Polarized Ketene Dithioacetals; 71.[1] Synthesis of 2,5-Substituted 3-Bis(methylthio)methylenetetrahydrofurans

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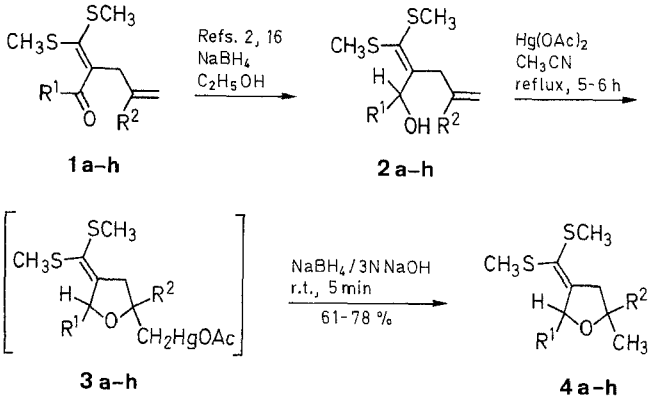
Synthesis of novel 2,5-substituted 3-bis(methylthio)methylenetetrahydrofurans **4** by oxymercuration–reduction of α- bis(methylthio)methylene-γ,δ-unsaturated alcohols **2** is reported. The carbinols **2** are obtained from the corresponding allyl-(or 2-methyl-2-propenyl)acylketene dithioacetals **1** by sodium borohydride reduction or by treatment with methylmagnesium iodide.

In a recent report,[2] we described a novel stereoselective synthesis of α-ylidene-γ-butyrolactones from allyl-(or 2-methyl-2-propenyl)acylketene dithioacetals **1**. The reaction sequence involves (a) sodium borohydride reduction of **1** to the corresponding carbinol acetals **2**, (b) methanolysis of the carbinol acetals **2** in the presence of ether-boron trifluoride complex in methanol to give the corresponding α-ylidene-γ,δ-unsaturated esters, and (c) cyclization of the esters in the presence of a mixture of formic acid and phosphoric acid to give the desired lactones. We now report that the intermediate carbinols undergo heterocyclization through an oxymercuration–reduction sequence to give the corresponding 2,5-substituted 3-bis (methylthio)methylenetetrahydrofurans **4**.

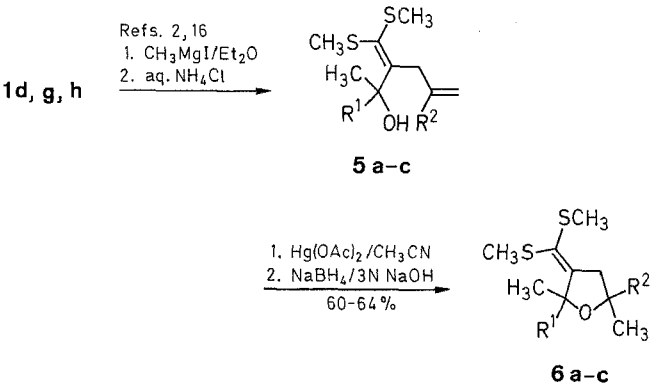


1a–h **2a–h** **3a–h** **4a–h**

1–4	R^1	R^2	1–4	R^1	R^2
a	C_6H_5	H	**e**	C_6H_5	CH_3
b	4-ClC_6H_4	H	**f**	4-ClC_6H_4	CH_3
c	4-$CH_3OC_6H_4$	H	**g**	4-$CH_3OC_6H_4$	CH_3
d	CH_3	H	**h**	CH_3	CH_3

Scheme **A**

The carbinol **2a**, prepared as described earlier,[2] was treated with mercuric acetate in acetonitrile, followed by sodium borohydride reduction of the intermediate organomercuric compound to yield the diastereoisomeric mixture of **4a** (72%) containing 85% of *trans* and 15% of *cis* isomer. The observed diastereoselectivity to give predominantly *trans* isomer is in agreement with similar mercuration studies on γ,δ-unsaturated alcohols to give cyclic ethers.[3–6] Similarly, the acyclic allyl alcohols are also known to undergo diastereoselective mercuration to give preferentially *erythro* isomers.[7] The other carbinols **2b–d** and **2e–h**, derived from the respective allyl-(**1b–d**) and 2-methyl-2-propenyl-(**1e–h**) ketene dithioacetals (Scheme **A**), were also shown to give the corresponding 2-aryl(or methyl)-5-methyl-(**4b–d**) and 5,5-dimethyl-(**4e–h**) tetrahydrofurans under identical conditions in 60–78% overall yields. The cyclization was found to be equally facile with the carbinols **5a–c**, obtained by addition of methylmagnesium iodide to the respective dithioacetals **1d**, **1g** and **1h**, to afford the corresponding 2,5-dimethyl-(**6a**) and 2,2-dimethyl-(**6b, c**) tetrahydrofurans in good yields (Scheme **B**). The structures of all the tetrahydrofurans were established by their spectral and analytical data (Table).

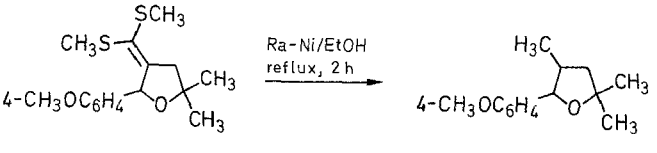


5a–c **6a–c**

5, 6	R^1	R^2
a	CH_3	H
b	4-$CH_3OC_6H_4$	CH_3
c	CH_3	CH_3

Scheme **B**

The 2,5-substituted tetrahydrofuran moiety is commonly found in many natural products, particularly among the polyether antibiotics. Hence, there has been considerable interest in devising viable synthetic methods for its construction.[3,8–10] The most common route involves electrophilic cyclization of γ,δ-unsaturated alcohols.[3–6,11–14] The present procedure involving cyclization of the carbinols **2** affords novel 2,5-substituted tetrahydrofurans carrying an additional bis(methylthio)methylene functionality, which is useful for further synthetic manipulations. Thus in one experiment, the product **4g** was subjected to reductive desulfurization in the presence of Raney nickel to give the corresponding 2-(4-methoxyphenyl)-3,5,5-trimethyltetrahydrofuran as a mixture of *cis*-**7** and *trans*-**7** isomers (40:60) in good yield.



4g **7**

An interesting feature of this reaction is the chemoselective mercuration of γ,δ-double bond with mercuric acetate, whereby the bis(methylthio)methylene functionality remains unaffected. These results are in conformity with the reported[15] studies of the relative reactivity of various substituted olefins towards oxymercuration, showing that terminal mono- and di-substituted olefins are more reactive than the corresponding tetrasubstituted derivatives.

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Table. 2,5-Substituted 3-Bis(methylthio)methylenetetrahydrofurans **4a–h** and **5a–c** Prepared

Product	*cis*/*trans*[a]	Yield (%)	mp (°C)	Molecular Formula[b]	IR (neat/KBr)[c] ν (cm^{-1})	^{1}H-NMR (CCl_4)[d] δ, J (Hz)	MS (70eV)[e] *m/z* (%)
4a	15 : 85	72	oil	$C_{14}H_{18}OS_2$ (266.4)	1604, 1490, 1447, 1425, 1382, 1281, 1091, 1055, 1017	1.20 (d, 3H, J = 7, CH_3 or *cis*); 1.30 (d, 3H, J = 7, CH_3 of *trans*); 1.68 (s, 3H, SCH_3 of *trans*); 1.95 (s, 3H, SCH_3 of *cis*); 2.18 (s, 3H, SCH_3 of *trans*); 2.25 (s, 3H, SCH_3 of *cis*); 2.30–2.88 (m, 1H, $\underline{H}_A-C-H_B$); 3.08 (dd, 1H, J = 17, 5, $H_A-C-\underline{H}_B$); 3.75–4.23 (m, 1H, H-5); 5.57 (d, 1H, J = 1.5, H-2 of *trans*); 5.65 (s, 1H, H-2 of *cis*); 7.23 (m, $5H_{arom}$)	266 (M^+, 19); 251 (33)
4b	20 : 80	78	65–66	$C_{14}H_{17}ClOS_2$ (300.9)	1610, 1486, 1383, 1359, 1261, 1168, 1089, 1009	1.25 (d, 3H, J = 7, CH_3 of *cis*); 1.38 (d, 3H, J = 7, CH_3 of *trans*); 1.78 (s, 3H, SCH_3 of *trans*); 2.05 (s, 3H, SCH_3 of *cis*); 2.25 (s, 3H, SCH_3 of *trans*); 2.27 (s, 3H, SCH_3 of *cis*); 2.33–2.98 (m, 1H, $\underline{H}_A-C-H_B$); 3.15 (dd, 1H, J = 17, 5, $H_A-C-\underline{H}_B$); 3.89–4.35 (m, 1H, H-5); 5.50 (d, 1H, J = 1.5, H-2 of *trans*); 5.70 (s, 1H, H-2 of *cis*); 7.25 (s, $4H_{arom}$)	
4c	22 : 78	69	oil	$C_{15}H_{20}O_2S_2$ (296.4)	1610, 1511, 1463, 1441, 1427, 1385, 1303, 1248, 1173, 1140, 1029, 1056, 1040, 1018	1.20 (d, 3H, J = 7, CH_3 of *cis*); 1.30 (d, 3H, J = 7, CH_3 of *trans*); 1.71 (s, 3H, SCH_3 of *trans*); 2.00 (s, 3H, SCH_3 of *cis*); 2.20 (s, 3H, SCH_3 of *trans*); 2.28 (s, 3H, SCH_3 of *cis*); 2.30–3.89 (m, 1H, $\underline{H}_A-C-H_B$); 3.08 (dd, 1H, J = 17, 5, $H_A-C-\underline{H}_B$); 2.72 (s, 3H, CH_3O); 3.75–4.28 (m, 1H, H-5); 5.48 (d, 1H, J = 1.5, H-2 of *trans*); 5.68 (s, 1H, H-2 of *cis*); 6.55–7.30 (dd, A_2B_2, $4H_{arom}$)	296 (M^+, 2); 266 (35); 218 (100)
4d	38 : 62	66	oil	$C_9H_{16}OS_2$ (204.35)	1604, 1443, 1427, 1384, 1365, 1288, 1248, 1186, 1095, 1077	1.11–1.41 (m, 6H, CH_3 of *cis* and *trans*); 2.32 (s, 3H, SCH_3); 2.33 (s, 3H, SCH_3); 2.40–3.08 (m, 2H, CH_2); 3.64–4.01 (distorted sext, 1H, H-5 of *cis*); 4.60 (qd, 1H, J = 7, 1.5, H-2 of *trans*); 4.78 (qd, 1H, J = 7, 1, H-2 of *cis*)	204 (M^+, 29); 156 (75)
4e	–	62	oil	$C_{15}H_{20}OS_2$ (280.4)	1604, 1491, 1450, 1425, 1366, 1293, 1249, 1183, 1149, 1024	1.20 (s, 3H, CH_3); 1.36 (s, 3H, CH_3); 1.73 (s, 3H, SCH_3); 2.20 (s, 3H, SCH_3); 2.59 (dd, 1H, J = 16, 1.5, $\underline{H}_A-C-H_B$); 2.94 (d, 1H, J = 16, $H_A-C-\underline{H}_B$); 5.50 (d, 1H, J = 1.5, H-2); 7.21 (s, $5H_{arom}$)	280 (M^+, 20); 265 (40)
4f	–	61	70	$C_{15}H_{19}ClOS_2$ (314.9)	1610, 1508, 1460, 1440, 1423, 1363, 1295, 1250, 1175, 1162, 1033	1.19 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 1.80 (s, 3H, SCH_3); 2.21 (s, 3H, SCH_3); 2.52 (dd, 1H, J = 16, 1.5, $\underline{H}_A-C-H_B$); 2.89 (d, 1H, J = 16, $H_A-C-\underline{H}_B$); 5.50 (d, 1H, J = 1.5, H-2); 7.20 (s, $4H_{arom}$)	316 (3); 314 (M^+, 10); 301 (10); 299 (20); 254 (8); 252 (28)
4g	–	66	oil	$C_{16}H_{22}O_2S_2$ (310.5)	1608, 1506, 1460, 1436, 1420, 1362, 1298, 1245, 1175, 1163, 1028	1.18 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 1.78 (s, 3H, SCH_3); 2.21 (s, 3H, SCH_3); 2.57 (dd, 1H, J = 16, 1.5, $\underline{H}_B-C-H_B$); 2.90 (d, 1H, J = 16, $H_A-C-\underline{H}_B$); 3.68 (s, 3H, OCH_3); 5.50 (d, 1H, J = 1.5, H-2); 6.62–7.22 (dd, A_2B_2, $4H_{arom}$)	310 (M^+, 22); 295 (77)
4h	–	68	oil	$C_{10}H_{18}OS_2$ (218.4)	1605, 1430, 1420, 1363, 1287, 1246, 1154, 1098, 1075, 1020	1.08 (s, 3H, CH_3); 1.28 (s, 3H, CH_3); 1.29 (d, 3H, J = 7, 2-CH_3); 2.20 (s, 6H, SCH_3); 2.39 (dd, 1H, J = 16, 1.5, $\underline{H}_A-C-H_B$); 2.73 (d, 1H, J = 16, $H_A-C-\underline{H}_B$); 4.61 (qd, 1H, J = 7, 1.5, H-2)	218 (M^+, 22)
5a	–	60	oil	$C_{10}H_{18}OS_2$ (218.4)	1590, 1450, 1430, 1420, 1380, 1350, 1252, 1160, 1132, 1083, 1050	1.23 (d, 3H, J = 7, CH_3); 1.39 (s, 3H, CH_3); 1.49 (s, 3H, CH_3); 2.12 (s, 3H, SCH_3); 2.26 (s, 3H, SCH_3); 2.27 (m, 1H, merged with SCH_3 signal, $\underline{H}_A-C-H_B$); 2.95 (dd, 1H, J = 17, 5.5, $H_A-C-\underline{H}_B$); 3.90 (distorted sext, 1H, H-5)	218 (M^+, 100) 203 (78)
5b	–	64	oil	$C_{17}H_{24}O_2S_2$ (324.5)	1607, 1505, 1460, 1438, 1420, 1361, 1293, 1247, 1174, 1162, 1088, 1033	1.18 (s, 3H, CH_3); 1.28 (s, 3H, SCH_3); 1.90 (s, 3H, SCH_3); 2.22 (s, 3H, SCH_3); 2.70 (d, 1H, J = 17, $\underline{H}_A-C-H_B$); 2.98 (d, 1H, J = 17, $H_A-C-\underline{H}_B$); 3.69 (s, 3H, CH_3O); 6.60–7.37 (dd, A_2B_2, $4H_{arom}$)	324 (M^+, 5); 309 (10); 218 (100)
5c	–	60	oil	$C_{11}H_{20}OS_2$ (232.4)	1540, 1450, 1430, 1420, 1360, 1295, 1252, 1163, 1138, 985	1.20 (s, 6H, CH_3); 1.47 (s, 6H, CH_3); 2.20 (s, 3H, SCH_3); 2.23 (s, 3H, SCH_3); 2.73 (s, 2H, CH_2)	232 (M^+, 15); 217 (81)

[a] Ratio of *cis*/*trans* isomers calculated from ^{1}H-NMR spectra.
[b] Satisfactory microanalyses obtained: C ±0.28, H ±0.31.
[c] Recorded on Perkin-Elmer 297 infrared spectrophotometer.
[d] Recorded on Varian EM-390 NMR spectrometer.
[e] Recorded on Jeol JMS-D 300 spectrometer.

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The required allyl-(**1a–d**) and 2-methyl-2-propenyl-(**1e–h**) acylketene dithioacetals and the corresponding carbinols **2a–h** and **5a–c** were prepared according to the earlier reported procedure,[2,16] and used without further purification.

2,5-Substituted 3-Bis(methylthio)methylenetetrahydrofurans (4a–h and 5a–c; General Procedure:

To a solution of carbinol **2** (0.01 mol) in CH_3CN (40 mL), $Hg(OAc)_2$ (7.90 g, 0.025 mol) is added. The reaction mixture is refluxed with stirring for 5–6 h, cooled, filtered and the residue washed with $CHCl_3$ (2×25 mL). The filtrate (< 90 mL) is then treated with 3 M NaOH (25 mL), followed by $NaBH_4$ (0.05 mol) in NaOH (30 mL), and stirred at room temperature for 5 min. The reaction mixture is then filtered through a sintered glass funnel to remove solid inorganic impurities, and the filtrate extracted with $CHCl_3$ (3×50 mL). The organic layer is washed with water (100 mL), dried (Na_2SO_4) and evaporated to give products **4** or **5**, which are further purified by passing through a small column of silica gel. (Table).

Reductive Desulfurization of 4g with Raney Nickel; 2-(4-Methoxyphenyl)-3,5,5-trimethyltetrahydrofuran (7):

To a solution of **4g** (0.50 g, 2.5 mmol) in EtOH (20 mL), W4 Raney nickel[17] (5 g) is added, and the mixture is refluxed with stirring for 2 h. After filtration and washing of the residue with $CHCl_3$ (15 mL), the combined filtrate is concentrated, and the product purified by passing through a silica gel column using hexane as eluent. Desulfurized product **7** was obtained as a light yellow viscous oil; yield: 0.29 (82%).

$C_{14}H_{20}O_2$	calc.	C 76.32	H 9.15
(220.3)	found	76.04	9.39

IR (neat): ν = 1615, 1513, 1248, 1165, 990 cm^{-1}.

^{1}H-NMR(CCl_4): δ = 0.58 (d, 3 H, J = 7 Hz, 3-CH_3 of *cis*-**7**); 0.91 (d, 3 H, J = 6 Hz, 3-CH_3 of *trans* **7**); 1.23, 1.28 (s, 3 H, each, 5-CH_3 of *trans* **7**); 1.35, 1.40 (s, 3 H, each, 5-CH_3 of *cis* **7**); 1.57–2.58 (m, 3 H, H-3 and 4-CH_2); 3.69 (s, 3 H, CH_3O); 4.18 (d, 1 H, J = 9 Hz, H-2 of *cis* **7**); 4.94 (d, 1 H, J = 7.5 Hz, H-2 of *trans* **7**); 6.64–7.30 (m, 4 H_{arom}).

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