The Total Synthesis and Biological Assessment of *trans*-Epothilone A

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Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

The total synthesis of (12*S*,13*S*)-*trans*-epothilone A (**1a**) was achieved based on two different convergent strategies. In a first-generation approach, construction of the C(11)–C(12) bond by Pd^0-catalyzed *Negishi*-type coupling between the C(12)-to-C(15) *trans*-vinyl iodide **5** and the C(7)-to-C(11) alkyl iodide **4** preceded the (nonselective) formation of the C(6)–C(7) bond by aldol reaction between the C(7)-to-C(15) aldehyde **25** and the dianion derived from the C(1)-to-C(6) acid **3**. The lack of selectivity in the aldol step was addressed in a second-generation approach, which involved construction of the C(6)–C(7) bond in a highly diastereoselective fashion through reaction between the acetonide-protected C(1)-to-C(6) diol **31** ('*Schinzer*'s ketone') and the C(7)-to-C(11) aldehyde **30**. As part of this strategy, the C(11)–C(12) bond was established subsequent to the critical aldol step and was based on *B*-alkyl *Suzuki* coupling between the C(1)-to-C(11) fragment **40** and C(12)-to-C(15) *trans*-vinyl iodide **5**. Both approaches converged at the stage of the 3-*O*, 7-*O*-bis-TBS-protected seco acid **27**, which was converted to *trans*-deoxyepothilone A (**2**) *via Yamaguchi* macrolactonization and subsequent deprotection. Stereoselective epoxidation of the *trans* C(12)–C(13) bond could be achieved by epoxidation with *Oxone*® in the presence of the catalyst 1,2:4,5-di-*O*-isopropylidene-L-*erythro*-2,3-hexodiuro-2,6-pyranose (**42a**), which provided a 8:1 mixture of **1a** and its (12*R*,13*R*)-epoxide isomer **1b** in 27% yield (54% based on recovered starting material). The absolute configuration of **1a** was established by X-ray crystallography. Compound **1a** is at least equipotent with natural epothilone A in its ability to induce tubulin polymerization and to inhibit the growth of human cancer cell lines *in vitro*. In contrast, the biological activity of **1b** is at least two orders of magnitude lower than that of epothilone A or **1a**.

Introduction. – Epothilones A and B (*Fig. 1*) are the main representatives of a family of bacterial natural products that exhibit potent antiproliferative activity against a broad range of human cancer cell lines. First isolated in 1993 by *Reichenbach*, *Höfle*, and co-workers [1], these compounds were subsequently shown by *Bollag et al.* to be microtubule depolymerization inhibitors [2] and, thus, to inhibit human cancer cell growth by the same mechanism of action as the renowned anticancer drug *Taxol*® (paclitaxel) [3]. At the time of this discovery, epothilones A and B, apart from paclitaxel and its analogs, were the only compounds recognized in the literature to act as microtubule-stabilizing agents[1]). However, in distinct contrast to paclitaxel, epothilones were found to be equally effective *in vitro* against drug-sensitive and multidrug-resistant cell lines [2][5–7], which immediately suggested that epothilone-derived anticancer agents could eventually be useful for the treatment of drug-resistant tumors.

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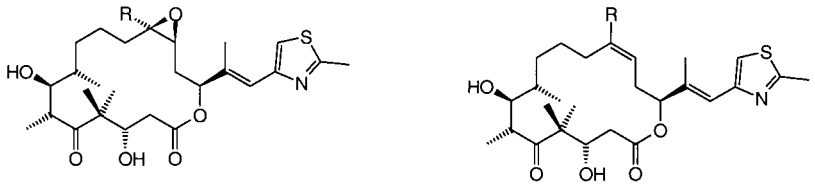
[1]) Several other natural products have recently been recognized to be microtubule depolymerization inhibitors. For a review, *cf.* [4].



Epothilone A R = H
Epothilone B R = CH_3

Deoxyepothilone A R = H
Deoxyepothilone B R = CH_3

Fig. 1. *Structures of epothilones A and B and of their deoxy variants.* Deoxyepothilones A and B are also known as epothilones C and D, respectively.

This very attractive *in vitro* profile, in combination with the knowledge that epothilones (and related analogs) are well within the realm of modern total synthesis techniques, presumably even on a scale sufficiently large to support clinical trials, has turned these compounds into important lead structures for anticancer drug discovery. More than 20 total syntheses of epothilones A and B have been published since their absolute configuration was disclosed in 1996 (for recent reviews, *cf.* [8–11]); at the same time, several hundred analogs have been prepared and their biological activities investigated, which has led to a remarkably comprehensive understanding of the structure-activity relationships (SAR) for epothilone-derived structures in a short period of time (for recent reviews, *cf.* [6][8][9][12]).

As part of their early SAR work, *Nicolaou* and co-workers reported in 1997 the intriguing observation that one of the two possible *trans*-epoxide isomers of epothilone A is virtually equipotent with natural epothilone A [13]. These *trans*-epoxides were obtained by nonselective epoxidation of *trans*-deoxyepothilone A (the C(12)=C(13) *trans* isomer of deoxyepothilone A, *cf. Fig. 1*), which, in turn, had been produced as a consequence of nonselective C=C formation between C(12) and C(13), rather than being the result of a directed synthetic effort. *trans*-Deoxyepothilone A had also been described by *Danishefsky* and co-workers [14], who were the first to characterize the biological activity of this analog *in vitro* [14a]. However, neither the stereoselective synthesis of *trans*-deoxyepothilone A nor the stereo- and regioselective epoxidation of *trans*-deoxyepothilones has been described in the literature so far, and, most importantly, the absolute configuration of the epoxide moiety in the more active isomer of *trans*-epothilones A had not been determined in *Nicolaou*'s work[2]).

To address this question, we have elaborated a stereoselective synthesis of *trans*-epothilones A, and we have determined the epoxide configuration in the more active isomer by X-ray crystallography. In this paper, we provide full details of our synthetic work, and we report additional data on the *in vitro* antiproliferative activity of *trans*-epothilones A[3]). The results of our biological experiments clearly reconfirm the conclusions previously derived by *Nicolaou* and co-workers and thus refute a more recent notion that *trans*-epothilones would be biologically inactive [18].

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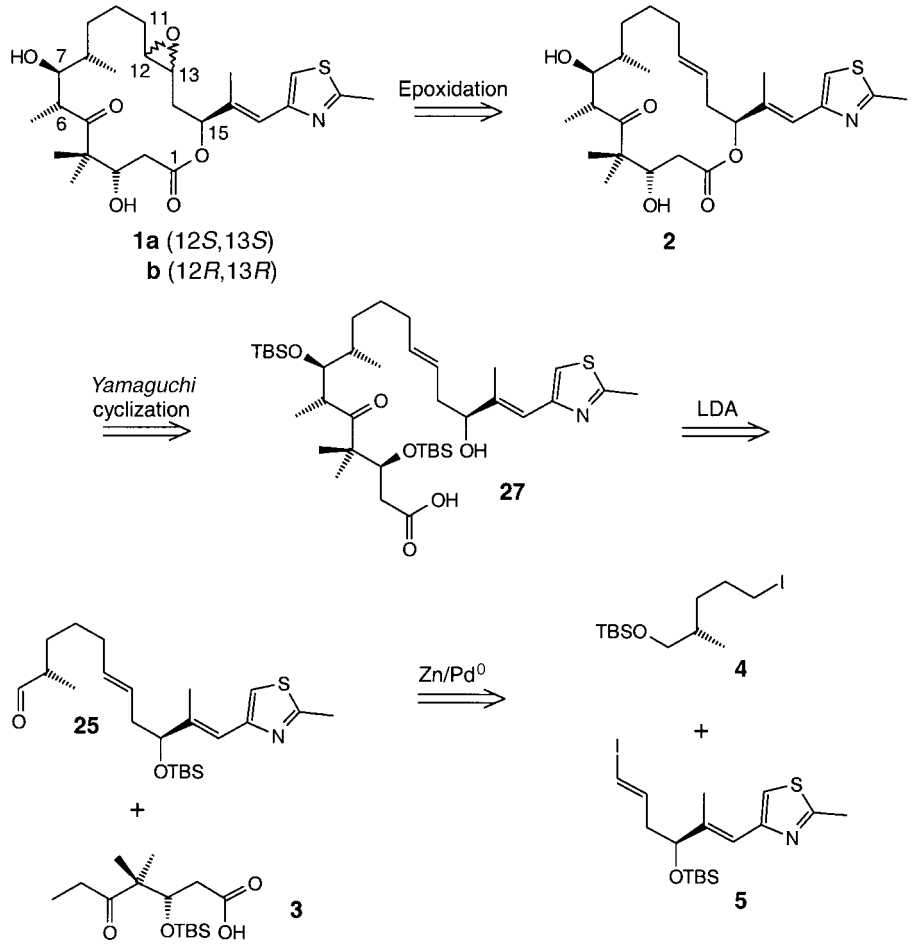
[2]) *Nicolaou* has recently reported a series of highly potent cyclopropyl analogs of *trans*-epothilone A, with the configuration of the C(12)–C(13) cyclopropyl moiety corresponding to that in the active *trans*-epothilone A isomer as determined in this work [15].

[3]) Preliminary accounts of this work, including the disclosure of the absolute configuration of the active *trans*-epothilone A isomer have been published [16][17].

Results and Discussion. – The general features of our initial approach to the synthesis of C(12), C(13) *trans* analogs of epothilone A are summarized in *Scheme 1*. This approach combined elements of the strategies previously developed by *Schinzer* and co-workers [19] and *Nicolaou* and co-workers [20] for the synthesis of natural epothilones and was conceived to be based on four key steps: *i*) Pd^0-catalyzed coupling of vinyl iodide **5** with the zincate derived from alkyl iodide **4**, *ii*) aldol reaction of aldehyde **25**, which would be derived from the product of coupling between **4** and **5**, and the dianion of carboxylic acid **3**, *iii*) macrolactonization of seco acid **27**, and *iv*) stereoselective epoxidation of *trans*-deoxyepothilone A (**2**), for which appropriate methodology needed to be developed. Based on literature precedent [20], the aldol reaction between **3** and **25** was expected to be essentially nonselective and to provide a

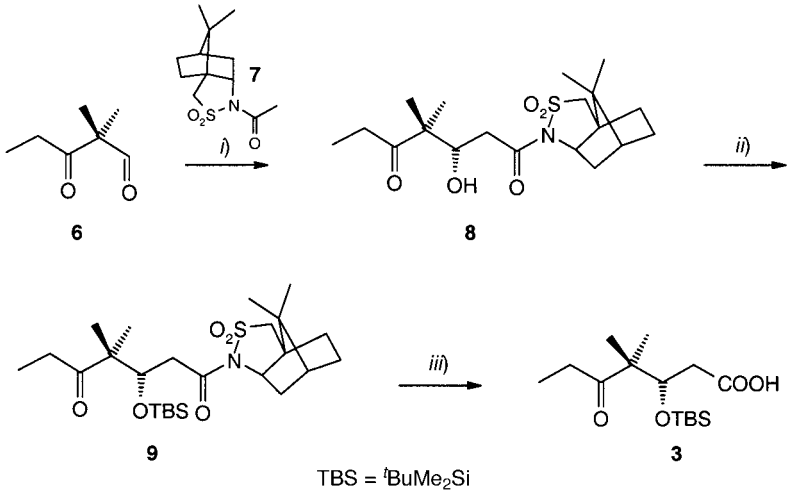
Scheme 1. retro-*Synthetic Analysis for the Synthesis of* trans-*Epothilones A* (**1**)



ca. 1:1 mixture of *syn* isomers at C(6) and C(7) ((6*S*,7*R*) and (6*R*,7*S*), resp.); however, assuming that these isomers could then be separated by chromatographic means, this approach appeared to provide the most-rapid access to *trans*-deoxyepothilone A (**2**), thus allowing the investigation of the crucial epoxidation step **2** → **1** and the development of the necessary methodology for stereoselective epoxide formation at C(12), C(13).

The synthesis of carboxylic acid **3** is summarized in *Scheme 2* and was based on *Oppolzer* chemistry [21] to establish the chiral center at C(3). Thus, reaction of aldehyde **6** with the boron enolate of acetylsultam **7** provided the desired aldol product **8** in 46% yield after purification by simple recrystallization (> 99% de). Protection of the free OH group in **8** as TBS ether (TBS = ^{t}BuMe$_2$Si) gave crystalline **9**, which was then converted to **3** by treatment with LiOOH in THF/H_2O in 76% yield.

Scheme 2



i) 1. **7**, $Et_3B \cdot OTf$, $^i Pr_2NEt$, 0°, 40 min; 2. + **6**, − 78°, 2 h; 46%. *ii*) TBS-OTf, − 78°, 1 h, − 78° → r.t., 16 h; 92%. *iii*) LiOH, H_2O_2, THF/H_2O 4:1, r.t., 7 h; 76%.

The crystallinity of compounds **8** and **9** allowed straightforward scale-up of this reaction sequence to produce multi-hundred-g quantities of **3**. It should be noted that this strategy for the synthesis of **3** was originally conceived by *De Brabander et al.* [22], but these investigators erroneously reported that **3** would be obtained by means of (2*S*)-*N*-acetylbornane-10,2-sultam (*i.e.*, the enantiomer of **7**, *ent*-**7**). We have repeated *De Brabander*'s work, and, based on X-ray crystallographic analysis, we were able to show that the aldol product obtained upon reaction of **6** with *ent*-**7** is, in fact, the enantiomer of **8** (*ent*-**8**) with the undesired (3*R*) configuration (*ca.* 9:1 selectivity in favor of *ent*-**8**; see structure of *ent*-**9** in *Fig. 2*). Subsequent to this discovery, *De Brabander et al.* published a corrigendum to their original paper [23], which corroborated our own experimental findings but, in our view, does not adequately clarify which compound is actually described in their original report. It should also be noted in this context that the optical rotation reported for carboxylic acid **3** by *Nicolaou* and co-workers ($[\alpha]_D = +16$) [20] is of the wrong sign.

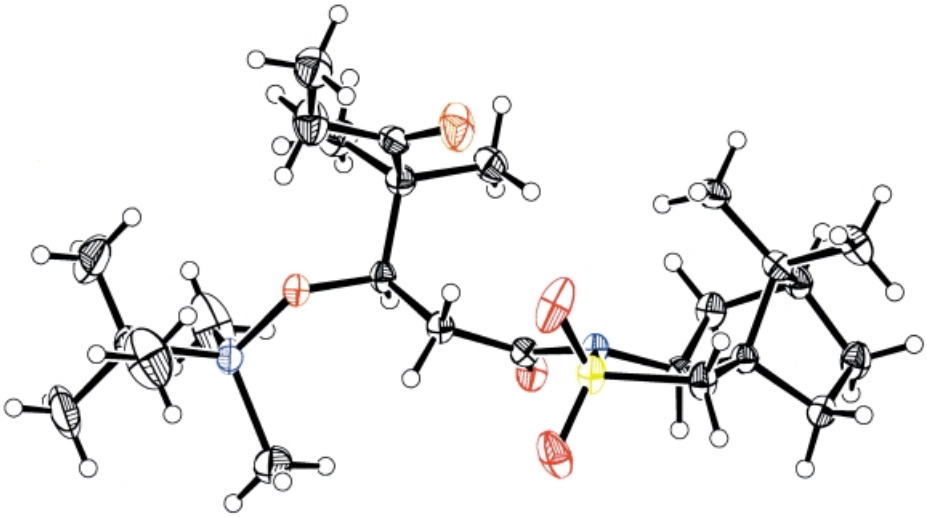
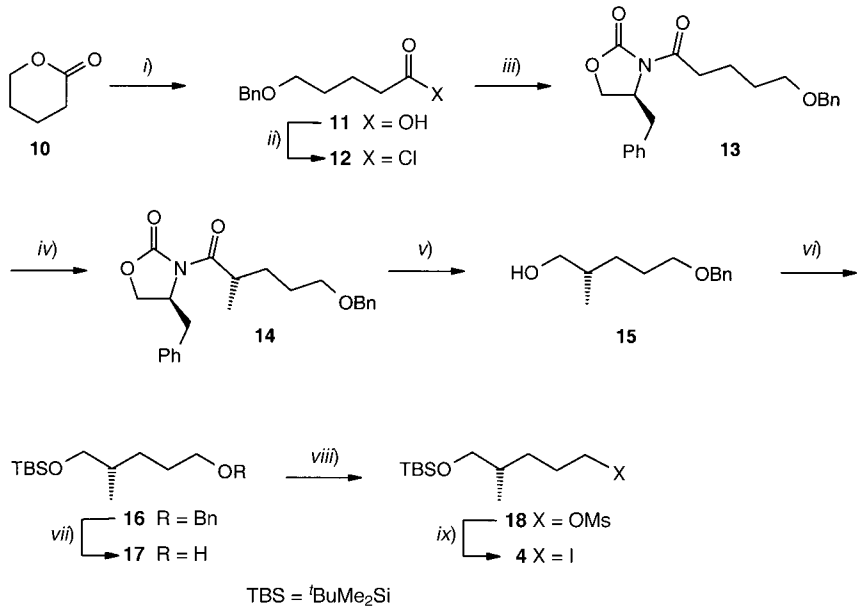


Fig. 2. *ORTEP Plot of* ent-**9** *with 30% displacement ellipsoids*

The preparation of alkyl iodide **4** has previously been described by *Schinzer* and co-workers [19], except for a different approach to the synthesis of carboxylic acid **11** and the use of a valine- rather than phenylalanine-derived *Evans* auxiliary in the crucial methylation step [**13** → **14**, *Scheme 3*). Our own synthesis of this building block is closely related to *Schinzer*'s approach (*Scheme 3*). In the initial step, pentano-5-lactone was converted to 5-(benzyloxy)pentanoic acid (**11**) by treatment with KOH and benzyl alcohol [24]. Treatment of **11** with oxalyl chloride gave the corresponding acid chloride **12**, which was reacted with the Li-salt of (4*S*)-4-benzyloxazolidin-2-one to provide acyloxazolidinone **13**. On a g-scale, acid chloride **12** could be purified by bulb-to-bulb distillation (50% yield), whereas, on larger-scale, attempts to distill the compound resulted in complete decomposition. Large-scale preparation of **13** was, thus, based on the reaction of the anion of (4*S*)-4-benzyloxazolidin-2-one with crude **12** (obtained by simple evaporation of the reaction mixture), which still provided **13** in a satisfactory 82% overall yield based on **11**. The choice of (4*S*)-4-benzyloxazolidin-2-one rather than (4*S*)-4-isopropyloxazolidin-2-one [19] as the chiral auxiliary in the ensuing methylation step was primarily based on the lower price of the former, which, in the anticipated subsequent scale-up of the synthesis of **4**, would be of significant importance. Methylation of the sodium enolate of **13** with MeI at $-78°$ furnished a 11:1 mixture of diastereoisomers (by reversed-phase HPLC) in favor of the desired **14** (91%). This mixture proved to be inseparable by TLC in a broad variety of solvent systems (>20 mixtures were investigated); fortunately, however, the material could eventually be purified by crystallization from AcOEt/hexane, which provided **14** in 46% yield and in diastereoisomerically pure form (>99.5%, as determined by HPLC on a chiral stationary phase). The relative configuration of **14** and, thus, the absolute configuration at the newly created chiral center were confirmed by X-ray crystallographic analysis (*Fig. 3*).

Scheme 3



i) KOH, benzyl chloride, toluene, reflux, 16 h; 50%. *ii*) $(COCl)_2$, DMF (cat.), toluene, r.t., 2 h, 50–60°, 1.75 h; 95% (crude). *iii*) (4*S*)-4-Benzyloxazolidin-2-one, BuLi, THF, −80°, 2 h; 86%. *iv*) 1. NaHMDS (sodium salt of hexamethyldisilazane), THF, −75 to −70°, 2.5 h; 2. MeI, THF, −78°, 2 h; 46%. *v*) $LiAlH_4$, 5°, 20 min, r.t., 1 h; 72%. *vi*) TBS-Cl, 1*H*-imidazole, DMF, 40°, 1 h; quant. *vii*) H_2, 10% Pd/C, MeOH/cyclohexane, 16 h; 94%. *viii*) Ms-Cl, Et_3N, CH_2Cl_2, 0°, 15 min; quant. *ix*) NaI, acetone, 50°, 25 h; 85%.

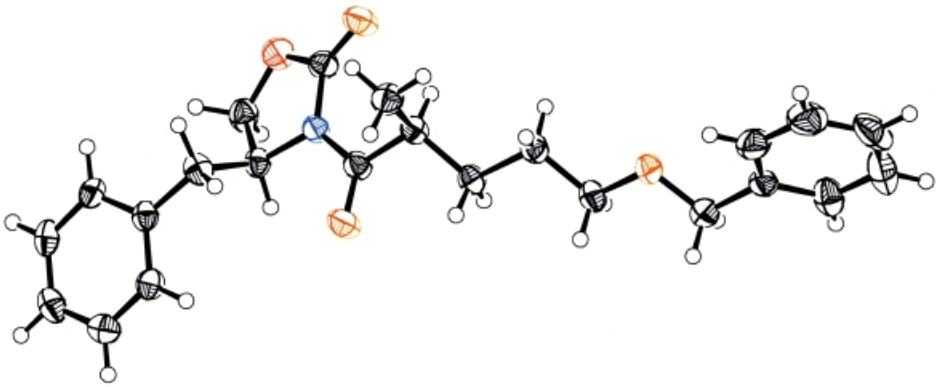


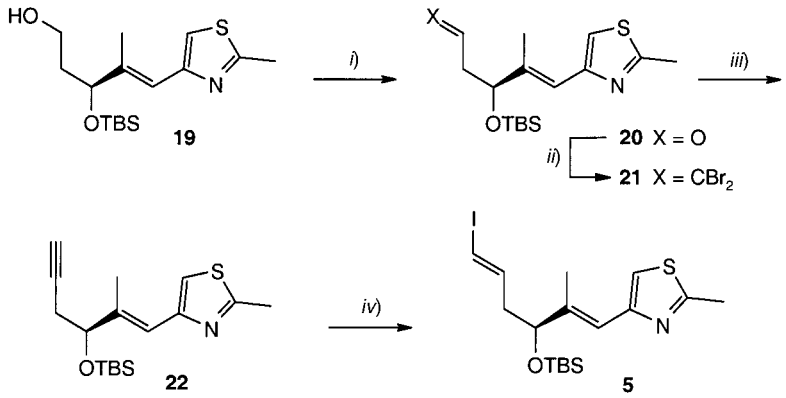
Fig. 3. *ORTEP Plot of* **14** *with 30% displacement ellipsoids*

It is important to note that methylation of the (4*S*)-*N*-acyl-4-isopropyl oxazolidinone analogous to **13** as described by *Schinzer* and co-workers [19] likewise led to a *ca.* 11:1 mixture of diastereoisomers, which, in our hands, was again inseparable by silica-gel chromatography in numerous solvent systems, including the one reported [19] to provide the diastereoisomerically pure methylation product. Reduction of **14** with

$LiAlH_4$ provided alcohol **15** in 72% yield after distillation, which was converted to the TBS ether **16** by treatment with TBS-Cl. Removal of the benzyl protecting group by catalytic hydrogenation over 10% Pd/C in MeOH/cyclohexane gave the mono-protected diol **17** in 94% yield. In contrast, attempted hydrogenation in MeOH led to the free diol, due to concurrent loss of both the benzyl as well as the TBS protecting groups. Alcohol **17** was then elaborated into the desired iodide **4** *via* the corresponding mesylate **18** in 85% overall yield. As for building block **3**, the chemistry outlined in *Scheme 3* allowed the synthesis of **4** on a multiple-hundred-g scale.

The synthesis of building block **5** is based on the known alcohol **19** [19] as an advanced intermediate (*Scheme 4*). *Swern* oxidation of **19** provided aldehyde **20** in 85% yield, which was then converted into dibromo-olefin **21** *via Corey-Fuchs* reaction [25]. Treatment of **21** with BuLi and subsequent quenching with H_2O gave acetylene **22**. Hydrozirconation of **22** with *Schwartz*'s reagent [26] followed by reaction with I_2 then furnished the desired *trans*-vinyl iodide **5** with high stereoselectivity and in 31% overall yield for the four-step sequence from **19**.

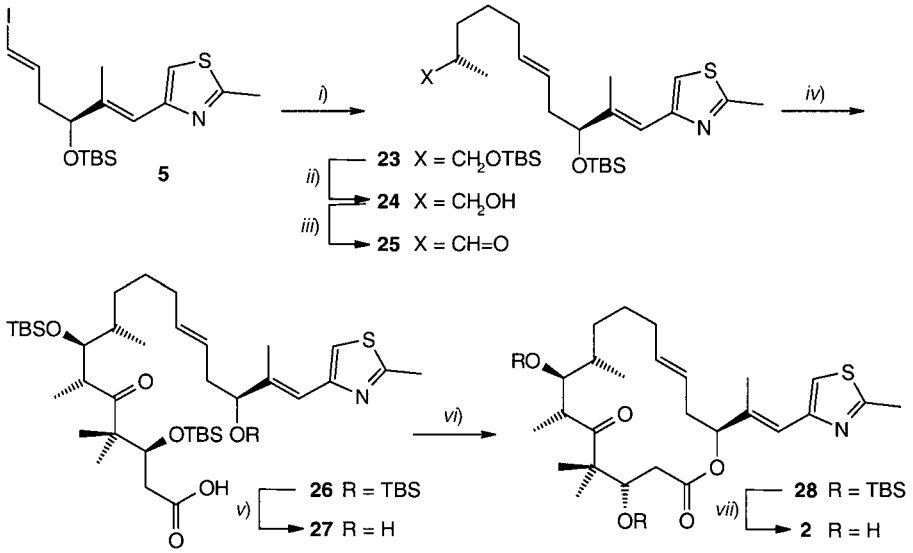
Scheme 4



i) 1. $(COCl)_2$, DMSO, CH_2Cl_2, −75°, 10 min; 2. +**19**, −70°, 40 min; 3. Et_3N, −60° → r.t., 1 h; 85%. *ii*) CBr_4, Ph_3P, CH_2Cl_2, r.t., 1 h; 80%. *iii*) BuLi, THF, −75°, 1 h, r.t., 1 h; 60%. *iv*) 1. $[ZrCl(Cp)_2H]$, THF, r.t., 30 min; 2. I_2, r.t., 20 min; 77%.

The construction of the epothilone macrocycle from building blocks **3**, **4**, and **5** is summarized in *Scheme 5*. The first step in this assembly process involved reductive coupling between vinyl iodide **5** and the preformed zincate derived from **4** in the presence of a Pd^0 catalyst [19], which provided *trans*-olefin **23** in 69% yield. Treatment of **23** with 1.1 equiv. of camphorsulfonic acid (CSA) in CH_2Cl_2/MeOH led to selective TBS removal from the primary OH group (80%), and the resulting free alcohol **24** underwent smooth *Swern* oxidation to furnish aldehyde **25** in good yield (79%). Aldol reaction of this aldehyde with the dianion generated from carboxylic acid **3** [20] gave a mixture of products, which was directly treated with excess TBS-OTf; subsequent treatment of the crude persilylated material with K_2CO_3 in MeOH gave the desired free carboxylic acid **26** in 31% yield (based on **25**) as a single diastereoisomer after purification by FC. The configuration of the newly formed stereogenic centers at C(6)

Scheme 5

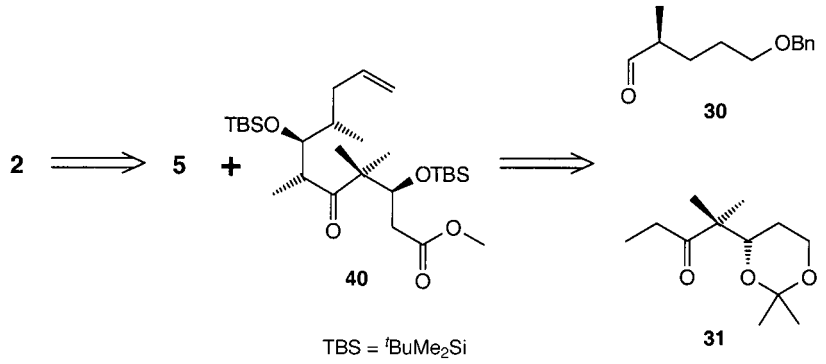


i) **4**, Zn–Cu, [Pd(Ph_3P)$_4$], benzene, 60–80°; 69%. *ii*) CSA, CH_2Cl_2/MeOH; 80%. *iii*) $(COCl)_2$/DMSO, CH_2Cl_2, –78°; 79%. *iv*) 1. **3**, LDA (lithium diisopropylamide), –78°; 2. TBS-OTf, lutidine; 3. K_2CO_3, MeOH, 31% (3 steps). *v*) Bu_4NF, THF, 64%. *vi*) 2,4,6-$Cl_3C_6H_2C(O)Cl$, Et_3N, DMAP (*N*,*N*-dimethylpyridin-4-amine), THF/toluene; 61%. *vii*) CF_3COOH/CH_2Cl_2; 91%.

and C(7) was confirmed by X-ray crystallographic analysis at the stage of *trans*-epothilone A (*vide infra*). No attempts were made to determine the ratio of diastereoisomers formed in the aldol step, as the reaction was expected to be essentially nonselective. As indicated above, the choice of carboxylic acid **4** as a partner in the aldol reaction to establish the C(6)–C(7) bond was primarily driven by the desire to obtain rapid access to *trans*-deoxyepothilone A (**2**) for subsequent epoxidation studies, while less emphasis was placed at an early stage on the stereoselectivity of each single step in the overall sequence to **1**. Treatment of **26** with 6 equiv. of Bu_4NF for 3.5 h rather surprisingly gave the desired mono-desilylated product **27** only in 35% yield together with substantial quantities of doubly deprotected material. The degree of selectivity in this reaction is thus significantly lower than described in the literature for related substrates (*cf.*, *e.g.*, [20]). The yield of **27** could be improved to 64% by reducing the initial excess of Bu_4NF and careful reaction monitoring, but the formation of over-deprotected products could be only partially suppressed. Fortunately, these byproducts were not lost, but could be recycled into **27** by treatment with excess TBS-OTf followed by cleavage of the TBS ester with K_2CO_3 in MeOH (*vide supra*). Cyclization of seco acid **27** by the method of *Yamaguchi et al.* [27] gave protected *trans*-deoxyepothilone A **28** in 61% yield. Deprotection of this material with 90% CF_3COOH/CH_2Cl_2 then furnished *trans*-deoxyepothilone A (**2**) in excellent yield (91%).

As will be outlined below, **2** could be successfully converted to the two diastereoisomeric *trans*-epothilone A isomers **1** in a stereoselective fashion. This

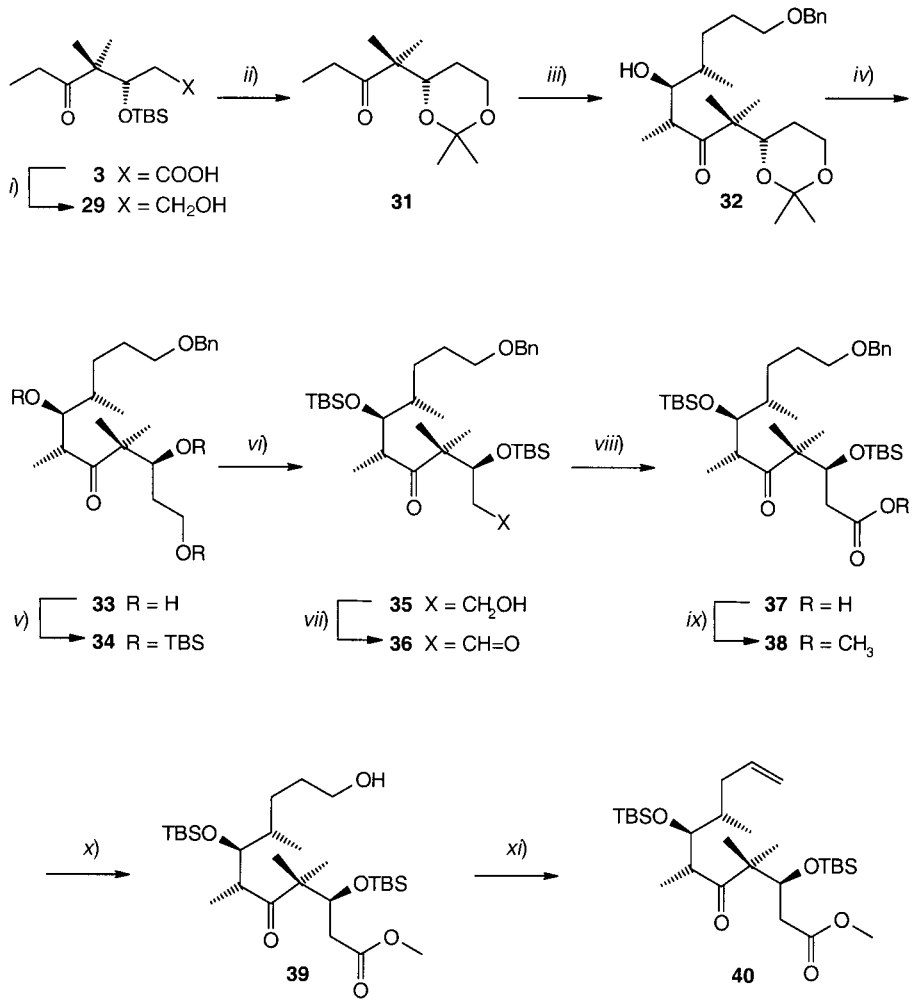
Scheme 6. retro-*Synthetic Analysis for a Second-Generation Approach to the Synthesis of* trans-*Deoxyepothilone A* (**2**)



finding has subsequently prompted us to investigate more selective routes to **2**, to establish a selective and efficient overall synthesis of **1**. However, apart from offering improved access to **1**, such a second-generation approach was also desired to provide straightforward access to analogs with modified heterocyclic side chains (attached to C(15)), which represent a major focus of our analog program [28]. As illustrated in *Scheme 6*, a conceivable strategy to achieve these objectives was to perform aldol-based construction of the C(6)–C(7) bond prior to formation of the C(11)–C(12) bond, which, in turn, would be achieved by a *Suzuki*-type coupling between vinyl iodide **5** and a trialkylborane generated *in situ* from olefin **40** [29][30]. Although this particular sequence of steps is not *a priori* a critical feature for the synthesis of *trans*-epothilone A itself, this strategy offers significant advantages in the synthesis of side-chain-modified analogs of **1**, as it obviates the need to repeat the critical aldol step for every new modification. Olefin **40** was planned to be derived from aldehyde **30** (to be obtained from alcohol **15**, *Scheme 3*) and *Schinzer*'s ethyl ketone **31** [31], which was thought to be readily accessible from carboxylic acid **3**. Aldol reactions of **31** with aldehydes related to **30** had been previously reported to proceed with high diastereoselectivity in favor of the desired (6*R*,7*S*) isomer [20][32]. The choice of an alternative coupling method for the construction of the C(11)–C(12) bond was mainly based on favorable prior experience with the alkyl *Suzuki* approach in the coupling of **40** with vinyl iodides other than **5** [28]. In addition, in preliminary experiments, the attempted coupling of the C(1)-to-C(11) ω-alkyl iodide corresponding to **40** with a vinyl iodide similar to **5** proceeded much less efficiently than that involving the C(7)-to-C(11) fragment **4**.

As illustrated in *Scheme 7*, the elaboration of carboxylic acid **3** into ketone **31** was readily achieved by borane-mediated reduction of the carboxylate moiety and subsequent acetalization of the resulting monoprotected diol **29** with 5% CF_3COOH/acetone in 52% yield. In contrast, treatment of **29** with $CuSO_4$ in acetone at reflux temperature gave only recovered starting material. This is contrary to the behavior of the isomer of **29** incorporating a primary TBS ether and a free secondary

Scheme 7



i) $BH_3 \cdot Me_2S$, $B(OMe)_3$, 0°, 2 h, 15°, 6 h; 56%). *ii*) CF_3COOH, acetone, 35°, 18 h; 93%. *iii*) 1. LDA (0.5 equiv.), THF, −78°, 80 min; 2. +**30** (0.5 equiv.), −78°, 75 min; 82%. *iv*) PPTS (pyridinium *p*-toluenesulfonate), MeOH, r.t., 22 h; 81%. *v*) TBS-OTf, 2,6-lutidine, CH_2Cl_2, r.t.; 81%. *vi*) CSA, MeOH/CH_2Cl_2, 0°, 1 h; 80%. *vii*) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°; 92%. *viii*) $NaClO_2$, isobutene, NaH_2PO_4, THF, ^{t}BuOH, H_2O, r.t., 4 h; 93%. *ix*) DCC, DMAP, MeOH, CH_2Cl_2, −20° → r.t., 4 h; 71%. *x*) H_2, Pd/C, MeOH, r.t., 1 atm., 1 h; 74%. *xi*) 1. 2-NO_2−C_6H_4−SeCN, Bu_3P, r.t., 1 h; 2. $NaHCO_3$, 30% H_2O_2 soln., r.t., 24 h; 93%.

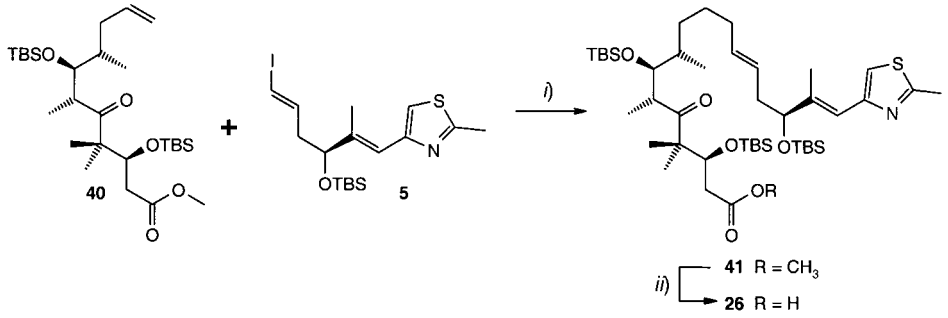
OH group, which can be efficiently acetalized under those conditions [31]. The 7-step synthesis of **31** from β-keto aldehyde **6** constitutes a significantly more efficient approach to this valuable building block than previously reported strategies, and it has allowed the preparation of multi-hundred-g quantities of material.

Aldol reaction of **31** (2 equiv.) with aldehyde **30** proceeded with excellent stereoselectivity, and, after purification by FC, the desired aldol product **32** was

obtained in diastereoisomerically pure form in 82% yield. Cleavage of the acetonide moiety in **32** gave free triol **33**, which was further elaborated into its partially protected analog **35** *via* persilylation (→**34**) and subsequent selective cleavage of the primary TBS ether with 1.03 equiv. of CSA in $MeOH/CH_2Cl_2$ in 65% overall yield. *Swern* oxidation of **35** followed by $NaClO_2$-mediated oxidation [20] of the resulting aldehyde **36** provided carboxylic acid **37**, which was converted to methyl ester **38** by *N*,*N*-dimethylpyridin-4-amine (DMAP)-catalyzed esterification with dicyclohexylcarbodiimide (DCC)/MeOH. Finally, removal of the benzyl protecting group gave primary alcohol **39**, which was then smoothly transformed into the desired terminal olefin **40** *via* the corresponding 2-nitrophenyl selenocyanate and *in situ* oxidation and elimination in 93% yield [33]. Thus, **40** could be obtained in remarkable 22% overall yield for the 9-step sequence from aldol product **32**.

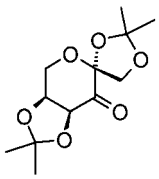
Alkyl-*Suzuki* coupling of **40** (*via* the *in situ* formed trialkylborane) with vinyl iodide **5** proceeded smoothly and gave the desired *trans*-olefin in 63% yield (*Scheme 8*). Saponification of the methyl ester in the coupling product **41** with LiOH/^{i}PrOH provided carboxylic acid **25**, which was then elaborated into *trans*-deoxyepothilone A (**2**) as outlined in *Scheme 5*.

Scheme 8

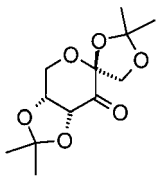


i) 1. Olefin **40**, 9-BBN (9-borabicyclo[3.3.1]nonane), THF, r.t.; 2. Cs_2CO_3, $[PdCl_2(dppf)_2]$, Ph_3As, vinyl iodide **5**, DMF, −10° to r.t.; 63%. *ii*) LiOH (6 equiv.), ^{i}PrOH/H_2O 4:1, 50°; 85%.

The most critical step in the synthesis of *trans*-epothilone A **1** proved to be the stereo- and chemoselective epoxidation of the *trans* C(12)=C(13) bond. Epoxidation of **2** with methyl(trifluoromethyl)dioxirane [35] has been reported by *Nicolaou* and co-workers to produce diastereoisomeric *trans*-epothilones A in 35 and 45% isolated yield, respectively, after separation by prep. TLC [34]. Unfortunately, we were not able to reproduce these results, and, in our hands, the epoxidation of **2** with methyl(trifluoromethyl)dioxirane gave a 1:1 mixture of diastereoisomeric *trans*-epothilones **1a**/**1b** (*cf. Scheme 1*) in only 28% isolated yield. Rather than trying to improve the chemical yield of this transformation and subsequently optimize the separation of the diastereoisomers **1a** and **1b**, we decided to explore the possibility of stereoselective epoxidation of the *trans* C(12)=C(13) bond. One of the most-sensible options available in this context appeared to be the use of fructose-derived epoxidation catalysts **42a**/**42b**, which have been demonstrated by *Shi* and co-workers to catalyze the *Oxone*®-mediated epoxidation of isolated *trans* C−C bonds with significant stereoselectivities [36].



42a

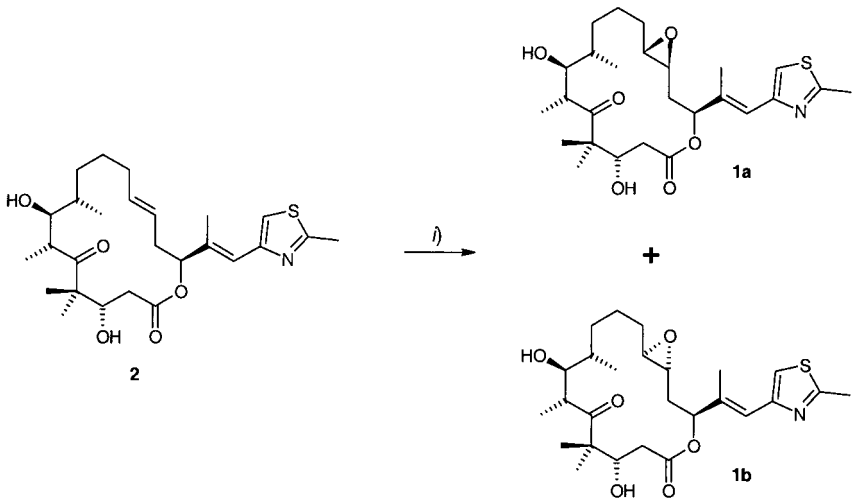


42b

Preliminary orientational experiments on an analytical scale indeed revealed that **42a** and **42b** each catalyzed the epoxidation of **2** with a *ca.* 9 : 1 selectivity in favor of **1a** and **1b**, respectively[4]). On a preparative scale, epoxidation of **2** (1 mmol) with *Oxone*® in the presence of 30% catalyst **42a**[4]) led to a 8 : 1 mixture of diastereoisomeric epoxides **1a**/**1b** in 27% isolated yield (54% based on recovered starting material) (*Scheme 9*).

Although the chemical yield of the epoxidation thus was not fully satisfactory, the results that the desired isomer **1a**[4]) was produced with almost 10 : 1 selectivity represented a significant improvement over the reaction with methyl(trifluoromethyl)dioxirane (which had been characterized by a complete lack of selectivity (*vide supra*)). The preferential formation of **1a** is particularly significant in view of our finding that the isolation of pure **1a** on a multi-mg scale was practical only by means of prep. HPLC. Pure **1a** was finally obtained in 11% yield (based on **2**; 22% based on

Scheme 9



i) *Oxone*®, **42a** (30 mol-%), $Bu_4N(HSO_4)$ (cat.), K_2CO_3, MeCN/1,2-dimethoxyethane/0.05M $Na_2B_4O_7 \cdot 10\ H_2O$ in $4 \cdot 10^{-4}$ M Na_2EDTA 2 : 1 : 2, r.t., 1 h; 27% (**1a**/**1b** 8 : 1; 50% recovered starting material).

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[4]) The absolute configuration of the epoxides produced in the presence of **42a**/**42b** at this point could be only inferred from the known stereochemical preferences of the *Shi* catalysts. However, based on biological studies with material obtained from the methyl(trifluoromethyl)dioxirane-mediated epoxidation of **2** *via* HPLC separation, it was clear that **42a** would lead to the biologically more-active isomer (which was later demonstrated to correspond to structure **1a**).

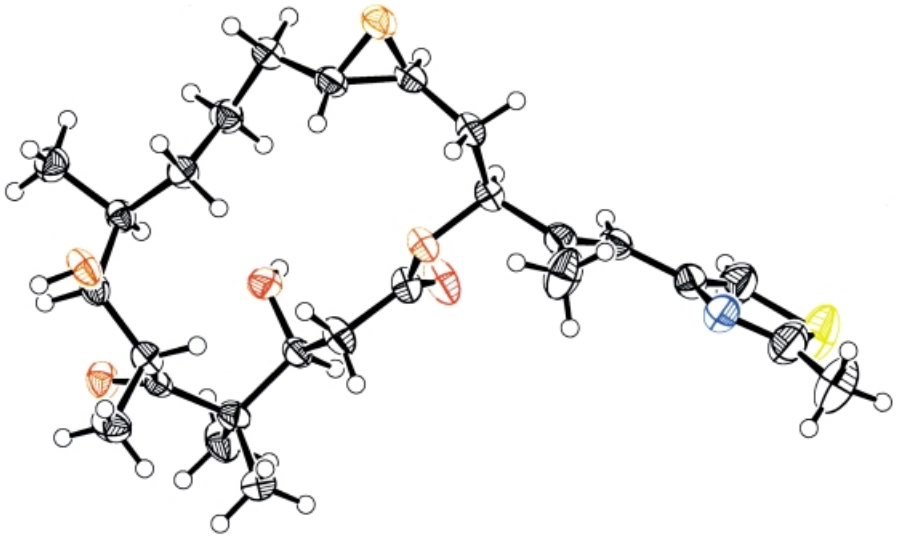

Fig. 4. *ORTEP Plot of* trans-*epothilone A* (**1a**) *with 30% displacement ellipsoids*

recovered starting material) after prep. HPLC purification in quantities, which were sufficient for broad biological profiling *in vitro* and *in vivo* (*in vivo* data not included in this paper). The relative and absolute configuration of (the biologically active) *trans*-epothilone A isomer **1a** was established by X-ray crystallography (*Fig. 4*) and is in line with the reported stereochemical preferences for epoxidation catalyst **42a** [36].

At the biological level, compounds **1a** and **1b** were both evaluated for their ability to induce tubulin polymerization *in vitro* and to inhibit the growth of human cancer cell lines derived from different types of human tumors. Induction of tubulin polymerization *in vitro* is commonly used as a measure of the strength of the interactions of microtubule-stabilizing agents with tubulin/microtubules; in general, the degree of tubulin-polymerization induction by such compounds reflects their ability to protect preformed microtubules against various types of depolymerizing stimuli [37]. As illustrated by the data summarized in *Table 1*, **1a** is a very potent inducer of tubulin polymerization, whose activity at the level of tubulin interactions is at least comparable with that of natural epothilone A. In contrast, **1b** did not show any measurable induction of tubulin polymerization under our experimental conditions, thus making this compound a significantly less-potent polymerization inducer than even *trans*-deoxyepothilone A (**2**) (*Table 1*). These data clearly indicate that the biological activity of *trans*-epothilone A is associated with a (12*S*,13*S*) configuration (natural configuration at C13).

As expected, similar findings were made in cancer cell growth-inhibition experiments, where the antiproliferative activity of **1a** proved to be comparable with that of epothilone A itself, whereas **1b** is more than two orders of magnitude less active (*Table 2*). *trans*-Epothilone A (**1a**) also retains the ability to inhibit the growth of multidrug-resistant cancer cell lines with the same potency as epothilone A, thus

Table 1. *Induction of Tubulin Polymerization of Epothilone Analogs.* Tubulin polymerization was determined by a modified version of the centrifugation assay described in [38].

	Tubulin polymerization [%][a])	EC_{50} [μM][b])
Epothilone A	65	4.61
Epothilone B	85	2.63
1a	85	3.86
1b[c])	0	> 50
2	48	n.d.[d])

[a]) Induction of polymerization of porcine brain microtubule protein by 2 μM of test compound relative to the effect of 25 μM of epothilone B, which gave maximal polymerization (85% of protein input). [b]) Concentration required to achieve half-maximal tubulin polymerization with purified bovine brain tubulin. [c]) **1b** was obtained by prep. HPLC purification from a 1:1 mixture **1a**/**1b** obtained in an initial epoxidation experiment with methyl(trifluoromethyl)dioxirane. The material used in these experiments was contaminated with *ca.* 5% of **1a**. [d]) Not determined.

indicating that the compound, like epothilones A and B [2][5–7], is a poor substrate for the P-gp efflux pump (*cf. Table 2*, data for KB-8511 and MCF-7/MDR cell lines). Overall, these findings reconfirm and extend the previous observation by *Nicolaou* and co-workers that changing the geometry of the epoxide moiety in epothilone A from *cis* to *trans* is very well tolerated (for one of the two *trans* epothilone A stereoisomers) and does not affect *in vitro* biological potency. We have not made any serious attempts, either experimental or computational, to rationalize the differences in activity between **1a** and **1b** (or the similar activities of **1a** and epothilone A) at the conformational level. However, it seems worth noting that significant deviations between the X-ray crystal structures of epothilone A and **1a** are observed only in the immediate vicinity of the epoxide moiety, while the remainder of the macrocycle is largely superimposable

Table 2. *Growth Inhibition of Human Carcinoma Cell Lines by Epothilones A and B*, trans-*Epothilones* **1a** *and* **1b**, *and Paclitaxel*[a])

Cell line (tissue type)	IC_{50} [nM]				
	Epo A	Epo B	PXT	**1a**	**1b**
KB-31 (epidermoid)	2.01 ± 0.43	0.17 ± 0.06	1.93 ± 0.36	1.01 ± 0.24	523, 212[d])
KB-8511 (epidermoid)[b])	1.67 ± 0.17	0.19 ± 0.04	351 ± 26	0.86 ± 0.34	400, 182[d])
MCF-7 (breast)	2.04 ± 0.30	0.23 ± 0.04	2.29 ± 0.56	1.01 ± 0.11	n.d.[e])
MCF-7/MDR (breast)[c])	32.5 ± 1.97	3.83 ± 0.70	7169 ± 709	24.7 ± 2.2	n.d.[e])
MDA-MB-231 (breast)	2.13 ± 0.88	0.18 ± 0.05	2.00 ± 0.48	0.88 ± 0.40	n.d.[e])
A549 (lung)	3.40 ± 0.13	0.27 ± 0.02	4.31 ± 0.78	1.63 ± 0.23	n.d.[e])
HCT-116 (colon)	3.13 ± 0.76	0.50 ± 0.17	2.84 ± 0.63	1.74 ± 0.92	n.d.[e])
PC-3M (prostate)	4.65 ± 0.62	0.63 ± 0.10	4.84 ± 1.05	2.15 ± 0.23	n.d.[e])

[a]) Cells were exposed to compounds for 3–5 days, allowing for at least two population doublings. Cell numbers were estimated by quantification of protein content of fixed cells by methylene blue staining [39]. For further experimental details, *cf.* [40]. Data are presented as mean ± s.d. based on three independent experiments. Epo A = epothilone A; Epo B = epothilone B; PXT = paclitaxel. [b]) Multidrug-resistant P-gp-overexpressing subline of the parental KB-31 line. [c]) Multidrug-resistant variant of the MCF-7 cell line (multiple resistance mechanisms). [d]) Values are from separate single experiments which were performed with two different batches of material. As this material still contained small amounts of **1a**, the true IC_{50} values for **1b** are higher than those listed. [e]) Not determined.

between the two structures. This suggests that the overall conformational preferences of the macrolactone ring do not significantly change as a function of epoxide geometry (as long as the (*S*)-configuration at C(13) is maintained), thus resulting in equivalent biological potency for the (12*R*,13*S*) *cis* and the (12*S*,13*S*) *trans* isomers.

Conclusions. – We have developed highly efficient and scaleable syntheses for epothilone fragments **3** (**31**), **4** (**30**), and **5**, which were subsequently employed in the total synthesis of *trans*-epothilones A **1**. While our first-generation approach to **1** suffered from a lack of stereoselectivity in the construction of the C(6)–C(7) bond, we have developed a second-generation strategy that allows the synthesis of *trans*-deoxyepothilone A (**2**) with high efficiency and stereoselectivity. This approach features the unsaturated C(1)-to-C(11) fragment **40** as a key intermediate, which can be accessed from **31** and **30** in excellent yield and which is of significant utility also for the preparation of epothilone analogs other than **1**. The C(12)=C(13) bond in **2** could be epoxidized with reasonable selectivity and in acceptable yield in the presence of fructose-derived epoxidation catalysts **42**. However, further improvments in the yield and also the selectivity of the epoxidation step are still desirable, especially in view of the fact that the separation of epoxide isomers **1a** and **1b** on a preparative scale proved to be exceedingly difficult. Nevertheless, the epoxidation of **2** with *Oxone*® in the presence of **42** proceeds with significantly higher selectivity than previously reported for other epoxidation systems, and it has given access to sufficient quantities of material of **1a** for detailed biological testing. X-Ray crystallographic analysis of **1a** (in combination with that of intermediates *ent*-**9** and **14**) unambiguously established the configuration of the epoxide moiety in the more potent isomer of *trans*-epothilones A (**1a**) to be (12*S*,13*S*).

Experimental Part

General. Abbreviations: 9-BBN, 9-borabicyclo[3.3.1]nonane; DMF, *N*,*N*-dimethylformamide; FC, flash chromatography; LDA, lithium diisopropylamide; Ms, methylsulfonyl; NaHDMS, sodium hexamethyldisilazide; PPTS, pyridinium *p*-toluenesulfonate; TBS, (*tert*-butyl)dimethylsilyl; TBS-OTf, TBS triflate. If not noted otherwise, all starting materials were purchased from commercial suppliers and used without further purification. Solvents were of reagent-grade purity and used as purchased without any additional distillation. Pre-dried THF from *Fluka* was used in H_2O-sensitive reactions. FC: *Merck* silica gel *60* (0.043–0.060 mm). NMR Spectra: 200 MHz, *Varian Gemini-200*; 300 MHz, *Varian Gemini-300*; 400 MHz, *Varian Mercury 400*; 500 MHz, *Bruker DRX-500*; δ in ppm *J* in Hz. Electrospray mass spectra: *Fisons Instruments VG Platform II*.

X-Ray Crystallography. Suitable crystals of compound **1a** were obtained from an Et_2O soln. by slow evaporation of the solvent. A *Nonius-CAD4* (**1a**) or a *Philips PW1100* (*ent*-**9** and **14**) automatic diffractometer were used for data collection with Mo$K\alpha$ radiation and a graphite monochromator. The structures were solved by direct methods (SHELXS). The parameters were refined by full-matrix least-squares calculations (SHELXL) with anisotropic displacement parameters for all non-H-atoms. Subsequent difference *Fourier* maps showed 34 out of 49 H-atoms for **1a**, 32 of 45 for *ent*-**9**, and 24 out of 27 for **14**. The positions of the remaining H-atoms were calculated based on normal geometry. H-Atom parameters were idealized and not refined. For **1a**, the positions of the H-atoms of the two OH groups were taken from the difference map and kept fixed.

Crystallographic data for the individual structures have been deposited in the *Cambridge Crystallographic Data Centre* as deposition Nos. CCDC-192930 (**1a**), CCDC-192932 (*ent*-**9**), and CCDC-192931 (**14**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

2,2-Dimethyl-3-oxopentanal (**6**). Procedure analogous to the one reported for 2,2-dimethyl-3-oxobutanal by *Inukai* and *Yoshizawa* [41]: To a soln. of 17.5 ml (0.200 mol) of propanoyl chloride in 50 ml of ^{t}BuOMe was

added dropwise at r.t. within 3 min a soln. of 28.2 g (0.200 mol) of 1-(morpholin-4-yl)isobutene [42] in 50 ml of ^{t}BuOMe. The resulting suspension was heated to reflux for 16 h and then allowed to cool to r.t. After dilution with 100 ml of Et_2O, the temp. was further lowered to 0°, and the precipitate was collected by filtration and then dried *in vacuo* (32.3 g of white crystals). This material was redissolved in 50 ml of H_2O and the pH adjusted to 5 by addition of sat. aq. $NaHCO_3$ soln. Et_2O was added, and the mixture was stirred at r.t. for 18 h. The aq. phase was extracted with Et_2O (3 × 50 ml), the combined org. phase washed with H_2O (1 × 50 ml), dried ($MgSO_4$), and evaporated, and the residue purified by fractionated distillation: 14.03 g (55%) of **6**. Colorless liquid. B.p. 62–64°/20 Torr. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.58 (*s*, 1 H); 2.45 (*q*, 2 H); 1.30 (*s*, 6 H); 1.00 (*t*, 3 H).

*1-[(1*S*,5*R*)-10,10-Dimethyl-3,3-dioxido-3-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl]-ethanone* (=*(3a*S*,6*R*,7a*R*)-1-Acetylhexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide*; **7**). To a soln. of 430.0 g (2.0 mol) of (+)-camphor-10,2-sultam (*Avocado*) in 16 l of THF was added 96.0 g (2.200 mol) of NaH (55% dispersion in oil) in portions within 25 min. After stirring at r.t. for 15 h, 170.0 ml (2.400 mol) of AcCl was added to the suspension (ice-cooling) within 30 min. After stirring at r.t. for additional 15 min, 400 ml of THF/H_2O 4:1 was added to the light yellow suspension within 10 min. The THF was then evaporated, and the soln. was diluted with 3 l of H_2O and extracted with AcOEt (3 × 2 l). The combined org. extract was washed with 2 l of brine, dried (Na_2SO_4), and concentrated to a volume of *ca.* 2 l, which resulted in the formation of a suspension. Addition of 3 l of hexanes and cooling to 0–5° for 1 h provided, after filtration and drying at 50°, 481.0 g (93%) of **7**. Light yellow crystals. M.p. 133–135. $[\alpha]_D^{r.t.} = -96.8$ ($c = 0.995$, AcOEt); −109.5 ($c = 1.015$, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 4.83 (*m*, 1 H); 3.45 (*dd*, 2 H); 2.39 (*s*, 3 H); 2.10 (*m*, 2 H); 1.85 (*m*, 3 H); 1.35 (*m*, 2 H); 1.13 (*s*, 3 H); 0.95 (*s*, 3 H). MS: 275 ($[M+Na]^+$).

Alternatively, compound **7** was prepared in comparable yield and quality without NaH according to the following procedure [43]: To a soln. of 50 g (0.232 mol) of (−)-camphor-10,2-sultam (*Fluka*) in 1 l of MeCN was added 41.3 ml (0.580 mol) of AcCl under Ar, and the mixture was heated under reflux for 4 h. Then 64.1 g of K_2CO_3 was added, and stirring at reflux temp. was continued for 2 h. The suspension was then cooled to r.t., and 750 ml of H_2O was added together with 250 ml of CH_2Cl_2. The aq. phase was extracted with CH_2Cl_2 (3 × 800 ml), the combined org. phase washed with 500 ml of sat. NaCl soln., dried ($MgSO_4$), and evaporated. Recrystallization of the residue from hot EtOH gave 56.58 g (95%) of **7**. White crystals.

*(3*S*)-1-[(1*S*,5*R*)-10,10-Dimethyl-3,3-dioxido-3-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-3-hydroxy-4,4,dimethylheptane-1,5-dione* (**8**). Under Ar, 336 ml (2.32 mol) of triethylborane was slowly added to 2.7 l of hexane at r.t. (*ca.* 25 min). To this soln. was added 187 ml (2.14 mol) of CF_3SO_3H under cooling. After rinsing the dropping funnel with 180 ml of CH_2Cl_2, the mixture was slowly warmed to 40° until gas evolution had ceased (*ca.* 70 min). It was then cooled, and a soln. of 459 g (1.78 mol) of **7** in 4 l of CH_2Cl_2 was added at 0–2° within 20 min followed by a soln. of 382 ml (2.23 mol) of ^{i}Pr$_2$NEt (*Hünig*'s base) in 1.5 l of CH_2Cl_2 (also at 0–2°; *ca.* 20 min). The mixture was then cooled to −75°, and a soln. of 320 g (2.50 mol) of **6** in 300 ml of CH_2Cl_2 was added at the same temp. within 35 min. After an additional 1.5 h at −70 to −75°, the reaction was quenched by addition of 400 ml of THF/H_2O 3:1 followed by 3.5 l of sat. NH_4Cl soln. The soln. was then concentrated and diluted with 2 l of AcOEt and 2 l of H_2O. The aq. phase was extracted with AcOEt (3 × 2 l) and the combined org. phase washed with H_2O (6 × 1 l) and brine (1 × 1 l). Drying (Na_2SO_4) and evaporation gave a semicrystalline yellow residue which was twice recrystallized from AcOEt/hexane: 316 g (46%) of **8** as a single diastereoisomer. White crystals. M.p. 121–122°. $[\alpha]_D^{r.t.} = -110$ ($c = 1.03$, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 4.30 (*m*, 1 H); 3.85 (*m*, 1 H); 3.45 (*dd*, 2 H); 3.25 (*m*, 1 H); 2.80 (*m*, 2 H); 2.55 (*q*, 2 H); 2.10 (*m*, 2 H); 1.90 (*m*, 3 H); 1.35 (*m*, 2 H); 1.17 (*s*, 3 H); 1.15 (*s*, 3 H); 1.10 (*s*, 3 H); 1.02 (*t*, 3 H); 0.97 (*s*, 3 H). MS: 386 ($[M+H]^+$).

*(3*S*)-3-[(*tert*-Butyl)dimethylsilyl)oxy]-1-[(1*S*,5*R*)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo[5.2.1.0^{1,5}]-dec-4-yl]-4,4-dimethylheptane-1,5-dione* (=*(3a*S*,6R,7a*R*)-1-{(3*S*)-3-[(*tert*-Butoxy)dimethylsilyl]oxy}-4,4-dimethyl-1,5-dioxoheptyl}-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide*; **9**). To a soln. of 409 g (1.06 mol) of **8** in 3 l of CH_2Cl_2 was added 185 ml (1.59 mol) of 2,6-lutidine (=2,6-dimethylpyridine) followed by a soln. of 292 ml of TBS-OTf (1.272 mol) in 200 ml of CH_2Cl_2 (both additions at *ca.* −75°). The mixture was stirred at −75° for 2.5 h and then allowed to warm to r.t. overnight. The mixture was then extracted with H_2O (3 × 1 l), the combined aq. extract back-extracted with CH_2Cl_2 (2 × 1 l), the combined org. extract evaporated, and the residue recrystallized from EtOH/H_2O: 485 g (92%) of **9**. White crystals M.p. 87–89°. $[\alpha]_D^{r.t.} = -68.7$ ($c = 0.95$, AcOEt). ^{1}H-NMR (200 MHz, $CDCl_3$): 4.75 (*t*, 1 H); 3.83 (*m*, 1 H); 3.45 (*dd*, 2 H); 2.95 (*dd*, 1 H); 2.65 (*dd*, 1 H); 2.50 (*q*, 2 H); 2.10 (*m*, 2 H); 1.85 (*m*, 3 H); 1.35 (*m*, 2 H); 1.13 (2*s*, 6 H); 1.03 (*s*, 3 H); 0.97 ('*m*', 6 H); 0.83 (*s*, 9 H); 0.06 (*s*, 3 H); 0.04 (*s*, 3 H). MS: 500 ($[M+H]^+$). Anal. calc. for $C_{25}H_{45}NO_5SSi$ (499.79): C 60.08, H 9.08, N 2.80, S 6.42, Si 5.62; found: C 60.28, H 8.96, N 2.99, S 6.43, Si 5.50.

*(3S)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-4,4-dimethyl-5-oxoheptanoic Acid* (**3**). To a soln. of 10.0 g (0.020 mol) of **9** in 100 ml of THF/H_2O 4:1 was added 0.772 g (0.032 mol) of LiOH, followed by 3.37 ml of 30% aq. H_2O_2 soln. After 7 h stirring at r.t., 3.78 g of Na_2SO_3 was added to the mixture, and the THF was evaporated. To the remaining aq. suspension was added 50 ml of AcOEt, and the pH was adjusted to 6 by addition of 1N HCl. The aq. phase was extracted with AcOEt (2×), the combined org. phase evaporated, and the residue suspended in 50 ml of hexane. After stirring at 0° for 1 h, the mixture was filtered, the filtrate evaporated, and the residue purified by FC (CH_2Cl_2/MeOH 97:3 → 95:1): 4.58 g (76%) of **3**. Oil.

^{1}H-NMR (200 MHz, $CDCl_3$): 4.45 (*m*, 1 H); 2.50 (*m*, 3 H); 2.30 (*dd*, 1 H); 1.12 (*s*, 3 H); 1.05 (*s*, 3 H); 1.00 (*t*, 3 H); 0.85 (*s*, 9 H). MS (neg.): 301 ($[M-H]^-$).

On larger scale, the crude material obtained from the hexane filtrate after trituration was used directly in the next step.

5-(Benzyloxy)pentanoic Acid (**11**). To a mixture of 150 ml (1.65 mol) of pentano-5-lactone (**10**), 462 g (8.25 mol) of KOH, and 3.5 l of toluene was added 608 ml (5.29 mol) of benzyl chloride under N_2, and the mixture was heated under reflux for 16 h. After cooling to r.t., 3 l of H_2O, was added, and the mixture was stirred. The aq. phase was then washed with 2 l of Et_2O, acidified by addition of conc. HCl soln., and extracted with Et_2O (3 × 3 l). The combined acid extract was washed with brine (2.5 l) and evaporated and the oily residue co-evaporated with toluene (2 × 200 ml) and then dried *in vacuo:* 172 g (50%) of crude **11**. Oil. This material was used directly in the next step without further purification. If desired, **11** can be purified by distillation (b.p. *ca.* 130°/0.0075 Torr). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.30 (*m*, 5 H); 4.48 (*s*, 2 H); 3.45 (*t*, 2 H); 2.35 (*t*, 2 H); 1.70 (*m*, 4 H).

5-(Benzyloxy)pentanoyl Chloride (**12**). To a soln. of 220 g (1.05 mol) of crude **11** in 1.1 l of toluene under Ar was added 0.9 ml of DMF followed by dropwise addition of 130 ml (1.47 mol) of oxalyl chloride at r.t. within 1.5 h. After stirring at r.t. for additional 30 min, the mixture was heated to 50–60° for 1.75 h, after which period the solvents and excess oxalyl chloride were evaporated at a bath temp. of 40°. The light yellow oily residue thus obtained (226 g, 95%) was >90% pure and used as such in the next step. Although feasible on small scale, attempts to purify this acid chloride by vacuum distillation resulted in lower-quality material and in greatly reduced yields. B.p. 120–122°/0.075 Torr. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.30 (*m*, 5 H); 4.48 (*s*, 2 H); 3.45 (*t*, 2 H); 2.93 (*t*, 2 H); 1.90–1.60 (*m*, 4 H).

(4S)-4-Benzyl-3-[5-(benzyloxy)pentanoyl]oxazolidin-2-one (**13**). To a soln. of 544 g (3.07 mol) of (4*S*)-4-benzyloxazolidin-2-one in 9 l of THF was added 1.75 l of 15% BuLi soln. in hexane (4.1 mol) under Ar at −80° within 2 h. To this soln. was then added a soln. of 757 g (3.34 mol) of **12** in 2 l of THF dropwise over 1.5 h at −80°, and the mixture was stirred at −80° for 30 min. After that time, the reaction mixture was allowed to warm to −20°, and 400 ml of THF/H_2O 4:1 was added, followed by 800 ml of sat. aq. NH_4Cl soln. The THF was evaporated at 40°, the residue diluted with CH_2Cl_2/H_2O (2000 ml/400 ml), the aq. phase extracted with CH_2Cl_2 (1 × 2 l), the combined org. phase washed with 1N NaOH (1 × 2 l) and brine (2 × 4 l), and evaporated, the residue co-evaporated with toluene (2 × 1 l), and the resulting light brown oil purified by CC (silica gel, ^{t}BuOMe/hexanes 1:1): 821 g (73%) of **13** as an oil. Rechromatography of 196 g of impure material gave additional 151 g (13%) of **13**. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.30 (*m*, 8 H); 7.20 (*m*, 2 H); 4.65 (*m*, 1 H); 4.50 (*s*, 2 H); 4.15 (*d*, 2 H); 3.51 (*t*, 2 H); 3.28 (*dd*, 1 H); 2.95 (*m*, 2 H); 2.74 (*dd*, 1 H); 1.90–1.60 (*m*, 4 H).

(4S)-4-Benzyl-3-[(2S)-5-(benzyloxy)-2-methylpentanoyl]oxazolidin-2-one (**14**). All non-aq. steps were carried out under Ar. A soln. of 205 g (0.558 mol) of **13** in 800 ml of THF was added dropwise at −75° to 690 ml of 1M NaHMDS in THF. After completion of the addition (*ca.* 2 h), the soln. was stirred for an additional 30 min at −70° after which time a soln. of 198 ml (3.18 mol) of MeI in 800 ml of THF was added dropwise at the same temp. (*ca.* 45 min). The mixture was then stirred at −70° for 75 min, the cooling bath removed, and the mixture allowed to warm to r.t. After addition of 300 ml of THF/H_2O 1:1 followed by 250 ml of sat. NH_4Cl soln., the aq. phase was extracted with ^{t}BuOMe (3 × 300 ml), the combined org. phase evaporated, and the residue purified by CC (silica gel, ^{t}BuOMe/hexane 1:1): *ca.* 11:1 mixture of diastereoisomers. Two-fold recrystallization of this material from AcOEt/hexane (*ca.* 1:10) gave 98.5 g (46%) of **14**, which was diastereoisomerically pure. White crystalline solid. M.p. 51.5–53.3°. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.30 (*m*, 8 H); 7.20 (*m*, 2 H); 4.62 (*m*, 1 H); 4.48 (*s*, 2 H); 4.10 (*m*, 2 H); 3.75 (*m*, 1 H); 3.45 (*t*, 2 H); 3.25 (*dd*, 1 H); 2.75 (*dd*, 1 H); 1.80 (*m*, 1 H); 1.70–1.45 (*m*, 3 H); 1.22 (*d*, 3 H).

(2S)-5-(Benzyloxy)-2-methylpentan-1-ol (**15**). To a soln. of 67.5 g (0.175 mol) of **14** in 700 ml of dry THF was added 150 ml of 1M $LiAlH_4$ in THF (0.150 mol) at 5° within 20 min. The mixture was stirred at r.t. for 1 h and then quenched by addition of 17 ml of THF/H_2O, 10:7 followed by 6.5 ml of 4N NaOH and 15 ml of H_2O. The resulting precipitate was removed by filtration, the residue washed with 250 ml of THF, and the filtrate evaporated. The residue of the evaporation was then redissolved in 250 ml of AcOEt and this soln. extracted

with 200 ml each of H_2O, 1N NaOH, H_2O, 1N HCl, and H_2O followed by 300 ml of brine. The solvent was evaporated and the residue co-evaporated with toluene (3 × 100 ml). Vacuum distillation of the residue at 105°/0.69 mbar gave 26 g (72%) of **15**. Colorless oil. $[\alpha]_D^{r.t.} = -8.7$ ($c = 1$, MeOH). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.35–7.25 (*m*, 5 H); 4.50 (*s*, 2 H); 3.45 (*m*, 4 H); 1.80–1.40 (*m*, 3 H); 1.30–1.10 (*m*, 1 H); 0.95 (*d*, 3 H). MS: 209 ($[M+H]^+$).

*{[(2*S*)-5-(Benzyloxy)-2-methylpentyl]oxy}(*tert*-butyl)dimethylsilane* (**16**): To a soln. of 256 g (1.22 mol) of **15** and 216 g (3.17 mol) of 1*H*-imidazole in 1 l of DMF at r.t. was added 248 g (1.59 mol) of TBS-Cl in 3 portions, and the mixture was then stirred at 40° for 1 h. After cooling to 10°, 500 ml of ice-cold H_2O was added and the soln. poured onto 1 l of AcOEt. The aq. phase was extracted with AcOEt (3 × 500 ml), the combined org. phase washed with H_2O (3 × 1 l) and brine (1 × 1.5 l) and evaporated, and the residue co-evaporated with toluene (1 ×) and then purified by FC (silica gel, AcOEt/hexanes 1:6). 395 g (quant.) of **16**. Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.35–7.25 (*m*, 5 H); 4.49 (*s*, 2 H); 3.50–3.30 (*m*, 4 H); 1.75–1.35 (*m*, 4 H); 0.88 (*d* + overlapping *s*, 3 H + 9 H); 0.02 (*s*, 6 H). MS: 323 ($[M+H]^+$).

*(4*S*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-4-methylpentan-1-ol* (**17**). Compound **16** (102 g, 0.31 mol) was hydrogenated in 1800 ml of EtOH/cyclohexane 2:1 over 10% Pd/C (10 g) at r.t. and atmospheric pressure for 16 h. After removal of the catalyst by filtration, the solvents were evaporated, and the residue was purified by FC (silica gel, hexane/AcOEt 6:1 → 1:1). 67.7 g (94%) of **17**. Colorless oil. $[\alpha]_D^{r.t.} = -3.4$ ($c = 1$, MeOH). ^{1}H-NMR (200 MHz, $CDCl_3$): 3.62 (*t*, 2 H); 3.40 (*m*, 2 H); 1.70–1.30 (*m*, 4 H); 1.25–1.00 (*m*, 1 H); 0.88 (*d* + overlapping *s*, 3 H + 9 H); 0.02 (*s*, 6 H). MS: 233 ($[M+H]^+$). Anal. calc. for $C_{12}H_{28}O_2Si$ (233.442): C 62.01, H 12.14, Si 12.08; found: C 61.8, H 12.0, Si 11.90.

*(*tert*-Butyl)[(2*S*)-5-iodo-2-methylpentyloxy]dimethylsilane* (**4**). Mesylation of **17**: To a soln. of 25 g (0.107 mol) of **17** in 200 ml of CH_2Cl_2 at 0° was added 22.4 ml (0.161 mol) of Et_3N followed by dropwise addition of 11.0 ml (0.14 mol) of MsCl. The resulting white suspension was stirred at 0° for 15 min and then carefully diluted with 100 ml of ^{t}BuOMe and 100 ml of H_2O. The org. layer was washed consecutively with 100 ml of 1N HCl, 100 ml of sat. $NaHCO_3$ soln., and 200 ml of brine. The brine extract was back-extracted with 50 ml of CH_2Cl_2. The combined org. extract was evaporated and the residue co-evaporated with toluene (1 ×) to provide 32 g (quant.) of **18** as a light yellow oil, which was used in the next step without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.20 (*t*, 2 H); 3.40 (*d*, 2 H); 3.00 (*s*, 3 H); 1.85–1.40 (*m*, 4 H); 1.25–1.05 (*m*, 1 H); 0.88 (*d* + overlapping *s*, 3 H + 9 H); 0.00 (*s*, 6 H). MS: 311 ($[M+H]^+$).

A mixture of 30 g (0.096 mol) of **18**, 30 g (0.193 mol) of NaI, and 200 ml of dry acetone was stirred at 50° for 25 h. After cooling to 15°, 70 ml of brine was added, insoluble material removed by filtration, and the filter-cake washed with 200 ml of AcOEt. The org. layer in the filtrate was then separated, the solvents were evaporated, and the residue was purified by FC (silica gel, hexanes/AcOEt 9:1): 28.0 g (85%) of **4**. Colorless oil. $[\alpha]_D^{r.t.} = -8.2$ ($c = 1.034$, MeOH). ^{1}H-NMR (200 MHz, $CDCl_3$): 3.40 (*m*, 2 H); 3.15 (*t*, 2 H); 1.95–1.75 (*m*, 2 H); 1.70–1.40 (*m*, 2 H); 1.25–1.00 (*m*, 1 H); 0.88 + 0.85 (*s* + overlapping *d*, 9 H + 3 H); 0.02 (*s*, 6 H). Anal. calc. for $C_{12}H_{27}IOSi$ (342.339): C 42.10, H 7.95, I 37.07, Si 8.20; found: C 42.45, H 8.29, I 37.13, Si 8.05.

*(3*S*,4*E*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-4-methyl-5-(2-methylthiazol-4-yl)pent-4-enal* (**20**). A soln. of 35.6 ml (0.414 mol) of oxalyl chloride in CH_2Cl_2 (600 ml) was treated at −70° under N_2 with a soln. of 61.4 ml (0.864 mol) of DMSO in 120 ml of CH_2Cl_2. After stirring at −75° for 10 min, a soln. of 117.9 g (0.36 mol) of alcohol **19** [19][31] in 300 ml of CH_2Cl_2 was added within 20 min, and stirring was continued for additional 30 min. To the clear mixture, Et_3N (250.9 ml, 1.8 mol) was then added within 15 min, such that the temp. was kept below −60°. After 5 min, the cooling bath was removed and the mixture allowed to warm to 0° within 1 h. H_2O (500 ml) was then added, the aq. phase extracted with CH_2Cl_2 (1 × 200 ml and 1 × 100 ml), the combined org. phase washed with brine, dried (Na_2SO_4), and evaporated and the resulting crude aldehyde purified by FC (hexanes, then hexanes/AcOEt 9:1 → 8:2): **20** (99.4 g, 85%). Slightly yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.78 (*m*, 1 H); 6.94 (*s*, 1 H); 6.55 (br. *s*, 1 H); 4.68 (*dd*, $J = 7.5, 3.5$, 1 H); 2.65–2.8 (*m*, 4 H); 2.49 (*ddd*, $J = 16, 4, 1$, 1 H); 2.03 (*s*, 3 H); 0.88 (*s*, 9 H); 0.03, 0.08 (2*s*, 6 H). MS: 326.3 ($[M+H]^+$).

*4-{(1*E*,3*S*)-6,6-Dibromo-3-{[(*tert*-butyl)dimethylsilyl]oxy}-2-methylhexa-1,5-dienyl}-2-methylthiazole* (**21**). A soln. of 32.51 g (0.123 mol) of triphenylphosphine in 58 ml of CH_2Cl_2 was added within 20 min to an ice-cooled soln. of 20.56 g (0.0620 mol) of tetrabromomethane in 150 ml of CH_2Cl_2 under N_2. The dark orange soln. was stirred for 10 min without cooling followed by addition of a soln. of 18.34 g (0.0563 mol) of **20** in 49 ml of CH_2Cl_2 over 30 min. During the addition of **20**, the temp. was kept between 18 and 23°. The resulting suspension was stirred for 1 h at r.t., cooled in an ice bath, and filtered. The solid filter cake was washed with CH_2Cl_2/hexane 1:1 (25 ml). The combined filtrates were stirred with H_2O (100 ml), and the mixture was neutralized by the addition of sat. aq. $NaHCO_3$ soln. The org. phase was then dried (Na_2SO_4), and evaporated and the residue purified by FC (hexane/AcOEt 8:2): **21** (21.77 g, 80%). Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.92 (*s*, 1 H);

6.51 (br. *s*, 1 H); 6.44 (*t*, 1 H); 4.24 (*dd*, 1 H); 2.70 (*s*, 3 H); 2.44 (*m*, 2 H); 2.01 (*s*, 3 H); 0.88 (*s*, 9 H); 0.03, 0.09 (2*s*, 6 H).

*4-{(1*E*,3*S*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-2-methylhex-1-en-5-ynyl}-2-methylthiazole* (**22**). Dibromoolefin **21** (24.05 g, 0.05 mol) was dissolved under N_2 in 150 ml of dry THF and the soln. cooled to $-75°$. Then 1.6M BuLi in hexanes (66 ml, 0.1056 mol) was added dropwise over 30 min, and the dark mixture was stirred for 1 h at $-75°$ and then 1 h at r.t. H_2O (100 ml) was added slowly to the mixture followed by Et_2O (300 ml). The aq. phase was extracted with Et_2O (2 × 100 ml), the combined org. phase washed with brine, dried (Na_2SO_4), and evaporated, and the crude product purified by FC (hexanes, then hexanes/AcOEt 99:1 → 92:8): 9.62 g (60%) of **22**. Yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.03, 0.09 (2*s*, 6 H); 0.88 (*s*, 9 H); 1.95 (*t*, *J* = 2, 1 H); 2.01 (*s*, 3 H); 2.44 (*dd*, *J* = 7.5, 2, 2 H); 2.70 (*s*, 3 H); 4.29 (br. *t*, *J* = 7.5, 1 H); 6.51 (br. *s*, 1 H); 6.94 (*s*, 1 H). MS: 322.3 ($[M+H]^+$).

*4-{(1*E*,3*S*,5*E*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-iodo-2-methylhexa-1,5-dienyl}-2-methylthiazole* (**5**). To a suspension of 26.1 g (0.0961 mol) of chlorobis(cyclopentadienyl)hydrozirconium (*Schwartz*'s reagent) in dry THF (200 ml) was added dropwise a soln. of 20.6 g (0.0641 mol) of **22** in dry THF (50 ml) at r.t. under N_2. After stirring at r.t. for 30 min, an almost clear soln. was obtained, which was treated with solid I_2 (0.0961 mol) over a period of 10 min. During the addition, the temp. was maintained at 20–25° with an ice-water bath. The dark mixture was stirred for additional 10 min and then added dropwise to 400 ml of sat. aq. $NaHCO_3$ soln. under stirring. Hexanes/AcOEt 9:1 (200 ml) was added and the mixture stirred for 5 min. The aq. phase was extracted with hexanes/AcOEt 9:1 (2 × 150 ml), the combined org. phase washed with brine (200 ml), dried (Na_2SO_4), and evaporated, and the resulting black oil purified by FC (toluene, then toluene/AcOEt 98:2 → 96:4): **5** (22.3 g, 77%). Brownish oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.91 (*s*, 1 H); 6.6–6.7 (*m*, 2 H); 6.04 (br. *d*, *J* = 15, 1 H); 4.13 (br. *t*, *J* = 7.5, 1 H); 2.69 (*s*, 3 H); 2.42–2.35 (*m*, 2 H); 1.98 (br. *s*, 3 H); 0.88 (*s*, 9 H); −0.01, 0.05 (2*s*, 6 H). MS: 450.1 ($[M+H]^+$).

*4-{(1*E*,3*S*,5*E*,10*S*)-3,11-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-2,10-dimethylundeca-1,5-dienyl}-2-methylthiazole* (**23**). To suspension of Zn–Cu couple (3.74 g, 0.057 mol) in dry benzene was added 0.27 ml (0.0032 mol) of ethylene bromide under N_2. The mixture was immersed in a preheated oil bath, refluxed for 30 s and cooled to r.t. (ice-water bath) followed by addition of Me_3SiCl (0.27 ml, 0.0022 mol) and stirring for 5 min. To this mixture was added a soln. of 12.7 g (0.037 mol) of **4** and 5.9 ml (0.063 mol) of *N*,*N*-dimethylacetamide in 31.5 ml of benzene within 5 min. The resulting mixture was heated to 60° for 2.5 h and then cooled to r.t. After addition of 0.16 ml (0.00069 mol) of TMS-OTf and 5.9 ml (0.063 mol) of *N*,*N*-dimethylacetamide, heating was continued for 1 h at 80°. After cooling to r.t., 1.09 g (0.00095 mol) of tetrakis(triphenylphosphine)palladium was added, and the mixture was stirred for 5 min. A soln. of 11.1 g (0.0247 mol) of **5** in 23 ml of benzene was then added dropwise and the mixture heated to 60° for 30 min and cooled to r.t. After addition of sat. aq. NH_4Cl soln. (39 ml) and 150 ml of ^{t}BuOMe, the resulting mixture was filtered through *Hyflo*, the aq. phase extracted with ^{t}BuOMe (2 × 50 ml), the combined org. phase washed with brine (50 ml), dried (Na_2SO_4), and evaporated, and the crude product purified by FC (hexanes, then hexanes/AcOEt 99:1 → 96:4): 9.16 g (69%) of **23**. Slightly yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.90 (*s*, 1 H); 6.43 (br. *s*, 1 H); 5.27–5.51 (*m*, 2 H); 4.08 (br. *t*, *J* = 7.5, 1 H); 2.69 (*s*, 3 H); 2.17–2.28 (*m*, 2 H); 3.25–3.47 (*m*, 2 H); 1.88–2.0 (*m*, 5 H); 1.15–1.4 (*m*, 4 H); 0.78–0.9 (*m*, 22 H); −0.02, 0.00, 0.09 (3*s*, 12 H). MS: 450.0 ($[M+H]^+$).

*(2*S*,6*E*,9*S*,10*E*)-9-{[(*tert*-Butyl)dimethylsilyl]oxy}-2,10-dimethyl-11-(2-methylthiazol-4-yl)undeca-6,10-dien-1-ol* (**24**). To a soln. of 18.24 g (0.0339 mol) of **23** in 500 ml of MeOH/CH_2Cl_2 1:1 was added solid (+)-camphor-10-sulfonic acid (7.88 g, 0.0339 mol) at 0° under N_2 in portions over 5 min. The mixture was then stirred at 0° for 30 min and subsequently for 2 h at r.t. After addition of sat. aq. $NaHCO_3$ soln. (31.1 ml), the solvents were evaporated, and the residue was partitioned between H_2O (50 ml) and CH_2Cl_2 (200 ml). The aq. phase was further extracted with CH_2Cl_2 (2 × 30 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the crude product purified by FC (hexanes/AcOEt 91:9 → 77:23): 11.53 g (80%) of **24**. Slightly yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.92 (*s*, 1 H); 6.44 (br. *s*, 1 H); 5.26–5.48 (*m*, 2 H); 4.10 (br. *t*, *J* = 7.5, 1 H); 3.35–3.5 (*m*, 2 H); 2.70 (*s*, 3 H); 2.15–2.34 (*m*, 2 H); 1.92–2.02 (*m*, 5 H); 1.2–1.5 (*m*, 4 H); 0.85–1.11 (*m*, 14 H); −0.01, 0.06 (2*s*, 6 H). MS: 424.3 ($[M+H]^+$).

*(2*S*,6*E*,9*S*,10*E*)-9-{[(*tert*-Butyl)dimethylsilyl]oxy}-2,10-dimethyl-11-(2-methylthiazol-4-yl)undeca-6,10-dienal* (**25**). A soln. of 0.185 ml (0.00215 mol) of oxalyl chloride in 4.6 ml of CH_2Cl_2 was treated at −70° under N_2 with a soln. of 0.334 ml (0.0047 mol) of DMSO in 1 ml of CH_2Cl_2. After stirring at −70° for 10 min, a soln. of 0.83 g (0.00196 mol) of **24** in 3 ml of CH_2Cl_2 was added within 10 min, and stirring was continued for 30 min. To the clear mixture, 1.365 ml (0.00979 mol) of Et_3N was added within 10 min such that the temp. was kept below −60°. The cooling bath was then removed, and the mixture was allowed to warm to r.t. within 1 h. H_2O (6 ml) was added, the aq. phase extracted with CH_2Cl_2 (1 × 5 ml and 1 × 3 ml), the combined org. phase dried

(Na_2SO_4) and evaporated and the crude aldehyde purified by FC (hexanes, then hexanes/AcOEt 95:5 → 80:20): 0.656 g (79%) of **25**. Slightly yellow oil. $[\alpha]_D^{21} = +20.16$ ($c = 2.465$, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 9.55 (d, $J = 2$, 1 H); 6.90 (s, 1 H); 6.43 (br. s, 1 H); 5.27–5.5 (m, 2 H); 4.09 (t, $J = 6.5$, 1 H); 2.69 (s, 3 H); 2.13–2.38 (m, 3 H); 1.9–2.05 (m, 5 H); 1.6–1.75 (m, 1 H); 1.22–1.44 (m, 3 H); 1.03 (d, $J = 7.5$, 3 H); 0.87 (s, 9 H); −0.02, 0.03 (2s, 6 H). MS: 422.2 ($[M+H]^+$).

*(5*S*)-5-[[(*tert*-Butyl)dimethylsilyl]oxy]-7-hydroxy-4,4-dimethylheptan-3-one* (**29**). To a soln. of 78 g of crude **3** in 300 ml of THF was aded dropwise 90 ml (0.800 mol) of trimethyl borate at 0° within 5 min followed by 50 ml (0.500 mol) of $BH_3 \cdot Me_2S$ within 15 min. The mixture was then stirred at ice-bath temp. for 22 h, at which point 200 g of crushed ice was added in portions, such that the temp. did not exceed +5°. The resulting emulsion was stirred at r.t. for 30 min. The solvents were then removed by evaporation (azeotropic removal of H_2O with toluene), and 2 l of hexanes were added to the milky residue followed by 80 g of H_2O and 100 g of Na_2SO_4. After stirring at r.t. for 1 h, the mixture was filtered and the filtrate evaporated. Purification of the residue by FC (CH_2Cl_2, 2 runs) gave 32.5 g (56%) of **29**. Clear colorless oil. $[\alpha]_D^{r.t.} = +31.1$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$; 1:2 equilibrium between the open-chain and the cyclic-hemiacetal form (major component), the latter being a diastereoisomer mixture; thus some of the integrals do not amount to signals of 1.0): 6.03 (d, 0.65 H, exchangeable with D_2O); 4.12, 4.00–3.82, 3.70–3.58 (dt, m, m, 3 H); 2.15 (m, 0.65 H); 1.80–1.40 (m, 3.35 H); 1.12–0.89 ('m', 19 H); 0.13 (d, 3.9 H); 0.08 (d, 2.1 H). MS: 271 ($[M-OH]^+$).

*2-[(4*S*)-2,2-Dimethyl-1,3-dioxan-4-yl]-2-methylpentan-3-one* (**31**). A soln. of 32.0 g (0.111 mol) of **29** in a mixture of 440 ml of acetone and 25.7 ml of CF_3COOH was stirred at r.t. for 18 h. After cooling to 2°, Et_3N (61.3 ml) was added within 10 min followed by 750 ml of Et_2O and 165 ml of H_2O. The emulsion was stirred at r.t. for 15 min, the Et_2O soln. back-extracted with H_2O (3 × 100 ml), the combined aq. extract in turn back-extracted with Et_2O (3 × 100 ml), the combined org. phase washed with brine (1 × 80 ml), dried, and evaporated, and the residue purified by FC (hexane/Et_2O 6:1 (+0.1% of Et_3N)): 22.0 g (93%) of **31**. Colorless oil, which solidified upon standing at −20°. $[\alpha]_D^{r.t.} = +13.0$ ($c = 1.335$, $CHCl_3$) ([31]: +12.4 ($c = 1.0$, $CHCl_3$)). ^{1}H-NMR (200 MHz, $CDCl_3$): 4.01 (dd, 1 H); 3.91 (dd, 1 H); 3.82 (m, 1 H); 2,50 (q, 2 H); 1,60 (m, 1 H); 1.40 (s, 3 H); 1.30 (s + overlapping m, 3 H + 1 H); 1.11 (s, 3 H); 0.98 (t, 3 H). MS: 215 ($[M+H]^+$), 157 (100, [M − acetone]$^+$).

*(2*S*)-5-(Benzyloxy)-2-methylpentanal* (**30**). To a soln. of 10.71 g (0.085 mol) of oxalyl chloride in 170 ml of CH_2Cl_2 was added a soln. of 13.19 g of DMSO (0.209 mol) in 15 ml of CH_2Cl_2 at −78° within 15 min. The soln. was stirred at −78° for 15 min, when a soln. of 8.79 g of **15** (0.043 mol) in 35 ml of CH_2Cl_2 was added dropwise within 15 min. The mixture was stirred at −78° for 45 min and then 25.62 g (0.254 mol) of Et_3N was added dropwise at −78° within 15 min. The cooling bath was removed and the mixture allowed to warm to r.t. (suspension). It was then recooled to −30°, and 110 ml of sat. aq. NH_4Cl soln. was added. Subsequently H_2O was added at r.t. until a clear biphasic soln. had formed. The org. phase was washed with 75 ml of 2% $KHSO_4$ soln., 75 ml of sat. aq. $NaHCO_3$ soln., and 75 ml of brine, dried ($MgSO_4$), and evaporated. The residue was purified by FC (AcOEt/hexane 3:7): 7.15 g (81%) of **30**. Oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.62 (d, 1 H); 7.32 (m, 5 H); 4.50 (s, 2 H); 3.50 (t, 2 H); 2.35 (m, 1 H); 1.82 (m, 1 H); 1.65 (m, 2 H); 1.60 (m, 1 H); 1.11 (d, 3 H). MS: 207 ($[M+H]^+$).

*(4*R*,5*S*,6*S*)-9-(Benzyloxy)-2-[(4*S*)-2,2-dimethyl-1,3-dioxan-4-yl]-5-hydroxy-2,4,6-trimethylnonan-3-one* (**32**). To a soln. of 9.6 ml (0.068 mol) of $^iPr_2NH$ in 100 ml of THF was added dropwise 42.46 ml of 1.6M BuLi (0.068 mol) in hexane at −5 to −0° within 10 min. The yellow soln. was stirred at 0° for 30 min and then cooled to −78°, and a soln. of 14.83 g (0.069 mol) of **31** in 100 ml of THF was added dropwise at −78° within 20 min. After one additional hour at −78°, a soln. of **30** (7.15 g, 0.0347 mol) in 125 ml of THF was added dropwise over 15 min. The mixture was then stirred at −78° for 1 h, when 150 ml of sat. aq. NH_4Cl soln. was added. The mixture was then allowed to warm to r.t., and 600 ml of Et_2O was added followed by H_2O until a clear biphasic soln. had formed. The aq. phase was extracted with Et_2O (2 × 600 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue purified by FC (hexane/AcOEt 3:2, 3 runs): 11.94 g (82%) of **32** as a single diastereoisomer (by NMR). ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.35 (s, 2 H); 7.33 (s, 3 H); 7.28 (m, 1 H); 4.50 (s, 2 H); 4.05 (dd, 1 H); 3.97 (m, 1 H); 3.86 (m, 1 H); 3.48 (m, 3 H); 3.38 (d, 1 H); 3.28 (q, 1 H); 1.85–1.70 (m, 2 H); 1.68–1.35 (m, 3 H; overlapping with s at 1.56, 3 H); 1.40 (s, 3 H); 1.35 (m, 1 H, overlapping with s at 1.34, 3 H); 1.08 (s, 3 H); 1.02 (d, 3 H); 0.85 (d, 3 H). MS: 421.4 ($[M+H]^+$).

*(3*S*,6*R*,7*S*,8*S*)-11-(Benzyloxy)-1,3,7-trihydroxy-4,4,6,8-tetramethylundecan-5-one* (**33**). To a soln. of 11.96 g (0.0284 mol) of **32** in 360 ml of MeOH was added 7.15 g (0.0284 mol) of PPTS, and the mixture was stirred at r.t. for 24 h. The solvent was evaporated and the residue purified by FC (Et_2O): 8.75 g (81%) of **33**. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.32 (m, 5 H); 4.50 (s, 2 H); 4.03 (m, 1 H); 3.85 (m, 2 H); 3.49 (m, 2 H); 3.42–3.23

(*m*, 4 H); 1.78 (*m*, 2 H); 1.65–1.50 (*m*, 4 H); 1.20 (*s*, 3 H); 1.15 (*s*, 3 H); 1.07 (*d*, 3 H); 0.88 (*d*, 3 H). MS: 403.0 ($[M+Na]^+$).

*(3S,6R,7S,8S)-11-(Benzyloxy)-1,3,7-tris-{[(*tert*-butyl)dimethylsilyl]oxy}-4,4,6,8-tetramethylundecan-5-one* (**34**). To a soln. of 8.75 g of **33** (0.023 mol) in 300 ml of CH_2Cl_2 was added 12.3 g (0.115 mol) of 2,6-lutidine followed by dropwise addition of 24.3 g (0.0919 mol) of TBS-OTf at 0–5° over 10 min. The mixture was stirred at r.t. for 20 h, concentrated to *ca.* 50% of its original volume, and then poured on a mixture of 800 ml of AcOEt and 500 ml of sat. aq. $NaHCO_3$ soln. The aq. soln. was extracted with 300 ml of AcOEt, the combined org. extract successively washed with H_2O, 5% $KHSO_4$ soln. (2×), brine (2×), and H_2O, dried ($MgSO_4$), and evaporated, and the residue purified by FC (3% hexane/Et_2O): 13.81 g (81%) of **34**. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.32 (*m*, 4 H); 7.28 (*m*, 1 H); 4.50 (*s*, 2 H); 3.89 (*dd*, 1 H); 3.78 (*dd*, 1 H); 3.66 (*m*, 1 H); 3.58 (*m*, 1 H); 3.46 (*t*, 2 H); 3.15 (*m*, 1 H); 1.70 (*m*, 1 H); 1.57 (*m*, 1 H); 1.48 (*m*, 2 H); 1.40–1.15 (*m*, 3 H, overlapping with *s* at 1.22, 3 H); 1.05 (*d*, 3 H); 1.02 (*s*, 3 H); 0.94 (*d*, 3 H); 0.92–0.84 ('*m*', 27 H); 0.11–0.01 (several *s*, 18 H). MS: 723.0 ($[M+H]^+$).

*(3S,6R,7S,8S)-11-(Benzyloxy-3,7-bis{[(*tert*-butyl)dimethylsilyl]oxy}-hydroxy-4,4,6,8-tetramethylundecan-5-one* (**35**). To a soln. of 12.8 g (0.0174 mol) of **34** in 700 ml of CH_2Cl_2/MeOH 1:1 at 0° was added 4.18 g (0.0180 mol) of camphorsulfonic acid portionwise over 5 min. The mixture was stirred at 0° for 1 h, when 2.5 ml (0.0179 mol) of Et_3N was added. The bulk of the CH_2Cl_2 was then evaporated, and 300 ml of AcOEt was added to the remaining soln. This was followed by removal of the bulk of MeOH by evaporation (no heating) and subsequent addition of additional 200 ml of AcOEt. This soln. was extracted with 400 ml of sat. aq. $NaHCO_3$ soln. and H_2O (2×), the combined aq. extract once back-extracted with 300 ml of CH_2Cl_2, the CH_2Cl_2 soln. washed several times with H_2O (each 100 ml), the combined org. extract dried ($MgSO_4$) and evaporated, and the residue purified by FC (hexane/Et_2O 2:1): 8.66 g (80%) of **35**. ^{1}H-NMR ((D$_6$)DMSO, 500 MHz): 7.30 (*m*, 5 H); 4.42 (*s*, 2 H); 4.38 (*t*, 1 H); 3.79 (*dd*, 1 H); 3.68 (*m*, 1 H); 3.46 (*m*, 1 H); 3.39 (*t*, 2 H); 3.35 (*m*, 1 H); 3.17 (*m*, 1 H); 1.62 (*m*, 1 H); 1.48 (*m*, 2 H); 1.32 (*m*, 3 H); 1.15 (*s*, 3 H; overlapping with *m*, 1 H); 0.98 (*d*, 3 H); 0.97 (*s*, 3 H); 0.90–0.84 ('*m*', 21 H); 0.07 (*s*, 3 H); 0.05 (*s*, 3 H); 0.04 (*s*, 6 H). MS: 631.3 ($[M+Na]^+$).

*(3R,6R,7S,8S)-11-(Benzyloxy)-3,7-bis{[(*tert*-butyl)dimethylsilyl]oxy}-4,4,6,8-tetramethyl-5-oxoundecanal* (**36**). To a soln. of 1.5 ml (0.0177 mol) of oxalyl chloride in 45 ml of CH_2Cl_2 was added 2.7 ml (0.0380 mol) of DMSO at −75° within 5 min. The soln. was stirred at −75° for 10 min, when a soln. of 9.25 g (0.0148 mol) of alcohol **35** in 45 ml of CH_2Cl_2 was added dropwise within 20 min. The mixture was stirred at −75° for 30 min, and then 12.0 ml (0.0884 mol) of Et_3N was added dropwise at −75° within 10 min. The mixture was allowed to warm to −10°, followed by addition of 200 ml of H_2O and 300 ml of CH_2Cl_2. The org. phase was washed with brine (2 × 300 ml), the combined aq. phase re-extracted with CH_2Cl_2 (1 × 200 ml), the combined org. extract dried ($MgSO_4$) and evaporated and the residue purified by FC (hexane/Et_2O 4:1) 8.51 g (92%) of **36**. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.76 (*d*, 1 H); 7.30 (*m*, 5 H); 4.50 (overlapping *s* and *m*, 3 H); 3.79 (*d*, 1 H); 3.47 (*t*, 2 H); 3.12 (*m*, 1 H); 2.50 (*dd*, 1 H); 2.40 (*dd*, 1 H); 1.72 (*m*, 1 H); 1.60–1.10 (*m*, 4 H; overlapping with *s* at 1.22, 3 H); 1.08 (*s*, 3 H); 1.05 (*d*, 3 H); 0.93 (*d*, 3 H); 0.90 (*s*, 9 H); 0.88 (*s*, 9 H); 0.09 (*s*, 3 H); 0.06 (*s*, 6 H); 0.04 (*s*, 3 H). MS: 607.3 ($[M+H]^+$).

*(3S,6R,7S,8S)-11-(Benzyloxy)-3,7-bis{[(*tert*-butyl)dimethylsilyl]oxy}-4,4,6,8-tetramethyl-5-oxoundecanoic Acid* (**37**). To a soln. of *ca.* 7 g (0.0875 mol) of isobutene in 40 ml of THF at 0° was added a soln. of 8.5 g (0.0137 mol) of **36** in 70 ml of *t*BuOH dropwise within 15 min followed by the dropwise addition of 14 ml of H_2O at 0°. Then 4.8 g of $NaClO_2$ (80%) and 2.9 g of $NaH_2PO_4 \cdot H_2O$ were added, and the mixture was stirred at r.t. for 4 h. The mixture was evaporated, the residue distributed between H_2O and CH_2Cl_2 (500 ml each), the pH of the separated aq. phase adjusted to 4.5 with 1N HCl, and the aq. phase recombined with the CH_2Cl_2 extract. After extraction, the aq. phase was extracted with CH_2Cl_2 (2 × 250 ml), the combined org. phase washed with H_2O (400 ml), dried, and evaporated, and the residue purified by FC (hexane/acetone 1:1): 8.10 g (93%) of **37**. Oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30 (*m*, 5 H); 4.50 (*s*, 2 H); 4.39 (*m*, 1 H); 3.80 (*d*, 1 H); 3.45 (*m*, 2 H); 3.15 (*m*, 1 H); 2.48 (*dd*, 1 H); 2.31 (*dd*, 1 H); 1.72 (*m*, 1 H); 1.45 (*m*, 1 H); 1.35–1.15 (*m*, 3 H; overlapping with *s* at 1.21, 3 H); 1.10 (*s*, 3 H); 1.06 (*d*, 3 H); 0.92 (*d*, 3 H); 0.90 (*s*, 9 H); 0.88 (*s*, 9 H); 0.10 (*s*, 3 H); 0.06 (*s*, 9 H). MS (neg.): 621.5 ($[M-H]^+$).

*(3S,6R,7S,8S)-11-(Benzyloxy)-3,7-bis{[(*tert*-butyl)dimethylsilyl]oxy}-4,4,6,8-tetramethyl-5-oxoundecanoic Acid Methyl Ester* (**38**). A soln. of 3.27 g (0.00513 mol) of **37** in 90 ml of CH_2Cl_2 was cooled to −20°, and 1.2 g (0.00582 mol) of dicyclohexylcarbodiimide, 3.5 ml (0.00865 mol) of MeOH, and 0.647 mg (0.00535 mol) of *N,N*-dimethylpyridin-4-amine were added. The mixture was allowed to warm to r.t., and after 4.5 h, it was diluted with 400 ml of CH_2Cl_2. This soln. was extracted with H_2O (2 × 200 ml), the combined aq. phase re-extracted with CH_2Cl_2 (2×), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue purified by FC (hexane/Et_2O 9:1). 2.478 g (71%) of **38**. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30 (*m*, 5 H); 4.50 (*s*, 2 H); 4.40

(*m*, 1 H); 3.80 (*d*, 1 H); 3.67 (*s*, 3 H); 3.47 (*m*, 2 H); 3.15 (*m*, 1 H); 2.42 (*dd*, 1 H); 2.28 (*dd*, 1 H); 1.72 (*m*, 1 H); 1.60–1.20 (*m*, 4 H); 1.20 (*s*, 3 H); 1.06 (*s*, 3 H); 1.05 (*d*, 3 H); 0.91 (*d*, 3 H); 0.89 (*s*, 9 H); 0.87 (*s*, 9 H); 0.09 (*s*, 3 H); 0.05 (*s*, 6 H); 0.03 (*s*, 3 H). MS: 659.2 ($[M+Na]^+$).

*(3*S*,6*R*,7*S*,8*S*)-3,7-Bis[[(*tert*-butyl)dimethylsilyl]oxy]-11-hydroxy-4,4,6,8-tetramethyl-5-oxoundecanoic Acid Methyl Ester* (**39**). Compound **38** (1.25 g, 0.00123 mol) was hydrogenated over 150 mg of 5% Pd/C in 50 ml of MeOH at r.t. and 1 atm. After 4 h, the catalyst was removed by filtration, the filtrate evaporated, and the residue purified by FC (hexane/Et_2O 1:1): 0.935 g (74%) of **39**. Oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.41 (*m*, 1 H); 3.80 (*d*, 1 H); 3.68 (*s*, 3 H); 3.64 (*t*, 2 H); 3.17 (*m*, 1 H); 2.43 (*dd*, 1 H); 2.29 (*dd*, 1 H); 1.65 (*m*, 1 H); 1.55–1.30 (*m*, 4 H); 1.22 (*s*, 3 H); 1.10 (*s*, 3 H); 1.07 (*d*, 3 H); 0.95 (*d*, 3 H); 0.91 (*s*, 9 H); 0.88 (*s*, 9 H); 0.10 (*s*, 3 H); 0.07 (*s*, 6 H); 0.02 (*s*, 3 H). MS: 569.3 ($[M+Na]^+$).

*(3*S*,6*R*,7*S*,8*S*)-3,7-Bis[[(*tert*-butyl)dimethylsilyl]oxy]-4,4,6,8-tetramethyl-5-oxoundec-10-enoic Acid Methyl Ester* (**40**). To a soln. of 5.0 g (0.00891 mol) of **39** and 6.44 g (0.0284 mol) of 2-nitrophenyl selenocyanate in 50 ml of THF was added 7.13 ml (0.0288 mol) of tributyl phosphine dropwise within 15 min such that the temp. did not exceed 35°. The mixture was stirred at r.t. for 1 h, at which point 23 g of solid $NaHCO_3$ was added, followed by dropwise addition of 31.2 ml of 30% aq. H_2O_2 soln., again such that the temp. did not exceed 35°. After 16 h at r.t., 185 ml of 5% $KHSO_4$ soln. was added to the mixture, which was then extracted with Et_2O (2 × 400 ml). The combined org. extract was washed with H_2O (200 ml), dried ($MgSO_4$), and evaporated. Purification of the residue by FC (hexane/AcOEt 95:5) gave 4.495 g (93%) of **40**. Yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.73 (*m*, 1 H); 5.02 (*d*, 1 H); 4.98 (*s*, 1 H); 4.41 (*m*, 1 H); 3.81 (*d*, 1 H); 3.68 (*s*, 3 H); 3.17 (*m*, 1 H); 2.43 (*dd*, 1 H); 2.29 (*dd*, 1 H); 2.25 (*m*, 1 H); 1.85 (*m*, 1 H); 1.40 (*m*, 1 H); 1.26 (*s*, 3 H); 1.10 (*s*, 3 H); 1.08 (*d*, 3 H); 0.96 (overlapping *d* and *s*, 12 H); 0.94 (*s*, 9 H); 0.10 (*s*, 1 H); 0.08 (*s*, 6 H); 0.03 (*s*, 3 H). MS: 529.1 ($[M+H]^+$).

*(3*S*,6*R*,7*S*,8*S*,12*E*,15*S*,16*E*)-3,7,15-Tris[[(*tert*-butyl)dimethylsilyl]oxy]-4,4,6,8,16-pentamethyl-17-(2-methylthiazol-4-yl)-5-oxoheptadeca-12,16-dienoic Acid Methyl Ester* (**41**). To a soln. of 2.00 g (0.00378 mol) of **40** in 35 ml of THF was added 8.32 ml of 0.5M 9-BBN in THF (*Aldrich*) under Ar, and the mixture was stirred at r.t. for 4 h (*soln. A*). In a separate flask, 1.28 g (0.00284 mol) of **5** was added to a mixture of 1.85 g (0.00567 mol) of Cs_2CO_3, 0.236 g (0.000756 mol) of Ph_3As, 0.261 g (0.00378 mol) of [$PdCl_2$(dppf)], dppf = 1,1′-bis(diphenylphosphino)ferrocene, and 0.612 ml (0.034 mol) of H_2O in 23 ml of DMF (*soln. B*). *Soln. B* was cooled to −10° and then *soln. A* was added. The mixture was allowed to warm to r.t. and stirred at r.t. for 24 h, when 400 ml of H_2O was added, followed by 400 ml of AcOEt. The aq. soln. was back-extracted with AcOEt (2 × 200 ml), the combined org. extract dried (Na_2SO_4) and evaporated, and the residue purified by FC (toluene/AcOEt 100:1): 1.534 g (63%) of **41**. Oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.90 (*s*, 1 H); 6.44 (*s*,1 H); 5.41 (*m*, 2 H); 4.40 (*dd*, 1 H); 4.08 (*m*, 1 H); 3.75 (*dd*, 1 H); 3.65 (*s*, 3 H); 3.13 (*m*, 1 H); 2.69 (*s*, 3 H); 2.44–2.16 (*m*, 4 H); 1.99 (*s*, 3 H); 1.95 (*m*, 2 H); 1.30 (*m*, 1 H); 1.23 (*s*, 3 H); 1.05 (*s*, 3 H); 1.03 (*d*, 3 H); 0.90–0.85 (3*s*, 27 H); 0.09 (*s*, 3 H); 0.05 (*s*, 9 H); 0.01 (*s*, 3 H); −0.01 (*s*, 3 H).

*(3*S*,6*R*,7*S*,8*S*,12*E*,15*S*,16*E*)-3,7,15-Tris[[(*tert*-butyl)dimethylsilyl]oxy]-4,4,6,8,16-pentamethyl-17-(2-methylthiazol-4-yl)-5-oxoheptadeca-12,16-dienoic Acid* (**26**). *Approach A:* To a soln. of LDA in THF (prepared from 47.2 ml of 1.6M BuLi in hexane (0.0755 mol) and 10.67 g (0.0755 mol) of ^{i}Pr_2NH in 100 ml of dry THF) was added a soln. of 9.14 g (0.03 mol) of **3** in 60 ml of dry THF at −70° under N_2 dropwise within 15 min. After completion of the addition, the mixture was stirred for 15 min at −70° and for 1 h at −35°. After re-cooling to −78°, a soln. of 10.6 g (0.025 mol) of **25** in 57 ml of dry THF was added dropwise within 15 min, the mixture was stirred at −78° for 1 h, warmed to −50°, and then quenched by the slow addition of sat. aq. NH_4Cl soln. (118.5 ml). The resulting suspension was warmed to 0° and treated with AcOH (12 ml) and AcOEt (250 ml). After extensive shaking, the aq. phase was re-extracted with AcOEt (3 × 50 ml) and the combined org. extract dried (Na_2SO_4) and evaporated: crude aldol product.

This material was dissolved in 250 ml of CH_2Cl_2 under N_2 and the soln. cooled in an ice bath. Then, 2,6-lutidine (18,97 ml, 0.1634 mol) was added followed by 24.9 ml (0.108 mol) of TBS-OTf, which was added dropwise over 10 min. The clear soln. was stirred at 0° for 2 h and then treated with 10% citric acid (250 ml). After efficient stirring, the aq. phase was separated and extracted with CH_2Cl_2 (2 × 50 ml). The combined org. extract was dried (Na_2SO_4) and evaporated to give the crude per-silylated hydroxy acid. This material was dissolved in 250 ml of MeOH, K_2CO_3 (8.3 g, 0.06 mol) and H_2O (8.2 ml) were added, and the mixture was stirred for 1 h at r.t. After this time, the suspension was filtered and the filtrate acidified to pH 4 by the addition of *Dowex® 50WX8* (100–200 mesh) and filtered again. The filtrate was evaporated and the residue redissolved in 200 ml of AcOEt. This soln. was washed with sat. aq. NH_4Cl soln., the aq. phase back-extracted with AcOEt (3 × 50 ml), and the combined org. phase dried (Na_2SO_4) and evaporated to give the crude product as a mixture of two diastereoisomers. These could be separated by six consecutive FC runs (run 1: toluene/acetone 95:5 →

70:30; run 2: toluene/AcOEt 95:5 → 70:30; run 3: CH_2Cl_2/MeOH 95:5 → 70:30; runs 4–6: hexanes/AcOEt 95:5 → 70:30): 6.5 g (31%) of the desired diastereoisomer **26** as a slightly yellow oil.

Approach B: To a soln. of 1.396 g (0.00164 mol) of **41** in 45 ml of ^{i}PrOH/H_2O 4:1 was added 0.240 g (0.0102 mol) of $LiOH \cdot H_2O$, and the mixture was heated to 60° for 18 h. The mixture was then diluted with H_2O (200 ml) and CH_2Cl_2 (400 ml) and acidified to pH 4 with 1N HCl. The aq. soln. was back-extracted with CH_2Cl_2, the combined org. phase dried (Na_2SO_4) and evaporated, and the residue purified by FC (hexane/AcOEt 9:1 → 8:2): 1.1662 g (85%) of **26**. $[\alpha]_D^{21} = -8.37$ ($c = 2.03$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.93 (*s*, 1 H); 6.47 (br. *s*, 1 H); 5.3–5.5 (*m*, 2 H); 4.35–4.4 (*m*, 1 H); 4.09 (*t*, $J = 6.5$, 1 H); 3.79 (*d*, $J = 7.5$, 1 H); 3.1–3.25 (*m*, 1 H); 2.71 (*s*, 3 H); 2.56 (*dd*, $J = 16$, 4.5, 1 H); 2.16–2.38 (*m*, 3 H); 1.87–2.01 (*m*, 5 H); 1.21 (*s*, 3 H); 1.14 (*s*, 3 H); 1.02–1.47 (*m*, 17 H, including 1.07 (*d*, $J = 7$, 3 H)); 0.75–0.93 (*m*, 30 H); 0.12 (*s*, 3 H); 0.09 (*s*, 3 H); 0.05 (*s*, 9 H); 0.01 (*s*, 3 H). MS: 837.9 ($[M+H]^+$).

*(3S,6R,7S,8S,12E,15S,16E)-3,7-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-15-hydroxy-4,4,6,8,16-pentamethyl-17-(2-methylthiazol-4-yl)-5-oxoheptadeca-12,16-dienoic Acid* (**27**). To a soln. of acid **26** (1.10 g, 0.00131 mol) in 20 ml of THF was added 3.9 ml (0.0039 mol) of 1M Bu_4NF in THF at r.t. The soln. was stirred at r.t. for 24 h, at which point additional Bu_4NF was added (0.001 mol). Stirring was continued for additional 16 h, and the mixture was then diluted with 150 ml of H_2O, 120 ml of sat. aq. NH_4Cl soln., and 400 ml of AcOEt. The org. phase was back-extracted with AcOEt (1 × 200 ml), the combined org. phase washed with H_2O (100 ml), dried ($MgSO_4$) and evaporated, and the resulting yellow oil purified by FC (CH_2Cl_2/MeOH 94:6): **27** (0.604 g, 64%). Yellow resin. $[\alpha]_D^{21} = -20.77$ ($c = 1.55$, $CHCl_3$). MS: 723.9 ($[M+H]^+$). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.94 (*s*, 1 H); 6.58 (br. *s*, 1 H); 5.57 (*td*, $J = 15$, 7.5, 1 H); 5.41 (*td*, $J = 15$, 7.5, 1 H); 4.35–4.42 (*m*, 1 H); 4.13–4.19 (*m*, 1 H); 3.79 (*d*, $J = 7.5$, 1 H); 3.08–3.2 (*m*, 1 H); 2.73 (*s*, 3 H); 2.53 (*dd*, $J = 16$, 4.5, 1 H); 2.22–2.45 (*m*, 3 H); 1.95–2.06 (*m*, 5 H); 1.14 (*s*, 3 H); 1.22 (*s*, 3 H); 1.02–1.5 (*m*, 14 H, including 1.07 (*d*, $J = 7$, 3 H)); 0.77–0.95 (*m*, 21 H); 0.11 (*s*, 3 H); 0.07, 0.08 (2*s*, 9 H).

*(4S,7R,8S,9S,13E,16S)-4,8-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methylthiazol-4-yl)ethenyl]oxacyclohexadec-13-ene-2,6-dione* (**28**). To a soln. of 2.35 g (0.00324 mol) of **27** in 38 ml of dry THF was added 2.71 ml (0.0194 mol) of Et_3N at 10° followed by dropwise addition of 2.54 ml (0.01626 mol) of 2,4,6-trichlorobenzoyl chloride. After stirring at 10° for 20 min, the soln. was diluted with dry toluene (360 ml), and the resulting thin suspension was added slowly (3.5 h) to a soln. of 3.965 g (0.03245 mol) of DMAP in 1.62 l of dry toluene at r.t. After completion of the addition, the mixture was stirred for 1 h and then filtered, and the filtrate was concentrated. The partially crystalline residue was stirred in Et_2O (250 ml), the mixture filtered, the filtrate evaporated, and the yellow resin obtained purified by FC (CH_2Cl_2/AcOEt 99:1 → 98:2): **28** (1.4 g, 61%). Colorless resin. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.95 (*s*, 1 H); 6.55 (*s*, 1 H); 5.43 (*m*, 2 H); 5.25 (*dd*, 1 H); 4.40 (*m*, 1 H); 3.92 (*m*, 1 H); 3.07 (*m*, 1 H); 2.72 (*s*, 3 H); 2.72–2.40 (*m*, 4 H); 2.13 (*s* + *m*, 4 H); 1.92 (*m*, 1 H); 1.59 (*m*, 3 H); 1.40 (*m*, 2 H); 1.17 (*s*, 3 H); 1.15 (*d*, 3 H); including 1.08 (*s*, 3 H)); 0.95 (*d*, 3 H); 0.89 (*s*, 3 H); 0.87 (*s*, 3 H); 0.11 (*s*, 3 H); 0.085 (*s*, 3 H); 0.075 (*s*, 3 H); 0.05 (*s*, 3 H). MS: 706.2 ($[M+H]^+$).

(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methylthiazol-4-yl)ethenyl]oxacyclohexadec-13-ene-2,6-dione (= trans-*Deoxyepothilone A*; **2**). To an ice-cooled soln. of 1.4 g (0.00198 mol) of **28** in 13 ml of CH_2Cl_2 was added slowly 3.23 ml of CF_3COOH and the slightly yellow soln. was stirred in the ice bath for 2.5 h. The solvent was then evaporated and the residue purified by FC (hexanes/AcOEt 67:33 → 50:50). Fractions containing pure product were collectively redissolved in CH_2Cl_2 (30 ml), and the soln. was washed with sat. $NaHCO_3$ soln./H_2O 1:1 and sat. NaCl soln./H_2O 1:1, dried (Na_2SO_4), and evaporated: **2** (0.864 g (91%). Colorless resin. $[\alpha]_D^{21} = -56.08$ ($c = 0.765$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.98 (*s*, 1 H); 6.57 (br. *s*, 1 H); 5.3–5.57 (*m*, 3 H); 4.20 (*dd*, $J = 9$, 2, 1 H); 3.7–3.77 (*m*, 1 H); 3.19–3.29 (*m*, 1 H); 2.72 (*s*, 3 H); 1.9–2.62 (*m*, *ca.* 10 H; including 2.08 (*s*, 3 H)); 1.30 (*s*, 3 H); 1.20 (*d*, $J = 7.5$, 3 H); 1.09 (*s*, 3 H); 0.8–1.75 (*m*, *ca.* 20 H; including 1.00 (*d*, $J = 7.5$, 3 H)). MS: 478.0 ($[M+H]^+$).

trans-*Epothilone A* (= *(1S,3S,7S,10R,11S,12S,16S)-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[(1E)-1-methyl-2-(2-methylthiazol-4-yl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione*; **1a**). To a soln. of **2** (0.477 g, 0.001 mol) in 15 ml of MeCN/1,2-dimethoxyethane 2:1 was added 10 ml 0.05M $Na_2B_4O_7 \cdot 10H_2O$ in $4 \cdot 10^{-4}$ M Na_2EDTA at r.t. followed by 15 mg of $Bu_4N(HSO_4)$ and 1,2:4,5-di-*O*-isopropylidene-L-*erythro*-2,3-hexodiuro-2,6-pyranose (**42a**, 0.0775 g, 0.0003 mol) [36b]. The well-stirred mixture was cooled to 0–5° and treated simultaneously, within 1 h, with small portions of *Oxone*® and a soln. of K_2CO_3 (0.932 g, 0.0067 mol) in H_2O (6.5 ml). After stirring at 0° for 1 h, the mixture was extracted with AcOEt (4 × 40 ml). The combined org. extract was dried (Na_2SO_4) and evaporated to give a yellow resin (*ca.* 300 mg), which, according to HPLC, was composed of roughly 50% of starting material and 50% of a mixture of the desired epoxide **1a** and its epimer **1b** in a ratio of 8:1. Unreacted starting material was removed by prep. TLC (silica gel, CH_2Cl_2/MeOH 9:1) providing 0.13 g (27%; 54% based on recovered starting material) of a 8:1 mixture **1a**/**1b**. Purification of this

material by prep. HPLC (*Prontosil 120-5-C18 AQ 5* μm (250 × 20 mm; *Bischoff*); 20 ml/min of MeCN/H_2O, 30 min at 28% MeCN, → 30% MeCN in 40 min, 110 min at 30% MeCN, → 100% MeCN in 110 min (no addition of CF_3COOH, 4 runs)) provided 57.6 mg (11%) of pure **1a**. $[\alpha]_D^{21} = -37.1$ ($c = 0.275$, $CHCl_3$). ([40]: $[\alpha]_D^{22} = -23.3$ ($c = 0.40$, $CHCl_3$)). ^{1}H-NMR (500 MHz, (D_6)DMSO)[5]: 7.34 (*s*, 1 arom. H); 6.50 (*s*, H–C(17)); 5.29 (*d*, *J* = 11, H–C(15)); 5.24 (*d*, *J* = 5.8 Hz, OH–C(3)); 4.53 (*d*, *J* = 6.0, OH–C(7)); 4.17 (*m*, H–C(3)); 3.51 (br. *t*, *J* = 8.0, H–C(7)); 3.11 (*m*, H–C(6)); 2.89 (*m*, H–C(12)); 2.83 (*m*, H–C(13)); 2.64 (*s*, Me–C(20)); 2.43, 2.38 (2*m*, CH_2)); 2.07 (*s*, Me–C(16)); 2.03, 1.73 (2*m*, CH_2(14)); 1.68 (*m*, 1 H, CH_2); 1.56 (*m*, 1 H, CH_2); 1.43 (*m*, 1 H, CH_2); 1.32 (*m*, 1 H, CH_2); 1.21 (*m*, 1 H, CH); 1.04 (*m*, 2 H, CH_2); 1.20 (*s*, Me–C(4)); 1.10 (*d*, *J* = 6.0, Me–C(6)); 0.89 (*s*, Me–C(4)); 0.87 (*d*, *J* = 6.0, Me–C(8)). MS: 494.1 ($[M+H]^+$).

The authors are indebted to *M. Hattenberger*, *W. Heinzelmann*, *R. Kesselring*, *J. Köppler*, *H. Lerch*, *J. Loretan*, *R. Reuter*, and *W. Vetterli* for excellent technical assistance in the synthesis (*W. H.*, *R. K.*, *H. L.*, *W. V.*) and biological evaluation (*M. H.*, *J. K.*, *J. L.*, *R. R.*) of the target compounds.

REFERENCES

[1] G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach, German patent disclosure DE 4138042, May 5, 1993 (Priority Nov. 19, 1991); K. Gerth, N. Bedorf, G. Höfle, H. Irschik, H. Reichenbach, *J. Antibiot.* **1996**, *49*, 560.
[2] D. M. Bollag, P. A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C. A. Woods, *Cancer Res.* **1995**, *55*, 2325.
[3] P. B. Schiff, J. Fant, S. B. Horwitz, *Nature (London)* **1979**, *277*, 665.
[4] K.-H. Altmann, *Curr. Opin. Chem. Biol.* **2001**, *5*, 42.
[5] R. J. Kowalski, P. Giannakakou, E. Hamel, *J. Biol. Chem.* **1997**, *272*, 2534.
[6] K.-H. Altmann, M. Wartmann, T. O'Reilly, *Biochim. Biophys. Acta* **2000**, *1470*, M79.
[7] P. Giannakakou, D. L. Sackett, Y. K. Kang, Z. Zhan, J. T. Buters, T. Fojo, M. S. Poruchynsky, *J. Biol. Chem.* **1997**, *272*, 17118.
[8] K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem., Int. Ed.* **1998**, *37*, 2014.
[9] C. R. Harris, S. J. Danishefsky, *J. Org. Chem.* **1999**, *64*, 8434.
[10] J. Mulzer, H. J. Martin, M. Berger, *J. Heterocycl. Chem.* **1999**, *36*, 1421.
[11] K. C. Nicolaou, A. Ritzen, K. Namoto, *Chem. Commun.* **2001**, 1523.
[12] M. Wartmann, K.-H. Altmann, *Curr. Rev. Med. Chem.–Anticancer Agents* **2002**, *2*, 123.
[13] K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature (London)* **1997**, *387*, 268.
[14] a) D. Meng, D. S. Su, A. Balog, P. Bertinato, E. J. Sorensen, S. J. Danishefsky, Y. H. Zheng, T. C. Chou, L. He, S. B. Horwitz, *J. Am. Chem. Soc.* **1997**, *119*, 2733; b) D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, *Angew. Chem., Int. Ed.* **1997**, *36*, 757.
[15] K. C. Nicolaou, K. Namoto, A. Ritzen, T. Ulven, M. Shoji, J. Li, G. D'Amico, D. Liotta, C. T. French, M. Wartmann, K.-H. Altmann, P. Giannakakou, *J. Am. Chem. Soc.* **2001**, *123*, 9313.
[16] N. End, G. Bold, G. Caravatti, M. Wartmann, K.-H. Altmann, 'Proceedings of ECSOC-4– The 4th International Electronic Conference on Synthetic Organic Chemistry', 2000, p. 1431 (accessible at: http://www.mdpi.org/ecsoc-4.htm).
[17] K.-H. Altmann, M. J. J. Blommers, G. Caravatti, A. Flörsheimer, K. C. Nicolaou, T. O'Reilly, A. Schmidt, D. Schinzer, M. Wartmann, 'Anticancer Agents – Frontiers in Cancer Chemotherapy', Eds. I. Ojima, G. D. Vite, and K.-H. Altmann, ACS Symposium Series 796, American Chemical Society, Washington DC, 2001, p. 112.
[18] 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.
[19] D. Schinzer, A. Bauer, J. Schieber, *Chem.–Eur. J.* **1999**, *5*, 2492.
[20] 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.
[21] W. Oppolzer, *Pure Appl. Chem.* **1990**, *62*, 1241; S. Bond, P. Perlmutter, *J. Org. Chem.* **1997**, *62*, 6397.
[22] J. De Brabander, S. Rosset, G. Bernardinelli, *Synlett* **1997**, 824.

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[5] For numbering, see *Scheme 1*.

[23] J. De Brabander, S. Rosset, G. Bernardinelli, *Synlett* **1998**, 328 (Errata and Addenda).
[24] L. Lermer, E. Neeland, J.-P. Ounsworth, R. J. Sims, S. A. Tischler, L. Weiler, *Can. J. Chem*. **1992**, *70*, 1427.
[25] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett*. **1972**, *36*, 3769.
[26] D. W. Hart, J. Schwartz, *J. Am. Chem. Soc*. **1974**, *96*, 8115; K. J. Stille, J. H. Simpson, *J. Am. Chem. Soc*. **1987**, *109*, 2138; S. L. Buchwald, S. J. LaMaire, R. B. Nielsen, B. T. Watson, S. M. King, *Org. Synth.* **1993**, *71*, 77.
[27] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
[28] K.-H. Altmann, G. Bold, G. Caravatti, A. Flörsheimer, V. Guagnano, M. Wartmann, *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2765.
[29] A. Suzuki, *J. Organomet. Chem*. **1999**, *576*, 147.
[30] A. Balog, D. Meng, T. Kamenecka, P. Bertinato, D.-S. Su, E.-J. Sorensen, S. J. Danishefsky, *Angew. Chem., Int. Ed.* **1996**, *35*, 2801; D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, S. J. Danishefsky, *J. Am. Chem. Soc*. **1997**, *119*, 10073.
[31] D. Schinzer, A. Limberg, O. Böhm, *Chem.–Eur. J.* **1996**, *2*, 1477.
[32] D. Schinzer, A. Bauer, O. M. Böhm, A. Limberg, M. Cordes, *Chem.–Eur. J.* **1999**, *5*, 2483.
[33] P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem*. **1976**, *41*, 1485.
[34] K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, J. L. Trujillo, *J. Am. Chem. Soc*. **1997**, *119*, 7960.
[35] D. Yang, M.-K. Wong, Y.-C. Yip, *J. Org. Chem*. **1995**, *60*, 3887.
[36] Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc*. **1996**, *118*, 9806; Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc*. **1996**, *118*, 9806.
[37] E. Hamel, *Med. Res. Rev*. **1996**, *16*, 207.
[38] C. M. Lin, Y. Q. Jiang, A. G. Chaudhary, J. M. Rimoldi, D. G. Kingston, E. Hamel, *Cancer Chemother. Pharmacol*. **1996**, *38*, 136.
[39] T. Meyer, U. Regenass, D. Fabbro, E. Alteri, J. Rösel, M. Müller, G. Caravatti, A. Matter, *Int. J. Cancer* **1989**, *43*, 851.
[40] K. C. Nicolaou, R. Scarpelli, B. Bollbuck, B. Werschkun, M. M. Pereira, M. Wartmann, K.-H. Altmann, D. Zaharevitz, R. Gussio, P. Giannakakou, *Chem. Biol*. **2000**, *7*, 593.
[41] T. Inukai, R. Yoshizawa, *J. Org. Chem*. **1967**, *32*, 404.
[42] E. Benzing, *Angew. Chem.* **1959**, *71*, 521.
[43] W. M. Clark, C. Bender, *J. Org. Chem*. **1998**, *63*, 6732.

Received August 12, 2002