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

A Novel Route to 5,7-Dimethoxy-6-hydroxyflavone

Mauricio Osorio-olivares [a], Bruce K. Cassels [b], Silvia Sepúlveda-Boza [c] & Marcos Caroli Rezende [a]

[a] Facultad de Química y Biología, Universidad de Santiago de Chile, Av. B. O'Higgins 3363, Santiago

[b] Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago

[c] Facultad de Ciencias Médicas, Universidad de Santiago de Chile, Av. B. O'Higgins 3363, Santiago, Chile

Version of record first published: 17 Sep 2007.

To cite this article: Mauricio Osorio-olivares, Bruce K. Cassels, Silvia Sepúlveda-Boza & Marcos Caroli Rezende (1999): A Novel Route to 5,7-Dimethoxy-6-hydroxyflavone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:5, 815-819

To link to this article: http://dx.doi.org/10.1080/00397919908086038

SYNTHETIC COMMUNICATIONS, 29(5), 815-819 (1999)

A NOVEL ROUTE TO 5,7-DIMETHOXY-6-HYDROXYFLAVONE

Mauricio Osorio-Olivares [a], Bruce K. Cassels *[b], Silvia Sepúlveda-Boza •[c] and Marcos Caroli Rezende [a]

(a) Facultad de Química y Biología, Universidad de Santiago de Chile, Av. B. O'Higgins 3363, Santiago; (b) Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago; (c) Facultad de Ciencias Médicas, Universidad de Santiago de Chile, Av. B. O'Higgins 3363, Santiago, Chile.

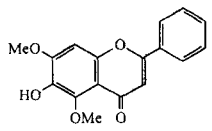
Abstract: A novel route to 5,7-dimethoxy-6-hydroxyflavone is described, involving the cyclization of an intermediate phosphorane as the key step.

7-O-Rhamnosylscutellarein (sorbarin) is the major flavonoid derivative present in the Brazilian toxic plant *Pseudocalymma elegans.*[1] The recent findings that oral administration of an ethanolic extract of this plant causes central nervous system stimulation, producing an anxiogenic-like effect in rats at low concentrations, and that the acute toxicity of *P. elegans* appears to be unrelated to these CNS actions,[2] might be associated with a possible action of sorbarin, presumably derhamnosylated in the gut. Reports on the interaction of flavonoids, in particular of scutellarein derivatives, with adenosine receptors [3] lend support to this hypothesis.

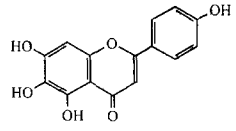
In order to be able to test the possible anxiogenic-like actions of scutellarein analogues, we became interested in developing general synthetic routes to such compounds. A promising approach seemed to us the method of Le Floc'h and

(*) - Authors to whom correspondence should be addressed

Lefeuvre [4] which employed as a key step the cyclization of a phosphorane prepared from an *ortho*-hydroxyacetophenone allowing divergent syntheses of variously B-ring-substituted flavones from a single precursor. We decided to test this route in the preparation of the known 5,7-dimethoxy-6-hydroxyflavone (**1**),[5] a target molecule related to scutellarein (**2**)

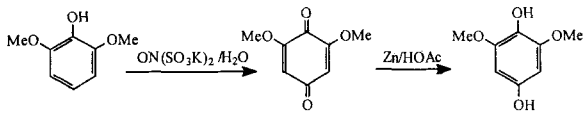


1



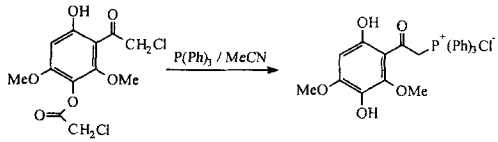
2

Our strategy required 2,6-dimethoxy-1,4-dihydroxybenzene (**3**) as starting material. This compound was readily prepared by oxidation of commercial 2,6-dimethoxyphenol with nitrosodisulphonate (Fremy salt),[6] followed by reduction of the resulting quinone with Zn/HOAc.[7]



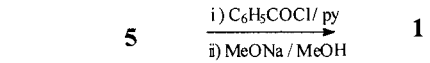
3

A Friedel-Crafts acylation of (**3**) with chloroacetyl chloride gave compound (**4**), which was converted into the triphenylphosphonium chloride (**5**) in 67 % yield.



4 **5**

Esterification of (**5**) with benzoyl chloride, followed by treatment of the resulting benzoate with base led to the target flavone (**1**), which was obtained in 77 % yield from the phosphonium salt (**5**).



In conclusion, the above route for the preparation of the scutellarein derivative 5,7-dimethoxy-6-hydroxyflavone (**1**) proved to be efficient and, in principle, versatile. The preparation of the intermediate phosphonium salt (**5**) turned out to be straightforward and could be achieved in reasonable yield. In addition, since the esterification of **5** may be carried out with a variety of aroyl chlorides, the above method represents a general route to a series of different 2-arylflavones with the scutellarein substitution pattern in ring A.

Experimental:

Melting points were obtained on a Kofler hot-stage apparatus and were not corrected. ^1H and ^{13}C nmr spectra were recorded on a Bruker AMX 300 MHz instrument, using tetramethylsilane as internal reference. Electron-impact mass spectra were obtained at low resolution with a Hewlett-Packard 5989 A spectrometer, and at high-resolution with a Kratos MS-50 apparatus.

The 2,6-dimethoxyphenol was purchased from Fluka, and triphenylphosphine and chloroacetyl chloride were from Aldrich. All other reagents used were of analytical quality.

2,6-Dimethoxyquinone was prepared in 81% yield by oxidation of 2,6-dimethoxyphenol, following a procedure described in the literature.[6] The product melted at 250-252 °C, lit.[6] m.p. 249-250 °C. Reduction of this compound with zinc in acetic acid gave 2,6-dimethoxy-1,4-dihydroxybenzene (**3**) in 62 % yield, m.p. 159-161 °C, lit.[7] m.p. 159-160 °C.

2-Chloroacetyl-4-chloroacetoxy-3,5-dimethoxyphenol (**4**) - To a stirred solution of 2,6-dimethoxy-1,4-dihydroxybenzene (2 g, 0.012 mol) in nitromethane (12 mL), kept under nitrogen, was added chloroacetyl chloride (7.6 mL, 0.09 mol) and then, in small portions, aluminum chloride (6.3 g, 0.05 mol). After the addition was complete the

reaction mixture was heated in an oil bath at 100 °C for 5 minutes. The mixture was then cooled in an ice bath, quenched with water (10 mL), and extracted with ethyl acetate (30 mL). The organic extract was then concentrated with a rotary evaporator, and the residue was taken up in methanol (30 mL) and stored overnight under nitrogen in a refrigerator. The 2-chloroacetyl-4-chloroacetoxy-3,5-dimethoxyphenol (**4**) which crystallized out was filtered, washed with a small volume of cold methanol and dried. The product weighed 1.55 g (40 % yield), m.p. 117-118 °C. HRMS: 322.0011 (M^+-1); calculated for $C_{12}H_{12}Cl_2O_6$, 323.0011. MS m/z (%) 322 (19), 273 (15), 246 (90), 197 (100), 182 (9), 77 (8) and 49 (12). ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H, 5-OCH_3); 3.98 (s, 3H, 3-OCH_3); 4.34 (s, 2 H, 4-$OCOCH_2Cl$); 4.80 (s, 2H, 2-$COCH_2Cl$); 6.33 (s, 1H, H-6); 12.90 (s, 1 H, 1-OH). ^{13}C NMR (DMSO-d_6) δ 41.45 (4-CH_2Cl); 51.70 (2-CH_2Cl); 57.34 (5-OCH_3); 62.86 (3-OCH_3); 97.00 (C-6); 109.37 (C-2); 125.41 (C-4); 153.43 (C-3); 157.55 (C-5); 160.61 (C-1); 166.65 (4-OC=O); 195.46 (2-C=O).

Triphenyl-[(2,4-dimethoxy-3,6-dihydroxy)benzoylmethyl phosphonium chloride (**5**) - A solution of 2-chloroacetyl-4-chloroacetoxy-3,5-dimethoxyphenol (**4**) (1 g, 3.1 mmol) and triphenylphosphine (1.62 g, 6.2 mmol) in acetonitrile (50 mL) was kept in a water bath at 55 °C for 6 h. The solvent was then removed in a rotary and diethyl ether (30 mL) was added. The insoluble phosphonium salt was filtered and redissolved in the smallest possible volume of chloroform at 50 °C. Addition of methanol precipitated, after cooling, the crude phosphonium chloride (**5**). Alternatively, purification of the product was achieved in better yield (1.06 g, 67 %) through column chromatography (silica gel, $CHCl_3$/ MeOH 10/1 as eluent), affording a product with m.p. 185-186 °C. Anal. found C, 65.65; H, 4.78 %; calcd. for $C_{28}H_{26}ClO_5P$ C, 66.08; H, 5.15 %. MS: m/z (%) 472 (5), 471 (10), 277 (100), 262 (54), 199 (24). ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3 H, 4-OCH_3) ; 3.84 (s, 3H, 2-OCH_3) ; 4.34 (s, 2 H, -CH_2 -); 6.27 (s, 1 H, H-5) ; 7.50-7.70 (m , 15 H, P(C_6H_5)$_3$). ^{13}C NMR (DMSO-d_6) δ 41.57 (-CH_2 P); 56.83 (4-OCH_3); 62.00 (2-OCH_3); 97.75 (C-5); 107.59 (C-1), 125.98, 126.71, 130.13, 130.22, 133.54, and 133.62 (Ar-C); 153.07 (C-2); 154.54 (C-4); 163.83 (C-3); 167.02 (C-6); 183.31 (C=O).

5,7-Dimethoxy-6-hydroxyflavone (**1**) - A mixture of triphenyl-[(2,4-dimethoxy-3,6-dihydroxy)benzoylmethyl phosphonium chloride (**5**) (1 g, 1.96 mmol), and benzoyl chloride (0.83 g, 0.70 mL, 5.89 mmol) in pyridine (12 mL) was heated with stirring under nitrogen for 24 h at 60 °C. The cooled solution was then diluted with water (20 mL), acidified with concentrated hydrochloric acid to pH 1-2, and extracted with ethyl acetate

(30 mL). The organic solvent was removed and the solid residue was boiled with petroleum ether and filtered. The insoluble crude benzoate was heated with stirring under nitrogen for 1 hour at 50 °C with 4 mL of a 1 M solution of sodium methoxide in methanol. The solvent was then evaporated and the residue was diluted with water, acidified with concentrated HCl and extracted with ethyl acetate. After removing the organic solvent, the solid residue was purified by column chromatography (silica gel 60, $CHCl_3$ / MeOH 10:1 as eluent) to give 0.45 g (77 % yield) of the flavone (**1**), m.p. 216 °C, lit.[5] m.p. 212-213 °C. ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3 H, 5-OCH_3); 3.95 (s, 3 H, 7-OCH_3); 6.79 (s, 1 H, H-3); 7.18 (s, 1 H, H-8); 7.58 (m, 3 H, H-2', 4', 6'); 8.06 (m, 2 H, H-3',5'); 9.03 (s, 1 H, 6-OH). ^{13}C NMR (DMSO-d_6) δ 57.16 (7-OCH_3); 62.12 (5-OCH_3); 97.64 (C-8); 108.17 (C-3); 112.91 (C-4a); 126.79 (C-5',3'); 129.93 (C-6',2'); 131.98 (C-1'); 132.25 (C-4'); 138.51 (C-2); 145.01 (C-5); 151.69 (C-8a); 154.31 (C-7); 160.81 (C-6); 176.75 (C-4). MS m/z (%) 298 (100); 297 (13); 283 (28); 280 (83); 252 (34); 251 (50); 181 (7); 166 (24); 153 (28); 102 (11).

Acknowledgements: We are grateful to Fundación Andes and DICYT (Universidad de Santiago de Chile), for supporting this work.

References:

1. H.C. Krebs, Naturforsch. 1987, 42b, 1361-1363.
2. R.A. Schutz, M.T.B. Schutz, M.E.M. Angelucci, E.M.A. Muñoz and C. Da Cunha, Brazil. J. Vet. Res. Animal Sci. 1996, 33, 182-188
3. (a) X.-d. Ji, N. Melman and K.A. Jacobson, J. Med. Chem. 1996, 39, 781-788; (b) Y. Karton, J.-I. Jiang, N. Melman, M.E. Olah, G.L. Stiles and K.A. Jacobson, J. Med. Chem. 1996, 39, 2293-2301.
4. (a) Y. Le Floc'h and M. Lefeuvre, Tetrahedron Lett. 1986, 27, 5503-5504; (b) Idem, ibid. 1986, 27, 2751-2752.
5. V.D.N. Sastri and T.R. Seshadri, Proc. Indian Acad. Sci. 1946, 23A, 273-275
6. H.J. Teuber and W. Rau, Chem. Ber. 1953, 86, 1036-1047.
7. L. Horner and S. Goewecke, Chem. Ber. 1961, 94, 1291-1298.

(Received in the USA 14 September 1998)