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# Microwave-assisted selective protection of glutaraldehyde and its symmetrical derivatives as monoacetals and -thioacetals

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ABSTRACT

Six monoprotected acetals and -thioacetals of glutaradehyde and its symmetrical dimethyl derivatives were synthesized. Microwave-assisted heating proved to be a substantially more selective method for monoprotection than conventional heating. All reactions were efficient and only traces of diprotected material were formed.

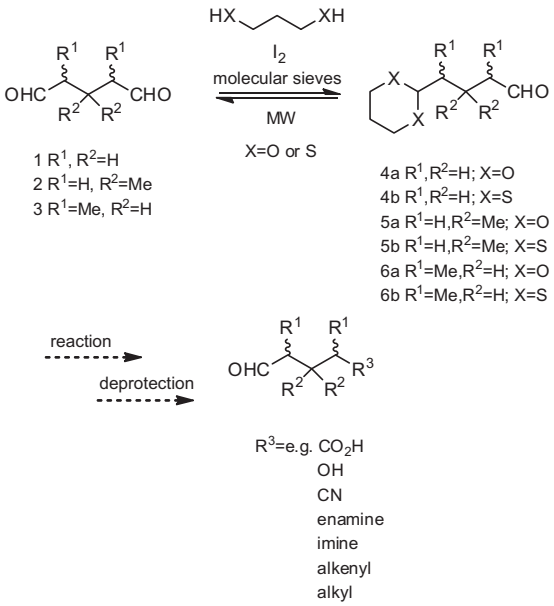


## 1. Introduction

The premise of this research stems from our ongoing studies to synthesize new organic molecules with pharmaceutical properties.[1] The use of simple, readily available reagents and microwave irradiation opens new prospects to green chemistry approaches. Microwave-assisted reactions are fast and the workup is simple. In this study microwave reactions of symmetrical dialdehydes **1**–**3** with propane-1,3-diol or propane-1,3-dithiol afforded monoprotected glutaraldehydes **4**–**6** with good selectivities and yields. These monoprotected glutaraldehydes can be used as building blocks for the preparation of numerous organic aldehydes with diverse carbon backbones and substitution patterns (Scheme 1). Moreover, glutaraldehyde monoacetals can be used as precursors in the synthesis of pyridines.

Particularly, we wanted to show that selective protection of only one aldehyde group in **1**–**3** is successful even when the dialdehyde has a symmetrical structure.

In this study, to the best of our knowledge, for the first time the selective protection of glutaraldehyde (**1**) and its symmetrical derivatives **2** and **3** to monoacetals **4a**–**6a** and monothioacetals **4b**–**6b** under microwave irradiation is introduced (Scheme 1).




**Scheme 1.** Synthesis of monoprotected glutaraldehydes.

## 2. Results and discussion

All reactions were performed using both conventional heating devices and microwave irradiation. In the microwave-assisted reactions only very small amounts, if any, of the diprotected compounds were formed, whereas under conventional heating in most cases the amount of the diprotected material increased substantially.

The microwave-assisted reaction between **1** and propane-1,3-diol afforded 4-(1,3-dioxan-2-yl)butanal (**4a**) and the corresponding diacetal in the ratio of 3:1 (yield 72%), respectively (Table 1). The total yield under conventional heating was 66%, which comprised 35% diprotected material. Only one microwave-assisted synthesis (yield 55%) for a 5-ring glutaraldehyde monoacetal could be found in the lit.[2]

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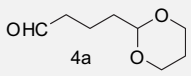
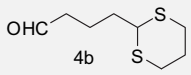
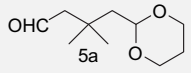
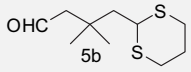
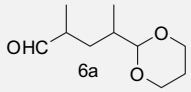
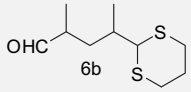
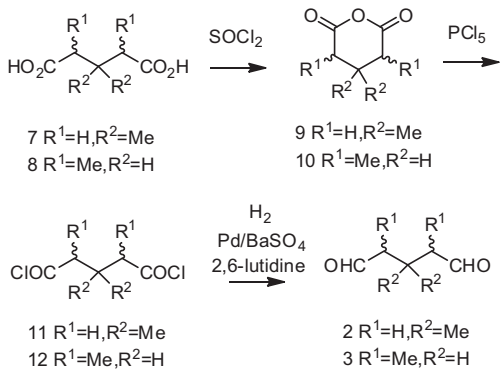
**Table 1**
Monoacetal and -thioacetal protected glutaraldehyde and their protected dimethyl derivatives obtained under microwave conditions

| Entry | Protected aldehyde | Conditions[a] | Total yield[b] % | Ratio of mono:di (thio)acetal |
|---|---|---|---|---|
| 1a |  4a | A | 72 | 3:1 |
| 1b |  4b | B | 51 | 1:0 |
| 1c |  5a | A | 84 | 5:1 |
| 1d |  5b | B | 70 | 10:1 |
| 1e |  6a | A | 73 | 1:0 |
| 1f |  6b | B | 75 | 3:2 |

[a] A: MW, THF, 100 W, 70 °C, $t_{ramp}$=1:30, $t_{hold}$=2:30; B: MW, $CH_2Cl_2$, 100 W, 70 °C, $t_{ramp}$=1:30, $t_{hold}$=2:30.
[b] Of mono and diprotected glutaraldehyde derivatives.

A few syntheses of 4-(1,3-dithian-2-yl)butanal (**4b**) have been described[3] but only one between glutaraldehyde (**1**) and propane-1,3-dithiol.[3a] However, this reaction was performed using conventional heating equipment (5 h, 60–70 °C). When microwave irradiation was used (70 °C, iodine catalyst, molecular sieves) the corresponding reaction was completed by us in only two minutes. In the reaction of **1** with propane-1,3-dithiol no diprotected compound[4] was formed (Table 1). It is known that prolonged heating easily results in polymerization of glutaraldehyde (**1**). Utilizing the short reaction time of the microwave reaction polymerization was totally hindered.

Some syntheses of 3,3-dimethylglutaraldehyde (**2**) have been described in the lit.[5] but none for its monoacetal **5a** or monothioacetal **5b**. Two references of a monoprotected acyclic dimethyl acetal of **2** were found.[5g,6] Dialdehyde **2** was prepared applying methods described in the literature (Scheme 2).[7b] A common feature of **2** is its instability,[5a] which turned out to be true also in our hands. Therefore, aldehyde **2** was immediately used in subsequent reactions without additional purification. The instability of the dialdehyde was further proved by the fact that monoprotected 3,3-glutaraldehyde acetal **5a** was not formed at all unless the reaction was performed under microwave conditions. In this case the yield




**Scheme 2.** Synthesis of compounds **2** and **3**.

of **5a** was 84% in the ratio of 5:1 (mono-:dithioacetal). Monothioacetal **5b** was synthesized correspondingly in 70% yield and in the ratio of 10:1 (mono-:dithioacetal).

Two syntheses for 2,4-dimethylglutaraldehyde (**3**) could be found in the lit.[8] Dialdehyde **3** was prepared correspondingly to **2** (Scheme 2). Racemic 2,4-dimethylglutaric acid (mixture of DL and *meso*) was used as starting compound. Reactions of **3** with propane-1,3-diol or propane-1,3-dithiol using microwaves afforded monoacetals **6a** and **6b**, respectively. In both cases the yields were >70%. In the reaction of **3** with propane-1,3-diol no diprotected compound was formed. The corresponding reaction using conventional heating equipment didn't take place at all, which was also true for propane-1,3-dithiol. When propane-1,3-dithiol was used under microwave conditions the amount of the diprotected thioacetal increased (3:2).

## 3. Conclusions

The microwave-assisted reaction of glutaraldehyde and its symmetrical methylated derivatives with propane-1,3-diol and propane-1,3-dithiol is an efficient method to prepare their monoacetal and monothioacetal derivatives. The reactions were fast and only traces of diprotected material were formed. On the average, best results were obtained when glutaraldehyde and its methyl derivatives were protected with propane-1,3-diol.

## 4. Experimental section

### 4.1. General

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. Non-aqueous reagents were transferred under argon via syringe and dried prior to use. THF and $CH_2Cl_2$ were obtained by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 solvent purification system). Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel $F_{254}$ (230–400 mesh) plates and analyzed by heating upon staining with $KMnO_4$ solution. For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted. The microwave reactions were performed in pressure vessels in a CEM Discover apparatus. $^1H$ (399.98 MHz) and $^{13}C$ NMR (100.59 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$. The chemical shifts are reported in ppm relative to TMS ($\delta$ 0.00) for $^1H$ NMR and in ppm relative to $CDCl_3$ ($\delta$ 77.0) for $^{13}C$ NMR. Melting points (mp) were determined in open capillaries using Stuart SMP3 melting point apparatus. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer. High resolution mass spectrometric data were obtained using MicroMass LCT Premier Spectrometer.

Glutaraldehydes **1**–**3** were prepared applying methods described in the literature. Water was removed from glutaraldehyde (**1**) by saturating it with NaCl. This was extracted five times with ether. The combined ether extracts were dried over $Na_2SO_4$ and the solvent evaporated. The crude product was distilled under reduced pressure (74 °C/9 mmHg).

3,3-Dimethylglutaraldehyde (**2**) was prepared using methods described in the literature. 3,3-Dimethylglutaric acid (**7**) was first converted to anhydride **9**,[7] then to the corresponding acyl chloride **11**[7b], which was hydrogenated ($H_2$/Pd) to 3,3-dimethylglutaraldehyde (**2**)[7b] (Scheme 2).

2,4-Dimethylglutaraldehyde (**3**) was prepared from diacid **8** (mixture of DL and *meso*), which was sequentially converted to the corresponding anhydride **10**,[9] acid chloride **12**,[10] and finally to dialdehyde **3**.[8] (Scheme 2).

### 4.2. Syntheses of dimethylglutaraldehydes 2 and 3

*4.2.1. 4,4-Dimethyldihydro-2H-pyran-2,6(3H)-dione (**9**).* Thionylchloride (5.40 mL, 74.92 mmol) and 3,3-dimethylglutaric acid (3.00 g, 18.73 mmol) were stirred for 4 h at room temperature. After removal of extra $SOCl_2$ the product was obtained as white crystals, mp 120 °C (lit.[11] 125 °C). Yield: 2.60 g (96%). IR: 1811, 1775 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 2.60 (4H, s, C$H_2$), 1.15 (6H, s, *Me*$_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 166.1, 43.8, 29.5, 27.6; HRMS *m*/*z* $[M+Na]^+$ calcd for $C_7H_{10}O_3$: 165.0528, found: 165.0520.

*4.2.2. 3,5-Dimethyldihydro-2H-pyran-2,6(3H)-dione (**10**).* White crystals, mp 90.5–91 °C (lit.[9e] 90–92 °C). Yield: 710 mg (95%). IR: 1803, 1762 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) mixture of diastereomers $\delta$: 2.89, 2.74, 2.72 (2H, sextet, *J*=7.0 Hz, C*H*Me), 2.06 (1H, dt, *J*=13.5, 5.5 Hz, C$H_aH_b$), 1.88 (2H, t, *J*=7.0 Hz, C$H_aH_b$), 1.59 (1H, ddd, *J*=13.5, 13.0 Hz, C$H_aH_b$), 1.39, 1.38 (6H, d, *J*=7.0 Hz, C*HMe*); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 170.0, 37.0, 33.3, 31.5, 16.0; HRMS *m*/*z* $[M+Na]^+$ calcd for $C_7H_{10}O_3$: 165.0528, found: 165.0536. Data in accordance with literature values.[9e]

*4.2.3. 3,3-Dimethylpentanedioyl dichloride (**11**).* Anhydride **10** (2.35 g, 16.54 mmol) and phosphorus pentachloride (4.34 g, 20.84 mmol) were heated to 105 °C and stirred for 24 h. The crude product was distilled under reduced pressure (52 °C/0.4 mmHg, lit.[5a] 59–60 °C/0.8 mmHg). The acid chloride was obtained as colorless oil. Yield: 2.50 g (78%). IR: 1803 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 3.12 (4H, s, C$H_2$), 1.18 (6H, s, *Me*$_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 171.8, 56.2, 34.4, 26.9.

*4.2.4. 2,4-Dimethylpentanedioyl dichloride (**12**).* Colorless oil, bp 80 °C/1.2 mmHg (lit.[10a] 94–95 °C/12 mmHg). Yield: 980 mg (82%). IR: 1783 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) mixture of diastereomers $\delta$: 2.98, 2.97 (2H, sextet, *J*=7.0 Hz, C*H*Me), 2.38, 1.65 (2H, dt, *J*=14.0, 7.0 Hz, C$H_2$), 1.95 (2H, t, *J*=7.0 Hz, C$H_2$), 1.37, 1.36 (6H, d, *J*=7.0 Hz, CH*Me*); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 177.1, 176.9, 49.4, 48.6, 36.7, 36.2, 17.8, 17.1.

*4.2.5. 3,3-Dimethylpentanedial (**2**).* To a stirred solution of THF (40 mL) and freshly distilled 2,6-lutidine (0.90 mL, 8.14 mmol), Pd/$BaSO_4$ (240 mg, 2.26 mmol) and acid chloride (790 mg, 4.03 mmol) were added. The reaction mixture was stirred under hydrogen for 13.5 h. The crude product was filtered through Celite® and the solvent evaporated. Dialdehyde **2** (481 mg, 93% containing 15% of unreacted anhydride **9**) was obtained as yellow oil. Due to instability of **2**, the product was used as such in the next reaction step. IR: 1719 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 9.83 (2H, t, *J*=2.5 Hz, C*H*O), 2.51 (4H, d, *J*=2.5 Hz, C$H_2$), 1.21 (6H, s, *Me*$_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 201.7, 54.3, 32.8, 28.0; HRMS *m*/*z* $[M+Na]^+$ calcd for $C_7H_{12}O_2$: 151.0735, found: 151.0732.

*4.2.6. 2,4-Dimethylpentanedial (**3**).* Yellow oil. Yield: 216 mg (35%). IR: 1722 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 9.64, 9.62 (2H, d, *J*=1.5 Hz, C*H*O), 2.47 (2H, 2× sextet, *J*=7.0 Hz, C*H*Me), 2.21, 1.31 (2H, dt, *J*=14.0, 7.0 Hz, C$H_2$), 1.74 (2H, t, *J*=7.0 Hz, C$H_2$), 1.15, 1.14 (6H, d, *J*=7.0 Hz, C*HMe*); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 204.0, 203.9, 43.9, 30.8, 30.7, 14.0, 13.7; HRMS *m*/*z* $[M+Na]^+$ calcd for $C_7H_{12}O_2$: 151.0735, found: 151.0742.

### 4.3. General procedure for the syntheses of monoprotected dimethylglutaraldehydes 2 and 3 using microwave irradiation

3,3-Dimethylpentanedial (**2**) or 2,4-dimethylpentanedial (**3**) were dissolved in dry $CH_2Cl_2$ or THF. Propane-1,3-dithiol or distilled propane-1,3-diol (60 mol %) and molecular sieves (5 Å) were added. Iodine (10 mol %) was added just before the microwave reaction. The reaction parameters were: *P*=100 W, *T*=70 °C, $t_{ramp}$=1.5 min, $t_{hold}$=2.5 min. Then $CH_2Cl_2$ was added and the mixture was washed with saturated $Na_2S_2O_3$(aq). The organic layer was dried over $Na_2SO_4$. The solvent was evaporated and the residue was purified with flash chromatography (EtOAc:Hex 1:3).

*4.3.1. 4-(1,3-Dioxan-2-yl)butanal (**4a**).* Yellow oil. Yield: 332 mg (52%). IR: 1723 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 9.76 (1H, t, *J*=1.5 Hz, C*H*O), 4.50 (1H, t, *J*=5.0 Hz, OC*H*O), 4.10 (2H, dt, *J*=11.0, 1.0 Hz, C$H_aH_b$OCHOC$H_aH_b$), 3.78–3.71 (2H, m, $CH_aH_b$OCHOC$H_aH_b$), 2.47 (2H, td, *J*=7.0, 1.5 Hz, OHCC$H_2$), 2.13–2.01 (1H, m, OCHO-$CH_aH_bCH_aH_b$), 1.76 (2H, p, *J*=7.0 Hz, OHCCH$_2$C$H_2$), 1.60 (2H, q, *J*=5.0 Hz, OHCCH$_2$CH$_2$C$H_2$), 1.37–1.30 (1H, m, OCHOC$H_aH_b$C$H_aH_b$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 202.4, 101.7, 66.9, 43.6, 34.3, 25.8, 16.6; HRMS *m*/*z* $[M+Na]^+$ calcd for $C_8H_{14}O_3$: 181.0841, found: 181.0842.

*4.3.2. 4-(1,3-Dithian-2-yl)butanal (**4b**).* Yellow oil. Yield: 297 mg (51%). IR: 1720 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 9.77 (1H, t, *J*=1.5 Hz, C*H*O), 4.04 (1H, t, *J*=6.5 Hz, SC*H*S), 2.92–2.80 (4H, m, C$H_aH_b$SCHSC$H_aH_b$), 2.48 (2H, td, *J*=7.0, 1.5 Hz, OHCC$H_2$), 2.16–2.09 (1H, m, SCH$_a$H$_b$C$H_a$H$_b$), 1.92–1.75 (5H, m, OHCCH$_2$C$H_2$CH$_2$CH-$SCH_aH_bCH_aH_b$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 201.7, 47.0, 43.2, 34.7, 30.3, 25.9, 19.3; HRMS *m*/*z* $[M+Na]^+$ calcd for $C_8H_{14}OS_2$: 213.0384, found: 213.0388. Data in accordance with literature values.[3a]

*4.3.3. 4-(1,3-Dioxan-2-yl)-3,3-dimethylbutanal (**5a**).* Yellow oil. Yield: 415 mg (70%, containing anhydride **9**). IR: 1718 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 9.82 (1H, t, *J*=3.0 Hz, C*H*O), 4.63 (1H, t, *J*=5.0 Hz, OC*H*O), 4.08 (2H, dt, *J*=10.5, 1.5 Hz, C$H_aH_b$OCHOC$H_aH_b$), 3.78–3.71 (2H, m, $CH_aH_b$OCHOC$H_aH_b$), 2.34 (2H, d, *J*=3.0 Hz, OHCC$H_2$), 2.13–2.01 (1H, m, OCHOC$H_aH_b$C$H_aH_b$), 1.69 (2H, d, *J*=5.0 Hz, OHCCH$_2$CH$_2$C$H_2$), 1.32 (1H, ddddd, *J*=13.5, 2.5, 2.5, 1.5, 1.5 Hz, OCHOC$H_aH_b$C$H_aH_b$), 1.10 (6H, s, *Me*$_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 203.5, 100.5, 66.8, 54.6, 46.9, 31.8, 28.5, 25.6; HRMS *m*/*z* $[M+Na]^+$ calcd for $C_{10}H_{18}O_3$: 209.1154, found: 209.1163.

*4.3.4. 4-(1,3-Dithian-2-yl)-3,3-dimethylbutanal (**5b**).* Yellow oil. Yield: 325 mg (64%, containing anhydride **10**). IR: 1718 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 9.84 (1H, t, *J*=3.0 Hz, C*H*O), 4.06 (1H, t, *J*=5.5 Hz, SC*H*S), 2.94 (2H, ddd, *J*=14.0, 12.0, 2,5 Hz, $CH_aH_b$SCH-$SCH_aH_b$), 2.80 (2H, ddd, *J*=14.0, 4.5, 3.0 Hz, C$H_aH_b$SCHSC$H_aH_b$), 2.43 (2H, d, *J*=3.0 Hz, OHCC$H_2$), 2.09 (1H, ddddd, *J*=14.0, 4.5, 4.5, 2.5, 2.5 Hz, SCH$_a$H$_b$C$H_a$H$_b$), 1.88–1.80 (1H, m, SCH$_a$H$_b$CH$_a$H$_b$), 1.76 (2H, d, *J*=5.5, CMe$_2$C$H_2$), 1.15 (6H, s, *Me*$_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 202.5, 54.4, 48.4, 43.0, 33.9, 31.2, 27.9, 25.2; HRMS *m*/*z* $[M+H]^+$ calcd for $C_{10}H_{18}OS_2$: 219.0877, found: 219.0886.

*4.3.5. 4-(1,3-Dioxan-2-yl)-2,4-dimethylbutanal(**6a**).* Yellow oil. Yield: 105 mg (73%). IR: 1723 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) mixture of diastereomers $\delta$: 9.62 (1H, d, *J*=2.0 Hz, C*H*O), 9.56 (1H, d, *J*=2.5 Hz, C*H*O), 4.33 (1H, d, *J*=4.5 Hz, OC*H*O), 4.10 (2H, dt, *J*=11.5, 1.0 Hz, C$H_aH_b$OCHOC$H_aH_b$), 3.76–3.70 (2H, m, $CH_aH_b$OCHOC$H_aH_b$), 2.78–2.65 (1H, m, CH$_2$C*H*Me), 2.53–2.42 (1H, m, OHCC*H*Me), 2.08–1.97 (1H, m, OCH$_a$H$_b$CH$_a$H$_b$), 1.62–1.54 (2H, m, CHMeC$H_2$), 1.22–1.12 (1H, m, OCH$_a$H$_b$C$H_a$H$_b$), 1.10 (3H, d, *J*=7.0, CH$_2$CH*Me*), 1.07 (3H, d, *J*=7.0 Hz, CH$_2$CH*Me*), 0.94 (3H, d, *J*=7.0 Hz, OHCCH*Me*), 0.93 (3H, d, *J*=7.0 Hz, OHCCH*Me*); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 205.4, 205.3, 104.9, 104.8, 67.0, 66.9, 43.9, 37.1, 32.8, 31.8, 14.9, 14.5, 14.0, 13.2; HRMS *m*/*z* $[M+Na]^+$ calcd for $C_{10}H_{18}O_3$: 209.1154, found: 209.1164.

*4.3.6. 4-(1,3-Dithian-2-yl)-2,4-dimethylbutanal (**6b**).* Yellow oil. Yield: 111 mg (45%). IR: 1724 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) mixture of four diastereomers $\delta$: 9.63 (1H, d, *J*=2.0 Hz, C*H*O), 9.59 (1H, d, *J*=2.5 Hz, C*H*O), 4.13 (2H, d, *J*=4.0 Hz, SC*H*S), 2.95–2.85 (4H, m, C$H_aH_b$SCHSC$H_aH_b$), 2.78–2.67 (2H, m, OHCC*H*MeCH$_2$C*H*Me), 2.23–

2.16, 1.92–1.85, 1.36–1.29 (2H, m, OHCCHMeC$H_2$), 2.12–2.03, 1.85–1.74 (2H, m, SCH$_a$H$_b$C$H_a$H$_b$), 1.22–1.05 (6H, d, $J$=7.0 Hz, *Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 203.9, 203.8, 55.3, 55.0, 46.3, 46.0, 34.6–34.5, 32.9–32.3, 31.1–29.6, 27.5–27.3, 23.2–22.6, 21.0–20.7, 18.5–17.8, 14.0–13.2; HRMS $m/z$ $[M+Na]^+$ calcd for $C_{10}H_{18}OS_2$: 241.0697, found: 241.0687. Data in accordance with literature values.[12]

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## References and notes

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