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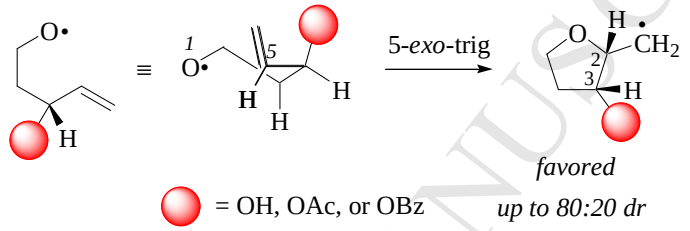

2,3-cis-Cyclization of 4-Pentenoxyl Radicals

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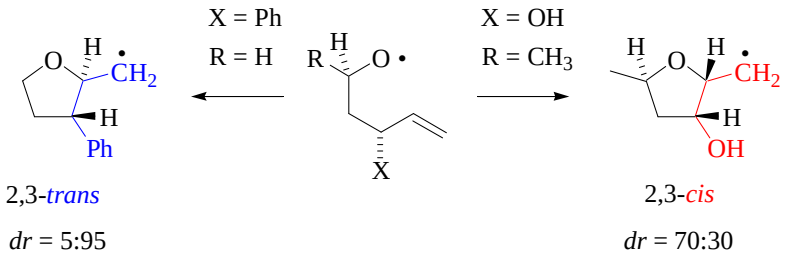
* Corresponding author. Tel.: +49-631-205-2431, Fax: +49-631-205-3921, e-mail: hartung@chemie.uni-kl.de

Keywords: Alkoxyl radical; Polar effect; Reactive conformer; Stereoselective synthesis; Tetrahydrofuran.

Abstract: 4-Pentenoxyl radicals cyclize 2,3-cis-selectively, when substituted by an allylic hydroxy, acetyloxy, or benzoyloxy group. Additional substituents increase or decrease the fraction of 2,3-cis-cyclized product, depending on relative configuration, positioning, and their chemical nature. The preference for 3-acceptor-subsituted pentenoxyl radicals to furnish products of 2,3-cis-ring closure arises from a secondary orbital interaction between the allylic oxygen substituent and the alkene entity, kinetically disfavoring the competing 2,3-trans-mode of 5-*exo*-cyclization. Aligning the β-C,O-bond in anticline orientation to the plane of the alkene, which is the preferred conformation for transition structures for 2,3-trans-cyclization, stabilizes the double bond by delocalizing π-electrons into the σ^*(C,O)-orbital. Along with energy decreases the affinity of π-electrons for adding the oxygen radical. In 2,3-cis-cyclization, a similar stabilizing effect cannot occur, because the allylic oxygen substituent and the alkene align synperiplanar. The kinetic effect of an allylic oxygen substituent becomes furthermore apparent in cyclization of the 3-hydroxynona-1,8-dien-5-oxyl radical, favoring intramolecular addition to the unsubstituted allylic double bond by a factor three.

1. Introduction

4-Pentenoxyl radicals cyclize 2,3-trans-selectively when substituted with an allylic alkyl or a phenyl group (Scheme 1).[1] The fraction of 2,3-trans-product increases with the size of the allylic substituent, from 80/20 for methyl to above 99/1 for *tert*-butyl.[2,3] Transition state theory[4] explains 2,3-trans-selectivity on the basis of cumulative 1,2- and 1,3-repulsion, progressively disfavoring 2,3-cis-addition as steric demand of the allylic substituent grows.[5,6]



Scheme 1. Stereoselectivity in 5-*exo*-cyclization of allyl substituted 4-pentenoxyl radicals.[2,3,7]

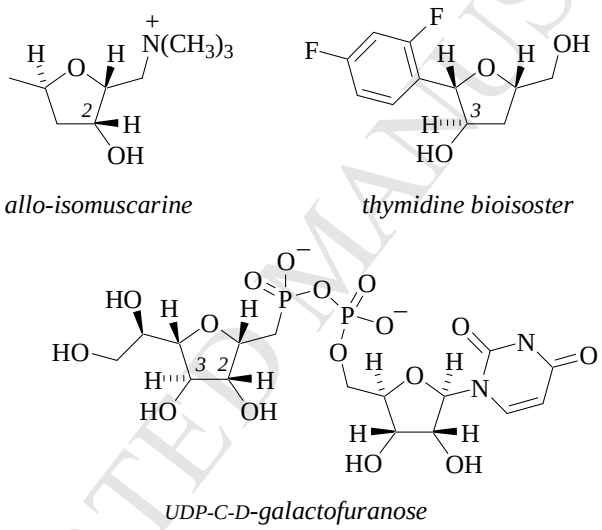


Figure 1. Structure formulas of bio-inspired 2- and 3-hydroxy-substituted tetrahydrofurans as targets in organic synthesis.[8,9,10]

Steric effects controlling selectivity in synthesis of 2,3-trans-substituted heterocycles by intramolecularly adding polar reactands[11,12] or radicals[13,14,15,16,17] to double bonds are well documented in the scientific literature. In the past decades, however, more and more reports

appeared describing selectivity not fitting into this stereochemical scheme. Alkenols bearing an allylic oxygen substituent, for example, show a marked propensity for cyclizing 2,3-cis-selectively, when treated with molecular iodine. A theory explaining this phenomenon starts to evolve, but is not yet consistent.[18,19,20,21]

The affinity of the allylic hydroxy group to direct cyclizations 2,3-cis-selectively also extends to oxygen radical additions, as recently outlined in synthesis of *allo*-isomuscarine (Scheme 1, Figure 1).[8] The alkene in this example poses the nucleophilic component and the radical oxygen the electrophilic, which is exactly opposed to the situation in electrophile-induced alkenol cyclization. A theory explaining 2,3-cis-selectivity in radical cyclization so far does not exist.

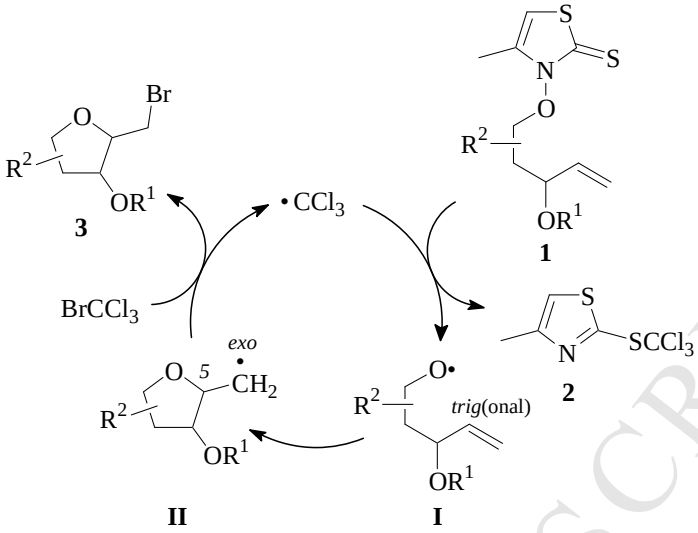
For uncovering the principles leading to 2,3-cis-selective ring closures, we investigated in the study summarized below, reactivity and selectivity of seven 4-pentenoxyl radicals, differing in substitution at the allylic carbon and at proximal positions. The results from this effort show that an allylic oxygen substituent reduces the rate of intramolecular 2,3-trans-addition, and leave the rate of the 2,3-cis-pathway largely unaffected. The rate effect of the allylic oxygen substituent is not restricted to stereocontrol but also controls selectivity in intramolecular addition of an oxyl radical to two chemically different C,C-double bonds. The 3-hydroxynona-1,8-dien-5-oxyl radical thus prefers adding to the unsubstituted allylic double bond by a partial rate factor three.

2. Results and Interpretation

2.1 Alkenoxyl radical generation, chain reaction, and design of alkenoxyl radicals for conducting the study

Based on the expertise from preceding mechanistic studies,[8,22] we used *O*-pentenyl esters of 1,3-thiazole-derived heterocyclic thiohydroxamic acids[23] as progenitors for generating oxygen radicals. Heating compounds of this kind, for example the 3-alkoxy-1,3-thiazole-2(3*H*)-thiones,[1] in the presence of a chemical initiator, or photoexciting the molecules with 350 nm-light, almost specifically breaks the N,O-bond, allowing to liberate oxygen radicals under pH-neutral and non oxidative conditions from otherwise stable compounds.

The mechanism operating for converting 3-alkoxy-1,3-thiazole-2(3*H*)-thiones into alkoxyl radicals is a chain reaction. The sequence starts by adding a chain propagating radical to the thione sulfur of the thiohydroxamate used as progenitor, providing oxygen radical **I** and substituted thiazole **2** (Scheme 2).[24] By extrapolating known kinetic data[2,25,26], we expect allyl-substituted derivatives to intramolecularly add with a rate constant between 10^8 s^{-1} and 10^9 s^{-1} to the C,C-double bond. In terms of regioselectivity the intramolecular addition should lead to a 5-*exo*/6-*endo*-distribution ranging from 98:2 (for X = CH_3) to 90:10 (for X = OH).[27] For terminating the sequence, cyclized radical **II** needs to be trapped by a mediator. In the present study, we used bromotrichloromethane for this purpose, providing 2-bromomethyltetrahydrofuran **3** as major oxygen radical-derived product.[8] The requested information on stereocontrolling effects of oxygen substituents in cyclizations then is stored in the cis/trans-ratio of bromocyclization product **3**. The second product of bromine atom transfer from bromotrichloromethane to carbon radical **II** is the trichloromethylradical, being essential for resuming the chain reaction.



Scheme 2. Chain reaction for bromomethyltetrahydrofuran synthesis from 3-alkenoxy-4-methylthiazole-2(3*H*)-thione **1** and $BrCCl_3$ (R^1 = H, Ac, Bz; R^2 = H, OAc, CH_3).[8,24]

For clarifying the role of the allylic oxygen substituent in stereoselectivity control for alkenoxyl radical 5-*exo*-cyclization, we conceived a set of six alkenoxyl radicals: three monosubstituted 4-pentenoxyl radicals (**Ia**–**c**), two homologues bearing acetyloxy groups in different relative configuration (*erythro*/*threo*-**Id**), and a third (**Ie**) having an allylic acyloxy group positioned next to two additional substituents (Figure 2). As we became aware of the kinetic role of the allylic oxygen substituent, we included nonadienyloxyl radical **If** into the study, for exploring regioselectivity effects.

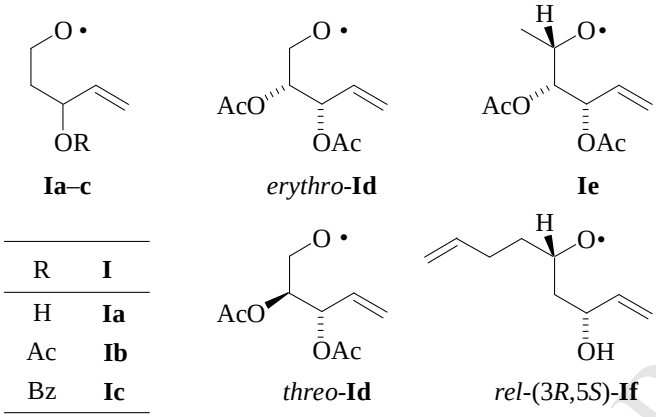
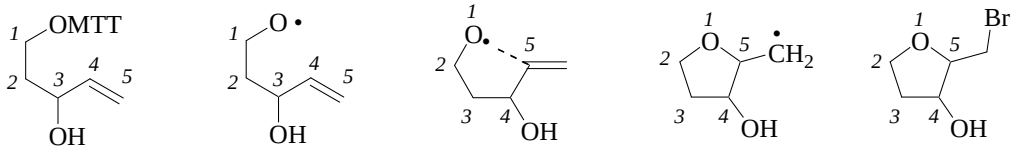


Figure 2. Structure formulas of 4-pentenoxyl radicals **Ia–f** conceived for uncovering the origin of 2,3-cis-selectivity in homolytic 5-*exo*-cyclization.

2.2 Convention used for numbering atom positions

Oxygen and carbon differ in priority for systematically naming aliphatic and heterocyclic compounds. For carbons in the aliphatic side chain of *O*-alkenyl esters **1**, and for the carbons of radical **I**, we adhered to the IUPAC-recommendation for aliphatic compounds.[28] A transition structure TS-**I** associated with 5-*exo*-cyclization, in the chosen stereochemical model, derives from tetrahydrofuran (cf. section 2.5.3). Numbering atoms in intermediate TS-**I**, similar to tetrahydrofuran core of cyclized carbon radical **II**, and bromocyclization product **3** thus follows the Hantzsch and Widman convention.[29,30]

For assigning configuration of vicinal stereocenters, we adhered in this article to descriptors *erythro* and *threo*. By this approach we feel, that the reader may easier follow differences in chemical selectivity, as configuration at one of the stereocenters changes.



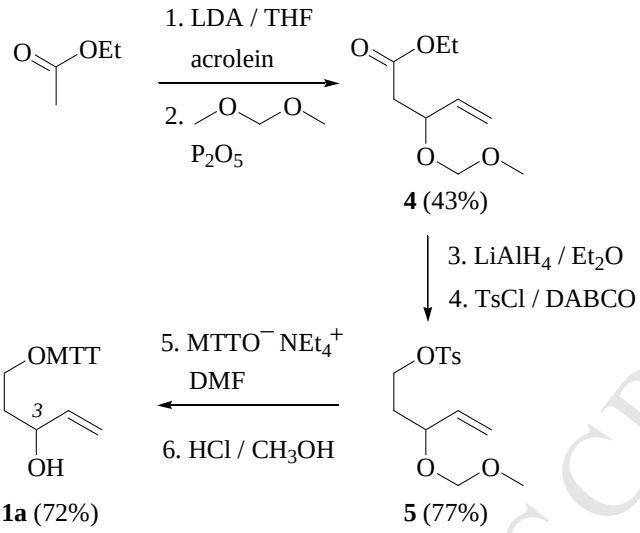
1a **Ia** TS-**Ia** **IIa** **3a**

Figure 3. Convention used in this article for numbering atoms in product classes associated with alkenoxyl radical cyclization, as exemplified for alkenoxythiazolethione **1a**, derived 4-alkenoxyl radical **Ia**, transition structure for 5-*exo*-cyclization TS-**Ia**, 5-*exo*-cyclized carbon radical **IIa**, and bromocyclization product **3a** (MTT = 4-methyl-2-thiooxo-1,3-thiaz-3-yl).

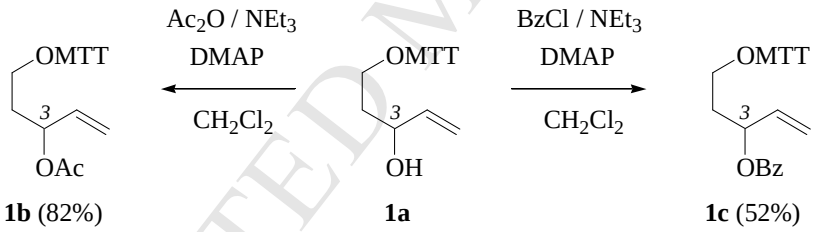
2.3 3-Alkenoxy-4-methylthiazole-2(3*H*)-thiones

2.3.1 Monosubstituted O-pentenyl thiohydroxamates

For constructing the alkenoxy group of thiohydroxamate **1a**, we connected in the initial step ethyl acetate to acrolein by a mixed aldol addition (Scheme 3).[31,32] The product formed in the addition, ethyl 3-hydroxypentenoate, eliminates water on standing. For preventing this elimination to occur, we converted the reactive hydroxy group into a methoxymethyloxy (MOMO)-group.[32,33] Subsequently, we transformed the ethoxycarbonyl group in ester **4** into primary alkyl sulfonate group in tosylate **5** by standard prodecures.[32,34] Displacing the sulfonate group in tosylate **5** by the 4-methyl-2-thiooxo-(3*H*)-1,3-thiazyl-1-oxide anion furnishes a MOM-protected *O*-alkenyl thiohydroxamate, which was treated with hot acidic methanol for solvolytically cleaving off the acetal-protecting group. Esterifying the hydroxy group in alcohol **1a** with acetic anhydride gives acetate **1b**. Using benzoyl chloride as acylation reagent provides benzoate **1c** (Scheme 4).



Scheme 3. Summary of functional group transformation for preparing 3-(3-hydroxypent-4-enyloxy)thiazolethione **1a** from ethyl acetate (MTTO = 4-methyl-2-thiooxo-1,3-thiazyl-3-oxy; cf. Figure 3).

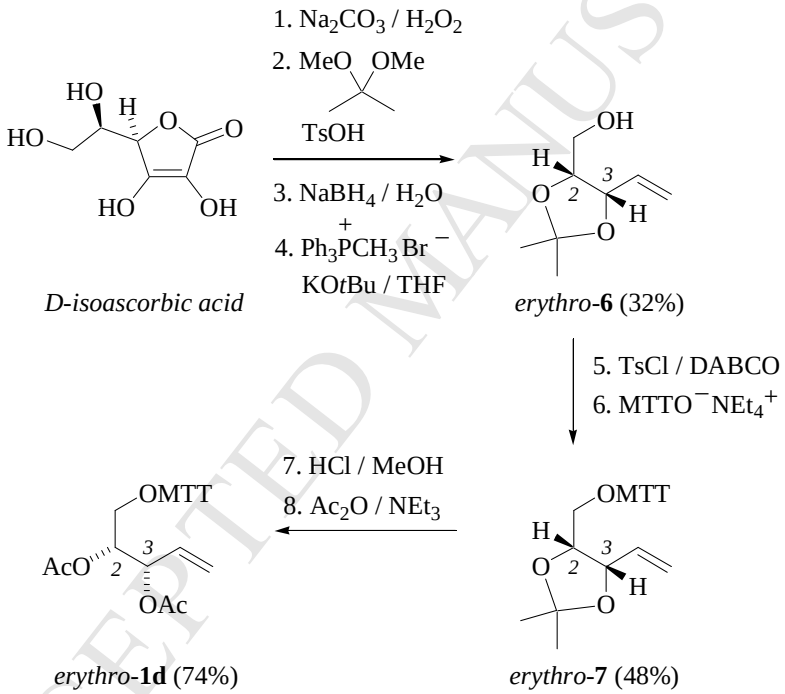


Scheme 4. *O*-Acylation of 3-(3-hydroxypent-4-enyloxy)thiazolethione **1a**.

2.3.2 Disubstituted O-pentenyl thiohydroxamates

For preparing the *erythro*-configured side chain of *O*-(2,3-*erythro*-bisacetyloxypentenyl) thiohydroxamate *erythro*-**1d**, we started from D-erythronolactone. The lactone is synthetically available from D-isoascorbic acid by oxidatively removing two carbon atoms (Scheme 5). For preventing oxidative side reactions, we protected the two hydroxy groups of the lactone with

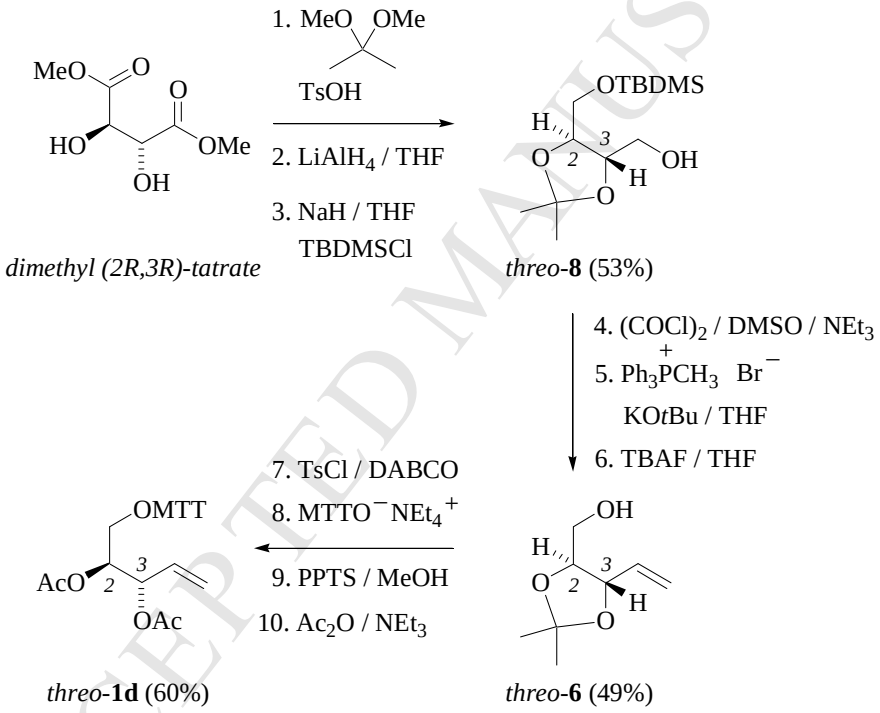
2,2-dimethoxypropane in acidic solution under kinetic control, leading to the derived acetonide. [35] Reducing the protected D-erythronolactone with sodium borohydride affords a lactol, which was treated with methanediyltriphenylphosphorous ylide to furnish alkenol *erythro*-**6**.[35,36,37] For converting alkenol *erythro*-**6** into *O*-alkenyl thiohydroxamate *erythro*-**7**, we adhered to methods already summarized in Scheme 3.[24,38,39] At the final stage, we again changed protecting groups at oxygen from acetonide, required for synthesis, to acyl required for alkenoxyl radical cyclization.[40]



Scheme 5. Preparing of 3-[2,3-*erythro*-2,3-bis-(acetyloxy)pent-4-en-1-oxy]thiazolethione *erythro*-**1d** from D-isoascorbic acid.

For preparing *O*-(*threo*-2,3-bisacetyloxypentenyl) thiohydroxamate *threo*-**1d**, we used dimethyl (2*R*,3*R*)-tartrate as starting material. The ester comprises two stereocenters in the

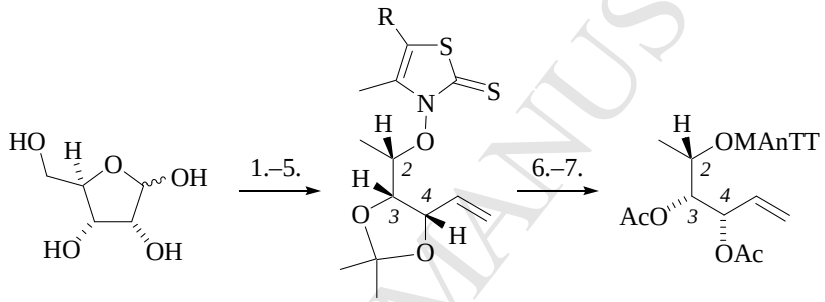
required configuration and two functional groups for building the carbon skeleton of target compound *threo*-**1d**. One of the ester groups served in a sequence adapted from synthesis of diastereomer *erythro*-**1d** for introducing the thiohydroxamate functional group at a primary carbon. The second ester group was used for constructing the alkene entity needed for conducting the alkenoxyl radical cyclization. By this strategy, we obtained monosilyl-protected diol *threo*-**8** as first key intermediate, acetonide-protected 4-pentenetriol *threo*-**6** as second and *O*-alkenyl thiohydroxamate *threo*-**1d** as final product.[41,42,43,44,45]



Scheme 6. Synthesis of 3-[2,3-*threo*-2,3-bis-(acetyloxy)pent-4-en-1-oxy]thiazolethione *threo*-**1d** from dimethyl (2*R*,3*R*)-tartrate.

*2.3.3 Trisubstituted O-pentenyl thiohydroxamate **1e***

For accomplishing synthesis of D-*arabino*-configured thiohydroxamate **1e** we extended the five carbon chain from D-ribose by one carbon in a Wittig-alkenylation, and inverted configuration at carbon C2 in the thiohydroxamate O-alkylation step (Scheme 7). For simplifying work-up procedures we, again, used the acetonide protecting group for the glycol segment. We also changed the thiohydroxamic acid to 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione, allowing to crystalline target compound **1e**, for additional purification in the final step.[46]

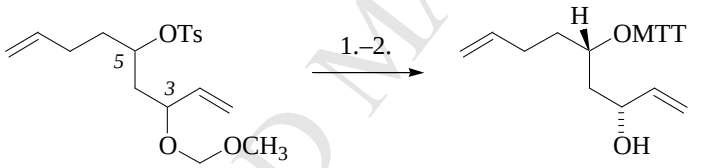


D-ribose **9** (15%) **1e** (43%)

Scheme 7. Synthesis of 2,3,4-*arabino*-configured 3-(hexenoxy)thiazolethione **1e** from D-ribose [R = 4-methoxyphenyl; reagents and conditions – 1. step: acetone, concentrated sulfuric acid (81% yield);[47] 2. step: iodine, imidazole, triphenylphosphine, toluene/acetonitrile (54% yield);[48,49] 3. step: palladium on charcoal, hydrogen, ethanol (97% yield);[50,51] 4. step: methyl triphenylphosphonium bromide, potassium *tert*-butoxide, tetrahydrofuran (67% yield); 5. step: 3-hydroxy-4-methyl-5-(4-methoxyphenyl)-1,3-thiazole-2(3*H*)-thione (MAnTTOH), diethyl azodicarboxylate, triphenylphosphine, benzene (54% yield); 6. step: hydrogen chloride, methanol (96% yield); 7. step: acetic anhydride, 4-(*N*,*N*-dimethylamino)pyridine, dichloromethane (45% yield)].

*2.3.4 O-(3-Hydroxy-5-nona-1,8-dienyl) thiohydroxamate **1f***

For preparing the C9-carbon skeleton of dienyl tosylate **10** we added but-3-en-1-yl magnesium bromide to 3-(methoxymethyloxy)pent-4-enal and esterified the resulting product, 3-(methoxymethyloxy)nona-1,8-dien-5-ol, with *p*-toluenesulfonyl chloride. Heating tosylate **10** with 3-hydroxy-4-methyl-1,3-thiazole-2(3*H*)-thione tetraethylammonium salt in DMF yields a MOM-protected *O*-dienyl thiohydroxamate as 50/50-mixture of stereoisomers. The diastereomers separate on the silica gel column, used for purifying the 3-(3-hydroxynona-1,8-dien-5-yl)thiazolethione **1f** after having solvolytically cleaved off the MOM-protecting group (Scheme 8). Only isomer *rel*-(3*R*,5*S*)-**1f** provided a correct combustion analysis and was therefore considered in the subsequent alkenoxyl radical study.



10 *rel*-(3*R*,5*S*)-**1f** (23%)

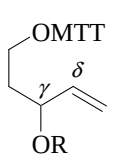
Scheme 8. Preparing 3-(3-hydroxynona-1,8-dien-5-yl)thiazolethione *rel*-(3*R*,5*S*)-**1f** from dienyl tosylate **10** (Supplementary data) [reagents and conditions – (1.): 3-hydroxy-4-methyl-1,3-thiazole-2(3*H*)-thione tetraethylammonium salt, DMF, 40 °C (67% yield); (2.): hydrogen chloride, methanol, and column chromatography for separating diastereomers {*rel*-(3*R*,5*S*)-**1f**: 35% yield}].

2.3.5 Stereochemical analysis

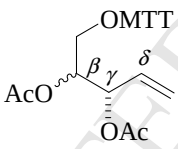
All stereocenters of *O*-alkenyl thiohydroxamates *erythro*-**1d**, *threo*-**1d**, and **1e** derive

from enantiopure natural products. All synthetic manipulations used for transforming the starting materials into the target compounds occurred stereospecifically, as concluded from single sets of resonances in proton- and carbon-13 NMR-spectra (Experimental). For unknown reasons, optical rotations recorded for *erythro*-**1d** and *threo*-**1d** scattered from batch to batch, and in one instance even changed sign. Since stereochemical information obtained by transforming single diastereomers suffice to answer all relevant question associated with the study, we refrained from emphasizing absolute configuration of *O*-alkenyl thiohydroxamates *erythro*/*threo*-**1d** and **1e** hereafter.

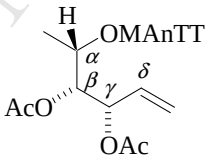
Table 1. Chemical shifts of oxygen-bound carbons and the inner alkene proton of *O*-alkenyl thiohydroxamates **1a**–**f** (in $CDCl_3$, ambient temperature)



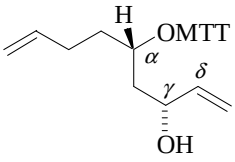
1a–**c**



erythro/*threo*-**1d**



1e



(±)-**1f**

entry	**1** / R	C^{α} / ppm	C^{β} / ppm	C^{γ} / ppm	H^{δ} / ppm
1	**1a** / H	73.1	35.1	68.5	5.94 (ddd)
2	**1b** / Ac	72.0	32.5	71.1	5.85 (ddd)
3	**1c** / Bz	72.0	32.6	71.7	5.97 (ddd)
4	*erythro*-**1d**	72.5	71.2	73.3	5.83 (ddd)
5	*threo*-**1d**	73.8	70.8	72.0	5.90 (ddd)
6	**1e**	74.0	72.1	76.9	5.79 (ddd)
7	(±)-**1f**	84.5	– [a]	71.0	5.94 (ddd)

[a] Not assigned; for entire sets of chemical shifts, see the Experimental.

2.4 Homolytic bromocyclization

2.4.1 Parameters for conducting alkenoxyl radical reactions

For studying the chemistry of 4-pentenoxyl radicals **Ia**–**f**, we adhered to a standardized protocoll derived from preceding mechanistic investigations.[8,22,24] Operational standards thereby relate to (i) the experimental set-up, (ii) methods for quantifying products, and (iii) structure analysis.

(i) *Experimental set-up*. For securing that yields and selectivity are not flawed by technical details associated with the initiating step, we used photochemical and thermal activation for initiating radical chain reactions. In the following, we assessed yields and product manifolds obtained from *O*-esters **1a** and **1b** under both conditions, for deciding which of the methods to use as standard.

The most effective way for initiating a radical reaction photochemically started from a 83-millimolar solution of **1a** in perdeuterobenzene containing bromotrichloromethane. The solution was irradiated in a Rayonet®-chamber reactor equipped with twelve 350-nm light bulbs. This set-up gave 2-methylsulfanylthiazole **2** in 59% and bromoethers **3a**/**11a** in 71% yield. For initiating the radical reaction thermally, we heated a likewise prepared solution of **1a** in the presence of azobisisobutyronitrile (AIBN) as chemical initiator. The therml version of the radical reaction gave 88% of bromoethers **3a**/**11a** in total, and co-product **2** in 81% yield.

The same trend for providing elevated yields under thermal conditions was seen for reactions between *O*-acetyl-substituted ester **1b** and bromotrichloronmethane. For example, heating **1b** in a 83-millimolar solution of perdeuterobenzene and bromotrichlormethane gave

O-acetyloxybromoethers **3b**/**11b** in 89% combined yield, and 90% of thiazole **2**. The photochemical reaction provided 77% of bromocyclization products **3b**/**11b** and 71% of co-product **2**. By comparing yields we finally decided to use the thermal method as standard for conducting alkenoxyl radical bromocyclizations of *O*-alkenylthio-hydroxamates **1a**–**f**. Benzoate **1c**, under such conditions, gave 95% of thiazole **2** and a combined yield of 94% for brominated ethers **3c**/**11c**.

Regarding reaction times, thermally initiated conversions of *O*-alkenyl esters **1a**–**c** took no longer than two hours for completion. Extending reaction times diminishes yields and causes side-products to appear.

Photoreactions of standardized solutions of esters **1a**–**b** were complete within one hour. In some of the experiments the reaction mixture turned in an unpredictable manner yellowish or turbid with some of the starting material still present. Extending the reaction time quantitatively turns over substrate **1**, however, by also leading to a higher product manifold.[22,52]

(ii) *Methods for quantifying products*. For obtaining the original stereochemical information of a bromocyclization product **3**, chemoselectivity for the reaction between thiohydroxamate **1** and $BrCCl_3$, and maximum yields, we injected samples taken directly from solutions of products in perdeuterobenzene into a gas chromatograph equipped with a flame ionization detector and coupled to a mass spectrometer. For cross-checking structural assignments, we analyzed samples from the same mixture by NMR-spectroscopy (proton and carbon-13).

(iii) *Structure analysis*. All products described in this article were characterized by high

resolution mass spectrometry, combustion analysis, and NMR-spectroscopy for constitution analysis. For assigning relative configuration of bromocyclization products (i.e. **3**), we relied on shift differences of carbon-13 resonances between cis/trans-isomers (vide infra). For deducing constitution and, wherever possible, relative configuration of brominated tetrahydropyrans, being formed in 13% yield and less (cf. section 2.5.2), we used mass spectrometry in combination with NMR-spectroscopy. In one instance (for **11a**), we independently prepared a bromotetrahydropyran for securing our interpretation.

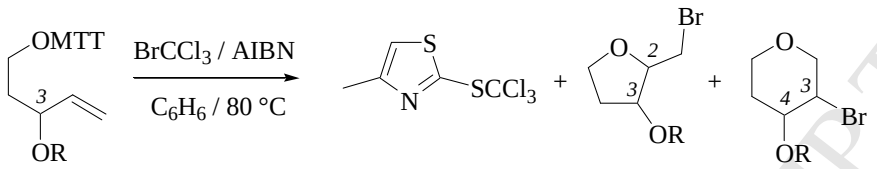
*2.4.2 Bromocyclization of monosubstituted O-(4-pentenyl) thiohydroxamates **1a**−**c***

(i) *Products*. In a larger scale-up experiment, conducted under thermal conditions, 1.12 mmol monosubstituted *O*-alkenyl thiohydroxamate **1a** gave 56% of 2-bromomethyl-tetrahydrofuran-3-ol (**3a**), 4% of 4-bromotetrahydropyran-3-ol (**11a**), and 84% of disubstituted thiazole **2** (Table 2, entry 1). Tetrahydrofuran **3a** was formed under such conditions as 74/26-mixture of 2,3-cis/trans-isomers.

O-Acetyl-substituted ester **1b** yielded 71% of tetrahydrofuran **3b** as 68/32-mixture of 2,3-cis/trans-isomers, 11% of tetrahydropyran **11b** and 94% of thiazole **2** under standard conditions (Table 2, entry 2).

O-Benzoyl-substituted thiohydroxamate **1c** provided 69% of disubstituted tetrahydrofuran **3c** as 68/32-mixture of 2,3-cis/trans-isomers, 12% of tetrahydropyran isomer **11c** and 75% of thiazole **2**, when heated with bromotrichloromethane (Table 2, entry 3).

Table 2. Products formed from *O*-(4-pentenoxy)thiazolethiones **1a**–**c** and bromotrichloromethane



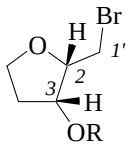
1a–c **2** **3a–c** **11a–c**

entry	**1** / R	**2** / %	**3** / % (*cis*:*trans*) [a]	**11** / % (*cis*:*trans*) [b]
1	**1a** / H	84	**3a**: 56 (74:26)	**11a**: 4 [c]
2	**1b** / Ac	94	**3b**: 71 (68:32)	**11b**: 11 (57:43)
3	**1c** / Bz	75	**3c**: 69 (68:32)	**11c**: 12 (50:50)

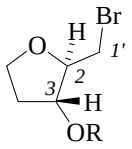
[a] Stereodescriptors refer to configuration at carbons C2 and C3. [b] Stereodescriptors refer to configuration at carbons C3 and C4. [c] 65/35-Mixture of stereoisomers.

(ii) *Stereochemical analysis*. For assigning relative configuration of 5-*exo*-bromocyclization product **3** we relied on a systematic highfield shift of resonances for carbons C2, C3, and for exocyclic bromomethyl carbon C1' in 2,3-cis-isomers. This guideline derives from a combined NMR-spectroscopy/X-ray-diffraction study on di- and trisubstituted tetrahydrofurans.[8,12] This phenomenon arises from steric deshielding of interacting nuclei (Table 3).[53]

Table 3. Carbon-13 NMR-chemical shifts for cis/trans-isomers of 2,3-substituted tetrahydrofurans **3a**–**c** (in $CDCl_3$, ambient temperature)



(±)-*cis*-**3a**–**c**



(±)-*trans*-**3a**–**c**

entry	**3** / R	C2 / ppm	C3 / ppm	C1' / ppm
1	*cis*-**3a** / H	82.2	71.9	29.0
2	*cis*-**3b** / Ac	80.8	73.7	28.4
3	*cis*-**3c** / Bz	81.2	74.5	28.7
4	*trans*-**3a** / H	85.1	75.1	32.8
5	*trans*-**3b** / Ac	83.2	77.4	33.1
6	*trans*-**3c** / Bz	83.3	78.0	33.2

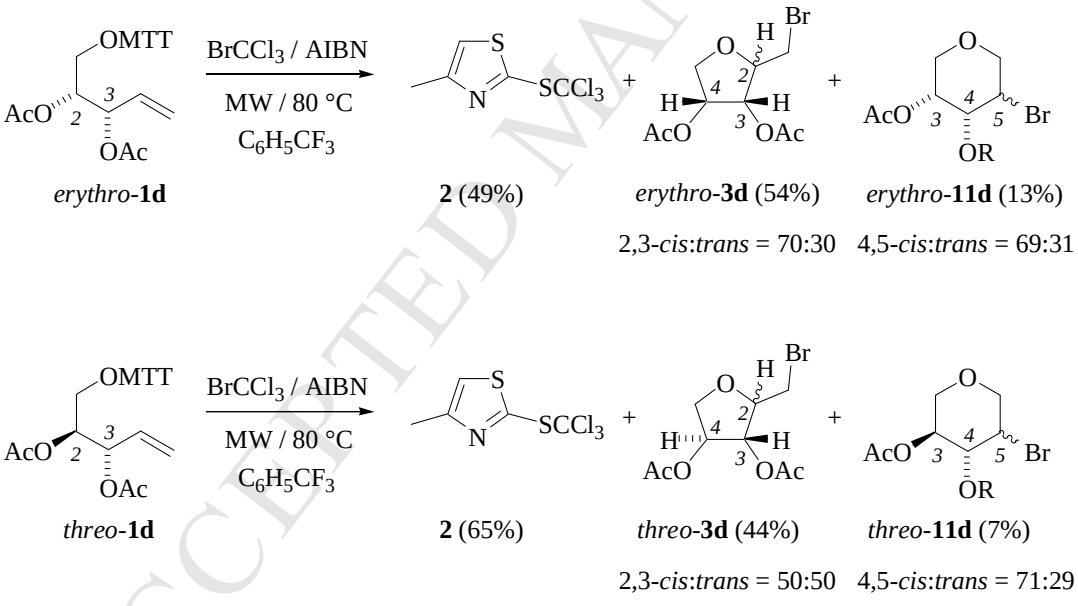
*2.4.3 Products from erythro/threo-isomers of 3-[2,3-bis-(acetyloxy)pent-4-enyloxy]-4-methyl-1,3-thiazole-2(3H)-thione **1d***

(i) *Products*. *O*-(2,3-Bisacetyloxypentenyl) thiohydroxamate *erythro*-**1d** furnished 67% of bromoethers *erythro*-**3d** and *erythro*-**11d** taken together, and 49% of disubstituted thiazole **2**, when heated in a laboratory microwave to 80 °C in a solution of α,α,α-trifluorotoluene under otherwise standard conditions (Scheme 9, top).

All attempts to chromatographically separate 2,3-cis/trans-isomers of bromoethers **3d** and **11d** always gave in our hands product mixtures, however in differing ratios. Superimposing information gained from such mixtures allowed to characterize all products by chemical shifts and fine structures of proton resonances. In high resolution mass spectrometra bisacetates *erythro*-**3d**/**11d** showed the peculiar phenomen of being by one proton heavier than calculated for the molecular formula $C_9H_{13}O_5Br$. This excess mass-per-charge unit is retained

throughout the fragmentation of *erythro*-**3d**/**11d**, until one of the acetyl groups dissociates off. Given consistent proton integrals and fine structures in underlying NMR-spectra, we assigned molecular ions $C_9H_{14}O_5Br^+$ to derivatives of *erythro*-**3d**/**11d**, generated in the mass spectrometer, having one proton chelated by two vicinal acetyloxy groups.

Heating stereoisomer *threo*-**1d** in a solution of α,α,α-trifluorotoluene (80 °C) containing bromotrichloromethane and AIBN gave 65% of thiazole **2**, and a combined yield of 51% for bromocyclization products *threo*-**3d** and *threo*-**11d** (Scheme 9, bottom). For assigning constitution and configuration, we, again, relied on information gained from analyzing sets of *threo*-**3d**/**11d**-mixtures containing differing isomer ratios.

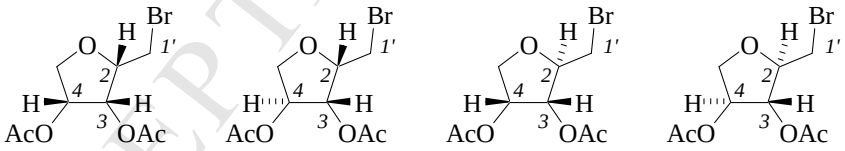


Scheme 9. Products formed from radical reactions between bromotrichloromethane and 3-[*erythro*-2,3-bis-(acetyloxy)pent-4-enoxy]thiazolethione *erythro*-**1d** [top; yields for experiment conducted via photochemical activation (λ = 350 nm, 22 °C, 30 minutes) on a 196-millimolar scale of **1d** in C_6D_6 containing 9.6 equivalents of $BrCCl_3$: 77% of **2**, 68% of *erythro*-**3d** and

erythro-**11d** taken together] and stereoisomer *threo*-**1d** [bottom; yields for experiment conducted via photochemical activation (λ = 350 nm, 22 °C, 30 minutes) on a 196-millimolar scale in C_6D_6, containing 9.0 equivalents of $BrCCl_3$: 53% of **2**, 72% of *threo*-**3d** and *threo*-**11d** taken together]; MW = microwave.

(ii) *Stereochemical analysis of tetrahydrofurans*. According to the stereochemical guideline for interpreting carbon-13 NMR-spectra described in section 2.4.2, the major stereoisomer formed from *O*-pentenyl ester *erythro*-**1d** is the all-cis-configured tetrahydrofuran $cis_{erythro}$-**3d**. This guideline in a similar manner allows to assigning spectral data of cis_{threo}-**3d** from the equimolar mixture of diastereoisomers.

Table 4. Selected carbon-13 NMR-chemical shifts of 3,4-bisacetyloxy-2-bromomethyl-tetrahydrofurans *erythro*/*threo*-**3d** (in C_6D_6, ambient temperature)

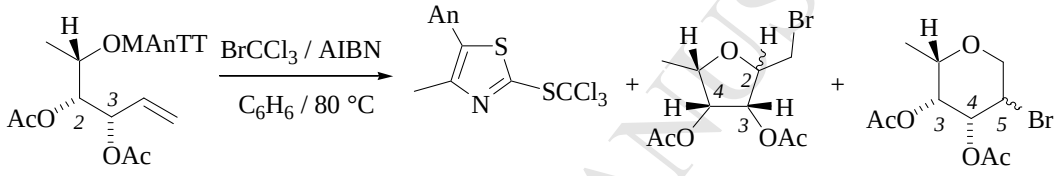


$cis_{erythro}$-**3d** cis_{threo}-**3d** $trans_{erythro}$-**3d** $trans_{threo}$-**3d**

entry	**3d**	C2 / ppm	C3 / ppm	C4 / ppm	C1' / ppm
1	$cis_{erythro}$	79.2	71.9	72.2	29.2
2	cis_{threo}	80.2	76.4	77.9	28.0
3	$trans_{erythro}$	79.6	74.5	72.3	33.3
4	$trans_{threo}$	83.9	80.2	78.4	32.2

*2.4.4 Products from 3-[arabino-3,4-bis-(acetyloxy)hex-5-enoxy]-1,3-thiazole-2(3H)-thione **1e***

(i) *Products*. *Arabino*-configured *O*-(3,4-bisacetyloxyhexenyl) thiohydroxamate **1e** reacted with bromotrichloromethane in boiling benzene containing AIBN to give 50% bromomethyltetrahydrofuran **3e**, and 10% of bromotetrahydropyran **11e**, and 55% of trisubstituted thiazole **12** (Scheme 10). Chromatography on silica gel allows to separate tetrahydropyran 4,5-*trans*-**11e** from all-cis-configured tetrahydropyran 4,5-*cis*-**11e**, and a 2,3-cis/trans-mixture of bromomethyltetrahydrofuran **3e**.



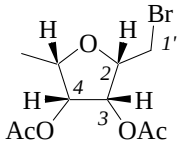
1e **12** (55%) **3e** (50%) **11e** (10%)

2,3-*cis*:*trans* = 30:70 4,5-*cis*:*trans* = 20:80

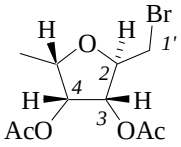
Scheme 10. Products formed from 3-[*arabino*-3,4-bis-(acetyloxy)hex-5-enoxy]-1,3-thiazole-2(3*H*)-thione **1e** and bromotrichloromethane.

(ii) *Stereochemical analysis*. From low field-shifted resonances of carbons C2–C4 and carbon C1' we concluded that the major 5-*exo*-bromocyclization product obtained from *arabino*-configured *O*-hexenoxyl radical **Ie** is the 2,3-trans-stereoisomer of tetrahydrofuran **3e**.

Table 5. Proton and carbon-13 chemical shift values used for distinguishing tetrasubstituted tetrahydrofuran *cis*-**3e** from isomer *trans*-**3e** ($CDCl_3$, ambient temperature)



cis-**3e**



trans-**3e**

entry	**3**	C2 / ppm	C3 / ppm	C4 / ppm	C1' / ppm
1	*cis*-**3e**	77.9	72.9	72.4	29.4
2	*trans*-**3e**	78.1	74.9	73.6	33.7

*2.4.5 Products from 3-[rel-(3R,5S)-3-hydroxynona-1,8-dien-5-oxy]-4-methyl-1,3-thiazole-2(3H)-thione **1f***

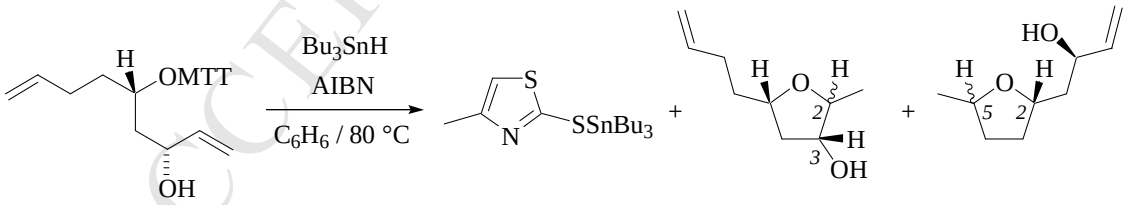
(i) *Products*. Heating or photolyzing *O*-nonadienyl thiohydroxamate **1f** in benzene/bromotrichloromethane-solutions gives products of sequential alkoxyl radical cyclization *and* bromotrichloromethane addition across the remaining carbon-carbon double bond.[52,54] For preventing such side reactions to occur, we changed the mediator from bromotrichloromethane to tributylstannane. This modification, in all instances studied so far, never changed stereo- and regioselectivity of alkenoxyl radical additions.[1,8]

Boiling a solution of *O*-nonadienyl ester **1f** in benzene in the presence of a 3.7-fold excess of tributylstannane, provided a 26/74-mixture of tetrahydrofurans **14** and **15** in a total yield of 76%, besides 79% of thiazole **13** (Scheme 11). Tin compound **13** fragments into 2-methylthiazole-2(3*H*)-thione and yet unidentified organotin derivatives when being contacted with silica gel, and therefore was characterized and quantified from the reaction mixture by proton-NMR spectroscopy.[24]

2,5-Substituted tetrahydrofuran **15** formed from *O*-nonadienyl ester **1f** and

tributylstannane as 27/73-mixture of cis/trans-isomers, which we used for stereochemical analysis. Based on a model developed from theory for predicting selectivity in 5-*exo*-cyclization of monosubstituted 4-pentenoxyl radicals, we think that the major stereoisomer is disubstituted tetrahydrofuran *trans*-**15**.[1] Since most resonances of *cis*/*trans*-**15** overlap, we unfortunately could not conduct a more sophisticated stereochemical analysis at this point.

From the reaction mixture we furthermore separated trisubstituted tetrahydrofuran **14** as 20/80-mixture of 2,3-cis/trans-isomers in a total yield of 20%. This mixture, however, was contaminated by 13 percent by weight with a third product, showing in high resolution mass spectra identical molecular masses to tetrahydrofurans **14** and **15**. From supplementary NMR-spectroscopic information we concluded that the third product is a tetrahydropyran formed from 6-*endo*-cyclization. Since the yield of the product was rather low (3%), we were not able to provide at this point a complete structure analysis (see also section 2.5.2). Given the propensity of hydroxyl-substituted alkoxyl radicals to afford a higher fraction of 6-*endo*-cyclized products, we propose that the third product arises from 6-*endo*-addition of **If** to the allylic alcohol segment.



rel-(3*R*,5*S*)-**1f** **13** (79%) **14** (20%) *dr* = 20:80 **15** (56%) *dr* = 27:73

Scheme 11. Products formed from 3-[*rel*-(3*R*,5*S*)-3-hydroxynona-1,8-dien-5-oxy]-4-methyl-1,3-thiazole-2(3*H*)-thione **1f** and tributylstannane.

(ii) *Analyzing regioselectivity in 5-exo-cyclization*. From a doublet of double-doublet fine structure for the inner alkene proton and larger shift dispersion for the two terminal protons, we concluded that the major cyclization product obtained from nonadien-5-yl ester **1f** is disubstituted tetrahydrofuran **15** (Figure 4, top and bottom). In tetrahydrofuranol **14**, the resonance of the inner alkene proton is split into a triplet of double-doublet and the terminal protons are less shift-dispersed (Figure 4, center).

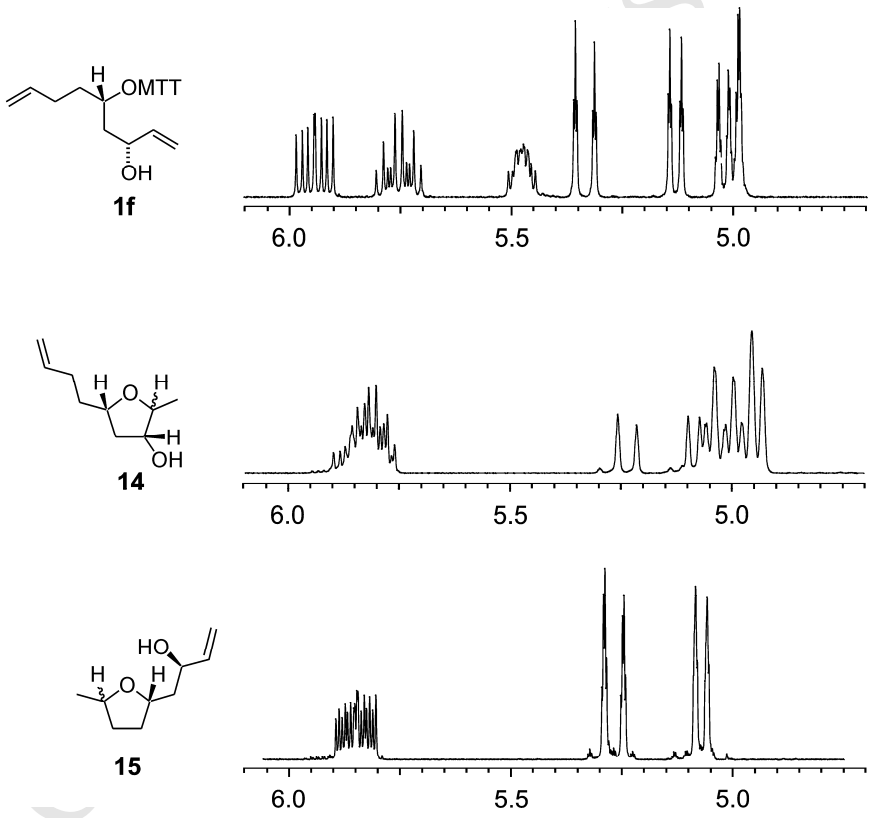


Figure 4. Section of proton NMR-spectra displaying resonances of inner and terminal alkene protons of tetrahydrofurans **14** and **15**, and *O*-[*rel*-(3*R*,5*S*)-3-hydroxynona-1,8-dien-5-yl] thiohydroxamate **1f** for comparison.

2.5 Mechanistic and stereochemical aspects

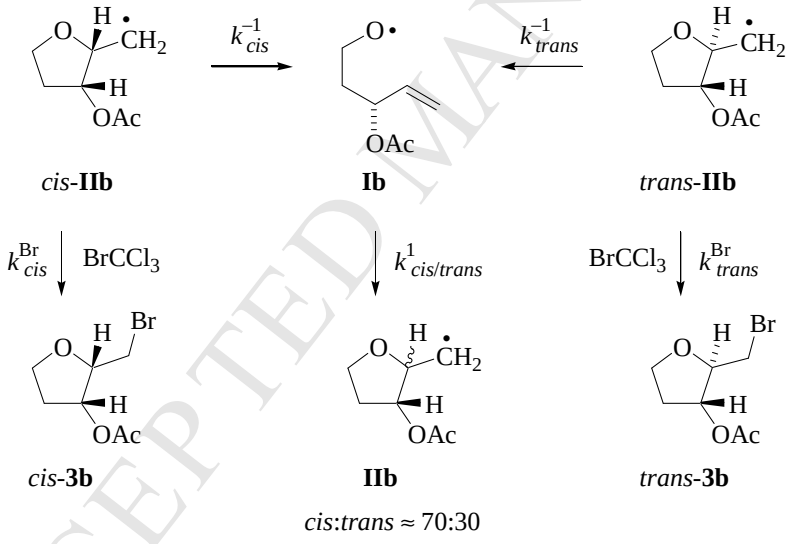
To find out what causes 3-substitued-4-pentenoxyl radicals **Ia**–**c** to cyclize 2,3-cis-selectively, we at first verified that the intramolecular addition follows kinetic control. For this purpose, we monitored stereochemical integrity of diastereomerically pure cyclized radicals *cis*-**IIb** and *trans*-**IIb** under conditions that extended their life-times by a factor 100.

2.5.1 On reversibility of 3-acyloxypent-4-en-1-oxyl radical 5-exo-cyclization

(i) *Kinetic approach*. In a kinetically controlled reaction a notable barrier would prevent tetrahydrofuranyl-2-methyl radical *cis*-**IIb** or stereoisomer *trans*-**IIb** from ring opening to alkenoxyl radical **I** in a β-fragmentation. If the oxygen radical formed, a de-novo-cyclization would become apparent by altering stereochemical integrity of previously pure *cis*-**IIb** and *trans*-**IIb** towards an equilibrium mixture presumably of 68/32 (Scheme 12 and eq. 1). By extending the life-time of radicals *cis*-**IIb** and *trans*-**IIb** by, for example, a factor 100 compared to conditions applied in bromocyclizations, the stereochemical fingerprint from a possible ring-opening should become evident.

The kinetic life-time of carbon radical **IIb** in bromocyclization is defined as inverse pseudo-first order rate constant for homolytic substitution for brominative trapping. This rate constant numerically derives from the product between the rate constant k^{Br} and concentration of bromotrichloromethane (eq. 2).[55] In bromocyclization starting from a 0.2 molar solution of *O*-alkyl thiohydroxamate **1b**, as used in the standard operational procedure, the concentration

of bromotrichloromethane declines from 1.49±0.01 M at the beginning towards 0.91±0.01 M by the end. The rate constant k^{Br} for trapping primary carbon radicals *cis*-**IIb** and *trans*-**IIb**, is approximately 3.9×10^{7} $M^{-1}s^{-1}$. This value derives from the experimental rate constant for hept-6-en-2-yl radical-trapping with bromotrichloromethane ($k^{Br} = 1.2\times10^{8}$ $M^{-1}s^{-1}$ at 26 °C in benzene) divided by three.[56] The factor three corrects for a polar rate effect arising from alkyl substitution at the radical center.[57] Since rate effects of β-substituents are in general small, we assumed that k^{Br}_{cis} and k^{Br}_{trans} are identical (approximation 1).[58] Based on these approximations, life-times of *cis*/*trans*-**IIb** in standard bromocyclizations are 1.7×10^{-8} s at the beginning of the reaction, and 2.8×10^{-8} s by the end.



$$\frac{d[\mathbf{3b}]}{dt} = k^{Br}[BrCCl_3][\mathbf{IIb}] \qquad \text{(eq. 1)}$$

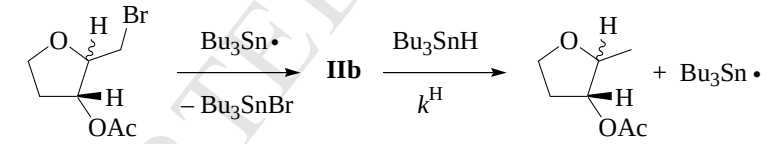
$$\textit{life-time} \text{ for } \mathbf{IIb}: \ \tau = \frac{1}{k^{Br}[BrCCl_3]} \qquad \text{(eq. 2)}$$

$$k^{Br}_{cis} = k^{Br}_{trans} \qquad \text{(app. 1)}$$

Scheme 12. Scheme of elementary reactions, kinetic equations (eqs. 1–2) and approximation

(app. 1) set up for identifying thermochemical contributions to 2,3-cis-selectivity in 5-*exo*-cyclization of 3-acetyloxypentenoxyl radical **Ib** (see also text).

For extending tetrahydrofuran-2-methyl radicals life-times, we changed the mediator to tributylstannane. The tin compound traps, primary carbon radicals, for example the 1-butyl radical with a rate constant of $k^{H} = 2.4\times10^{6}$ M^{-1} s^{-1} at 300 Kelvin in benzene, which is 16-times slower than the reaction with bromotrichloromethane. The ratio k^{Br}/k^{H} remains constant, if activation parameters for the two processes respond similar to a change in reaction temperature. On the basis of this assumption, we extrapolated that the life-time of primary alkyl radicals *cis*/*trans*-**IIb** in a 0.17 molar solution of tributylstannane, as used for conducting the controls, extends to 2.5×10^{-6} s.



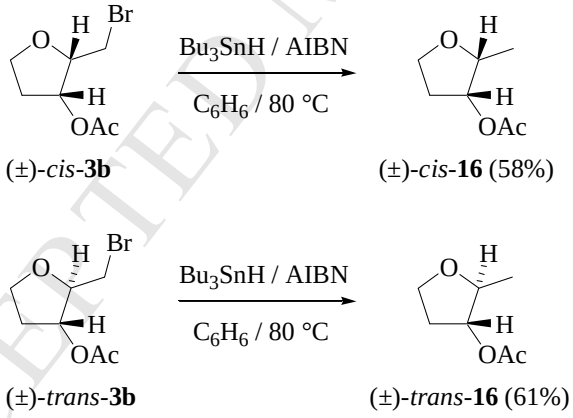
3b **16**

$$\frac{d\,[\mathbf{16}]}{d\,t} = k^{H}\,[\mathbf{IIb}][Bu_3SnH] \qquad \text{(eq. 3)}$$

Scheme 13. Elementary reactions (top) and differential equation (bottom) for comparing rates and life-time of alkyl radical trapping under reductive conditions (eq. is short for equation).

(ii) *Stereochemical study*. For putting our theoretical considerations on radical life-times

into practice, we heated a 0.07 molar solution of 2-bromomethyltetrahydrofuran-3-yl acetate *cis*-**3b** in benzene with an excess of tributylstannane (c_o = 0.17 M). The reduction furnishes diastereomerically pure 2-methyltetrahydrofuranyl acetate *cis*-**16**. Stereoisomer *trans*-**3b** reacts with tributylstannane under identical conditions to 3-acetyl-2-methyltetrahydrofuran *trans*-**16**. From gas chromatograms, we concluded that 2-methyltetrahydrofurans *cis*/*trans*-**16** form in essentially quantitative yield. The amount of products obtained after removing organotin compounds declined to 58–61%. Since no stereochemical scrambling occurs upon reducing the two diastereomers of 2-bromomethyltetrahydrofuryl acetates **3b** we concluded that carbon radicals *cis*/*trans*-**IIb** retain configuration in the environment used for conducting homolytic bromocyclization.



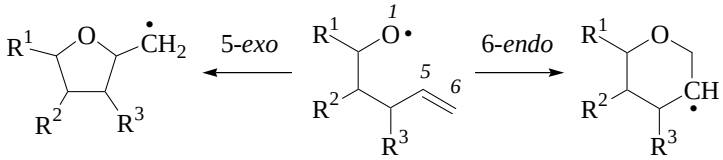
Scheme 14. Reducing 2-bromomethyltetrahydrofurans *cis*/*trans*-**3b** with tributylstannane (diastereomeric purity of all products >98:2, according to information from GC-MS in combination with proton NMR-spectroscopy; for reactand concentrations, refer to the text).

2.5.2 On 6-endo-cyclization

Bromotetrahydropyrans **11a**–**e** are by-products in homolytic bromocyclization of *O*-alkenyl thiohydroxamates **1a**–**e**. From arguments summarized in section 2.5.1, we expect 6-*endo*-cyclizations proceed kintically controlled as well. The experimental tetrahydropyran/tetrahydrofuran-ratio exceeds in most instances the expectation value of 2/98, derived from cyclizations of allylic carbon-substituted 4-pentenoxyl radicals, by a factor 6–7 (Table 7).[2] We think that the origin of declining regioselectivity and 2,3-cis-selectivity in tetrahydrofuran synthesis have same causes.

For elucidating constitution and configuration of minor cyclization products **11a**–**e**, we analyzed fragmentation pattern from electron impact spectra and carbon-13 NMR-chemical shift differences. A diagnostic tool for distinguishing a 2-bromomethyltetrahydrofuran from a 3-bromotetrahydropyran is the chemical shift of endocyclic ether carbons, which are high field-shifted by 1.7–14.0 ppm for the six-membered ring. For distinguishing cis- from trans-stereoisomers, we translated absolute values of vicinal coupling constants with the aid of the Karplus-relationship into dihedral angles, and assigned substituent positions accordingly to axial and equatorial locations in the chair conformation of tetrahydropyran.[59,60]

Table 7. Survey of selectivity data for cyclization of substituted 4-penten-1-oxyl radicals **Ia**–**e** (80 °C)



II **I** **III**

entry	**I**	R^1	R^2	R^3	**II**:**III** [a]	2,3-*cis*:*trans*-**II** [b]
1	**Ia**	H	H	OH	94:6	74:26
2	**Ib**	H	H	OAc	87:13	68:32
3	**Ic**	H	H	OBz	85:15	68:32
4	*erythro*-**Id**	H	OAc	OAc	81:19	70:30
5	*threo*-**Id**	H	OAc	OAc	86:14	50:50
6	**Ie**	CH_3	OAc	OAc	83:17	30:70

[a] Approximated from ratio of bromine atom-trapping. [b] Relative configuration of substituents at alkenoxyl radical carbons C2 and C3.

2.5.3 On the origin of 2,3-cis-selective pent-4-en-1-oxyl radical cyclization

(i) *Transition structures*. In transition structures associated with 5-*exo*-C,O-cyclization, the radical oxygen, the inner alkene carbon (C5), and the allylic carbon (C4) lie for stereoelectronic reason in a plane. Carbons C2 and C3 are offset into opposite directions from this plane, leading to distorted twist (T)-conformers $^2T_3$ (Figure 4, left) or $_2T^3$.

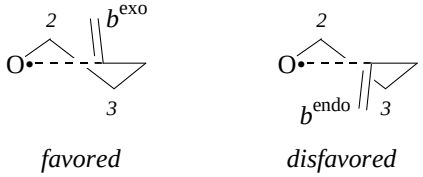


Figure 4. Twist-model for predicting lowest in energy transition structures of the 4-pentenoxyl radical in 5-*exo*-trig-cyclization, having the terminal vinyl group located in *exo*-bisectional

position (b^{exo}, favored), or *endo*-bisectional orientation (b^{endo}, disfavored).

(ii) *Preferred sites for placing substituents*. 2,3-cis-Cyclization, in the twist-model, proceeds via transition structures having the substituent at carbon C4 located pseudo-axially, forming a plane with the alkene carbons (Figure 5, left). Rotating the vinyl substituent by 180 degrees causes atoms C2 and C3, for arguments summarized in Figure 4, to interchange positions with respect to the twist plane. This conformational change causes carbon C2 to flip underneath, and carbon C3 above the twist plane, transforming a $^{2}T_{3}$- into a $_{2}T^{3}$-conformer. The allylic substituent thereby changes position in the twist-conformer from pseudo-axial to pseudo-equatorial. In pseudo-equatorial orientation, a sterically demanding group at carbon C4, for instance methyl, *tert*-butyl, or phenyl, experiences less strain from other substituents and the heterocyclic core (Figure 5, right).[2,7]

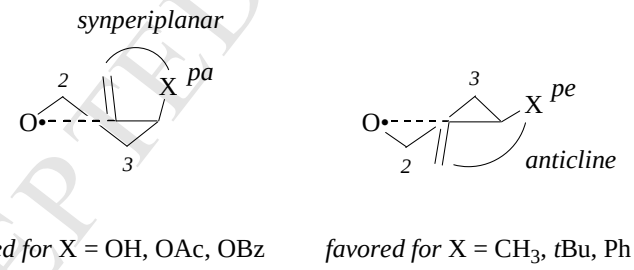


Figure 5. Twist-models for transition structures leading to 2,3-cis- (left; *pa* = pseudo-axial) or 2,3-trans-5-*exo*-cyclized products (right; *pe* = pseudo-equatorial) from 4-pentenoxyl radicals.

(iii) *Theory of reactive conformers*. Substituents favoring 2,3-cis-cyclization are able to overcompensate repulsion from synperiplanar orientation of the vinyl group and pseudo-

axially orientation of the substituent. Opponents to steric factors in chemical reactivity are polar effects. Alkoxyl radical additions to carbon-carbon double bonds are fast and exothermic reactions having, according to Hammond's postulate, transition structures located early on the reaction coordinate. A valid theory for interpreting selectivity based on polar effects in transition structures, located early on a reaction coordinate, is frontier molecular orbital (FMO)-theory.

The major difference between transition structures leading to 2,3-cis- and 2,3-trans-cyclization of a 3-substituted 4-pentenoxyl radical arises from relative orientation between allylic substituent X and the plane of the carbon-carbon double bond, which, in turn, effects the π(C,C)-bond energy. In transition structures associated with 2,3-trans-cyclization the alkene and the allylic oxygen substituent adopt an anticline conformation, allowing π-electrons to delocalize into the σ^*(C,O)-orbital (for X = O: Figure 6, right). In transition structures associated with 2,3-cis-cyclization, the alkene entity is not similarly stabilized and therefore a better electron donor for the singly occupied molecular orbital (SOMO) of the oxygen radical (for X = O: Figure 6, left).

In a kinetically controlled reaction, differences in transition structure energies translate into free activation energy differences for competing reaction pathways, as expressible in a selectivity parameter, for example, a relative rate constant. From this argument we concluded that the π(C,C) $\rightarrow \sigma^*$(C,O)-interaction reduces the rate constant for 2,3-trans-cyclization, allowing 2,3-cis-cyclization to become the more effective pathway for 5-*exo*-cyclization. Experimentally, the rate effect of an allylic hydroxy group becomes apparent in cyclization of the 3-hydroxynona-1,8-dien-5-oxyl radical **1f**, which favors addition to the unsubstituted

terminal double bond by a factor three.

Stabilizing FMO-interactions between an allylic hydroxy group and the alkene have been put forward earlier for explaining anticline conformation of but-3-en-2-ol in the ground state.[61] Rotating the hydroxy and the vinyl group about the σ(C2,C3)-bond uncouples π(C,C) $\rightarrow\sigma^*$(C,O)-electron delocalization, raising the HOMO-energy of but-3-en-2-ol, until the hydroxy group and the alkene align coplanar in the energetic maximum.

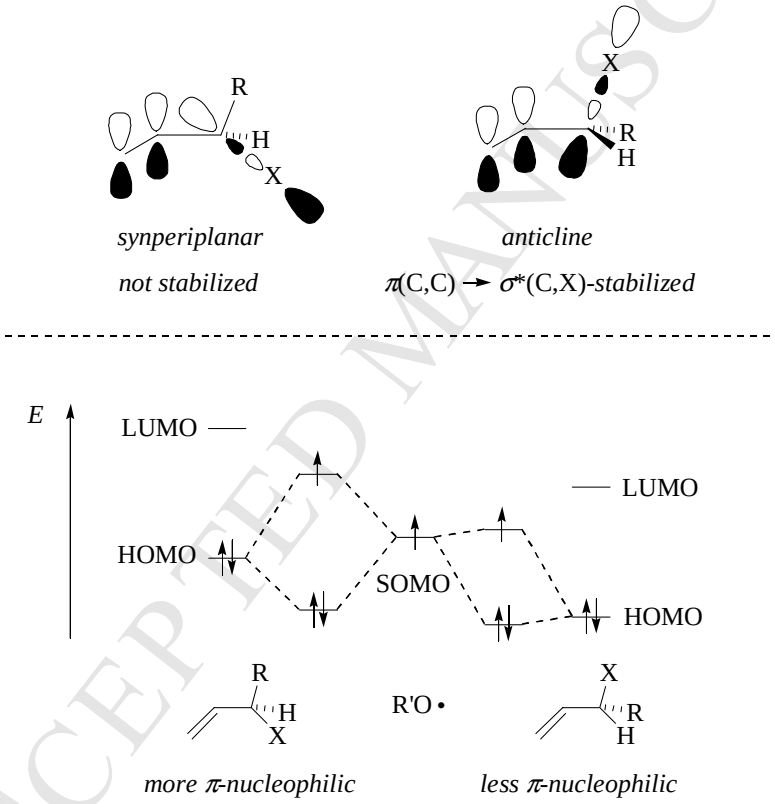


Figure 6. Correlation diagram describing angle dependency of frontier molecular orbital (FMO)-interactions in acceptor-substituted butenes used for explaining the kinetic origin of 2,3-cis-selectivity in oxygen radical additions (right; R = e.g. CH_3 or CH_2CH_2O•, R' = e.g.

primary, secondary, and tertiary alkyl; X = e.g. OH, OAc, OBz).

(iv) *2,3-cis-Directing effect in multiply substituted 4-pentenoxyl radicals*. In proposed transition structure TS-$cis_{erythro}$-**Id**, the allylic acetyloxy group and the π(C,C)-bond align synperiplanar. The second acetyloxy group adopts an equatorial position, which is the preferred position for steric reasons. Changing orientation of the underlying twist conformation directs both acetyloxy substituents in transition structure TS-$trans_{erythro}$-**Id** into unfavorable positions – pseudo-equatorial for the allylic group and axial for the substituent at carbon C2 (Figure 7, top). By favoring intermediate TS-$cis_{erythro}$-**Id** the reaction leads to all-cis-configured tetrahydrofuran $cis_{erythro}$-**3d** as major product from *O*-alkenyl thiohydroxamate *erythro*-**1d**.

In transition structure TS-cis_{threo}-**Id**, the allylic acetyloxy group aligns synperiplanar to the π-bond and the second axial. In diastereomorphic transition structure TS-$trans_{threo}$-**Id**, the situation for the two acetyloxy groups reverses – being electronically disfavored for the substituent in position 3 and sterically favored for position 2 (Figure 7, bottom). Polar and steric effects in both of the proposed transition structures seem to counterbalance, offering no obvious preferrence for either pathway and explaining a 50/50-stereoselectivity for homolytic bromocyclization of *O*-alkenyl thiohydroxamate *threo*-**1d**.

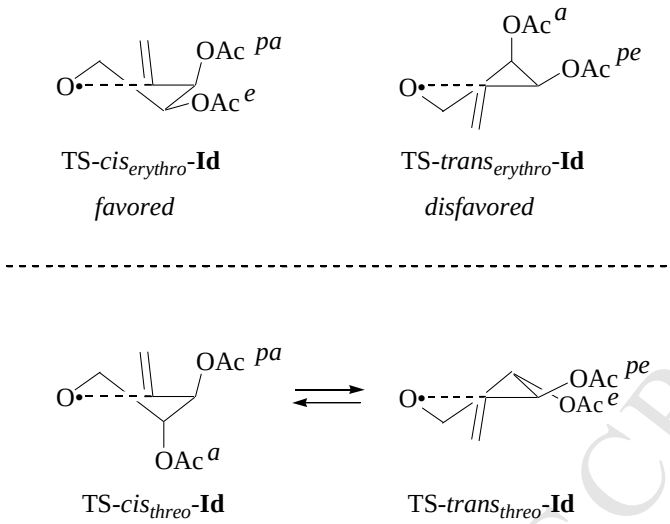
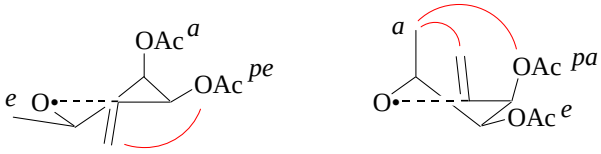


Figure 7. Transition structure models for explaining stereoselectivity in 5-*exo*-trig-cyclization on the basis of cumulative polar and steric substituent effects in 2,3-diacetyloxy-4-pentenoxyl radicals *erythro*-**Id** and *threo*-**Id** (*a* = axial, *pa* = pseudo-axial, *pe* = pseudo-equatorial, *e* = equatorial).

arabino-Configured 4-pentenoxyl radical **Ie** cyclizes 2,3-trans-selectively. The methyl substituent becomes the principal stereoinductor, guiding 5-*exo*-cyclization by steric effects (Figure 8). Density functional theory predicts the transition structure for 2,5-trans-cyclization of the 5-hexen-2-oxyl radical to be 3 kJ mol^{-1} lower in free activation energy than the transition structure leading to 2,5-cis-cyclization. This approximation poses an approximate upper limit for the 2,3-cis-directing effect of the acetyloxy group.



TS-*trans*-**Ie** TS-*cis*-**Ie**

favored *disfavored*

Figure 8. Transition structure models for explaining 2,5-trans-selectivity in 5-*exo*-trig-cyclisation of *arabino*-configured 3,4-bis(acetyloxy)-5-hex-2-oxyl radical **Ie** (*a* = axial, *pa* = pseudo-axial, *pe* = pseudo-equatorial, *e* = equatorial; arcs symbolize steric repulsion between interconnected substituents).

3. Concluding Remarks

2,3-cis-Selectivity arises from electrophilicity at oxygen in homolytic addition to non-activated double bonds on one side and a stereoelectronic effect exerted by an allylic hydroxy, acetyloxy or benzoyloxy substituent on the other. This combination kinetically disfavors 2,3-trans-ring closures of 3-acceptor-subsituted 4-pentenoxyl radicals, allowing to become a 2,3-cis-stereoisomer of a substituted tetrahydrofuran to become principal cyclization product.

According to theory, 2,3-cis-selectivity should extend to other acceptor groups X in allylic position and to other electrophilic radicals. The stronger X withdraws π-electrons toward the σ^*(C,X)-orbital, the more pronounced 2,3-cis-stereocontrol shall be. At some point, we expect steric repulsion between the vinyl group and X to counteract the polar 2,3-cis-directing effect. Using Winstein-Holness *A*-parameters[62,63] and electronegativity of atoms, we expect allylic halogens to be potential 2,3-cis-directing substituents. Nitrogen and sulfur

groups, on the other hand possibly are borderline cases.

Addressing questions of this kind will help to expand our knowledge about polar effects in oxygen radical chemistry and the role such effects play for controlling selectivity in homolytic carbon-oxygen bond formation.[8,64,65,66] This is particularly interesting because 2,3-cis-selectivity adds a component to synthesis of tetrahydrofurans in pH-neutral non-oxidative environment, not available so far from carbon substitution. The key for refining the existing reaction model, as far as we understand the mechanism, lies in the interplay between steric and polar substituent effects acting on transition structures. We will report in an upcoming article on this topic.

4. Experimental

4.1. General

For general laboratory practice and instrumentation see the Supplementary Data.

4.2 3-Alkenoxythiazole-2(3*H*)-thiones

4.2.1 General method for hydroxy group *O*-acetylation.

A solution of 3-alkenoxythiazole-2(3*H*)-thione MTTOR **1b** or **1d**−**e** (1 equiv.), triethylamine (0.5−3.8 equiv.), *N*,*N*-dimethylaminopyridine (DMAP, 0.1−0.35 equiv.) in dichloromethane (6−25 mL/mmol MTTOR) was treated at 0 °C with acetic anhydride (2.4−5.0 equiv.). The mixture was stirred for 12−22 hours at 22 °C and treated afterwards with water (7.5 mL/mmol MTTOR). Extracting the reaction mixture with diethyl ether (3 × 10 mL/mmol MTTOR)

furnishes an organic solution, which was successively washed with water, an aqueous saturated solution of $NaHCO_3$, and brine (je 15 mL/mmol MTTOR). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure (600 mbar, 40 °C) to leave a residue, which was crystallized from the solvent specified below, or purified by chromatography on silica gel (SiO_2) as stationary phase.

4.2.2 3-(3-Hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1a). A solution of 3-[3-(methoxymethyloxy)-pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione (2.51 g, 9.11 mmol; Supplementary data) in methanol (57 mL) was treated with aqueous hydrochloric acid [4.7 mL, 37 % (*w*/*w*)]. Stirring at 22 °C was continued for 3 days and 30 minutes. Water (60 mL) was afterwards added to furnish a mixture, which was extracted with diethyl ether (3 × 70 mL). Combined organic extracts were washed with an aqueous saturated solution of $NaHCO_3$ (70 mL) and brine (70 mL). The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C) to afford a residue that was purified by chromatography (diethyl ether). Yield: 1.81 g (7.82 mmol, 86%), pale yellow oil. R_f = 0.36 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.83 (dddd, 1 H, J = 14.8, 9.8, 5.0, 3.7 Hz), 2.07 (dddd, 1 H, J = 14.7, 9.8, 4.4, 3.4 Hz), 2.31 (d, 3 H, J = 1.0 Hz), 3.54 (s, 1 H, OH), 4.39−4.43 (m, 1 H), 4.59–4.64 (m, 2 H), 5.14 (dt, 1 H, J_d = 10.5 Hz, J_t = 1.5 Hz), 5.33 (dt, 1 H, J_d = 17.2 Hz, J_t = 1.6 Hz), 5.94 (ddd, 1 H, J = 17.2, 10.6, 5.5 Hz), 6.21 (d, 1 H, J = 1.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ13.3, 35.1, 68.5, 73.1, 103.2, 114.7, 137.8, 139.9, 180.4. Anal. Calcd. for $C_9H_{13}NO_2S_2$ (231.34): C, 46.73; H, 5.66; N, 6.05; S, 27.72. Found: C, 46.71; H, 5.76; N, 6.13; S, 27.89.

4.2.3 3-(3-Acetyloxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1b). From 3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1a**) (462 mg, 2.00 mmol), triethylamine (486 mg, 4.80 mmol), *N*,*N*-dimethylaminopyridine (DMAP, 24 mg, 0.20 mmol) and acetic anhydride (490 mg, 4.80 mmol) in dichloromethane (12 mL) according to procedure 4.2.1. Yield: 447 mg (1.64 mmol, 82%), colorless crystalline solid, m.p. 63−64 °C (from diethyl ether/pentane). R_f = 0.30 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ2.09 (s, 3 H, CH_3), 2.16–2.22 (m, 2 H), 2.26 (d, 3 H, J = 1.2 Hz), 4.39–4.45 (m, 1 H), 4.48–4.53 (m, 1 H), 5.24 (dt, 1 H, J_d = 10.5 Hz, J_t = 1.1 Hz), 5.33 (dt, 1 H, J_d = 17.2 Hz, J_t = 1.2 Hz), 5.47−5.52 (m, 1 H), 5.85 (ddd, 1 H, J = 17.2, 10.6, 6.3 Hz), 6.15 (d, 1 H, J = 1.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ13.4, 21.2, 32.5, 71.1, 72.0, 102.7, 117.6, 135.5, 137.5, 170.1, 180.4. Anal. Calcd. for $C_{11}H_{15}NO_3S_2$ (273.38): C, 48.33; H, 5.53; N, 5.12; S, 23.46 Found: C, 48.39; H, 5.58; N, 5.17; S, 23.38.

4.2.4 3-(3-Benzoyloxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1c). Pyridine (0.35 mL, 4.30 mmol) was added at room temperature to a solution of 3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1a**) (500 mg, 2.15 mmol) in dichloromethane (38 mL). The reaction mixture was cooled to 0 °C and treated at this temperature in a dropwise manner with benzoyl chloride (604 mg, 4.30 mmol). The resulting mixture was stirred for 20 hours at 22 °C and treated afterwards with water (20 mL). Extracting the reaction mixture with dichloromethane (3 × 20 mL) furnishes an organic solution which was washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure (600 mbar, 40 °C). The

remaining residue was purified by chromatography [SiO_2, diethyl ether/pentane = 1:1(*v*/*v*)]. Yield: 374 mg (1.11 mmol, 52%), pale yellow oil. R_f = 0.29 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ2.21 (d, 3 H, *J* = 1.4 Hz), 2.33−2.36 (m, 2 H), 4.42−4.47 (m, 1 H), 4.60−4.65 (m, 1 H), 5.28 (dt, 1 H, J_d = 10.5 Hz, J_t = 1.2 Hz), 5.42 (dt, 1 H, J_d = 17.2 Hz, J_t = 1.3 Hz), 5.75−5.79 (m, 1 H), 5.97 (ddd, 1 H, *J* = 17.1, 10.7, 6.1 Hz), 6.12 (d, 1 H, *J* = 1.3 Hz), 7.43−7.47 (m, 2 H), 7.56−7.59 (m, 1 H), 8.05−8.07 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ13.4, 32.6, 71.7, 72.0, 102.7, 117.7, 128.5, 129.6, 130.0, 133.2, 135.5, 137.6, 165.6, 180.4. Anal. Calcd. for $C_{16}H_{17}NO_3S_2$ (335.44): C, 57.29; H, 5.11; N, 4.18; S, 19.12 Found: C, 57.21; H, 5.22; N, 4.05; S, 19.05.

4.2.5 3-[(2*R*,3*S*)-2,3-Bis(acetyloxy)-pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *erythro*-(1d)

***erythro*-(1d)**. A Solution of 3-[(2*R*,3*S*)-isopropylidendioxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *erythro*-(**7**) (980 mg, 3.41 mmol) in methanol (70 mL) was treated with aqueous hydrochloric acid [2.76 mL, 37 % (*w*/*w*)]. The reaction mixture was stirred for 8 hours at 22 °C. Diethyl ether (20 mL) was added and the mixture was extracted with diethyl ether/petroleum ether = 2:1 (*v*/*v*) (3 × 30 mL). Combined organic solutions were concentrated under reduced pressure (370 mbar, 40 °C) to leave 3-[(2*R*,3*S*)-dihydroxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione as product, which was used as obtained in the succeeding step. Yield: 669 mg (2.73 mmol, 80%), colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ2.32 (d, 3 H, *J* = 1.2 Hz), 3.06 (brs, 1 H), 3.94 (d, 1 H, *J* = 1.2 Hz), 4.05 (brs, 1 H), 4.33 (brs, 1 H), 4.36 (dd, 1 H, *J* = 9.4, 6.8 Hz), 4.49 (dd, 1 H, *J* = 9.4, 3.8 Hz), 5.28 (d, 1 H, *J* = 10.6 Hz), 5.38−5.45 (m, 1 H), 5.95 (ddd, 1 H, *J* = 17.0, 10.8, 5.7 Hz), 6.23 (d, 1 H, *J* = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 100

MHz) δ 13.3, 71.7, 72.9, 78.7, 103.4, 117.3, 136.1, 138.0, 180.6. 3-[(2*R*,3*S*)-2,3-dihydroxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione (524 mg, 2.12 mmol), triethylamine (818 mg, 8.08 mmol, 1.12 mL), *N*,*N*-dimethylaminopyridine (DMAP, 26.0 mg, 0.21 mmol) and acetic anhydride (821 mg, 8.04 mmol, 0.76 ml) were dissolved in dichloromethane (50 mL) according to general procedure 4.2.1. Eluent used for chromatographic purification: ethyl acetate/pentane = 2:1 (*v*/*v*). Yield: 655 mg (1.98 mmol, 93%), yellow oil. R_f = 0.40 [petroleum ether/diethyl ether = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3 H), 2.11 (s, 3 H), 2.24 (d, 3 H, *J* = 1.2 Hz), 4.46 (dd, 1 H, *J* = 9.6, 7.0 Hz), 4.78 (dd, 1 H, *J* = 9.6, 2.5 Hz), 5.33–5.42 (m, 3 H), 5.57 (ddt, 1 H, J_d = 6.1, 4.8 Hz, J_t = 1.2 Hz), 5.83 (ddd, 1 H, *J* = 17.1, 10.6, 6.4 Hz), 6.15 (d, 1 H, *J* = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.2, 20.9, 21.0, 71.2, 72.5, 73.3, 102.7, 120.1, 131.3, 137.3, 169.6, 170.0, 180.4. Anal. Calcd for $C_{13}H_{17}NO_5S_2$ (331.41): C, 47.11; H, 5.17, N, 4.23; S, 19.35. Found: C, 47.02; H, 5.21; N, 4.28; S 19.53.

4.2.6 3-[(2*S*,3*S*)-Bis(acetyloxy)-pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *threo*-(1d). Pyridinium *p*-toluenesulfonate (434 mg, 1.73 mmol) was added to a solution of 3-[(*2R*,*3R*)-isopropylidenedioxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione (451 mg, 1.57 mmol; Supplementary data) in methanol (20 mL) to furnish a solution which was boiled under reflux for 2 days and 2 hours. Adding water (20 mL) at room temperature to the mixture affords a suspension, which was extracted with dichloromethane (3 × 50 mL). Combined organic solutions were concentrated under reduced pressure (370 mbar, 40 °C) to leave 3-[(2*S*,3*S*)-dihydroxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione as crude product, which was used as obtained in the succeeding step. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.32 (d, 3 H, *J* =

1.2 Hz), 3.06 (brs, 1 H), 3.91–3.98 (m, 1 H), 4.05 (brs, 1 H), 4.31–4.39 (m, 2 H), 4.49 (dd, 1 H, *J* = 9.4, 3.8 Hz), 5.28 (d, 1 H, *J* = 10.6 Hz), 5.38–5.44 (m, 1 H), 5.95 (ddd, 1 H, *J* = 17.0, 10.8, 5.7 Hz), 6.23 (d, 1 H, *J* = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ13.3, 71.2, 72.3, 79.0, 103.4, 117.5, 136.5, 137.9, 180.6. Crude 3-[(2*S*,3*S*)-dihydroxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione (477 mg), triethylamine (730 mg, 7.21 mmol, 1 mL), *N*,*N*-dimethylaminopyridine (DMAP, 22.0 mg, 0.18 mmol) and acetic anhydride (735 mg, 7.19 mmol, 0.68 mL) were dissolved in dichloromethane (50 mL) and treated as described in general procedure 4.2.1, to leave a crude product, which was purified by chromatography using ethyl acetate/pentane = 2:1 (*v*/*v*) as eluent. Yield: 431 mg (1.30 mmol, 83% for both steps), yellow oil. R_f = 0.21 [petroleum ether/diethyl ether = 1:1 (*v*/*v*)]. ^{1}H NMR (C_6D_6, 600 MHz) δ 1.52 (d, 3 H, *J* = 1.2 Hz), 1.68 (s, 3 H), 1.76 (s, 3 H), 4.27 (dd, 1 H, *J* = 9.1, 6.2 Hz), 4.41 (dd, 1 H, *J* = 9.1, 2.6 Hz), 5.05–5.09 (m, 1 H), 5.12 (d, 1 H, *J* = 1.2 Hz), 5.27 (dt, 1 H, J_d = 17.2 Hz, J_t = 1.2 Hz), 5.41 (td, 1 H, J_t = 5.9 Hz, J_d = 3.4 Hz), 5.67−5.70 (m, 1 H), 5.78 (ddd, 1 H, *J* = 17.0, 10.7, 6.0 Hz). ^{13}C NMR (C_6D_6, 150 MHz) δ13.1, 20.77, 20.79, 71.5, 72.5, 74.0, 102.2, 119.7, 132.6, 137.5, 169.3, 169.8, 181.0. Anal. Calcd for $C_{13}H_{17}NO_5S_2$ (331.41): C, 47.11; H, 5.17, N, 4.23; S, 19.35. Found: C, 46.95; H, 5.19; N, 4.02; S 18.68.

4.2.7 3-[(2*S*,3*S*,4*S*)-3,4-*O*-Bis(acetyloxy)-hex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione (1e). From 3-[(2*S*,3*S*,4*S*)-3,4-*O*-bishydroxyhex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione (880 mg, 2.39 mmol; Supplementary data), triethylamine (121 mg, 1.19 mmol, 167 μL), *N*,*N*-dimethylaminopyridine (DMAP, 35.0 mg, 287 μmol) and acetic anhydride (1.22 g, 12.0 mmol) in dichloromethane (28

mL) according to general procedure 4.2.1. Eluent used for chromatographic purification: diethyl ether/pentane = 1:1 (*v*/*v*). Yield: 480 mg (1.06 mmol, 45%), colorless solid. R_f = 0.16 [diethyl ether/pentane = 1:1 (*v*/*v*)]. $[\alpha]^{D}_{25}$ = 35.0 (*c* = 1.93 g/100 ml dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.22 (d, 3 H, *J* = 6.4 Hz), 2.08 (s, 3 H), 2.09 (s, 3 H), 2.26 (s, 3 H), 3.80 (s, 3 H), 5.26 (dd, 2 H, *J* = 4.1, 11.1 Hz), 5.30 (d, 1 H, *J* = 10.5 Hz), 5.38 (d, 1 H, *J* = 17.4 Hz), 5.53 (t, 1 H, *J* = 7.3 Hz), 5.79 (ddd, 1 H, *J* = 17.4, 10.2, 7.6 Hz), 5.93−5.98 (m, 1 H), 6.95 (d, 2 H, *J* = 8.6 Hz), 7.24 (d, 2 H, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.6, 14.5, 20.9, 21.5, 55.5, 72.1, 74.0, 76.9, 114.7, 119.4, 120.9, 122.6, 129.9, 132.4, 133.5, 160.0, 169.8, 170.2, 178.9. Anal. Calcd. for $C_{21}H_{25}NO_6S_2$ (451.55): C, 55.86; H, 5.58; N, 3.10. Found: C, 56.06; H, 5.70, N, 3.03.

4.2.8 3-(3-Hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3*H*)-thione (1f). A solution of 3-[3-(methoxymethyloxy)-nona-1,8-dien-5-oxy]-4-methylthiazole-2(3*H*)-thione (1.36 g, 4.12 mmol; Supplementary data) in methanol (27 mL) was treated with aqueous hydrochloric acid [37% (*w*/*w*), 0.92 mL, 9.45 mmol]. The reaction mixture was allowed to stir for 18 hours at 22 °C. Adding water (20 mL) and diethyl ether (20 mL) provided a two-phase system. The aqueous layer was extracted with diethyl ether (3 × 10 mL). Organic washings were combined with the organic layer from the reaction mixture and washed with an aqueous saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL). After drying ($MgSO_4$), the organic solvent was removed under reduced pressure (600 mbar, 30 °C) to leave a residue, which was purified by chromatography [diethyl ether/pentane = 1:2 (*v*/*v*)]. *rel-(3S,5S)-3-(3-Hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3H)-thione*. Yield: 457 mg (1.60 mmol, 39%), pale yellow liquid. R_f

= 0.35 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.63–1.75 (m, 2 H), 1.78–1.84 (m, 2 H), 1.94–2.14 (m, 2 H), 2.27 (d, 3 H, J = 1.1 Hz), 4.71–4.77 (m, 1 H), 4.98–5.03 (m, 2 H), 5.14 (dt, 1 H, J_d= 10.5 Hz, J_t = 1.5 Hz), 5.34 (dt, 1 H, J_d = 17.2 Hz, J_t = 1.6 Hz), 5.40–5.47 (m, 1 H), 5.74 (ddt, 1 H, J_d = 16.9, 10.4 Hz, J_t = 6.5 Hz), 5.93 (ddd, 1 H, J = 17.2, 10.5, 5.3 Hz), 6.26 (d, 1 H, J = 1.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ14.2, 29.2, 32.2, 40.4, 67.0, 81.3, 103.6, 114.3, 115.7, 136.7, 139.4, 139.9, 180.9. *rel-(3R,5S)-3-(3-Hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3H)-thione (**1f**)*. Yield: 418 mg (1.46 mmol, 35%), pale yellow liquid. R_f = 0.16 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.67–1.73 (m, 2 H), 1.84–1.92 (m, 2 H), 2.02–2.20 (m, 2 H), 2.25 (d, 3 H, J = 1.3 Hz), 4.56–4.60 (m, 1 H), 4.98–5.04 (m, 2 H), 5.13 (dt, 1 H, J_d = 10.5 Hz, J_t = 1.4 Hz), 5.33 (dt, 1 H, J_d = 17.2 Hz, J_t = 1.5 Hz), 5.45–5.51 (m, 1 H), 5.76 (ddt, 1 H, J_d = 17.0, 10.4 Hz, J_t = 6.5 Hz), 5.94 (ddd, 1 H, J = 17.2, 10.5, 5.5 Hz), 6.22 (d, 1 H, J = 1.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ14.1, 29.1, 32.1, 39.9, 71.0, 84.5, 103.3, 114.7, 115.6, 136.8, 139.2, 140.0, 180.8. Anal. Calcd for $C_{13}H_{21}NO_2S_2$ (285.43): C, 54.70; H, 6.71, N, 4.91; S, 22.47. Found: C, 54.57; H, 6.92; N, 4.91; S 22.19.

4.3 Radical Bromocyclizations

4.3.1 General method for thermally initiated radical reactions. Azobisisobutyronitrile (AIBN) (0.25 equiv.) was added to a solution of *N*-(alkenoxy)-4-methylthiazole-2(3*H*)-thione **1a**−**e** (1 equiv.) in benzene (5−10 mL/mmol MTTOR) and bromotrichloromethane (8−10 equiv.). The mixture is heated under reflux for 1–2 hours. The solution is allowed to cool to 22 °C and concentrated under reduced pressure (200 mbar, 40 °C). The residual oil is purified

by chromatography using silica gel (SiO_2) as stationary phase.

4.3.2 General method for thermally initiated radical reaction in a laboratory microwave. A solution of *N*-(alkenoxy)-4-methylthiazole-2(3*H*)-thione **1d** (1 equiv.) and bromotrichloromethane (8.6−9.25 equiv.) in α,α,α-trifluorotoluene (3 mL/mmol MTTOR) was treated with AIBN (0.25 equiv.) and heated for 30 minutes at 80 °C in a laboratory microwave (see Supplementary data). The reaction mixture is allowed to cool to room temperature and concentrated under reduced pressure (70 mbar, 40 °C). The remaining residue is purified by chromatography [pentane/diethyl ether = 1:2 (*v*/*v*)].

4.3.3 Conversion of 3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1a). Reactants: MTTOR **1a** (260 mg, 1.12 mmol), bromotrichloromethane (1.78 g, 0.89 mL, 9.00 mmol), and AIBN (46.0 mg, 0.28 mmol) in benzene (6.1 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 1:1 (*v*/*v*). *4-Methyl-2-(trichloromethylsulfanylthiazole (**2**).* Yield: 234 mg (0.94 mmol, 84%), yellow oil. R_f = 0.60 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ2.59 (s, 3 H), 7.33 (s, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ17.2, 96.8, 122.6, 153.5, 155.6.[67] *3-Bromotetrahydropyran-4-ol (**11a**).* Yield: 7.1 mg (39.3 µmol, 3.5%, as 65/35-mixture of 2,3-cis/2,3-trans-isomers) isolated as a mixture of tetrahydropyranol **11a** and tetrahydrofuranol *cis*-**3a** (**11a**/**3a** = 8/92), yellow oil. R_f = 0.19 [diethyl ether/pentane = 1:1 (*v*/*v*)]. *rel-(3S,4R)-3-Bromo-tetrahydropyran-4-ol cis-(**11a**)*: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.92−2.06 (m, 2 H),

3.62 (dt, 1 H, J_d = 11.5 Hz, J_t = 4.7 Hz), 3.79 (dd, 1 H, J = 11.8, 3.8 Hz), 3.83−3.96 (m, 3 H), 4.35 (dt, 1 H, J_d = 8.3 Hz, J_t = 3.4 Hz). Retention time (t_r) = 11.40 minutes (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 121 (35), 108 (44), 101 (26), 100 (70), 83 (100), 73 (59), 55 (37). HRMS (EI^+) *m*/*z* 179.9775/181.9759 [M^+]; calculated mass for $C_5H_9O_2Br^+$: 179.9786/181.9765. *rel-(3R,4R)-3-Bromotetrahydropyran-4-ol trans-(**11a**)*: t_r = 11.28 minutes: 122 (37), 108 (49), 106 (51), 101 (38), 83 (79), 73 (100), 57 (32). HRMS (EI^+) *m*/*z* 181.9772/179.9778 [M^+]; calculated mass for $C_5H_9O_2Br^+$: 181.9765/179.9786. *rel-(2S,3R)-2-Bromomethyltetrahydrofuran-3-ol cis-(**3a**)*. Yield: 81.9 mg (0.45 mmol, 40%), yellow oil. R_f = 0.16 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.85 (brs, 1 H, OH), 2.02 (dddd, 1 H, J = 13.4, 6.9, 3.7, 1.4 Hz), 2.16−2.25 (m, 1 H), 3.47−3.55 (m, 2 H), 3.92 (td, 1 H, J_t = 8.6 Hz, J_d = 3.6 Hz), 4.01 (ddd, 1 H, J = 8.3, 6.1, 3.5 Hz), 4.09 (td, 1 H, J_t = 8.7 Hz, J_d = 7.0 Hz), 4.50 (td, 1 H, J_t = 4.3 Hz, J_d = 1.4 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ29.0, 35.4, 67.2, 71.9, 82.2. HRMS (EI^+) *m*/*z* 181.9772/179.9778 [M^+]; calculated mass for $C_5H_9O_2Br^+$: 181.9765/179.9786; *m*/*z* 87.0443 [M^+-CH_2Br]; calculated mass for $C_4H_7O_2^+$: 87.0446. From a 92:8-mixture of tetrahydrofuranol *cis*-**3a** and tertrahydropyranol **11a**: Anal. Calcd. for $C_5H_9O_2Br$ (181.03): C, 33.17; H, 5.01. Found: C, 33.22; H, 5.07. *2-Bromomethyltetrahydrofuran-3-ol (**3a**)*. Yield (determined versus *para*-bromobenzaldehyde as internal NMR-standard): 17.3 mg (95.7 µmol, 9%, *cis*/*trans* = 15:85), yellow oil. R_f = 0.14 [diethyl ether/pentane = 1:1 (*v*/*v*)]. *cis*-**3a**: NMR data agreed with values from an authentic sample. *trans*-**3a**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.76 (brs, 1 H, OH), 1.94 (dddd, 1 H, J = 13.2, 6.3, 4.2, 3.2 Hz), 2.14−2.23 (m, 1 H), 3.32 (dd, 1 H, J = 10.4, 7.3 Hz), 3.45 (dd, 1 H, J = 10.5, 4.8 Hz), 3.96−4.03 (m, 3 H), 4.36 (dt, 1 H, J_d = 6.3 Hz, J_t = 3.1 Hz).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 32.8, 34.9, 67.5, 75.1, 85.1. HRMS (EI^+) *m*/*z* 87.0447 [M^+-CH_2Br]; calculated mass for $C_4H_7O_2^+$: 87.0446. *rel-(2R,3R)-2-Bromomethyltetrahydrofuran-3-ol trans-(**3a**).* Yield (determined versus *para*-bromobenzaldehyde as internal NMR-standard): 13.8 mg (76.0 µmol, 7%), yellow oil. R_f = 0.11 [diethyl ether/pentane = 1:1 (*v*/*v*)]. NMR data agreed with values from an authentic sample.

4.3.4 Conversion of 3-(3-acetyloxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1b). Reactants: MTTOR **1b** (334 mg, 1.22 mmol), bromotrichloromethane (1.94 g, 0.96 mL, 9.76 mmol), AIBN (51.0 mg, 0.31 mmol) in benzene (6.8 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 1:1 (*v*/*v*). *4-Methyl-2-(trichloromethylsulfanyl)thiazole (**2**).* Yield (determined versus pentachlorobenzene as internal NMR-standard): 250 mg (1.15 mmol, 94%), yellow oil. R_f = 0.61 [diethyl ether/pentane = 1:1 (*v*/*v*)]. NMR data agreed with values from an authentic sample. *rel-(3R,4R)-3-Bromotetrahydropyran-4-yl acetate trans-(**11b**).* Yield (determined versus pentachlorobenzene as internal NMR-standard): 12.4 mg (55.5 µmol, 4.5%), orange oil. R_f = 0.51 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.68−1.75 (m, 1 H), 2.11 (s, 3 H), 2.19 (ddt, 1 H, J_d = 13.2, 5.0 Hz, J_t = 2.6 Hz), 3.52−3.58 (m, 2 H), 3.90−4.01 (m, 2 H), 4.15 (dd, 1 H, *J* = 12.0, 4.3 Hz), 4.98 (td, 1 H, J_t = 9.8 Hz, J_d = 4.8 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.0, 32.6, 47.8, 66.0, 71.3, 73.7, 170.0. HRMS (EI^+) *m*/*z* 143.0711 [M^+-Br]; calculated mass for $C_7H_{11}O_3^+$: 143.0708. *2-Bromomethyltetrahydrofuran-3-yl acetate (**3b**).* Yield (determined versus pentchlorobenzene as internal NMR-standard): 194 mg

(0.87 mmol, 71%, *cis*/*trans* = 68:32), yellow oil. R_f = 0.45 [diethyl ether/pentane = 1:1 (*v*/*v*)]. *cis*-**3b**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.94−2.04 (m, 1 H), 2.07 (s, 3 H), 2.18−2.34 (m, 1 H), 3.41−3.55 (m, 2 H), 3.86−3.95 (m, 1 H), 4.00−4.15 (m, 2 H), 5.39 (ddd, 1 H, *J* = 5.5, 4.0, 1.7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ20.9, 28.4, 33.5, 66.9, 73.7, 80.8, 170.1. HRMS (EI^+) *m*/*z* 223.9880/221.9887 [M^+]; calculated mass for $C_7H_{11}O_3Br^+$: 223.9871/221.9892. *trans*-**3b**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.94−2.04 (m, 1 H), 2.05 (s, 3 H), 2.18−2.34 (m, 1 H), 3.41−3.55 (m, 2 H), 3.86−3.95 (m, 1 H), 4.00−4.15 (m, 2 H), 5.09 (dt, 1 H, J_d = 6.7 Hz, J_t = 2.3 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ20.94, 32.6, 33.1, 67.7, 77.4, 83.2, 170.6. HRMS (EI^+) *m*/*z* 129.0551 [M^+-CH_2Br]; calculated mass for $C_6H_9O_3^+$: 129.0552. *rel-(3S,4R)-3-Bromotetrahydropyran-4-yl acetate cis-(**11b**)*. Yield (determined versus pentachlorobenzene as internal NMR-standard): 15.3 mg (68.4 µmol, 6%), yellow oil. R_f = 0.43 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.85−1.91 (m, 1 H), 1.95−2.00 (m, 1 H), 2.13 (s, 3 H), 3.62−3.68 (m, 1 H), 3.83−3.89 (m, 2 H), 3.94−3.97 (m, 1 H), 4.30−4.33 (m, 1 H), 5.08 (dt, 1 H, J_d = 7.0 Hz, J_t = 3.3 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ20.99, 32.6, 49.1, 64.2, 69.1, 69.3, 170.0. HRMS (EI^+) *m*/*z* 223.9885/221.9902 [M^+]; calculated mass for $C_7H_{11}O_3Br^+$: 223.9871/221.9892.

4.3.5 Conversion of 3-(3-Benzyloxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1c). Reactants: MTTOR **1c** (324 mg, 0.97 mmol), bromotrichloromethane (1.54 g, 0.77 mL, 7.76 mmol), AIBN (39.0 mg, 0.24 mmol) in benzene (5.3 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 1:2 (*v*/*v*). *4-Methyl-2-(trichloromethylsulfanyl)thiazole (**2**)*. Yield: 181 mg (0.73 mmol, 75%),

yellow oil. R_f = 0.55 [diethyl ether/pentane = 1:2 (*v*/*v*)]. NMR data agreed with values from an authentic sample. *rel-(2R,3R)-2-Bromomethyltetrahydrofuran-3-yl benzoate trans-(**3c**)* [Yield (determined versus *para*-bromobenzaldehyde as internal NMR-standard): 54.7 mg (0.21 mmol, 22%)] and *rel-(3R,4R)-3-bromotetrahydropyran-4-bezoate trans-(**11c**)* [Yield (determined versus *para*-bromobenzaldehyde as internal NMR-standard): 16.2 mg (57 µmol, 6%)], yellow oil. R_f = 0.46 [diethyl ether/pentane = 1:2 (*v*/*v*)]. *rel-(2R,3R)-2-bromomethyltetrahydrofuran-3-yl benzoate trans-(**3c**)*. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ2.14–2.20 (m, 1 H), 2.33−2.41 (m, 1 H), 3.54−3.58 (m, 1 H), 3.61−3.67 (m, 1 H), 3.99−4.07 (m, 1 H), 4.15−4.22 (m, 1 H), 4.26 (td, 1 H, J_t = 5.0 Hz, J_d = 2.5 Hz), 5.38 (dt, 1 H, J_d = 6.6 Hz, J_t = 2.2 Hz), 7.44−7.49 (m, 2 H), 7.57−7.61 (m, 1 H), 8.02−8.09 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ32.8, 33.2, 68.0, 78.0, 83.3, 128.5, 129.7, 133.3, 166.2. HRMS (EI^+) *m*/*z* 286.0042/284.0068 [M^+]; calculated mass for $C_{12}H_{13}O_3Br^+$: 286.0028/284.0048. *rel-(3R,4R)-3-Bromotetrahydropyran-4-yl benzoate trans-(**11c**)*. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.80−1.91 (m, 1 H), 2.33−2.41 (m, 1 H), 3.61−3.67 (m, 2 H), 3.99−4.07 (m, 1 H), 4.09−4.14 (m, 1 H), 4.15−4.22 (m, 1 H), 5.22 (td, 1 H, J_t = 9.6 Hz, J_d = 4.8 Hz), 7.44−7.49 (m, 2 H), 7.57−7.61 (m, 1 H), 8.02−8.09 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 32.8, 47.7, 66.0, 71.3, 74.3, 128.5, 129.6, 129.7, 133.3, 166.2. HRMS (EI^+) *m*/*z* 286.0065/284.0062 [M^+]; calculated mass for $C_{12}H_{13}O_3Br^+$: 286.0028/284.0048. *rel-(2S,3R)-2-Bromomethyl-tetrahydrofuran-3-yl benzoate cis-(**3c**)*. Yield: 122 mg (0.46 mmol, 47%), yellow oil. R_f = 0.38 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ2.18−2.24 (m, 1 H), 2.43 (dtd, 1 H, J_d = 14.1, 5.5 Hz, J_t = 8.6 Hz), 3.52−3.61 (m, 2 H), 4.01 (td, 1 H, J_t = 8.6 Hz, J_d = 4.3 Hz), 4.12−4.18 (m, 1 H), 4.27 (td, 1 H, J_t = 6.9 Hz, J_d = 4.0 Hz), 5.67 (ddd, 1 H, J = 5.5,

3.9, 1.8 Hz), 7.45−7.48 (m, 2 H), 7.57−7.61 (m, 1 H), 8.02−8.05 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.7, 33.7, 67.1, 74.5, 81.2, 128.5, 129.6, 129.7, 133.4, 165.6. HRMS (EI^+) *m*/*z* 286.0028/284.0063 [M^+]; calculated mass for $C_{12}H_{13}O_3Br^+$: 286.0028/284.0048. Anal. Calcd. for $C_{12}H_{13}O_2Br$ (285.13): C, 50.55; H, 4.60. Found: C, 50.20; H, 4.65. *rel-(3S,4R)-3-Bromotetrahydropyran-4-yl benzoate cis-(**11c**)*. Yield (determined versus *para*-bromobenzaldehyde as internal NMR-standard): 16.5 mg (58 µmol, 6%), orange oil. R_f = 0.33 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ2.00−2.07 (m, 1 H), 2.17−2.30 (m, 1 H), 3.74 (ddd, 1 H, *J* = 11.7, 6.3, 4.0 Hz), 3.91−3.96 (m, 1 H), 3.98−4.04 (m, 1 H), 4.05−4.10 (m, 1 H), 4.43 (dt, 1 H, J_d = 7.0 Hz, J_t = 3.3 Hz), 5.35 (dt, 1 H, J_d = 6.9 Hz, J_t = 3.3 Hz), 7.45−7.50 (m, 2 H), 7.58−7.62 (m, 1 H), 8.09−8.12 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ30.0, 49.1, 64.2, 69.5, 69.6, 128.5, 129.67, 129.74, 133.3, 165.4. HRMS (EI^+) *m*/*z* 205.0870 [M^+−Br]; calculated mass for $C_{12}H_{13}O_3^+$: 205.0865.

4.3.6 Conversion of 3-[(2*R*,3*S*)-2,3-bis-(acetyloxy)-pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *erythro*-(1d). Reactants: 3-[(2*R*,3*S*)-2,3-bis-(acetyloxy)-pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *erythro*-(**1d**) (320 mg, 966 µmol), bromotrichloromethane (0.82 mL, 8.32 mmol), AIBN (40 mg, 0.24 mmol) in α,α,α-trifluorotoluene (3 mL) according to procedure 4.3.2. *4-Methyl-2-(trichloromethylsulfanyl)thiazole (**2**)*. Yield: 119 mg (478 µmol, 49%), yellow oil. R_f = 0.55 [pentane/diethyl ether = 1:2 (*v*/*v*)]. NMR data agreed with reference values from an authentic sample. *(2S,3R,4R)-2-Bromomethyltetrahydrofuran-3,4-diyl bisacetate cis$_{erythro}$-(**3d**)*. Yield: 103 mg (365 µmol, 38%), yellow oil. R_f = 0.55 [petroleum ether/diethyl ether = 1:2 (*v*/*v*)]. ^{1}H-NMR (400 MHz, C_6D_6) δ1.56 (s, 3 H), 1.65 (s, 3 H), 3.19

(d, 2 H, J = 7.0 Hz), 3.58–3.65 (m, 2 H), 3.80 (td, 1 H, J_t = 7.0 Hz, J_d = 4.8 Hz), 5.09 (td, 1 H, J_t = 6.2 Hz, J_d = 5.1 Hz), 5.29 (t, 1 H, J = 4.9 Hz). ^{13}C-NMR (100 MHz, C_6D_6) δ20.28, 20.33, 29.2, 69.7, 71.9, 72.2, 79.2, 169.2, 169.5. MS (EI) *m*/*z* 283 (1), 281 (1), 201 (26), 187 (76), 178 (5), 158 (17), 141 (42), 127 (37), 115 (100), 99 (20), 85 (45), 81 (77). *(2R,3R,4R)- 2-Bromomethyltetrahydrofuran-3,4-diyl bisacetate trans$_{erythro}$-(**3d**)*. Yield: 43.3 mg (154 μmol, 16%), yellow oil. R_f = 0.55 [petroleum ether/diethyl ether = 1:2 (*v*/*v*)]. ^{1}H-NMR (400 MHz, C_6D_6) δ1.62 (s, 3 H), 1.63 (s, 3 H), 3.03−3.14 (m, 2 H), 3.57−3.65 (m, 1 H), 3.74 (dd, 1 H, J = 10.2, 4.8 Hz), 3.98 (dt, 1 H, J_d = 6.6 Hz, J_t = 4.5 Hz), 5.14 (dd, 1 H, J = 6.6, 5.3 Hz), 5.23 (td, 1 H, J_t = 5.0 Hz, J_d = 3.5 Hz). ^{13}C-NMR (100 MHz, C_6D_6) δ20.4, 20.5, 33.3, 71.1, 72.3, 74.5, 79.6, 169.5, 169.6. MS (EI) *m*/*z* 283(1), 281(1), 201(14), 187(33), 141(50), 127(21), 115 (100), 99(12), 85(24), 81(41). Mixture of *cis$_{erythro}$*- and *trans$_{erythro}$*-(**3d**): HRMS (EI$^+$) *m*/*z* 283.0065/281.0023 $[M+H]^+$; calculated mass for $C_9H_{14}O_5Br^+$: 283.0004/281.0025; *m*/*z* 201.0767 $[M+H]^+-Br$; calculated mass for $C_9H_{13}O_5^+$: 201.0763. Anal. Calcd. for $C_9H_{13}BrO_5$ (281.17): C, 38.66; H, 4.66; Found: C, 38.64; H, 4.96. *(3R,4R,5R)-3-Bromotetrahydropyran-4,5-diyl bisacetate trans$_{erythro}$-(**11d**)*. Yield: 24.6 mg (87.5 μmol, 9%), yellow oil. R_f = 0.55 [petroleum ether/diethyl ether = 1:2 (*v*/*v*)]. ^{1}H-NMR (400 MHz, C_6D_6) δ1.65 (s, 3 H), 1.73 (s, 3 H), 2.80 (dd, 1 H, J = 13.1, 1.1 Hz), 3.07 (t, 1 H, J = 11.2 Hz), 3.50−3.54 (m, 1 H), 3.85 (ddd, 1 H, J = 11.6, 4.9, 1.1 Hz), 4.12 (td, 1 H, J_t = 10.8 Hz, J_d = 5.0 Hz), 5.03 (dd, 1 H, J =10.6, 3.5 Hz), 5.21−5.22 (m, 1 H). ^{13}C-NMR (100 MHz, C_6D_6) δ20.57, 20.65, 45.3, 68.7, 70.0, 71.6, 74.1, 169.6, 169.9. MS (EI) *m*/*z* 283 (1), 281 (1), 237 (5), 195 (17), 179 (5), 159 (5), 141 (100), 140 (29), 115 (4), 103 (12), 99 (66), 98 (58), 81 (17). *(3S,4R,5R)-3-Bromotetrahydropyran-4,5-diyl bisacetate cis$_{erythro}$-(**11d**)*. Yield: 10.6 mg (37.9 μmol, 4%),

yellow oil. R_f = 0.55 [petroleum ether/diethyl ether = 1:2 (*v*/*v*)]. ^{1}H-NMR (400 MHz, C_6D_6) δ1.60 (s, 3 H), 1.72 (s, 3 H), 3.32−3.37 (m, 1 H), 3.38−3.44 (m, 1 H), 3.47−3.49 (m, 2 H), 3.51−3.55 (m, 1 H), 4.82 (ddd, 1 H, *J* = 10.7, 5.3, 2.8 Hz), 5.62−5.64 (m, 1 H). ^{13}C-NMR (100 MHz, C_6D_6) δ20.48, 20.50, 44.3, 63.9, 67.5, 68.1, 69.5, 169.2, 169.6. MS (EI) *m*/*z* 283 (1), 281 (1), 222 (1), 209 (4), 207 (4), 195 (3), 178 (7), 177 (7), 159 (15), 141 (100), 140 (56), 103 (38), 99 (90), 98 (59), 81 (20). Mixture of *cis*$_{erythro}$- and *trans*$_{erythro}$-(**11d**): HRMS (EI$^+$) *m*/*z* 283.0043/281.0040 $[M+H]^+$; calculated mass for $C_9H_{14}O_5Br^+$: 283.0004/281.0025; *m*/*z* 238.9760/236.9976 $[M^+-C_2H_3O]$; calculated mass for $C_7H_{10}O_4Br^+$: 238.9742/236.9762.

4.3.7 Conversion of 3-[(2*S*,3*S*)-bis(acetyloxy)-pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *threo*-(1d). Reactants: 3-[(2*S*,3*S*)-Bis(acetyloxy)-pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *threo*-(**1d**) (200 mg, 603 µmol), bromotrichloromethane (0.55 ml, 5.58 mmol), AIBN (25 mg, 0.15 mmol) in α,α,α-trifluorotoluene (2 mL) according to procedure 4.3.2. *4-Methyl-2-(trichloromethylsulfanyl)thiazole (**2**)*. Yield: 97.0 mg (390 µmol, 65%), yellow oil. R_f = 0.55 [pentane/diethyl ether = 1:2 (*v*/*v*)]. NMR data agreed with reference values from an authentic sample. *(2S,3R,4S)-2-Bromomethyltetrahydrofuran-3,4-diyl bisacetate cis*$_{threo}$*-(**3d**)*. Yield: 38.3 mg (136 µmol, 22%), yellow oil. R_f = 0.56 [petroleum ether/methyl *tert*-butyl ether = 1:4 (*v*/*v*)]. ^{1}H-NMR (400 MHz, C_6D_6) δ1.48 (s, 3 H), 1.50 (s, 3 H), 3.16 (d, 2 H, *J* = 7.3 Hz), 3.58 (dd, 1 H, *J* = 10.5, 2.3 Hz), 4.00 (dd, 1 H, *J* = 10.7, 4.9 Hz), 4.14 (td, 1 H, J_t = 7.0 Hz, J_d = 3.8 Hz), 5.07−5.09 (m, 1 H), 5.37 (dd, 1 H, *J* = 3.7, 1.0 Hz). ^{13}C-NMR (100 MHz, C_6D_6,) δ20.3, 20.5, 28.0, 72.7, 76.4, 77.9, 80.2, 169.1, 169.4. MS (EI) *m*/*z* 283 (1), 281 (1), 201 (10), 187 (8), 178 (2), 158 (3), 141 (18), 127 (10), 115 (100), 99 (8), 85 (17), 81 (58).

*(2R,3R,4S)-2-Bromomethyltetrahydrofuran-3,4-diyl bisacetate trans$_{threo}$-(**3d**)*. Yield: 38.2 mg (136 μmol, 22%), yellow oil. R_f = 0.56 [petroleum ether/methyl *tert*-butyl ether = 1:4 (*v*/*v*)]. ^{1}H-NMR (400 MHz, C_6D_6) δ1.49 (s, 3 H), 1.50 (s, 3 H), 3.27−3.36 (m, 2 H), 3.69−3.72 (m, 1 H), 3.78−3.81 (m, 1 H), 3.86 (td, 1 H, J_t = 5.9 Hz, J_d = 3.5 Hz), 5.07 (dt, 1 H, J_d = 4.3 Hz, J_t = 1.6 Hz), 5.17−5.19 (m, 1 H). ^{13}C-NMR (100 MHz, C_6D_6) δ20.4, 20.5, 32.2, 72.5, 78.4, 80.2, 83.9, 169.5, 169.7. Mixture of *cis$_{threo}$*- and *trans$_{threo}$*-isomer: HRMS (EI$^+$) *m*/*z* 283.0000/281.0010 $[M+H]^+$; calculated mass for $C_9H_{14}O_5Br^+$: 283.0004/281.0025; *m*/*z* 187.0623 $[M^+-CH_3Br]$; calculated mass for $C_8H_{11}O_5^+$: 187.0606. Anal. Calcd. for $C_9H_{13}BrO_5$ (281.17): C, 38.66; H, 4.66; Found: C, 38.66; H, 4.90. *(3R,4R,5S)-4,5-Bis(acetyloxy)-3-bromomethyltetrahydropyran trans$_{threo}$-(**11d**)*. Yield: 8.09 mg (28.8 μmol, 2%), yellow oil. R_f = 0.56 [petroleum ether/methyl *tert*-butyl ether = 1:4 (*v*/*v*)]. ^{1}H-NMR (600 MHz, $CDCl_3$) δ2.11 (s, 3 H), 2.12 (s, 3 H), 3.31 (t, 1 H, *J* = 10.7 Hz), 3.50 (t, 1 H, *J* = 11.4 Hz), 3.83−3.91 (m, 1 H), 4.08–4.11 (m, 1 H), 4.14 (dd, 1 H, *J* = 11.6, 5.0 Hz), 4.89 (ddd, 1 H, *J* = 10.3, 9.2, 5.5 Hz), 5.21 (t, 1 H, *J* = 9.6 Hz). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ20.8, 20.9, 44.7, 67.8, 69.9, 71.2, 75.2, 169.4, 169.5. *(3R,4R,5S)-4,5-Bisacetyloxy-3-bromomethyltetrahydropyran cis$_{threo}$-(**11d**)*. Yield: 3.75 mg (13.3 μmol, 5%), yellow oil. R_f = 0.56 [petroleum ether/methyl *tert*-butyl ether = 1:4 (*v*/*v*)]. ^{1}H-NMR (600 MHz, $CDCl_3$) δ2.11 (s, 3 H), 2.12 (s, 3 H), 3.70 (dd, 1 H, *J* = 12.7, 3.9 Hz), 3.83−3.91 (m, 3 H), 4.47 (ddd, 1 H, *J* = 8.2, 4.3, 3.5 Hz), 4.95−4.97 (m, 1 H), 5.13–5.15 (m, 1 H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ20.8, 20.9, 45.3, 65.8, 68.2, 68.7, 69.1, 169.4, 169.5.

4.3.8 Conversion of 3-[(2*S*,3*S*,4*S*)-3,4-*O*-bis(acetyloxy)-hex-5-en-2-oxy]-4-methyl-5-(*p*-

methoxyphenyl)thiazole-2(3*H*)-thione (1e). Reactants: 3-[(2*S*,3*S*,4*S*)-3,4-*O*-Bis(acetyloxy)-hex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione (**1e**) (222 mg, 0.49 mmol), bromotrichloromethane (488 µl, 4.9 mmol), AIBN (20 mg, 0.12 mmol) in benzene (5 mL) according to procedure 4.3.1. Reaction time: 2.5 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 1/1 (*v*/*v*). *4-Methyl-5-(p-methoxyphenyl)-2-(trichloromethylsulfanyl)thiazole (**12**).* Yield: 96.9 mg (0.27 mmol, 55%), yellow crystals. R_f = 0.48 [diethyl ether/pentane = 1/1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ2.57 (s, 3 H), 3.85 (s, 3 H), 6.97 (d, 2 H, *J* = 8.6 Hz), 7.24 (d, *J* = 8.6 Hz). ^{13}C-NMR (150 MHz, C_6D_6) δ16.3, 54.9, 97.9, 114.6, 123.4, 129.9, 130.7, 141.6, 150.1, 150.8, 160.4. MS (EI) *m*/*z* 355 [M^+], 248 (8), 236 (100), 203 (28), 192 (17), 177 (38), 160 (22), 145 (27), 134 (8), 119 (5), 108 (9), 77 (8).[24] *(2S,3R,4R,5R)-5-Bromo-2-methyltetrahydropyran-3,4-diyl bisacetate trans-(**11e**).* Yield: 12.0 mg (40.8 µmol, 8%), yellow crystals. R_f = 0.36 [diethyl ether/pentane = 1/1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.14 (d, 3 H, *J* = 6.4 Hz,), 2.05 (s, 3 H), 2.16 (s, 3 H), 3.57−3.64 (m, 1 H), 3.74−3.79 (q, 1 H, *J* = 6.7 Hz), 4.14−4.21 (m, 2 H), 5.03 (dd, 1 H, *J* = 3.5, 10.8 Hz), 5.22 (dd, 1 H, *J* = 1.0, 3.2 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ16.6, 20.6, 20.7, 44.0, 71.3, 71.9, 74.0, 74.7, 169.8, 170.4. MS (EI) *m*/*z* 207/209 (4), 152/154 (24), 129 (22), 113 (75), 103 (14), 95 (16), 85 (16), 69 (100), 57 (13). *2-Brommethyl-5-methyltetrahydrofuran-3,4-diyl bisacetate (**3e**).* Yield: 72.7 mg (247 µmol, 50%), 30/70-mixture of 2,5-cis/2,5-trans-isomers, yellow oil. R_f = 0.24 [diethyl ether/pentane = 1/1 (*v*/*v*)]. *cis*-**3e**: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ1.21 (d, 3 H, *J* = 6.9 Hz,), 2.09 (d, 6 H, *J* = 2.2 Hz), 3.41−3.45 (m, 2 H), 4.17−4.29 (m, 2 H), 4.37−4.42 (m, 1 H), 5.36−5.40 (m, 1 H), 5.51 (t, 1 H, *J* = 5.5 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ15.4, 20.5, 20.9, 29.4, 72.4, 72.9, 75.3, 77.9, 169.6, 169.8. MS (EI) *m*/*z* 201 (15), 175/177 (19), 155

(93), 129 (58), 113 (18), 99 (100), 95 (60), 87 (16), 69 (39), 57 (17). *trans*-**3e**: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ1.23 (d, 3 H, *J* = 1.9 Hz), 2.04 (s, 3 H), 2.12 (s, 3 H), 3.49 (dd, 1 H, *J* = 4.4, 11.1 Hz), 3.59 (dd, 1 H, *J* = 4.4, 11.1 Hz), 4.17−4.29 (m, 1 H), 4.37−4.42 (m, 1 H), 5.29−5.32 (m, 1 H), 5.36−5.40 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ14.8, 20.6 (2C), 33.7, 73.6, 74.9, 76.1, 78.1, 169.8, 170.4. MS (EI) *m*/*z* 201 (15), 175/177 (19), 155 (93), 129 (58), 113 (18), 99 (100), 95 (60), 87 (16), 69 (39), 57 (17). Mixture of *cis*- and *trans*-isomer-**3e**: Anal. Calcd. for $C_{10}H_{15}BrO_5$ (295.13): C, 40.70; H, 5.12; Found: C, 41.02; H, 5.13.

*(2S,3R,4R,5S)-5-Bromo-2-methyltetrahydropyran-3,4-diyl bisacetate cis-(**11e**)*. Yield: 3.03 mg (10.3 μmol, 2%), yellow oil. R_f = 0.12 [diethyl ether/pentane = 1/1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.26 (d, 3 H, *J* = 6.7 Hz), 2.10 (s, 3 H), 2.17 (s, 3 H), 3.74−3.79 (m, 1 H), 3.93−3.98 (m, 1 H), 4.24−4.28 (m, 2 H), 5.09 (t, 1 H, *J* = 4.0 Hz), 5.15 (t, 1 H, *J* = 2.5 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ16.3, 20.9 (2C), 44.6, 68.9, 69.1, 70.3, 73.6, 170.0, 170.7. MS (EI) *m*/*z* 207/209 (4), 152/154 (24), 129 (22), 113 (75), 103 (14), 95 (16), 85 (16), 69 (100), 57 (13).

4.3.9 Conversion of *rel*-(3*R*,5*S*)-3-(3-hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3*H*)-thione (1f) with Bu_3SnH. A solution of *rel*-(3*R*,5*S*)-3-(3-hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3*H*)-thione (**1f**) (418 mg, 1.46 mmol) in benzene (17.0 mL) containing tributylstannane (1.57 g, 5.40 mmol) and AIBN (59.9 mg, 0.37 mmol) was boiled under reflux for 2 hours, while being heated in an oil bath (bath temperature 100 °C). The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure (200 mbar, 40 °C), to leave a residue which was purified by chromatography [SiO_2, diethyl ether/pentane

= 1:2 (*v*/*v*)]. *4-Methyl-2-(tributylstannylsulfanyl)thiazole (**13**)*. Yield: 1.15 mmol (79%, yield was determined via ^{1}H-NMR with pentachlorobenzene as internal standard before the chromatography). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.87–0.94 (m, 9 H), 1.24–1.68 (m, 18 H), 2.28 (s, 3 H), 6.54 (s, 1 H). *rel-(2'S,2R)-1-(5'-methyltetrahydrofuran-2'-yl)but-3-ene-2-ol (**15**)*. Yield: 127 mg (815 µmol, 56%), as a mixture of cis- and trans-isomers (A:B = 27:73), colorless liquid. R_f = 0.23 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (dd, 3 H, *J* = 6.1, 0.7 Hz, B), 1.24 (dd, 3 H, *J* = 6.1, 0.7 Hz, A), 1.40–1.70 (m, 4 H, A/B), 1.91–2.07 (m, 2 H, B), 2.09–2.16 (m, 2 H, A), 4.00–4.07 (m, 1 H, B), 4.11–4.18 (m, 1 H, B), 4.21–4.27 (m, 2 H, A), 4.31–4.35 (m, 1 H, A/B), 5.07 (d, 1 H, *J* = 10.4 Hz, A/B), 5.27 (d, 1 H, *J* = 17.2 Hz, A/B), 5.80–5.89 (m, 1 H, A/B). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 21.4, 32.1, 32.2, 33.0, 33.2, 42.6, 43.2, 72.8, 72.9, 75.1, 76.2, 79.0, 79.6, 114.0 (2C), 140.5 (2C). Retention time (t_r) = 12.2 minutes (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 138 (10), 127 (5), 111 (5), 98 (14), 85 (100), 79 (110), 67 (33), 57 (52). HRMS (EI^+) *m*/*z* 156.1146 [M^+]; calculated mass for $C_9H_{16}O_2^+$: 156.1150. t_r = 12.3 minutes: MS (EI) *m*/*z* 138 (10), 127 (5), 111 (5), 98 (14), 85 (100), 79 (110), 67 (33), 57 (52). HRMS (EI^+) *m*/*z* 156.1135 [M^+]; calculated mass for $C_9H_{16}O_2^+$: 156.1150. *rel-(3R,5S)-5-(But-3-en-1-yl)-2-methyltetrahydrofuran-3-ol (**14**)* and *Tetrahydropyran-derivative* as a 86/14-mixture. Yield: 53 mg (340 µmol, 23%), colorless liquid. R_f = 0.15 [diethyl ether/pentane = 1:1 (*v*/*v*)]. *rel-(3R,5S)-5-(But-3-en-1-yl)-2-methyltetrahydrofuran-3-ol (**14**)* as a mixture of cis- and trans-isomers (A:B = 20:80). *Main isomer B*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, 3 H, *J* = 6.3 Hz), 1.46−1.78 (m, 4 H), 2.02−2.20 (m, 2 H), 3.95−4.00 (m, 1 H), 4.14−4.17 (m, 1 H), 4.19−4.24 (m, 1 H), 4.93−5.10 (m, 2 H), 5.76−5.90 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ

14.2, 30.2, 35.4, 41.6, 74.1, 76.5, 77.3, 114.6, 138.2. Retention time (t_r) = 12.8 minutes: MS (EI) *m*/*z* 138 (1), 127 (14), 114 (57), 101 (57), 79 (29), 70 (29), 57 (100), 53 (10). HRMS (EI^+) *m*/*z* 156.1151 [M^+]; calculated mass for $C_9H_{16}O_2^+$: 156.1150; *m*/*z* 138.1042 [M^+-H_2O]; calculated mass for $C_9H_{14}O_1^+$: 138.1045. *Minor isomer A*: t_r = 12.6 minutes: MS (EI) *m*/*z* 138 (1), 127 (14), 114 (57), 101 (57), 79 (29), 70 (29), 57 (100), 53 (10). HRMS (EI^+) *m*/*z* 138.1036 [M^+-H_2O]; calculated mass for $C_9H_{14}O_1^+$: 138.1045. *Tetrahydropyran-derivative*. Retention time (t_r) = 13.6 minutes: MS (EI) *m*/*z* 137 (0.9), 114 (10), 101 (14), 83 (28), 79 (19), 67 (48), 55 (100), 51 (10). HRMS (EI^+) *m*/*z* 138.1042 [M^+-H_2O]; calculated mass for $C_9H_{14}O_1^+$: 138.1045.

4.4 Reduction of Bromomethyletrahydrofurans

4.4.1 General method. Tributylstannane (1.03 g, 3.40 mmol) and AIBN (25.0 mg, 0.15 mmol) were added to a solution of 2-bromomethyltetrahydrofuran-3-yl acetate (**3b**) (303 mg, 1.36 mmol) in dry benzene (20 mL). The reaction mixture was boiled under reflux for 1.5 hours and treated afterwards at room temperature with potassium fluoride (2.5 g, 43.0 mmol) and water (2 mL). Stirring was continued for 30 minutes at room temperature. The slurry was dried ($MgSO_4$) and filtrated. The solids were washed with methyl *tert*-butyl ether (3 × 30 mL). Organic washings were combined with the filtrate from potassium fluoride-treatment and concentrated under reduced pressure (300 mbar, 40 °C). The remaining oil was purified by chromatography [SiO_2, diethyl ether/pentane = 2:1 (*v*/*v*)].

4.4.2 *cis*-2-Methyltetrahydrofuran-3-yl acetate *cis*-(16). From *cis*-2-

bromomethyltetrahydrofuran-3-yl acetate *cis*-(**3b**) according to procedure 4.4.1. Yield: 114 mg (790 µmol, 58%), yellowish oil. R_f = 0.52 [diethyl ether/pentane = 2:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, 3 H, J = 6.5 Hz), 1.90–2.01 (m, 1 H), 2.08 (s, 3 H), 2.25–2.36 (m, 1 H), 3.75 (td, 1 H, J_t = 8.7 Hz, J_d = 6.5 Hz), 3.83–3.96 (m, 1 H), 4.02 (q, 1 H, J = 8.2 Hz), 5.26 (ddd, 1 H, J = 6.0, 4.0, 1.9 Hz). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ14.1, 20.9, 33.4, 65.8, 75.2, 77.3, 170.6.[68]

4.4.3 *trans*-2-Methyltetrahydrofuran-3-yl acetate *trans*-(16). From *trans*-2-bromomethyltetrahydrofuran-3-yl acetate *trans*-(**3b**) according to procedure 4.4.1. Yield: 120 mg (830 µmol, 61%), yellowish oil. R_f = 0.55 [diethyl ether/pentane = 2:1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.23 (d, 3 H, J = 6.5 Hz), 1.85–1.98 (m, 1 H), 2.06 (s, 3 H), 2.16–2.27 (m, 1 H), 3.79–4.04 (m, 3 H), 4.86 (dt, 1 H, J_d = 6.5 Hz, J_t = 2.4 Hz). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ19.0, 21.1, 32.0, 66.5, 79.6, 80.0, 170.3.[68]

Supplementary data. Instrumentation, precursors for the synthesis of 3-alkenoxythiazole-2(3*H*)-thiones **1a**–**f** (alkenols and alkenyl *p*-toluenesulfonates), ^{1}H NMR- and ^{13}C NMR spectra of selected 3-alkenoxythiazole-2(3*H*)-thiones, tetrahydrofurans and tetrahydropyrans (30 pages). Supplementary data associated with this article can be found in the online version at doi: xxx.

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Supplementary Data for

2,3-cis-Cyclization of 4-Pentenoxyl Radicals

Irina Kempter, Christine Schur, Ruth-Maria Bergsträßer, Benjamin Wolff, Thomas Kopf, and Jens Hartung*

Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

Contents

1 General Remarks

(i) Numbering of compounds in the Supplementary data is consistent with the accompanying article. (ii) Numbering of references refers exclusively to the Supplementary data.

2 Instrumentation and Solvent Purification

2.1 Nuclear magnetic resonance spectroscopy

Proton- and carbon-13 nuclear magnetic reonance (NMR)-spectra were recorded with FT-NMR DPX 200, DPX 400 and DMX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale. The resonances of residual $CHCl_3$ and of the carbon atom of $CDCl_3$ (δ_H 7.26, δ_C 77.0) were used as internal standards. NMR shift values of isomuscarine bromides in solutions of D_2O were referenced versus 1,4-dioxane as internal standard (δ_H 3.17, δ_C 67.1).

2.2 Electron impact mass spectrometry

Mass spectra (EI, 70 eV) were recorded with a Mass Selective Detector HP 6890 (*Hewlett Packard*).

2.3 High resolution mass spectrometry

Mass spectroscopy (EI, 70 eV), GCT Premier Micromass (*Waters*).

2.4 Combustion analysis

Combustion analysis was performed with a vario Micro cube CHNS (*Elementar Analysentechnik/Hanau*).

2.5 Thin layer chromatography

Reaction progress was monitored via thin layer chromatography (tlc) on aluminium sheets coated with silica gel (60 F_{254}, *Merck*). Compounds on developed tlc-sheets were detected with the aid of the UV/VIS indicator commercially disposed on the sheets, becoming apparent, for example, by a hand lamp emitting 254 nm light. As alternative method for detecting compounds on developed tlc-sheets is staining by Ekkert´s reagent, and subsequent heating, leading to blue-green spots for organobromines, blue spots for alcohols and yellow

spots for radical precursors.

2.6 Gas chromatography coupled to mass spectrometry

GC/MS-analysis was performed with a HP 6890 Series (*Hewlett Packard*) system and mass detector with a HP-5MS column (*Agilent*, 30 m × 0.25 mm, 0.25 μm). Temperature program: 40 °C (3 min), 10 °C min^{-1} → 280 °C, 280 °C (10 min).

2.7 Melting points

Melting points [°C] were determined on a Koffler hot-plate melting point microscope (*Reichert*) and are not corrected.

2.8 Photoreactor

Photochemically initiated reactions were performed in a Rayonet®-chamber reactor equipped with 350-nm light bulbs from the *Southern New England Ultraviolet* company.

2.9 Laboratory microwave

Microwave heating solutions in α,α,α-trifluorotoluene was performed in a Biotage Initiator 2.5 microwave, using a preselected temperature of 80 °C and using absorption settings for toluene available from the instrument menu.

2.10 Purification of solvents

The term "petroleum ether" refers to the fraction of hydrocarbons boiling between 40–55°C. All solvents were purified according to standard procedures.[1]

3 *O*-Alkenyl Thiohydroxamat Syntheses

3.1 General method for acid-catalyzed hydrolysis of di-*O*-isopropylidene protecting groups

groups. A solution of a di-*O*-isopropylidene-protected 3-alkenoxythiazole-2(3*H*)-thione in methanol was treated with aqueous hydrochloric acid [37 % (*w*/*w*)] and stirred for 8 hours at 22 °C. Water or diethyl ether was added at this temperature, and the product was extracted from this mixture with diethyl ether or dichloromethane. Combined organic washings were dried ($MgSO_4$) and concentrated under reduced pressure (600 mbar, 40 °C) to furnish a residue, which was purified by chromatography (SiO_2).

3.2 3-[3-(methoxymethyloxy)-pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione

3.2.1 Ethyl 3-hydroxypent-4-enoate.[2,3] In an atmosphere of dry nitrogen, a solution of diisopropylamine (9.71 g, 96.0 mmol, 13.6 mL) in dry tetrahydrofuran (80 mL) was cooled to −78 °C and treated in a dropwise manner with *n*-butyllithium (88.0 mmol, 35.2 mL, 2.5 M in hexane) over a period of 30 minutes. At this temperature ethyl acetate (7.05 g, 80.0 mmol) dissolved in dry tetrahydrofuran (35 mL) and afterwards acrolein (4.93 g, 88.0 mmol) dissloved in dry tetrahydrofuran (25 mL) were added in a dropwise manner. The reaction mixture was stirred for 15 minutes at −78 °C and then treated with an aqueous saturated solution of NH_4Cl (50 mL). The reaction mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 80 mL). Combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (600−300 mbar, 40 °C) to afford a residue, which was distilled under reduced pressure (5.0×10^{-1} mbar). Yield: 8.89 g (61.7 mmol, 77%), colorless

liquid, b.p. 67 °C (5.0×10^{-1} mbar). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3 H, J = 7.1 Hz), 2.47−2.59 (m, 2 H), 3.05 (brs, 1 H, OH), 4.16 (q, 2 H, J = 7.3 Hz), 4.52 (brs, 1 H), 5.14 (dt, 1 H, J_d = 10.5 Hz, J_t = 1.3 Hz), 5.30 (dt, 1 H, J_d = 17.3 Hz, J_t = 1.4 Hz), 5.87 (ddd, 1 H, J = 17.1, 10.5, 5.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 41.1, 60.7, 68.9, 115.3, 138.8, 172.2.

3.2.2 Ethyl 3-(methoxymethyloxy)pent-4-enoate (4).[3,4] Phosphorous pentoxide (14.0 g, 98.7 mmol) was added at 0 °C to a stirred solution of dimethoxymethane (34 mL) in chloroform (13 mL) in an at atmosphere of dry nitrogen at such rate that no clumping occurs. To this slurry, a solution of ethyl 3-hydroxypent-4-enoate (2.04 g, 14.2 mmol) in chloroform (13 mL) was added in a dropwise manner at 0 °C. The reaction mixture was allowed to warm to 22 °C and stirred for 1 hour at this temperature. Additional phosphorus pentoxide (14.0 g, 98.7 mmol) was added and the mixture was stirred for 2 hours at 22 °C. Solids were filtered off and washed with chloroform (3 × 30 mL). The solvent was removed under reduced pressure (200 mbar, 30 °C) to leave a residue, which was purified by chromatography [SiO_2, diethyl ether/pentane = 1:2 (*v*/*v*)]. Yield: 1.49 g (7.90 mmol, 56%), colorless liquid. R_f = 0.47 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3 H, J = 7.2 Hz), 2.47−2.66 (m, 2 H), 3.35 (s, 1 H), 4.11−4.19 (m, 2 H), 4.49 (td, 1 H, J_t = 7.9 Hz, J_d = 5.4 Hz), 4.55 (d, 1 H, J = 6.8 Hz), 4.69 (d, 1 H, J = 6.8 Hz), 5.23 (dt, 1 H, J_d = 10.3 Hz, J_t = 1.1 Hz), 5.30 (dt, 1 H, J_d = 17.3 Hz, J_t = 1.3 Hz), 5.73 (ddd, 1 H, J = 17.5, 10.1, 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 41.0, 55.5, 60.5, 73.8, 93.9, 118.1, 136.7, 170.7.

3.2.3 3-(Methoxymethyloxy)pent-4-en-1-ol.[3,5] In an atmosphere of dry nitrogen, a solution

of ethyl 3-(methoxymethyloxy)pent-4-enoate (**4**) (3.47 g, 18.44 mmol) in dry diethyl ether (78 mL) was cooled in an ice bath and treated with lithium aluminium hydride (700 mg, 18.44 mmol) at such a rate that the temperature of 0 °C is maintained. The reaction mixture was allowed to warm to 22 °C and stirred for 1.5 hours at this temperature. Water (0.72 mL) was added at room temperature and the suspension was stirred for 5 minutes, afterwards aqueous sodium hydroxide (2 M, 0.95 mL) was added and the suspension was stirred for 5 minutes. The reaction mixture was treated with additional water (2.20 mL) and stirred for 5 minutes, while solids were precipitated. The solids were filtered off and washed with diethyl ether (30 mL). The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C) to leave a residue that was purified by chromatography (SiO_2, diethyl ether). Yield: 2.37g (16.21 mmol, 88%), colorless liquid. R_f = 0.38 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80−1.85 (m, 2 H), 2.35 (brs, 1 H, OH), 3.39 (s, 1 H), 3.71−3.84 (m, 2 H), 4.23−4.28 (m, 1 H), 4.55 (d, 1 H, J = 6.6 Hz), 4.70 (d, 1 H, J = 6.8 Hz), 5.19−5.27 (m, 2 H), 5.72 (ddd, 1 H, J = 17.4, 10.1, 7.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.7, 55.6, 60.0, 76.3, 93.9, 117.4, 137.6.

3.2.4 3-(Methoxymethyloxy)pent-4-en-1-yl *p*-toluenesulfonate (5).[5] 3-(Methoxy-methyloxy)pent-4-en-1-ol (3.67 g, 25.11 mmol) was dissolved in dichloromethane (120 mL) and treated with 1,4-diazabicyclo[2.2.2]octane (5.63 g, 50.22 mmol) at room temperature. The reaction mixture was cooled in an ice bath and treated in portions with *p*-toluenesulfonyl chloride (7.18 g, 37.67 mmol) at such at rate that the temperature is kept at 0 °C. The reaction mixture was allowed to warm to 22 °C. Stirring at this temperature was continued for 16

hours, leading to a colorless deposit. Solids were filtered off and washed with dichloromethane (50 mL). The solution was washed with aqueous hydrochloric acid (2 M, 2 × 50 mL), an aqueous saturated solution of $NaHCO_3$ (50 mL) and brine (50 mL). Combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 1:1 (*v*/*v*)]. Yield: 6.54 g (21.76 mmol, 87%), colorless oil. R_f = 0.44 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81−1.94 (m, 2 H), 2.45 (s, 3 H), 3.29 (s, 1 H), 4.07−4.12 (m, 2 H), 4.16−4.22 (m, 1 H), 4.46 (d, 1 H, *J* = 6.6 Hz), 4.63 (d, 1 H, *J* = 6.8 Hz), 5.15−5.19 (m, 2 H), 5.55−6.64 (m, 1 H), 7.34 (d, 2 H, *J* = 8.1 Hz), 7.79 (d, 2 H, *J* = 8.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 34.6, 55.5, 67.0, 73.4, 93.9, 118.3, 127.9, 129.8, 133.1, 137.0, 144.7. Anal. Calcd. for $C_{14}H_{20}O_5S$ (300.37): C, 55.98; H, 6.71; S, 10.68. Found: C, 56.12; H, 6.62; S, 10.50.

3.2.5 3-[3-(Methoxymethyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione. To a solution of 3-hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (2.14 g, 7.74 mmol) in anhydrous dimethylformamide (8 mL) was added at 22 °C 3-(methoxymethyloxy)pent-4-en-1-yl *p*-toluenesulfonate (**5**) (2.12 g, 7.04 mmol) in anhydrous dimethylformamide (5.5 mL). The reaction mixture was stirred at 50 °C (oil bath temperature) for 2.5 hours. Water (50 mL) was added and the resulting suspension was extracted with dichloromethane (3 × 20 mL). Combined organic extracts were washed with aqueous sodium hydroxide (2 M, 3 × 20 mL) and brine (20 mL). The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C). The residue was purified by

chromatography [SiO_2, diethyl ether/pentane = 2:1 (*v*/*v*)]. Yield: 1.63 g (5.92 mmol, 84%), pale yellow oil. R_f = 0.33 [diethyl ether/pentane = 2:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03−2.18 (m, 2 H), 2.28 (d, 3 H, J = 1.4 Hz), 3.37 (s, 1 H), 4.23−4.29 (m, 1 H), 4.44−4.55 (m, 2 H), 4.58 (d, 1 H, J = 6.6 Hz), 4.71 (d, 1 H, J = 6.6 Hz), 5.24−5.32 (m, 2 H), 5.74 (ddd, 1 H, J = 17.4, 10.1, 7.4 Hz), 6.15 (d, 1 H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 33.7, 55.7, 72.9, 74.2, 94.1, 102.7, 118.2, 137.4, 137.6, 180.4. Anal. Calcd. for $C_{11}H_{17}NO_3S_2$ (275.39): C, 47.98; H, 6.22; N, 5.09; S, 23.29. Found: C, 48.18; H, 6.17; N, 5.14; S, 23.48.

3.3 3-[(2*R*,3*S*)-Isopropylidendioxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *erythro*-(7)

. 3-Hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (575 mg, 2.08 mmol) and [(*2R,3S*)-isopropylidendioxypent-4-en-1-yl] *p*-toluenesulfonate were dissolved in dimethylformamide (5 mL). The resulting clear solution was stirred for 16 hours at 40 °C. Afterwards water (50 mL) was added and the resulting mixture was extracted with diethyl ether (4 × 50 mL). Combined organic extracts were washed with aqueous sodium hydroxide (2 M, 50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure (600 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 2.5/1 (*v*/*v*)]. Yield: 361 mg (1.26 mmol, 78%), yellow oil. R_f = 0.65 [petroleum ether/diethyl ether = 1/3 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 3 H), 1.52 (s, 3 H), 2.31 (d, 3 H, J = 1.17 Hz), 4.12 (dd, 1 H, J = 9.3, 8.3 Hz), 4.58–4.74 (m, 3 H), 5.28 (dt, 1 H, J_d = 10.4 Hz, J_t = 1.1 Hz), 5.41 (dt, 1 H, J_d = 17.1 Hz, J_t = 1.3 Hz), 5.83 (ddd, 1 H, J = 17.2, 10.2, 7.1 Hz), 6.15 (d, 1 H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.5, 25.2,

27.8, 75.0, 75.7, 77.9, 102.6, 109.5, 119.4, 132.3, 138.0, 180.3. Anal. Calcd. for $C_{12}H_{17}NO_3S_2$ (287.39): C, 50.15; H, 5.96; N, 4.87; S, 22.31. Found: C, 50.26; H, 6.21; N, 4.97; S, 22.45.

3.4 3-[(2*S*,3*S*)-Isopropylidendioxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione. 3-Hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (2.07 g, 7.49 mmol) and [(2*R*,3*R*)-isopropylidendioxypent-4-en-1-yl] *p*-toluenesulfonate (1.80 g, 5.76 mmol) were dissolved in dimethylformamide (10 mL). The solution was stirred at 40 °C for 16 hours and then added to water (50 mL). The mixture was extracted with diethyl ether (4 × 50 mL). Combined organic extracts were washed with aqueous sodium hydroxide (2 M, 50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 2.5/1 (*v*/*v*)]. Yield: 1.40 g (4.87 mmol, 85%), yellow oil. R_f = 0.63 [petroleum ether/diethyl ether = 1/3 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.43 (d, 6 H, *J* = 6.2 Hz), 2.30 (d, 3 H, *J* = 1.2 Hz), 4.03 (ddd, 1 H, *J* = 8.5, 5.1, 3.4 Hz), 4.45 (t, 1 H, *J* = 7.8 Hz), 4.52–4.58 (m, 2 H), 5.30 (d, 1 H, *J* = 10.3 Hz), 5.49 (d, 1 H, *J* = 10.3 Hz), 5.86 (ddd, 1 H, *J* = 17.2, 10.3, 7.0 Hz), 6.16 (d, 1 H, *J* = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.3, 26.7, 26.9, 74.3, 78.0, 78.3, 102.6, 109.9, 119.7, 134.2, 137.9, 180.2. Anal. Calcd. for $C_{12}H_{17}NO_5S_2$ (287.39): C, 50.15; H, 5.96; N, 4.87; S, 22.31. Found: C, 50.23; H, 5.82; N, 4.82; S, 21.93.

3.5 3-[(2*S*,3*S*,4*S*)-3,4-*O*-Bishydroxyhex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione

3.5.1 (2*R*,3*R*,4*S*)-3,4-*O*-Isopropylidendioxyhex-5-en-2-ol. Potassium *tert*-butoxide (1.88 g, 16.8 mmol) and methyltriphenylphosphonium bromide (5.77 g, 16.2 mmol) were dissolved in

dry tetrahydrofuran (80 mL). The reaction mixture was stirred 2 hours at 25 °C. 2,3-*O*-Isopropyliden-5-*O*-desoxy-D-ribofuranose (1.10 g, 6.46 mmol) in tetrahydrofuran (20 mL) was added and the mixture was stirred 6 hours while being refluxed. The reaction mixture was treated with water (20 mL) at room temperature and the layers were separated. The aqueous layer was extracted with diethyl ether (5 × 20 mL). Combined organic extracts were washed with water (20 mL) and brine (20 mL). The solution was dried (Na_2SO_4) and the solvent was removed under reduced pressure (800 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 1/1 (*v*/*v*)]. Yield: 755 mg (4.37 mmol, 67%), colorless oil. R_f = 0.47 [diethyl ether/pentane = 1/1 (*v*/*v*)]. $[\alpha]^{D}_{25} = -21.3$ (*c* = 1.00 g/100 ml/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 3 H, *J* = 6.2 Hz), 1.37 (s, 3 H), 1.48 (s, 3 H), 1.74 (d, 1 H, *J* = 4.4 Hz, OH), 3.79–3.86 (m, 1 H), 3.93 (dd, 1 H, *J* = 7.9, 6.2Hz), 4.66 (dd, 1 H, *J* = 7.3, 6.4 Hz), 5.31 (ddd, 1 H, *J* = 17.3, 2.9, 1.7 Hz), 5.44 (ddd, 1 H, *J* = 12.0, 2.9, 1.4 Hz), 5.98−6.05 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 25.3, 27.7, 66.4, 78.8, 82.0, 108.7, 118.5, 134.6. Anal. Calcd. for $C_9H_{16}O_3$ (172.22): C, 62.77; H, 9.36. Found: C, 62.46; H, 9.58.

3.5.2 3-[(2*S*,3*S*,4*S*)-3,4-*O*-Isopropylidendioxyhex-5-en-2-oxy]-4-methyl-5-(*p*-methoxy-phenyl)thiazole-2(3*H*)-thione (9). In an atmosphere of dry nitrogen, (2*R*,3*R*,4*S*)-3,4-*O*-isopropylidendioxyhex-5-en-2-ol (750 mg, 4.36 mmol), 3-hydroxy-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione (1.66 g, 6.54 mmol) and triphenylphosphine (2.29 g, 8.72 mmol) were dissolved in benzene (50 mL). The solution was cooled to 0 °C and diethyl azodicarboxylate (3.04 g, 17.4 mmol) was added in a dropwise manner. The reaction mixture was stirred 48 hours at 25 °C and then treated with with aqueous sodium hydroxide (2 M, 15

mL). The resulting layers were separated and the aqueous layer was extracted with dichloromethane (4 × 20 mL). Combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure (600 mbar, 40 °C) to leave a residue, which was purified by chromatography [SiO_2, diethyl ether/pentane = 1/1 (*v*/*v*)]. Yield: 953 mg (2.35 mmol, 54%), yellow solid. R_f = 0.26 [diethyl ether/pentane = 1/1 (*v*/*v*)]. $[\alpha]^D_{25}$ = 28.9 (*c* = 11.2 g/100 ml/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (d, 6 H, *J* = 6.7 Hz), 1.43 (s, 3 H), 2.32 (s, 3 H), 3.83 (s, 3 H), 4.34 (dd, 2 H, *J* = 7.8, 6.2 Hz), 4.53 (dd, 1 H, *J* = 8.6, 6.2 Hz), 5.34 (t, 2 H, *J* = 8.3, Hz), 5.41−5.47 (m, 1 H), 5.97−6.05 (m, 1 H), 6.94 (d, 2 H, *J* = 8.0 Hz), 7.21 (d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.8, 15.2, 25.7, 28.0, 55.6, 79.8, 80.0, 80.8, 109.7, 114.7, 118.6, 120.4, 123.1, 130.0, 133.7, 134.3, 160.0, 178.7. Anal. Calcd. for $C_{20}H_{25}NO_4S_2$ (407.54): C, 58.94; H, 6.18; N, 3.44. Found: C, 58.75; H, 6.21; N, 3.63.

3.5.3 3-[(2*S*,3*S*,4*S*)-3,4-*O*-Bishydroxyhex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione. From 3-[(2*S*,3*S*,4*S*)-3,4-*O*-isopropylidendioxyhex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione (**9**) (1.14 g, 2.8 mmol), methanol (48 mL) and aqueous hydrochloric acid [2.96 mL, 37 % (*w*/*w*)] according to procedure 3.1. Water (60 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). This product was used as obtained in the succeeding step. Yield: 1.00 g (2.75 mmol, 96%), yellow oil. R_f = 0.0 [diethyl ether/pentane = 1/1 (*v*/*v*)]. $[\alpha]^D_{25}$ = 21.7 (*c* = 8.84 g/100 ml/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (d, 3 H, *J* = 6.7 Hz), 2.34 (s, 3 H), 3.58 (d, 1 H, *J* = 4.7 Hz), 3.83 (s, 3 H,), 4.42 (t, 1 H, *J* = 6.6 Hz), 5.32 (d, 1 H, *J* = 10.6 Hz), 5.43 (d, 1 H, *J* = 17.2 Hz), 5.49 (dd, 1 H, *J* = 9.4, 3.1 Hz), 6.10−6.01 (m, 1 H), 6.95 (d, 2 H, *J* = 9.0 Hz), 7.24 (d, *J* = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.9, 15.4, 55.5, 72.8, 76.2, 80.8, 114.6,

117.7, 120.1, 122.1, 129.9, 133.8, 137.2, 160.0, 178.8. Anal. Calcd. for $C_{17}H_{21}NO_4S_2$ (367.48): C, 55.56; H, 5.76; N, 3.81. Found: C, 55.31; H, 5.75; N, 4.04.

3.6 Synthesis of 3-(3-Hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3*H*)-thione (1f)

3.6.1 3-(Methoxymethyloxy)pent-4-enal. In an atmosphere of dry nitrogen, a solution of ethyl 3-(methoxymethyloxy)pent-4-enoate (9.49 g, 50.4 mmol) in dichloromethane (125 mL) was cooled to −78 °C, and treated in a dropwise manner at −78 °C with diisobutylaluminium hydride (50.4 mL, 1 M solution in hexane) and afterwards with methanol (99.5 mL). The reaction mixture was allowed to 22 °C and solids were filtered off over celite. The filtrate was concentrated under reduced pressure (650 mbar, 30 °C) to leave a residue, which was purified by chromatography [SiO_2, diethyl ether/pentane = 1:1 (*v*/*v*)]. Yield: 3.00 g (20.80 mmol, 41%), colorless liquid. R_f = 0.41 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.53–2.59 (m, 1 H), 2.67–2.70 (m, 1 H), 3.34 (s, 3 H), 4.53 (d, 1 H, J = 6.9 Hz), 4.57 (m, 1 H), 4.70 (d, 1 H, J = 6.9 Hz,), 5.23–5.26 (m, 1 H), 5.28–5.33 (m, 1 H), 5.70–5.78 (m, 1 H), 9.77–9.78 (dd, 1 H, J = 2.6, 1.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.9, 55.7, 72.2, 93.9, 118.2, 136.5, 200.5.

3.6.2 3-(Methoxymethyloxy)nona-1,8-dien-5-ol. In an atmosphere of dry nitrogen, a suspension of magnesium (450 mg, 18.5 mmol) in dry tetrahydrofuran (18.5 mL) was treated in a dropwise manner with bromobut-2-ene (2.50 g, 18.5 mmol) and afterwards with 3-(methoxymethyloxy)pent-4-enal (2.06 g, 14.20 mmol) at room temperature. The reaction mixture was stirred for 1 hour at 22 °C and then cooled to 0 °C. At 0 °C the reaction mixture

was treated with an aqueous saturated solution of NH_4Cl. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). Combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (650 mbar, 30 °C) and the residue was purified by chromatography [SiO_2, diethyl ether/pentane = 1:1 (*v*/*v*)]. Yield: 2.08 g (10.2 mmol, 70%), colorless liquid, as a 50/50-mixture of diastereomers. R_f = 0.53 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49–1.80 (m, 4 H), 2.10–2.24 (m, 2 H), 3.41 (s, 3 H), 3.83–3.92 (m, 1 H), 4.27–4.36 (m, 1 H), 4.54–4.59 (dd, 1 H, *J* = 13.6, 6.7 Hz), 4.68–4.75 (m, 1 H), 4.96–4.98 (m, 2 H), 5.18–5.28 (m, 2 H), 5.63–5.75 (m, 1 H), 5.77–5.90 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.7, 30.0, 36.4, 36.6, 42.2, 42.3, 55.8, 67.5, 70.3, 75.4, 77.6, 93.4, 94.4, 114.7, 116.8, 118.1, 137.4 (2C), 137.7 (2C), 138.5 (2C), 138.5 (2C). Retention time (t_r) = 14.8 minutes (for GC/MS conditions see section 2.7): MS (EI) *m*/*z* 138 (<1), 113 (24), 101 (28), 83 (57), 67 (57), 55 (100). HRMS (EI$^+$) *m*/*z* 168.1142 [M^+-OCH_3-H]; calculated mass for $C_{10}H_{16}O_2^+$: 168.1150. t_r = 14.9 minutes: MS (EI) *m*/*z* 138 (<1), 113 (24), 101 (28), 83 (57), 67 (57), 55 (100). HRMS (EI$^+$) *m*/*z* 168.1133 [M^+-OCH_3-H]; calculated mass for $C_{10}H_{16}O_2^+$: 168.1150.

3.6.3 3-(Methoxymethyloxy)nona-1,8-dien-5-yl-4-methyl *p*-toluenesulfonate (10). In an atmosphere of dry nitrogen, a solution of 3-(methoxymethyloxy)nona-1,8-dien-5-ol (1.30 g, 6.50 mmol) in dry dichloromethane (32 mL) was treated with 1,4-diazabicyclo[2.2.2]octane (1.46 g, 13.00 mmol) and the mixture was cooled in an ice bath. *p*-Toluenesulfonyl chloride (1.86 g, 9.75 mmol) was added in portions that the temperature does not exceed 0 °C. The resulting reaction mixture was allowed to warm to 22 °C and stirred for 19 hours at this

temperature. The precipitate formed was filtered off and washed with diethyl ether (3 × 30 mL). Filtrate and organic washings were washed with aqueous hydrochloric acid (2 M, 30 mL), an aqueous saturated solution of $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 30 °C) to leave a residue, which was purified by chromatography [SiO_2, diethyl ether/pentane = 1:3 (*v*/*v*)]. Yield: 1.85 g (5.20 mmol, 80%), pale yellow liquid, as a 50/50-mixture of diastereomers. R_f = 0.26 [diethyl ether/pentane = 1:3 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71–1.84 (m, 4 H), 1.99–2.06 (m, 2 H), 2.45 (s, 3 H), 3.33–3.39 (m, 3 H), 3.98–4.03 (m, 1 H), 4.47–4.51 (m, 1 H), 4.62–4.64 (m, 1 H), 4.80–4.86 (m, 1 H), 4.93–4.98 (m, 2 H), 5.15–5.21 (m, 2 H), 5.58–5.72 (m, 2 H), 7.35 (d, 2 H, J = 8.2 Hz), 7.80–7.83 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 28.5, 28.8, 33.3, 34.1, 39.9, 40.6, 55.7, 55.9, 73.8, 74.5, 80.4, 80.5, 93.6, 94.5, 115.3, 115.3, 117.6, 118.6, 127.7, 127.8, 129.7, 134.5, 134.7, 137.0, 137.1, 137.1, 137.8, 144.5.

3.6.4 3-[3-(Methoxymethyloxy)nona-1,8-diene-5-oxy]-4-methylthiazole-2(3*H*)-thione. 3-Hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (0.87 g, 5.90 mmol) was dissolved in anhydrous dimethylformamide (3.5 mL) and treated with 3-(methoxymethyloxy)nona-1,8-diene-5-yl-4-methyl *p*-toluenesulfonate (**10**) (1.85 g, 5.20 mmol) in anhydrous dimethylformamide (7 mL). The solution was stirred at 40 °C (oil bath temperature) for 2 hours and then allowed to cool to 22 °C. The mixture was treated with water (10 mL) and dichlormethane (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). Combined organic layers were washed with aqueous sodium hydroxide (2 M, 3 × 10 mL) and brine (3 × 25 mL). The organic solution was

dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 1:1 (*v*/*v*)]. Yield: 1.16 g (3.50 mmol, 67%), pale yellow liquid, as a 50/50-mixture of diastereomers. R_f = 0.35 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78–2.00 (m, 4 H), 2.20–2.27 (m, 5 H), 3.37–3.39 (m, 3 H), 4.17–4.20 (m, 1 H), 4.51–4.68 (m, 2 H), 4.98–5.07 (m, 2 H), 5.23–5.31 (m 2 H), 5.45–5.50 (m, 1 H), 5.67–5.83 (m, 2 H), 6.16–6.18 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 29.1, 31.7, 32.1, 38.4, 38.7, 55.8, 55.9, 74.0, 74.7, 81.9, 93.7, 94.5, 102.8, 115.2, 118.3, 137.3, 137.6, 137.8, 138.9, 181.0.

4 Synthesis of *rel*-(3*S*,4*R*)-3-bromotetrahydropyran-4-ol *cis*-(11a)

3-Bromotetrahydropyran-4-one (180 mg, 1.00 mmol) was dissolved in methanol (4 mL) and treated with sodium borohydride (46 mg, 1.20 mmol) at 22 °C.[6,7] The reaction mixture was stirred at 22 °C for 3 hours. The solvent was removed under reduced pressure (300 mbar, 40 °C). Ethyl acetate (20 mL) was added and the resulting solution was washed with brine (20 mL). The layers were separated and the organic layer was dried ($MgSO_4$). The solvent was removed under reduced pressure (200 mbar, 40 °C) and the residue was purified by chromatography [SiO_2, diethyl ether/pentane = 2:1 (*v*/*v*)]. Yield: 95.0 mg (0.52 mmol, 52%), pale yellow oil. R_f = 0.30 [diethyl ether/pentane = 2:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91–2.04 (m, 2 H), 3.62 (dt, 1 H, J_d = 11.7 Hz, J_t = 4.7 Hz), 3.79 (dd, 1 H, J = 11.9, 3.8 Hz), 3.89 (ddd, 1 H, J = 11.8, 8.5, 3.7 Hz), 3.95–3.99 (m, 2 H), 4.35 (dt, 1 H, J_d = 8.3 Hz, J_t = 3.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.6, 55.7, 63.3, 67.0, 68.1. MS (EI) *m*/*z* 124/122, 108/106, 101, 100, 83 (100), 73, 61, 55.

5 Bromocyclizations

5.1 General method for thermally initiated radical reactions. Bromotrichloromethane (10 equiv.) and azobisisobutyronitrile (AIBN) (0.25 equiv.) were added to a solution of 3-alkenoxythiazole-2(3*H*)-thione **1** (1 equiv., c_0 = 83 mM) in perdeuterobenzene. The solution was heated to reflux for 2 hours. For yields of 4-methyl-2-(trichloromethylsulfanyl)thiazole (**2**), tetrahydrofuran **3** and tetrahydropyran **11**, determined via proton-NMR using pentachlorobenzene or bromobenzaldehyde as internal standard, refer to section 2.4.1 of the associated publication.

5.2 General method for photochemically initiated radical reactions. Bromotrichloromethane (9−10 equiv.) were added to a solution of 3-alkenoxythiazole-2(3*H*)-thione **1** (1 equiv., c_0 = 83 or 196 mM) in perdeuterobenzene. The solution was photolyzed (350 nm) for 30−60 minutes. For yields of 4-methyl-2-(trichloromethylsulfanyl)thiazole (**2**), tetrahydrofuran **3** and tetrahydropyran **11**, determined via proton-NMR using pentachlorobenzene or bromobenzaldehyde as internal standard, refer to section 2.4.1 and Scheme 9 of the associated publication.

6 NMR Spectra

6.1 *O*-Alkenylthiohydroxamate

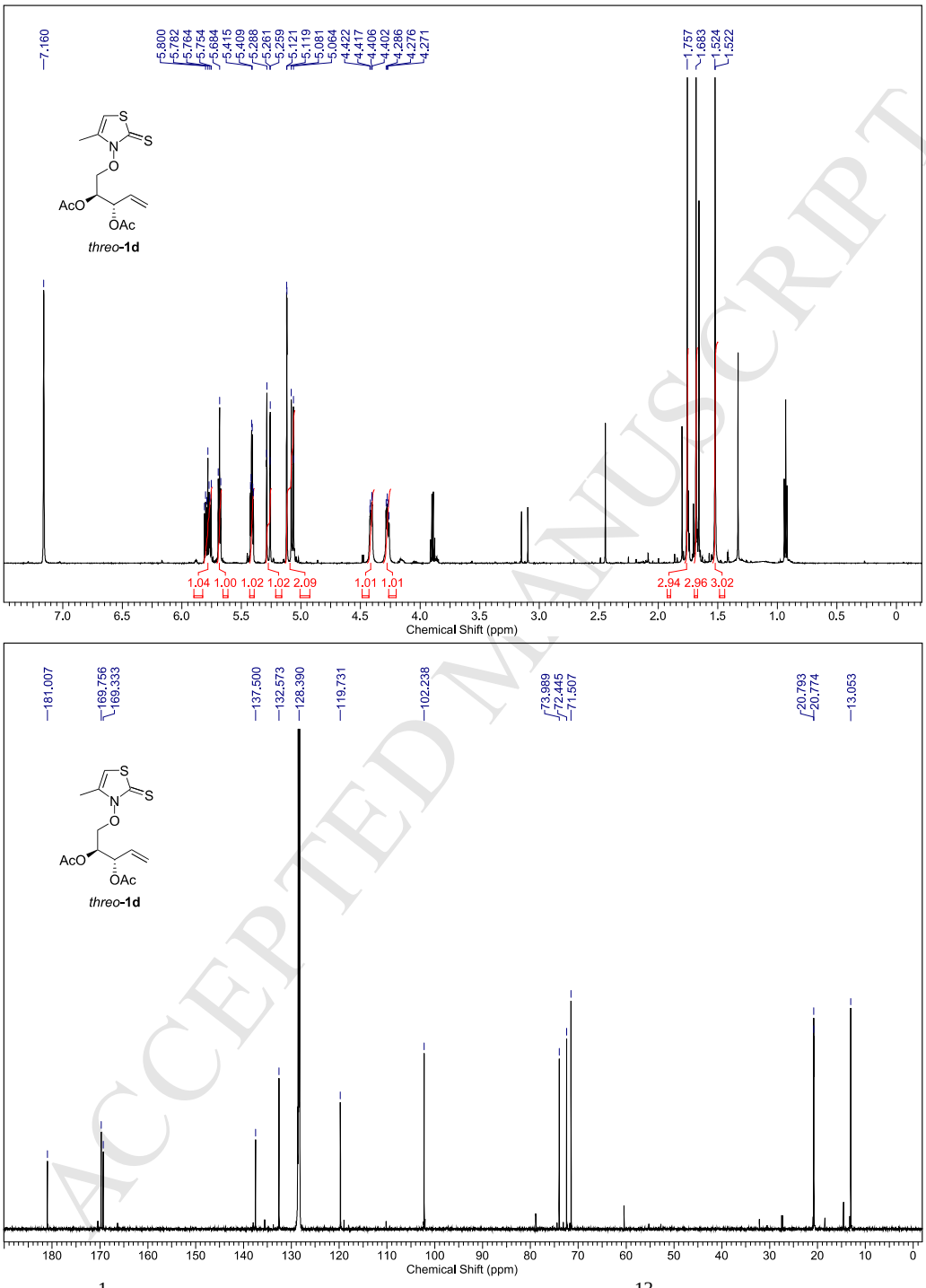

Figure 6.1 ^{1}H-NMR-spectrum (C_6D_6, 600 MHz, top) and ^{13}C-NMR-spectrum (C_6D_6, 150 MHz, bottom) of 3-[(2*S*,3*S*)-bis(acetyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *threo*-(**1d**).

6.2 Bromocyclization products of 1a

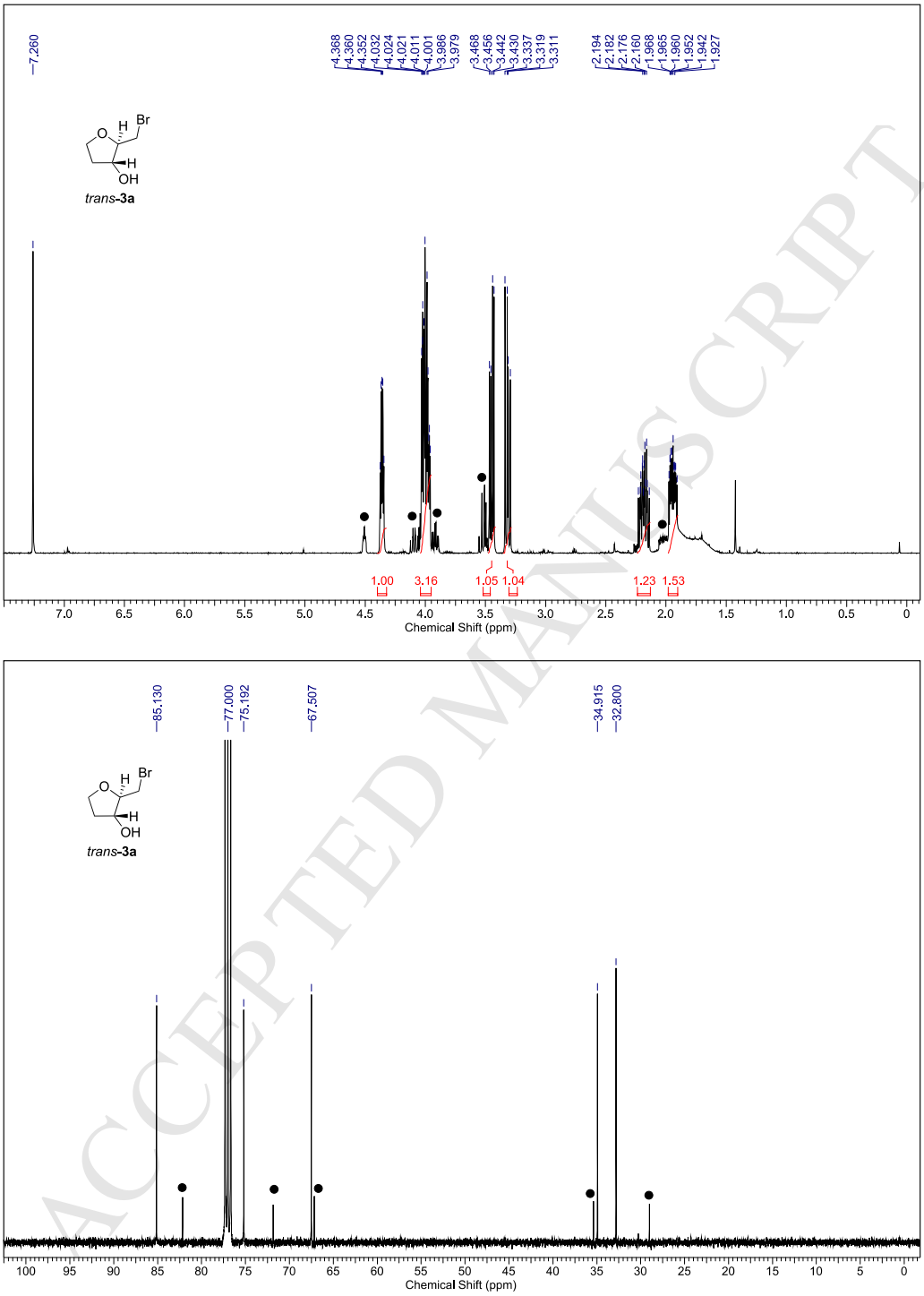

Figure 6.2 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(2*R*,3*R*)-2-bromomethyltetrahydrofuran-3-ol *trans*-(**3a**). Labeling (●) refer to *rel*-(2*S*,3*R*)-2-bromomethyltetrahydrofuran-3-ol *cis*-(**3a**).

6.3 Bromocyclization products of 1b

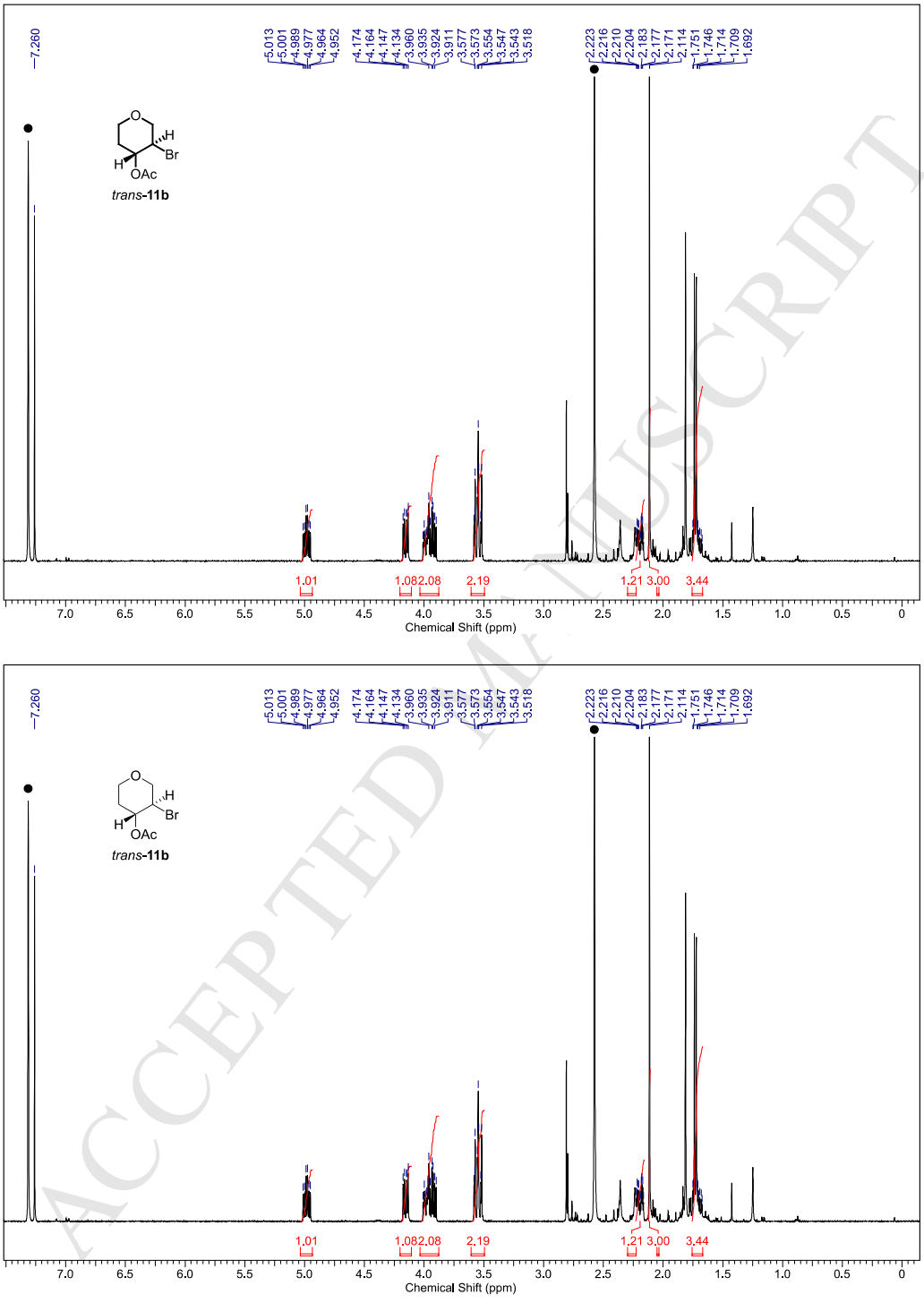

Figure 6.3 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(3*R*,4*R*)-3-bromotetrahydropyran-4-yl acetate *trans*-(**11b**). Labeling (●) refer to 4-methyl-2-(trichloromethylsulfanyl)thiazole (**2**).

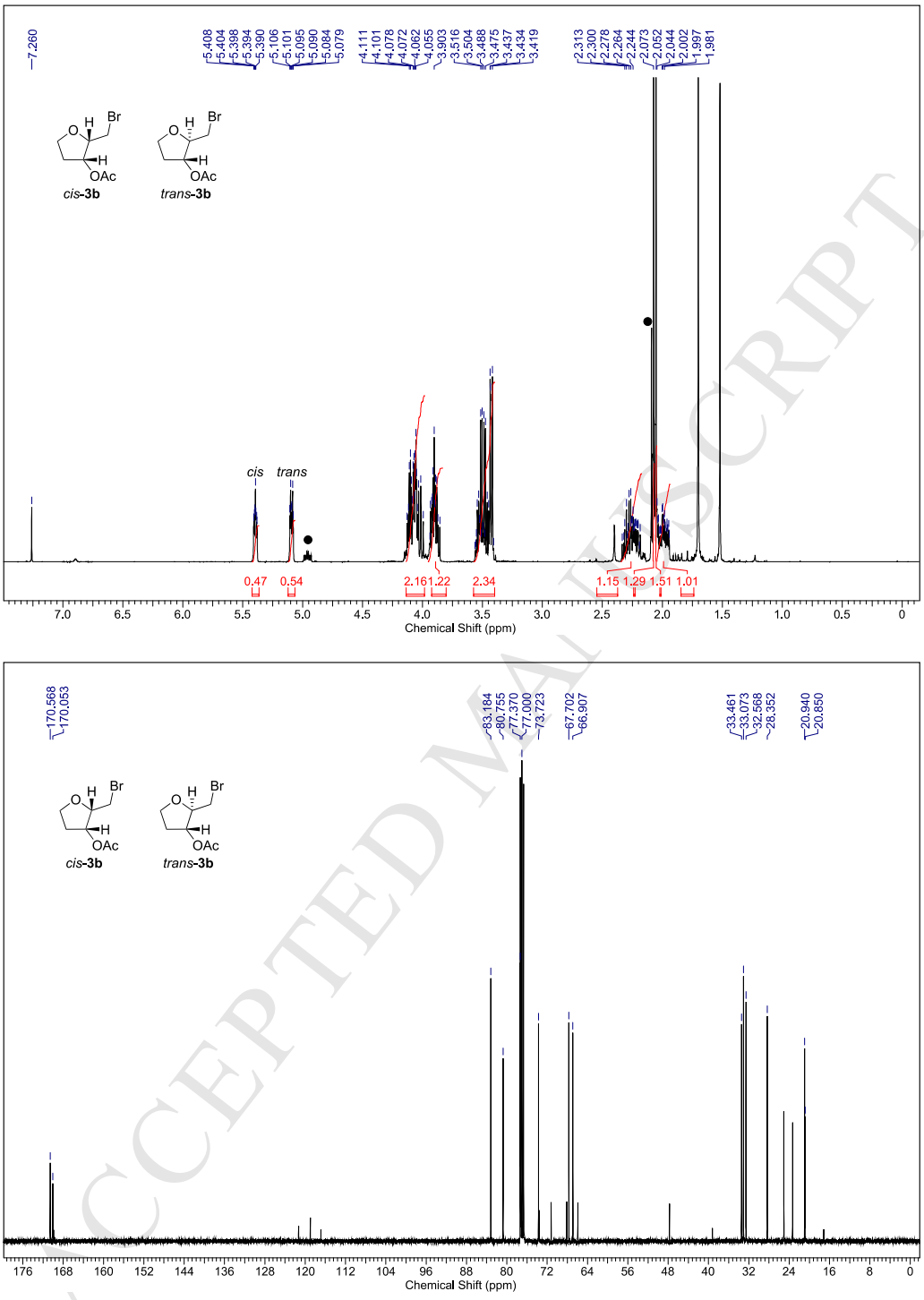

Figure 6.4 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of 2-bromomethyltetrahydrofuran-3-yl acetate (**3b**) (47/53-mixture of cis/trans-isomers). Labeling (●) refer to assignable resonances for *rel*-(3*R*,4*R*)-3-bromotetrahydropyran-4-yl acetate *trans*-(**11b**).

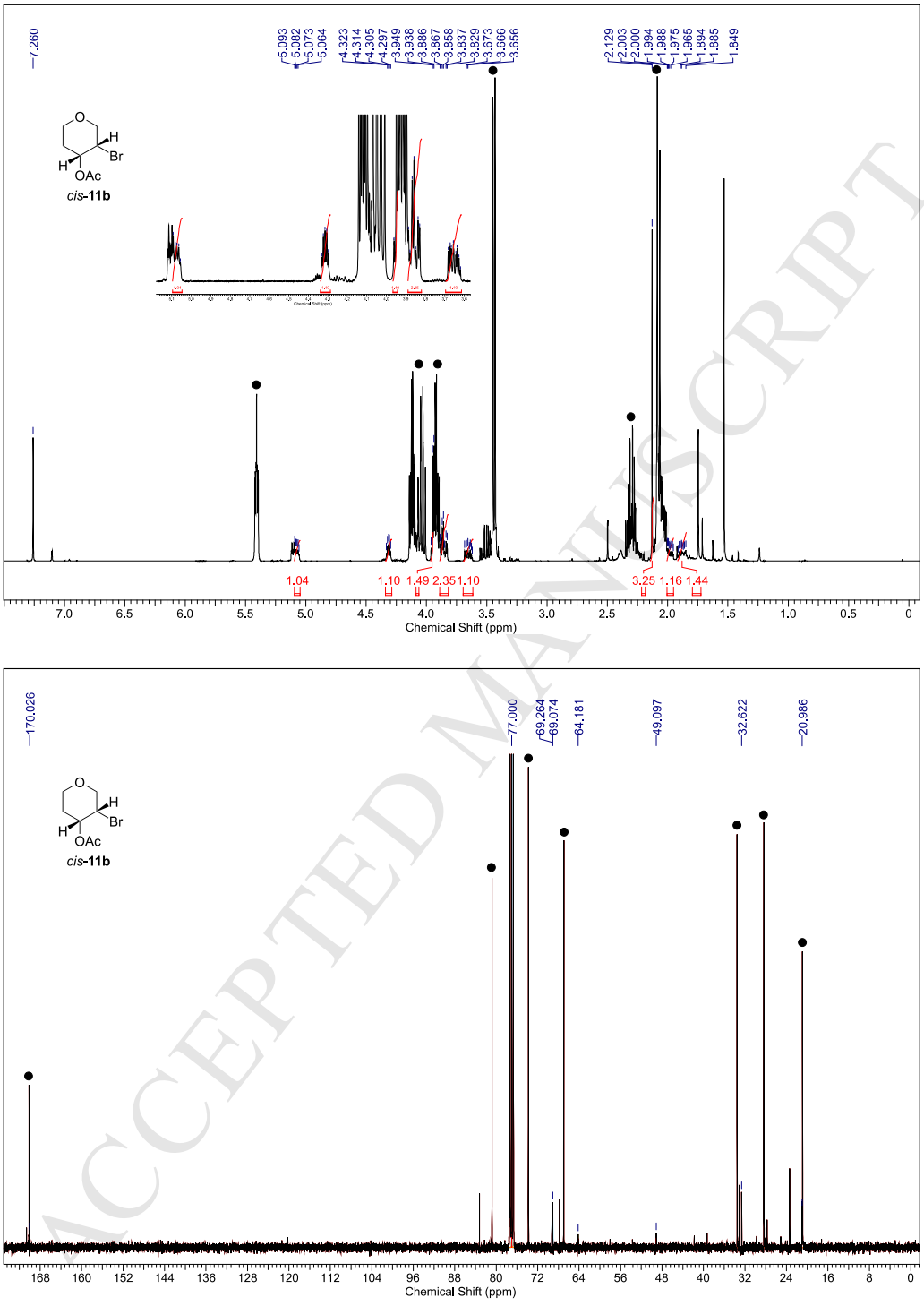

Figure 6.5 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(3*S*,4*R*)-3-bromotetrahydropyran-4-yl acetate *cis*-(**11b**). Labeling (●) refer to *rel*-(2*S*,3*R*)-2-bromomethyltetrahydrofuran-3-yl acetate *cis*-(**3b**).

6.4 Bromocyclization products of 1c

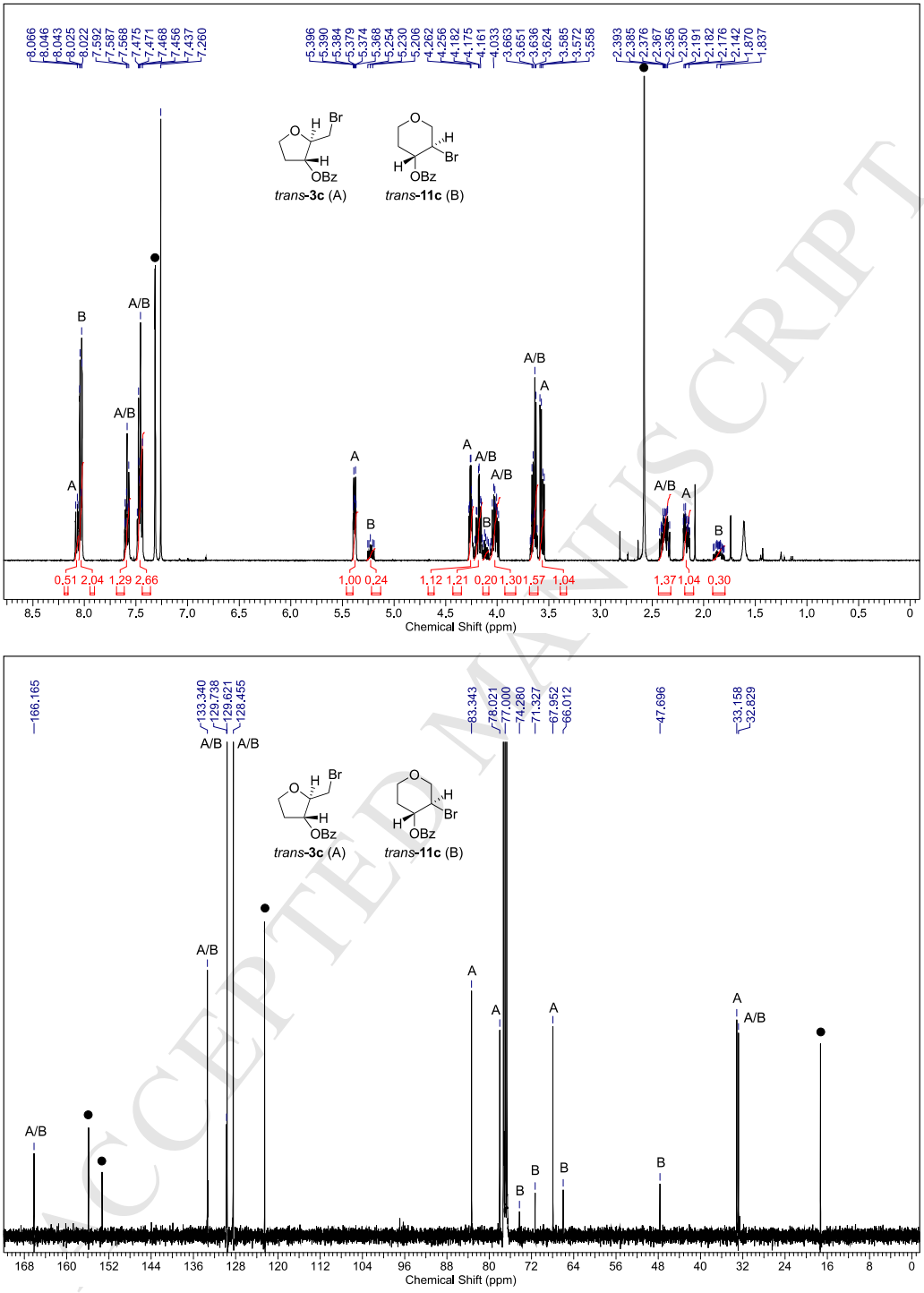

Figure 6.6 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(2*R*,3*R*)-2-bromomethyltetrahydrofuran-3-yl benzoate *trans*-(**3c**) and *rel*-(3*R*,4*R*)-3-bromotetrahydropyran-4-yl benzoate *trans*-(**11c**) (81/9- mixture of A/B-isomers). Labeling (●) refer to 4-methyl-2-(trichloromethylsulfanyl)thiazole (**2**).

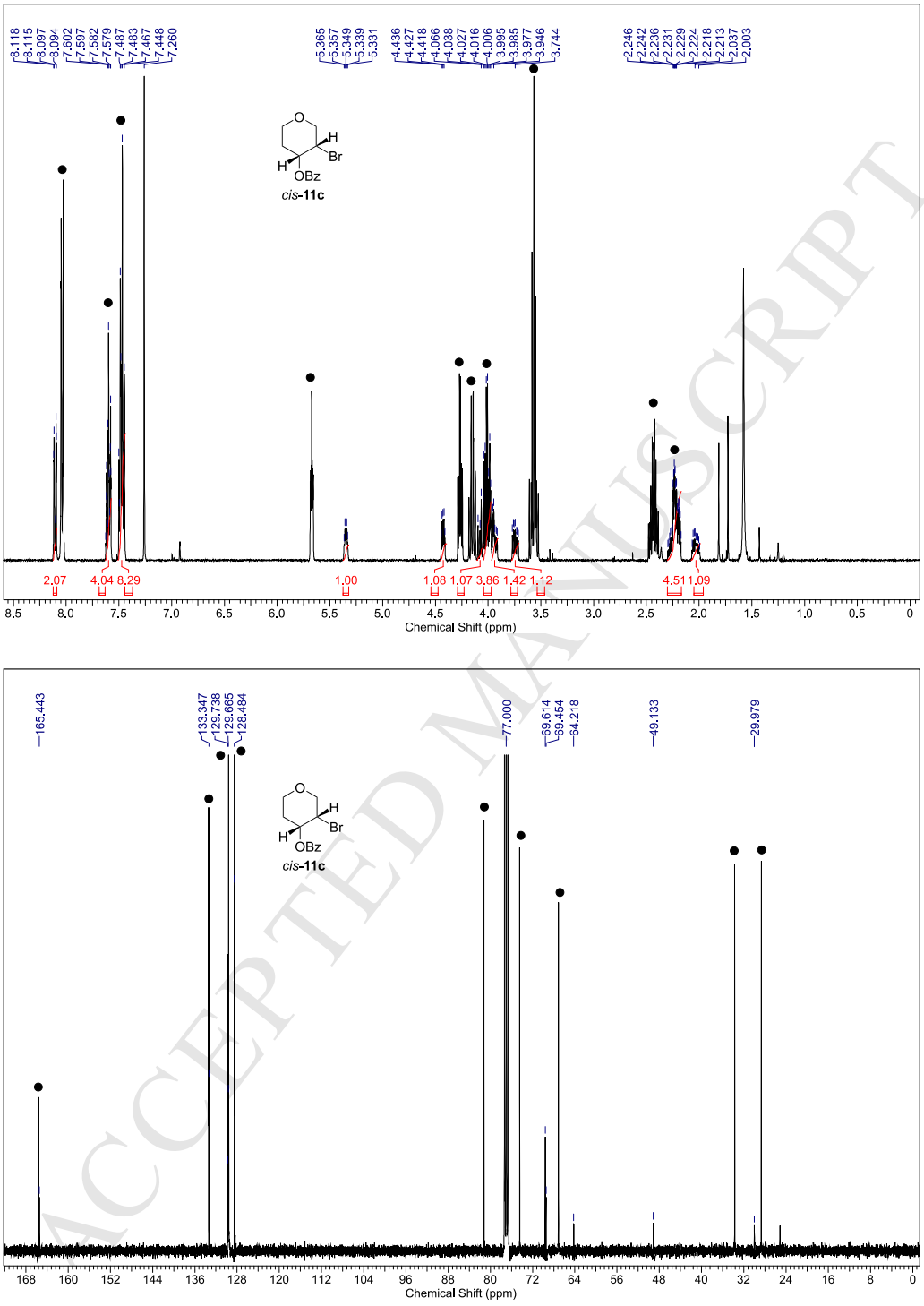

Figure 6.7 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(3*S*,4*R*)-3-bromotetrahydropyran-4-yl benzoate *cis*-(**11c**). Labeling (●) refer to *rel*-(2*S*,3*R*)-2-bromomethyltetrahydrofuran-3-yl benzoate *cis*-(**3c**).

6.5 Bromocyclization products of *erythro*-1d

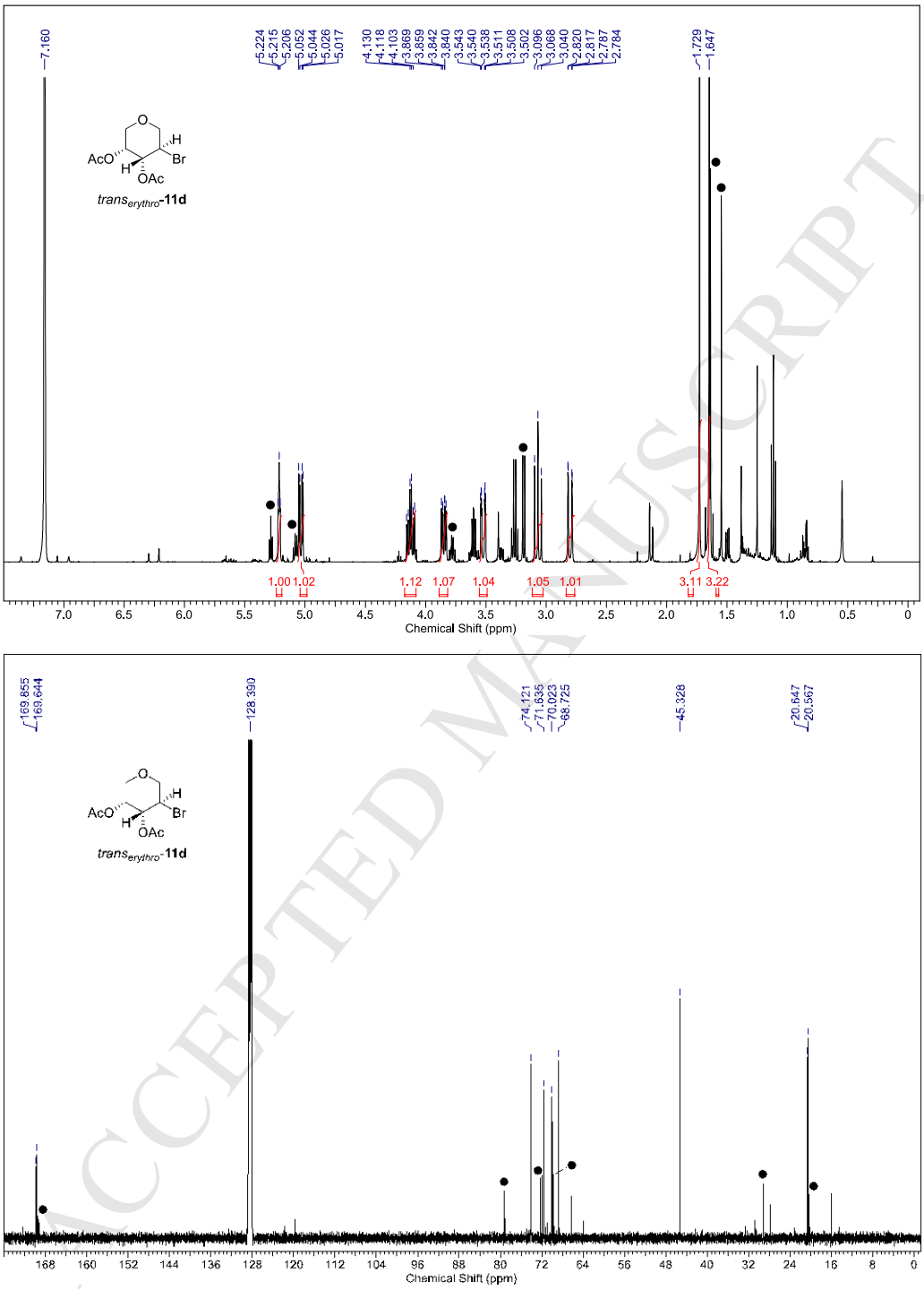

Figure 6.8 ^{1}H-NMR-spectrum (C_6D_6, 400 MHz, top) and ^{13}C-NMR-spectrum (C_6D_6, 100 MHz, bottom) of (3*R*,4*R*,5*R*)-3-bromotetrahydropyran-4,5-diyl bisacetate *trans*$_{erythro}$-(**11d**). Labeling (●) refer to (2*S*,3*R*,4*R*)-2-bromomethyltetrahydrofuran-3,4-diyl bisacetate *cis*$_{erythro}$-(**3d**).

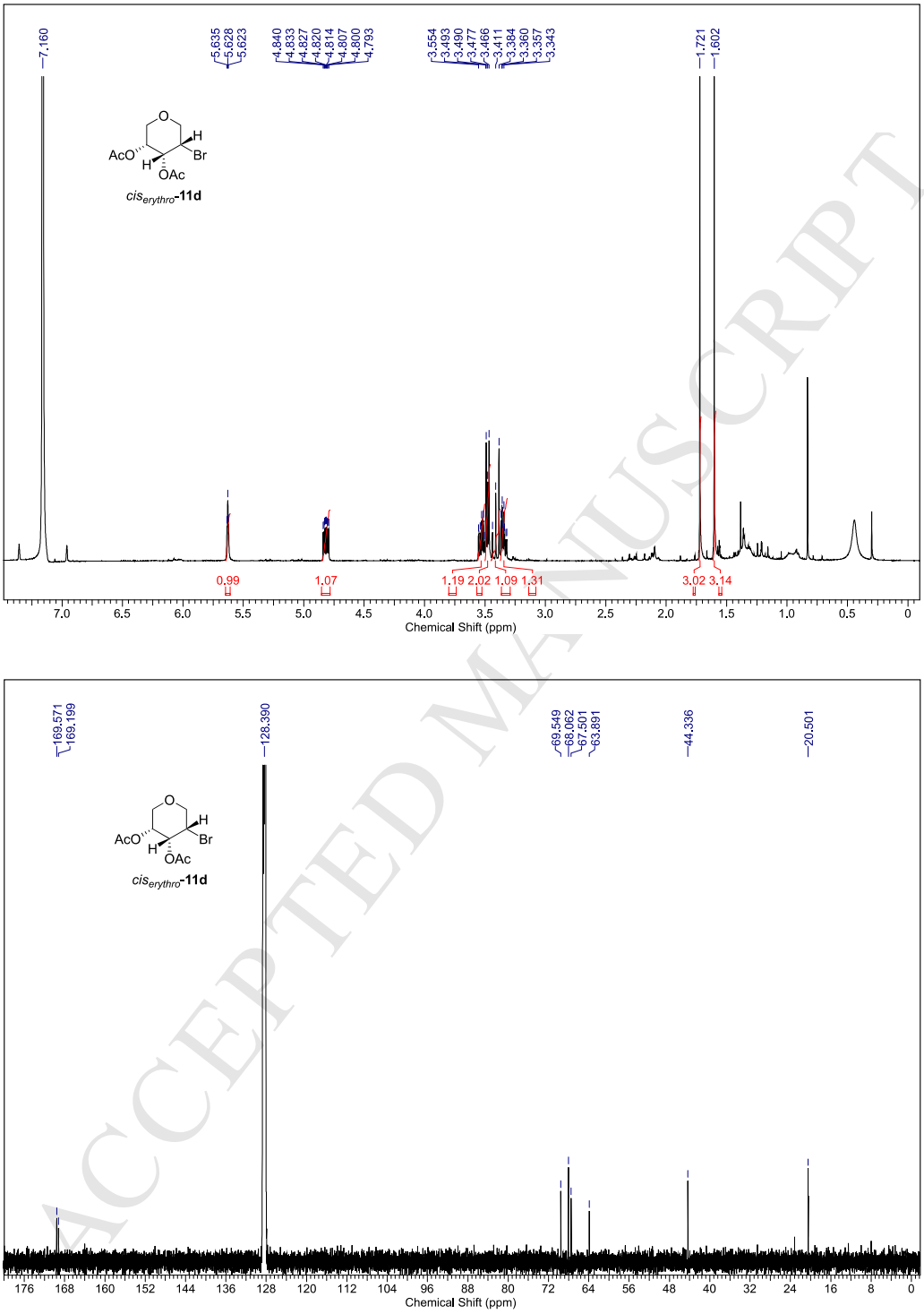

Figure 6.9 ^{1}H-NMR-spectrum (C_6D_6, 400 MHz, top) and ^{13}C-NMR-spectrum (C_6D_6, 100 MHz, bottom) of (3*S*,4*R*,5*R*)-3-bromotetrahydropyran-4,5-diyl bisacetate *cis*$_{erythro}$-(**11d**).

6.6 Bromocyclization products of *threo*-1d

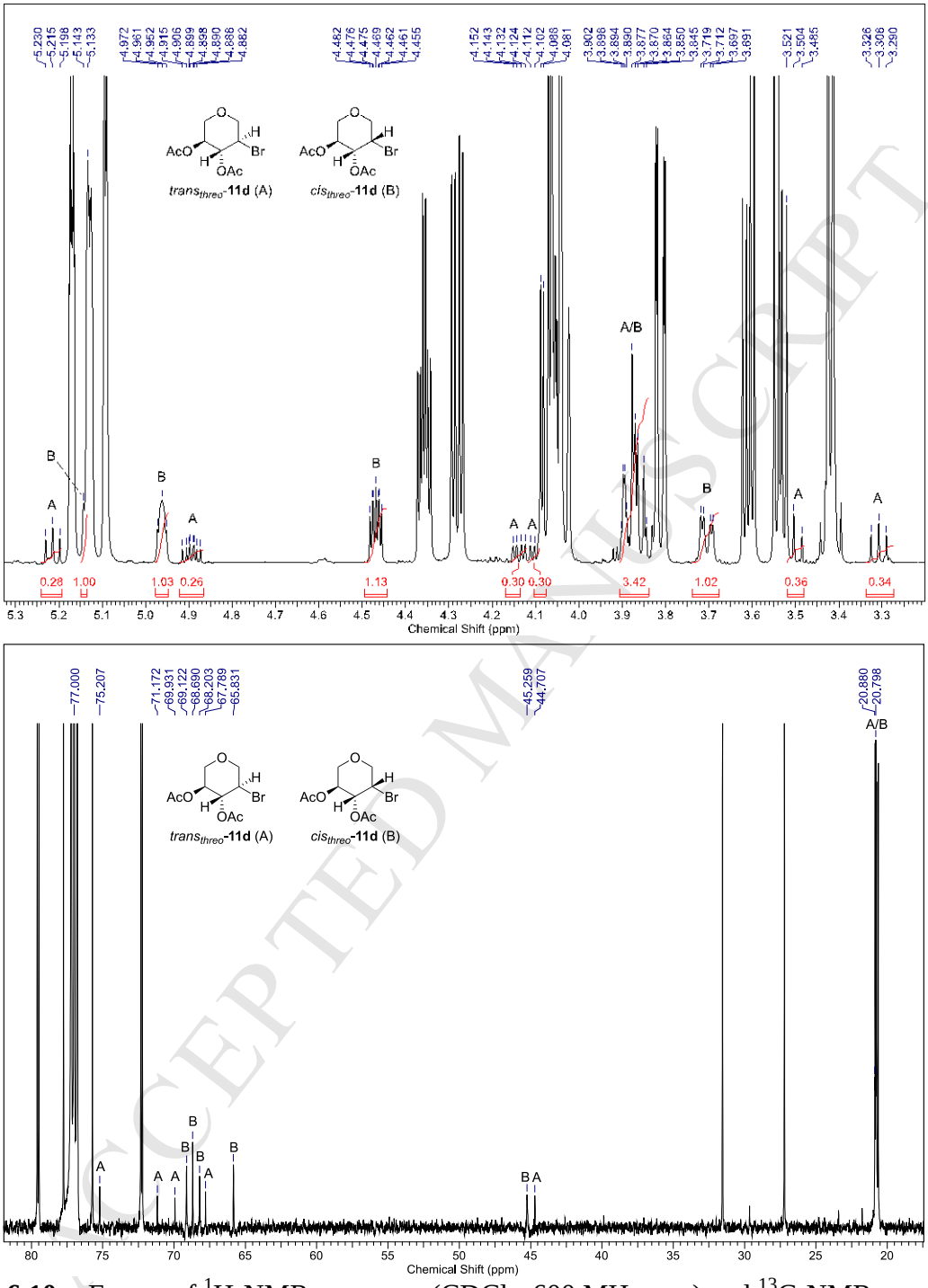

Figure 6.10 Expert of ^{1}H-NMR-spectrum ($CDCl_3$, 600 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 150 MHz, bottom) of (3*R*,4*R*,5*S*)-4,5-bis(acetyloxy)-3-bromomethyltetrahydropyran *trans*$_{threo}$-(**11d**) and (3*R*,4*R*,5*S*)-4,5-bisacetyloxy-3-bromomethyltetrahydropyran *cis*$_{threo}$-(**11d**) (80/20-mixture of cis/trans-isomers).

6.7 Bromocyclization products of 1f

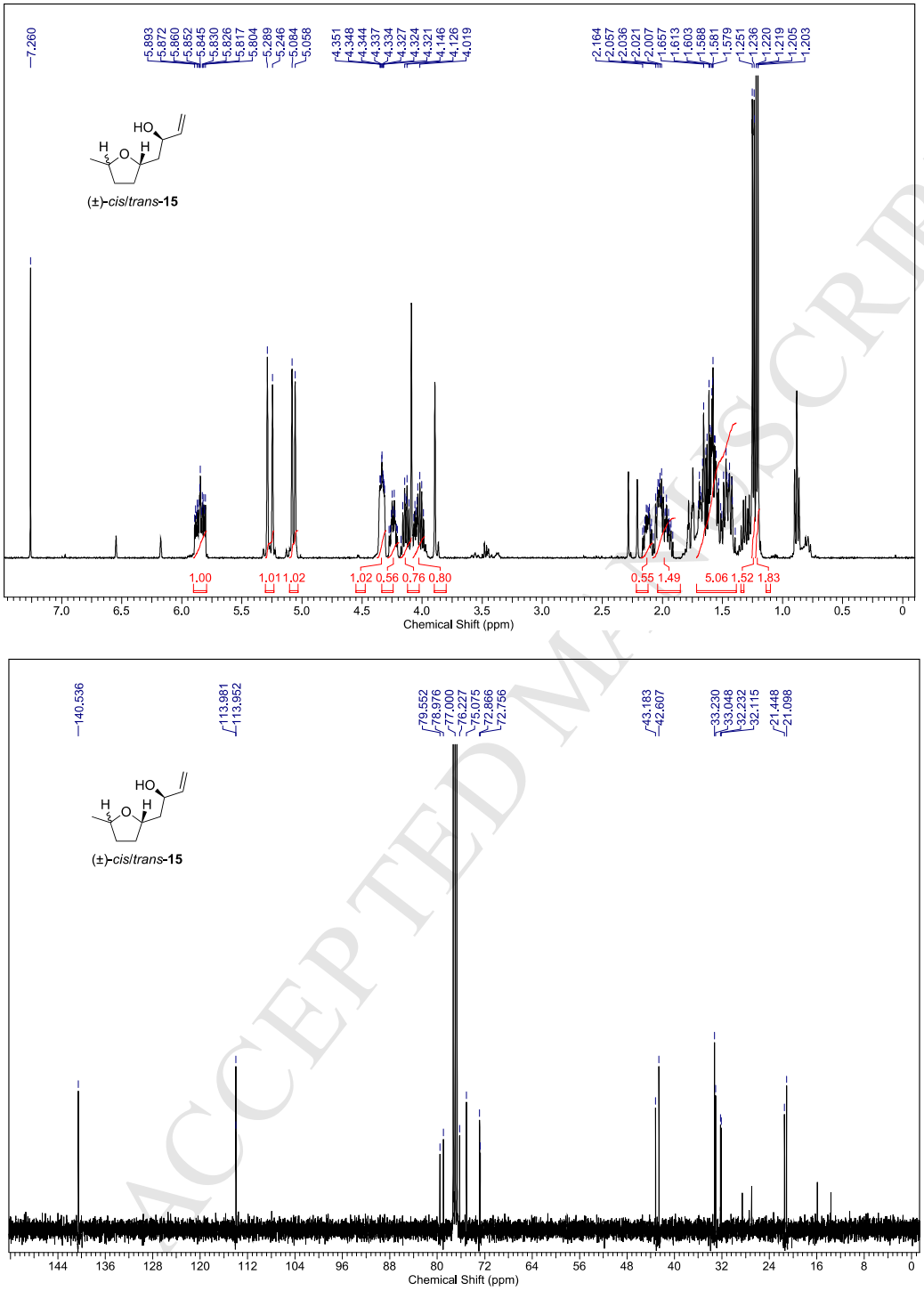

Figure 6.11 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(2'*S*,2*R*)-1-(5'-methyltetrahydrofuran-2'-yl)but-3-ene-2-ol (**15**) (27/73-mixture of A/B-isomers).

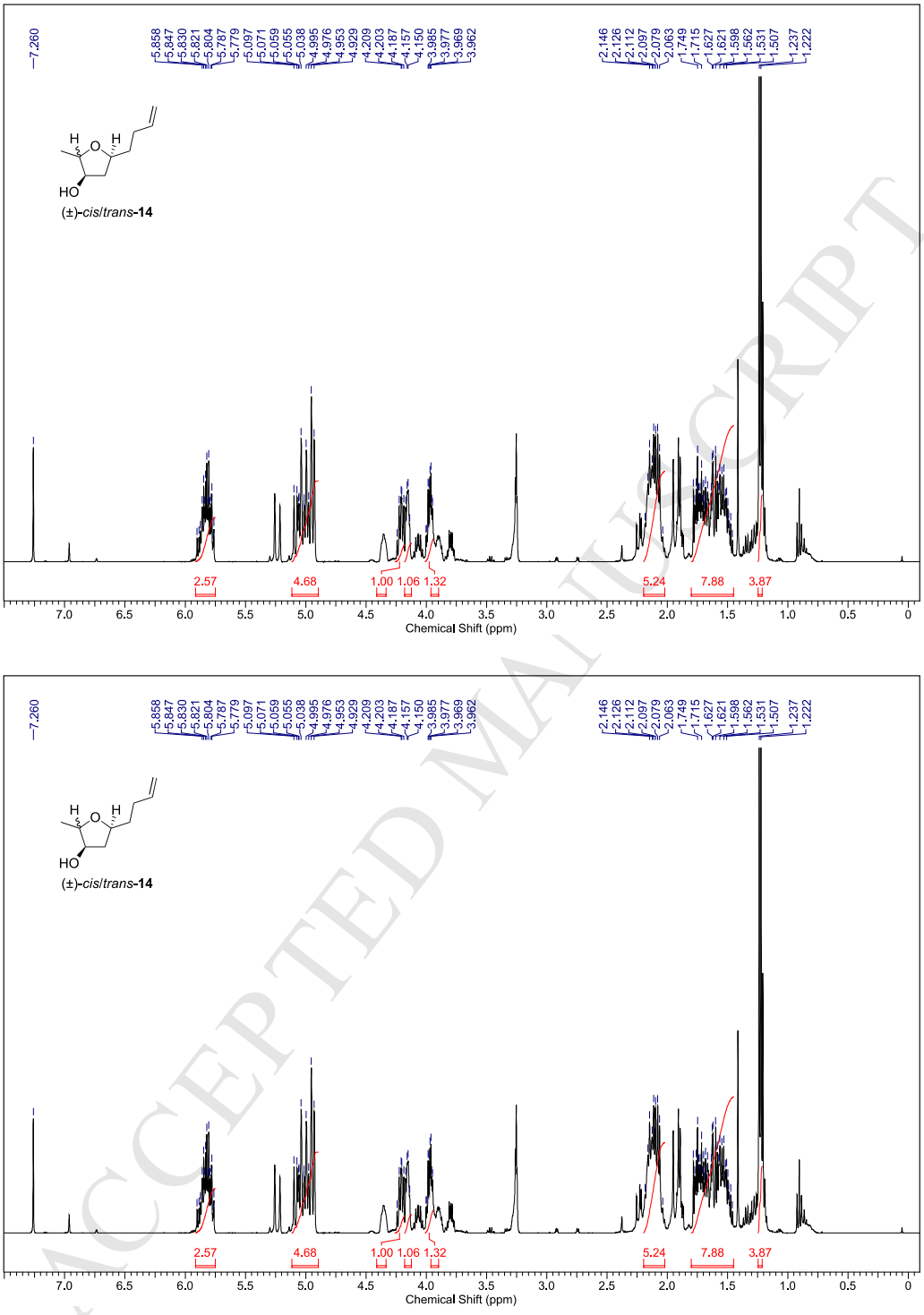

Figure 6.12 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) from the main isomer B of *rel*-(3*R*,5*S*)-5-(but-3-en-1-yl)-2-methyltetrahydrofuran-3-ol (**14**) (20/80-mixture A/B-isomers).

7 References

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