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Synthesis of New β-Hydroxychalcones: Pongapinone A and Ponganone II

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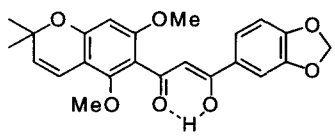
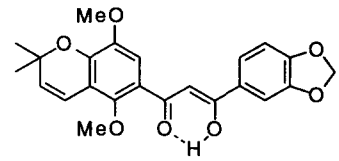
Abstract: Practical synthesis of new β-hydroxychalcones, pongapinone A (**1**) and ponganone II (**2**), is described. © 1997 Elsevier Science Ltd.

Flavonoid compounds such as flavones, flavanones, chalcones, β-diketones and β-hydroxychalcones are widely distributed in the plant kingdom.[1] Of this family, flavones are the most abundant members. Although a great amount of research has been devoted to the synthesis of the flavones,[2] to date, no naturally occurring pyrano-β-hydroxychalcones have been synthesized.[3] In 1991 and 1992, researchers in Gifu[4] and Osaka[5] independently reported the isolation and characterization of structurally related pyrano-β-hydroxychalcones, which were named pongapinone A (**1**) and ponganone II (**2**). Interestingly, pongapinone A inhibits the production of interleukin-1 *in vitro*.[6, 7] The combination of biological activity and the highly substituted aromatic rings of **1** and **2** prompted us to develop efficient synthetic routes in a regioselective manner, which could provide a flexible approach to a number of other members of this family.



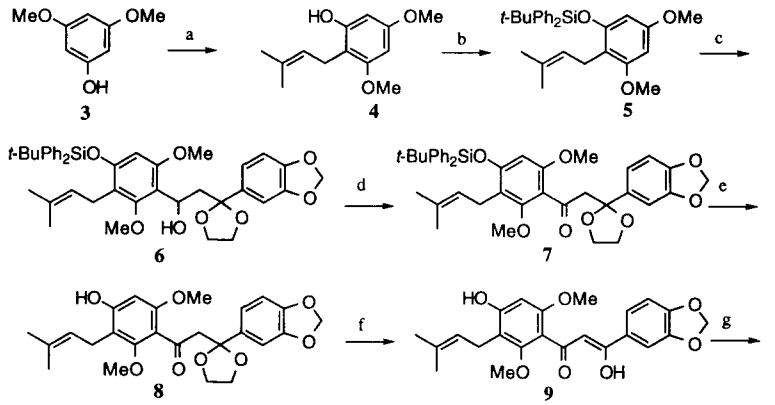
pongapinone A (**1**)



ponganone II (**2**)

The synthesis of pongapinone A (**1**) is summarized in Scheme 1. Commercially available phloroglucinol dimethyl ether (**3**), which has the required trioxygenated substitutions, was used as the starting material. Regioselective introduction of the prenyl and alcoholic moieties on **3** was accomplished through the following three-step sequence; phenolic C-alkylation of **3** with prenyl bromide in the presence of NaH gave **4**, which after phenolic hydroxy group protection with *t*-$BuPh_2Si$ group, was lithiated with 1.1 equiv. of BuLi (THF, 0 ℃, 30 min) and condensed with aldehyde **1** **5**[8] to afford, with complete regioselectivity, the alcohol **6** (61%).[9] We next examined several methods to oxidize **6**. Although both the Swern and the Collins oxidations failed, success was achieved with either Pr_4NRuO_4/4-methylmorpholine *N*-oxide (NMO)[10] or Dess-Martin periodinane.[11] The final steps of the pongapinone A synthesis were accomplished by deprotection of the silyl group and hydrolysis of the ketal in **7**, followed by oxidative cyclization of the prenyl group by DDQ. These steps afforded pongapinone A (**1**) in 68% yield (3 steps). The synthetic pongapinone A thus obtained proved to be identical with the natural material *via* all spectroscopic and chromatographic comparisons.[5, 12, 13]

Scheme 1[a]

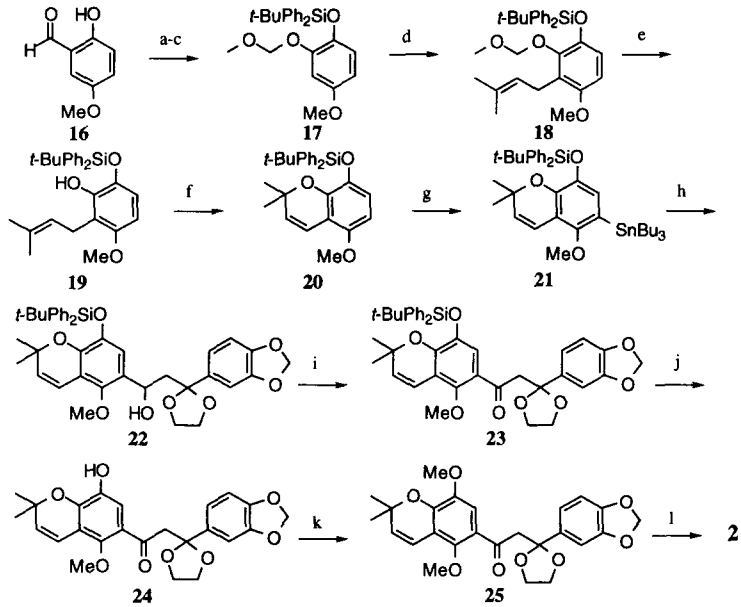


[a](a) prenyl bromide (1.1 equiv.), NaH (1.2 equiv.), THF, 25 ℃, 30%. (b) *t*-$BuPh_2SiCl$, imidazole, DMF, 25 ℃, 80%. (c) BuLi (1.1 equiv.), THF, -78 ~ 0 ℃, then **15** (1.1 equiv.), -78 ℃, 61%. (d) Pr_4NRuO_4, NMO, MS(4Å), CH_2Cl_2, 25 ℃, 76%; the Dess-Martin reagent, CH_2Cl_2, 25 ℃, 60%. (e) Bu_4NF, THF, 25 ℃, 95%. (f) conc. HCl, THF, 25 ℃, 96%. (g) DDQ, benzene, reflux, 75%.

Our studies on the synthesis of new β-hydroxychalcones were extended to the synthesis of ponganone II (**2**), which is illustrated in Scheme 2. After protection of the phenolic functionality of 2-hydroxy-5-methoxybenzaldehyde (**16**) with *t*-$BuPh_2Si$ group, the resulting silylated derivative underwent the Baeyer Villiger oxidation, with *m*-CPBA, to afford the required phenolic product, which was then converted to the methoxymethyl (MOM) ether **17** (51%, 3 steps). Subsequent lithiation of **17** at 0 ℃ in THF with 1.2 equiv. of *t*-BuLi followed by the addition of prenyl bromide provided **18** (75%). Acidic treatment of **18** cleaved the MOM protecting group, without affecting *t*-$BuPh_2Si$ group, to afford the phenolic product **19** (84%), which was then oxidatively cyclized by treatment with DDQ (benzene, reflux) to give the chromene **20** (63%). Unfortunately, the ortho-metallation of **20** with alkyllithiums failed under a variety of reaction conditions. Successful ortho-metallation was accomplished with BuLi/*t*-BuOK (Lochmann-Schlosser base)[14] according to Suzuki's procedure;[15] however, as the reaction of metallated **20** with aldehyde **15** failed, due to the inherent low reactivity of metallated **20**, an indirect sequence was employed. Metallation of **20** with BuLi/*t*-BuOK in THF followed by trapping with Bu_3SnOTf led to the stannyl chromene **21** in modest yield (22%). A lithium-tin transmetallation with BuLi at -78 ℃ followed by immediate condensation with **15** efficiently afforded the alcohol **22** (70%). Oxidation of **22** with Pr_4NRuO_4/NMO led to the corresponding ketone **23** (83%). After deprotection of *t*-$BuPh_2Si$ group in **23**, the resultant alcohol **24** was methylated with CH_3I/K_2CO_3 to give **25**, which was then exposed to catalytic conc. HCl in THF to provide **2** (91%, 3 steps). Synthetic **2** proved to be identical with the natural product on comparison of spectroscopic data.[4),13)]

In conclusion, we have achieved the first total synthesis of pongapinone A and ponganone II. With this practical synthesis of pyrano-β-hydroxychalcones now in hand, continued investigations into the biological properties of this class of compounds will be aided.

Scheme 2[a]

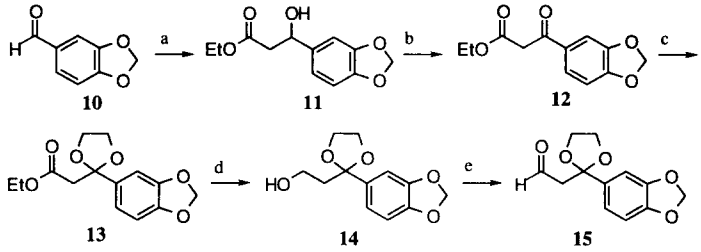


[a](a) *t*-$BuPh_2SiCl$, imidazole, THF, 25 °C, 90%. (b) *m*-CPBA, EtOAc, 25 °C, 93%. (c) MOMCl, NaH, THF, 25 °C, 61%. (d) *t*-BuLi (1.2 equiv.), THF, 0 °C; then prenyl bromide (1.2 equiv.), 25 °C, 75%. (e) conc. HCl, MeOH, 0 °C, 84%. (f) DDQ, benzene, reflux, 63%. (g) *t*-BuOK/BuLi (2.0 equiv.), THF, -78 °C; then Bu_3SnOTf (2.2 equiv.), -78 °C, 22%. (h) BuLi (1.1 equiv.), THF, -78 °C; then **15** (2.0 equiv.), -78 °C, 70%. (i) Pr_4NRuO_4, NMO, MS(4Å), CH_2Cl_2, 25 °C, 83%. (j) Bu_4NF, THF, 25 °C, 97%. (k) MeI, K_2CO_3, acetone, reflux, 98%. (l) conc. HCl, THF, 25 °C, 96%.

References and Notes

1. For reviews on a wide variety of biological activities, see: (a) Anton, R. *Prog. Clin. Biol. Res.* **1988**, *280*, 423. (b) Tripathi, V. D.; Rastogi, R. P. *J. Sci. Ind. Res.* **1981**, *40*, 116.
2. Ares, J. J.; Outt, P. E.; Kakodkar, S. V.; Buss, R. C.; Geiger, J. C. *J. Org. Chem.* **1993**, *58*, 7903 and references cited therein.
3. Pyrano-β-hydroxychalcones prepared through a Baker-Venkataraman reaction are often used as intermediates for the synthesis of flavones. See: (a) Banerji, A.; Devanand, L. L.; Prabhu, B. R. *Phytochemistry* **1988**, *27*, 3637. (b) Subrahmanyam, K.; Rao, J. M.; Rao, K. V. J. *Indian J. Chem., Sect B* **1977**, *15B*, 105. (c) Banerji, A.; Goomer, N. C. *Synth.Commun.* **1985**, *27*, 3637.
4. Tanaka, T.; Iimuna, M.; Yuki, K.; Fujii, Y.; Mizuno, M. *Chem. Pharm. Bull.* **1991**, *39*, 1473.
5. Kitagawa, I.; Zhang, R.-S.; Hori, K.; Thuchiya, K.; Shibuya, H. *Chem. Pharm. Bull.* **1992**, *40*, 2041.
6. There is compelling evidence that interleukin-1 (IL-1) plays a pivotal role in the pathogenesis of rheumatoid arthritis (RA), and recent studies have demonstrated that inhibition of IL-1 with IL-1 receptor antagonist resulted in significant clinical improvement of patients with active RA. For pertinent reviews, see: (a) Arend, W. P.; Dayer, J.-M. *Arthritis & Rheumatism* **1995**, *38*, 151. (b) Joosten, L. A. B.; Helsen, M. M. A.; Loo, F. A. J.; Berg, W. B. *Arthritis & Rheumatism* **1996**, *39*, 797.
7. IC_{50} = 6.1 μM. For detail, see: Kitagawa, I.; Shibuya, H.; Kimura, Y. Japan Patent 5170764, July 9, 1993.

8. The aldehyde **15** was synthesized from piperonal (**10**) as shown in the following scheme.



Reagents and reaction conditions: (a) CH_2=C(OLi)OEt, THF, -78 ℃, 86%. (b) PCC, CH_2Cl_2, 25 ℃, 60 %. (c) $HO(CH_2)_2OH$, *p*-TsOH, benzene, reflux, 43%. (d) $LiAlH_4$, Et_2O, 25 ℃, 73%. (e) PCC, CH_2Cl_2, 25 ℃, 58%.

9. (a) Trost, B. M.; Saulnier, M. G. *Tetrahedron Lett.* **1985**, *26*, 123. (b) Landi, J. J.; Ramig, K. *Synth. Commun.* **1991**, *21*, 167.
10. Griffith, W. W. P.; Ley, S. V. *Aldrichimica* **1990**, *23*, 13.
11. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
12. We are grateful to Professor Kitagawa, I., Osaka University, for supplying a natural sample of pongapinone A.
13. Selected physical data for: **7** ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.10 (s, 9 H), 1.68 (s, 3 H), 1.76 (s, 3 H), 2.99 (s, 3 H), 3.39-3.45 (m, 2 H), 3.41 (s, 2 H), 3.61 (s, 3 H), 3.71-3.73 (m, 2 H), 3.83-3.86 (m, 2 H), 5.20-5.31 (m, 1 H), 5.70 (s, 1 H), 5.89 (s, 2 H), 6.68 (dd, J = 0.9 and 7.6 Hz, 1 H), 6.93-6.96 (m, 2 H), 7.35-7.43 (m, 6 H), 7.68-7.72 (m, 4 H); EIMS 694 (3%, M^+); **9** ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.77 (s, 3 H), 1.83 (s, 3 H), 3.38 (d, J = 7.2 Hz, 2 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 5.22 (m, 1 H), 6.03 (s, 2 H), 6.27 (s, 1 H), 6.36 (s, 1 H), 6.85 (d, J = 7.9 Hz, 1 H), 7.40 (d, J = 1.6 Hz, 1 H), 7.52 (dd, J = 1.6 and 7.9 Hz, 1 H), 16.41 (bs, 1 H); EIMS 415 (15%, M^+); **1** ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44 (s, 6 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 5.53 (d, J = 10.1 Hz, 1 H), 6.03 (s, 2 H), 6.23 (s, 1 H), 6.36 (s, 1 H), 6.53 (dd, J = 0.6 and 10.1 Hz, 1 H), 6.85 (d, J = 8.2 Hz, 1 H), 7.40 (d, J = 1.7 Hz, 1 H), 7.52 (dd, J = 1.7 and 8.2 Hz, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 27.92 (2C), 56.01, 63.05, 76.89, 96.20, 99.90, 101.72, 107.18, 108.07, 108.14, 113.91, 116.56, 122.79, 127.68, 129.75, 148.08, 151.12, 155.19, 156.30, 158.37, 183.00, 185.50; EIMS 410 (31%, M^+); **2 2** ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.04 (s, 3 H), 1.05 (s, 3 H), 1.08 (s, 9 H), 1.90 (dd, J = 9.2 and 15.0 Hz, 1 H), 1.99 (dd, J = 2.3 and 15.0 Hz, 1 H), 3.57 (s, 3 H), 3.68-3.89 (m, 2 H), 4.01-4.15 (m, 3 H), 5.05 (m, 1 H), 5.44 (d, J = 10.0 Hz, 1 H), 5.95 (s, 2 H), 6.41 (d, J = 10.0 Hz, 1 H), 6.70 (s, 1 H), 6.76-6.96 (m, 3 H), 7.24-7.32 (m, 6 H), 7.68-7.74 (m, 4 H); EIMS 680 (11%, M^+); **2** ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.51 (s, 6 H), 3.75 (s, 3 H), 3.90 (s, 3 H), 5.71 (d, J = 9.9 Hz, 1 H), 6.05 (s, 2 H), 6.62 (d, J = 9.9 Hz, 1 H), 6.88 (d, J = 8.2 Hz, 1 H), 7.16 (s, 1 H), 7.37 (s, 1 H), 7.44 (d, J = 1.8 Hz, 1 H), 7.57 (dd, J = 1.8 and 8.2 Hz, 1 H), 17.02 (bs, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 27.85 (2C), 56.30, 62.49, 77.17, 96.17, 101.68, 107.04, 108.10, 112.04, 115.77, 116.63, 120.23, 122.62, 130.07, 130.62, 145.12, 146.39, 148.06, 150.18, 151.06, 183.02, 184.37; EIMS 410 (31%, M^+).
14. Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627.
15. Matsumoto, T.; Kakigi, H.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 4337.

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