Annulated and bridged tetrahydrofurans from alkenoxyl radical cyclization†‡

Christine Schur, a Harald Kelm, a Thomas Gottwald, b Arne Ludwig, b Rainer Kneuer b and Jens Hartung* a

Abstract

4-Pentenoxyl radicals sharing two or more carbon atoms with a cycloalkane cyclize in a predictable manner stereoselectively and regioselectively to afford in solutions of bromotrichloromethane cycloalkyl-fused or -bridged 2-bromomethyltetrahydrofurans in up to 95% yield. Stereoselectivity in alkenoxyl radical ring closures arises from cumulative steric effects. The substituent positioned the closest to the alkene carbon, which is being attacked by the oxygen radical, exerts the strongest stereodirecting effect. This principal inductor guides 5-exo-cyclization 2,3-trans- or 2,4-cis-selectively. The substituent located further from the attacked π-bond is the secondary inductor. A secondary inductor in the relative trans-configuration enhances stereodifferentiation by the primary inductor; a cis-configured secondary inductor decreases this effect. A secondary inductor is not able to overrule the guiding effect of a similar sized primary inductor. Intramolecular 4-pentenoxyl radical additions to a cyclohexene-bound exo-methylene group or to endocyclic double bonds proceed cis-specifically, as exemplified by synthesis of a diastereomerically pure bromobicyclo[2.2.1]heptyl-annulated tetrahydrofuran from the verbenylethoxyl radical. According to theory, the experimental 2,3-cis-specificity in alkoxyl radical cyclization to an endocyclic π-bond arises from strain associated with the 2,3-trans-ring closure.

1. Introduction

4-Pentenoxyl radicals add intramolecularly to the inner alkene carbon with rate constants of 108 per second and above.1-6 Alkyl or ortho-substituted aryl groups in position 1 exert a stereodirecting effect, leading to 2,5-trans-configured tetrahydrofurans as principal products. Carbon substituents at positions 2 and 3 direct 4-pentenoxyl radical cyclization 2,4-cis- and 2,3-trans-selectively.7-9 Stereodifferentiation by alkyl or aryl groups arises from steric effects, which gradually increases as the distance between a controlling substituent and the attacked π-bond shortens, for example from a 15/85-cis/trans-ratio at room temperature to <2/98 by shifting a tert-butyl group from position 1 to position 3.9 In synthesis, 5-exo-cyclized 4-pentenoxyl radicals are preferentially trapped by a heteroatom atom donor,10,11 for introducing halogen,12-14 alkylsulfanyl,15 or other synthetically useful functional groups.16

The model to explain stereodifferentiation by a carbon substituent in 4-pentenoxyl radical cyclization predicts that the intramolecular addition proceeds via a distorted twist-conformer of tetrahydrofuran as the favored transition structure (twist-model),8,17 differing from the cyclohexane-based Beckwith–Houk-model for carbon radical cyclization.18,19 Application of the alkoxyl radical approach to synthesis of more demanding targets, for example biologically active terpene-, acetogenin-, and fatty acid-derived cycloalkyl-fused tetrahydrofurans,20-22 requires to extend the model in order to predict the selectivity for constructing bicyclic compounds.7,21 Lessons from carbon radical chemistry have taught that stereodifferentiation in synthesis of bicyclic compounds is difficult to extrapolate by transferring results from monocycle to bicyclic formation, since transannular and other strain effects may superimpose in an unpredictable manner.24,25 To find out whether embedding two carbons of a 4-pentenoxyl radical into a cycloaliphatic framework conserves or changes guidelines for stereoselective tetrahydrofuran synthesis, we examined in this study bromocyclization of cis/trans-cycloalkyl-bridged alkenoxyl.
1. We used derivatives of 3-alkenoxy-4-methylthiazole-2(3H)-thiones (MTTORs) (type A–C) and alkenoxyl radicals having an endocyclic carbon–carbon double bond (type D–E; dotted red lines symbolize an alkyl bridge).

2. The most important finding from the study shows that cycloalkyl-bridged 4-pentenoxyl radicals cyclize in a predictable manner stereoselectively and regioselectively, to a terminal double bond, providing tetrahydrofuranylmethyl tosylates at room temperature in solutions of dimethyl sulfoxide-tetrahydrofuran.

3. In extension to previous studies, the MTTO + anion, in a SN2-reaction, 31 isomerizes to 2-(methylcyclohexenyl)ethyl tosylates at room temperature and liberating oxygen radicals in an addition/fragmentation sequence involving a mediator radical. The intermediate formed by adding, for example, the trichloromethyl radical to the thione sulfur of MTTO 1 dissociates into 2-(trichloromethylsulfanyl)-4-methylthiazole 2 and oxygen radical I (Scheme 1). 4-Pentenoxy radicals cyclize by intramolecularly adding with rate constants of $10^9$–$10^6$ s$^{-1}$ at room temperature to a terminal double bond, providing tetrahydrofuranylmethyl radicals, for example II, in a fingerprint 5-exo/6-endocycloalkylation selectivity of 98 : 2. 2. Trapping of carbon radical II by bromotrichloromethane yields bromomethyltetrahydrofuran 3 as a target product, and the trichloromethyl radical for propagating the chain reaction.

2.1.1 Alkenoxyl radical generation, intramolecular addition, and chain reaction. In extension to previous studies, we used derivatives of 3-alkenoxy-4-methylthiazole-2(3H)-thiones (MTTORs) 1 as progenitors for generating oxygen radicals under non-oxidative and pH-neutral conditions. 11,26,27 MTTORs (e.g. 1) are heterocyclic O-alkenyl thiohydroxamates, liberating oxygen radicals in an addition/fragmentation sequence involving a mediator radical. The intermediate formed by adding, for example, the trichloromethyl radical to the thione sulfur of MTTO 1 dissociates into 2-(trichloromethylsulfanyl)-4-methylthiazole 2 and oxygen radical I (Scheme 1). 14 4-Pentenoxy radicals cyclize by intramolecularly adding with rate constants of $10^9$–$10^6$ s$^{-1}$ at room temperature to a terminal double bond, providing tetrahydrofuranylmethyl radicals, for example II, in a fingerprint 5-exo/6-endocycloalkylation selectivity of 98 : 2. 17 Trapping of carbon radical II by bromotrichloromethane yields bromomethyltetrahydrofuran 3 as a target product, and the trichloromethyl radical for propagating the chain reaction.

2.1.2 Preparation and properties of 3-alkenoxy-4-methylthiazole-2(3H)-thiones (MTTORs). The standard approach to synthesis of O-alkenyl thiohydroxamate 1 is substitution of a leaving group from a carbon electrophile by the 4-methyl-2-thiooxothiazole-2(3H)-thione ion (MTTO$^-$; Scheme 2). 32 In the present study we used O-alkenyl tosylates as carbon electrophiles, obtained in 69–96% yield from an alkenol, 28–31 $p$-toluenesulfonyl chloride, and 1,4-diazabicyclo[2.2.2]octane for buffering in situ-liberated hydrogen chloride (ESI$^+$. 32 Some alkenol syntheses required modification of the original instruction, for example for preparing cis- and trans-isomers of 2-(methylprop-1-enyl)-cyclohexylmethanol (for 1e) 31,34 and $\beta$-verbenylethanol (for 1h; ESI$^+$. 35 Treating O-pentenyl tosylates at room temperature in solutions of dimethyl formamide with the tetraethylammonium salt of MTTO$^-$ furnished MTTOs 1a, 1b, and 1d–h in yields between 65% and 82% (Scheme 2). In position 2 substituted cyclohexyl tosylates toward the incoming nucleophile, the MTTO$^-$-anion, in a $S_{N}2$-reaction.

3. Alkenoxyl-4-methylthiazole-2(3H)-thiones obtained as described above are oils (1a–h, cis-1c, 1f) or crystalline solids (trans-1c, 1d–e, 1g, 1h), stable for months when stored in vials at room temperature. Recrystallizing 3-(methylcyclohexenyl)-
methylthiazole-2(3H)-thione 

The phenomenon of hindered rotation about the nitrogen-oxygen bond, becoming apparent in nuclear magnetic resonance spectra of, for example, 3-isopropoxy-4-methylthiazole-2(3H)-thione at -60 °C, and a twofold set of resonances below this temperature.40 The lowest in energy conformer has the ester carbon C7 o

The lowest conformer, which is the diastereomeric form at 150 K; the (R,P)-isomer was arbitrarily chosen from the racemate (R,P)/(S,M)-1g for presentation (50% probability level); hydrogen atoms are drawn as circles of an arbitrary radius; oxygen is depicted in red, nitrogen in blue, and sulfur in orange; for depiction of the minor diastereomer (S,P)/(R,M)-1g, see the ESIT].

Conformation of thiazolethione-derived O-alkyl thiohydroxamates in solution and in the gas phase. The crystals available for determining the structure of compound 1g were systematically disordered showing, according to the model used for solving and refining the structure, a 78/22-ratio of diastereomers at crystallographic independent sites.§ The diastereomers differ with respect to the configuration at C8/C8a (ESI§) and the helicity at the nitrogen-oxygen bond, showing both the characteristic offset of thiohydroxamate bound carbon 7 from the heterocyclic plane [major diastereomer (ds): C2–N3–O1–C7 = 91.0(2)°; minor ds: C2–N3a–O1a–C7a = 59.8(6)°] and bond lengths which are diagnostic for primary O-alkyl thiohydroxamates [major ds (Fig. 2): C2–S2 = 1.666(1) Å, C2–N3 = 1.358(2) Å, N3–O1 = 1.386(2) Å; minor ds (ESI‡): C2–N3a = 1.366(6) Å, N3a–O1a = 1.373(4) Å].

2.1.3 Numbering of atom positions in O-alkenyl thiohydroxamates, alkenoxyl radicals, and cyclized products. Oxygen and carbon differ in priority for systematically naming open chain and heterocyclic organic compounds according to the IUPAC convention. For the stereochemical discussion in this article we numbered the 4-pentenyl chain in O-radical progenitor I and alkenoxyl radical I as recommended by IUPAC for aliphatic compounds. A transition structure (TS)-I for 5-exocyclization in the twist model is a derivative of tetrahydrofuran, and thus numbered, similar to cyclized carbon radical II, according to the Hantzsch–Widman notation for heterocyclic compounds. For numbering positions in bicyclic bromocyclization product 3, we used the von Baeyer convention (Fig. 3).

2.2 Alkenoxyl radical addition to exocyclic double bonds

2.2.1 1,2-Annulation – 2-allylcycloalkyl-1-oxyl radical reactions. For elucidating principles of stereocontrol exerted by a cycloalkane fused in positions 1 and 2 to the 4-pentenoxyl radical we investigated the size effect of the cycloaliphatic ring,§ Crystallographic data (excluding structure factors) for the structure in this paper are deposited with the Cambridge Crystallographic Data Centre as supplementary publication [CCDC 1008593 (compound 1g)].
the relative configuration of substituents, and substitution at the terminal alkene carbon on reactivity and selectivity of type-A alkenoxyl radicals (Tables 1–4).

(i) Methods of alkenoxy radical generation and product analysis. Photolyzing solutions of O-alkenyl thiohydroxamates 1a–c in benzene containing 10 equivalents (1.67 M) of bromotrichloromethane, using Rayonet® chamber apparatus equipped with 350 nm illuminants, quantitatively consume the starting material within 30 minutes, as determined by thin layer chromatography. Reaction mixtures from photochemical experiments tended to turn turbid and yellow. A gas chromatogram (GC) recorded by the end of the reaction time provided information on the original product pattern and distribution.

### Table 1

<table>
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<tr>
<th>Entry</th>
<th>cis-1</th>
<th>Conditions</th>
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<th>cis-3a–b/% (1,3-cis : trans)</th>
<th>4a/%</th>
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<tr>
<td>1</td>
<td>1a</td>
<td>hν/25 °C</td>
<td>85</td>
<td>3a: 10 (70 : 30)</td>
<td>4a: 60</td>
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<td>2</td>
<td>1a</td>
<td>AIBN/80 °C</td>
<td>87</td>
<td>3a: 8 (71 : 29)</td>
<td>4a: 54</td>
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<tr>
<td>3</td>
<td>1b</td>
<td>hν/25 °C</td>
<td>73</td>
<td>3b: 49 (64 : 36)</td>
<td>4b: 33</td>
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<td>4</td>
<td>1b</td>
<td>AIBN/80 °C</td>
<td>75</td>
<td>3b: 34 (56 : 44)</td>
<td>4b: 35</td>
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### Table 2

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<th>Conditions</th>
<th>2/%</th>
<th>cis-3a/% (1,3-cis : trans)</th>
<th>4a/%</th>
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<tbody>
<tr>
<td>1</td>
<td>hν/25 °C</td>
<td>56</td>
<td>44 (14)³</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>AIBN/80 °C</td>
<td>85</td>
<td>73 (14)³</td>
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³Not detected (NMR). Figures in brackets refer to the yield of 5,7-dibromo-9,9,9-trichlorononanal.

### Table 3

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<th>Entry</th>
<th>Conditions</th>
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<th>cis-3c/% (6,8-cis : trans)</th>
<th>4c/%</th>
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<td>1</td>
<td>hν/25 °C</td>
<td>73</td>
<td>45 (89 : 11)</td>
<td>a</td>
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<tr>
<td>2</td>
<td>AIBN/80 °C</td>
<td>74</td>
<td>61 (68 : 32)</td>
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³Not detected (NMR).

### Table 4

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<th>Entry</th>
<th>Conditions</th>
<th>2/%</th>
<th>trans-3c/% (6,8-cis : trans)</th>
<th>4c/%</th>
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<tr>
<td>1</td>
<td>hν/25 °C</td>
<td>92</td>
<td>49 (8 : 92)</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>AIBN/80 °C</td>
<td>80</td>
<td>70 (13 : 87)</td>
<td>8</td>
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</tbody>
</table>

³Not detected (NMR).
Column chromatography furnished samples of purified 2-(trichloromethylsulfanyl)-4-methyl-1,3-thiazole (2), 5-exo-bromomethylated products 3a–c, and β-fragmented unsaturated 5-bromooctane 3a–b. For collecting analytical data (Tables 1–4, and Experimental). Solutions from thermally initiated reactions were in addition charged with 15 mole percent of azo-α,α-bis-(isobutyronitrile) (AIBN) as the initiator. Such mixtures remained clear but tended to turn yellow by the end of the reaction.

(ii) Product pattern and kinetic interpretation. Reactions between O-(2-allylcycloalkyl) thiohydroxamates cis-1a–c and bromomethylmethane furnish bromomethyltetrahydrofurans cis-3a–c, with the yields gradually decreasing for thermally initiated reactions from 61% for cis-3c to 34% for cis-3b to 8% for cis-3a (Table 1, entries 2 and 4; Table 3, entry 2). The reactions gave bromoaldehydes 4a–c as co-products in yields increasing from 12% for 4c, through 35% for 4b to 54% for 4a. Photolyzing or heating O-(2-allylcyclopentyl) thiohydroxamate trans-1a in the presence of bromomethylmethane provided bromooctanal 4a, but no bromomethyltetrahydrofururan trans-3a as secured by independent analysis of an authentic sample (ESI‡). The ratio of the bromomethylated product trans-3c and bromoaldehyde 4c obtained from O-cyclohexylallyl ester trans-1c is similar to the ratio of cis-3c and 4c obtained from the stereoisomer cis-1c (entry 2 in Tables 3 and 4). The pattern of products obtained from radical reactions conducted at 80 °C in summary is similar, except for bromoaldehyde 4c, which did not form in the room temperature experiments. None of the reactions furnished 2-allylcycloalkanols or 2-allylcycloalkanones in verifiable amounts (GC-MS).

In kinetically controlled reactions, the quotient between bromomethyltetrahydrofururan 3 and bromooctane 4 is equivalent to the relative rate constant for the addition (k_add) versus β-fragmentation (k_b) (Scheme 3). Kinetic control for oxygen radical addition to terminal double bonds is documented. For the following reason we suggest that the sequence leading to bromoaldehyde 4 under conditions chosen in this study also is kinetically controlled. In 1.67 molar solution of bromomethylmethane, the effective rate constant for bromine atom trapping by secondary alkyl radicals, such as III, is approximately 4.3 × 10^8 s⁻¹, based on k_b for the 6-hepten-2-yl radical (2.6 × 10^8 M⁻¹ s⁻¹; 26 °C) as a reference. The rate constant k_add for the 4-formylbutyl radical 5-exo-cyclization (8.7 × 10^8 s⁻¹; 80 °C) serving as a reference for the reaction III → I, is by almost three orders of magnitude slower than the effective rate of bromine atom transfer from bromomethylmethane to the secondary carbon radical III.

For comparing rates of 5-exo-cyclization to rates of β-fragmentation for intermediates 1a–c, we standardized reactant concentrations and used a tenfold molar excess of bromomethylmethane. Under such conditions, the ratio of bromide 3 to 4 corresponds to the quotient k_add/k_b, gradually increasing along the series of radicals trans-1a (k_rel = 0), cis-1a (0.2), cis-1b (1.0) to cis/trans-1c (k_rel = 5–9). Dividing k_add for the 4-penten-2-yl radical cyclization (5.2 × 10^8 s⁻¹; 26 °C) by k_b for the cyclopentenyl radical β-fragmentation (4.7 × 10^8 s⁻¹; 80 °C) for calibrating the competition system with the aid of absolute rate constants leads to a similar order of magnitude for the k_add/k_b ratio. The propensity of cyclopentane-fused 4-pentenoyl radicals to provide β-fragmented products, such as bromooctane 4a–b, arises from strain, being ~20 kJ mol⁻¹ higher for cyclohexane. Substituting methyl for hydrogen at the terminal alkene carbon increases the fraction of the 5-exo-cyclized product from cis-3a to cis-3b, which we address to a rate enhancing polar effect of the methyl group in oxygen radical additions.

(iii) Stereoelectronic guidelines. 1,2-Cycloalkyl-bridged 4-pentenoyl radicals 1a–c cyclize 2,4-cis-selectively showing that the substituent in position 2 is the principal stereoelector for 5-exo-cyclization of type-A radicals. A trans-arranged secondary inductor in position 1 enhances the directing effect of the principal inductor; a cis-configured secondary inductor decreases this effect.

(iv) On the origin of 2,4-cis-selectivity in 5-exo-cyclization of type-A 4-pentenoyl radicals. To understand the origin of 2,4-cis-selectivity, we modelled transition structures (TS) of 2-allyl-1-cyclohexyl-1-oxyl radical 5-exo-cyclization 1c → Ic, using assessed electronic structure methods. For stereochemical analysis, we considered transition structures for 2,4-cis-(TS1) and 2,4-trans-cyclization (TS2) of allyl-1-cyclohexyl radicals cis/trans-1c (Fig. 4 and ESI‡ see also section 2.4). Transition structure searches according to an established methodology (ESI‡) led to twist (T)-conformers of tetrahydrofuran (Fig. 4), similar to intermediates modelled for 5-exo-cyclization of monosubstituted 4-pentenoyl radicals. The radical oxygen in transition structures TS1 cis/trans-cyclohexyl-1-oxylic radical 5-exo-cyclization lies for stereoelectronic reasons in a plane defined by inner alkene carbon (C5) and the allylic carbon (C4). Carbons 2 and 3 are offset into opposite directions from this plane, leading to 24-trans-1c (TS2-cis-1c, TS2-trans-1c, and TS2-trans-1c) and 24-trans-1c (TS1-cis-1c, TS1-trans-1c, and TS1-trans-1c) favoring transition structures TS1 cis-1c and TS1-trans-1c. Favored transition structures furthermore have the cyclohexyl-
2.2.2 2,3-Annulation – 2-(vinylcyclohexyl)-methylthio radical reactions. For elucidating principles controlling the stereoselectivity in cyclization of 2,3-cyclohexyl-bridged 4-pentenyl radicals (type B), we investigated bromocyclization of 2-vinyl- and 3-(2-dimethylvinylcyclohexylmethyl)-thiazolethiones cis/trans-1d-e (Tables 5 and 6).

(i) Methods of alkenoxyl radical generation and product analysis. Thermally induced reactions between O-[2-(vinylcycloalkyl-1-methyloxy) thiohydroxamate cis/trans-1d/e and bromotrichloromethane furnish 81% of 7-bromomethyltetrahydrofuran cis-3d and 95% of bromoisopropyl derivative cis-3e (entry 2 in Tables 5 and 6). The former reaction provided in addition 5% of the diastereomerically pure 6-endo-cyclized product cis-5d, which was not obtained from dimethylvinyl-congener cis-1e (GC-MS).

Heating O-(2-vinycycloalkyl-1-methyloxy) thiohydroxamate cis-1d in the presence of bromotrichloromethane furnishes an 80/20-mixture of 5-exo/6-endo-bromocyclized products trans-3d and trans-5d, whereas O-[2-(dimethylvinyl)-cyclohexylmethyl] ester trans-1e affords bromopropyltetrahydrofuran trans-3e as a single diastereomer (Tables 5 and 6, entry 4). Photochemical reactions gave 13–20% lower yields of bromocyclization products 3 and 5 taken together, and 8–19% less thiazole 2, than thermally initiated reactions (entries 1 and 3 in Tables 5 and 6).

(ii) Effect of methyl substitution at the terminal alkene carbon. Substituting two hydrogens at the terminal alkene carbon by methyl improves the stereoselectivity and regioselectivity in cyclization of type-B 4-pentenyl radicals (Tables 5 and 6). Terminal methyl groups furthermore improve the regioselectivity of the intramolecular addition, occurring with 80/20-selectivity for trans-1d, 94/6 for cis-1d, and 5-exo-specifically for cis/trans-1e (GC-MS; Table 5, entries 2 and 4, and Table 6).

Table 5 Bromocyclization products formed from 3-[(2-vinylcyclohexyl)methyloxy]-thiazolethione 1d and BrCCl3

<table>
<thead>
<tr>
<th>Entry</th>
<th>1d</th>
<th>Conditions</th>
<th>2/%</th>
<th>3d/% (6,7-cis : trans)</th>
<th>5d/% (1,2-cis : trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cis</td>
<td>hv/25 °C</td>
<td>71</td>
<td>1,6-cis: 70 (20 : 80)</td>
<td>1,6-cis: 3 (99 : 1)</td>
</tr>
<tr>
<td>2</td>
<td>cis</td>
<td>AIBN/80 °C</td>
<td>88</td>
<td>1,6-cis: 81 (21 : 79)</td>
<td>1,6-cis: 5 (99 : 1)</td>
</tr>
<tr>
<td>3</td>
<td>trans</td>
<td>hv/25 °C</td>
<td>78</td>
<td>1,6-trans: 57 (7 : 93)</td>
<td>1,6-trans: 10 (30 : 50)</td>
</tr>
<tr>
<td>4</td>
<td>trans</td>
<td>AIBN/80 °C</td>
<td>97</td>
<td>1,6-trans: 70 (10 : 90)</td>
<td>1,6-trans: 17 (41 : 59)</td>
</tr>
</tbody>
</table>

Stereodescriptor referring to the configuration of bridgehead carbons in products 3d and 5d.
(iii) Stereochemical guidelines. 2,3-Cycloalkyl-bridged 4-pentenoxyl radicals 1d-e cyclize 2,3-trans-selectively, indicating that the principal stereoinducer in cyclization of type-B radicals is the substituent in position 3 of the radical. Fusing 4-pentenoxyl radicals in relative trans-positions of cyclohexane enhances stereodifferentiation by the principal inductor.

(iv) On the origin of 2,3-trans-selectivity in 5-exo-cyclization of type-B 4-pentenoxyl radicals. Models built as instructed in section 2.1 show that type-B cyclohexyl-bridged 4-pentenoxyl radicals cis/trans-1d-e cyclize 2,3-trans-selectively, because steric constraints disfavor the 2,3-cis-mode of ring closure. In transition structures for 2,3-cis-cyclization, van der Waals repulsion between the (E)-positioned alkene substituent and the axially arranged hydrogens raises conformational free energy. The second aspect raising conformational free energy thus disfavoring a transition structure is eclipsing of hydrogens bound to carbons 4 and 5 (for TS\textsuperscript{2}-trans-1d and TS\textsuperscript{2}-cis-1d; Fig. 5). Extending the size of the (E)-substituent from hydrogen to methyl raises transannular repulsion, explaining the stereo-directing effect of a terminal substituent in cyclization of cis/trans-1e.

2.2.3 3,4-Annulation – 2-(2-methylene cyclohexyl)-1-ethylpentenoxyl radical reactions. To explore the selectivity in intramolecular addition of a 3,4-cyclohexyl-bridged 4-pentenoxyl radical (type C), we investigated photochemical and thermal reactions between 3-[2-(2-methylene cyclohexyl)-ethoxy]-thiazolethione 1f and bromotrichloromethane (Table 7).

(i) Methods of alkoxyl radical generation and product analysis. 3-[2-(2-methylene cyclohexyl)-ethoxy]-thiazolethione 1f furnishes the 5-exo-bromocyclized product cis-3f as a single dia-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>2/%</th>
<th>cis-3f/%</th>
<th>5f/% (cis : trans)</th>
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<tbody>
<tr>
<td>1</td>
<td>hυ/25 °C</td>
<td>54</td>
<td>24</td>
<td>21 (19 : 81)</td>
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<tr>
<td>2</td>
<td>AIBN/80 °C</td>
<td>80</td>
<td>35</td>
<td>22 (32 : 68)</td>
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</table>

The 5-exo/6-endo-selectivity of radical If (53 : 47) at room temperature falls below the value reported for the 4-methyl-4-pentenoxyl radical (69 : 31) and is higher than the regioselectivity determined for the 4-tert-butyl-4-pentenoxyl radical (46 : 54). Regioselectivity in 4-pentenoxyl radical cyclization originates from a balance between FMO attractions, torsional strain, and steric shielding. A carbon substituent in position 4 lowers the barrier for 6-endo-addition based on favorable frontier molecular orbital (FMO) interactions for the C,O-addition to the terminal carbon. Steric blocking of the incoming oxygen radical gradually lowers the rate of 5-exo-addition as the size of the carbon substituent in position 4 increases. The fraction of bromotetrahydropyran 5f remained almost unchanged (Table 7, entry 1).

The 5-exo/6-endo-selectivity of radical If (53 : 47) at room temperature falls below the value reported for the 4-methyl-4-pentenoxyl radical (69 : 31) and is higher than the regioselectivity determined for the 4-tert-butyl-4-pentenoxyl radical (46 : 54). Regioselectivity in 4-pentenoxyl radical cyclization originates from a balance between FMO attractions, torsional strain, and steric shielding. A carbon substituent in position 4 lowers the barrier for 6-endo-addition based on favorable frontier molecular orbital (FMO) interactions for the C,O-addition to the terminal carbon. Steric blocking of the incoming oxygen radical gradually lowers the rate of 5-exo-addition as the size of the carbon substituent in position 4 increases. The fraction of bromo-tetrahydropyran 5f remained almost unchanged (Table 7, entry 1).

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Table 8 Products formed from 3-[[1-methylcyclohex-1-en-4-yl]-methyloxy]-thiazolethione 1g and BrCCl₃ and diagnostic proton-NMR shift values of bromocyclization product 3g

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>3g/% (1,2-cis : trans)</th>
<th>2/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>h₂/25 °C</td>
<td>69</td>
<td>64  (28 : 72)</td>
</tr>
<tr>
<td>2</td>
<td>AIBN/80 °C</td>
<td>76</td>
<td>72  (19 : 81)</td>
</tr>
</tbody>
</table>

* Protons experiencing deshielding by changing the position of the carbon–bromine bond from anti to syn, and vice versa, are printed in blue.

2.3 Cyclization onto endocyclic double bonds

For investigating the stereoselectivity in intramolecular addition to endocyclic double bonds we examined bromocyclization of 3-[[2-(methylencyclocyclohex-1-en-4-yl)-methyloxy]-thiazolethione 1g (type D; section 3.1) and verbenylethanol-derived thiohydroxamate 1h (type E; section 3.2).

2.3.1 The (cyclohexen-4-yl)-methyloxy radical cyclization. (i) Methods of alkoxyl radical generation and product analysis. Photochemical and thermal reactions between 3-[[1-methylencyclohex-1-en-4-yl]-methyloxy]-thiazolethione 1g and bromotrichloromethane furnish the 5-exo-bromocyclized product 3g and substituted thiazole 2 (Table 8, entries 1 and 2).

Bicyclic tetrahydrofuran 3g forms at 80 °C as a 19/81-mixture of 1,2-cis/trans-stereoisomers. Resonances of protons in β- and γ-positions to the carbon–bromine bond experience a shift dispersion by ~0.5 ppm upon changing orientation of the bromosubstituent from anticlinal or antiperiplanar to synclinal (Table 8). We address this phenomenon to magnetic anisotropy induced by the carbon–bromine bond, possibly in combination with three nonbonding electron pairs at bromine.54

(ii) Stereocchemical guideline. Cyclohexenylmethylthoxy radical 1g cyclizes 2,4-cis-specifically (Scheme 5).

2.3.2 The verbenylethoxy radical cyclization. (i) Products from photochemical activation. Verbenylethanol-derived thiohydroxamate 1h furnishes tricyclic bromides 6 and 7 in a total yield of 61%, besides 79% of 2-(trichloromethylsulfanyl)-4-methylthiazole 2, when photolyzed in the presence of bromotrichloromethane (Scheme 6).

(ii) Stereocchemical guideline. Cyclohexenylethoxy radical 1h cyclizes cis-specifically (Scheme 7).

(iii) Verbenylethoxy radical chemistry. In extension to the chemistry summarized in this article, we propose that tricyclic products 6 and 7 arise from a sequence composed of intramolecular addition 1h ← cis-IIIh, ring-opening of cyclobutylmethyl radical cis-IIIh, and bromine atom trapping by rearranged radicals V and VI (Scheme 7). 1,2-Shifting of the methylene bridge releases cyclobutyl strain in radical cis-IIIh, leading to the secondary carbon radical V. For steric reasons, we expect trapping of the bicyclic radical V by bromotrichloromethane to occur from the concave face due to shielding of the convex side with the vicinal exo-oriented methyl group. The minor product 7, according to the proposed model, results from 1,2-shifting of the dimethylthene bridge cis-IIIh → VI and subsequent homolytic bromination.

2.4 Strain effects in alkoxyl radical additions

For estimating differences in energy barriers associated with 2,3-cis- and 2,3-trans-cyclization of type-E alkoxyl radicals, we modelled energetics associated with 5-exo-cyclization using electronic structure methods.55,56 The 2-(cyclohexen-3-yl)-ethyloxyl radical Ii, in this approach, served as a truncated model for the verbenyl-4-ethyloxyl radical 1h, while the 4-pentenoxyl radical 5-exo-cyclization Ij → Ijj and the methoxyl radical addition to the inner carbon of propene served as references (Schemes 8 and 9).

(i) Density functional theory. For computing ground state energies of radicals and energies of transition structures, we used Becke’s three parameter Lee–Young–Parr-hybrid functional (B3LYP)57,58 and Becke’s half and half Lee–Young–Parr hybrid functional (BHandHLYP)59 in combination with 6-31+G** and 6-311G**-basis sets.60 All selected density functional/basis set-combinations reproduce experimental stereo- and regioselectivity for oxygen radical addition to carbon–carbon double bonds with a precision coming close to the accuracy for determining experimental selectivity.8,14,17,52,60

(ii) Theoretical approach. For calculating equilibrium structures of conformationally flexible molecules and transition structures associated with radical addition to carbon–carbon double bonds we used an established strategy.5,14 According to theory, the 2-(cyclohexen-3-yl)-ethyloxyl radical Ii favors...
pseudo-equatorial (pe) positioning of the ethyloxyl radical side to pseudo-axial (pa), as expressed by a modelled 90/10-mixture of pe/pa-conformers of $I_i$ at 298 K (B3LYP/6-31+G**; ESI‡). Both conformers served as starting points for modeling 5-exo-cyclizations.

Equilibrium structures of propene, alkoxyl radicals $I_i$–$k$, cyclized radicals $II_j$–$j$, and the addition product $VIII$ lack in negative eigenvalues of second derivatives of energy-minimized wavefunctions. Transition structures TS–I and TS–VII show one imaginary frequency $i$, describing the trajectory of oxygen radical addition to the inner alkene carbon (Table 9).61 Attempts to localize a transition structure for the trans-5-exo-cyclization of conformer pa-$I_i$ led to TS$^1$-trans-$I_i$, already available from conformer pe-$I_i$.

(iii) Quality of the models. Computed wavefunctions characterizing equilibrium structures show expectation values for the spin operator $\langle S^2 \rangle$ close to 0.75 for oxygen and carbon radicals (ESI‡), as expected for doublet states. Wavefunctions describing transition structures show $\langle S^2 \rangle$-values of $\sim$0.77 for B3LYP-calculated intermediates and 0.82–0.84 for BHandHLYP-calculated transition structures (ESI†). The effect of spin contamination in BHandHLYP-calculated transition structures was discussed previously, but is not considered relevant for attaining reasonable precision in determining computed relative energies.52

(iv) Methoxyl radical addition to propene. Theory predicts a lower barrier for methoxyl radical addition to the terminal carbon than for addition to the inner carbon of propene ($\Delta G^\circ_{298} = -5.0 \text{ to } -8.5 \text{ kJ mol}^{-1}$; ESI‡). The decision to compare structure and energetics from the disfavored mode of addition to data obtained for monocycle and bicycle formation was guided by structural similarity between TS–$II_j$ and TS–VII on one side, and derived addition products $II_j$–$j$, $VIII$ on the other (Table 9, Schemes 8 and 9).

(v) Thermochemistry. Cyclization of the 2-(cyclohexen-3-yl)-ethyloxyl radical $I_i$ $\rightarrow$ $II_j$, according to zero-point energy corrected reaction energies (B3LYP/6-31+G**), is for all considered

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Scheme 6 Formation of bicyclic products from 3-(verbenylethoxy)-thiazole-2(3H)-thione $1h$.

Scheme 7 Proposed pathways for product formation from verbenyl-ethyloxyl radical $1h$ (type E; from $1h$).

Scheme 8 Structure formulas of radicals and intermediates associated with the 1-(cyclohexen-3-yl)-ethyl-2-oxyl radical 5-exo-cyclization (pe = pseudo-equatorial; pa = pseudo-axial; a = axial; eq = equatorial).
paths strongly exothermic (\(\Delta_{E} = -35 \text{ to } -47 \text{ kJ mol}^{-1}\)), pointing to a notable barrier for the reverse reaction, the \(\beta\)-fragmentation. Computed energetics for the addition \(\text{i} \rightarrow \text{ii}\) are similar to the values calculated for the 4-pentenoxyl radical ring closure \(\text{j} \rightarrow \text{ii}j\) (\(\Delta_{E} = -41 \text{ kJ mol}^{-1}\)) and are less exothermic than the methoxyl radical addition to the inner carbon of propene (\(\Delta_{E} = -53 \text{ mol}^{-1}\)). BHandHLYP-calculations provide similar trends for reaction energies, except for a stronger driving force for the intermolecular addition (Table 10).

(vii) Transition structures. The distance \(d\) between the radical oxygen and the attacked carbon, as predicted by B3LYP theory for transition structures of cyclohexenylethylxyl radical cyclization (2.04–2.08 Å), 4-pentenoxyl radical cyclization (2.05 Å) and methoxyl radical addition to propene (2.06 Å), is marginally wider than those obtained from BHandHLYP-calculations (1.98–2.02 Å; Table 9). Values for the angle \(a\) describing oxygen radical attack to the inner alkene carbon are grouped for all calculated transition structures in the range between 98 and 104 degrees, being more acute than the angle calculated for the highest in the energy transition structure TS-trans-\(\text{ii}\) (121–122 degrees; Table 9). Absolute values of improper torsion angles \(\omega\) for transition structures TS-\(\text{ii}\), TS-\(\text{ij}\), and TS-VIII, according to B3LYP- and BHandHLYP-theory, are close to 160 degrees, indicating the hybridization change at the attacked carbon from sp\(^2\) (\(\omega = 180^\circ\) for propene) toward sp\(^3\) (122° for propane).

Superimposing atomic coordinates of 4-pentenoxyl radical cores illustrates that density functional-calculated favored transition structures for the cyclohexenylethylxyl radical cyclization and the 4-pentenoxyl radical ring closure are nearly identical (Fig. 6). A \(2T_3\)-conformer, as predicted by theory for TS-cis-\(\text{ii}\) (\(2T_4\)), is separated by only 36 degrees from a \(2T_3\)-conformer in TS-\(\text{ij}\) (\(2T_3\)) on the pseudorotatory cycle of tetrahydrofurane.

(vii) Energy barriers. The barrier for 2,3-cis-cyclization of cyclohexenylethylxyl radical \(\text{ii}\) (\(\Delta_{E} = 17 \text{ kJ mol}^{-1}\)) is similar to the barrier predicted by B3LYP-theory for the 4-pentenoxyl radical 5-exo-cyclization (20 kJ mol\(^{-1}\)) and the methoxyl radical addition to propene (21 kJ mol\(^{-1}\)). BHandHLYP-computed barriers for 2,3-cis-cyclization of \(\text{ii}\) and 5-exo-cyclization of \(\text{ij}\) are higher, but generally show the same trends (Table 10).

The computed relative Gibbs free energy of activation for the 2,3-trans-mode of cyclization is 55 kJ mol\(^{-1}\) above the value for the lowest in the energy pathway of 2,3-cis-ring closure (B3LYP; 58 kJ mol\(^{-1}\) for BHandHLYP calculations using either the 6-31+G** or the 6-311G** basis set; ESI\(^*\)). A Gibbs free activation energy difference of 55 kJ mol\(^{-1}\) translates for a kinetically controlled reaction and a temperature of 298.15 K into a relative rate constant of \(4 \times 10^6\) in favor of the 2,3-cis-cyclization. Detecting a 2,3-trans-bromocyclized product with such a precision was beyond the capability of analytic instruments used in the study.

(viii) Marcus analysis. For analyzing strain and electronic effects on barriers of 5-exo-alkenoxyl radical cyclization, we split zero-point vibrational energy-corrected electronic barriers (\(\Delta_{E}^\ddagger\)) into an intrinsic (\(\Delta_{E}^\ddagger_i\)) and a thermodynamic term (\(\Delta_{E}^\ddagger_{TD}\)), using Marcus theory (Fig. 7, Table 10, eqn (1)–(3)).\(^{63–65}\) The intrinsic part describes contributions of strain and steric repulsion in a thermoneutral degenerated reaction to the barrier \(\Delta_{E}^\ddagger_i\) in a transition structure located half way on the reaction coordinate (\(x^2 = 0.5\) between reactant(s) (\(x = 0\)) and product(s) (\(x = 1\); Fig. 7). The thermodynamic part of the barrier \(\Delta_{E}^\ddagger_{TD}\) describes energy changes arising from incipient bond forming and bond breaking in a transition structure.

\[
\Delta_{E}^\ddagger_i = \frac{\Delta_{E}^\ddagger - \Delta_{E} \pm \sqrt{(\Delta_{E}^\ddagger)^2 - (\Delta_{E} - \Delta_{E}^\ddagger)}}{2}
\]

\[
x^2 = \frac{1}{2} \left(1 + \frac{\Delta_{E}}{4\Delta_{E}^\ddagger}\right)
\]

\[
\Delta_{E}^\ddagger = \Delta_{E}^\ddagger_i + \Delta_{E}^\ddagger_{TD}
\]
The role of the intrinsic barrier. Intrinsic barriers modeled for 2,3-cis-cyclization of cyclohexenylethyl radical II ($\Delta E^i = 35-37 \text{ kJ mol}^{-1}$, B3LYP; for BHandHLYP-calculated values, refer to Table 10) and 5-exo-cyclization of 4-pentenoxyl radical Ij ($37 \text{ kJ mol}^{-1}$) are marginally smaller than the intrinsic barrier for methoxyl radical addition to the inner carbon of propene ($43 \text{ kJ mol}^{-1}$). An intrinsic barrier of 90 kJ mol$^{-1}$ predicted for 2,3-trans-cyclization of the cyclohexenylethyl radical II exceeds the value for the barriers of all other investigated oxygen radical additions in the study by far. From this information we concluded that the thermodynamic barrier is not the key parameter for explaining the experimental 2,3-cis-specificity of verbenylenylethyl radical cyclization.

(x) The role of the thermodynamic barrier. In transition structures associated with alkoxyl radical addition to alkenes, incipient carbon–oxygen bond formation and carbon–carbon $\pi$-bond breaking in summary is exothermic, lowering the intrinsic barrier by a thermodynamic contribution of $-19$ to $-20$ kJ mol$^{-1}$. This thermodynamic barrier $\Delta E^T_H$ is surprisingly similar for 2,3-cis- and 2,3-trans-ring cyclization of cyclohexenylethyl radical II ($-16$ to $-20$ kJ mol$^{-1}$), the 4-pentenoxyl radical 5-exo-cyclization Ij $\rightarrow$ Ijj ($-18$ kJ mol$^{-1}$; B3LYP/6-31+G**), and the barrier for methoxyl radical addition to the inner carbon of propene ($-23$ kJ mol$^{-1}$). BHandHLYP-computed energies lead to more negative thermodynamic barriers, but show otherwise similar trends. From the data we concluded that the thermodynamic barrier is not the key parameter for explaining the experimental 2,3-cis-specificity of verbenylenylethyl radical cyclization.

Table 10 Zero-point vibrational energy-corrected activation energies ($\Delta E^i$), reaction energies ($\Delta_R E$), intrinsic energy barriers ($\Delta E^i$), thermodynamic contribution $\Delta E^T_H$ to $\Delta E^i$, free energy differences $[\Delta G^{298}\text{propene}] = G^{298}(\text{II}) - G^{298}(\text{III})$ or $\Delta G^{298} = [G^{298}(\text{II}) + G^{298}(\text{propene})] - G^{298}(\text{VIII})$ and approximated transition location $x^i$ for alkoxyl radical additions (Schemes 8 and 9, eqn (1)–(3)).

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Method</th>
<th>$\Delta E^i$/kJ mol$^{-1}$</th>
<th>$\Delta_R E$/kJ mol$^{-1}$</th>
<th>$\Delta E^i$:/kJ mol$^{-1}$</th>
<th>$\Delta E^T_H$/kJ mol$^{-1}$</th>
<th>$x^i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>pe-li $\rightarrow$ cis-IIi (ax)</td>
<td>B3LYP/6-31+G**</td>
<td>16.7</td>
<td>-44.1</td>
<td>35.4</td>
<td>-18.6</td>
<td>0.2</td>
</tr>
<tr>
<td>pe-li $\rightarrow$ trans-IIi</td>
<td>B3LYP/6-31+G**</td>
<td>73.1</td>
<td>-34.5</td>
<td>89.5</td>
<td>-16.4</td>
<td>0.4</td>
</tr>
<tr>
<td>pa-li $\rightarrow$ cis-IIi (eq)</td>
<td>B3LYP/6-31+G**</td>
<td>74.0</td>
<td>-33.7</td>
<td>117.7</td>
<td>-17.2</td>
<td>0.5</td>
</tr>
<tr>
<td>lj $\rightarrow$ IIj</td>
<td>B3LYP/6-31+G**</td>
<td>19.8</td>
<td>-40.5</td>
<td>37.3</td>
<td>-17.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Ik + propene $\rightarrow$ VIII</td>
<td>B3LYP/6-31+G**</td>
<td>20.5</td>
<td>-53.8</td>
<td>43.2</td>
<td>-22.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

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3. Concluding remarks

Cycloalkyl-fused and -bridged 4-pentenoxyl radicals provide bicyclic and tricyclic tetrahydropyrans by 5-exo-cyclizations. The selectivity determining step is the intramolecular oxygen radical addition to the carbon–carbon double bond, occurring in most instances with notable stereochemical preference. From the observed stereoselectivities we concluded that a system exists, which can be summed up by two new directives for predicting the stereochemical outcome of similar cyclizations not exemplified in this article. The new guidelines supplement the set of existing directives, developed for predicting the major products in synthesis of monocyclic dissubstituted tetrahydropyrans by the oxygen radical method.7,14,67

The first of the new guidelines ranks the hierarchy of two similarly sized sterioinductors by the distance between the alkyl group and the alkene carbon which is being approached by the oxygen radical. This guideline states that the substituent positioned the closest to the attacked alkene carbon is the principal (primary) inductor, guiding 5-exo-cyclization 2,3-trans- and 2,4-cis-selectively. The substituent bound further from the attacked x-bond is the secondary inductor, enhancing stereodifferentiation exerted by the principal inductor in the case of the trans-configuration, and decreasing this effect in the case of the cis-configuration. A secondary inductor is not able to overrule the guiding effect of a similarly sized primary inductor. The first guideline applies to 5-exo-cyclization of type-A and type-B 4-pentenoxyl radicals (Fig. 1).

The second new directive states that 4-pentenoxyl radical 5-exo-cyclization to a cyclohexene-bound exo-methylene group or an endocyclic double bond occurs cis-specifically. The second guideline refers to intramolecular addition of type-C-E radicals (Fig. 1).

From the hierarchy of similar-sized inductors we expect a substituent located in position 3 to also control the stereo- and selectivity in 5-exo-cyclization of 4-pentenoxyl radicals having similar sized substituents attached to carbons 1, 2, and 3. According to the first new guideline, a group in position 2 will be secondary and a group in position 1 the least effective, the tertiary inductor. From today’s point of view we expect the stereoisomer of a 1,2,3-substituted 4-pentenoxyl radical corresponding to an all-trans-configured type-A and type-B radical to cyclize with notable 2,3-trans-, 2,4-cis-, and 2,5-trans-selectivity, possibly providing a single diastereomer. In the same model, a sterically more demanding substituent in position 2, for example tert-butyl, should be able to overrule the effect of a smaller group in position 3, such as methyl. Stereochemical questions of this kind attracted our attention and are being pursued at the moment in our laboratory, with the aim to provide new solutions to synthesis of functionalized ethers from oxygen radical addition to alkenes.

4. Experimental

4.1. General

For general laboratory practice and instrumentation see ref. 42 and the ESL‡

4.2. General methods

4.2.1 3-Hydroxy-4-methylthiazole-2(3H)-thione tetraethylammonium salt (MTTO‘NET4). A solution of 3-hydroxy-4-methylthiazole-2(3H)-thione (MTTOH; 1.3 mmol) in methanol (2 mL) was treated at 20 °C with a 1.5 M solution of tetraethylammonium hydroxide in methanol (0.87 mL, 1.3 mmol) and stirred for 1 hour. The solvent was removed under reduced pressure and the residue was freeze-dried for 12–14 hours.

4.2.2 Synthesis of O-alkenylthiohydroxamates. A suspension of 3-hydroxy-4-methylthiazole-2(3H)-thione tetraethylammonium salt (1.3 mmol) in anhydrous dimethyl formamide (1 mL) was treated at 20 °C with a solution of an alkyl p-toluenesulfonate (1 mmol) in anhydrous dimethyl formamide (1 mL) for the time span specified in section 3. The resulting solution was stirred at 20 °C or 40-50 °C (for specific information, see synthetic procedures in section 4.3) diluted with dichloromethane (10 mL) and washed with an aqueous 2 M solution of sodium hydroxide (10 mL) and water (3 × 10 mL). The organic layer was separated, dried (MgSO4), and concentrated under reduced pressure to leave a residue, which was purified by chromatography (SiO2) or crystallized (solvent specification in section 4.3).

4.3 3-Alkenoxy-4-methylthiazole-2(3H)-thiones

4.3.1 3-[cis-2-{Prop-2-en-1-yl}-cyclopent-1-yloxy]-4-methylthiazole-2(3H)-thione cis-(1a). From trans-2-{prop-2-en-1-yl}-cyclopent-1-yl 4-toluenesulfonate (4.22 g, 15.1 mmol); reaction time: 72 hours at 20 °C, the eluent used for chromatography: dichloromethane–pentane = 2:1 (v/v); Rf = 0.51. Yield: 2.67 g (10.5 mmol, 70%), colorless oil.16 1H-NMR (CDCl3, 600 MHz) δ 1.60–1.75 (m, 3 H), 1.80–1.84 (m, 1 H), 1.87–1.93 (m, 2 H), 2.03–2.06 (m, 1 H), 2.22 (d, J = 1.2 Hz, 3 H), 2.22–2.27 (m, 1 H), 2.67–2.71 (m, 1 H), 4.99–5.01 (m, 1 H), 5.08 (dq, Jd = 17.0, J = 1.7 Hz, 1 H), 5.74–5.77 (m, 1 H), 5.98–6.05 (m, 1 H), 6.16 (q, J = 0.9 Hz, 1 H). 13C-NMR (CDCl3, 150 MHz) δ 13.8, 21.9, 29.2, 29.3, 30.1, 45.2, 88.2, 102.9, 115.4, 137.9, 139.2, 181.0. UV (methanol): λmax (lg ε mol−1 cm−1) 319 nm (3.14), 210 nm (3.05). Anal. Caled for C12H17NOS2: C, 56.43; H, 6.71; N, 5.48; S, 25.11. Found: C, 56.48; H, 6.56; N, 5.68; S, 25.27.

4.3.2 3-[trans-2-{Prop-2-en-1-yl}-cyclopent-1-yloxy]-4-methylthiazole-2(3H)-thione trans-(1a). From cis-2-{prop-2-en-1-yl}-cyclopent-1-yl 4-toluenesulfonate (1.85 g, 6.60 mmol); reaction time: 1 hour at 45 °C; the eluent used for chromatography: diethyl ether–pentane = 1:1 (v/v); Rf = 0.38. Yield: 1.13 g (4.42 mmol, 67%), yellow oil.16 1H-NMR (CDCl3, 400 MHz) δ 1.28–1.37 (m, 1 H), 1.67–1.84 (m, 3 H), 1.86–1.93 (m, 1 H), 1.98–2.09 (m, 1 H), 2.21–2.30 (m, 2 H), 2.24 (d, Jf = 1.2 Hz, 3 H), 2.22–2.27 (m, 1 H), 4.97–5.05 (m, 2 H), 5.43–5.46 (m, 1 H), 5.78 (ddt, Jf = 17.0, 10.2, 6.8 Hz, 1 H), 6.16 (q, Jf = 1.4 Hz, 1 H). 13C-NMR (CDCl3, 100 MHz) δ 14.1, 23.2, 30.4, 30.6, 37.6, 43.7, 83.07 | 8299
92.1, 102.9, 116.3, 136.4, 138.8, 181.0. UV (methanol): \( \lambda_{\text{max}} \) (lg ε/mol·l\(^{-1}\)) 319 nm (3.17), 208 nm (3.09). Anal. Caled for C\(_{13}\)H\(_{19}\)NOS\(_2\) (269.42): C, 57.96; H, 7.11; N, 5.48; S, 25.11; Found: C, 56.49; H, 6.85; N, 5.46; S, 24.96.

4.3.3 \( \text{[cis-2-(3-Methylbut-2-en-1-yl)cyclopent-1-yl]-4-methylthiazole-2(3H)-thione cis (1b).} \) From \( \text{[trans-2-(3-methylbut-2-en-1-yl)cyclopent-1-yl]-4-toluenesulfonate (2.48 g, 8.04 mmol); reaction time: 21 hours at 20 °C; the eluent used for chromatography: diethyl ether–pentane = 1 : 2 (v/v), } R_f = 0.30. Yield: 1.49 g (5.26 mmol, 65%), colorless oil. \( ^{1}H\)-NMR (CDCl\(_3\), 400 MHz) \( \delta \) 1.59–1.76 (m, 3 H), 1.64 (s, 3 H), 1.71 (s, 3 H), 1.77–2.03 (m, 4 H), 2.18–2.30 (m, 1 H), 2.23 (d, \( J = 1.4 \) Hz, 1 H), 2.47–2.59 (m, 1 H), 3.53 (ddt, \( J_d = 7.9, 6.5, J_f = 1.5 \) Hz, 1 H), 5.72 (td, \( J_d = 4.5, J_f = 1.7 \) Hz, 1 H), 6.15 (d, \( J = 1.4 \) Hz, 1 H). \( ^{13}C\)-NMR (CDCl\(_3\), 100 MHz) \( \delta \) 13.5, 17.9, 21.9, 25.8, 27.1, 29.1, 29.4, 46.0, 88.5, 102.8, 123.5, 132.0, 181.0. UV (methanol): \( \lambda_{\text{max}} \) (lg ε/mol·l\(^{-1}\)) 210 nm (3.20), 207 nm (3.16).

4.3.4 \( \text{[cis-2-(Prop-2-en-1-yl)cyclohex-1-ylmethyl]-4-methylthiazole-2(3H)-thione cis (1c).} \) From \( \text{[trans-2-(prop-2-en-1-yl)cyclohex-1-ylmethyl]-4-toluenesulfonate (650 mg, 2.20 mmol); reaction time: 3 h at 40 °C; the eluent used for chromatography: diethyl ether–pentane = 1 : 2 (v/v), } R_f = 0.31. Yield: 466 mg (1.73 mmol, 79%), yellow oil, which crystallizes from diethyl ether to afford colorless crystals. M.p. = 51–52 °C.

4.3.5 \( \text{[trans-2-(Prop-2-en-1-yl)cyclohex-1-yl]-4-methylthiazole-2(3H)-thione trans (1d).} \) From \( \text{[trans-2-(prop-2-en-1-yl)cyclohex-1-yl]-4-toluenesulfonate (2.72 g, 8.44 mmol); reaction time: 2 hours at 45 °C; the eluent used for chromatography: diethyl ether–pentane = 1 : 2 (v/v), } R_f = 0.31. Yield: 761 mg (2.56 mmol, 78%), colorless oil, colorless crystals on standing at 20 °C. M.p. = 51–52 °C.

4.3.6 \( \text{[cis-2-(Eth-1-en-1-yl)cyclohex-1-ylmethyl]-4-methylthiazole-2(3H)-thione cis (1d).} \) From \( \text{[cis-2-(eth-1-en-1-yl)cyclohex-1-ylmethyl]-4-toluenesulfonate (2.72 g, 8.44 mmol); reaction time: 2 hours at 45 °C; the eluent used for chromatography: diethyl ether–pentane = 1 : 2 (v/v), } R_f = 0.31. Yield: 1.86 g (6.25 mmol, 74%), yellow oil, which crystallized from ethyl acetate to afford a colorless solid. M.p. = 47–48 °C.

4.3.7 \( \text{[trans-2-(Eth-1-en-1-yl)cyclohex-1-ylmethyl]-4-methylthiazole-2(3H)-thione trans (1e).} \) From \( \text{[trans-2-(ethyl-1-en-1-yl)cyclohex-1-ylmethyl]-4-toluenesulfonate (650 mg, 2.20 mmol); reaction time: 4 hours at 45 °C; the eluent used for chromatography: diethyl ether–pentane = 1 : 2 (v/v), } R_f = 0.31. Yield: 316 mg (1.25 mmol, 78%), colorless oil, colorless crystals on standing at 20 °C. M.p. = 78 °C.

4.3.8 \( \text{[trans-2-(2-Methylprop-1-en-1-yl)cyclohex-1-ylmethyl]-4-methylthiazole-2(3H)-thione trans (1e).} \) From \( \text{[trans-2-(2-methylprop-1-en-1-yl)cyclohex-1-ylmethyl]-4-toluenesulfonate (1.06 g, 3.28 mmol); reaction time: 4 hours at 50 °C; the eluent used for chromatography: diethyl ether–pentane = 1 : 2 (v/v), } R_f = 0.31. Yield: 61 mg (2.56 mmol, 78%), colorless oil, colorless crystals on standing at 20 °C. M.p. = 78 °C.
1.5 Hz, 1 H), 6.12 (d, J = 1.5 Hz, 1 H). 13C-NMR (CDCl3, 100 MHz) δ 13.2, 18.1, 25.6, 25.7, 25.8, 29.9, 33.4, 38.7, 42.1, 79.5, 102.5, 128.8, 131.7, 137.8, 180.2. UV (methanol): λmax (lg ε/mmol^(-1) cm^-1) 317 nm (3.13), 209 nm (3.02). Anal. Calcd for C16H23NOS2 (309.49): C, 62.09; H, 7.49; N, 4.53; S, 21.47.

4.4.3 3-[2-(1-Methylene-cyclohex-2-yl)-ethyl-1-yl-2-oxo]-4-methyl-thiazole-2(3H)-thione (1f). From [2-(1-methylene-cyclohex-2-yl)-ethyl] 4-toluenesulfonate (3.60 mg, 12.2 mmol); reaction time: 1 hour at 50 °C; the eluent used for chromatography: diethyl ether–pentane = 1:1 (v/v); Rf = 0.39. Yield: 2.57 g (9.54 mmol, 78%). yellow oil. 1H-NMR (CDCl3, 400 MHz) δ 1.25–1.38 (m, 1 H), 1.42–1.55 (m, 2 H), 1.56–1.74 (m, 2 H), 1.76–1.89 (m, 2 H), 2.03 (dd, J = 13.0, 8.5, 4.5 Hz, 1 H), 2.14 (td, Jt = 14.1, Jd = 7.2 Hz, 1 H), 2.20–2.39 (m, 2 H), 2.27 (d, J = 1.2 Hz, 3 H), 4.38 (q, J = 7.3 Hz, 1 H), 4.45 (q, J = 7.3 Hz, 1 H), 4.60 (s, 1 H), 4.70 (s, 1 H), 6.15 (d, J = 1.2 Hz, 1 H). 13C-NMR (CDCl3, 100 MHz) δ 13.4, 24.1, 28.6, 30.0, 34.0, 34.7, 39.4, 74.8, 102.6, 106.1, 137.7, 151.6, 180.3. UV (methanol): λmax (lg ε/mmol^(-1) cm^-1) 316 nm (3.18), 206 nm (3.10). Anal. Calcd for C11H13N2OS2 (269.42): C, 57.76; H, 7.12; N, 5.20; S, 23.08. Found: C, 57.74; H, 7.12; N, 5.14; S, 29.33.

4.4.4 Conversion of 3-[[1S,4S,5R]-2,6,6-Trimethyl-bicyclo[3.1.1]hept-2-en-4-yl]-eth-1-yl-2-oxo]-4-methyl-thiazole-2(3H)-thione (1h). From [2-[[1S,4S,5R]-2,6,6-trimethylbicyclo[3.1.1]hept-2-en-4-yl]-ethyl] 4-toluenesulfonate (686 mg, 2.05 mmol); reaction time: 20 hours at 20 °C; the eluent used for chromatography: diethyl ether–pentane = 1:2 (v/v); Rf = 0.28. Yield: 463 mg (1.50 mmol, 73%) colorless oil, which crystallizes on standing at 20 °C. [δ]D^25 = −52.9 (c = 1.02/ethanol). 1H-NMR (CDCl3, 600 MHz) δ 0.86 (s, 3 H), 1.15 (d, J = 9.0 Hz, 1 H), 1.29 (s, 3 H), 1.67 (t, J = 1.7 Hz, 3 H), 1.79 (dq, Jd = 14.0, Jq = 7.0 Hz, 1 H), 1.89 (dq, Jd = 13.8 Hz, Jq = 6.9 Hz, 1 H), 1.95–2.05 (m, 2 H), 2.21 (dt, Jd = 8.8, Je = 5.6 Hz, 1 H), 2.28 (d, J = 1.0 Hz, 3 H), 2.48–2.57 (m, 1 H), 4.41–4.52 (2 H, 1 H), 6.19 (d, J = 0.8 Hz, 1 H), 6.15 (d, J = 1.0 Hz, 1 H). 13C-NMR (CDCl3, 150 MHz) δ 13.5, 20.4, 22.9, 26.5, 27.8, 31.6, 36.4, 40.8, 45.1, 47.6, 75.0, 102.7, 119.3, 137.7, 145.5, 180.4. Anal. Calcd for C14H13N2OS2 (309.49): C, 62.09; H, 7.49; N, 4.53; S, 20.72; Found: C, 61.81; H, 7.51; N, 4.46; S, 21.09.

4.4 Alkyl radical reactions

4.4.1 Photochemical reactions. A solution of 3-alkoxythiazolthione 1 (1.00 mmol, cle = 0.17 M) and BrCCL3 (10 mmol, cleBrCCl3 = 1.67 M) in dry C6H6 (6 mL) was photolyzed at ~25 °C in a Rayonet® chamber reactor equipped with twelve 350 nm illuminants, until the starting material was completely consumed (~30 min, tlc). The solution was concentrated under reduced pressure (10 mbar, 40 °C) to leave an oil, which was purified by chromatography (SiO2).

4.4.2 Thermal reactions. A solution of 3-alkoxythiazolthione 1 (1.00 mmol, cle = 0.17 M), BrCCL3 (10 mmol, cleBrCCl3 = 1.67 M), and AIBN (25 mol%) in dry C6H6 (6 mL) was heated to 80 °C for 30 min. After complete consumption of 1 (tlc), the solvent was removed under reduced pressure (10 mbar, 40 °C) to leave a residue, which was purified by chromatography (SiO2).

4.4.3 Conversion of 3-[[cis-2-[(prop-2- en-1-yl)- cyclopent-1-yl]-4-methylthiazole-2(3H)-thione cис(1a). Photochemical reaction. cis-1a 528 mg (2.07 mmol); the eluent used for column chromatography: diethyl ether–pentane = 1:5 (v/v). 3-Bromomethyl-2-oxabicyclo[3.3.0]octane cis-3a. Yield: 42.3 mg (206 mmol, 10%), yellow liquid, 70%–30-mixture of 1,3-cis-trans-isomers, i.e. rel(1S,3R,5S)=3a/rel(1S,3R,5S)=3a. Rf = 0.48 for diethyl ether–pentane = 1:5 (v/v). Anal. Calcd for C15H23N2OS2 (341.43): C, 62.76; H, 7.94; N, 5.29; S, 24.07. Found: C, 62.73; H, 7.87; N, 5.28; S, 24.03.

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Like-5,7-dibromo-9,9,9-trichloronorannul. Yield: 36.8 mg (91.2 μmol, 11%), yellow liquid. 8. H-NMR (CDCl3, 100 MHz) δ 1.75-2.05 (m, 4 H), 2.40-2.67 (m, 4 H), 3.23 (dd, J = 15.9, 4.8 Hz, 1 H), 3.47 (dd, J = 16.0, 5.3 Hz, 1 H), 4.18-4.29 (m, 1 H), 4.37 (ddt, J = 8.0, 6.6, J= 5.1 Hz, 1 H), 9.80 (t, J = 1.5 Hz, 1 H). 11C-NMR (CDCl3, 100 MHz) δ 19.6, 35.8, 42.9, 44.8, 48.3, 51.9, 62.3, 96.6, 201.5. HRMS (EI+) m/z 408.8282/408.8250 (M – H); calculated mass for C9H15BrO2: 408.8281/408.8261. Like-5,7-dibromo-9,9,9-trichloronorannul. Yield: 192.5 mg (47.6 μmol, 5%), yellow liquid. Unlike-5,7-dibromo-9,9,9-trichloronorannul. Yield: 34.1 mg (84.5 μmol, 9%), yellow liquid.

Conversion of 3-cis-2-(3-methylbut-2-en-1-yl)-cyclo-1-lyoxy)-4-methylthiazole-2(3H)-thione cis-(1b). Photochemical reaction. cis-1b 296 mg (1.04 μmol); eluent used for column chromatography: diethyl ether-pentane = 1:5 (v/v). 3-(2-Bromoprop-2-yl)-2-oxabicyclo[3.3.0]octane cis-3b. Yield: 119 mg (510 μmol, 49%), 64/36-mixture of 1,3-cis/trans-isomers, i.e. rel-(1S,3S,5S)-3b-rel-(1S,3R,5S)-3a. 4-Methyl-2-(trichloromethylsulfanyl)-thiazole (2). Yield: 146 mg (1800 μmol, 87%), yellow liquid. 5-Bromoc-7-enal (4a). Yield: 230 mg (1.12 mmol, 54%), yellow liquid.
i.e. rel-(1R,6S,8S)-3c-rel-(1R,6S,8R)-3c, colorless liquid. R₁ = 0.50 for diethyl ether-pentane = 1 : 5 (v/v).

\( \text{rel-(1R,6S,8S)-3c: H-NMR (CDCl}_3, 400 \text{ MHz}) \delta 1.04-1.58 \text{ (m, 6 H), 1.67-2.13 \text{ (m, 5 H), 3.11 (dt, } J = 3.7 \text{ Hz, } J_t = 10.4 \text{ Hz, 1 H), 3.34 (dd, } J = 6.7, 10.1 \text{ Hz, 1 H), 3.42 (dd, } J = 4.9, 10.1 \text{ Hz, 1 H), 4.20-4.24 \text{ (m, 1 H).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 24.2, 25.7, 28.9, 31.2, 35.3, 36.3, 43.9, 76.7, 84.5. \text{rel-(1R,6S,8R)-3c: H-NMR (CDCl}_3, 400 \text{ MHz }) \delta 1.08-1.53 \text{ (m, 6 H), 2.18-2.24 \text{ (m, 1 H), 1.69-2.12 (m, 4 H), 3.23 (dt, } J = 4.0 \text{ Hz, } J_t = 10.4 \text{ Hz, 1 H), 3.41 (dd, } J = 6.5, 10.1 \text{ Hz, 1 H), 3.50 (ddd, } J = 5.3, 10.1 \text{ Hz, 1 H), 4.24-4.30 \text{ (m, 1 H).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 24.2, 25.5, 28.8, 31.3, 36.7, 37.1, 46.3, 77.3, 83.3. \text{Thermal reaction. cis-1c 111 mg (412 µmol); eluent used for chromatography: diethyl ether-pentane = 1 : 5 (v/v).} \)

\( \text{8-(Bromomethyl)-7-oxabicyclo[4.3.0]nonane trans-(3c). Yield: 63.1 mg (288 µmol, 70%).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 1.08-1.53 \text{ (m, 6 H), 2.18-2.24 (m, 1 H), 1.69-2.12 \text{ (m, 4 H), 3.23 (dt, } J = 4.0 \text{ Hz, } J_t = 10.4 \text{ Hz, 1 H), 3.41 (dd, } J = 6.5, 10.1 \text{ Hz, 1 H), 3.50 (ddd, } J = 5.3, 10.1 \text{ Hz, 1 H), 4.24-4.30 \text{ (m, 1 H).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 24.2, 25.5, 28.8, 31.3, 36.7, 37.1, 46.3, 77.3, 83.3. \text{Thermal reaction. cis-1c 111 mg (412 µmol); eluent used for chromatography: diethyl ether-pentane = 1 : 5 (v/v).} \)

\( \text{8-(Bromomethyl)-7-oxabicyclo[4.3.0]nonane trans-(3c). Yield: 63.1 mg (288 µmol, 70%).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 1.08-1.53 \text{ (m, 6 H), 2.18-2.24 (m, 1 H), 1.69-2.12 (m, 4 H), 3.23 (dt, } J = 4.0 \text{ Hz, } J_t = 10.4 \text{ Hz, 1 H), 3.41 (dd, } J = 6.5, 10.1 \text{ Hz, 1 H), 3.50 (ddd, } J = 5.3, 10.1 \text{ Hz, 1 H), 4.24-4.30 \text{ (m, 1 H).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 24.2, 25.5, 28.8, 31.3, 36.7, 37.1, 46.3, 77.3, 83.3. \text{Thermal reaction. cis-1c 111 mg (412 µmol); eluent used for chromatography: diethyl ether-pentane = 1 : 5 (v/v).} \)

\( \text{8-(Bromomethyl)-7-oxabicyclo[4.3.0]nonane trans-(3c). Yield: 63.1 mg (288 µmol, 70%).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 1.08-1.53 \text{ (m, 6 H), 2.18-2.24 (m, 1 H), 1.69-2.12 (m, 4 H), 3.23 (dt, } J = 4.0 \text{ Hz, } J_t = 10.4 \text{ Hz, 1 H), 3.41 (dd, } J = 6.5, 10.1 \text{ Hz, 1 H), 3.50 (ddd, } J = 5.3, 10.1 \text{ Hz, 1 H), 4.24-4.30 \text{ (m, 1 H).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 24.2, 25.5, 28.8, 31.3, 36.7, 37.1, 46.3, 77.3, 83.3. \text{Thermal reaction. cis-1c 111 mg (412 µmol); eluent used for chromatography: diethyl ether-pentane = 1 : 5 (v/v).} \)

\( \text{8-(Bromomethyl)-7-oxabicyclo[4.3.0]nonane trans-(3c). Yield: 63.1 mg (288 µmol, 70%).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 1.08-1.53 \text{ (m, 6 H), 2.18-2.24 (m, 1 H), 1.69-2.12 (m, 4 H), 3.23 (dt, } J = 4.0 \text{ Hz, } J_t = 10.4 \text{ Hz, 1 H), 3.41 (dd, } J = 6.5, 10.1 \text{ Hz, 1 H), 3.50 (ddd, } J = 5.3, 10.1 \text{ Hz, 1 H), 4.24-4.30 \text{ (m, 1 H).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 24.2, 25.5, 28.8, 31.3, 36.7, 37.1, 46.3, 77.3, 83.3. \text{Thermal reaction. cis-1c 111 mg (412 µmol); eluent used for chromatography: diethyl ether-pentane = 1 : 5 (v/v).} \)

\( \text{8-(Bromomethyl)-7-oxabicyclo[4.3.0]nonane trans-(3c). Yield: 63.1 mg (288 µmol, 70%).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 1.08-1.53 \text{ (m, 6 H), 2.18-2.24 (m, 1 H), 1.69-2.12 (m, 4 H), 3.23 (dt, } J = 4.0 \text{ Hz, } J_t = 10.4 \text{ Hz, 1 H), 3.41 (dd, } J = 6.5, 10.1 \text{ Hz, 1 H), 3.50 (ddd, } J = 5.3, 10.1 \text{ Hz, 1 H), 4.24-4.30 \text{ (m, 1 H).} \)

\( \text{13}^C\text{-NMR (CDCl}_3, 100 \text{ MHz }) \delta 24.2, 25.5, 28.8, 31.3, 36.7, 37.1, 46.3, 77.3, 83.3. \text{Thermal reaction. cis-1c 111 mg (412 µmol); eluent used for chromatography: diethyl ether-pentane = 1 : 5 (v/v).} \)
4.10 Conversion of 3-[cis-2-(2-methylprop-2-en-1-yl)cyclohex-1-ylmethyl]oxy-4-methylthiazole-2(3H)-thione cis(1e).

Photochemical reaction. cis-1e 161 mg (541 μmol); eluent used for chromatography: diethyl ether-pentane = 1:10 (v/v). Yield: 107 mg (433 μmol, 80%), i.e. rel-(1R,6S,7S)-3e, pale yellow liquid. Rf = 0.48 for diethyl ether-pentane = 1:10 (v/v).

1H-NMR (CDCl3, 600 MHz) δ 1.32–1.43 (m, 2 H), 1.45–1.55 (m, 3 H), 1.59–1.67 (m, 2 H) 1.68–1.76 (m, 7 H), 2.25–2.33 (m, 2 H) 3.63–3.69 (m, 2 H), 3.91 (dd, J = 8.2, 5.9 Hz, 1 H). 13C-NMR (CDCl3, 100 MHz) δ 23.1 (CH3, HMQC), 25.2, 28.1, 30.1, 30.9, 38.6, 40.3, 69.9, 72.6, 90.1. Anal. Calcld for C11H19BrO (247.17): C, 53.45; H, 7.75; Found: C, 53.32; H, 7.59. 4-Methyl-2-(trichloromethylsulfanyl)-thiazole (2). Yield: 110 mg (443 μmol, 82%), pale yellow liquid. Thermal reaction: cis-1e 151 mg (508 μmol); eluent used for chromatography: diethyl ether-pentane = 1:10 (v/v). 7-(2-Bromoprop-2-yl)-8-oxabicyclo[4.3.0]nonane cis(3e).

Yield: 119 mg (481 μmol, 95%), i.e. rel-(1R,6S,7S)-3e, pale yellow liquid. 4-Methyl-2-(trichloromethylsulfanyl)-thiazole (2). Yield: 114 mg (460 μmol, 90%), colorless liquid.

4.11 Conversion of 3-[trans-2-(2-methylprop-2-en-1-yl)cyclohex-1-ylmethyl]oxy-4-methylthiazole-2(3H)-thione trans(1e).

Photochemical reaction. trans-1e 140 mg (471 μmol); eluent used for chromatography: diethyl ether-pentane = 1:10 (v/v). 7-(2-Bromoprop-2-yl)-8-oxabicyclo[4.3.0]nonane trans(3e).

Yield: 94.4 mg (382 μmol, 81%), i.e. rel-(15S,6S,7S)-3e, colorless liquid. Rf = 0.39 for diethyl ether-pentane = 1:10 (v/v).

1H-NMR (CDCl3, 400 MHz) δ ppm 1.04–1.35 (m, 4 H) 1.46–1.58 (m, 1 H) 1.68–1.91 (m, 4 H) 1.74 (s, 3 H) 1.77 (s, 3 H) 2.06–2.14 (m, 1 H) 3.37 (dd, d = 11.3, 7.4 Hz, 1 H), 3.44 (dd, J = 9.2 Hz, 1 H) 3.92 (t, t = 7.1 Hz, 1 H). 13C-NMR (CDCl3, 150 MHz) δ 25.3, 25.9, 27.3, 30.5, 30.7, 31.0, 47.2, 47.8, 69.3, 72.1, 89.4. Anal. Calcld for C11H13BrO (247.17): C, 53.45; H, 7.75; Found: C, 53.62; H, 7.82. 4-Methyl-2-(trichloromethylsulfanyl)-thiazole (2). Yield: 92.4 mg (372 μmol, 79%), colorless liquid. Thermal reaction. trans-1e 147 mg (495 μmol); eluent used for chromatography: diethyl ether-pentane = 1:10 (v/v).

7-(2-Bromoprop-2-yl)-8-oxabicyclo[4.3.0]nonane trans(3e).

Yield: 115 mg (465 μmol, 94%), i.e. rel-(1S,6S,7S)-3e, colorless liquid. 4-Methyl-2-(trichloromethylsulfanyl)-thiazole (2). Yield: 120 mg (483 μmol, 98%), colorless liquid.

4.12 Conversion of 3-[2-(1-methylecyclohex-2-yl)-ethyl-oxo]-4-methylthiazole-2(3H)-thione (1f).

Photochemical reaction. 1f 275 mg (1.02 mmol); eluent used for chromatography: diethyl ether-pentane = 1:10 (v/v). Yield: 243 mg (977 μmol, 98%), colorless liquid. 91/9-mixture of exo/endo-isomers 7-Bromomethyl-[8-oxabicyclo[4.3.0]nonane trans(3d) and 2-Bromo-4-oxabicyclo[4.4.0]decanes trans(5d).

Yield: 168 mg (767 μmol, 77%), 90/10-mixture of 6,7-cis/6,7-trans-isomers, i.e. rel-(1S,6S,7R)-3d/rel-(1S,6S,7S)-3d and rel-(1S,2R,6S)-5d, pale yellow liquid.

4.13 Conversion of 3-[1-(cyclohex-1-yl)-4-methylthiazole-2(3H)-thione (1g).

Photochemical reaction. 1g 536 mg (2.10 mmol); eluent used for chromatography: diethyl ether-acetone-pentane = 1:1:15 (v/v/v). Yield: 213 mg (1.04 mmol, 50%), pale yellow liquid. Rf = 0.46 for diethyl ether-acetone-pentane = 1:1:15 (v/v/v).

1H-NMR (CDCl3, 400 MHz) δ 1.48–1.57 (m, 1 H) 1.77 (s, 3 H) 1.79–1.89 (m, 1 H) 1.90–1.96 (m, 1 H) 1.97–2.06 (m, 1 H) 2.33–2.39 (m, 1 H) 2.58 (d, J = 11.9 Hz, 1 H) 3.73–3.88 (m, 2 H) 4.10 (d, J = 5.8 Hz, 1 H). 13C-NMR (CDCl3, 100 MHz) δ 26.8, 32.3, 33.9, 35.4, 36.4, 67.9, 72.3, 83.0. Anal. Calcld for C9H12BrO (205.09): C, 46.85; H, 6.39; Found: C, 46.74; H, 6.36. 4-Methyl-2-(trichloromethylsulfanyl)-thiazole (2).

Yield: 358 mg (1.44 mmol, 69%), pale yellow liquid. Rf = 0.35 for diethyl ether-acetone-pentane = 1:1:1:15 (v/v/v/v).

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δ(1H) -0.85 (d, J = 11.2, 8.1, 6.4, 0.9 Hz, 1 H), 0.93 (s, 1 H), 1.05 (s, 1 H), 1.15 (s, 3 H), 3.13 (dd, J = 11.1, 1.7 Hz, 1 H), 1.35–1.41 (m, 1 H), 1.55 (dd, J = 11.3, 1.3 Hz, 1 H), 1.60 (s, 1 H), 2.04 (dddd, J = 12.1, 9.5, 5.8, 1.3 Hz, 1 H), 2.60–2.66 (m, 1 H), 3.40 (dd, J = 11.1, 8.6, 5.9 Hz, 1 H), 3.79 (s, 1 H), 3.88–3.97 (m, 2 H). 13C-NMR (CDCl3, 100 MHz): δ 15.4, 25.9, 30.3, 31.8, 34.9, 40.5, 41.8, 50.9, 53.4, 67.9, 72.1, 83.4. HRMS (EI) m/z 258.0612 (M+); calculated mass for C13H19OBr: 258.0442 260. 4-Methyl-2-(trichloromethylsulfonyl)-thiazole (2). Yield: 193 mg (774 μmol, 79%), colorless liquid. rel-1S,2S,6S,7S,9S-9-bromo-1,2,3,4,5,6,7,8,9,10-trimethyl-3-oxatricyclo[5.2.1.02,9]decane (7). Yield: 7.7 mg (3%). 1H-NMR (CDCl3, 400 MHz) δ 0.93 (s, 3 H), 1.05 (s, 6 H), 1.81–2.04 (m, 4 H), 2.32–2.42 (m, 1 H), 3.01 (tttd, J = 9.7, 4.7, J = 1.4 Hz, 1 H), 3.83–3.93 (m, 1 H), 4.30 (dd, J = 11.2, 5.8, 1.7 Hz, 1 H), 4.35–4.44 (m, 2 H). 13C-NMR (CDCl3, 100 MHz) δ 13.8, 20.4, 20.5, 26.0, 31.2, 43.0, 47.2, 51.8, 53.2, 53.8, 71.7, 91.2. HRMS (EI) m/z 258.0612/260.0612 (M+); calculated mass for C13H19OBr: 258.0619/260.0599.

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Notes and references


For 2-(3-methylbut-2-en-1-yl)-cyclopentan-1-ol: L. Streinz

For 2-(prop-2-en-1-yl)cyclopentan-1-ol: S. Baskaran, I. Islam


For 2-{(1-
