Sonication-Induced Halogenative Decarboxylation of Thiohydroxamic Esters

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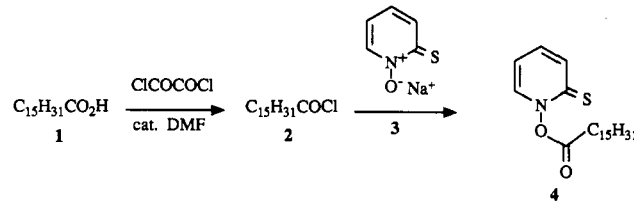
The sonication of primary, secondary, and tertiary thiohydroxamic esters in CCl_4 has led to their synthetic transformation to alkyl chlorides, bromides, or iodides. The high yields were comparable to the previous thermal- or photoinduced version of this same reaction. This radical reaction calls attention to the utility of ultrasound in production of trichloromethyl radical, which was concluded to initiate decomposition of the thiohydroxamic esters.

Introduction

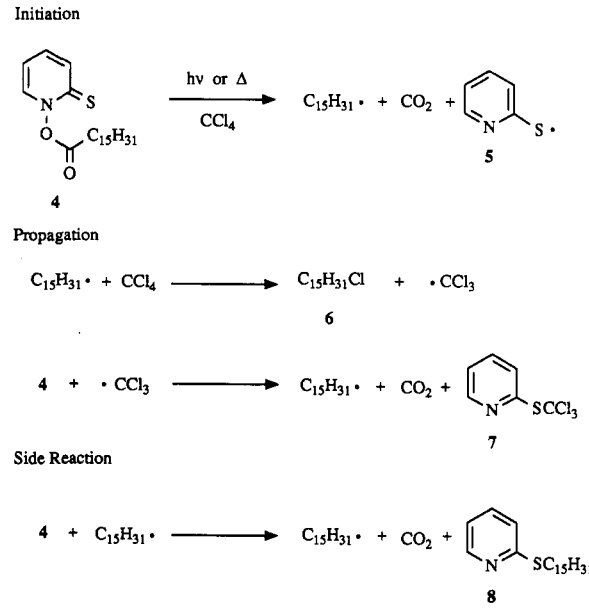
In the last few years there has been significant progress both in the understanding and the practical use of high-intensity ultrasonic waves (sonication) in organic synthesis. The phenomenon responsible for chemical effects (sonochemistry) observed during sonication in solution is acoustic cavitation. Cavitation is the formation and collapse of microbubbles produced while irradiating with ultrasonic waves.[1-11]

The use of sonication has been widely applied to heterogeneous systems where cavitation generally activates the solid present.[2-4,7,12-14] For homogeneous systems, aqueous solutions have been the focus of investigation, because for many years it was wrongly assumed that only water cavitated.[15,16] Aqueous sonochemistry is dominated by homolysis of water into H• and •OH which go on to carry out a variety of reactions.[17-23] Although cavitation of various organic solvents are well known, there are relatively few reports of sonochemistry in nonaqueous homogeneous solution.[24-27] The studies that have been done

Scheme I



Scheme II



suggest a variety of effects that include thermal effects in both the vapor zone of cavitation[28-31] and the liquid layer surrounding the collapsing bubble,[28,32-35] pressure effects,[36,37] and solvent disruption effects.[38-45]

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Table I. Various Concentrations of Ester

entry	conc, M	6, %	1, %	8, %
1	0.003	5	83	0
2	0.03	92	2	6
3	0.3	68	0	19

The major sonochemistry resulting from cavitation in homogeneous solutions is accepted to be generated during the collapse of a bubble, producing extremely high temperatures and pressures. The temperatures and pressures produced have been estimated by both theoretical and experimental means and are on the order of several thousand Kelvin (5200 K) and 1 kbar of pressure.[32] The solvent plus any volatile solutes which have diffused into the sonication bubble, therefore, can undergo reaction due to the direct (primary) action of cavitation.[30,32] The liquid layer surrounding the collapsing bubble has also been speculated to be a reaction zone.[28,32-35] This zone is thought to be heated (1900 K) and pressurized by the collapsing bubble but is quite thin (200 nm) and short lived (2 μs).[28] Fundamentally, therefore, in homogeneous reactions there are two reaction zones for cavitation to effect a reaction: the collapsing bubble and the liquid layer surrounding this collapsing bubble. With the few examples known, it is interesting to investigate what organic chemistry can be done in these reaction zones, making mechanistic generalizations possible, and along these lines, we have performed the following study.

The sonochemistry chosen to explore was the radical decomposition of thiohydroxamic esters (mixed anhydrides of a carboxylic acid and *N*-hydroxypyridine-2-thione). The mechanism and synthetic utility of these esters has already been extensively studied.[46-54] The design was to expose these thermally labile esters to the heat generated by cavitation. Since the esters are essentially nonvolatile, potentially the only direct exposure to cavitation would be in the liquid layer surrounding the collapsed bubble. The esters would undergo homolytic fragmentation, and ensuing radical chemistry could be realized.

Results and Discussion

The thiohydroxamic ester (mixed anhydride) that was chosen for general investigation was ester **4**.[48] Ester **4** was prepared from acid chloride **2** and the sodium salt of thiohydroxamic acid **3** in an overall yield of 98% (Scheme I). This general strategy was used to make all of the thiohydroxamic esters used throughout this study.

Scheme III

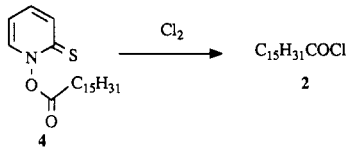

Table II. Temperature Effect

temp, °C	6, %	1, %	8, %
75	90	0	9
33	92	2	6
22	80	11	5
0	64	18	0

Table III. Alkyl Chloride Formation

entry	ester	products (%)
1	4	**6** (92), **7** (77)
2	12	**13** (80), **7** (73), **11** (5)
3	17	**18** (82), **7** (86)
4	22	**23** (76), **21** (10)

To investigate the sonochemistry of thiohydroxamic ester **4**, carbon tetrachloride (CCl_4) was chosen as the solvent. The radical process by which thiohydroxamic esters decompose in CCl_4 has been studied both under light conditions and thermal conditions.[55-59] The mechanism (Scheme II) involves initiation by decomposition of the thiohydroxamic esters into **5**, CO_2, and $C_{15}H_{31}^{\bullet}$, followed by propagation in chain fashion to give 1-chloropentadecane (**6**). This reaction sequence is a very useful synthetic procedure and also could be a sensitive probe of sonication, since thiohydroxamic esters are thermally labile, and the process follows a chain mechanism.

The ultrasonic irradiation (20 kHz, 40 W/cm^2) of thiohydroxamic ester **4** in CCl_4, under argon, produced a mixture of chromatographically separable compounds: $C_{15}H_{31}Cl$ (**6**) (92%), palmitic acid (**1**) (2%), thioether **7** (77%), and side product **8** (6%). The large amount of alkyl chloride **6** and thioether **7** suggests that a radical chain propagation, similar to the one for light and thermal conditions, must have been operating.[55,56]

To optimize this sonochemical radical reaction, various concentrations of ester **4** at 33 °C (20 °C external bath) were tried (Table I). In the low-concentration run (entry 1), carboxylic acid **1** was the major product isolated. Acid **1** was presumably a result of attack of chlorine (Cl_2) on the ester (Scheme III) followed by hydrolysis to the acid during chromatography. The Cl_2 was formed during sonication from the known sonochemical decomposition of CCl_4 to Cl_2.[60,61] The use of sonochemical halogen generation has previously been used to make metal halides.[62] The Cl_2 attack has become the major pathway in this case, because dilution has made the radical pathway less efficient. In a separate experiment, a solution of ester **4** was placed under an atmosphere of Cl_2, and acid chloride **2** was,

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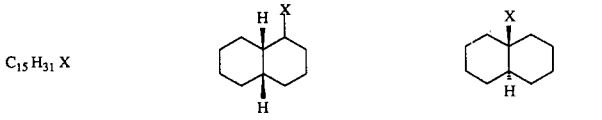
Table IV. Various Radical Traps

entry	ester	trap	equiv of trap in CCl_4	products (%)
1	4	$BrCCl_3$	15	**9** (83)
2	12	$BrCCl_3$	15	**14** (86), **7** (81)
3	17	$BrCCl_3$	15	**19** (85)
4	22	$BrCCl_3$	15	**24** (85), **7** (91)
5	4	$BrCCl_3$	neat	**9** (89), **7** (81)
6	26	$BrCCl_3$	neat	**27** (83), **7** (79)
7	4	CHI_3	1.2	**10** (80)
8	12	CHI_3	1.2	**15** (82)
9	17	CHI_3	1.2	**20** (84)

indeed, formed. In the high-concentration run (entry 3), $C_{15}H_{31}^{\bullet}$ reacted, competitively, with another molecule of ester **4** to produce **8** (Scheme II, side reaction) instead of selectively reacting with a CCl_4 solvent molecule. The optimal concentration of 0.03 M was maintained for all future studies.

The effect of temperature was studied on the sonication of ester **4** in CCl_4. The internal reaction temperatures chosen for study were from 0 °C to 75 °C (Table II). The higher temperatures produced less **1**, but an increasing amount of **8**. The increasing amount of **8** was attributed to the known increase in the rate of addition of $C_{15}H_{31}^{\bullet}$ with ester **4** (Scheme II) at higher temperatures.[48] The increasing amount of **1** at lower temperatures can be attributed to the increased solubility of Cl_2 at lower temperatures, which increased the rate of Cl_2 attack on ester **4** (Scheme III). At the higher temperatures, Cl_2 was simply degassed from the solution, before it had time to attack ester **4**. It should also be mentioned, that at 33 °C, the rate of formation of **6** was twice the rate at 75 °C, due to the lower vapor pressure of CCl_4 leading to more intense cavitation. The optimal temperature of 33 °C was chosen for all future studies.

With the general conditions (33 °C, 0.03 M) worked out for the formation of alkyl chloride **6**, a series of primary, secondary, and tertiary thiohydroxamic esters were sonicated in CCl_4 (Table III).[63] Entries 1–3 show that primary, secondary, and tertiary thiohydroxamic esters can undergo efficient conversion to alkyl chlorides using the sonication procedure. The thiohydroxamic ester **22** of the oleic acid run (entry 4) shows the compatibility of a double bond to the reaction conditions. For entries 1–3, thioether **7** was isolated, providing evidence that the propagation step in the proposed mechanism (Scheme II) was operating in all cases.



1) X= COOH
2) X= COCl
4) X= CO_2 N-S
6) X= Cl
8) X= S-2-Pyr
9) X= Br
10) X= I

11) X= COOH
12) X= CO_2 N-S
13) X=Cl
14) X= Br
15) X= I

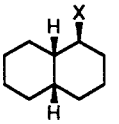
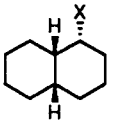
16) X= COOH
17) X= CO_2 N-S
18) X= Cl
19) X= Br
20) X= I

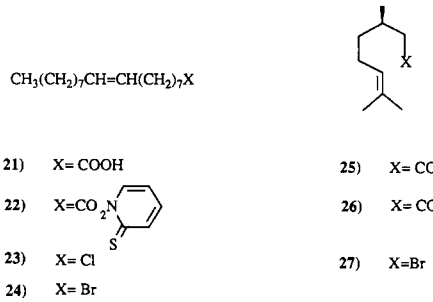
To further expand the scope of this reaction to bromides and iodides, other radical traps were sonicated with various thiohydroxamic esters in CCl_4 to generate differing functionality (Table IV). The reaction with $BrCCl_3$ (entries 1–6) gave very good yields of alkyl bromides (**9**, **14**, **19**, **24**, **27**). This reaction was done both in neat $BrCCl_3$ (entries 5,6) or with 15 equiv of $BrCCl_3$ in CCl_4 (entries 1–4) working nearly as well. The $BrCCl_3$ was obviously a much better trap than the CCl_4 for the carbon radical generated,[64–66] considering in entries 1–4, the bromides were produced exclusively in preference to chlorides.

Table V. Average Reaction Times

solvent	radical trap	average time required, min
$BrCCl_3$	solvent	10–15
CCl_4	solvent	20–30
CCl_4	$BrCCl_3$	20–25
CCl_4	CHI_3	45–50

Table VI. Ratio of Isomers

product	X		
13	Cl	8	1
14	Br	6.3	1
15	I	3	1



Thiohydroxamic ester **22** derived from oleic acid (entry 4) again showed the stability of a double bond to these conditions. The equivalent reaction using standard Hunsdieker methodology gives lower yields of monobrominated compound **24**.[67]

The ester derived from citronellic acid (**26**, entry 6) gave a high yield of the acyclic bromide **27**. This result was similar to a result (87% bromide) obtained by a photochemical process run previously.[56] The failure to close to a cyclopentane calls attention to the extremely fast quenching with $BrCCl_3$ in accord with known kinetic rates.[64–66]

To produce iodides, iodoform was added to a solution of the esters in CCl_4 (entries 7–9), and the material was sonicated. It was necessary to add only 1.2 equiv of CHI_3 to get selectively the iodides over any of the chlorides. At the end of the reaction using iodoform, the solution was highly colored, and the expected pyridylthio ether could not be isolated. Thus, in this case direct proof of the chain carrier was not found.

The average time required to consume 0.3 mmol of thiohydroxamic ester in 10 mL of solution under standard conditions was dependent on the radical trap present and solvent but independent of ester (Table V). The fastest reaction times were in $BrCCl_3$, presumeably because $BrCCl_3$ has a lower vapor pressure than CCl_4, thus it cavitates more violently, generating radicals more effi-

(63) Thiohydroxamic esters of *p*-methoxy- and *p*-nitrobenzoic acids yielded less than 10% aryl halide but gave the acid after standard reaction conditions.

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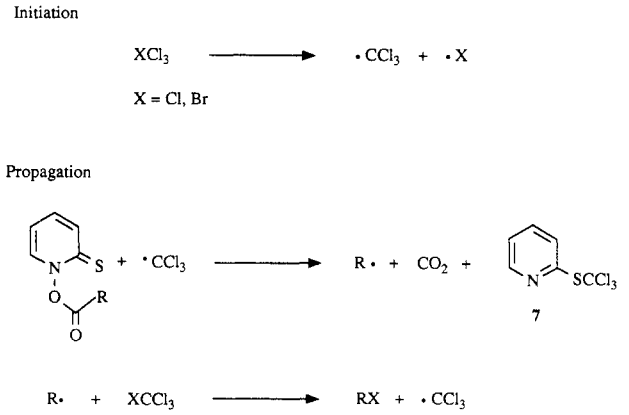
Scheme IV



ciently (faster initiation). The longest reaction times were when CHI_3 was used as the radical trap. This lengthy reaction time was probably related to the poorer propagation of the radical chain.

The secondary radical generated from cis,cis-ester **12** produced a mixture of diastereomers (Table VI). The tertiary radical generated from trans-ester **17** produced only the trans-decalin ring system (**18–20**).

To investigate what other radical sonochemistry could be done with thiohydroxamic esters, benzene was tried as the solvent. In the absence of a radical trap (i.e. CCl_4), thiohydroxamic esters are known to produce compound **8** (Scheme II) and dimer from a combination of R· with R·.[48] When ester **4** was sonicated for 18 h at 33 °C in benzene, the starting ester was recovered quantitatively. Another sonication reaction was also run in benzene with AIBN (azobisisobutyronitrile) added, but again no decomposition of ester **4** was observed. These findings demonstrate that thiohydroxamic ester must not be directly participating in the cavitation process. Therefore, ester **4** must not be in the cavitation bubble, which is not surprising, since it is nonvolatile, and ester **4** must not have felt the high temperature in the liquid layer surrounding the collapsing bubble, due either to this reaction zone being insignificant in size, or the high temperature in this zone was dissipated too quickly for reaction.

The cavitation in benzene can be assumed to be similar to the cavitation in CCl_4, therefore, thiohydroxamic ester **4** was not decomposing due to the high temperatures produced during sonication. Carbon tetrachloride is known to decompose under sonication conditions into Cl· and ·CCl_3.[60] The ·CCl_3 produced from cavitation must have been the species initiating the reaction.[68–70] Therefore, these sonication reactions were fundamentally different from the thermal or photoinduced halogenative decarboxylations, because the initiation step was not radical decomposition of the thiohydroxamic ester, but radical decomposition of CCl_4 during cavitation to produce ·CCl_3 as the initiator. The mechanism of the ultrasonic irradiation induced halogenative decarboxylation can be proposed (Scheme IV).

Methylene chloride and chloroform were tried as solvents to see if these chlorinate solvents would lead to radical species capable of initiating radical chemistry of thiohydroxamic ester **4**. The sonochemical decomposition of chloroform has been reported elsewhere[71,72] and does involve radicals, including ·CCl_3, and presumeably, methylene chloride would involve radical decomposition pathways as well.

The ultrasonic irradiation of ester **4** was carried out in anhydrous methylene chloride or chloroform. The results in both solvents turned out to be essentially identical. After silica gel chromatography, carboxylic acid **1** was isolated in high yield. The same reaction was done in deuterated chloroform and a ^1H NMR spectrum of various aliquots of the reaction mixture revealed that acid chloride **2** was actually the product formed during sonication. The isolated carboxylic acid was, therefore, simply an artifact from hydrolysis of the acid chloride during purification. The thiohydroxamic piece of the ester was not isolated nor seen in the ^1H NMR study. A white precipitate, however, was formed and was believed to be an insoluble hydrochloride salt of **3**. It has been shown that one of the principle sonication products of $CHCl_3$ is HCl. The HCl generated, therefore, could lead to the decomposition of ester **4** to give the acid chloride **2** and thiohydroxamic acid **3**, which, in turn, reacted with a second molecule of HCl to generate the insoluble hydrochloride salt of **3**. To confirm that HCl was capable of attacking ester **4**, a $CDCl_3$ solution of ester **4** was allowed to stand under an atmosphere of HCl, and, indeed, palmitoyl chloride (**2**) was produced along with the insoluble hydrochloride salt of **3**. Therefore, the sonochemically produced HCl attacks thiohydroxamic ester **4** faster than any sonochemically produced radicals in CH_2Cl_2 or $CHCl_3$ and/or the chain propagation was very inefficient in CH_2Cl_2 or $CHCl_3$.

Experimental Section

General Procedures. Methylene chloride was distilled from P_2O_5. Benzene was distilled from sodium and benzophenone. Carbon tetrachloride was distilled prior to use. All other reagents were obtained from commercial suppliers and used without further purification. Melting points were taken in Pyrex capillary and are uncorrected. IR spectra were determined with a Perkin-Elmer Model 281 infrared recording spectrophotometer. ^1H NMR spectra were determined with the following spectrometers: UCB-200 and UCB-250 (super-conducting, FT instruments operating at 200 and 250 MHz), and Bruker AM-400. ^{13}C NMR spectra were determined on the UCB-200 at 50.78 MHz. Chemical shifts are expressed in ppm downfield from tetramethylsilane using tetramethylsilane as an internal standard for ^1H NMR and chloroform (77.0) for ^{13}C NMR. ^1H NMR data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constants in hertz, proton assignment. Elemental analyses were performed by the Microanalytical Laboratory operated by the College of Chemistry, University of California. The ultrasonic waves were produced by a 250-W high intensity ultrasonic processor, Vibra Cell, from Sonics & Materials Inc. During our reactions the power meter showed an average power of 23% corresponding to a power of about 45 W cm^{-2}. Ultrasonic irradiation was carried out with the tip of the horn immersed directly in the solution.

General Preparation of Acid Chlorides. Acid chlorides were prepared immediately prior to use, by treatment of the acid (10 mmol) in methylene chloride (50 mL) with oxalyl chloride (20 mmol) and DMF (dimethylformamide) (1 drop) at room temperature under nitrogen with magnetic stirring for 2 h.[59] The reaction mixture was evaporated to dryness, redissolved in methylene chloride (30 mL), and evaporated to dryness again, yielding the crude acid chloride, which was used without further purification.

General Procedure for the Synthesis of Mixed Anhydrides "Thiohydroxamic Esters". These compounds are sensitive to light; therefore, the reaction vessel, chromatography column, etc.,

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were covered with aluminum foil and not exposed to direct lighting. To a solution of the acid chloride (10 mmol) in dry methylene chloride (50 mL) was added the sodium salt of *N*-hydroxy-2-thiopyridone (Fluka) (**3**) (10.5 mmol). After stirring for the desired time and at the appropriate temperature (see below), the reaction mixture was rapidly filtered and the solvent was evaporated without heating. The compounds obtained by this method are listed below.

1-[(1-Oxohexadecyl)oxy]-2(1*H*)-pyridinethione (4): reaction time 30 min at 20 °C; purified by flash chromatography on silica gel with methylene chloride as the eluent and crystallized from pentane/CH_2Cl_2 to give fluffy yellow crystals (98%); mp 72 °C (lit.[73] mp 75 °C).

1-[[(Decahydro-(1α,4aα,8aα)-naphthalen-1-yl)carbonyl]-oxy]-2(1*H*)-pyridinethione (12): reaction time 30 min at 20 °C; purified by flash chromatography on silica gel using methylene chloride as the eluent and crystallized from pentane/CH_2Cl_2 to give yellow crystals (78%); mp 93–94 °C; IR (solution cell, CH_2Cl_2) 1810 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.68 (dm, 1, J = 8 Hz), 7.54 (dm, 1, J = 7 Hz), 7.19 (tm, 1, J = 7 Hz), 6.62 (tm, 1, J = 7 Hz), 2.95 (m, 1), 2.35 (m, 1), 1.10–1.95 (m, 15). Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 65.92; H, 7.42; N, 4.75.

1-[[(Decahydro-(4aα)-naphthalen-8aβ-yl)carbonyl]-oxy]-2(1*H*)-pyridinethione (17): reaction time 40 h at 45 °C with a catalytic amount of dimethylaminopyridine; purified by flash chromatography on silica gel using methylene chloride as the eluent and crystallized from pentane/CH_2Cl_2 (66%); mp 119 °C dec; IR (solution cell, CH_2Cl_2) 1800 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.70 (dm, 1, J = 8 Hz), 7.43 (dm, 1, J = 7 Hz, 7.18 (tm, 1, J = 7 Hz), 6.62 (tm, 1, J = 8 Hz), 2.52 (d, 2, J = 13 Hz), 1.17–1.90 (m, 15); ^{13}C (200 MHz, $CDCl_3$) δ 176.75, 170.43, 137.90, 137.78, 133.09, 112.44, 48.79, 46.51, 37.87, 29.03, 26.33, 23.76. Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 66.16; H, 7.48; N, 4.84.

1-[(*cis*-1-Oxooctadec-9-enyl)oxy]-2(1*H*)-pyridinethione (22): reaction time 30 min at 20 °C; purified by flash chromatography on silica gel using methylene chloride as the eluent to give a yellow oil (84%); IR (solution cell, CH_2Cl_2) 1820, 1620, 1535 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.62 (dd, 1, J = 1.6, 8 Hz), 7.56 (dd, 1, J = 1.3, 7 Hz), 7.17 (dt, 1, J = 1.6, 8 Hz), 6.61 (dt, 1, J = 1.8, 7 Hz), 5.31 (m, 2, vinyl H), 2.68 (t, 2, J = 7 Hz, Hα of carbonyl), 1.97 (m, 4, allyl H), 1.77 (tt, 2, J = 7, 7 Hz, Hβ of carbonyl), 1.23 (s (br), 20 H), 0.84 (t, 3, J = 7 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 175.40, 168.69, 137.54, 136.88, 133.42, 129.69, 129.38, 112.42, 31.65, 31.29, 29.52, 29.41, 29.28, 29.07, 28.90, 28.79, 28.70, 26.96, 26.91, 24.06, 22.44, 13.91. Anal. Calcd for $C_{23}H_{37}NO_2S$: C, 70.54; H, 9.52; N, 3.61. Found: C, 70.48; H, 9.92; N, 3.61.

1-[[(3*R*)-3,7-Dimethyl-1-oxooct-6-enyl]oxy]-2(1*H*)-pyridinethione (26): reaction time 30 min at 20 °C; purified by flash chromatography on silica gel using methylene chloride as the eluent to give a yellow oil (60%); IR (solution cell, CH_2Cl_2) 1810 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60 (dm, 1, J = 7 Hz), 7.55 (dm, 1, J = 7 Hz), 7.18 (tm, 1, J = 7 Hz), 6.62 (tm, 1, J = 7 Hz), 5.03 (m, 1 H vinyl), 2.60 (m, 2), 2.01 (m, 2 + 1), 1.61 (s, 3), 1.20–1.60 (m, 2), 1.03 (d, 3, J = 5 Hz). Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.36; H, 7.70; N, 5.00.

General Procedure for the Decomposition of Esters by Sonication. The ester (0.3 mmol) was dissolved in solvent system listed and irradiated with ultrasonic waves until thin-layer chromatography indicated complete consumption of starting ester (see Table V for average reaction times) under an argon atmosphere. Typically, a 20 °C water bath was kept around the reaction vessel during sonication, and this maintained the internal reaction temperature from 20 °C, which quickly (5–10 min) rose to 33 °C, finally reaching a maximum of 35 °C. The variable-temperature (see Table II) runs were done with baths of −20 °C, 0 °C, 20 °C, and 60 °C, maintaining average internal temperatures of 0 °C, 22 °C, 33 °C, and 75 °C. There was no need to stir the reaction mixture during the sonication process. The solvent was then evaporated under reduced pressure, and the residue was purified by chromatography on silica gel using a solvent gradient, generally pentane, followed by ethyl acetate–pentane mixtures. The compounds obtained by this method are listed below.

1-Chloropentadecane (6). Sonication of ester **4** (81 mg, 0.22 mmol) in 10 mL of carbon tetrachloride gave, after chromatography (pentane), **6** as a colorless oil (50.4 mg, 92%): ^1H NMR (200 MHz, $CDCl_3$) δ 3.53 (t, 2, J = 7 Hz), 1.77 (tt, 2, J = 7 Hz), 1.26 (m (br), 24), 0.86 (t, 3, J = 7 Hz). Identical with reported literature spectrum.[59]

The column was further eluted (pentane 70%, ethyl acetate 30%) to give 2-(pentadecylthio)pyridine (**8**) (4 mg, 5.7%) as a pale yellow oil: ^1H NMR (200 MHz, $CDCl_3$) δ 8.42 (dm, 1, J = 5 Hz), 7.45 (tm, 1, J = 7.3 Hz), 7.16 (dm, 1, J = 8 Hz), 6.96 (tm, 1, J = 5 Hz), 3.16 (t, 2, J = 7 Hz), 1.70 (tt, 2, J = 7, 7 Hz), 1.28 (m (br), 24), 0.88 (t, 3, J = 7 Hz). Identical with reported literature spectrum.[59]

The column was further eluted (pentane 50%, ethyl acetate 50%) to give 2-[(trichloromethyl)thio]pyridine (**7**) (39 mg, 77%) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 8.73 (m, 1), 7.83 (m, 2), 7.41 (m, 1). Identical with reported literature spectrum.[74]

1-Bromopentadecane (9). Sonication of ester **4** (210.5 mg, 0.58 mmol) in 10 mL of bromotrichloromethane gave, after chromatography (pentane), **9** (148.5 mg, 88.7%) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 3.39 (t, 2, J = 7 Hz), 1.83 (tt, 2, J = 7, 7 Hz), 1.24 (m (br), 24), 0.86 (t, 3, J = 7 Hz). Identical with reported literature spectrum.[59]

The column was further eluted (pentane 50%, ethyl acetate 50%) to give compound **7** (106 mg, 81%).

Sonication of ester **4** (130.6 mg, 0.36 mmol) in 9.5 mL of carbon tetrachloride and 0.5 mL of bromotrichloromethane (15 equiv) gave, after chromatography (pentane), **9** (86.1 mg, 83%) identical with above.

1-Iodopentadecane (10). Sonication of ester **4** (86.7 mg, 0.24 mmol) and 1.22 equiv of iodoform (114 mg, 0.29 mmol) in 10 mL of carbon tetrachloride gave, after chromatography (pentane), **10** (72 mg, 83.7%) as a crystalline compound (pentane): mp 22–24 °C (the compound contained a very small amount of iodoform); ^1H NMR (200 MHz, $CDCl_3$) δ 3.17 (t, 2, J = 7 Hz), 1.80 (tt, 2, J = 7, 7 Hz), 1.23 (m (br), 24), 0.86 (t, 3, J = 7 Hz). Identical with reported literature spectrum.[59]

1-Chlorodecahydro-(1α,4aβ,8aβ)-naphthalene and 1-Chlorodecahydro-(1β,4aβ,8aβ)-naphthalene (13). Sonication of ester **12** (108.5 mg, 0.37 mmol) in 10 mL of carbon tetrachloride gave, after chromatography (pentane), **13** (51.3 mg, 80%) as a mixture of two diastereoisomers (ratio 1α/1β, 8/1): ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (ddd, 1, J = 3.7, 7.5, 7.5 Hz, major isomer), 4.11 (ddd, 1, J = 4.5, 4.5, 12.3 Hz, minor isomer), 1.20–2.20 (m (br), 16). Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.55; H, 9.92. Found: C, 69.34; H, 10.09.

The column was further eluted (pentane 50%, ethyl acetate 50%) to give compound **7** (62 mg, 73%).

1-Bromodecahydro-(1α,4aβ,8aβ)-naphthalene and 1-Bromodecahydro-(1β,4aβ,8aβ)-naphthalene (14). Sonication of ester **12** (75.7 mg, 0.26 mmol) in 9.5 mL of carbon tetrachloride and 0.5 mL of bromotrichloromethane gave, after chromatography (pentane), **14** (48.6 mg, 86.1%) as a mixture of two isomers (ratio 1α/1β, 6.3/1): ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (ddd, 1, J = 3.7, 7.4, 7.4 Hz, major isomer), 4.33 (ddd, 1, J = 4.6, 4.6, 12.5 Hz, minor isomer), 0.95–2.40 (m (br), 16). Anal. Calcd for $C_{10}H_{17}Br$: C, 55.31; H, 7.89. Found: C, 55.70; H, 8.01.

The column was further eluted (pentane 50%, ethyl acetate 50%) to give compound **7** (81%).

1-Iododecahydro-(1α,4aβ,8aβ)-naphthalene and 1-Iododecahydro-(1β,4aβ,8aβ)-naphthalene (15). Sonication of ester **12** (117.8 mg, 0.40 mmol) and 1.2 equiv of iodoform (207 mg, 0.53 mmol) in 10 mL of carbon tetrachloride gave, after chromatography (pentane), **15** (88 mg, 82.3%) as a mixture of two diastereoisomers (ratio 1α/1β, 3/1): ^1H NMR (400 MHz, $CDCl_3$) δ 4.63 (m, 1, major isomer), 4.55 (ddd, 1, J = 4.5, 4.5, 12.5 Hz, minor isomer), 1.20–2.20 (m, 16). Anal. Calcd for $C_{10}H_{17}I$: C, 45.47; H, 6.49. Found: C, 45.62; H, 6.44.

***trans*-4a-Chlorodecahydronaphthalene (18).** Sonication of ester **17** (108 mg, 0.37 mmol) in 10 mL of carbon tetrachloride

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gave, after chromatography (pentane), **18** (53 mg, 82%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–2.20 (m (br), 17); ^{13}C NMR (200 MHz, $CDCl_3$) identical with literature.[75]

The column was further eluted (pentane 50%, ethyl acetate 50%) to give compound **7** (73 mg, 86%).

***trans*-4a-Bromodecahydronaphthalene (19).** Sonication of ester **17** (92 mg, 0.32 mmol) in 9.5 mL of carbon tetrachloride and 0.5 mL of bromotrichloromethane gave, after chromatography (pentane), **19** (58 mg, 84.6%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–2.20 (m (br), 17); ^{13}C NMR (200 MHz, $CDCl_3$) identical with literature.[73] Anal. Calcd for $C_{10}H_{17}Br$: C, 55.31; H, 7.89. Found: C, 55.50; H, 8.07.

***trans*-4a-Iododecahydronaphthalene (20).** Sonication of ester **17** (95.1 mg, 0.33 mmol) and 1.2 equiv of iodoform (155 mg, 0.39 mmol) in 10 mL of carbon tetrachloride gave, after chromatography (pentane), **20** (72 mg, 83.7%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–2.15 (m (br), 17); ^{13}C NMR (200 MHz, $CDCl_3$) identical with literature.[75]

***cis*-1-Chloro-8-heptadecene (23).** Sonication of ester **22** (141.2 mg, 0.36 mmol) in 10 mL of carbon tetrachloride gave, after chromatography (pentane), **23** (75 mg, 76.2%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.35 (m, 2, H vinyl), 3.53 (t, 2, J = 7 Hz), 2.02 (m (br), 4), 1.78 (tt, 2, J = 7, 7 Hz), 1.28 (m (br), 20), 0.89 (t, 3, J = 7 Hz). Prepared previously.[67]

***cis*-1-Bromo-8-heptadecene (24).** Sonication of the ester **22** (131.8 mg, 0.34 mmol) in 9.5 mL of carbon tetrachloride and 0.5 mL of bromotrichloromethane (15 equivalents) gave, after chromatography (pentane), **24** (90.3 mg, 84.7%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.33 (m, 2, vinyl H), 3.38 (t, 2, J = 7 Hz), 2.00 (m, 4), 1.83 (tt, 2, J = 7, 7 Hz), 1.25 (m (br), 20 H), 0.86 (t, 3, J = 7 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 130.01, 129.60, 57.75, 33.95, 32.82, 31.91, 29.76, 29.62, 29.53, 29.33, 29.06, 28.79, 28.67, 28.15, 27.22, 27.13, 22.71, 14.13. Prepared previously.[67]

The column was further eluted (pentane 50%, ethyl acetate 50%) to give compound **7** (70 mg, 91%).

(6*R*)-7-Bromo-2,6-dimethyl-2-heptene (27). Sonication of ester **26** (107.6 mg, 0.38 mmol) in 10 mL of bromotrichloromethane gave, after chromatography (pentane 50%, ethyl acetate 50%), **27** (65 mg, 82.6%) as a colorless oil: ^{1}H NMR (200 MHz) δ 5.12 (tm, 1, 5, J = 7 Hz), 3.38 (m, 2, 1), 2.05 (m, 2), 1.71 (s, 3), 1.64 (s, 3), 1.20–1.80 (m (br), 3), 1.05 (d, 3, J = 5 Hz). Identical with reported literature spectrum.[76]

The column was further eluted (pentane 50%, ethyl acetate 50%) to give compound **7** (69 mg, 79%).

Sonication of Ester 4 in Chloroform or Methylene Chloride. Ester **4** (0.3 mmol) was dissolved in 10 mL of chloroform or methylene chloride and sonicated during 1 h under an argon atmosphere. A 20 °C water bath was used to maintain the reaction temperature below 35 °C. The reaction was followed by observing the disappearance of the yellow color characteristic of the ester. After chromatography the only compound isolated was acid **1** quantitatively.

A similar experiment executed in deuterochloroform gave acyl chloride **2** as the only identifiable product in the reaction mixture by taking ^{1}H NMR spectra of aliquots during the reaction.

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Registry No. **1**, 57-10-3; **2**, 112-67-4; **3**, 15922-78-8; **4**, 89025-67-2; **6**, 4862-03-7; **7**, 66832-24-4; **8**, 89025-53-6; **9**, 629-72-1; **10**, 35599-78-1; **12**, 123540-79-4; *cis*-**13**, 123540-80-7; *trans*-**13**, 123540-86-3; *cis*-**14**, 123540-81-8; *trans*-**14**, 123540-87-4; *cis*-**15**, 123540-82-9; *trans*-**15**, 123540-88-5; **17**, 123540-83-0; **18**, 5597-82-0; **19**, 7731-69-3; **20**, 82823-27-6; **22**, 119520-40-0; **23**, 123540-84-1; **24**, 81861-58-7; **26**, 123540-85-2; **27**, 106130-55-6; CCl_4, 56-23-5; (Z)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7COCl$, 112-77-6; (R)-$(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)CH_2COCl$, 77732-35-5; $BrCCl_3$, 75-62-7; CHI_3, 75-47-8; $CDCl_3$, 865-49-6; decahydro-(1α,4aα,8aα)-naphthalene-1-carbonyl chloride, 123540-78-3; *trans*-4a-decahydronaphthalenecarbonyl chloride, 3021-76-9.

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Synthesis of Deuterium-Labeled Sesquiterpene Lactones Isolated from *Inula helenium* L.

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Reduction of the vinyl sulfoxides **9** and **10** derived from isoalantolactone (**1**) and alantolactone (**2**) with $NaBD_4$ yielded deuterium-labeled lactones **11** and **12**. Amalgam reduction of sulfides **7** and **8** or sulfoxides **9** and **10** gave labeled products but not the expected deuterated lactones **11** and **12**. Satisfactory deuteration of alantolactone **2** could be achieved by CF_3COOD hydrolysis of (tributylstannyl)alantolactone (**23**) obtained in four steps from alantolactone **2**.

Introduction

Allergic contact dermatitis (ACD) to simple chemicals is a dermatologic problem concerning a number of patients in the world. It is believed that the allergy-producing molecules, also called *haptens*, are low molecular weight (~1000 Da maximum) with electrophilic properties, able to bind to nucleophilic groups of skin proteins.[1] The molecular mechanism of ACD is a clue to the understanding of this biological phenomenon and a better knowledge of the factors regulating ACD might enable one to effect prevention. In this respect, availability of isotope-labeled haptens is an important step for the study of hapten–protein interaction ultimately leading to ACD induction.

We have been involved for a number of years now in the synthesis of model α-methylene-γ-butyrolactones for the purpose of uncovering structure–activity relationships, including the stereospecificity of molecular recognition.[2]

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