The Homologation of Hagemann's Ester

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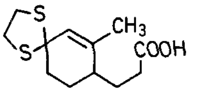
For the preparation of suitable polyenes for biomimetic cationic cyclizations[1], the acid **1** has proved to be an extremely useful synthon[2]. Its optical resolution has rendered possible the syntheses of optical active steroidal compounds[3].



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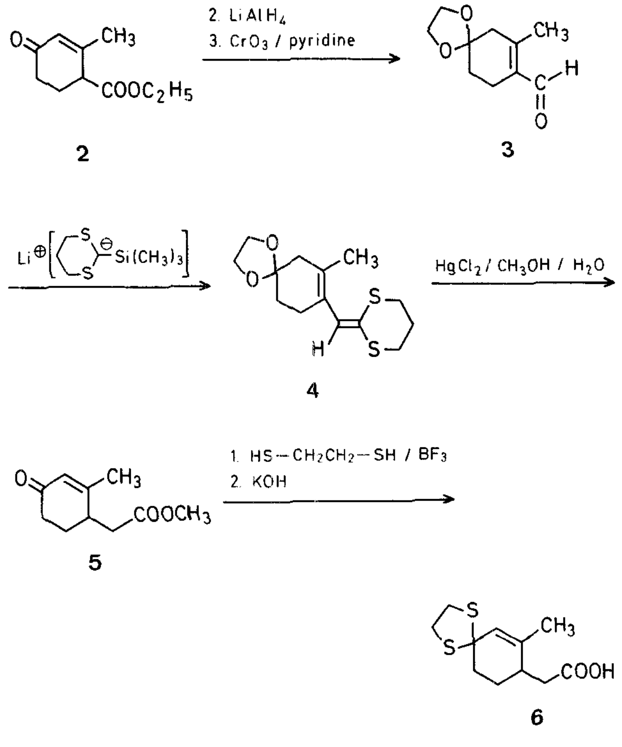
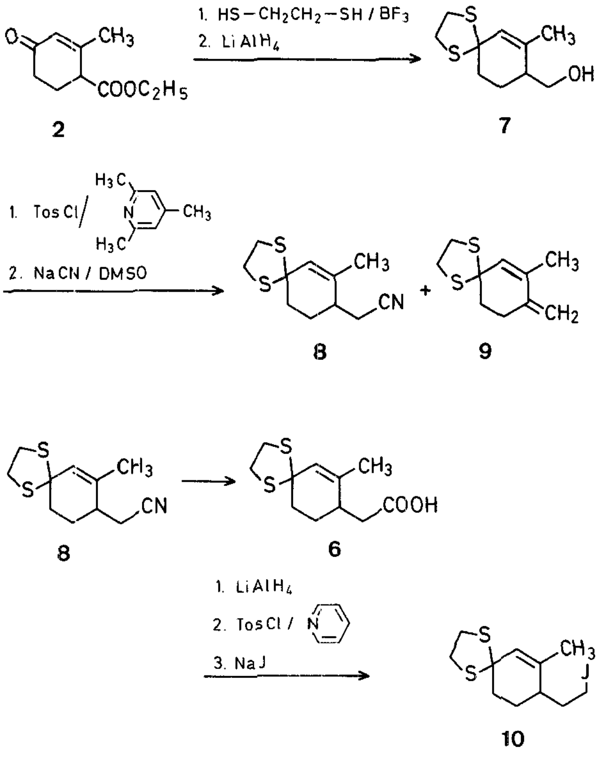
We now report two synthetic routes for the preparation of the acid **6**, containing one methylene group less than **1** in the side chain, which could be a synthon of similar usefulness.

In the first synthesis commercially available Hagemann's ester **2** (4-ethoxycarbonyl-3-methyl-2-cyclohexen-1-one) was converted to the known aldehyde **3**[4]. Condensation of **3** with the anion of 2-trimethylsilyl-1,3-dithiane[5] afforded the ketene-*S*,*S*-acetal **4** in nearly quantitative yield, which then was treated with mercury(II) chloride in methanol/water, furnishing the ester **5** in one step (42% from **3**). Ester **5** was converted to the *S*,*S*-acetal with 1,2-ethanedithiol and the ester group hydrolyzed to give the acid **6** (69% from **5**) as a colorless solid in 26% yield from Hagemann's ester.



The second synthesis involves simpler reactions and provides a higher overall yield of acid **6** (56%). If Hagemann's ester is *S*,*S*-acetalized with 1,2-ethanedithiol, the double bond does not migrate to the 3,4-position. Subsequent treatment with lithium aluminum hydride afforded alcohol **7** (84% from **2**), which was converted to its tosylate, then treated with sodium cyanide in dimethyl sulfoxide to give the nitrile **8** (77%). In the latter reaction the diene **9** was formed as a by-product (7%). Acid **6** was obtained by hydrolysis of **8** with potassium hydroxide in aqueous ethanol.

For further synthetic applications the iodide **10** can be prepared from the acid **6** (76%) using the same procedures which were employed for the conversion of the homologous acid **1** to the analogous iodide[2].



4-Methoxycarbonylmethyl-3-methyl-2-cyclohexen-1-one (5):
The procedure given by Seebach et al.[5] was used. Thus 2-trimethylsilyl-1,3-dithiane (7.17 g, 37.2 mmol) is allowed to react with *n*-butyllithium followed by addition of the aldehyde **3**[4] (6.64 g, 36.4 mmol). For work-up dichloromethane is used instead of pentane. The dichloromethane solution is washed with water and sodium chloride solution, dried with sodium sulfate, and concentrated in vacuo to give crude **4** (10.33 g) as an orange colored oil. The ^{1}H-N.M.R. of this product showed no major impurities, so that it was used without further purification. (Attempts to distil **4** resulted in decomposition.)

To a stirred solution of crude **4** (8.73 g) in methanol/water (9:1, 275 ml), mercury(II) chloride (19.0 g, 70 mmol) is added (N_2 atmosphere). The mixture is heated under reflux for 2.5 h. After cooling the brown precipitate is filtered off and washed with dichloromethane. The combined filtrates are diluted with water (500 ml) and extracted with dichloromethane. The organic layers are washed with water, concentrated ammonium chloride solution and sodium chloride solution, dried with magnesium sulfate, and concentrated in vacuo. The residue is distilled, chromatographed on silica gel with hexane/ether (1:1), and redistilled; yield: 2.44 g (42% from **3**); b.p. 155°/0.6 torr (colorless oil); $n_D^{20} = 1.4975$.

$C_{10}H_{14}O_3$	calc.	C 65.91	H 7.74
(181.2)	found	65.70	7.77

I.R. (liquid film): $\nu_{max} = 1767, 1700, 1642\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 5.86$ (s, br, 1H); 3.72 (s, 3H); 3.00–1.70 (m), 1.98 ppm (s, total 10H).

4,4-Ethanediyldithio-1-hydroxymethyl-2-cyclohexene (7):
To a stirred solution of 1,2-ethanedithiol (62.8 ml, 750 mmol) and Hagemann's ester[6] (**2**; 45.8 g, 251 mmol) in chloroform (500 ml) boron trifluoride etherate (11 ml, distilled from calcium hydride) is added (N_2-atmosphere). The mixture is stirred for 3.5 h, then poured into water (500 ml) and extracted with ether. The combined

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organic layers are quickly washed with 10% aqueous potassium hydroxide and then sodium chloride solution, dried with magnesium sulfate, and concentrated in vacuo. The crude product (62.9 g) is dissolved in dry ether (100 ml) and reduced with lithium aluminum hydride (27.8 g, 732 mmol) following the procedure given in Ref. [4]; yield: 45.6 g (84% from **2**); b.p. 126–132°/0.016 torr (colorless oil); $n_D^{20} = 1.5955$.

$C_{10}H_{16}OS_2$	calc.	C 55.51	H 7.45	S 29.64
(216.4)	found	55.37	7.53	29.36

I.R. (liquid film): $\nu_{max} = 3401, 2941, 1433, 1272, 1081, 1042, 1020\ cm^{-1}$.

^1H-N.M.R. ($CDCl_3$): $\delta = 5.68$ (s, br, 1 H); 3.80–3.52 (m, 2 H); 3.32 (s, 4 H); 2.42–1.63 (m), 1.73 ppm (s, total 8 H).

1-Cyanomethyl-4,4-ethanediyldithio-2-methyl-2-cyclohexene (8): The tosylation method developed by Marvel et al.[7], modified by Johnson et al.[8], was used. To an ice-cooled solution of the alcohol **7** (61.9 g, 286 mmol) in dry 2,4,6-trimethylpyridine (185 ml, distilled from potassium hydroxide) *p*-toluenesulfonyl chloride (78.0 g, 410 mmol) is added in several portions during 15 min (N_2 atmosphere). The reagents are stirred at 0° for 2 h, then 85% lactic acid (13.0 ml) is added by a syringe and stirring is continued for 30 min. The mixture is then poured into 10% aqueous hydrochloric acid (1 l) and extracted with ether. The ether layers are washed with 5% aqueous hydrochloric acid, water, and sodium chloride solution, dried with magnesium sulfate, and concentrated *in vacuo*. The remaining cotton-like solid is dried at 40°/1 torr for 1 h; yield: 106.5 g of crude tosylate; m.p. 66–69°.

Following the procedure of Pawson et al.[9] the tosylate is dissolved in dry dimethyl sulfoxide (600 ml) and sodium cyanide (53.0 g, 1.08 mol) is added. The mixture is stirred at 55–60° for 20 h. After cooling the solution is poured into water (2 l) and extracted with dichloromethane. The organic layers are washed with 5% aqueous ammonium chloride, saturated sodium hydrogen carbonate solution, water, and sodium chloride solution, dried with potassium carbonate, and concentrated in vacuo. The residue is chromatographed on silica gel. A first band is eluted with benzene and this product is isolated and distilled to give the diene **9**; yield: 3.84 g (7% from **7**); b.p. 190°/14 torr.

$C_{10}H_{14}S_2$	calc.	C 60.55	H 7.11
(198.35)	found	60.32	7.32

I.R. (liquid film): $\nu_{max} = 2985, 1600, 1456, 888\ cm^{-1}$.

^1H-N.M.R. ($CDCl_3$): $\delta = 5.76$ (s, 1 H); 4.95 (s, 1 H); 4.86 (s, br, 1 H); 3.32 (s, 4 H); 2.73–3.01 (m, 4 H); 1.80 ppm (s, br, 3 H).

After elution of the first band and removal of a yellow residual band from the top of the column by a pipette the nitrile **8** is washed from the column with benzene/ether (1:1). The solvent is removed in vacuo and the residue recrystallized from ethanol/water (4:1); yield: 49.55 g (77% from **7**); m.p. 59–62°.

$C_{11}H_{15}NS_2$	calc.	C 58.62	H 6.71	N 6.22	S 28.45
(225.4)	found	58.59	6.83	6.13	28.25

I.R. ($CHCl_3$): $\nu_{max} = 2932, 2247$ (w), 1435, 1416, 1269, 862 cm^{-1}.

^1H-N.M.R. ($CDCl_3$): $\delta = 5.72$ (s, 1 H); 3.33 (s, 4 H); 2.80–1.61 (m), 1.71 ppm (s, total 10 H).

(4,4-Ethanediyldithio-2-methyl-2-cyclohexenyl)-acetic Acid (6): Method A: from **8**: To a solution of the nitrile **8** (51.7 g, 229 mmol) in ethanol (130 ml) a solution of potassium hydroxide (40.0 g, 714 mmol) in water (200 ml) is added. The mixture is stirred at 80–95° for 50 h, then diluted with water (300 ml), and extracted with dichloromethane. The aqueous layer is acidified to pH 1 with 10% hydrochloric acid and extracted with dichloromethane. The organic layer from the latter extraction is washed with sodium chloride solution, dried with magnesium sulfate, and concentrated in vacuo. The residue is twice recrystallized from 50% aqueous ethanol and dried at 50°/0.7 torr; yield: 48.05 g (86%); m.p. 100.5–103°.

Method B: from **5**: The ester **5** (2.41 g, 13.2 mmol) is *S,S*-acetalized as previously described for **2**. Distillation (125°/0.022 torr) of the crude product affords 2.80 g of the *S,S*-acetal ester as a colorless oil, which is treated with potassium hydroxide (0.75 g) in methanol/water *(30 ml, 4:1) for 20 h. Then the solution is diluted with* water (15 ml) and extracted with ether. The aqueous layer is acidified and worked up as described above; yield: 2.22 g (69% from **5**); m.p. 102–103.5°.

$C_{11}H_{16}O_2S_2$	calc.	C 54.06	H 6.60	S 26.24
(244.4)	found	54.26	6.69	26.20

I.R. ($CHCl_3$): $\nu_{max} = 2941, 1709, 1430, 1288, 1109\ cm^{-1}$.

^1H-N.M.R. ($CDCl_3$): $\delta = 10.73$ (s, br, 1 H); 5.62 (s, br, 1 H); 3.30 (s, 4 H); 2.85–1.52 (m), 1.68 ppm (s, total 10 H).

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