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Synthesis of 4-*epi*-Parviflorons A, C and E: Structure-Activity Relationship Study of Antiproliferative Abietane Derivatives

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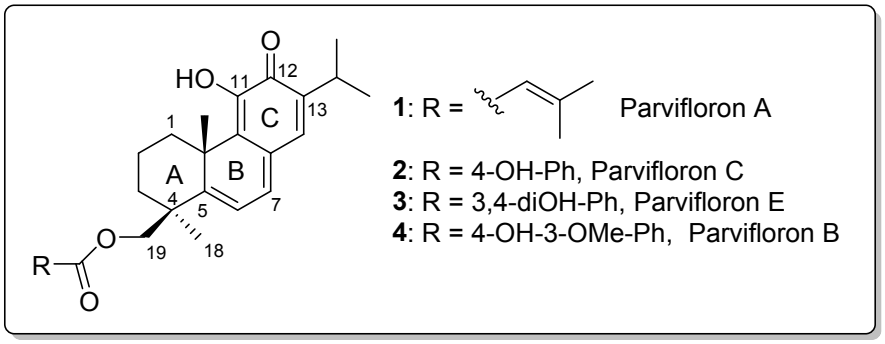
ABSTRACT

The first syntheses of 4-*epi*-parviflorons A, C, and E (4-*epi*-**1**–**3**) were achieved in 12–13 steps from commercially available (−)-abietic acid (**5**). All synthesized compounds, including intermediates and derivatives, were evaluated for antiproliferative activity against five human tumor cell lines. A structure-activity relationship study revealed no significant difference between Pf E and 4-*epi*-Pf E, the importance of two oxygen functional groups at C-11 and C-12 for antiproliferative activity, as well as a combination of carbomethoxy at C-4 and a benzoyl ester with electron-drawing group at C-12 or hydroxymethyl at C-4 and an appropriate oxidation state of ring-B/C for triple-negative breast cancer cell selectivity.

INTRODUCTION

Parviflorons (Pfs) are abietane diterpenes isolated from only the genus *Plectranthus* in the family Lamiaceae. These compounds were first isolated by Eugster *et al.*, Pfs A–F from *P. parviflorus* in 1978[1] and Pfs G and H from *P. strigosus* in 1984.[2] Pfs feature a conjugated *o*-hydroxy-*p*-quinone methide with an isopropyl group at C-13 and an oxygenated functional group on ring-A. They can be classified into three groups based on the position of the oxygenation, C-4 for Pfs A–C and E, (**1**–**4**, Figure 1), C-2 for Pfs D, F and G and C-2/-4 for Pf H. Among the eight compounds, we found that PFs C, E and F[3] displayed potent antiproliferative activities with IC_{50} values of 2.5–7.3 μM against several human tumor cell lines (HTCLs) including a multidrug resistant cell line (Figure 1).



Compound	Cell line/IC_{50} (μM)[a]				
	A549	KB	KB-VIN	MDA-MB-231	MCF-7
Parvifloron C (**2**)	3.1	3.1	3.4	3.4	3.7
Parvifloron E (**3**)	5.1	4.8	7.2	5.0	4.8

Figure 1. The structures of parviflorons A–C and E (**1**–**4**) and antiproliferative activities of **2** and **3**

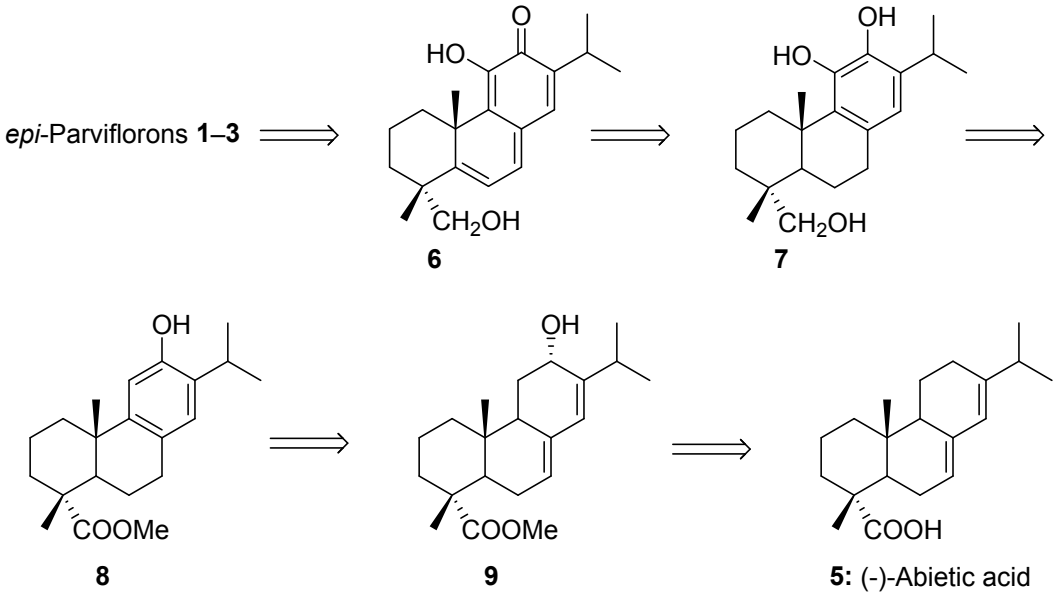
[a]A549 (lung carcinoma), KB (identical to cervical carcinoma HeLa derivative AV-3), KB-VIN (P-gp-overexpressing MDR subline of KB), MDA-MB-231 (triple-negative breast cancer), MCF-7 (estrogen receptor-positive & HER2-negative breast cancer). Antiproliferative activity expressed as IC_{50} values for each cell line, the concentration of compound that caused 50% reduction relative to untreated cells determined by the SRB assay.

We recently reported the first total synthesis of Pf F.[3] During this study, several derivatives showed selective activity against the MDA-MB-231 triple-negative breast cancer (TNBC) cell line. These results implied the possibility of developing more selective and potent anti-TNBC agents from Pf derivatives. TNBC, which accounts for 10–20% of all invasive breast cancers,[4] cannot be treated with standard hormonal or targeted therapies, due to the lack of estrogen/progesterone receptors (ER/PR) or HER2 overexpression. Thus, TNBC is associated with a poor prognosis and 30% of patients develop distant metastasis. More effective treatment depends urgently on the discovery of TNBC selective antitumor agents. To obtain more potent compounds and structure-activity relationship (SAR) information including the effects of substituents and stereocenter at C-4, we accomplished the syntheses of PFs with oxygenated functional groups at C-4, namely 4-*epi*-Pfs A, C and E, together with the related derivatives. All synthesized compounds were evaluated for antiproliferative activity against five human tumor cell lines (HTCLs), MDA-MB-231 (TNBC), MCF-7 (estrogen receptor-positive and HER2-negative breast cancer), A549 (lung carcinoma), KB (originally isolated from epidermoid carcinoma of the nasopharynx, while identical to cervical carcinoma HeLa derivative AV-3), and KB-VIN (a KB-subline exhibiting MDR phenotype with overexpression of P-gp).

RESULTS AND DISCUSSION

Our retrosynthetic analysis is outlined in Scheme 1. We selected commercially available (−)-abietic acid (**5**) as the starting material to maintain the chiral tricyclic framework, conceivably an important core structure for the biological activity. We planned to assay all synthetic intermediates to obtain important SAR, including the effect of the C-4 stereocenter on the cytotoxic activity as the 4-epimers of natural Pfs will be generated from **5** through our proposed reaction sequence. However, if necessary, we could invert the stereochemistry at C-4 via a reported method at the

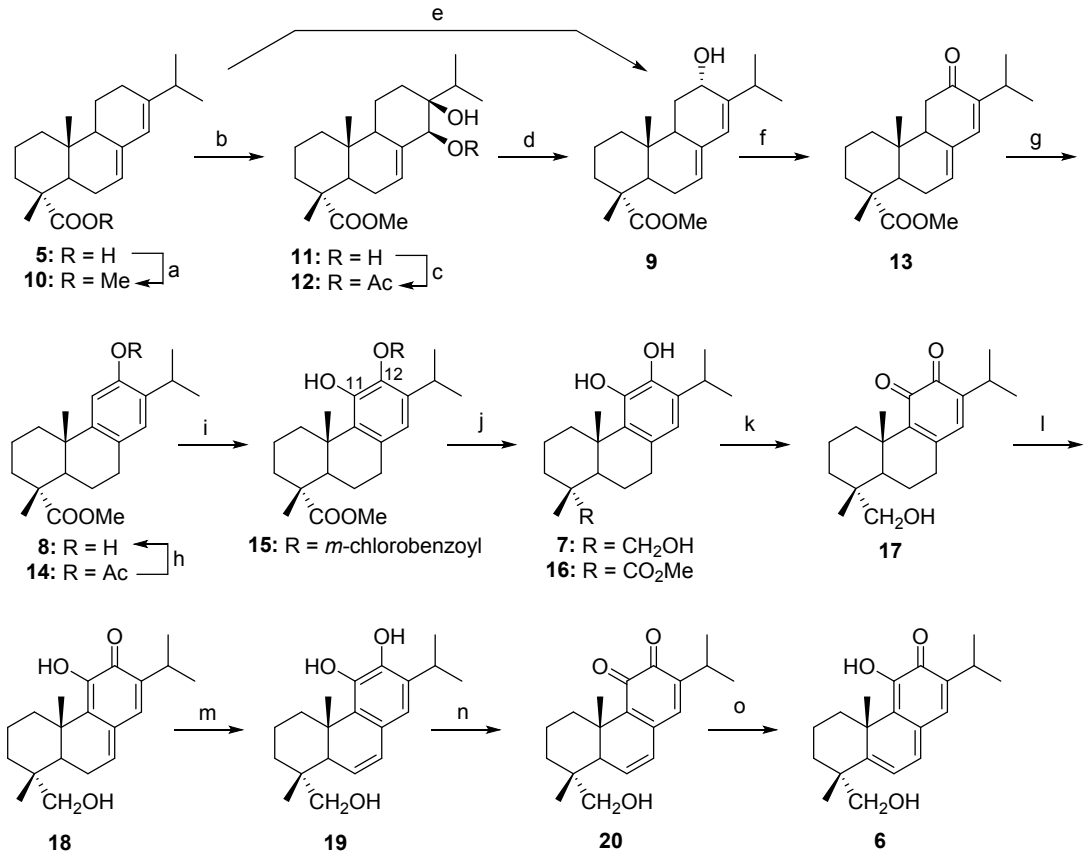
early stage.[5] Our synthetic strategy involved a final esterification of the hydroxymethyl group in **6**, prepared from catechol **7** through repeated oxidation and isomerization reactions (Scheme 1). We planned to obtain catechol **7** from phenol **8** by Tada's method using *m*-chlorobenzoyl peroxide (*m*CBPO).[6] Phenol **8** would be synthesized from (−)-abietic acid (**5**) through allylic oxidation to **9** followed by aromatization.



Scheme 1. Retrosynthetic analysis of 4-*epi*-parviflorons A, C, and E

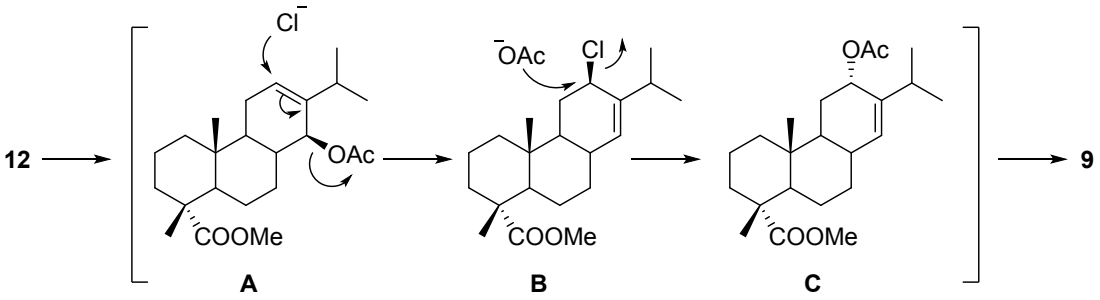
Using a known method,[7] we initially produced mono-acetate **12** by methylation of (−)-abietic acid (**5**), selective dihydroxylation at the $\Delta^{13,14}$ double bond with osmium (VIII) oxide, followed by acetylation of the secondary alcohol (Scheme 2). The treatment of **12** with thionyl chloride unexpectedly provided **9** with a hydroxyl rather than chloro group at C-12, even though water was strictly excluded from the reaction. Although the mechanism of this reaction has been obscure, 12β-chloroabietate **B** would be formed through S_N2' reaction from 14β-acetoxy intermediate **A**. S_N2 reaction of a resultant acetate anion to C-12 on 12β-chloroabietate **B** would provide 12α-acetoxyabietate **C**, which could be easily hydrolyzed to produce **9** (Scheme 3). Because the

dihydroxylation step proceeded slowly and the overall yield of **9** was low, we attempted to insert a hydroxyl group directly at the C-12 position of **10** using various allylic oxidation conditions. The use of an iron carbonyl complex to achieve allylic oxidation was reported in 1988.[8] In a model reaction, in which the carbomethoxy moiety at C-4 was first converted to methyl group, the desired allylic alcohol was obtained successfully via oxidative de-complexation of an iron carbonyl complex with I_2 in the presence of water. However, the same procedure with **10** did not produce the desired compound **9**. Other allylic oxidation conditions with different combinations of oxidants (TBHP or O_2) and metals [CuI, $Pd(OH)_2/C$, $RuCl_3$, $Fe(acac)_3$, etc] resulted in complex mixtures. However, under Wohl-Ziegler conditions, the desired 12-hydroxylated compound (**9**), rather than the 12-brominated compound, was obtained in 19% yield. The direct allylic oxidation from **10** and the three-step conversion from **6** produced **9** in similar overall yields. The resulting allylic alcohol **9** was then oxidized with pyridinium dichromate (PDC) and isomerized with sulfuric acid in acetic acid at reflux temperature to provide phenol **8** together with its acetate **14**, which was hydrolyzed readily to **8**. The *ortho*-oxidation of phenol **8** with *m*-chlorobenzoyl peroxide (*m*CBPO)[6] produced mainly 11-hydroxy-12-*m*-chlorobenzoyloxy **15** through an intramolecular ester exchange of 12-hydroxy-11-*m*-chlorobenzoyloxy **E**, derived by a [3.3]sigmatropic shift from 12-*m*-chlorobenzoperoxoate **D** (Scheme 4). The chemical structure of **15** was identified by HMBC, particularly from the correlation between the hydroxyl proton with C-11 and C-10. The treatment of **15** with 10 eq. mol of $LiAlH_4$ in THF at reflux temperature for 7 h generated alcohol **7**, while the reduction with 5.5 eq. mol of reagent and a shorter reaction time gave methyl ester **16** in good yield. Oxidation of **7** with Ag_2O, followed by heating in toluene produced *ortho*-hydroxy quinone methide **18**, which was isomerized to **19** by heating.[7] Further oxidation and isomerization of **19** produced **6**, the common intermediate to 4-*epi*-Pfs.

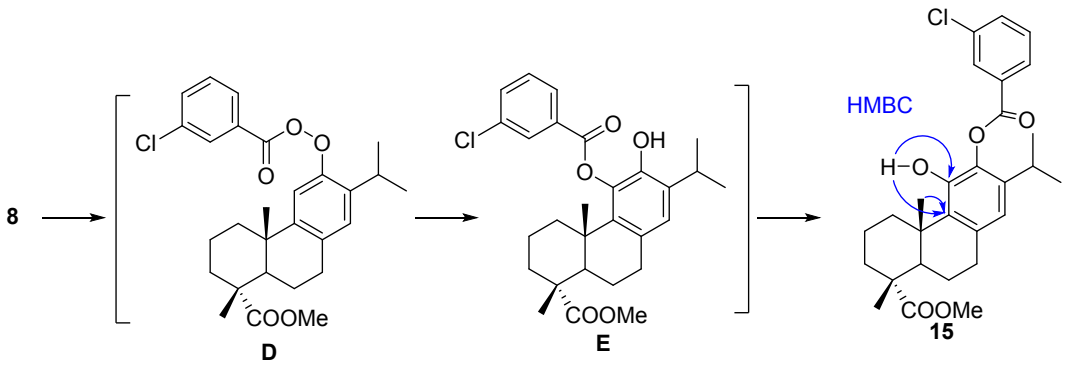


Scheme 2. Preparation of common intermediate **6**

Reagents and conditions: (a) MeI, K_2CO_3, acetone, reflux, 22 h, 87%; (b) OsO_4, py, CH_3NO, H_2O, *t*BuOH, reflux, 66 h, 57%; (c) Ac_2O, py, rt, 3 h, 92%; (d) $SOCl_2$, Et_3N, CH_2Cl_2, −78°C, 20 min, 56%; (e) NBS, AIBN, CCl_4, rt, 27 h, 19%; (f) PDC, py, MS4Å, CH_2Cl_2, rt, 1 h, 60%; (g) cH_2SO_4, HOAc, reflux, 3 h, 42% for **8**, 39% for **14**; (h) $NaHCO_3$, H_2O, MeOH, rt, 12.5 h, 95%; (i) *m*CPBO, CH_2Cl_2, rt, 23 h, 69%; (j) $LiAlH_4$ (10 eq. mol), THF, reflux, 4 h, 90% for **7**, $LiAlH_4$ (5.5 eq. mol), THF, reflux, 1 h, 69% for **16**; (k) Ag_2O, CH_2Cl_2, rt, 2 h, 86%; (l) toluene, reflux, 2 h, 96%; (m) neat, 115 °C, 3 h; (n) Ag_2O, CH_2Cl_2, rt, 1 h, 62% for 2 steps; (o) toluene, reflux, 5 h, 60%.



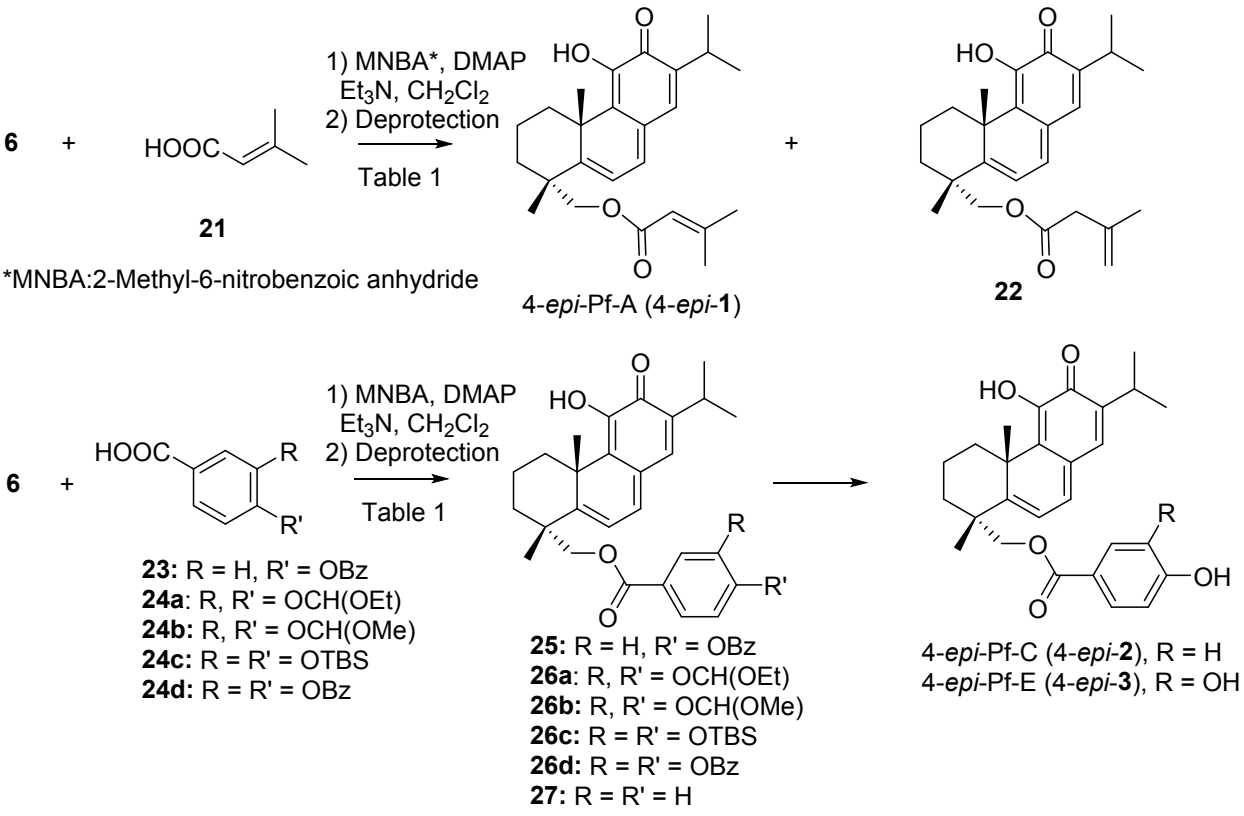
Scheme 3. A possible mechanism from **12** to **9**



Scheme 4. The reaction pathway from phenol **8** to benzoate **15**

Because compound **6** is unstable and acid sensitive,[9] no acidic conditions could be applied during subsequent esterification and deprotection steps. Only Shiina reagent proved successful for the esterification of **6**, although other condensation reagents, such as DCC, EDCI, and the use of pentafluorophenyl ester, did not produce the desired ester. The treatment of **6** with 3-methylcrotonic acid in the presence of Shiina reagent provided 4-*epi*-PF A (4-*epi*-**1**) in 11% yield along with **22** in 4% yield (Scheme 5). The target compound 4-*epi*-Pf C (4-*epi*-**2**) was prepared by reaction of **6** with benzoyl protected 4-hydroxybenzoic acid followed by deprotection of the benzoyl group (Table 1, entry 2). Various methods were investigated to protect/deprotect the catechol moiety of protocatechuic acid (Table 1, entries 3–6). While methyl and ethyl orthoesters (**24a,b**) gave reasonable yields in the esterification of **6**, the deprotection was inefficient under slightly acidic or even neutral conditions (Table 1, entries 3–4).[10] Esterification of **6** with

protocatechuic acid protected as a silyl ether (**24c**) failed to give the desired product **26c**, instead giving only the ortho-quinone **20** (Table 1, entry 5). While the dibenzoyl protecting groups on the desired esterified **26d** were removed easily to give 4-*epi*-Pf E (4-*epi*-**3**) in good yield under basic conditions using *n*BuNH$_2$,[11] the initial esterification of **6** not only gave **26d** in low yield (16%) but unexpectedly also produced **27** as well as **20** in lower (17%) and higher (56%) yields, respectively (Table 1, entry 6). Compound **27** was produced by a reaction with benzoyl protection moiety on **24d** rather than Shiina mixed anhydride.



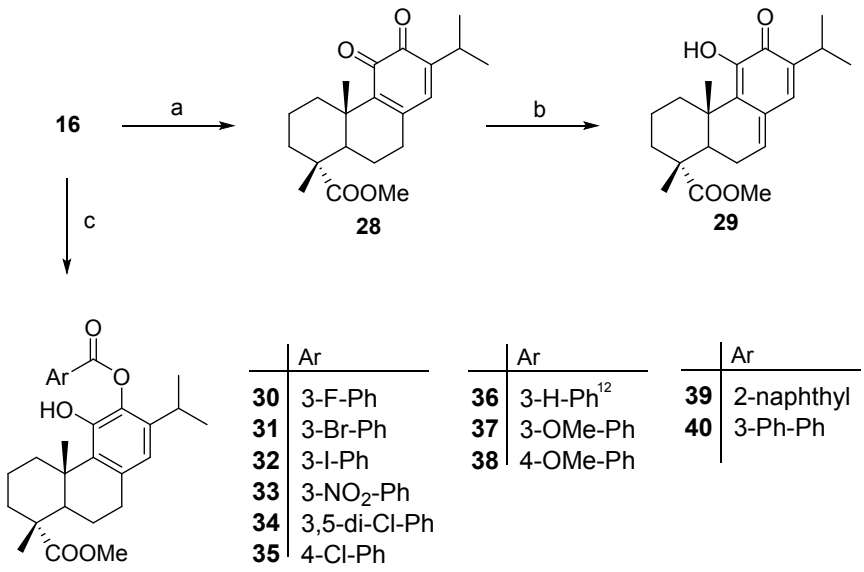
Scheme 5. Total synthesis of 4-*epi*-Pfs (4-*epi*-**1**–**3**) from **6**

Table 1. Reaction and yield of 4-*epi*-Pfs (4-*epi*-**1**–**3**)

Entry	Acids	Yields of ester products	Deprotection conditions	Yields of desired compounds
1	**21**	-	-	4-*epi*-**1** (11%), **22** (4%), **20** (38%)
2	**23**	**25** (45%), **20**	*n*-BuNH$_2$, PhH, rt, 7 h	4-*epi*-**2** (29%), **25** (4%)
3	**24a**	**26a** (59%), **20** (16%)	PPTS, dioxane, H$_2$O, rt, 4 d	4-*epi*-**3** (8%), **26a** (79%)

4	**24b**	**26b** (38%), **20** (13%)	Amberlyst 15, K_2HPO_4, KH_2PO_4, MeOH, THF, 45 °C	4-*epi*-**3** (0%)
5	**24c**	**26c** (0%), **20** (84%)	-	-
6	**24d**	**26d** (16%), **27** (17%), **20** (56%)	*n*-$BuNH_2$, PhH, rt, 1 h	4-*epi*-**3** (77%)

As shown in Table 2, Pf E (**3**) and its epimer (4-*epi*-**3**) showed comparable potency against the tested tumor cell lines; thus, the stereochemistry at C-4 did not affect the antiproliferative activity. Accordingly, we felt that the additional stereo inversion step at C-4 was unnecessary to our current study. In addition, we found that intermediate **15** with a *m*-chlorobenzoyloxy group on C-12 exhibited selective inhibition of TNBC cell proliferation. This interesting finding led us to synthesize related derivatives (**30**–**40**) with various aryloxy groups on C-12 (Scheme 6). Furthermore, because catechol **16** showed broad antiproliferative activity against all tested tumor cell lines, quinone methide **29** was also prepared to determine the effect of the oxidation state in ring B/C.



	Ar
30	3-F-Ph
31	3-Br-Ph
32	3-I-Ph
33	3-NO_2-Ph
34	3,5-di-Cl-Ph
35	4-Cl-Ph

	Ar
36	3-H-Ph[12]
37	3-OMe-Ph
38	4-OMe-Ph

	Ar
39	2-naphthyl
40	3-Ph-Ph

Scheme 6. Preparation of abietane derivatives **30**–**40**
Reagents and conditions: (a) Ag_2O, CH_2Cl_2, rt, 40 min, 99%; (b) toluene, reflux, 8 h, 89%; (c) ArCOOH, EDCI, DMAP, CH_2Cl_2, 0 °C, 18–62%.

According to the antiproliferative activity profiles against five HTCLs (Table 2), the compounds were divided into three categories based on their biological profiles, (I) selectively active against the TNBC cell line, (II) active ($IC_{50} \leq 5$ μM) against all tested HTCLs, including MDR, and (III) inactive against all tested HTCLs. The compounds belonging to group-I included **15**, **18**, **19**, and **30**–**35**. These compounds were four to five times more potent against MDA-MB-231 compared with the remaining four cell lines. The synthesized 4-*epi*-**3** and the intermediates **6**, **7**, **16**, **17**, **26a**, **26d** and **27** were classified as group-II. These eight compounds significantly inhibited the cell growth of all tested HTCLs (although the actual active compound might be **6**, which could be produced by de-esterification of 4-*epi*-**3** in the cell). Among them, compound **16** showed the most potent cell growth inhibitory effects ($IC_{50} < 3$ μM) against breast cancer cell lines, MDA-MB-231 and MCF-7, regardless of the hormonal receptor status. The remaining tested compounds were in group-III and generally did not display significant cell growth inhibition. From these observations, we determined the following SAR correlations, 1) two adjacent oxygenated functional groups at C-11 and -12 are potentially required for increased antiproliferative activity [early intermediate compounds **9**–**13** were weakly active or inactive, while **20** (11, 12-diketone) was an exception, 2) when a carbomethoxy group is present at C-4, TNBC selectivity was induced by a benzoyl ester substituted with an electronegative moiety at C-12 (compare **15** and **30**–**35** with **16** and **36**–**40**), 3) when a hydroxymethyl group is present at C-4, TNBC selectivity was dependent on the oxidation state in ring-B/C (compare **6**, **7**, **17** and **20** with **18**, **19** and **29**). When 3-H-Ph (**36**) was substituted by 3-F-Ph (**30**), TNBC selectivity was significantly increased. This observation suggests that 3-H-Ph may be a target of oxidative detoxification by ubiquitously expressing enzyme, and the halogens as well as nitrogen dioxide may be resistant (NO_2, F > Br > I) against detoxifying enzyme selectively expressed in MDA-MB-231. Overall, we demonstrates that TNBC selectivity can be

inducible by moiety modified at C-12, while chirality at C-4 may not be responsible for the TNBC selectivity.

Table 2. Antiproliferative Data of Synthesized Compounds

	Cell lines / IC_{50} (μM)[a]				
Compound	A549	KB	KB-VIN	MDA-MB-231	MCF-7
3 (Pf E)	5.1	4.8	7.2	5.0	6.1
4-*epi*-**3**	5.3	4.8	9.5	5.5	6.4
6	5.2	4.6	5.2	5.0	5.8
7	5.8	4.9	6.0	4.5	6.0
8	13.6	3.9	3.7	18.6	5.9
9	>40	34.9	35.7	>40	>40
10	>40	39.7	35.3	>40	>40
11	>40	>40	>40	>40	>40
12	>40	>40	>40	>40	>40
13	>40	29.2	16.8	>40	39.0
15	20.1	32.3	>40	5.6	20.4
16	5.0	5.2	6.1	2.7	2.8
17	6.9	5.0	6.5	4.8	6.4
18	17.9	6.5	17.2	4.9	7.1
19	18.5	17.2	18.4	6.7	17.6
20	>40	>40	>40	36.4	>40
26a	5.0	4.8	5.5	4.1	4.4
26d	7.0	13.5	21.6	6.3	8.1
27	4.9	4.9	5.2	5.0	5.2
29	21.8	22.2	23.7	11.6	17.1
30	29.4	29.9	32.9	5.2	17.9
31	>40	>40	>40	8.4	22.9
32	>40	>40	>40	11.5	27.2
33	24.3	26.2	33.9	5.1	20.9
34	19.2	21.4	34.6	3.9	17.0
35	23.4	28.7	35.9	4.0	19.1
36	39.2	31.0	33.6	21.4	26.3
37	33.7	29.8	30.1	11.0	21.9
38	22.0	16.8	17.1	23.4	24.1
39	29.5	26.6	23.9	17.9	34.2
40	>40	>40	>40	19.6	29.4
PXL[b](nM)	5.4	6.3	2352.8	8.7	10.9

Class-(I) selectively active against the TNBC cell line; Class-(II) active ($IC_{50} \leq 5$ μM) against all tested human tumor cell lines (HTCLs); Class-(III) inactive against all tested HTCLs

[a]Antiproliferative activity defined as IC_{50} value (μM) for each cell line, the concentration of compound that caused 50% reduction relative to untreated cells using the sulforhodamine B assay. [b] Paclitaxel

Because compounds that impact the cell cycle should inhibit cell growth in all tested tumor cell lines, we postulated that the TNBC-selective compounds do not affect the cell cycle progression. Thus, three group-I TNBC-selective compounds, **30**, **31**, and **33**, with an electron-withdrawing group at the *m*-position of the C-12 benzoyl ester, together with one less selective group-III compound, **37**, with an electron-donating group at the same position were assessed in a cell cycle progression assay in MDA-MB-231 using flow cytometry (Figure 2). As we expected, none of the four tested compounds displayed a significant effect on cell cycle progression or sub-G1 induction. These results support our hypothesis that our selective compounds target a protein required for cell growth expressed specifically in MDA-MB-231 cells but do not affect the proteins responsible for the S- and G2/M-phase progression, as well as apoptotic induction. We are now conducting studies to identify the target.

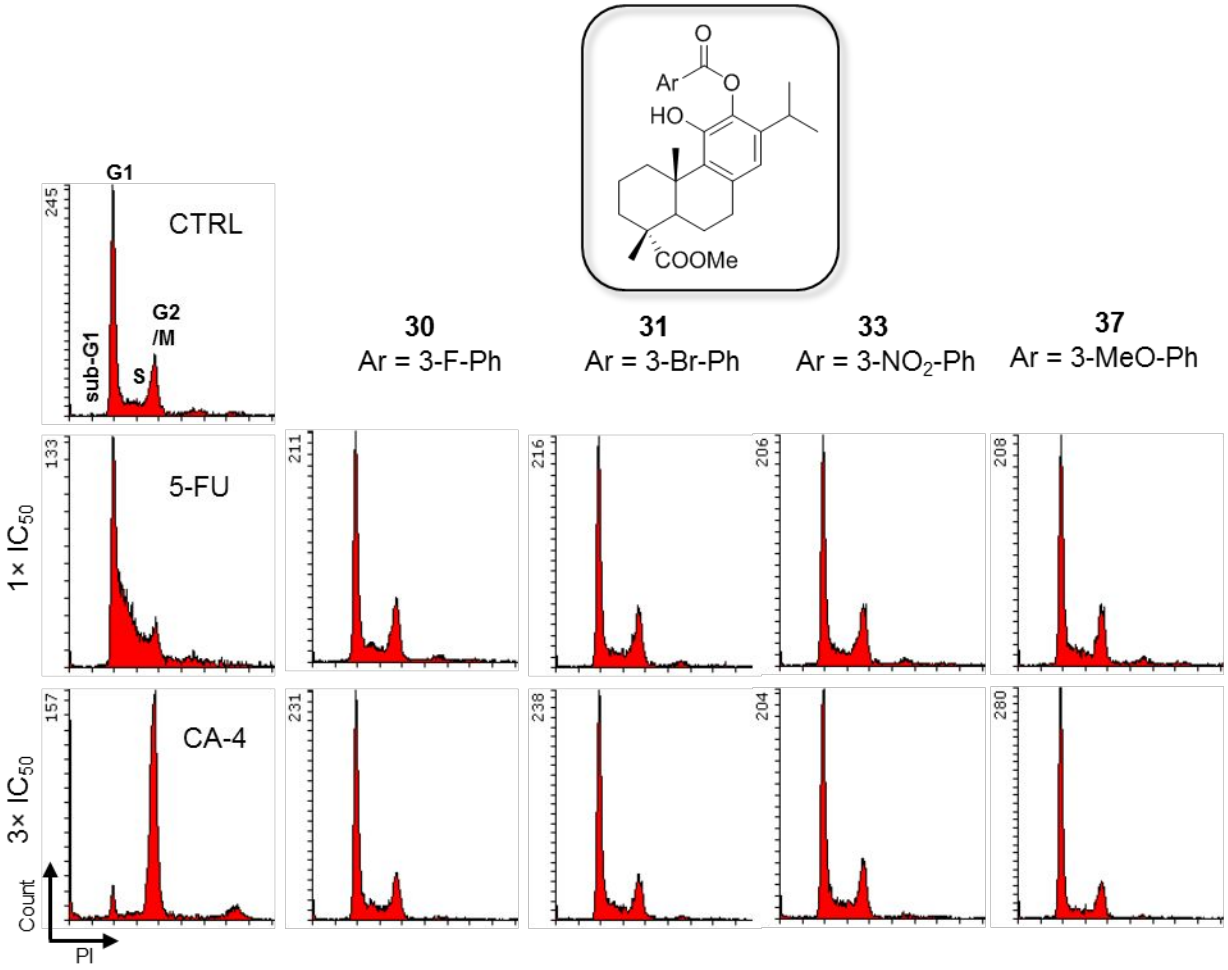


Figure 2. Effects of compounds on cell cycle progression.

Triple-negative breast cancer MDA-MB-231 cells were treated with compound for 24 h at concentration of 1× IC_{50} or 3× IC_{50} as indicated. DMSO was used as a vehicle control (CTRL). 25 μM (1× IC_{50}) 5-fluorouracil (5-FU) or 0.1 μM (3× IC_{50}) combretastatin A-4 (CA-4) was used for DNA replication (S-phase) or mitotic inhibitor, respectively. Cell cycle distributions of treated cells were analyzed by flow cytometry (LSRFortessa operated by FACS Diva software, BD Bioscience) after staining with propidium iodide (PI) in the presence of RNase.

In conclusion, we achieved the first total synthesis of 4-*epi*-Pfs with ester functional groups at C-4, including 4-*epi*-Pfs A, C and E, from (−)-abietic acid in 12–13 steps in 0.15% overall yield. The synthesized compounds, including intermediates and derivatives, were evaluated for antiproliferative activity against five HTCLs. We observed no significant difference of antiproliferative activity between Pf E and its 4-epimer. The SAR study suggested the importance

of two oxygenated functional groups at C-11 and C-12. Furthermore, the TNBC selective compounds required one of two conditions, a carbomethoxy group at C4 combined with a benzoyl ester substituted with an electron-drawing group or a hydroxymethyl group at C4 combined with an appropriate oxidation state of ring-B/C.

EXPERIMENTAL SECTION

General Procedures.

All chemicals and solvents were used as purchased. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a JEOL JMN-ECA600 or JMN-ECS400 spectrometers with tetramethylsilane (TMS) as an internal standard. All chemical shifts are described as δ values in ppm, apparent scalar coupling constants J in Hz. Mass spectroscopic data were obtained on a JMS-700 MStation (FAB) mass spectrometer with TOF analyzer. Analytical and preparative TLC was carried out on precoated silica gel $60F_{254}$ and RP-$18F_{254}$ plates (0.25 or 0.50 mm thickness; Merck).

General synthetic procedures for esterification:

Methyl 12-(3-chlorobenzoyloxy)-11-hydroxyabieta-8,11,13-trien-18-oate ***(15).*** *m*CBPO (161.7 mg, 0.52 mmol) was added to a solution of **8** (122.4 mg, 0.37 mmol) in anhyd CH_2Cl_2 (10.0 ml). After stirring at rt for 23 h under Ar, the reaction was quenched with aqueous 20% $Na_2S_2O_3$ (10.0 ml). The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography with hexane–CH_2Cl_2 (2 : 1) to afford **15** (114.7 mg, 0.24 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 1.23–1.26 (m,

1H), 1.29 (s, 3H), 1.31–1.33 (m, 1H), 1.38 (s, 3H), 1.40–1.47 (m, 2H), 1.59–1.64 (m, 1H), 1.71–1.80 (m, 3H), 2.24–2.31 (m, 1H), 2.78–2.98 (m, 4H), 3.12–3.17 (m, 1H), 3.69 (s, 3H), 5.09 (s, 1H), 6.61 (s, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.64–7.67 (m, 1H), 8.12 (br d, J = 7.6 Hz, 1H), 8.21 (t, J = 1.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.3, 22.1, 22.9, 23.1, 27.6, 32.2, 35.7, 36.5, 38.9, 46.8, 48.4, 51.9, 118.8, 128.5, 130.2, 130.4, 134.1, 134.2, 134.6, 135.1, 135.7, 137.6, 145.5, 163.9, 179.3; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{28}H_{33}ClO_5$, 484.2017; found, 484.2010.

*11,12-Dihydroxydehydroabietinol (**7**).* 1M LAH in THF (1.60 ml, 1.60 mmol) was added to a solution of **15** (110.4 mg, 0.23 mmol) in anhyd THF (3.0 ml) at 0 °C. After refluxing for 4 h under Ar, the reaction was quenched with 1N HCl (3.0 ml) at 0 °C. The mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography with hexane–acetone (7 : 1) to afford **7** (65.8 mg, 0.21 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (s, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.25 (d, J = 6.8 Hz, 3H), 1.27–1.30 (m, 1H), 1.33–1.36 (m, 1H), 1.38 (s, 3H), 1.44–1.53 (m, 2H), 1.57–1.65 (m, 3H), 1.67–1.81 (m, 2H), 2.78–2.83 (m, 2H), 2.97 (sept, J = 7.2 Hz, 1H), 3.07–3.12 (m, 1H), 3.21 (dd, J = 6.4, 11.2 Hz, 1H), 3.50 (dd, J = 6.0, 10.4 Hz, 1H), 4.52 (s, 1H), 5.68 (s, 1H), 6.43 (s, 1H); HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{20}H_{30}O_3$, 318.2195; found, 318.2194.

*Methyl 11,12-dihydroxydehydroabietate (**16**).* 1M LAH in THF (0.36 ml, 0.36 mmol) was added to a solution of **15** (175.8 mg, 0.36 mmol) in anhyd THF (3.0 ml) at −78 °C. After stirring at −78 °C for 40 min under Ar, the reaction was quenched with 1N HCl (2.0 ml). The mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography

with EtOAc–hexane (1 : 20) to afford **16** (107.7 mg, 0.31 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (d, J = 7.2 Hz, 3H), 1.25 (d, J = 7.2 Hz, 3H), 1.28 (s, 3H), 1.29–1.31 (m, 1H), 1.36 (s, 3H), 1.39–1.46 (m, 1H), 1.61–1.80 (m, 5H), 2.22 (d, J = 12.0 Hz, 1H), 2.73 (dd, J = 5.2, 16.0 Hz, 1H), 2.82–3.02 (m, 2H), 3.13 (br d, J = 12.4 Hz, 1H), 4.49 (s, 1H), 5.71 (s, 1H), 6.42 (s, 1H); HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{21}H_{30}O_4$, 346.2144; found, 346.2144.

*(4bS,8R)-8-(Hydroxymethyl)-2-isopropyl-4b,8-dimethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthrene-3,4-dione (**17**).* Ag_2O (50.1 mg, 0.22 mmol) was added to a solution of **7** (37.5 mg, 0.12 mmol) in anhyd CH_2Cl_2 (3.0 ml). After stirring at rt for 40 min under Ar, the mixture was filtered through celite with CH_2Cl_2 and the filtrate was concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1 : 5) to afford **17** (27.3 mg, 0.086 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83 (s, 3H), 1.08 (br s, 3H), 1.10 (br s, 3H), 1.27 (s, 3H), 1.31–1.34 (m, 2H), 1.39–1.51 (m, 3H), 1.56–1.62 (m, 1H), 1.65–1.83 (m, 2H), 2.44–2.46 (m, 2H), 2.71–2.76 (m, 1H), 2.86–2.93 (m, 1H), 3.16 (dd, J = 5.6, 10.4 Hz, 1H), 3.47 (dd, J = 6.4, 11.2 Hz, 1H), 6.39 (s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ: 17.6, 17.7, 18.1, 20.3, 21.4, 21.4, 26.8, 33.4, 34.9, 35.5, 37.6, 37.8, 44.4, 71.8, 137.8, 144.7, 146.7, 148.0, 180.1, 181.1; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{20}H_{28}O_3$, 316.2038; found, 316.2040.

*(4bS,8R)-4-Hydroxy-8-(hydroxymethyl)-2-isopropyl-4b,8-dimethyl-5,6,7,8,8a,9-hexahydrophenanthren-3(4bH)-one (**18**).* **17** (25.9 mg, 0.082 mmol) was dissolved in anhyd toluene (2.0 ml). After refluxing for 2 h under Ar, the solution was concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1 : 10) to afford **18** (25.0 mg, 0.079 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (s, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H), 1.22 (s, 3H), 1.30–1.35 (m, 2H), 1.48–1.60 (m, 2H), 1.66–1.78 (m, 2H), 1.93 (dd, J = 4.0, 12.0 Hz, 1H), 2.36–2.45 (m, 1H), 2.51–2.59 (m, 1H), 3.00–3.10 (m, 2H), 3.19 (dd, J = 6.0,

10.8 Hz, 1H), 3.19 (dd, *J* = 6.0, 10.8 Hz, 1H), 6.78–6.80 (m, 2H), 7.48 (s, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 18.0, 18.2, 18.9, 21.5, 21.8, 25.6, 26.6, 35.1, 36.3, 38.0, 38.4, 44.1, 71.9, 127.0, 131.6, 136.2, 140.5, 143.8, 148.6, 181.4; HRMS (FAB-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{29}O_3$, 317.2117; found, 317.2106.

(4bS,8R)-8-(Hydroxymethyl)-2-isopropyl-4b,8-dimethyl-4b,5,6,7,8,8a-hexahydrophenanthrene-3,4-diol ***(19)*** *and (4bS,8R)-8-(Hydroxymethyl)-2-isopropyl-4b,8-dimethyl-4b,5,6,7,8,8a-hexahydrophenanthrene-3,4-dione* ***(20)***. **18** (27.9 mg, 0.088 mmol) was heated for 3 h at 115 °C under Ar to afford **19**, which was used for the next reaction without purification due to its instability. After cooling of the reaction mixture to rt, anhyd CH_2Cl_2 (2.0 ml) and Ag_2O (36.9 mg, 0.16 mmol) were added to the residue. The mixture was stirring at rt for 1 h under Ar. The mixture was filtered through celite with CH_2Cl_2 and the filtrate was concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1 : 7) to afford **20** (17.1 mg, 0.054 mmol, 62%, 2 steps from **18**). **19:** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.00 (s, 3H), 1.19 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.29–1.52 (m, 2H), 1.74–1.95 (m, 4H), 2.48 (m, 1H), 2.84 (br d, *J* = 12.4 Hz, 1H), 3.00–3.07 (m, 1H), 3.26 (dd, *J* = 6.8, 10.8 Hz, 1H), 3.51 (dd, *J* = 5.6, 11.2 Hz, 1H), 5.09 (s, 1H), 5.60 (s, 1H), 5.80 (dd, *J* = 2.8, 9.6 Hz, 1H), 6.44 (dd, *J* = 3.2, 9.6 Hz, 1H), 6.49 (s, 1H); HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{20}H_{28}O_3$, 316.2038; found, 316.2031; **20:** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.26 (s, 3H), 1.49–1.54 (m, 2H), 1.58 (s, 3H), 1.67–1.76 (m, 2H), 1.92–2.04 (m, 1H), 3.16 (sept, *J* = 6.8 Hz, 1H), 3.28–3.34 (m, 1H), 3.44 (d, *J* = 11.6 Hz, 1H), 3.76 (d, *J* = 11.6 Hz, 1H), 6.40 (d, *J* = 6.8 Hz, 1H), 6.74 (d, *J* = 6.8 Hz, 1H), 6.93 (s, 1H), 7.74 (br s, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 15.7, 17.9, 18.7, 21.3, 21.5, 27.0, 34.0, 34.5, 37.3, 38.0, 46.4, 71.1, 127.1, 136.4, 139.2, 140.7,

141.3, 147.8, 181.7, 182.0; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{20}H_{26}O_3$, 314.1882; found, 314.1875.

*(4bS,8R)-4-Hydroxy-8-(hydroxymethyl)-2-isopropyl-4b,8-dimethyl-5,6,7,8-tetrahydrophenanthren-3(4bH)-one (**6**)*. **20** (23.9 mg, 0.076 mmol) was dissolved in anhyd toluene (1.0 ml). After refluxing for 4 h under Ar, the solution was concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1: 7) to afford **6** (14.2 mg, 0.045 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.26 (s, 3H), 1.49–1.54 (m, 2H), 1.58 (s, 3H), 1.67–1.76 (m, 2H), 1.92–2.04 (m, 1H), 3.16 (sept, *J* = 6.8 Hz, 1H), 3.28–3.34 (m, 1H), 3.44 (d, *J* = 11.6 Hz, 1H), 3.76 (d, *J* = 11.6 Hz, 1H), 6.40 (d, *J* = 6.8 Hz, 1H), 6.74 (d, *J* = 6.8 Hz, 1H), 6.93 (s, 1H), 7.74 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ: 17.7, 21.6, 21.8, 25.3, 25.7, 26.9, 33.0, 34.2, 42.6, 43.2, 71.5, 118.5, 127.5, 127.6, 133.2, 137.9, 141.6, 146.4, 163.5, 178.2; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{20}H_{26}O_3$, 314.1882; found, 314.1894.

*[(1R,4aS)-5-Hydroxy-7-isopropyl-1,4a-dimethyl-6-oxo-1,2,3,4,4a,6-hexahydrophenanthren-1-yl]methyl 2-methoxybenzo[d][1,3]dioxole-5-carboxylate (**26b**)*. Triethylamine (0.017 ml, 0.12 mmol), DMAP (0.5 mg, 0.0041 mmol), MNBA (15.9 mg, 0.046 mmol) and **24b** (8.6 mg, 0.044 mmol) were dissolved in anhyd CH_2Cl_2 (0.5 ml) and stirred at rt for 20 min. A solution of **6** (11.7 mg, 0.037 mmol) in anhyd CH_2Cl_2 (0.3 ml) was added to the mixture. After stirring at rt for 19.5 h, the reaction was quenched with aqueous sat. NH_4Cl (5.0 ml). The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1 : 7) to afford **26b** (7.0 mg, 0.014 mmol, 38%) and recovered **6** (1.5 mg, 0.0048 mmol, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.40 (s, 3H), 1.53–

1.58 (m, 1H), 1.61 (s, 3H), 1.67–1.77 (m, 3H), 1.96–2.06 (m, 1H), 3.17 (sept, *J* = 6.8 Hz, 1H), 3.35 (br d, *J* = 14.4 Hz, 1H), 3.42 (s, 3H), 4.21 (d, *J* = 11.2 Hz, 1H), 4.39 (d, *J* = 11.2 Hz, 1H), 6.34 (d, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 7.2 Hz, 1H), 6.91–6.93 (m, 3H), 7.51 (d, *J* = 1.2 Hz, 1H), 7.68 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.75 (s, 1H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ:17.7, 21.7, 21.9, 25.0, 25.6, 26.9, 33.3, 35.0, 41.2, 43.1, 50.2, 72.5, 107.9, 109.2, 118.5, 119.9, 124.2, 125.3, 127.61, 127.63, 133.2, 137.9, 141.7, 146.2, 146.3, 150.1, 162.2, 165.8, 178.37; HRMS (FAB-TOF) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{33}O_7$, 493.2226; found, 493.2227.

*4-({[(1R,4aS)-5-Hydroxy-7-isopropyl-1,4a-dimethyl-6-oxo-1,2,3,4,4a,6-hexahydrophenanthren-1-yl]methoxy}carbonyl)-1,2-phenylene dibenzoate (**26d**) and [(1R,4aS)-5-Hydroxy-7-isopropyl-1,4a-dimethyl-6-oxo-1,2,3,4,4a,6-hexahydrophenanthren-1-yl]methyl benzoate (**27**).* Triethylamine (0.012 ml, 0.086 mmol), DMAP (3.8 mg, 0.031 mmol), MNBA (10.4 mg, 0.030 mmol) and **24d** (11.5 mg, 0.032 mmol) were dissolved in anhyd CH_2Cl_2 (0.1 ml) and stirred at rt for 40 min. A solution of **6** (8.1 mg, 0.026 mmol) in anhyd CH_2Cl_2 (0.6 ml) was added to the mixture. After stirring at rt for 11 h, the reaction was quenched with aqueous sat. NH_4Cl (0.5 ml). The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by MPLC [RediSep®Rf Teledyne Isco 4g, EtOAc–hexane (1 : 19)] to afford **26d** (2.0 mg, 0.0030 mmol, 12%) and **27** (1.9 mg, 0.0045 mmol, 17%) along with recovery of **6** (4.5 mg, 56%). **26d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (d, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.42 (s, 3H), 1.57–1.60 (m, 1H), 1.61 (s, 3H), 1.70–1.77 (m, 3H), 1.95–2.08 (m, 1H), 3.15 (sept, *J* = 7.2 Hz, 1H), 3.35 (br d, *J* = 14.8 Hz, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 6.36 (d, *J* = 6.8 Hz, 1H), 6.73 (d, *J* = 6.8 Hz, 1H), 6.93 (s, 1H), 7.39 (q, *J* = 8.0 Hz, 4H), 7.49–7.59 (m, 3H), 7.74 (s, 1H), 8.02–8.07 (m, 6H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 17.7, 21.7, 21.8, 25.1, 25.6, 26.9, 33.2, 35.0, 41.2, 43.1, 72.9,

118.6, 123.8, 125.1, 127.6, 127.7, 128.2, 128.6, 130.2, 133.2, 133.93, 133.97, 137.9, 141.7, 146.3, 146.7, 162.0, 163.8, 164.1, 165.1, 178.4; HRMS (FAB-TOF) *m/z*: $[M+H]^+$ calcd for $C_{41}H_{39}O_8$, 659.2645; found, 659.2664; **27**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.41 (s, 3H), 1.57–1.59 (m, 1H), 1.61 (s, 3H), 1.69–1.78 (m, 3H), 1.95–2.07 (m, 1H), 3.16 (sept, *J* = 6.8 Hz, 1H), 3.33–3.38 (m, 1H), 4.24 (d, *J* = 10.8 Hz, 1H), 4.42 (d, *J* = 10.8 Hz, 1H), 6.36 (d, *J* = 6.4 Hz, 1H), 6.71 (d, *J* = 6.4 Hz, 1H), 6.92 (s, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.58 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.75 (s, 1H), 8.01–8.04 (m, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ: 17.8, 21.7, 21.9, 25.0, 25.6, 26.9, 33.3, 35.0, 41.2, 43.1, 72.5, 118.5, 127.6, 128.5, 129.6, 130.1, 133.1, 133.2, 138.0, 141.7, 146.3, 162.3, 166.5, 178.4; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{27}H_{30}O_4$, 418.2144; found, 418.2127.

*4-epi-Parvifloron A (4-epi-**1**)*[1] *and [(1R,4aS)-5-Hydroxy-7-isopropyl-1,4a-dimethyl-6-oxo-1,2,3,4,4a,6-hexahydrophenanthren-1-yl]methyl 3-methylbut-3-enoate (**22**).* Triethylamine (0.012 ml, 0.086 mmol), DMAP (2.2 mg, 0.018 mmol), MNBA (17.2 mg, 0.050 mmol) and 3-methylcrotonic acid (**21**, 6.1 mg, 0.061 mmol) were dissolved in anhyd CH_2Cl_2 (0.2 ml) and stirred at rt for 30 min. The mixture was added to a solution of **6** (6.9 mg, 0.022 mmol) in anhyd CH_2Cl_2 (0.3 ml). After stirring at rt for 5 h, the reaction was quenched with aqueous sat. NH_4Cl (4.0 ml). The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1 : 20) to afford the mixture of 4-*epi*-**1** and **22** [15.0 mg, 0.0033 mmol, 15%, 4-*epi*-**1** : **22** = 11 : 4 (determined from ^{1}H NMR)]. 4-*epi*-**1** : ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.31 (s, 3H),1.50–1.51 (m, 1H), 1.57 (s, 3H), 1.59–1.63 (m, 2H), 1.67–1.73 (m, 1H), 1.90 (d, *J* = 1.2 Hz, 3H), 1.91–2.03 (m, 1H), 2.16–2.17 (m, 3H), 3.16 (sept, *J* = 6.8 Hz, 1H), 3.31 (dd, *J* = 14.0, 4,0 Hz, 1H),3.99 (d, *J* = 11.2

Hz, 1H), 4.21 (d, *J* = 11.2 Hz, 1H), 5.69 (t, *J* =1.6 Hz, 1H), 6.29 (d, *J* = 6.8 Hz, 1H), 6.71 (d, *J* = 6.8 Hz, 1H), 6.93 (s, 1H), 7.73 (s, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 17.7, 20.4, 21.7, 21.9, 25.1, 25.6, 26.9, 27.5, 33.2, 34.8, 41.0, 43.1, 71.3, 115.9, 118.6, 127.5, 127.7, 133.2, 138.2, 141.6, 146.3, 157.3, 162.7, 166.7, 178.3; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{25}H_{32}O_4$, 396.2301; found, 396.2288. **22** : ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.31 (s, 3H), 1.40–1.51 (m, 1H), 1.57 (s, 3H), 1.60–1.63 (m, 1H), 1.63–1.73 (m, 2H), 1.80 (s, 3H), 1.89–2.00 (m, 1H), 3.06 (s, 2H), 3.16 (sept, *J* = 7.2 Hz, 1H), 3.30 (m, 1H), 3.98 (d, *J* = 11.2 Hz, 1H), 4.22 (d, *J* = 11.2 Hz, 1H), 4.85 (d, *J* = 0.8 Hz, 1H), 4.91(t, *J* = 1.6 Hz, 1H), 6.24 (d, *J* = 6.4 Hz, 1H), 6.70 (d, *J* = 6.4 Hz, 1H), 6.92 (s, 1H), 7.73 (s, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 17.7, 21.7, 21.9, 22.6, 25.2, 25.5, 26.9, 33.1, 34.7, 41.0, 43.0, 43.5, 72.3, 114.9, 118.6, 127.6, 133.2, 137.9, 141.7, 146.3, 162.2, 171.4, 178.4; HRMS (FAB-TOF) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{33}O_4$, 397.2379; found, 397.2380.

*[(1R,4aS)-5-Hydroxy-7-isopropyl-1,4a-dimethyl-6-oxo-1,2,3,4,4a,6-hexahydrophenanthren-1-yl]methyl 4-(benzoyloxy)benzoate (**25**).* Triethylamine (0.010 ml, 0.076 mmol), DMAP (0.6 mg, 0.050 mmol), MNBA (14.6 mg, 0.042 mmol) and **23** (9.3 mg, 0.038 mmol) were dissolved in anhyd CH_2Cl_2 (0.6 ml) and stirred at rt for 40 min. The mixture was added a solution of **6** (7.2 mg, 0.023 mmol) in anhyd CH_2Cl_2 (0.4 ml). After stirring at rt for 2 h, the reaction was quenched with aqueous sat. NH_4Cl (2.0 ml). The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1 :15) to afford to **25** (5.6 mg, 0.010 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.42 (s, 3H), 1.55–1.60 (m, 1H), 1.62 (s, 3H), 1.70–1.79 (m, 3H), 1.98–2.08 (m, 1H), 3.16 (sept, *J* = 6.8 Hz, 1H), 3.34–3.39 (m, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H),

6.36 (d, *J* = 6.8 Hz, 1H), 6.72 (d, *J* = 6.8 Hz, 1H), 6.93 (s, 1H), 7.29–7.33 (m, 2H), 7.51–7.55 (m, 2H), 7.64–7.69 (m, 1H), 7.75 (br s, 1H), 8.09–8.12 (m, 2H), 8.19–8.22 (m, 2H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 17.8, 21.7, 21.9, 25.1, 25.7, 26.9, 33.3, 35.0, 41.2, 43.1, 72.6, 118, 6, 122.0, 127.6, 127.7, 128.7, 130.3, 131.2, 133.2, 134.0, 137.9, 141.7, 146.4, 154.8, 162.1, 164.7, 165.8, 178.4; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{34}H_{34}O_6$, 538.2355; found, 538.2363.

*4-epi-Parvifloron C (4-epi-**2**).*[1] *n*-Butylamine (2.4 µl, 0.024 mmol) was added to a solution of **25** (2.6 mg, 0.0048 mmol) in benzene (0.2 ml). After stirring at rt for 42 h, the mixture was directly purified by silica gel column chromatography with EtOAc–hexane (1: 10) and RP-preparative TLC with acetonitrile–water (5 : 1) to afford 4-*epi*-**2** (0.6 mg, 0.0014 mmol, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 7.2 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.40 (s, 3H), 1.52–1,55 (m, 1H), 1.61 (s, 3H), 1.68–1.77 (m, 1H), 1.96–2.06 (m, 1H), 3.16 (sept, *J* = 7.2 Hz, 1H), 3.32–3.38 (m, 1H), 4.20 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 5.34 (br s, 1H), 6.35 (d, *J* = 6.8 Hz, 1H), 6.72 (d, *J* = 6.8 Hz, 1H), 6.86 (br d, *J* = 8.4 Hz, 2H), 6.93 (s, 1H), 7.74 (br s, 1H), 7.93 (d, *J* = 8.0 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 17.8, 21.7, 21.9, 25.0, 25.7, 26.9, 33.3, 35.0, 41.3, 43.2, 72.3, 115.3, 118.6, 122.6, 127.6, 127.9, 131.9, 133.3, 138.4, 141.6, 146.4, 160.1, 162.7, 166.2, 178.3; HRMS (FAB-TOF) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{31}O_5$, 435.2171; found, 435.2174.

*4-epi-Parvifloron E (4-epi-**3**).*[1] *n*-Butylamine (2.6 µl, 0.026 mmol) was added to a solution of **26d** (1.7 mg, 0.0026 mmol) in benzene (0.1 ml). After stirring at rt, for 1.5 h the mixture was directly purified by silica gel column chromatography with EtOAc–hexane (1: 3) to afford 4-*epi*-**3** (0.9 mg, 0.0020 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.39 (s, 3H), 1.41–1.46 (m, 1H), 1.61 (s, 3H), 1.67–1.76 (m, 3H), 1.96–2.95 (m, 1H), 3.16 (sept, *J* = 7.2 Hz, 1H), 3.35 (br d, *J* = 13.2 Hz, 1H), 3.55 (br s, 1H), 4.18 (d, *J* = 11.2 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 5.65 (br s, 1H), 6.34 (d, *J* = 6.4 Hz, 1H), 6.72 (d, *J* = 6.4 Hz, 1H), 6.90–6.92

(m, 2H), 7.51–7.58 (m, 2H), 7.69–7.73 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3CN, δ CD_3=1.3 ppm) δ: 18.3, 21.8, 22.0, 25.5, 25.9, 27.8, 34.0, 35.4, 42.1, 43.9, 72.7, 116.0, 117.1, 119.9, 123.2, 123.7, 128.3, 128.7, 134.3, 139.6, 142.2, 145.2, 147.2, 150.4, 163.2, 166.7, 179.0; HRMS (FAB-TOF) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{31}O_6$, 451.2121; found, 451.2113.

*Methyl (1R,4aS)-7-isopropyl-1,4a-dimethyl-5,6-dioxo-1,2,3,4,4a,5,6,9,10,10a-decahydrophenanthrene-1-carboxylate (**28**).* Ag_2O (30.8 mg, 0.13 mmol) was added to a solution of **15** (24.7 mg, 0.071 mmol) in anhyd CH_2Cl_2 (1.0 ml). After stirring at rt for 40 min under Ar, the mixture was filtered through celite with CH_2Cl_2 and the filtrate was concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1 : 20) to afford **28** (24.2 mg, 0.070 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.24 (s, 3H), 1.25 (s, 3H), 1.30–1.41 (m, 1H), 1.60–1.71 (m, 5H), 2.01 (d, *J* = 10.8 Hz, 1H), 2.46–2.49 (m, 2H), 2.75–2.78 (m, 1H), 2.90 (sept, *J* = 6.4 Hz, 1H), 3.68 (s, 3H), 6.38 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 16.5, 18.0, 20.2, 20.8, 21.4, 26.9, 33.3, 35.2, 36.7, 37.4, 45.5, 47.6, 52.0, 137.6, 144.1, 147.0, 148.0, 178.8, 179.9, 180.9; HRMS (FAB-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{28}O_4Na$, 367.1885; found, 367.1902.

*Methyl (1R,4aS)-5-hydroxy-7-isopropyl-1,4a-dimethyl-6-oxo-1,2,3,4,4a,6,10,10a-octahydrophenanthrene-1-carboxylate (**29**).* **28** (88.4 mg, 0.26 mmol) was dissolved in anhyd toluene (2.0 ml). After refluxing for 8 h under Ar, the solution was concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1 : 20) to afford **29** (79.6 mg, 0.23 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.22 (s, 3H), 1.32 (s, 3H), 1.63–1.81 (m, 5H), 2.13 (ddd, *J* = 2.4, 6.8, 19.2 Hz, 1H), 2.39–2.53 (m, 2H), 3.01–3.10 (m, 2H), 3.67 (s, 3H), 6.74 (dd, *J* = 3.2, 7.2 Hz, 1H), 6.78 (s, 1H), 7.47 (s, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 17.1, 18.2, 18.9, 21.5, 21.8, 26.6, 27.7, 36.0,

36.8, 38.1, 45.0, 47.3, 52.1, 126.5, 131.6, 136.1, 140.7, 143.8, 147.7, 178.5, 181.3; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{21}H_{28}O_4$, 344.1988; found, 344.1976.

*Methyl 12-(3-fluorobenzoyloxy)-11-hydroxyabieta-8,11,13-trien-18-oate (**30**).* 3-Fluorobenzoic acid (11.8 mg, 0.084 mmol), EDCI (0.014 ml, 0.079 mmol) and DMAP (1.1 mg, 0.009 mmol) were dissolved in anhyd CH_2Cl_2 (0.3 mL) and stirred at rt for 25 min. Then the mixture was added to a solution of **15** (22.9 mg, 0.066 mmol) in anhyd CH_2Cl_2 (0.7 mL). After stirring at rt for 210 min, the reaction was quenched with aqueous 10% NH_4Cl (4.0 ml). The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1 : 20) to afford **30** (10.5 mg, 0.022 mmol, 34%) and recovered **15** (10.1 mg, 0.029 mmol, 44%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.16 (d, *J* = 7.2 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 1.31–1.33 (m, 1H), 1.37 (s, 3H), 1.41–1.46 (m, 1H), 1.59–1.63 (m, 2H), 1.70–1.82 (m, 3H), 2.25 (d, *J* = 11.4 Hz, 1H), 2.79–2.85 (m, 2H), 2.89–2.96 (m, 1H), 3.13–3.17 (m, 1H), 3.68 (s, 3H), 5.12 (s, 1H), 6.61 (s, 1H), 7.39 (m, 1H), 7.52–7.55 (m, 1H), 7.90–7.92 (m, 1H), 8.03–8.05 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.3, 22.1, 22.9, 23.0, 27.6, 32.2, 35.7, 36.5, 38.9, 46.8, 48.4, 51.9, 117.2 (d, *J* = 23.1 Hz), 118.8, 121.3 (d, *J* = 21.6 Hz), 126.1, 130.6 (d, *J* = 7.2 Hz), 134.3, 134.7, 135.7, 137.7, 145.5, 162.7 (*J* = 247.1 Hz), 163.9, 179.3; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{28}H_{33}FO_5$, 468.2312; found, 468.2294.

*Methyl 12-(3-bromobenzoyloxy)-11-hydroxyabieta-8,11,13-trien-18-oate (**31**).* The same procedure as described for **30** was performed using 3-bromobenzoic acid (14.4 mg, 0.072 mmol) and **16** (21.0 mg, 0.061 mmol) with reaction time of 150 min to afford **31** (7.0 mg, 0.013 mmol, 22%) and recovered **16** (7.4 mg, 0.021 mmol, 35%).^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.16 (d, *J* = 7.2 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 1.30–1.33 (m, 1H), 1.37 (s, 3H), 1.40–1.45 (m,

1H), 1.59–1.63 (m, 1H), 1.70–1.82 (m, 3H), 2.25 (d, J = 11.4 Hz, 1H), 2.79–2.84 (m, 2H), 2.90–2.96 (m, 1H), 3.12–3.16 (m, 1H), 3.68 (s, 3H), 5.09 (s, 1H), 6.61 (s, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.81 (ddd, J = 1.2, 1.8, 7.8 Hz, 1H), 8.17 (ddd, J = 1.8, 1.8, 7.8 Hz, 1H), 8.37 (t, J = 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.3, 22.1, 22.9, 23.1, 27.6, 32.2, 35.7, 36.5, 38.9, 46.8, 48.4, 52.0, 118.8, 122.9, 128.9, 130.4, 130.5, 133.3, 134.2, 134.6, 135.7, 137.1, 137.7, 145.5, 163.7, 179.3; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{28}H_{33}BrO_5$, 528.1511; found, 528.1485.

*Methyl 11-hydroxyabieta-12-(3-iodebenzoyloxy)-8,11,13-trien-18-oate (**32**).* The same procedure as described for **30** was performed using 3-iodebenzoic acid (22.1 mg, 0.089 mmol) and **16** (26.0 mg, 0.075 mmol) with reaction time of 40 min to afford **32** (9.6 mg, 0.017 mmol, 22%) and recovered **16** (16.2 mg, 0.047 mmol, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.16 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.29 (s, 3H), 1.30–1.34 (m, 1H), 1.37 (s, 3H), 1.57–1.80 (m 5H), 2.25 (d, J = 10.8 Hz, 1H), 2.77–2.98 (m, 3H), 3.10–3.15 (m, 1H), 3.68 (s, 3H), 5.07 (s, 1H), 6.60 (s, 1H), 7.29–7.33 (m, 1H), 8.01 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 7.6 Hz, 1H), 8.56–8.57 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.3, 22.1, 22.9, 23.1, 27.6, 31.0, 32.2, 35.7, 36.5, 38.9, 46.8, 48.4, 52.0, 94.2, 118.8, 129.5, 130.5, 134.2, 134.6, 135.7, 137.7, 139.1, 142.9, 145.5, 163.6, 179.3; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{28}H_{33}IO_5$,576.1373; found,576.1358.

*Methyl 11-hydroxyabieta-12-(3-nitrobenzoyloxy)-8,11,13-trien-18-oate (**33**).* The same procedure as described for **30** was performed using 3-nitrobenzoic acid (12.2 mg, 0.073 mmol) and **16** (20.4 mg, 0.059 mmol) with reaction time of 30 min to afford **33** (5.3 mg, 0.011 mmol, 18%) and recovered **15** (6.0 mg, 0.017 mmol, 29%). ^1H NMR (600 MHz, $CDCl_3$) δ: 1.17 (d, J = 7.2 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H), 1.29 (s, 3H), 1.30–1.34 (m, 1H), 1.38 (s, 3H), 1.42–1.47 (m, 1H), 1.59–1.64 (m, 1H), 1.70–1.82 (m, 3H), 2.26 (d, J = 12.0 Hz, 1H), 2.79–2.85 (m, 2H), 2.91–2.97 (m, 1H), 3.12 (br d, J = 13.8 Hz, 1H), 3,69 (s, 3H), 5.03 (s, 1H), 6.63 (s, 1H), 7.78 (t, J = 7.8 Hz, 1H),

8.53–8.57 (m, 2H), 9.07–9.08 (m, 1H); $^{13}C\{^{1}H\}$ NMR (600 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.3, 22.0, 22.9, 23.1, 27.7, 32.2, 35.8, 36.4, 38.9, 46.7, 48.3, 52.0, 119.0, 125.2, 128.5, 130.2, 130.4, 134.5, 134.6, 135.9, 137.6, 145.3, 148.5, 163.0, 179.2; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{28}H_{33}NO_7$, 495.2257; found, 495.2249.

*Methyl 12-(3,5-dichlorobenzoyloxy)-11-hydroxyabieta-8,11,13-trien-18-oate (**34**)*. The same procedure as described for **33** was performed using 3,5-dichlorobenzoic acid (15.0 mg, 0.079 mmol) and **16** (22.7 mg, 0.066 mmol) to afford **34** (5.6 mg, 0.011 mmol, 19%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.16 (d, J = 6.6 Hz, 3H), 1.18 (d, J = 6.6 Hz, 3H), 1.29 (s, 3H), 1.31–1.33 (m, 1H), 1.36 (s, 3H), 1.40–1.46 (m, 1H), 1.59–1.63 (m, 2H), 1.69–1.82 (m, 3H), 2.23 (d, J = 12.0 Hz, 1H), 2.75–2.82 (m, 2H), 2.90–2.96 (m, 1H), 3.12 (br d, J = 13.8 Hz, 1H), 3.68 (s, 3H), 4.99 (s, 1H), 6.61 (s, 1H), 7.66–7.67 (m, 1H), 8.09–8.11 (m, 2H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.3, 22.1, 22.9, 23.1, 27.6, 32.2, 35.8, 36.4, 38.9, 46.7, 48.3, 51.9, 118.9, 128.66, 128.74, 131.5, 133.9, 134.4, 134.5, 135.8, 135.9, 137.6, 145.3, 162.8, 179.2; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{28}H_{32}Cl_2O_5$, 518.1627; found, 518.1638.

*Methyl 12-(4-chlorobenzoyloxy)-11-hydroxyabieta-8,11,13-trien-18-oate (**35**)*. The same procedure as described for **33** was performed using 4-chlorobenzoic acid (8.2 mg, 0.052 mmol) and **16** (14.9 mg, 0.043 mmol) to afford **35** (6.4 mg, 0.013 mmol, 31%) and recovered **16** (8.1 mg, 0.023 mmol, 54%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.15 (d, J = 7.2 Hz, 3H), 1.18 (d. J = 7.2 Hz, 3H), 1.29 (s, 3H), 1.30–1.32 (m, 1H), 1.37 (s, 3H), 1.40–1.45 (m, 1H), 1.59–1.63 (m, 2H), 1.70–1.82 (m, 3H), 2.25 (d, J = 11.4 Hz, 1H), 2.78–2.84 (m, 2H), 2.99–2.96 (m, 1H), 3.13–3.17 (m, 1H), 3.68 (s, 3H), 5.14 (s, 1H), 6.60 (s, 1H), 7.52 (d, J = 9.0 Hz, 2H), 8.17 (d, J = 7.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.3, 22.1, 22.9, 23.0, 27.6, 32.2, 35.7, 36.5, 38.9,

46.8, 48.4, 51.9, 118.8, 127.0, 129.3, 131.7, 134.3, 134.7, 135.6, 137.7, 140.8, 145.6, 164.2, 179.3; HRMS (FAB-TOF) *m/z*: $[M]^+$ calcd for $C_{28}H_{33}ClO_5$, 484.2017; found, 484.2019.

*Methyl 12-benzoyloxy-11-hydroxyabieta-8,11,13-trien-18-oate (**36**).* The same procedure as described for **30** was performed using benzoic acid (6.9 mg, 0.056 mmol) and **16** (15.7 mg, 0.045 mmol) with reaction time of 20 h to afford **36** (3.8 mg, 0.0084 mmol, 19%). ^{1}H NMR spectroscopic data was identical to those in the literature.[12]

*Methyl 11-hydroxyabieta-12-(3-methoxybenzoyloxy)-8,11,13-trien-18-oate (**37**).* The same procedure as described for **30** was performed using 3-methoxybenzoic acid (13.3 mg, 0.087 mmol) and **16** (25.3 mg, 0.073 mmol) with reaction time of 240 min to afford **37** (10.8 mg, 0.022 mmol, 22%) and recovered **16** (6.2 mg, 0.018 mmol, 25%).^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.16 (d, *J* = 7.2 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 1.30–1.34 (m, 1H), 1.37 (s, 3H), 1.41–1.45 (s, 1H), 1.59–1.63 (m, 2H), 1.70–1.82 (m, 3H), 2.26 (d, *J* = 11.4 Hz, 1H), 2.79–2.96 (m, 3H), 3.15–3.18 (m, 1H), 3.68 (s, 3H), 3.89 (s, 3H), 5.20 (s, 1H), 6.60 (s, 1H), 7.21–7.23 (m, 1H), 7.45 (t, *J* = 8.4 Hz, 1H), 7.73–7.74 (m, 1H), 7.84–7.85 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.2, 22.1, 22.9, 23.0, 27.6, 32.2, 35.7, 36.5, 38.9, 46.8, 48.4, 51.9, 55.6, 114.7, 118.7, 120.7, 122.7, 129.8, 129.9, 134.1, 134.8, 135.5, 137.8, 145.6, 159.8, 164.9, 179.3; HRMS (FAB-TOF) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{37}O_6$, 481.2590; found, 481.2578.

*Methyl 11-hydroxyabieta-12-(4-methoxybenzoyloxy)-8,11,13-trien-18-oate (**38**)*

The same procedure as described for **33** was performed using 4-methoxybenzoic acid (18.6 mg, 0.12 mmol) and **16** (35.7 mg, 0.043 mmol) to afford **38** (9.0 mg, 0.019 mmol, 19%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.16 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.29 (s, 3H), 1.30–1.32 (m, 1H), 1.37 (s, 3H), 1.40–1.45 (m, 1H), 1.59–1.62 (m, 2H), 1.70–1.82 (m, 3H), 2.25 (d, *J* = 11.4 Hz, 1H), 2.78–2.96 (m, 3H), 3.15–3.20 (m, 1H), 3.68 (s, 3H), 3.91 (s, 3H), 5.29 (s, 1H), 6.59 (s, 1H),

7.00–7.03 (m,2H), 8.18–8.20 (m, 2H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.2, 22.1, 22.9, 23.0, 27.6, 32.2, 35.7, 36.5, 38.9, 46.8, 48.4, 51.9, 55.6, 114.1, 118.6, 120.8, 132.6, 134.1, 134.9, 135.3, 137.9, 145.8, 164.3, 164.8, 179.3; HRMS (FAB-TOF) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{37}O_6$, 481.2590; found, 481.2602.

*Methyl 11-hydroxyabieta-12-naphthoyloxy-8,11,13-trien-18-oate (**39**).* The same procedure as described for **33** was performed using 2-naphthoic acid (14.4 mg, 0.084 mmol) and **16** (24.3 mg, 0.070 mmol) to afford **39** (9.7 mg, 0.019 mmol, 28%) and recovered **16** (15.0 mg, 0.043 mmol, 62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.30 (s, 3H), 1.31–1.34 (m, 1H), 1.39 (s, 3H), 1.42–1.48 (m, 1H), 1.59–1.63 (m, 2H), 1.72–1.81 (m, 3H), 2.28 (d, *J* = 10.8 Hz, 1H), 2.80–2.84 (m, 1H), 2.89–2.98 (m, 2H) 3.18 (br d, *J* = 14.4 Hz, 1H), 3.69 (s, 3H), 5.27 (s, 1H), 6.63 (s, 1H), 7.61 (br t, *J* = 6.6 Hz, 1H), 7.67 (br t, *J* = 7.2 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 8.22 (dd, *J* = 1.8, 8.4 Hz, 1H), 8.84 (s, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.2, 22.1, 22.9, 23.1, 27.6, 32.2, 35.7, 36.5, 38.9, 46.8, 48.4, 51.9, 118.7, 125.4, 125.7, 127.0, 127.9, 128.7, 129.0, 129.6, 132.3, 132.5, 134.1, 134.9, 135.5, 136.0, 137.9, 145.7, 165.2, 179.3; HRMS (FAB-TOF) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{37}O_5$, 501.2641; found, 501.2632.

*Methyl 12-(3-biphenyloxy)-11-hydroxyabieta-8,11,13-trien-18-oate (**40**).* The same procedure as described for **33** was performed using 3-biphenylcarboxylic acid (16.6 mg, 0.083 mmol) and **16** (24.0 mg, 0.069 mmol) to afford **40** (12.4 mg, 0.024 mmol, 34%) and recovered **16** (10.2 mg, 0.029 mmol, 43%).^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.18 (d, *J* = 7.2 Hz, 3H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 1.31–1.33 (m, 1H), 1.38 (s, 3H), 1.42–1.46 (m, 1H), 1.59–1.63 (m, 2H), 1.71–1.83 (m, 3H), 2.26 (d, *J* = 11.4 Hz, 1H), 2.79–2.97 (m, 3H), 3.17 (d, *J* = 13.8 Hz, 1H), 3.68 (s, 3H), 5.23 (s, 1H), 6.61 (s, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.62 (t, *J* = 7.8 Hz,

1H), 7.64–7.67 (m, 2H), 7.90–7.92 (m, 1H), 8.21–8.23 (m, 1H), 8.46 (t, J = 1.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (600 MHz, $CDCl_3$) δ: 16.9, 18.6, 20.2, 22.1, 23.0, 23.1, 27.6, 32.2, 35.7, 36.5, 38.9, 118.7, 127.2, 128.0, 129.0, 129.1, 129.2, 129.3, 132.7, 135.5, 137.8, 142.1, 145.6, 165.0, 179.3; HRMS (FAB-TOF) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{39}O_5$, 527.2797; found, 527.2789.

Antiproliferative Activity Assay. Antiprolierative activity of analogues was performed as described before.[13] Briefly, all stock celll lines were grown in T-75 flasks at 37 °C with 5% CO_2 in air. Freshly trypsinized cell suspensions were seeded in 96-well microtiter plates at densities of 4,000-11,000 cells per well with compounds. After 72 h in culture with test compounds, cells were fixed in 10% trichloroacetic acid and then stained with 0.04% sulforhodamine B. The absorbance at 515 nm was measured using a microplate reader (ELx800, BioTek) operated by Gen5 software (BioTek) after solubilizing the bound dye with 10 mM Tris base. The IC_{50} was calculated from at least three independent experiments of duplication for an assay. All values presented are statistically significant. A549, KB, MDA-MB-231 and MCF-7 were obtained from the Lineberger comprehensive Cancer Center (UNC-CH) or from ATCC (Manassas, VA). KB-VIN was a generous gift of Professor Y.-C. Cheng (Yale University). We confirmed our KB and KB-VIN are identical to AV-3 (ATCC number, CCL-21) as a HeLa (cervical carcinoma) contaminant by short tandem repeat (STR) profiling. Cells were cultured in RPMI-1640 medium supplemented with 2 mM $_L$-glutamine and 25 mM HEPES (Mediatech), supplemented with 10% fetal bovine serum (Specialized Media), 100 μg/mL streptomycin, and 100 IU penicillin. MDR stock cells (KB-VIN) were maintained in the presence of 100 nM vincristine.

Cell Cycle Analysis. Cell cycle was evaluated by measurement of the DNA content by propidium iodide (PI) (BD Biosciences) staining as described previously.[14] Briefly, 1×10^5 MDA-MB-231 cells were seeded in 12-well culture plate 24 h prior to treatment with compounds. Cells were

treated with 1 × and 3 × IC_{50} μM for **30**, **31**, **33**, and **37**, 25 μM (1× IC_{50}) 5-fluorouracil (5-FU), and 0.1 μM (3× IC_{50}) combretastatin A-4 (CA-4). Vehicle (DMSO) was used as a control. Harvested cells were washed with PBS and fixed in 70% EtOH at -20 °C for overnight followed by staining with PI containing RNase (BD Biosciences) at 37 °C for 30 min. Stained cells were analyzed by flow cytometer (LSRFortessa, BD Biosciences). Experiments were repeated a minimum of three times.

ASSOCIATED CONTENT

Supporting Information Available: These materials are available free of charge via the Internet at http://pubs.acs.org.

NMR spectra for compounds *epi*-**1**–**3**, **6**–**20**, **22**, **25**, **26b**, **26d**, and **27**–**40** as well as the standard deviation for Table 2. (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Rüedi, P.; Eugster, C. H. Diterpenoide Drüsenfarbstoffe aus Labiaten: 6 neue p - Chinomethane aus *Plectranthus parviflorus* WILLD, *Helv. Chim. Acta*, **1978**, *61*, 709–715.

(2) Alder, A. C. A.; Rüedi, P.; Eugster, C. H. Drüsenfarbstoffe aus tropischen Labiaten: Parviflorone aus *Plectranthus strigosus* BENTH. *Helv. Chim. Acta*, **1984**, *67*, 1531–1534.

(3) Saito, Y.; Goto, M.; Nakagawa-Goto, K. Total Synthesis of Antiproliferative Parvifloron F, *Org. Lett.* **2018**, *20,* 628–631.

(4) Kumar, P.; Aggarwal, R. An overview of triple-negative breast cancer, *Arch. Gynecol. Obstet*. **2016**, *293*, 247–269.

(5) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Ramos, J. M.; Guardia, J. J.; Messouri, I.; Chayboun, I.; Mansour, A. I.; Dahdouh, A. Synthesis of (+)-Hanagokenol A, (+)-Fortunins E, G, H, and (-)-Sugikurojin A from Abietic Acid, *Synthesis* **2010,** *20*, 3493–3503.

(6) Tada, M.; Ishimaru, K. Efficient ortho-Oxidation of Phenol and Synthesis of Anti-MRSA and Anti-VRE Compound Abietaquinone Methide from Dehydroabietic Acid, *Chem. Pharm. Bull*. **2006**, *54*, 1412–1417.

(7) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Lachkar, M.; Messouri, I. First Synthesis of Picealactone C. A New Route Toward Taxodione-related Terpenoids from Abietic Acid, *Tetrahedron Lett*. **2007**, *48*, 989–992.

(8) Haslinger, E.; Michl, G. Synthesis of (+)-Taxodione from (−)-Abietic Acid, *Tetrahedron Lett*. **1988**, *29*, 5751–5754.

(9) Simoes, M. F.; Rijo P., Duarte, A.; Matias, D.; Rodriguez, B. An Easy and Stereoselective Rearrangement of an Abietane Diterpenoid into a Bioactive Microstegiol Derivative, *Phytochemistry Lett.* **2010**, *3*, 234–237.

(10) Tofani, D.; Balducci, V.; Gasperi, T.; Incerpi, S.; Gambacorta, A. Fatty Acid Hydroxytyrosyl Esters: Structure/Antioxidant Activity Relationship by ABTS and in Cell-Culture DCF Assays, *J. Agric. Food Chem*. **2010**, *58*, 5292–5299.

(11) Bell, K. H. Facile Selective Aminolysis of Phenolic Benzoates with 1-Butanamine in Benzene, *Tetrahedron Lett*. **1986**, *27*, 2263–2264.

(12) Gigante, B.; Santos, C.; Silva, A. M.; Curto, M. J.; Nascimento, M. S.; Pinto, E.; Pedro, M.; Cerqueira, F.; Pinto, M. M.; Duarte, M. P.; Laires, A.; Rueff, J.; Gonçalves, J.; Pegado, M. I.; Valdeira, M. L. Catechols from Abietic Acid: Synthesis and Evaluation as Bioactive Compounds, *Bioorg. Med. Chem*. **2003**, *11*, 1631–1638.

(13) Nakagawa-Goto, K.; Oda, A.; Hamel, E.; Ohkoshi, E.; Lee, K. H.; Goto, M. Development of a Novel Class of Tubulin Inhibitor from Desmosdumotin B with a Hydroxylated Bicyclic B-Ring, *J. Med. Chem.* **2015**, *58*, 2378−2389.

(14) Nakagawa-Goto, K.; Taniguchi, Y.; Watanabe, Y.; Oda, A.; Ohkoshi, E.; Hamel, E.; Lee, K. H.; Goto, M. Triethylated Chromones with Substituted Naphthalenes as Tubulin Inhibitors, *Bioorg. Med. Chem*. **2016**, *24*, 6048−6057.

Graphical Abstract