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A Novel Synthetic Method for 3-Hydroxyhomoisoflavanone

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A novel synthetic method was developed for 3-hydroxyhomoisoflavanone. Treatment of aryllithium **14** to aldehyde **13** which was obtained from dihydroxylation of **10**, followed by cycloetherification to give 3-hydroxyhomoisoflavanones.

Key words : Dihydroxylation, 3-Hydroxyhomoisoflavanone, Cycloetherification

INTRODUCTION

Brazilin was isolated from *Caesalpinia sappan L.* (*Leguminosae*) (Cheveul *et al.*, 1808; Namikoshi *et al.*, 1987) which has long been used as traditional Chinese medicine. In the course of systematic screening for biological activity, brazilin was shown to have antibacterial activity (Pratt *et al.*, 1959), antiinflammatory activity (Hikino *et al.*, 1977) and hypoglycemia activity (Moon *et al.*, 1990). Structurally similar derivative, (+)-haematoxylin (Chevreul *et al.*, 1824) was isolated from *Haematoxylon campechianum* (*Leguminosae*). Haematoxylin exhibited the inhibition activity of the Bovine-Lens aldose reductase (Moon *et al.*, 1985) and 120 times higher sweatness than sucrose (Arnoldi *et al.*, 1995). The structure of both brazilin and haematoxylin as polyhydroxybenzindenopyrans is classified to tetracyclic homoisoflavanoid. The biosynthetic precusors of **1a,b** were known as homoisoflavanones **2a,b**. The pharmacological potentiailty attracted chemists to synthesize these tetracyclic homoisoflavanoids **1a,b** and its derivatives. Many synthetic methods has been reported for intermediates **2a,b** (Farkas *et al.*, 1968; Krishnamurty *et al.*, 1974; Chatterjea *et al.*, 1979; Davis *et al.*, 1990) which can be futher transformed to **1a,b** by reduction and acid catalyzed cyclization. Most of synthetic methods employed **3** or **4** as intermediate which was transformed to 3-hydroxyhomoisoflavanone derivatives by aldol condensation with corresponding benzaldehyde moiety. Different approach was accomplished by Chatterjea *et al* in 1974. They used intramolecular Friedel Craft type cyclization of cyanohydrin intermediate **5** as a key step. Now we report a new synthetic methodology for 3-hydroxyhomoisoflavanone *via* OsO_4-dihydroxylation and intramolecular etherification.

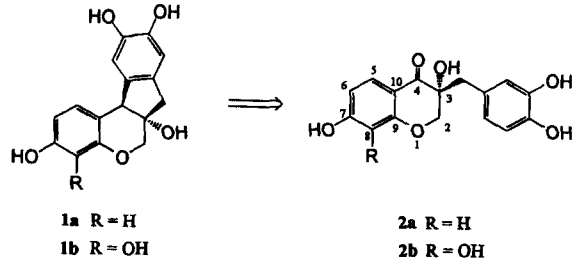

Fig. 1. Chemical structure of brazilin and haematoxylin.

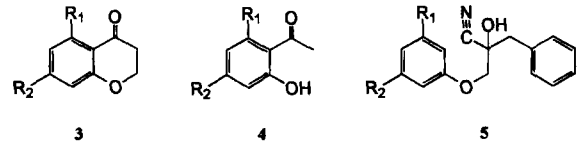

Fig. 2. Intermediates for 3-hydroxyhomoisoflavanone.

MATERIALS AND METHODS

IR spectra were recorded on a Perkin-Elmer 1710 FT spectrometer. ^{1}H-NMR spectra were measured on a Bruker WP 80 SY or JEOL JNM-GCX 400 spectrometer. Mass spectra were recorded on a VG Trio-2 GC-MS EI method at 70 eV or a JMS AX505WA by CI method at 200 eV. Chemical shifts (δ) are in parts per million (ppm) relatives to Me_4Si, and coupling constants (J values) are in hertz.

The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. Tetrahydrofuran was distilled from Na and benzophenone.

Ethyl 2,3-dihydroxy-2-benzylpropionate (11)

To a solution of 4-methylmorpholine *N*-oxide (1.35

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g, 11.542 mmol) and osmium tetroxide (67 mg, 0.528 mmol) in acetone-*tert*-butanol-water (2.5:1:12.5) mixture (64 mL) was added **10** (2.0 g, 10.513 mmol). The reaction was stirred at room temperature (18 h). Sodium thiosulfate (87 mg) and florisil (10 g) were added, stirred (10 min) and filtered. The filtrate was neutralized with 1 N aqueous HCl solution, and concentrated *in vacuo*. The residue was diluted with ethyl acetate (100 mL), washed with brine (30 mL) and dried over anhydrous magnesium sulfate (2 g). The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 33% ethyl acetate-hexane) to give a colorless oil **11**: yield, 2.03 g (86%); IR (neat) 3445, 2983, 1732 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.29 (t, *J*=7.2 Hz, 3 H), 2.27 (bs 1 H), 2,89. (d, *J*=13.6 Hz, 1 H), 2.99 (d, *J*= 13.6 Hz, 1 H), 3.70 (d, *J*=11.0 Hz, 1 H), 3.92 (d, *J*= 11.0 Hz, 1 H), 4.18-4.24 (m, 2 H), 7.18-7.30 (m, 5 H); MS (EI) 224 $[M]^+$, 206 $[M-H_2O]^+$.

Ethyl 2,3-*O*-isopropylidenedioxy-2-benzylpropionate (12)

To a tetrahydrofuran solution (15 mL) of **11** (1.19 g, 5.306 mmol) and p-toluenesulfonic acid monohydrate (100 mg, 0.53 mmol) was added 2,2-dimethoxypropane (1.11 g, 10.62 mmol). The reaction was stirred at room temperature (20 h) and concentrated *in vacuo*. The residue was diluted with ethyl acetate (100 mL), washed with aqueous $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL) and dried over anhydrous magnesium sulfate (2 g). The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 17% ethyl acetate-hexane) to give a colorless caramel **12**: yield, 1.16 g (83%); IR (neat) 2987, 1739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.22 (t, *J*=7.6 Hz, 3 H), 1.28 (s, 3 H), 1.43 (s, 3 H), 3.04 (d, *J*=14.0 Hz, 1 H), 3.19 (d, *J*=14.0 Hz, 1 H), 3.91 (d, *J*=8.8 Hz, 1 H), 4.13-4.22 (m, 2 H), 4.34 (d, *J*=8.8 Hz, 1 H), 7.21-7.30 (m, 5 H); MS (EI) 264 $[M]^+$.

2,3-*O*-Isopropylidenedioxy-2-benzylpropionaldehyde (13)

To a toluene solution (1 mL) of **12** (20 mg, 1.18 mmol) was added 1 M diisobutylaluminum hydride (0.08 mL, 0.08 mmol) at -78°C. The reaction was stirred at -78°C (0.5 h). The reaction was quenched with water and extracted with diethyl ether (25 mL × 2). The ether solution was washed with brine (10 mL) and dried over anhydrous magnesium sulfate (1 g). The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 17% ethyl acetate-hexane) to give a colorless oil **13**: yield, 10 mg (60%); IR (neat) 2988, 1732 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.25 (s, 3 H), 1.42 (s, 3 H), 2.90 (d, *J*=14.0 Hz, 1 H), 3.09 (d, *J*=14.0 Hz, 1 H), 3.82 (d, *J*=8.8 Hz, 1 H), 4.22 (d, *J*=8.8 Hz, 1 H), 7.19-7.31 (m, 5 H), 9.67 (s, 1 H); MS (+CI) 221 $[M + 1]^+$.

1-[2-(2-Methoxyethoxymethoxy)-4-methoxyphenyl]-2-benzyl-2,3-isopropylidene-dioxypropanol (15)

To a tetrahydrofuran solution (5 mL) of 1-bromo-2-(2-methoxyethoxymethoxy)-4-methoxybenzene (428 mg, 1.470 mmol) was added 1.2 M *n*-butyllithium (1.2 mL, 1.47 mmol) at -78°C. The reaction was stirred at -78°C (0.3 h). **13** (323 mg, 1.47 mmol) was added to the reaction and stirred at room temperature (18 h). The reaction was quenched with water and extracted with diethyl ether. The ether solution was washed with brine and dried over anhydrous magnesium sulfate. The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 50% ethyl acetate-hexane) to give a colorless caramel **15**: yield, 292 mg (45%); IR (neat) 3467, 2939 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 0.78 (s, 3 H), 1.24 (s, 3 H), 1.51 (bs, 1 H), 2.51 (d, *J*=14.0 Hz, 1 H), 3.14 (d, *J*=14.0 Hz, 1 H), 3.28 (s, 3 H), 3.42-3.57 (m, 4 H), 3.67 (d, *J*=8.8 Hz, 1 H), 4.15 (d, *J*=8.8 Hz, 1 H), 5.07 (s, 1 H), 5.14-5.20 (m, 2 H), 6.54 (dd, *J*=2, 8.4 Hz, 1 H), 6.69 (d, *J*=2 Hz, 1 H), 7.08-7.22 (m, 5 H), 7.44 (d, *J*=8.4 Hz, 1 H); MS (EI) 432 $[M]^+$.

2-Benzyl-2,3-isopropylidenedioxyethyl [2'-(2-methoxyethoxymethyl)-4'-methoxy] phenyl ketone (16)

To a methylenechloride suspension (3 mL) of PCC (218 mg, 0.979 mmol) and sodium acetate (17 mg, 0.210 mmol) was added **15** (292 mg, 0.660 mmol). The reaction was stirred at room temperature (16 h), diluted with ether (50 mL), passed through the florisil and silica gel layer and dried over anhydrous magnesium sulfate (1 g). The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 33% ethyl acetate-hexane) to give a colorless caramel **16**: yield, 204 mg (70%); IR (neat) 2952, 1610 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 0.896 (s, 3 H), 1.12 (s, 3 H), 3.03 (d, *J*=14.0 Hz, 1 H), 3.38 (s, 3 H), 3.48 (d, *J*=14.0 Hz, 2 H), 3.57 (t, *J*=2.4 Hz, 2 H), 3.85 (t, *J*=2.4 Hz, 2 H), 3.96 (d, *J*=8.8 Hz, 1 H), 4.31 (d, *J*=8.8 Hz, 1 H), 5.24 (s, 2 H), 6.45 (dd, *J*= 2.4, 8.8 Hz, 1 H), 6.77 (d, *J*=2.4 Hz, 1 H), 7.07 (d, *J*= 8.8 Hz, 1 H), 7.23-7.29 (m, 5 H); MS (EI) 430 $[M]^+$.

2-Benzyl-2,3-dihydroxyethyl 2'-hydroxy-4'methoxyphenyl ketone (17)

A concentrated HCl-methanol (1:16) solution (2 mL) of **16** (66 mg, 0.149 mmol) was stirred at 50°C (2 h). The reaction was concentrated, diluted with ethyl acetate (50 mL), washed with brine (10 mL) and dried over anhydrous magnesium sulfate (1 g). The excess solvent was removed *in vacuo* and the residue was

purified by column chromatography (SiO_2, 33% ethyl acetate-hexane) to give a colorless caramel **17**: yield, 42 mg (98%); IR (neat) 3436, 2926, 1625 cm^{-1}; ^{1}H-NMR (80 MHz, $CDCl_3$) 1.60 (bs, 3 H), 3.26 (d, J=14.0 Hz, 1 H), 3.70 (d, J=14.0 Hz, 2 H), 3.85 (s, 3 H), 3.87 (m, 1 H), 4.26 (m, 1 H), 6.47 (dd, J=2.4, 9.8 Hz, 1 H), 7.11-7.25 (m, 6 H), 8.24 (d, J=9.8 Hz, 1 H); MS (EI) 302 $[M]^+$.

3-Tosyloxy-2-hydroxy-2-benzylethyl 2'-hydroxy-4'-methoxyphenyl ketone (18)

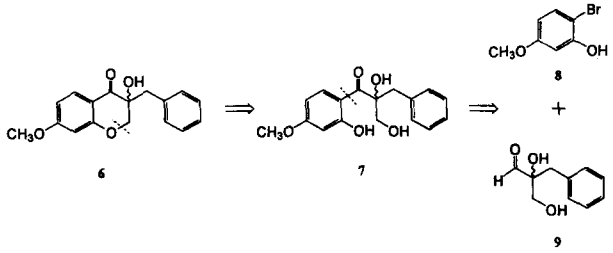
A chloroform solution (1.76 mL) of **17** (14 mg, 0.049 mmol), p-toluenesulfonyl cholride (13.2 mg, 0.069 mmol) and pyridine (0.235 mg, 0.003 mmol) was stirred at room temperature (43 h). The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 33% ethyl acetate-hexane) to give a colorless caramel **18**: yield, 12.4 mg (55%), IR (neat) 3469, 1626 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 2.16 (s, 2 H), 2.43 (s, 3 H), 3.14 (d, J=14.0 Hz, 1 H), 3.26 (d, J=14.0 Hz, 1 H), 3.85 (t, J=2.4 Hz, 2 H), 3.96 (s, 3 H), 4.23 (d, J=9.6 Hz, 1 H), 4.53 (d, J=9.6 Hz, 1 H), 6.35 (dd, J=2.4, 9.2 Hz, 1 H), 6.40 (d, J=2.4 Hz, 1 H), 7.00-7.02 (m, 2 H), 7.15-7.18 (m, 3 H), 7.28 (d, J=8.0 Hz, 1 H), 7.69 (d, J=8.0 Hz, 1 H), 8.10 (d, J= 9.2 Hz, 1 H); MS (EI) 457 $[M]^+$.

3-Hydroxy-7-methoxyhomoisoflavanone (6)

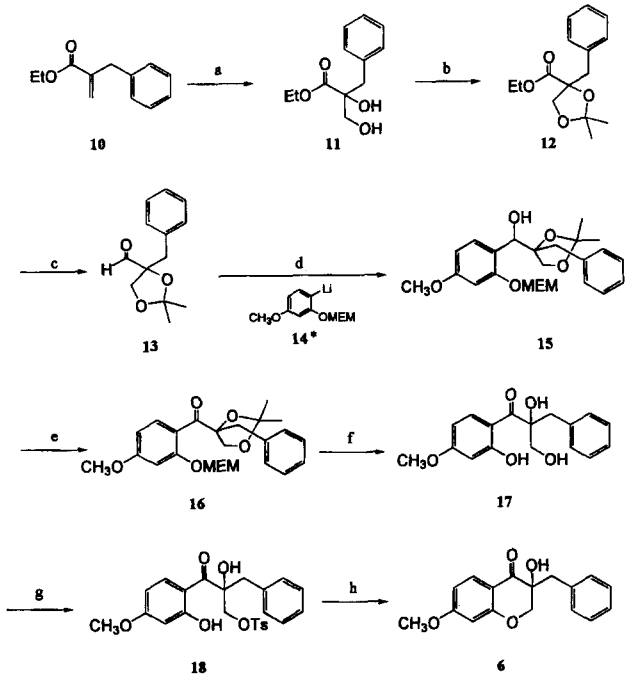
A methanol solution (1 mL) of **18** (12.4 mg, 0.0272 mmol) and potassium carbonate (6 mg, 0.043 mmol) was stirred at room temperature (5 h). The reaction solution was concentrated *in vacuo*, diluted with ethyl acetate (50 mL), washed with water (10 mL) and brine (10 mL) and dried over anhydrous magnesium sulfate (1 g). The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 25% ethyl acetate-hexane) to give a white solid **6**: yield, 5.7 mg (74%); IR (neat) 3464, 1619 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.56 (s, 1 H), 2.94 (d, J=14.0, 1 H), 3.01 (d, J=14.0, 1 H), 3.88 (s, 3 H), 4.09 (d, J=11.0 Hz, 1 H), 4.27 (d, J=11.0 Hz, 1 H), 6.49 (d, J=2.4 Hz, 1 H), 6.67 (dd, J=2.4, 9.2 Hz, 1 H), 7.20-7.32 (m, 5 H), 7.82 (d, J=9.2 Hz, 1 H); MS (EI) 284 $[M]^+$, 266 $[M\text{-}H_2O]^+$.

RESULTS AND DISCUSSION

Our retrosynthetic analysis is outlined in Scheme 1. 3-Hydroxyhomoisoflavanone 6 was prepared *via* three key reaction ; Dihydroxylation of **10**, Addition of lithiate **14** to aldehyde **13** and Intramolecular etherification of **18**. Diol **11** was prepared by dihydroxylation of α,β-unsaturated ester **10** using catalytic amount of OsO_4 and 4-methylmorpholine N-oxide. Then the diol **11** was protected with acetonide and the following reduction with DIBAL-H generated aldehyde **13**. Treatment of **13** with **14** provided **15** followed by oxidation with PCC to give ketone **16**. Acetonide and MEM group of **16** were deprotected simultaneously with 2% methanolic HCl solution. Selective tosylation of **17** furnished **18** and the following intramolecular etherification gave **6**. In summary, 3-hydroxyhomoisoflavanone **6** was prepared through 8 steps from **10** in overall yield 5.9%. High yield of OsO_4-catalytic dihydroxylation in preparation of diol **11** gave advantage for industrial application. Especially this method can be applied to prepare C(3)(*S*)-**6** by asymmetric dihydroxylation. The asymmetric synthesis of C(3)(*S*)-**6** is currently being investigated.



Scheme 1. Retrosynthetic analysis for 3-hydroxyhomoisoflavanone.



Scheme 2. Synthetic route to 3-hydroxyhomoisoflavanone. Reaction condition: (a) NMO, OsO_4, *tert*-BuOH, H_2O, acetone, rt, 18 h; 86%; (b) 2,2-dimethoxypropane, p-TsOH, THF, rt, 20h; 83%; (c) DIBAL-H, toluene, -78°C, 30 min; 60%; (d) **14**, THF, -78°C to rt, 18h; 56%; (e) PCC, NaOAc, CH_2Cl_2, rt, 16h; 79%; (f) 2% HCl in MeOH, 50°C, 2 h; 98%; (g) p-TsCl, pyridine, $CHCl_3$, rt, 43 h; 55%; (h) K_2CO_3, MeOH, rt, 5 h; 74%.

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REFERENCES CITED

Arnoldi, A., Bassoli, A., Borgonovo, G. and Merlin, L. Synthesis and Sweet taste of optically active (-)-haematoxylin and of some (±)-haematoxylin derivatives. *J. Chem. Soc. Perkin Trans.* 1, 2447 (1995).

Chatterjea, J. N., Singh, R. P. Lal, P.K. and Shaw, S. C. Homoisoflavanones: Part III Synthesis of 3-hydroxyhomoisoflavanones & a new synthesis of (±)-5,7-di-*O*-methyleucomol. *Indian J. of Chem.*, 17B, 42 (1979).

Chevreul, M. *Ann. Chim.* 66, 225 (1808).

Chevreul, M. Du mémoir sur le bois de camp che et sur la nature de principe colorant. *Ann. Chim.* 82, 53 (1824).

Davis, F. A. and Chen, B.-C. A highly enantioselective synthesis of (R)-and (S)-5,7-*O*-dimethyleucomol. *Tetrahedron Lett.*, 31, 6823 (1990).

Farkas, L., Gottsegen A. and Nogradi, M. Synthesis of eucomin and (±)-eucomol. *Tetrahedron Lett.*, 9, 4099 (1968).

Hikino, H., Taguchi, T., Fujimura, H. and Hiramatsu, Y. Antiinflammatory principles of *Caesalpinia sappan* wood and of *Haematoxylon caempechianum wood. Planta Med.*, 31, 214 (1977).

Krishnamurty, H. G., Parkash, B. and Seshadri, T. R., Synthesis of eucomin, 4'-demethyleucomin & 5,7-di-*O*-methyleucomol. *Indian J. of Chem.*, 12, June, 554 (1974).

Moon, C.K., Yun, Y. P., Lee, J. H., H. wagner and Shin, Y. S. Inhibition of Lens-aldose reductase activity by brazilin and haematoxylin. *Planta Med.*, 39, 66 (1985).

Moon, C. K., Lee, S. H., Chung, J. H., Kim, S. G., Chung, M. K. and Moon, C. H. Effects of brazilin on glucose metabolism in primary cultured rat hepatocyte. *Arch. Pharm. Res.*, 13, 355 (1990).

Namikosh, M., Nakata, H. and Saitoh, T. Homoisoflavonoids from *Caesalpinia sappan. Phytochemistry*, 26, 1831 (1987).

Pratt, R. and Yuzuriha, Y. Antibacterial activity of the hearwood of Haematoxylon braziletto. *J. Am. Pharm. Assoc.*, 48, 69 (1959).