Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Design, Synthesis, and Biological Evaluation of Novel Deguelin-Based Heat Shock Protein 90 (HSP90) Inhibitors Targeting Proliferation and Angiogenesis

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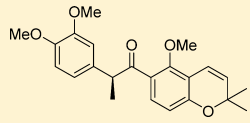
Supporting Information

ABSTRACT: Deguelin exhibits potent apoptotic and antiangiogenic activities in a variety of transformed cells and cancer cells. Deguelin also exhibits potent tumor suppressive effects in xenograft tumor models for many human cancers. Our initial studies confirmed that deguelin disrupts ATP binding to HSP90 and consequently induces destabilization of its client proteins such as HIF-1α. Interestingly, a fluorescence probe assay revealed that deguelin and its analogues do not compete with ATP binding to the N-terminus of HSP90, unlike most HSP90 inhibitors. To determine the key parts of deguelin that contribute to its potent HSP90 inhibition, as well as its antiproliferative and antiangiogenic activities, we have established a structure−activity relationship (SAR) of deguelin. In the course of these studies, we identified a series of novel and potent HSP90 inhibitors. In particular, analogues **54** and **69**, the B- and C-ring-truncated compounds, exhibited excellent antiproliferative activities with IC_{50} of 140 and 490 nM in the H1299 cell line, respectively, and antiangiogenic activities in zebrafish embryos in a dose dependent manner (0.25−1.25 μM).



INTRODUCTION

Molecular chaperones, such as heat-shock proteins (HSPs), are ubiquitous proteins that make use of ATP-dependent conformational changes to regulate the folding of client proteins for the purpose of activating nascent proteins, refolding of damaged proteins, or degrading severely damaged proteins.[1] In addition, chaperone proteins can prevent client protein aggregation and help membrane translocation of the client protein for intracellular deposition. HSP90 is a heat shock protein, and its molecular chaperone function is required for the stability and activation of numerous client proteins related to signal transduction in the cell.[2] Under standard, nonstress conditions, the amount of HSP90 comprises 1−2% of total cellular proteins, but under stress, levels of HSP90 increase about 2-fold. Oncogenic mutations of client proteins require increased HSP90 activity and consequently lead to the overexpression of HSP90, a phenotype that is common in human cancer.[3] HSP90 client proteins include ErbB2, Src, Met tyrosine kinases, mitogen-activated protein kinase kinase (MEK 1/2), Akt, Raf-1, cyclin-dependent serine kinases, steroid hormone receptors, telomerase, metalloprotein-2 (MMP-2), and hypoxia-inducible factor-1α (HIF-1α), all of which exist in various signaling pathways for the survival, proliferation, invasion, metastasis, and angiogenesis of cells and are known to contribute to the malignant phenotype.[4] Specifically, HIF-1α, a subunit of HIF-1 with constitutively expressed HIF-1β, is an oxygen-labile transcriptional factor that promotes angiogenesis at positions of vascular disruption and dysfunction by inducing the expression of vascular endothelial growth factor (VEGF), an angiogenesis-regulatory protein. Angiogenesis is the process of the formation of new blood vessels and is necessary for the repair, reproduction, and development of damaged blood vessels or metabolically active new tissues. However, pathological angiogenesis not only plays an important role in the growth and spread of tumors by their metastases but also induces bleeding, vascular leakage, and tissue destruction by abnormally rapid neovascularization.[5] As a result, pathological angiogenesis can lead to diverse angiogenesis-dependent diseases, including diabetic retinopathy (DR), age-related macular degeneration (AMD), and autoimmune diseases, as well as cancer.[6] Thus, HSP90 inhibition can be considered as an effective and novel therapy against angiogenesis-associated diseases, including cancer, with HSP90 inhibitors representing potentially promising chemotherapeutic agents for angiogenesis-dependent diseases.

HSP90 predominantly exists as a homodimer and is composed of three principal domains; N-terminal, middle,

Received: June 19, 2012
Published: November 27, 2012

dx.doi.org/10.1021/jm301488q | J. Med. Chem. 2012, 55, 10863−10884

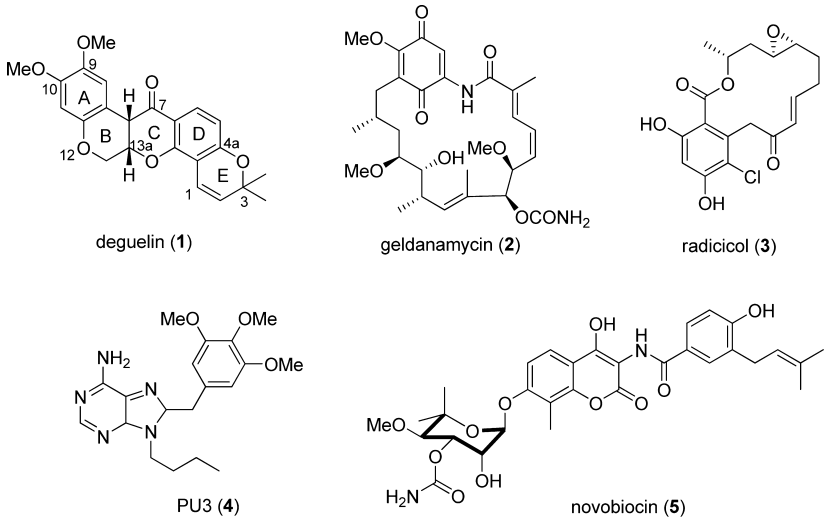
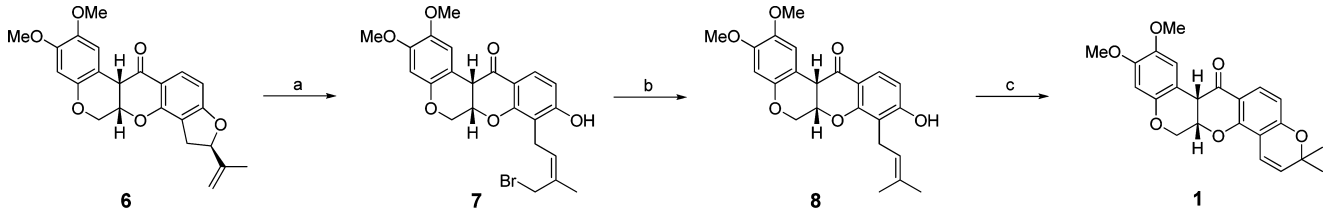


Figure 1. Chemical structures of deguelin (**1**) and other reported HSP90 inhibitors.

Scheme 1. Synthesis of Intermediate 8 and Deguelin[a]



[a]Reagents and conditions: (a) BBr_3, CH_2Cl_2, −10 °C; (b) $NaBH_3CN$, HMPA, 70 °C, 50% for two steps; (c) (i) PhSeCl, CH_2Cl_2, −30 °C, (ii) H_2O_2, THF, 0 °C, 61%.

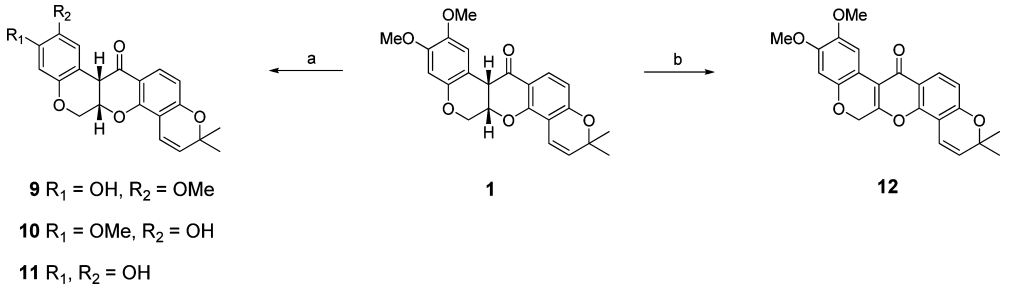
and C-terminal domains.[7] The N-terminal domain has an adenine nucleotide-binding pocket that contains an unusual structural motif known as the Bergerat fold, making this ATP-binding domain different from the ATP-binding pockets of chaperone HSP70 or other kinases.[8] This structural singularity suggests the possibility of discovering highly selective HSP90 inhibitors. Most HSP90 inhibitors, including geldanamycin (**2**),[9] the less toxic analogue 17-allylamino-17-demethoxygeldanamycin (17-AAG),[10] radicicol (**3**),[11] the more stable oxime analogues,[12] and the synthetic compound PU3 (**4**),[13] (Figure 1) are known to interact with the ATP-binding pocket in the N-terminal domain of HSP90, whereas novobiocin (**5**),[14] a natural antibiotic known as a DNA gyrase B inhibitor, has shown effective inhibitory activity by interacting with the ATP-binding pocket in the C-terminal domain of HSP90. These HSP90 inhibitors showed prominent chemopreventive effects against a diverse array of cancer cells in preclinical models by accelerating the degradation of numerous oncogenic HSP90 client proteins; a few HSP90 inhibitors, including 17-AAG, have entered phase II clinical trials. However, several clinical trials of HSP90 inhibitors have revealed various negative side effects with constitutional clinical symptoms.[15]

Deguelin (**1**), a rotenoid isolated from the African plant *Mundulea sericea* (Leguminosae),[16] has been reported to prevent tobacco carcinogen-induced lung carcinogenesis by blocking Akt activation[17] and has shown potent apoptotic and antiangiogenic activities against diverse transformed cells and cancer cells in vitro.[18] We recently reported that deguelin interferes with the chaperone function of HSP90 by inhibiting ATP binding, thereby inducing the destabilization of HIF-1α with consequent tumor growth reduction in xenograft models of various human cancers, such as lung, prostate, head and neck, and stomach cancers.[19] In addition, we proposed that deguelin binds to the N-terminal ATP-binding pocket of HSP90 using a structure−function analysis with a docking study of deguelin and HSP90.[19,20] However, our recent work has revealed no activity of deguelin and its analogues in a fluorescence polarization assay (FP assay)[21] using VER-00045864,[22] which is a fluorescence probe that binds to the ATP-binding pocket in the N-terminal domain of HSP90. This result suggested that deguelin does not bind to the ATP-binding pocket of the N-terminal domain of HSP90 but might bind to the other binding site in HSP90, distinguishing it from other HSP90 inhibitors. Recently, Hieronymus and Brandt reported that the HSP90 inhibitor gedunin showed unique HSP90 modulatory attributes.[23] Although the effective biological activities of deguelin as an HSP90 inhibitor have been evaluated by several biological methods, details of the deguelin-binding site in HSP90 remain undetermined.

In this article, we describe the design, synthesis, and biological evaluation of a novel series of synthetic HSP90 inhibitors based on the structure of deguelin to establish the structure−activity relationships between deguelin and HSP90 and to identify the congener responsible for the excellent biological activities of deguelin. Our effort also involves the identification of HSP90 inhibitors consisting of novel and simplified scaffolds based on the elucidated congener. Initially, 24 analogues were prepared from deguelin by semisynthetic procedures to elucidate the essential skeleton and functionalities for potent HSP90 inhibition. Additionally, nine HSP90

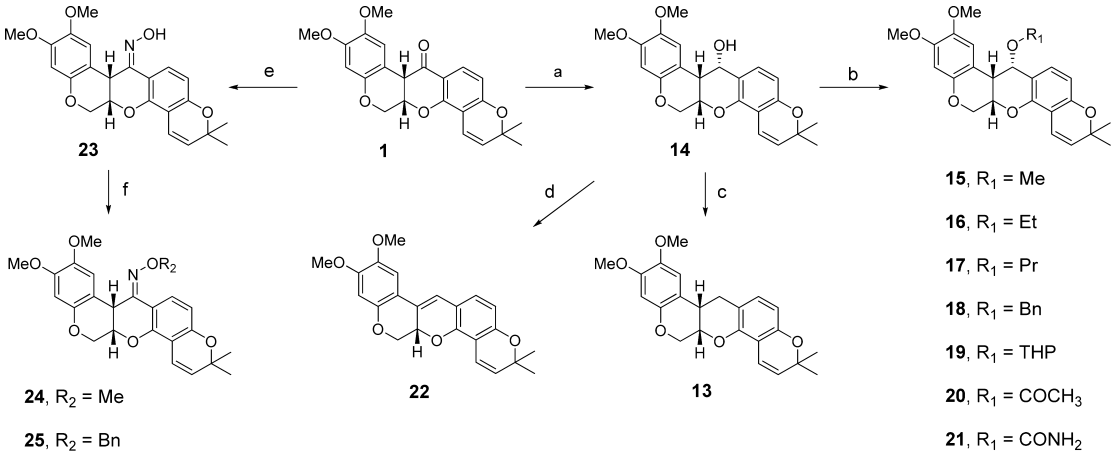
dx.doi.org/10.1021/jm301488q | J. Med. Chem. 2012, 55, 10863−10884

Scheme 2. Synthesis of the 9,10-Demethylated Analogues and α,β-Unsaturated Deguelin[a]



[a]Reagents and conditions: (a) BBr_3, CH_2Cl_2, −78 to 0 °C, 16% for **9**, 14% for **10**, 33% for **11**; (b) I_2, NaOAc, EtOH, reflux, 35%.

Scheme 3. Synthesis of the C7-Modified Deguelin Analogues[a]



[a]Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 100%. (b) R_1 = Me: CH_3I, *t*-BuOK, THF, 0 °C, 100%. R_1 = Et: EtI, *t*-BuOK, THF, 0 °C, 71%. R_1 = *n*-Pr: 1-PrI, *t*-BuOK, THF, 0 °C, 68%. R_1 = Bn: BnBr, *t*-BuOK, THF, 0 °C, 88%. R_1 = THP: PPTS, DHP, CH_2Cl_2, rt, 50%. R_1 = Ac: Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 82%. R_1 = $CONH_2$: CCl_3CONCO, CH_2Cl_2, 0 °C, then MeOH/water, 67%. (c) (i) CH_3I, CS_2, NaH, THF, 0 °C; (ii) Bu_3SnH, AIBN, toluene, reflux, 49%; (d) AcOH, 100 °C, 70%; (e) $NH_2OH{\cdot}HCl$, pyridine, 70 °C, 100%; (f) R_2 = Me: CH_3I, *t*-BuOK, THF, 0 °C, 57%. R_2 = Bn: BnBr, *t*-BuOK, THF, 0 °C, 33%.

inhibitors with a novel scaffold, designed on the basis of the ring-truncation strategy, were synthesized via concise and versatile synthetic procedures developed to produce a variety of ring-truncated analogues. The synthesized compounds were evaluated by the cell growth inhibition assay (MTS assay) against H1299 non-small-cell lung cancer (NSCLC) and by Western blot analysis of the HIF-1α protein, which is not only an important client protein of HSP90 but also a VEGF-regulatory transcriptional factor that induces angiogenesis. Antiangiogenic activities of the analogues possessing a potent HSP90 inhibitory activity in vitro were further evaluated using a zebrafish angiogenesis model.

CHEMISTRY

Deguelin was prepared by a known procedure[24] from a commercially available natural product, rotenone (**6**), and the structure of the synthesized deguelin was confirmed by comparison of the spectral data to those of natural deguelin.[25] Enantiomeric purity of the synthetic deguelin was confirmed by HPLC and optical rotation. Most of the deguelin analogues were synthesized from deguelin or intermediate **8**, shown in Scheme 1, while the ring-truncated analogues were prepared by the procedures developed by us.[26] We first synthesized the deguelin analogues to determine the role that each fragment and the overall conformation of deguelin play in HSP90 inhibition. The synthetic procedures are shown in Schemes 1−4.

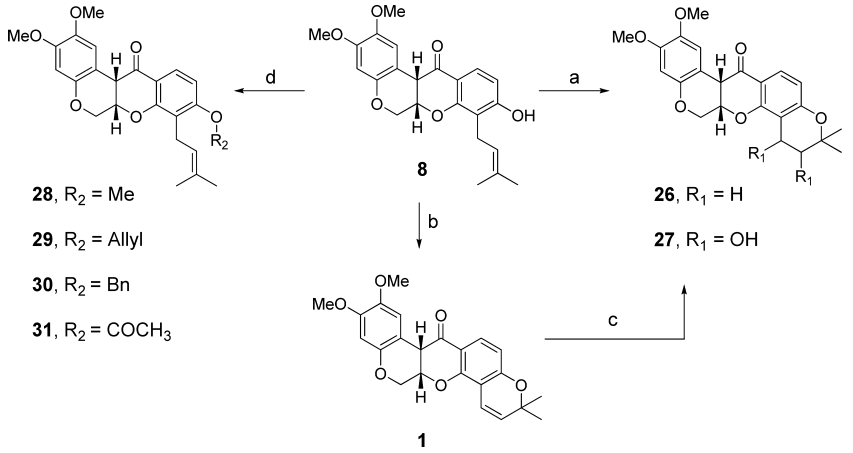
Syntheses of the C9 and/or C10-demethylated analogues **9**, **10**, and **11** are described in Scheme 2. Interestingly, treatment of deguelin with BBr_3 at −78 °C followed by warming to 0 °C afforded the desired analogues **9**, **10**, and **11** in a ratio of 1:1:2, whereas warming the reaction mixture to ambient temperature resulted in the production of catechol **11** as the major product. Iodination of deguelin and in situ treatment with NaOAc produced the α,β-unsaturated ketone **12**.

The C7-modified analogues were synthesized as outlined in Scheme 3. Reduction of deguelin with $NaBH_4$ produced the secondary alcohol **14** with a quantitative yield. Subsequent alkylation with various alkyl halides or acid-catalyzed THP protection of alcohol **14** afforded the corresponding alkyl ethers (**15**−**19**). Acetylation of **14** with Ac_2O in the presence of DMAP and Et_3N produced acetate **20**. Treatment of **14** with trichloroacetyl isocyanate followed by hydrolysis using a mixture of methanol and water afforded the desired carbamate **21**.

The Barton-McCombie radical reaction of **14** generated the deoxygenated product **13**.[27] Dehydration of **14** in boiling acetic acid produced styrene **22**. Treatment of deguelin with hydroxylamine in pyridine yielded oxime **23**, which was subsequently reacted with the appropriate alkyl halides to produce the oxime ethers **24** and **25**.

dx.doi.org/10.1021/jm301488q | J. Med. Chem. 2012, 55, 10863−10884

Scheme 4. Synthesis of the Terminal Pyran Ring-Modified Analogues[a]



[a]Reagents and conditions. (a) R_1 = H: PTSA, benzene, reflux, 99%; (b) (i) PhSeCl, CH_2Cl_2, −30 °C, (ii) H_2O_2, THF, 0 °C, 61%. (c) R_1 = OH: OsO_4, NMO, acetone/water (4:1), 0 °C to rt, 47%. (d) R_2 = Me: CH_3I, Cs_2CO_3, CH_3CN, 0 °C, 41%. R_2 = allyl: allyl iodide, Cs_2CO_3, CH_3CN, 0 °C, 39%. R_2 = Bn: BnBr, Cs_2CO_3, CH_3CN, 0 °C, 25%. R_2 = $COCH_3$: Ac_2O, DMAP, CH_2Cl_2, rt, 44%.

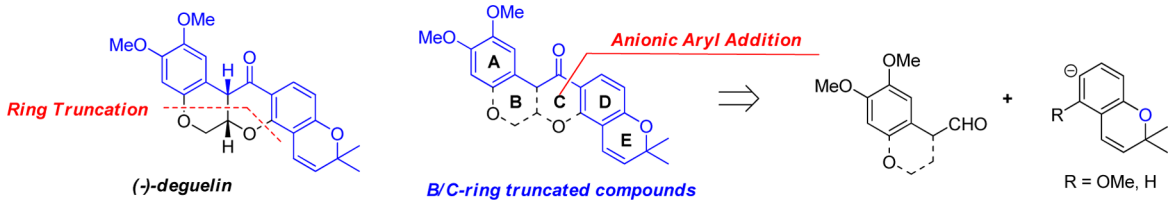
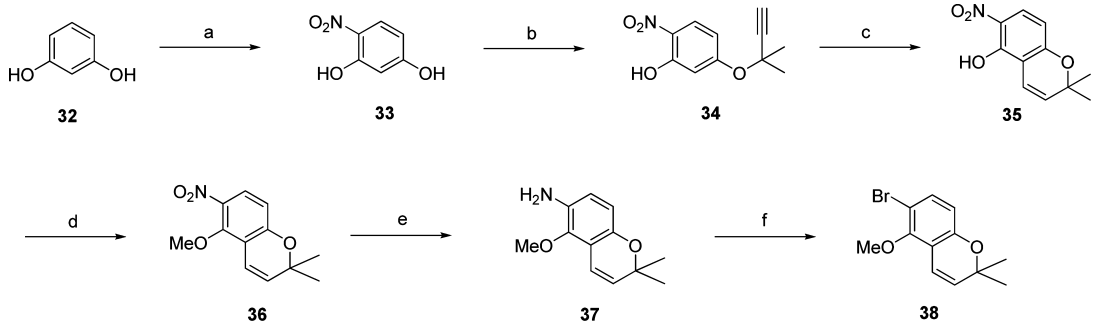


Figure 2. Ring-truncation strategy for the new HSP90 inhibitors.

Scheme 5. Synthesis of 6-Bromo-5-methoxy-2,2-dimethyl-2*H*-chromene (38)[a]



[a]Reagents and conditions: (a) HNO_3, AcOH, $CHCl_3$, rt, 55%; (b) 2-methyl-3-butyn-2-ol, DBU, TFAA, $CuCl_2$, CH_3CN, 0 °C, 45%; (c) *N*,*N*-diethylaniline, 130 °C, 91%; (d) CH_3I, K_2CO_3, acetone, 60 °C; (e) $SnCl_2{\cdot}2H_2O$, EtOH, reflux, 95% for two steps; (f) $NaNO_2$, HBr, CuBr, water, 0 to 65 °C, 88%.

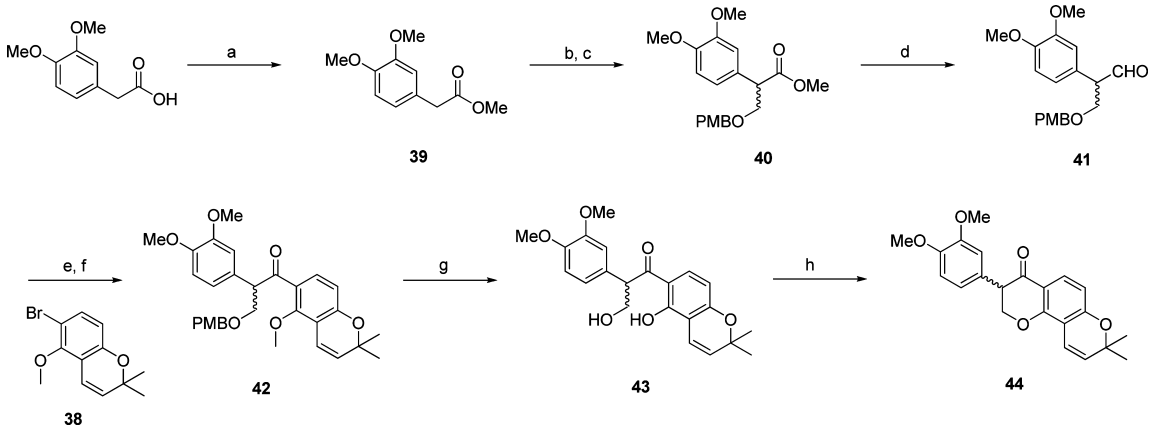
Syntheses of the terminal benzopyran-modified analogues **26**−**31** are outlined in Scheme 4. Acid-catalyzed cyclization of intermediate **8** produced dihydrobenzopyran **26**. Dihydroxylation of deguelin with OsO_4 in the presence of *N*-methylmorpholine *N*-oxide (NMO) produced the desired diol **27**. Treatment of intermediate **8** with Cs_2CO_3 followed by addition of the requisite alkyl halides at 0 °C gave the corresponding aryl ethers (**28**−**30**). Synthesis of acetate **31** from phenol **8** was accomplished by acetylation with Ac_2O in the presence of DMAP and Et_3N.

After successful completion of the syntheses of the deguelin analogues, we turned our attention to the discovery of new HSP90 inhibitors with a novel scaffold, avoiding the structural complexity of deguelin. Thus, we designed new HSP90 inhibitors, which are devoid of the middle dihydrobenzopyran units, by applying a ring-truncation strategy based on the initial SAR study of deguelin (Figure 2). Our unified synthetic procedure included addition of an aryl anion, which was prepared from **38** by halogen−metal exchange reaction, to the diverse aldehydes and seemed quite straightforward for the syntheses of the ring-truncated compounds.

First, our effort focused on the synthesis of aryl bromide **38** as a key precursor for the aryl anion (Scheme 5). Generally, 5-hydroxy-6-formyl-2,2-dimethyl-2*H*-chromenes are prepared by a propargylation of resorcinol and subsequent regioselective Claisen rearrangement.[28] However, 5-hydroxy-6-bromo-2,2-dimethyl-2*H*-chromene could not be prepared by the same reaction sequence largely because of the poor regioselectivity of the Claisen rearrangement. Thus, we prepared 5-hydroxy-6-nitro-2,2-dimethyl-2*H*-chromene **35** via propargylation of **33**

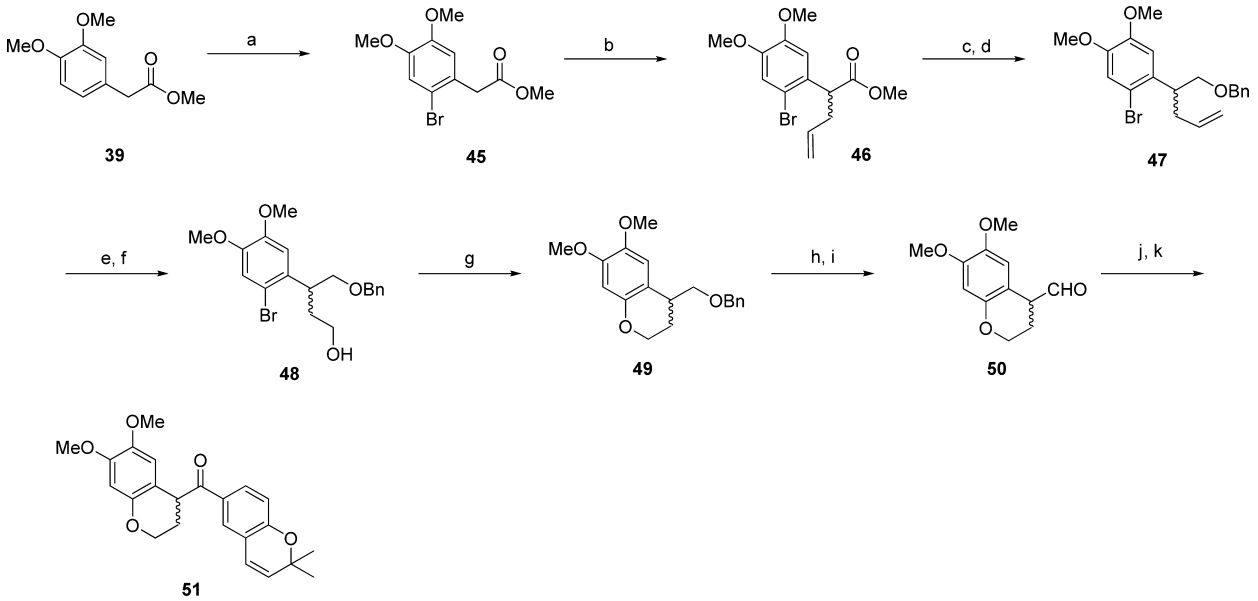
dx.doi.org/10.1021/jm301488q | *J. Med. Chem.* 2012, 55, 10863−10884

Scheme 6. Synthesis of the B-Ring-Truncated Analogue (44)[a]



[a]Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, 0 °C to rt, then MeOH, 89%; (b) NaOMe, $(CH_2O)_n$, DMSO, rt, 58%; (c) Bundle's reagent, CSA, CH_2Cl_2, rt, 100%; (d) (i) DIBAL-H, THF, −78 °C, 88%, (ii) DMP, CH_2Cl_2, rt, 71%; (e) **38**, *n*-BuLi, THF, −78 °C to rt, 72%; (f) DMP, CH_2Cl_2, 84%; (g) BCl_3, CH_2Cl_2, −78 °C, 75%; (h) DIAD, PPh_3, CH_2Cl_2, rt, 57%.

Scheme 7. Synthesis of the C-Ring-Truncated Analogue (51)[a]



[a]Reagents and conditions: (a) NBS, THF, −78 °C to rt, 96%; (b) allyl iodide, LHMDS, THF, −78 °C, 53%; (c) $LiAlH_4$, THF, 0 °C to rt, 88%; (d) NaH, BnBr, *n*-Bu_4NBr, THF, rt, 86%; (e) OsO_4, NMO, $NaIO_4$, acetone/water = 4:1, rt; (f) $NaBH_4$, MeOH, 0 °C, 73% for two steps; (g) $Pd_2(dba)_3$, 2-(di-*tert*-butylphosphino)biphenyl, *t*-BuONa, toluene, 50 °C, 75%; (h) (i) $Pd(OH)_2/C$, H_2, MeOH, rt; (ii) DMP, CH_2Cl_2, rt, 60% for two steps; (j) 6-bromo-2,2-dimethyl-2*H*-chromene, *n*-BuLi, THF, −78 °C to rt; (k) DMP, CH_2Cl_2, rt, 41% for two steps.

with 2-methyl-3-butyn-2-ol and a subsequent regioselective Claisen rearrangement. Methylation of **35** followed by reduction of the nitro group afforded the corresponding aniline **37**. Finally, aniline **37** was successfully converted to the aryl bromide **38** with a 88% yield under Sandmeyer condition using $NaNO_2$, CuBr, and HBr.[29]

The designed ring-truncated analogues containing a stereogenic center were synthesized as racemic mixtures; asymmetric synthesis of those analogues showing potent inhibitory activity was conducted later. Synthesis of the B-ring-truncated analogue is described in Scheme 6. Treatment of 3′,4′-dimethoxyphenylacetic acid with oxalyl chloride followed by an addition of excess methanol gave methyl ester **39**. An aldol reaction of **39** with paraformaldehyde followed by PMB protection of the resulting alcohol afforded ether **40**, which was converted into aldehyde **41** upon DIBAL-H reduction and subsequent Dess−Martin oxidation. Addition of the aryl anion of **38** to aldehyde **41** and subsequent Dess−Martin oxidation of the resulting alcohol produced the corresponding ketone **42**. Simultaneous removal of the PMB and methyl protecting groups of **42** with BCl_3 and a subsequent intramolecular Mitsunobu etherification using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine afforded the desired B-ring-truncated analogue **44**.

Regioselective bromination of ester **39** with NBS at −78 °C[30] followed by allylation of the resulting bromobenzene **45** with LHMDS and allyl iodide at −78 °C produced the allylated ester **46**. LAH reduction of **46** followed by protection of the resulting primary alcohol with benzyl bromide yielded benzyl ether **47**. Oxidative allyl cleavage of **47** with OsO_4 and $NaIO_4$ and subsequent $NaBH_4$ reduction of the resulting aldehyde

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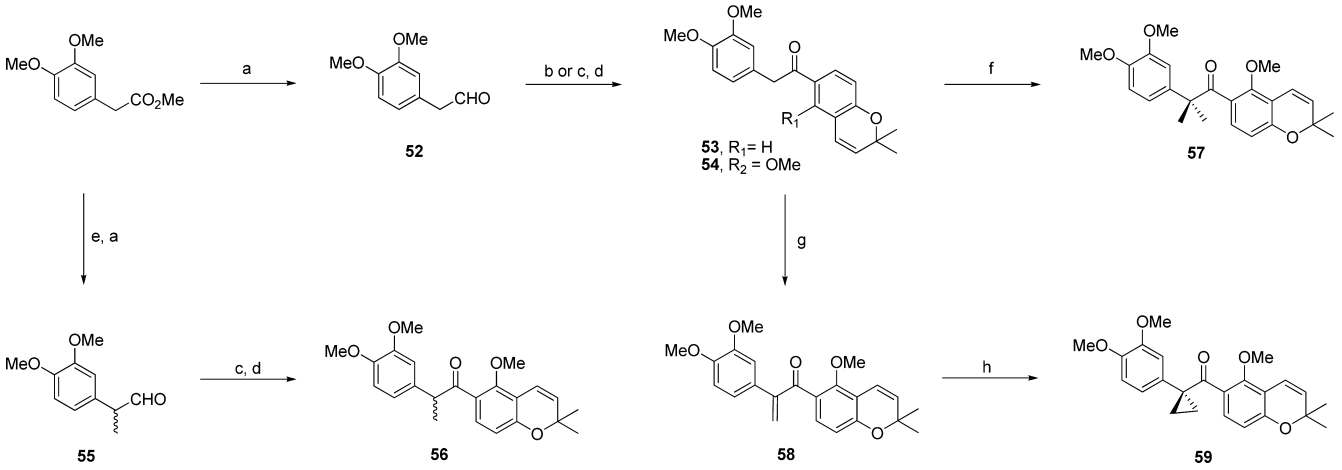
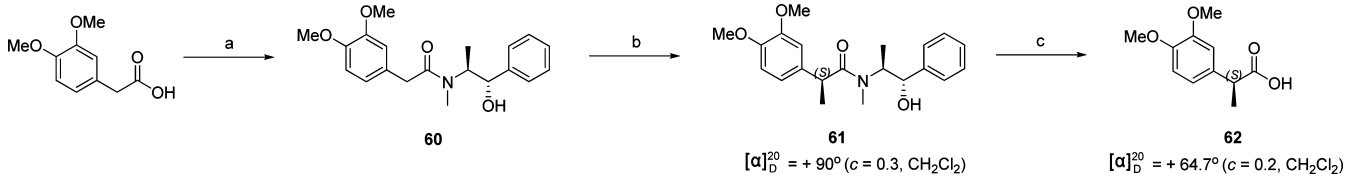
Scheme 8. Synthesis of the B- and C-Ring-Truncated Analogues[a]



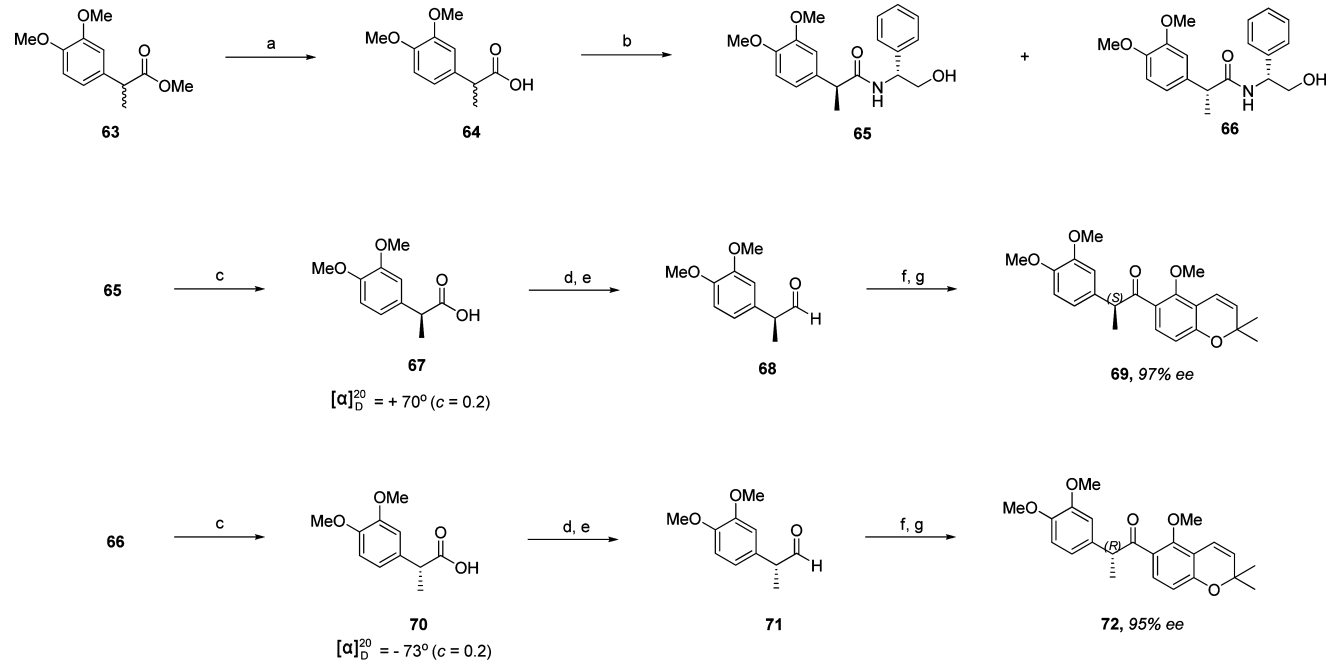
[a]Reagents and conditions: (a) DIBAL-H, THF, −78 °C. **52**: 68%. **55**: 61%. (b) **53**: *n*-BuLi, 6-bromo-2,2-dimethyl-2*H*-chromene, THF, −78 °C to rt. (c) **54**: *n*-BuLi, **38**, THF, −78 °C to rt; (d) DMP, CH_2Cl_2, rt. **53**: 46% for two steps. **54**: 48% for two steps. **56**: 64% for two steps. (e) LDA, CH_3I, THF, rt, −78 °C 79%; (f) NaH, CH_3I, THF, rt, 88%; (g) K_2CO_3, $(CH_2O)_n$, DMF, rt, 87%; (h) NaH, Me_3SOI, DMSO, rt, 91%.

Scheme 9. Synthesis of (*S*)-2-(3,4-Dimethoxyphenyl)propanoic Acid (62)[a]



[a]Reagents and conditions: (a) (i) $SOCl_2$, CH_2Cl_2, reflux, (ii) Et_3N, (+)-pseudoephedrine, CH_2Cl_2, rt, 73%; (b) CH_3I, LiCl, LDA, THF, −78 °C, 81%; (c) H_2SO_4, dioxane, 100 °C, 96%.

Scheme 10. Asymmetric Synthesis of the Optically Active Analogues 69 and 72[a]

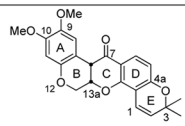
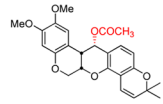
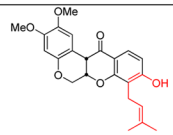
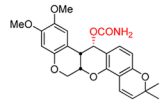
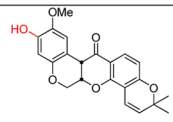
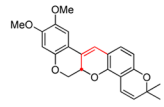
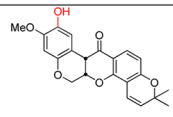
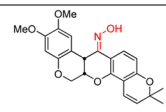
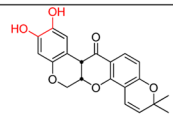
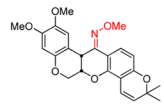
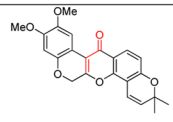
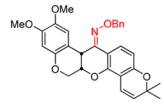
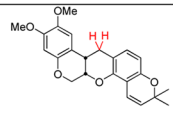
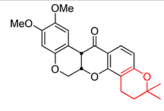
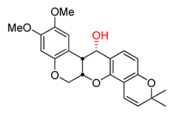
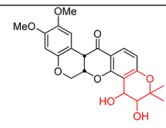
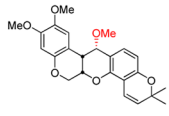
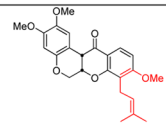
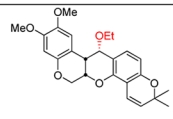
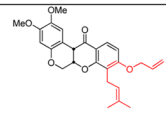
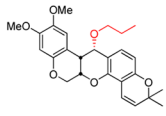
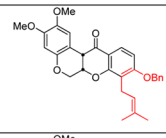
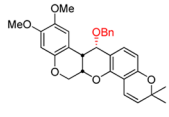
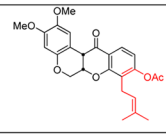
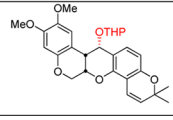


[a]Reagents and conditions: (a) LiOH·H_2O, THF/water (2:1), rt, 100%; (b) (−)-phenylglycinol, EDC, HOBt, *i*-Pr_2NEt, CH_2Cl_2, rt. **65**: 42%. **66**: 42%. (c) H_2SO_4, dioxane, 100 °C. **67**: 100%. **70**: 100%. (d) BH_3·SMe_2, ether, 0 °C to rt. **68**: 85%. **71**: 81%. (e) DMP, CH_2Cl_2, rt. **68**: 81%. **71**: 79%. (f) *n*-BuLi, $CeCl_3$, **38**, THF, −78 °C to rt. **69**: 80%. **72**: 48%; (g) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt. **69**: 84%. **72**: 71%.

produced alcohol **48**. Cyclization of **48** with *t*-BuONa in the presence of $Pd_2(dba)_3$ and 2-(di-*tert*-butylphosphino)biphenyl provided dihydrobenzopyrane **49**,[31] which was subjected to benzyl deprotection and Dess−Martin oxidation of the

dx.doi.org/10.1021/jm301488q | J. Med. Chem. 2012, 55, 10863−10884

Table 1. Cell Growth Inhibitions by Deguelin Analogues in the MTS Assay

Analogs[a]	Structure	IC_{50} (μM)[b] in H1299	Analogs[a]	Structure	IC_{50} (μM)[b] in H1299
Deguelin		0.11	**20**		0.68
8		9.8	**21**		0.11
9		0.87	**22**		N.A
10		0.97	**23**		0.3
11		10.1	**24**		4.3
12		N.A[c]	**25**		N.A
13		4.2	**26**		0.14
14		0.01	**27**		N.A
15		4.1	**28**		5.2
16		9.8	**29**		N.A
17		10.5	**30**		N.A
18		N.A	**31**		N.A
19		N.A			

[a]All compounds were purified by column chromatography and recrystallization (>95%). [b]IC_{50} values were determined as the mean of triplicate experiments, and standard deviations are within 15%. [c]No activity (NA) indicates that the analogue exhibits activity with an IC_{50} higher than 500 μM.

dx.doi.org/10.1021/jm301488q | J. Med. Chem. 2012, 55, 10863−10884

resulting alcohol to yield aldehyde **50**. The addition of the aryl anion, prepared from 6-bromo-2,2-dimethyl-2*H*-chromene,[31] to aldehyde **50** followed by oxidation of the resultant alcohol afforded the C-ring-truncated compound **51** (Scheme 7).

The B- and C-ring-truncated analogues were prepared as described in Scheme 8. Aldehyde **52**, which was prepared by the DIBAL-H reduction of methyl 3′,4′-dimethoxyphenyl acetate, was readily converted to **53** and **54** by the addition of the aryl anion, which was prepared from 6-bromo-2,2-dimethyl-2*H*-chromene and **38**, followed by Dess−Martin oxidation. The α-methylated analogue **56** was prepared by addition of the aryl anion prepared from **38** to aldehyde **55**, which was conveniently synthesized by α-alkylation of methyl 3′,4′-dimethoxyphenyl acetate using LDA and CH_3I, followed by ester reduction. Dimethylation of **54** with excess CH_3I and NaH afforded analogue **57**. Standard aldol condensation of **54** with paraformaldehyde gave enone **58**, which was subjected to Corey−Chaykovsky cyclopropanation[32] to yield analogue **59**.

We prepared the (*S*)- and (*R*)-enantiomers of racemate **56** to evaluate the HSP90 inhibitory activity of each enantiomer (Scheme 9). We initially synthesized the known acid **62** with an (*S*)-configuration to confirm the stereochemistries of both enantiomers of **56**, which were prepared by our own procedure shown in Scheme 10. Optically active amide **61** was synthesized by the amidation of 3′,4′-dimethoxyphenylacetic acid and the asymmetric methylation of (*S*,*S*)-pseudoephedrine amide **60**. Finally, optically active **62** was obtained in high yield by acid-catalyzed hydrolysis.[33]

The synthesis of each enantiomer of **56** is outlined in Scheme 10. The diastereomeric mixture of (−)-phenylglycinolamides **65** and **66** were prepared by the hydrolysis of racemic carboxylic ester **63**, followed by an EDC-assisted amide coupling of the resulting acid **64** with (−)-phenylglycinol.[34] The diastereomeric mixture of amides **65** and **66** was readily separated by flash chromatography, and each diastereomer was converted to the corresponding acid, **67** or **70**, by acid-catalyzed hydrolysis. The absolute configurations of **67** and **70** were confirmed by comparison of their spectral data, including optical rotation, with those of **62**. The reduction of acids **67** and **70** with the $BH_3{\cdot}SMe_2$ complex and subsequent Dess−Martin oxidation of the resulting alcohols produced aldehydes **68** and **71**. Aldehydes **68** and **71** were transformed into the corresponding ketones **69** and **72** via sequential condensation with an aryl anion, prepared from **38**, in the presence of $CeCl_3$ and Ley oxidation of the resulting alcohols (97 and 95% ee by chiral HPLC, respectively).

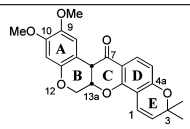
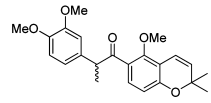
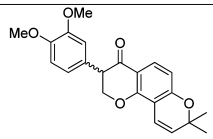
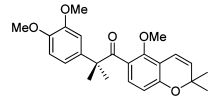
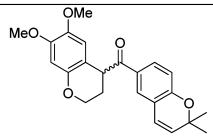
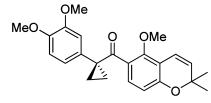
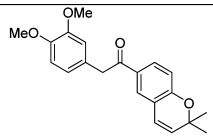
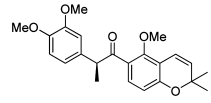
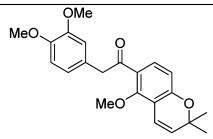
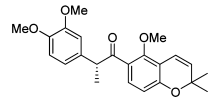
STRUCTURE−ACTIVITY RELATIONSHIP (SAR) BASED ON ANTIPROLIFERATIVE ACTIVITY

We previously reported that deguelin competes with ATP in binding to HSP90 and sensitively suppresses the interaction between HSP90 and its client proteins including HIF-1α.[19] For further confirmation of the HSP90 inhibitory activity of deguelin, we carried out an FP assay on deguelin and its analogues using VER-00045864 as a fluorescence probe for the N-terminal ATP-binding pocket of HSP90.[22] The HSP90 inhibitors in the FP assay are known to compete with the probe in binding to the N-terminal ATP-binding pocket of HSP90, resulting in a decrease of fluorescence polarization compared to the probe alone. Geldanamycin has been reported to have an IC_{50} of 348 nM in the FP assay using the VER-00045864 probe.[22] However, deguelin, which exhibited a significant HSP90 inhibitory activity at 100 nM level in our previous study,[19] did not show an inhibitory activity in the FP assay even at 20 μM (data not shown). These data suggested that deguelin binds to the other binding site of HSP90 and not to the ATP-binding pocket in the N-terminal domain of HSP90.[23] Thus, we attempted to establish the SAR between deguelin and HSP90 to obtain more detailed information about the deguelin binding mode. Ultimately, we desired to develop novel and effective HSP90 inhibitors based on the SAR study. Deguelin consists of five continuous rings including two aromatic rings, two cis-fused dihydropyrans (at C7a and C13a), and a hydrophobic 2,2-dimethyl-2*H*-chromene moiety. In addition, deguelin possesses two methoxy groups at C9 and C10 and a carbonyl group at C7, which is considered to be important for binding to HSP90.[20]

For the elucidation of the essential functions of each fragment and the proper conformation of the ring-fused systems required for potent HSP90 inhibition, we prepared 24 deguelin analogues. The synthesized analogues are classified as (i) the C9 and/or C10-methoxy-modified analogues **9**−**11**, (ii) the conformation-changed analogues **12**, **22**, (iii) the C7-carbonyl-modified analogues **13**−**21** and **23**−**25**, and (iv) the chromene-modified analogues **8** and **26**−**31**. The biological activities of the 24 analogues were evaluated by a cell growth inhibition assay (MTS assay) against H1299 non-small-cell lung cancer (NSCLC) cells. The results of the MTS assay are presented in Table 1. Initially, the effects of two methoxy groups at the C9 and C10-positions were analyzed. Analogues **9** and **10**, possessing monohydroxy groups on the A-ring, exhibited approximately 10-fold lower activity compared to deguelin, and analogue **11** with dihydroxyl groups showed 100-fold lower activity compared to deguelin. These results seem to imply that both of the methoxy groups are essential as H-bonding acceptors for the inhibitory activity of deguelin. The importance of maintaining a cis-conformation of deguelin is addressed by analogues **12** and **22**, as both analogues result in a complete loss of activity. Variation of the C7-carbonyl led to significant changes in the inhibitory activities. Removal of the C7-carbonyl group (**13**) caused significantly lower activity (IC_{50} of 4.2 μM); however, interestingly, reduction of the carbonyl to an alcohol (**14**) resulted in increased potency (IC_{50} of 10 nM) compared to that of deguelin, also revealing that the C7-oxygen atom is crucial for cell growth inhibition. However, the C7-alkoxy analogues **15**−**18** exhibited significantly decreased activity compared to deguelin and **14**, suggesting that the bulky substituents at the C7-position prevent the analogues from binding to HSP90. In fact, as the size of the alkyl groups increase (**15**−**19**), inhibitory activity decreases. H-Bonding of the C7-substituents also seems important for inhibitory activity. Analogue **14**, possessing a C7-hydroxyl group, exhibited the most potent activity, which was 10-fold more active than deguelin and 400-fold more active than the corresponding methyl ether **15**. Interestingly, the carbamate analogue **21** and the oxime analogue **23**, which possess H-bonding donors, also exhibited excellent cell growth inhibitory activities (IC_{50} of 110 and 300 nM, respectively). However, the corresponding oxime ethers **24** and **25** showed low or no activity. Overall, the presence of a bulky substituent at the C7-position seems to decrease or eliminate inhibitory activity; however, having H-bond donor groups at the C7-position can compensate or overcome the decrease of activity induced by the steric effect. We also examined the cell growth inhibitory activities of analogues **8** and **26**−**31** to learn the function of the terminal 2,2-dimethyl-2*H*-chromene moiety. Analogue **26**,

dx.doi.org/10.1021/jm301488q | J. Med. Chem. 2012, 55, 10863−10884

Table 2. Cell Growth Inhibition by the B- or/and C-Ring-Truncated Compounds in the MTS Assay

Analogs[a]	Structure	IC_{50} (μM)[b] in H1299	Aanlogs[a]	Structure	IC_{50} (μM)[b] in H1299
Deguelin		0.11	**56**		0.73
44		4.5	**57**		3.2
51		3.8	**59**		102
53		1.0	**69**		0.49
54		0.14	**72**		1.3

[a]All compounds were purified by column chromatography and recrystallization (>95%). [b]IC_{50} values were determined as the mean of triplicate experiments, and standard deviations are within 15%.

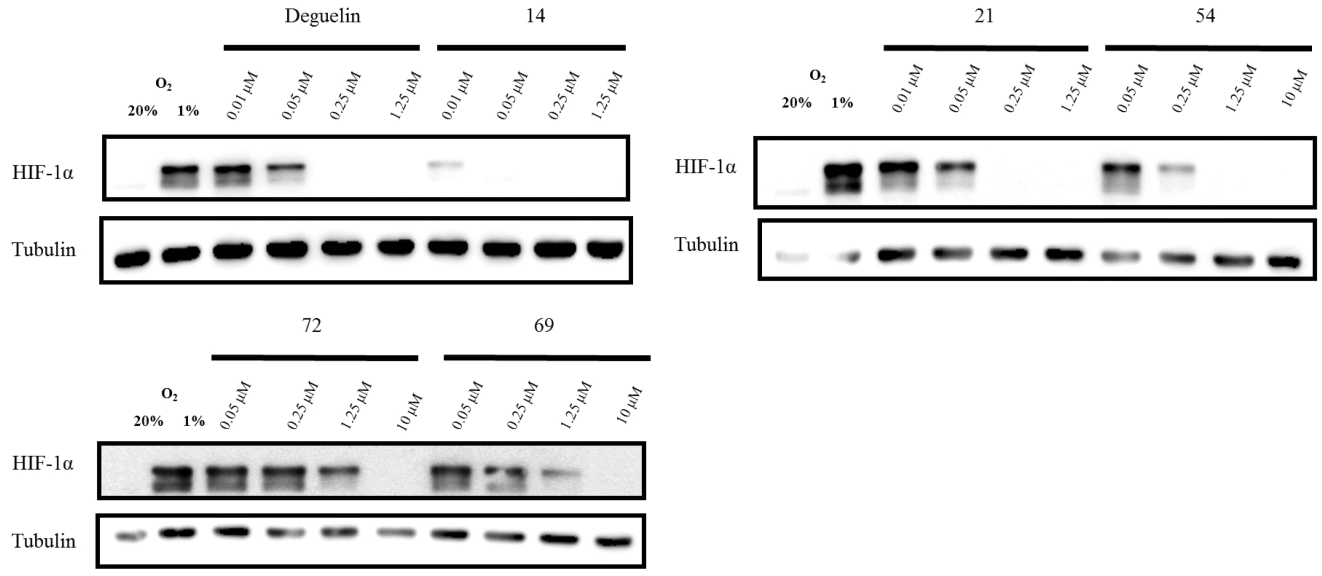


Figure 3. Western blot analysis of HIF-1α pretreated with deguelin and the potent deguelin analogues using H1299 cell lines.

possessing the olefin-reduced pyran system, exhibited similar inhibitory activity as deguelin. Diol **27** exhibited a complete loss of activity. Generally, olefin modification or pyran-ring opening in the terminal chromene moiety significantly reduced (**28**) or eliminated (**29**–**31**) inhibitory activity. These results imply that the HSP90 binding site interacting with the terminal 2,2-dimethyl-2*H*-chromene moiety consists of hydrophobic residues rather than hydrophilic residues and is sensitive to the size of the interacting counterpart.

Next, we focused on the B- and/or C-ring-truncated compounds. On the basis of the aforementioned SAR, we designed and prepared nine ring-truncated compounds for which activities were also evaluated by the MTS assay. The results are presented in Table 2.

The B- or C-ring-truncated compounds (**44**, **51**) exhibited significantly lower activity than deguelin, whereas compounds **54** and **56**, devoid of both the B- and C-rings, showed excellent inhibitory activities. Compound **54** exhibited the most potent activity, with an IC_{50} of 140 nM, which is almost equipotent to

dx.doi.org/10.1021/jm301488q | J. Med. Chem. 2012, 55, 10863−10884

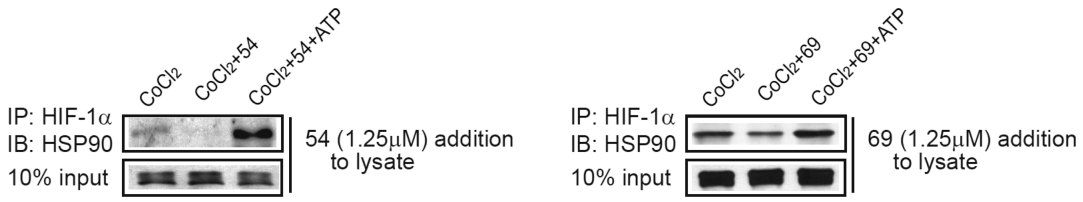


Figure 4. Inhibition of HSP90 and HIF-1α binding in vitro by analogues **54** and **69**.

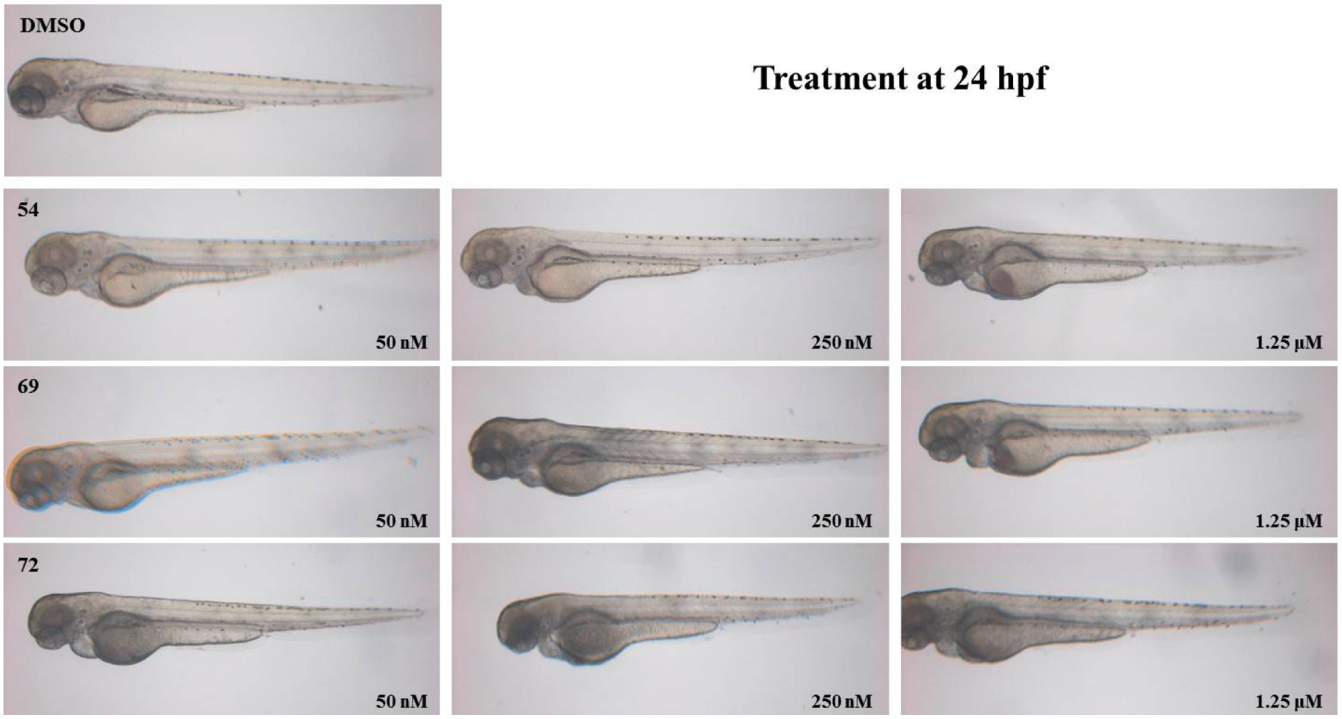


Figure 5. Effects of analogues **54**, **69**, and **72** on developmental defects in zebrafish embryos. Zebrafish embryos were incubated with the tested compounds at 50 nM, 250 nM, and 1.25 μM for 72 h.

deguelin. Noticeably, the deletion of the methoxy substituent in the terminal chromene moiety of **54** resulted in a significant decrease in antiproliferative activity (**53**), suggesting an important role for the methoxy group in inhibitory activity. The B- and C-ring-truncated compound **56**, possessing the *o*-methoxy substituent in the terminal chromene moiety and the α-methyl substituent, exhibited moderate activity with an IC_{50} of 730 nM. Incorporation of the dimethyl substituents at the benzylic position (**57**) resulted in a significantly decreased activity compared to those of the monomethyl substituted compound **56** or the nonsubstituted compound **54**. The decreased activities shown for **57** and **59** seem to imply that an appropriate constraint induced by the substituents is necessary in the ring-truncated compounds. The racemate **56** exhibited lower inhibitory activity than deguelin and **54**. However, we anticipated that the enantiomer of **56** would have different activities, as is the case for many chiral drugs.[35] Thus, we examined the cell growth inhibitory activities of each enantiomer. As presented in Table 2, the (*S*)-enantiomer **69**, with an IC_{50} of 490 nM, was approximately twice as potent as racemate **56**, whereas the (*R*)-enantiomer **72** was approximately 2-fold less active. Although compound **69** was less active in vitro than **54** without a methyl substituent, it seems that the stereochemistry is of much importance in determining the effectiveness of the HSP90 inhibitor.

HIF-1α INHIBITORY ACTIVITIES

To confirm the correlation between antiproliferative activities and HSP90 inhibitory activities of the synthesized compounds and to validate their antiangiogenic activities, we selected deguelin analogues and the ring-truncated compounds exhibiting excellent cell growth inhibition for further study. Because HIF-1α is one of the most well-known HSP90 client proteins and its transcriptional activity of vascular endothelial growth factor (VEGF) is important in terms of angiogenesis regulation,[19] the HIF-1α inhibitory activities of **14**, **21**, **54**, **69**, and **72** were analyzed by Western blot analysis using the H1299 cell line. As presented in Figure 3, HIF-1α was suppressed in a dose-dependent manner by all five test compounds. In addition, the tested compounds showed parallel correlations between the cell growth inhibitory activity and HIF-1α suppression.

Analogue **14**, which exhibited the most potent HIF-1α inhibition, showed higher HIF-1α suppression than the parent deguelin. The ring-truncated compound **54** was also quite potent in HIF-1α suppression. The B- and C-ring-truncated compound **69** in an optically active form exhibited higher HIF-1α inhibitory activity than its antipode **72** as observed in the MTS assay (Table 2). Involvement of HSP90 in the HIF-1α inhibition by analogues **54** and **69** was confirmed in vitro by immunoprecipitation and immunoblotting assays using H1299 cell lysates. The experiments were done at 1.25 μM **54** and **69**

dx.doi.org/10.1021/jm301488q | J. Med. Chem. 2012, 55, 10863−10884

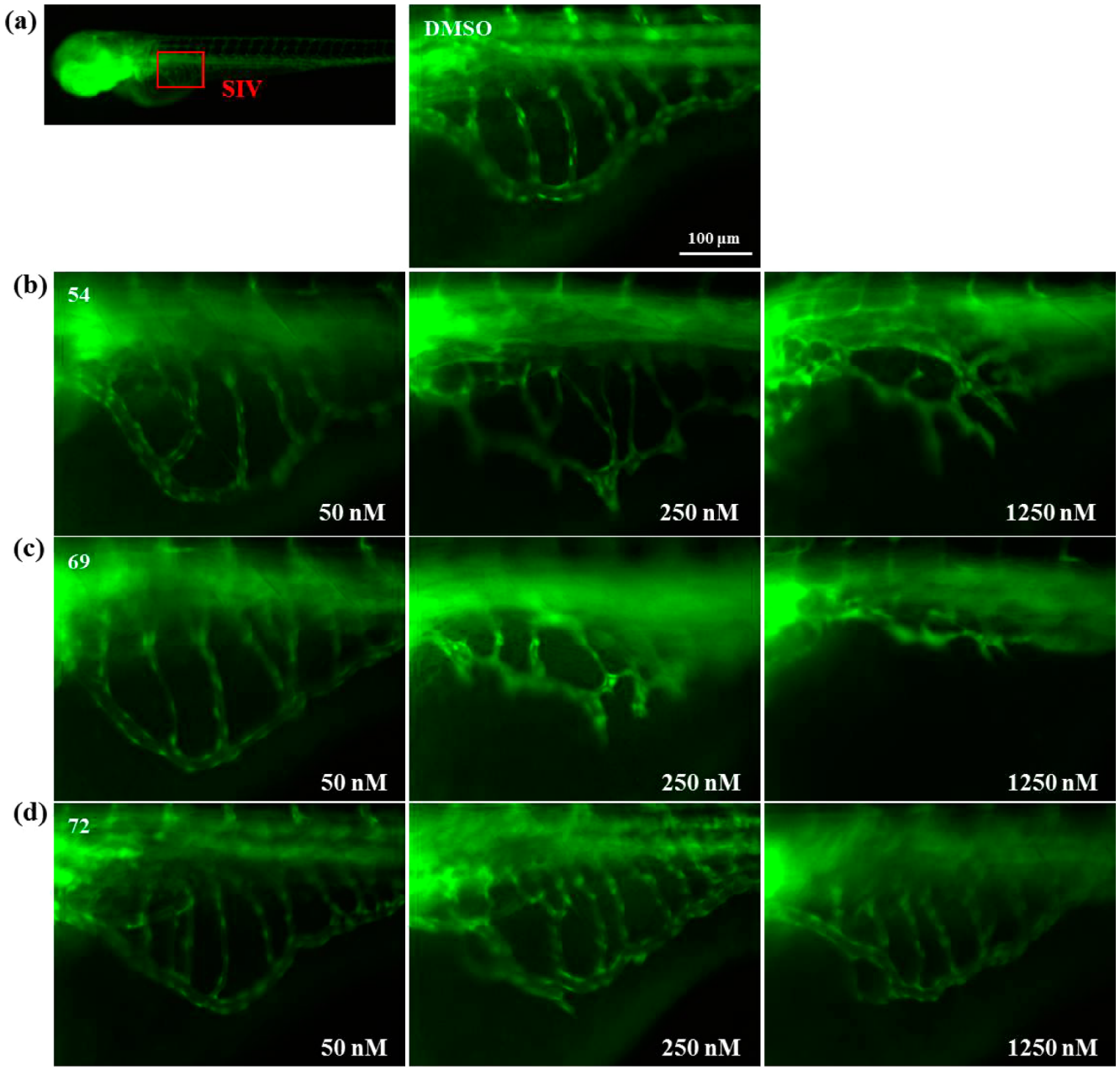


Figure 6. Antiangiogenic effects of **54**, **69**, and **72** in a zebrafish model. Zebrafish embryos were incubated with the tested compounds at 50, 250, and 1250 nM for 24 h. (a) A 72 hpf Tg(fli:EGFP)^{y1} larva treated with DMSO. Red box indicates SIV and negative control (DMSO). (b) Antiangiogenic effect of **54**. (c) Antiangiogenic effect of (*S*)-**69**. (d) Antiangiogenic effect of (*R*)-**72**. Scale bar, 100 μm.

because they exhibited evident HIF-1α inhibitions at the concentration. As shown in Figure 4, analogues **54** and **69** interrupted the interaction between HIF-1α and HSP90 in vitro, which was reversed by addition of excess ATP. These results strongly support that analogues **54** and **69** may inhibit the activity of HSP90 by competing with ATP at the ATP-binding site.

■ ANTIANGIOGENIC EFFECTS IN ZEBRAFISH EMBRYOS

Antiangiogenic effects of the ring-truncated compounds, which exhibited potent in vitro activities, were further confirmed using a transgenic zebrafish line.[36] HIF-1α proteins are known to contribute to the survival of tumor cells, inducing angiogenesis via VEGF transcription. We envisioned that inhibition of an interaction between HSP90 and HIF-1α using our potent analogues suppresses angiogenesis in zebrafish. Thus, we initially investigated conditions for the treatment stage and concentration, which does not induce a developmental defect in zebrafish embryos. We examined deguelin, **54**, **69**, and **72** in a dose dependent manner at 50% epiboly (5.3 hpf) using zebrafish embryos. We observed a developmental defect by deguelin at 50 nM to 10 μM. Interestingly, analogues **54**, **69**, and **72** exhibited the normal growth without affecting viability and showed no developmental defects at 50 nM to 1.25 μM (Supporting Information, Figure 1). However, developmental defects in zebrafish embryos were observed upon treatment with analogues **54**, **69**, and **72** at 10 μM (Supporting Information, Figure 2). Unfortunately, the initial incubation of zebrafish embryos in the presence of the deguelin analogues

dx.doi.org/10.1021/jm301488q | *J. Med. Chem.* 2012, 55, 10863−10884

14 and **21** at 0.05−1.25 μM did not affect angiogenesis in zebrafish. We assumed that the chemical or metabolic instability of analogues **14** and **21** induced the loss of activity in vivo model, which is partly supported by the mass spectral data of analogue **21**. We tested deguelin for antiangiogenic effect using zebrafish model. However, we could not observe any mature zebrafish showing the normal growth even at 50 nM. Deguelin also affected the zebrafish viability in a dose dependent manner (Supporting Information, Figure 3). On the basis of these results, the developmental defect by analogues **54**, **69**, and **72** were examined at 50 nM to 1.25 μM (24 hpf). As shown in Figure 5, analogues **54**, **69**, and **72** exhibited the normal growth of zebrafish embryos without developmental defect or malformation at the selected concentrations.

As shown in Figure 6, the B- and C-ring-truncated compound **54** exhibited a potent antiangiogenic effect, indicated by the depletion of subintestinal veins (SIV), in a dose-dependent manner at 72 hpf. Interestingly, optically active **69** showed the most potent antiangiogenic activity among the tested compounds. However, its antipode **72**, which was less active in the MTS assay and Western blot analysis, did not show significant antiangiogenic activity even at a high concentration of 1.25 μM. These results supported that the antiangiogenic effects of the deguelin analogues and the ring-truncated compounds were induced by blocking the action of HIF-1α via HSP90 inhibition. The excellent antiangiogenic activity of **69**, which appears more potent than **54**, is not clearly explained at present. Other mechanism of actions may partly explain the antiangiogenic activity of **69** in zebrafish model in addition to inhibition of an interaction between HIF-1α and HSP90.

■ CONCLUSION

In this work, we have elucidated the structural features of deguelin required for HSP90 inhibition using the MTS assay and Western blot analysis of the HSP90 client protein, HIF-1α. The established SAR revealed the importance of each fragment and the conformation of deguelin and provided crucial information for the development of novel and potent HSP90 inhibitors. We have identified new potent deguelin analogues (**14** and **21**) through the SAR studies. Ring-truncated compounds (**54** and **69**) designed based on the SAR studies exhibited excellent HIF-1α suppression and potent cell growth inhibition. In particular, we confirmed the excellent antiangiogenic activities of the ring-truncated compounds **54** and **69** using the in vivo zebrafish model. Our efforts in the design, synthesis, and biological evaluations of these novel HSP90 inhibitors have led to the development of promising antiangiogenic agents **54** and **69**, which consist of a novel scaffold. As we mentioned with respect to the assay for antiangiogenesis using zebrafish model, the higher antiangiogenic activity of **69** than that of **54** at a concentration of 1.25 μM is not clearly explained at present. Further intensive studies on the mechanism of antiangiogenesis and therapeutic applications of **54** and **69** are in progress.

■ EXPERIMENTAL SECTION

Chemistry. General Methods. Unless otherwise described, all commercial reagents and solvents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, acetonitrile, triethylamine, and pyridine were freshly distilled with calcium hydride. Flash column chromatography was carried out using silica gel 60 (230−400 mesh, Merck), and preparative thin layer chromatography was used with glass-backed silica gel plates (1 mm, Merck). Thin layer chromatography was performed to monitor reactions. All reactions were performed under dry argon atmosphere in flame-dried glassware. Rotenone as starting material of deguelin was purchased from Sigma-Aldrich. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-LA 300 (300 MHz), JEOL JNM-GCX (400 MHz), or Bruker AMX-500 (500 MHz) spectrometer. Chemical shifts are provided in parts per million (ppm, δ) downfield from tetramethylsilane (internal standard) with coupling constant in hertz (Hz). Multiplicity is indicated by the following abbreviations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad (br). Optical rotations were measured using JASCO DIP-1000 digital polarimeter at ambient temperature using a 100 mm cell of 2 mL capacity. Mass spectra and HRMS results were recorded on VG Trio-2 GC−MS instrument and JEOL JMS-AX instrument, respectively. All the final compounds were purified to more than 95% purity. The purity of the compounds was determined by normal phase high performance liquid chromatography (HPLC) (Gilson or Waters, Chiralpak AD-H (4.6 mm × 250 mm) or Chiralpak OD-H (4.6 mm × 250 mm)). The detailed analytical conditions are available in Supporting Information.

General Procedure A for Preparation of 15−18, 24, and 25. To a solution of **14** or **23** in THF were added the alkyl halides (1.5 equiv) and *t*-BuOK (1.0 M in THF, 1 equiv) at 0 °C. After completion of the reaction, which was monitored by TLC, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3 to 1:6) to afford the desired product.

General Procedure B for Preparation of 28−30. To a solution of phenol **8** and the corresponding alkyl halides (2 equiv) in acetonitrile was added Cs_2CO_3 (1.5 equiv) at 0 °C. After completion of the reaction, which was monitored by TLC, the resulting mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford the desired product.

General Procedure C for an Addition of Aryl Anion to Aldehyde. To a solution of aryl bromide (1.5 equiv) in THF was added dropwise *n*-BuLi solution in *n*-hexane (1.4 equiv) at −78 °C. The reaction mixture was stirred for 20 min at −78 °C, and aldehyde (1.0 equiv) was added. The reaction mixture was stirred for an additional 30 min and was warmed to ambient temperature. The reaction mixture was washed with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4 to 1:2) to afford the corresponding alcohol.

General Procedure D for Dess−Martin Oxidation. To a solution of alcohol in CH_2Cl_2 was added Dess−Martin periodinane (3.0 equiv). After being stirred for 1 h, the reaction mixture was diluted with CH_2Cl_2 and sodium thiosulfate solution (10%) was added. The mixture was stirred for 10 min and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6 to 1:2) to afford the corresponding oxidized product.

(6a*S*,12a*S*)-9-Hydroxy-2,3-dimethoxy-8-(3-methyl-2-butenyl)-6a,12a-dihydrochromeno[3,4-*b*]chromen-12(6*H*)-one (8). To a solution of rotenone **6** (200 mg, 0.50 mmol) in CH_2Cl_2 (5.0 mL) was added BBr_3 solution (0.53 mL of 1.0 M solution in CH_2Cl_2, 0.53 mmol) at −10 °C, and the reaction mixture was stirred for 5 min. The solvent was removed under reduced pressure, and methanol (1.0 mL) was added. The resulting white solid was filtered, and the residue of intermediate **7** was used for the next step without further purification. To a solution of **7** (130 mg, 0.27 mmol) in hexamethylphosphoramide (HMPA) was added $NaBH_3CN$ (69 mg,

1.1 mmol). The reaction mixture was heated to 70 °C, stirred for 3 h, and poured into water. The mixture was extracted with a mixture of diethyl ether and *n*-hexane (3:1). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on a silica gel (EtOAc/*n*-hexane = 1:2) to give 55 mg (50%) of **8** as pale yellow solid with a melting point of 193−195 °C: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, 1H, J = 8.7 Hz), 6.76 (s, 1H), 6.50 (d, 1H, J = 8.7 Hz), 6.41 (s, 1H), 6.00 (s, 1H), 5.19 (m, 1H), 4.87 (t, 1H, J = 3.0 Hz), 4.60 (dd, 1H, J = 11.9, 3.1 Hz), 4.14 (d, 1H, J = 11.9 Hz), 3.80 (m, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.34 (m 2H), 1.74 (s, 3H), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.4, 162.1, 160.1, 149.3, 147.5, 143.6, 134.0, 126.9, 121.1, 114.8, 112.5, 110.7, 110.5, 108.5, 104.7, 100.8, 72.0, 66.2, 56.2, 55.7, 44.1, 25.7, 22.0, 17.7. HRMS (FAB) calcd for $C_{23}H_{24}O_6$ (M^+): 396.1573. Found: 396.1575.

(7a*S*,13a*S*)-9,10-Dimethoxy-3,3-dimethyl-13,13a-dihydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromen-7(7a*H*)-one (1, Deguelin). To a solution of **8** (128 mg, 0.32 mmol) in CH_2Cl_2 (4.0 mL) was added PhSeCl (68 mg, 0.35 mmol) at −30 °C, and the mixture was stirred for 10 min at the same temperature. The reaction mixture was warmed to ambient temperature and stirred for an additional 1 h. The organic solvent was removed under reduced pressure, and the resulting residue was dissolved in THF (4.0 mL), followed by addition of H_2O_2 (30% in water, 0.06 mL) at 0 °C. After completion of the reaction, which was monitored by TLC, EtOAc (8.0 mL) and water (4.0 mL) were added. The organic layer was washed with 5% $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford 78 mg (61%) of **1** as pale yellow solid with a melting point of 85−87 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, 1H, J = 8.7 Hz), 6.77 (s, 1H), 6.62 (d, 1H, J = 10.0 Hz), 6.43 (s, 1H), 6.43 (d, 1H, J = 8.7 Hz), 5.53 (d, 1H, J = 10.0 Hz), 4.89 (m, 1H), 4.61 (dd, 1H, J = 12.0, 3.1 Hz), 4.17 (d, 1H, J = 12.0 Hz), 3.82 (d, 1H, J = 4.1 Hz), 3.78 (s, 3H), 3.75 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.2, 160.0, 156.9, 149.4, 147.4, 143.8, 128.6, 128.5, 115.7, 112.7, 111.4, 110.4, 109.1, 104.7, 100.9, 77.6, 72.4, 66.2, 56.3, 55.8, 44.3, 28.4, 28.1. HRMS (FAB) calcd for $C_{23}H_{23}O_6$ (M + H^+): 395.1495. Found: 395.1495.

(7a*S*,13a*S*)-9-Hydroxy-13,13a-dihydro-10-methoxy-3,3-dimethyl-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromen-7(7a*H*)-one (9). To a solution of deguelin **1** (100 mg, 0.25 mmol) in CH_2Cl_2 (7.0 mL) was added BBr_3 (0.25 mL, 0.25 mmol, 1.0 M solution in CH_2Cl_2) at −78 °C. The reaction mixture was stirred for 1 h and warmed to 0 °C. After being stirred for an additional 30 min, the resulting mixture was quenched with water (5.0 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane/CH_2Cl_2 = 1:3:1 to 1:2:1) to afford 16 mg (16%) of **9** as pale yellow solid with a melting point of 94−96 °C: ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.64 (d, 1H, J = 8.7 Hz), 7.60 (s, 1H), 6.67 (s, 1H), 6.59 (d, 1H, J = 10.1 Hz), 6.40 (d, 1H, J = 8.7 Hz), 6.30 (s, 1H), 5.66 (d, 1H, J = 10.1 Hz), 5.06 (m, 1H), 4.57 (dd, 1H, J = 12.2, 2.9 Hz), 4.22 (d, 1H, J = 12.2 Hz), 3.85 (d, 1H, J = 4.0 Hz), 3.62 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 190.2, 160.8, 158.2, 149.6, 148.6, 143.7, 130.4, 129.4, 116.6, 114.3, 112.2, 112.1, 110.3, 105.8, 105.2, 78.8, 74.0, 67.3, 57.3, 45.4, 29.0, 28.6. HRMS (FAB) calcd for $C_{22}H_{21}O_6$ (M + H^+): 381.1338. Found: 381.1327.

(7a*S*,13a*S*)-10-Hydroxy-13,13a-dihydro-9-methoxy-3,3-dimethyl-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromen-7(7a*H*)-one (10). Analogue **10** was obtained (14 mg, 14%) as pale yellow solid with a melting point of 116−118 °C by the procedure for analogue **9**: ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.64 (d, 1H, J = 8.6 Hz), 7.07 (s, 1H), 6.60 (s, 1H), 6.59 (d, 1H, J = 10.1 Hz), 6.39 (d, 1H, J = 8.6 Hz), 6.38 (s, 1H), 5.67 (d, 1H, J = 10.1 Hz), 5.06 (m, 1H), 4.59 (dd, 1H, J = 12.2, 2.9 Hz), 4.23 (d, 1H, J = 12.2 Hz), 3.82 (d, 1H, J = 4.0 Hz), 3.71 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 190.0, 160.8, 158.2, 149.1, 148.2, 142.1, 130.4, 129.4, 116.6, 114.5, 114.3, 112.1, 110.3, 107.2, 102.1, 78.8, 73.9, 67.4, 56.6, 45.4, 29.0, 28.6. HRMS (FAB) calcd for $C_{22}H_{21}O_6$ (M + H^+): 381.1338. Found: 381.1335.

(7a*S*,13a*S*)-13,13a-Dihydro-9,10-dihydroxy-3,3-dimethyl-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromen-7(7a*H*)-one (11). Analogue **11** was obtained by the procedure for analogue **9** and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane/CH_2Cl_2 = 1:3:1 to 1:2:1) to afford 32 mg (33%) of pale yellow solid with a melting point of 203−205 °C (decomposed): ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.75 (s, 1H), 7.63 (d, 1H, J = 8.7 Hz), 7.38 (s, 1H), 6.59 (s, 1H), 6.58 (d, 1H, J = 10.1 Hz), 6.39 (d, 1H, J = 8.7 Hz), 6.29 (s, 1H), 5.65 (d, 1H, J = 10.1 Hz), 5.03 (m, 1H), 4.55 (dd, 1H, J = 12.2, 2.9 Hz), 4.20 (d, 1H, J = 12.2 Hz), 3.79 (d, 1H, J = 4.0 Hz), 1.38 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 190.1, 160.8, 158.2, 148.4, 146.9, 140.7, 130.4, 129.3, 116.6, 114.9, 114.2, 112.1, 110.3, 106.2, 105.1, 78.8, 74.0, 67.2, 45.4, 29.0, 28.6. HRMS (FAB) calcd for $C_{21}H_{19}O_6$ (M + H^+): 367.1182. Found: 367.1179.

9,10-Dimethoxy-3,3-dimethyl-3*H*-chromeno[3,4-*b*]pyrano-[2,3-*h*]chromen-7-(13*H*)-one (12). To a solution of deguelin **1** (50 mg, 0.13 mmol) in ethanol (2.0 mL) were added NaOAc (21 mg, 0.25 mmol) and I_2 (290 mg, 1.14 mmol). The reaction mixture was refluxed for 12 h and cooled to ambient temperature. The resulting reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was crystallized from EtOAc and *n*-hexane (1:1) to afford 17 mg (35%) of α,β-unsaturated ketone **12** as pale yellow solid with a melting point of 233−235 °C (decomposed): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.42 (s, 1H), 8.01 (d, 1H, J = 8.7 Hz), 6.84 (d, 1H, J = 8.7 Hz), 6.73 (d, 1H, J = 10.0 Hz), 6.52 (s, 1H), 5.70 (d, 1H, J = 8.7 Hz), 4.99 (s, 2H), 3.93 (s, 3H), 3.84 (s, 3H), 1.47 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 157.1, 156.1, 151.0, 148.9, 146.2, 144.0, 130.5, 126.4, 118.4, 115.3, 114.6, 111.7, 110.5, 109.9, 109.0, 100.3, 77.7, 64.8, 56.2, 55.8, 28.1, 28.1. HRMS (FAB) calcd for $C_{23}H_{20}O_6$ (M^+): 392.1260. Found: 392.1263.

(7*S*,7a*R*,13a*S*)-9,10-Dimethoxy-3,3-dimethyl-7,7a,13,13a-tetrahydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromen-7-ol (14). To a solution of deguelin **1** (300 mg, 0.76 mmol) in methanol (10.0 mL) was added $NaBH_4$ (43 mg, 1.13 mmol) at 0 °C. The reaction mixture was stirred for 30 min and quenched with H_2O. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:1) to afford 300 mg (100%) of alcohol **14** as white solid with a melting point of 142−144 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.99 (d, 1H, J = 8.2 Hz), 6.68 (s, 1H), 6.64 (d, 1H, J = 10.0 Hz), 6.47 (s, 1H), 6.41 (d, 1H, J = 8.2 Hz), 5.56 (d, 1H, J = 10.0 Hz), 4.80 (m, 2H), 4.57 (d, 1H, J = 10.0 Hz), 4.21 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.36 (t, 1H, J = 4.9 Hz), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.3, 149.6, 149.4, 147.9, 143.8, 130.0, 129.1, 116.4, 113.6, 111.3, 109.8, 109.5, 108.7, 100.7, 76.0, 69.1, 66.3, 65.0, 56.5, 55.8, 37.9, 27.8, 27.7. HRMS (FAB) calcd for $C_{23}H_{24}O_6$ (M^+): 396.1560. Found: 396.1562.

(7a*S*,13a*S*)-9,10-Dimethoxy-3,3-dimethyl-7,7a,13,13a-tetrahydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromene (13). To a solution of **14** (40 mg, 0.10 mmol) in THF (2.0 mL) was added NaH (16 mg of 60% dispersion in mineral oil, 0.40 mmol) at 0 °C. The reaction mixture was stirred for 30 min at the same temperature, and carbon disulfide (0.06 mL, 1.00 mmol) was added. After addition of CH_3I (0.06 mL, 1.00 mmol) at 0 °C, the reaction mixture was warmed to ambient temperature and quenched with methanol (1.0 mL). The reaction mixture was concentrated under reduced pressure. The crude residue was extracted with EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6) to afford 35 mg (71%) of the xanthate intermediate. To the xanthate intermediate (21 mg, 0.04 mmol) dissolved in dry toluene (1.0 mL) were added tri-*n*-butyltin hydride (0.02 mL, 0.09 mmol) and AIBN (catalytic amount). The reaction mixture was refluxed until completion of the reaction (monitored by TLC) and concentrated under reduced

pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6) to afford 11 mg (69%) of **13** as pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.75 (d, 1H, J = 8.2 Hz), 6.63 (d, 1H, J = 10.0 Hz), 6.62 (s, 1H), 6.38 (s, 1H), 6.31 (d, 1H, J = 8.2 Hz), 5.52 (d, 1H, J = 10.0 Hz), 5.53 (d, 1H, J = 10.0 Hz), 4.67 (q, 1H, J = 4.7 Hz), 4.24 (d, 1H, J = 5.4 Hz), 3.79 (s, 6H), 3.26 (m, 1H), 2.99 (m, 2H), 1.38 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.2, 148.9, 148.7, 147.7, 143.5, 128.9, 128.5, 116.7, 113.0, 111.4, 111.2, 109.7, 108.8, 100.6, 75.6, 69.7, 65.6, 56.6, 55.8, 31.6, 29.4, 27.8, 27.6. HRMS (FAB) calcd for $C_{23}H_{24}O_5$ (M^+): 380.1624. Found: 380.1631.

(7*S*,7a*R*,3a*S*)-7,9,10-Trimethoxy-3,3-dimethyl-7,7a,13,13a-tetrahydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromene (15). Ether **15** was prepared from **14** according to the general procedure A and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford a colorless solid with a melting point of 66−68 °C (21 mg, 100%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.93 (d, 1H, J = 8.2 Hz), 6.77 (s,1H), 6.64 (d, 1H, J = 10.0 Hz), 6.42 (s, 1H), 6.37 (d, 1H, J = 8.2 Hz), 5.55 (d, 1H, J = 10.0 Hz), 4.78 (m, 1H), 4.51 (t, 1H, J = 10.0 Hz), 4.39 (d, 1H, J = 3.6 Hz), 4.22 (dd, 1H, J = 10.0, 3.9 Hz), 3.82 (s, 3H), 3.81 (s, 3H), 3.38 (m, 1H), 3.15 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.2, 149.1, 149.0, 148.4, 143.5, 129.3, 129.0, 116.5, 113.6, 111.5, 110.3, 110.0, 108.4, 100.4, 76.7, 75.9, 70.0, 65.8, 57.0, 56.5, 55.7, 37.2, 27.9, 27.8. HRMS (FAB) calcd for $C_{24}H_{26}O_6$ (M^+): 410.1729. Found: 410.1713.

(7*S*,7a*R*,3a*S*)-9,10-Dimethoxy-3,3-dimethyl-7-ethoxy-7,7a,13,13a-tetrahydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]-chromene (16). Ether **16** was prepared from **14** according to the general procedure A and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford a colorless solid with a melting point of 133−135 °C (23 mg, 71%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.95 (d, 1H, J = 8.0 Hz), 6.84 (s, 1H), 6.63 (d, 1H, J = 9.9 Hz), 6.39 (s, 1H), 6.35 (d, 1H, J = 8.3 Hz), 5.53 (d, 1H, J = 9.9 Hz), 4.75 (m, 1H), 4.58 (t, 1H, J = 9.7 Hz), 4.53 (d, 1H, J = 3.8 Hz), 4.20 (dd, 1H, J = 9.9, 4.2 Hz), 3.80 (s, 3H), 3.80 (s, 3H), 3.42 (m, 2H), 3.29 (m, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 1.00 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.9, 149.1, 148.9, 148.4, 143.3, 128.9, 128.6, 116.6, 114.4, 111.7, 110.1, 109.8, 108.5, 100.3, 75.8, 75.0, 70.1, 66.0, 64.9, 56.5, 55.7, 36.8, 29.6, 27.8, 27.8. HRMS (FAB) calcd for $C_{25}H_{28}O_6$ (M^+): 424.1886. Found: 424.1894.

(7*S*,7a*R*,3a*S*)-9,10-Dimethoxy-3,3-dimethyl-7-propoxy-7,7a,13,13a-tetrahydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]-chromene (17). Ether **17** was prepared from **14** according to the general procedure A and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:5) to afford a colorless solid with a melting point of 54−56 °C (15 mg, 68%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.94 (d, 1H, J = 8.2 Hz), 6.83 (s, 1H), 6.63 (d, 1H, J = 9.9 Hz), 6.39 (s, 1H), 6.34 (d, 1H, J = 8.2 Hz), 5.53 (d, 1H, J = 9.9 Hz), 4.77 (m, 1H), 4.57 (t, 1H, J = 9.9 Hz), 4.50 (d, 1H, J = 3.7 Hz), 4.21 (dd, 1H, J = 9.9, 4.2 Hz), 3.80 (s, 6H), 3.39 (m, 2H), 3.18 (m, 1H), 1.39 (s, 8H), 0.69 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.9, 149.1, 148.9, 148.3, 143.3, 128.9, 128.7, 116.6, 114.3, 111.7, 110.2, 109.8, 108.4, 100.3, 75.8, 75.3, 71.3, 70.1, 65.9, 56.5, 55.8, 36.8, 29.6, 27.9, 27.8, 22.9. HRMS (FAB) calcd for $C_{26}H_{31}O_6$ ($M + H^+$): 439.2121. Found: 439.2120.

(7*S*,7a*R*,3a*S*)-7-Benzyloxy-9,10-dimethoxy-3,3-dimethyl-7,7a,13,13a-tetrahydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]-chromene (18). Ether **18** was prepared from **14** according to the general procedure A and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6) to afford a colorless solid with a melting point of 142−144 °C (22 mg, 88%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 (m, 3H), 7.00 (m, 2H), 6.87 (d, 1H, J = 8.2 Hz), 6.66 (d, 1H, J = 9.9 Hz), 6.62 (s, 1H), 6.45 (s, 1H), 6.37 (d, 1H, J = 8.2 Hz), 5.56 (d, 1H, J = 9.9 Hz), 4.81 (m, 1H), 4.62 (t, 1H, J = 9.9 Hz), 4.54 (d, 1H, J = 3.2 Hz), 4.48 (AB quartet, 2H, J = 85.0, 12.5 Hz), 4.25 (dd, 1H, J = 14.2, 4.6 Hz), 3.84 (s, 3H), 3.72 (s, 3H), 3.36 (m, 1H), 1.42 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2, 149.1, 148.9, 148.7, 143.4, 137.9, 129.2, 129.0, 128.1, 127.6, 127.4, 127.2, 116.5, 113.8, 111.3, 110.1, 110.0, 108.4, 100.4, 75.9, 72.8, 69.9, 69.8, 65.8, 64.9, 56.2, 55.8, 37.3, 27.9, 27.8. HRMS (FAB) calcd for $C_{30}H_{30}O_6$ (M^+): 486.2042. Found: 486.2050.

(7*S*,7a*S*,13a*S*)-9,10-Dimethoxy-3,3-dimethyl-7-(tetrahydro-2*H*-pyran-2-yloxy)-7,7a,13,13a-tetrahydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromene (19). To a mixture of **14** (30 mg, 0.08 mmol) and DHP (13 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) was added pyridinium *p*-toluenesulfonate (5.8 mg, 0.02 mmol), and the reaction mixture was stirred for 1 h. The reaction was quenched with water (0.5 mL), and the resulting mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford 18 mg (50%, diastereomeric mixture) of **19** as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.06 (d, 1H, J = 8.2 Hz), 6.91 (d, 1H, J = 8.2 Hz), 6.84 (s, 1H), 6.72 (s, 1H), 6.63 (t, 1H, J = 9.9 Hz), 6.42 (s, 1H), 6.69 (s, 1H), 6.37 (d, 1H, J = 8.4 Hz), 6.33 (d, 1H, J = 8.2 Hz), 5.54 (t, 1H, J = 9.3 Hz), 4.85 (m, 4H), 4.75 (m, 1H), 4.63 (t, 1H, J = 10.0 Hz), 4.55 (t, 1H, J = 10.0 Hz), 4.33 (m, 1H), 4.21 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.70 (m, 1H), 3.40 (m, 3H), 3.29 (m, 1H), 3.11 (m, 1H), 1.71−1.19 (m, 12H), 1.40 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2, 153.7, 149.2, 149.1, 149.0, 148.9, 148.7, 148.7, 148.2, 148.2, 143.3, 143.2, 116.5, 116.4, 113.4, 113.1, 111.8, 111.7, 110.2, 110.0, 109.6, 109.6, 109.3, 109.3, 109.1, 108.2, 100.3, 100.2, 99.1, 93.2, 75.9, 75.8, 72.4, 69.8, 69.4, 69.1, 65.8, 65.2, 61.6, 60.4, 56.5, 56.5, 55.8, 55.8, 37.2, 36.8, 30.3, 30.2, 28.0, 27.9, 27.8, 27.7, 25.4, 25.3, 18.7, 18.1. HRMS (FAB) calcd for $C_{28}H_{32}O_7$ (M^+): 480.2148. Found: 480.2155.

(7*S*,7a*S*,13a*S*)-9,10-Dimethoxy-3,3-dimethyl-7,7a,13,13a-tetrahydro-3*H*-chromeno[3,4-*b*]pyrano[2,3,*h*]chromen-7-yl Acetate (20). To a solution of **14** (30 mg, 0.08 mmol) and DMAP (catalytic amount) in CH_2Cl_2 (1.0 mL) were added Et_3N (0.01 mL, 0.09 mmol) and acetic anhydride (0.06 mL, 0.64 mmol) at 0 °C. The reaction mixture was stirred for 10 min at ambient temperature and quenched with saturated NH_4Cl solution. The mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:5) to afford 27 mg (82%) of **20** as a white solid with a melting point of 111−113 °C: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.01 (d, 1H, J = 8.3 Hz), 6.63 (s, 1H), 6.63 (d, 1H, J = 9.9 Hz), 6.38 (s, 1H), 6.38 (d, 1H, J = 7.5 Hz), 6.24 (d, 1H, J = 4.4 Hz), 5.56 (d, 1H, J = 9.9 Hz), 4.86 (m, 1H), 4.43 (t, 1H, J = 10.2 Hz), 4.24 (m, 1H), 3.81 (s, 6H), 3.49 (m, 1H), 1.71 (s, 3H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 154.6, 149.3, 148.6, 148.5, 143.4, 130.5, 129.1, 116.2, 111.7, 110.9, 109.7, 109.6, 108.6, 100.1, 76.1, 69.0, 66.7, 64.5, 56.4, 55.8, 36.4, 27.9, 27.8, 20.8. HRMS (FAB) calcd for $C_{25}H_{26}O_7$ (M^+): 438.1679. Found: 438.1681.

(7*S*,7a*S*,13a*S*)-9,10-Dimethoxy-3,3-dimethyl-7,7a,13,13a-tetrahydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromen-7-yl Carbamate (21). To a solution of **14** (30 mg, 0.08 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise trichloroacetyl isocyanate (0.01 mL, 0.11 mmol) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C, and then methanol (1.0 mL) and water (0.2 mL) were added at 0 °C. The resulting mixture was stirred for 2.5 h and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:5) to give 21 mg (67%) of **21** as a colorless thick oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87 (d, 1H, J = 8.2 Hz), 6.62 (d, 1H, J = 10.0 Hz), 6.53 (s, 1H), 6.33 (s, 1H), 6.27 (d, 1H, J = 8.2 Hz), 5.46 (d, 1H, J = 10.0 Hz), 4.74 (m, 1H), 4.56 (dd, 1H, J = 11.7, 2.7 Hz), 4.49 (d, 1H, J = 2.7 Hz), 4.18 (d, 1H, J = 11.7 Hz), 3.73 (s, 3H), 3.72 (s, 3H), 3.41 (m, 1H), 1.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2, 149.6, 148.9, 148.3, 143.3, 130.6, 128.4, 116.6, 110.2, 110.1, 109.6, 108.6, 108.2, 100.9, 75.9, 75.1, 67.5, 65.9, 56.7, 55.8, 55.6, 35.5, 28.1, 27.6. HRMS (FAB) calcd for $C_{23}H_{22}O_5$ ($M^+ - CO_2NH_3$): 378.1467. Found: 378.1474.

(13a*S*)-9,10-Dimethoxy-3,3-dimethyl-13,13a-dihydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromene (22). A solution of **14** (3 mg, 8 μmol) in acetic acid (1.0 mL) was stirred for 2 h at 100 °C and treated with water (2.0 mL). The mixture was extracted with

diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:7) to afford 2 mg (70%) of **22** as pale yellow solid with a melting point of 152−154 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (s, 1H), 6.81 (d, 1H, J = 8.2 Hz), 6.60 (d, 1H, J = 10.0 Hz), 6.55 (s, 1H), 6.40 (s, 1H), 6.36 (d, 1H, J = 8.2 Hz), 5.59 (d, 1H, J = 10.0 Hz), 5.27 (m, 1H), 4.57 (dd, 1H, J = 10.0, 5.4 Hz), 4.13 (t, 1H, J = 10.0 Hz), 3.88 (s, 3H), 3.83 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.3, 150.3, 149.2, 148.2, 144.7, 129.7, 126.4, 123.7, 116.6, 116.2, 111.8, 110.6, 109.8, 109.6, 105.2, 100.9, 76.1, 71.1, 67.9, 56.3, 55.9, 28.0, 27.6. HRMS (FAB) calcd for $C_{23}H_{22}O_5$ (M^+): 378.1467. Found: 378.1474.

(7a*R*,13a*S*)-9,10-Dimethoxy-3,3-dimethyl-13,13a-dihydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromen-7(7a*H*)-one Oxime (23). To a solution of deguelin **1** (25 mg, 0.06 mmol) in pyridine (1.0 mL) was added hydroxylamine hydrochloride (14 mg, 0.19 mmol). The reaction mixture was heated to 70 °C and stirred until the reaction was completed (monitored by TLC). The resulting mixture was quenched with water (0.5 mL) and extracted with CH_2Cl_2. The organic layer was washed with 2 N HCl solution, water, and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford 26 mg (100%) of oxime **23** as a colorless thick oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26 (br, 1H), 7.59 (d, 1H, J = 8.7 Hz), 6.62 (m, 2H), 6.41 (s, 1H), 6.37 (d, 1H, J = 8.7 Hz), 5.49 (d, 1H, J = 10.0 Hz), 4.84 (d, 1H, J = 3.2 Hz), 4.61 (dd, 1H, J = 12.0, 2.4 Hz), 4.48 (m, 1H), 4.24 (d, 1H, J = 12.0 Hz), 3.79 (s, 3H), 3.72 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.7, 151.6, 151.3, 149.3, 147.7, 143.6, 128.6, 124.5, 116.2, 112.2, 110.7, 109.8, 108.2, 106.2, 100.6, 76.5, 69.6, 66.8, 56.4, 55.8, 31.6, 28.1, 27.8. HRMS (FAB) calcd for $C_{23}H_{23}NO_6$ (M^+): 409.1525. Found: 409.1513.

(7a*R*,13a*S*)-9,10-Dimethoxy-3,3-dimethyl-13,13a-dihydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromen-7(7a*H*)-one *O*-Methyloxime (24). The oxime ether **24** was prepared from **23** according to the general procedure A and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford a white solid with a melting point of 120−122 °C (12 mg, 57%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (d, 1H, J = 8.7 Hz), 6.61 (d, 1H, J = 10.0 Hz), 6.51 (s, 1H), 6.38 (m, 2H), 5.48 (d, 1H, J = 10.0 Hz), 4.71 (d, 1H, J = 3.3 Hz), 4.59 (dd, 1H, J = 12.0, 2.4 Hz), 4.45 (m, 1H), 4.21 (d, 1H, J = 12.0 Hz), 4.03 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.6, 151.2, 150.0, 149.2, 147.6, 143.5, 128.5, 124.7, 116.3, 111.9, 110.6, 109.7, 108.4, 106.3, 100.5, 76.5, 69.6, 66.9, 61.9, 56.3, 55.8, 32.3, 28.1, 27.8. HRMS (FAB) calcd for $C_{24}H_{25}NO_6$ (M^+): 423.1682. Found: 423.1677.

(7a*R*,13a*S*)-9,10-Dimethoxy-3,3-dimethyl-13,13a-dihydro-3*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromen-7(7a*H*)-one *O*-Benzyloxime (25). The oxime ether **25** was prepared from **23** according to the general procedure A and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:5) to afford white solid with a melting point of 80−82 °C (11 mg, 33%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, 1H, J = 8.7 Hz), 7.46 (d, 2H, J = 7.1 Hz), 7.31 (m, 3H), 6.62 (d, 1H, J = 10.0 Hz), 6.46 (s, 1H), 6.37 (m, 2H), 5.48 (d, 1H, J = 10.0 Hz), 5.27 (AB quartet, 2H, J = 50.7, 12.0 Hz), 4.76 (d, 1H, J = 3.0 Hz), 4.58 (dd, 1H, J = 12.0, 2.2 Hz), 4.44 (m, 1H), 4.20 (d, 1H, J = 12.0 Hz), 3.78 (s, 3H), 3.48 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.6, 151.2, 150.1, 149.1, 147.5, 143.5, 137.5, 128.7, 128.7, 128.5, 128.4, 128.4, 128.1, 124.8, 116.3, 111.7, 110.6, 109.7, 108.5, 106.4, 100.5, 76.6, 76.5, 69.6, 66.8, 56.0, 55.7, 32.3, 28.1, 27.8. HRMS (FAB) calcd for $C_{30}H_{29}NO_6$ (M^+): 499.1995. Found: 499.1999.

(7a*S*,13a*S*)-9,10-Dimethoxy-3,3-dimethyl-2,3,13,13a-tetrahydro-1*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]chromen-7(7a*H*)-one (26). A mixture of **8** (4 mg, 10 μmol) and *p*-toluenesulfonic acid (0.5 mg, 2.5 μmol) in benzene (1.0 mL) was stirred at 80 °C for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ (1.0 mL) solution and extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane/CH_2Cl_2 = 1:3:1 to 1:2:1) to afford 3.5 mg (99%) of **26** as white solid with a melting point of 145−147 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, 1H, J = 8.6 Hz), 6.79 (s, 1H), 6.43 (s, 1H), 6.43 (d, 1H, J = 8.7 Hz), 4.90 (m, 1H), 4.62 (dd, 1H, J = 12.0, 3.0 Hz), 4.17 (d, 1H, J = 12.0 Hz), 3.81 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.65 (m, 2H), 1.74 (t, 2H, J = 6.6 Hz), 1.33 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.4, 161.0, 159.9, 149.2, 147.3, 143.7, 126.3, 112.2, 111.6, 110.2, 108.8, 104.9, 100.7, 75.5, 72.2, 66.3, 56.2, 55.7, 44.1, 31.5, 26.9, 26.3, 16.5. HRMS (FAB) calcd for $C_{23}H_{25}O_6$ ($M + H^+$): 397.1651. Found: 397.1642.

(7a*S*,13a*S*)-1,2-Dihydroxy-9,10-dimethoxy-3,3-dimethyl-2,3,13,13a-tetrahydro-1*H*-chromeno[3,4-*b*]pyrano[2,3-*h*]-chromen-7(7a*H*)-one (27). To a solution of deguelin **1** (20 mg, 0.05 mmol) in a mixture of acetone and water (4.0 mL, 4:1) were added *N*-methylmorpholine *N*-oxide (18 mg, 0.15 mmol) and OsO_4 (20 μL of 0.1 M solution in toluene, 2 μmol) at 0 °C. After being stirred for 10 min, the reaction mixture was warmed to ambient temperature and stirred for an additional 72 h. The reaction mixture was quenched with saturated sodium sulfite solution at 0 °C, filtered through Celite pad, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 2:1 to EtOAc only) to afford 10 mg (47%, diastereomeric mixture) of **27** as pale yellow solid with a melting point of 87−89 °C. Isomer A: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 1H, J = 8.8 Hz), 6.48 (m, 3H), 4.98 (d, 1H, J = 4.7 Hz), 4.46 (m, 3H), 4.42 (s, 1H), 3.80 (s, 3H), 3.76 (t, 1H, J = 4.7 Hz), 3.71 (s, 3H), 3.45 (br, 1H), 3.34 (d, 1H, J = 4.5 Hz), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.7, 160.6, 160.4, 151.2, 148.2, 144.3, 128.7, 113.0, 110.5, 110.0, 109.1, 108.6, 101.1, 79.1, 76.3, 70.4, 67.3, 63.7, 61.9, 56.3, 55.9, 24.3, 22.5. Isomer B: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, 1H, J = 8.8 Hz), 6.47 (m, 3H), 4.97 (d, 1H, J = 4.7 Hz), 4.59 (m, 3H), 4.43 (s, 1H), 3.80 (s, 3H), 3.73 (m, 1H), 3.70 (s, 3H), 3.53 (br, 1H), 3.30 (d, 1H, J = 4.5 Hz), 1.43 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.8, 160.8, 160.6, 151.2, 148.2, 144.1, 128.8, 113.2, 110.8, 109.7, 109.2, 108.4, 101.0, 79.0, 76.7, 70.3, 67.2, 63.8, 62.0, 56.3, 55.8, 24.5, 22.5. HRMS (FAB) calcd for $C_{23}H_{24}O_8$ (M^+): 428.1471. Found: 428.1463.

2,3,9-Trimethoxy-8-(3-methylbut-2-enyl)-6a,12a-dihydro-6*H*-chromeno[3,4-*b*]chromen-12-one (28). Ether **28** was prepared from **8** according to the general procedure B and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford a white solid with a melting point of 130−132 °C (16 mg, 41%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, 1H, J = 8.8 Hz), 6.74 (s, 1H), 6.56 (d, 1H, J = 8.9 Hz), 6.41 (s, 1H), 5.11 (m, 1H), 4.87 (m, 1H), 4.58 (dd, 1H, J = 11.9, 3.3 Hz), 4.15 (d, 1H, J = 11.9 Hz), 3.83 (s, 3H), 3.81 (d, 1H, J = 4.1 Hz), 3.77 (s, 3H), 3.74 (s, 3H), 3.28 (m, 2H), 1.74 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.0, 163.6, 159.2, 149.3, 147.4, 143.6, 131.8, 126.9, 121.6, 117.4, 113.1, 110.3, 105.1, 104.6, 100.7, 71.8, 66.2, 56.2, 55.8, 55.8, 44.3, 25.7, 21.9, 17.6. HRMS (FAB) calcd for $C_{24}H_{26}O_6$(M^+): 410.1729. Found: 410.1735.

9-Allyloxy-2,3-dimethoxy-8-(3-methylbut-2-enyl)-6a,12a-dihydro-6*H*-chromeno[3,4-*b*]chromen-12-one (29). Ether **29** was prepared from **8** according to the general procedure B and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6) to afford a pale yellow solid with a melting point of 151−153 °C (12 mg, 39%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, 1H, J = 8.9 Hz), 6.75 (s, 1H), 6.53 (d, 1H, J = 8.9 Hz), 6.42 (s, 1H), 5.98 (m, 1H), 5.30 (m, 2H), 5.15 (m, 1H), 4.88 (m, 1H), 4.58 (m, 3H), 4.16 (d, 1H, J = 11.8 Hz), 3.81 (d, 1H, J = 2.0 Hz), 3.78 (s, 3H), 3.74 (s, 3H), 3.33 (m, 2H), 1.74 (s, 3H), 1.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.0, 162.6, 159.4, 149.4, 147.5, 143.7, 132.5, 131.7, 126.8, 121.6, 117.8, 117.6, 113.2, 110.5, 106.2, 104.7, 100.8, 72.0, 69.0, 66.3, 56.3, 55.8, 44.4, 25.7, 22.1, 17.8. HRMS (FAB) calcd for $C_{26}H_{28}O_6$ (M^+): 436.1886. Found: 436.1883.

9-Benzyloxy-2,3-dimethoxy-8-(3-methylbut-2-enyl)-6a,12a-dihydro-6*H*-chromeno[3,4-*b*]chromen-12-one (30). Ether **30** was prepared from **8** by the general procedure B and purified by

flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6) to afford a white solid with a melting point of 160−162 °C (12 mg, 25%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, 1H, J = 8.8 Hz), 7.31 (m, 5H), 6.74 (s, 1H), 6.60 (d, 1H, J = 8.8 Hz), 6.41 (s, 1H), 5.15 (m, 3H), 4.48 (m, 1H), 4.61 (dd, 1H, J = 11.9, 3.0 Hz), 4.16 (d, 1H, J = 11.9 Hz), 3.81 (d, 1H, J = 4.1 Hz), 3.78 (s, 3H), 3.73 (s, 3H), 3.35 (m, 2H), 1.66 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.0, 162.7, 159.3, 149.4, 147.5, 143.6, 136.3, 131.8, 129.7, 128.6, 128.0, 127.1, 126.9, 122.8, 121.7, 117.9, 113.4, 110.5, 106.3, 104.7, 100.8, 72.0, 70.3, 66.3, 56.3, 55.8, 44.4, 25.7, 22.2, 17.7. HRMS (FAB) calcd for $C_{30}H_{31}O_6$ ($M + H^+$): 487.2121. Found: 487.2113.

Acetic Acid 2,3-Dimethoxy-8-(3-methylbut-2-enyl)-12-oxo-6,6a,12,12a-tetrahydrochromeno[3,4-*b*]chromen-9-yl Ester (31). To a solution of **8** (25 mg, 0.06 mmol) and DMAP (catalytic amount) in CH_2Cl_2 (1.0 mL) were added Et_3N (0.01 mL, 0.07 mmol) and acetic anhydride (0.05 mL, 0.53 mmol) at 0 °C. The reaction mixture was stirred for 10 min at ambient temperature and quenched with saturated NH_4Cl solution. The mixture was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford 14 mg (44%) of **31** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, 1H, J = 8.6 Hz), 6.70 (d, 1H, J = 8.6 Hz), 6.68 (s, 1H), 6.42 (s, 1H), 5.02 (m, 1H), 4.93 (m, 1H), 4.60 (dd, 1H, J = 12.0, 3.2 Hz), 4.17 (d, 1H, J = 12.0 Hz), 3.87 (d, 1H, J = 4.0 Hz), 3.78 (s, 3H), 3.74 (s, 3H), 3.24 (m, 2H), 2.27 (s, 3H), 1.72 (s, 3H), 1.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.1, 168.6, 159.8, 154.9, 149.7, 147.6, 143.9, 132.5, 125.9, 123.0, 120.7, 116.4, 110.5, 104.0, 100.9, 72.3, 66.1, 56.3, 55.8, 44.4, 29.6, 25.6, 23.0, 20.8, 17.7. HRMS (FAB) calcd for $C_{25}H_{26}O_7$ (M^+): 438.1679. Found: 438.1681.

4-Nitrobenzene-1,3-diol (33). To a solution of resorcinol **32** (5.0 g, 44.96 mmol) in a mixture (2:1, 270 mL) of chloroform and acetic acid was slowly added a solution of nitric acid (3.6 mL) in acetic acid (70 mL). After being stirred for 1 h, the reaction mixture was quenched with water (100 mL) and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4 to EtOAc/*n*-hexane/CH_2Cl_2 = 1:4:2) to afford 3.8 g (55%) of nitroresorcinol **33** as yellow solid with a melting point of 120−122 °C: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.99 (d, 1H, J = 9.1 Hz), 6.43 (m, 2H).

5-(2-Methylbut-3-yn-2-yloxy)-2-nitrophenol (34). To a solution of 2-methyl-3-butyn-2-o1 (0.36 mL, 3.70 mmol) in acetonitrile (18 mL) at 0 °C was added DBU (0.63 mL, 4.19 mmol), followed by a dropwise addition of trifluoroacetic anhydride (0.58 mL, 4.19 mmol) over 30 min. The resulting yellow solution was stirred at 0 °C for 40 min. In a separate flask, a solution of phenol **33** (500 mg, 3.22 mmol) in acetonitrile (18 mL) at 0 °C was treated with DBU (0.63 mL, 4.19 mmol), followed by an addition of $CuC1_2$ (9 mg, 0.06 mmol). To this mixture at 0 °C was added dropwise the first acetonitrile solution over 40 min. The reaction mixture was stirred overnight at 0 °C and concentrated under reduced pressure. The residue was poured into water, and the aqueous solution was extracted with EtOAc. The organic layer was washed successively with 2 N HCI, 2 N KOH, and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:20 to 1:2) to afford 320 mg (45%) of **34** as yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.92 (s, 1H), 8.00 (d, 1H, J = 9.5 Hz), 6.99 (d, 1H, J = 2.6 Hz), 6.69 (dd, 1H, J = 9.5, 2.6 Hz), 2.69 (s, 1H), 1.72 (s, 6H). HRMS (FAB) calcd for $C_{11}H_{12}NO_4$ ($M + H^+$): 222.0766. Found: 222.0773.

2,2-Dimethyl-6-nitro-2*H*-chromen-5-ol (35). A solution of **34** (310 mg, 1.40 mmol) in *N*,*N*-diethylaniline (28 mL) was heated to 130 °C and stirred until the reaction was completed (monitored by TLC). The reaction mixture was poured into ice−water and extracted with EtOAc. The organic layer was washed with 2 N HCl and water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:15) to afford **35** (281 mg, 91%) as a pale yellow solid with a melting point of 135−137 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (d, 1H, J = 9.4 Hz), 6.70 (d, 1H, J = 10.0 Hz), 6.38 (d, 1H, J = 9.4 Hz), 5.63 (d, 1H, J = 10.0 Hz), 1.45 (s, 6H). HRMS (FAB) calcd for $C_{11}H_{12}NO_4$ ($M + H^+$): 222.0766. Found: 222.0775.

5-Methoxy-2,2-dimethyl-6-nitro-2*H*-chromene (36). A mixture of phenol **35** (294 mg, 1.33 mmol), K_2CO_3 (553 mg, 4.0 mmol), and CH_3I (0.25 mL, 3.98 mmol) in acetone (5.0 mL) was heated to 55 °C and stirred overnight. The mixture was concentrated, treated with water, and extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude **36**, which was used for the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (d, 1H, J = 8.9 Hz), 6.59 (m, 2H), 5.72 (d, 1H, J = 10.0 Hz), 3.89 (s, 3H), 1.44 (s, 6H). HRMS (FAB) calcd for $C_{12}H_{14}NO_4$ ($M + H^+$): 236.0923. Found: 236.0924.

5-Methoxy-2,2-dimethyl-2*H*-chromen-6-amine (37). A mixture of **36** (318 mg, 1.35 mmol) and $SnCl_2{\cdot}2H_2O$ (1.47 g, 6.52 mmol) in ethanol (13.0 mL) was refluxed for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc. The organic layer was washed with 2 N NaOH (20.0 mL) and water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford aniline **37** (258 mg, 95% for 2 steps) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.54 (m, 2H), 6.43 (d, 1H, J = 8.4 Hz), 5.63 (d, 1H, J = 9.9 Hz), 3.78 (s, 3H), 3.46 (br, 2H), 1.37 (s, 6H). HRMS (FAB) calcd for $C_{12}H_{15}NO_2$ (M^+): 205.1103. Found: 205.1104.

6-Bromo-5-methoxy-2,2-dimethyl-2*H*-chromene (38). Hydrogen bromide (1.6 mL, 48% in water) was slowly added to a solution of aniline **37** (260 mg, 1.27 mmol) in water (5.0 mL) that was cooled in advance to 0 °C. The resulting reaction mixture was stirred vigorously for 10 min at the same temperature. A solution of $NaNO_2$ (92 mg, 1.30 mmol) in water (1.0 mL) was slowly added, and the reaction mixture was kept below 5 °C. To a solution of CuBr (190 mg, 1.30 mmol) in water (5.0 mL) was added dropwise the above diazo solution at 65 °C. The reaction mixture was stirred until the reaction was completed. The resulting reaction mixture was cooled to ambient temperature and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:12) to yield the aryl bromide **38** (365 mg, 88%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 (d, 1H, J = 8.6 Hz), 6.52 (d, 1H, J = 10.0 Hz), 6.42 (d, 1H, J = 8.6 Hz), 5.59 (d, 1H, J = 10.0 Hz), 3.74 (s, 3H), 1.35 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.3, 152.7, 132.1, 131.2, 116.9, 116.6, 113.9, 107.3, 76.1, 61.5, 30.9, 27.7. HRMS (FAB) calcd for $C_{12}H_{13}BrO_2$ (M^+): 268.0099. Found: 268.0107.

Methyl 2-(3,4-Dimethoxyphenyl)acetate (39). To a solution of 3′,4′-dimethoxyphenylacetic acid (500 mg, 2.54 mmol) and dry DMF (catalytic amount) in CH_2Cl_2 (12 mL) was added oxalyl chloride (0.68 mL, 7.64 mmol) dropwise at 0 °C. After the mixture was stirred for 30 min at ambient temperature, absolute methanol (10 mL) was added and the mixture was stirred for 10 min. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford the desired product **39** (476 mg, 89%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.79 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.67 (s, 3H), 3.55 (s, 2H).

Methyl 2-(3,4-Dimethoxyphenyl)-3-(4-methoxybenzyloxy)-propanoate (40). Ester **39** (500 mg, 2.38 mmol) and paraformaldehyde (76 mg, 2.50 mmol) were suspended in DMSO (5 mL), and NaOMe (6.8 mg, 0.12 mmol) was added. The reaction mixture was stirred overnight and poured into ice-cold water (10 mL). The resulting mixture was neutralized with 2 N HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:1) to afford 331 mg (58%) of the aldol product as a pale

yellow thick oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.74 (m, 3H), 4.05 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.73 (m, 2H), 3.65 (s, 3H). HRMS (FAB) calcd for $C_{12}H_{16}O_5$ (M^+): 240.0998. Found: 240.1013.

To a solution of the above aldol product (36 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) were added *p*-methoxybenzyl 2,2,2-trichloroacetamidate (84 mg, 0.30 mmol) and a catalytic amount of CSA. The reaction mixture was stirred overnight and quenched with saturated $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford 54 mg (100%) of **40** as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.19 (d, 2H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.5 Hz), 6.78 (m, 3H), 4.46 (AB quartet, 2H, J = 33.4, 11.7 Hz), 3.98 (m, 1H), 3.83 (s, 6H), 3.80 (m, 2H), 3.77 (s, 3H), 3.67 (s, 3H). HRMS (FAB) calcd for $C_{20}H_{24}O_6$ (M^+): 360.1573. Found: 360.1569.

2-(3,4-Dimethoxyphenyl)-3-(4-methoxybenzyloxy)propanal (41). To a solution of methyl ester intermediate **40** (20 mg, 0.06 mmol) in THF (1.0 mL) was added methanol (0.003 mL, 0.07 mmol). The reaction mixture was cooled to −78 °C, and DIBAL-H (0.16 mL of 1.0 M solution in toluene, 0.16 mmol) was slowly added. The reaction mixture was stirred at −78 °C for 30 min and warmed to ambient temperature. Rochelle's solution was carefully added to the reaction mixture over 15 min, and the mixture was stirred vigorously for 1 h at 0 °C. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:1) to afford the corresponding alcohol (16 mg, 88%): ^{1}H NMR ($CDCl_3$,500 MHz) δ 7.21 (d, 2H, J = 8.5 Hz), 6.85 (d, 2H, J = 8.5 Hz), 6.77 (d, 1H, J = 8.6 Hz), 6.73 (m, 2H), 4.46 (s, 2H), 3.93 (m, 1H), 3.83 (s. 6H), 3.81 (m, 1H), 3.78 (s, 3H), 3.72 (m, 2H), 3.10 (quin, 1H, J = 6.5 Hz). HRMS (FAB) calcd for $C_{19}H_{24}O_5$ (M^+): 332.1624. Found: 332.1628.

The aldehyde **41** (11 mg, 71%) was prepared from the above alcohol according to the general procedure D and was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford 11 mg (71%) of pure **41** as a colorless oil: ^{1}H NMR ($CDCl_3$,300 MHz) δ 9.66 (d, 1H, J = 1.7 Hz), 7.14 (d, 1H, J = 8.4 Hz), 6.78 (m, 3H), 6.66 (m. 2H), 4.40 (d, 2H, J = 3.5 Hz), 3.99 (dd, 1H, J = 8.6, 6.9 Hz), 3.80 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.70 (m, 2H).

(*S*)-2-(3,4-Dimethoxyphenyl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-(4-methoxybenzyloxy)propan-1-one (42). Coupling of aldehyde **41** and aryl bromide **38** by the general procedure C afforded the alcohol intermediate (34 mg, 72%, diastereomeric mixture), which was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2).

Ketone **42** was prepared from the above alcohol by the general procedure D and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to give pure **42** (26 mg, 84%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (d, 1H, J = 8.6 Hz), 7.11 (d, 2H, J = 8.6 Hz), 6.73 (m, 5H), 6.50 (d, 1H, J = 10.0 Hz), 6.45 (d, 1H, J = 8.2 Hz), 5.57 (d, 1H, J = 9.9 Hz), 4.83 (dd, 1H, J = 8.9, 5.1 Hz), 4.39 (q, 2H, J = 11.5 Hz), 4.12 (t, 1H, J = 9.1 Hz), 3.75 (s, 6H), 3.71 (s, 3H), 3.57 (dd, 1H, J = 9.1, 5.1 Hz), 3.52 (s, 3H), 1.34 (s, 6H). HRMS (FAB) calcd for $C_{31}H_{35}O_7$ ($M + H^+$): 519.2383. Found: 519.2373.

(*S*)-2-(3,4-Dimethoxyphenyl)-3-hydroxy-1-(5-hydroxy-2,2-dimethyl-2*H*-chromen-6-yl)propan-1-one (43). To a solution of **42** (23 mg, 0.04 mmol) in CH_2Cl_2 (1.0 mL) was added BCl_3 (0.16 mL of 1.0 M solution in CH_2Cl_2, 0.16 mmol) at −78 °C. After being stirred for 1 h, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford 12 mg (75%) of **43** as pale yellow thick oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, 1H, J = 8.7 Hz), 6.76 (m, 3H), 6.53 (d, 1H, J = 11.1 Hz), 6.49 (d, 1H, J = 10.5 Hz), 5.63 (d, 1H, J = 9.9 Hz), 4.75 (dd, 1H, J = 8.7, 4.8 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.77 (m, 2H), 1.39 (s, 3H), 1.38 (s, 3H). HRMS (FAB) calcd for $C_{22}H_{24}O_6$ (M^+): 384.1573. Found: 384.1570.

(3*S*)-3-(3,4-Dimethoxyphenyl)-8,8-dimethyl-2,3-dihydro-4*H*,8*H*-pyrano[2,3-*f*]chromen-4-one (44). To a solution of **43** (10 mg, 0.03 mmol) in THF (1.0 mL) was added in one portion a solution of PPh_3 (65 mg, 0.25 mmol) and diisopropyl azodicarboxylate (0.02 mL, 0.12 mmol) in THF (0.5 mL). The reaction mixture was stirred until completion (monitored by TLC) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford 5.5 mg (57%) of **44** as white solid with a melting point of 109−111 °C: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, 1H, J = 8.7 Hz), 6.82 (s, 2H), 6.77 (s, 1H), 6.61 (d, 1H, J = 10.0 Hz), 6.47 (d, 1H, J = 8.7 Hz), 5.58 (d, 1H, J = 10.0 Hz), 4.94 (m, 1H), 4.63 (m, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 1.44 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.9, 159.5, 157.6, 149.1, 148.5, 128.9, 128.6, 127.8, 120.6, 115.6, 114.7, 111.8, 111.4, 111.2, 109.1, 77.5, 55.8, 51.3, 29.6, 28.2, 28.2, 21.7. HRMS (FAB) calcd for $C_{22}H_{23}O_5$ ($M + H^+$): 367.1545. Found: 367.1552.

Methyl 2-(2-Bromo-4,5-dimethoxyphenyl)acetate (45). To a solution of methyl ester **39** (500 mg, 2.38 mmol) in THF (12 mL) was added NBS (449 mg, 2.50 mmol) at −78 °C. The reaction mixture was stirred for 30 min and warmed to ambient temperature. The reaction mixture was filtered, washed with EtOAc, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford **45** (660 mg, 96%) as a pale yellow solid with a melting point of 63−65 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (s, 1H), 6.72 (s, 1H), 3.79 (s, 6H), 3.66 (s, 2H), 3.65 (s, 3H). HRMS (FAB) calcd for $C_{11}H_{13}BrO_4$ (M^+): 287.9997. Found: 287.9995.

Methyl 2-(2-Bromo-4,5-dimethoxyphenyl)pent-4-enoate (46). To a solution of ester **45** (150 mg, 0.52 mmol) in THF (2.0 mL) was added LHMDS (0.63 mL of 1.0 M solution in THF, 0.63 mmol) at −78 °C. The reaction mixture was stirred for 20 min, and allyl iodide (0.049 mL, 0.52 mmol) was added dropwise. The mixture was stirred for 1 h, and saturated NH_4Cl solution was added. The mixture was poured into water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:8) to afford 90 mg (53%) of **46**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.94 (s, 1H), 6.81 (s, 1H), 5.68 (m, 1H), 4.98 (m, 2H), 4.11 (dd, 1H, J = 8.2, 7.2 Hz), 3.78 (s, 6H), 3.61 (s, 3H), 2.69 (m, 1H), 2.42 (m, 1H). HRMS (FAB) calcd for $C_{14}H_{17}BrO_4$ (M^+): 328.0310. Found: 328.0316.

1-(1-(Benzyloxy)pent-4-en-2-yl)-2-bromo-4,5-dimethoxybenzene (47). To a solution of methyl ester **46** (84 mg, 0.25 mmol) in THF (2.0 mL) was slowly added $LiAlH_4$ (10 mg, 0.25 mmol) at 0 °C. The mixture was warmed to ambient temperature and stirred for 1 h. The mixture was then cooled to 0 °C, and saturated $NaHCO_3$ solution was carefully added over 30 min. The mixture was stirred vigorously for 1 h and poured into water. The mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6) to afford the alcohol intermediate (68 mg, 88%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.01 (s, 1H), 6.73 (s, 1H), 5.73 (m, 1H), 5.03 (d, 1H, J = 17.1 Hz), 4.97 (d, 1H, J = 10.1 Hz), 3.84 (s, 3H), 3.83 (s, 3H), 3.77 (d, 2H, J = 5.7 Hz), 3.41 (quin, 1H, J = 7.1 Hz), 2.50 (quin, 1H, J = 7.1 Hz), 2.37 (quin, 1H, J = 7.1 Hz). HRMS (FAB) calcd for $C_{13}H_{17}BrO_3$ (M^+): 300.0361. Found: 300.0356.

To a solution of the above alcohol (400 mg, 1.33 mmol) in THF (7.0 mL) was added NaH (64 mg, 1.59 mmol, 60% in mineral oil) at 0 °C. The reaction mixture was stirred for 30 min at ambient temperature, and *n*-Bu_4NBr (23 mg, 0.07 mmol) and benzyl bromide (0.19 mL, 0.59 mmol) were added. After being stirred overnight, the resulting mixture was treated with saturated NH_4Cl (5.0 mL) solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:8) to afford 448 mg (86%) of **47**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (m, 5H), 6.94 (s, 1H), 6.71 (s, 1H), 5.65 (m, 1H), 4.93 (m, 2H), 4.43 (s, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.53

(m, 3H), 2.53 (m, 1H), 2.30 (m, 1H). HRMS (FAB) calcd for $C_{20}H_{23}BrO_3$ (M^+): 390.0831. Found: 390.0839.

4-(Benzyloxy)-3-(2-bromo-4,5-dimethoxyphenyl)butan-1-ol (48). To a solution of olefin **47** (252 mg, 0.64 mmol) in a mixture of acetone and water (4:1, 25 mL) were added NMO (233 mg, 1.93 mmol) and OsO_4 (0.32 mL of 0.1 M solution in toluene, 0.03 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 6 h and extracted with EtOAc. The organic layer was washed with saturated sodium sulfite solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in a mixture of acetone and water (4:1, 25 mL), and $NaIO_4$ (413 mg, 1.93 mmol) was added. The reaction mixture was stirred for 0.5 h and extracted with EtOAc. The organic layer was washed with saturated sodium thiosulfate solution and concentrated under reduced pressure to give the crude aldehyde, which was used for the next step without further purification.

To a solution of the above aldehyde (0.64 mmol) in methanol (6.0 mL) was added $NaBH_4$ (49 mg, 1.29 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h, quenched with saturated NH_4Cl solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:1) to give 184 mg (73% for two steps) of **48** as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (m, 5H), 6.94 (s, 1H), 6.69 (s, 1H), 4.47 (s, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.54 (m, 4H), 2.01 (m, 2H), 1.81 (m, 1H). HRMS (FAB) calcd for $C_{19}H_{23}BrO_4$ (M^+): 394.0780. Found: 394.0774.

4-(Benzyloxymethyl)-6,7-dimethoxychroman (49). To a solution of $Pd_2(dba)_3$ (13 mg, 0.01 mmol) and 2-(di-*tert*-butylphosphino)biphenyl (7 mg, 0.02 mmol) in dry toluene (10 mL) were added alcohol **48** (379 mg, 0.96 mmol) and *t*-BuONa (124 mg, 1.25 mmol). The reaction mixture was heated to 50−55 °C and stirred overnight. The reaction mixture was cooled to ambient temperature, diluted with EtOAc (10 mL), and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6) to afford 226 mg (75%) of **49**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (m, 5H), 6.61 (s, 1H), 6.30 (s, 1H), 4.48 (q, 2H, J = 11.9 Hz), 4.03 (m, 2H), 3.73 (s, 3H), 3.70 (s, 3H), 3.61 (m, 1H), 3.49 (m, 1H), 2.98 (m, 1H), 1.95 (m, 2H). HRMS (FAB) calcd for $C_{19}H_{22}O_4$ (M^+): 314.1518. Found: 314.1518.

6,7-Dimethoxychroman-4-carbaldehyde (50). The mixture of **49** (191 mg, 0.61 mmol) and 20% $Pd(OH)_2$/C (38 mg) in methanol (5.0 mL) was stirred under hydrogen gas for 5 h at ambient temperature. The reaction mixture was filtered through a short pad of Celite, and the pad was washed with methanol (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:1) to afford 158 mg (100%) of alcohol: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.61 (s, 1H), 6.33 (s, 1H), 4.08 (m, 2H), 3.78 (m, 2H), 3.74 (s, 6H), 2.85 (m, 1H), 1.98 (m, 2H); LRMS (FAB) m/z 225 ($M + H^+$).

The aldehyde **50** was prepared from the above alcohol according to the general procedure D and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford 15 mg (60%) of pure **50**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.67 (d, 1H, J = 1.8 Hz), 6.58 (s, 1H), 6.42 (s, 1H), 4.13 (m, 3H), 3.81 (s, 6H), 2.32 (m, 1H), 2.06 (m, 1H).

(6,7-Dimethoxychroman-4-yl)(2,2-dimethyl-2*H*-chromen-6-yl)methanone (51). Coupling of aldehyde **50** with 6-bromo-2,2-dimethyl-2*H*-chromene according to the general procedure C afforded the alcohol intermediate (18 mg, 75%), which was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4). HRMS (FAB) calcd for $C_{23}H_{26}O_5$(M^+): 382.1780. Found: 382.1793.

Ketone **51** was prepared from the above alcohol according to the general procedure D and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6) to give 9.9 mg (55%) of pure **51** as colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (dd, 1H, J = 8.5, 2.1 Hz), 7.66 (d, 1H, J = 1.9 Hz), 6.81 (d, 1H, J = 8.4 Hz), 6.42 (s, 1H), 6.34 (m, 2H), 5.66 (d, 1H, J = 9.9 Hz), 4.61 (t, 1H, J = 5.8 Hz), 4.17 (m, 2H), 3.81 (s, 3H), 3.65 (s, 3H), 2.21 (m, 2H), 1.45 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.6, 157.7, 149.4, 149.2, 143.3, 131.3, 130.5, 129.0, 127.4, 121.5, 120.9, 116.3, 112.4, 110.6, 101.1, 77.7, 63.4, 56.4, 55.8, 41.6, 28.4, 28.4, 26.5. HRMS (FAB) calcd for $C_{23}H_{24}O_5$ (M^+): 380.1624. Found: 380.1621.

2-(3,4-Dimethoxyphenyl)acetaldehyde (52). To a solution of methyl 3′,4′-dimethoxyphenylacetate (1.94 g, 9.24 mmol) in dry diethyl ether was added dropwise DIBAL-H (11.1 mL of 1.0 M solution in THF, 11.1 mmol) at −78 °C. The reaction mixture was stirred for 1 h at the same temperature, and Rochelle's solution was carefully added over 15 min. The mixture was stirred vigorously for 1 h at 0 °C and then poured into water. The mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford aldehyde **52** as a yellow oil (1.13 g, 68%): ^{1}H NMR ($CDCl_3$,300 MHz) δ 9.66 (t, 1H, J = 2.5 Hz), 6.80 (d, 1H, J = 8.0 Hz), 6.68 (m, 1H), 6.64 (d, 1H, J = 1.8 Hz), 3.81 (s, 6H), 3.56 (d, 2H, J = 2.5 Hz).

2-(3,4-Dimethoxyphenyl)-1-(2,2-dimethyl-2*H*-chromen-6-yl)ethanone (53). Ketone **53** was prepared from 6-bromo-2,2-dimethyl-2*H*-chromene and aldehyde **52** according to the general procedures C and D and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford 37 mg (46% for 2 steps) of pure **53** as pale yellow solid with a melting point of 111−113 °C: ^{1}H NMR ($CDCl_3$,400 MHz) δ 7.76 (dd, 1H, J = 8.4, 2.2 Hz), 7.62 (d, 1H, J = 2.2 Hz), 6.76 (m, 4H), 6.29 (d, 1H, J = 9.8 Hz), 5.61 (d, 1H, J = 9.8 Hz), 4.10 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.3, 157.3, 148.8, 147.7, 131.0, 130.4, 129.4, 127.3, 127.1, 121.5, 121.4, 120.6, 116.0, 112.3, 111.2, 77.4, 55.7, 55.7, 44.5, 28.2, 28.2. HRMS (FAB) calcd for $C_{21}H_{23}O_4$ ($M + H^+$): 339.1596. Found: 339.1595.

2-(3,4-Dimethoxyphenyl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethanone (54). Ketone **54** was prepared from aryl bromide **38** and aldehyde **52** according to the general procedures C and D and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford 80 mg (48% for 2 steps) of pure **54** as a pale yellow solid with a melting point of 90−92 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43 (d, 1H, J = 8.4 Hz), 6.72 (s, 3H), 6.54 (d, 1H, J = 9.9 Hz), 6.52 (d, 1H, J = 8.4 Hz), 5.62 (d, 1H, J = 9.9 Hz), 4.12 (s, 2H), 3.77 (s, 6H), 3.69 (s, 3H), 1.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.7, 157.7, 156.3, 148.8, 147.8, 131.1, 130.5, 127.6, 124.8, 121.7, 116.5, 114.8, 112.8, 112.6, 111.2, 63.2, 55.8, 55.8, 50.3, 50.2, 28.1, 28.0. HRMS (FAB) calcd for $C_{22}H_{25}O_5$ ($M + H^+$): 369.1702. Found: 369.1705.

2-(3,4-Dimethoxyphenyl)propanal (55). To a solution of methyl 3′,4′-dimethoxyphenylacetate (4.76 g, 22.6 mmol) in THF (5 mL) was added dropwise LDA (18.1 mL of 2.0 M solution in THF, 36.2 mmol) at −78 °C. The reaction mixture was stirred for 30 min at the same temperature, and methyl iodide (2.82 mL, 45.3 mmol) was added. The mixture was stirred for 1 h, acidified with 2 N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:4) to give methyl 2-(3,4-dimethoxyphenyl)propanoate (4.01 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.80 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.64 (q, 1H, J = 7.1 Hz), 3.63 (s, 3H), 1.46 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.7, 148.9, 148.1, 133.0, 119.5, 111.2, 110.6, 55.8, 55.8, 51.9, 44.9, 18.6. HRMS (FAB) calcd for $C_{12}H_{16}O_4$ (M^+): 224.1049. Found: 224.1052.

To a solution of methyl 2-(3,4-dimethoxyphenyl)propanoate (3.0 g, 13.4 mmol) in THF (35 mL) was added dropwise DIBAL-H (16.0 mL of 1.0 M solution in THF, 16.0 mmol) at −78 °C. The reaction mixture was stirred for 1 h at the same temperature, and Rochelle's solution was carefully added over 15 min. The mixture was stirred vigorously for 1 h at 0 °C and poured into water. The mixture was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford **55** as a yellow oil (1.58 g, 61%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.63 (d, 1H, J = 1.5 Hz), 6.86 (d, 1H, J = 8.2 Hz), 6.74 (m, 1H), 6.66

dx.doi.org/10.1021/jm301488q | J. Med. Chem. 2012, 55, 10863−10884

(d, 1H, J = 2.0 Hz), 3.85 (s. 6H), 3.56 (q, 1H, J = 6.9 Hz), 1.40 (d, 3H, J = 6.9 Hz).

2-(3,4-Dimethoxyphenyl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)propan-1-one (56). Ketone **56** was prepared from aryl bromide **38** and aldehyde **55** according to the general procedures C and D and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford 11 mg (64% for 2 steps) of pure **56** as a colorless thick oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, 1H, J = 8.5 Hz), 6.76 (m, 3H), 6.55 (d, 1H, J = 10.0 Hz), 6.48 (d, 1H, J = 8.5 Hz), 5.62 (d, 1H, J = 10.0 Hz), 4.60 (q, 1H, J = 6.9 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.65 (s, 3H), 1.48 (d, 3H, J = 6.9 Hz), 1.39 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 157.1, 155.7, 149.0, 147.9, 133.8, 130.7, 130.5, 125.5, 120.2, 116.5, 112.3, 111.2, 77.2, 76.7, 63.3, 55.8, 55.7, 50.0, 43.1, 28.0, 28.0, 19.0. HRMS (FAB) calcd for $C_{23}H_{27}O_5$ (M + H$^+$): 383.1858. Found: 383.1853.

2-(3,4-Dimethoxyphenyl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-2-methylpropan-1-one (57). To a solution of **54** (15 mg, 0.04 mmol) in THF (1.0 mL) were added NaH (5 mg, 0.12 mmol, 60% in mineral oil) and CH_3I (0.02 mL, 0.16 mmol). The reaction mixture was stirred until the reaction was completed (monitored by TLC), and extraction was with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford 14 mg (88%) of **57** as pale yellow solid with a melting point of 111−113 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.87 (m, 3H), 6.52 (d, 1H, J = 9.9 Hz), 6.21 (q, 2H, J = 5.4 Hz), 5.61 (d, 1H, J = 9.9 Hz), 3.88 (s, 3H), 3.83 (s, 3H), 3.70 (s, 3H), 1.50 (s, 6H), 1.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.6, 155.1, 154.1, 148.9, 147.9, 136.2, 130.5, 127.8, 126.7, 118.2, 116.6, 115.0, 111.1, 111.0, 109.8, 77.2, 76.2, 63.6, 55.8, 55.8, 51.6, 27.9, 27.8, 26.3. HRMS (FAB) calcd for $C_{24}H_{29}O_5$ (M + H$^+$): 397.2015. Found: 397.2015.

2-(3,4-Dimethoxyphenyl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)prop-2-en-1-one (58). To a solution of ketone **54** (20 mg, 0.05 mmol) in anhydrous DMF (1 mL) were added K_2CO_3 (15 mg, 0.11 mmol) and paraformaldehyde (3 mg, 0.08 mmol). The reaction mixture was stirred for 4 h and then extracted with EtOAc. The organic layer was washed with saturated NH_4Cl solution, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford 18 mg (87%) of **58** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, 1H, J = 8.6 Hz), 6.95 (m, 2H), 6.78 (d, 1H, J = 8.0 Hz), 6.51 (m, 2H), 5.90 (s, 1H), 5.60 (d, 1H, J = 10.0 Hz), 5.55 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 1.38 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.5, 157.3, 156.2, 149.4, 149.1, 148.6, 131.7, 130.4, 129.7, 125.0, 121.7, 120.2, 116.5, 114.8, 111.8, 110.9, 110.7, 77.2, 76.8, 63.1, 55.8, 28.0, 27.9. HRMS (FAB) calcd for $C_{23}H_{25}O_5$ (M + H$^+$): 381.1702. Found: 381.1709.

1-(3,4-Dimethoxyphenyl)cyclopropyl)(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)methanone (59). To anhydrous DMSO (0.5 mL) were added NaH (1.2 mg, 0.03 mmol, 60% in mineral oil) and trimethylsulfoxonium iodide (6.5 mg, 0.03 mmol). The resulting mixture was stirred for 40 min, followed by an addition of a solution of α,β-unsaturated ketone **58** (10 mg, 0.03 mmol) in anhydrous DMSO (0.5 mL). After being stirred for 1 h, the reaction mixture was quenched with a saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl solution, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford 9 mg (91%) of **59** as white oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.98 (d, 1H, J = 8.4 Hz), 6.78 (m, 2H), 6.67 (d, 1H, J = 8.4 Hz), 6.48 (d, 1H, J = 10.0 Hz), 6.35 (d, 1H, J = 8.4 Hz), 5.58 (d, 1H, J = 10.0 Hz), 3.78 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 1.67 (q, 2H, J = 4.0 Hz), 1.35 (s, 6H), 1.28 (q, 2H, J = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.6, 155.4, 153.9, 148.4, 147.8, 133.0, 130.4, 128.7, 126.3, 121.4, 116.5, 114.7, 113.6, 111.4, 110.6, 76.2, 63.1, 55.7, 55.7, 37.1, 27.8, 27.8, 17.7, 17.7. HRMS (FAB) calcd for $C_{24}H_{26}O_5$ (M^+): 394.1780. Found: 394.1774.

2-(3,4-Dimethoxyphenyl)propanoic Acid (64). To a solution of ester **63** (400 mg, 1.78 mmol) in a mixture of THF and water (2:1, 9.0 mL) was added $LiOH{\cdot}H_2O$ (230 mg, 5.35 mmol), and the mixture was stirred for 5 h. The reaction mixture was extracted with EtOAc, and 2 N NaOH (20 mL) was added to the organic layer. The aqueous layer was acidified with aqueous 2 N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was used directly for the next reaction: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (m, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.66 (q, 1H, J = 7.3 Hz), 1.48 (d, 3H, J = 7.3 Hz). HRMS (FAB) calcd for $C_{11}H_{14}O_4$ (M^+): 210.0892. Found: 210.0907.

(*S*)-2-(3,4-Dimethoxyphenyl)-*N*-((*R*)-2-hydroxy-1-phenylethyl)propanamide (65) and (*R*)-2-(3,4-Dimethoxyphenyl)-*N*-((*R*)-2-hydroxy-1-phenylethyl)propanamide (66). To a solution of **64** (282 mg, 1.34 mmol) in CH_2Cl_2 (10 mL) were added *N*-(3-dimethylaminoproryl)-*N*′-ethylcarbodiimide hydrochloride (287 mg, 1.47 mmol), (*R*)-(−)-2-phenylglycinol (207 mg, 1.47 mmol), HOBt (230 mg, 1.47 mmol), and diisopropylethylamine (0.26 mL, 1.47 mmol) at 0 °C. The reaction mixture was stirred overnight at ambient temperature, quenched with saturated NH_4Cl solution, and diluted with CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/CH_2Cl_2/*n*-hexane = 3:2:1) to afford 187 mg (42%) of **65** and 186 mg (42%) of **66** as a pale yellow solid with a melting point of 115−117 °C (**65**) and 133−135 °C (**66**).

(*S*)-Diastereomer (**65**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (m, 3H), 7.03 (m, 2H), 6.81 (m, 2H), 6.73 (s, 1H), 6.05 (m, 1H), 5.02 (m, 1H), 3.86 (s, 3H), 3.80 (m, 2H), 3.78 (s, 3H), 3.58 (q, 1H, J = 7.1 Hz) 1.48 (d, 3H, J = 7.1 Hz). HRMS (FAB) calcd for $C_{19}H_{24}NO_4$ (M + H$^+$): 330.1705. Found: 330.1696.

(*R*)-Diastereomer (**66**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (m, 3H), 7.10 (m, 2H), 6.78 (m, 3H), 5.97 (m, 1H), 4.96 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.72 (d, 2H, J = 5.0 Hz), 3.50 (q, 1H, J = 7.1 Hz) 1.46 (d, 3H, J = 7.1 Hz). HRMS (FAB) calcd for $C_{19}H_{24}NO_4$ (M + H$^+$): 330.1705. Found: 330.1712.

(*S*)-2-(3,4-Dimethoxyphenyl)propanoic Acid (67). To a solution of **65** (186 mg, 0.56 mmol) in 1,4-dioxane (5.0 mL) was slowly added H_2SO_4 (5.0 mL, 4.0 M in water) at 0 °C. The reaction mixture was refluxed for 2 h, cooled to ambient temperature, and diluted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to afford carboxylic acid **67** (117 mg, 100%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (m, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.67 (q, 1H, J = 7.1 Hz), 1.47 (d, 3H, J = 7.1 Hz). HRMS (FAB) calcd for $C_{11}H_{14}O_4$ (M^+): 210.0892. Found: 210.0903; $[\alpha]_D^{25}$ +70° (c 0.2, CH_2Cl_2).

(*S*)-2-(3,4-Dimethoxyphenyl)propanal (68). A solution of (*S*)-**67** (115 mg, 0.55 mmol) in dry diethyl ether (8.0 mL) was cooled to 0 °C, and $BH_3{\cdot}SMe_2$ complex (1.5 mL, 3.0 mmol) was added dropwise. The reaction mixture was stirred for 1 h at the same temperature and then stirred 3 h at ambient temperature. The mixture was quenched with water at 0 °C, and 2 N NaOH was added dropwise until the evolution of H_2 gas was not observed. The aqueous layer was extracted with ether, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford 104 mg (85%) of the alcohol intermediate as a colorless oil. The enantiomeric excess (95% ee) was determined by chiral HPLC (Chiralcel OD-H, isopropanol/*n*-hexane = 1:3, 1.0 mL/min): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.78 (m, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.66 (m, 2H), 2.88 (sex, 1H, J = 6.9 Hz), 1.24 (d, 3H, J = 6.9 Hz). HRMS (FAB) calcd for $C_{11}H_{16}O_3$ (M^+): 196.1099. Found: 196.1106.

(*S*)-Aldehyde **68** was prepared from the above alcohol according to the general procedure D and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford 21 mg (85%) of pure (*S*)-**68** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.63 (d, 1H, J = 1.5 Hz), 6.86 (d, 1H, J = 8.2 Hz), 6.74 (dd, 1H, J = 8.2, 2.0 Hz), 6.66 (d, 1H, J = 2.0 Hz), 3.86 (s, 6H), 3.55 (q, 1H, J = 7.1 Hz), 1.40 (d, 3H, J = 7.1 Hz).

(*S*)-2-(3,4-Dimethoxyphenyl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)propan-1-one (69). $CeCl_3 \cdot 7H_2O$ (189 mg, 0.52 mmol) in a one-necked flask was heated gradually to 135−140 °C under reduced pressure (0.1 Torr) and stirred for 2 h. While the flask was still hot, argon gas was injected into the flask, which was then cooled in an ice bath. THF (1.0 mL) was added all at once with vigorous stirring. The ice bath was removed, and the suspension was stirred overnight at ambient temperature. The aryl anion, which was generated by an addition of *n*-BuLi (0.13 mL of 1.6 M solution in *n*-hexane, 0.21 mmol) to **38** (61 mg, 0.23 mmol) in THF (1.0 mL) at −78 °C, was added at −78 °C. After the mixture was stirred for 1.5 h at −78 °C, aldehyde **68** (20 mg, 0.10 mmol) was added and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford the corresponding alcohol (32 mg, 80%, diastereomeric mixture) as colorless oil. Isomer A: ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.22 (d, 1H, J = 8.4 Hz), 6.73 (m, 3H), 6.50 (m, 2H), 5.69 (d, 1H, J = 9.9 Hz), 4.95 (m, 1H), 3.70 (s, 6H), 3.61 (s, 3H), 3.07 (quin, 1H, J = 6.8 Hz), 1,35 (s, 6H), 1.28 (d, 3H, J = 6.9 Hz). Isomer B: ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.02 (d, 1H, J = 8.4 Hz), 6.75 (m, 3H), 6.55 (d, 1H, J = 10.0 Hz), 6.43 (d, 1H, J = 8.5 Hz), 5.70 (d, 1H, J = 9.9 Hz), 4.93 (dd, 1H, J = 7.5, 4.0 Hz), 3.72 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 2.95 (quin, 1H, J = 7.2 Hz), 1,34 (d, 6H, J = 11.8 Hz), 1.06 (d, 3H, J = 7.2 Hz).

To a solution of the above alcohol (32 mg, 0.08 mmol) in CH_2C1_2 (2.0 mL) were added 4 Å molecular sieves (41.0 mg) and *N*-methylmorpholine *N*-oxide (15 mg, 0.13 mmol). The reaction mixture was stirred for 10 min, and tetrapropylammonium perruthenate (3 mg, 0.01 mmol) was added. When the reaction was completed (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2. The mixture was washed with 10% sodium sulfite solution, brine, and saturated copper(II) sulfate solution. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford ketone **69** as a colorless oil (27 mg, 84%). The enantiomeric excess (97% ee) was determined by chiral HPLC (Chiralpak AD-H, isopropanol/*n*-hexane = 1:9, 1.0 mL/min): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, 1H, J = 8.5 Hz), 6.76 (m, 3H), 6.55 (d, 1H, J = 10.0 Hz), 6.48 (d, 1H, J = 8.5 Hz), 5.62 (d, 1H, J = 10.0 Hz), 4.60 (q, 1H, J = 6.9 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.65 (s, 3H), 1.48 (d, 3H, J = 6.9 Hz), 1.39 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 157.1, 155.7, 149.0, 147.9, 133.8, 130.7, 130.5, 125.5, 120.2, 116.5, 112.3, 111.2, 77.2, 76.7, 63.3, 55.8, 55.7, 50.0, 43.1, 28.0, 28.0, 19.0. HRMS (FAB) calcd for $C_{23}H_{27}O_5$ (M + H^+): 383.1858. Found: 383.1853.

(*R*)-2-(3,4-Dimethoxyphenyl)propanoic Acid (70). To a solution of **66** (217 mg, 0.66 mmol) in 1,4-dioxane (5.6 mL) was slowly added H_2SO_4 (5.6 mL, 4.0 M in water) at 0 °C. The reaction mixture was refluxed for 2 h, cooled to ambient temperature, and diluted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to afford acid **70** (138 mg, 100%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (m, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.67 (q, 1H, J = 7.1 Hz), 1.47 (d, 3H, J = 7.1 Hz). HRMS (FAB) calcd for $C_{11}H_{14}O_4$ (M^+): 210.0892. Found: 210.0911; $[\alpha]_D^{25}$ −73° (c 0.2, CH_2Cl_2).

(*R*)-2-(3,4-Dimethoxyphenyl)propanal (71). To a stirred solution of acid (*R*)-**70** (138 mg, 0.66 mmol) in dry diethyl ether (10 mL) was added dropwise $BH_3 \cdot SMe_2$ complex (1.8 mL, 3.61 mmol) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature and then for 3 h at ambient temperature. The reaction mixture was quenched with water and then 2 N NaOH at 0 °C. The aqueous layer was extracted with ether, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford 104 mg (81%) of alcohol as colorless oil. The enantiomeric excess (97% ee) was determined by chiral HPLC (Chiralcel OD-H, isopropanol/*n*-hexane = 1:3, 1.0 mL/min): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.78 (m, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.66 (m, 2H), 2.88 (sex, 1H, J = 6.9 Hz), 1.24 (d, 3H, J = 6.9 Hz). HRMS (FAB) calcd for $C_{11}H_{16}O_3$ (M^+): 196.1099. Found: 196.1112.

(*R*)-Aldehyde **71** was prepared from the above alcohol according to the general procedure D and purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to give 16 mg (79%) of pure (*R*)-**71** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.63 (d, 1H, J = 1.5 Hz), 6.86 (d, 1H, J = 8.2 Hz), 6.74 (dd, 1H, J = 8.2, 2.0 Hz), 6.66 (d, 1H, J = 2.0 Hz), 3.86 (s, 6H), 3.55 (q, 1H, J = 7.1 Hz), 1.40 (d, 3H, J = 7.1 Hz).

(*R*)-2-(3,4-Dimethoxyphenyl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)propan-1-one (72). The alcohol intermediate (12 mg, 48%) was prepared as a colorless oil from **38** (36 mg, 0.14 mmol) and aldehyde **71** (13 mg, 0.07 mmol) by the same procedure for the alcohol intermediate of ketone **69**. Isomer A: ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.22 (d, 1H, J = 8.4 Hz), 6.73 (m, 3H), 6.50 (m, 2H), 5.69 (d, 1H, J = 9.9 Hz), 4.95 (m, 1H), 3.70 (s, 6H), 3.61 (s, 3H), 3.07 (quin, 1H, J = 6.8 Hz), 1,35 (s, 6H), 1.28 (d, 3H, J = 6.9 Hz). Isomer B: ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.02 (d, 1H, J = 8.4 Hz), 6.75 (m, 3H), 6.55 (d, 1H, J = 10.0 Hz), 6.43 (d, 1H, J = 8.5 Hz), 5.70 (d, 1H, J = 9.9 Hz), 4.93 (dd, 1H, J = 7.5, 4.0 Hz), 3.72 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 2.95 (quin, 1H, J = 7.2 Hz), 1.34 (d, 6H, J = 11.8 Hz), 1.06 (d, 3H, J = 7.2 Hz).

Ketone **72** (10 mg, 71%) was prepared as a colorless oil from the above alcohol (14 mg, 0.036 mmol) by the same procedure as for ketone **69**. The enantiomeric excess (95% ee) was determined by chiral HPLC (Chiralpak AD-H, isopropanol/*n*-hexane = 1:9, 1.0 mL/min): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, 1H, J = 8.5 Hz), 6.76 (m, 3H), 6.55 (d, 1H, J = 10.0 Hz), 6.48 (d, 1H, J = 8.5 Hz), 5.62 (d, 1H, J = 10.0 Hz), 4.60 (q, 1H, J = 6.9 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.65 (s, 3H), 1.48 (d, 3H, J = 6.9 Hz), 1.39 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 157.1, 155.7, 149.0, 147.9, 133.8, 130.7, 130.5, 125.5, 120.2, 116.5, 112.3, 111.2, 77.2, 76.7, 63.3, 55.8, 55.7, 50.0, 43.1, 28.0, 28.0, 19.0. HRMS (FAB) calcd for $C_{23}H_{27}O_5$ (M + H^+): 383.1858. Found: 383.1849.

Biological Assay. MTS Assay and Western Blot Analysis of HIF-1α Expression. To analyze the antiproliferation effect of deguelin and its analogues against the non-small-cell lung cancer (NSCLC), H1299 cells were plated in 96-well plates at a density of 5 × 10^3 cells per well. Next day, the cells were treated with 0.1% DMSO as a dilution control or with various concentrations of deguelin and the tested analogues. Cell proliferation was assessed by the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) assay after 3 days. At least three replicate wells were used for each analysis. Western blot analysis of HIF-1α was utilized to evaluate the HSP90 inhibitory activities of the analogues after the same process. H1299 cells were untreated or treated with deguelin and the analogues at each concentration for 72 h, followed by incubation under hypoxic conditions (1% O_2) for 12 h. The resulting cell lysates were used for Western blot analysis with a monoclonal antibody against HIF-1α (BD Pharmingen).

Immunoprecipition and Immunoblotting Assay. In vitro assay was performed using the lysates of H1299 cells that had been treated with 100 μM $CoCl_2$ for 5 h. The cell lysates were incubated with 1.25 μM of analogue **54** or **69** in the presence or absence of 20 mM ATP for 30 min at 37 °C. The resulting samples were incubated with anti-HIF-1α antibody overnight at 4 °C. The antigen−antibody complex was then precipitated following incubation for 2 h at 4 °C with protein G-agarose. The immune complex was solubilized in 2× Laemmli buffer and boiled for 5 min. The samples were resolved and analyzed using 6% SDS−PAGE and then transferred to nitrocellulose membrane. They were then immunoblotted with the antibody directed against HSP90.

Antiangiogenic Effect on Zebrafish Embryos. Zebrafish embryos were used to determine the antiangiogenic effects of the tested compounds. The transgenic line Tg(fli1:EGFP)^{y1} zebrafish were obtained from the Zebrafish International Resource Center, University of Oregon, Eugene, OR (Lawson and Weinstein, 2002). Zebrafish embryos were generated by natural pairwise mating and raised at 28.5 °C in Danieau's solution. The Tg(fli1:EGFP)^{y1} embryos were

maintained in Danieau's solution at 28.5 °C, and the embryos were sorted for viability and the developmental stage (shield stage) at 6 hpf (hours postfertilization). The embryos were treated with 1-phenyl-2-thiourea (Sigma) to inhibit pigment formation at 12 hpf. The embryos were placed into each well of a 24-well plate containing 1 mL of Danieau's solution with or without the tested compounds at 24 hpf. The Danieau's solution was washed out at 48 hpf and examined for viability and gross morphological abnormalities. At 72 hpf, the embryos were anesthetized in tricaine (Sigma) and mounted in 6% methylcellulose (Sigma). The embryos were then photographed under a Leica DM5000B fluorescence microscope (Leica Microsystems, Wetzlar GmbH, Germany).

■ ASSOCIATED CONTENT

Supporting Information

HPLC data of the final compounds and supplementary figures on the zebrafish angiogenesis model. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a National Research Foundation grant funded by the Korea Government (MEST) (Grant No. 2012-0006019) and by the Global Core Research Center (GCRC) grant (Grant No. 2012-0001187) from the National Research Foundation (NRF), Ministry of Education, Science and Technology (MEST), Republic of Korea.

■ ABBREVIATIONS USED

HSP, heat shock protein; HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; DR, diabetic retinopathy; AMD, age-related macular degeneration; FP, fluorescence polarization; MTS, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium; NSCLC, non-small-cell lung cancer; DHP, dihydropyran; PTSA, *p*-toluenesulfonic acid; DMP, Dess–Martin periodinane; DIAD, diisopropyl azodicarboxylate; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBt, 1-hydroxybenzotriazole; SIV, subintestinal vein; hpf, hour postfertilization; CSA, camphor sulfonic acid

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