Synthesis of Naturally Occurring Prenylated Benzophenones. Vismiaphenone A, Vismiaphenone B, and Isovismiaphenone B

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2,4,6-Trihydroxybenzophenone on prenylation with 2-methyl-3-buten-2-ol in the presence of $(C_2H_5)_2O\cdot BF_3$ yielded 2,4,6-trihydroxy-3,5-diprenylbenzophenone (**3**), 2,6-dihydroxy-4-prenyloxybenzophenone, 2,6-dihydroxy-3-prenyl-4-prenyloxybenzophenone, a benzodipyran and 6-benzoyl-5,7-dihydroxy-2,2-dimethyl-3-prenylchroman. **3** on reaction with 2 moles of *p*-toluenesulfonyl chloride followed by methylation and detosylation gave a naturally occurring benzophenone, vismiaphenone A (**12**). Cyclodehydrogenation of 6-hydroxy-3,5-diprenyl-2,4-ditosyloxybenzophenone gave 8-benzoyl-2,2-dimethyl-6-prenyl-5,7-ditosyloxy-2*H*-1-benzopyran, which on detosylation gave another naturally occurring benzophenone, isovismiaphenone B, while cyclodehydrogenation of **3** gave vismiaphenone B, another naturally occurring benzophenone. 2,4-Dihydroxy-6-methoxybenzophenone on similar treatment with 2-methyl-3-buten-2-ol afforded **12** directly.

Monache *et al.*[1] recently reported the isolation of new prenylated benzophenones *viz.* vismiaphenone A (**12**), vismiaphenone B (**8**) and isovismiaphenone B (**9**) from the fruits of *Vismia decipiens*. The structures were assigned on the basis of spectroscopic and degradative studies. In order to confirm the proposed structures, we report the syntheses of these benzophenones starting from 2,4,6-trihydroxybenzophenone.

2,4,6-Trihydroxybenzophenone (**1**) (prepared by the condensation[2] of 1,3,5-trimethoxybenzene[3] with benzoyl chloride followed by demethylation) on reaction with 2-methyl-3-buten-2-ol in the presence of $(C_2H_5)_2O\cdot BF_3$ in dioxane at 25—30 °C furnished six products on TLC (benzene:hexane, 2:1), which were separated by column chromatography on silica gel and designated as compounds **A**, **B**, **C**, **D**, **E**, and **F**.

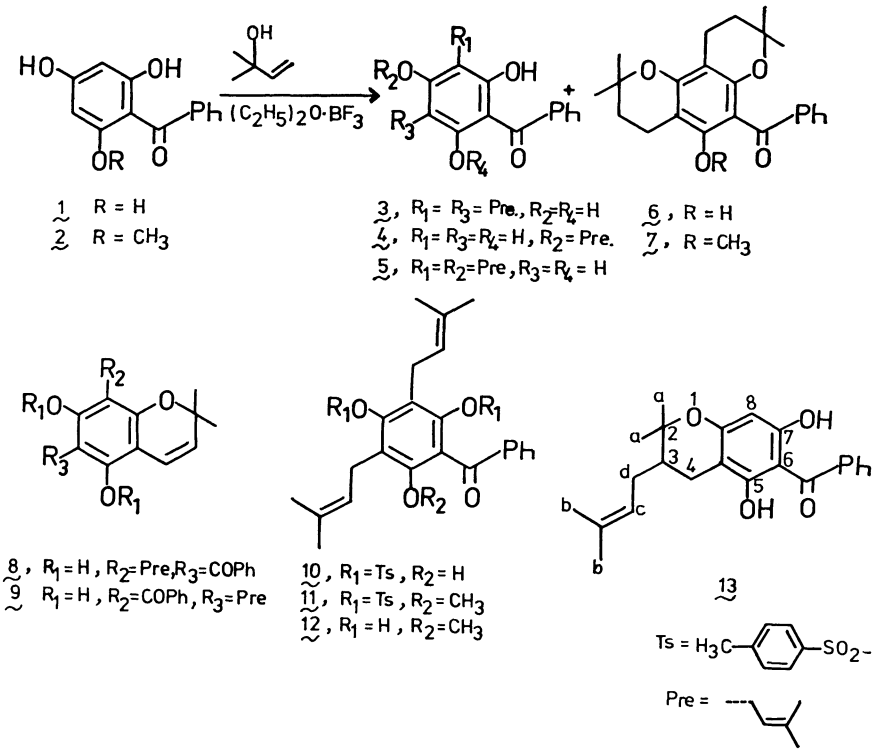
Compound **A** was obtained as yellow shining crystals, $C_{23}H_{26}O_4$, mp 94—95 °C. It exhibited positive iron(III) chloride reaction and negative Gibbs' reaction.[4] The infrared (IR) spectrum suggested the presence of hydroxyl groups (3350 and 3100 cm^{-1}) and carbonyl (1610 cm^{-1}) groups. Its ^1H NMR spectrum showed δ 7.33—7.65 (5H, m) due to the unsubstituted phenyl ring. It also indicated the presence of two prenyl groups [δ 1.77, 1.72 (6H, s each, $(CH_3)_2\times2$), 3.31 (4H, d, J=6.5 Hz, $-C\underline{H}_2-CH=\times2$), 5.2 (2H, t, J=6.5 Hz, $-CH_2-C\underline{H}=\times2$)] and three hydroxyl groups [δ 6.2 (1H), 8.85 (1H), 12.8 (1H) all exchangeable with deuterium]. Based on these data, compound **A** was assigned the structure 2,4,6-trihydroxy-3,5-diprenylbenzophenone (**3**), which was further confirmed by its acid cyclization to benzo[1,2-*b*:3,4-*b*']dipyran (**6**). Compound **3** was also reported earlier by us[5] in poor yields by the reaction of **1** with prenyl bromide in the presence of sodium methoxide.

Compound **B** was obtained as light yellow needles, $C_{18}H_{18}O_4$, mp 121 °C. It exhibited positive Gibbs' reaction and indicated a hydroxyl (3250 cm^{-1}) and a carbonyl (1620 cm^{-1}) groups in IR spectrum. Its ^1H NMR spectrum showed a singlet at δ 6.08 integrating for two protons assigned to C_3–H and C_5–H and a multiplet at δ 7.4—7.78 assigned to unsubstituted phenyl ring. It also indicated the presence of a prenyloxyl group [δ 1.78, 1.84 (3H, s each $(CH_3)_2$), 4.57 (2H, d, J=7 Hz, $-C\underline{H}_2-CH=$), 5.5 (1H, t, J=7 Hz, $-CH_2-C\underline{H}=$)] and two hydroxyl groups [δ 8.98 (1H, s), 12.84 (1H, s), both exchangeable with deuterium]. On this basis compound **B** was assigned the structure as 2,6-dihydroxy-4-prenyloxybenzophenone (**4**).

Compound **C** was a brown oil, $C_{23}H_{26}O_4$, gave a positive iron(III) chloride reaction as well as Gibbs' reaction. ^1H NMR spectrum indicated the presence of one prenyloxyl group and one *C*-prenyl group [δ 4.18 (2H, d, J=6.5 Hz, $-C\underline{H}_2-CH=$), 3.38 (2H, d, J=7 Hz, $-C\underline{H}_2-CH=$), 5.3, 4.67 (1H, bt each, J=6.5 Hz, $-CH_2-C\underline{H}=\times2$), 1.74, 1.78, 1.64, 1.57 (3H, s each, $(CH_3)_2\times2$)]. It also showed the presence of an aromatic proton δ 5.95 (1H, s), an unsubstituted phenyl ring δ 7.36—7.71 (5H, m) and two hydroxyl groups at δ 10.8 (2H, s, C_2– and C_6–OH). It was assigned the structure as 2,6-dihydroxy-3-prenyl-4-prenyloxybenzophenone (**5**).

Compound **D** was obtained as white crystals, mp 176 °C, having molecular formula $C_{23}H_{26}O_4$. It exhibited positive iron(III) chloride reaction and the ^1H NMR spectrum revealed the presence of two 2,2-dimethylchroman units [δ 0.86, 0.38 (6H, s each, $(CH_3)_2\times2$), 1.27, 1.03 (2H, t each, J=7 Hz, $CH_2-C\underline{H}_2\times2$), 2.13, 1.93 (2H, t each, J=7 Hz, $C\underline{H}_2-CH_2\times2$)], unsubstituted phenyl ring δ 6.68—6.97 (5H, m) and a chelated hydroxyl δ 12.4 (1H, s). On the basis of these data, it was assigned 2,2,8,8-tetramethyl-2*H*,10*H*-benzo[1,2-*b*:3,4-*b*'] benzopyran structure (**6**), which was further confirmed by its methylation to give **7**, which corresponded to that derived from **12**.

Compound **E** was a light brown oil, $C_{23}H_{26}O_4$, exhibited positive iron(III) reaction. A positive Gibbs' test along with a singlet at δ 5.91 indicated that C_8–H *para* to C_5–OH is free and thus C_5 position of benzophenone must be linked to the $C_{10}H_{18}$ unit. It also showed in its ^1H NMR spectrum (i) two methyl groups attached to a saturated centre at δ 1.26, 1.44 (3H, s each), (ii) two methyl groups attached to an unsaturated centre, δ 1.63, 1.74 (3H, s each), (iii) a multiplet integrating for three protons at δ 2.0—2.41 assignable to two protons at C_d and one proton at C_3, (iv) C_4 protons at δ 2.79 (2H, dd, J=16 and 5 Hz) and a methine proton δ 5.11—5.36 (1H, m, H_c). Unsubstituted phenyl ring protons were indicated at their usual position at δ 7.36—7.77 (5H, m). Thus, on the above basis compound **E** was formulated as



6-benzoyl-5,7-dihydroxy-2,2-dimethyl-3-prenylchroman (**13**). Compound **E** seems to arise by the attack of an isopentenyl carbonium ion, generated from 2-methyl-3-buten-2-ol, on the prenyl unit of 5-prenylbenzophenone.[6] Compound **F** was unreacted starting benzophenone **1**. Oxidative cyclodehydrogenation of **3** with DDQ afforded **8**, whose spectral data were in complete agreement with those reported for the natural sample of vismiaphenone B. Ditosylation of **3** with 2 mol of *p*-toluenesulfonyl chloride gave 6-hydroxy-3,5-diprenyl-2,4-ditosyloxybenzophenone (**10**) which on methylation followed by detosylation furnished **12**, identical in all respects with the reported data for vismiaphenone A. Compound **12** was also prepared by the reaction of 2,4-dihydroxy-6-methoxybenzophenone (**2**) (prepared by ditosylation of **1** followed by methylation and detosylation) with 2-methyl-3-buten-2-ol under similar reaction conditions as in **1**. This reaction showed the presence of two minor and two major products on TLC. The two major products were characterized to be **3** and **12**, while the minor products could not be identified.

Oxidative cyclodehydrogenation of **10**, followed by detosylation furnished **9**, identical with isovismiaphenone B in all respects.

Experimental

All melting points are uncorrected. IR and UV spectra were recorded on a Perkin-Elmer IR spectrophotometer Model-621 (ν_{max} in cm^{-1}) in KBr and on Perkin-Elmer UV spectrophotometer Model-554 (λ_{max} in nm) in methanol respectively. ^1H NMR spectra were measured on Perkin-Elmer R-32 (90 MHz) spectrometer in $CDCl_3$ or CCl_4 using tetramethylsilane as an internal standard (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad).

Reaction of 2-Methyl-3-buten-2-ol with 2,4,6-Trihydroxybenzophenone. **1** (10 g, 27.3 mmol) was dissolved in dry dioxane (50 ml) and stirred vigorously at 25—30 °C. $(C_2H_5)_2O \cdot BF_3$ (3 ml in 15 ml of dioxane) was added to the stirring solution in 1 h. The solution was stirred for 1 h more. Then 2-methyl-3-buten-2-ol (4.5 ml, 52.3 mmol, in 10 ml of dioxane) was added in 10 min and the solution stirred for another 4 h. The reaction mixture was left overnight and diluted with water. It was extracted with ethyl acetate (2×250 ml) and the organic phase was washed with 5% aqueous sodium hydrogencarbonate (100 ml) and water. It was dried (Na_2SO_4) and solvent evaporated. The resulting brownish liquid (8.5 ml) was chromatographed on silica gel. On elution with light petroleum (boiling range 60—80 °C) with the increasing amount of ethyl acetate, following compounds were separated.

*Compound **A** (**3**).* Obtained as yellow shining crystals (950 mg), (Found: C, 75.35; H, 7.20%. Calcd for $C_{23}H_{26}O_4$: C, 75.46; H, 7.06%). UV(qualitative) 254 and 311. IR: 3350 (br), 3100 (br), 1610, 1552, 1390, 1320, 1252, 1155, 1095 and 940.

*Compound **B** (**4**).* Crystallized from chloroform as light yellow needles (80 mg), (Found: C, 72.46; H, 6.10%. Calcd for $C_{18}H_{18}O_4$: C, 72.48; H, 6.04%). UV (qualitative) 248 and 308, IR: 3250(br), 2900, 1620, 1459, 1375, 1150, 1082, and 820.

*Compound **C** (**5**).* Obtained as brown oil (60 mg), (Found: C, 75.38; H, 7.14%. Calcd for $C_{23}H_{26}O_4$: C, 75.46; H, 7.06%). UV (qualitative) 248 and 308; IR: 3360, 3120, 1620, 1510, 1385, 1290, 1165, 1060, and 935.

*Compound **D** (**6**).* Crystallised from light petroleum–benzene mixture as white crystals (50 mg), (Found: C, 75.41; H, 7.16%. Calcd for $C_{23}H_{26}O_4$: C, 75.46; H, 7.06%); UV: 210 and 312; IR: 3390, 2910, 1585, 1440, 1418, 1330, 1318, 1291, 1271, 1250, 1228, 1150, 1110, and 952.

*Compound **E** (**13**).* Obtained as light brown oil (740 mg), (Found: C, 75.40; H, 7.12%. Calcd for $C_{23}H_{26}O_4$: C, 75.46; H, 7.06%). UV: 253 and 310; IR: 3320, 2920,

1620, 1585, 1424, 1300, 1167, 1120, 1078, and 920.

*Compound **F**.* Obtained as light yellow crystals and was characterized to be the unreacted benzophenone **1** (500 mg).

*2,4-Dihydroxy-6-methoxy-3,5-diprenylbenzophenone (**12**).* A mixture of **3** (200 mg, 0.55 mmol) and *p*-toluenesulfonyl chloride (280 mg, 1.47 mmol) was dissolved in dry acetone (5 ml) and the solution was refluxed with ignited potassium carbonate (300 mg) for 6 h. Dimethyl sulfate (0.2 ml, 1.6 mmol) and potassium carbonate (100 mg) were added and the reaction mixture was further refluxed for 12 h. Inorganic salts filtered and acetone evaporated. The residue was treated with 10% ethanolic potassium hydroxide (20 ml) for 2 h at 50—55 °C. The solution was cooled, diluted with water (200 ml), acidified with HCl and extracted with ether. The ethereal layer was washed with 5% sodium hydrogen carbonate solution (45 ml) followed by water (100 ml) and dried (Na_2SO_4). The solvent was evaporated and the residue on purification by column chromatography afforded **12** as a light yellow oil (35 mg), (Found C, 75.81; H, 7.46%). UV: 255 and 310. IR: 3410, 1620, 1602, 1582, 1442, 1375, 1320, 1175, 1150, 1002. ^{1}H NMR(CCl_4): δ 11.8 (1H, s, O<u>H</u> at C-2), 7.75—7.31(5H, m, phenyl ring protons), 6.2(1H, br s, O<u>H</u> at C-4), 5.2(2H, br t, J=7 Hz, CH_2–C<u>H</u>=×2), 3.3—3.44(4H, m, C<u>H</u>$_2$–CH=×2), 3.21(3H, s, OCH_3), 1.75, 1.76(6H, s each, $(CH_3)_2$×2).

*8-Benzoyl-5,7-dihydroxy-2,2-dimethyl-6-prenyl-2H-1-benzopyran (**9**).* A mixture of **3** (250 mg, 0.68 mmol), *p*-toluenesulfonyl chloride (350 mg, 1.84 mmol) and potassium carbonate (360 mg) was refluxed in dry acetone (7 ml) for 8 h. The potassium salts were filtered off and washed with hot acetone (50 ml). The filtrate and washing were mixed and the solvent evaporated. The residue on purification with column chromatography on silica gel gave **10** as waxy solid (180 mg), mp 57 °C, ^{1}H NMR(CCl_4): δ 13.18 (1H, chelated OH), 7.81 (4H, d, J=7 Hz, tosyl protons at C-3′ and C-5′×2), 7.28—7.49 (5H, m, phenyl protons), 7.14 (4H, d, J=7 Hz, tosyl protons at C-2′ and C-6′×2), 4.94—5.14 (2H, m), 3.12—3.36 (4H, m), 2.48, 2.39 (3H, s each, methyl protons of tosyl×2), 1.68, 1.56 (6H, s each, $(CH_3)_2$×2).

Compound **10** (120 mg, 0.17 mmol) was dissolved in benzene (5 ml), DDQ (150 mg, 0.66 mmol) was added and refluxed for 16 h. The reaction mixture was filtered through a short column of silica gel. Solvent evaporated and the residue was treated with 10% ethanolic KOH (15 ml) at 55—60 °C for 2 h. Solvent evaporated, residue was diluted with water, acidified and extracted with ether (50 ml). The ethereal layer was washed with water, dried (Na_2SO_4) and the solvent evaporated. The residue on purification with column chromatography on silica gel afforded **9** as light yellow solid (25 mg), mp 117—118 °C (lit,[1] mp 118—120 °C), (Found: C, 75.85; H, 6.68%). UV: 295 and 305; IR: 3390, 3350, 1643, 1615, 1592, 1575, 1175, 1130, and 880; ^{1}H NMR ($CDCl_3$): δ 12.9 (1H, s, OH at C-2), 7.3—7.55 (5H, m, phenyl ring protons), 6.4 (1H, d, J=9 Hz, proton at C-4), 6.2 (1H, s, OH at C-7), 5.3 (1H, d, J=9 Hz, proton at C-3), 4.9—5.15(1H, m, –C<u>H</u>=CH$(CH_3)_2$), 3.3(2H, J=7 Hz, –C<u>H</u>$_2$–CH=), 1.75, 0.85 (12H, s each, $(CH_3)_2$×2).

*6-Benzoyl-5,7-dihydroxy-2,2-dimethyl-8-prenyl-2H-1-benzopyran (**8**).* **3** (50 mg, 0.14 mmol) was dissolved in dry benzene (5 ml) and refluxed with DDQ (30 mg, 0.13 mmol) for 3 h. The reaction mixture filtered through a small column of silica gel. On evaporation of solvent, **8** was left as light yellow oil (15 mg), (Found: C, 75.82; H, 6.62%). UV: 280 and 319; IR: 3390, 3340, 1642, 1615, 1590, 1570, 1175, 1160, 1128, 1120, and 880; ^{1}H NMR ($CDCl_3$): δ 12.6(1H, s, OH), 8.9(1H, s, OH), 7.3—7.6(5H, m), 6.45 (1H, d, J=8 Hz, proton at C-4), 5.45(1H, d, J=8 Hz, proton at C-3), 5.0—5.21(1H, t, J=7 Hz, –CH_2–C<u>H</u>=), 3.31(2H, d, J=7 Hz, –C<u>H</u>$_2$–CH=), 1.77, 1.25(6H, s each, $(CH_3)_2$×2).

*Cyclization of **3**.* Compound **3** (50 mg, 0.14 mmol) was dissolved in chloroform (5 ml) and trifluoroacetic acid (0.5 ml) was added to it and left overnight. Solvent evaporated and the residue dissolved in benzene (25 ml) and filtered through a small column of silica gel. On evaporation of solvent, **6** was obtained as white crystals (30 mg).

*Methylation of **6**.* The mixture of **6** (20 mg, 0.06 mmol), dimethyl sulfate (0.1 ml) and potassium carbonate (50 mg) was refluxed in acetone (5 ml) for 10 h. On working up in the usual manner, **7** was obtained as white solid which crystallized from hexane as white crystals (15 mg), mp 144 °C (lit,[1] mp 145—146 °C). ^{1}H NMR (CCl_4): δ 7.55—7.72 (2H, m, phenyl ring protons), 7.14—7.38 (3H, m, phenyl ring protons), 3.52(3H, s, OCH_3), 2.56, 2.42(2H, t each, J=7 Hz, C<u>H</u>$_2$–CH_2×2), 1.65, 1.56(2H, t each, J=7 Hz, –CH_2–C<u>H</u>$_2$×2), 1.26, 0.96(6H, s each, $(CH_3)_2$×2).

*Reaction of **2** with 2-Methyl-3-buten-2-ol.* Compound **2** (800 mg, 3.3 mmol) was treated with 2-methyl-3-buten-2-ol (0.5 ml) in the presence of $(C_2H_5)_2O\cdot BF_3$ (0.2 ml) as mentioned in case of **1**. On working up a brown oil (750 mg) was obtained, which was chromatographed on silica gel. On elution with light petroleum, two main fractions were separated and were characterized to be **12** and **3** respectively.

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