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A Facile Phenol-Driven Intramolecular Diastereoselective Thermal/Base-Catalyzed Dipolar [2 + 2] Annulation Reactions: An Easy Access to Complex Bioactive Natural and Unnatural Benzopyran Congeners

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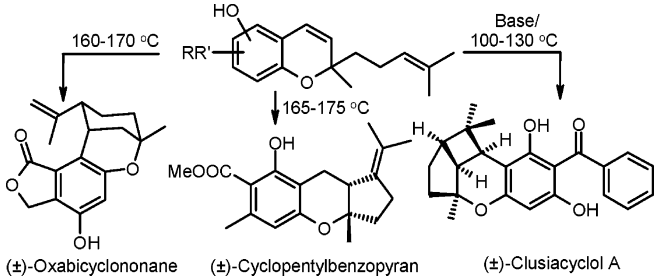

The complex bioactive natural and unnatural benzopyran congeners have been synthesized using one-/two-step approaches in very good yields from the reactions of two different dihydroxyphthalides, natural resorcyclic acid derivative, and trihydroxybenzophenone with citral and/or farnesal, via the phenol-driven intramolecular diastereoselective thermal/base-catalyzed dipolar [2 + 2] cycloaddition reactions and three different thermal intramolecular cyclization reactions. The effects of the nature and the position of phenolic groups in the starting materials on the course of these cycloaddition reactions have also been described. Depending upon the absence or presence of intramolecular hydrogen bonding of the phenolic group with the carbonyl moiety in the starting materials, these phenol-driven intramolecular thermal/base-catalyzed dipolar [2 + 2] cycloaddition reactions either furnished the kinetically controlled products or directly formed the thermodynamically controlled rearranged products, respectively.

Introduction

Several structurally complex compounds with a hexahydrooxacyclobutaindan moiety have been isolated as bioactive natural products and are depicted in Figure 1.[1−7] All of these oxacyclobutaindans bear the free phenolic group/groups, and one can easily make out that nature might be designing them by using the condensation reactions of phenolic compounds with citral and/or farnesal via [2 + 2] cycloaddition reactions. The natural products with oxabicyclononane units have been shown in Figure 2,[7,8] and one gets a feeling that Nature might be making them via intramolecular cyclization of phenolic groups with the correctly attached limonene moiety.[9] Among these, rhododaurichromanic acid A (from *Rhododendron dauricum*)[1] and

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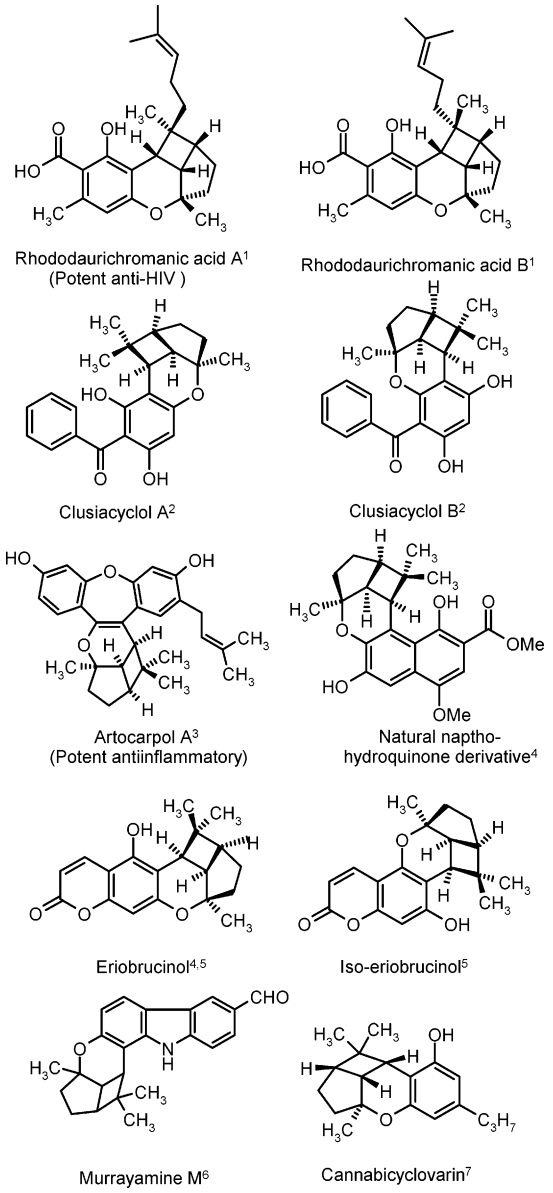


FIGURE 1. Naturally occurring hexahydrooxacyclobutaindans.

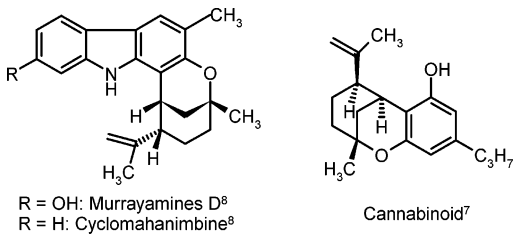
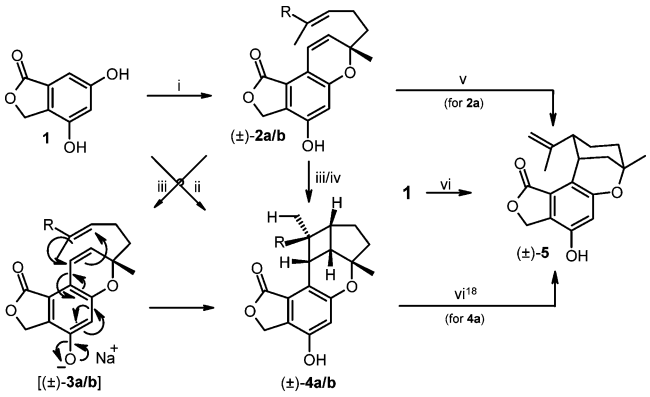


FIGURE 2. Naturally occurring oxabicyclononanes.

artocarpol A (from *Artocarpus rigida*) [3] are of current interest, as they possess potent anti-HIV and potent antiinflammatory activities, respectively.[1,3] Such types of natural and unnatural compounds with oxacyclobutaindan core units have been synthesized previously by using intramolecular [2 + 2] photochemical[1b,c,3c,5,9,10] or acid-catalyzed cationic[11] cycloaddition reactions of various suitably substituted benzopyrans. We reasoned that all these molecules bear a free phenolic group, and hence, the intramolecular phenol-driven thermal or base-catalyzed [2 + 2] cycloaddition reactions would be possible via the corresponding dipolar intermediates.[12] Hence, we prepared a plan to study the thermal/base-catalyzed cycloaddition reactions of four different types of natural/unnatural phenolic substrates with citral and/or farnesal. Here, we report an easy thermal/base-catalyzed diastereoselective access to several structurally interesting bioactive natural and unnatural benzopyran congeners (Schemes 1−4).

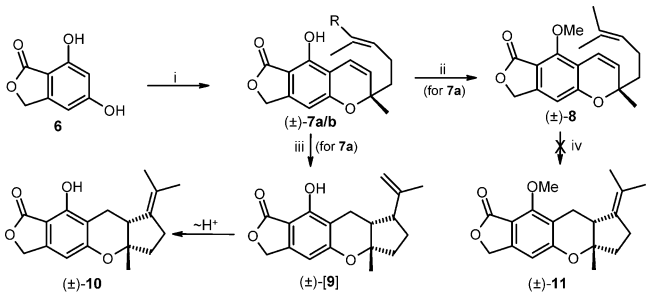
SCHEME 1. Synthesis of Unnatural Hexahydrooxacyclobutaindans 4a/b and Oxabicyclononane 5[a]



2a: R= CH_3; **2b**: R= $CH_2CH_2CH{=}C(CH_3)_2$; **4a**: R = CH_3; **4b**: R= $CH_2CH_2CH{=}C(CH_3)_2$

[a] Key: (i) citral/farnesal (5.00 equiv), $Ca(OH)_2$ (1.50 equiv), MeOH, 60 °C, 6 days (**2a**: 60%, **2b**: 63%); (ii) citral (5.00 equiv), 120−130 °C, 6 h (**4a**: 82%); (iii) (a) MeOH/2 N NaOH (5:1), 0 °C to rt, 8−10 h, (b) H^+/2 N HCl (**4a**: 80%, **4b**: 78%); (iv) 120−130 °C, 6 h (**4a**: 76%); (v) 160−170 °C, 6 h (82%); (vi) citral (5.00 equiv), 160−170 °C, 6 h (82%).

SCHEME 2. Thermal Annulation and Rearrangement of (±)-7 to (±)-10[a]



7a: R = CH_3; **7b**: R = $CH_2CH_2CH{=}C(CH_3)_2$

[a] Key: (i) citral/farnesal (5.00 equiv), DBU (1.10 equiv), MeCN, 50 °C, 24 h (**7a**: 65%, **7b**: 68%); (ii) acetone, K_2CO_3 (5.00 equiv), MeI (5.00 equiv), reflux, 6 h (99%); (iii) 165−170 °C, 6 h (**10**: 90%); (iv) rt to 200 °C, 6 h (0%).

Results and Discussion

The reaction of 4,6-dihydroxyphthalide (**1**)[13] with citral (5 equiv) at 120−130 °C exclusively furnished the corresponding

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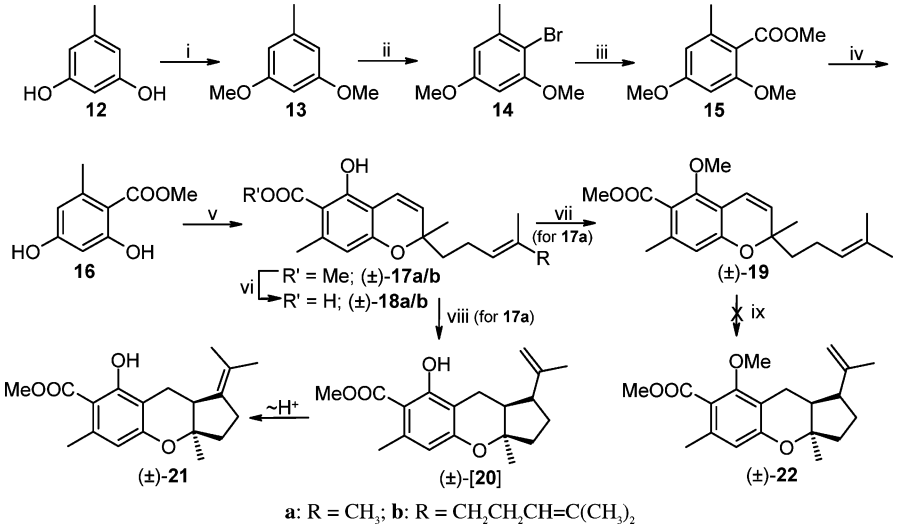
SCHEME 3. Synthesis of Cannabichromeorcinic Acid (18a), Daurichromenic Acid (18b), and Thermal Rearrangement to Benzopyran Derivative 21[a]



[a] Key: (i) acetone, K_2CO_3 (5.00 equiv), MeI (5.00 equiv), reflux, 6 h (~100%); (ii) CCl_4, NBS (1.00 equiv), reflux, 4 h (99%); (iii) (a) THF, −78 °C, *n*-BuLi (1.20 equiv), 1 h, (b) $ClCO_2Me$ (excess), −78 °C to rt (96%); (iv) DCM, 0 °C, $AlCl_3$ (6.00 equiv), rt, 12 h (98%); (v) MeOH, $Ca(OH)_2$ (2.00 equiv), citral/farnesal (5.00 equiv), rt, 72 h (**17a**: 72%, **17b**: 79%); (vi) MeOH/3 N KOH (3:1), rt, 72 h (**18a**: 82%, **18b**: 80%); (vii) acetone, K_2CO_3 (5.00 equiv), MeI (5.00 equiv), reflux, 6 h (98%); (viii) 175 °C, 6 h (98%); (ix) rt to 200 °C, 6 h (0%).

oxacyclobutaindan derivative (±)-**4a** with 82% yield via the benzopyran formation[14−16] **2a** followed by an in situ intramolecular [2 + 2] cycloaddition pathway tracing a highly diastereoselective route (Scheme 1). The structural assignment of **4a** was done on the basis of $^1H/^{13}C$ NMR and the X-ray crystallographic data.[17] The reaction of phthalide **1** with citral at 160−170 °C exclusively gave the oxabicyclononane (±)-**5** in 82% yield. The two vinylic protons in the ^1H NMR spectrum of **5** appeared at 3.80 and 4.47 ppm, and such an upfield shift could be due to the anisotropic effect of the lactone carbonyl group. The ^{13}C NMR and the corresponding DEPT spectra showed cleanly the presence of those two vinylic carbons, and finally, the structure of **5** was confirmed from the X-ray crystallographic data.[17] Both of the structural skeletons, oxacyclobutaindan and oxabicyclononane, exist in nature (Figures 1 and 2). To study the mechanism of formation of both **4a** and **5**, we synthesized the intermediate benzopyrans **2a**/**b**. The treatment of phthalide **1** with citral/farnesal in the presence of a catalytic amount of $Ca(OH)_2$ in methanol, respectively, gave the benzopyrans **2a**/**b** in 60/63% yields.[14,15] Herein, the observed regioselectivity could be a result of selective formation of the relatively more stable carbanion at the 3-position of phthalide **1** in comparison with the formation at 5-position. The benzopyran **2a** underwent a facile phenol-driven thermal dipolar [2 + 2] cycloaddition reaction at 120−130 °C to yield **4a** in 76% yield. Similarly, both the benzopyrans **2a**/**b** on treatment with aqueous 2 N sodium hydroxide solution at room temperature followed by acidification also exclusively gave the corresponding phenoxy anion driven dipolar [2 + 2] cycloaddition products **4a**/**b** in 80/78% yields via the corresponding intermediates **3a**/**b**. Both **2a** and **4a** on heating at 160−170 °C exclusively gave the rearranged product **5** in 80−82% yield. The formation of oxabicyclononane **5** from the benzopyran **2a** at elevated temperature could be a result of straight forward intramolecular cyclization to form **4a** at 120−130 °C followed by its thermal rearrangement at 160−170 °C. These observations revealed that in these reactions the oxacyclobutaindan **4a** is a kinetically controlled product and it undergoes a framework rearrangement at 160−170 °C to exclusively furnish the rearranged thermodynamically controlled product **5**.

We planned to verify the generality of the present phenol directed [2 + 2] cycloaddition reaction and designed the linear benzopyrans **7a**/**b** in 65/68% yields using the conditions[14] developed by us earlier for the regioselective coupling of α,β-unsaturated aldehydes at the 4-position of phthalide **6**[13] (Scheme 2). The benzopyran **7b** is structurally very similar to the naturally occurring potent anti-HIV agent daurichromenic acid A.[1,19] In our hands, the base-catalyzed intramolecular dipolar [2 + 2] cyclization of **7a** to the corresponding oxacyclobutaindan derivative met with failure and it could be a result of position of phenolic hydroxyl group which is intramolecularly hydrogen bonded with the adjacent carbonyl group and the higher stability of the corresponding phenoxy anion due to the conjugation with the carbonyl group. We heated neat the benzopyran **7a** up to 160 °C with a gradual increase in temperature, but did not observe any thermal reaction. The heating of the above reaction mixture at 165−175 °C directly furnished the isopropylidinecyclopentylbenzopyran (±)-**10**[20] in 90% yield and we were unable to arrest this reaction at the intermediate **9**. The structure of this rearranged product was assigned on the basis of $^1H/^{13}C$

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(17) For all of the details related to the X-ray crystallographic structures of compound **4a** and **5** and the corresponding data, see the Supporting Information.

(18) Addition of 5 equivalents of citral is essential, as the melting point of **4a** is 244−246 °C.

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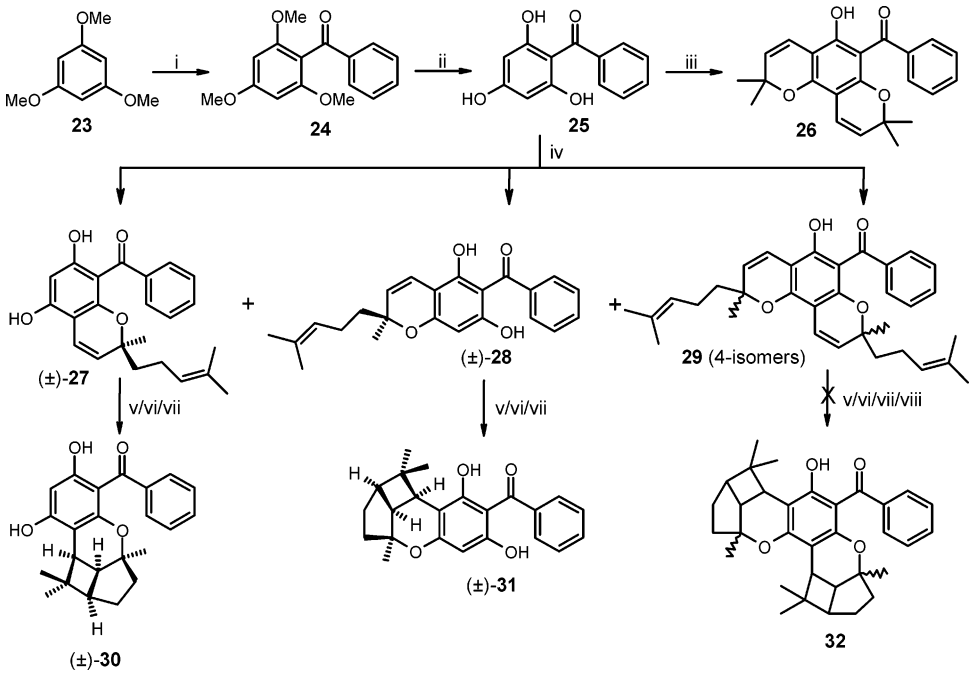
SCHEME 4. Synthesis of Naturally Occurring Clusiaphenone A (26), Clusiachromene C (27), Clusiacyclol A (30) and Clusiacyclol B (31)[a]



[a] Key: (i) $AlCl_3$ (1.50 equiv), DCM, 0 °C, benzoyl chloride (1.00 equiv), 0 °C to rt, 12 h (96%); (ii) DCM, BBr_3 (4.20 equiv), −78 °C to rt, 48 h (92%); (iii) MeOH, DBU (2.20 equiv), prenal (excess), rt, 36 h (94%); (iv) MeOH, DBU (0.80 equiv) 0 °C, citral (1.00 equiv), 6 h (**27**: 26%, **28**: 16%, **29**: 11%) or MeOH, $Ca(OH)_2$ (0.50 equiv), rt, citral (1.00 equiv), 96 h (**29**: 13%, **30**: 35%, **31**: 29%) or MeOH, DBU (2.20 equiv), rt, Citral (10.00 equiv), 36 h (**29**: 95%); (v) MeOH, $Ca(OH)_2$ (0.20 equiv), rt, 48 h (**30**: 79%, **31**: 76%); (vi) MeOH/0.1 N KOH (3:1), rt, 24 h (**30**: 75%, **31**: 70%); (vii) 100−110 °C, 6 h (**30**: 82%, **31**: 80%); (viii) 170−180 °C, 6 h (0%).

NMR data. The formation of **10** from **7a** at higher temperature could be a result of the possible intramolecular ene reaction[21] of **7a** to yield the intermediate **9**, followed by thermal isomerization to the more stable isopropylidinecyclopentylbenzopyran **10** with the tetrasubstituted carbon−carbon double bond. The methyl ether **8** failed to undergo any reaction[22] on heating up to 200 °C indicating that the presence of free phenolic hydroxyl group is essential to get the ene adduct. We surmise that the participation of phenolic hydroxyl group at elevated temperature can also lead to intramolecular dipolar [2 + 2] cycloaddition and hence the oxacyclobutaindan intermediate formation followed by rearrangement could be another possible pathway for the present reaction.

Similarly, we prepared a plan to synthesize the bioactive natural benzopyrans the cannabichromeorcinic acid (**18a**)[23] and daurichromenic acid (**18b**)[1,19] (*Rhododendron dauricum*) and to employ the present dipolar [2 + 2] annulation approach for the synthesis of rhododaurichromanic acid A[1a] (Scheme 3). Our synthesis of **18a**/**b** started with orcinol monohydrate (**12**) as a suitable starting material. The compound **12** on methylation followed by NBS-induced nuclear bromination exclusively furnished the expected bromo compound **14**[24] in ∼99% yield. The bromo compound **14** on lithiation followed by the treatment with methyl chloroformate gave the required ester **15**[25] in 96% yield, which on $AlCl_3$-induced demethylation provided the required phenolic ester **16** in 98% yield. The compound **16** is a natural product,[26] and therefore, our proposed route to **18a**/**b** appears to be biogenetic in nature. The treatment of the ester **16** with citral/farnesal in the presence of $Ca(OH)_2$ gave the desired benzopyrans **17a**/**b** in very good yields. The observed regioselectivity could be the result of a complexation of Ca^{2+} ion with both the phenolic groups, thus activating the 3-position of **16** for the condensation reaction.[14,15] Saponification of these esters **17a**/**b** provided the natural benzopyran carboxylic acids **18a**/**b** in 82 and 80% yields, respectively. The analytical and spectral data obtained for **18a**/**b** were in complete agreement with the reported data for the natural cannabichromeorcinic acid (**18a**) [22] and daurichromenic acid (**18b**).[1a] Next, we employed the phenol-driven dipolar approach on daurichromenic ester for further cyclization. As before, we heated the benzopyran ester **17a** to 160 °C and did not find any reaction, but the increase in temperature to 165−175 °C directly furnished the benzopyran (±)-**21** in 98% yield. Herein also, as indicated in Scheme 2, the reaction followed a similar course to yield the unisolable ene reaction intermediate **20** and its in situ isomerization furnished (±)-**21**. In our hands, an attempted base-induced [2 + 2] cyclization provided only the corresponding acid **18a** and not the desired cyclized product. Both **17b**/**18b** on heating at 175 °C provided only polymeric gummy materials. Herein

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also, a higher temperature was necessary to initiate the thermal reaction in **17a**, as the activating phenolic group is in conjugation and intramolecularly hydrogen bonded with the adjacent carbonyl moiety. As before, here also we noticed that the present reaction is possible only in the presence of free phenolic hydroxyl group of **17a**, as the methyl ether **19** failed to undergo any reaction[22] on heating up to 200 °C. Hence, the possibility of formation of the corresponding oxacyclobutaindan intermediate could be another possible pathway for the present reaction. Though we were unable to get the thermal [2 + 2] dipolar cycloaddition product from **17a**, a photochemical[1b,c] and cationic[11] conversion of **17b** to the rhododaurichromanic acid A and B is known.

Finally, we decided to synthesize the isomeric natural products clusiacyclol A and B (*Clusia multiflora*)[2] using the present phenol driven [2 + 2] dipolar cycloaddition strategy following the biogenetic type pathway (Scheme 4). We synthesized the required natural product[27] trihydroxybenzophenone **25** from the symmetrical trimethoxybenzene **23** via Friedel−Crafts benzoylation to obtain trimethoxybenzophenone **24**,[28] followed by its demethylation to obtain **25** in high yield. Initially, we planned for the synthesis of the relatively simple diprenylated natural product clusiaphenone A (**26**) (*Clusia sandiensis*).[29] The benzophenone derivative **25** in the presence of DBU underwent smooth condensation reactions with two molecules of the α,*β*-unsaturated aldehyde prenal to yield the natural product **26** in 94% yield. Later, we carried out systematic studies on condensation reaction of citral with **25**. The benzophenone **25** on reaction with citral in the presence of $Ca(OH)_2$/DBU furnished a mixture of three products (by TLC). The silica gel column chromatographic separation of the above mixture followed by examination of ^{1}H NMR spectra revealed that mixture of products **27** + **30** (inseparable), **28** + **31** (inseparable), and a diastereomeric mixture of **29** (inseparable) were formed. In both **27** and **30**, the methyl groups on the pyran ring were shielded due to the anisotropic effect of the adjacent phenyl group, which helped us to unambiguously discriminate them from the corresponding isomeric products **28** and **31**, respectively. Though both the positions in **25** are equivalent, one of the phenolic groups is involved in intramolecular hydrogen bonding and the other relatively free phenolic −OH group participates in the intramolecular cyclization to yield mixture of **27** + **30**, always as a major product. However it was not possible to achieve complete regioselectivity in the coupling of **25** with citral to exclusively obtain either **27** or **28**. However, it was possible to stop the reaction of **25** with citral to obtain the column separable mixture of **27** + **28** + **29** by using less equivalents of DBU or to obtain the column separable mixture of **29** + **30** + **31** by using an excess amount of $Ca(OH)_2$, in very good yields.

The naturally occurring pure (±)-clusiachromene C (**27**) (*Clusia multiflora*) on thermal/base-catalyzed [2 + 2] cycloaddition gave the desired natural product (±)-clusiacyclol B (**30**) in very good yield. We expect (±)-**28** also to be a natural product from the sources containing **31**. Similarly, **28** on thermal/base-catalyzed reaction furnished the natural product (±)-clusiacyclol A (**31**) in very good yield. Herein, we could stop the thermal reactions of **27** and **28** to obtain the kinetically controlled naturally occurring **30** and **31**, as the free non-hydrogen-bonded phenolic groups were available in both the compounds **27** and **28**, respectively. The analytical and spectral data obtained for these natural product **26**, **27**, **30** and **31** were in complete agreement with the reported data.[2,29] In the reaction of **25** with citral, we could force the reaction to exclusively obtain the double condensed product **29** in excellent yield by using excess amount (5 equiv) of citral, but as a diastereometic mixture in nearly 1:1 ratio. In our hands, the compound **29** showed great reluctance to form the further cycloaddition product **32** under both thermal and base-catalyzed conditions and only decomposed/polymeric materials were obtained.

Conclusions

In summary, we have demonstrated a simple and efficient phenol directed intramolecular diastereoselective dipolar thermal/base-catalyzed [2 + 2] cycloaddition approach to novel biologically important natural and unnatural benzopyran systems and the mechanistic aspects described in short are only the proposals. The present approach to these complex oxacyclobutaindans and the three different thermal framework rearrangements are noteworthy. These studies clearly reveal that in the present [2 + 2] cycloaddition approach, the presence of a free phenolic group is essential to design oxacyclobutaindans either thermally or by using base catalysis. If the free hydroxyl group is involved in intramolecular hydrogen bonding with an adjacent carbonyl group, a higher temperature is necessary and in such cases it was not possible to stop the reactions at the kinetically controlled products oxacyclobutaindans, instead the rearranged thermodynamically controlled benzopyran derivatives were obtained. The control experiments with *O*-methyl ethers of starting phenols also clearly revealed that though the role is not clear, the free phenolic groups are essential for these thermal reactions. Such types of oxabicyclononanes units are also present in natural products and oxacyclobutaindans can be the probable biogenetic intermediates. We feel that the present general approach to these important classes of compounds will be highly useful to design most of the natural products depicted in Figure 1 and several other natural products and natural product analogs/congeners for structure−activity relationship studies. Synthesis of chiral chromans[30] and application of the present strategy would provide an easy access to enantiomerically pure benzopyran systems.

Experimental Section

4-Hydroxy-7-methyl-7-(4-methylpent-3-enyl)-3*H*,7*H*-2,6-dioxacyclopenta[*a*]napthylen-1-one (2a). To a stirring mixture of **1** (2.00 g, 12.05 mmol) and $Ca(OH)_2$ (1.33 g, 18.07 mmol) in methanol (50 mL) at room temperature was added a solution of citral (10.42 mL, 60.24 mmol) in methanol (10 mL). After the reaction mixture was stirred for 6 days at 60 °C, methanol was removed in vacuo, and the reaction mixture was diluted with ethyl acetate (80 mL). The organic layer was washed with 2 N HCl, water, and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 15% ethyl acetate in petroleum ether gave **2a** (2.16 g, 60%) as a colorless thick oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.57 (s, 3H), 1.66 (s, 3H), 1.65−1.80 (m, 2H), 2.08 (t, J = 8 Hz, 2H), 5.09 (dt, J = 6, 2 Hz, 1H), 5.21 (s, 2H), 5.61 (d, J = 10 Hz, 1H), 6.54 (s, 1H), 7.26 (d, J =

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10 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.6, 22.6, 25.6, 26.4, 41.1, 68.3, 79.4, 109.2, 112.4, 117.2, 120.6, 123.7, 125.8, 129.3, 131.8, 151.1, 155.3, 172.9; IR ($CHCl_3$) 3238, 1713, 1622 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.02; H, 6.63.

7-(4,8-Dimethylnona-3,7-dienyl)-4-hydroxy-7-methyl-3*H*,7*H*-2,6-dioxacyclopenta[*a*]napthylen-1-one (2b). It was prepared similsrly using **1** (2.00 g, 12.05 mmol), $Ca(OH)_2$ (1.33 g, 18.07 mmol), and farnesal (13.27 g, 60.24 mmol). **2b** (2.79 g, 63%): colorless thick oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.57 (s, 3H), 1.59 (s, 3H), 1.65−1.80 (m, 2H), 1.67 (s, 3H), 1.85−2.20 (m, 6H), 5.10 (t, J = 6 Hz, 2H), 5.20 (s, 2H), 5.61 (dd, J = 10, 4 Hz, 1H), 6.51 (s, 1H), 7.27 (d, J = 10 Hz, 1H); IR ($CHCl_3$) 3383, 1751, 1734, 1626 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.02; H, 7.52.

10,10,6a-Trimethyl-4-hydroxy-6a,7,8,9,11,13-hexahydro-3*H*-2,6-dioxacyclobuta[*cd*]indano[*b,g*]benzofuran-1-one (4a). Method A. A stirring mixture of **1** (1.00 g, 6.02 mmol) and citral (5.21 mL, 30.12 mmol) was heated at 120−130 °C for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 15% ethyl acetate in petroleum ether furnished **4a** (1.48 g, 82%) as a colorless crystalline solid. **Method B.** Compound **2a** (500 mg, 1.66 mmol) was heated neat with stirring at 120−130 °C for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 15% ethyl acetate in petroleum ether furnished **4a** (380 mg, 76%) as a colorless crystalline solid. **Method C.** To a stirring solution of **2a** (500 mg, 1.66 mmol) in methanol (20 mL) at 0 °C was added 2 N KOH (4 mL) dropwise. The reaction mixture was allowed to attain room temperature, and after 8−10 h of stirring at room temperature, methanol was removed in vacuo and the reaction mixture was acidified slowly with 2 N HCl at 0 °C. The reaction mixture was extracted with ethyl acetate (30 mL × 2), and the combined organic layer was washed water and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 15% ethyl acetate in petroleum ether gave **4a** (400 mg, 80%) as a colorless crystalline solid: mp 256−258 °C (acetone); ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.55 (s, 3H), 1.30 (s, 3H), 1.42 (s, 3H), 1.50−1.65 (m, 3H), 1.78 (t, J = 10 Hz, 1H), 2.25−2.40 (m, 1H), 2.57 (t, J = 10 Hz, 1H), 3.45 (d, J = 8 Hz, 1H), 5.15 (s, 2H), 6.56 (s, 1H), 10.22 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 18.2, 25.2, 27.1, 33.4, 35.9, 37.8, 38.1, (one carbon signal below the DMSO-d_6 peaks), 46.5, 67.2, 83.9, 110.1, 113.9, 124.5, 127.8, 150.8, 154.8, 170.9; ^{1}H NMR (500 MHz, acetone-d_6) δ 0.63 (s, 3H), 1.35 (s, 3H), 1.49 (s, 3H), 1.55−1.75 (m, 3H), 1.85−2.00 (m, 1H), 2.42 (t, J = 5 Hz, 1H), 2.64 (t, J = 10 Hz, 1H), 3.56 (d, J = 10 Hz, 1H), 5.16 (s, 2H), 6.64 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 18.4, 25.9, 27.3, 33.8, 36.9, 39.0, 39.1, 40.9, 47.7, 67.5, 84.8, 110.8, 115.7, 125.9, 128.2, 151.3, 156.3, 171.4; IR (Nujol) 3236, 1717, 1622 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.85; H, 6.86.

10,6a-Dimethyl-10-(4-methylpent-3-enyl)-4-hydroxy-6a,7,8,9,-11,13-hexahydro-3*H*-2,6-dioxacyclobuta[*cd*]indano[*b,g*]benzofuran-1-one (4b). To a stirring solution of **2b** (500 mg, 1.35 mmol) in methanol (20 mL) at 0 °C was added 2 N KOH (4 mL) dropwise. The reaction mixture was allowed to attain room temperature, and after 10 h of stirring at room temperature, methanol was removed under vacuo and the reaction mixture was acidified slowly with 2 N HCl at 0 °C. The reaction mixture was extracted with ethyl acetate (30 mL × 2), and the organic layer was washed water and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether gave **4b** (390 mg, 78%) as a colorless thick oil: ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.55 (s, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 1.42 (s, 3H), 1.53−1.67 (m, 5H), 1.79 (t, J = 10 Hz, 1H), 1.90−2.15 (m, 2H), 2.25−2.40 (m, 1H), 2.60 (t, J = 10 Hz, 1H), 3.45 (d, J = 8 Hz, 1H), 5.07 (t, J = 6 Hz, 1H), 5.15 (s, 2H), 6.56 (s, 1H), 10.22 (s, 1H); IR (Nujol) 3215, 1697, 1616 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.11; H, 7.49.

9-Isopropenyl-6a-methyl-4-hydroxy-2,6-dioxabicyclo[3,3,1]-nonyl[*b,g*]-3*H*-benzofuran-1-one (5). Method A. A stirring mixture of **1** (500 mg, 3.01 mmol) and citral (2.60 mL, 15.06 mmol) was heated at 160−170 °C for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 15% ethyl acetate in petroleum ether furnished **5** (741 mg, 82%) as a colorless crystalline solid. **Method B.** A stirring mixture of **4a** (250 mg, 0.83 mmol) and citral (0.72 mL, 4.16 mmol) was heated at 160−170 °C for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 15% ethyl acetate in petroleum ether furnished **5** (205 mg, 82%) as a colorless crystalline solid. **Method C.** Compound **2a** (500 mg, 1.66 mmol) was heated neat with stirring at 160−170 °C for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 15% ethyl acetate in petroleum ether furnished **5** (410 mg, 82%) as a colorless crystalline solid: mp 244−246 °C (acetone); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.26 (dt, J = 12.5, 5 Hz, 2H), 1.30 (s, 3H), 1.57−1.66 (m, 1H), 1.75 (dt, J = 15, 5 Hz, 1H), 1.80 (s, 3H), 1.88 (dd, J = 12.5, 5 Hz, 1H), 1.99 (dd, J = 15, 5 Hz, 1H), 2.25 (dt, J = 7.5, 5 Hz, 1H), 3.80 (s, 1H, vinylic-H), 3.92 (s, 1H), 4.47 (s, 1H, vinylic-H), 5.04 (s, 2H), 6.47 (s, 1H), 10.13 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 23.2, 24.5, 28.6, 29.0, 36.1, 39.5, 48.3, 66.7, 75.0, 106.8, 109.1, 112.7, 124.3, 124.9, 147.8, 150.8, 158.0, 170.6; IR (Nujol) 3238, 1711, 1622 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.92; H, 6.79.

9-Hydroxy-6-methyl-6-(4-methylpent-3-enyl)-3*H*,6*H*-2,5-dioxacyclopenta[*b*]napthalen-1-one (7a). To a stirring solution of **6** (1.00 g, 6.02 mmol) and DBU (0.99 mL, 6.63 mmol) in acetonitrile (50 mL) at room temperature was added citral (5.21 mL, 30.12 mmol). After the mixture was stirred for 24 h at 50 °C, acetonitrile was removed in vacuo, and the reaction mixture was diluted with ethyl acetate (60 mL). The organic layer was washed with 2 N HCl, water, and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether gave **7a** (1.17 g, 65%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.56 (s, 3H), 1.60−1.85 (m, 2H), 1.65 (s, 3H), 2.08 (q, J = 9 Hz, 2H), 5.07 (t, J = 6 Hz, 1H), 5.19 (s, 2H), 5.58 (d, J = 12 Hz, 1H), 6.36 (s, 1H), 6.69 (d, J = 12 Hz, 1H), 7.77 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 22.6, 25.5, 26.8, 41.5, 70.4, 80.4, 102.0, 103.7, 108.6, 115.7, 123.7, 127.9, 131.9, 147.1, 152.1, 161.1, 172.5; IR ($CHCl_3$) 3440, 1729, 1639, 1460, 1216, 1153, 757 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.13; H, 6.99.

6-(4,8-Dimethylnona-3,7-dienyl)-9-hydroxy-6-methyl-3*H*,6*H*-2,5-dioxacyclopenta[*b*]napthalen-1-one (7b). Compound **7b** was prepared similarly using **6** (1.00 g, 6.02 mmol), DBU (0.99 mL, 6.63 mmol) in acetonitrile (50 mL), and farnesal (6.64 g, 30.12 mmol). **7b** (1.50 g, 68%): thick oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.57 (s, 3H), 1.59 (s, 3H), 1.65−1.85 (m, 2H), 1.67 (s, 3H), 1.90−2.20 (m, 6H), 5.08 (t, J = 6 Hz, 1H), 5.10 (t, J = 6 Hz, 1H), 5.21 (s, 2H), 5.60 (dd, J = 12, 6 Hz, 1H), 6.38 (s, 1H), 6.71 (d, J = 12 Hz, 1H), 7.76 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.8, 17.5, 22.4, 25.5, 26.4, 26.7, 39.5, 41.3, 70.2, 80.1, 101.8, 103.5, 108.4, 115.6, 123.3, 124.2, 127.7, 131.0, 135.4, 147.0, 151.9, 160.8, 172.3; IR (neat) 3420, 1734, 1640 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.09; H, 7.52.

9-Methoxy-6-methyl-6-(4-methylpent-3-enyl)-3*H*,6*H*-2,5-dioxacyclopenta[*b*]napthalen-1-one (8). To a stirring mixture of **7a** (500 mg, 1.66 mmol) and anhydrous K_2CO_3 (1.15 g, 8.33 mmol) in acetone (30 mL) was added methyl iodide (1.03 mL, 16.66 mmol), and the reaction mixture was refluxed for 6 h. After cooling, the reaction mixture was filtered through Celite. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether afforded **8** (518 mg, 99%) as a colorless oil: ^{1}H

NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.56 (s, 3H), 1.66 (s, 3H), 1.68−1.79 (m, 2H), 2.01−2.17 (m, 2H), 4.12 (s, 3H), 5.03−5.13 (m, 1H), 5.15 (s, 2H), 5.63 (d, J = 10 Hz, 1H), 6.53 (s, 1H), 6.75 (d, J = 10 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5, 22.6, 25.6, 26.9, 41.4, 62.8, 68.7, 80.1, 104.5, 108.8, 114.3, 116.6, 123.6, 129.1, 131.9, 149.6, 155.1, 160.2, 168.6; IR (neat) 1755, 1643, 1609 cm^{-1}; MS (*m/z*) 315, 232, 131, 103. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.41; H, 6.90.

10-Hydroxy-8-isopropyl-5a-methyl-5a,6,7,9-tetrahydro-3*H*-2,5-dioxadicyclopenta[*b,g*]napthalen-1-one (10). Compound **7a** (500 mg, 1.66 mmol) was heated neat with stirring at 165−170 °C for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 10% ethyl acetate in petroleum ether furnished **10** (450 mg, 90%) as a colorless waxy solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.50−1.59 (m, 1H), 1.67 (s, 3H), 1.73−1.83 (m, 2H), 1.87 (dd, J = 15, 5 Hz, 1H), 1.94 (d, J = 5 Hz, 3H), 1.99−2.05 (m, 1H), 2.47 (dd, J = 15, 5 Hz, 1H), 4.38 (s, 1H), 5.19 (s, 2H), 6.40 (s, 1H), 7.75 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.0, 20.5, 22.4, 28.3, 29.2, 36.2, 40.0, 70.1, 76.4, 101.1, 102.1, 112.9, 123.2, 130.0, 145.2, 153.9, 163.8, 172.7; IR (Nujol) 3516, 3445, 1742, 1641, 1607 cm^{-1}; MS (*m/z*) 301, 131, 103. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.10; H, 6.66.

1,3-Dimethoxy-5-methylbenzene (13). A stirring mixture of **12** (5.00 g, 35.17 mmol), anhydrous K_2CO_3 (24.30 g, 175.87 mmol), and methyl iodide (10.95 mL, 175.87 mmol) in acetone (100 mL) was refluxed for 6 h. After cooling, the reaction mixture was filtered through Celite. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 2% ethyl acetate in petroleum ether afforded **13** (5.35 g, ∼100%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.76 (s, 6H), 6.29 (d, J = 2 Hz, 1H), 6.34 (d, J = 2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6, 55.0, 97.4, 107.0, 140.0, 160.6; IR (neat) 2999, 2947, 2837, 1607, 1597 cm^{-1}. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.24; H, 7.88.

2-Bromo-1,5-dimethoxy-3-methylbenzene (14). To a solution of **13** (5.00 g, 32.85 mmol) in CCl_4 (60 mL) was added NBS (5.85 g, 32.85 mmol), and the reaction mixture was refluxed gently for 4 h. After cooling, the reaction mixture was filtered, and concentration of the filtrate in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 5% ethyl acetate in petroleum ether afforded **14** (7.51 g, 99%) as a low-melting solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 6.34 (d, J = 2 Hz, 1H), 6.42 (d, J = 4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.5, 55.4, 56.2, 97.2, 105.1, 107.2, 139.8, 156.6, 159.3; IR (neat) 2939, 2839, 1612, 1591, 1574 cm^{-1}; MS (*m/z*) 233, 231, 205, 203, 195, 181, 166, 122, 102. Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80; Br, 34.58. Found: C, 46.61; H, 4.92; Br, 34.69.

Methyl 2,4-Dimethoxy-6-methylbenzoate (15). To a stirring solution of **14** (7.00 g, 30.30 mmol) in THF (60 mL) at −78 °C was added *n*-BuLi (1.50 M, 24.24 mL, 36.36 mmol) dropwise. After the mixture was stirred at −78 °C for 1 h, freshly distilled methyl chloroformate (7.00 mL, 90.90 mmol) was added slowly. The reaction mixture was allowed to reach room temperature, and the reaction was quenched with a saturated solution of NH_4Cl. THF was removed in vacuo, ethyl acetate (150 mL) was added to the reaction mixture, and the separated organic layer was washed with water and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether afforded **15** (6.10 g, 96%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 6.31 (bs, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.4, 51.5, 54.8, 55.4, 95.7, 106.3, 116.0, 137.8, 157.9, 161.1, 168.3; IR (neat) 1728, 1607 cm^{-1}; MS (*m/z*) 211, 193, 179, 122, 102. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.93; H, 6.56.

Methyl 2,4-Dihydroxy-6-methylbenzoate (16). To a stirring mixture of $AlCl_3$ (20.95 g, 157.14 mmol) in DCM (100 mL) at 0 °C was added a solution of **15** (5.50 g, 26.19 mmol) in DCM (40 mL) dropwise. The reaction mixture was allowed to reach room temperature and stirred for a further 12 h. After removal of the DCM in vacuo, the residue was cooled to 0 °C, and water was added very slowly to decompose the formed complex. To this reaction mixture was added ethyl acetate (150 mL), and the separated organic layer was washed with water and brine and dried over Na_2SO_4. Removal of the solvent under vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 15% ethyl acetate in petroleum ether furnished **16** (4.67 g, 98%) as a colorless crystalline solid: mp 136−138 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.81 (s, 3H), 6.18 (bs, 2H), 10.01 (bs, 1H), 10.76 (bs, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 22.3, 51.9, 100.7, 107.5, 110.5, 141.1, 161.4, 161.5, 170.5; IR (Nujol) 3371, 3306, 1651, 1643 cm^{-1}. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.23; H, 5.47.

Methyl 2,7-Dimethyl-5-hydroxy-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran-6-carboxylate (17a). To a stirring mixture of **16** (1.00 g, 5.49 mmol) and $Ca(OH)_2$ (814 mg, 10.99 mmol) in methanol (25 mL) at room temperature was added citral (4.75 mL, 27.47 mmol). After the mixture was stirred for 72 h at room temperature, methanol was removed in vacuo, and the reaction mixture was diluted with ethyl acetate (60 mL). The separated organic layer was washed with 2 N HCl, water, and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 2% ethyl acetate in petroleum ether gave **17a** (1.25 g, 72%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.56 (s, 3H), 1.57−1.70 (m, 2H), 1.66 (s, 3H), 2.00−2.20 (m, 2H), 2.45 (s, 3H), 3.91 (s, 3H), 5.09 (t, J = 6 Hz, 1H), 5.47 (d, J = 10 Hz, 1H), 6.18 (s, 1H), 6.73 (d, J = 10 Hz, 1H), 11.99 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.6, 22.6, 24.4, 25.6, 27.0, 41.6, 51.7, 79.6, 104.9, 107.0, 111.6, 116.8, 123.9, 126.2, 131.7, 142.7, 157.8, 159.7, 172.4; IR (neat) 3017, 1726, 1659, 1651, 1645, 1620, 1614 cm^{-1}; MS (*m/z*) 317, 303, 301, 289, 285, 269, 233, 102. Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.02; H, 7.83.

Methyl 2,7-dimethyl-5-hydroxy-2-[(3*E*)-4,8-dimethyl-3,7-nonadienyl]-2*H*-1-benzopyran-6-carboxylate (17b). Compound **17b** was prepared similarly using **16** (1.00 g, 5.49 mmol), $Ca(OH)_2$ (814 mg, 10.99 mmol), and farnesal (6.05 g, 27.47 mmol). **17b** (1.66 g, 79%): colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.57 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.85−2.25 (m, 8H), 2.46 (s, 3H), 3.91 (s, 3H), 5.10 (t, J = 6 Hz, 2H), 5.48 (d, J = 10 Hz, 1H), 6.19 (s, 1H), 6.74 (d, J = 10 Hz, 1H), 11.99 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9, 17.6, 22.5, 24.3, 25.6, 26.6, 26.9, 39.6, 41.5, 51.6, 79.6, 104.8, 107.0, 111.6, 116.8, 123.7, 124.3, 126.1, 131.2, 135.3, 142.6, 157.8, 159.7, 172.3; IR (neat) 2968, 2926, 1653, 1618 cm^{-1}; MS (*m/z*) 385, 383, 369, 365, 353, 348, 317, 233, 209, 201, 125, 102. Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.11; H, 8.45.

2,7-Dimethyl-5-hydroxy-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran-6-carboxylic Acid (18a). To a stirring solution of **17a** (500 mg, 1.58 mmol) in methanol (15 mL) at 0 °C was added 3 N KOH (5 mL) slowly. The reaction mixture was allowed to attain room temperature, and after 72 h of stirring at room temperature, methanol was removed in vacuo. The reaction mixture was acidified with 2 N HCl at 0 °C and then extracted with ethyl acetate (50 mL × 2). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 15% ethyl acetate in petroleum ether gave **18a** (392 mg, 82%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.57 (s, 3H), 1.65−1.80 (m, 2H), 1.66 (s, 3H), 2.00−2.15 (m, 2H), 2.53 (s, 3H), 5.09 (t, J = 8 Hz, 1H), 5.48 (d, J = 8 Hz, 1H), 6.23 (s, 1H), 6.73 (d, J = 8 Hz, 1H), 11.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 22.7, 24.4, 25.6, 27.1, 41.7, 80.0, 103.6, 107.1, 112.1, 116.7, 123.9, 126.3, 131.9, 144.4, 158.9, 160.6, 176.0; IR (Nujol) 3061, 2700−2500, 1651, 1643, 1632, 1620, 1614

cm^{-1}; MS (*m/z*) 303, 301, 285, 279, 224, 219, 201, 199, 179, 157, 135, 102. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.39; H, 7.20.

2,7-Dimethyl-5-hydroxy-2-[(3*E*)-4,8-dimethyl-3,7-nonadienyl]-2*H*-1-benzopyran-6-carboxylic Acid (18b). Compound **18b** was prepared similarly using **17b** (500 mg, 1.30 mmol), methanol (15 mL), and 3 N KOH (5 mL). **18b** (385 mg, 80%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.57 (s, 3H), 1.59 (s, 3H), 1.60−1.71 (m, 1H), 1.67 (s, 3H), 1.72−1.82 (m, 1H), 1.92−1.98 (m, 2H), 1.99−2.14 (m, 4H), 2.53 (s, 3H), 5.00−5.15 (m, 2H), 5.48 (d, J = 8 Hz, 1H), 6.23 (s, 1H), 6.73 (d, J = 8 Hz, 1H), 11.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 17.7, 22.6, 24.4, 25.7, 26.7, 27.2, 39.7, 41.7, 80.1, 103.6, 107.1, 112.2, 116.7, 123.7, 124.3, 126.3, 131.3, 135.5, 144.4, 159.0, 160.6, 176.1; IR ($CHCl_3$) 3057, 2700−2500, 1643, 1618 cm^{-1}; MS (*m/z*) 369, 353, 301, 279, 247, 233, 225, 219, 211, 205, 181, 157, 148, 135, 102. Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.65; H, 8.04.

Methyl 2,7-Dimethyl-5-methoxy-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran-6-carboxylate (19). To a stirring mixture of **17a** (250 mg, 0.79 mmol) and anhydrous K_2CO_3 (550 mg, 3.95 mmol) in acetone (25 mL) was added methyl iodide (0.49 mL, 7.91 mmol), and the reaction mixture was refluxed for 6 h. After cooling, the reaction mixture was filtered through Celite. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 3% ethyl acetate in petroleum ether afforded **19** (255 mg, 98%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.57 (s, 3H), 1.66 (s, 3H), 1.89−2.20 (m, 4H), 2.25 (s, 3H), 3.79 (s, 3H), 3.90 (s, 3H), 5.08 (t, J = 8 Hz, 1H), 5.57 (d, J = 10 Hz, 1H), 6.43 (s, 1H), 6.57 (d, J = 10 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.6, 19.9, 22.6, 25.6, 26.4, 41.1, 51.9, 63.0, 78.7, 112.3, 113.8, 117.0, 120.0, 123.9, 128.8, 131.8, 137.7, 154.1, 155.2, 168.4; IR (neat) 1730, 1634, 1609 cm^{-1}; MS (*m/z*) 331, 313, 299, 130. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.59; H, 7.99.

Methyl 8-Hydroxy-3a,6-dimethyl-1-(propan-2-ylidene)-1,2,3,-3a,9,9a-hexahydrocyclopenta[*b*]chromene-7-carboxylate (21). Compound **17a** (250 mg, 0.79 mmol) was heated neat with stirring at 175 °C for a period of 6 h. After cooling, the obtained residue, on silica gel column chromatographic purification using a mixture of 2% ethyl acetate in petroleum ether, furnished **21** (245 mg, 98%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.48−1.56 (m, 1H), 1.65 (s, 3H), 1.74−1.79 (m, 1H), 1.82 (dd, J = 10, 5 Hz, 1H), 1.88−1.91 (m, 1H), 1.94 (d, J = 5 Hz, 3H), 1.96−2.20 (m, 1H), 2.43 (dd, J = 10, 5 Hz, 1H), 2.44 (s, 3H), 3.88 (s, 3H), 4.33 (s, 1H), 6.23 (s, 1H), 11.93 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1, 20.7, 22.7, 24.1, 28.5, 29.6, 37.0, 40.3, 51.5, 75.8, 103.7, 110.9, 111.0, 122.7, 130.8, 140.2, 160.7, 161.7, 172.6; IR ($CHCl_3$) 3381, 1651, 1620, 1576 cm^{-1}. Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.05; H, 7.78.

Phenyl (2,4,6-trimethoxyphenyl)methanone (24). To an ice-cooled stirring mixture of $AlCl_3$ (5.95 g, 44.59 mmol) in DCM (60 mL) was added benzoyl chloride (3.45 mL, 29.73 mmol) dropwise. After being stirred at 0 °C for 1 h, the reaction mixture was added slowly to a stirring solution of 1,3,5-trimethoxybenzene (5.00 g, 29.73 mmol) in DCM (50 mL) at 0 °C. The reaction mixture was allowed to attain room temperature, and after a further 12 h of stirring, the reaction mixture was poured slowly into ice-cooled 50% HCl (60 mL). The organic layer was diluted with DCM (50 mL), and the separated organic layer was washed with saturated $NaHCO_3$ solution, water, and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 20% ethyl acetate in petroleum ether gave **24** (7.76 g, 96%) as a white solid: mp 113−115 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.68 (s, 6H), 3.86 (s, 3H), 6.17 (s, 2H), 7.35−7.60 (m, 3H), 7.75−7.90 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.4, 55.7, 90.6, 110.8, 128.2, 129.3, 132.8, 138.1, 158.6, 162.3, 194.9; IR (Nujol) 1663, 1585 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.69; H, 5.84.

Phenyl (2,4,6-trihydroxyphenyl)methanone (25). To a stirring solution of **24** (7.00 g, 25.73 mmol) in DCM (100 mL) at −78 °C was added boron tribromide (10.21 mL, 108.09 mmol) quickly, and the reaction mixture was allowed to reach the room temperature slowly. After being stirred for 60 h at room temperature, the reaction mixture was cooled to 0 °C and very slowly quenched with water. DCM was removed in vacuo, and ethyl acetate (300 mL) was added to the reaction mixture. The separated organic layer was washed with water and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 45% ethyl acetate in petroleum ether gave **25** (5.45 g, 92%) as a faint yellow crystalline solid: mp 167−169 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.87 (s, 2H), 7.35−7.60 (m, 3H), 7.64 (d, J = 8 Hz, 2H), 9.86 (s, 1H), 10.11 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 94.7, 105.9, 128.2, 128.7, 132.0, 140.1, 159.7, 162.2, 196.8; IR (Nujol) 3192, 1626 cm^{-1}. Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.89; H, 4.44.

6-Benzoyl-5-hydroxy-2,2,8,8-tetramethyl-2*H*,8*H*-benzo(1,2-*b*:3′,4′-*b*′)dipyran (26). To a stirring solution of **25** (500 mg, 2.17 mmol) and DBU (0.71 mL, 4.78 mmol) in methanol (15 mL) at room temperature was added 3-methyl-2-butenal (prenal) (2.0 mL, 20.73 mmol). After the reaction mixture was stirred for 36 h at room temperature, methanol was removed in vacuo and the reaction mixture was diluted with ethyl acetate (50 mL). The separated organic layer was washed with 2 N HCl, water, and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 5% ethyl acetate in petroleum ether gave **26** (740 mg, 94%) as a faint yellow crystalline solid: mp 146−148 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 6H), 1.47 (s, 6H), 5.29 (d, J = 10 Hz, 1H), 5.50 (d, J = 10 Hz, 1H), 6.52 (d, J = 10 Hz, 1H), 6.71 (d, J = 10 Hz, 1H), 7.30−7.55 (m, 5H), 12.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 28.4, 77.8, 78.3, 102.0, 102.2, 105.0, 115.9, 116.1, 125.0, 125.4, 127.1, 127.5, 129.9, 142.8, 155.5, 156.0, 159.7, 200.3; IR (Nujol) 3175, 1649, 1643, 1599 cm^{-1}. Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.15; H, 6.33.

6-Benzoyl-5-hydroxy-2,8-dimethyl-2,8-bis(4-methylpent-3-enyl)-2*H*,8*H*-benzo(1,2-*b*:3′,4′-*b*′)dipyran (29). To a stirring solution of **25** (500 mg, 2.17 mmol) and DBU (0.71 mL, 4.78 mmol) in methanol (15 mL) at room temperature was added citral (3.76 mL, 21.73 mmol). After the mixture was stirred for 36 h at room temperature, methanol was removed in vacuo, and the reaction mixture was diluted with ethyl acetate (50 mL). The separated organic layer was washed with 2 N HCl, water, and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 2% ethyl acetate in petroleum ether gave **29** (1.03 g, 95%) as a faint yellow gum. **29** (diastereomeric mixture in nearly 1:1 ratio): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.00−1.35 (m, 4H), 1.44 (d, J = 2 Hz, 3H), 1.50 (s, 3H), 1.59 (s, 3H), 1.63 (s, 3H), 1.60−1.80 (m, 2H), 1.67 (s, 3H), 2.00−2.20 (m, 2H), 4.80−4.95 (m, 1H), 5.05−5.20 (m, 1H), 5.24 (d, J = 10 Hz, 1H), 5.44 (dd, J = 10, 2 Hz, 1H), 6.55 (d, J = 10 Hz, 1H), 6.74 (d, J = 10 Hz, 1H), 7.30−7.52 (m, 5H), 12.71 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5, 22.4, 22.6, 25.5/25.6, 25.9, 26.9, 27.0, 40.8, 41.5/41.6, 80.3, 80.5/80.6, 101.5/101.6, 101.8/101.9, 104.7/104.8, 116.3, 116.5, 123.9, 124.1/124.2, 127.0, 127.5, 128.2, 129.5, 129.9, 131.4, 131.6, 132.8, 142.8, 155.6, 156.1, 159.6, 200.0 (on expansion seven carbons showed diastereomeric splittings); IR ($CHCl_3$) 3410, 1640, 1590 cm^{-1}; MS (*m/z*) 499, 405, 389, 373, 357, 341, 325, 309, 301, 279, 275, 245, 231, 205. Anal. Calcd for $C_{33}H_{38}O_4$: C, 79.49; H, 7.68. Found: C, 79.58; H, 7.53.

[5,7-Dihydroxy-2-methyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran-8-yl]phenylmethanone (Clusiachromene C) (27) and [5,7-Dihydroxy-2-methyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran-6-yl]phenylmethanone (28). To a stirring solution of **25** (2.00

g, 8.69 mmol) and DBU (1.04 mL, 6.96 mmol) in methanol (50 mL) at 0 °C was added a solution of citral (1.50 mL, 8.69 mmol) in methanol (10 mL) dropwise. After the mixture was stirred for 6 h at 0 °C, methanol was removed in vacuo at 0 °C and the reaction mixture was diluted with ethyl acetate (75 mL). The separated organic layer was washed with 2 N HCl, water, and brine and dried over Na_2SO_4. Immediately after removal of the solvent in vacuo, the residue was purified by silica gel column chromatographic purification. Elution with a mixture of 2% ethyl acetate in petroleum ether afforded **29** (476 mg, 11%) as a faint yellow gum. Elution with a mixture of 5% ethyl acetate in petroleum ether afforded **28** (506 mg, 16%) as a faint yellow oil. Further elution with a mixture of 10% ethyl acetate in petroleum ether gave **27** (822 mg, 26%) as a faint yellow oil.

28: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20−1.45 (m, 2H), 1.42 (s, 3H), 1.55−1.80 (m, 2H), 1.67 (s, 3H), 1.74 (s, 3H), 5.08 (t, J = 6 Hz, 1H), 5.42 (d, J = 10 Hz, 1H), 5.89 (s, 1H), 6.65 (d, J = 10 Hz, 1H), 7.30−7.70 (m, 5H), 7.78 (s, 1H), 10.15 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.6, 22.6, 27.2, 27.5, 41.7, 80.5, 96.5, 102.4, 104.2, 116.3, 123.8, 124.6, 127.8, 128.8, 131.8, 131.9, 140.0, 158.1, 161.0, 161.4, 197.6; IR ($CHCl_3$) 3508, 3285, 1624, 1593 cm^{-1}; MS (*m/z*) 365, 327, 301, 210, 208, 192, 176, 103. Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.92; H, 6.65.

27: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.10−1.35 (m, 2H), 1.50 (s, 3H), 1.57−1.72 (m, 2H), 1.64 (s, 3H), 4.88 (t, J = 6 Hz, 1H), 5.26 (d, J = 10 Hz, 1H), 5.96 (s, 1H), 6.53 (d, J = 10 Hz, 1H), 7.30−7.70 (m, 5+1H), 12.38 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.6, 22.5, 25.6, 25.9, 40.8, 80.3, 95.8, 101.9, 105.4, 116.4, 123.8, 123.9, 127.1, 127.6, 130.1, 131.6, 142.6, 156.7, 158.9, 164.8, 200.3; IR ($CHCl_3$) 3522, 3504, 1632, 1620, 1594 cm^{-1}; MS (*m/z*) 365, 301, 279, 269, 253, 237, 231, 221, 207, 193, 191, 157, 135, 122, 102. Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.89; H, 6.81.

(1a,2,3,3a,8b,8c-Hexahydro-6,8-dihydroxy-1,1,3a-trimethyl-1*H*-4-oxanenzo [*f*]cyclobut[*cd*]inden-5-yl)phenylmethanone (Clusiacyclol B, 30). Method A. To a stirring solution of **27** (500 mg, 1.37 mmol) in methanol (20 mL) at room temperature was added $Ca(OH)_2$ (20 mg, 0.27 mmol). After the mixture was stirred for 48 h at room temperature, methanol was removed in vacuo, and the reaction mixture was diluted with ethyl acetate (50 mL). The organic layer was washed with 2 N HCl, water, and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether gave **30** (395 mg, 79%) as a white crystalline solid. **Method B.** To a stirring solution of **27** (500 mg, 1.37 mmol) in methanol (15 mL) at 0 °C was added 0.1 N KOH (5 mL) dropwise. The reaction mixture was allowed to attain room temperature, and after 24 h of stirring at room temperature, methanol was removed in vacuo and the reaction mixture was acidified slowly with 2 N HCl at 0 °C. The reaction mixture was diluted with ethyl acetate (60 mL), and the separated organic layer was washed with water and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether gave **30** (375 mg, 75%) as a white crystalline solid. **Method C.** Compound **27** (500 mg, 1.37 mmol) was heated neat at 100−110 °C for a period of 6 h with stirring. After cooling, the residue on silica gel column chromatographic purification using a mixture of 10% ethyl acetate in petroleum ether furnished **30** (410 mg, 82%) as a white crystalline solid: mp 179−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (s, 3H), 0.81 (s, 3H), 1.32 (s, 3H), 1.36−1.50 (m, 2H), 1.59−1.71 (m, 1H), 1.78−1.88 (m, 1H), 2.29 (t, J = 8 Hz, 1H), 2.39 (dd, J = 12, 8 Hz, 1H), 2.95 (d, J = 8 Hz, 1H), 5.96 (s, 1H), 6.02 (s, 1H), 7.30−7.50 (m, 5H), 12.43 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.7, 25.8, 26.4, 33.6, 35.7, 37.2, 37.8, 39.0, 45.9, 84.1, 95.8, 103.4, 106.3, 126.8, 127.5, 129.6, 143.2, 156.3, 162.4, 164.3, 200.6; IR ($CHCl_3$) 3327, 1624, 1603 cm^{-1}; MS (*m/z*) 365, 285, 102. Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.69; H, 6.52.

(1a,2,3,3a,8b,8c-Hexahydro-6,8-dihydroxy-1,1,3a-trimethyl-1*H*-4-oxanenzo [*f*]cyclobut[*cd*]inden-7-yl)phenylmethanone (Clusiacyclol A) (31). Method A. Compound **31** was prepared similarly using **28** (250 mg, 0.68 mmol), methanol (20 mL), and $Ca(OH)_2$ (10 mg, 0.14 mmol). **31:** white solid (190 mg, 76%). **Method B.** By using **28** (250 mg, 0.68 mmol), methanol (12 mL), and 0.1 N KOH (4 mL). **31** (175 mg, 70%): white solid. **Method C.** By heating **28** (250 mg, 0.68 mmol) neat. **31** (200 mg, 80%): white solid; mp 137−139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.55−1.65 (m, 1H), 1.65−1.75 (m, 2H), 1.92−2.00 (m, 1H), 2.41 (t, J = 10 Hz, 1H), 2.58 (dd, J = 10, 10 Hz, 1H), 3.06 (d, J = 10 Hz, 1H), 5.94 (s, 1H), 7.45 (s, 1H), 7.50 (t, J = 10 Hz, 2H), 7.57 (t, J = 10 Hz, 1H), 7.64 (d, J = 10 Hz, 2H), 10.20 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8, 25.6, 27.5, 33.6, 35.5, 37.3, 38.8, 39.0, 46.5, 84.8, 97.7, 104.3, 104.5, 127.9, 129.1, 132.1, 140.0, 158.8, 161.5, 161.6, 197.4; IR (Nujol) 3325, 1620, 1614, 1589 cm^{-1}; MS (*m/z*) 365, 301, 192, 131. Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.71; H, 6.75.

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Supporting Information Available: ^{1}H NMR spectra of **2a**,**b**, **4a**, **5**, **7a**,**b**, **8**, **10**, **16**, **17a**,**b**, **18a**,**b**, **19**, **21**, and **25**−**31**. ^{13}C NMR and DEPT spectra of **4a**, **5**, **7a**, **8**, **10**, **16**, **17a**,**b**, **18a**,**b**, **19**, **21**, and **25**−**31**. X-ray crystallographic data (CIF) and the ORTEP diagrams for compounds **4a** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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