Catalytic Antibody Route to the Naturally Occurring Epothilones: Total Synthesis of Epothilones A – F

Subhash C. Sinha,*[a] Jian Sun,[a] Gregory P. Miller,[a] Markus Wartmann,[b] and Richard A. Lerner*[a]

Abstract: Naturally occurring epothilones have been synthesized starting from enantiomerically pure aldol compounds **9** – **11**, which were obtained by antibody catalysis. Aldolase antibody 38C2 catalyzed the resolution of (±)-**9** by enantioselective retro-aldol reaction to afford **9** in 90% *ee* at 50% conversion. Compounds **10** and **11** were obtained in more than 99% *ee* at 50% conversion by resolution of their racemic mixtures using newly developed aldolase antibodies 84G3, 85H6 or 93F3. Compounds **9**, **10** and **11** were resolved in multigram quantities and then converted to the epothilones by metathesis processes, which were catalyzed by Grubbs' catalysts.

Keywords: antibodies · antitumor agents · chiral resolution · epothilones · retro-aldol reactions

Introduction

Since the inception of the concept of antibody catalysis,[1] a number of chemical transformations have been catalyzed by monoclonal antibody catalysts, which were generated against respective transition state analogues by normal immunization techniques.[2] Recently, the reactive immunization technique[3] was introduced to generate antibody catalysts. Two sets of catalytic aldolase monoclonal antibodies (38C2 and 33F12, and 84G3, 85H6 and 93F3) were raised against β-diketone haptens **I** and **II** (Figure 1), respectively, by the reactive immunization technique.[4, 5] Similar to natural aldolase enzymes, these antibody catalysts work by an enamine mechanism and were found to be very useful for synthetic organic chemistry.[6] These two sets of aldolase antibodies complement each other by having antipodal properties and thus produce compounds with opposite facial selectivities. Moreover, unlike natural aldolase enzymes, they accept a much broader range of substrates. In order to demonstrate the efficacy of antibody catalysis for natural product synthesis, we used these aldolase antibody catalysts in the total synthesis of epothilones, which are molecules of current interests due to their possible anticancer chemotherapeutic activity.[7]

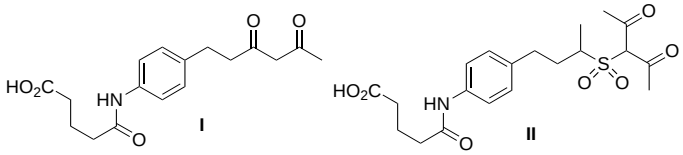

Figure 1. Structures of hapten **I** used to generate antibodies 38C2 and 33F12, and hapten **II** to generate 84G3, 85H6 and 93F3.

Epothilones A – F (**1** – **6**, see Figure 2) are sixteen-membered macrolides isolated from myxobacteria (*Sorangium cellulosum* strain 90).[7, 8] These compounds possess a taxol-like mode of action and function through the stabilization of cellular microtubules. They exhibit cytotoxicity even in taxol-resistant cell lines.[9] Epothilone B has been reported to be about 3400 times more active than taxol against the resistant human leukemic cell line CCRF-CEM/VBL in cell-culture cytotoxicity studies. Danishefsky and co-workers reported the first total synthesis of epothilones A and B (**1** and **2**).[10] Soon after, Nicolaou[11] and Schinzer[12] also reported syntheses of these compounds. Since then numerous syntheses of epothilones A – D have been achieved.[13] In addition, naturally occurring epothilone E,[14] and many analogues of **1** – **5** have also been synthesized and their biological studies have been reported.[15]

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author. ^{1}H and ^{13}C NMR spectra for selected compounds, syntheses of compounds (±)-**9**, (±)-**10** and (±)-**11**, ORTEP diagram of compound **15** (35 pages).

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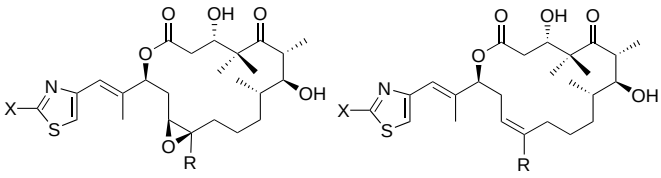


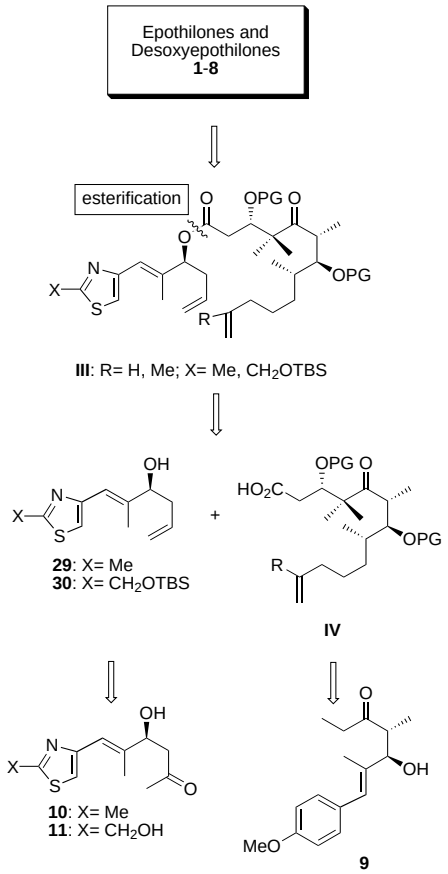
1: Epothilone A, and **3**: Epothilone C: R = H, X = Me
2: Epothilone B, and **4**: Epothilone D: R = X = Me
5: Epothilone E, and **7**: Deoxyepothilone E: R = H, X = CH_2OH
6: Epothilone F, and **8**: Deoxyepothilone F: R = Me, X = CH_2OH

Figure 2. Structures of epothilones and analogues.

Recently, we reported an antibody catalyzed route to the syntheses of epothilones A and C (**1** and **3**) and desoxyepothilone E (**7**) by the macrolactonization/metathesis approach starting from **9**–**11**.[16] Using the same precursors **9**–**11**, we have now synthesized epothilones B (**2**), D (**4**) and F (**6**). In this article, we describe, including full details of our previous communication,[16] syntheses of epothilones A–F (**1**–**6**).[17]

Results and Discussion

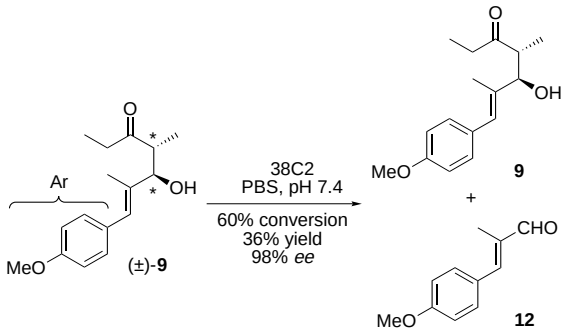
In several reported syntheses of compounds **1**–**4** by the metathesis approach, intermediate **III** in its partially or fully protected form have been used.[8] Considering the relevance of aldolase antibodies to the total syntheses of epothilones, we imagined that **III** could be synthesized through intermediates **IV** and **29**–**30**, starting from precursors **9**–**11** (Scheme 1).



Scheme 1. Retrosynthesis of epothilones **1**–**8**.

Monoclonal catalytic antibodies have been used effectively in the total synthesis of natural products as demonstrated by the construction of brevicomins,[18] multistriatin,[19] and other compounds.[20] In these cases, the antibody catalysts were used to catalyze stereoselective reactions with high rates, thereby yielding precursors to these molecules. The stereochemistry obtained by the antibody-catalyzed reactions guided the remaining configurations of the molecule. Following the same principle, we have now generated the chiral starting materials by using aldolase antibodies and converted these precursors to the naturally occurring epothilones.

Resolution of compound 9 by retro-aldol reaction using antibody 38C2: Based on previous studies on aldol and retro-aldol reactions with aldolase antibodies 38C2 and 33F12,[6] compound (±)-**9** was chosen as the substrate for resolution using antibody 38C2. When compound (±)-**9** was incubated with a catalytic amount of antibody 38C2, enantioselective retro-aldol reaction of (±)-**9** was observed affording aldehyde **12** and pentan-3-one. At 60% conversion, the reaction mixture contained essentially the enantiomerically pure compound **9**.[21] This reaction was also amenable to gram scale. Typically, 0.75 g (2.85 mmol) of compound (±)-**9** was resolved using antibody 38C2 (0.5 g, 0.00357 mmol, 0.125 molar percent) to afford enantiomerically pure **9** (0.3 g, 40% yield).[16a] Alternatively, in a step-wise process, comparatively lesser amount of antibodies were used to give similar results. Thus, compound (±)-**9** (0.825 g, 3.15 mmol) was first resolved with 38C2 (0.1 g, 0.67 μmol, 0.021 molar percent) to afford enantiomerically enriched (±)-**9** (60–70% *ee*). Using the same antibody an additional amount of (±)-**9** (0.5 g, 1.9 mmol) was first resolved in a similar manner to afford the additional amount of enantiomerically enriched (±)-**9** (60–70% *ee*). The combined enriched **9** (684 mg, 52%, 70% *ee*) from previous two experiments were resolved in a new container using the antibody 38C2 (25 mg, 0.179 μmol) to afford enantiomerically pure **9** (480 mg, 36%). Apparently, the aldehyde **12** is an inhibitor of this reaction and slows down the resolution as the former is produced.



Scheme 2. Resolution of (±)-**9** to **9** by antibody 38C2 catalyzed retro-aldol reaction of *ent*-**9** to aldehyde **12**. The other product, pentane-3-one, is not shown in the Scheme.

Production of 10 by aldol reaction and resolution of (±)-10 using aldolase antibody 38C2: Once again, our studies with the aldolase antibody 38C2 guided us to use aldol reaction of aldehyde **13** with acetone to produce compound **10**. As

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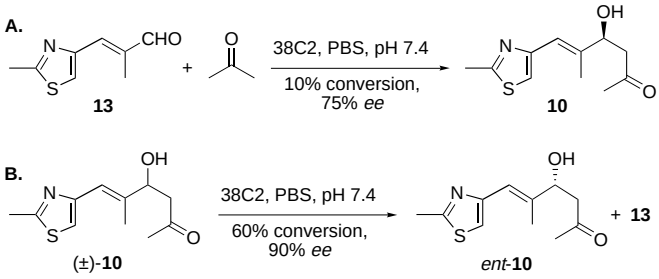
expected, the antibody 38C2 catalyzed this reaction. The enantiomeric excess of the aldol product **10** was found to reach 75% at 10% conversion (Scheme 3A), however, the enantiomeric purity decreased as the reaction progressed. The reason for this is that as higher concentrations of the aldol product were achieved, the retro-aldol process started and was significantly faster than the forward reaction. Hence, at 20% conversion of **13** the ratio between **10** and *ent*-**10** dropped to 4:1. Obviously, both the formation of **10** from **13** and acetone, and the conversion of **10** to **13** and acetone were catalyzed by antibody 38C2 and were faster than the analogous reactions for *ent*-**10**.

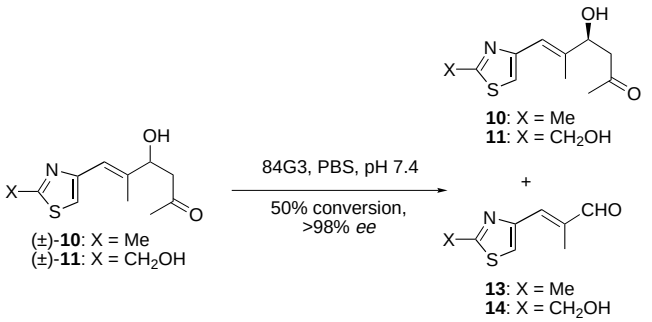


Scheme 3. Production of compounds **10** and *ent*-**10** by antibody 38C2 catalyzed reactions. A) Aldol reaction of aldehyde **13** with acetone, B) resolution of (±)-**10**.

In order to quantify the relative rate of the retro-aldol reactions of **10** and *ent*-**10** with antibody 38C2, we checked the resolution of their racemic mixture. It was found that the retro-aldol reaction of (±)-**10** was catalyzed by antibody 38C2 to afford a 5:1 selectivity in favor of *ent*-**10** at 50% conversion and this selectivity was increased up to 90–95% *ee* at a higher conversion. In a typical reaction, the retro-aldol reaction of (±)-**10** with 0.06 mol percent of antibody 38C2 afforded *ent*-**10** with an enantiomeric purity of 90% at 60% conversion.[22]

Resolution of compounds (±)-10 and (±)-11 by retro-aldol reaction using antibody 84G3, 85H6 or 93F3: Nine more aldolase antibodies were generated against hapten **II**,[5] three of which (84G3, 85H6 and 93F3) efficiently catalyzed the retro-aldol reaction of (±)-**10** to aldehyde **13** and acetone (Scheme 4).[16b] All three antibodies, 84G3, 85H6 and 93F3, showed complementarity with respect to antibody 38C2. Thus, the retro-aldol reaction of (±)-**10** with any of the three antibodies, 84G3, 85H6, and 93F3, afforded compound **10** as a major enantiomer. At 50% conversion of the starting racemic aldol (±)-**10**, compound **10**[23] was obtained in essentially enantiomerically pure form.[24]

Just as (±)-**10**, its analogue (±)-**11** was also resolved using any of the three antibodies 84G3, 85H6 and 93F3 to afford enantiomerically pure **11** at 50% conversion.[25] All three catalysts gave similar results with 84G3 and 93F3 demonstrating a rate enhancement slightly greater than with 85H6. These antibodies could also be used to resolve (±)-**10** and (±)-**11** on a synthetically useful scale. Here, antibody 84G3 was used to perform the gram-scale resolution of compounds (±)-**10** and (±)-**11**. We therefore incubated compounds (±)-**10** (16.8 g, 75.0 mmol) and (±)-**11** (1.45 g, 6.0 mmol) with antibody 84G3

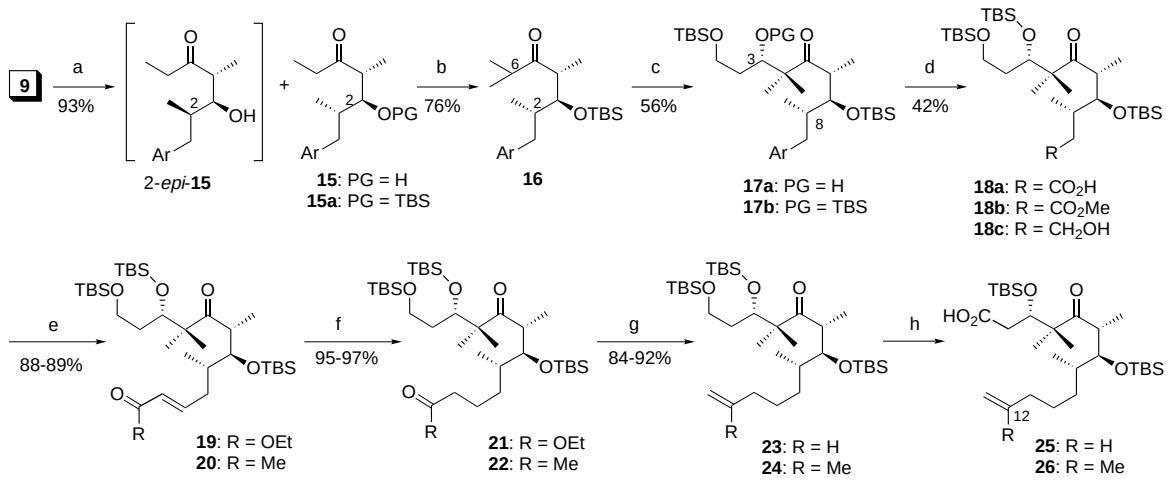


Scheme 4. Resolution of compounds (±)-**10** and (±)-**11** by retro-aldol reaction, catalyzed by antibody 84G3, to give compounds **10** and **11**. The other product, acetone, is not shown in the Scheme.

at 0.003 and 0.005 molar percent, respectively, (see Experimental Section). Progress of these reactions was followed by disappearance of the peak for *ent*-**10** and *ent*-**11** in the HPLC traces. In this way, the racemic mixture was resolved, affording **10** and **11** with more than 98% enantiomeric excess in 45 and 48% isolated yields, respectively. The corresponding aldehydes **13** and **14** were isolated in 40 and 45% yields, respectively. The thiazole aldehydes obtained from these reactions were reused to synthesize the aldol starting materials. Thus, even though the process is a kinetic resolution, the overall yield is good because the produced aldehydes can be recycled.

Conversion of compounds 9–11 to epothilones: With starting materials **9–11** in hand, syntheses of epothilones A, B, E and F (**1**, **2**, **5** and **6**) were achieved via their desoxyepothilones (**3**, **4**, **7** and **8**) using the metathesis approach (see Schemes 5 and 6).

Synthesis of acids 25 and 26 from compound 9: Compound **9** was hydrogenated using Rh/Al_2O_3 to afford a 1:1 mixture of compounds **15** and 2-*epi*-**15**, which were then separated by column chromatography over silica gel. The structure of **15**, which possessed three vicinal stereogenic centers (at C-6, C-7 and C-8) of epothilones, was confirmed by X-ray analysis.[26] The free alcohol function in compound **15** was silylated as its TBS ether using TBSCl and imidazole in dry DMF at 50 °C to afford **15a**. The latter compound was then monomethylated at the less substituted carbon alpha to the carbonyl function to give compound **16**. Aldol reaction of **16** with 3-*tert*-butyldimethylsilyloxy propanal took place at the same α-carbon mentioned above, affording the aldol product **17a** accompanied with 3-*epi*-**17a** in a 1.6:1 diastereomeric ratio at C-3 in favor of the desired isomer. The other possible product by aldol reaction at C-6 was not detected. The aldol product thus obtained was silylated as its TBS ether using TBSOTf and then purified from its minor 3-epimer to give **17b**. The methoxy substituted aromatic ring was exhaustively degraded to the corresponding carboxylic acid **18a**, using the $RuCl_3$/$NaIO_4$ system.[27] Esterification of the acid **18a** was achieved with diazomethane providing ester **18b**. Reduction of this ester afforded the corresponding primary alcohol in compound **18c**. The latter product was converted to the corre-



Scheme 5. Syntheses of acids **25** and **26** from the enantiomerically pure aldol compound **9**. Key steps: a) H_2, Rh/Al_2O_3, THF, 18 h; b) i) TBSCl, imidazole, DMF, 40–50 °C, 48 h, ii) LDA, THF, −78 °C, 2 h then MeI, HMPA, −78 to −40 °C, 4 h; c) i) LDA, THF, −78 to −40 °C, 2 h then $TBSOCH_2CH_2CHO$, −78 °C, 0.5 h (3*S*:3*R*, 1.6:1), ii) TBSOTf, lutidine, CH_2Cl_2, −78 to 0 °C, 4 h, 3-*epi*-**17b** was isolated in 35% (two steps); d) i) $RuCl_3$, $NaIO_4$, CCl_4/CH_3CN 1:1, PBS buffer (pH 7.4), 16 h, ii) CH_2N_2, $EtOH/Et_2O$, 0 °C, 12 h, iii) DIBAL-H, THF, −78 to −55 °C, 1 h; e) i) Dess–Martin reagent, CH_2Cl_2, 2 h, ii) for compound **19**: $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 0.5 h; for compound **20**: $MeCOCHPPh_3$, benzene, reflux, 4 h; f) H_2, Rh/Al_2O_3, THF; for compound **21**: 16 h, for compound **22**, 1 h; g) for compound **23**: i) DIBAL-H, THF, −78 °C, 2 h, ii) Dess–Martin reagent, CH_2Cl_2, 2 h, iii) $MePPh_3I$, *n*BuLi, THF, 0 °C, 0.5 h; for compound **24**: $MePPh_3I$, *n*BuLi, THF, 0 °C, 0.5 h; h) see ref. [12c] and [12d].

sponding aldehyde, which was used in the synthesis of both **25** and **26**.

The above mentioned aldehyde obtained from the oxidation of **18c** was olefinated by Wittig and Wittig–Horner reactions to afford alkenes **19** and **20**, respectively. The latter alkenes, **19** and **20**, were hydrogenated over Rh/Al_2O_3 to yield the saturated ester **21** and ketone **22**. The ester function in compound **21** was reduced to the corresponding alcohol, which was oxidized to the aldehyde and then olefinated by Wittig reaction with methylenetriphenylphosphorane to afford alkene **23**. Ketone **22** was also olefinated by Wittig reaction with methylenetriphenylphosphorane to afford compound **24**. The ^1H and ^{13}C NMR spectra of **23** and **24** were identical to those for the same compounds used in the Schinzer's synthesis of **1** and **3**.[12c,d] The selective deprotection of the primary hydroxy group in **23** and **24** with TsOH in methanol/CH_2Cl_2 at 0 °C followed by two-step oxidations of the primary alcohol via their corresponding aldehydes afforded acids **25** and **26**, respectively.[12c,d]

The thiazole fragments, **29** and **30**, to be used in the syntheses of **1**–**8**, were prepared starting from **10** and **11** respectively, as shown in Scheme 6. The hydroxy groups in compounds **10** and **11** were first protected as their TBS ethers to afford **10a** and **11a**. Reaction of **10a** and **11a** with lutidine and TMSOTf at −78 °C gave the corresponding trimethylsilyl enol ether derivatives, which were then oxidized using OsO_4/NMO to afford the primary hydroxy ketones, **27** and **28**, respectively.[28] Reduction of the ketone function in compounds **27** and **28** afforded the corresponding vicinal diols, which were then cleaved with $Pb(OAc)_4$ to give aldehydes **29a**[29] and **30a**. Wittig reactions of **29a** and **30a** with methylenetriphenylphosphorane afforded alkenes **29b** and **30b**. The TBS protecting group in compound **29b** was cleaved by exposure to TBAF yielding the corresponding alcohol **29**. Similar treatment with compound **30b** afforded the corresponding diol. The primary hydroxyl group of this product was then selectively protected with TBSCl to afford compound **30**.

Esterification of thiazole alcohol **29** with acids **25** and **26** yielded esters **31** and **32**, respectively. Similarly, thiazole alcohol **30** was esterified with acids **25** and **26** to afford compounds **33** and **34**, respectively. Metathesis of **31** and **33** was achieved with Grubbs' catalyst **V** (Figure 3) to afford the cyclized compounds **35** and **37** along with their *trans* isomers, (*E*)-**35** and (*E*)-**37**, in a ratio of 3:2 in favor of compounds **35** and **37**. Similar treatment of dienes **32** and **34** with Grubbs' catalyst **V**, however, resulted in their corresponding dimers after prolonged treatment. We also tested Hoveyda's modified catalyst, **VI**,[30] which gave similar results. At the time of these experiments, Grubbs reported a new catalyst, **VII**, which possesses comparable activity to Schrock's catalyst **VIII**,[31] and described it as a powerful catalyst using a wide variety of substrates.[32] Following the reported procedure by Grubbs,[32a] catalyst **VII** was synthesized which was proven to be fairly stable to air and moisture. Recently, we have used **VII** as a RCM catalyst for the synthesis of 13-alkyl epothilones.[33] Using the catalyst **VII**, metathesis of **32** and **34** in refluxing CH_2Cl_2 was successfully achieved to afford the mixture of cyclized olefins **36** and **38**, and their respective *trans* isomers in a ratio of 1.1:1 in favor of **36** and **38**. In fact, this is the first occasion that Grubbs' catalyst, **VII**, has been used as a RCM catalyst for macrocyclization in the synthesis of naturally occurring epothilones. The cyclized products in each case were deprotected using trifluoroacetic acid or HF/pyridine to afford desoxyepothilones **3**, **4**, **7** and **8** and their *trans* isomers. The physical and spectral data (^1H NMR, ^{13}C NMR, MS, optical rotation) of **3**, **4**, **7** and **8** were identical to the published data.[10–14, 17] Epoxidation of **3**, **4**, **7** and **8** was accomplished using methyl(trifluoromethyl)dioxirane to afford **1**, **2**, **5**, **6** and their α-stereoisomer, as previously reported.

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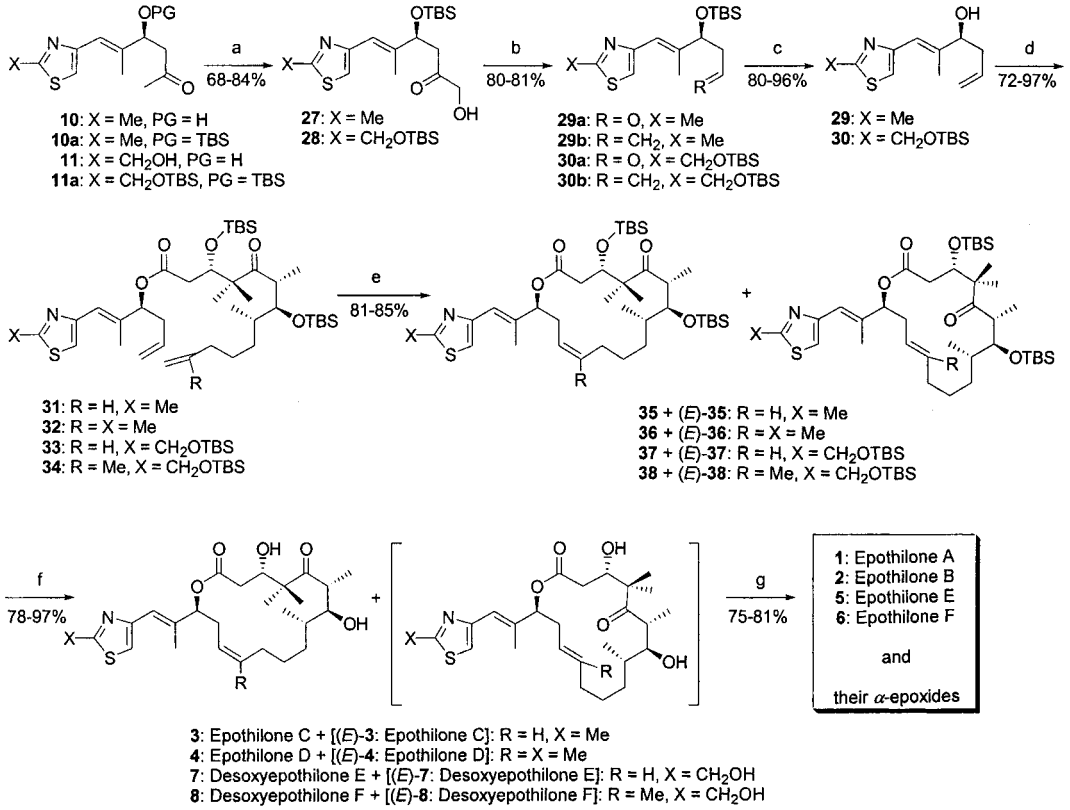

Scheme 6. Total syntheses of epothilones A–F (**1**–**6**) by metathesis approach. Key steps: a) i) TBSCl, imidazole, DMF, rt, 8 h, ii) TMSOTf, lutidine, CH_2Cl_2, −78 to 0 °C, 4 h then OsO_4, NMO, CH_2Cl_2, rt, 5 h; b) i) $NaBH_4$, MeOH, 0 °C, 0.5 h, ii) $Pb(OAc)_4$, CH_2Cl_2, 0 °C, 0.5 h, iii) $MePPh_3I$, *n*BuLi, THF, 0 °C, 0.5 h; c) for compound **29**: TBAF, THF, 0 °C, 1 h; for compound **30**: i) TBAF, THF, 0 °C, 1 h, ii) TBSCl, *i*Pr_2EtN, CH_2Cl_2, 0 °C to RT, 8 h; d) for compounds **31** and **33**: **25**, EDC, DMAP (cat.), CH_2Cl_2, 0 °C to RT, 5 h; for compounds **32** and **34**: **26**, EDC, DMAP (cat.), CH_2Cl_2, 0 °C to RT, 5 h; e) for compounds **35**, (*E*)-**35**, **37** and (*E*)-**37**: Grubbs' catalyst **V**, CH_2Cl_2, RT, 5 h; for compounds **36**, (*E*)-**36**, **38** and (*E*)-**38**: Grubbs' catalyst **VII**, CH_2Cl_2, reflux, 16 h; f) HF/pyridine, THF, RT, 2–6 h; g) CF_3COMe, oxone, $NaHCO_3$, CH_3CN, CH_2Cl_2, Na_2EDTA, 0 °C, 1 h.

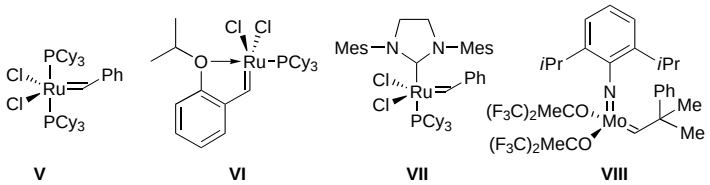

Figure 3. Structures of metathesis catalysts, **V**–**VIII**.

The biological effect of the synthetic epothilone F (**6**), desoxyepothilone F (**8**) and (*E*)-desoxyepothilone F [(*E*)-**8**] were studied using tubulin polymerization and cell growth inhibition experiments. Both the epothilone F and desoxyepothilone F produced 77% and 75% tubulin polymerization, respectively. As expected, (*E*)-desoxyepothilone F showed greatly reduced activty, producing less than 10% tubulin polymerization. Under the same conditions, epothilones A and B produced 67% and 84% tubulin polymerization, respectively. Epothilone F was eight times more potent than desoxyepothilone F with respect to growth inhibition of KB-31 epidermoid carcinoma cells, with IC_{50} values of 0.4 nM and 3.3 nM, respectively. Thus, epothilone F and desoxyepothilone F are almost equally potent to epothilone B and epothilone D, respectively.

In conclusion, we have achieved syntheses of naturally occurring epothilones A–F starting from enantiomerically pure *β*-hydroxy ketones **9**–**11**, which were obtained by resolution of their racemic mixtures using two aldolase antibodies. Three stereogenic centers of **9** and **10**–**11** were incorporated into the epothilone molecules by the antibody-catalyzed steps. The remaining four stereogenic centers including the epoxide ring were guided by the structure of the substrates. Metathesis of corresponding dienes to produce cyclized products, enroute to **2** and **6**, was catalyzed by the Grubbs' new catalyst **VII**. The catalyst **VII** was proven to be superior to other air- and moisture-sensitive catalysts. Biological evaluations suggest that epothilone F and desoxyepothilone F are equally potent to epothilones B and D, respectively.

Experimental Section

General: ^1H and ^{13}C NMR spectra were measured in $CDCl_3$. Positive ion mass spectra, using the fast ion bombardment (FIB) technique, were obtained on a VG ZAB-VSE double focusing, high-resolution mass spectrometer equipped with either a cesium or sodium ion gun. Optical rotations were measured in a one-decimeter (1.3 mL) cell using an Autopol III automatic polarimeter at room temperature (22–23 °C). TLC was performed on glass sheets precoated with silica gel (Merck, Kieselgel 60, F_{254}, Art. No. 5715). Column chromatographic separations were performed on silica gel (Mallinckrodt, 230–400 mesh, V150) under pressure. HPLC analyses were carried out using a reverse phase ODR column (Daicel Chemical Industries) monitored by a UV spectrophotometer at

$\lambda_{max} = 254$ nm. THF was dried and distilled over sodium/benzophenone. All antibody reactions were first degassed by passing a slow stream of argon through the reaction mixture and then carried out under an argon atmosphere.

Kinetic resolution of (±)-9 to 9 by antibody 38C2 catalyzed enantioselective retro-aldol reaction: In a typical process,[34] a dialysis bag containing antibody 38C2 (0.1 g, 0.714 μmol in 6.3 mL PBS buffer) was introduced to a mixture of compound (±)-**9** (0.825 g, 3.15 mmol in 50 mL CH_3CN) in PBS buffer (pH 7.4, 500 mL). Progress of the reaction was monitored by HPLC (see: Supporting Information) and when that slowed down substantially (at 60–70% *ee*), the reaction was interrupted. The dialysis bag was dialyzed (3 × 200 mL) with 10% CH_3CN in PBS buffer (pH 7.4) and introduced to a new batch of substrate (0.5 g, 1.9 mmol in 20 mL CH_3CN) in PBS buffer (pH 7.4, 200 mL). The process was repeated as above. The combined aqueous solution from dialysis was extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the resultant residue was purified by column chromatography to afford enriched **9** (684 mg, 52%, 70% *ee*). First part of the process was repeated using a new dialysis bag containing the antibody 38C2 (25 mg, 0.179 μmol), enriched **9** (684 mg, 2.61 mmol) in CH_3CN (20 mL) and PBS buffer (pH 7.4, 200 mL). At >98% consumption of one enantiomer as judged by HPLC analysis, the reaction mixture was worked up and purified, as above, to afford enantiomerically pure **9** (480 mg, overall 36%). $[\alpha]_D = +44.9^\circ$ ($c = 2.1$, $CHCl_3$); ^{1}H NMR (600 MHz): $\delta = 7.21$ (d, $J = 8.7$ Hz, 2H; ArH), 6.85 (d, $J = 8.7$ Hz, 2H; ArH), 6.51 (s, 1H; ArCH=C), 4.43 (br s, 1H; C*H*OH), 3.79 (s, 3H; OCH_3), 2.83 (m, 1H; C*H*$COCH_3$), 2.56 (m, 2H; CH_2CO), 1.81 (s, 3H; CH_3C=CH), 1.12 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.04 (t, $J = 7.2$ Hz, 3H; CH_3CH_2); ^{13}C NMR (150.9 MHz): $\delta = 216.0$, 158.1, 135.0, 125.5, 113.5, 75.9, 55.2, 48.3, 35.2, 15.1, 10.4, 7.6; MS (FAB): 262 $[M]^+$, 285 $[M+Na]^+$.

Kinetic resolutions of (±)-10 and (±)-11 to 10 and 11 by antibody 84G3 catalyzed enantioselective retro-aldol reactions

Compound 10: Antibody 84G3 (12.5 mg per mL, 27.2 mL, 0.34 g, 0.00227 mmol) was added to a degassed solution of compound (±)-**10** (16.8 g, 75 mmol) in PBS buffer (1.55 L, pH 7.4) and CH_3CN (140 mL), and the mixture was incubated under an argon atmosphere at 37 °C for 5 d. At more than 98% consumption of one enantiomer as judged by HPLC analysis (for HPLC conditions, see Supporting Information), the mixture was dialyzed using amicon membranes to recover the antibody and the filtrate was passed through a reverse phase column (C-18) to elute first water, and then the compounds were isolated using methanol as eluent. The solvents were removed under vacuum and the residue was purified over silica gel (hexanes/EtOAc 9:1 → 2:1) to afford compounds **10** (7.6 g, 45%, >98% *ee*) and the aldehyde **13** (5.29 g, 42%). For **10**: $[\alpha]_D = -34.3^\circ$ ($c = 1.62$, $CHCl_3$); ^{1}H NMR (600 MHz): $\delta = 6.89$ (s, 1H; ArH), 6.55 (s, 1H; ArCH=C), 4.58 (dd, $J = 9.3$, 2.2 Hz, 1H; C*H*OH), 3.72 (br s, 1H; OH), 2.72 (dd, $J = 16.7$, 9.4 Hz, 1H; CH_2CO), 2.65 (s, 3H; $ArCH_3$), 2.64 (dd, $J = 16.7$, 3.0 Hz, 1H; CH_2CO), 2.18 (s, 3H; CH_3CO), 1.98 (s, 3H; CH_3C=CH); ^{13}C NMR (150.9 MHz): $\delta = 208.9$, 164.7, 152.5, 140.5, 118.6, 115.7, 72.6, 48.7, 30.9, 19.0, 14.7; MS: 226 $[M+H]^+$, 248 $[M+Na]^+$.

Compound 11: In a similar manner as above (see compound **10** for the detailed process and Supporting Information for HPLC system), (±)-**11** (1.45 g, 6.0 mmol) and antibody 84G3 (45 mg, 0.0003 mmol) in PBS (pH 7.4, 90 mL) and CH_3CN (4 mL) were incubated for 96 h at 37 °C to afford compound **11** (0.69 g, 48%, >98% *ee*) and aldehyde **14** (0.44 g, 40%). For **11**: $[\alpha]_D = -26.7^\circ$ ($c = 0.9$, $CHCl_3$); ^{1}H NMR (500 MHz): $\delta =$ 7.07(s, 1H; ArH), 6.58 (s, 1H; ArC*H*=C), 4.92 (s, 2H; CH_2OH), 4.60 (m, 1H; C*H*OH), 3.32 (br, 1H; OH), 3.01 (br, 1H; OH), 2.73 (m, 2H; CH_2CO), 2.22 (s, 3H; CH_3CO), 2.03 (s, 3H; CH_3C=CH); ^{13}C NMR (125.75 MHz, $CDCl_3$): $\delta = 209.2$, 170.0, 152.8, 140.8, 118.5, 116.4, 72.6, 62.0, 48.6, 30.9, 14.8; MS: 264 $[M+Na]^+$.

Compounds 15 and 2-*epi*-15: A heterogeneous mixture of **9** (2.2 g, 8.4 mmol) and Rh/Al_2O_3 (10% *w*/*w*, 440 mg) in THF (85 mL) was stirred at room temperature under a H_2 atmosphere using balloon for 18 h. The solution was filtered through Celite, solvents were removed under vacuum and the residue was chromatographed over silica gel (hexanes/EtOAc 3:1) to give **15** (1.06 g, 48%) and 2-*epi*-**15** (0.99 g, 45%).

Physical data of 15: m.p. 68–70 °C; $[\alpha]_D = -3.3^\circ$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (600 MHz): $\delta = 7.10$ (d, $J = 8.3$ Hz, 2H; ArH), 6.81 (d, $J =$ 8.3 Hz, 2H; ArH), 3.77 (s, 3H; OCH_3), 3.63 (dd, $J = 9.0$, 1.8 Hz, 1H; C*H*OH), 3.11 (br s, 1H; OH), 3.09 (dd, $J = 13.5$, 3.3 Hz, 1H; CH_2Ar), 2.72 (qd, $J = 7.2$, 2.4 Hz, 1H; C*H*CO), 2.57 (dq, $J = 18.0$, 7.3 Hz, 1H; CH_2CH_3), 2.45 (dq, $J = 18.0$, 7.3 Hz, 1H; CH_2CH_3), 2.29 (dd, $J = 13.5$, 9.3 Hz, 1H; CH_2Ar), 1.75 (m, 1H; C*H*CH_2Ar), 1.12 (d, $J = 7.2$ Hz, 3H; CH_3CHCO), 1.05 (t, $J = 7.3$ Hz, 3H; CH_3CH_2), 0.71 (d, $J = 6.8$ Hz, 3H; CH_3CHCH_2); ^{13}C NMR (150.9 MHz): $\delta = 217.2$, 157.7, 132.6, 130.5, 113.5, 74.1, 55.2, 46.7, 38.0, 37.5, 34.8, 15.0, 9.1, 7.6; HRMS: calcd for $C_{16}H_{24}O_3Na$: 287.1623; found: 287.1624 $[M+Na]^+$.

Physical data of 2-*epi*-15: m.p. 94–96 °C; $[\alpha]_D = +7.0^\circ$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (600 MHz): $\delta = 7.04$ (d, $J = 8.6$ Hz, 2H; ArH), 6.82 (d, $J = 8.6$ Hz, 2H; ArH), 3.78 (s, 3H; OCH_3), 3.67 (t, $J = 5.7$ Hz, 1H; C*H*OH), 2.80 (qd, $J = 7.1$, 5.3 Hz, 1H; C*H*CO), 2.66 (dd, $J = 13.5$, 5.6 Hz, 1H; CH_2Ar), 2.51 (dq, $J = 18.0$, 7.3 Hz, 1H; CH_2CH_3), 2.43 (dq, $J = 18.0$, 7.3 Hz, 1H; CH_2CH_3), 2.37 (br s, 1H; OH), 2.29 (dd, $J = 13.5$, 9.2 Hz, 1H; CH_2Ar), 1.76 (m, 1H; C*H*CH_2Ar), 1.16 (d, $J = 7.1$ Hz, 3H; CH_3CHCO), 1.03 (t, $J =$ 7.3 Hz, 3H; CH_3CH_2), 0.88 (d, $J = 6.6$ Hz, 3H; CH_3CHCH_2); ^{13}C NMR (150.9 MHz): $\delta = 215.8$, 157.8, 132.3, 129.9, 113.7, 74.5, 55.2, 48.3, 39.0, 37.7, 34.9, 14.3, 11.5, 7.6; MS: 287 $[M+Na]^+$.

Compound 15a: TBSCl (1.1 g, 7.3 mmol) was added to a solution of compound **15** (0.96 g, 3.64 mmol) and imidazole (1.1 g, 16.2 mmol) in dry DMF (3 mL) and stirred at 40–50 °C for 48 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with Et_2O. The combined organic layer was washed with brine and dried over $MgSO_4$. Solvents were removed under vacuum and the crude silyl ether was purified over silica gel (hexanes/EtOAc 19:1) to afford pure silyl ether **15a** (1.15 g, 84%) and recovered **15** (0.15 g, 16%). ^{1}H NMR (600 MHz): $\delta = 7.02$ (d, $J = 8.4$ Hz, 2H; ArH), 6.81 (d, $J = 8.4$ Hz, 2H; ArH), 3.92 (dd, $J = 5.6$, 4.1 Hz, 1H; CHOTBS), 3.77 (s, 3H; OCH_3), 2.79 (dd, $J = 13.6$, 4.0 Hz, 1H; CH_2Ar), 2.76 (m, 1H; CHCO), 2.50 (qd, $J = 7.5$, 4.0 Hz, 1H; CH_2CH_3), 2.46 (qd, $J = 7.5$, 4.0 Hz, 1H; CH_2CH_3), 2.08 (dd, $J = 13.6$, 10.4 Hz, 1H; CH_2Ar), 1.72 (m, 1H; C*H*CH_2Ar), 1.11 (d, $J = 7.2$ Hz, 3H; CH_3CHCO), 1.04 (t, $J =$ 7.2 Hz, 3H; CH_3CH_2), 0.92 (s, 9H; $SiC(CH_3)_3$), 0.80 (d, $J = 7.2$ Hz, 3H; CH_3CHCH_2), 0.08 (s, 3H; $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz): $\delta = 214.0$, 157.7, 133.4, 129.9, 113.6, 76.7, 55.2, 49.7, 40.7, 37.4, 35.3, 26.1, 18.4, 16.4, 13.4, 7.7, −3.9, −4.2; HRMS: calcd for $C_{22}H_{39}O_3Si$: 379.2668; found: 379.2665 $[M+H]^+$.

Compound 16: *n*BuLi (1.6 M in hexanes, 2.4 mL, 3.8 mmol) was added dropwise to a solution of iPr_2NH (0.58 mL, 4.13 mmol) in dry THF (10 mL) at 0 °C. After stirring for 0.5 h, the mixture was cooled to −78 °C and compound **15a** (1.3 g, 3.44 mmol) in dry THF (5 mL) was added dropwise to the solution. After stirring for another 2 h, HMPA (0.58 mL, 4.1 mmol) and MeI (0.5 mL, 8.0 mmol) in dry THF (2 mL) were added dropwise to the solution. The reaction mixture was stirred at −78 to −40 °C for 4 h and then quenched with a saturated aqueous solution of NH_4Cl, diluted with water and extracted with Et_2O. The combined organic layer was washed with brine and dried over $MgSO_4$. Solvents were removed under vacuum to give crude product that was purified over silica gel (hexanes/EtOAc 49:1) to give **16** (1.02 g, 76%) and **15a** (0.17 g, 13%).

Physical data of **16**: $[\alpha]_D = -2.7^\circ$ ($c = 1.15$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 7.01$ (d, $J = 7.7$ Hz, 2H; ArH), 6.80 (d, $J = 7.7$ Hz, 2H; ArH), 3.90 (dd, $J = 6.5$, 3.2 Hz, 1H; CHOTBS), 3.77 (s, 3H; OCH_3), 2.97 (pentet, $J =$ 6.8 Hz, 1H; CH_3CHCO), 2.82 (m, 1H; $(CH_3)_2CHCO$), 2.76 (dd, $J = 13.7$, 4.0 Hz, 1H; $ArCH_2$), 2.13 (dd, $J = 13.7$, 10.6 Hz, 1H; $ArCH_2$), 1.70 (m, 1H; C*H*CH_2Ar), 1.11 (d, $J = 7.0$ Hz, 3H; CH_3CHCO), 1.10 (d, $J = 7.0$ Hz, 3H; $(CH_3)_2CH$), 1.09 (d, $J = 6.8$ Hz, 3H; $(CH_3)_2CH$), 0.92 (s, 9H; $SiC(CH_3)_3$), 0.81 (d, $J = 6.9$ Hz, 3H; CH_3CHCH_2), 0.09 (s, 3H; $Si(CH_3)_2$), 0.05 (s, 3H; $Si(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 217.2$, 157.7, 133.4, 129.9, 113.7, 76.8, 55.2, 48.1, 40.7, 40.2, 36.9, 26.1, 18.8, 18.4, 18.2, 16.7, 14.5, −3.8, −4.1; MS: 393 $[M+H]^+$, 415 $[M+Na]^+$.

Compounds 17a and 3-*epi*-17a: *n*BuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol) was added dropwise to a solution of iPr_2NH (0.45 mL, 3.2 mmol) in dry THF (10 mL) at 0 °C. After stirring for 0.5 h, the mixture was cooled to −78 °C and compound **16** (1.02 g, 2.6 mmol) in dry THF (5 mL) was added dropwise to the solution. After stirring for another 2 h at −78 to −40 °C, the reaction mixture was recooled to −78 °C and a solution of $TBSOCH_2CH_2CHO$ (0.98 g, 5.2 mmol) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 0.5 h and then quenched with a saturated aqueous solution of NH_4Cl, and worked-up with Et_2O and water. The combined organic layer was washed with brine, dried over $MgSO_4$ and solvents were removed under vacuum to give the crude

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product. Purification over silica gel (hexanes/EtOAc 49:1) gave the aldol product (diastereomeric ratio 1.6:1 in favor of the desired compound 1.54 g), which was contaminated with a small amount of small inseparable impurities. This product was taken to the next step without further purification. ^{1}H NMR (400 MHz): $\delta = 7.02$ (d, $J = 8.6$ Hz, 2H; ArH), 6.79/6.78 (d, $J = 8.6$ Hz; d, $J = 8.5$ Hz, together 2H; ArH), 4.06–3.75 (m, 4H; TBSOCH_2, CHOH, CH(OTBS)), 3.77/3.76 (2s, together 3H; OCH_3), 3.54/3.45 (2br s, together 1H; OH), 3.26 (m, 1H; CH_3CHCO), 2.79 (dd, $J = 13.8$, 3.8 Hz, 1H; $ArCH_2$), 2.25/2.24 (2dd, $J = 13.8$, 11.2 Hz each, together 1H; $ArCH_2$), 1.73 (m, 1H; CH_3CHCH_2), 1.56 (m, 2H; TBSOCH$_2$CH_2), 1.21/1.20 (2s, together 3H; $(CH_3)_2$C), 1.16/1.13 (2s, together 3H; $(CH_3)_2$C), 1.11/1.09 (2d, $J = 7.0$ Hz each, together 3H; CH_3CHCO), 0.94 (s, 9H; SiC$(CH_3)_3$), 0.88/0.87 (2s, together 9H; SiC$(CH_3)_3$), 0.80/0.79 (2d, $J = 7.2$ Hz each, together 3H; CH_3CHCH$_2$), 0.10/0.09/0.07/0.05 (4s, together 12H; Si$(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 219.9$, 157.6, 133.4, 129.9, 113.6, 77.4, 76.4/75.6, 63.0/62.6, 55.2, 52.3/52.1, 45.1/45.0, 40.5/40.2, 36.0/35.8, 35.6/33.3, 31.6, 26.3, 25.9, 22.2/22.0, 19.9/19.7, 18.6/18.2, 17.5/17.4, 16.1, 15.9, 14.1, −3.5, −3.7, −3.8, −5.5; MS: 581 $[M+H]^+$.

Compounds 17b and 3-*epi*-17b: TBSOTf (0.76 mL, 3.3 mmol) was added dropwise to a solution of the above-mentioned mixture of aldol products **17a** and 3-*epi*-**17a** (1.54 g, 2.66 mmol) and lutidine (0.45 mL, 3.84 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C and stirred at −78 → 0 °C for 4 h. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$, diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water and dried over anhydrous $MgSO_4$. Solvents were removed and the residue was chromatographed over silica gel (hexanes/EtOAc 49:1) to give **17b** (1.02 g, 56%) and 3-*epi*-**17b** (0.64 g, 35%) in two steps.

Physical data of 17b: ^{1}H NMR (400 MHz): $\delta = 7.03$ (d, $J = 8.6$ Hz, 2H; ArH), 6.80 (d, $J = 8.6$ Hz, 2H; ArH), 4.13 (t, $J = 5.2$ Hz, 1H; CH_2CHOTBS), 3.92 (dd, $J = 6.3$, 2.4 Hz, 1H; CHCHOTBS), 3.77 (s, 3H; OCH_3), 3.66 (m, 2H; TBSOCH_2), 3.17 (m, 1H; CH_3CHCO), 2.80 (dd, $J = 13.8$, 3.7 Hz, 1H; $ArCH_2$), 2.25 (dd, $J = 13.7$, 11.0 Hz, 1H; $ArCH_2$), 1.69 (m, 1H; CH_3CHCH_2), 1.52 (m, 2H; TBSOCH$_2$CH_2), 1.20 (s, 3H; $(CH_3)_2$C), 1.09 (d, $J = 7.0$ Hz, 3H; CH_3CHCO), 1.08 (s, 3H; $(CH_3)_2$C), 0.95/0.89/0.87 (3s, 27H; SiC$(CH_3)_3$), 0.82 (d, $J = 6.8$ Hz, 3H; CH_3CHCH$_2$), 0.11/0.04/0.02/0.01 (4s, 12H; Si$(CH_3)_2$), 0.10 (s, 6H; Si$(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 217.5$, 157.7, 133.3, 129.9, 113.6, 77.1, 72.2, 60.4, 55.2, 54.1, 45.0, 40.7, 37.6, 36.2, 26.3, 26.2, 25.9, 23.0, 19.2, 18.7, 18.4, 18.2, 17.4, 15.5, −3.5, −3.6, −3.8, −4.0, −5.3; MS: 717 $[M+Na]^+$.

Physical data of 3-*epi*-17b: ^{1}H NMR (400 MHz): $\delta = 7.03$ (d, $J = 8.6$ Hz, 2H; ArH), 6.81 (d, $J = 8.6$ Hz, 2H; ArH), 3.93 (dd, $J = 7.6$, 2.6 Hz, 1H; CH_2CHOTBS), 3.90 (dd, $J = 6.5$, 2.4 Hz, 1H; CHCHOTBS), 3.77 (s, 3H; OCH_3), 3.68 (m, 1H; TBSOCH_2), 3.59 (m, 1H; TBSOCH_2), 3.23 (m, 1H; CH_3CHCO), 2.82 (dd, $J = 13.8$, 3.7 Hz, 1H; $ArCH_2$), 2.26 (dd, $J = 13.8$, 11.1 Hz, 1H; $ArCH_2$), 1.70 (m, 1H; CH_3CHCH_2), 1.60 (m, 1H; TBSOCH$_2$CH_2), 1.52 (m, 1H; TBSOCH$_2$CH_2), 1.26 (s, 3H; $(CH_3)_2$C), 1.10 (s, 3H; $(CH_3)_2$C), 1.09 (d, $J = 6.6$ Hz, 3H; CH_3CHCO), 0.96/0.91/0.89 (3s, 27H; SiC$(CH_3)_3$), 0.81 (d, $J = 6.9$ Hz, 3H; CH_3CHCH$_2$), 0.10 (2s, together 9H; Si$(CH_3)_2$), 0.08 (s, 3H; Si$(CH_3)_2$), 0.02 (2s, together 6H; Si$(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 218.0$, 157.7, 133.3, 129.9, 113.6, 77.2, 74.0, 60.9, 55.2, 53.6, 45.5, 40.5, 38.1, 36.1, 26.3, 26.1, 26.0, 24.8, 19.4, 18.6, 18.3, 18.2, 17.4, 15.0, −3.5, −3.6, −3.8, −4.0, −5.2, −5.3; MS: 695 $[M+H]^+$.

Acid 18a: $RuCl_3 \cdot H_2O$ (69 mg, 0.31 mmol) was added to a heterogeneous mixture of compound **17b** (2.2 g, 3.2 mmol) and $NaIO_4$ (13.52 g, 63.2 mmol) in CCl_4 (21 mL), CH_3CN (21 mL) and phosphate buffer (0.25 M, pH 7.4, 21 mL) at room temperature and stirred for 16 h. The reaction mixture was diluted with water and EtOAc and filtered over Celite. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$. Solvents were removed under vacuum and the resultant residue was purified by chromatography over silica gel (hexanes/EtOAc 4:1) to afford acid **18a** (1.21 g) with trace of impurities, which was taken to the next step without further purification. ^{1}H NMR (400 MHz): $\delta = 3.88$ (dd, $J = 7.6$, 2.8 Hz, 1H; CH_2CHOTBS), 3.81 (dd, $J = 7.9$, 1.8 Hz, 1H; CHCHOTBS), 3.66 (m, 1H; TBSOCH_2), 3.58 (m, 1H; TBSOCH_2), 3.09 (m, 1H; CH_3CHCO), 2.48 (dd, $J = 15.7$, 3.3 Hz, 1H; CH_2CO_2H), 2.13 (dd, $J = 15.7$, 10.4 Hz, 1H; CH_2CO_2H), 1.87 (m, 1H; CHCH$_2$CO$_2$H), 1.56 (m, 1H; TBSOCH$_2$CH_2), 1.48 (m, 1H; TBSOCH$_2$CH_2), 1.21 (s, 3H; $(CH_3)_2$C), 1.06 (d, $J = 6.8$ Hz, 3H; CH_3CHCO), 1.04 (s, 3H; $(CH_3)_2$C), 1.00 (d, $J = 6.8$ Hz, 3H; CH_3CHCH$_2$), 0.90/0.88/0.87 (3s, 27H; SiC$(CH_3)_3$), 0.09/0.08/0.07/0.05 (4s, 12H; Si$(CH_3)_2$), 0.02 (s, 6H; Si$(CH_3)_2$); MS: 655 $[M+Na]^+$.

Ester 18b: A freshly distilled solution of CH_2N_2 (prepared from 10 mmol Diazald in ether/ethanol, 25 mL) was added to a cold (0 °C) solution of the crude acid **18a** (1.21 g) in Et_2O (10 mL) and the mixture was allowed to warm to room temperature overnight. Solvents were removed and the residue was purified over silica gel (hexanes/EtOAc 9:1) to afford pure ester **18b** (1.08 g, 53%, two steps). ^{1}H NMR (600 MHz): $\delta = 3.89$ (dd, $J = 7.8$, 2.6 Hz, 1H; CH_2CHOTBS), 3.81 (dd, $J = 7.8$, 1.8 Hz, 1H; CHCHOTBS), 3.66 (m, 1H; TBSOCH_2), 3.64 (s, 3H; CO_2CH_3), 3.58 (m, 1H; TBSOCH_2), 3.08 (m, 1H; CHCO), 2.45 (dd, $J = 15.6$, 3.2 Hz, 1H; CH_2CO_2), 2.11 (dd, $J = 15.6$, 10.6 Hz, 1H; CH_2CO_2), 1.85 (m, 1H; CHCH$_2$CO$_2$), 1.55 (m, 1H; TBSOCH$_2$CH_2), 1.50 (m, 1H; TBSOCH$_2$CH_2), 1.22 (s, 3H; $(CH_3)_2$C), 1.06 (s, 3H; $(CH_3)_2$C), 1.05 (d, $J = 6.7$ Hz, 3H; CH_3CHCO), 0.96 (d, $J = 6.8$ Hz, 3H; CH_3CHCH$_2$), 0.90/0.89/0.87 (3s, 27H; SiC$(CH_3)_3$), 0.08/0.076/0.068/0.055 (4s, 12H; Si$(CH_3)_2$), 0.021/0.019 (2s, 6H; Si$(CH_3)_2$); ^{13}C NMR (150.9 MHz): $\delta = 218.1$, 173.9, 73.8, 60.9, 53.7, 51.4, 46.0, 38.1, 35.7, 35.5, 26.2, 26.1, 25.9, 24.4, 19.1, 18.9, 18.5, 18.3, 18.2, 15.4, −2.74, −3.77, −3.99, −5.28, −5.31; MS (ESI): 669 $[M+Na]^+$, 681 $[M+Cl]^-$.

Alcohol 18c: A solution of DIBAL-H (1.0 M in toluene, 5 mL, 5 mmol) was added to a solution of compound **18b** (1.08 g, 1.67 mmol) in dry THF (20 mL) and the reaction was stirred at −78 to −55 °C for 1 h. The reaction mixture was quenched by careful addition of a saturated aqueous NH_4Cl and diluted with Et_2O. Celite was added and the mixture was stirred at 0 °C until all solid material precipitated out (ca. 0.5 h). Inorganic material was filtered off, solvents were removed, and the residue was purified over silica gel (hexanes/EtOAc 6:1) to afford pure alcohol **18c** (820 mg, 79%). ^{1}H NMR (600 MHz): $\delta = 3.92$ (dd, $J = 7.6$, 2.7 Hz, 1H; CH_2CHOTBS), 3.85 (dd, $J = 7.6$, 1.9 Hz, 1H; CHCHOTBS), 3.71 (m, 1H; CH_2OH), 3.68 (m, 1H; CH_2OH), 3.59 (m, 2H; TBSOCH_2), 3.18 (m, 1H; CHCO), 1.70 (m, 1H; CH_3CHCH$_2$), 1.60 (m, 2H; CH_2), 1.50 (m, 2H; CH_2), 1.22 (s, 3H; $(CH_3)_2$C), 1.06 (d, $J = 7.0$ Hz, 3H; CH_3CHCO), 1.05 (s, 3H; $(CH_3)_2$C), 0.95 (d, $J = 6.8$ Hz, 3H; CH_3CHCH$_2$), 0.91/0.89/0.88 (3s, 27H; SiC$(CH_3)_3$), 0.092/0.089/0.082/0.05/0.026/0.023 (6s, 18H; Si$(CH_3)_2$); ^{13}C NMR (150.9 MHz): $\delta = 218.5$, 77.9, 73.7, 61.1, 60.7, 53.8, 45.6, 38.1, 35.0, 33.7, 26.2, 26.1, 25.9, 24.8, 22.6, 18.9, 18.5, 18.3, 15.6, −3.63, −3.72, −3.93, −5.28; MS: 619 $[M+H]^+$, 641 $[M+Na]^+$.

Synthesis of compounds 19 and 20: Dess–Martin reagent (581 mg, 1.37 mmol) was added to a solution of alcohol **18c** (410 mg, 0.66 mmol) in CH_2Cl_2 (10 mL) at room temperature and the mixture was stirred for 2 h. The reaction was diluted with Et_2O (20 mL) and quenched with a saturated aqueous $NaHCO_3$ (5 mL) and a 10% aqueous solution of $Na_2S_2O_5$ (5 mL), stirred for 10 min and then extracted with Et_2O. The combined Et_2O layer was washed with brine and dried over anhydrous $MgSO_4$. Solvents were evaporated under vacuum and the residue was passed through a small bed of silica gel (hexanes/EtOAc 10:1) to afford the corresponding aldehyde (390 mg, 95%), which was used in the next step to synthesize compounds **19** and **20** immediately.

Compound 19: $(EtO)_2P(O)CH_2CO_2Et$ (0.2 mL, 1.0 mmol) was added dropwise to a mixture of NaH (40 mg, 1.0 mmol) in dry THF (2.0 mL) at 0 °C. After 10 min, a solution of the above-mentioned aldehyde (89 mg, 0.14 mmol) in THF (0.5 mL) was added and the reaction mixture was stirred at the same temperature for 0.5 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl, diluted with water and extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. The resultant residue was purified by column chromatography over silica gel (hexanes/EtOAc 15:1) to afford pure ester **19** (93 mg, 94%). ^{1}H NMR (600 MHz): $\delta = 6.88$ (ddd, $J = 15.2$, 8.5, 6.4 Hz, 1H; CH=CHCO$_2$), 5.80 (d, $J = 15.2$ Hz, 1H; CH=CHCO$_2$), 4.17 (q, $J = 7.1$ Hz, 2H; CO$_2$CH_2CH$_3$), 3.89 (dd, $J = 7.5$, 2.7 Hz, 1H; CH_2CHOTBS), 3.81 (dd, $J = 7.5$, 2.0 Hz, 1H; CHCHOTBS), 3.67 (m, 1H; TBSOCH_2), 3.57 (m, 1H; TBSOCH_2), 3.13 (m, 1H; CHCO), 2.35 (m, 1H; CH_2CH=CH), 2.01 (dt, $J = 14.5$, 9.7 Hz, 1H; CH_2CH=CH), 1.70–1.40 (m, 3H; CH_2, CH), 1.27 (t, $J = 7.1$ Hz, 3H; CO$_2$CH$_2$CH_3), 1.21 (s, 3H; $(CH_3)_2$C), 1.06 (d, $J = 6.8$ Hz, 3H; CH_3CHCO), 1.03 (s, 3H; $(CH_3)_2$C), 0.92 (d, $J = 6.9$ Hz, 3H; CH_3CHCH$_2$), 0.91/0.89/0.87 (3s, 27H; SiC$(CH_3)_3$), 0.09 (s, 3H; Si$(CH_3)_2$), 0.07/0.02 (2s, 12H; Si$(CH_3)_2$), 0.06 (s, 3H; Si$(CH_3)_2$); ^{13}C NMR (150.9 MHz): $\delta = 218.0$, 166.5, 148.4, 122.6, 77.6, 73.9, 60.9, 60.2, 53.7, 45.8, 38.1, 37.5, 33.7, 31.6, 26.2, 26.1, 25.9,

24.4, 22.6, 19.4, 18.6, 18.3, 15.5, 14.2, 14.1, −3.5, −3.6, −3.7, −4.0, −5.3; MS: 709 $[M+Na]^+$.

Compound 20: A solution of the aldehyde (37 mg, 0.063 mmol), obtained from the oxidation of alcohol **18c**, and $MeC(O)CHPPh_3$ (20 mg, 0.063 mmol) in dry benzene (1 mL), was refluxed for 4 h. Solvents were removed under vacuum and the residue was purified over silica gel (hexanes/EtOAc 15:1) to afford ketone **20** (38 mg, 93%). ^{1}H NMR (500 MHz): $\delta = 6.71$ (ddd, $J = 15.8$, 8.5, 6.6 Hz, 1H; C*H*=CHCO), 6.06 (d, $J = 15.8$ Hz, 1H; CH=C*H*CO), 3.89 (dd, $J = 7.8$, 2.9 Hz, 1H; $CH_2CHOTBS$), 3.82 (dd, $J = 7.4$, 1.9 Hz, 1H; CHC*H*OTBS), 3.65 (td, $J = 9.9$, 4.8 Hz, 1H; $TBSOCH_2$), 3.57 (dt, $J = 9.9$, 7.7 Hz, 1H; $TBSOCH_2$), 3.13 (m, 1H; CHCO), 2.37 (m, 1H; CH_2CH=CH), 2.22 (s, 3H; CH_3CO), 2.03 (m, 1H; CH_2CH=CH), 1.64–1.45 (m, 3H; CH_2, CH), 1.21 (s, 3H; $(CH_3)_2C$), 1.06 (d, $J = 6.6$ Hz, 3H; CH_3CHCO), 1.01 (s, 3H; $(CH_3)_2C$), 0.94 (d, $J = 6.3$ Hz, 3H; CH_3CHCH_2), 0.91 (s, 9H; $SiC(CH_3)_3$), 0.89 (s, 9H; $SiC(CH_3)_3$), 0.87 (s, 9H; $SiC(CH_3)_3$), 0.083/0.075/0.072/0.051/0.02/0.018 (6s, 18H; $Si(CH_3)_2$); ^{13}C NMR (125.75 MHz): $\delta = 217.9$, 198.3, 147.4, 132.5, 77.6, 73.9, 60.9, 53.7, 45.8, 38.1, 37.7, 34.0, 27.0, 26.2, 26.1, 25.9, 24.3, 19.6, 18.5, 18.3, 15.5, −3.5, −3.6, −3.7, −4.0, −5.2, −5.3; MS: 657 $[M+H]^+$, 679 $[M+Na]^+$, 691 $[M+Cl]^-$.

Compound 21: A mixture of **19** (411 mg, 0.6 mmol) and Rh/Al_2O_3 (10% *w*/*w*, 80 mg) in THF (10 mL) was stirred under H_2 atmosphere (using balloon) for 16 h. The reaction mixture was filtered over Celite to afford pure **21** (400 mg, 97%). ^{1}H NMR (400 MHz): $\delta = 4.10$ (q, $J = 7.6$ Hz, 2H; $CO_2CH_2CH_3$), 3.88 (dd, $J = 7.6$, 2.8 Hz, 1H; $CH_2CHOTBS$), 3.76 (dd, $J = 7.2$, 2.2 Hz, 1H; CHC*H*OTBS), 3.65 (td, $J = 9.8$, 5.1 Hz, 1H; $TBSOCH_2$), 3.56 (dt, $J = 9.8$, 7.5 Hz, 1H; $TBSOCH_2$), 3.10 (m, 1H; CHCO), 2.26 (m, 2H; CH_2CO), 1.69 (m, 1H), 1.68–1.39 (m, 5H), 1.24 (t, $J = 7.2$ Hz, 3H; $CO_2CH_2CH_3$), 1.21 (m, 1H), 1.21 (s, 3H; $(CH_3)_2C$), 1.03 (d, $J = 6.8$ Hz, 3H; CH_3CHCO), 1.01 (s, 3H; $(CH_3)_2C$), 0.92 (d, $J = 6.8$ Hz, 3H; CH_3CHCH_2), 0.88 (s, 18H; $SiC(CH_3)_3$), 0.86 (s, 9H; $SiC(CH_3)_3$), 0.07 (s, 3H; $Si(CH_3)_2$), 0.05 (s, 3H; $Si(CH_3)_2$), 0.04/0.01 (2s, 12H; $Si(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 218.2$, 173.6, 77.6, 73.8, 61.0, 60.2, 53.7, 45.2, 38.5, 38.1, 34.9, 30.3, 26.2, 26.1, 25.9, 24.5, 23.2, 19.2, 18.5, 18.3, 17.6, 15.3, 14.2, −3.6, −3.7, −3.8, −4.0, −5.3; MS: 711 $[M+Na]^+$.

Compound 22: In a similar manner as above, a mixture of **20** (35.0 mg, 0.053 mmol), Rh/Al_2O_3 (10% *w*/*w*, 20 mg) in THF (2 mL) was stirred under H_2 atmosphere (using balloon) for 1 h and filtered over Celite to afford pure **22** (33 mg, 95%). ^{1}H NMR (500 MHz): $\delta = 3.88$ (dd, $J = 7.7$, 2.6 Hz, 1H; $CH_2CHOTBS$), 3.76 (dd, $J = 7.0$, 2.2 Hz, 1H; CHC*H*OTBS), 3.65 (td, $J = 9.5$, 4.8 Hz, 1H; $TBSOCH_2$), 3.56 (dt, $J = 9.5$, 8.1 Hz, 1H; $TBSOCH_2$), 3.11 (m, 1H; CHCO), 2.39 (t, $J = 6.6$ Hz, 2H; CH_2CO), 2.11 (s, 3H; CH_3CO), 1.67–1.58 (m, 1H), 1.57–1.50 (m, 1H), 1.49–1.42 (m, 1H), 1.40–1.31 (m, 3H), 1.21 (s, 3H; $(CH_3)_2C$), 1.08 (m, 1H), 1.02 (d, $J = 7.0$ Hz, 3H; CH_3CHCO), 1.01 (s, 3H; $(CH_3)_2C$), 0.91 (d, $J = 6.6$ Hz, 3H; CH_3CHCH_2), 0.88 (s, 18H; $SiC(CH_3)_3$), 0.85 (s, 9H; $SiC(CH_3)_3$), 0.09 (s, 3H; $Si(CH_3)_2$), 0.06 (s, 6H; $Si(CH_3)_2$), 0.04 (s, 3H; $Si(CH_3)_2$), 0.01 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (125.75 MHz): $\delta = 218.2$, 208.8, 77.7, 73.9, 61.0, 53.7, 45.2, 44.2, 38.7, 38.1, 30.9, 30.4, 29.9, 26.2, 26.1, 25.9, 26.0, 24.5, 22.0, 19.2, 18.5, 18.3, 17.6, 15.3, 1.0, −3.6, −3.7, −3.9, −5.2, −5.3; MS: 659 $[M+H]^+$, 681 $[M+Na]^+$, 693 $[M+Cl]^+$.

Alkene 23: Compound **21** (400 mg, 0.58 mmol) was reduced with DIBAL-H (1M in toluene, 1.7 mL, 1.7 mmol) at −78 °C (for details, see preparation of **18c**) to afford the corresponding alcohol (355 mg, 95%) after purification over silica gel (hexanes/EtOAc 7:1). ^{1}H NMR (600 MHz): $\delta = 3.88$ (dd, $J = 7.6$, 2.6 Hz, 1H; $CH_2CHOTBS$), 3.77 (dd, $J = 6.9$, 2.0 Hz, 1H; CHC*H*OTBS), 3.67 (td, $J = 9.7$, 4.8 Hz, 1H; $TBSOCH_2$), 3.63 (t, $J = 6.6$ Hz, 2H; CH_2OH), 3.58 (dt, $J = 9.7$, 7.8 Hz, 1H; $TBSOCH_2$), 3.13 (m, 1H; CHCO), 1.75–1.15 (m, 9H), 1.22 (s, 3H; $(CH_3)_2C$), 1.04 (d, $J = 6.8$ Hz, 3H; CH_3CHCO), 1.02 (s, 3H; $(CH_3)_2C$), 0.91 (d, $J = 7.0$ Hz, 3H; CH_3CHCH_2), 0.90 (s, 9H; $SiC(CH_3)_3$), 0.89 (s, 9H; $SiC(CH_3)_3$), 0.87 (s, 9H; $SiC(CH_3)_3$), 0.08/0.06 (2s, 6H; $Si(CH_3)_2$), 0.05/0.02 (2s, 12H; $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz): $\delta = 218.3$, 77.4, 73.9, 62.9, 61.0, 53.7, 45.0, 38.9, 38.1, 33.3, 31.6, 30.7, 26.2, 26.1, 25.9, 24.5, 23.9, 22.6, 19.3, 18.5, 18.3, 17.5, 15.3, 14.1, −3.68, −3.71, −3.79, −3.99, −5.26, −5.29; MS: 779 $[M+Cs]^+$.

The above-mentioned alcohol (355 mg, 0.55 mmol) was oxidized with Dess–Martin reagent (466 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) at room temperature (for details, see oxidation of **18c** in the preparation of **19**). The corresponding aldehyde (350 mg, 99%) was obtained after purification over silica gel (hexanes/EtOAc 10:1) and was taken to the next step immediately.

BuLi (1.6M in hexane, 1.5 mL, 2.4 mmol) was added to a heterogeneous solution of $MePPh_3I$ (1.01 g, 2.5 mmol) in dry THF (15 mL) at 0 °C. After stirring for 0.5 h, a solution of the above-mentioned aldehyde (350 mg, 0.54 mmol) in dry THF (5 mL) was added to the reaction mixture. After stirring for an additional 0.5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and solvents were removed. The resulting residue was purified over silica gel (hexanes/EtOAc 9:1) to afford the known olefin **23** (310 mg, 89%). Physical and spectral data of compound **23** were identical to the reported data.[12c]

Alkene 24: *n*BuLi (1.6M in hexane, 54 μL, 86 μmol) was added to a heterogeneous solution of $MePPh_3I$ (38 mg, 0.091 mmol) in dry THF (0.1 mL) at 0 °C. After stirring for 0.5 h, a solution of ketone **22** (30 mg, 46 μmol) in dry THF (0.1 mL) was added to the reaction mixture. After stirring for an additional 20 min at room temperature, the reaction mixture was worked up as above (see synthesis of **23**) to afford known olefin **24** (28 mg, 92%) after purification over silica gel (hexanes/EtOAc 15:1). Physical and spectral data of compound **24** were identical to the reported data.[12d]

Conversion of compounds 23 and 24 to acids 25 and 26: For selective deprotection and subsequent oxidation of compounds **23** and **24** to acids **25** and **26**, see references [12c] and [12d]; physical and spectral data of the produced compounds were identical to the values reported in latter references.

Compounds 10a and 11a: TBSCl (402 mg, 2.66 mmol) was added to a solution of compound **10** (300 mg, 1.33 mmol) and imidazole (271 mg, 3.99 mmol) in dry DMF (1 mL) and stirred at room temperature for 8 h. The reaction mixture was diluted with Et_2O and water. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined ether layer was washed with brine and dried over anhydrous $MgSO_4$. Solvents were removed under vacuum and the residue was purified over silica gel (hexanes/EtOAc 10:1) to afford pure silyl ether **10a** (400 mg, 89%). $[\alpha]_D = -33.7°$ ($c = 1.18$, $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 6.90$ (s, 1H; ArH), 6.50 (s, 1H; ArCH=C), 4.62 (dd, $J = 9.0$, 3.6 Hz, 1H; CHOTBS), 2.79 (dd, $J = 14.8$, 9.2 Hz, 1H; CH_2CO), 2.68 (s, 3H; $ArCH_3$), 2.42 (dd, $J = 14.8$, 3.6 Hz, 1H; CH_2CO), 2.16 (s, 3H; $COCH_3$), 2.00 (s, 3H; CH_3C=CH), 0.84 (s, 9H; $SiC(CH_3)_3$), 0.03 (s, 3H; $Si(CH_3)_2$), −0.01 (s, 3H; $Si(CH_3)_2$); ^{13}C NMR (125.75 MHz): $\delta = 207.3$, 164.5, 152.8, 141.1, 119.0, 115.6, 75.2, 50.4, 31.8, 25.7, 25.6, 19.2, 18.0, 14.0, −4.7, −5.4; MS: 340 $[M+H]^+$, 362 $[M+Na]^+$.

In a similar manner, compound **11** (500 mg, 2.07 mmol) was treated with TBSCl (773 mg, 4.97 mmol) and imidazole (862 mg, 12.42 mmol) in dry DMF (2 mL) at room temperature for 8 h to afford **11a** (874 mg, 90%) after purification over silica gel (hexanes/EtOAc 20:1). $[\alpha]_D = -26.5°$ ($c = 1.70$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 7.00$ (s, 1H; ArH), 6.50 (s, 1H; ArCH=C), 4.93 (s, 2H; CH_2OTBS), 4.63 (dd, $J = 9.0$, 3.1 Hz, 1H; CHOTBS), 2.80 (dd, $J = 14.6$, 9.0 Hz, 1H; CH_2CO), 2.43 (dd, $J = 14.6$, 3.6 Hz, 1H; CH_2CO), 2.16 (s, 3H; $COCH_3$), 2.00 (d, $J = 1.2$ Hz, 3H; CH_3C=CH), 0.93 (s, 9H; $SiC(CH_3)_3$), 0.84 (s, 9H; $Si(CH_3)_2$), 0.11 (s, 6H; $Si(CH_3)_2$), 0.03 (s, 3H; $Si(CH_3)_2$), −0.01 (s, 3H; $Si(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 207.3$, 172.0, 153.1, 141.1, 119.1, 115.8, 75.2, 63.2, 50.4, 31.8, 25.7, 18.2, 18.1, 14.0, −4.7, −5.3, −5.5; MS: 470 $[M+H]^+$.

Keto alcohol 27: TMSOTf (1.07 mL, 5.9 mmol) was added to a solution of compound **10a** (1.0 g, 2.95 mmol) and lutidine (1.37 mL, 11.8 mmol) in dry CH_2Cl_2 (15 mL) at −78 °C. The reaction mixture was stirred at −78 to 0 °C for 4 h and then diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated to give the corresponding silyl enol ether derivative (1.1 g), which was taken to the next step without purification.

OsO_4 (0.2M in toluene, 0.5 mL, 0.1 mmol) and NMO (50% aqueous, 1.57 mL, 7.6 mmol) was added sequentially to a solution of the above-mentioned silyl enol ether (1.1 g) in CH_2Cl_2 (15 mL) and the mixture was stirred at room temperature for 5 h. After the reaction was complete, as judged by TLC, a solution of $Na_2S_2O_5$ (10% aqueous, 10 mL) was added and stirred for 10 min, and then extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$.

0947-6539/01/0708-1698 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 8

Solvents were removed under vacuum and the resultant residue was purified by column chromatography (silica gel, hexanes/EtOAc 4:1) to afford pure keto alcohol **27** (684 mg, 68 % from **10a**). Physical data of **27**: $[\alpha]_D = -52.8^\circ$ ($c = 1.52$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 6.92$ (s, 1H; ArH), 6.52 (s, 1H; ArCH=C), 4.64 (dd, $J = 9.3$, 3.4 Hz, 1H; CHOTBS), 4.25 (AB qd, $\Delta\tilde{\nu} = 12.9$ Hz, $J = 19.2$ Hz, 2H; CH_2OH), 3.14 (t, $J = 4.8$ Hz, 1H; OH), 2.78 (dd, $J = 13.8$, 9.3 Hz, 1H; CH_2CO), 2.69 (s, 3H; $ArCH_3$), 2.43 (dd, $J = 13.8$, 3.3 Hz, 1H; CH_2CO), 2.03 (s, 3H; CH_3C=CH), 0.84 (s, 9H; $SiC(CH_3)_3$), 0.01 (s, 3H; $Si(CH_3)_2$), −0.01 (s, 3H; $Si(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 208.4$, 164.7, 152.6, 140.4, 119.4, 116.0, 75.4, 70.0, 45.6, 25.7, 19.3, 18.0, 14.0, −4.8, −5.5; MS: 356 $[M+H]^+$, 378 $[M+Na]^+$.

Keto alcohol 28: In a similar manner as above, compound **11a** (795 mg, 1.7 mmol) was treated with TMSOTf (0.62 mL, 3.4 mmol) and lutidine (0.79 mL, 6.8 mmol) in dry CH_2Cl_2 (10 mL) at −78 to 0 °C for 4 h to afford the corresponding crude enol ether (1.0 g). The product was then treated with OsO_4 (0.2 M in toluene, 0.37 mL, 0.074 mmol) and NMO (50 % aqueous, 0.92 mL, 4.4 mmol) in CH_2Cl_2 (10 mL) at room temperature for 5 h to afford pure compound **28** (691 mg, 84 % from **11a**) after purification over silica gel (hexanes/EtOAc 6:1).

Physical data of 28: $[\alpha]_D = -45.3^\circ$ ($c = 0.8$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 7.01$ (s, 1H; ArH), 6.50 (s, 1H; ArCH=C), 4.93 (s, 2H; CH_2OTBS), 4.63 (dd, $J = 9.4$, 3.0 Hz, 1H; CHOTBS), 4.24 (ABq, $\Delta\nu = 11.0$, $J = 19.4$ Hz, 2H; CH_2OH), 3.22 (br s, 1H; OH), 2.75 (dd, $J = 14.1$, 9.4 Hz, 1H; CH_2CO), 2.42 (dd, J = 14.1, 3.2 Hz, 1H; CH_2CO), 2.01 (s, 3H; CH_3C=CH), 0.92/0.83 (2s, 18H; $SiC(CH_3)_3$), 0.11 (s, 6H; $Si(CH_3)_2$), 0.00 (s, 3H; $Si(CH_3)_2$), −0.03 (s, 3H; $Si(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 208.4$, 172.1, 152.8, 140.3, 119.4, 116.1, 75.3, 69.9, 63.1, 45.5, 25.7, 18.2, 18.0, 13.9, −4.8, −5.5; MS: 508 $[M+Na]^+$, 524 $[M+K]^+$, 520 $[M+Cl]^-$.

Aldehyde 29a: $NaBH_4$ (120 mg, 3.16 mmol) was added to a solution of **27** (561 mg, 1.58 mmol) in methanol (10 mL) at 0 °C. After the mixture was stirred for 0.5 h, acetone (5 mL) was added and stirring was continued for an additional 5 min. Saturated aqueous NH_4Cl (1 mL) and ethyl acetate (10 mL) were added sequentially. The mixture was filtered through Celite and the filtrate was passed through a small silica gel column to afford the corresponding diol (511 mg, 91 %), which contained two diastereomers (2.5:1, by ^{1}H NMR analysis). ^{1}H NMR (400 MHz): $\delta = 6.88/6.86$ (2s, together 1H; ArH), 6.51/6.45 (2s, together 1H; ArCH=C), 4.40 (m, 1H; CHOTBS), 3.86/3.77 (2m, together 1H; C*H*OH), 3.82/3.53 (2d, $J = 2.4$, 2.6 Hz, together 1H), 3.53 (m, 1H), 3.43 (m, 1H), 3.36/3.25 (2m, together 1H), 2.65 (s, 3H; $ArCH_3$), 1.95/1.93 (2d, $J = 0.9$, 1.2 Hz, together 3H; CH_3C=CH), 1.84–1.54 (m, 2H; CH_2CHOH), 0.86/0.85 (2s, together 9H; $SiC(CH_3)_3$), 0.064/0.056 (2s, together 3H; $Si(CH_3)_2$), −0.002, −0.02 (2s, together 3H; $Si(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 164.6$, 152.8, 152.4, 141.5, 119.4, 118.4, 115.3, 115.2, 78.1, 75.4, 70.5, 68.8, 66.8, 66.5, 38.9, 38.7, 25.7, 19.1, 19.0, 18.1, 17.9, 14.7, 13.5, −4.6, −4.8, −5.2, −5.3; MS: 380 $[M+Na]^+$, 356 $[M-H]^-$.

Lead(IV) acetate (500 mg, 1.13 mmol) was added to a solution of the above mentioned diol (190 mg, 0.53 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After the reaction mixture was stirred for 0.5 h at this temperature, it was quenched by addition of silica gel. The heterogeneous mixture was then loaded over a silica gel column and eluted with hexane/EtOAc 4:1 to afford the known aldehyde **29a** (170 mg, 99 %). Physical and spectral data of **29a** were identical to the reported data (see refs. [10d] and [12c]).

Aldehyde 30a: In a similar manner as above, compound **28** (667 mg, 1.38 mmol) was treated with $NaBH_4$ (120 mg, 3.16 mmol) in methanol (10 mL) to provide the corresponding diol (620 mg, 92 %) after purification, which contained two diastereomers (2.5:1 by ^{1}H NMR analysis). ^{1}H NMR (400 MHz): $\delta = 7.00/6.98$ (2s, together 1H; ArH), 6.52/6.46 (2s, together 1H; ArCH=C), 4.92 (s, 2H; CH_2OTBS), 4.40 (m, 1H; CHOTBS), 3.80 (m, 1H), 3.73 (br s, 1H), 3.47 (m, 2H), 3.05 (br s, 1H; OH), 1.96/1.95 (2s, together 3H; CH_3C=CH), 1.80/1.61 (2m, together 2H; CH_2CHOH), 0.92 (s, 9H; $SiC(CH_3)_3$), 0.88/0.87 (2s, together 9H; $SiC(CH_3)_3$), 0.12 (s, 6H; $Si(CH_3)_2$), 0.08/0.07 (2s, together 3H; $Si(CH_3)_2$), 0.01/0.00 (2s, together 3H; $Si(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 172.1$, 171.9, 153.1, 152.7, 141.3, 119.5, 118.6, 115.6, 115.4, 78.3, 75.5, 70.8, 68.9, 66.8, 66.6, 63.1, 63.0, 38.9, 38.5, 25.8, 25.7, 18.2, 18.1, 17.9, 14.8/14.1, 13.6, −4.5, −4.8, −5.2, −5.3, −5.5, −5.6; MS 488 $[M+H]^+$, 510 $[M+Na]^+$, 486 $[M-H]^-$.

The above-mentioned diol (620 mg, 1.27 mmol) was treated with $Pb(OAc)_4$ (1.27 g, 2.72 mmol) in CH_2Cl_2 (10 mL) at 0 °C to afford compound **30a** (550 mg, 95 %) after purification over silica gel (hexanes/EtOAc 10:1). $[\alpha]_D = -0.36^\circ$ ($c = 1.11$, $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 9.77$ (t, $J = 2.6$ Hz, 1H; CHO), 7.03 (s, 1H; ArH), 6.54 (s, 1H; ArCH=C), 4.94 (s, 2H; CH_2OTBS), 4.67 (dd, $J = 8.4$, 4.1 Hz, 1H; CHOTBS), 2.72 (ddd, $J = 15.8$, 8.4, 2.9 Hz, 1H; CH_2CHO), 2.50 (ddd, $J = 15.4$, 4.1, 2.2 Hz, 1H; CH_2CHO), 2.03 (d, $J = 1.1$ Hz, 3H; CH_3C=CH), 0.94 (s, 9H; $SiC(CH_3)_3$), 0.87 (s, 9H; $SiC(CH_3)_3$), 0.12 (s, 6H; $Si(CH_3)_2$), 0.07/0.02 (2s, 6H; $Si(CH_3)_2$); ^{13}C NMR (125.75 MHz): $\delta = 201.4$, 172.1, 152.9, 140.4, 119.4, 116.0, 73.9, 63.2, 50.1, 25.7, 14.1, −4.6, −5.2, −5.5; MS: 456 $[M+H]^+$.

Compound 29b: *n*BuLi (1.6 M in hexane, 0.6 mL, 0.96 mmol) was added to a heterogeneous solution of $MePPh_3I$ (404 mg, 1 mmol) in dry THF (5 mL) at 0 °C. After stirring for 0.5 h, a solution of aldehyde **29a** (170 mg, 0.52 mmol) in dry THF (2 mL) was added to the reaction mixture. After the reaction mixture was stirred for an additional 0.5 h, it was quenched with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Solvents were removed under vacuum and the resultant residue was purified over silica gel (hexanes/EtOAc 9:1) to afford olefin **29b** (152 mg, 90 %). The physical and spectral data of compound **29b** were identical to the reported data (see refs. [10d] and [12c]).

Compound 30b: In a similar manner as above, compound **30a** (330 mg, 0.73 mmol) was treated with the Wittig reagent, prepared from $MePPh_3I$ (590 mg, 1.46 mmol) and *n*BuLi (1.6 M in hexane, 0.87 mL, 1.39 mmol) in dry THF (5 mL), at 0 °C to afford compound **30b** (300 mg, 91 %) after purification over silica gel (hexanes/EtOAc 15:1). $[\alpha]_D = -19.5^\circ$ ($c = 1.08$, $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 7.01$ (s, 1H; ArH), 6.44 (s, 1H; ArCH=C), 5.77 (m, 1H; C*H*=CH_2), 5.00 (m, 2H; CH=CH_2), 4.95 (s, 2H; CH_2OTBS), 4.14 (t, $J = 6.3$ Hz, 1H; CHOTBS), 2.30 (m, 2H; CH_2CH=CH_2), 1.99 (s, 3H; CH_3C=CH), 0.95/0.88 (2s, 18H; $SiC(CH_3)_3$), 0.12 (s, 6H; $Si(CH_3)_2$), 0.05/0.00 (2s, 6H; $Si(CH_3)_2$); ^{13}C NMR (125.75 MHz): $\delta = 172.3$, 153.8, 142.4, 135.8, 119.3, 117.0, 115.7, 78.8, 63.7, 41.8, 26.2, 18.7, 14.4, 1.5, −4.2, −4.5, −5.0; MS: 454 $[M+H]^+$.

Deprotection of 29b[35] **and 30b**: TBAF (1 M in THF, 2.5 mL, 2.5 mmol) was added to a solution of olefin **30b** (290 mg, 0.64 mmol) in dry THF (3.0 mL) at 0 °C. After the reaction mixture was stirred for 1 h at this temperature, it was worked-up with ether and water. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. Solvents were removed under vacuum and the residue was purified over silica gel (hexanes/EtOAc 1:1) to afford the corresponding diol (138 mg, 96 %). $[\alpha]_D = -8.6^\circ$ ($c = 1.49$, $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 7.05$ (s, 1H; ArH), 6.52 (s, 1H; ArCH=C), 5.80 (m, 1H; C*H*=CH_2), 5.11 (m, 2H; CH=CH_2), 4.89 (s, 2H; CH_2OH), 4.18 (dd, $J = 7.4$, 5.3 Hz, 1H; CHOH), 2.52 (br s, 1H; OH), 2.45–2.31 (m, 2H; CH_2CH=CH_2), 1.99 (s, 3H; CH_3C=CH); ^{13}C NMR (150.9 MHz): $\delta = 170.0$, 152.9, 142.1, 134.4, 118.7, 118.0, 116.1, 76.3, 61.9, 39.9, 14.4; MS: 226 $[M+H]^+$.

TBSCl (115 mg, 0.74 mmol) was added to a solution of the above-mentioned diol (138 mg, 0.61 mmol) and *i*Pr_2EtN (0.22 mL, 1.23 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C and the reaction mixture was stirred at 0 °C to room temperature for 8 h. Work-up (CH_2Cl_2 and water) and purification over silica gel (hexanes/EtOAc 3:1) afforded pure **30** (180 mg, 83 %). $[\alpha]_D = -13.4^\circ$ ($c = 0.37$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 7.01$ (s, 1H; ArH), 6.52 (s, 1H; ArCH=C), 5.81 (m, 1H; C*H*=CH_2), 5.11 (m, 2H; CH=CH_2), 4.93 (s, 2H; CH_2OTBS), 4.18 (t, $J = 6.7$ Hz, 1H; C*H*OH), 2.40 (m, 3H; CH_2CH=CH_2, OH), 2.00 (s, 3H; CH_3C=CH), 0.93 (s, 9H; $SiC(CH_3)_3$), 0.11 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 172.1$, 153.0, 141.4, 134.6, 119.0, 117.8, 115.6, 76.4, 63.2, 40.0, 25.7, 18.2, −5.5; MS: 340 $[M+H]^+$, 362 $[M+Na]^+$.

Esterification of acids 25 and 26 with alcohols 29 and 30 to esters 31–34[36]

Compound 33: EDC (38 mg, 0.2 mmol) was added to a solution of alcohol **30** (64 mg, 0.19 mmol), acid **25** (85 mg, 0.16 mmol) and DMAP (2 mg, 0.016 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C to room temperature and the crude mixture was chromatographed over a column of silica gel (hexanes/EtOAc 10:1) to afford pure ester **33** (99 mg, 72 % based on acid **25**) and recovered alcohol **30** (9 mg).

Physical data of 33: $[\alpha]_D = -31.2^\circ$ ($c = 2.50$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 7.04$ (s, 1H; ArH), 6.47 (s, 1H; ArCH=C), 5.74 (m, 2H; 2 × C*H*=CH_2), 5.28 (t, $J = 6.7$ Hz, 1H; CO_2CHCH_2), 5.08 (d, $J = 17.1$ Hz, 1H; CH=CH_2), 5.02 (d, $J = 10.2$ Hz, 1H; CH=CH_2), 4.97 (d, $J = 17.2$ Hz, 1H; CH=CH_2), 4.94 (s, 2H; CH_2OTBS), 4.92 (d, $J = 10.3$ Hz, 1H; CH=CH_2), 4.33 (dd, $J = 6.0$, 3.6 Hz, 1H; TBSOC*H*CH_2), 3.72 (dd, $J = 7.0$, 2.2 Hz, 1H; TBSOC*H*CH), 3.14 (pentet, $J = 6.8$ Hz, 1H; CHCO), 2.48 (m, 3H), 2.27

(dd, $J = 17.0$, 6.1 Hz, 1H), 2.05 (s, 3H; CH_3C=CH), 1.98 (m, 2H), 1.50–1.10 (m, 5H), 1.22 (s, 3H; $(CH_3)_2C$), 1.02 (s, 3H; $(CH_3)_2C$), 1.02 (d, $J = 6.8$ Hz, 3H; CH_3CHCO), 0.94 (s, 9H; $SiC(CH_3)_3$), 0.88 (s, 9H; $SiC(CH_3)_3$), 0.88 (d, $J = 6.8$ Hz, 3H; CH_2CHCH_3), 0.86 (s, 9H; $SiC(CH_3)_3$), 0.11 (s, 6H; $Si(CH_3)_2$), 0.09 (s, 3H; $Si(CH_3)_2$), 0.04 (s, 3H; $Si(CH_3)_2$), 0.02 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 217.7$, 172.0, 171.1, 152.8, 138.9, 136.7, 133.4, 121.2, 117.8, 116.5, 114.4, 78.7, 77.6, 74.0, 63.2, 53.3, 45.2, 40.3, 38.8, 37.5, 34.3, 30.4, 27.0, 26.2, 26.0, 25.8, 23.2, 20.3, 18.5, 18.2, 17.6, 15.4, 14.5, −3.7, −3.8, −4.3, −4.7, −5.5; HRMS: calcd for $C_{46}H_{85}NO_6SSi_3Cs$: 996.4460; found: 996.4494 $[M+Cs]^+$.

Compound 34: In a similar manner as above, alcohol **30** (90 mg, 0.27 mmol) was treated with acid **26** (177 mg, 0.32 mmol), EDC (156 mg, 0.80 mmol) and DMAP (3.3 mg, 0.027 mmol) to afford pure ester **34** (225 mg, 97%). $[\alpha]_D = -31.7^\circ$ ($c = 1.17$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 7.04$ (s, 1H; ArH), 6.47 (s, 1H; ArCH=C), 5.70 (m, 1H; CH=CH_2), 5.28 (t, $J = 6.8$ Hz, 1H; CO_2CHCH_2), 5.08 (d, $J = 17.1$ Hz, 1H; CH=CH_2), 5.02 (d, $J = 10.2$ Hz, 1H; CH=CH_2), 4.93 (s, 2H; CH_2OTBS), 4.67 (s, 1H; CH_2=CCH_3), 4.64 (s, 1H, CH_2=CCH_3), 4.33 (m, 1H; $TBSOCHCH_2$), 3.72 (dd, $J = 10.1$, 3.1 Hz, 1H; $TBSOCHCH$), 3.14 (pentet, $J = 10.1$ Hz, 1H; CHCO), 2.54–2.43 (m, 3H), 2.27 (dd, $J = 17.0$, 6.1 Hz, 1H), 2.05 (d, $J = 1.8$ Hz, 3H; CH_3C=CH), 1.96 (m, 1H), 1.68 (s, 3H; CH_3C=CH_2), 1.53–1.44 (m, 1H), 1.40–1.28 (m, 2H), 1.27–1.19 (m, 2H), 1.22 (s, 3H; $(CH_3)_2C$), 1.03 (d, J = 6.8 Hz, 3H; CH_3CHCO), 1.02 (s, 3H; $(CH_3)_2C$), 0.94 (s, 9H; $SiC(CH_3)_3$), 0.89 (s, 9H; $SiC(CH_3)_3$), 0.88 (d, $J = 6.8$ Hz, 3H; CH_2CHCH_3), 0.86 (s, 9H; $SiC(CH_3)_3$), 0.11 (s, 6H; $Si(CH_3)_2$), 0.09 (s, 3H; $Si(CH_3)_2$), 0.03 (s, 3H; $Si(CH_3)_2$), 0.02 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (100.6 MHz): $\delta = 217.7$, 172.0, 171.1, 152.7, 145.9, 136.7, 133.4, 121.2, 117.7, 116.5, 109.8, 78.6, 77.6, 74.0, 63.2, 53.3, 45.2, 40.3, 38.7, 38.3, 37.5, 31.5, 30.5, 26.2, 25.9, 25.7, 25.6, 23.1, 20.3, 18.5, 18.2, 18.1, 17.6, 15.4, 14.5, −3.7, −3.8, −4.3, −4.8, −5.5; MS: 878 $[M+H]^+$.

Conversion of esters 31–34 to desoxyepothilones and epothilones[37]

Epothilone B (2) and D (4): Grubbs' catalyst **VII** (3.4 mg, 0.004 mmol) was added to a solution of **32** (15 mg, 0.02 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred at reflux for 8 h. Solvents were evaporated and the residue was purified over silica gel (hexanes/EtOAc 20:1) to afford an inseparable mixture (1.1:1, by ^{1}H NMR analysis) of stereoisomeric alkenes **36** and (*E*)-**36** (11.7 mg, 81%). For the conversion of the above-mentioned mixture to **4** and then to epothilone B (**2**), see references [10d], [11d], and [12d].

Desoxyepothilone E (7) and (*E*)-desoxyepothilone E [(*E*)-7]: Grubbs' catalyst **V** (10 mg, 0.012 mmol) was added to a solution of **33** (50 mg, 0.058 mmol) in degassed CH_2Cl_2 (10 mL) and the solution was stirred at room temperature for 5 h. Solvents were removed under vacuum and the residue was purified by chromatography over silica gel (hexanes/EtOAc 50:1) to afford a (1:1) mixture (41 mg, 85%) of **37** and (*E*)-**37**, which was taken to the next step without separation. A small amount of pure **37** and (*E*)-**37** was purified by preparative TLC (hexanes/EtOAc 20:1) for analysis.

Physical data of 37: ^{1}H NMR (500 MHz): $\delta = 7.06$ (s, 1H; ArH), 6.52 (s, 1H; ArCH=C), 5.52 (td, $J = 11.0$, 3.0 Hz, 1H; CH=CH), 5.37 (m, 1H; CH=CH), 5.00 (d, $J = 10.5$ Hz, 1H; CO_2CHCH_2), 4.95 (s, 2H; CH_2OTBS), 4.02 (d, $J =$ 9.5 Hz, 1H; $TBSOCHCH_2$), 3.88 (d, $J = 9.0$ Hz, 1H; $TBSOCHCH$), 3.00 (m, 1H; CHCO), 2.76 (m, 1H), 2.66 (dd, $J = 16.5$, 10.0 Hz, 1H), 2.35 (m, 1H), 2.10 (s, 3H; CH_3C=CH), 2.06 (dd, $J = 13.5$, 5.5 Hz, 1H), 1.85 (m, 1H), 1.52 (m, 2H), 1.27 (m, 3H), 1.18 (s, 3H; $(CH_3)_2C$), 1.13 (s, 3H; $(CH_3)_2C$), 1.08 (d, $J = 7.0$ Hz, 3H; CH_3CHCO), 0.95 (m, 12H), 0.93 (s, 9H; $SiC(CH_3)_3$), 0.84 (s, 9H; $SiC(CH_3)_3$), 0.12 (s, 6H; $Si(CH_3)_2$), 0.11 (s, 3H; $Si(CH_3)_2$), 0.10 (s, 3H; $Si(CH_3)_2$), 0.09 (s, 3H; $Si(CH_3)_2$), −0.11 (s, 3H; $Si(CH_3)_2$); ^{13}C NMR (127.75 MHz): $\delta = 215.0$, 172.1, 171.3, 152.7, 138.5, 135.0, 122.8, 119.6, 116.3, 79.6, 76.7, 76.4, 63.2, 53.4, 38.9, 37.8, 31.8, 31.3, 29.7, 29.2, 28.4, 26.3, 26.0, 25.7, 24.9, 24.2, 18.7, 18.6, 17.7, 15.1, 14.1, −3.2, −3.4, −3.7, −5.4, −5.8; HRMS: calcd for $C_{44}H_{82}NO_6SSi_3$: 836.5171; found: 836.5141 $[M+H]^+$.

Physical data of compound (*E*)-37: ^{1}H NMR (500 MHz): $\delta = 7.03$ (s, 1H; ArH), 6.53 (s, 1H; ArCH=C), 5.43 (m, 1H; CH=CH), 5.37 (m, 1H; CH=CH), 5.22 (dd, $J = 8.0$, 3.0 Hz, 1H; CO_2CHCH_2), 4.95 (s, 2H; CH_2OTBS), 4.00 (dd, $J = 6.5$, 4.0 Hz, 1H; $TBSOCHCH_2$), 3.91 (d, $J =$ 6.0 Hz, 1H; $TBSOCHCH$), 3.05 (m, 1H; CHCO), 2.76 (m, 1H), 2.64 (dd, $J = 15.5$, 4.0 Hz, 1H), 2.54 (m, 1H), 2.45 (m, 1H), 2.12 (s, 3H; CH_3C=CH), 1.90 (m, 1H), 1.68–1.48 (m, 3H), 1.24 (m, 2H), 1.17 (s, 3H; $(CH_3)_2C$), 1.14 (d, $J = 7.0$ Hz, 3H; CH_3CHCO), 0.94 (m, 12H), 0.89 (s, 9H; $SiC(CH_3)_3$), 0.86 (s, 9H; $SiC(CH_3)_3$), 0.13 (s, 6H; $Si(CH_3)_2$), 0.09 (s, 3H; $Si(CH_3)_2$), 0.07 (s, 3H; $Si(CH_3)_2$), 0.06 (s, 3H; $Si(CH_3)_2$), 0.03 (s, 3H; $Si(CH_3)_2$); ^{13}C NMR (127.75 MHz): $\delta = 216.3$, 172.1, 170.5, 152.8, 137.7, 134.3, 125.6, 119.6, 116.4, 78.7, 76.8, 73.8, 63.2, 53.9, 45.3, 41.3, 39.8, 36.4, 32.4, 30.0, 27.1, 26.4, 26.2, 26.0, 25.7, 23.5, 21.5, 18.5, 18.4, 15.5, 14.5, −3.6, −3.7, −4.0, −4.6, −5.4; HRMS: calcd for $C_{44}H_{82}NO_6SSi_3$: 836.5171; found: 836.5140 $[M+H]^+$.

HF/pyridine (0.5 mL) was added dropwise to a solution of the above-mentioned mixture of **37** and (*E*)-**37** (41 mg, 0.049 mmol) in THF (1 mL) at room temperature. The mixture was stirred at room temperature for 2 h and then slowly poured into a cold saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. Solvents were removed under vacuum and the residue was chromatographed over silica gel (hexanes/EtOAc 1:1) to afford pure **7** (9 mg, 37%) and (*E*)-**7** (10 mg, 41%). For **7**: $[\alpha]_D = -43.7^\circ$ ($c = 0.3$, $CHCl_3$), lit.:[14a] -44.2° ($c = 0.6$, $CHCl_3$); for (*E*)-**7**: $[\alpha]_D = -41.1^\circ$ ($c = 0.29$, $CHCl_3$), lit.:[14a] -31.5° ($c = 0.6$, $CHCl_3$). For the conversion of **7** to epothilone E (**5**), and physical and spectral data of **5** and its precursors see reference [14a,b].

Desoxyepothilone F (8) and (*E*)-desoxyepothilone F [(*E*)-8]: Using the same process as above for the conversion of **32** to **36**, compound **34** (97 mg, 0.11 mmol) was metathesized by using Grubbs' catalyst **VII** (21 mg, 0.024 mmol) in CH_2Cl_2 (30 mL) at reflux for 16 h to afford **38** (40 mg, 43%) and (*E*)-**38** (39 mg, 42%) after purification by preparative TLC (hexanes/EtOAc 49:1).

Physical data of compound 38: $[\alpha]_D = -22.5^\circ$ ($c = 1.14$, $CHCl_3$); ^{1}H NMR (600 MHz): $\delta = 7.05$ (s, 1H; ArH), 6.54 (s, 1H; ArCH=C), 5.15 (t, $J =$ 8.0 Hz, 1H; CH=$C(CH_3)CH_2$), 4.95 (d, $J = 10.1$ Hz, 1H; CO_2CHCH_2), 4.94 (s, 2H; CH_2OTBS), 4.01 (d, $J = 10.0$ Hz, 1H; $TBSOCHCH_2$), 3.88 (d, $J = 9.0$ Hz, 1H; $TBSOCHCH$), 3.01 (m, 1H; CHCO), 2.80–2.62 (m, 3H), 2.44 (m, 1H), 2.09 (s, 3H; CH_3C=CH), 2.04 (m, 1H), 1.72–1.67 (m, 3H), 1.66 (s, 3H; CH=$C(CH_3)CH_2$), 1.60–1.48 (m, 3H), 1.17 (s, 3H; $(CH_3)_2C$), 1.12 (s, 3H; $(CH_3)_2C$), 1.07 (d, $J = 6.9$ Hz, 3H; CH_3CHCO), 0.96 (d, $J =$ 6.9 Hz, 3H; CH_3CHCH_2), 0.94/0.93/0.83 (3s, 27H; $SiC(CH_3)_3$), 0.12 (s, 6H; $Si(CH_3)_2$), 0.095 (s, 3H; $Si(CH_3)_2$), 0.091/0.06/−0.13 (3s, 9H; $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz): $\delta = 215.1$, 172.0, 152.7, 138.7, 119.5, 119.1, 116.1, 79.9, 76.3, 63.2, 53.4, 39.1, 32.4, 31.9, 31.4, 30.9, 29.2, 27.4, 26.4, 26.2, 25.7, 24.6, 24.3, 23.1, 18.7, 18.6, 18.3, 17.8, 15.2, −3.3, −3.7, −5.5, −5.7; MS: 850 $[M+H]^+$, 884 $[M+Cl]^-$.

Physical data of compound (*E*)-38: $[\alpha]_D = -27.7^\circ$ ($c = 0.82$, $CHCl_3$); ^{1}H NMR (600 MHz): $\delta = 7.02$ (s, 1H; ArH), 6.53 (s, 1H; ArCH=C), 5.26 (dd, $J = 8.1$, 2.9 Hz, 1H; CO_2CHCH_2), 5.16 (t, $J = 7.0$ Hz, 1H; CH=$C(CH_3)CH_2$), 4.95 (s, 2H; CH_2OTBS), 4.47 (t, $J = 5.2$ Hz, 1H; $TBSOCHCH_2$), 3.88 (dd, $J = 6.2$, 2.6 Hz, 1H; $TBSOCHCH$), 3.05 (pentet, $J = 6.6$ Hz, 1H; CHCO), 2.61 (dd, $J = 15.8$, 5.5 Hz, 1H), 2.57 (m, 1H), 2.47 (m, 2H), 2.12 (s, 3H; CH_3C=CH), 2.09 (m, 1H), 1.91 (m, 1H), 1.73–1.64 (m, 1H), 1.56 (s, 3H), 1.54–1.47 (m, 2H), 1.32–1.21 (m, 4H), 1.17 (s, 3H; $(CH_3)_2C$), 1.11 (d, $J = 7.0$ Hz, 3H; CH_3CHCO), 1.07 (s, 3H; $(CH_3)_2C$), 0.95 (s, 9H; $SiC(CH_3)_3$), 0.91 (d, $J = 7.3$ Hz, 3H; CH_3CHCH_2), 0.89 (s, 9H; $SiC(CH_3)_3$), 0.88 (s, 9H; $SiC(CH_3)_3$), 0.12 (s, 6H; $Si(CH_3)_2$), 0.086/0.084/ 0.07/0.04 (4s, 12H; $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz): $\delta = 216.3$, 172.0, 170.5, 153.0, 138.0, 137.5, 120.0, 119.4, 116.3, 79.1, 73.0, 63.3, 54.0, 44.0, 41.9, 40.3, 39.3, 31.9, 26.1, 26.0, 25.7, 24.7, 22.7, 22.6, 20.2, 18.4, 18.3, 18.2, 16.8, 16.0, 15.7, 15.4, 14.1, −3.6, −4.0, −4.3, −4.4, −5.5; MS: 850 $[M+H]^+$, 884 $[M+Cl]^-$.

According to the process for the conversion of **37** to **7**, the above-mentioned compound **38** (33 mg, 0.039 mmol) was treated with HF/pyridine (0.4 mL) in THF (0.8 mL) at room temperature for 6 h to afford **8** (19 mg, 97%) after purification over silica gel (hexanes/EtOAc 1:1). $[\alpha]_D = -75.5^\circ$ ($c =$ 0.93, $CHCl_3$); ^{1}H NMR (600 MHz): $\delta = 7.08$ (s, 1H; ArH), 6.58 (s, 1H; ArCH=C), 5.23 (d, $J = 9.2$ Hz, 1H; CO_2CHCH_2), 5.12 (dd, $J = 9.7$, 4.8 Hz, 1H; CH=$C(CH_3)CH_2$), 4.85 (s, 2H; CH_2OH), 4.30 (d, $J = 11.0$ Hz, 1H; $CH(OH)CH_2$), 3.90 (br s, 1H; $CH(OH)CH$), 3.67 (br s, 1H; OH), 3.11 (m, 1H; CHCO), 3.09 (br s, 1H; OH), 2.60 (m, 1H), 2.44 (dd, $J = 14.5$, 11.0 Hz, 1H), 2.29–2.21 (m, 3H), 2.02 (s, 3H; CH_3C=CH), 1.88 (m, 1H), 1.73 (m, 1H), 1.68–1.59 (m, 1H), 1.64 (s, 3H; CH=$C(CH_3)CH_2$), 1.32 (s, 3H; $(CH_3)_2C$), 1.28–1.20 (m, 3H), 1.17 (d, $J = 7.0$ Hz, 3H; CH_3CHCO), 1.01 (s, 3H; $(CH_3)_2C$), 0.99 (d, $J = 7.0$ Hz, 3H; CH_3CHCH_2); ^{13}C NMR (150.9 MHz): $\delta = 220.7$, 170.3, 170.2, 152.2, 139.6, 138.3, 120.9, 118.4, 116.3, 78.6, 74.2, 71.9, 61.3, 53.7, 41.4, 39.6, 38.5, 32.4, 31.6, 31.4, 29.2, 25.2, 23.1, 22.9, 17.4, 16.2, 15.5, 13.4; HRMS: calcd for $C_{27}H_{41}NO_6SNa$: 530.2547; found: 530.2541 $[M+Na]^+$.

0947-6539/01/0708-1700 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 8

In a similar manner as above, (*E*)-**38** (40 mg, 0.047 mmol) was treated with HF/pyridine (0.4 mL) in THF (0.8 mL) at room temperature for 6 h to afford (*E*)-**8** (23 mg, 96 %). $[\alpha]_D = -89.0^\circ$ ($c = 0.90$, $CHCl_3$); ^{1}H NMR (600 MHz): $\delta = 7.10$ (s, 1H; ArH), 6.59 (s, 1H; ArCH=C), 5.40 (t, $J =$ 4.8 Hz, 1H; C*H*=C(CH_3)CH_2), 5.06 (t, $J = 6.6$ Hz, 1H; CO_2CHCH_2), 4.86 (d, $J = 1.7$ Hz, 2H; CH_2OH), 4.41 (dd, $J = 10.1$, 2.6 Hz, 1H; C*H*(OH)CH_2), 3.63 (t, $J = 3.7$ Hz, 1H; C*H*(OH)CH), 3.24 (m, 1H; CHCO), 2.56 (ddd, $J =$ 15.3, 7.9, 3.8 Hz, 1H; CH_2CH=CCH_3), 2.49 (dd, $J = 15.4$, 10.1 Hz, 1H; CH_2CO_2), 2.45–2.36 (m, 2H), 2.13 (m, 1H), 2.03 (s, 3H; CH_3C=CHAr), 1.94 (m, 1H), 1.60 (m, 2H), 1.56 (s, 3H; CH=C(CH_3)CH_2), 1.36 (m, 1H), 1.27 (m, 2H), 1.25 (s, 3H; (CH_3)$_2$C), 1.15 (d, $J = 6.6$ Hz, 3H; CH_3CHCO), 1.01 (s, 3H; (CH_3)$_2$C), 0.96 (d, $J = 6.6$ Hz, 3H; CH_3CHCH$_2$); ^{13}C NMR (100.6 MHz): $\delta = 220.0$, 170.2, 170.0, 152.3, 138.3, 137.7, 119.2, 118.7, 116.0, 76.5, 71.5, 61.3, 60.4, 52.9, 43.2, 39.6, 39.4, 37.4, 30.5, 29.2, 24.4, 21.1, 19.5, 16.4, 16.3, 15.8, 14.7, 14.2; HRMS: calcd for $C_{27}H_{41}NO_6S$: 508.2727; found: 508.2712 $[M+H]^+$.

Epothilone F (6): Oxone (38 mg, 0.062 mmol) and $NaHCO_3$ (8.4 mg, 0.1 mmol) were added in portions to a mixture of **8** (18 mg, 0.036 mmol), an aqueous solution of Na_2EDTA (4×10^{-4} M, 0.31 mL) and 1,1,1-trifluoroacetone (0.3 mL, 3.35 mmol) in CH_3CN (0.42 mL) and CH_2Cl_2 (0.21 mL). After the reaction was complete as determined by TLC, the mixture was diluted with EtOAc and passed quickly through a pad of silica gel. Solvents were removed under vacuum and the residue was purified by preparative TLC (CH_2Cl_2/MeOH 18:1) to afford epothilone F and its α-epoxide (15 mg, 81 %, β:α = 5:1). A second preparative TLC (hexanes/EtOAc 1:2) afforded pure epothilone F (11 mg, 59 %). $[\alpha]_D = -25.0^\circ$ ($c = 0.1$, methanol); ^{1}H NMR (600 MHz): $\delta = 7.12$ (s, 1H; ArH), 6.59 (s, 1H; ArCH=C), 5.43 (dd, $J = 7.4$, 3.1 Hz, 1H; CO_2CHCH_2), 4.92 (s, 2H; CH_2OH), 4.17 (m, 1H; C*H*(OH)CH_2), 4.01 (m, 1H; C*H*(OH)CH), 3.76 (brs, 1H; OH), 3.29 (m, 1H; CHCO), 2.86 (brs, 1H; OH), 2.80 (dd, $J = 7.4$, 5.3 Hz, 1H; CH-O(epoxide)), 2.59 (brs, 1H; OH), 2.54 (dd, $J = 14.0$, 10.1 Hz, 1H; CH_2CO_2), 2.38 (dd, $J = 14.0$, 3.1 Hz, 1H; CH_2CO_2), 2.09 (s, 3H; CH_3C=CH), 2.06 (m, 1H), 1.93 (dt, $J = 15.4$, 7.4 Hz, 1H), 1.74–1.67 (m, 2H), 1.49 (m, 1H), 1.46–1.36 (m, 4H), 1.35 (s, 3H; CH_3C-O(epoxide)), 1.27 (s, 3H; (CH_3)$_2$C), 1.16 (d, $J = 6.6$ Hz, 3H; CH_3CHCO), 1.07 (s, 3H; (CH_3)$_2$C), 0.99 (d, $J = 7.0$ Hz, 3H; CH_3CHCH$_2$); ^{13}C NMR (100.6 MHz): $\delta = 220.6$, 170.6, 170.0, 152.2, 137.6, 119.5, 116.9, 73.2, 62.2, 61.5, 61.3, 60.4, 52.8, 43.1, 39.1, 36.4, 32.1, 31.8, 30.7, 29.7, 22.8, 22.5, 21.2, 20.2, 17.1, 15.8, 14.2; HRMS: calcd for $C_{27}H_{41}NO_7SNa$: 546.2456; found: 546.2479 $[M+Na]^+$.

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[24] A solution (100 μL) of compound (±)-**10** (0.01 M in CH_3CN, 10 μL) and antibody 84G3 (6 μM, 90 μL in PBS buffer, pH 7.4) was kept at room temperature under argon atmosphere for 12 h. The reaction mixture was then shown to contain only one enantiomer of (±)-**10** by HPLC analysis equipped with a chiral reverse phase column (Daicel Chemical Industries; for HPLC conditions see: Supporting Information).

[25] Compound (±)-**11** (0.01 M solution in CH_3CN, 10 μL) was incubated with the antibody 84G3, 85H6 or 93G3 (6 μM antibody solution in PBS buffer, pH 7.4, 90 μL) and the progress of the reaction was followed by HPLC equipped with a chiral reverse phase ODR column. The absolute stereochemistry was determined by comparison of the specific rotation and HPLC trace of **11** with those of **10**.

[26] Crystallographic data (excluding structure factors) for structure **15** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-146207. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk); see also Supporting Information.

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[36] Esterification of acids **25** and **26** with alcohols **29** and **30**, respectively, to produce **31** and **32** were achieved as reported (see refs. [11c], [12c], and [12d]). Physical and spectral data of the products matched the reported data (see refs. [10d], [11c], [12c], and [12d]).

[37] Epothilones A (**1**) and C (**3**): Following a known method, compound **31** was metathesized to produce a mixture of **35** and (*E*)-**35**, which was deprotected using HF/pyridine and the crude product was separated to afford **3** and (*E*)-**3**. Compound **3** was then converted to epothilone A (**1**) and its α-epoxide. Physical and spectral data of **1**, **3** and all the intermediates were identical to the reported data (see refs. [10d], [11c]).

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