Synthesis and Biological Evaluation of (±)-Abyssinone II and Its Analogues as Aromatase Inhibitors for Chemoprevention of Breast Cancer

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An efficient and economical synthesis of the naturally occurring aromatase inhibitor abyssinone II was performed. The synthesis features an optimized aromatic prenylation reaction in which an arylcopper intermediate is reacted with prenyl bromide to afford a key intermediate that was converted to a prenylated aromatic aldehyde. Condensation of the aldehyde with an *o*-hydroxyacetophenone under Claisen−Schmidt conditions afforded a chalcone that was deprotected and cyclized in the presence of sodium acetate in refluxing ethanol to afford (±)-abyssinone II. The synthesis proved to be versatile enough to provide an array of abyssinone II derivatives that were evaluated as aromatase inhibitors. Methylation of the 4′-hydroxyl group of (±)-abyssinone II resulted in a significant increase in aromatase inhibitory activity, and further smaller increases in activity resulted from the methylation of the 7-hydroxyl group and removal of the prenyl side chain. As a result of these structural changes, the most active flavanone of the series was 20 times more potent than (±)-abyssinone II (IC_{50} 40.95 μM).

Introduction

Breast cancer, the second leading cause of cancer deaths, is the most commonly diagnosed cancer among postmenopausal women. The World Health Organization has estimated that more than 1.2 million people will be diagnosed with breast cancer this year worldwide, including more than 180 000 in the United States.[1] The role of estrogens in the development of breast cancer is well established, with the majority of postmenopausal women having hormone receptor-positive tumors.[2−4] One strategy for the treatment of these cancers is to decrease estrogen production.[5,6] Aromatase, a key cytochrome P450 enzyme, catalyzes the rate-limiting aromatization step for the conversion of androgens (testosterone and androstenedione) to estrogens (estradiol and estrone).[7] This pathway is the main source of estrogen in postmenopausal women. Because estrogen production is the last step in the biosynthetic sequence of steroid production, selective inhibition of aromatase would not interfere with the production of other useful steroids, such as adrenal corticoids. Therefore, aromatase inhibitors (AIs[a]) have become attractive therapeutic agents in the treatment of estrogen-dependent breast cancers.[8−14] Additionally, a role for estrogens in prostate neoplasia has been recently postulated.[5,6]

In the last two decades, several classes of steroidal and nonsteroidal AIs such as aminoglutethimide and imidazole or triazole derivatives have been designed.[8−14] The first FDA-approved AI, aminoglutethimide, has shown some clinical benefit in breast cancer trials, but lack of selectivity and its weak aromatase inhibitory activity has limited its usefulness.[10] Other AIs recently approved by the FDA include the nonsteroidals anastrazole[15] and letrozole,[16] as well as the steroid exemestane[17] that, like all AIs, inhibit the synthesis of estrogen in tissues other than the ovaries and also causes several severe adverse effects.

Besides the development of synthetic AIs, there is a continuing search for new classes of natural products that inhibit aromatase to discover novel breast cancer chemopreventive agents. Prenylated flavonoids are of current interest due to their unique structures and aromatase inhibitory activities. (2*S*)-Abyssinone II, a naturally occurring prenylated flavonoid from the Chinese medicinal plant *Broussonetia papyrifera*, has recently become a focal point of our ongoing program for isolation, structure elucidation, and biological investigation of chemopreventive natural products.[18−23] Previous results from our group have shown significant inhibitory activity of (2*S*)-abyssinone II **(1)** in the aromatase assay, with an IC_{50} of 0.37 μM observed using the radiometric method.[23] Abyssinone II was selected as one of the chemopreventive agents for further studies under the Rapid Access to Preventive Intervention Development (RAPID) program of the National Cancer Institute. Recently, Moriarty et al. reported IC_{50} values of 0.6 μM (radiometric method) and 62 μM (fluorimetric high throughput method) of their synthetic racemic abyssinone II.[24] The excellent potency of abyssinone II and limited availability from natural sources, as well as the recently reported low-yielding synthesis by Moriarty et al.,[24] prompted us to explore the development of an efficient and economical synthetic route to racemic abyssinone II that would allow access to large quantities for testing in animal models.

In this article, we describe a practical synthesis and in vitro biological evaluation of racemic abyssinone II and a series of structurally analogous AIs, together with a discussion of their structure−activity relationships. All of the new analogues were tested in a CYP 19 (aromatase) inhibition assay to obtain a preliminary biological profile of the series that will be useful in the further design and development of flavonoid AIs.

Chemistry

A retrosynthetic analysis of (±)-abyssinone is outlined in Scheme 1. The key steps are the application of an aryl−allyl

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[a] Abbreviations: AI, aromatase inhibitor; MOMCl, methoxymethylene chloride, DIPEA, *N*,*N*-diisopropylethylamine; LiHMDS, lithium hexamethyldisilazide; THF, tetrahydrofuran.

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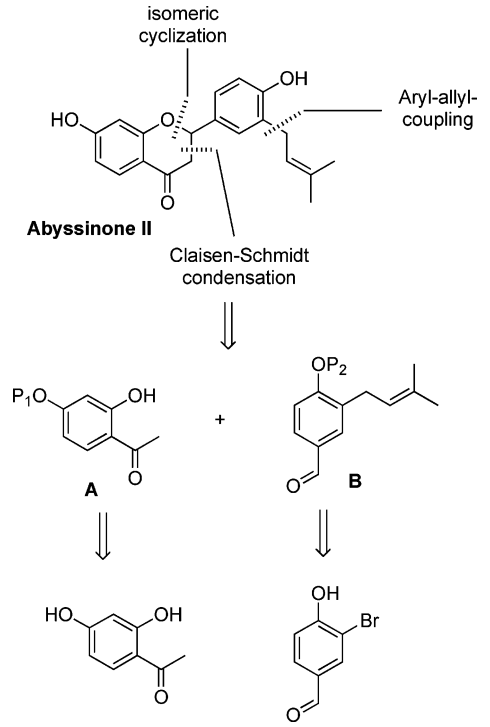
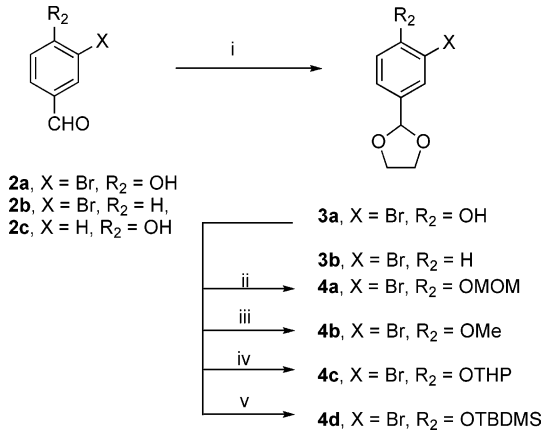
Scheme 1. Retrosynthetic Analysis for the Synthesis of Abyssinone II and Its Analogues



Scheme 2[a]



[a] Reagents and conditions: (i) $(CH_2OH)_2$, *p*-TsOH, Dean−Stark trap, toluene, reflux, 24 h; (ii) MOMCl, DIPEA, CH_2Cl_2, rt; (iii) K_2CO_3, $(CH_3)_2SO_4$, CH_3COCH_3, rt; (iv) DHP, CH_2Cl_2, *p*-TsOH, rt; (v) TBDMSCl, imidazole, CH_2Cl_2.

coupling reaction using an alkyl cuprate as a coupling reagent to introduce the prenyl side chain and a Claisen−Schmidt condensation and cyclization to produce the desired flavanone.

Our strategy toward efficient large scale synthesis of abyssinone II was based on the development of a practical procedure to synthesize a key prenylated synthon. Aldehyde protection of commercially available 3-bromo-4-hydroxybenzaldehyde (**2a**)[25] with ethylene glycol under acidic conditions using a Dean−Stark trap produced bromophenol **3a**[26] in 95% yield, as shown in Scheme 2. The phenol was then protected using methoxymethylene chloride (MOMCl) and *N*,*N*-diisopropylethylamine (DIPEA) in dry dichloromethane to afford compound **4a**[26] in 94% yield. Several different approaches to aromatic prenylation, including Pd-catalyzed Stille coupling,[27] pi-allyl nickel bromide complex mediated allylation,[28] and allylation through aryl cuprate,[29,30] were performed as shown in Scheme 3 and Table 1. The prenylation step was very sensitive to modification of

Scheme 3

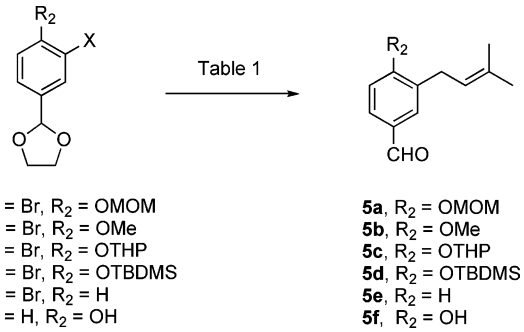


Table 1. Prenylation of Aromatic Compounds

starting material	reaction conditions	product	yield[a] (%)
2c	KOH/MeOH, 3,3-dimethylallyl bromide, rt[31]	**5f**	7
2c	BF_3·OEt_2, 3,3-dimethylallyl bromide, rt[32]	**5f**	4
2c	BaO·Al_2O_3, 3,3-dimethylallyl bromide, rt[33]	**5f**	9
4b	$Pd(PPh_3)_4$, tributyl(3-methyl-2-butenyl)tin, 100 °C[27]	**5b**	34[b]
4b	$Ni(COD)_2$, 3,3-dimethylallyl bromide, rt[28]	**5b**	8
4b	*t*-BuLi, CuCN·2LiCl, 3,3-dimethylallyl bromide rt[29]	**5b**	45
4b	BuLi, CuBr·DMS, 3,3-dimethylallyl bromide, 0 °C−rt[30]	**5b**	85
4a	BuLi, CuBr·DMS, 3,3-dimethylallyl bromide, rt	**5a**	83
4c	BuLi, CuBr·DMS, 3,3-dimethylallyl bromide, rt	**5c**	0
4d	BuLi, CuBr·DMS, 3,3-dimethylallyl bromide, rt	**5d**	0
3b	BuLi, CuBr·DMS, 3,3-dimethylallyl bromide, −78 °C	**5e**	10

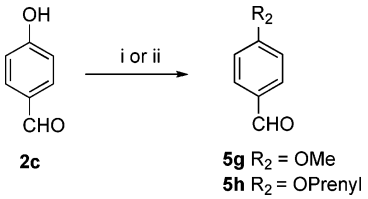
[a] The yield was not optimized. [b] It was very difficult to remove tributyl tin impurity from the product.

the reaction parameters. The best yielding procedure was found to use CuBr·DMS reagent at 0 °C to room temperature. After a bromine−lithium exchange using *n*-BuLi, followed by transmetallation with CuBr·DMS, the resulting cuprate was treated with prenyl bromide to afford the prenylated product. A number of different phenol protecting groups were tested for the prenylation step and it was found that the TBDMS-protected compound failed to produce any prenylated products, possibly due to steric hindrance. However, the MOM and methoxy ethers were stable under the reaction conditions and prenylation occurred in very high yield. Aldehydes **5g**[34] and **5h**[35] were also synthesized in excellent yield, as shown in Scheme 4.

2,4-Dihydroxyacetophenone was regioselectively monoprotected on the nonhydrogen-bonded phenol using K_2CO_3 in dry acetone and MOMCl at room temperature to provide acetophenone **6a** in 88% yield (Scheme 5). The corresponding monomethyl ether **6b** was also obtained in 87% yield by reaction with Me_2SO_4.

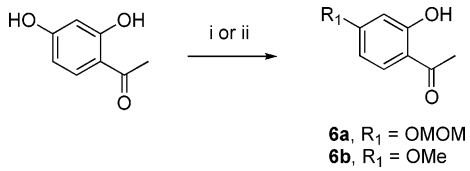
Condensation of **5a** and **6a** under Claisen−Schmidt conditions using 60% KOH in methanol provided the desired enone **7a** in 76% yield (Scheme 6). Deprotection of the MOM groups using HCl in methanol at room temperature yielded chalcone **7b** in 95% yield. The subsequent cyclization was carried out with NaOAc in 55% yield (96% based on recovered starting material) in refluxing EtOH for 48 h to yield (±)-abyssinone II **(8b)** as a bright yellow solid. The ^{1}H NMR, ^{13}C NMR, IR, and mass spectral data of the synthetic product were consistent with those reported for natural (2*S*)-abyssinone II.[23] Several abyssinone II

Scheme 4[a]



[a] Reagents and conditions: (i) K_2CO_3, Me_2CO, Me_2SO_4, room temperature or (ii) K_2CO_3, Me_2CO, prenyl bromide, room temperature.

Scheme 5[a]



[a] Reagents and conditions: (i) K_2CO_3, Me_2CO, MOMCI, room temperature; (ii) K_2CO_3, Me_2CO, Me_2SO_4, room temperature.

analogues were designed based on initial biological results and synthesized as outlined in Schemes 6 and 7.

During our initial attempts to synthesize (±)-abyssinone II **(8b)**, the reaction of the acetophenone derivative **6b** with the substituted aldehyde **5b** was carried out with lithium hexamethyldisilazide (LiHMDS) in dry tetrahydrofuran (THF) instead of KOH in methanol (Claisen−Schmidt conditions), followed by neutralization with aqueous ammonium chloride. This resulted in the isolation of the covalently hydrated chalcone **9** instead of either the chalcone **7b** or the (±)-abyssinone II **(8b)** (Scheme 8).

Aromatase (CYP 19) Inhibitory Activity. An aromatase inhibition assay was performed on synthetic racemic abyssinone II and its various analogues, as described in the Experimental Section. The IC_{50} values of compounds **7a**−**7k**, **8a**−**8k**, and **9** are reported in Table 2.

Our synthetic racemic abyssinone II **8b** was determined to have an IC_{50} value of 40.95 ± 11.31 μM, whereas the corresponding chalcone **7b** was inactive in aromatase inhibition assays. All of the chalcone intermediates were inactive except **7d**. The data reported in Table 2 support the hypothesis that coordination of the carbonyl oxygen with the heme iron of the CYP19 enzyme is responsible for the inhibitory activity. In the chalcones, the *ortho*-phenolic hydroxyl group hydrogen bonds with the keto oxygen and hence reduces its affinity toward the heme iron, leading to loss of aromatase inhibitory activity.

The 4′-methoxy analogue **8d** (IC_{50} = 4.08 ± 2.10 μM), the 7-methoxy derivative **8f** (IC_{50} = 4.75 ± 0.61 μM), and the 4′,7-dimethoxy analogue **8g** (IC_{50} = 3.67 ± 1.61 μM) were about 10 times more potent than racemic abyssinone II itself. To analyze the influence of the 7-methoxy group on aromatase inhibitory activity, the 7-unsubstituted analogue **8h** (IC_{50} = 12.10 ± 3.24 μM) was synthesized and evaluated. The IC_{50} value of this compound, compared to that of **8d** and **8g**, suggests that electron-donating substituents in the 7 position increase aromatase inhibitory activity in the flavanone series, perhaps by increasing electron density on the carbonyl oxygen and thus improving its ability to coordinate effectively the iron atom of aromatase.

A previous study of the aromatase inhibitory activity of nonprenylated flavanones reported that the presence of a 4′-methoxy group decreases the aromatase inhibitory activity.[36] The 4′-hydroxy **8f** and 4′-unsubstituted **8i** (IC_{50} = 4.67 ± 2.15 μM) analogues were synthesized to determine if this would also be true with the prenylated flavanones. Both of them showed similar aromatase inhibitory activity compared to **8g**. The insignificant contribution of the 4′-methoxy group in **8g** to the enzyme inhibitory activity can be expected because, as opposed to the 7-methoxy group, it is not conjugated with the carbonyl oxygen.

The nonprenylated flavanone **8j** was synthesized to investigate the influence of prenyl substitution on aromatase inhibition. Surprisingly, **8j** (IC_{50} = 1.86 ± 0.37 μM) was slightly more active than its prenylated analogue **8g** (IC_{50} = 3.67 ± 1.61 μM), suggesting that prenyl substitution in this series actually has a weakly negative effect on the aromatase inhibitory activity.

Conclusion

An efficient total synthesis of (±)-abyssinone II and a series of abyssinone II-based flavonoid AIs has been successfully carried out. A detailed study of aromatic prenylation provided the foundation of this synthesis. Interestingly, all the flavanone analogues reported here (**8a**, **8c**−**8k**) show human aromatase inhibitory activity that is superior to that of the racemic form of the parent natural product, abyssinone II. Methylation of the two phenols and elimination of the prenyl group of abyssinone II resulted in the most active compound in the series **8j**.

Experimental Section

NMR spectra were determined at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$ using $CHCl_3$ as internal standard. Flash chromatography was performed with 230−400 mesh silica gel. TLC was carried out using commercially available precoated glass silica gel plates of 250 μm thickness. Melting points are uncorrected. Unless otherwise stated, chemicals and solvents were of reagent grade and used as obtained from commercial sources without further purification. THF and diethyl ether were freshly distilled from sodium/benzophenone ketyl radical prior to use. Benzene was distilled from phosphorus pentoxide and acetone was freshly distilled from potassium carbonate prior to use.

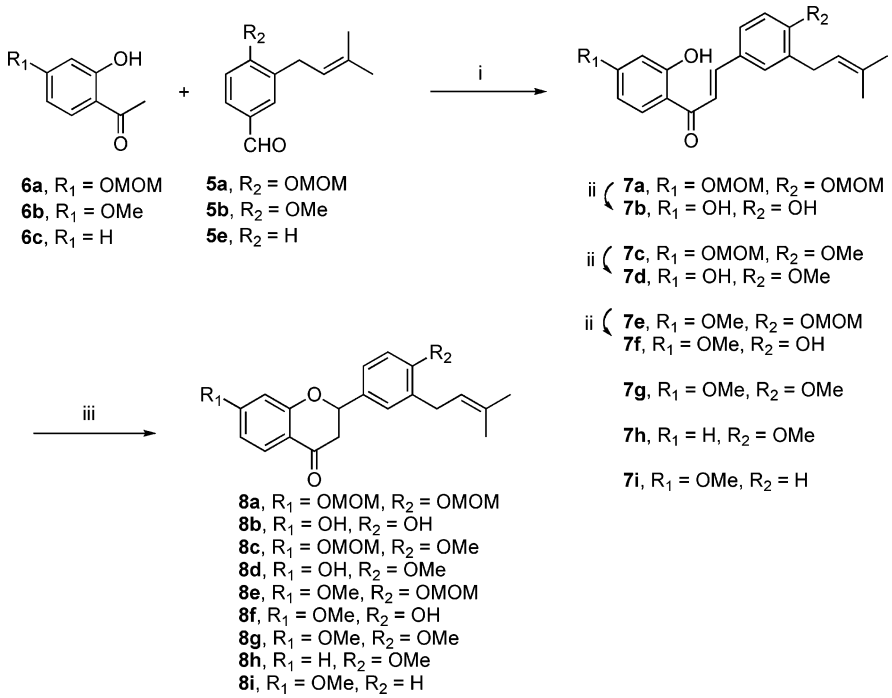
2-Bromo-4-(1,3-dioxolan-2-yl)phenol (3a). Compound **3a** was isolated as a crystalline solid in 95% yield using a literature procedure, as described in reference 26.

2-[3-Bromo-4-(methoxymethoxy)phenyl]-1,3-dioxolane (4a). Compound **4a** was isolated as a colorless liquid in 94% yield according to literature procedure, as described in reference 26.

2-(3-Bromo-4-methoxyphenyl)-1,3-dioxolane (4b). Compound **4b** was isolated as colorless oil in 91% yield according to literature procedure, as described in reference 25.

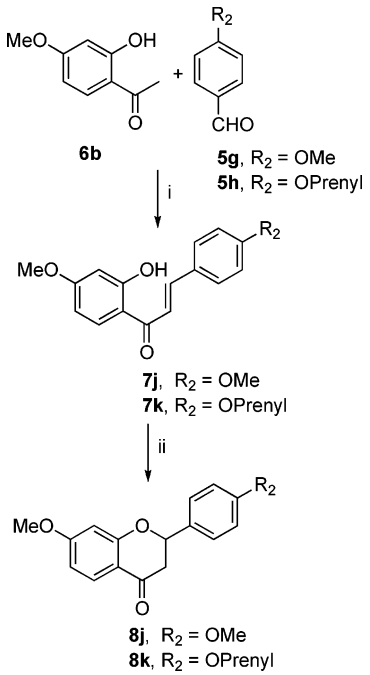
General Prenylation Procedure to Synthesize Compounds 5a−**5d.** Diprotected bromo compound (6.9 mmol) was dissolved in benzene (18 mL) and anhydrous ether (36 mL) and ground 5 Å molecular sieves (1.0 g) were added. After a dropwise addition of *n*-BuLi (3.2 mL, 2.5 M in hexanes, 8.0 mmol) at 0 °C, the reaction mixture was stirred for another 30 min at room temperature, and then solid CuBr·DMS (700 mg, 3.5 mmol) was added carefully while cooling the reaction mixture on an ice water bath. The reaction mixture was allowed to stir for 60 min at room temperature and then prenyl bromide (1.0 mL, 8.3 mmol) was added. After the reaction mixture was stirred for 5 h, it was quenched by the addition of saturated NH_4Cl (10 mL), followed by addition of 1 N HCl (10 mL), and the mixture was stirred for 20 min. The aqueous layer was extracted with ether and the ether extract was washed with 20% aqueous acetic acid (20 mL) and then concentrated in vacuo. Most of the ketal converted to aldehyde during this process. The initial oil was dissolved in CH_2Cl_2 (15 mL), SiO_2 (1.0 g) was added, and the mixture was stirred for 30 min at room temperature for complete ketal deprotection. The solvent was removed and the solid was chromatographed on a silica gel column (2 × 12 in., containing 140 g of SiO_2, particle size 40−63 μm), eluting with 25% ethyl acetate in hexanes, to afford prenylated aldehyde as a light yellow oil.

Scheme 6[a]



[a] Reagents and conditions: (i) 60% aq KOH (w/v)/MeOH, room temperature, 24−36 h; (ii) HCl, MeOH, room temperature, 18−24 h; (iii) NaOAc, EtOH, reflux, 24−48 h.

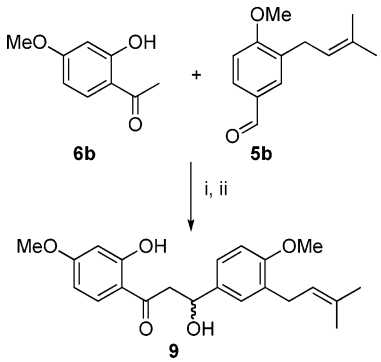
Scheme 7[a]



[a] Reagents and conditions: (i) 60% aq KOH (w/v)/MeOH, room temperature, 24−36 h; (ii) NaOAc, EtOH, reflux, 24−48 h.

4-(Methoxymethoxy)-3-(3-methylbut-2-enyl)benzaldehyde (5a). The compound was isolated as clear light yellow oil in 83% yield. R_f = 0.58 (25% EtOAc−hexanes); IR (neat) 2912, 1689, 1599, 1494, 1255, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1 H), 7.64 (m, 2 H), 7.14 (d, J = 9.3 Hz, 1 H), 5.26 (s, 2 H), 5.25 (m, 1 H), 3.45 (s, 3 H), 3.34 (d, J = 7.2 Hz, 2 H), 1.72 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 159.8, 133.4, 131.5, 130.6, 130.3, 130.2, 121.3, 113.1, 93.9, 56.2, 28.5, 25.8, 17.7; EIMS (*m*/*z*, rel intensity) 234 (M^+, 17), 202 (100), 187 (62), 173 (36), 159 (56), 91 (27); HRMS *m*/*z* calcd for $C_{14}H_{18}O_3$, 234.1256; found, 234.1255.

Scheme 8[a]



[a] Reagents and conditions: (i) LiHMDS, THF, −20 °C to room temperature; (ii) aq NH_4Cl.

4-Methoxy-3-(3-methylbut-2-enyl)benzaldehyde (5b). The compound was isolated as clear light yellow oil in 85% yield. R_f = 0.62 (25% EtOAc−hexanes); IR (neat) 2966, 2914, 2733, 1687, 1599, 1579, 1497, 1441, 1255, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1 H), 7.63 (m, 2 H), 6.87 (d, J = 8.4 Hz, 1 H), 5.24 (t, J = 7.2 Hz, 2 H), 3.85 (s, 3 H), 3.28 (d, J = 1.2 Hz, 2 H), 1.70 (s, 3 H), 1.65 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 162.2, 133.3, 130.8, 130.5, 130.0, 129.4, 121.1, 114.1, 55.5, 28.0, 25.6, 17.6; HRMS *m*/*z* calcd for $C_{13}H_{16}O_2$, 204.1150; found, 204.1149.

4-Methoxybenzaldehyde (5g). Compound **5g** was isolated as a colorless solid in 90% yield according to the literature procedure, as described in reference 34.

4-(3-Methylbut-2-enyloxy)benzaldehyde (5h). Compound **5h** was isolated as a colorless liquid in 92% yield according to the literature procedure, as described in reference 35.

1-[2-Hydroxy-4-(methoxymethoxy)phenyl]ethanone (6a). A mixture of 2,4-dihydroxy acetophenone (2.0 g, 13.2 mmol) and oven-dried potassium carbonate (4.0 g, 30.0 mmol) in dry acetone (30 mL) was stirred for 10 min. MOMCl (1.62 mL, 17.2 mmol) was added dropwise to the reaction mixture, and the mixture was stirred at room temperature for 24 h. Solvent was evaporated under reduced pressure and water (25 mL) was added. The mixture was extracted with chloroform (3 × 100 mL) and the organic phase

Table 2. Inhibition of Aromatase by Abyssinone II and Its Analogues

cmpd	IC_{50} (μM)
7a	>242.4
8a	13.95 ± 6.09
7b	>308.3
8b	40.95 ± 11.31
7c	>261.5
8c	7.67 ± 3.27
7d	82.94 ± 44.27
8d	4.08 ± 2.10
7e	>261.5
8e	25.14 ± 6.38
7f	>295.5
8f	4.75 ± 0.61
7g	>283.75
8g	3.67 ± 1.61
7h	>310.17
8h	12.10 ± 3.24
7i	>310.2
8i	4.67 ± 2.15
7j	>351.7
8j	1.86 ± 0.37
7k	>271.4
8k	28.65 ± 7.96
9	54.67 ± 11.93
aminoglutethimide	0.27

was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was column chromatographed on silica gel eluting with 20% ethyl acetate in hexanes to afford acetophenone **6a** (2.2 g, 87% yield) as a very low melting solid. R_f = 0.51 (25% EtOAc−hexanes); mp 38−39 °C; IR (KBr) 2959, 2829, 1632, 1579, 1504, 1367, 1262, 1142 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.7 Hz, 1 H), 6.51 (m, 2 H), 5.15 (s, 2 H), 3.42 (s, 3 H), 2.51 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 164.7, 163.4, 132.3, 114.6, 108.0, 103.6, 93.8, 56.2, 26.1; EIMS (*m*/*z*, rel intensity) 196 (M^+, 100), 181 (6), 164 (9), 151 (32), 137 (24).

1-(2-Hydroxy-4-methoxyphenyl)ethanone (6b). Compound **6b** was prepared in 88% yield as a crystalline solid using the procedure described in reference 37.

General Procedure for the Synthesis of Chalcones 7a, 7c, 7e, and 7g−7k. A solution of 60% aqueous KOH (1.5 mL) was added dropwise to a well-stirred mixture of acetophenone **6** (1.0 mmol) and aldehyde **5** (1.0 mmol) at room temperature. After 24−36 h, the pH of the reaction mixture was brought back to 7.0 by the careful addition of 1 N HCl solution (~5 mL). The aqueous layer was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and then concentrated in vacuo. The residue was column chromatographed on silica gel, eluting with 15% ethyl acetate in hexanes, to afford chalcones **7** in high yield.

1-[2-Hydroxy-4-(methoxymethoxy)phenyl]-3-(4-[methoxymethoxy)-3-(3-methylbut-2-enylphenyl]prop-2-en-1-one (7a). The compound was isolated as a yellow semisolid in 76% yield. R_f = 0.26 (15% EtOAc−hexanes); IR (neat) 2910, 1634, 1571, 1497, 1359, 1242, 1151, 1077, 997 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, J = 12.3, 3.3 Hz, 2 H), 7.44 (m, 3 H), 7.07 (d, J = 9.0 Hz, 1 H), 6.60 (m, 2 H), 5.28 (t, J = 7.2 Hz, 1 H), 5.22 (s, 2 H), 5.19 (s, 2 H), 3.45 (s, 6 H), 3.34 (d, J = 7.2 Hz, 2 H), 1.73 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 166.0, 163.3, 157.1, 144.7, 133.0, 131.3, 130.1, 128.0, 127.8, 121.8, 117.8, 114.9, 113.7, 108.0, 103.8, 93.9, 56.3, 56.1, 28.6, 25.7, 17.8; EIMS (*m*/*z*, rel intensity) 412 (M^+, 81), 380 (12), 367 (16), 219 (67), 187 (100), 181 (55), 151 (36), 69 (45); HRMS *m*/*z* calcd for $C_{24}H_{28}O_6$, 412.1886; found, 412.2884. Anal. ($C_{24}H_{28}O_6$·1.75H_2O) C, H.

1-[2-Hydroxy-4-(methoxymethoxy)phenyl]-3-[4-methoxy-3-(3-methylbut-2-enyl)phenyl]prop-2-en-1-one (7c). The compound was isolated as yellow solid in 65% yield: mp 53−55 °C; R_f = 0.52 (20% EtOAc−hexanes); IR (neat) 2912, 2837, 1682, 1634, 1568, 1502, 1361, 1255, 1233, 1155, 1079, 999 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 5.8 Hz, 1 H), 7.80 (s, 1 H), 7.46 (dd, J = 9.0, 2.4 Hz, 1 H), 7.42 (d, J = 5.1 Hz, 1 H), 7.38 (s, 1 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.60 (d, J = 2.1 Hz, 1 H), 6.56 (dd, J = 8.7, 2.1 Hz, 1 H), 5.27 (t, J = 6.9 Hz, 1 H), 5.19 (s, 2 H), 3.85 (s, 3 H), 3.46 (s, 3 H), 3.31 (d, J = 7.2 Hz, 2 H), 1.74 (s, 3 H), 1.70 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 166.0, 163.2, 159.6, 144.9, 133.0, 131.1, 130.7, 129.6, 128.3, 126.9, 121.6, 117.1, 114.9, 110.2, 107.9, 103.8, 93.8, 56.2, 55.4, 28.3, 25.7, 17.7; CIMS (*m*/*z*, rel intensity) 383 (MH^+, 100), 351 (12), 327 (17), 229 (30), 181 (51), 151 (11); HRMS *m*/*z* calcd for $C_{23}H_{26}O_5$, 382.1780; found, 382.1783. Anal. ($C_{23}H_{26}O_5$·1.0H_2O) C, H.

1-(2-Hydroxy-4-methoxyphenyl)-3-[4-(methoxymethoxy)-3-(3-methylbut-2-enyl)phenyl]prop-2-en-1-one (7e). The compound was isolated as yellow semisolid in 80% yield. R_f = 0.55 (25% EtOAc−hexanes); IR (neat) 2923, 2853, 1634, 1578, 1497, 1363, 1221, 1152, 1129, 1078 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 7.2 Hz, 2 H), 7.42 (m, 3 H), 7.06 (d, J = 8.4 Hz, 1 H), 6.47 (d, J = 2.7 Hz, 1 H), 6.44 (d, J = 2.4 Hz, 1 H), 5.29 (t, J = 6.9 Hz, 1 H), 5.23 (s, 2 H), 3.82 (s, 3 H), 3.45 (s, 3 H), 3.33 (d, J = 7.2 Hz, 2 H), 1.73 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 166.5, 165.9, 157.0, 144.6, 133.0, 131.3, 131.1, 130.1, 128.1, 127.8, 121.8, 117.9, 114.1, 113.7, 107.6, 101.0, 94.0, 56.1, 55.5, 28.7, 25.8, 17.8; EIMS (*m*/*z*, rel intensity) 382 (M^+, 44), 350 (7), 337 (11), 219 (30), 187 (52), 151 (100), 69 (83); HRMS *m*/*z* calcd for $C_{23}H_{26}O_5$, 382.1780; found, 382.1779. Anal. ($C_{23}H_{26}O_5$·0.5H_2O) C, H.

1-(2-Hydroxy-4-methoxyphenyl)-3-[4-methoxy-3-(3-methylbut-2-enyl)phenyl]prop-2-en-1-one (7g). The compound was isolated as yellow solid in 75% yield: mp 82−84 °C; R_f = 0.48 (25% EtOAc−hexanes); IR (neat) 2964, 2944, 1633, 1567, 1504, 1442, 1362, 1252, 1219, 1128, 1121 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.7 Hz, 1 H), 7.79 (d, J = 2.1 Hz, 1 H), 7.47 (dd, J = 8.1, 2.1 Hz, 1 H), 7.42 (d, J = 4.8 Hz, 1 H), 7.39 (d, J = 8.7 Hz, 1 H), 6.85 (d, J = 9.0 Hz, 1 H), 6.48 (d, J = 2.4 Hz, 1 H), 6.44 (d, J = 2.4 Hz, 1 H), 5.27 (t, J = 7.2 Hz, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.31 (d, J = 7.2 Hz, 2 H), 1.74 (s, 3 H), 1.70 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 166.5, 165.9, 159.6, 144.8, 133.1, 131.0, 130.8, 129.6, 128.3, 127.1, 121.7, 117.3, 110.3, 107.5, 106.4, 101.0, 55.563, 55.527, 28.4, 25.8, 17.8; EIMS (*m*/*z*, rel intensity) 352 (M^+, 100), 321 (25), 283 (14), 202 (18), 189 (100), 115 (18), 69 (35); HRMS *m*/*z* calcd for $C_{22}H_{24}O_4$, 352.1675; found, 324.1675. Anal. ($C_{22}H_{24}O_4$·3.0H_2O) C, H.

1-(2-Hydroxyphenyl)-3-[4-methoxy-3-(3-methylbut-2-enyl)-phenyl]prop-2-en-1-one (7h). The compound was isolated as yellow solid in 55% yield: mp 74−76 °C; R_f = 0.5 (15% EtOAc−hexanes); IR (neat) 3428, 2934, 1714, 1661, 1497, 1416, 1391, 1256, 1103 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 5.4 Hz, 1 H), 7.84 (s, 1 H), 7.50 (m, 3 H), 7.43 (s, 1 H), 6.99 (d, J = 8.1 Hz, 1 H), 6.91 (t, J = 7.5 Hz, 1 H), 6.85 (d, J = 8.4 Hz, 1 H), 5.28 (t, J = 7.2 Hz, 1 H), 3.86 (s, 3 H), 3.31 (d, J = 7.2 Hz, 2 H), 1.74 (s, 3 H), 1.70 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 163.5, 159.9, 145.9, 136.0, 133.2, 130.9, 129.8, 129.5, 128.5, 126.9, 121.6, 120.1, 118.7, 117.1, 110.3, 55.5, 28.4, 25.8, 17.8; EIMS (*m*/*z*, rel intensity) 322 (M^+, 35), 291 (10), 253 (14), 189 (34), 171 (12), 147 (31), 121 (89), 115 (24), 69 (100); HRMS *m*/*z* calcd for $C_{21}H_{22}O_3$, 322.1569; found, 322.1575. Anal. ($C_{21}H_{22}O_3$·0.25H_2O) C, H.

1-(2-Hydroxy-4-methoxyphenyl)-3-[3-(3-methylbut-2-enyl)-phenyl]prop-2-en-1-one (7i). The compound was isolated as yellow semisolid in 81% yield. R_f = 0.5 (15% EtOAc−hexanes); IR (neat) 3420, 2964, 1634, 1574, 1505, 1441, 1359, 1260, 1233, 1127 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (m, 2 H), 7.47 (m, 3 H), 7.30 (t, J = 7.5 Hz, 1 H), 7.21 (d, J = 8.7 Hz, 1 H), 6.47 (d, J = 2.1 Hz, 1 H), 6.44 (s, 1 H), 5.31 (t, J = 6.0 Hz, 1 H), 3.82 (s, 3 H), 3.35 (d, J = 7.2 Hz, 2 H), 1.74 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 166.6, 166.1, 144.7, 142.6, 134.7, 133.2, 131.2, 130.8, 128.9, 128.6, 125.8, 122.5, 120.0, 114.0, 107.7, 101.0, 55.5, 34.1, 25.7, 17.8; EIMS (*m*/*z*, rel intensity) 322 (M^+, 74), 305 (6), 253 (22), 177 (100), 151 (77), 115 (18), 95 (18), 69 (24); HRMS *m*/*z* calcd for $C_{21}H_{22}O_3$, 322.1569; found, 322.1567. Anal. ($C_{21}H_{22}O_3$·1.25H_2O) C, H.

1-(2-Hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (7j). The compound was isolated as a bright yellow crystalline solid in 85% yield: mp 106−108 °C; R_f = 0.52 (15%

EtOAc−hexanes); IR (KBr) 3002, 2956, 2935, 2832, 1632, 1569, 1510, 1442, 1365, 1283, 1258, 1220, 1171, 1128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (m, 2 H), 7.58 (m, 2 H), 7.43 (d, J = 15.3 Hz, 1 H), 6.91 (m, 2 H), 3.83 (s, 3 H), 3.82 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 166.5, 165.9, 161.7, 144.2, 131.0, 130.3, 127.4, 117.7, 114.4, 114.1, 107.5, 101.0, 55.5, 55.4; ESIMS (*m*/*z*, rel intensity) 285 (MH^+, 100), 267 (1), 239 (1), 160 (10), 151 (14), 150 (9); HRMS *m*/*z* calcd for $C_{17}H_{16}O_4$, 284.1049; found, 284.1047. Anal. ($C_{17}H_{16}O_4$) C, H.

1-(2-Hydroxy-4-methoxyphenyl)-3-[4-(3-methylbut-2-enyloxy)phenyl]prop-2-en-1-one (7k). The compound was isolated as a bright yellow crystalline solid in 80% yield: mp 95−97 °C; R_f = 0.5 (15% EtOAc−hexanes); IR (KBr) 3052, 2917, 2849, 1633, 1604, 1578, 1566, 1508, 1363, 1264, 1219, 1172, 1128, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (m, 2 H), 7.57 (m, 2 H), 7.44 (d, J = 15.6 Hz, 1 H), 6.93 (m, 2 H), 6.44 (m, 2 H), 5.46 (m, 1 H), 4.53 (d, J = 6.6 Hz, 2 H), 3.82 (s, 3 H), 1.78 (s, 3 H), 1.73 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 166.5, 165.9, 161.1, 144.3, 138.8, 131.0, 130.3, 127.3, 119.0, 117.6, 115.0, 114.0, 107.5, 101.0, 64.9, 55.5, 25.8, 18.2; ESIMS (*m*/*z*, rel intensity) 339 (MH^+, 100), 271 (30), 215 (7), 151 (1); HRMS *m*/*z* calcd for $C_{17}H_{16}O_4$, 284.1049; found, 284.1047. Anal. ($C_{17}H_{16}O_4$) C, H.

General Procedure for Deprotection of the MOM Group from Chalcones to Synthesize 7b, 7d, and 7f. Concd HCl (0.25 mL/MOM group) was added to a solution of chalcone (1 mmol) in methanol (10 mL) at room temperature, and the reaction mixture was stirred for 18−24 h until disappearance of starting material occurred. The solvent was evaporated under reduced pressure, and the residue was column chromatographed on silica gel, eluting with 25% ethyl acetate in hexanes, to afford flavanone in high yield.

1-(2,4-Dihydroxyphenyl)-3-[4-hydroxy-3-(3-methylbut-2-enyl)-phenyl]-prop-2-en-1-one (7b). The compound was isolated as a bright reddish-yellow crystalline solid in 95% yield: mp 167−168 °C; R_f = 0.47 (25% EtOAc−hexanes); IR (KBr) 3302, 2966, 2925, 1625, 1501, 1365, 1227, 1132 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.86 (d, J = 9.3 Hz, 1 H), 7.67 (d, J = 14.7 Hz, 1 H), 7.47 (d, J = 14.7 Hz, 1 H), 7.34 (dd, J = 2.4, 8.4, 1 H), 7.33 (m, 1 H), 6.72 (d, J = 8.1 Hz, 1 H), 6.32 (dd, J = 8.7, 2.7 Hz, 1 H), 6.18 (d, J = 2.1, 1 H), 5.24 (t, J = 7.2 Hz, 1 H), 3.22 (m, 2 H), 1.658 (s, 3 H), 1.654 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 166.0, 163.1, 157.0, 145.1, 135.3, 132.0, 131.0, 128.3, 127.7, 121.0, 117.2, 116.2, 114.1, 108.0, 103.6, 29.4, 25.7, 17.9, 14.0; EIMS (*m*/*z*, rel intensity) 324 (M^+, 46), 268 (8), 188 (20), 175 (100), 137 (77), 69 (34); HRMS *m*/*z* calcd for $C_{20}H_{20}O_4$, 324.1362; found, 324.1357. Anal. ($C_{20}H_{20}O_4 \cdot 0.25H_2O$) C, H.

1-(2,4-Dihydroxyphenyl)-3-[4-methoxy-3-(3-methylbut-2-enyl)-phenyl]prop-2-en-1-one (7d). The compound was isolated as light yellow solid in 85% yield. R_f = 0.45 (25% EtOAc−hexanes); mp 166−168 °C; IR (KBr) 3306, 2928, 1630, 1601, 1564, 1500, 1370, 1255, 1230, 1141 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 9.51 (s, 1 H), 8.07 (d, J = 8.4 Hz, 1 H), 7.78 (m, 4 H), 7.02 (d, J = 8.4 Hz, 1 H), 6.44 (d, J = 8.7 Hz, 1 H), 6.34 (dd, J = 3.0, 16.2 Hz, 1 H), 5.30 (t, J = 7.2 Hz, 1 H), 3.89 (s, 3 H), 3.33 (d, J = 7.2 Hz, 2 H), 1.72 (s, 3 H), 1.70 (s, 3 H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 192.5, 167.3, 165.8, 160.4, 145.0, 134.1, 133.0, 132.6, 131.1, 130.6, 129.4, 127.9, 122.9, 118.4, 114.2, 111.3, 108.4, 103.5, 55.7, 25.6, 17.6; negative ESIMS (*m*/*z*, rel intensity) 337 ($M - H^+$, 100); positive ESIMS (*m*/*z*, rel intensity) 339 (MH^+, 79), 322 (100); HRESIMS *m*/*z* calcd for $C_{21}H_{23}O_4$, 339.1591; found, 339.1591. Anal. ($C_{21}H_{22}O_4 \cdot 2.25H_2O$) C, H.

3-[4-Hydroxy-3-(3-methylbut-2-enyl)phenyl]-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one (7f). The compound was isolated as a yellow solid in 89% yield: mp 80−82 °C; R_f = 0.34 (20% EtOAc−hexanes); IR (neat) 3317, 2923, 2852, 1628, 1571, 1504, 1365, 1242, 1154, 1129 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 3.9 Hz, 1 H), 7.78 (m, 1 H), 7.41 (m, 3 H), 6.82 (d, J = 8.1 Hz, 1 H), 6.47 (d, J = 2.7 Hz, 1 H), 6.44 (br s, 1 H), 5.51 (s, 1 H), 5.30 (t, J = 7.2 Hz, 1 H), 3.82 (s, 3 H), 3.36 (d, J = 6.6 Hz, 2 H), 1.775 (s, 3 H), 1.772 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 166.5, 165.9, 156.9, 144.6, 136.4, 135.7, 130.9, 128.3, 127.4, 121.0, 117.5, 116.3, 114.1, 107.6, 106.4, 101.0, 55.5, 29.7, 25.8, 17.9; EIMS (*m*/*z*, rel intensity) 338 (M^+, 53), 282 (9), 165 (100), 151 (100), 133 (27), 69 (34); HRMS *m*/*z* calcd for $C_{21}H_{22}O_4$, 338.1518; found, 338.1513. Anal. ($C_{21}H_{22}O_4 \cdot 3.1H_2O$) C, H.

General Procedure for the Synthesis of Flavanones 8a−8k. Chalcones **7a−7k** (0.2 mmol) and sodium acetate (2.0 mmol) were heated in refluxing ethanol (2 mL) for 24−48 h. The mixture was then allowed to cool to room temperature and poured into ice water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was column chromatographed on silica gel, eluting with 15−25% ethyl acetate in hexanes, to afford flavanones **8a−8k**.

7-(Methoxymethoxy)-2-[4-(methoxymethoxy)-3-(3-methylbut-2-enyl)phenyl]-chroman-4-one (8a). The compound was isolated as a clear light yellow oil in 45% (isolated) and 91% (based on recovered starting material) yield. R_f = 0.25 (15% EtOAc−hexanes); IR (neat) 2931, 1682, 1608, 1573, 1496, 1447, 1360, 1247, 1153, 1130, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.7 Hz, 1 H), 7.24 (m, 2 H), 7.09 (d, J = 8.1 Hz, 1 H), 6.68 (m, 2 H), 5.39 (dd, J = 13.5, 2.7 Hz, 1 H), 5.31 (t, J = 7.2 Hz, 1 H), 5.21 (s, 2 H), 5.18 (s, 2 H), 3.47 (s, 3 H), 3.46 (s, 3 H), 3.36 (d, J = 7.2 Hz, 2 H), 3.03 (dd, J = 13.5, 3.3 Hz, 1 H), 2.78 (dd, J = 16.8, 2.7 Hz, 1 H), 1.73 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 163.5, 163.3, 155.2, 132.8, 131.6, 131.2, 128.7, 127.7, 125.0, 122.0, 115.6, 113.8, 111.0, 103.6, 94.2, 94.0, 79.8, 56.3, 56.0, 44.1, 28.7, 25.8, 17.8; EIMS (*m*/*z*, rel intensity) 412 (M^+, 59), 380 (37), 335 (4), 219 (48), 187 (100), 151 (19), 115 (12), 69 (22); HRMS *m*/*z* calcd for $C_{24}H_{28}O_6$, 412.1886; found, 412.1876. Anal. ($C_{24}H_{28}O_4 \cdot 1.5H_2O$) C, H.

7-Hydroxy-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]chroman-4-one [(±)-Abyssinone II, 8b]. The compound was isolated as a bright yellow crystalline solid in 55% (isolated) and 96% (based on recovered starting material) yield: mp 76−78 °C; R_f = 0.47 (25% EtOAc−hexanes); IR (KBr) 3301, 1927, 1599, 1504, 1367, 1237, 1128, 1028 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.68 (d, J = 8.7 Hz, 1 H), 7.13 (m, 2 H), 6.76 (d, J = 8.7 Hz, 1 H), 6.48 (dd, J = 2.3, 8.7 Hz, 1 H), 6.33 (d, J = 2.3 Hz, 1 H), 5.35 (dd, J = 2.8, 13.4 Hz, 1 H), 5.31 (t, J = 7.2 Hz, 1 H), 3.29 (d, J = 7.2 Hz, 2 H), 3.02 (dd, J = 3.7, 13.4 Hz, 1 H), 2.67 (dd, J = 2.9, 16.9 Hz, 1 H), 1.72 (s, 3 H), 1.70 (s, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 193.5, 166.7, 165.5, 156.5, 133.1, 131.1, 129.8, 129.4, 128.9, 126.1, 123.7, 115.6, 114.9, 111.6, 103.8, 81.1, 44.9, 29.3, 25.9, 17.8; EIMS (*m*/*z*, rel intensity) 324 (M^+, 53), 307 (15), 255 (10), 189 (6), 175 (100), 137 (87), 69 (49); HRMS *m*/*z* calcd for $C_{20}H_{20}O_4$, 324.1362; found, 324.1353. Anal. ($C_{20}H_{20}O_4 \cdot 0.6H_2O$) C, H.

2-[4-Methoxy-3-(3-methylbut-2-enyl)phenyl]-7-(methoxymethoxy)chroman-4-one (8c). The compound was isolated as a clear light yellow oil in 45% (isolated) and 89% (based on recovered starting material) yield. R_f = 0.5 (20% EtOAc−hexanes); IR (neat) 2962, 1683, 1610, 1574, 1503, 1446, 1333, 1251, 1154, 1128, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.7 Hz, 1 H), 7.26 (m, 2 H), 6.88 (d, J = 8.1 Hz, 1 H), 6.89 (m, 2 H), 5.39 (dd, J = 13.8, 2.7 Hz, 1 H), 5.31 (t, J = 6.0 Hz, 1 H), 5.19 (s, 2 H), 3.85 (s, 3 H), 3.47 (s, 3 H), 3.34 (d, J = 6.9 Hz, 2 H), 3.06 (dd, J = 13.8, 3.3 Hz, 1 H), 2.78 (dd, J = 14.4, 2.7 Hz, 1 H), 1.75 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 163.5, 163.3, 157.6, 132.8, 130.5, 130.3, 128.8, 127.4, 125.0, 121.9, 115.5, 110.9, 110.1, 103.5, 93.9, 79.9, 56.3, 55.4, 44.1, 28.4, 25.7, 17.7; EIMS (*m*/*z*, rel intensity) 382 (M^+, 100), 351 (26), 337 (13), 207 (15), 202 (29), 189 (85), 147 (28), 115 (29), 91 (32), 69 (26), 55(15); HRMS *m*/*z* calcd for $C_{23}H_{26}O_5$, 382.1780; found, 382.1781. Anal. ($C_{23}H_{26}O_5$) C, H.

7-Hydroxy-2-[4-methoxy-3-(3-methylbut-2-enyl)phenyl]chroman-4-one (8d). The compound was isolated as a light yellow oil in 30% (isolated) and 90% (based on recovered starting material) yield. R_f = 0.44 (25% EtOAc−hexanes); IR (neat) 3218, 2963, 2927, 1660, 1600, 1504, 1463, 1330, 1257, 1157, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.7 Hz, 1 H), 7.23 (dd, J = 8.4, 2.1 Hz, 1 H), 7.21 (d, J = 2.4 Hz, 1 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.52 (dd, J = 7.2, 1.2 Hz, 1 H), 6.44 (d, J = 2.1 Hz, 1

H), 5.35 (dd, J = 13.2, 2.7 Hz, 1 H), 5.26 (t, J = 7.2 Hz, 1 H), 3.82 (s, 3 H), 3.32 (d, J = 7.2 Hz, 2 H), 3.06 (dd, J = 13.2, 3.9 Hz, 1 H), 2.77 (dd, J = 17.1, 3.0 Hz, 1 H), 1.71 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 167.4, 163.9, 157.7, 132.9, 130.6, 130.2, 129.3, 127.5, 125.1, 121.8, 118.1, 110.2, 103.4, 79.8, 55.4, 28.4, 25.8, 17.7; EIMS (*m*/*z*, rel intensity) 338 (M^+, 100), 307 (20), 269 (17), 189 (76), 137 (51), 115 (25), 69 (23); HRMS *m*/*z* calcd for $C_{21}H_{22}O_4$, 338.1518; found, 338.1522. Anal. ($C_{21}H_{22}O_4 \cdot 3.25H_2O$) C, H.

7-Methoxy-2-[4-(methoxymethoxy)-3-(3-methylbut-2-enyl)-phenyl]chroman-4-one (8e). The compound was isolated as a clear light yellow oil in 50% (isolated) and 97% (based on recovered starting material) yield. R_f = 0.53 (25% EtOAc−hexanes); IR (neat) 2911, 1686, 1610, 1574, 1503, 1446, 1374, 1332, 1292, 1250, 1154, 1128 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 9.3 Hz, 1 H), 7.23 (m, 2 H), 7.07 (d, J = 8.4 Hz, 1 H), 6.57 (dd, J = 8.7, 2.7 Hz, 1 H), 6.44 (d, J = 2.4 Hz, 1 H), 5.36 (dd, J = 13.2, 3.0 Hz, 1 H), 5.27 (t, J = 7.8 Hz, 1 H), 5.20 (s, 2 H), 3.80 (s, 3 H), 3.45 (s, 3 H), 3.34 (d, J = 7.2 Hz, 2 H), 3.03 (dd, J = 13.2, 3.6 Hz, 1 H), 2.75 (dd, J = 17.1, 3.3 Hz, 1 H), 1.70 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 166.1, 163.6, 155.2, 132.8, 131.6, 131.2, 128.7, 127.7, 125.0, 122.0, 114.7, 113.8, 110.1, 100.8, 94.2, 79.9, 55.9, 55.6, 44.1, 28.7, 25.8, 17.8; positive ESIMS (*m*/*z*, rel intensity) 383 (MH^+, 100), 351 (15), 283 (16), 214 (10), 150 (14); HRMS *m*/*z* calcd for $C_{23}H_{26}O_5$, 382.1780; found, 382.1778. Anal. ($C_{23}H_{26}O_5 \cdot 0.25H_2O$) C, H.

2-[4-Hydroxy-3-(3-methylbut-2-enyl)phenyl]-7-methoxychroman-4-one (8f). The compound was isolated as a yellow semisolid in 40% (isolated) and 88% (based on recovered starting material) yield. R_f = 0.31 (20% EtOAc−hexanes); IR (neat) 3338, 2924, 1663, 1605, 1573, 1508, 1443, 1364, 1335, 1260, 1159, 1115 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 1 H), 7.37 (m, 2 H), 6.84 (m, 1 H), 6.57 (dd, J = 8.7, 2.1 Hz, 1 H), 6.45 (m, 1 H), 5.82 (s, 1 H), 5.31 (m, 2 H), 3.79 (s, 3 H), 3.45 (s, 3 H), 3.35 (d, J = 6.6 Hz, 2 H), 3.03 (dd, J = 13.8, 3.3 Hz, 1 H), 2.76 (dd, J = 16.8, 2.7 Hz, 1 H), 1.75 (s, 3 H), 1.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 166.4, 163.0, 155.4, 132.7, 131.6, 130.7, 128.6, 126.1, 122.4, 116.3, 106.9, 101.3, 80.4, 56.1, 45.7, 26.3, 17.5; CIMS (*m*/*z*, rel intensity) 339 (MH^+, 73), 327 (9), 299 (24), 215 (15), 177 (76), 151 (38), 123 (11); HRMS *m*/*z* calcd for $C_{21}H_{22}O_4$, 338.1518; found, 338.1520. Anal. ($C_{21}H_{22}O_4 \cdot 0.3H_2O$) C, H.

7-Methoxy-2-[4-methoxy-3-(3-methylbut-2-enyl)phenyl]chroman-4-one (8g). The compound was isolated as a clear light yellow oil in 56% (isolated) and 99% (based on recovered starting material) yield. R_f = 0.47 (20% EtOAc−hexanes); IR (neat) 3341, 2924, 2851, 1679, 1607, 1499, 1443, 1334, 1254, 1159 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.7 Hz, 1 H), 7.23 (dd, J = 8.4, 2.1 Hz, 1 H), 7.19 (d, J = 2.4 Hz, 1 H), 6.85 (d, J = 8.1 Hz, 1 H), 6.58 (dd, J = 8.7, 2.7 Hz, 1 H), 6.45 (d, J = 2.4 Hz, 1 H), 5.37 (dd, J = 13.8, 3.0 Hz, 1 H), 5.27 (t, J = 7.2 Hz, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.31 (d, J = 7.5 Hz, 2 H), 3.03 (dd, J = 13.5, 3.3 Hz, 1 H), 2.75 (dd, J = 17.1, 2.7 Hz, 1 H), 1.71 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 166.0, 163.6, 157.6, 132.8, 130.5, 130.3, 128.6, 127.5, 125.0, 121.9, 114.7, 110.1, 100.8, 79.9, 55.4, 44.2, 28.4, 25.8, 17.7; EIMS (*m*/*z*, rel intensity) 352 (M^+, 73), 321 (21), 283 (11), 202 (25), 189 (100), 151 (55), 115 (22), 69 (17); HRMS *m*/*z* calcd for $C_{22}H_{24}O_4$, 352.1675; found, 352.1676. Anal. ($C_{22}H_{24}O_4 \cdot 3.0H_2O$) C, H.

2-[4-Methoxy-3-(3-methylbut-2-enyl)phenyl]chroman-4-one (8h). The compound was isolated as a clear light yellow oil in 65% (isolated) and 97% (based on recovered starting material) yield. R_f = 0.49 (15% EtOAc−hexanes); IR (neat) 2975, 1689, 1606, 1577, 1500, 1464, 1305, 1254, 1223, 1148, 1119 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.7 Hz, 1 H), 7.32 (m, 4 H), 7.15 (d, J = 7.2 Hz, 1 H), 6.56 (dd, J = 8.7, 2.1 Hz, 1 H), 6.49 (s, 1 H), 5.39 (dd, J = 13.2, 2.7 Hz, 1 H), 5.28 (t, J = 7.2 Hz, 1 H), 5.20 (s, 2 H), 3.78 (s, 3 H), 3.33 (d, J = 7.2 Hz, 2 H), 3.01 (dd, J = 13.8, 2.7 Hz, 1 H), 2.76 (dd, J = 16.5, 2.1 Hz, 1 H), 1.71 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 161.8, 157.6, 136.0, 132.9, 130.5, 130.2, 127.5, 126.9, 125.0, 121.9, 121.3, 120.8, 118.1, 110.1, 79.5, 55.4, 44.3, 28.4 25.7, 17.7; EIMS (*m*/*z*, rel intensity) 322 (M^+, 73), 267 (10), 253 (23), 189 (46), 147 (72), 121 (100), 92 (60), 65 (36), 55 (21). Anal. ($C_{21}H_{22}O_3$) C, H.

7-Methoxy-2-[3-(3-methylbut-2-enyl)phenyl]chroman-4-one (8i). The compound was isolated as a clear very light yellow oil in 55% (isolated) and 95% based on recovered starting material) yield. R_f = 0.48 (15% EtOAc−hexanes); IR (neat) 2923, 1683, 1607, 1574, 1442, 1259, 1158, 1113 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.7 Hz, 1 H), 7.32 (m, 4 H), 7.15 (d, J = 7.2 Hz, 1 H), 6.56 (dd, J = 8.7, 2.1 Hz, 1 H), 6.49 (s, 1 H), 5.39 (dd, J = 13.2, 2.7 Hz, 1 H), 5.28 (t, J = 7.2 Hz, 1 H), 5.20 (s, 2 H), 3.78 (s, 3 H), 3.33 (d, J = 7.2 Hz, 2 H), 3.01 (dd, J = 13.8, 2.7 Hz, 1 H), 2.76 (dd, J = 16.5, 2.1 Hz, 1 H), 1.71 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6, 166.0, 163.5, 142.5, 138.7, 132.9, 128.8, 128.5, 126.2, 123.5, 122.6, 114.7, 110.1, 100.8, 80.1, 55.6, 44.2, 34.2, 25.7, 16.9; EIMS (*m*/*z*, rel intensity) 322 (M^+, 88), 253 (29), 177 (100), 151 (77), 122 (55), 107 (53), 69 (71), 55 (73); HRMS *m*/*z* calcd for $C_{21}H_{22}O_3$, 322.1569; found, 322.1571; Anal. ($C_{21}H_{22}O_3 \cdot 0.2H_2O$) C, H.

7-Methoxy-2-(4-methoxyphenyl)chroman-4-one (8j). The compound was isolated as a yellow solid in 65% (isolated) and 99% (based on recovered starting material) yield: mp 79−81 °C; R_f = 0.5 (15% EtOAc−hexanes); IR (neat) 3003, 2961, 1680, 1609, 1574, 1515, 1444, 1275, 1257, 1158, 1113 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.7 Hz, 1 H), 7.36 (m, 2 H), 6.92 (m, 2 H), 6.57 (dd, J = 8.7, 2.7 Hz, 1 H), 6.44 (d, J = 2.4 Hz, 1 H), 5.37 (d, J = 13.8, 3.3 Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.01 (dd, J = 13.2, 3.3 Hz, 1 H), 2.76 (dd, J = 17.1, 3.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 166.0, 163.5, 159.8, 130.7, 128.6, 127.7, 114.7, 114.1, 110.1, 100.8, 79.7, 55.5, 55.3, 44.0; EIMS (*m*/*z*, rel intensity) 284 (M^+, 80), 269 (7), 177 (13), 134 (100), 121 (53), 108 (9), 91 (24); HRMS *m*/*z* calcd for $C_{17}H_{16}O_4$, 284.1049; found, 284.1051. Anal. ($C_{17}H_{16}O_4$) C, H.

7-Methoxy-2-[4-(3-methylbut-2-enyloxy)phenyl]chroman-4-one (8k). The compound was isolated as a solid in 50% (isolated) and 88% (based on recovered starting material) yield: mp 108−110 °C; R_f = 0.31 (25% EtOAc−hexanes); IR (neat) 2917, 1723, 1680, 1609, 1513, 1444, 1385, 1257, 1158, 1113 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.7 Hz, 1 H), 7.36 (m, 2 H), 6.93 (m, 2 H), 6.57 (dd, J = 8.7, 2.1 Hz, 1 H), 6.44 (d, J = 2.1 Hz, 1 H), 5.46 (m, 1 H), 5.37 (dd, J = 13.2, 2.7 Hz, 1 H), 4.50 (d, J = 6.6 Hz, 2 H), 3.79 (s, 3 H), 3.03 (dd, J = 13.8, 3.9 Hz, 1 H), 2.76 (dd, J = 17.1, 3.3 Hz, 1 H), 1.77 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 166.1, 163.5, 159.1, 138.4, 130.6, 128.6, 127.6, 119.3, 114.8, 110.1, 100.8, 79.7, 64.7, 55.5, 44.0, 25.8, 18.1; CIMS (*m*/*z*, rel intensity) 339 (MH^+, 100), 299 (5), 271 (30), 215 (6), 177 (32), 151 (6); HRMS *m*/*z* calcd for $C_{21}H_{22}O_4$, 338.1518; found, 338.1522. Anal. ($C_{21}H_{22}O_4$) C, H.

3-Hydroxy-1-(2-hydroxy-4-methoxyphenyl)-3-[4-methoxy-3-(3-methylbut-2-enyl)phenyl]propan-1-one (9). A solution of LiHMDS in THF (1 M, 7.2 mL, 7.2 mmol) was added to a well-stirred solution of acetophenone **6b** (500 mg, 3.0 mmol) in THF (15 mL) under argon at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and at −10 °C for 2 h and was cooled again to −78 °C, and a solution of aldehyde **5b** (615 mg, 3.0 mmol) in THF (2 mL) was added in one portion. Stirring was continued at −78 °C for 30 min and then the cooling bath was removed and the reaction mixture was stirred at room temperature. Stirring was continued for 24 h and the reaction mixture was quenched by the addition of saturated NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and then concentrated in vacuo. The residue was column chromatographed on silica gel, eluting with 50% ethyl acetate in hexanes, to afford compound **15** as a clear oil (430 mg, 39% yield). R_f = 0.27 (50% EtOAc−hexanes); IR (neat) 1631 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.67 (s, 1 H), 7.65 (d, J = 10.0 Hz, 1 H), 7.20 (m, 2 H), 6.88 (d, J = 5.0 Hz, 1 H), 6.44 (m, 2 H), 5.31 (t, J = 2.7 Hz, 1 H), 5.28 (dd, J = 8.3, 1.2 Hz, 1 H), 3.83 (s, 6 H), 3.33 (m, 4 H), 1.79 (s, 3 H), 1.77 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 166.5, 165.6, 157.0, 134.8, 132.6, 131.9, 130.4, 127.0, 124.4, 122.4, 113.7, 110.3, 108.0, 101.0, 70.0, 55.7, 55.6, 46.8, 28.7, 25.9, 17.9; EIMS (*m*/*z*, rel intensity) 370 (M^+, 1), 352 (5),

321 (1), 218 (10), 203 (12), 189 (9), 135 (12), 108 (15), 91 (32), 69 (100), 43 (60); negative ion ESIMS (*m*/*z*, rel intensity) 369 [$(M - H)^-$]; HRMS calcd for $C_{22}H_{26}O_5$, 370.1780; found, 370.1783. Anal. ($C_{22}H_{28}O_5$) C, H.

Assay for Inhibition of Aromatase Activity. The synthetic (±)-abyssinone II and (±)-analogues were tested for aromatase inhibition. Aromatase inhibition is quantified by measuring the fluorescent intensity of fluorescein, the hydrolysis product of dibenzylfluorescein, by aromatase. In brief, the test substance (10 μL) is preincubated with the NADPH regenerating system (90 μL of 2.6 mM $NADP^+$, 7.6 mM glucose 6-phosphate, 0.8 U/mL glucose 6-phosphate dehydrogenase, 13.9 mM $MgCl_2$, and 1 mg/mL albumin in 50 mM potassium phosphate, pH 7.4) for 10 min at 37 °C before 100 μL of the enzyme and substrate mixture [80 μL/mL enzyme (CYP19, BD Biosciences, San Jose, CA), 0.4 μM dibenzylfluorescein, and 4 mg/mL albumin in 50 mM potassium phosphate, pH 7.4] are added. Then, the reaction mixture is incubated for 30 min at 37 °C to allow aromatase to generate the product and quenched with 75 μL of 2 N NaOH. After the reaction is terminated, shaking for 5 min followed by an incubation for 2 h at 37 °C enhances the noise/background ratio, and fluorescence is measured at 485 nm (excitation) and 530 nm (emission). Three independent experiments were performed in duplicate, and the average values were used to construct the dose−response curves. At least four concentrations of each test substance were used, and the IC_{50} values were calculated (Table 2).

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Supporting Information Available: ^1H NMR, ^{13}C NMR, and elemental analyses for compounds **7a**−**7k**, **8a**−**8k**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) American Cancer Society web site. http://www.cancer.org. and www.imaginis.com (accessed on April 5, 2007).
(2) Vogel, C. L. Hormonal Approaches to Breast Cancer Treatment and Prevention: An Overview. *Semin. Oncol.* **1996**, *23*, 2−9.
(3) Reddy, P. A Review of the Newer Aromatase Inhibitors in the Management of Metastatic Breast Cancer. *J. Clin. Pharm. Ther.* **1998**, *23*, 81−90.
(4) Tobias, J. S. Endocrine Approaches for the Treatment of Early and Advanced Breast Cancer in Postmenopausal Women. *Int. J. Biochem. Cell Biol.* **2004**, *36*, 2112−2119.
(5) Karr, J. P.; Kaburagi, Y.; Mann, C. F.; Sandberg, A. A. The Potential Significance of Aromatase in the Etiology and Treatment of Prostatic Disease. *Steroids* **1987**, *50*, 449−457.
(6) Henderson, D.; Habenicht, U.-F.; Nishino, Y.; el Etreby, M. F. Estrogens and Benign Prostatic Hyperplasia: The Basis for Aromatase Inhibitor Therapy. *Steroids* **1987**, *50*, 219−233.
(7) Siiteri, P. K. Review of Studies on Estrogen Biosynthesis in the Human. *Cancer Res.* **1982**, *42*, 3269s−3273s.
(8) Attar, E.; Bulun, S. E. Aromatase Inhibitors: The Next Generation of Therapeutics for Endometriosis. *Fertil. Steril.* **2006**, 1307−1318.
(9) Geisler, J.; Lonning, E. Aromatase Inhibition: Translation into Successful Therapeutic Approach. *Clin. Cancer Res.* **2005**, *11*, 2809−2821.
(10) Michaud, L. B. Adjuvant Use of Aromatase Inhibitors in Postmenopausal Women with Breast Cancer. *Am. J. Health-Syst. Pharm.* **2005**, *62*, 266−273.
(11) Brueggemeier, R. W.; Hackett, J. C.; Diaz-Cruz, E. S. Aromatase Inhibitors in the Treatment of Breast Cancer. *Endocr. Rev.* **2005**, *26*, 331−345.
(12) Miller, W. R. Aromatase Inhibitors: Mechanism of Action and Role in the Treatment of Breast Cancer. *Semin. Oncol.* **2003**, *30*, 3−11.
(13) Recanatini, M.; Cavalli, A.; Valenti, P. Nonsteroidal Aromatase Inhibitors: Recent Advances. *Med. Res. Rev.* **2002**, *22*, 282−304.
(14) Kelloff, G. J.; Lubet, R. A.; Lieberman, R.; Eisenhauer, K.; Steele, V. E.; Crowell, J. A.; Hawk, E. T.; Boone, C. W.; Sigman, C. C. Aromatase Inhibitors as Potential Cancer Chemopreventives. *Cancer Epidemiol. Biomarkers Prev.* **1998**, *7*, 65−78.
(15) Howell, A.; Robertson, J. F. R.; Vergote, I. A. Review of the Efficacy of Anastrozole in Postmenopausal Women with Advanced Breast Cancer with Visceral Metastases. *Breast Cancer Res. Treat.* **2003**, *82*, 215−222.
(16) Scott, J. L.; Keam, J. S. Letrozole: In Postmenopausal Hormone-Responsive Early-Stage Breast Cancer. *Drugs* **2006**, *66*, 353−362.
(17) Lonning, P. E.; Bajetta, E.; Murray, R.; Tubiana-Hulin, M.; Eisenberg, P. D.; Mickiewicz, E.; Celio, L.; Pitt, P.; Mita, M.; Aaronson, N. K.; Fowst, C.; Arkhipov, A.; di Salle, E.; Polli, A.; Massimini, G. Activity of Exemestane in Metastatic Breast Cancer After Failure of Nonsteroidal Aromatase Inhibitors: A Phase II Trial. *J. Clin. Oncol.* **2000**, *18*, 2234−2244.
(18) Carcache-Blanco, E. J.; Cuendet, M.; Park, E. J.; Su, B.-N.; Rivero-Cruz, J. F.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. Potential Cancer Chemopreventive Agents from *Arbutus unedo*. *Nat. Prod. Res.* **2006**, *20*, 327−334.
(19) Cuendet, M.; Oteham, C. P.; Moon, R. C.; Pezzuto, J. M. Quinone Reductase Induction as a Biomarker for Cancer Chemoprevention. *J. Nat. Prod.* **2006**, *69*, 460−463.
(20) Kinghorn, A. D.; Su, B.-N.; Jang, D. S.; Chang, L. C.; Lee, D.; Gu, J.-Q.; Carcache-Blanco, E. J.; Pawlus, A. D.; Lee, S. K.; Park, E. J.; Cuendet, M.; Gills, J. J.; Bhat, K.; Park, H.-S.; Mata-Greenwood, E.; Song, L. L.; Jang, M.; Pezzuto, J. M. Natural Inhibitors of Carcinogenesis. *Planta Med.* **2004**, *70*, 691−705.
(21) Kinghorn, A. D.; Su, B.-N.; Lee, D.; Gu, J.-Q.; Pezzuto, J. M. Cancer Chemopreventive Agents Discovered by Activity-Guided Fractionation: An Update. *Curr. Org. Chem.* **2003**, *7*, 213−226.
(22) Maiti. A.; Cuendet, M.; Kondratyuk, T.; Croy, V. L.; Pezzuto, J. M.; Cushman, M. Synthesis and Cancer Chemopreventive Activity of Zapotin, a Natural Product from *Casimiroa edulis*. *J. Med. Chem.* **2007**, *50*, 350−355.
(23) Lee, D.; Bhat, K. P.; Fong, H. H. S.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. Aromatase Inhibitors from *Broussonetia papyrifera*. *J. Nat. Prod.* **2001**, *64*, 1286−1293.
(24) Moriarty, M. R.; Grubjesic, S.; Surve, B. C.; Chandersekera, S. N.; Prakash, O.; Naithani, R. Synthesis of Abyssinone II and Related Compounds as Potential Chemopreventive Agents. *Eur. J. Med. Chem.* **2006**, *41*, 263−267.
(25) Anson, C. E.; Creaser, C. S.; Malkov, A. V.; Mojovic, L.; Stephenson, G. R. Flavonoid Derivatives as Organometallic Bioprobes. *J. Organomet. Chem.* **2003**, *668*, 101−122.
(26) Mitsuru, S.; Toshifumi, W. Preparation of Antihypertensive and Antianginal Phenyl Pyridyl Detone Oximes and Oxime Ethers with Potassium Channel-Opening Activity. Eur. Pat. Appl. EP 623597 A1, 1994; p 130.
(27) Bach, T.; Kruger, L. The Preparation of 2,3,5-Tri and 2,3-Disubstituted Furans by Regioselective Palladium(0) Catalyzed Coupling Reactions: Application to the Syntheses of Rosefuran and the F5 Furan Fatty Acid. *Eur. J. Org. Chem.* **1999**, 2045−2057.
(28) Knölker, H.-J.; Baum, E.; Reddy, K. R. Transition Metal Complexes in Organic Synthesis. Part 58: First Enantioselective Total Synthesis of the Potent Neuronal Cell Protecting Substance Carquinostatin A from (*R*)-Propene Oxide. *Tetrahedron Lett.* **2000**, *41*, 1171−1174.
(29) Tucker, C. E.; Majid, T. N.; Knochel, P. Preparation of Highly Functionalized Magnesium, Zinc, and Copper Aryl and Alkenyl Organometallics via the Corresponding Organolithiums *J. Am. Chem. Soc.* **1992**, *114*, 3938−3984.
(30) Odejinmi, S. I.; Wiemer, D. F. Application of Benzyl Protecting Groups in the Synthesis of Prenylated Aromatic Compounds. *Tetrahedron Lett.* **2005**, *46*, 3871−3874.
(31) Kyogoku, K. K.; Hatayama, K.; Yokomori, S.; Sek, T.; Tanaka, I. Synthesis of Prenyl Chalcone Sophoradin, Isolated from *Sophora subprostrata*. *Agric. Biol. Chem.* **1975**, *1*, 133−138.
(32) Jain, A. C.; Prasad, A. K. Synthesis of Amorilin (Euchrenone a3) and 5,7-Dihydroxy-6",6"-dimethyl-6,8-di-C-prenylpyrano[2",3",4",3"]-flavanone. *Indian J. Chem.* **1990**, *29B*, 525−528.
(33) Glusenkamp, K.-H.; Büchi, G. C-Prenylation of Phenols Promoted by Aluminium Oxide Surfaces. *J. Org. Chem.* **1986**, *51*, 4481−4483.
(34) Gray G. W.; Jones B. Mesomorphism and Chemical Constitution. II. The *trans-p-n*-Alkoxycinnamic Acids. *J. Chem. Soc.* **1954**, 1467−1470.
(35) Chari, V. M.; Aurnhammer, G.; Wagner, H. Synthese von (±)-4′-γ,γ-Dimethylallyl-naringenin (Selinon). *Tetrahedron Lett.* **1970**, 3079−3080.
(36) Pouget, C.; Fagnere, C.; Basly, J.-P.; Besson, A.-E.; Champavier, Y.; Habrioux, G.; Chulia, A.-J. Synthesis and Aromatase Inhibition Activity of Flavanones. *Pharm. Res.* **2002**, *19*, 286−291.
(37) Tsuji, Y.; Huh, K.-T.; Watanabe, Y. Ruthenium Complex Catalyzed *N*-Heterocyclization. Syntheses of Quinolines and Indole Derivatives from Aminoarenes and 1,3-Propanediol of Glycols. *J. Org. Chem.* **1987**, *52*, 1673−1680.

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