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Graphical Abstract

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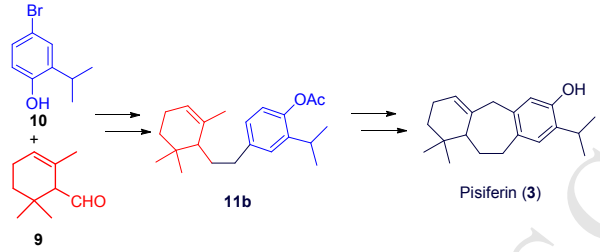

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ABSTRACT

A concise total synthesis of (±)-pisiferin has been accomplished from commercially available compounds α-cyclocitral (**9**) and 4-bromo-2-isopropylphenol (**10**) via Suzuki coupling and F-C alkylation as key reaction in five steps with an overall yield of 22%. The feature of this concise synthesis is a convergent strategy coupled by Suzuki reaction. This work not only provides a strategy to approach the total synthesis of pisiferin itself but also serves as an additional correlation origin to which many related icetaxane-type diterpenes can be referred.

1. Introduction

The icetaxane diterpenoid natural products exhibit an array of interesting biological activities, which coupled with their unique structural features. Thus they have generated significant interests from the isolation and synthetic community.[1] Recently more and more icetaxane and dimeric icetexane diterpenoids have been isolated from a variety of terrestrial plant sources.[2] Most of those compounds in this family exhibit significant cytotoxicities against human cancer lines, such as compounds **1** and **2**[2a], premnalatifolin A[2b] and przewalskone[2d] (Figure 1).

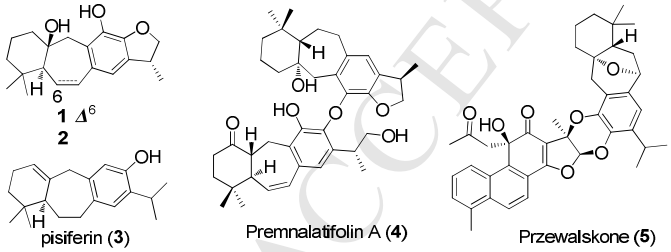
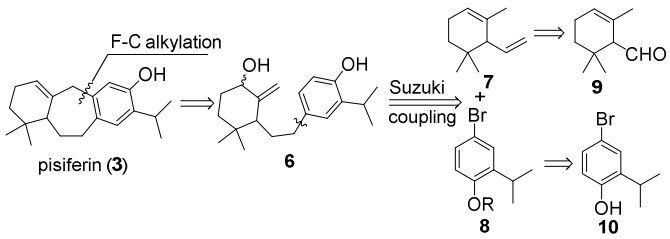


Figure 1. Selected member of icetaxane diterpenoid natural products

New, simple or enantioselective synthesis of the icetaxane products have also been reported.[3] Our target molecule pisiferin (**3**) is a subclass of the icetaxane family which has been isolated from the leaves and the seeds of *Chamaecyparis pisifera*.[4] The first total synthesis of (±)-pisiferin was reported by Matsumoto[5] and co-workers in 1986, which was also the first example for synthesis of an icetexane diterpenoid. The second total synthesis of (±)-pisiferin and the first total synthesis of (±)-isopisiferin was reported by Honda and co-workers.[6] The third total synthesis of (±)-pisiferin was reported by Majetich and co-workers by using cyclialkylation reaction as key reaction.[7] The total synthesis of (±)-isopisiferin was also reported by Liu and Shia[3a] and Ghatak[8]. Previous efforts directed toward the synthesis of pisiferin and other congeners fall into more steps, more complicated methods and produced isomers.[5-7] It was notable, most of isomers were inseparable, for example pisiferin and isopisiferin.[6,7] The particular interests on the biogenetic synthesis relationship of ictexane diterpene and other diterpene led us to choose Pisiferin as our synthetic target molecule. Herein we describe the realization of this goal.



Scheme 1. Retrosynthetic Analysis of pisiferin

Our retrosynthetic analysis of pisiferin is shown in scheme 1. Of the many possible disconnection of the 6, 7, 6-tricyclic backbone, we chose a two-step procedure. We envisioned that pisiferin could be synthesized from compound **6** via a Lewis-acid catalyzed F-C alkylation. In previous paper, isomer of pisiferin (isopisiferin) was produced in cleavage of the methyl ether or under strong acidic conditions. Thus the F-C alkylation condition should be controlled in order to exclusively obtain the target molecular. The compound **6** would be derived from **7** and **8** by

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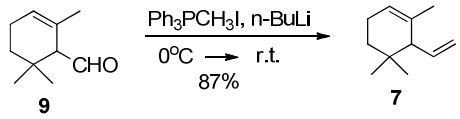
using a Suzuki-coupling, and then an allylic oxidation. Further retrosynthetic disconnection of compounds **7** and **8** were envisioned to follow a Wittig reaction to prepare the diene **7** from racemic α-cyclocitral (**9**) and to prepare the bromide derivative **8** from **10**. This retrosynthesis of the target molecule was concise and novel compared to the reported works by other chemists.[5-7]

2. Results and Discussion

In the forward direction, compounds **9** and **10** are commercial available. The diene **7** was prepared via Wittig reaction from racemic aldehyde **9** in 87% yield.[9] (Shown in Scheme 2)

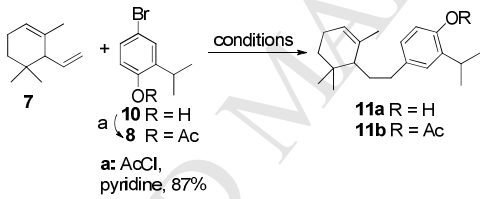


Scheme 2. Synthesis of compound **7**.

With compound **7** in hand, we want to try the Suzuki coupling with phenol **10** without protecting the phenol group, concerned on the green chemistry principle. However the Suzuki coupling of **10** and the borohydride diene **7** did not work as expected under the typical Suzuki coupling condition.[10] (Table 1, entry 1) A screen of the bases and solvents for Suzuki coupling were taken into consideration to accomplish the coupling procedure (Table 1, entry 2 ~4). The complex products were obtained in these conditions, which strongly suggested that the hydroxyl group of the phenol would complicate the coupling reaction. Thus, it needs a protecting group before the coupling procedure.

With these realizations in mind, two tenets were confirmed that (i) the protect group must tolerate the ambient which the Suzuki reaction needs and (ii) the condition of deprotection should be non-acid and easily to deprotect the hydroxyl group. Therefore, the acetyl group was then taken into consideration and chosen as the protecting group. Therefore, the compound **8** was prepared in by acetylating of **10** with AcCl and pyridine (Table 1).[11] Under the condition[12] stated as Table 1 entry 5, we firstly got the desired coupling product in 19% yield. In order to improve the yield of this reaction, different Pd-catalyst, base and solvents were screen. When $Pd(PPh_3)_4$ was subjected to the reaction instead of $Pd(OAc)_2$ and SPhos, the desired product cannot be obtained no matter using DMF and THF as solvents or THF and H_2O (Table 1 entry 6, 7). Changing the base as CsF, the desired coupling product was obtained in 17% yield (Table 1 entry 8). When we changed the solvent to THF, the reaction resulted in 7% of **11a** and 58% of **11b** (entry 9). This could be rationlized by the better solubility of the base CsF in THF. By utilization a considerable weak base, CsF, the acetyl group was envisioned to be maintained during Suzuki coupling reaction. However, changing the base as KF, the desired product was not obtained (Table 1 entry 10).

Table 1. Conditions of the Suzuki coupling [a]



Entry	Aryl halides	*catalysts*	*base*	*solvents*	*Yields* [b]
1	**10**	$Pd(PPh_3)_4$	3N NaOH (5.0 equiv)	THF	Complex product
2	**10**	$Pd(PPh_3)_4$	$K_3PO_4 \cdot 3H_2O$ (3.0 equiv)	THF : H_2O = 40 : 3	Complex product
3	**10**	$Pd(PPh_3)_4$	$K_3PO_4 \cdot 3H_2O$ (3.0 equiv)	THF : H_2O = 5 : 1	Complex product
4 [c]	**10**	$Pd(OAc)_2$	K_3PO_4 (3.0 equiv)	DMF : THF = 1 : 1	Complex product
5 [c]	**8**	$Pd(OAc)_2$	K_3PO_4 (3.0 equiv)	DMF : THF = 1 : 1	19 %
6	**8**	$Pd(PPh_3)_4$	K_3PO_4 (3.0 equiv)	DMF : THF = 1 : 1	Undesired product
7	**8**	$Pd(PPh_3)_4$	K_3PO_4 (3.0 equiv)	THF : H_2O = 5 : 1	Undesired product
8	**8**	$Pd(PPh_3)_4$	CsF (3.0 equiv)	DMF : THF = 1 : 1	17 %
9	**8**	$Pd(PPh_3)_4$	CsF (3.0 equiv)	THF	**11a** 7%; **11b** 58 %
10	**8**	$Pd(PPh_3)_4$	KF (3.0 equiv)	THF	Undesired product

[a] All reactions were carried out under the following conditions, unless otherwise noted: alkenylboranes were generate in situ from the diene **7** (2.0 mmol, 1.5 equiv) heated with 9-BBN. And 1.0 equiv of aryl halides, catalysts (0.1 equiv) refluxed for 3 h under Ar atmosphere.

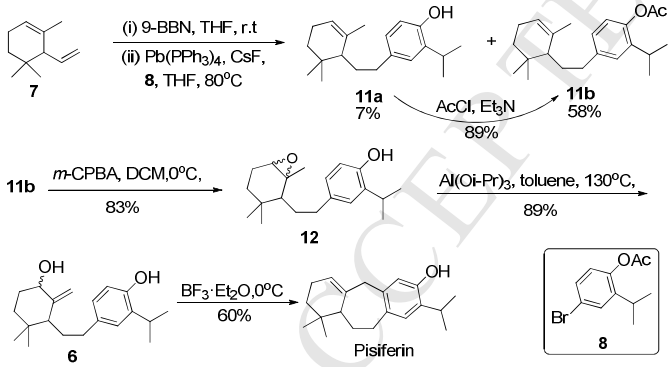
[b] Isolated yield.

[c] Add the ligand 0.2 equiv of SPhos.

With this optimized condition in hand, the Suzuki coupling was utilized to generate **11b.** This convergent synthesis of **11b** was operated in one-pot procedure. Diene **7** was mixed with 9-BBN stirred over night at r.t. then stirred for another 6h at 70 °C. This hydroboration product was used without any purification to accomplish the Suzuki coupling.[13] Then the coupled compound **11b** and the deprotection compound **11a** was achieved. (Shown in Scheme. 3) As expected, most of the acetyl group remained. Moreover, the compound **11a** was transformed to **11b** in 89% yield by use of AcCl and Et_3N.

When we finally got this coupling compound **11a**, we were able to move on and approach to the target molecule. As it was shown in the retrosynthesis the compound **11a** was needed to be transformed to **6** for F-C alkylation to construct the 6, 7, 6-fused tricycles. At this time the construction of compound **6** was the key. In order to accomplish this transformation, an allylic

oxidation of **11a** was first conducted with SeO_2.[14] However, only few desired product was obtained in company with other isomers in this case. As a result we chose a two-step procedure to finish this transformation. The compound **11a** was first treated with *m*-CPBA to generate the corresponding epoxide product **12** (diastereoisomer mixture) in 83%, which following rearrangement of the formed epoxide yielded diol **6** in 89% with addition of Al(Oi-Pr)$_3$ at 130 ^oC.[15] (Shown in Scheme 3) And with this two-step procedure we accomplished the transformation as expected. As the temperature of the rearrangement step was a little severe, another condition of open epoxide rearrangement was utilized. We tried to use iodine to accomplish this transformation.[16] However the result was disappointing. So we did not change the condition. In these steps the new chiral centers were generated. But all these generated chirality would dismiss in the final step. So the diastereoisomer mixture **12** and **6** were not separated. The diol **6** was pursued a F-C alkylation under Lewis-acid catalyzed condition[10] to construct the 7-member ring. When using $BF_3 \cdot Et_2O$ as Lewis-acid catalyst, the target molecule, pisiferin (along its 10% isomer) was obtained in 60%. (Shown in Scheme 3) The reaction time need be controlled, when the reaction mixture was turned to a pale-purple, then the reaction was quenched with saturated $NaHCO_3$ (aq), extracted with ethyl acetate. In order to reduce the ratio of the isomer or obtain the target exclusively, with the $BF_3 \cdot Et_2O$ as the Lewis acid the reaction was conducted under the low temperature such as -78 ^oC, -48 ^oC, - 10 ^oC, all these efforts resulted in no reaction. The weaker Lewis acid such as $FeCl_3$ was also tried, but the cyclization did not occur either. When we chose the other transition metal Lewis acid such as Sc(OTf)$_3$, the result was the same as the $BF_3 \cdot Et_2O$ condition. As result, pisiferin (along with the isomer 10% detected) was achieved in 22% yield with only 5 steps from the commercially available **10**. It was disappointed that the control of the reaction time did not result in giving the pisiferin exclusively. The isomer of the pisiferin was still existed in the product mixture according to the NMR result. This fact strongly suggested that the Lewis acid promoted F-C alkylation would cause the isomerization of the pisiferin.



Scheme 3. Synthesis of pisiferin

3. Summary

Even though this strategy did not give the pisiferin without its isomers as expected, the strategy we designed to approach the backbone of pisiferin is concise. And this elegant strategy can be referred as an additional correlation origin to which many related icetaxane-type diterpenes. Our work also can give some light on the construction of the 6-7-6 backbone of the icetaxane-type diterpenes. Further studies on synthesis of icetaxane-type diterpenes by new strategy of construction the 7-member ring are ongoing in our group.

4. Experimental section

4.1. General

All moisture-sensitive reactions were performed under an atmosphere of Ar. Glassware was flame dried prior to use. THF was dried by distillation over Na/K. CH_2Cl_2 was dried by distillation over CaH_2. Unless otherwise stated, solvents and reagents were used as received. Column chromatography was generally performed on silica gel (200-300 mesh) and TLC inspections were on silica gel GF_{254} plates. ^1H NMR spectra were recorded at 400 MHz spectrometers. Chemical shifts (δ) are reported in ppm downfield from $Si(CH_3)_4$ with the partially-deuterated solvent as the internal standard ($CDCl_3$ δ 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, b = broad, q = quartet, m = multiplet). ^{13}C NMR spectra were recorded at 100 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$ δ 77.0). IR spectra were recorded on a Nicolet 670 FTIR spectrophotometer and reported in wave numbers (cm-1). HRMS data were determined on a Bruker Daltonics APEXII 47e FT-ICR spectrometer.

4.2. Experimental procedures and data of synthetic intermediates

4.2.1. *1,5,5-trimethyl-6-vinylcyclohex-1-ene (***7**)

To a 50 ml round bottom flask equipped with a stir bar was added $CH_3P(Ph_3)I$ (4.85 g, 12 mmol, 1.2 equiv). Then 20 ml THF was added under Ar atmosphere. This solution was cooled to 0^oC, upon which *n*-BuLi (2.5 M in THF; 4.4 ml, 11 mmol, 1.1 equiv) was added dropwise via syringe, resulted a yellow mixture and a solution of aldehyde **9** (1.35 g, 8.9 mmol, 1.0 equiv) in THF (12 ml) was added successfully. The result mixture was warmed to room temperature and stirred for 2 h. Then the reaction was quenched with saturated NH_4Cl (aq). The resulting mixture was extracted with petroleum ether (bp. 30-60 ^oC). The organic layer was washed with water followed by brine, and dried over Na_2SO_4. The extraction was filtered and concentrated in vacuo. The resulted residue was purified by column chromatography (petroleum ether bp.30-60 ^oC), provided diene **7** (1.17 g, 87%) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 – 5.49 (m, 1H), 5.40 (s, 1H), 5.09 – 4.98 (m, 2H), 4.98 – 4.93 (m, 1H), 2.10 (d, *J* = 9.4 Hz, 1H), 2.00 (m, 2H), 1.59 (d, *J* = 1.7 Hz, 3H), 1.49 – 1.35 (m, 1H), 1.17 (d, *J* = 13.2 Hz, 1H), 0.89 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.13, 134.69, 121.71, 121.68, 116.56, 78.12, 77.80, 77.48, 56.58, 32.48, 32.41, 28.19, 27.75, 23.87, 23.55. IR(film): 3389, 2925, 1720, 1656, 1458, 1374, 1253, 1122, 917, 502 cm^{-1}.

4.2.3. *4-bromo-2-isopropylphenyl acetate (**8**)*[11]

To a 25 ml round bottom flask equipped with a stir bar were added 4-bromo-2-isopropylphenol **10** (913.7 mg, 4.248 mmol, 1 equiv) and DCM (10 ml). This solution was stirred at room temperature, then pyridine (0.68 ml, 8.496 mmol, 2.0 equiv) was added dropwise via syringe. After addition of the pyridine, acetyl chloride (0.57 ml, 8.071 mmol, 1.9 equiv) was added dropwise via syringe, resulted in a pale yellow mixture. After stirring for 3 h, the reaction was quenched with saturated NH_4Cl (aq). The resulting mixture was extracted with ethyl acetate. The organic layer was washed with water followed by brine, and dried over Na_2SO_4. It was filtered and concentrated in vacuo. The residue was purified by column chromatography (8:1 petroleum ether/ethyl acetate), provided 4-bromo-2-isopropylphenyl acetate (**8**) (951.8 mg, 87%) as a pale yellow liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.2 Hz, 1H), 7.31 (dd, *J* = 8.5, 2.3 Hz, 1H),

6.88 (d, *J* = 8.5 Hz, 1H), 2.98 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.32 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.45, 147.20, 142.63, 130.08, 129.78, 124.21, 119.66, 77.48, 77.16, 76.84, 27.70, 22.90, 21.02. IR(film): 2967, 1765, 1688, 1369, 1207, 1177, 1095, 758 cm^{-1}.

4.2.4. *2-isopropyl-4-(2-(2,6,6-trimethylcyclohex-2-en-1-yl)ethyl) phenol (**11a**) and 2-isopropyl-4-(2-(2,6,6-trimethylcyclohex-2-en-1-yl)ethyl)phenyl acetate (**11b**)*

To a 10 ml round bottom flask equipped with a stir bar was added diene **7** (295 mg, 1.967 mmol, 1.5 equiv) and 9-BBN (0.5 M in THF; 5.25 ml, 2.62 mmol, 2.0 equiv) under Ar atmosphere. The resulted reaction mixture was stirred at room temperature overnight, then heated to 70 ^{o}C for another 6 h. To another 25 ml two neck round bottom flask equipped with a stir bar was added CsF (611.8 mg, 4.03 mmol, 3.1 equiv) which was flame dried, and $Pd(PPh_3)_4$ (150.9 mg, 0.1306 mmol, 0.1 equiv) under Ar atmosphere. Then a solution of phenyl acetate **8** (335.6 mg, 1.31 mmol, 1.0 equiv) in 4 ml THF was added to this flask, followed by addition of the 9-BBN and diene **7** reaction mixture which was already prepared. The resulted mixture was heated to 80 ^{o}C, refluxed for 3 h and 30 min. The reaction mixture was then quenched with saturated NH_4Cl (aq), extracted with ethyl acetate. The organic layer was washed with water followed by brine, and dried over Na_2SO_4. The extraction was filtered and concentrated *in vacuo*, resulted a brownish black liquid. The residue was purified by column chromatography (30:1 petroleum ether/ethyl acetate), provided phenyl acetate **11b** (246 mg, 58%) and phenol **11a** (31.2 mg, 7%).

11a : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 4.75 (s, 1H), 3.27 – 3.05 (m, 1H), 2.46 – 2.33 (m, 1H), 1.88 (s, 1H), 1.64 – 1.48 (m, 4H), 1.24 (d, *J* = 6.9 Hz, 6H).

11b : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.31 (s, 1H), 2.99 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.63 (t, *J* = 8.4 Hz, 2H), 2.28 (s, 3H), 1.97 (s, 2H), 1.72 (dd, *J* = 13.5, 7.9 Hz, 1H), 1.53 – 1.41 (m, 2H), 1.20 (d, *J* = 6.9 Hz, 6H), 0.97 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.66, 145.96, 140.99, 139.60, 136.34, 126.41, 126.40, 121.90, 120.17, 77.32, 77.00, 76.68, 48.90, 36.21, 33.12, 32.53, 31.56, 27.47, 27.43, 27.41, 23.39, 22.99, 22.90, 20.82; IR(film): 3400, 2962, 2926, 2855, 1767, 1737, 1603, 1451, 1413, 1261, 1097, 1023, 797, 700 cm^{-1}; HRMS (ESIMS) calculated for $C_{22}H_{32}O_2$ [M + Na]+ 351.2300, found 351.2295.

4.2.5. *2-isopropyl-4-(2-(1,3,3-trimethyl-7-oxabicyclo[4.1.0] heptan-2-yl)ethyl)phenyl acetate (**12**)*

To a 50 ml round bottom flask equipped with a stir bar was added the phenyl acetate **9** (246.0 mg, 0.7489 mmol, 1 equiv) and 10 ml DCM. The solution was cooled to 0 ^{o}C, upon which *m*-CPBA (197.9 mg, 1.147 mmol, 1.5 equiv) was added. The resulted mixture was stirred for 2h and 10 min at 0 ^{o}C. Then the reaction was quenched with saturated $NaHCO_3$ (aq), extracted by DCM. The organic layer was washed with water followed by brine, and dried over Na_2SO_4. Then the resulted extraction was filtered, concentrated in vacuo. The residue was purified by column chromatography (8:1 petroleum ether/ethyl acetate), provided epoxide (204.1 mg, 83%) as pale yellow liquid. And the ^{1}H NMR analysis suggested that the epoxide **12** was a racemic mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 1.5 Hz, 1H), 7.07 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 3.10 – 2.94 (m, 2H), 2.94 – 2.83 (m, 1H), 2.70 – 2.50 (m, 1H), 2.32 (s, 3H), 2.05 – 1.90 (m, 1H), 1.90 – 1.75 (m, 1H), 1.67 (ddd, *J* = 12.9, 10.6, 5.8 Hz, 2H), 1.57 (d, *J* = 2.3 Hz, 1H), 1.45 (dd, *J* = 8.8, 5.2 Hz, 1H), 1.35 (d, *J* = 10.8 Hz, 3H), 1.32 – 1.13 (m, 7H), 0.90 (s, 3H), 0.81 (d, *J* = 12.9 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.83, 146.02, 141.14, 139.67, 126.68, 126.57, 121.94, 77.32, 77.00, 76.68, 60.15, 59.55, 47.03, 35.50, 31.50, 29.71, 27.81, 27.51, 27.35, 26.92, 26.89, 22.99, 22.96, 22.12, 20.95; IR(film): 3449, 3023, 2978, 2934, 2368, 1736, 1374, 1246, 1098, 1047, 758, 668 cm^{-1}; HRMS (ESIMS) calculated for $C_{22}H_{32}O_3$ [M + Na]$^{+}$ 367.2249, found 367.2244.

4.2.6. *4-(2-(5-hydroxy-2,2-dimethyl-6-methylenecyclohexyl)ethyl) -2-isopropylphenol (**6**)*

To a 25 ml two neck round bottom flask equipped a stir bar was added $Al(O\text{-}iPr)_3$ (353.0 mg, 1.728 mmol, 3.0 equiv). And a solution of the corresponding epoxide **12** (198.4 mg, 0.5759 mmol, 1.0 equiv) in 10 ml toluene was added to this flak via syringe under Ar atmosphere. The resulted mixture was heated to 130 ^{o}C and refluxed for 3h. The reaction was then quenched with saturated NH_4Cl, extracted with ethyl acetate. The organic layer was washed with water followed by brine, and dried over Na_2SO_4. The extraction was filtered and concentrated in vacuo. The residue was purified by column chromatography (8:1 then 4:1 petroleum ether/ethyl acetate), provided diol **6** (154.9 mg, 89%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.88 (d, *J* = 6.3 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.42 – 5.04 (m, 2H), 4.84 (d, *J* = 28.0 Hz, 1H), 4.26 (s, 1H), 4.00 (d, *J* = 9.7 Hz, 1H), 3.59 (q, *J* = 10.6 Hz, 1H), 3.23 (dt, *J* = 12.7, 6.3 Hz, 1H), 2.74 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.67 – 2.48 (m, 1H), 2.36 (dt, *J* = 13.6, 8.3 Hz, 1H), 2.14 – 2.01 (m, 1H), 2.01 – 1.87 (m, 1H), 1.80 (dd, *J* = 14.1, 7.8 Hz, 2H), 1.71 (d, *J* = 6.3 Hz, 1H), 1.65 – 1.52 (m, 1H), 1.52 – 1.34 (m, 3H), 1.27 (d, *J* = 6.8 Hz, 7H), 1.12 (s, 1H), 1.04 (s, 1H), 0.95 (s, 2H), 0.89 (d, *J* = 9.6 Hz, 1H), 0.72 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.83, 146.02, 141.14, 139.67, 126.68, 126.57, 121.94, 77.32, 77.00, 76.68, 60.15, 59.55, 47.03, 35.50, 31.50, 29.71, 27.81, 27.51, 27.35, 26.92, 26.89, 22.99, 22.96, 22.12, 20.95; IR(film): 3365, 2960, 2868, 1505, 1461, 1431, 1258, 1216, 1170, 1081, 1036, 1022, 901, 756, 668 cm^{-1}; HRMS (ESIMS) calculated for $C_{20}H_{30}O_2$ [M + Na]$^{+}$ 325.2143, found 325.2584.

4.2.7. *Pisiferin (**3**)*

To a 25 ml round bottom flask equipped with a stir bar was added a solution of diol **6** (35.1 mg, 0.1160 mmol, 1.0 equiv) in 6 ml DCE under Ar. The solution was cooled to 0 ^{o}C, upon which BF_3•Et_2O (49.4 mg, 0.3481 mmol, 3.0 equiv) was added via microsyringe under Ar atmosphere. The resulted mixture was stirred for 3h 20min at 0 ^{o}C, resulted a pale-purple like mixture. Then the reaction was quenched with saturated $NaHCO_3$ (aq), extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The resulted extraction was filtered and concentrated in vacuo. The residue was purified by column chromatography (20:1 then 16:1 petroleum ether/ethyl acetate), provided pisiferin (19.7 mg, 60%) as a colorless liquid. The resulted pisiferin contained a inseparable isomer with 10:1 (pisiferin/isopisiferin). The NMR spectrum was complicated by the existing isomer of the pisiferin. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.54 (s, 1H), 5.43 (s, 1H), 4.50 (s, 1H), 3.26 (s, 2H), 3.14 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.80 (dd, *J* = 13.0, 4.5 Hz, 2H), 2.15 – 1.95 (m, 2H), 1.90 (d, *J* = 17.9 Hz, 1H), 1.79 (d, *J* = 11.7 Hz, 1H), 1.24 (t, *J* = 6.9 Hz, 10H), 0.91 (d, *J* = 11.5 Hz, 7H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.80, 139.84, 138.42, 133.70, 131.06, 127.02, 121.23, 114.99, 77.21, 77.00, 76.79, 51.76, 44.70, 42.31, 37.27, 35.90, 35.72, 34.48, 32.12, 31.93, 31.25, 31.10, 30.92, 30.52, 30.46, 29.70, 27.81, 27.73, 27.14, 26.74, 25.90, 24.19, 23.20, 22.88, 22.69, 22.52, 21.98, 21.81, 20.11, 17.67, 14.11; HRMS (ESIMS) calculated for $C_{20}H_{30}O_2$ [M + H]$^{+}$ 285.2140, found 285.2213.

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at

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