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Reactivity of unsaturated sultones synthesized from unsaturated alcohols by ring-closing metathesis. Application to the racemic synthesis of the originally proposed structure of mycothiazole

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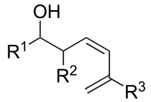
Abstract—Unsaturated sultones have been synthesized from various primary or secondary alkenols by ring-closing metathesis of the corresponding unsaturated sulfonates. By treatment with a strong base, β,γ-unsaturated sultones can be metalated and subsequently alkylated with electrophiles. When iodomethylmagnesium chloride was selected as the electrophile, seven-membered ring β,γ-unsaturated sultones were converted into homoallylic conjugated (*Z*)-dienols. This methodology was applied to the racemic synthesis of the originally proposed structure of the marine natural product mycothiazole.

1. Introduction

Homoallylic conjugated (*Z*)-dienols of type **A** (Fig. 1) and their derivatives are present in a variety of biologically active natural products such as palytoxin,[1] ostreocin,[2] discodermolide,[3] dictyostatin,[4] neodihydrohistrionicotoxin,[5] and mycothiazole.[6] As illustrated in the total synthesis of some of these natural products or in synthetic approaches, various strategies have been developed to synthesize conjugated (*Z*)-dienols of type **A** in a stereoselective manner (Scheme 1).



A

Figure 1. Structure of the homoallylic conjugated (*Z*)-dienols of type **A**.

A first approach involves palladium- or nickel-catalyzed cross-coupling reactions[7] between (*Z*)-alkenyl iodides (X=I)[8,9] or enol carbamates and triflates [X=OCON(*i*-Pr$_2$) or OTf][10] of type **B**, respectively, with an alkenyl metal of type **C** [route (a), Scheme 1]. The (*Z*)-alkenyl iodides of type **B** (X=I) can also undergo a Nozaki–Hiyama–Kishi coupling with an aldehyde (R^{3}CHO) followed by oxidation of the resulting allylic alcohol and subsequent methylenation of the carbonyl group [route (b), Scheme 1].[11] The (*Z*)-alkenyl iodides of type **B** are generally prepared from the aldehydes of type **D** by a Wittig olefination with (iodomethylene)triphenylphosphorane,[12] but the direct conversion of these latter aldehydes to the conjugated (*Z*)-dienols of type **A** can also be achieved by reaction with allylic organometallic species of type **E** such as an allyltitanium bearing a diphenylphosphanyl group (Z=PPh$_2$) and subsequent elimination of phosphine oxide,[13] or an allylchromium[14] or an allylborane[15] bearing a trimethylsilyl group (Z=SiMe$_3$) followed by Peterson elimination [route (c), Scheme 1].[16] Another strategy relies on a copper-promoted coupling of the alkynylsilane moiety in the homopropargylic alcohols of type **F** with vinyl iodide, followed by an intramolecular hydrosilylation of the carbon–carbon triple bond [route (d), Scheme 1].[17] As the reduction of lactones of type **G** followed by Wittig methylenation can provide access to subunits of type **A**, an alternative route has been developed from homoallylic alcohols of type **H** that relies on a ring-closing metathesis reaction (RCM) of the corresponding derived acrylates [route (e), Scheme 1].[18] Whereas a R^3 substituent (R$^3 \neq$H) can be introduced in the first two routes [routes (a) and (b), Scheme 1], the other strategies have only been reported for the synthesis of subunits of type **A** bearing a terminal olefin (R^3=H).

The development of an alternative complementary route to subunits of type **A** from homoallylic alcohols of type **H**[19] was considered that would rely on an unsaturated heterocyclic intermediate generated by RCM for the control of (*Z*) configuration of the α,β-disubstituted double bond and

Keywords: Ring-closing metathesis; Sultones; Conjugated dienes; Natural products.

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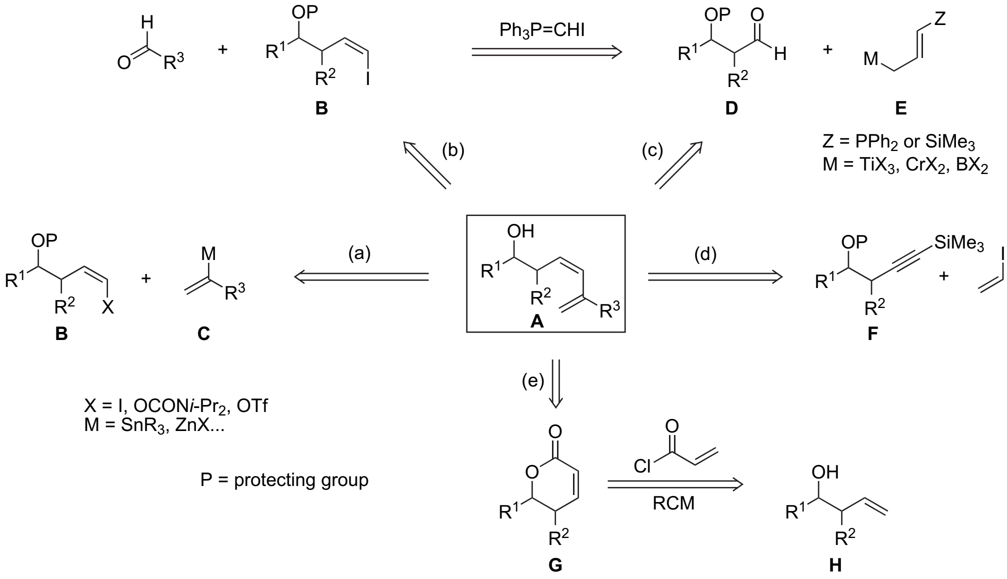
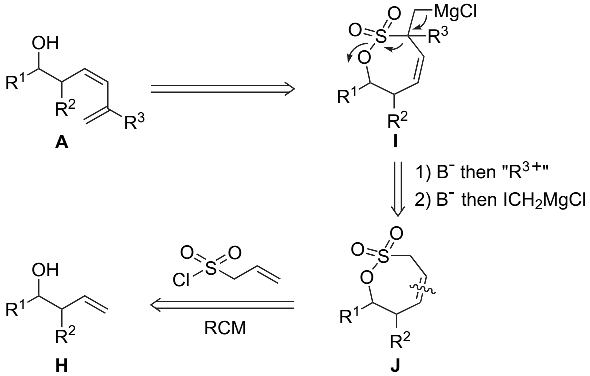


Scheme 1. Synthetic approaches toward homoallylic conjugated (*Z*)-dienols of type **A**.

would enable the introduction of a R^3 substituent. Based on literature precedents, subunits of type **A** should be generated from the β-metalated sultones of type **I** by β-elimination of the sulfonyl moiety and loss of sulfur dioxide.[20,21] Such intermediates of type **I** should be accessible from the unsaturated sultones of type **J** by sequential metalation and electrophilic trapping, first by an appropriate alkylating reagent containing the R^3 moiety and then with the carbenoid reagent ICH_2MgCl.[21] A RCM could be used to elaborate the unsaturated sultones of type **J** from the corresponding unsaturated sulfonates derived from homoallylic alcohols of type **H** (Scheme 2).



Scheme 2. Synthesis of subunits of type **A** from unsaturated sultones.

Herein, we would like to report a full account of our results concerning the synthesis of unsaturated sultones by RCM, their subsequent transformation to homoallylic conjugated (*Z*)-dienols of type **A** as well as the application of this methodology to the racemic synthesis of the originally proposed structure of the marine natural product mycothiazole.

2. Synthesis of unsaturated sultones by RCM

The RCM catalyzed by ruthenium–carbene complexes is a particularly attractive strategy for the synthesis of unsaturated carbocycles as well as oxygen, nitrogen, or phosphorous containing heterocycles that would be difficult to obtain by other routes.[22] When we initially started our investigations on this subject, the preparation of unsaturated sultones by RCM had not been described, although the synthesis of sulfur-containing heterocycles by this strategy had already been the subject of several reports.[23] Thus, it was initially reported that, unlike the more reactive Schrock's molybdenum carbene catalyst, the ruthenium–carbene complex **I**,[24] the so-called first generation Grubbs' catalyst (Fig. 2) was not suitable for the generation of cyclic sulfides due to its poisoning by low-valent organosulfur compounds.[25,26] However, it was later demonstrated that the second generation ruthenium catalysts bearing an *N*-heterocyclic carbene (such as **II** or its dehydro analogue) could be used successfully in some cases, depending on the substitution pattern of the substrates.[27] However, the ruthenium catalysts are compatible with the higher oxidation states of the sulfur atom as illustrated by the numerous reports concerning the synthesis of unsaturated sulfoxides,[28] sulfones,[29] sulfonamides,[30] and sulfamides[31] by RCM using the ruthenium–carbene catalysts **I** or **II** (Fig. 2).

In order to demonstrate that a variety of sultones could be generated by RCM, and not only those of type **J** required for our synthetic approach toward homoallylic conjugated (*Z*)-dienols of type **A**, a variety of primary alkenols were treated with vinyl-, allyl-, or homoallylsulfonyl chlorides[32] in the presence of Et_3N (CH_2Cl_2, 0 °C to rt) to generate the corresponding primary unsaturated sulfonates **1a–f** (40–90%). These sulfonates underwent a RCM in the

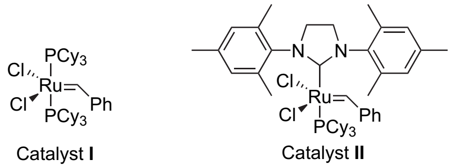
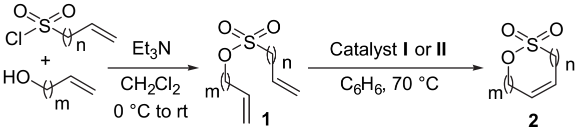
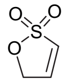
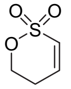
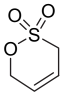
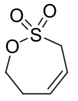
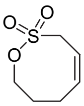
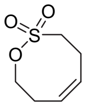


Figure 2. RCM catalysts.

Table 1. Synthesis of unsaturated sultones from primary alkenols

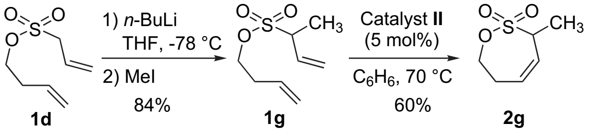


m	*n*	Sulfonate **1** (yield%)	Sultone **2** (yield%)
1	0	**1a** (40)	 **2a** (100)
2	0	**1b** (87)	 **2b** (90)
1	1	**1c** (76)	 **2c** (51)[a] (99)
2	1	**1d** (90)	 **2d** (60)[a] (100)
3	1	**1e** (83)	 **2e** (94)[a]
2	2	**1f** (90)	 **2f** (99)[a] (51)

[a] Yields refer to the use of catalyst **I**.

presence of catalyst **I** or **II** (C_6H_6, 70 °C) and the corresponding unsaturated sultones **2a–f** were obtained in good to virtually quantitative yields (Table 1). The second generation catalyst **II**, which is less sensitive to steric and electronic effects compared to catalyst **I**,[24] was used to achieve the RCM of the unsaturated sulfonates **1a** and **1b**, which provided the corresponding α,β-unsaturated five- and six-membered ring sultones **2a** (100%) and **2b** (90%), respectively. It was observed that catalyst **I** was considerably less efficient than catalyst **II** for the formation of the six- and seven-membered ring β,γ-unsaturated sultones **2c** (51% compared to 99%) and **2d** (60% compared to 100%), respectively. Similar results were disclosed, prior to our first report, by Metz and co-workers who achieved the formation of five- to nine-membered and fifteen-membered ring sultones from primary unsaturated sulfonates using catalyst **II** in refluxing CH_2Cl_2.[33] Despite the well-known difficulties associated with the formation of medium-size rings by RCM, we observed that the less reactive catalyst **I** was particularly efficient in promoting the RCM reaction of the unsaturated sulfonates **1e** and **1f** leading to the eight-membered ring sultones **2e** (94%) and **2f** (99%), respectively, whereas the latter was obtained in considerably lower yield (51%) when catalyst **II** was employed (Table 1).[34]

It was also demonstrated that primary unsaturated sulfonates could be substituted prior to RCM. Thus, the sulfonate **1d** was metalated by treatment with *n*-BuLi in THF at −78 °C[35] and subsequent addition of methyl iodide regioselectively afforded the α-substituted sulfonate **1g** in good yield (84%). After treatment with catalyst **II** (C_6H_6, 70 °C), the α-methyl-β,γ-unsaturated seven-membered ring sultone **2g** (60%) was produced (Scheme 3).

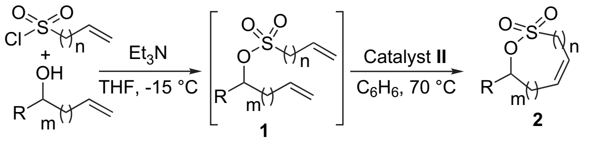


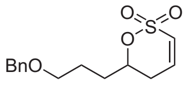
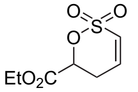
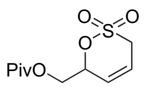
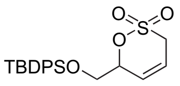
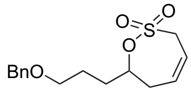
Scheme 3. Alkylation of acyclic unsaturated sulfonates.

The synthesis of unsaturated sultones derived from secondary alkenols was next investigated. It turned out that the sulfonates **1h–l** derived from secondary allylic or homoallylic alcohols were considerably less stable than those derived from primary ones, but their preparation could be achieved by reaction with vinyl or allylsulfonyl chlorides in the presence of Et_3N in THF at −15 °C.[36] The latter solvent provided better results than CH_2Cl_2 presumably because of the lower solubility of triethylamine hydrochloride, which may be responsible for side reactions. Nevertheless, the crude intermediate secondary sulfonates **1h–l** were not purified and immediately treated with catalyst **II** in C_6H_6 at 70 °C. Under these conditions, the corresponding functionalized α,β- or β,γ-unsaturated sultones **2h–l** were obtained in satisfactory overall yields (54–76%) from the corresponding secondary alkenols (Table 2).

These results demonstrate that a wide variety of sultones can be easily synthesized by RCM of the corresponding sulfonates derived from either primary or secondary alkenols.[33,34] The unsaturated sultones **2** should constitute interesting heterocyclic building blocks in organic synthesis since they possess multiple sites of reactivity.[37,38]

Table 2. Synthesis of unsaturated sultones from secondary alkenols

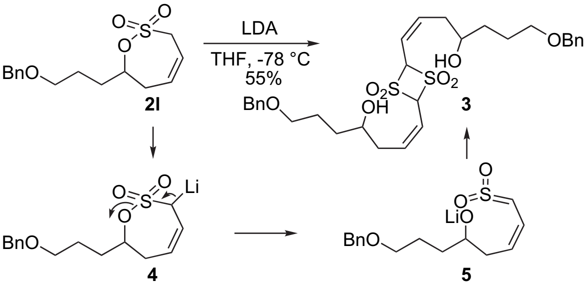


m	*n*	R		Sultones **2** (yield%)
1	0	$(CH_2)_3OBn$	**1h**	 **2h** (76)
1	0	CO_2Et	**1i**	 **2i** (54)
0	1	CH_2OPiv	**1j**	 **2j** (74)
0	1	$CH_2OTBDPS$	**1k**	 **2k** (65)
1	1	$(CH_2)_3OBn$	**1l**	 **2l** (65)

Following our initial goal, the transformation of the β,γ-unsaturated seven-membered ring sultones of type **J** such as **2d** and **2l** into homoallylic conjugated (*Z*)-dienols of type **A** was investigated (Scheme 2). This operation implies that these unsaturated sultones should be metalated at the α-position of the sulfonyl moiety and functionalized by reaction with appropriate electrophiles.

3. Synthesis of conjugated (*Z*)-dienols of type A

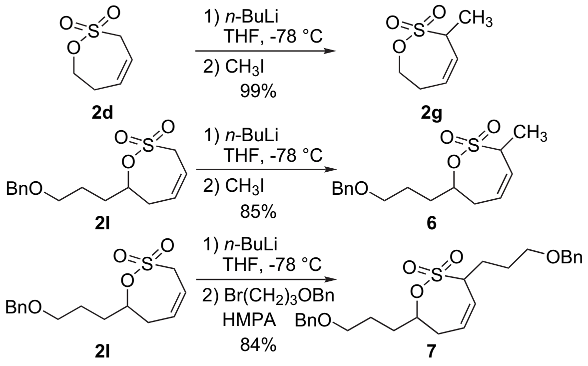
Sultones can be metalated at the α-position of the sulfonyl group using a strong base such as an alkyllithium reagent.[39] In the case of β,γ-unsaturated sultones of type **J**, the acidity of the hydrogens at the α-position should be improved compared to the saturated analogues, and the use of a milder base such as LDA was considered for achieving the metalation. However, when sultone **2l** was treated with LDA in THF at −78 °C, the formation of the 1,3-dithietane tetraoxide **3** took place rapidly prior to the introduction of any electrophilic agent. The latter compound was isolated in 55% yield in the apparent form of a 60:40 mixture of *trans*/*cis*-diastereomers (unassigned relative configuration) bearing double bonds of (*Z*) configuration, as indicated by the analysis of the ^{1}H NMR spectrum. The formation of **3** may be explained by the transformation of the α-lithiated sultone **4** into the corresponding sulfene **5** that dimerized under these conditions to **3** (Scheme 4).[40]



Scheme 4. Metalation of sultone **2l** with LDA.

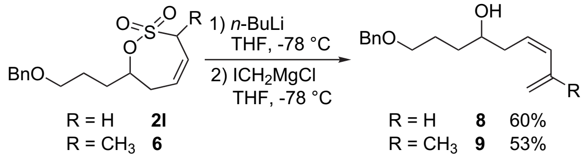
Fortunately, this side-reaction was not observed when sultone **2l** was metalated with *n*-BuLi in THF at −78 °C and subsequent addition of methyl iodide cleanly provided the α-methyl β,γ-unsaturated seven-membered ring sultone **6** in 85% yield as a single diastereomer (unassigned relative configuration) (Scheme 5). Although, the different behavior of the α-lithiated sultone **4** under these two sets of experimental conditions has not been fully elucidated, it appeared obvious that the presence of excess LDA and/or diisopropylamine modified the reactivity of the carbon–lithium bond in the latter species and was responsible for its transformation to sulfene **5**. Indeed, when **2l** was metalated with an excess of *n*-BuLi, the subsequent addition of diisopropylamine also triggered the formation of 1,3-dithietane tetraoxide **3**.

Metalation of sultone **2d** derived from a primary alkenol with *n*-BuLi in THF at −78 °C followed by addition of methyl iodide afforded α-methylated sultone **2g**, a substrate that was previously synthesized by alkylation of the acyclic sulfonate **1d** and subsequent RCM (Scheme 3). Besides methyl iodide, other less reactive alkylating agents such as the alkyl bromide $Br(CH_2)_3OBn$ could be used successfully provided that the polar co-solvent HMPA was added. Under these conditions, sultone **2l** was effectively converted into the α-alkylated sultone **7** (84%, single diastereomer of unassigned relative configuration) (Scheme 5).



Scheme 5. Alkylation of sultones **2d** and **2l**.

In order to demonstrate that conjugated (*Z*)-dienols of type **A** could be generated from unsaturated sultones of type **J**, substrates **2l** and **6** were metalated with *n*-BuLi in THF at −78 °C and the resulting organolithium reagents were alkylated with ICH_2MgCl[41] (generated from CH_2I_2 and *i*-PrMgCl, THF, −78 °C). As anticipated, this carbenoid reagent behaved as an electrophilic species and the Grignard reagents initially generated by this alkylation reaction underwent β-elimination and loss of sulfur dioxide to deliver the homoallylic alcohols **8** (60%) and **9** (53%) bearing a 1,3-diene unit with an internal (*Z*)-disubstituted double bond and either a terminal or an α,α-disubstituted olefin, respectively (Scheme 6).



Scheme 6. Synthesis of the conjugated (*Z*)-dienols of type **A**.

Having demonstrated that conjugated (*Z*)-dienols of type **A** could be synthesized from homoallylic alcohols, we envisaged to highlight the interest of this methodology by its application to the total synthesis of biologically active natural products. In order to fully benefit from the intermediacy of an unsaturated sultone in this strategy, natural products bearing a subunit of type **A** with an α,α-disubstituted double bond appeared rather interesting targets and the marine natural product mycothiazole was selected.

4. Total synthesis of the originally proposed structure of mycothiazole

Over the past few years, natural products of marine origin have continued to be of interest due to their wide spectrum of biological and pharmacological properties. Mycothiazole was first isolated in 1988 from the marine sponge *Spongia mycofijiensis* collected from the Vanuatu islands.[6] Its presence was also detected recently in the extracts of another

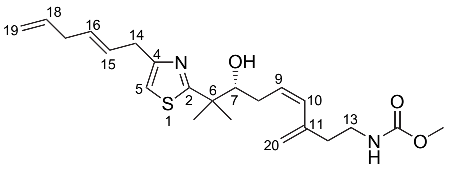


Figure 3. Originally proposed structure of (−)-mycothiazole.

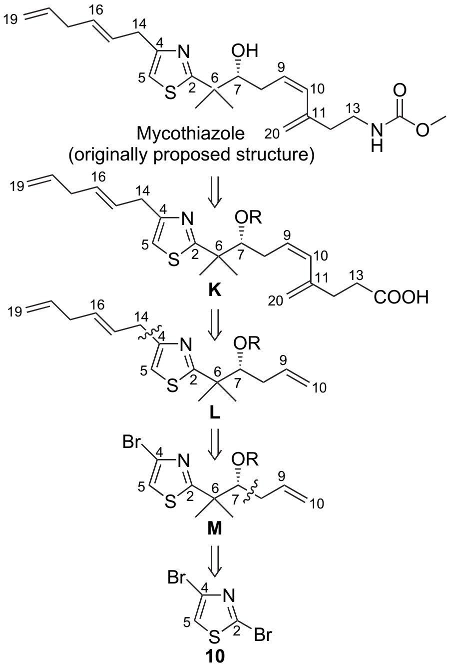
marine sponge of the genus *Dactylospongia*.[42] Mycothiazole was found to exhibit an antihelminthic activity in vitro.[6] Moreover, screening assays by the National Cancer Institute (NCI) in the United States indicated that mycothiazole exhibits a rather selective toxicity against a small cell lung cancer line.[43] The originally proposed structure of mycothiazole was established after extensive NMR analysis and confirmed by the exhaustive interpretation of a HREIMS spectrum (Fig. 3).[6] The synthesis and biological evaluation of simplified analogues of mycothiazole are still currently being investigated.[44]

The main structural feature of this natural product is a 2,4-disubstituted thiazole ring, which is embedded between two acyclic dienic side chains. The C2 side-chain includes a nitrogen substituent at C13 (methyl carbamate), a conjugated diene moiety consisting of a (*Z*)-disubstituted double bond (C9–C10) and a methylene group (C11–C20), a quaternary carbon at C6 substituted by a *gem*-dimethyl group, and a secondary alcohol at C7 that constitutes the unique stereocenter of mycothiazole having a (*R*) configuration. The C4 substituent is a 2,5-hexadienyl chain containing a disubstituted double bond (C15–C16) to which an (*E*) configuration was originally assigned and a terminal olefin (C18–C19). A conjugated (*Z*)-dienol subunit of type **A** is easily recognized in the C7–C11 fragment of this natural product.[45]

The first total synthesis of the proposed structure of mycothiazole features the formation of the thiazole ring by condensation of L-cysteine methyl ester with a carboxylic acid followed by oxidation with activated MnO_2 to form the 2,4-disubstituted thiazole, an enantioselective aldol condensation for the control of configuration at the C7 stereocenter, and the stepwise construction of the 2,5-hexadienyl side-chain at C4 by two sequential Stille coupling reactions (C15–C14 and C17–C18 bond formation). A third Stille coupling enabled the construction of the C10–C11 bond and hence the elaboration of the subunit of type **A** [according to route (a), Scheme 1].[9] The assignment of the (*R*) absolute configuration to mycothiazole was based on the comparison of the signs of optical rotations of the synthetic sample and the natural product. The discrepancies observed between the values were attributed to the lability of mycothiazole upon storage.[9] Synthetic approaches have also been reported toward a C4–C7 subunit containing the 2,4-disubstituted thiazole[46] and the C8–C13 fragment containing the conjugated diene by an ene–yne cross-metathesis, which occurred without stereoselectivity.[47,48]

4.1. Retrosynthetic analysis

In our retrosynthetic analysis of the originally proposed structure of mycothiazole, the installation of the methyl carbamate at C13 was envisaged by a Schmidt reaction applied to the carboxylic acid of type **K**. The key stage would be the elaboration of the conjugated (*Z*)-dienol moiety in compound **K** from the corresponding homoallylic alcohol derivative of type **L**, through an intermediate sultone, using the previously described strategy. The introduction of the side-chain at C4 in compound **L** should be achieved from the substituted 4-bromothiazole of type **M**. In this latter compound, the secondary homoallylic alcohol at C7 would be created by allylation of an intermediate aldehyde whose preparation was envisaged from the readily available 2,4-dibromothiazole **10**[49] (Scheme 7).



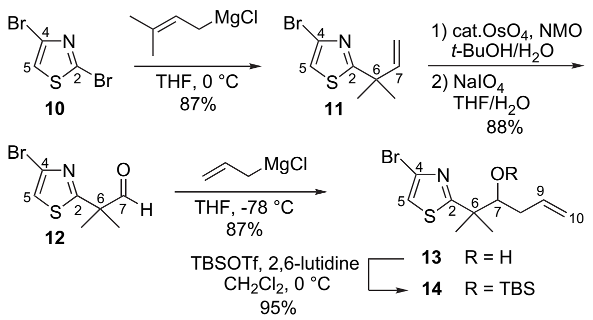
Scheme 7. Retrosynthetic analysis.

The selection of this latter compound as a starting material would also be potentially attractive for the synthesis of structural analogues of the natural product bearing a different side-chain at C4.

4.2. Synthesis of the C4–C10 subunit

Our synthesis of the originally proposed structure of mycothiazole first required the chemoselective substitution of bromine at C2 in 2,4-dibromothiazole **10**. Prenylmagnesium chloride chemoselectively reacted with **10** in THF at 0 °C with complete allylic transposition (S_E2' process)[50] to produce 2,4-disubstituted thiazole **11** (87%). The terminal olefin in compound **11** was subjected to a dihydroxylation (cat. OsO_4, NMO, *t*-BuOH/H_2O) and the resulting intermediate 1,2-diol was not purified but underwent an oxidative cleavage with $NaIO_4$ in THF/H_2O to afford aldehyde **12** (88%). This compound was treated with allylmagnesium bromide and the resulting secondary alcohol **13** (87%) was protected as a *tert*-butyldimethylsilyl ether (TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C) to produce compound **14** (95%) containing the C4–C10 subunit of mycothiazole (Scheme 8).

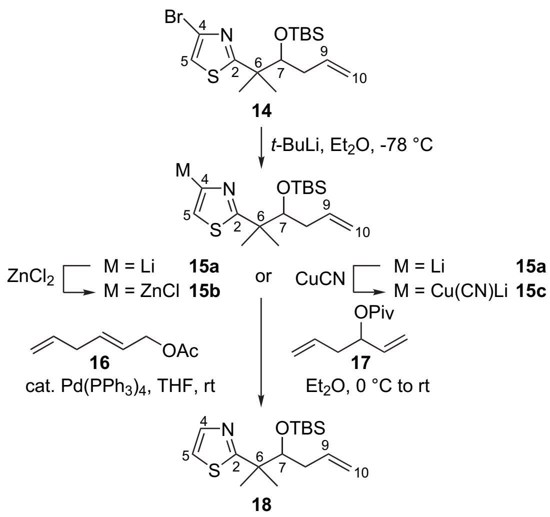
The next task was to install the 2,5-hexadienyl side-chain at C4 on the thiazole ring.



Scheme 8. Synthesis of the C4–C10 subunit.

4.3. Installation of the unsaturated side-chain at C4

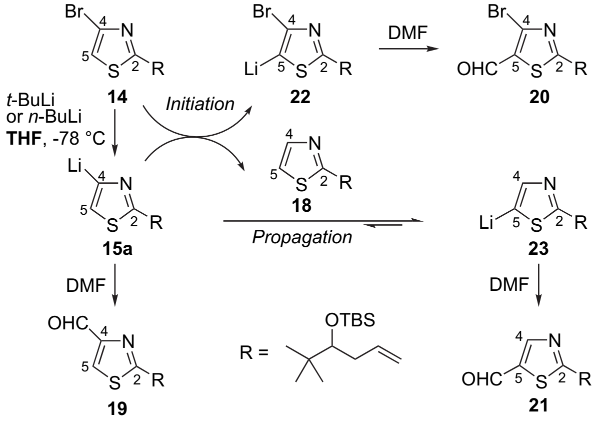
Our initial plan was to create the C4–C14 bond by a cross-coupling reaction. Thus, the substituted 4-bromothiazole **14** underwent lithium–bromine exchange with *tert*-butyllithium in ether at −78 °C.[51] The corresponding organolithium reagent **15a** was transmetalated with zinc chloride, but the resulting organozinc reagent **15b** did not react with the allylic acetate **16**[52] in the presence of a catalytic amount of Pd(PPh$_3$)$_4$ in THF.[53] A transmetalation of **15a** with copper cyanide was also attempted but the resulting lower order cyanocuprate **15c** did not achieve the S_N2' substitution of the allylic ester **17**[54] and presumably decomposed upon warming to rt. In both cases, only the mono-substituted thiazole **18** resulting from the protonation of the carbon–metal bond at C4 was recovered after hydrolysis of the reaction mixture (Scheme 9).



Scheme 9. Attempts to form the C4–C14 bond.

These two initial unsuccessful attempts of introducing the side-chain at C4 by direct formation of the C4–C14 bond, although not optimized, led us to consider an alternative plan in which the 2,5-hexadienyl side-chain at C4 would be installed by the formation of the C14–C15 bond. This strategy required at first the homologation of the substituted 4-bromothiazole **14** and this operation was envisaged by the introduction of a formyl group at C4.

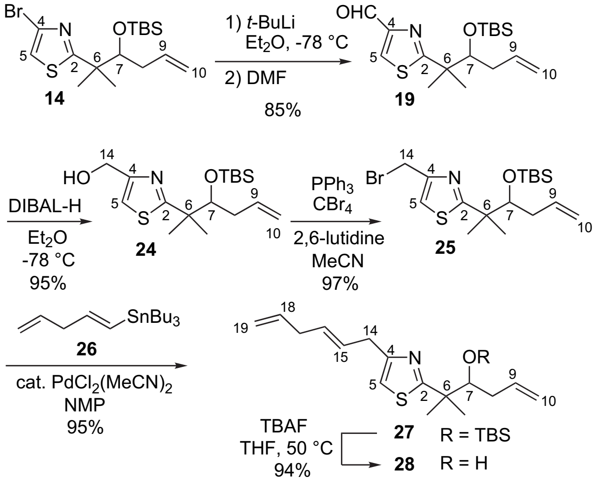
The substituted 4-bromothiazole **14** was subjected to lithium–bromine exchange with *tert*-butyllithium or *n*-butyllithium[51] but these reactions were initially inadvertently carried out in THF as the solvent. In this case, subsequent formylation with DMF afforded mixtures of products containing the desired disubstituted thiazole **19** formylated at C4 as the minor component, the mono-substituted thiazole **18**, the substituted 4-bromo-5-formylthiazole **20** as well as the corresponding regioisomeric thiazole **21** formylated at C5. The relative proportions of these compounds differ considerably from one experience to another and were presumably affected by the rate of addition of alkyllithium as well as the reaction time at −78 °C before DMF was introduced, although the aldehyde **21** (formyl group at C5) was clearly the major component (43–72% isolated yields) (Scheme 10).



Scheme 10. Lithium–bromine exchange of **14** carried out in THF.

Indeed, the order of acidity of the hydrogens on thiazoles is H2>H5>H4 and it is well-known that thiazol-4-yl metals are destabilized by the adjacent nitrogen atom's lone-pair effect, as in the imidazole series.[55] Thus, as the organolithium **15a** was gradually generated by lithium–bromine exchange of **14**, it may abstract a hydrogen at C5 on the parent bromide **14** and generate the protonated compound **18**, as well as the substituted 4-bromothiazol-5-yllithium **22**, which accounted for the formation of **20** after addition of DMF. The small amount of **18** generated during this initiation phase is then able to subsequently catalyze the equilibration of the organolithium **15a** at C4 to the thermodynamically more stable regioisomeric thiazol-5-yllithium **23** (Scheme 10).[56] This mechanism shares some similarities with the so-called 'halogen dance reaction' observed when 2-trimethylsilyl-4-bromothiazole was deprotonated with LDA, the propagation being ensured in this case by a 4,5-dibrominated thiazole preferentially undergoing Br–Li exchange at C5.[57] However, such an equilibration does not take place in ether as the organolithium **15a** displays a lower basic character in this less-coordinating solvent compared to THF. In fact, examination of literature results indicates that halogen–metal exchange reactions on 4-halothiazoles have been generally carried out in ether.[51]

Thus, the substituted 4-bromothiazole **14** underwent a clean lithium–bromine exchange with *tert*-butyllithium in ether at −78 °C[51] and subsequent formylation with DMF cleanly afforded aldehyde **19** (85%). Subsequent reduction (DIBAL-H, Et$_2$O, −78 °C) afforded the primary alcohol **24** (95%), which was treated with PPh$_3$ and CBr$_4$ in THF.[9] Under these conditions, the corresponding bromide **25** was obtained in modest yield (52%) due to a slow and incomplete reaction, despite the use of a large excess of reagents. When carried out in acetonitrile in the presence of 2,6-lutidine,[58] bromination of **20** proceeded considerably faster and led to **25** in excellent yield (97%). With the aim of installing the unsaturated side-chain of the originally proposed structure of mycothiazole at C4 in a single operation, the bromide **25** was subjected to a Stille coupling with (*E*)-1-tributylstannylpenta-1,4-diene **26**[59] in the presence of a catalytic amount of $PdCl_2(MeCN)_2$ in *N*-methylpyrrolidinone (NMP)[9] and the 1,4-diene **27** was obtained in 95% yield. Subsequent deprotection of the hindered hydroxyl group at C7 with TBAF in THF at 50 °C finally afforded the homoallylic alcohol **28** (94%) (Scheme 11).



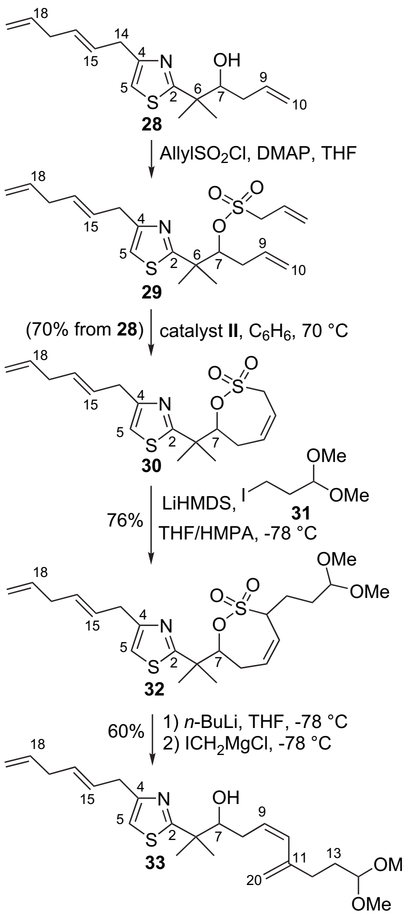
Scheme 11. Synthesis of the C10–C19 subunit.

With compound **28** in hand, the formation of the conjugated (*Z*)-dienol moiety (C9–C13 subunit), that constitutes the pivotal stage of our synthetic approach toward mycothiazole, could be tested.

4.4. Formation of the conjugated (*Z*)-dienol moiety

Following our synthetic plan, the elaboration of the conjugated (*Z*)-dienol moiety of mycothiazole from the homoallylic alcohol **28** required at first the preparation of the key intermediate unsaturated sultone **30**. The sterically hindered secondary alcohol **28** did not react with allylsulfonyl chloride in the presence of triethylamine in THF at rt, but switching to DMAP as the base enabled the synthesis of intermediate sulfonate **29**. The latter compound was not purified and underwent RCM by treatment with catalyst **II** (C_6H_6, 70 °C). Under these conditions, the unsaturated sultone **30** was obtained in 70% yield (two steps from alcohol **28**).

The next task was to alkylate the unsaturated sultone **30** with an appropriate electrophile, precursor of the (*N*-carbomethoxyamino)ethyl substituent (C12–C13) of mycothiazole. We selected the readily available 1,1-dimethoxy-3-iodopropane **31**[60] as the alkylating agent since the acetal moiety could then be deprotected to the aldehyde and the latter could be oxidized to the carboxylic acid required for the subsequent Schmidt reaction. The alkylation of sultone **30** with the functionalized alkyl iodide **31** turned out to be difficult to achieve since dialkylation was often observed as a side-reaction. After optimization, it was discovered that addition of LiHMDS to a mixture of sultone **30** and iodide **31** in the presence of HMPA (THF, −78 °C) cleanly afforded monoalkylated sultone **32** (76%) as a 1:1 mixture of diastereomers.[61] The sultone **32** was then efficiently deprotonated with *n*-butyllithium in THF at −78 °C and subsequent addition of ICH_2MgCl provided the desired conjugated (*Z*)-dienol **33** in 60% yield (Scheme 12).

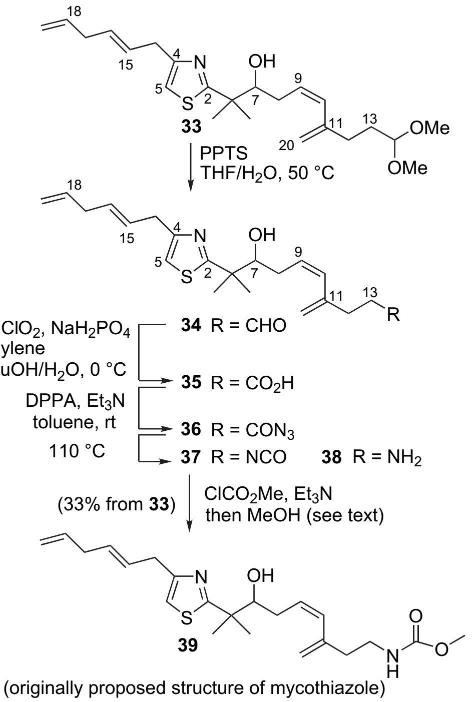


Scheme 12. Elaboration of the homoallylic conjugated (*Z*)-dienol.

Having successfully accomplished the key transformation of our synthesis, only functional group manipulations were required in order to complete the total synthesis of the originally proposed structure of mycothiazole.

4.5. Completion of the synthesis of the originally proposed structure of mycothiazole

Hydrolysis of the dimethyl acetal in compound **33** (PPTS, THF/H_2O, 50 °C) quantitatively afforded aldehyde **34**, which was not purified but directly chemoselectively oxidized by $NaClO_2$ in the presence of amylene and excess NaH_2PO_4 in *t*-BuOH/H_2O.[62] However, upon completion of the oxidation, acidification of the reaction mixture with hydrochloric acid should be absolutely avoided as the decomposition of the resulting carboxylic acid **35** occurred. This extremely sensitive compound could be in fact directly extracted from the reaction mixture with EtOAc and immediately treated with diphenylphosphoryl azide (DPPA) and Et_3N in toluene.[63] After formation of the acylazide **36**, the reaction mixture was heated at reflux in order to induce Curtius rearrangement to the corresponding isocyanate **37**. As the latter was apparently not readily converted into the proposed structure of mycothiazole when MeOH was added to the reaction mixture at reflux, we initially thought that **37** had probably accidentally hydrolyzed to amine **38**. However, the compound obtained after purification by preparative TLC on silica gel did not react with $ClCO_2Me$ in the presence of Et_3N. This result suggested that the rather robust isocyanate **37** had been isolated and therefore, the reaction mixture was treated with an excess of MeOH. Under these conditions, a surprisingly smooth methanolysis took place,[64] which produced compound **39** in 33% overall yield from dimethyl acetal **33** (four steps) (Scheme 13).



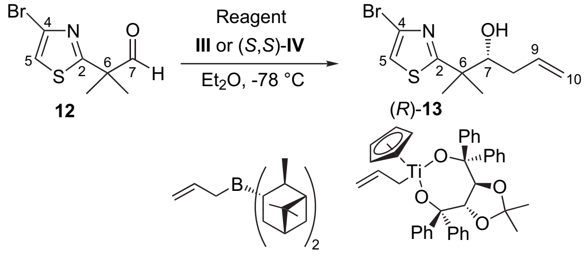
Scheme 13. Completion of the synthesis of the originally proposed structure of mycothiazole.

Although the ^1H NMR data of compound **39** were in good agreement with those previously reported for natural mycothiazole,[6] as well as for the synthetic material corresponding to the originally proposed structure [compound (−)-**39**],[9] the ^{13}C NMR data were only in perfect agreement with those of the synthetic material. Indeed, some discrepancies were noted between the chemical shifts of some carbons of the 2,5-hexadienyl side-chain at C4 and those reported for the natural product. In particular, signals corresponding to C14 and C17 (present numbering system) in compound **39** appeared significantly upfield. Differences between the observed analytical data of mycothiazole and the synthetic sample were initially attributed to the lability of the natural product,[6,9] but recently the configuration of the C14–C15 disubstituted double bond was reassigned to (*Z*) on the basis of a 600 MHz ^1H NMR spectrum and NOE experiments.[65]

We had thus completed a racemic synthesis of the originally proposed structure of mycothiazole and not of the natural product itself.[66]

4.6. Formal enantioselective approach

As mycothiazole contains a single stereocenter at C7, we investigated a formal enantioselective approach relying on the preparation of the optically active alcohol (*R*)-**13**. Thus, addition of the chiral allylic borane **III** [generated from allylmagnesium bromide and (+)-*B*-chlorodiisopinocampheyl borane ((+)-DIPCl)][67] to aldehyde **12** in ether at −78 °C led to the corresponding secondary homoallylic alcohol (*R*)-**13** (70%) with low optical purity (ee=54%). Although this result could have been probably optimized by modifying the reaction conditions, an enantioselective allyltitanation of aldehyde **12** with the allyltitanium complex (*S*,*S*)-**IV** [generated from allylmagnesium chloride and the corresponding ((*S*,*S*)-TADDOL)CpTiCl complex][68] in THF/Et_2O at −78 °C afforded (*R*)-**13** in much better yield and enantiomeric excess (82% yield, ee=99%) (Scheme 14).



Reagent	III	(*S*,*S*)-IV
Yield of (*R*)-**13**	70%	82%
ee of (*R*)-**13**	54%	99%

Scheme 14. Formal enantioselective approach.

The (*R*) configuration of the homoallylic alcohol **13** obtained from these reactions was attributed on the basis of the known face-selectivities of the chiral allylating reagents and particularly the allyltitanium complex **IV**, which displays an extremely high face-selectivity regardless of the nature of the aldehydes.[68]

5. Conclusion

In summary, unsaturated sultones have been generated from primary or secondary unsaturated alcohols by RCM of the corresponding unsaturated sulfonates. The β,γ-unsaturated seven-membered ring sultones have been converted to homoallylic conjugated (*Z*)-dienols by sequential metalation and electrophilic trapping, first with an alkyl halide and then with the carbenoid ICH_2MgCl. This methodology has been applied to the synthesis of originally proposed structure of (±)-mycothiazole, which has been achieved in 18 steps from 2,4-dibromothiazole with an overall yield of 5%. The side-chain at C2 was introduced in a stepwise fashion by using a chemoselective prenylation, an aldehyde allylation, a chain-extension of a homoallylic alcohol to a conjugated (*Z*)-dienol, proceeding through an intermediate unsaturated sultone, and a Curtius rearrangement. The installation of the side-chain at C4 was based on a one carbon homologation followed by a Stille coupling. A formal enantioselective approach has also been demonstrated with the preparation of the secondary homoallylic alcohol **13** in high enantiomeric purity (ee=99%). In principle, we could effectively access to mycothiazole by a similar strategy described herein, using

(*Z*)-1-tributylstannylpenta-1,4-diene[69] instead of its (*E*) geometric isomer in Stille coupling that served to elaborate the 2,5-hexadienyl side-chain at the C4 position of the thiazole ring.

6. Experimental

6.1. General procedures

IR spectra were recorded on a Perkin–Elmer 298. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ and data were reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or overlap of nonequivalent resonances), integration. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ and data were reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s=quaternary C, d=CH, t=CH_2, q=CH_3). THF and diethyl ether were distilled from sodium/benzophenone. CH_2Cl_2, benzene, toluene, Et_3N, NMP, *i*-Pr_2NEt, DMF, and HMPA were distilled from CaH_2. Other reagents were obtained from commercial suppliers and used as received. TLC was performed on silica gel plates visualized either with a UV lamp (254 nm), or by using solutions of *p*-anisaldehyde/sulfuric acid/acetic acid in EtOH or $KMnO_4$/K_2CO_3 in water followed by heating. Flash chromatography was performed on silica gel (230–400 mesh).

6.2. Synthesis of unsaturated sultones by RCM

6.2.1. Synthesis of unsaturated sulfonates derived from primary alcohols.

6.2.1.1. General procedure. To a solution of an unsaturated primary alcohol (1.0–1.1 equiv) and Et_3N (1.1–1.2 equiv) in CH_2Cl_2 (1 M) at 0 °C was added dropwise a solution of an unsaturated sulfonyl chloride (1.0 equiv) in CH_2Cl_2 (1 M). After 0.5 to 1 h at rt, the reaction mixture was diluted with pentane and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel.

6.2.1.2. Allyl vinylsulfonate (1a). This compound was prepared from allyl alcohol (300 μL, 4.35 mmol, 1.1 equiv), Et_3N (610 μL, 4.35 mmol, 1.1 equiv), and vinylsulfonyl chloride (500 mg, 3.95 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography, (petroleum ether/EtOAc 80:20), 150 mg (40%) of **1a** were obtained as a colorless oil; IR 3060, 1650, 1610, 1360, 1175, 940 (br), 920, 845, 810, 740 cm^{-1}; ^{1}H NMR δ 6.52 (dd, *J*=16.5, 9.5 Hz, 1H), 6.37 (d, *J*=16.5 Hz, 1H), 6.12 (d, *J*=9.5 Hz, 1H), 5.89 (ddt, *J*=17.3, 10.3, 5.9 Hz, 1H), 5.38 (dq, *J*=17.3, 1.5 Hz, 1H), 5.31 (dq, *J*=10.3, 1.5 Hz, 1H), 4.57 (dt, *J*=5.9, 1.5 Hz, 2H); ^{13}C NMR δ 132.5 (d), 130.2 (t), 130.1 (d), 120.5 (t), 71.0 (t).

6.2.1.3. But-3-enyl vinylsulfonate (1b). This compound was prepared from but-3-en-1-ol (360 μL, 4.15 mmol, 1.05 equiv), Et_3N (610 μL, 4.35 mmol, 1.1 equiv), and vinylsulfonyl chloride (500 mg, 3.95 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography (petroleum ether/EtOAc 80:20), 650 mg (87%) of **1b** were obtained as a colorless oil; IR 3060, 1640, 1360, 1175, 960, 910, 835, 800, 735 cm^{-1}; ^{1}H NMR δ 6.50 (dd, *J*=16.6, 9.9 Hz, 1H), 6.34 (d, *J*=16.6 Hz, 1H), 6.11 (d, *J*=9.9 Hz, 1H), 5.71 (ddt, *J*=16.9, 10.3, 6.6 Hz, 1H), 5.15–5.04 (m, 2H), 4.09 (t, *J*=6.6 Hz, 2H), 2.43 (apparent q, *J*=6.6 Hz, 2H); ^{13}C NMR δ 132.3 (d), 132.2 (d), 130.2 (t), 118.2 (t), 69.7 (t), 33.0 (t); EIMS *m*/*z* (relative intensity) 121 ($M-C_3H_5^+$, 31), 91 (100), 55 (13), 54 (69). Anal. Calcd for $C_6H_{10}O_3S$: C, 44.43; H, 6.21. Found: C, 44.26; H, 6.35.

6.2.1.4. Allyl allylsulfonate (1c). This compound was prepared from allyl alcohol (380 μL, 5.60 mmol, 1.05 equiv), Et_3N (820 μL, 5.90 mmol, 1.1 equiv), and allylsulfonyl chloride (750 mg, 5.30 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography (petroleum ether/EtOAc 70:30), 660 mg (76%) of **1c** were obtained as a colorless oil; IR 1640, 1355, 1160, 960, 940, 925, 880, 825 cm^{-1}; ^{1}H NMR δ 6.01–5.82 (m, 2H), 5.50–5.43 (m, 2H), 5.45 (dq, *J*=17.0, 1.5 Hz, 1H), 5.36 (dq, *J*=10.3, 1.1 Hz, 1H), 4.71 (dt, *J*=5.9, 1.5 Hz, 2H), 3.86 (dt, *J*=7.4, 1.1 Hz, 2H); ^{13}C NMR δ 130.4 (d), 124.3 (t and d, 2C), 120.4 (t), 70.9 (t), 55.0 (t); EIMS *m*/*z* (relative intensity) 121 ($M-C_3H_5^+$, 3), 106 (21), 97 (8), 83 (29), 81 (16), 80 (21), 79 (14), 69 (59), 67 (57), 57 (80), 56 (44), 55 (64), 54 (100). Anal. Calcd for $C_6H_{10}O_3S$: C, 44.43; H, 6.21. Found: C, 44.45; H, 6.24.

6.2.1.5. But-3-enyl allylsulfonate (1d). This compound was prepared from but-3-en-1-ol (485 μL, 5.60 mmol, 1.05 equiv), Et_3N (825 μL, 5.86 mmol, 1.1 equiv), and allylsulfonyl chloride (750 mg, 5.33 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography (petroleum ether/EtOAc 75:25), 850 mg (90%) of **1d** were obtained as a colorless oil; IR 3080, 1640, 1360, 1170, 960, 910, 820, 740, 640 cm^{-1}; ^{1}H NMR δ 5.88 (ddt, *J*=16.2, 10.6, 7.3 Hz, 1H), 5.76 (ddt, *J*=17.2, 10.3, 6.6 Hz, 1H), 5.48–5.40 (m, 2H), 5.19–5.09 (m, 2H), 4.25 (t, *J*=6.6 Hz, 2H), 3.82 (dt, *J*=7.3, 1.5 Hz, 2H), 2.47 (apparent qt, *J*=6.6, 1.3 Hz, 2H); ^{13}C NMR δ 132.3 (d), 124.3 (d), 124.0 (t), 118.0 (t), 69.4 (t), 54.3 (t), 33.2 (t). Anal. Calcd for $C_7H_{12}O_3S$: C, 47.71; H, 6.86. Found: C, 47.81; H, 6.94.

6.2.1.6. Pent-4-enyl allylsulfonate (1e). This compound was prepared from pent-4-en-1-ol (400 μL, 3.92 mmol, 1.1 equiv), Et_3N (600 μL, 4.27 mmol, 1.2 equiv), and allylsulfonyl chloride (500 mg, 3.56 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography (petroleum ether/EtOAc 90:10 to 80:20), 560 mg (83%) of **1e** were obtained as a colorless oil; IR 3070, 1640, 1350, 1160, 970, 920, 830, 640 cm^{-1}; ^{1}H NMR δ 5.86 (ddt, *J*=16.9, 9.9, 7.3 Hz, 1H), 5.74 (ddt, *J*=16.9, 10.3, 6.6 Hz, 1H), 5.42 (dq, *J*=10.3, 1.5 Hz, 1H), 5.41 (dq, *J*=16.9, 1.5 Hz, 1H), 5.05–4.95 (m, 2H), 4.19 (t, *J*=6.6 Hz, 2H), 3.79 (dt, *J*=7.0, 1.1 Hz, 2H), 2.13 (m, 2H), 1.79 (m, 2H); ^{13}C NMR δ 136.5 (d), 124.4 (d), 124.1 (t), 115.7 (t), 69.9 (t), 54.5 (t), 29.2 (t), 28.2 (t). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42. Found: C, 50.36; H, 7.48.

6.2.1.7. But-4-enyl but-3-ene-1-sulfonate (1f). This compound was prepared from but-3-en-1-ol (0.85 mL, 9.8 mmol, 1.0 equiv), Et_3N (1.5 mL, 11 mmol, 1.1 equiv), and (but-3-enyl)sulfonyl chloride (1.5 g, 9.8 mmol, 1.0 equiv) according to the general procedure. After purification by flash chromatography (petroleum ether/EtOAc 70:30), 1.7 g (90%) of **1f** were obtained as a colorless oil; IR 3080, 1640, 1360, 1170, 1160, 955, 905, 825 cm^{-1}; ^{1}H NMR δ 5.84–5.67 (m, 2H), 5.16–5.04 (m, 4H), 4.20 (t, *J*=6.6 Hz, 2H), 3.15–3.09 (m, 2H), 2.58–2.49 (m, 2H), 2.49–2.40 (m, 2H); ^{13}C NMR δ 133.6 (d), 132.4 (d), 118.2 (t), 117.1 (t), 68.6 (t), 49.4 (t), 33.3 (t), 27.5 (t); EIMS *m*/*z* (relative intensity) 136 ($M-C_4H_6^+$, 0.5), 119 (6), 108 (3), 93 (4), 79 (3), 67 (5), 55 (100), 54 (80). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.41. Found: C, 50.20; H, 7.61.

6.2.2. Synthesis of unsaturated sultones derived from primary alcohols.

6.2.2.1. General procedure. To a degassed solution of an unsaturated sulfonate **1a–f** in C_6H_6 (0.05–0.01 M) (argon bubbling, 15 min) was added catalyst **I** or catalyst **II** (0.015–0.05 equiv) and the resulting solution was heated at 70 °C. After 0.5 to 3 h, the reaction mixture was cooled to rt, concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel.

6.2.2.2. 5*H*-[1,2]Oxathiole-2,2-dioxide (2a). This compound was prepared from **1a** (150 mg, 1.03 mmol) by using catalyst **II** (21 mg, 0.025 mmol, 0.025 equiv) in C_6H_6 (33 mL) at 70 °C for 1 h. After purification by flash chromatography (petroleum ether/EtOAc 70:30), 121 mg (100%) of **2a** were obtained as pale brown solid; mp 85 °C; IR 1610, 1345, 1180, 1090, 1000, 920, 870, 750 cm^{-1}; ^{1}H NMR δ 7.03 (dt, *J*=6.6, 2.0 Hz, 1H), 6.81 (dt, *J*=6.6, 2.4 Hz, 1H), 5.11 (dd, *J*=2.4, 2.0 Hz, 2H); ^{13}C NMR δ 136.8 (d), 124.3 (d), 72.2 (t); EIMS *m*/*z* (relative intensity) 120 (M$^+$, 40), 91 (24), 66 (100), 65 (28), 56 (10), 55 (11). Anal. Calcd for $C_3H_4O_3S$: C, 29.99; H, 3.36. Found: C, 30.10; H, 3.47.

6.2.2.3. 5,6-Dihydro-[1,2]oxathiine-2,2-dioxide (2b). This compound was prepared from **1b** (400 mg, 2.47 mmol) by using catalyst **II** (42 mg, 0.049 mmol, 0.02 equiv) in C_6H_6 (50 mL) at 70 °C for 3 h. After purification by flash chromatography (petroleum ether/EtOAc 60:40), 300 mg (90%) of **2b** were obtained as pale brown solid; mp 90 °C; IR 1620, 1355, 1345, 1180, 970, 920, 860, 825 cm^{-1}; ^{1}H NMR δ 6.60–6.49 (m, 2H), 4.79 (t, *J*=5.7 Hz, 2H), 2.57–2.51 (m, 2H); ^{13}C NMR δ 137.0 (d), 126.7 (d), 69.4 (t), 24.4 (t); EIMS *m*/*z* (relative intensity) 134 (M$^+$, 50), 104 (100), 76 (23), 70 (15), 69 (39), 68 (11), 55 (100). Anal. Calcd for $C_4H_6O_3S$: C, 35.81; H, 4.51. Found: C, 35.86; H, 4.65.

6.2.2.4. 3,6-Dihydro-[1,2]oxathiine-2,2-dioxide (2c). This compound was prepared from **1c** (400 mg, 2.50 mmol) by using catalyst **II** (52 mg, 0.06 mmol, 0.025 equiv) in C_6H_6 (82 mL) for 3 h at 70 °C. After purification by flash chromatography (petroleum ether/EtOAc 60:40), 335 mg (99%) of **2c** were obtained as a waxy beige solid; mp<50 °C; IR 1640, 1360, 1170, 1130, 1030, 940, 885, 860, 800, 720 cm^{-1}; ^{1}H NMR δ 5.95–5.88 (m, 1H), 5.84–5.77 (m, 1H), 5.07–5.03 (m, 2H), 3.82–3.78 (m, 2H); ^{13}C NMR δ 123.6 (d), 119.0 (d), 72.5 (t), 46.6 (t); EIMS *m*/*z* (relative intensity) 134 (M$^+$, 1), 70 ($M-SO_2^+$, 100), 69 (33), 65 (10), 54 (22), 53 (13); HRMS (CI$^+$, CH_4) calcd for $C_4H_7O_3S$ (M+H$^+$): 135.0116. Found: 135.0118.

6.2.2.5. 2,7-3*H*-Dihydro-[1,2]oxathiepine-2,2-dioxide (2d). This compound was prepared from **1d** (100 mg, 0.568 mmol) by using catalyst **II** (24 mg, 0.028 mmol, 0.02 equiv) in C_6H_6 (57 mL) for 2 h at 70 °C. After purification by flash chromatography (petroleum ether/EtOAc 75:25), 84 mg (100%) of **2d** were obtained as a pale brown solid; mp 78 °C; IR 1650, 1370, 1270, 1160, 975, 910, 880, 840, 805, 740 cm^{-1}; ^{1}H NMR δ 6.25–6.16 (m, 1H), 5.80–5.71 (m, 1H), 4.52–4.48 (m, 2H), 4.02 (apparent br d, *J*=6.2 Hz, 2H), 2.65 (m, 2H); ^{13}C NMR δ 134.8 (d), 119.4 (d), 72.5 (t), 51.1 (t), 28.8 (t); EIMS *m*/*z* (relative intensity) 148 (M$^+$, 1), 83 (4), 67 (100), 55 (18), 54 (87), 53 (14). Anal. Calcd for $C_5H_8O_3S$: C, 40.53; H, 5.44. Found: C, 40.61; H, 5.60.

6.2.2.6. 3,4,7,8-Tetrahydro-[1,2]oxathiocine-2,2-dioxide (2e). This compound was prepared from **1e** (150 mg, 0.788 mmol) by using catalyst **I** (33 mg, 0.040 mmol, 0.05 equiv) in C_6H_6 (75 mL) for 3 h at 70 °C. After purification by flash chromatography (petroleum ether/ether 95:5 to 90:10), 120 mg (94%) of **2e** were obtained as a pale brown waxy solid; mp<50 °C; IR 1650, 1380, 1275, 1265, 1250, 1150, 1060, 990, 945, 930, 820, 790, 760 cm^{-1}; ^{1}H NMR δ 6.03–5.93 (m, 1H), 5.77–5.69 (m, 1H), 4.36 (t, *J*=5.9 Hz, 2H), 3.91 (apparent dd, *J*=7.7, 0.8 Hz, 2H), 2.42–2.32 (m, 2H), 1.99–1.91 (m, 2H); ^{13}C NMR δ 136.6 (d), 118.6 (d), 71.0 (t), 48.5 (t), 26.6 (t), 22.9 (t); EIMS *m*/*z* (relative intensity) 162 (M$^+$, 3), 98 ($M-SO_2^+$, 74), 97 (52), 80 (35), 67 (87), 57 (31), 56 (100), 53 (32); HRMS (CI$^+$, CH_4) calcd for $C_6H_{11}O_3S$ (M+H$^+$): 163.0429. Found: 163.0427.

6.2.2.7. 3,4,7,8-Tetrahydro-[1,2]oxathiocine-2,2-dioxide (2f). This compound was prepared from **1f** (650 mg, 3.42 mmol) by using catalyst **I** (140 mg, 0.170 mmol, 0.05 equiv) in C_6H_6 (350 mL) for 4 h at 70 °C. After purification by flash chromatography (petroleum ether/ether 50:50), 550 mg (99%) of **2f** were obtained as a pale brown solid; mp 62 °C; IR 1350, 1165, 1010, 980, 965, 920, 880, 770, 740 cm^{-1}; ^{1}H NMR δ 5.97–5.79 (m, 2H), 4.25 (t, *J*=5.9 Hz, 2H), 3.31–3.27 (m, 2H), 2.63–2.52 (m, 4H); ^{13}C NMR δ 130.4 (d), 127.8 (d), 68.9 (t), 53.7 (t), 26.9 (t), 20.8 (t); EIMS *m*/*z* (relative intensity) 162 (M$^+$, 2), 80 (66), 79 (13), 68 (78), 67 (100), 53 (26). Anal. Calcd for $C_6H_{10}O_3S$: C, 44.43; H, 6.21. Found: C, 44.55; H, 6.30.

6.2.3. Preparation of sultone 2g from 1d.

6.2.3.1. But-3-enyl but-1-ene-3-sulfonate (1g). To a solution of sulfonate **1d** (1.0 g, 5.7 mmol) in THF (30 mL) at −78 °C was added *n*-BuLi (2.3 mL, 2.5 M in hexanes, 5.7 mmol, 1.0 equiv). After 1.5 h at −78 °C, CH_3I (1.1 mL, 17 mmol, 3.0 equiv) was added. After a further 1.5 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. After purification by flash chromatography (petroleum ether/EtOAc 80:20), 900 mg (84%) of **1g** were obtained as a colorless oil; IR 3080, 1640, 1350, 1170, 960, 910, 820, 790, 650 cm^{-1}; ^{1}H NMR δ 5.88 (ddd, *J*=17.3, 10.3, 7.7 Hz, 1H), 5.74

(ddt, J=17.0, 10.0, 6.6 Hz, 1H), 5.38 (dt, J=17.0, 1.1 Hz, 1H), 5.37 (dt, J=10.0, 1.1 Hz, 1H), 5.16–5.07 (m, 2H), 4.22 (t, J=6.6 Hz, 2H), 3.80 (m, 1H), 2.44 (apparent qt, J=6.6, 1.5 Hz, 2H), 1.50 (d, J=7.0 Hz, 3H); ^{13}C NMR δ 132.4 (d), 130.9 (d), 121.3 (t), 118.1 (t), 69.3 (t), 60.1 (d), 33.5 (t), 14.2 (q); EIMS *m/z* (relative intensity) 148 (M^+, 0.1), 136 (4), 81 (2), 71 (3), 56 (5), 55 (100), 54 (22), 53 (6). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42. Found: C, 50.15; H, 7.63.

6.2.3.2. 3-Methyl-6,7-dihydro-3*H*-[1,2]oxathiepine-2,2-dioxide (2g). To a solution of **1g** (900 mg, 4.74 mmol) in C_6H_6 (100 mL) was added catalyst **II** (10 mg, 0.12 mmol, 0.025 equiv). After 2 h at 70 °C, the reaction mixture was cooled to rt, concentrated under reduced pressure, and the crude material was purified by flash chromatography (petroleum ether/ether 70:30) to afford 450 mg (60%) of **2g** as a colorless oil; IR 3030, 1460, 1355, 1275, 1170, 1005, 975, 950, 890, 840, 780, 750 cm^{-1}; ^{1}H NMR δ 6.11 (dddd, J=11.2, 7.7, 5.9, 1.8 Hz, 1H), 5.55 (ddd, J=11.2, 5.1, 1.8 Hz, 1H), 4.60–4.53 (m, 1H), 4.46–4.39 (m, 1H), 4.19–4.09 (m, 1H), 2.73–2.60 (m, 1H), 2.52–2.42 (m, 1H), 1.60 (d, J=7.4 Hz, 3H); ^{13}C NMR δ 132.8 (d), 127.5 (d), 72.7 (t), 57.3 (d), 28.4 (t), 15.3 (q); EIMS *m/z* (relative intensity) 162 (M^+, 0.5), 120 (10), 97 (17), 83 (36), 81 (28), 80 (16), 69 (18), 68 (100), 67 (60), 55 (16), 53 (24).

6.2.4. Synthesis of unsaturated sultones derived from secondary alcohols.

6.2.4.1. General procedure. To a solution of the unsaturated secondary alcohols **1h–l** and Et_3N (1.1–2.0 equiv) in THF at −15 °C was added dropwise a solution of the appropriate sulfonyl chloride (1.1–1.5 equiv) in THF. After 1 h at −15 °C, an additional quantity of sulfonyl chloride (0.2–0.5 equiv) was generally added to ensure complete conversion. After 1 h at −15 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was filtered through a short plug of silica gel (Et_2O) and the filtrate was evaporated under reduced pressure. The crude sulfonates **2h–l** were dissolved in benzene (0.08–0.06 M) and to the resulting degassed solution (argon bubbling, 15 min) was added catalyst **II** (0.01–0.05 equiv). After 1 h at 70 °C, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel.

6.2.4.2. 6-[(3-Benzyloxy)propyl]-5,6-dihydro-[1,2]oxathiine-2,2-dioxide (2h). This compound was synthesized according to the general procedure from 7-benzyloxyhept-1-en-4-ol (2.0 g, 9.0 mmol), Et_3N (1.5 mL, 11 mmol, 1.2 equiv), and vinylsulfonyl chloride (1.40+0.28 g, 11.0+2.2 mmol, 1.2+0.2 equiv) in THF (30 mL). The crude sulfonate was then treated with catalyst **II** (55 mg, 0.070 mmol, 0.011 equiv) in C_6H_6 (150 mL). After purification by flash chromatography (petroleum ether/EtOAc 70:30), 1.60 g (65%) of **2h** were obtained as a pale brown waxy solid; IR 3030, 1615, 1330, 1170, 1150, 1090, 880, 820, 735, 700 cm^{-1}; ^{1}H NMR δ 7.40–7.26 (m, 5H), 6.54 (ddd, J=10.7, 2.6, 1.3 Hz, 1H), 6.47 (ddd, J=10.7, 4.4, 2.3 Hz, 1H), 4.98 (m, 1H), 4.51 (s, 2H), 3.60–3.48 (m, 2H), 2.51–2.29 (m, 2H), 1.97–1.68 (m, 4H); ^{13}C NMR δ 138.2 (s), 136.6 (d), 128.3 (d, 2C), 127.5 (d, 3C), 126.0 (d), 82.0 (d), 72.8 (t), 70.0 (t), 31.5 (t), 30.1 (t), 24.7 (t); EIMS *m/z* (relative intensity) 282 (M^+, 4), 173 (4), 161 (5), 107 (50), 105 (12), 91 (100), 79 (12), 65 (10). Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43. Found: C, 59.39; H, 6.59.

6.2.4.3. Ethyl (2,2-dioxo-5,6-dihydro-2λ^6-[1,2]oxathiine-6-yl)formate (2i). This compound was synthesized according to the general procedure from ethyl 2-hydroxypent-4-enoate (1.75 g, 12.2 mmol), Et_3N (1.88 mL, 13.4 mmol, 1.1 equiv), and vinylsulfonyl chloride (1.69+0.31 g, 13.4+2.4 mmol, 1.1+0.2 equiv) in THF (30 mL). The crude sulfonate was then treated with catalyst **II** (200 mg, 0.235 mmol, 0.02 equiv) in C_6H_6 (120 mL). After purification by flash chromatography (petroleum ether/EtOAc 80:20), 1.35 g (54%) of **2i** were obtained as a pale brown oil; IR 3060, 1750, 1360, 1330, 1305, 1230, 1180, 1155, 1030, 950, 910, 835, 730, 685 cm^{-1}; ^{1}H NMR δ 6.64–6.51 (m, 2H), 5.36 (dd, J=9.2, 6.6 Hz, 1H), 4.29 (q, J=7.2 Hz, 2H), 2.73 (m, 2H), 1.31 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 165.7 (s), 135.9 (d), 126.2 (d), 76.2 (d), 62.5 (t), 27.0 (t), 13.9 (q); EIMS *m/z* (relative intensity) 178 ($M-Et^+$, 2), 161 ($M-OEt^+$, 4), 134 (12), 133 ($M-CO_2Et^+$, 100), 125 (33), 115 (10), 106 (6), 97 (45), 89 (22), 87 (12), 85 (11), 69 (22), 68 (29), 57 (9); HRMS (CI$^+$, CH_4) calcd for $C_7H_{11}O_5S$ ($M+H^+$): 207.0327. Found: 207.0327.

6.2.4.4. (2,2-Dioxo-3,6-dihydro-2*H*-2λ^6-[1,2]oxathiine-6-yl)methyl-2,2-dimethyl propanoate (2j). This compound was synthesized according to the general procedure from 2-hydroxybut-3-enyl 2,2-dimethyl propanoate (2.10 g, 12.2 mmol), Et_3N (3.4 mL, 24.4 mmol, 2.0 equiv), and allylsulfonyl chloride (1.9+0.34 g, 13.5+2.4 mmol, 1.1+0.2 equiv) in THF (30 mL). The crude sulfonate was then treated with catalyst **II** (49 mg, 0.057 mmol, 0.05 equiv) in C_6H_6 (120 mL). After purification by flash chromatography (petroleum ether/EtOAc 80:20), 2.24 g (74%) of **2j** were obtained as a colorless oil; IR 1730, 1625, 1480, 1360, 1280, 1160, 915, 805, 770, 740, 680, 630 cm^{-1}; ^{1}H NMR δ 5.94–5.81 (m, 2H), 5.38 (m, 1H), 4.43 (dd, J=12.3, 6.0 Hz, 1H), 4.29 (dd, J=12.3, 3.5 Hz, 1H), 3.91–3.80 (m, 1H), 3.78–3.66 (m, 1H), 1.20 (s, 9H); ^{13}C NMR δ 177.8 (s), 124.0 (d), 120.9 (d), 82.1 (d), 63.1 (t), 46.0 (t), 38.7 (s), 26.9 (q, 3C); EIMS *m/z* (relative intensity) 249 ($M+H^+$, 0.1), 233 ($M-Me^+$, 0.1), 218 (1), 146 ($M-t\text{-}BuCO_2H^+$, 14), 128 (5), 85 (31), 81 (6), 69 (12), 67 (9), 57 (100); HRMS (CI$^+$, CH_4) calcd for $C_{10}H_{17}O_5S$ ($M+H^+$): 249.0797. Found: 249.0798.

6.2.4.5. 6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2,2-dioxo-3,6-dihydro-2*H*-2λ^6-[1,2]oxathiine (2k). This compound was synthesized according to the general procedure from 1-(*tert*-butyldimethylsilyloxy)but-3-en-2-ol (1.6 g, 4.9 mmol), Et_3N (1.4 mL, 10 mmol, 2.05 equiv), and allylsulfonyl chloride (0.78+0.34 g, 5.5+2.5 mmol, 1.1+0.5 equiv) in THF (22 mL). The crude sulfonate was then treated with catalyst **II** (42 mg, 0.05 mmol, 0.01 equiv) in C_6H_6 (75 mL). After purification by flash chromatography (petroleum ether/EtOAc 90:10 to 85:15), 1.3 g (65%) of **2k** were obtained as a white solid; mp 106–108 °C; ^{1}H NMR δ 7.71–7.66 (m, 4H), 7.50–7.39 (m, 6H), 5.97–5.91 (m, 1H), 5.89–5.82 (m, 1H), 5.27 (m, 1H), 3.95 (dd, J=11.4, 5.1 Hz, 1H), 3.89 (dd, J=11.4, 5.1 Hz, 1H), 3.83 (m, 1H), 3.74–3.65 (m, 1H), 1.09 (s, 9H); ^{13}C NMR δ 135.4 (d, 4C), 132.6 (s, 2C), 129.9 (d, 2C), 127.7 (d, 4C), 125.4 (d), 119.7 (d), 84.3 (d), 64.1 (t), 46.2 (t), 26.6 (q, 3C), 19.1 (s); EIMS *m/z* (relative intensity) 266 (24, $M-SO_2-C_4H_8^+$), 265 ($M-SO_2-t\text{-}Bu^+$, 100), 247 (6), 237 (11), 199 (43), 197 (12), 187 (42), 183 (12), 181 (10). Anal. Calcd for $C_{21}H_{26}O_4SSi$: C, 62.65; H, 6.51. Found: C, 62.49; H, 6.68.

6.2.4.6. 7-[3-(Benzyloxy)propyl]-6,7-dihydro-3*H*-[1,2]oxathiepine-2,2-dioxide (2l). This compound was synthesized according to the general procedure from 7-benzyloxy-hept-1-en-3-ol (1.0 g, 4.5 mmol), Et_3N (1.3 mL, 9.2 mmol, 2.0 equiv), and allylsulfonyl chloride (1.0+0.34 g, 7.1+2.4 mmol, 1.5+0.5 equiv) in THF (21 mL). The crude sulfonate was treated with catalyst **II** (98 mg, 0.12 mmol, 0.025 equiv) in C_6H_6 (75 mL). After purification by flash chromatography (petroleum ether/EtOAc 70:30), 0.88 g (65%) of **2l** were obtained as a colorless oil; IR 3030, 1495, 1450, 1360, 1180, 1160, 1100, 965, 905, 820, 740, 705, 700 cm^{-1}; ^{1}H NMR δ 7.39–7.26 (m, 5H), 6.13 (dddd, J=11.0, 8.8, 4.8, 2.4 Hz, 1H), 5.74 (dddd, J=11.0, 8.1, 4.8, 2.6 Hz, 1H), 4.84–4.76 (m, 1H), 4.50 (s, 2H), 4.16–4.08 (m, 1H), 3.83 (dd, J=15.8, 8.5 Hz, 1H), 3.57–3.45 (m, 2H), 2.74–2.62 (m, 1H), 2.39 (ddd, apparent br d, J=16.6, 8.5, 1.1 Hz, 1H), 1.88–1.68 (m, 4H); ^{13}C NMR δ 138.3 (s), 133.9 (d), 128.3 (d, 2C), 127.5 (d, 2C), 127.4 (d), 119.3 (d), 85.1 (d), 72.8 (t), 69.1 (t), 50.5 (t), 34.2 (t), 32.2 (t), 25.2 (t); EIMS *m/z* (relative intensity) 296 (M^+, 3), 215 ($M-SO_3-H^+$, 16), 173 (4), 161 (4), 160 (4), 131 (4), 117 (3), 108 (11), 107 (46), 92 (16), 91 (10), 80 (12), 79 (17), 71 (20), 67 (11), 54 (10). Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.74; H, 6.94.

6.3. Synthesis of conjugated (*Z*)-dienols of type A

6.3.1. *trans*- and *cis*-2,4-Bis((1*Z*)-7-benzyloxy-4-hydroxy-hept-1-enyl)[1,3]dithietane-1,1,3,3-tetroxide (3). To a solution of $i\text{-}Pr_2NH$ (0.14 mL, 1.0 mmol, 3.0 equiv) in THF (2 mL) at −78 °C was added *n*-BuLi (0.40 mL, 2.5 M in hexanes, 1.0 mmol, 3.0 equiv). After 15 min at 0 °C, the resulting LDA solution was cooled to −78 °C and a solution of sultone **2l** (100 mg, 0.337 mmol) in THF (2 mL) was added. After 1 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 60:40 to 50:50) to afford 55 mg (55%) of **3** as a colorless oil and as an apparent 60:40 mixture of diastereomers; IR 3400 (br), 3020, 1640, 1450, 1350, 1155, 1080, 845, 740, 700 cm^{-1}; MS (CI^+, NH_3) *m/z* (relative intensity) 610 ($M+NH_4^+$, 77), 548 (10), 482 (22), 431 (20), 252 (16), 196 (100), 141 (13), 102 (55).

Major diastereomer: ^{1}H NMR δ 7.38–7.25 (m, 10H), 6.70 (d, J=9.6 Hz, 2H), 6.27 (dd, J=11.0, 7.7 Hz, 2H), 5.89 (dd, apparent br t, J=11.0, 9.6 Hz, 2H), 4.51 (s, 4H), 3.70–3.61 (m, 2H), 3.55–3.44 (m, 4H), 3.16 (br s, 2H, OH), 2.33–2.22 (m, 4H), 1.78–1.45 (m, 8H); ^{13}C NMR δ 140.0 (d, 2C), 137.8 (s, 2C), 128.3 (d, 6C), 127.7 (d, 4C), 113.3 (d, 2C), 97.0 (d, 2C), 73.0 (t, 2C), 70.2 (d, 2C), 69.8 (t, 2C), 36.4 (t, 2C), 34.7 (t, 2C), 26.2 (t, 2C).

Minor diastereomer: ^{1}H NMR δ 7.38–7.25 (m, 10H), 6.45 (d, J=9.9 Hz, 2H), 6.25 (dd, J=10.7, 7.7 Hz, 2H), 6.06 (dd, apparent br t, J=10.7, 9.9 Hz, 2H), 4.51 (s, 4H), 3.70–3.61 (m, 2H), 3.55–3.44 (m, 4H), 3.16 (br s, 2H, OH), 2.33–2.22 (m, 4H), 1.78–1.45 (m, 8H); ^{13}C NMR δ 140.4 (d, 2C), 137.8 (s, 2C), 128.3 (d, 6C), 127.7 (d, 4C), 114.7 (d, 2C), 98.8 (d, 2C), 73.0 (t, 2C), 70.1 (d, 2C), 69.8 (t, 2C), 36.2 (t, 2C), 34.6 (t, 2C), 26.2 (t, 2C).

6.3.2. (3*R or *S**,7*S**)-7-[(3-Benzyloxy)propyl]-3-methyl-3*H*-[1,2]oxathiepine-2,2-dioxide (6).** To a solution of sultone **2l** (100 mg, 0.336 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (200 μL, 2.5 M in hexanes, 0.500 mmol, 1.5 equiv). After 1 h at −78 °C, CH_3I (84 μL, 1.34 mmol, 4.0 equiv) was added. After 15 min at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ether 80:20) to afford 87 mg (85%) of **6** as a colorless oil and as a single diastereomer (unassigned relative configuration); IR 3020, 1450, 1340, 1170, 1160, 1100, 945, 910, 810, 740, 700 cm^{-1}; ^{1}H NMR δ 7.39–7.26 (m, 5H), 5.92 (ddd, J=12.0, 7.7, 4.4 Hz, 1H), 5.69 (ddd, J=12.0, 7.0, 2.0 Hz, 1H), 4.82 (m, 1H), 4.50 (s, 2H), 3.97 (apparent quintet, J=7.2 Hz, 1H), 3.59–3.41 (m, 2H), 2.64 (m, 1H), 2.44–2.34 (m, 1H), 1.90–1.67 (m, 4H), 1.62 (d, J=7.4 Hz, 3H); ^{13}C NMR δ 138.3 (s), 130.8 (d), 128.2 (d, 2C), 127.5 (d, 2C), 127.4 (d), 125.6 (d), 83.6 (d), 72.8 (t), 69.1 (t), 56.3 (d), 34.3 (t), 32.1 (t), 25.3 (t), 14.9 (q); EIMS *m/z* (relative intensity) 310 (M^+, 2), 229 ($M-SO_3H^+$, 13), 160 (8), 123 (14), 107 (40), 95 (11), 94 (12), 93 (12), 92 (15), 91 (100), 81 (16), 79 (15), 71 (18), 68 (18), 67 (16), 65 (10).

6.3.3. 3-Methyl-6,7-dihydro-3*H*-[1,2]oxathiepine-2,2-dioxide (2g). To a solution of sultone **2d** (150 mg, 1.01 mmol) in THF (15 mL) at −78 °C, was added dropwise *n*-BuLi (425 μL, 2.5 M in hexanes, 1.06 mmol, 1.05 equiv). After 1 h at −78 °C, CH_3I (190 μL, 3.03 mmol, 3.0 equiv) was added. After 15 min at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ether 80:20) to afford 162 mg (92%) of **2g** as a colorless oil. This compound has previously been synthesized from sulfonate **1d** by methylation and subsequent RCM, see Section 6.2.3.

6.3.4. (3*R or *S**,7*R**)-3,7-Bis[(3-benzyloxy)propyl]-6,7-dihydro-3*H*-[1,2]oxathiepine-2,2-dioxide (7).** To a solution of sultone **2l** (150 mg, 0.507 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (250 μL, 2.5 M in hexanes, 0.625 mmol, 1.25 equiv). After 1 h at −78 °C, a solution of 3-benzyloxy-1-bromopropane (130 μL, 0.760 mmol, 1.5 equiv) and HMPA (350 μL, 2.03 mmol, 4.0 equiv) in THF (2 mL) was added dropwise. After 1.5 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ether

80:20 to 75:25) to afford 188 mg (84%) of **7** as a colorless oil and as a single diastereomer (unassigned relative configuration); IR 3030, 1495, 1450, 1360, 1160, 1100, 910, 740, 705, 690 cm^{-1}; ^1H NMR δ 7.89–7.28 (m, 10H), 5.96 (ddd, J=12.0, 7.5, 4.4 Hz, 1H), 5.68 (ddd, J=12.0, 7.5, 2.2 Hz, 1H), 4.80 (m, 1H), 4.49 (s, 4H), 3.92 (m, 1H), 3.57–3.47 (m, 4H), 2.68–2.56 (m, 1H), 2.44–2.22 (m, 2H), 2.18–2.04 (m, 1H), 1.88–1.68 (m, 6H); ^{13}C NMR δ 138.3 (s), 138.1 (s), 131.4 (d), 128.3 (d, 2C), 128.2 (d, 2C), 127.5 (d, 4C), 127.4 (d, 2C), 124.6 (d), 83.6 (d), 72.9 (t), 72.8 (t), 69.4 (t), 69.1 (t), 60.7 (d), 34.4 (t), 32.1 (t), 26.8 (t, 2C), 25.3 (t).

6.3.5. (6*Z*)-1-(Benzyloxy)nona-6,8-dien-4-ol (8). To a solution of sultone **2l** (157 mg, 0.531 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (320 μL, 2.5 M in hexanes, 0.796 mmol, 1.5 equiv). After 1 h at −78 °C, a solution of iodomethylmagnesium chloride [prepared from CH_2I_2 (150 μL, 1.86 mmol, 3.5 equiv) and *i*-PrMgCl (930 μL, 2 M in THF, 1.86 mmol, 3.5 equiv) in THF (3 mL), −78 °C, 1 h] was transferred via a cannula into the reaction mixture. After 1 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 80:20) to afford 79 mg (60%) of **8** as a colorless oil; IR 3400, 3030, 1495, 1450, 1365, 1270, 1205, 1095, 1030, 910, 740, 705 cm^{-1}; ^1H NMR δ 7.48–7.27 (m, 5H), 6.65 (dddd, J=16.9, 11.0, 10.3, 1.1 Hz, 1H), 6.16 (dd, apparent t, J=11.0 Hz, 1H), 5.53 (m, 1H), 5.24 (dd, J=16.9, 1.8 Hz, 1H), 5.15 (br d, J=10.3 Hz, 1H), 4.53 (s, 2H), 3.68 (m, 1H), 3.52 (t, J=5.9 Hz, 2H), 2.59 (br s, 1H, OH), 2.41–2.36 (m, 2H), 1.82–1.62 (m, 3H), 1.58–1.43 (m, 1H); ^{13}C NMR δ 138.1 (s), 132.0 (d), 131.6 (d), 128.3 (d, 2C), 128.1 (d), 127.6 (d, 2C), 127.5 (d), 117.7 (t), 72.9 (t), 71.1 (d), 70.3 (t), 35.6 (t), 34.0 (t), 26.1 (t).

6.3.6. (6*Z*)-1-Benzyloxy-8-methylnona-6,8-dien-4-ol (9). To a solution of sultone **6** (130 mg, 0.419 mmol) in THF (4 mL) at −78 °C was added *n*-BuLi (252 μL, 2.5 M in hexanes, 0.629 mmol, 1.5 equiv). After 1 h at −78 °C, a solution iodomethylmagnesium chloride [prepared from CH_2I_2 (120 μL, 1.46 mmol, 3.5 equiv) and *i*-PrMgCl (730 μL, 2M in THF 1.46 mmol, 3.5 equiv) in THF (3 mL), −78 °C, 1 h] was transferred via a cannula into the reaction mixture. After 1 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 85:15) to afford 58 mg (53%) of **9** as a colorless oil; IR 3400, 1595, 1580, 1490, 1450, 1360, 1275, 1205, 1175, 1100, 910, 740, 705 cm^{-1}; ^1H NMR δ 7.39–7.27 (m, 5H), 6.00 (dd, J=11.8, 1.1 Hz, 1H), 5.49 (dt, J=11.8, 7.4 Hz, 1H), 4.98 (br s, 1H), 4.89 (br s, 1H), 4.53 (s, 2H), 3.71–3.64 (m, 1H), 3.52 (t, J=5.9 Hz, 2H), 2.56–2.39 (m, 3H), 1.90 (s, 3H), 1.79–1.50 (m, 4H); ^{13}C NMR δ 141.4 (s), 138.1 (s), 133.1 (d), 128.3 (d, 2C), 127.6 (d, 2C), 127.5 (d), 127.1 (d), 115.6 (t), 72.9 (t), 71.5 (d), 70.3 (t), 36.4 (d), 34.1 (d), 26.1 (d), 23.2 (q); EIMS *m*/*z* (relative intensity) 260 (M^+, 1), 259 (45), 152 (16), 137 (37), 105 (100), 95 (22), 93 (12), 82 (53), 79 (17), 71 (15), 67 (32).

6.4. Total synthesis of the originally proposed structure of mycothiazole

6.4.1. Synthesis of the C4–C10 subunit.

6.4.1.1. 2,4-Dibromothiazole (10). A mixture of thiazolidine-2,4-dione (3.4 g, 29 mmol) and phosphorous oxybromide (25 g, 87 mmol, 3.0 equiv) was heated at 110 °C. After 3 h, the reaction mixture was cooled to rt and cautiously hydrolyzed with crushed ice. The resulting mixture was extracted with ether and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by chromatography (pentane/ether 99.5:0.5) to afford 4.8 g (68%) of **10** as a white solid; mp 80–84 °C; IR 3120, 1460, 1390, 1240, 1070, 1020, 880, 820, 740 cm^{-1}; ^1H NMR δ 7.22 (s, 1H); ^{13}C NMR δ 136.2 (s), 124.1 (s), 120.7 (d); EIMS *m*/*z* (relative intensity) 245 ($M[^{81}Br_2]^+$, 52), 243 ($M[^{79}Br^{81}Br]^+$, 100), 241 ($M[^{79}Br]^+$, 52), 138 (30), 136 (30), 13 (30), 83 (13), 57 (27).

6.4.1.2. 4-Bromo-2-(1,1-dimethylallyl)thiazole (11). To a suspension of magnesium turnings (3.46 g, 142 mmol, 5.7 equiv) in THF (20 mL) was added dropwise a solution of prenyl chloride (8.0 mL, 71 mmol, 2.9 equiv) in THF (150 mL) (internal temperature maintained between 5–10 °C). After a further 0.5 h stirring at rt, the resulting solution of prenylmagnesium chloride was transferred via a cannula to a solution of **10** (6.00 g, 24.7 mmol) in THF (20 mL) at 0 °C. After 1 h at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 99.5:0.5) to afford 4.98 g (87%) of **11** as a volatile colorless liquid; IR 3120, 3080, 1640, 1480, 1460, 1395, 1260, 1240, 1080, 1020, 920, 890, 840, 820, 740 cm^{-1}; ^1H NMR δ 7.09 (s, 1H), 6.13 (dd, J=17.3, 10.5 Hz, 1H), 5.17 (dd, J=17.3, 0.7 Hz, 1H), 5.14 (dd, J=10.5, 0.7 Hz, 1H), 1.54 (s, 6H); ^{13}C NMR δ 179.8 (s), 154.0 (s), 144.4 (d), 116.0 (d), 113.3 (t), 45.6 (s), 27.8 (q, 2C); EIMS *m*/*z* (relative intensity) 233 ($M[^{81}Br]^+$, 3), 232 ($M[^{81}Br]-H^+$, 3), 231 ($M[^{79}Br]^+$, 4), 230 ($M[^{79}Br]-H^+$, 3), 218 ($M[^{81}Br]-Me^+$, 99), 216 ($M[^{79}Br]-Me^+$, 100), 203 (13), 201 (12), 192 (3), 190 (4), 152 (2), 138 (4), 137 (6), 136 (8).

6.4.1.3. 2-(4-Bromothiazol-2-yl)-2-methylpropanal (12). To a solution of **11** (3.80 g, 16.3 mmol) in *t*-BuOH/H_2O (1:1, 60 mL) at rt were successively added OsO_4 (4.0 mL, 4% in water, 0.65 mmol, 0.04 equiv) and NMO (2.10 g, 17.9 mmol, 1.1 equiv). After stirring overnight at rt, a mixture of powdered $Na_2S_2O_3$ (7.5 g) and Celite (15 g) was added. After 0.5 h, the resulting mixture was filtered through Celite (EtOAc). The organic layer was separated and the aqueous phase was extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude resulting 1,2-diol was dissolved in THF/H_2O (1:1, 300 mL) and $NaIO_4$ (8.70 g, 40.8 mmol, 2.5 equiv) was added to the resulting solution. After 1 h at rt, the reaction mixture was filtered through Celite (EtOAc). The filtrate was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by filtration through a short plug of silica gel (petroleum ether/ether 90:10) to afford 3.37 g (88%) of aldehyde **12** as a pale yellow oil, which was directly engaged in the next step; ^1H NMR δ 9.67 (s, 1H), 7.25 (s, 1H), 1.40 (s, 6H); ^{13}C NMR δ 199.0 (d), 172.8 (s), 125.2 (s), 117.1 (d), 51.7 (s), 22.6 (q, 2C).

6.4.1.4. 2-(4-Bromothiazol-2-yl)-2-methylhex-5-en-3-ol (13). To a solution of **12** (3.34 g, 14.3 mmol) in THF (25 mL) at −78 °C was added a solution of allylmagnesium bromide (21.5 mL, 1 M in ether, 21.5 mmol, 1.5 equiv) in ether (30 mL). After 1 h at rt, the reaction mixture was hydrolyzed with a 1 M solution of hydrochloric acid and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/ether 85:15 to 80:20) to afford 3.47 g (87%) of **13** as a colorless oil; IR 3420, 3130, 1640, 1470, 1370, 1260, 1080, 1055, 920, 890, 845, 740 cm^{-1}; ^1H NMR δ 7.14 (s, 1H), 5.86 (dddd, J=17.6, 9.6, 7.7, 6.3 Hz, 1H), 5.13–5.06 (m, 2H), 3.80 (m, 1H), 3.05 (m, 1H, OH), 2.31 (m, 1H), 1.98 (m, 1H), 1.45 (s, 6H); ^{13}C NMR δ 179.6 (s), 135.5 (d), 124.0 (s), 117.4 (t), 115.9 (d), 77.2 (d), 45.2 (s), 36.5 (t), 26.0 (q), 24.0 (q); EIMS *m/z* (relative intensity) 277 ($M[^{81}Br]^+$, 0.4), 275 ($M[^{79}Br]^+$, 0.4), 236 ($M[^{81}Br]-C_3H_5^+$, 13), 234 ($M[^{79}Br]-C_3H_5^+$, 13), 207 (100), 206 (39), 205 (98), 204 (32), 192 (41), 190 (36).

6.4.1.5. 4-Bromo-2-{2-[(*tert*-butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazole (14). To a solution of **13** (700 mg, 2.54 mmol) and 2,6-lutidine (740 µL, 6.35 mmol, 2.5 equiv) in CH_2Cl_2 (15 mL) at 0 °C was added dropwise TBSOTf (1.2 mL, 5.1 mmol, 2.0 equiv). After 3 h at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 99:1) to give 940 mg (95%) of **14** as a colorless oil; IR 3120, 3080, 1640, 1465, 1390, 1365, 1255 (br), 1090, 915, 840, 780 cm^{-1}; ^1H NMR δ 7.09 (s, 1H), 5.71 (m, 1H), 4.96–4.88 (m, 2H), 4.02 (t, J=5.3 Hz, 1H), 2.35–2.25 (m, 1H), 2.16–2.06 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), −0.10 (s, 3H); ^{13}C NMR δ 179.6 (s), 135.8 (d), 123.8 (s), 116.2 (t), 115.9 (d), 78.7 (d), 46.6 (s), 38.6 (t), 26.0 (q, 3C), 25.3 (q), 24.9 (q), 18.1 (s), −3.6 (q), −4.8 (q); EIMS *m/z* (relative intensity) 376 ($M[^{81}Br]-Me^+$, 3), 374 ($M[^{79}Br]-Me^+$, 3), 350 ($M[^{81}Br]-C_3H_5^+$, 13), 348 ($M[^{79}Br]-C_3H_5^+$, 12), 335 ($M[^{81}Br]-C_4H_8^+$, 19), 334 ($M[^{81}Br]-t\text{-}Bu^+$, 100), 333 ($M[^{79}Br]-C_4H_8^+$, 19), 332 ($M[^{79}Br]-t\text{-}Bu^+$, 96), 186 (12), 185 (70), 129 (10), 127 (13), 115 (14), 99 (12), 75 (31), 73 (61). Anal. Calcd for $C_{16}H_{28}BrNOSSi$: C, 49.22; H, 7.23; N, 3.59. Found: C, 49.32; H, 7.23; N, 3.72.

6.4.2. Br–Li exchange of 14 with *n*-BuLi in THF and subsequent formylation. To a solution of *n*-BuLi (1.1 mL, 2.5 M in hexanes, 2.8 mmol, 1.5 equiv) in THF (10 mL) at −78 °C was added dropwise a solution of **14** (730 mg, 1.88 mmol) in THF (10 mL). After 15 min at −78 °C, freshly distilled DMF (295 mL, 3.76 mmol, 2.0 equiv) was added. After 0.5 h, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/ether 97:3 to 85:15) to afford 175 mg (22%) of **20**, 200 mg (34%) of **18**, 92 mg (14%) of **19**, and 90 mg (14%) of **21** as pale yellow oils.

6.4.2.1. 2-{2-[(*tert*-Butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazole (18). IR 3080, 1705, 1680, 1640, 1470, 1390, 1360, 1260, 1090, 1060, 1040, 1005, 910, 840, 770, 740, 725 cm^{-1}; ^1H NMR δ 7.66 (d, J=3.3 Hz, 1H), 7.14 (d, J=3.3 Hz, 1H), 5.63 (dddd, J=16.5, 10.3, 7.7, 6.6 Hz, 1H), 4.89–4.80 (m, 2H), 3.99 (dd, J=6.3, 4.6 Hz, 1H), 2.26–2.16 (m, 1H), 2.09–1.99 (m, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 0.85 (s, 9H), 0.02 (s, 3H), −0.06 (s, 3H); ^{13}C NMR δ 178.3 (s), 141.5 (d), 135.9 (d), 117.8 (d), 115.8 (t), 78.9 (d), 46.0 (s), 38.5 (t), 26.0 (q), 25.9 (q, 3C), 24.5 (q), 18.0 (s), −3.7 (q), −4.8 (q); EIMS *m/z* (relative intensity) 311 (M^+, 1), 296 ($M-Me^+$, 5), 270 ($M-C_3H_5^+$, 16), 256 (10), 254 (100), 198 (12), 185 (35), 180 (11), 138 (8), 127 (31), 115 (7), 99 (6), 75 (11), 73 (39).

6.4.2.2. 2-{2-[(*tert*-Butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazole-4-carboxaldehyde (19). IR 3080, 1710, 1640, 1485, 1470, 1390, 1365, 1260, 1135, 1090, 1055, 1005, 915, 840, 780, 700 cm^{-1}; ^1H NMR δ 10.0 (s, 1H), 8.08 (s, 1H), 5.67 (dddd, J=16.9, 10.3, 7.7, 6.6 Hz, 1H), 4.93–4.84 (m, 2H), 3.99 (dd, apparent t, J=5.1 Hz, 1H), 2.36–2.26 (m, 1H), 2.15–2.05 (m, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), −0.08 (s, 3H); ^{13}C NMR δ 184.9 (d), 179.4 (s), 153.9 (s), 135.4 (d), 127.4 (d), 116.2 (t), 78.7 (d), 46.7 (s), 38.5 (t), 26.1 (q), 25.9 (q, 3C), 25.2 (q), 18.1 (s), −3.7 (q), −4.8 (q); EIMS *m/z* (relative intensity) 324 ($M-Me^+$, 3), 298 ($M-C_3H_5^+$, 21), 284 (10), 283 (20), 282 (100), 213 (13), 212 (76), 185 (34), 166 (5), 155 (5), 115 (6), 75 (10), 73 (38).

6.4.2.3. 4-Bromo-2-{2-[(*tert*-butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazole-5-carboxaldehyde (20). IR 3080, 1675, 1640, 1480, 1460, 1365, 1250, 1090, 1005, 915, 840, 780, 740, 680 cm^{-1}; ^1H NMR δ 9.94 (s, 1H), 5.70 (dddd, J=16.9, 10.7, 7.7, 6.4 Hz, 1H), 4.97–4.88 (m, 2H), 4.03 (t, J=5.2 Hz, 1H), 2.36–2.26 (m, 1H), 2.19–2.09 (m, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), −0.10 (s, 3H); ^{13}C NMR δ 186.9 (s), 182.8 (d), 135.1 (d), 133.6 (s), 131.7 (s), 116.5 (t), 78.3 (d), 47.6 (s), 38.5 (t), 25.8 (q, 3C), 25.4 (q), 24.3 (q), 18.0 (s), −3.8 (q), −4.9 (q); EIMS *m/z* (relative intensity) 404 ($M[^{81}Br]-Me^+$, 2), 402 ($M[^{79}Br]-Me^+$, 2), 378 ($M[^{81}Br]-C_3H_5^+$, 14), 376 ($M[^{79}Br]-C_3H_5^+$, 13), 363 ($M[^{81}Br]-C_4H_8^+$, 21), 362 ($M[^{81}Br]-t\text{-}Bu^+$, 100), 361 ($M[^{79}Br]-C_4H_8^+$, 20), 360 ($M[^{79}Br]-t\text{-}Bu^+$, 96), 185 (48), 127 (20), 115 (11), 99 (14), 75 (25), 73 (60).

6.4.2.4. 2-{2-[(*tert*-Butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazole-5-carboxaldehyde (21). IR 3080, 1680, 1640, 1510, 1470, 1420, 1390, 1360, 1260, 1100, 1040, 1005, 910, 840, 780 cm^{-1}; ^1H NMR δ 9.98 (s, 1H), 8.29 (s, 1H), 5.66 (dddd, J=16.9, 10.3, 7.4, 6.6 Hz, 1H), 4.94–4.84 (m, 2H), 4.03 (dd, apparent t, J=5.3 Hz, 1H), 2.27 (m, 1H), 2.11 (m, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), −0.08 (s, 3H); ^{13}C NMR δ 187.3 (s), 182.1 (d), 150.6 (d), 138.6 (s), 135.4 (d), 116.3

(t), 78.5 (d), 47.3 (s), 38.6 (t), 25.8 (q, 3C), 25.4 (q), 25.0 (q), 18.0 (s), −3.8 (q), −4.8 (q); EIMS *m/z* (relative intensity) 324 (M−Me$^+$, 4), 298 (M−$C_3H_5^+$, 16), 283 (M−$C_4H_8^+$, 21), 282 (M−*t*-Bu$^+$, 100), 269 (6), 256 (3), 226 (8), 185 (29), 166 (6), 156 (4), 127 (9), 115 (7), 99 (7), 75 (14), 73 (46), 59 (8).

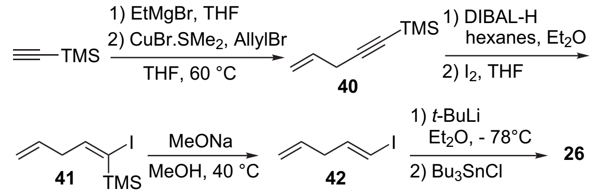
6.4.3. Installation of the unsaturated side-chain at C4.

6.4.3.1. Br–Li exchange of 14 with *t*-BuLi in ether and subsequent formylation. To a solution of *t*-BuLi (3.1 mL, 1.7 M in pentane, 5.3 mmol, 3.0 equiv) in ether (17 mL) at −78 °C was added dropwise a solution of **14** (676 mg, 1.74 mmol) in ether (17 mL). After 5 min at −78 °C, freshly distilled DMF (410 μL, 5.22 mmol, 3.0 equiv) was added dropwise. After 0.5 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/Et_2O: 90:10) to afford 500 mg (85%) of **19** as a yellow oil, see Section 6.4.2.2.

6.4.3.2. ({2-[2-(*tert*-Butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}thiazol-4-yl)methanol (24). To a solution of aldehyde **19** (960 mg, 2.83 mmol) in ether (35 mL) at −78 °C was added DIBAL-H (4.75 mL, 1 M in hexanes, 4.75 mmol, 1.7 equiv). After 0.5 h at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of Rochelle's salt and diluted with ether. After 2 h at rt, the organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 910 mg (95%) of **24** as a colorless oil, which was directly engaged in the next step without purification; IR 3300, 3070, 1640, 1470, 1390, 1365, 1260, 1100, 1040, 910, 840, 780 cm^{-1}; ^{1}H NMR δ 7.04 (s, 1H), 5.68 (m, 1H), 4.93–4.86 (m, 2H), 4.73 (br d, *J*=5.0 Hz, 2H), 4.00 (dd, *J*=5.9, 4.8 Hz, 1H), 3.38 (t, *J*=5.0 Hz, 1H, OH), 2.31–2.21 (m, 1H), 2.14–2.04 (m, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), −0.09 (s, 3H); ^{13}C NMR δ 179.3 (s), 155.3 (s), 136.1 (d), 116.0 (t), 113.7 (d), 78.9 (d), 60.8 (t), 46.4 (s), 38.6 (t), 26.0 (q, 3C), 25.8 (q), 24.8 (q), 18.3 (s), −3.6 (q), −4.7 (q); EIMS *m/z* (relative intensity) 341 (M$^+$, 1), 300 (M−$C_3H_5^+$, 33), 285 (22), 284 (100), 262 (64), 214 (49), 192 (23), 185 (100), 183 (28), 168 (40), 157 (22), 140 (29), 115 (22), 75 (31), 73 (79). Anal. Calcd for $C_{17}H_{31}NO_2SSi$: C, 59.77; H, 9.15; N, 4.10. Found: C, 59.66; H, 9.30; N, 4.14.

6.4.3.3. 4-Bromomethyl-2-{2-[(*tert*-butyldimethylsilyl)-oxy]-1,1-dimethylpent-4-enyl}thiazole (25). To a solution of **24** (640 mg, 1.92 mmol), 2,6-lutidine (92 μL, 0.79 mmol, 0.4 equiv), and PPh_3 (830 g, 3.21 mmol, 1.7 equiv) in MeCN (16 mL) at rt was added portionwise CBr_4 (1.1 g, 3.2 mmol, 1.7 equiv). After 0.5 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/ether 95:5) to afford 740 mg (97%) of **25** as a colorless oil; IR 3070, 1640, 1470, 1385, 1365, 1255, 1085, 1040, 1000, 910, 835, 775 cm^{-1}; ^{1}H NMR δ 7.17 (s, 1H), 5.71 (dddd, *J*=16.9, 10.3, 7.3, 6.6 Hz, 1H), 4.95–4.87 (m, 2H), 4.57 (s, 2H), 4.04 (dd, *J*=5.9, 4.8 Hz, 1H), 2.34–2.24 (m, 1H), 2.17–2.06 (m, 1H), 1.44 (s, 3H), 1.38 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), −0.09 (s, 3H); ^{13}C NMR δ 179.2 (s), 151.1 (s), 136.0 (d), 117.0 (d), 116.0 (t), 78.9 (d), 46.4 (s), 38.6 (t), 27.6 (t), 26.0 (q, 3C), 25.5 (q), 25.0 (q), 18.3 (s), −3.6 (q), −4.6 (q); EIMS *m/z* (relative intensity) 364 (M[^{81}Br]−$C_3H_5^+$, 12), 362 (M[^{79}Br]−$C_3H_5^+$, 12), 348 (M[^{81}Br]−*t*-Bu$^+$, 87), 346 (M[^{79}Br]−*t*-Bu$^+$, 83), 324 (2), 252 (7), 192 (30), 186 (17), 185 (100), 168 (31), 140 (10), 139 (13), 129 (13), 115 (15), 95 (17), 75 (14), 73 (56).

6.4.4. Preparation of organostannane 26.



6.4.4.1. Trimethylpent-4-en-1-ylsilane (40). To a solution of EtMgBr (34 mL, 3 M in THF, 102 mmol, 1.2 equiv) in THF (120 mL) was slowly added trimethylsilylacetylene (12 mL, 85 mmol) (exothermic reaction, internal temperature between 25 and 30 °C). The resulting mixture was heated at 50 °C for 2 h and cooled to rt. To the reaction mixture was added CuBr·SMe_2 (1.75 g, 8.49 mmol, 0.1 equiv) in one portion followed by allyl bromide (11.0 mL, 127 mmol, 1.5 equiv) dropwise (exothermic reaction, internal temperature 50 °C). After 2 h at 60 °C, the reaction mixture was hydrolyzed with a 1 M aqueous solution of hydrochloric acid and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by distillation under reduced pressure to afford 9.2 g (79%) of **40** as a colorless oil; bp 45 °C/15 mmHg; IR 2180, 1640, 1420, 1250, 1030, 1000, 915, 890, 840, 700 cm^{-1}; ^{1}H NMR δ 5.82 (ddt, *J*=17.0, 10.3, 5.2 Hz, 1H), 5.34 (dq, *J*=17.0, 1.7 Hz, 1H), 5.13 (dq, *J*=10.3, 1.7 Hz, 1H), 3.01 (dt, *J*=5.2, 1.7 Hz, 2H), 0.17 (s, 9H); ^{13}C NMR δ 132.1 (d), 116.1 (t), 103.3 (s), 87.0 (s), 24.1 (t), 0.00 (q, 3C).

6.4.4.2. (*E*)-1-Iodo-1-trimethylsilylpenta-1,4-diene (41). A solution of DIBAL-H (70 mL, 1 M in hexanes, 70 mmol, 1.2 equiv) was diluted with ether (7.2 mL, 70 mmol, 1.2 equiv) and a solution of **40** (8.00 g, 58.0 mmol) in ether (145 mL) was slowly added at 0 °C. After 1.5 h at rt and 2 h at 40 °C, the reaction mixture was cooled to −78 °C and a solution of iodine (36.8 g, 145 mmol, 2.5 equiv) in THF (150 mL) was added dropwise. The reaction mixture was warmed to rt, hydrolyzed with a 1 M aqueous solution of hydrochloric acid, and extracted with ether. The combined organic extracts were successively washed with a saturated aqueous solution of $NaHCO_3$ and a 25% aqueous solution of $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by distillation under reduced pressure (in the presence of a small amount of Cu powder) to afford 11.3 g (73%) of **41** as a colorless oil; bp 85 °C/10 mmHg; IR 3070, 1640, 1580, 1250, 990, 915, 840, 760, 690 cm^{-1}; ^{1}H NMR δ 7.16 (t, J=8.0 Hz, 1H), 5.77 (ddt, J=17.3, 9.6, 6.1 Hz, 1H), 5.11–5.03 (m, 2H), 2.83 (ddt, J=8.0, 6.1, 1.5 Hz, 2H), 0.29 (s, 9H); ^{13}C NMR δ 152.7 (d), 134.6 (d), 116.0 (t), 107.8 (s), 38.8 (t), 1.0 (q, 3C); EIMS m/z (relative intensity) 266 (M$^+$, 21), 185 (80), 139 (M−I$^+$, 4), 83 (11), 73 (100).

6.4.4.3. (*E*)-1-Iodopenta-1,4-diene (42). To a solution of MeONa [prepared by portionwise addition of sodium pieces (3.85 g, 167 mmol, 4.0 equiv) in MeOH (100 mL), 20–45 °C] at rt was added a solution of **41** (11.1 g, 41.7 mmol) in MeOH (30 mL). After 4 h at 40 °C, the reaction mixture was hydrolyzed with H_2O (100 mL) and extracted with pentane. The combined organic extracts were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by distillation under reduced pressure (in the presence of a small amount of Cu powder) to afford 6.0 g (74%) of **42** as a slightly yellow oil; bp 60–70 °C/35 mmHg; IR 1640, 1605, 1430, 1250, 1230, 1175, 1115, 990, 950, 915, 860, 840 cm^{-1}; ^{1}H NMR δ 6.55 (dt, J=14.3, 6.4 Hz, 1H), 6.07 (dt, J=14.3, 1.5 Hz, 1H), 5.79 (ddt, J=17.3, 10.3, 6.4 Hz, 1H), 5.12–5.05 (m, 2H), 2.81 (ddq, apparent tq, J=6.4, 1.5 Hz, 2H); ^{13}C NMR δ 143.6 (d), 134.2 (d), 116.5 (t), 72.8 (d), 39.7 (t).

6.4.4.4. (*E*)-1-Tributylstannylpenta-1,4-diene (26). To a solution of **42** (580 mg, 3.00 mmol) in ether (15 mL) at −78 °C was added *t*-BuLi (4.0 mL, 1.7 M in pentane, 6.8 mmol, 2.3 equiv). After 0.5 h at −78 °C, the reaction mixture was warmed to 0 °C and *n*-Bu_3SnCl (0.89 mL, 3.3 mmol, 1.1 equiv) was added rapidly. After 0.5 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude alkenylstannane **26** was directly engaged in the next step without further purification (purification by flash chromatography on silica gel resulted in extensive protodestannylation). An analytical sample of **26** was obtained by rapid filtration on silica gel (pentane); ^{1}H NMR δ 6.11–5.96 (m, 2H), 5.87 (ddt, J=16.9, 10.3, 6.6 Hz, 1H), 5.05 (dq, J=17.0, 1.5 Hz, 1H), 5.03 (dq, J=10.3, 1.5 Hz, 1H), 2.94–2.89 (m, 2H), 1.58–1.46 (m, 6H), 1.40–1.26 (m, 6H), 0.95–0.86 (m, 15H); ^{13}C NMR δ 146.4 (d), 136.7 (d), 129.0 (d), 115.2 (t), 41.9 (t), 29.3 (t, 3C), 27.4 (t, 3C), 13.7 (q, 3C), 9.4 (t, 3C).

6.4.4.5. 2-{2-[(*tert*-Butyldimethylsilyl)oxy]-1,1-dimethylpent-4-enyl}-(2*E*)-4-(hexa-2,5-dienyl)thiazole (27). To a degassed solution of bromide **25** (65 mg, 0.16 mmol) and stannane **26** (72 mg, 0.20 mmol, 1.25 equiv) in freshly distilled NMP (2.5 mL) (argon bubbling, 10 min) at rt was added $PdCl_2(CH_3CN)_2$ (4 mg, 0.02 mmol, 0.1 equiv). After 0.5 h at rt, the reaction mixture was hydrolyzed with a 20% aqueous solution of NH_4OH, stirred for 0.5 h and extracted with ether. The combined organic extracts were washed with a 1 M aqueous solution of $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/ether 95:5) to afford 62 mg (95%) of **27** as a colorless oil; IR 3070, 1640, 1515, 1470, 1460, 1430, 1385, 1360, 1255, 1090, 1040, 1000, 970, 910, 835, 775, 740 cm^{-1}; ^{1}H NMR δ 6.74 (s, 1H), 5.86 (ddt, J=16.6, 10.2, 6.4 Hz, 1H), 5.77–5.52 (m, 3H), 5.10–4.98 (m, 2H), 4.96–4.85 (m, 2H), 4.07 (dd, J=6.0, 4.5 Hz, 1H), 3.50 (br d, J=6.4 Hz, 2H), 2.81 (apparent br t, J=6.4 Hz, 2H), 2.28 (m, 1H), 2.10 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), −0.11 (s, 3H); ^{13}C NMR δ 178.2 (s), 155.1 (s), 136.8 (d), 136.3 (d), 129.8 (d), 128.0 (d), 115.8 (t), 115.0 (t), 112.0 (d), 78.9 (d), 46.1 (s), 38.5 (t), 36.5 (t), 34.8 (t), 25.9 (q, 3C), 25.6 (q), 24.4 (q), 18.1 (s), −3.7 (q), −4.8 (q); EIMS m/z (relative intensity) 391 (M$^+$, 3), 376 (M−Me$^+$, 4), 350 (M−$C_3H_5^+$, 15), 336 (12), 335 (27), 334 (M−*t*-Bu$^+$, 100), 260 (20), 207 (41), 186 (12), 185 (72), 129 (13), 115 (14), 75 (10), 73 (54).

6.4.4.6. 2-[((2*E*)-4-Hexa-2,5-dienyl)thiazol-2-yl]-2-methylhex-5-en-3-ol (28). To a solution of **27** (300 mg, 0.777 mmol) in THF (10 mL) at rt was added *n*-Bu_4NF (2.3 mL, 1 M in THF, 2.3 mmol, 3.0 equiv). After 1.5 h at 50 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/Et_2O 75:25) to give 200 mg (94%) of **28** as a colorless oil; IR 3400 (br), 3070, 1640, 1520, 1470, 1430, 1365, 1050, 990, 970, 910, 740 cm^{-1}; ^{1}H NMR δ 6.75 (s, 1H), 5.91 (ddt, J=17.0, 10.2, 6.8 Hz, 1H), 5.82 (ddt, J=16.9, 10.2, 6.4 Hz, 1H), 5.72–5.50 (m, 2H), 5.10–4.96 (m, 4H), 4.52 (br d, J=5.7 Hz, 1H), 3.73 (m, 1H), 3.46 (br d, J=6.0 Hz, 2H), 2.78 (apparent br t, J=6.4, 2H), 2.32–2.24 (m, 1H), 2.05–1.94 (m, 1H), 1.44 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 178.9 (s), 155.4 (s), 136.8 (d), 136.3 (d), 130.3 (d), 127.7 (d), 116.5 (t), 115.2 (t), 111.9 (d), 77.9 (d), 44.6 (s), 36.6 (t, 2C), 34.7 (t), 26.9 (q), 24.3 (q); EIMS m/z (relative intensity) 277 (M$^+$, 1), 236 (M−$C_3H_5^+$, 19), 208 (19), 207 (100), 206 (21), 192 (16), 166 (9), 139 (11), 138 (12), 126 (9), 97 (6), 71 (10); HRMS (CI$^+$, CH_4) calcd for $C_{16}H_{24}NOS$ (M+H$^+$): 278.1579. Found: 278.1575.

6.4.5. Synthesis of the originally proposed structure of mycothiazole.

6.4.5.1. 2-[1-(2,2-Dioxo-2,3,6,7-tetrahydro-2λ^6-[1,2]-oxathiepin-7-yl)-1-methylethyl]-4-((2*E*)-hexa-2,5-dienyl)-thiazole (30). To a solution of **28** (110 g, 0.405 mmol) and DMAP (97 mg, 0.80 mmol, 2.0 equiv) in THF (3 mL) at rt was added dropwise a solution of allylsulfonyl chloride (84 mg, 0.60 mmol, 1.5 equiv) in THF (2 mL). After 2 h at rt, a solution of DMAP (97 mg, 0.80 mmol, 2.0 equiv) and allylsulfonyl chloride (84 mg, 0.60 mmol, 1.5 equiv) in THF (2 mL) was added. After 1 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined organic extracts were washed with an aqueous solution of $CuSO_4$, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was filtered through silica gel (ether) and after evaporation of the solvent under reduced pressure, the crude sulfonate **29** was dissolved in C_6H_6 (40 mL). To the resulting degassed solution (argon bubbling, 15 min) at 70 °C was added catalyst **II** [(51 mg, 0.06 mmol, 0.15 equiv) in three portions at 1 h interval]. After a further 1 h at 70 °C, the reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 70:30) to afford 98 mg (70%) of **30** as a colorless oil; IR

3080, 3015, 3030, 1640, 1515, 1430, 1360, 1170, 1055, 970, 910, 875, 830, 740, 700, 690 cm^{-1}; ^1H NMR δ 6.85 (s, 1H), 6.09 (m, 1H), 5.87 (ddt, J=17.3, 10.2, 6.4 Hz, 1H), 5.80–5.52 (m, 3H), 5.12–5.00 (m, 3H), 4.14 (m, 1H), 3.90 (apparent br dd, J=15.5, 8.1 Hz, 1H), 3.58–3.48 (m, 2H), 2.84 (apparent br t, J=6.4 Hz, 2H), 2.59 (m, 1H), 2.42 (dd, J=16.2, 8.5 Hz, 1H), 1.55 (s, 3H), 1.54 (s, 3H); ^{13}C NMR δ 174.5 (s), 156.0 (s), 136.9 (d), 134.5 (d), 130.3 (d), 127.8 (d), 119.1 (d), 115.2 (t), 113.1 (d), 90.1 (d), 50.5 (t), 44.6 (s), 36.6 (t), 34.8 (t), 29.8 (t), 26.9 (q), 22.4 (q); EIMS *m/z* (relative intensity) 353 (M^+, 39), 338 ($M-Me^+$, 7), 324 (10), 313 (19), 312 ($M-C_3H_5^+$, 100), 272 ($M-[CH_2{=}CH{-}CH_2{-}CH{=}CH]^+$, 12), 218 (37), 207 (58), 206 (95), 192 (22), 164 (28), 152 (22), 139 (28), 138 (58), 97 (19), 71 (23), 55 (21).

6.4.5.2. 2-{1-[3-(3,3-Dimethoxypropyl)-2,2-dioxo-2,3,6,7-tetrahydro-2λ^6-[1,2]oxathiepin-7-yl]-1-methylethyl}-4-((2*E*)-hexa-2,5-dienyl)thiazole (32). To a solution of **30** (142 mg, 0.402 mmol), iodide **31** (111 mg, 0.482 mmol, 1.2 equiv), and HMPA (280 μL, 1.61 mmol, 4.0 equiv) in THF (10 mL) at −78 °C was added dropwise LiHMDS (0.48 mL, 1 M in THF, 0.48 mmol, 1.2 equiv). After 20 min at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 65:35) to afford 139 mg (76%) of **30** as a colorless oil and as a nearly 1:1 mixture of diastereomers. In order to facilitate characterization, the two diastereomers were partially separated by resubjecting an analytical sample of the mixture to purification by flash chromatography.

First eluting diastereomer: IR 1640, 1520, 1460, 1360, 1170, 1130, 1055, 970, 905, 740, 690 cm^{-1}; ^1H NMR δ 6.82 (s, 1H), 6.08 (m, 1H), 5.94–5.47 (m, 4H), 5.18–4.96 (m, 3H), 4.38 (apparent td, J=5.5, 2.0 Hz, 1H), 4.09 (m, 1H), 3.49 (br d, J=6.4 Hz, 2H), 3.33 (s, 6H), 2.81 (apparent br t, J=6.4 Hz, 2H), 2.57–2.15 (m, 4H), 2.08–1.67 (m, 2H), 1.51 (s, 6H); ^{13}C NMR δ 174.6 (s), 155.9 (s), 136.9 (d), 133.8 (d), 130.3 (d), 127.8 (d), 126.9 (d), 115.2 (t), 113.0 (d), 104.0 (d), 91.4 (d), 61.0 (d), 53.2 (q, 2C), 44.7 (s), 36.6 (t), 34.8 (t), 29.7 (t), 29.1 (t), 27.0 (q), 24.6 (t), 22.5 (q); EIMS *m/z* (relative intensity) 424 ($M-OMe^+$, 10), 423 (38), 382 (31), 344 (20), 326 (12), 316 (15), 288 (13), 235 (13), 218 (12), 208 (15), 207 (70), 206 (57), 194 (13), 192 (15), 139 (15), 138 (27), 97 (13), 91 (14), 79 (14), 77 (13), 71 (100); HRMS (CI^+, CH_4) calcd for $C_{22}H_{34}NO_5S_2$ ($M+H^+$): 456.1878. Found: 456.1875.

Second eluting diastereomer: IR 1640, 1520, 1460, 1420, 1360, 1170, 1125, 1060, 970, 905, 740, 690 cm^{-1}; ^1H NMR δ 6.82 (s, 1H), 5.95–5.77 (m, 2H), 5.74–5.50 (m, 3H), 5.17–4.97 (m, 3H), 4.38 (br t, J=5.5 Hz, 1H), 3.96 (m, 1H), 3.50 (br d, J=6.4 Hz, 2H), 3.34 (s, 3H), 3.33 (s, 3H), 2.81 (apparent br t, J=6.4 Hz, 2H), 2.56 (m, 1H), 2.39–2.17 (m, 2H), 2.00 (m, 1H), 1.80–1.69 (m, 2H), 1.55 (s, 3H), 1.52 (s, 3H); ^{13}C NMR δ 174.5 (s), 156.0 (s), 136.9 (d), 132.2 (d), 130.3 (d), 127.8 (d), 124.1 (d), 115.2 (t), 113.1 (d), 104.0 (d), 88.2 (d), 60.4 (d), 53.2 (q), 53.1 (q), 44.5 (s), 36.6 (t), 34.8 (t), 29.7 (t), 29.6 (t), 27.0 (q), 25.0 (t), 22.5 (q); EIMS *m/z* (relative intensity) 384 (21), 383 (16), 336 (20), 168 (13), 167 (75), 166 (100), 97 (13), 75 (31), 71 (64); HRMS (CI^+, CH_4) calcd for $C_{22}H_{34}NO_5S_2$ ($M+H^+$): 456.1878. Found: 456.1875.

6.4.5.3. (5*Z*)-2-[(4-(2*E*)-Hexa-2,5-dienyl)thiazol-2-yl]-10,10-dimethoxy-2-methyl-7-methylenedec-5-en-3-ol (33). To a solution of **32** (139 mg, 0.305 mmol) in THF (10 mL) at −78 °C was added a solution of *n*-BuLi (0.25 mL, 2.5 M in hexanes, 0.625 mmol, 2.5 equiv). After 0.5 h at −78 °C, a solution of ICH_2MgCl [prepared from CH_2I_2 (576 mg, 2.15 mmol, 7 equiv) and *i*-PrMgCl (1.1 mL, 2 M in THF, 2.2 mmol, 7 equiv) in THF (10 mL), −80 °C, 1 h] was added via a cannula to the reaction mixture. After 15 min at −78 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/ether 70:30) to afford 74 mg (60%) of **33** as a colorless oil; IR 3420, 1640, 1520, 1450, 1380, 1365, 1125, 1055, 970, 910 cm^{-1}; ^1H NMR δ 6.77 (s, 1H), 5.92–5.53 (m, 5H), 5.18–4.98 (m, 2H), 4.98 (br s, 1H), 4.85 (br s, 1H), 4.63 (m, 1H), 4.35 (apparent t, J=5.8 Hz, 1H), 3.73 (m, 1H), 3.47 (apparent br d, J=6.4 Hz, 2H), 3.32 (s, 6H), 2.80 (apparent br t, J=6.4 Hz, 2H), 2.49 (m, 1H), 2.24–2.09 (m, 3H), 1.75–1.66 (m, 2H), 1.44 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 179.0 (s), 155.4 (s), 144.7 (s), 136.9 (d), 131.0 (d), 130.4 (d), 129.7 (d), 127.7 (d), 115.2 (t), 113.7 (t), 111.9 (d), 104.1 (d), 78.7 (d), 52.8 (q, 2C), 44.7 (s), 36.6 (t), 34.7 (t), 32.2 (t), 31.2 (t), 31.1 (t), 27.0 (q), 24.2 (q); MS (CI^+, CH_4) *m/z* (relative intensity) 406 ($M+H^+$, 74), 390 ($M-Me^+$, 64), 374 (37), 368 (38), 358 (35), 318 (30), 280 (26), 236 (36), 183 (28), 169 (33), 127 (29), 70 (100); HRMS (CI^+, CH_4) calcd for $C_{23}H_{36}NO_3S$ ($M+H^+$): 406.2416. Found: 406.2422.

6.4.5.4. (4*Z*)-8-[((2*E*)-4-Hexa-2,5-dienyl)thiazol-2-yl]-7-hydroxy-8-methyl-3-methylenenon-4-enylmethyl carbamate (39) (originally proposed structure of mycothiazole). To a solution of **33** (15 mg, 37 μmol) in THF/H_2O (1:1, 6 mL) at rt was added PPTS (19 mg, 74 μmol, 2.0 equiv). After 18 h at 50 °C, the reaction mixture was hydrolyzed with water and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude aldehyde **34** was dissolved in *t*-BuOH/H_2O (3:1, 2 mL) and to the resulting solution at 0 °C were successively added 2-methylbut-2-ene (43 μL, 0.41 mmol, 11 equiv), $NaH_2PO_4 \cdot H_2O$ (69 mg, 0.44 mmol, 12 equiv), and $NaClO_2$ (24 mg, 0.22 mmol, 6 equiv). After 1 h at 0 °C, the reaction mixture was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude highly sensitive carboxylic acid **35**, which was immediately dissolved in toluene (5 mL). To the resulting solution at rt were successively added Et_3N (20 μL, 0.14 mmol, 3.9 equiv) and diphenylphosphoryl azide (24 μL, 0.11 mmol, 3.0 equiv). After 1 h at rt, the reaction mixture was heated at 110 °C. After 1 h, MeOH (3 mL) was added and the reaction mixture was further heated at reflux for 1 h. After concentration under reduced pressure, the residue was purified by preparative chromatography on silica gel (pentane/ether 50:50) to afford 10 mg of the isocyanate **37**. This compound (which was initially mistaken with the amine **38**) was dissolved in CH_2Cl_2 (3 mL), and to the resulting solution at rt were successively added Et_3N (20 μL, 0.14 mmol) and $ClCO_2Me$ (8 μL, 0.10 mmol). After 0.5 h, additional quantities of Et_3N (50 μL, 0.36 mmol) and $ClCO_2Me$ (28 μL, 0.36 mmol) were added. As no reaction apparently occurred, MeOH (2 mL) was added to the reaction mixture. After 1 h at rt, the reaction mixture was concentrated under reduced pressure and the residue was purified by preparative chromatography on silica gel (petroleum ether/EtOAc 50:50) to afford 5 mg (33%) of **39**; R_f (petroleum ether/EtOAc) 0.5; ^1H NMR δ 6.77 (s, 1H), 5.92–5.52 (m, 5H), 5.43 (br s, 1H, NH), 5.09–4.86 (m, 4H+OH), 3.79 (br d, J=9.8 Hz, 1H), 3.63 (s, 3H), 3.46 (d, J=6.4 Hz, 2H), 3.35–3.14 (m, 2H), 2.80 (t, J=6.0 Hz, 2H), 2.48–2.17 (m, 4H), 1.43 (s, 3H), 1.39 (s, 3H); EIMS 404 (M^+, 5), 373 ($M-OMe^+$, 2), 316 (21), 236 (42), 208 (15), 207 (100), 206 (10), 192 (6), 138 (5), 105 (8), 88 (9); HRMS (EI) calcd for $C_{22}H_{32}N_2O_3S$ (M^+): 404.2134. Found: 404.2133.

6.5. Comparison of the ^1H and ^{13}C NMR data

See Tables 3 and 4.

6.6. Formal enantioselective approach

6.6.1. Synthesis of (*R*)-13 by an enantioselective allylboration. To a solution of (+)-DIPCl (390 mg, 1.20 mmol, 1.2 equiv) in ether (10 mL) at −78 °C was added dropwise allylmagnesium bromide (1.1 mL, 1 M in ether, 1.1 mmol, 1.1 equiv). After 3 h at −78 °C, a solution of aldehyde **12** (230 mg, 1.00 mmol) in ether (2 mL) was added. After 2 h at −78 °C, the reaction mixture was warmed to rt and hydrolyzed by addition of a 3 M aqueous solution of NaOH (2 mL) and a 30% aqueous solution of H_2O_2 (1 mL). After 1 h at 40 °C, the resulting mixture was filtered through Celite (ether) and the filtrate was extracted with EtOAc. The

Table 3. Table of comparison of the ^1H NMR data

H	Synthetic compound **39** present study 300 MHz, $CDCl_3$	Synthetic compound (−)-**39**[9] previous total synthesis 270 MHz, $CDCl_3$	(−)-Mycothiazole natural product[6] 300 MHz, $CDCl_3$
H5	6.77 (s)	6.77 (s)	6.73 (t)
H7	3.79 (br d, J=9.8 Hz)	3.78 (dd, J=9.6, 3.0 Hz)	3.74 (dd, J=10.2, 3.0 Hz)
H8	2.48–2.17 (m)	2.43–2.18 (m)	2.39 (m), 2.24 (m)
H9	5.92–5.52 (m)	5.91–5.52 (m)	5.65 (m)
H10	5.92–5.52 (m)	5.91–5.52 (m)	5.83 (m)
H12	2.48–2.17 (m)	2.43–2.18 (m)	2.29 (m), 2.18 (m)
H13	3.35–3.14 (m)	3.33–3.16 (m)	3.23 (m), 3.14 (m)
H14	3.46 (d, J=6.4 Hz)	3.46 (d, J=5.6 Hz)	3.46 (d, J=7.2 Hz)
H15	5.92–5.52 (m)	5.91–5.52 (m)	5.68 (br m)
H16	5.92–5.52 (m)	5.91–5.52 (m)	5.50 (m)
H17	2.80 (br t, J=6.0 Hz)	2.80 (t, J=6.0 Hz)	2.84 (dt, J=6.3, 1.5 Hz)
H18	5.92–5.52 (m)	5.91–5.52 (m)	5.73 (m)
H19	5.09–4.86 (m)	5.09–4.88 (m)	4.96 (m), 4.96 (m)
H20	5.09–4.86 (m)	5.09–4.88 (m)	4.96 (m), 4.83 (m)
H21	1.43 (s)	1.43 (s)	1.39 (s)
H22	1.39 (s)	1.39 (s)	1.35 (s)
H24	3.63 (s)	3.63 (s)	3.56 (s)
NH	5.43 (br s)	5.43 (br s)	Not indicated
OH	5.09–4.86 (m)	5.09–4.88 (m)	Not indicated

Table 4. Table of comparison of the ^{13}C NMR data

C	Synthetic compound **39** present study 75 MHz, $CDCl_3$	Synthetic compound (−)-**39** previous total synthesis[9] 67.5 MHz, $CDCl_3$	(−)-Mycothiazole natural product[6] 75 MHz, $CDCl_3$
C2	Not accurately assigned (low signal/noise ratio)	179.4	179.4
C4	155.4	155.4	154.9
C5	112.0	112.0	111.8
C6	44.6	44.5	44.5
C7	78.1	78.1	78.1
C8	30.6	30.6	30.6
C9	130.6	130.6	130.8
C10	130.9	130.9	130.8
C11	Not accurately assigned (low signal/noise ratio)	142.5	142.4
C12	37.1	37.1	37.1
C13	39.4	39.4	39.4
C14	**34.7**	**34.7**	29.4
C15	**127.6**	**127.6**	126.7
C16	**130.5**	**130.4**	128.8
C17	**36.6**	**36.6**	31.5
C18	136.8	136.8	136.4
C19	115.2	115.2	115.0
C20	115.9	115.8	115.8
C21	26.7	26.7	26.6
C22	23.9	23.9	23.9
C23	157.2	157.1	157.1
C24	51.8	51.8	51.8

combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 90:10 to 85:15) to afford 190 mg (70%) of (*R*)-**13** as a colorless oil. The ee value (ee=54%) was determined by HPLC: Chiral OD-H column, elution rate: 1 mL/min, eluent: hexane, detection: 230–260 nm, injection: 10 μL (of a 2 mg/mL solution), retention times: (*S*)-enantiomer, 48.4 min; (*R*)-enantiomer, 55.5 min.

6.6.2. Synthesis of (*R*)-13 by an enantioselective allyltitanation. To a solution of ((*S*,*S*)-TADDOL)CpTiCl (980 mg, 1.60 mmol, 1.6 equiv) in ether (16 mL) at 0 °C was added dropwise allylmagnesium chloride (650 μL, 2 M in THF, 1.30 mmol, 1.3 equiv). After 3 h at 0 °C, a solution of aldehyde **12** (230 mg, 1.00 mmol) in ether (4 mL) was added at −78 °C. After 5 h at −78 °C, the reaction mixture was warmed to rt and hydrolyzed with a 45% aqueous solution of NH_4F. After stirring overnight at rt, the resulting mixture was filtered through Celite (ether). The organic layer was separated and washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was taken-up in pentane and the precipitated (*S*,*S*)-TADDOL (634 mg, 1.36 mmol, 85% recovery) was separated by filtration. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography (pentane/ether 90:10 to 85:15) to afford 226 mg (82%) of (*R*)-**13** as a colorless oil. The ee value (ee=99%) was determined by HPLC with chiral OD-H column; $[\alpha]_D^{20}$ +20.2 (*c* 1.0, MeOH).

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