DOI: 10.1002/chem.200802605

The Laulimalide Family: Total Synthesis and Biological Evaluation of Neolaulimalide, Isolaulimalide, Laulimalide and a Nonnatural Analogue

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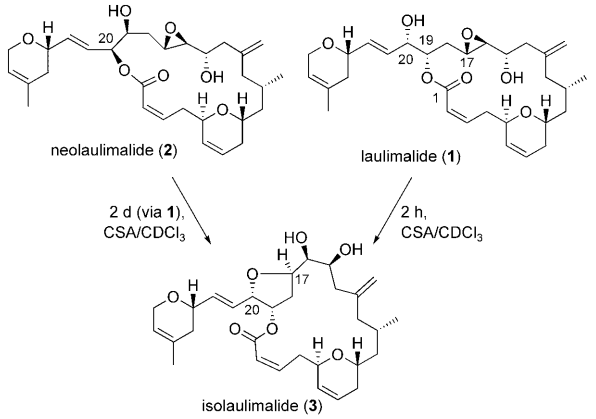
Abstract: We herein describe in full detail the first total synthesis of the antitumor agents neolaulimalide and isolaulimalide as well as a highly efficient route to laulimalide. A Kulinkovich reaction followed by a cyclopropyl–allyl rearrangement is used to install the *exo*-methylene group. The C_2–C_{16} aldehyde fragment is coupled with the C_{17}–C_{28} sulfone fragments by a highly (*E*)-selective Julia–Lythgoe–Kocienski olefination to deliver the key intermediates of all three syntheses. Various conditions for the Yamaguchi macrolactonization are applied to close the individual macrocycles. Finally a carefully elaborated endgame was developed to solve the problem of acyl migration in the case of neolaulimalide. All compounds were tested against several cell lines. The cytotoxicity of neolaulimalide could be confirmed for the first time since its original isolation and it could be shown that it induces tubulin polymerization as efficiently as laulimalide.

Keywords: acyl migration · antitumor agents · natural products · olefination · total synthesis

Introduction

The laulimalides (Scheme 1), also known as fijianolides, are a family of polyketide natural products obtained from various marine sources.[1] The 20-membered macrolide laulimalide (fijianolide B, **1**) and its isomer isolaulimalide (fijianolide A, **3**) have been isolated almost contemporaneously by two groups from the marine sponges *Cacospongia mycofijiensis*,[1a] respectively *Hyatella sp.* and a nudibranch predator, *Chromodoris lochi*[1b] back in 1988. A third isomer named neolaulimalide (**2**) was isolated along with **1**, **3** and other cytotoxic compounds from the sponge *Fasciospongia rimosa* in 1996.[1c,d] Reisolation from *Cacospongia mycofijiensis* unearthed, in addition to **1** and **3**, six additional fijianolides (D–I) each varying with respect to the oxidation state and/or substitution pattern of the C_{20} sidechain.[1e]

Laulimalide (**1**) and neolaulimalide (**2**) inhibit the proliferation of several tumor cell lines with IC_{50} values in the low nanomolar range (**1**: KB $IC_{50}=15$ nM, MDA-MB-435 $IC_{50}=6$–7 nM;[1b,2] **2**: P-388 $IC_{50}=50$ nM, A-549 = 10 nM, HT-29 $IC_{50}=25$ nM, MEL 28 $IC_{50}=25$ nM[1c,d]) whereas isolaulimalide (**3**) and fijianolides D-I show reduced activity (**3**: HT-29 $IC_{50}=20$–97 μM, MDA-MB-435 $IC_{50}=20$ μM).[1d,e,2] In 1999 the group of Mooberry discovered that **1** stabilizes microtubules similar to paclitaxel.[2] Later this was confirmed



Scheme 1. The laulimalides (CSA = camphorsulfonic acid).

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200802605.

by different groups along with the result that **1** binds to tubulin in a similar fashion as paclitaxel does, however, the binding site is different.[3] Laulimalide is synergistic with other anticancer agents and is also very potent against cell lines showing multidrug-resistance (MDR).[3] According to a first in vivo study **1** does not generate significant tumor-growth inhibition within the limit of acceptable toxicity,[4a] whereas a second evaluation by a different group reports significant inhibition of growth in HCT-116 tumors.[4b]

Due to its epoxide function **1** is an intrinsically unstable compound. On exposure to acid, it rearranges to **3** within two hours via an acid-catalyzed S_N2-type attack of the C_{20}-hydroxyl group on the C_{17} position of the epoxide (Scheme 1).[1b] Compound **2** shows an appreciably reduced lability towards acid.[1c,d] First it undergoes ring contraction to **1**, which then isomerizes to **3** as expected. After two days, the rearrangement is complete.

Owing to its potential as an anticancer lead, the total synthesis of **1** and the preparation of analogues thereof is a hot topic for over a decade now.[5,6] However, since acid lability has been identified as a major drawback in developing **1** as an anticancer drug,[6a] **2** should be considered as a promising alternative lead compound. To our surprise the equally active isomer **2** has been completely ignored since its discovery. Moreover, **2** has been isolated only once and so we decided to develop a first total synthesis for a re-evaluation of the promising biological properties.[7]

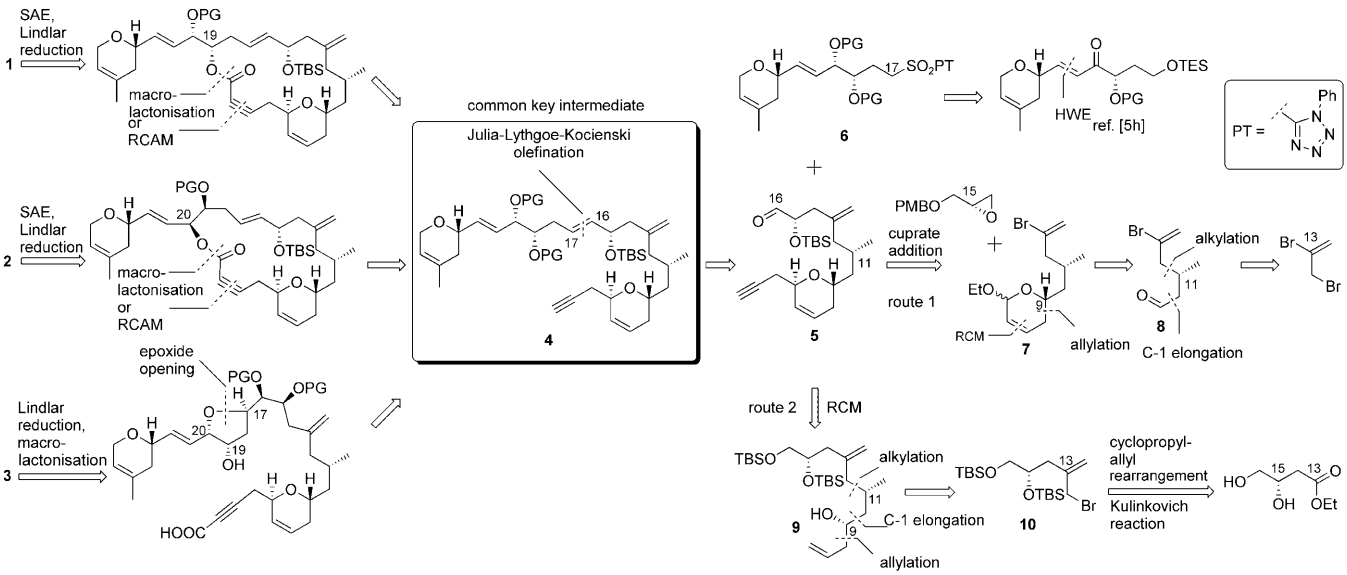
We see a potential for **3** as an alternative perfectly stable lead compound as well. Hence we aimed for a flexible first total synthesis of **3** which should open the space for the preparation of biological active analogues.[7] Finally, we realized that the material for the in vivo testing of **1** is still partly obtained from marine sources and not by total synthesis.[4b] This stimulated us to develop a late generation route to **1** as well, which should be suited for the acquisition of larger quantities of material.

Results and Discussion

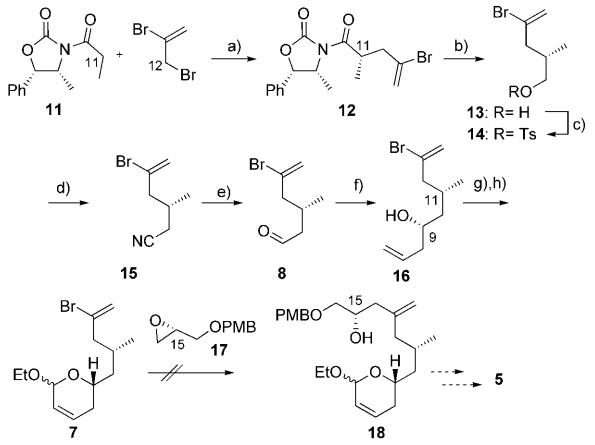
Strategic consideration: Our retrosynthesis (Scheme 2) was focused on the development of a common key intermediate that could be used for the preparation of all three laulimalides.

It was obvious that we have to install the labile epoxide and 2,3-(*Z*)-enoate functions of **1** and **2** at the end of the synthesis, after generating the macrocycle. For the synthesis of **3** we envisaged the formation of the characteristic tetrahydrofuran moiety via an epoxide opening prior to macrocyclization. These considerations guided us to the common key intermediate **4** which should be adapted to the different tasks by a proper choice of the protecting groups. For optimal convergency the C_{16}–C_{17} double bond in **4** was disconnected to deliver aldehyde **5** and sulfone **6** suitable for a Julia-Lythgoe-Kocienski olefination.[5a–c,8]

Preparation of the fragments—The aldehyde fragment 5: For the preparation of the C_2–C_{16} fragment **5**, which was used in all three syntheses, we envisioned two routes (Scheme 2). In the first approach (Scheme 3) the C_{11} stereocenter was generated by alkylating the sodium enolate of **11** with 2,3-dibromo-1-propene to obtain **12** in 70% yield. Reductive removal of the auxiliary led to alcohol **13**[9] which was subjected to a C-1 elongation by standard tosylation and S_N2 displacement with sodium cyanide. Nitrile **14** was reduced to the volatile aldehyde **8**. Allylation with (−)-Ipc–allylborane gave the homoallylic alcohol **16** in 85% yield and a 14:1 d.r.[10] The dihydropyran **7** was generated by



Scheme 2. Retrosynthesis of **1**, **2** and **3** (PG = protecting group, HWE = Horner–Wadsworth–Emmons olefination, PMB = *para*-methyloxybenzyl, PT = 1-phenyl-1*H*-tetrazole, RCAM = ring-closing alkyne metathesis, RCM = ring-closing metathesis, SAE = Sharpless asymmetric epoxidation, TBS = *tert*-butyldimethylsilyl).

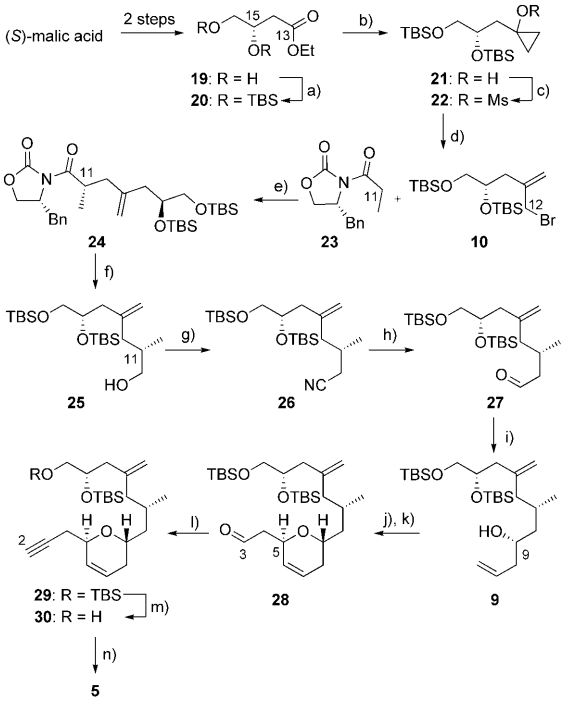


Scheme 3. Synthesis of aldehyde **5**, first generation approach. a) NaHMDS, THF, −78 to −30°C (70%); b) $LiBH_4$, H_2O, Et_2O, 0°C (93%); c) TsCl, DMAP, pyridine, RT (97%); d) NaCN, DMSO, 85°C (99%); e) DIBALH, CH_2Cl_2, −78°C to RT (80%); f) (−)-Ipc-allylborane, pentane, Et_2O, −100°C (86%); g) $(EtO)_2CHCH{=}CH_2$, PPTS, toluene, 40°C; h) $[Cl_2(PCy_3)_2Ru{=}CHPh]$, CH_2Cl_2, reflux (80% over two steps) (DIBALH = diisobutylaluminium hydride, DMAP = *N*,*N*-dimethylaminopyridine, DMSO = dimethylsulfoxide, Ipc = isopinocampheyl, NaHMDS = sodium bis(trimethylsilyl)amide, PPTS = pyridinium toluene-4-sulfonate, THF = tetrahydrofuran, Ts = *p*-toluenesulfonyl).

forming the mixed allylic acetal and subsequent ring-closing metathesis (RCM).[11] However, several attempts to open epoxide **17** with differnt cuprate species generated from vinyl bromide **7** failed in our hands.

Since our first route to aldehyde **5** had misfired we focused on the development of a second, more robust and reliable approach. Thus we decided to start with commercially available diol **19** which can be obtained from very cheap natural (*S*)-malic acid in two steps and provides us with the correct configuration at C_{15}.[12] The TBS-protected diol **20** was used in a Kulinkovich reaction[13] to generate cyclopropanol **21** which was used without further purification in the next step. Mesylation of **21** and treatment of the crude product with $MgBr_2{\cdot}OEt_2$ in refluxing CH_2Cl_2 resulted in a rapid cyclopropyl–allyl rearrangement furnishing allylbromide **10** in 73% yield over three steps.[13] This sequence could be carried out without problems on a 30 gram scale. Alkylation of *N*-propionyloxazolidinone **23** with **10** proceeded in good yields. The auxiliary was removed by reduction with $LiBH_4$ and gave alcohol **25**. At this stage we used a Mitsunobu reaction for C-1 elongation to the cyanide alternative to tosylation and S_N2 displacement with sodium cyanide.[14] Reduction of nitrile **26** with DIBALH led to aldehyde **27** and subsequent Brown allylation[10] gave us alcohol **9** in very good yield and a high d.r. of 16:1. The formation of the dihydropyran unit could be streamlined as well. After generation of the mixed allylic acetal we were able to perform RCM[11] and the subsequent installation of the C_2–C_3 sidechain, by addition of vinyloxytrimethylsilane and montmorilonite K10, in one pot. The resulting aldehyde **28** was converted into the terminal alkyne with the Bestmann-Ohira reagent in 75% yield.[15] Selective deprotection of the primary TBS ether and oxidation with 2-iodoxybenzoic acid (IBX) to the aldehyde delivered fragment **5** in 21% yield over 14 linear steps.

The sulfone fragments 6a–e (Scheme 4**)**: The syntheses of sulfones **6a**, **6b** and **6c** started with the removal of the TES-ether from the known intermediate **31a**[5h] with HF·pyridine

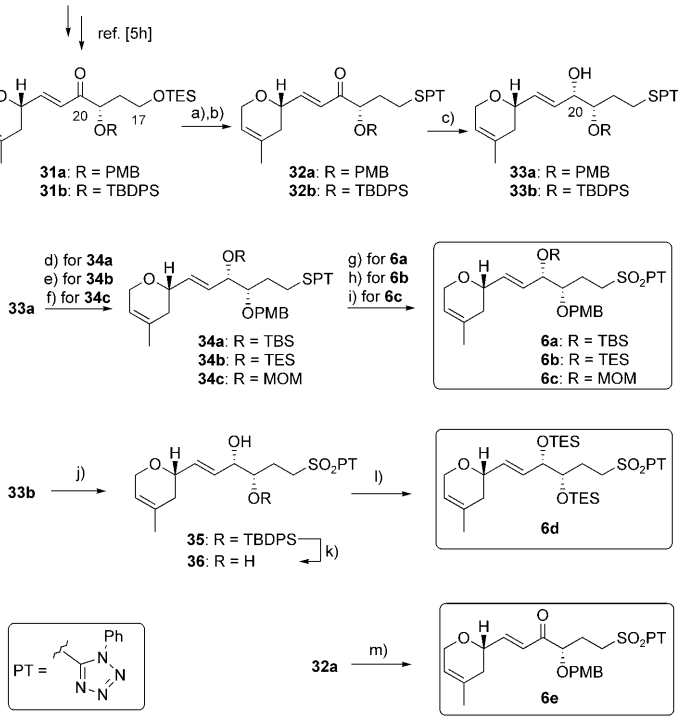


Scheme 4. Synthesis of aldehyde **5**, second-generation approach. a) TBSCl, Im, CH_2Cl_2, RT (99%); b) $Ti(OiPr)_4$, EtMgBr, 10°C, Et_2O; c) MsCl, NEt_3, 0°C; d) $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, reflux (73% over three steps); e) NaHMDS, THF, −78 to −30°C, (77%, 79% conversion); f) $LiBH_4$, H_2O, Et_2O, 0°C (97%); g) PPh_3, DIAD, acetone cyanohydrin, THF, RT (94%); h) DIBALH, CH_2Cl_2, −78°C to RT (92%); i) (−)-Ipc-allylborane, pentane, Et_2O, −100°C (95%); j) $(EtO)_2CHCH{=}CH_2$, PPTS, toluene, 40°C; k) $[Cl_2(PCy_3)_2Ru{=}CHPh]$, CH_2Cl_2, reflux, then montmorilonite K10, vinyloxytrimethylsilane, RT (70% over two steps); l) K_2CO_3, dimethyl-1-diazo-2-oxopropylphosphonate, MeOH, RT (75%); m) NH_4F, EtOH, RT (93%, 71% conversion); n) IBX, MeCN, reflux (98%) (Bn = benzyl, DIAD = diisopropyl azodicarboxylate, Im = imidazole, IBX = 2-iodoxybenzoic acid, Ms = methanesulfonyl).

to give the primary alcohol, which was immediately transformed into sulfide **32a** (90% over two steps) by a Mitsunobu reaction with 1-phenyl-1*H*-tetrazol-5-thiol (PT-SH). Luche[16] reduction of **32a** at low temperatures delivered the *syn*-product **33a** in almost quantitative yield and good diastereoselectivity (d.r. 17:1). The newly generated OH group at C_{20} was protected as TBS-, TES- and MOM-ethers **34a–c** which were oxidized to the sulfones **6a**, **6b** and **6c**. This worked well for **6a** and **6c**. In the case of the very labile allylic OTES ether in **6b** we had to use buffered heptamolybdate[17] and carefully monitor the reaction progress to avoid desilylation and subsequent epoxidation of the allylic alcohol.

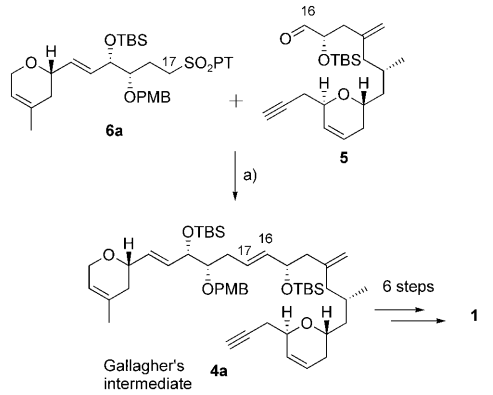
For the synthesis of **6d** we started from **31b** and transformed it to sulfide **32b** as described above for **32a** Scheme 5. The Luche reduction of **32b** gave even better diastereoselectivity (d.r. > 20:1) and excellent yields. The resulting alcohol **33b** was oxidized to the sulfone, the TBDPS-ether was removed with 70% HF·pyridine and the obtained vicinal diol was capped with TES groups to furnish **6d**.

The sulfonyl ketone **6e** was obtained by oxidizing sulfide **32a**.



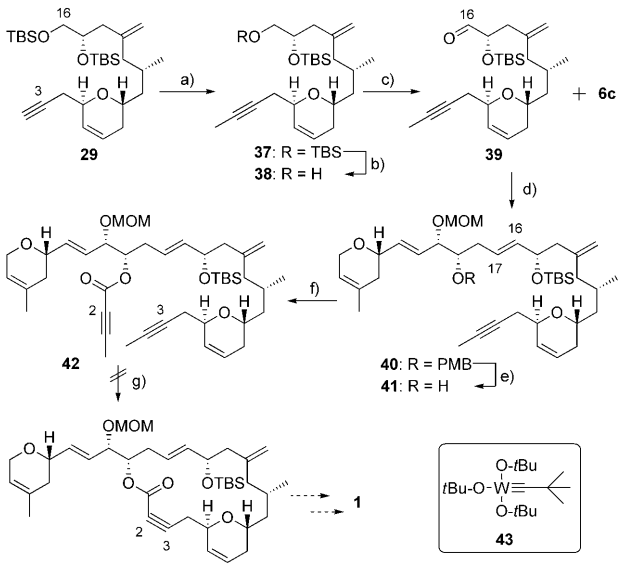
Scheme 5. Synthesis of the sulfone fragments **6a–e**. a) 7% HF·pyridine, THF, RT (98% both cases); b) PPh_3, PTSH, DEAD, THF, 0°C to RT (92% both cases); c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78°C (**33b**), −100°C (**33a**) (**33b**: 97%, d.r. > 20:1; **33a**: 98%, d.r. 17:1); d) TBSOTf, 2,6-lutidine, CH_2Cl_2, −20°C to RT (93%); e) TESOTf, 2,6-lutidine, CH_2Cl_2, −30°C to RT (97%); f) MOMCl, $NEtiPr_2$, CH_2Cl_2, RT (98%); g) H_2O_2, $(NH_4)_6Mo_7O_{24}$, EtOH, RT (73%); h) H_2O_2, $(NH_4)_6Mo_7O_{24}$, EtOH, pH 7 buffer, RT (61%) i) H_2O_2, $(NH_4)_6Mo_7O_{24}$, EtOH, RT (76%); j) H_2O_2, $(NH_4)_6Mo_7O_{24}$, EtOH, RT (70%); k) 70% HF·pyridine, THF, 0°C to RT (94%); l) TESOTf, 2,6-lutidine, CH_2Cl_2, −20°C to RT (97%); m) H_2O_2, $(NH_4)_6Mo_7O_{24}$, EtOH, RT (73%) (DEAD = diethyl azodicarboxylate, MOM = methyloxymethyl, OTf = trifluoromethanesulfonate, TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl).

Total synthesis of laulimalide (1)—The Gallagher intermediate: After the successful coupling of aldehyde **5** with sulfone **6a** via a completely (*E*)-selective Julia–Lythgoe–Kocienski olefination[8] we obtained intermediate **4a** in excellent yield (Scheme 6). This compound had been used as a 1:1 mixture of diastereomers at C_{15} in a gram scale synthesis of **1** by Gallagher *et al* that provided material for an in vivo study.[5k] We can now provide a shorter, higher yielding and stereoselective route to **4a**.



Scheme 6. Synthesis of the Gallagher Intermediate **4a**. a) KHMDS, THF, −78°C (87%) (KHMDS = potassium bis(trimethylsilyl)amide).

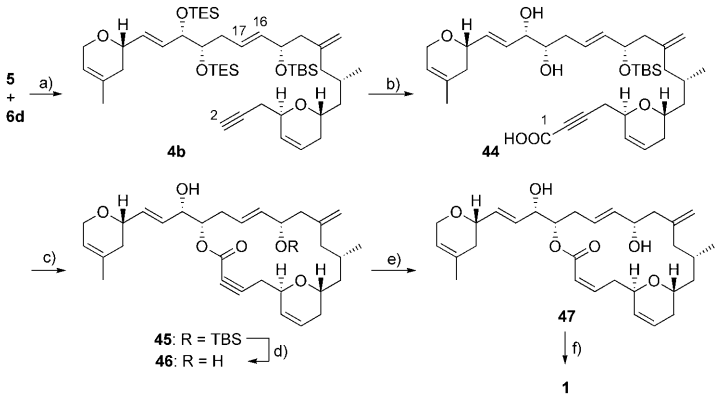
Alkyne-metathesis approach to 1: After having achieved a formal access to **1** we envisioned the development of a more effective endgame and considered RCAM (ring-closing alkyne metathesis) as a promising alternative method for closing the macrocycle (Scheme 7), since this method has been successful on several occasions.[18] We therefore methylated the terminal alkyne of **29** and cleaved the primary TBS-ether with NH_4F. Oxidation of alcohol **38** with IBX delivered aldehyde **39** which was used in a Julia–Lythgoe–Kocienski olefination with sulfone **6c** to deliver intermediate **40** in 74% yield. After oxidative cleavage of the PMB group with DDQ the resulting alcohol **41** was esterified with 2-butynoic acid and DIC to furnish the required RCAM precursor **42**. To our disappointment treatment of **42** with the commercially available Schrock alkyne metathesis catalyst **43**[19]



Scheme 7. Alkyne metathesis approach to **1**: a) *n*BuLi, MeI, THF, −78°C (85%); b) NH_4F, EtOH, RT (89%, 65% conversion); c) IBX, MeCN, reflux (98%) d) KHMDS, THF, −78°C (74%); e) DDQ, phosphate buffer pH 7, CH_2Cl_2, RT (89%) f) DIC, 2-butynoic acid, DMAP, CH_2Cl_2, 0°C to RT (70%); g) Schrock catalyst **43**, PhH (DIC = *N,N'*-diisopropylcarbodiimide).

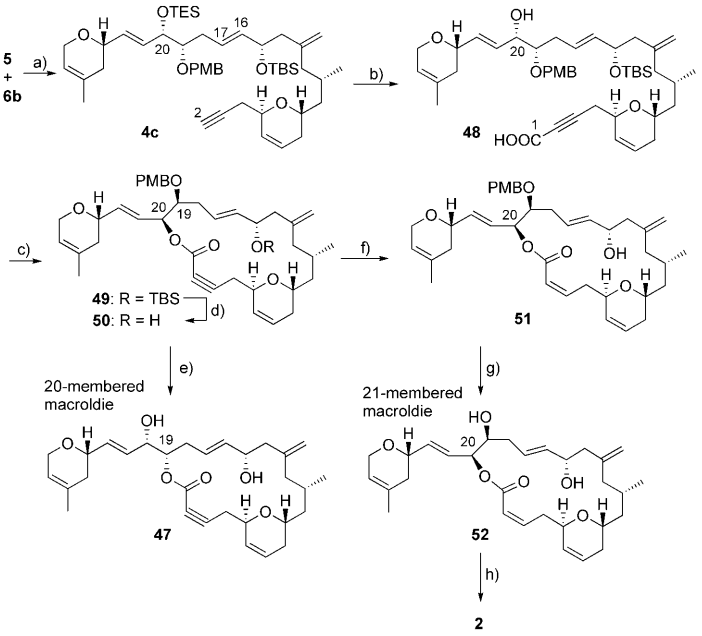
under several conditions[20] did not produce the desired product. We mainly isolated unconverted **43** along with unidentified decomposition products. The ester function next to a triple bond in **43** might be a reason for our failure since Fürstner reported a related case earlier.[21]

Macrolactonization approach to 1: We next aspired an effective macrolactonization approach (Scheme 8). Julia–Lythgoe–Kocienski olefination of **5** and sulfone **6d** again gave us fragment **4b** in excellent yield and (*E*)-selectivity. Then, we were able to generate seco acid **44** in just one operation as C-1 elongation with *n*BuLi and carbon dioxide followed by selective deprotection of the TES groups with 7% HF·pyridine could be performed in the same pot. Yamaguchi macrolactonization under Yonemitsu conditions[22] delivered the 20-membered ring **45** exclusively in good yields. The macrocycle was desilylated to **46** and Lindlar-reduction of the triple bond led to desoxylaulimalide (**47**). Finally, Sharpless asymmetric epoxidation (SAE) furnished **1** in 75% yield.[4c] All analytical data of **1** were in full accord with the ones reported.[1]



Scheme 8. Synthesis of **1**. a) KHMDS, THF, −78°C (80%); b) *n*BuLi, CO_2 then 7% HF·pyridine, THF, −78°C to RT (87%); c) 2,4,6-$Cl_3C_6H_3C(O)Cl$, NEt_3, DMAP, benzene, RT (75%); d) 35% HF·pyridine, THF, 0°C to RT (95%); e) H_2, Lindlar cat., quinoline, EtOAc/cyclohexene, RT (85%); f) Ti(O*i*Pr)$_4$, (+)-DIPT, *t*BuOOH, 4 Å MS, CH_2Cl_2, −20°C (75%) (DIPT = diisopropyl tartrate, MS = molecular sieves).

Total synthesis of neolaulimalide (2): For the synthesis of **2** the macrolactonization had to generate the obviously unfavored 21-membered macrocycle, an objective which had to be enforced by appropriate protective group manipulations. Hence we coupled aldehyde **5** with sulfone **6b** to **4c** (Scheme 9) and obtained seco acid **48** in one pot by C-1 elongation and subsequent desilylation in good yield. Our first Yamaguchi macrolactonization attempts again under Yonemitsu conditions delivered unacceptable 1:1 mixtures of the desired macrocycle **49** and its dimer in moderate combined yield. A change to classical Yamaguchi conditions[22,23] and higher dilution reduced dimer formation to 4% and yielded **49** in 35%. With the 21-membered macrocycle in hands we expected that the simple endgame we used for **1**

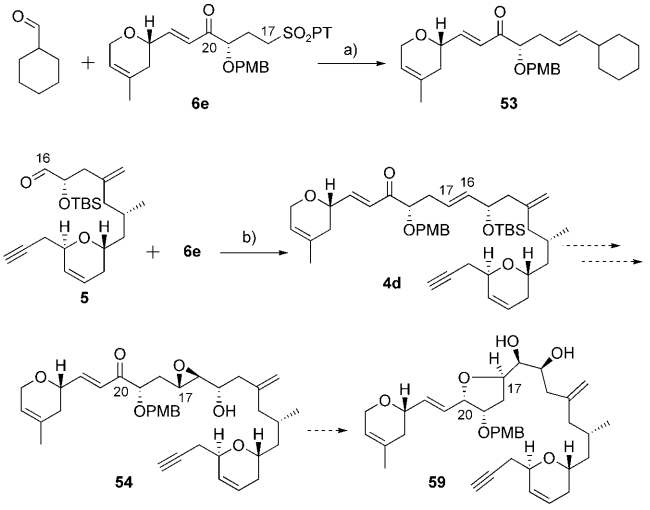


Scheme 9. First total synthesis of **2**. a) KHMDS, THF, −78°C (76%), b) *n*BuLi, CO_2 then 7% HF·pyridine, THF, −78°C to RT (85%); c) 2,4,6-$Cl_3C_6H_3C(O)Cl$, NEt_3, DMAP, PhH, RT (35% + 4% dimer); d) 35% HF·pyridine, THF, 0°C to RT (87%); e) DDQ, phosphate buffer pH 7, CH_2Cl_2, RT (90%); f) Lindlar cat., quinoline, EtOAc/cyclohexene (98%); g) DDQ, phosphate buffer pH 7, CH_2Cl_2, ultrasound, 32–42°C (96%); h) Ti(O*i*Pr)$_4$, (+)-DIPT, *t*BuOOH, 4 Å MS, CH_2Cl_2, −20°C (73%).

would provide us **2** as well. In fact desilylation of the TBS ether proceeded smoothly with 35% HF·pyridine and delivered **50** in 87% yield. However, on attempting to remove the remaining OPMB protecting group, we realized how strong the driving force was to restore the more favorable 20-membered lactone. Thus on treatment of **22** with an excess of DDQ in CH_2Cl_2/phosphate buffer pH 7 the desired oxidative cleavage of the PMB ether was ensued by a rapid acyl migration and macrolactone **47** was isolated as the sole product. Model studies indicated that the ring strain which disfavors the larger macrolide would be much reduced in the (*Z*)-enoate. Due to this considerations we generated the labile (*Z*)-enoate prior to the crucial deprotection by Lindlar reduction to **51**. After intensive experimentation we were delighted to see that ultrasound treatment of **51** with DDQ under strictly neutral conditions during reaction and workup gave desoxyneolaulimalide (**52**) in excellent yield. During our deprotection studies we found that the notoriously acid labile macrocycle is even more sensitive to base promoted trans-acylation. To avoid this complication in the final step of our synthesis we had to develop a modified non-basic work up for the SAE reaction. Therefore, after successful epoxidation we were able to obtain **2** in 73% yield. All analytical data perfectly matched those in the literature.[1c]

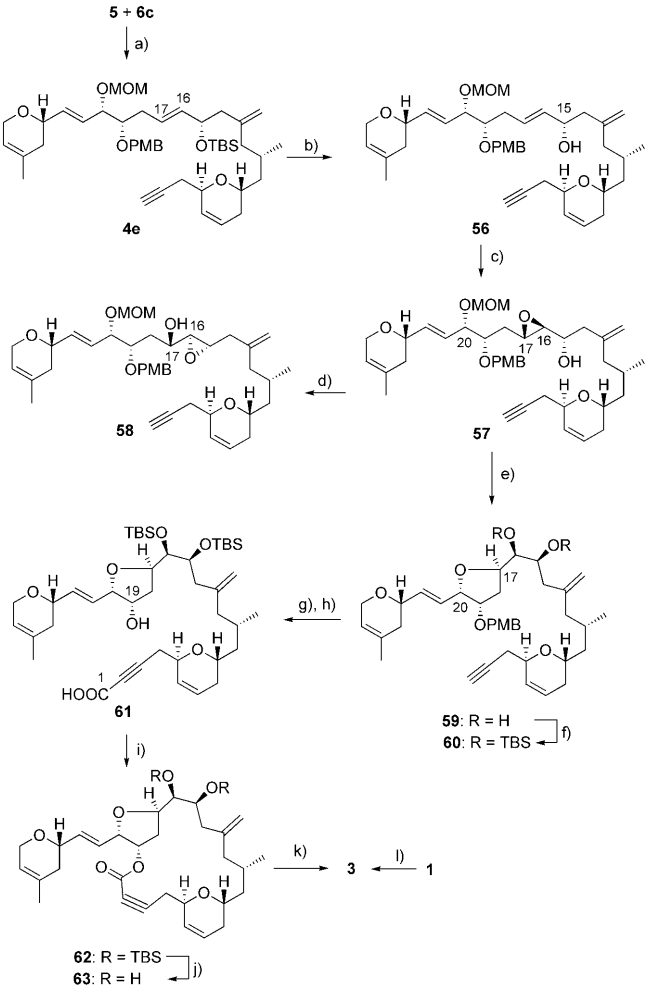
Total synthesis of isolaulimalide (3): To generate the THF ring we envisioned an efficient reduction/epoxide opening

sequence to convert **54** into **59** (Scheme 10). Therefore we had to perform a Julia olefination with unsaturated sulfone **6e** and **5**. Since difficulties were expected, we started our investigations with a model system. Treatment of **6e** and an excess of cycohexanecarbaldehyde under Barbier conditions with KHMDS lead to enone **53** in 69% yield. To our disappointment the analogous reaction of aldehyde **5** with **6e** never gave yields higher than 24%, when we used both components in stoichiometric amounts. At this point we had to reconsider our synthesis and change the strategy. Nevertheless we obtained the valuable information that even an unsaturated ketone such as **6e** can be applied in Julia olefinations though with limited success.



Scheme 10. First approach to **3**. a) KHMDS, THF, −78°C (70%); b) KHMDS, THF, −78°C (24%).

Our next approach started with the formation of intermediate **4e** from sulfone **6c** and **5** in excellent yield (Scheme 11). Desilylation of the TBS-ether with HF·pyridine led to allylic alcohol **56**. Its SAE delivered **57** as a modified cyclisation precursor. First attempts to deprotect the OMOM ether and subsequent opening of the epoxide with various acids or Lewis acids did not deliver the desired tetrahydrofuran. Instead, along with unidentified decomposition products, epoxide **58** was isolated as the product of an acid-catalyzed Payne rearrangement. After extensive experimentation we found that when we removed the OMOM protecting group with $BF_3{\cdot}OEt_2$ and PhSH at −20 to 0°C, intramolecular opening of the epoxide occurred to give tetrahydrofuran **59** in 70% yield. TBS protection of the resulting vicinal diol led to compound **60**, whose PMB deprotection and C-1 elongation delivered seco-acid **61**. We suspected that macrolactonization would not be facile, due to the transannular strain exerted by the rigid tetrahydrofuran ring. Therefore we were pleased to isolate, from a Yamaguchi macrolactonization, the desired macrolactone in 38% yield, along with 9% of the dimer. This mixture was difficult to separate; however, after removal of the TBS-protecting



Scheme 11. First total synthesis of **3**. a) KHMDS, THF, −78°C (86%); b) 70% HF·pyridine, THF, 0°C to RT (95%); c) Ti(O*i*Pr)$_4$, (+)-DIPT, *t*BuOOH, 4 Å MS, CH_2Cl_2, −20°C (73%); d) several acidic conditions (e.g. HCl, EtOH; TMSBr, DCM); e) $BF_3{\cdot}Et_2O$, PhSH, THF, −20°C to 0°C (70%); f) TBSOTf, 2,6-lutidine, CH_2Cl_2, −20°C to RT (87%); g) DDQ, phosphate buffer pH 7, CH_2Cl_2 (90%); h) *n*BuLi, CO_2, THF, −78°C (86%); i) 2,4,6-$Cl_3C_6H_3C(O)Cl$, NEt_3, DMAP, benzene, RT; j) 70% HF·pyridine, THF, 0°C to RT (32% over two steps); k) H_2, Lindlar cat., quinoline, EtOAc/cyclohexene (97%); l) cat. CSA, $CDCl_3$ (90%).

groups monomer **63** could be easily isolated by chromatography. Reduction of the triple bond to the (*Z*)-enoate finally gave **3** which was identical with the sample we obtained from **1** by treatment with a catalytic amount of acid (Scheme 11, Figure 1). All analytical data of **3** matched those reported in literature.[1a,b]

Synthesis of an C-20 O ester analogue (67): During our synthesis of **1** we observed that ester **64** was generated when we used an excess of 2,4,6-trichlorobenzoyl chloride in the macrolactonization of seco-acid **44** (Scheme 12). We converted this intermediate to the laulimalide analogue **67** by subsequent desilylation, Lindlar reduction and SAE. This sequence might be used for the generation of a library of C-20 OH ester analogues by simply adding the corresponding acid chlorides to the reaction mixture after macrolactoniza-

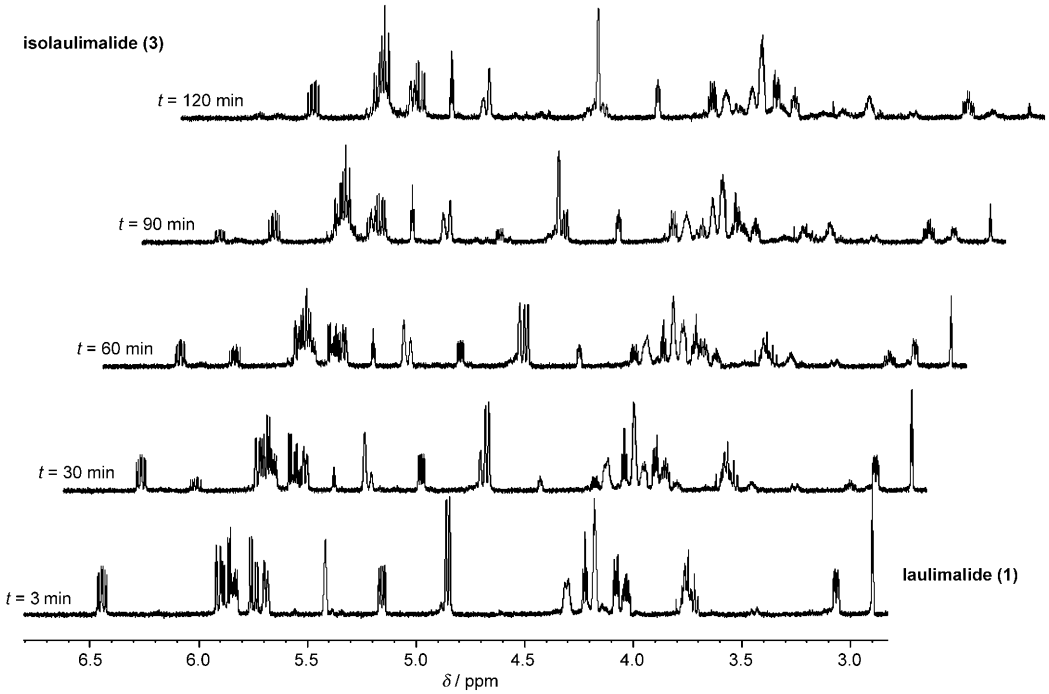
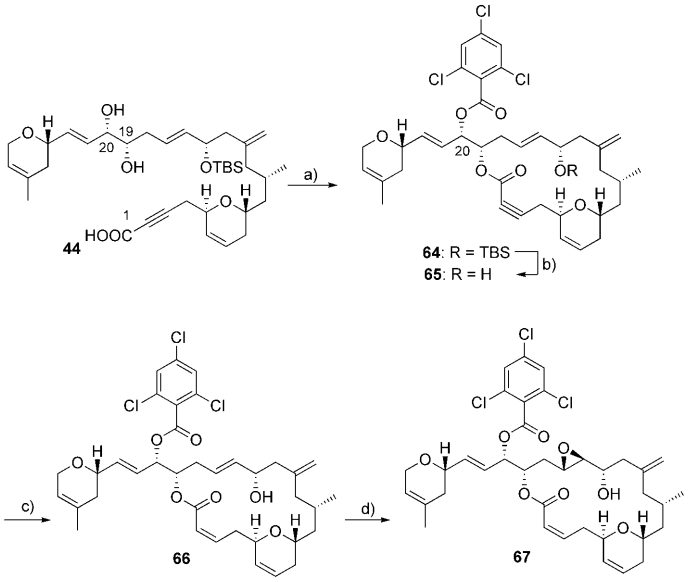


Figure 1. Conversion of laulimalide (**1**) to isolaulimalide (**3**) by treatment with a catalytic amount of TFA in $CDCl_3$, followed by ^1H NMR (600 MHz).



Scheme 12. Synthesis of analogue **67**. a) 2,4,6-$Cl_3C_6H_3C(O)Cl$ (3 equiv), NEt_3, DMAP, benzene, RT (72%); b) 35% HF·pyridine, THF, 0°C to RT (86%); c) H_2, Lindlar cat., quinoline, EtOAc/cyclohexene, RT (70%); d) $Ti(OiPr)_4$, (+)-DIPT, *t*BuOOH, 4 Å MS, CH_2Cl_2, −20°C (71%).

tion. This should enable the synthesis of unnatural analogues like **67** without adding steps to the synthesis.

Biological activities: All synthetic laulimalides (**1**–**3**) were tested for their effects on the proliferation of three tumor cell lines (Table 1), along with the standard epothilone A. **2** showed the same activity as reported in the original isolation publication[1c] and is as active **1**. As expected **3** showed only marginal cytotoxicity. The unnatural analogue **67** was almost inactive. The EC_{50} values for tubulin polymerization (Table 2) showed that neolaulimalide (**2**) induces tubulin polymerization as potent as **1** and epothilone A and is therefore a potent member of the MSAA family.

Table 1. Inhibition of proliferation.[a]

cell line compound	MCF-7	PC-3M IC_{50} [nM]	HCT-116
laulimalide (**1**)	11.6±0.5	5.9±0.3	7.8±0.8
neolaulimalide (**2**)	13.2±0.6	8.4±0.7	4.5±0.6
isolaulimalide (**3**)	4900±200	4400±300	4800±300
67	>10000	>10000	>10000
epothilone A	2.9±0.3	6.4±1.5	2.8±0.4

[a] Cells were treated with varying concentrations of the compounds for 72 h. The values represent the means of three experiments ±SD.

Table 2. Potency for tubulin polymerization of all compounds.[a]

compound	EC_{50} values (αβ-tubulin polymerization)
laulimalide (**1**)	4.0±0.5 μM
neolaulimalide (**2**)	3.9±0.4 μM
isolaulimalide (**3**)	> 10 μM
67	> 10 μM
epothilone A	4.4±0.3 μM

[a] The EC_{50} (half maximal effective concentration) values represent the means of three experiments±SD.

Conclusion

We described a fully stereoselective and flexible approach to the laulimalide family including the first total synthesis of neolaulimalide (**2**) in 21 steps along the longest linear sequence in 3% overall yield. As the compound is now available again for the first time, the biological re-evaluation of **2** was possible and we could prove the promising cytotoxic properties.[1c,d] The more acid stable **2** is as active as **1** and polymerizes tubulin in the same concentration range. Secondly, isolaulimalide (**3**) was synthesized for the first time. This approach which proceeded in 2% yield and 24 linear steps enables the preparation of a range of analogues not accessible from **1** by modifications of the fully stable late stage intermediates **59**/**60**. Finally we made further improvements towards the preparation of larger amounts of laulimalide (**1**) and are now able to present a robust synthesis that starts from cheap materials and produces the compound in 7% yield over 20 linear steps.

Experimental Section

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Anhydrous toluene and Et_2O were distilled from sodium/benzophenone under argon. Anhydrous CH_2Cl_2 was distilled from CaH_2 under argon or reduced pressure, respectively. Anhydrous THF (tetrahydrofurane) was purchased from Acros (99.85%, water $<$ 50 ppm). All other solvents were HPLC grade. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) with E. Merck silica gel 60-F254 plates. Flash column chromatography was performed with Merck silica gel (0.04–0.063 mm, 240–400 mesh) under pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on either Bruker Avance DRX 400 or DRX 600 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal (^1H, $\delta = 7.26$ ppm; ^{13}C, $\delta = 77.16$ ppm). All ^1H and ^{13}C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; br = broad signal). Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy. Optical rotations were measured on a P 341 Perkin-Elmer polarimeter. Mass spectra were measured on a Micro mass, trio 200 Fisions Instruments. High resolution mass spectra (HRMS) were performed with a Finnigan MAT 8230 with a resolution of 10000. The Supporting Information of this paper includes experimental details for compounds **7**, **8**, **14**–**16**; **37**–**42**; **6e**, **53**–**54**, **64**–**67** and NMR spectra of all new compounds.

(S)-1-(2,3-Bis(*tert*-butyldimethylsilyloxy)propyl)cyclopropanol (21): To a stirred solution of TBS-protected diol **20** (21.20 g, 56.3 mmol) in THF (170 mL) at 10°C was added $Ti(OiPr)_4$ (4.80 g, 61.7 mmol). A solution of EtMgBr (56.3 mL, 3 M in Et_2O, 168.9 mmol) was added dropwise over the period of 4 h. After the addition the black solution was stirred for another 1 h at the same temperature. The solvent was removed under vacuum and the oily, black residue was diluted with CH_2Cl_2 (250 mL) and cooled to 0°C. The solution was quenched with aq. sat. NH_4Cl solution (35 mL). The resulting mixture was filtered and the precipitate was washed with CH_2Cl_2 (5×60 mL). The filtrate was washed with aq. sat. $NaHCO_3$ solution, the organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. Crude cyclopropanol **21** (18.9 g) was obtained as a yellow, viscous oil and was used in the next step without further purification. An analytical sample was obtained by column chromatography (silica gel, hexane/EtOAc 20:1) as a clear, colorless oil. $[\alpha]_D^{20} = +13.7$ ($c = 1.15$, in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 4.02–3.95 (m, 1H), 3.70–3.61 (m, 2H), 2.00 (ddd, $J = 14.7$, 5.6, 1.0 Hz, 2H), 1.68 (dd, $J = 14.6$, 5.3 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.79–0.68 (m, 2H), 0.52–0.46 (m, 1H), 0.43–0.37 (m, 1H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 73.6$ (CH), 67.1 (CH_2), 54.0 (C_q), 42.2 (CH_2), 26.0 (3×CH_3), 25.9 (3×CH_3), 18.4 (C_q), 18.1 (C_q), 13.6 (CH_2), 12.6 (CH_2), −4.3 (CH_3), −4.7 (CH_3), −5.2 (CH_3), −5.3 ppm (CH_3); IR (film): $\tilde{\nu} = 3443$, 2956, 2930, 2886, 2858, 1463, 1257, 1119, 837, 778 cm^{-1}; HRMS(EI): m/z: calcd for $C_{18}H_{40}O_3Si_2$: 360.2516, found: 360.2523.

(*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(1-(methylsulfonyloxy)cyclopropyl)-propyl methanesulfonate (22): To a stirred solution of crude **21** (18.8 g) in absolute Et_2O (80 mL) at 0°C was added Et_3N (1.99 g, 197.1 mol). Methanesulfonyl chloride (11.28 g, 98.5 mmol) was added dropwise over a period of 30 min and the reaction was stirred for another 45 min at the same temperature. The reaction was quenched by adding water (80 mL) and the aqueous layer was extracted three times with Et_2O. The organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. Crude mesylate **22** (21.4 g) was obtained as a yellow, viscous oil and was used in the next step without further purification. An analytical sample was obtained by column chromatography (silica gel, hexane/EtOAc 15:1) as a clear, colorless oil. $[\alpha]_D^{20} = -5.0$ ($c =$ 1.10 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.07$–4.00 (m, 1H), 3.63 (dd, $J = 10.1$, 4.3 Hz, 1H), 3.50 (dd, $J = 10$, 6.0 Hz, 1H), 2.99 (s, 3H), 2.42 (dd, $J = 15.2$, 4.0 Hz, 1H), 1.67–1.60 (m, 1H), 1.34–1.25 (m, 1H), 1.24–1.15 (m, 1H), 0.93–0.79 (m, 19H), 0.78–0.71 (m, 1H), 0.09 (s, 6H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 70.7$ (CH), 67.2 (CH_2), 64.4 (C_q), 40.5 (CH_2), 40.1 CH_3), 26.1 (3×CH_3), 26.0 (3x CH_3), 18.5 (C_q), 18.1 (C_q), 12.7 (CH_2), 11.4 (CH_2), −4.3 (CH_3), −4.5 (CH_3), −5.2 ppm (2×CH_3); IR (film): $\tilde{\nu} = 2930$, 2857, 1472, 1361, 1256, 1165, 836, 776, 668 cm^{-1}; HRMS(EI): m/z: calcd for $C_{19}H_{42}O_5SSi_2$: 438.2291, found: 438.2281.

Allylbromide 10: To a stirred solution of crude mesylate **22** (21.4 g) in CH_2Cl_2 (200 mL) was $MgBr_2{\cdot}Et_2O$ (40.7 g, 157.6 mmol). The reaction mixture was refluxed for 3 h, then cooled to 0°C and quenched with H_2O (150 mL). The aqueous layer was extracted three times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained yellow oil was purified by column chromatography (silica gel, hexane/EtOAc 15:1), yielding **10** as clear, colorless oil (17.5 g, 41.3 mmol, 73% over three steps). $[\alpha]_D^{20} = +0.9$ ($c = 1.50$ in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.25$ (brs, 1H), 5.02 (brs, 1H), 4.07 (d, $J = 9.9$ Hz, 1H), 4.01 (d, $J = 9.7$ Hz, 1H), 3.86–3.78 (m, 1H), 3.52 (dd, $J = 10.0$, 5.1 Hz, 1H), 3.41 (dd, $J = 10.0$, 6.7 Hz, 1H), 2.57 (dd, $J = 14.1$, 4.7 Hz, 1H), 2.28 (dd, $J = 14.1$, 6.7 Hz, 1H), 0.90–0.87 (m, 18H), 0.07–0.04 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.8$ (C_q), 118.2 (CH_2), 72.3 (CH), 66.8 (CH_2), 38.2 (CH_2), 37.8 (CH_2), 26.1 (3×CH_3), 26.0 (3×CH_3), 18.5 (C_q), 18.2 (C_q), −4.3 (CH_3), −4.5 (CH_3), −5.2 ppm (2×CH_3); IR (film): $\tilde{\nu} = 2956$, 2930, 2858, 1472, 1256, 1117, 1083, 836, 811, 776 cm^{-1}; HRMS(EI): m/z: calcd for $C_{18}H_{39}O_2BrSi_2$: 422.1672, found: 422.1656.

(*R*)-4-Benzyl-3-((2*S*,6*S*)-6,7-bis(*tert*-butyldimethylsilyloxy)-2-methyl-4-methyleneheptanoyl)oxazolidin-2-one (24): To a stirred solution of Evans *N*-propionyloxazolidinone **23** (9.07 g, 38.9 mmol) in THF (150 mL) was added NaHMDS (44.74 mL, 44.74 mmol, 1 M solution in THF) at −78°C in 30 min. The solution was stirred for 15 min at the same temperature before allylbromide **10** (8.21 g, 19.45 mmol) was added. The reaction was allowed to reach −30°C and stirred for 8 h at this temperature. The reaction was warmed to 0°C and quenched by adding aq. sat. NH_4Cl (150 mL). The aqueous layer was extracted three times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 20:1 → 6:1), yielding **24** as clear, colorless oil (6.82 g, 11.85 mmol, 61%) and unconsumed **10** (1.73 g, 4.085 mmol, 21%). $[\alpha]_D^{20} = 25.1$ ($c = 1.15$ in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$–7.26 (m, 3H), 7.23–7.19 (m, 2H), 4.88 (brs, 1H), 4.86 (brs, 1H), 4.71–4.64 (m, 1H), 4.20–4.12 (m, 2H), 4.03 (dt, $J =$ 14.1, 7.0 Hz, 1H), 3.86–3.79 (m, 1H), 3.52 (dd, $J = 10.1$, 5.3 Hz, 1H), 3.46 (dd, $J = 10.0$, 5.7 Hz, 1H), 3.29 (dd, $J = 13.3$, 3.4 Hz, 1H), 2.67 (dd, $J =$ 13.4, 9.9 Hz, 1H), 2.58 (dd, $J = 14.4$, 7.6 Hz, 1H), 2.34 (dd, $J = 13.9$, 4.8 Hz, 1H), 2.20–2.11 (m, 2H), 1.18 (d, $J = 6.8$ Hz, 3H), 0.89 (brs, 9H),

0.88 (brs, 9H), 0.06 (brs, 3H), 0.05 (brs, 3H), 0.04 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (C_q), 153.2 (C_q), 143.9 (C_q), 135.6 (C_q), 129.6 (2×CH), 129.0 (2×CH), 127.4 (CH), 114.3 (CH_2), 72.3 (CH), 67.3 (CH_2), 66.1 (CH_2), 55.6 (CH), 41.1 (CH_2), 40.4 (CH_2), 38.2 (CH_2), 35.9 (CH), 26.2 (3×CH_3), 26.1 (3×CH_3), 18.5 (C_q), 18.3 (C_q), 17.4 (CH_3), −4.1 (CH_3), −4.5 (CH_3), −5.2 ppm (CH_3); IR (film): $\tilde{\nu}$ = 2955, 2929, 2857, 1784, 1386, 1251, 1103, 835, 776 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{31}H_{53}NO_5Si_2$: 575.3462, found: 575.3457.

(2*S*,6*S*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-2-methyl-4-methyleneheptan-1-ol (25): Compound **24** (6.80 g, 11.81 mmol) was dissolved in Et_2O (150 mL), H_2O (215 μL) was added and the mixture was cooled to 0 °C. $LiBH_4$ (334 mg, 15.35 mmol) was added portionwise over 30 min and the reaction was stirred for another 5 h at the same temperature. The reaction was quenched by adding 0.1 N aq. NaOH (150 mL). The aqueous layer was extracted three times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 7:1), yielding **25** as viscous, colorless oil (4.62 g, 11.47 mmol, 97 %). $[\alpha]_D^{20}$ = −1.2 (*c* = 1.05 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.84 (brs, 1H), 4.82 (brs, 1H), 3.81–3.74 (m, 1H), 3.55–3.49 (m, 2H), 2.48–3.40 (m, 2H), 2.32 (dd, *J* = 13.8, 4.9 Hz, 1H), 2.22–2.12 (m, 1H), 2.07 (dd, *J* = 13.9, 7.1 Hz, 1H), 1.90–1.80 (m, 1H), 1.33 (t, *J* = 5.7 Hz, 1H, OH), 0.92–0.86 (m, 21H), 0.06–0.03 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0 (C_q), 114.0 (CH_2), 72.4 (CH), 68.5 (CH_2), 67.3 (CH_2), 40.9 (CH_2), 40.8 (CH_2), 34.0 (CH), 26.1 (3×CH_3), 26.0 (3×CH_3), 18.5 (C_q), 18.3 (C_q), 16.8 (CH_3), −4.2 (CH_3), −4.5 (CH_3), −5.1 (CH_3), −5.2 ppm (CH_3); IR (film): $\tilde{\nu}$ = 2930, 2859, 1739, 1683, 1652, 1538, 1471, 1464, 1257, 1121, 834, 671 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{21}H_{46}O_3Si_2$: 402.2985, found: 402.2974.

(3*S*,7*S*)-7,8-Bis(*tert*-butyldimethylsilyloxy)-3-methyl-5-methyleneoctane-nitrile (26): Alcohol **25** (300 mg, 0.746 mmol) was dissolved in Et_2O (10 mL) and cooled to 0 °C. PPh_3 (401 mg, 1.490 mmol) and DIAD (301 mg, 1.490 mmol) were added followed by acetone cyanohydrin (137 μL, 128 mg, 1.490 mmol). The yellow reaction mixture was stirred at 0 °C for 1 h and allowed to warm to RT overnight. The reaction mixture was flashed through a short pad of silica gel and the solvent was removed under vacuum. The crude product was purified by column chromatography (silica gel, hexane/EtOAc 20:1), yielding **26** as slightly yellow oil (288 mg, 0.699 mmol, 94 %). $[\alpha]_D^{20}$ = +3.2 (*c* = 1.45 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (brs, 1H), 4.85 (brs, 1H), 3.79–3.72 (m, 1H), 3.52 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.41 (dd, *J* = 10.0, 6.4 Hz, 1H), 2.38–2.27 (m, 2H), 2.21 (dd, *J* = 16.8, 6.7 Hz, 1H), 2.14–1.99 (m, 4H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.89 (brs, 9H), 0.87 (brs, 9H), 0.06–0.04 (m, 9H), 0.04 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6 (C_q), 118.8 (C_q), 115.1 (CH_2), 72.5 (CH), 67.0 (CH_2), 43.5 (CH_2), 40.4 (CH_2), 28.7 (CH), 26.1 (3×CH_3), 26.0 (3×CH_3), 24.2 (CH_2), 19.6 (CH_3), 18.5 (C_q), 18.3 (C_q), −4.2 (CH_3), −4.6 (CH_3), −5.2 ppm (2×CH_3); IR (film): $\tilde{\nu}$ = 2956, 2930, 2858, 1733, 1557, 1505, 1472, 1464, 1257, 1115, 835, 777 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{22}H_{45}NO_2Si_2$: 411.2989, found: 411.2986.

(3*S*,7*S*)-7,8-Bis(*tert*-butyldimethylsilyloxy)-3-methyl-5-methyleneoctanal (27): Cyanide **26** (2.63 g, 6.387 mmol) was dissolved in CH_2Cl_2 (65 mL) and cooled to −78 °C. DIBAL (6.39 mL, 9.581 mmol, 1.5 M in toluene) was added drop wise over 15 min and the reaction was stirred for 45 min at the same temperature before it was allowed to warm to RT. The reaction was stirred for 5 h at RT and then cooled again to −78 °C. EtOAc (2 mL) was added and the reaction was allowed to warm to 0 °C before it was poured into a flask containing sat. aq. KNa-tartrate (200 mL) and EtOAc (200 mL). The cloudy mixture was stirred vigorous for 6 h. The aqueous layer was extracted three times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 10:1), yielding **27** as colorless oil 2.43 g (5.856 mmol, 92 %). $[\alpha]_D^{20}$ = −6.8 (*c* = 1.05 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (t, *J* = 2.0 Hz, 1H), 4.87 (brs, 1H), 4.80 (brs, 1H), 3.80–3.73 (m, 1H), 3.52 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.42 (dd, *J* = 10.0, 6.2 Hz, 1H), 2.47–2.40 (m, 1H), 2.31 (ddd, *J* = 14.0, 4.9, 0.8 Hz, 1H), 2.27–2.16 (m, 2H), 2.09–2.01 (m, 2H), 1.98 (dd, *J* = 13.9, 7.1 Hz, 1H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.89 (brs, 9H), 0.87 (brs, 9H), 0.05–0.04 (m, 9H), 0.03 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7 (C_q), 144.4 (C_q), 114.7 (CH_2), 72.5 (CH), 67.2 (CH_2), 50.9 (CH_2), 44.4 (CH_2), 40.6 (CH_2), 26.5 (CH), 26.1 (3×CH_3), 26.0 (3×CH_3), 20.1 (CH_3), 18.5 (C_q), 18.3 (C_q), −4.2 (CH_3), −4.5 (CH_3), −5.1 (CH_3), −5.2 ppm (CH_3); IR (film): $\tilde{\nu}$ = 2956, 2930, 2858, 1729, 1472, 1361, 1256, 1119, 1006, 836, 776 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{22}H_{46}O_3Si_2$: 414.2985, found:. 414.2988.

(4*S*,6*S*,10*S*)-10,11-Bis(*tert*-butyldimethylsilyloxy)-6-methyl-8-methylene-undec-1-en-4-ol (9): Aldehyde **27** (2.40 g, 5.786 mmol) was dissolved in Et_2O (70 mL) and cooled to −100 °C. A solution of (−)-Ipc-allylborane (10.49 mL, 8.390 mmol, 0.8 M solution in pentane) was added precooled (−78 °C) via a cannula in 20 min. The reaction was stirred at −100 °C for 2 h and quenched by adding MeOH (4 mL). The reaction was warmed to RT and the solvent was removed under vacuum. The residue was taken up in H_2O/THF 1:1 (120 mL), $NaBO_3{\cdot}4H_2O$ (2.23 g, 14.465 mmol) was added and the mixture was stirred overnight. The solution was diluted with brine (100 mL) and extracted three times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 40:1), yielding **9** as colorless oil (2.43 g, 5.509 mmol, 95 %, d.r. 16:1 determined by HPLC). $[\alpha]_D^{20}$ = +9.5 (*c* = 1.05 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89–5.77 (m, 1H), 5.17–5.13 (m, 1H), 5.13–5.10 (m, 1H), 4.82 (brs, 1H), 4.78 (brs, 1H), 3.81–3.71 (m, 2H), 3.51 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.43 (dd, *J* = 9.9, 5.8 Hz, 1H), 2.32–2.23 (m, 2H), 2.20–2.11 (m, 1H), 2.08–1.99 (m, 2H), 1.92–1.84 (m, 2H), 1.54–1.46 (m, 1H), 1.44 (d, *J* = 4.2 Hz, 1H, OH), 1.27–1.11 (m, 1H), 0.90–0.88 (m, 12H), 0.87 (brs, 9H), 0.05–0.04 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9 (C_q), 135.0 (CH), 118.2 (CH_2), 113.9 (CH_2), 72.3 (CH), 68.6 (CH), 67.4 (CH_2), 45.1 (CH_2), 44.4 (CH_2), 43.0 (CH_2), 40.9 (CH_2), 27.5 (CH), 26.2 (3×CH_3), 26.1 (3×CH_3), 19.4 (CH_3), 18.5 (C_q), 18.3 (C_q), −4.1 (CH_3), −4.5 (CH_3), −5.1 (CH_3), −5.2 ppm (CH_3); IR (film): $\tilde{\nu}$ = 3368, 2929, 2858, 1643, 1472, 1361, 1256, 1117, 991, 836, 776 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{25}H_{52}O_3Si_2$: 456.3455, found: 456.3451.

2-((2*R*,6*R*)-6-((2*S*,6*S*)-6,7-Bis(*tert*-butyldimethylsilyloxy)-2-methyl-4-methyleneheptyl)-5,6-dihydro-2*H*-pyran-2-yl)acetaldehyde (28): Acrolein diethyl acetal (6 mL) and a catalytic amount of PPTS were added to homoallylalcohol **9** (2.41 g, 5.275 mmol) in toluene (75 mL). The mixture was rotated on a rotary evaporator at 80 mbar and 40 °C to remove the liberated EtOH. The volume of the reaction was kept constant by adding toluene occasionally. After 90 min the reaction was concentrated to about 5 mL and purified by column chromatography (silica gel, hexane/EtOAc 50:1 + 1 % Et_3N). The obtained mixed acetal was used immediately for the next step. Grubbs' catalyst 1st gen. (224 mg, 0.264 mmol) was added in one portion to the mixed acetal dissolved in degased CH_2Cl_2 (300 mL) at 40 °C and the reaction was refluxed overnight. The reaction was cooled to RT and air was bubbled through the reaction for 10 min. The solvent was reduced to 20 mL and vinyloxytrimethylsilane (3.07 g, 26.375 mmol) and montmorillonite K10 (2.5 g) were added. After sirring for 10 min the reaction was filtered through a short pad of silica gel and concentrated in vacuum. The obtained brown oil was purified by column chromatography (silica gel, hexane/EtOAc 20:1), yielding **28** as colorless oil (1.89 g, 3.699 mmol, 70 %, over two steps). $[\alpha]_D^{20}$ = −32.0 (*c* = 1.12 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82–9.79 (m, 1H), 5.90–5.85 (m, 1H), 5.72–5.76 (m, 1H), 4.82 (brs, 1H), 4.80–4.71 (m, 2H), 3.80–3.71 (m, 2H), 3.49 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.44 (dd, *J* = 10.0, 5.6 Hz, 1H), 2.73 (ddd, *J* = 16.2, 8.9, 3.0 Hz, 1H), 2.53 (ddd, *J* = 16.2, 4.8, 1.8 Hz, 1H), 2.25 (dd, *J* = 13.8, 5.6 Hz, 1H), 3.09–1.81 (m, 6H), 1.69–1.60 (m, 1H), 1.15–1.06 (m, 1H), 0.90–0.83 (m, 21H), 0.05 (brs, 3H), 0.04–0.03 ppm (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1 (CH), 144.9 (C_q), 128.0 (CH), 125.8 (CH), 113.8 (CH_2), 72.4 (CH), 68.0 (CH), 67.5 (CH_2), 65.7 (CH_2), 48.1 (CH_2), 45.1 (CH_2), 42.4, (CH_2), 41.0 (CH_2), 31.1 (CH_2), 26.9 (CH), 26.2 (3×CH_3), 26.1 (3×CH_3), 19.4 (CH_3), 18.5 (C_q), 18.3 (C_q), −4.2 (CH_3), −4.5 (CH_3), −5.1 (CH_3), −5.2 ppm (CH_3); IR (film): $\tilde{\nu}$ = 2928, 1730, 1472, 1361, 1256, 1097, 835, 775 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{28}H_{54}O_4Si_2$: 510.3561, found:. 510.3556.

TBS-ether 29: To a solution of aldehyde **28** (1.87 g, 3.660 mmol) in MeOH (10 mL) was added K_2CO_3 (1.01 g, 7.320 mmol) and Bestman–

Ohira reagent (879 mg, 4.575 mmol). After stirring for 4 h at RT the reaction was quenched by adding sat. aq. $NaHCO_3$ solution (10 mL), diluted with H_2O (10 mL) and extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 30:1), yielding **29** as colorless oil (1.39 g, 2.737 mmol, 75%). $[\alpha]_D^{20} = -49.5$ ($c = 1.00$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.93$–5.82 (m, 2H), 4.81 (brs, 1H), 4.78 (brs, 1H), 4.36–4.28 (m, 1H), 3.85–3.73 (m, 2H), 3.54–3.40 (m, 2H), 2.55–2.39 (m, 2H), 2.32–2.23 (m, 1H), 2.10–1.83 (m, 7H), 1.68–1.57 (m, 1H), 1.16–1.07 (m, 1H), 0.90–0.80 (m, 21H), 0.06–0.03 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 145.0$ (C_q), 128.1 (CH), 125.7 (CH), 113.8 (CH_2), 81.2 (C_q), 72.4 (CH), 70.9 (CH), 70.2 (CH), 67.5 (CH_2), 66.1 (CH), 45.1 (CH_2), 42.6 (CH_2), 41.0 (CH_2), 31.3 (CH_2), 27.0 (CH), 26.2 ($3\times CH_3$), 26.1 ($3\times CH_3$), 24.7 (CH_2), 19.4 (CH_3), 18.5 (C_q), 18.3 (C_q), −4.1 (CH_3), −4.5 (CH_3), −5.1 (CH_3), −5.2 ppm (CH_3); IR (film): $\tilde{\nu} = 3314$, 2954, 2928, 1642, 1472, 1255, 1093, 835, 776, 708 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{29}H_{54}O_3Si_2$: 506.3611, found: 506.3604.

(2*S*,6*S*)-2-(*tert*-Butyldimethylsilyloxy)-6-methyl-4-methylene-7-((2*R*,6*R*)-6-(prop-2-ynyl)-3,6-dihydro-2*H*-pyran-2-yl)heptan-1-ol (30): To a stirred solution of compound **29** (1.38 g, 2.72 mmol) in MeOH (10 mL) was added NH_4F (4 g) and stirred at RT for 32 h. To the reaction was added H_2O (50 mL) and it was extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 20:1 → 10:1), yielding **30** as colorless oil (699 mg, 1.78 mmol, 65%, 95% based on recovered starting material) along with recovered **29** (408 mg, 0.80 mmol). $[\alpha]_D^{20} = -57.0$ ($c = 1.00$, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.92$–5.88 (m, 1H), 5.86–5.83 (m, 1H), 4.82 (brs, 1H), 4.80 (brs, 1H), 4.35–4.30 (m, 1H), 3.90–3.84 (m, 1H), 3.83–3.78 (m, 1H), 3.60–3.55 (m, 1H), 3.47–3.42 (m, 1H), 2.51 (ddd, $J = 16.4$, 6.9, 2.7 Hz, 1H), 2.43 (ddd, $J = 16.6$, 7.1, 2.6 Hz, 1H), 2.25–2.18 (m, 2H), 2.01 (t, $J = 2.8$ Hz, 1H), 2.00–1.95 (m, 3H), 1.95–1.87 (m, 3H), 1.65–1.59 (m, 1H), 1.08 (ddd, $J = 14.0$, 9.4 3.0 Hz, 1H), 0.91–0.89 (m, 12H), 0.10 (brs, 3H), 0.09 ppm (brs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 144.4$ (C_q), 128.1 (CH), 125.8 (CH), 114.1 (CH_2), 81.2 (C_q), 71.6 (CH), 71.0 (CH), 70.2 (CH), 66.2 (CH_2), 65.9 (CH), 45.1 (CH_2), 42.3 (CH_2), 40.6 (CH_2), 31.3 (CH_2), 27.0 (CH), 26.0 ($3\times CH_3$), 24.6 (CH_2), 19.6 (CH_3), 18.3 (C_q), −4.1 (CH_3), −4.5 ppm (CH_3); IR (film): $\tilde{\nu} = 3452$, 3312, 2928, 1256, 1092, 837, 777, 611 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{23}H_{40}O_3Si_2$: 392.2747, found: 392.2751.

(2*S*,6*S*)-2-(*tert*-Butyldimethylsilyloxy)-6-methyl-4-methylene-7-((2*R*,6*R*)-6-(prop-2-ynyl)-3,6-dihydro-2*H*-pyran-2-yl)heptanal (5): To a refluxing solution of alcohol **30** (550 mg, 1.40 mmol) in MeCN was added IBX (784 mg, 2.80 mmol) in one portion. The reaction was refluxed for 20 min, cooled to RT and filtered over celite. The solvent was removed under vacuum and the obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 10:1), yielding **5** as colorless oil (535 mg, 1.37 mmol, 98%). $[\alpha]_D^{20} = -72.4$ ($c = 1.00$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.59$ (d, $J = 1.8$ Hz, 1H), 5.93–5.89 (m, 1H), 5.86–5.81 (m, 1H), 4.87 (brs, 1H), 4.86 (brs, 1H), 4.36–4.30 (m, 1H), 4.09 (ddd, $J = 7.6$, 5.3, 1.8 Hz, 1H), 3.84–3.76 (m, 1H), 2.51 (ddd, $J = 16.5$, 7.0, 2.7 Hz, 1H), 2.42 (ddd, $J = 16.4$, 7.0, 2.7 Hz, 1H), 2.38 (dd, $J = 14.1$, 4.9 Hz, 1H), 2.29 (dd, $J = 14.2$, 7.5 Hz, 1H), 2.06–2.00 (m, 1H), 2.02 (t, $J = 2.7$ Hz, 1H), 2.00–1.85 (m, 4H), 1.61 (ddd, $J = 13.8$, 9.9, 3.4 Hz, 1H), 1.11 (ddd, $J = 13.9$, 9.1, 3.1 Hz, 1H), 0.90 (brs, 9H), 0.89 (d, $J = 6.2$ Hz, 3H), 0.07 (brs, 3H), 0.05 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 203.5$ (CH), 142.7 (C_q), 128.1 (CH), 125.8 (CH), 115.2 (CH_2), 81.2 (C_q), 76.7 (CH), 71.2 (CH), 70.2 (CH), 66.2 (CH), 44.9 (CH_2), 42.6 (CH_2), 39.0 (CH_2), 31.3 (CH_2), 26.9 (CH), 25.9 ($3\times CH_3$), 24.6 (CH_2), 19.3 (CH_3), 18.3 (C_q), −4.5 (CH_3), −4.7 ppm (CH_3); IR (film): $\tilde{\nu} = 3314$, 2929, 1737, 1092, 839, 778, 611 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{23}H_{38}O_3Si$: 390.2590, found: 390.2586.

(*S*,*E*)-4-(4-Methoxybenzyloxy)-1-((*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)-6-(1-phenyl-1*H*-tetrazol-5-ylthio)hex-1-en-3-one (32a): To a solution of compound **31a** (3.77 g, 8.184 mmol) in THF (35 mL) was added 7% HF/pyridine (13 mL) over a period of 5 min at RT. The reaction was stirred 30 min and quenched with sat. aq. $NaHCO_3$ solution (90 mL) and extracted four times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 1:1 + 1% Et_3N), yielding the labile alcohol as colorless, viscous oil (2.76 g, 7.98 mmol, 98%) which was immediately used for the next step. A solution of OTES deprotected **31a** (2.71 g, 7.823 mmol) in THF (35 mL) was cooled to 0 °C and added PPh_3 (3.08 g, 11.734 mmol), 1-phenyl-1*H*-tetrazol-5-thiol (2.09 g, 11.734 mmol) and DEAD (2.45 g, 14.081 mmol). The reaction was stirred at 0 °C for 1 h and 4 h at RT. The reaction was quenched by adding sat. aq. $NaHCO_3$ solution (60 mL) and extracted four times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 3:1), yielding sulfide **32a** as colorless oil (3.66 g, 7.224 mmol, 92%). $[\alpha]_D^{20} = -97.5$ ($c = 1.10$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$–7.51 (m, 5H), 7.28–7.22 (m, 2H), 7.03 (dd, $J = 15.7$, 4.0 Hz, 1H), 6.85 (d, $J = 8.6$ Hz, 2H), 6.74 (dd, $J = 15.8$, 1.8 Hz, 1H), 5.45 (brs, 1H), 4.56 (d, $J = 11.4$ Hz, 1H), 4.32 (d, $J = 11.3$ Hz, 1H), 4.28–4.15 (m, 3H), 4.10 (dd, $J = 8.7$, 4.4 Hz, 1H), 3.79 (s, 3H), 3.54–3.40 (m, 2H), 2.30–2.12 (m, 2H), 2.11–1.93 (m, 2H), 1.72 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 200.5$ (C_q), 159.7 (C_q), 154.1 (C_q), 147.7 (CH), 133.8 (C_q), 131.2 (C_q), 130.2 (CH), 130.1 ($2\times CH$), 129.9 ($2\times CH$), 129.3 (C_q), 123.9 ($2\times CH$), 122.8 (CH), 119.9 (CH), 114.1 ($2\times CH$), 81.6 (CH), 72.7 (CH), 72.7 (CH_2), 65.9 (CH_2), 55.5 (CH), 35.1 (CH_2), 31.7 (CH_2), 29.5 (CH_2), 23.0 ppm (CH_3); IR (film): $\tilde{\nu} = 3469$, 2930, 2150, 1692, 1612, 1384, 1302, 1247, 1090, 761, 516 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{27}H_{30}O_4N_4SNa$: 529.1885, found: 529.1878.

(3*S*,4*S*,*E*)-4-(4-Methoxybenzyloxy)-1-((*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)-6-(1-phenyl-1*H*-tetrazol-5-ylthio)hex-1-en-3-ol (33a): Compound **32a** (3.61 g, 7.097 mmol) was dissolved in MeOH (35 mL) and cooled to −100 °C. $CeCl_3 \cdot 7H_2O$ (4.49 g, 12.066 mmol) was added and stirred for 10 min. Following $NaBH_4$ (398 mg, 10.646 mmol) was added in three portions and stirred for 90 min at the same temperature. The reaction was quenched by adding EtOAc (2 mL) and warmed to RT. H_2O (60 mL) was added and extracted four times with EtOAc. The combined organic phase was washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 1:1), yielding alcohol **33a** as colorless oil (3.53 g, 6.940 mmol, 98%). $[\alpha]_D^{20} = -59.4$ ($c = 1.20$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$–7.54 (m, 5H), 7.27 (d, $J = 7.6$ Hz, 2H), 6.86 (d, $J = 7.8$ Hz, 2H), 5.89 (dd, $J = 15.7$, 4.9 Hz, 1H), 5.80 (ddd, $J = 15.7$, 5.8, 1.0 Hz, 1H), 5.41 (brs, 1H), 4.62- 4.55 (m, 2H), 4.21–4.15 (m, 3H), 4.07–4.01 (m, 1H), 3.79 (s, 3H), 3.58–3.52 (m, 1H), 3.49–3.40 (m, 2H), 2.39 (d, $J = 4.8$ Hz, 1H, OH), 2.21–2.11 (m, 1H), 2.10–2.00 (m, 2H), 1.95–1.87 (m, 1H), 1.70 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.6$ (C_q), 154.4 (C_q), 133.8 (C_q), 133.5 (CH), 131.5 (C_q), 130.2 (CH), 130.1 (C_q), 130.0 ($4\times CH$), 129.8 (CH), 124.0 ($2\times CH$), 119.8 (CH), 114.1 ($2\times CH$), 80.2 (CH), 73.7 (CH), 73.4 (CH), 72.9 (CH_2), 65.8 (CH_2), 55.4 (CH_3), 35.8 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 23.1 ppm (CH_3); IR (film): $\tilde{\nu} = 3430$, 2359, 1612, 1513, 1384, 1247, 1174, 1032, 762 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{27}H_{32}O_4N_4S$: 508.2144, found: 508.2158.

Sulfide 34a: To a stirred solution of **33a** (85 g, 0.136 mmol) in CH_2Cl_2 (2 mL) at −30 °C was added 2,6-lutidine (25.5 mg, 0.238 mmol) and dropwise TESOTf (54 mg, 0.204 mmol). The reaction was stirred at the same temperature for 20 min, then allowed to warm to RT and stirred for another 3 h. The reaction was quenched with aq. sat. $NaHCO_3$ (5 mL) and extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained viscous oil was purified by column chromatography (silica gel, hexane/EtOAc 10:1), yielding sulfide **34a** as colorless, viscous oil (83 mg, 0.127 mmol, 93%). $[\alpha]_D^{20} = -50.8$ ($c = 1.50$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.56$–7.53 (m, 5H), 7.25 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 5.82 (dd, $J = 15.7$, 3.8 Hz, 1H), 5.76 (dd, $J = 15.7$, 4.5 Hz, 1H), 5.40 (brs, 1H), 4.64 (d, $J = 11.4$ Hz, 1H), 4.47 (d, $J = 11.4$ Hz, 1H), 4.38 (t, $J = 4.3$ Hz, 1H), 4.16 (brs, 2H), 4.07–4.01 (m, 1H), 3.78 (s, 3H), 3.54–3.46 (m, 2H), 3.39–3.32 (m, 1H), 2.14–1.99 (m, 2H), 1.89 (brd, $J = 17.7$ Hz, 1H), 1.85–1.73 (m, 1H), 1.70 (brs, 3H), 0.85 (brs, 9H), 0.02 (brs, 3H), 0.01 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.5$ (C_q), 154.5 (C_q), 134.0 (C_q), 132.2 (CH), 131.6 (C_q), 130.5 (C_q),

130.1 (CH), 129.9 (2×CH), 129.8 (2×CH), 129.5 (CH), 123.9 (2×CH), 119.9 (CH), 114.0 (2×CH), 80.0 (CH), 73.6 (CH), 72.4 (CH), 72.2 (CH_2), 65.7 (CH_2), 55.4 (CH_3), 35.9 (CH_2), 30.5 (CH_2), 29.0 (CH_2), 25.9 (3×CH_3), 23.1 (CH_3), 18.3 (C_q), −4.4 (CH_3), −4.8 ppm (CH_3); IR (film): $\tilde{\nu}$= 3400, 2930, 2856, 1718, 1611, 1512, 1500, 1249, 1073, 976, 837, 778, 694 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{33}H_{46}O_4N_4SSiNa$: 645.2907, found: 645.2912.

Sulfide 34b: To a stirred solution of **33a** (1.21 g, 2.379 mmol) in CH_2Cl_2 (20 mL) at −30 °C was added 2,6-lutidine (446 mg, 4.163 mmol) and dropwise TESOTf (943 mg, 3.569 mmol). The reaction was stirred at the same temperature for 20 min, then allowed to warm to RT and stirred for another 2 h. The reaction was cooled to −30 °C again and Et_3N (1 mL) was added. The reaction was quenched with aq. sat. $NaHCO_3$ (20 mL), warmed to RT and extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained viscous oil was purified by column chromatography (silica gel, hexane/EtOAc 10:1 + 1% Et_3N), yielding sulfide **34b** as colorless, viscous oil (1.38 g, 2.215 mmol, 93%). $[\alpha]_D^{20}=-69.4$ ($c=1.00$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.57$–7.52 (m, 5H), 7.25 (d, $J=8.9$ Hz, 2H), 6.84 (d, $J=8.9$ Hz, 2H), 5.81–5.78 (m, 2H), 5.41 (brs, 1H), 4.64 (d, $J=11.4$ Hz, 1H), 4.47 (d, $J=11.4$ Hz, 1H), 4.38–4.35 (m, 1H), 4.19–4.14 (m, 2H), 4.06–4.00 (m, 1H), 3.78 (s, 3H), 3.54–3.46 (m, 2H), 3.40–3.31 (m, 1H), 2.13–1.98 (m, 2H), 1.89 (brd, $J=17.0$ Hz, 1H), 1.85–1.73 (m, 1H), 1.70 (brs, 3H), 0.91 (t, $J=7.9$ Hz, 9H), 0.56 ppm (q, $J=7.9$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 159.5 (C_q), 154.6 (C_q), 134.0 (C_q), 132.3 (CH), 131.6 (C_q), 130.6 (C_q), 130.1 (CH), 129.9 (2×CH), 129.8 (2×CH), 129.5 (CH), 123.9 (2×CH), 119.9 (CH), 114.0 (2×CH), 80.1 (CH), 73.6 (CH), 72.5 (CH), 72.5 (CH_2), 65.7 (CH_2), 55.4 (CH_3), 35.9 (CH_2), 30.5 (CH_2), 29.2 (CH_2), 23.1 (CH_3), 7.0 (3×CH_3), 5.0 ppm (3×CH_2); IR (film): $\tilde{\nu}$=2954, 1611, 1512, 1500, 1456, 1382, 1246, 1173, 1014, 974, 744; HRMS(EI): *m/z*: calcd for $C_{33}H_{46}O_4N_4SSiNa$: 645.2907, found: 645.2916.

Sulfide 34c: To a solution of **33a** (2.12 g, 4.168 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added EtN*i*Pr_2 (5.39 g, 41.680 mmol) and subsequent dropwise MOMCl (1.68 g, 20.840 mmol). The reaction was allowed to reach RT and was stirred for 24 h. The reaction was quenched by adding sat. aq. NH_4Cl solution (20 mL) and extracted four times with Et_2O. The combined organic phase was washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained colorless oil was purified by column chromatography (silica gel, hexane/EtOAc 3:1), yielding sulfide **34c** as colorless oil (2.26 g, 4.089 mmol, 98%). $[\alpha]_D^{20}=-62.1$ ($c=1.00$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.57$–7.52 (m, 5H), 7.25 (d, $J=8.6$ Hz, 2H), 6.83 (d, $J=$ 8.6 Hz, 2H), 5.83 (ddd, $J=15.7$, 5.4, 0.8 Hz, 1H), 5.67 (ddd, $J=15.7$, 6.8, 1.3 Hz, 1H), 5.41 (brs, 1H), 4.71–4.67 (m, 2H), 4.57 (d, $J=6.8$ Hz, 1H), 4.50 (d, $J=11.2$ Hz, 1H), 4.26–4.21 (m, 1H), 4.19–4.14 (m, 2H), 4.07–4.00 (m, 1H), 3.77 (s, 3H), 3.65–3.59 (m, 1H), 3.51–3.43 (m, 1H), 3.34 (s, 3H), 2.13–2.05 (m, 1H), 2.04–1.99 (m, 1H), 1.97–1.85 (m, 2H), 1.69 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.5$ (C_q), 154.5 (C_q), 133.9 (C_q), 131.5 (C_q), 130.4 (CH), 130.0 (2×CH), 129.9 (2×CH), 126.9 (CH), 123.9 (2×CH), 119.8 (CH), 114.0 (2×CH), 94.6 (CH_2), 78.8 (CH), 77.4 (CH), 73.4 (CH), 72.8 (CH_2), 65.8 (CH_2), 55.8 (CH_3), 55.4 (CH_3), 35.9 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 23.0 ppm (CH_3); IR (film): $\tilde{\nu}$=2931, 1612, 1513, 1500, 1384, 1247, 1032, 821, 762, 694 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{29}H_{36}O_5N_4SNa$: 575.2304, found: 575.2321.

Sulfone 6a: Ammonium molybdate (59 mg) was added to H_2O_2 (30% aqueous solution, 0.33 mL) at 0 °C and stirred for 15 min. The yellow solution was added dropwise to a solution of **34a** (130 mg, 0.209 mmol) in EtOH (4 mL) at 0 °C and stirred for 30 min before it was allowed to reach RT. After stirring for another 3.5 h the reaction was diluted with aq. sat. $NaHCO_3$ (10 mL) and extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 4:1), yielding sulfone **6a** as viscous oil (100 mg, 0.153 mmol, 73%). $[\alpha]_D^{20}=-61.9$ ($c=1.10$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.68$–7.64 (m, 2H), 7.62–7.56-(m, 5H), 7.25 (d, $J=6.4$ Hz, 2H), 6.89 (d, $J=6.4$ Hz, 2H), 5.85–5.76 (m, 2H), 5.41 (brs, 1H), 4.62 (d, $J=11.4$ Hz, 1H), 4.48 (d, $J=11.4$ Hz, 1H), 4.39–4.36 (m, 1H), 4.17 (brs, 2H), 4.07–4.02 (m, 1H), 3.81 (s, 3H), 3.80–3.73 (m, 1H), 3.69–3.59 (m, 1H), 3.53 (ddd, $J=9.0$, 4.4, 4.3 Hz, 1H), 2.19 (ddd, $J=19.3$, 9.7, 4.6 Hz, 1H), 2.08–1.86 (m, 3H), 1.70 (brs, 3H), 0.88 (brs, 9H), 0.03 ppm (brs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.7$ (C_q), 153.6 (C_q), 133.3 (C_q), 132.7 (CH), 131.5 (CH), 130.1 (2×C_q), 129.9 (2×CH), 129.8 (2×CH), 128.7 (CH), 125.3 (2×CH), 119.9 (CH), 114.2 (2×CH), 79.3 (CH), 73.4 (CH), 72.4 (CH_2), 72.4 (CH), 65.7 (CH_2), 55.5 (CH_3), 53.3 (CH_2), 35.9 (CH_2), 26.0 (3×CH_3), 23.1 (CH_3), 22.6 (CH_2), 18.3 (C_q), −4.4 (CH_3), −4.8 ppm (CH_3); IR (film): $\tilde{\nu}=2954$, 2856, 1611, 1513, 1498, 1342, 1249, 1150, 1101, 836, 762 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{33}H_{46}O_6N_4SSiNa$: 677.2805, found: 677.2803.

Sulfone 6b: Ammonium molybdate (1.1 g, 0.98 mmol) was added to H_2O_2 (30% aqueous solution, 2.4 mL) and phosphate buffer (0.5 M, 1.2 mL) at 0 °C and stirred for 15 min. The yellow solution was added dropwise to a solution of **34b** (950 mg, 1.525 mmol) in EtOH (20 mL) at 0 °C and stirred for 30 min before it was allowed to reach RT. After stirring for another 4 h the reaction was diluted with aq. sat. $NaHCO_3$ (35 mL) and extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 4:1), yielding sulfone **6b** as viscous oil (612 mg, 0.935 mmol, 61%). $[\alpha]_D^{20}=-27.5$ ($c=1.10$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.61$–7.55 (m, 5H), 7.25 (d, $J=8.6$ Hz, 2H), 6.89 (d, $J=8.6$ Hz, 2H), 5.84–5.76 (m, 2H), 5.41 (brs, 1H), 4.62 (d, $J=11.4$ Hz, 1H), 4.48 (d, $J=11.4$ Hz, 1H), 4.39–4.35 (m, 1H), 4.19–4.14 (m, 2H), 4.08–4.02 (m, 1H), 3.81 (s, 3H), 3.80–3.73 (m, 1H), 3.68–3.59 (m, 1H), 3.54–3.49 (m, 1H), 2.24–2.13 (m, 1H), 2.08–1.98 (m, 2H), 1.98–1.86 (m, 2H), 1.70 (brs, 3H), 0.91 (t, $J=7.9$ Hz, 9H), 0.56 (q, $J=7.9$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.7$ (C_q), 153.6 (C_q), 133.2 (C_q), 132.8 (CH), 131.6 (CH), 130.1 (2×C_q), 129.9 (2×CH), 129.8 (2×CH), 128.8 (CH), 125.3 (2×CH), 119.9 (CH), 114.1 (2×CH), 79.4 (CH), 73.4 (CH), 72.6 (CH), 72.5 (CH_2), 65.7 (CH_2), 55.5 (CH_3), 53.3 (CH_2), 35.8 (CH_2), 23.1 (CH_3), 22.6 (CH_2), 7.0 (3×CH_3), 5.0 (3×CH_3); IR (film): $\tilde{\nu}=$ 2954, 2875, 1611, 1513, 1498, 1342, 1248, 1150, 1100, 821, 743 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{33}H_{46}O_6N_4SSiNa$: 677.2805, found: 677.2814.

Sulfone 6c: Ammonium molybdate (1.1 g, 0.87 mmol) was added to H_2O_2 (30% aqueous solution, 4.4 mL) at 0 °C and stirred for 15 min. The yellow solution was added dropwise to a solution of **34c** (2.21 g, 4.000 mmol) in EtOH (40 mL) at 0 °C and stirred for 45 min before it was allowed to reach RT. After stirring for another 3.5 h the reaction was diluted with H_2O (50 mL) and extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 4:1), yielding sulfone **6c** as white crystals (1.77 g, 3.027 mmol, 76%). M.p. 85–86 °C; $[\alpha]_D^{20}=$ −34.1 ($c=1.10$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.68$–7.55 (m, 5H), 7.26 (d, $J=8.2$ Hz, 2H), 6.88 (d, $J=6.8$ Hz, 2H), 5.85 (dd, $J=$ 15.8, 5.3 Hz, 1H), 5.68 (dd, $J=15.8$, 6.7 Hz, 1H), 5.41 (brs, 1H), 4.68 (d, $J=6.8$ Hz, 1H), 4.67 (d, $J=11.4$ Hz, 1H), 4.57 (d, $J=6.8$ Hz, 1H), 4.50 (d, $J=11.4$ Hz, 1H), 4.25 (t, $J=5.9$ Hz, 1H), 4.19–4.15 (m, 2H), 4.08–4.01 (m, 1H), 3.84–3.75 (m, 1H), 3.81 (s, 3H), 3.67–3.59 (m, 2H), 3.36 (s, 3H), 2.26–2.16 (m, 1H), 2.09–1.98 (m, 2H), 1.90 (brd, $J=16.7$ Hz, 1H), 1.70 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.6$ (C_q), 153.6 (C_q), 135.6 (CH), 133.2 (C_q), 131.6 (CH), 131.5 (C_q), 130.0 (2×CH), 129.9 (C_q), 129.8 (2×CH), 126.1 (CH), 125.3 (2×CH), 119.8 (CH), 114.1 (2×CH), 94.6 (CH_2), 77.8 (CH), 77.0 (CH), 73.3 (CH), 72.7 (CH_2), 65.7 (CH_2), 55.9 (CH_3), 55.4 (CH_3), 53.0 (CH_2), 35.8 (CH_2), 23.5 (CH_2), 23.0 ppm (CH_3); IR (film): $\tilde{\nu}=2913$, 2358, 1613, 1513, 1341, 1248, 1151, 1101, 1033, 764, 689 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{29}H_{36}O_7N_4SNa$: 607.2202, found: 607.2217.

(*S*,*E*)-4-(*tert*-Butyldiphenylsilyloxy)-1-((*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)-6-(1-phenyl-1*H*-tetrazol-5-ylthio)hex-1-en-3-one (32b): To a solution of compound **31b** (3.98 g, 6.874 mmol) in THF (30 mL) was added 7% HF·pyridine (12 mL) over a period of 5 min at RT. The reaction was stirred 30 min, quenched with sat. aq. $NaHCO_3$ solution (80 mL) and extracted four times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography

(silica gel, hexane/EtOAc 3:1 + 1% Et_3N), yielding labile alcohol as colorless, viscous oil (3.14 g, 6.757 mmol, 98%) which was immediately used for the next step. A solution of alcohol OTES deprotected **31b** (3.12 g, 6.714 mmol) in THF (30 mL) was cooled to 0°C and added PPh_3 (2.29 g, 8.728 mmol), 1-phenyl-1*H*-tetrazol-5-thiol (1.79 g, 10.044 mmol) and DEAD (1.75 g, 10.048 mmol). The reaction was stirred at 0°C for 1 h and 3 h at RT. The reaction was quenched by adding sat. aq. $NaHCO_3$ solution (50 mL) and extracted three times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 7:1), yielding sulfide **32b** as colorless, viscous oil (3.85 g, 6.154 mmol, 92%). $[\alpha]_D^{20} = -40.9$ ($c = 1.40$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$–7.56 (m, 4H), 7.56–7.47 (m, 5H), 7.41–7.28 (m, 6H), 6.87 (dd, $J = 15.7$, 3.8 Hz, 1H), 6.76 (dd, $J = 15.8$, 1.5 Hz, 1H), 5.43 (brs, 1H), 4.40 (t, $J = 6.0$ Hz, 1H), 4.22–4.11 (m, 3H), 3.38–3.22 (m, 2H), 2.29–2.19 (m, 1H), 2.18–2.09 (m, 1H), 2.02–1.87 (m, 2H), 1.72 (brs, 3H), 1.11 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.8$ (C_q), 154.0 (C_q), 147.2 (CH), 136.1 (2×CH), 136.0 (2×CH), 133.8 (C_q), 133.1 (C_q), 132.7 (C_q), 131.2 (C_q), 130.1 (3×CH), 129.9 (2×CH), 127.9 (2×CH), 127.8 (2×CH), 123.8 (2×CH), 122.9 (CH), 119.9 (CH), 77.0 (CH), 72.5 (CH), 65.8 (CH_2), 35.0 (CH_2), 34.2 (CH_2), 28.7 (CH_2), 27.1 (3×CH_3), 23.0 (CH_3), 19.5 ppm (C_q); IR (film): $\tilde{\nu} = 2931$, 1630, 1500, 1427, 1111, 762, 703 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{35}H_{40}O_3N_4SSiNa$: 647.2488, found: 647.2502.

((3*S*,4*S*,*E*)-4-(*tert*-Butyldiphenylsilyloxy)-1-((*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)-6-(1-phenyl-1*H*-tetrazol-5-ylthio)hex-1-en-3-ol (33b): Compound **32b** (3.48 g, 5.569 mmol) was dissolved in MeOH (30 mL) and cooled to −78°C. $CeCl_3 \cdot 7H_2O$ (2.72 g, 7.239 mmol) was added and stirred for 10 min. Following $NaBH_4$ (270 mg, 7.223 mmol) was added in three portions and stirred for 30 min at the same temperature. The reaction was quenched by adding sat. aq. NH_4Cl (50 mL) solution, warmed to RT and extracted four times with EtOAc. The combined organic phase was washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 2:1), yielding alcohol **33b** as colorless, viscous oil (3.39 g, 5.401 mmol, 97%). $[\alpha]_D^{20} = -23.3$ ($c = 1.05$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.69$–7.63 (m, 4H), 7.56–7.46 (m, 5H), 7.42–7.31 (m, 6H), 5.87 (dd, $J = 15.8$, 4.8 Hz, 1H), 5.80 (dd, $J = 15.9$, 4.8 Hz, 1H), 5.41 (brs, 1H), 4.22–4.14 (m, 3H), 4.02–3.96 (m, 1H), 3.86 (dd, $J = 10.5$, 5.3 Hz, 1H), 3.33–3.17 (m, 2H), 2.34 (d, $J = 6.1$ Hz, 1H, OH), 2.10–1.97 (m, 2H), 1.70 (brs, 3H), 1.07 ppm (brs, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 154.2$ (C_q), 136.1 (4×CH), 133.8 (C_q), 133.4 (C_q), 133.3 (C_q), 133.1 (CH), 131.6 (C_q), 130.1 (4×CH), 129.9 (2×CH), 128.0 (2×CH), 127.0 (2×CH), 123.9 (2×CH), 119.8 (CH), 75.0 (CH), 74.0 (CH), 73.4 (CH), 65.7 (CH_2), 35.8 (CH_2), 32.8 (CH_2), 29.4 (CH_2), 27.2 (3×CH_3), 23.1 (CH_3), 19.7 ppm (C_q); IR (film): $\tilde{\nu} = 3286$, 2931, 1500, 1427, 1110, 741, 704 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{35}H_{42}O_3N_4SSiNa$: 649.2645, found: 649.2648.

(3*S*,4*S*,*E*)-4-(*tert*-Butyldiphenylsilyloxy)-1-((*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hex-1-en-3-ol (35): Ammonium molybdate (2.1 g, 1.70 mmol) was added to H_2O_2 (30% aqueous solution, 10 mL) at 0°C and stirred for 15 min. The yellow solution was added dropwise to a solution of **33b** (3.38 g, 5.392 mmol) in EtOH (55 mL) at 0°C and stirred for 45 min before it was allowed to reach RT. After stirring for another 3 h the reaction was diluted with H_2O (80 mL) and extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 3:1), yielding sulfone **35** as colorless, viscous oil (2.47 g, 3.750 mmol, 70%). $[\alpha]_D^{20} = -27.1$ ($c = 1.05$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$–7.54 (m, 9H), 7.48–7.35 (m, 6H), 5.86 (dd, $J = 15.9$, 5.1 Hz, 1H), 5.78 (dd, $J = 15.9$, 5.3 Hz, 1H), 5.41 (brs, 1H), 4.19–4.14 (m, 3H), 4.03–3.96 (m, 1H), 3.88 (dd, $J = 10.2$, 5.1 Hz, 1H), 3.79–3.69 (m, 1H), 3.62–3.53 (m, 1H), 2.20–2.07 (m, 1H), 2.07–1.96 (m, 3H), 1.87 (brd, $J = 16.9$ Hz, 1H), 1.70 (brs, 3H), 1.09 ppm (brs, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.4$ (C_q), 136.1 (2×CH), 136.0 (2×CH), 133.6 (CH), 133.2 (C_q), 133.0 (C_q), 132.9 (C_q), 132.5 (C_q), 131.5 (C_q), 130.4 (CH), 130.3 (CH), 129.8 (2×CH), 129.2 (CH), 128.1 (4×CH), 125.3 (2×CH), 119.8 (CH), 74.3 (CH), 74.1 (CH), 73.2 (CH), 65.7 (CH_2), 52.8 (CH_2), 35.6 (CH_2), 27.3 (3×CH_3), 25.9 (CH_2), 23.1 (CH_3), 19.6 ppm (C_q); IR (film): $\tilde{\nu} = 2930$, 1701, 1685, 1560, 1497, 1426, 1341, 1104, 702, 508 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{35}H_{42}O_5N_4SSiNa$: 681.2543, found: 681.2552.

(3*S*,4*S*,*E*)-1-((*S*)-4-Methyl-3,6-dihydro-2*H*-pyran-2-yl)-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hex-1-ene-3,4-diol (36): To a stirred solution (PVC flask) of compound **35** (2.46 g, 3.734 mmol) in THF (15 mL) was added HF·pyridine (70%, 15 mL) at 0°C dropwise over 15 min. The reaction was stirred at the same temperature for 30 min before it was allowed to warm to RT and stir for another 10 h. The reaction was diluted with CH_2Cl_2 (100 mL), cooled to 0°C and quenched carefully with sat. aq. $NaHCO_3$ (200 mL). The phases were separated and the aqueous phase extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1 → EtOAc), yielding diol **34** as colorless oil (1.48 g, 3.520 mmol, 94%). $[\alpha]_D^{20} = -66.5$ ($c = 1.2$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$–7.66 (m, 2H), 7.64–7.57 (m, 3H), 5.90 (dd, $J = 15.8$, 4.9 Hz, 1H), 5.76 (ddd, $J = 15.7$, 6.5, 1.1 Hz, 1H), 5.41 (brs, 1H), 4.20–4.14 (m, 2H), 4.06–3.94 (m, 3H), 3.90–3.80 (m, 1H), 3.08–2.42 (brs, 2H, OH), 2.24–2.14 (m, 1H), 2.13–2.06 (m, 1H), 2.05–2.00 (m, 1H), 1.91 (brd, $J = 16.7$ Hz, 1H), 1.70 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.6$ (C_q), 134.8 (CH), 133.1 (C_q), 131.6 (CH), 131.5 (C_q), 129.8 (2×CH), 129.1 (CH), 125.3 (2×CH), 119.7 (CH), 75.3 (CH), 73.0 (CH), 72.1 (CH), 65.9 (CH_2), 53.3 (CH_2), 35.7 (CH_2), 26.1 (CH_2), 23.1 ppm (CH_3); IR (film): $\tilde{\nu} = 3401$, 2133, 1634, 1498, 1341, 1154, 976, 764, 689 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{19}H_{24}O_5N_4SNa$: 443.1365, found: 443.1358.

Sulfone 6d: To a stirred solution of diol **36** (1.45 g, 3.448 mmol) in CH_2Cl_2 (30 mL) at −20°C was added 2,6-lutidine (1.035 g, 9.656 mmol) and dropwise TESOTf (1.869 g, 7.586 mmol). The reaction was allowed to reach RT and was stirred for 1 h. Et_3N (2 mL) was added, cooled to −5°C and quenched with sat. aq. $NaHCO_3$ (50 mL). The phases were separated and the aqueous phase extracted three times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 10:1 + 1% NEt_3), yielding sulfone **6d** as colorless, viscous oil (2.17 g, 3.345 mmol, 97%). $[\alpha]_D^{20} = -50.3$ ($c = 0.9$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.70$–7.67 (m, 2H), 7.63–7.56 (m, 3H), 5.88–5.78 (m, 2H), 5.41 (brs, 1H), 4.27–4.34 (m, 1H), 4.19–4.15 (m, 2H), 4.10–4.04 (m, 1H), 3.87–3.74 (m, 3H), 2.23–2.12 (m, 1H), 2.10–1.99 (m, 1H), 1.98–1.89 (m, 2H), 1.70 (brs, 3H), 1.00–0.89 (m, 18H), 0.67–0.55 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.6$ (C_q), 133.3 (C_q), 132.4 (CH), 131.6 (C_q), 131.5 (C_q), 129.8 (2×CH), 128.6 (CH), 125.3 (2×CH), 119.9 (CH), 74.6 (CH), 73.5 (2×CH), 65.7 (CH_2), 53.4 (CH_2), 35.8 (CH_2), 24.4 (CH_2), 23.1 (CH_3), 7.0 (6×CH_3), 5.1 (3×CH_2), 5.0 ppm (3×CH_2); IR (film): $\tilde{\nu} = 3568$, 2956, 2877, 1498, 1345, 1107, 975, 743, 688 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{29}H_{47}O_5N_4SSi_2$ (= M - CH_2CH_3): 619.2806, found: 619.2802.

Total synthesis of laulimalide (1)

TBS ether 4a: To a stirred solution of **6a** (28 mg, 0.043 mmol) in THF (1 mL) at −78°C was added KHMDS (74 μL, 0.049 mmol, 0.5 M in toluene) dropwise over 4 min. The yellow solution was allowed to stir for 3 min before **5** (15 mg, 0.039 mmol, in 0.5 mL THF) was added dropwise over 5 min. After stirring for another 90 min at the same temperature the reaction was quenched by adding H_2O (4 mL) and warmed to RT. The phases were separated and the aqueous phase was extracted four times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 15:1), yielding compound **4a** as viscous oil (28 mg, 0.034 mmol, 87%). $[\alpha]_D^{20} = -67.8$ ($c = 0.73$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 5.92–5.87 (m, 1H), 5.87–5.78 (m, 2H),5.75 (dd, $J = 15.8$, 4.9 Hz, 1H), 5.63 (dt, $J = 15.5$, 6.8 Hz, 1H), 5.47 (dd, $J = 15.5$, 6.6 Hz, 1H), 5.41 (brs, 1H), 4.78 (brs, 1H), 4.77 (brs, 1H), 4.52 (brs, 2H), 4.34–4.25 (m, 2H), 4.20–4.14 (m, 3H), 4.06–4.00 (m, 1H), 3.83–3.77 (m, 4H), 3.32 (ddd, $J = 8.6$, 5.3, 3.0 Hz, 1H), 2.50 (ddd, $J = 16.4$, 6.6, 2.8 Hz, 1H), 2.42 (ddd, $J = 16.4$, 7.3, 2.8 Hz, 1H), 2.33–2.19 (m, 2H), 2.11 (dd, $J = 13.9$, 6.3 Hz, 1H), 2.08–1.85 (m, 9H), 1.70 (brs,

3H), 1.63 (ddd, J=13.9, 9.9, 3.3 Hz, 1H), 1.09 (ddd, J=13.9, 9.2, 3.1 Hz, 1H), 0.90–0.86 (m, 21H), 0.03 (brs, 3H), 0.01 (brs, 6H), 0.00 ppm (brs, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=159.3 (C_q), 144.8 (C_q), 135.2 (CH), 131.6 (C_q), 131.6 (CH), 131.2 (C_q), 130.4 (CH), 129.5 (2×CH), 128.1 (CH), 127.5 (CH), 125.7 (CH), 119.9 (CH), 113.9 (CH_2), 113.9 (2×CH), 82.9 (CH), 82.0 (C_q), 73.8 (CH), 72.9 (CH), 72.6 (CH), 72.6 (CH_2), 70.9 (CH), 70.2 (CH), 66.0 (CH), 65.7 (CH_2), 55.4 (CH_3), 45.3 (CH_2), 45.1 (CH_2), 42.5 (CH_2), 35.8 (CH_2), 32.9 (CH_2), 31.3 (CH_2), 26.9 (CH), 26.1 (3×CH_3), 26.0 (3×CH_3), 24.6 (CH_2), 23.1 (CH_3), 19.5 (CH_3), 18.4 (C_q), 18.3 (C_q), −4.0 (CH_3), −4.3 (CH_3), −4.5 (CH_3), −4.7 ppm (CH_3); IR (film): $\tilde{\nu}$=3310, 2929, 1617, 1513, 1250, 1090, 836, 776 cm^{-1}; HRMS(EI): m/z: calcd for $C_{49}H_{78}O_6Si_2Na$: 841.5235, found: 841.5233.

TBS-ether 4b: To a stirred solution of **6d** (289 mg, 0.445 mmol) in THF (5 mL) at −78 °C was added KHMDS (1.024 mL, 0.512 mmol, 0.5 M in toluene) dropwise over 4 min. The yellow solution was allowed to stir for 3 min before **5** (174 mg, 0.445 mmol, in 1 mL THF) was added dropwise over 5 min. After stirring for another 90 min at the same temperature the reaction was quenched by adding H_2O (5 mL) and warmed to RT. The phases were separated and the aqueous phase was extracted four times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 30:1), yielding compound **4d** as viscous oil (289 mg, 0.355 mmol, 80%). $[\alpha]_D^{20}$=−76.8 (c=0.94 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.93–5.80 (m, 2H), 5.83 (dd, J=15.9, 4.3 Hz, 1H), 5.77 (dd, J=15.9, 5.2 Hz, 1H), 5.47–5.38 (m, 1H), 5.41 (brs, 1H), 4.78 (brs, 1H), 4.77 (brs, 1H), 4.35–4.29 (m, 1H), 4.05 (ddd, J=9.3, 4.6, 4.6 Hz, 1H), 3.85–3.77 (m, 1H), 3.59 (ddd, J=8.5, 4.2, 4.2 Hz, 1H), 2.51 (ddd, J=16.4, 6.7, 2.6 Hz, 1H), 2.43 (ddd, J=16.3, 7.0, 2.6 Hz, 1H), 2.33–2.25 (m, 1H), 2.23 (dd, J=13.8, 7.7 Hz, 1H), 2.14–2.03 (m, 2H), 2.01 (t, J=2.7 Hz, 1H), 1.99–1.86 (m, 7H), 1.71 (brs, 3H), 1.63 (ddd, J=13.6, 10.0, 3.5 Hz, 1H), 1.09 (ddd, J=13.6, 9.1, 3.5 Hz, 1H), 0.99–0.92 (m, 18H), 0.90–0.85 (m, 12H), 0.64–0.59 (m, 12H), 0.03 (s, 3H), 0.01 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=144.8 (C_q), 135.1 (CH), 131.7 (C_q), 131.3 (CH), 130.3 (CH), 128.1 (CH), 127.7 (CH), 125.7 (CH), 119.9 (CH), 113.8 (CH_2), 81.2 (C_q), 76.2 (CH), 74.8 (CH), 73.9 (CH), 72.7 (CH), 71.0 (CH), 70.2 (CH), 66.0 (CH), 65.7 (CH_2), 45.3 (CH_2), 45.0 (CH_2), 42.5 (CH_2), 35.9 (CH_2), 34.9 (CH_2), 31.3 (CH_2), 27.0 (CH), 26.1 (3×CH_3), 24.6 (CH_2), 23.1 (CH_3), 19.5 (CH_3), 18.4 (C_q), 7.2 (4×CH_3), 7.1 (2×CH_3), 5.3 (4×CH_2), 5.1 (2×CH_2), −4.0 (CH_3), −4.5 ppm (CH_3); IR (film): $\tilde{\nu}$=3314, 2955, 2122, 1644, 1460, 1361, 1093, 1005, 973, 836, 756 cm^{-1}; HRMS(EI): m/z: calcd for $C_{47}H_{84}O_5Si_3Na$: 835.5524, found: 835.5531.

Seco-acid 44: To a stirred solution of compound **4d** (168 mg, 0.2064 mmol) in THF (3 mL) at −78 °C was added nBuLi (0.206 mL, 0.3304 mmol) dropwise over a period of 5 min. The bright yellow solution was stirred for 5 min and then CO_2(g) was bubbled through the reaction for 10 min. Now HF·pyridine (7%, 3 mL) was added dropwise over 5 min to the colorless reaction mixture. The reaction was allowed to warm to RT and stirred for another 90 min. The reaction was quenched by slow addition of aq. sat. $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (15 mL). The pH of the aqueous phase was set to pH 3 by addition of HCl (1 N in H_2O), the phases were separated and the aqueous phase was extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 5:1), yielding seco acid **44** as viscous oil (113 mg, 0.1797 mmol, 87%). $[\alpha]_D^{20}$=−46.7 (c=1.15 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.88–5.79 (m, 3H), 5.76 (dd, J=15.7, 6.3 Hz, 1H), 5.63–5.50 (m, 2H), 5.39 (brs, 1H), 4.77 (brs, 1H), 4.75 (brs, 1H), 4.38–4.29 (m, 1H), 4.25–4.17 (m, 2H), 4.17–4.11 (m, 2H), 4.08–3.96 (m, 2H), 3.81–3.71 (m, 1H), 3.64–3.55 (m, 1H), 2.57 (dd, J=16.4, 7.1 Hz, 1H), 2.52–2.43 (m, 1H), 2.39–2.27 (m, 1H), 2.23–1.75 (m, 9H), 1.69 (brs, 3H), 1.64–1.55 (m, 1H), 1.15–1.05 (m, 1H), 0.86–0.82 (m, 12H), 0.00 (brs, 3H), −0.01 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.5 (C_q), 144.8 (C_q), 137.6 (CH), 133.9 (CH), 131.6 (C_q), 130.0 (CH), 128.3 (CH), 125.5 (CH), 125.0 (CH), 119.8 (CH), 114.1 (CH_2), 94.8 (C_q), 79.5 (C_q), 74.3 (CH), 73.5 (CH), 73.3 (CH), 72.1 (CH), 70.5 (CH), 65.9 (CH), 65.7 (CH_2), 45.2 (CH_2), 44.7 (CH_2), 42.6 (CH_2), 36.1 (CH_2), 35.7 (CH_2), 31.2 (CH_2), 27.2 (CH), 26.8 (3×CH_3), 24.8 (CH_2), 23.1 (CH_3), 19.6 (CH_3), 18.4 (C_q), −4.0 (CH_3), −4.6 ppm (CH_3); IR (film): $\tilde{\nu}$=3307, 2928, 2236, 1582, 1363, 1254, 1074, 972, 836, 777, 708 cm^{-1}; HRMS(EI): m/z: calcd for $C_{36}H_{56}O_7SiNa$: 651.3693, found: 651.3702.

Macrolactone 45: To a stirred solution of seco acid **44** (57 mg, 0.0906 mmol) in benzene (2 mL) at RT was added Et_3N (25.2 μL, 0.1812 mmol) and dropwise 2,4,6-trichlorobenzoyl chloride (14.2 μL, 0.0997 mmol). The solution was stirred for 4 h before it was diluted with benzene (100 mL). DMAP (110.6 mg, 0.9057 mmol) in benzene (20 mL) was added over 6 h via a syringe pump. After additional 6 h, aq. sat. $NaHCO_3$ (70 mL) was added and the mixture was stirred for 20 min. The phases were separated and the aqueous layer was extracted three times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 3:1), yielding compound macrolactone **45** as viscous oil (41.3 mg, 0.0676 mmol, 75%). $[\alpha]_D^{20}$=−39.2 (c=0.65 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.94–5.85 (m, 2H), 5.75 (ddd, J=15.6, 5.8, 1.3 Hz, 1H), 5.64–5.57 (m, 2H), 5.42 (brs, 1H), 5.00 (dd, J=13.1, 6.9 Hz, 1H), 4.78 (brs, 1H), 4.76 (brs, 1H), 4.42 (d, J=10.9 Hz, 1H), 4.24–4.15 (m, 4H), 4.05 (ddd, J=9.7, 4.7, 4.7 Hz, 1H), 3.74–3.65 (m, 1H), 2.71 (dd, J=17.5, 11.5 Hz, 1H), 2.39 (dd, J=17.5, 2.6 Hz, 1H), 2.32 (t, J=6.8 Hz, 1H), 2.12–2.02 (m, 4H), 1.98–1.91 (m, 4H), 1.89–1.82 (m, 1H), 1.70 (brs, 3H), 1.62–1.54 (m, 1H), 1.08 (ddd, J=14.0, 9.9, 1.7 Hz, 1H), 0.86–0.83 (m, 12H), −0.01 (brs, 3H), −0.03 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.4 (C_q), 145.1 (C_q), 138.6 (CH), 134.2 (CH), 131.5 (C_q), 128.7.0 (CH), 127.7 (CH), 127.1 (CH), 123.3 (CH), 119.9 (CH), 114.4 (CH_2), 87.6 (C_q), 77.8 (CH), 73.7 (CH), 73.4 (C_q), 73.3 (CH), 71.6 (CH), 71.2 (CH), 65.8 (CH), 65.7 (CH_2), 45.8 (CH_2), 43.9 (CH_2), 43.1 (CH_2), 35.8 (CH_2), 32.8 (CH_2), 31.5 (CH_2), 26.6 (CH), 26.0 (3×CH_3), 24.2 (CH_2), 23.1 (CH_3), 19.2 (CH_3), 18.4 (C_q), −4.0 (CH_3), −4.7 ppm (CH_3); IR (film): $\tilde{\nu}$=3392, 2235, 1638, 1246, 1070, 833, 775, 704 cm^{-1}; HRMS(EI): m/z: calcd for $C_{36}H_{54}O_6SiNa$: 633.3587, found: 633.3595.

Diol 46: To a stirred solution (PVC flask) of compound **45** (40 mg, 0.655 mmol) in THF (2 mL) at 0 °C was added HF·pyridine (70%, 550 μL) dropwise in 10 min. After stirring at 0 °C for another 10 min the reaction was allowed to reach RT and stirred for 40 min. The mixture was diluted with CH_2Cl_2 (10 mL), cooled to 0 °C and quenched by slow addition of aq. sat. $NaHCO_3$ (35 mL). The phases were separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1), yielding compound **46** as viscous oil (31 mg, 0.0624 mmol, 95%). $[\alpha]_D^{20}$=−34.3 (c=0.75 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.94–5.87 (m, 2H), 5.75 (ddd, J=15.7, 6.1, 1.3 Hz, 1H), 5.69–5.65 (m, 2H), 5.64–5.58 (m, 1H), 5.42 (brs, 1H), 5.03 (dd, J=13.4, 6.7 Hz, 1H), 4.89 (brs, 2H), 4.43 (brd, J=11.5 Hz, 1H), 4.29 (brd, J=10.5 Hz, 1H), 4.24–4.15 (m, 3H), 4.05 (ddd, J=9.8, 4.6, 4.4 Hz, 1H), 3.66 (dt, J=9.3, 3.4 Hz, 1H), 2.70 (dd, J=17.4, 11.1 Hz, 1H), 2.41–2.27 (m, 4H), 2.15 (dd, J=13.1, 6.1 Hz, 1H), 2.10–1.87 (m, 8H), 1.70 (brs, 3H), 1.61–1.59 (m, 1H), 1.08 (ddd, J=13.8, 10.3, 1.3 Hz, 1H), 0.85 ppm (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.4 (C_q), 145.1 (C_q), 137.1 (CH), 134.3 (CH), 131.4 (C_q), 128.0 (CH), 127.7 (CH), 127.1 (CH), 124.9 (CH), 119.9 (CH), 114.4 (CH_2), 87.7 (C_q), 76.8 (CH), 73.6 (CH), 73.3 (C_q), 73.2 (CH), 71.4 (CH), 69.2 (CH), 65.8 (CH_2), 65.6 (CH), 45.7 (CH_2), 42.8 (2×CH_2), 35.7 (CH_2), 33.0 (CH_2), 31.4 (CH_2), 26.3 (CH), 24.1 (CH_2), 23.1 (CH_3), 19.2 ppm (CH_3); IR (film): $\tilde{\nu}$=3401, 2923, 2235, 1708, 1435, 1245, 1067, 971 cm^{-1}; HRMS(EI): m/z: calcd for $C_{30}H_{40}O_6Na$: 519.2723, found: 519.2735.

Desoxylaulimalide (47): To a stirred solution of compound **46** (21 mg, 0.0423 mmol) in a 1:1 mixture of EtOAc and cyclohexene (2 mL) at RT was added quinoline (17.5 mg). H_2 (balloon) was bubbled through the reaction and Lindlar catalyst (16.5 mg) was added. After 2 h the reaction was filtered through a short pad of celite, to remove the catalyst and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1), yielding desoxylaulimaldie **47** as colorless oil (18 mg, 0.0361 mmol, 85%), that was identical in every aspect with the compound derived from prior laulimalide syntheses.[5]

Laulimalide (1): To a stirred suspension of powdered molecular sieves 4 Å (300 mg) in CH_2Cl_2 (3.5 mL) at −20 C, was added (+)-diisopropyl tartrate (57 μL, 0.0287 mmol, 0.5 M in CH_2Cl_2) and $Ti(OiPr)_4$ (48 μL 0.02429 mmol, 0.5 M in CH_2Cl_2). The mixture was stirred for 30 min at the same temperature before *tert*-butyl hydroperoxide (44 μL, 0.0485, 1.1 M in CH_2Cl_2, dried over molecular sieves 4 Å) was added dropwise. The mixture was stirred for another 30 min before a solution of **47** (11 mg, 0.022 mmol, in 0.4 mL CH_2Cl_2) was added dropwise. The reaction was stirred for 3.5 h at −20 °C before it was quenched by addition of aq NaOH (3 mL, 1 M in brine). After stirring for 10 min the mixture was diluted with CH_2Cl_2 and brine, the phases were separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1), yielding laulimalide (**1**) as white solid (8.5 mg, 0.0165 mmol, 75 %), that was identical in every aspect with the compound derived from prior laulimalide syntheses and the reported data of the natural compound.[1,5] $[\alpha]_D^{20} = -198.4$ ($c = 0.25$ in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 6.45$ (ddd, J = 11.4, 10.0, 3.7 Hz, 1H), 5.91 (ddd, $J = 11.5$, 2.5,1.3 Hz, 1H), 5.87 (ddd, $J = 15.7$, 5.4, 1.2 Hz, 1H), 5.85–5.82 (m, 1H), 5.75 (ddd, $J = 15.7$, 5.7, 1.2 Hz, 1H), 5.71–5.67 (m, 1H), 5.42 (brs, 1H), 5.15 (ddd, $J = 11.2$, 5.3, 1.6 Hz, 1H), 4.86 (brs, 1H), 4.85 (brs, 1H), 4.33–4.28 (m, 1H), 4.22 (brq, $J = 5.3$, 1H), 4.19–4.16 (m, 2H), 4.10–4.06 (m, 1H), 4.05–4.01 (m, 1H), 3.78–3.69 (m, 2H), 3.06 (ddd, $J = 9.2$, 3.5, 2.4 Hz, 1H), 2.90 (brt, $J = 2.5$ Hz, 1H), 2.39–2.35 (m, 2H), 2.22 (d of m, $J = 16.7$ Hz, 1H), 2.12 (brd, $J = 15.7$ Hz, 1H), 2.06–2.00 (m, 2H), 1.99 (dd, $J = 15.7$, 8.7 Hz, 1H), 1.95–1.85 (m, 4H), 1.78 (dd, $J = 13.1$, 10.0 Hz, 1H), 1.74–1.70 (m, 1H), 1.69 (brs, 3H), 1.50 (ddd, $J = 14.4$, 11.1, 9.3 Hz, 1H), 1.45 (dt, $J = 14.9$, 7.6 Hz, 1H), 1.32 (ddd, $J = 14.4$, 4.7, 3.5 Hz, 1H), 0.83 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 166.1$ (C_q), 150.4 (CH), 145.0 (C_q), 134.0 (CH), 131.4 (C_q), 128.8 (CH), 128.6 (CH), 125.3 (CH), 120.6 (CH), 119.8 (CH), 112.6 (CH_2), 73.6 (CH), 73.3 (CH), 73.2 (CH), 72.4 (CH), 68.0 (CH), 66.7 (CH), 65.8 (CH_2), 60.8 (CH), 52.2 (CH), 45.7 (CH_2), 43.5 (CH_2), 37.2 (CH_2), 35.7 (CH_2), 33.9 (CH_2), 33.5 (CH_2), 31.8 (CH_2), 29.7 (CH_3), 23.1 (CH), 20.9 ppm (CH_3); IR (film): $\tilde{\nu} = 3424$, 3073, 3030, 2847, 1720, 1642, 1424, 1214, 1170, 895 cm^{-1}; HRMS(EI): m/z: calcd for $C_{30}H_{42}O_7Na$: 537.2828, found: 537.2833.

Total synthesis of neolaulimalide (2)

TBS-ether 4c: To a stirred solution of **6b** (202 mg, 0.313 mmol) in THF (4 mL) at −78 °C was added KHMDS (0.688 mL, 0.344 mmol, 0.5 M in toluene) dropwise over 4 min. The yellow solution was allowed to stir for 3 min before **5** (122 mg, 0.313 mmol, in 0.7 mL THF) was added dropwise over 5 min. After stirring for another 90 min at the same temperature the reaction was quenched by adding H_2O (4 mL) and warmed to RT. The phases were separated and the aqueous phase was extracted four times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 15:1 + 1% Et_3N), yielding compound **4c** as viscous oil (195 mg, 0.238 mmol, 76 %). $[\alpha]_D^{20} = -79.3$ ($c = 1.2$ in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.91–5.85 (dt, $J = 2.5$, 1.1 Hz, 1H), 5.84–5.82 (m, 1H), 5.81 (ddd, $J = 15.4$, 4.6, 1.1 Hz, 1H), 5.76 (ddd, $J = 15.5$, 5.3, 1.1 Hz, 1H), 5.65–5.58 (m, 1H), 5.47 (dd, $J = 15.5$, 6.4 Hz, 1H), 5.41 (brs, 1H), 4.79 (brs, 1H), 4.77 (brs, 1H), 4.53 (brs, 2H), 4.34–4.30 (m, 1H), 4.26 (t, $J = 4.9$ Hz, 1H), 4.19–4.15 (m, 3H), 4.03 (ddd, $J = 10.0$, 4.7, 4.3 Hz, 1H), 3.82–3.72 (m, 1H), 3.80 (s, 3H), 3.31 (ddd, $J = 8.6$, 5.2, 3.3 Hz, 1H), 2.50 (ddd, $J = 16.5$, 6.7, 2.7 Hz, 1H), 2.43 (ddd, $J = 16.5$, 7.2, 2.7 Hz, 1H), 2.29 (ddd, $J = 14.7$, 7.2, 3.0 Hz, 1H), 2.23 (dd, $J = 13.8$, 6.6 Hz, 1H), 2.11 (dd, $J = 13.8$, 6.6 Hz, 1H), 2.06–1.85 (m, 8H), 1.70 (s, 3H), 1.63 (ddd, $J = 13.9$, 9.9, 3.4 Hz, 1H), 1.09 (ddd, $J = 14.0$, 9.5, 3.4 Hz, 1H), 0.92 (t, $J = 7.9$ Hz, 9H), 0.89 (d, $J = 6.4$ Hz, 3H), 0.87 (s, 9H), 0.58–0.53 (m, 6H), 0.03 (brs, 3H), 0.01 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 159.3$ (C_q), 144.7 (C_q), 135.2 (CH), 131.6 (C_q), 131.6 (CH), 131.1 (C_q), 130.4 (CH), 129.5 (2×CH), 128.1 (CH), 127.4 (CH), 125.7 (CH), 119.9 (CH), 113.9 (CH_2), 113.8 (2×CH), 82.9 (CH), 82.0 (C_q), 73.7 (CH), 73.0 (CH), 72.6 (CH_2), 71.5 (CH), 70.9 (CH), 70.2 (CH), 66.0 (CH), 65.7 (CH_2), 55.4 (CH_3), 45.3 (CH_2), 45.1 (CH_2), 42.5 (CH_2), 35.8 (CH_2), 32.9 (CH_2), 31.3 (CH_2), 26.9 (CH), 26.1 (3×CH_3), 24.6 (CH_2), 23.1 (CH_3), 19.4 (CH_3), 18.4 (C_q), 7.1 (3×CH_3), 5.0 (3×CH_2), −4.0 (CH_3), −4.6 ppm (CH_3); IR (film): $\tilde{\nu} = 3312$, 2929, 1612, 1513, 1302, 1248, 1091, 1039, 1006, 836, 776 cm^{-1}; HRMS(EI): m/z: calcd for $C_{49}H_{78}O_6Si_2Na$: 841.5235, found: 841.5241.

Seco-acid 48: To a stirred solution of compound **4c** (165 mg, 0.2013 mmol) in THF (3 mL) at −78 °C was added *n*BuLi (0.214 mL, 0.342 mmol, 1.6 M in hexane) dropwise over a period of 5 min. The bright yellow solution was stirred for 5 min and then CO_2(g) was bubbled through the reaction for 10 min. Now HF·pyridine (7 %, 2.8 mL) was added dropwise over 5 min to the colorless reaction mixture and it was allowed to warm to RT and stirred for another 90 min. The reaction was quenched by slow addition of aq. sat. $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (15 mL). The pH of the aqueous phase was set to pH 3 by addition of HCl (1 N), the phases were separated and the aqueous phase was extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 6:1), yielding seco acid **48** as viscous oil (136 mg, 0.182 mmol, 85 %). $[\alpha]_D^{20} = -25.2$ ($c = 1.10$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.1$ Hz, 2H), 6.87 (d, $J = 8.1$ Hz, 2H), 5.95–5.87 (m, 1H), 5.72 (dd, $J = 15.3$, 6.3 Hz, 1H), 5.84 (dd, $J = 15.3$, 5.4 Hz, 1H), 5.72–5.65 (m, 1H), 5.60–5.52 (m, 2H), 5.41 (brs, 1H), 4.80 (brs, 1H), 4.78 (brs, 1H), 5.63 (d, $J = 11.3$ Hz, 1H), 4.46 (d, $J = 11.3$ Hz, 1H), 4.39 (brs, 1H), 4.23–4.16 (m, 3H), 4.11 (t, $J = 6.2$ Hz, 1H), 4.05 (ddd, $J = 9.6$, 4.8, 4.6 Hz, 1H), 3.80 (s, 3H), 3.80–3.74 (m, 1H), 3.40 (dd, $J = 11.1$, 5.6 Hz, 1H), 2.64 (dd, $J = 17.2$, 9.0 Hz, 1H), 2.47 (dd, $J = 17.3$, 4.3 Hz, 1H), 2.44–2.37 (m, 1H), 2.33–2.24 (m, 1H), 2.17 (d, $J = 6.3$ Hz, 2H), 2.12–1.79 (m, 7H), 1.70 (brs, 3H), 1.62 (ddd, $J = 12.9$, 10.0, 3.0 Hz, 1H), 1.05 (t, $J = 12.2$ Hz, 1H), 0.88–0.85 (m, 12H), 0.02 (s, 3H), 0.00 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.6$ (C_q), 154.9 (C_q), 144.6 (2×C_q), 137.7 (CH), 133.1 (CH), 131.6 (C_q), 130.6 (CH), 129.9 (2×CH), 127.6 (CH), 126.7 (CH), 124.0 (CH), 119.5 (CH), 114.4 (CH_2), 114.0 (2×CH), 86.7 (C_q), 81.3 (CH), 74.5 (C_q), 73.9 (CH), 72.8 (CH), 72.1 (CH_2), 71.8 (CH), 70.7 (CH), 66.0 (CH), 65.6 (CH_2), 55.4 (CH_3), 45.4 (CH_2), 44.3 (CH_2), 43.2 (CH_2), 35.8 (CH_2), 32.8 (CH_2), 31.4 (CH_2), 26.8 (CH), 26.1 (3×CH_3), 24.5 (CH_2), 23.1 (CH_3), 19.4 (CH_3), 18.4 (C_q), −4.0 (CH_3), −4.6 ppm (CH_3); IR (film): $\tilde{\nu} = 3450$, 2928, 2238, 1708, 1513, 1382, 1249, 1174, 1091, 835, 777, 610 cm^{-1}; HRMS(EI): m/z: calcd for $C_{44}H_{64}O_8SiNa$: 771.4268, found: 771.4284.

Macrolactone 49: To a stirred solution of *seco* acid **48** (35 mg, 0.0467 mmol) in benzene (1 mL) at RT was added Et_3N (13.0 μL, 0.0934 mmol) and dropwise 2,4,6-trichlorobenzoyl chloride (14.4 μL, 0.0794 mmol). The solution was stirred for 4 h before it was diluted with benzene (20 mL) and added over 6 h *via* a syringe pump into a stirred solution of DMAP (57 mg, 0.4673 mmol) in benzene (200 mL). After additional 6 h the mixture was concentrated to about 20 mL, aq. sat. $NaHCO_3$ (30 mL) was added and the mixture was stirred for 20 min. The phases were separated and the aqueous layer was extracted four times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 10:1 → 8:1), yielding compound **49** as viscous oil (12 mg, 0.0164 mmol, 35 %) and the dimer of **49** (3 mg, 0.0021 mmol, 4 %). $[\alpha]_D^{20} = -22.4$ ($c = 0.78$ in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 5.95–5.81 (m, 1H), 5.84–5.82 (m, 2H), 5.63–5.60 (m, 1H), 5.52–5.50 (m, 1H), 5.43–5.40 (m, 3H), 4.76 (brs, 2H), 4.56 (d, $J = 11.7$ Hz, 1H), 4.53 (d, $J = 11.7$ Hz, 1H), 4.46–4.42 (m, 1H), 4.22–4.16 (m, 3H), 4.04 (ddd, $J = 10.5$, 3.6, 3.6 Hz, 1H), 3.80 (s, 3H), 3.76–3.72 (m, 1H), 3.13 (ddd, $J = 7.0$, 7.0, 2.8 Hz, 1H), 2.61 (dd, $J = 17.4$, 10.0 Hz, 1H), 2.48 (dd, $J = 17.4$, 2.5 Hz, 1H), 2.36–2.30 (m, 2H), 2.22 (dd, $J = 13.9$, 7.9 Hz, 1H), 2.14 (dd, $J = 13.9$, 5.4 Hz, 1H), 2.10 (dd, $J = 13.6$, 5.4 Hz, 1H), 2.08–2.04 (m, 1H), 1.98–1.87 (m, 4H), 1.74 (dd, $J = 13.6$, 10.0 Hz, 1H), 1.70 (brs, 3H), 1.62 (ddd, $J = 13.9$, 9.8, 3.9 Hz, 1H), 1.13 (ddd, $J = 13.9$, 9.7, 2.8 Hz, 1H), 0.86 (m, 9H), 0.83 (d, $J = 6.6$ Hz, 3H), 0.01 (brs, 3H), 0.00 ppm (brs, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 159.4$ (C_q), 153.1 (C_q), 144.5 (C_q), 136.9 (CH), 134.5 (CH), 131.5 (C_q), 130.3 (C_q), 129.7 (2×CH), 127.7 (CH), 127.0 (CH), 124.7 (CH), 124.5 (CH), 119.9 (CH), 113.9 (2×CH_2), 88.1 (C_q), 77.9 (CH), 77.5 (CH), 73.5 (C_q), 73.4 (CH), 71.8 (CH), 71.4 (CH), 71.2 (CH), 66.0 (CH), 65.8 (CH_2), 55.4 (CH_3), 45.0

(CH_2), 44.0 (CH_2), 43.4 (CH_2), 35.8 (CH_2), 34.4 (CH_2), 31.3 (CH_2), 27.1 (CH), 26.0 ($3\times CH_3$), 24.4 (CH_2), 23.1 (CH_3), 19.0 (CH_3), 18.4 (C_q), −4.0 (CH_3), −4.6 ppm (CH_3); IR (film): $\tilde{\nu}$ = 2926, 2854, 2234, 1709, 1513, 1460, 1247, 1070, 969, 835, 776 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{44}H_{62}O_7SiNa$: 753.4162, found: 753.4149.

Alcohol 50: To a stirred solution (PVC flask) of macrolactone **49** (10 mg, 0.0137 mmol) in THF (0.75 mL) at 0 °C was added HF·pyridine (35%, 500 μL) dropwise in 5 min. After stirring at 0 °C for another 10 min the reaction was allowed to reach RT and stirred for 5 h. The mixture was diluted with CH_2Cl_2 (4 mL), cooled to 0 °C and quenched by slow addition of aq. sat. $NaHCO_3$ (7 mL). The phases were separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1), yielding compound **50** as colorless oil (7.3 mg, 0.0119 mmol, 87%). $[\alpha]_D^{20} = -38.0$ (c = 0.38 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.94–5.90 (m, 1H), 5.87–5.80 (m, 2H), 5.62–5.55 (m, 3H), 5.51 (dd, J = 15.5, 6.5 Hz, 1H), 5.43 (brs, 1H), 4.88 (brs, 2H), 4.57 (d, J = 11.7 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 4.45 (brd, J = 9.9 Hz, 1H), 4.25 (ddd, J = 9.8, 6.4, 3.4 Hz, 1H), 4.20–4.17 (m, 2H), 4.06–4.01 (m, 1H), 3.80 (s, 3H), 3.69–3.64 (m, 1H), 3.58 (ddd, J = 6.8, 5.3, 2.8 Hz, 1H), 2.58 (dd, J = 17.3, 10.1 Hz, 1H), 2.47 (dd, J = 17.3, 2.3 Hz, 1H), 2.43–2.36 (m, 2H), 2.34 (dd, J = 13.9, 3.7 Hz, 1H), 2.22–2.16 (m, 2H), 2.11–2.04 (m, 1H), 2.02–1.89 (m, 4H), 1.88–1.83 (m, 2H), 1.70 (brs, 3H), 1.66 (ddd, J = 14.0, 10.5, 2.6 Hz, 1H), 1.10 (ddd, J = 14.0, 10.3, 1.6 Hz, 1H), 0.86 ppm (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.5 (C_q), 153.2 (C_q), 144.5 (C_q), 135.5 (CH), 134.2 (CH), 131.5 (C_q), 130.2 (C_q), 129.7 ($2\times$CH), 127.7 (CH), 127.0 (CH), 125.9 (CH), 124.5 (CH), 119.9 (CH), 114.0 ($2\times CH_2$), 88.5 (C_q), 77.2 (CH), 77.8 (CH), 73.4 (CH), 73.2 (C_q), 71.6 (CH), 71.3 (CH), 69.3 (CH), 66.0 (CH), 65.8 (CH_2), 55.4 (CH_3), 45.7 (CH_2), 43.6 (CH_2), 43.0 (CH_2), 35.8 (CH_2), 34.8 (CH_2), 31.4 (CH_2), 26.8 (CH), 24.3 (CH_2), 23.1 (CH_3), 19.1 ppm (CH_3); IR (film): $\tilde{\nu}$ = 2925, 2234, 1707, 1513, 1248, 1070 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{38}H_{48}O_7Na$: 639.3298, found: 639.3315.

Enone 51: To a stirred solution of compound **50** (8.1 mg, 0.01314 mmol) in a 1:1 mixture of EtOAc and cyclohexene (3 mL) at RT was added quinoline (18 μL). H_2 (balloon) was bubbled through the reaction and Lindlar catalyst (15 mg) was added. After 1 h the reaction was filtered through a short pad of celite and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 5:1 to 1:1), yielding **51** as colorless oil (8.0 mg, 0.01293 mmol, 89%). $[\alpha]_D^{20} = 38.6$ (c = 0.70 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.43 (ddd, J = 11.5, 9.4, 7.2 Hz, 1H), 5.95 (d, J = 11.5 Hz, 1H), 5.88 (dd, J = 15.9, 5.3 Hz, 1H), 5.85–5.77 (m, 2H), 5.69 (dd, J = 10.4, 2.0 Hz, 1H), 5.61–5.51 (m, 1H), 5.46 (dd, J = 15.5, 5.7 Hz, 1H), 5.44–5.38 (m, 2H), 4.87 (brs, 1H), 4.85 (brs, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 11.6 Hz, 1H), 4.25–4.12 (m, 4H), 4.06–4.01 (m, 1H), 3.99–3.92 (m, 1H), 3.80 (s, 3H), 3.64 (ddd, J = 8.6, 5.4, 3.2 Hz, 1H), 3.22 (ddd, J = 13.5, 9.1, 4.1 Hz, 1H), 2.47–2.26 (m, 5H), 2.34–2.26 (m, 2H), 2.12–2.00 (m, 2H), 1.89 (brd, J = 16.6 Hz, 1H), 1.81–1.71 (m, 4H), 1.70 (brs, 3H), 0.99 (ddd, J = 13.8, 8.4, 3.6 Hz, 1H), 0.86 ppm (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4 (C_q), 159.4 (C_q), 147.3 (C_q), 145.0 (C_q), 135.8 (CH), 133.2 (CH), 131.5 (C_q), 130.2 (C_q), 129.7 ($2\times$CH), 129.3 (CH), 126.4 (CH), 125.9 (CH), 124.1 (CH), 121.4 (CH), 119.9 (CH), 114.7 (CH_2), 113.9 ($2\times$CH), 78.4 (CH), 73.9 (CH), 73.5 (CH), 71.9 (CH_2), 70.2 (CH), 70.1 (CH), 67.8 (CH), 65.8 (CH_2), 55.4 (CH_3), 45.2 (CH_2), 43.0 (CH_2), 40.7 (CH_2), 35.8 (CH_2), 35.2 (CH_2), 34.2 (CH_2), 30.3 (CH_2), 27.0 (CH), 23.1 (CH_3), 19.4 ppm (CH_3); IR (film): $\tilde{\nu}$ = 3469, 2917, 1714, 1513, 1247, 1168, 1033, 819, 447, 419 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{38}H_{50}O_7Na$: 641.3454, found: 641.3450.

Desoxyneolaulimalide (52): To a solution of **51** (6.5 mg, 0.0105 mmol) in a biphasic 1:1 mixture of CH_2Cl_2/aq. (pH 7) buffer (6 mL) was added DDQ (4 mg) in one portion. The flask was closed with a septum and placed into an ultrasound bath at 35 °C. After 1 h additional DDQ (4 mg) was added and the same after 2.5 h. The reaction was diluted with H_2O (10 mL) and CH_2Cl_2 (5 mL) after a total reaction time of 3.5 h. The phases were separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic layer was washed four times with H_2O and dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1 to 1:1), yielding **52** as white solid (5.0 mg, 0.01003 mmol, 96%). $[\alpha]_D^{20} = 12.9$ (c = 0.21 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (ddd, J = 11.4, 9.2, 7.5 Hz, 1H), 5.95 (d, J = 11.4 Hz, 1H), 5.88 (dd, J = 15.8, 4.4 Hz, 1H), 5.85–5.77 (m, 2H), 5.74–5.60 (m, 2H), 5.52 (dd, J = 15.5, 5.6 Hz, 1H), 5.42 (brs, 1H), 5.25 (dd, J = 5.2, 3.5 Hz, 1H), 4.89 (brs, 1H), 4.86 (brs, 1H), 4.26–4.15 (m, 4H), 4.06 (ddd, J = 10.2, 4.0, 4.0 Hz, 1H), 3.98–3.90 (m, 1H), 3.89–3.81 (m, 1H), 3.15–3.07 (m, 1H), 2.53 (ddd, J = 12.6, 8.5, 8.4 Hz, 1H), 2.48–2.39 (m, 1H), 2.28–2.11 (m, 4H), 2.11–1.99 (m, 1H), 1.92 (brd, J = 16.9 Hz, 1H), 1.86–1.67 (m, 5H), 1.69 (brs, 3H), 1.04–0.95 (m, 1H), 0.88 ppm (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3 (C_q), 144.8 (C_q), 136.6 (CH), 135.0 (CH), 131.5 (C_q), 129.1 (CH), 126.0 (CH), 125.0 (CH), 124.2 (CH), 121.6 (CH), 119.8 (CH), 114.6 (CH_2), 75.4 (CH), 73.2 (CH), 72.1 (CH), 70.8 (CH), 70.3 (CH), 67.9 (CH), 65.8 (CH_2), 45.0 (CH_2), 43.5 (CH_2), 41.3 (CH_2), 37.1 (CH_2), 35.8 (CH_2), 35.5 (CH_2), 30.4 (CH_2), 27.1 (CH), 23.1 (CH_3), 19.5 ppm (CH_3); IR (film): $\tilde{\nu}$ = 3401, 2920, 2851, 1716, 1260, 1079, 799, 473, 446, 405 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{30}H_{42}O_6Na$: 521.2879, found: 521.2882.

Neolaulimalide (3): To a stirred suspension of powdered molecular sieves 4 Å (160 mg) in CH_2Cl_2 (1.7 mL) at −20 °C, was added (+)-diisopropyl tartrate (25.6 μL, 0.0128 mmol, 0.5 M in CH_2Cl_2) and Ti(O*i*Pr)$_4$ (21.4 μL 0.0107 mmol, 0.5 M in CH_2Cl_2). The mixture was stirred at the same temperature for 10 min before *tert*-butyl hydroperoxide (27.3 μL, 0.0150, 0.55 M in CH_2Cl_2, dried over molecular sieves 4 Å) was added dropwise. The mixture was stirred for another 30 min before a solution of **52** (4.4 mg, 0.00882 mmol, in 0.3 mL CH_2Cl_2) was added dropwise. The reaction was stirred for 2.5 h at −20 °C before it was quenched by addition of aq. sat. NH_4Cl (2 mL) and warmed to RT. After stirring for 4 min the mixture was diluted with Et_2O and sat. aq. KNa-tartrate and stirred for 45 min, the phases were separated and the aqueous layer was extracted four times with Et_2O. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1 → 1:2), yielding neolaulimalide (**1**) as white solid (3.3 mg, 0.00641 mmol, 73%), that was identical in every aspect with the reported data of the natural compound. $[\alpha]_D^{20} = -53.3$ (c = 0.30 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.35 (ddd, J = 11.7, 8.1, 8.1 Hz, 1H), 5.91 (ddd, J = 15.7, 4.9, 0.9 Hz, 1H), 5.90 (d, J = 11.7 Hz, 1H), 5.86–5.83 (m, 1H), 5.83 (ddd, J = 15.9, 6.8, 1.5 Hz, 1H), 5.73–5.70 (m, 1H), 5.42 (brs, 1H), 5.32 (dd, J = 6.8, 4.9 Hz, 1H), 4.95 (brs, 1H), 4.90 (brs, 1H), 4.29–4.25 (m, 1H), 4.18 (brs, 2H), 4.10–4.07 (m, 1H), 4.07–4.03 (m, 1H), 3.96–3.91 (m, 1H), 3.83–3.80 (m, 1H), 3.19 (dt, J = 6.4, 2.5 Hz, 1H), 3.02 (t, J = 2.5 Hz, 1H), 2.95–2.89 (m, 1H), 2.89–2.83 (m, 1H), 2.76 (d, J = 6.4 Hz, 1H, OH), 2.37 (dd, J = 14.5, 6.4 Hz, 1H), 2.18 (dd, J = 14.5, 6.8 Hz, 1H), 2.11–2.08 (m, 1H), 2.06–2.00 (m, 3H, $1\times$OH), 1.99–1.97 (m, 1H), 196–1.93 (m, 1H), 1.92–1.89 (m, 1H), 1.89–1.85 (m, 1H), 1.80–1.74 (m, 1H), 1.69 (brs, 3H), 1.68–1.64 (m, 1H), 1.63–1.60 (m, 1H), 1.10 (ddd, J = 13.9, 8.6, 4.8 Hz, 1H), 0.90 ppm (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6 (C_q), 144.8 (CH), 143.8 (C_q), 136.0 (CH), 131.5 (C_q), 128.6 (CH), 125.2 (CH), 124.8 (CH), 122.5 (CH), 119.7 (CH), 114.1 (CH_2), 77.1 (CH), 73.0 (CH), 72.3 (CH), 70.6 (CH), 67.4 (CH), 66.5 (CH), 65.8 (CH_2), 60.8 (CH), 52.4 (CH), 46.4 (CH_2), 41.9 (CH_2), 38.6 (CH_2), 35.7 (CH_2), 35.4 (CH_2), 35.3 (CH_2), 31.0 (CH_2), 27.0 (CH), 23.0 (CH_3), 20.1 ppm (CH_3); IR (film): $\tilde{\nu}$ = 3437, 2919, 2850, 1715, 1640, 1607, 1168, 855, 407 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{30}H_{42}O_6Na$: 537.2828, found: 537.2831.

Total synthesis of isolaulimalide (3)

TBS-ether 4e: To a stirred solution of **6c** (253 mg, 0.4327 mmol) in THF (8 mL) at −78 °C was added KHMDS (0.952 mL, 0.4760 mmol, 0.5 M in toluene) dropwise over 5 min. The yellow solution was allowed to stir for 3 min before **5** (144 mg, 0.369 mmol, in 1.0 mL THF) was added dropwise over 5 min. After stirring for another 90 min at the same temperature the reaction was quenched by adding H_2O (7 mL) and warmed to RT. The phases were separated and the aqueous phase was extracted four times

with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 4:1), yielding compound **4e** as viscous oil (273 mg, 0.3164 mmol, 86%). $[\alpha]_D^{20} = -49.6$ ($c = 0.72$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.5$ Hz, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 5.92–5.81 (m, 2H), 5.79 (dd, $J = 15.7$, 5.3 Hz, 1H), 5.68 (dd, $J = 15.7$, 6.7 Hz, 1H), 5.64–5.56 (m, 1H), 5.51 (dd, $J = 15.4$, 6.0 Hz, 1H), 5.42 (brs, 1H), 4.79 (brs, 1H), 4.77 (brs, 1H), 4.68 (d, $J = 6.6$ Hz, 1H), 4.58 (d, $J = 6.6$ Hz, 1H), 4.55 (s, 2H), 4.35–4.28 (m, 1H), 4.22–4.11 (m, 4H), 4.06–3.99 (m, 1H), 3.85–3.77 (m, 1H), 3.79 (s, 3H), 3.46–3.40 (m, 1H), 3.35 (s, 3H), 2.50 (ddd, $J = 16.4$, 6.8, 2.5 Hz, 1H), 2.42 (ddd, $J = 16.4$, 7.0, 2.6 Hz, 1H), 2.38–2.29 (m, 1H), 2.27–2.16 (m, 2H), 2.27–2.16 (m, 9H), 1.70 (brs, 3H), 1.62 (ddd, $J = 13.5$, 10.1, 3.2 Hz, 1H), 1.09 (ddd, $J = 13.6$, 9.5, 3.2 Hz, 1H), 0.92–0.84 (m, 12H), 0.03 (brs, 3H), 0.01 ppm (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.4$ (C_q), 144.7 (C_q), 135.9 (CH), 134.5 (CH), 131.5 (C_q), 131.0 (C_q), 129.6 (2×CH), 128.1 (CH), 127.8 (CH), 126.4 (CH), 125.7 (CH), 119.9 (CH), 113.9 (CH_2), 113.8 (2×CH), 94.6 (CH_2), 81.5 (C_q), 81.4 (CH), 77.4 (CH), 73.5 (CH), 72.7 (CH_2), 72.5 (CH), 70.9 (CH), 70.3 (CH), 66.5 (CH), 65.7 (CH_2), 55.8 (CH_3), 55.4 (CH_3), 45.3 (CH_2), 45.0 (CH_2), 42.5 (CH_2), 35.9 (CH_2), 33.7 (CH_2), 31.3 (CH_2), 27.0 (CH), 26.1 (3×CH_3), 24.6 (CH_2), 23.1 (CH_3), 19.5 (CH_3), 18.4 (C_q), −4.0 (CH_3), −4.6 ppm (CH_3); IR (film): $\tilde{\nu} = 3855$, 2927, 1700, 1653, 1513, 1249, 1038, 835, 668 cm^{-1}; HRMS(EI): m/z: calcd for $C_{45}H_{68}O_7Na$: 771.4632, found: 771.4626.

Alcohol 56: To a stirred solution (PVC flask) of compound **4e** (235 mg, 0.3137 mmol) in THF (3.5 mL) at 0°C was added HF·pyridine (70%, 1.0 mL) dropwise in 10 min. After stirring at 0°C for another 10 min the reaction was allowed to reach RT and stirred for 2 h. The mixture was diluted with CH_2Cl_2 (50 mL), cooled to 0°C and quenched by slow addition of aq. sat. $NaHCO_3$ (100 mL). The phases were separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1), yielding alcohol **56** as viscous oil (189 mg, 0.2977 mmol, 95%). $[\alpha]_D^{20} = -69.0$ ($c = 1.40$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.27$ (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 5.92–5.87 (m, 1H), 5.86–5.76 (m, 3H), 5.74–5.64 (m, 2H), 5.59–5.48 (m, 1H), 5.42 (brs, 1H), 4.89 (brs, 1H), 4.88 (brs, 1H), 4.69 (dd, $J = 13.2$, 6.2 Hz, 1H), 4.61–4.52 (m, 3H), 4.35–4.29 (m, 1H), 4.22–4.13 (m, 4H), 4.03 (ddd, $J = 9.7$, 4.7, 4.7 Hz, 1H), 3.85–3.76 (m, 1H), 3.79 (s, 3H), 3.47 (ddd, $J = 7.5$, 5.0, 5.0 Hz, 1H), 3.37 (s, 3H), 2.51 (ddd, $J = 16.5$, 7.0, 2.6 Hz, 1H), 2.42 (ddd, $J = 16.5$, 6.8, 2.6 Hz, 1H), 2.37–2.31 (m, 1H), 2.29–2.12 (m, 3H), 2.12–2.02 (m, 2H), 2.02 (t, $J = 2.7$ Hz, 1H), 2.01–1.79 (m, 5H), 1.70 (brs, 3H), 1.63 (ddd, $J = 14.0$, 9.9, 3.4 Hz, 1H), 1.14 (ddd, $J = 14.0$, 9.6, 3.2 Hz, 1H), 0.89 ppm (d, $J = 6.3$ Hz, 3H); NMR (100 MHz, $CDCl_3$): $\delta = 159.3$ (C_q), 144.8 (C_q), 135.0 (CH), 134.7 (CH), 131.5 (C_q), 131.0 (C_q), 129.8 (2×CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 125.8 (CH), 119.9 (CH), 114.5 (CH_2), 113.8 (2×CH), 94.5 (CH_2), 81.2 (C_q), 80.9 (CH), 77.7 (CH), 73.5 (CH), 72.8 (CH_2), 71.1 (CH), 70.2 (CH), 70.0 (CH), 66.1 (CH), 65.7 (CH_2), 55.8 (CH_3), 55.4 (CH_3), 44.6 (CH_2), 44.3 (CH_2), 42.7 (CH_2), 35.9 (CH_2), 33.9 (CH_2), 31.3 (CH_2), 27.0 (CH), 24.6 (CH_2), 23.1 (CH_3), 19.5 ppm (CH_3); IR (film): $\tilde{\nu} = 3468$, 2912, 1612, 1513, 1247, 1091, 1034, 707 cm^{-1}; HRMS(EI): m/z: calcd for $C_{39}H_{54}O_7Na$: 657.3767, found: 657.3777.

Epoxide 57: To a stirred suspension of powdered molecular sieves 4 Å (1.4 g) in CH_2Cl_2 (4.5 mL) at −20°C, was added (+)-diisopropyl tartrate (708 μL, 0.354 mmol, 0.5 M in CH_2Cl_2) and $Ti(OiPr)_4$ (590 μL 0.295 mmol, 0.5 M in CH_2Cl_2). The mixture was stirred for 30 min at the same temperature before *tert*-butyl hydroperoxide (749 μL, 0.412, 0.55 M in CH_2Cl_2, dried over molecular sieves 4 Å) was added dropwise. The mixture was stirred for another 30 min before a solution of **56** (155 mg, 0.244 mmol, in 1.2 mL CH_2Cl_2) was added dropwise. The reaction was stirred for 3.5 h at −20°C before it was quenched by addition of aq NaOH (4 mL, 1 M in brine). After stirring for 10 min the mixture was diluted with CH_2Cl_2 and brine, the phases were separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 3:1), yielding epoxide **57** as colorless oil (115 mg, 0.177 mmol, 73%). $[\alpha]_D^{20} = -82.5$ ($c = 1.18$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$ (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.92–5.86 (m, 1H), 5.85–5.77 (m, 2H), 5.67 (dd, $J = 15.9$, 6.8 Hz, 1H), 5.41 (brs, 1H), 4.90 (brs, 1H), 4.88 (brs, 1H), 4.71–4.66 (m, 2H), 4.62–4.56 (m, 2H), 4.35–4.29 (m, 1H), 4.24–4.19 (m, 1H), 4.17 (brs, 2H), 4.03 (ddd, $J = 9.8$, 4.7, 4.5 Hz, 1H), 3.82–3.76 (m, 1H), 3.79 (s, 3H), 3.71 (ddd, $J = 9.3$, 5.1, 3.7 Hz, 1H), 3.36 (s, 3H), 3.17–3.12 (m, 1H), 2.79 (dd, $J = 4.0$, 2.3 Hz, 1H), 2.51 (ddd, $J = 16.5$, 7.1, 2.7 Hz, 1H), 2.42 (ddd, $J = 16.5$, 6.8, 2.7 Hz, 1H), 2.30 (dd, $J = 14.3$, 3.9 Hz, 1H), 2.17 (dd, $J = 14.4$, 9.1 Hz, 1H), 2.11–2.00 (m, 3H), 1.99–1.83 (m, 6H), 1.83–1.77 (m, 1H), 1.70 (brs, 3H), 1.65–1.59 (m, 3H), 1.13 (ddd, $J = 13.8$, 9.5, 3.2 Hz, 1H), 0.89 ppm (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.5$ (C_q), 144.2 (C_q), 134.9 (CH), 131.5 (C_q), 130.7 (C_q), 129.8 (2×CH), 128.1 (CH), 127.1 (CH), 125.8 (CH), 119.9 (CH), 114.5 (CH_2), 113.8 (2×CH), 94.6 (CH_2), 81.3 (C_q), 78.5 (CH), 77.4 (CH), 73.5 (CH), 73.2 (CH_2), 71.1 (CH), 70.3 (CH), 67.5 (CH), 66.1 (CH), 65.7 (CH_2), 61.5 (CH), 55.8 (CH_3), 55.4 (CH_3), 53.4 (CH), 44.6 (CH_2), 42.7 (CH_2), 40.5 (CH_2), 35.9 (CH_2), 33.7 (CH_2), 31.3 (CH_2), 27.1 (CH), 24.6 (CH_2), 23.1 (CH_3), 19.4 ppm (CH_3); IR (film): $\tilde{\nu} = 2927$, 1653, 1617, 1513, 1248, 1093, 1035, 668 cm^{-1}; HRMS(EI): m/z: calcd for $C_{39}H_{54}O_8Na$: 673.3716, found: 673.3728.

Diol 59: To a stirred solution of epoxide **57** (83 mg, 0.1275 mmol) in THF (2 mL) at −20°C was added thiophenol (114 μL, 1.02 mmol) and dropwise $BF_3{\cdot}Et_2O$ (61.4 μL, 0.4845 mmol). The mixture was stirred at the same temperature for 6 h and then allowed to warm to RT and stirred for another 3 h. Et_3N (1.4 mL) was added, the reaction, quenched with aq. sat. $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (12 mL). The phases were separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 4:1 → 1:1), yielding diol **59** as colorless oil (54 mg, 0.0890 mmol, 70%). $[\alpha]_D^{20} = -51.4$ ($c = 1.05$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$ (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.96 (ddd, $J = 15.7$, 7.3, 1.0 Hz, 1H), 5.92–5.86 (m, 1H), 5.85–5.78 (m, 2H), 5.42 (brs, 1H), 4.92 (brs, 1H), 4.91 (brs, 1H), 4.52 (d, $J = 11.7$ Hz, 1H), 4.44 (d, $J = 11.7$ Hz, 1H), 4.43–4.39 (m, 2H), 4.36–4.29 (m, 1H), 4.19 (brs, 2H), 4.10–4.03 (m, 2H), 3.82–3.73 (m, 3H), 3.80 (s, 3H), 2.56–2.46 (m, 2H), 2.42 (ddd, $J = 16.5$, 6.9, 2.6 Hz, 1H), 2.31–2.25 (m, 2H), 2.22 (ddd, $J = 13.1$, 6.3, 1.8 Hz, 1H), 2.17–2.02 (m, 4H), 1.98–1.84 (m, 5H), 1.70 (brs, 3H), 1.67–1.59 (m, 2H), 1.16 (ddd, $J = 13.8$, 9.0, 3.2 Hz, 1H), 0.89 ppm (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.3$ (C_q), 145.0 (C_q), 134.1 (CH), 131.6 (C_q), 130.6 (C_q), 129.2 (2×CH), 128.0 (CH), 127.9 (CH), 125.8 (CH), 119.9 (CH), 114.8 (CH_2), 113.9 (2×CH), 83.1 (CH), 81.3 (C_q), 80.8 (CH), 78.7 (CH), 75.1 (CH), 73.8 (CH), 71.4 (CH_2), 71.1 (CH), 70.3 (CH), 69.8 (CH), 66.2 (CH), 65.7 (CH_2), 55.4 (CH_3), 44.3 (CH_2), 42.6 (CH_2), 39.9 (CH_2), 35.9 (CH_2), 33.4 (CH_2), 31.3 (CH_2), 27.2 (CH), 24.6 (CH_2), 23.1 (CH_3), 19.4 ppm (CH_3); IR (film): $\tilde{\nu} = 3436$, 2913, 1613, 1513, 1248, 1174, 1037, 706 cm^{-1}; HRMS(EI): m/z: calcd for $C_{37}H_{50}O_7Na$: 629.3454, found: 629.3446.

TBS-ether 60: To a stirred solution of diol **59** (52 mg, 0.0857 mmol) in CH_2Cl_2 (2 mL) at −20°C was added 2,6-lutidine (55 mg, 0.510 mmol) and dropwise TBSOTf (114 mg, 0.431 mmol). The reaction was allowed to reach RT after addition and was stirred for 8 h. The mixture was cooled to 0°C, diluted with CH_2Cl_2 (70 mL) and quenched with sat. aq. $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase extracted three times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, hexane/EtOAc 10:1 → 5:1), yielding compound **60** as colorless, viscous oil (62 mg, 0.0742 mmol, 87%). $[\alpha]_D^{20} = -82.3$ ($c = 0.65$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 5.94 (ddd, $J = 15.6$, 7.3, 0.9 Hz, 1H), 5.91–5.86 (m, 1H), 5.85–5.81 (m, 1H), 5.78 (dd, $J = 15.6$, 6.0 Hz, 1H), 5.42 (brs, 1H), 4.84 (brs, 1H), 4.80 (brs, 1H), 4.50 (d, $J = 11.6$ Hz, 1H), 4.43 (d, $J = 11.6$ Hz, 1H), 4.34–4.27 (m, 3H), 4.19 (brs, 2H), 4.09–4.03 (m, 1H), 4.03–3.98 (m, 1H), 3.90–3.86 (m, 1H), 3.85–3.82 (m, 1H), 3.82–3.77 (m, 2H), 3.80 (s, 3H), 2.49 (ddd, $J = 16.4$, 6.7, 2.7 Hz, 1H), 2.42 (ddd, $J = 16.4$, 7.2, 2.7 Hz, 1H), 2.20 (dd, $J = 14.3$, 6.9 Hz, 1H), 2.16–2.05 (m, 4H), 2.00 (t, $J = 2.7$ Hz, 1H), 1.98–1.85 (m, 6H), 1.70 (brs, 3H), 1.68–1.59 (m, 1H), 1.13–

1.02 (m, 1H), 0.94–0.82 (m, 21H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (C_q), 144.7 (C_q), 133.4 (CH), 131.8 (C_q), 130.9 (C_q), 129.2 (2×CH), 128.8 (CH), 128.1 (CH), 125.7 (CH), 119.9 (CH), 114.4 (CH_2), 113.9 (2×CH), 83.9 (CH), 81.4 (CH), 81.2 (C_q), 78.0 (CH), 77.3 (CH), 74.3 (CH), 74.0 (CH_2), 71.3 (CH), 70.8 (CH), 70.2 (CH), 65.9 (CH), 65.8 (CH_2), 55.4 (CH_3), 44.9 (CH_2), 42.3 (CH_2), 40.6 (CH_2), 35.9 (CH_2), 33.8 (CH_2), 31.2 (CH_2), 27.1 (CH), 26.2 (6×CH_3), 24.6 (CH_2), 23.1 (CH_3), 19.6 (CH_3), 18.4 (C_q), 18.3 (C_q), −3.8 (CH_3), −3.9 (CH_3), −4.5 ppm (2×CH_3); IR (film): $\tilde{\nu}$ = 2928, 1514, 1249, 1091, 835, 776 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{49}H_{78}O_7Si_2Na$: 857.5184, found: 857.5195.

Alcohol 60a: To a stirred solution of compound **60** (52 mg, 0.06225 mmol) in a biphasic 1:1 mixture of CH_2Cl_2/aq. (pH 7) buffer (4 mL) was added DDQ (55 mg, 0.2573 mmol) portion wise at RT. The reaction was stirred overnight and diluted with aq. sat. $NaHCO_3$ (15 mL) and CH_2Cl_2 (10 mL). The phases were separated and the aqueous layer was extracted with four times with CH_2Cl_2. The combined organic layer was washed two times with aq. sat. $NaHCO_3$, dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 10:1 → 4:1), yielding **60a** as viscous oil (41 mg, 0.05733 mmol, 90%). $[\alpha]_D^{20}$ = −43.7 (*c* = 1.23 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93–5.86 (m, 2H), 5.85–5.79 (m, 2H), 5.42 (brs, 1H), 4.84 (brs, 1H), 4.80 (brs, 1H), 4.37–4.29 (m, 3H), 4.27–4.23 (m, 1H), 4.18 (brs, 2H), 4.09–4.03 (m, 1H), 3.95–3.91 (m, 1H), 3.84 (brd, *J* = 4.1 Hz, 1H), 3.82–3.77 (m, 1H), 2.50 (ddd, *J* = 16.4, 6.8, 2.8 Hz, 1H), 2.42 (ddd, *J* = 16.4, 7.2, 2.8 Hz, 1H), 2.24 (dd, *J* = 14.4, 6.6 Hz, 1H), 2.21–2.02 (m, 4H), 2.01 (t, *J* = 2.6 Hz, 1H), 2.00–1.83 (m, 6H), 1.70 (brs, 3H), 1.68–1.59 (m, 1H), 1.10 (ddd, *J* = 13.7, 9.6, 3.1 Hz, 1H), 0.93–0.85 (m, 21H), 0.10 (s, 3H), 0.05 (s, 6H), 0.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8 (C_q), 134.5 (CH), 131.6 (C_q), 128.1 (CH), 127.3 (CH), 125.8 (CH), 119.8 (CH), 114.4 (CH_2), 82.6 (CH), 81.2 (C_q), 78.0 (CH), 77.8 (CH), 74.7 (CH), 74.1 (CH), 73.7(CH), 70.9 (CH), 70.2 (CH), 66.0 (CH), 65.8 (CH_2), 44.9 (CH_2), 42.5 (CH_2), 40.1 (CH_2), 37.5 (CH_2), 35.9 (CH_2), 31.3 (CH_2), 27.0 (CH), 26.2 (6×CH_3), 24.6 (CH_2), 23.1 (CH_3), 19.4 (CH_3), 18.4 (C_q), 18.3 (C_q), −3.7 (CH_3), −4.0 (CH_3), −4.5 (CH_3), −4.6 ppm (CH_3); IR (film): $\tilde{\nu}$ = 3313, 2929, 2856, 1407, 1254, 1123, 836, 777, 636 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{41}H_{70}O_6Si_2Na$: 737.4609, found: 737.4625.

Seco-acid 61: To a stirred solution of compound **60a** (35 mg, 0.0489 mmol) in THF (1.5 mL) at −78 °C was added *n*BuLi (0.122 mL, 0.195 mmol, 1.6 M in hexane) dropwise over a period of 5 min. The bright yellow solution was stirred for 5 min and then CO_2(g) was bubbled through the reaction for 15 min. The reaction was warmed to RT, quenched by addition of aq. sat. NH_4Cl (7 mL) and diluted with CH_2Cl_2 (10 mL), the phases were separated and the aqueous phase was extracted four times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The obtained oil was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 6:1), yielding compound **61** as viscous oil (32 mg, 0.0421 mmol, 86%). $[\alpha]_D^{20}$ = −37.8 (*c* = 0.88 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93–5.82 (m, 4H), 5.40 (brs, 1H), 4.84 (brs, 1H), 4.80 (brs, 1H), 4.37–4.27 (m, 4H), 4.20 (brs, 2H), 4.11–4.05 (m, 1H), 3.96–3.90 (m, 1H), 3.82 (brd, *J* = 3.9 Hz, 1H), 3.87–3.70 (m, 1H), 2.57 (dd, *J* = 16.3, 5.8 Hz, 1H), 2.48 (dd, *J* = 16.3, 7.9 Hz, 1H), 2.24–1.94 (m, 8H), 1.94–1.79 (m, 4H), 1.69 (brs, 3H), 1.67–1.08 (m, 1H), 1.16–1.08 (m, 1H), 0.91–0.86 (m, 21H), 0.11 (s, 3H), 0.05 (s, 6H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1 (C_q), 144.7 (C_q), 134.1 (CH), 131.5 (C_q), 128.2 (2×CH), 125.8 (CH), 119.7 (CH), 114.4 (CH_2), 88.6 (C_q), 82.8 (CH), 78.3 (CH), 78.1 (CH), 74.8 (CH), 74.0 (CH), 73.1 (C_q), 73.7(CH), 70.4 (CH), 66.4 (CH), 65.8 (CH_2), 45.2 (CH_2), 42.5 (CH_2), 37.5 (CH_2), 37.5 (CH_2), 31.6 (CH_2), 29.9 (CH_2), 27.2 (CH), 26.3 (6×CH_3), 24.9 (CH_2), 23.1 (CH_3), 19.6 (CH_3), 18.4 (C_q), 18.3 (C_q), −3.7 (CH_3), −3.9 (CH_3), −4.5 (CH_3), −4.6 ppm (CH_3); IR (film): $\tilde{\nu}$ = 2929, 2857, 1580, 1388, 1254, 1046, 835, 777 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{42}H_{70}O_8Si_2Na$: 781.4507, found: 781.4519.

Macrolactone 63: To a stirred solution of seco acid **61** (15.0 mg, 0.0198 mmol) in benzene (1 mL) at RT was added Et_3N (8.2 μL, 0.0812 mmol) and dropwise 2,4,6-trichlorobenzoyl chloride (7.6 μL, 0.0312 mmol). The solution was stirred for 4 h before it was diluted with benzene (10 mL) and added over 6 h via a syringe pump into a stirred solution of DMAP (24.2 mg, 0.1982 mmol) in benzene (130 mL). After additional 6 h the mixture was concentrated to about 20 mL, aq. sat. $NaHCO_3$ (15 mL) was added and the mixture was stirred for 20 min. The phases were separated and the aqueous layer was extracted four times with EtOAc. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 10:1 → 7:1), yielding a 4:1 mixture of **62** and its dimer as viscous oil (8.4 mg) that was used without further separation in the next step. To a stirred solution (PVC flask) of the 4:1 mixture of compound **62** and the dimer (7 mg) in THF (1 mL) at 0 °C was added HF·pyridine (70%, 400 μL) dropwise in 5 min. After stirring at 0 °C for another 10 min the reaction was allowed to reach RT and stirred for 5 h. The mixture was diluted with CH_2Cl_2 (5 mL), cooled to 0 °C and quenched by slow addition of aq. sat. $NaHCO_3$ (8 mL). The phases were separated and the aqueous layer was extracted five times with CH_2Cl_2. The combined organic phase was dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1 → 1:2), yielding diol **63** as colorless oil (3.2 mg, 0.00619 mmol, 32% over two steps). $[\alpha]_D^{20}$ = 26.2 (*c* = 0.13 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.93–5.89 (m, 1H), 5.86–5.84 (m, 2H), 5.63–5.60 (m, 1H), 5.43–5.41 (m, 2H), 4.92 (brs, 2H), 4.55 (dd, *J* = 6.2, 4.9 Hz, 1H), 4.43 (brd, *J* = 10.6 Hz, 1H), 4.29 (ddd, *J* = 11.7, 3.8, 1.5 Hz, 1H), 4.20 (brs, 1H), 4.20–4.16 (m, 2H), 3.78–3.73 (m, 1H), 2.72 (dd, *J* = 18.0, 11.1 Hz, 1H), 2.41 (dd, *J* = 18.0, 2.3 Hz, 1H), 2.34 (d, *J* = 2.6 Hz, 1H), 2.22 (ddd, *J* = 13.6, 11.7, 3.4 Hz, 1H), 2.17–2.08 (m, 3H), 2.05 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.03–1.98 (m, 1H), 1.98–1.92 (m, 3H), 1.86 (dd, *J* = 13.6, 11.0 Hz, 1H), 1.70 (brs, 3H), 1.60 (ddd, *J* = 14.0, 10.6, 3.0 Hz, 1H), 1.15 (ddd, *J* = 14.0, 11.1, 2.6 Hz, 1H), 0.80 ppm (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.1 (C_q), 144.2 (C_q), 135.8 (CH), 131.5 (C_q), 127.6 (CH), 126.6 (CH), 126.0 (CH), 119.8 (CH), 113.9 (CH_2), 87.7 (C_q), 80.9 (CH), 78.7 (CH), 78.3 (CH), 73.8 (C_q), 73.6 (CH), 71.8 (CH), 71.1 (CH), 69.7 (CH), 65.7 (CH_2), 64.4 (CH), 46.2 (CH_2), 44.4 (CH_2), 35.8 (CH_2), 35.4 (CH_2), 34.6 (CH_2), 31.6 (CH_2), 25.8 (CH), 24.2 (CH_2), 23.1 (CH_3), 17.3 ppm (CH_3); IR (film): $\tilde{\nu}$ = 2924, 2853, 2236, 1713, 1459, 1247, 1071, 672 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{30}H_{40}O_7Na$: 535.2672, found: 535.2682.

Isolaulimalide (3): To a stirred solution of diol **63** (3.1 mg, 0.00602 mmol) in EtOAc/cyclohexene 1:1 (1 mL) at RT was added quinoline (3.6 μL). H_2 (balloon) was bubbled through the reaction and Lindlar catalyst (3 mg) was added. After 2 h the reaction was filtered through a short pad of celite, subsequently the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1 to 1:2). Yielding isolaulimalide (**3**) as white solid (3.0 mg, 0.00583 mmol, 97%), that was identical in every aspect with the reported data of the natural compound. $[\alpha]_D^{20}$ = −17.9 (*c* = 0.28 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.19 (ddd, *J* = 11.7, 10.6, 6.8 Hz, 1H), 5.90 (ddd, *J* = 15.7, 5.8, 1.4 Hz, 1H), 5.88–5.84 (m, 2H), 5.76–5.72 (m, 1H), 5.70 (ddd, *J* = 15.7, 5.9, 1.4 Hz, 1H), 5.56 (t, *J* = 4.0 Hz, 1H), 5.37 (brs, 1H), 4.89 (brs, 1H), 4.88 (brs, 1H), 4.63–4.60 (m, 1H), 4.36 (ddd, *J* = 10.9, 4.8, 4.8 Hz, 1H), 4.32–4.27 (m, 1H), 4.15–4.11 (m, 3H), 4.06 (brd, *J* = 9.4 Hz, 1H), 4.00–3.96 (m, 1H), 3.66–3.61 (m, 1H), 3.18 (dddd, *J* = 12.0, 10.5, 5.3, 1.5 Hz, 1H), 2.51 (dddd, *J* = 12.1, 9.7, 6.9, 0.8 Hz, 1H), 2.36 (ddd, *J* = 13.7, 10.9, 4.4 Hz, 1H), 2.30–2.24 (m, 1H), 2.21 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.23–2.17 (m, 2H), 2.12–2.08 (m, 1H), 2.02–1.92 (m, 4H), 1.87–1.81 (m, 2H), 1.67 (brs, 3H), 1.51 (ddd, *J* = 14.0, 9.2, 2.2 Hz, 1H), 1.13 (ddd, *J* = 14.0, 9.4, 2.6 Hz, 1H), 0.86 ppm (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.5 (C_q), 145.0 (C_q), 143.2 (CH), 134.1 (CH), 131.5 (C_q), 128.3 (CH), 125.9 (CH), 125.7 (CH), 123.1 (CH), 119.9 (CH), 113.8 (CH_2), 81.6 (CH), 78.2 (CH), 76.8 (CH), 74.6 (CH), 73.5 (CH), 73.0 (CH), 70.6 (CH), 66.9 (CH), 65.6 (CH_2), 45.7 (CH_2), 43.0 (CH_2), 36.0 (CH_2), 35.7 (CH_2), 35.5 (CH_2), 34.7 (CH_2), 31.9 (CH_2), 27.5 (CH), 23.1 (CH_3), 19.9 ppm (CH_3); IR (film): $\tilde{\nu}$ = 3425, 2917, 1713, 1644, 1033 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{30}H_{42}O_7$: 514.2931, found: 514.2922.

Cytotoxicity assay (Table 1**)**: The MCF-7 (breast cancer), HCT116 (colon carcinoma) and PC-3 M (prostate cancer) cell lines originate from the American Type Culture (ATCC) and were obtained as a generous gift

from Markus Wartmann, Novartis AG, Switzerland. Cells were seeded at 1.5×10^3 per well into 96-well microtiter plates and incubated overnight. Compounds were added in serial dilutions on day 1. Subsequently, the plates were incubated for 72 h and then fixed with 3.3% v/v glutaraldehyde, washed with water and stained with 0.05% methylene blue. After washing, the dye was eluted with 3% v/v HCl and the optical density measured at 665 nm with a GeniosPro photometer (Tecan, Switzerland). IC_{50} values were determined by the GraphPad Prim software (San Diego, USA) using the formula $(OD_{treated}-OD_{start})/(OD_{control}-OD_{start})\times100$. IC_{50} is defined as the drug concentration which leads to 50% of cells per well as compared to control cultures (100%) at the end of the incubation period. Experiments were performed three times on different days.

Tubulin polymerization assay (Table 2**)**: Pure αβ-tubulin (> 95%) was isolated from fresh pig brain according to the method of Castoldi and Popov with slight modifications as previously reported.[24,25] For the tubulin polymerization assays freshly thawed solutions of αβ-tubulin in BRB80 buffer (80 mM PIPES, 1 mM $MgCl_2$, 1 mM EGTA adjusted to pH 6.8 with KOH) were centrifuged at 5000 g for 5 min at 5 °C. This solution was incubated with additional BRB80 and test compounds, as 2 mM DMSO solutions, were then added on ice. Experiments were carried out in a 96-well quartz plate in 100 μL volumes at a concentration of 30 μM tubulin and 30 μM test compound. The polymerization was monitored by following the increase in absorption at 340 nm in a temperature-controlled TECAN GeniosPro spectrophotometer at RT (actual measuring temperature was 24–27 °C). The concentration of DMSO used in the polymerization experiments was found to be highly critical; concentrations >2% DMSO induced considerable microtubule formation even in the absence of test compounds. All experiments, along with both negative (untreated αβ-tubulin) and vehicle (DMSO) controls, were carried out in triplicate. The maximal polymerization for each compound was determined using the GraphPad Prim software (San Diego, USA) and the EC_{50} (half maximal effective concentration) values were calculated from the concentration-effect curve. Experiments were performed with at least two different αβ-tubulin batches.

Acknowledgements

We gratefully acknowledge financial support from The Austrian Science Fund (FWF project L202-N19). We thank Dr. H. Kählig, Dr. L. Brecker and S. Felsinger, Universität Wien, for NMR spectra, M. Zinke and S. Schneider, Universität Wien, for HPLC analysis and M. Wartmann, Novartis AG, Switzerland, for donation of the cell lines for the cytotoxicity assays.

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Received: December 11, 2008
Published online: April 28, 2009

