Enantioselective Total Synthesis of Epothilones A and B Using Multifunctional Asymmetric Catalysis

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Received June 6, 2000

Abstract: An enantioselective total synthesis of epothilones A (**1**) and B (**2**) using multifunctional asymmetric catalysis such as a cyanosilylation of an aldehyde, an aldol reaction of an unmodified ketone with an aldehyde, and a protonation in the conjugate addition of a thiol to an α,β-unsaturated thioester has been achieved. We divided **1** and **2** into fragment A, fragment B, and fragment C. A catalytic asymmetric synthesis of fragments A and B was accomplished using a catalytic asymmetric cyanosilylation as a key step. An enantiocontrolled synthesis of fragment C was achieved in two ways. One is the use of a direct catalytic asymmetric aldol reaction of an unmodified ketone with an aldehyde as a key step, and the other utilizes a catalytic asymmetric protonation in the conjugate addition of a thiol to an α,β-unsaturated thioester as a key step. Suzuki cross-coupling of fragment A with fragment C followed by Yamaguchi lactonization as key steps led to an enantiocontrolled synthesis of epothilone A (**1**). On the other hand, Suzuki cross-coupling of fragment B with fragment C followed by Yamaguchi lactonization accomplished an enantiocontrolled synthesis of epothilone B (**2**).

Introduction

Epothilones (see Scheme 1 for epothilones A (**1**) and B (**2**)) show potent antitumor activity by binding and stabilizing microtubles in the same way as taxol, and they are promising drug candidates. Epothilones A (**1**) and B (**2**) were isolated from the myxobacteria of the genus *Sorangium*, and their structures were determined by Höfle et al.[1] Highly efficient total syntheses were disclosed by the research groups of Danishefsky, Nicolaou, Schinzer, and others,[2] making possible structure−activity relationships of epothilones. An enantioselective total synthesis, however, using simple asymmetric catalysts has not been achieved, although an enantioselective total synthesis of epothilone A (**1**) has been accomplished using antibody catalysts[2k] or an enzyme.[2t] Herein we report a full account of an enantioselective total synthesis of epothilones A (**1**) and B (**2**) using multifunctional asymmetric catalysts for a direct aldol reaction, a cyanosilylation, and a conjugate addition/enantioselective protonation, demonstrating the usefulness of these reactions for the catalytic asymmetric synthesis of complex molecules.

Retrosynthetic Analysis. Scheme 1 shows our retrosynthetic analysis of **1** and **2** using multifunctional asymmetric catalysis to control all the chiral centers included in **1** and **2**. The 16-membered rings of **1** and **2** were expected to be constructed by Suzuki coupling of fragments A and C and/or fragments B and C followed by Yamaguchi lactonization. Fragments A and B could be obtained by a catalytic asymmetric cyanosilylation of aldehyde **7** controlled by the Lewis acid−Lewis base bifunctional catalyst as a key step.[3] Fragment C could be synthesized by a catalytic asymmetric epoxidation and aldol reaction as key steps.[4,5] Alternatively, aldehyde **9** was expected to be constructed using a catalytic asymmetric protonation in the conjugate addition of thiol **17** to **18** as the key step.[6]

Synthesis of Fragments A and B. The requisite α,β-unsaturated aldehyde **7** for the catalytic asymmetric cyanosilylation was first synthesized according to reported procedures.[2h] With large amounts of **7** in hand, a catalytic asymmetric cyanosilylation was carefully examined, and the results are summarized in Table 1. The Lewis acid−Lewis base bifunctional asymmetric catalyst was prepared starting from Et_2AlCl

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10.1021/ja002024b CCC: $19.00
Published on Web 10/18/2000

Scheme 1. Molecular Structure and Retrosynthetic Analysis of Epothilone A (**1**) and B (**2**)

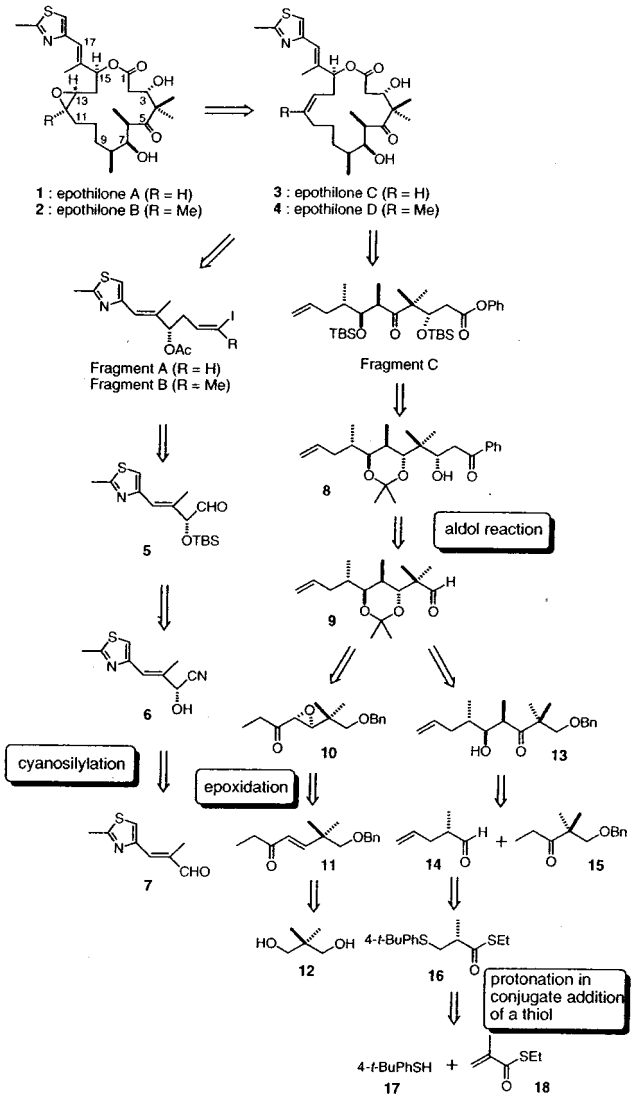


Table 1. Catalytic Asymmetric Synthesis of **6**

entry	concn (M)	cat. (mol %)	TMSCN (equiv)	slow addition of TMSCN (h)	time (h)	yield (%)	ee (%)
1	0.3	20	3	10	86	83	98
2	0.3	20	1.8	10	51	97	99
3	0.6	20	1.8	10	90	70	97
4	0.6	20	1.2	10	74	97	99
5	0.3	10	1.2	24	84	95	99
6	0.3	5	1.2	48	50	97	99

and the chiral ligand **19** according to the established procedure in our group (Scheme 2).[3]

The reaction was first carried out using 20 mol % of catalyst in the presence of *n*-$Bu_3P{=}O$ (80 mol %) and TMSCN (3 equiv, slow addition over 10 h) at −40 °C, giving the corresponding cyanohydrin **6** in 83% and 98% ee after acidic workup. The absolute configuration of **6** is already known,[3] and the ee was unequivocally determined by HPLC analysis after converting **6** to the TBS ether (DAICEL CHIRALPAK AD, hexane/2-propanol (100:1, v/v), flow rate 1.0 mL/min, retention times 7.5 min (*R*) isomer and 8.0 min (*S*) isomer, detection at 254 nm). In an attempt to improve the reactivity of the above-mentioned catalytic asymmetric cyanosilylation, further reactions using different conditions were examined. As shown in Table 1, finally we were pleased to find that the desired cyanohydrin **6** was obtained in 97% and in 99% ee in the presence of 5 mol % of catalyst by adding 1.2 equiv of TMSCN over 48 h. This result shows that the ratio of the catalyst and TMSCN is quite important to promote the reaction effectively. This tendency is very unusual in our catalytic asymmetric cyanosilylation of aldehydes, strongly indicating the following fact. It seems that the thiazole functional group activates TMSCN by the coordination to Si of TMSCN, allowing the substitution of Cl in the catalyst with CN. The asymmetric catalyst generated from Et_2-AlCN and the ligand **19** was shown to be rather unreactive for a catalytic asymmetric cyanosilylation of aldehydes in our group.[7] On the basis of the mechanistic studies,[3] the reaction should proceed through the proposed transition state shown in Figure 1. At present, however, the possibility that the actual reagent structure is TMSNC cannot be excluded. With large quantities of **6** in hand, the synthesis of fragments A and B was pursued. Direct conversion of **6** to the aldehyde **5** using DIBAL was first attempted (Scheme 3). The yield, however, was moderate, giving **5** only in about 40%. On the other hand, ethanolysis using HCl in ethyl alcohol followed by hydrolysis gave rise to the ester **20** in good yield accompanied by a small

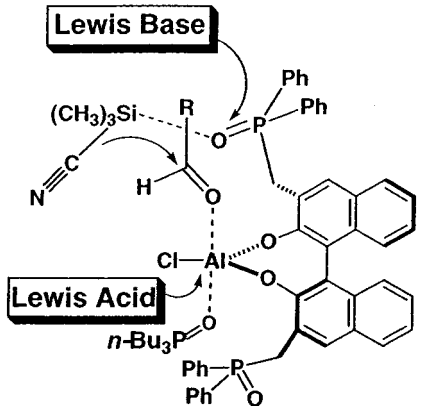
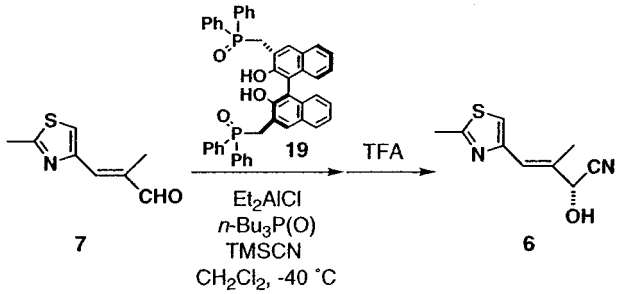


Figure 1. Proposed transition state for the catalytic asymmetric cyanosilylation.

Scheme 2. Catalytic Asymmetric Cyanosilylation



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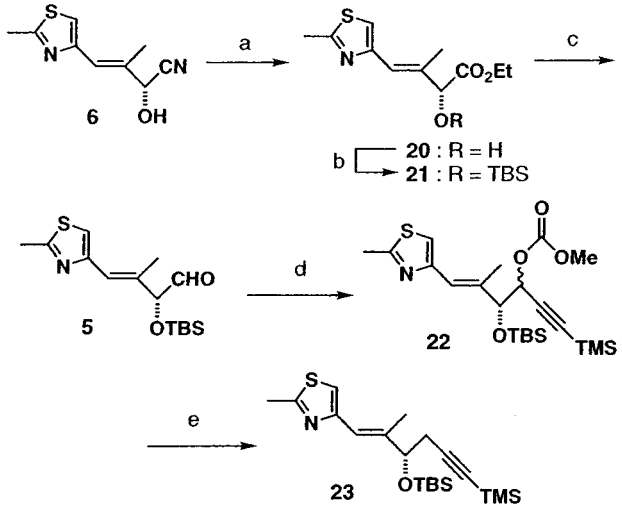
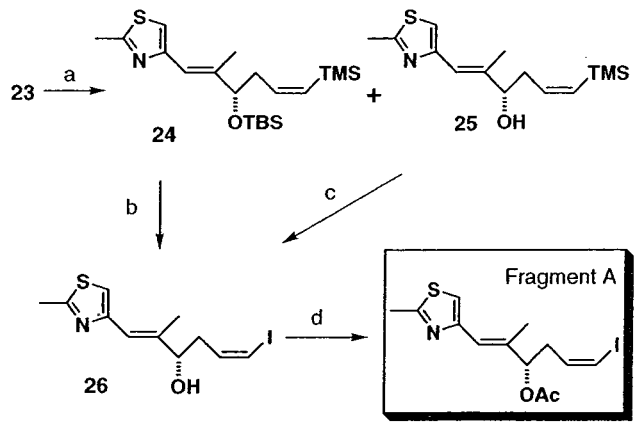
Scheme 3. Synthesis of Compound **23**[a]



[a] (a) HCl, EtOH, H_2O, 90 °C, 83%; (b) TBSCl, imidazole, DMF, 99%; (c) DIBAL, toluene, −78 °C, 94%; (d) TMSC≡CLi, THF, −78 °C; then $ClCO_2Me$, 79%; (e) $Pd(OAc)_2$, *n*-Bu_3P, HCO_2NH_4, benzene, 50 °C 51%.

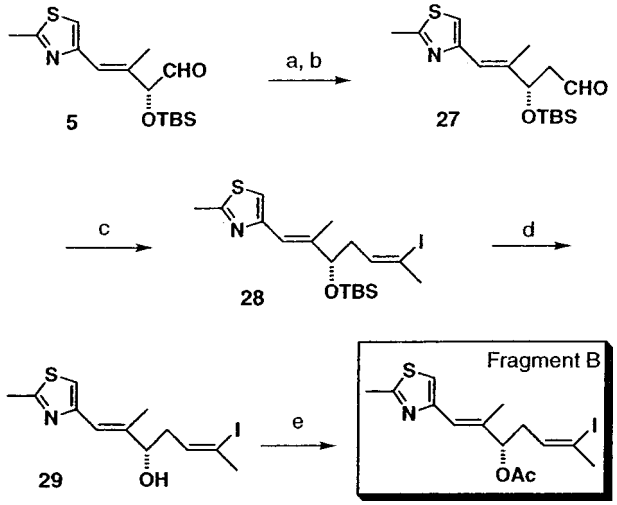
Scheme 4. Synthesis of Fragment A[a]



[a] (a) Ti(O*i*Pr)$_4$, *i*PrMgBr, Et_2O, −78 to −50 °C, 69% for **24**, 29% for **25**; (b) i. I_2, CH_2Cl_2; ii. HF·pyridine, THF, 75% (for two steps); (c) I_2, CH_2Cl_2, 59%; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 100%.

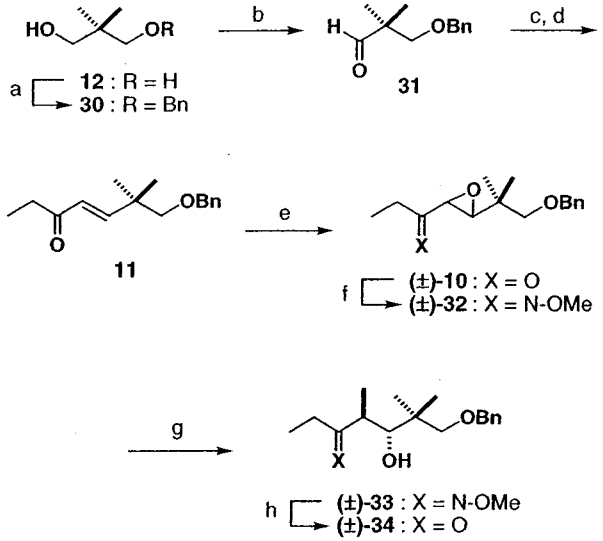
amont of the corresponding carboxylic acid. Since racemization was observed when the above reaction was carried out at ≥ 100 °C, the actual ethanolysis was performed at 90 °C. After protection of the alcohol as a TBS ether, the resulting ester **21** was reduced with DIBAL to give the desired aldehyde **5** in 77% overall yield from **6**. Reaction of **5** with the lithium acetylide followed by treatment with $ClCO_2Me$ afforded **22** in a mixture of diastereomers (79%), which underwent reduction with a catalytic amount of $Pd(OAc)_2$, *n*-Bu_3P, and HCO_2NH_4, giving **23** in 51% yield.[8] Then conversion of **23** to fragment A was first examined. In contrast to our expectation, hydroalumination of **23** using DIBAL did not afford the desired product under a variety of reaction conditions. On the other hand, hydrotitanation[9] proceeded well, giving **24** (69%) and **25** (26%) after acidic workup (Scheme 4). This successful transformation might be ascribed to lower Lewis acidity of low-valent titanium than DIBAL, thereby making the undesired coordination of the thiazole moiety to low-valent titanium unlikely. The silylalkene

Scheme 5. Synthesis of Fragment B[a]



[a] (a) $Ph_3P^+CH_2OMeCl^-$, LHMDS, THF, 68%; (b) $Hg(OAc)_2$ *n*-Bu_4NI, THF, H_2O, 60%; (c) $Ph_3P^+CH_2CH_3I^-$, *n*-BuLi, THF then I_2, then NaHMDS, 50%; (d) HF·pyridine, THF, 100%; (e) Ac_2O Et_3N, DMAP, CH_2Cl_2, 96%.

Scheme 6. Synthesis of Compound **34**[a]



[a] (a) i. PhCHO, TsOH·H_2O, benzene, reflux, ii. DIBAL, CH_2Cl_2 85%; (b) SO_3·Py, DMSO, Et_3N, 96%; (c) LDA, butanone, THF, −78 °C, 81%; (d) trifluoroacetic anhydride, CH_2Cl_2, then DBU 100%; (e) H_2O_2, NaOH aq, MeOH, 66%; (f) NH_2OMe·HCl AcONa, MeOH, 83%; (g) CuCN, MeLi, Et_2O, −78 °C, 60%; (h) Raney nickel (W2), H_2, H_3BO_3, acetone, THF, MeOH, H_2O 78%.

24 was successively treated with I_2 and HF·pyridine to give the *cis*-iodoalkene **26** (75%). Similarly, **25** was treated with I_2, furnishing **26** (59%). The resulting alcohol **26** was then protected as an acetate to provide fragment A (99% ee). The stereochemistry of the carbon−carbon double bond was confirmed by the ^1H NMR coupling constant (7.5 Hz). Transformation to fragment B was attempted next. Conversion of **23** to fragment B was first attempted under a variety of reaction conditions. However, this attempt was found to be unfruitful.

Thus, **5** was transformed into the aldehyde **27** using the Wittig reaction followed by hydrolysis in 41% overall yield,[10] which was further treated with iodophosphorane, giving **28** exclusively

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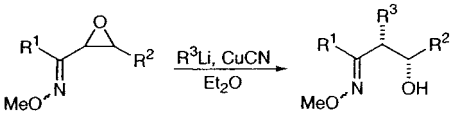
(9) Sato, F.; Ishikawa, H.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 85−88.

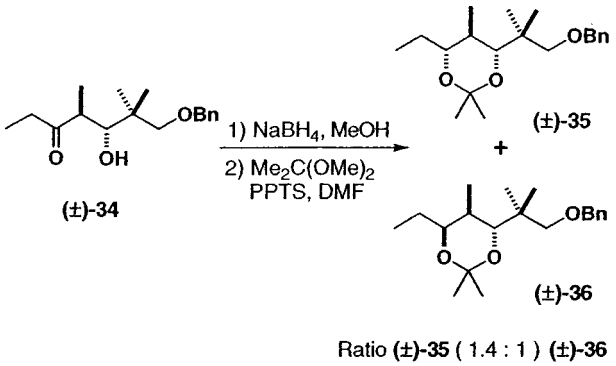
(10) Corey, E. J.; Narasaka, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1976**, *98*, 6417−6418.

Table 2. Epoxide Opening of *cis* Epoxy-oximes by Cuprate Reagents



entry	R^1	R^2	R^3	yield (%)
1	Me	pentyl	Me	77
2	propyl	pentyl	Me	72
3	phenethyl	pentyl	Me	85
4	phenethyl	pentyl	Bu	80
5	phenethyl	pentyl	Ph	80
6	phenethyl	pentyl	vinyl	50
7	pentyl	phenethyl	Me	81

Scheme 7. Conversion of (±)-**34** to Acetonides (±)-**35** and (±)-**36**



in 50% yield (Scheme 5).[11] Removal of the protecting group followed by acetylation gave rise to fragment B (99% ee) in 96% overall yield. The stereochemistry of the trisubstituted carbon−carbon double bond was determined by precedent.[2i]

Synthesis of Fragment C. According to the retrosynthetic analysis shown in Scheme 1, the synthesis of optically active fragment C was investigated. The requisite α,*β*-unsaturated ketone **11** was first synthesized starting from neopentyl glycol (**12**) as shown in Scheme 6. A catalytic asymmetric epoxidation of **11** was examined using the lanthanoid-containing asymmetric catalysts developed in our group.[4] Unfortunately, however, because of the steric hindrance of the quaternary carbon atom in the α-position to the double bond, only small amounts of the epoxide were obtained with low ee values. This unfortunate result led us to another strategy for the synthesis of optically active **8**. We envisioned that a direct aldol reaction of acetophenone with (±)-**9** (see Scheme 1) promoted by the heteropolymetallic asymmetric catalyst would give desired **8** by an effective catalyst control. Toward this aim **11** was oxidized with H_2O_2 to the epoxy ketone (±)-**10** which was then converted into the methyloxime (±)-**32**. The epoxide opening to give the *anti*-aldol (±)-**34** was achieved by using the cuprate reagent (→ (±)-**33**) and subsequent reduction with Raney nickel followed by hydrolysis.[12] To the best of our knowledge, this is a new method to prepare an *anti*-aldol).[13] The relative stereochemistry of (±)-**34** was determined by NOE experiments (Scheme 7) of the corresponding acetonides (±)-**35** and (±)-**36** obtained by $NaBH_4$ reduction followed by treatment with 2,2-dimethoxypropane and PPTS as shown in Figure 2.

(11) Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827−2828.

(12) For the related reaction, see: Corey, E. J.; Melvin, L. S., Jr.; Haslanger, M. F. *Tetrahedron Lett.* **1975**, 3117−3120.

(13) It is also possible to prepare *syn* aldols from *cis* enones by this method (Table 2).

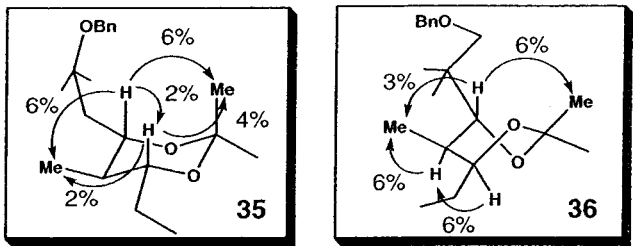


Figure 2. NOE results for (±)-**35** and (±)-**36**.

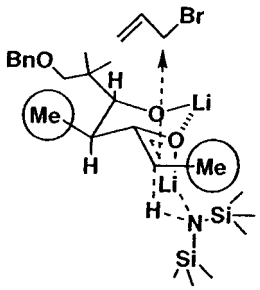
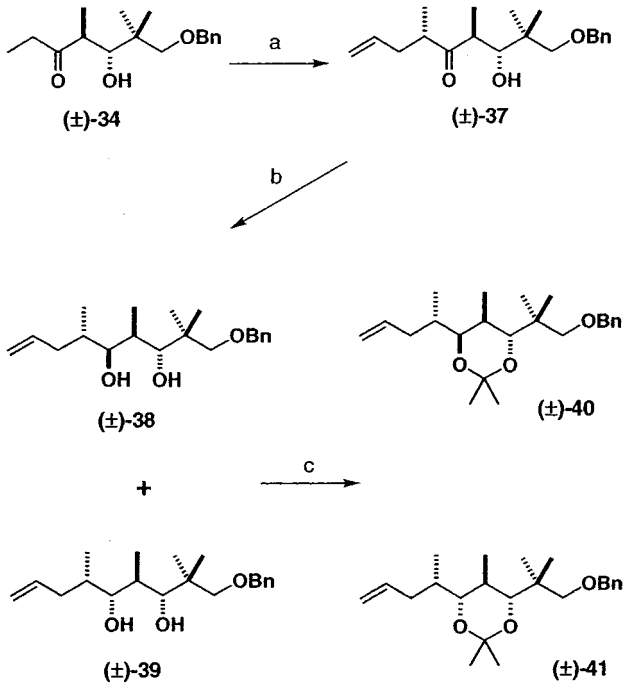


Figure 3. Formation of the (*Z*)-*O* enolate followed by alkylation.

Scheme 8. Synthesis of Compound (±)-**40** and (±)-**41**[a]



[a] (a) LHMDS, allyl bromide, DMPU, THF, −78 °C, 48% (recovery of **34**, 52%); (b) $Me_4NBH(OAc)_3$, AcOH, MeCN, 79% for **38**, 11% for **39**; (c) methoxypropene, TsOH, DMF, 96% for **40**, 73% for **41**.

Toward the synthesis of fragment C, the next step was the stereocontrolled allylation of (±)-**34**. After protection of the hydroxyl group of (±)-**34** as a TBS ether, the allylation was examined. Unfortunately, however, although the reaction proceeded well, only a low stereoselectivity was observed. In striking contrast to this result, when the allylation was carried out using nonprotected (±)-**34** in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), only the desired product was formed albeit in modest yield (48%, conversion yield 100%). This highly stereoselective allylation seems to proceed through the (*Z*)-*O* enolate shown in Figure 3. The reason the chemical yield is just modest might be ascribed to the generation of LiBr, which prevents the reaction from proceeding effectively. When alkali metals other than lithium

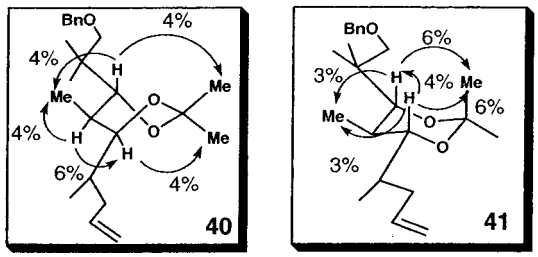
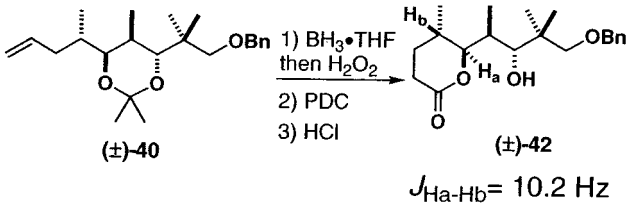
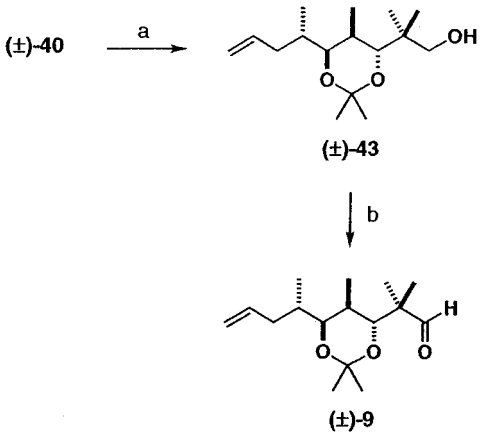


Figure 4. NOE results for (±)-**40** and (±)-**41**.

Scheme 9. Determination of the Stereochemistry of the Allylation



Scheme 10. Synthesis of (±)-**9**[a]

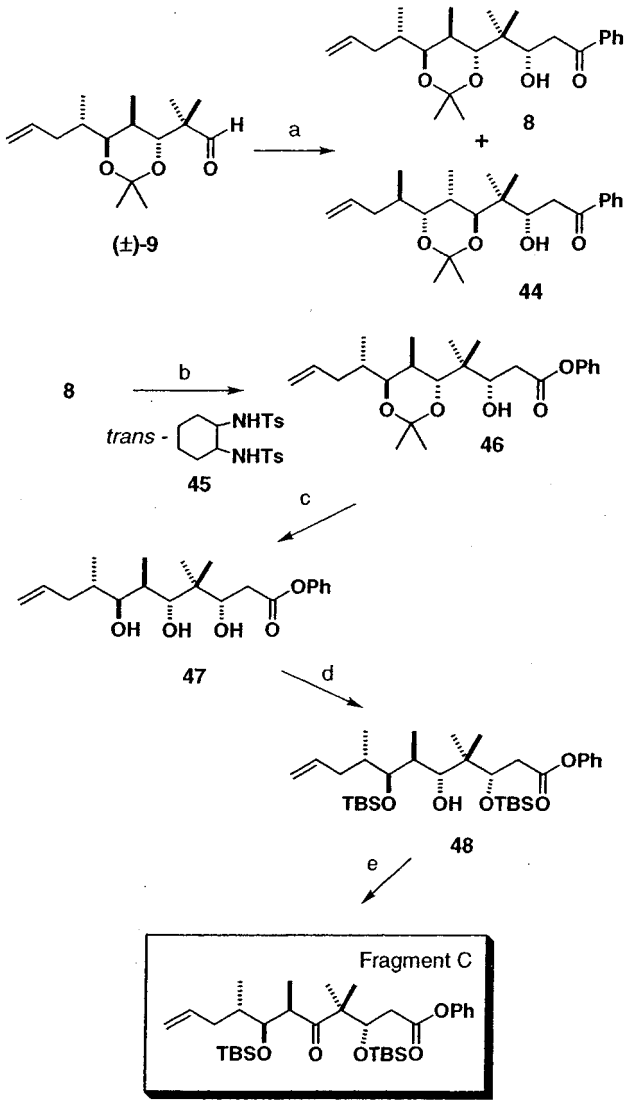


[a] (a) Li, liquid NH_3, *t*-BuOH, THF, 100%; (b) TPAP, NMO, MS 4A, CH_2Cl_2, 89%.

were utilized, a lower stereoselectivity was observed. Stereoselective reduction of (±)-**37** with $Me_4NBH(OAc)_3$[14] (Scheme 8) resulted in the formation of the desired alcohol **38** (79%) together with the undesired alcohol **39** (11%). The stereochemistry of the resulting secondary alcohol was unequivocally determined by NOE experiments of the corresponding acetonides (±)-**40** and (±)-**41** (Figure 4). At this stage, the stereochemistry of the allylation was determined as follows. Hydroboration of (±)-**40** followed by oxidative workup and further oxidation with PDC gave the corresponding carboxylic acid. Treatment of this carboxylic acid with HCl resulted in the removal of the protecting group and the subsequent lactonization, giving the lactone (±)-**42**. The coupling constant between H_a and H_b of (±)-**42** was shown to be 10.2 Hz, confirming the stereochemistry of the allylation (Scheme 9). Birch reduction of (±)-**40** and subsequent oxidation with TPAP gave rise to the requisite (±)-aldehyde **9** in 89% overall yield (Scheme 10).

In the next step, the direct catalytic asymmetric aldol reaction with acetophenone was carefully examined (Scheme 11). After several attempts, it was found that treatment of (±)-**9** with 8 equiv of acetophenone in the presence of the heteropolymetallic asymmetric catalyst generated from (*R*)-$LaLi_3$tris(binaphthoxide)

Scheme 11. Catalytic Asymmetric Aldol Reaction and Subsequent Conversion to Fragment C[a]



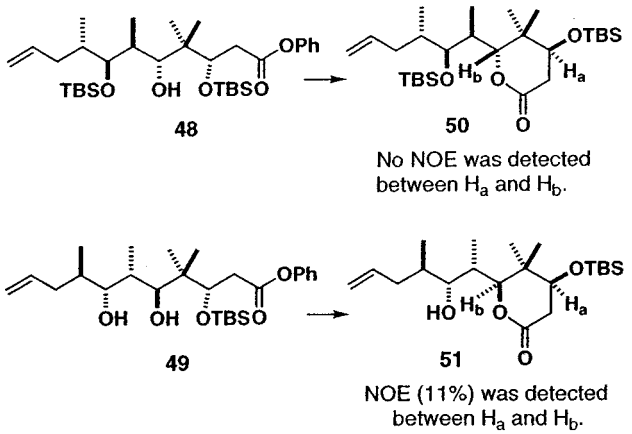
[a] (a) Acetophenone, (*R*)-LLB, KHMDS, H_2O, THF, −20 °C, 30% (89% ee) for **8**, 29% (88% ee) for **44** (recovery of **9** 36%); (b) BTSP, $SnCl_4$, MS 4A, ligand **45**, K_2CO_3, CH_2Cl_2, 69%; (c) BCl_3 CH_2Cl_2, −78 °C, 87%; (d) TBSOTf, *i*Pr_2NEt, CH_2Cl_2; (e) Dess−Martin periodinane, CH_2Cl_2, 65% (for two steps).

(LLB) (20 mol %), KHMDS (18 mol %), and H_2O (40 mol %)[5] at −20 °C for 168 h gave the desired aldol product **8** in 30% and in 89% ee together with the diastereomer **44** in 29% and in 88% ee. Under these reaction conditions, 36% of (±)-**9** was recoverd and the excess acetophenone was also completely recovered. It appeared that the reaction became sluggish as the aldol reaction proceeded. In addition, when the reaction was worked up, a trace amount of the dehydrated product was observed. The stereochemistry of the newly formed secondary alcohol in both **8** and **44** was determined to be *S* by the Mosher method.[15] As far as we know, this is the first example of a catalytic resolution of a racemic compound in an aldol reaction using a simple asymmetric catalyst.[2k,t] The desired diastereomer **8** underwent Baeyer−Villiger oxidation with bis(trimethylsilyl) peroxide (BTSP), $SnCl_4$, and ligand (±)-**45** to give the ester **46** in 69% yield (conversion yield 88%).[16] Treatment of the ester **46** with BCl_3 (87%) followed by selective protection as a TBS

(14) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

(15) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

Scheme 12. Determination of the Stereochemistry of Aldol Products **8** and **44**



ether furnished **48**, and subsequent oxidation with Dess−Martin periodinane gave fragment C in 65% overall yield. The stereochemistry of **8** and the diastereomer **44** was determined as follows (Scheme 12). Treatment of **48** and/or **49** with acid afforded the lactones **50** and **51**, respectively, and NOE experiments of the lactones resulted in the determination of the stereochemistry of **8** and **44**. It should be mentioned that a strategy of this type would be useful for exploring the diversity of epothilones in terms of medicinal chemistry. On the basis of the mechanistic studies,[5] the transition model for this aldol reaction is proposed to be as shown in Figure 5.

As shown above, we have succeeded in synthesizing fragment C in 89% ee. Unfortunately, however, the above synthesis is not effective due to the necessity of a catalytic resolution, although we believe that the synthesis is quite interesting in terms of an asymmetric synthesis of the requisite compound. Therefore, we further investigated the feasibility of a catalytic asymmetric synthesis of the aldehyde **9**. As already mentioned in the retrosynthetic analysis of fragment C, we envisioned that a catalytic asymmetric protonation in the conjugate addition of a thiol to an α,β-unsaturated thioester[6] would lead to a catalytic asymmetric synthesis of **9**. Reaction of **17** with **18** in the presence of 5 mol % of (*S*)-$SmNa_3$tris(binaphthoxide) (SmSB) gave **16** in 92% yield and 88% ee, which was then reduced with $LiAlH_4$ followed by protection of the resulting primary alcohol as a MPM ether, furnishing **53** in 93% overall yield (Scheme 13). The absolute configuration of **16** is already known,[6] and the ee was determined by HPLC analysis (see the Experimental Section). The transition state model is proposed to be as shown in Figure 6. The sulfide **53** was oxidized with *m*CPBA, and the subsequent Pummerer rearrangement[17] gave rise to the corresponding aldehyde **54**, which was reduced with $NaBH_4$ to afford the alcohol **55**. The primary alcohol of **55** was brominated, and the resulting bromide **56** was reacted with lithium divinylcuprate to yield the alkene **57**. Deprotection of the MPM group in **57** with DDQ and subsequent oxidation gave the very volatile aldehyde **14**. Carefully handling, the aldol reaction of **14** with the ketone **15** successfully procceeded to give the desired aldol product **13** (60%, 4:1 ratio).[2s] After protection of the secondary alcohol as a TBS ether, reduction using DIBAL afforded the alcohol with the desired stereochemistry, which was converted to the opticlly active acetonide **40**.

As already discussed, **40** was transformed into the aldehyde **9**. During the synthetic route mentioned above (**16** → **9**), no racemization was observed. Thus, although the synthesis involves relatively many steps, we have succeeded in synthesizing optically active **9** in a catalytic asymmetric manner using multifunctional asymmetric catalysis.

(16) Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971−973.

(17) Konno, K.; Hashimoto, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1986**, *27*, 3865−3868.

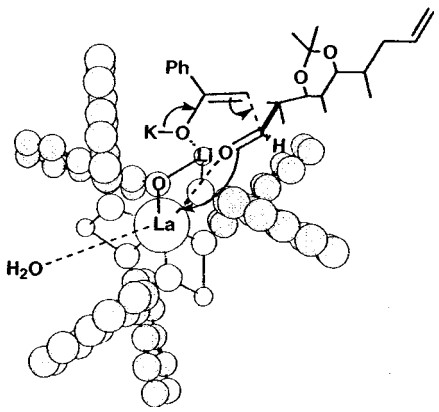
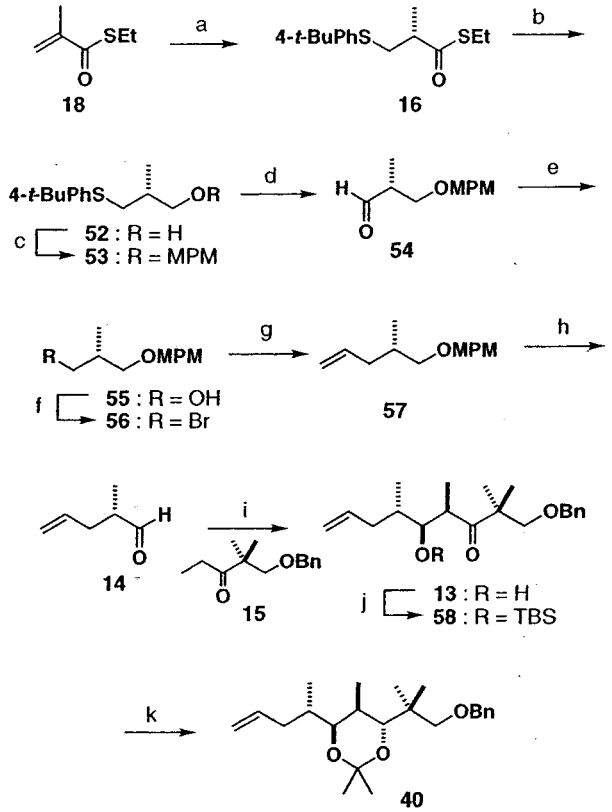


Figure 5. Proposed transition state of the catalytic asymmetric aldol reaction.

Scheme 13. Synthesis of Optically Active **40** Using Catalytic Aymmetric Protonation in the Conjugate Addition of a Thiol to a Conjugated Thioester[a]



[a] (a) (*S*)-SmSB (5 mol %), 4-*t*-BuPhSH (**17**), CH_2Cl_2, 92%, 88% ee; (b) LAH, Et_2O, 95%; (c) MPMCl, NaH, DMF, 98%; (d) i. *m*CPBA, CH_2Cl_2, −20 °C, ii. trifluoroacetic anhydride, pyridine CH_2Cl_2, 78%; (e) $NaBH_4$, MeOH, 100%; (f) CBr_4, PPh_3, CH_2Cl_2, 100%; (g) CuCN, MeLi, tetravinyltin, THF, −78 °C → rt 88%; (h) i. DDQ, H_2O, CH_2Cl_2, ii. TPAP, NMO, MS 4A CH_2Cl_2; (i) LDA **15**, THF, −78 °C, 60% for three steps (4:1); (j) TBSOTf, iPr_2NEt, CH_2Cl_2, 100%; (k) i. DIBAL, toluene −78 °C, ii. methoxypropene, TsOH, DMF, 91%.

Total Synthesis of Epothilones A and B. Having synthesized the requisite fragments A, B and C, first of all, the synthesis of epothilone A (**1**) was examined (Scheme 14). Following mainly the synthesis achieved by Danishefsky et al.,[2a,i] however, it was found that, in our case, hydroboration of fragment C (89% ee)

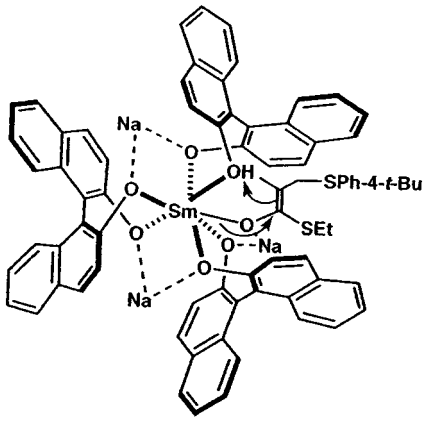
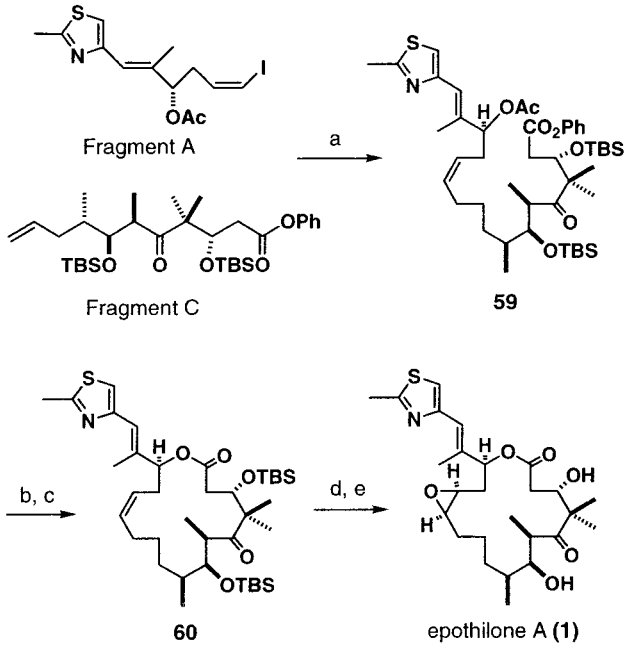


Figure 6. Proposed transition state of the catalytic asymmetric protonation in the conjugate addition of a thiol to a conjugated thioester.

Scheme 14. Total Synthesis of Epothilone A (**1**)[a]



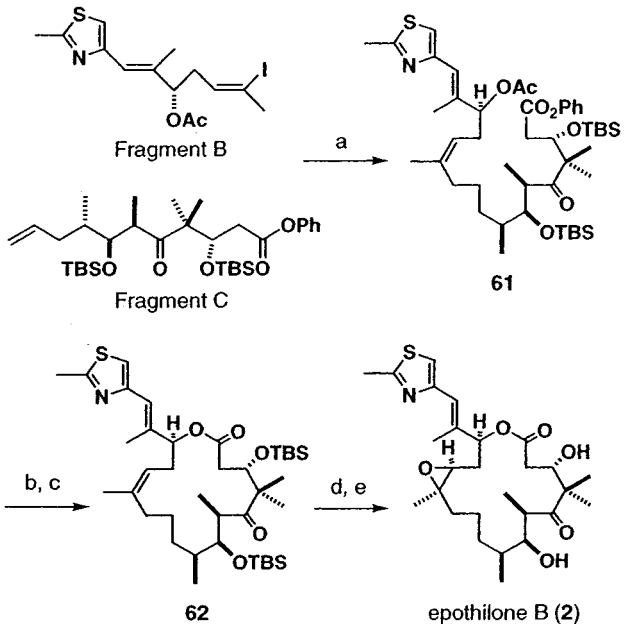
[a] (a) 9-BBN (2 molar equiv), ultrasound, THF, then $PdCl_2$(dppf) (50 mol %), K_3PO_4, DMF, H_2O, 60 °C, 50%; (b) NaOH, MeOH, H_2O, 84%; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, 88%; (d) HF·pyridine, THF, 99%; (e) 3,3-dimethyldioxirane, CH_2Cl_2, −35 °C, 49%.

using 9-BBN did not proceed well. Fortunately this reaction proceeded well with ultrasound,[18] and the subsequent coupling reaction with fragment A in the presence of $PdCl_2$(dppf) gave the desired product **59** (99% ee) in 50% yield together with a trace amount of the diastereomer (less polar). Hydrolysis of **59** with NaOH in MeOH furnished the hydroxy acid in 84%, which was followed by Yamaguchi lactonization, affording the lactone **60** (88%). Finally, treatment of **60** with HF·pyridine followed by epoxidation gave rise to epothilone A (**1**) in 99% ee [4 (desired):1 (undesired) ratio]. The structure of **1** was unequivocally confirmed (^{1}H and ^{13}C NMR spectra) by comparison with the spectral data kindly provided by Prof. K. C. Nicolaou.

Similarly, the total synthesis of epothilone B (**2**) was achieved. Suzuki cross-coupling of fragment B with fragment C gave **61** (99% ee) in 50% yield (Scheme 15), again accompanied by the formation of a trace amount of the diastereomer (less polar).

(18) Brown, H. C.; Racherla, U. S. *Tetrahedron Lett.* **1985**, *26*, 2187−2190.

Scheme 15. Total Synthesis of Epothilone B (**2**)[a]



[a] (a) 9-BBN (2 molar equiv), ultrasound, THF, then $PdCl_2$(dppf) (20 mol %), K_3PO_4, DMF, H_2O 60 °C, 50%; (b) NaOH, MeOH H_2O, 93%; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, 90%; (d) HF·pyridine, THF, 92%; (e) 3,3-dimethyldioxirane, CH_2Cl_2, −35 °C 97%.

Hydrolysis of **61** followed by Yamaguchi lactonization and the subsequent removal of the silyl group gave epothilone D (**4**) in 84% overall yield. Finally, we were pleased to obtain epothilone B (**2**) by treatment with 3,3-dimethyldioxirane in 97% yield, which was identified by comparison with an authentic sample (^{1}H and ^{13}C NMR spactra) kindly provided by Prof. K. C. Nicolaou.

Conclusions

We have achieved an enantioselective total synthesis of epothilones A (**1**) and B (**2**) by controlling all the chiral centers using multifunctional asymmetric catalysis. These syntheses have succeeded in demonstrating the usefulness of multifunctional asymmetric catalysis such as a cyanosilylation, an aldol reaction, and a conjugate addition/protonation for the synthesis of complex molecules. Although the practicability of the shown synthesis is still unsatisfactory, we would like to emphasize that this is the first step of enantiocontrolled syntheses of complex molecules using multifunctional asymmetric catalysis. To improve the practicability of the total synthesis, further investigations are currently under way.

Experimental Section

(2*R*,3*E*)-2-Hydroxy-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butenenitrile (6). In a flame-dried flask **19** (64 mg, 0.0895 mmol) was placed and dried at 50 °C for 2 h under the reduced pressure. Then 3 mL of dichloromethane was added, followed by the addition of diethylaluminum chloride (93 μL, 0.089 mmol, 0.96 M in hexane) under an argon atmosphere. After stirring for 10 min, tributylphosphine oxide (78 mg, 0.358 mmol) in dichloromethane (1.2 mL) was added at room temperature. The resulting mixture was stirred at the same temperature for 1 h to give a clear solution. To this stirred solution of the catalyst was added aldehyde **7** (300 mg, 1.79 mmol) in dichloromethane (1.4 mL) at −40 °C. After 30 min, TMSCN (287 μL, 2.15 mmol) was slowly added over 48 h using a syringe pump. (CAUTION! TMSCN should be added dropwise from the top of the flask, where the temperature may be above 15 °C, because the melting point of

TMSCN is 11−12 °C.) The reaction mixture was allowed to stir for 39 h at the same temperature. Trifluoroacetic acid (2.0 mL) was added at −40 °C, and the mixture was stirred vigorously at room temperature for 1 h to hydrolyze the trimethylsilyl ether of the product. After the addition of ethyl acetate (30 mL), the mixture was stirred for a further 30 min. The organic layer was separated and washed with water. The aqueous layer was extracted with ethyl acetate (30 mL × 2). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude product was further purified by flash chromatography (ethyl acetate/hexane 1:3) to give cyanohydrin **6** (337 mg, 97%): $[\alpha]^{25}_D$ +16.5 (*c* 0.7, $CHCl_3$) (99% ee); IR (neat) 3039, 2821, 2694, 2361, 1508, 1450, 1381, 1277, 1197, 1166, 1091, 980, 901, 813, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.74 (m, 1H), 4.98 (m, 1H), 2.73 (s, 3H), 2.19 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 151.3, 134.8, 122.0, 118.8, 117.9, 66.7, 19.3, 15.3; EI-MS *m*/*z* 194 (M^+); EI-HRMS calcd for $C_9H_{10}N_2OS$ (M^+).

(2*R*,3*E*)-Ethyl 2-Hydroxy-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butanoate (20). Cyanohydrin **6** (348 mg, 1.79 mmol) was dissolved in a ca. 5.6 M HCl ethanol solution (10 mL) containing concentrated HCl aq (5 mL). The reaction mixture was heated at 90 °C for 5 h and then poured into saturated aqueous $NaHCO_3$ (100 mL) at 0 °C. The mixtire was extracted with AcOEt (100 mL) three times, and the combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:1) to give ester **20** (359 mg, 1.486 mmol; 83%) as a solid: $[\alpha]^{23}_D$ −116 (*c* 0.72, $CHCl_3$) (99% ee); IR (neat) 3465, 2980, 2925, 1733, 1444, 1192, 1080, 1024, 879, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.63 (s, 1H), 4.64 (d, J = 5.6 Hz, 1H), 4.27 (dq, J = 3.5, 7.0 Hz, 1H), 4.25 (dq, J = 3.5, 7.0 Hz, 1H), 3.29 (d, J = 5.6 Hz, 1H), 2.71 (s, 3H), 2.07 (m, 3H), 1.27 (dd, J = 7.0, 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 165.1, 152.8, 136.2, 123.1, 117.1, 77.0, 62.6, 19.6, 14.5, 14.5; EI-MS *m*/*z* 241 (M^+); EI-HRMS calcd for $C_{11}H_{15}NO_3S$ (M^+) 241.0772, found 241.0771.

(2*R*,3*E*)-Ethyl 2-(*tert*-Butyldimethylsilyloxy)-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butenoate (21). To a solution of ester **20** (309 mg, 1.28 mmol) in DMF (2 mL) were added imidazole (262 mg, 3.84 mmol) and TBSCl (290 mg, 1.92 mmol) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. A saturated aqueous $NaHCO_3$ (20 mL) was added to the mixture followed by the addition of AcOEt (20 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue that was purified by silica gel flash chromatography (AcOEt/hexane, 1:10) to give the silyl ether **21** (451 mg, 1.27 mmol; 99%) in 99% ee as a colorless oil: $[\alpha]^{22}_D$ −41.8 (*c* 0.85, $CHCl_3$) (99% ee); IR (neat) 2929, 2857, 1752, 1472, 1252, 1115, 1030, 893, 838, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.63 (s, 1H), 4.67 (m, 1H), 4.17 (q, J = 7.0 Hz, 2H), 2.71 (s, 3H), 2.09 (m, 3H), 1.26 (t, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 164.9, 153.1, 137.4, 121.6, 116.7, 78.5, 61.3, 26.1, 19.6, 18.7, 14.6, 14.5, −4.7, −4.7; EI-MS *m*/*z* 355 (M^+); EI-HRMS calcd for $C_{17}H_{29}NO_3SiS$ (M^+) 355.1637, found 355.1636. The enantiomeric excess was determined by chiral stationary phase HPLC analysis [DAICEL CHIRALPAK AD, hexane/2-propanol (250:1, v/v), flow rate 1.0 mL/min, retention time 9.5 min (*S*)-isomer and 11.5 min (*R*)-isomer, detection at 254 nm].

(2*R*,3*E*)-2-(*tert*-Butyldimethylsilyloxy)-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butenal (5). Ester **21** (105 mg, 0.3 mmol) was dissolved in toluene (20 mL) and cooled to −78 °C. DIBAL (325 μL, 1 M solution in toluene, 0.32 mmol) was added dropwise to maintain the temperature at −78 °C. After the addition was complete, the reaction mixture was stirred at the same temperature for 1 h. A saturated aqueous Rochelle salt solution (40 mL) and AcOEt (30 mL) were successively added, and the quenched mixture was allowed to warm to room temperature and stirred for 2 h. The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:10) to give the aldehyde **5** (86 mg, 0.28 mmol; 94%) as a colorless oil: $[\alpha]^{20}_D$ +148.9 (*c* 0.75, $CHCl_3$) (99% ee); IR (neat) 2929, 2857, 2360, 1732, 1471, 1254, 1109, 839, 780, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.37 (d, J = 1.37 Hz, 1H), 6.99 (s, 1H), 6.71 (s, 1H), 4.42 (m, 1H), 2.71 (s, 3H), 2.05 (m, 3H), 0.94 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 165.2, 152.8, 134.6, 121.9, 117.0, 83.3, 26.1, 19.6, 18.6, 15.3, −4.5, −4.6; EI-MS *m*/*z* 311 (M^+); EI-HRMS calcd for $C_{15}H_{25}NO_2SiS$ (M^+) 311.1375, found 311.1378.

(1*E*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1-hexen-5-yne (23). (Trimethylsilyl)-acetylene (198 μL, 1.4 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. Butyllithium (903 μL, 1.55 M hexane solution, 1.4 mmol) was added, and the reaction mixture was stirred at the same temperature for 20 min. Then aldehyde **5** (218 mg, 0.7 mmol) in THF (1 mL) was added to the reaction mixture. After 40 min methyl chloroformate (216 μL, 2.8 mmol) was added and the whole mixture was stirred for additional 30 min. A saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:10) to give a diastereomixture of carbonate **22** (259 mg, 0.55 mmol; 79%) as a colorless oil. To a solution of carbonate **22** (65 mg, 0.14 mmol), palladium acetate (6.2 mg, 0.028 mmol), and ammonium formate (35 mg, 0.56 mmol) in benzene (2 mL) was added tributylphosphine, and the mixture was heated at 50 °C. After 24 h the mixture was evaporated under reduced pressure and the residue was purified by silica gel flash chromatography (AcOEt/hexane, 1:100) to give alkyne **23** (28 mg, 0.07 mmol; 51%) as a colorless oil: $[\alpha]^{24}_D$ +31.3 (*c* 0.5, $CHCl_3$) (99% ee); IR (neat) 2956, 2856, 2177, 1730, 1471, 1249, 1083, 933, 843, 777, 642 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.45 (s, 1H), 4.32 (dd, J = 5.0, 7.2 Hz, 1H), 2.71 (s, 3H), 2.50 (dd, J = 7.2, 16.7 Hz, 1H), 2.43 (dd, J = 5.0, 16.7 Hz, 1H), 2.01 (m, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.12 (s, 9H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 153.1, 141.2, 119.4, 115.6, 104.8, 86.2, 76.9, 29.0, 25.9, 19.3, 18.4, 13.8, 0.14, −4.6, −4.8; EI-MS *m*/*z* 393 (M^+); EI-HRMS calcd for $C_{20}H_{35}NOSi_2S$ (M^+) 393.1978, found 393.1984.

(1*E*,3*S*,5*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadiene (24) and (1*E*,3*S*,5*Z*)-2-Methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadien-3-ol (25). Alkyne **23** (60 mg, 0.15 mmol) was dissolved in Et_2O (3 mL) and cooled to −78 °C. Ti(O-*i*-Pr)$_4$ (225 μL, 0.76 mmol)and then *i*-PrMgCl (762 μL, 2.0 M Et_2O solution, 1.52 mmol) were added, and the mixture was warmed to −50 °C and stirred for 1 h. A saturated aqueous NH_4Cl solution (20 mL) was added to the mixture followed by the addition of AcOEt (20 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:20 → 1:2) to give alkene **24** (42 mg, 0.105 mmol; 69%) and **25** (11 mg, 0.04 mmol; 26%). **24**: $[\alpha]^{25}_D$ +12.5 (*c* 0.45, $CHCl_3$) (99% ee); IR (neat) 2927, 2855, 1731, 1461, 1249, 1078, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.47 (s, 1H), 6.30 (m, 1H), 5.56 (m, 1H), 4.17 (dd, J = 5.2, 7.3 Hz, 1H), 2.71 (s, 3H), 2.44 (m, 1H), 2.35 (m, 1H), 2.01 (m, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.06 (s, 9H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 153.7, 145.9, 142.8, 131.3, 119.5, 115.7, 79.4, 41.1, 26.5, 19.8, 18.9, 14.5, 0.85, −4.0, −4.3; EI-MS *m*/*z* 395 (M^+); EI-HRMS calcd for $C_{20}H_{37}NOSi_2S$ (M^+) 395.2134, found 395.2134. **25**: $[\alpha]^{22}_D$ −7.8 (*c* 0.23, $CHCl_3$) (99% ee); IR (neat) 3388, 2955, 2855, 1725, 1600, 1443, 1248, 1074, 838, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.51 (s, 1H), 6.26 (m, 1H), 5.63 (m, 1H), 4.15 (m, 1H), 2.65 (s, 3H), 2.42 (m, 2H), 2.00 (m, 3H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 147.6, 144.0, 141.5, 128.6, 119.2, 115.8, 100.7, 39.3, 19.3, 14.5, 0.34; EI-MS *m*/*z* 281 (M^+); EI-HRMS calcd for $C_{14}H_{23}NOSiS$ (M^+) 281.1270, found 281.1275.

(1*E*,3*S*,5*Z*)-2-Methyl-6-iodo-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadien-3-ol (26). To a solution of alkene **24** (9 mg, 0.023 mmol) in CH_2Cl_2 (1.5 mL) was added iodine (17 mg, 0.068 mmol), and the mixture was stirred at room temperature for 12 h. The mixture was evaporated under reduced pressure, and the residue was purified by silica gel flash

chromatography (CH_2Cl_2) to give a mixture of iodoalkenes which was directly used for the next step. To a mixture of iodoalkenes in THF (1 mL) was added HF·Py (0.5 mL) at 0 °C, and the mixture was stirred at room temperature for 12 h. Then the mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) at 0 °C and extracted with AcOEt (20 mL) three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue that was successively purified by silica gel flash chromatography (AcOEt/hexane, 1:1) and preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1:1.5) to give hydroxyalkene **26** (5.7 mg, 0.017 mmol; 75% in two steps): $[\alpha]^{26}_D$ −11.0 (*c* 0.25, $CHCl_3$) (99% ee); IR (neat) 3388, 2922, 1653, 1507, 1439, 1290, 1189, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.57 (s, 1H), 6.35 (dt, J = 1.4, 7.5 Hz, 1H), 6.28 (dt, J = 6.3, 7.5 Hz, 1H), 4.33 (t, J = 6.5 Hz, 1H), 2.71 (s, 3H), 2.51 (m, 2H), 2.08 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 152.7, 141.2, 137.5, 119.5, 116.0, 84.8, 76.2, 40.6, 19.3, 14.5; EI-MS *m*/*z* 335 (M^+); EI-HRMS calcd for $C_{11}H_{14}NOSI$ (M^+) 334.9841, found 334.9839.

(1*E*,3*S*,5*Z*)-2-Methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadien-3-yl acetate (Fragment A). To a solution of alkene **26** (4.5 mg, 0.013 mmol) in CH_2Cl_2 (1.5 mL) were added triethylamine (7.5 μL, 0.054 mmol), acetic anhydride (2.5 μL, 0.027 mmol), and then small amounts of DMAP. The mixture was stirred at room temperature for 6 h, and then a saturated aqueous NH_4Cl solution (20 mL) was added to the mixture followed by the addition of AcOEt (20 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:4) to give fragment A (5.1 mg, 0.013 mmol; quant): $[\alpha]^{26}_D$ −27.7 (*c* 0.5, $CHCl_3$) (99% ee); IR (neat) 2923, 1737, 1369, 1234, 1019 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.53 (s, 1H), 6.35 (dt, J = 1.3, 7.5 Hz, 1H), 6.18 (dt, J = 6.5, 7.5 Hz, 1H), 5.40 (t, J = 6.4 Hz, 1H), 2.71 (s, 3H), 2.60 (m, 2H), 2.10 (m, 3H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 165.1, 152.7, 137.0, 136.6, 121.2, 116.8, 85.5, 77.2, 38.8, 21.5, 19.6, 15.3; EI-MS *m*/*z* 377 (M^+); EI-HRMS calcd for $C_{13}H_{16}NO_2SI$ (M^+) 376.9947, found 376.9949.

(1*E*,3*S*,5*Z*)-2-Methyl-6-iodo-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadien-3-ol (26). To a solution of alkene **25** (11 mg, 0.039 mmol) in CH_2Cl_2 (1 mL) was added iodine (50 mg, 0.2 mmol), and the mixture was stirred at room temperature for 12 h. The mixture was evaporated under reduced pressure, and the residue was successively purified by silica gel flash chromatography (CH_2Cl_2) and then preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1:1.5) to give iodoalkene **26** (7.7 mg, 0.023 mmol; 59%).

(3*S*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)-4-pentenal (27). To a suspension of (methoxymethyl)-triphenylphosphonium chloride (216 mg, 0.63 mmol) in THF (4 mL) was added LHMDS (630 μL, 1.0 M THF solution, 0.63 mmol) at 0 °C, and the mixture was stirred at room temperature for 20 min. Then the mixture was cooled to −78 °C, aldehyde **5** (131 mg, 0.42 mmol) in THF (1 mL) was added to the mixture, which was then allowed to warm to room temperature gradually and stirred for 2 h. H_2O (20 mL) was added to the mixture followed by the addition of AcOEt (20 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by alumina flash chromatography (AcOEt/hexane, 1:30) to give the enol ether (91 mg, 0.27 mmol; 68%) which was immediately used in the next step.

To a solution of the enol ether (91 mg, 0.27 mmol) in THF (4 mL) and H_2O (0.4 mL) was added mercury acetate (402 mg, 1.26 mmol), and the mixture was stirred for 2.5 h. Tetrabutylammonium iodide (1.55 g, 4.2 mmol) was added to the solution, and the whole was stirred for an additional 2 h. Saturated aqueous NH_4Cl (20 mL) was added to the mixture followed by the addition of AcOEt (20 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:6) to give aldehyde **27** (52 mg, 0.16 mmol; 60%) as a colorless oil: $[\alpha]^{19}_D$ −21.8 (*c* 2.4, $CHCl_3$) (99% ee); IR (neat) 2928, 2856, 1726, 1389, 1254, 1083, 838, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (dd, J = 2.9, 2.9 Hz, 1H), 6.94 (s, 1H), 6.56 (s, 1H), 4.69 (dd, J = 3.9, 8.1 Hz, 1H), 2.73 (ddd, J = 2.9, 8.1, 10.1 Hz, 1H) 2.70 (s, 3H), 2.50 (ddd, J = 2.9, 3.9, 10.1 Hz, 1H), 2.04 (m, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 165.0, 153.0, 140.7, 119.6, 116.2, 74.3, 50.4, 26.0, 19.5, 18.4, 14.4, −4.3, −4.9; EI-MS *m*/*z* 325 (M^+); EI-HRMS calcd for $C_{16}H_{27}NO_2SiS$ (M^+) 325.1532, found 325.1630.

(1*E*,3*S*,5*Z*)-3-(*tert*-Butyldimethylsilyloxy)-6-iodo-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-heptadiene (28). To a suspension of (ethyl)triphenylphosphonium iodide (200 mg, 0.48 mmol) in THF (1 mL) was added butyllithium (315 μL, 1.52 M hexane solution, 0.48 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. Then the mixture was added to a solution of iodine (122 mg, 0.48 mmol) in THF (2 mL) at −78 °C, and the whole mixture was allowed to warm to −20 °C. NaHMDS (463 μL, 1 M THF solution, 0.46 mmol) was then added to the mixture. After 15 min the mixture was cooled to −78 °C again and aldehyde **27** (52 mg, 0.16 mmol) in THF (1 mL) was added to the mixture, which was then warmed to −20 °C gradually. After 1.5 h saturated aqueous NH_4Cl (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (CH_2Cl_2) followed by a second silica gel flash chromatography (AcOEt/hexane, 1:50) to give iodoalkene **28** (37 mg, 0.08 mmol; 50%) as a colorless oil: $[\alpha]^{21}_D$ +14.2 (*c* 1.63, $CHCl_3$) (99% ee); IR (neat) 2954,2927, 2855, 2360, 1733, 1653, 1506, 1471, 1387, 1360, 1251, 1183, 1068, 951, 884, 835, 776, 727, 457 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.49 (s, 1H), 5.46 (dt, J = 1.3, 6.6 Hz, 1H), 4.22 (t, J = 6.2 Hz, 1H), 2.71 (s, 3H), 2.48 (d, J = 1.3 Hz, 3H), 2.36 (m, 2H), 2.02 (m, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 153.4, 142.1, 132.5, 119.3, 115.6, 102.7, 77.6, 44.1, 34.0, 26.2, 19.6, 18.6, 14.5, −4.3, −4.6; EI-MS *m*/*z* 448 ($M^+ - CH_3$), 406 ($M^+ - t$-Bu); EI-HRMS calcd for $C_{14}H_{21}NOSiSI$ ($M^+ - t$-Bu) 406.0158, found 406.0166.

(1*E*,3*S*,5*Z*)-3-Hydroxy-6-iodo-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-heptadiene (29). To a solution of iodoalkene **28** (34 mg, 0.073 mmol) in THF (2 mL) was added HF·Py (1 mL) at 0 °C, and the mixture was stirred at room temperature for 12 h. Then the mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) at 0 °C and extracted with AcOEt (30 mL) three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:2) to give hydroxyalkene **29** (26 mg, 0.073 mmol; quant): $[\alpha]^{21}_D$ −8.4 (*c* 0.85, $CHCl_3$) (99% ee); IR (neat) 3370, 2951, 2919, 2848, 1725, 1654, 1508, 1427, 1375, 1288, 1188, 1150, 1096, 1053, 1021, 965, 881, 813, 728, 450 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.57 (s, 1H), 5.53 (dt, J = 1.3, 6.5 Hz, 1H), 4.27 (t, J = 6.2 Hz, 1H), 2.71 (s, 3H), 2.51 (d, J = 1.3 Hz, 3H), 2.45 (m, 2H), 2.17 (brs, 1H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 153.0, 141.8, 131.8, 119.5, 116.1, 103.7, 76.8, 42.8, 34.1, 19.5, 14.8; EI-MS *m*/*z* 349 (M^+); EI-HRMS calcd for $C_{12}H_{16}NOSI$ (M^+) 348.9998, found 348.9988.

(1*E*,3*S*,5*Z*)-6-Iodo-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-heptadien-3-yl Acetate (Fragment B). To a solution of alkene **29** (23 mg, 0.066 mmol) in CH_2Cl_2 (1.5 mL) were added triethylamine (12 μL, 0.13 mmol), acetic anhydride (37 μL, 0.26 mmol), and then small amounts of DMAP. The mixture was stirred at room temperature for 6 h, and saturated aqueous NH_4Cl (20 mL) was added to the mixture followed by the addition of AcOEt (20 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:4) to give fragment B (25 mg, 0.063 mmol; 96%): $[\alpha]^{24}_D$ −24.6 (*c* 1.2, $CHCl_3$) (99% ee); IR (neat) 3454, 3110, 2958, 2916, 2855, 1736, 1655, 1503, 1428, 1369, 1295, 1234, 1184, 1130, 1105, 1019, 964, 872, 730 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.52 (s, 1H), 5.41 (dt, J = 1.5, 6.5 Hz, 1H), 5.34 (t, J = 6.4 Hz, 1H), 2.71 (s, 3H), 2.54 (m, 2H), 2.49 (d, J = 1.5 Hz, 3H), 2.09 (m, 3H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 165.0, 152.8, 137.3, 130.7, 121.0, 116.7, 104.0, 77.7, 40.7, 34.1, 21.6, 19.6, 15.3; EI-MS m/z 391 (M^+); EI-HRMS calcd for $C_{14}H_{18}NO_2SI$ (M^+) 391.0103, found 391.0102.

Benzyloxy-3-hydroxy-2,2,4,6-tetramethyl-8-nonen-5-one, a Mixture of (3*R*,4*S*,6*S*) and (3*S*,4*R*,6*R*) Isomers (37). To a solution of hydroxy ketone **34** (1.073 g, 3.85 mmol) in THF (5.5 mL) and DMPU (2 mL) was added LHMDS (8.48 mL, 1.0 M THF solution, 8.48 mmol) at −78 °C followed by the addition of DMPU (9.5 mL) again. After 40 min, allyl bromide (1.67 mL, 19.3 mmol) was added to the mixture, which was stirred at the same temperature for 1.5 h. Saturated aqueous NH_4Cl (50 mL) was added to the mixture followed by the addition of AcOEt (50 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane/CH_2Cl_2, 1:20:10) to give allyl ketone **37** (589 mg, 1.85 mmol; 48%) as a colorless oil and the starting material **34** (558 mg, 2.0 mmol). **37**: IR (neat) 3743, 2971, 2929, 2876, 1691, 1455, 1379, 1097, 1002, 916, 737, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 5H), 5.60 (m, 1H), 4.95 (m, 2H), 4.44 (d, J = 12.2 Hz, 1H), 4.38 (d, J = 12.2 Hz, 1H), 4.04 (brs, 1H), 3.49 (d, J = 3.6 Hz, 1H), 3.27 (d, J = 9.0 Hz, 1H), 3.13 (d, J = 9.0 Hz, 1H), 2.91 (dq, J = 3.6, 7.0 Hz, 1H), 2.64 (m, 1H), 2.34 (m, 1H), 1.96 (m, 1H), 1.16 (d, J = 6.8 Hz), 0.96 (d, J = 7.0 Hz, 3H), 0.84 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ; EI-MS m/z 318 (M^+); EI-HRMS calcd for $C_{20}H_{30}O_3$ (M^+) 318.2195, found 318.2193.

Procedure for the Preparation of (*R*)-LLB Complex (Which Was Used for (*R*)-Heteropolymetallic Asymmetric Catalyst). To a stirred solution of (*R*)-binaphthol (3.50 g, 12.2 mmol), in THF (39.7 mL) at 0 °C, was added a solution of La(O-*i*-Pr)$_3$ (20.4 mL, 4.07 mmol, 0.2 M in THF, freshly prepared from the powder of La(O-*i*-Pr)$_3$ purchased from Kojundo Chemical Co., Ltd., 5-1-28, Chiyoda, Sakato, Saitama, 350-02, Japan (Fax: +81-492-84-1351) and dry THF). The solution was stirred for 30 min at room temperature, and then the solvent was evaporated under reduced pressure. The resulting residue was dried for 1 h under reduced pressure (ca. 5 mmHg) and dissolved in THF (60.5 mL). The solution was cooled to 0 °C, and *n*-BuLi (7.45 mL, 12.2 mmol, 1.64 M in hexane) was added. The mixture was stirred for 12 h at room temperature to give a 0.06 M (*R*)-LLB solution, which was used for the preparation of (*R*)-heteropolymetallic asymmetric catalyst. This catalyst solution can be stored for several months under an atmosphere of argon. (CAUTION: The powder of La(O-*i*-Pr)$_3$ should be used immediately after opening the ampule.)

(3*S*,4′*R*,5′*R*,6′*S*,4″*S*)-3-Hydroxy-4-methyl-4-[2,2,5-trimethyl-6-(1-pente-4-yl)-1,3-dioxan-4-yl]pentophenone (8) and (3*S*,4′*S*,5′*S*,6′*R*,4″*R*)-3-Hydroxy-4-methyl-4-[2,2,5-trimethyl-6-(1-pente-4-yl)-1,3-dioxan-4-yl]pentophenone (44). To a stirred solution of potassium bis(trimethylsilyl)amide (KHMDS, 532 μL, 0.266 mmol, 0.5 M in toluene) at 0 °C was added a solution of water (590 μL, 0.59 mmol, 1.0 M in THF). The resulting solution was stirred for 20 min at 0 °C, and then (*R*)-LLB (2.95 mL, 0.295 mmol, 0.1 M in THF) was added and the mixture was stirred at 0 °C for 30 min. The pale yellow solution thus obtained was then cooled to −20 °C, and acetophenone (1.38 mL, 11.8 mmol) was added. The solution was stirred for 20 min at this temperature, and then aldehyde **9** (397 mg, 1.48 mmol) was added and the reaction mixture was stirred for 168 h at −20 °C. The mixture was quenched by addition of 1 N HCl (4 mL), and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO_2, ethyl acetate/hexane 1/30) to give **8** (172 mg, 0.177 mmol; 30%) in 89% ee as a colorless oil, **44** (166 mg, 0.171 mmol; 29%) in 88% ee as a colorless oil, and starting material **9** (143 mg, 0.532 mmol; 36%). **8**: $[\alpha]^{29}_D$ −16.0 (*c* 0.895, $CHCl_3$) (89% ee); IR (neat) 3500, 2974, 2936, 2876, 1681, 1598, 1449, 1378, 1221, 1024, 997, 753, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 5.77 (m, 1H), 5.02 (m, 2H), 4.23 (ddd, J = 1.7, 2.9, 8.6 Hz, 1H), 3.70 (d, J = 1.7 Hz, 1H), 3.42 (d, J = 6.1 Hz, 1H), 3.30 (dd, J = 3.0, 9.9 Hz, 1H), 3.13 (dd, J = 8.6, 15.3 Hz, 1H), 3.08 (dd, J = 2.9, 15.3 Hz, 1H), 2.49 (m, 1H), 1.97 (m, 1H), 1.77 (m, 1H), 1.61 (m, 1H), 1.36 (s, 3H), 1.29 (s, 3H), 1.04 (s, 3H), 0.97 (d, J = 6.1 Hz, 3H), 0.88 (s, 3H), 0.81 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 137.7, 137.4, 133.5, 128.9, 128.6, 116.5, 100.7, 81.5, 74.9, 73.8, 41.7, 40.9, 37.8, 33.3, 32.8, 26.4, 24.0, 20.2, 16.6, 14.7, 14.0; EI-MS m/z 388 (M^+); EI-HRMS calcd for $C_{24}H_{36}O_4$ (M^+) 388.2613, found 388.2622. **44**: $[\alpha]^{24}_D$ −62.0 (*c* 0.97, $CHCl_3$) (88% ee); IR (neat) 3511, 2972, 2934, 2878, 1682, 1598, 1449, 1378, 1290, 1221, 996, 753, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 5.77 (m, 1H), 5.02 (m, 2H), 4.33 (ddd, J = 2.4, 4.2, 9.6 Hz, 1H), 3.67 (d, J = 4.2 Hz), 3.50 (d, J = 6.1 Hz, 1H), 3.34 (dd, J = 3.3, 10.3 Hz, 1H), 3.16 (dd, J = 9.6, 15.9 Hz, 1H), 2.98 (dd, J = 2.4, 15.9 Hz, 1H), 2.50 (m, 1H), 2.03 (m, 1H), 1.77 (m, 1H), 1.63 (m, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.95 (d, J = 6.3 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 200.7, 137.9, 137.4, 133.4, 128.9, 128.5, 116.5, 100.9, 81.1, 73.9, 73.5, 41.2, 41.2, 37.8, 33.0, 32.8, 26.3, 23.8, 20.1, 20.0, 14.7, 14.1; EI-MS m/z 389 (M^+ + 1); EI-HRMS calcd for $C_{24}H_{37}O_4$ (M^++1) 389.2692, found 389.2695. The enantiomeric excesses were determined by chiral stationary phase HPLC analysis [DAICEL CHIRALPAK AD, hexane/2-propanol (100:1, v/v), flow rate 1.0 mL/min, retention time 11 min (*S*)-isomer and 12.5 min (*R*)-isomer, detection at 254 nm for **8**; DAICEL CHIRALPAK AD, hexane/2-propanol (100:1, v/v), flow rate 1.0 mL/min, retention time 10 min (*S*)-isomer and 12 min (*R*)-isomer, detection at 254 nm for **44**].

(3*S*,4′*R*,5′*R*,6′*S*,4″*S*)-Phenyl-3-hydroxy-4-methyl-4-[2,2,5-trimethyl-6-(1-pente-4-yl)-1,3-dioxan-4-yl]pentanoate (46). In a flame-dried flask MS4A (11 mg) was added and dried at 180 °C for 12 h under reduced pressure. Ligand **45** (5.7 mg, 0.0135 mmol) and K_2CO_3 (15 mg, 0.108 mmol) were added, followed by CH_2Cl_2 (400 μL) under an argon atmosphere. To the suspension were added $SnCl_4$ (14 μL, 0.0135 mmol, 1 M in CH_2Cl_2) and BTSP (230 μL, 0.216 mmol, 0.94 M in CH_2Cl_2) at 0 °C. After 10 min aldol **8** (21 mg, 0.054 mmol) in CH_2Cl_2 (600 μL) was added to the mixture and the whole mixture was stirred for 10 h at the same temperature. Saturated aqueous $Na_2S_2O_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1:10) to give ester **46** (15 mg, 0.0373 mmol; 69%) as a colorless oil and starting material **8** (4.6 mg, 0.0119 mmol; 22%). **46**: $[\alpha]^{30}_D$ +2.7 (*c* 1.55, $CHCl_3$) (89% ee); IR (neat) 3493, 2975, 2934, 2883, 1759, 1594, 1493, 1378, 1198, 1138, 688 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (m, 2H), 7.20 (m, 1H), 7.10 (m, 2H), 5.77 (m, 1H), 5.03 (m, 2H), 4.16 (dd, J = 3.0, 9.8 Hz, 1H), 3.39 (d, J = 6.1 Hz), 3.31 (dd, J = 2.9, 10.2 Hz, 1H), 2.75 (dd, J = 3.0, 14.7 Hz, 1H), 2.64 (dd, J = 9.8, 14.7 Hz, 1H), 2.51 (m, 1H), 1.97 (m, 1H), 1.77 (m, 1H), 1.63 (m, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.01 (s, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.86 (s, 3H), 0.82 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.4, 152.4, 138.2, 130.6, 126.6, 122.8, 117.1, 101.2, 81.8, 75.5, 74.5, 42.2, 38.6, 38.6, 34.1, 33.7, 26.8, 24.3, 20.3, 17.2, 15.2, 14.5; EI-MS m/z 389 (M^+ − Me), 405 (M^+ + 1); EI-HRMS calcd for $C_{23}H_{33}O_5$ (M^+ − Me) 389.2328, found 389.2320.

(3*S*,5*R*,6*R*,7*S*,8*S*)-Phenyl-3,5,7-trihydroxy-4,4,6,8-tetramethyl-10-undecenoate (47). Ester **46** (80 mg, 0.2 mmol) was dissolved in CH_2Cl_2 (3 mL), and the solution was cooled to −78 °C. BCl_3 (990 μL, 0.989 mmol, 1 M in xylene) was added to the solution, which was stirred at the same temperature for 20 min. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:2) to give triol **47** (63 mg, 0.172 mmol; 87%) as a colorless oil: $[\alpha]^{30}_D$ −10.0 (*c* 1.05, $CHCl_3$) (89% ee); IR (neat) 3432, 2925, 2854, 1730, 1381, 1195, 1136, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.26 (m, 1H), 7.10 (m, 2H), 5.85 (m, 1H), 5.06 (m, 2H), 4.09 (dd, J = 2.4, 10.3 Hz, 1H), 3.76 (dd, J = 1.5, 9.6 Hz), 3.69 (d, J = 2.7 Hz, 1H), 2.83 (dd, J = 2.4, 16.3 Hz, 1H), 2.72

(dd, J = 10.3, 16.3 Hz, 1H), 2.50 (m, 1H), 2.03 (m, 1H), 1.95 (m, 1H), 1.70 (m, 1H), 1.09 (s, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.88 (s, 3H), 0.84 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.6, 151.9, 138.4, 130.2, 126.6, 122.5, 117.0, 85.3, 78.0, 76.6, 42.2, 38.7, 37.8, 37.0, 35.1, 21.8, 16.1, 16.1, 14.0; EI-MS m/z 364 (M^+); EI-HRMS calcd for $C_{21}H_{32}O_5$ (M^+) 364.2250, found 364.2247.

(3*S*,6*R*,7*S*,8*S*)-Phenyl 3,7-Di-*tert*-butyldimethylsilyloxy-4,4,6,8-tetramethyl-5-oxo-10-undecenoate (Fragment C) and (3*R*,5*S*,2′*R*,3′*S*,4′*S*)-5-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-3-[3-(*tert*-butyldimethylsilyloxy)-4-methyl-6-hepten-2-yl]tetrahydro-2-pyrone (50). To a solution of triol **47** (63 mg, 0.172 mmol) in CH_2Cl_2 (3 mL) were added diisopropylethylamine (150 μL, 0.86 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (120 μL, 0.86 mmol), and the mixture was stirred for 30 min. AcOEt (30 mL) was added to the mixture followed by the addition of saturated aqueous NH_4Cl (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:10) to give silyl ether **48** as a colorless oil which was used for the next step quickly.

To a solution of silyl ether **48** in CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (220 mg, 0.516 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous $Na_2S_2O_3$ (30 mL) were added to the mixture. Then AcOEt (30 mL) was added and the organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:5) to give the mixture. Further preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1:30) furnished fragment C (66 mg, 0.112 mmol; 65% in two steps) and lactone **50** (4 mg, 0.0086 mmol; 5% in 2 steps). Fragment C: $[\alpha]^{29}_D$ −23.8 (*c* 0.77, $CHCl_3$) (89% ee); IR (neat) 2930, 2857, 1762, 1693, 1472, 1377, 1255, 1197, 1144, 1089, 989, 837, 776 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.19 (m, 2H), 7.10 (m, 1H), 6.95 (m, 2H), 5.84 (m, 1H), 5.10 (m, 2H), 4.79 (dd, J = 3.3, 6.0 Hz, 1H), 4.06 (dd, J = 1.8, 6.8 Hz), 3.22 (m, 1H), 2.87 (dd, J = 3.5, 16.7 Hz, 1H), 2.65 (dd, J = 6.3, 16.7 Hz, 1H), 2.43 (m, 1H), 2.04 (m, 1H), 1.65 (m, 1H), 1.19 (s, 3H), 1.18 (d, J = 7.5 Hz, 3H), 1.16 (s, 3H), 1.06 (m, 12H), 1.00 (s, 9H), 0.23 (s, 3H) 0.18 (s, 3H), 0.16 (s, 3H),0.15 (s, 3H);^{13}C NMR(125 MHz,C_6D_6) δ 217.7, 171.1, 152.3, 138.8, 130.3, 126.6, 122.7, 116.9, 78.7, 74.8, 54.5, 46.5, 41.6, 39.6, 36.8, 27.3, 27.1, 24.5, 20.2, 19.6, 19.3, 18.9, 16.6, −2.6, −2.7, −3.2, −3.8; EI-MS m/z 533 ($M^+ - t$-Bu), 521 ($M^+ - C_5H_9$); EI-HRMS calcd for $C_{28}H_{49}O_5Si_2$ (M^+) 521.3118, found 521.3119. **50:** $[\alpha]^{29}_D$ +20.5 (*c* 0.1, $CHCl_3$) (89% ee); IR (neat) 2929, 2857, 1379, 1471, 1362, 1256, 1088, 1038, 836, 775 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.90 (m, 1H), 5.14 (m, 2H), 4.47 (d, J = 9.1 Hz, 1H), 4.34 (dd, J = 0.9, 6.9 Hz, 1H), 3.16 (dd, J = 3.0, 3.4 Hz, 1H), 2.66 (m, 1H), 2.40 (m, 2H), 2.00 (m, 1H), 1.82 (m, 1H), 1.77 (m, 1H), 1.10 (s, 9H), 1.00 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.95 (s, 9H), 0.93 (s, 3H), 0.61 (s, 3H), 0.39 (s, 3H), 0.33 (s, 3H), −0.03 (s, 6H); ^{13}C NMR(125 MHz,C_6D_6) δ 168.7, 139.1, 116.9, 84.1, 77.3, 75.3, 39.7, 39.2, 38.4, 38.0, 37.9, 28.4, 27.4, 26.7, 26.0, 19.5, 18.9, 16.9, 13.5, −2.3, −3.1, −3.7, −4.1; EI-MS m/z 429 ($M^+ - t$-Bu); EI-HRMS calcd for $C_{26}H_{54}O_4Si_2$ ($M^+ - t$-Bu) 429.2856, found 429.2856.

Preparation of CH_2Cl_2 Solution of (*S*)-$SmNa_3$tris(binaphthoxide) Complex (SmSB). To a stirred solution of (*S*)-BINOL (43 mg, 0.15 mmol) in THF were added a solution of Sm(O-*i*-Pr)$_3$ (0.05 mmol; purchased from Kojundo Chemical Co., Ltd., 5-1-28, Chiyoda, Sakato, Saitama 350-02, Japan (Fax: +81-492-84-1351)) in THF (0.5 mL) and a solution of NaO-*t*-Bu (0.15 mmol) in THF (0.3 mL) at 0 °C. After being stirred for 2 h at room temperature, the THF solution of (*S*)-SmSB was concentrated under reduced pressure. The resulting (*S*)-SmSB powder was redissolved in CH_2Cl_2 (3 mL). This solution was directly used as a catalyst.

***S*-Ethyl (*S*)-3-(4-*tert*-Butylphenylthio)-2-methylpropanethioate (16).** To a solution of (*S*)-SmSB (0.2 mmol) in CH_2Cl_2 (3 mL) were successivery added ethylthio methacrylate (**18**) (527 mg, 4 mmol) and 4-*tert*-butylthiophenol (**17**) (680 μL, 4 mmol) at −78 °C. After being stirred for 7 h at the same temperature, the reaction mixture was quenched with 1 N HCl (2 mL) and then extracted with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:1) to give **16** (1.15 g, 3.88 mmol; 92%): $[\alpha]^{24}_D$ −102 (*c* 0.87, $CHCl_3$) (93% ee); IR (neat) 2964, 1686, 964 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 4H), 3.26−3.32 (m, 1H), 2.80−2.92 (m, 1H),1.31 (s 9H), 1.28 (d, J = 6.7 Hz, 3H), 1.25 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 149.8, 132.0, 130.2, 126.0, 48.1, 37.8, 34.5, 31.2, 23.3, 17.3, 14.6; EI-MS m/z 296 (M^+). Anal. Calcd for $C_{16}H_{24}OS_2$: C, 64.81; H, 8.16. Found: C, 64.52; H, 8.20.

(4*R*,5*S*,6*S*)-1-Benzyloxy-5-hydroxy-2,2,4,6-tetramethyl-8-nonen-3-one (13). To a solution of **57** (336 mg, 1.53 mmol) in CH_2Cl_2 (3 mL) was added DDQ (380 mg, 1.68 mmol) at 0 °C, and the mixture was stirred for 2 h at room temperature. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture followed by Et_2O (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice by the addition by the addition of Et_2O (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated by distillaiton to a final volume of 10 mL, which was purified by silica gel flash chromatography (Et_2O/pentane, 1:8 → 1:3) to give alcohol in Et_2O/pentane solution. Then the solution was diluted by CH_2Cl_2 (3 mL) and cooled to 0 °C. To the solution of alcohol were added NMO (250 mg, 2.13 mmol), MS4A (710 mg), and then TPAP (32 mg, 0.071 mmol), and the mixture was allowed to stir for 1 h at room temperature. The mixture was filtered through $MgSO_4$, Celite, and silica gel; then the mixture was concentrated by distillaiton to a final volume of 10 mL, which was added to the next reaction.

To a solution of *N*,*N*-diisopropylamine (232 μL, 1.66 mmol) in THF (20 mL) was added butyllithium (1.04 mL, 1.52 M hexane solution, 1.6 mmol) at −78 °C. The mixture was allowed to warm to 0 °C and stirred for 40 min and then cooled to −78 °C again, and ketone **15** (332 μL, 1.51 mmol) in THF (2 mL) was added to the mixture. After 1 h aldehyde **14** in Et_2O/CH_2Cl_2 solution (2 mL) was added to the mixture and the whole mixture was stirred for 1 h. Saturated aqueous NH_4Cl (40 mL) was added to the mixture followed with AcOEt (40 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:20) to give aldol **13** (289 mg, 0.906 mmol; 60%) as a colorless oil: $[\alpha]^{24}_D$ −27.5 (*c* 0.22, $CHCl_3$) (87% ee); IR (neat) 3500, 2969, 1689, 1455, 1381, 1099, 1029, 910, 737, 698, 506 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.28 (m, 3H), 5.76 (m, 1H), 5.00 (m, 2H), 4.48 (s, 2H), 3.54 (m, 1H), 3.47 (s, 2H), 3.39 (m, 1H), 3.24 (dq, J = 1.5, 6.8 Hz, 1H), 2.51 (m, 1H), 1.86 (m, 1H), 1.62 (m, 1H), 1.20 (s, 3H), 1.17 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.9, 138.2, 137.4, 128.7, 128.0, 127.9, 116.6, 77.5, 74.5, 73.8, 49.9, 40.5, 37.6, 35.4, 22.2, 22.1, 15.4, 10.0; EI-MS m/z 318 (M^+), 303 (M^+ − Me); EI-HRMS calcd for $C_{19}H_{23}O_3$ (M^+ − Me) 303.196, found 303.196.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-Phenyl 3,7-Di-*tert*-butyldimethylsilyloxy-15-methoxycarbonyl-4,4,6,8,16-pentamethyl-17-(2-methyl-1,3-thiazol-4-yl)-5-oxo-12,16-heptadecadienoate (59). To a solution of fragment C (10 mg, 0.0169 mmol) in THF (0.5 mL) was added 9-BBN (69 μL, 0.5 M solution in THF, 0.0338 mmol) at 0 °C, and the mixture was stirred in the ultrasonic bath cleaner (28 °C) for 50 min. H_2O (50 μL) was added to the mixture at 0 °C followed by the addition of fragment A (10.1 mg, 0.0266 mmol) in DMF (1 mL), $PdCl_2$(dppf) (7 mg, 0.00846 mmol), and $K_3PO_4 \cdot 3H_2O$ (14 mg, 0.0508 mmol). After degassing (FPTmethod), the mixture was stirred for 5 h at 60 °C. A saturated aqueous NH_4Cl (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:1) and then preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1:2) to give coupled product **59** (7.1 mg, 0.00846 mmol; 50%): $[\alpha]^{21}_D$ −38.9 (*c* 0.325, $CHCl_3$); IR (neat) 2929, 2856, 1739, 1693, 1472, 1370, 1237, 1196, 1144, 1088, 988, 837, 776 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ

7.21 (m, 2H), 7.11 (m, 1H), 6.94 (m, 2H), 6.69 (s, 1H), 6.54 (s, 1H), 5.59 (m, 2H), 5.53 (m, 1H), 4.79 (dd, J = 3.5, 6.1 Hz, 1H), 4.07 (dd, J = 2.2, 6.3 Hz, 1H), 3.27 (dq, J = 2.2, 6.6 Hz, 1H), 2.92 (dd, J = 3.4, 16.8 Hz, 1H), 2.68 (m, 1H), 2.54 (m, 1H), 2.35 (m, 3H), 2.31 (s, 3H), 2.17 (m, 2H), 1.78 (s, 3H), 1.60 (m, 3H), 1.35 (m, 2H), 1.24 (s, 3H), 1.23 (s, 3H), 1.22 (d, J = 6.6 Hz, 3H), 1.09 (s, 9H), 1.06 (d, J = 6.6 Hz, 3H), 1.01 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H), 0.20 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3, 170.9, 170.5, 165.0, 152.9, 151.1, 137.7, 133.0, 129.7, 126.1, 124.4, 121.9, 121.0, 116.5, 78.9, 78.0, 74.0, 53.9, 45.6, 40.9, 39.2, 31.4, 31.0, 28.3, 28.2, 27.5, 27.4, 24.0, 21.6, 19.8, 19.6, 18.9, 18.6, 18.1, 15.9, 15.2, −3.3, −3.3, −3.9, −4.3. Anal. Calcd for $C_{46}H_{75}NO_7Si_2S$: C, 65.59; H, 8.97; N, 1.66. Found: C, 65.38; H, 8.94; N, 1.68.

(4*S*,7*R*,8*S*,9*S*,13*Z*,16*S*,1′*E*)-4,8-Di-*tert*-butyldimethylsilyloxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione (60). To a solution of coupled product **59** (7.1 mg, 0.00846 mmol) in MeOH (1 mL) was added 3 N aqueous NaOH (1 mL), and the mixture was stirred at 50 °C for 36 h. Saturated aqueous NH_4Cl (20 mL) was added to the mixture followed by the addition of AcOEt (20 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:1) to give hydroxy acid (5.1 mg, 0.00708 mmol; 84%).

To a solution of hydroxy acid (5.1 mg, 0.00708 mmol) in THF (500 μL) were added Et_3N (12 μL, 0.0845 mmol) and 2,4,6-trichlorobenzoyl chloride (11 μL, 0.0704). The mixture was stirred at room temperature for 20 min, diluted with toluene (500 μL), and added dropwise over a period of 3 h to a solution of DMAP (17 mg, 0.141 mmol) in toluene (6 mL). After complete addition, the mixture was stirred for an additional 1 h and concentrated in vacuo. Purification of the residue by silica gel flash chromatography (AcOEt/hexane, 1:10) gave lactone **60** (4.4 mg, 0.0062 mmol; 88%). The spectral data of **60** thus obtained were identical with those of an authentic sample.[2h,i]

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-Phenyl 3,7-Di-*tert*-butyldimethylsilyloxy-15-methoxycarbonyl-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)-5-oxo-12,16-heptadecadienoate (61). To a solution of fragment C (10.6 mg, 0.0179 mmol) in THF (0.5 mL) was added 9-BBN (72 μL, 0.5 M solution in THF, 0.0359 mmol) at 0 °C, and the mixture was stirred in the ultrasonic bath cleaner (28 °C) for 1.5 h. H_2O (50 μL) was added to the mixture at 0 °C followed by the addition of fragment B (9.8 mg, 0.0251 mmol) in DMF (1 mL), $PdCl_2$(dppf) (3 mg, 0.00359 mmol), and $K_3PO_4 \cdot 3H_2O$ (14 mg, 0.0538 mmol). After degassing (FPTmethod), the mixture was stirred for 1 h at 60 °C. A saturated aqueous NH_4Cl (30 mL) was added to the mixture followed by the addition of AcOEt (30 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:1) and then preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1:2) to give coupled product **61** (5.7 mg, 0.00664 mmol; 37%): $[\alpha]^{22}_D$ −32.3 (*c* 0.45, $CHCl_3$); IR (neat) 2930, 2856, 1739, 1693, 1472, 1370, 1239, 1197, 1145, 1088, 989, 836, 776 cm^{-1}); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.21 (m, 1H), 7.14 (m, 2H), 6.69 (s, 1H), 6.51 (s, 1H), 5.23 (m, 1H), 5.07 (m, 1H), 4.46 (dd, J = 3.6, 5.8 Hz, 1H), 3.79 (dd, J = 1.8, 6.9 Hz, 1H), 3.18 (m, 1H), 2.74 (dd, J = 3.5, 16.5 Hz, 1H), 2.70 (s, 3H), 2.53 (dd, J = 6.0, 16.5 Hz, 1H), 2.40 (m, 2H), 2.06 (s, 3H), 2.05 (s, 3H), 2.00 (m, 1H), 1.66 (s, 3H), 1.40 (m, 6H), 1.30 (s, 3H), 1.12 (s, 3H), 1.09 (d, J = 6.5 Hz, 3H), 0.91 (m, 12H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3, 170.9, 170.5, 164.9, 153.0, 151.1, 138.7, 137.9, 129.7, 126.1, 121.9, 120.9, 119.8, 116.5, 79.3, 78.0, 74.1, 53.9, 45.6, 40.9, 39.2, 32.9, 32.0, 31.2, 26.6, 26.5, 26.4, 24.0, 23.8, 21.6, 19.9, 19.6, 18.9, 18.6, 18.1, 15.9, 15.2, −3.3, −3.4, −3.9, −4.3. Anal. Calcd for $C_{47}H_{77}NO_7Si_2S$: C, 65.92; H, 9.06; N, 1.64. Found: C, 65.66; H, 8.80; N, 1.61.

(4*S*,7*R*,8*S*,9*S*,13*Z*,16*S*,1′*E*)-4,8-Di-*tert*-butyldimethylsilyloxy-5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione (62). To a solution of coupled product **61** (5 mg, 0.00584 mmol) in MeOH (1 mL) was added 3 N aqueous NaOH (1 mL), and the mixture was stirred at 50 °C for 36 h. Saturated aqueous NH_4Cl (20 mL) was added to the mixture followed by the addition of AcOEt (20 mL). The organic layer was separated, and the aqueous phase was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was purified by silica gel flash chromatography (AcOEt/hexane, 1:1) to give hydroxy acid (4 mg, 0.00543 mmol; 93%).

To a solution of hydroxy acid (3.9 mg, 0.00528 mmol) in THF (200 μL) were added Et_3N (8.3 μL, 0.0528 mmol) and 2,4,6-trichlorobenzoyl chloride (8.8 μL, 0.0634). The mixture was stirred at room temperature for 20 min, diluted with toluene (700 μL), and added dropwise over a period of 3 h to a solution of DMAP (32 mg, 0.264 mmol) in toluene (5.1 mL). After complete addition, the mixture was stirred for an additional 1 h and concentrated in vacuo. Purification of the residue by silica gel flash chromatography (AcOEt/hexane, 1:5) and then preparative thin-layer chromatography (silica gel, AcOEt/hexane, 1:6) gave lactone **62** (3.4 mg, 0.00475 mmol; 90%). The spectral data of **62** thus obtained were identical with those of an authentic sample.[2h]

Acknowledgment. Financial support was provided by CREST, The Japan Science and Technology Corporation (JST), and RFTF of Japan Society for the Promotion of Science. We thank Prof. K. C. Nicolaou for sending us spectral data of epothilones A and B.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of products and experimental procedures not described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

JA002024B