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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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**To cite this article:** Raju M. Walunj, Arun D. Natu, Madhusudan V. Paradkar & Supada R. Rojatkar (2016): An Efficient Total Synthesis of Naturally Occurring anti-TMV Compound Gramniphenol G, Synthetic Communications, DOI: 10.1080/00397911.2016.1207782

**To link to this article:** http://dx.doi.org/10.1080/00397911.2016.1207782

# An efficient total synthesis of naturally occurring anti-TMV compound Gramniphenol G

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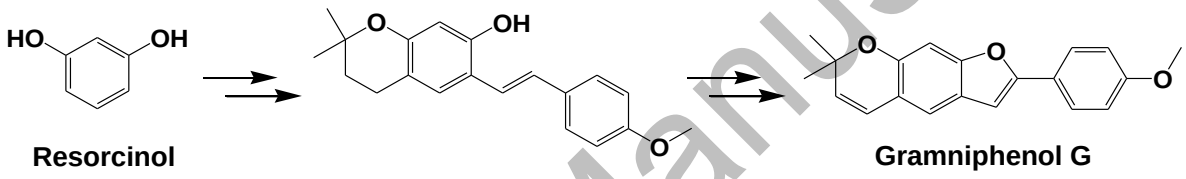
## GRAPHICAL ABSTRACT




## INTRODUCTION

Benzofurans and their analogues constitute a major group of naturally occurring compounds.[1] Many 2-arylbenzofurans exhibit broad range of biological activities including anticancer,[2] antiviral,[3] immunosuppressive,[4] antioxidative,[5] and anti-inflammatory.[6] Recently, several new compounds were isolated [7] from the plant *Arundina gramnifolia* belonging to orchidaceae family which is used in Chinese folkloric medicine as a detoxifying and diuretic agent, as well as for the treatment of arthritis and inflammation.[8] Two compounds namely Gramniphenol G **(1)** and Gramniphenol F **(2)** from this plant belong to a new class of compounds wherein a pyran ring is fused to a benzofuran ring system. The structures of Gramniphenol G **(1)** and Gramniphenol F **(2)**

as depicted below comprising of a pyranobenzofuran ring system were elucidated on the basis of NMR and Mass analysis.[7]

Prompted by the unique structures of **(1)** and **(2)** and their potential *in vitro* anti-tobacco mosaic virus activity (anti-TMV)[7] we decided to undertake total synthesis of **(1)**. Retrosynthetic analysis (Scheme 1) indicated that **(1)** can originate from resorcinol involving the oxidative cyclization of ortho-vinyl phenol as a key step.

## RESULTS AND DISCUSSION

On the basis of this retrosynthetic analysis, following synthetic route (Scheme 2) was first planned for the key intermediate **(10)** starting from resorcinol **(3)**.

We started the synthesis with Friedel-Crafts acylation of resorcinol **(3)** using 3,3-dimethyl acrylic acid **(4)** in presence of zinc chloride and phosphorous oxychloride as per the methods reported in literature.[9] After completion of reaction, usual work up gave crude compound **(5)** which on subsequent heterocyclization in alkaline medium provided a pink solid of 2,2-dimethyl-7-Hydroxy chroman-4-one **(6)** in 86% overall yield. Subsequent reduction of **(6)** using amalgamated zinc in dilute HCl provided phenol **(7)** in 85% yield.[10] Synthesis of **(10)** further involved condensation of phenol **(7)** and phenyl acetic acid **(8)** followed by Fries rearrangement. Condensation of phenol **(7)** with phenyl acetic acid **(8)** to provide **(9)** was accomplished by condensation of acyl chloride of phenyl acetic acid **(8)** and phenol **(7)** to provide an oil which on column chromatographic purification provided ester **(9)** in 95% yield. Subsequently, Fries rearrangement of ester

**(9)** using anhydrous aluminium chloride at 150 to 180°C provided required intermediate **(10)** in 50% yield.

With Fries product **(10)** in hand we decided to transform it first in to key intermediate **(12)**, followed by intermediate **(13)** which on dehydrogenation should provide the target molecule Gramniphenol G **(1) (**Scheme 3).

Reduction of carbonyl group in compound **(10)** using sodium borohydride in methanol as solvent at ambient temperature gave benzylic alcohol **(11)** in 95% yield. Dehydration of alcohol **(11)** in N,N-dimethylformamide as solvent at reflux temperature provided ortho-vinylphenol **(12)** in 85% yield. Now formation of compound **(13)** involved oxidative cyclization of ortho-vinylphenol **(12)** following the reported method.[11] This was achieved using iodine as an oxidative reagent and potassium carbonate as base in 40% yield. During the course of this reaction, formation of **(13)** involves an intermediate which was isolated and characterized as 2-aryl-3- iodo dihydropyranobenzofuran **(14)**.

Finally, synthesis of Gramniphenol G namely 2-(4'-methoxyphenyl)-7,7-dimethyl-7H-furo[3,2-g]chromene **(1)** was achieved by dehydrogenation of **(13)** with 2,3-dicyno-5-6-dichloro-p-benzoquinone (DDQ) in 1,4-dioxane as solvent and at reflux temperature in 95% yield.

Gramniphenol G **(1)** thus obtained was an orange solid having m. p. 179-181°C. However, as mentioned earlier Gramniphenol G was originally isolated from *Arundina*

*gramnifolia* (orchidaceae family) and was reported to be an orange gum [7] may be due to small impurities. Moreover, recently total synthesis of Gramniphenol G **(1)** obtained as a solid with m. p. 181-183℃ has been reported.[12]

The reported IR spectrum showed a peak at 3342 $cm^{-1}$. [7] There is no hydroxyl group in the synthetically prepared Gramniphenol G and does not contain this peak. Gramniphenol F isolated from the same plant contains a hydroxyl group and showed a band at 3344 $cm^{-1}$ in IR.[7] It is quite possible that isolated Gramniphenol G might be contaminated with Gramniphenol F. The mass analysis showed the molecular ion peak at [M+Na] = 329.1 suggesting the molecular formula $C_{20}H_{18}O_3$. Its $^1H$, $^{13}C$, and DEPT NMR spectral data (Table 1) exhibited signals for all 20 carbons and 18 protons, suggesting the presence of the following partial structures: a 2-arylbenzofuran system bearing seven aromatic protons, a gem-dimethylchromene moiety and a methoxy group. Observation of long-range correlations (Fig. 2) of H-1″ with C-4, C-6, and C-3", as well as those of H-2″ with C-3" and C-5 led to the proposal of an angularly fused gemdimethylchromene at C-5 and C-6. The location of the methoxy group at C-4′ was established on the basis of HMBC correlation (Fig. 2) of methoxy protons with C-4′ and further confirmed by NOESY correlation (Fig.3), the methoxy group showed the NOE correlation between methoxy group with H-3′ and H-5′.

The relationships of the olefinic protons H-1″/H-2″ and the aromatic proton signals H-2′ /H-3′ and H-5′ /H-6′ were well displayed in the $^1H$-$^1H$ COSY correlations (Fig, 2). Thus, the structure **(1)** was established as Gramniphenol G namely 2-(4'-methoxyphenyl)-7, 7-

dimethyl-7H-furo[3,2-g]chromene on the basis of the above discussed physical and 1D, 2-D NMR spectral data.

## CONCLUSION

In conclusion, we have described an efficient total synthesis of Gramniphenol G namely 2-(4'-methoxyphenyl)-7,7-dimethyl-7H-furo[3,2-g]chromene **(1)** starting with resorcinol and using easily accessible reagents.

## EXPERIMENTAL

All solvents were purified and dried by standard procedures prior to use. Thin-layer chromatography (TLC) was performed on Merck 60 F254 silica-gel plates and visualization was accomplished by ultraviolet (UV) irradiation or iodine. Melting points were determined using open capillary tubes and are uncorrected. Crude products were purified by column chromatography on 100- to 200-mesh silica gel or neutral alumina. The yields reported are the yields obtained after the column chromatographic separation. Mass spectra were recorded on a Perkin-Elmer instrument. Infrared (IR) spectra were recorded on a Perkin-Elmer BX 2 Fourier transform (FT)–IR instrument as a thin film or KBr pellets and are expressed in $cm^{-1}$. $^{1}H$ and $^{13}C$ NMR spectra are recorded on Varian Mercury spectrometer on 400 and 100MHz respectively using $CDCl_3$ as solvent. Chemical shifts are reported in δ ppm with reference to tetramethylsilane (TMS) as an internal standard.

**PREPARATION OF 1-(7-HYDROXY-2,2-DIMETHYLCHROMAN-6-YL)-2-(4'-METHOXYPHENYL) ETHANONE (10)**

A homogeneous mixture of **(9)** (10.0 g, 0.030 mol) and anhydrous $AlCl_3$ (7.3 g, 0.054 mol) was heated at 150-180°C for one hour. The course of the reaction was monitored by TLC. The reaction mixture was then cooled and decomposed over HCl (1:1) which provided an oily product. It was extracted with diethyl ether, washed with water and dried over anhydrous $Na_2SO_4$. Removal of solvent gave thick oil which was further purified by column chromatography using hexane- ethyl acetate gradient as eluent to provide **(10)** as an off white solid. Yield: 5.0 g (50%); mp: 134-136°C; IR (KBr): υ max; 2976, 1637, 1147 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ ppm 1.36 (s, 6H, $CH_3$), 1.81-1.85 (t, 2H, $CH_2$), 2.73-2.76 (t, 2H, $CH_2$), 3.80 (s, 3H, $OCH_3$), 4.15 (s, 2H, $CH_2$), 6.33 (s, 1H, aryl H), 6.88-6.91 (broad d, 2H, aryl H), 7.19-7.21 (d, *J* = 8.0 Hz, 2H, aryl H), 7.58 (s, 1H, aryl H), 12.35 (s, 1H, aryl OH); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ ppm 21.70 ($CH_2$), 26.90 ($CH_3$), 32.63 ($CH_2$), 43.70 ($CH_2$), 55.18 ($OCH_3$), 75.90 (C), 104.73, 112.76, 114.09, 126.47, 130.33, 131.84, 158.55 (aryl C-OH), 161.38, 163.30, (aryl C and CH), 201.97 (carbonyl); Mass: [M+1] = 327.1; Anal. calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79; O, 19.61. Found: C, 73.61; H, 6.87; O, 19.52.

**PREPARATION OF 2-(4'-METHOXYPHENYL)-7,7-DIMETHYL-6,7-DIHYDRO-5H-FURO[3,2-G] CHROMENE (13)**

To the solution of stilbene **(12)** (5.0 g, 0.0161 mol) in THF (250 ml) was added anhydrous $K_2CO_3$ (13.3 g, 0.096 mol), iodine (24.5 g, 0.096 mol) and the contents were stirred at ambient temperature until **(12)** was consumed. The course of reaction was

monitored by TLC. The mixture was poured into saturated aqueous $NaHCO_3$ and treated with saturated aqueous $NaHSO_3$ to consume the excess iodine. The mixture was extracted with dichloromethane, washed with water and the organic layer was dried over anhydrous sodium sulphate. Removal of solvent provided a residue which on column chromatography using hexane-ethyl acetate gradient as eluent provided **(13)** as an off white solid.

**Compound (13)** ; Yield: 2.0 g (40%); mp: 201-202°C; IR (KBr): υ max 2972, 2945, 1147 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ ppm 1.38 (s, 6H, $CH_3$), 1.84-1.87 (t, 2H, $CH_2$), 2.88-2.92 (t, 2H, $CH_2$), 3.86 (s, 3H, $OCH_3$), 6.75 (s, 1H, aryl H), 6.94-6.95 (d, *J* = 4.0 Hz, 2H, aryl H), 6.97 (s, 1H, aryl H), 7.20 (s, 1H, aryl H), 7.74-7.76 (d, *J* = 8.0 Hz, 2H, aryl H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ ppm 22.76 ($CH_2$), 26.87 ($CH_3$), 33.02 ($CH_2$), 55.32 ($OCH_3$), 74.30 (C), 99.06, 99.19, 114.13, 117.05, 119.84, 122.54, 123.76, 125.92, 151.82, 154.47, 155.01, 159.49 (aryl C and CH); Mass: [M+1] = 309.1; Anal. calcd. for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54; O, 15.57. Found: C, 77.85; H, 6.70; O, 15.45.

## PREPARATION OF GRAMNIPHENOL G (1)

Chroman **(13)** (0.5 g, 0.0016 mol) was dissolved in 1, 4-dioxane (50 ml). To the resulting solution, DDQ (0.40 g, 0.0017 mol) was added and the mixture was refluxed for 6 hrs until **(13)** was completely consumed as evident from TLC. Solvent was evaporated under vacuum and the yellow residue obtained was purified by column chromatography using hexane-ethyl acetate gradient as eluent to provide an orange solid which was caracterized as Gramniphenol G **(1)**.

**Gramniphenol G (1)**; Yield: 0.47 g (94%); mp: 179-181°C (lit.[12] mp: 181-183°C); IR (KBr): υ max; 2978, 2933, 1587, 1462, 1126, 1033 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ ppm 1.47 (s, 6H, $CH_3$), 3.83 (s, 3H, $OCH_3$), 5.64 (d, *J* = 10.0 Hz, 1H, =CH), 6.43 (d, *J* = 10.0 Hz,1H, =CH), 6.76 (s, 1H, aryl H), 6.96 (broad d, 2H, aryl H), 6.97 (s, 1H, aryl H) 7.12 (s, 1H, aryl H), 7.74 (broad d, 2H, aryl H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ ppm 27.76 ($CH_3$), 55.32 ($OCH_3$), 76.20 (C), 99.46, 114.18, 117.27, 118.12, 122.83, 123.53, 125.92, 129.87, 151.04, 155.31, 159.58 (aryl C and CH); Mass: [M+23] = 329.1; Anal. calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92; O, 15.67. Found: C, 78.21; H, 5.80; O, 15.99. (spectral data are in accordance with Reference 7).


## ACKNOWLEDGMENTS

Authors are grateful to Principal Dr. S. G. Gupta, Abasaheb Garware College and Dr. R. C. Chikate, Head, Department of chemistry for providing the necessary facilities, Dr. D. G. Naik, Agharkar Research Institute, Pune, for providing spectral analysis and valuable discussions.


## SUPPORTING INFORMATION

Full experimental details and $^1H$ and $^{13}C$ NMR spectra for all the intemediates and final compound can be accessed via supplementary information section of this article's webpage.

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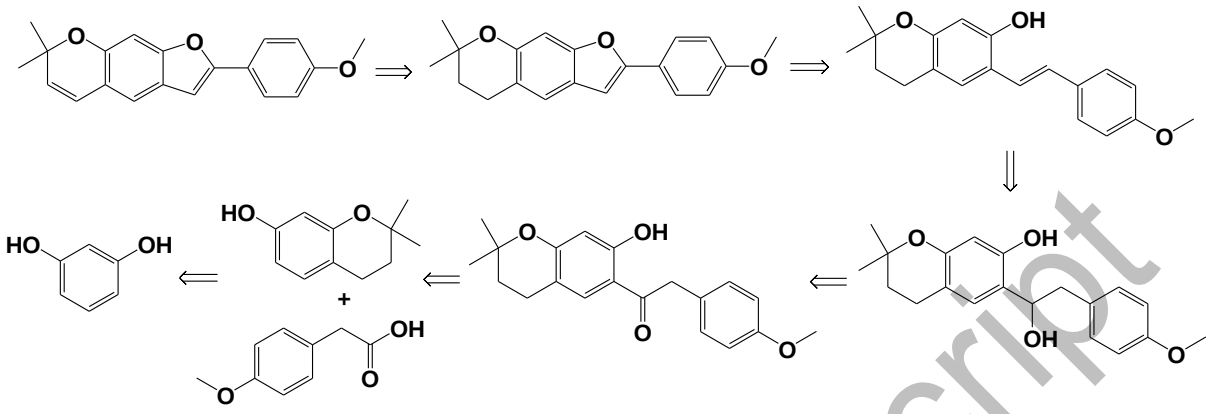
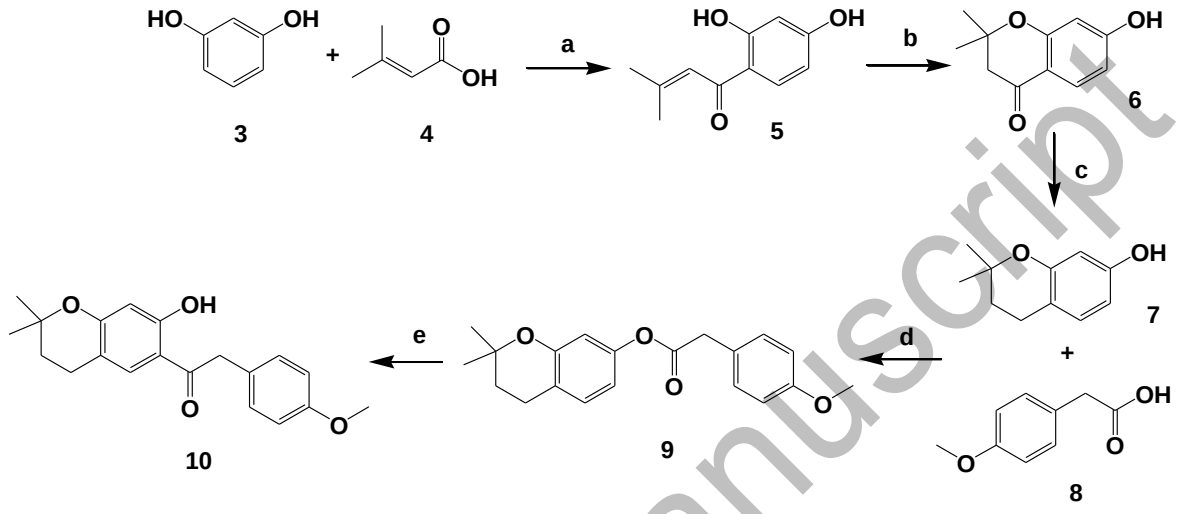
**Table 1.** $^{1}H$, $^{13}C$ NMR, and HMBC Correlations Data of Compound 1(δ in ppm, in $CDCl_3$)

| **Position** | **$\delta_H$ (*J* in Hz)** | **$\delta_C$** | **HMBC** |
|---|---|---|---|
| 2 | - | 155.31 (s) | |
| 3 | 6.76 (s) | 99.46 (d) | 122.83, 155.31 |
| 4 | 7.12 (s) | 117.27 (d) | 99.46, 122.83, 151.04,155.31 |
| 5 | - | 118.12 (s) | - |
| 6 | - | 151.04 (s) | - |
| 7 | 6.97 (s) | 99.46 (d) | 151.04 |
| 3a | - | 122.83 (s) | - |
| 7a | - | 155.31 (s) | - |
| 1' | - | 123.53 (s) | - |
| 2', 6' | 7.74 (br d) | 125.92 (d) | 125.92, 155.31, 159.58 |
| 3', 5' | 6.96 (br d) | 114.18 (d) | 114.18, 123.53, 159.58 |
| 4' | - | 159.58 (s) | - |
| 1" | 6.43 (d, *J*= 10Hz) | 122.84 (d) | 76.20, 117,27, 151.04 |
| 2" | 5.64 (d, *J*= 10Hz) | 129.87 (d) | 76.20, 118.12 |
| 3" | - | 76.20 (s) | - |
| 4", 5" | 1.47 (s) | 27.76 (q) | 27.76, 76.20, 129.87 |
| -OMe | 3.83 (s) | 55.33 (q) | 159.58 |

**Scheme 1.** Retrosynthetic analysis of Gramniphenol G



**Scheme 2.** Reagents and conditions: (a) $ZnCl_2$, $POCl_3$, ambient temperature (b) 2 % aq. NaOH, 5-10°C (c) Zn, conc. HCl, $HgCl_2$, water (d) i. Thionyl chloride, reflux temperature ii. Distillation, 60-70°C (e) Anhydrous $AlCl_3$, 150-180°C



**Scheme 3.** Reagents and conditions: (a) $NaBH_4$, methanol, ambient temperature (b) N,N-dimethylformamide, 150°C (c) Iodine, $K_2CO_3$, THF, ambient temperature (d) DDQ, dioxane.

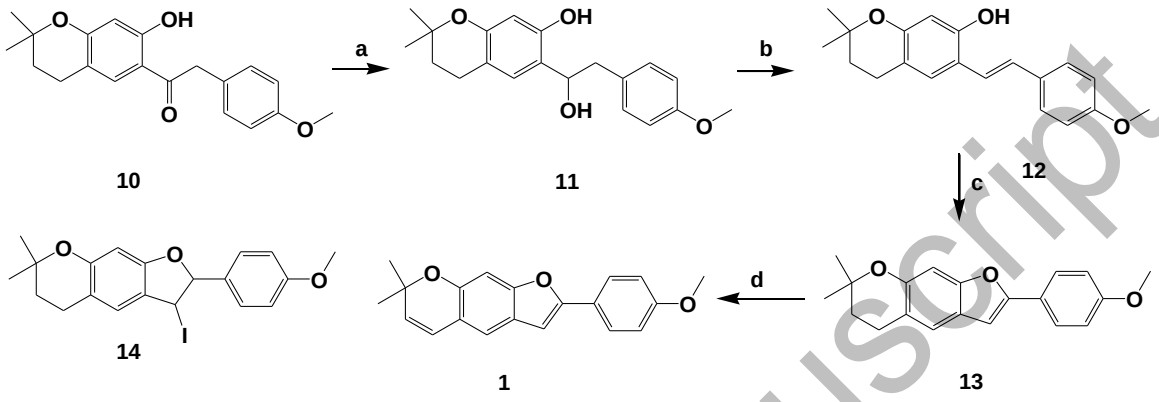
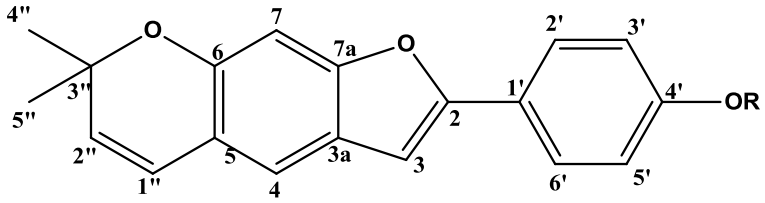


**Figure1.** Structures of Gramniphenol G **(1)** and Gramniphenol F **(2)**




**1, R = Me**

**2, R = H**

**Figure 2.** $^{1}H$-$^{1}H$ COSY (▬) and $^{1}H$-$^{13}C$ HMBC (⟶) correlations of compound **(1)**

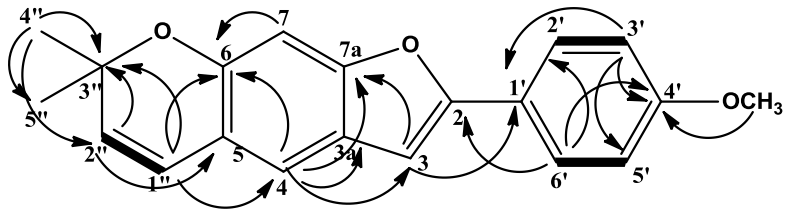


**Figure 3.** NOESY (⟷) correlations of compound **(1)**