Synthesis of Benzoylbenzo[b]furan and Derivatives

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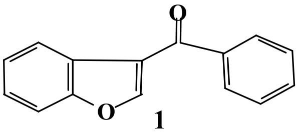
Abstract

3-Benzoylbenzofuran is a part of the structure of natural product such as Daphnodorins A and B extracted from *Daphne odora* roots and flowers, herbal medicine. The compounds present in very limited amount. A prototype of benzoylbenzo[b]furan(1) and its derivatives were synthesized from 2-hydroxybenzil(21) as a model for natural product synthesis that contains 3-benzoylbenzofuran as its fundamental structure. 3-Benzoylbenzofurans(22) and isoflavones(23) were successfully synthesized by refluxing 2-(carboxyalkoxy)benzils(21) with sodium acetate, acetic acid and acetic anhydride in good yields. The starting compounds for our synthesis are 2-hydroxybenzils(20), which were readily prepared by the reaction of ester derivatives(19) with LDA at -78 ^{o}C. Conversion of 2-hydroxybenzils(20) to 2-(carboxyalkoxy)benzils(21) was accomplished by reaction with ethyl bromoacetate and subsequent hydrolysis. Demethylation of compounds(22) by refluxing with 48% hydrobromic acid and acetic acid afforded compound(24) as the model compounds (46% yield).

Introduction

Natural products have been increasingly used as environmental friendly chemicals for many purposes. Benzofurans of the basic structure(1) are considerably rare natural products and are important in pharmaceutical industries. However, these types of compounds have been isolated in only small amounts from plants. Brady et. al[1]. have reported a synthesis of 3-benzoylbenzofuran and derivatives *via* intramolecular cyclization of 2-(carboxymethoxy)benzil(2). The corresponding isoflavone(3) has also been produced from the reaction. Some important natural products contain the basic unit of benzofuran have also been extensively investigated[2-6].



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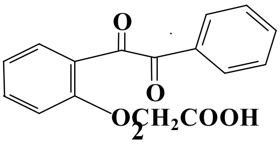

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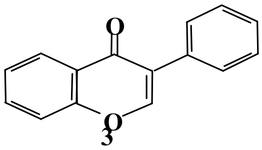

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Baba et. al.[7] reported the isolation of new flavans, daphnodorin A (4) and daphnodorin B (5) from *Daphne odora*. These compounds show striking activity as a pain reliever. Calodinins (6-7) which have been isolated from many plants[8-10] also show some potential in antifungal activities.

Isoflavones, found in several plants, have been widely investigated due to some of them possess interesting biological activities[11-14]. Flemiphilippinin A (8) and flamiphilippin B (9) have been isolated from *Flemingia philippinensis*[15]. These compounds have been shown to possess some activities against P_{388} lympocytic leukemia cells. A group of isoflavones (10-15), isolated from soybean, has been shown to possess anti-cancer activities, especially breast cancer[16-18]. Moreover, dihydroxyflavone of (10) has been found to have greater anti-cancer activity than the parent compound[18-19].

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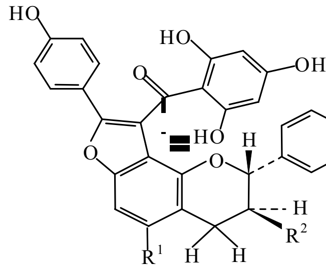
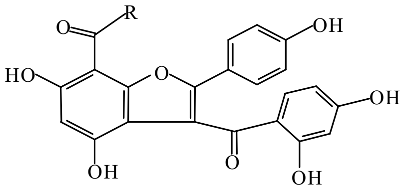
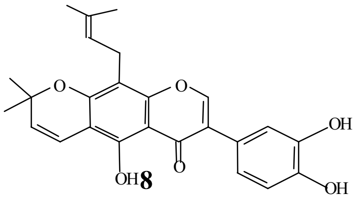


4, R^1 = OH, R^2 = H
5, R^1 = H, R^2 = OH



6, R = p-$HOC_6H_4CH=CH$-
7, R = p-$HOC_6H_4CH_2CH_2$-



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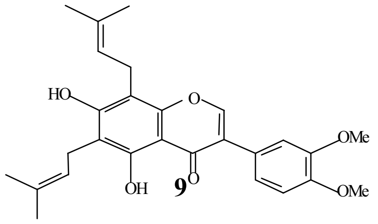

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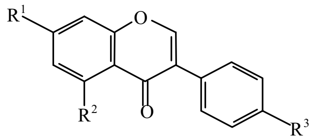
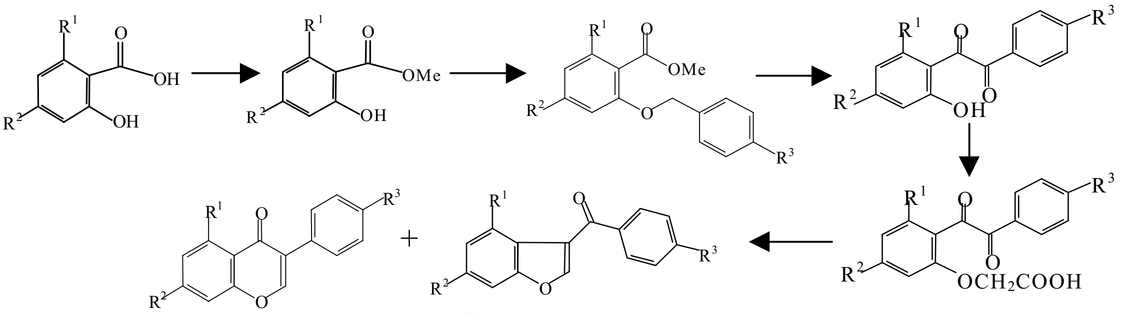


10, R^1 = OH, R^2 = H, R^3 = OH
11, R^1 = O-Glu, R^2 = H, R^3 = OH
12, R^1 = OH, R^2 = H, R^3 = OMe
13, R^1 = R^2 = R^3 = OH
14, R^1 = O-Glu, R^2 = R^3 = OH
15, R^1 = R^2 = OH, R^3 = OMe

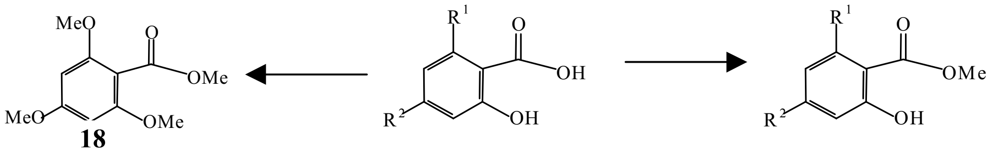
Of those flavanoid compounds mentioned, daphnodorins A and B are new isoflavanoid compounds that have been shown potential use as pain reliever. However, they can only be isolated in tiny quantity from plants. Synthesis is an alternative approach to obtain quantitative amounts of the compounds. In this study, synthetic approach to benzoylbenzo[b]furan and its derivatives have been proposed (Scheme 1). These would lead to the total synthesis of daphnodorins A and B as well as their derivatives.



Scheme 1

Results and discussion

Our work is to investigate the possibility of the synthesis of some derivatives of 3-benzoylbenzo[b]furan (1). These compounds would lead to the complicated structures of the natural products daphnodorins A (4) and B (5). According to the report[1], synthesis of 3-benzoylbenzo[b]furan also resulted in the formation of an isoflavone. Synthetic sequences leading to the benzofurans and isoflavones have been proposed as shown in Scheme 1. Hence, acids 16a and 16b were converted to the corresponding methyl esters 17a and 17b under the normal esterification conditions (Scheme 2) in good yields[20]. The structures of the methyl esters have been confirmed spectroscopically and on their physical properties.



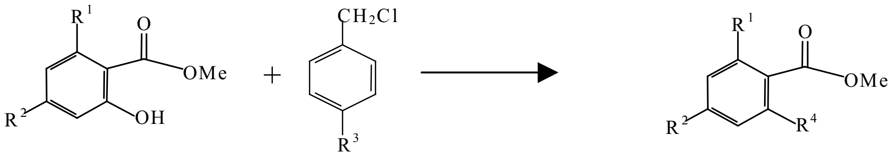
18

16a, R^1 = H, R^2 = OH
b, R^1 = R^2 = OH

17a, R^1 = H, R^2 = OH
b, R^1 = R^2 = OH
c, R^1 = R^2 = OMe
d, R^1 = H, R^2 = OMe

Scheme 2

The methyl esters 17(a,b,c) were reacted with either benzyl chloride or 4-methoxybenzyl chloride to afford the corresponding benzylated products (Scheme 3)[21-23]. However, the methyl esters 17a gave only 17% yield of the completed benzylated product (19k) and 51% yield of the 2-hydroxy-4-methoxybenzyloxy-benzoate (19f). While high yields of 19i and 19j were the only products obtained from the reactions of 17b with the corresponding benzyl chlorides. It was found that compounds with more than one hydroxyl group, the introduction of benzyl group to all the hydroxyl position is unlikely to occur. The synthesis was further complicated with the reaction of methyl 2,4-dibenzyloxybenzoate (19e) with LDA at –78°C. The products obtained from the reaction were difficult to separate and the mixture contains several components of unwanted products.



17a, R^1 = H, R^2 = OH
b, R^1 = R^2 = OH
c, R^1 = R^2 = OMe
d, R^1 = H, R^2 = OMe
e, R^1 = R^2 = H

R^3 = H, OMe

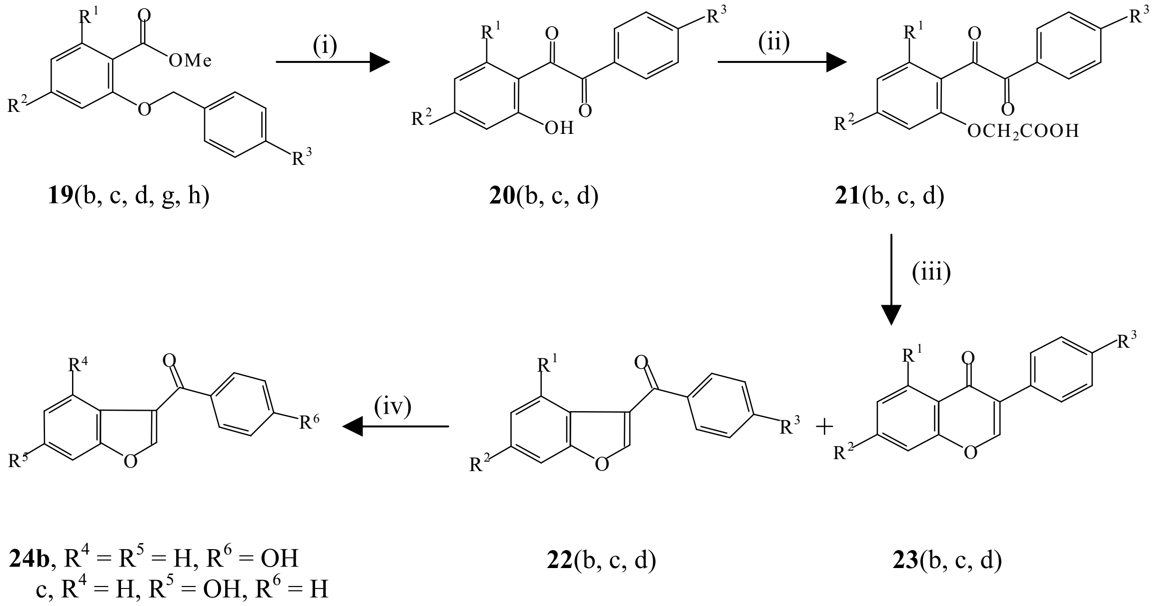
Bz = Benzyl
MPM = 4-Methoxybenzyl

19a, R^1 = R^2 = H, R^4 = OBz
b, R^1 = R^2 = H, R^4 = OMPM
c, R^1 = H, R^2 = OMe, R^4 = OBz
d, R^1 = H, R^2 = OMe, R^4 = OMPM
e, R^1 = H, R^2 = R^4 = OBz
f, R^1 = H, R^2 = OMPM, R^4 = OH
g, R^1 = R^2 = OMe, R^4 = OBz
h, R^1 = R^2 = OMe, R^4 = OMPM
i, R^1 = OH, R^2 = OBz, R^4 = OH
j, R^1 = R^2 = OMPM, R^4 = OH
k, R^1 = H, R^2 = R^4 = OMPM

Scheme 3

Due to the problems mentioned above, it has been designed to protect some of the hydroxyl groups except hydroxyl group at position 2 prior to their further benzylation. By taking the advantages of the steric effect, the remote hydroxyl groups would be reacted first. It was found that 17a reacted smoothly with dimethyl sulfate in sodium carbonate[21] to give methyl 2-hydroxy-4-methoxybenzoate (17d) in 81% yield. The melting point and spectroscopic data of the compound have been confirmed. On the other hand, methyl 2-hydroxy-4,6-dimethoxybenzoate (17c) could be obtained directly from 2, 4, 6-trihydroxybenzoic acid (16b) by reaction with dimethyl sulfate and sodium carbonate in moderate yield.

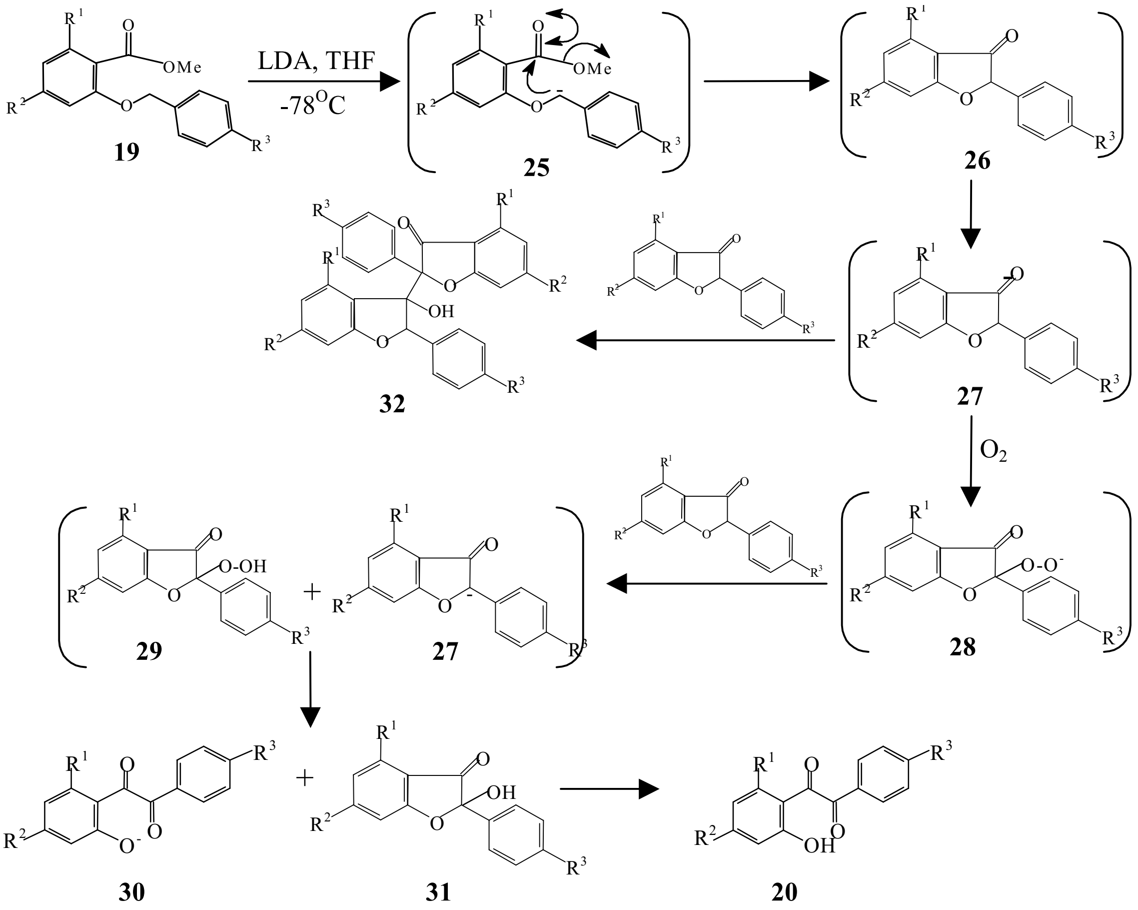
Further reactions of methyl esters 17(c,d,e) with either benzyl chloride or 4-methoxybenzyl chloride as usual manner (Scheme 3)[22] to give the corresponding benzylated products 19(b,c,d,g,h) in good yields. The physical properties including their spectroscopic data were found to agree very well with their structures. Having prepared the benzylated products, 19 (b,c,d,g,h), the next step has been the reaction of 19 with LDA at –78°C under nitrogen (Scheme 4-i). It was found that benzylated products 19(b,c,d) reacted as expected to give the corresponding benzil derivatives 20(b,c,d) in fair yields. It has been suggested that mechanism[23] of the formation of benzil derivatives would go through the benzylic carbanion intermediates (Scheme 5).



(i) LDA/THF, -78°C
(ii) K_2CO_3/acetone, then ethyl bromoacetate/reflux
(iii) Ac_2O-AcOH-NaOAc/reflux
(iv) 48%HBr-AcOH/reflux

Scheme 4

The benzylic carbanion (25) would reacts *via* intermediates 26-31 to afford both 20 and 32, respectively. The molecular oxygen would play an important role in this transformations. The diketones 20(b,c,d) were clearly confirmed by mass spectra on their molecular ions at m/z 256 (for both 20b and 20c) and 286 for 20d. The diketone 20b was further confirmed by its fragmentations at m/z 121(5%) and 135(100%). While the diketone 20c fragmented to give m/z at 151(100%) and 105(2%). However, fragmentations of diketone 20d gave m/z at 151(100%) and 135(42%) instead. Besides the products mentioned there also obtained coumarones 26b and 26d from the reactions. On the other hand, 19c resulted in the formation of dimer 32c. The structures of all compounds were confirmed by their physical properties and spectroscopic data. Under the same reaction conditions, several attempts have been made to bring about the transformation of compounds 19g and 19h were failed. It is clearly that the presence of the methoxy group at position 6 would form chelation with lithium ion and forces the base out of the right position for abstracting the benzylic protons[23].



Scheme 5

In the step (ii) of Scheme 4, benzils 20(b,c,d) were easily transformed to the corresponding acids 21(b,c,d) in good yields. The reactions were accomplished by refluxing the acids with ethyl bromoacetate in weak base and followed by hydrolysis. The structures of products have been confirmed by their melting points and spectroscopic data. The products 21(b,c,d) obtained were then converted to the corresponding benzo[b]furans 22(b,c,d) and isoflavones 23(b,c,d) in step (iii) by refluxing the acids 21(b,c,d) with Ac_2O-AcOH-AcONa[24-27]. Again, the melting points and spectroscopic data, especially the mass spectra of the products all agree with the structures. It is worth to note that 22b and 23b show the same molecular weight in mass spectra as well as those 22c and 23c, and 22d and 23d. However, further fragmentations will be characteristic patterns of each compound. The mechanism of the reactions have been suggested to be intramolecular cycloaddition *via* ketene intermediate[1].

The final step (Scheme 4-iv) is the demethylation 22(b,c,d) under reflux of 48%HBr and acetic acid[28]. It was found that only 22b and 22c were successfully converted to the corresponding hydroxy compounds 24b and 24c. However, it was failed to isolate 24d from the reaction mixture.

Experimental

R-1500 FT-NMR spectrometer (Hitachi, 60MHz) has been used as routine analyses, and high resolution ^{1}H NMR 200 MHz and ^{13}C NMR spectrometers (Bruker AM 200) have been used to record all the reference spectra. The infrared spectra were recorded on FT-IR spectrometer 2000 (Perkins Elmer) and the CHN analyses were recorded on the Perkins Elmer elemental analyzer (PE 2400 series II CHNS/O analyzer). All the solvents and reagents, if necessary, were freshly prepared and distilled or recrystallized and dried prior to use.

1. Preparation of methyl 2,4-dihydroxybenzoate (17a)

To a 100-mL round-bottomed flask were added 12.01g (0.08 mol) of 2,4-dihydroxybenzoic acid (16a), methanol (50 mL), and conc. sulfuric acid (5 mL) and the resulting mixture was heated at reflux for 22 h with stirring. The reaction mixture (brownish solution produced was gradually changed to greenish brown solution) was allowed to cool to room temperature and the solvent was evaporated. The crude product was poured into water (100 mL). The white precipitate was filtered and recrystallized from ethyl acetate-hexane to give methyl 2,4-dihydroxybenzoate (17a) 10.40g (79%) as pale green crystals, m.p. 118-120^{o}C (m.p. reported 116-118^{o}C)[29].

IR (KBr): ν_{max} 3339, 1642, 1505 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.90(s, 3H), 6.40(m, 2H), 7.80(d, J = 10.0Hz ,1H), 11.00(s, 2H)

MS m/z (% relative intensity): 168(M^+,100), 136 (90.04), 108(43.17)

2. Preparation of methyl 2,4,6-trihydroxybenzoate (17b)

The reaction was carried out in an analogous manner as reaction 1. After the crude product in water was extracted with ethyl acetate, the combined organic phases were washed with sodium hydrogen carbonate and followed by a solution of sodium chloride. The organic phase was dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica gel-ethyl acetate-hexane) to give brown oil of methyl 2,4,6-trihydroxybenzoate (17b) in 40% yield.

IR (Neat) : ν_{max} 3402, 1702, 1602 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.80(s, 3H), 6.15(s, 2H)

MS m/z (% relative intensity): 184(M^+, 0.09), 154(100), 125(61.56), 95(6.86)

3. Preparation of methyl 2-hydroxy-4,6-dimethoxybenzoate (17c)

To a 100-mL round-bottomed flask were added 11.99g (0.07 mol) of 2,4,6-trihydroxybenzoic acid (16b), dimethyl sulfate (25 mL, 250 mmol), sodium carbonate (26.50g, 0.25 mol), and acetone (2.5 mL) and the resulting mixture was heated at reflux with stirring for 8 h. The reaction mixture was allowed to cool to room temperature, filtered, and acetone was evaporated. The resulting mixture was diluted with toluene and stirred at room temperature for 1 hr, and the undissolved material was filtered off. The crude product was extracted with diluted solution of sodium hydroxide twice and the aqueous layer was acidified with 6M HCl to give a solution of pH 1-2. The resulting solution was extracted with toluene (3x25 mL). The combined organic phases were added (anhydrous Na_2SO_4), activated charcoal, filtered, and evaporated to dryness. The crude product was purified by recrystallization with toluene-heptane (2:1) to give methyl 2-hydroxy-4,6-dimethoxybenzoate (17c) 6.0g (40%) as colorless crystals, m.p. 102-104^{o}C (m.p. reported 108-109^{o}C)[30]. Together with 17c, methyl 2,4,6-trimethoxybenzoate (18) was obtained 1.02g (6%) as a yellow oil.

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70 Found: C, 56.48; H, 5.80

IR (Nujol): ν_{max} 1642, 1614 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.85(s, 3H), 3.90(s, 3H), 4.05(s, 3H), 6.05(d, J = 2.2 Hz, 1H), 6.20 (d, J = 2.6 Hz, 1H), 12.05(s, 1H)

MS m/z (% relative intensity): 212(M^+, 65.73), 180(100), 152(37.84), 137(20.09), 96(3.45)

4. Preparation of methyl 2-hydroxy-4-methoxybenzoate (17d)

The reaction was carried out in an analogous manner as reaction 3. The crude product was purified by recrystallization with toluene-heptane (2:1) to give methyl 2-hydroxy-4-methoxybenzoate (17d) as colorless crystals, m.p. 38-40°C (m.p. reported 39-41°C)[31] in 81% yield.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.38; H, 5.53 Found: C, 59.06; H, 5.73

IR (KBr): ν_{max} 1667, 1585 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.80(s, 3H), 3.90(s, 3H), 6.30-6.50(m, 2H), 6.70(d, J = 10.0 Hz ,1H), 11.00(s, 1H)

MS m/z (% relative intensity): 182(M^+, 90.61), 168(13.98), 150(100), 122(44.82), 107(14.20), 79 (6.86)

5. Preparation of methyl 2,4,6-trimethoxybenzoate (18)

The reaction was carried out in an analogous manner as reaction 3. The crude product was purified by preparative-layer chromatography (silica gel), developed by a mixture of ethyl acetate-hexane (3:7) to give methyl 2,4,6-trimethoxybenzoate (18) as a yellow oil in 83% yield.

IR (Neat): ν_{max} 1728, 1610 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.75(s, 3H), 3.78(s, 3H), 3.80(s, 3H), 3.85(s, 3H), 6.05(s, 2H)

MS m/z (% relative intensity): 226(M^+, 40.4), 195(100), 152(5.76)

6. Preparation of methyl 2-benzyloxybenzoate (19a)

To a mixture of 11.83g (0.08 mol) of methyl salicylate (17e), potassium carbonate (20.70g, 0.15 mol), and benzyl chloride (12 mL, 0.1 mol) dissolved in dimethylformamide (50 mL) were placed into a 100-mL round-bottomed flask. The resulting mixture was heated at 110°C with stirring for 4 h, and then allowed to cool to 25°C. The reaction mixture was poured into water and extracted with ethyl acetate (3x25 mL). The combined organic phases were washed with water followed by a solution of sodium chloride. The mixture was then dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness. The crude material was purified by column chromatography (silica gel-ethyl acetate-hexane) to give a colorless oil of methyl 2-benzyloxybenzoate (19a) 18.64g (99%).

IR (Neat): ν_{max} 1727, 1600 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.95(s, 3H), 5.20(s, 2H), 6.90-7.55(m, 8H), 7.85(dd, J = 2.0, 8.0 Hz)

MS m/z (% relative intensity): 242(M^+, 6.41), 210(100), 91(58.23)

7. Preparation of methyl 2-(4-methoxybenzyloxy)benzoate(19b)

To a mixture of 3.80g (0.025 mol) of methyl salicylate (17e) and potassium carbonate (5.52g, 0.04 mol) dissolved in dimethylformamide (25 mL) was placed into a 100-mL round-bottomed flask and the resulting mixture was stirred at 0°C. After 15 min, 4-methoxybenzyl chloride (3.4 mL, 0.025 mol) was added and the resulting mixture was heated at 110°C with stirring for 8 h, and then allowed to cool to 25°C. The reaction mixture was poured into water and extracted with ethyl acetate (3x25 mL). The combined organic phases were washed with water followed by a solution of sodium chloride. The mixture was then dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness. The crude material was purified by column chromatography (silica gel-ethyl acetate-hexane) to give a white solid. After recrystallization with petroleum ether, 6.73g (99%) of methyl 2-(4-methoxybenzyloxy)benzoate (19b) was obtained as colorless crystals, m.p. 50-52°C (m.p. reported 57-58°C)[32].

IR (KRr): ν_{max} 1715, 1597, 1515, 1227 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.75(s, 3H), 3.90(s, 3H), 5.10(s, 2H), 6.80-7.50(m, 7H), 7.80(dd, J = 2.0, 8.0 Hz,1H)

MS m/z (% relative intensity): 272(M^+,1.09), 121(100), 91(5.54), 78 (4.62)

8. Preparation of methyl 2-benzyloxy-4-methoxybenzoate (19c)

The reaction was carried out in an analogous manner as reaction 6 to give a colorless oil of methyl 2-benzyloxy-4-methoxybenzoate (19c) in 98% yield.

Anal. Calcd. for $C_{16}H_{16}O_4$[33]: C, 70.58; H, 5.92 Found: C, 70.78; H, 6.12

IR (Neat): ν_{max} 1722, 1609, 1577, 1255 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.80(s, 3H), 3.90(s, 3H), 5.15(s, 2H), 6.40-6.60(m, 2H), 7.20-7.60 (m, 5H), 7.90(d, J = 10.0 Hz, 1H)

MS m/z (% relative intensity): 272(M^+, 20.56), 241(24.16), 240(100), 213(2.54), 91(31.72)

9. Preparation of methyl 4-methoxy-2-(4-methoxybenzyloxy)benzoate (19d)

The reaction was carried out in an analogous manner as reaction 7. The crude material was purified by column chromatography (silica gel-ethyl acetate-hexane) to give methyl 4-methoxy-2-(4-methoxybenzyloxy)benzoate (19d) as a white solid, m.p. 56-58°C in 80% yield.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00 Found: C, 67.80; H, 5.53

IR (KBr): ν_{max} 1722, 1581, 1503, 1022 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.80(s, 3H), 3.90(s, 6H), 5.15(s, 2H), 6.40-6.60(m, 2H), 6.90(d, J = 10.0 Hz, 2H), 7.40(d, J = 10.0 Hz, 2H), 7.85(d, J = 10.0 Hz, 1H)

MS m/z (% relative intensity): 302(M^+, 34.13), 270(16.55), 242(10.37), 121(100), 91(4.81)

10. Preparation of methyl 2,4-dibenzyloxybenzoate (19e)

The reaction was carried out in an analogous manner as reaction 6. The product, methyl 2,4-dibenzyloxybenzoate (19e), was obtained as white crystals, m.p. 60-62°C (m.p. reported 62-65°C)[29] in 97% yield.

IR (Nujol): ν_{max} 1727, 1606 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.90(s, 3H), 5.10(s, 2H), 5.20(s, 2H,), 6.60-6.70(m, 2H), 7.25-7.65 (m, 10H), 7.95(dd, J = 9.0, 9.0 Hz,1H)

MS m/z (% relative intensity): 348(M^+,18.44), 316(47.70), 181(46.92), 91(100)

11. Preparation of methyl 2-benzyloxy-4,6-dimethoxybenzoate (19g)

The reaction was carried out in an analogous manner as reaction 6. The crude material was purified by column chromatography (silica gel-ethyl acetate-hexane) and followed by recrystallization (isopropyl alcohol) to give methyl 2-benzyloxy-4,6-dimethoxybenzoate (19g) as colorless crystals, m.p. 66-68°C, in 97% yield.

Anal. Calcd. for $C_{17}H_{18}O_5$[34]: C, 67.54; H, 6.00 Found: C, 67.86; H, 5.54

IR (KBr): ν_{max} 1727, 1613, 1499, 1279 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.88(s, 3H), 3.91(s, 3H), 3.99(s, 3H), 5.19(s, 2H), 6.23(d, J = 1.8 Hz, 1H), 6.27(d, J = 1.8 Hz), 7.40-7.50(m, 5H)

MS m/z (% relative intensity): 302(M^+, 35.81), 270(80.77), 271(44.03), 243(38.07), 91(100)

12. Preparation of methyl 2-(4-methoxybenzyloxy)-4,6-dimethoxybenzoate (19h)

The reaction was carried out in an analogous manner as reaction 7. The crude product was purified by preparative-layer chromatography followed by recrystallization in ethyl acetate-hexane to give methyl 4,6-dimethoxy-2-(4-methoxybenzyloxy)benzoate (19h) as colorless crystals, m.p. 76-78°C, in 69% yield.

Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.06 Found: C, 64.87; H, 5.80

IR (KBr): ν_{max} 1728, 1614, 1514, 1268 cm^{-1}

^{1}H NMR, 200MHz ($CDCl_3$): δ 3.77(s, 3H), 3.80(s, 6H), 3.84(s, 3H), 5.00(s, 2H), 6.13(d, J = 1.8 Hz, 1H) 6.15(d, J = 2.2 Hz, 1H), 6.85(d, J = 8.0 Hz, 2H), 7.25-7.32(d, J = 8.0, 2H)

MS m/z (% relative intensity): 332 (M^+, 38.82), 300(45.72), 121(100)

13. Preparation of methyl 2-hydroxy-4-(4-methoxybenzyloxy) benzoate(19f)

To a mixture of 1.68g (0.01 mol) of methyl 2,4-dihydroxybenzoate (17a) and sodium hydride (55% w/w) (1.2g, 0.0275 mol) dissolved in dimethylformamide (25 mL) were placed in a 100-mL round-bottomed flask. The reaction mixture was stirred at 0°C for 15 min, 4-methoxybenzyl chloride (3.38 mL, 0.025 mol) was added and then the temperature allowed to raise to room temperature with stirring for 2.5 h. After the completion, the reaction mixture was quenched with sat. ammonium chloride solution and extracted with ethyl acetate (3x25 mL). The combined organic phases were washed with water, and followed by a solution of sodium chloride. The organic layer was dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness. The crude material was purified by column chromatography (silica gel-ethyl acetate-hexane) to give methyl 2-hydroxy-4-(4-methoxybenzyloxy)benzoate (19f) 1.4608g (51%) as a white solid, m.p. 60-62°C, and a yellow oil of methyl 2,4-bis(4-methoxybenzyloxy)benzoate (19k) 0.72g (18%)[35].

(19f): IR (Nujol): ν_{max} 1672, 1616, 1586, 1248 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.85(s, 3H), 3.95(s, 3H), 5.0(s, 2H,), 6.40-7.40(m, 6H), 6.75(d, J = 9.0 Hz, 1H), 11.05(s,1H)

MS m/z (% relative intensity): 288(M^+, 5.20), 121(100), 91(4.92)

(19k): IR (Neat): ν_{max} 1722, 1609, 1515, 1249 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.75(s, 6H), 3.85(s, 3H), 4.95(s, 2H), 5.05(s, 2H), 6.55-7.45(m, 10H), 7.85(d, J=10.0 Hz, 1H)

MS m/z (% relative intensity): 288(100), 256(67.96), 228(67.78), 197(22.20)

14. Preparation of methyl 4-benzyloxy-2,6-dihydroxybenzoate (19i)

The reaction was carried out in an analogous manner as reaction 13. The combined organic phases were washed with water and followed by a solution of sodium chloride. The organic layer was dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness. The crude product was purified by preparative-layer chromatography (silica gel), developed by ethyl acetate:hexane (3:7) to give a yellow oil of methyl 4-benzyloxy-2,6-dihydroxybenzoate (19i) in 95% yield.

IR (Neat): ν_{max} 3435, 1724,1602 cm^{-1}

^{1}H NMR, 200MHz ($CDCl_3$): δ 3.67(s, 3H), 4.95(s, 2H), 6.8(d, J = 2.2 Hz), 6.15(d , J = 2.0 Hz), 7.25-7.40(m, 5H)

MS m/z (% relative intensity): 274(M^+,42.71), 166(3.77), 121(100), 91(3.78)

15. Preparation of methyl 2-hydroxy-4,6-bis(4-methoxybenzyloxy)benzoate (19j)

The reaction was carried out in an analogous manner as reaction 13. The combined organic phases were washed with water and followed by a solution of sodium chloride. The organic layer was dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness. The crude product was purified by preparative-layer chromatography (silica gel), developed by a mixture of chloroform-ethyl acetate-hexane (2:2:6) to give a yellow oil of methyl 2-hydroxy-4,6-bis(4-methoxy)benzoate (19j) in 85% yield.

IR (Neat): ν_{max} 1719, 1611, 1514, 1249 cm^{-1}

^{1}H NMR, 200MHz ($CDCl_3$): δ 3.75(s, 9H), 4.40(s, 2H), 4.88(s, 2H), 6.10(d, J = 1.8 Hz, 1H), 6.17 (d, J = 2.2 Hz), 6.85-6.97(m, 4H), 7.20-7.40(m, 4H), 9.88(s ,1H)

MS m/z (% relative intensity): 424(M^+, 0.01), 258(23.52), 150(20.70), 122(100), 119(21.44), 107 (10.09), 91(9.58)

16. Reaction of methyl 2-(4-methoxybenzyloxy)benzoate (19b) with LDA

To a solution of diisopropylamine (4.3 mL, 0.030 mol) and tetrahydrofuran (150 mL) in a 250-mL two-neck flask was slowly added a solution of *n*-butyllithium in hexane (36.4 mL, 0.028 mol) under nitrogen atmosphere at 0°C. The reaction mixture was then cooled to –78°C (dry ice/acetone) and was slowly added 3.80g (0.014 mol) of methyl 2-(4-methoxybenzyloxy)benzoate (19b) dissolved in tetrahydrofuran (15 mL) and the resulting mixture was stirred for 2 h. The color of the solution was gradually changed from orange to deep red and allowed to warm to room temperature. The reaction mixture was neutralized by 2M hydrochloric acid and stirred at room temperature for 1 h. The organic solvent was partially evaporated and extracted with dichloromethane (3x25 mL). The combined organic phases were washed with 1M sodium carbonate, water, and a solution of sodium chloride. The organic phase was dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness. The reaction mixture was separated by, first column chromatography, and followed by preparative-layer chromatography, developed by ethyl acetate-hexane (3:7) to give a yellow oil of 1-(2-hydroxyphenyl)-2-(4-methoxyphenyl)ethanedione(20b) [36]1.09g (30%) and a yellow liquid which was recrystallized from methanol as colorless crystals, m.p. 215-217°C, 0.1279g (3.8%) characterized as 26b.

(20b): IR (Neat): ν_{max} 1668 & 1628, 1597 cm^{-1}

^1H NMR, 200 MHz ($CDCl_3$): δ 3.90(s, 3H), 6.80-7.60(m), 7.90(d, J = 8.4 Hz, 2H), 11.50(s, 1H)

MS m/z (% relative intensity): 256(M^+, 1.20), 135(100), 121(5.29), 77(9.82)

(26b): Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03 Found: C, 75.29; H, 3.99

IR (KBr): ν_{max} 1721, 1610 cm^{-1}

^1H NMR, 200 MHz ($CDCl_3$): δ 3.77(s, 3H), 6.77(d, J=9.2 Hz, 2H), 7.00(m, 2H), 7.40(d, J = 8.8 Hz, 1H), 7.45-7.55(m, 2H), 7.62(dd, J = 0.8, 0.6 Hz,1H)

^{13}C NMR ($CDCl_3$): δ 196.69, 170.97, 160.12, 137.66, 129.3, 124.67, 122.99, 122.03, 121.38, 112.70, 112.57, 90.11, 55.17

MS m/z (% relative intensity): 240(M^+, 16.41), 239(100), 211(2.31), 210(4.12), 209(1.08)

17. Reaction of methyl 2-benzyloxy-4-methoxybenzoate (19c) with LDA

The reaction was carried out in an analogous manner as reaction 16. After purification, it was obtained a yellow solid and a yellow liquid. The yellow solid (16% yield), m.p. 77-79°C (m.p. reported 82-83°C)[37] was characterized as 1-(2-hydroxy-4-methoxyphenyl)-2-phenylethanedione (20c). The yellow liquid recrystallized from methanol as colorless crystals (1.4% yield), m.p. 236-238°C, was characterized as 32c.

(20c): IR ($CHCl_3$): ν_{max} 3415,1715 & 1687,1613, 1503, 1220 cm^{-1}

^1H NMR, 200MHz ($CDCl_3$): δ 3.95(s, 3H), 6.45(dd, J = 2.6, 2.6 Hz, 1H), 6.52(d, J = 2.2 Hz), 7.30-7.57(m, 3H), (d, J = 7.4 Hz,1H), 8.00(d, J = 7.4 Hz, 2H), 11.87(s,1H)

MS m/z (% relative intensity): 256(M^+, 3.98), 151(100), 105(1.76), 95(4.72)

(32c): Anal. Calcd. for $C_{30}H_{24}O_6$: C, 74.99; H, 5.03 Found: C, 74.34; H, 5.23

IR (KBr): ν_{max} 3469, 1679, 1609 cm^{-1}

^1H NMR, 200 MHz ($CDCl_3$): δ 3.74(s, 3H), 3.79(s, 3H), 5.27(s, 1H), 5.80(d, J = 8.8 Hz, 1H), 6.15 (dd, J = 2.2, 2.2 Hz,1H), 6.52(m, 2H), 6.70(d, J = 2.2 Hz,1H), 7.20-7.66(m, 11H)

^{13}C NMR ($CDCl_3$): δ 194.47, 164.53, 162.63,161.06, 157.63, 136.16, 134.86, 133.43, 129.71, 129.01, 128.37, 128.05, 127.87 127.29, 126.89, 118.24, 117.33, 110.57, 107.99, 103.56, 102.73, 95.68, 89.50, 86.29, 55.53, 55.41.

MS m/z % relative intensity): 480(M^+, 0.03), 313(14.29), 240(100), 226(10.67)

18. Reaction of methyl 2-(4-methoxybenzyloxy)-4-methoxybenzoate (19d) with LDA

The reaction was carried out in an analogous manner as reaction of 16. After purification, a yellow solid and yellow liquid were obtained. The yellow solid (16% yield), m.p. 94-96°C (reported m.p. 99-101°C)[37] was characterized as 1-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)ethanedione (20d). The yellow liquid recrystallized from methanol to give colorless crystals (1% yield), m.p. 235-237°C, was characterized as 26d.

(20d): Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93 Found: C, 66.71; H, 5.71

IR (Nujol): ν_{max} 1662 & 1628, 1592 cm^{-1}

^1H NMR, 200MHz ($CDCl_3$): δ 3.85(s, 3H), 3.95(s, 3H), 6.40(dd, J=2.6, 2.6 Hz), 6.50(d, J = 2.2 Hz, 1H), 7.00(d, J = 9.0 Hz, 2H), 7.40(d, J = 9.0 Hz), 7.95(d, J = 9.0 Hz, 2H), 11.95 (s,1H)

MS m/z (% relative intensity): 286(M^+, 9.42), 151(100) ,135(41.95), 107(2.95), 77(5.54)

(26d): IR (KBr): ν_{max} 1706, 1611 cm^{-1}

^1H NMR, 200 MHz ($CDCl_3$): δ 3.76 (s, 3H), 3.82(s, 3H), 6.48(d, J = 2.2 Hz,1H), 6.58(d, J = 1.6 Hz,1H), 6.74(d, J = 8.8 Hz, 2H), 7.35-7.50(m)

^{13}C NMR ($CDCl_3$): δ 194.66, 173.57, 168.20, 159.95, 129.18, 125.64, 123.97, 14.45, 112.67, 111.58, 96.16, 90.61, 55.83, 55.18
MS m/z (% relative intensity): 270(M^+,19.77), 269(100), 241(1.29), 240(3.06), 239(1.55), 238(1.13), 225 (1.04)

19. Preparation of $2''$-carboxymethoxy-$4'$-methoxy-1,2-diphenylethanedione (21b)

To a mixture of 0.25g (0.001 mol) of 1-(2-hydroxyphenyl)-2-(4-methoxyphenyl) ethanedione (20b) and potassium carbonate (0.2g, 0.0015 mol) dissolved in acetone were placed into a 100-mL round-bottomed flask. The resulting mixture was stirred at room temperature for 15 min, ethyl bromoacetate (0.5 mL, 0.0045 mol) was added and the resulting mixture was heated at reflux with stirring for 8 h. The yellow solution was gradually changed to colorless which indicates the reaction was completed. The reaction mixture was allowed to cool to room temperature, filtered, the acetone was evaporated, and the resulting mixture was hydrolyzed with potassium hydroxide (0.2g) in 90% ethanol and stirred for 30 min. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate (3x25 mL). The combined organic phases were washed with water followed by a solution of sodium chloride. The mixture was then dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness. The crude mixture was recrystallized from ethyl acetate-hexane to give $2''$-carboxymethoxy-$4'$-methoxy-1,2-diphenylethanedione (21b) 0.2000g (64%) as pale yellow crystals, m.p. 110-112°C.
Anal. Calcd. for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49 Found: C, 64.80; H, 4.86
IR (KBr): ν_{max} 3349, 1752 & 1656, 1598 cm^{-1}
^1H NMR, 200 MHz ($CDCl_3$): δ 3.20(s, broad,1H), 3.90(s, 3H), 4.60(s, 2H), 6.85-7.25(m, 5H), 7.55-7.65(m,1H), 7.90-8.00(m, 2H)
MS m/z (% relative intensity): 314(M^+, 34.69), 255(13.64), 179(26.01), 151(22.19), 135(100), 121(14.16)

20. Preparation of methyl $2''$-carboxymethoxy-$4''$-methoxy-1,2-diphenylethanedione (21c)

The reaction was carried out in an analogous manner as reaction 19 to give pale yellow crystals, m.p. 116-118 °C, of methyl $2''$-carboxymethoxy-$4''$-methoxy-1,2-diphenylethanedione (21c) in 39% yield.
Anal. Calcd. for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49 Found: C, 64.38; H, 3.65
IR (KBr): ν_{max} 3399, 1746 & 1678,1600, 1251 cm^{-1}
^1H NMR, 200 MHz ($CDCl_3$): δ 3.51(s, broad,1H), 3.90(s, 3H), 4.55(s, 2H), 6.40(d, J = 2.2 Hz,1H), 6.70(dd, J = 1.8, 2.2 Hz,1H), 7.40-7.70(m, 3H), 7.90-8.00(m, 3H)
MS m/z (% relative intensity): 314(M^+, 0.11), 209(100), 181(35.14), 15(48.08)

21. Preparation of $2''$-carboxymethoxy-$4',4''$-dimethoxy-1,2-diphenylethanedione (21d)

The reaction was carried out in an analogous manner as in reaction 19 to give pale yellow crystals, m.p. 169-171°C, of $2''$-carboxymethoxy-$4',4''$-dimethoxy-1,2-diphenylethanedione (21b) in 74% yield.
Anal. Calcd. for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68 Found: C, 61.35; H, 4.97
IR (KBr): ν_{max} 3399,1745 & 1665, 1619, 1502, 1252 cm^{-1}
^1H NMR, 200 MHz ($CDCl_3$): δ 3.891(s, 3H), 3.896(s, 3H), 4.60(s, 2H), 6.40(d, J = 2.2 Hz,1H), 6.65(dd, J = 2.2, 6.6 Hz, 1H), 6.95(d, J = 8.8 Hz, 2H), 7.85-7.96(m, 3H)
MS m/z (% relative intensity): 344(M^+, 1.63), 209(100), 181(33.82), 151(32.50), 135 (23.02)

22. Thermal cyclization of $2''$-carboxymethoxy-$4'$-methoxy-1,2-diphenylethanedione (21b)

To a mixture of 0.185g (0.0006 mol) of $2''$-carboxymethoxy-$4'$-methoxy-1,2-diphenylethanedione (21b), sodium acetate (0.15g), acetic anhydride (4 mL), and acetic acid (1 mL) were placed into a 100-mL round-bottomed flask. The resulting mixture was heated at reflux with stirring for 10 h. The resulting mixture was allowed to cool to room temperature and extracted with dichloromethane (3x25 mL). The combined organic phases were washed with 1M sodium carbonate, water, and a solution of sodium chloride. The organic layer was dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness. The crude mixture was purified by preparative-layer chromatography, developed by dichloromethane-hexane (1:1) to give colorless crystals, m.p. 83-85°C (m.p. reported = 89-90°C)[38], of 3-(4-methoxybenzoyl)benzo[b]furan (22b) 0.0370g (25%) and colorless crystals, m.p. 135-137°C (reported m.p. 141-142°C)[39], of $4^{\prime}$-methoxyisoflavone (23b) 0.028g (19%).

(22b): Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80 Found: C, 74.25; H, 5.28

IR (KBr): ν_{max} 1630, 1604, 1546 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.90(s, 3H), 7.05(d, J = 8.6 Hz, 2H), 7.30-7.60(m, 3H), 7.96(d, J = 7.0 Hz, 2H), 8.10(s, 1H), 8.16-8.20(m, 1H)

MS m/z (% relative intensity): 252(M^+, 100), 221(19.09),145(8.63), 135(7.06)

(23b): IR (KBr): ν_{max} 1633, 1613, 1567, 1511 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.85(s, 3H), 7.00(d, J = 8.8 Hz, 2H), 7.40-7.75(m, 5H), 8.00(s, 1H), 8.30(dd, J = 1.8, 1.8 Hz, 1H)

MS m/z (% relative intensity): 252(M^+, 100), 251(66.29), 237(22.18), 209(8.17), 181(4.06), 153 (2.03), 132(5.45), 120(0.19), 92(0.62)

23. Thermal cyclization of $2^{\prime\prime}$-carboxymethoxy-$4^{\prime\prime}$-methoxy-1,2-diphenylethanedione(21c)

The reaction was carried out in an analogous manner as in reaction 22 to give a yellow liquid of 6-methoxy-3-benzoylbenzo[b]furan (22c) in 24% yield and a yellow solid which was recrystallized from methanol as colorless crystals, m.p. 150-152°C (reported m.p. 156°C)[40], of 7-methoxyisoflavone (23c) in 21% yield.

(22c): Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80 Found: C, 74.18; H, 5.75

IR ($CHCl_3$): ν_{max} 1647, 1546 cm^{-1}

^{1}H NMR, 200 MHz (CDCl3): δ 3.80(s, 3H), 6.93(d, J = 2.6 Hz), 6.95-7.01(m, 1H), 7.40-7.55(m, 3H), 7.70-7.95(dd, J = 1.4, 2.0 Hz, 2H), 7.92(s, 1H), 8.00(d, 1H, J = 8.4 Hz)

MS m/z (% relative intensity): 252(M^+, 100), 237(11.92), 209(14.98), 181(7.06), 175(20.84), 105 (1.57)

(23c): IR ($CHCl_3$): ν_{max} 1634, 1500, 1458 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.92(s, 3H), 6.80(d, J = 2.2 Hz, 1H), 7.00(dd, J = 2.2, 2.6 Hz), 7.38-7.60(m, 5H), 7.96(s, 1H), 8.20(d, J = 9.6 Hz, 1H)

MS m/z (% relative intensity): 252(M^+, 60.16), 251(100), 150(2.35), 122(2.97)

24. Thermal cyclization of $2^{\prime\prime}$-carboxymethoxy-$4^{\prime}$,$4^{\prime\prime}$-dimethoxy-1,2-diphenylethanedione (21d)

The reaction was carried out in an analogous manner as in reaction 22 to give colorless crystals of 6-methoxy-3-($4^{\prime}$-methoxybenzoyl)benzo[b]furan (22d), m.p. 93-95°C, in 26% yield and a yellow solid which was recrystallized from methanol as colorless crystals, m.p. 158-160°C (reported m.p. 162-163°C)[41], which is characterized as 7,$4^{\prime}$-dimethoxyisoflavone (23d) in 24% yield.

(22d): Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 4.99 Found: C, 72.35; H, 4.11

IR (KBr): ν_{max} 1650, 1605, 1570 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.80(s, 3H), 3.90(s, 3H), 6.95-7.10(m, 4H), 7.85(d, 2H, J = 8.0 Hz), 8.00(s, 1H), 8.05(d, J = 8.0 Hz, 1H)

MS m/z (% relative intensity): 282(M^+, 100), 267(12.19), 251(16.34), 239(14.36), 175(3.79), 135 (4.17)

(23d): IR (KBr): ν_{max} 1632 , 1610, 1574 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 3.85(s, 3H), 3.92(s, 3H), 6.84(d, J = 2.2 Hz), 6.93-7.03(m, 3H), 7.50(d, J = 9.2 Hz, 2H), 7.93(s, 1H), 8.25(d , J = 9.2 Hz, 1H)

MS m/z (% relative intensity): 282(M^+, 100), 281(74.46), 267(13.33), 239(6.55), 150(1.57), 132 (12.93), 122(1.79)

25. Demethylation of 3-(4$^{/}$-methoxybenzoyl)benzo[b]furan (22b)

To a mixture of 0.06g (0.00024 mol) of 3-(4$^{/}$-methoxybenzoyl)benzo[b]furan (22b), 48% hydrobromic acid (3 mL), and acetic acid (3 mL) were placed into a 100-mL round-bottomed flask. The resulting mixture was heated at reflux with stirring for 4 h. The color of the solution was gradually changed from yellow to brown, allowed to cool to room temperature. The solution was diluted with water and extracted with ethyl acetate (3x25 mL). The combined organic phases were washed with water, solution of sodium chloride. The organic layer was dried (anh.Na_2SO_4) and evaporated to dryness. The crude product was purified by preparative-layer chromatography, developed by ethyl acetate-hexane (3:7), and followed by recrystallization from methanol to give yellow crystals, m.p. 172-175^{o}C, of 3-(4$^{/}$-hydroxybenzoyl)benzo[b]furan (24b) in 0.026g (46%).

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23 Found: C, 75.41; H, 3.68

IR (KBr): ν^{max} 3411, 1727, 1612 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 6.76(s, 1H), 6.86(d, J = 8.4 Hz, 2H) , 7.10-7.20(m, 2H), 7.35-7.50 (m, 2H), 7.65(d , J = 8.8 Hz, 2H)

MS m/z (% relative intensity): 238(M$^+$, 3.13), 210(100), 182(26.06), 180(11.22), 153(8.92), 121 (1.25)

26. Demethylation of 3-benzoyl-6-methoxybenzo[b]furan (22c)

The reaction was carried out in an analogous manner as in reaction 25 to give yellow crystals of 3-benzoyl-6-hydroxybenzo[b]furan (24c), m.p. 148-151^{o}C, in 21% yield.

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23 Found: C, 73.96; H, 3.85

IR (KBr): ν_{max} 3414,1725, 1613 cm^{-1}

^{1}H NMR, 200 MHz ($CDCl_3$): δ 4.39(s, broad), 6.85-7.30(m, 5H), 7.45-7.60(m, 2H), 7.75(d, J = 7.2 Hz, 2H)

MS m/z (% relative intensity): 238(M$^+$, 0.05), 210(100), 209(18.46), 181(24.11) 182(19.32), 153 (10.66)

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