°C and $P(OMe)_3$ (16 mL, 16.8 g, 0.135 mol) was added over a period of 30 min. The mixture was warmed to room temperature and then poured into a 1-L three-necked flask containing a sodium naphthoxide solution [prepared from 1-naphthol (14.5 g, 0.10 mol) and NaH (2.4 g, 0.10 mol) in *t*-BuOH (400 mL, dried over 3-Å powdered molecular sieves) under nitrogen] and a stir bar. Ti(O-*i*-Pr)$_4$ (36 mL, 34.4 g, 0.12 mol) was added, and the mixture was stirred overnight at room temperature under nitrogen.

The reaction mixture was filtered through a pad of Celite and the pad washed with EtOAc (300 mL). The filtrate was concentrated to ca. one-fourth of its volume, 10% H_2SO_4 (200 mL) was added, and the mixture was stirred vigorously for 1 h. Phase separation, several ether extractions of the aqueous phase, and concentration of the combined organic phases at 60 °C (first at 20 mm and then at 0.5 mm) were followed by hydrolysis of the tartrate ester (150 mL ether and 100 mL 1 N NaOH, stirred for 45 min at room temperature). The phases were separated, the aqueous layer was extracted with portions of ether, and the combined organic layers were washed with saturated NH_4Cl and brine, dried (Na_2SO_4), and concentrated to provide crude (2*S*)-3-(1-naphthoxy)-1,2-propanediol. It was recrystallized from hot CCl_4 to yield the analytically pure product: 11.8 g (54%); mp 105–106 °C; $[\alpha]^{25}_D$ +7.3° (*c* 0.48, EtOH) [lit.[9b] $[\alpha]^{25}_D$ +7.7° (*c* 1.0, EtOH)]; ^{1}H NMR ($CDCl_3$) δ 8.21 (m, 1 H), 7.91 (m, 1 H), 7.33–7.52 (m, 4 H), 6.82 (d, J = 7.5 Hz, 1 H), 4.16–4.31 (m, 3 H), 3.93 (dd, J = 3.0, 11.4 Hz, 1 H), 3.86 (dd, J = 5.8, 11.2 Hz, 1 H), 2.61 (br, 2 H); IR (Nujol) 3240, 3070, 2930, 2860, 1600, 1560, 1510, 1460, 1405, 1380, 1275, 1245, 1105, 1075, 1070, 990, 790, 775, 770 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.50; H, 6.51.

The 1-naphthoxydiol was converted to the bis Mosher ester, which was analyzed by ^{1}H NMR and observed to be ca. 90% ee.

Acknowledgment. We are grateful to the National Institutes of Health (Grant GM28384) and Eli Lilly and Co. for financial support.

Registry No. **3**, 97798-48-6; **4**, 86884-91-5; **5**, 105183-41-3; **5** (diacetate), 105183-42-4; **6**, 56715-19-6; allyl alcohol, 107-18-6; *N*-isopropylbenzylamine, 102-97-6; 1-naphthol, 90-15-3; benzenethiol, 108-98-5; methallyl alcohol, 513-42-8.

Biomimetic Approach to Biflavonoids: Oxidative Coupling of 2′-Hydroxychalcones with I_2 in Alkaline Methanol

Syed Mashhood Ali and Mohammad Ilyas*

Department of Chemistry, Aligarh Muslim University, Aligarh-202001, India

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Biflavonoids are formed in nature from flavonoid C_6.C_3.C_6 precursors produced by the condensation of acetate–malonate units onto a cinnamic acid starter molecule.[1] While the chalcone–flavanone couple is accepted as the first biogenetic entity whereby all biflavonoids are produced in plants, the question whether the chalcones or flavonones are more immediate precursors is not yet resolved. There is some evidence from the competitive feeding experiments[2] that chalcones are more immediate precursors, but the ready enzymic chalcone–flavanone isomerization still leaves some doubts.

Biflavonoids differ not only in the interflavonoid linkage but also in their oxygenation patterns and oxidation level of the central three carbons.[3,4a] A general survey of the structures of natural biflavonoids reveals that compounds having an oxidation level of the C_3 unit either equal to or higher than the chalcone–flavanone couple prevail in large numbers. The oxygenation pattern in their benzene rings is typical: ring A generally has three alternate oxygens at positions 2′, 4′, and 6′ in the open formula, while ring B has, in most cases, a para oxygen function with respect to the central three carbons.

It is now generally believed that all natural biflavonoids are produced in vivo by the oxidative coupling of chalcones to bichalcones followed by modification of the C_3 chain.[3,4a,5] To the best of our knowledge, there is neither a chemical analogy to this hypothesis nor any report on the isolation of bichalcones from a natural source. Attempts have occasionally been made to mimic the synthetic strategy in vitro in the production of biflavonoids from chalcones[6,7] as well as flavanones.[7] However, in no case could oxidative coupling be achieved and the products of these oxidation reactions were either aurones or flavones. The present paper describes oxidative coupling of 2′-hydroxy-4,4′,6′-trimethoxychalcone (**1**) and 2′-hydroxy-4,4′-dimethoxychalcone (**3**) to 2′,2‴-dihydroxy-4,4′,4″,4‴,6′,6‴-hexamethoxy[5′,5‴]bichalcone (**2**) and 2′,2‴-dihydroxy-4,4′4″,4‴-tetramethoxy[3′,5‴]bichalcone (**4**), respectively, with iodine in alkaline methanol, which provides evidence in fav or of the generation of a radical on ring A of chalcone.

Results and Discussion

The Ullmann coupling reaction comprises major route to biflavonoids. The reported synthetic approaches employ The Ullmann reaction in two ways: one involves coupling of two iodinated flavonoid nuclei[8], whereas the other is based on the synthesis of suitably substituted biphenyls followed by heteroannulation.[9] Because of the poor yield in the coupling step and the fact that iodo derivatives are not trivial to prepare, this route to biflavonoids is not practical. In the event of failure of our initial efforts to prepare bichalcones by this route,[10] we directed attention to phenol oxidative coupling. Added impetus for pursuing this approach came from the fact that oxidative coupling of chalcones is considered to be the intermidiate step in the biogenesis of biflavonoids.

To avoid possible chalcone–flavonone isomerization during coupling reaction, we desired to study the reaction under basic conditions. Although alkaline potassium ferricyanide is a recommended oxidant for achieving oxidative coupling,[11] it has not proved successful in the case of chalcones. We selected the I_2/$^-$OH system[12] for this purpose. The chalcones selected for the study were those having the typical oxygenation pattern of biflavonoids. All the hydroxy groups except that at the 2′ position were protected by methylation.

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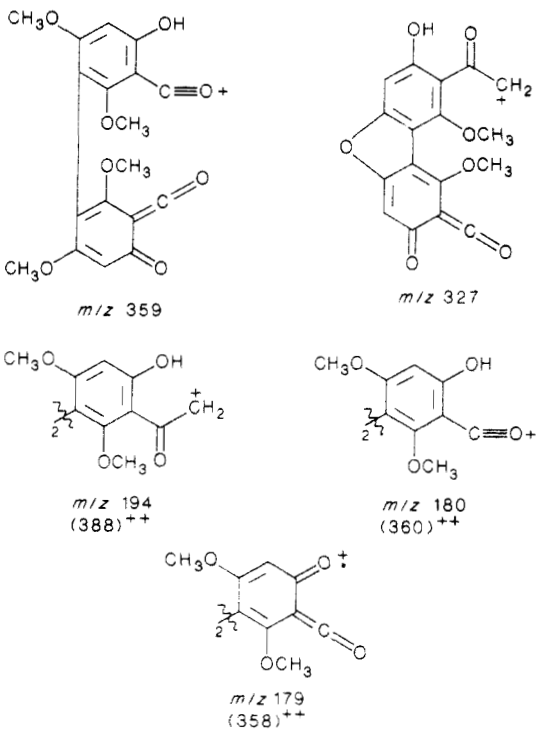
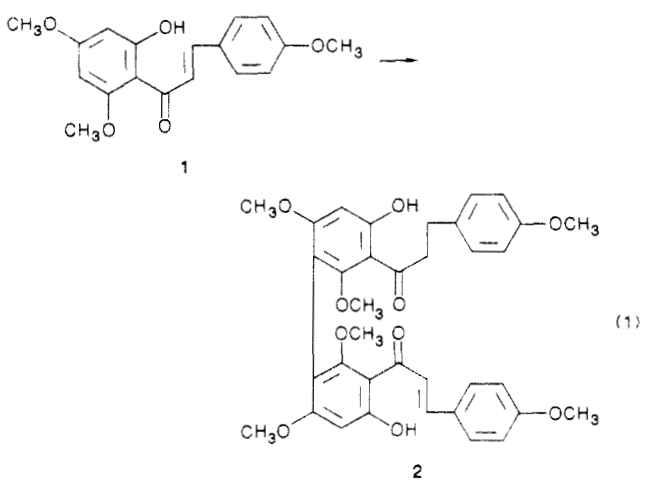
Chart I



Treatment of 2′-hydroxy-4,4′,6′-trimethoxychalcone (**1**) with iodine in methanol in the presence of potassium hydroxide afforded a known bichalcone, 2′,2‴-dihydroxy-4,4′,4″,4‴,6′,6‴-hexamethoxy[5′,5‴]bichalcone (**2**), characterized by spectral methods (IR, UV, NMR, and mass) (eq 1). The interchalcone linkage of two chalcone units



in **2** through A rings was indicated by the fragments at m/z 359, 327, 194, 180, and 179 in the mass spectrum (Chart I).[4b] A cursory examination of the NMR spectrum of **2** revealed high symmetry in the molecule. The possibility of [3′,5‴]-linkage was, therefore, ruled out. A shielded singlet in the aromatic region for two protons at δ 5.62 was ascribed to the 3′ and 3‴ protons. Unequivocal evidence in support of the 5′,5‴-linkage was obtained by the oxidation of **2** with SeO_2 in isoamyql alcohol to give a biflavone, which was found to be identical with an authentic sample of succedaneaflavone hexamethyl ether[13] (Co-TLC, characteristic UV shade and NMR).

2′-Hydroxy-4,4′-dimethoxychalcone (**3**) when treated with iodine under almost identical conditions furnished

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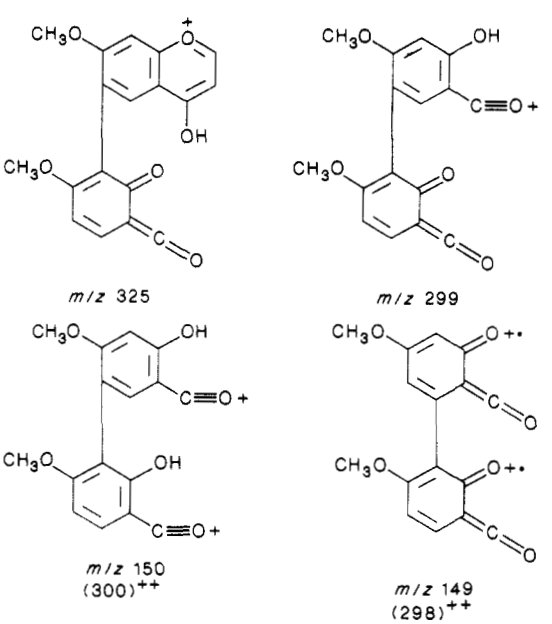
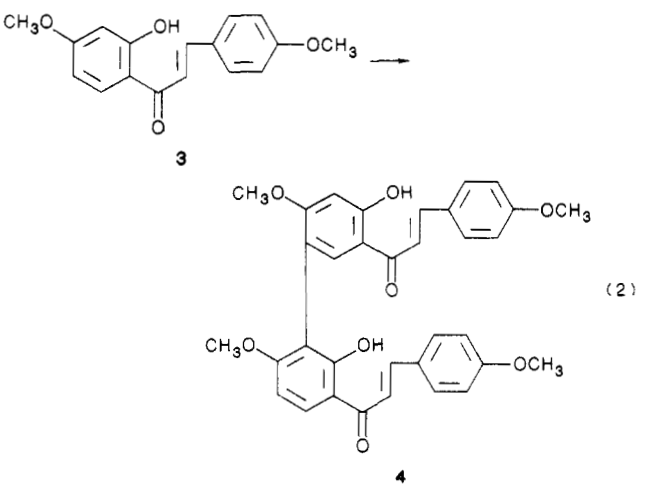
Chart II



the hitherto unknown 2′,2‴-dihydroxy-4,4′,4″,4‴-tetramethoxy[3′,5‴]bichalcone (**4**) (eq 2). Although IR and



UV spectra of **4** helped in the preliminary characterization, the position of the linkage was established mainly from NMR and mass spectral data. The involvement of both the A rings in the linkage was supported by the ions at m/z 325, 299, 150, and 149 in the mass spectrum of **4** (Chart II). The NMR spectrum of **4** displayed methoxyl signals as a compact group in the region δ 3.70–4.40. Two singlets at δ 6.65 and 8.30, each for one proton, were assigned to 3‴ and 6‴ protons, respectively. Signals for the remaining aromatic protons as well as four olefinic protons appeared as two complex multiplets, each integrating for seven protons.

The transformation of 2′-hydroxychalcones to bichalcones proves that a phenolic A ring radical has been formed. Our results are interesting both from biogenetic as well as synthetic points of view. The oxidative coupling of chalcones, described in this paper, is the first in vitro experiment in support of the hypothesis for the biogenesis of biflavonoids and supports the idea that chalcones may be precursors in the biosynthesis of biflavonoids. The reaction provides evidence in favor of generation of a radical of ring A of chalcone, a serious limitation of previous studies. The methodology developed for the synthesis of bichalcones, besides being most closely related to the process that is believed to occur in nature, is a

complement to previously reported methods. Bichalcones serve as important synthetic intermediates in the syntheses of various biflavonoids differing in the oxidation level of the C_3 unit. Our procedure should therefore be applicable to nearly all natural biflavonoids through the intermediacy of bichalcones prepared from suitably substituted chalcones. Moreover, our results indicate that iodine in alkaline methanol is a simple and very useful reagent for phenol oxidative coupling. Its synthetic utility could well be exploited in those instances where the phenolic groups are hydrogen bonded. The hydrogen-bonded hydroxyls have been reported[7] to resist oxidation.

Experimental Section

Melting points were determined on a Kofler microscopical hot stage and are uncorrected. IR and UV spectra were obtained on Pye Unicam SP3-100 and PU 8800 spectrophotometers, respectively. NMR spectra were measured with a Varian A-60D instrument, and mass spectra with a JEOL JMS-D300 instrument.

Preparation of 2′-Hydroxy-4,4′,6′-trimethoxychalcone (1). To a mixture of phloroacetophenone-4,6-dimethyl ether (5 g, 25.5 mmol) and *p*-anisaldehyde (3.47 g, 25.5 mmol) in alcohol was added a hot 50% aqueous solution of sodium hydroxide (10 g). The resulting mixture was heated at 50 °C for 30 min. The contents were then cooled and poured into cold water and neutralized with dilute HCl. A yellow solid was obtained that was filtered, washed, and dried. Crystallization from alcohol yielded yellow needles of **1** (5.85 g, 73%), mp 112–114 °C (lit.[14] mp 113–114 °C).

Preparation of 2′-Hydroxy-4,4′-dimethoxychalcone (3). To a cold suspension of equimolar amounts of 2-hydroxy-4-methoxyacetophenone (8 g, 50 mmol) and *p*-anisaldehyde (7 g, 50 mmol) in alcohol (160 mL) was added a cold 60% aqueous solution of potassium hydroxide (95 g). The flask was stoppered securely and allowed to stand at room temperature for 1 week with occasional shaking. The contents were then poured on to crushed ice and neutralized with dilute HCl to give a yellow precipitate. The crude solid was filtered, washed with water, dried, and crystallized from methanol to afford yellow needles of **3** (10.4 g, 74%), mp 89–91 °C (lit.[7] mp 90–91 °C).

2′,2‴-Dihydroxy-4,4′,4″,4‴,6′,6‴-hexamethoxy[5′,5‴]bichalcone (2). 2′-Hydroxy-4,4′,6′-trimethoxychalcone (314 mg, 1 mmol) was dissolved in methanol, and a methanolic solution of potassium hydroxide (0.5 g) was added to it. To the resulting mixture was added iodine (127 mg, 0.5 mmol) with shaking. The contents were stirred at room temperature for 3 h and poured into ice-cold water. A red solid precipitated that was filtered, washed with water, and dried. Crystallization from alcohol yielded red crystals of **2** (220 mg, 70%), mp 189–191 °C (lit.[13] mp 191–192 °C): UV λ_{max} (MeOH) 228, 350, 370 nm; IR ν_{max} (KBr) 3440, 1625, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 3.80–4.00 (18 H, s, 4,4′,4″,4‴,6′,6‴-OCH_3), 5.62 (2 H, s, 3′,3‴-H), 6.90 (4 H, d, J = 9 Hz, 3,5,3″,5″-H), 7.50 (4 H, d, J = 9 Hz, 2,6,2″,6″-H), 7.65 (4 H, s, $\alpha,\beta,\alpha',\beta'$-H), 14.35 (2 H, s, 2′,2‴-OH); MS, m/z (relative intensity) 626 (M, 80.68), 611 (8.62), 519 (3.56), 493 (6.54), 492 (13.56), 491 (10.10), 465 (15.48), 464 (22.49), 463 (56.86), 461 (20.19), 358 (16.42), 357 (3.14), 327 (21.43), 314 (20.24), 313 (8.92), 312 (11.73), 301 (11.64), 194 (16.37), 179 (12.16), 180 (4.50), 161 (19.41), 134 (60.21), 133 (22.85), 121 (100).

Oxidation of 2. A mixture of **2** (100 mg) and SeO_2 (0.5 g) in isoamyl alcohol was refluxed for 24 h. The contents were then poured on the crushed ice. A solid precipitated that was filtered, washed with water, and dried. Crystallization from a chloroform/methanol mixture gave succedaneaflavone hexamethyl ether. Melting point, TLC, and NMR spectrum were in good agreement with that reported in the literature.[13]

2′,2‴-Dihydroxy-4,4′,4″,4‴-tetramethoxy[3′,5‴]bichalcone (4). The reaction was performed in the previously described manner. Thus, 2′-hydroxy-4,4′-dimethoxychalcone (500 mg, 1.76 mmol) was dissolved in methanol and a methanolic solution of potassium hydroxide (1 g) was added to it with shaking. Iodine (112 mg, 0.88 mmol) was added to the resulting mixture and the contents were stirred at room temperature for 3 h and poured into ice-cold water. The organic material was extracted with ethyl acetate and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a yellow solid, which was crystallized from alcohol to give crystals of **4** (370 mg, 74%), mp 180–181 °C; UV λ_{max} (MeOH) 210, 230, 330, 380 nm; IR ν_{max} (KBr) 3440, 1620 cm^{-1}; NMR ($CDCl_3$) δ 3.85, 3.90, 4.00, 4.03 (3 H, each, s, 4,4′,4″,4‴-OCH_3), 6.65 (1 H, s, 3‴-H), 6.90 (7 H, mc, 5′,α,α',3,5,3″,5″-H), 7.75 (7 H, mc, 6′,β,β',2,6,2″,6″-H), 8.30 (1 H, s, 6‴-H), 13.60 (1 H, s, 2′-OH), 14.00 (1 H, s, 2‴-OH); MS, m/z (relative intensity) 567 (3.21), 566 (M, 19.23), 565 (30.64), 459 (4.62), 458 (3.29), 433 (14.19), 432 (19.61), 405 (45.23), 404 (67.32), 326 (16.73), 325 (28.11), 299 (18.31), 271 (8.67), 163 (7.35), 161 (67.32), 150 (1 4.59), 149 (10.95), 135 (24.45), 134 (100), 133 (34.56), 121 (28.91).

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Registry No. 1, 3420-72-2; 2, 57290-97-8; 3, 2198-19-8; 4, 105281-48-9; phloroacetophenone 4,6-dimethyl ether, 90-24-4; 2-hydroxy-4-methoxyacetophenone, 552-41-0; *p*-anisaldehyde, 123-11-5; succedaneflavone hexamethyl ether, 57290-98-9.

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Practical Conversion of Artemisinic Acid into Desoxyartemisinin

Mankil Jung,*[1] Hala N. ElSohly, and Edward M. Croom[2]

Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, Mississippi 38677

Andrew T. McPhail and Donald R. McPhail

Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

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Artemisinin (Qinghaosu, **2**) isolated from *Artemisia annua* has recently been used in China as a new type of antimalarial drug with rapid action and low toxicity against chloroquine-resistant malaria.[3,4] Artemisinin is a novel sesquiterpene lactone bearing an unusual cyclic peroxide function. The combination of an interesting biological activity, a novel chemical structure, and a low yield from natural sources prompted us to search for a new synthesis of artemisinin and related compounds. Although interesting syntheses[5-7] of artemisinin and desoxyartemisinin were reported recently, these complex syntheses do not provide feasible methods for large-scale production. *A. annua* has been found to contain approximately 8–10 times more artemisinic acid than artemisinin.[8] We therefore attempted a new synthesis that embodies highly stereospecific conversion of artemisinic acid (**1**) into artemisinin (**2**) (Scheme I). Stereoselective reduction[7] of artemisinic acid (**1**) [$LiBH_4$ (5.3 equiv), $NiCl_2{\cdot}6H_2O$ (0.49 equiv), CH_3OH, room temperature, 2 h] into the dihydro compound **3a** (quantitative yield), followed by ozonolysis[7] of **3a** (O_3, CH_2Cl_2/CH_3OH = 1/1.5, −78 °C for 1 h and then CH_3SCH_3 workup), gave the keto aldehyde **4**, 75%.

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(2) Department of Pharmacognosy, University of Mississippi.
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