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Towards the Synthesis of the 4,19-Diol Derivative of (–)-Mycothiazole: Synthesis of a Potential Key Intermediate

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The synthesis of a potential key intermediate for the synthesis of the 4,19-diol derivative of (–)-mycothiazole using convergent strategies is described in this paper. Several approaches have been tested, including cross metathesis and a Julia–Kocienski olefination. Finally, the formation of the 1,1-dialkyl-1,2-ethanediol motif through C4–C5 bond construction was realized by nucleophilic addition of a vinyl iodide derivative to a keto ester after halogen/lithium exchange followed by reduction of the resulting hydroxy ester.

Introduction

(–)-Mycothiazole (**1**; Figure 1) was first isolated from the marine sponge *Cacospongia mycofijiensis*.[1] It exhibits toxicity towards lung cancer cells[2] and very recently was proven to be a valuable novel prototype of mitochondrial complex I inhibitor.[3] Its unique structure as well as its potential pharmacological activities make it a good target for laboratories interested in the total synthesis of biologically active natural compounds. There are only two total syntheses of mycothiazole (**1**)[2,4] and three partial syntheses published so far[5] but these lead to the wrong stereochemistry at the C14–C15 double bond, which was first claimed to be *E* and finally revised to *Z*.[6] Compound **2**, which possesses the same skeleton as **1** but with a 4,19-diol group, was isolated along with **1** (Figure 1).[6] Its structure was elucidated by comparison of the NMR spectra of **1** and **2**, but the configuration at C4 remains unknown. To the best of our knowledge, no synthesis of compound **2** has been reported so far and considering the potential interest in (–)-mycothiazole (**1**) itself, access to its derivatives presents a valuable challenge for organic chemists. The main difference between **1** and **2** is the presence of a conjugated homoallylic *Z* dienol in mycothiazole (**1**) and an allylic 1,1-dialkyl-1,2-ethanediol group in **2** (Figure 1).

The two previously described strategies for the synthesis of mycothiazole (**1**) used a standard Stille coupling reaction to create the C6–C19 diene, as reported by Shioiri and coworkers,[4a] or a chain extension of a homoallylic alcohol proceeding through an unsaturated sultone intermediate

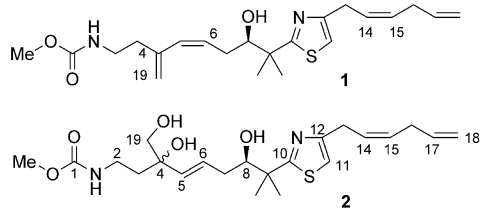

Figure 1. (–)-Mycothiazole (**1**) and mycothiazole-4,19-diol (**2**).

generated by ring-closing metathesis, as reported by Cossy and co-workers.[4b] Neither of these approaches turned out to be valuable for the synthesis of 4,19-diol **2**. A nonexhaustive survey of the literature showed that the 1,1-dialkyl-1,2-ethanediol motif is present in relatively few natural products, the total syntheses of which, in general, have not yet been described.[7] Nevertheless, some methods have been published in the literature that give access to such a group, for example, by addition of a phenylboronic acid to an α-keto ester catalyzed by rhodium,[8] by addition of an alcohol to a vinyl epoxide in the presence of a catalytic amount of trialkylborane and palladium,[9] or by rearrangement of 2-(1-hydroxyalkyl)-1-cyclopropanols using organozinc catalysis.[10] The classical dihydroxylation of double bonds[11] or reduction of hydroxy esters[12] can also be used. Other 1,1-dialkyl-1,2-ethanediol intermediates have also been reported in the total syntheses of natural products, but they are obtained by tedious, not straightforward methods.[13] Herein we report our efforts to synthesize a key intermediate of mycothiazole-4,19-diol (**2**) and more especially to build the allylic 1,1-dialkyl-1,2-ethanediol moiety.

Results and Discussion

As the synthesis of the 1,4-diene lateral side-chain[14] and the introduction of the carbamate moiety[4] have already

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been well described, we focused our efforts on the synthesis of the allylic 1,1-dialkyl-1,2-ethanediol group, the two aforementioned parts being introduced at the end of the synthesis. In our synthetic strategy outlined in Figure 2, we envisaged a convergent, late-stage assembly of the two advanced fragments by a cross-metathesis reaction to build the C5–C6 double bond, which seemed reasonable considering the *E* configuration of this olefin. The first fragment **3** could be obtained by dihydroxylation of the benzodioxepine **4** followed by the substitution of the mesyl group by potassium phthalimidate, **4** being easily obtained from the commercially available dimethyl itaconate (**5**). The advantage of compound **4** is its possible selective cleavage by hydrogenolysis and its ability to perform π-stacking with aromatic chiral auxiliaries in the case of asymmetric dihydroxylation, as reported by Oi and Sharpless.[15] The construction of the second fragment **6** could be achieved by condensation of 2,2-dimethylpropanediol (**7**) and cysteine (**8**) followed by aromatization of the resulting thiazolidine and a few straightforward functional group manipulations.

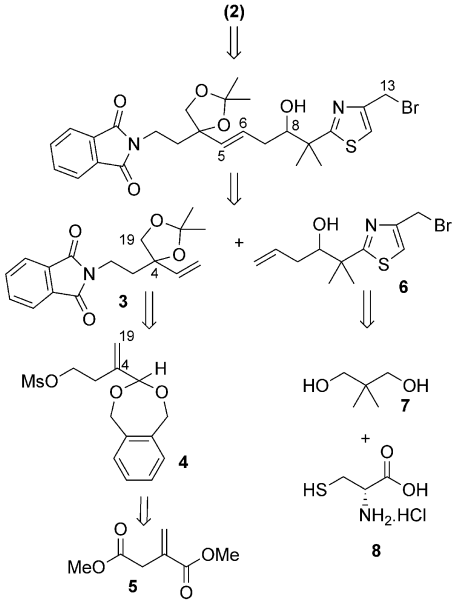
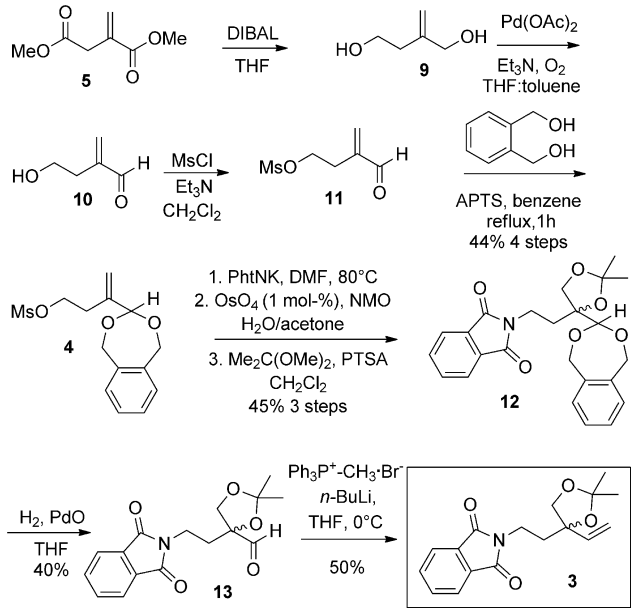


Figure 2. Retrosynthetic analysis of mycothiazole-4,19-diol (**2**).

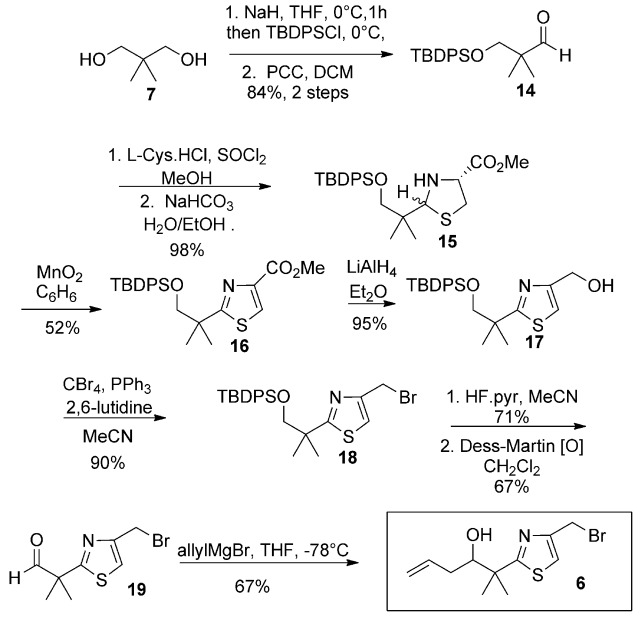
As shown in Scheme 1, our initial approach to building subunit **3** started from commercially available dimethyl itaconate (**5**). Reduction of **5** with DIBAL in THF led to diol **9**, which was selectively oxidized to **10** according to our recently reported method.[16] Mesylation of **10** followed by protection of the aldehyde group as the 1,2-benzenedimethanol acetal[17] delivered **4** in 44% yield over the four steps. Substitution of the mesyl group by potassium phthalimidate followed by dihydroxylation according to the classical conditions described by Van Rheenen et al.[18] and subsequent protection of the resulting diol as the diacetal gave product **12** with an overall yield of 45% for the three steps. Literature precedent predicted selective removal of the benzodioxepine moiety using catalytic PdO in THF at room temperature under 1 atm of H_2,[15,19] however, in our case, 20 atm of hydrogen and a temperature of 100 °C were necessary to obtain **13**. Poisoning of the catalyst by the nitrogen atom could be an explanation for this low reactivity even though good results were published by others with nitrogen containing substrates.[19] Finally, a classical Wittig reaction delivered the first fragment **3** (50%). The entire sequence was realized in nine steps from commercially available and inexpensive **5** in 4% overall yield.



Scheme 1. Synthesis of intermediate **3** from dimethyl itaconate.

As for the thiazole ring, the different approaches to mycothiazole (**1**) reported in the literature used either 2,4-dibromothiazole,[4b] commercially available but very expensive, or a cyclodehydration reaction based on the Hantzsch synthesis, for which numerous steps are necessary as well as the use of the strongly odorous Lawesson reagent.[5] Therefore we decided to synthesize the thiazole ring by oxidation of the corresponding thiazolidine as proposed by Shioiri and co-workers (Scheme 2).[4a]

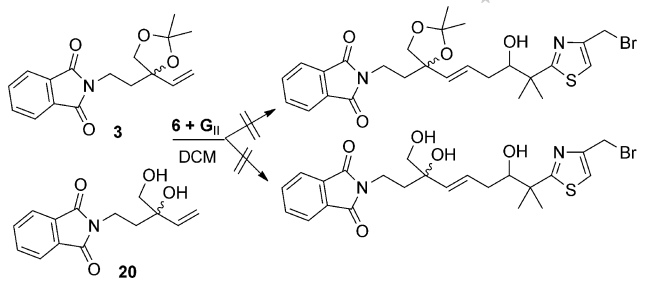
We started the synthesis of subunit **6** by monoprotection of the commercial diol **7** according to the method described by Mc Dougal et al.[20] followed by PCC oxidation (two steps, 84% isolated yield). Condensation of the resulting aldehyde **14**[4a] with L-cysteine methyl ester gave compound **15**[4a] as a diastereomeric mixture (98%). Oxidation of thiazolidines to thiazoles is most conveniently performed with chemical manganese dioxide (CMD), as reported by Shioiri and co-workers.[21] Owing to the difficulties involved in accessing this reagent, we tested several other methods by using NBS and alkyl peroxides,[22] NiO_2,[23] and standard manganese dioxide. After some experimentation, we found that the procedure performed in benzene using MnO_2 synthesized in our laboratory following the method of Fatiadi[24] was the most promising. Thus, thiazole **16**[4a] was obtained in 52% yield by using 20 equiv. of MnO_2, which compares with the 62% yield obtained with 60 equiv. of



Scheme 2. Synthesis of intermediate **6** from 2,2-dimethylpropanediol (**7**).

CMD by Shioiri and co-workers.[4a] Reduction of ester **16** with $LiAlH_4$ furnished alcohol **17**,[4a] which upon exposure to PPh_3 and CBr_4 in the presence of 2,6-lutidine provided the corresponding bromide derivative **18**.[4a] Deprotection of the TBDPS ether using the HF·pyridine complex (71% yield) followed by oxidation to the corresponding aldehyde with Dess–Martin periodinane (67%) afforded **19**, whereas deprotection with TBAF and oxidation with PCC led to degradation products. Finally, alkylation with allylmagnesium bromide provided **6** in an overall yield of 12% over the ten steps.

With these two fragments in hand we tried to apply our initial strategy: The connection of fragments **3** and **6** by cross metathesis (CM; Figure 2). According to Grubbs' model,[25] olefins can be divided into four types depending upon their reactivity. Thus, compound **3**, bearing a quaternary center next to the double bond can be considered as a type III olefin, not being very reactive and not being able to homodimerize, whereas compound **6** can be considered a type I olefin, capable of fast homodimerization and thus much more reactive. Such types of double bonds have already been subjected with success to CM using Grubbs' second-generation catalyst.[26] Nevertheless, whatever the conditions used (% catalyst, solvent, temperature, microwaves,[27] etc.), every attempt to obtain the coupling product resulted in recovery of the starting material. The Grubbs–Hoveyda catalyst was also tried without success. The presence of the bulky dioxolane group might explain this lack of reactivity, preventing [2+2] cycloaddition with the carbenic species and thus inhibiting the reaction. Therefore we tried CM with diol **20** obtained by acidic deprotection of **3** (98% yield). However, only dimerization products of compound **6** and starting materials (**3** or **20**) were obtained (Scheme 3).



Scheme 3. CM between olefin **6** and olefins **3** and **20**.

It is clear to us that the main problem was the steric bulkiness at the C4 center. We therefore explored two alternative syntheses using CM as the key reaction followed by introduction of the diol group. We first planned to perform CM between thiazole **6** and compound **22** bearing a terminal double bond, an epoxide group as the diol precursor, and a primary alcohol protected by a TBDPS group, which could later be transformed into a methyl carbamate as described by Shioiri and co-workers[4a] (Figure 3).

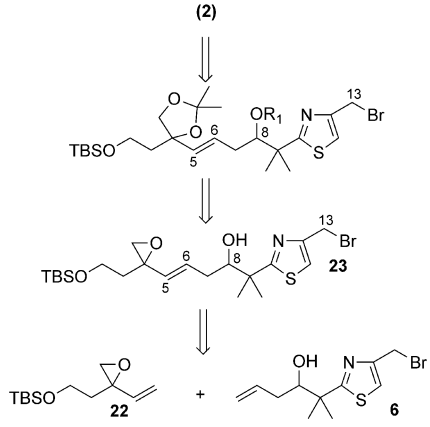
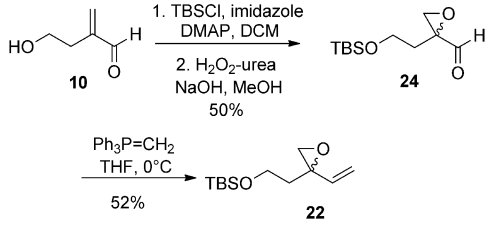


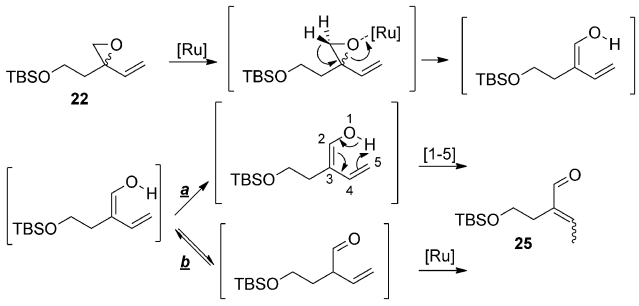
Figure 3. Alternative retrosynthetic approach to **2**.

Protection of **10** as the corresponding silyl ether followed by 1,4-addition of hydrogen peroxide ions formed in situ from a H_2O_2–urea complex gave epoxide **24** (50% yield, two steps). A classical Wittig reaction ended this sequence with the synthesis of **22** and a modest overall yield of 14% in five steps starting from dimethyl itaconate **5** (Scheme 4).



Scheme 4. Access to epoxide **22**.

G_I and G_{II} catalysts were both tested in CH_2Cl_2 at reflux for the CM reaction between intermediates **6** and **22** without the formation of the desired product. Thiazole **6** was recovered but epoxide **22** was transformed into aldehyde **25**. We proposed the mechanism depicted in Scheme 5 to explain this reaction.



Scheme 5. Rearrangement of epoxide **22** catalyzed by the G_{II} catalyst.

Ru might be considered as a Lewis acid, which, after chelation with the oxygen of the epoxide, could open it by a [1,2] hydride shift leading to a nonisolated conjugated dienol. Two routes could be considered to lead to the aldehyde: Route **a** based on a [1,5] sigmatropic rearrangement promoted by the heating of the reaction mixture or route **b** catalyzed again by Ru, which is known to allow olefin isomerization to the α,β-unsaturated aldehyde.[28] Whatever the mechanism, the epoxide rearrangement proceeded faster than CM. Therefore, we decided to follow the synthetic strategy outlined in Figure 4.

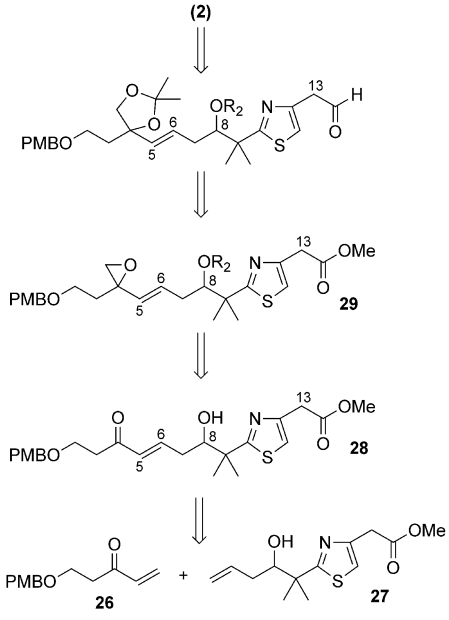
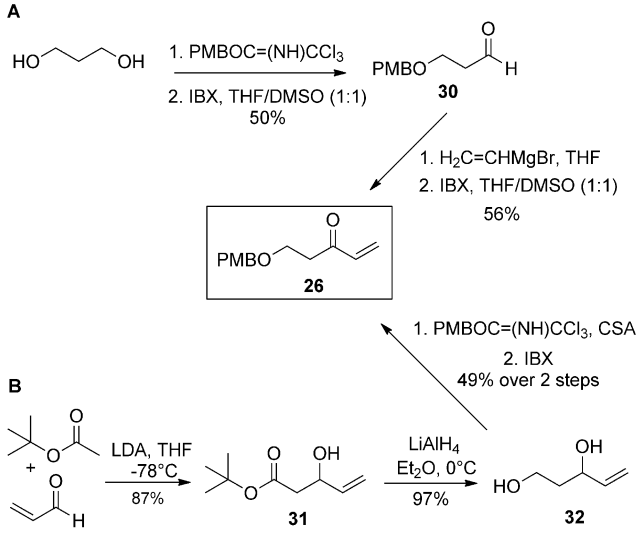


Figure 4. Access to **2** by enone metathesis.

As with the previous strategy, the diol group would be formed after the coupling between the thiazole part and the diol precursor by CM. Metathesis using olefin **26** (type II according to the Grubbs model) and olefin **27** (type I) could be performed stereoselectively to provide the *E* isomer of enone **28**, which could lead to epoxide **29** by a Corey–Chaykovsky[29] reaction. Two alternative syntheses of intermediate **26** were thus explored (Scheme 6).

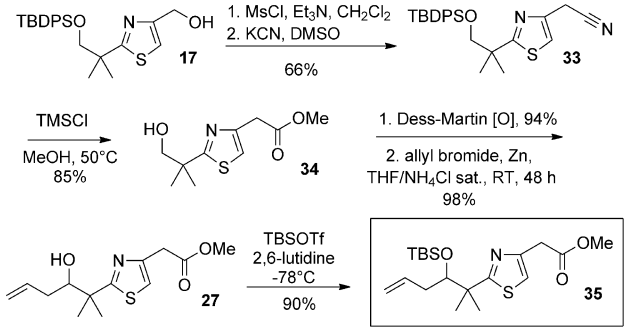


Scheme 6. Two alternative syntheses of enone **26**.

Starting from 1,3-propanediol, we proceeded with its monoprotection with the 4-methoxybenzyl (PMB) group and subsequent oxidation to aldehyde **30** by IBX (*o*-iodoxybenzoic acid; 50%, two steps). Treatment of the protected aldehyde thus obtained with vinylmagnesium bromide followed by another IBX oxidation gave vinyl ketone **26** in 29% yield over the four steps. Because of this low yield, we tested another strategy based on the condensation of *tert*-butyl acetate with acrolein to provide β-hydroxy ester **31**, which was reduced with $LiAlH_4$ to diol **32** and selectively monoprotected and oxidized to furnish enone **26** in 41% overall yield.

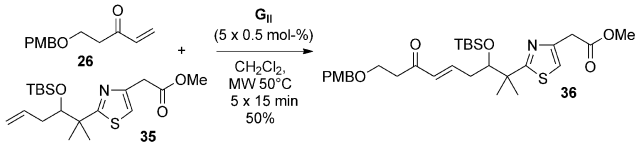
Considering the strategy developed by Rodriguez and coworkers[14] for the introduction of the 2,5-hexadienic lateral chain by a Wittig reaction, a one-carbon homologation of the ester side-chain in compound **16** was necessary. Direct homologation following the method of Kowalski et al.[30] provided degradation products. We chose to transform alcohol **17** into a leaving group and to substitute it with potassium cyanide (Scheme 7). Nitriles are known to be metathesis catalyst poisons, therefore it was necessary to elaborate this group before testing the CM. Exposure of compound **33** to chlorotrimethylsilane in MeOH[31] provided the ester function with concomitant cleavage of the silyl ether due to the acidic conditions and afforded compound **34** in a good yield of 85% over two steps. Oxidation with Dess–Martin periodinane followed by a chemoselective allylation using Barbier conditions gave the homoallylic alcohol **27**, which upon exposure to TBSOTf in the presence of 2,6-lutidine provided the corresponding TBS ether in 81% yield over the last three steps.

After some experimentation, we found that the cross-metathesis reaction between compounds **26** and **35** led to the desired coupled product **36** in 50% isolated yield under



Scheme 7. Access to thiazole **35**.

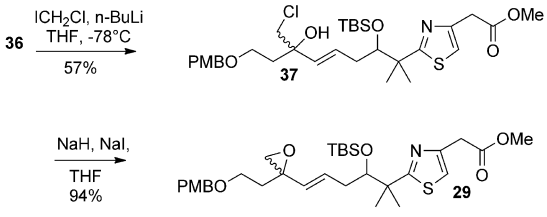
optimized conditions (G_{II} catalyst and microwave irradiation,[27] which enables one to lower both the catalyst quantity and the reaction time as compared with classical thermal conditions). This moderate yield was due to the fact that it is not possible to achieve more than 60% conversion. Nevertheless, always unreacted starting material was recovered (Scheme 8).



Scheme 8. Successful coupling of **26** and **35** by CM.

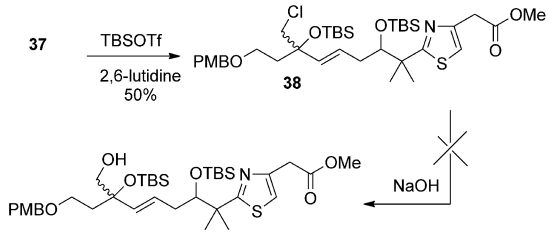
Note that CM with the unprotected alcohol **27** gave the coupled product but that further protection of the hydroxy group as a silyl ether was not possible in our hands.

In our synthetic strategy outlined in Figure 4, we envisaged building the diol part of the molecule by opening the epoxide **29** obtained from enone **36**. The Corey–Chaykovsky[29] reaction first considered gave only degradation products. We thus decided to construct the epoxide in two steps. Addition of chloroiodomethane and *n*BuLi to the enone **36** afforded chlorohydrin **37**, which upon exposure to basic conditions led to the desired epoxide **29** (Scheme 9). This molecule could not be purified over silica and caution had to be taken over its storage.



Scheme 9. Synthesis of epoxide **29**.

With epoxide **29** now available, several conditions could be tested for its opening. Despite extensive experimentation, all of our attempts remained unsuccessful when using either basic, acidic, or neutral conditions,[32,33] leading only to degradation products. To circumvent this problem, we tried to directly obtain the dioxolane adduct. $Cu(OTf)_2$ in acetone is known to selectively open vinylic epoxides,[34] but in our case only the starting material **29** was recovered. The use of $BF_3{\cdot}Et_2O$ in acetone gave a mixture of degradation products.[35] A final attempt was performed with chlorohydrin **37**: Exposure of this compound to TBSOTf in the presence of 2,6-lutidine provided the corresponding TBS ether **38** in 50% yield, which was then treated with sodium hydroxide without success (Scheme 10).[36]



Scheme 10. Silylation of compound **37**.

Considering the difficulties encountered during our metathesis approach, we decided to test olefination reactions to build the C5–C6 double bond. We chose two approaches from the various methods available, the Horner–Wadsworth–Emmons reaction and the modified Julia olefination, which presented the advantage of having a common intermediate, aldehyde **42**, the methyl carbamate function and the lateral 2,5-hexadienic side-chain being introduced at the end of the synthesis (Figure 5).

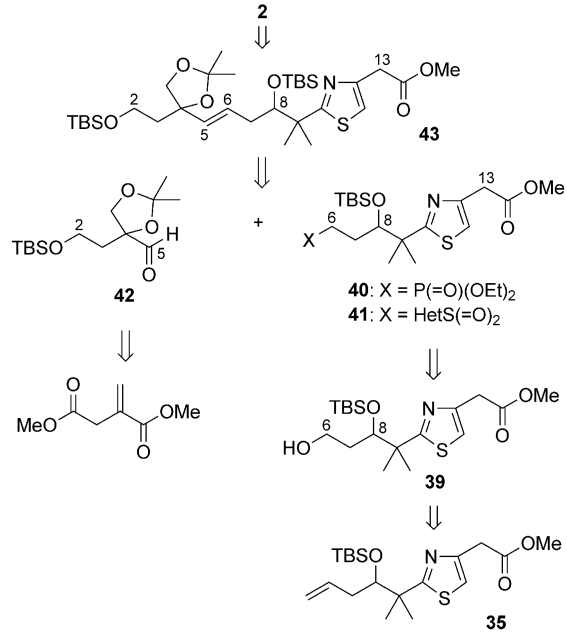
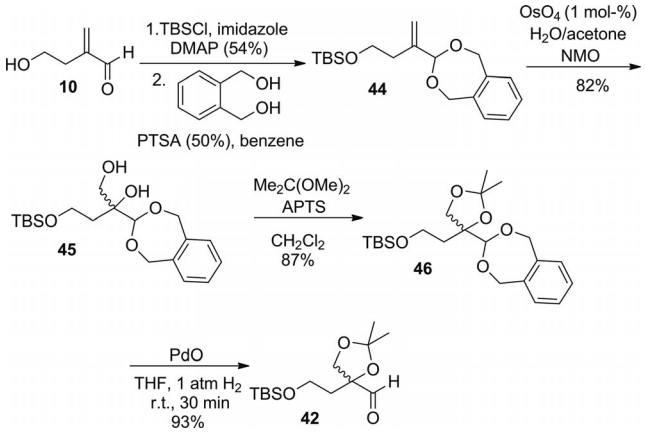


Figure 5. Double-bond construction through olefination reactions.

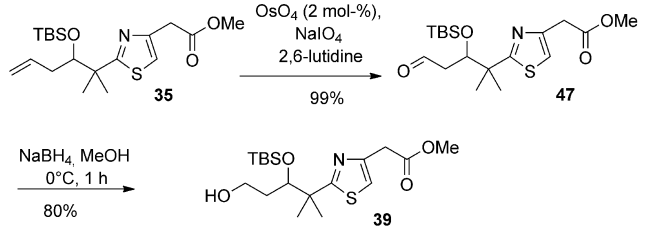
Aldehyde **42** was synthesized from dimethyl itaconate via aldehyde **10** (Scheme 11). Protection of the alcohol group as a silyl ether and protection of the aldehyde group under mild conditions gave benzodioxepine **44** in moderate yield (27%, two steps). Dihydroxylation led to diol **45**, which was subsequently protected as diacetal **46**. Finally, hydro-

genolysis using PdO under an atmospheric pressure of hydrogen afforded aldehyde **42** in 16% overall yield (seven steps).



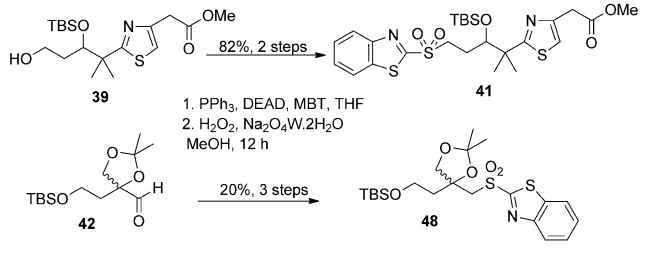
Scheme 11. Synthesis of aldehyde **42**.

Phosphonate **40** could be prepared starting from thiazole **35**, the synthesis of which has been developed previously for the cross-metathesis strategy. Oxidative cleavage of the terminal double bond followed by chemoselective reduction of the aldehyde group by $NaBH_4$ furnished alcohol **39** in 80% isolated yield over the two steps (Scheme 12).



Scheme 12. Synthesis of alcohol **39**.

We then planned to introduce the phosphonate group by an Arbuzov reaction,[37] which necessitated the presence of a halogen in place of the alcohol. Unfortunately, every attempt to obtain this intermediate was unsuccessful. Hence the Arbuzov reaction could not be tested. Therefore we turned our attention to the Julia–Kocienski-type reagent **41**, which was obtained in two steps and 82% isolated yield from alcohol **39** (Scheme 13).



Scheme 13. Synthesis of the Julia–Kocienski intermediates.

Two sets of experimental conditions were tested for this coupling reaction: The Barbier protocol or premetalation depending on the steric bulk of the sulfone.[38] In our case, none of these conditions was efficient and only starting materials were recovered. The steric hindrance of aldehyde **42** was proposed to explain this result as the modified Julia reaction was successfully performed in our group with sulfone **41** and *p*-nitrobenzaldehyde. We thus decided to put the aldehyde group on the thiazole fragment (compound **47**, Scheme 12) and the sulfone on the protected diol (compound **48**, Scheme 13). This last product turned out to be particularly unstable after deprotonation with LiHMDS as only unidentified degradation products were recovered at the end of the reaction.

Considering the difficulties encountered in achieving the C5–C6 connection, we turned our attention to an alternative convergent strategy and the subsequent formation of the diol by the formation of the C4–C5 bond. By analogy with the preceding retrosyntheses, the methyl carbamate function and the lateral 2,5-hexadienic side-chain would be introduced at the end of the synthesis. The key step in this approach would be a nucleophilic addition of the vinyl iodide derivative **49** to the α-hydroxy ketone **51** (Figure 6).

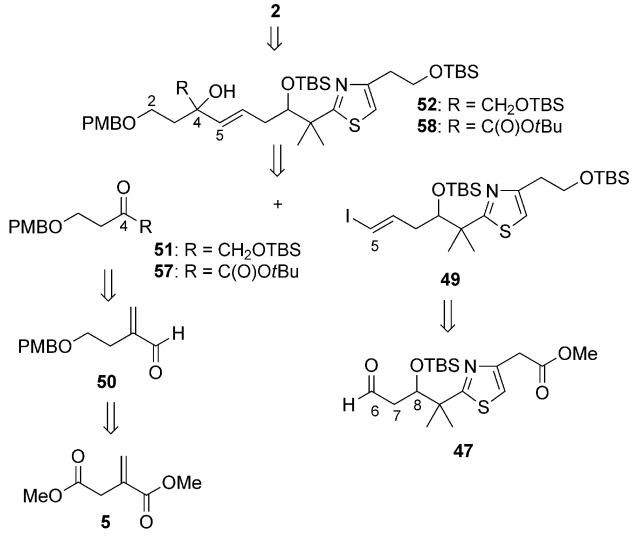
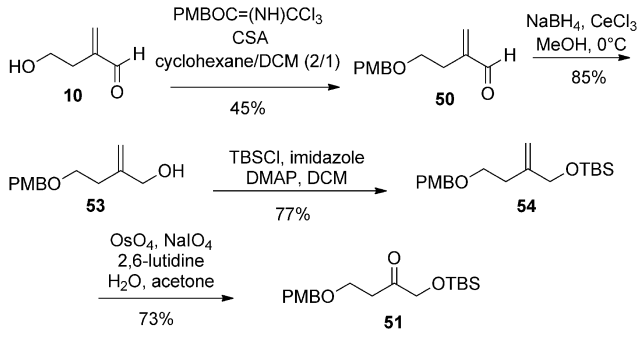


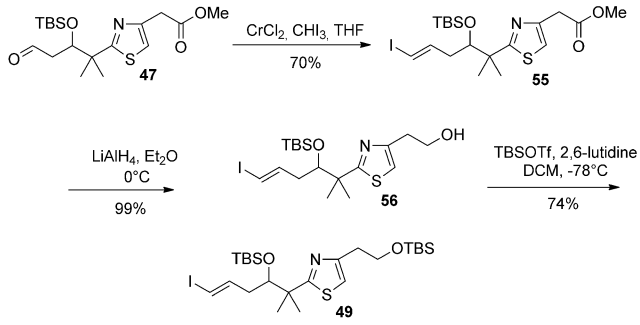
Figure 6. Alternative strategies through C4–C5 bond formation.

Thus, hydroxy aldehyde **10**, upon exposure to the corresponding trichloroacetamidate, provided the PMB ether **50**, which after Luche reduction and treatment with TBSCl furnished compound **54** (65%, two steps). The carbonyl function was then generated by oxidative cleavage giving ketone **51** in four steps and a 21% overall yield (Scheme 14).

Concerning the synthesis of the second key fragment, the vinyl iodide derivative **49** was synthesized in 15 steps and a 14.8% overall yield from 2,2-dimethylpropanediol via aldehyde **47** by a Takai reaction (product **55**, 70% isolated yield),[39] quantitative reduction of the ester group with $LiAlH_4$ (alcohol **56**), and subsequent primary alcohol protection to the TBS ether (Scheme 15).



Scheme 14. Synthesis of ketone **51**.

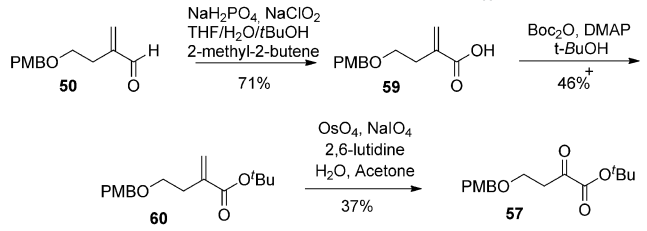


Scheme 15. Vinyl iodide subunit synthesis.

With these fragments in hand, we investigated the coupling step. We first tested Grignard conditions as described by Kogen and co-workers[40] for the synthesis of (+)-benzastatine or by Eustache and co-workers[13b] for the fumagilline series, but only the starting materials were recovered, which indicates that the magnesium insertion did not take place.

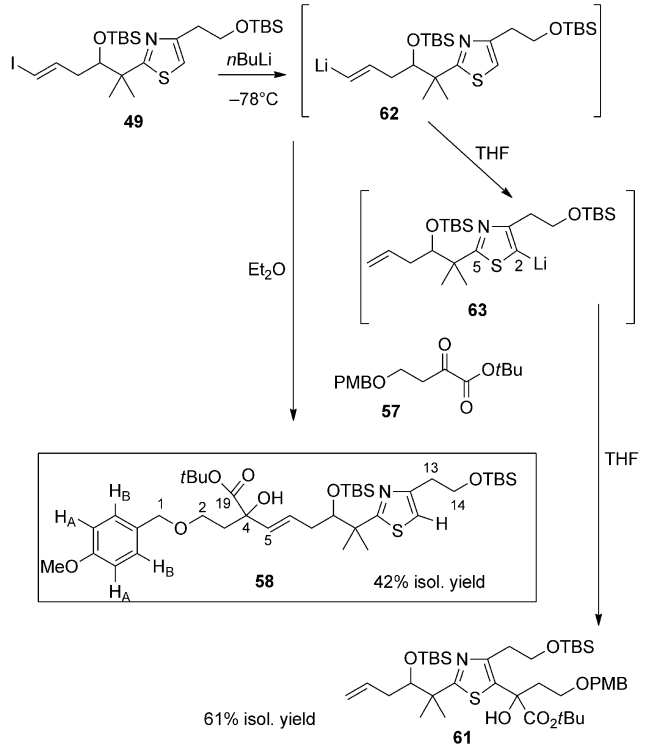
The method developed by Knochel and co-workers, using isopropylmagnesium bromide[41a] or an *i*PrMgCl·LiCl complex[41b] to carry out the iodide/magnesium exchange, was not successful either, even though the exchange was proven as the olefin was observed after loss of iodide. An alternative approach based on an iodide/lithium exchange followed by a transmetalation with $MgBr_2$ gave the same result.[42] Use of *t*BuLi only gave degradation products as well. Finally, the Nozaki–Hiyama–Kishi reaction[43] gave only ketone **51** and the olefin analogue of **49**. All these results show that the exchange takes place but that the reactivity of the ketone has to be increased. Addition of a Lewis acid was first envisaged but abandoned due to the fragility of the different substrates. Introduction of an electron-withdrawing group at the α position of the ketone could be a solution, leading to an α-hydroxy ester, which could be reduced to the desired diol (Figure 6).

Therefore we turned our attention to the synthesis of keto ester **57** (Scheme 16). Oxidation of aldehyde **50** according to the Pinnick reaction[44] gave acid **59**, which – after esterification and dihydroxilation/oxidation – gave keto ester **57** with a 12% overall yield.



Scheme 16. Synthesis of keto ester **57**.

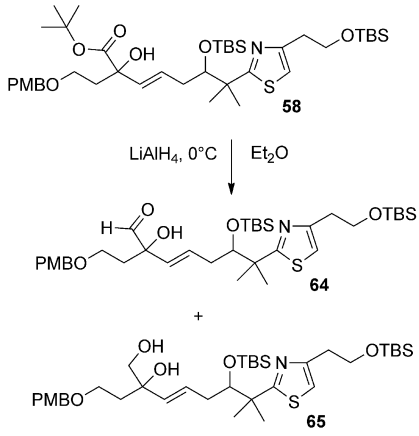
Of all the conditions tested on the preceding α-hydroxy ketone, we chose the simple iodide/lithium exchange in the presence of *n*BuLi at –78 °C (Scheme 17). By using THF as solvent, compound **61** was isolated due to the acidity of the proton at the 2-position in the thiazole ring and the concomitant formation of the supposed intermediate **63**. In Et_2O, a less coordinating solvent than THF, **62** displayed less basic character and the addition could be performed with the keto ester **57** more rapidly than deprotonation at C2, leading to the desired coupling product **58** in a 42% isolated yield and recovery of excess of keto ester **57**. This difference in selectivity in THF and Et_2O has already been described by Cossy and co-workers during the formylation of bromothiazole derivatives.[4c] Analysis of the ^1H NMR spectrum (see the Supporting Information) showed two different signals in the aromatic area: One doublet at δ = 7.24 ppm, which integrated for two protons, and another doublet at δ = 6.84 ppm, which integrated for three protons. NOESY experiments allowed the different signals to be assigned: Thus, the doublet at δ = 7.24 ppm was assigned to



Scheme 17. Access to the desired coupling product **58**.

the two aromatic protons H_A due to the correlation with the singlet signal of the methoxy group at δ = 3.81 ppm. Part of the signal at δ = 6.84 ppm was attributed to the two H_B aromatic protons, which correlate with the CH_2 group (C1) at δ = 4.37 ppm, and the other proton was unambiguously assigned to the aromatic proton on the thiazole ring. This proton signal correlates with that of the C13 protons at 2.93–2.97 ppm. These NMR experiments confirmed the successful coupling that led to compound **58**.

The hydroxy ester **58** was reduced with $LiAlH_4$ and a mixture of diol **65** and aldehyde **64** was thus obtained (Scheme 18). These two products were easily separated by flash chromatography. Aldehyde **64** was reduced to diol **65** by repeating the same procedure (35% isolated yield in the two steps, unoptimized).



Scheme 18. Synthesis of the diol **65**.

With compound **65** in hand, we now have at our disposal a valuable key intermediate for the 4,19-diol skeleton. The two lateral side-chains can be introduced according to the previously described methods: The 1,4-diene part by a Wittig reaction, as proposed by Rodriguez and co-workers,[14] and the carbamate moiety by introduction of a tosylate function in place of the PMB group, according to the synthesis of Shioiri and co-workers.[2] This leaving group could then be substituted by NaN_3, the azide obtained reduced with triphenylphosphane, and upon treatment with methyl chlorocarbonate we could have access to the desired carbamate. To perform such reactions, there has to be a careful choice of protecting groups that can be selectively cleaved. Protection of the diol function as a ketal also has to be considered.

Conclusions

We have reported herein the first approach to the skeleton of the 4,19-diol derivative of mycothiazole. To the best of our knowledge, no synthesis, neither total nor partial, has been reported so far. One has to bear in mind that the structure of the 4,19-diol derivative of the mycothiazole has not yet been fully established. The asymmetric version of this synthesis would have to be considered if we were to prove the absolute configuration of the two chiral centers. One of our intermediates, alcohol **27**, could be obtained in its chiral form by an asymmetric allylation under Barbier conditions with the addition of chiral auxiliaries such as amino alcohols,[45] camphor derivatives,[46] or cinchonine.[47] Oxidation of the alcohol function and subsequent Corey–Bakshi–Shibata[48] reduction may be another possibility for controlling the center at C8. As for the chiral center at C4, there are several possibilities. The coupling could be performed diastereoselectively under the control of the C8 center. If not, the two diastereoisomers could be separated at the hydroxy ester level or at the diol level. Derivatization of the diol with a chiral auxiliary could also lead to separable isomers. Replacement in compound **57** of the *tert*-butyl group by a bulky chiral moiety like 8-phenylmenthol could also be considered. Further studies are in progress in our laboratory to test these different possibilities and to propose a complete synthesis and a definitive reliable assignment of the different stereogenic centers of the 4,19-diol derivative of mycothiazole.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded either in $CDCl_3$ or in C_6D_6 solvent with a Bruker AM 300 MHz, 500 MHz, or 75 MHz spectrometer at ambient temperature, which provided all the necessary data for the full assignment of each compound. Chemical shifts δ are given in ppm, coupling constants J are in Hz. The chemical shifts are reported in ppm upfield from TMS as an internal standard and signal patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet; m, multiplet, br., broad singlet. High-resolution mass spectrometry (HRMS) analyses were conducted by using a ThermoFinigan-MAT 95 XL instrument. Optical rotations were measured with a digital polarimeter using a 5 mL cell with a 1 dm pathlength. IR spectra were measured with a Perkin–Elmer Spectrum One FT-IR spectrometer. TLC analyses were performed on plates (layer thickness 0.25 mm) and were visualized with UV light, phosphomolybdic acid, or *p*-anisaldehyde solution. Column chromatography was performed on silica gel (40–63 μm) using technical-grade ethyl acetate (EtOAc) and petroleum ether (EP). When appropriate, solvents and reagents were dried by distillation over an appropriate drying agent prior to use. Diethyl ether and tetrahydrofuran were distilled from Na/benzophenone and used fresh. Dichloromethane was distilled from CaH_2. All the reactions were performed under nitrogen in flame- or oven-dried glassware with magnetic stirring.

2-[2-(2,2-Dimethyl-4-vinyl-1,3-dioxolan-4-yl)ethyl]isoindoline-1,3-dione (3): *n*BuLi (1 M in hexane, 2.49 mL, 2.49 mmol) was added to a solution of methyltriphenylphosphonium bromide (889 mg, 2.48 mmol) in THF (11 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C and then for 45 min at room temperature then cooled again to 0 °C before a solution of compound **13** (520 mg, 1.66 mmol) in THF (5 mL) was added dropwise. The resulting solution was stirred at room temperature for an additional 2 h and then quenched by an aqueous saturated NH_4Cl solution (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic phases washed with water (10 mL) and brine (10 mL), and then dried ($MgSO_4$). After evaporation of the solvent, compound **3** was obtained by flash chromatography (hexanes/

EtOAc, 85:15) in 50% isolated yield (323 mg, 0.77 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.46 (s, 3 H), 1.99 (ddd, J = 23.9, 10.3, 5.4 Hz, 2 H), 3.62–3.89 (m, 2 H), 3.85 (d, J = 5.5 Hz, 2 H), 5.19 (dd, J = 10.9, 1.3 Hz, 1 H), 5.40 (dd, J = 17.3, 1.3 Hz, 1 H), 5.88 (dd, J = 17.3, 10.9 Hz, 1 H), 7.67–7.86 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3, 27.3, 33.9, 36.6, 74.0, 82.3, 110.4, 115.3, 123.3, 132.4, 134.0, 139.4, 168.4 ppm. In agreement with reported data.[49]

3-(1,5-Dihydrobenzo[*e*][1,3]dioxepin-3-yl)but-3-en-1-yl Methanesulfonate (4): A solution of **11** (1.72 g, 9.66 mmol), benzenedimethanol (2 g, 14.5 mmol), and *p*-toluenesulfonic acid (183 mg, 0.96 mmol) in benzene (75 mL) was heated at reflux for 1 h using a Dean Stark apparatus. The reaction mixture was quenched by the addition of a saturated Na_2CO_3 solution (10 mL) and washed with brine (10 mL). After separation, the organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue thus obtained was purified by flash chromatography (hexanes/EtOAc, 7:3) to give **4** as a colorless oil (44% isolated yield from **5**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61 (t, J = 6.4 Hz, 2 H), 2.98 (s, 3 H), 4.37 (t, J = 6.4 Hz, 2 H), 4.89 (s, 4 H), 5.17 (s, 1 H), 5.29 (s, 1 H), 5.45 (s, 1 H), 7.12–7.28 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.2, 37.8, 68.9, 71.3, 106.8, 116.7, 127.6, 127.8, 139.1, 140.9 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2873, 1451, 1357, 1196, 1081, 1042, 754 cm^{-1}.

2-[4-(Bromomethyl)thiazol-2-yl]-2-methylhex-5-en-3-ol (6): A solution of magnesium bromide (1 M in Et_2O, 0.23 mL, 0.23 mmol) was added dropwise to a solution of aldehyde **19** (59 mg, 0.23 mmol) in anhydrous THF (4 mL) at –78 °C under nitrogen. After 35 min of stirring at this temperature, the solution was quenched by addition of a saturated NH_4Cl solution (5 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (hexanes/EtOAc, 95:5) gave the homoallylic alcohol **6** as a colorless oil in 67% isolated yield (borsm). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 1.45 (s, 3 H), 1.94–2.08 (m, 1 H), 2.12–2.35 (m, 1 H), 3.76 (dd, J = 10.0, 2.7 Hz, 1 H), 4.53 (s, 2 H), 5.04–5.10 (m, 2 H), 5.87 (ddt, J = 16.9, 10.1, 6.7 Hz, 1 H), 7.18 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6, 27.0, 27.4, 36.9, 45.3, 77.9, 116.8, 117.2, 136.3, 151.7, 180.1 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3412, 2969, 2925, 1640, 1463, 1421, 1360, 1199, 1051, 910, 732 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}BrNOS$ $[M + H]^+$ 290.0209; found 290.0205.

2-Methylenebutane-1,4-diol (9): DIBAL (100 mL of a 1 M solution in hexanes, 100 mmol) was added to a 0 °C solution of dimethyl itaconate (**5**; 3.19 mL, 22.7 mmol) in THF (150 mL) . After stirring for 5 h at room temperature, the reaction mixture was quenched by the addition of a H_2SO_4 solution (5 M) until pH 1. The precipitate was then filtered off and the aqueous layer was extracted with EtOAc (5 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford diol **9** (98% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (t, J = 5.9 Hz, 2 H), 2.60 (br. s, 1 H, OH), 3.75 (t, J = 5.9 Hz, 2 H), 4.10 (s, 2 H), 4.97 (s, 1 H), 5.13 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.0, 61.6, 66.0, 113.3, 146.2 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3340, 2931, 1652, 1435, 1044, 909 cm^{-1}. In agreement with reported data.[50]

3-Formylbut-3-en-1-yl Methanesulfonate (11): Et_3N (426 μL, 3.3 mmol) and mesyl chloride (378 mg, 3.3 mmol) were added to a solution of **10** (220 mg, 2.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was quenched by the addition of ca. 20 mL of a saturated NH_4Cl solution. The organic phase was then evaporated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford quantitatively **11** as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68 (t, J = 6.4 Hz, 2 H), 2.95 (s, 3 H), 4.29 (t, J = 6.4 Hz, 2 H), 6.16 (s, 1 H), 6.42 (s, 1 H), 9.52 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.7, 37.7, 67.6, 137.5, 144.8, 194.2 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2947, 2847, 1770, 1712, 1449, 1402, 1371, 1330, 1191, 1103, 1044, 724 cm^{-1}.

2-{2-[4-(1,5-Dihydrobenzo[*e*][1,3]dioxepin-3-yl)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}isoindoline-1,3-dione (12): A solution of compound **4** (1.26 g, 4.23 mmol) and potassium phthalimide (2.34 g, 12.68 mmol) was stirred in DMF (40 mL) at 80 °C for 2 h. After cooling, the reaction mixture was quenched by the addition of water (20 mL). The aqueous phase was extracted with EtOAc (3 × 40 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 85:15) to yield the phthalimidate intermediate in 57% isolated yield (841 mg, 2.41 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (t, J = 7.1 Hz, 2 H), 3.85 (t, J = 7.1 Hz, 2 H), 4.82 (br. s, 4 H), 5.08 (s, 1 H), 5.35 (s, 1 H), 5.36 (s, 1 H), 7.02–7.19 (m, 4 H), 7.58–7.80 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.1, 37.0, 70.1, 104.8, 115.3, 123.2, 127.0, 127.2, 132.2, 133.9, 138.9, 142.4, 168.3 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3063, 2924, 2853, 1771, 1713, 1457, 1444, 1396, 1357, 1266, 1189, 1125, 1027, 926, 869, 719 cm^{-1}.

OsO_4 (4% in water, 284 μL, 46.4 μmol) and NMO (627 mg, 4.64 mmol) were added to a solution of the preceding intermediate (811 mg, 2.32 mmol) in a mixture of water/acetone (1:1, 20 mL). The reaction mixture was stirred at room temperature for 2 d and then extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the corresponding diol in 96% isolated yield (854 mg, 2.22 mmol); m.p. 156.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85–2.11 (m, 2 H), 3.01 (br. s, 2 H), 3.57 (d, J_{AB} = 11.5 Hz, 1/2 AB), 3.78 (d, J_{AB} = 11.5 Hz, 1/2 AB), 3.84–3.95 (m, 2 H), 4.81–4.99 (m, 4 H), 5.01 (s, 1 H), 7.11–7.30 (m, 4 H), 7.63–7.85 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.5, 33.4, 65.4, 74.4, 74.9, 112.3, 123.4, 128.4, 132.5, 134.1, 139.4, 168.3 ppm. HRMS (ESI): calcd. for $C_{21}H_{21}NNaO_6$ $[M + Na]^+$ 406.1261; found 406.1258.

A solution of the crude product (854 mg, 2.22 mmol), 2,2-dimethoxypropane (593 μL, 4.83 mmol), and *p*-toluenesulfonic acid (23 mg, 0.12 mmol) in CH_2Cl_2 (25 mL) was stirred for 2 h at room temperature. The reaction mixture was quenched by the addition of a saturated $NaHCO_3$ solution (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 80:20 then 50:50) to yield compound **12** in 83% isolated yield (782 mg, 1.85 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3 H), 1.50 (s, 3 H), 2.10 (ddd, J = 6.4, 3.9, 2.6 Hz, 2 H), 3.88 (ddd, J = 6.4, 3.9, 2.1 Hz, 2 H), 3.93 (d, J_{AB} = 9 Hz, 1/2 AB), 4.18 (d, J_{AB} = 9 Hz, 1/2 AB), 4.86–5.02 (m, 5 H), 7.12–7.28 (m, 4 H), 7.62–7.88 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7, 27.1, 32.4, 33.8, 70.3, 74.4, 83.1, 110.8, 110.9, 123.3, 128.2, 132.5, 134.0, 139.5, 168.4 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3412, 3052, 2987, 2847, 1771, 1722, 1449, 1372, 1265, 1198, 1105, 1060, 736 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{25}NNaO_6$ $[M + Na]^+$ 446.1574; found 446.1569.

4-[2-(1,3-Dioxoisoindolin-2-yl)ethyl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (13): A solution of compound **12** (500 mg, 1.18 mmol) and PdO (1.4 mg, 11.08 μmol) in THF (1.2 mL) was heated at 100 °C under 20 bar H_2 in a stainless steel pressure apparatus for 20 h. After cooling, the residue was filtered and washed with Et_2O. Evaporation of the solvent gave the pure aldehyde **13** in 40% iso-

lated yield (144 mg, 0.472 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 6 H), 2.11 (ddd, J = 14.0,7.9, 2.3 Hz, 2 H), 3.77 (ddd, J = 14.0, 7.9, 1.3 Hz, 2 H), 3.85 (d, J_{AB} = 9.1 Hz, 1/2 AB), 4.13 (d, J_{AB} = 9.0 Hz, 1/2 AB), 7.68–7.39 (m, 4 H), 9.67 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 32.0, 33.5, 70.5, 86.4, 112.2, 123.5, 132.5, 134.3, 168.4, 203.0 ppm.

2-[4-(Bromomethyl)thiazol-2-yl]-2-methylpropanal (19): HF·pyridine (8 μL, 0.11 mmol) was added to a solution of compound **18** (54 mg, 0.11 mmol) in CH_3CN (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated and the crude product purified by flash chromatography on silica gel (hexanes/EtOAc, 70:30) to afford the corresponding alcohol in 71% isolated yield (19 mg, 78 μmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 6 H), 3.72 (s, 2 H), 4.54 (s, 2 H), 7.19 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1, 27.3, 40.9, 71.4, 116.6, 151.3, 180.0 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3401, 2919, 1198, 1055 cm^{-1}.

Dess–Martin periodinane (15 wt.-%, 514 mL, 0.24 mmol) was added at 0 °C under nitrogen to a solution of the alcohol (50 mg, 0.20 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was stirred at room temperature for 3 h. A 1:1 saturated $NaHCO_3$/$Na_2S_2O_3$ solution (2 mL) was then added. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Purification of the residue by flash chromatography on silica gel (hexanes/EtOAc, 95:5) gave aldehyde **19** as a colorless oil in 67% isolated yield (33 mg, 0.13 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 6 H), 4.58 (s, 2 H), 7.29 (s, 1 H), 9.69 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3, 27.3, 52.3, 118.2, 152.9, 172.9, 200.0 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2934, 2927, 2710, 1736, 1199 cm^{-1}.

2-[3-Hydroxy-3-(hydroxymethyl)pent-4-en-1-yl]isoindoline-1,3-dione (20): A solution of **3** (15 mg, 43 μmol) in THF/HCl (1 M, 1:1, 1 mL) was heated at reflux for 10 h. After cooling, the mixture was extracted with EtOAc (3 × 5 mL) and the combined organic phases dried ($MgSO_4$), filtered, and concentrated in vacuo to provide **20** in 98% isolated yield (11 mg; 42 μmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88–2.05 (m, 2 H), 2.87 (br. s, 2 H, OH), 3.47 (s, 2 H), 3.81 (t, J = 7.0 Hz, 1 H), 5.15 (dd, J = 10.9, 0.7 Hz, 1 H), 5.35 (dd, J = 17.3, 0.7 Hz, 1 H), 5.75 (dd, J = 17.3, 10.9 Hz, 1 H), 7.68–7.85 (m, 4 H) ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_4$ [M + Na]$^+$ 284.0893; found 284.0893.

***tert*-Butyldimethyl[2-(2-vinyloxiran-2-yl)ethoxy]silane (22):** A solution of methylenetriphenylphosphonium bromide (959 mg, 2.68 mmol) in THF (20 mL) was treated with *n*Buli (1.3 M in hexane, 1.79 mL, 2.32 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C and then at 45 min at room temperature and then cooled again to 0 °C before a solution of aldehyde **24** (412 mg, 1.79 mmol) in THF (20 mL) was added dropwise. The resulting solution was stirred at room temperature for an additional 30 min and then quenched by the addition of a saturated NH_4Cl solution (10 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic phases were washed with water (20 mL) and brine and (20 mL) then dried ($MgSO_4$). After evaporation of the solvent, compound **22** was obtained by flash chromatography (hexanes/EtOAc, 98:2) as a colorless oil in 50% isolated yield (204 mg, 0.89 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.01 (s, 6 H), 0.83 (s, 9 H), 1.72–1.99 (m, 2 H), 2.60 (d, J_{AB} = 5.5 Hz, 1/2 AB), 2.83 (d, J_{AB} = 5.5 Hz, 1/2 AB), 3.67 (td, J = 6.7, 1.7 Hz, 2 H), 5.13 (dd, J = 10.7, 1.1 Hz, 1 H), 5.27 (dd, J = 17.1, 1.1 Hz, 1 H), 5.73 (dd, J = 17.1, 10.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3, 18.3, 26.0, 36.7, 55.2, 56.8, 59.5, 116.4, 137.7 ppm.

2-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}oxirane-2-carbaldehyde (24): A solution of γ-hydroxy aldehyde **10** (4.20 g, 42 mmol), imidazole (3.43 g, 50.4 mmol), and DMAP (154 mg, 1.3 mmol) in CH_2Cl_2 (150 mL) was treated with TBSCl (7.59 g, 50.4 mmol) for 30 min. The reaction mixture was then quenched with water (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (hexanes/EtOAc, 95:5) gave the TBS ether as a colorless oil in 54% isolated yield (4.85 g, 22.7 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.87 (s, 9 H), 2.47 (t, J = 6.4 Hz, 2 H), 3.69 (t, J = 6.4 Hz, 2 H), 6.06 (s, 1 H), 6.37 (s, 1 H), 9.53 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4, 18.2, 25.9, 31.4, 61.0, 135.8, 147.1, 194.4 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2956, 2930, 2858, 1693, 1472, 1462, 1256, 1101, 1055, 925, 835, 776 cm^{-1}.

The urea–H_2O_2 complex (35 wt.-%, 2.95 g, 10.64 mmol) was added to the TBS ether (759 mg, 3.54 mmol) in MeOH (35 mL). After complete dissolution, a 1 M solution of NaOH (1 mL, 1 mmol) was added at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was treated with brine (10 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (hexanes/EtOAc, 95:5) gave the epoxy aldehyde **24** as a colorless oil in 50% isolated yield (407 mg, 1.77 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.84 (s, 9 H), 1.98–2.12 (m, 2 H), 3.01 (d, J_{AB} = 4.9 Hz, 1/2 AB), 3.13 (d, J_{AB} = 9.7 Hz, 1/2 AB), 3.69–3.81 (m, 2 H), 8.93 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4, 18.3, 25.9, 31.2, 50.3, 58.6, 59.4, 198.9 ppm.

2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]but-2-enal (25): A solution of epoxide **22** (46 mg, 0.2 mmol) and alcohol **6** (58 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was heated at reflux for 6 h with the G_I catalyst (4.2 mg, 5.1 μmol). The reaction mixture was cooled, concentrated in vacuo and the crude product purified by flash chromatography (hexanes/EtOAc, 98:2). Compound **6** was recovered untouched and aldehyde **25** was obtained in 95% isolated yield (43 mg, 0.19 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.86 (s, 9 H), 2.01 (d, J = 7.0 Hz, 3 H), 2.50 (t, J = 6.6 Hz, 2 H), 3.61 (t, J = 6.6 Hz, 2 H), 6.67 (q, J = 7.0 Hz, 1 H), 9.37 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2, 15.4, 18.4, 26.0, 27.6, 61.5, 141.7, 152.0, 195.1 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2946, 2929, 2857, 1685, 1472, 1256, 1131, 836 cm^{-1}. HRMS (CI): calcd. for $C_{12}H_{25}O_2Si$ 229.1624; found 229.1619.

5-[(4-Methoxybenzyl)oxy]pent-1-en-3-one (26). Route A: A solution of vinylmagnesium bromide (0.7 M in THF, 43 mL, 30.3 mmol) was added to a solution of aldehyde **30** (4.90 g, 25.2 mmol) in THF (100 mL) at 0 °C. After stirring for 1 h at this temperature, the reaction mixture was quenched by the addition of a saturated NH_4Cl solution (50 mL). THF was evaporated in vacuo and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), and dried ($MgSO_4$). After filtration and concentration, the residue was purified by flash chromatography (hexanes/EtOAc, 80:20) to give the intermediate alcohol in 81% isolated yield (4.56 g, 20.5 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78–1.91 (m, 2 H), 3.15 (br. s, 1 H, OH), 3.53–3.68 (m, 2 H), 3.79 (s, 3 H), 4.33 (dt, J = 6.0, 5.7 Hz, 1 H), 4.45 (s, 2 H), 5.09 (dd, J = 10.4, 1.5 Hz, 1 H), 5.25 (dd, J = 17.1, 1.5 Hz, 1 H), 5.87 (ddd, J = 17.1, 10.4, 6.0 Hz, 1 H), 6.88 (d, J = 8.7 Hz, 2 H), 7.25 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.3, 55.2, 67.8, 71.5, 72.8, 113.7, 114.2, 129.3, 130.0, 140.6, 159.2 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3349, 2944, 2873, 1423, 1129, 1054, 991, 924 cm^{-1}.

Compound 26: To a solution of this intermediate in THF (100 mL) was added a solution of IBX (7.97 g, 28.6 mmol) in DMSO (15 mL). After stirring for 6 h, water (20 mL) was added. After filtration, the residue was washed with CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc, 90:10), and compound **26** was recovered in 80% isolated yield (3.53 g, 25.5 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.89 (t, J = 6.4 Hz, 2 H), 3.77 (t, J = 6.4 Hz, 2 H), 3.80 (s, 3 H), 4.45 (s, 2 H), 5.86 (dd, J = 10.1, 1.3 Hz, 1 H), 6.22 (dd, J = 17.7, 1.3 Hz, 1 H), 6.33 (dd, J = 17.7, 10.1 Hz, 1 H), 6.87 (d, J = 8.7 Hz, 2 H), 7.24 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.2, 54.7, 64.6, 72.4, 113.4, 128.1, 128.9, 129.9, 136.3, 158.8, 198.3 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2928, 2906, 2868, 1731, 1680, 1613, 1513, 1247, 1098, 1034 cm^{-1}.

Route B: The conditions described for the synthesis of compound **30** from butanediol were applied to compound **32** to yield **26** (see below).

Methyl 2-[2-(3-Hydroxy-2-methylhex-5-en-2-yl)thiazol-4-yl]acetate (27): Compound **34** was oxidized according to the procedure described for compound **19** (94% isolated yield). Zinc (4.04 g, 62.2 mmol) and allyl bromide (5.40 mL, 62.2 mmol) were added to a solution of the resulting aldehyde (3.53 g, 15.5 mol) in a 1:1 mixture of THF/saturated NH_4Cl solution (50 mL) at 0 °C. After 48 h stirring at room temperature, the solution was filtered, THF evaporated in vacuo, and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc, 80:20) and alcohol **27** was recovered in 98% isolated yield (4.09 g, 15.2 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.45 (s, 3 H), 1.93–2.03 (m, 1 H), 2.24–2.36 (m, 1 H), 3.68–3.76 (m, 4 H), 3.81 (s, 2 H), 5.02–5.12 (m, 2 H), 5.90 (ddt, J = 17.0, 10.3, 7.1 Hz, 1 H), 7.07 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 26.5, 36.6, 36.7, 44.7, 52.0, 77.8, 114.9, 116.5, 136.2, 147.9, 170.6, 178.7 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3422, 2966, 1740, 1640, 1523, 1436, 1161, 1052, 914 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{20}NO_3S$ [M + H]$^+$ 2709.1158; found 270.1158.

Methyl (*E*)-2-{2-[3-(*tert*-Butyldimethylsilyl)oxy]-6-(2-{2-[(4-methoxybenzyl)oxy]ethyl}oxiran-2-yl)-2-methylhex-5-en-2-yl]thiazol-4-yl}acetate (29): A solution of chlorohydrin **37** (141 mg, 0.23 mmol), NaI (7 mg, 45 μmol), and NaH (60% in oil, 11 mg, 0.27 mmol) in THF (1 mL) was stirred at 0 °C for 2 h and at room temperature for an additional 30 min. The reaction was quenched with a saturated NH_4Cl solution (1 mL), the aqueous phase extracted with EtOAc (3 × 5 mL), and the combined organic layers dried ($MgSO_4$). After filtration and evaporation in vacuo, vinyl epoxide **29** was obtained quantitatively (135 mg, 0.23 mmol) and used in the following step without further purification as a colorless oil (mixture of two diastereoisomers, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.11 (s, 3 H), 0.03 (s, 3 H), 0.87 (s, 9 H), 1.34 (s, 3 H), 1.39 (s, 3 H), 1.98–2.15 (m, 3 H), 2.19–2.35 (m, 1 H), 2.60 (d, J = 5.2 Hz, 1 H), 2.82 (d, J = 5.2 Hz, 1 H), 3.49 (t, J = 6.6 Hz, 2 H), 3.71 (s, 3 H), 3.72–3.82 (m, 5 H), 3.99 (t, J = 5.0 Hz, 1 H), 4.40 (s, 2 H), 5.24 (d, J = 15.6 Hz, 1 H), 5.74 (dt, J = 15.6, 7.2 Hz, 1 H), 6.87 (d, J = 8.5 Hz, 2 H), 7.02 (s, 1 H), 7.23 (d, J = 8.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.6, –3.6, 18.2, 21.1, 24.8, 25.9, 26.1, 33.7, 36.9, 37.3, 46.3, 52.0, 54.7, 55.3, 56.4, 66.1, 72.7, 78.8, 113.8, 115.1, 129.2, 130.4, 130.4, 130.9, 147.7, 159.2, 170.9, 178.1 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2950, 2929, 2856, 1743, 1613, 1514, 1463, 1249, 1095, 1038, 836 cm^{-1}. HRMS (ESI): calcd. for $C_{31}H_{47}NO_6SSi$ [M + H]$^+$ 590.2972; found 590.2972.

3-[(4-Methoxybenzyl)oxy]propanal (30): Camphorsulfonic acid (1.16 g, 5 mmol) and *p*-methoxybenzyl trichloroacetamidate (29.06 g, 100 mmol) were added to a solution of 1,3-propanediol (7.36 mL, 101 mmol) in a mixture of cyclohexane/CH_2Cl_2 (2:1, 100 mL). After stirring for 10 h, the reaction mixture was quenched with a saturated $NaHCO_3$ solution (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc, 80:20) and the desired monoprotected diol was recovered in 59% isolated yield (11.36 g, 58 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55 (quint., J = 6.0 Hz, 2 H), 2.87 (br. s, 1 H, OH), 3.59 (t, J = 6.0 Hz, 2 H), 3.72 (t, J = 6.0 Hz, 2 H), 3.76 (s, 3 H), 4.42 (s, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 7.23 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.2, 55.2, 62.2, 68.6, 72.8, 113.8, 129.3, 130.2, 159.2 ppm.

The alcohol (5.88 g, 30 mmol) was treated with a solution of IBX (10.04 g, 36 mmol) in DMSO (20 mL). After stirring for 4 h water (50 mL) was added to the reaction mixture, which was then filtered through Celite and the insoluble residue was washed with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (3 × 50 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 85:15) and aldehyde **30** was recovered in 85% isolated yield (4.94 g, 25.5 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55 (dt, J = 6.0, 1.9 Hz, 2 H), 3.65 (t, J = 6.0 Hz, 2 H), 3.67 (s, 3 H), 4.34 (s, 2 H), 6.77 (d, J = 8.7 Hz, 2 H), 7.14 (d, J = 8.7 Hz, 2 H), 9.65 (t, J = 1.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.8, 55.1, 63.4, 72.8, 113.8, 129.3, 129.9, 159.2, 201.2 ppm. In agreement with reported data.[51]

***tert*-Butyl 3 Hydroxy-4-pentenoate (31):** Freshly distilled diisopropylamine (15.55 mL, 110 mmol) was diluted in dried THF (500 mL) and to this solution was added dropwise at –78 °C *n*Buli (1.6 M in hexane, 68.75 mL, 110 mmol). After stirring for 1.5 h at this temperature, *tert*-butyl acetate (13.51 mL, 100 mmol) was added dropwise. After another 1.5 h of stirring at –78 °C, acrolein (8.91 mL, 120 mmol) was introduced dropwise. The mixture was stirred at –78 °C for a further 10 min and the reaction was quenched at this temperature by the addition of a 1 M solution of HCl (50 mL). The resulting solution was allowed to warm to room temperature and then concentrated. The organic layer was extracted with Et_2O (3 × 100 mL) and the organic extracts were combined, washed with water (50 mL) and brine (50 mL), and dried ($MgSO_4$). After concentration, the crude product was purified by flash chromatography (hexanes/EtOAc, 80:20). Compound **26** was recovered in 87% isolated yield (14.98 g, 87 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 2.42 (dd, J_{AB} = 16.2, 8.0 Hz, 1/2 AB), 2.51 (dd, J_{AB} = 16.2, 4.3 Hz, 1/2 AB), 4.45–4.51 (m, 1 H), 5.14 (dd, J = 10.5, 1.3 Hz, 1 H), 5.30 (dd, J = 15.6, 1.3 Hz, 1 H), 5.87 (ddd, J = 16.0, 10.5, 5.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0, 42.2, 69.0, 81.3, 115.0, 139.0, 171.6 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3442, 3014, 2980, 2933, 1732, 1646, 1457, 1394, 1369, 1257, 1157, 1040, 993, 924, 880 cm^{-1}. In agreement with reported data.[52]

4-Pentene-1,3-diol (32): Ester **31** (1 g, 5.8 mmol) in Et_2O (10 mL) was added dropwise to a suspension of $LiAlH_4$ (440 mg, 11.6 mmol) in Et_2O (20 mL) at 0 °C. After stirring at this temperature for 1 h, the mixture was quenched by the addition of water (440 μL), 2 M NaOH (440 μL), and water again (880 μL). The reaction mixture was stirred for 30 min at room temperature, dried ($MgSO_4$), and concentrated in vacuo to give diol **32** nearly quanti-

tatively (602 mg, 5.8 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.88 (m, 2 H), 2.16 (br. s, 2 H, OH), 3.79–3.91 (m, 2 H), 4.40 (dddd, J = 12.0, 6.2, 5.9, 1.0 Hz, 1 H), 5.14 (d, J = 10.6 Hz, 1 H), 5.28 (d, J = 17.3 Hz, 1 H), 5.87 (ddd, J = 17.3, 10.6, 5.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.3, 60.6, 72.2, 114.6, 140.6 ppm. IR (film, NaCl): $\tilde{\nu}$ = 885, 924, 990, 1055, 1428, 2945, 3390 cm^{-1}. In agreement with reported data.[53]

Oxidation Procedure: See the synthesis of compound **30**.

2-(2-{1-[(*tert*-Butyldiphenylsilyl)oxy]-2-methylpropan-2-yl}thiazol-4-yl)acetonitrile (33): Mesyl chloride (32 μL, 0.42 mmol) and Et_3N (59 μL, 0.42 mmol) were added to a solution of alcohol **17** (136 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After stirring for 1 h at room temperature, the solvent was removed in vacuo and the residue dissolved in Et_2O (10 mL) and a saturated NH_4Cl solution (5 mL). The aqueous phase was then extracted with Et_2O (3 × 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and evaporated to give the mesyl intermediate quantitatively (160 mg, 0.32 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (s, 9 H), 1.45 (s, 6 H), 2.96 (s, 3 H), 3.73 (s, 2 H), 5.32 (s, 2 H), 7.32 (s, 1 H), 7.33–7.43 (m, 6 H), 7.52–7.73 (m, 4 H) ppm.

Potassium cyanide (59 mg, 0.91 mmol) was added to the crude product in DMSO (3 mL) at 0 °C. After stirring for 1 h at room temperature, H_2O (5 mL) and EtOAc (5 mL) were added. The aqueous phase was then extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (2 × 5 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 95:5) to give compound **33** in 66% isolated yield over the two steps (86 mg, 0.19 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 9 H), 1.44 (s, 6 H), 3.73 (s, 2 H), 3.84 (s, 2 H), 7.18 (s, 1 H), 7.35–7.46 (m, 6 H), 7.52–7.62 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 20.6, 25.4, 26.8, 43.3, 72.6, 115.5, 127.7, 129.7, 133.4, 135.7, 143.9, 179.5 ppm. HRMS (ESI): calcd. for $C_{25}H_{31}N_2OSSi$ [M + H]$^+$ 435.1921; found 435.1915.

Methyl 2-[2-(1-Hydroxy-2-methylpropan-2-yl)thiazol-4-yl]acetate (34): A solution of compound **33** (150 mg, 0.34 mmol) and TMSCl (175 μL, 1.38 mmol) in MeOH (3 mL) was heated for 15 h at 50 °C. After cooling, a saturated $NaHCO_3$ solution (5 mL) was added dropwise and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo to give compound **34** in 85% isolated yield (66 mg, 0.28 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 6 H), 3.68 (s, 2 H), 3.72 (s, 3 H), 3.79 (s, 2 H), 7.06 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1, 36.6, 42.1, 52.1, 71.4, 114.8, 147.6, 170.7, 178.8 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3412, 2956, 2252, 1738, 1437, 1253, 1051, 910, 733 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{16}NO_3S$ [M + H]$^+$ 230.0845; found 230.0847.

Methyl 2-(2-{3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylhex-5-en-2-yl}thiazol-4-yl)acetate (35): A solution of alcohol **27** (1.62 g, 6.02 mmol) and 2,6-lutidine (841 μL, 7.22 mmol) in CH_2Cl_2 (30 mL) was treated with TBSOTf (1.66 mL, 7.22 mmol) for 1 h at –78 °C. The reaction mixture was quenched with a saturated NH_4Cl solution, the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 95:5) to yield 2.07 g (5.42 mmol, 90%) of the TBS ether **35** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.01 (s, 3 H), 0.14 (s, 3 H), 0.98 (s, 9 H), 1.46 (s, 3 H), 1.52 (s, 3 H), 2.11–2.42 (m, 2 H), 3.81 (s, 3 H), 3.92 (s, 2 H), 4.13 (t, J = 4.7 Hz, 1 H), 4.92–5.04 (m, 2 H), 5.79 (ddt, J = 16.8, 10.5, 7.5 Hz, 1 H), 7.13 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.6, –3.4, 18.3, 24.7, 25.9, 26.1, 37.1, 38.7, 46.3, 52.1, 79.0, 115.1, 116.1, 136.4, 147.8, 171.1, 178.4 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2954, 2928, 2857, 1746, 1472, 1255, 1093, 836, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{34}NO_3SSi$ [M + H]$^+$ 384.2023; found 384.2028.

Methyl (*E*)-2-(2-{3-[(*tert*-Butyldimethylsilyl)oxy]-9-[(4-methoxybenzyl)oxy]-2-methyl-7-oxonon-5-en-2-yl}thiazol-4-yl)acetate (36): A solution of enone **26** (1.34 g, 6.11 mmol) and thiazole **35** (1.56 g, 4.07 mmol) in anhydrous CH_2Cl_2 (20 mL) was purged by bubbling with N_2 for 10 min. Then Grubbs' second-generation catalyst (17 mg, 20 μmol, 0.5 mol-%) was added and the reaction mixture was submitted to microwave irradiation at 50 °C for 15 min. This procedure (catalyst addition, microwave irradiation) was repeated five times (5 × 0.5 mol-% G_{II}) to give 66% conversion. The solvent was evaporated in vacuo and the residue purified by flash chromatography (hexanes/EtOAc, 90:10) to give compound **36** [1.17 g, 2.03 mmol, 83% isolated yield (borsm)] as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.05 (s, 3 H), 0.02 (s, 3 H), 0.89 (s, 9 H), 1.36 (s, 3 H), 1.40 (s, 3 H), 2.20–2.45 (m, 2 H), 2.72 (t, J = 6.6 Hz, 2 H), 3.70 (t, J = 6.6 Hz, 2 H), 3.70 (s, 3 H), 3.78 (s, 2 H), 3.79 (s, 3 H), 4.01 (t, J = 5.2 Hz, 1 H), 4.43 (s, 2 H), 5.90 (d, J = 16.0 Hz, 1 H), 6.64 (dt, J = 16.0, 7.6 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.01 (s, 1 H), 7.23 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.7, –3.8, 18.2, 24.2, 25.9, 26.3, 36.8, 37.3, 39.7, 46.0, 51.9, 55.2, 65.1, 72.8, 78.1, 113.7, 115.4, 129.3, 130.3, 131.5, 144.7, 147.9, 159.2, 170.8, 177.2, 198.0 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2954, 2934, 2856, 1740, 1670, 1613, 1513, 1362, 1249, 1095, 1038, 836, 776 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{46}NO_6SSi$ [M + H]$^+$ 576.2810; found 576.2796.

Methyl (*E*)-2-(2-{3-[(*tert*-Butyldimethylsilyl)oxy]-7-(chloromethyl)-7-hydroxy-9-[(4-methoxybenzyl)oxy]-2-methylnon-5-en-2-yl}thiazol-4-yl)acetate (37): *n*BuLi (0.6 M in hexane, 2.59 mL, 1.51 mmol) was added dropwise to a solution of enone **36** (796 mg, 1.38 mmol) and chloroiodomethane (151 μL, 2.07 mmol) in anhydrous THF (5 mL) at –78 °C. The resulting mixture was stirred at this temperature for 2 h and quenched with a saturated NH_4Cl solution (5 mL). The mixture was allowed to warm to room temperature and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 90:10) to give chlorohydrin **37** as a colorless oil (495 mg, 0.79 mmol) in 57% isolated yield (mixture of two diastereoisomers, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.10–0.02 (m, 3 H), 0.02–0.19 (m, 3 H), 0.89 (s, 4.5 H), 0.90 (s, 4.5 H), 1.37 (s, 3 H), 1.42 (s, 3 H), 1.68–1.88 (m, 1 H), 2.01–2.21 (m, 2 H), 2.25–2.44 (m, 1 H), 3.34–3.49 (m, 2 H), 3.54–3.66 (m, 2 H), 3.70 (s, 3 H), 3.76–3.82 (m, 5 H), 4.00 (t, J = 5.1 Hz, 1 H), 4.42 (s, 2 H), 5.37 (dm, J = 15.6 Hz, 1 H), 5.74 (dt, J = 15.6, 8.2 Hz, 1 H), 6.86 (d, J = 8.0 Hz, 2 H), 7.02 (s, 1 H), 7.21 (d, J = 8.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.3, –3.3, 18.6, 25.1, 26.2, 26.2, 26.4, 36.8, 36.9, 37.2, 37.7, 37.8, 46.7, 52.4, 52.6, 55.6, 67.1, 73.4, 74.7, 74.8, 79.4, 114.2, 115.6, 129.4, 129.7, 130.1, 133.3, 133.5, 148.0, 148.1, 159.7, 171.4, 178.5, 178.6 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3478, 2954, 2923, 2856, 1742, 1613, 1514, 1463, 1250, 1093, 836 cm^{-1}. MS (ESI): m/z (%) = 648.2 (95) [M + Na]$^+$; calcd. for $C_{31}H_{48}ClNNaO_6SSi$ [M + Na]$^+$ 648.2555; found 648.2555.

Methyl (*E*)-2-(2-{3,7-Bis[(*tert*-butyldimethylsilyl)oxy]-7-(chloromethyl)-9-[(4-methoxybenzyl)oxy]-2-methylnon-5-en-2-yl}thiazol-4-yl)acetate (38): Thiazole **37** (100 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was treated as described for compound **35** with 2,6-lutidine (22 μL, 0.19 mmol) and TBSOTf (44 μL, 0.19 mmol) to give after purification (hexanes/EtOAc, 95:5) compound **38** (59.2 mg, 0.08 mmol) as

a colorless oil in 50% isolated yield (mixture of two diastereoisomers, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.11 (s, 3 H), 0.04 (s, 9 H), 0.84 (s, 9 H), 0.85 (s, 9 H), 1.34 (s, 3 H), 1.40 (s, 3 H), 1.88–2.02 (m, 2 H), 2.05–2.39 (m, 2 H), 3.41–3.48 (m, 2 H), 3.48–3.59 (m, 2 H), 3.71 (s, 3 H), 3.75–3.85 (m, 5 H), 3.92–4.09 (m, 1 H), 4.40 (s, 2 H), 5.40 (d, J = 15.7 Hz, 0.5 H), 5.42 (d, J = 15.7 Hz, 0.5 H), 5.67 (dt, J = 15.7, 7.1 Hz, 1 H), 6.86 (d, J = 6.1 Hz, 2 H), 7.03 (s, 1 H), 7.23 (d, J = 6.1 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8, –3.6, –2.0, –1.9, 18.3, 18.6, 25.3, 25.6, 26.0, 26.1, 37.0, 37.7, 37.8, 38.0, 46.5, 51.7, 51.9, 52.1, 55.4, 66.0, 72.8, 76.1, 76.3, 78.9, 79.0, 113.9, 115.2, 128.5, 128.7, 129.4, 130.6, 134.1, 134.2, 147.8, 159.3, 171.1, 178.4 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2856, 2929, 2856, 1746, 1614, 1514, 1471, 1361, 1250, 1093, 836, 775 cm^{-1}.

Methyl 2-(2-{3-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-2-methyl-2-pentyl}thiazol-4-yl)acetate (39): $NaBH_4$ (339 mg, 8.96 mmol) was added portionwise to a solution of aldehyde **47** (2.65 g, 6.85 mmol) in MeOH (35 mL) at 0 °C. After stirring for 1 h at 0 °C, water (30 mL) was added with caution. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 70:30) to give alcohol **39** (2.12 g, 5.48 mmol) in 80% isolated yield.^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.11 (s, 3 H), 0.90 (s, 9 H), 1.38 (s, 3 H), 1.41 (s, 3 H), 1.55–1.70 (m, 2 H), 2.16 (br. s, 1 H, OH), 3.35–3.58 (m, 2 H), 3.72 (s, 3 H), 3.80 (s, 2 H), 4.17 (dd, J = 6.0, 4.2 Hz, 1 H), 7.03 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.5, –4.00, 18.2, 24.1, 26.0, 36.7, 37.2, 45.9, 52.1, 59.6, 75.8, 115.2, 147.7, 171.1, 178.7 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3411, 2955, 2930, 2886, 2856, 1742, 1472, 1256, 1098, 1051, 837, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{34}NO_4SSi$ $[M + H]^+$ 388.1972; found 388.1973.

Methyl 2-(2-{5-(Benzo[*d*]thiazol-2-ylsulfonyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpentan-2-yl}thiazol-4-yl)acetate (41): DEAD (264 μL, 1.68 mmol) was added to a solution of alcohol **39** (500 mg, 1.29 mmol), 2-mercaptobenzothiazole (281 mg, 1.68 mmol), and triphenylphosphane (440 mg, 1.68 mmol) in THF (15 mL) at 0 °C. The solution was stirred at room temperature for 1 h before the addition of a saturated $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the resulting organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 95:5) to give the intermediate thioether (623 mg, 1.16 mmol) in 90% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.04 (s, 3 H), 0.13 (s, 3 H), 0.92 (s, 9 H), 1.38 (s, 3 H), 1.44 (s, 3 H), 1.88–2.11 (m, 2 H), 3.00–3.18 (m, 1 H), 3.21–3.39 (m, 1 H), 3.71 (s, 3 H), 3.80 (s, 2 H), 4.13 (dd, J = 6.3, 4.0 Hz, 1 H), 7.04 (s, 1 H), 7.28 (td, J = 7.0, 1.1 Hz, 1 H), 7.74 (td, J = 7.0, 1.1 Hz, 1 H), 7.75 (d, J = 7.0 Hz, 1 H), 7.85 (d, J = 7.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.4, –3.7, 18.3, 24.5, 26.1, 30.7, 33.6, 36.9, 46.0, 52.0, 78.2, 115.3, 120.9, 121.5, 124.1, 125.9, 135.2, 147.8, 153.3, 166.6, 170.8, 177.7 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2953, 2928, 2856, 1743, 1462, 1428, 1256, 1094, 1048, 997, 837, 775, 756, 727 cm^{-1}.

The above-mentioned thioether (330 mg, 0.615 mmol) in MeOH (6 mL) was treated at 0 °C with $Na_2O_4W{\cdot}2H_2O$ (101 mg, 0.31 mmol) and H_2O_2 (35% H_2O, 210 μL, 2.46 mmol) was added dropwise. The resulting mixture was stirred for 14 h until total conversion before the reaction was quenched by the addition of a saturated $Na_2S_2O_3$ solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 85:15) to give sulfone **41** (384 mg, 0.55 mmol) in 90% isolated yield as a white solid; m.p. 78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.07 (s, 3 H), 0.00 (s, 3 H), 0.86 (s, 9 H), 1.34 (s, 3 H), 1.40 (s, 3 H), 1.90–2.10 (m, 2 H), 3.24 (td, J = 11.6, 5.0 Hz, 1 H), 3.38 (td, J = 11.7, 5.0 Hz, 1 H), 3.68 (s, 3 H), 3.73 (s, 2 H), 4.07 (t, J = 5.1 Hz, 1 H), 7.01 (s, 1 H), 7.55–7.69 (m, 2 H), 8.02 (d, J = 7.2 Hz, 1 H), 8.20 (d, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8, –4.18, 18.0, 24.7, 25.8, 26.0, 26.4, 36.7, 45.7, 51.6, 51.9, 76.8, 115.6, 122.2, 125.2, 127.5, 127.9, 136.6, 147.9, 152.5, 165.4, 170.5, 176.6 ppm.

4-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (42): PdO (6 mg, 50 μmol) was added to a degassed solution of ketal **46** (1.03 g, 2.52 mmol) in THF (2.5 mL). The reaction mixture was stirred at room temperature under 1 atm H_2 for 30 min and then filtered through Celite. The residue was rinsed with CH_2Cl_2 (3 × 10 mL). Evaporation of the solvent led to the pure aldehyde **42** (671 mg, 2.33 mmol) as a colorless oil in 93% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.86 (s, 9 H), 1.42 (s, 6 H), 1.79–2.18 (m, 2 H), 3.62–3.80 (m, 2 H), 3.83 (d, J = 8.9 Hz, 1 H), 4.22 (d, J = 8.9 Hz, 1 H), 9.65 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.5, –5.4, 18.3, 26.0, 26.6, 26.7, 38.9, 58.3, 70.8, 86.4, 110.9, 203.1 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2950, 2931, 2858, 1732, 1472, 1372, 1256, 1217, 1091, 836, 777 cm^{-1}.

***tert*-Butyl{[3-(1,5-dihydroxbenzo[*e*][1,3]dioxepin-3-yl)but-3-en-1-yl]oxy}dimethylsilane (44):** A solution of γ-hydroxy aldehyde **10** (4.20 g, 42 mmol) in CH_2Cl_2 (150 mL) was stirred with imidazole (3.43 g, 50.4 mmol), DMAP (154 mg, 1.3 mmol), and TBSCl (7.59 g, 50.4 mmol) at room temperature for 30 min. After the addition of water (100 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 95:5) to give the TBS ether as a colorless oil (4.85 g, 22.7 mmol) in 54% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.87 (s, 9 H), 2.47 (t, J = 6.4 Hz, 2 H), 3.69 (t, J = 6.4 Hz, 2 H), 6.06 (s, 1 H), 6.37 (s, 1 H), 9.53 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4, 18.2, 25.9, 31.4, 61.0, 135.8, 147.1, 194.4 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2956, 2930, 2858, 1693, 1472, 1462, 1256, 1101, 1055, 925, 835, 776 cm^{-1}.

1,2-Benzenedimethanol (5.25 g, 38.0 mmol), trimethyl orthoformate (4.57 mL, 41.8 mmol), and PTSA (361 mg, 1.9 mmol) in 1,2-dimethoxyethane (13 mL) were stirred at room temperature for 30 min. The solution was then diluted with Et_2O (100 mL), washed with a saturated $NaHCO_3$ solution (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the benzodioxepine (6.71 g, 37.2 mmol), which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.47 (s, 3 H), 4.71 (d, J_{AB} = 14.1 Hz, 1/2 AB), 5.08 (d, J_{AB} = 14.1 Hz, 1/2 AB), 5.48 (s, 1 H), 7.06–7.21 (m, 4 H) ppm.

A solution of the TBS ether (3.63 g, 16.9 mmol) in 1,2-dimethoxyethane (80 mL), PTSA (160 mg, 0.84 mmol) and the benzodioxepine obtained as described above (6.10 g, 33.8 mmol) was stirred for 12 h until total conversion and then quenched with a saturated $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 99:1) to give compound **44** as a colorless oil (2.83 g, 8.45 mmol) in 50% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.91 (s, 9 H), 2.40 (t, J = 7.1 Hz, 2 H), 3.78 (t, J = 7.1 Hz, 1 H), 4.70–4.98 (m, 4 H), 5.10 (s, 1 H), 5.29 (s, 1 H), 5.40

(s, 1 H), 7.10–7.27 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2, 18.4, 26.0, 35.8, 62.6, 70.0, 105.5, 114.4, 127.0, 127.2, 139.0, 142.8 ppm.

4-[(*tert*-Butyldimethylsilyl)oxy]-2-(1,5-dihydrobenzo[*e*]dioxepin-3-yl)butane-1,2-diol (45): A solution of olefin **44** (1.17 g, 3.50 mmol) was treated as described for compound **12** to give after flash chromatography (hexanes/EtOAc, 80:20) diol **45** (1.05 g, 2.87 mmol) as a colorless oil in 82% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.89 (s, 9 H), 1.78–1.99 (m, 2 H), 3.61 (d, J_{AB} = 11.5 Hz, 1/2 AB), 3.66 (d, J_{AB} = 11.5 Hz, 1/2 AB), 3.82–3.99 (m, 2 H), 4.88–5.03 (m, 5 H), 7.16–7.31 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.9, 18.1, 25.8, 34.5, 59.5, 65.5, 74.2, 74.9, 112.1, 127.8, 139.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{32}NaO_5Si$ $[M + Na]^+$ 391.1911; found 391.1905.

***tert*-Butyl{2-[4-(1,5-dihydroxbenzo[*e*][1,3]dioxepin-3-yl)-2,2-dimethyl-1,3-dioxolan-4-yl]ethoxy}dimethylsilane (46):** A solution of diol **45** (1.07 g, 2.90 mmol) was treated as described for compound **12** to give after flash chromatography (hexanes/EtOAc, 95:5) ketal **46** (1.03 g, 2.52 mmol) as a colorless oil in 87% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.86 (s, 9 H), 1.42 (s, 3 H), 1.46 (s, 3 H), 1.89 (dt, J = 14.0, 6.8 Hz, 1 H), 2.04 (dt, J = 14.0, 7.1 Hz, 1 H), 3.79 (t, J = 7.0 Hz, 2 H), 3.97 (d, J = 8.9 Hz, 1 H), 4.11 (d, J = 8.9 Hz, 1 H), 4.83–4.98 (m, 5 H), 7.15–7.27 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2, 18.4, 26.1, 26.8, 27.0, 36.3, 59.2, 70.3, 74.2, 83.3, 110.0, 111.0, 128.0, 139.5 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2955, 2928, 2856, 1471, 1462, 1370, 1255, 1216, 1107, 1056, 836, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{36}NaO_5Si$ $[M + Na]^+$ 431.2224; found 431.2219.

Methyl 2-(2-{3-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-5-oxopentan-2-yl}thiazol-4-yl)acetate (47): A solution of olefin **35** (2.74 g, 7.15 mmol) in a mixture dioxane/water (3:1, 40 mL) was treated at room temperature with 2,6-lutidine (1.66 mL, 14.3 mmol), $NaIO_4$ (6.12 g, 28.6 mmol), and OsO_4 (4% in water, 437 µL, 71.5 µmol). After stirring for 1 h, CH_2Cl_2 (100 mL) and water (50 mL) were added. After separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 90:10) to give aldehyde **47** as a colorless oil (2.73 g, 7.07 mmol) in 99% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.01 (s, 3 H), 0.01 (s, 3 H), 0.86 (s, 9 H), 1.37 (s, 3 H), 1.41 (s, 3 H), 2.44 (ddd, J_{AB} = 17.1, J = 5.0, 2.3 Hz, 1/2 AB), 2.61 (dd, J_{AB} = 17.1, J = 5.0 Hz, 1/2 AB), 3.70 (s, 3 H), 3.79 (s, 2 H), 4.51 (t, J = 5.0 Hz, 1 H), 7.05 (s, 1 H), 9.54 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8, –4.1, 18.2, 24.4, 25.9, 37.0, 45.9, 48.7, 52.2, 73.9, 115.7, 148.1, 170.9, 176.8, 200.9 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2955, 2931, 2857, 1743, 1725, 1523, 1472, 1362, 1256, 1159, 1098, 1006, 838, 777 cm^{-1}.

2-[(4-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-2,2-dimethyl-1,3-dioxolan-4-yl)methylsulfonyl]benzo[*d*]thiazole (48): Compound **48** was obtained from aldehyde **42** according to the procedure described for sulfone **41** from aldehyde **47**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.86 (s, 9 H), 1.09 (s, 3 H), 1.25 (s, 3 H), 1.99–2.12 (m, 1 H), 2.50 (dt, J = 14.3, 4.5 Hz, 1 H), 3.78–4.12 (m, 6 H), 7.52–7.68 (m, 2 H), 8.00 (dd, J = 8.0, 1.5 Hz), 8.19 (dd, J = 7.6, 1.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2, –5.1, 18.5, 26.2, 26.5, 26.8, 39.5, 59.4, 60.4, 74.6, 80.7, 110.2, 122.6, 125.7, 127.9, 128.2, 137.2 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2983, 2950, 2929, 2851, 1472, 1372, 1333, 1256, 1155, 1091, 1058, 836 cm^{-1}.

(*E*)-2-{3-[(*tert*-Butyldimethylsilyl)oxy]-6-iodo-2-methylhex-5-en-2-yl}-4-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}thiazole (49): A solution of alcohol **56** (45 mg, 93.5 µmol) in anhydrous CH_2Cl_2 (1 mL) and 2,6-lutidine (13 µL, 112.2 µmol) was treated at –78 °C with TBSOTf (26 µL, 112.2 µmol) and stirred at this temperature for 1 h. The reaction was quenched by the addition of a saturated NH_4Cl solution (2 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 99:1) to give compound **49** (41 mg, 69 µmol) as a colorless oil in 74% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.07 (s, 3 H), 0.00 (s, 6 H), 0.07 (s, 3 H), 0.86 (s, 9 H), 0.90 (s, 9 H), 1.34 (s, 3 H), 1.39 (s, 3 H), 2.02–2.13 (m, 1 H), 2.16–2.23 (m, 1 H), 2.96 (t, J = 6.6 Hz, 2 H), 3.87–3.94 (m, 2 H), 4.03 (dd, J = 6.5, 4.3 Hz, 1 H), 5.85 (dd, J = 14.7, 1.2 Hz, 1 H), 6.28 (ddd, J = 14.7, 8.3, 6.8 Hz, 1 H), 6.83 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2, –4.3, –3.5, 18.4, 24.1, 26.1, 26.2, 35.4, 40.6, 46.2, 62.5, 76.2, 78.2, 113.7, 144.2, 153.8, 177.2 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2950, 2928, 2856, 1471, 1254, 1098, 836, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{47}INO_2SSi$ $[M + H]^+$ 596.1912; found 596.1911.

4-[(4-Methoxybenzyl)oxy]-2-methylenebutanal (50): Compound **50** was obtained from alcohol **10** according to the procedure described for **30**: To a solution of compound **10** (1.02 g, 10.2 mmol) in a mixture of cyclohexane/CH_2Cl_2 (2:1) (10 mL) were added camphorsulfonic acid (118 mg, 0.51 mmol) and *p*-methoxybenzyl trichloroacetamidate (3.16 g, 11.2 mmol). After stirring for 10 h, the reaction mixture was quenched with a saturated $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc, 95:5), and the desired product 50 was recovered with 45% isolated yield (1.01 g, 4.58 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (t, J = 6.4 Hz, 2 H), 3.55 (t, J = 6.4 Hz, 2 H), 3.79 (s, 3 H), 4.42 (s, 2 H), 6.06 (s, 1 H), 6.36 (s, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.22 (d, J = 8.7 Hz, 2 H), 9.52 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1, 55.2, 67.6, 72.4, 113.7, 129.2, 130.2, 135.8, 146.9, 159.1, 194.5 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2934, 2857, 2829, 1686, 1612, 1513, 1248, 1175, 1098, 1034, 822 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{16}NaO_3$ $[M + Na]^+$ 243.0992; found 243.0998.

1-[(*tert*-Butyldimethylsilyl)oxy]-4-[(4-methoxybenzyl)oxy]butan-2-one (51): A solution of olefin **54** (275 mg, 0.82 mmol) in dioxane/water (3:1, 10 mL) was treated at room temperature with 2,6-lutidine (191 µL, 1.63 mmol), $NaIO_4$ (700 mg, 3.27 mmol), and OsO_4 (4% in water, 50 µL, 8.2 µmol). After 12 h stirring at room temperature, CH_2Cl_2 (10 mL) and water (10 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the resulting organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 95:5) to give alcohol **51** (202 mg, 0.60 mmol) in 73% isolated yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.91 (s, 9 H), 2.76 (t, J = 6.2 Hz, 2 H), 3.72 (t, J = 6.2 Hz, 2 H), 3.80 (s, 3 H), 4.19 (s, 2 H), 4.43 (s, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 7.24 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.5, 18.3, 25.8, 38.9, 55.2, 64.7, 69.7, 72.9, 113.8, 129.3, 130.2, 159.3, 208.9 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2956, 2930, 2857, 1722, 1613, 1514, 1463, 1362, 1249, 1172, 1100, 838 cm^{-1}. In agreement with reported data.[54]

4-[(4-Methoxybenzyl)oxy]-2-methylenebutan-1-ol (53): Sodium borohydride (125 mg, 3.31 mmol) was added portionwise to a stirred solution of **50** (663 mg, 3.01 mmol) and cerium chloride

heptahydrate (1.23 g, 3.31 mmol) in MeOH (8 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, after which water (10 mL) was added to destroy the residual sodium borohydride. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the resulting organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 80:20) to give alcohol **53** (568 mg, 2.55 mmol) in 85% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (br. s, 1 H, OH), 2.40 (t, J = 6.2 Hz, 2 H), 3.58 (t, J = 6.2 Hz, 2 H), 3.80 (s, 3 H), 4.06 (s, 2 H), 4.46 (s, 2 H), 4.92 (s, 1 H), 5.05 (s, 1 H), 6.87 (d, J = 8.7 Hz, 2 H), 7.24 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.6, 55.1, 65.9, 69.1, 72.6, 111.7, 113.7, 129.3, 129.9, 146.5, 159.2 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3400, 2923, 2851, 1712, 1612, 1513, 1248, 1033, 819 cm^{-1}. In agreement with reported data.[55]

***tert*-Butyl{4-[(4-methoxybenzyl)oxy]-2-methylenebutoxy}dimethylsilane (54):** A solution of alcohol **53** (240 mg, 1.08 mmol) was treated as described for compound **24** to give after flash chromatography (hexanes/EtOAc, 99:1) TBS ether **54** (277 mg, 0.82 mmol) as a colorless oil in 77% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.90 (s, 9 H), 2.33 (t, J = 7.0 Hz, 2 H), 3.56 (t, J = 7.0 Hz, 2 H), 3.80 (s, 3 H), 4.07 (s, 2 H), 4.44 (s, 2 H), 4.86 (s, 1 H), 5.08 (s, 1 H), 6.87 (d, J = 8.6 Hz, 2 H), 7.26 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3, 18.4, 26.0, 33.2, 55.2, 66.1, 68.9, 72.6, 110.1, 113.8, 129.3, 130.6, 145.9, 159.2 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2950, 2929, 2856, 1613, 1514, 1463, 1361, 1249, 1172, 1098, 836 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{30}NaO_4Si$ [M + Na]$^+$ 361.1806; found 361.1807. In agreement with reported data.[56]

Methyl (*E*)-2-(2-{3-[(*tert*-Butyldimethylsilyl)oxy]-6-iodo-2-methylhex-5-en-2-yl}thiazol-4-yl)acetate (55): A solution of aldehyde **47** (1.39 g, 3.61 mmol) and CH_3I (2.84 g, 7.22 mmol) in anhydrous THF (15 mL) was added at 0 °C to a solution of $CrCl_2$ (2.66 g, 21.66 mmol) in anhydrous THF (20 mL) and the resulting mixture was stirred for 18 h at room temperature before being hydrolyzed with water (20 mL). The aqueous phase was then extracted with EtOAc (3 × 20 mL) and the resulting organic layers were washed with a saturated $Na_2S_2O_3$ solution (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 90:10) to give compound **55** (1.29 g, 2.53 mmol) as a colorless oil in 70% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.07 (s, 3 H), 0.06 (s, 3 H), 0.89 (s, 9 H), 1.35 (s, 3 H), 1.40 (s, 3 H), 2.01–2.10 (m, 1 H), 2.12–2.33 (m, 1 H), 3.72 (s, 3 H), 3.82 (s, 2 H), 4.02 (dd, J = 6.4, 4.4 Hz, 1 H), 5.85 (dt, J = 14.3, 1.4 Hz, 1 H), 6.25 (ddd, J = 14.3, 8.2, 6.9 Hz, 1 H), 7.04 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.4, –3.5, 18.3, 24.2, 26.1, 26.5, 37.1, 40.6, 46.1, 52.2, 76.4, 78.1, 115.5, 144.0, 148.0, 171.1, 177.8 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2953, 2929, 2856, 1744, 1522, 1471, 1435, 1361, 1255, 1093, 1046, 837, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{33}INO_2SSi$ [M + H]$^+$ 482.1040; found 482.1031.

(*E*)-2-(2-{3-[(*tert*-Butyldimethylsilyl)oxy]-6-iodo-2-methylhex-5-en-2-yl}thiazol-4-yl)ethanol (56): A solution of ester **55** (1.29 g, 2.53 mmol) in anhydrous Et_2O (10 mL) was added to a solution of $LiAlH_4$ (192 mg, 5.06 mmol) in anhydrous Et_2O (15 mL) at 0 °C under argon. After stirring for 1 h at room temperature, water (192 μL), a 2 M NaOH solution (192 μL), and water (384 μL) were added at 0 °C. After stirring for 1 h at room temperature, the aluminium salts were filtered off and the filtrate was concentrated in vacuo to give thiazole **56** (1.20 g, 2.50 mmol), which was used without further purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.06 (s, 3 H), 0.06 (s, 3 H), 0.90 (s, 9 H), 1.29 (s, 3 H), 1.34 (s, 3 H), 2.05–2.14 (m, 1 H), 2.17–2.34 (m, 1 H), 2.96 (t, J = 5.2 Hz, 2 H), 3.87–3.98 (m, 3 H), 5.85 (dd, J = 14.6, 1.3 Hz, 1 H), 6.28 (ddd, J = 14.6, 8.2, 6.9 Hz, 1 H), 6.84 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.5, –3.5, 18.3, 24.7, 26.1, 26.3, 33.6, 40.5, 46.1, 62.3, 76.3, 78.2, 113.6, 143.6, 154.1, 178.2 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3394, 2929, 1522, 1473, 1256, 1094, 957, 837, 775, 739 cm^{-1}.

***tert*-Butyl 4-[(4-Methoxybenzyl)oxy]-2-oxobutanoate (57):** A solution of olefin **60** (246 mg, 0.84 mmol) was treated as reported for the synthesis of compound **51** from **54** to give keto ester **57** (93 mg, 0.31 mmol) in 37% isolated yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 9 H), 3.03 (t, J = 6.2 Hz, 2 H), 3.73 (t, J = 6.2 Hz, 2 H), 3.77 (s, 3 H), 4.42 (s, 2 H), 6.83 (d, J = 8.7 Hz, 2 H), 7.22 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 39.6, 55.3, 64.2, 72.9, 83.9, 113.8, 129.3, 130.0, 159.3, 160.2, 193.6 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2978, 2933, 2862, 1742, 1723, 1614, 1515, 1463, 1370, 1248, 1173, 1098, 1033 cm^{-1}. In agreement with reported data.[57]

***tert*-Butyl (*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-7-{4-[2-(*tert*-butyldimethylsilyloxy)ethyl]thiazol-2-yl}-2-hydroxy-2-{2-[(4-methoxybenzyl)oxy]ethyl}-7-methyloct-3-enoate (58):** A solution of **49** (91 mg, 0.152 mmol) in anhydrous Et_2O (1.5 mL) was treated at –78 °C with *n*BuLi (1.2 M in heptanes, 180 μmol) and stirred at this temperature for 1 h before the dropwise addition of keto ester **57** (90 mg, 0.3 mmol). After an additional 1.5 h of stirring at –78 °C, the solution was quenched with a saturated NH_4Cl solution (2 mL). The reaction mixture was allowed to warm to room temperature and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 95:5) to give compound **58** (39 mg, 64 μmol) as a colorless oil in 42% isolated yield (two diastereoisomers, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.11 (s, 3 H), 0.00 (s, 6 H), 0.04 (s, 3 H), 0.87 (s, 18 H), 1.34 (s, 3 H), 1.40 (s, 3 H), 1.43 (s, 9 H), 1.84–1.93 (m, 1 H), 2.05–2.17 (m, 2 H), 2.24–2.33 (m, 1 H), 2.97 (t, J = 6.5 Hz, 2 H), 3.50–3.58 (m, 3 H), 3.81 (s, 3 H), 3.92 (t, J = 6.5 Hz, 2 H), 4.04 (br. s, 1 H), 4.39 (s, 2 H), 5.46 (dd, J = 15.4, 3.9 Hz, 1 H), 5.86 (dt, J = 15.4, 6.9 Hz, 1 H), 6.83 (s, 1 H), 6.84 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $C6D_6$): δ = –5.0, –4.4, –3.3, 18.5, 25.4, 25.9, 26.3, 28.2, 30.0, 35.3, 37.4, 38.7, 38.9, 46.7, 55.6, 62.6, 66.0, 73.2, 79.2, 82.8, 114.1, 120.4, 128.6, 129.8, 130.6, 133.5, 159.5, 174.4 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3412, 2929, 2857, 1722, 1514, 1463, 1250, 1098, 836, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{40}H_{70}NO_7SSi_2$ [M + H]$^+$ 764.4409; found 764.4406.

4-[(4-Methoxybenzyl)oxy]-2-methylenebutanoic Acid (59): A solution of aldehyde **50** (865 mg, 3.93 mmol) in a mixture of THF/H_2O/*t*BuOH (4:4:1, 90 mL) was treated at 0 °C with 2-methyl-2-butene (10 mL, 94.1 mmol), NaH_2PO_4 (3.77 g, 31.4 mmol), and $NaClO_2$ (1.77 g, 15.7 mmol) and stirred for 4 h at room temperature. A saturated NH_4Cl solution (50 mL) was added. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the resulting organic layers were washed with a saturated $NaHCO_3$ solution (3 × 50 mL). The basic aqueous layers were washed with EtOAc (3 × 20 mL) and then acidified with 1 M HCl (50 mL). The acidic aqueous phase thus obtained was extracted with EtOAc (3 × 50 mL). The organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to give acid **59** (656 mg, 2.77 mmol) in 71% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61 (t, J = 6.5 Hz, 2 H), 3.61 (t, J = 6.5 Hz, 2 H), 3.79 (s, 3 H), 4.46 (s, 2 H), 5.75 (s, 1 H), 6.35 (s, 1 H), 6.86 (d, J = 8.6 Hz, 2 H), 7.25 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 31.7, 55.2, 68.2, 72.4, 113.7, 128.8, 129.3, 130.1, 136.9, 159.1, 171.9 ppm. IR (film, NaCl): $\tilde{\nu}$ = 3050, 2936, 1698, 1613, 1514, 1442, 1249, 1173, 1095, 1035 cm^{-1}. In agreement with reported data[58]

***tert*-Butyl 4-[(4-Methoxybenzyl)oxy]-2-methylenebutanoate (60):** A solution of acid **59** (522 mg, 2.21 mmol) in *t*BuOH (10 mL) was treated at 0 °C with Boc_2O (1.01 g, 4.64 mmol) and DMAP (81 mg, 0.66 mmol) and stirred at room temperature for 8 h. After evaporation of the solvent, the residue was diluted in Et_2O (10 mL) and brine (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL) and the resulting organic layers washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 95:5) to give ester **60** (300 mg, 1.02 mmol) as a colorless oil in 46% isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 9 H), 2.62 (t, *J* = 6.7 Hz, 2 H), 3.61 (t, *J* = 6.7 Hz, 2 H), 3.81 (s, 3 H), 4.47 (s, 2 H), 5.57 (s, 1 H), 6.15 (s, 1 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 7.27 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0, 32.3, 55.1, 68.4, 72.4, 80.4, 113.7, 125.3, 129.1, 130.5, 139.0, 159.1, 166.1 ppm. IR (film, NaCl): $\tilde{\nu}$ = 2978, 2934, 2857, 1713, 1613, 1514, 1367, 1249, 1151, 1098 cm^{-1}. In agreement with reported data.[59]

***tert*-Butyl 2-(2-{3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylhex-5-en-2-yl}-4-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}thiazol-5-yl)-2-hydroxy-4-[(4-methoxybenzyl)oxy]butanoate (61):** A solution of **49** (33 mg, 55 μmol) in anhydrous THF (0.5 mL) was treated at –78 °C with *n*BuLi (1.2 M in heptanes, 61 μmol) and the mixture was stirred at this temperature for 1 h before the dropwise addition of keto ester **57** (32 mg, 110 μmol). After an additional 1.5 h of stirring at –78 °C, the solution was quenched with a saturated NH_4Cl solution (2 mL). The reaction mixture was allowed to warm to room temperature and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 95:5) to give compound **61** (26 mg, 34 μmol) as a colorless oil in 61% isolated yield as a 1:1 mixture of diastereoisomers. ^1H NMR (300 MHz, $CDCl_3$): δ = –0.12–0.04 (m, 9 H), 0.82–0.89 (m, 15 H, H), 1.38–1.43 (m, 21 H), 1.99–2.13 (m, 1 H), 2.20–2.39 (m, 2 H), 2.49–2.64 (m, 1 H), 2.99–3.16 (m, 2 H), 3.52 (t, *J* = 6.7 Hz, 1 H), 3.62 (t, *J* = 6.7 Hz, 1 H), 3.80 (s, 3 H), 3.89 (t, *J* = 6.5 Hz, 2 H), 3.96–4.04 (m, 1 H), 4.41 (s, 2 H), 4.85 (m, 2 H), 5.67 (m, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 6.98 (s, OH), 7.24 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3, –5.2, –4.3, –4.2, –3.4, 18.4, 18.6, 21.3, 23.0, 24.4, 25.5, 26.1, 26.2, 27.9, 28.1, 30.5, 38.8, 38.9, 39.7, 41.0, 46.2, 46.3, 55.4, 63.1, 65.7, 65.9, 72.9, 74.6, 74.7, 76.0, 77.3, 78.9, 113.9, 116.1, 125.7, 128.4, 129.6, 130.4, 135.9, 151.7, 159.3, 172.4 ppm. MS: (ESI) *m/z* = 764.2 (100) $[M + H]^+$, 786.2 (49) $[M + Na]^+$, 1549.7 (6) $[2M + Na]^+$. HRMS (ESI): calcd. for $C_{40}H_{69}NO_7SSi_2Na$ $[M + Na]^+$ 786.4235; found 786.4235.

(*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-7-(4-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}thiazol-2-yl)-2-hydroxy-2-{2-[(4-methoxybenzyl)oxy]ethyl}-7-methyloct-3-enal (64) and (*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-7-(4-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}thiazol-2-yl)-2-hydroxy-2-{2-[(4-methoxybenzyl)oxy]ethyl}-7-methyloct-3-ene-1,2-diol (65): A solution of hydroxy ester **58** (39 mg, 0.051 mmol) in anhydrous Et_2O (1 mL) was added to $LiAlH_4$ (5.8 mg, 0.15 mmol) covered with a minimum of Et_2O (300 μL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. Then H_2O (6 μL), 2.5 M NaOH (6 μL), and again H_2O (12 μL) were added and the solution stirred for an additional 20 min. A precipitate was thus formed, filtered, washed with Et_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 90:10) to give compound **64** (10 mg, 14.5 μmol, 28% isolated yield) and compound **65** (10 mg, 15 μmol, 28% isolated yield) as colorless oils, each as a 1:1 mixture of diastereoisomers. The same procedure applied again to the mixture led to 35% isolated yield of the diol.

Product 64: ^1H NMR (500 MHz, $CDCl_3$): δ = –0.1 (s, 3 H), –0.09 (s, 3 H), –0.01 (s, 6 H), 0.02 (s, 3 H), 0.04 (s, 3 H), 0.86 (s, 18 H), 1.25 (s, 3 H), 1.35 (s, 3 H), 1.43 (s, 3 H), 1.62 (m, 3 H), 1.79–1.85 (m, 1 H), 2.14–2.19 (m, 2 H), 2.27–2.29 (m, 1 H), 2.98 (m, 2 H), 3.47–3.55 (m, 2 H), 3.79 (s, 3 H), 3.91 (t, *J* = 6.5 Hz, 3 H), 4.04 (br. s, 1 H), 4.30 (q, *J* = 11.3 Hz, 2 H), 5.24–5.28 (m, 1 H), 5.75–5.82 (m, 1 H), 6.86 (d, *J* = 8.9 Hz, 2 H), 6.87 (s, 1 H), 7.18 (d, *J* = 8.9 Hz, 2 H), 9.32 (s, 1 H), 9.34 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.4, –4.6, –3.6, 18.2, 18.3, 25.9, 26.0, 36.7, 37.4, 46.2, 55.3, 62.2, 65.2, 72.9, 78.6, 79.7, 113.8, 128.9, 129.5, 129.8, 131.4, 153.1, 159.3, 177.5, 199.6 ppm. HRMS (ESI): calcd. for $C_{36}H_{62}NO_6SSi_2$ $[M + H]^+$ 692.3831; found 692.3828.

Product 65: ^1H NMR (300 MHz, $CDCl_3$): δ = –0.08 (s, 3 H), –0.01 (s, 6 H), 0.07 (s, 3 H), 0.85, 0.87, 0.88 (s, 18 H), 1.25 (s, 3 H), 1.38 (s, 3 H), 1.44 (s, 3 H), 1.55–1.63 (m, 3 H), 2.02–2.34 (m, 3 H), 2.99 (m, 2 H), 3.36 (s, 2 H), 3.49–3.67 (m, 2 H), 3.80 (s, 3 H), 3.91 (t, *J* = 6.5 Hz, 2 H), 4.40 (s, 2 H), 5.28–5.38 (m, 1 H), 5.70–5.80 (m, 1 H), 6.86 (d, *J* = 8.9 Hz, 2 H), 6.88 (s, 1 H), 7.18 (d, *J* = 8.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.0, –4.4, –4.3, –3.4, –3.3, 18.5, 18.6, 26.0, 26.2, 26.3, 30.1, 36.5, 36.6, 37.8, 38.0, 55.7, 67.0, 67.1, 69.4, 73.4, 75.4, 75.5, 78.1, 79.1, 114.3, 128.5, 129.8, 129.9, 130.1, 130.5, 134.8, 159.7 ppm. HRMS (ESI): calcd. for $C_{36}H_{64}NO_6SSi_2$ $[M + H]^+$ 694.3973; found 694.3987.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all new compounds.

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