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Short Communication

A Modified Synthesis of (±)-(*E*)-7-Methyl-1,6-dioxaspiro[4,5]decane

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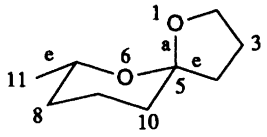
(*E*)-(*S*)-7-Methyl-1,6-dioxaspiro[4,5]decane (**1**) is a component of the volatiles produced by several kinds of wasp, bee, and beetle.[1] As a simple model of the spiroketal structures that have been found in many natural products, compound **1** has received considerable attention since the early 1980s. Quite a few synthetic[1] and structural[2] studies have appeared in the literature. However, the assignment of most of the signals in both ^1H and ^{13}C NMR spectra still remains to be done, and, owing to its use in the pheromone-based pest management program, the need[2] for practical routes still exists.



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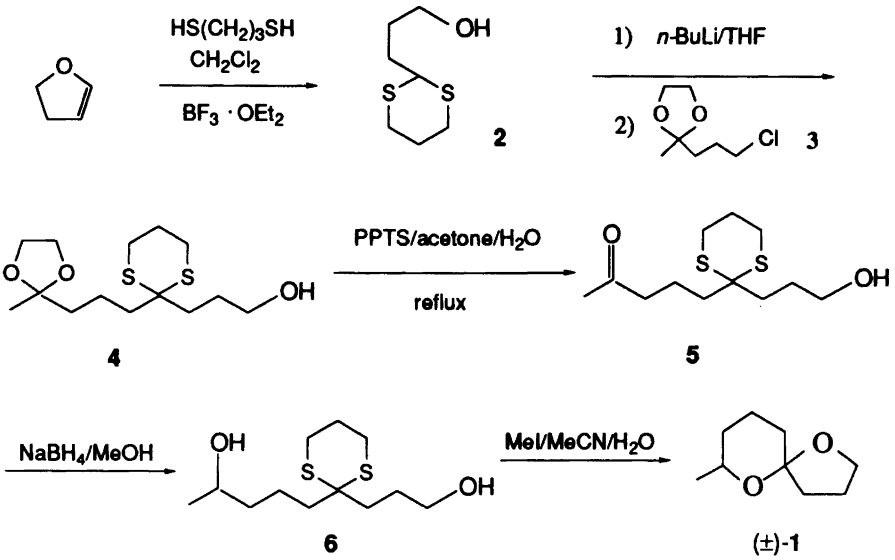
The most practical synthesis of the (±)-**1** so far documented is probably the one reported by Ramaswamy and Oehlschlager.[1d] Unfortunately, in this route the yields of the first and the last steps were quite low (<43% and 44%, respectively) and one of the building blocks was not commercially available. In an effort to circumvent these shortcomings we developed a modified route as shown in Scheme 1.

The reason for the low yield of the first step in the previous work [1d] seemed to be an incorrect experimental procedure. We observed that the dithiol reacted with 2,3-dihydrofuran very violently in the presence of acidic catalysts. To avoid forming undesired by-products, it was of critical importance to introduce the dihydrofuran last, at a rather slow rate and with sufficient cooling. With these modifications, the yield of **2** was easily raised to 87%.

Alkylation of the dianion of dithiane **2** was realized with the commercially available chloride **3** (which also could be conveniently prepared from the corresponding ketone with ethylene glycol in benzene in the presence of



Scheme 1.

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p-TsOH). Selective hydrolysis of the *O*-ketal (which failed with 3% HCl[3] in THF) was cleanly effected in aqueous acetone by use of pyridium *p*-toluenesulfonate (PPTS)[4] as a catalyst. Subsequent reduction with $NaBH_4$ in MeOH gave the diol **6** as the only product. Finally, the thioketal was converted into the spiroketal **1** in 77% yield by treatment with CH_3I in aqueous acetonitrile (containing 20% water).

What deserves to be mentioned here is the unique function of water and the remarkable stability of **1** in acidic aqueous solution. It is known that most ketals hydrolyze rapidly in strongly acidic aqueous solution. Considering that several equivalents of HI are generated in the dethioketalization, one might well expect that the absence of water in the final step would significantly increase the yield of **1**. However, with anhydrous acetonitrile as the solvent the yield turned out to be only 27%. The reaction mixture became brown soon after the mixing of **6** and CH_3I and darkened rapidly with time. Upon addition of water to the reaction mixture, the dark-brown species went into the aqueous phase and the colour vanished within minutes. Obviously, in addition to the expected alkylation[1d] with CH_3I at the sulfur atoms and the substitution of the resulting sulfonium groups by the alcohol oxygens, some other reactions (which are probably suppressed by water) occurred in the non-aqueous system.

Experimental

All NMR spectra were recorded on a Varian XL-400 NMR spectrometer (operating at 400 MHz for ^1H) with Me_4Si as an internal standard and $CDCl_3$ as the solvent. The assignment of the ^1H and ^{13}C NMR spectra of compound **1** is based on standard 2D experiments (COSY-90 and HETCOR). IR spectra were collected on a Perkin-Elmer 1600 FT infrared spectrometer. Mass spectra (GC–MS) were obtained on a modified Finnigan Mat 1020B instrument (electron impact mode, 70 eV). The relative intensity of the peaks is given in parentheses after the corresponding *m/z* value. Elemental analysis was performed by Mikro Kemi AB, Uppsala, Sweden.

2,3-Dihydrofuran (97%), 5-chloro-2-pentanone ethyleneketal (97%), and *n*-BuLi (1.6 M in hexane) were purchased from Aldrich Chemie Co. Boron trifluoride–diethyl ether (48%), 1,3-propanedithiol (97%), sodium borohydride (85%), iodomethane (99%), and pyridinium toluene-4-sulfonate (PPTS, 99%) were purchased from Fluka AG.

2-(3-Hydroxypropyl)-1,3-dithiane (**2**).[1d] To a 100 ml flask were added CH_2Cl_2 (30 ml), the dithiol (2.6 ml, 25 mmol), $BF_3 \cdot OEt_2$ (0.5 ml, 48% solution), and, with cooling (−70° bath) and stirring, the dihydrofuran (2.0 ml, 26 mmol, added dropwise). After the completion of the addition, the cold bath was removed and the mixture was stirred at room temperature for 41 h. The reaction mixture was diluted with diethyl ether (500 ml), washed with saturated aqueous $NaHCO_3$ (2 × 50 ml), water (2 × 200 ml) and brine (30 ml), and dried over Na_2SO_4. After filtration and evaporation, the oily residue was chromatographed on silica gel (eluting with diethyl ether) to give the dithiane **2** as a yellowish oil (3.88 g, 22 mmol, 87%). IR: 3430 cm^{-1}; ^1H NMR: δ 1.4 (1 H, br s, OH), 1.74–1.92 (5 H, m), 2.08–2.16 (1 H, m), 2.80–2.93 (4 H, m), 3.68 (2 H, br t, *J* 5.9 Hz), 4.1 (2 H, t, *J* 6.6 Hz); ^{13}C NMR: δ 25.9, 29.7, 30.4 (2 C), 31.9, 47.2, 62.3; GC–MS: 178 (M^+, 35.1), 119 (100), 85 (20.3), 71 (71.8), 61 (13.1), 60 (21.8), 47 (28.0), 46 (55.6).

8,8-Ethylenedioxy-4,4-trimethylenedithiononan-1-ol (**4**). With cooling (−70°C bath) and stirring *n*-BuLi (29.0 ml, 1.6 M) was added dropwise (via a syringe) to a solution of the dithiane **2** (3.88 g, 22 mmol) and Ph_3CH (8 mg, as an indicator) in dry THF (70 ml, freshly distilled from Na–Ph_2CO under Ar) under argon. The bath was allowed to warm to −20°C and the magenta solution was stirred at that temperature for 4 h, before the chloride (3.5 ml, 23 mmol) was introduced via a syringe. After further stirring at 0°C for 3 h, the reaction flask was kept in a 0°C refrigerator for 4 days. The mixture was diluted with diethyl ether (150 ml) and washed with water (2 × 100 ml) and brine (100 ml). The aqueous phases were back-extracted with diethyl ether (100 ml) and the resulting ethereal phase was washed with brine (50 ml). The ethereal phases were then combined and dried over Na_2SO_4. The oily residue after filtration and evaporation was chromatographed on silica gel (eluting with diethyl ether) to give compound **4** as a sticky oil (4.62 g, 15 mmol, 69%). IR: 3433 cm^{-1}; ^1H NMR: δ 1.32 (3 H, s), 1.43 (1 H, br s, OH), 1.50–1.60 (2 H, m), 1.61–1.69 (2 H, m), 1.69–1.76 (2 H, m), 1.85–1.91 (2 H, m), 1.91–2.01 (4 H, m), 2.76–2.88 (4 H, m), 3.68 (2 H, br t, *J* 6.3 Hz), 3.92–3.97 (4 H, m); ^{13}C NMR: δ 18.63, 23.85, 25.39, 25.98 (2 C), 27.63, 34.38, 38.57, 39.09, 52.96, 62.84, 64.63 (2 C), 109.86; Anal. for $C_{14}H_{26}O_3S_2$: C, H.

9-Hydroxy-6,6-trimethylenedithiononan-2-one (**5**). A mixture of the ketal **4** (4.49 g, 14.7 mmol) and PPTS (1.23 g, 4.89 mmol) in aqueous acetone (140 ml of acetone plus 15 ml of water) was heated to reflux with stirring for 3 h, when TLC showed the hydrolysis to be complete. The mixture was diluted with diethyl ether (450 ml) and washed with water (50 ml) and brine (70 ml). The aqueous phases were back-extracted with diethyl ether. The ethereal phases were washed as above, combined with the first one, and dried over Na_2SO_4. Filtration and evaporation followed by column chromatography on silica gel (eluting with diethyl ether) gave the ketone **5** as a colourless oil (3.42 g, 13.0 mmol, 89%). IR: 1740 cm^{-1}; ^1H NMR: δ 1.48 (1 H, br s), 1.74 (4 H, m), 1.88 (2 H, m), 1.98 (4 H, m), 2.16 (3 H, s), 2.48 (2 H, t, *J* 6.7 Hz), 2.82 (4 H, m), 3.68 (2 H, br t, *J* 6.5 Hz); ^{13}C NMR: δ 18.33, 25.35, 25.95 (2 C), 27.43, 29.99, 34.32, 37.48, 43.20, 52.71, 62.70, 208.59. The crude ketone could also be used directly in the next step.

2-(4-Hydroxypentyl)-2-(3-hydroxypropyl)-1,3-dithiane (**6**).[1d] With cooling (ice–water bath) and stirring, $NaBH_4$ (600 mg) was carefully added (in small portions) to a solution of the ketone **5** (3.37 g, 12.8 mmol) in methanol (60 ml). When the addition was complete, the mixture was stirred at 0°C for 30 min. An additional amount of $NaBH_4$ (100 mg) was introduced. When TLC showed a complete reduction, the mixture was diluted with diethyl ether (100 ml) and washed with water (50 ml) and brine (40 ml). The combined aqueous phases were back-extracted with diethyl ether (2 × 75 ml). The ethereal phases were washed as above, combined with the first one and dried over Na_2SO_4. After filtration and evaporation, the oily residue was chromatographed on silica gel (eluting with diethyl ether) to afford the diol **6** as an oil (3.36 g, 12.7 mmol, 99%). IR: 3374 cm^{-1}; ^1H NMR: δ 1.21 (3 H, d, *J* 6.2 Hz), 1.4–1.75 (8 H, m), 1.85–2.04 (6 H, m), 2.82 (4 H, m), 3.69 (2 H, br t, *J* 6.3 Hz), 3.84 (br q, 1 H); ^{13}C NMR: δ 20.26, 23.61, 25.39, 25.98 (2 C), 27.58, 34.34, 38.24, 39.18, 52.92, 62.76, 67.76.

(E)-*7-Methyl-1,6-dioxaspiro[4,5]decane* (**1**).[1d] To a 100 ml flask were added the diol **6** (1.68 g, 6.35 mmol), acetonitrile (24 ml), water (6 ml) and CH_3I (6.3 ml). The mixture was stirred at room temperature for 24 h before being diluted with pentane (100 ml), washed with water (30 ml), saturated aqueous $NaHCO_3$ (50 ml) and brine (30 ml), and dried over Na_2SO_4. The colourless solution was then filtered through a short pad of silica gel (ϕ 0.8 × 5 cm, eluting with pentane) and the filtrate was concentrated on a rotary evaporator (aspirator, cold-water bath). The residue was then flash distilled (Kugelrohr, oil pump) to give a colourless liquid (760 mg, 4.87 mmol, 77%), which was highly pure as shown by GC and ^1H and ^{13}C NMR spectroscopy. ^1H NMR: δ 1.10 (3 H, d, *J* 6.4 Hz, H-11), 1.17 (1 H, m, H-8), 1.56 (1 H, m, H-8), 1.59–1.71 (4 H, m, from upfield to downfield, H-10), H-9, H-4 and H-10), 1.76–1.87 (2 H, m, from upfield to downfield, H-9 and H-3), 1.87–1.94 (1 H, m, H-4), 2.03 (1 H, m, H-3), 3.85 (1 H, m, H-7), 3.86 (2 H, t, *J* 7.1 Hz, H-2); ^{13}C NMR: δ 20.40 (C-9), 22.01 (C-11), 23.72 (C-3), 32.57 (C-8), 32.77 (C-10), 37.93 (C-4), 66.41 (C-7), 66.74 (C-2), 105.95 (C-5, missing in HETCOR); GC–MS: 156 (M^+, 2.3), 141 (1.3), 126 (1.8), 112 (12.2), 97 (26.2), 87 (98.4), 84 (100), 69 (15.3), 55 (46.4).

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