A Facile Synthesis of Biogenetic Precursor, Puerarone, Isolated from *Pueraria* sp

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Puerarone was synthesized using chalcone oxidation with thallium (III) trinitrate and chromenation of the resulting isoflavone using 3-hydroxyisovaleraldehyde dimethylacetal. The key demethylation step was achieved with boron tribromide.

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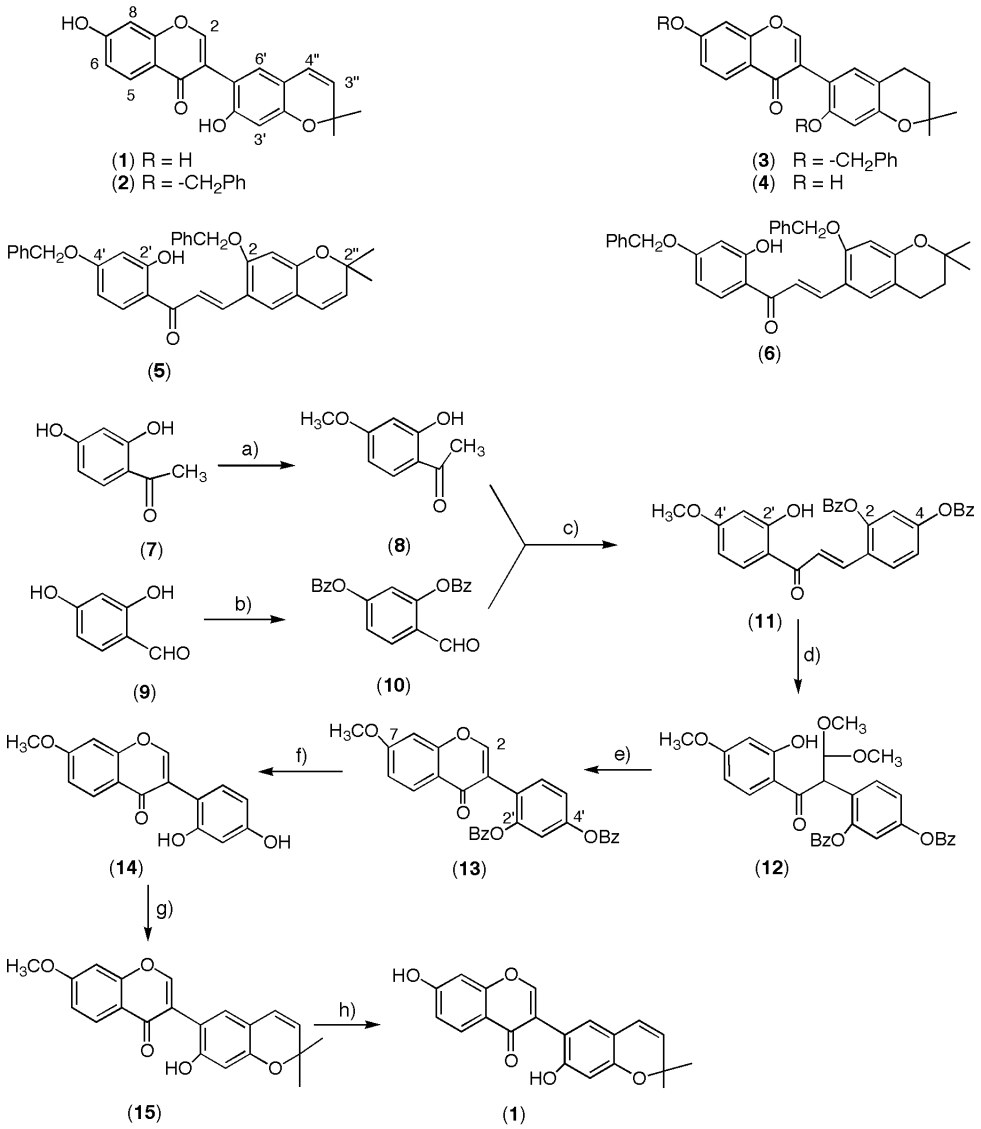
Synthesis of the chromenoisoflavone, puerarone **1,** which is considered to be the precursor in biosynthesis of *Pueraria* pterocarponoids [1], has been attempted. Jain *et al.* [2] reported the synthesis of dihydropuerarone **4**, in an attempt to synthesize puerarone **1** from 2,4'-dibenzyloxy-2'-hydroxy-2",2"-dimethyl-2*H*-pyrano-[2,3-*c*]-chalcone **5.** The conversion of chalcone **5** to the chromenoisoflavone, 2',7-dibenzyloxypuerarone **2** was attempted by thallium(III) nitrate-methanol oxidation. The approach was abandoned for the preparation of dihydropyranochalcone **6**, which gave dihydropuerarone **4** from 2',7-dibenzyloxydihydropuerarone **3**. However, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) dehydrogenation of 2',7-dibenzyloxydihydropuerarone **3** furnished **1**, but there is no experimental detail given and no spectro-analytical support provided [2].

In the present study, the total synthesis of puerarone **1** is achieved utilizing 2,4-dibenzyloxy-2'-hydroxy-4'-methoxychalcone **11** as the key intermediate (Scheme 1) which was converted to 2',4'-dihydroxy-7-methoxyisoflavone **14** and later to 7-methoxypuerarone **15** which on demethylation using boron tribromide furnished the desired product, puerarone **1**.

The chalcone **11** was obtained by condensation of 2-hydroxy-4-methoxyacetophenone **8** and 2,4-dibenzyloxybenzaldehyde **10** in aqueous sodium hydroxide [3,4]. The formation of chalcone **11** was confirmed by IR, ^{1}H NMR, MS & UV spectral analysis. The presence of absorptions at 1630 and 1540 cm^{-1} in the IR spectrum corresponding to an α,β-unsaturated carbonyl group, the observation of molecular ion peak at m/z 466 in the MS spectrum and the lack of methyl ketone singlet and of aldehydic protons of the corresponding starting materials in the ^{1}H NMR spectrum confirmed the chalcone structure **11** [5,6]. The chalcone **11** on reacting with thallium(III) nitrate [7] in dry methanol at room temperature for 6 hours, afforded the acetal **12** which was cyclised using 10% aqueous hydrochloric acid to give the desired product, 2',4'-dibenzyloxy-7-methoxyisoflavone **13** after purification by silica gel column chromatography in 76% yield. The IR spectrum of **13** exhibited absorptions at 1650 and 1620 cm^{-1} corresponding to the conjugated carbonyl while the ^{1}H NMR spectrum showed characteristic one proton C_2 isoflavone singlet at δ 7.90, a methoxy singlet at δ 3.78, two benzylic methylenes at δ 5.00 as singlet. The MS spectrum of compound **13** showed molecular ion peak at m/z 464 along with prominent ion peak at m/z 373, formed by the loss of one benzyl group, which together established the structure of isoflavone **13**. The hydrogenolysis of **13** in acetone on 10% palladium-carbon as catalyst furnished a mixture of products which was purified to give 2',4'-dihydroxy-7-methoxyisoflavone **14** and this on condensation with 3-hydroxyisovaleraldehyde dimethylacetal in pyridine furnished the chromenoisoflavone, 7-methoxypuerarone, **15**. The ^{1}H NMR spectrum of **15** showed the $C_{3'}$ and $C_{6'}$ proton singlets at δ 7.30 and δ 7.10 respectively, and a characteristic one proton C_2 isoflavone singlet at δ 8.13. In the mass spectrum molecular ion peak at m/z 350 along with prominent ion peak at m/z 335 formed by the loss of one methyl group, which is characteristic for 2",2"-dimethyl chromene ring system in the molecule **15** [8], is observed. The isoflavone **15** was demethylated using boron tribromide [9] at -78 °C in dry dichloromethane under nitrogen atmosphere to furnish the puerarone **1,** as an oil, identified by spectroscopic means and comparison with the natural sample. The UV spectrum of **1** showed absorption values at λmax 230 and 305 nm, IR absorptions are observed at 3400 cm^{-1} corresponding to the hydroxyl group and at 1665 cm^{-1} corresponding to the conjugated carbonyl. In the mass spectrum of **1**, molecular ion peak at m/z 336 and prominent ion peak at m/z 321, due to the loss of one methyl group from the 2",2"-dimethylchromene moiety [8], are observed. The ^{1}H NMR of **1** displayed characteristic C_2 isoflavone proton singlet at δ 8.34, a six protons singlet at δ 1.40 and a set of AB quartets for the $C_{3"}$ and $C_{4"}$ protons at δ 5.62 and δ 6.35 (J = 10.0 Hz, both) for the 2",2"-dimethylchromene ring [8]. The protons at C_5, C_6 and C_8 are observed at δ 8.14 (d, J = 8.5 Hz), δ 7.20 (dd, J = 8.5, 2.0 Hz) and δ 7.02 (d,J = 2.0 Hz) respectively while protons at $C_{3'}$ and $C_{6'}$ resonate at δ 6.37 & δ 7.04 as singlets in the ^{1}H NMR spectrum of **1,** which confirms the structure **1**. A comparison of the ^{1}H NMR spectrum of **1** with the reported ^{1}H NMR data of naturally occurring puerarone [1] showed a downfield shift, *i.e.*, a maximum shift of δ 0.12 for individual resonances (*e.g.*, $C_{3"}$) and an overall downfield shift of δ 0.09 for the whole spectrum. The observed chemical shift values are close to the reported ^{1}H NMR data and the spectral analyses (UV, IR, ^{1}H NMR & MS) of **1** unequivocally established the puerarone structure **1**.

Scheme 1



Reagents and conditions: a) CH_3I, acetone, K_2CO_3, reflux b) $PhCH_2Cl$, K_2CO_3, NaI, EtOH, reflux c) 50% aq. NaOH, EtOH, reflux d) $Th(III)NO_3$, dry MeOH e) 10% aq. HCl, reflux f) 10% Pd-C, H_2, acetone g) 3-Hydroxy isovaleraldehyde dimethylacetal, pyridine, reflux h) dry CH_2Cl_2, -78 °C , BBr_3.

EXPERIMENTAL

General.

Melting points are uncorrected and expressed in degree Celsius. UV spectra were recorded on Hitachi-320 spectrophotometer and IR spectra were recorded on Perkin-Elmer 157 as potassium bromide pellets, unless otherwise stated. The ^1H NMR spectra were acquired on Perkin-Elmer R-32 and Bruker WM 400 FT spectrometer. The mass spectra were recorded on Jeol JMS D-300 instrument in EI mode at 70 eV. Precoated silica gel TLC plates (Merck, Darmstadt) were used and visualized by spraying with a 2 *N* sulphuric acid solution of Ceric Sulfate.

2-Hydroxy-4-methoxyacetophenone (**8**).

To a stirred solution of 2,4-dihydroxyacetophenone (**7**) (15.0 g) in dry acetone (150 ml), anhydrous potassium carbonate (15.0 g) and methyl iodide (40 ml) were added. The reaction mixture was refluxed for 4 hours, cooled, filtered and washed with hot acetone. The evaporation of solvent yielded a residue that was dissolved in chloroform, washed with water, dried over anhydrous sodium sulphate and the solvent evaporated to give an oil that was crystallized from hexane-ether (1:1) to furnish (**8**) , 12.4 g, 75.7%. mp 47 °C.

2,4-Dibenzyloxybenzaldehyde (**10**).

2,4-Dihydroxybenzaldehyde (**9**) (15.0 g) in ethanol (150 ml) was mixed with potassium carbonate (30.0 g), benzyl chloride (30 ml) and sodium iodide (0.5 g). The suspension was refluxed

for 6 hours and the solvent evaporated to afford a residue that was crystallized from hexane-dichloromethane (1:1) to give (**10**), 27.5 g, 72.3%. mp 82 °C.

2,4-Dibenzyloxy-2'-hydroxy-4'-methoxychalcone (**11**).

To a mixture of 2-hydroxy-4-methoxyacetophenone (**8**) (10.0 g) and 2,4-dibenzyloxybenzaldehyde (**10**) (20.0 g) in ethanol (250 ml) was added 50% aqueous sodium hydroxide (30.0 ml) and the mixture was refluxed for 2 hours to furnish a yellow precipitate that was filtered and washed with dilute hydrochloric acid and water. Recrystallization from ether-dichloromethane (1:1) yielded yellow crystals (**11**), 13.6 g, 46.6%, mp 155 °C. IR (KBr): 1630, 1540, 1320, 1225, 1150,1010 and 825 cm^{-1}. ^1H NMR ($CDC1_3$): δ 3.70 (S,3H,OCH_3), 5.00 (S, 4H, 2xPhCH_2-O-), 6.00-6.70 (m, 3H, H-3, 3' 5'), 7.15-7.82 (m, 13H, ArH). MS (m/z): 466 (M^+).

2', 4'-Dibenzyloxy-7-methoxyisoflavone (**13**).

To stirred suspension of chalcone (**11**) (15.0 g) in methanol (450 ml) was added thallium(III) nitrate (20.0 g) in four small portions in 1 hour and stirring continued for a total of 6 hours at room temperature. The reaction mixture was filtered and 10% HCl (30.0 ml) was added to the filtrate. The acidified filtrate was refluxed for 4 hours, concentrated to give a mass to which water was added and extracted with chloroform. Evaporation of the solvent gave an oil product, which was purified by silica gel column chromatography using hexane-benzene (1:1) to give (**13**), 11.4 g, 76%, mp 139 °C. IR (KBr): 1650, 1620, 1440, 1260, 1240, 1035 and 840 cm^{-1}. ^1H NMR (acetone-d_6): δ 3.78 (s, 3H, OCH_3), 5.00 (s, 4H, 2xPhCH_2-O), 6.60-7.50(m, 16H, Ar*H*), 7.90 (s, 1H, C_2-H). MS (m/z): 464 (M^+), 373.

2', 4'-Dihydroxy-7-methoxyisoflavone (**14**).

To a stirring solution of 2',4'-dibenzyloxy-7-methoxyisoflavone (**13**) (10 g) in acetone (150 ml) was added 10% Pd-C (1.0 g) and stirring was continued for 3 hours under hydrogen. The catalyst was filtered, acetone was evaporated and the oily residue obtained purified by column chromatography over silica gel to furnish 2',4'-dihydroxy-7-methoxyisoflavone (**14**), 1.6 g, 27%, mp 210 °C. UV (MeOH): 248, 264, 290 nm^{-1}. IR (KBr): 3400,1640,1620 cm^{-1}. ^1H NMR (acetone-d_6 + DMSO-d_6): δ 3.85 (s, 3H, $ArOCH_3$), 6.25-6.60 (m, 2H, H-3', 5'), 6.70-7.45 (m, 3H, H-6, 8, 6'), 8.00(s, 1H, H-2), 8.15(d, 1H, J = 8.5 Hz, H-5). MS (m/z): 284 (M^+), 267, 254, 151, 134.

7-Methoxypuerarone (**15**).

The mixture of 2',4'-dihydroxy-7-methoxyisoflavone (**14**) (2.0 g) and 3-hydroxyisovaleraldehyde dimethylacetal (10 ml) in pyridine (50 ml) was refluxed at 150 °C for 48 hours. The reaction mixture was concentrated under vacuum and the residue obtained was chromatographed over a silica gel column eluting with chloroform to give 7-methoxypuerarone (**15**) as an oil, 1.4 g, 55.6%. UV (MeOH): 248, 310 cm^{-1}. IR (Neat): 3400, 1660, 1570, 1480, 835 cm^{-1}. ^1H NMR (acetone-d_6): δ 1.26 (s, 6H, 2 x CH_3), 3.90 (s, 3H,Ar-OCH_3), 5.35 (d, IH, J = 10.0 Hz, H-3"), 6.54 (d, 1H, J = 10.0 Hz, H-4"), 6.82 (m, 1H, H-6), 7.10 (s, 1H, H-6'), 7.30 (s, 1H, H-3'), 7.83 (m, 2H, H-5, 8), 8.13 (s, 1H, H-2). MS (m/z): 350 (M^+), 335, 174, 163.

Puerarone (**1**).

To the stirring solution of 7-methoxypuerarone (**15**) (1.0 g) in dry dichloromethane, cooled by dry ice and acetone at -78 °C under nitrogen atmosphere was added boron tribromide (20 ml) in 2 portions and stirring continued for 30 minutes. The reaction mixture was allowed to warm to room temperature and the solvent was removed under vacuum to afford an oil which on preparative thin layer chromatographic purification using hexane-ethyl acetate (2:1) furnished puerarone (**1**) as an oil, 482 mg, 50.2%. UV (MeOH) 230, 305 cm^{-1}. IR (Neat): 3400, 1665, 1450, 1050, 840. ^1H NMR (acetone-d_6): δ 1.40 (s, 6H, 2xCH_3), 5.62 (d, 1H, J = 10.0 Hz, H-3"), 6.35 (d, IH, J = 10.0 Hz, H-4"), 6.37 (s, 1H, H-3'), 7.02 (d, 1H, J = 2.0 Hz, H-8), 7.04(s, IH, H-6'), 7.20 (dd, IH, J = 8.5,2.0 Hz, H-6), 8.14 (d, IH, J = 8.5 Hz, H-5), 8.34 (s, 1H, H-2). MS (m/z): 336 (M^+), 321, 200, 185, 170, 134.

REFERENCES AND NOTES

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[1] K.V. Ramakrishna, R. A. Khan and R. S. Kapil, *Indian J. Chem*., **27 B**, 285 (1988).

[2] A. C. Jain and P. Paliwal, *Indian J. Chem*., **29B,**757 (1990).

[3] G. N. Vyas and N. M. Shahi, *J. Indian Chem. Soc*., **27**, 189 (1950).

[4] J. L. Ingham and P. M. Dewick, *Phytochemistry*, **17**, 535 (1978).

[5] A. V. K. Prasad, R. S. Kapil and S. P. Popli, *J. Chem. Soc. Perkin I*, 1561 (1986).

[6] L. Farkas, A. Gottsegen, M. Nogardi and S. Antus, *J. Chem. Soc. Perkin I*, 305 (1974).

[7] Thallium(III) nitrate; [CAS: 13453-38-8]. Primary target organs skin, eyes and upper respiratory tracts, handling and storage precautions to be strictly followed. 'Sigma-Aldrich Library of Chemical Safety Data', Edition II, Vol. **2**, p. 3317, Robert E. Lenga (Editor), Sigma-Aldrich Corporation, Milwaukee, WI 53201, USA, 1988.

[8] C. S. Barnes, J. L. Occolowitz, N. L. Dutta, P. M. Nair, P. S. Phadke and K. Venketraman, *Tetrahedran. Lett*., **5**, 281(1963).

[9] Boron tri bromide; [CAS: 10294-33-4]. Extremely destructive to the tissues of mucous membrane & respiratory tract. Reacts with water to give toxic fumes, explodes on heating, incompatible with Sodium and Potassium.'Hazardous Chemicals Desk Reference', IIIrd ed., p. 188, Richard J. Lewis Sr. (Editor), Van Nostrand Reinhold, New York,1993.