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THE DIELS-ALDER APPROACH TO MUSK ODOR TYPE ARENES

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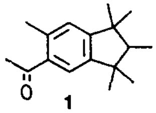
Summary : The readily accessible 2-halogeno-1-trimethylsilyloxy-1,3-butadienes react smoothly with dimethyl acetylenedicarboxylate to afford 4-halophthalic esters. One of these cycloadducts was subsequently converted into heterocyclic analogues of phantolide like musk fragrances.

Phantolide (1), Tonalide (2) and Versalide (3) belong to a class of acetophenones which carry two quarternary carbon atoms as bulky substituents in the *meta* and *para* positions and which exhibit the characteristic musk odor together with some woody undertones. [1, 2] Despite its valuable olfactive properties, Versalide (3) had to be withdrawn from the market because of hepatotoxic and neurotoxic side effects and the others (1 and 2) are suspected of poor biodegradability.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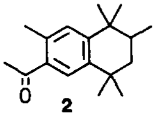
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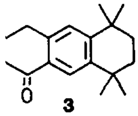
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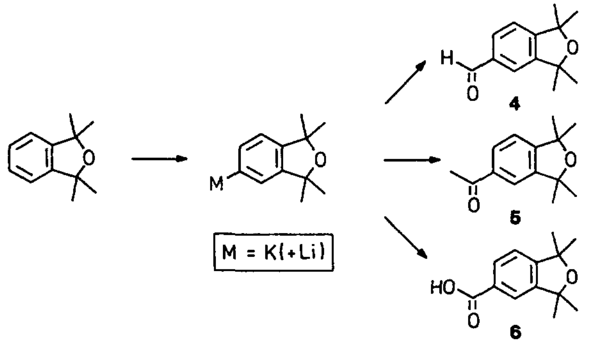
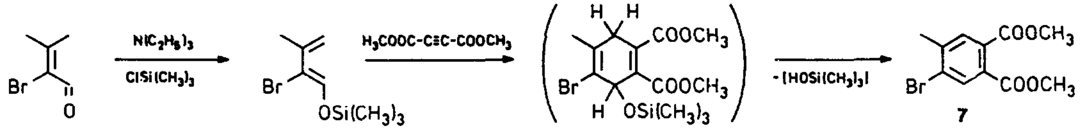
We wondered whether the replacement of a part of the saturated carbocycle by a heteroatom would make such compounds metabolically more vulnerable and thus improve their environmental compatibility. 1,1,3,3-Tetramethyl-1,3-dihydroisobenzofuran [3] being easily available, we submitted it to the metalation with the superbasic mixture of butyllithium and potassium *tert*-butoxide [4]. The organometallic intermediate was trapped with standard electrophiles to give the aldehyde 4 (50%), the ketone 5 (45%) and the acid 6 (79%), respectively.

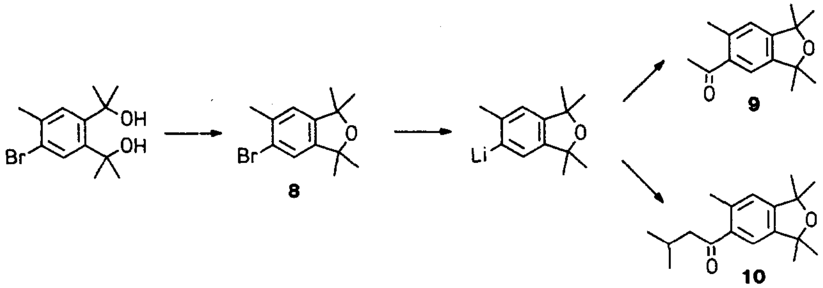


No simple method, however, exists for the subsequent introduction of the lacking methyl group next to the carbonyl function. Although 1,1,3,3,5-pentamethyl-1,3-dihydroisobenzofuran could be readily prepared by treatment of the organometallic intermediate with methyl iodide, it did not sustain the conditions of a Friedel-Crafts acylation reaction. Therefore, we opted for the [4+2] cycloaddition approach using electron-rich dienes [5] as the key components. So far, only few arenes [6] have been constructed in this way and no haloarenes at all.

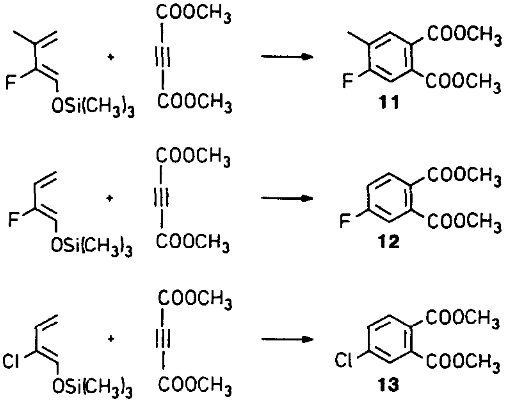
2-Bromo-3-methyl-2-butenal was converted into (*Z*)-2-bromo-3-methyl-1,3-butadienyl trimethylsilyl ether (87%) by treatment with chlorotrimethylsilane in the presence of triethylamine. It reacted with dimethyl acetylenedicarboxylate in refluxing toluene to give dimethyl 4-bromo-5-methylphthalate (7, 86%).



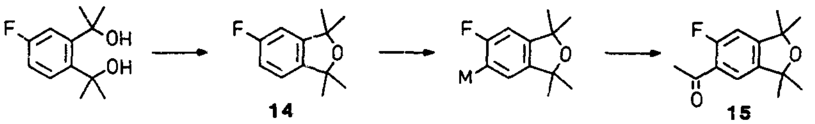
Four equivalents of methylmagnesium chloride were added to the *ortho* diester and the resulting diol (78%) was cyclized to afford 5-bromo-1,1,3,3,6-pentamethyl-1,3-dihydroisobenzofuran (8, 98%). This compound underwent a quantitative halogen/metal permutation reaction with butyllithium. The organolithium intermediate was acylated with *S*-2-pyridyl ethanethioate or isovaleryl chloride to give the ketones 9 (82%) and 10 (93%).



Analogous cycloaddition reactions between 2-fluoro-3-methyl-1,3-butadienyl trimethylsilyl ether, 2-fluoro-1,3-butadienyl trimethylsilyl ether [7] or 2-chloro-1,3-butadienyl trimethylsilyl ether [7] and dimethyl acetylenedicarboxylate as the dienophile were carried out. Dimethyl 4-fluoro-5-methylphthalate (11, 84%), dimethyl 4-fluorophthalate (12, 70%) and dimethyl 4-chlorophthalate (13, 83%) were obtained as the sole products.



The fluorophthalate 12 was converted to the diol and the latter was dehydrated to give the tetrahydroisobenzofuran 14. Superbase metalation [8] generated an intermediate that was carboxylated to afford the corresponding acid which was ultimately converted into the fluorinated ketone 15 (51%).



None of the compounds 4, 5, 9, 10 and 15 exhibited a typical musk odor. Apparently, oxygen is not always a good mimic of carbon.

EXPERIMENTAL PART

1. General

The molecular peaks (M^+) listed of chlorides and bromide refer to the ^{37}Cl and ^{81}Br isotopes. - For standard laboratory practice, techniques and abbreviations, see related articles, *e.g.*, ref. [9].

2. Dienyl Trimethylsilyl Ethers

1-Trimethylsilyloxy-1,3-butadiene [10 - 11]: 75% of the (*E*)-isomer [11] (from 2-butenal); bp 62 - 64 °C/60 mmHg; n_D^{20} 1.4466. - ^1H-NMR : δ 6.55 (1 H, dm, *J* 11.9), 6.27 (1 H, dt, *J* 16.9, 10.5), 5.74 (1 H, ddm, *J* 11.9, 10.5), 5.01 (1 H, dm, *J* 16.9), 4.83 (1 H, dm, *J* 10.3), 0.22 (9 H, s).

Working procedure for the preparation of halogenated derivatives : Under nitrogen atmosphere, a mixture of the 2-halo-2-alkenal (0.20 mol), chlorotrimethylsilane (30 mL, 28 g, 0.24 mol), triethylamine (50 mL, 36 g, 0.36 mol) and zinc dichloride (0.7 g, 5 mmol) [10] in anhydrous benzene (50 mL) was heated to reflux temperature for several hours. A precipitate was formed. Pentane (0.1 L) was added and the mixture was filtered. The filtrate was concentrated by evaporation and the residue distilled under reduced pressure.

2-Fluoro-1-trimethylsilyloxy-1,3-butadiene : 67% (from 2-fluoro-2-butenal [12], 5 h of reflux); bp 59 - 61 °C/40 mmHg; n_D^{20} 1.4457. - ^1H-NMR : δ 6.00 (1 H, ddd, *J* 27.0, 17.5, 11.5), 5.88 (1 H, d, *J* 11.5), 5.34 (1 H, d, *J* 21.5), 4.99 (1 H, d, *J* 17.5), 0.26 (9 H, s). - ^{19}F-NMR : δ -86.0 (dd, *J* 26.5, 21.0). - Analysis : calc. for $C_7H_{13}FOSi$ (160.26) C 52.46, H 8.18; found C 52.34, H 8.03%.

2-Chloro-1-trimethylsilyloxy-1,3-butadiene : 81% (from 2-chloro-2-butenal [13]; 3 h of reflux); bp 66 - 67 °C/14 mmHg; n_D^{20} 1.4747. - ^1H-NMR : δ 6.66 (1 H, s, broad), 6.31 (1 H, dd, *J* 16.4, 10.7), 5.45 (1 H, ddd, *J* 10.7, 1.0, 0.5), 5.04 (1 H, ddd, *J* 16.4, 1.0, 0.5), 0.28 (9 H, s). - Analysis : calc. for $C_7H_{13}ClOSi$ (176.72) C 47.58, H 7.41; found C 47.99, H 7.30%.

2-Fluoro-3-methyl-1-trimethylsilyloxy-1,3-butadiene : 78% (from 2-fluoro-3-methyl-2-butenal [12], 8 h of reflux); bp 56 - 58 °C/13 mmHg; (*Z*/*E*)-mixture in the ratio of 90 : 10. - ^1H-NMR : δ 6..59 (0.1 × 1 H, d, *J* 10.1), 6.00 (0.9 × 1 H, d, *J* 21.9), 5.2 (0.1 × 1 H, m), 5.20 (0.9 × 1 H, hept, *J* 0.7), 4.89 (0.1 × 1 H, hept, *J* 1.6), 4.81 (0.9 × 1 H, symm. m), 2.02 (0.1 × 3 H, symm. m), 1.78 (0.9 × 3 H, symm. m, narrow), 0.25 (0.9 × 9 H, s), 0.22 (0.1 × 9 H, s). - ^{19}F-NMR : δ -80.6 (0.9 × 1 F, dm, *J* 21.9), -97.0 (0.1 × 1 F, dm, *J* 10.1). - Analysis : calc. for $C_8H_{15}FOSi$ (174.28) C 55.13, H 8.68; found C 54.98, H 8.98%.

2-Bromo-3-methyl-1-trimethylsilyloxy-1,3-butadiene : 86% (from 2-bromo-3-methyl-2-butenal [14], 3 h of reflux); bp 69 - 71 °C/3 mmHg; (*Z*/*E*)-mixture in the ratio of 92 : 8. - ^1H-NMR : δ 6.82 (0.9 × 1 H, t-like s, *J* ~ 0.5), 6.68 (0.1 × 1 H, s, broad), 5.34 (0.9 × 1 H, symm.), 5.3 (0.1 × 1 H, m), 5.1 (0.1 × 1 H, m), 4.96 (0.9 × 1 H, pent-like m, *J* ~ 1.5), 2.09 (0.1 × 1 H, symm. m), 1.97 (0.9 × 1 H, dd, *J* 1.5, 0.7), 0.28 (0.9 × 9 H, s), 0.23 (0.1 × 9 H, s). - Analysis : calc. for $C_8H_{15}BrOSi$ (235.20) C 40.85, H 6.43; found C 40.96, H 6.36.

3. Dimethyl phthalates

Working procedure : A mixture consisting of the dienyl trimethylsilyl ether (50 mmol), dimethyl acetylenedicarboxylate (6.1 mL, 7.1 g, 50 mmol), a little hydroquinone (approximately 20 mg) and toluene (30 mL) was placed for 15 h in a 120 °C hot oil bath. After the addition of a small amount of aluminum trichloride (about 50 mg), the heating was continued for an additional hour. The product was isolated by distillation under reduced pressure.

Dimethyl phthalate [15] : 75%.

Dimethyl 4-fluorophthalate (12) : 70%; mp -32 to -34 °C; bp 89 - 91 °C/1 mmHg; n_D^{20} 1.4989. - ^{1}H-NMR : δ 7.80 (1 H, dd, *J* 8.5, 5.5), 7.35 (1 H, dd, *J* 8.5, 2.5), 7.21 (1 H, dt, *J* 8.5, 2.5), 3.93 (3 H, s), 3.90 (3 H, s). - ^{19}F-NMR : δ -44 (dt, *J* 8.2, 5.5). - MS : 212 (6%, M^+), 181 (100%). Analysis : calc. for $C_{10}H_9FO_4$ (212.18) C 56.61, H 4.27; found C 57.00, H 3.96%.

Dimethyl 4-chlorophthalate (13) : 83%; mp 31 - 32 °C; bp 116 - 118 °C/0.05 mmHg. - ^{1}H-NMR : δ 7.70 (1 H, d, *J* 8.5), 7.67 (1 H, d, *J* 2.0), 7.50 (1 H, dd, *J* 8.5, 2.0), 3.92 (3 H, s), 3.90 (3 H, s). - MS : 230 (5%, M^+), 199 (31%), 197 (100%). - Analysis : calc. for $C_{10}H_9ClO_4$ (228.63) C 52.53, H 3.97; found C 52.92, H 3.76%.

Dimethyl 4-fluoro-5-methylphthalate (11) : 84%; mp 60 - 61 °C; bp 90 - 92 °C/0.05 mmHg. - ^{1}H-NMR : δ 7.54 (1 H, d, *J* 7.4), 7.30 (1 H, d, *J* 9.5), 3.85 (3 H, s), 3.84 (3 H, s), 2.28 (3 H, d, *J* 1.5), - ^{19}F-NMR : δ -48.5 (ddq, *J* 9.5, 7.4, 1.5). - MS : 226 (22%, M^+), 195 (100%). - Analysis : calc. for $C_{11}H_{11}FO_4$ (226.20) C 58.41, H 4.90; found C 58.45, H 4.91%.

Dimethyl 4-bromo-5-methylphthalate (7) : 85%; mp 57 - 59 °C; bp 134 - 136 °C/0.07 mmHg. - ^{1}H-NMR : δ 7.92 (1 H, s), 7.56 (1 H, s), 3.90 (6 H, s), 2.48 (3 H, s). - MS : 288 (13%, M^+), 257 (86%), 255 (100%). - Analysis : calc. for $C_{11}H_{11}BrO_4$ (287.11) C 46.02, H 3.86; found C 45.91, H 3.84%.

4. 2,2'-*o*-Phenylenebis(2-propanol) Derivatives

Working Procedure : A 3.0 M solution (0.20 L) of methylmagnesium chloride (0.60 mol) in tetrahydrofuran was added dropwise, in the course of 30 min, to the dimethyl phthalate (0.10 mol) in tetrahydrofuran (0.10 L) kept in an ice-bath. After being heated 24 h under reflux, the mixture was poured into a saturated aqueous solution (0.40 L) of ammonium chloride. Extraction with diethyl ether (3 × 0.10 L), washing of the combined organic layers with brine (2 × 0.20 L), drying and evaporation of the solvent gave a residue which crystallized upon trituration with hexane.

***o*-Phenylenebis-2,2'-(2-propanol)** [3] : 70% (lit. : 40%).

2,2'-(4-Fluoro-1,2-phenylene)bis(2-propanol) : 71%; mp 152 - 154 °C. - ^{1}H-NMR : δ 7.30 (1 H, dd, *J* 8.8, 6.1), 7.03 (1 H, dd, *J* 11.7, 2.7), 6.87 (1 H, ddd, *J* 8.8, 7.0, 2.7), 5.48 (1 H, s, broad), 4.95 (1 H, s, broad), 1.71 (6 H, s), 1.70 (6 H, s). - ^{19}F-NMR : δ – 54.2 (ddd, *J* 11.7, 7.0, 6.1). - MS : 197 (14%, M^+ – 15), 179 (100%). - Analysis : calc. for $C_{12}H_{17}FO_2$ (212.26) C 67.90, H 8.07; found C 68.26, H 8.08%.

2,2'-(4-Bromo-5-methyl-1,2-phenylene)bis(2-propanol) : 78%; mp 158 - 160 °C. - ^{1}H-NMR : δ 7.45 (1 H, s), 7.16 (1 H, s), 5.84 (2 H, s, splitted), 2.35 (3 H, s), 1.69 (6 H, s). - MS : 273 (15%, M^+ - 15), 255 (97%), 253 (100%). - Analysis : calc. for $C_{13}H_{19}BrO_2$ (287.20) C 54.37, H 6.67; found C 54.48, H 6.58%. - With only half the amount of methylmagnesium chloride (0.30 mol) a mixture of **5-bromo-1-hydroxy-1,3,3,6-tetramethyl-1,3-dihydroisobenzofuran** and of **6-bromo-1-hydroxy-1,3,3,5-tetramethyl-1,3-dihydroisobenzofuran** was obtained; 89%; mp 125 - 127 °C. - ^{1}H-NMR : δ 7.51 (0.4 × 1 H, s), 7.31 (0.6 × 1 H, s), 7.22 (0.6 × 1 H, s), 7.01 (0.4 × 1 H, s), 3.06 (1 H, s), 2.43 (3 H, s), 1.75 (3 H, s), 1.56 (3 H, s), 1.48 (3 H, s). - MS : 254 (17%, M^+ – 18), 239 (100%). - Analysis : calc. for $C_{12}H_{15}BrO_2$ (271.15) C 53.16, H 5.58; found C 53.19, H 5.75%.

5. Dihydroisobenzofurans

By dehydration of 2,2'-o-phenylenebis(2-propanols) : A suspension of the 2,2'-*o*-phenylenebis(2-propanol) (40 mmol) in 60% sulfuric acid (0.10 L) was vigorously stirred 1 h at 50 °C. The mixture was poured into water and extracted with hexane (3 × 0.10 L). The organic layers were washed with a sat. aqu. solution of sodium hydrogen carbonate (2 × 0.10 L) and brine (0.10 L) and evaporated to dryness to afford the crystalline material.

1,1,3,3-Tetramethyl-1,3-dihydroisobenzofuran [3] : 98%; mp 70 - 72 °C. - ^{1}H-NMR : δ 7.29 (2 H, symm. m), 7.11 (2 H, symm. m), 1.54 (12 H, s).

5-Fluoro-1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran (14) : 98%; mp 41 - 42 °C. - ^{1}H-NMR : δ 7.08 (1 H, dd, *J* 8.5, 5.0), 6.96 (1 H, dt, *J* 8.5, 2.2), 6.77 (1 H, dd, *J* 8.5, 2.2), 1.52 (6 H, s), 1.51 (6 H, s). - ^{19}F-NMR : δ -53.5 (td, *J* 8.5, 5.0). - MS : 179 (100%, $M^+ - 15$), 161 (23%). - Analysis : calc. for $C_{12}H_{15}FO$ (194.25) C 74.20, H 7.78; found C 74.29, H 7.82%.

5-Bromo-1,1,3,3,6-pentamethyl-1,3-dihydroisobenzofuran (8) : 98%; mp 81 - 82 °C. ^{1}H-NMR : δ 7.26 (1 H, s), 6.96 (1 H, s), 2.42 (3 H, s), 1.50 (12 H, s). - MS : 270 (3%, M^+), 255 (98%), 253 (100%). - Analysis : calc. for $C_{13}H_{17}BrO$ (269.18) C 58.01, H 6.37; found C 58.33, H 6.32%.

By metalation of 1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran and subsequent electrophilic substitution : Potassium *tert*-butoxide (2.5 g, 22 mmol) was added to the solution of 1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran (3.5 g, 20 mmol) and butyllithium (22 mmol) in hexane (45 mL). The mixture was sonicated 2 h at 25 °C before being quenched with the electrophile.

1,1,3,3,5-Pentamethyl-1,3-dihydroisobenzofuran : 25% (after the addition of methyl iodide); mp 51 - 53 °C. - ^{1}H-NMR : δ 7.11 (1 H, d, *J* 7.7), 7.00 (1 H, d, *J* 7.7), 6.91 (1 H, s), 2.37 (3 H, s), 1.53 (12 H, s). - MS : 175 (100%, $M^+ - 15$), 157 (17%).

5-Formyl-1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran (4) : 50% (after consecutive treatment of the reaction mixture with equimolar quantities of lithium bromide, dissolved in tetrahydrofuran, and dimethylformamide); mp 83 - 85 °C. - ^{1}H-NMR : δ 10.03 (1 H, s), 7.82 (1 H, dd, *J* 7.8, 1.2), 7.65 (1 H, d, *J* 1.2), 7.26 (1 H, d, *J* 7.8), 1.58 (6 H, s), 1.57 (6 H, s). - MS : 205 (13%, $M^+ + 1$), 189 (100%, M^+), 171 (5%). - Analysis : calc. for $C_{13}H_{16}O_2$ (204.27) C 76.44, H 7.89; found C 76.76, H 8.01%.

5-Carboxy-1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran (6) : 79% (after having poured the reaction mixture onto dry ice); mp 202 - 204 °C. - ^{1}H-NMR : δ 8.08 (1 H, dd, *J* 8.0, 1.2), 7.87 (1 H, d, *J* 1.2), 7.21 (1 H, d, *J* 8.0), 1.58 (6 H, s), 1.57 (6 H, s). - MS : 205 (100%, $M^+ - 15$), 187 (6%); 115 (21%). - Analysis : calc. for $C_{13}H_{16}O_3$ (220.27) C 70.89, H 7.32; found C 70.73, H 7.35%.

5-Acetyl-1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran (5) : 45% (the reaction mixture being first poured onto dry ice, then evaporated and the residue finally treated 30 min at 25 °C with a slight excess of 1.8 M ethereal methyllithium); mp 70 - 71 °C.- ^{1}H-NMR : δ 7.92 (1 H, dd, *J* 7.9, 1.5), 7.72 (1 H, d, broad, *J* 1.5), 7.19 (1 H, d, broad, *J* 7.9), 2.64 (3 H, s), 1.56 (6 H, s), 1.55 (6 H, s). - MS : 219 (6%, $M^+ + 1$), 203 (100%), 185 (3%). - Analysis : calc. for $C_{14}H_{18}O_2$ (218.29) C 77.03, H 8.31; found C 77.23, H 8.38%.

By metalation of 5-fluoro-1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran and subsequent electrophilic substitution : Precooled (-90 °C) tetrahydrofuran (25 mL), 5-fluoro-1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran, (14, 3.9 g, 20 mmol) and potassium *tert*-butoxide (2.5 g, 22 mmol) were consecutively added to butyllithium (22 mmol) from which the commercial solvent (hexane) had been previously stripped off under reduced pressure. After 2 h of vigorous stirring at -90 °C, an excess of freshly crushed dry ice was introduced into the reaction vessel. The reaction mixture was allowed to reach 25 °C and was then purged with a stream of nitrogen. At 0 °C, a 1.8 M solution (12 mL) of methyllithium (22 mmol) in diethyl ether was added. After 1 h of stirring at 0 °C, the mixture was brought with anhydrous formic acid (3.0 ml, 3.7 g, 80 mmol) to pH 5, concentrated and absorbed on silica gel (10 g). The dry powder was poured on top of a column filled with fresh silica gel suspended in hexane. Elution with a 1 : 9 (v/v) mixture of ethyl acetate and hexane afforded 2.4 g (51%) of **5-acetyl-6-fluoro-1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran (16)**; mp 95 - 97 °C. - ^{1}H-NMR : δ 7.86 (1 H, d, *J* 10.5), 7.62 (1 H,d, *J* 6.4), 2.67 (3 H, d, *J* 5.1), 1.53 (6 H, s), 1.52 (6 H, s). - ^{19}F-NMR : δ −48.4 (ddq, *J* 10.5, 6.4, 5.1). MS : 237 (22%, $M^+ + 1$), 221 (100%). - Analysis : calc. for $C_{14}H_{17}FO_2$ (236.28) C 71.17, H 7.25; found C 71.22, H 7.17%.

By treatment of 5-bromo-1,1,3,3,6-pentamethyl-1,3-dihydroisobenzofuran with butyllithium and subsequent electrophilic substitution : A 1.6 M solution (7.5 mL) of butyllithium (12 mmol) in hexane and of the dihydroisobenzofuran 8 (10 mmol) in diethyl ether (20 mL) were mixed at 25 °C. The white suspension was cooled to -75 °C and after addition of *S*-2-pyridyl ethanethioate [16] or isovaleryl chloride, was stirred 30 min before being allowed to warm up. The mixture was slightly acidified (pH ~ 5) with anhydrous formic acid, the solvents were evaporated and the residue absorbed on silica gel (10 g). The dry powder was poured on top of a column filled with fresh silica gel (40 g) and hexane. The product was isolated by elution with a 1 : 9 (v/v) mixture of ethyl acetate and hexane.

5-Acetyl-1,1,3,3,6-pentamethyl-1,3-dihydroisobenzofuran (9) : 82%; mp 106 - 108 °C. - ^{1}H-NMR : δ 7.37 (1 H, s), 6.95 (1 H, s), 2.59 (3 H, s), 2.53 (3 H, s), 1.52 (6 H, s), 1.50 (6 H, s). - MS : 232 (1%, M^+), 217 (100%). - Analysis : calc. for $C_{15}H_{20}O_2$ (232.32) C 77.55, H 8.68; found C 77.85, H 8.69%.

5-Isovaleryl-1,1,3,3,6-pentamethyl-1,3-dihydroisobenzofuran (10) : 93%; mp 80 - 82 °C. - ^{1}H-NMR : δ 7.26 (1 H, s), 6.94 (1 H, s), 2.78 (2 H, d, *J* 6.7), 2.50 (3 H, s), 2.29 (1 H, hept-like symm. m, *J* 6.7), 1.53 (6 H, s), 1.51 (6 H, s), 1.00 (6 H, d, *J* 6.7). - MS : 274 (2%, M^+), 259 (100%). - Analysis : calc. for $C_{18}H_{26}O_2$ (274.40) C 78.79, H 9.55; found 79.07, H 9.66%.

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