Preparation of 3-methylthiodecanal, a flavour compound

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1-Undecen-4-ol was converted into its benzyl ether in 92% yield by reaction with benzyl chloride in the presence of NaH and was then oxidised with a ruthenium catalysis to give the corresponding aldehyde, which was treated directly with ethylene glycol in the presence of pyridinium *p*-toluenesulfonate to produce 2-(2´-benzyloxynonyl)-1,3-dioxolane in an overall yield of 87%. This intermediate underwent deprotection of the benzyloxy group and mesylation to give 2-(2´-mesyloxynonyl)-1,3-dioxolane in 90% yield, treatment of which with sodium methyl mercaptide followed by cleavage of the 1,3-dioxolane group afforded 3-methylthiodecanal in 81% yield.

Keywords: 3-methylthiodecanal, 1-undecen-4-ol, oxidation, preparation, flavour compounds

Volatile sulfur-containing compounds play an important role in the aromas of many foods, such as tropical fruits, vegetables of the *Allium* species (garlic, onion, chive) and *Cruciform* families (Brussels sprouts, broccoli, cabbage, cauliflower), and thermally processed foods (roasted meat, chicken, seafood, coffee).[1] The polyfunctional thiols and their derivatives have attracted a lot of attention due to their unique odour characteristics in recent years,[2-7] among which many compounds possessing the tropical, fruity or vegetable odour notes feature a 1,3-oxygen-sulfur functionality, a so-called 'olfactophore'.[8] More and more compounds containing this olfactophore have been reported to occur in nature[9-12] and many have been approved as safe flavour ingredients by the Flavour and Extract Manufacturers' Association (FEMA).[13]

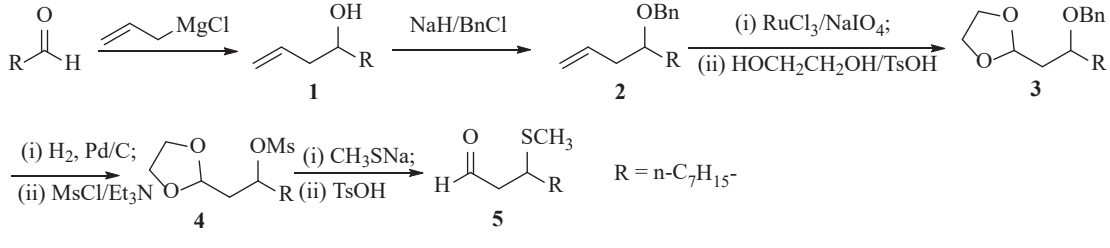
The homologues of 3-methylthioalkanals, which contain a 1,3-oxygen-sulfur functionality occur widely as volatile aroma components of various plants,[14-17] fruit,[18] vegetables,[19] and cooked beef liver[20] and seafoods.[21] Five of these homologues have obtained FEMA numbers, including 3-methylthiopropanal (FEMA No. 2747), 3-methylthiobutanal (FEMA No. 3374), 3-methylthiohexanal (FEMA No. 3877), 3-methylthioheptanal (FEMA No. 4183), and 3-methylthiodecanal (FEMA No. 4734). 3-Methylthiodecanal is a relatively new flavour compound, which was added to the GRAS (Generally Recognized as Safe) list in 2013.[22] However, the preparation of this flavour compound has not been reported so far. The most common method of their preparation in the literature is by conjugate addition of methanethiol to α,β-unsaturated aldehydes which affords the corresponding 3-methylthioalkanals directly,[23-26] a route limited only by the availability of the corresponding α,β-unsaturated aldehydes. In this work, we investigated a synthetic route starting from 1-undecen-4-ol which involved the oxidation of its double bond and transformation of its hydroxyl group to afford 3-methylthiodecanal. We chose this starting material in view of its accessibility of 1-undecen-4-ol *via* a Grignard reaction.

Results and discussion

Our efficient eight-step synthesis of 3-methylthiodecanal **5** is shown in Scheme 1. 1-Undecen-4-ol **1**, prepared by the Grignard reaction of allylmagnesium chloride with octanal, was converted to the corresponding benzyl ether **2** in 92% yield by treatment with benzyl chloride in the presence of NaH to protect the hydroxyl group from oxidation in subsequent steps.

Although ozonolysis is one of the most common methods for the oxidative cleavage of the C=C bond, we chose the Ru-catalysed oxidation reported by Niggemann *et al.*,[27] which was more easily carried out than ozonolysis due to the inconvenient preparation of ozone gas in the laboratory. 4-Benzyloxy-1-undecene **2** was oxidised by 5 mol % of $RuCl_3$ and 2 equiv. of $NaIO_4$ in acetone/acetonitrile/water to afford the corresponding aldehyde. However, unexpectedly we found that the aldehyde was unstable and decomposed on a silica column during purification or on standing overnight. Therefore, the crude aldehyde was used in the next step directly. Initially, the deprotection of the benzyloxy group of the aldehyde was attempted by hydrogenolysis catalysed by Pd/C in methanol solution so as to protect the carbonyl group by the concurrent formation of a dimethyl acetal. Unfortunately, it failed and gave a complex mixture. It was thus decided that protection of the carbonyl group of the crude oxidation product should precede the deprotection of the benzyloxy group. This was carried out by treatment of the crude oxidation product with ethylene glycol in the presence of pyridinium *p*-toluenesulfonate to give 2-(2´-benzyloxynonyl)-1,3-dioxolane **3** in an overall yield of 87% in these two steps.

After the deprotection of the benzyloxy group of **3**, by hydrogenolysis using 10% Pd–C, mesylation produced 2-(2´-mesyloxynonyl)-1,3-dioxolane **4**. Both the deprotection and mesylation went smoothly in an overall yield of 90%. The final product 3-methylthiodecanal **5** was obtained through a nucleophilic substitution reaction of **4** with sodium methyl



Scheme 1

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mercaptide followed by the cleavage of the 1,3-dioxolane group. The overall yield of the nucleophilic substitution and deprotection of the carbonyl group was 81%.

The solution of 3-methylthiodecanal (0.1% in propylene glycol) possessed a typical odour of long white radish soup and a slight fatty scent. It is well known that the stereoisomers of chiral flavours usually present different odour properties. Among these homologues, (*R*)-3-methylthiobutanal presented a typical odour of cooked potato, whereas the opposite enantiomer was odourless. In contrast, the enantiomers of 3-methylthiohexanal and 3-methylthioheptanal showed no stereospecific differences in their organoleptic properties.[28] However, the odours of the enantiomers of 3-methylthiodecanal are still unknown. To settle this issue, we planned to prepare its enantiomers based on the synthetic route designed for the racemate, but using an optically active 1-undecen-4-ol as starting material.

In summary, 3-methylthiodecanal was easily prepared from the corresponding homoallylic alcohol 1-undecen-4-ol by the Ru-catalysed oxidation of its double bond and nucleophilic substitution by methylthiolate of its hydroxyl group through its mesylate. The protection and deprotection steps of the hydroxyl group and the aldehyde group derived from the oxidation proceeded smoothly in high yields although they made this synthetic route a little tedious. Overall, it is worthy of consideration for the preparation of 3-methylthiodecanal due to the easy availability of starting material, operational simplicity and the very good yield of each individual step.

Experimental

Allyl chloride, *n*-octanal, and sodium periodate were purchased from the Beijing Bailingwei Science and Technology Company, ruthenium (III) chloride from Sigma-Aldrich Chemical Co., and the other chemicals from the Beijing Huaxue Shiji Company. NMR spectra were obtained on a Bruker AV 300 spectrometer (^{1}H NMR at 300 MHz, ^{13}C NMR at 75 MHz) in $CDCl_3$ using TMS as an internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. The high resolution mass spectra were obtained on a Bruker Apex IV FTMS.

1-Undecen-4-ol (**1**): The Grignard reaction of allyl magnesium chloride with octanal, using a method reported by us previously,[29] gave 1-undecen-4-ol **1** as a colourless oil (85%), b.p. 63–65 °C (1.1 mbar); ^{1}H NMR δ 0.88 (t, *J* = 6.9 Hz, 3 H, H-C11), 1.17–1.52 (m, 12 H, H-C5-C10), 1.57 (d, *J* = 3.9 Hz, 1 H, -OH), 2.13 (m, 1 H, H-C3), 2.31 (m, 1 H, H´-C3), 3.63 (m, 1 H, H-C4), 5.12 (m, 2 H, H-C1), 5.83 (m, 1 H, H-C2); ^{13}C NMR δ 14.0 (C11), 22.6 (C10), 25.6 (C6), 29.3 (C8), 29.6 (C7), 31.8 (C9), 36.8 (C5), 41.9 (C3), 70.7 (C4), 117.9 (C1), 134.9 (C2). The NMR data were consistent with the literature data.[30]

4-Benzyloxy-1-undecene (**2**): Sodium hydride (60% dispersion, 2.4 g, 60 mmol) in one portion was added to a stirred solution of **1** (8.5 g, 50 mmol) in THF (100 mL) and DMF (10 mL) and the resultant suspension was refluxed for 0.5 h. Benzyl chloride (8.6 mL, 75 mmol) was then added and the reaction mixture was refluxed for a further 16 h. On cooling, the reaction mixture was poured into iced water (100 mL) and extracted with ether (100 mL ×3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil, which was purified by column chromatography over silica gel (petroleum ether/ethyl acetate, 30:1) to yield the benzyl ether as a light yellow oil (11.96 g, 92%). ^{1}H NMR δ 0.88 (t, *J* = 7.2 Hz, 3 H, H-C11), 1.20–1.62 (m, 12 H, H-C5-C10), 2.33 (m, 2H, H-C3), 3.44 (m, 1 H, H-C4), 4.49 (d, *J* = 11.7 Hz, 1 H, C<u>H</u>$_2$(benzyl)), 4.57 (d, *J* = 11.7 Hz, 1 H, C<u>H</u>$_2$(benzyl)), 5.02–5.15 (m, 2 H, H-C1), 5.86 (m, 1 H, H-C2), 7.26-7.42 (m, 5 H, phenyl); ^{13}C NMR δ 14.1 (C11), 22.7 (C10), 25.4 (C6), 29.3 (C8), 29.7 (C7), 31.9 (C9), 33.8 (C5), 38.3 (C3), 70.9 (<u>C</u>H$_2$(benzyl)), 78.6 (C4), 116.8 (C1), 127.4 (C4 (phenyl)), 127.7 (C3 and C5 (phenyl)), 128.3 (C2 and C6 (phenyl)), 135.2 (C2), 139.0 (C1 (phenyl)). The NMR data were consistent with the literature data.[31]

2-(2´-Benzyloxynonyl)-1,3-dioxolane (**3**)

Oxidation of the double bond: 4-Benzyloxy-1-alkene **2** (10.4 g, 40 mmol) was dissolved in acetone (80 mL), acetonitrile (80 mL) and water (68 mL). A solution of $RuCl_3$ (1 M, 2 mL, 2 mmol, 5 mol %) and $NaIO_4$ (17.12 g, 80 mmol) was added. After stirring for 20 min, the mixture was diluted with ethyl acetate (30 mL), filtered, and the filter cake was washed with ethyl acetate (10 mL × 3). The filtrate was washed with saturated Na_2SO_3 solution (80 mL) and saturated $NaHCO_3$ solution (30 mL) sequentially. Phases were separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (80 mL) and dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The light brown crude aldehyde was not purified and was used in the next step directly.

Protection of the carbonyl group: A mixture of the aldehyde obtained above, ethylene glycol (18.6 g, 0.3 mol), pyridinium *p*-toulenesulfonate (2.4 g) and toluene (70 mL) was stirred and heated under reflux for 3 h. The water formed during the reaction was removed by a Dean–Stark trap. The cooled reaction mixture was sequentially washed with saturated aqueous $NaHCO_3$, water, and brine. The solvent was evaporated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 30:1) to give 2-(2´-benzyloxynonyl)-1,3-dioxolane **3** as a colourless oil (10.65 g, 87%). ^{1}H NMR δ 0.88 (t, *J* = 6.9 Hz, 3 H, H-C9´), 1.18–1.48 (m, 10 H, H-C4´-C8´), 1.48–1.70 (m, 2 H, H-C-3´), 1.79 (ddd, *J* = 13.8, 6.3, 4.8 Hz, 1 H, H-C1´), 2.00 (ddd, *J* = 13.8, 7.5, 3.9 Hz, 1 H, H´-C1´), 3.62 (m, 1 H, H-C2´), 3.80–4.02 (m, 4 H, H-C4 and H-C5), 4.53 (m, 2 H, C<u>H</u>$_2$ (benzyl)), 5.00 (dd, *J* = 6.3, 4.2 Hz, 1 H, H-C2), 7.26–7.40 (m, 5 H, phenyl); ^{13}C NMR δ 14.2 (C-9´), 22.7 (C-8´), 25.1 (C-4´), 29.3 (C-5´), 29.7 (C-6´), 31.8 (C-7´), 34.5 (C3´), 38.8 (C1´), 64.7 (C5), 64.8 (C4), 71.2 (<u>C</u>H$_2$ (benzyl), 75.9 (C2´), 102.5 (C2), 127.4 (C4 (phenyl)), 127.8 (C3 and C5 (phenyl)), 128.3 (C2 and C6 (phenyl)), 138.9 (C1 (phenyl)); HRESIMS, *m/z* 329.20827 [M + Na$^+$] (calcd. for $C_{19}H_{30}NaO_3$, 329.20872).

2-(2´-Mesyloxynonyl)-1,3-dioxolane **4**

Cleavage of the benzyloxy group: 10% Pd–C (0.525 g) was added to a solution of the 1,3-dioxolane **3** (4.6 g, 15 mmol) in methanol (50 mL). After stirring under an atmosphere of hydrogen for 0.5 h, the reaction mixture was filtered through a pad of celite and concentrated. The residue was used directly for the next step without purification. ^{1}H NMR δ 0.86 (t, *J* = 6.9 Hz, 3 H, H-C9´), 1.19–1.59 (m, 12 H, H-C3´-C8´), 1.76 (m, 1 H, H-C1´), 1.89 (m, 1 H, H´-C1´), 2.92 (d, *J* = 2.4 Hz, 1 H, -OH), 3.80–4.05 (m, 5 H, H-C4, H-C5 and H-C2´), 5.02 (dd, *J* = 5.1, 3.9 Hz, 1 H, H-C2).

Mesylation of the hydroxyl group: Triethylamine (4.2 mL, 30 mmol) followed by methanesulfonyl chloride (1.4 mL, 18 mmol) was added to a solution of the alcohol obtained above in CH_2Cl_2 (40 mL) at 0 ºC. The mixture was stirred at 0 ºC for 0.5 h and at room temperature overnight. Then water was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ether. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 10:1) to give the corresponding mesylate as a colourless oil (3.97 g, 90%). ^{1}H NMR δ 0.87 (t, *J* = 6.9 Hz, 3 H, H-C9´), 1.18–1.46 (m, 10 H, H-C4´-C8´), 1.70–1.80 (m, 2 H, H-C3´), 1.94 (ddd, *J* = 14.7, 5.4, 4.5 Hz, 1 H, H-C1´), 2.12 (ddd, *J* = 14.7, 7.8, 4.2 Hz, 1 H, H´-C1´), 3.02 (s, 3 H, Me(mesyl)), 3.82–4.02 (m, 4 H, H-C4 and H-C5), 4.87 (m, 1 H, H-C2´), 4.98 (dd, *J* = 5.4, 4.2 Hz, 1 H, H-C2); ^{13}C NMR δ 13.9 (C-9´), 22.4 (C-8´), 24.5 (C-4´), 28.9 (C-5´), 29.1 (C-6´), 31.6 (C-7´), 35.3 (C-3´), 38.3 (Me-S), 38.6 (C-1´), 64.7 (C-5), 64.8 (C-4), 80.1 (C-2´), 101.2 (C-2); HRESIMS, *m/z* 317.13959 [M + Na$^+$] (calcd for $C_{13}H_{26}NaSO_5$, 317.13932).

3-Methylthiodecanal **5**

Methanethiol was bubbled into an aqueous solution of 2M NaOH (20 mL) until it was saturated. To the solution was added DMF (20 mL) and the mesylate **4** (2.94 g, 10 mmol). The mixture was heated at

80 °C for 2 h. On cooling, ethyl acetate (30 mL) was added to dilute the reaction mixture. The aqueous layer was separated and extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue obtained was treated with *p*-toluenesulfonic acid monohydrate (0.95 g, 5 mmol) in acetone (60 mL) and water (30 mL). The mixture was stirred at 50 °C for 6 h. On cooling, the mixture was extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography (*n*-hexane/ether, 10:1) to give 3-methylthiodecanal **5** as a light yellow oil (1.64 g, 81%). ^{1}H NMR δ 0.88 (t, *J* = 6.9 Hz, 3 H, H-C10), 1.20-1.34 (m, 8 H, H-C6-C9), 1.43 (m, 2 H, H-C5), 1.59 (m, 2 H, H-C4), 2.06 (s, 3 H, C$\underline{H}_3$S-), 2.61–2.69 (m, 2 H, H-C2), 3.04 (quintet, *J* = 6.9 Hz, 1 H, H-C3), 9.77 (t, *J* = 2.1 Hz, 1 H, -C$\underline{H}$O); ^{13}C NMR δ 12.6 (Me-S), 14.0 (C-10), 22.6 (C-9), 26.8 (C-5), 29.1 (C-6), 29.3 (C-7), 31.7 (C-8), 34.3 (C-4), 40.3 (C-3), 48.1 (C-2), 200.9 (C-1); HRESIMS, *m/z* 225.12840 [M + Na$^+$] (calcd for $C_{11}H_{22}NaSO$, 225.12836).

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