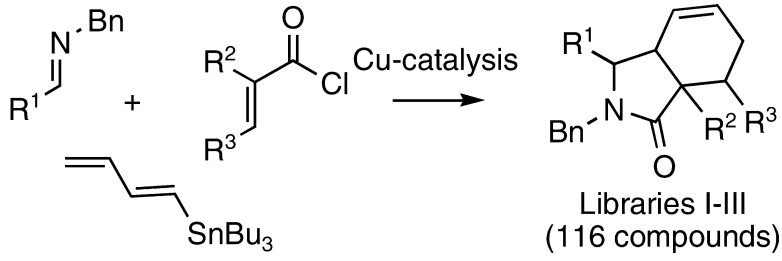
JOURNAL OF combinatorial CHEMISTRY

Article

Solution-Phase Parallel Synthesis of Hexahydro-1*H*-isoindolone Libraries via Tactical Combination of Cu-Catalyzed Three-Component Coupling and Diels–Alder Reactions

Lei Zhang, Gerald H. Lushington, Benjamin Neuenswander, John C. Hershberger, and Helena C. Malinakova

J. Comb. Chem., **2008**, 10 (2), 285-302• DOI: 10.1021/cc700151m • Publication Date (Web): 01 February 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Solution-Phase Parallel Synthesis of Hexahydro-1*H*-isoindolone Libraries via Tactical Combination of Cu-Catalyzed Three-Component Coupling and Diels–Alder Reactions

Lei Zhang, Gerald H. Lushington, Benjamin Neuenswander, John C. Hershberger, and Helena C. Malinakova*

Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, and the Center for Methodology and Library Development at the University of Kansas, 1501 Wakarusa Drive, Lawrence, Kansas 66047

Received September 13, 2007

Parallel solution-phase synthesis of combinatorial libraries of hexahydro-1*H*-isoindolones exploiting a novel "tactical combination" of Cu-catalyzed three-component coupling and Diels–Alder reactions was accomplished. Three distinct libraries consisting of 24 members (library I), 60 members (library II), and 32 members (library III) were constructed. Variation of three substituents on the isoindolone scaffold in library I was exclusively achieved by the choice of the building blocks. In the syntheses of libraries II and III, sublibraries of isoindolone scaffolds were prepared initially in a one-pot/two-step process and were further diversified via Pd-catalyzed Suzuki cross-coupling reaction with boronic acids at two different diversification points. The Lipinski profiles and calculated ADME properties of the compounds are also reported.

Introduction

Solution-phase parallel synthesis of combinatorial libraries has proven to be a valuable tool in drug discovery.[1] For this reason, the development of novel and synthetically powerful combinations of reactions or reaction cascades,[2] which would deliver medicinally relevant heterocyclic scaffolds, is critical to further advancement in the combinatorial chemistry field. In particular, transformations that would dramatically increase molecular complexity in just a few synthetic steps and be well-suited for automated parallel solution-phase synthesis are of substantial interest.

Considering that an overwhelming majority of currently marketed medicinal agents possess a nitrogen-containing heterocyclic skeleton,[3] we were attracted to the possibility to design tactical combinations of reactions,[2] which would first assemble an α-*N*-substituted amide scaffold **I**, and subsequently realize different modes of cyclization among the substituents R^1-R^4 to afford hypothetical heterocyclic scaffolds **II**, **III**, and **IV** (Figure 1). Recently, we have reported the first demonstration of this concept,[4] involving a new tandem copper-catalyzed three-component coupling/Diels–Alder sequence for a modular assembly of substituted isoindolones **III** (pathway i, Figure 1). In this study,[4] we have extended the scope of the copper-catalyzed three-component coupling originally reported by Arndtsen[5] to permit an in situ assembly of α-*N*-substituted amides **I** with functional groups poised for a facile intramolecular Diels/Alder reaction.

Preparation of discovery libraries of hexahydro-1*H*-isoindolones represents a valuable goal because the hydroisoindoline core is present in both synthetic and naturally occurring compounds that exert a wide range of pharmacological activities. For example, heterocycles **V** and **VI** (Figure 2), have been recognized as tachykinin NK1 receptor antagonists useful in the treatment of variety of disorders associated with an excess of tachykinines, including emesis, urinary incontinence, depression, and anxiety.[6] Naturally occurring cytotoxic fungal metabolites cytochalasins (cytochalasin B, Figure 2) also possess the hydroisoindolone skeleton along with a macrocyclic ring.[7] The principal activity of cytochalasins involves disruption of actin filaments and actin-associated structures. Structure–activity studies indicated that certain important activities, for example, a strong acceleration of the actin assembly, are retained in analogs lacking the macrocyclic ring.[8] Thus, compound **VII** was shown to possess similar accelerating activity to cytochalasin B in the fluorescence photobleaching recovery assay (Figure 2).[8]

The more recently discovered cytochalasin L-696,474 exhibited inhibitory activity against HIV-1 protease.[9] To the best of our knowledge, no combinatorial libraries of hexahydro-1*H*-isoindolones have been synthesized to date. There are few reports on the synthesis of libraries of isoindolines possessing an aromatic ring fused to the pyrrole or pyrrolidone rings. Thus, a 1000-member library of dimeric isoindoline-5,6-diamides was synthesized in solution phase and screened for binding to erythropoietin receptor (EPOr).[10] A solid-phase synthesis of isoindoline libraries was realized via Rh-catalyzed [2 + 2 + 2]-cyclotrimerization.[11] As a part of a program aimed at the diversity-oriented synthesis (DOS) of natural-product-like molecules, a solution-phase protocol exploiting a tandem Ugi four-component coupling/intramo-

* To whom the correspondence should be addressed. E-mail: hmalina@ku.edu. Phone: 785-864-4743.

10.1021/cc700151m CCC: $40.75
Published on Web 02/01/2008

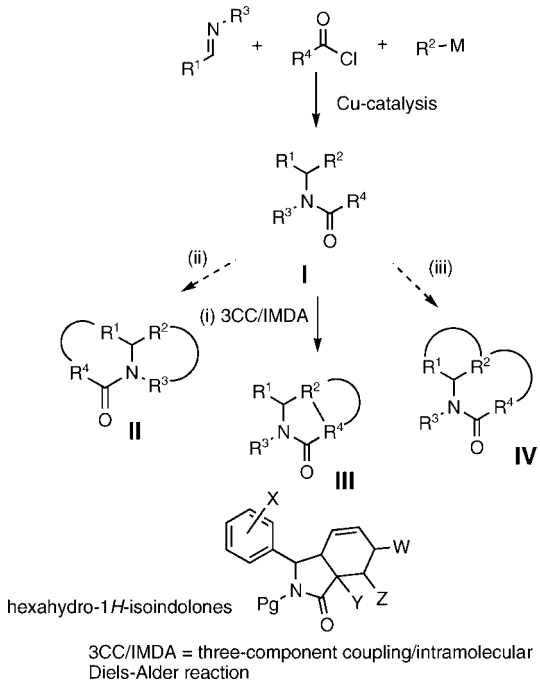


Figure 1. Tactical combination of reactions using α-*N*-substituted amides.

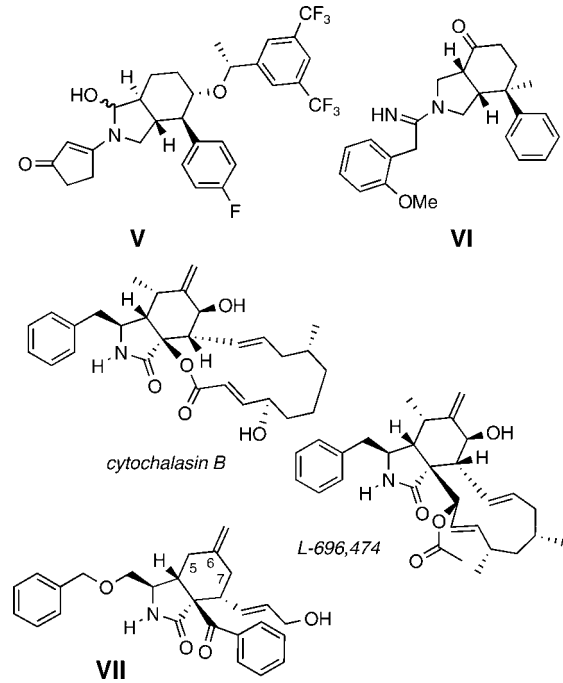


Figure 2. Biologically active hydroisoindolines and hydroisoindolones.

lecular Diels–Alder reaction for the preparation of isoindolones have been described.[12] Among the established classical procedures for the synthesis of hydroisoindolines and hydroisoindolones,[13] methods exploiting an intramolecular Diels–Alder reactions of amides are known.[14] In comparison to these traditional approaches, our three-component coupling/Diels–Alder reaction sequence offers the advantage of modularity, allowing us to incorporate up to three elements of diversity into the automated parallel synthesis of combinatorial libraries.

Herein, we report parallel solution phase synthesis of three combinatorial libraries **I**−**III** (Figure 3) of hexahydro-1*H*-isoindolones consisting of 24, 60, and 32 members, respectively, using our three-component coupling/Diels–Alder methodology with subsequent diversification of the scaffolds via Pd-catalyzed Suzuki cross-coupling reaction. The study demonstrates the value of our method in parallel synthesis, delivering all the libraries in excellent purities (measured by UV at 214 nm) reaching >95% purity for 89% of the library members.[15]

Results and Discussion

For the synthesis of library **I**, the design involving a one-pot/two-step three-component coupling of *N*-benzyl imines with differentially substituted acroyl chlorides and 1,3-butadienyl(tributyl)stannane was chosen (Scheme 1). The design endows the library with two elements of diversity, and both the imine component (six building blocks) and the acroyl chloride component (four building blocks) were chosen to contribute substantially to the diversity of library **I**. We anticipated that the diversity in the imine component **1**{*1–6*} (Figure 4), using electron-rich or -deficient aromatic and heteroaromatic *N*-benzyl-protected imines, would be well-tolerated. Our prior studies confirmed that the α- or *β*-methyl-substituted acroyl chlorides **2**{*1–2*} were compatible with the reaction sequence,[4] and the extension to *β*-ethyl-substituted acroyl chlorides appeared obvious. In contrast, we opted to evaluate the reactivity of conjugated *trans*-cinnamoyl chloride **2**{*4*} (Figure 4) in a classical synthetic format prior to the library synthesis (Scheme 2). Gratifyingly, the treatment of the *N*-benzylimine of 2-bromophenylcarboxaldehyde with *trans*-cinnamoyl chloride **2**{*4*} and dienylstannane **3** under CuCl catalysis in acetonitrile/methylene chloride mixture at room temperature, followed by solvent removal under reduced pressure, injection of toluene, and heating to reflux (16 h), afforded a good yield of the anticipated hexahydro-1*H*-isoindolone **4d** as a mixture of two diastereomers **4da** and **4db** in a 2:1 ratio as established by ^{1}H NMR. Diffusion-controlled crystallization of the mixture afforded single crystals of the minor diastereomer **4db**. X-ray crystallographic analysis of the singles crystals of **4db** revealed the relative stereochemistry at carbons C-3, C-3a, C-7, and C-7a as shown in Scheme 2. However, the relative stereochemistry of the major diastereomer **4da** (Scheme 2) could not be unequivocally assigned in the absence of the

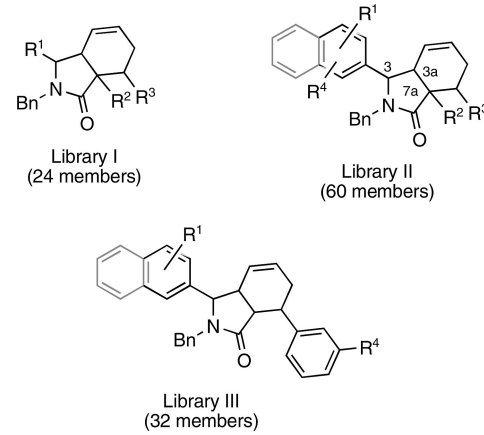
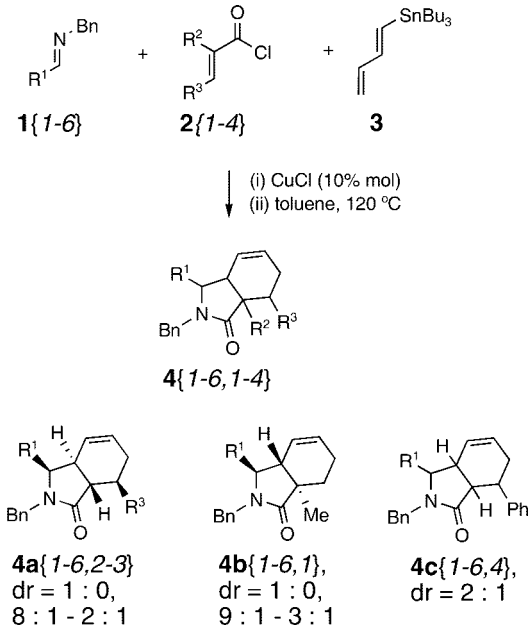


Figure 3. Overview of the prepared libraries.

Scheme 1. Synthetic Route to Library **I**



X-ray crystallographic evidence because the comparison of the *J* coupling constants in the ^{1}H NMR spectra to the data for isoindolones with known stereochemistry[4] proved to be inconclusive, and the NOE analyses were found not to be informative in our prior studies.[4] The success in the synthesis of isoindolones **4d** led us to include *trans*-cinnamoyl chloride **2**{*4*} among the library components **2** for the synthesis of library **I** (Figure 4). We aimed to produce 24 distinct hexahydro-1*H*-isoindolones according to the process outlined in Scheme 1. The library synthesis was carried out in MiniBlock XT synthesizer fitted with 24 (17 × 110 mm) reaction vials. The vials were charged with the CuCl catalyst (10 mol%), stock solutions of imines **1**{*1–6*}[16] in acetonitrile (1.0 equiv), and neat commercially available acroyl chlorides **2**{*1–4*} (1.3 equiv), consecutively. To the stirred reaction vessels was injected the stock solution of dienylstannane **3**[17] in methylene chloride (2.0 equiv), and the reaction system was heated to 45 °C under a stream of dry argon overnight. Solvents were removed by parallel evaporation in the GeneVac EZ-2 plus evaporator, and toluene (5 mL) was added to each vial. The reaction vials were heated in the MiniBlock XT synthesizer to reflux overnight, and the crude mixtures were individually filtered through 24 PrepSep silica columns. To remove tin-containing byproducts, the filtrates were treated overnight with KF on Celite (50%). The crude products obtained after filtration through 24 individual PrepSep silica columns and evaporation (GeneVac EZ-2) were analyzed by HPLC (UV 214 nm) and purified via preparative HPLC with mass-directed fractionation to obtain the final 24 library members **4**{*1–6,1–4*} (Table 1). Seven of the twelve isoindolones **4a**{*1–6,2–3*} (entries 7–18, Table 1) were obtained as single diastereomers, and six products **4b**{*1–6,1*} were isolated in diastereomeric ratios of 1:0−3:1 (entries 1–6, Table 1). The relative stereochemistry of the major diastereomers **4a** and **4b** as shown in Scheme 1 and Table 1 was assigned on the basis of the structure elucidation studies described in our prior communication and the comparison of the characteristic *J* coupling constants in the ^{1}H NMR spectra (see Tables S-10 and Tables S-11 in the Supporting Information),[4] whereas the relative stereochemistry for the major diastereomer in products **4c**{*1–6,4*} could not be unequivocally assigned (vide supra).

As summarized in Table 1, the above-described one-pot/two-step protocol successfully afforded all anticipated 24 library **I** members in 37–64% isolated yields (21–67 mg). Purities measured by UV detection at 214 nm of 21 members (87%) were higher than 97%, and the remaining three products were obtained in 92%, 90%, and 63% UV (214 nm) purity.

Aiming to further expand the diversity of hexahydro-1*H*-isoindolone libraries accessible by our methodology, we incorporated a subsequent diversification via palladium-catalyzed Suzuki cross-coupling into the library design (libraries **II** and **III**), endowing the libraries with three elements of diversity. In the first approach, the requisite Csp^2-Br-activating functionality was placed into the *N*-benzyl imine component, employing both electron-rich and -deficient bromoaryl imines **5**{*1–4*} (Figure 4) in the initial one-pot/two-step three-component coupling with α- and *β*-methyl-substituted acroyl chlorides **2**{*1–2*} and dienylstannane **3** (Scheme 3). The preparation of a series of eight bromoisoindolones was performed in a parallel format using the MiniBlock XT synthesizer fitted with 8 (24 × 150 mm) reaction vials according to the experimental protocol described above for the synthesis of isoindolones **4** except for the purification procedure. Thus, filtration of the crude solutions of the reaction mixtures in toluene through Celite and evaporation (GeneVac EZ-2) was followed by individual flash chromatography over silica to afford the corresponding bromoisoindolones **6**{*1–4,1–2*} as pure compounds in 55–71% yields (0.49–0.60 g) (Scheme 3). Bromoisoindolones **6**{*1–4,2*} bearing a methyl substituent (R^3) at C7 were isolated as single diastereomers,[18] whereas bromoisoindolones **6**{*1–4,1*} bearing a methyl substituent (R^2) at C7a were obtained as mixtures of three diastereomers with diastereomeric ratios ranging from dr = 4:92:4 to 7:84:9 (by GC).[19] Bromoisoindolones **6** were fully characterized. Subsequently, the stock solutions of the eight bromoisoindolones **6**{*1–4,1–2*} in THF (1 equiv) were added to 48 vials (11.5 × 110 mm) in the 8 × 6 position MiniBlock XT synthesizer containing $Pd(OAc)_2$ (5 mol%), 2-(dicyclohexylphosphino)-2′-(*N,N*-dimethylamine)biphenyl (ligand L1, Scheme 3) (10 mol %), CsF (4 equiv), and boronic acids **7**{*1–6*} (Figure 4) to perform the final diversification using modified literature conditions for the Suzuki cross-coupling (reflux at 60 °C overnight).[20] The boronic acids **7**{*1–6*} were selected to evaluate the efficiency of coupling to electron-rich and -deficient aromatic, as well as vinylic, boronic acids. The crude reaction mixtures were concentrated and filtered through 48 individual PrepSep silica columns eluting with methylene chloride, and the solutions were evaporated (GeneVac EZ-2) to afford crude products **8**. The crude products were analyzed by HPLC (UV 214 nm) and purified via preparative HPLC with mass-directed fractionation to obtain the final 48 library members **8**{*1–4,1–2,1–6*} (Scheme 3). The structures of the major diastereomers **8a**{*1–4,1,1–6*} arising from the coupling to the diastereomeric mixtures of

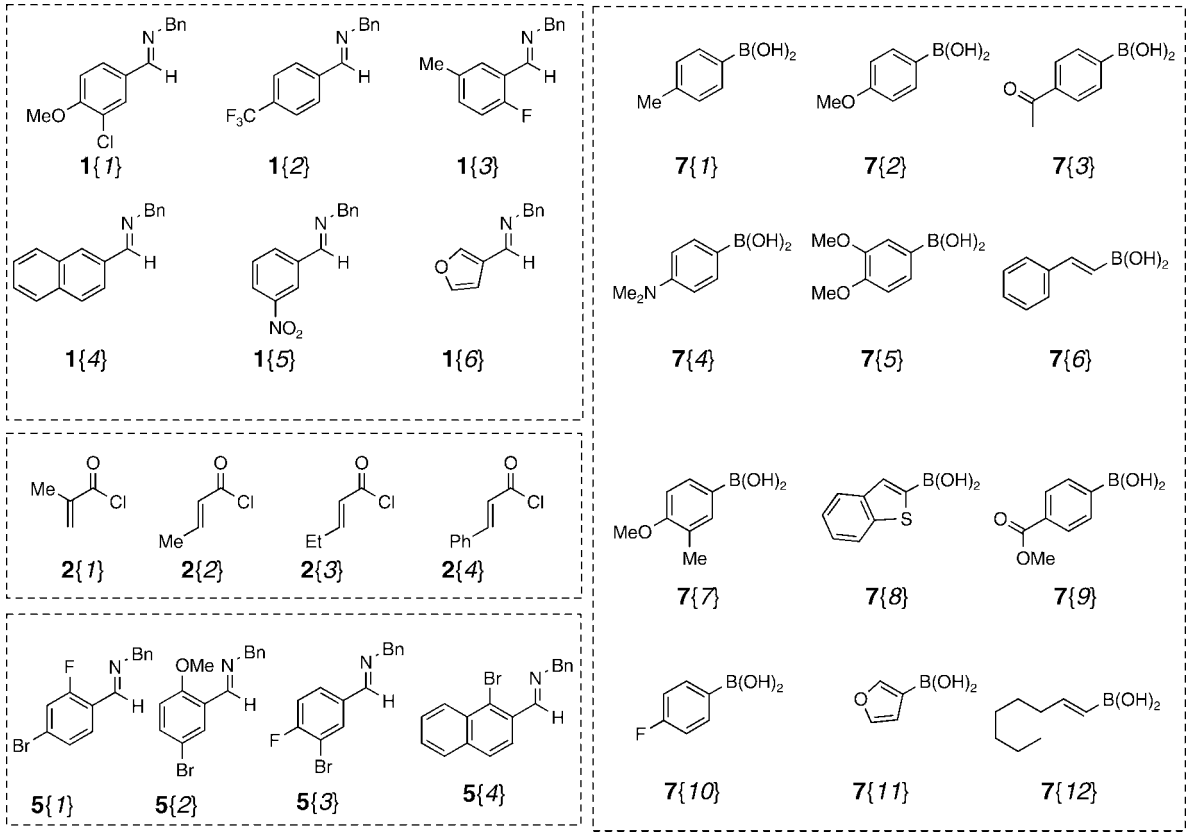
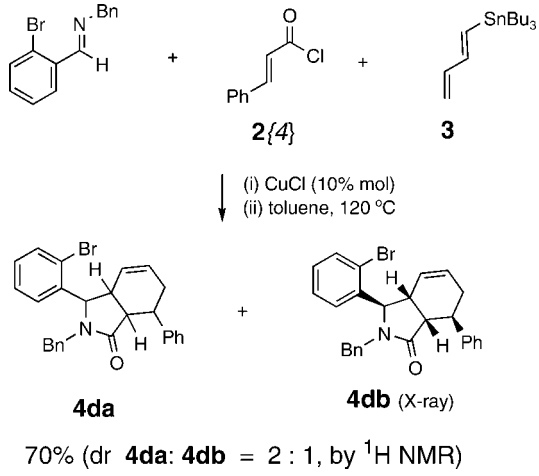


Figure 4. Library components for libraries **I**−**III**.

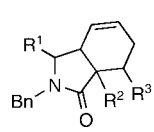
Scheme 2. Preliminary Study on the Reactivity of *trans*-Cinnamoyl Chloride



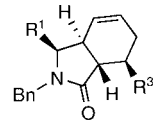
the corresponding bromoisoindolones **6**{*1–4,1*} (vide infra), as well as the structure of the single diastereomers **8b**{*1–4*, *2*, *1–6*} from coupling to single diastereomers of bromoisoindolones **6**{*1–4*, *2*} are shown in Scheme 3.[19] The assignment of the relative stereochemistry for major diastereomers of heterocycles **6** and **8** is based on analogy with our results reported in prior communication.[4]

The results of the synthesis of library **II** (part I) are summarized in Table 2. Overall, only two entries (entries 43 and 45, Table 2) failed to afford the anticipated heterocycles **8**. However, the yields of Suzuki cross-coupling to isoindolones **6**{*4,1–2*}, featuring the naphthalene ring at C3 (R^1), proved to be rather low (7–19%) regardless of the structure of the boronic acid, affording the corresponding twelve isoindolones **8**{*4,1–2,1–6*} in 5–10% yields over the entire three-step reaction sequence. In contrast, the remaining 36 library members underwent the cross-coupling in 9–74% yields, corresponding to 6–53% overall yields, providing 4–34 mg of the heterocycles **8**{*1–3,1–2,1–6*} (Table 2). Consistently, somewhat lower yields were noted in the cross-coupling reactions with the electron deficient boronic acid **7**{*3*} (Figure 4). The purities measured by UV detection at 214 nm for 42 members (88%) were higher than 94%, and for 4 members were 26%, 57%, 87%, and 91% (Table 2), attesting to the effectiveness of the preparative HPLC purification. Overall, analysis of the data in Table 2 indicates that the scope and economy (overall yields) in the preparation of library **II** could be significantly improved by optimization of the conditions for the Suzuki cross-coupling to the challenging sterically hindered naphthyl-substituted isoindolones **6**{*4,1–2*}. Indeed, a brief survey of the effect of the choice of the auxiliary phosphine ligand on the yields of the Suzuki cross-coupling between the isoindolone **6**{*4,2*} and *p*-methoxyphenylboronic acid **7**{*2*} revealed that a significant increase in the yield of the corresponding isoindolone **8**{*4,2,2*} resulted from replacing 2-(dicyclohexylphosphino)-2′-(*N,N*-dimethylamine)biphenyl (L1) (16% yield) with 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl (L2) (90%) (Scheme 4).[21] To evaluate the generality of these improved Suzuki conditions in the context of parallel library synthesis, we decided to prepare a part II of library **II**, aiming to repeat the coupling of boronic acids **7**{*1–6*} to naphthyl-substituted sterically encumbered isoindolones **6**{*4,1–2*}, as well as to expand the diversity of the boronic acid components to encompass heteroaryl and vinyl boronic acids. Thus, we

Table 1. Results Summary for Library **I**

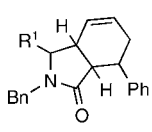


4{*1-6,1-4*}



4a{*1-6,2-3*}
dr = 1 : 0,
8 : 1 - 2 : 1

4b{*1-6,1*},
dr = 1 : 0,
9 : 1 - 3 : 1

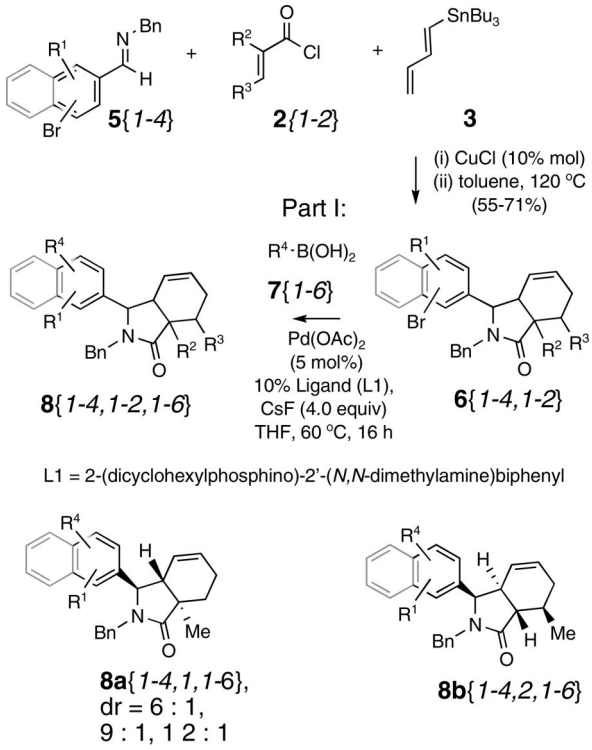


4c{*1-6,4*},
dr = 2 : 1

entry	compd	R^1	R^2	R^3	yield[a] (%)	dr[b]	purity[c] (%)	HRMS[d]
1	**4**{*1,1*}	4-MeO-3-ClC_6H_3	Me	H	64	9:1	100	382.1584
2	**4**{*2,1*}	4-$CF_3C_6H_4$	Me	H	48	5:1	99	386.1738
3	**4**{*3,1*}	2-F-3-MeC_6H_3	Me	H	57	1:0	100	350.1952
4	**4**{*4,1*}	$C_{10}H_7$ naphthyl	Me	H	63	7:1	99	368.2022
5	**4**{*5,1*}	3-$NO_2C_6H_4$	Me	H	47	3:1	98	373.1723
6	**4**{*6,1*}	C_4H_3O 3-furyl	Me	H	56	6:1	63	308.1612
7	**4**{*1,2*}	4-MeO-3-ClC_6H_3	H	Me	42	8:1	99	382.1559
8	**4**{*2,2*}	4-$CF_3C_6H_4$	H	Me	43	1:0	91	386.1714
9	**4**{*3,2*}	2-F-3-MeC_6H_3	H	Me	44	1:0	99	350.1925
10	**4**{*4,2*}	$C_{10}H_7$ naphthyl	H	Me	61	7:1	100	368.2012
11	**4**{*5,2*}	3-$NO_2C_6H_4$	H	Me	41	1:0	97	363.1708
12	**4**{*6,2*}	C_4H_3O 3-furyl	H	Me	37	3:1	92	308.1655
13	**4**{*1,3*}	4-MeO-3-ClC_6H_3	H	Et	38	1:0	99	396.1741
14	**4**{*2,3*}	4-$CF_3C_6H_4$	H	Et	51	4:1	99	400.1871
15	**4**{*3,3*}	2-F-3-MeC_6H_3	H	Et	52	1:0	100	364.2074
16	**4**{*4,3*}	$C_{10}H_7$ naphthyl	H	Et	34	1:0	99	382.2191
	4{*4,3*}[e]				17	1:0	99	
17	**4**{*5,3*}	3-$NO_2C_6H_4$	H	Et	59	2:1	90	377.1877
18	**4**{*6,3*}	C_4H_3O 3-furyl	H	Et	47	1:0	99	322.1795
19	**4**{*1,4*}	4-MeO-3-ClC_6H_3	H	Ph	46	2:1	99	444.1718
20	**4**{*2,4*}	4-$CF_3C_6H_4$	H	Ph	60	2:1	99	448.1909
21	**4**{*3,4*}	2-F-3-MeC_6H_3	H	Ph	55	2:1	99	412.2061
22	**4**{*4,4*}	$C_{10}H_7$ naphthyl	H	Ph	20	1:0	99	430.2187
	4{*4,4*}[e]				34	2:1	99	
23	**4**{*5,4*}	3-$NO_2C_6H_4$	H	Ph	47	2:1	98	425.1862
24	**4**{*6,4*}	C_4H_3O 3-furyl	H	Ph	37	2:1	98	370.1802

[a] Isolated yield after HPLC purification. [b] dr = ratio of the diastereomers in the final product established by HPLC. [c] UV purity determined at 214 nm after HPLC purification. [d] The HRMS data for the M + 1 molecular ion of the compound **4** detected in the corresponding product. [e] A second minor fraction of the product was separated and isolated by the HPLC with mass-directed fractionation. The identity of the product in the minor fraction was confirmed by ^{1}H NMR.

Scheme 3. Synthetic Route to Library **II** (Part I)



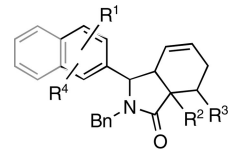
8a{*1-4,1,1-6*},
dr = 6 : 1,
9 : 1, 1 2 : 1

8b{*1-4,2,1-6*}

tested the coupling of isoindolones **6**{*1–2,2*} to boronic acids **7**{*7–12*} leading to 12 new library members **8**{*1–2,2,7–12*} (Scheme 5). A protocol identical to that for the synthesis of library **II** (part I) was employed. The results of the synthesis of library **II** (Part II) are summarized in Table 3. Indeed, the yields of Suzuki cross-coupling to isoindolones **6**{*4,1–2*} featuring the naphthalene ring at C3 (R^1) dramatically improved reaching 24–86% to afford the corresponding isoindolones **8**{*4,1–2,1–6*} in 16–56% yield (11–41 mg) over the entire three-step sequence. Furthermore, products **8** were obtained in excellent purities (98%–100% by UV at 214 nm) (entries 1–12, Table 3). The additional boronic acids **7**{*7–12*} proved to be competent coupling partners, providing the corresponding new isoindolones **8**{*1–2,2,7–12*} in 24–100% cross-coupling yields, 15–60% overall yields (12–47 mg), and purities higher than 95% (UV at 214 nm) (entries 13–24, Table 3). In only two cases involving the cross-coupling of 2-benzothiophenyl boronic acids, the cross-coupling yields dropped to 43% and 24%, respectively (entries 14 and 20, Table 3).

In summary, when the initial low-yielding preparation of isoindolones **8**{*4,1–2,1–6*} (Table 2, entries 37–48) is disregarded, the two-pot three-step protocol for the synthesis of isoindolones, followed by diversification via Suzuki cross-coupling at a carbon in the aryl substituent at C3 (R^1), afforded 60 new isoindolones **8** (3–49 mg) in 6–60% overall yields and higher than 90% purity in 59 cases (one compound had a purity of 87% by UV at 214 nm) (Tables 2 and 3).

Table 2. Results Summary for Library **II** (Part I)



Library II
(48 members)

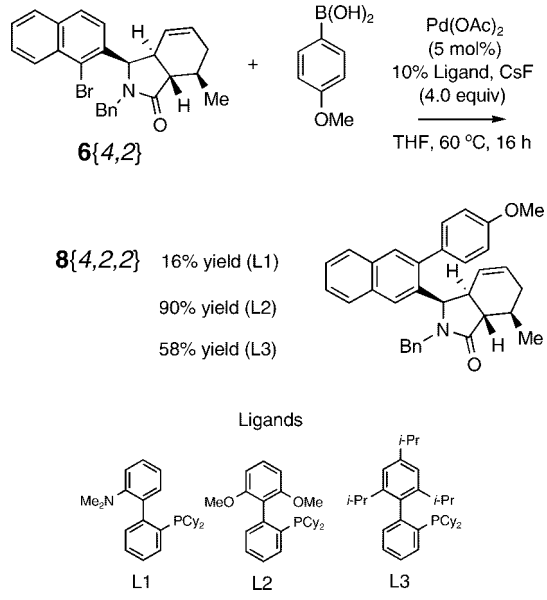
8{*1-4,1-2,1-6*}

entry	compd	R^1	R^2	R^3	R^4	yield (1)[a] (%)	yield (2)[b] (%)	dr[c]	purity[d] (%)	HRMS[e]
1	**8**{*1,1,1*}	2-F-4-C_6H_4−	Me	H	4-MeC_6H_4	70	43	6:1	99	426.2233
2	**8**{*1,1,2*}	2-F-4-C_6H_4−	Me	H	4-MeOC_6H_4	61	37	6:1	100	442.2173
3	**8**{*1,1,3*}	2-F-4-C_6H_4−	Me	H	4-Me(*C*=O)C_6H_4	44	27	6:1	99	454.2187
4	**8**{*1,1,4*}	2-F-4-C_6H_4−	Me	H	4-$Me_2N$$C_6H_4$	62	38	6:1	94	455.2485
5	**8**{*1,1,5*}	2-F-4-C_6H_4−	Me	H	4,3-$(MeO)_2C_6H_3$	56	34	6:1	99	472.2295
6	**8**{*1,1,6*}	2-F-4-C_6H_4−	Me	H	*trans*-PhCH=CH	65	40	6:1	100	438.2234
7	**8**{*1,2,1*}	2-F-4-C_6H_4−	H	Me	4-MeC_6H_4	65	39	1:0	100	426.2253
8	**8**{*1,2,2*}	2-F-4-C_6H_4−	H	Me	4-MeOC_6H_4	65	39	1:0	100	442.2182
9	**8**{*1,2,3*}	2-F-4-C_6H_4−	H	Me	4-Me(*C*=O)C_6H_4	14	8	1:0	100	454.2189
10	**8**{*1,2,4*}	2-F-4-C_6H_4−	H	Me	4-$Me_2N$$C_6H_4$	64	38	1:0	95	455.2494
11	**8**{*1,2,5*}	2-F-4-C_6H_4−	H	Me	4,3-$(MeO)_2C_6H_3$	43	26	1:0	99	472.2284
12	**8**{*1,2,6*}	2-F-4-C_6H_4−	H	Me	*trans*-PhCH=CH	67	40	1:0	100	438.2242
13	**8**{*2,1,1*}	2-MeO-5-C_6H_4−	Me	H	4-MeC_6H_4	74	53	6:1	91	438.2433
14	**8**{*2,1,2*}	2-MeO-5-C_6H_4−	Me	H	4-MeOC_6H_4	71	50	6:1	100	454.2394
15	**8**{*2,1,3*}	2-MeO-5-C_6H_4−	Me	H	4-Me(*C*=O)C_6H_4	41	29	6:1	99	466.2394
16	**8**{*2,1,4*}	2-MeO-5-C_6H_4−	Me	H	4-$Me_2N$$C_6H_4$	73	52	6:1	96	467.2698
17	**8**{*2,1,5*}	2-MeO-5-C_6H_4−	Me	H	4,3-$(MeO)_2C_6H_3$	71	51	6:1	99	484.2491
18	**8**{*2,1,6*}	2-MeO-5-C_6H_4−	Me	H	*trans*-PhCH=CH	66	47	6:1	96	450.2439
19	**8**{*2,2,1*}	2-MeO-5-C_6H_4−	H	Me	4-MeC_6H_4	74	47	1:0	100	438.2422
20	**8**{*2,2,2*}	2-MeO-5-C_6H_4−	H	Me	4-MeOC_6H_4	59	37	1:0	100	454.2404
21	**8**{*2,2,3*}	2-MeO-5-C_6H_4−	H	Me	4-Me(*C*=O)C_6H_4	28	18	1:0	99	466.2367
22	**8**{*2,2,4*}	2-MeO-5-C_6H_4−	H	Me	4-$Me_2N$$C_6H_4$	67	42	1:0	94	467.2680
23	**8**{*2,2,5*}	2-MeO-5-C_6H_4−	H	Me	4,3-$(MeO)_2C_6H_3$	51	32	1:0	91	484.2476
24	**8**{*2,2,6*}	2-MeO-5-C_6H_4−	H	Me	*trans*-PhCH=CH	60	38	1:0	100	450.2435
25	**8**{*3,1,1*}	4-F-3-C_6H_4−	Me	H	4-MeC_6H_4	31	21	9:1	99	426.2220
26	**8**{*3,1,2*}	4-F-3-C_6H_4−	Me	H	4-MeOC_6H_4	58	40	9:1	100	442.2180
27	**8**{*3,1,3*}	4-F-3-C_6H_4−	Me	H	4-Me(*C*=O)C_6H_4	9	6	9:1	96	454.2189
28	**8**{*3,1,4*}	4-F-3-C_6H_4−	Me	H	4-$Me_2N$$C_6H_4$	56	39	9:1	94	455.2491
29	**8**{*3,1,5*}	4-F-3-C_6H_4−	Me	H	4,3-$(MeO)_2C_6H_3$	49	34	9:1	87	472.2291
30	**8**{*3,1,6*}	4-F-3-C_6H_4−	Me	H	*trans*-PhCH=CH	49	34	9:1	100	438.2219
31	**8**{*3,2,1*}	4-F-3-C_6H_4−	H	Me	4-MeC_6H_4	64	43	1:0	100	426.2218
32	**8**{*3,2,2*}	4-F-3-C_6H_4−	H	Me	4-MeOC_6H_4	52	35	1:0	100	442.2177
33	**8**{*3,2,3*}	4-F-3-C_6H_4−	H	Me	4-Me(*C*=O)C_6H_4	38	25	1:0	98	454.2190
34	**8**{*3,2,4*}	4-F-3-C_6H_4−	H	Me	4-$Me_2N$$C_6H_4$	31	21	1:0	94	455.2501
35	**8**{*3,2,5*}	4-F-3-C_6H_4−	H	Me	4,3-$(MeO)_2C_6H_3$	31	21	1:0	97	472.2271
36	**8**{*3,2,6*}	4-F-3-C_6H_4−	H	Me	*trans*-PhCH=CH	63	42	1:0	100	438.2227
37	**8**{*4,1,1*}	2-naphthalene-1-yl	Me	H	4-MeC_6H_4	11	7	12:1	100	458.2465
38	**8**{*4,1,2*}	2-naphthalene-1-yl	Me	H	4-MeOC_6H_4	10	6	12:1	95	474.2432
39	**8**{*4,1,3*}	2-naphthalene-1-yl	Me	H	4-Me(*C*=O)C_6H_4	15	9	12:1	26	486.2428
40	**8**{*4,1,4*}	2-naphthalene-1-yl	Me	H	4-$Me_2N$$C_6H_4$	7	5	12:1	97	487.2738
41	**8**{*4,1,5*}	2-naphthalene-1-yl	Me	H	4,3-$(MeO)_2C_6H_3$	10	6	12:1	99	504.2527
42	**8**{*4,1,6*}	2-naphthalene-1-yl	Me	H	*trans*-PhCH=CH	19	12	12:1	100	470.2485
43	**8**{*4,2,1*}	2-naphthalene-1-yl	H	Me	4-MeC_6H_4	0	0	1:0	NA	NA
44	**8**{*4,2,2*}	2-naphthalene-1-yl	H	Me	4-MeOC_6H_4	19	11	1:0	96	474.2416
45	**8**{*4,2,3*}	2-naphthalene-1-yl	H	Me	4-Me(*C*=O)C_6H_4	2	1	1:0	57	486.2455
46	**8**{*4,2,4*}	2-naphthalene-1-yl	H	Me	4-$Me_2N$$C_6H_4$	11	6	1:0	97	487.2715
47	**8**{*4,2,5*}	2-naphthalene-1-yl	H	Me	4,3-$(MeO)_2C_6H_3$	16	9	1:0	90	504.2539
48	**8**{*4,2,6*}	2-naphthalene-1-yl	H	Me	*trans*-PhCH=CH	15	8	1:0	100	470.2479

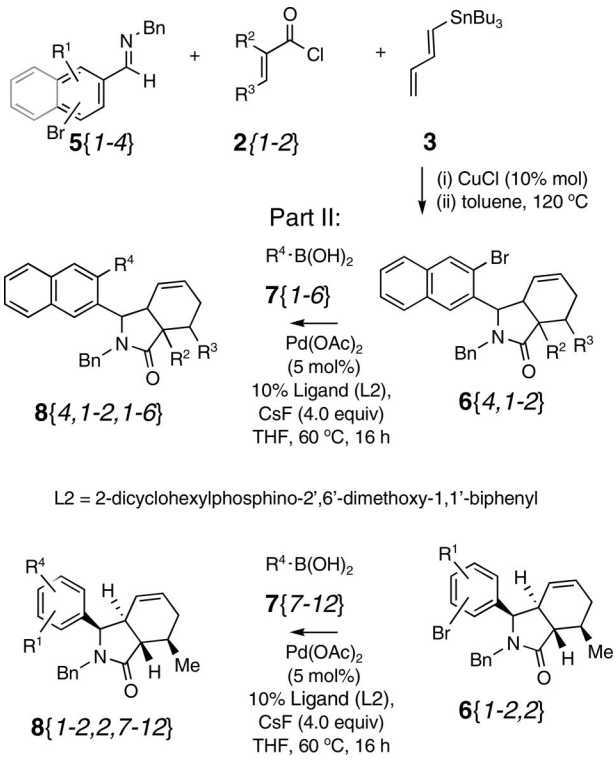
[a] Isolated yield after HPLC purification calculated for the final cross-coupling step. [b] Overall yield for the entire sequence of the three steps (three-component coupling, Diels–Alder, cross-coupling). [c] dr = ratio of the diastereomers in the final product established by HPLC. [d] UV purity determined at 214 nm after HPLC purification. [e] The HRMS data for the M + 1 molecular ion of the compound **8** detected in the corresponding product.

Successful application of *trans*-cinnamoyl chloride **2**{*4*} as a diversity element in the synthesis of library **I** opened up an access to isoindolones bearing the phenyl substituent at the C7 position. Following the precedent of library **II**, we decided to investigate further diversification of hexahydro-1*H*-isoindolones bearing bromoaryl substituents at the C7 position via the Suzuki cross-coupling reaction. Our strategy for the construction of library **III** is outlined in Scheme 6. According to this plan (Scheme 6), library **III** was designed to feature two elements of diversity, for example, the imines **1**{*1–4*} and boronic acids **7**{*1,2,4,6*} (Scheme 6). The preparation of a series of four C7-bromoarylisoindolones **10** via coupling of four imines **1**{*1–4*} with *m*-bromocinnamoyl chloride **9** and diennylstannene **3** was performed in a parallel format using the MiniBlock XT synthesizer fitted with 4 (24 × 150 mm) reaction vials proceeding according to the experimental protocol described above for the synthesis of isoindolones **4** and **6**. Thus, filtration of the crude reaction

Scheme 4. Ligand Effects in the Suzuki Cross-Coupling



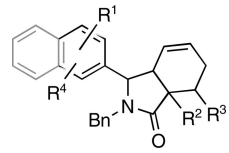
Scheme 5. Synthetic Route to Library **II** (Part II)



mixtures in toluene through Celite and evaporation (GeneVac EZ-2) was followed by individual flash chromatography over silica to afford the corresponding bromoisoindolones **10**{*1*−*4*} as pure compounds in 58–70% yields. Isoindolones **10** were obtained as mixtures of two diastereomers inseparable on a preparative scale in dr 2:1 and were fully characterized. However, as discussed above for compounds **4da** and **4db**, the relative stereochemistry for the major diastereomer of isoindolones **10** could not be unequivocally assigned in the absence of X-ray crystallographic evidence.[22] Subsequently, the stock solutions of the four bromoisoindolones **10**{*1–4*} in THF (1 equiv) were added to 16 vials (11.5 × 110 mm) in the 8 × 6 position MiniBlock XT synthesizer containing $Pd(OAc)_2$ (5 mol%), 2-(dicyclohexylphosphino)-2′-(*N,N*-dimethylamine)biphenyl (10 mol %), CsF (4 equiv), and selected boronic acids **7**{*1,2,4,6*} (Figure 4) to perform the final diversification via Suzuki cross-coupling. The crude reaction mixtures were concentrated and filtered through 16 individual PrepSep silica columns eluting with methylene chloride, and the solutions were evaporated (GeneVac EZ-2) to afford crude products **11**. The crude products were analyzed by HPLC (UV 214 nm) and purified via preparative HPLC with mass-directed fractionation. The preparative HPLC succeeded in separating each product **11** into two fractions, each significantly enriched or exclusively containing either the major or minor diastereomers of isoindolones **11**{*1–4,1,2,4,6*}. Thus, the synthesis of library **III** in fact delivered 32 distinct library members **11**. The results from preparation of the library **III** are summarized in Table 4. Combined yields of the Suzuki cross-coupling for both fractions of diastereomers of isoindolones **11** ranged from 27 to 76%, corresponding to 17–53% yields over the entire three-step sequence, affording acceptable quantities of products, for example, 8–29 mg for fractions with major diastereomers of **11** and 5–25 mg for fractions with the minor diastereomers of **11** (Table 4). The fractions with major diastereomers were isolated in high diastereomeric purities, for example, 1:0 (six entries) and 9:1–33:1 (10 entries) as established by HPLC and ^{1}H NMR. Diastereomeric ratios in the fractions featuring predominantly the minor diastereomer varied more broadly from 1:1 to 9/10:1 ratios (Table 4). The purities of isoindolones **11** contained in all the fractions were excellent (99–100% by UV at 214 nm) with a single exception for the major diastereomer of isoindolone **11**{*3,4*}, which was isolated in 80% UV purity (entry 11a, Table 4). Interestingly, the yields of the cross-coupling to the isoindolone **10**{*1*} proved to be consistently lower 27–44% than the yields of the coupling to the remaining isoindolones **10**{*2–4*},which were between 49% and 76% with a single exception (33% yield of **11**{*4,4*} (entry 16a, Table 4). It is not clear if these results are connected to the presence of the potentially reactive aryl chloride functionality. Further improvements in the efficiency of the cross-coupling protocol might be achieved by replacing the ligand 2-(dicyclohexylphosphino)-2′-(*N,N*-dimethylamine)biphenyl (L1) with the ligand 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl used in the preparation of library **II** (part II, vide supra), and this possibility will be explored in future studies. Success in preparation of library **III** opens up an access to scaffolds with quite distinct shapes and therefore possibly extends the range of biologically relevant properties of the isoindolones available by this methodology.

To confirm the purity and identity of compounds in libraries **I**−**III**, additional analyses were performed. The bromophenyl isoindolones **6**{*1–4,1–2*} and **10**{*1–4*} were fully characterized following the preparation as described above without further purification. In addition to the purities established by UV (214 nm) and the structure confirmation via MS detection of the corresponding molecular ion indicated for each entry from libraries **I**−**III** in Tables 1−4, all the members of libraries **I**−**III** were analyzed by ^{1}H NMR, and selected members of libraries **I** (6 compounds),

Table 3. Results Summary for Library **II** (Part II)



Library II
(24 members)

8{*4,1-2,1-6*}

8{*1-2,2,7-12*}

entry	compd	R^1	R^2	R^3	R^4	yield (1)[a] (%)	yield (2)[b] (%)	dr[c]	purity[d] (%)	HRMS[e]
1	**8**{*4,1,1*}	2-naphthalene-1-yl	Me	H	4-MeC_6H_4	52	34	12:1	100	485.2500
2	**8**{*4,1,2*}	2-naphthalene-1-yl	Me	H	4-MeOC_6H_4	24	16	12:1	100	474.2451
3	**8**{*4,1,3*}	2-naphthalene-1-yl	Me	H	4-Me(*C*=O)C_6H_4	37	24	12:1	100	486.2434
4	**8**{*4,1,4*}	2-naphthalene-1-yl	Me	H	4-$Me_2NC_6H_4$	60	39	12:1	100	487.2748
5	**8**{*4,1,5*}	2-naphthalene-1-yl	Me	H	4,3-$(MeO)_2C_6H_3$	38	25	12:1	100	504.2521
6	**8**{*4,1,6*}	2-naphthalene-1-yl	Me	H	*trans*-PhCH=CH	86	56	12:1	100	470.2475
7	**8**{*4,2,1*}	2-naphthalene-1-yl	H	Me	4-MeC_6H_4	53	29	1:0	100	458.2503
8	**8**{*4,2,2*}	2-naphthalene-1-yl	H	Me	4-MeOC_6H_4	76	42	1:0	99	474.2420
9	**8**{*4,2,3*}	2-naphthalene-1-yl	H	Me	4-Me(*C*=O)C_6H_4	27	15	1:0	98	486.2419
10	**8**{*4,2,4*}	2-naphthalene-1-yl	H	Me	4-$Me_2NC_6H_4$	48	27	1:0	100	487.2742
11	**8**{*4,2,5*}	2-naphthalene-1-yl	H	Me	4,3-$(MeO)_2C_6H_3$	55	30	1:0	100	504.2525
12	**8**{*4,3,6*}	2-naphthalene-1-yl	H	Me	*trans*-PhCH=CH	85	47	1:0	100	470.2469
13	**8**{*1,2,7*}	2-F-4-C_6H_4−	H	Me	4-Me-4-MeOC_6H_3	92	55	1:0	100	456.2324
14	**8**{*1,2,8*}	2-F-4-C_6H_4−	H	Me	2-benzothiophenyl	43	26	1:0	100	468.1783
15	**8**{*1,2,9*}	2-F-4-C_6H_4−	H	Me	4-MeO(*C*=O)C_6H_4	99	59	1:0	100	470.2130
16	**8**{*1,2,10*}	2-F-4-C_6H_4−	H	Me	4-FC_6H_4	100	60	1:0	100	430.1981
17	**8**{*1,2,11*}	2-F-4-C_6H_4−	H	Me	3-furyl	56	34	1:0	98	402.1868
18	**8**{*1,2,12*}	2-F-4-C_6H_4−	H	Me	*trans*-1-octene1-yl	77	46	1:0	97	446.2854
19	**8**{*2,2,7*}	2-MeO-5-C_6H_4−	H	Me	4-Me-4-MeOC_6H_3	100	63	1:0	95	468.2540
20	**8**{*2,2,8*}	2-MeO-5-C_6H_4−	H	Me	2-benzothiophenyl	24	15	1:0	100	480.1978
21	**8**{*2,2,9*}	2-MeO-5-C_6H_4−	H	Me	4-MeO(*C*=O)C_6H_4	55	35	1:0	100	482.2320
22	**8**{*2,2,10*}	2-MeO-5-C_6H_4−	H	Me	4-FC_6H_4	88	55	1:0	100	442.2174
23	**8**{*2,2,11*}	2-MeO-5-C_6H_4−	H	Me	3-furyl	78	49	1:0	100	414.2075
24	**8**{*2,2,12*}	2-MeO-5-C_6H_4−	H	Me	*trans*-1-octene-1-yl	90	57	1:0	100	458.3060

[a] Isolated yield after HPLC purification calculated for the final cross-coupling step. [b] Overall yield for the entire sequence of the three steps (three-component coupling, Diels–Alder, cross-coupling). [c] dr = ratio of the diastereomers in the final product established by HPLC. [d] UV purity determined at 214 nm after HPLC purification. [e] The HRMS data for the M + 1 molecular ion of the compound **8** detected in the corresponding product.

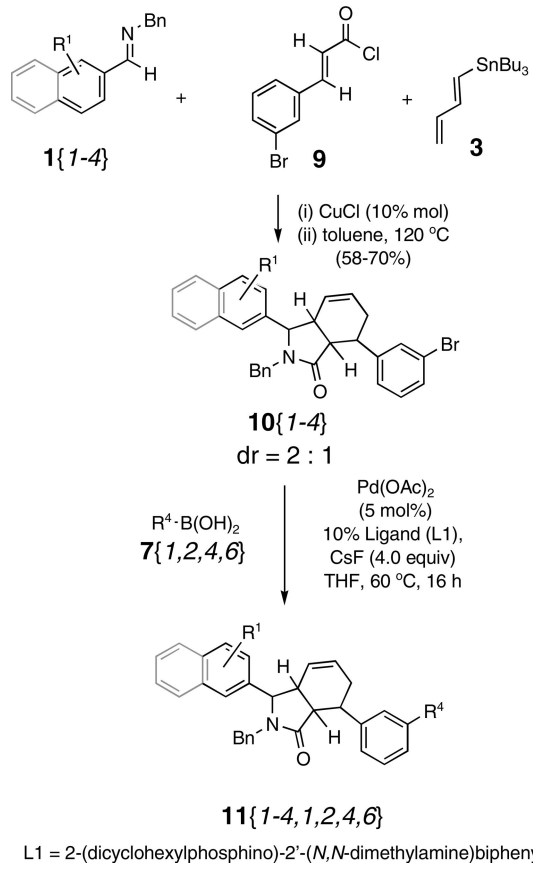
II (10 compounds), and (8 compounds) were fully characterized after the mass-directed fractionation by HPLC without further purification (data is provided in the Experimental Section (see below)). These analyses provided in all cases satisfactory evidence of the compound identity and purity, comparable to the results of the purity measurements by UV (214 nm). All the compounds reported herein were produced as racemates.

Prior to screening of the compounds for biological activity, a total of one hundred compounds prepared in this study, including 24 members **4** of library **I**, 60 members of library **II** represented by **8**{*1–4,1–2,1–6*} and **8**{*1–2,2,7–12*}, and the 16 major diastereomer fractions containing products **11** from library **III** were evaluated computationally for their drug-like properties on the basis of Lipinski's "rule of five".[23] Overall, 23% of compounds had two or more Lipinski's rule violations; 65% had one violation, and 12% had zero. The most common violation was *C*log*P* (88% of compounds) for which the mean value over the entire library was 6.37 (standard deviation = 1.25). The molecular weight distribution shown in Figure 5 indicates the desirable centering around 400–500 g/mol[23] with 50% of compounds having the molecular weight in this range. Standard absorption−distribution−metabolism−excretion (ADME) properties were calculated using the VolSurf[24] program and are presented in the Supporting Information. Finally, chemical diversity analysis relative to the PubChem collection (performed via DiverseSolutions)[25] revealed that approximately 35% of compounds occupy rather unexplored regions of the PubChem space (diversity scores < 24), and 48% of compounds was found in moderately explored PubChem space (diversity scores from 24 to 94). Only the balance (17%) of compounds are present in regions of PubChem space that already have substantial populations (diversity scores from 95 to 146), albeit without duplicating any known entities.

Conclusions

A new and highly efficient method for synthesis of combinatorial libraries of hexahydro-*1H*-isoindolones relying on a tactical combination[2] of Cu-catalyzed three-component coupling process with an intramolecular Diels–Alder reaction was applied to the preparation of combinatorial libraries. The one-pot/two-step sequence rapidly assembled substituted isoindolone scaffolds, which were further diversified by Pd-catalyzed Suzuki cross-coupling reactions. Overall, three distinct combinatorial libraries comprising a total of 116 pure compounds or mixtures of diastereomers were synthesized in high purities (>95% for 89 compounds) and good quantities (5–50 mg). The application of parallel synthesis methods and automated purification techniques allowed us to complete the library preparation within only three weeks.

Scheme 6. Synthetic Route to Library **III**



The evaluation of biological activities of the compounds prepared in this study in high-throughput screens is currently underway.

Experimental Section

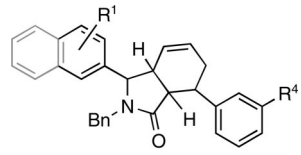
General. All imines were prepared according to a modified literature procedure[26] by condensation of a 1:1 mixture of aldehyde and amine in benzene at 65 °C in the presence of activated 3 Å (8–12 mesh) molecular sieves (4–6 h, monitored by GC), followed by filtration through Celite and removal of solvent under vacuum. Dienylstannane **3** was prepared according to a modified literature protocol.[27] Other chemicals were used as purchased from commercial suppliers. Tetrahedrofuran (THF) was freshly distilled from sodium/benzophenone. Benzene, acetonitrile, toluene, and methylene chloride were kept over 3 Å (8–12 mesh) molecular sieves under an atmosphere of dry argon; other solvents were used as received. Reactions with air-sensitive materials were carried out in oven-dried (at least 6 h at 140 °C) glassware under a stream of dry argon using standard syringe techniques. The parallel syntheses were performed on a MiniBlock XT synthesizer obtained from Mettler-Toledo AutoChem. PrepSep silica gel SPE cartridges were obtained from Fisher Scientific. Automated weighing was performed using the Bohdan Balance Automator (Mettler-Toledo Auto-Chem). Parallel evaporation was performed on the GeneVac EZ-2 plus evaporator system. Flash chromatography was performed with 32–63 μm silica gel (Sorbent). Analytical thin-layer chromatography (TLC) was carried out on commercial Merck silica gel 60 plates, 250 μm thickness, with fluorescent indicator (F-254) or stained with aqueous $KMnO_4$ solution. IR spectra were measured as thin films on salt (NaCl) plates on a Shimadzu FTIR-8400S spectrophotometer. Melting points were determined using the Thomas-Hoover capillary melting-point apparatus (Uni-Melt).

^{1}H NMR spectra were recorded on a Bruker-500 DRX (500 MHz) or a Bruker Avance 400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from TMS (0 ppm). Data are reported as follows: chemical shift, multiplicity (app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublets, m = multiplet, br = broad), coupling constants, and integration. ^{13}C NMR spectra were recorded on a Bruker-500 DRX (125 MHz) spectrometer using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of $CDCl_3$ (77.2 ppm) as an internal standard.

HPLC analyses were carried out using a Xterra MS C-18 column (5 μm, 4.6 × 150 mm) and gradient elution (10% CH_3CN/water to 100% CH_3CN) on a Waters mass-directed fractionation instrument using a Waters 2767 sample manager, Waters 2525 HPLC pump, a 2487 dual λ absorbance detector, and Waters/MicroMass ZQ (quadrupole) MS ELSD detector (Sedex 85) connected to a PC with a MassLynx workstation. Purification was carried out using an Xterra MS C-18 column (5 μm, 10 × 150 mm), a gradient elution (40% CH_3CN/water to 100% CH_3CN) with a UV fraction trigger. High-resolution mass spectra (HRMS) [ESI$^+$] were obtained using Waters/MicroMass LCT Premier (TOF instrument).

(±)-2-Benzyl-3-(2-bromophenyl)-7-phenyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (4da) and (±)-(3*R*,3*aR*,7*R*,7*aS*)-2-Benzyl-3-(2-bromophenyl)-7-phenyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (4db). To a solution of *N*-(2-bromobenzylidene)-1-phenylmethanamine (0.137 g, 0.5 mmol, 1.0 equiv) and acid chloride **2**{*4*} (0.109 g, 0.65 mmol, 1.3 equiv) in acetonitrile (4 mL) was added CuCl (5.0 mg, 0.05 mmol, 10 mol%) while stirring. Dienylstannane **3** (0.343 g, 1.0 mmol, 2.0 equiv) in methylene chloride (3 mL) was added, and the reaction mixture was heated to 45 °C overnight. Solvents were removed in vacuo; the crude product was dissolved in toluene (10 mL), and the reaction mixture was refluxed overnight. The resulting dark precipitate was filtered off; the solvent was removed in vacuo providing the crude product, which was purified by flash chromatography over silica, eluting with ethyl acetate/hexanes (1:4) to afford a mixture of isoindolones **4da** and **4db** (0.161 g, 70%, **4da**/**4db** = 2:1). Partial separation of **4da** and **4db** was realized via preparative TLC to afford **4da** as a colorless oil and **4db** as a white solid, which was further purified by recystallization (CH_2Cl_2/pentane) providing a single crystal for X-ray crystallographic analysis. **4da**: R_f = 0.45 (EtOAc/hexane 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.9 Hz, 1 H), 7.44–7.21 (m, 10 H), 7.20–7.11 (m, 3 H), 5.92 (dq, J = 9.9, 2.0 Hz, 1 H), 5.57 (dq, J = 9.9, 3.3 Hz, 1 H), 5.07 (d, J = 14.5 Hz, 1 H), 5.05 (d, J = 8.3 Hz, 1 H), 3.53 (d, J = 14.5 Hz, 1 H), 3.20 (td, J = 10.6, 7.0 Hz, 1 H), 3.18–3.12 (m, 1 H), 2.87 (t, J = 12.1 Hz, 1 H), 2.58–2.48 (m, 1 H), 2.15 (ddq, J = 19.2, 9.7, 3.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 143.6, 136.4, 134.5, 133.7,

Table 4. Results Summary for Library **III**



Library III
(32 members)

11{*1-4,1,2,4,6*}

entry	compd	R^1	R^4	yield (1)[a] (%)	yield (2)[b] (%)	yield (3)[c] (%)	dr[d]	purity[e] (%)	HRMS[f]
1a	**11**{*1,1*}	3-Cl-4-MeOC_6H_3	4-MeC_6H_4	25	42	25	14:1	99	534.2165
1b[g]				17			9:1	100	
2a	**11**{*1,2*}	3-Cl-4-MeOC_6H_3	4-MeOC_6H_4	18	30	17	33:1	100	550.2137
2b				12			1:0	99	
3a	**11**{*1,4*}	3-Cl-4-MeOC_6H_3	4-$Me_2NC_6H_4$	28	44	26	16:1	100	563.2479
3b				16			1:0	100	
4a	**11**{*1,6*}	3-Cl-4-MeOC_6H_3	*trans*-PhCH=CH	18	27	17	16:1	99	546.2171
4b				9			1:0	100	
5a	**11**{*2,1*}	4-$CF_3C_6H_4$	4-MeC_6H_4	35	59	35	1:0	100	538.2318
5b				24			9:1	100	
6a	**11**{*2,2*}	4-$CF_3C_6H_4$	4-MeOC_6H_4	35	65	38	1:0	100	554.2302
6b				30			3:1	100	
7a	**11**{*2,4*}	4-$CF_3OC_6H_4$	4-$Me_2NC_6H_4$	34	49	29	1:0	99	567.2589
7b				15			1:0	100	
8a	**11**{*2,6*}	4-$CF_3C_6H_4$	*trans*-PhCH=CH	29	50	30	33:1	100	550.2402
8b				21			3:1	100	
9a	**11**{*3,1*}	2-F-5-MeC_6H_4	4-MeC_6H_4	24	53	33	1:0	99	502.2555
9b				29			2:1	100	
10a	**11**{*3,2*}	2-F-5-MeC_6H_4	4-MeOC_6H_4	21	70	43	1:0	100	518.2457
10b				49			1:1	99	
11a	**11**{*3,4*}	2-F-5-MeC_6H_4	4-$Me_2NC_6H_4$	17	58	36	24:1	99	531.2798
11b				41			1:1	100	
12a	**11**{*3,6*}	2-F-5-MeC_6H_4	*trans*-PhCH=CH	21	55	34	26:1	80	514.2573
12b				34			1:1	100	
13a	**11**{*4,1*}	2-naphthyl	4-MeC_6H_4	47	67	47	19:1	99	520.2629
13b				20			1:0	99	
14a	**11**{*4,2*}	2-naphthyl	4-MeOC_6H_4	36	56	40	1:0	100	536.2560
14b				20			1:0	99	
15a	**11**{*4,4*}	2-naphthyl	4-$Me_2NC_6H_4$	53	76	53	9:1	100	549.2891
15b				23			10:1	100	
16a	**11**{*4,6*}	2-naphthyl	*trans*-PhCH=CH	24	33	23	14:1	99	532.2654
16b				9			1:0	100	

[a] Isolated yield after HPLC purification calculated for the final cross-coupling step. [b] Combined yield of the cross-coupling step for both the major and minor diastereomer fractions. [c] Overall yield for the entire sequence of the three steps (three-component coupling, Diels–Alder, cross-coupling) combined for both the major and minor diastereomer fractions. [d] dr = ratio of the diastereomers in the final product established by HPLC. [e] UV purity determined at 214 nm after HPLC purification. [f] The HRMS data for the M + 1 molecular ion of the compound **11** detected in the corresponding product. [g] Entries *xx*b give data for the fraction containing the minor diastereomer.

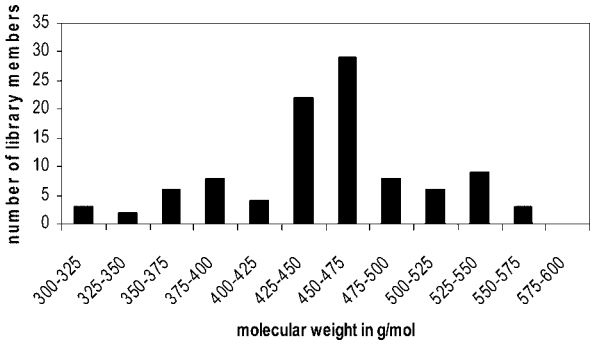


Figure 5. Molecular weight distribution diagram for members of libraries **I**−**III**.

129.9, 129.5, 128.9 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.0, 127.8, 127.6, 126.5, 124.9, 124.1, 59.9, 44.7, 44.4, 44.2, 42.4, 37.3; IR (neat, cm^{-1}) 1699 (s); HRMS (ES^+) calcd for $C_{27}H_{25}BrNO$ ($M + H^+$) 458.1119, found 458.1120. **4db**: mp 100–102 °C; R_f = 0.42 (EtOAc/hexane 1:4); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.9 Hz, 1 H), 7.44–7.10 (m, 12 H), 7.08 (d, J = 7.7 Hz, 1 H), 6.12–6.05 (m, 1 H), 5.92–5.85 (m, 1 H), 5.31 (d, J = 15.0 Hz, 1 H), 4.50 (s, 1 H), 3.75–3.71 (m, 1 H), 3.64 (d, J = 15.0 Hz, 1 H), 2.93 (d, J = 7.0 Hz, 1 H), 2.70–2.60 (m, 2 H), 2.40–2.29 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 144.9, 138.1, 135.8, 133.7, 129.3, 128.9, 128.6 (2C), 128.5 (2C), 127.9 (2C), 127.8 (2C), 127.6, 127.5, 127.4, 126.3, 126.1, 123.3, 64.8, 44.8, 44.6, 38.7, 35.7, 26.6; IR (neat, cm^{-1}) 1695 (s); HRMS (ES^+) calcd for $C_{27}H_{25}BrNO$ ($M + H^+$) 458.1119, found 458.1127.

General Procedure for the Synthesis of Library 4{*1–6, 1–4*}. Initially, stock solutions of six imines **1**{*1–6*} in acetonitrile and dienylstannane **3** in methylene chloride were prepared. To a 4 × 6 position Bohdan MiniBlock fitted with 24 (17 × 110 mm) reaction vials, under an atmosphere of argon, were added CuCl (2.5 mg, 0.025 mmol, 10 mol%) and solutions of imines **1**{*1-6*} (2 mL, 0.25 mmol, 1.0 equiv) at the appropriate positions, followed by the addition of neat acyl chlorides **2**{*1*−*4*} (0.33 mmol, 1.3 equiv). While stirring,

dienylstannane **3** (1.5 mL, 0.5 mmol, 2.0 equiv) was added, and the 24 reaction vials were heated to 45 °C overnight. After removal of solvents by parallel evaporation in the GeneVac EZ-2 plus evaporator, the reaction vials were transferred back to the MiniBlock. Toluene (5 mL) was added, and the reaction mixture was refluxed overnight under Ar. Then toluene was removed by parallel evaporation, and the residue was dissolved in ethyl acetate (EtOAc, 1 mL). The EtOAc solutions were transferred individually to 24 PrepSep silica gel columns (500 mg/6 mL). The PrepSep columns containing the crude products were then washed with EtOAc (4 mL). To the EtOAc fractions was added 50% KF on Celite (1 g), and the 24 suspensions were stirred overnight, followed by filtration though 24 PrepSep silica gel columns (500 mg/6 mL). Filtrates were evaporated in parallel to dryness in a GeneVac EZ-2 plus evaporator. The products were submitted for LC/MS analyses followed by preparative LC to obtain the pure products.

(±)-(3*R*,3*aR*,7*a*R)-2-Benzyl-3-(3-chloro-4-methoxyphenyl)-7*a*-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 4{*1*,*1*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.24 (m, 3 H), 7.18 (s, 1 H), 7.04–6.94 (m, 4 H), 5.60 (dq, J = 10.0, 3.1 Hz, 1 H), 5.54–5.41 (m, 1 H), 5.11 (d, J = 14.3 Hz, 1 H), 3.95 (s, 3 H), 3.85 (d, J = 10.9 Hz, 1 H), 3.46 (d, J = 14.3 Hz, 1 H), 2,71–2.56 (m, 1 H), 2.26–2.20 (m, 2 H), 2.05–1.99 (m, 1 H), 1.84 (q, J = 10.5 Hz, 1 H), 0.96 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 153.0, 134.6, 128.5, 127.7, 127.6 (2C), 127.2 (2C), 127.0, 126.8, 126.6, 125.6, 120.1, 110.3, 59.2, 54.3, 49.6, 42.3, 40.8, 27.1, 21.8, 12.0; IR (neat, cm^{-1}) 1689; HRMS (ES$^+$) calcd for $C_{23}H_{25}ClNO_2$ (M + H$^+$) 382.1574, found 382.1584.

(±)-(3*R*,3*aS*,7*R*,7*a*S)-2-Benzyl-3-(2-fluoro-5-methylphenyl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 4{*3*,*2*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.06 (m, 6 H), 6.98 (dd, J = 10.0, 8.3, 1 H), 6.89 (d, J = 7.1 Hz, 1 H), 5.83–5.77 (m, 1 H), 5.65–5.58 (m, 1 H), 5.23 (d, J = 15.0 Hz, 1 H), 4.40 (d, J = 2.9 Hz, 1 H), 3.62 (d, J = 15.0 Hz, 1 H), 2.73–2.68 (m, 1 H), 2.60 (dd, J = 7.3, 5.2 Hz, 1 H), 2.42–2.28 (m, 1 H), 2.33 (s, 3 H), 1.86–1.77 (m, 1 H), 1.72–1.64 (m, 1 H), 1.10 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 158.2, 156.2, 134.2, 132.1, 127.9, 126.5 (2C), 126.2, 126.0 (2C), 125.8, 125.7, 124.3, 113.8, 57.7, 42.8, 42.6, 38.0, 27.3, 22.5, 18.9, 17.1; IR (neat, cm^{-1}) 1692; HRMS (ES$^+$) calcd for $C_{23}H_{25}FNO$ (M + H$^+$) 350.1920, found 350.1925.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-7-ethyl-3-(2-fluoro-5-methylphenyl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one4{*3*,*3*}: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18–7.08 (m, 4 H), 6.96–6.91 (m, 2 H), 6.82 (dd, J = 10.0, 8.3 Hz, 1 H), 6.72 (d, J = 7.2 Hz, 1 H), 5.66–5.61 (m, 1 H), 5.48–5.42 (m, 1 H), 5.10 (d, J = 15.0 Hz, 1 H), 4.23 (br s, 1 H), 3.47 (d, J = 15.0 Hz, 1 H), 2.58 (dd, J = 7.3, 4.4 Hz, 1 H), 2.52–2.48 (m, 1 H), 2.18 (s, 3 H), 2.18–2.09 (m, 1 H), 2.06–2.00 (m, 1 H), 1.79–1.72 (m, 1 H), 1.35–1.15 (m, 2 H), 0.98 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 157.8, 155.9, 134.2, 132.1, 127.9, 127.8 (2C), 126.6, 126.0 (2C), 125.5, 124.5, 114.0, 113.6, 57.7, 42.7, 41.0, 37.7, 30.4, 24.0, 23.5, 19.0, 10.1; IR (neat, cm^{-1}) 1699; HRMS (ES$^+$) calcd for $C_{24}H_{27}FNO$ (M + H$^+$) 364.2077, found 364.2074.

(±)-(3*R*,3*aR*,7*aR*)-2-Benzyl-7*a*-methyl-3-(naphthalen-2-yl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 4{*4*,*1*} (Major Isomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95–7.83 (m, 3 H), 7.65 (s, 1 H), 7.58–7.40 (m, 2 H), 7.35–7.22 (m, 4 H), 6.97 (d, J = 5.7 Hz, 2 H), 5.63–5.55 (m, 1 H), 5.52–5.47 (m, 1 H), 5.20 (d, J = 14.3 Hz, 1 H), 4.12 (d, J = 10.7 Hz, 1 H), 3.52 (d, J = 14.3 Hz, 1 H), 2.82–2.77 (m, 1 H), 2.30–2.25 (m, 2 H), 2.07 (dd, J = 13.4, 7.3 Hz, 1 H), 1.90 (q, J = 10.7 Hz, 1 H), 1.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 134.7, 133.0, 131.4, 127.1 (2C), 126.9 (2C), 126.8, 126.6, 126.5, 126.4, 126.3, 126.2, 126.0, 125.9, 124.1, 123.6, 119.6, 60.2, 49.5, 42.0, 40.9, 24.8, 21.7, 12.0; IR (neat, cm^{-1}) 1690; HRMS (ES$^+$) calcd for $C_{26}H_{26}NO$ (M + H$^+$) 368.2014, found 368.2022.

(±)-2-Benzyl-3-(3-nitrophenyl)-7-phenyl-2,3,3*a*,6,7,7*a*-hexahydro-1H-isoindol-1-one 4{*5*,*4*}: ^{1}H NMR (500 MHz, $CDCl_3$, major product reported, 1:1 rotamers) δ 8.24 (t, J = 8.9 Hz, 1 H), 8.03 (br s, 1 H), 7.64–7.15 (m, 11 H), 7.85 (d, J = 7.5 Hz, 1 H), 5.78 (dq, J = 10.0, 3.3 Hz, 0.5 H), 5.72–5.60 (m, 1.5 H), 5.15 (d, J = 15.0 Hz, 0.5 H), 4.95 (d, J = 14.8 Hz, 0.5 H), 4.66 (d, J = 7.6 Hz, 0.5 H), 4.12 (d, J = 9.9 Hz, 0.5 H), 3.64 (d, J = 15.0 Hz, 0.5 H), 3.61 (d, J = 14.8 Hz, 0.5 H), 3.30–3.18 (m, 1 H), 2.79 (t, J = 12.1 Hz, 0.5 H), 2.71 (t, J = 11.8 Hz, 0.5 H), 2.65–2.50 (m, 2 H), 2.39–2.29 (m, 0.5 H), 2.20–2.10 (m, 0.5 H); ^{13}C NMR (125 MHz, $CDCl_3$, all isomers reported) δ (174.9, 173.9, 173.6), (148.8, 148.7, 148.6), (144.1, 143.1, 143.0), (141.9, 139.9, 138.0), (136.3, 136.2, 135.7), (133.9, 132.9, 132.2), (130.5, 130.4, 130.2), (130.1, 130.0, 129.7), 128.8, 128.7, 128.6 (3 C), 128.4, 128.1, 127.8, 127.7, 127.5 (2C), 127.4, 126.8, 126.7, 126.6, 126.1, 123.6, 125.5, 123.2 (3 C), 122.9, 122.0, 121.5, (65.3, 63.6, 60.4), 49.5, 48.8, 44.8, 44.7, 44.6, 44.4, 44.0, 42.3, 42.2, 41.2, 37.5, 37.4, 36.3, 28.2; IR (neat, cm^{-1}) 1689; HRMS (ES$^+$) calcd for $C_{27}H_{25}N_2O_3$ (M + H$^+$) 425.1865, found 425.1862.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(furan-3-yl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 4{*6*,*2*} (Major Isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (br s, 1 H), 7.34–7.24 (m, 4 H), 7.09 (d, J = 7.1 Hz, 2 H), 6.32 (br s, 1 H), 5.84–5.77 (m, 1 H), 5.56–5.49 (m, 1 H), 5.18 (d, J = 14.9 Hz, 1 H), 4.01 (d, J = 5.1 Hz, 1 H), 3.60 (d, J = 14.8 Hz, 1 H), 2.77–2.70 (m, 1 H), 2.56 (t, J = 7.4 Hz, 1 H), 2.29–2.25 (m, 0.5 H), 2.25–2.21 (m, 0.5 H), 2.17–2.05 (m, 1 H), 1.90–1.75 (m, 1 H), 1.19 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 144.2, 140.4, 136.6, 128.5 (2C), 128.3, 127.9 (2C), 127.3, 124.9, 124.0, 108.6, 57.8, 45.9, 43.9, 40.2, 30.6, 26.2, 19.2; IR (neat, cm^{-1}) 1685; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{20}H_{22}NO_2$(M+H$^+$) 308.1651, found 308.1655.

General Procedure for the Synthesis of Bromoisoindolones 6{*1–4*,*1–2*}. Initially, stock solutions of four imines **5**{*1–4*} in acetonitrile and dienylstannane **3** in methylene chloride were prepared. To a 4 × 3 position Bohdan MiniBlock fitted with 8 (24 × 150 mm) reaction vials, under an atmosphere of argon, were added CuCl (40.0 mg, 0.40 mmol, 20 mol%) and solutions of imines **5**{*1−4*} (10 mL,

2.0 mmol, 1.0 equiv) at the appropriate positions, followed by the addition of neat acyl chlorides **2**{*1*−*2*} (2.6 mmol, 1.3 equiv). While the mixture was stirred, dienylstannane **3** (10 mL, 3.0 mmol, 1.5 equiv) was added, and the 8 reaction vials were heated to 45 °C overnight. Solvents were removed by parallel evaporation in the GeneVac EZ-2 plus evaporator. The reaction vials were then transferred back to the MiniBlock. The residue was dissolved in toluene (15 mL), and the reaction mixture was refluxed overnight. The resulting dark precipitate was filtered off though Celite, and the solvent was removed in a GeneVac EZ-2 plus evaporator providing the crude product, which was purified individually by flash chromatography over silica gel, eluting with ethyl acetate/hexanes (1:4) to afford the corresponding bromoisoindolones.

(±)-(3*R*,3*aR*,7*aR*)-2-Benzyl-3-(4-bromo-2-fluorophenyl)-7*a*-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 6{*1*,*1*}: 0.505 g; yield 61%; dr = 7:84:9 (GC); major diastereomer reported; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.10 (m, 6 H), 7.00–6.94 (m, 2 H), 5.60 (dq, J = 9.9, 3.3 Hz, 1 H), 5.55–5.45 (m, 1 H), 5.14 (d, J = 14.3 Hz, 1 H), 4.40 (br s, 1 H), 3.50 (d, J = 14.3 Hz, 1 H), 2.55 (br s, 1 H), 2.30–2.20 (m, 2 H), 2.03 (ddd, J = 12.8, 6.6, 1.6 Hz, 1 H), 1.82 (dt, J = 12.8, 9.3 Hz, 1 H), 0.96 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 161.6, 159.7, 129.4 (2C), 128.8 (3 C), 128.6, 128.3, 127.7, 124.0, 122.3, 121.2, 119.5, 53.2, 51.5, 44.2, 42.9, 29.0, 23.5, 13.9; IR (neat, cm^{-1}) 1699; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{22}H_{22}BrFNO$ (M + H$^+$) 414.0869, found 414.0865.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(4-bromo-2-fluorophenyl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 6{*1*,*2*}: 0.498 g; yield 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5 H), 7.19 (d, J = 7.6 Hz, 2 H), 6.93 (t, J = 8.0 Hz, 1 H), 5.67–5.59 (m, 1 H), 5.52 (dq, J = 10.0, 3.3 Hz, 1 H), 5.19 (d, J = 14.8 Hz, 1 H), 4.81 (d, J = 7.9 Hz, 1 H), 3.64 (d, J = 14.8 Hz, 1 H), 3.03–2.94 (m, 1 H), 2.36–2.31 (m, 0.5 H), 2.31–2.26 (m, 0.5 H), 2.19–2.06 (m, 1 H), 2.02 (t, J = 12.0 Hz, 1 H), 1.72–1.62 (m, 1 H), 1.39 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 161.7, 159.7, 136.5, 130.7, 128.7 (2C), 128.2 (2C), 127.7, 123.6, 122.2, 121.8, 119.7, 119.5, 55.0, 45.5, 44.7, 44.4, 36.5, 30.9, 18.9; IR (neat, cm^{-1}) 1699; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{22}H_{22}BrFNO$ (M+H$^+$) 414.0869, found 414.0875.

(±)-(3*R*,3*aR*,7*aR*)-2-Benzyl-3-(5-bromo-2-methoxyphenyl)-7*a*-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 6{*2*,*1*}: 0.605 g; yield 71%; dr = 6:85:9 (GC); major diastereomer reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 8.7, 2.4 Hz, 1 H), 7.31 (d, J = 2.4 Hz, 1 H), 7.26–7.20 (m, 3 H), 6.98–6.92 (m, 2 H), 6.79 (d, J = 8.8 Hz, 1 H), 5.57 (dq, J = 9.8, 3.0 Hz, 1 H), 5.50 (dq,J = 9.8, 1.8 Hz, 1 H), 5.09 (d, J = 14.2 Hz, 1 H), 4.56 (d, J = 10.7 Hz, 1 H), 3.67 (s, 3 H), 3.53 (d, J = 14.2 Hz, 1 H), 2.55 (dt, J = 8.2, 2.4 Hz, 1 H), 2.28–2.20 (m, 2 H), 2.01 (ddd, J = 12.7, 6.5, 2.2 Hz, 1 H), 1.84 (dt, J = 12.9, 9.3 Hz, 1 H), 0.96 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 157.0, 136.4, 132.5, 131.6, 130.5 (2C), 129.4 (2C), 128.4, 127.4, 125.7, 122.1, 113.6, 112.8, 55.6, 53.4, 52.0, 44.2, 43.0, 29.1, 23.6, 14.1; IR (neat, cm^{-1}) 1692; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{23}H_{25}BrNO_2$(M+H$^+$) 426.1069, found 426.1070.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(5-bromo-2-methoxyphenyl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 6{*2*,*2*}: 0.538 g; yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.6, 2.4 Hz, 1 H), 7.31–7.22 (m, 3 H), 7.12 (d, J = 2.4 Hz, 1 H), 7.09 (d, J = 7.6 Hz, 2 H), 6.79 (d,J = 8.7 Hz, 1 H), 5.79 (dq, J = 9.9, 2.6 Hz, 1 H), 5.62–5.59 (m, 1 H), 5.26 (d, J = 15.1 Hz, 1 H), 4.43 (br s, 1 H), 3.80 (s, 3 H), 3.63 (d, J = 15.1 Hz, 1 H), 2.64–2.56 (m, 2 H), 2.52–2.46 (m, 1 H), 2.39–2.34 (m, 0.5 H), 2.34–2.30 (m, 0.5 H), 1.80 (d, J = 19.6 Hz, 1 H), 1.05 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 156.2, 136.3, 131.4, 130.2, 128.7 (2C), 128.4 (2C), 127.7, 127.4, 127.3, 126.2, 113.2, 112.5, 60.3, 55.7, 44.5, 44.3, 39.0, 28.6, 25.3, 19.1; IR (neat, cm^{-1}) 1692; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{23}H_{25}BrNO_2$(M+H$^+$) 426.1069, found 426.1078.

(±)-(3*R*,3*aR*,7*aR*)-2-Benzyl-3-(3-bromo-4-fluorophenyl)-7*a*-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1H-isoindol-1-one 6{*3*,*1*}: 0.572 g; yield 69%; dr = 6:85:9 (GC); major diastereomer reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 6.5, 2.1 Hz, 1 H), 7.32–7.24 (m, 3 H), 7.20–7.06 (m, 2 H), 6.98–6.94 (m, 2 H), 5.63 (dq, J = 9.8, 3.3 Hz, 1 H), 5.45 (dq, J = 9.8, 2.2 Hz, 1 H), 5.13 (d, J = 14.4 Hz, 1 H), 3.87 (d, J = 10.8 Hz, 1 H), 3.48 (d, J = 14.4 Hz, 1 H), 2.60 (dt, J = 10.6, 2.7 Hz, 1 H), 2.26–2.20 (m, 2 H), 2.03 (ddd, J = 13.0, 6.8, 1.6 Hz, 1 H), 1.84 (dt, J = 13.0, 9.2 Hz, 1 H), 0.96 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 159.9, 157.9, 136.2, 135.2, 132.8, 129.5, 128.7 (2C), 128.4 (2C), 127.7, 120.9, 116.9, 116.4, 61.0, 51.7, 44.0, 42.7, 29.0, 23.6, 13.9; IR (neat, cm^{-1}) 1699; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{22}H_{22}BrFNO$ (M + H$^+$) 414.0869, found 414.0864.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(3-bromo-4-fluorophenyl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 6{*3*,*2*}: 0.556 g; yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 6.5, 2.2 Hz, 1 H), 7.32–7.24 (m, 3 H), 7.14 (t, J = 8.3 Hz, 1 H), 7.09–7.00 (m, 3 H), 5.82 (dtd, J = 10.0, 3.9, 1.8 Hz, 1 H), 5.50 (ddt, J = 10.0, 3.4, 1.8 Hz, 1 H), 5.20 (d, J = 14.8 Hz, 1 H), 3.97 (d, J = 4.8 Hz, 1 H), 3.50 (d, J = 14.8 Hz, 1 H), 2.68–2.60 (m, 1 H), 2.55 (t, J = 7.8 Hz, 1 H), 2.31–2.26 (m. 0.5 H), 2.26–2.21 (m, 0.5 H), 2.16 (quint, J = 6.2 Hz, 1 H), 2.85–1.75 (m, 1 H), 1.16 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 159.7, 157.8, 137.1, 136.0, 131.7, 128.6 (2C), 127.5 (2C), 127.2, 126.9, 124.6, 117.1, 116.9, 65.3, 45.4, 44.2, 41.7, 30.4, 26.1, 19.1; IR (neat, cm^{-1}) 1699; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{22}H_{22}BrFNO$ (M + H$^+$) 414.0869, found 414.0874.

(±)-(3*R*,3*aR*,7*aR*)-2-Benzyl-3-(1-bromonaphthalen-2-yl)-7*a*-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 6{*4*,*1*}: 0.584 g; yield 65%; dr = 4:94:4 (GC); major diastereomer reported; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.5 Hz, 1 H), 7.91 (t, J = 7.9 Hz, 2 H), 7.68 (t, J = 7.5 Hz, 1 H), 7.62 (t, J = 7.5 Hz, 1 H), 7.38 (d, J = 8.6 Hz, 1 H), 7.30–7.20 (m, 3 H), 7.00–6.94 (m, 2 H), 5.67 (dq, J = 9.9, 1.9 Hz, 1 H), 5.58 (dq, J = 9.9, 3.0 Hz, 1 H), 5.20 (d, J = 14.2 Hz, 1 H), 4.96 (d, J = 10.6 Hz, 1 H), 3.46 (d, J = 14.2 Hz, 1 H), 2.69 (dt, J = 10.6, 2.5 Hz, 1 H), 2.29–2.22 (m, 2 H), 2.06 (ddd, J = 13.0, 5.6, 3.0 Hz, 1 H), 1.87 (dt, J = 13.0, 9.2 Hz, 1 H), 1.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9, 136.0, 134.8, 134.3, 132.4, 129.1 (2C), 128.8 (2C), 128.6, 128.2, 127.9, 127.7, 127.6, 127.2, 127.1,

127.0, 124.7, 121.8, 61.0, 51.9, 44.5, 43.2, 29.2, 23.6, 14.1; IR (neat, cm^{-1}) 1692; HRMS (ESI^+, *m/z*) calcd for $C_{26}H_{25}BrNO$ ($M + H^+$) 446.1120, found 446.1112.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(1-bromonaphthalen-2-yl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 6{*4,2*}: 0.492 g; yield 55%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, $J = 8.5$ Hz, 1 H), 7.88 (dd, $J = 7.8, 4.1$ Hz, 2 H), 7.66 (t, $J = 7.3$ Hz, 1 H), 7.59 (t, $J = 7.4$ Hz, 1 H), 7.30–7.20 (m, 4 H), 7.12–7.05 (m, 2 H), 5.82 (br s, 2 H), 5.34 (d, $J = 14.9$ Hz, 1 H), 4.82 (br s, 1 H), 3.59 (d, $J = 14.9$ Hz, 1 H), 2.82–2.76 (m, 1 H), 2.63 (dd, $J = 7.1, 4.7$ Hz, 1 H), 2.52–2.43 (m, 1 H), 2.42–2.33 (m, 1 H), 1.86–1.82 (m, 0.5 H), 1.82–1.77 (m, 0.5 H), 1.07 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 136.9, 136.0, 134.1, 132.7, 128.5 (2C), 128.4, 128.2 (2C), 128.0, 127.9, 127.7, 127.5, 127.2, 126.9, 125.8, 123.7, 123.3, 65.7, 44.8 (2C), 39.9, 28.9, 25.5, 19.1; IR (neat, cm^{-1}) 1692; HRMS (ESI^+, *m/z*) calcd for $C_{26}H_{25}BrNO$ ($M + H^+$) 446.1120, found 446.1112.

General Procedure for the Synthesis of Library 8{*1–4,1–2,1–6*}. Initially, stock solutions of eight bromoisoindolones **6**{*1–4,1–2*} in THF were prepared. To a 8 × 6 position Bohdan MiniBlock fitted with 48 (11.5 × 110 mm) reaction vials, under an atmosphere of argon, were added palladium acetate (1.2 mg, 0.005 mmol, 5 mol%), 2-(dicyclohexylphosphino)-2′-(*N,N*-dimethylamino)biphenyl (3.6 mg, 0.010 mmol, 10 mmol%), cesium fluoride (0.061 g, 0.4 mmol, 4.0 equiv), and boronic acids **7**{*1−6*} (0.2 mmol, 2.0 equiv) at the appropriate positions, followed by addition of solutions of bromoisoindolones **6**{*1−4,1–2*} (1.0 mL, 0.1 mmol, 1.0 equiv). After they were refluxed at 60 °C overnight, the reaction mixtures were concentrated via parallel evaporation. The residues were transferred individually to 48 PrepSep silica gel columns (500 mg/6 mL). The PrepSep columns containing the crude products were then washed with methylene chloride (5 mL). Filtrates were evaporated in parallel to dryness in a GeneVac EZ-2 plus evaporator. The crude products were submitted for LC/MS analyses, followed by preparative LC to obtain the pure products.

General Procedure for the Synthesis of Libraries 8{*4,1–2,1–6*} and 8{*1–2,2,7–12*}. Initially, stock solutions of eight bromoisoindolones **6**{*4,1–2*} and **6**{*1–2,2*} in THF were prepared. To a 8 × 6 position Bohdan MiniBlock fitted with 24 (11.5 × 110 mm) reaction vials, under an atmosphere of argon, were added palladium acetate (1.2 mg, 0.005 mmol, 5 mol %), 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl (4.1 mg, 0.010 mmol, 10 mmol%), cesium fluoride (0.061 g, 0.4 mmol, 4.0 equiv), and boronic acids **7**{*1−6*} for library **8**{*4,1–2,1–6*} or boronic acids **7**{*7–12*} for library **8**{*1–2,2,7–12*} (0.2 mmol, 2.0 equiv) at the appropriate positions, followed by the addition of solutions of isoindolones **6**{*4,1–2*} for library **8**{*4,1–2,1–6*} or **6**{*1–2,2*} for library **8**{*1–2,2,7–12*} (1.0 mL, 0.1 mmol, 1.0 equiv). After they were refluxed at 60 °C overnight, the reaction mixtures were concentrated via parallel evaporation. The residues were transferred individually to 24 PrepSep silica gel columns (500 mg/6 mL). The PrepSep columns containing the crude products were then washed with methylene chloride (5 mL). Filtrates were evaporated in parallel to dryness in a GeneVac EZ-2 plus evaporator. The crude products were submitted for LC/MS analyses, followed by preparative LC to obtain the pure products.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(3-fluoro-4′-methoxybiphenyl-4-yl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 8{*1,2,2*}: ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, $J = 8.7$ Hz, 2 H), 7.36 (d, $J = 8.0$ Hz, 1 H), 7.32–7.26 (m, 4 H), 7.15 (t, $J = 8.0$ Hz, 1 H), 7.09 (d, $J = 7.7$ Hz, 2 H), 7.01 (d, $J = 8.7$ Hz, 2 H), 5.85–5.78 (m, 1 H), 5.65–5.60 (m, 1 H), 5.27 (d, $J = 15.0$ Hz, 1 H), 4.43 (d, $J = 3.1$ Hz, 1 H), 3.89 (s, 3 H), 3.64 (d, $J = 15.0$ Hz, 1 H), 2.78–2.74 (m, 1 H), 2.63 (dd, $J = 7.3, 5.3$ Hz, 1 H), 2.41–2.34 (m, 1 H), 2.32 (dm, $J = 17.5$ Hz, 1 H), 1.80 (dm, $J = 17.5$ Hz, 1 H), 1.12 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 160.0, 142.7, 136.7, 131.8, 130.5 (3 C), 128.7 (3 C), 128.2 (2C), 128.0 (2C), 127.2, 122.5, 114.4 (3 C), 114.0, 59.6, 55.4, 44.9, 44.4, 40.0, 29.3, 26.5, 19.1; IR (neat, cm^{-1}) 1690; HRMS (ES^+) calcd for $C_{29}H_{29}FNO_2$ ($M + H^+$) 442.2182, found 442.2182.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(4′-(dimethylamino)-4-methoxybiphenyl-3-yl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 8{*2,2,4*}: ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, $J = 8.4, 2.3$ Hz, 1 H), 7.45 (d, $J = 8.7$ Hz, 2 H), 7.30–7.24 (m, 3 H), 7.18 (d, $J = 2.3$ Hz, 1 H), 7.11 (d, $J = 7.9$ Hz, 2 H), 6.96 (d, $J = 8.5$ Hz, 1 H), 6.90–6.80 (m, 2 H), 5.80 (dquint, $J = 10.0, 2.5$ Hz, 1 H), 5.71–5.65 (m, 1 H), 5.27 (d, $J = 15.2$ Hz, 1 H), 4.53 (d, $J = 1.5$ Hz, 1 H), 3.86 (s, 3 H), 3.70 (d, $J = 15.2$ Hz, 1 H), 3.04 (s, 6 H), 2.74–2.68 (m, 1 H), 2.64 (dd, $J = 7.4, 4.0$ Hz, 1 H), 2.52–2.45 (m, 1 H), 2.41–2.36 (m, 0.5 H), 2.36–2.31 (m, 0.5 H), 1.83–1.80 (m, 0.5 H), 1.80–1.75 (m, 0.5 H), 1.06 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 155.8, 149.8, 136.7, 134.0, 129.9, 129.3 (2C), 128.3 (2C), 128.0 (2C), 127.9, 127.7, 127.4, 127.3, 127.1, 127.0, 126.2, 112.9, 111.1, 60.7, 55.6, 44.4 (2C), 40.7, 40.5, 39.1, 28.8, 25.4, 19.1; IR (neat, cm^{-1}) 1695; HRMS (ES^+) calcd for $C_{31}H_{35}N_2O_2$ ($M + H^+$) 467.2699, found 467.2680.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(4-fluoro-3-styrylphenyl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 8{*3,2,6*}: ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, $J = 7.5$ Hz, 2 H), 7.41 (t, $J = 7.5$ Hz, 2 H), 7.38–6.98 (m, 11 H), 5.86–5.80 (m, 1 H), 5.58–5.53 (m, 1 H), 5.22 (d, $J = 14.8$ Hz, 1 H), 4.03 (d, $J = 5.2$ Hz, 1 H), 3.56 (d, $J = 14.8$ Hz, 1 H), 2.74–2.68 (m, 1 H), 2.58 (t, $J = 7.5$ Hz, 1 H), 2.32–2.27 (m, 0.5 H), 2.27–2.22 (m, 0.5 H), 2.15 (quint, $J = 6.4$ Hz, 1 H), 1.87–1.82 (m, 0.5 H), 1.82–1.77 (m, 0.5 H), 1.20 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 161.0, 159.0, 136.9, 136.3, 135.3, 133.3, 129.2 (2C), 128.5 (2C), 128.3, 128.1 (2C), 127.5, 127.2, 127.0 (2C), 126.5, 126.2, 120.3, 116.5, 116.4, 65.9, 45.7, 44.0, 41.9, 30.7, 26.3, 19.2; IR (neat, cm^{-1}) 1692; HRMS (ES^+) calcd for $C_{30}H_{29}FNO$ ($M + H^+$) 438.2233, found 438.2227.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-3-(4-(Benzo[*b*]thiophen-2-yl)-2-fluorophenyl)-2-benzyl-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 8{*1,2,8*}: ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, $J = 7.5$ Hz, 1 H), 7.83 (dd, $J = 6.9, 1.7$ Hz, 1 H), 5.79 (s, 1 H), 5.52 (dd, $J = 8.0, 1.6$ Hz, 1 H), 7.46 (dd, $J = 11.2, 1.6$ Hz, 1 H), 7.39 (quintd, $J = 7.1, 1.6$ Hz, 2 H), 7.34–7.23 (m, 3 H), 7.18 (t, $J = 8.0$ Hz, 1 H), 7.10 (d, $J =$

7.7 Hz, 2 H), 5.87–5.80 (m, 1 H), 5.67–5.60 (m, 1 H), 5.29 (d, J = 15.0 Hz, 1 H), 4.44 (d, J = 3.1 Hz, 1 H), 3.65 (d, J = 15.0 Hz, 1 H), 2.80–2.74 (m, 1 H), 2.62 (t, J = 6.3 Hz, 1 H), 2.42–2.28 (m, 2 H), 1.87–1.82 (m, 0.5 H), 1.82–1.77 (m, 0.5 H), 1.15 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 161.9, 159.9, 142.1, 140.4, 139.6, 136.0, 128.8 (2C), 128.6, 128.0 (2C), 127.7, 127.6, 127.5, 126.6, 125.3, 124.9, 123.9, 122.5, 120.6, 114.0, 113.8, 59.7, 44.9, 44.5, 40.0, 29.3, 25.6, 19.1; IR (neat, cm^{-1}) 1695; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{30}H_{27}FNOS$ (M + H$^+$) 468.1797, found 468.1783.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(2-fluoro-4-(furan-3-yl)phenyl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 8{*1*,*2*,*11*}: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (t, J = 1.1 Hz, 1 H), 7.52 (t, J = 1.7 Hz, 1 H), 7.33–7.25 (m, 4 H), 7.22 (dd, J = 11.3, 1.6 Hz, 1 H), 7.12 (t, J = 7.9 Hz, 1 H), 7.09–7.06 (m, 2 H), 6.70 (dd, J = 1.7, 1.1 Hz, 1 H), 5.85–5.78 (m, 1 H), 5.61 (dq, J = 10.2, 2.5 Hz, 1 H), 5.26 (d, J = 15.0 Hz, 1 H), 4.41 (d, J = 7.2 Hz, 1 H), 3.60 (d, J = 15.0 Hz, 1 H), 2.77–2.71 (m, 1 H), 2.60 (dd, J = 7.4, 5.2 Hz, 1 H), 2.40–2.33 (m, 1 H), 2.32 (dquint, J = 17.5, 2.7 Hz, 1 H), 1.85–1.80 (m, 0.5 H), 1.80–1.75 (m, 0.5 H), 1.12 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 162.0, 160.0, 144.1, 139.1, 136.1, 134.3, 128.8 (2C), 127.9 (2C), 127.6, 127.4, 125.4, 125.2, 121.8, 113.4, 113.2, 108.6, 59.6, 44.9, 44.7, 40.0, 29.4, 25.6, 19.1; IR (neat, cm^{-1}) 1685; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{26}H_{25}FNO_2$ (M + H$^+$) 402.1869, found 402.1868.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(2-fluoro-4-((*E*)-oct-1-enyl)phenyl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 8{*1*,*2*,*12*}: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.24 (m, 3 H), 7.15–7.01 (m, 5 H), 6.37 (d, J = 16.0 Hz, 1 H), 6.28 (dt, J = 15.8, 6.5 Hz, 1 H), 5.83–5.77 (m, 1 H), 5.62–5.56 (m, 1 H), 5.25 (d, J = 14.9 Hz, 1 H), 4.37 (d, J = 3.2 Hz, 1 H), 3.58 (d, J = 14.9 Hz, 1 H), 2.74–2.68 (m, 1 H), 2.58 (t, J = 6.3 Hz, 1 H), 2.38–2.27 (m, 2 H), 2.24 (q, J = 7.1 Hz, 2 H), 1.84–1.79 (m, 0.5 H), 1.79–1.74 (m, 0.5 H), 1.50 (quint, J = 7.1 Hz, 2 H), 1.42–1.28 (m, 6 H), 1.11 (d, J = 6.9 Hz, 3 H), 0.93 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 161.9, 160.0, 140.0, 136.2, 133.3, 128.6 (2C), 128.5, 127.9 (2C), 127.3, 127.0, 125.4, 124.8, 113.0, 112.8, 59.7, 45.0, 44.4, 40.0, 33.0, 31.7, 29.4, 29.2, 28.9, 25.7, 22.6, 19.1, 14.1; IR (neat, cm^{-1}) 1692; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{30}H_{37}FNO$ (M + H$^+$) 446.2859, found 446.2854.

(±)-Methyl 3′-((1*R*,3*aS*,4*R*,7*aS*)-2-benzyl-4-methyl-3-oxo-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-isoindol-1-yl)-4′-methoxybiphenyl-4-carboxylate 8{*2*,*2*,*9*}: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.5 Hz, 2 H), 7.58 (d, J = 8.5 Hz, 3 H), 7.30–7.25 (m, 4 H), 7.12 (d, J = 7.8 Hz, 2 H), 7.01 (d, J = 8.5 Hz, 1 H), 5.80 (dq, J = 10.0, 2.5 Hz, 1 H), 5.71–5.65 (m, 1 H), 5.25 (d, J = 15.1 Hz, 1 H), 4.55 (d, J = 1.6 Hz, 1 H), 3.97 (s, 3 H), 3.87 (s, 3 H), 3.74 (d, J = 15.1 Hz, 1 H), 2.74–2.68 (m, 1 H), 2.62 (dd, J = 7.2, 4.1 Hz, 1 H), 2.53–2.44 (m, 1 H), 2.36 (dquint, J = 17.7, 2.7 Hz, 1 H), 1.86–1.81 (m, 0.5 H), 1.81–1.76 (m, 0.5 H), 1.07 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 167.0, 157.4, 144.8, 136.5, 132.5, 130.2 (2C), 128.6 (2C), 128.5 (2C), 128.4 (2C), 127.8 (2C), 127.5, 126.6 (2C), 126.4, 124.4, 111.2, 60.8, 55.7, 52.1, 44.6, 44.5, 39.2, 28.8, 25.4, 19.1; IR (neat, cm^{-1}) 1723, 1692; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{31}H_{32}NO_4$ (M + H$^+$) 482.2331, found 482.2320.

(±)-(3*R*,3*aR*,7*aR*)-3-(1-(4-Acetylphenyl)naphthalen-2-yl)-2-benzyl-7*a*-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 8{*4*,*1*,*3*}: ^{1}H NMR (400 MHz, $CDCl_3$, major diasteromer reported) δ 8.01 (d, J = 8.3 Hz, 2 H), 7.94 (d, J = 8.3 Hz, 1 H), 7.59 (dd, J = 8.3, 1.6 Hz, 1 H), 7.53 (d, J = 8.3 Hz, 1 H), 7.47 (d, J = 8.3 Hz, 1 H), 7.39 (td, J = 8.3, 1.6 Hz, 1 H), 7.34–7.21 (m, 4 H), 7.18 (d, J = 8.3 Hz, 1 H), 6.87 (d, J = 7.4 Hz, 2 H), 6.08 (dd, J = 8.0, 1.6 Hz, 1 H), 5.55 (dq, J = 9.9, 3.2 Hz, 1 H), 5.43 (dq, J = 9.9, 2.1 Hz, 1 H), 5.31 (d, J = 15.2 Hz, 1 H), 4.24 (d, J = 10.6 Hz, 1 H), 3.59 (d, J = 15.2 Hz, 1 H), 2.82–2.74 (m, 1 H), 2.67 (s, 3 H), 2.31–2.15 (m, 2 H), 2.08–1.98 (m, 1 H), 1.88 (dt, J = 13.6, 9.7 Hz, 1 H), 0.94 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 180.1, 142.6, 138.9, 137.0, 136.0, 133.5, 132.9, 131.5, 131.2, 129.1, 128.9 (3 C), 128.7, 128.1 (2C), 127.9, 127.7, 127.6, 127.5, 126.8, 126.6, 126.3, 123.8, 121.9, 58.4, 52.2, 42.9, 42.8, 29.3, 26.6, 23.5, 14.6; IR (neat, cm^{-1}) 1689; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{34}H_{32}NO_2$ (M + H$^+$) 486.2437, found 486.2434.

(±)-(3*R*,3*aR*,7*aR*)-2-Benzyl-3-(1-(4-(dimethylamino)phenyl)naphthalen-2-yl)-7*a*-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 8{*4*,*1*,*4*}: ^{1}H NMR (400 MHz, $CDCl_3$, major diasteromer reported) δ 7.91 (d, J = 9.5 Hz, 2 H), 7.50 (t, J = 7.2 Hz, 1 H), 7.42 (d, J = 9.5 Hz, 2 H), 7.37 (t, J = 7.2 Hz, 1 H), 7.30–7.18 (m, 3 H), 7.03 (dd, J = 8.5, 2.1 Hz, 1 H), 6.91 (d, J = 7.2 Hz, 2 H), 6.77 (dd, J = 8.5, 2.8 Hz, 1 H), 6.39 (dd, J = 8.5, 2.8 Hz, 1 H), 6.04 (dd, J = 8.5, 2.2 Hz, 1 H), 5.52 (br s, 2 H), 5.22 (d, J = 15.0 Hz, 1 H), 4.49 (d, J = 10.6 Hz, 1 H), 3.62 (d, J = 15.0 Hz, 1 H), 3.00 (s, 6 H), 2.81–2.74 (m, 1 H), 2.30–2.18 (m, 2 H), 2.06–1.98 (m, 1 H), 1.88 (dt, J = 13.6, 9.7 Hz, 1 H), 0.96 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 149.4, 140.9, 137.2, 133.7, 133.0, 132.1, 131.5, 130.3, 129.1, 128.6 (3 C), 128.0 (3 C), 127.7, 127.5, 127.4, 127.1, 126.0, 124.9, 123.9, 122.2, 112.0, 111.8, 58.7, 52.3, 44.5, 43.7, 40.5, 29.7, 29.3, 23.6, 14.7; IR (neat, cm^{-1}) 1692; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{34}H_{35}N_2O$ (M + H$^+$) 487.2739, found 487.2748.

(±)-(3*R*,3*aS*,7*R*,7*aS*)-2-Benzyl-3-(1-(4-methoxyphenyl)-naphthalen-2-yl)-7-methyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one 8{*4*,*2*,*2*}: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.5 Hz, 2 H), 7.50 (ddd, J = 7.9, 4.8, 3.1 Hz, 1 H), 7.45–7.17 (m, 6 H), 7.11 (dd, J = 8.3, 2.0 Hz, 1 H), 6.98 (dd, J = 8.4, 2.6 Hz, 1 H), 6.96–6.93 (m, 2 H), 6.70 (dd, J = 8.4, 2.6 Hz, 1 H), 6.58 (dd, J = 8.4, 2.0 Hz, 1 H), 5.66–5.57 (m, 1 H), 5.25 (d, J = 15.1 Hz, 1 H), 5.02–4.93 (m, 1 H), 4.19 (d, J = 2.5 Hz, 1 H), 3.87 (s, 3 H), 3.57 (d, J = 15.1 Hz, 1 H), 2.75 (dd, J = 7.2, 4.9 Hz, 1 H), 2.68–2.62 (m, 1 H), 2.47–2.38 (m, 1 H), 2.30–2.25 (m, 0.5 H), 2.25–2.20 (m, 0.5 H), 1.82–1.67 (m, 1 H), 1.06 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 158.8, 138.7, 136.2, 135.1, 133.5, 132.9, 131.5, 130.5, 129.7, 128.5 (2C), 128.4 (3 C), 127.8, 127.2, 127.0, 126.7, 126.3, 125.9, 125.6, 112.4, 113.9, 113.6, 62.9, 55.3, 45.1, 44.4, 40.2, 28.9, 25.6, 20.7; IR (neat, cm^{-1}) 1692; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{33}H_{32}NO_2$ (M + H$^+$) 474.2433, found 474.2420.

General Procedure for the Synthesis of Bromoisoindolones 10{*1–4*}. Initially, stock solutions of four imines **1**{*1–4*} in acetonitrile and dienylstannane **3** in methylene chloride were prepared. To a 4 × 3 position Bohdan MiniBlock fitted with 4 (24 × 150 mm) reaction vials, under an atmosphere of argon, were added CuCl (40.0 mg, 0.40 mmol, 20 mol%) and the solutions of imines **1**{*1−4*} (10 mL, 2.0 mmol, 1.0 equiv) at the appropriate positions, followed by the addition of neat acyl chloride **9** (2.6 mmol, 1.3 equiv). While the mixture was stirred, the solution of dienylstannane **3** (10 mL, 3.0 mmol, 1.5 equiv) was added. The General Procedure for Synthesis of Bromosoindolones **6**{*1–4*,*1–2*} was followed to carry out the reactions to afford the corresponding bromoisoindolones as mixtures of diasteromers (dr ≈ 2:1). For analytical purposes, small samples of isoindolones **6** were partially separated via preparative TLC to afford small amounts of pure diastereomers in each case.

(±)-2-Benzyl-3-(3-chloro-4-methoxyphenyl)-7-(3-bromophenyl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (major) and (±)-(3*R*,3*aR*,7*R*,7*aS*)-2-Benzyl-3-(3-chloro-4-methoxyphenyl)-7-(3-bromophenyl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (minor) 10{*1*}: 0.300 g; yield 58%; dr = 2:1. **Major isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (br s, 1 H), 7.42 (dt, J = 7.3, 1.7 Hz, 1 H), 7.32–7.22 (m, 5 H), 7.17 (d, J = 2.0 Hz, 1 H), 7.03 (dd, J = 8.4, 2.0 Hz, 1 H), 6.98–6.90 (m, 3 H), 5.73 (dq, J = 11.2, 2.7 Hz, 1 H), 5.77–5.65 (m, 1 H), 4.95 (d, J = 14.6 Hz, 1 H), 3.97 (s, 3 H), 3.93 (d, J = 10.0 Hz, 1 H), 3.54 (d, J = 14.6 Hz, 1 H), 3.19 (td, J = 10.6, 6.8 Hz, 1 H), 2.73–2.64 (m, 1 H), 2.59 (t, J = 11.8 Hz, 1 H), 2.62–2.57 (m, 0.5 H), 2.57–2.52 (m, 0.5 H), 2.32–2.20 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 155.2, 145.7, 136.5, 130.6, 130.0 (2C), 129.8, 129.4, 128.6 (3 C), 128.5 (4 C), 127.4, 126.3, 124.0, 122.5, 112.2, 63.2, 56.3, 49.2, 48.7, 44.0, 42.0, 37.3; IR (neat, cm^{-1}) 1700; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{28}H_{26}BrClNO_2$ (M + H$^+$) 522.0835, found 522.0829. **Minor isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–6.95 (m, 12 H), 5.71–5.56 (m, 1 H), 5.58 (dq,J = 10.1, 2.9 Hz, 1 H), 5.16 (d, J = 14.8 Hz, 1 H), 4.47 (d, J = 7.4 Hz, 1 H), 3.96 (s, 3 H), 3.54 (d, J = 14.8 Hz, 1 H), 3.16 (td, J = 10.7, 6.9 Hz, 1 H), 3.10–3.00 (m, 1 H), 2.78 (t, J = 12.1 Hz, 1 H), 2.57–2.52 (m, 0.5 H), 2.52–2.47 (m, 0.5 H), 2.18–2.05 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 154.8, 145.9, 136.5, 130.6, 130.5, 130.3, 130.1, 129.7 (2C), 128.8 (2C), 128.7, 128.6, 128.5, 128.4, 128.2, 127.8, 126.4, 124.4, 112.3, 59.9, 56.2, 46.0, 44.6, 44.0, 42.1, 37.2; IR (neat, cm^{-1}) 1700; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{28}H_{26}BrClNO_2$ (M + H$^+$) 522.0835, found 522.0858.

(±)-2-Benzyl-3-(4-(trifluoromethyl)phenyl)-7-(3-bromophenyl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (major) and (±)-(3*R*,3*aR*,7*R*,7*aS*)-2-Benzyl-3-(4-(trifluoromethyl)phenyl)-7-(3-bromophenyl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (minor) 10{*2*}: 0.311 g; yield 59%; dr = 2:1. **Major isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 2 H), 7.49 (br s, 1 H), 7.43 (dt, J = 7.2, 1.8 Hz, 1 H), 7.35–7.20 (m, 7 H), 6.90–6.85 (m, 2 H), 5.74 (dq, J = 9.8, 3.0 Hz, 1 H), 5.71–5.65 (m, 1 H), 5.00 (d, J = 14.6 Hz, 1 H), 4.05 (d, J = 9.9 Hz, 1 H), 3.54 (d, J = 14.6 Hz, 1 H), 3.19 (td, J = 10.7, 6.9 Hz, 1 H), 2.77–2.72 (m, 0.5 H), 2.72–2.67 (m, 0.5 H), 2.63 (t, J = 11.7 Hz, 1 H), 2.58 (d, J = 19.0 Hz, 1 H), 2.34–2.22 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 145.5, 141.5, 136.2, 131.0, 130.8, 130.6, 130.0, 129.8, 129.7, 128.6 (4 C), 128.3, 127.6, 126.3, 126.0 (2C), 125.0, 123.6, 122.6, 63.7, 49.4, 48.8, 44.2, 42.0, 37.2; IR (neat, cm^{-1}) 1706; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{28}H_{24}BrF_3NO$ (M + H$^+$) 526.0993, found 526.0984. **Minor isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 2 H), 7.45 (br s, 1 H), 7.41 (dt, J = 7.2, 1.8 Hz, 1 H), 7.35–7.24 (m, 7 H), 7.19–7.14 (m, 2 H), 5.67–5.61 (m, 1 H), 5.57 (dq, J = 9.9, 3.0 Hz, 1 H), 5.19 (d, J = 14.8 Hz, 1 H), 4.60 (d, J = 7.5 Hz, 1 H), 3.59 (d, J = 14.8 Hz, 1 H), 3.18 (td, J = 10.5, 6.9 Hz, 1 H), 3.16–3.10 (m, 1 H), 2.76 (t, J = 12.2 Hz, 1 H), 2.60–2.51 (m, 0.5 H), 2.51–2.45 (m, 0.5 H), 2.16–2.03 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 145.7, 139.5, 136.4, 130.5, 130.3, 130.0, 129.8, 129.7, 128.6 (2C), 128.4 (2C), 128.1, 127.8, 127.4 (2C), 126.3, 126.0 (2C), 124.0, 122.6, 60.5, 44.6, 44.5, 44.0, 42.0, 37.1; IR (neat, cm^{-1}) 1706; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{28}H_{24}BrF_3NO$ (M + H$^+$) 526.0993, found 526.1002.

(±)-2-Benzyl-3-(2-fluoro-5-methylphenyl)-7-(3-bromophenyl)-2,3,3*a*,6,7,7*a*-hexahydro-1H-isoindol-1-one (major) and (±)-(3*R*,3*aR*,7*R*,7*aS*)-2-Benzyl-3-(2-fluoro-5-methylphenyl)-7-(3-bromophenyl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (minor) 10{*3*}: 0.304 g; yield 62%; dr = 2:1. **Major isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.02 (m, 10 H), 6.96 (dd, J = 10.0, 8.5 Hz, 1 H), 6.85 (d, J = 7.2 Hz, 1 H), 6.03 (dq, J = 10.0, 2.4 Hz, 1 H), 5.79–5.73 (m, 1 H), 5.25 (d, J = 14.9 Hz, 1 H), 4.46 (br s, 1 H), 3.67 (d, J = 14.9 Hz, 1 H), 3.62–3.58 (m, 1 H), 2.96 (dd, J = 7.0, 4.0 Hz, 1 H), 2.70–2.63 (m, 1 H), 2.59 (dquint, J = 18.2, 3.1 Hz, 1 H), 2.32 (s, 3 H), 2.34–2.29 (m, 0.5 H), 2.29–2.24 (m, 0.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 159.8, 157.8, 147.1, 136.0, 134.1, 130.6, 130.0, 129.9, 129.5 (2C), 128.6 (2C), 128.4, 128.0, 127.6, 126.7, 126.2, 122.5, 115.8, 115.6, 59.5, 44.8, 44.7, 39.6, 36.1, 27.1, 20.9; IR (neat, cm^{-1}) 1702; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{28}H_{26}BrFNO$ (M + H$^+$) 490.1182, found 490.1175. **Minor isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 10.4 Hz, 1 H), 7.45–7.10 (m, 7 H), 7.03 (dd,J = 10.0, 8.5 Hz, 1 H), 7.00 (dd, J = 9.9, 8.5 Hz, 1 H), 6.96–6.91 (m, 1 H), 6.89 (d, J = 7.0 Hz, 1 H), 5.87–5.57 (m, 2 H), 5.14 (d, J = 14.7 Hz, 1 H), 4.92 (d, J = 7.5 Hz, 1 H), 3.63 (d, J = 14.8 Hz, 1 H), 3.25–3.14 (m, 1 H), 2.77 (t, J = 12.1 Hz, 1 H), 2.63 (t, J = 11.9 Hz, 1 H), 2.56–2.52 (m, 0.5 H), 2.51–2.46 (m, 0.5 H), 2.39 (s, 3 H), 2.35–2.20 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 160.1, 158.2, 146.0, 136.5, 134.1, 130.7, 130.6, 130.4, 130.2, 130.0 (2C), 129.9 (2C), 129.2, 127.6, 126.2, 124.5, 122.5, 121.9, 115.7, 55.1, 48.8, 44.9, 44.0, 42.1, 37.2, 21.0; IR (neat, cm^{-1}) 1696; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{28}H_{26}BrFNO$ (M + H$^+$) 490.1182, found 490.1187.

(±)-2-Benzyl-3-(naphthalen-2-yl)-7-(3-bromophenyl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (major) and (±)-(3*R*,3*aR*,7*R*,7*aS*)-2-Benzyl-3-(naphthalen-2-yl)-7-(3-bromophenyl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (minor) 10{*4*}: 0.356 g; yield 70%; dr = 2:1. **Major isomer:** ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 rotamers) δ 7.97–7.90 (m, 2.5 H), 7.89–7.83 (m, 0.5 H), 7.66 (br s, 1

H), 7.64–7.48 (m, 3 H), 7.44 (t, $J = 7.6$ Hz, 1 H), 7.38–7.18 (m, 7 H), 6.95–6.90 (m, 1 H), 5.79–5.69 (m, 1.5 H), 5.52 (dq, $J = 10.0$, 3.2 Hz, 0.5 H), 5.29 (d, $J = 14.9$ Hz, 0.5 H), 5.06 (d, $J = 14.6$ Hz, 0.5 H), 4.75 (d, $J = 7.4$ Hz, 0.5 H), 4.21 (d, $J = 10.2$ Hz, 0.5 H), 3.68 (d, $J = 14.8$ Hz, 0.5 H), 3.58 (d, $J = 14.6$ Hz, 0.5 H), 3.24 (td, $J = 11.2$, 6.8 Hz, 0.5 H), 3.22 (td, $J = 11.2$, 6.8 Hz, 0.5 H), 3.20–3.15 (m, 0.5 H), 2.93 (t, $J = 12.0$ Hz, 0.5 H), 2.92–2.84 (m, 0.5 H), 2.68 (t, $J = 11.9$ Hz, 0.5 H), 2.64–2.45 (m, 1 H), 2.34–2.25 (m, 0.5 H), 2.22–2.03 (m, 0.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (173.7 and 173.6), (146.0 and 145.8), (136.8 and 136.7), 134.5, 133.5, 133.4, 133.3, 133.1, 132.6, 130.7, 130.6, 130.0 (2C), 129.7, 129.6, 129.3, 129.2, 129.0, 128.8, 128.7 (2C), 128.4 (2C), 128.0, 127.9, 127.8 (2C), 127.6, 127.4, 126.6, 126.5, 126.3 (2C), 125.6, 125.2, 124.6, 124.3, 122.5, (64.3, 60.9), (49.2, 48.9), (44.9, 44.1), (44.6, 44.2), (42.2, 42.1), (37.3, 37.1); IR (neat, cm^{-1}) 1699; HRMS (ESI^+, *m*/*z*) calcd for $C_{31}H_{27}BrNO$ ($M + H^+$) 508.1276, found 508.1274. **Minor isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.82 (m, 3 H), 7.60 (br s, 1 H), 7.58–7.50 (m, 2 H), 7.43 (br s, 1 H), 7.36–7.25 (m, 5 H), 7.24 (d, $J = 5.7$ Hz, 1 H), 7.15 (t, $J = 6.0$ Hz, 1 H), 7.12–7.08 (m, 2 H), 6.07–6.01 (m, 1 H), 5.78–5.72 (m, 1 H), 5.31 (d, $J = 14.3$ Hz, 1 H), 4.30 (d, $J = 3.3$ Hz, 1 H), 3.63 (d, $J = 14.8$ Hz, 1 H), 3.46 (q, $J = 5.2$ Hz, 1 H), 3.08 (t, $J = 6.5$ Hz, 1 H), 2.76 (m, 1 H), 2.57 (dhex, $J = 18.2$, 2.8 Hz, 1 H), 2.36–2.31 (m, 0.5 H), 2.31–2.26 (m, 0.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 146.8, 136.5, 136.3, 133.1, 130.7, 133.3, 130.0, 129.6, 129.3, 128.6, 128.5 (2C), 128.2 (2C), 127.9, 127.8, 127.6, 127.0, 126.7, 126.3, 126.2, 125.1, 124.1, 122.5, 66.0, 45.0, 44.5, 41.1, 36.7, 28.3; IR (neat, cm^{-1}) 1692; HRMS (ESI^+, *m*/*z*) calcd for $C_{31}H_{27}BrNO$ ($M + H^+$) 508.1276, found 508.1269.

General Procedure for Synthesis of Library 11{*1–4*, *1*,*2*,*4*,*6*}. Initially, stock solutions of four bromoisoindolones (mixtures of diastereomers in each case) **10**{*1–4*} in THF were prepared. To a 8 × 6 position Bohdan MiniBlock fitted with 24 (11.5 × 110 mm) reaction vials, under an atmosphere of argon, were added palladium acetate (1.2 mg, 0.005 mmol, 5 mol%), 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl (3.6 mg, 0.010 mmol, 10 mmol%), cesium fluoride (0.061 g, 0.4 mmol, 4.0 equiv), and boronic acids **7**{*1*,*2*,*4*,*6*} (0.2 mmol, 2.0 equiv) at the appropriate positions, followed by the addition of solutions of isoindolones **10**{*1–4*} (1.0 mL, 0.1 mmol, 1.0 equiv). After they were refluxed at 60 °C overnight, the reaction mixtures were concentrated via parallel evaporation. The residues were transferred individually to 48 PrepSep silica gel columns (500 mg/6 mL). The PrepSep columns containing the crude products were then washed with methylene chloride (5 mL). Filtrates were evaporated in parallel to dryness in a GeneVac EZ-2 plus evaporator. The products were submitted for LC/MS analyses, followed by preparative LC to obtain the pure products.

(±)-2-Benzyl-3-(3-chloro-4-methoxyphenyl)-7-(4′-(dimethylamino)biphenyl-3-yl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (Major) and (±)-(3*R*,3*aR*,7*R*,7*aS*)-2-Benzyl-3-(3-chloro-4-methoxyphenyl)-7-(4′-(dimethylamino)biphenyl-3-yl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (Minor) 11{*1*,*4*}. Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, $J = 8.9$ Hz, 2 H), 7.54–6.90 (m, 12 H), 6.85 (d, $J = 8.9$ Hz, 2 H), 5.76 (dq, $J = 10.0$, 3.0 Hz, 1 H), 5.72–5.67 (m, 1 H); 4.99 (d, $J = 14.7$ Hz, 1 H), 3.97 (s, 3 H), 3.93 (d, $J = 9.9$ Hz, 1 H), 3.54 (d, $J = 14.7$ Hz, 1 H), 3.29 (td, $J = 10.6$, 7.0 Hz, 1 H), 3.04 (s, 6 H), 2.77–2.70 (m, 1 H), 2.68 (t, $J = 11.6$ Hz, 1 H), 2.68–2.63 (m, 0.5 H), 2.63–2.58 (m, 0.5 H), 2.40–2.30 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 155.1, 149.9, 143.7, 141.1, 136.7, 130.5, 129.8, 129.7, 128.9, 128.8 (2C), 128.7 (2C), 128.5, 128.3, 128.0 (2C), 127.8, 127.5, 125.9, 125.2, 124.9, 124.0, 112.9 (2C), 112.2, 63.2, 56.2, 49.4, 48.9, 44.1, 42.5, 40.7 (2C), 37.6; IR (neat, cm^{-1}) 1696; HRMS (ES^+) calcd for $C_{36}H_{36}ClN_2O_2$ ($M + H^+$) 563.2465, found 563.2479. **Minor isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, $J = 8.9$ Hz, 2 H), 7.50–7.15 (m, 10 H), 7.05 (d, $J = 8.9$ Hz, 1 H), 6.98 (d, $J = 8.9$ Hz, 1 H), 6.83 (d, $J = 8.9$ Hz, 2 H), 5.68–5.64 (m, 1 H), 5.63–5.59 (m, 1 H), 5.18 (d, $J = 14.7$ Hz, 1 H), 4.48 (d, $J = 7.4$ Hz, 1 H), 3.95 (s, 3 H), 3.59 (d, $J = 14.7$ Hz, 1 H), 3.27 (td, $J = 10.6$, 7.0 Hz, 1 H), 3.13–3.05 (m, 1 H), 3.02 (s, 6 H), 2.86 (t, $J = 12.1$ Hz, 1 H), 2.62–2.57 (m, 0.5 H), 2.57–2.52 (m, 0.5 H), 2.25–2.16 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 154.7, 149.9, 143.8, 141.3, 136.8, 129.9, 129.7, 129.0, 128.9, 128.8 (2C), 128.4 (2C), 128.0 (2C), 127.7, 127.4, 126.5, 125.9, 125.1, 124.9, 124.4, 123.0, 112.8 (2C), 112.3, 59.9, 56.2, 44.8, 44.4, 44.1, 42.5, 40.7 (2C), 37.5.

(±)-2-Benzyl-7-(4′-methylbiphenyl-3-yl)-3-(4-(trifluoromethyl)phenyl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (Major) and (±)-(3*R*,3*aR*,7*R*,7*a*S)-2-Benzyl-7-(4′-methylbiphenyl-3-yl)-3-(4-(trifluoromethyl)phenyl)-2,3,3a,6,7,7a-hexahydro-1*H*-isoindol-1-one (Major) 11{*2*, *1*}: Major isomer: (1: 1 rotamers) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65–6.75 (m, 17 H), 6.08–6.03 (m, 0.5 H), 6.02–5.95 (m, 0.5 H), 5.63–5.55 (m, 1 H), 5.18 (d, $J = 15.0$ Hz, 0.5 H), 5.05 (d, $J = 15.1$ Hz, 0.5 H), 4.08 (d, $J = 2.8$ Hz, 0.5 H), 4.03 (s, 0.5 H), 3.44 (d, $J = 15.1$ Hz, 0.5 H), 3.42 (d, $J = 15.0$ Hz, 0.5 H), 3.26–3.14 (m, 1 H), 2.98 (t, $J = 6.1$ Hz, 0.5 H), 2.87–2.83 (m, 0.5 H), 2.77 (ddd, $J = 17.1$, 10.8, 2.6 Hz, 0.5 H), 2.65–2.47 (m, 1.5 H), 2.39–2.25 (m, 1 H), 2.30 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (174.1, 173.9), 144.7, 143.6, 141.3, 141.0, 138.7, 138.4, 137.1, 136.9, 135.9, 135.7, 130.9, 130.0, 129.6 (2C), 129.5 (2C), 129.4 (2C), 129.0, 128.9, 128.7 (2C), 128.6, 128.5 (2C), 128.4, 128.3, 128.1 (2C), 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2 (2C), 127.0 (2C), 126.8, 126.7 (2C), 126.6 (2C), 126.5, 126.4, 126.2, 126.1, 125.5, 125.4, 125.3, 123.6, (65.5, 64.6), (45.1, 44.6), (44.4, 44.0), (42.4, 41.0), (38.9, 36.6), (28.1, 27.0), 21.1; IR (neat, cm^{-1}) 1695; HRMS (ES^+) calcd for $C_{35}H_{31}F_3NO$ ($M + H^+$) 538.2358, found 538.2318. **Minor isomer:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, $J = 8.6$ Hz, 2 H), 7.55 (d, $J = 8.6$ Hz, 2 H), 7.52–7.48 (m, 2 H), 7.46 (t, $J = 7.6$ Hz, 1 H), 7.35–7.25 (m, 8 H), 7.18 (d, $J = 7.6$ Hz, 2 H), 5.68–5.63 (m, 1 H), 5.62 (dq, $J = 10.0$, 3.5 Hz, 1 H), 5.20 (d, $J = 14.9$ Hz, 1 H), 4.61 (d, $J = 7.6$ Hz, 1 H), 3.59 (d, $J = 14.9$ Hz, 1 H), 3.29 (td, $J = 10.6$, 7.0 Hz, 1 H), 3.21–3.14 (m, 1 H), 2.85 (t, $J = 12.1$ Hz, 1 H), 2.62–2.57 (m, 0.5 H), 2,57–2.52 (m, 0.5 H), 2.43 (s, 3 H), 2.25–2.16 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 143.6, 141.3, 139.7, 138.7, 136.8, 136.5, 131.0, 129.4 (2C), 128.8, 128.7 (2C), 128.4 (2C), 127.7, 127.5 (2C), 127.3 (2C),

126.3, 126.2, 125.9 (4 C), 125.4, 123.9, 60.5, 44.7, 44.6, 44.2, 42.4, 37.4, 21.1.

(±)-2-Benzyl-3-(2-fluoro-5-methylphenyl)-7-(4′-methylbiphenyl-3-yl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (Major) and (±)-(3*R*,3*aR*,7*R*,7*aS*)-2-Benzyl-3-(2-fluoro-5-methylphenyl)-7-(4′-methylbiphenyl-3-yl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (Minor) 11{*3*, *1*}. Major isomer: (1: 1 rotamers) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 0.5 H), 7.55–6.85 (m, 13.5 H), 6.79 (t, J = 7.1 Hz, 1 H), 6.10–6.02 (m, 1 H), 5.75–5.71 (m, 1 H), 5.70–5.67 (m, 0.5 H), 5.25 (d, J = 15.0 Hz, 0.5 H), 5.13 (d, J = 15.1 Hz, 0.5 H), 4.43 (s, 0.5 H), 4.37 (s, 0.5 H), 3.72–3.69 (m, 0.5 H), 3.63 (d, J = 15.0 Hz, 0.5 H), 3.57 (d, J = 15.1 Hz, 0.5 H), 2.60 (dm, J = 15.1 Hz, 0.5 H) 3.22 (dd, J = 6.6, 3.0 Hz, 0.5 H), 3.18 (dt, J = 11.4, 3.9 Hz, 0.5 H), 2.99 (dd, J = 6.8, 3.5 Hz, 0.5 H), 2.97–2.93 (m, 1 H), 2.90–2.81 (m, 1 H), 2.42–2.30 (m, 1 H), 2.37 (s, 3 H), 2.26 (s, 1.5 H), 2.24 (s, 1.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (174.0, 173.1), (158.3, 158.2), (156.4, 156.3), (143.9, 141.7), (139.8, 139.4), (137.3, 136.9), (135.6, 135.4), (134.6, 134.5), (132.6, 132.5), 129.0, 128.4, 128.3 (2C), 128.2, 128.1 (2C), 128.0 (2C), 127.9, 127.4 (2C), 127.2, 127.1, 127.0 (2C), 126.9, 126.5, 126.4 (2C), 126.1 (2C), 126.0, 125.9, 125.8, 125.7 (2C), 125.6, 125.2, 125.1, 124.9, 124.6, 123.8, 123.6, (114.3, 114.1), (58.0, 57.2), (43.5, 43.3), (43.0, 42.9), (42.4, 38.0), (37.7, 34.7), (25.6, 25.3), 19.7, (19.5, 19.4); IR (neat, cm^{-1}) 1692; HRMS (ES^+) calcd for $C_{35}H_{32}FNO$ ($M + H^+$) 502.2546, found 502.2555. **Minor isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 2 H), 7.53–6.85 (m, 13 H), 5.86–5.81 (m, 1 H), 5.62 (dq, J = 10.0, 3.3 Hz, 1 H), 5.18 (d, J = 14.9 Hz, 1 H), 4.92 (d, J = 7.6 Hz, 1 H), 3.62 (d, J = 14.9 Hz, 1 H), 3.29 (td, J = 10.9, 6.6 Hz, 1 H), 3.22–3.14 (m, 1 H), 2.85 (t, J = 12.1 Hz, 1 H), 2.62–2.57 (m, 0.5 H), 2.57–2.52 (m, 0.5 H), 2.43 (s, 3 H), 2.38 (s, 3 H), 2.26–2.18 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 160.1, 158.2, 144.0, 141.2, 138.7, 136.8, 136.6, 134.0, 130.3, 130.1, 129.5, 128.9 (2C), 128.8, 128.6 (2C), 128.5 (2C), 128.3, 127.9, 127.6, 127.2, 127.0, 126.0, 115.7, 115.5, 55.0, 45.0, 44.7, 44.0, 42.4, 37.5, 21.1, 20.9.

(±)-2-Benzyl-7-(4′-methoxybiphenyl-3-yl)-3-(naphthalen-2-yl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (Major) and (±)-(3*R*,3*aR*,7*R*,7*aS*)-2-Benzyl-7-(4′-methoxybiphenyl-3-yl)-3-(naphthalen-2-yl)-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-isoindol-1-one (major) 11{*4*,*2*}: Major isomer: (3:2 rotamers) ^{1}H NMR (400 MHz, $CDCl_3$,) δ 8.20–6.88 (m, 20 H), 5.81–5.76 (m, 0.4 H), 5.75 (br s, 1.2 H), 5.56 (dq, J = 10.0, 3.1 Hz, 0.4 H), 5.29 (d, J = 14.8 Hz, 0.4 H), 5.07 (d, J = 14.9 Hz, 0.6 H), 4.76 (d, J = 7.5 Hz, 0.4 H), 4.22 (d, J = 10.0 Hz, 0.6 H), 3.99 (s, 1.8 H), 3.98 (s, 1.2 H), 3.68 (d, J = 14.8 Hz, 0.4 H), 3.58 (d, J = 14.6 Hz, 0.6 H), 3.42–3.31 (m, 1 H), 3.28–3.18 (m, 0.4 H), 3.01 (t, J = 12.1 Hz, 0.4 H), 2.92 (t, J = 11.1 Hz, 0.6 H), 2.78 (t, J = 11.9 Hz, 0.6 H), 2.70–2.50 (m, 1 H), 2.38 (ddd, J = 18.7, 10.3, 3.7 Hz, 0.6 H), 2.24–2.14 (m, 0.4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0 (2C), 167.2, 146.1, 146.0, 144.4, 144.2, 140.1, 140.0, 136.8, 136.7, 134.7 (2C), 133.5, 133.4, 133.3, 133.1, 132.7, 131.7, 130.0 (2C), 129.5, 129.4, 129.0 (2C), 128.7 (4 C), 128.4 (2C), 128.0, 127.9, 127.8, 127.6 (2C), 127.4, 127.3, 127.2, 126.8, 126.7, 126.6, 126.5, 126.3, 125.7, 125.6, 125.3, 124.7, 124.3, 115.2, (64.4, 60.9), 52.1, (49.3, 49.0), (45.0, 44.6), (44.3, 44.1), (42.6, 42.5), (37.6, 37.4); IR (neat, cm^{-1}) 1694; HRMS (ES^+) calcd for $C_{38}H_{34}NO_2$ ($M + H^+$) 536.2589, found 536.2560. **Minor isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 2 H), 7.90–7.07 (m, 18 H), 6.11–6.05 (m, 1 H), 5.80–5.74 (m, 1 H), 5.32 (d, J = 14.9 Hz, 1 H), 4.32 (d, J = 3.3 Hz, 1 H), 3.96 (s, 3 H), 3.64 (d, J = 14.9 Hz, 1 H), 3.62–3.54 (m, 1 H), 3.16 (t, J = 6.4 Hz, 1 H), 2.84–2.76 (m, 1 H), 2.67–2.62 (m, 0.5 H), 2.62–2.57 (m, 0.5 H), 2.45–2.41 (m, 0.5 H), 2.40–2.36 (m, 0.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 167.0, 145.8, 145.2, 140.1, 136.6, 136.3, 133.3, 133.1, 130.0 (2C), 129.2, 129.0, 128.6 (2C), 128.4 (2C), 128.1 (2C), 127.8, 127.7, 127.5, 127.3, 127.1, 127.0, 126.7, 126.6, 126.3, 125.4, 125.1, 124.2, 66.1, 52.1, 45.2, 44.5, 41.2, 37.0, 28.6.

Acknowledgment. This work was supported by the National Institutes of Health, Kansas University Chemical Methodologies and Library Development Center of Excellence (P50 GM069663). We thank our colleagues Dr. Frank Schoenen for his assistance with the organization of the library synthesis and Dr. Victor W. Day for his assistance with X-ray crystallography.

Supporting Information Available. Description of the experimental procedure for the computational study, the summary of the results, molecular structure of **4db** established by X-ray crystallography, and copies of ^{1}H and ^{13}C NMR spectra and HPLC traces for compounds reported in the Experimental Section above. The material is available free of charge via the Internet at at http://pubs.acs.org.

References and Notes

(1) An, H.; Cook, P. D. *Chem. Rev.* **2000**, *100*, 3311.
(2) (a) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (b) Corey, E. J.; Cheng, X.-M. In *The Logic of Chemical Synthesis*; Wiley: New York, 1989, p 31.
(3) Foye, W. O. In *Principles of Medicinal Chemistry*, 3rd ed.; Lea & Febiger: Philadelphia, 1989.
(4) Zhang, L.; Malinakova, H. C. *J. Org. Chem.* **2007**, *72*, 1484.
(5) (a) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 1991. (b) Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2005**, *70*, 5133. (c) Davis, J. L.; Dhawan, R.; Arndsen, B. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 590.
(6) (a) Jiang, J.; Devita, R. J.; Kumar, S.; Mills, S. G.; Tschirret-Guth, R. A. Int. Patent WO 2007002457, 2007. (b) Kuethe, J. T.; Yin, J.; Huffman, M. A.; Journet, M. Int. Patent WO 2007008564, 2007. (c) Rudd, J. A.; Ngan, M. P.; Wai, M. K. *Eur. J. Pharmacol.* **1999**, *366*, 243.
(7) (a) Haidle, A. M.; Myers, A. G. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12048. (b) Thilly, W. G.; Liber, H. L.; Wogan, G. N. *Front. Biol.* **1978**, *46*, 53.
(8) Walling, E. A.; Drafft, G. A.; Ware, B. R. *Arch. Biochem. Biophys.* **1988**, *264*, 321.
(9) Linghan, R. B.; Hsu, A.; Silverman, K. C.; Bills, G. F.; Dombrowski, A.; Goldman, M. E.; Darke, P. L.; Huang, L.; Koch, G.; Ondeyka, J. G.; Goetz, M. A. *J. Antiob.* **1992**, *45*, 686.
(10) Goldberg, J.; Jin, Q.; Ambroise, Y.; Satoh, S.; Desharnais, J.; Capps, K.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 544.
(11) Young, D. D.; Senaiar, R. S.; Deiters, A. *Chem.—Eur. J.* **2006**, *12*, 5563.
(12) Chand, Y. *J. Comb. Chem.* **2005**, *7*, 958.

(13) (a) Clayden, J.; Knowles, F. E.; Baldwin, I. R. *J. Am. Chem. Soc.* **2005**, *127*, 2412. (b) Sohar, P.; Csampai, A.; Magyarfalvi, G.; Szabo, A. E.; Stajr, G. *Monatsh. Chem.* **2004**, *135*, 1519. (c) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Org. Lett.* **2000**, *2*, 4229. (d) Brettle, R.; Jafri, I. A. *J. Chem. Soc, Perkin Trans. 1* **1983**, 387. (e) Brette, R.; Cummings, D. P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2385.

(14) (a) Sun, S.; Murray, W. V. *J. Org. Chem.* **1999**, *64*, 5941. (b) Crisp, G. T.; Gebauer, M. G. *J. Org. Chem.* **1996**, *61*, 8425.

(15) From the total of 116 distinct I−III library members reported in this communication, 103 members (89%) had the UV (214 nm) purity higher than 95%.

(16) For the protocol for the preparation of the imines, see: Iovel, I.; Golomba, L.; Fleisher, M.; Popelis, J.; Grinberga, S.; Lukevics, E. *Chem. Heterocycl. Compd.* **2004**, *40*, 701.

(17) For the protocol for the preparation of the diennyl stannane, see: (a) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555. (b) Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967.

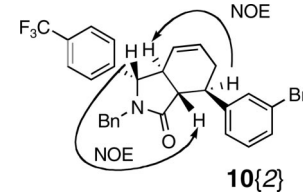
(18) The assignment of the relative stereochemistry for isoindolones **6** (R^3 = Me) is based on an X-ray crystallographic analysis of an analogous isoindolone obtained in our previous work (ref 4). ^{1}H NMR data demonstrating the analogous spectral features of the isoindolones **6** and the previously characterized compounds (ref 4) are presented in the Supporting Information (see page S-103).

(19) However, following the Pd-catalyzed cross-coupling reaction, only two diastereomers of the corresponding isoindolones **8** were isolated after purification by preparative HPLC. The assignment of the relative stereochemistry for isoindolones **8** is derived directly from the assignment of the relative stereochemistry for isoindolones **6**, from which the corresponding isoindolones **8** were produced via Pd-catalyzed cross-coupling to a Csp^2−Br bond.

(20) Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998.

(21) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(22) In our prior studies (ref 4), repeated attempts to unequivocally assign the relative stereochemistry of isoindolones on the basis of NOE experiments proved to be inconclusive, as noted for cases where a direct comparison to X-ray crystallographic evidence became possible. We have tabulated the characteristic *J* coupling constants in the ^{1}H NMR of selected compounds **4da**, **4c**, and **10** (see Table S-12 in the Supporting Information) and performed 2D NMR analyses as well as ^{1}H NMR NOE experiments on the major diastereomer of compound **10**{*2*}. The data available to date are consistent with the structure of the major diastereomer of compound **10**{*2*} as shown below. However, the assignment is only *tentative* and has yet to be confirmed by X-ray crystallography. For additional discussion regarding the structures of compounds **4da**, **4c**, **10**, and **11**, see the Supporting Information page S-103.



10{*2*}

(23) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3–25.

(24) Cruciani, G.; Meniconi, M.; Carosati, E.; Zamora, I.; Mannhold, R. In *Methods and Principles in Medicinal Chemistry*; van de Waterbeemd, H.; Lennernäs, H.; Artursson, P., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2003.

(25) Pearlman, R. S.; Smith, K. M. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 28–35.

(26) Iovel, I.; Golomba, L.; Fleisher, M.; Popelis, J.; Grinberga, S.; Lukevics, E. *Chem. Heterocycl. Compd.* **2004**, *40*, 701.

(27) (a) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555. (b) Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967.

CC700151M