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# Studies towards the synthesis of epothilone A *via* organoboranes†

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Studies towards the synthesis of epothilone A *via* organoboranes have been described. A modified procedure for the large-scale preparation of *B*-γ,γ-dimethylallyldiisopinocampheylborane from prenyl alcohol has been developed. This reagent, upon reaction with various aldehydes, provides the corresponding α,α-dimethylhomoallylic alcohols in high enantioselectivities. The application of this reagent for the synthesis of the $C_1$–$C_6$ subunit of epothilone has been demonstrated. Alternatively, inter- and intramolecular asymmetric reduction protocols have also been utilized for the synthesis of the $C_1$–$C_6$ subunit of epothilone A. The synthesis of the $C_7$–$C_{21}$ fragment of epothilone A involving asymmetric alkoxyallyl- and crotylboration using α-pinene-derived reagents has also been described.

## Introduction

Microtubules play an important role in normal cellular processes and have become a key target for cancer chemotherapeutic drugs. The success of Paclitaxel (Taxol™) as an anti-cancer drug has led to an invigorated quest for novel compounds with a mechanism of action similar to that of Taxol, with greater efficacy towards Taxol-resistant cells. One such compound is epothilone, which not only binds to the microtubules in a paclitaxel-like manner, but is much more active.[1] Naturally occurring epothilone is a mixture of epothilone A and B (Fig. 1). Epothilone A (**1a**) turned out to be as active as Paclitaxel, whereas epothilone B is 50 times more active.[1,2a–c] This simple structure and promising biological properties led to extensive efforts towards the synthesis of epothilone[2] and its analogs.[3]

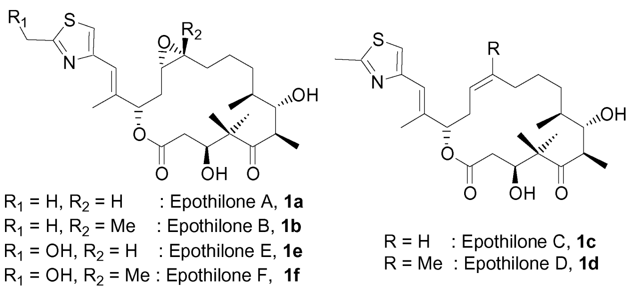


**Fig. 1** Naturally occurring epothilones.

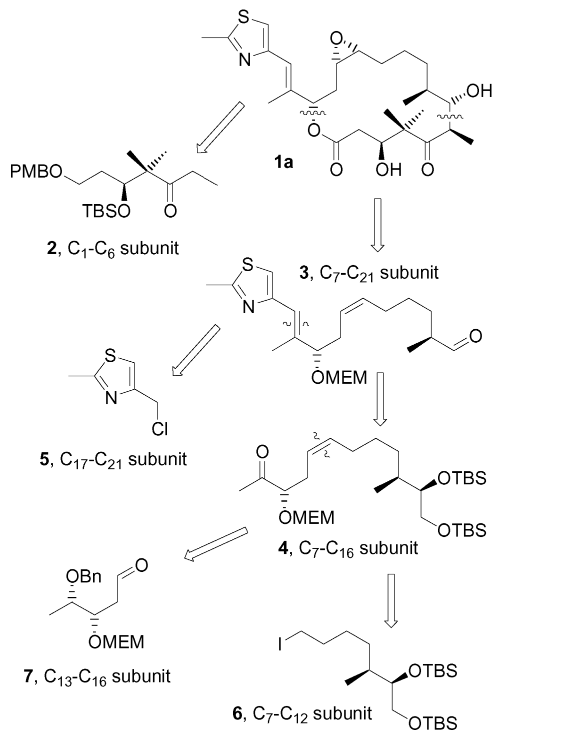


**Fig. 2** Retrosynthetic analysis for epothilone A.

As part of our program on the development and applications of pinane-based versatile organoborane reagents[4] for organic synthesis,[5] we undertook the synthesis of epothilones.[6] Our retrosynthetic analysis of **1a** is shown in Fig. 2. We envisaged that the required subunits $C_1$–$C_6$ (**2**) and $C_7$–$C_{21}$ (**3**) could be prepared *via* α-pinene-derived asymmetric alkoxyallyl- and crotylboration and dimethylallylboration protocols. We also envisioned that the total synthesis of epothilone could be achieved *via* an aldol coupling between the ethyl ketone **2** and the aldehyde **3**, followed by a macrolactonization under Yamaguchi conditions. Several approaches towards the synthesis of these two subunits are described in this manuscript. The $C_1$–$C_6$ subunit **2** was realized *via* an asymmetric dimethylallylboration strategy. Wittig olefination and alkoxyallyl- and crotylboration chemistry was used for the synthesis of **3**.

† Electronic supplementary information (ESI) available: $^1H$ and $^{13}C$ NMR spectra. See http://dx.doi.org/10.1039/b508001k

## Results and discussion

### Synthesis of the $C_1$–$C_6$ subunit of epothilone

*B*-Chlorodiisopinocampheylborane is an excellent chiral reducing agent, which has been extensively used in the literature for the asymmetric reduction of a wide variety of ketones.[7] We visualized the application of $Ipc_2BCl$ for the intermolecular reduction of an acetylenic ketone[8] *en route* to the synthesis of the $C_1$–$C_6$ subunit of epothilone. We initiated the synthesis with the reaction of propionaldehyde and dimethylallylzinc bromide furnishing the homoallylic alcohol **10** (Scheme 1). Oxidation of the alcohol, followed by ozonolysis, afforded the keto-aldehyde **11** in 70% combined yield. Treatment with ethynylmagnesium bromide resulted in the chemoselective addition of the Grignard to the aldehyde, which upon oxidation yielded the diketone **12** in 80% yield. With our prior knowledge that the rate of reduction of tertiary ketones[9] with $Ipc_2BCl$ is extremely slow, the diketone **12** was reacted with $Ipc_2BCl$, and to our delight, reduction of the

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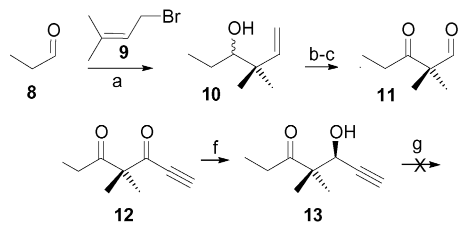
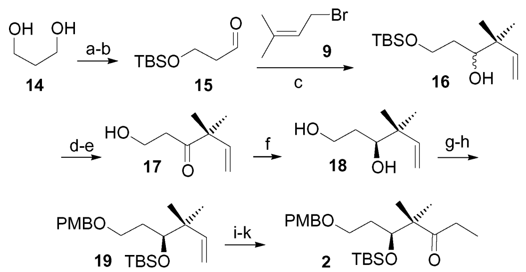



**Scheme 1** Chemoselective reduction of the acetylenic ketone. *Reagents and conditions*: (a) Zn, 80%; (b) DMP, 87%; (c) $O_3$, $Me_2S$, 80%; (d) HCëiCMgBr, 69%; (e) DMP, 80%; (f) $Ipc_2BCl$, 76% yield, 96% ee; (g) $Cy_2BH$, $Cl_2BH$, $BH_3{\cdot}Me_2S$, *etc.*

acetylenic ketone occurred highly regioselectively (rather than reduction of the ethyl ketone), to give the propargylic alcohol **13** in 76% yield and 96% ee. At this stage, our efforts towards the hydroboration of alkyne did not materialize, and resulted in the formation of a complex mixture of products (Scheme 1). Having failed to achieve the hydroboration of the propargylic alcohol, we diverted our attention towards the intramolecular reduction of β-hydroxyketones for the synthesis of **2**.

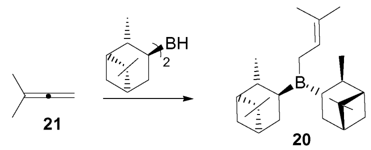
Hydroxyketones[10] and keto-acids[11] undergo intramolecular reduction with $Ipc_2BH$ (or $Ipc_2BCl$) yielding the corresponding diols or hydroxyacids respectively in very high ee. We planned the synthesis of the $C_1$–$C_6$ subunit *via* this intramolecular reduction protocol. Monosilylation of 1,3-propanediol, followed by Dess–Martin periodinane (DMP)[12] oxidation provided 3-silyloxypropionaldehyde **15** (Scheme 2). Allylation with the prenylzinc reagent furnished the homoallylic alcohol **16** in 71% yield. Oxidation and deprotection of the silyl ether afforded the β-hydroxyketone **17**. Intramolecular reduction of the β-hydroxyketone with $Ipc_2BH$ provided the diol **18** in 75% yield and in very high ee (98%). Sequential protection of the primary alcohol as the PMB ether and the secondary alcohol as the TBS ether yielded **19**. Ozonolytic cleavage of the olefin afforded the aldehyde, which upon reaction with ethylmagnesium bromide, followed by DMP oxidation yielded **2**, the $C_1$–$C_6$ subunit of epothilone A (Scheme 2) in 77% yield.




**Scheme 2** Intramolecular reduction of the β-hydroxy ketone. *Reagents and conditions*: (a) TBSCl, imidazole, 89%; (b) DMP, 81%; (c) Zn, 71%; (d) DMP, 83%; (e) HCl, 80%; (f) (+)-$Ipc_2BH$, NaOH, $H_2O_2$, 75% yield, 98% ee; (g) $MeOC_6H_4CH_2OC(NH)CCl_3$, CSA, 80%; (h) TBSCl, imidazole, 86%; (i) $O_3$, $Me_2S$, 78%; (j) EtMgBr, 76%; (k) DMP, 77%.

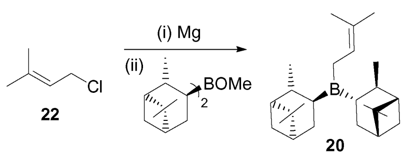
Even though we were able to synthesize the subunit with high stereoselectivity, we were not satisfied with the overall yield and number of steps required for the synthesis. With the intent of overcoming these shortcomings, we concentrated our efforts on the development of an asymmetric dimethylallylboration protocol.

**Improved procedure for the synthesis of *B*-γ,γ-dimethylallyldiisopinocampheylborane[6a].** "Allyl"boration is one of the most important carbon–carbon bond forming reactions in organic synthesis.[13] Over the past two decades, we have developed several highly functionalized "allyl"boranes based on terpenes.[4] While some of these reagents have been well utilized by the synthetic organic community for the total synthesis of a variety of complex natural products,[14] others have been sparsely used, probably due to the difficulty in their preparation or the cost of the starting materials. One such reagent is *B*-γ,γ-dimethylallyldiisopinocampheylborane **20**,[15] which upon reaction with aldehydes provides α,α-dimethylhomoallylic alcohols. Several natural products, such as artemesia alcohol,[16] bryostatin,[17] epothilone, pederin,[18] and mycalamide[19] contain an α,α-dimethylhydroxy unit in them, and one could envisage the use of **20** for the preparation of the α,α-dimethylalcohol moiety. Following Brown's initial report of the synthesis of artemesia alcohol,[15] only Schinzer has described the application of **20** for the synthesis of epothilones.[20] Brown's original preparation of **20** involved the hydroboration of relatively expensive 1,1-dimethylallene **21** with diisopinocampheylborane, thus making it impractical for large-scale applications (Scheme 3). The wide range of potential applications as well as the highly expensive starting materials involved in the preparation of **20** persuaded us to develop an inexpensive method for the large-scale synthesis of this reagent.




**Scheme 3** Literature synthesis of **20**.

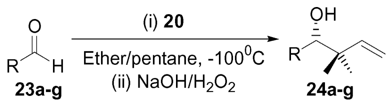
The traditional preparation of *B*-allyldialkylboranes involves the reaction of the corresponding allyl Grignard reagent with *B*-halodialkylborane or *B*-methoxydialkylborane. We envisioned the use of dimethylallyl Grignard, which can be readily prepared from the commercially available and relatively inexpensive prenyl alcohol. The reaction of prenyl alcohol with $PBr_3$ produced the corresponding bromide. However, the reaction of the dimethylallyl bromide with magnesium turnings was not satisfactory and resulted in the predominant formation of homocoupling products. The subsequent addition of (+)-$Ipc_2BOMe$ to the reaction mixture resulted in very low yields of the allylborane **20** (∼10% on the basis of $^{11}B$ NMR spectroscopy). Consequently, the bromide was replaced with chloride on the basis that the chloride might reduce the risk of homocoupling. Accordingly, the dimethylallyl chloride **22** was prepared by the reaction of prenyl alcohol with thionyl chloride. Temperature played a crucial role in the formation of the Grignard. When the temperature was too high, homocoupling dominated, and when the temperature was kept below 0 °C, the formation of the Grignard reagent was arrested. Grignard formation was finally achieved by carefully keeping the reaction temperature in the range 0–5 °C. Upon successful formation of the Grignard, the reaction mixture was transferred to a solution of (+)-$Ipc_2BOMe$ in ether at 0 °C to furnish the required dimethylallylborane **20** in essentially quantitative yield (Scheme 4).[6a] The methoxymagnesium chloride salt was filtered using a Kramer's filter under nitrogen, and the solvent was evaporated under vacuum to provide 90% yield of **20** ($^{11}B$ NMR peak at δ 79). Similarly, starting from (−)-$Ipc_2BOMe$, the antipode of the reagent **20** was prepared. The reagent was tested for its large-scale applicability by carrying out the reaction on a 0.5 mole scale – highly reproducible results were obtained.

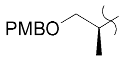
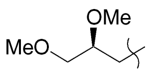



**Scheme 4** Modified procedure for the synthesis of **20**.

We then examined **20** for the allylboration of various aldehydes. The reaction with aliphatic aldehydes such as propionaldehyde **23a**, isobutyraldehyde **23b**, pivalaldehyde **23c** (Table 1, entries 1–3), took place smoothly and the product homoallylic

**Table 1** Dimethylallylboration of aldehydes




| Entry | Aldehyde | R | Homoallylic alcohol | Yield (%) | ee/de (%) |
|---|---|---|---|---|---|
| 1 | **23a** | $CH_3CH_2$- | **24a** | 81 | 97 |
| 2 | **23b** | $(CH_3)_2CH$- | **24b** | 85 | 95 |
| 3 | **23c** | $(CH_3)_3C$- | **24c** | 88 | 95 |
| 4 | **23d** | $C_6H_5$- | **24d** | 92 | 95 |
| 5 | **23e** | $C_6H_5CH{=}CH$- | **24e** | 90 | 87 |
| 6 | **23f** | $PMBOCH_2CH_2$- | **24f** | 82 | 95 |
| 7. | **23g** |  | **24g** | 90 | 92 |
| 8 | **23h** |  | **24h** | 93 | 95 |

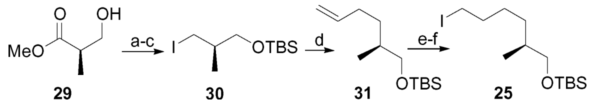
alcohols **24a–c** were obtained in very good yields (81–88%) and in excellent ee (95–97%). The ee was determined by making the *p*-nitrobenzoate esters of the homoallylic alcohols, and analyzing them by HPLC. Similarly, benzaldehyde **23d** and cinnamaldehyde **23e** (entries 4 and 5) provided alcohols **24d** and **24e** in excellent yield and ee. The reaction with α-chiral (**23g**) and β-chiral aldehydes (entries 7 and 8) took place in a reagent-controlled manner, and the homoallylic alcohols **24g** and **24h** were obtained in 92% and 95% de, respectively.

The modified synthesis of dimethylallylborane was then utilized in the synthesis of the $C_1$–$C_6$ subunit **2** of epothilone. Dimethylallylboration of aldehyde **23f** using **20** at −100 °C furnished the homoallylic alcohol **24f** in 82% yield and 95% ee. The completion of the synthesis of the $C_1$–$C_6$ subunit was achieved without any difficulty by a silyl protection, ozonolysis, alkylation, and oxidation sequence as described earlier (Scheme 2).

### Synthesis of the $C_7$–$C_{21}$ subunit of epothilone

We envisaged the synthesis of the $C_7$–$C_{21}$ subunit (**3**) by the convergence of the three subunits $C_7$–$C_{12}$ (**25**), $C_{13}$–$C_{16}$ (**26**), and $C_{17}$–$C_{21}$ (**5**) using a sequential Wittig coupling protocol. Our initial plan was to couple thiazolyl chloride **5** with **26** to yield **27**, followed by a second Wittig coupling with the primary iodide **25** (path A, Fig. 3). Alternatively, a Wittig coupling between **25** and **26** would provide **28**, which after another Wittig coupling with thiazolyl chloride should also provide the required $C_7$–$C_{21}$ subunit of epothilone (path B, Fig. 3). Our results are discussed below.

The $C_7$–$C_{12}$ segment (iodide **25**) was prepared as shown in Scheme 5. Silyl protection of the commercially available (*R*)-3-hydroxy-2-methylpropionate (Roche ester, **29**), reduction of the ester using $BH_3{\cdot}Me_2S$, and iodination with $I_2$/$PPh_3$ furnished the iodide **30**. Nucleophilic substitution of the iodide with higher-order allyl cuprate,[21] generated by the reaction of allyl Grignard with $Li_2CuCl_4$ or CuI, provided the olefin **31** in 22–50% yield. Attempts towards obtaining a higher yield for the substitution proved futile even after an extensive study of reagents and conditions. Hydroboration-oxidation of the olefin **31** to the primary alcohol, followed by iodination provided the required iodide **25** (Scheme 5).




**Scheme 5** Preparation of the $C_7$–$C_{12}$ segment **33**. *Reagents and conditions*: (a) TBSCl, imidazole, DMF, 0 °C, 90%; (b) $BH_3{\cdot}Me_2S$, $NEt_3$, MeOH, THF, 25 °C, 78%; (c) $I_2$, $PPh_3$, imidazole, $CH_2Cl_2$, 8 h, 87%; (d) allylMgBr, $Li_2CuCl_4$, THF, −78 °C, 30–50%; (e) $BH_3{\cdot}Me_2S$, 3 h, NaOH, $H_2O_2$, 3 h, 40%; (f) $I_2$, $PPh_3$, imidazole, $CH_2Cl_2$, 8 h, 80%.

The synthesis of $C_{13}$–$C_{16}$ segment proved to be challenging. The synthesis was initiated with the alkoxyallylboration[22] of acetaldehyde with *B*-γ-methoxyethoxymethoxyallyldiisopinocampheylborane to furnish the homoallylic alcohol **33** (Scheme 6). The corresponding alkoxyallylborane reagent was prepared by the reaction of lithiated allyl methoxyethoxymethyl ether **32** with *B*-methoxydiisopinocampheylborane. Attempts towards the oxidation of the homoallylic alcohol under Jones ($CrO_3$) or Swern [$Me_2SO$, $(COCl)_2$] conditions, to our dismay, led to isomerization yielding the α,β-unsaturated ketone **34**. Oxidation of the homoallylic alcohol **33** was finally achieved with Dess–Martin periodinane to yield the ketone **35** in 76% yield. Hydroboration of **35** proved futile and we could not

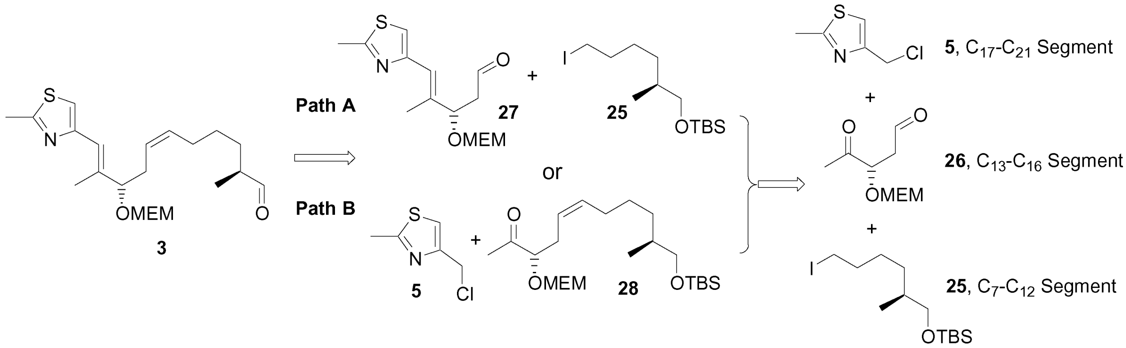
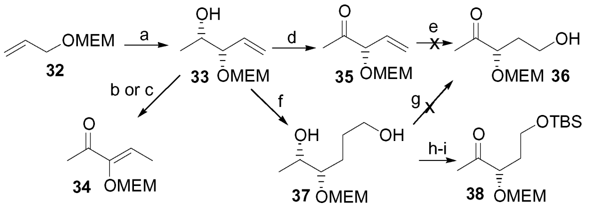



**Fig. 3** Retrosynthetic analysis for the $C_7$–$C_{21}$ subunit.



**Scheme 6** Preparation of the $C_{13}$–$C_{16}$ segment **38**. *Reagents and conditions*: (a) *s*-BuLi, THF, 0.5 h, (+)-Ipc$_2$BOMe, 1 h, $BF_3$·$Et_2O$, 5 min, $CH_3CHO$, −78 °C, 3 h, (ii) NaOH, $H_2O_2$, 3 h, 75% yield, 95% ee; (b) $CrO_3$, $CH_2Cl_2$; (c) $Me_2SO$, $(COCl)_2$, $NEt_3$; (d) DMP, $CH_2Cl_2$, 25 °C, 76%; (e) $BH_3$·THF, $Cy_2BH$, 9-BBN, $Cl_2BH$, CatBH/RhCl$(PPh_3)_3$ *etc.* (f) $Cy_2BH$, NaOH, $H_2O_2$, 76%; (g) (i) $Br_2$, $Na_2CO_3$, MeOH, 0 °C; or (ii) $Br_2$, HMPT, $NaHCO_3$, $H_2O$, $CH_2Cl_2$, 25 °C; or (iii) $(Bu_3Sn)_2O$, $Br_2$, $CH_2Cl_2$, 25 °C; or (iv) NaOCl, $CH_3COOH$, 25 °C; or (v) $KBrO_3$, $NaHSO_3$, $CH_3CN$, $H_2O$; or (vi) $(NH_4)_2Ce(NO_3)_6$, $KBrO_3$, $CH_3CN$, 80 °C *etc.* (h) TBSCl, imidazole, DMF, 25 °C, 87%; (i) DMP, $CH_2Cl_2$, 25 °C, 80%.

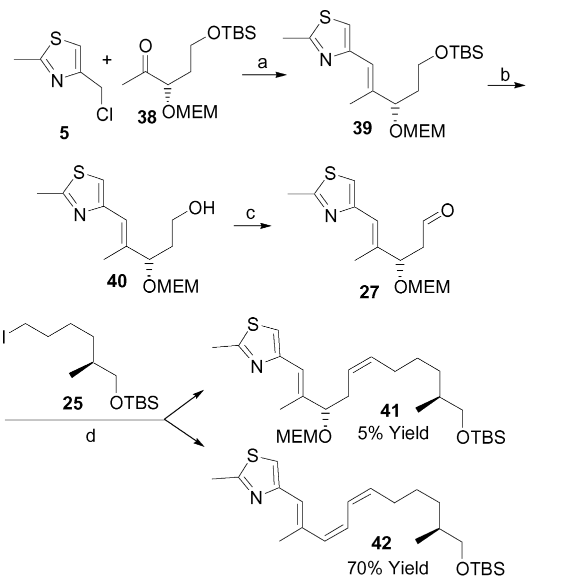
realize the formation of the hydroxyketone **36**, irrespective of the borane reagents used, such as $BH_3$, $Cy_2BH$, 9-BBN, $Cl_2BH$, catecholborane *etc.* (Scheme 6).

Selective oxidation of secondary alcohols in the presence of a primary alcohol is a well-studied field of chemistry,[23] and we attempted to use this reaction in our synthesis. Hydroboration of the homoallylic alcohol **33** was achieved by treatment with 2.5 eq. of dicyclohexylborane, and the 1,4-diol **37** was obtained in 76% yield and >98% regioselectivity. However, selective oxidation of the secondary alcohol in **37** did not work under a variety of conditions. Oxidizing agents such as $Br_2/Na_2CO_3$, $Br_2$/HMPT, $Br_2/(Bu_3Sn)_2O$, NaOCl, $KBrO_3/NaHSO_3$, CAN/$KBrO_3$ *etc.* did not provide the required hydroxyketone. As a final resort, a two-step indirect formation of the $C_{13}$–$C_{16}$ subunit **38** was achieved by selective protection of the primary alcohol as the silyl ether, followed by oxidation of the secondary alcohol to the corresponding ketone **38** in 70% combined yield (Scheme 6).

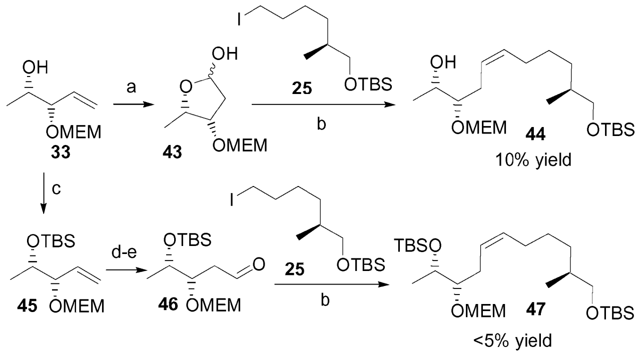
Having achieved the synthesis of the segments $C_7$–$C_{12}$ (**25**, Scheme 5), $C_{13}$–$C_{16}$ (**38**, Scheme 6), and $C_{17}$–$C_{21}$ (**5**[24]), we proceeded further towards the coupling of these pieces by path A, Fig. 3. Formation of the Wittig salt was realized by refluxing **5** with tri-*n*-butylphosphine (the Schlosser modification of the Armstrong protocol).[25] Treatment of the Wittig salt with NaHMDS, followed by the addition of the ketone **38** furnished the olefin **39**. Protolytic cleavage of the silyl ether, followed by DMP oxidation provided the aldehyde **27**. Wittig coupling of the aldehyde **27** with the $C_7$–$C_{12}$ subunit (iodide, **25**) under standard highly basic conditions led to extensive β-elimination of the alkoxy (MEM) group to furnish the conjugated trienyl thiazole **42** as the major coupling product (Scheme 7).

With the intent of increasing the yield for the Wittig coupling, we used the alternative Wittig olefination protocol shown in path B, Fig. 3. Partial oxidation of the primary alcohol in the diol **37** yielded the γ-lactol, **43**. Treatment of this hemiacetal with the Wittig ylide generated from the primary iodide **25** resulted in very low yields of the olefinic alcohol **44** (Scheme 8). Having failed to optimize the yields in the Wittig olefination of the γ-lactol, we resorted to a protected aldehyde for the coupling. Thus, the homoallylic alcohol **33** was protected as the silyl ether **45**. Hydroboration of the olefin **45** with dicyclohexylborane furnished the primary alcohol in >98% regioselectivity. Oxidation of the primary alcohol to the aldehyde **46**, followed by a Wittig coupling with the ylide obtained from the primary iodide **25**, yielded the olefin **47** in <5% yield (Scheme 8).

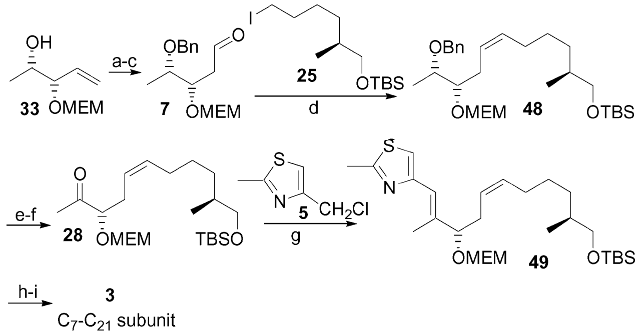
In order to overcome the low yields in the Wittig coupling in our synthesis, we used the relatively non-labile benzyl ether as the protecting group. Thus, the protection of the homoallylic alcohol **33** as its benzyl ether, followed by hydroboration and oxidation using DMP yielded aldehyde **7** (Scheme 9). Although one of the chiral centers derived from alkoxyallylboration will be converted



**Scheme 7** Coupling of **5**, **25** and **38**. *Reagents and conditions*: (a) (i) $PBu_3$; (ii) NaHMDS, 74%; (b) AcOH, 83%; (c) DMP, 85%; (d) (i) **25**, $PPh_3$; (ii) NaHMDS.



**Scheme 8** Wittig olefination of γ-lactol **55** with iodide **33**. *Reagents and conditions*: (a) (i) $Cy_2BH$, NaOH, $H_2O_2$, 76%; (ii) TPAP, NMO, 85%; (b) (i) 25, $PPh_3$; (ii) NaHMDS; (c) TBSCl, imidazole, 25 °C , 89%; (d) $Cy_2BH$, NaOH, $H_2O_2$, 25 °C, 3 h, 78%; (e) DMP, 25 °C, 0.3 h, 97%.

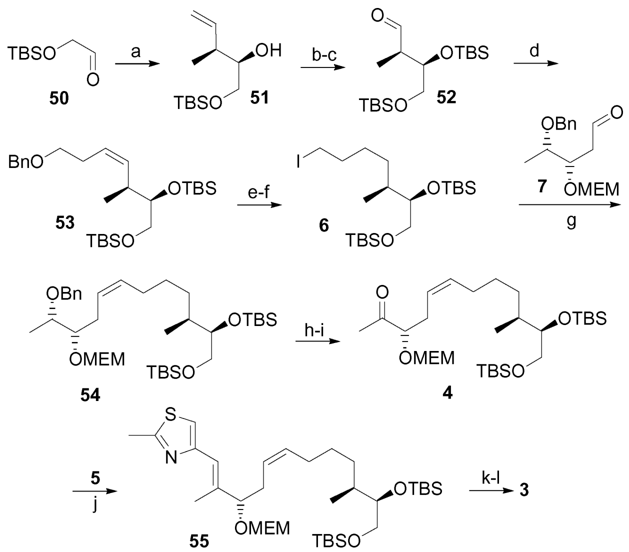


**Scheme 9** Preparation of the $C_7$–$C_{21}$ subunit. *Reagents and conditions*: (a) NaH, BnBr, THF, 0–25 °C , 78%; (b) $BH_3$·$Me_2S$, 0 °C, 4 h, NaOH, $H_2O_2$, 25 °C, 3 h, 82%; (c) DMP, $CH_2Cl_2$, 25 °C, 0.3 h, 97%; (d) (i) **25**, $PPh_3$, benzene, 80 °C, 12 h; (ii) NaHMDS, HMPA, THF, −78 °C, (iii) **7**, 25 °C, 58%; (e) Li, $NH_3$(l), THF, −78 °C, 3.5 h, MeOH–$NH_4Cl$, 25 °C, 15 h, 85%; (f) DMP, $CH_2Cl_2$, 25 °C, 8 h, 95%; (g) (i) **5**, $PBu_3$, 3 h, 70 °C; (ii) NaHMDS, THF, 0 °C, 0.8 h; (iii) **28**, 0 °C, 6 h, 98%; (h) AcOH–$H_2O$–THF (3 : 1 : 1), 25 °C, 18 h, 80%; (i) DMP, $CH_2Cl_2$, 25 °C, 3 h, 98%.

to the ketone at a later stage of the synthesis, the protocol does not necessitate any additional steps to create this chiral center. Wittig coupling of aldehyde **7** with the primary iodide **25** provided the olefin **48** in 58% yield (∼9 : 1 *Z* : *E*). Debenzylation, under Birch reduction conditions, furnished the alcohol, which upon DMP oxidation provided the ketone **28** in 95% yield.

A modified Wittig coupling between thiazolyl chloride **5** and the ketone **28** yielded **49**. Silyl deprotection and DMP oxidation furnished the required $C_7$–$C_{21}$ subunit **3** of epothilone in 98% yield.

Even though the synthesis of the $C_7$–$C_{21}$ subunit of epothilone was achieved, the unreliable yields during the allyl substitution of the primary iodide **30** compelled us to modify the synthetic scheme. We designed a protocol utilizing α-pinene-based crotylboration.[26] This procedure is advantageous because it replaces the relatively expensive Roche ester **29**. We began our synthesis with the *Z*-crotylboration of *tert*-butyldimethylsiloxyacetaldehyde **50** to furnish the homoallylic alcohol **51**. Silyl protection, followed by oxidative cleavage of the olefin furnished the aldehyde **52**. Wittig coupling of **52** with 3-benzyloxypropyl iodide,[27] under standard conditions, led to the stereoselective formation of *Z*-olefin **53**. Pd-catalyzed hydrogenation resulted in the simultaneous debenzylation and reduction of the double bond yielding the primary alcohol, which upon iodination provided **6**. Formation of the Wittig ylide of **6**, followed by treatment with the aldehyde **7**, furnished the coupled olefin **54**. It is noteworthy that the *Z*-olefin was formed selectively and in high yield (85%) from the substrate, which is prone to β-elimination, as was the case in the earlier protocols. Birch reduction afforded the debenzylated secondary alcohol, which underwent oxidation, yielding the ketone **4**. Wittig coupling of the ketone **4** with thiazolyl chloride **5** using the Schlosser modification of the Armstrong protocol provided **55** in 83% yield. Selective deprotection of the two silyl groups using dilute HCl, followed by $Pb(OAc)_4$ cleavage provided the required $C_7$–$C_{21}$ subunit **3** (Scheme 10).




**Scheme 10** Revised procedure for the preparation of the $C_7$–$C_{21}$ subunit. *Reagents and conditions*: (a) (i) *n*-BuLi, *cis*-2-butene, $KO^tBu$, THF, −45 °C, 0.3 h; (+)-$Ipc_2BOMe$, −78 °C, 1 h; $BF_3{\cdot}Et_2O$, 5 min; **67**, −78 °C, 3 h; (ii) NaOH, $H_2O_2$, 25 °C, 3 h, 82%; (b) TBSCl, imidazole, DMF, 25 °C, 9 h, 89%; (c) (i) $OsO_4$, NMO, acetone–water (3 : 1), 25 °C, 4 h; (ii) $NaIO_4$, acetone–water (3 : 1), 25 °C, 2.5 h, 90%; (d) (i) **71**, $PPh_3$, *p*-xylene, 150 °C, 12 h; (ii) NaHMDS, 0 °C, THF, **70**, 3 h, 77%; (e) $H_2$, Pd/C, EtOAc, 8 h, 60%; (f) $I_2$, $PPh_3$, imidazole, $CH_2Cl_2$, 8 h, 78%; (g) (i) **6**, $PPh_3$, *p*-xylene, 150 °C, 3 h; (ii) NaHMDS, HMPA, THF, −78 °C, 2 h; (iii) 7, −78–25 °C, 15 h, 85%; (h) Li, $NH_3$(l), THF, −78 °C, 3.5 h, MeOH–$NH_4Cl$, 25 °C, 15 h, 95%; (i) DMP, $CH_2Cl_2$, 25 °C, 0.3 h, 98%; (j) (i) **5**, $PBu_3$, 3 h, 70 °C; (ii) NaHMDS, THF, 0 °C, 0.7 h; (iii) **4**, 0 °C, 15 h, 83%; (k) THF–$H_2O$–HCl (8 : 1 : 1), 0.3 h; (l) $Pb(OAc)_4$, benzene, 25 °C, 0.3 h, 70% (overall).

## Conclusions

In conclusion, we have developed a simple and inexpensive procedure for the large-scale synthesis of both antipodes of *B*-γ,γ-dimethylallyldiisopinocampheylborane, and have examined the reactivity of the reagent with a wide variety of aldehydes, providing homoallylic alcohols in high diastereo- and enantioselectivities. We have further demonstrated the application of this reagent for the synthesis of the $C_1$–$C_6$ subunit of the potent anti-cancer agent epothilone B. With an economical procedure, we believe that this reagent will find further applications in organic synthesis. We have also achieved the synthesis of the $C_7$–$C_{21}$ subunit of epothilone A using a Wittig reaction and pinane-based alkoxyallyl- and crotylboration as key steps. The present study provides subunits that should be amenable to conversion into epothilone, since similar subunits have been successfully utilized previously for the synthesis of epothilone.[2k]

## Experimental

### (±)-4,4-Dimethylhex-5-en-3-ol, $C_8H_{16}O$, 10

A solution of dimethylallylbromide **9** (10.0 g, 67.1 mmol) was added to a suspension of zinc (8.8 g, 134.2 mmol) and propionaldehyde (9.8 mL, 134.2 mmol) in 100.0 mL THF. A saturated solution of $NH_4Cl$ was added dropwise to the reaction mixture and stirred for 3 h at 25 °C. After the completion of reaction as indicated by TLC, the reaction mixture was filtered under suction and the residue was worked up with ether and 10% HCl. The combined organic layers were dried ($MgSO_4$), concentrated under vacuum, and purified by column chromatography (silica gel, pentane–ether, 4 : 1) to obtain 6.9 g (80%) of the homoallylic alcohol **10**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.80 (1 H, dd, *J* 10.8 and 17.4), 4.98–5.06 (2 H, m), 3.13 (1 H, dd, *J* 1.9 and 10.4), 1.49–1.62 (1 H, m), 1.11–1.28 (1 H, m), 0.99 (3 H, s), 0.98 (3 H, s), 0.97 (3 H, t, *J* 7.3); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 145.6, 113.1, 80.0, 41.7, 24.3, 23.1, 22.2, 11.6.

### 4,4-Dimethylhex-5-en-3-one, $C_8H_{14}O$, keto-10

Alcohol **10** (6.0 g, 46.9 mmol) was added to a suspension of Dess–Martin periodinane (29.8 g, 70.4 mmol) in 70.0 mL $CH_2Cl_2$ and stirred for 2 h at 25 °C. After the completion of reaction, the reaction mixture was filtered and washed with pentane. The combined organic layers were concentrated under vacuum and purified by column chromatography (silica gel, pentane–ether, 5 : 1) to obtain 5.1 g (87%) of the ketone **keto-10**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.91 (1 H, dd, *J* 10.5 and 17.6), 5.09–5.14 (2 H, m), 2.47 (2 H, q, *J* 7.3), 1.20 (6 H, s), 0.99 (3 H, t, *J* 7.3); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 213.8, 142.8, 114.0, 50.7, 30.6, 23.6, 8.3.

### 2,2-Dimethyl-3-oxopentanal, $C_7H_{12}O_2$, 11

A solution of the olefinic ketone **keto-10** (5.0 g, 39.7 mmol) in $CH_2Cl_2$–$CH_3OH$ (1 : 1) was cooled to −78 °C and ozone gas was bubbled through the solution until the formation of the ozonide was complete, as indicated by the deep blue color of the solution. The resulting ozonide was quenched with $Me_2S$ (14.6 mL, 200.0 mmol) and stirred at 25 °C for 4 h. The reaction mixture was concentrated under vacuum to obtain 4.0 g (80%) yield of the crude product. The resultant crude keto-aldehyde **11** was used for the next step without further purification. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 9.62 (1 H, s), 2.47 (2 H, q, *J* 7.3), 1.38 (6 H, s), 0.98 (3 H, t, *J* 7.3); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 209.9, 201.2, 60.2, 32.3, 19.3, 7.6.

### (±)-4,4-Dimethyl-5-hydroxyhept-6-yn-3-one, $C_9H_{14}O_2$, OH-11

A solution of the keto-aldehyde **11** (4.0 g, 31.2 mmol) in 60.0 mL ether was cooled to 0 °C and ethynylmagnesium bromide (31.5 mL, 1.0 M solution, 31.5 mmol) was added dropwise to the reaction mixture. The reaction was warmed to 25 °C and stirred for 2 h. After the completion of the reaction as indicated by TLC, the reaction mixture was quenched with dilute HCl and worked up with ether. The combined organic layers were dried ($MgSO_4$), concentrated under vacuum, and purified by column chromatography (silica gel, hexanes–ethyl acetate, 5 : 1) to obtain 2.9 g (69%) of the alcohol **OH-11**.

### 4,4-Dimethylhept-1-yn-3,5-dione, $C_9H_{12}O_2$, 12

Procedure similar to that for **keto-10**, providing **12** in 87% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 3.36 (1 H, s), 2.46 (2 H, t, *J* 7.3), 1.38 (6 H, s), 1.05 (3 H, t, *J* 7.3).

### (5*S*)-4,4-Dimethyl-5-hydroxyhept-6-yn-3-one, $C_9H_{14}O_2$, 13

A solution of the diketone **12** (2.0 g, 13.2 mmol) in 25.0 mL ether was cooled to 0 °C and 4.6 g (14.5 mmol) of *B*-chlorodiisopinocampheylborane (DipCl) was added to it. The reaction mixture was warmed to room temperature. After the completion of the reaction as indicated by $^{11}B$ NMR spectroscopy, the reaction mixture was oxidized with NaOAc and $H_2O_2$, and worked up with ether and water. The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The crude alcohol was purified by column chromatography (silica gel, hexanes–ethyl acetate, 5 : 1) to obtain 1.5 g (76%) of the hydroxy-ketone **13**. The ee was determined to be 96% by HPLC analysis.

### (±)-1-*tert*-Butyldimethylsilyloxy-4,4-dimethylhex-5-en-3-ol, $C_{14}H_{30}O_2Si$, 16

A solution of dimethylallylbromide **9** (10.0 g, 67.1 mmol) was added to a suspension of zinc (6.6 g, 100.0 mmol) and aldehyde **15** (6.3 g, 33.6 mmol) in 60.0 mL THF. A saturated solution of $NH_4Cl$ was added dropwise to the reaction mixture and stirred for 3 h at 25 °C. After completion of the reaction as indicated by TLC, the reaction mixture was filtered under suction and the residue was worked up with ether and 10% $NH_4Cl$. The combined organic layers were dried ($MgSO_4$), concentrated under vacuum, and purified by column chromatography (silica gel, pentane–ether, 4 : 1) to obtain 6.9 g (80%) of the homoallylic alcohol **16**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.82–5.94 (1 H, m), 4.94–5.08 (2 H, m), 3.72–3.90 (2 H, m), 3.52 (1 H, m), 3.25 (1 H, br s), 1.44–1.72 (2 H, m), 1.02 (6 H, s), 0.89 (9 H, s), 0.05 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 145.7, 112.3, 78.5, 63.3, 33.4, 25.9, 22.9, 22.5, 18.2, −5.5.

### 1-*tert*-Butyldimethylsilyloxy-4,4-dimethylhex-5-en-3-one, $C_{14}H_{28}O_2Si$, keto-16

Procedure similar to that of **keto-10**, providing **keto-16** in 87% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.90 (1 H, dd, *J* 10.5 and 17.6), 5.12–5.18 (2 H, m), 3.85 (2 H, t, *J* 6.4), 2.67 (2 H, t, *J* 6.5), 1.22 (6 H, s), 0.87 (9 H, s), 0.04 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 211.6, 142.3, 114.5, 58.9, 50.9, 40.4, 25.9, 23.2, 18.3, −5.5.

### 1-Hydroxy-4,4-dimethylhex-5-en-3-one, $C_8H_{14}O_2$, 17

A solution of the ketone **keto-16** (5.5 g, 21.5 mmol) was dissolved in 40.0 mL of $CH_3OH$, and 10.0 mL of 10% HCl was added to the reaction mixture. After the completion of the reaction as indicated by TLC, the reaction mixture was concentrated *in vacuo* and worked up with ether and water. The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. The crude hydroxyketone was purified by column chromatography (silica gel, hexanes–ethyl acetate, 4 : 1) to obtain 2.4 g (80%) of the pure hydroxyketone **17**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.84–5.94 (1 H, m), 5.12–5.18 (2H, m), 3.79 (2 H, t, *J* 5.4), 2.71 (2 H, t, *J* 5.0), 2.52 (1 H, br s), 1.22 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 214.3, 142.1, 114.8, 58.2, 50.9, 39.4, 23.4.

### (3*S*)-4,4-Dimethylhex-5-ene-1,3-diol, $C_8H_{16}O_2$, 18

A solution of the hydroxyketone **17** (2.4 g, 17.2 mmol) in 20.0 mL ether was cooled to 0 °C, and 5.4 g (18.9 mmol) of diisopinocampheylborane ($Ipc_2BH$) was added to it. The reaction mixture was warmed to room temperature. After the completion of the reaction, as indicated by $^{11}B$ NMR spectroscopy, the reaction mixture was oxidized with NaOAc and $H_2O_2$ and worked up with ether and water. The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The crude alcohol was purified by column chromatography (silica gel, hexanes–ethyl acetate, 5 : 1) to obtain 1.9 g (76%) of the diol **18**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.84–5.94 (1 H, m), 5.12–5.18 (2 H, m), 3.75–3.85 (2 H, m), 3.54–5.64 (1 H, m), 2.9–3.1 (2 H, br s), 1.41–1.75 (2 H, m), 0.98 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 145.1, 113.4, 78.3, 62.1, 41.5, 32.8, 22.8, 22.1.

### (3*S*)-1-*p*-Methoxybenzyloxy-4,4-dimethylhex-5-en-3-ol, $C_{16}H_{24}O_3$, PMB-18

Diol **18** (1.8 g, 12.5 mmol) was added dropwise to a suspension of NaH (0.7 g, 50% dispersion in mineral oil, 15.0 mmol) in 30.0 mL ether at 0 °C and stirred for 2 h. 6.3 g (31.2 mmol) of PMBBr was added dropwise to the reaction mixture and stirred overnight at 25 °C. After the completion of the reaction as indicated by TLC, the reaction mixture was quenched with 10% HCl and worked up with ether and water. The combined organic layers were dried, concentrated under vacuum and purified by column chromatography (silica gel, hexanes–ethyl acetate, 5 : 1), to obtain 2.6 g (80%) of mono-protected alcohol **PMB-18**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.25 (1 H, d, *J* 8.2), 6.88 (2 H, d, *J* 8.6), 5.86 (1 H, dd, *J* 6.1 and 11.1), 4.99–5.06 (2 H, m), 4.45 (2 H, s), 3.79 (3 H, s), 3.48–3.73 (3 H, m), 2.89 (1 H, br s), 1.55–1.92 (2 H, m), 1.05 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 159.3, 145.6, 130.1, 129.3, 113.9, 112.6, 77.9, 73.0, 69.7, 55.3, 41.3, 31.3, 22.9, 22.5.

### (3*S*)-3-*tert*-Butyldimethylsilyloxy-1-*p*-methoxybenzyloxy-4,4-dimethylhex-5-ene, $C_{22}H_{38}O_3Si$, 19

Alcohol **PMB-18** (2.5 g, 9.5 mmol) was dissolved in 38 mL dimethylformamide. *tert*-Butyldimethylsilylchloride (1.7 g, 11.3 mmol) and imidazole (1.2 g, 17.0 mmol) were added at 0 °C and the mixture stirred for 3 h. After the completion of the reaction as indicated by TLC, the reaction mixture was worked up with ether and water. The organic layer was dried over $MgSO_4$, concentrated under aspirator vacuum to obtain 2.8 g (80%) of silyl ether **19**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.25 (2 H, d, *J* 7.9), 6.88 (2 H, d, *J* 8.7), 5.86 (1 H, dd, *J* 10.4 and 18.0), 4.93–4.98 (2 H, m), 4.40 (2 H s), 3.81 (3 H, s), 3.42–3.52 (3 H, m), 1.53–1.93 (2 H, m), 0.97 (6 H, s), 0.89 (9 H, s), 0.04 (3 H, s), 0.03 (3 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 159.1, 146.1, 130.8, 129.3, 113.8, 111.6, 76.4, 72.5, 67.8, 55.3, 42.5, 33.9, 26.2, 24.5, 22.6, 18.4, −3.8; EI-MS: 309 [$(M - C(CH_3)_2CH{=}CH_2)^+$], 121 [100%, $^+CH_2C_6H_4OCH_3$], 73, 59; CI-MS: 379 [$(M + H)^+$], 121 [100%, $CH_2C_6H_4OCH_3^+$], 81, 69; HRMS-CI: $(M^+)$ 378.2608 (actual), 378.2590 (calcd); $(M + H)^+$ 379.2662 (actual), 379.2669 (calcd).

### (3*S*)-3-*tert*-Butyldimethylsilyloxy-5-*p*-methoxybenzyloxy-2,2-dimethylpentanal, $C_{21}H_{36}O_4Si$, ald-19

Procedure similar to that of **11**. 78% pure aldehyde **ald-19** was obtained. The resulting aldehyde was used for the next step without further purification. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 9.54 (1 H, s), 7.25 (2 H, d, *J* 8.5), 6.88 (2 H, d, *J* 8.5), 4.40 (2 H, s), 3.96 (1 H, dd, *J* 3.51 and 7.41), 3.81 (3 H, s), 3.48 (2 H, dd, *J* 6.0 and 7.4), 1.61–1.91 (2 H, m), 1.05 (3 H, s), 1.00 (3 H, s), 0.85 (9 H, s), 0.05 (3 H, s), 0.03 (3 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 206.3, 159.2, 130.4, 129.3, 113.8, 73.3, 72.6, 66.7, 55.3, 51.3, 33.6, 26.0, 19.1, 18.2, 17.6, −4.0, −4.2.

**(5*S*)-5-*tert*-Butyldimethylsilyloxy-7-*p*-methoxybenzyloxy-4,4-dimethylheptan-3-ol, $C_{23}H_{42}O_4Si$, OH-19**

Aldehyde **ald-19** (1.0 g, 2.6 mmol) was dissolved in 5.0 mL THF and cooled to 0 °C. Ethylmagnesium bromide (2.9 mL, 1.0 M solution in THF, 2.9 mmol) was added to it dropwise and stirred for 1 h. The reaction mixture was quenched with sat. $NH_4Cl$, worked up with ether and the combined organic layers were dried ($MgSO_4$), and concentrated under vacuum to obtain crude alcohol **OH-19**, which was used for the next step without further purification.

**(5*S*)-5-*tert*-Butyldimethylsilyloxy-7-*p*-methoxybenzyloxy-4,4-dimethylheptan-3-one, $C_{23}H_{40}O_4Si$, 2**

Procedure similar to that for **keto-10**, providing **2** (the $C_1$–$C_6$ subunit of epothilone) in 88% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.24 (2 H, d, *J* 8.6), 6.87 (2 H, d, *J* 8.6), 4.40 (2 H, s), 4.05 (1 H, dd, *J* 3.1 and 7.4), 3.80 (3 H, s), 3.42–3.47 (2 H, m), 2.39–2.61 (2 H, m), 1.50–1.76 (2 H, m), 1.10 (3 H, s), 1.05 (3 H, s), 0.99 (3 H, t, *J* 7.1), 0.86 (9 H, s), 0.04 (3 H, s), 0.01 (3 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 159.2, 130.6, 129.2, 113.8, 74.0, 72.5, 67.3, 55.3, 53.0, 34.3, 31.7, 26.1, 22.0, 20.2, 18.3, 7.8, −4.0, −4.1; EI-MS: *m/z* 309 [$(M - C(CH_3)_2COCH_2CH_3)^+$], 121 [100%, $^+CH_2C_6H_4OCH_3$], 77, 75; CI-MS: 409 [$(M + H)^+$], 271, 121 [100%, $^+CH_2C_6H_4OCH_3$], 81, 69; HRMS-CI: ($M^+$) 408.2696 (calcd), 408.2677 (actual); $(M + H)^+$ 409.2774 (calcd), 409.2787 (actual).

***B*-γ,γ-Dimethylallyldiisopinocampheylborane 20**

1-Chloro-3-methyl-2-butene (90.2 mL, 1.0 mol) was added dropwise to a stirred suspension of magnesium (120 g, 2.5 mol) in 200 mL ether and was stirred for 1 h. Meanwhile, a flame-dried round-bottomed flask was cooled under an inert atmosphere and *B*-methoxydiisopinocampheylborane (158.2 g, 0.5 mol) was weighed into the flask under nitrogen. The borinate was dissolved in 500 mL ether and cooled to 0 °C. The previously made Grignard reagent was then transferred into the borinate solution and stirred for 4 h. After the completion of the reaction as monitored by $^{11}B$ NMR (δ 79), the reaction mixture was filtered under nitrogen using a Kramer's filter and was washed repeatedly with ether. The organic layer was concentrated under vacuum in nitrogen atmosphere. Spectroscopic grade pentane was added to it using a cannula, stirred for 5 min and the precipitate (unreacted Grignard reagent and the magnesium salts) allowed to settle. The supernatant liquid was then transferred *via* a cannula into another round-bottomed flask under nitrogen and the solvent was evaporated off under vacuum. After repeated washing with pentane, the concentrate (90%, 159.4 g, 450.0 mmol) was dissolved in 450 mL pentane so as to prepare a 1 M stock solution of the reagent in pentane. This stock solution was used for reaction with various aldehydes.

Typical procedure for the reaction of **20** with an aldehyde: *B*-γ,γ-dimethylallyldiisopinocampheylborane, **20** (24.0 mL, 1.0 M solution in pentane, 24.0 mmol) was dissolved in 24.0 mL ether and cooled to −100 °C. The aldehyde (20.0 mmol) was dissolved in 10.0 mL ether, cooled to −78 °C, and transferred to the reaction mixture using a cannula. The reaction mixture was monitored using $^{11}B$ NMR (δ 56). After completion, the reaction mixture was oxidized using 3.0 M NaOH and 30% $H_2O_2$ and stirred at room temperature for 6 h. The reaction mixture was worked up with ether and water, the combined organic layers were dried ($MgSO_4$), concentrated under vacuum, and purified by column chromatography (silica gel, hexanes–ethyl acetate) to afford pure homoallylic alcohol.

**(3*S*)-1-*p*-Methoxybenzyloxy-4,4-dimethylhex-5-en-3-ol, $C_{16}H_{24}O_3$, 24f**

Aldehyde **23f** (7.8 g, 40.4 mmol) was added to a stirred solution of (−)-*B*-γ,γ-dimethylallyldiisopinocampheylborane (96.9 mL of a 0.5 M solution in ether–pentane) at −100 °C and maintained at that temperature for 2 h. The progress of the reaction was followed by $^{11}B$ NMR spectroscopy (δ 56). Upon completion, the mixture was oxidized with 19.4 mL of 3.0 M NaOH and 19.4 mL of 30% $H_2O_2$, stirred for 4 h at room temperature and extracted with ether. The organic layer was dried over $MgSO_4$, concentrated under vaccum, purified by column chromatography (silica gel, hexanes–ethyl acetate, 3 : 2) to obtain 8.7 g (82%) of the pure alcohol **24f**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.25 (2 H, d, *J* 8.2), 6.88 (2 H, d, *J* 8.6), 5.86 (1 H, dd, *J* 6.1 and 11.1), 4.99–5.06 (2 H, m), 4.45 (2 H, s), 3.79 (3 H, s), 3.48–3.73 (3 H, m), 2.89 (1 H, d, *J* 2.7), 1.55–1.92 (2 H, m), 1.05 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 159.3, 145.6, 130.1, 129.4, 129.3, 113.9, 112.6, 77.9, 73.0, 69.7, 55.3, 41.3, 31.3, 22.9, 22.5.

**(2*S*,3*S*)-1-*p*-Methoxybenzyloxy-2,4,4-trimethylhex-5-en-3-ol, $C_{17}H_{26}O_3$, 24g**

Procedure as described above for the dimethylallylboration of aldehydes. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.23 (2 H, d, *J* 8.3), 6.87 (2 H, d, *J* 8.5), 5.98 (1 H, dd, *J* 6.8 and 10.8), 4.95–5.08 (2 H, m), 4.41 (2 H, dd, *J* 6.3 and 7.1), 3.79 (3 H, s), 3.20–3.60 (4 H, m), 1.91–2.07 (1 H, m), 1.05 (3 H, s), 1.05 (3 H, s), 0.94 (3 H, d, *J* 6.9); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 159.3, 145.9, 129.3, 129.2, 113.8, 111.6, 83.2, 79.2, 76.5, 73.7, 73.0, 55.3, 42.3, 34.6, 24.2, 23.8, 18.4, 11.5.

**(2*S*)-1-Benzyloxypent-4-en-2-ol, $C_{12}H_{16}O_2$, Bn-OH-23h**

To a solution of *B*-allyldiisopinocampheylborane (20.0 mL, 1.0 M solution, 20.0 mmol) in ether–pentane was added benzyloxyacetaldehyde (3.3 g, 22.0 mmol), and the mixture stirred for 3 h at −100 °C. After the completion of the reaction as indicated by $^{11}B$ NMR spectroscopy (δ 79), the reaction mixture was oxidized using 8.0 mL of 3.0 M NaOH and 8.0 mL of 30% $H_2O_2$, and the mixture worked up with ether and water. The combined organic layers were dried, concentrated and used in the next step without further purification. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.30–7.37 (5 H, m), 5.77–5.90 (1 H, m), 5.08–5.17 (2 H, m), 4.57 (2 H, s), 3.85–3.93 (1 H, m), 3.52 (1 H, dd, *J* 3.4 and 9.4), 3.38 (1 H, dd, *J* 7.4 and 9.5), 2.24–2.30 (3 H, m); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 138.0, 134.3, 128.5, 127.8, 127.7, 117.8, 73.9, 73.4, 69.8, 37.9.

**(2*S*)-2-*tert*-Butyldimethyldimethylsilyloxy-1-benzyloxypent-4-ene, $C_{18}H_{30}O_2$, Bn-TBS-23h**

Procedure similar to that for **19**, providing the pure silyl ether **Bn-TBS-23h** in 82% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.30–7.40 (5 H, m), 5.73–5.91 (1 H, m), 5.05–5.20 (2 H, m), 4.56 (2 H, s), 3.86–3.97 (1 H, m), 3.38 (2 H, s), 2.24–2.30 (2 H, m), 0.90 (9 H, s), 0.1 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 138.5, 135.0, 128.4, 127.6, 127.5, 117.1, 74.3, 73.4, 71.3, 39.5, 25.9, 18.3, −4.4, −4.6.

**(2*S*)-2-*tert*-Butyldimethyldimethylsilyloxypent-4-en-1-ol, $C_{11}H_{24}O_2$, OH-TBS-23h**

The silylated benzyl ether **Bn-TBS-23h** (1.6 g, 5.9 mmol) was dissolved in 12.0 mL THF and transferred to a pre-cooled solution of lithium (0.2 g, 28.6 mmol) in liquid ammonia (60.0 mL) and stirred for 3 h at −78 °C. The reaction mixture was slowly quenched with $NH_4Cl$ and MeOH, warmed to room temperature, stirred overnight and worked up with ether and water. The organic layer was dried ($MgSO_4$), concentrated under aspirator vacuum, purified by column chromatography (silica gel, hexanes–ethyl acetate, 5 : 1) to obtain 0.8 g (68%) of alcohol **OH-TBS-23h**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.65–5.86 (1 H, m), 4.94–5.15 (2 H, m), 3.37–3.78 (4 H, m), 2.24–2.30 (2 H, m), 0.90 (9 H, s), 0.10 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 134.5, 117.4, 71.2, 66.5, 37.6, 25.9, 18.3, −5.3, −5.4.

### (2*S*)-Pent-4-ene-1,2-diol, $C_5H_{10}O_2$, diol-23h

A solution of the silyl alcohol **OH-TBS-23h** (0.5 g, 2.7 mmol) was dissolved in 6.0 mL $CH_3OH$, and 1.5 mL of 10% HCl added. The reaction was stirred for 2 h, and monitored by TLC. The reaction mixture was concentrated under vacuum, and worked up with ether and water. The combined organic layers were dried, concentrated and purified by column chromatography (silica gel, hexanes–ethyl acetate, 2 : 3) to obtain 0.23 g (84%) of the diol **diol-23h**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.71–5.85 (1 H, m), 5.05–5.11 (2 H, m), 3.83 (2 H, br s), 3.70 (1 H, ddd, *J* 2.9, 6.6 and 13.8), 3.59 (1 H, dd, *J* 2.9 and 11.5), 3.40 (1 H, dd, *J* 7.6 and 11.2), 2.19 (2 H, t, *J* 6.9); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 134.2, 117.8, 71.5, 66.1, 37.8; EI-MS: *m/z* 85 [M + H − $H_2O$], 61, 43; CI-MS: 103 [(M + H)$^+$], 85 [(M + H − $H_2O$)$^+$], 67 [100%, M + H − $2H_2O$].

### (2*S*)-1,2-Dimethoxypent-4-ene, $C_7H_{14}O_2$, diMe-23h

A solution of **diol-23h** (0.5 g, 5.0 mmol) in 10.0 mL ether was added dropwise to a pre-cooled suspension of NaH (0.36 g, 50% dispersion in mineral oil, 7.5 mmol) in ether. $CH_3I$ (2.1 g, 15.0 mmol) was added to the reaction mixture and stirred overnight at 25 °C. After the completion of the reaction, the reaction mixture was quenched with dilute HCl and worked up ether and water. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, hexanes–ethyl acetate, 4 : 1) to obtain 0.48 g (74%) of the dimethyl ether **diMe-23h**.

### (3*S*)-3,4-Dimethoxybutanal, $C_6H_{12}O_3$, 23h

Procedure similar to that for **11**, to provide the aldehyde **23h** in 68% yield.

### (2*S*,4*S*)-1, 2-Dimethoxy-5,5-dimethylhept-6-en-4-ol, $C_{11}H_{22}O_3$, 24h

Procedure as described earlier for the dimethylallylboration of aldehydes. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.85 (1 H, dd, *J* 5.7 and 11.1), 4.97–5.04 (2 H, m), 3.35–3.55 (5 H, m), 3.43 (3 H, s), 3.36 (3 H, s), 1.67–1.74 (1 H, m), 1.44–1.54 (1 H, m), 1.01 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 145.5, 112.4, 80.9, 77.5, 74.2, 59.2, 57.4, 41.3, 33.3, 23.1, 22.1; EI-MS: *m/z* 157, 133, 125, 101 [100%], 89, 69, 59; CI-MS: 203 [M + H], 185 [(M + H − $H_2O$)$^+$], 153, 133, 121, 101; HRMS-CI: (M + H − $H_2O$)$^+$ 185.1547 (actual), 185.1542 (calcd).

### 1-*tert*-Butyldimethylsilyloxy-2-methylhex-5-ene, $C_{13}H_{28}OSi$, 31

A solution of the iodide **30** (10.0 g, 3.2 mmol) was dissolved in 6.0 mL $CH_2Cl_2$ and cooled to −78 °C. Lithium tetrachlorocuprate (16.0 mL, 0.1 M solution, 1.6 mmol) and allylmagnesium bromide (6.4 mL, 1 M solution, 6.4 mmol) were added to the reaction mixture and stirred at −78 °C for 4 h. After complete reaction of the starting material, the reaction mixture was worked up with $NH_4Cl$ and ether. The combined organic layers were dried, concentrated *in vacuo*, and purified by column chromatography (silica gel, hexanes–ethyl acetate, 9 : 1) to obtain 3.6 g (50%) of the olefin **31**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.77–5.86 (1 H, m), 5.94–5.03 (2 H, m), 3.35–3.48 (2 H, m), 1.96–2.17 (2 H, m), 1.44–1.65 (2 H, m), 1.09–1.22 (1 H, m), 0.90 (9 H, s), 0.88 (3 H, d, *J* 6.5), 0.05 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 139.3, 114.2, 68.2, 35.3, 32.2, 25.9, 19.0, 18.4, 16.6, −5.3; EI-MS: *m/z* 213 [M − $CH_3$], 171 [M − $C_4H_9$], 141, 115, 99, 89, 75 [100%, $(HOSi(CH_3)_2)^+$]; CI-MS: *m/z* 229 [(M + H)$^+$], 213 [M + H − $CH_4$], 171, 145, 133, 115; HRMS-CI: (M + H)$^+$ 229.1982 (actual), 229.1988 (calcd).

### 6-*tert*-Butyldimethylsilyloxy-5-methylhexan-1-ol, $C_{13}H_{30}O_2Si$, OH-31

Olefin **31** (3.5 g, 15.4 mmol) was dissolved in 30.0 mL ether. $BH_3{\cdot}Me_2S$ (1.2 mL, 10 M solution, 12.0 mmol) was added at 0 °C and the mixture stirred overnight at room temperature. The reaction mixture was oxidized with 14.4 mL of 3.0 M sodium hydroxide and 14.4 mL of 30% hydrogen peroxide and stirred for 10 h at 25 °C. The reaction mixture was worked up with ether and water. The organic layer was dried over $MgSO_4$, and evaporated under aspirator vacuum to obtain 1.5 g (40%) of alcohol **OH-31**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 3.63 (2 H, t, *J* 7.0), 3.42 (1 H, dd, *J* 6.0 and 11.0), 3.35 (1 H, dd, *J* 7.0 and 11.0), 1.57–1.53 (3 H, m), 1.42–1.39 (3 H, m), 1.16–1.06 (1 H, m), 0.88 (9 H, s), 0.85 (3 H, d, *J* 6.5), 0.03 (3 H, s), 0.02 (3 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 68.2, 62.7, 35.6, 32.9, 32.8, 25.7, 23.0, 18.2, 16.5, −5.5; EI-MS: *m/z* 189, 171, 97, 75, 55 [100%, $C_4H_7^+$], 47; CI-MS: *m/z* 247 [(M + H)$^+$], 231, 189, 155, 143, 133, 115 [M + H − $HOSi(CH_3)_2C(CH_3)_3$]; HRMS-CI: (M + H)$^+$ 247.2088 (actual), 247.2093 (calcd).

### 6-*tert*-Butyldimethylsilyloxy-1-iodo-5-methylhexane, $C_{13}H_{29}OISi$, 25

Alcohol **OH-31** (1.5 g, 6.1 mmol) was dissolved in 12.0 mL $CH_2Cl_2$. Iodine (3.1 g, 12.2 mmol), triphenylphosphine (3.2 g, 12.2 mmol) and imidazole (0.8 g, 12.2 mmol) were added to the reaction mixture, which was stirred for 8 h. After the completion of the reaction as indicated by TLC, the reaction mixture was worked up with ether and water. The organic layers were dried, concentrated under vacuum and purified by column chromatography (silica gel, hexanes–ethyl acetate, 19 : 1) to afford 1.7 g (80%) of **25**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 3.42 (1 H, dd, *J* 6.5 and 10.0), 3.38 (1 H, dd, *J* 6.0 and 10.0), 3.19 (2 H, t, *J* 7.0), 1.85–1.78 (2 H, m), 1.61–1.55 (1 H, m), 1.47–1.33 (3 H, m), 1.10–1.02 (1 H, m), 0.89 (9 H, s), 0.87 (3 H, d, *J* 6.7), 0.04 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 68.1, 35.4, 33.7, 31.8, 27.8, 25.8, 18.2, 16.5, 7.1, −5.5; EI-MS: *m/z* 299 [M − $C_4H_9$], 215, 185, 97 (100%), 75, 55; CI-MS: *m/z* 357 [(M + H)$^+$], 341, 299, 229 [M + H − HI], 133 [$(HOSi(CH_3)_2C(CH_3)_3 + H)^+$], 115; HRMS-CI: (M + H)$^+$ 357.1103 (actual), 357.1111 (calcd).

### (2*S*,3*S*)-3-(2-Methoxyethoxymethoxy)pent-4-en-2-ol, $C_9H_{18}O_4$, 33

*sec*-Butyllithium (193.0 mL, 231.7 mmol) was added dropwise to a well-stirred solution of allyloxymethoxyethoxymethane **32** (35.6 g, 243.8 mmol) in 500.0 mL THF at −78 °C and stirred for 0.5 h. (+)-$Ipc_2BOMe$ ((+)-*B*-methoxy-diisopinocampheylborane) (92.6 g, 292.7 mmol, 1.0 M solution in THF) was added to the reaction mixture and stirred for 1 h at −78 °C. $BF_3{\cdot}Et_2O$ (55.6 mL, 439.0 mmol) was added and the reaction mixture was cooled to −100 °C. Acetaldehyde (13.7 mL, 243.9 mmol) dissolved in 25 mL THF was cooled to −78 °C and was added dropwise to the reaction mixture. The reaction was stirred at −100 °C for 2 h and then warmed to −78 °C and stirred overnight. The reaction mixture was oxidized with 117.2 mL of 3.0 M sodium hydroxide and 117.2 mL of 30% hydrogen peroxide and stirred for 10 h at room temperature. The product was extracted with ether, washed with water, and dried over $MgSO_4$. The solvent was removed under aspirator vacuum. The byproducts isopinocampheol and α-pinene were vacuum-distilled and the crude product was purified by silica gel column chromatography (hexane–ethyl acetate, 7 : 3) to obtain 33.0 g (75%) of the homoallylic alcohol **33**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.64 (1 H, ddd, *J* 7.8, 10.6 and 17.8), 5.27–5.32 (2 H, m), 4.78 (1 H, d, *J* 7.0), 4.69 (1 H, d, *J* 7.0), 3.78–3.86 (2 H, m), 3.63–3.73 (2 H, m), 3.53–3.56 (2 H, m), 3.38 (3 H, s), 2.85 (1 H, br s), 1.13 (3 H, d, *J* 6.3); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 134.7, 119.6, 92.9, 82.9, 71.7, 69.3, 67.3, 58.8, 18.5; EI-MS: *m/z* 89 [100%, $^+CH_2OCH_2CH_2OCH_3$], 77, 70, 59, 45, 43; CI-MS: *m/z* 191 [(M + H)$^+$], 115.

**(3*S*)-3-(2-Methoxyethoxymethoxy)pent-4-en-2-one, $C_9H_{16}O_4$, 35**

Procedure similar to that for **keto-10**, providing the ketone **35** in 76% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.77 (1 H, ddd, *J* 6.6, 10.3 and 17.1), 5.36–5.51 (2 H, m), 4.80 (1 H, d, *J* 6.9), 4.76 (1 H, d, *J* 6.9), 4.60 (1 H, d, *J* 6.6), 3.65–3.80 (2 H, m), 3.53 (2 H, t, *J* 4.4), 3.37 (3 H, s), 2.19 (3 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 206.1, 132.3, 119.8, 93.6, 82.8, 71.6, 67.4, 58.8, 25.7; EI-MS: *m/z* 145 [(M − $CH_3CO$)$^+$], 113, 89 [100%, $CH_2OCH_2CH_2OCH_3^+$], 77, 59, 43; CI-MS: *m/z* 189 [(M + H)$^+$], 113, 89 [100%, $^+CH_2OCH_2CH_2OCH_3$].

**(3*S*,4*S*)-3-(2-Methoxyethoxymethoxy)pentane-1,4-diol, $C_9H_{20}O_5$, 37**

Olefin **33** (5.0 g, 26.3 mmol) was added to a suspension of dicyclohexylborane (11.7 g, 65.8 mmol) in 60.0 mL ether at 0 °C and stirred overnight at room temperature. The reaction mixture was oxidized with 26.2 mL of 3.0 M sodium hydroxide and 26.2 mL of 30% hydrogen peroxide and stirred for 10 h at room temperature. The reaction mixture was worked up with ether and water. The organic layer was dried over $MgSO_4$, and evaporated under aspirator vacuum to obtain 4.1 g (76%) of alcohol **37**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 4.72–4.84 (2 H, m), 3.62–3.78 (5 H, m), 3.46–3.58 (3 H, m), 3.37 (3 H, s), 2.90–3.10 (2 H, br s), 1.72–1.86 (1 H, m), 1.54–1.68 (1 H, m), 1.14 (3 H, d, *J* 6.2); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 96.5, 82.1, 71.7, 69.6, 67.7, 59.0, 58.7, 33.9, 19.0.

**(2*S*,3*S*)-5-*tert*-Butyldimethylsilyloxy-3-(2-methoxyethoxymethoxy)pentan-2-ol, $C_{15}H_{34}O_5Si$, TBS-37**

Procedure similar to that for **Bn-TBS-23h**, providing the silyl ether **TBS-37** in 87% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 4.80 (1 H, d, *J* 6.9), 4.76 (1 H, d, *J* 6.9), 3.45–3.82 (8 H, m), 3.36 (3 H, s), 1.73–1.83 (1 H, m), 1.53–1.64 (1 H, m), 1.14 (3 H, d, *J* 6.4), 0.86 (9 H, s), 0.02 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 96.5, 82.8, 71.7, 69.4, 67.7, 59.1 (2 carbons), 34.4, 25.9, 18.9, 18.2, −5.3, −5.4.

**(3*S*)-5-*tert*-Butyldimethylsilyloxy-3-(2-methoxyethoxymethoxy)pentan-2-one, $C_{15}H_{32}O_5Si$, 38**

Procedure similar to that for **keto-10**, providing the ketone **38** in 80% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 4.72 (2 H, s), 4.18 (1 H, dd, *J* 4.5 and 7.5), 3.66–3.73 (4 H, m), 3.46–3.49 (2 H, m), 3.35 (3 H, s), 2.15 (3 H, s), 1.78–1.87 (2 H, m), 0.86 (9 H, s), 0.02 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 209.1, 95.6, 79.5, 71.7, 67.6, 59.0, 58.5, 35.0, 26.4, 25.9, 18.9, −5.4, −5.5.

**4-((3*S*)-5-*tert*-Butyldimethylsilyloxy-3-methoxyethoxymethoxy-2-methylpent-1-enyl)-2-methylthiazole, $C_{20}H_{37}O_4SNSi$, 39**

Thiazolyl chloride **5** (2.1 g, 14.1 mmol) was heated at 80 °C with tri-*n*-butylphosphine (42.3 mL of a 1.0 M solution, 42.3 mmol) for 3 h. The reaction mixture was cooled to 0 °C and diluted with 30.0 mL THF. NaHMDS (13.4 mL, 1.0 M solution, 13.4 mmol) was added dropwise to the reaction mixture and stirred at 0 °C for 20 min. Ketone **38** (3.0 g, 9.4 mmol) was added to the reaction mixture and stirred overnight. After the completion of the reaction as indicated by TLC, the reaction mixture was quenched with $NH_4Cl$ and worked up with ether and water. The combined organic layers were dried, concentrated and purified by column chromatography (silica gel, hexanes–ethyl acetate, 9 : 1) to obtain 2.9 g (74%) of the coupled olefin **39**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 6.89 (1 H, s), 6.45 (1 H, s), 4.68 (1 H, d, *J* 6.7), 4.59 (1 H, d, *J* 6.8), 4.25 (1 H, dd, *J* 5.4 and 8.0), 3.47–3.80 (6 H, m), 3.32 (3 H, s), 2.65 (3 H, s), 1.95 (3 H, s), 1.67–1.91 (2 H, m), 0.84 (9 H, s), 0.01 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 164.4, 152.9, 138.5, 121.3, 115.9, 92.8, 78.5, 71.8, 67.0, 59.7, 59.0, 37.3, 25.9, 19.2, 18.2, 13.6, −5.3, −5.4.

**4-((3*S*)-5-Hydroxy-3-(2-methoxyethoxymethoxy)-2-methylpent-1-enyl)-2-methylthiazole, $C_{14}H_{23}O_4SN$, 40**

A solution of the silyl ether **39** (2.8 g, 6.7 mmol) was dissolved in 10.0 mL of $CH_3OH$, and 2.0 mL of AcOH was added to the reaction mixture. After the completion of the reaction as indicated by TLC, the reaction mixture was concentrated *in vacuo* and worked up with ether and water. The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. The crude hydroxyketone was purified by column chromatography (silica gel, hexanes–ethyl acetate, 4 : 1) to obtain 1.7 g (83%) of the pure alcohol **39**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 6.85 (1 H, s), 6.43 (1 H, s), 4.63 (1 H, d, *J* 6.9), 4.53 (1 H, d, *J* 6.9), 4.30 (1 H, dd, *J* 4.7 and 8.9), 3.45–3.83 (6 H, m), 3.30 (3 H, s) 2.60 (3 H, s), 1.92 (3 H, s), 1.71–1.79 (2 H, m); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 164.6, 152.6, 138.5, 120.8, 116.0, 92.3, 78.7, 71.8, 67.0, 59.1, 59.0, 36.8, 19.2, 14.0.

**4-((3*S*)-5-Oxo-3-(2-methoxyethoxymethoxy)-2-methylpent-1-enyl)-2-methylthiazole, $C_{14}H_{21}O_4SN$, 27**

Procedure similar to that for **keto-10**, providing the aldehyde **27** in 85% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 9.77 (1 H, s), 6.93 (1 H, s), 6.53 (1 H, s), 4.67–4.72 (2 H, m), 4.60 (1 H, d, *J* 6.9), 3.47–3.79 (4 H, m), 3.34 (3 H, s), 2.77 (1 H, ddd, *J* 2.9, 9.3 and 16.2), 2.66 (3 H, s), 2.52 (1 H, ddd, *J* 1.7, 4.0 and 16.2), 2.01 (3 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 200.7, 164.8, 152.3, 136.6, 121.8, 116.7, 92.6, 76.2, 71.7, 67.3, 59.0, 47.8, 19.2, 13.9.

**4-((1*E*,3*Z*,5*Z*,10*S*)-11-*tert*-butyldimethylsilyloxy-2,10-dimethylundeca-1,3,5-trienyl)-2-methylthiazole, $C_{23}H_{39}OSNSi$, 42**

A mixture of iodide **25** (4.7 g, 13.1 mmol) and $Ph_3P$ (3.8 g, 14.4 mmol, 1.1 equiv.) was heated neat at 100 °C for 2 h to provide the phosphonium salt (7.4 g, 91%) as a white solid: The salt was dissolved in THF (120 mL, 0.1 M), and the solution was cooled to 0 °C. Sodium hexamethyldisilylamide (NaHMDS, 12.0 mL, 12.0 mmol, 1 M solution in THF) was slowly added at the same temperature, and the resulting mixture was stirred for 15 min, before aldehyde **27** (3.2 g, 9.8 mmol) was slowly added. Stirring was continued for another 15 min at 0 °C, and then the mixture was quenched with saturated aqueous $NH_4Cl$. The reaction mixture was worked up with ether and water. The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude product. Purification by column chromatography (silica gel, hexane–ethyl acetate, 9 : 1) furnished olefin **42** with extensive β-elimination.

**(2*S*,3*S*)-2-*tert*-Butyldimethylsilyloxy-3-(2-methoxyethoxymethoxy)pent-4-ene, $C_{15}H_{32}O_4Si$, 45**

Procedure similar to that for **19**, providing the silyl ether **45** in 89% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.73 (1 H, ddd, *J* 6.8, 10.4 and 17.3), 5.20–5.27 (2 H, m), 4.74 (1 H, d, *J* 6.9), 4.70 (1 H, d, *J* 6.9), 3.73–3.94 (3 H, m), 3.58–3.64 (1 H, m), 3.50–3.54 (2 H, m), 3.36 (3 H, s), 1.07 (3 H, d, *J*), 0.86 (9 H, s), 0.04 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 134.9, 118.2, 93.6, 81.2, 71.8, 70.3, 66.8, 59.0, 25.9, 19.2, 18.1, −4.6, −4.7.

**(3*S*,4*S*)-4-*tert*-Butyldimethylsilyloxy-3-(2-methoxyethoxymethoxy)pentan-1-ol, $C_{15}H_{34}O_5Si$, OH-45**

Procedure similar to that for **37**, providing the alcohol **OH-45** in 78% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 4.83 (1 H, d, *J* 6.9), 4.73 (1 H, d, *J* 6.9), 3.53–3.90 (8 H, m), 3.38 (3 H, s), 3.00 (1 H, br s), 1.86 (1 H, ddd, *J* 4.9, 9.6 and 14.4), 1.50–1.61 (1 H, m), 1.11 (3 H, d, *J* 6.3), 0.87 (9 H, s), 0.07 (3 H, s), 0.06 (3 H, s);

$\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 96.1, 80.0, 71.7, 70.2, 67.4, 59.4, 59.1, 32.6, 25.8, 18.3, 18.0, −4.7, −4.8.

**(3*S*,4*S*)-4-*tert*-Butyldimethylsilyloxy-3-(2-methoxyethoxymethoxy)pentanal, $C_{15}H_{32}O_5Si$, 46**

Procedure similar to that for **keto-10**, providing the pure aldehyde **46** in 97% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 9.72 (1 H, s), 4.71 (2 H,s), 3.95–4.04 (2 H, s), 3.59–3.62 (2 H, m), 3.47–3.49 (2 H, m), 3.33 (3 H, s), 2.43–2.68 (2 H, m), 1.05 (3 H, d, *J* 6.2), 0.81 (9 H, s), 0.01 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 201.2, 95.7, 76.5, 71.6, 68.6, 67.2, 59.0, 43.8, 25.7, 17.9, 17.5, −4.7, −4.9.

**(2*S*,3*S*,5*Z*,10*S*)-2,11-Bis(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)undec-5-ene, $C_{28}H_{60}O_5Si_2$, 47**

Procedure similar to that for **42**, providing the olefin **47** in <5% yield.

**(2*S*,3*S*)-2-Benzyloxy-3-(2-methoxyethoxymethoxy)pent-4-ene, $C_{16}H_{24}O_4$, Bn-33**

A solution of homoallylic alcohol **33** (10.0 g, 52.6 mmol) was added dropwise to a suspension of NaH (3.8 g, 50% dispersion in mineral oil, 79.0 mmol) in 100.0 mL ether at 0 °C. Benzyl bromide (12.0 mL, 105.2 mmol) was added to the reaction mixture and stirred overnight at room temperature. The reaction mixture was quenched with $NH_4Cl$ and worked up with ether and water. The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes–ethyl acetate 19 : 1) to obtain 11.5 g (78%) of the benzyl ether **Bn-33**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.24–7.42 (5 H, m), 5.81 (1 H, ddd, *J* 7.2, 10.3 and 17.6), 5.24–5.34 (2 H, m), 4.79 (1 H, d, *J* 6.8), 4.73 (1 H, d, *J* 6.9), 4.65 (1 H, d, *J* 12.0), 4.60 (1 H, d, *J* 11.9), 4.14 (1 H, dd, *J* 5.7 and 6.4), 3.78–3.85 (1 H, m), 3.45–3.65 (4 H, m), 3.34 (3 H, s), 1.18 (3 H, d, *J* 6.3); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 138.9, 134.9, 128.3, 127.8, 127.5, 118.6, 93.2, 79.8, 76.8, 71.8, 71.6, 66.9, 58.9, 16.0; ESI-MS: 303 [Na adduct]; HRMS-ESI: (Na adduct) 303.1573 (actual), 303.1572 (calcd).

**(3*S*,4*S*)-4-Benzyloxy-3-(2-methoxyethoxymethoxy)pentan-1-ol, $C_{16}H_{26}O_5$, Bn-OH-33**

Procedure similar to that for **37**, providing the alcohol **Bn-OH-33** in 82% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.26–7.34 (5 H, m), 4.85 (1 H, d, *J* 6.9), 4.76 (1 H, d, *J* 6.9), 4.62 (1 H, d, *J* 11.8), 4.51 (1 H, d, *J* 11.8), 3.52–3.89 (8 H, m), 3.38 (3 H, s), 2.74–2.84 (1 H, br s), 1.87 (1 H, ddd, *J* 4.6, 9.1 and 13.9), 1.63 (1 H, ddd, *J* 4.6, 8.8 and 14.1), 1.18 (3 H, d, *J* 6.3); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 138.5, 128.4, 127.7, 127.6, 96.0, 77.7, 76.5, 71.7, 71.3, 67.4, 59.1 (2 carbons), 32.9, 15.0; ESI-MS: 321 [Na adduct].

**(3*S*,4*S*)-4-Benzyloxy-3-(2-methoxyethoxymethoxy)pentanal, $C_{16}H_{24}O_5$, 7**

Procedure similar to that for **keto-10**, providing the pure aldehyde **7** in 97% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 9.72–9.75 (1 H, m), 7.26–7.32 (5 H, m), 4.75 (2 H, s), 4.57 (1 H, d, *J* 12.1), 4.44 (1 H, d, *J* 11.8), 4.18–4.25 (1 H, m), 3.46–3.72 (5 H, m), 3.33 (3 H, s), 2.52–2.75 (2 H, m), 1.15 (3 H, d, *J* 6.3); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 201.1, 138.3, 128.4, 127.8, 127.7, 95.7, 75.0, 74.7, 71.6, 71.1, 67.3, 59.0, 44.5, 14.5.

**(2*S*,3*S*,5*Z*,10*S*)-2-benzyloxy-11-*tert*-butyldimethylsilyloxy-3-(2-methoxyethoxymethoxy)undec-5-ene, $C_{29}H_{52}O_5Si$, 48**

Procedure similar to that for **42**, providing the olefin **48** in 58% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.25–7.33 (5 H, m), 5.42 (2 H, d, *J* 5.3), 4.79 (2 H, s), 4.61 (1 H, d, *J* 12.0), 4.50 (1 H, d, *J* 11.9), 3.41–3.71 (8 H, m), 3.37 (3 H, s), 2.25–2.43 (2 H, m), 2.02–2.03 (2 H, m), 1.26–1.57 (4 H, m), 1.19 (3 H, d, *J* 5.3), 1.02–1.10 (1 H, m), 0.88 (9 H, s), 0.86 (3 H, d, *J* 7.2), 0.04 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 138.8, 131.9, 128.3, 127.6, 127.4, 125.8, 95.5, 79.9, 75.8, 71.8, 71.3, 68.4, 67.0, 59.0, 35.7, 32.9, 28.1, 27.8, 27.1, 26.0, 18.4, 16.8, 15.3, −5.3.

**(2*S*,3*S*,5*Z*,10*S*)-11-*tert*-Butyldimethylsilyloxy-3-(2-methoxyethoxymethoxy)undec-5-en-2-ol, $C_{22}H_{46}O_5Si$, OH-48**

Procedure similar to that for **OH-TBS-23h**, providing the alcohol **OH-48** in 85% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.32–5.48 (2 H, m), 4.76 (2 H, s), 3.63–3.79 (3 H, m), 3.50–3.53 (2 H, m), 3.27–3.42 (6 H, m), 2.85–2.89 (1 H, br s), 2.12–2.36 (2 H, m), 1.89–2.03 (2 H, m), 1.50–1.54 (1 H, m), 1.22–1.36 (3 H, m), 1.12 (3 H, d, *J* 6.3), 0.98–1.10 (1 H, m), 0.84 (9 H, s), 0.79 (3 H, d, *J* 7.2), 0.01 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 132.3, 124.6, 95.8, 83.9, 71.7, 68.9, 68.3, 67.6, 59.0, 35.6, 32.8, 29.0, 27.7, 26.9, 25.9, 19.1, 18.3, 16.7, −5.4.

**(3*S*,5*Z*,10*S*)-11-*tert*-Butyldimethylsilyloxy-3-(2-methoxyethoxymethoxy)undec-5-en-2-one, $C_{22}H_{44}O_5Si$, 28**

Procedure similar to that for **keto-10**, providing the pure ketone **28** in 95% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.28–5.52 (2 H, m), 4.74 (1 H, d, *J* 7.0), 4.69 (1 H, d, *J* 7.0), 4.06 (1 H, dd, *J* 6.1 and 6.3), 3.66–3.70 (2 H, m), 3.47–3.50 (2 H, m), 3.28–3.42 (5 H, m), 2.42 (2 H, dd, *J* 5.9 and 6.6), 2.15 (3 H, s), 1.94–2.03 (2 H, m), 1.50–1.53 (1 H, m), 1.22–1.38 (3 H, m), 1.00–1.03 (1 H, m), 0.86 (9 H, s), 0.82 (3 H, d, *J* 6.7), 0.01 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 209.2, 133.3, 123.3, 95.2, 82.1, 71.6, 68.3, 67.5, 59.0, 35.7, 32.8, 29.9, 27.7, 26.9, 26.6, 26.0, 18.3, 16.7, −5.4.

**4-((1*E*,3*S*,5*Z*10*S*)-11-*tert*-Butyldimethylsilyloxy-3-(2-methoxyethoxymethoxy)-2,10-dimethylundeca-1,5-dienyl)-2-methylthiazole, $C_{27}H_{49}O_4SNSi$, 49**

Procedure similar to that for **39**, providing the coupled olefin **49** in 98% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 6.93 (1 H, s), 6.48 (1 H, s), 5.32–5.48 (2 H, m), 4.72 (1 H, d, *J* 6.9), 4.64 (1 H, d, *J* 6.8), 4.13 (1 H, dd, *J* 6.6 and 6.9), 3.80–3.86 (1 H, m), 3.53–3.64 (3 H, m), 3.30–3.45 (5 H, m), 2.70 (3 H, s), 2.30–2.45 (2 H, m), 1.91–2.05 (5 H, m), 1.22–1.58 (4 H, m), 0.99–1.09 (1 H, m), 0.88 (9 H, m), 0.84 (3 H, d, *J* 6.8), 0.03 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 164.6, 152.8, 138.4, 132.0, 125.2, 121.5, 115.9, 92.8, 81.7, 71.8, 68.4, 67.0, 59.0, 35.7, 32.9, 31.9, 27.8, 27.1, 26.0, 19.3, 18.4, 16.8, 13.8, −5.3.

**4-((1*E*,3*S*,5*Z*,10*S*)-11-Hydroxy-3-(2-methoxyethoxymethoxy)-2,10-dimethylundeca-1,5-dienyl)-2-methylthiazole, $C_{21}H_{35}O_4SN$, OH-49**

The silyl ether **49** (2.0 g, 3.9 mmol) was dissolved in 8.0 mL of THF, and 2.0 mL of AcOH and 2.0 mL of $H_2O$ were added to the reaction mixture. After the completion of the reaction as indicated by TLC, the reaction mixture was concentrated *in vacuo* and worked up with ether and water. The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. The crude hydroxyketone was purified by column chromatography (silica gel, hexanes–ethyl acetate, 4 : 1) to obtain 1.2 g (80%) of the pure alcohol **OH-49**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 6.95 (1 H, s), 6.49 (1 H, s), 5.34–5.47 (2 H, m), 4.72 (1 H, d, *J* 6.9), 4.64 (1 H, d, *J* 6.8), 4.14 (1 H, t, *J* 6.9), 3.80–3.87 (1 H, m), 3.39–3.64 (5 H, m), 3.38 (3 H, s), 2.71 (3 H, s), 2.31–2.47 (2 H, m), 1.98–2.08 (6 H, m), 1.08–1.60 (5 H, m), 0.89 (3 H, d, *J* 6.7); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 164.7, 152.7, 138.5, 131.9, 125.5, 121.5, 115.9, 92.8, 81.8, 71.8, 68.2, 67.0, 59.1, 35.7, 32.8, 31.9, 27.7, 19.2, 16.6, 13.8.

**4-((1*E*,3*S*,5*Z*,10*S*)-3-(2-Methoxyethoxymethoxy)-2,10-dimethyl-11-oxoundeca-1,5-dienyl)-2-methylthiazole, $C_{21}H_{33}O_4SN$, 3**

Procedure similar to that for **keto-10**, providing the pure aldehyde **3** (the $C_7$–$C_{21}$ subunit of epothilone) in 98% yield.

$\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 9.58 (1 H, d, *J* 2.0), 6.94 (1 H, s), 6.47 (1 H, s), 5.39–5.43 (2 H, m), 4.71 (1 H, d, *J* 6.8), 4.63 (1 H, d, *J* 6.9), 4.12 (1 H, t, *J* 6.8), 3.78–3.85 (1 H, m), 3.51–3.63 (3 H, m), 3.37 (3 H, s), 2.69 (3 H, s), 2.27–2.42 (3 H, m), 1.97–2.07 (5 H, m), 1.33–1.41 (4 H, m), 1.06 (3 H, d, *J* 7.0); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 205.1, 164.6, 152.8, 138.3, 131.1, 126.0, 121.5, 116.0, 92.8, 81.6, 71.8, 67.1, 59.1, 46.2, 32.0, 30.1, 27.4, 26.9, 19.3, 13.8, 13.3; EI-MS: *m*/*z* 256, 89 [100%, $CH_3OCH_2CH_2OCH_2^+$]; CI-MS: *m*/*z* 396 [(M + H)$^+$], 290 [100%, M + H − $HOCH_2OCH_2CH_2OCH_3$], 256, 168, 89; HRMS-CI: (M + H) 396.2205 (actual), 396.2209 (calcd).

### (2*R*,3*S*)-1-*tert*-Butyldimethylsilyloxy-3-methylpent-4-en-2-ol, $C_{12}H_{26}O_2Si$, 51

Potassium *tert*-butoxide (56.7 mL, 1.0 M solution, 56.7 mmol) was dissolved in 100.0 mL THF at −78 °C and *trans*-2-butene (12.0 mL, 128.9 mmol) was added to it. *n*-Butyllithium (22.7 mL, 2.5 M solution, 56.7 mmol) was added to it and stirred for 20 min at −45 °C. The reaction mixture was cooled to −78 °C and (+)-*B*-methoxydiisopinocampheylborane [(+)-$Ipc_2BOMe$] (22.0 g, 69.6 mmol) dissolved in 50.0 mL THF was added to it and stirred for 1 h. Aldehyde **50** (9.0 g, 51.6 mmol) was dissolved in 20.0 mL of THF pre-cooled to −78 °C, transferred to the reaction mixture *via* a cannula at −78 °C and stirred for 3 h. The reaction mixture was oxidized with 27.8 mL 3 M NaOH and 27.7 mL 30% $H_2O_2$ and stirred overnight. The reaction mixture was worked up with ether and water. The organic layer was dried over $MgSO_4$, concentrated under vacuum and purified by column chromatography (silica gel, hexane–ethyl ether, 3 : 2) to obtain 9.7 g (82%) of pure alcohol **51**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.66–5.78 (1 H, m), 4.98–5.07 (2 H, m), 3.61–3.68 (1 H, m), 3.40–3.49 (2 H, m), 2.48 (1 H, d, *J* 2.8), 2.22–2.34 (1 H, m), 1.08 (3 H, d, *J* 6.8), 0.89 (9 H, s), 0.06 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 140.5, 114.9, 74.7, 64.2, 41.0, 25.9, 18.3, 16.0, −5.4.

### (2*R*,3*S*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-3-methylpent-4-ene, $C_{18}H_{40}O_2Si_2$, TBS-51

Procedure similar to that for **19**, providing the silyl ether **TBS-51** in 89% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 5.79–5.91 (1 H, m), 4.96–5.09 (2 H, m), 3.44–3.62 (2 H, m), 2.39–2.45 (1 H, m), 0.98 (3 H, d, *J* 6.9), 0.90 (9 H, s), 0.89 (9 H, s), 0.06 (12 H, s).; $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 142.3, 113.7, 76.5, 75.4, 40.3, 26.0, 25.9, 18.4, 18.2, 13.6, −4.7 (2 carbons), −5.3, −5.4.

### (2*R*,3*R*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-2-methylbutanal, $C_{17}H_{38}O_3Si_2$, 52

NMO (6.8 g, 58.2 mmol) was added to the olefinic ether **TBS-51** (10.0 g, 29.1 mmol) dissolved in acetone–water (4 : 1, 60.0 mL) at 0 °C. $OsO_4$ (0.7 g, 2.9 mmol) was added to the above solution and stirred for 6 h at room temperature, and the product was extracted with ether, washed with a saturated solution of sodium sulfite and dried over $MgSO_4$. The solvent was removed under aspirator vacuum. The crude product was dissolved in acetone–water (4 : 1, 50.0 mL) and stirred at room temperature, followed by the slow addition of $NaIO_4$ (12.4 g, 58.2 mmol). The mixture was stirred for 0.5 h at room temperature and the product was extracted with ether, and washed with a saturated solution of sodium thiosulfate. The solvent was removed under aspirator vacuum and the crude product was purified by column chromatography (silica gel, hexane–ethyl acetate, 3 : 2) to obtain 9.0 g (90%) of **52**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 9.77 (1 H, s), 4.12–4.18 (1 H, m), 3.62 (1 H, dd, *J* 4.8 and 10.0), 3.50 (1 H, dd, *J* 6.0 and 9.0), 2.54–2.62 (1 H, m), 1.06 (3 H, d, *J* 6.9), 0.87 (9 H, s), 0.86 (9 H, s), 0.05 (12 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 204.6, 72.2, 64.4, 49.6, 25.9, 25.7, 18.3, 18.0, 7.6, −4.2, −4.9, −5.4 (2 carbons).

### (2*R*,3*S*,4*Z*)-7-Benzyloxy-1,2-bis(*tert*-butyldimethylsilyloxy)-3-methylhept-4-ene, $C_{27}H_{50}O_3Si_2$, 53

A mixture of 1-benzyloxy-3-iodopropane (2.0 g, 7.4 mmol) and $Ph_3P$ (1.9 g, 7.4 mmol) was heated in xylene at 100 °C for 10 h. Evaporation of the xylene provided white crystals of the phosphonium salt. The solid was submerged in THF with occasional heating. The solution was cooled to 0 °C and NaHMDS (6.9 mL, 6.9 mmol) was added slowly. The clear red solution was stirred for 20 min at room temperature and recooled to 0 °C. Aldehyde **52** (1.7 g, 4.9 mmol) was added to the solution and stirred at 0 °C for 2 h. The reaction mixture was extracted with ether and water. The combined organic layers were dried, concentrated under vacuum and purified by column chromatography (silica gel, hexanes–ethyl acetate, 9 : 1) to provide 1.8 g (77%) of olefin **53**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.26–7.38 (5 H, m), 5.33–5.45 (2 H, m), 4.51 (2 H, s), 3.41–3.56 (5 H, m), 2.64–2.76 (1 H, m), 2.32–2.46 (2 H, m), 0.93 (3 H, d, *J* 6.8), 0.89 (18 H, s), 0.05 (12 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 138.6, 129.5, 128.4, 127.6, 127.5, 124.7, 76.9, 72.9, 70.1, 65.7, 34.2, 28.2, 26.1, 26.0, 18.4, 18.3, 15.0, −4.0, −4.7, −5.2, −5.3.

### (5*S*,6*R*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-5-methylheptan-1-ol, $C_{20}H_{46}O_3Si_2$, OH-6

Benzyl ether **53** (1.6 g, 3.3 mmol) was dissolved in ethyl acetate (10.0 mL). 0.15 g of 10% w/v palladium-on-charcoal was added to it and hydrogen gas bubbled through the reaction mixture for 6 h. The reaction mixture was filtered over silica gel and purified by column chromatography (silica gel, hexanes–ethyl acetate, 3 : 1) to obtain 0.78 g (60%) of pure alcohol **OH-6**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 3.65 (2 H, t, *J* 6.6), 3.57–3.61 (1 H, m), 3.47 (2 H, d, *J* 6.4), 1.51–1.67 (3 H, m), 1.30–1.45 (2 H, m), 1.16–1.29 (2 H, m), 0.88 (9 H, s), 0.87 (9 H, s), 0.82 (3 H, d, *J* 6.8), 0.04 (12 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 75.9, 65.3, 63.1, 35.3, 33.4, 33.1, 26.0, 25.9, 23.8, 18.2 (2 carbons), 13.3, −3.9, −4.8, −5.2, −5.4.

### (2*R*,3*S*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-7-iodo-3-methylheptane, $C_{20}H_{45}IO_2Si_2$, 6

Alcohol **OH-6** (0.3 g, 0.8 mmol) was dissolved in $CH_2Cl_2$. Iodine (0.3 g, 1.15 mmol), triphenylphosphine (0.3 g, 1.2 mmol) and imidazole (0.2 g, 2.3 mmol) were added and stirred for 8 h. After the completion of the reaction as indicated by TLC, the reaction mixture was worked up with ether and water. The organic layers were dried, concentrated under vacuum and purified by column chromatography (silica gel, hexanes–ethyl acetate, 19 : 1) to afford 0.3 g (78%) of **6**. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 3.57–3.62 (1 H, m), 3.47 (2 H, d, *J* 6.1), 3.47 (2 H, t, *J* 7.0), 1.77–1.86 (2 H, m), 1.60–1.70 (1 H, m), 1.34–1.47 (3 H, m), 1.15–1.19 (1 H, m), 0.89 (9 H, s), 0.88 (9 H, s), 0.82 (3 H, d, *J* 6.6), 0.05 (12 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 75.8, 65.2, 35.1, 33.8, 32.5, 28.6, 26.0, 25.9, 18.4 (2 carbons), 13.3, 7.2, −3.9, −4.8, −5.2, −5.3.

### (2*S*,3*S*,5*Z*,10*S*,11*R*)-2-Benzyloxy-11,12-bis(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-10-methyldodec-5-ene, $C_{36}H_{68}O_6Si_2$, 54

Procedure similar to that for **42**, providing the olefin **54** in 85% yield. $\delta_H$(300 MHz; $CDCl_3$; $Me_4Si$) 7.26–7.36 (5 H, m), 5.43 (2 H, ddd, *J* 6.4, 11.4 and 17.4), 4.79 (2 H, s), 4.61 (1 H, d, *J* 11.9), 4.50 (1 H, d, *J* 11.8), 3.47–3.53 (4 H, m), 3.57–3.73 (5 H, m), 3.37 (3 H, s), 2.23–2.44 (2 H, m), 1.96–2.08 (2 H, m), 1.62–1.65 (1 H, m), 1.27–1.43 (3 H, m), 1.09–1.42 (1 H, m), 1.19 (3 H, d, *J* 5.5), 0.90 (9 H, s), 0.89 (9 H, s), 0.81 (3 H, d, *J* 6.6), 0.05 (6 H, s), 0.04 (6 H, s); $\delta_C$(75.5 MHz; $CDCl_3$; $Me_4Si$) 138.8, 132.0, 128.3, 127.6, 127.4, 125.7, 95.5, 79.9, 75.9, 71.8, 71.3, 67.0, 65.4, 59.0 (2 carbons), 35.3, 33.5, 28.1, 27.7 (2 carbons), 26.0, 25.9, 18.4, 18.2, 15.3, 13.4, −4.0, −4.7, −5.2, −5.3. ESI: *m*/*z* 675 [Na adduct]; HRMS-ESI: (Na adduct) 675.4460 (actual), 675.4452 (calcd).

### (2*S*,3*S*,5*Z*,10*S*,11*R*)-11,12-Bis(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-10-methyldodec-5-en-2-ol, $C_{29}H_{62}O_6Si_2$, OH-54

Procedure similar to that for **OH-TBS-23h**, providing **OH-54** in 95% yield. $\delta_H$(300 MHz; CDCl$_3$; Me$_4$Si) 5.35–5.51 (2 H, m), 4.79 (2 H, s), 3.67–3.82 (3 H, m), 3.52–3.60 (3 H, m), 3.44–3.46 (2 H, m), 3.37 (3 H, s), 3.35–3.36 (1 H, m), 2.95–2.97 (1 H, br s), 2.18–2.38 (2 H, m), 1.98–2.05 (2 H, m), 1.58–1.66 (1 H, m), 1.16–1.41 (4 H, m), 1.14 (3 H, d, *J* 6.4), 0.87 (9 H, s), 0.86 (9 H, s), 0.79 (3 H, d, *J* 6.8), 0.03 (3 H, s), 0.02 (3 H, s), 0.01 (6 H, s); $\delta_C$(75.5 MHz; CDCl$_3$; Me$_4$Si) 132.4, 124.5, 95.8, 84.0, 75.8, 71.7, 68.9, 67.6, 59.0, 35.2, 33.4, 29.1, 27.7, 27.6, 26.0, 25.9, 19.1, 18.3, 18.2, 13.3, −4.0, −4.8, −5.3, −5.4; ESI: *m/z* 585 [Na adduct]; HRMS-ESI: (Na adduct) 585.3981 (actual), 585.3983 (calcd).

### (3*S*,5*Z*,10*S*,11*R*)-11,12-Bis(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-10-methyldodec-5-en-2-one, $C_{29}H_{60}O_6Si_2$, 4

Procedure similar to that for **keto-10**, providing the pure aldehyde **4** in 98% yield. $\delta_H$(300 MHz; CDCl$_3$; Me$_4$Si) 5.48–5.56 (1 H, m), 5.32–5.40 (2 H, m), 4.77 (1 H, d, *J* 7.1), 4.73 (1 H, d, *J* 7.1), 4.09 (1 H, t, *J* 6.2), 3.45–3.73 (6 H, m), 3.37 (3 H, s), 2.45 (2 H, t, *J* 6.6), 2.17 (3 H, s), 1.99–2.05 (2 H, m), 1.61–1.64 (1 H, m), 1.12–1.42 (4 H, m), 0.88 (9 H, s), 0.87 (9 H, s), 0.80 (3 H, d, *J* 6.8), 0.07 (3 H, s), 0.04 (6 H, s), 0.03 (3 H, s); $\delta_C$(75.5 MHz; CDCl$_3$; Me$_4$Si) 209.2, 133.3, 123.2, 95.2, 82.1, 75.8, 71.7, 67.5, 65.3, 59.0, 35.2, 33.4, 29.9, 27.6, 27.5, 26.5, 26.0, 25.9, 18.3, 18.2, 13.3, −4.0, −4.8, −5.3, −5.4; EI-MS: *m/z* 427, 147, 133, 89 [100%, $CH_2OCH_2CH_2OCH_3^+$], 73, 59; CI-MS: *m/z* 561 [(M + H)$^+$], 485 [(M + H − HOCH$_2$CH$_2$OCH$_3$)$^+$], 353 [(M + H − HOCH$_2$CH$_2$OCH$_3$ − HOSi(CH$_3$)$_2$C(CH$_3$)$_3$)$^+$], 221, 89 [100%, $CH_2OCH_2CH_2OCH_3^+$]; HRMS-CI: (M + H) 561.4008 (actual), 561.4007 (calcd).

### 4-(((1*E*,3*S*,5*Z*,10*S*,11*R*)-11,12-Bis(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-2,10-dimethyldodeca-1,5-dienyl)-2-methylthiazole, $C_{34}H_{65}O_5SNSi_2$, 55

Procedure similar to that for **39**, providing the coupled olefin **55** in 83% yield. $\delta_H$(300 MHz; CDCl$_3$; Me$_4$Si) 6.92 (1 H, s), 6.48 (1 H, s), 5.40 (2 H, ddd, *J* 6.9, 12.2 and 18.7), 4.71 (1 H, d. *J* 6.9), 4.63 (1 H, d, *J* 6.9), 4.12 (1 H, t, *J* 6.8), 3.78–3.86 (1 H, m), 3.52–3.63 (4 H, m), 3.45–3.47 (2 H, m), 3.37 (3 H, s), 2.69 (3 H, s), 2.30–2.46 (2 H, m), 1.94–2.05 (5 H, m), 1.58–1.63 (1 H, m), 1.07–1.43 (4 H, m), 0.87 (9 H, s), 0.86 (9 H, s), 0.79 (3 H, d, *J* 6.9), 0.03 (6 H, s), 0.02 (6 H, s); $\delta_C$(75.5 MHz; CDCl$_3$; Me$_4$Si) 164.5, 152.8, 138.4, 132.0, 125.2, 121.5, 115.9, 92.7, 81.7, 75.8, 71.8, 67.0, 65.3, 59.0, 35.2, 33.4, 31.9, 27.8, 27.7, 26.0, 25.9, 19.2, 18.4, 18.2, 13.8, 13.4, −4.0, −4.8, −5.3, −5.4; ESI: *m/z* 656, 678 [Na adduct]; HRMS-ESI: (Na adduct) 656.4202 (actual), 656.4200 (calcd).

### 4-((1*E*,3*S*,5*Z*,10*S*)-3-(2-Methoxyethoxymethoxy)-2,10-dimethyl-11-oxoundeca-1,5-dienyl)-2-methylthiazole, $C_{21}H_{33}O_4NS$, 3

The silyl ether **55** (0.5 g, 0.7 mmol) was dissolved in 2.0 mL of THF, and 0.5 mL of AcOH and 0.5 mL of $H_2O$ were added to the reaction mixture. After the completion of the reaction as indicated by TLC, the reaction mixture was concentrated *in vacuo* and worked up with ether and water. The combined organic layers were dried (MgSO$_4$), and concentrated under reduced pressure. The crude diol **OH-55** was utilized for the next step without further purification. The diol **OH-55** was dissolved in benzene (4.0 mL) and stirred at 25 °C. Pb(OAc)$_4$ (0.7 g, 1.5 mmol) was added to the reaction mixture and stirred for 20 min. After the completion of the reaction as indicated by TLC, the reaction mixture was worked up with ether and water. The combined organic layers were dried over MgSO$_4$ and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, hexanes–ethyl acetate, 4 : 1), to provide the required $C_7$–$C_{21}$ subunit of epothilone **3** in 0.2 g (70% overall yield for the two steps). $\delta_H$(300 MHz; CDCl$_3$; Me$_4$Si) 9.58 (1 H, d, *J* 2.0), 6.94 (1 H, s), 6.47 (1 H, s), 5.39–5.43 (2 H, m), 4.71 (1 H, d, *J* 6.8), 4.63 (1 H, d, *J* 6.9), 4.12 (1 H, t, *J* 6.8), 3.78–3.85 (1 H, m), 3.51–3.63 (3 H, m), 3.37 (3 H, m), 2.69 (3 H, s), 2.27–2.42 (3 H, m), 1.97–2.07 (5 H, m), 1.33–1.41 (4 H, m), 1.06 (3 H, d, *J* 7.0); $\delta_C$(75.5 MHz; CDCl$_3$; Me$_4$Si) 205.1, 164.6, 152.8, 138.3, 131.1, 126.0, 121.5, 116.0, 92.8, 81.6, 71.8, 67.1, 59.1, 46.2, 32.0, 30.1, 27.4, 26.9, 19.3, 13.8, 13.3; EI-MS: *m/z* 256, 89 [100%, $CH_3OCH_2CH_2OCH_2^+$]; CI-MS: *m/z* 396 [(M + H)$^+$], 290 [100%, M + H − HOCH$_2$OCH$_2$CH$_2$OCH$_3$], 256, 168, 89; HRMS-CI: (M + H) 396.2205 (actual), 396.2209 (calcd).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27 3-Benzyloxypropyl iodide was conveniently prepared in 2 steps starting from 1,3-propanediol, by monobenzylation followed by iodination.

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