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Total Synthesis of Antiproliferative Parvifloron F

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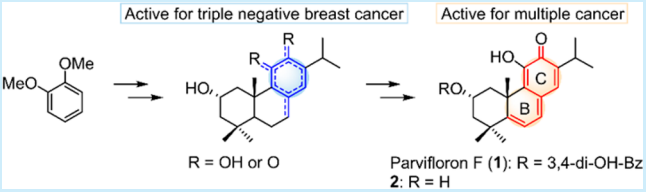
Supporting Information

ABSTRACT: The first total synthesis of parvifloron F, a bioactive highly oxidized abietane diterpene, was achieved. The abietane skeleton was constructed by Lewis acid promoted cyclization. Preliminary structure−activity relationship correlations were established for the synthetic intermediates against human tumor cell lines. Certain compounds showed unique selective antiproliferative activity against triple-negative breast cancer. The oxidation level of the abietane ring affected the selectivity.



Plectranthus, a genus of family Lamiaceae, contains about 300 species. It has been widely used as traditional medicine in Tropical Africa, Asia, and Australia for digestive, skin, and respiratory diseases.[1] Phytochemical studies on *Plectranthus* have discovered various types of abietane diterpenes, such as parviflorons (Pfs).[2] Among them, Pfs-D, -F (**1**), and -G contain a different benzoate group at the C-2 position (Figure 1). Pf-F

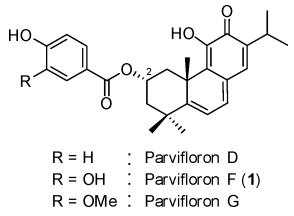
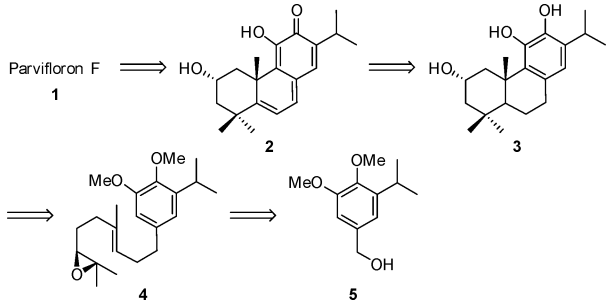


Figure 1. Structure of parvifloron D, F, and G.

(**1**) was first isolated from *P. parviflorus* together with Pf-D and Pf-G was separated from *P. strigosus* by Eugster et al. in 1978[3] and 1984,[4] respectively. In 2001, **1** was also isolated from *P. nummularius* by Narukawa et al.[5] Compound **1** exhibits multiple biological effects, including DPPH radical scavenging activity (EC_{50} 0.13 mM),[5] antibacterial activity against *Listeria monocytogenes* (MIC 31.2 μg/mL) and *Mycobacterium tuberculosis* (MIC 95 μg/mL), antiproliferative activity against the Vero cell line (IC_{50} 1.6 μg/mL), and tyrosinase inhibitory activity.[6] In addition, our original study revealed potent antiproliferative activity against several human tumor cell lines (HTCLs). However, the total synthesis and structure−activity relationship (SAR) correlations of **1** have not been reported despite its attractive biological activities. Herein, we describe the first total synthesis of **1** and the antiproliferative activity of synthetic intermediates against HTCLs.

As shown in Scheme 1, a retrosynthetic analysis suggested that esterification of quinone methide **2** with protocatechuic acid

Scheme 1. Retrosynthetic Analysis of Parvifloron F



would provide **1**. Intermediate **2** could be generated through the repeated oxidation and isomerization of catechol **3**, prepared by biomimetic cyclization of epoxide **4**. Epoxide **4** could be synthesized by an S_N2 reaction of a dithiane intermediate produced by reacting benzylalcohol **5** with a chiral epoxygeranyl bromide.

Accordingly, benzylalcohol **5** was synthesized via isopropylation[7] of veratrole followed successively by a Friedel−Crafts acylation,[8] haloform reaction,[8] and reduction.[9] IBX oxidation of **5** gave benzaldehyde **6**, which was converted to the desired dithioacetal **7**[10] (Scheme 2). Lithiation of **7** with *t*-BuLi followed by addition of chiral epoxygeranyl bromide **8**[11] provided epoxide **9** in 76% yield. Reductive desulfurization of the dithiane moiety[12] on **9** with AIBN and Bu_3SnH afforded the cyclization precursor **4** in 86% yield.

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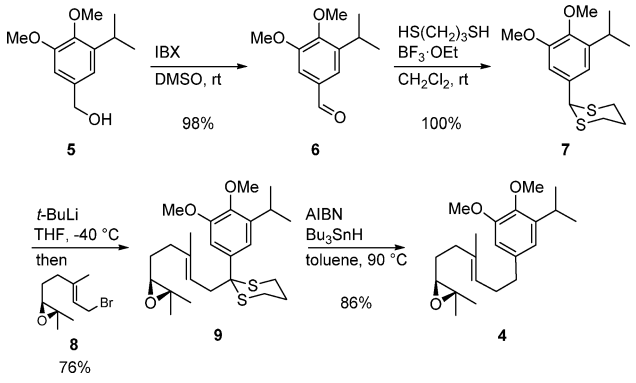
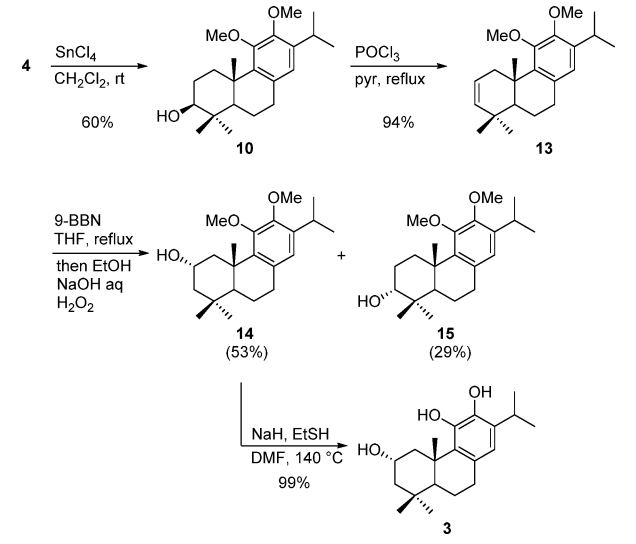
Scheme 2. Synthesis of Epoxide 4



Cyclization of **4** was successfully accomplished by the use of tin(IV) chloride as a Lewis acid[13] at room temperature to provide the desired product **10** in good yield (Scheme 3). Other Lewis

Scheme 3. Synthesis of Catechol 3



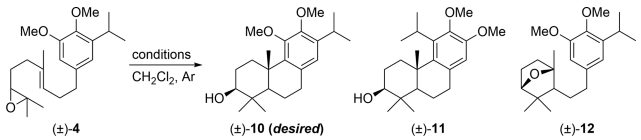
acids, such as boron trifluoride diethyl etherate and titanium(IV) chloride, were tested under various conditions for the cyclization of (±)-**4**, which was prepared separately. However, the desired (±)-**10** was obtained in poor yield due to the formation of (±)-**11**, which was formed by cyclization at an undesired position, and oxabicyclo[2.2.1]heptane[14] [(±)-**12**] (Table 1).

Olefination of **10** with phosphoryl chloride[15] proceeded well to generate **13**. Hydroboration−oxidation of **13** with 9-BBN gave **14** with a hydroxyl at C-2 in 53% yield and its regioisomer **15** with a hydroxyl at C-3 in 29% yield. Deprotection of the methoxy groups using sodium hydride and ethanethiol with heating[16] provided catechol **3**.

Oxidation of **3** with Ag_2O[17] provided quinone **16**, and subsequent isomerization under reflux afforded *o*-hydroxy-*p*-quinone methide **17** in good yield (Scheme 4). Unexpectedly, compound **17** did not isomerize to the related catechol **18** under the reflux conditions.[17] However, when the reaction was carried out under neat conditions, further isomerization did occur to produce **18** in 58% yield (77%, based on recovered starting material; brsm). The same reaction sequence from **3** to **17** was then applied to **18** to obtain the ester precursor **2**. The subsequent esterification step was more difficult than expected, likely because the compound skeleton was unstable under acidic conditions and migration/decomposition could occur readily through a C-10 carbonium cation.[18] In fact, the esterification of **2** with protocatechuic acid protected as its orthoester proceeded in moderate yield, but the subsequent deprotection of the protecting group with *p*-toluenesulfonic acid monohydrate or Amberlyst 15 resulted in low yield and reproducibility. When the esterification reaction was attempted with unprotected protocatechuic acid, only the starting material (**2**) was recovered. Finally, because phenolic benzoates can be removed under mild basic conditions,[19] compound **2** was esterified successfully via a Shiina reaction under basic conditions[20] with protocatechuic acid protected as its dibenzoate (**20**).[21] The condensation produced the desired **21** in 24% yield along with the unexpected unsubstituted benzoate **22** in 31% yield. The latter compound was produced when the hydroxyl group of **2** attacked the protected benzoate moiety rather than the activated carboxylic anhydride. The selective removal of the phenolic benzoate groups in **21** using *n*-butyl amine[22] proceeded smoothly to give **1** in 68% yield. It should be noted that the reaction proceeded well in spite of the presence of a nucleophile. The spectroscopic data of the synthetic sample were identical with those of the natural product.

We next focused on the antiproliferative activity of the synthetic compounds against HTCLs.[23] Compounds **10**, **13**, and **14** containing methoxy groups exhibited moderate activity. Interestingly, catechol **3**, *o*-quinone **16**, and *o*-hydroxy-*p*-quinone methide **17** showed 4-fold selectivity against triple-negative breast cancer (TNBC) cell line MDA-MB-231 compared with A549 (Table 2).

Table 1. Cyclization Conditions of Racemic 4 Using Several Lewis Acids



entry	conditions	temp	workup	products
1	BF_3·OEt_2 (1.2 equiv), 1.5 h	−78 °C	H_2O	**10** (19%), **12** (33%)
2	BF_3·OEt_2 (1.2 equiv), 1 h	−78 °C	TEA (1.2 equiv), $NaHCO_3$ aq	**10**:**11** = 1:1 (40%), **12** (16%)
3	$SnCl_4$ (1.2 equiv), 1 h	−78 °C	TEA (1.2 equiv), $NaHCO_3$ aq	**10**:**11** = 5:4 (36%), **12** (23%)
4	BF_3·OEt_2 (1.2 equiv), 1 h	−20 to 0 °C	H_2O	**10** (27%), **12** (49%)
5	$SnCl_4$ (1.2 equiv), 2 h	−20 to 0 °C	H_2O	**10** (47%), **12** (30%)
6	$TiCl_4$ (1.2 equiv), 2 h	−20 to 0 °C	H_2O	**10** (35%), **12** (8%)
7	$SnCl_4$ (1.2 equiv), 1 h	room temp	H_2O	**10** (60%), **12** (5%)

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Scheme 4. Synthesis of Parvifloron F

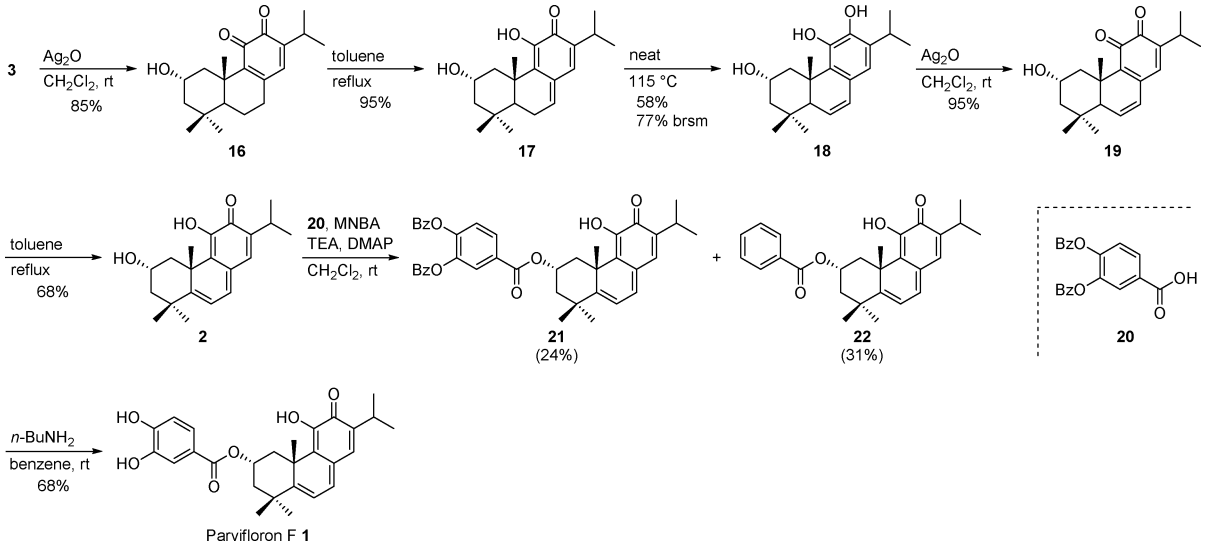

Table 2. Antiproliferative Activity of Synthetic Compounds against Human Tumor Cell Lines

	cell lines[a]/IC_{50} (μM)[b]				
compd	A549	KB	KB-VIN	MDA-MB-231	MCF-7
compounds containing methoxy group					
10	>40	>40	>40	>40	>40
13	>40	>40	>40	>40	39.70
14	25.38	22.34	20.50	>40	30.73
compounds showing selectivity against triple-negative breast cancer					
3	19.45	15.72	19.89	5.13	13.53
16	20.44	18.49	21.43	5.14	15.17
17	20.12	19.36	21.42	5.18	16.19
compounds showing broad spectrum antiproliferative activity					
19	8.36	8.04	19.59	5.16	10.11
2	4.91	5.47	5.62	5.01	5.02
1	4.64	4.49	4.75	4.99	4.67
1 (NP)[c]	4.92	4.74	4.70	4.91	4.74
(±)-**1**	4.67	5.03	4.97	5.15	5.36
PXL (nM)	6.97	6.63	1969	8.96	10.96

[a]Lung carcinoma (A549), originally isolated from epidermoid carcinoma of the nasopharynx (KB), MDR subline of KB overexpressing P-glycoprotein (KB-VIN), triple-negative breast cancer (MDA-MB-231) and breast cancer (MCF-7) were used for antiproliferative activity evaluation of synthetic compounds. [b]Antiproliferative activity as IC_{50} values for each cell line; the concentration of compound that caused 50% reduction of cell growth relative to untreated cells determined by the sulforhodamine B assay. [c]Natural Product (NP).

The results suggested that the oxidation level of the abietane ring might be important for the selective TNBC antiproliferative activity. Compound **2** with a free hydroxyl at C-2 was equipotent to the natural product **1**. Thus, the ester moiety of **1** did not affect the antiproliferative activity against the tested HTCLs and presumably is hydrolyzed by cellular esterase. In addition, the stereochemistry did not influence the activity, since (±)-**1**, prepared by the same reaction sequence using (±)-**8**, and **1** were equipotent.

In summary, we have achieved the first total synthesis of Pf-F (**1**) with 0.94% overall yield from benzylalcohol **5**. All synthesized abietane derivatives were evaluated for antiproliferative activity against several HTCLs. The SAR study indicated that the oxidation level of the abietane ring affected antiproliferative selectivity against HTCLs. Compounds **3**, **16**, and **17** showed selective activity against TNBC MDA-MB-231.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03763.

Experimental procedures and spectroscopic data for synthetic compounds (PDF)

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Notes

The authors declare no competing financial interest.

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