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Aromatic Ring Synthesis by 1,3-Michael-Claisen Annulation : Formation of Dihydrobenzofurans and Tetrahydrochromans from α-Methylene γ-Butyrolactone and δ-Valerolactone.

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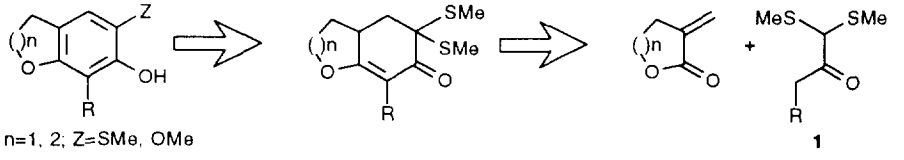
Abstract: Substituted dihydrobenzofurans and tetrahydrochromans have been prepared from respectively α-methylene-γ-butyrolactone and δ-valerolactone *via* a 1,3-Michael-Claisen reaction from two 3-carbon units, 1,1-bis-(methylthio)-2-propanone or butanone, and an α-methylene lactone.

Formation of aromatic rings is of great importance in the synthesis of natural products and biologically active compounds[1]. Construction of benzenoid aromatic systems from aliphatic sources via annulation reactions has the great advantage to control the position of substituents at the initial stage of the synthesis.

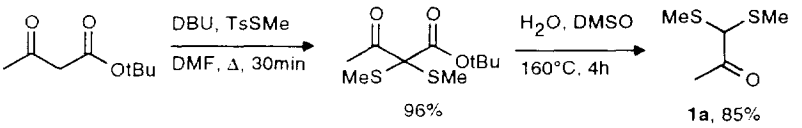
We describe in this paper the preparation of substituted dihydrobenzofurans and tetrahydrochromans from respectively α-methylene γ-butyrolactone and δ-valerolactone *via* a 1,3-Michael-Claisen annulation reaction as shown on the retrosynthetic scheme.



Our approach is based on the work of Kim [1b, 2] who showed that phenolic compounds could be readily made via an 1,3-Michael-Claisen annulation from two 3-carbon units, such as 1,1-bis-(methylthio)-2-propanone **1a** (R=H), and an α,β-unsaturated ketone or an α-methylene lactone.

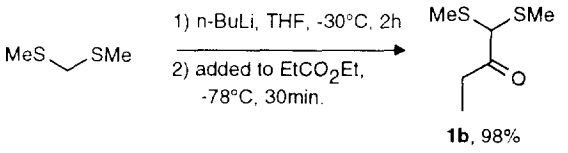
This methodology allowed us to describe, using new experimental conditions, short syntheses of highly substituted dihydrobenzofurans and tetrahydrochromans.

1,1-bis-(methylthio)-2-propanone **1a** was readily prepared from t-butyl acetoacetate which was first disulfenylated with methylthiotosylate[3] and decarboxylated in modified Krapcho conditions[4] (without addition of salts like NaCN), (Scheme I).



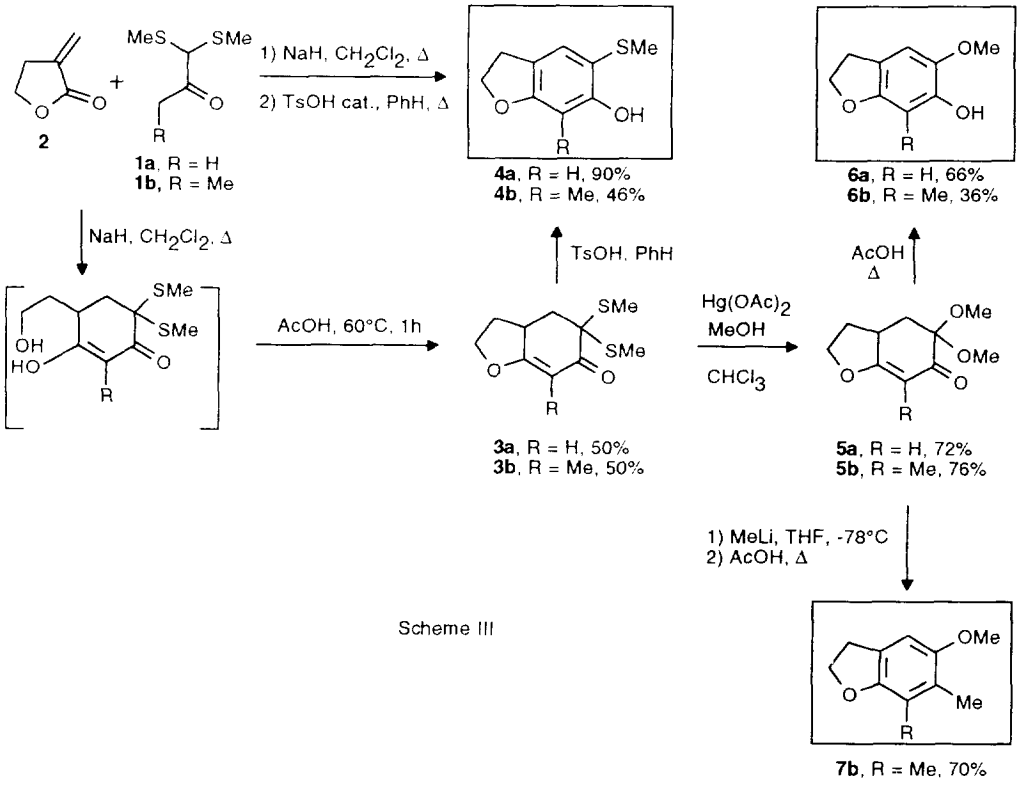
Scheme I

1,1-bis(methylthio)-2-butanone **1b** was obtained by condensation of the anion of bis(methylthio)-methane on ethyl propionate (Scheme II).



Scheme II

In refluxing a mixture of α-methylene-γ-butyrolactone[5] **2**, the thioacetal **1a** and sodium hydride (2 eq) in CH_2Cl_2, we observed the formation of the Michael adduct as a mixture of the three possible enols. This mixture was directly cyclized in acetic acid to give the tetrahydrobenzofuran **3a** in 50% overall yield (Scheme III).



Scheme III

Aromatisation was carried out in presence of p-TsOH to give the dihydrobenzofurane **4a** in 90% yield.
The formation of **4a** was readily improved in heating directly the Michael adduct in presence of p-TsOH affording a 2 steps synthesis of the dihydrobenzofurane **4a** in 90% yield.

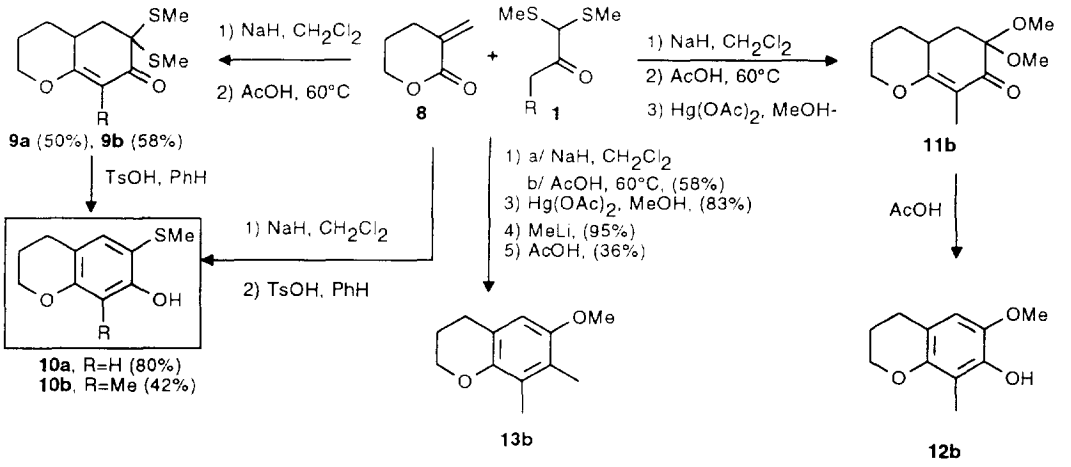
Compound **4b** was obtained in similar conditions with 46% yield. The lower yield is due to the chromatographic purification.

Ozaki and Kim[2a] hydrolyzed the thioacetal function of type **3** intermediates in order to get catechol derivatives with mercuric chloride or perchlorate in rather poor yields. We found that transacetalization with mercuric acetate in methanol to the corresponding acetal **5** proceeded with a much better yield.
Finally aromatization in boiling acetic acid afforded the corresponding catechol derivatives **6**. Once again the stability of **6b** led to a lower yield.

Finally it was shown that the addition of MeLi to **5b**, followed by aromatisation in acetic acid yielded the methylated benzofuran **7b** in 70% yield.

Substituted tetrahydrochromans were also prepared by the same procedure from α-methylene δ-valerolactone[6] **8** (Scheme IV).

A few remarks concerning the syntheses of the tetrahydrochromans of Scheme IV must be pointed out. Tetrahydrochroman **10a**, obtained in 80% yield (from NMR), was contaminated by about 20% of the starting thioacetal **1a** which could not be separated by chromatography (same Rf). Therefore in this case it is necessary to make first the tetrahydrochroman derivative **9a** (50%) in acetic acid and then get **10a** by aromatisation with p-TsOH.



Scheme IV

On the other hand, the direct 2 steps synthesis of **10b** was faster than usual, it was necessary to heat the reaction mixture with p-TsOH only 4h (16h in the other cases).
For the synthesis of **12b**, the first 3 steps gave the expected products in high yields, but the last step, the aromatisation of the product **11b**, gave only 36% yield due to the low stability of **12b** on silicagel.

Finally, in the synthesis of **13b**, the last step, the aromatisation step in acetic acid gave a small amount of the corresponding phenol (20%) which could not be separated from **13b** by chromatography.

Experimental Section.

1,1-Bis(methylthio)-2-propanone, 1a

1) 2,2-bis(methylthio)-t-butyl-acetoacetate : DBU (2 eq, 25.13 mL, 168 mmol) and methyl thiotosylate[3] (2 eq, 34 g, 168 mmol) were successively added to a solution of t-butyl acetoacetate (1 eq, 13.3 g, 84 mmol) in DMF (300 mL). The mixture was heated at 80°C during 30 min, allowed to cool and poured onto cold water (800 mL). The aqueous phase was extracted with a 1/1 ether-hexane mixture (3 x 200 mL), the combined organic layers were washed with 200 mL of a 10% HCl solution and water (200 mL), dried over Na_2SO_4 and concentrated under vacuum to yield 2,2-bis(methylthio)-t-butyl-acetoacetate (19.9g, 79.8 mmol, 95%) as yellow cristals.

IR (CCl_4) : 3020-2840 (C-H), 1720 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.51 (s, 9H, t-Bu), 1.98 (s, 6H, SCH_3), 2.37 (s, 3H, H-4). ^{13}C NMR (50 MHz, $CDCl_3$) : 11.82 (SCH_3), 25.29 (C-4), 27.44 (t-Bu), 75.85 (C-2), 83.94 (C-5), 165.20 (C-1), 195.07 (C-3)

Anal. Cald for $C_{10}H_{18}O_3S_2$: C, 47.97 ; H, 7.39. Found : C, 48.13 ; H, 7.25.

2) A solution of DMSO (100 mL), 2,2-bis(methylthio)-t-butyl-acetoacetate (1 eq, 19.9 g, 77 mmol) and water (1 eq, 1.43 mL, 77 mmol) was heated at 160°C during 4h. After cooling, the mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the joined organic layers were washed with water (100 mL), dried over Na_2SO_4 and concentrated under vacuum. The oily residue was distilled in a bulb to bulb Büchi apparatus (bp = 60°C/0,1 mmHg, apparatus temperature) to yield a pale yellow oil (9.8 g, 65.4 mmol, 85%).

IR (CCl_4) : 3020-2820 (C-H), 1720 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 2.08 (s, 6H, SCH_3), 2.36 (s, 3H, H-3), 4.37 (s,1H, H-1). ^{13}C NMR (50 MHz, $CDCl_3$) : 11.62 (SCH_3), 25.72 (C-3), 60..70 (C-1), 198.45 (C-2)

Anal. Cald for $C_5H_{10}OS_2$: C, 39.97 ; H, 6.71. Found : C, 39.62 ; H, 6.71.

1,1-Bis(methylthio)-2-butanone, 1b

A solution of bis(methylthio)methane (2 eq, 5 mL, 48.9 mmol) in THF (100 mL) was cooled at -78°C and n-butyllithium (2 eq, 33.3 mL of a 1.47M solution in hexane , 48.9 mmol) was added dropwise. The resulting mixture was stirred at -78°C during 2 h and added via a canula to a solution of ethyl propionate (60 mL) in THF (100 mL) previously cooled to -78°C. Stirring at -78°C was maintained during 30 min and hydrolysis performed by adding sat. NH_4Cl solution (100 mL). The mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the joined organic layers were washed with water (100 mL), dried over Na_2SO_4 and concentrated under vacuum (12 mmHg to remove the solvents and then 48 hours under 0.5 mmHg to remove starting materials in excess). A pale yellow oil (3.98 g, 24.2 mmol, 98 %) was obtained.

IR (CCl_4) : 3020-2820 (C-H), 1720 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.10 (t, 3H, J=7.3 Hz, H-4), 2.05 (s, 6H, SCH_3), 2.69 (q, 2H, J=7. 3 Hz, H-3), 4.37 (s, 1H, H-1). ^{13}C NMR (50 MHz, $CDCl_3$) : 7.87 (C-4), 12.23 (SCH_3), 32.03 (C-3), 60.30 (C-1), 201.92 (C-2).

Anal. Cald for $C_6H_{12}OS_2$: C, 43.87 ; H, 7.36. Found : C, 43.86 ; H, 7.54.

General procedure for the preparation of α-methylthio-β-hydroxy compounds.

In a three-necked round bottomed flask equipped with a dropping funnel, a suspension of NaH (2 eq) in CH_2Cl_2 (1 mL/mmol NaH) was cooled at 0°C with an ice bath. Thioacetal **1a** or **1b** (1 eq) in CH_2Cl_2 (1 mL/mmol thioacetal) was added dropwise to the suspension. After stirring for 10 min at 0°C, α-methylenelactone **2** or **8** (1 eq) dissolved in CH_2Cl_2 (1 mL/mmol lactone) was added dropwise and the ice bath was replaced by a heating bath. The suspension was refluxed for 16 h, allowed to cool down and poured onto a 10% aqueous HCl solution (10 mL/mmol thioacetal). The organic layer was decanted, the aqueous layer extracted with CH_2Cl_2 and the joined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was dissolved in benzene (5ml/mmol thioacetal) and a catalytic amount of p-TsOH added. The resulting solution was refluxed with a Dean-Stark apparatus during **x**h. After cooling and distillation of benzene under vacuum, the product was submitted to flash-chromatography (see products description).

2,3-Dihydro-5-methylthio-6-hydroxy-benzofuran, 4a

Prepared from compounds **1a** and **2**. Refluxing time **x** = 120h. Chromatography : CH_2Cl_2. Yield : 90%, pale pink cristals, R_f : 0,50 (CH_2Cl_2), mp : 62-63°C.

IR (CCl_4) : 3400 (OH), 3000-2860 (C-H). ^1H NMR (200 MHz, $CDCl_3$) : δ = 2.25 (s, 3H, SCH_3), 3.13 (t, 2H, J=8.5Hz, H-3), 4.58 (t, 2H, J=8.5Hz, H-2), 6.47 (s, 1H, H-7), 6.80 (s, 1H, OH), 7.29 (bs, 1H, H-4). ^{13}C NMR (50 MHz, $CDCl_3$) : 20.60 (S-CH_3), 28.67 (C-3), 72.04 (C-2), 96.40 (C-7), 110.70 (C-5), 119.46 (C-9), 130.85 (C-4), 158.93 (C-6), 162.55 (C-8).

Anal. Cald for $C_9H_{10}O_2S$: C, 59.48 ; H, 5.57. Found : C, 59.32 ; H, 5.53.

2,3-Dihydro-6-methylthio-7-hydroxy-benzopyran, 10a

Prepared from compounds **8** and **1a**. Refluxing time **x** = 72h. Yield : 80% (^1H NMR, could not be separated from **1a**). R_f : 0,67 (CH_2Cl_2).

^1H NMR (200 MHz, $CDCl_3$) : δ = 1.98 (tt, 2H, J_{3-4}=6.5Hz, J_{3-2}=5Hz, H-3), 2.26 (s, 3H, SCH_3), 2.71 (t, 2H, J=6.5Hz, H-4), 4.16 (t, 2H, J=5Hz, H-2), 6.44 (s, 1H, H-8), 6.58 (s, 1H, OH), 7.17 (bs, 1H, H-5)

2,3-Dihydro-5-methylthio-6-hydroxy-7-methyl-benzofuran, 4b

Prepared from compounds **1b** and **2**. Refluxing time **x** = 2.5h. Chromatography : CH_2Cl_2/hexane 20/80. Yield : 46%, pale yellow oil. R_f : 0,51 (CH_2Cl_2/hexane 50/50).

1. IR (CCl_4) : 3400 (OH), 3000-2860 (C-H). ^1H NMR (200 MHz, $CDCl_3$) : δ = 2.14 (s, 3H, CH_3), 2.25 (s, 3H, S-CH_3), 3.15 (t, 2H, J=8.5Hz, H-3), 4.58 (t, 2H, J=8.5Hz, H-2), 6.89(s, 1H, OH), 7.17 (bs, 1H, H-4). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 20.92 (S-CH_3), 29.49 (C-3), 71.82 (C-2), 106.43 (C-7), 110.60 (C-5), 118.36 (C-9), 127.84 (C-4), 155.15 (C-6), 160.95 (C-8).

Anal. Cald for $C_{10}H_{12}O_2S$: C, 61.20 ; H, 6.16. Found : C, 61.11 ; H, 6.33.

2,3-Dihydro-6-methylthio-7-hydroxy-8-methyl-benzopyran, 10b

Prepared from compounds **8** and **1b**. Refluxing time **x** = 4h. Chromatography : CH_2Cl_2. Yield : 68%, a pale yellow oil, R_f : 0,95 (CH_2Cl_2).

IR (CCl_4) : 3400 (OH), 3000-2840 (C-H). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.98 (tt, 2H, J_{3-4}=6.5Hz, J_{3-2}=5Hz, H-3), 2.14 (s, 3H, CH_3), 2.27 (s, 3H, SCH_3), 2.73 (t, 2H, J_{4-3}=6.5Hz, H-4), 4.22 (t, 2H, J_{2-3}=5Hz, H-2), 6.75 (s, 1H, OH), 7.07 (bs, 1H, H-5). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 8.78 (CH_3), 20.57 (S-CH_3), 22.32 (C-3), 24.46 (C-4), 66.57 (C-2), 110.93 (C-8), 111.27 (C-6), 114.37 (C-10), 132.73 (C-5), 153.46 (C-7), 154.78 (C-9).

Anal. Cald for $C_{11}H_{14}O_2S$: C, 62.83 ; H, 6.71. Found : C, 62.74 ; H, 6.76.

General procedure for the preparation of annulation intermediates 3 and 9.

In a three-necked round bottomed flask equiped with a dropping funnel, a suspension of NaH (2 eq) in CH_2Cl_2 (1 mL/mmol NaH)was cooled at 0°C with an ice bath. Thioacetal **1a** or **1b** (1 eq) in CH_2Cl_2 (1 mL/mmol thioacetal) was added dropwise to the suspension. After stirring for 10 min at 0°C, α-methylenelactone **2** or **8** (1 eq) dissolved in CH_2Cl_2 (1 mL/mmol lactone) was added dropwise and the ice bath was replaced by a heating bath. The suspension was refluxed for 16h, allowed to stand and poured onto a 10% aqueous HCl solution (10 mL/mmol thioacetal). The organic layer was decanted, the aqueous layer extracted with CH_2Cl_2 and the joined organic layers washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was dissolved in acetic acid (5ml/mmol thioacetal) and the solution heated at 60°C during 1 hour. After cooling and distillation of acetic acid under vacuum, the product was submitted to flash-chromatography.

2,3,9,4-Tetrahydro-5,5-bis(methylthio)-6-one-benzofuran, 3a

Prepared from compounds **1a** and **2**. Chromatography : CH_2Cl_2/MeOH 99/1. The analytical sample was recristallized from CH_2Cl_2/hexane. Yield : 50%, white cristals, R_f : 0.27 (CH_2Cl_2/MeOH 99/1), mp : 111-111.5°C.

IR (CCl_4) : 2980-2820 (C-H), 1635 (C=O). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.83 (qd, 1H, $J_{3ax-3eq}$=12Hz, $J_{3ax-2ax}$=$J_{3ax-9ax}$=12Hz, $J_{3ax-2eq}$=8.5Hz, H-3ax), 2.07 (s, 3H, SCH_3), 2.13 (s, 3H, SCH_3), 2.28 (B part of ABX, 1H, $J_{4ax-4eq}$=13Hz, $J_{4ax-9ax}$=12Hz, H-4ax), 2.35 (ddd, 1H, $J_{3eq-3ax}$=12Hz, $J_{3eq-2ax}$=5Hz, $J_{3eq-2eq}$=0, $J_{3eq-9ax}$=8Hz, H-3eq), 2.60 (A part of ABX, 1H, $J_{4eq-4ax}$=13Hz, $J_{4eq-9ax}$=5Hz, H-4eq), 3.34 (dtd(d), 1H, $J_{9ax-3ax}$=12Hz, $J_{9ax-3eq}$=8Hz, $J_{9ax-4ax}$=12Hz,J $_{9ax-4eq}$=5Hz; J_{9ax-7}=2Hz, H-9), 4.30 (ddd, 1H; $J_{2ax-2eq}$=8.5Hz, $J_{2ax-3ax}$=12Hz, $J_{2ax-3eq}$=5Hz, H-2ax), 4.56 (t, 1H, $J_{2eq-2ax}$=$J_{2eq-3ax}$=8.5Hz, $J_{2eq-3eq}$=0, H-2eq), 5.43 (bs, 1H, H-7). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 11.05 (SCH_3), 11.85 (SCH_3), 29.90 (C-3), 37.47 (C-9), 40.40 (C-4), 62.39 (C-5), 73.18 (C-2), 97.09 (C-7), 180.40 (C-8), 191.75 (C-6)

Anal. Cald for $C_{10}H_{14}O_2S_2$: C, 52.14 ; H, 6.13. Found : C, 52.08 ; H, 5.91.

2,3,10,5-Tetrahydro-6,6-bis(methylthio)-7-one-benzopyran, 9a

Prepared from compounds **8** and **1a**. Chromatography : CH_2Cl_2/MeOH 99/1. The analytical sample was recristallized from CH_2Cl_2/hexane. Yield : 50%, white cristals, R_f : 0.29 (CH_2Cl_2/MeOH 99/1), mp : 102-104 °C.

IR (CCl_4) : 2980-2840 (C-H), 1650 (C=O), 1615 (C=C). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.41 (m, 1H, H-3 or H-4), 1.97 (m, 3H, H-3 and H-4), 2.05 (s, 3H, SCH_3), 2.07 (s, 3H, SCH_3), 2.32 (m, 2H, H-5), 2.85 (m, 1H, H-10), 3.97 (m, 1H, H-2), 4.29 (m, 1H, H-2), 5.47 (d, 1H, $J_{8\text{-}10}$=2Hz, H-8). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 10.87 (SCH_3), 11.82 (SCH_3), 23.12 (C-4), 25.50 (C-3), 32.30 (C-10), 41.56 (C-5), 62.93 (C-6), 68.31 (C-2), 104.54 (C-8), 175.90 (C-9), 190.91 (C-7).

Anal. Cald for $C_{11}H_{16}O_2S_2$: C, 54.07 ; H, 6.60. Found : C, 53.85 ; H, 6.42.

2,3,9,4-Tetrahydro-5,5-bis(methylthio)-6-one-7-methyl-benzofuran, 3b

Prepared from compounds **1b** and **2**. Chromatography : CH_2Cl_2. Yield : 50%, white cristals. R_f : 0.50 (CH_2Cl_2/MeOH 99/1), mp : 98-99 °C

IR (CCl_4) : 3000-2860 (C-H), 1675 (C=O), 1640 (C=C). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.70 (bs, 3H, CH_3), 1.78 (m, 1H, H-3ax), 2.04 (s, 3H, SCH_3), 2.08 (s, 3H, SCH_3), 2.27 (m, 2H, H-3eq + H-4ax), 2.55 (A part of ABX, 1H, $J_{4eq\text{-}4ax}$=13Hz, $J_{4eq\text{-}9ax}$=5Hz, H-4eq), 3.26 (m, 1H, H-9), 4.25 (ddd, 1H, $J_{2ax\text{-}2eq}$=8.5Hz, $J_{2ax\text{-}3ax}$=11.5Hz, $J_{2ax\text{-}3eq}$=5Hz, H-2ax), 4.53 (t, 1H, $J_{2eq\text{-}2ax}$=$J_{2eq\text{-}3ax}$=8.5Hz, H-2eq). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 7.77 (CH_3), 11.26 (SCH_3), 11.99 (SCH_3), 30.77 (C-3), 36.93 (C-9), 40.42 (C-4), 62.67 (C-5), 72.60 (C-2), 104.43 (C-7), 174.98 (C-8), 190.50 (C-6).

Anal. Cald for $C_{11}H_{16}O_2S_2$: C, 54.07 ; H, 6.60. Found : C, 53.88 ; H, 6.57.

2,3,10,5-Tetrahydro-6,6-bis(methylthio)-7-one-8-methyl-benzopyran, 9b

Prepared from compounds **8** and **1b**. Chromatography : CH_2Cl_2 to CH_2Cl_2/MeOH 98/2 by 1%. Yield : 58%, white cristals. R_f : 0.43 (CH_2Cl_2/MeOH 99/1), mp : 106-107 °C.

IR (CCl_4) : 3000-2860 (C-H), 1700 (C=O), 1650 (C=C). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.39 (m, 1H, H-3 or H-4), 1.71 (bs, 3H, CH_3), 1.93 (m, 3H, H-3 + H-4), 2.08 (bs, 6H, SCH_3), 2.20 (m, 2H, H-5), 2.82 (m, 1H, H-10), 3.98 (m, 1H, H-2), 4.31 (m, 1H, H-2). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 7.83 (CH_3) , 10.96 (SCH_3), 11.93 (SCH_3), 23.28 (C-3), 26.48 (C-4), 32.03 (C-10), 41.18 (C-5), 63.05 (C-6), 68.03 (C-2), 111.38 (C-8), 169.83 (C-9), 190.91 (C-7).

Anal. Cald for $C_{12}H_{18}O_2S_2$: C, 55.78, H ; 7.02. Found : C, 55.95 ; H, 6.99.

Transacetalization compounds

The cyclic dithioacetal **3a**, **3b**, **9a** or **9b** (1 eq) was dissolved in anhydrous $CHCl_3$ (5 mL/mmol thioacetal). Mercury acetate (2.5 eq) in MeOH (2 mL/mmol thioacetal) was added dropwise and the resulting solution stirred at room temperature for 16h. Unsoluble mercury salts were formed and the solution became pink. The solvents were removed under reduced pressure and the residue suspended in CH_2Cl_2 (5 mL/mmol thioacetal).The suspension was filtrated on celite to remove mercury salts. The clear filtrate was washed first with a 10% solution of sodium hydrogenosulfite, then with brine. The organic layer was decanted, dried over sodium sulfate and the solvent removed to give a yellow-brown wax. The crude product was purified by flash-chromatography on silica gel with the appropriate eluent (see products description).

2,3,9,4-Tetrahydro-5,5-bis(methoxy)-6-one-benzofuran, 5a

Prepared from compound **3a**. Chromatography : CH_2Cl_2/MeOH 98/2. Yield : 72%, a pale pink solid. Rf : 0.25 (CH_2Cl_2/MeOH 98/2)

^1H NMR (200 MHz, $CDCl_3$) : δ = 1.75 (m, 2H, H-3ax + H-4ax), 2.32 (m, 1H, H-3eq), 2.68 (A part of ABX, 1H, $J_{4eq-4ax}$=12.5Hz, J_{4a-9ax}=5Hz, H-4eq), 3.23 (s, 3H, OCH_3), 3.28 (m, 1H, H-9), 3.35 (s, 3H, OCH_3), 4.29 (ddd, 1H, $J_{2ax-2eq}$=8.5Hz, $J_{2ax-3ax}$=12Hz, $J_{2ax-3eq}$=5Hz, H-2ax), 4.55 (t, 1H, $J_{2eq-2ax}$=$J_{2eq-3ax}$=8.5Hz, H-2eq), 5.42 (bs, 1H, H-7). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 30.23 (C-3), 36.03 (C-4), 37.72 (C-9), 48.71 (OCH_3), 50.55 (OCH_3), 73.49 (C-2), 96.20 (C-5), 98.51 (C-7), 182.08 (C-8), 191.26 (C-6).

2,3,9,4-Tetrahydro-5,5-bis(methoxy)-6-one-7-methyl-benzofuran, 5b

Prepared from compound **3b**. Chromatography : ethyl acetate/hexane 1/1. Yield : 76%, pale pink cristals. The analytical sample was recritallized in ethyl acetate/hexane to yield white cristals. Rf : 0.31 (CH_2Cl_2/MeOH 95/5), mp : 97-98 °C.

IR (CCl_4) : 3040-2860 (C-H), 1675 (C=O), 1650 (C=C). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.64-1.88 (m, 2H, H-3ax + H-4ax), 1.72 (bs, 3H, CH_3), 2.32 (m, 1H, H-3eq), 2.66 (A part of ABX, 1H, $J_{4eq-4ax}$=12.5Hz, $J_{4eq-9ax}$=5Hz, H-4eq), 3.16 (m, 1H, H-9), 3.21 (s, 3H, OCH_3), 3.35 (s, 1H, OCH_3), 4.29 (ddd, 1H, $J_{2ax-2eq}$=8.5Hz, $J_{2ax-3ax}$=12Hz, $J_{2ax-3eq}$=5Hz; H-2ax), 4.55 (t, 1H, $J_{2eq-2ax}$=$J_{2eq-3ax}$=8.5Hz, H-2eq); ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 7.19 (CH_3), 30.64 (C-3), 35.88 (C-4), 36.47 (C-9), 48.58 (OCH_3), 50.24 (OCH_3), 72.51 (C-2), 95.84 (C-5), 105.49 (C-7), 176.39 (C-8), 190.61 (C-6).

Anal. Cald for $C_{11}H_{16}O_4$: C, 62.25 ; H, 7.60. Found : C, 62.40 ; H, 7.82.

2,3,10,5-Tetrahydro-6,6-bis(methoxy)-7-one-8-methyl-benzopyran, 11b

Prepared from compound **9b**. Chromatography : CH_2Cl_2/MeOH 98/2. Yield : 83%, a pale pink wax. Rf : 0.25 (CH_2Cl_2/MeOH 95/5).

IR (CCl_4) : 3000-2840 (C-H), 1675 (C=O), 1630 (C=C). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.33 (m, 1H, H-4ax), 1.56 (A part of ABX, 1H, $J_{5ax-5eq}$=13Hz, $J_{5ax-10ax}$=4.5Hz, H-5ax,), 1.65 (bs, 3H, CH_3), 1.88 (m, 3H, H-3 + H-4eq), 2.36 (B part of ABX, 1H, $J_{5eq-5ax}$=13Hz; $J_{5eq-10ax}$=2.5Hz, H-5eq)), 2.74 (m, 1H, H-10), 3.10 (s, 3H, OCH_3), 3.28 (s, 1H, OCH_3), 3.96 (m, 1H, H-2ax), 4.26 (m, 1H, H-2eq). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 7.43 (CH_3), 23.21 (C-4), 26.56 (C-3), 31.72 (C-10), 36.78 (C-5), 48.58 (OCH_3), 50.47 (OCH_3), 67.87 (C-2), 96.14 (C-6), 112.34 (C-8), 171.80 (C-9), 191.50 (C-7).

Anal. Cald for $C_{12}H_{18}O_4$: C, 63.70 ; H, 8.02. Found : C, 63.70 ; H, 7.96.

Preparation of catechol monoethers

Dimethoxyacetal **5a**, **5b** or **11b** was dissolved in acetic acid (10 mL/mmol acetal) and the solution was refluxed during 2h. After removal of the solvent under reduced pressure, the residue was purified by flash-chromatography with the appropriate eluent (see products description).

2,3-Dihydro-5-methoxy-6-hydroxy-benzofuran, 6a

Prepared from compound **5a**. Chromatography : CH_2Cl_2. Yield : 66%, a colorless oil. Rf : 0.52 (CH_2Cl_2/MeOH 95/5)

IR (CCl_4) : 3560 (O-H), 3050-2840 (C-H). ^1H NMR (200 MHz, $CDCl_3$) : δ = 3.14 (t, 2H, J=8.5Hz, H-3), 3.84 (s, 3H, OCH_3), 4.54 (t, 2H, J=8.5Hz, H-2), 5.62 (bs, 1H, OH), 6.46 (s, 1H, H-7), 6.75 (s, 1H, H-4). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 29.90 (C-3), 57.07 (OCH_3), 71.55 (C-2), 97.21 (C-7), 108.36 (C-4), 116.54 (C-9), 140.76 (C-6), 145.65 (C-5), 154.41 (C-8).
Anal. Cald for $C_9H_{10}O_3$: C, 65.05 ; H, 6.07. Found : C, 65.33 ; H, 6.24.

2,3-Dihydro-5-methoxy-6-hydroxy-7-methyl-benzofuran, 6b

Prepared from compound **5b**. Chromatography : CH_2Cl_2/hexane 1/1. Yield : 36%, an unstable oil which becomes red. R_f : 0.23 (CH_2Cl_2/hexane 1/1).
IR (CCl_4) : 3550 (O-H), 3020-2840 (C-H). ^1H NMR (200 MHz, $CDCl_3$) : δ = 2.15 (s, 3H, CH_3), 3.15 (t, 2H, J=8.5Hz, H-3), 3.83 (s, 3H, OCH_3), 4.53 (t, 2H, J=8.5Hz, H-2), 5.70 (bs, 1H, OH), 6.63 (s, 1H, H-4).

2,3-Dihydro-6-methoxy-7-hydroxy-8-methyl-benzopyran, 12b

Prepared from compound **11b**. Chromatography : CH_2Cl_2. Yield : 36%, a pale yellow oil. R_f : 0.25 (CH_2Cl_2
IR (CCl_4) : 3560 (O-H), 3000-2840 (C-H); ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.99 (tt, 2H, J_{3-2}=5Hz, J_{3-4}=6.5Hz, H-3), 2.13 (s, 3H, CH_3), 2.73 (t, 2H, J_{4-3}=6.5Hz, H-4), 3.83 (s, 3H, OCH_3), 4.17 (t, 2H, J_{2-3}=5Hz, H-2), 5.65 (bs, 1H, OH), 6.41 (s, 1H, H-5). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 8.21 (CH_3), 22.71 (C-4), 24.80 (C-3), 56.33 (OCH_3), 66.27 (C-2), 108.52 (C-5), 111.59 (C-8), 140.23 (C-7), 142.47 (C-6)
Anal. Cald for $C_{11}H_{14}O_3$: C, 68.02, H, 7.27. Found : C, 67.92; H, 7.36.

Addition of methyllithium to cyclic acetals

1) Cyclic acetal **5b** or **11b** (1 eq) dissolved in anhydrous THF (10 mL/mmol acetal) was cooled at -78°C. Methyl lithium [1,6M/ether (2 eq)] was added dropwise. Starting material disappearance was monitored by TLC. Workup was performed by addition of a saturated ammonium chloride solution (10 mL/mmol acetal) and extraction of the medium with CH_2Cl_2 (3 x 10 mL/mmol acetal). The combined organic layers were dried over sodium sulfate and concentrated under vacuum to yield an unstable colorless oil which was used without further purification in the next step.
2) The preceeding alcohols were aromatised in acetic acid (10 mL/mmol alcohol) by heating at 60°C (oil bath temperature) during 1h. The acid was removed under reduced pressure and the residue purified by flash-chromatography with the appropriate eluent.

2,3-Dihydro-5-methoxy-6,7-dimethyl-benzofuran, 7b.

Prepared from compound **5b**. Chromatography : CH_2Cl_2/hexane 1/1. Yield : 69.5%, a pale yellow oil. R_f : 0.48 (CH_2Cl_2/hexane 1/1)
IR (CCl_4) : 3000-2840 (C-H). ^1H NMR (200 MHz, $CDCl_3$) : δ = 2.14 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.20 (t, 2H, J=8.5Hz, H-3), 3.78 (s, 3H, OCH_3), 4.53 (t, 2H, J=8.5Hz, H-2), 6.66 (s, 1H, H-4). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 11.76 (CH_3), 12.27 (CH_3), 30.77 (C-3), 56.65 (OCH_3), 70.58 (C-2), 105.77 (C-4), 119.20 (C-9), 122.61 (C-6), 124.79 (C-7), 151.95 (C-5), 152.65 (C-8).

2,3-Dihydro-6-methoxy-7,8-dimethyl-benzopyran, 13b

Prepared from compound **11b**. Chromatography : CH_2Cl_2/hexane 1/1. Yield : 64% (80/20 mixture of ether **13b** and the corresponding phenol), a pale yellow oil. R_f : 0.26 (CH_2Cl_2/hexane 1/1)
IR (CCl_4) : 3010-2840 (C-H). ^1H NMR (200 MHz, $CDCl_3$) : δ = 1.99 (tt, 2H, J_{3-2}=5Hz, J_{3-4}=6.5Hz, H-3), 2.14 (bs, 6H, CH_3), 2.79 (t, 2H, J_{4-3}=6.5Hz, H-4), 3.77 (s, 3H, OCH_3), 4.18 (t, 2H, J_{2-3}=5Hz, H-2), 6.43 (s, 1H, H-5).

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