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Enantiospecific syntheses of hongoquercin A, B and chromazonarol

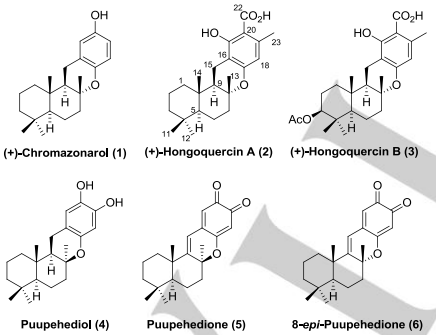
Dattatraya H. Dethe,*[a] Ganesh M. Murhade,[a] Balu D. Dherange[a] and Susanta Kumar Sau[a]

Dedication ((optional))

Abstract: Environmentally benign and highly atom economic catalytic Friedel-Crafts alkylation reaction and diastereoselective C-O bond formation reaction has been developed. The scope and generality of this reaction was amply illustrated by synthesis of chromazonarol, hongoquercin A and B and analogues thereof.

Introduction

Meroterpenoids are the natural products of mixed biosynthetic origin, partially derived from terpenoids.[1] This class of natural products displays a wide range of structural diversity and holds considerable promise as rich source of lead structures in drug discovery. In 1975 Cimino et al. isolated (+)-chromazonarol (**1**) from marine sponge *Disidea pallescens*.[2] Although the biological activity of this compound is not known, its structurally related molecule (+)-hongoquercin A (**2**) and B (**3**) exhibit antibacterial properties towards methicillin resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. (+)-Hongoquercin A (**2**) and B (**3**) were isolated by Roll et al. in 1998 from an unidentified terrestrial fungus.[3] Other related metabolites such as Puupehediol (**4**), Puupehedione (**5**), 8-*epi*-Puupehedione (**6**), are angiogenesis inhibitor with potential antileukemic activity.[4] Over last two decades, various metabolites of this family are shown to have a wide variety of biological properties, including antitumor, antiviral, antibiotic, antituberculosis, antimalarial, antioxidant, insecticidal and antifungal.[5] Due to unique structural features and important biological activities, this class of natural products has attracted attention of many synthetic chemists worldwide. In year 2000, Mori and co-workers reported the synthesis of (+)-hongoquercin A (**2**) from (–)-sclareol and established its absolute configuration as *5R, 8R, 9R,10S*.[6a] In the same year, same group also reported the total synthesis of (+)-hongoquercin B (**3**).[6b] In 2006 Hsung and co-workers reported the synthesis of (±)/(+)-hongoquercin A (**2**), using unusual polyene cyclization and cationic [2+2] cycloaddition reaction.[7] Alvarez-Manzaneda and coworkers[8] reported synthesis of puupehenone related bioactive metabolites using palladium (II)-mediated diastereoselective cyclization of a drimenylphenol. Same group also reported synthesis of (+)-chromazonarol (**1**), (+)-hongoquercin A (**2**), 8-*epi*-puupehenol (**6**) and 8-*epi*-puupehedione (**6**) using Diels Alder cycloaddition reaction as a key step.[9] In 2009, Alvarez-Manzaneda and coworkers reported cationic resin promoted Michael type Friedel-Crafts alkylation of alkoxyarenes with an α,β-unsaturated ketone[10] (Scheme 1, eq. 2). Recently Barrett



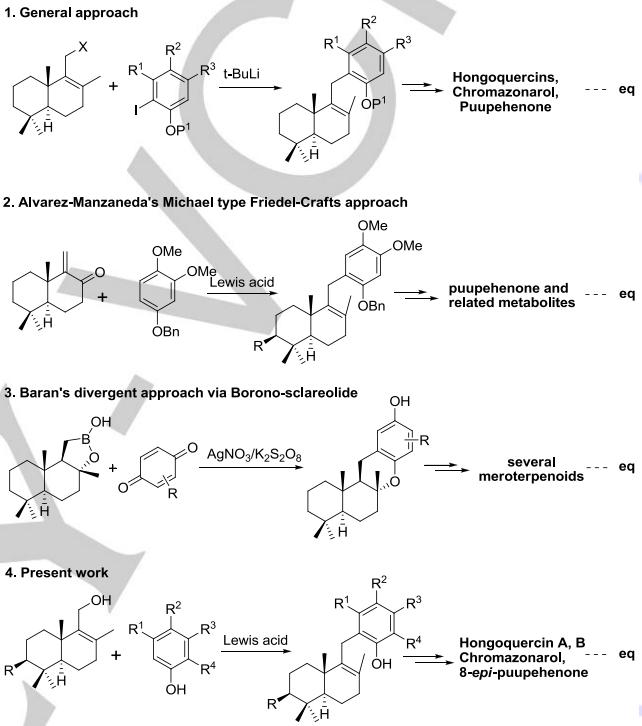


Figure 1. Representive examples of tetracyclic merosesquiterpenes.

Scheme 1. Various methods used for C-C bond formation in meroterpenoid natural product.

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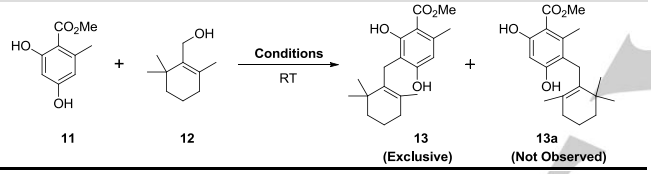
and co-workers reported dual biomemetic route for synthesis of (+)-hongoquercin B (**3**) using a palladium catalyzed decarboxylative π-farnesyl rearrangement of a diketo-dioxinone ester, aromatization and cationic diene-epoxide cyclization as key steps.[11] Most of the earlier approaches have relied upon the addition of a suitably protected arene nucleophile generated using pyrophoric *t*-BuLi, to cyclic terpenoid moiety.[8,12] Divergent strategies to synthesize this entire natural product family from a single building block are lacking[13] with exception of one report. Baran and co-workers[14] have reported scalable synthesis of bioactive meroterpenoids using borono-sclareolide, a terpenyl radical precursor as a single building block. In this manuscript we report diversity oriented synthesis of all above mentioned meroterpenoid natural products **1-3** and **6** (Fig. 1) and analogues thereof, using a highly regioselective Friedel-Crafts reaction and diastereoselective C-O bond formation reaction as key steps. Recently we have developed a protecting group free direct coupling of secondary allylic alcohol with electron rich aromatic compounds.[15] Although primary hydroxyl group is considered to be less reactive compared to secondary alcohol, we were curious about the outcome of Friedel-Crats reaction[16] between

Table 1. Optimisation table for acid catalysed Friedel-Crafts alkylation reaction.



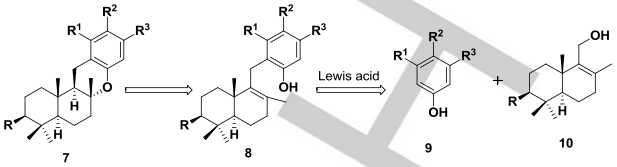
11 12 13 (Exclusive) 13a (Not Observed)

Entry	catalyst	mol %	solvent	yield [%]
1	$FeCl_3$	10	CH_2Cl_2	CRM[a]
2	$FeCl_3$	10	toluene	CRM[a]
3	$Cu(OTf)_2$	10	CH_2Cl_2	CRM[a]
4	$Bi(OTf)_3$	10	CH_2Cl_2	CRM[a]
5	$Fe(OTf)_3$	10	CH_2Cl_2	CRM[a]
6	$Yb(OTf)_3$	10	CH_2Cl_2	N. R. [b]
7	$In(OTf)_3$	10	CH_2Cl_2	N. R. [b]
8	AgOTf	10	CH_2Cl_2	N. R. [b]
9	$BF_3{\cdot}OEt_2$	10	THF	N. R. [b]
10	*p*-TSA	10	CH_2Cl_2	56
11	$Sc(OTf)_3$	10	CH_2Cl_2	30
12	$BF_3{\cdot}OEt_2$	10	CH_2Cl_2	81

[a] CRM = Complex reaction mixture. [b] N.R. = No reaction

electron rich phenols and primary allylic alcohol, which could give access to diverse meroterpenoids such as hongoquercin A, B, chromazonarol and related meroterpenoids.

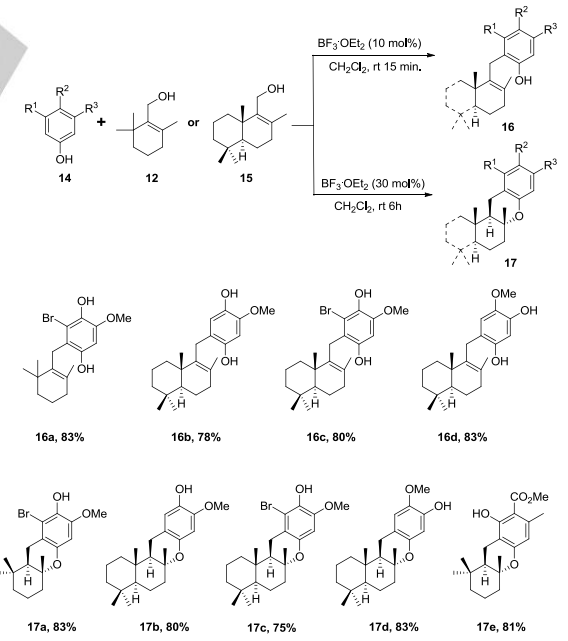
Results and Discussion



7 8 9 10

Scheme 2. Retrosynthetic plan for merosesquiterpenes.

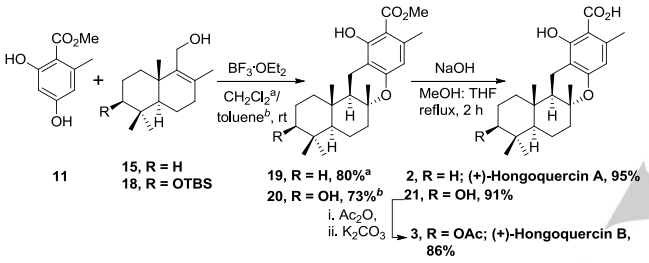
According to our retrosynthetic plan, it was envisioned that meroterpenoids skeleton (**7**) could be prepared from compound **8** by diastereoselective C-O bond formation. Required compound **8** could be obtained by Friedel-Crafts reaction between suitably substituted aromatic ring **9** and primary allylic alcohol **10** (Scheme 2). To check the feasibility of our strategy, various *Lewis* acids were screened for Friedel-Crafts alkylation of easily and commercially available resorcinol derivative **11** with cyclogeraniol **12** (Table 1). A mixture of compounds **11** and **12** was treated with 10 mol% of $FeCl_3$ in CH_2Cl_2 or toluene as solvent at room temperature. To our disappointment, it resulted in formation of a complex reaction mixture (Table 1, Entry 1 and 2). Similar results were obtained when 10 mol% of $Cu(OTf)_2$, $Bi(OTf)_3$ and $Fe(OTf)_3$ were used in CH_2Cl_2 or toluene at room temperature (Table 1, Entry 3, 4 and 5). Among the catalysts tested $Yb(OTf)_3$, $In(OTf)_3$, AgOTf in CH_2Cl_2 and $BF_3{\cdot}OEt_2$ in THF failed to generate any product and both starting materials were recovered (Table 1, entry 6, 7, 8 and 9). Interestingly, a mixture



Scheme 3. Synthesis of various meroterpenoid analogues.

of compounds **11** and **12** on treatment with 10 mol% *p*-TSA in CH_2Cl_2 afforded compound **13** exclusively, in 56% yield, while

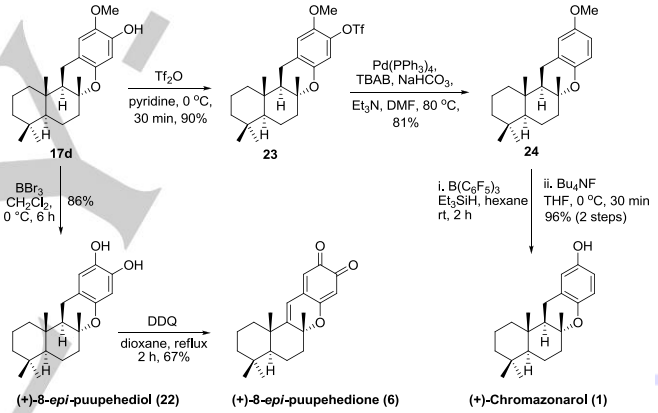
another possible regioisomer **13a** was not observed at all. (Table 1, Entry 10). Use of $Sc(OTf)_3$ also afforded compound **13** in 30% yield (Table 1, entry 11). To our delight, a mixture of **11** and **12** on treatment with 10 mol% of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature for 10 min afforded compound **13** in 81% yield (Table 1, Entry 12). More interestingly when 30 mol% of $BF_3{\cdot}OEt_2$ was used and the reaction mixture was allowed to stir for 6 h, formation of a pyran ring was also observed yielding derivative **17** in good yield with excellent regio- and diastereoselectivity[12b] (*dr* ≥19:1, confirmed by crude ^{1}H NMR) (Scheme 3). Excellent diastereoselectivity was observed possibly due to the formation of thermodynamically more stable *trans* decalin type system. To evaluate the scope and limitations of this reaction, various sesquiterpene derivatives were prepared using C–C and C–O bond formation reaction between various allylic alcohols and aromatic phenols (Scheme 3). Reaction of alcohol **12/15** with a variety of aromatic derivatives **14** using 30 mol% $BF_3{\cdot}OEt_2$ in CH_2Cl_2 afforded compounds **16a-16d** and **17a-17e** in good yields (Scheme 3).



Scheme 4. Total synthesis of (+)-hongoquercin A (**2**) and B (**3**).

After finding appropriate condition for the C–C and C–O bond formation, next we directed our attention towards the total synthesis of various hongoquercin skeletal and meroterpenoids. Initially, we focused on total synthesis of (+)-hongoquercin A (**2**) and (+)-hongoquercin B (**3**). The required terpenoids **15** (for hongoquercin A) and **18** (for hongoquercin B) were prepared from (+)-sclareolide[17] and 1,3-cyclohexanedione (see supporting information for preparation) respectively. Individual treatment of alcohol **15** and **18** with resorcinol derivative **11** as expected generated compound **19** (80%) and **20** (73%) respectively in highly regio- and diastereoselective manner. Compound **19** was subjected to ester hydrolysis using aq. NaOH in 1:1 mixture of methanol and THF to furnish (+)-hongoquercin A (**2**) in 95% yield, whose spectral data (IR, ^{1}H, ^{13}C, and HRMS) were in complete agreement with those reported in literature[14b] (Scheme 4). Compound **20** was transformed into (+)-hongoquercin B (**3**) after three steps. Thus, compound **20** was subjected to ester hydrolysis using aq. NaOH in 1:1 mixture of methanol and THF to give acid **21** in 91% yield. Acetylation of compound **21** using acetic anhydride, followed by selective hydrolysis of phenolic acetyl of the resultant diacetate compound using potassium carbonate in aq. methanol generated (+)-hongoquercin B (**3**) in 57.1% overall yield from known alcohol **18** (3 steps), whose spectral data (IR, ^{1}H, ^{13}C, and HRMS) were in complete agreement with those reported in literature.[3]

After completion of total synthesis of (+)-hongoquercin A (**2**) and B (**3**), next we targeted total synthesis of (+)-chromazonarol (**1**) and 8-*epi*-puupehedione (**6**). It was envisioned that deprotection of methyl ether of previously prepared compound **17d** could generate 8-*epi*-puupehedione (**6**) *via* 8-*epi*-puupehenol (**22**) and removal of extra hydroxyl group in **17d,** through triflate formation, followed by demethylation of resultant compound could generate (+)-chromazonarol (**1**). Accordingly, compound **17d** when subjected to reaction with BBr_3 in CH_2Cl_2, at 0 °C for 6 h, generated 8-*epi*-puupehediol (**22**). Without further purification, when this compound was subjected to reaction with DDQ in dioxane under reflux condition[9a] for 12 h, afforded 8-*epi*-puupehedione (**6**) in 67% yield (Scheme 5). On the other hand, treatment of compound **17d** with Tf_2O and pyridine at 0 °C in CH_2Cl_2 for 30 min afforded triflate **23** in 90% yield. Palladium catalyzed reductive cleavage of triflate group in compound **23** furnished methyl chromazonarol **24** in 81% yield. Initially, demethylation of compound **24** was attempted using BBr_3 and BCl_3, but under these reaction conditions decomposition of **24** and formation of a complex reaction



Scheme 5. Synthesis of (+)-chromazonarol (**1**) and 8-*epi*-puupehedione (**7**).

mixture was observed. Later, two steps protocol was used for the demethylation of methyl chromazonarol **24**. Thus compound **24** on treatment with $B(C_6F_5)_3$ and Et_3SiH in hexane at room temperature for 2 h, followed by deprotection of resultant silyl ether using TBAF in THF at 0 °C for 30 min afforded (+)-chromazonarol (**1**) in 96% yield. Structures of (+)-chromazonarol (**1**) and 8-*epi*-puupehedione (**6**) were further confirmed by comparing the spectral data (^{1}H and ^{13}C) with that reported in the literature by Baran and co-workers.[14a]

Conclusions

Lewis acid-catalyzed Friedel-Crafts alkylation and diastereoselective C-O bond formation reaction between resorcinol derivatives with primary allylic alcohol have been developed. Systematic study was performed to solve reactivity and regioselectivity problem by varying the substitution on

aromatic coupling partner and allylic alcohol. The developed method was applied for the highly atom economic syntheses of (+)-chromazonarol (**1**), (+)-hongoquercin A (**2**) and B (**3**).

Experimental Section

General: All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise mentioned. All the chemicals were purchased commercially, and used without further purification. Anhydrous THF and diethyl ether were distilled from sodium-benzophenone and dichloromethane was distilled from calcium hydride. Yields refer to chromatographically pure material, unless otherwise stated. Reaction were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as a visualizing agent and an p-anisaldehyde or ninhydrin stain, and heat as developing agents. Merck silica gel (particle size 100-200 and 230-400 mesh) was used for flash column chromatography. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. NMR spectra were recorded on Bruker Avance 500 (^{1}H: 500MHz, ^{13}C: 125MHz) in $CDCl_3$ having TMS 0.03% as internal standard. Mass spectrometric data were obtained using WATERS-Q-T of Premier-ESI-MS.

General procedure A for the C–C bond formation.

A mixture of the corresponding phenol (1 equiv.) and alcohol (1 equiv.) in anhydrous CH_2Cl_2 was stirred at room temperature for 5 min. Then $BF_3{\cdot}OEt_2$ (10 mol %) was added. The reaction mixture was stirred at room temperature for 15 min. When completion of the reaction was noted by TLC, a saturated solution of $NaHCO_3$ was added and the resultant reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent and purification of the residue on silica gel column chromatography using EtOAc/hexane as eluent afforded the monocouple product.

Methyl 2,4-dihydroxy-6-methyl-3-((2,6,6-trimethylcyclohex-1-enyl)methyl)benzoate (13): yellow oil (137 mg, 81%); IR (neat) υ_{max}/cm^{-1} 3339, 2930, 1655, 1620, 1540, 1478, 1136; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 6H), 1.46–1.53 (m, 2H), 1.63–1.69 (m, 2H), 1.72 (s, 3H), 2.06 (t, *J* = 6.3 Hz, 2H), 2.41–2.47 (m, 3H), 3.50 (s, 2H), 3.90 (s, 3H), 6.14 (s, 1H), 7.59 (s, 1H), 12.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 20.6, 24.0, 24.7, 27.9, 29.7, 32.8, 35.5, 39.4, 51.8, 104.4, 109.6, 112.0, 134.4, 136.5, 140.2, 160.8, 162.6, 172.8; HRMS m/z calcd for $C_{19}H_{25}O_4$ [(M – H)$^+$] 317.1753, found 317.1752.

3-bromo-5-methoxy-2-((2,6,6-trimethylcyclohex-1-enyl)methyl)benzene-1,4-diol (16a): brown oil (67 mg, 83%); IR (neat) υ_{max}/cm^{-1} 3380, 2925, 1610, 1488, 1450, 1020; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (br s, 6H), 1.45–1.53 (m, 2H), 1.63–1.70 (m, 2H), 1.72 (s, 3H), 2.07 (t, *J* = 6.2 Hz, 2H), 3.62 (s, 2H), 3.83 (s, 3H), 5.55 (s, 1H), 6.33 (s, 1H), 6.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 20.8, 28.1, 32.3, 33.0 (2 Carbon), 35.5, 39.6, 56.1, 99.7, 111.2, 115.6, 134.6, 136.0, 136.9, 145.4, 149.4; HRMS m/z calcd for $C_{17}H_{24}BrO_3$ [(M + H)$^+$] 355.0909, found 355.0915.

2-methoxy-5-(((4a*S*,8a*S*)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)benzene-1,4-diol (16b): yellow oil (193 mg, 78%); $[\alpha]_D^{30}$ = +42° (*c* 0.4, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 2928, 1647, 1603, 1208, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3 H), 0.90 (s, 3 H), 0.98 (s, 3 H), 1.57 (s, 3 H), 3.27 (s, 2 H), 3.83 (s, 3 H), 6.38 (s, 1 H), 6.61 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 18.8, 20.0, 20.0, 21.5, 27.5, 29.4, 33.0, 33.1, 33.3, 36.1, 38.9, 41.4, 51.5, 55.8, 99.8, 114.8, 118.1, 129.9, 137.5, 138.9, 144.6, 146.9; HRMS m/z calcd for $C_{22}H_{33}O_3$ [(M + H)$^+$] 345.2430, found 345.2436.

3-bromo-5-methoxy-2-(((4a*S*,8a*S*)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)benzene-1,4-diol (16c): viscous oil (124 mg, 80%); $[\alpha]_D^{30}$ = +37° (*c* 0.34, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 3380, 2925, 1580, 1488, 1020; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.90 (s, 3H), 1.10–1.20 (m, 3H), 1.37 (d, *J* = 12.7 Hz, 2H), 1.49–1.66 (m, 4H), 1.72 (s, 3H), 2.06–2.23 (m, 2H), 3.55 (br s, 2H), 3.83 (s, 3H), 5.54 (s, 1H), 6.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7 (2 Carbon), 20.0, 20.6, 21.7 (2 Carbon), 31.8, 33.1, 33.3, 33.5, 39.5, 41.4, 51.3, 56.1, 99.8 (2 Carbon), 111.3, 136.8, 139.6 (2 Carbon), 145.3, 149.4; HRMS m/z calcd for $C_{22}H_{32}BrO_3$ [(M + H)$^+$] 423.1535, found 423.1535.

4-methoxy-6-(((4a*S*,8a*S*)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)benzene-1,3-diol (16d): (102 mg, 83%) as a yellow oil; $[\alpha]_D^{30}$ = +52° (*c* 0.3, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 3412, 2937, 1615, 1518, 1462, 1374, 1241, 1193; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (s, 3H), 0.88–0.91 (m, 3H), 0.99 (s, 3H), 1.02–1.14 (m, 2H), 1.19 (dd, *J* = 12.6, 2.0 Hz, 1H), 1.33–1.40 (m, 2H), 1.48–1.57 (m, 2H), 1.58–1.60 (m, 3H), 1.65 (d, *J* = 4.4 Hz, 1H), 1.71–1.76 (m, 1H), 2.08–2.24 (m, 2H), 3.31 (s, 2H), 3.79 (s, 3H), 5.28 (br s, 1H), 5.49 (br s, 1H), 6.41 (s, 1H), 6.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 19.0, 20.3, 20.3, 21.7, 27.7, 33.3, 33.3, 33.5, 36.3, 39.1, 41.6, 52.0, 56.8, 102.9, 112.6, 117.1, 130.0, 138.0, 140.5, 144.1, 148.2; HRMS m/z calcd for $C_{22}H_{33}O_3$ [(M + H)$^+$] 345.2430, found 345.2433.

General procedure B for the C–C and C–O bond formation.

A mixture of the corresponding phenol (1 equiv) and alcohol (1 equiv) in anhydrous CH_2Cl_2 was stirred at room temperature for 5 min. Then $BF_3{\cdot}OEt_2$ (30 mol %) was added. The reaction mixture was stirred for 6 h at room temperature. When completion of the reaction was noted by TLC a saturated solution of $NaHCO_3$ was added and the resultant reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent and purification of the residue on a silica gel column chromatography using EtOAc/hexane as eluent furnished the cyclised product.

8-bromo-6-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-ol (17a): brown oil (54 mg, 83%); IR (neat) υ_{max}/cm^{-1} 3513, 2925, 1619, 1585, 1491, 1446, 1377, 1270, 1191, 1128; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.03 (s, 3H), 1.17 (s, 3H), 1.32–1.37 (m, 1H), 1.47–1.51 (m, 1H), 1.53–1.59 (m, 2H), 1.62–1.68 (m, 2H), 1.91–1.98 (m, 1H), 2.33 (dd, *J* = 16.7, 13.2 Hz, 1H), 2.71 (dd, *J* = 16.8, 5.1 Hz, 1H), 3.82 (s, 3H), 5.50 (br s, 1H), 6.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 19.7, 20.5, 24.2, 32.1, 33.4, 39.6, 41.5, 48.3, 56.1, 77.0, 99.9, 110.7, 114.2, 136.8, 145.8, 146.8; HRMS m/z calcd for $C_{17}H_{23}BrO_3$ [M]$^+$ 354.0831, found 354.0844.

(4a*S*,6a*R*,12a*R*,12b*S*)-9-methoxy-4,4,6a,12b-tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthen-10-ol (17b): semi-solid (98 mg, 80%); $[\alpha]_D^{30}$ = +35° (*c* 0.4, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 3414, 2933, 1586, 1480, 1250, 1158; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.87 (s, 3H), 0.90 (s, 3H), 1.18 (s, 3H), 1.39–1.47 (m, 2H), 1.61 (dd, *J* = 18.9, 11.5 Hz, 4H), 1.70 (br s, 1H), 1.76 (br s, 1H), 1.99–2.05 (m, 1H), 2.46–2.52 (m, 2H), 3.80 (s, 3H), 5.14 (br s, 1H), 6.33 (s, 1H), 6.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 18.5, 19.7, 20.6, 21.6, 21.7, 33.2, 33.4, 36.8, 39.2, 41.1, 41.8, 52.3, 55.9, 56.1, 76.7,

100.2, 113.8, 114.4, 138.9, 145.4, 146.1; HRMS: m/z calcd for $C_{22}H_{33}O_3$ [(M + H)$^+$] 345.2430, found 345.2422.

(4a*S*,6a*R*,12a*R*,12b*S*)-11-bromo-9-methoxy-4,4,6a,12b-tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthen-10-ol (17c): brown oil (73 mg, 75%); $[\alpha]_D^{30}$ = +27° (*c* 0.3, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 3513, 2925, 1619, 1491, 1446, 1377, 1270, 1191, 1128; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.91 (d, *J* = 2.06 Hz, 6H), 0.98–1.06 (m, 2H), 1.15 (s, 3H), 1.17–1.22 (m, 1H), 1.40–1.51 (m, 2H), 1.56–1.65 (m, 3H), 1.74–1.80 (m, 2H), 2.02–2.08 (m, 1H), 2.34 (dd, *J* = 16.8, 13.0 Hz, 1H), 2.63 (dd, *J* = 16.8, 5.3 Hz, 1H), 3.82 (s, 3H), 5.49 (br s, 1H), 6.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 18.5, 19.7, 20.4 (2 Carbon), 21.6, 23.4, 33.2, 33.4, 36.8, 39.2, 40.7, 41.8, 52.3, 56.1, 76.8, 99.9, 110.9, 114.0, 136.7, 145.7, 146.7; HRMS (EI) m/z calcd for $C_{22}H_{31}BrO_3$ [M]$^+$ 422.1457, found 422.1458.

(4a*S*,6a*R*,12a*R*,12b*S*)-10-methoxy-4,4,6a,12b-tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthen-9-ol (17d): semi-solid (204 mg, 83%); $[\alpha]_D^{30}$ = +30° (*c* 0.72, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 3400, 2937, 1615, 1518, 1438, 1374, 1241, 1170, 1193, 1170, 1088, 1020; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.88 (s, 3H), 0.90 (s, 3H), 0.95–1.05 (m, 2H), 1.17 (s, 3H), 1.35–1.50 (m, 3H), 1.60–1.79 (m, 5H), 2.03 (dt, *J* = 12.4, 3.2 Hz, 1H), 2.50–2.56 (m, 2H), 3.81 (s, 3H), 6.38 (s, 1H), 6.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 18.5, 19.7, 20.6, 21.6, 22.0, 33.2, 33.4, 36.8, 39.2, 41.0, 41.8, 52.3, 56.1, 56.5, 76.6, 103.5, 111.7, 112.6, 140.5, 144.6, 147.3; HRMS m/z calcd for $C_{22}H_{33}O_3$ [(M + H)$^+$] 345.2430, found 345.2422.

Methyl 8-hydroxy-1,1,4a,6-tetramethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene-7-carboxylate (17e): yellow oil (92 mg, 81%); IR (neat) υ_{max}/cm^{-1} 3330, 2830, 1644, 1620, 1560, 1150; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.03 (s, 3H), 1.21 (s, 3H), 1.32–1.36 (m, 1H), 1.48 (d, *J* = 1.8 Hz, 1H), 1.59–1.69 (m, 3H), 1.94–1.99 (m, 1H), 2.25–2.32 (m, 1H), 2.44 (s, 3H), 2.48 (d, *J* = 2.7 Hz, 1H), 2.74 (s, 1H), 2.80 (s, 1H), 3.91 (s, 3H), 6.18 (s, 1H), 12.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 19.7 (2 Carbon), 20.6, 24.1, 32.1, 33.5, 39.7, 41.5, 47.6, 51.7, 78.4, 103.8, 108.2, 112.2, 140.0, 157.8, 162.7, 172.8; HRMS m/z calcd for $C_{19}H_{27}O_4$ [(M + H)$^+$] 319.1909, found 319.1909.

(4a*S*,6a*R*,12a*R*,12b*S*)-methyl 11-hydroxy-4,4,6a,9,12b-pentamethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene-10-carboxylate (19): colourless oil (111 mg, 69%); $[\alpha]_D^{30}$ = +143° (*c* 0.6, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 1931, 1646, 1578, 1406, 1453, 1318, 1281, 1189, 1156, 1124; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.90 (s, 3H), 0.97–1.03 (m, 2H), 1.12–1.16 (m, 1H), 1.40–1.50 (m, 3H), 1.64–1.70 (m, 2H), 1.75–1.82 (m, 2H), 2.05–2.08 (m, 1H), 2.26–2.32 (m, 1H), 2.44 (s, 3H), 2.66–2.71 (m, 1H), 3.91 (s, 3H), 6.17 (s, 1H), 12.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 16.7, 18.5, 19.7, 20.7, 21.6, 24.1, 33.2, 33.4, 36.9, 39.2, 40.8, 41.8, 51.6, 51.7, 56.1, 78.1, 103.8, 107.9, 112.1, 139.9, 157.8, 162.9, 172.7; HRMS m/z calcd for $C_{24}H_{35}O_4$ [(M + H)$^+$] 387.2535, found 387.2535.

(3*S*,4a*R*,6a*R*,12a*R*,12b*S*)-methyl 3,11-dihydroxy-4,4,6a,9,12b-pentamethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene-10-carboxylate (20): white solid (161 mg, 73%); M.p. 184 – 186 °C; $[\alpha]_D^{30}$ = +98.8° (*c* 0.28, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3415 (br), 2932, 1646, 1580, 1453, 1331, 1277, 1126, 806; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (s, 3 H), 0.91 (s, 3 H), 0.97 (d, *J*=2.29 Hz, 1 H), 1.01 (s, 3 H), 1.12 (dd, *J*=12.36, 4.58 Hz, 1 H), 1.39 - 1.45 (m, 1 H), 1.50 (dd, *J*=13.28, 5.04 Hz, 1 H), 1.61 - 1.69 (m, 3 H), 1.74 - 1.79 (m, 1 H), 1.84 (dt, *J*=13.05, 3.55 Hz, 1 H), 2.07 (dt, *J*=12.36, 3.21 Hz, 1 H), 2.25 - 2.33 (dd, *J*=16.9, 13.3 Hz, 1 H), 2.42 (s, 3 H), 2.66 (dd, *J*=16.94, 5.04 Hz, 1 H), 3.23 (dd, *J*=11.22, 4.81 Hz, 1 H), 3.89 (s, 3 H), 6.16 (s, 1 H), 12.08 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 15.9, 17.1, 19.8, 21.0, 24.4, 27.5, 28.5, 37.1, 37.8, 39.1, 41.1, 51.8, 52.0, 55.4, 78.2, 79.0, 104.3, 108.1, 112.5, 140.4, 158.0, 163.2, 173.1; HRMS: m/z calcd for $C_{24}H_{35}O_5$ [M+H]$^+$: 403.2484; found: 403.2474.

(+)-Hongoquercin A (2): To a solution of **19** (30.0 mg, 0.078 mmol) in methanol (1 mL) and THF (1.5 mL) was added 6 M aq. NaOH (1.5 mL). The reaction mixture was refluxed for 2 h then it was acidified with 2% aq. HCl, and the resultant reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent and purification of the residue on a silica gel column chromatography using EtOAc/hexane as eluent afforded the product 2 (27 mg, 95%) as a white powder; M.p. 145 – 147 °C; $[\alpha]_D^{30}$ = +144° (*c* 0.6, MeOH); IR (neat) υ_{max}/cm^{-1} 2936, 2867, 1623, 1580, 1492, 1455, 1368, 1264, 1177, 1126, 1079, 1031; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.91 (s, 3H), 0.92 (s, 3H), 0.97 (ddd, *J* = 13.5, 3.1 Hz, 1H), 1.03 (dd, *J* = 12.2, 1.4 Hz, 1H), 1.17 (ddd, *J* = 13.5, 13.5, 3.7 Hz, 1H), 1.20 (s, 3H), 1.36 (ddd, *J* = 13.7, 13.7, 3.2 Hz, 1H), 1.42 (d, *J* = 12.4 Hz, 1H), 1.49 (m, 1H), 1.55 (dd, *J* = 13.2, 4.9 Hz, 1H), 1.62 (m, 1H), 1.67 (ddd, *J* = 13.2, 13.2, 4.1 Hz, 1H), 1.78 (m, 1H), 1.81 (m, 1H), 2.07 (ddd, *J* = 12.5, 3.0, 3.0 Hz, 1H), 2.28 (dd, *J* = 16.6, 13.3 Hz, 1H), 2.52 (s, 3H), 2.69 (dd, *J* = 16.8, 4.8 Hz, 1H), 6.21 (s, 1H), 11.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 16.9, 18.7, 20.0, 21.0, 21.8 (2 Carbon), 24.4, 33.4, 33.7, 37.2, 39.4, 41.1, 42.1, 51.8, 56.4, 78.7, 108.3, 112.9, 141.7, 159.1, 164.1, 176.3; HRMS m/z calcd for $C_{23}H_{32}O_4$ [(M + H)$^+$] 372.2301, found 372.2307.

(3*S*,4a*R*,6a*R*,12a*R*,12b*S*)-3,11-dihydroxy-4,4,6a,9,12b-pentamethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene-10-carboxylic acid (21): To a magnetically stirred solution of **20** (50 mg, 0.12 mmol) in a mixture of methanol (0.7 mL) and THF (1.5 mL) was added NaOH (10 mg, 0.25 mmol in 0.2 mL water) and the mixture was refluxed for 3 h. The reaction mixture was cooled and acidified to pH 2-3 followed by extraction with dichloromethane. The extract was washed with water and brine, dried with sodium sulphate. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:3) as eluent furnished the acid (+)-21 (44 mg, 91%) as a white solid; M.p. 149 – 151 °C; $[\alpha]_D^{30}$ = +138.2° (*c* 0.14, MeOH); IR (neat): ν_{max}/cm^{-1} 3490 (br), 2927, 2854, 1620, 1579, 1452, 1376, 1262, 1177, 1126, 1038; ^{1}H NMR (400 MHz, Methanol-d_3): δ 0.81 (s, 3 H), 0.95 (s, 3 H), 1.00 (s, 3 H), 1.03 (dd, *J*=12, 1.8 Hz),1.10 - 1.15 (m, 1 H), 1.17 (s, 3 H), 1.45 (dd, *J*=12.4, 5.0 Hz, 1 H), 1.52 (dd, *J*=13.3, 4.6 Hz, 1 H), 1.59 - 1.69 (m, 3 H), 1.79 (m, 2 H), 2.02 - 2.06 (dd, *J*= 12.0, 3.2 Hz, 1 H), 2.27 (dd, *J*=16.94, 13.40 Hz, 1 H), 2.44 (s, 3 H), 2.62 (dd, *J*=16.86, 5.01 Hz, 1 H), 3.19 (dd, *J*=11.02, 5.24 Hz, 1 H), 6.09 (s, 1 H); ^{13}C NMR (100 MHz, Methanol-d_3): δ 15.4, 16.2, 17.8, 20.5, 21.0, 24.2, 27.9, 28.7, 37.8, 38.8, 39.9, 42.1, 53.0, 56.5, 78.8, 79.4, 105.0, 108.7, 112.8, 141.8, 158.8, 164.5, 175.6; HRMS: m/z calcd for $C_{23}H_{33}O_5$ [M+H]$^+$: 389.2328; found: 389.2310.

(+)-Hongoquercin B (3): To a magnetically stirred solution of **21** (20 mg, 51 µmol) in pyridine (0.5 mL) was added acetic anhydride (24 µL, 0.26 mmol) at room temperature. After stirring for 24 h, the resulting solution was diluted with water (3 mL) and extracted with dichloromethane, washed with 1 N HCl, sat. $CuSO_4$ solution, water and brine, dried over sodium sulphate and concentrated under reduced pressure to afford diacetate. Crudre diacetate was dissolved in methanol (1 mL) and water (0.1 mL), followed by addition of K_2CO_3 (11 mg, 77 µmol) at room temperature. After stirring for 5 h, at same temperature, the resulting mixture was acidified to pH 2-3, and extracted with dichloromethane. The extract was washed with water and brine, dried with sodium sulphate. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc-hexane (1:3) as eluent furnished (+)-Hongoquercin B (3) (19 mg, 86%) as a white solid; M.p. 156 – 158 °C; $[\alpha]_D^{30}$ = +158.6° (*c* 0.14, MeOH); IR (neat): ν_{max}/cm^{-1} 2928,1732, 1621, 1580, 1371, 1262,

1126, 1034; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (s, 3 H), 0.91 (s, 3 H), 0.95 (s, 3 H), 1.10 (dd, *J*=12.0, 1.9 Hz, 1 H), 1.19 (br s, 1 H), 1.20 (s, 3 H), 1.42 - 1.47 (m, 1 H), 1.53 (dd, *J*=13, 4.9 Hz, 1 H), 1.66 (br. s., 2 H), 1.60 - 1.80 (m, 4 H), 1.86 (ddd, *J*=13.3, 3.3, 3.3 Hz, 1 H), 2.06 (s, 3 H), 2.09 (dt, *J*=12.6, 3.2 Hz, 1 H), 2.30 (dd, *J*=16.8, 13.2 Hz, 1 H), 2.51 (s, 3 H), 2.66 (dd, *J*=16.8, 4.9 Hz, 1 H), 4.51 (dd, *J*=11.4, 4.9 Hz, 1 H), 6.21 (s, 1 H), 11.87 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 16.8, 16.9, 19.5, 20.8, 21.4, 23.7, 24.3, 28.3, 36.8, 37.3, 37.9, 40.8, 51.4, 55.3, 78.1, 80.6, 102.8, 107.9, 112.7, 141.7, 158.8, 164.0, 171.2, 175.6; HRMS: m/z calcd for $C_{25}H_{33}O_6$ $[M-H]^+$: 429.2277; found: 429.2269.

(4a*S*,6a*R*,12a*R*,12b*S*)-10-methoxy-4,4,6a,12b-tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthen-9-yl trifluoromethanesulfonate (23): To a cold (0 °C), magnetically stirred solution of the **17d** (57 mg, 0.16 mmol) and dry pyridine (0.017 mL, 0.20 mmol) in anhydrous CH_2Cl_2 (4 mL) was added slowly Tf_2O (0.033 mL, 0.20 mmol). The reaction mixture was stirred for 30 min. at 0 °C. The reaction mixture was then quenched with H_2O and the resultant reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent and purification of the residue on a silica gel column chromatography using EtOAc/hexane as eluent afforded the product 23 (71 mg, 90%) as a yellow oil: R_f = 0.4 (EtOAc/hexane 1/9); $[\alpha]_D^{30}$ = +45° (*c* 0.32, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 2938, 1504, 1465, 1422, 1389, 1211, 1142, 1092, 1021; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.88 (s, 3H), 0.91 (s, 3H), 1.01–1.04 (m, 1H), 1.60–1.68 (m, 4H), 1.74–1.79 (m, 1H), 2.02–2.06 (m, 1H), 2.57–2.63 (m, 2H), 3.83 (s, 3H), 6.65 (s, 1H), 6.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (2 Carbon), 18.5, 19.7, 20.7, 21.5, 22.5, 33.1, 33.4, 36.8, 39.1, 40.8, 41.7, 51.7, 56.0, 56.6, 77.3, 111.0, 114.0, 122.9, 137.1, 144.6, 146.9; HRMS m/z calcd for $C_{23}H_{31}F_3O_5S$ $[M]^+$ 476.1844, found 476.1845.

(+)-8-*epi*-puupehedione (6): To a magnetically stirred solution of the **17d** (50 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) was added BBr_3 (72 mg, 0.29 mmol) at room temperature and reaction mixture was stirred for 6 h. Crushed ice was then added to the reaction mixture, extracted with CH_2Cl_2 (7 mL x 3), washed with brine and dried over Na_2SO_4. Evaporation of the solvent obtained as a crude product, which was used in the next step without further purification. Then 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (165 mg, 0.72 mmol) was added to a solution of *epi*-puupehediol (22) (*c* 0.14 mmol) in 1,4-dioxane (7 mL) and the mixture refluxed for 2 h. Then the solvent was evaporated under reduced pressure and the residue was diluted with ether (10 mL) and washed with sat. $NaHCO_3$ (3 x 7 mL) The organic phase was dried and the solvent was evaporated to yield a crude which after chromatography on silica gel furnish the product 6 (32 mg, 67%) as a red solid; $[\alpha]_D^{30}$ = +104° (*c* 0.5, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 2926, 1669, 1643, 1601, 1564, 1458, 1402, 1240, 1129; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 0.93 (s, 3H), 1.19 (s, 3H), 1.13–1.21 (m, 2H), 1.40–1.49 (m, 1H), 1.51–1.59 (m, 1H), 1.59 (s, 3H), 1.63–1.95 (m, 6H), 2.20–2.25 (m, 1H), 5.93 (s, 1H), 6.13 (s, 1H), 6.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 19.3, 21.8, 22.1, 30.8, 33.3, 34.2, 37.8, 40.4, 41.2, 41.3, 53.2, 83.1, 108.2, 114.5, 122.3, 137.9, 164.3, 166.4, 179.7, 181.2; HRMS m/z calcd for $C_{21}H_{27}O_3$ $[(M + H)^+]$ 327.1960, found 327.1964.

(4a*S*,6a*R*,12a*R*,12b*S*)-10-methoxy-4,4,6a,12b-tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene (24): Compound **23** (50 mg, 0.10 mmol), dry sodium formate (9 mg, 0.13 mmol), dry TBAB (64 mg, 0.21 mmol) and TEA (0.03 mL, 0.23 mmol) was dissolve in DMF (3 mL). Resultant mixture was degassed by bubbling argon for 30 min. then added $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) to this solution. The reaction mixture was heated for an additional 8 h at 80 °C. Upon cooling, the reaction mixture was diluted with Et_2O (100 mL) and filtered through a plug of celite. The mixture was poured into Et_2O (7 mL) and H_2O (7 mL) and the aqueous layer was thoroughly extracted with Et_2O (10 mL x 5). The combined organic layers were washed with 1 N HCl (5 mL), 1N NaOH, dried over Na_2SO_4. Evaporation of solvent and purification of the residue on a silica gel column chromatography using EtOAc/hexane as eluent furnish the product 24. (28 mg, 81%) as a colourless oil; $[\alpha]_D^{30}$ = +26° (*c* 0.47, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 2928, 2865, 1612, 1496, 1463, 1377, 1232; 1127, 1041; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.88 (s, 3H), 0.91 (s, 3H), 1.05 (s, 1H), 1.18 (s, 3H), 1.27–1.57 (m, 4H), 1.60–1.80 (m, 5H), 2.05 (dt, *J* = 12.4, 3.1 Hz, 1H), 2.51–2.69 (m, 2H), 3.74 (s, 3H), 6.61 (d, *J* = 2.0 Hz, 1H), 6.64–6.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 18.5, 19.7, 20.7, 21.6, 22.6, 33.2, 33.4, 36.8, 39.2, 41.1, 41.8, 52.1, 55.7, 56.1, 76.6, 113.0, 114.3, 117.4, 122.9, 147.1, 152.9; HRMS m/z calcd for $C_{22}H_{33}O_2$ $[(M + H)^+]$ 329.2481, found 329.2471.

(+)-Chromazonarol (1): To a solution of 24 (25 mg, 0.076 mmol) in hexane (1 mL) was added a 0.2 M solution of $B(C_6F_5)_3$ in toluene (17 µL, 0.0038 mmol) and $HSiEt_3$ (8 µL, 0.05 mmol) at room temperature. After stirring for one day, the reaction mixture was poured into brine and extracted with ether. The ether extracts were dried over $MgSO_4$ and concentrated to obtain chromazonarol triethylsilyl ether as a crude product, which was used in the next step without further purification. To a solution of chromazonarol triethylsilyl ether (ca. 0.076 mmol) in THF (0.7 mL) was added a 1 M solution of tetrabutyl ammonium fluoride (TBAF) in THF (0.06 mL, 0.06 mmol) at 0 °C. After stirring for 30 min, THF was removed in vacuo and the residue was purified on a silica gel column using EtOAc/hexane to furnish the product 1 (23 mg, 96%) as a white powder; M.p. 126 – 129 °C; $[\alpha]_D^{30}$ = +41° (*c* 0.4, $CHCl_3$); IR (neat) υ_{max}/cm^{-1} 3387, 2925, 1616, 1494, 1451, 1377, 1232, 1127; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.88 (s, 3H), 0.90 (s, 3H), 0.94–0.99 (m 1H), 1.02 (dd, *J* = 12.2, 2.2 Hz, 1H), 1.22–1.13 (m, 4H) 1.17 (s, 1H), 1.31–1.51 (m, 3H), 1.71–1.58 (m, 4H), 1.72–1.78 (m, 1H), 2.04 (dt, *J* = 12.4, 3.3 Hz, 1H), 2.5–2.58 (m, 2H), 6.55–6.57 (m, 2H), 6.63 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 18.6, 19.8, 20.8, 21.7, 22.6, 33.3, 33.5, 36.9, 39.3, 41.2, 41.9, 52.1, 56.2, 76.8, 114.3, 115.9, 117.6, 123.4, 147.2, 148.7; HRMS m/z calcd for $C_{21}H_{30}O_2$ $[(M + H)^+]$ 314.2246, found 314.2247.

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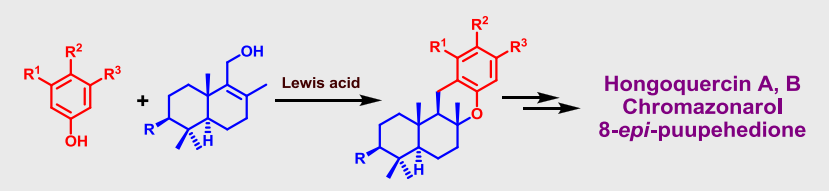

Environmentally benign and highly atom economic catalytic Friedel-Crafts alkylation reaction and diastereoselective C-O bond formation reaction has been developed. The scope and generality of this reaction was amply illustrated by protecting group free total synthesis of chromazonarol, hongoquercin A and B and analogues thereof.

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