

Rapid Communication

Synthesis of dimethyl ether of marsupsin

A Srikrishna* & M Mathews

Department of Organic Chemistry, Indian Institute of Science,
Bangalore 560 012, India

E-mail: ask@orgchem.iisc.ernet.in

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Total synthesis of the dimethyl ether of marsupsin, in seven steps starting from phloroglucinol, is described.

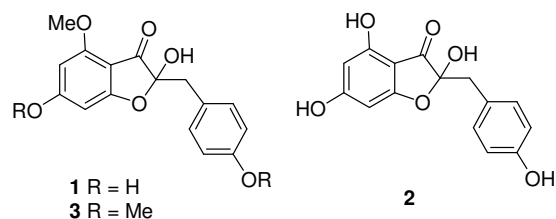
Keywords: Marsupsin, aurones, aurone hydrate, hemiacetal, aldol condensation

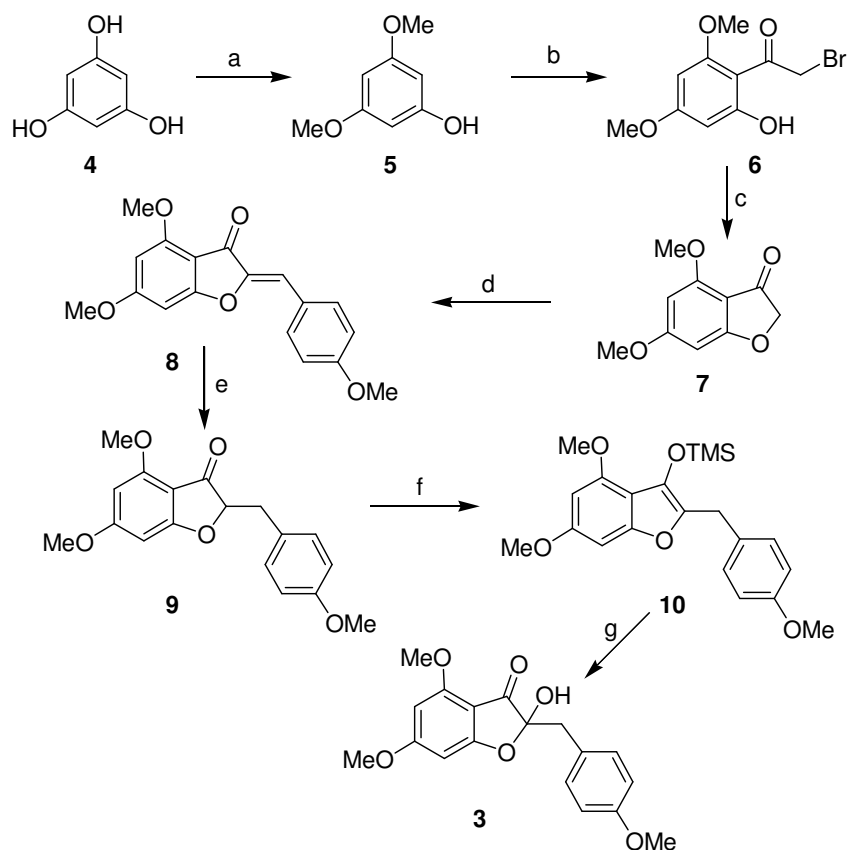
Pterocarpus marsupium Roxb, also known as Indian Kino tree or Bija Sar, is a large medicinal tree present in the forests of central and peninsular India. Extracts of the leaves, flowers and gum of *P. marsupium* have been used in the treatment of diarrhoea, toothache, fever, and urinary tract and skin infections, while extracts of bark and heartwood have been used in the treatment of diabetes in the Ayurvedic system of medicine. In 1982, two research groups simultaneously reported the isolation and structure elucidation of a hydrated aurone **1** from the heartwood of *P. marsupium* Roxb. While Subba Rao and Mathew¹ named it as carpusin, Schiff and co-workers² named it as marsupsin. The structure of marsupsin **1** was established on the basis of spectral studies and chemical transformations, and identified as the mono methyl ether of maesopsin **2**, an hydrated aurone isolated³ from the heartwood of *Maesopsis eminii*. Interestingly, very recently (2005), Hu *et al.* reported⁴ the isolation of marsupsin (claimed as new compound and named as carasinaurone) from the aerial parts of the chinese folk-medicinal plant *Caragana sinica*. The antihyperglycemic activity of marsupsin **1** has been well established⁵. Presence of an interesting carbon framework incorporating a hemiacetal and the associated biological properties made marsupsins attractive synthetic targets. Although synthesis of di- and trimethyl ethers of marsupsin were reported⁶, so far there is no report on the total synthesis of marsupsin **1** in the literature. Herein, we report the synthesis of the dimethyl ether of marsupsin **3**.

The synthetic sequence starting from phloroglucinol **4** is depicted in **Scheme I**. Controlled etherification of phloroglucinol **4** in refluxing methanol in the presence of Conc. sulfuric acid furnished the dimethyl ether **5** in 77% yield. Friedel-Craft's acylation of the phenol **5** with bromoacetyl bromide and anhydrous aluminum chloride in refluxing carbon disulfide generated the acetophenone **6** in 76% yield. Potassium carbonate mediated intramolecular etherification of the bromide **6** in methanol furnished the benzofuranone **7** in 72% yield. The benzofuranone **7** underwent a very facile aldol condensation with 4-methoxybenzaldehyde in the presence of potassium carbonate in methanol to furnish the aurone **8** in 74% yield.

As a number of reactions carried out to hydrate the enol ether **8**, both directly and indirectly, were unsuccessful due to the facile dehydration of aurone hydrates to aurones under acidic conditions, a longer route was chosen for the conversion of the aurone **8** into the dimethyl ether of marsupsin **3**. Hydrogenation of the olefin in **8** with 10% palladium over carbon as the catalyst in ethyl acetate furnished the dihydroaurone **9** in 86% yield⁶. Introduction of the hydroxy group at the α -position of **9** was carried out *via* the corresponding trimethylsilyl enol ether **10**. Thus, reaction of the benzofuranone **9** with lithium diisopropylamide (LDA) in THF followed by treatment of the resultant enolate with trimethylsilyl chloride furnished the TMS enol ether **10**. Epoxidation of the TMS enol ether **10** with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride in the presence of sodium bicarbonate, followed by cleavage of the TMS group with tetrabutylammonium fluoride (TBAF) furnished the dimethyl ether of marsupsin **3**, whose structure was established from its spectral data.

In conclusion, a convenient methodology starting from phloroglucinol has been developed for the synthesis of the dimethyl ether of marsupsin.





Scheme I — Reagents and conditions: (a) CH_3OH , H_2SO_4 (catalytic), reflux, 3 hr, 77%; (b) BrCH_2COBr , an. AlCl_3 , CS_2 , reflux, 4 hr, 76%; (c) K_2CO_3 , MeOH , RT, 4 hr, 72%; (d) K_2CO_3 , MeOH , 4-anisaldehyde, RT, 10 hr, 74%; (e) H_2 , 10%Pd-C, EtOAc, RT, 1 atm, 8 hr, 86% (f) LDA, THF; TMSCl, -70°C to RT, 3 hr; (g) i. MCPBA, CH_2Cl_2 , NaHCO_3 , 0°C , 2 hr; ii. TBAF, CH_2Cl_2 , RT, 4 hr, 48% (2 steps).

Experimental Section

4,6-Dimethoxybenzofuran-3(2H)-one 7: IR (neat): 3106, 1702, 1618, 1589, 1217, 1102, 826 cm^{-1} ; ^1H NMR ($\text{CDCl}_3 + \text{CCl}_4$): δ 6.10 (1 H, d, $J = 1.8$ Hz), 5.96 (1 H, d, $J = 1.8$ Hz), 4.55 (2 H, s), 3.92 (3 H, s), 3.86 (3 H, s); ^{13}C NMR ($\text{CDCl}_3 + \text{CCl}_4$): δ 194.3 (C), 177.0 (C), 169.5 (C), 158.8 (C), 104.8 (C), 92.9 (CH), 88.8 (CH), 75.3 (CH_2), 55.8 (CH_3), 55.7 (CH_3).

4,6-Dimethoxy-2-(4-methoxyphenylmethylene)-benzofuran-3(2H)-one 8: m.p. 167–69 $^\circ\text{C}$; IR (neat): 1696, 1615, 1600, 1248, 1093 cm^{-1} ; ^1H NMR ($\text{CDCl}_3 + \text{CCl}_4$): δ 7.45 (2 H, d, $J = 8.7$ Hz), 6.88 (2 H, d, $J = 8.7$ Hz), 6.65 (1 H, s), 6.29 (1 H, d, $J = 1.8$ Hz), 6.03 (1 H, d, $J = 1.8$ Hz), 3.91 (3 H, s), 3.86 (3 H, s), 3.79 (3 H, s); ^{13}C NMR ($\text{CDCl}_3 + \text{CCl}_4$): δ 180.1 (C), 168.7 (C), 168.4 (CH), 160.4 (C), 159.2 (C), 146.6 (C), 132.8 (2 C, CH), 125.3 (C), 114.2 (2 C, CH), 110.7 (C), 105.4 (C), 93.8 (CH), 89.0 (CH), 55.9 (CH_3), 55.8 (CH_3), 55.1 (CH_3).

4,6-Dimethoxy-2-(4-methoxyphenylmethyl)benzofuran-3(2H)-one 9: m.p. 122–24 $^\circ\text{C}$; IR (neat):

1700, 1618, 1594, 1512, 1250, 1215, 1155, 1105 cm^{-1} ; ^1H NMR ($\text{CDCl}_3 + \text{CCl}_4$): δ 7.17 (2 H, d, $J = 8.4$ Hz), 6.76 (2 H, d, $J = 8.4$ Hz), 6.06 (1 H, d, $J = 1.8$ Hz), 5.91 (1 H, d, $J = 1.8$ Hz), 4.66 (1 H, dd, $J = 8.4$ and 3.6 Hz), 3.86 (3 H, s), 3.82 (3 H, s), 3.75 (3 H, s), 3.24 (1 H, dd, $J = 14.7$ and 3.6 Hz), 2.89 (1 H, dd, $J = 14.7$ and 8.4 Hz); ^{13}C NMR ($\text{CDCl}_3 + \text{CCl}_4$): δ 195.5 (C), 175.6 (C), 169.7 (C), 158.9 (C), 158.4 (C), 130.4 (2 C, CH), 128.2 (C), 113.8 (2 C, CH), 104.7 (C), 92.9 (CH), 88.7 (CH), 86.8 (CH), 55.8 (CH_3), 55.7 (CH_3), 54.9 (CH_3), 36.7 (CH_2).

4,6-Dimethoxy-2-hydroxy-2-(4-methoxyphenylmethyl)benzofuran-3(2H)-one 3: IR (neat): 3388, 1699, 1614, 1512, 1464, 819 cm^{-1} ; ^1H NMR ($\text{CDCl}_3 + \text{CCl}_4$): δ 7.16 (2 H, d, $J = 8.7$ Hz), 6.72 (2 H, d, $J = 8.7$ Hz), 5.97 (1 H, d, $J = 1.8$ Hz), 5.79 (1 H, d, $J = 1.8$ Hz), 3.80 (3 H, s), 3.79 (3 H, s), 3.72 (3 H, s), 3.80–3.70 (1 H, brs), 3.14 and 3.05 (2 H, 2 $\times$ d, $J = 13.8$ Hz); ^{13}C NMR ($\text{CDCl}_3 + \text{CCl}_4$): δ 193.7 (C), 173.2 (C), 170.5 (C), 159.4 (C), 158.7 (C), 131.7 (2 C, CH), 125.1 (C), 113.7 (2 C, CH), 105.4 (C), 102.9

(C), 92.7 (CH), 88.7 (CH), 55.9 (CH₃), 55.8 (CH₃), 55.0 (CH₃), 40.8 (CH₂).

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