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A Concise Sultone Route to Highly Oxygenated 1,10-*seco*-Eudesmanolides – Enantioselective Total Synthesis of the Antileukemic Sesquiterpene Lactones (–)-Eriolanin and (–)-Eriolangin

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Dedicated to Professor Günter Domschke on the occasion of his 75th birthday

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Using a sultone as the key intermediate, the first enantioselective total synthesis of the antileukemic 1,10-*seco*-eudesmanolides (–)-eriolanin (**1**) and (–)-eriolangin (**2**) was achieved, which also established the hitherto unknown absolute configuration of these sesquiterpene lactones. Starting from 2-bromo-1-(2-furyl)ethanone, 24 steps were required to generate the common basic structure and two additional steps in each case for completion of the natural products. The effect of **1** and **2** on the cell cycle of human leukemia (HL-60) cells was investigated by flow cytometry.

Introduction

Eriolanin (**1**) and eriolangin (**2**) isolated from the plant *Eriophyllum lanatum*[1] are highly oxygenated members of the 1,10-*seco*-eudesmanolide family of sesquiterpene lactones, which also includes the britannilactones **3a**–**c**[2,3] and ivangulin (**4**)[4] (Figure 1). For lactones **1**–**3**, interesting bioactivities have been reported. Thus, **1** and **2** inhibit the in vitro growth of the human KB tumor cell line and additionally display a significant antileukemic activity in vivo in mice.[1] Likewise, compounds **3** have been shown to be cytotoxic in cancer cells.[5] Moreover, **3b** inhibits inducible nitric oxide synthase,[6] and **3c** effects cell cycle arrest at the G_2+M phase as well as polymerization of microtubules.[5b]

The constitution and relative configuration of the 1,10-*seco*-eudesmanolides **1** and **2** was elucidated by NMR techniques and X-ray analysis[1] and confirmed by several syntheses of racemic **1**[7,8] and one of racemic **2**,[7] whereas the absolute configuration of these compounds was unknown prior to our work. Herein we give a full account of our sultone approach[9] culminating in the first enantioselective total synthesis[10] of (–)-eriolanin (**1**) and (–)-eriolangin (**2**) that also opens a synthetic access toward the less highly

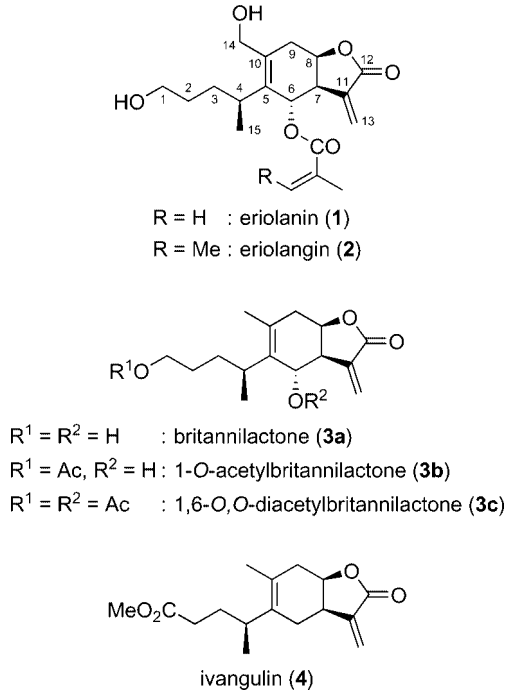

Figure 1. Representatives of the 1,10-*seco*-eudesmanolides.

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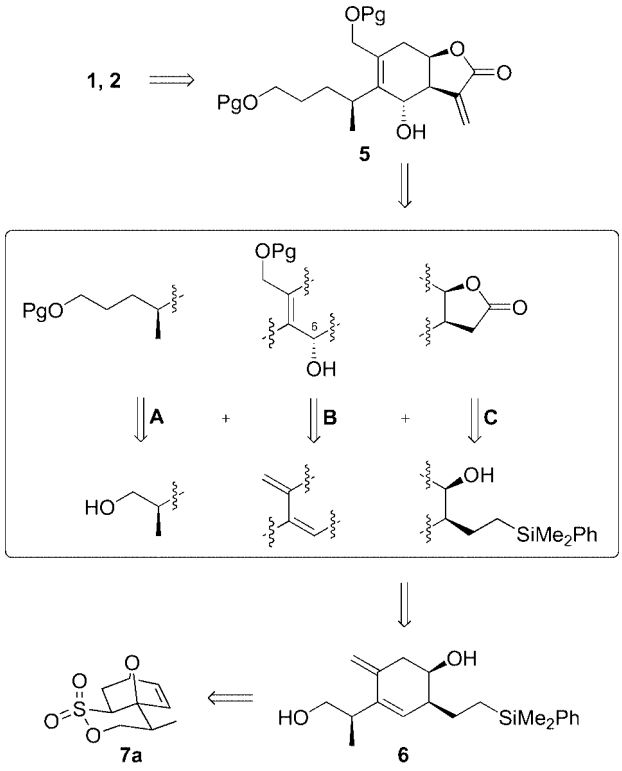
oxygenated, cytotoxic britannilactone (**3a**) and its derivatives **3b**,**c**. Furthermore, we disclose our investigations on the effects of **1** and **2** on the cell cycle of human leukemia (HL-60) cells by flow cytometry.

Results and Discussion

Synthetic Plan

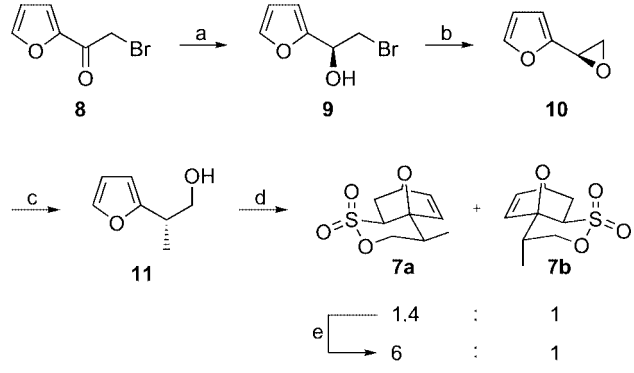
According to our synthetic plan, both target molecules **1** and **2** would be derived from the common alcohol precursor **5** and thus, their syntheses would differ only in the penultimate esterification step (Scheme 1). Further retrosynthetic disconnection of **5** leads to the highly functionalized methylenecyclohexene **6** revealing three major tasks: A) elongation of the side chain by a C_2 unit, B) generation of the enediol fragment with correct configuration at C6 (eudesmane numbering) from a semicyclic 1,3-diene subunit, and C) construction of the γ-lactone moiety by elaboration of the latent 1,4-diol already present in **6**. The key intermediate **6** was envisioned to be accessible from the sultone **7a**, the racemic mixture of which already enabled a short and highly diastereoselective synthesis of the 1,10-*seco*-eudesmanolide ivangulin **4**,[11] through a one-pot elimination/alkoxide-directed 1,6-addition/desulfurization with simultaneous methylenation.[12]



Scheme 1. Retrosynthetic analysis for eriolanin (**1**) and eriolangin (**2**).

Synthesis of Enantiopure Sultone 7a

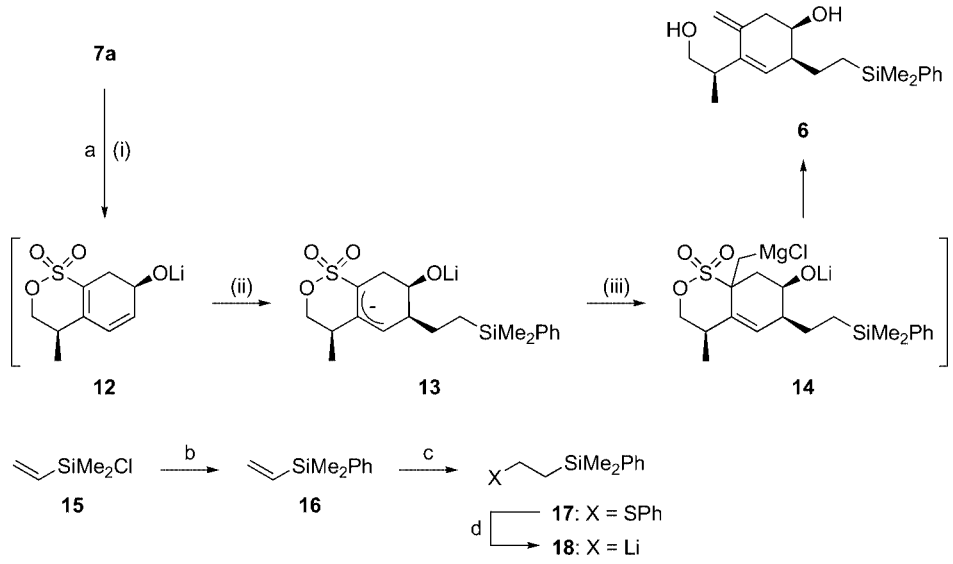
Initially, we focused on the development of a multi-gram-scale synthesis of the enantiomerically pure hydroxyalkylfuran **11**[13] (Scheme 2). To this end, we subjected the α-bromo ketone **8**[14] to a catalytic enantioselective transfer hydrogenation under conditions modified from those reported for α-chloro ketone derivatives.[15] The resulting bromohydrin **9** was obtained in excellent optical purity (>99% *ee* according to capillary GC) and delivered the highly sensitive epoxide **10** after mild basic treatment. As already reported for the racemic series,[16] ring opening of **10** with methylmagnesium bromide or methylcyanocuprate took place with good (MeMgBr: 10:1) to complete [MeCu(CN)Li] regioselectivity at the sterically more hindered position to give a primary alcohol. The stereochemical course, however, was strongly dependent on the nature of the methyl nucleophile. While the reaction proceeded with extensive racemization (<20% *ee* according to capillary GC) in case of methylmagnesium bromide, complete inversion of configuration to give **11** was observed for the less Lewis acidic cyanocuprate. Subsequent treatment of **11** with β-chloroethanesulfonic acid chloride[17] and triethylamine triggered a domino process consisting of dehydrohalogenation, esterification, and intramolecular Diels–Alder reaction to afford a mixture of the *exo* sultones **7a** and **7b**. Following thermal equilibration,[11] the required diastereomer **7a** was isolated in excellent yield by recrystallization.



Scheme 2. Preparation of sultone **7a**: a) 0.2 mol-% [Cp*RhCl((*R*,*R*)-tsdpen)], HCO_2H, Et_3N, EtOAc, 0 °C, >99% *ee*; b) K_2CO_3, MeCN, room temp.; c) MeCu(CN)Li, Et_2O, –78 °C to room temp., 50% (3 steps), >98.5% *ee*; d) β-chloroethanesulfonic acid chloride, Et_3N, CH_2Cl_2, room temp.; e) cat. BHT, EtOAc, 120 °C, microwaves, 80% **7a** (2 steps).

Synthesis of the Cyclohexene Core

The one-pot sequential transformation[12] of the sultone **7a** to the methylenecyclohexene **6** was initiated by deprotonation of **7a** using one equivalent of methyllithium to bring about cleavage of the oxo bridge by β-elimination with formation of the intermediate **12** (Scheme 3). This electron-deficient 1,3-diene underwent a completely regio- and diastereoselective alkoxide-directed 1,6-addition upon treatment with the lithiosilane **18** prepared by reductive lithiation of the thio ether **17**,[18] which in turn was derived from the vinylsilane **16**[19] through radical addition[20] of thiophenol. The resulting allyllithium species **13** was then regioselectively alkylated using (iodomethyl)magnesium chlo-



Scheme 3. Sequential one-pot transformation of the sultone **7a** to the methylenecyclohexene **6**: a) (i) MeLi, THF, –78 °C, (ii) **18**, –78 °C to –20 °C, (iii) ICH_2MgCl, THF, –78 °C to room temp., 61%; b) PhMgBr, THF, reflux, 83%; c) PhSH, AIBN, 100 °C, 87%; d) LiDBB, THF, –78 °C.

ride[21] to furnish the β-metallosultone **14**, which upon warming to room temperature collapsed by β-elimination with rupture of the δ-sultone to give the methylenecyclohexene **6** in good yield. In a single synthetic operation, the prefunctions for a γ-lactone were unfolded, an activation for 1,4-dioxygenation was created by virtue of the 1,3-diene, and the primary hydroxy group was liberated for side-chain elongation. At this stage, both the relative and absolute configuration of compound **6** were determined by X-ray diffraction analysis using anomalous scattering (Figure 2).[22,23]

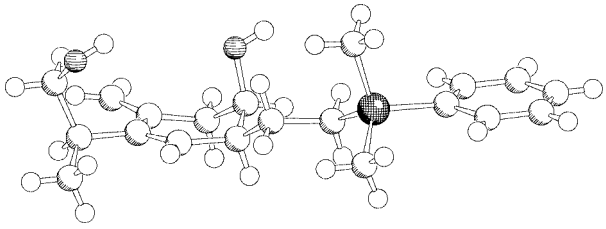
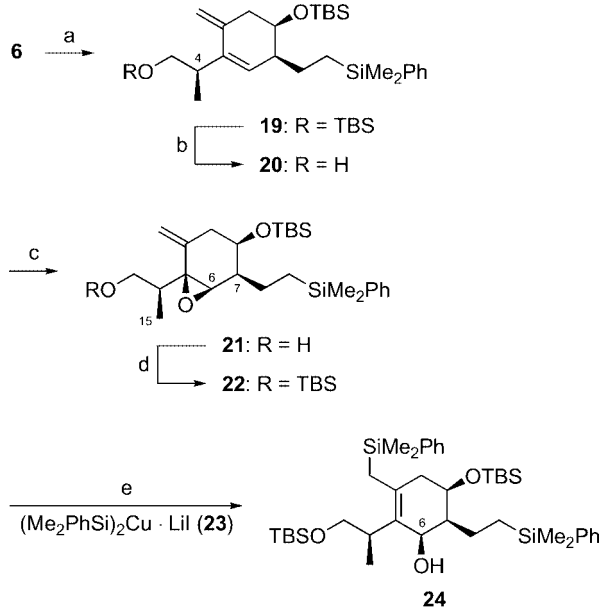


Figure 2. Crystal structure of the methylenecyclohexene **6**.[22,23]

1,4-Difunctionalization, Part I

Our first attempts to eventually 1,4-dioxygenate the 1,3-diene moiety of **6** are depicted in Scheme 4. Conversion of **6** to the bis(silyl) ether **19** followed by chemoselective monodeprotection furnished the primary alcohol **20**. The array of functional groups present in **20** appeared to provide an ideal basis for a chemoselective hydroxy-directed epoxidation[24] of the more electron-rich endocyclic double bond *trans* to the substituents on the six-membered ring. Unfortunately, the undesired diastereomer **21** was always the major product. Using *m*-chloroperbenzoic acid,[25] compound **21** was obtained as a single regio- and stereoisomer in quantitative yield. If the alcohol **20** adopts a conformation in solution similar to the crystal structure of the corresponding diol **6** (Figure 2), this selectivity is readily understood. Due to minimization of $A^{1,3}$ strain, the hydrogen atom at C4 points toward the *exo* methylene unit, which forces the hydroxymethyl group up to deliver the epoxidation reagent from the top face. The relative configuration of the epoxide **21** was clearly revealed by a 2D NOESY investigation (strong NOEs between C6-H and C7-H and between C6-H and C15-H_3). Whereas efforts to generate an enediol fragment through S_N2' ring opening of the vinyl



Scheme 4. 1,4-Difunctionalization of the 1,3-diene subunit, part I: a) TBSCl, imidazole, DMAP, DMF, room temp., 99%; b) TBAF, THF, 0 °C, 81% **20** + 17% **6**; c) *m*CPBA, $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C; d) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C; e) **23**, THF, Et_2O, –20 °C to 0 °C, 50% (3 steps).

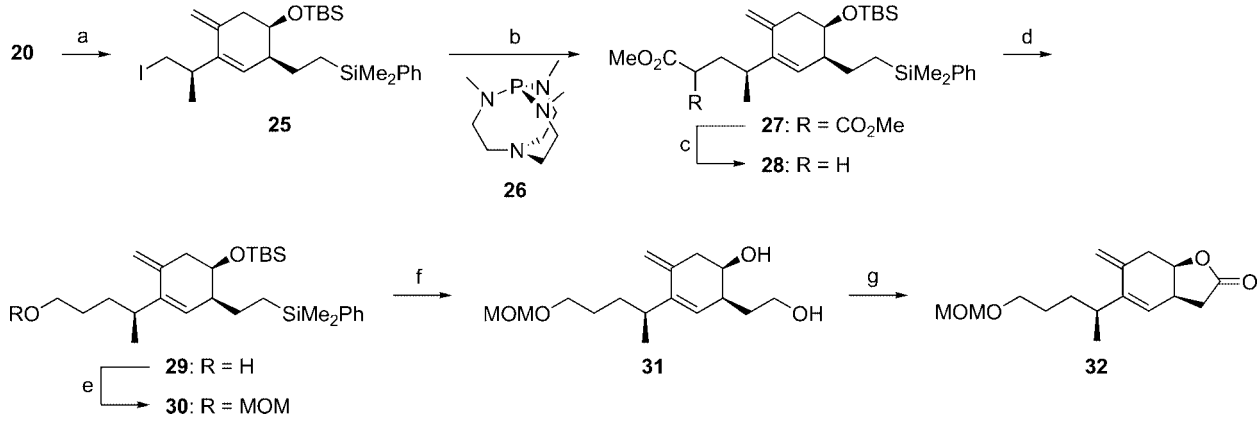
epoxide with oxygen nucleophiles met with failure in our hands,[7] this mode of attack was accomplished in the reaction of the silyl ether **22** with the silicon nucleophile **23** as a latent hydroxy anion equivalent.[26] However, experiments to amend the configuration at C6 of the resulting allylsilane **24** by Mitsunobu inversion[27] failed and additionally revealed an extreme sensitivity of **24** toward acid-triggered elimination with reformation of the 1,3-diene **19**. Because of this instability and the chemoselectivity problems that might be encountered after Tamao–Fleming oxidation of both carbon–silicon bonds in **24**,[28] we decided to elongate the side chain before taking care of the enediol.

Side-Chain Elongation and Construction of the γ-Lactone Moiety

For side-chain elongation, we applied a strategy similar to the one used in our synthesis of ivangulin (**4**) (Scheme 5).[11] After conversion[29] of the alcohol **20** to the iodide **25**, the required C_2 unit was attached by alkylation with dimethyl malonate. Since **25** was prone to undergo dehydrohalogenation, utilization of proazaphosphatrane **26**[30] was essential for efficient conversion to **27**. Mild demethoxycarbonylation[11,31] of **27** followed by reduction and protection afforded the MOM ether **30**. For construction of the γ-lactone moiety, we took full advantage of the Tamao–Fleming oxidation,[28,32] which smoothly delivered the diol **31**. Addition of molecular sieves (4 Å) in the first step caused a significant increase in yield, presumably due to enhancing the reactivity of tetrabutylammonium fluoride. Subsequent chemoselective oxidative ring closure of **31** to give the lactone **32** proved to be unexpectedly difficult, and only ultrasound-accelerated[33] TPAP oxidation[34] led to an acceptable yield of **32**. Unfortunately, attempted 1,4-dioxygenation of the 1,3-diene subunit of **32** by epoxidation followed by S_N2' ring opening led to complex mixtures of regio- and diastereoisomers. Due to the lack of selectivity at this stage, we opted for generation of the enediol prior to setting up the γ-lactone.

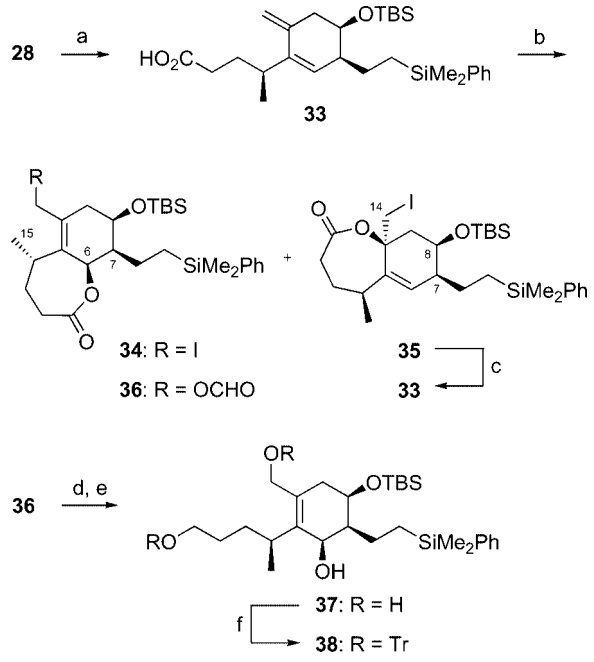
1,4-Difunctionalization, Part II

An intramolecular protocol was eventually decisive for the efficient generation of the enediol fragment of the target molecules (Scheme 6). Encouraged by reports of Rousseau on the facile iodolactonization of ω-heptenoic acids to give ε-lactones,[35] we envisioned an access to the enediol subunit through such a cyclofunctionalization of the dienylcarboxylic acid **33** and subsequent iodine–acyloxy exchange. To this end, the methyl ester **28** was saponified, and the resulting acid **33** was treated with bis(*s*-collidine)iodine(I) hexafluorophosphate[35] in toluene as the solvent of choice, whereupon the unstable iodolactone **34** along with small amounts of the regioisomer **35** were formed. Addition of silver acetate and dimethylformamide[36] to this reaction mixture selectively converted **34** to the formyloxy ε-lactone **36** in a one-pot procedure, whereas the minor isomer **35** proved to be completely unreactive under these conditions and could be reductively[37] eliminated to return **33** in a separate operation. Apparently, the intermediate allylcarbenium ion generated from the allylic iodide **34** is trapped by the solvent dimethylformamide as the nucleophile to give an iminium ion, which is converted into the formate **36** during aqueous workup. In line with this rationale, exchange of dimethylformamide against acetonitrile[36] did not allow conversion of **34**. Replacement of the formylation of **34** by reductive deiodination[38,39] should allow a straightforward access to britannilactone (**3a**) and its derivatives **3b**,**c**. The relative configuration of **36** was elucidated by 2D NOESY investigations at the stage of iodolactone **34** isolated on an analytical scale prior to addition of silver acetate and dimethylformamide in the racemic series (strong NOEs between C6-H and C7-H and between C6-H and C15-H_3). Likewise, the relative configuration of the iodolactone **35** was determined by 2D NOESY experiments (strong NOEs



Scheme 5. Side-chain elongation and synthesis of the lactone **32**: a) I_2, Ph_3P, imidazole, THF, MeCN, –20 °C to room temp., 84%; b) **26**, dimethyl malonate, MeCN, room temp., 91%; c) PhSH, K_2CO_3, DMF, 90 °C, 89%; d) $LiAlH_4$, Et_2O, 0 °C, 100%; e) MOMCl, Et(*i*Pr)$_2$N, CH_2Cl_2, 0 °C to room temp., 99%; f) (i) TBAF, MS (4 Å), THF, reflux, (ii) KF, H_2O_2, $NaHCO_3$, THF, MeOH, reflux, 87%; g) 10 mol-% TPAP, NMO, MS (4 Å), MeCN, 15 °C to 20 °C, ultrasound, 65%.

between C14-H_a and C7-H and between C14-H_a and C8-H). Reduction of the diester **36** with lithium aluminum hydride at 0 °C smoothly gave a hydroxy lactol after aqueous workup. Because increasing the reaction temperature in order to achieve complete reduction of **36** caused desilylation of the secondary alcohol, the hydroxy lactol was further reduced with lithium borohydride to afford the triol **37** in excellent overall yield. Chemoselective tritylation of the two primary alcohols in **37** cleanly afforded the bis(trityl) ether **38**. While this reaction sequence effected a rapid construction of the enediol moiety, the undesired configuration at C6 set up in the iodolactonization event had to be corrected subsequently.



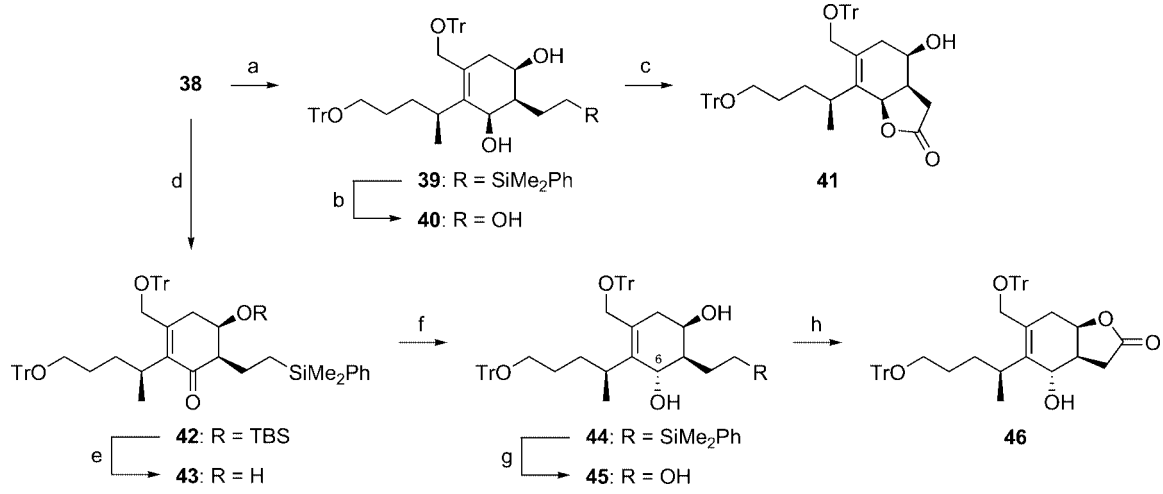
Scheme 6. 1,4-Difunctionalization, part II: a) KOH, MeOH, H_2O, reflux, 100%; b) (i) $I(col)_2PF_6$, PhMe, 0 °C, (ii) AgOAc, DMF, PhMe, 0 °C to room temp., 67% **36** + 15% **35**; c) zinc dust, HOAc, H_2O, THF, 0 °C to room temp., 86%; d) $LiAlH_4$, Et_2O, –10 °C to 0 °C; e) $LiBH_4$, Et_2O, 0 °C to room temp., 91% (2 steps); f) TrCl, DMAP, pyridine, CH_2Cl_2, room temp., 90%.

Completion of the Bicyclic Framework

Because experiments toward Mitsunobu inversion at C6 in **38** were not successful, presumably due to steric reasons, we tried to assemble the sterically less demanding γ-lactone subunit prior to inversion. Deprotection of **38** gave the diol **39**, which was subsequently transformed to the triol **40** by a modified Tamao–Fleming oxidation (Scheme 7). However, TEMPO oxidation of **40** utilizing *N*-chlorosuccinimide as the cooxidant under biphasic conditions[40] afforded exclusively the undesired γ-lactone **41**. Finally, correction of the configuration at C6 was cleanly achieved by an oxidation/reduction strategy. Dess–Martin oxidation[41] of **38** to give the enone **42** followed by desilylation under mild conditions[42] in order to avoid base- or acid-promoted degradation led to the β-hydroxy ketone **43**. Hydroxy-directed[24] reduction of **43** with the sodium aluminum dihydride Red-Al furnished the desired 6α allyl alcohol **44** with excellent diastereoselectivity (*dr* = 24:1). Exposure of this compound to the modified Tamao–Fleming oxidation conditions furnished the triol **45** featuring the completely oxygenated skeleton of the target molecules with correct configuration at all stereogenic centers. To our delight, chemoselective oxidation[43] of the triol **45** efficiently provided the requisite hydroxy γ-lactone **46**.

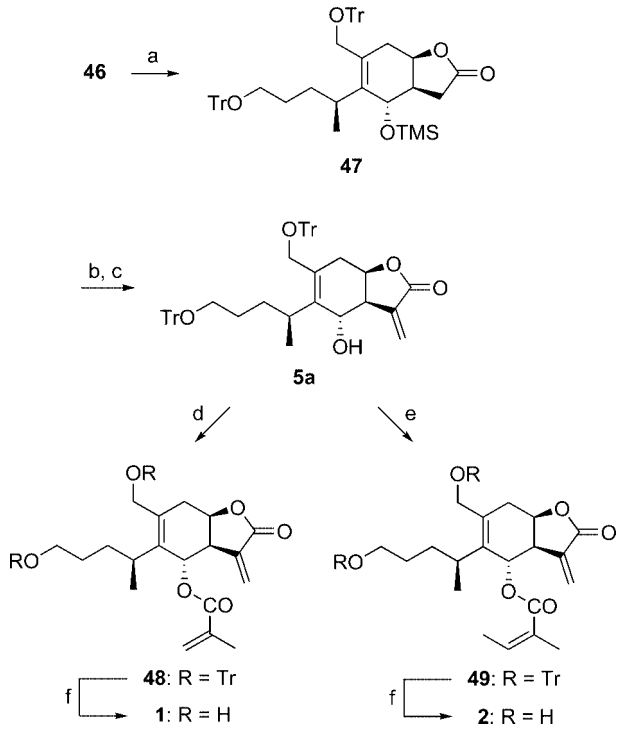
Final Steps Toward the Target Molecules

The final stage of our route to **1** and **2** was initiated by protection of the secondary hydroxy group in **46** followed by a one-step α-methylenation of the silyl ether **47** using



Scheme 7. Synthesis of lactone **41** and completion of the bicyclic framework **46**: a) TBAF, HOAc, THF, room temp., 97%; b) (i) TBAF, MS (4 Å), THF, 100 °C, sealed tube, (ii) KF, H_2O_2, $NaHCO_3$, THF, MeOH, 100 °C, sealed tube, 88%; c) cat. TEMPO, NCS, TBACl, K_2CO_3, $NaHCO_3$, CH_2Cl_2, H_2O, room temp., 84%; d) Dess–Martin periodinane, pyridine, CH_2Cl_2, room temp., 99%; e) TBAF, HOAc, THF, room temp., 96%; f) Red-Al, CH_2Cl_2, PhMe, –20 °C to room temp., 90%; g) (i) TBAF, MS (4 Å), THF, reflux, (ii) KF, H_2O_2, $NaHCO_3$, THF, MeOH, reflux, 99%; h) cat. TEMPO, bis(acetoxy)iodobenzene, CH_2Cl_2, room temp., 75%.

sodium hydride and paraformaldehyde (Scheme 8).[44] After desilylation, the lactone **5a**, the common alcohol precursor to both target esters **1** and **2**, was isolated in good overall yield. Preparation[7] of the methacrylate **48** as well as detritylation to give **1** proceeded uneventfully and delivered (–)-eriolanin, which proved to be identical to the natural product by comparison of spectral[7] and optical rotation data.[1] Using a modified Yamaguchi esterification,[45] the lactone **5a** could be smoothly transformed to angelate **49** without *Z*/*E* isomerization.[7] Deblocking to give compound **2** delivered (–)-eriolangin, which likewise turned out to be identical to the natural product by comparison of spectral[7] and optical rotation data.[1] Thus, our synthesis of **1** and **2** also clarifies the previously unknown absolute configuration of these sesquiterpene lactones, because the absolute configuration of the hydroxyalkylfuran **11** was unambiguously established.[13] In addition, X-ray diffraction analyses of **6** (Figure 2) and our synthetic product **1** (Figure 3)[10] provided further independent prove of the absolute configuration by anomalous X-ray scattering.



Scheme 8. Final steps of the synthesis of (–)-eriolanin (**1**) and (–)-eriolangin (**2**): a) TMSCl, imidazole, CH_2Cl_2, room temp., 96%; b) NaH, paraformaldehyde, THF, 100 °C, sealed tube; c) TBAF, THF, 0 °C, 61% (2 steps); d) methacrylic acid anhydride, Et_3N, DMAP, THF, 0 °C to room temp., 85%; e) (i) angelic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, PhMe, room temp., (ii) **5a**, 100 °C, 60%; f) cat. *p*TsOH, MeOH, room temp., 97% **1** from **48**, 85% **2** from **49**.

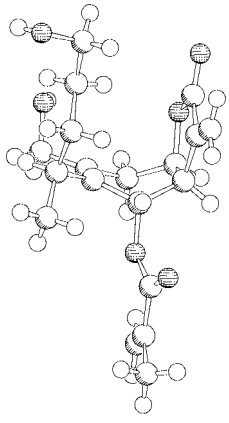


Figure 3. Crystal structure of synthetic (–)-eriolanin (**1**).[10,23]

Biological Investigations

We examined the effect of (–)-eriolanin (**1**), (–)-eriolangin (**2**) and, as a reference, the compound taxol on the cell cycle of human leukemia (HL-60) cells in vitro. This cell line was chosen because it is well characterized and gives a rather uniform response to distinct apoptotic stimuli.[46–48] Apoptosis can conveniently be quantified by flow cytometry. The criteria used (sub-G_1 DNA content) was shown previously to reflect the apoptotic process as determined with other genetic or biochemical methods.[49,50] After staining with propidium iodide (PI), the fractions of cells in different phases of the cell cycle (G_{0+1}, S and G_2+M phases) were quantified and populations of proliferating, arrested and apoptotic cells distinguished (Figure 4). In control cultures the fraction of apoptotic cells is low and was determined to be 4 ± 2% (Table 1).

Cell cultures were incubated in parallel with different concentrations of the test compounds for 1, 2, and 4 days. After 1 day of incubation, the reference compound taxol produced, as expected, a cell cycle arrest at the G_2+M stage[51] at all concentrations tested (66 ± 3% for 0.01 μM, 83 ± 5% for 0.1 μM and 94 ± 4 for 1.0 μM, $p < 0.05$). When the cells were exposed for 2 or 4 days to 0.1 μM taxol, the cells remained blocked (Figure 4, Table 1). At lower concentrations (0.01 μM), a large fraction of cells was released from the block and became apoptotic thus producing a "tail" of decreasing DNA content in two-dimensional plots (Figure 4). We have no evidence that the blocked cells reenter the cell cycle during 4 days of culture and hence, all cells in this tail were classified as apoptotic (Table 1). When the substances (–)-eriolanin (**1**) or (–)-eriolangin (**2**) were tested at low concentrations (0.1–10.0 μM), no significant effect with reference to the control cultures was noticed ($p > 0.05$, data not shown). At 30 μM concentration both compounds produced a strong G_2+M block similar to taxol (Figure 4). Already after 1 day culture a large fraction of cells was in this phase (26 ± 3% for **1** and 33 ± 3% for **2**, for both values $p < 0.05$). However, a small fraction of cells escaped the block and remained cycling. This effect was stronger for **1**, and after exposure for 4 days a prominent population of cells was in the third or fourth round of cell division similar to untreated control cultures (Figure 4). At intermediate concentrations (20 μM), when the G_2+M block was incomplete and some cells continued cycling, the largest fraction of apoptotic cells was observed (Table 1). At higher concentrations, the cell cycle block was more complete and fewer cells could enter the apoptotic pathway.

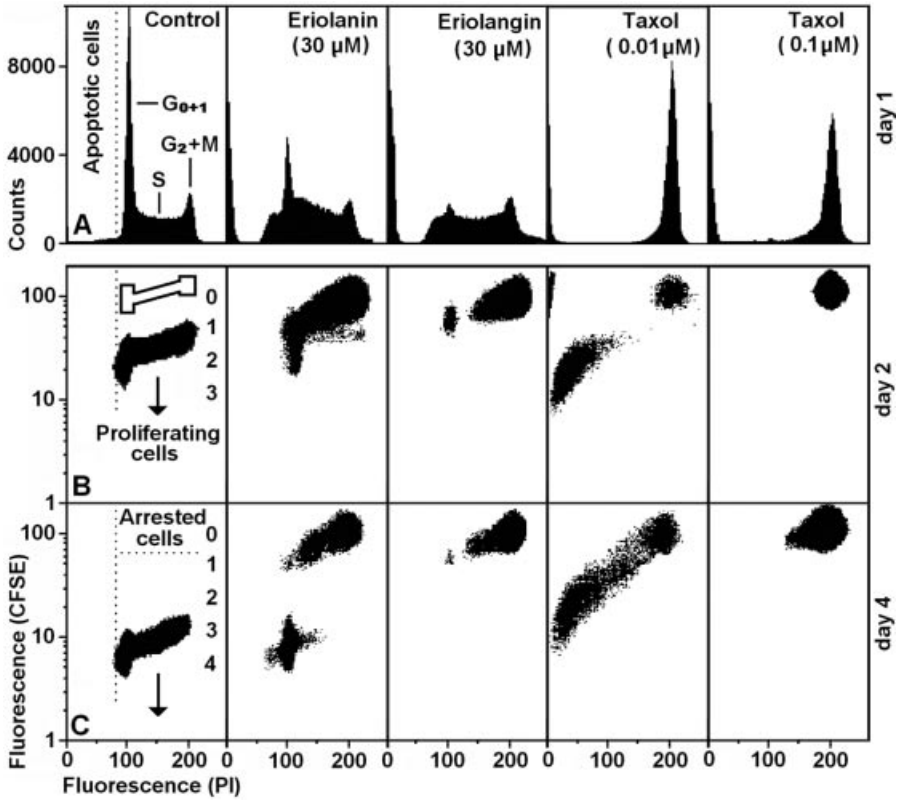


Figure 4. Effect of (–)-eriolanin (**1**), (–)-eriolangin (**2**), and taxol on cell proliferation: Asynchronously proliferating HL-60 cells were stained with carboxyfluorescein diacetate succinimidyl ester (CFSE; area defined as division 0) and after 1 h treated with **1** and **2** (30 µmol/L). An additional control culture was exposed to taxol in concentrations, which lead to cell cycle arrest at the G_2+M phase (0.01 and 0.1 µmol/L). After 1, 2, and 4 days, the cells were fixed, stained with propidium iodide (PI) and characterized by single-parameter (**A**: PI) or by two-parameter analysis (**B** and **C**: PI/CFSE). Cycling cells of different cell generations (labeled 1–4) and arrested cells (delayed at the position of the division 0) can be distinguished on the basis of their CFSE content. Furthermore, the presence of apoptotic cells (hypodiploid, left of the dashed line in **A**–**C**) and the cell cycle phases can be quantified in the respective cell generations.

Table 1. Effect of (–)-eriolanin (**1**), (–)-eriolangin (**2**), and taxol on cell proliferation.

Test substance	Concentration [µmol/L]	2 days after exposure[a] Apoptotic cells [%]	Cycling cells [%]	Arrested cells [%]	4 days after exposure[a] Apoptotic cells [%]	Cycling cells [%]	Arrested cells [%]
control	–	4±2	90±5	6±3	4±2	94±4	2±2
taxol	0.01	**55±2**	**n.q.**	**45±5**	**80±4**	**n.q.**	**20±4**
taxol	0.1	8±4	**n.q.**	**92±5**	8±4	**n.q.**	**92±5**
1	5	8±3	84±5	8±3	10±4	85±5	5±3
1	10	10±4	80±5	10±4	**16±4**	82±5	2±3
1	20	**20±4**	**50±5**	**30±3**	**20±4**	**60±4**	**20±3**
1	30	12±4	**24±5**	**64±4**	**15±4**	**45±5**	**40±5**
1	60	11±3	**11±5**	**78±4**	**17±4**	**10±5**	**73±6**
2	5	6±3	86±5	8±4	**17±4**	80±5	3±2
2	10	10±4	**70±4**	**20±4**	**20±4**	**73±4**	**7±4**
2	20	**14±4**	**26±5**	**60±4**	**20±2**	**36±5**	**47±4**
2	30	12±5	**16±5**	**72±3**	12±5	**11±5**	**77±3**
2	60	12±4	**16±5**	**72±3**	15±4	**10±5**	**75±3**

[a] The data show the effect of the test substances on the proliferation of HL-60 cells after exposure for 2 and 4 days (average ± standard deviation of 4 independent experiments). Statistically significant differences ($p < 0.05$) to control cultures are printed in **bold**; n.q. = not quantified (see text for explanation).

Conclusion

In conclusion, the first enantioselective total synthesis of the bioactive 1,10-*seco*-eudesmanolides (–)-eriolanin (**1**) and (–)-eriolangin (**2**) has been developed. Due to the sultone strategy applied, a rapid access to the key methylenecyclohexene **6** was achieved and thus, our route to **1** and **2** requires only 26 steps from the α-bromo ketone **8**. Average yields of 87% for **1** and 86% for **2** highlight the efficacy of our approach as well as a novel one-pot iodolactonization–

formylation and a high-yielding modified Tamao–Fleming oxidation. Using flow cytometry, both **1** and **2** were shown to cause a strong G_2+M block in human leukemia (HL-60) cells similar to taxol at 30 μM concentration. The selective manipulation of the diverse hydroxy groups on the 1,10-*seco*-eudesmanolide framework possible with our approach offers great flexibility with respect to the assembly of synthetic analogs. Along these lines, an enantioselective synthesis of britannilactone (**3a**) and its derivatives **3b**,**c** from iodolactone **34** is currently under investigation.

Experimental Section

General Remarks: All reactions requiring exclusion of moisture were run under argon using flame-dried glassware. Solvents were dried by distillation from Na/K and benzophenone (THF), Na (toluene), CaH_2 (Et_2O, MeCN), or by passing through activated alumina (CH_2Cl_2). All commercially available compounds were used as received unless otherwise stated. Flash chromatography: Merck silica gel 60 (40–63 μm). Thin layer chromatography: Merck silica gel 60 F_{254} plates. Melting points: Kleinfeld Labortechnik Electrothermal IA 9100 apparatus. Chiral capillary GC: Shimadzu 9A GC coupled with a Shimadzu C-R3A integrator and a Hydrodex®-β-6-TBDM column (25 m length, 0.25 mm i.d.). Optical rotation: Perkin–Elmer 341 polarimeter, solvent: $CHCl_3$. ^1H and ^{13}C NMR: Bruker DRX-500 (^1H: 500 MHz, ^{13}C: 126 MHz, calibrated to the residual resonance of the solvent). FT-IR: Nicolet 205 and Nicolet Avatar 360 spectrometer. Mass spectra: Hewlett–Packard 5890 GC coupled with a Hewlett–Packard 5972 detector and Agilent 6890N GC coupled with an Agilent 5973N detector (GC/MS); Bruker Esquire-LC (direct injection as a methanolic NH_4OAc solution, CID). Exact mass: Finnigan MAT 95 (EI, 70 eV). Elemental analysis: Carlo–Erba Instruments EA 1108 and Hekatech EA 3000. X-ray: Bruker Kappa CCD diffractometer.

Cell Culture and Analysis of Cell Cycle Effects by Flow Cytometry: Acute myeloid leukemia cells (HL-60, DSMZ, Germany) were maintained in RPMI 1640 medium with 10% heat-inactivated foetal calf serum (Gibco, France). Cells were grown at 37 °C in humidified 5% CO_2 and maintained at a density of $2\cdot10^5$–$1\cdot10^6$ cells/mL. Cell cultures ($0.5\cdot10^6$ cells/mL, 10 mL per flask) were exposed for 1, 2, and 4 days to different concentrations of (–)-eriolanin (**1**) and (–)-eriolangin (**2**) ranging from 0.1 μM to 60.0 μM. For comparison, paclitaxel ("taxol", from *Taxus brevifolia*, Sigma, Germany) was used at concentrations of 0.01 μM, 0.1 μM, and 1.0 μM. The stock solutions of the compounds were prepared in DMSO, and the final concentration of DMSO in all cell cultures was adjusted to 0.1%. The cells were characterized by flow cytometry using two criteria: the DNA content by staining with propidium iodide (PI; Fluka, Germany) and the fluorescence of the dye carboxyfluorescein diacetate succinimidyl ester (CFSE; Molecular Probes, Eugene, OR, USA), which reacts with cellular proteins and allows to analyze the dynamics of cell proliferation due to the decreasing fluorescent signal in successive cell generations. The technique has been applied to HL-60 cells before.[46] Briefly, HL-60 cells were stained with 10 μM CFSE in phosphate-buffered saline (PBS) for 10 min at 37 °C. The cells were washed with PBS, and culture medium was added. After different incubation times (see results), cells were removed from the culture, washed with PBS and centrifuged at 100 g for 10 min. The cell pellet was resuspended in PBS (100 μL), fixed in 70% (vol/vol) ethanol by adding cold (–20 °C) ethanol (1 mL) and stored overnight at –20 °C. The cells were spun down again, and the pellet was resuspended in PBS (1.5 mL) at room temperature. After centrifugation, the cell pellet was resuspended in DNA staining solution (1 mL) containing propidium iodide (PI; 50 μg/mL; Sigma, Germany) and RNase (0.2 mg/mL; Sigma, Germany) and incubated for at least 45 min at room temperature in the dark. The same number of cells ($5\cdot10^5$) per sample was analyzed by flow cytometry (CyFlow, Partec, Germany). The excitation wavelength was 473 nm, and green (520 nm for CFSE) and red fluorescence (>590 nm for PI) were recorded. For each variable (exposure conditions, culture periods etc.) a minimum of 4 samples was quantified. The fraction of cells present in different cell generations, their representation in the respective cell cycle phases, and percentage of apoptotic cells were calculated using CyFlow software (Partec, Germany).

Bromohydrin 9. 1. Preparation of the [Cp*RhCl((*R*,*R*)-tsdpen)] Solution: (Pentamethylcyclopentadienyl)rhodium chloride dimer (68.5 mg, 0.1 mol-%) and (1*R*,2*R*)-(–)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine (82.3 mg, 0.2 mol-%) were stirred in a solution (1.5 mL) of Et_3N and HCO_2H [HCO_2H (4.45 mL, 118 mmol) and Et_3N (14.45 mL, 148 mmol)] at room temperature for 45 min.

2. Transfer Hydrogenation: To a solution of the bromo ketone **8** (21.43 g, 114 mmol) in EtOAc (220 mL) was added the solution of [Cp*RhCl((*R*,*R*)-tsdpen)] diluted with EtOAc (10 mL) at 0 °C followed by addition of the remaining Et_3N/HCO_2H solution (described above) within 60 min. The resultant solution was stirred at 0 °C for 4 h, quenched with aqueous $NaHCO_3$ (300 mL, 5%), extracted with EtOAc (3 × 100 mL), washed with brine (100 mL), and dried with $MgSO_4$. $MgSO_4$ was separated by filtration through a pad of silica gel followed by removal of the solvent and distillation of the crude mixture in the dark, which gave **9** (15.2 g, approx. 70%) along with small amounts of inseparable impurities as an extremely light-sensitive, colorless liquid. Attempts at further purification by chromatography led to the decomposition of **9**. R_f = 0.44 (pentane/Et_2O, 2:1). b.p. 50–52 °C (2×10^{-2} mbar). >99% *ee* (chiral GC, 110 °C, isothermal). ^1H NMR ($CDCl_3$): δ = 2.54 (d, J = 5.5 Hz, 1 H), 3.72 (dd, J = 6.8, 10.5 Hz, 1 H), 3.74 (dd, J = 4.8, 10.5 Hz, 1 H), 4.96 Hz (ddd, J = 5.5, 6.8, 4.8 Hz, 1 H), 6.38 (2 d, 2 × J = 1.3 Hz, 2 H), 7.44 (dd, J = 1.3, 1.3 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 36.66 (t), 67.74 (d), 107.46 (d), 110.42 (d), 142.53 (d), 152.78 (s) ppm.

(*R*)-2-Oxiranylfuran (10): To a solution of the slightly impure bromohydrin **9** (15.2 g) in MeCN (160 mL) was added K_2CO_3 (22.0 g, 160 mmol). The mixture was vigorously stirred at room temperature for 14 h in the dark followed by filtration of the solid. The solvent was evaporated at 30 °C to afford **10** (7.22 g, approx. 80%) as an extremely light-, moisture-, and acid-sensitive red liquid in approx. 90% purity (^1H NMR integration). For spectral data see ref.[52].

(*S*)-2-(Furan-2-yl)propan-1-ol (11): To a suspension of CuCN (10.50 g, 117 mmol) in Et_2O (120 mL) was added MeLi (73 mL, 117 mmol, 1.6 M in Et_2O) at –78 °C within 15 min. The mixture was warmed to 0 °C and stirred until it turned to a black solution, which was cooled again to –78 °C, and a solution of the crude epoxide **10** (7.22 g, approx. 80%) in Et_2O (80 mL) was added over 30 min. The mixture was allowed to reach ambient temperature overnight, carefully quenched with an aqueous buffer (300 mL, satd. NH_4Cl/NH_3 25%, 1:1) at 0 °C and extracted with Et_2O (3 × 150 mL). The combined extracts were washed with brine (100 mL), dried with $MgSO_4$, and after filtration and removal of the solvent, the residue was purified by distillation to afford **11** (7.22 g, 50% from **8**) as a colorless liquid. >98.5% *ee* (chiral GC,

70 °C, isothermal). $[\alpha]_D^{20}$ = +20.6 (*c* = 0.99); ref.[13] $[\alpha]_D^{25}$ = +6.5 (*c* = 1.00 in $CHCl_3$). For further data see ref.[13].

Sultone 7a: To a solution of the alcohol **11** (13.4 g, 106.3 mmol) and Et_3N (58.8 mL, 425 mmol) in CH_2Cl_2 (1000 mL) was added dropwise β-chloroethanesulfonic acid chloride (19.0 g, 117 mmol) diluted with CH_2Cl_2 (200 mL) at room temperature. The resultant solution was stirred for 16 h at ambient temperature and heated under reflux for 2 h. The reaction was quenched with H_2O (300 mL), extracted with CH_2Cl_2 (3×100 mL), washed with brine (150 mL), dried with $MgSO_4$, and filtered through a pad of silica gel. After evaporation of the solvent, the residue was dissolved in a small amount of EtOAc, and **7a** along with the diastereomer **7b** (21.5 g, 94%, *dr* = 1.4:1) were crystallized by addition of pentane. To a solution of **7a** and **7b** (5.75 g, 26.6 mmol) in EtOAc (300 mL) was added a small amount of BHT, and the solution was heated in a sealed tube by microwaves to 120 °C (5 min → 120 °C, 120 °C for 30 min, 15 min → 20 °C). After removal of the solvent, the crude product was suspended in Et_2O/pentane (300 mL, 1:1), stirred overnight and filtered to afford **7a** along with the diastereomer **7b** (5.70 g, 99%, *dr* = 6:1). Pure **7a** was finally obtained by recrystallization from EtOAc. For collection of the analytical data, a sample of both isomers was chromatographically separated (pentane/Et_2O/EtOAc, 2:1:2). **7a:** R_f = 0.47 (pentane/Et_2O/EtOAc, 2:1:2). $[\alpha]_D^{30}$ = –15.5 (*c* = 1.00). M.p. 143 °C. ^1H NMR ($CDCl_3$): δ = 1.04 (d, *J* = 7.1 Hz, 3 H), 1.83 (dd, *J* = 7.9, 12.3 Hz, 1 H), 2.54 (ddd, *J* = 3.5, 4.6, 12.3 Hz, 1 H), 3.16 (m, 1 H), 3.16 (dd, *J* = 3.5, 7.9 Hz, 1 H), 4.31 (dd, *J* = 5.2, 11.8 Hz, 1 H), 4.50 (dd, *J* = 11.8, 11.9 Hz, 1 H), 5.23 (dd, *J* = 1.6, 4.6 Hz, 1 H), 6.23 (d, *J* = 5.6 Hz, 1 H), 6.58 (dd, *J* = 1.6, 5.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.93 (q), 29.70 (t), 31.68 (d), 57.47 (d), 73.04 (t), 78.62 (d), 91.06 (s), 135.02 (d), 140.34 (d) ppm. IR (KBr): $\tilde{\nu}$ = 3040, 2922, 1330, 1308, 1235, 1148, 1105, 948, 881, 764, 715, 694 cm^{-1}. GC/MS: *m*/*z* (%) = 216 (1), 108 (100), 95 (99), 91 (9), 81 (19), 79 (10), 67 (17), 41 (17). $C_9H_{12}O_4S$ (216.25): calcd. C 49.99, H 5.59; found C 50.04, H 5.66. **7b:** R_f = 0.42 (pentane/Et_2O/EtOAc, 2:1:2). $[\alpha]_D^{25}$ = +43.8 (*c* = 0.99). M.p. 107 °C. ^1H NMR ($CDCl_3$): δ = 1.46 (d, *J* = 7.2 Hz, 3 H), 1.74 (dd, *J* = 7.9, 12.3 Hz, 1 H), 2.41 (m, 1 H), 2.60 (ddd, *J* = 3.3, 4.7, 12.3 Hz, 1 H), 3.26 (dd, *J* = 3.3, 7.9 Hz, 1 H), 4.23 (dd, *J* = 1.4, 11.7 Hz, 1 H), 4.98 (dd, *J* = 2.3, 11.7 Hz, 1 H), 5.21 (dd, *J* = 1.8, 4.7 Hz, 1 H), 6.05 (d, *J* = 5.7 Hz, 1 H), 6.63 (dd, *J* = 1.8, 5.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.38 (q), 29.48 (t), 30.77 (d), 55.99 (d), 73.99 (t), 78.60 (d), 91.90 (s), 132.72 (d), 141.07 (d) ppm. IR (KBr): $\tilde{\nu}$ = 3040, 2922, 1330, 1308, 1235, 1148, 1105, 1067, 1034, 948, 881, 764, 715, 694 cm^{-1}. GC/MS: identical to **7a**. $C_9H_{12}O_4S$ (216.25): calcd. C 49.99, H 5.59; found C 50.12, H 5.63.

Dimethyl(phenyl)vinylsilane (16): For the preparation of the Grignard reagent a mixture of Mg chips (6.12 g, 252 mmol) in THF (26 mL) was treated with neat bromobenzene (1.3 mL, 12.4 mmol). After initiation of the reaction, bromobenzene (25.1 mL, 238.5 mmol) in THF (70 mL) was slowly added, and the mixture was heated under reflux for 8 h. To the resulting solution was added dropwise chlorodimethylvinylsilane (**15**) (26.4 mL, 192 mmol) diluted with THF (70 mL) followed by heating under reflux for 6 h and quenching with ice water. The organic layer was separated, the aqueous layer extracted with Et_2O (100 mL), and the combined organic layers were dried with $MgSO_4$. After filtration and evaporation of the solvent, the crude product was purified by distillation to give **16** (25.75 g, 83%) as a colorless liquid. B.p. 67 °C (18 mbar). ^1H NMR ($CDCl_3$): δ = 0.20 (s, 6 H), 5.60 (dd, *J* = 3.9, 20.1 Hz, 1 H), 5.92 (dd, *J* = 3.9, 14.6 Hz, 1 H), 6.14 (dd, *J* = 14.6, 20.1 Hz, 1 H), 7.19–7.22 (m, 3 H), 7.37–7.39 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –2.92 (q, 2 C), 127.79 (d, 2 C), 128.99 (d), 132.78 (t), 133.84 (d, 2 C), 138.03 (d), 138.44 (s) ppm. IR (neat): $\tilde{\nu}$ = 3069, 3050, 2959, 1592, 1428, 1404, 1250, 1113, 1008, 953, 836, 818, 776, 731, 701 cm^{-1}. GC/MS: *m*/*z* (%) = 162 (25), 147 (100), 148 (15), 135 (26), 121 (56), 120 (4), 105 (23), 104 (21), 77 (20). $C_{10}H_{14}Si$ (162.30): calcd. C 74.00, H 8.69; found C 73.71, H 8.38.

Dimethyl(phenyl)(2-phenylsulfanylethyl)silane (17): A mixture of the vinylsilane **16** (13.0 g, 80.0 mmol), thiophenol (13.2 g, 132.2 mmol) and a catalytic amount of AIBN was stirred at 100 °C for 24 h. At room temperature the solution was diluted with Et_2O (30 mL), extracted with aqueous KOH (45 mL, 2 M), washed with brine (25 mL), and dried with $MgSO_4$. After filtration and evaporation of the solvent, the crude product was purified by distillation to give **17** (19.0 g, 87%) as colorless crystals. B.p. 134 °C ($4\cdot10^{-2}$ mbar). M.p. 36 °C. R_f = 0.13 (pentane/CH_2Cl_2, 9:1). ^1H NMR ($CDCl_3$): δ = 0.20 (s, 6 H), 1.02–1.08 (m, 2 H), 2.79–2.84 (m, 2 H), 7.00–7.07 (m, 1 H), 7.13 (m, 4 H), 7.24–7.27 (m, 3 H), 7.36–7.39 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –3.15 (q, 2 C), 16.11 (t), 29.28 (t), 125.66 (d), 127.89 (d, 2 C), 128.79 (d, 2 C), 128.95 (d, 2 C), 129.17 (d), 133.56 (d, 2 C), 136.89 (s), 138.00 (s) ppm. IR (neat): $\tilde{\nu}$ = 3052, 3020, 2954, 1584, 1480, 1439, 1426, 1263, 1250, 836, 818, 736, 700 cm^{-1}. GC/MS: *m*/*z* (%) = 272 (20), 244 (62), 229 (22), 137 (69), 136 (80), 135 (100), 109 (34), 105 (30), 91 (17). $C_{16}H_{20}SSi$ (272.48): calcd. C 70.53, H 7.40; found C 70.63, H 7.44.

Methylenecyclohexene 6. (A) Preparation of the Lithium Alkoxide 12: To a –78 °C cold solution of the sultone **7a** (7.12 g, 33.0 mmol) in THF (170 mL) was added MeLi (20.6 mL, 33.0 mmol, 1.6 M in Et_2O) within 20 min, and the solution was further stirred at the same temperature for 20 min to give a solution of **12**. **(B) Preparation of the Lithiated Silane 18:** To oxide-free lithium chips (750 mg, 108 mmol) in THF (250 mL) was added 4,4′-di-*tert*-butylbiphenyl (DBB) (21.9 g, 82 mmol) at 0 °C, and stirring was maintained for 12 h. The turquoise solution of LiDBB was cooled to –78 °C, silane **17** (9.43 g, 34.7 mmol) in THF (125 mL) was added within 30 min, and the solution was stirred at the same temperature for additional 20 min. **(C) (Iodomethyl)magnesium Chloride:** A solution of *i*PrMgCl (100 mL, 200 mmol, 2 M in THF) was diluted with THF (330 mL) and cooled to –90 °C. Under vigorous mechanical stirring CH_2I_2 (53.4 g, 200 mmol) was added over 2 h, and the resulting grey suspension was stirred for another 2 h at –90 °C. **(D) 1,6-Addition Reaction to Give 13:** The –78 °C cold solution of **12** [described in paragraph (A)] was cannulated into the solution of **18** [described in paragraph (B)] at –78 °C within 20 min. The resulting brown solution was then stirred for 30 min at –78 °C, for 30 min at –20 °C and recooled to –78 °C to give **13**. **(E) Methylenation with Simultaneous Desulfurization to Give 6:** The –78 °C cold solution of **13** [described in paragraph (D)] was cannulated into the suspension of (iodomethyl)magnesium chloride [described in paragraph (C)] at –90 °C within 30 min. The resulting grey suspension was warmed to ambient temperature overnight. Aqueous $NaHCO_3$ (200 mL, 2%) was added carefully at 0 °C, and the separated aqueous layer was neutralized with HCl (6 M). The organic layer was washed with the neutralized aqueous layer, which was then extracted with Et_2O (3×200 mL). The combined extracts were washed successively with satd. aqueous $Na_2S_2O_3$ (100 mL) and brine (100 mL), dried with $MgSO_4$, and filtered. After evaporation of the solvent, the residue was filtered through a pad of silica gel (pentane) in order to remove DBB. Subsequent rinsing with EtOAc furnished the crude product, which was then purified by flash chromatography (Et_2O/CH_2Cl_2, 1:1 + 0.5% Et_3N) to afford **6** (6.64 g, 61%) as a white solid. R_f = 0.35 (Et_2O/CH_2Cl_2, 1:1). M.p. 66–68 °C. $[\alpha]_D^{26}$ = +49.5 (*c* = 0.99). ^1H NMR ($CDCl_3$): δ = 0.27 (s, 3 H), 0.28 (s, 3 H), 0.78 (ddd, *J* = 4.4, 12.8, 14.0 Hz, 1 H), 0.92 (ddd, *J* = 4.6, 12.9, 14.0 Hz, 1 H), 1.07 (d, *J* = 6.6 Hz, 3 H), 1.36 –1.43 (m, 1 H), 1.50–1.60 (m, 1 H), 2.19–2.22 (m, 1 H), 2.48 (ddd,

J = 2.1, 4.5, 14.8 Hz, 1 H), 2.60 (dd, *J* = 4.6, 14.8 Hz, 1 H), 2.81 (ddq, *J* = 6.0, 6.0, 6.6 Hz, 1 H), 3.54 (dd, *J* = 6.0, 10.6 Hz, 1 H), 3.59 (dd, *J* = 6.0, 10.6 Hz, 1 H), 4.02–4.06 (m, 1 H), 4.91 (broad s, 1 H), 5.16 (broad s, 1 H), 5.35 (broad s, 1 H), 7.25–7.36 (m, 3 H), 7.50–7.52 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –3.19 (q), –3.07 (q), 12.95 (t), 16.96 (q), 25.59 (t), 36.04 (d), 40.54 (t), 44.75 (d), 66.50 (d), 67.00 (t), 111.55 (t), 127.12 (d), 127.78 (d, 2 C), 128.89 (d), 133.55 (d, 2 C), 137.70 (s), 139.21 (s), 139.36 (s) ppm. IR (neat): $\tilde{\nu}$ = 3350, 3068, 3018, 2955, 2928, 2877, 1451, 1421, 1343, 1259, 1141, 958, 837, 817, 731, 701 cm^{-1}. GC/MS: *m*/*z* (%) = 331 (3), 315 (4), 281 (12), 279 (12), 234 (55), 145 (24), 135 (100), 121 (11), 105 (12), 91 (7). $C_{20}H_{30}O_2Si$ (330.54): calcd. C 72.67, H 9.15; found C 72.27, H 8.76.

Bis(silyl) Ether 19: To a solution of the diol **6** (2.64 g, 8.0 mmol) in dry DMF (50 mL) was successively added imidazole (2.73 g, 40.0 mmol), DMAP (1.96 g, 16.0 mmol), and TBSCl (3.57 g, 24.0 mmol), and the solution was stirred for 18 h at room temperature. The slightly yellowish suspension was diluted with pentane (50 mL) and poured into aqueous $NaHCO_3$ (100 mL, 5%). The aqueous layer was extracted with pentane (3 × 50 mL), and the combined extracts were washed with brine (30 mL), dried with $MgSO_4$, and filtered. After evaporation of the solvent, the crude product was purified by filtering through a pad of silica gel (pentane/Et_2O, 10:1) to give **19** (4.42 g, 99%) as a colorless viscous liquid. R_f = 0.84 (pentane/Et_2O, 10:1). $[\alpha]_D^{27}$ = +61.5 (*c* = 0.98). ^{1}H NMR ($CDCl_3$): δ = –0.01 (s, 3 H), 0.02 (s, 3 H), 0.03 (s, 3 H), 0.03 (s, 3 H), 0.26 (s, 3 H), 0.27 (s, 3 H), 0.72–0.90 (m, 2 H), 0.82 (s, 9 H), 0.89 (s, 9 H), 1.11 (d, *J* = 6.7 Hz, 3 H), 1.20–1.27 (m, 1 H), 1.64–1.70 (m, 1 H), 2.11–2.14 (m, 1 H), 2.32 (ddd, *J* = 1.5, 1.5, 14.5 Hz, 1 H), 2.59 (dd, *J* = 8.0, 14.5 Hz, 1 H), 2.71 (ddq, *J* = 6.7, 6.7, 8.7 Hz, 1 H), 3.21 (dd, *J* = 8.7, 9.6 Hz, 1 H), 3.59 (dd, *J* = 6.7, 9.6 Hz, 1 H), 3.95–3.90 (m, 1 H), 4.74 (broad s, 1 H), 5.04 (broad s, 1 H), 5.49 (d, *J* = 3.5 Hz, 1 H), 7.33–7.37 (m, 3 H), 7.49–7.53 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.43 (q), –5.31 (q), –4.80 (q), –5.27 (q), –3.20 (q), –3.08 (q), 13.37 (t), 16.80 (q), 18.05 (s), 18.33 (s), 24.61 (t), 25.78 (q, 3 C), 25.91 (q, 3 C), 36.24 (d), 39.70 (t), 45.46 (d), 68.57 (t), 68.59 (d), 108.56 (t), 127.76 (d, 2 C), 128.19 (d), 128.77 (d), 133.54 (d, 2 C), 137.70 (s), 139.48 (s), 141.68 (s) ppm. IR (neat): $\tilde{\nu}$ = 2955, 2893, 2857, 1460, 1252, 1113, 1091, 836, 813, 775 cm^{-1}. GC/MS: *m*/*z* (%) = 558 (0.1), 501 (1), 263 (5), 209 (34), 147 (12), 135 (100), 73 (38), 43 (17). $C_{32}H_{58}O_2Si_3$ (559.06): calcd. C 68.75, H 10.46; found C 68.73, H 10.22.

Alcohol 20: To an ice-cold solution of the bis(silyl) ether **19** (12.40 g, 22.3 mmol) in THF (180 mL) was added TBAF (36 mL, 36 mmol, 1 M in THF) over 8 h. The solution was maintained at this temperature for additional 30 h and then quenched with aqueous Na_2CO_3 (200 mL, 5%). The aqueous layer was extracted with Et_2O (3 × 200 mL), and the combined extracts were washed with brine (100 mL), dried with $MgSO_4$, and filtered. After evaporation of the solvent, the crude mixture was chromatographically purified (pentane/Et_2O, 4:1 → CH_2Cl_2/Et_2O, 1:1) to give **20** (8.00 g, 81%) as a colorless viscous liquid and **6** (1.30 g, 17%). R_f = 0.38 (pentane/Et_2O, 4:1). $[\alpha]_D^{24}$ = +77.1 (*c* = 0.99). ^{1}H NMR ($CDCl_3$): δ = –0.03 (s, 3 H), 0.00 (s, 3 H), 0.24 (s, 3 H), 0.26 (s, 3 H), 0.76–0.87 (m, 2 H), 0.78 (s, 9 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 1.22–1.33 (m, 1 H), 1.51–1.65 (m, 1 H), 2.10–2.14 (m, 1 H), 2.36 (ddd, *J* = 2.2, 2.2, 14.9 Hz, 1 H), 2.49 (dd, *J* = 6.0, 14.9 Hz, 1 H), 2.66–2.75 (m, 1 H), 3.45 (dd, *J* = 5.4, 10.5 Hz, 1 H), 3.51 (dd, *J* = 5.3, 10.5 Hz, 1 H), 3.96–4.01 (m, 1 H), 4.77 (broad s, 1 H), 5.05 (broad s, 1 H), 5.45 (broad s, 1 H), 7.30–7.34 (m, 3 H), 7.45–7.50 (m, 2 H) ppm.^{13}C NMR ($CDCl_3$): δ = –4.90 (q), –4.19 (q), –3.07 (q), –2.97 (q), 13.36 (t), 16.40 (q), 17.99 (s), 25.54 (t), 25.73 (q, 3 C), 35.48 (d), 40.12 (t), 45.60 (d), 66.68 (t), 68.06 (d), 109.68 (t), 127.73 (d, 2 C), 128.49 (d), 128.82 (d), 133.51 (d, 2 C), 136.63 (s), 139.23 (s), 140.86 (s) ppm. IR (neat): $\tilde{\nu}$ = 3100–3650 cm^{-1} (broad), 2929, 2893, 2857, 1472, 1463, 1428, 1250, 1114, 1093, 880, 836, 774, 700 cm^{-1}. GC/MS: *m*/*z* (%) = 444 (2), 387 (3), 209 (25), 149 (12), 135 (100), 124 (42), 73 (28). $C_{26}H_{44}O_2Si_2$ (444.80): calcd. C 70.21, H 9.97; found C 69.83, H 9.88.

Epoxide 21: Racemic **20** was used. To a vigorously stirred biphasic solution of alcohol *rac*-**20** (511 mg, 1.15 mmol) in CH_2Cl_2 (10 mL) and aqueous satd. $NaHCO_3$ (20 mL) was added a solution of *m*CPBA (258 mg, 1.50 mmol, 100%) in CH_2Cl_2 (10 mL) at 0 °C within 4 h. After stirring at 0 °C for additional 60 min, the solution was diluted with H_2O (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and filtered through a pad of silica gel (CH_2Cl_2). Evaporation of the solvent gave **21** (563 mg, >100%) as an extremely sensitive colorless liquid in high purity [approx. 90% (^{1}H NMR integration)], which was used without further purification. R_f = 0.30 (pentane/Et_2O, 7:3 + 2% Et_3N). ^{1}H NMR (C_6D_6): δ = 0.07 (s, 3 H), 0.08 (s, 3 H), 0.39 (s, 3 H), 0.42 (s, 3 H), 0.82 (d, *J* = 6.6 Hz, 3 H), 0.85 (ddd, *J* = 4.4, 12.6, 13.8 Hz, 1 H), 1.20 (ddd, *J* = 4.4, 12.6, 12.8 Hz, 1 H), 1.02 (s, 9 H), 1.84–1.90 (m, 1 H), 1.91–1.97 (m, 1 H), 2.01 (dd, *J* = 3.2, 13.2 Hz, 1 H), 2.01–2.08 (m, 1 H), 2.62–2.68 (m, 2 H), 3.39 (d, *J* = 4.4 Hz, 1 H), 3.43 (dd, *J* = 5.0, 11.4 Hz, 1 H), 3.47 (dd, *J* = 8.2, 11.4 Hz, 1 H), 3.78 (ddd, *J* = 3.2, 6.3, 10.9 Hz, 1 H), 5.14 (s, 1 H), 5.24 (s, 1 H), 7.29–7.36 (m, 3 H), 7.62–7.65 (m, 2 H) ppm. ^{13}C NMR (C_6D_6): δ = –4.88 (q), –4.55 (q), –3.25 (q), –2.86 (q), 13.65 (t), 14.34 (q), 18.25 (s), 19.11 (t), 25.96 (q, 3 C), 35.11 (d), 38.13 (t), 42.74 (d), 58.63 (d), 64.14 (t), 64.59 (s), 70.86 (d), 114.89 (t), 128.14 (d, 2 C), 129.16 (d, C), 133.93 (d, 2 C), 139.40 (s), 143.87 (s) ppm. IR (neat): $\tilde{\nu}$ = 3430 cm^{-1} (broad), 2954, 2929, 2885, 2856, 1463, 1250, 1098, 1044, 899, 868, 833, 815, 772, 728, 699 cm^{-1}.

Bis(silyl) Ether 22: To a solution of the alcohol **21** (60 mg, approx. 130 μmol) in CH_2Cl_2 (1.5 mL) was successively added at 0 °C imidazole (44 mg, 650 μmol), DMAP (5 mg, 40 μmol) and TBSCl (39 mg, 260 μmol), and stirring was maintained for 2 h. The solution was treated with Et_3N (100 μL) and rapidly filtered through a pad of silica gel (pentane/Et_2O, 40:1 + 2% Et_3N). Evaporation of the solvent gave **22** (67 mg, approx. 94%) in high purity as an extremely sensitive colorless oil, which was used without further purification. R_f = 0.66 (pentane/Et_2O, 40:1). ^{1}H NMR (C_6D_6): δ = –0.01 (s, 3 H), 0.01 (s, 3 H), 0.04 (s, 3 H), 0.05 (s, 3 H), 0.31 (s, 3 H), 0.33 (s, 3 H), 0.94 (s, 9 H), 0.98 (s, 9 H), 0.90–1.00 (m, 1 H), 1.12 (d, *J* = 6.9 Hz, 3 H), 1.20–1.33 (m, 1 H), 1.72–2.07 (m, 4 H), 2.37 (q, *J* = 6.9 Hz, 1 H), 2.70 (dd, *J* = 12.3, 12.3 Hz, 1 H), 3.45 (d, *J* = 4.3 Hz, 1 H), 3.56 (dd, *J* = 6.6, 9.8 Hz, 1 H), 3.76–3.84 (m, 2 H), 5.07 (s, 1 H), 5.19 (s, 1 H), 7.18–7.28 (m, 3 H), 7.51–7.58 (m, 2 H) ppm. ^{13}C NMR (C_6D_6): δ = –4.90 (q), –4.85 (q), –4.34 (q), –4.09 (q), –2.74 (q), –2.34 (q), 14.24 (t), 14.81 (q), 18.77 (s), 18.93 (s), 19.44 (t), 26.48 (q, 3 C), 26.62 (q, 3 C), 37.55 (d), 39.06 (t), 43.54 (d), 61.23 (d), 63.92 (s), 65.07 (t), 71.93 (d), 114.47 (t), 128.36 (d, 2 C), 129.59 (d), 134.74 (d, 2 C), 139.60 (s), 145.27 (s) ppm.

Silane 24: To oxide-free lithium chips (70 mg, 10 mmol) in THF (4 mL) was added dropwise with stirring at –10 °C chlorodimethylphenylsilane (340 mg, 2.0 mmol). The mixture was stirred at the same temperature for another 24 h to give a red solution of lithiodimethylphenylsilane (approx. 0.5 M). To a suspension of CuI (26 mg, 137 μmol) in Et_2O (0.7 mL) was added a solution of lithiodimethylphenylsilane (600 μL, approx. 300 μmol, 0.5 M in THF, preparation described above) at –20 °C within 5 min. The mixture was placed in an ice bath and additionally stirred for 15 min. The resulting purple solution of the silylcuprate **23** was cooled to –20 °C, and

vinyl epoxide **22** (50 mg, 91 μmol) diluted in Et_2O (500 μL) was added dropwise. Stirring was maintained at the same temperature for 2.5 h, followed by addition of lithiodimethylphenylsilane (450 μL, approx. 225 μmol). The mixture was stirred for 1 h at 0 °C and quenched with aqueous $NaHCO_3$ (5 mL, 5%). The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined extracts were dried with $MgSO_4$ and filtered. Removal of the solvent and subsequent purification by flash chromatography (pentane/Et_2O, 30:1) afforded **24** (34 mg, 50% from **20**) as an acid sensitive colorless liquid. R_f = 0.31 (pentane/Et_2O, 30:1). ^1H NMR ($CDCl_3$): δ = –0.04 (s, 3 H), –0.02 (s, 3 H), 0.01 (s, 3 H), 0.02 (s, 3 H), 0.27 (s, 3 H), 0.28 (s, 3 H), 0.29 (s, 3 H), 0.29 (s, 3 H), 0.68–0.84 (m, 2 H), 0.81 (s, 9 H), 0.88 (s, 9 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 1.16–1.21 (m, 1 H), 1.46–1.54 (m, 1 H), 1.53 (d, *J* = 13.9 Hz, 1 H), 1.65–1.76 (m, 1 H), 2.00 (dd, *J* = 1.6, *J* = 14.7 Hz, 1 H), 2.04 (d, *J* = 13.9, 1 H), 2.06 (dd, *J* = 3.7, 14.7 Hz, 1 H), 2.69 (tq, *J* = 6.9, 6.9 Hz, 1 H), 3.18 (d, *J* = 10.8 Hz, 1 H), 3.60 (d, *J* = 6.9 Hz, 2 H), 3.95 (dd, *J* = 3.6, 10.8 Hz, 1 H), 3.97–3.99 (m, 1 H), 7.30–7.35 (m, 6 H), 7.46–7.53 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.21 (q, 2 C), –5.05 (q), –4.67 (q), –3.22 (q), –3.14 (q), –2.26 (q), –2.18 (q), 13.07 (t), 14.90 (q), 23.30 (t), 23.38 (t), 17.75 (s), 18.35 (s), 25.68 (q, 3 C), 26.02 (q, 3 C), 38.60 (d), 42.81 (t), 46.03 (d), 66.21 (d), 67.93 (t), 70.01 (d), 126.80 (s), 127.71 (d, 2 C), 127.75 (d, 2 C), 128.78 (d), 128.98 (d), 132.81 (s), 133.46 (d, 2 C), 133.59 (d, 2 C), 139.24 (s), 139.46 (s) ppm. IR (neat): $\tilde{\nu}$ = 3530 cm^{-1} (broad), 2953, 2929, 2886, 2858, 1469, 1426, 1361, 1250, 1112, 1068, 1030, 922, 829, 773, 728, 697 cm^{-1}. MS (CID, –25 V): *m*/*z* (%) = 769 (100). $C_{40}H_{70}O_3Si_4$ (711.32): calcd. C 67.54, H 9.92; found C 67.73, H 10.11.

Iodide 25: To a solution of alcohol **20** (8.00 g, 18.00 mmol) in a mixture of THF (250 mL) and MeCN (100 mL) were added imidazole (7.85 g, 125 mmol) and Ph_3P (15.09 g, 57.6 mmol). The mixture was cooled to –20 °C, I_2 (14.52 g, 57.6 mmol) was added, and the resulting solution was stirred in the dark for 1 h at –20 °C and for 4 h at room temperature. The reaction was quenched with aqueous $NaHCO_3$ (200 mL, 5%) and extracted with pentane (3 × 200 mL). The combined extracts were successively washed with aqueous satd. $Na_2S_2O_3$ (50 mL) and brine (200 mL) and dried with $MgSO_4$. After filtration and evaporation of the solvent, the crude mixture was purified by filtering through a pad of silica gel (pentane + 1% Et_3N) to furnish **25** (8.37 g, 84%) essentially pure as a light sensitive colorless liquid. R_f = 0.29 (pentane). $[\alpha]_D^{25}$ = +108.8 (*c* = 1.01). ^1H NMR ($CDCl_3$): δ = 0.00 (s, 3 H), 0.03 (s, 3 H), 0.26 (s, 3 H), 0.27 (s, 3 H), 0.74 (ddd, *J* = 4.4, 13.8, 13.8 Hz, 1 H), 0.83 (s, 9 H), 0.90 (ddd, *J* = 4.3, 13.8, 13.8 Hz, 1 H), 1.21 (d, *J* = 6.7 Hz, 3 H), 1.22–1.33 (m, 1 H), 1.67–1.77 (m, 1 H), 2.11–2.16 (m, 1 H), 2.31 (ddd, *J* = 1.5, 1.5, 14.4 Hz, 1 H), 2.49 (dd, *J* = 8.5, 14.4 Hz, 1 H), 2.68–2.75 (m, 1 H), 3.08 (dd, *J* = 8.1, 9.5 Hz, 1 H), 3.35 (dd, *J* = 4.0, 9.5 Hz, 1 H), 3.94–3.97 (m, 1 H), 4.79 (broad s, 1 H), 4.94 (broad s, 1 H), 5.58 (d, *J* = 3.9 Hz, 1 H), 7.33–7.35 (m, 3 H), 7.49–7.53 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.84 (q), –4.29 (q), –3.22 (q), –3.01 (q), 13.36 (t), 16.02 (t), 18.04 (s), 19.71 (q), 24.33 (t), 25.79 (q, 3 C), 35.76 (d), 39.38 (t), 45.40 (d), 68.64 (d), 108.83 (t), 127.71 (d, 2 C), 128.79 (d), 128.88 (d), 133.56 (d, 2 C), 138.04 (s), 139.38 (s), 141.11 (s) ppm. IR (neat): $\tilde{\nu}$ = 2955, 2928, 2893, 2857, 1250, 1113, 1093, 883, 858, 836, 813, 774, 729, 700 cm^{-1}. GC/MS: *m*/*z* (%) = 501 (2), 413 (1), 385 (2), 291 (2), 263 (6), 209 (35), 147 (12), 136 (13), 135 (100), 73 (35). $C_{26}H_{43}IOSi_2$ (554.69): calcd. C 56.30, H 7.81; found C 56.10, H 7.79.

Malonate 27: To a solution of the proazaphosphatrane **26** (1.74 g, 8.0 mmol) in MeCN was added dimethyl malonate (1.32 g, 10.0 mmol) diluted with MeCN (15 mL). The solution was stirred at room temperature for 15 min, then treated with iodide **25** (2.77 g, 5.0 mmol), diluted with a mixture of toluene (10 mL) and MeCN (10 mL), and heated under reflux for 2 h. For precipitation and isolation of **26**×HI, the resulting clear solution was concentrated at 40 °C (100 mbar) and filtered. After evaporation of the remaining solvent and purification by flash chromatography (pentane/Et_2O, 9:1 + 0.5% Et_3N), **27** (2.52 g, 91%) was isolated as a colorless viscous liquid. R_f = 0.37 (pentane/Et_2O, 9:1). $[\alpha]_D^{23}$ = +77.5 (*c* = 1.00). ^1H NMR ($CDCl_3$): δ = –0.01 (s, 3 H), 0.02 (s, 3 H), 0.25 (s, 3 H), 0.26 (s, 3 H), 0.74 (ddd, *J* = 4.6, 13.8, 14.2 Hz, 1 H), 0.82 (s, 9 H), 0.90 (ddd, *J* = 4.4, 14.2, 18.1 Hz, 1 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 1.27 (dddd, *J* = 4.6, 8.5, 12.9, 18.1 Hz, 1 H), 1.64–1.72 (m, 1 H), 1.97 (ddd, *J* = 6.9, 8.6, 14.8 Hz, 1 H), 2.05 (ddd, *J* = 6.0, 8.5, 14.8 Hz, 1 H), 2.10–2.15 (m, 1 H), 2.31 (ddd, *J* = 1.5, 1.5, 14.4 Hz, 1 H), 2.47 (dd, *J* = 7.8, 14.4 Hz, 1 H), 2.57–2.61 (m, 1 H), 3.41 (dd, *J* = 8.6, 6.0 Hz, 1 H), 3.67 (s, 3 H), 3.68 (s, 3 H), 3.94–3.98 (m, 1 H), 4.72 (s, 1 H), 4.96 (s, 1 H), 5.54 (d, *J* = 3.3 Hz, 1 H), 7.32–7.36 (m, 3 H), 7.48–7.53 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.91 (q), –4.23 (q), –3.23 (q), –3.14 (q), 13.31 (t), 18.02 (s), 20.95 (q), 24.71 (t), 25.76 (q, 3 C), 30.88 (d), 35.90 (t), 39.76 (t), 45.33 (d), 49.56 (d), 52.27 (q), 52.35 (q), 68.67 (d), 108.89 (t), 127.57 (d), 127.57 (d, 2 C), 128.77 (d), 133.53 (d, 2 C), 139.43 (s, 2 C), 141.35 (s), 170.19 (s), 170.26 (s) ppm. IR (neat): $\tilde{\nu}$ = 2953, 2925, 1753, 1736, 1435, 1248, 1152, 1113, 1091, 884, 811, 771, 729, 699 cm^{-1}. GC/MS: *m*/*z* (%) = 558 (0.3), 527 (0.5), 501 (24), 469 (5), 395 (2), 317 (3), 279 (17), 229 (5), 209 (19), 135 (100), 113 (12). $C_{31}H_{50}O_5Si_2$ (558.90): calcd. C 66.62, H 9.02; found C 66.71 H 9.16.

Methyl Ester 28: To a solution of the malonate **27** (7.37 g, 13.2 mmol) in DMF (130 mL) were added thiophenol (2.94 g, 26.4 mmol) and K_2CO_3 (1.82 g, 13.2 mmol) at 90 °C. The resulting suspension was stirred at the same temperature for 100 min, diluted with aqueous $NaHCO_3$ (250 mL, 5%) at room temperature, and extracted with pentane (3 × 200 mL). The combined extracts were washed successively with aqueous NaOH (50 mL, 2 M), H_2O (50 mL), brine (50 mL), dried and filtered. The residue was purified by flash chromatography (pentane/CH_2Cl_2, 7:3 + 0.5% Et_3N) to afford **28** (5.89 g, 89%) as a colorless liquid. R_f = 0.23 (pentane/CH_2Cl_2, 7:3). $[\alpha]_D^{22}$ = +96.7 (*c* = 1.00). ^1H NMR ($CDCl_3$): δ = –0.02 (s, 3 H), –0.01 (s, 3 H), 0.25 (s, 3 H), 0.26 (s, 3 H), 0.74–0.80 (m, 2 H), 0.81 (s, 9 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 1.20–1.29 (m, 1 H), 1.63–1.80 (m, 3 H), 2.09–2.15 (m, 1 H), 2.17–2.29 (m, 2 H), 2.31 (ddd, *J* = 1.5, 1.5, 14.5 Hz, 1 H), 2.47 (dd, *J* = 7.9, 14.5 Hz, 1 H), 2.59 (ddq, *J* = 6.8, 6.8, 6.9 Hz, 1 H), 3.62 (s, 3 H), 3.94–3.98 (m, 1 H), 4.73 (s, 1 H), 4.99 (s, 1 H), 5.49 (d, *J* = 3.3 Hz, 1 H), 7.31–7.35 (m, 3 H), 7.48–7.52 (m, 2 H) ppm.^{13}C NMR ($CDCl_3$): δ = –4.89 (q), –4.22 (q), –3.27 (q), –3.09 (q), 13.33 (t), 18.02 (s), 20.44 (q), 24.77 (t), 25.76 (q, 3 C), 31.70 (t, 2 C), 32.24 (d), 39.78 (t), 45.32 (d), 51.32 (q), 68.64 (d), 108.78 (t), 127.23 (d), 127.70 (d, 2 C), 128.76 (d), 133.52 (d, 2 C), 139.41 (s), 139.67 (s), 141.58 (s), 174.53 (s) ppm. IR (neat): $\tilde{\nu}$ = 2954, 2929, 2888, 2857, 1741, 1435, 1250, 1169, 1113, 1093, 1065, 876, 837, 814, 774, 729, 700 cm^{-1}. GC/MS: *m*/*z* (%) = 500 (0.3), 485 (0.2), 469 (0.3), 443 (19), 385 (1), 351 (6), 305 (3), 221 (19), 209 (23), 135 (100), 119 (7). $C_{29}H_{48}O_3Si_2$ (500.86): calcd. C 69.54, H 9.66; found C 69.88, H 9.57.

Alcohol 29: Racemic **28** was used. A solution of methyl ester *rac*-**28** (2.13 g, 4.25 mmol) in Et_2O (40 mL) was treated with $LiAlH_4$ (242 mg, 6.37 mmol) at 0 °C, and stirring was maintained for 90 min. The resulting suspension was diluted with Et_2O (100 mL), quenched with aqueous $NaHCO_3$ (130 mL, 5%), stirred at 0 °C for 30 min and at room temperature for 30 min. The inorganic salts were separated by filtration and carefully rinsed with Et_2O, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined extracts were washed brine (50 mL), dried, filtered and the solvents evaporated. The crude product was purified by flash chromatog-

raphy (pentane/Et_2O, 4:1 + 0.5% Et_3N) to afford **29** (57 mg, 100%) as a colorless liquid. R_f = 0.34 (pentane/Et_2O, 4:1). ^1H NMR ($CDCl_3$): δ = 0.00 (s, 3 H), 0.03 (s, 3 H), 0.26 (s, 3 H), 0.27 (s, 3 H), 0.75 (ddd, J = 4.8, 12.9, 14.2 Hz, 1 H), 0.80–0.87 (m, 1 H), 0.82 (s, 9 H), 1.06 (d, J = 6.9 Hz, 3 H), 1.20–1.28 (m, 1 H), 1.38–1.43 (m, 1 H), 1.46–1.54 (m, 3 H), 1.69 (ddt, J = 5.1, 13.2, 5.1 Hz, 1 H), 2.01–2.16 (m, 1 H), 2.32 (ddd, J = 1.5, 1.5, 14.4 Hz, 1 H), 2.47 (dd, J = 8.0, 14.4 Hz, 1 H), 2.52–2.56 (m, 1 H), 3.58 (t, J = 6.0 Hz, 2 H), 3.95–3.99 (m, 1 H), 4.74 (s, 1 H), 5.00 (s, 1 H), 5.51 (d, J = 3.5 Hz, 1 H), 7.32–7.35 (m, 3 H), 7.49–7.52 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.84 (q), –4.25 (q), –3.27 (q), –3.04 (q), 13.38 (t), 18.05 (s), 20.73 (q), 24.66 (t), 25.78 (q, 3 C), 30.50 (t), 32.68 (d), 32.84 (t), 39.74 (t), 45.29 (d), 63.23 (t), 68.83 (d), 108.49 (t), 126.91 (d), 127.70 (d, 2 C), 128.77 (d), 133.59 (d, 2 C), 139.49 (s), 140.42 (s), 141.81 (s) ppm. IR (neat): $\tilde{\nu}$ = 3380 cm^{-1} (broad), 2954, 2929, 2893, 2857, 2360, 2333, 1462, 1428, 1250, 1113, 1095, 1065, 837, 814, 774, 729, 700 cm^{-1}. GC/MS: *m/z* (%) = 472 (0.1), 415 (0.2), 323 (2), 251 (3), 245 (3), 209 (13), 187 (4), 136 (14), 135 (100), 119 (8), 75 (22). $C_{28}H_{48}O_2Si_2$ (472.85): calcd. C 71.12, H 10.23; found C 71.27, H 10.43.

MOM Ether 30: To a solution of the alcohol **29** (2.00 g, 4.24 mmol) in CH_2Cl_2 (50 mL) was added DIPEA (2.1 mL, 12.72 mmol) and MOMCl (840 µL, 10.62 mmol) at 0 °C. The resulting solution was allowed to reach room temperature overnight. The mixture was filtered through a pad of silica gel to afford essentially pure **30** (2.16 g, 99%) as a colorless viscous liquid. R_f = 0.42 (pentane/Et_2O, 19:1). ^1H NMR ($CDCl_3$): δ = –0.04 (s, 3 H), 0.00 (s, 3 H), 0.22 (s, 3 H), 0.23 (s, 3 H), 0.67–0.90 (m, 2 H), 0.79 (s, 9 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.15–1.28 (m, 1 H), 1.35–1.42 (m, 1 H), 1.44–1.56 (m, 3 H), 1.61–1.73 (m, 1 H), 2.07–2.14 (m, 1 H), 2.28 (dd, J = 3.0, 14.4 Hz, 1 H), 2.45 (dd, J = 8.0, 14.4 Hz, 1 H), 2.52–2.55 (m, 1 H), 3.31 (s, 3 H), 3.44 (t, J = 6.0 Hz, 2 H), 3.93 (ddd, J = 3.0, 4.5, 8.0 Hz, 1 H), 4.56 (s, 2 H), 4.70 (s, 1 H), 4.97 (s, 1 H), 5.49 (d, J = 3.7 Hz, 1 H), 7.29–7.32 (m, 3 H), 7.46–7.49 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.83 (q), –4.24 (q), –3.22 (q), –3.07 (q), 13.36 (t), 18.05 (s), 20.66 (q), 24.61 (t), 25.80 (q, 3 C), 27.47 (t), 32.80 (d), 33.42 (t), 39.70 (t), 45.31 (d), 55.05 (q), 68.10 (t), 68.89 (d), 96.37 (t), 108.47 (t), 126.92 (d), 127.71 (d, 2 C), 128.76 (d), 133.54 (d, 2 C), 139.48 (s), 140.52 (s), 141.86 (s) ppm. IR (neat): $\tilde{\nu}$ = 2952, 2935, 2929, 2895, 2883, 2858, 1471, 1428, 1250, 1113, 1098, 1045, 919, 874, 837, 814, 774, 700 cm^{-1}. GC/MS: *m/z* (%) = 516 (2), 485 (0.3), 459 (1), 385 (0.6), 353 (1), 209 (13), 159 (6), 135 (100), 136 (14), 75 (18). $C_{30}H_{52}O_3Si_2$ (516.90): calcd. C 69.71, H 10.14; found C 69.73, H 10.24.

Diol 31: To activated molecular sieves (4 Å, 4.00 g) was added a solution of the silane **30** (2.10 g, 4.07 mmol) in a fresh charge of TBAF (24.4 mL, approx. 24.4 mmol, 1 M in THF), and the resulting dark grey suspension was heated under reflux for 3.5 h. KF (842 mg, 14.51 mmol), $NaHCO_3$ (354 mg, 4.1 mmol), MeOH (30 mL), and H_2O_2 (8.2 mL, 30% in H_2O) were added sequentially, and the mixture was heated under reflux for an additional 1 h. The resulting white suspension was poured at room temperature into aqueous diluted $NaHCO_3$ (250 mL) and extracted with EtOAc (4 × 150 mL). The combined extracts were washed with brine (50 mL), dried, filtered and the solvents evaporated. The residue was purified by flash chromatography (EtOAc + 0.5% Et_3N) to give **31** (1.00 g, 87%) as a colorless viscous liquid. R_f = 0.24 (EtOAc). ^1H NMR ($CDCl_3$): δ = 1.04 (d, J = 6.9 Hz, 3 H), 1.37–1.45 (m, 1 H), 1.49–1.60 (m, 3 H), 1.64–1.69 (m, 1 H), 1.78–1.85 (m, 1 H), 2.48–2.60 (m, 4 H), 3.33 (s, 3 H), 3.48 (dt, J = 1.0, 5.1 Hz, 2 H), 3.71 (ddd, J = 4.6, 7.3, 10.9 Hz, 1 H), 3.76 (ddd, J = 4.7, 6.7, 10.9 Hz, 1 H), 4.01 (ddd, J = 3.2, 3.2, 6.1 Hz, 1 H), 4.58 (s, 2 H), 4.89 (s, 1 H), 5.12 (s, 1 H), 5.33 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.67 (q), 27.63 (t), 32.90 (t), 33.13 (d), 34.03 (t), 39.69 (d), 39.95 (t), 55.10 (q), 60.59 (t), 67.45 (d), 67.97 (t), 96.30 (t), 110.98 (t), 125.57 (d), 139.45 (s), 141.26 (s) ppm. IR (neat): $\tilde{\nu}$ = 3380 cm^{-1} (broad), 2937, 2879, 1455, 1453, 1443, 1148, 1111, 1042, 919, 880, 866 cm^{-1}. GC/MS: *m/z* (%) = 283 (0.5), 267 (1), 235 (4), 204 (16), 191 (9), 185 (22), 175 (24), 159 (30), 147 (31), 131 (33), 119 (50), 105 (56), 91 (59), 79 (30), 45 (100). $C_{16}H_{28}O_4$ (284.39): calcd. C 67.57, H 9.92; found C 67.27, H 10.05.

Lactone 32: A solution of the diol **31** (98 mg, 345 µmol) in MeCN (2 mL) was treated with NMO (412 mg, 3.52 mmol) in an ultrasound bath at 15–20 °C for 10 min followed by addition of TPAP (14.5 mg, 35 µmol). After sonication at the same temperature for additional 50 min, the green mixture was filtered through a pad of silica gel (EtOAc). The solvent was removed, and the crude product was purified by flash chromatography (CH_2Cl_2/Et_2O, 19:1 + 0.5% Et_3N) to afford **32** (63 mg, 65%) as a colorless viscous liquid. R_f = 0.26 (CH_2Cl_2/Et_2O, 19:1). ^1H NMR ($CDCl_3$): δ = 1.05 (d, J = 6.8 Hz, 3 H), 1.37–1.44 (m, 1 H), 1.48–1.58 (m, 3 H), 2.30 (dd, J = 4.0, 17.2 Hz, 1 H), 2.53 (ddq, J = 6.7, 6.7, 6.7 Hz, 1 H), 2.57 (dddd, J = 1.6, 1.6, 3.3, 14.7 Hz, 1 H), 2.73 (dd, J = 5.7, 14.7 Hz, 1 H), 2.79 (dd, J = 8.8, 17.2 Hz, 1 H), 3.14 (ddd, J = 3.9, 9.1, 9.1 Hz, 1 H), 3.33 (s, 3 H), 3.47 (dd, J = 6.1, 8.6 Hz, 2 H), 4.58 (s, 2 H), 4.74 (ddd, J = 3.5, 5.7, 5.7 Hz, 1 H), 4.98 (s, 1 H), 5.19 (s, 1 H), 5.31 (d, J = 3.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.51 (q), 27.70 (t), 32.90 (t), 33.86 (d), 35.57 (d), 35.64 (t), 36.16 (t), 55.11 (q), 67.80 (t), 77.62 (d), 96.37 (t), 112.80 (t), 121.45 (d), 136.73 (s), 143.73 (s), 176.05 (s) ppm. IR (neat): $\tilde{\nu}$ = 2934, 2871, 1766, 1459, 1429, 1186, 1156, 1105, 1071, 1035, 995, 944, 915, 885, 866 cm^{-1}. GC/MS: *m/z* (%) = 281 (0.1), 249 (3), 218 (11), 217 (16), 205 (7), 189 (28), 179 (23), 175 (13), 171 (31), 159 (28), 157 (18), 133 (27), 119 (30), 105 (40), 91 (44), 45 (100). $C_{16}H_{24}O_4$ (280.36): calcd. C 68.54, H 8.63; found: C 68.55, H 8.66.

Carboxylic Acid 33: To a solution of the methyl ester **28** (5.89 g, 11.78 mmol) in MeOH (60 mL) and H_2O (30 mL) was added KOH (6.60 g, 118 mmol), and the resulting suspension was heated under reflux for 90 min. The clear solution was concentrated at 40 °C (100 mbar), diluted with EtOAc (200 mL), and carefully neutralized with aqueous HCl (2 M). The aqueous layer was extracted with EtOAc (2 × 200 mL), and the combined extracts were successively washed with aqueous satd. NH_4Cl (50 mL) and brine (50 mL). After drying over $MgSO_4$, filtration and removal of the solvent, the crude product was rinsed through a pad of silica gel (Et_2O) to afford essentially pure **33** (5.73 g, 100%) as a colorless liquid. R_f = 0.61 (pentane/Et_2O, 1:1). $[\alpha]_D^{21}$ = +98.2 (c = 1.01). ^1H NMR ($CDCl_3$): δ = –0.01 (s, 3 H), 0.02 (s, 3 H), 0.25 (s, 3 H), 0.26 (s, 3 H), 0.72–0.87 (m, 2 H), 0.81 (s, 9 H), 1.08 (d, J = 6.7 Hz, 3 H), 1.21–1.30 (m, 1 H), 1.64–1.83 (m, 3 H), 2.10–2.16 (m, 1 H), 2.21–2.36 (m, 3 H), 2.49 (dd, J = 7.7, 14.5 Hz, 1 H), 2.61 (ddq, J = 6.7, 6.7, 6.7 Hz, 1 H), 3.94–3.99 (m, 1 H), 4.74 (s, 1 H), 5.00 (s, 1 H), 5.50 (d, J = 3.5 Hz, 1 H), 7.31–7.35 (m, 3 H), 7.47–7.52 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.94 (q), –4.27 (q), –3.34 (q), –3.16 (q), 13.32 (t), 17.97 (s), 20.40 (q), 24.72 (t), 25.71 (q, 3 C), 31.35 (t), 31.48 (t), 32.19 (d), 39.74 (t), 45.28 (d), 68.58 (d), 108.81 (t), 127.29 (d), 127.65 (d, 2 C), 128.71 (d), 133.47 (d, 2 C), 139.35 (s), 139.49 (s), 141.48 (s), 179.55 (s) ppm. IR (neat): $\tilde{\nu}$ = 3050 cm^{-1} (broad), 2954, 2929, 2857, 1708, 1426, 1250, 1111, 1093, 876, 836, 774, 700 cm^{-1}. MS (CID, –25 V): *m/z* (%) = 567 (40), 485 (100). $C_{28}H_{46}O_3Si_2$ (486.83): calcd. C 69.08, H 9.52; found C 69.20, H 9.57.

Preparation of the Formyloxy ε-Lactone 36: To a solution of carboxylic acid **33** (49 mg, 100 µmol) in toluene (1.5 mL) was added bis(*sym*-collidine)iodine(I) hexafluorophosphate (69 mg, 135 µmol)

at 0 °C. After stirring at this temperature for 14 h in the dark, DMF (1.5 mL) and AgOAc (25 mg, 150 μmol) were added to the mixture. The resulting suspension was stirred at 0 °C for 2 h and an additional 1 h at room temperature. The solids were removed, the filtrate was poured into aqueous $NaHCO_3$ (5 mL, 5%), and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined extracts were washed successively with aqueous satd. $Na_2S_2O_3$ (5 mL), H_2O (5 mL) and brine (5 mL), dried with $MgSO_4$ and filtered. After evaporation of the solvent, the crude mixture was purified by flash chromatography (pentane/Et_2O, 3:2) to give **36** (35.5 mg, 67%) and **35** (8 mg, 15%) as extremely light sensitive colorless liquids. **36:** R_f = 0.34 (pentane/Et_2O, 3:2). $[\alpha]_D^{25}$ = +52.4 (c = 1.00). ^{1}H NMR ($CDCl_3$): δ = –0.01 (s, 3 H), 0.00 (s, 3 H), 0.28 (s, 3 H), 0.29 (s, 3 H), 0.67 (ddd, J = 4.7, 12.9, 13.9 Hz 1 H), 0.76 (ddd, J = 4.7, 12.9, 13.9 Hz, 1 H), 0.84 (s, 9 H), 1.08 (d, J = 7.3 Hz, 3 H), 1.31–1.36 (m, 1 H), 1.53–1.65 (m, 1 H), 1.68–1.80 (m, 2 H), 1.84–1.92 (m, 1 H), 2.25 (dd, J = 4.2, 18.4 Hz, 1 H), 2.34 (dd, J = 1.6, 18.4 Hz, 1 H), 2.43 (ddd, J = 1.3, 8.2, 15.0 Hz, 1 H), 2.84 (ddd, J = 1.3, 12.0, 15.0 Hz, 1 H), 3.19–3.26 (m, 1 H), 4.03 (dd, J = 1.6, 1.6 Hz, 1 H), 4.63 (d, J = 12.1 Hz, 1 H), 4.74 (d, J = 4.1 Hz, 1 H), 4.77 (d, J = 12.1 Hz, 1 H), 7.33–7.36 (m, 3 H), 7.49–7.53 (m, 2 H), 8.06 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.85 (q), –4.49 (q), –3.27 (q), –3.14 (q), 13.07 (t), 17.96 (q), 17.96 (s), 22.93 (t), 25.60 (q, 3 C), 28.57 (t), 30.06 (t), 32.26 (d), 38.58 (t), 45.90 (d), 62.79 (t), 65.37 (d), 69.73 (d), 127.79 (d, 2 C), 128.33 (s), 128.88 (d), 133.56 (d, 2 C), 136.65 (s), 139.22 (s), 160.74 (d), 174.30 (s) ppm. IR (neat): $\tilde{\nu}$ = 2953, 2926, 2856, 1722, 1426, 1250, 1149, 1113, 1089, 1025, 832, 809, 771, 729, 699 cm^{-1}. MS (CID, –10 V): m/z (%) = 588 (100). $C_{29}H_{46}O_5Si_2$ (530.84): calcd. C 65.61, H 8.73; found C 65.71, H 8.94. **35:** R_f = 0.60 (pentane/Et_2O, 3:2). $[\alpha]_D^{21}$ = +92.8 (c = 1.00) ppm. ^{1}H NMR ($CDCl_3$): δ = 0.05 (s, 3 H), 0.09 (s, 3 H), 0.26 (s, 3 H), 0.27 (s, 3 H), 0.69 (ddd, J = 4.5, 13.2, 13.2 Hz, 1 H), 0.81–0.96 (m, 1 H), 0.84 (s, 9 H), 1.15 (d, J = 6.8 Hz, 3 H), 1.14–1.25 (m, 2 H), 1.79–1.85 (m, 1 H), 1.95 (ddd, J = 13.5, 9.3, 1.2 Hz, 1 H), 2.01–2.10 (m, 2 H), 2.31 (ddd, J = 13.0, 5.0, 1.8 Hz, 1 H), 2.35 (dd, J = 13.5, 4.0 Hz, 1 H), 2.47–2.55 (m, 2 H), 3.22 (d, J = 11.0 Hz, 1 H), 3.45 (dd, J = 11.0, 1.2 Hz, 1 H), 3.95 (ddd, J = 4.0, 9.3, 9.3 Hz, 1 H), 5.67 (d, J = 3.9 Hz, 1 H), 7.32–7.35 (m, 3 H), 7.47–7.49 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.90 (q), –4.14 (q), –3.51 (q), –3.07 (q), 13.42 (t), 15.57 (t), 18.03 (s), 18.20 (q), 23.91 (t), 25.81 (q, 3 C), 30.67 (d), 32.68 (t), 34.17 (t), 40.56 (t), 45.58 (d), 67.20 (d), 81.53 (s), 126.81 (d), 127.79 (d, 2 C), 128.96 (d), 138.41 (d, 2 C), 138.87 (s), 139.09 (s), 171.92 (s) ppm. IR (neat): $\tilde{\nu}$ = 2952, 2931, 1728, 1452, 1246, 1207, 1149, 1112, 1095, 1015, 834, 815, 772, 696, 674 cm^{-1}. MS (CID, –25 V): m/z (%) = 671 (100). $C_{28}H_{45}IO_3Si_2$ (612.73): calcd. C 54.89, H 7.40; found C 54.97, H 7.22. *rac*-**34** from *rac*-**33:** R_f = 0.50 (pentane/Et_2O, 3:2). ^{1}H NMR (C_6D_6): δ = 0.20 (s, 3 H), 0.22 (s, 3 H), 0.50 (s, 6 H), 0.77–0.88 (m, 2 H), 0.79 (d, J = 7.1 Hz, 3 H), 1.05–1.10 (m, 1 H), 1.10–1.16 (m, 1 H), 1.19 (s, 9 H), 1.55 (ddd, J = 5.1, 12.5, 12.7 Hz, 1 H), 1.69 (dddd, J = 5.0, 6.3, 12.8, 18.6 Hz, 1 H), 2.03–2.12 (m, 1 H), 2.24 (dd, J = 1.6, 17.8 Hz, 1 H), 2.25–2.32 (m, 1 H), 2.33 (dd, J = 4.7, 17.8 Hz, 1 H), 2.47 (ddd, J = 1.1, 12.5, 13.9 Hz, 1 H), 2.67 (ddq, J = 4.9, 5.1, 7.1 Hz 1 H), 3.47 (d, J = 9.5 Hz, 1 H), 3.53 (d, J = 9.5 Hz, 1 H), 3.82 (m, 1 H), 4.52 (d, J = 4.2 Hz, 1 H), 7.31–7.35 (m, 1 H), 7.37–7.42 (m, 2 H), 7.68–7.71 (m, 2 H) ppm. ^{13}C NMR (C_6D_6): δ = –4.72 (q), –3.95 (q), –3.12 (q), –2.92 (q), 6.35 (t), 13.17 (t), 16.91 (q), 18.43 (s), 23.59 (t), 26.13 (q, 3 C), 28.20 (t), 29.84 (t), 32.48 (d), 38.95 (t), 46.00 (d), 66.30 (d), 69.13 (d), 128.29 (d, 2 C), 129.37 (d), 131.30 (s), 133.96 (d, 2 C), 135.29 (s), 139.19 (s), 172.68 (s) ppm. IR (neat): $\tilde{\nu}$ = 2953, 2926, 2856, 1726, 1447, 1362, 1247, 1149, 1111, 1084, 1023, 960, 916, 832, 810, 771, 728, 698, 674 cm^{-1}. MS (CID, 25 V): m/z (%) = 613 (100), 630 (20), 635 (20). $C_{28}H_{45}IO_3Si_2$ (612.73): calcd. C 54.89, H 7.40; found C 55.22, H 7.63.

Recycling of 35: To a solution of the iodolactone **35** (533 mg, 869 μmol) in THF (17 mL) were added zinc dust (554 mg, 8.53 mmol), HOAc (120 μL, 2.1 mmol), and H_2O (120 μL) at 0 °C. The mixture was stirred for 30 min at this temperature and at room temperature overnight. After complete conversion, the solids were removed, the filtrate was poured into aqueous satd. NH_4Cl, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined extracts were washed with aqueous satd. $Na_2S_2O_3$ (10 mL), dried with $MgSO_4$ and filtered. After evaporation of the solvent, the crude mixture was purified by flash chromatography (pentane/Et_2O, 3:2) to afford **33** (365 mg, 86%) as a colorless viscous liquid.

Triol 37: $LiAlH_4$ (547 mg, 14.48 mmol) was added within 30 min to a solution of the lactone **36** (3.82 g, 7.21 mmol) in Et_2O (350 mL) at –10 °C. The resulting mixture was stirred at –10 °C for 30 min and was then warmed to 0 °C within 3 h. If any remaining **36** was detectable, additional $LiAlH_4$ (137 mg, 3.62 mmol) was added and the reaction time was extended for 1 h. The reaction was quenched with H_2O (4 mL) and heated under reflux for 15 min. The white solid was separated by filtering through a pad of silica gel (Et_2O), and the filtrate was concentrated to dryness to give a mixture of reduced derivatives of **36**, which was then dissolved in Et_2O (80 mL), placed in an ice bath and treated with $LiBH_4$ (536 mg, 24.36 mmol). The solution was stirred at 0 °C for 10 min, warmed to room temperature and stirred for additional 2 h. The resulting suspension was diluted with Et_2O (30 mL), successively treated with acetone (2 mL) and aqueous $NaHCO_3$ (30 mL, 5%) and stirred until gas evolution has ceased. The aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined extracts were washed with brine (50 mL), dried and filtered. After removal of the solvent, the crude product was purified by flash chromatography (Et_2O) to afford **37** (2.93 g, 91%) as a colorless viscous liquid. R_f = 0.34 (Et_2O). $[\alpha]_D^{25}$ = +11.4 (c = 0.96). ^{1}H NMR ($CDCl_3$): δ = 0.01 (s, 3 H), 0.06 (s, 3 H), 0.29 (s, 6 H), 0.67 (ddd, J = 4.4, 13.9, 13.9 Hz, 1 H), 0.81–0.88 (m, 1 H), 0.82 (s, 9 H), 1.04 (d, J = 6.9 Hz, 3 H), 1.26–1.30 (m, 1 H), 1.44–1.52 (m, 1 H), 1.53–1.60 (m, 3 H), 1.72–1.83 (m, 2 H), 2.30 (dd, J = 4.0, 18.0 Hz, 1 H), 2.43 (dd, J = 1.3, 18.0 Hz, 1 H), 2.78–2.83 (m, 1 H), 3.60 (dt, J = 10.4, 6.0 Hz, 1 H), 3.63 (dt, J = 10.4, 6.0 Hz, 1 H), 3.88 (d, J = 10.2 Hz, 1 H), 4.08 (dd, J = 4.1, 10.2 Hz 1 H), 4.09 (d, J = 12.0 Hz, 1 H), 4.16–4.18 (m, 1 H), 4.20 (d, J = 12.0 Hz, 1 H), 7.33–7.36 (m, 3 H), 7.51–7.54 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.15 (q), –4.62 (q), –3.24 (q), –3.21 (q), 12.90 (t), 17.72 (s), 20.58 (q), 23.19 (t), 25.60 (q, 3 C), 31.09 (t), 32.12 (t), 34.98 (d), 38.18 (t), 45.57 (d), 62.34 (t), 62.82 (t), 66.84 (d), 70.07 (d), 127.73 (d, 2 C), 128.19 (s), 128.28 (d), 133.57 (d, 2 C), 139.25 (s), 140.61 (s) ppm. IR (neat): $\tilde{\nu}$ = 3383 cm^{-1} (broad), 2953, 2929, 2858, 1467, 1426, 1250, 1113, 1056, 1004, 829, 774, 729, 698 cm^{-1}. MS (CID, –25 V): m/z (%) = 565 (100). $C_{28}H_{50}O_4Si_2$ (506.87): calcd. C 66.35, H 9.94; found C 66.45, H 10.04.

Bis(trityl) Ether 38: Triol **37** (3.13 g, 6.20 mmol) was dissolved in CH_2Cl_2 (300 mL), and pyridine (975 μL, 124 mmol), DMAP (908 mg, 7.44 mmol), and trityl chloride (4.89 g, 17.56 mmol) were added. The resulting mixture was stirred at room temperature for 40 h. The solvent was evaporated, and the residue was filtered through a pad of silica gel (pentane/Et_2O, 9:1). Final purification was achieved by flash chromatography (pentane/Et_2O, 9:1 + 0.5% Et_3N) to give **38** (5.51 g, 90%) as a cured foam. R_f = 0.37 (pentane/Et_2O, 9:1). $[\alpha]_D^{21}$ = –4.1 (c = 1.00). ^{1}H NMR ($CDCl_3$): δ = 0.00 (s, 3 H), 0.03 (s, 3 H), 0.29 (s, 6 H), 0.75 (ddd, J = 4.4, 13.9, 13.9 Hz, 1 H), 0.82 (ddd, J = 4.7, 13.9, 13.9 Hz, 1 H), 0.79 (s, 9 H), 0.87 (d,

J = 6.9 Hz, 3 H), 1.20–1.24 (m, 1 H), 1.24–1.27 (m, 1 H), 1.38–1.48 (m, 3 H), 1.49–1.58 (m, 1 H), 1.70–1.79 (m, 1 H), 2.29–2.33 (m, 1 H), 2.36 (dd, *J* = 4.0, 18.1 Hz, 1 H), 2.47 (dd, *J* = 1.3, 18.1 Hz, 1 H), 2.82–2.91 (m, 2 H), 3.47 (d, *J* = 10.8 Hz, 1 H), 3.56 (d, *J* = 10.7 Hz, 1 H), 3.65 (d, *J* = 10.7 Hz, 1 H), 3.96 (dd, *J* = 3.5, 10.8 Hz, 1 H), 4.15 (broad s, 1 H), 7.16–7.27 (m, 18 H), 7.32–7.35 (m, 3 H), 7.36–7.40 (m, 6 H), 7.41–7.45 (m, 6 H), 7.50–7.54 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.13 (q), –4.58 (q), –3.23 (q), –3.18 (q), 12.93 (t), 17.73 (s), 19.58 (q), 23.19 (t), 25.65 (q, 3 C), 29.01 (t), 32.84 (t), 35.57 (d), 38.17 (t), 45.63 (d), 63.24 (t), 64.04 (t), 67.33 (d), 69.97 (d), 86.08 (s), 86.44 (s), 125.88 (s), 126.67 (d, 3 C), 126.88 (d, 3 C), 127.59 (d, 6 C) 127.70 (d, 8 C), 128.67 (d, 6 C), 128.71 (d, 6 C), 128.77 (d), 133.59 (d, 2 C), 139.41 (s), 140.41 (s), 144.15 (s, 3 C), 144.57 (s, 3 C) ppm. IR (neat): $\tilde{\nu}$ = 3510 cm^{-1} (broad), 3058, 2952, 2929, 2858, 1558, 1489, 1447, 1251, 1112, 1059, 1031, 987, 831, 771, 745, 698 cm^{-1}. MS (CID/75 V): *m*/*z* (%) = 1014 (100). $C_{66}H_{78}O_4Si_2$ (991.49): calcd. C 79.95, H 7.93; found C 79.43, H 8.23.

Diol 39: To a solution of the silyl ether **38** (50 mg, 50 μmol) in THF (1.5 mL) was added a mixture of TBAF (250 μL, approx. 250 μmol, 1 M in THF) and HOAc (5 μL, 88 μmol). The solution was stirred at room temperature for 3 h, diluted with Et_2O (2 mL), and quenched with aqueous $NaHCO_3$ (0.5 mL, 5%). The aqueous layer was extracted with Et_2O (3×2 mL), and the combined extracts were dried, filtered and the solvents evaporated. The residue was purified by flash chromatography (pentane/Et_2O, 7:3) to afford **39** (43 mg, 97%) as a cured white foam. R_f = 0.66 (pentane/Et_2O, 1:1). $[\alpha]_D^{22}$ = +3.8 (*c* = 1.01). ^{1}H NMR ($CDCl_3$): δ = 0.30 (s, 6 H), 0.84 (ddd, *J* = 5.5, 5.5, 11.0 Hz, 2 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 1.17–1.26 (m, 1 H), 1.32–1.45 (m, 4 H), 1.63–1.70 (m, 1 H), 1.72–1.79 (m, 1 H), 2.31–2.35 (m, 1 H), 2.41 (d, *J* = 5.0 Hz, 1 H), 2.48 (dd, *J* = 1.0, 18.6 Hz, 1 H), 2.57 (dd, *J* = 4.4, 18.6 Hz, 1 H), 2.86 (d, *J* = 8.1 Hz, 1 H), 2.89 (t, *J* = 6.5 Hz, 2 H), 3.50 (d, *J* = 10.4 Hz, 1 H), 3.72 (d, *J* = 10.5 Hz, 1 H), 4.08 (dd, *J* = 2.9, 7.8 Hz, 1 H), 4.14–4.17 (m, 1 H), 7.17–7.28 (m, 18 H), 7.33–7.36 (m, 3 H), 7.36–7.39 (m, 6 H), 7.41–7.44 (m, 6 H), 7.52–7.55 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –3.16 (q), –3.12 (q), 12.88 (t), 19.77 (q), 22.70 (t), 28.68 (t), 32.43 (t), 35.40 (d), 38.91 (t), 45.26 (d), 63.32 (t), 64.01 (t), 66.96 (d), 68.45 (d), 86.39 (s), 86.49 (s), 126.78 (d, 3 C), 126.93 (d, 3 C), 127.53 (s), 127.65 (d, 6 C), 127.74 (d, 6 C), 127.77 (d, 2 C), 128.66 (d, 6 C), 128.69 (d, 6 C), 128.85 (d), 133.59 (d, 2 C), 139.39 (s), 139.55 (s), 144.10 (s, 3 C), 144.41 (s, 3 C) ppm. IR (neat): $\tilde{\nu}$ = 3360 cm^{-1} (broad), 3058, 3024, 2931, 1489, 1448, 1247, 1218, 1113, 1054, 1029, 987, 834, 763, 745, 699 cm^{-1}. MS (CID/75 V): *m*/*z* (%) = 899 (100). $C_{60}H_{64}O_4Si$ (877.23): calcd. C 82.15, H 7.35; found C 81.78, H 7.32.

Triol 40: To activated molecular sieves (4 Å, 90 mg) was added a solution of silane **39** (50 mg, 57 μmol) in a fresh charge of TBAF (1.0 mL, approx. 1.0 mmol, 1 M in THF), and the mixture was heated in a sealed tube at 100 °C for 14 h. To the resulting grey suspension were sequentially added KF (12 mg, 208 μmol), $NaHCO_3$ (10 mg, 120 μmol), MeOH (0.5 mL), and H_2O_2 (0.2 mL, 30% in H_2O) at room temperature. The mixture was then heated at 90 °C for 90 min and cooled to room temperature. The molecular sieves were separated by filtration and sequentially washed with EtOAc (3 mL) and H_2O (3 mL). The filtrate was neutralized with aqueous satd. NH_4Cl, and the aqueous layer was extracted with EtOAc (3×5 mL). The combined extracts were washed with brine (5 mL), dried with $MgSO_4$, filtered and the solvents evaporated. The residue was purified by flash chromatography (EtOAc) to give **40** (37 mg, 88%) as a cured white foam. R_f = 0.53 (EtOAc). $[\alpha]_D^{22}$ = +5.0 (*c* = 1.00). ^{1}H NMR ($CDCl_3$): δ = 0.89 (d, *J* = 7.0 Hz, 3 H), 1.18–1.28 (m, 1 H), 1.34–1.46 (m, 3 H), 1.69–1.75 (m, 1 H), 1.89–1.96 (m, 1 H), 2.04–2.12 (m, 1 H), 2.34 (ddq, *J* = 7.0, 7.0, 7.0 Hz, 1 H), 2.52 (d, *J* = 18.5 Hz, 1 H), 2.66 (dd, *J* = 4.4, 18.5 Hz, 1 H), 2.89 (t, *J* = 6.5 Hz, 2 H), 3.51 (d, *J* = 10.5 Hz, 1 H), 3.75 (d, *J* = 10.5 Hz, 1 H), 3.81–3.90 (m, 2 H), 4.13 (broad s, 2 H), 7.18–7.22 (m, 6 H), 7.22–7.28 (m, 12 H), 7.36–7.39 (m, 6 H), 7.40–7.44 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.65 (q), 28.84 (t), 31.51 (t), 32.49 (t), 35.38 (d), 38.51 (t), 39.97 (d), 60.89 (t), 63.29 (t), 64.00 (t), 67.21 (d), 68.85 (d), 86.36 (s), 86.50 (s), 126.76 (d, 3 C), 126.93 (d, 3 C), 127.63 (d, 6 C), 127.84 (d, 6 C), 127.73 (s) 128.64 (d, 6 C), 128.67 (d, 6 C), 139.13 (s), 144.06 (s, 3 C), 144.40 (s, 3 C) ppm. IR (neat): $\tilde{\nu}$ = 3330 cm^{-1} (broad), 3057, 2927, 2863, 1447, 1372, 1220, 1155, 1055, 1032, 986, 899, 763, 746, 700 cm^{-1}. MS (CID/50 V): *m*/*z* (%) = 797 (9), 781 (100). $C_{52}H_{54}O_5$ (758.98): calcd. C 82.29, H 7.17; found C 82.24, H 7.22.

Lactone 41: Triol **40** (65 mg, 86 μmol), TEMPO (4 mg, 26 μmol), and TBACl (4 mg, 9 μmol) in a biphasic mixture of CH_2Cl_2 (1.5 mL) and an aqueous solution of $NaHCO_3$ (0.5 M) and K_2CO_3 (0.05 M) were vigorously stirred at room temperature. NCS (63 mg, 474 μmol) was added, and stirring was maintained for 3 h. The resulting mixture was diluted with H_2O (1 mL) and extracted with CH_2Cl_2 (4×3 mL). The combined extracts were washed with brine (5 mL), dried with $MgSO_4$, filtered and the solvents evaporated. The residue was purified by flash chromatography (Et_2O) to give **41** (54.5 mg, 84%) as a cured white foam. R_f = 0.30 (Et_2O). $[\alpha]_D^{22}$ = +0.3 (*c* = 0.91). ^{1}H NMR ($CDCl_3$): δ = 0.94 (d, *J* = 7.0 Hz, 3 H), 1.15–1.21 (m, 1 H), 1.23–1.32 (m, 2 H), 1.39–1.46 (m, 2 H), 2.34 (ddq, *J* = 7.0, 7.0, 7.0 Hz, 1 H), 2.51 (dd, *J* = 4.3, 17.8 Hz, 1 H), 2.55–2.71 (m, 4 H), 2.85–2.92 (m, 2 H), 3.56 (d, *J* = 10.8 Hz, 1 H), 3.80 (d, *J* = 10.8 Hz, 1 H), 3.98–4.03 (m, 1 H), 4.90 (d, *J* = 5.6 Hz, 1 H), 7.17–7.28 (m, 18 H), 7.30–7.37 (m, 6 H), 7.37–7.42 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.07 (q), 28.78 (t), 31.85 (t), 32.99 (t), 34.60 (t), 35.04 (d), 39.02 (d), 63.08 (t), 63.78 (t), 66.08 (d), 76.49 (d), 86.28 (s), 86.83 (s), 126.80 (d, 3 C), 127.14 (d, 3 C), 127.68 (d, 6 C), 127.86 (d, 6 C), 128.64 (d, 6 C), 128.67 (d, 6 C), 131.20 (s), 134.78 (s), 143.73 (s, 3 C), 144.39 (s, 3 C), 176.40 (s) ppm. IR (neat): $\tilde{\nu}$ = 3450 cm^{-1} (broad), 3058, 2927, 2857, 1773, 1490, 1447, 1183, 1155, 1056, 1032, 984, 900, 763, 746, 699 cm^{-1}. MS (CID/100 V): *m*/*z* (%) = 777 (100). $C_{52}H_{50}O_5$ (754.95): calcd. C 82.73, H 6.68; found C 82.85, H 6.58.

Cyclohexenone 42: Bis(trityl) ether **38** (990 mg, 1.00 mmol) was dissolved in CH_2Cl_2 (60 mL), and pyridine (600 μL, 6.00 mmol) and Dess–Martin periodinane (850 mg, 2.00 mmol) were added. The resulting solution was stirred in the dark at room temperature for 3.5 h. The reaction mixture was directly subjected to flash chromatography (pentane/Et_2O, 9:1) to give **42** (980 mg, 99%) as a cured white foam. R_f = 0.37 (pentane/Et_2O, 9:1). $[\alpha]_D^{25}$ = –3.3 (*c* = 1.00). ^{1}H NMR ($CDCl_3$): δ = –0.03 (s, 3 H), 0.00 (s, 3 H), 0.26 (s, 3 H), 0.27 (s, 3 H), 0.63 (ddd, *J* = 4.2, 14.1, 14.1 Hz, 1 H), 0.71–0.79 (m, 1 H), 0.75 (s, 9 H), 0.94 (d, *J* = 6.0 Hz, 3 H), 1.26–1.37 (m, 3 H), 1.48–1.58 (m, 2 H), 1.76–1.85 (m, 1 H), 2.16 (ddd, *J* = 2.8, 7.3, 7.3 Hz, 1 H), 2.34–2.46 (m, 1 H), 2.65 (dd, *J* = 4.7, 18.7 Hz, 1 H), 2.70 (dd, *J* = 3.8, 18.7 Hz, 1 H), 2.84 (t, *J* = 6.4 Hz, 2 H), 3.70 (d, *J* = 12.3 Hz, 1 H), 3.85 (d, *J* = 12.3 Hz, 1 H), 4.26–4.30 (m, 1 H), 7.18–7.33 (m, 21 H), 7.37–7.41 (m, 6 H), 7.37–7.41 (m, 6 H), 7.48–7.51 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.92 (q), –4.42 (q), –3.22 (q), –3.16 (q), 13.08 (t), 17.87 (s), 18.93 (t), 19.20 (q), 25.62 (q, 3 C), 28.88 (t), 31.44 (t), 32.76 (d), 36.85 (t), 56.85 (d), 63.38 (t), 63.81 (t), 68.25 (d), 86.15 (s), 86.97 (s), 126.71 (d, 3 C), 127.15 (d, 3 C), 127.60 (d, 6 C), 127.71 (d, 2 C), 127.88 (d, 6 C), 128.61 (d, 6 C), 128.67 (d, 6 C), 128.78 (d), 133.54 (d, 2 C), 138.30 (s), 139.30 (s), 143.64 (s, 3 C), 144.47 (s, 3 C), 147.91 (s), 200.23 (s) ppm. IR (neat): $\tilde{\nu}$ = 3059, 3021, 2947, 2856, 1671, 1447, 1250, 1111, 1067, 1032, 987, 834, 771, 745, 699 cm^{-1}. MS (CID/50 V): *m*/*z* (%)

= 1027 (30), 1011 (5), 243 (100). $C_{66}H_{76}O_4Si_2$ (989.48): calcd. C 80.11, H 7.74; found C 80.17, H 7.78.

Alcohol 43: To a solution of the silyl ether **42** (980 mg, 0.99 mmol) in THF (30 mL) was added a mixture of TBAF (4.8 mL, 4.8 mmol, 1 M in THF) and HOAc (90 μL, 1.55 mmol). The solution was stirred at room temperature for 26 h and then poured into aqueous $NaHCO_3$ (20 mL, 5%). The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined extracts were washed with brine (20 mL), dried, filtered and the solvents evaporated. The residue was purified by flash chromatography (pentane/Et_2O, 3:2 + 0.1% Et_3N) to afford **43** (830 mg, 96%) as a cured white foam. R_f = 0.28 (pentane/Et_2O, 3:2). $[\alpha]_D^{25}$ = –2.5 (*c* = 1.01). ^{1}H NMR ($CDCl_3$): δ = 0.27 (s, 6 H), 0.69 (ddd, *J* = 4.6, 13.6, 14.3 Hz, 1 H), 0.71 (ddd, *J* = 4.7, 12.9, 13.6 Hz, 1 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 1.23–1.54 (m, 5 H), 1.85–1.93 (m, 1 H), 2.26 (ddd, *J* = 2.8, 7.3, 7.3 Hz, 1 H), 2.36–2.44 (m, 1 H), 2.70 (dd, *J* = 4.3, 18.8 Hz, 1 H), 2.80–2.86 (m, 3 H), 3.71 (d, *J* = 12.2 Hz, 1 H), 3.91 (d, *J* = 12.2 Hz, 1 H), 4.31–4.33 (m, 1 H), 7.17–7.33 (m, 18 H), 7.30–7.33 (m, 3 H) 7.36–7.39 (m, 6 H), 7.40–7.43 (m, 6 H), 7.48–7.50 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –3.24 (q), –3.16 (q), 12.80 (t), 18.98 (q + t, 2 C), 28.91 (t), 31.43 (t), approx. 32.5 (d, signal detectable only via HSQC and COSY), 36.36 (t), 55.71 (d), 63.49 (t), 63.82 (t), 67.62 (d), 86.21 (s), 89.09 (s), 126.74 (d, 3 C), 127.20 (d, 3 C), 127.63 (d, 6 C), 127.77 (d, 2 C), 127.91 (d, 6 C), 128.59 (d, 6 C), 128.64 (d, 6 C), 128.88 (d), 133.53 (d, 2 C), 138.67 (s), 139.12 (s), 143.59 (s, 3 C), 144.43 (s, 3 C), 147.90 (s), 199.83 (s) ppm. IR (neat): $\tilde{\nu}$ = 3450 cm^{-1} (broad), 3058, 3026, 2929, 2868, 1666, 1447, 1247, 1112, 1065, 984, 834, 764, 745, 699 cm^{-1}. MS (CID/–10 V): *m*/*z* (%) = 931 (100). $C_{60}H_{62}O_4Si$ (875.22): calcd. C 82.34, H 7.14; found C 82.41, H 7.29.

Diol 44: To a solution of enone **43** (1.20 g, 1.37 mmol) in CH_2Cl_2 (140 mL) was added Red-Al (1.6 mL, approx. 5.5 mmol, 3.5 M in toluene) at –20 °C within 1 h. The mixture was allowed to reach room temperature overnight. After quenching with aqueous satd. NH_4Cl, the mixture was stirred until gas evolution ceased and dried with $MgSO_4$. The mixture was filtered, the solvent was removed, and the crude mixture was purified by flash chromatography (Et_2O) to give **44** (1.08 g, 90%) and **39** (43 mg, 4%) as cured white foams. **44:** R_f = 0.39 (Et_2O). $[\alpha]_D^{22}$ = –21.9 (*c* = 1.01). ^{1}H NMR ($CDCl_3$): δ = 0.15 (s, 3 H), 0.20 (s, 3 H), 0.71–0.75 (m, 2 H), 0.93 (d, *J* = 7.0 Hz, 3 H), 0.96–1.04 (m, 1 H), 1.10–1.29 (m, 3 H), 1.19 (d, *J* = 6.3 Hz, 1 H), 1.37–1.41 (m, 1 H), 1.56–1.62 (m, 1 H), 1.70 (ddt, *J* = 3.8, 8.0, 8.0 Hz, 1 H), 2.13 (dd, *J* = 9.2, 17.6 Hz, 1 H), 2.22–2.26 (m, 1 H), 2.53 (dd, *J* = 5.7, 17.6 Hz, 1 H), 2.84–2.93 (m, 2 H), 3.53 (d, *J* = 10.5 Hz, 1 H), 3.58 (d, *J* = 10.5 Hz, 1 H), 4.11 (dd, *J* = 3.8, 6.3 Hz, 1 H), 4.25 (ddd, *J* = 5.7, 8.0, 9.2 Hz, 1 H), 7.18–7.29 (m, 21 H), 7.38–7.45 (m, 14 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –3.33 (q), –3.03 (q), 13.60 (t), 17.99 (t), 20.39 (q), 28.54 (t), 32.10 (t), 34.25 (t), 34.53 (d), 50.08 (d), 62.81 (t), 63.80 (t), 65.74 (d), 69.34 (d), 86.29 (s), 86.52 (s), 126.82 (d, 3 C), 126.95 (d, 3 C), 127.67 (d, 6 C), 127.75 (d, 6 C), 127.72 (d, 2 C), 128.62 (d, 6 C), 128.65 (d, 6 C), 128.84 (d), 131.14 (s), 133.46 (d, 2 C), 137.73 (s), 139.14 (s), 143.99 (s, 3 C), 144.35 (s, 3 C) ppm. IR (neat): $\tilde{\nu}$ = 3450 cm^{-1} (broad), 3057, 2924, 2868, 1489, 1448, 1427, 1247, 1220, 1113, 1056, 1031, 987, 812, 761, 744, 696 cm^{-1}. MS (CID/25 V): *m*/*z* (%) = 894 (100). $C_{60}H_{64}O_4Si$ (877.23): calcd. C 82.15, H 7.35; found C 81.78, H 7.32.

Triol 45: To activated molecular sieves (4 Å, 1.50 g) was added a solution of the silane **44** (841 mg, 0.96 mmol) in a fresh charge of TBAF (10.0 mL, approx. 10.0 mmol, 1 M in THF), and the resulting dark grey suspension was heated under reflux for 4 h. KF (195 mg, 3.37 mmol), $NaHCO_3$ (186 mg, 2.21 mmol), MeOH (8 mL), and H_2O_2 (3.4 mL, 30% in H_2O) were added sequentially at room temperature, and the mixture was then heated under reflux for 1 h. The resulting white suspension was cooled to room temperature, the molecular sieves were separated by filtration and washed sequentially with EtOAc (20 mL) and H_2O (20 mL). The filtrate was neutralized with aqueous satd. NH_4Cl, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (20 mL), dried, filtered and the solvents evaporated. The residue was purified by flash chromatography (EtOAc) to give **45** (722 mg, 99%) as a cured white foam. R_f = 0.29 (EtOAc). $[\alpha]_D^{22}$ = –23.7 (*c* = 1.00). ^{1}H NMR ($CDCl_3$): δ = 0.96 (d, *J* = 7.0 Hz, 3 H), 1.20–1.31 (m, 5 H), 1.56–1.65 (m, 1 H), 2.06 (ddt, *J* = 3.5, 4.0, 8.0 Hz, 1 H), 2.22 (dd, *J* = 9.6, 17.7 Hz, 1 H), 2.23–2.28 (m, 1 H), 2.70 (dd, *J* = 5.8, 17.7 Hz, 1 H), 2.90 (t, *J* = 6.3 Hz, 2 H), 3.52 (d, *J* = 10.6 Hz, 1 H), 3.59–3.64 (m, 1 H), 3.67 (d, *J* = 10.6 Hz, 1 H), 3.70–3.74 (m, 1 H), 4.05 (d, *J* = 3.5 Hz, 1 H), 4.32 (ddd, *J* = 4.0, 5.8, 9.6 Hz, 1 H), 7.17–7.22 (m, 6 H), 7.23–7.28 (m, 12 H), 7.35–7.39 (m, 6 H), 7.41–7.44 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.47 (q), 28.49 (t), 29.73 (t), 32.19 (t), 34.16 (t), 34.31 (d), 45.95 (d), 62.07 (t), 62.74 (t), 63.63 (t), 65.66 (d), 69.66 (d), 86.29 (s), 86.66 (s), 126.85 (d, 3 C), 126.98 (d, 3 C), 127.68 (d, 6 C), 127.78 (d, 6 C), 128.62 (d, 6 C), 128.67 (d, 6 C), 131.77 (s), 136.98 (s), 143.98 (s, 3 C), 144.34 (s, 3 C) ppm. IR (neat): $\tilde{\nu}$ = 3320 cm^{-1} (broad), 3057, 2926, 2863, 1448, 1378, 1220, 1182, 1055, 1030, 1001, 899, 762, 745, 696 cm^{-1}. MS (CID/100 V): *m*/*z* (%) = 797 (32), 781 (100). $C_{52}H_{54}O_5$ (758.98): calcd. C 82.29, H 7.17; found C 82.34, H 7.15.

Lactone 46: To a solution of the triol **45** (457 mg, 603 μmol) in CH_2Cl_2 (7 mL) were added TEMPO (18 mg, 115 μmol) and bis(acetoxy)iodobenzene (388 mg, 1.20 mmol) at room temperature. After stirring for 3 h in the dark, the same amount of oxidant and cooxidant were added, and stirring was maintained for 6 h. The resulting orange solution was directly subjected to flash chromatography (Et_2O) to afford **46** (341 mg, 75%) as a cured white foam. R_f = 0.31 (Et_2O). $[\alpha]_D^{24}$ = –11.0 (*c* = 1.04). ^{1}H NMR ($CDCl_3$): δ = 1.00 (d, *J* = 6.8 Hz, 3 H), 1.05–1.12 (m, 1 H), 1.21–1.33 (m, 3 H), 1.57 (s, 1 H), 2.03 (dd, *J* = 5.3, 18.6 Hz, 1 H), 2.30–2.34 (m, 1 H), 2.66–2.78 (m, 3 H), 2.88–2.94 (m, 2 H), 2.96–3.03 (m, 1 H), 3.77 (d, *J* = 11.0 Hz, 1 H), 3.80 (d, *J* = 11.0 Hz, 1 H), 4.10 (broad s, 1 H), 5.03 (ddd, *J* = 2.4, 4.0, 8.0 Hz, 1 H), 7.18–7.23 (m, 6 H), 7.25–7.30 (m, 12 H), 7.37–7.42 (m, 12 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.18 (q), 28.08 (t), 30.90 (t), 30.59 (t), 32.39 (t), 33.60 (d), 39.44 (d), 62.99 (t), 63.09 (t), 66.72 (d), 77.97 (d), 86.32 (s), 86.78 (s), 126.82 (d, 3 C), 127.04 (d, 3 C), 127.69 (d, 6 C), 127.82 (d, 6 C), 128.59 (d, 6 C), 128.65 (d, 6 C), 132.51 (s), 139.70 (s), 143.98 (s, 3 C), 144.25 (s, 3 C), 175.92 (s) ppm. IR (neat): $\tilde{\nu}$ = 3480 cm^{-1} (broad), 3054, 2926, 2851, 1762, 1715, 1489, 1448, 1183, 1150, 1054, 1026, 899, 760, 746, 696 cm^{-1}. MS (CID/50 V): *m*/*z* (%) = 793 (93), 777 (100). $C_{52}H_{50}O_5$ (754.95): calcd. [M$^+$] 754.3658; found [M$^+$] 754.3667.

Silyl Ether 47: To a solution of alcohol **46** (184 mg, 244 μmol) in CH_2Cl_2 (7 mL) were added imidazole (83 mg, 1.22 mmol) and TMSCl (61 μL, 488 μmol) at room temperature. The solution was stirred for 30 min and then filtered rapidly through a pad of silica gel (Et_2O). After evaporation of the filtrate, essentially pure **47** (193 mg, 96%) was obtained as a cured white foam. R_f = 0.42 (pentane/Et_2O, 3:2). $[\alpha]_D^{24}$ = –26.4 (*c* = 1.00). ^{1}H NMR ($CDCl_3$): δ = 0.14 (s, 9 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 1.05–1.15 (m, 1 H), 1.19–1.37 (m, 3 H), 2.07 (dd, *J* = 6.6, 18.4 Hz, 1 H), 2.30–2.34 (m, 1 H), 2.61 (dd, *J* = 11.2, 18.4 Hz, 1 H), 2.66 (dd, *J* = 2.1, 16.1 Hz, 1 H), 2.77 (dd, *J* = 4.8, 16.1 Hz, 1 H), 2.85–2.95 (m, 3 H), 3.51 (d, *J* = 10.6 Hz, 1 H), 3.62 (d, *J* = 10.6 Hz, 1 H), 4.15 (d, *J* = 2.4 Hz, 1 H), 5.00 (ddd, *J* = 2.1, 4.8, 7.4 Hz, 1 H), 7.16–7.30 (m, 18 H), 7.37–

7.43 (m, 12 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 0.68 (q, 3 C), 19.00 (q), 28.27 (t), 30.86 (t), 31.00 (t), 32.05 (t), 33.91 (d), 40.40 (d), 62.76 (t), 63.23 (t), 67.05 (d), 78.06 (d), 86.31 (s), 86.58 (s), 126.83 (d, 3 C), 126.92 (d, 3 C), 127.69 (d, 6 C), 127.76 (d, 6 C), 128.65 (d, 6 C), 128.67 (d, 6 C), 131.02 (s), 139.51 (s), 144.04 (s, 3 C), 144.30 (s, 3 C), 176.10 (s) ppm. IR (neat): $\tilde{\nu}$ = 3058, 2953, 2864, 1772, 1490, 1448, 1356, 1250, 1183, 1154, 1056, 1030, 899, 878, 838, 745, 696 cm^{-1}. MS (CID/10 V): *m/z* (%) = 849 (100), 845 (20). $C_{55}H_{58}O_5Si$ (827.13): calcd. C 79.86, H 7.07; found C 79.89, H 7.12.

α-Methylene-γ-lactone 5a: To a solution of the lactone **47** (60 mg, 72 μmol) in THF (3 mL) in a sealed tube was added dry paraformaldehyde (66 mg, 2.2 mmol) and NaH (10.4 mg, 432 μmol). The colorless mixture was stirred for 15–120 min at 100 °C. A change in color of the mixture to yellowish brown within this time period indicates termination of the reaction, and the heating source was removed immediately. The resulting solution was cooled to room temperature, diluted with Et_2O (4 mL) and filtered rapidly through a pad of silica gel. After evaporation of the solvent, the crude mixture was dissolved in THF (6 mL) and placed in an ice bath. TBAF (95 μL, approx. 95 μmol, 1 M in THF) was added, and the solution was stirred at this temperature for 20 min. The reaction was quenched with aqueous satd. NH_4Cl (2 mL), and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined extracts were washed with brine (2 mL), dried with $MgSO_4$, filtered and the solvents evaporated. The residue was purified by flash chromatography (pentane/Et_2O, 1:9) to give **5a** (33.5 mg, 61% from **47**) as a cured white foam. R_f = 0.34 (pentane/Et_2O, 1:9). $[\alpha]_D^{24}$ = +34.7 (*c* = 1.00). ^{1}H NMR ($CDCl_3$): δ = 0.80–0.88 (m, 1 H), 0.92–1.02 (m, 1 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 1.04–1.12 (m, 1 H), 1.26–1.34 (m, 1 H), 2.21–2.29 (m, 1 H), 2.69–2.75 (m, 1 H), 2.71 (dd, *J* = 4.3, 16.1 Hz, 1 H), 2.84 (dd, *J* = 2.3, 16.1 Hz, 1 H), 2.85–2.90 (m, 1 H), 3.42 (d, *J* = 11.1 Hz, 1 H), 3.47–3.50 (m, 1 H), 3.82 (d, *J* = 11.1 Hz, 1 H), 4.11 (s, 1 H), 5.00–5.03 (m, 1 H), 5.55 (s, 1 H), 6.04 (d, *J* = 2.1 Hz, 1 H), 7.16–7.30 (m, 18 H), 7.39–7.42 (m, 12 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.37 (q), 27.84 (t), 30.57 (t), 31.31 (t), 33.33 (d), 44.68 (d), 62.79 (t), 63.16 (t), 68.33 (d), 75.64 (d), 86.13 (s), 86.82 (s), 123.98 (t), 126.78 (d, 3 C), 127.04 (d, 3 C), 127.65 (d, 6 C), 127.83 (d, 6 C), 128.61 (d, 6 C), 128.66 (d, 6 C), 132.01 (s), 136.48 (s), 140.11 (s), 144.00 (s, 3 C), 144.30 (s, 3 C), 169.66 (s) ppm. IR (neat): $\tilde{\nu}$ = 3510 cm^{-1} (broad), 3056, 2958, 2929, 2861, 1760, 1490, 1448, 1275, 1183, 1062, 1030, 1002, 899, 746, 704 cm^{-1}. MS (CID/75 V): *m/z* (%) = 789 (100), 805 (20). $C_{53}H_{50}O_5$ (766.96): calcd. C 83.00, H 6.57; found C 83.33, H 6.69.

Acrylate 48: To an ice-cold solution of the alcohol **5a** (30 mg, 39 μmol) in THF (0.5 mL) were added successively Et_3N (80 μL, 590 μmol), DMAP (2.3 mg, 18.8 μmol), and methacrylic anhydride (11.6 μL, 78.4 μmol). The mixture was stirred at 0 °C for 1 h and at room temperature for additional 2 h. MeOH (25 μL) was added, and stirring was maintained for 10 min. After evaporation of the volatile compounds, the crude mixture was purified by flash chromatography (pentane/Et_2O, 1:1) to give **48** (27.7 mg, 85%) as a cured white foam. R_f = 0.43 (pentane/Et_2O, 1:1). $[\alpha]_D^{26}$ = –30.9 (*c* = 0.91). ^{1}H NMR ($CDCl_3$): δ = 0.81 (d, *J* = 6.9 Hz, 3 H), 0.88–0.97 (m, 1 H), 1.02–1.14 (m, 2 H), 1.28–1.38 (m, 1 H), 1.96 (s, 3 H), 2.24–2.32 (m, 1 H), 2.71 (dd, *J* = 3.8, 16.2 Hz, 1 H), 2.71–2.75 (m, 1 H), 2.88 (dt, *J* = 8.8, 5.8 Hz, 1 H), 2.96 (dd, *J* = 1.9, 16.2 Hz, 1 H), 3.46 (d, *J* = 11.0 Hz, 1 H), 3.55 (dddd, *J* = 1.9, 2.2, 2.8, 7.6 Hz, 1 H), 3.79 (d, *J* = 11.0 Hz, 1 H), 4.99 (ddd, *J* = 1.9, 3.8, 7.6 Hz, 1 H), 5.29 (d, *J* = 1.9 Hz, 1 H), 5.62 (s, 1 H), 5.83 (d, *J* = 2.2 Hz, 1 H), 6.09 (s, 1 H), 6.15 (d, *J* = 2.8 Hz, 1 H), 7.18–7.24 (m, 6 H), 7.25–7.30 (m, 12 H), 7.36–7.39 (m, 6 H), 7.41–7.44 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.19 (q), 18.69 (q), 27.89 (t), 30.56 (t), 31.16 (t), 33.57 (d), 42.43 (d), 62.85 (t), 62.89 (t), 69.33 (d), 75.63 (d), 86.13 (s), 86.81 (s), 125.09 (t), 126.20 (t), 126.78 (d, 3 C), 127.04 (d, 3 C), 127.69 (d, 6 C), 127.84 (d, 6 C), 128.57 (d, 6 C), 128.66 (d, 6 C), 134.40 (s), 135.71 (s), 135.83 (s), 136.18 (s), 143.93 (s, 3 C), 144.30 (s, 3 C), 167.05 (s), 169.33 (s) ppm. IR (neat): $\tilde{\nu}$ = 3057, 2927, 2866, 1765, 1710, 1490, 1448, 1274, 1150, 1065, 1031, 1003, 978, 943, 899, 745, 704, 697 cm^{-1}. MS (CID/50 V): *m/z* (%) = 873 (61), 857 (100). $C_{57}H_{54}O_6$ (835.04): calcd. C 81.99, H 6.52; found C 81.78, H, 6.68.

(–)-Eriolanin (1): A solution of bis(trityl) ether **48** (24.5 mg, 29.3 μmol) in MeOH (1.5 mL) containing *p*TsOH×H_2O (1.1 mg, 5.9 μmol) was stirred at room temperature for 17 h and then diluted with EtOAc (3 mL). The solvent was evaporated without a heating source, and the residue was purified by flash chromatography (EtOAc) to give (–)-**1** (10.0 mg, 97%) as colorless crystals. R_f = 0.34 (EtOAc); m.p. 133–134 °C; ref.[1] 126.5–128 °C. $[\alpha]_D^{25}$ = –88.6 (*c* = 0.97); ref.[1] $[\alpha]_D^{25}$ = –93 ($CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.88 (d, *J* = 6.9 Hz, 3 H), 1.02–1.12 (m, 2 H), 1.21–1.34 (m, 2 H), 1.92 (s, 3 H), 2.62 (dd, *J* = 3.3, 16.1 Hz, 1 H), 2.28 (tq, *J* = 3.5, 6.9 Hz, 1 H), 2.94 (dd, *J* = 2.3, 16.1 Hz, 1 H), 3.43 (dt, *J* = 12.1, 6.2 Hz, 1 H), 3.52–3.56 (m, 1 H), 3.53 (dt, *J* = 12.1, 6.0 Hz, 1 H), 4.18 (d, *J* = 12.6 Hz, 1 H), 4.24 (d, *J* = 12.6 Hz, 1 H), 5.03 (ddd, *J* = 2.3, 3.3, 7.5 Hz, 1 H), 5.26 (d, *J* = 1.6 Hz, 1 H), 5.58 (t, *J* = 1.6 Hz, 1 H), 6.01 (d, *J* = 2.3 Hz, 1 H), 6.04 (s, 1 H), 6.39 (d, *J* = 2.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.19 (q), 18.83 (q), 29.78 (t), 30.88 (t), 30.91 (t), 33.06 (d), 43.12 (d), 61.43 (t), 62.63 (t), 69.49 (d), 75.53 (d), 126.03 (t), 126.35 (t), 135.45 (s), 136.02 (s), 136.07 (s), 136.32 (s), 167.05 (s), 170.45 (s) ppm. IR (neat): $\tilde{\nu}$ = 3360 cm^{-1} (broad), 2935, 2877, 2850, 1751, 1710, 1658, 1634, 1410, 1316, 1270, 1156, 1137, 1053, 1026, 1007, 976, 901, 818, 745, 665 cm^{-1}. MS (CID/10 V): *m/z* (%) = 391 (34), 368 (100), 351 (8).

Methacrylate 49: To a solution of angelic acid (20 mg, 200 μmol) in toluene (100 μL) were added 2,4,6-trichlorobenzoyl chloride (48.8 mg, 200 μmol) and Et_3N (27.8 μL, 200 μmol). After stirring for 3.5 h at room temperature, alcohol **5a** (14.0 mg, 18.3 μmol) was added, and the solution was stirred at 100 °C for 8 h. The mixture was cooled to room temperature, diluted with Et_2O (2 mL), and filtered. The solvent was removed, and the residue was purified by flash chromatography (pentane/Et_2O, 7:5) to afford **49** (9.3 mg, 60%) as a cured white foam. R_f = 0.41 (pentane/Et_2O, 7:5). $[\alpha]_D^{25}$ = –27.8 (*c* = 1.00). ^{1}H NMR ($CDCl_3$): δ = 0.85 (d, *J* = 6.7 Hz, 3 H), 0.88–0.97 (m, 1 H), 1.00–1.12 (m, 2 H), 1.30–1.38 (m, 1 H), 1.89 (dd, *J* = 1.2, 1.2 Hz, 3 H), 2.04 (dd, *J* = 1.4, 7.3 Hz, 3 H), 2.25–2.33 (m, 1 H), 2.72 (dt, *J* = 8.6, 7.0 Hz, 1 H), 2.77 (dd, *J* = 3.7, 16.4 Hz, 1 H), 2.86 (dt, *J* = 8.6, 5.8 Hz, 1 H), 2.90 (dd, *J* = 1.9, 16.4 Hz, 1 H), 3.36 (d, *J* = 10.7 Hz, 1 H), 3.55 (dddd, *J* = 1.7, 2.2, 2.7, 7.8 Hz, 1 H), 3.80 (d, *J* = 10.7 Hz, 1 H), 4.99 (ddd, *J* = 1.9, 3.7, 7.8 Hz, 1 H), 5.34 (d, *J* = 1.7 Hz, 1 H), 5.83 (d, *J* = 2.2 Hz, 1 H), 6.13 (d, *J* = 2.7 Hz, 1 H), 6.15 (dq, *J* = 1.2, 7.3 Hz, 1 H), 7.18–7.23 (m, 6 H), 7.24–7.29 (m, 12 H), 7.35–7.37 (m, 6 H) 7.38–7.42 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.82 (q), 18.85 (q), 20.61 (q), 27.87 (t), 30.89 (t), 31.15 (t), 33.67 (d), 42.53 (d), 62.84 (t), 63.01 (t), 68.55 (d), 74.08 (d), 86.14 (s), 86.73 (s), 125.11 (t), 126.78 (d, 3 C), 127.04 (d, 3 C), 127.55 (s), 127.67 (d, 6 C), 127.84 (d, 6 C), 128.55 (d, 6 C), 128.67 (d, 6 C), 134.22 (s), 135.84 (s), 136.01 (s), 139.15 (d), 143.95 (s, 3 C), 144.31 (s, 3 C), 167.56 (s), 169.39 (s) ppm. IR (neat): $\tilde{\nu}$ = 3062, 2927, 2859, 1764, 1707, 1490, 1448, 1273, 1226, 1147, 1133, 1031, 978, 945, 899, 745, 704, 696 cm^{-1}. MS (CID/10 V): *m/z* (%) = 866 (100). $C_{58}H_{56}O_6$ (849.06): calcd. C 82.05, H 6.65; found C 82.12, H 6.51.

(–)-Eriolangin (2): A solution of the bis(trityl) ether **49** (21.0 mg, 24.7 μmol) in MeOH (2 mL) containing *p*TsOH×H_2O (1.5 mg,

8.3 μmol) was stirred at room temperature for 24 h and then diluted with EtOAc (3 mL). The mixture was filtered through a pad of silica gel, evaporated and purified by chromatography (EtOAc) to give (–)-**2** (7.6 mg, 85%) as colorless crystals. R_f = 0.37 (EtOAc); m.p. 95–97 °C; ref.[1] 94–96 °C. $[\alpha]_D^{24}$ = –87.5 (*c* = 1.05); ref.[1] $[\alpha]_D^{25}$ = –91 ($CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.91 (d, *J* = 6.9 Hz, 3 H), 1.01–1.16 (m, 2 H), 1.23–1.36 (m, 2 H), 1.84 (dd, *J* = 1.5, 1.5 Hz, 3 H), 1.97 (dd, *J* = 1.5, 7.2 Hz, 3 H), 2.64 (dd, *J* = 3.2, 16.1 Hz, 1 H), 2.74–2.78 (m, 1 H), 2.93 (dd, *J* = 2.5, 16.1 Hz, 1 H), 3.43 (dt, *J* = 12.1, 6.3 Hz, 1 H), 3.53 (dt, *J* = 12.1, 6.1 Hz, 1 H), 3.55 (dddd, *J* = 1.7, 2.2, 2.5, 7.5 Hz, 1 H), 4.16 (d, *J* = 12.5 Hz, 1 H), 4.24 (d, *J* = 12.5 Hz, 1 H), 5.05 (ddd, *J* = 2.5, 3.2, 7.5 Hz, 1 H), 5.31 (d, *J* = 1.7 Hz, 1 H), 6.05 (d, *J* = 2.2 Hz, 1 H), 6.11 (qq, *J* = 1.5, 7.2 Hz, 1 H), 6.39 (d, *J* = 2.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.76 (q), 18.95 (q), 20.50 (q), 29.91 (t), 30.92 (t, 2 C), 33.16 (d), 43.27 (d), 61.51 (t), 62.68 (t), 68.69 (d), 75.56 (d), 126.00 (t), 127.39 (s), 135.71 (s), 136.09 (s), 136.15 (s), 139.23 (d), 167.49 (s), 170.44 (s) ppm. IR (neat): $\tilde{\nu}$ = 3250 cm^{-1} (broad), 2956, 2913, 2870, 2849, 1752, 1696, 1461, 1409, 1388, 1269, 1251, 1228, 1134, 1065, 1051, 1026, 1014, 994, 976, 933, 902, 820, 741 cm^{-1}. MS (CID/10 V): *m*/*z* (%) = 382 (100).

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