Natural product-derived building blocks for combinatorial synthesis. Part 1. Fragmentation of natural products from myxobacteria

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Novel and unique chiral building blocks of high structural diversity were obtained by selective chemical fragmentation of natural products from myxobacteria. Subsequent modification reactions provided primary alcohol and carboxylic acid derivatives, which are suitable for the construction of combinatorial chemical libraries. The single SPOT synthesis of a hybrid structure on a polypropylene membrane was employed to demonstrate the chemical recombination of such rare building blocks on a micro-scale.

Introduction

Natural products continue to play an important role in drug discovery,[1–4] especially in the field of anti-tumor and anti-infective agents. Recently, there has been an increasing interest in the synthesis of natural product-based combinatorial libraries[5–8] with high structural diversity for the search of new lead structures and for the identification of new targets emerging from the growing efforts in genomics and proteomics.[9,10]

At present, two main strategies are applied for the combinatorial synthesis of non-oligomeric natural product-based libraries. The target-oriented library synthesis is based on the systematic structural modification of a natural product skeleton for the optimisation of existing leads (*focused libraries*) by either semisynthetic or, with the possibility of introducing broader structural variations, total synthesis approaches.[5–7,11] Diversity-oriented approaches on the other hand utilise either common structural motifs of natural products that are capable of interacting with a wide range of biological targets ('*privileged structures*') for the synthesis of structural complex and diverse small-molecule libraries[12–14] or multifunctional scaffolds (*e.g.* steroids or carbohydrates) for generating diversity by introducing variable side chains.[15–17]

Here we report on a novel strategy for the construction of diversity-oriented natural product-based libraries by combinatorial chemical synthesis of hybrid structures *via* recombination of complex fragments of natural products. The synthesis of a unique collection of structural diverse chiral building blocks by chemical fragmentation of a range of natural products from myxobacteria is described. Myxobacteria are a rich source of bioactive secondary metabolites,[18] and during the past years we isolated highly diverse natural products, such as the antifungal macrolide soraphen A (**1**),[19] the β-methoxyacrylate fungicide myxothiazol A (**2a**),[20–22] the macrolide-polyether antibiotic sorangicin A (**3**),[23–25] the anticancer drug candidate epothilone A (**4**),[26–28] the antifungal compound ambruticin S (**5**),[29,30] or the cytostatic macrolide apicularen A (**6**)[31,32] (Scheme 1). So far, we have focused on cleavage reactions that result in most easily accessible and stable primary alcohol derivatives. Additional functional groups were selectively protected to provide chiral building blocks suitable for the solid-phase synthesis of single compound combinatorial libraries. Moreover, the conversion to carboxylic acid fragments was investigated in order to increase diversity in the coupling chemistry for library synthesis. The SPOT technique[33,34] allows the simultaneous synthesis of large numbers of compounds on a nanomolar scale and is therefore especially suited for library synthesis with valuable and rare building blocks. Our strategy for the preparation of *non-target* directed combinatorial libraries is demonstrated by the solid-phase synthesis of a hybrid structure containing two natural product-derived fragments.

Results and discussion

Reductive ring opening of the macrolide soraphen A (**1**) with $LiAlH_4$ in THF[35] and subsequent silylation of the 1,17-diol with *tert*-butyldimethylsilyl chloride (TBSCl)–imidazole gave access to the known *tert*-butyldimethylsilyl (TBS)-protected intermediate **7**.[36] Selective cleavage of the $\Delta^{9,10}$ double bond by ozonolysis, followed by reduction with $NaBH_4$ afforded the primary alcohol fragments **8** (66%) and **9** (57%) (Scheme 2). The former was oxidised with pyridinium dichromate (PDC) in DMF to the corresponding carboxylic acid derivative **10**, isolated as the triethylammonium salt in 61% yield.

The 5-*O*-methylated derivative **12** was obtained in an analogous reaction sequence by ozonolysis of the TBS-protected 5-*O*-methyl compound **11**, which was derived from soraphen A by 3,5-di-*O*-methylation with MeI and NaH in HMPA, acid catalysed removal of the C-3-OMe group and subsequent reductive cleavage of the lactone bond in 47% overall yield.

Reaction of soraphen A with H_2SO_4 in MeOH provided, in a complex reaction sequence, the γ-lactone **13**[35] (Scheme 3) in 81% yield. When the reaction was performed in CD_3OD an exchange of the 3-OMe and 17-OMe groups was found. We assume that the reaction takes places by a concerted mechanism with elimination of the hydroxy group at C-5 and cleavage of the macrocyclic lactone with inversion of the stereocenter at C-17 (no H/D-exchange was found when **13** was reacted with H_2SO_4 in CD_3OD). The structure elucidation was performed by ^1H–^1H COSY, ^1H–^1H TOCSY, and ^1H–^{13}C HMBC experiments. The illustrated stereochemistry at C-3 and C-4 was derived from NOE difference NMR spectra and NOE correlations in the ^1H–^1H ROESY spectrum of compound **15**. The 3-OMe and 4-OMe signals show significant differences in their chemical shifts (3.48 and 3.39 ppm, respectively). NOE correlations were

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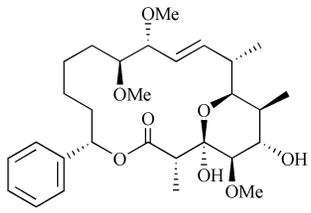
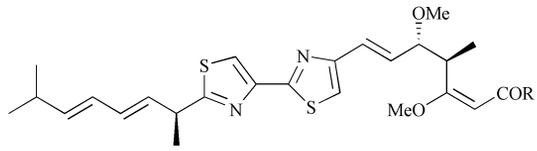
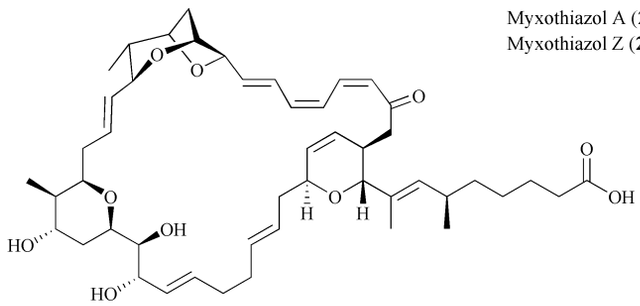


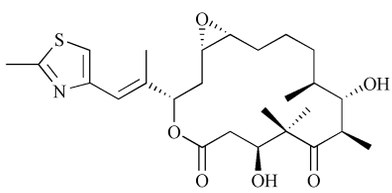
Soraphen A (**1**)



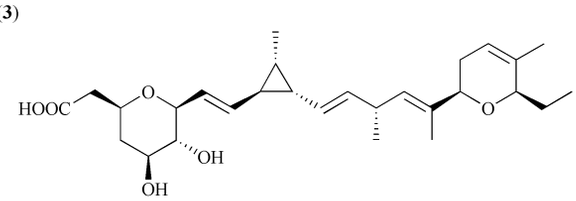
Myxothiazol A (**2a**): R = NH_2
Myxothiazol Z (**2b**): R = OMe



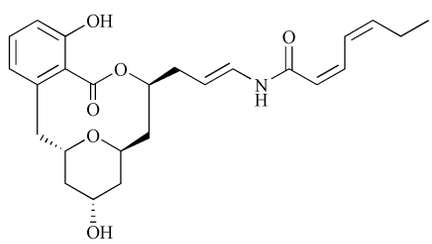
Sorangicin A (**3**)



Epothilone A (**4**)



Ambruticin S (**5**)



Apicularen A (**6**)

Scheme 1 Natural products from myxobacteria.

found between 2-Me and 3-OMe, 5-H_b and 4-OMe, and 6-Me and 5-H_b.

As ozonolysis of γ-lactone **13** gave after reductive work-up compound **14** as a single product, the $\Delta^{9,10}$ double bond was finally dihydroxylated by catalytic OsO_4 oxidation in the presence of 4-methylmorpholine *N*-oxide (NMO)[37] and the 1,2-glycol was cleaved with $NaIO_4$. Subsequent reduction with $NaBH_4$ afforded both alcohol fragments **14** and **15** in 72% and 74% yields, respectively. Oxidation of **15** with PDC provided after column chromatography the carboxylic acid **17** (56%). TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl)-catalysed oxidation[38,39] of the primary alcohol **14** in the presence of sodium chlorite ($NaClO_2$) and NaOCl gave on the other hand in comparable yields the carboxylic acid **16** (60%).

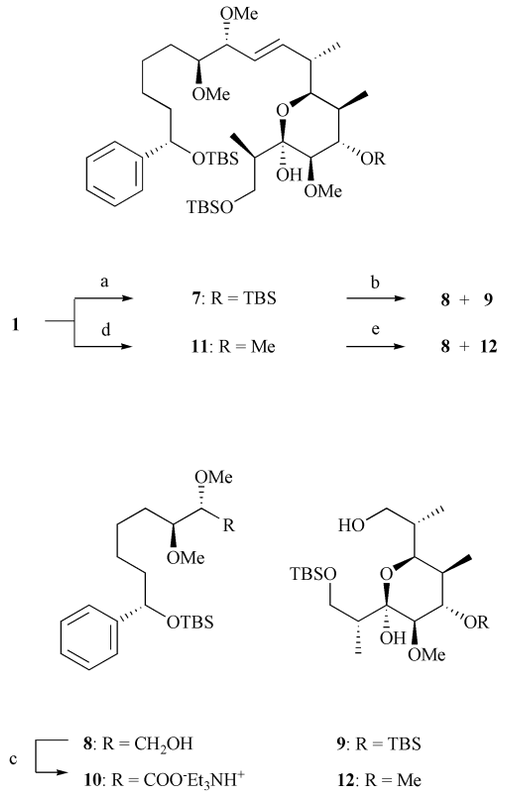
Myxothiazol Z (**2b**),[40,41] the ester-analog and co-metabolite of myxothiazol A (**2a**), was synthesised following established methods from myxothiazol A by conversion of the amide into an ester group.[42] OsO_4-oxidation without affecting the $\Delta^{2,3}$ double bond of the β-methoxy acrylate followed by diol cleavage with $NaIO_4$ and subsequent $NaBH_4$ reduction provided bis-thiazole **18** (78%) as racemate and the β-methoxyacryloyl ester **19** (67%) (Scheme 4). The racemic bis-thiazole **18** is formed by cleavage of the $\Delta^{15,16}$ double bond as a result of a rearrangement reaction during oxidation with OsO_4 which is in accordance with the results obtained by ozone-degradation followed by an oxidative work-up of myxothiazol A.[21]

Silylation of diol **18** with TBSCl–imidazole furnished in 85% yield bis-silyl ether **20**. Subsequent selective deprotection of the primary silyl-group with 0.2 equivalents of camphorsulfonic acid[43] (CSA) in MeOH–CH_2Cl_2 provided **21** in 83% yield.

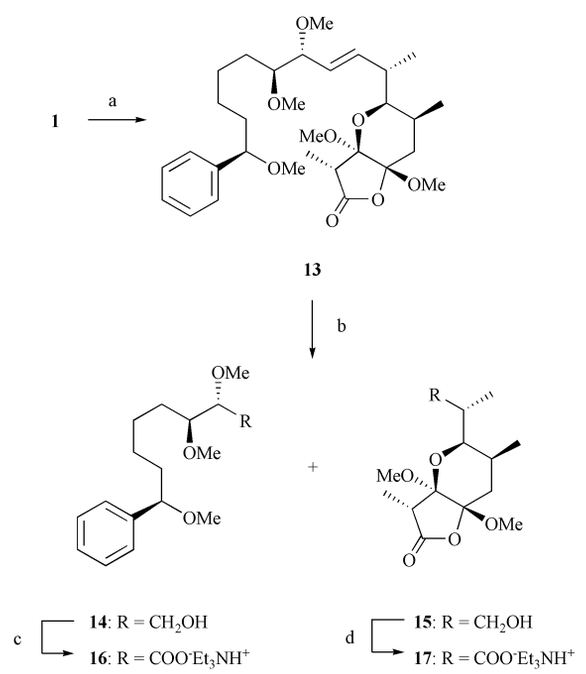
Oxidation of the primary alcohol **21** with TEMPO–KBr–NaOCl provided the carboxylic acid **22** (51%). DIBAL-H-reduction of the TBS-protected ester **23** which was obtained in 82% yield from **19** also gave access to the primary alcohol **24** (71%).

Acetylation of sorangicin A (**3**) with acetic anhydride in pyridine provided the corresponding 21,22,25-tri-*O*-acetate[44] which was cleaved by ozonolysis followed by reaction with Me_2S and subsequent reduction with borohydride ion exchange resin[45] (Scheme 5). The substituted tetrahydropyran derivative **25** and the bicyclic ether **26** were isolated by column chromatography in 79% and 84% yields, respectively, after simple removal of the polymer-supported reagent by filtration. Selective protection of the diol **25** was then achieved by deacetylation with NaOMe in MeOH, introduction of TBS-protecting groups to provide the fully silylated compound **27** (58% overall yield), and subsequent selective deprotection with CSA in MeOH–CH_2Cl_2 to afford the primary alcohol **28** (41%) and the diol **29** (44%). Selective silylation of **29** with TBSCl–Et_3N–DMAP in anhydrous CH_2Cl_2 provided on the other hand the primary alcohol **30** (38%). Both **28** and **30** contain traces of the other regioisomer and were finally purified by HPLC.

TBS-protection of diol **26** gave the TBS-protected bicyclic ether **31** in 57% yield which upon reaction with 0.2 equivalents of CSA in CH_2Cl_2–MeOH furnished in 42% yield a 1 : 1



Scheme 2 *Reagents*: a) 1. $LiAlH_4$, 2. TBSCl, imidazole; b) 1. O_3, 2. $NaBH_4$; c) 1. PDC, 2. Et_3N; d) 1. MeI, NaH, HMPA, 2. HCl, 3. $LiAlH_4$, 4. TBSCl, imidazole; e) 1. O_3, 2. $NaBH_4$.

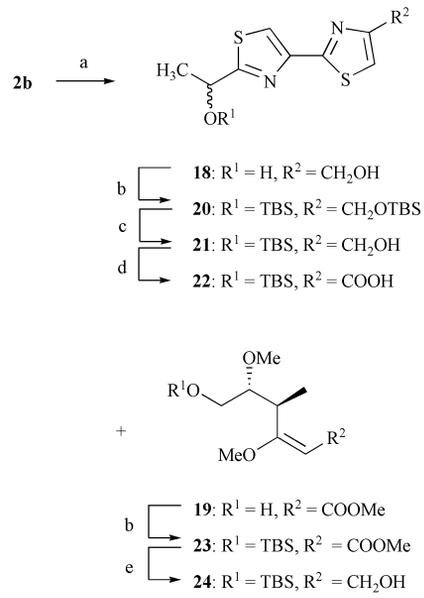


Scheme 3 *Reagents*: a) H_2SO_4, MeOH; b) 1. OsO_4, NMO, 2. $NaIO_4$, 3. $NaBH_4$; c) 1. TEMPO, NaOCl, $NaClO_2$, 2-methylbut-2-ene, 2. Et_3N; d) 1. PDC, 2. Et_3N.

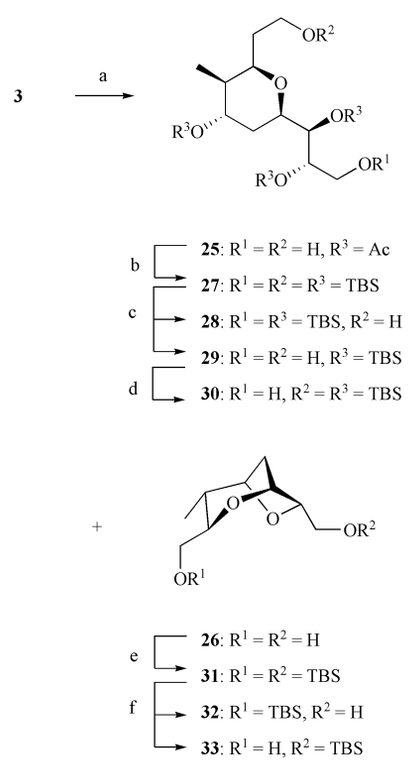
mixture of the primary alcohols **32** and **33**. Separation of the regioisomers was finally achieved by column chromatography.

Treatment of epothilone A (**4**) with a 0.5 M solution of sodium hydroxide in MeOH–H_2O afforded *via* a retro-aldol reaction[46] in 24% yield compound **34** and additionally, by cleavage of the lactone bond, the acid **35** in 65% yield (Scheme 6).

Treatment of epoxide **34** with H_2SO_4 in THF–H_2O provided diol **36** which gave upon periodate oxidation and subsequent



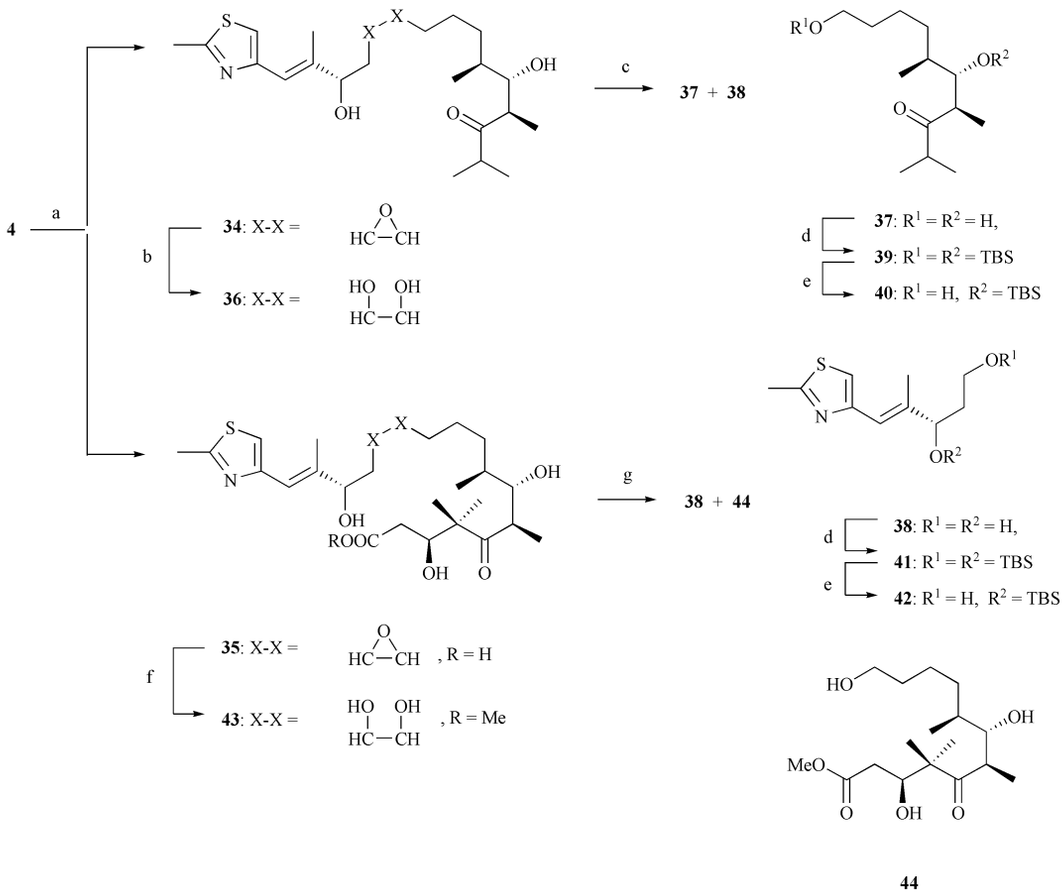
Scheme 4 *Reagents*: a) 1. OsO_4, NMO, 2. $NaIO_4$, 3. $NaBH_4$; b) TBSCl, imidazole; c) CSA; d) TEMPO, KBr, NaOCl,; e) DIBAL-H.



Scheme 5 *Reagents*: a) 1. Ac_2O, pyridine, 2. O_3, 3. Me_2S, 4. BH_4^- ion exchange resin; b) 1. NaOMe, MeOH, 2. TBSCl, imidazole; c) CSA; d) TBSCl, Et_3N, DMAP; e) TBSOTf, Et_3N; f) CSA.

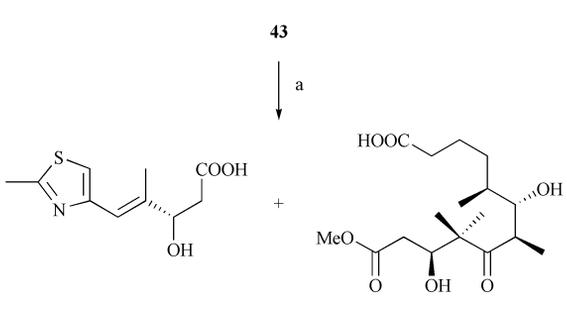
reduction with BH_4^- ion exchange resin the fragments **37** (48%) and **38** (55%), isolated by preparative HPLC. Here, the use of polymer-supported BH_4^- is particularly advantageous as it makes the isolation of polar compounds like **37** feasible by avoiding an aqueous work-up. Moreover, probably due to steric hindrance, no reduction of the carbonyl group at C-3 of compound **37** was found. Introduction of TBS-groups [**37** → **39** (71%) and **38** → **41**[47] (85%)] and subsequent selective CSA-deprotection provided the primary alcohols [**39** → **40** (79%) and **41** → **42**[43] (88%), respectively].

Reaction of epoxide **35** with H_2SO_4 in THF–H_2O, followed by methyl ester formation with TMS–diazomethane gave **43** in 54% yield. Subsequent reaction with $NaIO_4$ and then BH_4^- ion exchange resin provided diol **38** (49%) and ester **44** (41%) which



Scheme 6 *Reagents*: a) NaOH, MeOH; b) H_2SO_4; c) 1. $NaIO_4$, 2. BH_4^- ion exchange resin; d) TBSOTf, Et_3N; e) CSA; f) 1. H_2SO_4, 2. TMS–CH_2N_2; g) 1. $NaIO_4$ 2. BH_4^- ion exchange resin.

were separated by preparative HPLC. Alternatively, the diol **43** was cleaved to the carboxylic acids **45** and **46** in 86% and 49% yields, respectively, by reaction with sodium periodate and subsequent oxidation of the aldehyde fragments with sodium chlorite in the presence of 2-methylbut-2-ene as a HOCl scavenger[48] (Scheme 7). Whereas compounds **44** and **46** were

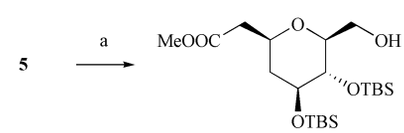


Scheme 7 *Reagents*: a) 1. $NaIO_4$, $NaClO_2$, 2-methylbut-2-ene.

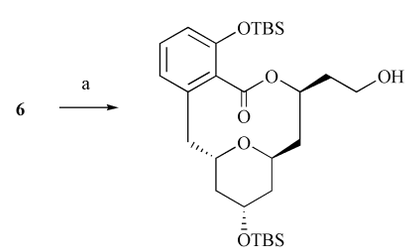
readily traceable by analytical HPLC using a light scattering detector, fragment **37** was hardly detected and analytical TLC was required.

The antifungal compound ambruticin S (**5**)[29,30] (Scheme 8) was esterified with diazomethane and the C-5 and C-6 hydroxy groups were protected as TBS-ethers by treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of triethylamine. Subsequent ozonolysis followed by sodium borohydride reduction afforded the primary alcohol **47** in 40% overall yield.

The cytostatic macrolide apicularen A (**6**)[31,32] provided the 10-membered lactone fragment **48** by ozonolysis of the TBS-protected derivative (Scheme 9). Reaction of **6** with TBSCl–



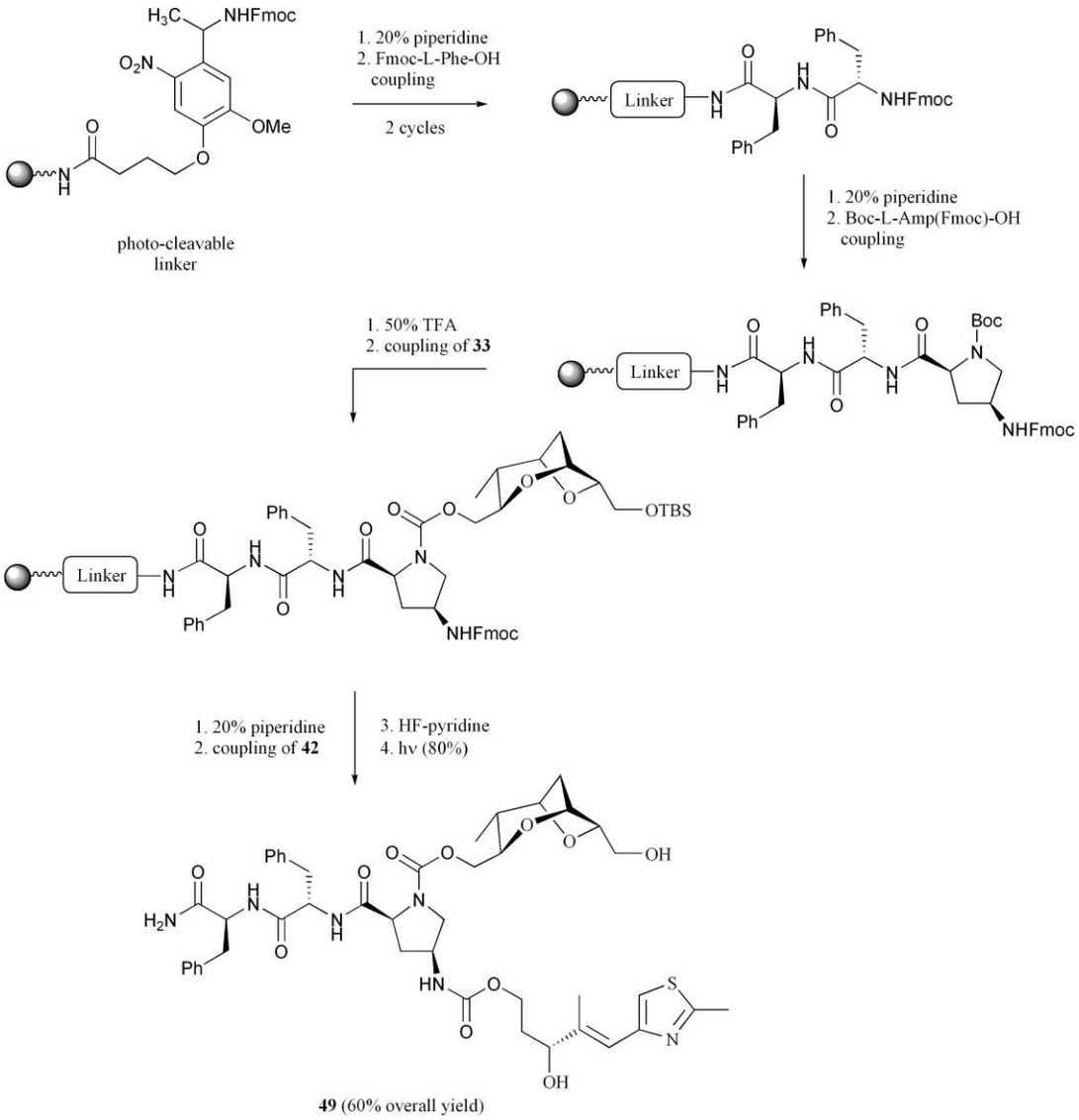
Scheme 8 *Reagents*: a) 1. CH_2N_2, 2. TBSOTf, Et_3N, 3. O_3, 4. $NaBH_4$.



Scheme 9 *Reagents*: a) 1. TBSCl, imidazole, 2. O_3, 3. Me_2S, 4. $NaBH_4$.

imidazole followed by cleavage of the $\Delta^{17,18}$ double bond by ozonolysis (O_3–Me_2S) and subsequent reduction with sodium borohydride afforded lactone **48** in 80% yield.

Thus, selective fragmentation of a series of natural products from myxobacteria and subsequent chemical modifications gave access to twenty-three diverse primary alcohol building blocks. Fragmentation reactions used so far cover the cleavage of double bonds either by ozonolysis or OsO_4-oxidation and subsequent oxidative cleavage with $NaIO_4$, lactone ring opening by either hydrolysis or reductive cleavage, and acid-catalysed epoxide hydrolysis followed by oxidative diol cleavage. The conversion to carboxylic acids was achieved by either oxidation of primary alcohol building blocks or by aldehyde oxidation. The



Scheme 10 SPOT synthesis of a natural product-derived hybrid structure on a photolinker-modified APEG membrane. *Reagents*: (a) amino acid coupling (5 equiv.): HOBt, DIC, NMP, (b) coupling of natural product-derived fragments (7–8 equiv.): *p*-nitrophenyl chloroformate, DMAP, pyridine, NMP (yield: >80%).

application of other fragmentation strategies and the introduction of different functional groups for solid-phase coupling reactions are presently under investigation.

The solid-phase synthesis of natural product-derived hybrid structures is exemplified by selective chemical coupling of sorangicin and epothilone fragments **33** and **42** *via* a single SPOT-synthesis on a 100 nmol scale (Scheme 10). The combination of the natural product building blocks is achieved employing a membrane-linked spacer. To obtain a broad range of molecular structures both the exchange of the natural product building blocks and variation of the connective spacer is intended in combinatorial library synthesis. Here, *cis*-4-amino-L-proline (Amp) is used as the spacer, which is attached *via* two L-phenylalanine (Phe) residues to a photolinker-derivatised membrane. First, the Fmoc-protected aminoethyl photolinker[49] was anchored to the commercially available amino-functionalised polypropylene membrane by activation with hydroxybenzotriazole (HOBt) and *N*,*N*-diisopropylcarbodiimide (DIC) in *N*-methylpyrrolidin-2-one (NMP) followed by capping of unreacted amino functions by acetylation with acetic anhydride. The initial spot loading is determined by the given membrane loading (600 nmol cm^{-2}), the spot size (1.2 µl per spot, ~0.28 cm^2), and the fact that the photolinker was added in a threefold excess. Stepwise elongation by two L-phenylalanine residues and the 4-amino-L-proline spacer was performed by three reaction cycles of Fmoc-deprotection with 20% piperidine in DMF and subsequent amino acid coupling. Rapid and nearly quantitative transformations were achieved by using reactants in large excess. The precise spot loading was determined to be 170 nmol by base-catalysed cleavage of the Fmoc-group of the Phe–Phe–Amp tripeptide and subsequent quantification of the dibenzofulvene–piperidine adduct by UV.[50] The phenylalanine residues were introduced to simplify the analysis of intermediates by RP-HPLC and MALDI-MS providing a UV-label and additional mass. In library synthesis they will be omitted or replaced by other amino acids to increase diversity. The orthogonal Boc and Fmoc protecting groups for the amino-functions at the 4-aminoproline allow the subsequent attachment of different natural product-derived fragments. First, the Boc protecting group of the 4-aminoproline was removed with 50% TFA. The sorangicin-derived fragment **33** was reacted with *p*-nitrophenyl chloroformate and DMAP in a 1 : 1 (v/v) mixture of pyridine and NMP and was subsequently coupled to give a carbamate linkage. After Fmoc-cleavage, the epothilone-derived building block **42** was coupled to the second amino-function using the same coupling procedure. The coupling reactions require a 7- to 8-fold excess of the natural product fragment in order to reach a yield of >80%. Then, all TBS-protecting groups were cleaved by reaction with HF–pyridine and the product finally removed from

the solid-support by exposure to UV light at 365 nm with an average product recovery of 80%. Analysis by reverse-phase HPLC ESI-MS revealed that compound **49** with a molecular mass of 876 was formed as the main product (70%) as determined by peak area integration of the HPLC chromatograms at 254 nm and 211 nm, respectively. Besides compound **49** a by-product (10%) and a number of very minor components, which add up to about 20% were detected. According to the molecular mass of 901 the by-product contains two epothilone fragments linked to the aminoproline spacer and is thus formed due to an incomplete reaction of the sorangicin fragment **33** in the first coupling step. Based on an initial spot loading of 170 nmol and a product recovery of 80% from the solid-support we can calculate that ~100 nmol of compound **49** were formed corresponding to an overall yield of 60%.

In summary, we have prepared a collection of natural product-derived chiral building blocks for the synthesis of combinatorial compound libraries with high structural diversity. The applicability of the primary alcohol fragments in solid-phase synthesis was exemplarily demonstrated with the SPOT-synthesis technique. The building blocks are currently being used for the automated highly parallel 10 nmol-scale synthesis of natural product hybrid structures, which will be tested for biological activity using a miniaturised ultra-high throughput screening system.

Experimental

General methods

Analytical TLC was performed on silica gel Si 60 F_{254} aluminium sheets, 0.2 mm (Merck). Products were visualised by either UV absorption at 254 nm or staining with cerium(IV) sulfate–phosphomolybdic acid in sulfuric acid followed by charring. Silica gel 60 (0.063–0.200 mm) was used for preparative column chromatography and precoated silica gel Si 60 F_{254} plates of 0.25, 0.5, 1.0 or 2.0 mm layer thickness for preparative TLC. Analytical HPLC was carried out on 250 × 4 Nucleosil 100–7 C-18 (Column A) and Nucleosil 100–7 (Column B) columns (Machery-Nagel) with detection by either UV absorption or light scattering. Preparative HPLC was carried out on 16 × 250 columns of either Nucleosil 100–7 C-18, Machery-Nagel (Column A) or Nucleosil 100–7, Knauer (Column B). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded from samples in KBr pellets on a Nicolet 20DXB FT-IR spectrometer. NMR spectra were measured on Bruker AM-300 [300 MHz (^{1}H); 75.5 MHz (^{13}C)] or Bruker WM-400 [(400 MHz (^{1}H); 100.6 MHz (^{13}C)]. *J* values are given in Hz. High-resolution mass spectra (HRMS) were measured on a MAT 95 Finnigran (DCI) or Kratos MS 50 RFTC (FAB) spectrometer from peak matching $M/\Delta M$ = 10000. Elemental analyses were carried out by Mikroanalytisches Laboratorium I. Beetz (Kronach, Germany). HPLC-MS was performed on ET 125/2 Nucleosil 120–5 C-18, Machery-Nagel, Hewlett-Packard 1050 diode array detector, PE Sciex Api-2000™ LC/MS/MS. THF was distilled from sodium–benzophenone and CH_2Cl_2 from CaH_2 prior to use. Ozonolysis was performed with a Sander Labor-Ozonisator. Polymer-supported borohydride on Amberlite® IRA-400 (~2.5 mmol BH_4^- g^{-1} resin) and HF–pyridine complex were supplied by Sigma-Aldrich Chemie GmbH (Taufkirchen, Germany). The primary alkyl amino-derivatised polypropylene APEG-membrane (loading 600 nmol cm^{-2}) was obtained from AIMS Scientific Products GmbH (Braunschweig, Germany). N^{α}-Fmoc-L-phenylalanine (Fmoc–Phe–OH) and the 4-{4-[1-(Fmoc-amino)ethyl]-2-methoxy-5-nitrophenoxy}butanoic acid photolinker were purchased from Calbiochem-Novabiochem GmbH (Bad Soden, Germany). Protected *cis*-4-amino-L-proline [Boc-L-Amp(Fmoc)-OH] was obtained from Neosystem (Strasbourg, France). Photolytic cleavage was performed using a Vilber Lourmat TFP-35.L transilluminator at 365 nm.

(2*R*,3*S*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-2,3-dimethoxy-8-phenyloctan-1-ol 8 and (2*R*,3*R*,4*S*,5*S*,6*S*)-2-[(1*R*)-2-(*tert*-butyldimethylsilyloxy)-1-methylethyl]-4-(*tert*-butyldimethylsilyloxy)-6-[(1*S*)-2-hydroxy-1-methylethyl]-3-methoxy-5-methyltetrahydro-2*H*-pyran-2-ol 9 and

Soraphen A (**1**) (500 mg, 0.97 mmol) was added at 0 °C to a solution of $LiAlH_4$ (220 mg, 5.80 mmol) in anhydrous THF (10 ml). The reaction mixture was stirred under a N_2 atmosphere for 6 h at room temperature, then treated at 0 °C with 1 M HCl and extracted three times with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate, then with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was dissolved in anhydrous DMF (5 ml) containing *tert*-butyldimethylsilyl chloride (1.38 g, 9.16 mmol) and imidazole (0.63 g, 9.25 mmol). After stirring for 48 h at room temperature, the reaction mixture was diluted with water and extracted three times with diethyl ether. The combined organic layers were washed with H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 14 : 1) gave 1,5,17-tris(*tert*-butyldimethylsilyloxy)-1,17-secosoraphen **7**[36] (492 mg, 59%) as a colourless oil; R_f 0.65 (petroleum ether–ethyl acetate 5 : 1). Compound **7** (241 mg, 0.277 mmol) was dissolved in CH_2Cl_2 (16 ml) and ozone was introduced at −70 °C for 5 min. After addition of MeOH (16 ml), the reaction mixture was treated at 0 °C with $NaBH_4$ (35 mg, 0.93 mmol) and stirred for 1.5 h at room temperature. The reaction mixture was then treated with a 1 M aqueous solution of NaH_2PO_4–K_2HPO_4 (pH 7) and extracted three times with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 5 : 1, then 2 : 1) gave **8** (73.0 mg, 66%) and **9** (78.2 mg, 57%) as colourless oils.

8. R_f (petroleum ether–ethyl acetate 5 : 1) 0.11; $[\alpha]_D^{22}$ −24.5 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3465m, 2930s, 2857s, 1472m, 1257m, 1111s, 1066m, 837s, 775m, 700m; δ_H (400 MHz; $CDCl_3$) −0.16, 0.01 [6 H, 2 × s, $Si(CH_3)_2$], 0.87 [9 H, s, $C(CH_3)_3$], 3.15 (1 H, dt, *J* 4.6 and 4.6, 2-H), 3.29 (1 H, m, 3-H), 3.39, 3.41 (6 H, 2 × s, 2-OMe, 3-OMe), 3.70 (2 H, m, 1-H_2), 4.63 (1 H, dd, *J* 5.0 and 7.1, 8-H), 7.18–7.31 (5 H, m, C8-Phenyl); δ_C (100.6 MHz; $CDCl_3$) −4.9, −4.6 [$Si(CH_3)_2$], 18.2 [$C(CH_3)_3$], 25.9 [$C(CH_3)_3$], 25.4, 25.7, 30.8, 40.9 (C-4, C-5, C-6, C-7), 57.8, 58.6 (2-Me, 3-OMe), 61.0 (C-1), 75.0 (C-8), 81.6 (C-3), 82.6 (C-2), 125.9, 126.8, 128.0, 145.8 (8-Phenyl); *m/z* (FAB) 419 (M + Na^+, 100%), 265 [(M – TBSO) + Na^+, 65]; HRMS found (M + Na^+) 419.2594; $C_{22}H_{40}O_4Si$ requires 419.2582.

9. R_f 0.47 (petroleum ether–ethyl acetate 5 : 1); $[\alpha]_D^{22}$ −3.5 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3449m, 2954s, 2930s, 2886m, 2857m, 1472m, 1255m, 1111m, 1030s, 838s, 778m; δ_H (300 MHz; $CDCl_3$) 0.03, 0.04, 0.11, 0.13 [12 H, 4 × s, 2 × $Si(CH_3)_2$], 0.79 (3 H, d, *J* 6.8, $CHCH_3$), 0.87, 0.90 [18 H, 2 × s, 2 × $C(CH_3)_3$], 0.97 (3 H, d, *J* 6.8, $CHCH_3$), 1.03 (3 H, d, *J* 7.1, 5-Me), 1.70 (1 H, m, 5-H), 1.93 (1 H, m, $CHCH_3$), 2.10 (1 H, m, $CHCH_3$), 2.97 (1 H, dd, *J* 1.1 and 3.0, 3-H), 3.37 (3 H, s, 3-OMe), 3.51 (1 H, dd, *J* 9.4 and 9.7, CH_{2a}), 3.63 (2 H, m, CH_2), 3.91 (1 H, dd, *J* 3.4 and 9.7, CH_{2b}), 3.99 (1 H, dd, *J* 2.6 and 10.5, 6-H), 4.08 (1 H, dd, *J* 2.6 and 2.6, 4-H); δ_C (100.6 MHz; $CDCl_3$) −5.4, −5.3, −5.1, −5.0 [2 × $Si(CH_3)_2$], 10.8 (5-Me), 11.8, 13.1 (2 × $CHCH_3$), 18.3, 18.0 [2 × $C(CH_3)_3$], 25.7, 26.0 [2 × $C(CH_3)_3$], 35.4 (C-5), 36.1, 41.3 (2 × $CHCH_3$), 57.5 (3-OMe), 63.5, 67.7 (2 × CH_2), 70.5, 70.7 (C-4, C-6), 77.9 (C-3), 100.5 (C-2); *m/z* (FAB) 529 (M + Na^+, 40%), 489 [(M – H_2O) + H^+, 100]; HRMS found (M + Na^+) 529.3357; $C_{25}H_{54}O_6Si_2$ requires 529.3349.

Triethylammonium (2*R*,3*S*,8*S*)-8-(*tert*-butyldimethylsilyloxy)-2,3-dimethoxy-8-phenyloctanoate 10

Compound **8** (5.0 mg, 12.6 μmol) was added to a solution of pyridinium dichromate (PDC) (42 mg, 0.112 mmol) in anhydrous DMF (250 μl). The reaction mixture was stirred for 40 h at room temperature, then diluted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (CH_2Cl_2–MeOH 90 : 10, 1% triethylamine) gave **10** (3.9 mg, 61%); R_f 0.34 (CH_2Cl_2–MeOH 90 : 10); δ_H (300 MHz; CD_3OD) −0.12, 0.08 [6 H, 2 × s, $Si(CH_3)_2$], 0.92 [9 H, s, $C(CH_3)_3$], 1.35 [9 H, t, $N(CH_2CH_3)_3$], 3.24 [6 H, q, $N(CH_2CH_3)_3$], 3.41, 3.42 (6 H, 2 × s, 2-OMe, 3-OMe), 3.48 (1 H, m, 3-H), 3.95 (1 H, d, *J* 3.4, 2-H), 4.72 (1 H, dd, *J* 5.3 and 7.6, 8-H), 7.20–7.34 (5 H, m, C8-Phenyl); δ_C (100.6 MHz; $CDCl_3$) −4.7, −4.4 [$Si(CH_3)_2$], 9.2 [$N(CH_2CH_3)_3$], 19.0 [$C(CH_3)_3$], 26.3 [$C(CH_3)_3$], 47.9 [$N(CH_2CH_3)_3$], 26.6, 26.7, 31.2, 41.9 (C-4, C-5, C-6, C-7), 58.1, 58.9 (2-OMe, 3-OMe), 76.4 (C-8), 83.0 (C-2), 83.6 (C-3), 127.0, 128.0, 129.1, 147.0 (8-Phenyl), 175.1 (C-1); *m*/*z* (FAB) 409 ($M - H^-$, 15%), 305 (40), 153 (100); HRMS found ($M - H^-$) 409.2373; $C_{22}H_{38}O_5Si$ requires 409.2410.

1,17-Bis(*tert*-butyldimethylsilyloxy)-5-methoxy-1,17-seco-soraphen 11

Soraphen A (**1**) (395 mg, 0.89 mmol) was dissolved in anhydrous hexamethylphosphoramide (HMPA) (5 ml) under a N_2 atmosphere and subsequently treated with iodomethane (1.0 ml, 16 mmol) and sodium hydride (80%, 200 mg, 6.7 mmol). The reaction mixture was stirred for 25 min at 55–60 °C, then cooled to 5 °C, treated with a 1 M aqueous solution of NaH_2PO_4–K_2HPO_4 (pH 7), and extracted with diethyl ether. The organic phase was washed with NaH_2PO_4–K_2HPO_4 (pH 7), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 3 : 1) gave 3,5-di-*O*-methylsoraphen (403 mg, 83%) as a colourless oil; R_f 0.37 (petroleum ether–ethyl acetate 2 : 1). 3,5-Di-*O*-methylsoraphen (185 mg, 0.33 mmol) was dissolved in THF (12.2 ml) and 1 M HCl (6.1 ml), and stirred for 3 days at room temperature. THF was removed *in vacuo*, the reaction mixture was treated with a 5% aqueous solution of sodium hydrogen carbonate, and was extracted three times with ethyl acetate. The combined organic layers were washed with a 1 M aqueous solution of NaH_2PO_4–K_2HPO_4 (pH 7), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 3 : 1) gave 5-*O*-methylsoraphen (180 mg, 98%) as a colourless oil; R_f 0.33 (petroleum ether–ethyl acetate 2 : 1).

A solution of 5-*O*-methyl-soraphen (245 mg, 0.46 mmol) in anhydrous THF (2 ml) was added to a solution of $LiAlH_4$ (110 mg, 2.90 mmol) in anhydrous THF (2 ml). The reaction mixture was stirred under a N_2 atmosphere for 4.5 h at room temperature, was then treated at 0 °C with 1 M HCl, and was extracted three times with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate, then with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was dissolved under N_2 atmosphere in anhydrous DMF (2.8 ml) containing *tert*-butyldimethylsilyl chloride (685 mg, 4.54 mmol) and imidazole (312 mg, 4.58 mmol). After stirring for 72 h at room temperature, the reaction mixture was diluted with water and extracted three times with diethyl ether. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 10 : 1) gave **11** (201 mg, 58%) as a colourless oil; R_f 0.46 (petroleum ether–ethyl acetate 6 : 1); ν_{max}(KBr)/cm^{-1} 3479w, 2930s, 2857s, 1472m, 1257m, 1090s, 837s, 775m; δ_H (400 MHz; $CDCl_3$) 0.86, 0.87 [18 H, 2 × s, 2 × $C(CH_3)_3$], 0.95 (3 H, d, *J* 6.6, 8-Me), 1.00, 1.01 (6 H, 2 × d, 2-Me, 6-Me), 1.54–1.75 (2 H, m, 16-H_2), 1.92 (1 H, m, 6-H), 2.06 (1 H, m, 2-H), 2.43 (1 H, m, 8-H), 3.08–3.15 (2 H, m, 4-H, 12-H), 3.25, 3.37, 3.41 (12 H, 3 × s, 4-OMe, 5-OMe, 11-OMe, 12-OMe, 3.45 (1 H, m, 5-H), 3.54 (1 H, dd, *J* 3.6 and 8.6, 11-H), 3.69 (1 H, dd, *J* 2.6 and 9.7, 1-H_a), 3.93 (1 H, dd, *J* 1.5 and 8.7, 7-H), 4.07 (1 H, dd, *J* 5.0 and 9.7, 1-H_b), 4.60 (1 H, dd, *J* 5.1 and 7.6, 17-H), 7.15–7.30 (5 H, m, C17-Phenyl); δ_C (100.6 MHz; $CDCl_3$) −5.3, −5.2, −4.9, −4.6 [2 × $Si(CH_3)_2$], 11.1, 11.9 (2-Me, 8-Me), 16.7 (6-Me), 18.2, 18.3 [2 × $C(CH_3)_3$], 25.7, 25.8 (C-14, C-15), 25.9, 26.0 [2 × $C(CH_3)_3$], 30.6 (C-13), 31.1 (C-6), 37.3 (C-8), 39.4 (C-2), 41.0 (C-16), 56.4, 57.4, 57.7, 58.5 (4-OMe, 5-OMe, 11-OMe, 12-OMe), 64.8 (C-1), 70.0 (C-7), 75.1 (C-17), 76.4 (C-4), 79.6 (C-5), 84.0 (C-12), 84.6 (C-11), 100.3 (C-3), 125.9, 126.7, 128.0, 146.0 (C-10, 17-Phenyl), 140.0 (C-9); *m*/*z* (FAB) 789 ($M + Na^+$, 15%), 157 (70), 73 (100); HRMS found ($M + Na^+$) 789.5176; $C_{42}H_{78}O_8Si_2$ requires 789.5133.

(2*R*,3*S*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-2,3-dimethoxy-8-phenyloctan-1-ol 8 and (2*R*,3*R*,4*S*,5*S*,6*S*)-2-[(1*R*)-2-(*tert*-butyldimethylsilyloxy)-1-methylethyl]-3,4-dimethoxy-6-[(1*S*)-2-hydroxy-1-methylethyl]-5-methyltetrahydro-2*H*-pyran-2-ol 12

Compound **11** (200 mg, 0.262 mmol) was dissolved in CH_2Cl_2 (15 ml) and ozone was introduced at −75 °C for 5 min. After addition of MeOH (13 ml), the reaction mixture was treated at 0 °C with $NaBH_4$ (33 mg, 0.87 mmol) and stirred for 1.5 h at room temperature. The reaction mixture was then treated with a 1 M aqueous solution of NaH_2PO_4–K_2HPO_4 (pH 7) and extracted three times with ethyl acetate. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane–ethyl acetate 3 : 1) gave **8** (75.5 mg, 73%) and **12** (19.4 mg, 18%) as colourless oils.

12. R_f 0.19 (hexane–ethyl acetate 3 : 1); $[\alpha]_D^{22}$ −24.9 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 0.06, 0.07 [6 H, 2 × s, $Si(CH_3)_2$], 0.83 (3 H, d, *J* 6.8, $CHCH_3$), 0.88 [9 H, s, $C(CH_3)_3$], 1.01 (3 H, d, *J* 7.4, $CHCH_3$), 1.04 (3 H, d, *J* 7.1, 5-Me), 2.10 (1 H, m, $CHCH_3$), 3.13 (1 H, dd, *J* 1.1 and 2.3, 3-H), 3.38, 3.42 (6 H, 2 × s, 3-OMe, 4-OMe); *m*/*z* (FAB) 429 ($M + Na^+$, 100%), 389 [($M - H_2O$) + H^+, 40]; HRMS found ($M + Na^+$) 429.2695; $C_{20}H_{42}O_6Si$ requires 429.2648.

Preparation of γ-lactone 13

Soraphen A (**1**) (1.0 g, 1.92 mmol) was dissolved in MeOH (44 ml) and treated with 95% H_2SO_4 (1.3 ml). After stirring for 24 h at room temperature, the reaction mixture was concentrated *in vacuo*, then treated with a 5% aqueous solution of sodium hydrogen carbonate and extracted three times with ethyl acetate. The combined organic layers were washed with a 1 M aqueous solution of NaH_2PO_4–K_2HPO_4 (pH 7), then with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 5 : 2, then 1 : 1) gave **13**[35] (858 mg, 81%) as a colourless oil; R_f 0.72 (CH_2Cl_2–acetone 90 : 10); $[\alpha]_D^{24}$ −69.4 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2980s, 2945s, 2840m, 2820m, 1795s, 1465s, 1460s, 1380m, 1360m, 1330m, 1270m, 1215m, 1195m, 1100m, 1030m, 1005m, 975m, 920m, 760m, 720m, 705s; δ_H (300 MHz; $CDCl_3$) 0.95 (6 H, d, *J* 7.0, 6-Me, 8-Me), 1.31 (3 H, *J* 7.2, 2-Me), 1.20–1.45 (6 H, m, 13-H_2, 14-H_2, 15-H_2), 1.62 (1 H, m, 6-H_a), 1.77 (1 H, m, 6-H_b), 1.95–2.06 (2 H, m, 5-H_a, 6-H), 2.27 (1 H, m, 5-H_b), 2.38 (1 H, m, 8-H), 3.02 (1 H, q, *J* 7.2, 2-H), 3.12 (1 H, m, 12-H), 3.18 (17-OMe), 3.23 (11-OMe), 3.36 (12-OMe), 3.39 (4-OMe), 3.40 (3-OMe), 3.49 (1 H, m, 11-H), 5.43 (1 H, dd, *J* 8.2 and 15.6, 10-H), 5.68 (1 H, dd, *J* 7.7 and 15.6, 9-H), 7.24–7.35 (5 H, m, 8-Phenyl); δ_C (75.5 MHz; $CDCl_3$) 9.2 (2-Me), 12.3 (8-Me), 16.4 (6-Me), 25.8, 26.0 (C-14, C-15), 27.9 (C-6), 30.8 (C-13), 32.3 (C-5), 38.2 (C-8, C-16), 42.2 (C-2), 50.0 (4-OMe), 51.4 (3-OMe), 56.5 (11-OMe), 56.6 (17-OMe), 58.7 (12-OMe), 74.8 (C-7), 83.7 (C-12), 84.1 (C-17), 84.8 (C-11), 101.2 (C-3), 102.2 (C-4), 127.4 (C-10), 138.6 (C-9),

126.7, 127.5, 128.4, 142.5 (8-Phenyl), 175.8 (C-1); *m/z* (DCI) 566 (M + NH_4^+, 100%), HRMS found (M + NH_4^+) 566.3620; $C_{14}H_{24}O_6$ requires 566.3693 (Found: C, 67.80; H, 8.8. Calc. for $C_{31}H_{48}O_8$: C, 67.84; H 8.8%).

(2*R*,3*S*,8*R*)-2,3,8-Trimethoxy-8-phenyloctan-1-ol 14 and bicyclic lactone 15

Compound **13** (86.4 mg, 0.157 mmol) was dissolved in acetone (1.6 ml) and H_2O (170 µl). 4-Methylmorpholine *N*-oxide (NMO) (85 mg, 4.0 equiv.) was added, followed by OsO_4 (300 µl, 2.5 wt% solution in *tert*-butanol, 0.15 equiv.). The reaction mixture was stirred for 24 h at room temperature, then the solvent was removed with a flow of nitrogen, the residue was partitioned between ethyl acetate and H_2O, and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in THF (1.7 ml) and treated with a solution of $NaIO_4$ (130 mg, 0.60 mmol) in H_2O (800 µl). After stirring for 40 min at room temperature, the organic solvent was removed *in vacuo*, brine was added, and the reaction mixture was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (3 ml) and MeOH (6 ml) and treated at 0 °C with $NaBH_4$ (16 mg, 0.42 mmol). After stirring for 2 h at room temperature, the reaction mixture was treated with acetic acid and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and a 1 M aqueous solution of NaH_2PO_4–K_2HPO_4 (pH 7), and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 1 : 1, then 1 : 2) gave **14** (33.7 mg, 72%) and **15** (33.6 mg, 74%) as colourless oils.

14. R_f 0.28 (petroleum ether–ethyl acetate 1 : 1); $[\alpha]_D^{22}$ +35.1 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3449m, 2936s, 2859m, 2823m, 1453m, 1108, 703m; δ_H (400 MHz; $CDCl_3$) 1.20–1.50 (6 H, m, 4-H_2, 5-H_2, 6-H_2), 1.64 (1 H, m, 7-H_a), 1.81 (1 H, m, 7-H_b), 3.14 (1 H, dt, *J* 4.6 and 4.6, 2-H), 3.28 (1 H, m, 3-H), 3.19 (3 H, s, 8-OMe), 3.38 (3 H, s, 3-OMe), 3.41 (3 H, s, 2-OMe), 3.70 (2 H, m, 1-H_2), 4.07 (1 H, t, *J* 6.1, 8-H), 7.24–7.35 (5 H, m, 8-Phenyl); δ_C (100.6 MHz; $CDCl_3$) 25.4, 26.0, 30.8, 38.1 (C-4, C-5, C-6, C-7), 56.7 (8-OMe), 57.8, 58.6 (2-OMe, 3-OMe), 61.0 (C-1), 81.6 (C-3), 82.6 (C-2), 84.1 (C-8), 125.9, 126.8, 128.0, 145.8 (8-Phenyl); *m/z* (EI) 296 ([M$^{\bullet}$]$^+$, 40%), 237 (100); HRMS found [M$^{\bullet}$]$^+$ 296.1995; $C_{17}H_{28}O_4$ requires 296.1988 (Found: C, 68.82; H, 9.5. Calc. for $C_{17}H_{28}O_4$: C, 68.87; H 9.5%).

15. R_f 0.16 (petroleum ether–ethyl acetate 1 : 1); $[\alpha]_D^{22}$ −111.9 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3533m, 2966m, 2946m, 1793s, 1460m, 1271m, 1197m, 1117s, 1028s, 971s, 951m; δ_H (400 MHz; $CDCl_3$) 0.87 (3 H, d, *J* 7.1, 8-Me), 0.95 (3 H, d, *J* 7.1, 6-Me), 1.35 (3 H, d, *J* 7.1, 2-Me), 1.86 (1 H, m, 8-H), 1.98–2.05 (2 H, m, 5-H_a, 6-H), 2.28 (1 H, m, 5-H_b), 3.07 (1 H, q, *J* 7.1, 2-H), 3.39 (3 H, s, 4-OMe), 3.48 (3 H, s, 3-OMe), 3.65–3.77 (3 H, m, 7-H, 9-H_2); δ_C (100.6 MHz; $CDCl_3$) 9.3 (2-Me), 12.3 (8-Me), 12.8 (6-Me), 27.8 (C-6), 32.0 (C-5), 36.5 (C-8), 41.9 (C-2), 50.0 (4-OMe), 51.5 (3-OMe), 66.6 (C-9), 74.6 (C-7), 101.5 (C-3), 102.2 (C-4), 175.5 (C-1); *m/z* (DCI) 306 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 306.1967; $C_{14}H_{24}O_6$ requires 306.1917 (Found: C, 58.36; H, 8.4. Calc. for $C_{14}H_{24}O_6$: C, 58.30; H 8.4%).

Triethylammonium (2*R*,3*S*,8*R*)-2,3,8-trimethoxy-8-phenyloctanoate 16

Compound **14** (45.1 mg, 0.15 mmol) was dissolved in acetone (470 µl) and treated at 0 °C with a 5% aqueous solution of sodium hydrogen carbonate (470 µl), containing KBr (1.9 mg, 0.015 mmol). 2,2,6,6-Tetramethylpiperidine-1-oxyl (36 mg, 0.23 mmol) was added, followed by the dropwise addition of sodium hypochlorite (aqueous 4–6%, 400 µl) over 20 min. Then 2-methylbut-2-ene (900 µl) and a solution of sodium chlorite (81 mg) and NaH_2PO_4 (61 mg) in H_2O (1.2 ml) were added. After stirring for 1.5 h at 0 °C, the reaction was quenched by the addition of a 10% aqueous solution of Na_2SO_3. Saturated aqueous NH_4Cl was added and the resulting mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (CH_2Cl_2–MeOH 95 : 5, 1% triethylamine) gave **16** (37.2 mg, 60%); R_f 0.24 (CH_2Cl_2–MeOH 90 : 10); ν_{max}(KBr)/cm^{-1} 2936s, 2860m, 2825m, 2677m, 1747s, 1454m, 1190m, 1113s, 761m, 702s; δ_H (300 MHz; CD_3OD) 1.35 (9 H, t, NCH_2CH_3), 1.81 (1 H, m, 7-H_a), 3.21 (3 H, s, 8-OMe), 3.25 (6 H, q, NCH_2CH_3), 3.42, 3.41 (6 H, 2 × s, 2-OMe, 3-OMe), 3.47 (1 H, m, 3-H), 3.94 (1 H, d, *J* 3.8, 2-H), 4.16 (1 H, t, *J* 7.1, 8-H); δ_C (100.6 MHz; CD_3OD) 9.2 (NCH_2CH_3), 26.6, 26.7 (C-5, C-6), 31.1 (C-4), 38.9 (C-7), 47.9 (NCH_2CH_3), 56.8 (8-OMe), 58.1, 58.9 (2-OMe, 3-OMe), 82.9 (C-2), 83.5 (C-3), 85.3 (C-8), 127.8, 128.7, 129.4 (8-Phenyl), 175.0 (C-1); *m/z* (DCI) 328 (M + NH_4^+, 100%), 127 (60), 110 (100); HRMS found (M + NH_4^+) 328.2131; $C_{17}H_{26}O_5$ requires 328.2124.

Oxidation of 15 to carboxylic acid 17

Compound **15** (24.1 mg, 0.084 mmol) was dissolved in anhydrous DMF (200 µl) and treated with a solution of PDC (285 mg, 0.76 mmol) in anhydrous DMF (1.5 ml). After stirring for 27 h at room temperature, Florisil (activated magnesium silicate) was added, the reaction mixture was diluted with ethyl acetate, filtered over silica gel, and concentrated *in vacuo*. Purification of the residue by column chromatography (CH_2Cl_2–MeOH 95 : 5, 2% triethylamine) gave **17** (19.1 mg, 56%); R_f 0.39 (CH_2Cl_2–MeOH 90 : 10); ν_{max}(KBr)/cm^{-1} 3429s, 2976s, 2940s, 2677s, 1791s, 1730m, 1463m, 1196m, 1142m, 1120s, 1027m, 973m, 954m; δ_H (300 MHz; CD_3OD) 0.96 (3 H, d, *J* 7.5, 6-Me), 1.11 (3 H, d, *J* 6.8, 8-Me), 1.32–1.38 (12 H, m, 2-Me, NCH_2CH_3), 2.05–2.15 (2 H, m, 5-H_a, 6-H), 2.36 (1 H, m, 5-H_b), 2.53 (1 H, m, 8-H), 3.06 (1 H, q, *J* 7.1, 2-H), 3.24 (6 H, q, NCH_2CH_3), 3.39, 3.46 (6 H, 2 × s, 3-OMe, 4-OMe), 4.06 (1 H, dd, *J* 1.9 and 10.6, 7-H); δ_C (100.6 MHz; CD_3OD) 9.25 (NCH_2CH_3), 9.4, 12.6, 13.9 (2-Me, 6-Me, 8-Me), 28.2 (C-6), 33.0 (C-5), 43.2 (C-2), 44.1 (C-8), 47.9 (NCH_2CH_3), 50.2, 52.2 (3-OMe, 4-OMe), 74.5 (C-7), 102.4, 103.7 (C-3, C-4), 177.7, 180.8 (C-1, C-9); *m/z* (DCI) 320 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 320.1757; $C_{14}H_{22}O_7$ requires 320.1710.

(1*RS*)-1-[4-(Hydroxymethyl)-2,4′-bi-1,3-thiazol-2′-yl]ethanol 18 and methyl (2*E*,4*R*,5*R*)-6-hydroxy-3,5-dimethoxy-4-methylhex-2-enoate 19

Myxothiazol Z (**2b**)[42] (576 mg, 1.14 mmol) was dissolved in acetone (11.3 ml) and H_2O (1.2 ml). 4-Methylmorpholine *N*-oxide (NMO) (619 mg, 0.03 equiv.) was added, followed by OsO_4 (435 µl, 2.5 wt% solution in *tert*-butanol). The reaction mixture was stirred for 24 h at room temperature, then the solvent was removed with a flow of nitrogen, the residue was partitioned between ethyl acetate and brine, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in THF (15.3 ml) and treated with a solution of $NaIO_4$ (1.10 g, 5.1 mmol) in H_2O (7.6 ml). After stirring for 40 min at room temperature, the organic solvent was removed *in vacuo*, brine was added, and the reaction mixture was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 ml) and MeOH (40 ml), and treated at 0 °C with $NaBH_4$ (290 mg, 7.67 mmol). After stirring for 2 h at room temperature, the reaction mixture was treated with acetic acid and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and a 1 M

aqueous solution of NaH_2PO_4–K_2HPO_4 (pH 7), and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by column chromatography (CH_2Cl_2–MeOH 95 : 5, 93 : 7, then 90 : 10) gave **18** (215 mg, 78%) and **19** (167 mg, 67%) as colourless oils.

18. R_f 0.12 (CH_2Cl_2–MeOH 95 : 5); ν_{max}(KBr)/cm^{-1} 3309s, 3113s, 2982m, 2930m, 1539m, 1435m, 1362m, 1307m, 1176s, 1139s, 1027s, 1018s, 964m, 802m, 773m; δ_H (400 MHz; CD_3OD) 1.64 (3 H, d, *J* 6.6, CHCH_3), 4.77 (2 H, s, CH_2O), 5.12 (1 H, q, *J* 6.6, C*H*CH_3), 7.44, 8.06 (2 H, 2 × s, 2 × SCH); δ_C (100.6 MHz; CD_3OD) 26.7 (CH*C*H_3), 63.6 (CH_2O), 71.2 (*C*HCH_3), 118.9, 119.5 (2 × SCH), 152.3, 161.5, 167.1, 182.8 (4 × C); *m*/*z* (DCI) 260 (M + NH_4^+, 100%), 243 (M + H^+, 100); HRMS found (M + NH_4^+) 260.0532; $C_9H_{10}N_2O_2S_2$ requires 260.0527.

19. R_f 0.35 (CH_2Cl_2–MeOH 95 : 5); $[\alpha]_D^{22}$ +83.8 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3445m, 2934m, 1711s, 1623s, 1382m, 1266m, 1194m, 1151s, 1088s, 1061m, 1040m; δ_H (300 MHz; $CDCl_3$) 1.17 (3 H, d, *J* 6.8, 4-Me), 3.27 (1 H, m, 5-H), 3.39–3.50 (4 H, m, 6-H_a, 5-OMe), 3.57–3.75 (7 H, m, 6-H_b, 1-OMe, 3-OMe), 4.09 (1 H, dq, *J* 7.0 and 7.0, 4-H), 5.03 (1 H, s, 2-H); δ_C (100.6 MHz; $CDCl_3$) 14.5 (4-Me), 36.0 (C-4), 51.3 (1-OMe), 55.6, 58.1 (3-OMe, 5-OMe), 61.4 (C-6), 83.6 (C-5), 91.5 (C-2), 168.7 (C-1), 176.5 (C-3); *m*/*z* (DCI) 236 (M + NH_4^+, 100%), 204 (100); HRMS found (M + NH_4^+) 236.1549; $C_{10}H_{18}O_5$ requires 236.1498.

2′-[(1*RS*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(*tert*-butyldimethylsilyloxymethyl)-2,4′-bi-1,3-thiazole 20

Compound **18** (37.6 mg, 0.155 mmol) was dissolved in anhydrous DMF (1 ml) containing *tert*-butyldimethylsilyl chloride (150 mg, 1.0 mmol) and imidazole (68 mg, 1.0 mmol). After stirring under a N_2 atmosphere for 48 h at room temperature, the reaction mixture was diluted with water and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by preparative TLC (petroleum ether–ethyl acetate 10 : 1) gave **20** (62.3 mg, 85%) as a colourless oil; R_f 0.54 (petroleum ether–ethyl acetate 10 : 1); ν_{max}(KBr)/cm^{-1} 2955s, 2929s, 2885m, 2857s, 1472m, 1462m, 1258m, 1178m, 1102s, 939m, 836s, 813m, 778s; δ_H (400 MHz; $CDCl_3$) 0.11, 0.12, 0.13, 0.14 [12 H, 4 × s, 2 × $Si(CH_3)_2$], 0.96, 0.96 [18 H, 2 × s, 2 × $C(CH_3)_3$], 1.60 (3 H, d, *J* 6.6, CHCH_3), 4.90 (2 H, s, CH_2O), 5.12 (1 H, q, *J* 6.0, C*H*CH_3), 7.19, 7.80 (2 H, 2 × s, 2 × SCH); δ_C (100.6 MHz; $CDCl_3$) −5.3, −5.0, −4.6 [2 × $Si(CH_3)_2$], 18.1, 18.4 [2 × *C*$(CH_3)_3$], 25.4 (CH*C*H_3), 25.8, 26.0 [2 × C(*C*$H_3)_3$], 62.4 (CH_2O), 69.5 (*C*HCH_3), 113.9, 115.3 (2 × SCH), 149.4, 158.3, 162.9 178.9 (4 × C); *m*/*z* (DCI) 471 (M + H^+, 100%); HRMS found (M + H^+) 471.1990; $C_{21}H_{38}N_2O_2S_2Si_2$ requires 471.1992.

{2′-[(1*RS*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2,4′-bi-1,3-thiazol-4-yl}methanol 21

Compound **20** (60.6 mg, 0.129 mmol) was dissolved in CH_2Cl_2 (1 ml) and MeOH (0.5 ml). A solution of camphorsulfonic acid (6.0 mg, 0.025 mmol) in MeOH (0.5 ml) was added at 0 °C and the reaction mixture was stirred for 3 h at room temperature. After neutralization with triethylamine, the solvent was evaporated and the residue was purified by preparative TLC (CH_2Cl_2–MeOH 90 : 10) to give **21** (38.2 mg, 83%) as a colourless oil; R_f 0.50 (CH_2Cl_2–MeOH 95 : 5); ν_{max}(KBr)/cm^{-1} 3320m, 3111m, 2957s, 2856m, 1471m, 1431m, 1334m, 1257m, 1182s, 1110s, 1057m, 1023m, 943s, 835s, 773s, 814m, 678m; δ_H (300 MHz; $CDCl_3$) 0.11, 0.14 [6 H, 2 × s, $Si(CH_3)_2$], 0.96 [9 H, s, $C(CH_3)_3$], 1.60 (3 H, d, *J* 6.4, CHCH_3), 4.81 (2 H, s, CH_2O), 5.17 (1 H, q, *J* 6.2, C*H*CH_3), 7.19, 7.86 (2 H, 2 × s, 2 × SCH); δ_C (100.6 MHz; $CDCl_3$) −5.0, −4.6 [$Si(CH_3)_2$], 18.1 [*C*$(CH_3)_3$], 25.1 (CH*C*H_3), 25.4 [C(*C*$H_3)_3$], 61.1 (CH_2O), 69.5 (*C*HCH_3), 115.1, 115.9 (2 × SCH), 149.0, 157.2, 163.6, 179.1 (4 × C); *m*/*z* (DCI) 357 (M + H^+, 100%); HRMS found (M + H^+) 357.1103; $C_{15}H_{24}N_2O_2S_2Si$ requires 357.1127.

2′-[(1*RS*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2,4′bi-1,3-thiazole-4-carboxylic acid 22

Compound **21** (23.8 mg, 0.067 mmol) was dissolved in acetone (400 µl) and treated at 0 °C with a 5% aqueous solution of sodium hydrogen carbonate (200 µl), containing KBr (0.8 mg). 2,2,6,6-Tetramethylpiperidine-1-oxyl (16 mg, 0.115 mmol) was added, followed by the dropwise addition of sodium hypochlorite (aqueous 4–6%, 300 µl) over 15 min. After stirring for 40 min at room temperature, a second portion of sodium hypochlorite (aqueous 4–6%, 300 µl) was added dropwise over 15 min at 0 °C and the reaction mixture was stirred for 2 h at room temperature. Saturated aqueous NH_4Cl was added and the resulting mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by preparative TLC (CH_2Cl_2–MeOH 75 : 25) gave **22** (20.2 mg, 51%) as a colourless oil; *m*/*z* (DCI) 388 (M + NH_4^+, 30%), 127 (30), 110 (100); HRMS found (M + NH_4^+) 388.1185; $C_{15}H_{22}N_2O_3S_2Si$ requires 388.1211.

Methyl (2*E*,4*R*,5*R*)-6-(*tert*-butyldimethylsilyloxy)-3,5-dimethoxy-4-methylhex-2-enoate 23

Compound **19** (72.4 mg, 0.332 mmol) was treated with *tert*-butyldimethylsilyl chloride and imidazole as described in the synthesis of **20**. The resulting product was purified by column chromatography (cyclohexane–diethyl ether 6 : 1) to yield **23** (90.0 mg, 82%) as a colourless oil; R_f 0.34 (cyclohexane–diethyl ether 5 : 1); $[\alpha]_D^{22}$ +56.5 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2954s, 2929s, 2857m, 1716s, 1624s, 1472m, 1382m, 1257m, 1141s, 1100m, 837s, 778m; δ_H (300 MHz; $CDCl_3$) 0.03 [6 H, s, $Si(CH_3)_2$], 0.88 [9 H, s, $C(CH_3)_3$], 1.15 (3 H, d, *J* 7.0, 4-Me), 3.34 (1 H, ddd, *J* 3.2, 6.8 and 8.1, 5-H), 3.47 (3 H, s, 5-OMe), 3.54 (1 H, dd, *J* 6.8 and 11.1, 6-H_a), 3.59–3.68 (7 H, m, 6-H_b, 1-OMe, 3-OMe), 4.01 (1 H, dq, *J* 7.0 and 8.1, 4-H), 4.97 (1 H, s, 2-H); δ_C (100.6 MHz; $CDCl_3$) −5.4, −5.3 [$Si(CH_3)_2$], 14.6 (4-Me), 18.4 [C(*C*$H_3)_3$], 25.9 [*C*$(CH_3)_3$], 36.6 (C-4), 50.8 (1-OMe), 55.5, 59.4 (3-OMe, 5-OMe), 65.0 (C-6), 84.3 (C-5), 90.8 (C-2), 167.5 (C-1), 177.2 (C-3); *m*/*z* (DCI) 350 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 350.2399; $C_{16}H_{32}O_5Si$ requires 350.2363.

(2*E*,4*R*,5*R*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethoxy-4-methylhex-2-en-1-ol 24

To a solution of compound **23** (165 mg, 0.50 mmol) in anhydrous THF (5 ml) was added under a N_2 atmosphere at −78 °C a 1 M solution of DIBAL-H in CH_2Cl_2 (1 ml). After stirring for 45 min at this temperature, the reaction was quenched with a saturated. aqueous solution of potassium sodium tartrate (5 ml). The reaction mixture was then treated with ethyl acetate (5 ml) and stirred vigorously for 1.5 h at room temperature. The aqueous layer was extracted three times with ethyl acetate, the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (heptane–ethyl acetate 5 : 1, 3% triethylamine) gave **24** (107 mg, 71%) as a colourless oil; R_f 0.33 (heptane–ethyl acetate 2 : 1); $[\alpha]_D^{22}$ +27.6 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3467m, 2953s, 2930s, 2857m, 1656m, 1463m, 1253m, 1142m, 1100s, 837s, 776m; δ_H (400 MHz; $CDCl_3$) 0.06, 0.07 [6 H, 2 × s, $Si(CH_3)_2$], 0.88 [9 H, s, $C(CH_3)_3$], 1.12 (3 H, d, *J* 6.8, 4-Me), 3.01 (1 H, dq, *J* 6.8 and 6.8, 4-H), 3.14 (1 H, ddd, *J* 2.6, 4.6 and 7.9, 5-H), 3.41–3.51 (7 H, m, 6-H_a, 3-OMe, 5-OMe), 3.78 (1 H, dd, *J* 2.5 and 11.7, 6-H_b), 3.91 (1 H, m, 1-H_a), 4.15 (1 H, dd, *J* 8.9 and 12.0, 1-H_b), 4.84 (1 H, dd, *J* 8.4 and 8.4, 2-H); δ_C (100.6 MHz; $CDCl_3$) −5.4, −5.1 [$Si(CH_3)_2$], 15.1 (4-Me), 18.6 [C(*C*$H_3)_3$], 26.0 [*C*$(CH_3)_3$], 35.3

(C-4), 54.2, 58.8 (3-OMe, 5-OMe), 57.6 (C-1), 62.7 (C-6), 84.7 (C-5), 97.6 (C-2), 162.1 (C-3); *m/z* (DCI) 322 (M + NH_4^+, 100%), 304 (70), 292 (50); HRMS found (M + NH_4^+) 322.2431; $C_{15}H_{32}O_4Si$ requires 322.2414.

Fragmentation of sorangicin A

Sorangicin A (**3**) (100 mg, 0.124 mmol) was dissolved in anhydrous pyridine (2 ml) and treated at 0 °C with acetic anhydride (2 ml) and a catalytic amount of DMAP. After stirring for 18 h at room temperature, the reaction mixture was concentrated, the residue dissolved in MeOH (5 ml) and H_2O (0.1 ml), then stirred for 30 min at room temperature. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (column A, eluent: MeOH–H_2O 80 : 20) to give 21,22,25-tri-*O*-acetylsorangicin A[44] (48.7 mg, 42%) as a colourless oil. 21,22,25-Tri-*O*-acetylsorangicin A (35.4 mg, 0.038 mmol) was dissolved in CH_2Cl_2 (440 µl) and methanol (1.3 ml), and ozone was introduced for 5 min at −65 °C. Dimethyl sulfide (150 µl) was added and the reaction mixture was stirred for 45 min at room temperature, then evaporated *in vacuo*. The residue was then dissolved in MeOH (10 ml) and treated with polymer-supported borohydride (0.5 g). After stirring for 3 h at room temperature, the reaction mixture was filtered and the solvent removed *in vacuo*. Purification of the residue by column chromatography (CH_2Cl_2–MeOH 95 : 5, then 90 : 10) gave **25** (11.3 mg, 79%) and **26** (6.0 mg, 84%) as colourless oils.

25. R_f 0.46 (CH_2Cl_2–MeOH 90 : 10); *m/z* (DCI) 394 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 394.2046; $C_{17}H_{28}O_8$ requires 394.2077.

26. R_f 0.30 (CH_2Cl_2–MeOH 90 : 10); δ_H (300 MHz; CD_3OD) 0.95 (3 H, d, *J* 6.8, 6-Me), 1.63 (1 H, m, 6-H), 1.88 (1 H, dd, *J* 1.5 and 11.7, 4-H_a), 2.05 (1 H, ddd, *J* 2.6, 6.8 and 11.7, 4-H_b), 3.48–3.62 (2 H, m, 7-H, 8-H_a), 3.68 (1 H, dd, *J* 1.9 and 11.3, 8-H_b), 3.82–3.93 (2 H, m, 1-H_2), 3.98 (1 H, m, 2-H), 4.23 (1 H, m, 5-H), 4.40 (1 H, m, 3-H); δ_C (100.6 MHz; CD_3OD) 16.1 (6-Me), 37.9 (C-6), 39.1 (C-4), 60.8 (C-1), 64.5 (C-8), 75.4 (C-3), 80.3 (C-7), 80.7 (C-5), 84.8 (C-2); *m/z* (DCI) 206 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 206.1453; $C_9H_{16}O_4$ requires 206.1392.

Deacetylation of 25 and silylation to compound 27

Compound **25** (85.9 mg, 0.228 mmol) was dissolved in anhydrous MeOH (9.7 ml) and treated with NaOMe (52 mg, 0.96 mmol). After stirring for 24 h at room temperature, the reaction mixture was neutralized with Dowex 50 W X 8 (H^+) ion exchange resin, the reaction mixture was filtered and the solvent was removed *in vacuo.* The residue was dissolved in anhydrous DMF (3.2 ml) containing *tert*-butyldimethylsilyl chloride (970 mg, 6.43 mmol) and imidazole (436 mg, 6.40 mmol). After stirring under a N_2 atmosphere for 72 h at room temperature, the reaction mixture was diluted with water and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–diethyl ether 50 : 1) gave **27** (109.1 mg, 58%) as a colourless oil; R_f 0.35 (petroleum ether–diethyl ether 50 : 1); ν_{max}(KBr)/cm^{-1} 2956s, 2929s, 2885m, 2858s, 1472m, 1257s, 1087s, 836s, 775s; δ_C (100.6 MHz; $CDCl_3$) 11.2 (7-Me), 31.1 (C-9), 36.7 (C-5), 39.4 (C-7), 61.0 (C-10), 65.2 (C-1), 70.7 (C-6), 71.3, 72.5, 77.8 (C-3, C-4, C-8), 76.3 (C-2); *m/z* (ESI) 843.5 (M + Na^+, 100%).

Synthesis of 28 and 29 by CSA-desilylation of 27

Compound **27** (19.7 mg, 0.024 mmol) was treated with camphorsulfonic acid as described in the synthesis of **21** and the residue was purified by column chromatography (petroleum ether–diethyl ether 50 : 1, petroleum ether–ethyl acetate 20 : 1, then 1 : 1) to give **27** (1.6 mg, 8%), **28** (7.0 mg, 41%), and **29** (6.3 mg, 44%) as colourless oils.

28. Purification by preparative HPLC (column B, eluent: heptane–ethyl acetate 50 : 1). Analytical HPLC: R_t 11.6 min (column B, eluent: heptane–ethyl acetate 50 : 1); R_f 0.23 (petroleum ether–ethyl acetate 15 : 1); $[\alpha]_D^{22}$ +17.9 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2956s, 2929s, 2885m, 2858s, 1472m, 1257s, 1086s, 1072s, 836s, 776s; δ_C (100.6 MHz; $CDCl_3$) 11.3 (7-Me), 18.1, 18.2, 18.3, 18.5 [4 × $C(CH_3)_3$], 31.3 (C-9), 35.1 (C-5), 39.7 (C-7), 62.2 (C-10), 65.0 (C-1), 71.1, 73.1, 74.2, 77.0 (C-3, C-4, C-6, C-8), 76.6 (C-2); *m/z* (DCI) 724 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 724.5230; $C_{35}H_{78}O_6Si_4$ requires 724.5219.

29. R_f 0.10 (petroleum ether–ethyl acetate 15 : 1); ν_{max}(KBr)/cm^{-1} 3411m, 2956s, 2929s, 2885m, 2858s, 1473m, 1256s, 1071s, 836s, 776s; δ_C (100.6 MHz; $CDCl_3$) −4.9, −4.8, −4.5, −4.4, −4.3, −4.2 [3 × $Si(CH_3)_2$], 18.1, 18.2, 18.3 [3 × $C(CH_3)_3$], 25.8–26.1 [$C(CH_3)_3$], 11.3 (7-Me), 30.6 (C-9), 35.1 (C-5), 39.7 (C-7), 62.0 (C-10), 63.8 (C-1), 70.8 (C-8), 73.8, 74.6 (C-2, C-3), 74.7 (C-6), 78.2 (C-4); *m/z* (DCI) 610 (M + NH_4^+, 100%), 593 [M + H^+, 40]; HRMS found (M + NH_4^+) 610.4386; $C_{29}H_{64}O_6Si_3$ requires 610.4355.

Synthesis of 30 by silylation of diol 29

Compound **29** (74.3 mg, 0.125 mmol) was dissolved in anhydrous CH_2Cl_2 (200 µl) and triethylamine (20 µl, 0.14 mmol), *tert*-butyldimethylsilyl chloride (20 mg, 0.132 mmol), and a catalytic amount of DMAP were added at 0 °C. After stirring for 22 h at room temperature, the reaction mixture was diluted with water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether/diethyl ether 50 : 1, then petroleum ether–ethyl acetate 20 : 1, then 1 : 1) gave **27** (13.1 mg, 13%), **30** (28.2 mg, 38%), and **29** (28.2 mg, 38%) as colourless oils.

30. Purification by preparative HPLC (column B, eluent: heptane–ethyl acetate 50 : 1).

Analytical HPLC: R_t 9.1 min (column B, eluent: heptane–ethyl acetate 50 : 1); R_f 0.28 (petroleum ether–ethyl acetate 15 : 1); $[\alpha]_D^{22}$ +19.0 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2956s, 2929s, 2885m, 2858s, 1472m, 1256s, 1072s, 836s, 776s; δ_C (100.6 MHz; $CDCl_3$) 11.2 (7-Me), 30.9 (C-9), 36.3 (C-5), 39.4 (C-7), 60.2 (C-10), 63.9 (C-1), 71.0, 71.0, 73.2, 73.9, 79.0 (C-2, C-3, C-4, C-6, C-8); *m/z* (DCI) 724 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 724.5221; $C_{35}H_{78}O_6Si_4$ requires 724.5219.

Synthesis of 31 by silylation of diol 26

Compound **26** (117 mg, 0.62 mmol) was dissolved under a N_2 atmosphere in anhydrous DMF (1.9 ml) and anhydrous CH_2Cl_2 (9.6 ml). Anhydrous triethylamine (347 µl, 2.47 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (434 µl, 1.89 mmol) were then added at 0 °C. After stirring for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 20 : 1, then 10 : 1) gave **31** (148 mg, 57%) as a colourless oil; R_f 0.36 (petroleum ether–ethyl acetate 10 : 1); ν_{max}(KBr)/cm^{-1} 2956s, 2930s, 2882m, 2857s, 1472m, 1256s, 1130s, 1097s, 1057m, 1016m, 838s, 777s; δ_H (400 MHz; $CDCl_3$) 0.89, 0.90 [18 H, 2 × s, 2 × $C(CH_3)_3$], 0.91 (3 H, d, *J* 7.1, 6-Me), 1.60 (1 H, m, 6-H), 1.77 (1 H, dd, *J* 1.0 and 11.2, 4-H_a), 1.94 (1 H, ddd, *J* 2.5, 6.6 and 11.7, 4-H_b), 3.47 (1 H, m, 7-H), 3.59 (1 H, dd, *J* 4.1 and 11.2, 8-H_a), 3.67 (1 H, dd, *J* 3.0 and 11.2, 8-H_b), 3.82–3.94 (3 H, m, 1-H_2, 2-H), 4.18 (1 H, d, *J* 6.6, 5-H), 4.33 (1 H, br s, 3-H); δ_C (100.6 MHz; $CDCl_3$) −5.2, −5.1 [$Si(CH_3)_2$], 16.0 (6-Me), 18.5 [$C(CH_3)_3$], 26.0 [$C(CH_3)_3$], 37.1 (C-6), 38.1 (C-4), 61.2

(C-1), 65.1 (C-8), 74.0 (C-3), 79.0 (C-7), 79.3 (C-5), 83.7 (C-2); *m*/*z* (DCI) 434 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 434.3151; $C_{21}H_{44}O_4Si_2$ requires 434.3122.

Synthesis of 32 and 33 by CSA-desilylation of 31

Compound **31** (238 mg, 0.57 mmol) was treated with camphorsulfonic acid as described in the synthesis of **21** and the residue was purified by column chromatography (petroleum ether–ethyl acetate 3 : 1, then ethyl acetate–MeOH 5 : 1) to give **31** (71.1 mg, 30%), a 1 : 1 mixture of **32** and **33** (72.2 mg, 42%), and **26** (16.6 mg, 15%). Compounds **32** and **33** were separated by column chromatography (hexane–ethyl acetate 3 : 2).

32. R_f 0.13 (petroleum ether–ethyl acetate 2 : 1); $[\alpha]_D^{22}$ −68.4 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3433m, 2957s, 2930s, 2882m, 2858m, 1256m, 1129s, 1098m, 1055m, 837s, 777s; δ_H (300 MHz; $CDCl_3$) 0.04, 0.05 (6 H, 2 × s, $Si(CH_3)_2$], 0.89 [9 H, s, $C(CH_3)_3$], 0.92 (3 H, d, *J* 6.8, 6-Me), 1.66 (1 H, m, 6-H), 1.80 (1 H, dd, *J* 1.7 and 11.7, 4-H_a), 1.97 (1 H, ddd, *J* 2.8, 6.6 and 11.7, 4-H_b), 3.53 (1 H, m, 7-H), 3.58 (1 H, dd, *J* 4.1 and 10.9, 8-H_a), 3.67 (1 H, dd, *J* 2.6 and 10.9, 8-H_b), 3.82–4.02 (3 H, m, 1-H_2, 2-H), 4.22 (1 H, d, *J* 6.4, 5-H), 4.37 (1 H, m, 3-H); δ_C (100.6 MHz; $CDCl_3$) −5.3, −5.1 [$Si(CH_3)_2$], 16.1 (6-Me), 18.4 [$C(CH_3)_3$], 26.0 [$C(CH_3)_3$], 36.9 (C-6), 38.2 (C-4), 61.3 (C-1), 64.8 (C-8), 74.1 (C-3), 79.2 (C-7), 79.5 (C-5), 82.8 (C-2); *m*/*z* (DCI) 320 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 320.2231; $C_{15}H_{30}O_4Si$ requires 320.2257.

33. R_f 0.29 (petroleum ether–ethyl acetate 2 : 1); $[\alpha]_D^{22}$ −76.2 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3443m, 2956s, 2930s, 2882m, 2857m, 1257m, 1091s, 838s, 778s; δ_H (300 MHz; $CDCl_3$) 1.60 (1 H, m, 6-H), 1.77 (1 H, dd, *J* 1.5 and 11.7, 4-H_a), 2.00 (1 H, ddd, *J* 2.6, 6.6 and 11.7, H-4$_b$), 3.46 (1 H, m, 8-H_a), 3.56 (1 H, m, 7-H), 3.68 (1 H, m, 8-H_b), 3.86–3.94 (3 H, m, 1-H_2, 2-H), 4.21 (1 H, d, *J* 6.6, 5-H), 4.38 (1 H, m, 3-H); δ_C (100.6 MHz; $CDCl_3$) −5.3, −5.2 [$Si(CH_3)_2$], 15.8 (6-Me), 18.4 [$C(CH_3)_3$], 26.0 [$C(CH_3)_3$], 36.7 (C-6), 38.3 (C-4), 60.8 (C-1), 63.9 (C-8), 74.1 (C-3), 78.4 (C-7), 78.9 (C-5), 83.5 (C-2); *m*/*z* (DCI) 320 (M + NH_4^+); HRMS found (M + NH_4^+, 100%) 320.2226; $C_{15}H_{30}O_4Si$ requires 320.2257.

Fragmentation of epothilone A

Epothilone A (**4**) (670 mg, 1.36 mmol) was dissolved in MeOH (16.8 ml), a 1 M aqueous solution of NaOH (16.8 ml) was added, and the reaction mixture was stirred for 5 min at room temperature. After addition of a 1 M aqueous solution of NaH_2PO_4, the organic solvent was removed *in vacuo* and the aqueous layer extracted four times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (CH_2Cl_2–MeOH 95 : 5, then 80 : 20) provided **34** (141 mg, 24%) and **35** (451 mg, 65%) as colourless oils.

34. R_f 0.68 (CH_2Cl_2–MeOH 85 : 15); *m*/*z* (DCI) 424 (M + H^+, 100%), 324 (20); HRMS found (M + H^+) 424.2506; $C_{23}H_{37}NO_4S$ requires 424.2522.

35. R_f 0.44 (CH_2Cl_2–MeOH 85 : 15); *m*/*z* (DCI) 512 (M + H^+, 10%), 424 (30), 324 (100), 206 (90).

(4*R*,5*S*,6*S*)-5,10-Dihydroxy-2,4,6-trimethyldecan-3-one 37 and (3*S*,4*E*)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)pent-4-ene-1,3-diol 38

Compound **34** (155 mg, 0.366 mmol) was dissolved in THF (1.4 ml) and H_2O (1.4 ml). A 1 M aqueous solution of H_2SO_4 (730 μl) was added at 0 °C and the reaction mixture was stirred for 5 h at room temperature. After addition of saturated aqueous sodium hydrogen carbonate, THF was removed *in vacuo* and the aqueous layer extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by column chromatography (CH_2Cl_2–MeOH 95 : 5) gave diol **36** (111.2 mg, 69%) as a colourless oil; R_f 0.55 (CH_2Cl_2–MeOH 85 : 15).

Compound **36** (111.2 mg, 0.252 mmol) was dissolved in MeOH (6.3 ml) and treated with a solution of $NaIO_4$ (80.7 mg, 0.377 mmol) in H_2O (6.3 ml). After stirring for 45 min at room temperature, the organic solvent was removed *in vacuo*, brine was added, and the reaction mixture was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeOH (15 ml) and treated with polymer-supported borohydride (0.76 g). After stirring for 3 h at room temperature, the reaction mixture was filtered and the solvent removed *in vacuo*. Isolation by preparative HPLC (column A, eluent: MeOH–H_2O 50 : 50) gave **37** (28.0 mg, 48%) and **38** (29.4 mg, 55%) as colourless oils.

37. Analytical HPLC: R_t 10.8 min (column A, eluent: MeOH–H_2O 50 : 50); ν_{max}(KBr)/cm^{-1} 3422s, 2968s, 2935s, 2875m, 1703s, 1466m, 1011m; *m*/*z* (DCI) 248 (M + NH_4^+, 50%), 148 (100).

38. Analytical HPLC: R_t 5.2 min (column A, eluent: MeOH–H_2O 50 : 50); R_f 0.62 (CH_2Cl_2–MeOH 85 : 15); $[\alpha]_D^{22}$ −25.7 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3377s, 2946m, 1508m, 1441m, 1190m, 1057s; δ_H (300 MHz; $CDCl_3$) 1.86 (2 H, m, 2-H_2), 1.99 (3 H, d, *J* 1.1, 4-Me), 2.68 (3 H, s, 8-Me), 3.82 (2 H, m, 1-H_2), 4.40 (1 H, t, *J* 6.0, 3-H), 6.59 (1 H, s, 5-H), 6.92 (1 H, s, 7-H); δ_C (100.6 MHz; $CDCl_3$) 14.7 (4-Me), 19.1 (8-Me), 36.7 (C-2), 61.4 (C-1), 77.1 (C-3), 115.5 (C-7), 118.4 (C-5), 142.2 (C-4), 152.7 (C-6), 164.9 (C-8); *m*/*z* (DCI) 214 (M + H^+, 100%); HRMS found (M + H^+) 214.0892; $C_{10}H_{15}NO_2S$ requires 214.0902.

(4*R*,5*S*,6*S*)-5,10-Bis(*tert*-butyldimethylsilyloxy)-2,4,6-trimethyldecan-3-one 39

Compound **37** (25.7 mg, 0.112 mmol) was dissolved under a N_2 atmosphere in anhydrous CH_2Cl_2 (2.2 ml) and at 0 °C were added anhydrous triethylamine (63 μl, 0.44 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (77 μl, 0.33 mmol). After stirring for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 20 : 1) gave **39** (36.6 mg, 71%) as a colourless oil; R_f 0.73 (petroleum ether–ethyl acetate 10 : 1); $[\alpha]_D^{22}$ −20.1 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2957s, 2930s, 2858m, 1710m, 1472m, 1256m, 1101m, 1005m, 837s, 774s; δ_H (300 MHz; $CDCl_3$) 0.88, 0.89 [18 H, 2 × s, 2 × $C(CH_3)_3$], 0.89 (3 H, d, *J* 7.0, 6-Me), 1.04, 1.06, 1.08 (9 H, 3 × d, 4-Me, 2-Me, 1-H_3), 2.75 (1 H, qqd, *J* 6.6 and 7.1, 2-H), 2.88 (1 H, dq, *J* 7.1 and 7.1, 4-H), 3.58 (2 H, t, *J* 6.6, 10-H_2), 3.83 (1 H, dd, *J* 3.3 and 6.6, 5-H); δ_C (100.6 MHz; $CDCl_3$) −5.2, −4.0, −3.9 [2 × $Si(CH_3)_2$], 18.4 [2 × $C(CH_3)_3$], 26.1, 26.0 [2 × $C(CH_3)_3$], 14.7 (4-Me), 16.6 (6-Me), 18.4, 18.8 (2-Me, C-1), 23.8 (C-8), 31.7, 33.1 (C-7, C-9), 39.0 (C-6), 40.4 (C-2), 47.6 (C-4), 63.2 (C-10), 76.6 (C-5), 217.3 (C-3); *m*/*z* (DCI) 476 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 476.3934; $C_{25}H_{54}O_3Si_2$ requires 476.3955.

(4*R*,5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-10-hydroxy-2,4,6-trimethyldecan-3-one 40

Compound **39** (47.2 mg, 0.103 mmol) was treated with camphorsulfonic acid as described in the synthesis of **21** and the residue was purified by column chromatography (petroleum ether–ethyl acetate 4 : 1) to give **40** (28.0 mg, 79%) as a colourless oil; R_f 0.34 (petroleum ether–ethyl acetate 4 : 1); $[\alpha]_D^{22}$ −22.0 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2958s, 2933s, 2858m, 1708s, 1464m, 1257m, 1063m, 1005s, 837s, 774s; δ_H (300 MHz; $CDCl_3$) 0.88 [9 H, s, $C(CH_3)_3$], 0.90 (3 H, d, *J* 7.0, 6-Me), 1.05, 1.06, 1.08 (9 H, 3 × d, 4-Me, 2-Me, 1-H_3), 2.76 (1 H, qqd, *J* 6.8 and 7.0, 2-H), 2.88 (1 H, dq, *J* 7.0 and 7.0, 4-H), 3.61 (2 H, t, *J* 6.4, 10-H_2), 3.84 (1 H, dd, *J* 3.2 and 6.8, 5-H); δ_C (100.6 MHz;

$CDCl_3$) −4.0, −3.9 [Si(CH_3)$_2$], 18.4 [C(CH_3)$_3$], 26.1 [C(CH_3)$_3$], 14.8 (4-Me), 16.5 (6-Me), 18.2, 18.8 (2-Me, C-1), 23.8 (C-8), 31.7, 33.1 (C-7, C-9), 38.9 (C-6), 40.4 (C-2), 47.6 (C-4), 62.8 (C-10), 76.6 (C-5), 217.5 (C-3); *m*/*z* (DCI) 362 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 362.3083; $C_{19}H_{40}O_3Si$ requires 362.3090.

(3*S*,4*E*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)pent-4-ene 41

Compound **38** (19.6 mg, 0.092 mmol) was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate as described in the synthesis of **39**. Purification of the residue by preparative TLC (petroleum ether–ethyl acetate 10 : 1) gave **41**[47] (34.5 mg, 85%) as a colourless oil; R_f 0.63 (petroleum ether–ethyl acetate 10 : 1); $[a]_D^{22}$ + 4.1 (*c* 1.0 in $CHCl_3$); *m*/*z* (DCI) 442 (M + H^+, 100%); HRMS found (M + H^+) 442.2609; $C_{22}H_{43}NO_2SSi_2$ requires 442.2631.

(3*S*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)pent-4-en-1-ol 42

Compound **41** (206.8 mg, 0.468 mmol) was treated with camphorsulfonic acid as described in the synthesis of **21** and the residue was purified by column chromatography (petroleum ether–ethyl acetate 5 : 2, then 2 : 1) to give **42**[43] (134 mg, 88%) as a colourless oil; R_f 0.36 (petroleum ether–ethyl acetate 2 : 1); $[a]_D^{22}$ −32.9 (*c* 1.0 in $CHCl_3$); *m*/*z* (DCI) 328 (M + H^+, 100%); HRMS found (M + H^+) 328.1759; $C_{16}H_{29}NO_2SSi$ requires 328.1767.

(3*S*,4*E*)-4-Methyl-5-(2-methyl-1,3-thiazol-4-yl)pent-4-ene-1,3-diol 38 and methyl (3*S*,6*R*,7*R*,8*R*)-3,7,12-trihydroxy-4,4,6,8-tetramethyl-5-oxododecanoate 44

Compound **35** (111.8 mg, 0.218 mmol) was treated with a 1 M aqueous solution of H_2SO_4 as described in the synthesis of **36**. The crude product was dissolved in MeOH (2.1 ml) and toluene (2.1 ml), and subsequently treated with a 2.0 M solution of (trimethylsilyl)diazomethane (250 µl) in portions over 2 h. After stirring for 0.5 h at room temperature, the reaction mixture was concentrated *in vacuo*. Purification of the residue by preparative TLC (CH_2Cl_2–MeOH 85 : 15) gave **43** (63.8 mg, 54%) as a colourless oil; R_f 0.58 (CH_2Cl_2–MeOH 85 : 15); *m*/*z* (DCI) 544 (M + H^+, 10%), 422 (60), 342 (50), 220 (100).

Compound **43** (63.8 mg, 0.117 mmol) was subsequently treated with $NaIO_4$ and polymer-supported borohydride as described for the synthesis of **37** and **38**. Isolation by preparative HPLC (column A, eluent: MeOH–H_2O 50 : 50) gave **38** (19.6 mg, 49%) and **44** (17.7 mg, 41%) as colourless oils.

44. Analytical HPLC: R_t 8.5 min (column A, eluent: MeOH–H_2O 50 : 50); ν_{max}(KBr)/cm^{-1} 3361m, 2940m, 1739s, 1688m, 1438m, 994m; δ_H (300 MHz; $CDCl_3$) 0.84 (3 H, d, *J* 6.8, 8-Me), 1.04 (3 H, d, *J* 7.0, 6-Me), 1.13, 1.19 (6 H, 2 × s, 4-Me), 2.37 (1 H, dd, *J* 10.0 and 16.2, 2-H_a), 2.46 (1 H, dd, *J* 2.8 and 16.2, 2-H_b), 3.63 (2 H, t, *J* 6.2, 12-H_2), 3.37 (1 H, m, 7-H), 3.25 (1 H, m, 6-H), 3.71 (3 H, s, COOMe), 4.25 (1 H, m, 3-H); δ_C (100.6 MHz; $CDCl_3$) 10.0 (8-Me), 15.6 (6-Me), 18.9, 21.3 (2 × 4-Me), 22.7 (C-10), 32.3 (C-11), 33.0 (C-9), 35.4 (C-8), 36.4 (C-2), 40.9 (C-6), 52.1 (C-4, 1-OMe), 62.9 (C-12), 72.4 (C-3), 74.8 (C-7), 173.4 (C-1), 222.3 (C-5); *m*/*z* (DCI) 350 (M + NH_4^+, 100%), 248 (30), 220 (50), 148 (40); HRMS found (M + NH_4^+) 350.2523; $C_{17}H_{32}O_6$ requires 350.2543.

(3*S*,4*E*)-3-Hydroxy-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)pent-4-enoic acid 45 and (5*R*,6*R*,7*R*,10*S*)-6,10-dihydroxy-12-methoxy-5,7,9,9-tetramethyl-8,12-dioxododecanoic acid 46

Compound **43** (215 mg, 0.40 mmol) was dissolved in MeOH (9.9 ml) and treated with a solution of $NaIO_4$ (126 mg, 0.56 mmol) in H_2O (9.9 ml). After stirring for 45 min at room temperature, the MeOH was removed *in vacuo*, the aqueous layer was diluted with brine, extracted three times with ethyl acetate, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in *tert*-butanol (12.8 ml), 2-methylbut-2-ene (2.4 ml) was added, then a solution of $NaClO_2$ (207 mg, 2.29 mmol) and NaH_2PO_4 (158 mg) in H_2O (3 ml). The reaction mixture was stirred for 1 h at room temperature, then a second portion of $NaClO_2$ (207 mg, 2.29 mmol) and NaH_2PO_4 (158 mg) in H_2O (3 ml) was added. After stirring for further 2 h at room temperature, the solvent was removed *in vacuo*, the residue was partitioned between ethyl acetate and brine, and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by preparative HPLC (column A, MeOH–H_2O, 50 mM NH_4OAc, pH 5.5) and subsequent extraction of product containing fractions after removal of MeOH at pH 4 gave **45** (77.6 mg, 86%) and **46** (67.2 mg, 49%) as colourless oils.

45. R_f 0.32 (CH_2Cl_2–MeOH 85 : 15); $[a]_D^{22}$ +2.5 (*c* 1.0 in $CHCl_3$); $[a]_D^{22}$ −18.7 (*c* 1.0 in MeOH); δ_H NMR (300 MHz; CD_3OD) 1.34 (t, *J* 7.3, NCH_2CH_3), 2.05 (3 H, d, *J* 1.1, 4-Me), 2.50–2.66 (2 H, m, 2-H_2), 2.72 (3 H, s, 8-Me), 3.24 (q, *J* 7.3, NCH_2CH_3), 4.60 (1 H, m, 3-H), 6.61 (1 H, s, 5-H), 7.23 (1 H, s, 7-H); δ_C (100.6 MHz; CD_3OD) 9.2 (NCH_2CH_3), 14.6 (4-Me), 18.6 (8-Me), 42.4 (C-2), 47.8 (NCH_2CH_3), 75.1 (C-3), 117.1 (C-7), 119.6 (C-5), 143.0 (C-4), 153.7 (C-6), 166.8 (C-8), 176.0 (C-1); *m*/*z* (DCI) 228 (M + H^+, 100%); HRMS found (M + H^+) 228.0701; $C_{10}H_{13}NO_3S$ requires 228.0694.

46. R_f 0.58 (CH_2Cl_2–MeOH 85 : 15); δ_C (100.6 MHz; CD_3OD) 12.5 (8-Me), 16.8 (6-Me), 20.4, 21.3 (2 × 4-Me), 23.8 (C-10), 32.2 (C-9), 37.3 (C-8), 38.7 (C-2, C-11), 44.1 (C-6), 52.2 (1-OMe), 53.8 (C-4), 73.6 (C-3), 76.8 (C-7), 174.3 (C-1, C-12), 221.1 (C-5); *m*/*z* (DCI) 364 (M + NH_4^+, 100%), 220 (45), 162 (40); HRMS found (M + NH_4^+) 364.2351; $C_{17}H_{30}O_7$ requires 364.2335.

Methyl [(2*S*,4*S*,5*R*,6*S*)-4,5-bis(*tert*-butyldimethylsilyloxy)-6-hydroxymethyltetrahydro-2*H*-pyran-2-yl] acetate 47

Ambruticin S (**5**) (106 mg, 0.216 mmol) was dissolved in ethanol (8 ml) and treated with a freshly prepared solution of diazomethane in diethyl ether. Excess diazomethane was destroyed by addition of acetic acid and the reaction mixture was concentrated *in vacuo*. The residue was dissolved under a N_2 atmosphere in anhydrous CH_2Cl_2 (4 ml) and treated at 0 °C with triethylamine (120 µl, 0.87 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (150 µl, 0.65 mmol). After stirring for 1 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous sodium hydrogen carbonate. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*; R_f 0.44 (hexane–ethyl acetate 9 : 1). The crude product was dissolved in CH_2Cl_2 (2.5 ml). To 1.0 ml of this solution was added MeOH (3 ml), and ozone was introduced for 3 min at −74 °C. The reaction mixture was evaporated *in vacuo*, the residue dissolved in MeOH (4 ml) and CH_2Cl_2 (2.5 ml), and treated at 0 °C with sodium borohydride (40 mg). After stirring for 1 h at room temperature, the reaction mixture was treated with a 1 M aqueous solution of NaH_2PO_4–K_2HPO_4 (pH 7) and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 9 : 2) gave **47** (14.3 mg, 40%) as a colourless oil; R_f 0.67 (petroleum ether–ethyl acetate 2 : 1); ν_{max}(KBr)/cm^{-1} 2955s, 2929s, 2857s, 1744s, 1473m, 1258m, 1115s, 837s, 779m; δ_H (300 MHz; $CDCl_3$) 0.88, 0.90 [18 H, 2 × s, 2 × C(CH_3)$_3$], 1.38 (1 H, m, 4-H_a), 1.99 (1 H, ddd, *J* 1.1, 3.4, and 9.5, H-4$_b$), 2.41 (1 H, dd, *J* 3.8 and 11.4, 2-H_a), 2.56 (1 H, dd, *J* 5.7 and 11.4, 2-H_b), 3.22 (1 H, m, 7-H), 3.31 (1 H, dd, *J* 6.1 and 6.9, 6-H), 3.57 (1 H, m, 8-H_a), 3.65–3.72 (4 H, m, 5-H, 1-OMe), 3.78 (1 H, m, 8-H_b), 3.87 (1 H, m, 3-H); δ_C (100.6 MHz; $CDCl_3$) −4.5, −4.1, −2.9, −2.8 [2 × Si(CH_3)$_2$],

18.4, 18.1 [2 × $C(CH_3)_3$], 26.3, 26.1 [2 × C(CH_3)$_3$], 40.5 (C-2), 40.7 (C-4), 51.8 (1-OMe), 63.0 (C-8), 72.1 (C-3), 73.6 (C-6), 74.8 (C-5), 80.8 (C-7), 171.2 (C-1); *m/z* (DCI) 466 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 466.3020; $C_{29}H_{50}O_6Si_2$ requires 466.3008.

Fragmentation of apicularen A

Apicularen A (**6**) (10.7 mg, 0.024 mmol) was treated with *tert*-butyldimethylsilyl chloride and imidazole as described in the synthesis of **20**. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 9 : 2, 2% triethylamine) gave 3,11-di-*O*-*tert*-butyldimethylsilylapicularen A (11.4 mg, 71%) as a colourless oil; R_f 0.39 (petroleum ether–ethyl acetate 4 : 1); *m/z* (DCI) 687 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 687.4225; $C_{37}H_{59}NO_6Si_2$ requires 687.4274.

3,11-Di-*O*-*tert*-butyldimethylsilylapicularen A (11.4 mg, 0.017 mmol) was dissolved in CH_2Cl_2 (0.5 ml) and methanol (1.5 ml), and ozone was introduced for 5 min at −75 °C. Dimethyl sulfide (200 µl) was added and the reaction mixture was stirred for 45 min at room temperature, then concentrated *in vacuo*. The residue was dissolved in MeOH (2 ml) and CH_2Cl_2 (1 ml), and treated at 0 °C with $NaBH_4$ (5 mg). After stirring for 2 h at room temperature, the reaction mixture was partitioned between ethyl acetate and a 1 M aqueous solution of NaH_2PO_4–K_2HPO_4 (pH 7), and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (petroleum ether–ethyl acetate 3 : 1, 1% triethylamine) gave **48** (7.5 mg, 80%) as a colourless oil; R_f 0.51 (petroleum ether–ethyl acetate 2 : 1); δ_H (300 MHz; $CDCl_3$) 0.89, 0.96 [18 H, 2 × s, 2 × C(CH_3)$_3$], 2.38 (1 H, dd, *J* 1.3 and 14.9, 8-H_a), 3.47 (1 H, dd, *J* 10.2 and 14.9, 8-H_b), 3.93–4.08 (2 H, m, 9-H, 11-H), 4.31 (1 H, m, 13-H), 5.70 (1 H, m, 15-H), 6.68–6.74 (2 H, m, 4-H, 6-H), 7.11 (1 H, dd, *J* 7.9 and 7.9, 5-H); δ_C (75.5 MHz; $CDCl_3$) −4.7, −4.1, −3.9 [2 × Si(CH_3)$_2$], 18.5, 18.1 [2 × $C(CH_3)_3$], 25.9 [2 × C(CH_3)$_3$], 37.5 (C-16), 38.5 (C-14), 39.1 (C-10), 39.3 (C-12), 39.5 (C-8), 59.1 (C-17), 65.6 (C-11), 66.2 (C-13), 72.1 (C-15), 73.9 (C-9), 117–3 (C-4), 123.2 (C-6), 128.1 (C-2), 129.6 (C-5), 139.5 (C-7), 151.9 (C-3), 169.9 (C-1); *m/z* (DCI) 568 (M + NH_4^+, 100%); HRMS found (M + NH_4^+) 568.3490; $C_{29}H_{50}O_6Si_2$ requires 568.3521.

SPOT synthesis of a natural product-derived hybrid structure

General procedures. All steps were carried out with the membrane placed in a polypropylene tray with a tight cover. Except for spotting reactions, the membrane was covered with respective solvents and reagent solutions and gently agitated on a rocker plate for the times indicated. Reaction conditions were optimised with model compounds to reach best possible results in coupling, deprotection, and cleavage reactions. The spot-size for manual spot synthesis with a spot volume of 1.2 µl is ~0.28 cm².

1 Coupling of the Fmoc-aminoethyl photolinker onto the APEG-membrane. 4-{4-[1-(Fmoc-amino)ethyl]-2-methoxy-5-nitrophenoxy}butanoic acid (0.2 M), 1-hydroxybenzotriazole (HOBt) (1.7 equiv.) and *N*,*N*-diisopropylcarbodiimide (DIC) (1.3 equiv.) were dissolved in *N*-methylpyrrolidin-2-one (NMP). After 30 min the solution was spotted onto the membrane (2 × 1.2 µl per spot, 3 equiv.) and the reaction was allowed to proceed for 60 min. The membrane was washed three times with DMF and twice with ethanol. The remaining amino-groups were then capped by acetylation with 2% acetic anhydride in DMF overnight and the membrane was washed again three times with DMF and twice with ethanol.

2 Fmoc-deprotection. The membrane was treated with 20% piperidine in DMF and the reaction was allowed to proceed for 30 min. The membrane was washed with DMF (3×) and DCM (3×).

3 Coupling of amino acids. The protected amino acid (0.3 M), 1-hydroxybenzotriazole (HOBt) (1.7 equiv.) and *N*,*N*-diisopropylcarbodiimide (DIC) (1.3 equiv.) was dissolved in NMP. After 30 min the mixture was spotted onto the membrane (2 × 1.5 µl per spot, 5 equiv.) and the reaction was allowed to proceed for 60 min. The membrane was washed with DMF (3×) and DCM (3×).

4 Determination of membrane loading. A single spot was cut out and placed in an Eppendorf vial and a solution of 20% piperidine in DMF (1 ml) was added. After 30 min the absorbance at 301 nm was measured and loading calculated using the molar absorption coefficient of the dibenzofulvene–piperidine adduct (ε = 7800). The spot loading of the Phe–Phe–Amp tripeptide was determined to be 170 nmol.

5 Boc-deprotection. The membrane was treated with 50% TFA (2 × 45 min), then washed with a 5% solution of diisopropylethylamine (DIEA) in DMF (3×), then with DMF (×) and DCM (3×).

6 Coupling of natural product fragments. The primary alcohol fragment (0.3 M), *p*-nitrophenyl chloroformate (0.9 equiv.) and DMAP (1.0 equiv.) were dissolved in a 1 : 1 (v/v) mixture of pyridine and NMP. After 30 min the precipitate was removed by centrifugation and the solution was spotted onto the membrane (3 × 1.3 µl per spot, 7–8 equiv.). The reaction was allowed to proceed for 2 h and the membrane was washed with DMF (3 ×) and DCM (3 ×). Coupling yields were found to be >80%.

7 TBS-deprotection. A solution of HF (70% in pyridine) was diluted 1 : 1 with DMF (**caution!**) and cooled to room temperature. The membrane was treated with the HF-solution for 3 h and was then washed with DMF (3×) and DCM (3×).

8 Photolytic cleavage. A single spot was cut out and placed in an Eppendorf vial. Cleavage from the membrane was performed in MeOH by irradiating for 3 h with UV light at 365 nm. The average compound recovery by cleavage from the linker was determined to be 80%. The product was analysed by HPLC-MS.

Analysis was performed by reverse-phase HPLC ESI-MS measured at 254 nm and 211 nm. For peak area integration the different molar absorption coefficients of epothilone A (ε = 17800 l mol^{-1} cm^{-1}) and phenylalanine (ε = 11700 l mol^{-1} cm^{-1}) measured in MeOH at 211 nm were taken into account. At 254 nm all compounds to which the epothilone fragment **42** is coupled give intensive signals whereas the absorption of the phenylalanine residues at this wavelength is negligible. The chromatogram measured at 211 nm reveals on the other hand additionally impurities that derive from Phe–Phe-linked intermediates, which contain no epothilone fragment.

Compound 49. ~100 nmol (60% overall yield); R_t 13.2 min (linear gradient of 5–95% aqueous CH_3CN, 5 mM NH_4OAc, pH 5.5 over 20 min); *m/z* (ESI) 877.0 (M + H^+); $C_{44}H_{56}N_6O_{11}S$ requires 877.4.

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