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A new approach to annelated furans. The total synthesis of (±)-euryfuran

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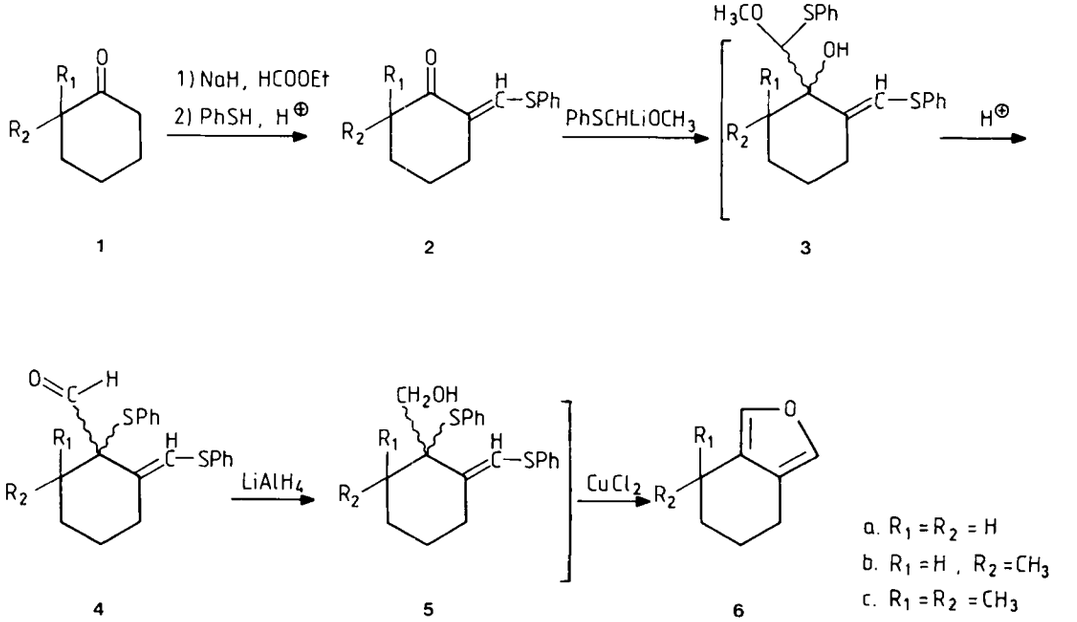
Abstract. A new approach to annelated furans has been developed starting from ketones. Formylation of the enolate, protection of the aldehyde function as its (phenylthio)- or (*n*-butylthio)methylene derivative and addition of methoxy(phenylthio)methyllithium gave adducts with the necessary functionalized carbon atoms. Rearrangement of these adducts to phenylthio aldehydes, followed by reduction, led to alcohols which spontaneously cyclized to furans. The method has been demonstrated in the total synthesis of (±)-euryfuran. An unusual rearrangement was found upon hydrolysis of the adducts mentioned above in that a ring expansion leading to γ-oxo α,β-unsaturated aldehydes was observed.

Introduction

The synthesis of drimanes has been strongly stimulated by the discovery of the potent insect-antifeedant properties of several members of this class of sesquiterpenes[1]. A suitable starting compound for the synthesis of drimanes is decalone **7**, which can be easily prepared on a good scale[2–4]. It was necessary to develop procedures for the construction of annelated butenolides, furans and lactols to convert decalone **7** into drimanes such as isodrimenin, confertifolin, euryfuran or valdiviolide[5].

A new route to annelated furans, starting from ketones, has been developed as described in Scheme 1. The ketones **1** were formylated and the aldehyde function was protected as its (phenylthio)methylene derivative **2**. Addition of methoxy(phenylthio)methyllithium[6,7] gave a diastereomeric mixture of unstable adducts **3**. Complete or partial rearrangement of these adducts occurred during the isolation procedure[8]. The adducts **3b** and **3c** required a short treatment with acid to effect complete conversion into the phenylthio aldehydes **4**. These phenylthio aldehydes **4** were not particularly stable and reduction to the alcohols **5** directly followed by treatment with $CuCl_2$ in collidine[9] proved to be the best procedure for the preparation of the furans **6a-c**. The furans were obtained in overall yields of about 30%. These somewhat modest isolated yields were partly due to



1 2 3 4 5 6

Scheme 1

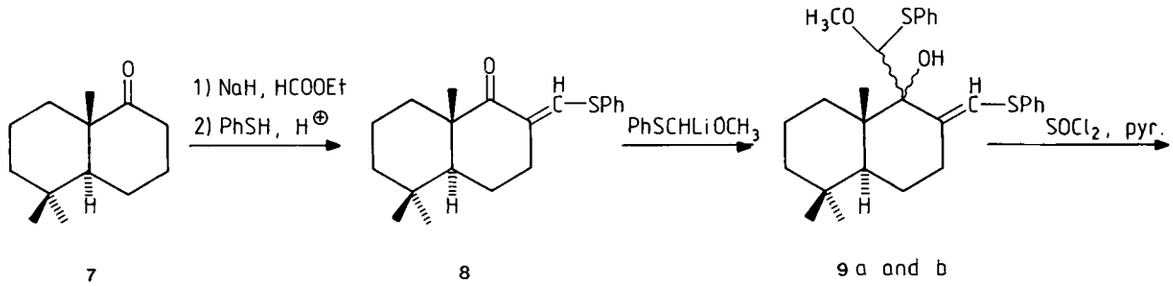
losses which occurred during the isolation procedure. The phenylthio group was used as protective group in **2** instead of the more usual *n*-butylthio group to avoid the formation of mixed disulfides in the last step of the sequence; this facilitates the purification of the furans. Extensive purification of the intermediates is not necessary.

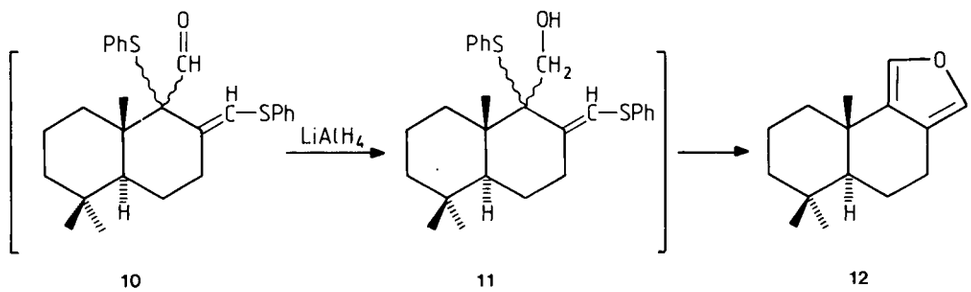
For the preparation of euryfuran (**12**), decalone **7** was first converted into its (phenylthio)methylene derivative **8**. Addition of methoxy(phenylthio)methyllithium gave a mixture of stable diastereomers **9a** and **9b** which could be separated into two fractions which were epimeric at C-1[10].

Rearrangement of the adducts **9a** and **9b** and reduction of the aldehydes **10** were again performed in one continuous operation since these intermediates proved to have limited stability. The alcohols **11** cyclized spontaneously to euryfyran (**12**)[11,12]. When the (*n*-butylthio)methylene was used as protecting group for the aldehyde function as in **13** (see Scheme 3), the rearranged aldehydes[10] and alcohols were stable compounds and treatment with $CuCl_2$ in collidine was necessary to convert the (*n*-butylthio)methylene alcohol into euryfuran. This new approach towards the array of functional groups as present in compounds **5** and **11** and their facile conversion into furans[9,13-15] is particularly useful in the synthesis of annelated *c*-furans.

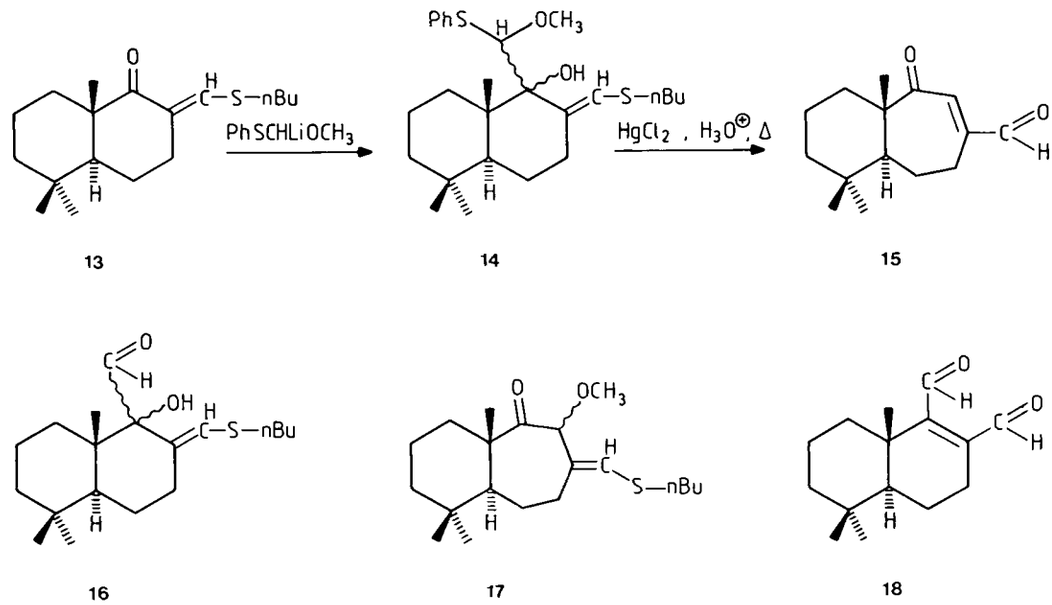
An attractive intermediate to annelated furans or butenolides would be the dialdehyde **18** which might be obtained after hydrolysis and dehydration of adducts **14**.

Mild hydrolysis of **14** gave diastereomeric mixtures of hydroxy aldehydes **16** and/or an unexpected rearranged product, which could be identified as the ring-expanded ketone **17**. When the hydrolysis of **14** was performed at reflux temperature in the presence of $HgCl_2$ and hydrochloric acid, the ring-expanded γ-oxo α,β-unsaturated aldehyde **15** was isolated as the sole product in 85% yield[16].

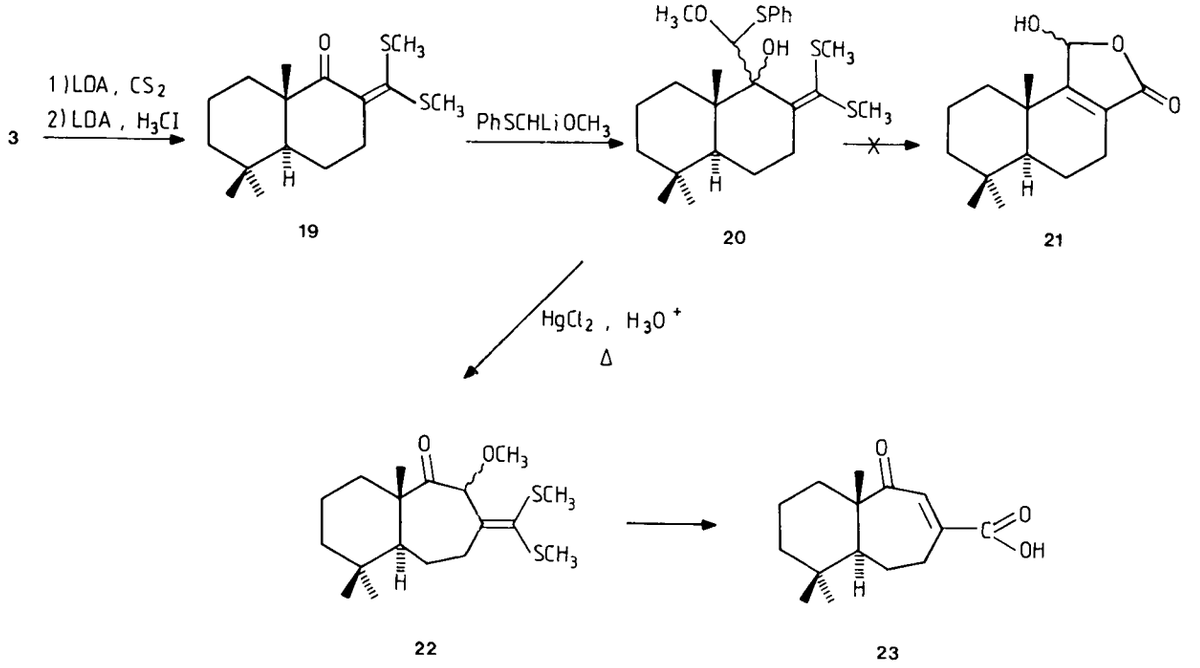




Scheme 2



Scheme 3



Scheme 4

The same type of rearrangement frustrated our attempts to produce annelated lactols, as indicated in Scheme 4, required for a total synthesis of valdiviolide (**21**). Therefore, decalone **3** was first converted into ketene dithioacetal **19**. Subsequent addition of methoxy(phenylthio)methyllithium afforded a mixture of diastereoisomeric adducts **20**. The hydrolysis of these adducts gave results comparable with those observed for **14** and the ring-expanded ketone **22** was isolated in 70% yield. Further hydrolysis of **22** could be accomplished in 61% yield by treatment with $HgCl_2$ and hydrochloric acid in methanol followed by treatment with potassium hydroxide.

Experimental

Boiling points and melting points are uncorrected. ^{1}H NMR spectra were determined on a Varian EM-390 or an Hitachi Perkin-Elmer R-24B spectrometer. Chemical shifts are reported in δ units with reference to tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded using a Varian XL-100 or a Bruker CXP-300 spectrometer in the pulse-FT mode with tetramethylsilane as the internal standard. Mass-spectral data and exact mass measurements were obtained using AEI MS 902 and VG micromass 7070F spectrometers. Unless indicated otherwise, the drying agent for organic solutions was $MgSO_4$. When no temperature is specified, the reaction was carried out at room temperature, *ca.* 20°C. The petroleum ether used for column chromatography had a boiling range of 40–60°C.

General procedure for the preparation of furans from (phenylthio)-methylene ketones

The preparation of the (phenylthio)methylene ketones **2a-c** and the addition of methoxy(phenylthio)methyllithium were performed as previously described[10]. The ethereal solution containing 30 mmol of the adducts **3a-c** was concentrated and dissolved in a mixture of 50 ml of dioxane and 20 ml of 2N hydrochloric acid. This reaction mixture was stirred for 30 min and water and ether were then added. The water solution was extracted with ether and the combined ethereal solutions were washed with brine and dried. The resulting solution of the phenylthio aldehydes **4a-c** was concentrated and added to a suspension of 10 mmol of $LiAlH_4$ in 50 ml of ether at 0°C. This reaction mixture was stirred for 30 min and then 0.2 ml of water, 0.2 ml of 4N NaOH and again 0.6 ml of water were added. After stirring for 15 min, the solution was dried over Na_2SO_4 overnight and filtered. The ether was evaporated *in vacuo* and the alcohols **5a-c** were dissolved in THF. To this solution were added 60 mmol of $CuCl_2$ and 120 mmol of collidine and the reaction mixture as refluxed for 2 h. The THF solution was decanted and the residue was extracted with ether. The combined solutions were washed with 2N hydrochloric acid, water and dried. The solvent was evaporated and the residue was purified by chromatography over silica gel using hexane as eluent.

4,5,6,7-Tetrahydroisobenzofuran (**6a**) was isolated as an unstable oil in 34% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.50–1.90 (m, 4H), 2.30–2.60 (m, 4H), 6.98 (s, 2H). MS *(m/e):* 122 ($M^{+\bullet}$, 100); 94 (51); 93 (35); 91 (25); 79 (35); 77 (25).

4-Methyl-4,5,6,7-tetrahydroisobenzofuran (**6b**) was isolated as an unstable oil in 35% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.18 (d, 3H), 1.50–2.00 (m, 4H), 2.30–2.60 (m, 3H), 7.05 (br s, 2H). MS *(m/e):* 136 ($M^{+\bullet}$, 80); 121 (100); 108 (12); 107 (12); 93 (22); 91 (24); 77 (26).

4,4-Dimethyl-4,5,6,7-tetrahydroisobenzofuran (**6c**) was isolated as a colourless oil in 23% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.20 (s, 6H), 1.40–2.00 (m, 4H), 2.50 (t, 2H), 6.97 (br s, 1H), 7.08 (br s, 1H). MS *(m/e):* 150 ($M^{+\bullet}$, 28); 135 (100), 107 (9); 105 (9); 91 (18); 77 (10).

(±)-Euryfuran (**12**)

The preparation of the (phenylthio)methylene ketone **8**, the adducts **9** and the rearranged phenylthio aldehydes **10** was performed as previously described[10]. The crude products **10** were purified by chromatography over silica gel using petroleum ether/2% ether as eluent. The phenylthio aldehydes **10** were obtained in 91% yield as an unstable oil which was directly converted into the alcohols **11**. ^{1}H NMR of **10** (one epimer) δ (ppm): 0.84, 0.90 and 1.00 (CH_3 signals), 1.1–2.1 (m, 9H), 2.2–3.0 (m, 2H), 6.10 (s, 1H), 7.1–7.5 (m, 10H), 9.37 (s, 1H).

A solution of 700 mg (1.6 mmol) of phenylthio aldehydes **10** in 5 ml of dry ether was added to a suspension of 40 mg (1.1 mmol) of $LiAlH_4$ in 100 ml of dry ether at 0°C. The reaction mixture was stirred for 15 min and then 5 drops of water, 5 drops of 4N NaOH and a further 10 drops of water were added. The mixture was stirred for 1 h and Na_2SO_4 was added to dry the solution. The mixture was then filtered and the solvent evaporated *in vacuo*. The residue was set aside at room temperature for 2 h, which was

sufficient time for the complete transformation of the reduced products to euryfuran. The final product was chromatographed over silica gel using petroleum ether as eluent. Euryfuran (**12**) was obtained in 80% yield as a colourless oil. The spectral properties were in agreement with those reported in the literature[11,12]. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.94, 0.97 and 1.23 (CH_3 signals), 1.3–2.1 (m, 9H), 2.2–2.9 (m, 2H), 7.07 (s, 2H). Acc. mass $C_{15}H_{22}O$ calcd.: 218.1674; found: 218.1653.

trans-2-[(n-Butylthio)methylene]-1β-hydroxy-5,5,8a-trimethylperhydronaphthalene-1α-carboxaldehyde (**16**) *and trans-4-[(n-butylthio)methylene]-3-methoxy-1,8,8-trimethylbicyclo[5.4.0]-undecan-2-one* (**17**)

A solution of 245 mg (0.55 mmol) of a mixture of adducts **14**, 262 mg (1.21 mmol) of yellow HgO and 328 mg (1.21 mmol) of $HgCl_2$ in 9 ml of acetone and 1 ml of water was stirred for 15 min at room temperature. Dilute hydrochloric acid (10 ml) was added and the mixture was extracted with ether. The ethereal solution was washed with 10 ml of 1N hydrochloric acid, with saturated $NaHCO_3$ solution and with brine and then dried. The residue was chromatographed over silica gel using petroleum ether/5% ether as eluent. The aldehydes **16** were eluted first as a mixture of two epimers and were obtained in 50% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.90 and 0.96 (CH_3 signals), 1.1–2.4 (m, 15H), 2.6–2.77 (t, *J* 7.2 Hz, 2H), 3.67 and 3.70 (2s, 1H), 6.23 and 6.26 (2s, 1H), 10.00 and 10.10 (2s, 1H). Acc. mass $C_{19}H_{32}O_2S$ calcd.: 324.2123; found: 324.2124.

The epimeric mixture of rearranged ketones **17** was eluted as the second fraction and obtained in 42% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.87, 0.93 and 1.20 (CH_3 signals), 1.2–2.6 (m, 18H), 2 65 (t, *J* 7.2 Hz, 2H), 3.30 and 3.33 (2s, 3H), 4.33 and 4.82 (2s, 1H), 6.2 (br s, 1H). Acc. mass $C_{20}H_{34}O_2S$ calcd.: 338.2280; found: 338.2278.

A solution of 224 mg (0.5 mmol) of adducts **14** and 816 mg (3 mmol) of $HgCl_2$ in 40 ml of acetone and 9 ml of 1N hydrochloric acid was stirred for 2 h at room temperature. Dilute hydrochloric acid was added and the mixture was extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ solution and with brine and then dried. The solvent was evaporated *in vacuo* and the residue was chromatographed over silica gel using petroleum ether/10% ether as eluent. An epimeric mixture of ring-enlarged ketones **17** was obtained in 76% yield.

trans-2-Oxo-1,8,8-trimethylbicyclo[5.4.0]undec-3-ene-4-carboxaldehyde (**15**)

A solution of 112 mg (0.25 mmol) of adducts **14** and 408 mg (1.1 mmol) of $HgCl_2$ in 20 ml of acetone and 4 ml of 1N hydrochloric acid was refluxed for 4 h. The reaction mixture was cooled and solid $NaHCO_3$ was added. The mixture was filtered and the solvent was evaporated *in vacuo*. Water and ether were added and the water solution was extracted with ether. The ethereal solution was washed with brine and dried. The solvent was evaporated *in vacuo* and the residue was purified by means of preparative TLC using petroleum ether/10% ether as eluent. The oxo aldehyde **15** was obtained in 85% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.92, 0.95 and 1.25 (CH_3 signals), 1.1–2.8 (m, 11H), 6.65 (br s, 1H), 9.58 (s, 1H). Acc. mass $C_{15}H_{22}O_2$ calcd.: 234.1620; found: 234.1622. The aldehydes **16** and the ring-enlarged ketones **17** were also transformed into keto aldehyde **15** when treated as described for compound **14**.

trans-2-[Bis(methylthio)methylene]-5,5,8a-trimethylperhydronaphthalen-1-one (**19**)[17]

A solution of lithium hexamethyldisilazane (LHMDS) (15.5 mmol) was generated at 0°C and under nitrogen by addition of 11 ml of butyllithium (15.5 mmol) to a solution of 2.5 g (15.5 mmol) HMDS in 20 ml of dry THF. The solution was cooled to −78°C and 2.7 ml (15.5 mmol) of hexamethylphosphoric triamide (HMPT) was added.

A solution of 2.8 g (15.5 mmol) of ketone **3** in 10 ml of dry THF was added and the mixture was stirred for 20 min at −78°C. 1.18 g (15.5 mmol) of carbon disulfide was then added and the temperature of the solution was allowed to rise to 0°C over 2 h. The solution was cooled to −78°C and 15.5 mmol of LHMDS in 20 ml of dry THF was added. The solution was stirred for ½ h, 2 ml (15.5 mmol) of methyl iodide was added at −78°C and the reaction mixture was slowly warmed to room temperature and stirred overnight. The solution was diluted with saturated NH_4Cl and extracted with ether. The ether extracts were washed with brine and dried. The solvent was evaporated *in vacuo* and the residue was chromatographed over silica gel using petroleum ether/2% ether as eluent. Compound **19** was obtained in 70% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.95 and 1.10 (CH_3 signals), 1.2–1.9 (m, 11H), 2.30 and 2.35 ($-S-CH_3$ signals).

trans-2-[Bis(methylthio)methylene]-1α-[(phenylthio)methoxymethyl)]-5,5,8a-trimethylperhydronaphthalen-1β-ol (**20**)

The addition of (phenylthio)methoxymethyllithium to compound **19** was performed as previously described[10]. The diastereoisomers **20** were separated by chromatography over silica gel using petroleum ether/4% ether as eluent. Epimers **20a** were obtained in 44% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.86, 0.90 and 1.00 (CH_3 signals), 1.1–2.0 (m, 11H), 2.30 and 2.35 ($-S-CH_3$ signals), 2.35–2.55 (m, 1H), 3.35 (s, 3H), 4.95 (s, 1H), 7.15–7.63 (m, 5H). MS *(m/e):* 299 (100); 295 (44); 267 (45); 234 (14); 187 (18); 177 (24); 161 (17); 153 (19); 145 (14); 110 (16); 109 (18). FD: 452 (M^+).

Epimers **20b** were obtained in 35% yield as a white solid, m.p. 93–95°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.83, 0.90 and 0.93 (CH_3 signals), 1.1–1.8 (m, 11H), 2.30 and 2.43 ($-S-CH_3$ signals), 3.52 (s. 3H), 5.42 (s, 1H), 7.2–7.5 (m, 5H). MS *(m/e):* 299 (100); 295 (37); 267 (25); 234 (8); 187 (12); 177 (15); 153 (15); 110 (47); 109 (17); FD: 452 (M^+). Anal. $C_{24}H_{36}O_2S_3$ calcd.: C 63.67, H 8.02; found: C 63.43, H 8.16%.

4-[Bis(methylthio)methylene]-3-methoxy-1,8,8-trimethylbicyclo[5.4.0]undecan-2-one (**22**)

A solution of 171 mg (0.35 mmol) of epimers **20b** and 0.57 g (2.1 mmol) of $HgCl_2$ in 30 ml of acetone and 6 ml of 1N hydrochloric acid was refluxed for 2 h. The reaction mixture was cooled and solid $NaHCO_3$ was added. The mixture was filtered and the solvent was evaporated *in vacuo*. Water and ether were added and the water solution was extracted with ether. The ether extracts were washed with brine and dried. The solvent was evaporated *in vacuo* and the residue was chromatographed over silica gel using petroleum ether/5% ether as eluent. Compound **22** was obtained as a 6/1 mixture of two epimers in 71% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.88 (br s, 6H), 1.20 (s, 3H), 1.2–2.1 (m, 11H), 2.27, 2.30 and 2.34 (3s, 6H), 3.05–3.25 (m, 1H), 3.34 and 3.38 (2s, 3H), 4.83 and 5.15 (2s, 1H). Acc. mass $C_{18}H_{30}O_2S_2$ calcd.: 342.1688; found: 342.1683.

2-Oxo-1,8,8-trimethylbicyclo[5.4.0]undec-3-ene-4-carboxylic acid (**23**)

To a solution of 200 mg (0.58 mmol) of **22** in 15 ml of methanol was added 238 mg of $HgCl_2$ and 5 ml of 4N hydrochloric acid. The solution was then refluxed for 24 h. The mixture was filtered and the solvent was evaporated. The crude product was dissolved in 15 ml of methanol and 800 mg of potassium hydroxide was added. The reaction mixture was stirred for one day at room temperature and poured into water. The solution was extracted twice with 100 ml of ether. The aqueous layer was acidified with 5 ml of 1N hydrochloric acid and extracted with 100 ml of ether. The ethereal solution was washed with brine and then dried. The solvent was evaporated, leaving a white solid, which was recrystallized from petroleum ether b.p. 40–60. Acid **23** was obtained in 61% yield as a white crystalline compound, m.p. 152–154°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.92 (s, 3H), 0.95 (s, 3H), 1.26 (s, 3H), 1.3–1.7 (m, 8H), 1.70–1.95 (m, 1H), 2.4–2.7 (m, 2H), 7.03 (s, 1H). MS *(m/e):* 250 ($M^{+\bullet}$, 58); 235 (15); 232 (5); 222 (11); 217 (6); 207 (14); 123 (81); 112 (100); 109 (58); 95 (48); 82 (60); 69 (74). Acc. mass $C_{15}H_{22}O_3$ calcd.: 250.1569; found: 250.1572. Anal. $C_{15}H_{22}O_3$ calcd.: C 71.97, H 8.86; found: C 71.86, H 8.97%.

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