Novel Synthesis of Flavonoids of *Scutellaria baicalensis* GEORGI

Wen-Hsin HUANG, Pei-Yu CHIEN, Ching-Huey YANG, and An-Rong LEE*

School of Pharmacy, National Defense Medical Center; Taipei, Taiwan.
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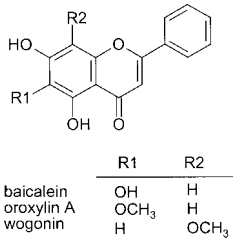
A concise and efficient total synthesis of the flavonoids baicalein, oroxylin A and wogonin was described. Intramolecular oxidative cyclization followed by demethylation of chalcone 1, readily prepared from trimethoxyphenol, afforded, depending upon the controlled conditions, baicalein or oroxylin A in excellent yields. Demethylation of 1 yielded 3, which, by oxidation with I_2/dimethyl sulfoxide (DMSO), was readily converted to oroxylin A and wogonin after column chromatography.

Key words baicalein; oroxylin A; wogonin

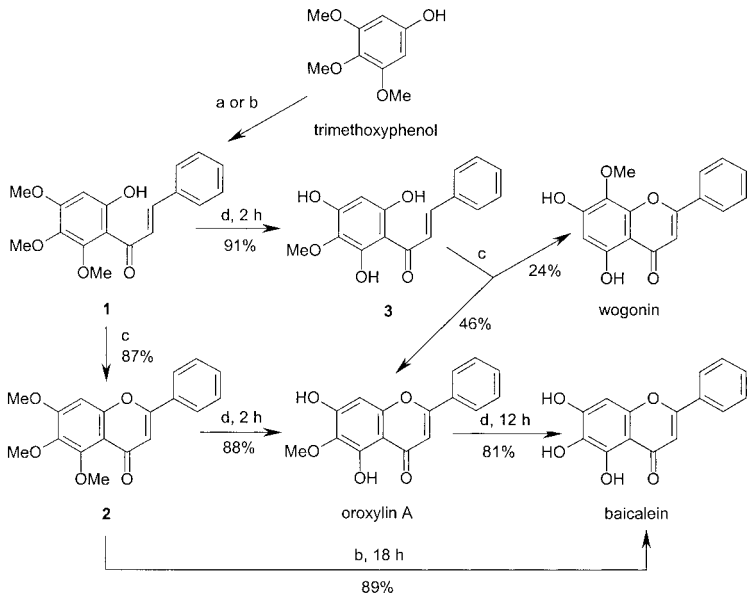
Baicalein, oroxylin A and wogonin are the three major flavonoids of *Scutellaria baicalensis* GEORGI, a traditional Chinese herb used since the ancient time, characterized by possessing a very broad spectrum of biological activities, notably anti-oxidant.[1] In literature, there have been no appropriate approaches available for a facile synthesis of those structurally similar flavonoids. Our interests in their unique pharmacological properties prompted us to pursue a pertinent route toward the very efficient preparation of such highly prized targets.

In general, procedures for laboratory synthesis of flavonoids are still based today on the approaches originally developed by Robinson[2] or exerted by the Baker–Venkataraman rearrangement,[3,4] synthesis *via* chalcones,[5] and synthesis *via* an intramolecular Wittig reaction.[6] At the outset, we followed the reported methods specifically for the synthesis of baicalein,[7,8] oroxylin A[9] and wogonin.[10] However, we found that they all suffered either from involving a number of steps giving too low overall yields or from encountering considerable challenges due to irreproducible workout. Attempts to synthesize baicalein from trimethoxyphenol by either the modified conventional Baker–Venkataraman approach[11] proved to be impractical (below 10% yield) or the Wittig strategy[6] completely failed. Therefore, our strategy for synthesis of baicalein turned to employing chalcone **1** as the starting material while the demethylation was performed at the last stage.

Our approaches (Chart 1) for construction of baicalein, oroxylin A and wogonin relied on the preparation of flavone



	R1	R2
baicalein	OH	H
oroxylin A	OCH_3	H
wogonin	H	OCH_3



(a) cinnamoyl chloride, BF_3-Et_2O, 15 min, 90 %; (b) acetic acid, BF_3-Et_2O, 15 min; benzaldehyde, EtOH, KOH; 66%; (c) I_2, DMSO, 2 h; (d) 47% HBr/HOAc.

Chart 1

* To whom correspondence should be addressed. e-mail: lar@ndmctsgh.edu.tw

2 and chalcone **3** as penultimate targets derived from chalcone **1**, readily prepared by treatment of easily accessible trimethoxyphenol with excessive acetic acid in the presence of BF_3–Et_2O,[12] followed by a Claisen-Schmidt condensation with equimolar benzaldehyde,[3,4] best catalyzed by KOH, in 66% overall yield. Alternatively, a better yield (90%) was achieved by direct acylation of trimethoxyphenol with equimolar cinnamoyl chloride, also in the presence of BF_3–Et_2O.

One of the most common methods in preparation for flavonoids such as **2** involves an intramolecular oxidative cyclization of chalcone,[5] *i.e.* **1**. However, formation of the prerequisite flavone **2** triggered by SeO_2/EtOH[7,13] or $Pd(OAc)_2$/AcCN[14] consistently led to extremely low yields (below 10%). This difficulty of cyclization, the phenyl ring bearing polyphenols (more than 3 OH's) later turned out to be the culprit, made us turn to non-metal oxidants. Among them, I_2/dimethyl sulfoxide (DMSO)[15] proved to be the most promising and the reaction proceeded smoothly and ended up with **2** in a much superior yield (87%). Surprisingly, attempted demethylation of **2** to obtain baicalein in a solution of 47% HBr/AcOH (1 : 2) at reflux for 2 h gave, after isolation, an unexpected yet desired product oroxylin A (88%) exclusively, validated by fruitless acetonidation in addition to spectroscopy.[16] Further reaction under the same condition over 12 h yielded baicalein (81%). Alternatively, a straight 18-h hydrolysis of **2** proceeded in the same methodology also afforded baicalein in excellent yield (89%).

In a similar fashion, demethylation of **1** in a solution of 47% HBr/HOAc (1 : 2) at reflux for 2 h gave **3** (91%) which was susceptible to oxidation with I_2/DMSO to procure a mixture of oroxylin A (46%) and wogonin (24%), readily separated by flash chromatography.

In conclusion, we have successfully attained an extremely efficient route for the preparation of baicalein, oroxylin A, and wogonin. To our best knowledge, for total synthesis of these three pharmacologically diversified flavonoids, our approach is the only practical path featuring in beginning with a common starting material, using affordable reagents and proceeding under mild conditions and thus suitable for large-scale pilot-plant synthesis. Various flavone derivatives are now being prepared in our laboratory by the above-mentioned methodology with a view to extensively evaluating their biological activities. The experimental details and biological data will be published shortly.

Experimental

Melting points were determined on a Buchi-530 melting point apparatus (uncorrected). IR spectra were recorded on a Perkin-Elmer FT-IR 1600 series FT-IR spectrophotometer. ^{1}H-NMR spectra were determined on a Varian Gemini-300 NMR instrument. Mass spectra were recorded on a Finnigan MAT TSQ-46 or Finnigan MAT TSQ-700 mass spectrometer. UV spectra were recorded on a Shimadzu UV-160A spectrophotometer.

1-(2,3,4-Trimethoxy-6-hydroxyphenyl)-3-phenylpropen-1-one (1) A mixture of 3,4,5-trimethoxyphenol (3.7 g, 20 mmol) and cinnamoyl chloride (3.7 g, 22 mmol) was dissolved in BF_3–Et_2O complex (20 ml) and heated to reflux for 15 min, and then quenched with excess of water. Filtration and recrystallization from hexane : EtOAc (3 : 1) gave chalcone **1** (5.6 g, 90%) as reddish-yellow crystals. Alternatively, **1** could be prepared by acylation of 3,4,5-trimethoxyphenol[12] and, without further purification, followed by condensation with benzaldehyde in the presence of KOH[3,4] (66%): mp 98—100 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s), 3.96 (3H, s), 4.03 (3H, s), 6.34 (1H, s), 7.45—7.48 (3H, m), 7.67 (2H, d, J=9.3 Hz), 8.06 (2H, d, J=15.5 Hz), 8.33 (2H, d, J=15.5 Hz). IR (KBr) cm^{-1}: 3419, 1608. MS *m/z*: 315 (MH^+).

5,6,7-Trimethoxyflavone (2) A mixture of **1** (7.2 g, 23 mmol) and iodine (200 mg) in DMSO (25 ml) was refluxed for 2 h, and then carefully poured onto crushed ice (200 g). The precipitate was filtered and washed with 20% Na_2SO_3. Purification by flash column chromatography (SiO_2, hexane : EtOAc = 3 : 1) yielded 6.3 g (87%) of **2** as white crystals, which turned into pale yellow after standing for about one month, and recovered 0.8 g (2.5%) of **1**: mp 146—147 °C (lit.[17] 164—165 °C). ^{1}H-NMR (DMSO-d_6) δ: 3.93 (3H, s), 3.97 (3H, s), 3.99 (3H, s), 6.72 (1H, s), 6.83 (1H, s), 7.50 (3H, m), 7.88 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1633. MS *m/z*: 313 (MH^+).

Oroxylin A A solution of **2** (0.20 g, 0.64 mmol) in 47% HBr (5 ml) and glacial acetic acid (10 ml) was refluxed for 2 h, and then carefully poured onto crushed ice (200 g). The resulting yellow precipitate was filtered and collected. Recrystallization from ethanol afforded 160 mg (88%) of oroxylin A as bright yellow crystals: mp 203—204 °C. (lit.[9] 195—197 °C). ^{1}H-NMR (DMSO-d_6) δ: 3.91 (3H, s), 6.94 (1H, s), 6.98 (1H, s), 7.59 (3H, m), 8.10 (2H, d, J=6.3 Hz), 8.77 (1H, s), 12.49 (1H, s). IR (KBr) cm^{-1}: 3435, 1667. UV λ_{max} (EtOH) nm (log ε): 322 (4.12), 278 (4.35), 216 (4.42). MS *m/z*: 285 (MH^+).

Baicalein Baicalein, as bright yellow crystals, was prepared by the modified procedure outlined above either from oroxylin A (reflux, 12 h) or **2** (reflux, 18 h) in 81% and 89% yield, respectively: mp 258—260 °C (lit.[7] 263—264 °C). ^{1}H-NMR (DMSO-d_6) δ: 6.61 (1H, s), 6.92 (1H, s), 7.56 (3H, m), 8.05 (2H, d, J=8.1 Hz), 8.81 (1H, s), 10.57 (1H, s), 12.65 (1H, s). IR (KBr) cm^{-1}: 3411, 1654. UV λ_{max} (EtOH) nm (log ε): 326 (4.17), 276 (4.42), 215 (4.49). MS *m/z*: 270 (M^+).

Wogonin Pure **3** (0.52 g, 1.8 mmol), prepared by the procedure outlined above (reflux, 2 h) from chalcone **1** (0.62 g, 2.0 mmol) in 91% yield, was subject to oxidative cyclization as previously described. Purification by flash chromatography (silica gel, CH_2Cl_2→hexane/EtOAc (3/1)→CH_2Cl_2/EtOAc (5/1)) and then recrystallization from ethanol gave oroxylin A (238 mg, 46%) and bright yellow crystals of wogonin (124 mg, 24%), respectively. Chalcone **3**: mp 121—122 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.78 (1H, d, J=13.4 Hz), 3.82 (3H, s), 5.56 (1H, d, J=13.4 Hz), 6.27 (1H, s), 7.40—7.54 (5H, m), 8.21 (1H, s), 11.72 (1H, s). IR (KBr) cm^{-1}: 3445, 1666. FAB-MS *m/z*: 287 (MH^+); Wogonin: mp 198—199 °C. (lit.[10] 203 °C). ^{1}H-NMR (DMSO-d_6) δ: 3.81 (3H, s), 6.30 (1H, s), 7.00 (1H, s), 7.37 (1H, s), 7.64 (3H, m), 8.10 (2H, d, J=6.3 Hz), 12.51 (1H, s). IR (KBr) cm^{-1}: 3445, 1667. UV λ_{max} (EtOH) nm (log ε): 321 (4.15), 276 (4.36), 216 (4.44). FAB-MS *m/z*: 285 (MH^+).

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References

1) Gao D., Sakuria K., Chen J., Ogiso T., *Res. Commun. Mol. Pathol. Pharm.*, **90**, 103—114 (1995).
2) Allan J., Robinson R., *J. Chem. Soc.*, 2192—2194 (1924).
3) Mahal H. S., Venkataraman K., *Curr. Sci.*, **4**, 214—216 (1933).
4) Wheeler T. S., "Organic Syntheses," Collective Vol. IV, 2nd ed. by Rabojohn N., John Wiley & Sons, New York, 1967, pp. 478—481.
5) Iinuma M., Iwashima K., Matsuura S., *Chem. Pharm. Bull.*, **32**, 4935—4941 (1984).
6) Hercouet A., LeCorre M., LeFloc'h Y., *Synthesis*, **1982**, 597—598 (1982).
7) Schonberg A., Badran N., Starkowsky N. A., *J. Am. Chem. Soc.*, **77**, 5390—5392 (1955).
8) Agasimundin Y. S., Siddappa S., *J. Chem. Soc., Perkin Trans. I*, 503—505 (1973).
9) Popova T. P., *Chem. Nat. Compd.* (*Engl. Transl.*), **11**, 97—99 (1975).
10) Hattori S., Hayashi K., *Chem. Ber.*, **66**, 1279—1280 (1933).
11) Ares J. J., Outt P. E., Kakodkar S. V., Buss R. C., Geiger J. C., *J. Org. Chem.*, **58**, 7903—7905 (1993).
12) Chiba K., Takakuwa T., Tada M., Yoshii T., *Biosci. Biotechnol. Biochem.*, **56**, 1769—1772 (1992).
13) Price W. A., Silva A. M. S., Cavaleiro J. A. S., *Heterocycles*, **36**, 2601—2612 (1993).
14) Kasahara A., Izumi T., Oshima M., *Bull. Chem. Soc. Jpn.*, **47**, 2526—2528 (1974).
15) Pinto D. C. G. A., Silva A. M. S., Cavaleiro J. A. S., *J. Heterocyclic Chem.*, **33**, 1887—1893 (1996).
16) Levene P. A., Raymond A. L., *J. Biol. Chem.*, **102**, 317—346 (1933).
17) McGarry L. W., Detty M. R., *J. Org. Chem.*, **55**, 4349—4356 (1990).