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Synthesis of 1,4-Bis-(2,4-Dimethoxyphenyl)-2,3-Bis-(4-methoxybenzyl)-Butane-1,4-Dione

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ABSTRACT

Brackenin, an unusual biflavonoid which consists of two α , α' -coupled dihydrochalcones, has been isolated from *Brackenridgea zanguebarica*. To date it is the only naturally occurring compound in this class. Brackenin appears to possess the symmetrical structure of a meso compound and is composed of two dihydroisoliquiritigenin units linked by a carbon-carbon bond between the two α -carbon atoms. It represents the first biflavonoid in this class. The present paper describes the synthesis of 1,4-Bis-(2,4-dimethoxyphenyl)-2,3-bis-(4-methoxybenzyl)-butane-1,4-dione, a brackenin like molecule in a few high yielding steps utilizing green methodologies from readily available raw materials (Scheme 1 and Scheme 2).

Keywords: Brackenin, Biflavonoids, Synthesis, Green solvents, 2,4-dimethoxy acetophenone, 2,4-dimethoxy aldehyde, Mannich reaction.

INTRODUCTION

Brackenridgea zanguebarica Oliv. (Ochnaceae) is a tree that can reach a height of up to 10 m. The species occurs in dry lowland forests and woodland of Tanzania and other countries in southern and eastern Africa. The tree is believed to have magical powers in warding off evil spirits and in protecting from lightning strikes [1]. Brackenin, an unusual biflavonoid which consists of two α , α' -coupled dihydrochalcones, has been isolated from *Brackenridgea zanguebarica* [2,3]. To date it is the only naturally occurring compound in this class. It has been reported that the powdered bark is used to treat wounds: "the yellow bark is powdered and sprinkled on" [4]. Yellow-coloured powdered roots are utilised in the same way [5]. A bark decoction is applied as eyewash in the treatment of conjunctivitis and the boiled bark is used in preparations of porridge against jaundice [6].

Brackenin appears to possess the symmetrical structure of a meso compound and is composed of two dihydroisoliquiritigenin units linked by a carbon-carbon bond between the two α -carbon atoms. It represents the first biflavonoid in this class. The present paper describes facile route to the synthesis of 1,4-Bis-(2,4-

dimethoxyphenyl)-2,3-bis-(4-methoxybenzyl)-butane-1,4-dione, a brackenin like molecule in a few high yielding steps utilizing green methodologies from readily available raw materials (Scheme 1 and Scheme 2).

MATERIALS AND METHODS

Chemical and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E.Merck AL silica gel 60 F254 plates and visualized under UV light. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. The ¹H NMR spectra were recorded in CDCl₃ on a Varian EM-360 spectrometer (400MHz). The ¹³C NMR spectra recorded in CDCl₃ on a Varian EM-360 spectrometer operating at 100MHz. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS.

3-(N,N-dimethylamino)-1-(2,4-dimethoxyphenyl)propan-1-one (2)

To a stirred mixture of 2,4-dimethoxy acetone (10 g, 55.50 mmol), 40% aq soln. dimethyl amine (10 g, 222 mmol) and paraformaldehyde (3.35 g, 2.0 mmol) in distilled water (15 mL) was added methanesulphonic acid (10 mol%) solution was refluxed for 12 h. The completion of reaction was monitored by periodic TLC. The reaction mixture was evaporated under reduced pressure and the resulting residual viscous liquid was extracted with isopropyl acetate. The organic layer was washed with water, followed by brine solution, dried over Na₂SO₄, and concentrated to afford mannich product **2** as brown viscous liquid (12.5 g, Yield: 95%) which was utilized as such in the next step.

1-(2,4-dimethoxyphenyl)prop-2-en-1-one (4)

A solution of mannich base **2** (12.5 g, 52.70 mmol) and methyl iodide (11.22 g, 79.05 mmol) in isopropyl acetate (75 mL) was stirred under nitrogen at room temperature for 6 h. The precipitated methiodide salt **3** was removed by filtration and dried *in vacuo* overnight at room temperature. The methiodide salt **3** was suspended in water (150 mL) and isopropyl acetate (150 mL) and heated under reflux with rapid stirring for 3 h. The mixture was cooled and the pale yellow organic layer was removed. Fresh isopropyl acetate (50 mL) was added, the mixture was once again heated under reflux for 1 h, and the process was repeated once again. The organic extracts were combined, washed with brine, dried over MgSO₄, and evaporated to afford **4**. Off-white solid; m.p. 105-106 °C. Yield: 9.7 g, 96%; IR (neat): ν_{\max} 3040, 2840, 1661, 1578, 1475, 1272, 1154, 873 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.86 (s, 3 H), 3.88 (s, 3 H), 5.72 (dd, 1 H, *J* = 2.0 & 8.0 Hz), 6.30 (dd, 1 H, *J* = 2.0 & 16.0 Hz), 6.45 (s, 1 H), 6.55 (d, 1 H, *J* = 9.0 Hz), 7.18 (dd, 1 H, *J* = 8.0 & 16.0 Hz), 7.75 (d, 1 H, *J* = 9.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 56.08, 97.92, 107.24, 122.66, 127.22, 129.11, 133.82, 160.92, 164.57, 196.72. EI-MS: *m/z* (rel.abund.%) 193.1 (M⁺, 100).

1-(2,4-Dimethoxyphenyl)prop-2-en-1-ol (6)

Vinyl bromide (12 mmol) in 2-MeTHF (15 mL) was added to a stirred mixture of zinc (0.79 g, 12 mmol) in 2-MeTHF (20 mL) and after stirring for 1 h, 2,4-dimethoxy benzaldehyde (2 g, 12 mmol) in 2-MeTHF (10 mL) was added. The mixture was stirred 3 h, and then saturated aqueous NH₄Cl solution (25 mL) was added. After 0.5 h the reaction mixture was filtered to remove the remaining zinc, 10% methanesulphonic acid (10 mL) was added and organic layer was separated. The aqueous layer was extracted with small portions of 2-Me THF; the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo* to afford compound **6**. Pale yellow liquid; Yield: 2.6 g, 93%; IR (neat): ν_{\max} 3500, 3410, 1670, 1571, 1478, 1279, 1161, 877 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.86 (s, 3 H), 3.88 (s, 3 H), 4.96 (dt, 1 H, *J* = 2.0 & 8.0 Hz), 5.12 (d, 1H, *J* = 8.0 Hz), 5.18 (dt, 1H, *J* = 2.0 & 8 Hz), 5.30 (br.t, 1H, *J* = 3.0 Hz), 5.98-5.86 (m, 1H), 6.48 (d, 1H, *J* = 8.0 Hz), 6.50 (s, 1 H), 7.20 (d, 1H, *J* = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 55.78, 98.82, 107.24, 122.71, 133.92, 137.21, 138.06, 147.82, 161.67, 166.41.

Conversion of compound 6 to compound 4 (oxidation procedure in air)

Under air, a reaction tube was charged with CsOH (30.9 mg, 20 mol %), compound **6** (2g, 10.30 mmol) and toluene (30 mL). The mixture was heated under air at 110 °C for 24 h, and then cooled to room temperature. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on a silica gel to give the desired product compound **4**. Yield: 3.79 g, 96%.

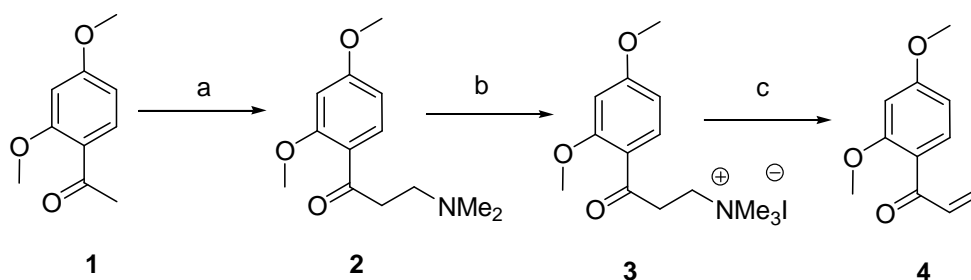
1,4-Bis(2,4-dimethoxyphenyl)butane-1,4-dione (7)

To a stirred suspension of catalyst (0.55 g, 2.1 mmol) in [bmim] [PF₆] (5 mL) were added Et₃N (2.2 mL, 14 mmol), compound **4** (5 g, 26 mmol) and compound **5** (5 g, 30 mmol) at room temperature. The temperature was raised to 80 °C and the reaction mixture stirred for 12 h. After completion of the reaction, as indicated by TLC, the product was

extracted with Et₂O (4 x 25 mL). The organic phase was dried and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO₂ to afford compound 7. Pale yellow solid; m.p. 146 °C; Yield: 6.33 g, 68%; IR (neat): ν_{\max} 1647, 1621, 1572, 1497, 1464, 1419, 1393, 1314, 1288, 1247, 1212, 1183, 1162, 1024, 976, 831 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 3.39 (s, 4 H), 3.83 (s, 6 H), 3.88 (s, 6 H), 6.45 (s, 2 H), 6.50 (dd, 2 H, *J* = 3.0 and 8.8 Hz), 7.84 (d, 2 H, *J* = 8.7 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 38.10, 55.39, 98.22, 105.13, 120.96, 132.57, 160.90, 164.27, 198.90; EI-MS: *m/z* 359.27 (M+1).

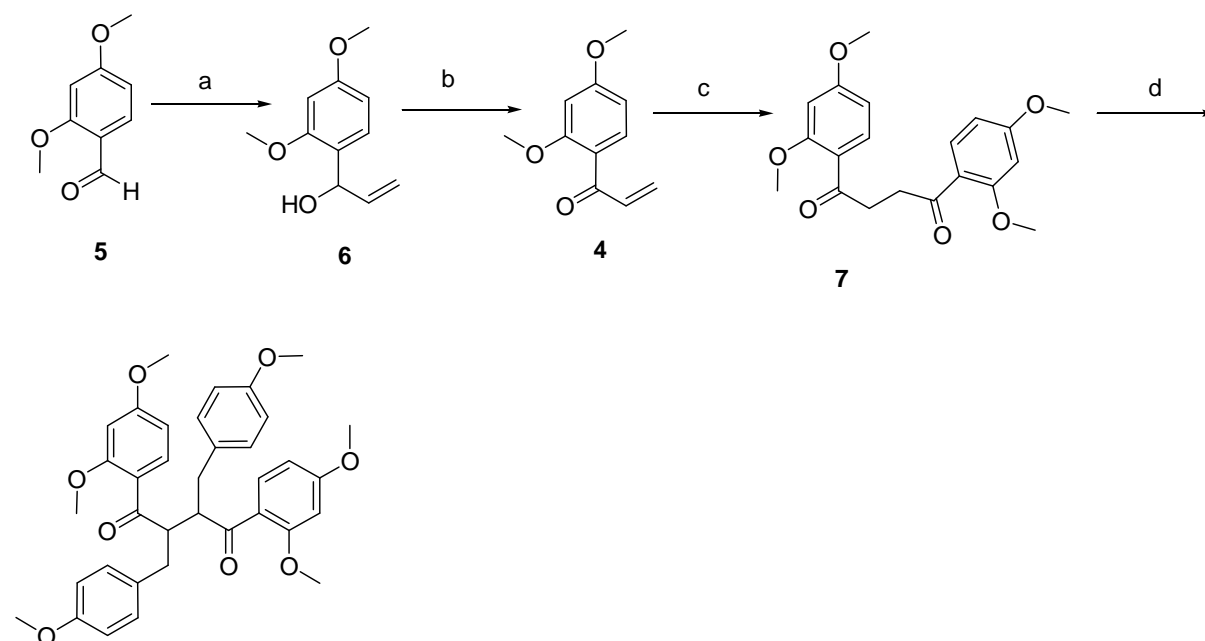
RESULTS AND DISCUSSION

In considering various alternatives for its synthesis (title compound) we choose to regard brackenin simply as a substituted 1,4-dicarbonyl. We have earlier reported the title compound using 2,4-dimethoxy benzaldehyde adopting the dimerisation procedure under non-green reaction conditions [7]. In this paper, we wish to report the synthesis of title compound applying green methodologies, from readily available 2,4-dimethoxy acetophenone and 2,4-dimethoxy benzaldehyde. Vinyl ketone **4** (Scheme 1) was obtained in three steps from 2,4-dimethoxy acetophenone by modifications of the previously described procedures [8,9]. Mannich reaction of 2,4-dimethoxy acetophenone was carried out using aqueous; 40% dimethyl amine solution in presence of water as solvent and methane sulphonic acid as an efficient organocatalyst. The presence of water and methane sulphonic acid makes the reaction medium as an entirely green and highly efficient one-pot Mannich reaction [10,11]. Isopropyl acetate was used as the solvent of choice during the conversion of Mannich base **2** to the vinyl ketone **4**. Isopropyl acetate was preferred over ethyl acetate as an extraction solvent since the relatively high solubility of EtOAc in water (and water in EtOAc) due to which the aqueous waste is contaminated with more organic material, thus making it difficult to dispose off and also the product could be lost in the aqueous layer.



Scheme 1: Experimental conditions: a) paraformaldehyde (HCHO), aqueous 40%; dimethyl amine, water, methane sulphonic acid (10 mol%), reflux, 12 hours; b) MeI, Isopropyl acetate, r.t., 6 hours; d) H₂O, Isopropyl acetate, reflux, 3 hours.

The synthesis of the title compound is outlined in Scheme 2. Conversion of aldehyde **5** to carbinol **6** was achieved using Barbier reaction conditions over the Grignard reaction. Aldehyde **5** was treated with vinyl bromide in presence of zinc metal in 2-Methyltetrahydrofuran at r.t. for 3 hours. The reaction is similar to the Grignard reaction but the crucial difference is that the Barbier reaction is a one-pot synthesis whereas a Grignard reagent is prepared separately before addition of the carbonyl compound. Barbier reactions are nucleophilic addition reactions that usually take place with relatively inexpensive and water insensitive metals or metal compounds in contrast to Grignard reagents or organolithium reagents thus making the procedure part of green chemistry. Furthermore, 2-Methyl tetrahydrofuran (2-MeTHF) which is derived from renewable resources such as corncobs and bagasse was used as a choice of solvent during Barbier reaction, when used as an organometallic solvent, 2-MeTHF offers both economical and environmentally friendly advantages over tetrahydrofuran. Oxidation of carbinol **6** using CsOH in presence of air [12] in toluene at 90 °C for 16 hours resulted in the formation of vinyl ketone **4**. Conversion of vinyl ketone **4** to 1,4-diketone **7** was achieved by Stetter reaction using thiazolium catalyst [13-17] in presence of triethyl amine in [bmim] [PF₆] as ionic liquid. The Stetter reaction can be performed in imidazolium type RTILs (room temperature ionic liquids) as solvents [18], with thiazolium salts and triethyl amine as catalysts. In these conditions the 1,4-diketones were isolated in good yields, usually higher than those obtained in classical organic solvents. Furthermore, it was possible to recycle and reuse the ionic liquid but not the catalyst. Finally the synthesis of the title compound was achieved by reacting 1,4-diketone **7** with 4-methoxy benzylbromide in presence of LDA in HMPTA as reported earlier 7.

**Meso (8) + racemic (9)**

Scheme 2: Experimental conditions: a) Vinyl bromide, Zn, aq; NH₄Cl, 2-MeTHF, r.t., 3 hours; b) CsOH, air, toluene, 90 °C, 16 hours; c) 2,4-Dimethoxy benzaldehyde, Thiazolium catalyst, Triethyl amine, [bmim] [PF₆], 80 °C, 10 hours; d) LDA-Lithium di-isopropyl amide, HMPTA-Hexamethylphosphoric triamide, 4-methoxy benzylbromide, -78 °C-r.t., 12 hours.

CONCLUSION

In conclusion, the present paper describes facile route to the synthesis of 1,4-Bis-(2,4-dimethoxyphenyl)-2,3-bis-(4-methoxybenzyl)-butane-1,4-dione, a brackenin like molecule in a few high yielding steps utilizing green methodologies from readily available raw materials.

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