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Synthesis of enantiopure (2*R*)-configured muscarine alkaloids via selective alkoxyl radical ring-closure reactions

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Abstract—A new synthesis of (−)-muscarine, (+)-*allo*-muscarine, (−)-*epi*-muscarine, and (−)-*epiallo*-muscarine has been devised which utilizes selective alkoxyl radical cyclizations for constructing tri-substituted tetrahydrofuran units. Photolysis of (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione in the presence of $BrCCl_3$ provided (2*R*,3*S*,5*S*)-3-benzoyloxy-5-bromomethyl-2-methyltetrahydrofuran as the major product and the corresponding (2*R*,3*S*,5*R*)-isomer as the minor. These building blocks were converted into enantiomerically pure (+)-*allo*-muscarine (from the major alkoxyl radical cyclization product) and (−)-muscarine (from the minor product). Temperature and substituent effects on the diastereoselectivity of the underlying alkoxyl radical cyclization have been investigated. (−)-*epi*-Muscarine and (−)-*epiallo*-muscarine have been prepared likewise, starting from (2*R*,3*R*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione.

1. Introduction

The observation that (+)-muscarine chloride reliably reproduces some of the responses to a stimulation of the parasympathetic nervous system is generally regarded as the beginning of modern pharmacology.[1,2] The significance of this alkaloid and its naturally occurring three diastereomers has led to a growing demand which at present cannot be covered from the current natural resources, such as fungi of the genera *Amanita*,[3] *Clitocybe*[4] and *Inocybe*[5] alone. Therefore, methods for selectively preparing enantiomerically pure (+)-muscarine *ent*-**1a**,[6] the major muscarine alkaloid from *Amanita muscaria*,[7] and its diastereomers (−)-*allo*-muscarine *ent*-**1b**,[8] (+)-*epi*-muscarine *ent*-**1c**,[9] and (+)-*epiallo*-muscarine *ent*-**1d**,[10] have received considerable attention over the last few decades.[11] Two major strategies have evolved for this purpose: (i) selective transformations of monosaccharides[12] and (ii) electrophile-induced ring-closure reactions of ex-chiral pool-derived substituted bis(homoallylic) alcohols.[13,14] The latter approach has been supplemented recently by a concept that utilizes a selective alkoxyl radical cyclization for the construction of the heterocyclic core of *allo*-muscarine **1b** under mild and neutral (i.e. non oxidative) conditions.[15,16] In view of this achievement and the relevance of muscarine alkaloids in particular, we have extended our preliminary investigation to address three major areas. (i) The development of a synthesis of (2*R*,3*S*)- and (2*R*,3*R*)-(3-benzoyloxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione. (ii) Accomplishment of a synthesis of all four (2*R*)-configured muscarine alkaloids **1a**–**d** (Fig. 1) starting from alkoxyl

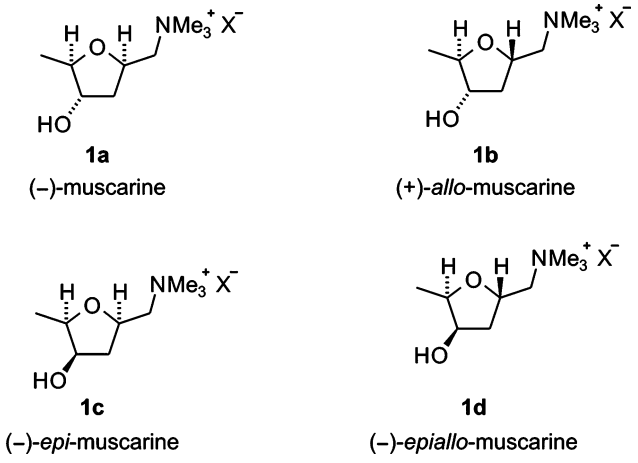

Figure 1. Structures of (2*R*)-configured muscarine alkaloids **1a**–**d**. X^- = monovalent anion.

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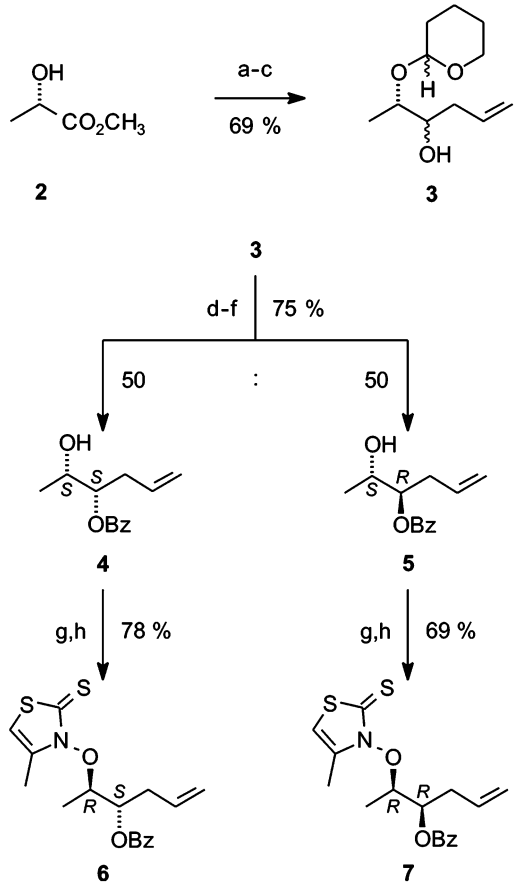
radial cyclization products. (iii) An investigation of the substituent and temperature effects on the diastereoselectivity of 5-*exo*-trig cyclizations using 2,3-*unlike*-configured 3-substituted 5-hexen-2-oxyl radicals.[15,17]

2. Results

2.1. Synthesis of alkoxyl radical precursors

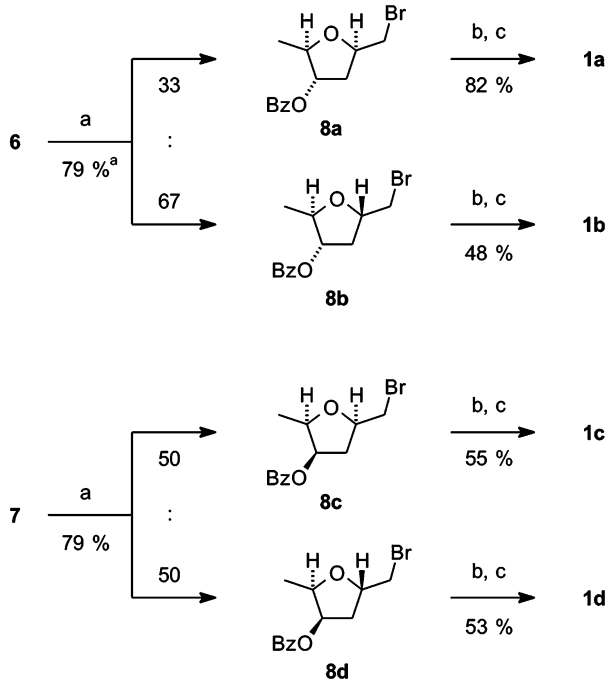
The selective *O*-protection of methyl (*S*)-lactate **2** using 3,4-dihydro-2*H*-pyran and pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2 provided (2*S*)-(2-tetrahydropyranyloxy)propanal (92%, not shown in Scheme 1)[18] which was treated with 1.5 equiv. of diisobutylaluminum hydride (DIBAH) in hexane/Et_2O and subsequently with allyl magnesium bromide in Et_2O (both steps at −78°C) to furnish 2-tetrahydropyranyloxy-5-hexen-3-ol **3** as a mixture of diastereomers (69% starting from **2**, Scheme 1). *O*-Acylation of compound **3** was achieved with a mixture of 1,4-diazabicyclo-[2.2.2]octane (DABCO)[19] and benzoyl chloride in CH_2Cl_2 (82%). This step was followed by removal of the THP protecting group under acidic conditions[20] to yield a 54:46 mixture of 3-benzoyloxy-5-hexen-2-ols **4** and **5**. Separation of this mixture into equal amounts of (2*S*,3*S*)-configured alkenol **4** and its (2*S*,3*R*)-stereoisomer **5** was accomplished on a preparative scale by HPLC (**4**:**5** = 50:50). Both purified products **4** and **5** were esterified with the combination of *p*-toluenesulfonyl chloride and DABCO[19] in dry CH_2Cl_2 (94% for both transformations, not shown in Scheme 1) followed by treatment with *N*-hydroxy-4-methylthiazole-2(3*H*)thione tetraethylammonium salt[21] in anhydrous DMF to provide 83% of (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazolethione **6** and 73% of its (2*R*,3*R*)-diastereomer **7**, respectively both as tan oils.



Scheme 1. Preparation of (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazolethione **6** and its (2*R*,3*R*)-diastereomer **7**. *Reagents and conditions*: (a) 3,4-Dihydro-2*H*-pyran, PPTS, CH_2Cl_2, 41°C (92%); (b) DIBAH in hexanes/Et_2O, −78°C; (c) $H_2C{=}CH{-}CH_2MgBr$, Et_2O, −78→0°C (75% for steps b and c); (d) BzCl, DABCO, CH_2Cl_2, 20°C (82%); (e) PPTS, EtOH, 78°C; (f) HPLC (91% for steps e and f); (g) TsCl, DABCO, CH_2Cl_2, 20°C (94% for conversion of **4** and **5**); (h) *N*-hydroxy-4-methylthiazole-2(3*H*)thione tetraethylammonium salt, DMF, 20°C (83% of **6** and 73% of **7**).

2.2. Preparation of muscarine alkaloids

A solution of (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazolethione **6** ($c_o = 0.18$ M) and $BrCCl_3$ ($c_o = 1.4$ M) was photolyzed at 20°C in a Rayonet® photoreactor equipped with 350 nm light bulbs (Scheme 2). The starting material **6** was consumed within 25 min to afford after work-up 26% of (2*R*,3*S*,5*R*)-tetra-



Scheme 2. Formation of (2*R*)-configured muscarine alkaloids **1a**–**d** starting from (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazolethione **6** and its (2*R*,3*R*)-diastereomer **7**. *Reagents and conditions*: (a) 8 equiv. of $BrCCl_3$, *hv* (350 nm), C_6H_6, 20°C, column chromatography; (b) NaOH, CH_3OH, 20°C (92% from **8a**, 66% from **8b**, 84% from **8c**, 78% from **8d**); (c) $N(CH_3)_3$, EtOH, 60°C (89% for **1a**, 73% for **1c**, 65% for **1c**, 68% for **1d**). [a] In addition, 77% of 2-trichloromethylsulfanyl-4-methylthiazole **9** were isolated (also see Fig. 3).

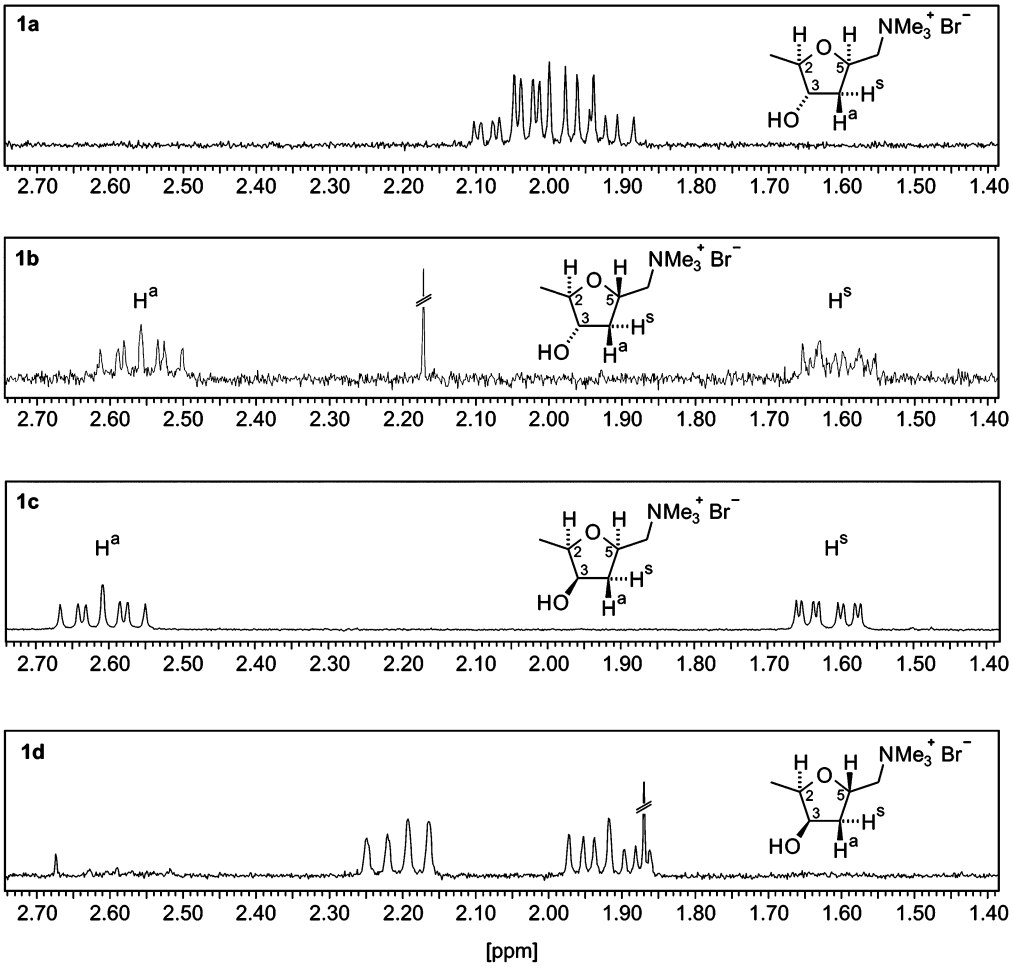


Figure 2. ^{1}H NMR spectra of muscarine alkaloids **1a**–**d** (D_2O) showing the resonances of protons attached to C-4 (see text).

hydrofuran **8a**, 53% of the (2*R*,3*S*,5*S*)-diastereomer **8b**, and 77% of 2-trichloromethylsulfanyl-4-methylthiazole **9** (for structure see Fig. 3). Benzoates **8a** and **8b** were saponified using a solution of NaOH in CH_3OH to yield the corresponding 5-bromomethyl-2-methyltetrahydrofuran-2-ols (92% from **8a** and 66% from **8b**, both not shown in Scheme 2). These products were treated in a hot solution of $N(CH_3)_3$ (4.2 M) in EtOH for 7 days to furnish, after work-up, analytically pure (−)-muscarine **1a** in 89% yield {$[\alpha]_D^{25} = -15.5$ (*c* 0.64, EtOH)} and (+)-*allo*-muscarine **1b** in 73% yield {$[\alpha]_D^{25} = +36.8$ (*c* 0.57, EtOH)}.[22]

(−)-*epi*-Muscarine **1c** and (−)-*epiallo*-muscarine **1d** were obtained starting from (2*R*,3*R*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazolethione **7** (Scheme 2). Near UV-light photolysis of a 0.18 M solution of thione **7** in the presence of 8 equiv. of $BrCCl_3$ afforded an equimolar ratio of (2*R*,3*R*,5*R*)-3-benzoyloxy-5-bromomethyl-2-methyltetrahydrofuran **8c** along with its (2*R*,3*R*,5*S*)-stereoisomer **8d** in a total yield of 79%. Products **8c** and **8d** were separated by column chromatography and subsequently treated with NaOH in CH_3OH to furnish the corresponding tetrahydrofuranols (not shown in Scheme 2) which were heated in a solution of $N(CH_3)_3$ in EtOH to yield (−)-*epi*-muscarine **1c** {$[\alpha]_D^{25} = -62.7$ (*c* 0.42, EtOH)} and (−)-*epiallo*-muscarine **1d** {$[\alpha]_D^{25} = 0.0$ (*c* 0.33, EtOH)}.[†,22]

The determined specific rotations of likewise prepared alkaloids **1a** and **1b** were in accord with the reported values for enantiomerically pure compounds.[22]

2.3. Stereochemical analysis

Relative configurations of alkoxyl radical cyclization products **8a**–**d** and alkaloids **1a**–**d** were established from ^{1}H NMR analysis (chemical shifts and NOE experi-

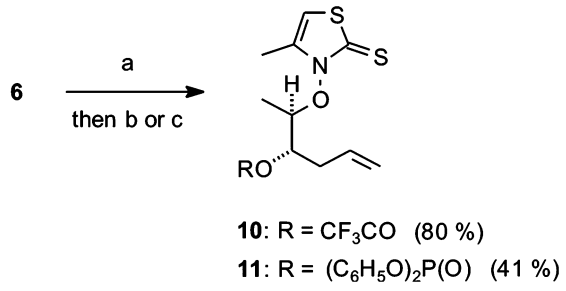
[†] A specific rotation of $[\alpha]_D^{25} \leq 0$ has been reported for enantiopure (−)-*epiallo*-muscarine **1d**.[22] The negative sign for the specific rotation of alkaloid (−)-**1d** has been assigned in extension to Ref. 22 where the authors recorded negative α-values at 578, 546, 436, and 365 nm, but no specific roation at 589 nm for an enantiomerically pure sample.

ments). A chemical shift difference of ~0.6–1.0 ppm between both protons at C-4 was indicative of a 3,5-*cis*-configuration [i.e. tetrahydrofurans **1b**, **1c** (Fig. 2) and **8b**, **8c** (Scheme 2)].[16] Smaller $\Delta\delta$ values of ~0–0.5 between signals for 4-H^s and 4-H^a pointed to 3,5-*trans*-diastereomers **1a**, **1d** (Fig. 2) and **8a**, **8d** (Scheme 2).[16] A 2,5-*cis*-arrangement of substituents at C-2 and C-5 such as in **1a**, **1d** and **8a**, **8d**, was derived from the positive results of the NOE experiments: Upon irradiation at 2-H enhancements were observed at 5-H and vice versa.

The enantiomeric purity of bromocyclization products **8a–d** was determined via their derived (*R*)-Mosher esters[23] which exhibited, in all instances, a single set of resonances (^{1}H NMR). This result was indicative of >96% ee for heterocycles **8a–d** for the following reason: The enantiomers of **8a–d** (>96% ee) and enantiomerically enriched tetrahydrofurans **8a** and **8b** (34% ee) were available from earlier studies.[14,15] These samples were converted into the corresponding (*R*)-configured Mosher esters. Their ^{1}H NMR spectra exhibited either a double set of resonances in a 68:32 ratio [i.e. for (*R*)-Mosher esters obtained from partially racemized **8a** and **8b** (both 34% ee)[15]] or markedly shifted signals (from *ent*-**8a–d**).[14]

2.4. Temperature and substituent effects in the cyclizations of 2,3-*unlike*-configured 3-substituted 5-hexen-2-oxyl radicals

Temperature effects on the diastereoselectivity of 5-*exo*-trig reactions were investigated using an enantiomerically enriched sample of (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazolethione **6** (34% ee).[15] 3-*O*-Substituted derivatives of the alkoxyl radical precursor **6** were prepared in two steps. Saponification of the benzoate functionality was accomplished via the treatment of ester **6** with a solution of NaOH in CH_3OH. This step provided (2*R**,3*S**)-*N*-(3-hydroxy-5-hexen-2-oxy)-thiazole-2(3*H*)thione[24] (not shown in Scheme 3) which was treated with DABCO and either trifluoroacetic acid anhydride (formation of trifluoroacetate **10**, 81% from **6**) or diphenylchlorophosphate (synthesis of mixed phosphate **11**, 41% from **6**).



Scheme 3. Preparation of 2,3-*unlike*-configured 5-hexen-2-oxythiazolethiones **10** and **11**. *Reagents and conditions*: (a) NaOH, CH_3OH, 20°C (97%); (b) $(CF_3CO)_2O$, DABCO, CH_2Cl_2, 20°C (82%); (c) $(C_6H_5O)_2P(O)Cl$, DABCO, 20°C (42%).

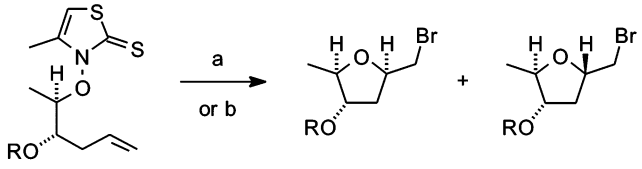
Addition of O_2 into a solution of 2,3-*unlike*-3-benzoyloxy-*N*-hexenoxythiazolethione **6**, $BrCCl_3$, and BEt_3[25] in C_6H_6 at −10°C provided tetrahydrofurans **8a–b** in 75% yield (**8a**:**8b** = 27:73, Table 1). If the same experiment was conducted at −78°C, only 32% of the target compounds **8a–b** were formed (**8a**:**8b** = 21:79).

Photolysis of 2,3-*unlike*-*N*-(3-trifluoroacetyloxy-5-hexen-2-oxy)thiazolethione **10** in the presence of $BrCCl_3$ at 20°C furnished 64% (^{1}H NMR) of trisubstituted tetrahydrofurans **12a–b** (**12a**:**12b** = 30:70). The conversion of the mixed phosphate **11**, under these conditions provided 69% of cyclic ethers **13a–b** (^{1}H NMR, **13a**:**13b** = 29:71).

3. Discussion

The results from the present study indicate that alkoxyl radicals serve as useful intermediates[26] for the construction of the heterocyclic core of enantiomerically pure muscarine alkaloids **1a–d** via selective ring-closure reactions. Key issues to be addressed in the present investigation were associated with the synthesis of (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazole-2(3*H*)-thione **6**, its 3-epimer **7** and a study on substituent and temperature effects in cyclizations of 2,3-*unlike* 3-substituted 5-hexen-2-oxyl radicals (e.g. **14**, Fig. 3).

Table 1. Substituent and temperature effects on the synthesis of tetrahydrofurans **8**, **12**, and **13**[a]



6, 10, 11 **8a, 12a, 13a** **8b, 12b, 13b**

Entry	R	*T* °C	Cond.	Products	Yield **a**+**b** (%)	Selectivity **a**:**b**
1	C_6H_5CO	−10	a	**8a**, **8b**	75	27:73
2	C_6H_5CO	−78	a	**8a**, **8b**	32	21:79
3	CF_3CO	20	b	**12a**, **12b**	64	30:70
4	$(C_6H_5O)_2P(O)$	20	b	**13a**, **13b**	69	29:71

[a] *Reagents and conditions*: (a) $BrCCl_3$, BEt_3/O_2, C_6H_6; (b) $BrCCl_3$, C_6D_6, *hv*.

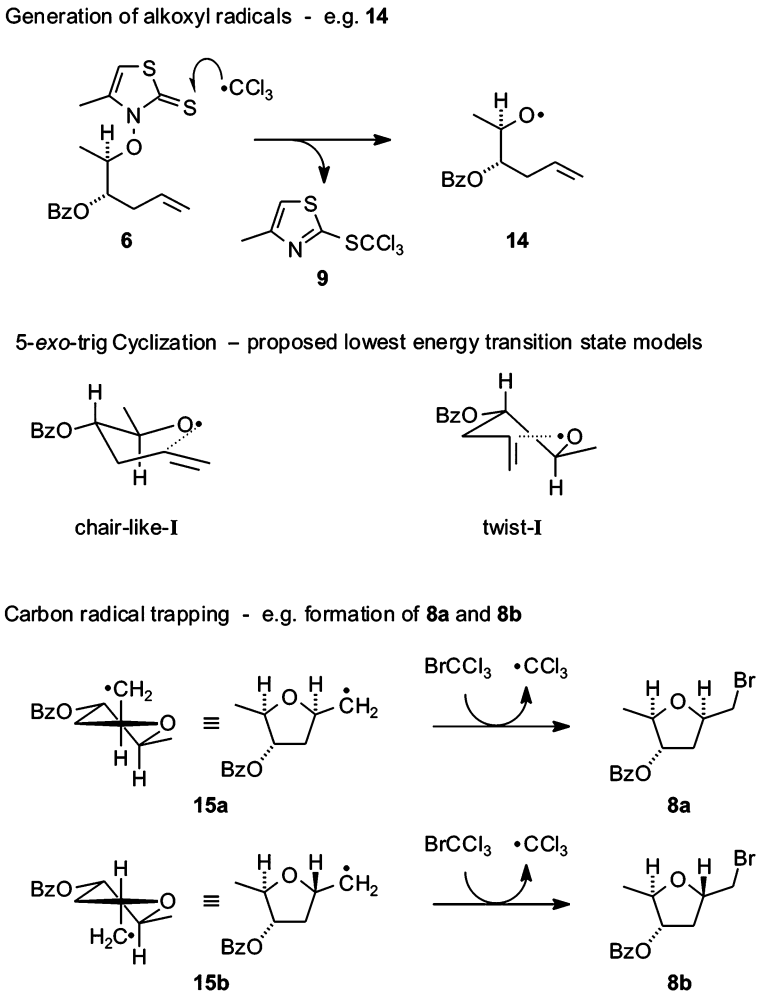


Figure 3. The synthesis of muscarine and *allo*-muscarine precursors **8a** and **8b** starting from (2*R*,3*S*)-(3-benzoyloxy-5-hexen-2-oxy)thiazolethione **6** and $BrCCl_3$—selected elementary steps and transition state models.

3.1. Stereoselective synthesis of alkoxyl radical precursors and functional group interconversion

The synthesis of (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazole-2(3*H*)thione **6** and its (2*R*,3*R*)-diastereomer **7** has been achieved in six synthetic steps starting from methyl (*S*)-lactate **2** (Scheme 1). The strategy to THP-protect the hydroxyl substituent in the starting material **2** was the key to conserving the stereointegrity at C-2, which had been the major obstacle in previous investigations.[15,27] The synthetic sequence which is outlined in Scheme 1 provided alkenol **3** as a mixture of four diastereomers. No attempts were made at this stage of the synthesis to purify and characterize any of these compounds, since the separation of (2*S*,3*S*)-3-benzoyloxy-5-hexen-2-ol **4** and its (2*S*,3*R*)-diastereomer **5** was attainable via HPLC. Alkenols **4** and **5** were converted into their derived tosylates (not shown in Scheme 1) which served as selective *O*-alkylation reagents for the synthesis of alkoxyl radical precursors **6** and **7** starting from *N*-hydroxy-4-methylthiazole-2(3*H*)thione tetraethylammonium salt. According to TLC analysis, this step was not associated with the formation of the isomeric (*S*)-alkylation products (i.e. 2-alkenylsulfanylthiazole-*N*-oxides).[28]

Functional group interconversion starting from thione **6** was feasible and provided trifluoroacetate **10** and mixed phosphate **11** in two synthetic steps. This result is noteworthy since the compatibility of cyclic thiohydroxamic acid *O*-esters in selective transformations was until then largely unexplored.[29,30] It was, however refrained from preparing the same derivatives starting from (2*R*,2*R*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)thiazolethione **7** because the *like*-configured 5-hexen-2-oxyl radical **16** underwent 5-*exo*-trig cyclizations without notable facial selectivity (Fig. 4, Scheme 2).

3.2. Generation and ring-closure reactions of 3-substituted 5-hexen-2-oxyl radicals

Photochemically induced or BEt_3/O_2-initiated reactions between (2*R*,3*S*)-(3-benzoyloxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione **6** and $BrCCl_3$ furnished bromocyclization products **8a** and **8b** in synthetically

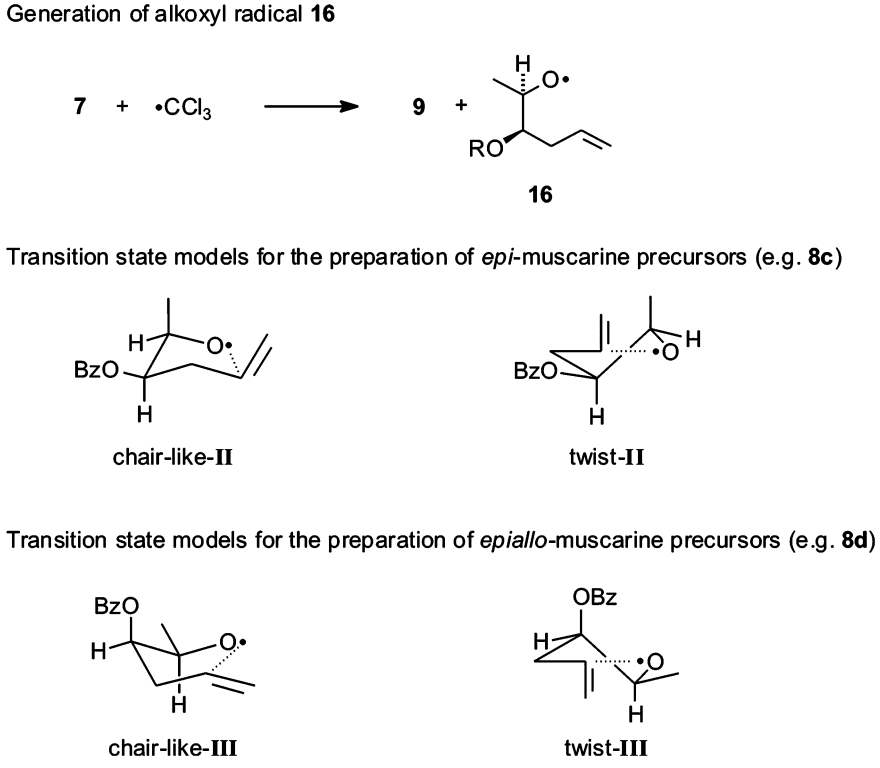


Figure 4. Generation of the (2*R*,3*R*)-3-benzoyloxy-5-hexen-2-oxyl radical **16** from thiazolethione **7** (top) and transition state models for the synthesis of *epi*-muscarine (center) or *epiallo*-muscarine precursors (bottom).

useful yields (Fig. 3). Signals of 6-*endo*-cyclized products (i.e. substituted tetrahydropyrans) were not noted in ^{1}H NMR spectra of the crude or purified products.[31,32] The underlying radical chain reaction of this sequence started either with a photochemical excitation of the radical precursor **6**[33] or the addition of suitable radicals to the C,S π-bond of this compound (BEt_3/O_2 system) in order to induce selective N,O-homolysis. This step provided the (2*R*,3*S*)-(3-benzoyloxy-5-hexen-2-oxyl radical **14** which underwent diastereoselective 5-*exo*-trig ring closures. Subsequent bromine atom trapping of cyclized intermediates **15a** and **15b** furnished (+)-*allo*-muscarine precursor **8b** as the major product and the (2*R*,3*S*,5*R*)-diastereomer **8a** as the minor. The CCl_3 radical, which was formed in the latter reaction, added preferentially to the C,S double bond in thione **6** thus leading to 2-mercaptothiazole derivative **9** in a yield that nearly matched that of the bromides **8a** and **8b** when taken together. No efforts were made to use alternative bromine atom donors for the synthesis of products **8a**–**b** since this aspect had been addressed in an earlier investigation.[16]

The stereochemical preference for the formation of bromocyclization product **8b** increased from 34% de at 20°C to 58% de upon lowering the reaction temperature to −78°C. Since it had been shown in previous work that under these conditions 4-penten-1-oxyl radical 5-*exo*-trig cyclizations follow kinetic control, the temperature–selectivity data compiled in Table 1 were used to estimate differences in activation parameters for both modes of ring closure ($\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{\mathbf{14\rightarrow 15a}} - \Delta H^{\ddagger}_{\mathbf{14\rightarrow 15b}} =$ 3.0 kJ mol^{-1}, $\Delta\Delta S^{\ddagger} = \Delta S^{\ddagger}_{\mathbf{14\rightarrow 15a}} - \Delta S^{\ddagger}_{\mathbf{14\rightarrow 15b}} = -3\times10^{-3}$ kJ mol^{-1} K^{-1}).[32,34] Based on this estimate, the observed diastereoselectivity for the *O*-radical reaction **14→15b** predominantly originated from its favorable activation enthalpy. This result in combination with data from earlier experimental[32] and theoretical investigations[35] was translated into stereochemical models (Figs. 3 and 4). An approach of reacting entities in intermediate **14** leads to a restriction of conformational freedom—from freely rotating to a cyclic intermediate with a long and therefore weak C,O-bond. In this picture, a methylene, methyl, and a benzoyloxy group will be preferentially arranged in positions that resemble equatorial locations in cyclohexane (see chair-like **I**, Beckwith–Houk model).[36–38] These stereochemical requirements are also fulfilled in the intermediate twist-**I**. This geometry is based on an ab-initio-calculated lowest transition structure for the 4-penten-1-oxyl radical cyclization.[35] A similar arrangement has recently been located as lowest energy transition structure in ab initio calculations dealing with 5-*exo*-trig cyclizations of anomeric carbon radicals.[39] Geometry twist-**I**, which probably reflects substituent effects onto the conformational behavior of such energetically favored transition structures more adequately, transposes the benzoyloxy and the methyl group into equatorial positions whereas the methylene end of the radical chain resides in the bisectional[40] location that has the largest distance from the C-1–C-2

bond (hereafter *exo*-bisectional). Both models favor an attack of the *O*-radical onto the *Si* face of C-4 thus leading to *allo*-muscarine precursor **8b** as major bromocyclization product. Cyclization onto the *Re* face of C-4 on the intermediate **14**, e.g. by transposing the methylene group into an axial (Beckwith–Houk model) or an *endo*-bisectional location (twist-model, both not shown), is for steric reasons associated with higher activation enthalpies (see above) and therefore disfavors the formation of product **8a**. By virtue of the same arguments the lack in diastereoselectivity in ring-closure reactions of the (2*R*,3*R*)-(3-benzoyloxy)-5-hexen-2-oxyl radical **16** was realized. The use of either chair-like-**II** and **III** (Beckwith–Houk) or twist-**II** and **III** as stereochemical models indicated no significant preference for any of the given structures.

The observation that β-trifluoroacetyloxy- and β-(diphenyl)phosphatyl-substituted 5-hexen-2-oxyl radicals furnished upon cyclisation and subsequent bromine atom trapping trisubstituted tetrahydrofurans (i.e. **12a**–**b** and **13a**–**b**) served in combination with results from the sequence **6**→**8a**,**8b** to establish the following guideline: β-*O*-acceptor-substituted 5-hexen-2-oxyl radicals prefer 5-*exo*-trig cyclization to β-C,C-cleavage. In turn, β-hydroxy-, a β-*tert*-butyldimethylsilyloxy and, less pronounced, β-benzyloxy substituent in 5-hexen-2-oxyl radicals favor β-C,C-cleavages to intramolecular additions.[15,24] This observation may be indicative of additional secondary orbital interactions within the RO–C–C–O$^{\bullet}$ fragment that, however, have not been considered in the models which are depicted in Figures 3 and 4.[41] Effects of a β-CF_3CO_2 or a pseudo tetrahedral $(C_6H_5O)_2P(O)O$ group on alkoxyl radical 5-*exo*-trig cyclizations in this study were qualitatively similar to that of the $C_6H_5CO_2$ substituent, but furnished slightly improved diastereoselectivities (**8b**: 34% de, **12b**: 40% de, **13b**: 42% de, Scheme 3, Table 1).

3.3. Synthesis and stereochemical analysis of muscarine alkaloids

The final steps in the synthesis of (2*R*)-configured muscarine alkaloids **1a**–**d** were performed starting from enantiomerically pure alkoxyl radical cyclization products **8a**–**d**. 5-Bromomethyl-2-methyltetrahydrofuranols, which were prepared in the initial step turned out to be surprisingly volatile compounds. Therefore, it was advisable not to completely remove the solvent in the work-up step on a synthetic scale, but to purify target compounds **1a**–**d** via two consecutive crystallizations. The stereochemical purity of target compounds **1a**–**d** has been verified at different stages of the synthesis. The overall yields of likewise prepared alkaloids **1** starting from methyl (*S*)-lactate **2** ranged from 4% (**1a**, **1c**, and **1d**) to 5% (**1b**). These values were competitive to results obtained from syntheses that applied polar bromocyclizations for constructing the tetrahydrofuran nucleus, e.g. of *allo*-muscarine **1b** and *epi*-muscarine **1c**.[14]

4. Conclusion

Ring-closure reactions of the (2*R*,3*S*)-3-benzoyloxy-5-hexen-2-oxyl radical **14** and its (2*R*,3*R*)-diastereomer **16** have been investigated and applied for the synthesis of enantiomerically pure (−)-muscarine **1a**, (+)-*allo*-muscarine **1b** (both from **14**), and (−)-*epi*-muscarine **1c**, (−)-*epiallo*-muscarine **1d** (the latter two from **16**). Cyclizations of the *unlike*-configured 5-hexen-2-oxyl radical **14** exhibited a marked 2,5-*trans*-3,5-*cis* selectivity that was improved upon lowering the reaction temperature. In addition, diastereoselectivities of cyclizations using *unlike*-configured 3-trifluoroacetyloxy- and 3-diphenylphosphatyl-substituted 5-hexen-2-oxyl radicals have been investigated. In both instances minor improvements in diastereoselectivity were noted in comparison to the ring closure of the 3-benzoyloxy derivative **14**.[13,14]

5. Experimental

5.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded with Bruker AC 200, AC 250, WM 400, AC 400 instruments at 20°C in $CDCl_3$ solutions unless otherwise noted. Residual protons of deuterated solvents [e.g. $\delta_H = 7.26$ ($CDCl_3$)] and the corresponding carbon resonances in ^{13}C NMR spectra [e.g. $\delta_C = 77.0$ ($CDCl_3$)] were taken as internal standards. Optical rotations were measured using a Perkin Elmer 241 polarimeter. IR spectra were recorded on either NaCl plates or samples embedded in KBr disks using a Perkin Elmer FT/IR 1600 spectrometer. C,H,N,S analyses were carried out in the Microanalytical Laboratory in the department of Inorganic Chemistry at the Universität Würzburg using Carlo Erba 1106 or LECO CHNS-932 machines. MS spectra were recorded with a Varian MATCH 7 spectrometer (electroimpact, EI, 70 eV). Column chromatography was performed with the use of SiO_2 (Merck, 0.063–0.2 mm). Photoreactions were carried out using a Southern New England Ultraviolet RPR-100 Rayonet® photoreactor, equipped with RPR 350 nm lamps. All solvents were distilled prior to use and were purified according to standard procedures.[42] Methyl (*S*)-lactate **2**, diisobutylaluminum hydride (DIBAH, 1 M in hexanes), 1,4-diazabicyclo[2.2.2]octane (DABCO), pyridinium *p*-toluenesulfonate (PPTS), diphenylchlorophosphate, trifluoroacetic acid anhydride, $BrCCl_3$, BEt_3 (1 M in hexane), (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride, $N(CH_3)_3$ (4.2 M in EtOH) were obtained from commercial sources (Fluka, Aldrich and Merck) and were used as received. Methyl 2-(tetrahydropyran-2-yl)-oxypropanoat,[18] *N*-hydroxy-4-methylthiazole-2(3*H*)-thione[43] and the corresponding tetraalkylammmonium salt[21] were prepared according to literature procedures. Petroleum ether refers to the fraction boiling between 35 and 50°C.

5.2. Preparation of alkoxyl radical precurors

5.2.1. 2-(Tetrahydropyran-2-yl)oxy-5-hexen-3-ol 3. A solution of methyl 2-(tetrahydropyran-2-yl)oxypropanoat[18] (1.18 g, 6.28 mmol) in dry Et_2O (30 mL) was treated under argon at −78°C dropwise with a solution of DIBAH (9.4 mL, 1 M in hexanes). The reaction mixture was stirred for 30 min at −78°C and treated at this temperature dropwise with a solution of allyl magnesium bromide in Et_2O prepared from magnesium turnings (336 mg, 13.8 mmol) and allyl bromide (1.52 g, 12.6 mmol) in dry Et_2O (13 mL). The reaction mixture was stirred for 16 h at −78°C and allowed to warm to 0°C. A saturated aqueous solution of NH_4Cl (25 mL) was added. The aqueous phase was separated from this mixture and was extracted with Et_2O (2×20 mL). The combined organic phases were successively washed with a saturated solution of aq. $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure to provide an oil which was then purified by chromatography [SiO_2, petroleum ether/AcOEt, 5:1 (v/v)]. Yield: 955 mg (4.77 mmol, 76%), colorless liquid as a mixture of diastereomers; $R_f = 0.37$ (petroleum ether/AcOEt, 5:1). ^{1}H NMR (250 MHz): δ 1.16–1.29 (m, 3H, 1-H), 1.44–1.83 (m, 6H, CH_2), 2.14–2.39 (m, 2H, 4-H), 3.33–4.03 (m, 4H, 2-H, 3-H, OCH_2), 4.98–5.21 (m, 3H, 6-H, OCHO), 5.73–5.94 (m, 1H, 5-H). ^{13}C NMR (63 MHz): δ 14.1, 17.1, 17.7, 18.0, 19.3, 19.5, 19.9, 20.6, 25.4, 29.6, 30.7, 32.5, 33.9, 34.2, 34.5, 36.2, 36.7, 36.8, 36.9, 38.0, 62.2, 62.6, 67.3, 69.8, 73.7, 74.9, 77.7, 77.8, 81.2, 81.3, 82.6, 82.6, 98.7, 103.2, 103.3, 107.8, 117.5, 117.5, 118.0, 118.1, 133.7, 133.7, 134.3, 134.8. MS (70 eV, EI): m/z (%) = 127 (14) [$C_7H_{11}O_2^+$], 84 (89) [$C_5H_8O^+$], 83 (48) [$C_5H_7O^+$], 75 (100) [$C_3H_7O_2^+$], 71 (34) [$C_4H_7O^+$], 57 (100) [$C_3H_5O^+$]; $C_{11}H_{20}O_3$ (200.3) calcd: C, 65.97; H, 10.07. Found: C, 65.46; H, 10.28.

5.2.2. 3-Benzoyloxy-2-(tetrahydropyran-2-yl)oxy-5-hexene. A solution of 2-(tetrahydropyran-2-yl)oxy-5-hexen-3-ol **3** (481 mg, 2.40 mmol) and DABCO (538 mg, 4.80 mmol) in dry CH_2Cl_2 (2.4 mL) was treated at 0°C dropwise with neat benzoyl chloride (506 mg, 3.60 mmol). The reaction mixture was stirred for 30 min at 20°C and was then diluted with Et_2O (10 mL). The precipitated salts were dissolved in 2 M HCl (10 mL). The organic phase was separated and the aqueous layer was extracted with Et_2O (2×5 mL). The combined organic phases were successively washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure to provide an oil that was purified by chromatography [SiO_2, petroleum ether/Et_2O, 5:1 (v/v)]. Yield: 596 mg (1.96 mmol, 82%), colorless oil, mixture of diastereomisomers. $R_f = 0.65$ (petroleum ether/Et_2O, 5:1). ^{1}H NMR (250 MHz): δ 1.16–1.33 (m, 3H, 1-H), 1.45–1.85 (m, 6H, CH_2), 2.41–2.62 (m, 2H, 4-H), 3.41–3.56 (m, 1H, OCH), 3.80–4.10 (m, 2H, OCH), 4.71–5.31 (m, 4H, 3-H, 6-H, OCHO), 5.74–5.92 (m, 1H, 5-H), 7.40–7.71 (m, 3H, Ar-H), 8.01–8.18 (m, 2H, Ar-H). ^{13}C NMR (63 MHz): δ 17.37, 17.97, 18.56, 19.46, 19.52, 19.88, 20.13, 20.16, 25.79, 25.86, 25.93, 31.10, 31.21, 31.26, 31.32, 34.82, 34.88, 34.96, 35.67, 62.28, 62.40, 63.19, 63.34, 68.86, 69.37, 71.21, 74.98, 75.23, 76.38, 77.77, 78.03, 95.06, 95.67, 98.99, 100.7, 118.1, 118.2, 118.2, 118.6, 128.7, 128.8, 128.8, 129.3, 130.0, 130.1, 130.5, 130.9, 131.0, 133.2, 133.3, 133.5, 133.7, 134.0, 134.2, 134.4, 134.9, 162.8, 166.4, 166.4, 166.7. MS (70 eV, EI): m/z (%) = 122 (70) [$C_7H_6O_2^+$], 105 (100) [$C_7H_5O^+$], 85 (15) [$C_5H_9O^+$], 77 (68) [$C_6H_5^+$]. $C_{18}H_{24}O_4$ (304.4) calcd: C, 71.03; H, 7.95. Found: C, 70.98; H, 7.66.

5.2.3. (2*S*,3*S*)-3-Benzoyloxy-5-hexen-2-ol 4 and (2*S*,3*R*)-3-benzoyloxy-5-hexen-2-ol 5. A solution of (2*S*,3*S*)-3-benzoyloxy-2-(tetrahydropyran-2-yl)oxy-5-hexene or the corresponding (2*S*,3*R*)-diastereomer (491 mg, 1.61 mmol) in EtOH (16 mL) was treated at 20°C with PPTS (40.5 mg, 0.160 mmol). The reaction mixture was refluxed for 6 h. Afterwards, the solvent was removed under reduced pressure to afford an oil, which was purified by chromatography [SiO_2, petroleum ether/Et_2O, 1:1 (v/v)]. Yield: 323 mg (1.47 mmol, 91%), colorless oil as a mixture of diastereomers (**4**:**5** = 54:46). Diastereomeric pure alkenols **4** and **5** were obtained via HPLC [Nova Pak HR column, silica 6–8 μm, 19 mm× 30 cm, 2-propanol/*n*-hexane, 99:1 (v/v)]; isomer **4**: $[\alpha]_D^{20} = -4.1$ (*c* 0.63, $CHCl_3$). isomer **5**: $[\alpha]_D^{20} = +13.0$ (*c* 0.64, $CHCl_3$). Spectroscopic data of the alkenols **4** and **5** are in accord with published values.[15]

5.2.4. (2*S*,3*S*)-3-Benzoyloxy-5-hexen-2-yl *p*-toluenesulfonate, (2*S*,3*R*)-3-benzoyloxy-5-hexen-2-yl-*p*-toluenesulfonate. (2*S*,3*S*)-3-Benzoyloxy-5-hexen-2-yl *p*-toluenesulfonate {$[\alpha]_D^{20} = -1.5$ (*c* 0.63, $CHCl_3$)} and (2*S*,3*R*)-3-benzoyloxy-5-hexen-2-yl *p*-toluenesulfonate {$[\alpha]_D^{20} = -43.9$ (*c* 0.73, $CHCl_3$)} were prepared by a literature procedure. All spectroscopic data of the compounds **8a** and **8b** were in accord with published values.[15]

5.2.5. (2*R*,3*S*)-*N*-(3-Benzoyloxy-5-hexen-2-oxy)-4-methylthiazol-2(3*H*)thione 6. Compound **6** was prepared from (2*S*,3*S*)-3-benzoyloxy-5-hexen-2-yl *p*-toluenesulfonate by adapting a published procedure {$[\alpha]_D^{20} = -50.2$ (*c* 0.81, $CHCl_3$)}. All spectroscopical data of thione **6** were in agreement with those reported for an enantiomerically enriched sample.[15]

5.2.6. (2*R*,3*R*)-*N*-(3-Benzoyloxy-5-hexen-2-oxy)-4-methylthiazol-2(3*H*)thione 7. A flame-dried round-bottomed flask was charged with *N*-hydroxy-4-methylthiazole-2(3*H*)thione tetraethylammmonium salt[21] (174 mg, 0.630 mmol) and (2*S*,3*R*)-3-benzoyloxy-5-hexen-2-yl *p*-toluenesulfonate[15] (216 mg, 0.577 mmol) in dry DMF (3 mL) under argon. The reaction mixture was sealed with a drying tube ($CaCl_2$), wrapped in aluminium foil, and stirred for 5 days at 20°C to furnish a dark brown solution which was poured into H_2O (10 mL) and subsequently extracted with Et_2O (3×10 mL). The combined organic phases were successively washed with 2 M NaOH (20 mL) and brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford an oil that was purified by chromatography [SiO_2, petroleum ether/Et_2O, 1:1 (v/v)]. Yield: 104 mg (0.298

mmol, 73%, based on a conversion of 71% of (2*S*,3*R*)-3-benzoyloxy-5-hexen-2-yl *p*-toluenesulfonate, which was recovered in 62.5 mg (0.167 mmol, 29%), tan oil. R_f = 0.36 (petroleum ether/Et_2O, 1:1). $[\alpha]_D^{20}$ = −108.4 (*c* 0.39, $CHCl_3$); ^1H NMR (250 MHz): δ 1.28 (d, 3H, ^3J = 6.6 Hz, 1-H), 2.25 (d, 3H, ^4J = 1.2 Hz, CH_3), 2.60–2.72 (m, 1H, 4-H), 2.79–2.89 (m, 1H, 4-H), 5.09 (d, 1H, ^3J = 10.1 Hz, 6-H), 5.18 (d, 1H, ^3J = 17.1 Hz, 6-H), 5.41 (m_c, 1H, 3-H), 5.79–5.93 (m, 2H, 2-H, 5-H), 6.12 (q, 1H, ^4J = 1.2 Hz, 5′-H), 7.45 (m_c, 2H, Ar-H), 7.58 (m_c, 1H, Ar-H), 8.06 (m_c, 2H, Ar-H). ^{13}C NMR (100 MHz): δ 13.94, 14.64 (C-1, CH_3), 35.26 (C-4), 74.50, 79.93 (C-2, C-3), 102.9 (C-5′), 118.6 (C-6), 128.4, 129.7, 130.8, 132.8, 133.2, 138.9 (C-4′), 165.9 (C=O), 180.7 (C=S). MS (70 eV, EI): *m*/*z* (%) = 131 (6) [$C_4H_5NS_2^+$], 105 (100) [$C_7H_5O^+$], 77 (35) [$C_6H_5^+$]. $C_{17}H_{19}NO_3S_2$ (349.5) calcd: C, 58.43; H, 5.48; N, 4.01; S, 18.35. Found: C, 58.26; H, 5.37; N, 3.97; S, 17.95.

5.3. Preparation of muscarine alkaloids 1a–d

5.3.1. Formation of 3-benzoyloxy-5-bromomethyl-2-methyltetrahydrofurans 8a and 8b. A solution of (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)-4-methylthiazol-2(3*H*)thione **6** (377 mg, 1.08 mmol) and $BrCCl_3$ (1.71 g, 8.64 mmol) in dry C_6H_6 (6 mL) was flushed for 5 min at 20°C with a gentle stream of argon. This solution was photolyzed for 25 min at 20°C in a Rayonet® chamber photoreactor and was subsequently concentrated under reduced pressure to furnish an oil that was purified by chromatography [SiO_2, petroleum ether/Et_2O, 5:1 (v/v)]. **8a**: R_f = 0.42 (petroleum ether/Et_2O, 5:1), 84.4 mg (0.282 mmol, 26%), colorless oil. $[\alpha]_D^{20}$ = +2.2 (*c* 0.69, $CHCl_3$). **8b**: R_f = 0.39 (petroleum ether/Et_2O, 5:1), 172 mg (0.574 mmol, 53%), colorless oil. $[\alpha]_D^{20}$ = −28.7 (*c* 0.59, $CHCl_3$); All spectroscopic data of the compounds **8a** and **8b** were in agreement with published values.[15]

5.3.1.1. 2-Trichloromethylsulfanyl-4-methylthiazole 9[24]. R_f = 0.52 [petroleum ether/Et_2O/acetone, 10:1:1 (v/v/v)], 207 mg (77%). ^1H NMR (250 MHz): δ 2.57 (d, 3H, CH_3), 7.31 (q, 1H, CH). $C_5H_4Cl_3NS_2$ (248.6): MS (70 eV, EI): *m*/*z* (%) = 247/249/251/253 (15/13/5/2) [M^+], 212/214/216 (53/38/9) [M^+–Cl], 130 (100) [M^+–CCl_3].

5.3.2. Synthesis of 3-benzoyloxy-5-bromomethyl-2-methyltetrahydrofurans 8c and 8d. A solution of (2*R*,3*R*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione (**7**) (212 mg, 0.607 mmol) and $BrCCl_3$ (963 mg, 4.86 mmol) in dry C_6H_6 (3.4 mL) was flushed for 5 min at 20°C with a gentle stream of argon This solution was photolyzed for 25 min at 20°C in a Rayonet® chamber photoreactor and was subsequently concentrated under reduced pressure to furnish an oil that was purified by chromatography [SiO_2, petroleum ether/Et_2O, 5:1 (v/v)]. **8c**: R_f = 0.29 (petroleum ether/Et_2O, 5:1), yield: 72.4 mg (0.242 mmol, 40%), colorless oil. $[\alpha]_D^{20}$ = +16.2 (*c* 0.53, $CHCl_3$); **8d**: R_f = 0.37 (petroleum ether/Et_2O, 5:1), 71.2 mg (0.238 mmol, 39%), colorless oil. $[\alpha]_D^{20}$ = −45.1 (*c* 0.20, $CHCl_3$). All spectroscopic data of the compounds **8c** and **8d** were in agreement with published values.[15]

5.3.3. Saponification of bromomethyltetrahydrofurans 8a–d (general procedure). 3-Benzoyloxy-5-bromomethyl-2-methyltetrahydrofuran **8** was dissolved in a solution of NaOH (0.18 M) in CH_3OH. The reaction mixture was stirred for 1 h at 20°C and subsequently poured into a mixture of Et_2O (20 mL) and H_2O (20 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent removed under reduced pressure to furnish an oil that was purified by chromatography [SiO_2, petroleum ether/Et_2O, 1:1 (v/v)].

5.3.3.1. (2*R*,3*S*,5*R*)-5-Bromomethyl-2-methyltetrahydrofuran-3-ol. A solution of **8a** (87.4 mg, 0.292 mmol) was treated with a solution of NaOH in CH_3OH (5.7 mL, 0.18 M) as outlined above. R_f = 0.26 (petroleum ether/Et_2O, 1:2), 53.0 mg (0.272 mmol, 92%), colorless liquid. ^1H NMR (250 MHz): δ 1.25 (d, 3H, ^3J = 6.4 Hz, CH_3), 1.95 (s br., 1H, OH), 2.02 (m_c, 2H, 4-H), 3.43–3.49 (m, 2H, CH_2Br), 3.95 (dq, 1H, ^3J_d = 3.5 Hz, ^3J_q = 6.4 Hz, 2-H), 4.06 (dt, 1H, ^3J_d = 3.5 Hz, ^3J_t = 4.7 Hz, 3-H), 4.37 (m_c, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 19.6, 35.8, 39.3, 76.9, 77.4, 83.1.

5.3.3.2. (2*R*,3*S*,5*S*)-5-Bromomethyl-2-methyltetrahydrofuran-3-ol. A solution of **8b** (36.7 mg, 0.123 mmol) was treated with a solution of NaOH in CH_3OH (2.4 mL, 0.18 M) as described previously. R_f = 0.40 (petroleum ether/Et_2O, 1:2), 15.9 mg (81.5 μmol, 66%), colorless liquid. ^1H NMR (250 MHz): δ 1.19 (d, 3H, ^3J = 6.4 Hz, CH_3), 1.83–1.92 (m, 2H, 4-H, OH), 2.44 (ddd, 1H, ^3J = 6.1, 7.9 Hz, ^2J = 14.0 Hz, 4-H), 3.52 (d, 2H, ^3J = 5.8 Hz, CH_2Br), 4.01–4.11 (m, 2H, 3-H, 2-H), 4.34 (ddd, 1H, ^3J = 5.8, 7.9, 11.3 Hz, 2-H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 18.5, 36.5, 38.5, 76.6, 77.2, 82.2.

5.3.3.3. (2*R*,3*R*,5*R*)-5-Bromomethyl-2-methyltetrahydrofuran-3-ol. A solution of **8c** (51.7 mg, 0.173 mmol) was treated with a solution of NaOH in CH_3OH (3.4 mL, 0.18 M) as outlined above. R_f = 0.42 (petroleum ether/Et_2O, 1:2), 28.2 mg (0.145 mmol, 84%), colorless liquid. ^1H NMR (250 MHz): δ 1.30 (d, 3H, ^3J = 6.4 Hz, CH_3), 1.83 (s. br., 1H, OH), 1.88 (ddd, 1H, ^3J = 1.4, 4.9 Hz, ^2J = 14.3 Hz, 4-H), 2.41 (ddd, 1H, ^3J = 6.0, 8.9 Hz, ^2J = 14.3 Hz, 4-H), 3.50 (dd, 1H, ^3J = 4.6 Hz, ^2J = 10.4 Hz, CH_2Br), 3.61 (dd, 1H, ^3J = 5.3 Hz, ^2J = 10.4 Hz, CH_2Br), 3.86 (dq, 1H, ^3J_d = 3.1 Hz, ^3J_q = 6.4 Hz, 2-H), 4.13–4.22 (m, 2H, 3-H, 5-H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 14.1, 36.5, 40.5, 74.2, 76.1, 79.0.

5.3.3.4. (2*R*,3*R*,5*S*)-5-Bromomethyl-2-methyltetrahydrofuran-3-ol. A solution of **8d** (17.4 mg, 5.82 μmol) was treated with a solution of NaOH in CH_3OH (1.1 mL, 0.18 M) as described above. R_f = 0.39 (petroleum ether/Et_2O, 1:2), 8.9 mg (4.56 μmol, 78%), colorless liquid. ^1H NMR (250 MHz): δ 1.27 (d, 3H, ^3J = 6.3 Hz, CH_3), 1.69 (s. br., 1H, OH), 2.04 (ddd, 1H, ^3J = 4.7, 9.2 Hz, ^2J = 13.8 Hz, 4-H), 2.20 (ddd, 1H, ^3J = 1.2, 6.7 Hz, ^2J = 13.8 Hz, 4-H), 3.46 (d, 1H, ^3J = 5.8 Hz, CH_2Br), 3.46 (d, 1H, ^3J = 4.9 Hz, CH_2Br), 4.12 (dq, 1H, ^3J_d = 2.8 Hz, ^3J_q = 6.3 Hz, 2-H), 4.25 (m_c, 1H, 3-H), 4.43–4.53 (m, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 13.9, 36.7, 39.8, 73.3, 76.4, 79.7.

5.3.4. Conversion of 5-bromomethyl-2-methyltetrahydrofuran-3-ols into (*R*)-configured Mosher esters (general procedure). A 1 M solution of the corresponding 5-bromomethyl-2-methyltetrahydrofuran-3-ol (5–20 μmol) CH_2Cl_2 (1 mL) was treated with dimethylaminopyridine (DMAP, 2.0 equiv.) at 0°C. Neat (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (1.5 equiv.) was added dropwise at 0°C and the mixture was stirred for 1 h at 20°C. The solution was diluted with Et_2O (2 mL). It was washed with 2N HCl, a satd aq. solution of $NaHCO_3$ and brine (2 mL each). Drying ($MgSO_4$) and concentration of the organic phase under reduced pressure afforded the derived Mosher esters in quantitative yields.

5.3.4.1. (*R*)-Mosher-ester of (2*R*,3*S*,5*R*)-5-bromomethyl-2-methyltetrahydrofuran-3-ol (derived from 8a). ^{1}H NMR (250 MHz): δ 1.31 (d, 3H, 6.6 Hz, CH_3), 2.13–2.18 (m, 2H, 4-H), 3.46 (m_c, 2H, CH_2Br), 3.53 (q, 3H, ^5J=1.2 Hz, OCH_3), 4.07 (dq, 1H, ^3J_d=2.7 Hz, ^3J_t=6.6 Hz, 2-H), 4.24 (m_c, 1H, 5-H), 5.12 (m_c, 1H, 3-H), 7.39–7.45 (m, 3H, Ar-H), 7.49–7.52 (m, 2H, Ar-H).

5.3.4.2. (*R*)-Mosher-ester of (2*R*,3*S*,5*S*)-5-bromomethyl-2-methyltetrahydrofuran-3-ol (derived from 8b). ^{1}H NMR (250 MHz): δ 1.23 (d, 3H, 6.4 Hz, CH_3), 2.09 (ddd, 1H, ^3J=2.9, 3.5 Hz, ^3J=14.5 Hz, 4-H), 2.56 (ddd, 1H, ^3J=6.6, 7.9 Hz, ^3J=14.5 Hz, 4-H), 3.16 (dd, 1H, ^3J=7.9 Hz, ^2J=10.1 Hz, CH_2Br), 3.30 (dd, 1H, ^3J=5.6 Hz, ^2J=10.1 Hz, CH_2Br), 3.53 (q, 3H, ^5J=1.2 Hz, OCH_3), 4.21 (dq, 1H, ^3J_d=2.4 Hz, ^3J_t=6.4 Hz, 2-H), 4.39 (m_c, 1H, 5-H), 5.14 (m_c, 1H, 3-H), 7.41–7.46 (m, 3H, Ar-H), 7.48–7.54 (m, 2H, Ar-H).

5.3.4.3. (*R*)-Mosher-ester of (2*R*,3*R*,5*R*)-5-bromomethyl-2-methyltetrahydrofuran-3-ol (derived from 8c). ^{1}H NMR (250 MHz): δ 1.22 (d, 3H, 6.6 Hz, CH_3), 1.83 (m_c, 1H, 4-H), 2.49 (m_c, 1H, 4-H), 2.91 (m_c, 1H, CH_2Br), 3.18 (m_c, 1H, CH_2Br), 3.51 (q, 3H, ^5J=1.2 Hz, OCH_3), 3.92–4.16 (m, 2H, 2-H, 5-H), 5.31 (m_c, 1H, 3-H), 7.30–7.39 (m, 3H, Ar-H), 7.41–7.51 (m, 2H, Ar-H).

5.3.4.4. (*R*)-Mosher-ester of (2*R*,3*R*,5*S*)-5-bromomethyl-2-methyltetrahydrofuran-3-ol (derived from 8d). ^{1}H NMR (250 MHz): δ 1.20 (d, 3H, 6.4 Hz, CH_3), 2.18–2.23 (m, 2H, 4-H), 3.43 (m_c, 2H, CH_2Br), 3.54 (q, 3H, ^5J=1.2 Hz, OCH_3), 4.21–4.36 (m, 2H, 2-H, 5-H), 5.46 (m_c, 1H, 3-H), 7.38–7.46 (m, 3H, Ar-H), 7.52–7.54 (m, 2H, Ar-H).

5.3.5. Muscarine alkaloids 1a–d (general procedure). Bromomethyl-2-methyltetrahydrofuran-3-ols (derived from **8a**–**d**, see above) were dissolved in a solution of $N(CH_3)_3$ in EtOH (4.2 M). The solution was stirred in a sealed tube for 6–7 days at 60°C. The solvent was removed under reduced pressure. Products **1a**–**d** crystallized from the residue upon addition of Et_2O The crude material was recrystallized from petroleum ether/acetone.

5.3.5.1. (2*R*,3*S*,5*R*)-Muscarine 1a. (2*R*,3*S*,5*R*)-5-Bromomethyl-2-methyltetrahydrofuran-3-ol (34.9 mg, 0.179 mmol) was dissolved in a solution of $N(CH_3)_3$ in EtOH (0.51 mL, 4.2 M). The reaction mixture was stirred for 6 days at 60°C and worked up as described above to furnish 40.4 mg (0.159 mmol, 89%) of the alkaloid **1a** as colorless hygroscopic crystals. $[\alpha]_D^{20}$=−15.5 (*c* 0.64, EtOH). ^{1}H NMR (250 MHz, D_2O): δ 1.16 (d, 3H, ^3J=6.4 Hz, CH_3), 1.94 (ddd, 1H, ^3J=5.2, 9.5 Hz, ^2J=13.7 Hz, 4-H), 2.06 (ddd, 1H, ^3J=2.8, 6.4 Hz, ^2J=13.7 Hz, 4-H), 3.15 (s, 9H, NCH_3), 3.42 (dd, 1H, ^3J=9.2 Hz, ^2J=14.0 Hz, CH_2N), 3.55 (dd, 1H, ^3J=1.8 Hz, ^2J=14.0 Hz, CH_2N), 4.01 (dq, 1H, ^3J_d=2.4 Hz, ^3J_q=6.4 Hz, 2-H), 4.08 (ddd, 1H, ^3J=2.4, 2.8, 5.2 Hz, 3-H), 4.61 (m_c, 1H, 5-H).

5.3.5.2. (2*R*,3*S*,5*S*)-*allo*-Muscarine 1b. (2*R*,3*S*,5*S*)-5-Bromomethyl-2-methyltetrahydrofuran-3-ol (12.2 mg, 62.5 μmol) was dissolved in a solution of $N(CH_3)_3$ in EtOH (0.20 mL, 4.2 M). The reaction mixture was stirred for 7 days at 60°C and worked up as described above to afford 11.6 mg (45.6 μmol, 73%) of alkaloid **1b** as colorless hygroscopic crystals. $[\alpha]_D^{20}$=+36.8 (*c* 0.57, EtOH). ^{1}H NMR (250 MHz, D_2O): δ 1.16 (d, 3H, ^3J=6.1 Hz, CH_3), 1.55–1.65 (m, 1H, 4-H), 2.56 (ddd, 1H, ^3J=6.4, 8.2 Hz, ^2J=14.8 Hz, 4-H), 3.14 (s, 9H, NCH_3), 3.36 (dd, 1H, ^3J=1.8 Hz, ^2J=14.0 Hz, CH_2N), 3.63 (dd, 1H, ^3J=10.1 Hz, ^2J=14.0 Hz, CH_2N), 4.03 (m_c, 2H, 3-H, 2-H), 4.67 (m_c, 1H, 5-H).

5.3.5.3. (2*R*,3*R*,5*R*)-*epi*-Muscarine 1c. (2*R*,3*R*,5*R*)-5-Bromomethyl-2-methyltetrahydrofuran-3-ol (15.5 mg, 79.5 μmol) was dissolved in a solution of $N(CH_3)_3$ in EtOH (0.22 mL, 4.2 M). The reaction mixture was stirred for 7 days at 60°C and worked up as described above to provide 13.1 mg (51.5 μmol, 65%) of alkaloid **1c** as colorless hygroscopic crystals. $[\alpha]_D^{20}$=−62.7 (*c* 0.42, EtOH). ^{1}H NMR (250 MHz, D_2O): δ 1.24 (d, 3H, ^3J=6.4 Hz, CH_3), 1.62 (ddd, 1H, ^3J=1.8, 5.8 Hz, ^2J=14.0 Hz, 4-H), 2.61 (ddd, 1H, ^3J=6.1, 8.9 Hz, ^2J=14.0 Hz, 4-H), 3.18 (s, 9H, NCH_3), 3.50 (dd, 1H, ^3J=3.1 Hz, ^2J=14.0 Hz, CH_2N), 3.58 (dd, 1H, ^3J=8.5 Hz, ^2J=14.0 Hz, CH_2N), 3.95 (dq, 1H, ^3J_d=3.4 Hz, ^3J_q=6.4 Hz, 2-H), 4.24 (ddd, 1H, ^3J=1.8, 3.4, 6.1 Hz, 3-H), 4.46 (m_c, 1H, 5-H).

5.3.5.4. (2*R*,3*R*,5*S*)-*epiallo*-Muscarine 1d. (2*R*,3*R*,5*S*)-5-Bromomethyl-2-methyltetrahydrofuran-3-ol (10.1 mg, 51.8 μmol) was dissolved in a solution of $N(CH_3)_3$ in EtOH (0.14 mL, 4.2 M). The reaction mixture was stirred for 7 days at 60°C and worked up as described above to yield 8.9 mg (35.0 μmol, 68%) of the alkaloid **1d** as colorless hygroscopic crystals. $[\alpha]_D^{20}$=0.0 (*c* 0.41, EtOH). ^{1}H NMR (250 MHz, D_2O): δ 1.19 (d, 3H, ^3J=6.4 Hz, CH_3), 1.92 (ddd, 1H, ^3J=4.9, 8.5 Hz, ^2J=14.0 Hz, 4-H), 2.20 (dd, 1H, ^3J=7.0 Hz, ^2J=14.0 Hz, 4-H), 3.16 (s, 9H, NCH_3), 3.35 (dd, 1H, ^3J=1.8 Hz, ^2J=14.0 Hz, CH_2N), 3.50 (dd, 1H, ^3J=9.7 Hz, ^2J=14.0 Hz, CH_2N), 4.07 (dq, 1H, ^3J_d=2.7 Hz, ^3J_q=6.4 Hz, 2-H), 4.21 (dd, 1H, ^3J=2.7, 4.9 Hz, 3-H), 4.58 (m_c, 1H, 5-H).

5.4. Preparation of 3-substituted *N*-hexenoxythiazolethiones

5.4.1. (2*R,3*S**)-*N*-(3-Hydroxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione**. (2*R*,3*S*)-*N*-(3-Hydroxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione (**6**, 37.8 mg, 0.108 mmol, 34% ee)[15] was dissolved in a solution of NaOH in CH_3OH (2.1 mL, 0.18 M). The reaction mixture was stirred for 16 h at 20°C and then poured into a mixture of Et_2O (20 mL) and H_2O (20 mL). The aqueous phase was separated and extracted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to afford an oil which was purified by chromatography [SiO_2, petroleum ether/Et_2O, 1:2 (v/v)]. $R_f=0.16$ (petroleum ether/Et_2O, 1:2), 25.6 mg (0.104 mmol, 97%), tan oil. ^{1}H NMR (250 MHz): δ 1.36 (d, 3H, $^3J=6.4$ Hz, 1-H), 2.08–2.22 (m, 1H, 4-H), 2.27–2.39 (m, 1H, 4-H), 2.31 (d, 3H, $^4J=1.2$ Hz, CH_3), 4.03–4.13 (m, 2H, 3-H, OH), 4.50 (dq, 1H, $^3J_d=1.5$ Hz, $^3J_q=6.4$ Hz, 2-H), 5.09 (d, 1H, $^3J=10.7$ Hz, 6-H), 5.14 (d, 1H, $^3J=17.1$ Hz, 6-H), 5.83 (ddt, 1H, $^3J_d=10.7$, 17.1 Hz, $^3J_t=7.0$ Hz, 5-H), 6.25 (q, 1H, $^4J=1.2$ Hz, 5′-H). ^{13}C NMR (63 MHz): δ 11.3, 13.7 (C-1, CH_3), 36.6 (C-4), 68.6 (C-3), 87.6 (C-2), 104.0 (C-5′), 117.5 (C-6), 134.2 (C-5), 138.7 (C-4′), 182.4 (C=S). IR (NaCl): $\nu=3381$ cm^{-1} (s), 3078 (m), 2937 (s), 1643 (m), 1594 (m), 1434 (m), 1391 (m), 1318 (s), 1175 (m), 1141 (m), 1040 (s), 1011 (s), 983 (s), 917 (m), 835 (w), 720 (s). MS (70 eV, EI): m/z (%) = 245 (2) [M^+], 147 (100) [$C_4H_5NOS_2^+$], 131 (34) [$C_4H_5NS_2^+$], 71 (23) [$C_4H_7O^+$]. $C_{10}H_{15}NO_2S_2$ (245.4) calcd: C, 48.95; H, 6.16; N, 5.71; S, 26.14. Found: C, 49.04; H, 5.97; N, 5.61; S, 25.89.

5.4.2. (2*R,3*S**)-*N*-(3-Trifluoroacetyloxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione 10**. A solution of (2*R**,3*S**)-*N*-(3-hydroxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione (100 mg, 0.408 mmol) and DABCO (91.4 mg, 0.815 mmol) in dry CH_2Cl_2 (0.4 mL) was treated at 0°C dropwise with neat trifluoroacetic anhydride (129 mg, 0.612 mmol). The reaction mixture was stirred for 2 h at 20°C. Afterwards it was diluted with *tert*-butyl methyl ether (2 mL). The precipitated salts were dissolved in 2N HCl (2 mL). The organic phase was separated. and washed with a saturated aq. solution of $NaHCO_3$ (2 mL) and brine (2 mL). The combined organic phases were then dried over $MgSO_4$ and concentrated under reduced pressure to furnish an oil that was purified by chromatography [SiO_2, petroleum ether/Et_2O, 1:1 (v/v)]. $R_f=0.34$ (petroleum ether/Et_2O, 1:1), 114 mg (0.333 mmol, 82%), tan oil. ^{1}H NMR (250 MHz): δ 1.33 (d, 3H, $^3J=6.4$ Hz, 1-H), 2.18 (d, 3H, $^4J=1.2$ Hz, CH_3), 2.53 (m_c, 2H, 4-H), 5.18 (d, 1H, $^3J=12.2$ Hz, 6-H), 5.19 (d, 1H, $^3J=17.4$ Hz, 6-H), 5.58 (dt, 1H, $^3J_d=2.4$ Hz, $^3J_d=7.3$ Hz, 3-H), 5.68–5.84 (m, 2H, 2-H, 5-H), 6.19 (q, 1H, $^4J=1.2$ Hz, 5′-H). ^{13}C NMR (100 MHz): δ 12.2, 13.6 (C-1, CH_3), 35.0 (C-4), 77.0, 79.8 (C-2, C-3), 103.0 (C-5′), 114.5 (q, $^1J_{C,F}=286$ Hz, CF_3), 120.0 (C-6), 131.0 (C-5), 138.6 (C-4′), 156.6 (q, $^2J_{C,F}=42.9$ Hz, C=O), 180.8 (C=S). MS (70 eV, EI): m/z (%) = 341 (19) [M^+], 147 (84) [$C_4H_5NOS_2^+$], 131 (100) [$C_4H_5NS_2^+$]. HRMS ($C_{12}H_{14}F_3NO_3S_2$, M^+) calcd: 341.0367. Found: 341.0360.

5.4.3. (2*R,3*S**)-*N*-(3-Diphenoxyphosphoryl-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione 11**. A solution of (2*R**,3*S**)-*N*-(3-hydroxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*)thione (22.1 mg, 90.1 μmol) and DABCO (20.2 mg, 0.180 mmol) in dry CH_2Cl_2 (0.2 mL) was treated dropwise at 0°C with neat diphenylchlorophosphate (36.3 mg, 0.135 mmol). The reaction mixture was stirred for 24 h at 20°C and subsequently diluted with *tert*-butyl methyl ether (2 mL). The precipitated salts were dissolved in 2 M HCl (2 mL) and the organic phase separated. and washed with a saturated aq. solution of $NaHCO_3$ (2 mL) and brine (2 mL). After drying over $MgSO_4$ the organic solvent was removed under reduced pressure to provide an oily residue that was purified by chromatography [SiO_2, petroleum ether/*tert*-butyl methyl ether, 1:2 (v/v)]. $R_f=0.46$ (petroleum ether/*tert*-butyl methyl ether, 1:2), 20.1 mg (42.1 μmol, 47%), tan oil. ^{1}H NMR (250 MHz): δ 1.29 (d, 3H, $^3J=6.6$ Hz, 1-H), 2.08 (d, 3H, $^4J=1.2$ Hz, CH_3), 2.47 (m_c, 1H, 4-H), 2.71 (m_c, 1H, 4-H), 5.09–5.20 (m, 3H, 2-H, 6-H), 5.62 (m_c, 1H, 3-H), 5.80 (ddt, 1H, $^3J_d=10.4$, 16.9 Hz, $^3J_t=6.7$ Hz, 5-H), 6.10 (d, 1H, $^4J=1.2$ Hz, 5′-H), 7.14–7.36 (m, 10H, Ar-H); ^{13}C NMR (63 MHz): δ 12.1, 13.8 (CH_3, C-1), 36.7 (d, $^3J_{C,P}=2.9$ Hz, C-4), 80.0 (d, $J_{C,P}=6.7$ Hz), 80.9 (d, $J_{C,P}=6.7$ Hz) (C-2, C-3), 102.6 (C-5′), 119.3, 120.0 (d, $^3J_{C,P}=4.8$ Hz), 120.1 (d, $^3J_{C,P}=5.7$ Hz), 125.3, 129.7, 129.8, 131.5, 139.1, 150.6 (d, $^2J_{C,P}=8.6$ Hz), 180.7 (C=S). MS (70 eV, EI): m/z (%) = 264 (52) [$C_{13}H_{13}O_4P$], 131 (75) [$C_4H_5NS_2$], 77 (67) [$C_6H_5^+$]. $C_{22}H_{24}NO_5PS_2$ (477.5) calcd: C, 55.33; H, 5.07; N, 2.93; S, 13.45. Found: C, 54.00; H, 5.19; N, 2.72; S, 12.25.

5.5. Photolysis of thiazolethiones 10 and 11 in the presence of $BrCCl_3$

5.5.1. General procedure. A Schlenk flask was charged with a solution of thiazolethione **10** or **11** in the dark ($c_0=0.18$ M). A defined amount of anisole or 2,2-dichloro-5,5-dimethylcyclohexane-1,3-dione (internal standards for ^{1}H NMR analysis) was then added. The flask was closed with a rubber septum and cooled to liquid-nitrogen temperature. The flask was evacuated (1×10^{-2} mbar) and subsequently flushed with argon after which $BrCCl_3$ was added. The sample was degassed by two freeze–pump–thaw cycles, subsequently thermostated to 18°C (H_2O bath) and then photolyzed for 25 min in a Rayonet® photoreactor to furnish a reaction mixture that was immediately analyzed by either ^{1}H NMR or GC.

5.5.1.1. 5-Bromomethyl-3-trifluoroacetyloxy-2-methyltetrahydrofuran 12 and 12b. To a solution of thiazolethione **10** (17.4 mg, 51.0 μmol) and $BrCCl_3$ (80.9 mg, 0.408 mmol) in dry deoxygenated C_6D_6 (0.8 mL) was added anisole (internal standard, ^{1}H NMR). The solution was treated as described in the general procedure and analyzed by ^{1}H NMR and MS. Yield: 32.9 μmol (64%), mixture of diastereomers (**12a**:**12b** = 29:71). $C_8H_{10}O_3BrF_3$ (291.1). HRMS ($C_7H_8F_3O_3$, M^+-CH_2Br) calcd: 197.0426. Found: 197.0425. MS (70 eV,

EI): m/z (%) = 197 (100) [$C_7H_8O_3F_3^+$], 167 (39) [$C_6H_6O_2F_3^+$], 83 (54) [$C_5H_7O^+$], 43 (85) [$C_2H_3O^+$]. **12a**: ^{1}H NMR (250 MHz, C_6D_6): δ 0.88 (d, 3H, ^3J = 6.6 Hz, CH_3), 1.47–1.57 (m, 2H, 4-H), 2.85–2.93 (m, 2H, CH_2Br), 3.66–3.75 (m, 2H, 2-H, 5-H), 4.45 (m_c, 1H, 3-H). **12b**: ^{1}H NMR (250 MHz, C_6D_6): δ 0.70 (d, 3H, ^3J = 6.6 Hz, CH_3), 1.37–1.45 (m, 1H, 4-H), 1.75 (ddd, 1H, ^3J = 6.6, 7.6 Hz, ^2J = 14.5 Hz, 4-H), 2.89 (dd, 1H, ^3J = 7.6 Hz, ^2J = 10.1 Hz, CH_2Br), 3.01 (dd, 1H, ^3J = 5.5 Hz, ^2J = 10.1 Hz, CH_2Br), 3.77–3.87 (m, 2H, 2-H, 5-H), 4.40 (dt, 1H, J_t = 3.1 Hz, J_q = 6.6 Hz, 3-H).

5.5.1.2. (5-Bromomethyl-2-methyltetrahydrofuran-3-yl)diphenoxyphosphate 13a and 13b. To a solution of thiazolethione **11** (14.1 mg, 29.5 μmol) and $BrCCl_3$ (47.6 mg, 0.239 mmol) in dry and deoxygenated C_6D_6 (0.8 mL) was added 2,2-dichloro-5,5-dimethylcyclohexane-1,3-dione. The solution was treated as described in the general procedure to provide a reaction mixture that was analyzed by ^{1}H NMR and MS. Yield: 20.4 μmol (69%), mixture of diastereomers (**13a**:**13b** = 30:70). $C_{18}H_{20}O_5PBr$ (427.2). MS (70 eV, EI): m/z (%) = 264 (100) [$C_{13}H_{13}O_4P^+$], 251 (15) [$C_{12}H_{12}O_4P^+$], 170 (66) [$C_6H_5PO_4^+$], 94 (36) [$C_6H_6O^+$], 77 (82) [$C_6H_5^+$]. **13a**: ^{1}H NMR (250 MHz, C_6D_6): δ 0.95 (d, 3H, ^3J = 6.4 Hz, CH_3), 1.25–1.40 (m, 2H, 4-H), 2.89 (d, 2H, ^3J = 4.9 Hz, CH_2Br), 3.84–4.01 (m, 1H, 5-H), 4.09 (dq, ^3J_d = 2.8 Hz, ^3J_t = 6.4 Hz, 2-H), 4.58–4.68 (m, 1H, 3-H), 6.79–6.87 (m, 2H, Ar-H), 6.92–7.02 (m, 4H, Ar-H), 7.23–7.30 (m, 4H, Ar-H). **13b**: ^{1}H NMR (250 MHz, C_6D_6): δ 0.83 (d, 3H, ^3J = 6.4 Hz, CH_3), 1.13–1.18 (m, 1H, 4-H), 1.53–1.66 (m, 1H, 4-H), 2.99 (dd, 1H, ^3J = 7.6 Hz, ^2J = 10.1 Hz, CH_2Br), 3.09 (dd, 1H, ^3J = 5.5 Hz, ^2J = 10.1 Hz, CH_2Br), 3.84–4.01 (m, 1H, 5-H), 4.16 (dq, ^3J_d = 3.4 Hz, ^3J_t = 6.4 Hz, 2-H), 4.55–4.62 (m, 1H, 3-H), 6.79–6.87 (m, 2H, Ar-H), 6.92–7.02 (m, 4H, Ar-H), 7.23–7.30 (m, 4H, Ar-H).

5.6. BEt_3/O_2-initiated reactions

5.6.1. General procedure and reaction at −78°C. A Schlenk flask was charged with a solution of thiazolethione **6** (70.2 mg, 0.201 mmol, 34% ee)[15] in CH_2Cl_2 (1.2 mL) in the dark (c_0 = 0.18). The flask was sealed with a rubber septum, cooled to liquid-nitrogen temperature and evacuated (1×10^{-2} mbar). Afterwards, the sample was flushed with argon. $BrCCl_3$ (319 mg, 1.61 mmol) was then added and the reaction mixture deaerated in two freeze–pump–thaw cycles after which it was allowed to warm to 18°C (H_2O bath). A solution of BEt_3 (0.1 mL, 1 m in hexane) was and the reaction mixture cooled to −78°C. O_2 (4.4 mL) was then bubbled through the reaction mixture (syringe pump) over a period of 30 min The solvent was removed under reduced pressure and the residue purified by chromatography [SiO_2, petroleum ether/Et_2O, 2:1 (v/v)] to furnish 19.2 mg (64.2 μmol, 32%) of a 21:79-mixture of tetrahydrofurans **8a** and **8b** as a colorless oil.

5.6.2. Reaction at −10°C. A solution of thiazolethione **6** (116 mg, 0.332 mmol, 34% ee),[15] $BrCCl_3$ (658 mg, 3.32 mmol), and BEt_3 (0.17 mL, 1 M in hexane) in dry CH_2Cl_2 (1.8 mL) was prepared as outlined above. O_2 (7.4 mL) was then bubbled through the reaction mixture using a syringe pump over a period of 30 min at −10°C. The solvent was removed under reduced pressure and the residue purified by chromatography [SiO_2, petroleum ether/Et_2O, 2:1 (v/v)] to furnish 74.5 mg (0.249 mmol, 75%) of a 27:73 mixture of tetrahydrofurans **8a** and **8b** as a colorless oil.

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