Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: J. M. Vierfond , A. Reynet , H. Moskowitz & C. Thal (1992) New Synthetic Route to Pummerer's Ketone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:12, 1783-1792, DOI: 10.1080/00397919208020498

To link to this article: http://dx.doi.org/10.1080/00397919208020498

SYNTHETIC COMMUNICATIONS, 22(12), 1783-1792 (1992)

NEW SYNTHETIC ROUTE TO PUMMERER'S KETONE

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Abstract - Pummerer's ketone **1** is obtained with an overall yield of 55 % by the following sequence: Claisen rearrangement of an arylcyclohexylether **3**; allylic oxidation of the methylcycloalkylphenolic derivative **4b**, then spontaneous cyclisation during demethylation to give **2**. **1** is obtained by dehydrogenation of **2**. NMR data agree with a *cis* stereochemistry at C_{4a} and C 9_b.

A strategy to morphinic analogs with a tetrahydrodibenzofuran framework has been developed from Pummerer's ketone **1**[1-4]; unfortunately oxidative coupling of *p*-cresol gives only

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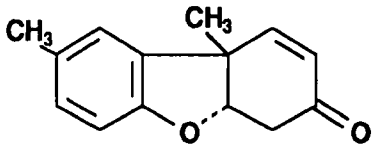
poor yields (22[5a] - 25[5b] %).



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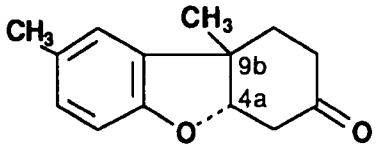

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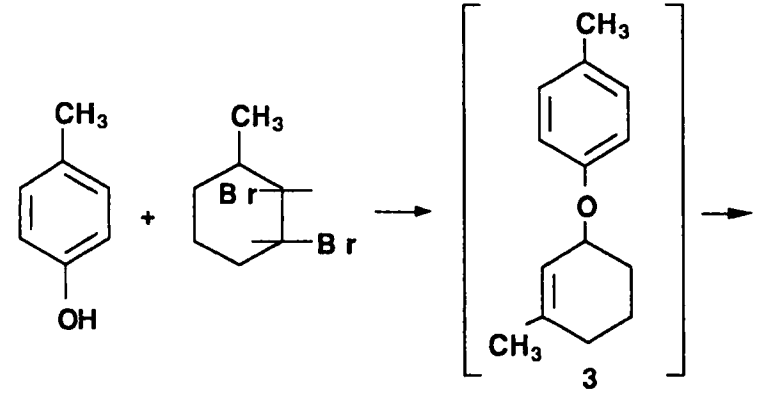
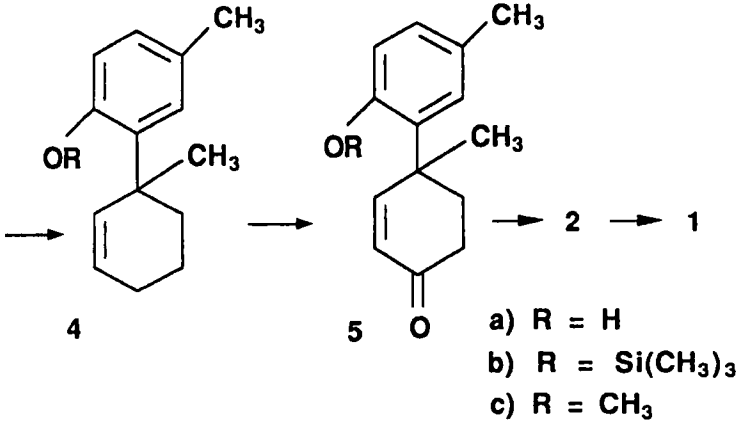
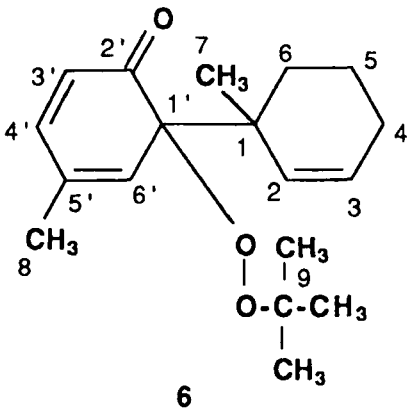
Our previous studies in the field of hexahydrodibenzofurans[6] and the marked antitussive activity exhibited by certain derivatives of Pummerer's ketone[7] prompted us to study an original synthetic approach to **1** and **2**. We describe here an easy sequence allowing overall yields of 55% for **1** and 60% for **2**, from the dibromo compound.





Previously, we have published a Claisen rearrangement from gaïacol and 2,3-dibromo-1-methyl cyclohexane[8] (obtained by addition of Br_2 on 1-methylcyclohex-2-ene). This procedure is useful in the case of *p*-cresol to prepare compound **4** *via* the non isolated ether **3** . The preparation consists of stirring the *p*-cresol and the dibromo derivative with NaH in DMF and heating at 120 °C during 6 hours. The solvent is evaporated and the reaction is heated to 200 °C for half an hour. Then, the mixture is chromatographed on silica-gel (pentane as eluant) to obtain compound **4a** (77%).

The second step is the allylic oxydation of compound **4a** . A first attempt in this way, was the reaction of the product **4a** and *t*BuOOH, $Cr(CO)_6$ in acetonitrile[9] at 50 °C during 48 hours to give intractable tar. A second attempt was realised from *o*-trimethylsilyl phenol **4b** in place of compound **4a** . The sole product which can be isolated was the dienone **6** resulting from ortho addition of *t* BuOOH on the phenol :



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Then the phenol protection was realised by phase transfer in a mixture water-benzene with benzyltriethylammonium chloride and by addition of CH_3I; after stirring 12 hours, the methoxy derivative **4c** (yield 100%) is obtained . Then the phenol **4c** dissolved in acetonitrile, is stirred at 50 °C during 48 hours with *t* BuOOH and $Cr(CO)_6$. The compound **5** is obtained with 88% yield from **4c**, after purification.

The one pot demethylation is easily realised in $CHCl_3$ with $Si(CH_3)_3I$ to obtain compound **2** (yield 85%). The stereochemistry of $-CH_3$ at C_{9b} and -H at C_{4a} is *cis* as in morphine (NOE effect between $-CH_3$ at 9b and H 4a). The last step is the dehydrogenation of ketone **2** to Pummerer's ketone **1**. This dehydrogenation is obtained by reaction of the phenylselenium chloride at room temperature followed by treatement with hydrogen peroxyde[11].

All compounds had correct microanalyses and their IR, ^1H NMR and ^{13}C NMR spectra were in conformity with their proposed structures.

EXPERIMENTAL

1-(2-hydroxy-5-methylphenyl)-1-methylcyclohex-2-ene **4a**

To a mixture of 1.8 g (0.06 mole) NaH and anhydrous DMF (50 ml) under nitrogen was added with stirring 6.06 g (0.06 mole) of *p*-cresol in DMF (10 ml). After half an hour, 5.12 g (0.02 mole) of 2,3-dibromo-1-methylcyclohexane was introduced. Then, the reaction was heated during 6 hours at 120

°C. The solvent was removed by distillation and the residue was heated to 200 °C under nitrogen during half an hour. Water (20 ml) was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried, evaporated and the residue chromatographed on silica gel (pentane as eluent) to give 3.12 g of a colourless liquid (yield from dibromo compound : 77%).

- ^1H NMR ($CDCl_3$) 200MHz : 7.1 (s, $H_{6'}$); 7 (d, $H_{3'}$); 6.8 (d, $H_{4'}$); 6.2 (s, OH); 6.1 (m); 5.85 (d, H_2); 2.3 (s, 3H); 2.0-2.2 (m, 3H); 1.7-1.8 (m, 3H); 1.5 (s, 3H).

- ^{13}C NMR ($CDCl_3$) 50 MHz: 152 ($C_{2'}$); 135.9 (C_2); 133.2 ($C_{1'}$); 130 ($C_{3'}$); 129.1 ($C_{5'}$); 128 (C_3); 127.4 ($C_{4'}$); 117.2 ($C_{6'}$); 38.1 (C_1); 35.7 (C_4); 29.6 (C_5) ; 26.7 (CH_3) ; 24.8 (C_6); 20.8 (CH_3) .

-Anal. calc. for C_{14} H_{18} O : C = 83.16; H = 8.91; found: C = 82.91; H = 8.85 .

4-(2-methoxy-4-methylphenyl)-4-methylcyclohex-2-ene **4c**

To a mixture of 0.6 g (0.015 mole) NaOH in water (1ml), C_6H_6 (4 ml) and 2.27 g (0.01 mole) of benzyltriethylammonium chloride was added 2.02 g (0.01 mole) of compound **4a** . The mixture was allowed to stir at room temperature for half an hour then, 2.13 g (0.015 mole) of methyliodide was added dropwise. After 12 hours at 25 °C, the mixture was extracted with diethyloxide, the organic layer dried (Na_2SO_4) and evaporated to

give 2.15 g (100%) of compound **4c** as a yellow oil wich was used without further purification.

- ^1H NMR ($CDCl_3$) 200MHz : 7.1 (s, $H_{6'}$); 6.9 (d, $H_{3'}$); 6.65 (d, $H_{4'}$); 5.75 (m, H_2, H_3); 3.7 (s, -OCH_3); 2.4 (m, 1H); 2.2 (s, CH_3); 2-1.85 (m, 2H); 1.60-1.45 (m, 3H); 1.45 (s, 3H).

- Anal. calc. for $C_{15}H_{20}O$: C = 83.35 ; H = 9.25;
found : C = 83.50 ; H = 9.28 .

4-(2-methoxy-5-methylphenyl)-4-methylcyclohex-2-en-1-one **5**

A solution of 0.648 g (0.03 mole) of compound **4c** in acetonitrile (20 ml) with *t*-BuOOH 90% (1.2 eq) and $Cr(CO)_6$ (0.25 eq) was stirred during 48 hours at 50 °C . Then, the solution was filtred, evaporated and chromatographed on silica gel (CH_2Cl_2) to obtain 0.60 g of compound **5** (yield 88%).

- ^1H NMR ($CDCl_3$) 200 MHz : 7.65 -7.60 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{6'}$); 7.35 (d, J = 10 Hz, H_3); 6.35 (d, J = 10 Hz, H_2); 3.65 (s, 3H, CH_3 in 2'); 2.35 (m, 1H); 2.02-1.95 (m, 2H); 1.75 (s, 3H, CH_3 in 5'); 1.35 (m, 1H); 1.0 (s, 3H, CH_3 in 4).

- ^{13}C NMR ($CDCl_3$) 50 MHz: 198.8 (C_1); 159.4 (C_3); 155.6 ($C_{2'}$); 132.2 ($C_{1'}$); 128.3 ($C_{5'}$); 128.2 ($C_{3'}$, $C_{4'}$); 126,4 (C_2); 111.7 ($C_{6'}$); 54.9 (OCH_3); 39.3 (C_4); 34.5 (C_5); 33.9 (C_6) ; 25.8 (CH_3 in 4) ; 20.7 (CH_3 in 5').

-Anal. calc. for $C_{15}H_{18}O_2$: C = 78.26; H = 7.82;
found: C = 78.02; H = 7.75.

cis-3-oxo-8,9b-dimethyl-1,2,3,4,4a,9b-hexahydrodibenzofuran **2**

To a solution of 0.46 g (0.02 mole) of compound **5** in anhydrous $CHCl_3$, under argon, was added dropwise 0.40 g (0.02 mole) of $Si(CH_3)_3I$. The reaction was allowed to stir at 25 °C during three hours.Then, water (10 ml) was added and the mixture was extracted with CH_2Cl_2.The product **2** was isolated by column chromatography (silica gel / CH_2Cl_2) as a yellow oil (0.37 g; 85 % yield).

- ^1H NMR 200 MHz ($CDCl_3$): 6.90-6.80 (m, 2H); 6.55 (m, 1H); 4.6 (t, H_{4a}); 2.8 (dd J_{a-b} =14Hz; J_{a-c} = 3Hz) 1H; 2.6 (dd J_{a-b} = 14Hz; J_{a-c} = 3Hz) 1H); 2.2 (s, 3H, CH_3 at 8); 1.90-1.75 (m, 2H); 1.4 (s, 3H, CH_3 at 9b); 1.30-1.10 (m, 2H).
- ^{13}C NMR 50 MHz ($CDCl_3$): 209.4 (C_3); 156.2 (C_{5a}); 133.5 (C_{9a}); 130.4 (C_8); 129.0 (C_7); 123.4 (C_6); 108.9 (C_9); 87.2 (C_{4a}); 43.6 (C_{9b}); 41.06 (C_4);35.7 (C_2); 34.3 (C_1); 26.9 (C_{10}); 20.7 (C_{11}).
-Anal. calc. for $C_{14}H_{16}O_2$: C = 77.7; H = 7.4;
found: C = 77.6; H = 7.28.

4a,9b-dihydro-8,9b-dimethyl-3-(4H)-dibenzofuranone (Pummerer's ketone) **1**

To a solution of 0.216 g (0.01 mole) of compound **2** in anhydrous ethyl acetate was added 0.23 g (0.012 mole) of phenylselenium chloride at 25 °C until decoloration. After

hydolysis with 4 ml of water, the organic layer was removed; 5 ml of THF and 2 ml of hydrogen peroxide (35%) was added to the residue and the solution was stirred during 24 hours. The mixture was washed successively with 10 ml of sodium sulfite, 10 ml of sodium hydrogenocarbonate and 10 ml of water. The organic layer was evaporated and the residue chomatographed on silica gel with $CHCl_3$ as eluent to give colorless crystals (0.205 g, 95% yield). m.p. = 124 °C.

- ^1H NMR 200 MHz ($CDCl_3$) : 7.15-6.90 (m, 2H); 6.71 (d, J = 8.6Hz, 1H); 6.45 (d, J = 10.1Hz, 1H); 5.95 (d,J = 10.1 Hz, 1H); 4.70 (m, 1H, H_{4a}); 3.05 (dd, Jgem = 17.5Hz; J = 3 Hz, 1H); 2,8 (dd, Jgem = 17.5Hz; J = 3Hz, 1H); 2.35 (s, 3H, CH_3 at 8); 1.55 (s, 3H, CH_3 at 9b).

- ^{13}C NMR 50 MHz ($CDCl_3$): 195.1 (C_3); 156.6 (C_{5a}); 149.6 (C_1); 132.1 (C_{9a}); 131.06 (C_8); 129.6 (C_7); 125.7 (C_2); 123.5 (C_6); 110.0 (C_9); 86.4 (C_{4a}); 45.06 (C_{9b}); 37.5 (C_4); 21.0 and 22.0 (CH_3 at 9b and 8).

-Anal. calc. for $C_{14}H_{18}O_2$: C = 78.50; H = 6.54; found: C = 78.30; H = 6.45.

1'-tert.-butyldioxy-5'-methylcyclohexadien-2-one -1'-(1-methylcyclohex-2-ene) **6**

To a precooled solution of 2.02 g (0.01 mole) of compound **4a** in freshly distillated pyridine, was added dropwise 6.48 g (0.06 mole) of $Si(CH_3)_3$ Cl . The mixture was stirred for 12

hours at 60 °C, then the dilution with ether gives a white precipitate which is removed by filtration . The organic layer was evaporated and a colorless oil **4b** is obtained .

-Anal. calc. for C_{17} H_{26} O Si : C = 74.45; H = 9.48;

found: C = 74.39; H = 9.45.

The compound **4b** was treated in the same experimental conditions than **4c** and 1.20 g (60%) of compound **6** was isolated by column chromatography (silica gel / CH_2Cl_2) .

- Mass m/z (%) : 291 (29); 246 (6); 230 (25); 217 (20); 202 (100) .

-^{1}H NMR 200 MHz ($CDCl_3$) : 6.8 (dd, J = 9Hz, J = 3Hz, $H_{4'}$); 6.70 (t, J = 3Hz, H_6); 6.10 (d, J = 3Hz, $H_{3'}$); 5.8 (d,J = 12Hz, H_3); 5.5 (d, J = 12Hz, H_2); 2.35 (m) H_{4a}; 1.95 (m, H_5); 1.55 (m, H_2, H_{4b},H_{6b}); 1.36 (m, H_{6a}); 1.26 (d, J = 3Hz, CH_3); 1.25 (s, CH_3); 1.12 (s, CH_3); 1.10 (2s, $2CH_3$).

- ^{13}C NMR 50 MHz ($CDCl_3$) : 185 ($C_{2'}$); 149.0 ($C_{6'}$); 148.9 ($C_{4'}$); 142.9 ($C_{5'}$); 134.6 (C_2); 130.0 ($C_{3'}$); 126.9 (C_3); 79.1 ($C_{1'}$, C_9); 39.0 (C_1); 33.0 (C_4); 26.9 (3 CH_3); 26.2 (C_8); 25.2 (C_5); 23.1 (C_7); 19 .0 (C_6) .

-Anal. calc. for C_{18} H_{26} O_3 : C = 74.48; H = 8.88;

found: C = 74.22; H = 8.79 .

Acknowledgement:

Financial support from the DRED (réseau de recherche "Pharmacochimie") is greatly appreciated.

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(Received in USA 20 February, 1992)