Ring Closure Reactions of Substituted 4-Pentenyl-1-oxy Radicals. The Stereoselective Synthesis of Functionalized Disubstituted Tetrahydrofurans†

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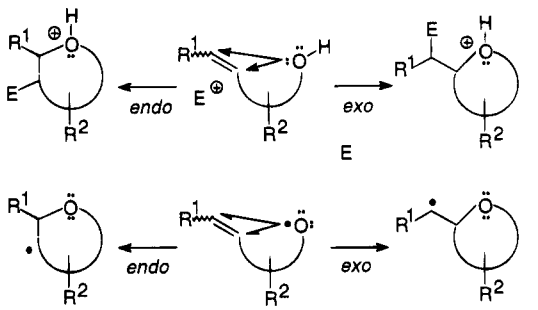
N-(Alkyloxy)pyridine-2(1*H*)-thiones **3** and benzenesulfenic acid *O*-esters **5** have been synthesized from substituted 4-pentenols **1** or the derived tosylates. Compounds **3** and **5** are efficient sources of *free* alkoxy radicals **6** which undergo synthetically useful fast ring closure reactions **6** → **8** [k^{exo} = (2 ± 1) × 10^8 s^{-1} to (6 ± 2) × 10^9 s^{-1} (T = 30 ± 0.2 °C)]. Tetrahydrofurfuryl radicals **8** can be trapped with, e.g., hydrogen or chlorine atom donors to afford either *trans*- or *cis*-disubstituted tetrahydrofurans **10** or **12** depending on the substitution pattern of the 4-pentenyloxy radical. Substituted tetrahydropyrans **11** or **13** are formed in the minor 6-*endo-trig* cyclization. According to the data of competition kinetics, the observed stereoselectivities in *free* alkoxy radical cyclizations arise from steric interactions between the substituents in the transition state of the ring closure reactions. Alkyl substituents cause small differences in the measured relative rate constants of 5-*exo* cyclizations which are reminiscent of the data obtained from the rearrangements of alkyl-substituted 5-hexenyl radicals. Likewise, a stereochemical model for oxygen radical cyclization is proposed where the pentenyloxy chain adopts a six-membered, chairlike transition state with the alkyl substituents preferentially situated in the pseudoequatorial positions leading to 2,5-*trans*-, 2,4-*cis*-, and 2,3-*trans*-substituted tetrahydrofurfuryl radicals **8** as the major intermediates.

Introduction

The substituted tetrahydrofuran nucleus plays an important role in antibiotically active compounds,[1] as a building block in organic synthesis,[2] chiral auxiliary,[3] or as the structural unit of metabolites in marine biology.[4] In spite of the synthetic efforts of several groups the stereoselective synthesis of this class of compounds from simple precursors is still a challenge because of the high flexibility of the transition states leading to the oxolane system.[5] Besides, five-membered oxygen-containing saturated heterocycles themselves show little energetic discrimination against pseudoaxial or pseudoequatorial substituents, because the lowest energy conformations of the envelopes and half-chairs are separated only by a few kJ/mol on the pseudorotatory cycle.[6] Thus, only a few cases are known where thermodynamic factors favor one of the two isomeric disubstituted tetrahydrofurans in the heterocycle synthesis. Among the different strategies available, the electrophilic activation of the double bond of a pentenol **1** with subsequent nucleophilic attack of the oxygen atom of the hydroxyl group has been used most in organic synthesis.[7] The umpolung of this reaction leads to an approach where electrophilic alkoxy radicals add intramolecularly to C–C double bonds (Scheme 1).[8]

Scheme 1



For a long time, the ring closure of the 4-pentenyloxy radical **6a** seemed different from the common carbon[9] and nitrogen[10] radical. Gilbert and co-workers were not able to measure the rate constant of the 5-*exo-trig* reaction of the 4-pentenyl-1-oxy radical (**6a**) by ESR spectroscopy[11] and assumed that the rate constant k^{exo} must exceed 10^8

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† Dedicated to Professor Athelstan L. J. Beckwith on the occasion of his 65th birthday.

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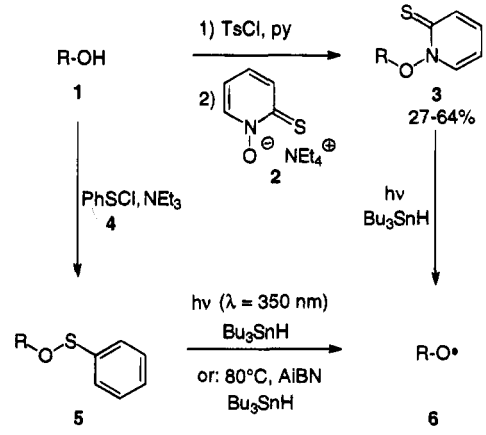
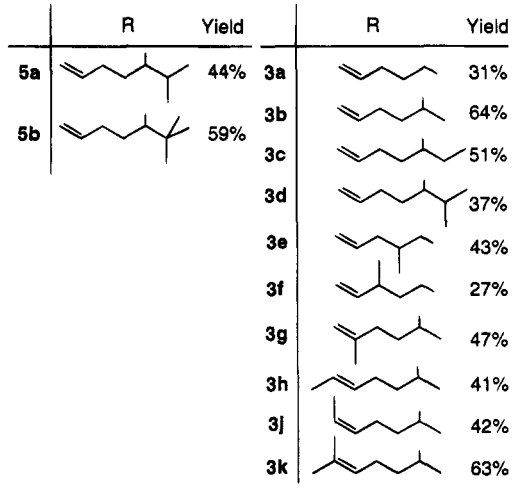
s^{-1} (T = 25 °C). This was confirmed by Beckwith *et al.*, who estimated $k^{exo} = 5.2 \times 10^8$ s^{-1} (T = 80 °C) from a competition experiment.[12] All authors agreed that the products of alkoxy radical cyclizations arose from an exclusive 5-*exo* rearrangement of the 4-pentenyloxy radical **6a**, while the 5-hexenyl radical 5-*exo-trig* cyclization is in many cases accompanied by a minor 6-*endo-trig* reaction.[9] Although *free* carbon radical cyclizations are among the widest spread reactions in the application of *free* radical chemistry,[13] the development of *free* alkoxy radical chemistry has been long hampered by the lack of suitable, easy-to-handle radical precursors having sufficient shelf life. Recent developments in the Beckwith group led to the synthesis of several arylsulfenic acid *O*-esters **5**[12] and *N*-(alkyloxy)pyridine-2(1*H*)-thiones **3**[14] which cleanly fragmented in a radical chain reaction to yield heteroradicals **6** upon addition of thiophilic tin radicals to the sulfur functional groups.

The present study was initiated by our interest in stereoselective tetrahydrofuran synthesis as a source of useful building blocks in organic synthesis. Thus, we were interested in both the basic mechanistic principles and the synthetic scope of alkoxy radical rearrangements in tetrahydrofuran synthesis which could take profit from the mild and neutral conditions in radical chemistry.

Results

Alkoxy radical precursors **3** and **5** were synthesized from substituted 4-penten-1-ols **1**[15] or the derived tosylates.[16] The reaction of 2-thioxopyridine *N*-oxide tetraethylammonium salt (**2**) and the pentenyl tosylates in DMF yields thiohydroxamic acid esters **3** in 27–64% yield as yellow oils, which are fairly stable if protected from visible light. The low yields of the desired products **3** arose from competitive side reactions of the tosylates with the ambident anion of the salt **2** which led to the formation of *S*-alkylated pyridine *N*-oxides.[14] Upon storage at 5 °C in the dark, primary (alkyloxy)pyridinethiones decompose faster than the secondary ones leading to the corresponding aldehydes. Thus, **3a**, **3e**, and **3f** were purified by column chromatography prior to use. Secondary esters **3b–d,g–k** were stable for about 6 months. For sterically demanding 2,2-dimethyl-6-hepten-3-ol (**1m**) the corresponding benzenesulfenic acid *O*-ester **5b** was the alkoxy radical precursor of choice because neither the derived tosylate nor the bromide of the alcohol **1m** could be reacted with the tetraethylammonium salt **2** to yield the *N*-(2,2-dimethyl-6-heptenyl-3-oxy)pyridine-2(1*H*)-thione in sufficient amounts. The straightforward synthesis of **5a** and **5b** from benzenesulfenyl chloride (**4**) in CH_2Cl_2 in the presence of triethylamine afforded **5a** and **5b** as crude products in 85–90% yield.[17] Polar side products which are presumably the corresponding sulfones[18] can be removed by careful distillation at temperatures below 110 °C. Thus, the isolated yields of analytically pure samples of **5a** and **5b** dropped to 44% and 59%, respectively.





All substituted tetrahydrofurans **10**[19] and -pyrans **11**,[20] which were prepared as authentic samples for NMR and GC, GC/MS analysis of the reaction mixtures of the alkoxy radical reactions, are known compounds. Still, no detailed spectroscopic data such as NMR chemical shift values have been published for *trans*- and *cis*-2-(2′-propyl)-5-methyltetrahydrofuran (**10d**), *trans*- and *cis*-2,4-methyltetrahydrofuran (**10e**), trans- and *cis*-2-*tert*-butyl-5-methyltetrahydrofuran (**10m**), and 2-(2′-propyl)-tetrahydropyran (**11d**). The structures of these compounds and the stereochemistry of the substituted tetrahydrofurans were derived from (H,H) and (C,H) COSY and from NOE experiments. An analytically pure sample of 2-*tert*-butyltetrahydropyran was obtained in a new synthesis starting from methyl 4,4-dimethyl-3-oxopentanoate because the literature procedure[20e] failed in our hands.

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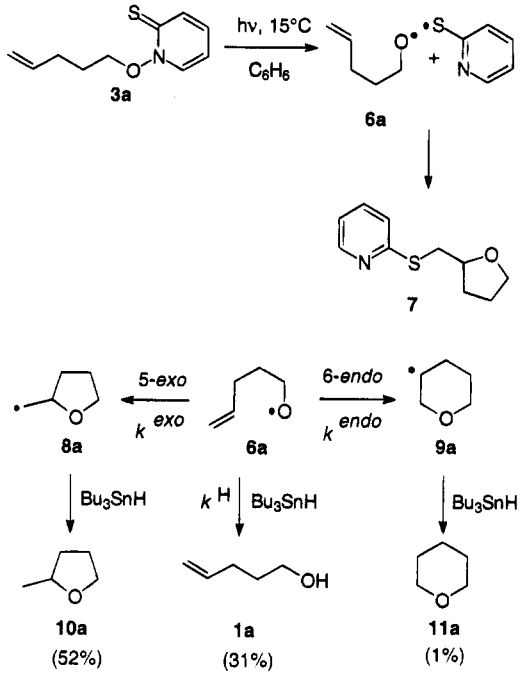
In order to standardize our analytical methods the ring closure of the 4-pentenyloxy radical **6a** was reinvestigated[11,13] using pyridinethione **3a** as the radical precursor. Photolysis of **3a** in benzene affords the rearranged product **7** in 64% yield. Addition of the hydrogen atom donor tri-*n*-butylstannane to a photolyzed solution of **3a** in *tert*-butylbenzene (TBB) affords three new products.



It is interesting to note that a small peak next to the signal arising from the 2-methyltetrahydrofuran (**10a**) in the gas chromatogram of the reaction mixture originated from the long sought-after tetrahydropyran (**11a**), which was the product of the 6-*endo* ring closure of the 4-pentenyl-1-oxy radical **6a**. The ratio of **10a**:**11a** was 98:2 (T = 15 °C), which was similar to the *exo*:*endo* ratio obtained from the rearrangement of the carbon-centered 5-hexenyl radical. Alkoxy radical **6a** could cyclize unimolecularly via 5-*exo*-*trig* **6a** → **8a** or 6-*endo*-*trig* **6a** → **9a** pathways or it was trapped by the hydrogen donor Bu_3SnH. Thus, the product distribution of 4-pentenol **1a**, 2-methyltetrahydrofuran (**10a**), and tetrahydropyran (**11a**) was a *snapshot* of the tin hydride concentration in solution, which was varied from [Bu_3SnH] = 2.00 M (**1a**:**10a** = 2.26) to [Bu_3SnH] = 0.07 M (**1a**:**10a** = 0.05). The rate constant of the 5-*exo* reaction (k^{exo} (30 °C) = (4 ± 2) × 10^8 s^{-1}) was measured by the radical clock technique[21] using the hydrogen transfer from tri-*n*-butylstannane to the *tert*-butoxy radical (k^H (30 °C) = (5 ± 2) × 10^8 $L{\cdot}mol^{-1}{\cdot}s^{-1}$)[22,23] as a reference reaction. The result was well in accord with the literature estimation of k^{exo} = 5.2 × 10^8 s^{-1} (T = 80 °C).[13] In a similar approach, numerical analysis of competition experiments using naphthalene-2-thiol (NpSH) as hydrogen donor and the new k^{exo} value derived from the tin hydride experiments afforded the rate constant of hydrogen transfer from NpSH to the 4-pentenyloxy radical **6a**. The thiol trapped the radical **6a** 1.4 times faster than the tin hydride. The total yield of the products **1a**, **10a**, and **11a** of the photoreaction of the pyridinethione **3a** with NpSH often exceeded 95%. Besides, formation of 4-pentenal, presumably derived from the disproportionation of the parent alkoxy radical **6a** at tin hydride concentrations below 0.07 M, was suppressed if the thiol NpSH was used as hydrogen donor in equivalent concentrations.

The ring closure reactions of substituted pentenyloxy radicals **6b**–**m** to *trans*- and *cis*-disubstituted tetrahydrofurfuryl radicals were studied in three different ways which are summarized in Table 1.

In the first series of experiments *N*-(alkyloxy)pyridine-2(1*H*)-thiones (**3**) were photolyzed with 1.2 equiv of NpSH in C_6D_6. The resulting yellow solutions were analyzed by ^1H NMR spectroscopy. Almost all samples showed a clean conversion of the precursors **3** to a *trans*–*cis* mixture of the corresponding tetrahydrofurans **10** and 2-pyridyl-2′-naphthyl disulfide (Scheme 2). The latter was isolated in quantitative yield by preparative thin layer chromatography from the reaction mixtures. ^1H-NMR signals arising from the parent pentenols **1** were detected in trace amounts in the spectra. Although the 5-*exo* cyclization of alkoxy radicals was a fast reaction, the introduction of alkyl substituents in position 1 of the 4-pentenyloxy chain allowed stereoselective ring closures and left *trans*-tetrahydrofurans **10b**–**d**,**m** as the major products. The observed stereoselectivities increased from methyl *via* ethyl, 2-propyl to *tert*-butyl from 61:39 to 85:15 (*trans*:*cis*, T = 15 °C). In all cases the NMR samples were subjected to GC analysis showing *trans*:*cis* ratios that were comparable within the experimental error. The ratio of five- to corresponding six-membered ring ethers was 98:2.[24] A methyl group at carbon 2 changed the stereochemical outcome of the reaction. The 2-methyl-4-pentenyl-1-oxy radical (**6e**) closed preferentially to the *cis*-2,4-dimethyltetrahydrofuryl radical (*cis*-**8e**), which was than trapped by the thiol to yield cis-2,4-dimethyltetrahydrofuran (*cis*-**10e**) (*trans*:*cis* = 25:75). Cyclization of the 3-methyl-4-pentenyl-1-oxy radical (**6f**) was the most selective reaction among the methyl-substituted radicals studied. Thus, the photolysis of precursor **3f** and NpSH in C_6D_6 (T = 15 °C) yielded a 86:14 mixture of *trans*- and *cis*-2,3-dimethyltetrahydrofuran (**10f**).

Methyl substituents at the terminal carbon atom of the double bond in the pentenyloxy chain increased the *trans*-selectivity of the ring closure from 61:39 in the unsubstituted case **6b** → **8b** to 72:28 (**6h** → **8h**) and 74:26 (**6j** → **8j**, **6k** → **8k**), respectively.

(21) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

(22) It is assumed that the reactive alkoxy radicals **6** and the *tert*-butoxy radical abstract a hydrogen atom from Bu_3SnH with the same rate constant. The latter was measured by J. A. Lusztyk, unpublished results cited in ref 13.

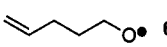
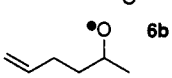
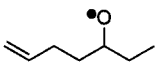
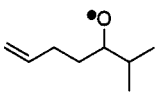
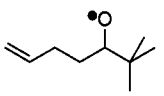
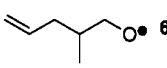
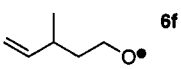
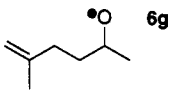
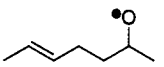
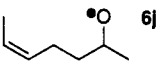
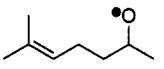
(23) k^{exo} was calculated from the slope of a linear correlation of a

$$\frac{[\mathbf{1}]}{[\mathbf{10}]} = \frac{k^H}{k^{exo}}[Bu_3SnH]$$

series of experiments (five data points consisting of three individual experiments) at different Bu_3SnH concentrations. The corresponding ratios of pentenol **1** and substituted tetrahydrofuran **10** were monitored by GC. The equation is derived from a kinetic model which is based on an irreversible rearrangement **6** → **8**: k^H refers to the rate constant of hydrogen transfer from *n*-tributylstannane to the *tert*-butoxy radical and k^{exo} to the rate constant of the 5-*exo*-*trig* rearrangement. [**1a**]:[**10a**] = (1.37 ± 0.06)[Bu_3SnH] − 0.02 (R_2 = 0.999). The reverse reaction **8** → **6** was ruled out by reducing 2-(bromomethyl)tetrahydrofuran (Bresson, A.; Dauphin, G.; Geneste, J.-M.; Kergomard, A.; Lacourt, A. *Bull. Soc. Chim. Fr.* **1973**, 1080) and 2-(bromomethyl)-5-*tert*-butyltetrahydrofuran (*trans*:*cis* = 63:37) (Colonge, J.; lagier, A. *Bull. Soc. Chim. Fr.* **1947**, 15) in TBB/AiBN, Bu_3SnH at T = 80 °C. Both transformations afford the cyclic products (2-methyltetrahydrofuran (**10a**): 62%, 2-*tert*-butyl-5-methyltetrahydrofuran (*trans*:*cis* = 65:35) (**10m**): 90%) without traces of alkenols **1a** or **1m**.

(24) For *exo*:*endo* selectivity in 5-hexenyl radical cyclizations see: Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

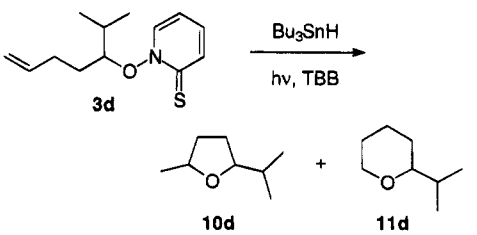
Table 1. Stereo- and Regioselective Ring Closure Reactions of Substituted 4-Pentenyl-1-oxy Radicals 6

alkoxy radical	reaction condns (i)[a] X = H: 10[d] *trans:cis*	10:11[e] *exo:endo*	11[e] *trans:cis*	reaction condns (ii)[b] X = H: 10[f] yield (*trans:cis*) (%)	10:11[g] *exo:endo*	11[f] yield (*trans:cis*) (%)	1[f] yield (%)	reaction condns (iii)[c] X = Cl: 12[h] yield (*trans:cis*) (%)	13[h] yield (%)
 **6a**		98:2		52	98:2	1	31	j	j
 **6b**	61:39	98:2		69 (64:36)	98:2	1	29	85 (63:37)	
 **6c**	66:34	98:2		82 (65:35)	98:2	2	7	89 (62:38)	
 **6d**	75:25	98:2		69 (69:31)	98:2	2	8	96 (70:30)	
 **6m**[k]				82 (85:15)	98:2	2	7	j	
 **6e**	25:75	98:2		70 (−)[m]	98:2	1	9	j	
 **6f**	86:14	99:1		66 (80:20)[n]	99:1	<1	16	j	
 **6g**		81:19[p]	92:8	73 (−)	82:18	16 (92:8)	8	75 (68:32)	18[q]
 **6h**	72:28	96:4	92:8	91 (71:29)	96:4	3 (92:8)	2	67 (74:26)[r]	
 **6j**	74:26	99:1	57:43	82 (73:27)	99:1	<1 (57:43)	4	70 (84:24)[r]	
 **6k**	74:26			90 (70:30)			2	91 (69:31)	

[a] Conditions (i): *hν*, 15 °C, 1.2 equiv of NpSH, C_6D_6. [b] Conditions (ii): *hν*, 30 °C, 2.5 equiv of Bu_3SnH, TBB or DCB. [c] Conditions (iii): *hν*, 30 °C, CCl_4. [d] *Trans:cis* ratios were determined by ^1H NMR; stereochemical assignments of the products were derived from NOE, (H, H) and (H, C) COSY experiments. Yields of cyclized products > 95%; experimental error of *trans:cis* ratios: ±3%. Pentenols **1** are formed in photoreactions of **3b**, **3f**, and **3g** in minor amounts (<5%). [e] GC/MS analysis of every experiment and comparison of the results with samples of independently synthesized tetrahydrofurans and -pyrans **10** and **11**. The *exo:endo* ratios vary within ±0.2% in absolute values. [f] Photoreaction of **3a−d,g−j** were performed in TBB and DCB, **3e,f,k** in TBB. All yields were determined *versus* n-$C_{14}H_{30}$ as internal standard (experimental error: ±5%). Due to the volality of each of the isomeric compounds **10** in the reaction mixtures every run was checked by GC analysis of samples with known *trans:cis* ratios (^1H NMR). [g] The *exo:endo* ratios vary within ±0.2% in the absolute values. [h] Isolated yield. [j] Not determined. [k] Photoreaction of the corresponding benzenesulfenic acid *O*-ester **5b** in THF, Bu_3SnH in a Rayonet photoreactor (λ = 350 nm). Control experiments using ester **5a** under the same reaction conditions afford **10d**, 73% (*trans:cis* = 68:32), **10d**: **11d** = 98:2, **11d**, 2%, **1d**, 14%. [m] The *trans*- and *cis*-isomers cannot be separated on the chosen GC column (DB 225). [n] Due to the very different boiling points of *trans*- and *cis*-**10f** and hence different volatilities of the two ethers this value is recalculated by calibrating ^1H NMR and GC results from a standard sample of **10f**. [p] ^1H NMR and GC. [q] *trans*-3-Chloro-3,6-dimethyltetrahydropyran (*trans*-**13g**). [r] 68:32 mixtures of the *like*, *unlike* isomers. No separation of the isomers was possible.

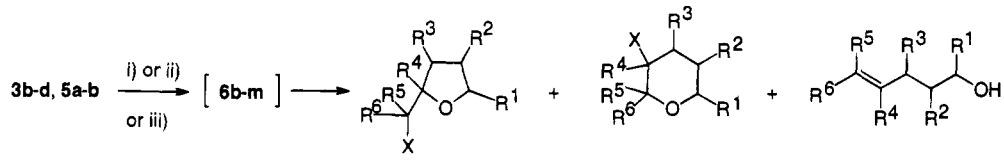
The intramolecular addition of the 5-methyl-5-hexenyl-2-oxy radical to the disubstituted double bond in **6g** was different from the rest of the radicals investigated because the product of 6-*endo* cyclization was formed in significant amounts to allow direct ^1H NMR analysis of the tetrahydropyran **11g**. The *trans*-2,5-dimethyltetrahydropyran (*trans*-**11g**) was the major product, while its *cis*-isomer was only detected by GC/MS analysis.

The second set of experiments was performed by photolyzing *N*-alkoxypyridine-2(1*H*)-thiones **3** in TBB and tri-*n*-butylstannane (exept for the photolysis of **5b**, which was done in THF at T = 15 °C) at 30 °C. The cyclization products **1**, **10**, and **11** were identified by addition of authentic samples of alkenols **1**, tetrahydrofurans **10**, and tetrahydropyrans **11** (Table 1) to the reaction mixtures and subsequent GC analysis of the samples. In some cases the observed stereoselectivities of the disubstituted tetrahydrofurans **10** were lower than those found in the photoreactions of **3** and NpSH in hexadeuteriobenzene. These findings were attributed to the temperature dependence of the ring closure reactions and checked by analyzing the reaction products of the photolyses of thiohydroxamic acid ester **3d** and Bu_3SnH at different temperatures (Table 2).



The data in Table 2 indicated that the temperature had a more dramatic effect on the *trans*-selectivity of rearrangement **6d** → **8d**, changing from 75:25 (15 °C) to 60:40 (140 °C), than on the *exo:endo* ratio which marginally decreased in the same temperature interval from 98:2 to 94:6.

Scheme 2[a]



1, 10-13	R^1	R^2	R^3	R^4	R^5	R^6
b	CH_3	H	H	H	H	H
c	C_2H_5	H	H	H	H	H
d	$CH(CH_3)_2$	H	H	H	H	H
e	H	CH_3	H	H	H	H
f	H	H	CH_3	H	H	H
g	CH_3	H	H	CH_3	H	H
h	CH_3	H	H	H	H	CH_3
j	CH_3	H	H	H	CH_3	H
k	CH_3	H	H	H	CH_3	CH_3
m	$C(CH_3)_3$	H	H	H	H	H

[a] Reagents and conditions: (i) *hν*, 15 °C, 1.2 equiv of NpSH, C_6D_6; (ii) *hν*, 30 °C, 2.5 equiv of Bu_3SnH, TBB or DCB; (iii) *hν*, 30 °C, CCl_4.

Table 2. Temperature Dependence of *trans*-,*cis*-Stereoselectivity and 5-*exo* *versus* 6-*endo* Regioselectivity of the Rearrangements 6d → 8d and 6d → 9d

T (°C)	10d *trans*:*cis*[b]	10d:11d[a]
15 ± 0.2	75:25[c]	98:2
30 ± 0.1	69:31[d]	98:2
57 ± 1	66:34[d]	96:4
102 ± 2	64:36[d]	95:5
140 ± 2	60:40[d]	94:6

[a] Experimental error ±0.2 in absolute values. [b] Experimental error ±3%. [c] Photoreaction of **3d** in C_6D_6, 1.2 equiv of NpSH, ^1H NMR. [d] Photoreaction of **3d** in TBB, Bu_3SnH, GC.

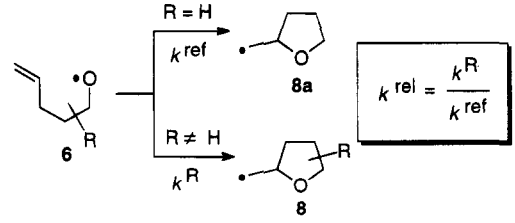
The synthetic scope of the new stereoselective tetrahydrofuran synthesis was demonstrated by the third set of experiments. This time, *N*-(alkyloxy)pyridine-2(1*H*)-thiones **3** were irradiated in carbon tetrachloride, and the intermediate cyclized carbon-centered radicals **8** and **9** were trapped by the chlorine atom donor to afford the chlorinated ethers **12** and **13**. This photoreaction was a very efficient process, and the GC analysis of the decolorized crude reaction mixtures showed essentially quantitative formation of the halogenated ethers **12** and **13**, which exhibited similar *trans*:*cis* ratios as the products **10** from the two series of experiments described above.[25] However, some of the chlorinated products **12** and **13** were difficult to separate from the solvents, and isolated yields dropped in a few instances down to 67%.

In order to shed light onto the origin of the stereoselectivity of the alkoxy radical ring closures the relative rate constants k^{rel} for *trans*- and *cis*-cyclization of all alkoxy radicals **6** except **6m** were measured at T = 30 °C using radical **6a** as the reference (k^{ref} **6a** = 1.00 ± 0.05). In general, the k^{rel} values (Table 3) refer to the solvent TBB. However, some relative rate constants had to be measured in 1,2-dichlorobenzene (DCB) in order to separate the pentenol signal from the solvent peak in the gas chromatogram.[26] The data obtained from these experiments are summarized in Table 3 and discussed in the following section.

Table 3. Relative Rate Constants for 5-*exo*-*trig* Ring Closure Reactions 6 → 8[23,26]

	k^{rel}	
alkoxy radical	k_{cis}^{rel}	k_{trans}^{rel}
6a	$k^{ref} \equiv 1.00 \pm 0.05$[a]	
6b	0.78 ± 0.07[b]	1.2 ± 0.1[b]
6c	0.73 ± 0.07[c]	1.2 ± 0.1[c]
6d	0.98 ± 0.09[b]	2.0 ± 0.2[b]
6e	1.7 ± 0.2[b]	0.56 ± 0.05[b]
6f	0.32 ± 0.03[b]	1.3 ± 0.1[b]
6g	1.8 ± 0.2[c]	
6h	2.9 ± 0.3[c]	7.1 ± 0.6[c]
6j	2.1 ± 0.2[c]	5.7 ± 0.5[c]
6k	5.7 ± 0.5[b]	12 ± 1[b]

[a] Reaction was run in TBB and DCB. [b] Photolysis in TBB. [c] Photoreactions in DCB.



Discussion

A reexamination of the 4-pentenyloxy radical cyclization provides two distinct results. First, the application

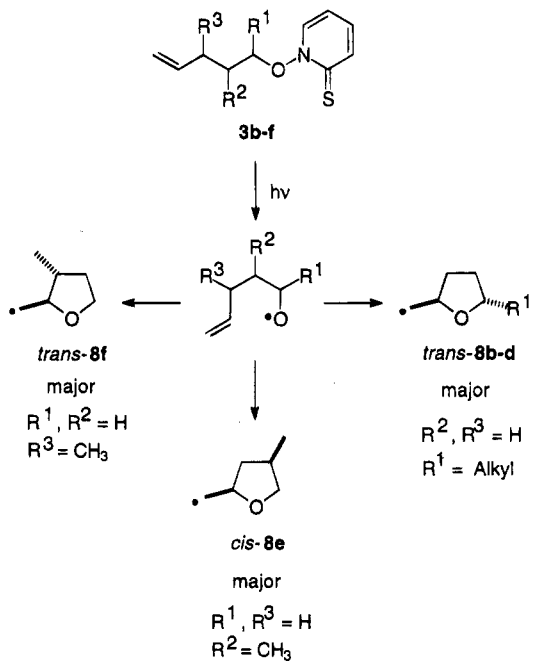
(25) Trichloromethyl 2-pyridylsulfide is formed in yields ranging from 92 to 98% and was isolated as colorless crystals: mp 71–103 °C (subl., dec), $C_6H_4Cl_3NS$ (228.5); MS (EI) *m*/*z* (rel intensity) 227, 229, 231, 233 (10, 9, 3, 1), 192, 194, 196 (100, 67, 15), 78 (76). Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron Lett.* **1985**, *26*, 5939.

(26) The k^{rel} values in Table 3 are based on the assumption that Bu_3SnH delivers its reactive hydrogen atom to all alkoxy radicals **6** with the same rate constant k^H:

$$k^{rel} = \frac{k^R}{k_R^H}\frac{k^{ref}}{k_{ref}^H} \approx \frac{k^R}{k^{ref}}\frac{k_{ref}^H}{k_R^H} = \frac{k^R}{k^{ref}}$$

Control experiments indicate no solvent effect on k^{rel} shifting from TBB to DCB using radical **6a** as the probe.

Scheme 3



of the radical clock technique shows that the ring closure **6a** → **8a** ($k^{exo} = 5 \pm 2 \times 10^8$ s^{-1}) belongs to the fastest radical cyclizations known so far. In the course of this reaction an oxygen–carbon bond is formed at the expense of a C–C double bond which renders the cyclization by about 12 kJ/mol more exothermic than the corresponding 5-hexenyl radical cyclization.[27] According to the Bell–Evans–Polanyi principle these differences could in part account for the differences in k^{exo} of alkoxy radical **6a** and the 5-hexenyl radical.[28] Second, the oxygen-centered radical **6a** does not exclusively form the 5-*exo* product **8a** but also the tetrahydropyranyl radical **9a**. Radicals **8a** and **9a** should be trapped by hydrogen donors such as Bu_3SnH with similar rate constants. Therefore, the ratio of five- and six-membered ring ethers **10a** and **11a** should reflect the quantities of initially formed 5-*exo* and 6-*endo* products **8a** and **9a**. It is surprising to note (Tables 1–3) that methyl and other alkyl substituents in the 4-pentenyloxy chain exhibit small effects on the rates and hence on the stereochemistry of the individual ring closure reactions in spite of the high k^{exo} values. Alkyl substituents at C-1 increase the rate of rearrangements **6** → *trans*-**8**, whereas **6** → *cis*-**8** is slightly reduced ($R^1 = CH_3$, C_2H_5) or remains constant within the experimental error ($R^1 = CH(CH_3)_2$). A methyl group at C-2 reverses the situation, enhancing the **6e** → *cis*-**8e** reaction, whereas **6e** → *trans*-**8e** gets less efficient, and therefore, *trans*-2,4-dimethyltetrahydrofuran (*trans*-**10e**) is the minor product of the photoreaction. Moving the methyl group in the pentenyloxy chain one position further away from the radical center yields the 3-methyl-

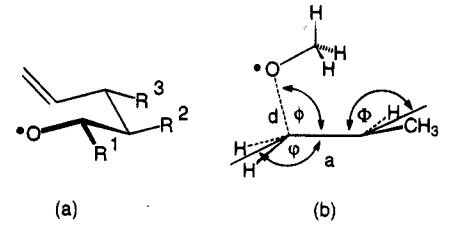
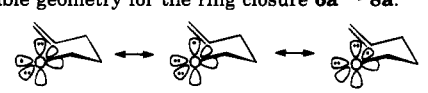


Figure 1. (a) Proposed chairlike transition state model for stereoselective alkoxy radical cyclization. The substituents in the 4-pentenyloxy chain preferably occupy the pseudoequatorial positions leading to *trans*-2,3-, *cis*-2,4-, and *trans*-2,5-disubstituted tetrahydrofurans as major reaction products. (b) Calculated transition geometry for the addition of the methoxy radical to propene by Houk *et al.* (d = 1.886 Å, a = 1.395 Å, ϕ = 108.2°, φ = 153.4°, and Φ = 172.5° (*ab initio*, UHF, 3-21-G).[30]

4-pentenyl-1-oxy radical (**6f**) as a mechanistic probe. Radical **6f** prefers to rearrange to *trans*-**8f** than to *cis*-**8f**, and NMR analysis of the trapped tetrahydrofurfuryl radicals **8f** shows a *trans*:*cis* ratio of 86:14 (T = 15 °C). The high selectivity is likely to arise from steric interactions between the C–C double bond and the neighboring methyl substituent in the transition state of the C–O bond formation. The preferential *trans*-ring closure for 1- and 3-substituted and *cis*-cyclization for 2-substituted alkoxy radicals may serve as a useful guideline in the following discussion.

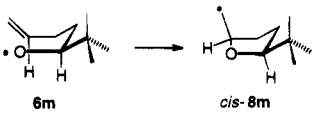
In general, the alternating *trans*-2,3-, *cis*-2,4-, and *trans*-2,5-stereoselectivities of the radical reactions and the substituent effects on k^{rel} values in Table 3 are reminiscent of the results obtained with 5-hexenyl radical cyclizations.[12,24] Likewise, the transition state of the 4-pentenyloxy radical ring closure should adopt the well-known chairlike transition state (Figure 1a).[29] According to the proposed model, this transition state favors products derived from intermediates having most of the substituents arranged in the pseudoequatorial position ($k^{rel} > 1$ for terminal unsubstituted olefins). Likewise, substituents which are aligned pseudoaxially slow down the ring closures presumably by 1,3-pseudoaxial interactions ($k^{rel} < 1$ if terminal unsubstituted olefins are studied). According to this transition state model, the 5-*exo* attack of the oxygen radical onto the C–C double bond should be favored by stereoelectronic effects over the 6-*endo* cyclization which would furnish the thermodynamically more stable secondary alkyl radical **11a**. However, the 6-*endo* product is a constant companion of the five-membered ring ether, and the observed *endo*:*exo* selectivities of 2:98 point to a very similar geometry of the 5-hexenyl and 4-pentenyloxy radical in the transion state. This is well in accord with the calculations of Houk *et al.*,[30] who investigated the addition of the methoxy

(27) This estimation was calculated using the following bond energies: C–C 370 kJ/mol, C=C 685 kJ/mol, C–O 382 kJ/mol: Kerr, J. A. *Chem. Rev.* **1966**, *66*, 465. Benson, S. W. *J. Chem. Educ.* **1965**, *42*, 502. It is likely that the SOMO of alkoxy radical **6a** mixes with the two oxygen lone pairs which would lead to a reactive intermediate with very favorable geometry for the ring closure **6a** → **8a**.



(28) Bell, R. P. *Proc. R. Soc. London, Ser. A* **1936**, *154*, 141. Evans, M. G.; Polanyi, M. *J. Chem. Soc., Faraday Trans.* **1936**, *32*, 1340.

(29) This description only takes the small methyl and ethyl substituent into account. The transition state of the sterically encumbered 2-*tert*-butyl-substituted radical **6m** is likely to avoid an axial *tert*-butyl group and should accommodate a boatlike geometry.



For similar aspects in carbon radical cyclisations see: Beckwith, A. L. J.; Zimmermann, J. *J. Org. Chem.* **1991**, *56*, 5791.

(30) (a) Houk, K. N.; Paddon-Row, M. N.; Spellmeyer, D. C.; Rondan, N. G.; Nagase, S. *J. Org. Chem.* **1986**, *51*, 2874. (b) Geometrical parameters (*ab initio*, UHF, 3-21-G) for addition of the methyl radical to propene taken from ref 33a: d = 2.262 Å, the C–C bond length a = 1.379 Å, the angles ϕ = 104.2°, φ = 158.8°, and Φ = 175.5°.

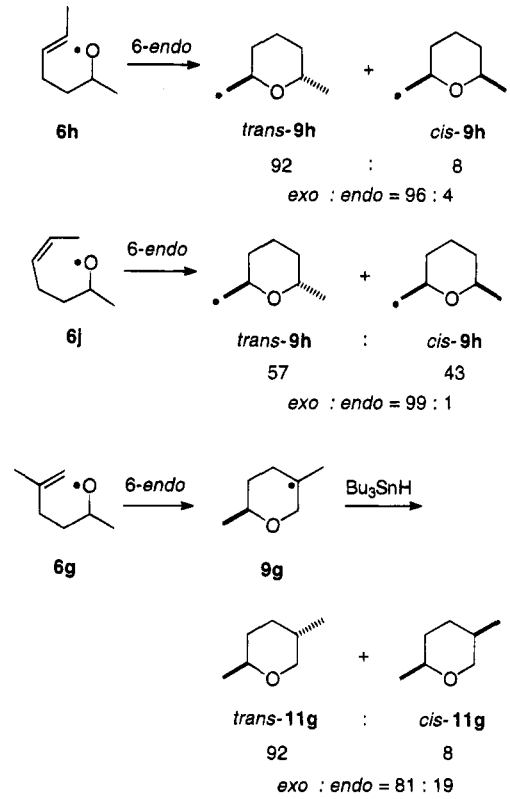
radical to propene (Figure 1b). The alkoxy radical was found to approach the olefin orthogonal to the nodal plane of the π-orbital. The C–O distance in the transition state was d = 1.886 Å, the C–C bond length a = 1.395 Å, the angles ϕ = 108.2°, φ = 153.4°, and Φ = 172.5° (*ab initio*, UHF, 3-21-G). Thus, the calculated geometry is similar to the one found for $CH_3^\bullet$ addition to propene, which shows an early transition state on the reaction coordinate and a slight rehybridization of the attacked sp^2 carbon toward sp^3. The only major difference between the carbon and the oxygen radical arises from the distances d which could point to a tighter transition state in the alkoxy radical reaction where substituents would exhibit a larger effect than one would expect from the high rate constants k^{exo}.

Alkoxy radicals are electrophilic reactive intermediates.[31] Therefore, it is straightforward that the substitution of hydrogens by methyl groups at the terminal double bond in radicals **6** increases the k^{exo} rate constant in the case of radicals **6g–k** compared to the 5-hexenyl-2-oxy radical (**6b**). However, the degree of rate enhancement in **6g–k** → **8g–k** differs from marginal (**6g** → **8g**: 1.5 times faster than **6b** → *trans*-**8b**) to significant (10-fold increase going from **6b** → *trans*-**8b** to **6k** → *trans*-**8k**). The high reactivity of the 5-methyl-5-hexenyl-2-oxy radical (**6g**) is surprising because alkyl substituents are known to reduce the rate constants of radical attack at the substituted sp^2 carbon.[32] However, alkoxy radical **6g** cyclizes 1.5 faster than the 5-unsubstituted derivative **6b** although 16–19% 6-*endo* cyclized product points to the steric hindrance of the methyl group on the 5-*exo-trig* reaction.

It is interesting to note that (*E*)- and (*Z*)-5-hexenyloxy radicals **6h** and **6j** rearrange similarly fast concerning the 5-*exo* reaction, affording after hydrogen transfer a *trans*:*cis* ratio of 2-ethyl-5-methyltetrahydrofuran (**10c**) of 72:28 and 74:26. These results were not expected from simple transition state models. However, this qualitative description cannot predict the rigidity of the transition geometry, and therefore, the rationalization of minor steric contributions (*i.e.*, (*E*)- or (*Z*)-geometry in **6h** or **6j**) on the preferred stereochemical reaction pathway cannot be deduced from our results and has to await detailed theoretical investigations. The major differences in the reactions of the two isomeric 5-heptenyloxy radicals **6h, 6j** originate from the observed stereoselectivities of the 6-*endo* cyclization which is *trans*-selective for the (*E*)-substituted olefin (92:8) and unselective for the (*Z*)-substituted double bond (57:43).

The 6-*endo* product formed by ring closure of the 5-methyl-5-hexenyloxy radical **6g** is a tertiary radical which is trapped by the hydrogen donors NpSH and *n*-Bu_3SnH preferentially from the axial side[33] to yield *trans*-2,5-dimethyltetrahydropyran (*trans*-**11g**) as the major product from the 6-*endo* ring closure (^1H NMR analysis). The ratio of *trans*-**11g**:*cis*-**11g** is 92:8 (GC).

The synthesis of the chlorinated ethers **12** and **13** by photoreacting alkyloxypyridinethiones **3** and CCl_4 deserves two further comments. It is important to run the reaction in concentrations of **3** below 5 mM in order to avoid the competitive addition of the tetrahydrofurfuryl



or the respective tetrahydropyranyl radical **8** or **9** to the thiocarbonyl group of the starting material **3**. This reaction would lead to derivatives of the thioether **7** instead of the desired organochlorine compounds **12** and **13**. The high yields of chlorinated products **12** and **13** are in parts ascribed to the efficient radical chain reaction carried by the $CCl_3^\bullet$ radical and the reluctance of the O–Cl bond to form from the uncyclized alkoxy radicals **6**. Given the vast chemistry associated with synthetic applications of organohalogens this reaction should be of further use wherever functionalized tetrahydrofurans are needed in organic synthesis.

Conclusion

Substituted 4-pentenyl-1-oxy radicals **6** undergo efficient and stereoselective 5-*exo-trig* ring closure reactions to yield tetrahydrofurylmethyl radicals **8**, which can be trapped, e.g., with hydrogen or chlorine atom donors. The observed *trans*:*cis* ratios range from 25:75 to 86:14 at room temperature and depend largely on the substitution pattern and the steric bulk of alkyl substituents of the 4-pentenyloxy radical. The 5-membered ring formation is in almost all cases accompanied by a small fraction of 6-*endo* product. The data derived from competition kinetics point to a chairlike transition state of the cyclization which should be similar to the one found in the 5-hexenyl radical rearrangement. Thus, the major products arise from transition geometries with the substituents aligned in pseudoequatorial positions.

Although highly reactive, 4-pentenyloxy radicals can be transformed smoothly and stereoselectively into saturated heterocyclic ethers, taking advantage of the mild and neutral reaction conditions of radical chemistry.

Experimental Section

The following abbreviations have been used throughout the paper: *tert*-butylbenzene (TBB), 1,2-dichlorobenzene (DCB), naphthalene-2-thiol (NpSH), methyl *tert*-butyl ether (MTB),

(31) Jones, M. J.; Moad, G.; Rizzardo, E.; Solomon, D. H. *J. Org. Chem.* **1989**, *54*, 1607.
(32) Giese, B. *Angew. Chem.* **1983**, *95*, 771; *Angew. Chem., Int. Ed. Engl.* **1983**, *95*, 771.
(33) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067.

lithium aluminum hydride (LAH). All compounds used in this study are racemic. Tri-*n*-butyltin hydride was purchased from Fluka (purum, 98%) and used as obtained. The purity of the reagent was checked by NMR.

NMR spectra were recorded unless otherwise noted in $CDCl_3$. UV spetrca were measured in ethanol in 1 cm quarz cuvettes and IR spectra in CCl_4 in NaCl cuvettes (0.5 mm). GC analysis: Carlo Erba GC 6000 (Vega Series), FID, connected to Spetra Physics integrator 4290. Helium at a flow rate of 2 mL/min (equals 80 kPa pressure) was used as carrier gas; injector and detector temperature 240 °C; DB-225 column from J&W Scientific. Preparative thin layer chromatography: 1 mm silica gel plates on glass (Merck). All solvents were distilled prior to use and purified according to standard procedures.[34]

Preparation of the Alcohols. 5-Hexen-2-ol (**1b**), 5-methyl-5-hexen-2-ol (**1g**), and 6-methyl-5-hepten-2-ol (**1k**) were prepared according to Johnson *et al.*[35] 6-Hepten-3-ol (**1c**), 2-methyl-6-hepten-3-ol (**1d**), 2,2-dimethyl-6-hepten-3-ol (**1m**), and (*E*)-5-hepten-2-ol (**1h**) were obtained from the parent acetoacetates, 2-methyl-4-pentenol (**1e**) and 3-methyl-4-pentenol (**1f**) from diethyl malonate, and the respective allylic halides by the method of Schechter *et al.*[15] and reduction of the ketones or carboxylic acids with LAH. (*Z*)-5-Hepten-2-ol (**1j**) was synthesized by Lindlar reduction[36] of 5-heptyn-2-one[15] and subsequent reduction of the carbonyl group using LAH. The stereochemical purity of both (*E*)- and (*Z*)-5-hepten-2-ol was 96:4 (GC major:minor).

Preparation of the Tosylates. The tosylates of the above alcohols were prepared by the method of Schleyer in 75–90% yield and purified by column chromatography on silica gel using toluene as eluent.[16]

Preparation of the Tetrahydrofurans. 2-Ethyl-5-methyltetrahydrofuran (**10c**), 2-(2′-propyl)-5-methyltetrahydrofuran (**10d**), and 2-(2′-methyl-2′-propyl)-5-methyltetrahydrofuran (**10m**) were prepared by solvomercuration of the appropriate alkenols **1** and subsequent sodium borohydride reduction of the mercury acetates.[19d] *trans*-2-(2′-propyl)-5-methyltetrahydrofuran (*trans*-**10d**):[19e] ^{1}H NMR (250 MHz) δ 0.82 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.32–1.64 (m, 2H), 1.65 (sept, J = 6.7 Hz, 1H), 1.78–2.04 (m, 4H), 3.65 (m_c, 1H), 4.02 (m_c, 1H); ^{13}C NMR (63 MHz) δ 18.5, 19.6, 21.6, 33.3, 33.6, 34.5, 75.1, 85.2. *cis*-2-(2′-propyl)-5-methyltetrahydrofuran (*cis*-**10d**):[19e] ^{1}H NMR (250 MHz) δ 0.85 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.1 Hz, 3H), 1.32–1.64 (m, 2H), 1.78–2.04 (m, 2H), 3.51 (m_c, 1H), 3.92 (m_c, 1H); ^{13}C NMR (63 MHz) δ 18.6, 19.6, 21.5, 28.8, 33.3, 33.6, 75.3, 84.5. *trans*-2-*tert*-Butyl-5-methyltetrahydrofuran (*trans*-**10m**):[19e] ^{1}H NMR (250 MHz) δ 0.87 (s, 9H), 1.21 (d, J = 6.1 Hz, 3H), 1.11–1.87 (m, 3H), 1.87–2.04 (m, 1H), 3.69 (dd, J = 6.7, 9.2 Hz, 1H), 3.98 (m_c, 1H); ^{13}C NMR (63 MHz) δ 21.5, 26.0, 27.2, 34.5, 34.9, 75.8, 87.1. *cis*-2-*tert*-Butyl-5-methyltetrahydrofuran (*cis*-**10m**):[19e] ^{1}H NMR (250 MHz) δ 0.88 (s, 9H), 1.19 (d, J = 6.1 Hz, 3H), 1.11–1.87 (m, 4H), 3.53 (t, J = 7.6 Hz, 1H), 3.98 (m_c, 1H); ^{13}C NMR (63 MHz) δ 21.4, 26.1, 26.6, 33.6, 34.5, 75.3, 87.8. 2,3-Dimethyltetrahydrofuran (**10f**) was obtained by the procedure published by Frauenrath *et al.*[19c] 2,4-Dimethyltetrahydrofuran (**10e**) was obtained from section 3.1.

Synthesis of Tetrahydropyrans. 2-Methyltetrahydropyran (**11b**), 2-ethyltetrahydropyran (**11c**), and 2-(2′-propyl)-tetrahydropyran (**11d**) were synthesized from 3,4-dihydro-2*H*-pyran, triflic acid, dimethyl sulfide, and the respective alkylmagnesium bromide.[20b] 4-Methyltetrahydropyran (**11f**) and *trans*- and *cis*-2,6-dimethyltetrahydropyran (*trans*- and *cis*-**11h**) were obtained by dehydrating the parent diols[19a,20a,c] with thionyl chloride in anhydrous ether. 2-(2′-Propyl)tetrahydropyran (**11d**):[20d] ^{1}H NMR (250 MHz) δ 0.86 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 1.23 (m_c, 1H), 1.34–1.62 (m, 4H), 1.60 (sept, J = 6.7 Hz, 1H), 2.93 (ddd, J = 2.1, 6.4, 11.0 Hz, 1H), 3.38 (td, J = 3.4, 11.3 Hz, 1H), 3.94–4.01 (m, 1H); ^{13}C NMR (63 MHz) δ 18.6, 18.9, 24.0, 26.6, 28.6, 33.5, 68.9, 83.3. 2-*tert*-Butyltetrahydropyran (**10m**). A solution of 31.64 g (0.20 mol) of methyl 4,4-dimethyl-3-oxopentanoate in ethanolic sodium ethoxide (4.60 g (0.20 mol) of sodium in 150 mL of ethanol) and 38.02 g (0.21 mol) of ethyl 3-bromopropionate was reacted at room temperature (14 h) according to Schechter *et al.*[15] Usual workup of the reaction mixture afforded 17.81 g (31%) of diethyl (1-pivaloyl)glutarate: bp 118–120 °C (0.1 mbar); ^{1}H NMR (200 MHz) δ 1.20 (s, 9H), 1.21 (q, J = 7.2 Hz, 3H), 1.23 (q, J = 7.1 Hz, 3H), 1.96–2.22 (m_c, 2H), 2.33 (t, J = 6.3 Hz, 2H), 3.98–4.17 (m, 5H); ^{13}C NMR (50.3 MHz) δ 14.2, 14.3, 24.9, 26.3, 31.8, 45.6, 31.8, 45.6, 51.2, 60.5, 60.7, 169.6, 173.0; MS (EI) m/z (rel intensity) 272 (0.8, M^+), 227 (12.9), 215 (21.3), 169 (59.2), 57 (100). Anal. Calcd for $C_{14}H_{24}O_5$ (272.4): C, 61.74; H, 8.88. Found: C, 61.53; H, 8.77. Saponification of 17.81 g (0.07 mol) of diester with 8.07 g (0.14 mol) of potassium hydroxide in 100 mL water for 3 d at 5 °C and subsequent decarboxylation of the acidified aqueous solution by addition of a solution of 7 mL of H_2SO_4 in 14 mL of water and common workup yielded 4.93 g (46%) of 6,6-dimethyl-5-oxoheptanoic acid: bp 95–98 °C (0.1 mbar); ^{1}H NMR (400 MHz) δ 1.10 (s, 9H), 1.85 (quint, J = 7.4 Hz, 2H), 2.34 (t, J = 7.0 Hz, 2H), 11.6 (s br, 1H); ^{13}C NMR (100.6 MHz) δ 19.0, 26.3, 33.3, 35.4, 44.3, 179.2, 215.0; MS (EI) m/z (rel intensity) 172 (0.9, M^+), 155 (11.5), 143 (72.7), 115 (100), 57 (87.4). Anal. Calcd for $C_9H_{16}O_3$ (172.2): C, 62.77; H, 9.63. Found: C, 62.58; H, 9.76. 6,6-Dimethyl-5-oxoheptanoic acid (4.50 g, 0.03 mol) was subjected to LAH reduction to afford after usual workup and distillation 3.51 g (81%) of 6,6-dimethylheptane-1,5-diol: bp 95 °C (0.1 mbar); mp 44–45 °C; ^{1}H NMR (400 MHz) δ 0.86 (s, 9H), 1.22–1.40 (m, 2H), 1.45–1.55 (m, 2H), 1.56–1.68 (m, 2H), 2.59 (s br, 2H), 3.15 (d, J = 10.3 Hz, 1H), 3.61 (t, J = 6.2 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 23.4, 26.0, 31.1, 32.7, 35.2, 62.6, 79.0; MS (EI) m/z (rel intensity) 127(2.4, M^+ – 33), 103 (17.3), 85 (100). Anal. Calcd for $C_9H_{20}O_2$ (172.2): C, 67.45; H, 12.60. Found: C, 67.20; H, 12.91. An solution of 1.50 g (9.4 mmol) of 6,6-dimethylheptane-1,5-diol in 35 mL of anhydrous diethyl ether was treated with 0.75 mL (1.22 g, 10.3 mmol) of freshly distilled (from crystalline sulfur) thionyl chloride at room temperature. The flask was closed with a drying tube ($CaCl_2$) and the mixture stirred for 7 d at ambient temperature. The ether was stripped off, and the resulting oily residue was distilled from K_2CO_3 *in vacuo* to afford 0.52 g (39%) of 2-*tert*-butyltetrahydropyran (**11m**) as a pleasant smelling colorless liquid: bp 75 °C (15 mbar); ^{1}H NMR (250 MHz) δ 0.87 (s, 9H), 1.23 (m_c, 1H), 1.30–1.60 (m, 4H), 1.81–1.88 (m, 1H), 2.85 (dd, J = 1.7, 10.7 Hz, 1H), 3.37 (td, J = 3.5, 11.2 Hz, 1H), 3.98 (m_c, 1H); ^{13}C NMR (63 MHz) δ 24.1, 25.8, 26.1, 26.4, 34.1, 69.1, 86.1; MS (EI) m/z (rel intensity) 142 (1.4), 85 (17.9), 57 (100). Anal. Calcd for $C_9H_{18}O$ (142.2): C, 76.00; H, 12.76. Found: C, 75.59; H, 13.08.

1. Preparation of *N*-(Alkyloxy)pyridine-2(1*H*)-thiones 3. A flame-dried round-bottom flask was charged with 1.36 g (5.30 mmol) of 2-mercaptopyridine *N*-oxide tetraethylammonium salt (**2**)[14] and 5.30 mmol of pentenol tosylate dissolved in 25 mL anhydrous DMF under argon. The reaction mixture was stirred for 14 h in the dark. The solvent was stripped *in vacuo* and the orange oil taken up with 20 mL of 0.1 N sodium hydroxide and 30 mL of methyl *tert*-butyl ether (MTB). The organic layer was separated and the aqueous phase extracted three times with 20 mL of MTB. The combined etheral extracts were washed with saturated sodium bicarbonate (25 mL) and saturated sodium chloride (25 mL) and dried ($MgSO_4$), leaving a lemon yellow solution. The solvent was removed *in vacuo*, affording a yellow oil which was purified by silica gel column chromatography (MTB) in the dark.

***N*-(5-Hexenyl-2-oxy)pyridine-2(1*H*)-thione (3b):** yield 0.71 g (64%); yellow oil; UV λ_{max} (log ϵ) 362 (3.78), 288 nm (4.17); IR ν 3081, 2977, 2933, 1610, 1560, 1527, 1446, 1409, 1275, 1132 cm^{-1}; ^{1}H NMR (250 MHz) δ 1.17 (d, J = 6.3 Hz, 3H), 1.53–1.71 (m, 1H), 1.72–1.88 (m, 1H), 2.04–2.18 (m, 2H), 4.81–4.97 (m, 2H), 5.06 (sx, J = 5.8 Hz, 1H), 5.71 (ddt, J = 6.4, 10.3, 17.0 Hz, 1H), 6.50 (td, J = 1.8, 6.9 Hz, 1H), 7.03 (td, J = 1.8, 7.1 Hz, 1H), 7.53 (dt, J = 1.8, 6.9 Hz, 1H), 7.57 (dt, J = 1.8, 6.9 Hz, 1H); ^{13}C NMR (63 MHz) δ 17.1, 28.5, 32.9, 80.2,

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112.1, 114.7, 132.3, 137.5, 139.5, 175.8; MS (EI) *m/z* (rel intensity) 209 (4.5) 127 (81.9), 111 (100). Anal. Calcd for $C_{11}H_{15}NOS$ (209.3): C, 63.12; H, 7.22; N, 6.69; S, 15.32. Found: C, 62.95; H, 7.00; N, 6.54; S, 15.24.

***N*-(6-Heptenyl-3-oxy)pyridine-2(1*H*)-thione (3c):** yield 0.60 g (51%); yellow oil; UV λ_{max} (log ϵ) 363 (3.76), 291 nm (4.11); IR ν 3086, 2973, 2934, 2867, 1610, 1527, 1447, 1406, 1274, 1176, 1130 cm^{-1}; ^1H NMR (200 MHz) δ 0.96 (t, J = 7.4 Hz, 3H), 1.58–1.83 (m, 4H), 2.18 (q, J = 9.0 Hz, 2H), 4.87–5.07 (m, 3H), 5.76 (ddt, J = 6.6, 10.3, 17.0 Hz, 1H), 6.53 (td, J = 1.1, 6.9 Hz, 1H), 7.06 (td, J = 1.5, 6.9 Hz, 1H), 7.56–7.60 (m, 2H); ^{13}C NMR (50.3 MHz) δ 8.3, 23.3, 28.5, 29.4, 84.5, 112.2, 114.9, 132.3, 137.6, 137.9, 139.5, 176.2; MS (EI) *m/z* (rel intensity) 223 (4.0), 190 (5.3), 127 (88.3), 111 (100). Anal. Calcd for $C_{12}H_{17}NOS$ (223.3): C, 64.54; H, 7.67; N, 6.27; S, 14.36. Found: C, 64.36; H, 7.45; N, 6.01; S, 14.11.

***N*-[(2-Methyl-6-heptenyl)-3-oxy]pyridine-2(1*H*)-thione (3d):** yield 0.47 g (37%); yellow oil; UV λ_{max} (log ϵ) 361 (3.78), 290 nm (4.11); IR ν 3079, 2968, 2929, 1611, 1592, 1527, 1446, 1407, 1274 cm^{-1}; ^1H NMR (200 MHz) δ 0.95 (d, J = 7.1 Hz, 3H), 1.07 (d, J = 7.1 Hz, 3H), 1.60–1.70 (m, 2H), 1.99 (septd, J = 3.5, 6.8 Hz, 1H), 2.21–2.36 (m, 2H), 4.91–5.10 (m, 3H), 5.80 (ddt, J = 6.4, 11.3, 17.0 Hz, 1H), 6.54 (td, J = 2.0, 6.9 Hz, 1H), 7.09 (td, J = 1.5, 6.9 Hz, 1H), 7.57–7.65 (m, 2H); ^{13}C NMR (50.3 MHz) δ 16.7, 17.5, 26.9, 28.4, 29.9, 87.7, 112.2, 114.9, 132.1, 138.0, 138.4, 139.5, 176.2; MS (EI) *m/z* (rel intensity) 237 (2.7), 204 (4.4), 128 (100), 127 (88.8). Anal. Calcd for $C_{13}H_{19}NOS$ (237.4): C, 65.78; H, 8.07; N, 5.90; S, 13.51. Found: C, 65.49; H, 8.26; N, 5.66; S, 13.71.

***N*-[(2-Methyl-4-pentenyl)-1-oxy]pyridine-2(1*H*)-thione (3e):** yield 0.48 g (43%); yellow oil; UV λ_{max} (log ϵ) 360 (3.76), 289 nm (4.12); IR ν 3079, 2964, 2878, 1846, 1608, 1527, 1446, 1411, 1277 cm^{-1}; ^1H NMR (200 MHz) δ 1.03 (d, J = 6.5 Hz, 3H), 1.97–2.17 (m, 2H), 2.21–2.33 (m, 1H), 4.12–4.28 (m, 2H), 4.98–5.02 (m, 2H), 5.78 (ddt, J = 6.9, 10.1, 17.2 Hz, 1H), 6.58 (td, J = 1.8, 6.8 Hz, 1H), 7.10 (td, J = 1.7, 8.7 Hz, 1H), 7.58 (dd, J = 1.8, 8.7 Hz, 1H), 7.69 (dd, J = 1.2, 6.9 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 16.4, 31.8, 37.5, 80.6, 113.2, 116.7, 132.7, 135.7, 137.7, 137.9, 175.6. MS (EI) *m/z* (rel intensity) 209 (3.0), 176 (7.8), 127 (100), 111 (57.7). Anal. Calcd for $C_{11}H_{15}NOS$ (209.3): C, 63.12; H, 7.22; N, 6.69; S, 15.32. Found: C, 62.91; H, 7.33; N, 6.47; S, 15.28.

***N*-[(3-Methyl-4-pentenyl)-1-oxy]pyridine-2(1*H*)-thione (3f):** yield 0.30 g (27%); yellow oil; UV λ_{max} (log ϵ) 359 (3.78), 288 nm (4.13); IR ν 3088, 2964, 2876, 1845, 1608, 1527, 1447, 1416, 1277 cm^{-1}; ^1H NMR (200 MHz) δ 1.03 (d, J = 6.5 Hz, 3H), 1.74–1.88 (m, 2H), 2.36 (sept, J = 6.9 Hz, 1H), 4.23–4.46 (m, 2H), 4.90–4.96 (m, 2H), 5.66 (ddd, J = 7.8, 10.1, 19.6 Hz, 1H), 6.54 (td, J = 1.8, 6.9 Hz, 1H), 7.09 (ddd, J = 1.5, 6.8, 9.0 Hz, 1H), 7.57 (dd, J = 1.8, 8.7 Hz, 1H), 7.69 (dd, J = 1.2, 6.9 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 20.3, 33.7, 34.4, 74.8, 75.9, 113.1, 113.6, 132.7, 137.8, 143.1, 175.5; MS (EI) *m/z* (rel intensity) 209 (0.4), 127 (55.5), 111 (47.8), 67 (100). Anal. Calcd for $C_{11}H_{15}NOS$ (209.3): C, 63.12; H, 7.22; N, 6.69; S, 15.32. Found: C, 63.24; H, 6.83; N, 6.33; S, 15.13.

***N*-[(5-Methyl-5-hexenyl)-2-oxy]pyridine-2(1*H*)-thione (3g):** yield 0.56 g (47%); yellow oil; UV λ_{max} (log ϵ) 362 (3.83), 291 nm (4.16); IR ν 3077, 2973, 2935, 2295, 2294, 2008, 1855, 1549, 1447, 1408, 1379, 1253, 1221, 1132 cm^{-1}; ^1H NMR (400 MHz) δ 1.18 (d, J = 6.3 Hz, 3H), 1.62 (s, 3H), 1.64 (m_c, 1H), 1.88 (m_c 1H), 2.07 (m_c, 2H), 4.59 (m_c, 2H), 5.05 (sx, J = 5.5, 1H), 6.50 (td, J = 1.8, 6.7 Hz, 1H), 7.04 (ddd, J = 1.7, 6.9, 8.5 Hz, 1H), 7.50–7.60 (m, 2H); ^{13}C NMR (100.6 MHz) δ 17.1, 22.1, 31.6, 32.5, 80.5, 110.0, 112.2, 132.4, 137.6, 139.6, 144.4, 175.8; MS (EI) *m/z* (rel intensity) 223 (0.8), 126 (5.3), 111 (8.2), 81 (41.5), 43 (100). Anal. Calcd for $C_{12}H_{17}NOS$ (223.3): C, 64.54; H, 7.67; N, 6.27; S, 14.35. Found: C, 64.27; H, 7.68; N, 6.40; S, 14.31.

***N*-[(*E*)-6-Heptenyl-2-oxy]pyridine-2(1*H*)-thione (3h):** yield 0.49 g (41%); yellow oil; UV λ_{max} (log ϵ) 361 (3.81), 289 nm (4.12); IR ν 2964, 2934, 2856, 2359, 2354, 2001, 1854, 1550, 1447, 1408, 1260, 1218 cm^{-1}; ^1H NMR (400 MHz) δ 1.21 (d, J = 6.3 Hz, 3H), 1.55 (d, J = 4.8 Hz, 3H), 1.52–1.62 (m, 1H), 1.75–1.83 (m, 2H), 2.00–2.14 (m, 2H), 5.09 (sx, J = 5.9 Hz, 1H), 5.30–5.43 (m, 2H), 6.51 (td, J = 1.8, 7.0 Hz, 1H), 7.06 (ddd, J = 1.5, 6.6, 8.5 Hz, 1H), 7.55–7.59 (m, 2H); ^{13}C NMR (100.6 MHz) δ 17.8, 18.0, 28.1, 34.2, 81.1, 112.4, 125.8, 130.3, 132.7, 138.2, 140.1, 176.6; MS (EI) *m/z* (rel intensity) 223 (2.6), 150 (22.0), 139 (41.5), 111 (45.7), 85 (100). Anal. Calcd for $C_{12}H_{17}NOS$ (223.3): C, 64.54; H, 7.67; N, 6.27; S, 14.35. Found: C, 64.20; H, 7.42; N, 6.12; S, 14.26.

***N*-[(*Z*)-6-Heptenyl-2-oxy]pyridine-2(1*H*)-thione (3j):** yield 0.50 g (42%); yellow oil; UV λ_{max} (log ϵ) 361 (3.71), 289 nm (4.06); IR ν 3016, 2974, 2933, 2861, 2362, 1610, 1525, 1446, 1408, 1276, 1176 cm^{-1}; ^1H NMR (400 MHz) δ 1.22 (dd, J = 1.5, 6.6 Hz, 3H), 1.52 (d, J = 6.62, 3H), 1.54–1.63 (m, 1H), 1.75–1.82 (m, 1H), 2.09–2.16 (m, 2H), 5.10 (sx, J = 5.9 Hz, 1H), 5.27–5.41 (m, 2H), 6.52 (t, J = 6.62 Hz, 1H), 7.06 (dd, J = 7.4, 8.5 Hz, 1H), 7.56–7.60 (m, 2H); ^{13}C NMR (100.6 MHz) δ 12.6, 17.6, 22.2, 33.8, 80.6, 112.1, 124.5, 129.2, 132.3, 137.9, 139.7, 176.3; MS (EI) *m/z* (rel intensity) 223 (4.3), 190 (5.2), 127 (29.6), 111 (68.2), 85 (100). Anal. Calcd for $C_{12}H_{17}NOS$ (223.3): C, 64.54; H, 7.67; N, 6.27; S, 14.35. Found: C, 64.31; H, 7.56; N, 6.29; S, 14.51.

***N*-[(6-Methyl-6-heptenyl)-2-oxy]pyridine-2(1*H*)-thione (3k):** yield 0.79 g (63%); yellow oil; UV λ_{max} (log ϵ) 363 (3.75), 290 nm (4.09); IR ν 3110, 2973, 2930, 2858, 1610, 1525, 1447, 1408, 1276 cm^{-1}; ^1H NMR (200 MHz) δ 1.26 (d, J = 6.3 Hz, 3H), 1.58 (s, 3H), 1.65 (s, 3H), 1.54–1.69 (m, 1H), 1.72–1.90 (m, 1H), 2.09 (q, J = 7.5 Hz, 2H), 5.03–5.19 (m, 2H), 6.54 (td, J 1.7, 6.9 Hz, 1H), 7.09 (1.7, 6.7 Hz, 1H), 7.59–7.65(m, 2H); ^{13}C NMR (50.3 MHz) δ 17.5, 17.6, 23.4, 25.5, 34.0, 80.9, 112.1, 123.2, 132.2, 132.4, 138.0, 139.7, 176.3; MS (EI) *m/z* (rel intensity) 237 (8.2), 204 (28.6), 126 (62.3), 95 (100). Anal. Calcd for $C_{13}H_{19}NOS$ (237.4): C, 65.78; H, 8.07; N, 5.90; S, 13.51. Found: C, 65.54; H, 7.84; N, 5.67; S, 13.77.

2. Synthesis of Benzenesulfenic Acid *O*-Esters 5. A solution of 0.50 g (3.90 mmol) of 2-methyl-6-hepten-3-ol (**1d**) and 0.99 g (9.70 mmol) of triethylamine in 20 mL of anhydrous CH_2Cl_2 was reacted with 0.71 g (4.90 mmol) of neat benzenesulfenyl chloride (**4**)[37] under nitrogen at −40 °C. The reaction mixture was stirred for 15 min at −40 °C and then allowed to warm to room temperature. The colorless solution was washed with cold water, 2 N hydrochloric acid, and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil is distilled in a Kugelrohr oven to yield 0.41 g (44%) of (2-methyl-6-hepten-3-yl)benzenesulfenic acid *O*-ester (**5a**) as a colorless liquid (bp 100 °C, 10^{-4} mbar): IR ν 3077, 2963, 2874, 1734, 1641, 1583, 1476, 1439, 1388, 1368, 1346 cm^{-1}; ^1H NMR (200 MHz) δ 0.79 (d, J = 6.7 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H), 1.45–1.64 (m, 2H), 1.85–2.13 (m, 3H), 3.32 (dt, J = 6.9 Hz, 1H), 4.80–4.91 (m, 2H), 5.64 (ddt, J = 6.6, 9.7, 16.3 Hz, 1H), 7.09–7.36 (m, 5H); ^{13}C NMR (63 MHz) δ 17.6, 18.4, 29.7, 30.0, 30.8, 92.4, 115.0, 126.7, 127.7, 129.0, 138.5, 141.1; MS (EI) *m/z* (rel intensity) 236 (13.9), 218 (97.3), 109 (80.0), 95 (68.3), 69 (100). Anal. Calcd for $C_{14}H_{20}OS$ (236.4): C, 71.14; H, 8.53; S, 13.56. Found: C, 70.78; H, 8.51; S, 13.43.

(2,2-Dimethyl-6-hepten-3-yl)benzenesulfenic acid *O*-ester (5b): yield 0.58 g (59%); bp 110 °C (10^{-4} mbar, Kugelrohr); UV λ_{max} (log ϵ) 308 (2.93), 271 (3.49), 245 nm (3.95); IR ν 3077, 2959, 2870, 1640, 1582, 1487, 1439, 1365 cm^{-1}; ^1H NMR (200 MHz) δ 0.80 (s, 9H), 1.40–1.63 (m, 2H), 1.73–1.92 (m, 1H), 1.93–2.09 (m, 1H), 3.20 (dd, J = 3.7, 7.1 Hz, 1H), 4.74–4.84 (m, 2H), 5.62 (ddt, J = 6.3, 10.4, 16.7 Hz, 1H), 7.15–7.43 (m, 5H); ^{13}C NMR (63 MHz) δ 26.5, 30.9, 31.9, 36.1, 98.3, 115.0, 127.4, 128.7, 129.0, 140.7; MS (EI) *m/z* (rel intensity) 250 (5,0), 109 (69.5), 57 (100). Anal. Calcd for $C_{15}H_{22}OS$ (250.4): C, 71.95; H, 8.86; S, 12.80. Found: C, 71.84; H, 8.89; S, 13.08.

3.1. Photolysis of Thiohydroxamic Acid Ester 3 in C_6D_6/NpSH. In a typical run 0.10 mmol of ester **3** and 19.2 mg (0.12 mmol) of NpSH were dissolved in 1.0 mL of C_6D_6 in a small Schlenk flask. The reaction vessel was closed with a rubber septum, wrapped with aluminum foil, and frozen to liquid nitrogen temperature. After thorough evacuation the flask was flushed with argon, thermostated in a water bath at T = 15 °C, and photolyzed with incandescent light (Philips 150W Spotline R80) for 5 min. The yellow reaction mixture was transferred into a NMR tube. After having recorded the

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NMR and GC spectra the sample was degassed with three consecutive freeze–pump–thaw cycles and sealed for NOE experiments. Preparative thin layer chromatography (hexane: ethyl acetate 3:1) of several runs yielded 2-pyridyl-2′-naphthyl disulfide: mp 95–96 °C; ^{1}H NMR (250 MHz) δ 7.08 (ddd, J = 1.2, 4.9, 7.3 Hz, 1H) 7.46 (m_c, 2H), 7.55–7.84 (m, 6H), 7.99 (d, J = 1.8 Hz, 1H), 8.48 (m_c, 1H); ^{13}C NMR (63 MHz) δ 119.9, 121.1, 125.4, 126.2, 126.5, 127.1, 127.7, 128.1, 129.3, 132.7, 133.7, 137.6, 149.9, 159.9; MS (EI) m/z (rel intensity) 269 (0.4), 220 (100), 156 (86.9), 111 (32.8). Anal. Calcd for $C_{15}H_{11}NS_2$ (269.4): C, 66.88; H, 4.12; N, 5.20; S, 23.80. Found: C, 67.63; H, 4.33; N, 4.73; S, 23.23.

trans-2,4-dimethyltetrahydrofuran (*trans*-**10e**): ^{1}H NMR (250 MHz) δ 0.75 (d, J = 6.7 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H), 1.24–135 (m, 1H), 1.40–1.58 (m, 1H), 1.94–2.17 (m, 1H), 3.14 (dd, J = 6.7, 8.2 Hz, 1H), 3.79–3.97 (m, 2H). *cis*-2,4-dimethyltetrahydrofuran (*cis*-**10e**): ^{1}H NMR (250 MHz) δ 0.79 (d, J = 6.7, 3H), 0.83 (q, J = 12.5 Hz, 1H), 1.20 (d, J = 6.1 Hz, 3H), 1.73–1.82 (m, 1H), 1.88–2.08 (m, 1H), 3.32 (t, J = 7.0 Hz, 1H), 3.75 (t, J = 7.6 Hz, 1H), 3.81–3.99 (m, 1H); ^{13}C NMR (63 MHz) δ 18.7, 22.0, 35.3, 43.4, 74.9, 76.3.

3.2. Photolysis of Thiohydroxamic Acid Ester 3 in TBB or DCB/Bu_3SnH. In a typical run 0.10 mmol of ester **3** was dissolved in 2.0 mL of TBB or DCB in a small Schlenk flask. A definitive amount of olefin free *n*-tetradecane (Fluka, standard for GC) was added, and the reaction vessel was closed with a rubber septum, wrapped with aluminum foil, and frozen to liquid nitrogen temperature. After thorough evacuation the flask was flushed with argon and thermostated in a water bath at T = 30 °C. Addition of 0.1 mL (0.11 g, 0.37 mmol) of tri-*n*-butylstannane under argon to the reaction mixture was followed by photolysis of the reaction mixture with incandescent light (Philips 150W Spotline R80) for 1 min. The decolorized solution was immediately subjected to GC analysis.

3.3. (2-Pyridyl)tetrahydrofurfuryl Sulfide (7). A 81.74 mg (0.43 mmol) sample of *N*-(4-pentenyl-1-oxy)pyridine-2(1*H*)-thione (**3a**) was dissolved in 4 mL of anhydrous benzene and treated as described in section 3.1 without addition of NpSH. The reaction mixture was purified by preparative thin layer chromatography (hexane:ethyl acetate 3:1) to afford 54.23 mg (64%) of thioether **7** as a colorless oil: ^{1}H NMR (250 MHz) δ 1.55–1.70 (m, 1H), 1.74–1.90 (m, 2H), 1.90–2.07 (m, 2H), 3.30 (dd, J = 1.5, 6.4 Hz, 2H), 3.84 (qd, J = 1.2, 7.3 Hz, 1H), 4.09 (quint, J = 6.4 Hz, 1H), 6.88 (ddd, J = 0.9, 5.8, 7.3 Hz, 1H), 7.12 (dt, J = 0.9, 8.2, 1H), 7.38 (ddd, 1.8, 7.3, 8.2 Hz, 1H), 8.33 (ddd, J = 0.9, 2.1, 4.9 Hz, 1H); ^{13}C NMR (63 MHz) δ 26.3, 31.1, 34.8, 68.6, 78.1, 119.6, 122.6, 136.1, 149.6, 158.9; MS (EI) m/z (rel intensity) 195 (1.8), 136 (20.8), 125 (34.9), 111 (100). Anal. Calcd for $C_{10}H_{13}NOS$ (195.3): C, 61.50; H, 6.43; N, 7.17; S, 16.42. Found: C, 61.26; H, 6.71; N, 7.11; S, 16.31.

3.4. Competition Kinetics. A Schlenk flask (standard glassware) was charged with 1.0 mL of a 0.020 M TBB or DCB solution of the ester **3** in the dark. The flask was closed with a rubber septum, wrapped with aluminum foil, and frozen to liquid nitrogen temperature. After thorough evacuation the reactor was flushed with argon and thermostated in a water bath at T = 30 ± 0.2 °C. After 15 min 0.20–0.80 mL of a 1.30 M solution of tri-*n*-butylstannane (thermostated in the same water bath at T = 30 ± 0.2 °C) were added. Ten min later the aluminum foil was removed, and the yellow reaction mixture was photolyzed for 1 min with incandescent light (Philips 150W Spotline R80). The decolorized solution was immediately subjected to GC analysis. Five data points composed of three single runs each were recorded for every radical precursor **3**.

3.5. Photolysis of Benzenesulfenic Acid *O*-Ester in THF/Bu_3SnH. In a typical run 0.40 mmol of radical precursor **5**, 0.2 mL (0.22 g, 0.74 mmol) tri-*n*-butylstannane, and a definitive amount of olefin-free *n*-tetradecane (Fluka, standard for GC) were dissolved in 10.0 mL of anhydrous THF in a Pyrex apparatus and subjected to UV-light photolysis (λ = 350 nm) at T = 15 °C in a Rayonet photoreactor. The reaction was monitored by GC.

4. Photolysis of Thiohydroxamic Acid Ester 3 in CCl_4. Solutions of 0.8 mmol of pyridinethione **3** in 200 mL of anhydrous CCl_4 were photolyzed for 15 min at T = 30 °C. The colorless solution was concentrated at room temperature *in vacuo* (200 mbar), and the remaining liquid was purified by column chromatography (silica gel, petroleum ether bp 50–55 °C:diethyl ether 9:1).

***trans*- and *cis*-2-(chloromethyl)-5-methyltetrahydrofuran (*trans*- and *cis*-12b):**[38] yield 91.52 mg (85%); *trans*-**12b**, ^{1}H NMR (250 MHz) δ 1.23 (d, J = 6.1 Hz, 3H), 1.30–1.61 (m, 1H), 1.62–1.82 (m, 1H), 1.83–2.13 (m, 2H), 3.44–3.58 (m, 2H), 4.07–4.20 (m, 1H), 4.26 (quint, J = 6.4 Hz, 1H); ^{13}C NMR (63 MHz) δ 21.2, 30.3, 34.0, 47.6, 76.3, 78.3; *cis*-**12b**, ^{1}H NMR (250 MHz) δ 0.79–0.97 (m, 1H), 1.25 (d, J = 6.4 Hz, 3H), 1.30–1.61, (m, 1H), 1.83–2.13 (m, 2H), 3.42–3.58 (m, 1H), 4.07–4.20 (m, 1H); ^{13}C NMR (63 MHz) δ 21.4, 29.7. 32.9, 47.4, 77.5, 78.8.

***trans*- and *cis*-2-(chloromethyl)-5-ethyltetrahydrofuran (*trans*- and *cis*-12c):** yield 105.80 mg (89%); MS (EI) m/z (rel intensity) 119, 120 (59.2, 18.2, M^+ − 15), 83 (27.3), 55 (100). Anal. Calcd for $C_7H_{13}ClO$ (148.6): C, 56.57; H, 8.82. Found: C, 56.60; H, 8.85. *trans*-**12c**: ^{1}H NMR (250 MHz) δ 0.88 (t, J = 7.9 Hz, 3H), 1.39–1.81 (m, 4H), 1.87–2.14 (m, 2H), 3.38–3.56 (m, 2H), 3.91 (quint, J = 6.4 Hz, 1H), 4.18 (quint, J = 6.4 Hz, 1H); ^{13}C NMR (63 MHz) δ 10.4, 28.8, 29.3, 31.5, 47.5, 78.2, 81.7. *cis*-**12c**: ^{1}H NMR (250 MHz) δ 0.89 (t, J = 7.6 Hz, 1.39–1.81 (m, 4H), 1.87–2.14 (m, 2H), 3.38–3,56 (m, 2H), 3.80 (quint, J = 6.1 Hz, 1H), 4.09 (quint, J = 6.1 Hz, 1H); ^{13}C NMR (63 MHz) δ 10.3, 28.7, 29.3, 30.1, 47.2, 78.6, 82.1.

***trans*- and *cis*-2-(chloromethyl)-5-(2′-propyl)tetrahydrofuran (*trans*- and *cis*-12d):** yield 124.92; mg (96%); MS (EI) m/z (rel intensity) 119, 121 (100, 36.3), 55 (58.7); MS (CI) m/z 180 ($M^+ + NH_4^+$). Anal. Calcd for $C_8H_{15}ClO$ (162.7): C, 59.07; H, 9.30. Found: C, 59.19; H, 9.58. *trans*-**12d**: ^{1}H NMR (250 MHz) δ 0.85 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 1.48–2.10 (m, 5H), 3.47 (dd, J = 6.1, 10.7 Hz, 1H), 3.58 (dd, J = 5.2, 11.0 Hz, 1H), 3.70 (m_c, 1H), 4.19 (m_c, 1H); ^{13}C NMR (63 MHz) δ 18.4, 19.5, 28.3, 29.3, 31.2, 47.2, 76.8, 86.2. *cis*-**12d**: ^{1}H NMR (250 MHz) δ 0.86 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H), 1.48–2.10 (m 5H), 3.46 (dd, J = 6.1, 10.7 Hz, 1H), 3.53 (dd, J = 5.2, 11.0 Hz, 1H), 3.70 (m_c, 1H), 4.19 (m_c, 1H); ^{13}C NMR (63 MHz) δ 18.5, 19.5, 28.3, 29.3, 31.1, 47.2, 76.8, 86.2.

***trans*- and *cis*-2-(chloromethyl)-2,5-dimethyltetrahydrofuran (*trans*- and *cis*-12g):** yield: 89.70 mg (75%). Anal. Calcd for $C_7H_{13}ClO$ (148.6): C, 56.57; H, 8.82. Found: C, 56.60; H, 8.85. *trans*-**12g**: ^{1}H NMR (250 MHz) δ 1.23 (d, J = 6.1Hz, 3H), 1.33 (s, 3H), 1.47–1.63 (m, 2H), 1.93–2.13 (m, 2H), 3.45 (s, 2H), 4.03–4.18 (m, 1H); ^{13}C NMR (63 MHz) δ 21.6, 23.0, 26.0, 31.8, 52.0, 76.5, 82.6; MS (EI) m/z (rel intensity) 133, 135 (5, 2, M^+ − 15), 99 (93), 43 (100). *cis*-**12g**: ^{1}H NMR (250 MHz) δ 1.20 (d, J = 6.1 Hz, 3H), 1.31 (s, 3H), 1.47–1.63 (m, 2H), 1.93–2.13 (m, 2H), 3.41 (d, J = 1.83 Hz, 2H), 4.03–4.18 (m, 1H); ^{13}C NMR (63 MHz) δ 21.0, 25.2, 25.5, 36.3, 52.0, 75.9, 82.8; MS (EI) m/z (rel intensity) 133, 135 (5, 2, M^+ − 15), 99 (67), 43 (100).

***trans*- and *cis*-2-(1′-chloroethyl)-5-methyltetrahydrofuran (*trans*- and *cis*-12h):** yield 79.64 mg (67%); MS (CI) m/z 166 ($M^+ + NH_4^+$). Anal. Calcd for $C_7H_{13}ClO$ (148.6): C, 56.57; H, 8.82. Found: C, 56.52; H, 8.92. *trans*-**12h**: ^{1}H NMR (250 MHz) δ 1.16 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.4 Hz, 3H), 1.57–2.10 (m, 4H), 3.80–4.14 (m, 3H); ^{13}C NMR (63 MHz) δ 19.9, 20.3, 28.3, 33.2, 59.3, 75.5, 81.2. *cis*-**12h**: ^{1}H NMR (250 MHz) δ 1.18 (d, J = 5.8 Hz, 3H), 1.42 (d, J = 6.7 Hz, 1.57–2.10 (m, 4H), 3.80–4.14 (m, 3H); ^{13}C NMR (63 MHz) δ 19.6, 20.8, 27.3, 32.0, 58.6, 76.5, 81.6.

***trans*- and *cis*-2-(1′-chloro-1′-methylethyl)-5-methyltetrahydrofuran (*trans*- and *cis*-12k):** yield 118.44 mg (91%); MS (EI) m/z (rel intensity) 126 (34.8, M^+ − HCl), 85 (100). Anal. Calcd for $C_8H_{15}ClO$ (162.7): C, 59.07; H, 9.30. Found: C, 59.01; H, 9.20. *trans*-**12k**: ^{1}H NMR (250 MHz) δ 1.22 (d, J = 6.1 Hz, 3H), 1.05–1.18 (m, 1H), 1.51 (s, 3H), 1.56 (s, 3H), 1.85–2.10 (m, 3H), 3.99 (dd, J = 6.4, 7.9 Hz, 1H), 4.11–4.22 (m, 1H); ^{13}C NMR (63 MHz) δ 21.2, 28.6, 28.8, 29.3, 34.6, 72.6, 76.9, 85.9. *cis*-**12k**: ^{1}H NMR (250 MHz) δ 1.24 (d, J = 6.1

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Hz, 3H), 1.44–1.56 (m, 1H), 1.53 (s, 3H), 1.54 (s, 3H), 1.85–2.10 (m, 3H), 3.89 (t, J = 7.0 Hz, 1H), 4.11–4.22 (m, 1H); ^{13}C NMR (63 MHz) δ 21.2, 22.8, 27.1, 27.9, 33.3, 71.3, 76.6, 86.4.

***trans*-3-chloro-3,6-dimethyltetrahydropyran (*trans*-13g):** yield 21.38 mg (18%); ^{1}H NMR (250 MHz) δ 1.20 (d, J = 6.10 Hz, 3H), 1.42 (s, 3H), 1.47–1.63 (m, 2H), 1.93–2.13 (m, 2H), 3.35–3.50 (m, 1H), 3.41 (d, J = 12.4 Hz, 1H), 3.85 (dd, J = 3.1, 12.4 Hz, 1H); ^{13}C NMR (63 MHz) δ 19.7, 27.9, 39.0, 41.6, 65.0, 74.0, 77.4; MS (EI) m/z (rel intensity) 148, 150 (18, 6), 133, 135 (100, 37). Anal. Calcd for $C_7H_{13}ClO$ (148.6): C, 56.57; H, 8.82. Found: C, 56.52; H, 8.91.

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