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Total Synthesis of (-)-Phomoarcherin C

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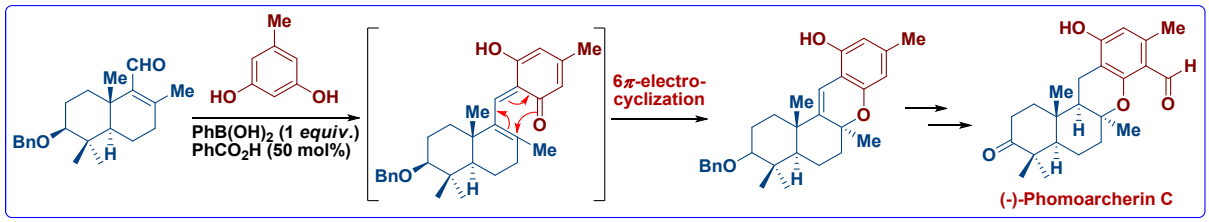


ABSTRACT: A full account on the first total synthesis of chroman meroterpenoid, (-)-phomoarcherin C has been described. Key synthetic transformations include phenyl boronic acid mediated 6π-electrocyclization reaction, a stereospecific hydrogenation driven by thermodynamic, conformational stability of the product and regioselective formylation. The strategy employed is considerably short, atom economical and can open the doors to provide access to various other natural products of the kind.

INTRODUCTION

Terpenoids constitute most diversified and the largest class of metabolites derived from plants and fungi.[1] Meroterpenoids, a subclass of terpenoids, are molecules with part of their structure derived from terpenoid unit. Like many other natural sources, fungi have been rich source of secondary metabolites including meroterpenoids.[2] For instance, endophytic fungi belonging to the genus *Phomopsis,* is an ample source of bioactive natural products.[3] Recently, three new sesquiterpenes, phomoarcherins A-C (**1-3**), were isolated from *phomopsis archeri*.[4] Phomoarcherins are tetracyclic terpenes containing an orcinol or an aromatic lactone moiety. All these phomoarcherins were tested and proven to show moderate to excellent anticancer properties. Most notably, phomoarcherin B (**2**) showed prominent activity against human cholongiocarcinoma cell lines, KKU-M139 (with IC_{50} value 0.1 μg/mL) and KKU-M156 (with IC_{50} value 2.0 μg/mL), which is very much comparable with the control drug, ellipticine. In addition, the compound showed prominent antimalarial activity with IC_{50} value 0.79 μg/mL.[5] Phomoarcherins are tetracyclic skeletons containing a characteristic *trans*-A/B decalin system fused with a dihydrobenzopyran framework with *cis*-B/C ring junction (Figure 1).

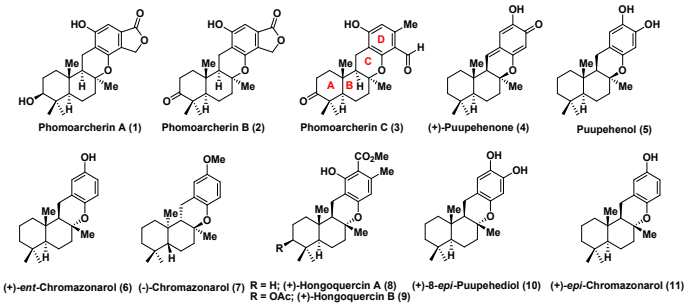
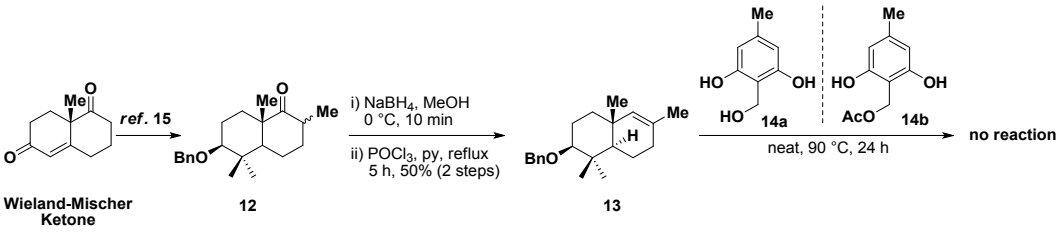


Figure 1: Meroterpenoid families of natural products

Presence of a benzopyran fused mono/sesqui terpenoid unit with a *cis* stereochemistry at the B/C ring junction makes these natural products challenging and interesting targets for synthetic community. There are several reports addressing the synthesis of such type of molecular frameworks such as total syntheses of puupehenol (**4**) and puupehenone (**5**),[6] (+)-*ent*-chromazonarol (**6**),[7] (-)-chromazonarol (**7**),[8] and hongoquercin A (**8**).[9] We also have recently reported total synthesis of hongoquercins A (**8**) and B (**9**), (+)-8-*epi*-puupehediol (**10**) and (+)-*epi*-chromazonarol (**11**).[10] But almost all of these methods are to construct the *trans*-B/C fused skeleton. To our knowledge, there are very few reports to synthesize such scaffolds. Although, they are indirect methods requiring more number of steps to achieve *cis*-B/C stereochemistry.[11] Therefore there has been an unmet need of developing novel strategy which provides a direct access to these kinds of molecules in a much efficient manner.

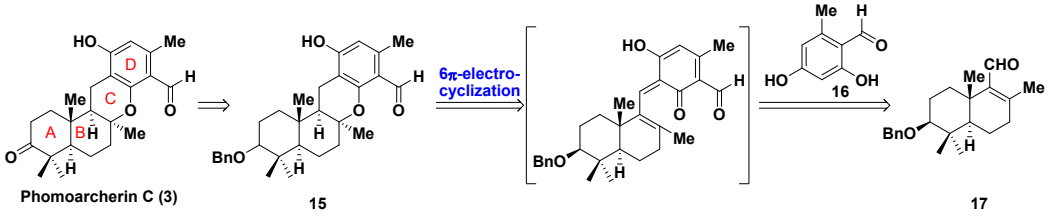


Scheme 1: Unsuccessful attempts towards the synthesis of phomoarcherin core

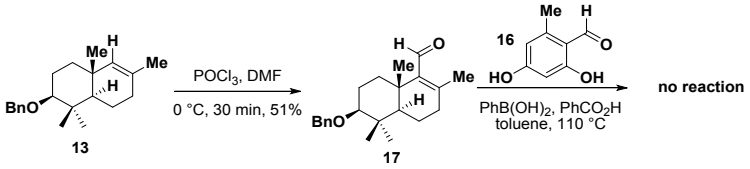
RESULTS AND DISCUSSION

In continuation to our ongoing research interest in total synthesis of natural products having tetrahydro benzopyran/chromane core,[12] we became interested to develop an efficient synthetic strategy that gives access to phomoarcherin family of natural products also. Typically, chromanes are outcomes of hetero Diels-Alder reaction (HDA) between *o*-quinone methide and an appropriate olefin.[13] We have reasoned that an HDA between appropriate *o*-quinone methides

and olefins would be a perfect synthetic tool to achieve the core skeleton of the aforementioned natural products. *O*-quinone methides are transient and highly reactive due to their extreme tendency to undergo rearomatization reacting either by Michael addition fashion with nucleophiles or by a cycloaddition with 2π systems to yield benzopyrans.[14]

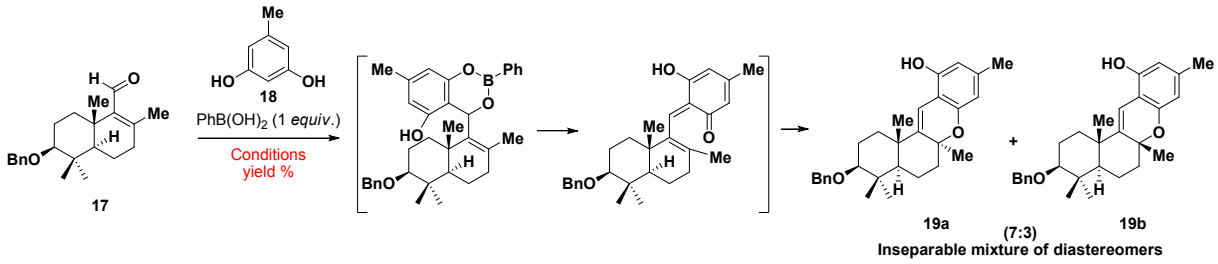


Scheme 2: Retrosynthetic analysis to execute 6π-electrocyclization



Scheme 3: Unsuccessful attempt of 6π-electrocyclization to give tetracyclic core

Table 1: Optimization of 6π-electrocyclization reaction



S. N.	Reagent	Additive	Solvent	Conc. mL/mmol	Time (h)	Temp (°C)	Yield
1	Pyridine	--	--	--	24	115	trace
2	$PhB(OH)_2$	$CH_3CH_2CO_2H$ (20 mol%)	Toluene	5	24	110	20
3	$PhB(OH)_2$	CH_3CO_2H (20 mol%)	Toluene	5	24	110	15
4	$PhB(OH)_2$	$PhCO_2H$ (20 mol%)	Benzene	5	15	80	30
5	$PhB(OH)_2$	$PhCO_2H$ (20 mol%)	Toluene	5	15	110	35

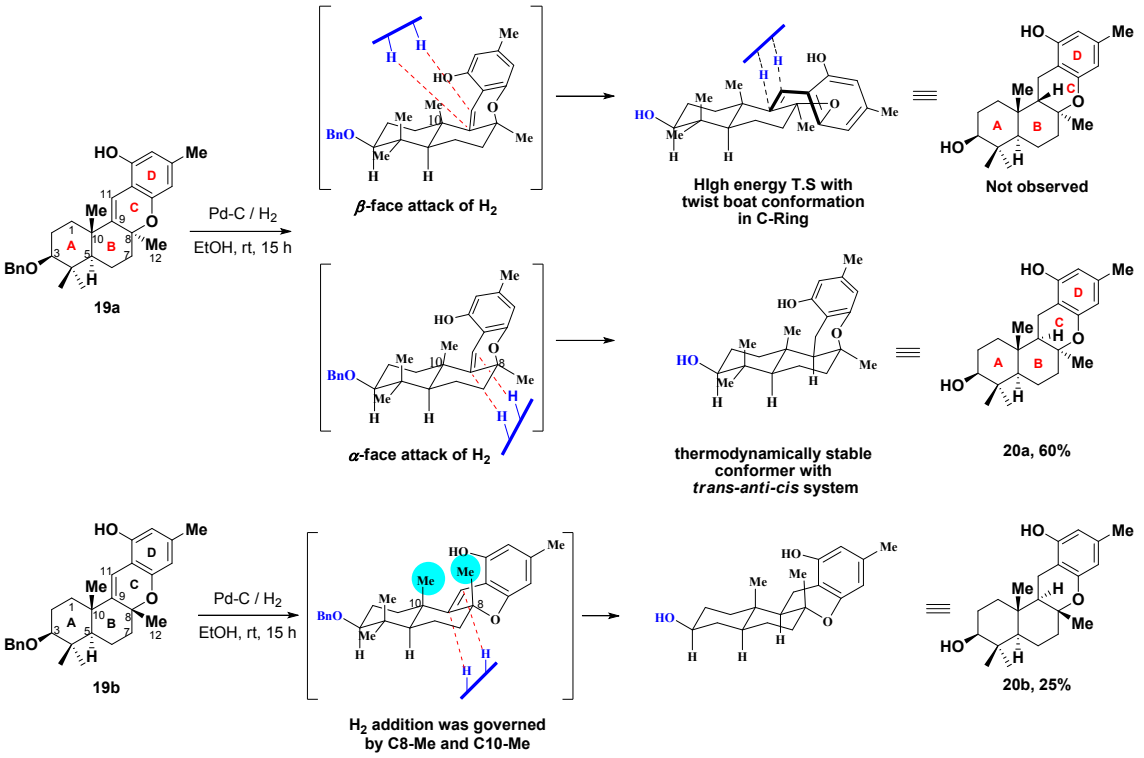
6	$PhB(OH)_2$	$PhCO_2H$ (20 mol%)	Xylene	5	15	140	33
7	$PhB(OH)_2$	$PhCO_2H$ (50 mol%)	Toluene	5	15	110	40
8	$PhB(OH)_2$	$PhCO_2H$ (50 mol%)	Toluene	5	15	160 (seal tube)	40
9	$PhB(OH)_2$	$PhCO_2H$ (50 mol%)	Toluene	0.5	15	110	60

a = All the reaction were carried out taking 1 equivalent of $PhB(OH)_2$

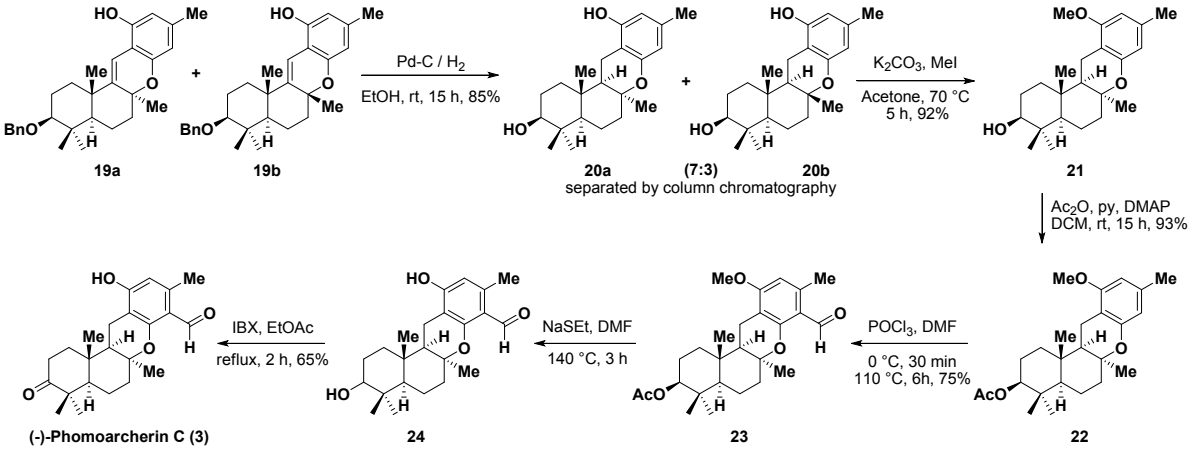
Over the years, many research groups have been engaged in developing new and efficient strategies to generate *o*-quinone methides.[15] One among such methods constitutes a Knoevenagel condensation of phenolic derivative and an aldehyde in basic medium to generate various *o*-quinone methides. In this respect, it was conceived that members of phomoarcherin family of natural products could be targeted by using terpenoids in combination with appropriate *o*-quinone methides by HDA strategy. Unfortunately, our initial attempts to operate HDA reactions between olefin **13**, prepared from a known ketone **12**,[16] and precursors of *o*-quinone methides (**14a** or **14b**) were unsuccessful to generate the desired benzopyran products resulting in the decomposition of aryl partners (**14a** or **14b**) with the olefin left unreacted in the reaction mixture (Scheme 1). We attribute these results to the low reactivity of olefin **13** due to severe steric hindrance exerted by methyl groups from either sides of the double bond.

This prompted us to adopt a different strategy. In this context, we believed that an electrophilic activation property of aryl boronic acids[17] may promote a *6π*-electrocyclization[18] between intermediate **16** and **17** through the formation of an intermediate with required *6π*-electronic system (Scheme 2). Advantages with alkyl boronic acid catalysis are i) they are considerably less toxic, ii) they are mild *Lewis* acids with wide range of chemical properties and iii) most of them are air stable with extended shelf lives. Aryl boronic acids are known to be important in many crucial chemical transformations.[19] Barrero *et al*. has reported an efficient synthesis of puupehedione and related compounds employing *6π*-electrocyclization.[20] Therefore we have envisioned that aryl boronic acids can activate the carbonyl compounds enabling them to get attacked by a nucleophile such as ocinol derivative **16** in our case. Accordingly, compound **17** was prepared from olefin **13** through Vilsmeier-Haack formylation. Then a reaction was set up between enal **17** and orcinol derivative **16** using phenyl boronic acid (1 *equiv.*), benzoic acid (20 mol%) as co-catalyst in toluene at 110 °C (Scheme 3). There was no any reaction occurred

even after prolonged heating for up to 24 h resulting in unreacted starting compounds left over in the reaction mixture. This is might be due to the deactivation of compound **16** by electron withdrawing formyl group.



Scheme 4: Schematic explanation for the stereoselective hydrogenation



Scheme 5: Completion of total synthesis of phomoarcherin C (3)

Eventually, orcinol **18** was employed in the same reaction with enal **17** in presence of phenyl boronic acid (1 *equiv.*) and benzoic acid (20 mol%). This time, to our delight, a 7:3

diastereomeric mixture of annulation products **19a** and **19b** was formed in 30% combined yield (Table 1). Phenyl boronic acid might be activating the enal **17** to form a boronate intermediate which upon disproportionation forms an intermediate with perfect 6π-electronic system that readily underwent electrocyclization to give the cyclic products (**19a** and **19b**). The two isomers differ in stereochemistry at C-8 methyl group and were inseparable by silica gel column chromatography. In order to improve the yield, we sought to screen several bronsted acid and solvent systems, keeping the phenyl boronic acid constant (Table 1) and found that the reaction at high concentration was affording highest conversion rate with best yield i.e. 60%. We proceeded for next step with the mixture of diastereomers.

Compounds **19a** and **19b** were then subjected to a Pd-C hydrogenation protocol to reduce the double bond and also to deprotect the benzyl group in one-pot. Only two diastereomeric diols **20a** and **20b** were obtained instead of four. Formation of **20b** is essentially because of the preferential *α*-face addition of hydrogen onto the double bond of **19a** which would be governed by the steric hindrance posed by both C8-*β*-Me and C10-*β*-Me present on either sides of the double bond.[21] On the other hand, diastereomer **20a** might be forming through a preferential *α*-face addition of hydrogen onto the double bond of **19a**. In this case, addition of hydrogen could not be completely governed by the C10-*β*-Me. Because, among the two adjacent angular methyl groups, C8-Me is in *α*-face and the C10-Me is in *β*-face. At this juncture, the formation of **20a** can be rationalised by the kinetic control of the reaction. If the hydrogen adds onto the double bond of the substrate **19a**, through *β*-face, it would generate a high energetic transition state with twist boat conformation in the ring-D. Therefore addition of the hydrogen onto the double bond of **19a** was taking place preferentially through the *α*-face to produce the tetracyclic skeleton with a thermodynamically stable *trans-anti-cis* A/B/C system (Scheme 4). This observation confirms the stereochemistry and relative configuration of the major isomer **20a** as 3*S*, 5*R*, 8*S, 9R* and 10S. At this stage, fortunately, the two diastereomers **20a** and **20b** were separated by careful silica gel column chromatography. In order to perform formylation on the aromatic ring, anticipating that both the free aliphatic and aromatic OH groups would possibly interfere, they were protected successively as acetyloxy and methoxy groups to get compound **22**. A Vilsmeier-Haack formylation on the compound **22** afforded aldehyde **23** in 75% yield. BBr_3 mediated methoxy deprotection was always a disappointment resulting in either decomposition or benzopyran ring opening reaction of **23**. Alternatively a reaction using excess of sodium ethyl

thiolate, to our delight, resulted in the deprotection of not only the methoxy group but also the acetyl group to afford dihydroxy compound **24** which was directly preceded for next step without further purification. IBX oxidation of **24** afforded the natural product, (-)-phomoarcherin C (**3**) in 65% yield (Scheme 5). Spectroscopic data and optical rotation of synthesized **3** was identical with those of isolated natural product (Tables S1-S3; see supporting information).

In conclusion, a structurally intriguing benzopyran natural, Phomoarcherin C has been synthesized for the first time in considerably concise route. A 6π-electrocyclization strategy catalysed by boronic acid-bronsted acid co-catalyst system was employed for the synthesis of the natural product in 9 steps from the known ketone **12** in 29.83 % overall yield. With the synthesis of this natural product, we have, in addition to confirming the structure of the molecule, also established its absolute configuration.

EXPERIMENTAL SECTION

General Information: All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise mentioned. All the chemicals and reagents used were purchased commercially, and used without further purification. Anhydrous diethyl ether was prepared by distilling from sodium - benzophenone. Dichloromethane was distilled from calcium hydride. DMF was distilled from dry KOH. Yields refer to chromatographically pure material, unless otherwise stated. Reactions were monitored by Agilent Infinite Series LC-MS and thin layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV-light as a visualizing agent and *p*-anisaldehyde stain as coloring agent, and heat as developing agent. Merck silica gel (particle size 100-200 and 230-400 mesh) was used for flash column chromatography. NMR spectra were recorded on JEOL ECX 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) in $CDCl_3$ having TMS 0.03% as internal standard. EI-MS/ESI-MS was recorded on a Waters Micromass Quattro Micro triplequadrupole mass spectrometer.

The following abbreviations were used to explain the multiplicities: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *dd* = doublet of doublet, *ddd* = doublet of a doublet of a doublet, *dt* = doublet of a triplet, *td* = triplet of a doublet, *m* = multiplet, *br* = broad.

Preparation of (3S,8aR)-3-(benzyloxy)-4,4,7,8a-tetramethyl-1,2,3,4,4a,5,6,8a-octahydro naphthalene (13):

Ketone **12** (314 mg, 1 mmol) was dissolved in MeOH (5 mL) and cooled to 0 °C. $NaBH_4$ (113 mg, 3 mmol) was added in portion wise to the above mixture at the same temperature. Once the addition of $NaBH_4$ is over, the reaction mixture was stirred for 10 min at the same temperature and reaction progress was monitored by TLC. Methanol was evaporated under reduced pressure followed by the addition of ice cold water (10 mL) and DCM (10 mL). Organic layer was separated through separating funnel. Aqueous layer was extracted twice (2 x 10 mL) with DCM. Combined organic layers were washed with brine, dried over $NaSO_4$, evaporated to obtain the crude alcohol which was preceded for the next step without further purification.

The above crude alcohol was dissolved in pyridine (5 mL) and cooled to 0 °C, prior to the gentle addition of $POCl_3$ (0.28 mL, 3 mmol). Reaction mixture was slowly allowed to attain room temperature then refluxed for 5 h. Once the reaction is completed as monitored by TLC, crushed ice was added to quench unreacted $POCl_3$ followed by extracting the reaction mixture with DCM (2 x 10 mL). The combined organic layers were washed initially with 1N HCl to remove pyridine, then with brine. Organic layer was dried over $NaSO_4$, evaporated to get crude olefin **13** which was purified by silica gel column chromatography using hexane/EtOAc (99:1) to get pure olefin **13** as colorless oil. Yield = 149 mg (50% over two steps). R_f = 0.5 in 100% hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 5.06 (d, *J* = 1.4 Hz, 1H), 4.68 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 2.96 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.00 – 1.82 (m, 3H), 1.73 – 1.65 (m, 1H), 1.59 (s, 3H), 1.52 – 1.42 (m, 2H), 1.20 (td, *J* = 13.4, 3.9 Hz, 2H), 1.05 (d, *J* = 2.0 Hz, 1H), 1.01 (s, 3H), 0.94 (s, 3H), 0.86 (s, 3H); **^{13}C NMR** {^{1}H} (100 MHz, $CDCl_3$) δ 139.6, 135.2, 130.4, 128.3, 128.3, 127.6, 127.6, 127.3, 87.0, 71.6, 58.3, 50.7, 38.8, 37.9, 35.1, 32.0, 23.6, 23.3, 21.7, 18.9, 16.4; **HRMS (ESI)** *m*/*z* calcd. for $C_{21}H_{31}O$ $[M+H]^+$ 299.2375, found 299.2368.

Preparation of 6-(benzyloxy)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (17):

To an ice cold DMF (1.9 mL, 50 mmol), was added slowly, $POCl_3$ (0.07 mL, 1.5 mmol) and the mixture was stirred vigorously under inert atmosphere at 0 °C for 30 minutes until a thick colorless syrup has formed. To this syrup, was added a solution of compound **13** (150 mg, 0.5 mmol) in 0.5 mL of dry DMF under inert atmosphere. The reaction mixture was stirred for 30

minutes at room temperature and reaction progress was monitored by TLC, after which, it was poured into crushed ice and then extracted with EtOAc twice (2x10 mL).

The combined organic layers were dried over $NaSO_4$, evaporated to get crude **17** which was purified by silica gel column chromatography using hexane/EtOAc (9:1) to get pure aldehyde **17** as colorless oil. Yield = 82 mg (51%). R_f = 0.5 in 10% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.35 – 7.32 (m, 5H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.42 (d, *J* = 11.9 Hz, 1H), 2.95 (dd, *J* = 11.8, 4.4 Hz, 1H), 2.68 (dt, *J* = 13.4, 3.5 Hz, 1H), 2.33 – 2.25 (m, 2H), 2.04 (s, 3H), 1.90 (ddd, *J* = 10.6, 7.6, 3.6 Hz, 2H), 1.73 (ddd, *J* = 7.6, 4.0, 2.3 Hz, 2H), 1.64 – 1.56 (m, 2H), 1.19 (s, 3H), 1.02 (s, 3H), 0.88 (s, 3H); **HRMS (ESI)** *m*/*z* calcd. for $C_{21}H_{31}O$ $[M+H]^+$ 227.2324, found 227.2332.

Preparation of (3S,4aR,6aS,12aR,12bS)-4,4,6a,9,12b-pentamethyl-2,3,4,4a,5,6,6a,12, 12a,12b-decahydro-1*H*-benzo[a]xanthene-3,11-diol (20a) and (3S,4aR,6aR,12aR,12bS)-4,4,6a,9,12b-pentamethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1*H*-benzo[a]xanthene-3,11-diol (20b):

A mixture of aldehyde **17** (326 mg, 1 mmol), orcinol **18** (196 mg, 1.5 mmol), $PhB(OH)_2$ (122 mg, 1 mmol) and $PhCO_2H$ (61 mg, 0.5 mmol) were taken in 0.5 mL of dry toluene and refluxed for 15 h under nitrogen atmosphere. Once the aldehyde was consumed as monitored by TLC, reaction mixture was diluted with 2 mL of DCM, absorbed on silica gel and directly purified by column chromatography using hexane/EtOAc (99:1 to 95:5) to get 7:3 mixture of diastereomers **19a** and **19b** as colorless oil. Yield = 206 mg (60% combined yield for **19a** and **19b**). Yield = 149 mg (50% over two steps). R_f = 0.5 in 5% EtOAc-hexane. Since the diastereomers were inseparable by column chromatography, next reaction was done on the mixture of diastereomers.

A mixture of **19a** and **19b** was dissolved in EtOH at room temperature and added with 300 mg of Pd/C (10 %) (2 w/v with respect to the starting compound) and stirred under hydrogen pressure (applied with balloon) for 15 h. Once the reaction was completed as monitored by TLC, palladium charcoal was filtered off and the solvents were evaporated to get crude product. Purification was done by silica gel column chromatography using hexane/EtOAc (97:3 to 90:10) to get 71 mg of **20a**, Yield = 60%, and 30 mg of **20b**, Yield = 25%.). R_f = 0.3 in 20% EtOAc-hexane.

Spectroscopic data of major compound 20a: ; $[\alpha]_D^{28}$ = -4.22 (c 1.02, $CHCl_3$); **IR (neat):** υ_{max}/cm^{-1} 3345, 2925, 2853, 1626, 1590, 1461, 1350, 1166, 1133, 1064, 1018, 997, 823; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.21 (s, 1H), 6.14 (s, 1H), 3.24 (dd, *J* = 11.5, 4.6 Hz, 1H), 2.74 – 2.55 (m, 3H), 2.20 (s, 3H), 2.15 (d, *J* = 10.9 Hz, 1H), 1.91 (dt, *J* = 13.0, 3.5 Hz, 1H), 1.71 – 1.58 (m, 5H), 1.55 – 1.52 (m, 1H), 1.35 (d, *J* = 7.6 Hz, 1H), 1.16 (s, 3H), 1.07 (dd, *J* = 13.1, 3.8 Hz, 1H), 1.02 (s, 3H), 0.93 – 0.86 (m, 2H), 0.78 (s, 3H), 0.71 (s, 3H); **^{13}C NMR** {^{1}H} (100 MHz, $CDCl_3$) δ 155.9, 153.4, 137.1, 110.5, 107.6, 107.0, 79.4, 75.3, 54.7, 49.1, 41.0, 39.1, 38.5, 38.4, 28.9, 27.5, 27.3, 21.5, 18.3, 17.5, 16.0, 14.5; **HRMS (ESI)** *m/z* calcd. for $C_{22}H_{33}O_3$ $[M+H]^+$ 345.2430, found 345.2422.

Preparation of (3S,4aR,6aS,12aR,12bS)-11-methoxy-4,4,6a,9,12b-pentamethyl- 2,3,4,4a,5, 6, 6a,12,12a,12b-decahydro-1H-benzo[a]xanthen-3-ol (21) :

Major diastereomer **20a** (70 mg, 0.2 mmol) was dissolved in acetone, added with K_2CO_3 (84 mg, 0.6 mmol) followed by MeI (0.04 mL, 0.6 mmol) at room temperature. The reaction mixture was slowly heated to reflux for 5h under nitrogen atmosphere. Once the reaction is completed as monitored by TLC, reaction mixture was filtered to get clear solution which was then evaporated under reduced pressure to get crude compound. Purification of the crude compound was done by silica gel column chromatography using hexane/EtOAc (97:3 to 95:5) to get **21** as a colorless oil. Yield = 66 mg (92%). R_f = 0.5 in 20% EtOAc-hexane. ; $[\alpha]_D^{28}$ = -4.65 (c 1.02, $CHCl_3$); **IR (neat):** υ_{max}/CM^{-1} 3359, 2928, 1618, 1587, 1496, 1463, 1352, 1327, 1303, 1277, 1225, 1165, 1133, 1112, 1022, 1002, 948, 934, 909, 888, 843, 811, 670, 580; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.23 (d, *J* = 15.0 Hz, 2H), 3.79 (s, 3H), 3.23 (dd, *J* = 11.5, 4.8 Hz, 1H), 2.71 (d, *J* = 18.4 Hz, 1H), 2.55 (dd, *J* = 18.4, 8.2 Hz, 1H), 2.26 (s, 3H), 2.18 – 2.10 (m, 1H), 1.92 (dt, *J* = 13.1, 3.5 Hz, 1H), 1.72 – 1.44 (m, 7H), 1.31 (d, *J* = 8.1 Hz, 1H), 1.15 (s, 3H), 1.02 (s, 3H), 0.93 – 0.84 (m, 1H), 0.78 (s, 3H), 0.70 (s, 3H); **^{13}C NMR** {^{1}H} (100 MHz, $CDCl_3$) δ 157.3, 155.4, 136.7, 110.6, 108.5, 103.0, 79.4, 75.2, 55.6, 54.7, 49.2, 41.0, 39.1, 38.5, 38.4, 28.8, 27.5, 27.2, 22.0, 18.3, 17.7, 16.0, 14.5. **HRMS (ESI)** *m/z* calcd. for $C_{23}H_{35}O_3$ $[M+H]^+$ 359.2586, found 359.2589.

Preparation of (3S,4aR,6aS,12aR,12bS)-11-methoxy-4,4,6a,9,12b-pentamethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthen-3-yl acetate (22):

Compound **21** (66 mg, 0.18 mmol) was dissolved in dry DCM (2 mL) and added with pyridine (0.09 mL, 1.1 mmol), acetic anhydride (0.1 mL, 1.1 mmol) and catalytic amount of N,N-dimethyl amino pyridine at room temperature. The reaction mixture was then stirred for 15 h under nitrogen atmosphere. Once the reaction was completed, as monitored by TLC, it was cooled to 0 °C and 1N HCl (5 mL) was added to the mixture. Two layers were separated. The aqueous layer was extracted twice with DCM (2 x 5 mL). Combined organic fractions were washed with brine, dried over $NaSO_4$ and evaporated under reduced pressure to get crude compound. Purification of the crude compound was done by silica gel column chromatography using hexane/EtOAc (99:1 to 95:5) to get **22** as a colorless oil. Yield = 72 mg (93%). R_f = 0.5 in 10% EtOAc-hexane; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = -4.0 (c 1.02, $CHCl_3$); **IR (neat):** υ_{max}/CM^{-1} 3; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.24 (s, 1H), 6.20 (s, 1H), 4.49 (dd, *J* = 11.5, 4.8 Hz, 1H), 3.79 (s, 3H), 2.69 (d, *J* = 18.4 Hz, 1H), 2.56 (dd, *J* = 18.4, 8.1 Hz, 1H), 2.26 (s, 3H), 2.18 – 2.10 (m, 1H), 2.04 (s, 3H), 1.92 (dt, *J* = 13.2, 3.4 Hz, 1H), 1.73 – 1.62 (m, 2H), 1.51 – 1.55 (m, 2H), 1.32 (d, *J* = 8.0 Hz, 1H), 1.15 (s, 3H), 1.10 (dd, *J* = 13.4, 3.9 Hz, 1H), 1.02 – 0.93 (m, 2H), 0.89 (s, 3H), 0.85 (s, 3H), 0.72 (s, 3H); **^{13}C NMR** {^{1}H} (100 MHz, $CDCl_3$) δ 171.4, 157.3, 155.4, 136.7, 110.6, 108.5, 103.0, 81.3, 75.2, 55.6, 54.8, 49.1, 40.9, 38.3, 38.2, 38.0, 28.8, 27.2, 23.8, 22.0, 21.7, 18.2, 17.8, 17.1, 14.5; **HRMS (ESI)** *m*/*z* calcd. for $C_{25}H_{37}O_4$ $[M+H]^+$ 401.2692, found 401.2688.

Preparation of (3S,4aR,6aS,12aR,12bS)-8-formyl-11-methoxy-4,4,6a,9, 12b-pentamethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthen-3-yl acetate (23):

Dry DMF (0.02 mL, 0.27 mmol) was taken in a round bottom flask under nitrogen atmosphere and cooled to 0 °C. Distilled $POCl_3$ (0.025 mL, 0.27 mmol) was added slowly to the dry DMF with vigorous stirring at 0 °C and kept stirring for 30 min at the same temperature to get thick colorless syrup. Then compound **22** (72 mg, 0.18 mmol) in dry DMF (2 mL) was added to the above syrup at 0 °C. Reaction mixture was gradually warmed to room temperature and then heated at 110 °C for 6 h. Once the starting compound was consumed completely as shown in TLC, crushed ice was added to cease the reaction and the mixture was extracted thrice with EtOAc (3x5 mL). Combined organic fractions were washed with brine, dried over $NaSO_4$ and evaporated under reduced pressure to get crude aldehyde. Purification of the crude compound was done by silica gel column chromatography using hexane/EtOAc (95:5 to 90:10) to get **23** as a colorless oil. Yield = 55 mg (72%). R_f = 0.3 in 10% EtOAc-hexane; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = -5.6 (c 1.02,

$CHCl_3$); **IR (neat):** υ_{max}/CM^{-1} 2925, 2852, 1732, 1674, 1603,1570,1463, 1394, 1371, 1342, 1312, 1280, 1245, 1217, 1167, 1085, 1028, 1005, 936, 886, 803, 555; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 6.24 (s, 1H), 4.52 (dd, *J* = 11.6, 4.7 Hz, 1H), 3.88 (s, 3H), 2.72 (d, *J* = 18.4 Hz, 1H), 2.63 (d, *J* = 8.0 Hz, 1H), 2.59 (s, 3H), 2.26 – 2.21 (m, 1H), 2.07 (s, 3H), 1.95 – 1.91 (m, 1H), 1.73 – 1.69 (m, 2 H), 1.61 – 1.57 (m, 3H), 1.39 (d, *J* = 8.0 Hz, 1H), 1.22 (s, 3H), 1.16 (d, *J* = 3.6 Hz, 1H), 1.02 (d, *J* = 10.6 Hz, 1H), 0.93 (s, 3H), 0.88 (s, 3H), 0.75 (s, 3H); **^{13}C NMR** {^{1}H} (100 MHz, $CDCl_3$) δ 191.6, 171.4, 161.1, 160.3, 141.5, 117.5, 109.1, 105.6, 81.1, 76.5, 55.8, 54.6, 48.4, 40.6, 38.3, 38.1, 38.0, 28.8, 27.3, 23.8, 22.7, 21.7, 18.1, 17.7, 17.2, 14.5; **HRMS (ESI)** *m*/*z* calcd. for $C_{26}H_{37}O_5$ $[M+H]^+$ 429.2641, found 429.2647.

Preparation of phomoarcherin C (3):

To a mixture of NaH (26 mg, 0.65 mmol) in dry DMF at 0 °C under nitrogen atmosphere, was added EtSH (0.055 mL, 0.77 mmol) and stirred for 30 min at the same temperature. A solution of compound **23** (55 mg, 0.13 mmol) in dry DMF was slowly added to the above sodium ethane thiolate mixture at 0 °C and allowed to warm gradually to room temperature. Then the reaction mixture was heated 140 °C for 3 h. Once the reaction was completed as indicated by TLC, it was cooled down to 0 °C and was quenched by adding crushed ice. Reaction mixture was extracted thrice with EtOAc (3x5 mL) and the combined organic fractions were washed with brine (2x5 mL), dried over $NaSO_4$ and evaporated to get crude compound **24** which was preceded for the next step without purification.

The above crude compound **24** was dissolved in EtOAc (2 mL) and added with IBX (108 mg, 0.38 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was refluxed for 2 h. Once the reaction was completed as shown in TLC, it was cooled to room temperature and the solids were filtered off. The clear solution obtained so was evaporated under reduced pressure and purified by silica gel column chromatography using hexane/EtOAc (95:5 to 90:10) to get **Phomoarcherin C (3)** as a colorless oil. Yield = 31 mg (65% over two steps). R_f = 0.6 in 20% EtOAc-hexane; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = -2.6 (c 1.02, $CHCl_3$); **IR (neat):** υ_{max}/CM^{-1} 2924, 2853, 1695, 1647, 1584, 1510, 1449, 1424, 1385, 1324, 1238, 1083, 1014, 813, 520; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 6.23 (s, 1H), 2.76 (s, 2H), 2.56 (m, 1H), 2.52 (s, 3H), 2.47 – 2.39 (m, 1H), 2.30 – 2.23 (m, 1H), 2.17 – 2.09 (m, 1H), 1.85 – 1.76 (m, 1H), 1.67 (dd, *J* = 13.4, 3.4 Hz, 1H), 1.54 – 1.48 (m, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 1.05 (s, 3H), 0.84 (s, 3H); **^{13}C NMR** {^{1}H} (100 MHz,

$CDCl_3$) δ 217.3, 191.0, 160.8, 158.3, 141.6, 116.8, 110.4, 106.9, 76.1, 54.1, 47.3, 47.1, 39.7, 38.4, 37.6, 34.1, 26.8, 26.7, 21.9, 21.6, 19.0, 17.4, 14.0; **HRMS (ESI)** *m/z* calcd. for $C_{23}H_{31}O_4$ $[M+H]^+$ 371.2222, found 371.2229.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of 1H and 13C spectra for all products and table of results from kinetics NMR experiments

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.Conflicts of interest

There are no conflicts to declare.

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