Hydrindanone Synthesis: An Incisterol Model

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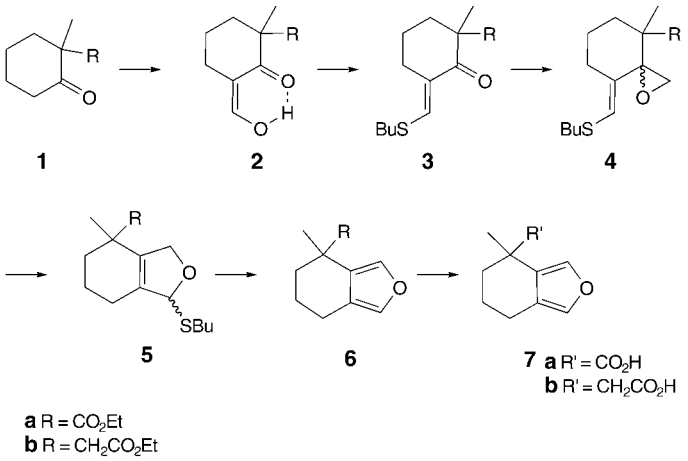
Ethyl 1-methyl-2-oxocyclohexanecarboxylate (**1a**) and its homologue **1b** were converted to hydroisobenzofuran acids **7** (*via* 6-[(butylsulfanyl)methylene] and epoxide derivatives), one of which furnished hexalone derivative **11** (*via* an intermediate diazomethyl ketone derivative). The above-mentioned starting esters were converted to ethylene ketals, the free-radical oxidations of which led to hydrobenzofuran acids. One of the latter led to a hydrindanone (*via* a diazomethyl ketone), whose further chemical elaboration yielded an incisterol model. A second hydrobenzofuran acid gave a cyclobutenone (*via* the diazomethyl ketone), which was transformed into a more-stable cyclopentenone isomer by treatment with *Lewis* acid.

Introduction. – A recent, new hydrindanone synthesis made use of the *Kanematsu* transformation for the construction of hydrobenzofuran structures, *en route* to the desired bicycles [1]. It became of interest to pursue an alternative synthesis of hydrobenzofurans as well as to develop a protocol for the production of hydrobenzofurans and their application to yet other hydrindanone syntheses.

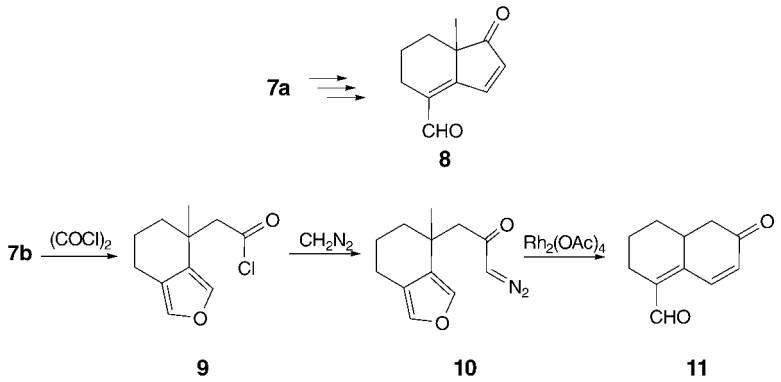
Results and Discussion. – Ethyl 1-methyl-2-oxocyclohexanecarboxylate (**1a**) [2] and its homologue ethyl (1-methyl-2-oxocyclohexyl)acetate (**1b**), prepared by alkylation of 2-methylcyclohexanone under thermodynamic control with ethyl bromoacetate and lithium diisopropylamide (LDA) in dioxane, were formylated with HCO_2Et/EtO^-Na^+, and the products **2a** and **2b** converted to thioenol ethers **3a** and **3b**, respectively, with BuSH and TsOH in benzene. Treatment of **3a** and **3b** with Me_3S^+ $MeOSO_3^-$ and OH^- in CH_2Cl_2 yielded epoxides **4a** and **4b**, which, during filtration through a silica pad, isomerized to dihydrofurans **5a** and **5b**, respectively. Thiol elimination from these compounds under the influence of acid (2N HCl in THF) furnished furans **6a** and **6b**, which were saponified to produce hydroisobenzofuran acids **7a** and **7b** (*Scheme 1*).

Compound **7a** was identical to the acid obtained in the *Kanematsu* reaction procedure from which hydrindanone **8** had been constructed (*Scheme 2*) [1]. Duplication of the **7a** → **8** transformation starting with acid **7b**, led to formation of acid chloride **9** (with $SOCl_2$) and diazomethyl ketone **10** (with CH_2N_2), which, upon catalysis with $Rh_2(OAc)_4$ in CH_2Cl_2, decomposed to afford the synthetically useful hexalone derivative **11** (*Scheme 2*).

Scheme 1



Scheme 2

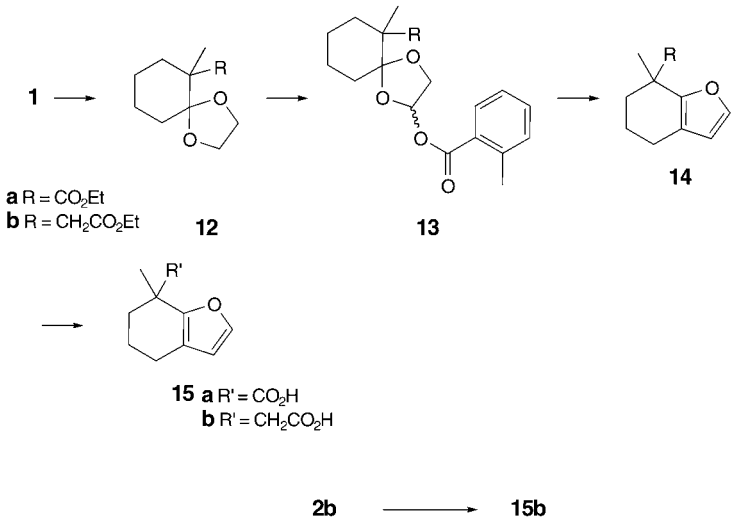


Two procedures were used for the synthesis of hydrobenzofurans. One, a general, flexible approach, involved the radical oxidation of ethylene ketals followed by acid-catalyzed rearrangement [3]. Thus, ketoesters **1a** and **1b** were converted ($HO(CH_2)_2OH$, $HC(OEt)_3$, H_2SO_4) to ketals **12a** and **12b**. Oxidation of the ketals with *t*-butyl 2-methylbenzenecarboperoxoate and CuBr led to **13a** and **13b**, respectively, and subsequent treatment with 2-methylbenzoic acid afforded hydrobenzofurans **14a** and **14b**. Saponification of the esters furnished acids **15a** and **15b** (*Scheme 3*).

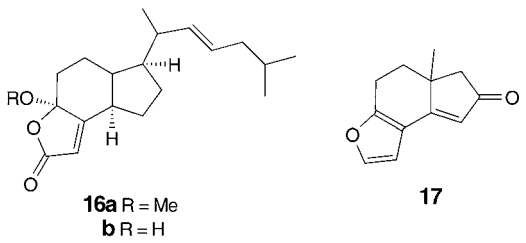
The second procedure, however, applied only to the formation of hydrobenzofuran **15b**, involved *C*-alkylation of **2b** with chloroacetaldehyde and K_2CO_3 in acetone, NaOH-induced ester hydrolysis, and aldehyde deformylation and HCl-catalyzed furan ring closure (*Scheme 3*).

With hydrobenzofuran **15b** in hand (*Scheme 3*), the time had arrived to choose a steroidal C/D ring compound, one that resembles a natural product, whose synthesis

Scheme 3

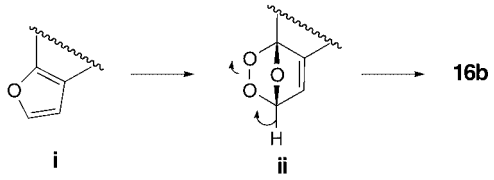


from **15b** *via* diazoketone chemistry could be readily anticipated. Incisterol **16a** [4][1]) was selected as the naturally occurring substance for which tricycle **17** was to be the synthetic relative.



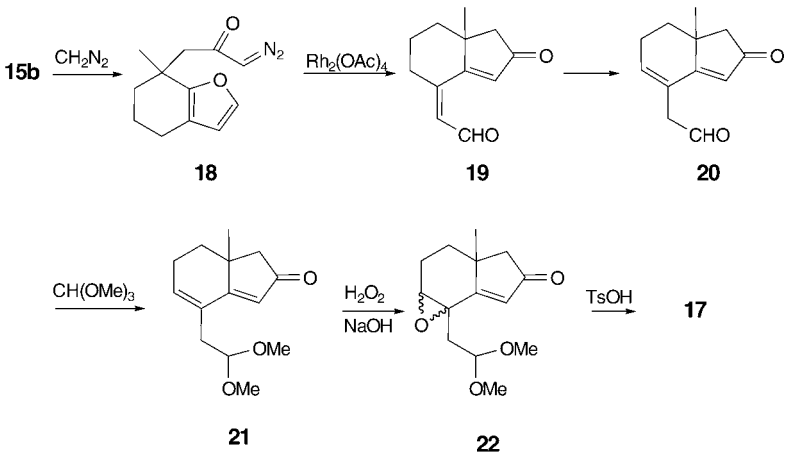
Treatment of acid **15b** with oxalyl chloride (CH_2Cl_2) and subsequently with CH_2N_2 (Et_2O, Et_3N) yielded diazoketone **18**, which, under catalytic decomposition ($Rh_2(OAc)_4$, CH_2Cl_2) afforded ketoaldehyde **19**. Acid-induced isomerization (conc. HI) of the latter furnished **20**, acetylation (CH_2Cl_2, MeOH, $HC(OMe)_3$, *p*-TsOH) of

[1]) The methyl ether **16a** is undoubtedly, an artifact of the MeOH extraction of the Mediterranean sponge *Dictyonella incisa* [4], the pseudoacid **16b** being the actual natural product. In view of the **i** → **ii** → **16b** reaction sequence, which constitutes the biosynthetic evolution of the γ-hydroxybutenolide moiety [4], furan **17** was an especially propitious choice for synthesis.



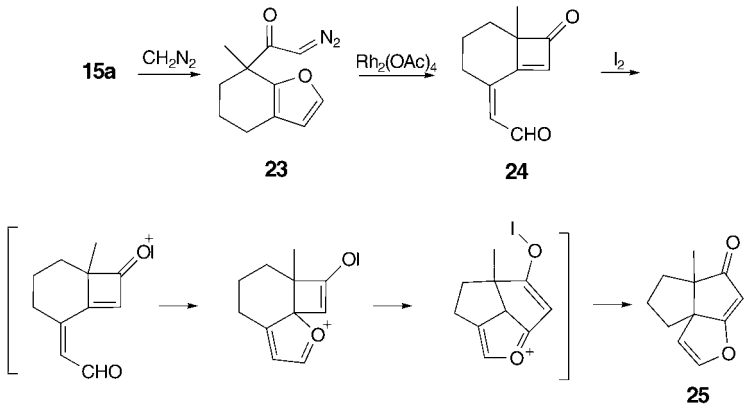
which produced ketoacetal **21**. Oxidation (H_2O_2, 6N NaOH, MeOH) of the latter gave epoxide **22**, which, upon treatment with acid (*p*-TsOH, THF) liberated the ketone **17** (*Scheme 4*).

Scheme 4



The availability of hydrobenzofuran carboxylic acid **15a** opened the possibility for the investigation of some long-postponed diazoketone chemistry. As illustrated in the conversions of **7a** → **8**, **10** → **11**, and **18** → **19**, cyclopentenones and cyclohexenones are the main (or only) products of rhodium-assisted decomposition of diazoketones when the diazo C-atom is related spatially 1,5 or 1,6 with the furan α-C-atom. The unanswered question had always been, what takes place in the case of a 1,4-relationship? Such was the situation in diazoketone **23**, derived from acid **15a** (with $SOCl_2$ followed by CH_2N_2, in Et_2O). Rh-Catalyzed decomposition of diazoketone **23** ($Rh_2(OAc)_4$, CH_2Cl_2) led to keto aldehyde **24** (fairly stable liquid, surviving > 10 days at $-20°$; decomposes on SiO_2), which was isomerized (I_2, CH_2Cl_2) to yield tricycle **25** (*Scheme 5*).

Scheme 5



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Experimental Part

General: See [1].

Ethyl 1-Methyl-2-oxocyclohexylacetate (**1b**). A soln. of 2-methylcyclohexanone (200 mg, 1.78 mmol) in dry dioxane (1 ml) was added dropwise to a stirring mixture of LDA (2.0 mmol) in dry dioxane (2 ml), and the combined mixture was stirred at 95° for 3 h. A soln. of ethyl bromoacetate (355 mg, 2.13 mmol) in dry dioxane (1 ml) was added dropwise to the mixture at r.t., and the stirring was continued for 2 h. The mixture was neutralized with 2% citric acid/H_2O and extracted with CH_2Cl_2 (3×20 ml). The extract was dried and evaporated *in vacuo*. Chromatography (CH_2Cl_2) of the residue yielded 180 mg (51%) of **1b**. Yellow oil. IR: 1734, 1708. ^{1}H-NMR: 1.13 (*s*, 3 H); 1.18 (*t*, *J* = 7.2, 3 H); 1.58–1.96 (*m*, 6 H); 2.32–2.41 (*m*, 2 H); 2.46–2.56 (*m*, 2 H); 4.03 (*q*, *J* = 7.2, 2 H). ^{13}C-NMR: 14.4; 21.1; 23.3; 26.7; 38.3; 38.4; 42.6; 47.5; 60.1; 171.3; 213.7. GC/MS 189 ($M^{+\cdot}$). Anal. calc. for $C_{11}H_{18}O_3$ (198.26): C 66.64, H 9.15; found: C 66.62, H 9.18.

Ethyl 3-(Hydroxymethylidene)-1-methyl-2-oxocyclohexane-1-carboxylate (**2a**). Keto ester **1a** (3.00 g, 16.3 mmol) was added to a suspension of 0.41 g (17.0 mmol) of NaH in 50 ml of anh. benzene at 5°, and the mixture was stirred for 0.5 h. *tert*-Butyl formate (2.50 g, 34.0 mmol) was added, and the temp. was allowed to rise to 25°. The mixture was stirred for 12 h and extracted with cold H_2O. The aq. extract was neutralized with 3N HCl to afford 1.80 g (8.5 mmol) of liquid **2a** (1.40 g, 97% based on amount of **1a** consumed (7.60 mmol of **1a** was recovered from the org. layer)). IR: 2400–3600, 1725, 1638, 1582. ^{1}H-NMR: 1.25 (*t*, *J* = 7.0, 3 H); 1.46 (*s*, 3 H); 1.60–1.80 (*m*, 6 H); 4.19 (*q*, *J* = 7.0, 2 H); 8.69 (br. *s*, 1 H); 14.40 (*s*, 1 H). ^{13}C-NMR: 13.9; 19.2; 22.0; 23.3; 34.1; 49.4; 61.2; 108.3; 173.6; 183.7; 187.7. GC/MS 212 ($M^{+\cdot}$). Anal. calc. for $C_{11}H_{16}O_4$ (212.25): C 62.25, H 7.60; found: C 62.24, H 7.58.

Ethyl [3-(Hydroxymethylidene)-1-methyl-2-oxocyclohexyl]acetate (**2b**). A soln. of **1b** (180 mg, 0.91 mmol) in dry Et_2O (3 ml) was added dropwise to a stirred suspension of freshly prepared EtONa (126 mg, 1.82 mmol) and ethyl formate (405 mg, 5.46 mmol) in Et_2O (4 ml) over a period of 1 h, and the mixture was stirred for 5 h at r.t. The white precipitate formed was collected by vacuum filtration and resuspended in AcOEt (10 ml). To this suspension, 10 ml of a 2% soln. of citric acid was added, and the resulting biphasic soln. was stirred for 20 min. The org. phase was separated, dried and concentrated *in vacuo* to yield 110 mg of **2b** as a yellow oil (53%). IR: 3500 (br.), 1732, 1636. ^{1}H-NMR: 1.12 (*t*, *J* = 7.3, 3 H); 1.18 (*s*, 3 H); 1.32–2.26 (*m*, 6 H); 2.28–2.78 (*m*, 2 H); 3.99 (*q*, *J* = 7.3, 2 H); 6.60 (br. *s*, 1 H); 8.22 (*s*, 1 H). ^{13}C-NMR: 14.1; 19.4; 24.2; 25.9; 29.6; 34.0; 40.3; 43.5; 60.3; 171.2; 182.6; 192.9. GC/MS: 226 ($M^{+\cdot}$). Anal. calc. for $C_{12}H_{18}O_4$ (226.27): C 63.70, H 8.02; found: C 63.74, H 8.01.

Ethyl 3-[(Butylsulfanyl)methylidene]-1-methyl-2-oxocyclohexane-1-carboxylate (**3a**). A soln. of 1.50 g (7.10 mmol) of **2a**, 0.53 g (5.90 mmol) of butane-1-thiol and 20 mg of *p*-TsOH in 30 ml of dry benzene was refluxed under a *Dean–Stark* water separator. After 1 equiv. of H_2O had been collected, the mixture was cooled, washed with 10% aq. Na_2CO_3 soln. and then with H_2O, and dried. The solvent was removed under reduced pressure, and the residue was chromatographed to afford 1.80 g (6.90 mmol) of **3a** (89%) as a yellow oil. IR: 1725, 1660, 1525. ^{1}H-NMR: 0.93 (*t*, *J* = 7.0, 3 H); 1.23 (*t*, *J* = 7.0, 3 H); 1.39 (*s*, 3 H); 1.30–1.50, 1.60–1.90 (2*m*, 6 H); 2.30–2.50 (*m*, 4 H); 2.86 (*t*, *J* = 7.0, 3 H); 4.08–4.24 (*m*, 2 H); 7.65 (br. *s*, 1 H). ^{13}C-NMR: 13.3; 13.9; 18.7; 21.4; 21.8; 27.3; 32.4; 34.2; 34.6; 54.4; 60.9; 129.2; 144.0; 173.6; 194.4. GC/MS: 284 ($M^{+\cdot}$). Anal. calc. for $C_{15}H_{24}O_3S$ (284.41): C 63.35, H 8.51; found: C 63.38, H 8.49.

Ethyl {3-[(Butylsulfanyl)methylidene]-1-methyl-2-oxocyclohexyl}acetate (**3b**). As described for **3a**, with **2b** (1.10 g, 4.90 mmol); 1.32 g (4.40 mmol) of **3b** (90%) as a yellow oil. IR: 1724, 1656, 1601. ^{1}H-NMR: 0.93 (*t*, *J* = 7.0, 3 H); 1.16 (*s*, 3 H); 1.22 (*t*, *J* = 7.0, 3 H); 1.35–1–95 (*m*, 7 H); 2.05–2.15 (*m*, 1 H); 2.30 (*d*, *J* = 16.0, 1 H); 2.30–2.40 (*m*, 1 H); 2.56 (*d*, *J* = 16.0, 1 H); 2.84 (*t*, *J* = 7.0, 2 H); 2.97 (*d*, *J* = 16.0, 1 H); 4.00–4.15 (*m*, 2 H); 7.59 (br. *s*, 1 H). ^{13}C-NMR: 13.3; 13.9; 19.5; 21.3; 25.0; 27.7; 32.3; 34.0; 34.6; 44.0; 59.9; 129.5; 142.6; 171.3; 199.2. GC/MS: 298 ($M^{+\cdot}$). Anal. calc. for $C_{16}H_{26}O_3S$ (298.44): C 64.39, H 8.78; found: C 64.38, H 8.77.

Ethyl 4,5,6,7-Tetrahydro-4-methyl-2-benzofuran-4-carboxylate (**6a**). A mixture of 568 mg (2.00 mmol) of **3a** and 565 mg (3.00 mmol) of Me_3SSO_4Me in 30 ml of CH_2Cl_2/50% aq. NaOH 1:1 was stirred at r.t. for 36 h. The layers were separated and the aq. layer extracted three times with 30 ml of Et_2O each. The org. layer and org. extract were combined, washed, dried, and evaporated, giving 480 mg (1.62 mmol, 82%) of *ethyl 8-[(butylsulfanyl)methylene]-5-methyl-1-oxaspiro[2.5]octane-5-carboxylate* (**4a**) as a 2:1 diastereoisomer mixture (by NMR analysis). Filtration of the diastereoisomer mixture through SiO_2 transformed them into *ethyl 1-(butylsulfanyl)-4-methyl-1,3,4,5,6,7-hexahydro-2-benzofuran-4-carboxylate* (**5a**; 427 mg, 1.44 mmol 89%; 1:1

mixture of diastereoisomers) as an oil. Treatment of esters **5a** with 1 ml of 2N HCl in 5 ml of THF gave 334 mg of a crude mixture. Chromatography afforded 292 mg (1.40 mmol) of **6a** (97%) as a colorless oil. IR: 1720. ^{1}H-NMR: 1.49 (*s*, 3 H); 1.50–1.80 (*m*, 3 H); 2.25 (*ddd*, *J* = 13.0, 6.0, 6.0, 1 H); 2.40–2.70 (*m*, 2 H); 7.11 (*d*, *J* = 1.0, 1 H); 7.38 (br. *s*, 1 H). ^{13}C-NMR: 13.9; 19.5; 20.2; 27.9; 34.1; 41.1; 60.6; 120.5; 125.1; 136.8; 139.3; 176.1. GC/MS: 208 ($M^{+\bullet}$). Anal. calc. for $C_{12}H_{16}O_3$ (208.26): C 69.21, H 7.74; found: C 69.23, H 7.76.

Data of **4a**: Major isomer: ^{1}H-NMR: 0.91 (*t*, *J* = 7.0, 3 H); 1.09 (*s*, 3 H); 1.25 (*t*, *J* = 7.0, 3 H); 1.20–1.75 (*m*, 6 H); 2.05–2.45 (*m*, 3 H); 2.64 (*t*, *J* = 7.0, 2 H); 2.55–2.75 (*m*, 1 H); 2.86 (*d*, *J* = 5.0, 1 H); 3.01 (*d*, *J* = 5.0, 1 H); 4.00–4.30 (*m*, 2 H); 5.96 (br. *s*, 1 H). ^{13}C-NMR: 13.4; 13.9; 19.3; 21.3; 22.3; 28.6; 32.1; 33.3; 36.3; 48.1; 51.4; 60.3; 63.1; 122.1; 134.3; 174.2. GC/MS: 298 ($M^{+\bullet}$). Anal. calc. for $C_{16}H_{26}O_3S$: C 64.39, H 8.78; found: C 64.37, H 8.77. Minor isomer: ^{1}H-NMR: 0.93 (*t*, *J* = 7.0, 3 H); 1.07 (*s*, 3 H); 1.26 (*t*, *J* = 7.0, 3 H); 1.20–1.75 (*m*, 6 H); 2.34 (*d*, *J* = 6.0, 1 H); 2.05–2.45 (*m*, 3 H); 2.65 (*t*, *J* = 7.0, 3 H); 2.55–2.75 (*m*, 1 H); 2.88 (*d*, *J* = 6.0, 1 H); 4.00–4.30 (*m*, 2 H); 6.02 (*d*, *J* = 1.0, 1 H). ^{13}C-NMR: 13.4; 13.9; 20.1; 21.4; 22.4; 29.4; 32.1; 34.1; 36.3; 47.9; 50.2; 60.3; 62.3; 118.7; 134.5; 174.2. GC/MS: 298 ($M^{+\bullet}$). Anal. calc. for $C_{16}H_{26}O_3S$ (298.44): C 64.39, H 8.78; found: C 64.38, H 8.79.

Ethyl (4,5,6,7-Tetrahydro-4-methyl-2-benzofuran-4-yl)acetate (**6b**). A mixture of 2.00 g (6.70 mmol) of **3b** and 1.90 g (10.00 mmol) of Me_3SSO_4Me in 30 ml of CH_2Cl_2 and 30 ml 50% aq. NaOH was heated at 48° for 24 h. Workup as for **4a** produced 1.70 g (5.40 mmol) of crude *ethyl [8-[(butylsulfanyl)methylidene]-5-methyl-1-oxaspiro[2.5]oct-5-yl]acetate* (**4b**) as a viscous oil. NMR Analysis showed the presence of two diastereoisomers in a ratio of *ca.* 4:3. Filtration of oxiranes **4b** through a SiO_2 pad converted them to *ethyl [1-(butylsulfanyl)-1,3,4,5,6,7-hexahydro-4-methyl-2-benzofuran-4-yl]acetate* (**5b**; 1.60 g, 5.10 mmol, 94%; mixture of diastereoisomers) as a liquid. A mixture of **5b** and 3 ml of 2N HCl in 5 ml of THF was stirred at r.t. for 3 h and then saturated with $CaCO_3$. The layers were separated, the aq. portion extracted with Et_2O, and the combined org. solns. washed, dried, and evaporated. Flash chromatography of the residue provided 1.05 g (4.70 mmol) of liquid **6b** (92%). IR: 1718. ^{1}H-NMR: 1.22 (*t*, *J* = 7.0, 3 H); 1.36 (*s*, 3 H); 1.50–1.90 (*m*, 2 H); 2.52 (*s*, 2 H); 2.45–2.55 (*m*, 2 H); 4.10 (*q*, *J* = 7.0, 2 H); 7.08 (*d*, *J* = 1.0, 1 H); 7.24 (br. *s*, 1 H). ^{13}C-NMR: 14.0; 19.5; 19.6; 29.0; 32.0; 36.3; 47.1; 59.8; 120.3; 129.6; 136.7; 137.7; 171.3. GC/MS: 222 ($M^{+\bullet}$). Anal. calc. for $C_{13}H_{18}O_3$ (222.28): C 70.24, H 8.16; found: C 70.26, H 8.18.

4,5,6,7-Tetrahydro-4-methyl-2-benzofuran-4-carboxylic Acid (**7a**). Alkaline hydrolysis of 250 mg (1.20 mmol) of **6a**, as described for **7b** (*vide infra*), gave 180 mg (1.00 mmol) of **7a** (83%) as a colorless, viscous oil, which solidified on standing (spectra data identical to that reported in [1]). GC/MS: 180 ($M^{+\bullet}$). Anal. calc. for $C_{10}H_{12}O_3$ (180.20): C 66.65, H 6.71; found: C 66.67, H 6.70.

(4,5,6,7-Tetrahydro-4-methyl-2-benzofuran-4-yl)acetic Acid (**7b**). A mixture of 500 mg (2.20 mmol) and 10 ml of 25% aq. NaOH was heated at 85° for 3 h. Upon normal work-up 320 mg (1.60 mmol) of **7b** (73%) was obtained. IR: 2400–3600, 1700. ^{1}H-NMR: 1.39 (*s*, 3 H); 1.55–1.90 (*m*, 4 H); 2.51 (*t*, *J* = 6.0, 2 H); 2.57 (*s*, 2 H); 7.09 (*d*, *J* = 1.0, 1 H); 7.26 (*d*, *J* = 1.0, 1 H); 11.2 (br. *s*, 1 H). ^{13}C-NMR: 19.5; 19.6; 28.9; 32.0; 36.2; 46.9; 120.3; 129.5; 136.9; 137.7; 178.1. GC/MS: 194 ($M^{+\bullet}$). Anal. calc. for $C_{11}H_{14}O_3$ (194.23): C 68.02, H 7.27; found: C 68.01, H 7.25.

2,3,4,4a,5,6-Hexahydro-6-oxonaphthalene-1-carbaldehyde (**11**). Conversion of **7b** to *(4,5,6,7-tetrahydro-4-methyl-2-benzofuran)acetyl chloride* (**9**) and *1-diazo-3-(4,5,6,7-tetrahydro-4-methyl-2-benzofuran-4-yl)propan-2-one* (**10**) was performed according to a standard procedure ([1] and refs. cit. therein). A soln. of 20 mg (0.09 mmol) of **10** and a few crystals of $Rh_2(OAc)_4$ in 2 ml of CH_2Cl_2 were stirred at r.t. for 1 h and then worked up in the usual manner to give 14 mg (0.07 mmol) of **11** (78%). ^{1}H-NMR: 1.27 (*s*, 3 H); 1.60–2.20 (*m*, 8 H); 6.18 (*d*, *J* = 10.0, 1 H); 8.02 (*d*, *J* = 10.0, 1 H); 10.4 (*s*, 1 H). ^{13}C-NMR: 16.5; 23.8; 25.7; 36.8; 38.1; 52.1; 130.0; 137.0; 189.6. GC/MS: 190 ($M^{+\bullet}$). Anal. calc. for $C_{12}H_{14}O_2$ (176.22): C 75.76, H 7.42; found: C 75.77, H 7.44.

Ethyl 6-Methyl-1,4-dioxaspiro[4.5]decane-6-carboxylate (**12a**). A mixture of 880 mg (5.0 mmol) of **1a**, 340 mg (5.5 mmol) of ethylene glycol, 2 ml of triethoxymethane and 2 drops of conc. H_2SO_4 was allowed to stand at r.t. for 18 h. It was filtered through a SiO_2 pad and the solvents were evaporated, providing 1.10 g (4.81 mmol) of **12a** (96%). B.p. 106–107° (4 mm Hg). IR: 1721. ^{1}H-NMR: 1.24 (*s*, Me 3 H); 1.26 (*t*, *J* = 7.0, Me 3 H); 1.35–1.70 (*m*, 6 H); 1.82–1.95 (*m*, 1 H); 2.06 (*ddd*, *J* = 13.0, 7.0, 5.0, 1 H); 3.85–4.02 (*m*, 2 H); 4.15 (*q*, *J* = 7.0, 3 H). ^{13}C-NMR: 13.9; 18.8; 21.3; 23.1; 31.5; 34.4; 50.7; 59.9; 64.3; 65.0; 110.3; 174.5. GC/MS: 228 ($M^{+\bullet}$). Anal. calc. for $C_{12}H_{20}O_4$ (228.29): C 63.14, H 8.83; found: C 63.11, H 8.85.

Ethyl (6-Methyl-1,4-dioxaspiro[4.5]dec-6-yl)acetate (**12b**). According to the procedure described above for **12a**, with 2.00 g (10.0 mmol) of **1b** to give 2.40 g (9.90 mmol, 99%) of liquid **12b**. IR: 1721. ^{1}H-NMR: 1.11 (*s*, 3 H); 1.25 (*t*, *J* = 7.0, 3 H); 1.40–1.80 (*m*, 8 H); 2.37 (*d*, *J* = 14.0, 1 H); 2.39 (*d*, *J* = 14.0, 1 H); 3.90–4.00 (*m*, 2 H); 4.10 (*q*, *J* = 7.0, 3 H). ^{13}C-NMR: 14.0; 19.6; 20.6; 23.2; 30.0; 34.6; 40.0; 41.5; 59.5; 64.6; 111.6; 172.4. GC/MS: 242 ($M^{+\bullet}$). Anal. calc. for $C_{13}H_{22}O_4$ (242.32): C 64.44, H 9.15; found: C 64.42, H 9.16.

Ethyl 6-Methyl-2-[(2-methylbenzoyl)oxy]-1,4-dioxaspiro[4.5]decane-6-carboxylate (**13a**). A mixture of 6.20 g (27.2 mmol) of **12a** and 80 mg of CuBr in 60 ml of anh. benzene was heated under reflux and N_2. A soln. of 11.0 g (52.8 mmol) of *tert*-butyl 2-methylbenzenecarboperoxoate in 20 ml of dry benzene was added dropwise to the stirring mixture over a period of 2.5 h (the soln. becoming deeply blue) and then heated for another 20 h. The mixture was extracted with 10% Na_2CO_3 soln., the aq. phase was washed with Et_2O and the combined org. phases were dried. Solvent removal of the latter *in vacuo* and MPLC (4:1 hexane/AcOEt) separation of the residue led to 4.80 g (13.2 mmol) of **13a** as a colorless liquid as well as 2.00 g (13.3 mmol) of recovered **12a**. The product yield was 49% based on consumed starting material. NMR Spectral analysis revealed the product to consist of two diastereoisomers. Careful chromatographic separation gave the slightly less polar, major component in pure form. IR: 1718, 1604, 1578. ^{1}H-NMR: 1.26 (*t*, *J* = 7.0, 3 H); 1.28 (*s*, 3 H); 1.40–2.60 (*m*, 8 H); 2.61 (*s*, 3 H); 4.16 (*q*, *J* = 7.0, 2 H); 4.20 (*dd*, *J* = 9.4, 1 H); 4.31 (*dd*, *J* = 9.4, 1 H); 6.62 (*dd*, *J* = 4.1, 1 H); 7.20–7.30 (*m*, 2 H); 7.42 (br. *t*, *J* = 7.0, 1 H); 7.91 (*dd*, *J* = 7.1, 1 H). ^{13}C-NMR: 13.9; 18.7; 21.0; 21.6; 23.2; 33.8; 34.0; 50.7; 60.2; 71.6; 96.2; 114.6; 125.6; 128.6; 130.5; 131.6; 132.2; 140.5; 166.2; 174.2. GC/MS: 362 ($M^{+\bullet}$). Anal. calc. for $C_{20}H_{26}O_6$ (362.42): C 66.28, H 7.23; found: C 66.30, H 7.20. Minor component: ^{1}H-NMR: 2.60 (*s*, 3 H). ^{13}C-NMR: 14.0; 18.9; 21.3; 21.6; 23.2; 33.7; 34.2; 51.7; 60.3; 69.8; 95.4; 114.4; 125.7; 128.6; 130.5; 131.7; 132.2; 140.6; 166.4; 174.7.

Ethyl {6-Methyl-2-[(2-methylbenzoyl)oxy]-1,4-dioxaspiro[4.5]decan-6-yl}acetate (**13b**). As described for **13a**, with 2.42 g (10.0 mmol) of **12b**, 4.16 g (19.9 mmol) of *tert*-butyl 2-methylbenzenecarboperoxoate, and 50 mg of CuBr in 30 ml of dry benzene. By-products were removed from the crude mixture on a SiO_2 column, and 2.3 g of the chromatographically inseparable components were submitted to vacuum distillation to give 0.85 mg (3.69 mmol) of recovered **12b** and 1.45 g (3.69 mmol) of viscous **13b** (57% yield on the basis of consumed starting material) as a mixture of four diastereoisomers. ^{1}H-NMR: 4.00–4.40 (*m*, 2 H); 6.50–6.70 (*m*, 1 H). ^{13}C-NMR (major): 71.0; 71.2; 95.4; 95.5; 115.2; 115.3; (minor): 69.6; 69.8; 94.3; 115.6; 115.7. GC/MS: 376 ($M^{+\bullet}$). Anal. calc. for $C_{21}H_{28}O_6$ (376.45): C 67.00, H 7.50; found: C 67.02, H 7.51.

Ethyl 4,5,6,7-Tetrahydro-7-methyl-1-benzofuran-7-carboxylate (**14a**). A mixture of 400 mg (1.10 mmol) of **13a** and 20 mg of 2-methylbenzoic acid was placed in a 5 ml round-bottomed flask (equipped with a short-path distillation unit) and the flask was heated in an oil bath at 230° for 10 min. The residue, combined with the distillate, was washed with 10% Na_2CO_3, dried, and evaporated. Separation of the mixture on a MPLC column (20:1 hexane/AcOEt) gave 200 mg (0.96 mmol) of liquid **14a** (87%). IR: 1723. ^{1}H-NMR: 1.13 (*t*, *J* = 7.0, 3 H); 1.42 (*s*, 3 H); 1.40–1.80 (*m*, 3 H); 2.20–2–40 (*m*, 3 H); 4.05 (*q*, *J* = 7.0, 2 H); 6.10 (*d*, *J* = 1.5, 1 H); 7.20 (*d*, *J* = 1.5, 1 H). ^{13}C NMR: 13.9; 20.6; 22.0; 23.1; 35.7; 43.6; 60.7; 109.9; 117.6; 141.0; 150.5; 174.9. GC/MS: 208 ($M^{+\bullet}$). Anal. calc. for $C_{12}H_{16}O_3$ (208.26): C 69.21, H 7.74; found: C 69.18, H 7.72.

Ethyl (4,5,6,7-Tetrahydro-7-methyl-1-benzofuran-7-yl)acetate (**14b**). As described for **14a**, with 530 mg (1.41 mmol) of **13b**, to give 250 mg (1.13 mmol) of **14b** (80%). IR: 1718. ^{1}H-NMR: 1.20 (*t*, *J* = 7.0, 3 H); 1.35 (*s*, 3 H); 1.60–1.80 (*m*, 3 H); 1.90–2.00 (*m*, 1 H); 2.40 (*t*, *J* = 6.8, 1 H); 2.54 (*d*, *J* = 14.0, 1 H); 2.61 (*d*, *J* = 14.0, 1 H); 4.00–4.20 (*m*, 2 H); 6.14 (*d*, *J* = 1.5, 1 H); 7.22 (*d*, *J* = 1.5, 1 H). ^{13}C-NMR: 14.1; 20.1; 22.3; 25.4; 34.6; 36.1; 44.4; 59.9; 110.0; 116.2; 140.3; 154.8; 171.4. GC/MS: 222 ($M^{+\bullet}$). Anal. calc. for $C_{13}H_{18}O_3$ (222.28): C 70.24, H 8.16; found: C 70.23, H 8.18.

4,5,6,7-Tetrahydro-7-methyl-1-benzofuran-7-carboxylic Acid (**15a**). Hydrolysis of 300 mg (1.44 mmol) of **14a** with 25% NaOH soln. at 85° for 3h, followed by the usual work-up, gave 250 mg of crude product. Crystallization thereof from hexane/Et_2O 10:1 led to 200 mg (1.11 mmol) of **15a** (77%). M.p. 75–76°. IR: 2400–3600, 1702. ^{1}H-NMR: 1.53 (*s*, 3 H); 1.50–1.90 (*m*, 3 H); 2.30–2.50 (*m*, 3 H); 6.17 (*s*, 1 H); 7.27 (*s*, 1 H); 11.90 (br. *s*, 1 H). ^{13}C-NMR: 20.5; 21.9; 22.9; 35.6; 43.5; 110.0; 118.2; 141.3; 149.7; 181.9. GC/MS: 180 ($M^{+\bullet}$). Anal. calc. for $C_{10}H_{12}O_3$ (180.22): C 66.65, H 6.71; found: C 66.63, H 6.70.

(4,5,6,7-Tetrahydro-7-methyl-1-benzofuran-7-yl)acetic Acid (**15b**). To a stirred soln. of ester **2b** (300 mg, 1.32 mmol) and 1.46 g (10.56 mmol) of K_2CO_3 in 5 ml of acetone, 1.65 ml of a 50% aq. soln. of chloroacetaldehyde (830 mg, 10.56 mmol) was added, and the resulting suspension was refluxed for 18 h. The acetone was evaporated *in vacuo*, the residue was diluted with 5 ml of a 20% NaOH soln., and the resulting soln. was stirred for 30 min at 50°. The soln. was acidified with 10% HCl and extracted with AcOEt (4 × 20 ml). The combined org. phases were dried and evaporated *in vacuo*. Chromatography of the residue and elution with CH_2Cl_2/MeOH 20:1 yielded 100 mg (0.52 mmol) of **15b** (39%) as colorless solid. M.p. 52–53°. IR: 2500–3500, 1702. ^{1}H-NMR: 1.38 (*s*, 3 H); 1.70–1.80 (*m*, 3 H); 1.90–2.00 (*m*, 1 H); 2.41 (*t*, *J* = 6.8, 1 H); 2.57 (*d*, *J* = 14.0, 1 H); 2.70 (*d*, *J* = 14.0, 1 H); 6.14 (*d*, *J* = 1.5, 1 H); 7.23 (*d*, *J* = 1.5, 1 H). ^{13}C-NMR: 20.0; 22.2; 25.1; 34.5; 35.8; 44.0; 110.0; 116.2; 140.5; 154.6; 177.8. GC/MS: 194 ($M^{+\bullet}$). Anal. calc. for $C_{11}H_{14}O_3$ (194.23): C 68.02, H 7.27; found: C 68.03, H 7.23.

1-Diazo-3-(4,5,6,7-tetrahydro-7-methyl-1-benzofuran-7-yl)propan-2-one (**18**). Ethanedioyl dichloride (200 mg, 1.56 mmol) was added to a stirred soln. of 150 mg of **15b** (0.78 mmol) in 3.5 dry CH_2Cl_2 (3.5 ml), and the mixture was stirred at 30° for 4 h. The solvent was evaporated *in vacuo* and the residue, dissolved in 2 ml dry Et_2O, was added dropwise over 15 min to 21 ml of a soln. of CH_2N_2 and Et_3N (0.19 ml) in Et_2O at 0°. The mixture was stirred for 18 h, the solvent was evaporated *in vacuo*, and the residue was purified by chromatography on Al_2O_3 (activity III; elution with CH_2Cl_2) to yield 80 mg (0.82 mmol) of **18** (47%) as an oil. IR: 2110, 1645. ^{1}H-NMR: 1.31 (*s*, 3 H); 1.47–2.01 (*m*, 6 H); 2.37–2.52 (*m*, 2 H); 4.93 (*s*, 1 H); 6.19 (*d*, J = 1.2, 1 H); 7.22 (*d*, J = 1.2, 1 H). ^{13}C-NMR 19.8; 22.6; 29.1; 32.2; 39.6; 51.5; 55.9; 107.3; 115.9; 140.8; 150.1; 195.9. Anal. calc. for $C_{12}H_{14}N_2O_2$ (218.26): C 66.04, H 6.47, N 12.84; found: C 66.01, H 6.44, N 12.85.

*(1,2,5,6,7,7a-Hexahydro-7a-methyl-2-oxo-4*H*-inden-4-ylidene)ethanal* (**19**). A soln. of 80 mg of **18** (0.366 mmol) in 2 ml of dry CH_2Cl_2 was added dropwise over 30 min. to a well-stirred suspension of 1 mg of Rh catalyst in 2 ml dry CH_2Cl_2. The resulting mixture was stirred at r.t. for 2 h. The solvent was evaporated *in vacuo*, and the residue purified by chromatography (CH_2Cl_2/MeOH 100:1) to yield 40 mg (0.21 mmol) of **19**. Yellow solid. M.p. 75–77°, 58%. IR: 1710, 1675, 1630. ^{1}H-NMR: 1.25 (*s*, 3 H); 1.72–2.09 (*m*, 5 H); 2.35–2.46 (*m*, 2 H); 2.65–2.68 (*m*, 1 H); 6.05 (*s*, 1 H); 6.12–6.14 (*m*, 1 H); 9.40 (*s*, 1 H). ^{13}C-NMR: 22.8; 24.2; 37.3; 39.6; 45.9; 51.4; 128.3; 130.2; 157.5; 177.6; 190.7; 205.8. GC/MS: 190 ($M^{+\bullet}$). Anal. calc. for $C_{12}H_{14}O_2$ (190.24): C 75.76, H 7.42; found: C 75.73, H 7.46.

*(2,6,7,7a-Tetrahydro-7a-methyl-2-oxo-1*H*-inden-4-yl)ethanal* (**20**). To a stirred soln. of 115 mg (0.58 mmol) **19** in 5 ml of CH_2Cl_2, at 0°, conc. HI (one drop) was added, and the stirring was continued for 2 h. The mixture was washed twice with a 5% soln. of $NaHCO_3$ and once with a 1% soln. of $Na_2S_2O_3$. The org. phase was dried and the solvent evaporated *in vacuo* to yield 100 mg (0.48 mmol) of **20** (86%). Yellow solid. M.p. 77–79°. IR: 1705, 1670. ^{1}H-NMR: 1.21 (*s*, 3 H); 1.65–1.93 (*m*, 3 H); 2.26–2.40 (*m*, 2 H); 2.48 (*m*, 1 H); 3.28–3.42 (*m*, 2 H); 5.79 (*s*, 1 H); 6.17 (*m*, 1 H); 9.75 (*s*, 1 H). ^{13}C-NMR: 21.9; 30.4; 38.2; 40.8; 48.1; 60.3; 119.0; 126.9; 128.5; 167.2; 196.2; 201.1. GC/MS: 190 ($M^{+\bullet}$). Anal. calc. for $C_{12}H_{14}O_2$ (190.24): C 75.76, H 7.42; found: C 75.78, H 7.39.

*4-[2,2-Bis(methoxy)ethyl]-1,6,7,7a-tetrahydro-7a-methyl-2*H*-inden-2-one* (**21**). Trimethoxymethane (120 mg, 1.13 mmol) was added to a stirred soln. of 100 mg of **20** (0.52 mmol) in 20 ml of CH_2Cl_2 and 0.04 ml of MeOH, and the mixture was stirred at r.t. for 18 h. The solvent was evaporated *in vacuo* to yield 100 mg (0.43 mmol) of **21** (82%). Yellow oil. IR: 1705. ^{1}H-NMR: 1.16 (*s*, 3 H); 1.64 (*m*, 2 H); 1.89 (*dd*, J = 14.0, 5.2, 1 H); 2.23–2.39 (*m*, 2 H); 2.41 (*d*, J = 5.2, 1 H); 2.53 (*m*, 1 H); 2.61 (*m*, 1 H); 3.35, 3.39 (2*s*, 6 H); 4.47 (*m*, 1 H); 5.89 (*s*, 1 H); 6.10 (*m*, 1 H). ^{13}C-NMR: 21.9; 30.8; 37.9; 40.8; 47.1; 55.3; 55.3; 61.2; 103.9; 121.6; 124.1; 128.8; 170.0; 196.2. GC/MS: 236 ($M^{+\bullet}$). Anal. calc. for $C_{14}H_{20}O_3$ (236.31): C 71.16, H 8.53; found: C 71.12, H 8.55.

*6b-[2,2-Bis(methoxy)ethyl]-1a,2,3,3a,4,6b-hexahydro-3a-methyl-5*H*-indeno[4,5-*b*]oxiren-5-one* (**22**). A soln. of 100 mg of **21** (0.42 mmol), 7.05 mmol of H_2O_2 and 0.5 ml of 6N NaOH in 14 ml of MeOH was stirred at r.t. for 4 h. Then, 10 mol of a 5% soln. of Na_2SO_3 was added, and the stirring was continued for 30 min. The soln. was extracted with 3 × 10 ml of CH_2Cl_2, and the org. phases were dried and concentrated *in vacuo*. Chromatography of the residue and elution with CH_2Cl_2 yielded 90 mg (0.36 mmol) of **22** (85%). Yellow oil. IR: 1708. ^{1}H-NMR: 1.15 (*s*, 3 H); 1.78–1.92 (*m*, 4 H); 2.21–2.33 (*m*, 2 H); 2.56–2.62 (*m*, 2 H); 3.33, 3.35 (2*s*, 6 H); 3.43 (*m*, 1 H); 4.32 (*m*, 1 H); 6.21 (*s*, 1 H). ^{13}C-NMR: 21.5; 22.9; 30.6; 32.9; 38.4; 52.6; 52.6; 61.3; 62.9; 64.0; 100.9; 124.8; 185.1; 196.7. GC/MS: 252 ($M^{+\bullet}$). Anal. calc. for $C_{14}H_{20}O_4$ (252.31): C 66.65, H 7.99; found: C 66.61, H 8.02.

*4,5,5a,6-Tetrahydro-5a-methyl-7*H*-indeno[5,4-*b*]furan-7-one* (**17**). A mixture of 90 mg (0.36 mmol) of **22** and a crystal of *p*-TsOH in 10 ml of dry THF was refluxed for 6 h. Then, 1 ml of a 5% soln. of $NaHCO_3$ was added, and the soln. was diluted with 10 ml of H_2O and extracted 3 × with 10 ml of CH_2Cl_2. The combined org. phases were dried and concentrated *in vacuo*. Chromatography of the residue (elution with CH_2Cl_2) led to 30 mg (0.16 mmol) of **17** (44%). Yellow oil. IR: 1700. ^{1}H-NMR: 1.32 (*s*, 3 H); 1.85–2.05 (*m*, 4 H); 2.21–2.32 (*m*, 2 H); 5.84 (*s*, 1 H); 6.46. (*d*, J = 1.7, 1 H); 7.31 (*d*, J = 1.7, 1 H). ^{13}C-NMR: 19.5; 21.9; 37.4; 45.2; 60.3; 99.0; 118.3; 128.0; 140.9; 154.2; 162.8; 196.5. GC/MS: 188 ($M^{+\bullet}$). Anal. calc. for $C_{12}H_{12}O_2$ (188.23): C 76.57, H 6.43; found: C 76.59, H 6.46.

2-Diazo-1-(4,5,6,7-tetrahydro-7-methyl-1-benzofuran-7-yl)ethanone (**23**). Yellow oil (83%). IR: 2102, 1625. ^{1}H-NMR: 1.44 (*s*, 3 H); 1.30–1.90 (*m*, 3 H); 2.30–2.50 (*m*, 3 H); 5.09 (*s*, 1 H); 6.24 (*d*, J = 1.0, 1 H); 7.33 (*d*, J = 1.0, 1 H). ^{13}C-NMR: 20.6; 22.0; 22.8; 35.5; 47.5; 53.8; 110.5; 119.3; 141.3; 150.9; 197.5.

[6-Methyl-7-oxobicyclo[4.2.0]oct-1(8)-en-2-ylidene]ethanal (**24**). A mixture of 140 mg (0.68 mmol) of **23** and 5 mg of $Rh_2(OAc)_4$ in 29 ml of CH_2Cl_2 was stirred for 15 min. The catalyst was filtered off on a *Celite* pad and the filtrate was evaporated, leaving 110 mg of a viscous oil. Spectral analysis showed the residue to be a 4:1 mixture of two components, the major one of which proved to be **24**. IR: 1760, 1678, 1572. ^{1}H-NMR: 1.35 (*s*, 3 H); 2.74 (br. *d*, J = 14.0, 1 H); 6.08 (*dd*, J = 8.2, 1 H); 6.10 (*s*, 1 H); 9.86 (*d*, J = 8.0, 1 H). ^{13}C-NMR: 17.9; 22.1;

32.0; 34.9; 66.7; 127.9; 131.5; 154.7; 176.7; 190.4; 192.6. GC/MS: 176 ($M^{+\cdot}$). Anal. calc. for $C_{11}H_{12}O_2$ (176.22): C 74.98, H 6.86; found: C 74.99, H 6.84.

*4,5,6,6a-Tetrahydro-6a-methyl-7*H-*pentaleno[1,6a*-b*]furan-7-one* (**25**). A soln. of the mixture containing **24** and 2 crystals of I_2 in 5 ml of CH_2Cl_2 was kept at r.t. for 1 h, whereupon the solvent was evaporated *in vacuo*. The residue was chromatographed on a chromatron (2 mm plate, 20:1 hexane/AcOEt elution) to give 100 mg (0.57 mmol) of liquid **25** (83% based on **23**). UV: 238 (1.27×10^{-4}). IR: 1695, 1628, 1571. ^{1}H-NMR: 1.15 (*s*, 3 H); 1.28–1.73 (*m*, 4 H); 1.94 (*dd*, $J = 13.6$, 1 H); 5.47 (*s*, 1 H); 5.57 (*d*, $J = 3.0$, 1 H); 6.75 (*d*, $J = 3.0$, 1 H). ^{13}C-NMR: 20.6; 22.1; 36.0; 38.0; 63.7; 65.6; 103.1; 112.7; 146.9; 196.7; 212.2. GC/MS: 176 ($M^{+\cdot}$). Anal. calc. for $C_{11}H_{12}O_2$ (176.22): C 74.98, H 6.86; found: C 74.96, H 6.87.

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