The 12,13-Diol Cyclization Approach for a Truly Stereocontrolled Total Synthesis of Epothilone B and the Synthesis of a Conformationally Restrained Analogue

Harry J. Martin,* Peter Pojarliev, Hanspeter Kählig, and Johann Mulzer*[a]

Abstract: A highly convergent and stereocontrolled synthesis of epothilone B (**1**) has been developed. The epoxide moiety in **1** was generated by regioselective mesylation and base treatment of the 12,13-diol **30** which was formed by a chelate Cram controlled Grignard addition of **14** and methyl ketone **13**. Both fragments were synthesized from the chiral carbon pool precursors (*S*)-citronellol and (*S*)-lactic acid, respectively. A highly diastereoselective aldol additon of epoxy-aldehyde **7** and the known Southern hemisphere ketone **8** delivered the full carbon skeleton, containing all the stereogenic centers of **1**. Functional group manipulation, macrolactonization and removal of two protecting groups then yielded **1**. The spatial closeness of the C4-β-methyl and C6-methyl group in the crystal structure of **1** inspired us to connect them through a methylene bridge to give a cyclohexanone derivative. Thus, the Northern hemisphere aldehyde **7** was added to the enolate of the cyclohexanone **47**. Further manipulations and macrolactonization delivered the conformationally restrained epothilone derivative **42**.

Keywords: carbonyl addition · epothilones · epoxidation · stereoselective synthesis · total synthesis

Introduction

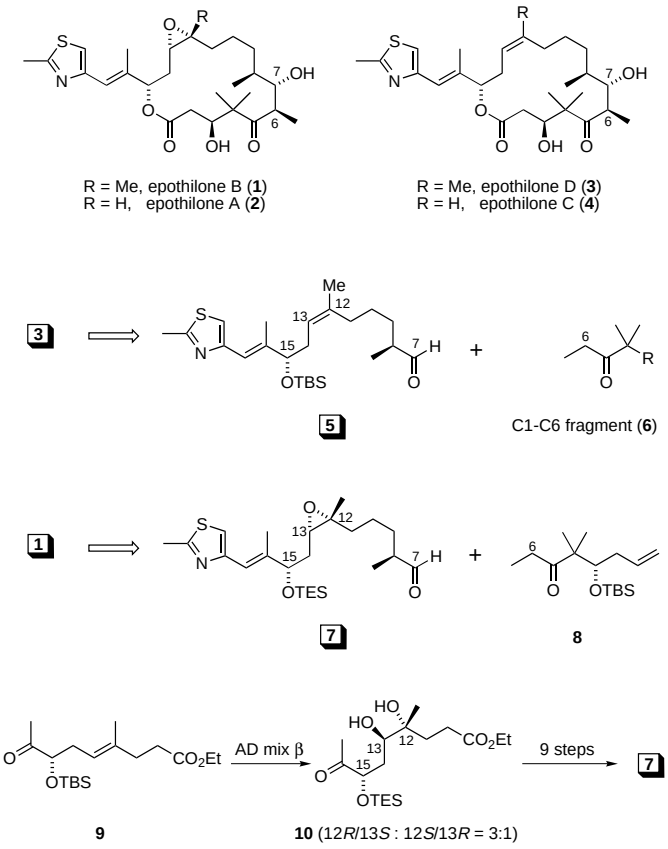
Epothilone B (**1**)[1] shows outstanding microtubule binding affinities and cytotoxity against tumor cells and multiple drug resistant tumor cell lines.[2] The role of **1** as a potential paclitaxel successor has initiated intense interest in its synthesis, resulting in several total syntheses of **1** and numerous derivatives thereof.[3, 4]

Apart from the objective to procure material for biological tests these syntheses were increasingly carried out in the intention to use **1** and the simpler epothilone A (**2**) as a testbed for the application of novel methodology. Thus, ring closing metathesis was used to generate the 12,13-olefin,[5] and ring closing aldol addition to form the 2,3-bond.[6] For the formation of the C-11,12-bond an interesting sp^2-sp^3-connecting Suzuki coupling was employed.[3a,c,e] Another issue was the introduction of stereogenic centers through chiral catalysis. For instance in the synthesis of **2** Shibasaki applied multifunctional catalysis for the construction of C15 (hydrocyanation) and C3 (aldol addition),[7] and the Lerner group prepared non-racemic fragments of **2** with the aid of catalytic antibodies.[8] In view of the extensive efforts which have been spent on developing stereocontrolled approaches to **1**/**2** it is more than surprising that the stereoproblem of introducing the 12,13-epoxide in pure (12*R*,13*S*) configuration still awaits a satisfactory solution. (Scheme 1). Usually the epoxide is generated through epoxidation of the corresponding 12,13-olefins (epothilone D, **3**, and epothilone C, **4**) either with *m*CPBA or dimethyl or trifluorodimethyl dioxirane. The high stereocontrol initially reported by Danishefsky[3a,c] could not be reproduced by Nicolaou, who found a virtually reagent independent ratio of 4:1 instead.[3b] Additionally, the two epoxide diastereomers are difficult to separate (TLC) and the application of peroxidic epoxidizing agents does not appear acceptable for the industrial scale. Recently Nicolaou reported a solution of the problem by using a 12-hydroxymethylene substituent in a stereocontrolled Sharpless epoxidation, however, this methodology requires several additional steps and does not appear satisfactory.[4e]

Though to a lesser degree the introduction of C6/C7 in the correct (6*R*,7*S*)-configuration still poses a problem. Usually, the C-6,7-bond is formed by an aldol addition of ketone **6** to the 12,13-unsaturated aldehyde **5** (or shorter fragments thereof). The diastereomeric ratio of 6*R*,7*S*:6*S*,7*R*-diastereomers routinely is about 3–4:1. Only Schinzer[3e] and White[3h] reported stereoselectivities of >90:10. This degree of selectivity was also recently achieved in Nicolaou's synthesis of some epothilone B derivatives.[4e] Remarkably, on reviewing the various syntheses of **1** there is not one synthesis so far, in which all stereogenic units are introduced with a selectivity of

[a] Dr. H. J. Martin, Prof. Dr. J. Mulzer, Dr. P. Pojarliev, Dr. H. Kählig
Institut für Organische Chemie der Universität Wien
Währinger Strasse 38, 1090 Wien (Austria)
Fax: (+43) 1-4277-52189
E-mail: harry.martin@univie.ac.at
johann.mulzer@univie.ac.at

  0947-6539/01/0710-2261 $ 17.50+.50/0

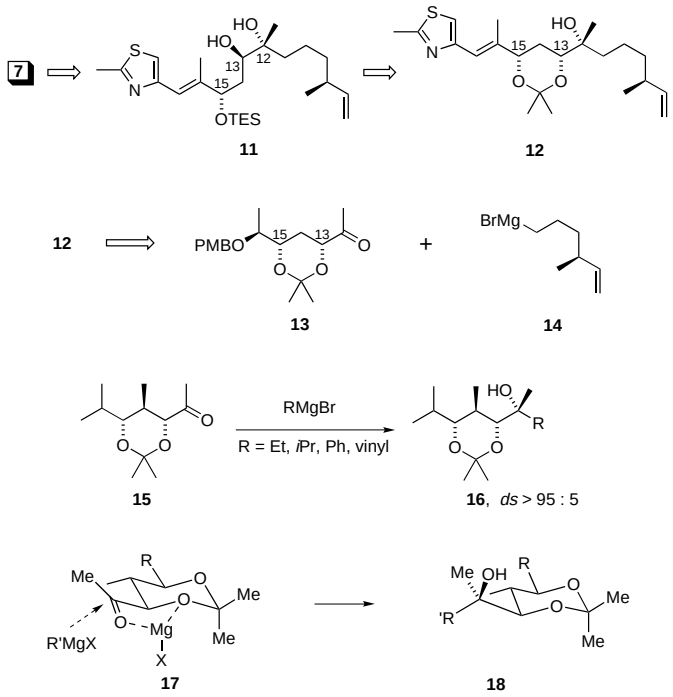


Scheme 1. Retrosynthetic analysis I for the synthesis of epothilone B.

>95:5, which would be desirable for any up-to-date-methodology.

Recently we reported a novel approach to the introduction of the epoxide function in **1** (Scheme 1). The key step of the synthesis was the highly stereoselective (*ds* >95:5) aldol addition of ketone **8** to the epoxy aldehyde **7**.[3j] The epoxide moiety in **7** was prepared through a regiocontrolled cyclization of diol **10**, which was readily available from the olefinic ester **9** by Sharpless AD reaction. In this way the epoxide was introduced very early in the synthesis and turned out to be surprisingly stable over a variety of synthetic operations. However, there were two flaws in this synthesis: the introduction of the 12,13-diol through Sharpless AD reaction of olefin **9** to form diol **10** was not stereoselective and the 15-O-protective group had to be changed from TBS to TES later in the synthesis to allow the final 15-O-deprotection under mild conditions.

We now report a new synthesis of **7** which eliminates the previous drawbacks and makes use of simple and reliable reactions which are applicable on the larger scale without problems, and most gratifyingly, create all stereogenic units with the required >95% stereoselectivity. The synthesis of **7** was centered around the 13,15-*syn* diol acetonide moiety represented in intermediate **12**, which, in the synthetic direction, had to be transformed into **7** via the 15-O-silylated triol **11**. Acetonide **12**, in turn, was prepared from ketone **13** through a chelate Cram controlled addition of the Grignard reagent **14**.[9] The high stereocontrol of this addition was to be expected from previous experiments in our group which showed that ketone acetonides **15** underwent highly selective additions with various Grignard reagents to form the *syn*-triols **16** in about 90% isolated yields (Scheme 2).[10] The mechanistic interpretation implies a chelate Cram intermediate **17** which is attacked at the carbonyl group from the less hindered face. In this way the trajectory is antiperiplanar to the endocyclic C–O-bond to give *syn*-triol **18**.



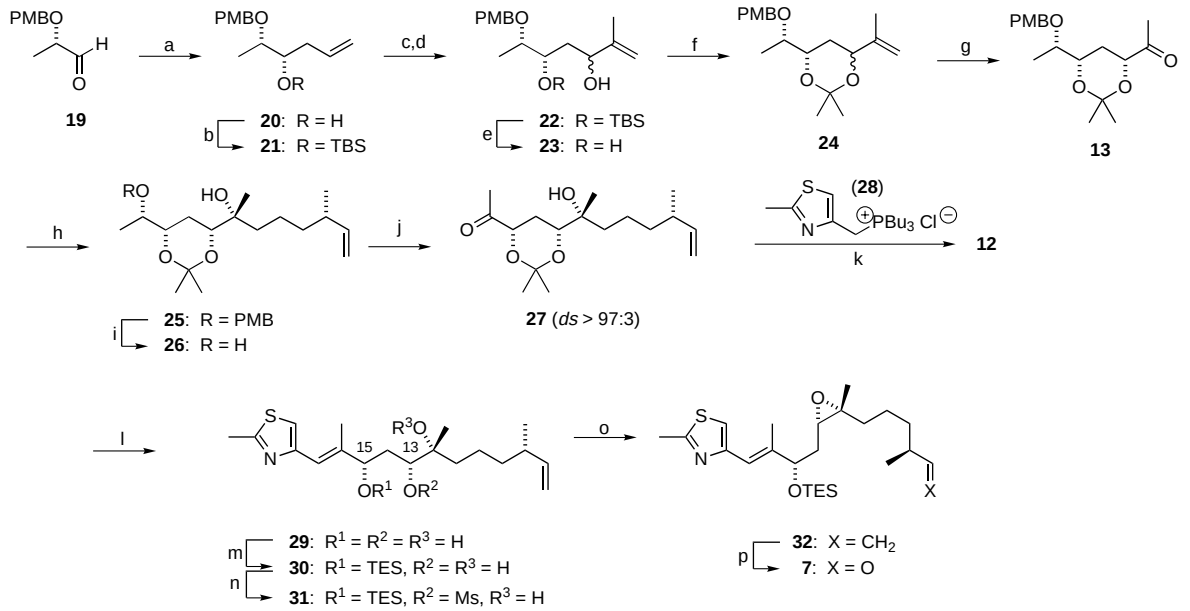
Scheme 2. Retrosynthetic analysis II for the convergent synthesis of the Northern hemisphere aldehyde.

Results and Discussion

Our synthesis started with the known addition of allyltrimethylsilane to aldehyde **19** (Scheme 3), which furnishes the *syn*-adduct **20** with >95:5 diastereoselectivity.[11] Subsequent O-silylation of **20** gave **21** which was treated with ozone followed by addition of isopropenyl magnesium bromide to form the triol **22** as a 3:2-mixture of diastereomers which was converted into the acetonide **24**. After oxidation of **24** to the ketone, the epimeric mixture was treated with mild base to achieve complete equilibration to the *syn*-diastereomer **13**.[12]

The addition of the Grignard reagent **14** (readily available from the known alcohol via the bromide)[13] to ketone **13** proceeded with high chelate Cram selectivity as expected to furnish the tertiary alcohol **25**. After PMB deprotection and oxidation, ketone **27** was transferred into the thiazolyl olefin **12** by an *E*-selective Wittig reaction.[3g] Global O-deprotection led to the triol **29** which, much to our surprise, underwent completely regioselective O-silylation at the 15-position to generate **30**, even when 3 mol equivalents of TESCl had to be applied for a complete conversion! Subsequent 13-O-mesylation also proceeded with perfect regiocontrol to convert **30** into **31**. The stage was now set for the base catalyzed formation of the 12,13-epoxide **32** under inversion at C13

0947-6539/01/0710-2262 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10

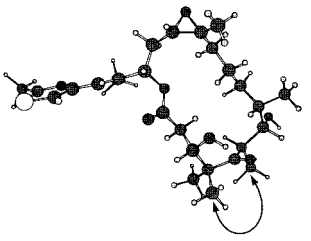


Scheme 3. a) See ref. [11]; b) TBSCl, imidazole, DMF, 22 °C, 24 h, 97 % c) O_3, CH_2Cl_2/MeOH, −78 °C, then PPh_3, 98 %; d) isopropenyl magnesium bromide, THF, −10 °C, 45 min, 89 % as a 3:2-mixture of diastereomers; e) 1.2 equiv TBAF, THF, 1 h, 25 °C, 99 %; f) 2,2-dimethoxypropane, cat. TsOH, 99 %; g) O_3/PPh_3, CH_2Cl_2, −78 °C, then 2.0 equiv K_2CO_3, MeOH, 1 h, 25 °C, (94 % in two steps); h) $MgBr_2$, CH_2Cl_2, −78 °C, 3.0 equiv **14**, 3 h, (78 %, *ds* = 96:4); i) 1.2 equiv DDQ, CH_2Cl_2, 45 min, 25 °C, (98 %); j) 1.5 equiv Dess–Martin-periodinane, CH_2Cl_2, 2 h, 25 °C, 95 %; k) 5.0 equiv **28**, KHMDS, 0 °C, 40 min, then **27**, 45 °C, 20 min, THF, 80 %; l) 15 % HCl, MeOH, 12 h, 25 °C, 99 %; m) 3.0 equiv TESCl, Et_3N, CH_2Cl_2, 12 h, 25 °C, 90 %; n) MsCl, Et_3N, 92 %; o) K_2CO_3, MeOH, 1 h, 25 °C, 90 %; p) NMO, OsO_4, $NaIO_4$, (62 % in two steps). TBS = *tert*-butyldimethylsilyl; TBAF = tetrabutylammonium fluoride; Ts = 4-toluenesulfonyl; DDQ = 2,3-dichloro-3,4-dicyanobenzoquinone; KHMDS = potassium hexamethyldisilazide; TES = triethylsilyl; Ms = methanesulfonyl, NMO = 4-methylmorpholine-*N*-oxide.

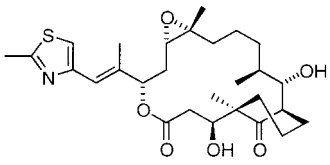
and retention at C12. Regioselective dihydroxylation of the terminal olefin followed by glycol cleavage delivered the desired aldehyde **7**.

Next we set about a stereocontrolled synthesis of ketone **8** (see Scheme 4). This compound had been made by a Brown allylation of aldehyde **34** with moderate enantioselectivity (*ee* ≈ 84 %).[3b] We applied Duthaler's allylation protocol[14] and to our delight we found that reagent **33** converted aldehyde **34** into adduct **35** with an *ee* > 98 %. Additionally we found the workup much more convenient than for Brown's method which implied repeated and tedious column chromatography to remove the boron containing side products. Aldol addition of the lithium enolate of ketone **8** to aldehyde **7** proceeded with excellent diastereoselectivity (> 95:5) to form the adduct **36** which was protected to give the 7-OTroc derivative **37**. The further success of the synthesis crucially depended on the handling of the O-protective groups. Thus, **37** was first converted into the aldehyde and then 15-O-desilylated to give hydroxy aldehyde **38** which was oxidized to the acid **39** with Pinnick's reagent.[15] Yamaguchi macrolactonization[16] furnished lactone **40** which was first deprotected at 7-O to give **41** and after removal of the 3-TBS group, epothilone B (**1**) which was identical in all pertinent analytical data with the natural compound described. In effect we have thus achieved a truly stereocontrolled synthesis of **1**, in addition to the one reported earlier.[3m]

Encouraged by this result we turned to the synthesis of a conformationally restricted analogue. On inspecting the crystal structure of **1** and on the basis of the conformational analysis of epothilone A in solution[17] it occurred to us that the (pro-*R*)-4- and the 6-methyl groups are closely together, and hence could be connected by a one carbon bridge to form a cyclohexane analogue **42** in which the "South East" (C3–C7) fragment can be expected to underly a significant conformational restriction. (Figure 1).



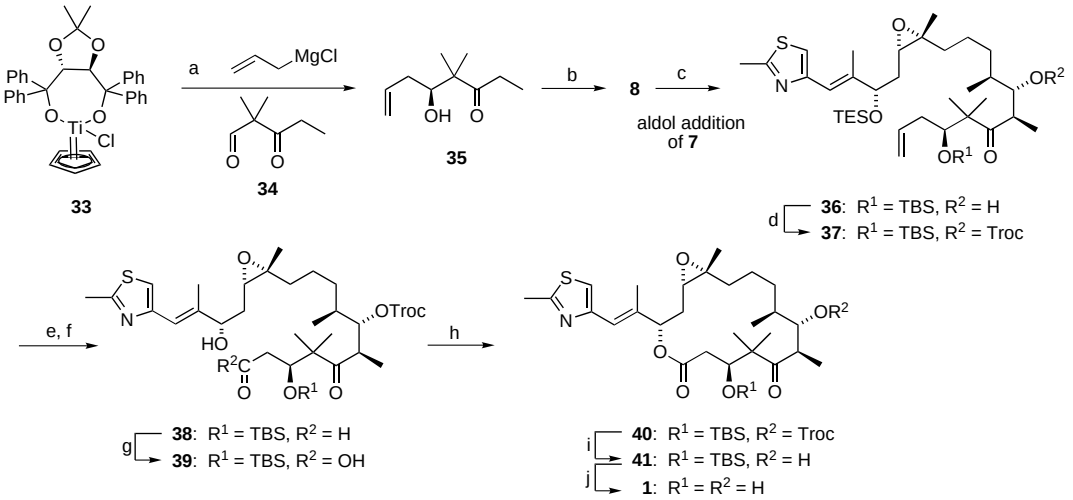
crystal structure of epothilone B (**1**)



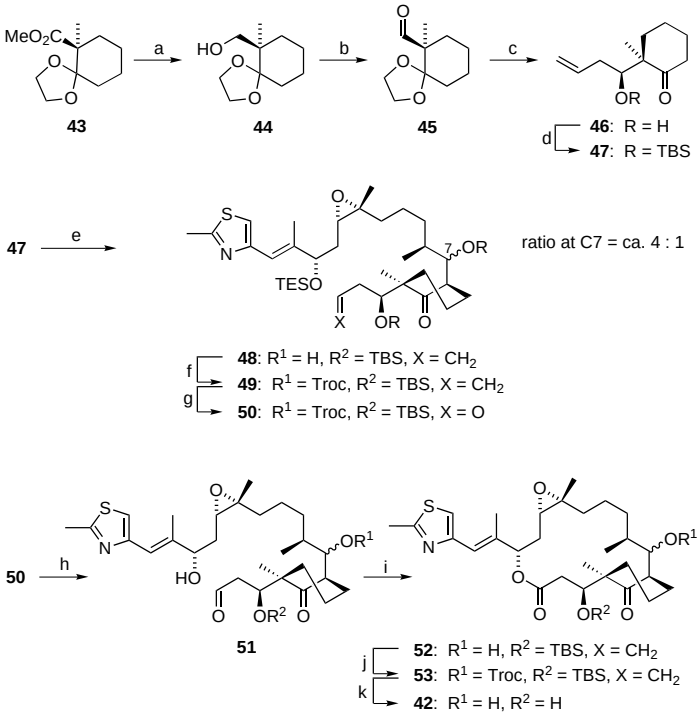
42: C4β - and C6 - methyl groups are connected via a CH_2 bridge to form a cyclohexane ring

Figure 1. Design of a conformationally restrained epothilone analogue.

The synthesis of **42** started from the cyclohexane derivative **43**, which was provided by the Schering (ZK 204027, *ee* > 98 %) (Scheme 5). Reduction with LAH furnished alcohol **44**, which was oxidized to aldehyde **45** and then subjected to an asymmetric Brown allylation followed by acetal hydrolysis to furnish **46** with a *ds* = 6:1. This value is much lower than the one observed for the acyclic analogue **34** (92:8), so that the allylation of **45** may be assumed to be a mismatched case. After TBS protection of the hydroxyl group the ketone **46** was used in the aldol condensation with aldehyde **7** to form the diastereomeric adducts **48** in a ratio of 4:1. After protection, 7-OTroc derivative **49** was oxidized to the aldehyde **50** with OsO_4/NMO followed by glycol cleavage with $NaIO_4$. Depro-



Scheme 4. a) **33**, allylmagnesium chloride, THF, 0 °C, 90 min, then add **34**, −74 °C, 3 h, 61 %; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h, 87 %; c) diisopropylamine, *n*BuLi (1.6 M in hexanes), THF, 0 °C, 20 min, then add **8** (in THF), −78 °C to −40 °C, 30 min, then add **7** (in THF), −78 °C, 15 min, 92 %; d) TrocCl, CH_2Cl_2, pyridine, 20 °C, 30 min, 91 %; e) NMO, OsO_4 (5 mol %), THF/*t*BuOH/H_2O 10:10:1, 25 °C, 16 h, workup with $Na_2S_2O_3$; crude diol in EtOH/H_2O, $NaIO_4$, 25 °C, 1 h, 78 % over two steps; f) HF/pyridine, THF, 22 °C, 20 min, 91 %; g) $NaClO_2$, 2,3-dimethyl-2-butene, NaH_2PO_4, *t*BuOH, H_2O, 22 °C, 45 min, 92 %; h) **38**, 2,4,6-trichlorobenzoyl chloride, triethylamine, DMAP, 0.02 M solution in toluene, 22 °C, 90 min, 65 % i) Zn, ammonium chloride, EtOH, reflux, 20 min, 92 %; j) HF/pyridine, 35 °C, **7d**, 67 %. Tf = trifluormethanesulfonyl; TrocCl = 2,2,2-trichloroethyl chloroformate; DMAP = 4-dimethylaminopyridine.



Scheme 5. a) LAH, Et_2O, 25 °C, 3 h, 97 %; b) oxalylchloride, DMSO, CH_2Cl_2, −78 °C, 15 min, then NEt_2iPr, 0 °C, 1 h, 90 %; c) (−)-Ipc_2B(allyl), allylmagnesium bromide, Et_2O, THF, −78 °C, 3 h, workup with H_2O_2, NaOH, *ds* = 6:1, 50 %; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 96 %; e) LDA, THF, −78 °C, 10 min, then **7**, −78 °C, 10 min, 78 %; f) TrocCl, pyridine, CH_2Cl_2, 25 °C, 40 min, 98 %; g) OsO_4, NMO, *t*BuOH, THF, 25 °C, 16 h, then $NaIO_4$, H_2O, EtOH, 25 °C, 1 h, 64 %; h) HF, pyridine, THF, 25 °C, 20 min, 88 %; i) $NaClO_2$, butanol, 2,3-dimethyl-but-2-ene, H_2O, NaH_2PO_4, 25 °C, 2 h, then 2,4,6-trichlorobenzoyl chloride, NEt_3, toluene, DMAP, 25 °C, 30 min, 36 %; j) Zn, EtOH, NH_4Cl, reflux, 30 min, 95 %; k) HF, pyridine, 40 °C, 4 d, 50 %. Ipc = isopinocampheyl; LDA = lithium diisopropylamide.

tection of O-15 and Pinnick oxidation of the resulting aldehyde **51** led to the seco acid which was converted without purification into the macrolactone **52** through Yamaguchi lactonization. Sequential deprotection furnished **53** and, eventually, the desired epothilone B analogue **42**. Careful analysis by two-dimensional NMR spectroscopy revealed the (*R*) configuration at C6 which established a *cis*-relationship of the two carbon appendages around the cyclohexane ring. However, the configuration of C7 could not be assigned with certainty. We did not insist on this point, as no biological activity of **42** towards tumor cell line MCF-7 was observed.

In conclusion, we have established a fully stereocontrolled synthesis of epothilone B, essentially based on well established methodology which starts from inexpensive materials. This methodology has also been successfully applied to the synthesis of a conformationally restricted epothilone analogue.

Experimental Section

Unless otherwise stated, solvents were dried by distillation under argon, from Na (toluene), Na/K (Et_2O, abbreviated as ether), potassium (THF), CaH_2 (Et_3N, DMF), P_2O_5 (CH_2Cl_2), KOH (pyridine) and Mg (MeOH, EtOH). All other commercially available reagents were used without further purification unless specified otherwise. All reactions were performed in oven-dried glassware under argon. Chromatography refers to flash column chromatography on silica gel 60 (230–400 mesh). Thin-layer chromatography (TLC) was performed on Al-backed plates (Merck silica gel 60 F_{254}) and visualised by using either a UV lamp, phosphomolybdic acid, sulphuric acidic/anisaldehyde or potassium permanganate solutions. Melting points (m.p.) are uncorrected. Optical rotations are reported in g per 100 mL. Infrared spectra (IR) were measured as evaporated films on single crystal silica plates and reported in wave numbers (cm^{-1}) with broad signals denoted by (br). High resolution mass spectra were obtained using electron ionisation (EI), field ionisation (FI) or fast atom bombardment

0947-6539/01/0710-2264 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10

(FAB). ^{1}H and ^{13}C NMR were recorded on a Bruker AC 250 (250 MHz), AM 400 (400 MHz) or AM 600 (600 MHz) spectrometer. Chemical shifts are reported using the solvent resonance internal standard (chloroform, $\delta = 7.26$ and 77.0).

Silyl ether 21, **silylation of alcohol 20**: A solution of alcohol **20** (8.95 g, 38.0 mmol) in dry DMF (180 mL) was treated with imidazole (15.5 g, 227 mmol) and TBS chloride (8.00 g, 53.0 mmol). After stirring over a period of 16 h at room temperature, the reaction mixture was added to hexane/ether (1:1 mixture, 400 mL) and washed with saturated aqueous $NaHCO_3$ solution (2×100 mL), water (100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexane/EtOAc 50:1 → 20:1) afforded silyl ether **21** as a colorless oil (12.94 g, 97 %). $[\alpha]_D^{20} = -0.4$ ($c = 2.40$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2955, 2857, 1642, 1613, 1587, 1514, 1464, 1249, 1098, 1039\ cm^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.83 (ddt, $J = 17.0, 10.0, 7.3$ Hz, 1H), 5.04 (d, $J = 17.0$ Hz, 1H), 5.01 (d, $J = 10.0$ Hz, 1H), 4.52 (d, $J = 12.0$ Hz, 1H), 4.44 (d, $J = 12.0$ Hz, 1H), 3.80 (s, 3H), 3.72 (qn, $J = 4.0$ Hz, 1H), 3.47 (dq, $J = 4.0, 6.5$ Hz, 1H), 2.42–2.34 (m, 1H), 2.17–2.08 (m, 1H), 1.12 (d, $J = 6.5$ Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 159.5, 136.6, 131.5, 129.5, 116.8, 114.1, 77.4, 74.2, 71.1, 55.7, 36.7, 26.3, 18.5, 14.4, -4.1$ (two signals); EI HRMS: m/z: 293.1581 $[M - C_4H_9]^+$, calcd for $C_{20}H_{34}O_3Si$: 350.2277.

Alcohol 22, **ozonolysis of alkene 21 and Grignard reaction**: Ozone was passed through a solution of alkene **21** (8.02 g, 25 mmol) in CH_2Cl_2 (200 mL) and methanol (10 mL) at −78 °C until a blue color appeared. Excess ozone was removed by purging with air (2 min), then PPh_3 (19.7 g, 75 mmol) was added and the mixture was allowed to warm to room temperature. The solvents were removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes/EtOAc/CH_2Cl_2 40:1:10, then hexanes/EtOAc 20:1 → 10:1) to give aldehyde (7.90 g, 98 %) as a colorless liquid. $[\alpha]_D^{20} = +2.8$ ($c = 2.20$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2934, 1728, 1612, 1514, 1466, 1250, 1101, 1037\ cm^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.75$ (s, 1H), 7.25–7.17 (m, 2H), 6.88–6.82 (m, 2H), 4.50 (d, $J = 11.5$ Hz, 1H), 4.38 (d, $J = 11.5$ Hz, 1H), 4.32–4.25 (m, 1H), 3.78 (s, 3H), 3.56–3.48 (m, 1H), 2.68–2.60 (m, 1H), 2.50–2.41 (m, 1H), 1.11 (d, $J = 6.5$ Hz, 3H), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 202.2, 159.6, 130.9, 129.6, 114.2, 76.6, 71.0, 69.4, 55.7, 46.4, 26.1, 18.3, 13.9, -4.2, -4.5$; EI HRMS: m/z: 295.1366 $[M - C_4H_9]^+$, calcd for $C_{19}H_{32}O_4Si$: 352.2070.

A solution of the above aldehyde (7.82 g, 22.2 mmol) in dry THF (20 mL) was slowly added at −10 °C to a solution of isopropenyl magnesium bromide (0.5 M solution in THF, 53.0 mL, 26.5 mmol). The mixture was allowed to warm to 0 °C and was quenched by addition to a saturated aqueous NH_4Cl solution (100 mL) and ether (100 mL). The aqueous layer was extracted with ether (2×40 mL), the combined organic phases were dried and concentrated. Purification by flash column chromatography (silica gel, hexanes/EtOAc 10:1) furnished allylic alcohol **22** (7.79 g, 89 %, mixture of diastereomers ca. 3:2) as a colorless oil. IR (thin film): $\tilde{\nu}_{max} =$ 3438 (br), 2955, 1650, 1613, 1514, 1463, 1250, 1086 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28–7.21$ (m, 2H), 6.90–6.84 (m, 2H), 4.99 (s, 1H), 4.84 (s, 0.6H), 4.81 (s, 0.4H), 4.56–4.44 (m, 2H), 4.23–4.15 (m, 1H), 4.00 (dt, $J = 7.0, 4.5$ Hz, 0.4H), 3.95 (dt, $J = 8.5, 4.5$ Hz, 0.6H), 3.80 (s, 3H), 3.62–3.50 (m, 1H), 3.10 (d, $J = 2.5$ Hz, 0.6H), 2.81 (d, $J = 3.5$ Hz, 0.4H), 1.95–1.76 (m, 1H), 1.73 (s, 3H), 1.68–1.58 (m, 1H), 1.16 (d, $J = 6.5$ Hz, 1.8H), 1.14 (d, $J = 6.5$ Hz, 1.2H), 0.88 (s, 9H), 0.07 (s, 1.8H), 0.06 (s, 1.2H), 0.00 (s, 3H); EI HRMS: m/z: 337.1849 $[M - C_4H_9]^+$, calcd for $C_{22}H_{38}O_4Si$: 394.2539.

Diol 23, **desilylation of 22**: A solution of silyl ether **22** (2.5 g, 6.3 mmol) in dry THF (60 mL) at 0 °C was treated with TBAF (1 M solution in THF, 7.6 mL, 7.6 mmol). After stirring for 1 h at 25 °C, the reaction mixture was diluted with ether (60 mL) and washed with saturated aqueous NH_4Cl solution (60 mL). The aqueous phase was extracted with ether (3×50 mL), and the combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash column chromatography (hexane/EtOAc 4:1) to provide diol **23** (1.75 g, 99 %) as a colorless liquid. IR (thin film): $\tilde{\nu}_{max} = 3418$ (br), 2969, 2934, 2868, 1612, 1513, 1248, 1106 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.28–7.18$ (m, 2H), 6.90–6.81 (m, 2H), 5.03 (br s, 0.4H), 4.98 (br s, 0.6H), 4.85 (br s, 0.4H), 4.80 (s, 0.6H), 4.58 (d, $J = 11.2$ Hz, 1H), 4.35 (d, $J = 11.2$ Hz, 1H), 4.36–4.23 (m, 1H), 3.79 (s, 3H), 3.81–3.63 (m, 1H), 3.50–3.33 (m, 1H), 3.1 (br s, 0.6 × OH), 2.93 (d, $J = 5$ Hz, 0.4 × OH), 2.87 (d, $J = 3$ Hz, 1 × OH), 1.72–1.53 (m, 2H), 1.70 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 1.8H), 1.15 (d, $J = 6.2$ Hz, 1.2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 159.4, 147.3, 130.3, 129.4, 114.0, 113.9, 110.8, 110.3, 77.9, 77.8, 75.6, 75.4, 72.5, 72.4, 70.7, 70.3, 55.3, 55.3, 37.6, 36.9, 18.7, 17.8, 15.4, 15.2$; EI HRMS: m/z: 280.1682 $[M]^+$, calcd for $C_{16}H_{24}O_4$: 280.1675.

Acetonide 24: A solution of diol **23** (1.75 g, 6.25 mmol) in 2,2-dimethoxypropane (50 mL) and catalytic amount of p-TsOH · H_2O (50 mg) was stirred for 3 h at 25 °C. The reaction mixture was diluted with ice-water (50 mL) and ether (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous phase was extracted with ether (3×50 mL) and the combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash column chromatography (hexane/EtOAc 15:1) to provide acetonide **24** (2.0 g, 99 %) as a colorless oil. IR (thin film): $\tilde{\nu}_{max} = 2989, 2937, 2870, 2836, 1613, 1248\ cm^{-1}$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.29–7.22$ (m, 2H), 6.89–6.81 (m, 2H), 4.95 (br s, 0.4H), 4.91 (br s, 0.6H), 4.81 (br s, 0.4H), 4.77 (br s, 0.6H), 4.61–4.48 (m, 2H), 4.28–4.24 (m, 0.4H), 4.23–4.18 (m, 0.6H), 3.98–3.81(m, 1H), 3.78 (s, 3H), 3.57–3.44 (m, 1H), 1.9–1.56 (m, 2H), 1.73 (s, 3H), 1.45 (s, 0.9H), 1.43 (s, 0.9H), 1.38 (s, 1.2H), 1.13 (d, $J = 6.4$ Hz, 1.2H), 1.11 (d, $J = 6.4$ Hz, 1.8H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 159.0, 145.2, 129.2, 113,7, 110,3, 100.5, 75.9, 71.3, 70.0, 69.7, 55.2, 32.4, 25.0, 24.5, 18.6, 15.3$; EI HRMS: m/z: 320.1977 $[M]^+$, calcd for $C_{19}H_{28}O_4$: 320.1988.

Ketone 13, **ozonolysis of alkene 24**: Alkene **24** (2.0 g, 6.25 mmol) was dissolved in a mixture of CH_2Cl_2 and MeOH (8:1, 65 mL), and the solution was cooled to −78 °C. Oxygen was bubbled through the solution for 2 min, after which ozone was passed through until the reaction mixture had a pale blue color (ca. 15 min). The solution was then purged with air for 2 min at −78 °C (until disappearance of blue color) and PPh_3 (2.46 g, 9.38 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h at 25 °C. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexane/EtOAc 40:1 to 10:1) to provide a 1:1 epimeric mixture of ketone **13**. The mixture of epimers were dissolved in dry MeOH (100 mL) and treated with dry K_2CO_3 (1.73 g, 12.5 mmol) at 25 °C. After stirring for 1 h at 25 °C, a mixture of ether (50 mL) and ice-water (50 mL) was added and the reaction mixture was neutralised with saturated aqueous NH_4Cl solution. The organic phases were separated and the aqueous phase was extracted with ether (3×50 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (hexane/EtOAc 10:1) furnished the pure ketone **13** (1.9 g, 94 % for two steps) as a single diastereomer. $[\alpha]_D^{20} = +23.8$ ($c = 2.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2993, 2939, 2837, 1718, 1613, 1514, 1380, 1107, 973\ cm^{-1}$; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.27–7.20$ (m, 2H), 6.88–6.80 (m, 2H), 4.56 (d, $J = 11.6$ Hz, 1H), 4.49 (d, $J = 11.6$ Hz, 1H), 4.21 (dd, $J = 12.0, 3.0$ Hz, 1H), 3.93 (ddd, $J = 11.7, 5.5, 2.5$ Hz, 1H), 3.77 (s, 3H), 3.53–3.41 (m, 1H), 2.17 (s, 3H), 1.66 (dt, $J = 13.0, 2.7$ Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.36 (dd, $J = 13.0, 1.0$ Hz, 1H), 1.15 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 208.9, 159.1, 130.9, 129.2, 113.7, 98.9, 76.1, 74.8, 72.0, 71.3, 55.3, 29.9, 27.7, 25.4, 19.5, 15.0$; EI HRMS: m/z: 322.1776 $[M]^+$, calcd for $C_{18}H_{26}O_5$: 322.1780.

Alcohol 25, **Grignard reaction of ketone 13**: Mg cuttings (365 mg, 15 mmol) were moistened with dry THF (0.2 mL). (3*S*)-6-Bromo-3-methyl-hex-1-ene (2.21 g, 12.5 mmol), dissolved in dry THF (12.5 mL), was slowly added at 25 °C under argon atmosphere. After the exothermic reaction was complete, the solution was stirred for 30 min at 25 °C. The dark-brown solution of **14** was separated from the mixture via syringe and used in the next step.

$MgBr_2 \cdot Et_2O$ (1.48 g, 5.4 mmol) was added in portions to a cooled (−78 °C) solution of ketone **13** (1.45 g, 4.5 mmol) in dry CH_2Cl_2 (30 mL). After stirring for 30 min, the homogeneous mixture was treated dropwise with Grignard compound **14** (1 M in THF, 13.5 mL, 13.5 mmol) at −78 °C and stirred for 1 h at this temperature. The mixture was allowed to warm to 25 °C and stirred for 1 h. Ice-water (30 mL) was added and the solution was treated with saturated aqueous NH_4Cl solution (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3×25 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash column chromatography (hexane/EtOAc 8:1) to give a mixture of diastereomers (*syn*:*anti* = 24:1 by HPLC analysis). Separation of these diastereomers was carried out by HPLC (Nucleosil 50–5, 237 × 32 mm, 15 % EtOAc in hexane, 80 mL min^{-1}, UV_{254},

10.0 min for the *syn*-product) to yield pure **25** (1.48 g, 78%) as a colorless oil. $[\alpha]_D^{20} = -7.5$ ($c = 2.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3572$ (br), 2939, 1639, 1613, 1513, 1379 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 7.30-7.21$ (m, 2H), 6.91–6.88 (m, 2H), 5.75–5.59 (m, 1H), 4.99–4.85 (m, 2H), 4.57 (d, $J = 11.7$ Hz, 1H), 4.50 (d, $J = 11.7$ Hz, 1H), 3.88 (dq, $J = 11.2$, 3.0 Hz, 1H), 3.78 (s, 3H), 3.64 (dd, $J = 11.2$, 3.0 Hz), 3.54–3.42 (m, 1H), 2.24 (br s, 1 × OH), 2.17–2.04 (m, 1H), 1.45–1.22 (m, 8H), 1.40 (s, 3H), 1.38 (s, 3H), 1.11 (d, $J = 6.4$ Hz, 3H), 1.04 (s, 3H), 0.96 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 144.7$, 131.1, 129.2, 113.7, 112.4, 98.6, 73.4, 73,2, 72.0, 71.3, 55.2, 38.9, 37.6, 37.2, 30.0, 25.3, 21.1, 21.1, 20.2, 19.8, 15.0; EI HRMS: m/z: 420.2866 $[M]^+$, calcd for $C_{25}H_{40}O_5$: 420.287.

Compound 26, **PMB-deprotection of 25**: DDQ (926 mg, 4.08 mmol) was added in small portions at 0 °C within 5 min to a solution of PMB-ether **25** (1.43 g, 3.4 mmol) in a mixture of CH_2Cl_2 and H_2O (10:1, 55 mL). After stirring for 45 min at 25 °C, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (50 mL) and aqueous $Na_2S_2O_3$ solution (1M, 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated. The crude mixture was purified by flash column chromatography (hexane/EtOAc 4:1) to provide **26** (1.0 g, 98%) as a colorless oil. $[\alpha]_D^{20} = +1.74$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3453$ (br), 3075, 2971, 1640, 1461, 1379, 911 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): $\delta =$ 5.78–5.62 (m, 1H), 5.03–4.92 (m, 2H), 3.75–3.55 (m, 3H), 2.60 (br s, 1 × OH), 2.25 (br s, 1 × OH), 2.23–2.07 (m, 8H), 1.42 (s, 3H), 1.39 (s, 3H), 1.18 (d, $J = 6$ Hz, 3H), 1.08 (s, 3H), 1.01 (d, $J = 7$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 144.7$, 112.5, 98.9, 73.7, 73.2, 73.1, 70.7, 38.9, 37.7, 37.2, 30.0, 26.4, 21.2, 21.1, 20.2, 20.0, 17.7; EI HRMS: m/z: 285.2057 $[M]^+$, calcd for $C_{16}H_{29}O_4$: 285.2066.

Ketone 27, **Dess–Martin oxidation of 26**: Dry pyridine (1.0 mL) and Dess–Martin periodinane (445 mg, 1.0 mmol) were added at 0 °C to a solution of **26** (200 mg, 0.67 mmol) in dry CH_2Cl_2 (15 mL). After stirring for 2 h at 25 °C, the reaction was quenched with a 1:1 mixture of aqueous $Na_2S_2O_3$ solution (1M) and saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The crude mixture was purified by flash column chromatography (hexane/EtOAc 6:1) to provide ketone **28** (190 mg, 95%) as a colorless foam. $[\alpha]_D^{20} = -24.2$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3508$ (br), 2942, 1720, 1381 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 5.74-5.56$ (m, 1H), 4.88–4.83 (m, 2H), 4.21 (dd, $J = 11.7$, 3.2 Hz, 1H), 2.19 (s, 3H), 2.18–2.04 (m, 1H), 1.68 (dt, $J = 13.0$, 2.7 Hz, 1H), 1.50–1.20 (m, 8H), 1.44 (s, 3H), 1.41 (s, 3H), 1.04 (s, 3H), 0.96 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 209.1$, 144.7, 112.5, 99.1, 74.9, 73.4, 73.3, 38.8, 37.7, 37.2, 29.9, 26.7, 25.4, 21.2, 21.1, 20.2, 19.6.

Thiazolyl olefin 12, **Wittig reaction of 27**: A solution of Wittig salt **28** (1.12 g, 3.2 mmol) in dry THF (10 mL) was cooled to −78 °C and treated dropwise with KHMDS (0.5M in toluene, 6.4 mL, 3.2 mmol). After stirring for 45 min at −78 °C ketone **27** (190 mg, 0.64 mmol), dissolved in dry THF (1.0 mL), was added to the reaction mixture at −78 °C. The cooling bath was removed and the reaction mixture was stirred for 45 min at 40 °C. Ether (20 mL) was added and the reaction was quenched by the addition of a cooled solution (0 °C) of saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted with ether (3 × 15 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The crude mixture ($E/Z = 28:1$, by ^1H NMR analysis) was purified by flash column chromatography (hexane/EtOAc 6:1) to provide pure compound **12** (202 mg, 80%) as a colorless oil. $[\alpha]_D^{20} = +5.2$ ($c = 1.5$, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 6.93$ (s, 1H), 6.58 (br s, 1H), 5.78–5.55 (m, 1H), 5.04–4.88 (m, 2H), 4.35 (dd, $J = 4.5$, 3.5 Hz, 1H), 3.78 (dd, $J = 5.5$, $J =$ 4.5 Hz, 1H), 2.71 (s, 3H), 2.28 (br s, 1 × OH), 2.22–2.08 (m, 1H), 2.08 (dd, $J = 0.9$ Hz, 3H), 1.62–1.25 (m, 8H), 1.52 (s, 3H), 1.49 (s, 3H), 1.09 (s, 3H), 1.01 (d, $J = 6.7$ Hz, 3H); EI HRMS: m/z: 393.2336 $[M]^+$, calcd for $C_{22}H_{35}NO_3S$: 393.2338.

Triol 29, **global O-deprotection of 12**: A 15% aqueous HCl solution (10 mL) was added to a solution of acetonide **12** (190 mg 0.48 mmol) in ethanol (20 mL) and the reaction mixture was stirred for 12 h at 25 °C. The reaction was quenched by the addition of ice-water (20 mL) and neutralised by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and ether (2 × 20 mL). The combined organic phases were then washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The crude mixture was purified by flash column chromatography (hexane/EtOAc 1:2) to provide triol **29** (168 mg, 99%) as a colorless oil. $[\alpha]_D^{20} = +8.1$ ($c = 1.6$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3384$ (br), 2955, 2865, 1452, 1374, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 6.90$ (s, 1H), 6.54 (br s, 1H), 5.74–5.57 (m, 1H), 4.97–4.83 (m, 2H), 4.41–4.31 (m, 1H), 3.72–3.63 (m, 1H), 2.64 (s, 3H), 2.17–2.03 (m, 1H), 1.98 (d, $J = 0.9$ Hz, 3H), 1.74–1.64 (m, 2H), 1.50–1.20 (m, 6H), 1.07 (s, 3H), 0.95 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 165.0$, 152.5, 144.8, 142.3, 118.7, 115.6, 112.5, 77.9, 77.2, 74.4, 38.9, 37.7, 37.2, 35.8, 21.4, 21.1, 20.2, 19.0, 14.4; EI HRMS: m/z: 353.2032 $[M]^+$, calcd for $C_{19}H_{31}NO_3S$: 353.2025.

Silyl ether 30, **monosilylation of 29**: Dry triethylamine (212 mg, 1.8 mmol) followed by triethylchlorosilane (68 mg, 0.45 mmol) was added to a cooled (0 °C) solution of triol **29** (160 mg, 0.45 mmol) in dry CH_2Cl_2 (25 mL). After stirring for 3 h at 25 °C, the reaction mixture was treated with additional TESCl (136 mg, 0.90 mmol) and the reaction mixture was stirred for an additional 16 h at 25 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The crude mixture was purified by flash column chromatography (hexane/EtOAc 3:1) to provide pure silyl ether **30** (192 mg, 90%) as a colorless oil. $[\alpha]_D^{20} = -4.7$ ($c = 1.5$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3451$ (br), 2956, 2910, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 6.93$ (s, 1H), 6.48 (br s, 1H), 5.73–5.57 (m, 1H), 4.96–4.82 (m, 2H), 4.41 (dd, $J = 8.5$, 4.8 Hz, 1H), 3.71 (br s, 1 × OH), 3.58 (dd, $J = 9.0$, 0.9 Hz, 1H), 2.68 (s, 3H); 2.15–2.02 (m, 1H), 1.99 (d, $J =$ 0.9 Hz, 3H), 1.75–1.62 (m, 2H), 1.50–1.20 (m, 6H), 1.05 (s, 3H), 0.98–0.87 (m, 12H), 0.68–0.55 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 164.5$, 152.6, 144.7, 141.5, 119.6, 115.6, 112.3, 79.9, 76.2, 74.0, 38.7, 37.7, 37.2, 37.1, 21.4, 21.0, 20.1, 19.1, 13.8, 6.7, 4.7; EI HRMS: m/z: 467.2896 $[M]^+$, calcd for $C_{25}H_{45}NO_3SSi$: 467.2889.

Mesylate 31, **monomesylation of 30**: Dry triethylamine (46 mg, 0.45 mmol) followed by methanesulfonyl chloride (44 mg, 0.38 mmol) was added to a cooled (−20 °C) solution of diol **31** (70 mg, 0.15 mmol) in dry CH_2Cl_2 (6 mL). After stirring for 3.5 h at −20 °C the reaction was quenched by addition of ice-water (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The crude mixture was purified by flash column chromatography (hexane/EtOAc 4:1 to 3:1) to provide unstable mesylate **32** (75 mg, 92%) as a colorless oil. ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 6.95$ (s, 1H), 6.56 (br s, 1H), 5.70–5.53 (m, 1H), 4.91–4.80 (m, 2H), 4.54 (dd, $J = 8.0$, 3.0 Hz, 1H), 4.36 (dd, $J = 8.5$, 5.0 Hz, 1H), 3.1 (s, 3H), 2.68 (s, 3H), 2.1 (br s, 1 × OH), 2.09–1.96 (m, 1H), 2.02 (d, $J = 1.1$ Hz, 3H), 1.81 (ddd, $J = 13.0$, 8.0, 5.0 Hz, 1H), 1.46–1.17 (m, 7H), 1.25 (s, 3H), 1.0–0.80 (m, 3 × TES-CH_3, 1 × Me, 12H), 0.67–0.52 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 164.5$, 152.4, 144.5, 141.6, 119.8, 116.4, 112.6, 86.2, 75.6, 74.1, 39.1, 38.9, 37.8, 37.8, 37.7, 37.1, 21.6, 20.4, 20.1, 13.0, 6.8, 4.7; EI HRMS: m/z: 545.2672 $[M]^+$, calcd for $C_{26}H_{47}O_5NS_2Si$: 545.2665.

Oxirane 32: Dry K_2CO_3 (36 mg, 0.26 mmol, 2.0 equiv) was added in portions at 25 °C to a solution of mesylate **31** (70 mg, 0.13 mmol) in dry MeOH (5 mL) and the mixture was stirred for 1 h at 25 °C. The reaction was quenched by the addition of ice-water (10 mL), ether (10 mL) and saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated. The crude mixture was purified by flash column chromatography (hexane/EtOAc 10:1) to provide pure oxirane **32** (53 mg, 90%) as a colorless oil. $[\alpha]_D^{20} = -7.6$ ($c = 0.25$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2956$, 2876, 1455, 1377, 1261, 1182, 1082, 1006, 962, 908, 739 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 6.91$ (s, 1H), 6.50 (br s, 1H), 5.74–5.58 (m, 1H), 4.99–4.85 (m, 2H), 4.32 (dd, $J = 8.9$, 3.7 Hz, 1H), 2.86 (dd, $J = 7.5$, 4.3 Hz, 1H), 2.68 (s, 3H), 2.17–2.02 (m, 1H), 2.01 (d, $J = 1.1$ Hz, 3H), 1.88 (ddd, $J = 13.9$, 8.9, 4.3 Hz, 1H), 1.59 (ddd, $J = 14.0$, 7.8, 4.3 Hz, 1H), 1.52–1.20 (m, 6H), 1.25 (s, 3H), 0.99–0.82 (m, 3 × TES-CH_3, 1 × Me, 12H), 0.66–0.55 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 164.8$, 153.1, 144.6, 142.3, 118.7, 115.3, 112.6, 76.2, 62.0, 61.7, 37.8, 36.8, 36.1, 33.1, 23.1, 20.1, 19.2, 14.1, 14.0, 6.8, 4.8; EI HRMS: m/z: 449.2784 $[M]^+$, calcd for $C_{25}H_{43}NO_2SSi$: 449.2774.

Aldehyde 7, **glycolization and cleavage of alkene 32**: *N*-Methylmorpholine-*N*-oxide (0.7M aqueous solution, 0.14 mL) followed by osmium tetroxide [0.13 mL, 0.04M solution (10 mg mL^{-1}) in *t*BuOH, ca. 5 mol%] was added at 0 °C to a cooled (0 °C) solution of alkene **33** (45 mg, 0.1 mmol) in a

  0947-6539/01/0710-2266 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10

mixture of THF and *t*BuOH (1:1, 1.5 mL). After stirring for 16 h at 25 °C the reaction was quenched by the addition of ice-water (5 mL), $Na_2S_2O_3$ (74 mg) and CH_2Cl_2 (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated. The crude mixture was filtered through silica gel (hexane/EtOAc 1:1), concentrated and redissolved in a 5:1 mixture of ethanol and water (6 mL). $NaIO_4$ (42 mg, 0.2 mmol) was added at 25 °C. After stirring for 1 h at 25 °C, the reaction was quenched with the addition of ice-water (5 mL), saturated aqueous $NaHCO_3$ solution (5 mL) and ether (10 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), concentrated and purified by flash column chromatography (hexane/EtOAc 4:1) to provide pure aldehyde **7** (28 mg, 62 % in two steps) as a colorless oil. $[\alpha]_D^{20} = -10.6$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2956, 2876, 1726, 1459, 1378, 1183, 1079, 1006, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.61$ (d, $J = 2.0$ Hz, 1H), 6.93 (s, 1H), 6.52 (s, 1H), 4.34 (dd, $J = 9.0$, 4.0 Hz, 1H), 2.89 (dd, $J = 7.0$, 4.5 Hz, 1H), 2.70 (s, 3H), 2.33–2.25 (m, 1H), 2.02 (s, 3H), 1.89 (ddd, $J = 14.0$, 9.0, 4.5 Hz, 1H), 1.74–1.66 (m, 1H), 1.60 (ddd, $J = 14.0$, 7.0, 4.0 Hz, 1H), 1.53–1.32 (m, 5H), 1.27 (s, 3H), 1.09 (d, $J = 7.0$ Hz, 1H), 0.94 (t, $J = 7.8$ Hz, 9H), 0.61 (q, $J = 7.8$ Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 205.2$, 164.9, 153.4, 142.6, 119.2, 115.8, 76.5, 62.4, 61.1, 46.7, 36.4, 33.3, 31.0, 23.2, 22.6, 19.6, 14.2, 13.7, 7.2, 5.2; EI HRMS: *m/z*: 451.2559 $[M]^+$, calcd for $C_{24}H_{41}NO_3SSi$: 451.2576.

Hydroxy ketone 35, **Hafner–Duthaler allylation**: A solution of allylmagnesium chloride (2.0 M solution in 5.5 mL THF, 11.0 mmol) was added slowly at 0 °C to a solution of titanium reagent **33** (7.36 g, 12.0 mmol) in dry ether (100 mL) and the mixture was stirred at 0 °C for 1.5 h. The reaction mixture then was cooled to −78 °C and keto aldehyde **34** (1.41 g, 11.0 mol), dissolved in ether (10 mL), was added. The mixture was stirred for additional 3 h at −78 °C, then ammonium fluoride (45 % solution in water, 50 mL) was added and the mixture was stirred at room temperature overnight. After filtration through celite and extraction with ether (2 × 50 mL), the combined organic phases were washed with brine (50 mL) dried and concentrated. The solid residue was stirred with pentane (50 mL), filtered and concentrated. Purification by flash column chromatography (silica gel, hexane/EtOAc/CH_2Cl_2 9:1:5) afforded hydroxy ketone **35** (1.14 g, 61 %) as a colorless oil, containing traces of chiral ligand (*ee* > 98 %, by chiral HPLC). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.85–5.79$ (m, 1H), 5.10–5.06 (m, 2H), 3.73 (dd, $J = 10.0$, 2.5 Hz, 1H), 2.54–2.38 (m, 3H), 2.24–2.17 (m, 1H), 2.03–1.95 (m, 1H), 1.14 (s, 3H), 1.10 (s, 3H), 0.98 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 217.2$, 135.6, 117.7, 75.5, 51.2, 36.3, 31.3, 21.7, 19.5, 7.8.

Silyl ether 8, **silylation of hydroxy ketone 35**: 2,6-Lutidine (0.70 mL, 6.0 mmol) and TBS triflate (1.15 mL, 5.0 mmol) were added at −78 °C to a solution of alcohol **35** (425 mg, 2.5 mmol) in dry CH_2Cl_2 (15 mL). After 1 h, saturated aqueous NH_4Cl solution (10 mL) was added and the mixture was allowed to warm to room temperature. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (silica gel, hexane/EtOAc 40:1) afforded silyl ether **8** (616 mg, 87 %) as a colorless oil. $[\alpha]_D^{20} = +3.6$ ($c = 2.08$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2957, 2886, 1706, 1472, 1090, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.74$ (m, 1H), 5.02–4.94 (m, 2H), 3.96 (dd, $J = 6.5$, 5.0 Hz), 2.48 (dq, $J = 11.3$, 7.0 Hz, 2H), 2.19–2.08 (m, 2H), 1.09 (s, 3H), 1.06 (s, 3H), 0.96 (t, $J = 7.0$ Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 215.8$, 136.2, 116.5, 76.7, 52.9, 39.0, 31.9, 26.0, 22.4, 20.2, 7.7, −3.6, −4.4; FI MS: *m/z*: 227 $[M - C_4H_9]^+$, 185, 83, 57; elemental analysis calcd for $C_{16}H_{32}O_2Si$ (284): C 67.54, H 11.34; found: C 67.78, H 11.24.

Hydroxy ketone 36, **aldol addition of ketone 8 and aldehyde 7**: Diisopropylamine (0.19 mL, 1.36 mmol) in dry THF (3.5 mL) was treated with *n*BuLi (0.84 mL, 1.6 M in hexane, 1.36 mmol) at −40 °C. After 20 min at 0 °C, the solution was cooled to −78 °C and ketone **8** (382 mg, 1.34 mmol), dissolved in THF (0.5 mL), was added dropwise (3 min). After stirring for 15 min at −78 °C and the mixture was allowed to warm to −40 °C over a period of 0.5 h. The mixture was cooled to −78 °C and aldehyde **7** (390 mg, 0.86 mmol), dissolved in THF (0.5 mL), was added dropwise (3 min). After 15 min at −78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl solution and ether (5 mL), the cooling bath was removed and water (5 mL) was added. The aqueous layer was extracted with ether (2 × 10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. Purification by column chromatography (silica gel, hexane/EtOAc 5:1) provided aldol product **36** (582 mg, 92 %, *ds* > 95:5, by ^1H NMR analysis) as a colorless oil. $[\alpha]_D^{20} = -17.0$ ($c = 1.05$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3502, 2956, 2877, 1683, 1472, 1082, 1003, 837, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.93$ (s, 1H), 6,52 (s, 1H), 5.78 (ddt, $J = 17.0$, 10.0, 7.0 Hz, 1H), 5.05–4.98 (m, 2H), 4.34 (dd, $J = 9.0$, 4.0 Hz, 1H), 3.93 (dd, $J = 6.5$, 4.5 Hz, 1H), 3.50 (s, 1H, OH), 3.31 (d, $J = 9.0$ Hz, 1H), 3.25 (q, $J = 7.0$ Hz, 1H), 2.89 (dd, $J = 7.5$, 4.5 Hz, 1H), 2.70 (s, 3H), 2.22–2.16 (m, 1H), 2.14–2.08 (m, 1H), 2.02 (s, 3H), 1.90 (ddd, $J = 14.0$, 9.0, 4.5 Hz, 1H), 1.81–1.74 (m, 1H), 1.61 (ddd, $J = 14.0$, 7.5, 4.0 Hz, 1H), 1.57–1.44 (m, 4H), 1.40–1.32 (m, 1H), 1.28 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 1.03 (d, $J = 7.0$ Hz, 1H, 0.95 (t, $J = 7.8$ Hz, 9H), 0.90 (s, 9H), 0.83 (d, $J = 6.5$ Hz, 3H), 0.62 (q, $J = 7.8$ Hz, 6H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 222.9$, 164.8, 153.5, 142.7, 136.7, 119.1, 117.1, 115.7, 76.9, 76.5, 75.3, 62.5, 61.4, 54.7, 41.5, 40.0, 36.4, 36.0, 33.8, 33.5, 26.4, 23.8, 23.1, 22.7, 19.8, 19.6, 18.6, 15.7, 14.4, 10.1, 7.2, 5.2, −3.1, −3.7; EI HRMS: *m/z*: 735.4773 $[M]^+$, calcd for $C_{40}H_{73}NO_5SSi_2$: 735.4748.

Trichloroethyl carbonate 37, **protection of alcohol 36**: A well stirred solution of aldol **36** (516 mg, 0.70 mmol) in dry CH_2Cl_2 (25 mL) and pyridine (1 mL) at 15 °C was treated with 2,2,2-trichloroethyl chloroformate (0.57 mL, 4.2 mmol). After stirring at 20 °C for 0.5 h, saturated aqueous $NaHCO_3$ solution (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexanes/EtOAc 10:1) provided **37** (580 mg, 91 %) as a pale yellow oil. $[\alpha]_D^{20} = -34.6$ ($c = 2.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2956, 2878, 1760, 1699, 1464, 1383, 1251, 1082, 992, 928, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.93$ (s, 1H), 6.52 (s, 1H), 5.77 (ddt, $J = 17.0$, 10.0, 7.0 Hz, 1H), 5.03–4.95 (m, 2H), 4.84 (d, $J = 12.0$ Hz, 1H), 4.81 (dd, $J = 7.5$, 4.5 Hz, 1H), 4.68 (d, $J = 12.0$ Hz, 1H), 4.33 (dd, $J = 9.0$, 3.5 Hz, 1H), 3.75 (dd, $J = 6.3$, 4.3 Hz, 1H), 3.44 (dq $J = 4.5$, 7.0 Hz, 1H), 2.88 (dd, $J = 7.5$, 4.5 Hz, 1H), 2.70 (s, 3H), 2.28–2.19 (m, 1H), 2.05–1.95 (m, 1H), 2.01 (d, $J = 1.0$ Hz, 3H), 1.87 (ddd, $J = 14.0$, 9.0, 4.5 Hz, 1H), 1.75–1.66 (m, 1H), 1.56 (ddd, $J = 14.0$, 7.5, 3.5 Hz, 1H), 1.54–1.38 (m, 4H), 1.30 (s, 3H), 1.28–1.22 (m, 1H), 1.26 (s, 3H), 1.20–1.10 (m, 1H), 1.07 (d, $J = 7.0$ Hz, 3H), 0.97–0.91 (t, $J = 8.0$ Hz, 9H+3H), 0.89 (s, 9H), 0.61 (q, $J = 8.0$ Hz, 6H), 0.06 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 216.0$, 164.8, 154.6, 153.4, 142.6, 136.8, 119.2, 117.0, 115.7, 95.2, 83.2, 78.5, 77.0, 76.5, 62.5, 61.1, 54.4, 42.7, 39.8, 36.4, 35.4, 33.7, 32.2, 26.5, 24.3, 23.1, 22.7, 20.4, 19.6, 18.6, 16.5, 14.4, 11.9, 7.2, 5.2, −3.3, −3.5; FAB HRMS: *m/z*: 1042.2865 $[M+Cs]^+$, calcd for $C_{43}H_{74}Cl_3NO_7SSi_2$: 909.3790.

Hydroxy aldehyde 38, **glycolization and cleavage of alkene 37**: OsO_4 (0.43 mL, 10 mg mL^{-1} in *t*BuOH, ≈5 mol %) and NMO (1.7 mL, 0.2 M in H_2O, 0.34 mmol) were added to a solution of alkene **37** (311 mg, 0.34 mmol) in THF (7.5 mL) and *t*BuOH (7.5 mL). The mixture was stirred for 16 h at room temperature, then $Na_2S_2O_3$ (0.25 g), water (25 mL) and CH_2Cl_2 (25 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was dissoved in hexane/ethyl acetate 1:1 and filtered through silica gel to give crude diol (302 mg), which was used without further purification. A solution of crude diol (302 mg) in ethanol (15 mL) and water (3 mL) was treated with sodium periodate (214 mg, 1.0 mmol) and stirred for 1 h at room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ solution (25 mL), diluted with water (25 mL) and extracted with ether (3 × 25 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (silica gel, hexanes/EtOAc 10:1 → 5:1) afforded aldehyde **38** (242 mg, 78 %) as a colorless oil. $[\alpha]_D^{20} = -43.4$ ($c = 1.00$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2956, 1759, 1726, 1698, 1464, 1383, 1252, 1083, 1003, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.74$ (s, 1H), 6.93 (s, 1H), 6.52 (s, 1H), 4.83 (d, $J = 12.0$ Hz, 1H), 4.74 (dd, $J = 7.5$, 4.0 Hz, 1H), 4.67 (d, $J = 12.0$ Hz, 1H), 4.36–4.31 (m, 2H), 3.44 (dq, $J = 4.5$, 6.5 Hz, 1H), 2.88 (dd, $J = 7.5$, 4.5 Hz, 1H), 2.70 (s, 3H), 2.67 (ddd, $J = 18.0$, 4.5, 1.0 Hz, 1H), 2.39 (ddd, $J = 18.0$, 5.0, 2.0 Hz, 1H), 2.02 (s, 3H), 1.86 (ddd, $J = 14.0$, 9.0, 4.5 Hz, 1H), 1.77–1.67 (m, 1H), 1.60–1.10 (m, 6H), 1.56 (ddd, $J = 14.0$, 7.5, 4.0 Hz, 1H), 1.33 (s, 3H), 1.26 (s, 3H), 1.06 (d, $J = 6.5$ Hz, 3H), 1.03 (s, 3H), 0.96 (d, $J = 6.5$ Hz, 3H), 0.94 (t, $J = 8.0$ Hz, 9H), 0.87 (s, 9H), 0.62 (q, $J = 8.0$ Hz, 6H), 0.11 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 215.8$, 200.8, 164.8, 154.6, 153.4, 142.6, 119.2, 115.8, 95.1, 82.7, 77.1, 76.5, 72.7, 62.5, 61.1, 53.8, 49.7, 42.6, 36.4, 35.3, 33.7, 32.3, 26.3, 23.4, 23.0,

22.5, 20.4, 19.6, 18.5, 16.4, 14.9, 11.6, −4.0, −4.1; EI HRMS: *m/z*: 854.2844 $[M-C_4H_9]^+$, calcd for $C_{42}H_{72}Cl_3NO_8SSi_2$: 911.3583.

Hydroxy aldehyde 38, **monodesilylation of 37**: In a polypropylene flask, a solution of the aldehyde **37** (204 mg, 0.22 mmol) in dry THF (4 mL) was treated with an HF/py stock solution (6 mL; prepared from 5 mL HF/pyridine complex, 15 mL pyridine and 10 mL THF). After stirring over a period of 20 min at room temperature, the reaction mixture was carefully added to a well stirred mixture of saturated aqueous $NaHCO_3$ solution (100 mL) and ether (20 mL). The layers were separated and the aqueous phase was extracted with ether (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (deactivated silica gel, hexanes/EtOAc 2:1 → 1:1) to give compound **38** (204 mg, 91%) as a pale yellow oil. $[\alpha]_D^{20} = -57.6$ ($c = 0.50$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2957, 1758, 1725, 1698, 1471, 1384, 1252, 1090, 992, 928, 838, 778\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.74$ (s, 1H), 6.95 (s, 1H), 5.70 (s, 1H), 4.84 (d, $J = 12.0$ Hz, 1H), 4.75 (dd, $J = 7.8$, 4.3 Hz, 1H), 4.68 (d, $J = 12.0$ Hz, 1H), 4.41–4.32 (m, 2H), 3.44 (dq, $J = 4.0$, 7.0 Hz, 1H), 2.96 (dd, $J = 8.0$, 4.0 Hz, 1H), 2.70 (s, 3H), 2.67 (dd, $J = 17.5$, 4.0 Hz, 1H), 2.40 (ddd, $J = 17.5$, 5.5, 2.0 Hz, 1H), 2.09 (d, $J = 3.5$ Hz, 1H), 2.06 (s, 3H), 1.94 (ddd, $J = 14.0$, 9.0, 4.0 Hz, 1H), 1.78–1.70 (m, 1H), 1.67 (ddd, $J = 14.0$, 8.0, 4.0 Hz, 1H), 1.58–1.42 (m, 4H), 1.38–1.15 (m, 2H), 1.34 (s, 3H), 1.28 (s, 3H), 1.07 (d, $J = 6.5$ Hz, 1H), 1.04 (s, 3H), 0.98 (d, $J = 7.0$ Hz, 1H), 0.87 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 215.8$, 200.9, 165.0, 154.6, 153.1, 142.1, 119.3, 116.2, 95.1, 82.7, 77.1, 75.8, 72.6, 62.2, 61.1, 53.8, 49.7, 42.6, 35.3, 34.5, 33.6, 32.3, 26.3, 23.4, 23.0, 22.5, 20.4, 19.6, 18.5, 16.4, 14.9, 11.6, −4.0, −4.1; FAB HRMS (CsI): *m/z*: 930.1764 $[M+Cs]^+$, calcd for $C_{36}H_{58}Cl_3NO_8SSi$: 797.2718.

Hydroxy acid 39, **Pinnick oxidation of aldehyde 38**: A solution of sodium chlorite (55 mg, 0.51 mmol) and NaH_2PO_4 (55 mg) in water (1 mL) was added to a solution of aldehyde **38** (151 mg, 0.188 mmol) in *t*BuOH (5 mL) and 2,3-dimethyl-2-butene. The mixture was stirred at room temperature for 45 min and quenched by addition of saturated aqueous NH_4Cl solution (10 mL) and water (10 mL). After extraction with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried ($MgSO_4$) and concentrated to give crude seco-acid **39** (148 mg) which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H), 6.75 (s, 1H), 4.91 (d, $J =$ 12.0 Hz, 1H), 4.77 (dd, $J = 8.5$, 4.0 Hz, 1H), 4.67 (d, $J = 12.0$ Hz, 1H), 4.47 (dd, $J = 7.5$, 2.0 Hz, 1H), 4.32 (t, $J = 7.0$ Hz, 1H), 3.46–3.38 (m, 1H), 2.85 (t, $J = 6.0$ Hz, 1H), 2.70 (s, 3H), 2.59 (dd, $J = 17.0$, 2.0 Hz,1H), 2.35 (dd, $J =$ 17.0, 7.5 Hz, 1H), 2.00 (s, 3H), 1.82–1.20 (m, 9H), 1.26 (s, 3H), 1.17 (s, 3H), 1.12 (d, $J = 6.5$ Hz, 3H), 1.11 (s, 3H), 1.04 (d, $J = 7.0$ Hz, 1H), 0.89 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H).

Lactone 40, **Yamaguchi cyclization of hydroxy acid 39**: Dry triethylamine (0.06 mL, 0.42 mmol) and 2,4,6-trichlorobenzoyl chloride (0.053 mL, 0.28 mmol) were added at 0 °C to a solution of crude seco-acid **39** (140 mg, 0.170 mmol) in dry toluene (1.5 mL). After stirring the mixture at room temperature for one hour, it was diluted with dry toluene (3.5 mL) and slowly added to a solution of DMAP (208 mg, 1.70 mmol) in toluene (95 mL) via syringe pump over a period of 1 h. After addition was completed, stirring was continued for 0.5 h, then the reaction mixture was concentrated to a ≈20 mL volume and filtered through silica gel. The solution was concentrated and purified by column chromatography (silica gel, hexane/EtOAc 4:1) to provide lactone **40** (88 mg, 65%) as a colorless oil. $[\alpha]_D^{20} = +4.8$ ($c = 1.00$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2958, 2934, 1760, 1698, 1464, 1380, 1248, 1158, 1100, 1067, 930, 827, 778\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.99$ (s, 1H), 6.56 (s, 1H), 5.21–5.14 (m, 2H), 4.87 (d, $J = 12.0$ Hz, 1H), 4.75 (d, $J = 12$ Hz, 1H), 4.05 (d, $J = 9.8$ Hz, 1H), 3.30 (dq, $J = 10.2$, 6.3 Hz, 1H), 2.82 (dd, $J = 10.3$, 4.0 Hz, 1H), 2.79 (dd, $J = 16.5$, 1.5 Hz, 1H), 2.71 (s, 3H), 2.64 (dd, $J = 16.5$, 10.0 Hz, 1H), 2.25–2.21 (m, 1H), 2.11 (s, 3H), 1.93–1.64 (m, 4H), 1.55–1.42 (m, 2H), 1.32–1.24 (m, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.16–1.08 (m, 1H), 1.12 (d, $J =$ 6.7 Hz, 3H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.88 (s, 9H), 0.16 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (150.1 MHz, $CDCl_3$): $\delta = 212.8$, 171.2, 165.2, 155.0, 95.2, 86.7, 77.9, 77.0, 76.5, 63.1, 62.3, 53.8, 46.1, 39.6, 35.5, 34.5, 31.9, 31.6, 26.5, 25.5, 24.5, 24.2, 23.0, 19.6, 19.5, 19.0, 16.7, 14.7, −3.1, −5.3; EI HRMS: *m/z*: 795.2541 $[M]^+$, calcd for $C_{36}H_{56}Cl_3NO_8SSi$: 795.2562.

Hydroxy lactone 41: Zinc powder (200 mg) and NH_4Cl (200 mg) were added to a solution of lactone **40** (32 mg, 0.040 mmol) in dry ethanol (3 mL). After refluxing over a period of 20 min, the mixture was cooled to room temperature, diluted with EtOAc (10 mL) and filtered through celite. The solution was concentrated and purified by flash column chromatography (silica gel, hexane/EtOAc 2:1 → 1:1) to give **41** (23 mg, 92%) as a colorless oil. $[\alpha]_D^{20} = -38.2$ ($c = 1.02$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3524, 2935, 1745, 1695, 1463, 1380, 1256, 1196, 1158, 1100, 1068, 978, 837, 777, 757\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H), 6.55 (s, 1H), 5.17 (br d, $J = 10.0$ Hz, 1H), 4.07 (dd, $J = 10.0$, 2.0 Hz, 1H), 3.88 (dd, $J = 6.0$, 2.5 Hz, 1H), 3.07 (qn, $J = 6.7$ Hz, 1H), 2.82–2.75 (m, 2H), 2.70 (s, 3H), 2.66 (dd, $J = 16.0$, 10.0 Hz, 1H), 2.37 (br s, 1H), 2.20 (ddd, $J = 15.0$, 3.0, 2.0 Hz, 1H), 2.10 (s, 3H), 1.87 (dt, $J = 15.0$, 10.0 Hz, 1H), 1.80–1.70 (m, 2H), 1.52–1.20 (m, 5H), 1.28 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H), 1.14 (d, $J = 6.5$ Hz, 3H), 1.03 (d, $J = 7.0$ Hz, 3H), 0.86 (s, 9H), 0.14 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 216.8$, 171.3, 165.2, 152.6, 137.8, 120.9, 117.0, 77.8, 76.4, 75.3, 63.3, 62.3, 53.8, 45.3, 39.8, 37.5, 34.3, 32.3, 32.1, 26.4, 25.0, 24.4, 23.6, 22.9, 19.6, 19.0, 18.7, 15.4, 15.1, −3.2, −5.2; EI HRMS: *m/z*: 621.3531 $[M]^+$, calcd for $C_{33}H_{35}NO_6SSi$: 621.3519.

Epothilone B (1): In a polypropylene flask, a solution of **41** (10.5 mg, 0.017 mmol) was dissolved in dry pyridine (1.6 mL) and treated with HF/pyridine complex (0.4 mL). After stirring over a period of 7 d at 35 °C, the reaction mixture was carefully added to a well stirred mixture of saturated aqueous $NaHCO_3$ solution (25 mL) and ether (15 mL). The layers were separated and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica gel, hexanes/EtOAc 2:1 → 1:1) to give epothilone B (5.8 mg, 67%) as a colorless oil, which crystallized upon standing (m.p. 90–92 °C). $[\alpha]_D^{20} = -35.5$ ($c = 0.20$, MeOH); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H), 6.59 (s, 1H), 5.41 (dd, $J = 7.8$, 2.8 Hz, 1H), 4.26–4.21 (m, 1H), 4.18 (br d, $J = 6.0$ Hz, 1H; OH), 3.77 (dd, $J = 5.5$, 3.5 Hz, 1H), 3.30 (dq, $J = 4.2$, 6.8 Hz, 1H), 2.81 (dd, $J = 7.5$, 4.5 Hz, 1H), 2.70 (s, 3H), 2.65 (br s, 1H, OH), 2.54 (dd, $J = 14.0$, 10.2 Hz, 1H), 2.37 (dd, $J = 14.0$, 3.0 Hz, 1H), 2.11 (dd, $J = 3.5$, 4.5 Hz), 2.09 (s, 3H), 1.92 (ddd, $J = 15.6$, 7.8, 7.6 Hz, 1H), 1.77–1.68 (m, 2H), 1.54–1.46 (m, 2H), 1.45–1.37 (m, 3H), 1.37 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H), 1.16 (d, $J = 6.8$ Hz, 3H), 1.08 (s, 3H), 1.00 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 220.6$, 170.6, 165.1, 151.8, 137.5, 119.7, 116.1, 76.7, 74.1, 72.9, 61.6, 61.3, 53.1, 42.9, 39.2, 36.4, 32.3, 32.0, 30.8, 22.7, 22.3, 21.4, 19.7, 19.1, 17.0, 15.8, 13.6.

Alcohol 44, **reduction of 43**: A cooled (0 °C) solution of methyl ester **43** (Schering, ZK 204027, 3.0 g, 14 mmol) in ether (200 mL) was treated portionwise with $LiAlH_4$ (531 mg, 14 mmol). The reaction mixture was stirred for 3.5 h at 25 °C and then quenched by dropwise addition of ice-water (50 mL) and saturated aqueous NH_4Cl solution (50 mL). The phases were separated, the aqueous phase was extracted twice with ether, and the combined organic phases were washed with brine (30 mL) and dried over $MgSO_4$. Purification by flash column chromatography (hexane/EtOAc 5:1) gave the alcohol **44** (2.53 g, 97%) as a colorless liquid. $[\alpha]_D^{20} = -13.7$ ($c =$ 6.1, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3453$ (br), 2937, 1464, 1415, 1332, 1276, 1178, 1095, 1031, 949 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 3.97-3.91$ (m, 4H), 3.59 (dd, $J = 11.2$, 5.3 Hz, 1H), 3.44 (dd, $J = 11.2$, 6.2 Hz, 1H), 2.87 (dd, $J = 5.9$, 5.5 Hz, 1H), 1.75–1.28 (m, 8H), 0.98 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 113.8$, 68.8, 64.5, 64.3, 41.9, 33.3, 30.5, 23.5, 20.5, 18.7; elemental analysis calcd for $C_{10}H_{18}O_3$ (186): C 64.49; H 9.74; found: C 64.26, H 9.87.

Aldehyde 45, **Swern oxidation of 44**: DMSO (3.25 mL, 42.9 mmol, 3.75 equiv) was added dropwise at −78 °C to a solution of oxalyl chloride (1.3 mL, 14.3 mmol) in CH_2Cl_2 (40 mL). After stirring for 15 min at −78 °C, a solution of the above alcohol **44** (2.13 g, 11.44 mmol), dissolved in dry CH_2Cl_2 (20 mL), was added dropwise at −78 °C. The solution was stirred for 15 min, then DIPEA (13 mL, 75.6 mmol) was added. After 10 min the mixture was allowed to warm to 0 °C over a 1 h. The mixture was diluted with CH_2Cl_2 (60 mL) and quenched by addition of ice-water (60 mL) and saturated aqueous NH_4Cl solution (30 mL). The phases were separated, the aqueous phase was extracted twice with CH_2Cl_2, and the combined organic phases were washed with brine (30 mL) and dried over $MgSO_4$. After filtration through a short pad of silica gel (hexane/EtOAc 10:1), the solvent was removed under reduced pressure and the unstable crude aldehyde **45** (1.9 g, 90%) was subjected to the next reaction without further purification. IR (thin film): $\tilde{\nu}_{max} = 3262$ (br), 2939, 1722, 1461, 1353, 1277, 1182, 1044, 1018, 991 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 9.7$ (s, 1H), 4.05–3.90 (m, 4H), 2.05–1.90 (m, 1H), 1.80–1.40 (m, 8H), 1.1 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 205.7$, 110.8, 65.1, 64.7, 53.7, 32.2, 31.2, 23.3, 20.8, 16.3.

Alcohol 46, **Brown allylation**: A solution of $MgBr_2 \cdot Et_2O$ (3.1 mL, 1M solution in ether, 3.1 mmol) was added to a cooled solution (−78 °C) of

0947-6539/01/0710-2268 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10

(−)-DIPCl (Aldrich No. 31,702–0, 988 mg, 3.08 mmol) in dry ether (20 mL). The reaction mixture was stirred for 30 min, and then warmed to room temperature without removing the precipitated magnesium salts. The suspension was cooled to −78 °C and the above aldehyde **45** (474 mg, 2.57 mmol), dissolved in dry THF (3 mL), was added dropwise with stirring over a period of 3 h. The magnesium salts were removed, the mixture was treated with 3 N NaOH (3 mL, 9 mmol) and 30 % H_2O_2 (1.2 mL) and then stirred at 50 °C overnight. The organic layer was separated and washed with saturated aqueous NH_4Cl solution (50 mL) and brine (20 mL), and dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (hexane/EtOAc 10:1) to give 283 mg a mixture of epimers in ca. 6:1 ration (by ^{1}H NMR analysis). The mixture was dissolved in acetone/water 3:2 (30 mL) and treated with *p*-TsOH·H_2O (30 mg) at 25 °C. The reaction mixture was stirred overnight and quenched by addition of saturated aqueous $NaHCO_3$ solution (10 mL) and ether (20 mL). The organic layer was separated and the aqueous phase was extracted with ether (5 × 20 mL). The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure, and the crude mixture was purified by flash column chromatography (hexane/EtOAc 5:1). The mixture of epimers was separated by HPLC (Supersphere Si60, 241 × 16 mm, 15 % EtOAc in hexane, 20 mL min^{-1}, UV_{254}, 10.0 min for **46** and 11.0 min for ***epi*-46**) to give pure 202 mg **46** und 33 mg ***epi*-46** (50 % yield in two steps).

(*S*,*R*)-Isomer 46: $[\alpha]_D^{20} = -10.2$ ($c = 1.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3483$ (br), 2938, 1699, 1452, 1054, 910, 610 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.98-5.78$ (m, 1H), 5.18–5.01 (m, 2H), 3.91 (ddd, $J = 9.8$, 4.6, 3.2 Hz, 1H), 2.55–1.50 (m, 10 H, 1 × OH), 1.11 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 216.9$, 136.2, 116.9, 73.8, 53.0, 39.2, 35.0, 32.7, 26.6, 20.7, 20.0; EI HRMS: *m*/*z*: 182.1312 $[M]^+$, calcd for $C_{11}H_{18}O_2$: 182.1307.

(*R*,*R*)-Isomer *epi*-46: $[\alpha]_D^{20} = -55.4$ ($c = 1.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} =$ 3483 (br), 2938, 1699, 1452, 1054, 910, 610 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.99-5.80$ (m, 1H), 5.14–5.02 (m, 2H), 3.83 (dt, $J = 10.0$, 3.0 Hz, 1H), 3.18 (d, $J = 3.0$ Hz, 1 × OH), 2.58–2.42 (m, 1H), 2.37–2.50 (m, 1H), 2.24–1.50 (m, 8H), 1.16 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 218.3$, 136.1, 116.8, 74.7, 52.2, 38.9, 36.2, 34.9, 27.2, 20.8, 16.8; EI HRMS: *m*/*z*: 182.1313 $[M]^+$, calcd for $C_{11}H_{18}O_2$: 182.1307.

Silyl ether 47: 2,6-Lutidine (1.0 mL, ca. 8.7 mmol) and TBS triflate (1.35 mL, 5.86 mmol) were added sequentially to a cooled (0 °C) solution of **46** (534 mg, 2.93 mmol) in dry CH_2Cl_2 (30 mL). After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (hexane/EtOAc 30:1) to give **47** as colorless liquid (834 mg, 96 %). $[\alpha]_D^{20} = +99.5$ ($c = 2.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} =$ 2934, 2857,1707, 1471, 1462, 1252, 1094, 911 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.87-5.69$ (m, 1H), 5.04–4.93 (m, 2H), 4.22 (dd, $J = 6.4$, 5.0 Hz, 1H), 2.36–2.27 (m, 2H), 2.20–2.07 (m, 3H), 1.93–1.55 (m, 4H), 1.47–1.35 (m, 1H), 0.98 (s, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 214.9$, 136.3, 116.9, 73.5, 54.8, 40.0, 38.0, 34.8, 26.9, 26.0, 20.8, 18.6, 18.3, −3.6, −4.3; EI HRMS: *m*/*z*: 296.2161 $[M]^+$, calcd for $C_{17}H_{32}O_2Si$: 296.2172.

Hydroxy ketones 48, aldol addition of ketone 47 and aldehyde 7: A solution of ketone **47** (241 mg, 0.81 mmol) in dry THF (0.5 mL) was added dropwise to a freshly prepared solution of LDA [2.7 mL, 0.81 mmol; *n*BuLi (1.55 mL, 1.6 M solution in hexanes, 2.5 mmol) was added to diisopropylamine (0.35 mL, 2.5 mmol) in 6.1 mL dry THF at 0 °C] at −78 °C. After stirring for 10 min, the solution was allowed to warm to −40 °C, and after 30 min at that temperature, it was recooled to −78 °C. A solution of aldehyde **7** (244 mg, 0.54 mmol) in dry THF (0.5 mL) was added dropwise. The resulting mixture was stirred for 10 min at −78 °C and then quenched by slow addition of saturated aqueous NH_4Cl solution (3 mL). The reaction mixture was warmed to 0 °C, and ether (5 mL) was added, followed by addition of ice-water (5 mL). The organic layer was separated, and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic phases was dried over $MgSO_4$ and concentrated under reduce pressure to afford a mixture of aldol products (6*R*,7*R*)-isomer **48** and one isomer in a ca. 4:1 ratio (78 %, by ^{1}H NMR analysis). Purification by flash column chromatography (hexane/EtOAc 10:1) and HPLC [Supersphere Si60-4, 241 × 16 mm, 13 % EtOAc in hexane, 20 mL min^{-1}, UV_{254}, 8.0 min for (6*R*,7*R*)-isomer **48** and 12.2 min for its isomer] gave pure **48** (201 mg), 52 mg of its isomer and 50 mg unreacted aldehyde **7**.

(6*R*,7*R*)-Hydroxy ketone 48: $[\alpha]_D^{20} = +19.0$ ($c = 0.7$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} =$ 3105 (br), 2957, 2757, 2708, 1726, 1505, 1459, 1378, 1240, 1005 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.90$ (s, 1H), 6.5 (br s, 1H), 5.82–5.63 (m, 1H), 5.04–4.92 (m, 2H), 4.31 (dd, $J = 8.7$, 3.7 Hz, 1H), 4.19 (dd, $J = 6.6$, 4.8 Hz, 1H), 3.76–3.65 (m, 1H), 3.16 (d, $J = 3.2$ Hz, 1 × OH), 2.85 (dd, $J =$ 7.3, 4.3 Hz, 1H), 2.67 (s, 3H), 2.55–2.41 (m, 1H), 2.30–1.78 (m, 6H), 1.99 (d, $J = 1.4$ Hz, 3H), 1.65–1.20 (m, 11H), 1.25 (s, 3H), 0.90–0.79 (m, (1 × TBS-*t*Bu, 3 × TES-CH_3, 2 × Me, 24H), 0.65–0.52 (m, 6H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 219.1$, 164.4, 153.1, 142.3, 135.4, 118.7, 117.7, 115.3, 76.1, 73.0, 72.8, 62.1, 61.0, 56.2, 51.6, 38.6, 37.2, 36.1, 34.4, 33.6, 33.2, 30.7, 26.0, 23.2, 22.3, 20.1, 19.2, 18.3, 16.7, 14.0, 12.5, 6.8, 4.8, −3.4, −4.2; EI HRMS: *m*/*z*: 747.4722 $[M]^+$, calcd for $C_{41}H_{73}NO_5SSi_2$: 747.4748.

Trichloroethyl carbonate 49, protection of alcohol 48: A solution of alcohol **48** (106 mg, 0.14 mmol) in dry CH_2Cl_2 (5 mL) was treated with dry pyridine (0.25 mL) and TrocCl (0.1 mL, 0.74 mmol) at 0 °C. After stirring for 40 min at 25 °C, the reaction mixture was quenched by addition of ice-water (10 mL), saturated aqueous $NaHCO_3$ solution (5 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (hexane/EtOAc/CH_2Cl_2 5:0.3:2) gave pure **49** (127 mg, 98 %) as a colorless oil: $[\alpha]_D^{20} = +35.64$ ($c = 0.55$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} =$ 2954, 1765, 1711, 1461, 1378 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.9$ (s, 1H), 6.49 (br s, 1H), 5.82–5.64 (m, 1H), 5.18 (dd, $J = 9.1$, 1.8 Hz, 1H), 5.10–4.97 (m, 2H), 4.72 (s, 2H), 4.31 (dd, $J = 9.1$, 3.4 Hz, 1H), 4.20 (dd, $J = 6.6$, 5.0 Hz, 1H), 2.86 (dd, $J = 7.5$, 4.1 Hz, 1H), 2.82–2.69 (m, 1H), 2.67 (s, 3H), 2.30–1.74 (m, 6H), 2.00 (d, $J = 1.1$ Hz, 3H), 1.68–1.12 (m, 11H), 1.25 (s, 3H), 0.97–0.83 (m, (1 × TBS-*t*Bu, 3 × TES-CH_3, 2 × Me, 24H), 0.66–0.53 (m, 6H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 212.8$, 164.4, 153.9, 153.1, 142.3, 135.2, 118.7, 117.9, 115.3, 94.9, 79.2, 76.5, 76.2, 72.9, 62.1, 60.9, 56.2, 50.0, 38.7, 37.9, 36.0, 33.7, 33.1, 30.9, 29.7, 25.9, 23.2, 22.3, 20.5, 19.2, 18.3, 16.4, 14.0, 12.8, 6.8, 4.8, −3.4, −4.2; EI HRMS: *m*/*z*: 921.3813 $[M]^+$, calcd for $C_{44}H_{74}Cl_3NO_7SSi_2$: 921.3790.

Aldehyde 50, glycolization and cleavage of alkene 49: *N*-Methylmorpholine-*N*-oxide (0.7 M aqueous solution, 0.3 mL) followed by osmium tetroxide [0.26 mL, 0.04 M solution (10 mg mL^{-1}) in *t*BuOH, ca. 5 mol %] was added at 0 °C to a cooled (0 °C) solution of alkene **49** (190 mg, 0.206 mmol) in a mixture of THF and *t*BuOH (1:1, 4 mL). After stirring for 16 h at 25 °C the reaction was quenched by the addition of ice-water (10 mL), $Na_2S_2O_3$ (148 mg) and CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The crude mixture was filtered through silica gel (hexane/EtOAc 1:1), concentrated and redissolved in a 5:1 mixture of ethanol and water (15 mL). $NaIO_4$ (84 mg, ≈0.2 mmol) was added at 25 °C. After stirring for 1 h at 25 °C the reaction was quenched with the addition of ice-water (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL) and ether (20 mL). The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), concentrated and purified by flash column chromatography (hexane/EtOAc 9:1) to provide pure aldehyde **50** (120 mg, 64 % in two steps) as a colorless oil. $[\alpha]_D^{20} = +33.0$ ($c = 1.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} =$ 2954, 1765, 1711, 1461, 1378 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 9.71$ (d, $J = 0.9$ Hz, 1 × CHO), 6.91 (s, 1H), 6.50 (br s, 1H), 5.12 (dd, $J = 9.4$, 2.3 Hz, 1H), 4.93 (dd, $J = 5.5$, 3.7 Hz, 1H), 4.81 (d, $J = 12.1$ Hz, 1H), 4.61 (d, $J = 11.9$ Hz, 1H), 4.31 (dd, $J = 8.9$, 3.7 Hz, 1H), 2.86 (dd, $J = 7.5$, 4.1 Hz, 1H), 2.8–2.69 (m, 1H), 2.67 (s, 3H), 2.57 (dd, $J = 5.7$, 1.4 Hz, 0.3H), 2.49 (dd, $J = 5.7$, 1.4 Hz, 0.7H), 2.36 (d, $J =$ 3.7 Hz, 0.7H), 2.28 (d, $J = 3.7$, 0.3H), 2.28–2.16 (m, 1H), 2.07–1.83 (m, 3H), 2.00 (d, $J = 1.4$ Hz, 3H), 1.74–1.12 (m, 11H), 1.25 (s, 3H), 0.98–0.79 (m, 1 × TBS-*t*Bu, 3 × TES-CH_3, 2 × Me, 24H), 0.65–0.53 (m, 6H), 0.14 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 213.0$, 199.9, 164.4, 153.8, 153.1, 142.3, 118.7, 115.3, 94.9, 79.5, 76.5, 76.2, 65.2, 62.1, 60.9, 55.9, 50.3, 48.5, 36.8, 36.0, 33.6, 33.1, 30.2, 29.7, 25.8, 23.1, 22.3, 20.6, 19.2, 18.1, 16.5, 14.0, 12.8, 6.8, 4.8, −4.6, −4.8; EI HRMS: *m*/*z*: 923.3554 $[M]^+$, calcd for $C_{43}H_{72}Cl_3NO_8SSi_2$: 923.3583.

Hydroxy aldehyde 51, monodesilylation of 50: A solution of **50** (90 mg, 0.097 mmol) in dry THF (4 mL) was treated with a stock solution of HF/py (3 mL) [prepared from HF/pyridine complex (5 mL), dry pyridine (15 mL)

and dry THF (10 mL)]. After stirring for 20 min at 25 °C, the reaction mixture was cooled at 0 °C and quenched by addition of saturated aqueous $NaHCO_3$ solution (50 mL) and ether (10 mL). The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The crude mixture was filtered through silica gel (hexane/EtOAc 2:1) and gave compound **51** (68 mg, 88 %) as a colorless oil. $[\alpha]_D^{20} = +33.9$ ($c = 1.25$, $CHCl_3$); $R_f = 0.23$ (2.5 % MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3396$(br), 2955, 2932, 2857, 1765, 1711, 1507, 1379 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 9.71$ (d, $J = 0.9$ Hz, 1 × CHO), 6.93 (s, 1H), 6.58 (br s, 1H), 5.14 (dd, $J =$ 9.1, 2.1 Hz, 1H), 4.92 (dd, $J = 5.5$, 3.2 Hz, 1H), 4.79 (d, $J = 11.9$ Hz, 1H), 4.61 (d, $J = 11.9$ Hz, 1H), 4.40 – 4.30 (m, 1H), 2.93 (dd, $J = 7.8$, 4.3 Hz, 1H), 2.80 – 2.69 (m, 1H), 2.67 (s, 3H), 2.57 (dd, $J = 5.7$, 1.4 Hz, 0.3H), 2.49 (dd, $J = 5.7$, 1.4 Hz, 0.7 Hz), 2.36 (d, $J = 3.4$ Hz, 0.7H), 2.28 (d, $J = 3.4$, 0.3H), 2.26 – 2.15 (m, 1H, 1 × OH), 2.05 (d, $J = 1.1$ Hz, 3H), 2.03 – 1.89 (m, 3H), 1.74 – 1.12 (m, 11H), 1.25 (s, 3H), 0.95 – 0.80 (m, 1 × TBS-*t*Bu, 2 × Me, 15H), 0.13 (s, 3H), − 0.02 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 213.0$, 199.9, 164.6, 153.9, 152.8, 141.8, 118.8, 115.7, 94.6, 79.3, 76.5, 75.4, 65.2, 61.9, 60.9, 55.9, 50.3, 48.6, 36.8, 36.1, 33.7, 33.7, 33.2, 30.3, 25.8, 23.3, 22.1, 20.6, 19.2, 18.1, 16.5, 14.6, 13.0, − 4.3, − 4.8; EI HRMS: m/z: 809.2685 $[M]^+$, calcd for $C_{37}H_{58}Cl_3NO_8SSi$: 809.2718.

Lactone 52, **Pinnick oxidation and Yamaguchi macrolactonization**: A solution of $NaClO_2$ (21 mg, 0.23 mmol) and NaH_2PO_4 (21 mg) in water (0.5 mL) was added to a solution of hydroxy aldehyde **51** (57 mg, 0.07 mmol) in *t*BuOH/2,3-dimethyl-but-2-ene (1:1, 4.4 mL) and the reaction was stirred for 2 h at 25 °C. The solution was concentrated under reduced pressure and subjected to flash column chromatography (silica gel, 2.5 % MeOH in CH_2Cl_2) to give seco-acid (28 mg, 48 %) as a colorless oil: $R_f = 0.12$ (2.5 % MeOH in CH_2Cl_2). A solution of the above seco-acid (28 mg, 0.034 mmol) in dry toluene (1 mL) was treated at 0 °C with dry Et_3N (0.14 mmol) and 2,4,6-trichlorobenzoyl chloride (0.07 mmol). The reaction mixture was stirred at 0 °C for 1 h and then added (over 3 h) to a solution of DMAP (50 mg, 0.3 mmol) in dry toluene (100 mL) at 25 °C and stirred at that temperature for 30 min. The reaction mixture was concentrated under reduced pressure to a small volume and filtered through silica gel. The residue was washed with 40 % EtOAc in hexane (20 mL), and the resulting solution was concentrated. Purification by flash column chromatography (hexane/EtOAc 5:1) furnished lactone **52** (10 mg, 36 %) as a colorless oil. $[\alpha]_D^{20} = +7.2$ ($c = 0.5$, $CHCl_3$); $R_f = 0.43$ (hexane/EtOAc 4:1); IR (thin film): $\tilde{\nu}_{max} = 2925$, 2854, 1755, 1709, 1656, 1379, 1250, 1111 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 6.99$ (s, 1H), 6.55 (br s, 1H), 5.31 (t, $J = 7.0$ Hz, 1H), 4.85 (d, $J = 12.1$ Hz, 1H), 4.68 (d, $J = 12.0$ Hz, 1H), 4.61 (t, $J = 5.5$ Hz, 1H), 4.44 (dd, $J = 10.3$, 2.3 Hz, 1H), 3.18 – 3.07 (m, 1H), 2.75 – 2.67 (m, 1H), 2.69 (s, 3H), 2.48 – 2.00 (m, 4H), 2.39 (dd, $J = 5.3$, 3.7 Hz, 2H), 2.16 (d, $J = 1.4$ Hz, 3H), 1.96 – 1.12 (m, 11H), 1.25 (s, 3H), 0.98 – 0.80 (m, 1 × TBS-*t*Bu, 2 × Me, 15H), 0.01 (s, 3H), − 0.02 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 210.2$, 170.7, 164.8, 155.2, 152.1, 135.8, 122.6, 117.1, 94.9, 85.2, 79.0, 76.7, 68.7, 61.8, 61.0, 56.0, 48.1, 39.5, 37.1, 36.2, 33.8, 32.2, 31.9, 29.4, 25.8, 25.5, 22.7, 22.0, 19.3, 18.2, 16.3, 14.8, 14.1, − 4.0, − 4.6; EI HRMS: m/z: 807.2587 $[M]^+$, calcd for $C_{37}H_{56}Cl_3NO_8SSi$: 807.2561.

Hydroxy lactone 53, **Troc-deprotection of 52**: A solution of **52** (8.0 mg, 0.01 mmol) in dry EtOH (2 mL) was treated with Zn powder (40 mg) and NH_4Cl (40 mg) at a rate sufficient to maintain a gentle reflux for 30 min. EtOAc (5 mL) was added at 0 °C and the mixture was filtered through silica gel. The resulting solution was concentrated under reduced pressure. Purification by flash column chromatography (hexane/EtOAc 3:1 → 2:1) gave pure product **53** (6 mg, 95 %). $[\alpha]_D^{20} = +22.0$ ($c = 0.7$, $CHCl_3$); $R_f = 0.14$ (hexane/EtOAc 4:1); ^1H NMR (250 MHz, $CDCl_3$): $\delta = 6.99$ (s, 1H), 6.56 (br s, 1H), 5.38 (t, $J = 7.0$ Hz, 1H), 4.66 (t, $J = 5.5$ Hz, 1H), 3.03 – 2.89 (m, 1H), 2.84 (dd, $J = 7.0$, 2.2 Hz, 1H), 2.78 (br s, 1 × OH), 2.76 – 2.71 (m, 1H), 2.70 (s, 3H), 2.35 (t, $J = 5.7$ Hz, 2H), 2.31 – 2.10 (m, 2H), 2.16 (d, $J = 1.2$ Hz, 3H), 2.09 – 1.99 (m, 2H), 1.93 – 1.18 (m, 11H), 1.25 (s, 3H), 1.04 (d, $J =$ 6.4 Hz, 3H), 0.93 (s, 3H), 0.89 – 0.78 (s, 9H), 0.00 (s, 3H), − 0.03 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 217.3$, 170.5, 164.8, 152.1, 136.0, 122.5, 117.0, 79.5, 78.7, 69.1, 62.1, 61.1, 56.6, 49.2, 39.7, 38.5, 38.3, 33.2, 32.5, 31.9, 29.4, 25.9, 25.6, 22.7, 22.0, 19.2, 18.3, 16.0, 14.7, 14.1, − 3.9, − 4.6; EI HRMS: m/z: 633.3536 $[M]^+$, calcd for $C_{34}H_{55}NO_8SSi$: 633.3519.

Epothilone B analogue 42, **desilylation of 53**: A solution of silyl ether **53** (5 mg, 0.008 mmol) in dry pyridine (1 mL) was treated with 0.5 mL of a stock solution of HF/py [prepared from HF/pyridine complex (0.4 mL) and dry pyridine (0.6 mL)]. After stirring for 4 d at 40 °C, the reaction mixture was cooled at 0 °C and quenched by addition of saturated aqueous $NaHCO_3$ solution (10 mL) and ether (5 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (hexane/EtOAc 1:1 → 1:2) and HPLC (Supersphere Si60-4, 250 × 4 mm, 10 % *i*PrOH in hexane, 2 mL min^{-1}, UV_{254}, 8.0 min) furnished lactone **42** (1.9 mg, 50 %) as a colorless wax. $[\alpha]_D^{20} = +8.1$ ($c = 0.25$, $CHCl_3$); $R_f = 0.44$ (hexane/EtOAc 1:2); ^1H NMR (250 MHz, $CDCl_3$): $\delta = 6.94$, (s, 1H), 6.58 (br s, 1H), 5.28 (d, $J = 3.2$ Hz, 1H), 4.83 – 4.76 (m, 1H), 3.97 (d, $J = 5.5$ Hz, 1H), 3.17 (d, $J = 3.0$ Hz, 1H), 2.95 – 2.83 (m, 1H), 2.79 (dd, $J = 9.7$, 2.2 Hz, 1H), 2.65 (s, 3H), 2.38 (dd, $J = 9.0$, 2.3 Hz, 1H), 2.20 (dd, $J = 9.0$, 4.4 Hz, 1H), 2.12 – 1.90 (m, 2H), 2.03 (d, $J = 1.1$ Hz, 3H), 1.80 – 1.40 (m, 14H), 1.25 (s, 3H), 1.07 (d, $J = 6.6$ Hz, 3H), 0.9 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$ 218.5, 170.5, 165.6, 153.0, 139.6, 119.0, 115.4, 78.7, 76.1, 68.4, 63.0, 62.0, 56.0, 49.2, 38.9, 38.7, 38.0, 36.3, 34.3, 32.9, 32.7, 25.1, 22.1, 20.7, 18.9, 17.7, 16.0, 15.3; EI HRMS: m/z: 519.2667 $[M]^+$, calcd for $C_{28}H_{41}NO_6S$: 519.2655.

Acknowledgement

Financial support by the Austrian Science Foundation (FWF) (Project P-12677-CHE) and by the Schering AG, Berlin is gratefully acknowledged. We also thank Prof. W. Skuballa, Schering AG for providing us with the compound ZK 204027, Dr. U. Klar, Schering AG for performing the biological tests with compound **42** and Sabine Schneider for HPLC support.

[1] G. Höfle, N. Bedorf, H. Steinmetz, D. Schomburg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, *108*, 1671; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567.

[2] a) D. M. Bollag, P. A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C. M. Woods, *Cancer Res.* **1995**, *55*, 2325; b) reviews of the chemistry and biology of the epothilones, see K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem.* **1998**, *110*, 2120; *Angew. Chem. Int. Ed*. **1998**, *37*, 2014; J. Mulzer, *Chem. Mon.* **2000**, *131*, 205.

[3] Syntheses of epothilone B: a) D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky,Y. H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem*. **1997**, *109*, 775; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 757; b) K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, Z. Yang, *J. Am. Chem. Soc*. **1997**, *119*, 7974; c) D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, S. J. Danishefsky, *J. Am. Chem. Soc*. **1997**, *119*, 10073; d) S. A. May, P. A. Grieco, *Chem. Commun*. **1998**, 1597; e) D. Schinzer, A. Bauer, J. Schieber, *Synlett* **1998**, 861; f) A. Ballog, C. Harris, K. Savin, X.-G. Zhang, T.-C. Chou, S. J. Danishefsky, *Angew. Chem*. **1998**, *110*, 2821; *Angew. Chem. Int. Ed*. **1998**, *37*, 2675; g) J. Mulzer, A. Mantoulidis, E. Öhler, *Tetrahedron Lett*. **1998**, *39*, 8633; h) J. D. White, R. G. Carter, K. F. Sundermann, *J. Org. Chem*. **1999**, *64*, 684; i) James D. White, K. F. Sundermann, R. G. Carter, *Org. Lett*. **1999**, *1*, 1431; j) H. J. Martin, M. Drescher, J. Mulzer, *Angew. Chem.* **2000**, *112*, 591; *Angew. Chem. Int. Ed*. **2000**, *39*, 581; k) J. Mulzer, A. Mantoulidis, E. Öhler, *J. Org. Chem*. **2000**, *65*, 7456; l) D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc*. **2000**, *122*, 10521; m) J. Mulzer, G. Karig P. Pojarliev, *Tetrahedron Lett*. **2000**, *41*, 7635

[4] Syntheses of epothilone analogues: a) see ref. [2b]; b) R. M. Borzilleri, X. Zheng, R. J. Schmidt, J. A. Johnson, S.-H. Kim, J. D. DiMarco, C. R. Fairchild, J. Z. Gougoutas, F. Y. F. Lee, B. H. Long, G. D. Vite, *J. Am. Chem. Soc*. **2000**, *122*, 8890; c) S. J. Stachel, M. D. Chappell, C. B. Lee, S. J. Danishefsky, T.-C. Chou, L. He, S. B. Horwitz, *Org. Lett*. **2000**, *2*, 1637; d) J. Johnson, S.-H. Kim, M. Bifano, J. DiMarco, C. Fairchild, J. Gougoutas, F. Lee, B. Long, J. Tokarski, G. Vite, *Org. Lett*. **2000**, *2*, 1537; e) K. C. Nicolaou, D. Hepworth, N. P. King, M. R. V. Finlay, R. Scarpelli, M. M. A. Pereira, B. Bollbuck, A. Bigot, B. Werschkun, N. Winssinger, *Chem. Eur. J*. **2000**, *6*, 2783; f) D. Schinzer, K.-H. Altmann, F. Stuhlmann, A. Bauer, M. Wartmann, *ChemBioChem* **2000**, *1*, 67; g) K. C. Nicolaou, Y. He, F. Roschangar, N. P. King, D. Vourloumis, T. Li, *Angew. Chem*. **1998**, *110*, 89; *Angew. Chem. Int. Ed*. **1998**, *37*, 84, h) K. C. Nicolaou, F. Sarabia, S. Ninkovic, M. R. V. Finlay, C. N. C. Boddy, *Angew. Chem.* **1998**, *110*, 85; *Angew. Chem. Int. Ed*. **1998**, *37*, 81; i) K. C. Nicolaou, H. Vallberg, N. P. King, F.

  0947-6539/01/0710-2270 $ 17.50+.50/0

Roschangar, Y. He, D. Vourloumis, C. G. Nicolaou, *Chem. Eur. J.* **1997**, *3*, 1957; j) K. C. Nicolaou, F. Sarabia, M. R. V. Finlay, S. Ninkovic, N. P. King, D. Vourloumis, Y. He, *Chem. Eur. J.* **1997**, *3*, 1971; k) K. C. Nicolaou, D. Vourloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschangar, N. P. King, M. R. V. Finlay, P. Giannakakou, P. Verdier-Pinard, E. Hamel, *Angew. Chem.* **1997**, *109*, 2181; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2097; l) J. D. Winkler, J. M. Holland, J. Kasparec, P. H. Axelsen, *Tetrahedron* **1999**, *55*, 8199; m) K. C. Nicolaou, M. Ray, V. Finlay, S. Ninkovic, F. Sarabia, *Tetrahedron* **1998**, *54*, 7127; n) K. C. Nicolaou, M. Ray, V. Finlay, S. Ninkovic, Y. He, Z. Yang, T. Li, F. Sarabia, D. Vourloumis, *Chem. Biol.* **1998**, *5*, 365.

[5] a) Z. Yang, Y. He, D. Vourloumis, H. Vallberg, K. C. Nicolaou, *Angew. Chem.* **1997**, *109*, 170; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166; b) D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm, M. Cordes, *Angew. Chem.* **1997**, *109*, 543; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 523; c) D. Schinzer, A. Bauer, O. M. Böhm, A. Limberg, M. Cordes, *Chem. Eur. J.* **1999**, *5*, 2483; d) K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 7974; e) D. Meng, P. Bertinato, A. Balog, D. S. Su, T. Kamenecka, E. J. Sorensen, S. J. Danishefsky, *J. Am. Chem. Soc.* **1997**, *119*, 10073.

[6] A. Balog, D. Meng, P.Kamenecka, T. Bertinato, D. S. Su, E. J. Sorensen, S. J. Danishefsky, *Angew. Chem.* **1996**, *108*, 2976; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801.

[7] D. Sawada, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 215; *Angew. Chem. Int. Ed.* **2000**, *39*, 209.

[8] S. C. Sinha, C. F. Barbas III, R. A. Lerner, *Proc. Natl. Acad. Sci. USA* **1998**, *39*, 8633.

[9] Review: R. M. Devant, H.-E. Radunz, *Houben Weyl*, *Methods of Organic Chemistry*, *Vol. E21b*: Stereoselective Synthesis (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, p. 1151.

[10] H. Kühne, "Konformationskontrolle durch cyclische Ketale bei Carbonyladditionen metallorganischer Reagenzien", *Diploma Thesis*, Freie Universität Berlin, **1992**.

[11] K. Gerlach, M. Quitschalle, M. Kalesse, *Tetrahedron Lett.* **1999**, *40*, 3553.

[12] a) J. Mulzer, H. M. Kirstein, J. Buschmann, C. Lehmann, P. Luger, *J. Am. Chem. Soc.* **1991**, *113*, 910; b) N. K. Kochetkov, A. F. Sviridov, M. S. Ermolenko, D. V. Vashunsky, V. S. Borodkin, *Tetrahedron Lett.* **1987**, *28*, 235; c) N. K. Kochetkov, A. F. Sviridov, M. S. Ermolenko, D. V. Vashunsky, V. S. Borodkin, *Tetrahedron* **1989**, *45*, 5109; d) G. Stork, I. Patterson, F. K. C. Lee, *J. Am. Chem. Soc.* **1982**, *104*, 4686.

[13] L. A. Paquette, D. G. Maynard, *J. Am. Chem. Soc.* **1992**, *114*, 5018.

[14] R. O. Duthaler, A. Hafner, *Chem. Rev.* **1992**, *92*, 807.

[15] B. S. Bal, W. E. Childers Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091.

[16] I. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

[17] R. E. Taylor, J. Zajicek, *J. Org. Chem.* **1999**, *64*, 7224.

Received: November 20, 2000 [F2878]