Tetrahedron 64 (2008) 7920–7928

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 12-aza analogs of epothilones and (*E*)-9,10-dehydroepothilones

Fabian Feyen [†], Andrea Jantsch [‡], Kurt Hauenstein, Bernhard Pfeiffer, Karl-Heinz Altmann [*]

Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology (ETH) Zürich, HCI H405, Wolfgang-Pauli-Str. 10, CH-8093 Zürich, Switzerland

ARTICLE INFO

Article history:
Received 8 May 2008
Received in revised form 4 June 2008
Accepted 6 June 2008
Available online 10 June 2008

ABSTRACT

N-Boc-12-aza-epothilone analog (azathilone) **1** is a potent inhibitor of human cancer cell growth and represents a structurally new class of natural product-derived microtubule-stabilizing agents. Compound **1** has been prepared employing a convergent strategy that is based on the consecutive assembly of building blocks **3**, **4**, and **19** into diene **20** and subsequent RCM-mediated macrocycle formation. The aldol reaction between aldehyde **3** and ketone **4** delivered the required 6*R*,7*S* diastereoisomer **5** with good selectivity and provided a reliable entry into the stereoselective synthesis of carboxylic acid **12**. RCM with diene **20** was highly *E*-selective, thus giving efficient access to (*E*)-9,10-dehydro-**1** (**2**). The latter is a key analog in SAR studies with **1**.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

Natural products are a unique source of lead structures for drug discovery and development, and a substantial part of modern pharmacotherapy is based on compounds that are either natural products themselves or derived from natural product leads.[1] Traditionally, the organic chemistry of natural product-based drug discovery, for reasons of technical feasibility, has mainly focused on the preparation of semisynthetic derivatives as potential new drug candidates,[2] while de novo total synthesis has generally been more important for the resolution of structural and stereochemical questions.[3] In cases of severely limited availability of a natural product, a problem particularly notorious with compounds of marine origin, total synthesis has also been a means of providing material for extended biological testing and, in particular, of analogs for initial SAR studies.[4] More recently, however, a number of total synthesis-based concepts have been developed that directly aim at the discovery of new drug leads that are not genuine natural products, but (still) exhibit natural product-like structural features. This includes the preparation of screening libraries either by diversity- or biology-oriented synthesis (DOS[5] or BIOS,[6] respectively), but also the design and synthesis of natural product hybrids[7] or 'non-natural' natural products.[8] In this context, we have recently reported on the potent antiproliferative activity of 12-aza-epothilone ('azathilone') **1** (Fig. 1),[8b,9] which is an epothilone-derived non-natural natural product that inhibits human cancer cell growth in vitro with sub-100 nM IC_{50} values.

The corresponding natural products epothilones A/B (Fig. 1) are microtubule-stabilizing agents with pronounced in vitro and in vivo antitumor activity[10] and have served as successful lead structures for the development of a series of clinical candidates for cancer chemotherapy[11].

Following the discovery of **1**, we have also investigated a (limited) number of structural variants with alternative carbamoyl- or acyl-substituents on N^{12};[9] however, while some of these analogs retained significant antiproliferative activity, all of them were less potent than lead structure **1**. In addition to the exploration of different N^{12}-substituents, our initial structure–activity relationship (SAR) studies with **1** were focused on structural modifications that had been demonstrated for natural epothilones to lead to enhanced antiproliferative activity. Based on work by Danishefsky and coworkers this includes the incorporation of a *E* double bond between C^9 and C^{10},[12,13] thus resulting in azathilone **2** (Fig. 1) as an important target structure for synthesis. Access to **2**, however, was not

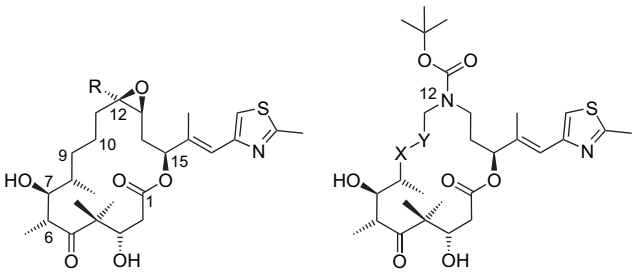


Figure 1.

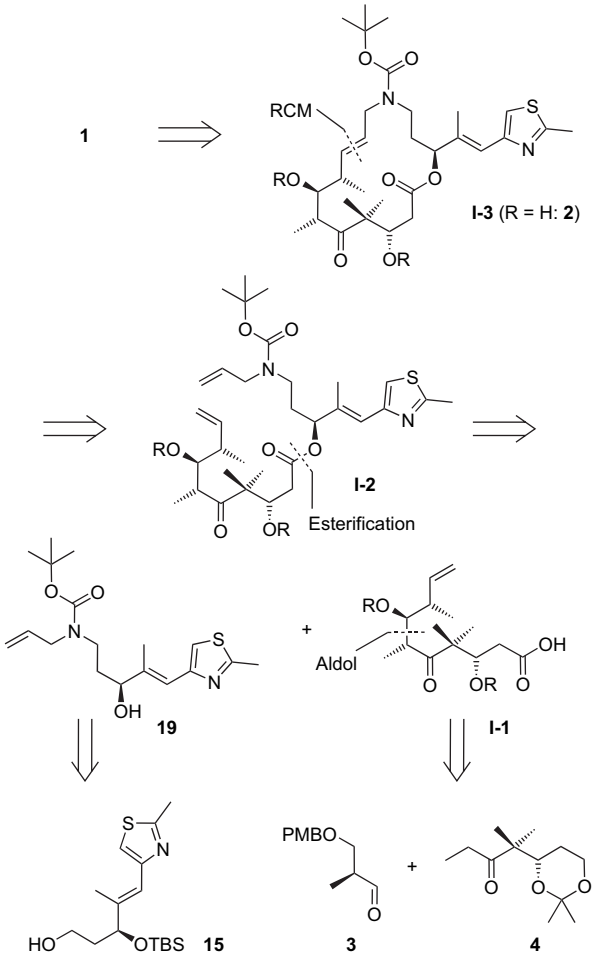
* Corresponding author. Tel.: +41 44 633 73 90; fax: +41 44 633 13 69.
E-mail address: karl-heinz.altmann@pharma.ethz.ch (K.-H. Altmann).
† Present address: Carbogen-Amcis AG, CH-5502 Hunzenschwil, Switzerland.
‡ Present address: Lonza AG, CH-3930 Visp, Switzerland.

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.06.017

possible based on our first generation strategy for the synthesis of **1**,[9,13] which did not proceed through an appropriate unsaturated intermediate (or even a precursor with a masked double bond between C^9 and C^{10}). As a consequence, we had to establish a new, independent route to **2**; as the reduction of **2** directly leads to **1**, this approach would simultaneously constitute a new route to azathilone **1**. In this paper we now disclose full experimental details for the synthesis of **2**,[14] which is based on a highly stereoselective ring-closing olefin metathesis (RCM) reaction, and its subsequent conversion to **1** by diimide reduction.

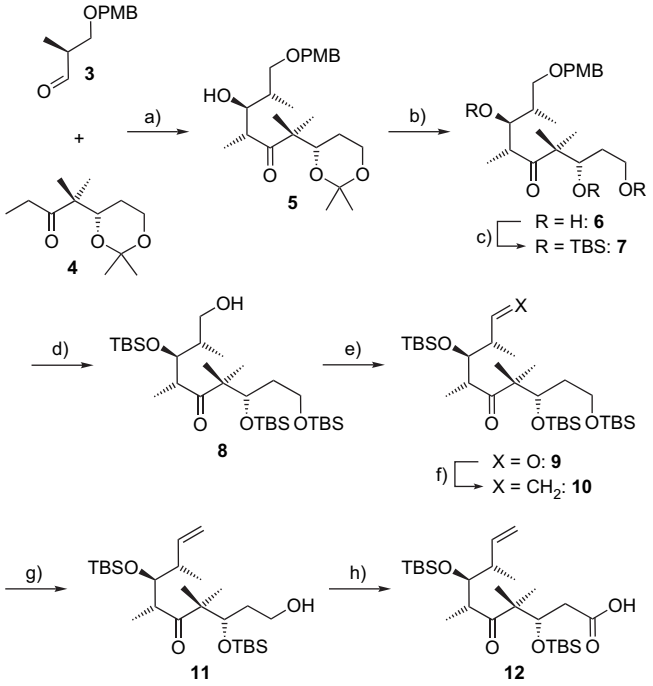
2. Results and discussion

As illustrated in Scheme 1, our retrosynthesis of **2** involved the RCM-based ring closure of a diene precursor **I-2** as the ultimate key disconnection. Compound **1** would then be obtained through selective reduction of the 9/10-double bond in **2** or an appropriately protected precursor thereof (**I-3**). Although the stereoselectivity of the ring-closure reaction was difficult to predict a priori, based on previous studies by Danishefsky and co-workers on related (N-free) systems the *E*-configured macrocyclic alkene was expected to be formed preferentially, although perhaps not with complete selectivity.[12b–e] Diene **I-2** was envisioned to be derived from alcohol **19** and a protected carboxylic acid **I-1** by simple esterification. Building block **19** was planned to be elaborated from the known alcohol **15**,[15,22] while intermediate **I-1** was assumed to be accessible from aldehyde **3**[15c,16] and the Schinzer ketone **4**,[15a,17] as aldol reactions between **4** and α-chiral aldehydes related to **3** have been consistently reported to show good to excellent selectivity in favor of the formation of the desired 6*R*,7*S* isomer.[15a,b,17b,18]



Scheme 1. Retrosynthesis of target structures **1** and **2**. R=protecting group or H. Protecting groups can vary independently.

As shown in Scheme 2, our expectations on the stereochemical outcome of the critical aldol step were borne out by the experimental results, such that the reaction between aldehyde **3** and the Li-enolate derived from ketone **4** produced a 8/1 mixture of 6,7-*syn* diastereoisomers. While the respective absolute configurations of these isomers could not be rigorously established, due to a lack of crystalline intermediates for the entire sequence leading from **3**/**4** to the target structures **2**/**1**, prior experience in our own laboratory[8a,15a] as well as a significant amount of literature precedence for aldol reactions with **4**[15b,17b,18,19] clearly suggest that the major product must be compound **5** with the desired 6*R*,7*S* configuration.



Scheme 2. (a) **4**, LDA, −78 °C, 5 h, then addition of **3**, −90 °C, 75 min, 76%, dr=8/1; (b) PPTS, MeOH, rt, 20 h, 86%; (c) (i) TBSOTf, 2,6-lutidine, −78 °C→rt, 1.5 h; (ii) flash chromatography, 76% (single isomer); (d) H_2/Pd–C, MeOH, rt, 20 h, 86%; (e) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 1 h; (f) $MePPh_3Br$, LiHMDS, THF, 0 °C, 1.5 h, 76% (two steps); (g) CSA (1.0 equiv), CH_2Cl_2/MeOH 1/1, 0 °C, 1 h, 87%; (h) PDC (11 equiv), DMF, rt, 64 h, 85%.

As a possible alternative entry into the synthesis of building block **I-1** we have also investigated the aldol reaction between aldehyde **3** and the Ti-enolate of γ-keto imide **13** (Fig. 2),[20] which already incorporates the required carboxylate oxidation state at C1 (epothilone numbering, see Fig. 1). Unfortunately, the desired aldol product was obtained only with variable selectivities and in variable and low yields (10–30%; dr=1:1–4:1) and this approach was not further pursued.

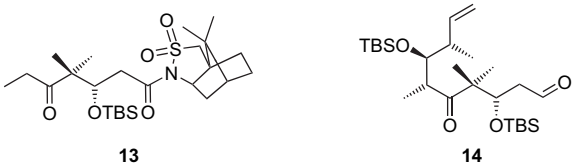
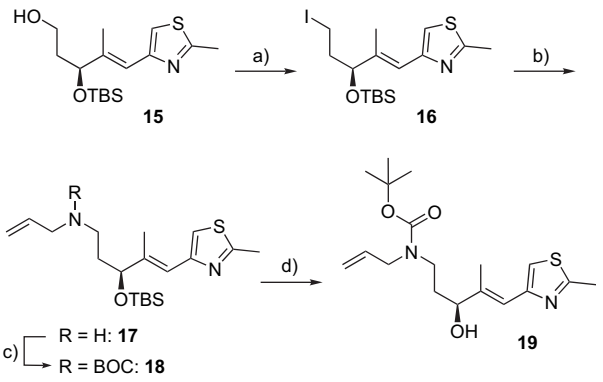


Figure 2.

While the separation of the mixture of isomers produced in the reaction between **3** and **4** was possible at the stage of the immediate aldol products, it was more conveniently performed after

conversion of this product mixture to fully protected tetrol **7** via acetal cleavage with PPTS, to produce **6**, and subsequent persilylation with TBSOTf (Scheme 2). After flash chromatography compound **7** was isolated as a single isomer in 48% overall yield for the three-step sequence from aldehyde **3**. Catalytic hydrogenation of **7** provided the partially protected tetrol **8** in excellent yield (86%) and this was further converted to aldehyde **9** by TPAP oxidation.[21] Subsequent Wittig reaction with $[Ph_3PCH_3]^+I^-$ gave olefin **10** in 76% yield (based on **8**). The elaboration of **10** into the desired carboxylic acid **12** (=**I-1** with R=TBS; Scheme 1) was then achieved in excellent overall yield (74%) through selective cleavage of the primary TBS ether followed by oxidation of the resulting free alcohol **11** with an excess of PDC in DMF. Alternatively, **12** could also be obtained from **11** in a two-step sequence that involved Swern oxidation to aldehyde **14** (Fig. 2) followed by further oxidation of the crude aldehyde with $NaClO_2$, 2-methyl-2-butene, ^tBuOH, and NaH_2PO_4[22] in similar overall yield as for the one-step approach with PDC.[23]

The synthesis of building block **19** from protected alcohol **15**[15,22] (Scheme 3) involved conversion of the latter to iodide **16**[22] through treatment with I_2, Ph_3P, and imidazole and subsequent reaction of **16** with an excess of allylamine to provide *O*-TBS-protected amino alcohol **17** in high yield (79%).

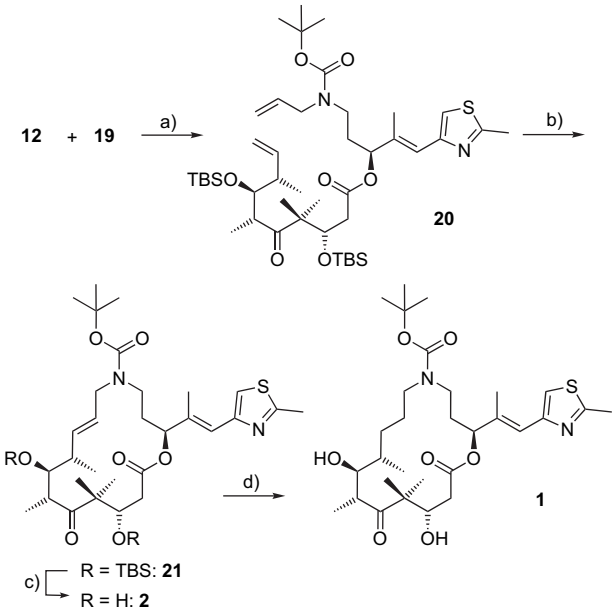


Scheme 3. (a) I_2, Ph_3P, imidazole, Et_2O/CH_3CN 3/1, 0 °C→rt, 30 min, 79%; (b) CH_2=$CHCH_2NH_2$ (11 equiv), Et_2O, refl, 20 h, 79%; (c) BOC_2O, Et_3N, DMAP (cat), THF, 0 °C, 5 h, 92%; (d) TBAF, aq THF, rt, 2 h, 81%.

Carbamoylation of the allylic amino group with BOC_2O then gave *N*/*O*-bis-protected derivative **18**, whose treatment with TBAF furnished the desired free alcohol **19** in 46% overall yield for the four-step sequence from **15**.

Initial attempts at the esterification of alcohol **19** and acid **12** with either DCC or EDC and DMAP gave the desired ester **20** only in moderate and somewhat variable yields of 25–57%. A significant improvement in the efficiency of the reaction could be realized, however, through rigorous drying of both starting materials (co-evaporation with toluene immediately before use) and the use of a 20% excess of alcohol **19** over acid **12**. Thus, under optimized conditions (dried starting materials, 1.0 equiv **12**, 1.2 equiv **19**, 1.3 equiv DCC, 0.3 equiv DMAP) ester **20** was consistently obtained in yields between 76 and 82% (Scheme 4).

With diene **20** in hand, our first attempt at ring closure involved the use of first generation Grubbs catalyst in boiling CH_2Cl_2 as the solvent,[24] but no macrocycle formation was observed under these conditions (only recovered starting material was isolated). In contrast, the use of second generation Grubbs catalyst led to efficient and highly stereoselective macrocyclization, thus furnishing the desired 9,10-*E*-configured cycloalkene **21** in 70% isolated yield. These findings mirror previous observations by Danishefsky and co-workers[25] as well as Sun and Sinha[26] on RCM-based macrocyclizations with the related diene **22** (Fig. 3), which did not undergo RCM with first generation Grubbs catalyst, whereas it was



Scheme 4. (a) DCC (1.3 equiv), DMAP (0.3 equiv), CH_2Cl_2, 0 °C, 15 min, rt, 15 h, 77%; (b) 2nd generation Grubbs catalyst (0.15 equiv, incremental addition), CH_2Cl_2, refl, 18 h, 70%; (c) HF·Pyr, pyridine, THF, 4.5 h, rt, 65%; (d) KO_2C-N=N-CO_2K (excess), AcOH, CH_2Cl_2, 52%.

converted to the corresponding cycloalkene in good yield in the presence of the second generation catalyst.[26]

In contrast to the transformation **20**→**21** (Scheme 4), however, the cyclization of **22** was completely non-selective, i.e., the product was obtained as a 1/1 mixture of double bond isomers.[26] Completely *E*-selective RCM reactions mediated by second generation Grubbs catalyst have been reported by Danishefsky and co-workers for dienes **23a**/**b**, but the yields of the desired cyclization products were severely compromised by the fact that the major reaction pathway for these substrates involves RCM between the double bonds C^{10}–$C^{10'}$ and C^{16}–C^{17} (rather than C^{10}–$C^{10'}$ and C^{9}–$C^{9'}$; epothilone numbering, Fig. 1).[12b,27] Interestingly, none of the corresponding alternative cyclization product was isolated from RCM reactions with diene **20**. The cyclization of **20**, however, was consistently accompanied by the formation of a minor by-product, which we initially assumed to be the 9,10-*Z* isomer of **21**. In order to investigate the biological activity of this purported *Z* isomer, the compound was isolated from one of our larger scale (ca. 900 mg of diene **20**) RCM reactions in 3.5% yield and ca. 90% purity. After deprotection and HPLC purification spectral analysis clearly indicated the resulting product to be an isomer of **2**, but, quite surprisingly, it also suggested the presence of an *E* rather than a *Z* double bond as part of the macrocycle (based on ^3J=15.5 Hz and the absence of a NOE between the two alkene protons). As this was outside of the scope of our study, we have made no further attempts to ascertain the identity of the side product formed in RCM reactions with **20**, but it should be noted that Zeng et al. have recently reported the epimerization of the stereocenter α to the

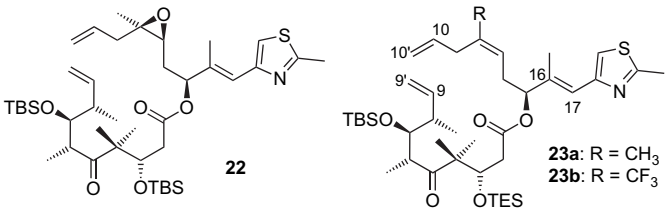


Figure 3.

double bond in a vinyl cyclopropane in the course of an RCM reaction.[28] Whether or not the minor product obtained in the RCM-based cyclization of diene **20** may be the result of an analogous epimerization at C8 (epothilone numbering; Fig. 1) remains to be elucidated.

The conversion of the fully protected cycloalkene **21** to our major target structure **2** then required the selective removal of the TBS protecting groups on O^3 and O^7 without concomitant loss of the crucial BOC moiety on N^{12}. This transformation could be achieved in good yield (65%) by treatment of **21** with HF·pyridine in THF under carefully controlled conditions. Continuous reaction monitoring proved to be absolutely mandatory in this case, as different batches of HF·pyridine (or even the same batch used at different times) can lead to different reaction kinetics and, thus, highly variable yields for otherwise identical reaction conditions. While cycloalkene **2** was our primary synthetic target, we have also investigated the possible conversion of this analog or its protected precursor **21** to the saturated azathilone **1**. Obviously, the reduction of the 9/10-double bond in **2**/**21** is complicated by the presence of a second alkene functionality in the C15 side chain; it was, therefore, not surprising that catalytic hydrogenation methods mostly gave mixtures of mono- and bis-hydrogenated products (in addition to unchanged starting material; according to MS-analysis of crude reaction mixtures). The use of H_2/Ra-Ni with **2** in EtOH did not give any conversion. Interestingly, hydrogenation of **21** in the presence of Wilkinson's catalyst, Rh(I)-$(PPh_3)_3Cl$, in EtOH for 2 h resulted in selective reduction of the trisubstituted side-chain double bond, providing analog **25** (Fig. 4) in 70% isolated yield.

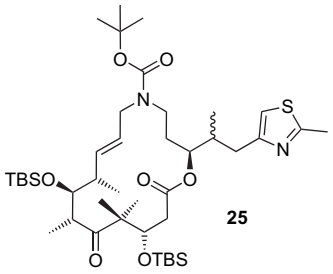


Figure 4.

In light of these difficulties we finally resorted to the use of in situ generated diimide as the reducing agent,[29] which had been successfully employed by Danishefsky and co-workers for the conversion of various 9,10-dehydroepothilones to the saturated parent compounds.[12b–d] More recently, we have also employed this methodology in the synthesis of a new 12,13-*trans*-cyclopropane-based Epo A analog.[30] After initial unsuccessful attempts with mesitylenesulfonyl hydrazine as a diimide source,[31] the desired transformation could finally be achieved with dipotassium diazodicarboxylate (PADA)/AcOH[32] in boiling CH_2Cl_2, although the reaction proved to be extremely slow. Thus, treatment of **2** with a total of 164 equiv of PADA (prepared according to Ref. 33) and 328 equiv of AcOH for 4 h gave the desired azathilone **1** in 15% isolated yield after HPLC purification together with 50% of recovered starting material. Purification of the target compound by RP-HPLC was indispensable, as no separation of **2** and **1** was achievable by conventional silica gel flash chromatography. When the reaction time was extended to 8 days and the total amount of PADA/AcOH was increased to ca. 680/1360 equiv (added in 11 separate portions) the total yield could be increased to 52% (after HPLC purification). The conversion of **2** to **1** is thus feasible in acceptable yield, but, clearly, additional optimization work would be required to establish a truly practical approach for this transformation.

As we have reported earlier,[8,14] the antiproliferative activity of 9,10-dehydro analog **2** is at least 30-fold lower than for the saturated parent compound **1**, which stands in stark contrast to the effects associated with the incorporation of a 9,10-*E* double bond in natural epothilones. While the molecular origin of this discrepancy is not understood at this point, it may be speculated that the data are indicative of differences in the bioactive conformation between the polyketide-based natural products and the azamacrolide-based azathilones. NMR-based structural studies are currently in progress to address this question as is the synthesis of additional azathilone analogs for more extensive SAR studies.

In summary, we have achieved the synthesis of the desatured azathilone **2**, which is a key derivative in the elucidation of the SAR of this new class of tubulin modulators. We have also demonstrated that **2** can be converted to **1** in good yield, although the reaction conditions for this transformation still require further optimization. Both **2** and **1** may serve as key intermediates for the preparation of additional azathilones for more extensive future SAR studies.

3. Experimental section

3.1. General

All solvents used for reactions were purchased as anhydrous grade from Fluka and used without further processing. Solvents for extractions, column chromatography and TLC were of commercial grade and distilled before use. TLC was performed on Merck TLC aluminum sheets (silica gel 60 F_{254}). Spots were visualized with UV light (λ=254 nm) or through staining with phosphomolybdic acid or $KMnO_4$. Flash column chromatography (FC) was performed using Fluka silica gel 60 for preparative column chromatography (40–63 μm), unless specifically noted otherwise. NMR spectra were recorded on a Bruker AV-400 (400 MHz) and a Bruker DRX-500 (500 MHz) spectrometer at 298 K or the temperature specifically indicated with the analytical data. Infrared spectra (IR) were recorded on a Jasco FT/IR-6200 instrument. Optical rotations were measured on a Jasco P-1020 polarimeter. RP-HPLC analyses were carried out on a Waters Symmetry column (C18, 3.5 μm, 4.6×100 mm) at a detection wavelength of 254 nm. Compounds were eluted with water (A)/CH_3CN (B) 50/50 for 2 min followed by a gradient A/B 50/50→A/B 10/90 from 2 to 9 min. Preparative RP-HPLC was carried out using a Waters Symmetry column (C18, 5 μm, 19×100 mm) using the same solvent system as above. Elution was performed with A/B 50/50 for 2 min followed by a gradient of A/B 50/50→A/B 30/70 from 2 to 9 min.

*3.1.1. (4R,5S,6S)-7-(4-Methoxybenzyloxy)-2-((S)-2,2-dimethyl-1,3-dioxan-4-yl)-5-hydroxy-2,4,6-trimethylheptan-3-one (**5**)*

A solution of ketone **4** (4.02 g, 18.75 mmol) in 10 ml of THF was added to a solution of LDA (freshly prepared from 11.2 ml of 1.6 M *n*-BuLi in hexane (17.90 mmol) and 2.53 ml (17.90 mmol) of diisopropylamine in 20 ml of THF) at −78 °C and the mixture was stirred at this temperature for 5 h. It was then cooled to −90 °C and aldehyde **3** (crude; prepared through Swern oxidation of 3.25 g (19.0 mmol) of the corresponding alcohol[15c]) was added in 10 ml of THF. After 75 min at −90 °C the reaction was quenched by addition of MeOH (2.5 ml), the mixture was diluted with AcOEt and water, and the phases were separated. Re-extraction of the aqueous solution with AcOEt, drying of the combined organic extracts over $MgSO_4$, and removal of the solvent under reduced pressure gave a residue that was purified by FC (AcOEt/hexane 1/4). The aldol product **5** was obtained as a clear oil (6.03 g, 76%) as a 8/1 mixture of diastereoisomers that was not separated at this point.

It should be noted that the reaction has also been carried out successfully on the same scale, when the enolate of **4** was generated

over only 75 min and the addition of aldehyde **3** was performed at −78 °C rather than −90 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J*=8.8 Hz, 2H); 6.85 (d, *J*=8.7 Hz, 2H); 4.42 (s, 2H); 4.03 (dd, *J*=11.8, 2.5 Hz, 1H); 3.97–3.88 (m, 1H); 3.86–3.80 (m, 1H); 3.78 (s, 3H); 3.63–3.55 (m, 2H); 3.52–3.40 (m, 2H); 3.40 (br s, 1H); 3.23–3.15 (m, 1H); 2.17 (s, 3H); 1.85–1.75 (m, 1H); 1.70–1.50 (m, 1H); 1.35 (s, 3H); 1.28 (s, 3H); 1.21 (s, 3H); 1.08 (s, 3H); 1.04 (d, *J*=7.0 Hz, 3H); 0.96 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.0, 159.1, 130.7, 129.2, 113.7, 98.4, 74.8, 72.9, 72.6, 72.5, 60.0, 55.2, 51.4, 41.8, 36.1, 29.7, 25.1, 21.7, 19.0, 18.5, 14.2, 10.0. IR (film): 3489 (br), 2962, 2937, 2876, 1687, 1609, 1513, 1369, 1244, 1097, 1033, 972, 850, 819. MS (ESI) *m*/*z* (rel intensity) 445 ([MNa^+], 88), 405 (18), 223 (6), 140 (3), 83 (7). HRMS (ESI) ($C_{24}H_{38}O_6$) calcd 445.2561 (MNa^+), found 445.2565 (MNa^+). NMR signals for major diastereoisomer.

3.1.2. (2S,3S,4R,7S)-1-(4-Methoxybenzyloxy)-3,7,9-trihydroxy-2,4,6,6-tetramethylnonan-5-one (**6**)

To a solution of the aldol product **5** (4.0 g, 9.47 mmol) in 150 ml of MeOH was added pyridinium-*p*-toluene sulfonate (1.98 g, 10.41 mmol) and the mixture was stirred at rt for 20 h. Satd aq $NaHCO_3$ was then added and the solution was extracted with AcOEt (4×100 ml). The combined organic extracts were dried over $MgSO_4$, the solvent was evaporated in vacuo, and the residue purified by FC (AcOEt/hexane 2/1) to provide 3.11 g (86%) of the title compound **6** (mixture of diastereoisomers).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J*=8.6 Hz, 2H); 6.85 (d, *J*=8.6 Hz, 2H); 4.42 (s, 2H); 4.05 (m, 1H); 3.88–3.80 (m, 1H); 3.78 (s, 3H); 3.67–3.60 (dd, *J*=8.7, 1.5 Hz, 1H); 3.60–3.52 (m, 1H); 3.51–3.43 (m, 1H); 3.30–3.00 (br m, 4H); 1.90–1.80 (m, 1H); 1.65–1.50 (m, 2H); 1.19 (s, 3H); 1.10 (s, 3H); 1.08 (d, *J*=7.0 Hz, 3H); 0.96 (d, *J*=6.9 Hz, 3H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ 217.0, 159.1, 130.3, 129.3, 113.7, 100.8, 76.2, 73.1, 72.9, 61.8, 55.2, 52.6, 41.8, 36.0, 32.5, 21.7, 18.5, 14.1, 10.4. IR (film): 3445 (br), 2966, 2360, 1688, 1613, 1513, 1248, 1076, 1037, 733, 704. MS (MALDI) *m*/*z* (rel intensity) 405 ([MNa^+], 100), 331 (7), 235 (7), 202 (5), 72 (3). HRMS (MALDI) ($C_{21}H_{34}O_6$) calcd 405.2248 (MNa^+), found 405.2255 (MNa^+).

3.1.3. (2R,3R,4S,7S)-1-(4-Methoxybenzyloxy)-3,7,9-tris(tert-butyldimethylsilyloxy)-2,4,6,6-tetramethylnonan-5-one (**7**)

To a solution of compound **6** (1.51 g, 3.92 mmol) and 3.49 g (19.5 mmol) of 2,6-lutidine in 30 ml of CH_2Cl_2 was added a solution of TBSOTf (5.65 g, 19.5 mmol) in 10 ml of CH_2Cl_2 dropwise at −78 °C. After 15 min at −78 °C and 1.5 h at rt, the reaction was quenched by addition of aq $NaHCO_3$ followed by extractive work-up with AcOEt. Purification of the residue obtained after drying of the extracts and evaporation of solvent by FC (Et_2O/hexane 1/25) gave 2.167 g (76%) of the fully protected tetrol **7** as a single diastereoisomer.

$[\alpha]_D^{20}$ −13.1 (*c* 1.78, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ 7.25–7.19 (m, 2H); 6.83–6.77 (m, 2H); 4.40–4.31 (m, 2H); 4.21 (dd, *J*=7.7, 2.7 Hz, 1H); 4.12 (dd, *J*=7.0, 2.5 Hz, 1H); 3.80–3.73 (m, 2H); 3.67 (dd, *J*=9.2, 6.3 Hz, 1H); 3.48–3.40 (m, 1H); 3.31 (s, 3H); 3.28 (dd, *J*=9.1, 6.6 Hz, 1H); 2.10–1.97 (m, 1H); 1.85–1.74 (m, 1H); 1.70–1.60 (m, 1H); 1.20 (s, 3H); 1.19 (s, 3H); 1.15 (d, *J*=7.0, 3H); 1.07 (d, *J*=7.1 Hz, 3H); 1.01 (s, 9H); 1.00 (s, 9H); 0.98 (s, 9H); 0.15 (s, 3H); 0.13 (s, 3H); 0.11 (s, 3H); 0.10 (s, 3H); 0.08 (s, 3H); 0.07 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.21 (m, 2H); 6.88–6.83 (m, 2H); 4.39 (s, 2H); 3.87 (dd, *J*=7.6, 2.8 Hz, 1H); 3.83 (dd, *J*=7.4, 2.3 Hz, 1H); 3.80 (s, 3H); 3.70–3.52 (m, 3H); 3.33–3.24 (m, 1H); 3.18 (dd, *J*=9.2, 7.5 Hz, 1H); 1.78–1.67 (m, 1H); 1.59–1.42 (m, 2H); 1.14 (s, 3H); 1.02 (d, *J*=5.9 Hz, 3H); 1.00 (s, 3H); 0.96 (d, *J*=7.1 Hz, 3H); 0.90 (s, 9H); 0.89 (s, 9H); 0.88 (s, 9H); 0.11–0.01 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.5, 159.1, 130.8, 129.3, 113.7, 76.4, 74.0, 72.9, 71.6, 61.1, 55.2, 53.7, 45.9, 38.8, 38.1, 26.2, 26.1, 26.0, 24.6, 18.6, 18.5, 18.3, 18.3, 16.7, 15.2, −3.6, −3.7, −3.7, −3.9, −5.2, −5.3. MS (ESI) *m*/*z* (rel intensity) 785 (85), 748 ([MNa^+], 100), 579 (65), 140 (13), 96 (32), 83 (43). HRMS (ESI-pos) ($C_{39}H_{76}O_6Si_3$) calcd 747.4842 (MNa^+), found 747.4865 (MNa^+).

3.1.4. (2S,3S,4R,7S)-3,7,9-Tri-tert-butyldimethylsilyloxy-1-hydroxy-2,4,6,6-tetramethylnonan-5-one (**8**)

Protected tetrol **7** (2.25 g, 3.09 mmol) was hydrogenated over 10%-Pd/C (0.7 g) at rt and atmospheric pressure in 60 ml of EtOH for 2 h. The catalyst was then removed by filtration and subsequently extracted with 300 ml of warm (60 °C) AcOEt. The combined filtrates and extracts were evaporated under reduced pressure and the residue was purified by FC (hexane/AcOEt 30/1) to provide 1.60 g (86%) of the title compound **8** as a viscous oil.

$[\alpha]_D^{20}$ −17.1 (*c* 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98–3.88 (m, 2H); 3.72–3.50 (m, 4H); 3.30–3.20 (m, 1H); 2.25 (br s, 1H); 1.65–1.45 (m, 3H); 1.17 (s, 3H); 1.12 (d, *J*=6.3 Hz, 3H); 1.05 (s, 3H); 1.00 (d, *J*=7.1 Hz, 3H); 0.92 (s, 9H); 0.88 (s, 9H); 0.85 (s, 9H); 0.12 (s, 3H); 0.08 (s, 3H); 0.08 (s, 3H); 0.07 (s, 3H); 0.04 (s, 3H); 0.02 (s, 3H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ 218.5, 73.9, 64.8, 61.0, 53.8, 53.0, 46.7, 38.1, 37.5, 26.4, 26.2, 26.1, 26.0, 19.1, 18.4, 18.4, 18.3, 15.8, 15.4, −3.6, −3.7, −3.8, −3.9, −5.2, −5.3. IR (film): 2948, 2930, 2851, 1688, 1509, 1469, 1252, 1091, 983, 836, 768. MS (ESI): *m*/*z*=627.16 [M+Na^+]. HRMS (MALDI) ($C_{31}H_{68}O_5Si_3$) calcd 627.4267 (MNa^+), found 627.4258 (MNa^+).

3.1.5. (2R,3S,4R,7S)-3,7,9-Tris(tert-butyldimethylsilyloxy)-2,4,6,6-tetramethyl-5-oxononanal (**9**)

To a stirred mixture of alcohol **8** (1.6 g, 2.64 mmol) and dried, powdered 4 Å molecular sieves in 80 ml of CH_2Cl_2 were added 0.81 g (6.02 mmol) of *N*-methylmorpholine-*N*-oxide (NMO) followed by tetra-*n*-propylammonium perruthenate (TPAP) (49 mg, 0.14 mmol). The mixture was stirred at rt for 1 h followed by filtration through a short plug of silica, washing with AcOEt, and evaporation of the filtrate to give 1.66 g of crude aldehyde **9** (quant), which was directly used in the next step.

$[\alpha]_D^{20}$ −43.4 (*c* 1.30, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J*=2.1 Hz, 1H); 4.06 (dd, *J*=8.0 Hz, 2.2 Hz, 1H); 3.88 (dd, *J*=7.5 Hz, 2.8 Hz, 1H); 3.64 (m, 1H); 3.57 (m, 1H); 3.22 (qi, *J*=7.0 Hz, 1H); 2.30 (m, 1H); 1.60–1.53 (m, 1H); 1.52–1.42 (m, 1H); 1.21 (s, 3H); 1.12 (d, *J*=7.0 Hz, 3H); 1.09 (d, *J*=7.0 Hz, 3H); 1.03 (s, 3H); 0.87 (s, 9H); 0.87 (s, 9H); 0.86 (s, 9H); 0.09 (s, 3H); 0.07 (s, 3H); 0.07 (s, 3H); 0.04 (s, 3H); 0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.9, 204.2, 76.2, 73.8, 60.9, 53.8, 50.8, 46.5, 38.1, 26.1, 26.0, 25.9, 24.5, 19.2, 18.3, 18.3, 15.5, 12.4, −3.7, −3.9, −5.2, −5.3. MS (ESI): *m*/*z*=625.27 [M+Na]$^+$ and 641.26 [M+K]$^+$. HRMS (ESI-pos) ($C_{31}H_{66}O_5Si_3$) calcd 625.41103 (MNa^+), found 625.41046 (MNa^+).

3.1.6. (3S,6S,7R,8R)-1,3,7-Tris(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyldec-9-en-5-one (**10**)

LiHMDS (3.40 ml of a 1 M solution in THF) was added dropwise to a solution of Ph_3PCH_3I (1.25 g, 3.5 mmol) in 20 ml of THF at 0 °C and the mixture was stirred at this temperature for 30 min. Solution (30 ml) of the above crude aldehyde **9** in THF were then added dropwise via syringe and stirring at 0 °C was continued for 45 min. Satd aq NH_4Cl (30 ml) was added followed by water (30 ml) and Et_2O (100 ml) and the phases were separated. The aqueous solution was re-extracted with Et_2O (2×100 ml), the combined organic extracts were dried over $MgSO_4$ and the solvent was removed by evaporation. Purification of the residue by FC (Et_2O/hexane 1/100→1/50) gave 1.20 g of olefin **10** as a colorless oil (76% over two steps).

$[\alpha]_D^{20}$ −23.1 (*c* 3.66, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99–5.88 (m, 1H); 5.07–4.97 (m, 2H); 3.92 (dd, *J*=7.5, 2.9 Hz, 1H); 3.88 (dd, *J*=7.0, 2.1 Hz, 1H); 3.71–3.62 (m, 1H); 3.61–3.53 (m, 1H); 3.10–3.02 (m, 1H); 2.16–2.08 (m, 1H); 1.61–1.45 (m, 2H); 1.19 (s, 3H); 1.05–1.00 (m, 9H); 0.92 (s, 9H); 0.89 (s, 9H); 0.87 (s, 9H); 0.10 (s, 3H); 0.09 (s, 3H); 0.08 (s, 3H); 0.06 (s, 3H); 0.04 (s, 3H); 0.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 218.5, 140.0, 115.3, 76.2, 73.8, 61.0, 53.7, 45.9, 43.5, 38.1, 26.2, 26.1, 26.0, 24.9, 18.8, 18.7, 18.5, 18.4, 18.3, 15.0, −3.5, −3.7, −3.8, −3.9, −5.2, −5.3. IR (film): 2954, 2930, 2858, 1691, 1469, 1254, 1092, 984, 837, 766. MS (MALDI) *m*/*z* (rel intensity) 623 ([MNa^+], 100), 601 ([MH^+], 4), 509 (12), 506 (22), 481 (17), 456 (9), 345 (14), 303 (29), 301 (15), 279 (29), 235 (26), 199 (11), 183 (14), 140 (14). HRMS (MALDI) ($C_{32}H_{68}O_4Si_3$) calcd 623.4321 (MNa^+), found 623.4330 (MNa^+).

3.1.7. (3S,6S,7R,8R)-3,7-Bis(tert-butyldimethylsilyloxy)-1-hydroxy-4,4,6,8-tetramethyl-dec-9-en-5-one (**11**)

Camphorsulfonic acid was added to a solution of olefin **10** (1.64 g, 2.73 mmol) in 50 ml of CH_2Cl_2/MeOH 1/1 at 0 °C and the mixture was stirred at 0 °C for 1 h. Aq $NaHCO_3$ was then added, the phases were separated, and the aqueous solution was re-extracted with CH_2Cl_2 (4×50 ml). The combined organic extracts were washed with brine and dried over $MgSO_4$. Subsequent evaporation of the solvent gave 1.15 g (87%) of a colorless oil that was homogenous by TLC and was directly used in the next step. Analytical data are for material from a different experiment that was submitted to FC (AcOEt/hexane 1/9).

$[\alpha]_D^{20}$ −9.3 (*c* 0.71, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99–5.88 (m, 1H); 5.08–4.97 (m, 2H); 4.07 (dd, *J*=6.7, 3.7 Hz, 1H); 3.89 (dd, *J*=7.5, 1.8 Hz, 1H); 3.64 (t, *J*=6.0 Hz, 2H); 3.08–3.01 (m, 1H); 2.13–2.06 (m, 1H); 1.82 (br s, 1H); 1.62–1.50 (m, 2H); 1.19 (s, 3H); 1.10 (s, 3H); 1.05 (d, *J*=7.0 Hz, 3H); 1.03 (d, *J*=7.0 Hz, 3H); 0.92 (s, 9H), 0.90 (s, 9H); 0.12 (s, 3H); 0.10 (s, 3H); 0.09 (s, 3H); 0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.7, 139.8, 115.5, 76.3, 73.0, 60.2, 53.9, 46.1, 43.3, 38.3, 26.0, 25.8, 25.2, 19.0, 18.5, 18.3, 17.4, 15.5, −3.5, −3.6, −3.8, −3.9. IR (film): 2955, 2930, 2858, 1702, 1473, 1252, 1087, 983, 829, 775. MS (MALDI) *m*/*z* (rel intensity) 509 ([MNa^+], 100), 345 (14), 301 (6), 235 (12), 184 (18), 162 (14), 140 (7). HRMS (MALDI) ($C_{26}H_{54}O_4Si_2$) calcd 509.3453 (MNa^+), found 509.3463 (MNa^+).

3.1.8. (3S,6R,7S,8S)-3,7-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4,6,8-tetramethyl-5-oxodec-9-enal (**14**)

To a solution of alcohol **11** (270 mg, 0.55 mmol) in CH_2Cl_2 (12 ml) were added $NaHCO_3$ (121 mg, 1.44 mmol), H_2O (13 μl), and DMP (611 mg, 1.44 mmol, as a 15% (w/v) solution in CH_2Cl_2). The suspension was stirred for 1.5 h, when TLC (hexane/AcOEt 10/1) indicated complete conversion. The mixture was diluted with Et_2O and then washed with satd aq $NaHCO_3$. The phases were separated and the aqueous solution was re-extracted with Et_2O. The combined organic extracts were then dried over $MgSO_4$, the solution was concentrated in vacuo, and the resulting semi-solid residue was purified by FC (hexane/AcOEt 50/1) to provide 243 mg (91%) of the target aldehyde **14** as a slightly yellow oil.

$[\alpha]_D^{20}$ −43.4 (*c* 1.30, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J*=2.1 Hz, 1H); 4.06 (dd, *J*=8.0 Hz, 2.2 Hz, 1H); 3.88 (dd, *J*=7.5 Hz, 2.8 Hz, 1H); 3.64 (m, 1H); 3.57 (m, 1H); 3.22 (qi, *J*=7.0 Hz, 1H); 2.30 (m, 1H); 1.60–1.53 (m, 1H); 1.52–1.42 (m, 1H); 1.21 (s, 3H); 1.12 (d, *J*=7.0 Hz, 3H); 1.09 (d, *J*=7.0 Hz, 3H); 1.03 (s, 3H); 0.87 (s, 9H); 0.87 (s, 9H); 0.86 (s, 9H); 0.09 (s, 3H); 0.07 (s, 3H); 0.07 (s, 3H); 0.04 (s, 3H); 0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.9, 204.2, 76.2, 73.8, 60.9, 53.8, 50.8, 46.5, 38.1, 26.1, 26.0, 25.9, 24.5, 19.2, 18.3, 18.3, 15.5, 12.4, −3.7, −3.9, −5.2, −5.3. MS (ESI): *m*/*z*=625.27 $[M+Na]^+$ and 641.26 $[M+K]^+$. HRMS (ESI-pos) ($C_{31}H_{66}O_5Si_3$) calcd 625.41103 (MNa^+), found: 625.41046 (MNa^+).

3.1.9. (3S,6S,7R,8R)-3,7-Bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxodec-9-enoic acid (**12**)

Procedure A: To a solution of aldehyde **14** (240 mg, 0.49 mmol) in a mixture of THF (13 ml), ^{t}BuOH (23 ml), and 2-methyl-2-butene (18.4 ml, 36.8 mmol) were added $NaClO_2$ (173 mg, 1.53 mmol) and NaH_2PO_4 (143 mg, 1.03 mmol) in water (5 ml) and the mixture was stirred at rt for 3 h. It was then concentrated in vacuo and the residue was partitioned between AcOEt and brine. The phases were separated and the aqueous solution was extracted with AcOEt. The combined organic extracts were then dried over $MgSO_4$, the solvent was evaporated and the resulting mixture was purified by FC (hexane/AcOEt 20/1→10/1→4/1) to yield (after two columns) 230 mg (94%) of acid **12** as a yellow oil.

Procedure B: To solution of alcohol **11** (1.15 g, 2.4 mmol) in 70 ml of DMF was added pyridinium dichromate (PDC) and the resulting solution was stirred at rt for 64 h. It was then poured into 150 ml of brine, 50 ml of water were added, and the solution was extracted with AcOEt (7×100 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Purification of the resulting residue by FC (AcOEt/hexane 1/6→1/2 (+5% MeOH)) gave 1.0 g (85%) of acid **12** as a light-yellow oil that could be converted to a white solid by co-evaporation with toluene.

$[\alpha]_D^{20}$ −21.0 (*c* 0.82, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.98 (br s, 1H); 5.99–5.88 (m, 1H); 5.08–4.98 (m, 2H); 4.40 (dd, *J*=6.7, 3.0 Hz, 1H); 3.87 (dd, *J*=7.5, 1.8 Hz, 1H); 3.08–3.01 (m, 1H); 2.49 (dd, *J*=16.4, 3.0 Hz, 1H); 2.31 (dd, *J*=16.4, 6.7 Hz, 1H); 2.13–2.06 (m, 1H); 1.19 (s, 3H); 1.10 (s, 3H); 1.05 (d, *J*=7.0 Hz, 3H); 1.02 (d, *J*=7.0 Hz, 3H); 0.91 (s, 9H), 0.87 (s, 9H); 0.08 (s, 3H); 0.07 (s, 3H); 0.07 (s, 3H); 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.4, 177.5, 139.8, 115.5, 76.3, 73.3, 53.6, 46.2, 43.4, 40.1, 26.2, 26.0, 24.1, 19.0, 18.7, 18.5, 18.2, 15.5, −3.5, −3.8, −4.3, −4.6. IR (film): 2956, 2930, 2858, 1714, 1681, 1386, 1254, 1087, 998, 837, 775, 707, 671. MS (MALDI) *m*/*z* (rel intensity) 523 ([MNa^+], 100), 501 ([MH^+], 3), 456 (6), 345 (11), 303 (5), 285 (6), 235 (14), 140 (11). HRMS (MALDI) ($C_{26}H_{52}O_5Si_2$) calcd 523.3246 (MNa^+), found 523.3255 (MNa^+).

3.1.10. 4-[(1E,3S)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-iodo-2-methyl-1-pentenyl]-2-methylthiazole (**16**)[15c]

To a solution of 10.0 g (30.35 mmol) of alcohol **15** in 180 ml of a 3/1 mixture of Et_2O and CH_3CN were successively added Ph_3P (12.0 g, 45.79 mmol), imidazole (6.24 g, 91.4 mmol) and iodine (11.6 g, 45.8 mmol) at 0 °C. The mixture was stirred at rt for 30 min followed by the addition of 35 ml of satd aq $Na_2S_2O_3$ and 400 ml of Et_2O. The layers were separated and the organic solution was washed with 35 ml of brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by FC (15% Et_2O/hexane) to provide 10.6 g (79%) of iodide **5** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (s, 1H); 6.52 (s, 1H); 4.22 (dd, *J*=7.5, 3.4 Hz, 1H); 3.20 (dd, *J*=7.4, 6.5 Hz, 2H); 2.70 (s, 3H); 2.15–2.00 (m, 2H), 2.00 (s, 3H); 0.91 (s, 9H); 0.11 (d, *J*=2.9 Hz, 3H); 0.04 (d, *J*=3.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 152.9, 141.1, 119.4, 115.5, 78.2, 40.4, 25.9, 19.2, 18.2, 14.0, 3.1, −4.5, −4.9.

3.1.11. (S,E)-N-Allyl-3-(tert-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-amine (**17**)

To a solution of iodide **16** (4.0 g, 9.14 mmol) in 60 ml of Et_2O was added allylamine (6.10 g, 100.7 mmol) with a syringe and the mixture was refluxed for 20 h. After cooling to rt 20 ml of satd aq $NaHCO_3$ were added, the phases were separated, and the aqueous solution was extracted with AcOEt. The combined organic extracts were then dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the residue by FC (AcOEt/MeOH/Et_3N 100/3/1) gave 2.73 g (81%) of the title compound as honey-yellow oil.

$[\alpha]_D^{20}$ −9.3 (*c* 1.33, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 1H); 6.41 (s, 1H); 5.80–5.70 (m, 1H); 5.02 (dd, *J*=17.1, 1.6 Hz, 1H); 4.92 (dd, *J*=10.2, 1.3 Hz, 1H); 4.11 (dd, *J*=7.4, 5.0 Hz, 1H); 3.09 (d, *J*=6.0 Hz, 3H); 2.58–2.47 (m, 1H); 2.54 (s, 3H); 1.88 (d, *J*=0.9 Hz,

3H); 1.75–1.50 (m, 2H); 1.23 (br s, 1H); 0.77 (s, 9H); 0.00 (s, 3H); −0.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 153.1, 142.1, 136.9, 118.5, 115.5, 115.0, 77.6, 52.5, 46.0, 36.6, 25.8, 19.1, 18.1, 13.9, −4.7, −5.2. IR (film): 2951, 2922, 2861, 1463, 1252, 1076, 836, 768, 288. MS (ESI) *m*/*z* (rel intensity) 389 ([MNa^+], 62), 367 ([MH^+], 100), 235 (11). HRMS (ESI-pos) ($C_{19}H_{34}N_2OSSi$) calcd 367.2234 (M+H), found 367.2240 (M+H).

3.1.12. (S,E)-tert-Butyl-allyl-(3-(tert-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-enyl)-carbamate (**18**)

To a solution of amine **17** (1.50 g, 4.09 mmol) and Et_3N (1.71 ml, 12.72 mmol) in 40 ml of THF was added BOC_2O (938 mg, 438 mmol) at 0 °C. After 5 min 30 mg (0.25 mmol) of DMAP were added and the mixture was stirred at 0 °C for 5 h. Aq satd NH_4Cl (25 ml) was then added, the phases were separated, and the aqueous solution was extracted with AcOEt. The combined organic extracts were washed with water and brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by FC (AcOEt/hexane 1/10) gave 1.764 g (92%) of the title compound as a colorless oil.

$[\alpha]_D^{20}$ −0.7 (*c* 0.74, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 1H); 6.38 (s, 1H); 5.81–5.70 (m, 1H); 5.10–5.00 (m, 2H); 4.10 (br s, 1H); 3.80 (br s, 2H); 3.22 (br m, 2H); 2.68 (s, 3H); 1.99 (s, 3H); 1.87–1.70 (m, 2H); 1.43 (s, 9H); 0.88 (s, 9H); 0.05 (s, 3H); 0.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 155.1, 152.9, 141.7, 134.1, 118.7, 116.2, 115.1, 79.3, 76.6, 49.7, 43.9, 34.8, 28.4, 25.8, 19.1, 18.1, 13.9, −4.7, −5.2. IR (film): 2955, 2926, 2855, 1688, 1465, 1405, 1248, 1166, 1065, 836, 771. MS (ESI) *m*/*z* (rel intensity) 489 ([MNa^+], 100), 467 ([MH^+], 10), 280 (10), 279 (49), 235 (21), 96 (16), 83 (20). HRMS (ESI-pos) ($C_{24}H_{42}N_2O_3SSi$) calcd 489.2578 (MNa^+), found 489.2585 (MNa^+).

3.1.13. (S,E)-tert-Butyl-allyl(3-hydroxy-4-methyl-5-(2-methylthiazol-4-yl)pent-4-enyl)-carbamate (**19**)

A 1 M solution of TBAF in 5% aq THF (5.2 ml) was added dropwise to a solution of fully protected amino alcohol **18** (1.30 g, 2.78 mmol) in 30 ml of THF over a period of 10 min at rt. The mixture was then stirred at rt for 2 h, when TLC indicated complete consumption of starting material. After addition of 25 ml of satd aq NH_4Cl and phase separation the aqueous solution was extracted with AcOEt. The combined organic extracts were washed with water and brine (50 ml each), dried over Na_2SO_4, and the solvent was removed in vacuo. Purification of the residue by FC (AcOEt/hexane 1/1) gave 793 mg (81%) of alcohol **19** as a colorless oil.

$[\alpha]_D^{20}$ +7.7 (*c* 1.43, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (s, 1H); 6.39 (s, 1H); 5.68–5.55 (m, 1H); 5.00–4.90 (m, 2H); 4.41 (br s, 1H); 4.10–4.00 (br s, 1H); 3.76–3.38 (br m, 3H); 3.10–2.95 (m, 1H); 2.51 (s, 3H); 1.85 (s, 3H); 1.78–1.50 (m, 2H); 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 156.8, 152.9, 142.0, 134.0, 118.1, 116.2, 115.1, 79.7, 73.7, 50.0, 43.7, 34.0, 28.2, 18.9, 14.5. IR (film): 3428 (br), 1972, 2930, 1691, 1469, 1412, 1364, 1254, 1168, 920, 873, 779. MS (ESI) *m*/*z* (rel intensity) 375 ([MNa^+], 100), 353 ([MH^+], 28), 279 (16), 257 (4), 188 (5), 177 (5), 96 (4), 82 (5). HRMS (ESI-pos) ($C_{18}H_{28}N_2O_3S$) calcd 375.1713 (MNa^+), found 375.1720 (MNa^+).

3.1.14. (3S,6R,7S,8S)-((S,E)-5-(tert-Butoxycarbonyl)-2-methyl-1-(2-methylthiazol-4-yl)-pent-1-en-3-yl)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxodec-9-enoate (**20**)

A solution of DCC (402 mg, 1.95 mmol) in 2 ml of CH_2Cl_2 was added dropwise to a solution of alcohol **19** (633 mg, 1.80 mmol), carboxylic acid **12** (750 mg, 1.50 mmol) (both dried by co-evaporation with toluene), and DMAP (55 mg, 0.45 mmol) in 8 ml of CH_2Cl_2 at 0 °C. After stirring at 0 °C for 30 min and 6 h at rt, the mixture was evaporated and the residue was purified by FC (hexane/AcOEt 9/1) to provide 968 mg (77%) of ester **20** as a colorless oil.

$[\alpha]_D^{20}$ −25.3 (*c* 0.63, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (s, 1H); 6.46 (s, 1H); 5.95–5.86 (m, 1H); 5.80–5.70 (m, 1H); 5.20 (dd, *J*=6.2, 3.5 Hz, 1H); 5.13–4.95 (m, 4H); 4.35 (dd, *J*=6.2, 3.4 Hz, 1H); 3.85–3.72 (m, 3H); 3.20–3.08 (m, 2H); 3.07–3.01 (m, 1H); 2.67 (s, 3H); 2.50 (dd, *J*=17.0, 3.4 Hz, 1H); 2.27 (dd, *J*=17.0, 5.9 Hz, 1H); 2.12–2.08 (m, 1H); 2.09 (s, 3H); 2.00–1.90 (m, 2H); 1.42 (s, 9H); 1.20 (s, 3H); 1.08 (s, 3H); 1.05 (d, *J*=7.0 Hz, 3H); 1.02 (d, *J*=7.0 Hz, 3H); 0.90 (s, 9H); 0.86 (s, 9H); 0.10 (s, 3H); 0.03 (s, 3H); 0.02 (s, 3H); 0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.9, 171.2, 164.6, 155.3, 152.4, 139.9, 136.5, 134.2, 120.9, 116.5, 116.3, 115.4, 79.6, 77.5, 76.2, 73.8, 53.4, 49.7, 46.1, 43.7, 43.5, 40.3, 31.6, 28.4, 26.2, 26.1, 23.6, 19.8, 19.2, 18.8, 18.5, 18.2, 15.1, 14.4, −3.5, −3.9, −4.2, −4.7. IR (film): 2958, 2933, 2858, 1739, 1695, 1466, 1409, 1366, 1252, 1169, 986, 836, 779. MS (MALDI) *m*/*z* (rel intensity) 857 ([MNa^+], 100), 523 (38), 429 (5), 357 (7), 335 (9), 279 (14), 235 (24), 166 (4). HRMS (MALDI) ($C_{44}H_{78}N_2O_7SSi_2$) calcd 857.4961 (MNa^+), found 857.4941 (MNa^+).

3.1.15. (E)-(2S,9S,10S,11R,14S)-10,14-Bis-(tert-butyldimethylsilanoxy)-9,11,13,13-tetramethyl-2-[(E)-1-methyl-2-(2-methylthiazol-4-yl)-vinyl]-12,16-dioxo-1-oxa-5-aza-cyclohexadec-7-ene-5-carboxylic acid tert-butylester (**21**)

Grubbs second generation catalyst ([1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenyl-methylene)-(tricyclohexylphosphine)-ruthenium; 9 mg, 0.16 mmol) was added to a solution of diene **20** (96.0 mg, 0.114 mmol) in 48 ml of CH_2Cl_2 and the mixture was refluxed for 16 h. At this point additional catalyst was added (6 mg) and refluxing was continued for 2 more hours. The mixture was then filtered through Celite and the filtrate was concentrated under reduced pressure. Purification of the residue by FC (hexane/Et_2O 5/3, 20 g of silica gel 15–40 μm, low pressure) gave 64.8 mg (70%) of fully protected cycloalkene **21**.

$[\alpha]_D^{20}$ +3.2 (*c* 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (s, 1H); 6.56 (s, 1H); 5.40 (d, *J*=9.9 Hz, 1H); 5.35–5.20 (m, 2H); 4.41–4.25 (m, 2H); 4.00 (m, 1H); 3.60–3.50 (m, 1H); 3.30–3.18 (m, 1H); 3.10 (t, *J*=11.7 Hz, 1H); 3.02–2.94 (m, 1H); 2.70 (s, 3H); 2.60 (dd, *J*=16.6, 6.4 Hz, 1H); 2.52–2.40 (m, 2H); 2.12 (s, 3H); 2.11–2.00 (m, 1H); 1.98–1.87 (m, 1H); 1.42 (s, 9H); 1.23 (s, 3H); 1.16 (s, 3H); 1.13 (d, *J*=6.8 Hz, 3H); 1.07 (d, *J*=7.0 Hz, 3H); 0.89 (s, 9H); 0.87 (s, 9H); 0.15 (s, 3H); 0.12 (s, 3H); 0.05 (s, 3H); 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.0, 170.4, 164.6, 155.6, 152.5, 137.3, 134.3, 124.4, 120.4, 116.5, 79.5, 77.1, 76.8, 73.1, 54.3, 48.0, 43.7, 42.9, 42.4, 32.1, 29.1, 26.0, 25.9, 23.7, 22.6, 19.2, 19.0, 18.4, 18.2, 15.1, 14.1, 12.6, −3.6, −4.3, −4.4, −5.0. IR (film): 2952, 2926, 2858, 1691, 1743, 1248, 1169, 1076, 986, 829, 771, 733. MS (MALDI) *m*/*z* (rel intensity) 829 ([MNa^+], 60), 807 ([MH^+], 3), 773 (28), 707 (100), 575 (11), 542 (13), 523 (6), 414 (4), 354 (5), 178 (23). HRMS (MALDI) ($C_{42}H_{74}N_2O_7SSi_2$) calcd 829.4648 (MNa^+), found 829.4632 (MNa^+).

3.1.16. (E)-(2S,9S,10S,11R,14S)-10,14-Bis-(tert-butyldimethylsilanoxy)-9,11,13,13-tetramethyl-2-[(E)-1-methyl-2-(2-methylthiazol-4-yl)-vinyl]-12,16-dioxo-1-oxa-5-aza-cyclohexadec-7-ene-5-carboxylic acid tert-butylester (**2**)

To a cooled (0 °C) solution of the protected cylcoalkene **21** (32.0 mg, 0.039 mmol) in 3 ml of THF was added pyridine (0.5 ml) followed by slow dropwise addition of HF·Pyr (0.6 ml). The mixture was stirred at rt for 2 h at which point additional HF·Pyr (0.6 ml) was added (after cooling to 0 °C) and stirring was continued for additional 2.5 h (rt). The mixture was then carefully (dropwise) added to 30 ml of ice-cold satd aq $NaHCO_3$ (CAUTION: strong foaming) and the aqueous solution was extracted with AcOEt (6×20 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed by evaporation. Purification of the resulting residue by FC (hexane/AcOEt 1/1) gave 14.8 mg (65%) of the target compound **2**.

$[\alpha]_D^{20}$ −83.8 (*c* 0.47, $CHCl_3$). ^1H NMR (DMSO-d_6, 500 MHz, 318 K): δ 7.29 (s, 1H); 6.49 (s, 1H); 5.92 (dd, *J*=15.5, 4.8 Hz, 1H); 5.38–5.30 (m, 1H); 5.13 (dd, *J*=7.6, 2.6 Hz, 1H); 5.08 (d, *J*=6.1 Hz, 1H); 4.54 (d, *J*=6.2 Hz, 1H); 4.44–4.37 (m, 1H); 3.97 (dd, *J*=14.3, 6.2 Hz, 1H); 3.71 (dd, *J*=14.8, 7.7 Hz, 1H); 3.54–3.48 (m, 1H); 3.27–3.17 (m, 2H); 3.16–3.08 (m, 1H); 2.65 (s, 3H); 2.41–2.33 (m, 2H); 2.07 (s, 3H); 2.11–2.03 (m, 1H); 2.03–1.93 (m, 1H); 1.85–1.76 (m, 1H); 1.40 (s, 9H); 1.16 (s, 3H); 1.08 (d, *J*=6.7 Hz, 3H); 1.02 (d, *J*=6.9 Hz, 3H); 0.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.9, 170.4, 165.6, 155.6, 151.3, 137.8, 124.9, 120.4, 117.5, 115.2, 79.7, 77.2, 74.2, 71.0, 54.7, 49.5, 42.9, 41.3, 39.9, 38.1, 33.8, 29.7, 28.5, 21.7, 18.7, 16.1, 13.7, 10.9; IR (film): 3460 (br), 1977, 2926, 2360, 2332, 1735, 1688, 1466, 1413, 1366, 1283, 1248, 1166, 986, 746. MS (MALDI) *m*/*z* (rel intensity) 601 ([MNa^+], 75), 579 ([MH^+], 5), 567 (17), 545 (49), 523 (21), 506 (18), 479 (100), 457 (20), 413 (19), 391 (27), 314 (20), 235 (15), 178 (31). HRMS (ESI) ($C_{30}H_{46}N_2O_7S$) calcd 601.2918 (MNa^+), found 601.2919 (MNa^+).

*3.1.17. (E)-(2S,9S,10S,11R,14S)-10,14-Dihydroxy-9,11,13,13-tetramethyl-2-[(E)-1-methyl-2-(2-methylthiazol-4-yl)-vinyl]-12,16-dioxo-1-oxa-5-aza-cyclohexadecane-5-carboxylic acid tert-butylester (**1**)*

To a solution of cycloalkene **2** (24 mg, 0.046 mmol) in CH_2Cl_2 (10 ml) were added 500 mg (2.58 mmol) of dipotassium diazodicarboxylate (PADA)[33] followed by AcOH (100 μl, 1.72 mmol). Two additional aliquots of AcOH (100 μl each) were added after 40 min and 60 min, respectively (5.16 mmol of AcOH in total), and the mixture was stirred at rt. This procedure was repeated after 18 h, 21 h, and 24 h. The progress of the reaction was monitored by ESI-MS (M+K peaks at m/z 617 and 619 for **2** and **1**, respectively). After 40 h the mixture was filtered through HYFLO® and the filter was washed with three 5 ml portions of CH_2Cl_2. The combined filtrates were evaporated, the residue was redissolved in CH_2Cl_2 (10 ml) and PADA and AcOH were added in the same amounts and by the same procedure as described above, with additional PADA and AcOH being added after 56 h, 60 h, and 64 h (total reaction time). After 80 h the mixture was worked up as for the 40 h time point, the product mixture was redissolved in 10 ml of CH_2Cl_2 and PADA and AcOH were added as before. Additional aliquots of PADA/AcOH were added after 170 h and 174 h, bringing the total amount of PADA/AcOH added in the course of the reaction to 28.38 mmol/56.76 mmol. After 190 h the mixture was worked up by filtration through HYFLO®; the filter was washed with CH_2Cl_2 (3×5 ml) and the combined filtrates were evaporated. The residue was submitted to FC in AcOEt/hexane providing 21.8 mg (91%) of a 4/1 mixture of **1** and **2** (according to analytical RP-HPLC). Purification of this material by preparative RP-HPLC gave 7.6 mg of pure **1** together with 1.0 mg (4%) of starting material **2**. A second chomatographic run with mixed fractions from the first separation gave additional 4.8 mg of **1** bringing the total yield to 12.4 mg (52%).

$[\alpha]_D^{20}$ −4.3 (*c* 0.98, $CHCl_3$). ^1H NMR (500 MHz, 318 K, $CDCl_3$): δ 7.01 (s, 1H); 6.64 (s, 1H); 5.18 (d, *J*=9.7 Hz, 1H); 4.38 (d, *J*=9.7 Hz, 1H); 3.72 (dd, *J*=7.2, 3.0 Hz, 1H); 3.63–3.45 (br m, 1H); 3.38–3.30 (m, 1H); 3.30–3.12 (m, 2H); 3.10–2.94 (br m, 1H); 2.93–2.86 (m, 1H); 2.78 (s, 3H); 2.50 (dd, *J*=14.4, 11.2 Hz, 1H); 2.40 (dd, *J*=14.3, 2.1 Hz, 1H); 2.30–2.10 (br m, 1H); 2.07 (s, 3H); 1.88–1.75 (m, 2H); 1.70–1.52 (m, 3H); 1.50–1.45 (m, 1H); 1.45 (s, 9H); 1.42 (s, 3H); 1.40–1.30 (m, 1H); 1.14 (d, *J*=6.9 Hz, 3H); 1.07 (s, 3H); 0.97 (d, *J*=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.7, 171.0, 170.2, 155.0, 151.7, 139.6, 117.5, 115.4, 79.5, 76.6, 71.7, 71.4, 53.9, 48.2, 43.6, 41.4, 39.2, 35.1, 33.8, 28.2, 27.8, 23.7, 21.4, 18.5, 17.6, 16.1, 15.7, 11.2. IR (film): 3460 (br), 2969, 2926, 2358, 2339, 1731, 1681, 1473, 1419, 1369, 1287, 1252, 1151, 976, 740. MS (MALDI) *m*/*z* (rel intensity) 603 ([MNa^+], 57), 581 ([MH^+], 23), 547 (18), 525 (100), 481 (73), 262 (6), 178 (9). HRMS (ESI) ($C_{30}H_{48}N_2O_7S$) calcd 603.3074 (MNa^+), found 603.3075 (MNa^+).

Acknowledgements

The excellent support by the mass spectrometry facility at the Laboratory of Organic Chemistry of the ETH Zürich is gratefully acknowledged.

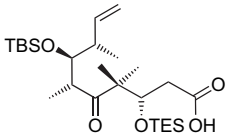
Supplementary data

^1H NMR spectra of compounds **1** and **2**. Analytical RP-HPLC traces of compounds **1** and **2** and the FC-purified mixture of **1** and **2** obtained after diimide reduction of **2**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.017.

References and notes

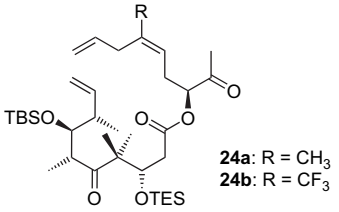
1. (a) Cragg, G. M.; Newman, D. J. *Pure Appl. Chem.* **2005**, *77*, 7–24; (b) *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; CRC: Boca Raton, FL, 2005; (c) Cragg, G. M.; Newman, D. J.; Snader, K. M. *Nat. Prod. Rep.* **2000**, *17*, 215–234.
2. Selected reviews: (a) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141–2153; (b) Hamann, M. T. *Curr. Pharm. Des.* **2003**, *9*, 879–889.
3. For an example where total synthesis has served to provide material of a complex natural product (discodermolide) for Phase I clinical studies see: Mickel, S. J. *Curr. Opin. Drug Discov. Dev.* **2004**, *7*, 869–881.
4. For examples from the area of microtubule-stabilizing natural products see: Altmann, K.-H.; Gertsch, J. *Nat. Prod. Rep.* **2007**, *24*, 327–357.
5. Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58.
6. Nören-Müller, A.; Reis-Corrêa, I., Jr.; Prinz, H.; Rosenbaum, C.; Saxena, K.; Schwalbe, H. J.; Vestweber, D.; Cagna, G.; Schunk, S.; Schwarz, O.; Schiewe, H.; Waldmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *103*, 10606–10611.
7. Tietze, L. F.; Bell, H. P.; Chandrasekar, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3996–4028.
8. (a) Feyen, F.; Cachoux, F.; Gertsch, J.; Wartmann, M.; Altmann, K.-H. *Acc. Chem. Res.* **2008**, *41*, 21–31; (b) Feyen, F.; Gertsch, J.; Wartmann, M.; Altmann, K.-H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5880–5885.
9. Altmann, K.-H.; Flörsheimer, A.; Bold, G.; Caravatti, G.; Wartmann, M. *Chimia* **2004**, *58*, 686–690.
10. For recent reviews on the chemistry, biology, and clinical applications of epothilones see: (a) Altmann, K.-H.; Pfeiffer, B.; Arseniyadis, S.; Pratt, B. A.; Nicolaou, K. C. *ChemMedChem* **2007**, *2*, 396–423; (b) Höfle, G.; Reichenbach, H. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; CRC: Boca Raton, FL, 2005; pp 413–450.
11. Larkin, J. M. G.; Kaye, S. B. *Expert Opin. Invest. Drugs* **2006**, *15*, 691–702.
12. (a) Chou, T. C.; Dong, H. J.; Zhang, X. G.; Tong, W. P.; Danishefsky, S. J. *Cancer Res.* **2005**, *65*, 9445–9454; (b) Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Chou, T. C.; Dong, H. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 10913–10922; (c) Yoshimura, F.; Rivkin, A.; Gabarda, A. E.; Chou, T. C.; Dong, H. J.; Sukenick, G.; Morel, F. F.; Taylor, R. E.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2518–2521; (d) Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Chou, T. C.; Dong, H. J.; Tong, W. P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 2899–2901; (e) Chou, T. C.; Dong, H. J.; Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Tong, W. P.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4761–4767.
13. For a side-chain-modified analog of **1** with enhanced antiproliferative activity cf. Ref. 8b.
14. A preliminary account of this work has appeared as a short conference report: Feyen, F.; Gertsch, J.; Wartmann, M.; Altmann, K.-H. *Chimia* **2007**, *61*, 143–146.
15. (a) Altmann, K.-H.; Bold, G.; Caravatti, G.; Denni, D.; Flörsheimer, A.; Schmidt, A.; Rihs, G.; Wartmann, M. *Helv. Chim. Acta* **2002**, *85*, 4086–4110; (b) Schinzer, D.; Bauer, A.; Schieber, J. *Chem.—Eur. J.* **1999**, *5*, 2492–2500; (c) Mulzer, J.; Mantoulidis, A.; Oehler, E. *J. Org. Chem.* **2000**, *65*, 7456–7467.
16. White, J. D.; Carter, R. G.; Sundermann, K. F.; Wartmann, M. *J. Am. Chem. Soc.* **2001**, *123*, 5407–5413.
17. (a) Klar, U.; Röhr, B.; Kuczynski, F.; Schwede, W.; Berger, M.; Skuballa, W.; Buchmann, B. *Synthesis* **2005**, 301–305; (b) Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem.—Eur. J.* **2001**, *7*, 5299–5317; (c) Taylor, R. E.; Galvin, G. M.; Hilfiker, K. A.; Chen, Y. *J. Org. Chem.* **1998**, *63*, 9580–9583; (d) Schinzer, D.; Limberg, A.; Böhm, O. *Chem.—Eur. J.* **1996**, *2*, 1477–1482.
18. (a) Klar, U.; Buchmann, B.; Schwede, W.; Skuballa, W.; Hoffmann, J.; Lichtner, R. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 7942–7948; (b) Taylor, R. E.; Chen, Y.; Galvin, G. M.; Pabba, P. K. *Org. Biomol. Chem.* **2004**, *2*, 127–132.
19. (a) Schinzer, D.; Bourguet, E.; Ducki, S. *Chem.—Eur. J.* **2004**, *10*, 3217–3224; (b) Schinzer, D.; Böhm, O.; Altmann, K.-H.; Wartmann, M. *Synlett* **2004**, 1375–1378.
20. Koch, G.; Loiseleur, O.; Fuentes, D.; Jantsch, A.; Altmann, K.-H. *Synlett* **2004**, 693–697.
21. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.

22. Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974–7991.
23. The synthesis of carboxylic acid **12** has been reported previously by Sinha and co-workers in Ref. 26. While this group has employed different starting materials, their overall strategy to **12** is similar to ours. In particular, the synthesis also proceeds through fully protected triol **10** as a key intermediate. However, no experimental details or analytical data are disclosed in Ref. 26 (including the associated Supplementary data), except for ^{1}H and ^{13}C data for **12**. It should also be noted that several discrepancies exist between the ^{13}C data reported for **12** by Sinha and co-workers and those reported in this paper. The Supplementary data to Ref. 26 lists 22 carbon signals for **12**, which does correspond to the total number of non-equivalent C-atoms. At the same time, however, the signal for the carboxylate carbon is missing from the list.
Danishefsky and co-workers have described the synthesis of carboxylic acid **12a**, but following a strategy different from the one discussed in this paper (Refs. 12b,d):



12a

24. For recent reviews on olefin metathesis cf., e.g.: (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140; (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
25. Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092.
26. Sun, J.; Sinha, S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1381–1383.
27. This problem was eventually overcome by the (uncomplicated and still *E*-selective) RCM of dienes **24a**/**b** and introduction of the side chain subsequent to macrocyclization:



28. Zeng, X.; Wei, X.; Farina, V.; Napolitano, E.; Xu, Y.; Zhang, L.; Haddad, N.; Yee, N. K.; Grinberg, N.; Shen, S.; Senanayake, C. H. *J. Org. Chem.* **2007**, *71*, 8864–8875.
29. Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91–155.
30. Kuzniewski, C. N.; Gertsch, J.; Wartmann, M.; Altmann, K.-H. *Org. Lett.* **2008**, *10*, 1183–1186.
31. Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157–2162.
32. (a) Corey, E. J.; Mock, W. L.; Pasto, D. J. *Tetrahedron Lett.* **1961**, 347–352; (b) Hünig, S.; Müller, H. R.; Their, W. *Tetrahedron Lett.* **1961**, 353–357; (c) van Tamelen, E. E.; Dewey, R. S.; Timmons, R. J. *J. Am. Chem. Soc.* **1961**, *83*, 3725–3726.
33. Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488–2501.