A New Synthetic Route for Natural Products with the Pyranobenzophenone Moiety: Clusiacitran A, Vismiaphenone B, Isovismiaphenone B, and Myrtiaphenone B

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Molecules with pyranobenzophenone moiety are widely distributed in nature.[1] They have a range of biological and pharmacological properties.[2] Among these, clusiacitran A (**1**) with a citran nucleus was isolated as an optically inactive racemate along with clusiacitran B (**2**) from an extract of the fruits of *Clusia multiflora* (Figure 1).[3] Recently, clusiacitran A (**1**) was also isolated from *Gaucinia schombrugkiana* Pierre, which was collected from Songkla area in southern Thailand along with clusiacitran B (**2**) and fluorinated clusiacitrans A (**3**) and B (**4**).[4] This plant is used in the treatment of coughs and diabetes as well as for improving the menstrual blood quality. The crude hexane extract of the stems of this plant has also shown antimalarial activity with an EC_{50} value of 2.2 μg mL^{-1}.[4] Although the structures of these materials **1**-**4** have been determined by spectral and X-ray analysis,[4] there are no synthetic approaches to these compounds.

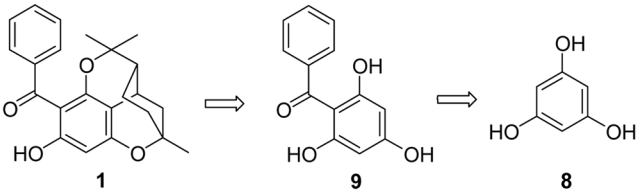
Both vismiaphenone B (**5**) and isovismiaphenone B (**6**) with prenylated benzophenone moiety were isolated from the fruits of either *Vismia decipiens*[5] or *Clusia ellipticifolia*.[6] Although one synthetic approach to vismiaphenone B (**5**) and isovismiaphenone B (**6**) has been reported, this synthetic route is limited by its many reaction steps, harsh reaction conditions, and low yield involving many side reactions.[7] Myrtiaphenone B (**7**) was isolated from both *Garcinia myrtifolia*[8] and *Garcinia pseudoguttifera*.[9] The biosynthetic approaches to myrtiaphenone B (**7**) have been described, but there are no reports on the synthesis of compound **7**.[8,9]

Recently, we reported a new methodology for preparing citrans and cyclols with polycycles by ethylenediamine diacetate (EDDA)-catalyzed reactions of substituted trihydroxybenzenes to citral or *trans*,*trans*-farnesal.[10] We also reported a new methodology for synthesizing benzopyrans *via* ethylenediamine diacetate (EDDA)-catalyzed reactions of resorcinols to α,β-unsaturated aldehydes.[11] As a part of an ongoing study into the synthetic efficacy of these two methodologies, this study examined the synthesis of naturally occurring molecules with the pyranobenzophenone moiety. This paper reports an efficient and concise synthesis of clusiacitran A (**1**), vismiaphenone B (**5**), isovismiaphenone B (**6**), and myrtiaphenone B (**7**).

Results and Discussion

Scheme 1 shows the retrosynthetic strategy. The synthesis of natural clusiacitran A (**1**) could be prepared using tandem electrocyclization of 2,4,6-trihydroxybenzophenone (**9**) and citral using the method previously developed by our group.[10] Compound **9** could be prepared from commercially available phloroglucinol (**8**) using a Friedel-Crafts acylation reaction.[12]

Reaction of phloroglucinol (**8**) with benzoyl chloride in the presence of $AlCl_3$ gave compound **9** in 48% yield (Scheme 2).[12] The treatment of compound **9** with 2.0 equiv of citral in the presence of 20 mol% of EDDA at 100 °C for 10 h in DMF afforded naturally occurring compound **1** in 54% yield as a sole product without any expected regio-



Scheme 1

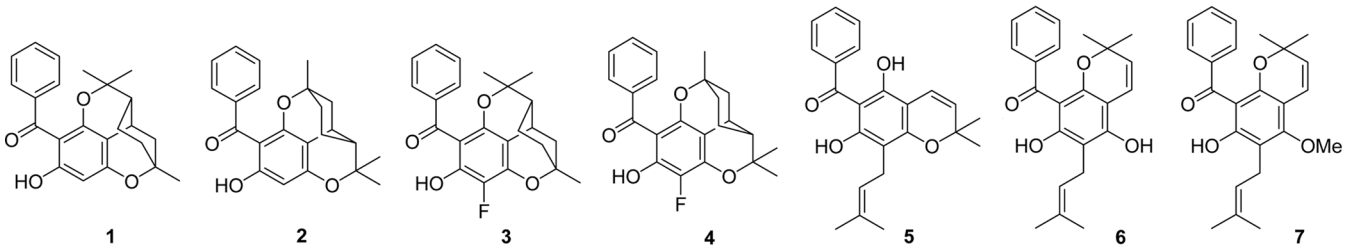
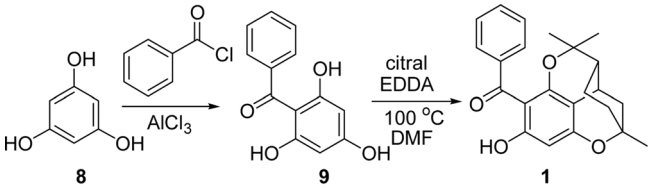


Figure 1. Selected naturally occurring molecules with benzophenone moiety.



Scheme 2

isomer.[13] The structure of synthetic compound **1** was easily identified through a comparison with data reported for the natural product.[3]

As a model study for the synthesis of natural products with oxabicyclononane skeletons, the acid-catalyzed reaction of compound **1** was next investigated. Compounds **10**-**15** with oxabicyclononane rings have been isolated from *Thai cannabis*[14] or *Murraya euchrestifolia*[15] (Figure 2). In particular, plants containing these molecules have been used in traditional medicine as analgesics and local anesthetics as well as for the treatment of rheumatism, dropsy, eczema, abdominal pain, stomach-ache, toothache, diarrhea, thrombosis, and oedema.[15b] They have been also widely used as an expectorant, anticonvulsant, anodyne, and detoxification reagent.[15b]

Treatment of compound **1** in refluxing AcOH for 2 h afforded compound **16** with oxabicyclononane moiety in 85% yield (Scheme 3). The assignment of compound **16** was confirmed by ^{1}H NMR analysis of the expected chemical shifts of two vinylic protons at δ 4.63 and 4.42.

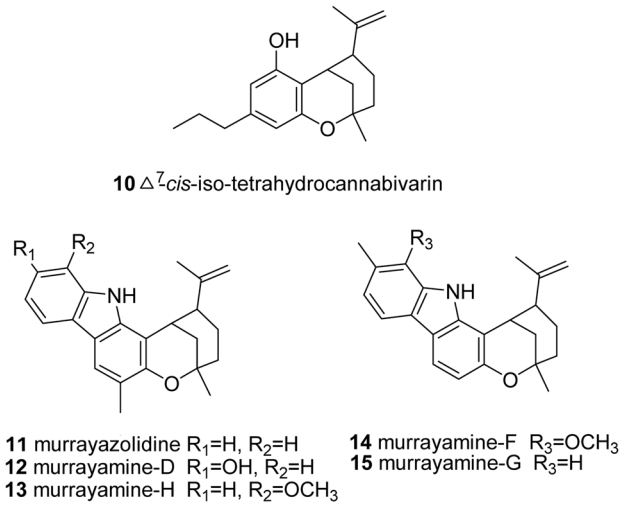
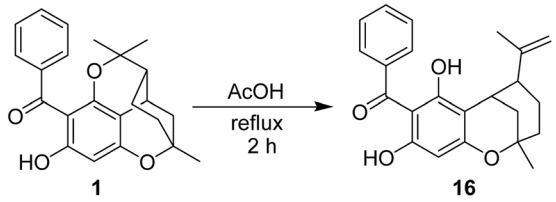


Figure 2. Selected naturally occurring molecules with oxabicyclononane moiety.

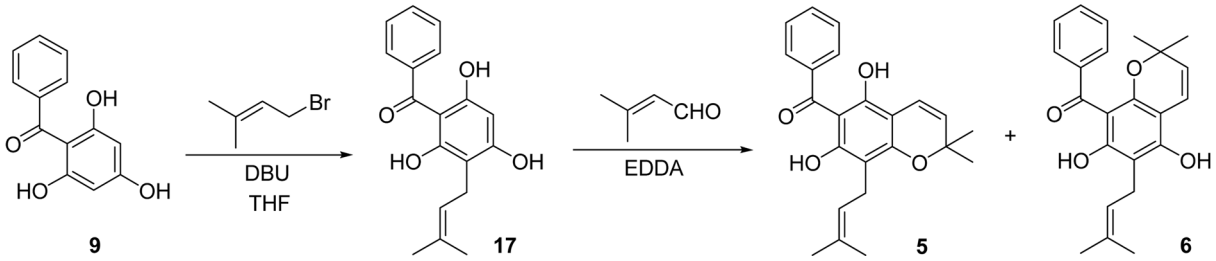


Scheme 3

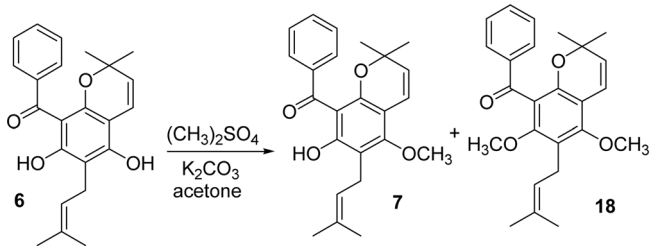
The synthesis of vismiaphenone B (**5**) and isovismiaphenone B (**6**) was next attempted as shown in Scheme 4. The C-prenylation of 2,4,6-trihydroxyacetophenone with prenyl bromide in KOH solution has been reported. However, following this method, the prenylated product **17** was only produced in 30% yield. In order to increase the yield, the base was changed to DBU. Interestingly, a reaction of 2,4,6-trihydrobenzophenone (**9**) with 1-bromo-3-methyl-2-butene in the presence of DBU in THF at room temperature for 24 h afforded the prenylated benzopheneone **17** in 42% yield. Treatment of compound **17** with 3-methyl-2-butenal in the presence of 20 mol% of EDDA in methylene chloride at room temperature for 5 h provided the naturally occurring products **5** and **6** in 31 and 51% yields, respectively. The assignment of compounds **5** and **6** was made by a comparison with the data reported for the natural products.[5,7] The ^{1}H NMR spectrum of compound **5** showed signals of two vinylic protons on 2*H*-pyranyl ring at δ = 6.58 (d, J = 10.0 Hz) and 5.47 (d, J = 10.0 Hz), whereas that of compound **6** showed signals of two vinylic protons at δ = 6.45 (d, J = 10.0 Hz) and 5.26 (d, J = 10.0 Hz).

Finally, the synthesis of natural product myrtiaphenone B (**7**) was attempted by a methylation reaction of compound **6**. A reaction of compound **6** with dimethylsulfate in the presence of K_2CO_3 in acetone at room temperature for 1 h produced the natural product **7** and its derivative **18** in 75 and 11% yield, respectively. The spectroscopic data of the synthetic material **7** was same as that reported in the literature.[8]

In conclusion, a new synthetic route for biologically interesting natural products clusiacitran A (**1**), vismiaphenone B (**5**), isovismiaphenone B (**6**), and myrtiaphenone B (**7**) with a pyranobenzophenone moiety was developed starting from phloroglucinol. The key strategy in this synthetic route is a Freidel-Crafts acylation followed by EDDA-catalyzed electrocyclization. The acid-catalyzed cleavage reaction of compound **1** was described as a model study for the synthesis of other natural products with oxabicyclononane moiety.



Scheme 4



Scheme 5

The synthesis of natural products with an oxabicyclononane skeleton is currently underway in our laboratory.

Experimental Section

All the experiments were carried out in a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ or DMSO-d_6. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. The MS spectra were carried out at the Korea Basic Science Institute.

2,4,6-Trihydroxybenzophenone (9). Alumium trichloride (5.334 g, 40.0 mmol) was added to a stirred mixture of phloroglucinol (**8**) (1.261 g, 10.0 mmol) in nitrobenzene (50 mL) and stirred for 30 min at room temperature. Then, benzoyl chloride (1.406 g, 10.0 mmol) was injected and heated to 60 °C for 3 h, and the reaction mixture was cooled to room temperature. The mixture was poured onto ice water and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with 1 N NaOH solution, water (2 × 30 mL), and brine (2 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to give residue. The residue was purified by column chromatography on silica gel using hexane/ethylacetate (5:1) to give **9** (1.105 g, 48%) as a solid: mp 169-170 °C; ^{1}H NMR (300 MHz, DMDO-d_6) δ 10.08 (1H, s), 9.82 (1H, s), 7.61 (2H, m), 7.51 (1H, t, J = 7.4 Hz), 7.43 (1H, t, J = 7.7 Hz), 5.84 (2H, s); ^{13}C NMR (75 MHz, DMDO-d_6) δ 196.5, 161.9, 159.4, 139.9, 131.8, 128.5, 128.0, 105.7, 94.4; IR (KBr) 3371, 3267, 1642, 1579, 1572, 1470, 1451, 1323, 1290, 1240, 1154, 1060, 920, 824, 756, 700 cm^{-1}; EIMS m/z (%) 230 (M^+, 50), 229 (100), 153 (38), 152 (5), 105 (9), 77 (13).

Clusiacitran A (1). To a solution of **9** (0.23 g, 1.0 mmol) and citral (0.304 g, 2.0 mmol) in DMF (20 mL) was added ethylenediamine diacetate (0.036 g, 0.2 mmol) at room temperature. The reaction mixture was heated to 100 °C for 10 h and then cooled to room temperature. Evaporation of solvent and purification by column chromatography on silica gel using hexane/ethylacetate (15:1) gave **1** (0.197 g, 54%) as a solid: mp 211-213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.64 (1H, s), 7.60-7.32 (5H, m), 6.10 (1H, s), 2.70-2.53 (1H, m), 2.22-2.12 (2H, m), 1.92-1.85 (2H, m), 1.48-1.38 (1H, m), 1.37 (3H, s), 1.27-1.18 (1H, m), 1.08 (3H, s), 0.8-0.7 (1H, m), 0.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 164.3, 163.2, 159.2, 142.1, 130.3, 127.6, 127.1, 197.8, 107.3, 97.2, 85.7, 76.1, 45.6, 37.4, 34.6, 29.1, 28.5, 27.6, 23.4, 21,5; IR (KBr) 3455, 2975, 2926, 1624, 1562, 1478, 1352, 1323, 1308, 1165, 1140, 1073, 1042, 951, 880, 820, 704 cm^{-1}; EIMS m/z (%) 364 (M^+, 45), 349 (13), 321 (5), 283 (14), 282 (31), 281 (100), 203 (16), 105 (33), 77 (29).

Compound 16. Compound **1** (0.073 g, 0.2 mmol) in acetic acid (5 mL) was refluxed for 2h and then cooled to room temperature. Water (30 mL) was added and the solution was extracted with ethyl acetate (3 × 30 mL). The organic layer was washed saturated sodium bicarbonate solution (2 × 30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to give residue. The residue was purified by column chromatography on silica gel using hexane/ethylacetate (10:1) to give **16** (0.062 g, 85%) as a solid: mp 149-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (1H, s), 7.6-7.43 (5H, m), 6.11 (1H, s), 4.63 (1H, s), 4.42 (1H, s), 3.50-3.40 (1H, m), 2.44-2.25 (1H, m), 2.00-1.45 (6H, m), 1.81 (3H, s), 1.37 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 164.3, 160.0, 159.8, 148.2, 140.1, 131.8, 128.9, 128.1, 109.5, 103.7, 95.6, 76.4, 48.2, 39.2, 37.3, 29.8, 28.4, 23.0, 22.8; IR (KBr) 2932, 1626, 1449, 1304, 1167, 1136, 1090, 883, 822, 739 cm^{-1}; EIMS m/z (%) 364 (M^+, 19), 349 (5), 321 (5), 281 (100), 203 (12), 105 (17), 77 (19).

3-Prenyl-2,4,6-trihydroxybenzophenone (17). A mixture of **9** (0.276 g, 1.2 mmol), prenyl bromide (0.179 g, 1.2 mmol), and DBU (0. 183 g, 1.2 mmol) in dry THF (10 mL) was stirred at room temperature for 24 h. Addition of 2N HCl solution (30 mL), and extraction with ethyl acetate (3 × 30 mL), washing with brine (30 mL), drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel using hexane/ethylacetate (7:1) gave **17** (0.151 g, 42%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.3 (1H, s), 7.63-7.45 (5H, m), 6.42 (1H, br s), 5.90 (1H, s), 5.23-5.20 (1H, m), 3.32 (2H, d, J = 7.1 Hz), 1.77 (3H, s), 1.73 (3H, s), ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 162.0, 161.5, 158.3, 140.1, 132.0, 129.0, 127.7, 103.8, 101.7, 96.8, 32.0, 26.7, 16.1; IR (neat) 3389, 2977, 2924, 1625, 1516, 1449, 1321, 1383, 1321, 1176, 1119, 1074, 821, 736 cm^{-1}; EIMS m/z (%) 298 (M^+, 100), 297 (24), 283 (32), 255 (20), 243 (90), 241 (36), 229 (20), 205 (18), 165 (71), 129 (21), 77 (23).

Vismiaphenone B (5) and isovismiaphenone B (6). To a solution of **17** (0.089 g, 0.3 mmol) and 3-methyl-2-butenal (0.051 g, 0.6 mmol) in methylene chloride (10 mL) was added ethylenediamine diacetate (0.011 g, 0.06 mmol) at room temperature. The reaction mixture was stirred at room temperature for 5 h. Water (30 mL) was added and the solution was extracted with methylene chloride (3 × 30 mL). Evaporation of solvent and purification by column chromatography on silica gel using hexane/ethylacetate (20:1) gave products **5** (0.034 g, 31%) and **6** (0.056, 51%). Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (1H, s), 8.72 (1H, s), 7.63-7.47 (5H, m), 6.58 (1H, d, J = 10.0 Hz), 5.47 (1H, d, J

= 10.0 Hz), 5.15 (1H, t, *J* = 7.0 Hz), 3.24 (2H, d, *J* = 7.0 Hz), 1.74 (3H, s), 1.66 (3H, s), 1.43 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 159.3, 159.0, 155.1, 140.0, 132.5, 132.2, 129.2, 127.8, 127.1, 125.8, 122.1, 116.1, 108.4, 104.5, 102.4, 77.9, 28.4, 25.8, 21.4, 17.9; IR (neat) 3503, 2976, 2924, 1616, 1449, 1377, 1323, 1177, 1134, 885, 746 cm^{-1}; EIMS m/z (%) 364 (M^+, 43), 350 (24), 349 (100), 347 (13), 309 (12), 294 (16), 293 (80), 215 (30), 105 (28), 77 (14).

Compound **6**: mp 119-120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.80 (1H, s), 7.46-7.35 (5H, m), 6.45 (1H, d, *J* = 10.0 Hz), 6.34 (1H, s), 5.30 (1H, t, *J* = 7.0 Hz), 5.26 (1H, d, *J* = 10.0 Hz), 3.41 (2H, d, *J* = 7.0 Hz), 1.84 (3H, s), 1.78 (3H, s), 0.95 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 162.0, 157.9, 154.5, 142.9, 136.7, 129.9, 127.5, 127.1, 125.2, 121.7, 115.9, 105.3, 105.0, 101.8, 77.3, 27.3, 25.9, 21.7, 17.9; IR (KBr) 3432, 2924, 1601, 1422, 1319, 1275, 1169, 1136, 817 cm^{-1}; EIMS m/z (%) 364 (M^+, 52), 350 (24), 349 (100), 347 (11), 294 (20), 293 (99), 215 (35), 129 (19), 105 (19), 77 (11).

Myrtiaphenone B (7) and its derivative 18. K_2CO_3 (0.097 g, 0.70 mmol) was added to a solution of **6** (0.051 g, 0.14 mmol) in acetone (10 mL) at room temperature. Dimethyl sulfate (0.018 g, 0.14 mmol) was then added dropwise, and the mixture was stirred at room temperature for 1 h. A saturated NH_4Cl solution (30 mL) was added and the mixture was extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to leave an oily residue. The residue was then purified by column chromatography on silica gel using hexane/ethyl acetate (30:1) to give products **7** (0.040 g, 75%) and **18** (0.006 g, 11%). Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.03 (1H, s), 7.50-7.33 (5H, m), 6.40 (1H, d, *J* = 10.0 Hz), 5.31 (1H, d, *J* = 10.0 Hz), 5.24 (1H, t, *J* = 6.9 Hz), 3.76 (3H, s), 3.30 (2H, d, *J* = 6.9 Hz), 1.78 (3H, s), 1.69 (3H, s), 0.97 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 162.0, 160.6, 158.0, 142.4, 131.5, 130.4, 127.5, 127.3, 126.0, 123.8, 116.8, 114.7, 111.5, 107.9, 77.0, 62.0, 27.3, 25.8, 22.2, 17.9; IR (neat) 2926, 1599, 1419, 1389, 1296, 1215, 1171, 1136, 1111, 966, 752 cm^{-1}; EIMS m/z (%) 378 (M^+, 30), 363 (100), 307 (20), 323 (86), 105 (70).

Compound **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.84 (2H, m), 7.55-7.50 (1H, m), 7.43-7.38 (2H, m), 6.50 (1H, d, *J* = 10.0 Hz), 5.50 (1H, d, *J* = 10.0 Hz), 5.18 (1H, t, *J* = 6.7 Hz), 3.75 (3H, s), 3.60 (3H, s), 3.27 (2H, d, *J* = 6.7 Hz), 1.73 (3H, s), 1.67 (3H, s), 1.17 (6H, s); IR (neat) 2975, 1674, 1580, 1451, 1418, 1316, 1283, 1215, 1128, 1100, 1005, 966, 889, 729 cm^{-1}; EIMS m/z (%) 392 (M^+, 10), 368 (34), 286 (45), 284 (61), 277 (89), 197 (66), 106 (58), 78 (100), 69 (48), 57 (51), 55 (42).

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