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# Synthesis and Sensorial Properties of 2-Alkylalk-2-enals and 3-(Acetylthio)-2-alkyl Alkanals

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Parallel synthesis was applied to prepare a series of 3-(acetylthio)-2-alkyl alkanals by Michael addition of thioacetic acid under alkaline conditions to $\alpha,\beta$-unsaturated 2-alkyl-substituted aldehydes, which were obtained by aldol condensation of the corresponding primary aldehydes as starting materials. The target compounds were characterized in terms of GC, MS, and NMR data. The sensory properties of the odorants, such as odor quality and odor detection threshold value, were determined with a trained panel. Structure−activity relationships are discussed, suggesting that the 1,3-oxygen−sulfur functionality, required for the "olfactophore" of tropical/vegetable notes, can further be extended to the acetylthio derivatives.

**KEYWORDS: Parallel synthesis; 2-alkylalk-2-enals; 3-(acetylthio)-2-alkyl alkanals; odorants; GC-MS; NMR; odor thresholds; sensory description**

## INTRODUCTION

Volatile organic sulfur compounds contribute to the aroma of many vegetables, fruits, and food products (*1*, *2*). In general, thiols and sulfides belong to the most intense and characteristic aroma substances, with sulfury, vegetable-like, and fruity notes perceived at low concentrations. In bell peppers, we have recently identified 2-heptanethiol as an odor-active compound (*3*). However, the identification of thiols and sulfides is generally a challenging task due to their instability and low concentration. Therefore, sulfur compounds can easily be overlooked in complex mixtures. The sensory relevance of such odorants is due to their low threshold values. For example, (2*R*,3*S*)-3-mercapto-2-methylpentan-1-ol, a character-impact constituent of fresh onions, shows an odor threshold of 0.03 $\mu$g/kg of water (*4*).

Identification of sensory relevant compounds can be achieved by applying a combinatorial approach. Vermeulen and co-workers (*5*−*7*) have prepared a series of sulfur-containing odorants by reacting various precursors in one reaction vessel. Odor-active compounds were screened by gas chromatography−olfactometry (GC-O) techniques for identification experiments, which are facilitated due to higher concentrations as compared to natural extracts. An alternative approach is to run several reactions in parallel in different reactors, a method called parallel synthesis frequently used in pharmaceutical research (*8*). In general, combinatorial approaches are easy to run; however, their analysis is demanding because complex mixtures of many products are obtained. The parallel approach has the advantage of simple automation leading to several isolated compounds, which can easily be characterized.

The objective of this paper was (i) the synthesis of various 2-alkylalk-2-enals and 3-(acetylthio)-2-alkyl aldehydes as reference compounds and (ii) the description of their sensory properties. The odorants were characterized in terms of GC, MS, and NMR data to facilitate their identification in complex mixtures.

## EXPERIMENTAL PROCEDURES

**Materials.** The chemicals were commercially available as follows: propanal (>98%), butanal (>98%), pentanal (>98%), hexanal (>98%), heptanal (>98%), octanal (>98%), thioacetic acid (>95%), piperidine (>99%), deuterochloroform ($C^2HCl_3$, >99%) (Fluka/Aldrich, Buchs, Switzerland); hydrochloric acid (HCl, 37%), magnesium sulfate ($MgSO_4$, 98%), sodium sulfate ($Na_2SO_4$), sodium bicarbonate ($NaHCO_3$), sodium hydroxide (NaOH), silica gel 60 (Merck, Darmstadt, Germany). Diethyl ether ($Et_2O$) was from Merck and freshly distilled over sodium/benzophenone (Fluka/Aldrich) prior to use. Air-sensitive reactions were carried out under nitrogen atmosphere.

**Syntheses** were achieved using conventional (*9*) and parallel synthesis, the latter using a Quest 205 apparatus from Argonaut Technologies (Basel, Switzerland). Combination of parallel synthesis with on-line workup and sample collection allows synthesis procedures using a single instrument. Each reaction vessel has a port at the top, a drain valve at the bottom, and inert gas to control draining time. This gives a number of options for on-line workup such as liquid−liquid extraction or solvent evaporation.

*Synthesis of 2-Alkylalk-2-enals* ***2a*****−*****f*****.** A three-neck flask (50 mL) was fitted with a sealed stirrer, an efficient reflux condenser, and a dropping funnel containing the freshly redistilled aldehyde (0.3 mol). A NaOH solution (1 M, 10 mL) was placed in the flask and heated to 80 °C. The aldehyde was added rapidly under vigorous stirring, and

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then the reaction mixture was refluxed for 1 h. After cooling to room temperature, the organic layer was separated and distilled without further treatment under reduced pressure using a fractionating column (17 × 2 cm). The yields were between 40 and 70%. In each case, one of the stereoisomers was formed in high excess: except for (*E*)-2-methylpent-2-enal (**2a**), the *Z*-isomer was preponderant. The GC and MS data for the *E*/*Z* isomers are given below. The NMR data refer to the major isomer.

*(E)-2-Methylpent-2-enal (**2a**):* distillation, 110 °C, 1 bar; purity, >95% by NMR, >99% by GC; GC ratio for *E*/*Z* (%), 99.2/0.8; GC, RI(PONA) = 810/810, RI(DB-Wax) = 1175/1172; MS (EI, *m*/*z*, rel %) 98 ($M^+$, 48/62), 83 (17/24), 69 (32/32), 55 (31/35), 53 (14/22), 43 (15/20), 41 (100/100), 39 (52/53); $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 1.07 (t, 3H, $CH_3$, $^3J$ = 7.6 Hz), 1.69 (d, 3H, $CH_3$, $^4J$ = 1.3 Hz), 2.33 (dq, 2H, $CH_2$, $^3J$ = 7.4 Hz, $^3J$ = 7.6 Hz), 6.44 (tq, 1H, CH, $^3J$ = 7.4 Hz, $^4J$ = 1.3 Hz), 9.30 (s, 1H, CH═O); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 9.3 ($CH_3$), 13.1 ($CH_3$), 22.6 ($CH_2$), 139.1 (Cq), 156.6 (CH), 195.7 (C═O).

*(Z)-2-Ethylhex-2-enal (**2b**):* distillation, 35 °C, 130 mbar; purity, >95% by NMR, 98.5% by GC; GC ratio for *E*/*Z* (%), 1.8/98.2; GC, RI(PONA) = 989/982, RI(DB-Wax) = 1322/1318; MS (EI, *m*/*z*, rel %) 126 ($M^+$, 36/36), 111 (27/23), 97 (72/53), 93 (27/19), 69 (32/24), 67 (30/24), 55 (100/100), 43 (36/25), 41 (89/73), 39 (61/53); $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 0.88−0.96 (2t, 6H, 2 $CH_3$, $^3J$ = 7.1 Hz), 1.45 (tq, 2H, $CH_2$, $^3J$ = 7.4 Hz, $^3J$ = 7.1 Hz), 2.18 (dt, 2H, $CH_2$, $^3J$ = 7.4 Hz, $^3J$ = 7.4 Hz), 2.26 (q, 2H, $CH_2$, $^3J$ = 7.1 Hz), 6.35 (t, 1H, CH, $^3J$ = 7.4 Hz), 9.28 (s, 1H, CH═O); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 13.2 ($CH_3$), 13.8 ($CH_3$), 17.2 ($CH_2$), 21.9 ($CH_2$), 30.6 ($CH_2$), 145.3 (Cq), 154.5 (CH), 195.0 (C═O).

*(Z)-2-Propylhept-2-enal (**2c**):* distillation, 35 °C, 25 mbar; purity, >95% by NMR, 98.2% by GC; GC ratio for *E*/*Z* (%), 0.3/99.7; GC, RI(PONA) = 1177/1168, RI(DB-Wax) = 1503/1496; MS (EI, *m*/*z*, rel %) 154 ($M^+$, 50/49), 125 (72/51), 111(27/26), 107 (32/23), 97 (22/25), 83 (68/51), 79 (43/35), 69 (33/37), 67 (34/29), 55 (100/86), 41 (98/100); $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 0.85 (t, 3H, $CH_3$, $^3J$ = 7.2 Hz), 0.90 (t, 3H, $CH_3$, $^3J$ = 7.2 Hz), 1.29−1.49 (m, 6H, 3 $CH_2$), 2.18 (t, 2H, $CH_2$, $^3J$ = 7.4 Hz), 2.32 (q, 2H, $CH_2$, $^3J$ = 7.4 Hz), 6.42 (t, 1H, CH, $^3J$ = 7.4 Hz), 9.32 (s, 1H, CH═O); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 13.8 ($CH_3$), 14.0 ($CH_3$), 21.9 ($CH_2$), 22.4 ($CH_2$), 25.9 ($CH_2$), 28.6 ($CH_2$), 30.8 ($CH_2$), 143.5 (Cq), 155.5 (CH), 195.3 (C═O).

*(Z)-2-Butyloct-2-enal (**2d**):* distillation, 110 °C, 70 mbar; purity, >95% by NMR, 97.7% by GC; GC ratio for *E*/*Z* (%), 5/95; GC, RI(PONA) = 1371/1361, RI(DB-Wax) = 1697/1688; MS (EI, *m*/*z*, rel %) 182 ($M^+$, 48/54), 139 (41/56), 125 (25/37), 111 (38/75), 97 (26/40), 95 (58/48), 83 (67/58), 79 (39/40), 69 (43/41), 67 (36/44), 55 (87/99), 41 (100/100); $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 0.85 (t, 3H, $CH_3$, $^3J$ = 7.2 Hz), 0.90 (t, 3H, $CH_3$, $^3J$ = 7.2 Hz), 1.25−1.40 (m, 8H, 4 $CH_2$), 1.55 (m, 2H, $CH_2$), 2.22 (t, 2H, $CH_2$, $^3J$ = 7.4 Hz), 2.35 (q, 2H, $CH_2$, $^3J$ = 7.4 Hz), 6.42 (t, 1H, CH, $^3J$ = 7.4 Hz), 9.34 (s, 1H, CH═O); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 13.8 ($CH_3$), 14.0 ($CH_3$), 22.4 ($CH_2$), 22.7 ($CH_2$), 23.7 ($CH_2$), 28.3 ($CH_2$), 28.8 ($CH_2$), 30.9 ($CH_2$), 31.5 ($CH_2$), 143.8 (Cq), 155.3 (CH), 195.3 (C═O).

*(Z)-2-Pentylnon-2-enal (**2e**):* distillation, 72 °C, 20 mbar; purity, >95% by NMR, 97.0% by GC; GC ratio for *E*/*Z* (%), 5/95; GC, RI(PONA) = 1570/1555, RI(DB-Wax) = 1900/1884; MS (EI, *m*/*z*, rel %) 210 ($M^+$, 21/19), 153 (32/24), 139 (24/21), 125 (12/35), 111 (17/19), 109 (20/19), 97 (29/34), 95 (31/29), 83 (47/45), 69 (34/37), 67 (43/40), 55 (69/75), 41 (100/100); $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 0.83 (t, 3H, $CH_3$, $^3J$ = 7.2 Hz), 0.86 (t, 3H, $CH_3$, $^3J$ = 7.2 Hz), 1.21−1.50 (m, 14H, 7 $CH_2$), 2.18 (t, 2H, $CH_2$, $^3J$ = 7.1 Hz), 2.31 (q, 2H, $CH_2$, $^3J$ = 7.4 Hz), 6.40 (t, 1H, CH, $^3J$ = 7.4 Hz), 9.31 (s, 1H, CH═O); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 13.9 ($CH_3$), 14.0 ($CH_3$), 22.4 ($CH_2$), 22.5 ($CH_2$), 23.9 ($CH_2$), 24.8 ($CH_2$), 28.4 ($CH_2$), 28.6 ($CH_2$), 28.9 ($CH_2$), 30.9 ($CH_2$), 31.5 ($CH_2$), 143.8 (Cq), 155.3 (CH), 195.3 (C═O).

*(Z)-2-Hexyldec-2-enal (**2f**):* purity, >90% by NMR, 93.6% by GC; GC ratio for *E*/*Z* (%), 4.5/95.5; GC, RI(PONA) = 1769/1752, RI(DB-Wax) = 2101/2086; MS (EI, *m*/*z*, rel %) 238 ($M^+$, 14/16), 167 (20/19), 153 (16/19), 139 (10/32), 97 (26/32), 95 (29/43), 83 (41/44), 69 (37/41), 67 (35/39), 55 (72/74), 43 (80/79), 41 (100/100); $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 0.87−0.92 (2t, 6H, 2 $CH_3$, $^3J$ = 7.2 Hz), 1.24−1.66 (m, 18H, 9 $CH_2$), 2.28 (t, 2H, $CH_2$, $^3J$ = 7.1 Hz), 2.35 (q, 2H, $CH_2$, $^3J$ = 7.3 Hz), 6.46 (t, 1H, CH, $^3J$ = 7.3 Hz), 9.37 (s,1H, CH═O); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 14.46 ($CH_3$), 14.48 ($CH_3$), 22.99 ($CH_2$), 23.02 ($CH_2$), 23.05 ($CH_2$), 24.40 ($CH_2$), 29.10 ($CH_2$), 29.30 ($CH_2$), 29.47 ($CH_2$), 29.74 ($CH_2$), 32.04 ($CH_2$), 32.12 ($CH_2$), 32.23 ($CH_2$), 144.21 (Cq), 155.83 (CH), 195.70 (C═O).

*Synthesis of 3-(Acetylthio)-2-alkyl Alkanals.* Piperidine (100 $\mu$L) was added to alkenals **2a**−**e** (34 mmol) under nitrogen at 10 °C in separated cylinders of the Quest 205 apparatus. Thioacetic acid (3.68 mL, 51.6 mmol) was then added dropwise at 10 °C. Thereafter, the reaction mixture was stirred for another 18 h at room temperature. The mixture was diluted with $Et_2O$ (10 mL), washed first with HCl (10 mL, 1 N) and then twice with a saturated $NaHCO_3$ solution (10 mL). The organic phases were dried over $Na_2SO_4$. All of these steps were carried out at the same time in the Quest 205 device. Then, the solvent was evaporated for each sample. The GC purity of the crude products was 50−90%, depending on the starting alkenal. In each case, a mixture of the two diastereomers was obtained. In general, only small differences were found for the NMR data of the two diastereomers (A/B), which are explicitly reported below. The GC and MS data for the two diastereomers (A/B) are given below.

*3-(Acetylthio)-2-methylpentanal (**3a**):* conversion yield, > 98% by GC; boiling point, 120 °C (1.5 mbar); purity, 95% by NMR, 96.5% by GC; A/B ratio (GC, %), 49.5/50.5; GC, RI(PONA) = 1209/1213, RI(DB-Wax) = 1812/1825; MS (EI, *m*/*z*, rel %) 174 ($M^+$, <1/<1), 131 (15/9), 103 (13/11), 77 (9/12), 70 (34/30), 61 (12/9), 55 (21/19), 43 (100/100); MS data are close to those reported in ref *10*; $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 0.92/0.96 (t, 3H, $CH_3$, $^3J$ = 7.2 Hz), 1.06/1.10 (d, 3H, $CH_3$, $^3J$ = 7.0 Hz), 1.47−1.74 (m, 2H, $CH_2$), 2.29/2.31 (s, 3H, $CH_3$), 2.60−2.70 (m, 1H, CH), 3.76/3.94 (dt, 1H, S−CH, $^3J$ = 4.8/4.1 Hz, $^3J$ = 4.6/4.4 Hz), 9.56/9.57 (d, 1H, CH═O, $^3J$ = 0.9/1.7 Hz); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 10.2/11.3 ($CH_3$), 11.9/12.1 ($CH_3$), 25.3/26.5 ($CH_2$), 31.0/31.1 ($CH_3$), 46.1/46.3 (CH), 50.2/50.7 (S−CH), 195.3/195.7 (S−C═O), 202.9/203.1 (C═O).

*3-(Acetylthio)-2-ethylhexanal (**3b**):* conversion yield (GC), 90%; boiling point, 85 °C (0.3 mbar); purity, 95% by NMR; A/B ratio (GC, %), 69/31; GC, RI(PONA) = 1373/1368, RI(DB-Wax) = 1942/1932; MS (EI, *m*/*z*, rel %) 202 ($M^+$, <1/<1), 159 (4/10), 131 (10/11), 98 (28/28), 97 (13/16), 69 (15/19), 55 (38/47), 43 (100/100); $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 0.87 (t, 3H, $CH_3$, $^3J$ = 7.0 Hz), 0.89 (t, 3H, $CH_3$, $^3J$ = 7.4 Hz), 1.30−1.79 (m, 6H, 3 $CH_2$), 2.34/2.36 (s, 3H, $CH_3$), 2.40−2.45 (m, 1H, CH), 3.92/3.88 (dt, 1H, S−CH, $^3J$ = 4.6 Hz, $^3J$ = 5.0 Hz), 9.62/9.57 (s, 1H, CH═O); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 12.4 ($CH_3$), 14.0 ($CH_3$), 19.7/20.5 ($CH_2$), 20.6/20.5 ($CH_2$), 31.0/30.9 ($CH_2$), 34.8/35.5 ($CH_3$), 43.6/43.3 (CH), 57.8/58.0 (S−CH), 195.4/195.7 (S−C═O), 203.4/203.3 (C═O).

*3-(Acetylthio)-2-propylheptanal (**3c**):* conversion yield (GC), 80%; boiling point, 109 °C (0.3 mbar); purity, 95% by NMR; A/B ratio (GC, %), 66/34; GC, RI(PONA) = 1543/1536, RI(DB-Wax) = 2087/2074; MS (EI, *m*/*z*, rel %) 230 ($M^+$, <1/<1), 187 (3/6), 159 (10/11), 155 (5/3), 126 (27/22), 97 (10/12), 83 (15/19), 69 (32/38), 55 (30/35), 43 (100/100); $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 0.78−0.84 (2t, 6H, 2 $CH_3$, $^3J$ = 7.0 Hz), 1.14−1.39 (m, 10H, 5 $CH_2$), 2.24/2.25 (s, 3H, $CH_3$), 2.39−2.47 (m, 1H, CH), 3.78/3.72 (dt, 1H, S−CH, $^3J$ = 4.8 Hz, $^3J$ = 5.0 Hz), 9.53/9.55 (s, 1H, CH═O); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 14.3 ($CH_3$), 14.4 ($CH_3$), 21.2/21.1 ($CH_2$), 22.6/22.7 ($CH_2$), 28.6/29.3 ($CH_2$), 29.6/29.5 ($CH_2$), 31.1 ($CH_2$), 32.4/33.1 ($CH_3$), 44.1/43.7 (CH), 55.9/56.1 (S−CH), 195.5/195.7 (S−C═O), 203.5/203.3 (C═O).

*3-(Acetylthio)-2-butyloctanal (**3d**):* conversion yield (GC), 72%; boiling point, 130 °C (0.3 mbar); purity, 95% by NMR; A/B ratio (GC, %), 70/30; GC, RI(PONA) = 1726/1720, RI(DB-Wax) = 2260/2247; MS (EI, *m*/*z*, rel %) 258 ($M^+$, <1/<1), 215 (2/5), 187 (12/14), 183 (5/4), 154 (26/21), 117 (10/9), 115 (8/13), 111 (9/10), 97 (18/23), 83 (22/25), 69 (22/28), 55 (42/49), 43 (100/100); $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 0.83−0.88 (2t, 6H, 2 $CH_3$, $^3J$ = 7.0 Hz), 1.17−1.76 (m, 14H, 7 $CH_2$), 2.32/2.31 (s, 3H, $CH_3$), 2.44−2.52 (m, 1H, CH), 3.80/3.85 (dt, 1H, S−CH, $^3J$ = 4.8 Hz, $^3J$ = 5.0 Hz), 9.52/9.58 (d, 1H, CH═O, $^3J$ = 2.8/2.2 Hz); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 14.2 ($CH_3$), 14.3 ($CH_3$), 22.8 ($CH_2$), 23.1/23.0 ($CH_2$), 26.3/26.9 ($CH_2$), 27.1/27.0 ($CH_2$), 30.1/30.0 ($CH_2$), 31.1 ($CH_2$), 31.7/31.8 ($CH_2$), 32.6/323.3 ($CH_3$),

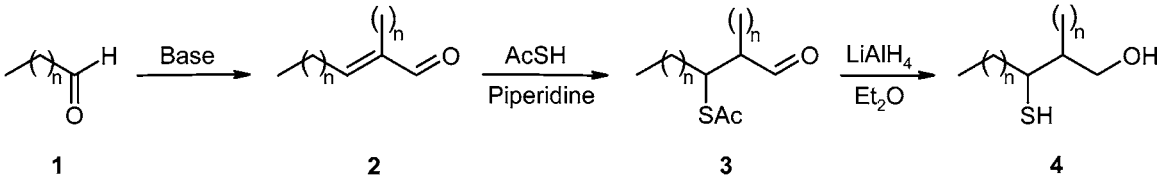


**Figure 1.** Synthetic pathway from *n*-aldehydes to 3-(acetylthio)-2-alkyl alkanals and the corresponding mercaptoalcohols.

44.2/43.8 (CH), 56.1/56.3 (S−CH), 195.5/195.7 (S−C═O), 203.6/203.4 (C═O).

*3-(Acetylthio)-2-pentylnonanal (**3e**):* conversion yield (GC), 62%; boiling point, 160 °C (0.12 mbar); purity, 95% by NMR; 93.7 by GC; A/B ratio (GC, %), 61/39; GC, RI(PONA) = 1917/1909, RI(DB-Wax) = 2449/2436; MS (EI, *m*/*z*, rel %) 286 ($M^+$, no signal), 243 (1/3), 215 (10/13), 211 (5/3), 182 (19/17), 131 (9/8), 129 (6/12), 111 (8/10), 97 (19/22), 83 (19/20), 69 (26/33), 55 (38/42), 43 (100/100); $^1$H NMR (360 MHz, $C^2HCl_3$) $\delta$ 0.83−0.88 (2t, 6H, 2 $CH_3$), 1.17−1.76 (m, 18H, 9 $CH_2$), 2.32 (s, 3H, $CH_3$), 2.45−2.55 (m, 1H, CH), 3.85/3.90 (m, 1H, S−CH), 9.55/9.60 (d, 1H, CH═O, $^3J$ = 2.80 Hz); $^{13}$C NMR (90 MHz, $C^2HCl_3$) $\delta$ 14.3/14.4 ($CH_3$), 14.4/14.5 ($CH_3$), 22.8 ($CH_2$), 22.9 ($CH_2$), 25.3 ($CH_2$), 26.4 ($CH_2$), 27.1 ($CH_2$), 30.9/27.3 ($CH_2$), 31.8/29.2 ($CH_2$), 32.1 ($CH_3$), 44.0 (CH), 56.1 (S−CH), 195.3 (S−C═O), 203.4 (C═O).

**Gas Chromatography−Mass Spectrometry/Olfactometry (GC-MS/O).** Mass spectra of the synthesized compounds and their retention indices (RIs) were acquired using a gas chromatograph GC 5890 (Agilent, Geneva, Switzerland) equipped with two splitless injectors heated at 260 °C and coupled with a quadrupole mass spectrometer MS 5970 (Agilent) operating in the electron impact ionization (EI) mode at 70 eV. Acquisitions were carried out over a mass range of 10−350 Da. Separations were performed on a 100% dimethyl polysiloxane apolar stationary phase (Ultra-1 PONA, 50 m × 0.20 mm i.d., 0.5 $\mu$m film thickness, Agilent) and on a polyethylene glycol polar stationary phase (DB-Wax, 60 m × 0.25 mm i.d., 0.5 $\mu$m film thickness, J&W, Folsom, CA). See ref *3* for more details concerning operating conditions.

**Nuclear Magnetic Resonance (NMR) Spectroscopy.** The samples for NMR spectroscopy were prepared in Wilmad 528-PP 5 mm Pyrex NMR tubes using deuterochloroform as solvent (0.7 mL). The NMR spectra were acquired on a Bruker AM-360 spectrometer equipped with a quadrinuclear 5 mm probe head, at 360.13 MHz for $^1$H and at 90.03 MHz for $^{13}$C under standard conditions (*11*). All chemical shifts are cited in parts per million relative to the solvent signal.

**Odor Threshold Determination.** Orthonasal detection thresholds were determined in water (Vittel) by seven panelists using the triangle test method, as recently described (*3*). Threshold values correspond to >70% of correct answers.

## RESULTS AND DISCUSSION

**Syntheses.** In an attempt to identify the main odor-active compounds in home-style prepared vegetables, we synthesized polyfunctional thiols and derivatives thereof, because such sulfur-containing odorants are known to contribute to the sensory properties of food products. Several 3-(acetylthio)-2-alkyl alkanals with different chain lengths were prepared by parallel synthesis to obtain reference materials and compare their sensory properties. Their precursors, the 2-alkylalk-2-enals, were also characterized. In addition, 3-(acetylthio)-2-alkyl alkanals can easily be reduced to the corresponding thioalcohols, known for their attractive organoleptic properties (*4*).

*2-Alkylalk-2-enals.* As shown in **Figure 1**, the first step was an aldol-type condensation of an *n*-alkanal, which results in the corresponding 2-alkyl-$\alpha$,$\beta$-unsaturated aldehyde. Depending on the starting aldehyde, the yields varied between 40 and 70%. Most of them occurred in the *Z*-isomeric form. However, a switch from *Z*- to *E*-stereochemistry was observed for the lower homologue **2a** containing only one carbon atom in the side chain. The multiplicity (tq) and the coupling constant of $^4J$ = 1.3 Hz for the alkene proton in **2a** clearly indicate the *E*-isomeric form, whereas such a pattern was not detected in **2b** and in the higher homologues. This difference in configuration is most likely due to a competitive steric hindrance between the side chain and the carbonyl group, which is probably due to the increasing van der Waals volume of the 2-alkyl group.

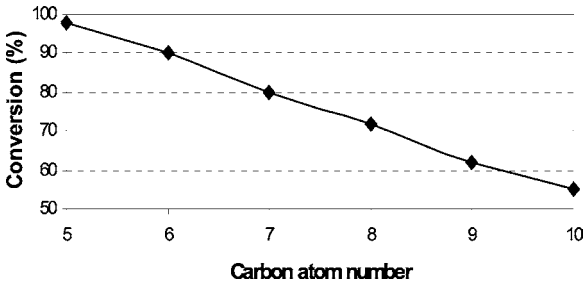


**Figure 2.** Conversion yields of the Michael addition as a function of the alkenal chain length ($R^2$ = 0.9982).

*3-(Acetylthio)-2-alkyl Alkanals.* The alkenals **2a**−**f** were mixed with thioacetic acid under alkaline condition to introduce regioselectively the acetylthio function in the aldehyde backbone. As $\alpha$,$\beta$-unsaturated aldehydes are well-known Michael acceptors and thioacetate is a soft nucleophile, the addition occurred exclusively in the $\beta$-position. For the entire series of products synthesized, a mixture of the *syn* and *anti* diastereomers was observed. Structure characterization and purity control were carried out on the basis of GC, GC/O, GC-MS, and NMR data. The purity of the products obtained by distillation was ≥95%, as measured by NMR.

The conversion of the reaction linearly decreased with the length of the alkenal backbone. As shown in **Figure 2**, almost complete conversion was achieved with 2-methylpent-2-enal (**2a**), whereas it was only 55% with 2-hexyldec-2-enal (**2f**). Both steric effects and physicochemical properties may explain this difference in reactivity. As the reactions were carried out without external solvents, the proper physicochemical properties of the reactant may directly influence the reaction. With increasing carbon chain length, the lipophilicity of the alkenal increases as well. Consequently, a polar nucleophile, such as $AcS^-$, can hardly access the electrophilic site of the alkenal for reaction. According to our experimental results obtained, the conversion yields are directly linked to the hydrophilic−lipophilic balance (HLB) of the Michael acceptor (2-alkylalk-2-enal).

To obtain the corresponding mercaptoalcohols, both the acetylthio and aldehyde functions can be reduced with lithium aluminum hydride under inert conditions (*7*; **Figure 1**). The mercaptoalcohols were also obtained as a mixture of diastereomers. In general, conversion yields were ∼80% in all cases as indicated by GC. Only 3-mercapto-2-methyl-1-pentanol was isolated in pure form and characterized by GC-MS and NMR. The data were in good agreement with those reported in the literature (*4*).

**Sensorial Properties.** The detection threshold values were obtained orthonasally using the triangular test procedure. By definition, the threshold value corresponded to ≥70% of correct answers of a trained panel composed of at least seven panelists

**Table 1.** Sensory Properties of 2-Alkyl α,β-Unsaturated Aldehydes

| compound | odor description[a] | threshold[b] | occurrence[c] |
|---|---|---|---|
| (*E*)-2-methylpent-2-enal (**2a**) | pungent, almond | 250 | boiled egg, fruits (grape, guava, cranberry, papaya, plum), vegetables (*Allium* species, mustard), potato (French fries), cheese, fish, oyster, meat, coffee, tea, mate, beer, cognac |
| (*Z*)-2-ethylhex-2-enal (**2b**) | lemon, apple, fruity | 125 | potato (French fries) |
| (*Z*)-2-propylhept-2-enal (**2c**) | apple, green, fatty | 150 | nd |
| (*Z*)-2-butyloct-2-enal (**2d**) | green, fatty, savory, meaty | 20 | pineapple, cooked rice |
| (*Z*)-2-pentylnon-2-enal (**2e**) | mushroom, metallic | 200 | nd |
| (*Z*)-2-hexyldec-2-enal (**2f**) | orange, metallic, bloody | 100 | bitter orange peel oil |

[a] Odor description at a concentration of ~1–2 mg/L. [b] Detection threshold in μg/L water was obtained by orthonasal measurements performed by seven panelists. [c] These data were taken from ref *13*; nd, not detected. The stereochemistry is not always specified.

**Table 2.** Sensory Properties of 3-(Acetylthio)-2-alkyl Alkanals

| compound | odor description[a] | threshold[b] |
|---|---|---|
| 3-(acetylthio)-2-methylpentanal (**3a**) | leek, onion, bouillon | 5 |
| 3-(acetylthio)-2-ethylhexanal (**3b**) | fruity, tropical, grapefruit | 15 |
| 3-(acetylthio)-2-propylheptanal (**3c**) | fruity, tropical, grapefruit | 50 |
| 3-(acetylthio)-2-butyloctanal (**3d**) | fruity, grapefruit, green vegetables, cauliflower | 200 |
| 3-(acetylthio)-2-pentylnonanal (**3e**) | green, fruity, citrus | 500 |

[a] Odor description was performed at a concentration of 0.5–5 mg/L. [b] Detection threshold in μg/L water was obtained by orthonasal measurements performed by seven panelists

(*3*). The odor quality was described at higher concentrations, usually 10−50 times the threshold concentration. The odor characteristics of the target compounds were identical with those of the distilled samples. The samples were also evaluated by GC/O to make sure that the target compound was the major odor-active substance. For example, (*Z*)-2-butyloct-2-enal (**2d**) exhibited a characteristic ham-like, meaty, savory note, which was confirmed by GC/O. In general, no or only weak-smelling impurities were found, which did not interfere with the sensory evaluation of the target compounds.

*2-Alkylalk-2-enals.* Compound **2a** derived from propanal showed a characteristic almond-like note with the highest threshold value of the alkenals synthesized (**Table 1**). Fruity notes dominated in compounds **2b** and **2c**, whereas the fatty and savory characters were more pronounced in **2d**. Compounds **2e** and **2f** showed metallic notes reminiscent of mushroom and orange, respectively. In general, a certain trend was found from sweet to savory notes with the elongation of the carbon chain length. The threshold values of the alkenals synthesized were in the range of 100−250 μg/L of water except for odorant **2d** derived from *n*-hexanal, which showed a relatively low threshold of 20 μg/L of water, which is close to that of vanillin (*12*). Therefore, 2-butyloct-2-enal (**2d**), having an attractive Parma ham note, may find interest in savory applications.

Some of the 2-alkyl-α,β-unsaturated aldehydes studied here have been widely found in nature and in many food products (**Table 1**), such as 2-methylpent-2-enal (**2a**) in fruits, vegetables, cheese, fish, meat, coffee, beer, and other beverages (*13*). 2-Ethylhex-2-enal (**2b**) is also used as feed preservative (*14*). However, the sensory contribution of 2-alkylalk-2-enals known so far is generally limited, most likely due to their moderate odor thresholds and low concentrations found in food products (*13*).

*3-(Acetylthio)-2-alkyl Alkanals.* The sensory properties of the acetylthio aldehydes are shown in **Table 2**. They are predominantly characterized by fruity notes, such as tropical and grapefruit-like, in particular odorants **3b**−**e**. On the contrary,

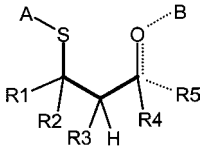


**Figure 3.** "Olfactophore" for tropical/vegetable notes with (A) H, $SCH_3$, ring; (B) H, $CH_3$, acyl, absent if carbonyl; (R1, R2) H, alkyl; (R3) H, alkyl, ring; (R4) H, $CH_3$, ring, OR; and (R5) H, absent if carbonyl. Adapted from ref *16*.

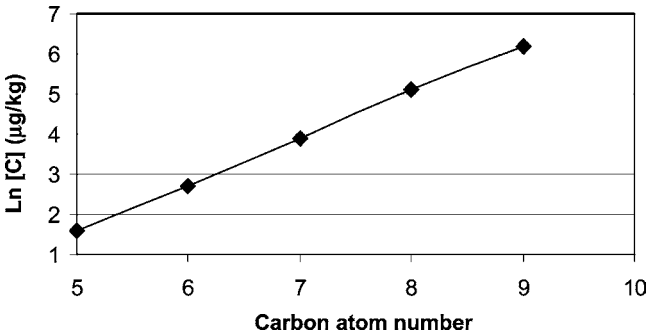


**Figure 4.** Odor threshold concentrations as function of the 3-(acetylthio)-2-alkyl alkanal chain length.

the lower homologue 3-(acetylthio)-2-methylpentanal (**3a**) showed savory characters such as leek, onion, and bouillon-like. Surprisingly, 3-(acetylthio)-2-butyloctanal (**3d**) was described as fresh, green, and vegetable-like, reminiscent of crude cauliflower when it is smelled neat. These organoleptic properties described in **Table 2** correspond to diastereomeric mixtures, the composition of which varied from 50:50 to 70:30. The odor quality of the individual isomers may differ; however, their characterization was not the aim of this study.

From a structural point of view, these data are in good agreement with the tropical/vegetable "olfactophore" recently proposed by Rowe (*15*, *16*). On the basis of our results, the model of 1,3-oxygen−sulfur structure can further be generalized by adding the acetyl group for substituent A in **Figure 3** (*16*). This is well in agreement with the citrus/grapefruit notes recently reported for 3-(acetylthio)hexanal and 3-(acetylthio)hexanol (*17*).

Interestingly, the threshold concentration increased exponentially with the carbon chain length (**Figure 4**). The lowest volatility of the heaviest compounds may explain the differences. In general, none of the 3-(acetylthio)-2-alkyl aldehydes studied here have been found in food or in nature so far. Only 3-(acetylthio)-2-methylpentanal (**3a**) has been reported in the patent literature as a precursor of the corresponding thioalcohol (*10*, *18*), but without describing its sensory properties, and in a paper dealing with the synthesis of bisamides (*19*).

In conclusion, parallel synthesis and, more generally, combinatorial chemistry, comprise an attractive approach in aroma research to help identify new odorants with interesting sensory properties. It allows rapid synthesis of a large number of reference compounds in a reasonable time, which can be very useful for structure elucidation of unknown odorants.

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