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Copper-Catalyzed Multicomponent Cascade Process for the Synthesis of Hexahydro-1*H*-isoindolones

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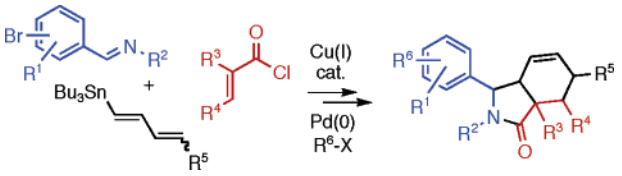

Copper-catalyzed coupling of imines, dienylstannanes, and acryloyl chlorides followed by a Diels−Alder reaction afforded hexahydro-1*H*-isoindolones. Diversification of the core via Pd-catalyzed cross-coupling defines a new modular approach to isoindolone combinatorial libraries.

Multicomponent and cascade reactions represent a cornerstone of combinatorial chemistry.[1] Given the role of heterocyles in drug discovery,[2] the present lack of methods for combinatorial synthesis of biologically relevant[3] isoindolone cores is quite surprising.[4] Herein, we report a new tandem copper-catalyzed three-component coupling/Diels−Alder sequence for a modular assembly of substituted isoindolones (Figure 1). For the first time, dienylstannanes **III** and substituted acryloyl chlorides **II** were used in a three-component coupling with imines **I** developed by Arndtsen,[5] and an appropriate choice of catalyst permitted the use of imines **I** bearing an aryl bromide functionality. In most cases, the entire reaction sequence providing heterocycles **V** occurred in a one-pot operation. Only the synthesis of isoindolones **V** bearing a substituent R^6 (R^6 = Me) required the isolation of amides **IV**.[6] Elaboration of the Csp^2−Br bond in templates **V** via Pd-catalyzed C−C bond-forming reactions afforded diversified products **VI**.[7] In contrast to traditional isoindolone syntheses,[8] diverse substitution patterns could be created via the choice of the building blocks. This study provides a proof of concept for a general application of α-*N*-substituted amides[9] as templates in diversity oriented synthesis, exploiting just one of many possible methods for an intramolecular cyclization of two of the four available side chains.

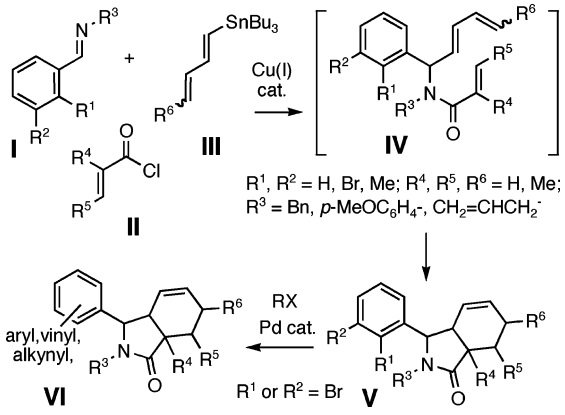

FIGURE 1. Synthetic strategy.

Initially, the Pd-catalyzed model reactions of benzoyl chloride, (ethenyl)tributylstannane, and *o*-bromo- or *m*- bromo-substituted imines of arylcarboxaldehydes **1a**,**b** afforded low yields of the desired α-substituted amides **2a**,**b** (method A, Scheme 1).[10] In contrast, the Cu-catalyzed protocol (method B)[5b] led to good (>70%) yields of the corresponding amides **2a**,**b** (Scheme 1).

To establish the substitution pattern required for Diels−Alder reaction in amides **IV**, the unprecedented application of a dienylstannane in the three-component coupling process[5] was investigated (Table 1). Gratifyingly, under the conditions of the Cu-catalyzed protocol (method B, Scheme 1) the intramolecular Diels−Alder reaction proved to be quite facile, providing isoindolones **3** and **5** in a single step, albeit in low yields (30−40%).[11] Reasoning that the Sn−Cu transmetalation[12] might represent a slow step, an excess of the dienylstannane was employed (2 equiv, method C, Table 1) providing the best yields (71−75%) of isoindolones **3**−**5** as inseparable mixtures of major *exo* (vide infra) and minor diastereomers accompanied by traces of a third diastereomer (entries 1−3, Table 1).[13]

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(9) For a closely related approach to yohimbine and protoberberine-type alkaloids, see: Yamaguchi, R.; Hamasaki, T.; Utimoto, K.; Kozima, S.; Takaya, H. *Chem. Lett.* **1990**, 2161.
(10) Arndtsen reported that the Pd-catalyzed coupling proceeded successfully with *m*-iodo-substituted aryl imines, see ref 5c.
(11) An attempted optimization by variations in the Cu(I) salts, additives (Bu_4NBr), temperature, and the catalyst loading led only to a minimal improvement.
(12) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973.
(13) The relative configuration of the minor diastereomer and the third diastereomer could not be assigned.

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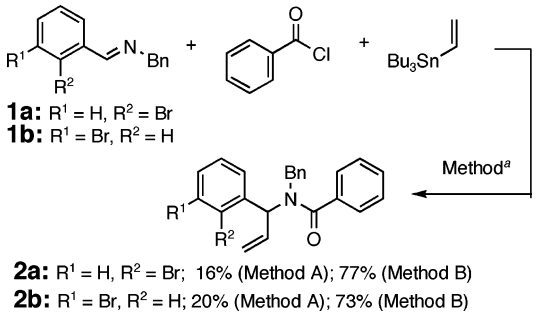
SCHEME 1[a]

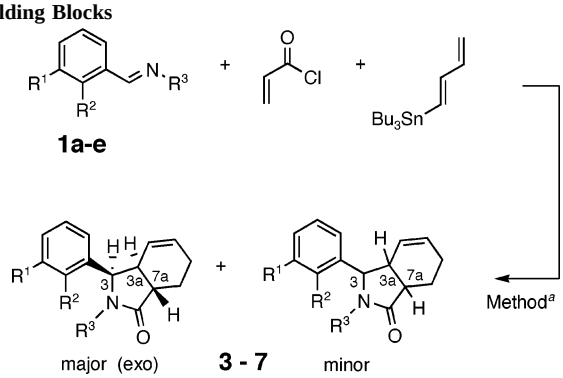


[a] Method A: Pd_2dba_3 (2.5%), $MeCN/CH_2Cl_2$, rt, 24 h, molar ratios of reagents: imine/acyl chloride/stannane = 1:1:1. Method B: CuCl (10%), $MeCN/CH_2Cl_2$, 45 °C, 16 h, molar ratios of reagents: imine/acyl chloride/stannane = 1:1.3:1.

The *N*-protecting group provides an additional point of diversity. *N*-Allyl imine **1d** reacted with acryloyl chloride and the dienylstannane (Method C) to afford the corresponding isoindolone **6** (entry 4, Table 1) as an inseparable mixture of diastereomers with compositions analogous to isoindolones **3**−**5**. In contrast, using method C, *N*-PMP imine **1e** provided only the corresponding amide, and heating in toluene was required to induce the intramolecular Diels−Alder reaction. Ultimately, a one-pot preparation of isoindolone **7** was realized via a modified protocol (method D), involving the removal of $MeCN/CH_2Cl_2$ solvent under reduced pressure and heating to reflux in toluene to afford two diastereomers of isoindolones **7.1** (52%) and **7.2** (5%) as pure compounds (entry 5, Table 1). The relative stereochemistry of the major diastereomer of isoindolones **3**−**7** was assigned as *exo* on the basis of the comparison of the *J* coupling constants for protons on the adjacent carbons C3, C3a, and C7a, e.g., $J^{3a,7a}$ and $J^{3,3a}$ with the data for structurally closely related compound **13**, the structure of which could be established by X-ray crystallography.[14]

Aiming to expand the structural diversity of the diene and acyl chloride building blocks, the reactivity of substituted acryloyl chlorides as well as 1-tributylstannyl-1,3-pentadiene, prepared as a mixture of *E*/*Z* isomers (1:2.5),[15] was studied (Table 2). Reactions of imines **1a** and **1c** with acryloyl chloride and the terminally substituted dienylstannane employing method C afforded exclusively the corresponding amides **8a** and **8c**. Application of method D (Table 1) gave mixtures of heterocycles **9** and **10** with amides **8**. The best results were realized in a two-pot protocol (method E), incorporating the isolation and purification of amides **8a,c** prior to a reflux in toluene. Imine **1a** yielded isoindolones **9.1** (69%) and **9.2** (11%), each as one diastereomer, and **9.1** accompanied by traces of an additional

TABLE 1. Reactions with Unsubstituted Acyl Chloride and Diene Building Blocks



	subst	R^1	R^2	R^3	method[a]	prdt	yield (%)	dr[b]
1	**1a**	H	Br	Bn	C	**3**	74	5.0:1[c]
2	**1b**	Br	H	Bn	C	**4**	75	2.6:1[c]
3	**1c**	Me	H	Bn	C	**5**	71	2.3:1[c]
4	**1d**	Me	H	allyl[d]	C	**6**	68	2.0:1[c]
5	**1e**	H	Br	PMP[e]	D	**7.1**	52[f]	(exo)
						7.2	5[f]	

[a] Method C (one pot/one step): CuCl (10%), $MeCN/CH_2Cl_2$, 45 °C, 16 h, imine/acyl chloride/stannane = 1:1.3:2.0. Method D (one pot/two steps): (i) CuCl (10%), $MeCN/CH_2Cl_2$, 45 °C, 16 h, imine/acyl chloride/stannane = 1:1.3:2.0; (ii) remove solvents under reduced pressure; (iii) toluene, 110 °C, 16 h. [b] dr = major/minor diastereomers as shown. [c] Trace quantities of a third diastereomer were detected in the inseparable mixture of two diastereomers. [d] Allyl = $CH_2CH{=}CH_2$. [e] PMP = *p*-$MeOC_6H_4$. [f] Yield of an isolated single diastereomer.

diastereomer[16] (entry 1, Table 2). Imine **1c** gave a mixture of four diastereomers of isoindolone **10** consisting of a major, a minor, and two trace diastereomers[16] (entry 2, Table 2). Experiments outlined in entries 3−6 (Table 2) demonstrate for the first time a successful coupling with substituted acryloyl chlorides, as well as a minimal effect of the additional substitution on the rates of intramolecular Diels−Alder reactions.[6] The coupling of imine **1a** with the α-substituted acryloyl chloride and 1-butadienyl(tributyl)stannane proceeded in one step (method C) to afford isoindolone **11** (66%, entry 3, Table 2). The one-pot/two-step protocol (method D) afforded good yields of isoindolones **12**−**14** from the reactions of imines **1c**, **1b**, and **1a** with *β*-substituted acryloyl chloride and 1-butadienyl(tributyl)stannane (entries 4−6, Table 2). Isoindolone **11** was isolated as a mixture of two (major and minor) inseparable diastereomers accompanied by traces of a third unidentified diastereomer.[13] In contrast, a single diastereomer of isoindolones **12**−**14** was produced. Crystallization of the mixture of diastereomers **11** afforded a single crystal of the major diastereomer **11.1**, and a single crystal of isoindolone **13** has also been obtained. X-ray crystallographic analyses indicated the *exo* stereochemistry in both the heterocycles **11.1** and **13**, with opposite configurations at the C3a carbons[17] (Table 2). The relative stereochemistry in the major diastereomers of heterocycles **3**−**7**, **9**−**10**, **12**, and **14** was assigned on the basis of comparable values of the key *J* coupling constants with the values for isoindolone **13** (Tables 1 and 2).[18] The available spectral data did not permit an unequivocal assignment of the relative stereochemistry at the remote C-6 stereocenter in isoindolones **9**−**10**, and the stereochemistry of the minor and trace diastereomers.[13,18]

The configurations of the major products suggest the operation of transition states **VII** and **VIII** (Figure 2). The relative

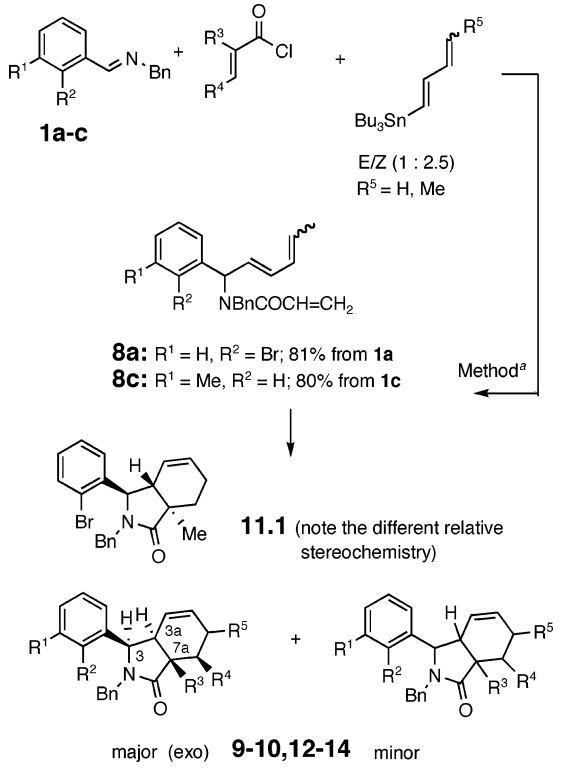
(14) The values of the coupling constants $J^{3a,7a}$ and $J^{3,3a}$ for the major products **3**−**7.1** were analogous to those found for product **13** (see reference 18). In the major (*exo*) products **3**−**7.1**, the $J^{3a,7a}$ coupling constants equal approximately 7.0 Hz, and $J^{3,3a}$ coupling constants are in the range of 0−4.5 Hz. However, the structures of the minor products **3**−**7.2** could not be assigned. The following values for the coupling constants were found in the minor products: $J^{3a,7a}$ equal approximately 12.5 Hz, and $J^{3,3a}$ are approximately 7.5 Hz. Results of additional NOE experiments are presented in the Supporting Information.

(15) Wender, P.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967.

(16) The presence of additional diastereomers arises likely from the two different configurations at the C-6 position (R^5), reflecting the presence of *E*/*Z* isomers of the diene.

(17) The spectroscopic data available for the minor product **11.2** did not permit a conclusive assignment of the relative stereochemistry.

TABLE 2. Reactions with Substituted Acyl Chloride and Diene Building Blocks



	method[a]	R^1	R^2	R^3	R^4	R^5	prdt	yield (%)	dr[b]
1	E	H	Br	H	H	Me	**9.1**	69[c]	(exo)
							9.2	11[d]	
2	E	Me	H	H	H	Me	**10**	83	2.0:1[e]
3	C	H	Br	Me	H	H	**11**	66	7.0:1[f]
4	D	Me	H	H	Me	H	**12**	70[d]	(exo)
5	D	Br	H	H	Me	H	**13**	69[d]	(exo)
6	D	H	Br	H	Me	H	**14**	66[d]	(exo)

[a] Methods C and D (see Table 1). Method E (two pot/two steps): step 1: CuCl (10%), MeCN/CH_2Cl_2, 45 °C, 16 h, imine/acyl chloride/stannane = 1:1.3:2.0; step 2: toluene reflux (110 °C). [b] dr = molar ratio of major/minor diastereomers as shown; note the different structure of **11.1**. [c] Yield of an isolated mixture of the major diastereomer accompanied by traces of an additional diastereomer. Yield is based on amide **8a**. [d] Isolated yield of a pure single diastereomer. [e] Trace quantities of two additional diastereomers were detected in the inseparable mixture of two (major and minor) diastereomers. Yield is based on amide **8c**. [f] Trace quantities of a third diastereomer were detected in the inseparable mixture of two diastereomers. Structure of compound **11.1** shown indicates the different relative stereochemistry observed in this case.

stereochemistry at C3 and C3a is reversed in transition state **VIII**, apparently due to the presence of the α-methyl group in the amide side-chain, seeking to relieve the strain that would be caused by the eclipsed Me and Ar substituents (Figure 2).

Additional diversification of both the *m*-bromophenyl and *o*-bromophenyl substituted isoindolones was achieved via classical Pd-catalyzed carbon−carbon bond-forming reactions (Table 3).[7] Thus, Suzuki, Heck, and Sonogashira coupling to isoindolones **13** and **14** afforded the anticipated functionalized heterocycles **15**−**18** in excellent yields (70−95%), demonstrating the value of the protocol for the construction of diverse combinatorial libraries.

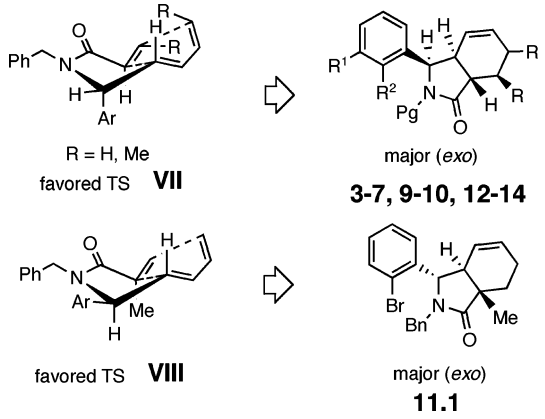
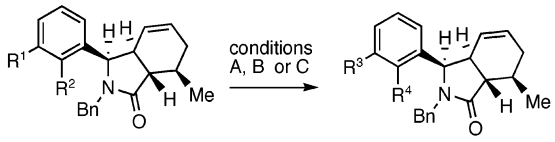
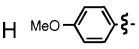
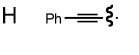
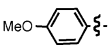


FIGURE 2. Proposed transition states for Diels−Alder reactions.

TABLE 3



	subst	condn[a]	R^1	R^2	R^3	R^4	prdt	yield (%)
1	**13**	A	Br	H		H	**15**	83
2	**13**	B	Br	H		H	**16**	70
3	**13**	C	Br	H		H	**17**	95
4	**14**	A	H	Br	H		**18**	88

[a] Conditions A: *p*-$MeOC_6H_4B(OH)_2$, $PdCl_2(PPh_3)_2$ (10%), K_2CO_3, DMF/H_2O, 60 °C, 12 h. [b] Conditions B: methyl acrylate, $Pd(OAc)_2$ (5%), Na_2CO_3, Bu_4NCl, DMF, 80 °C, 24 h. [c] Conditions C: phenylacetylene, $PdCl_2$ (20%), PPh_3 (40%), CuI (40%), diethylamine, 48 h.

In conclusion, a new convergent method for a rapid construction of hexahydro-1*H*-isoindolones via a tandem Cu-catalyzed three-component coupling/intramolecular Diels−Alder reaction has been described. The structures of the isoindolone products feature up to six substituents that can be diversified by the new protocol, showcasing the utility of α-*N*-substituted amides as templates in diversity oriented synthesis. Studies toward the application of the protocol to the construction of combinatorial libraries are ongoing.

Experimental Section

General Procedure for One-Pot/One-Step Synthesis of Isoindolones (Method C). A solution of the imine (0.5 mmol, 1.0 equiv) and acid chloride (0.65 mmol, 1.3 equiv) in acetonitrile (3 mL) was added to a solution of CuCl (5.0 mg, 0.05 mmol, 10 mol %) in acetonitrile (1 mL). A solution of the dienylstannane (1.0 mmol, 2.0 equiv) in methylene chloride (3 mL) was added, and the reaction mixture was heated to 45 °C overnight. The reaction mixture was then concentrated in vacuo and redissolved in ethyl acetate (50 mL).

(18) In the major (*exo*) products **9.1**−**10** and **12**−**14** the $J^{3a,7a}$ coupling constants equal approximately 7.0 Hz, and $J^{3,3a}$ coupling constants are in the range of 0−4.5 Hz (compare to data in reference 14). In the minor products **9.2**−**10**, the $J^{3a,7a}$ equals approximately 12 Hz, and $J^{3,3a}$ coupling constant are 7 Hz. Notably, the $J^{3,3a}$ coupling constant for isoindolone **11.1** equals 10.6 Hz. Results of additional NOE experiments are presented in the Supporting Information.

Saturated aqueous KF solution (15 mL) was added, the mixture was stirred for 2 h, and the resulting white solid was filtered off through Celite. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), solvents were removed in vacuo, and the crude product was purified by flash chromatography over silica eluting with ethyl acetate/hexanes (1:9 followed by 1:4) to afford the corresponding heterocycles.

(±)-(3*R*,3a*S*,7a*S*)-2,3,3a,6,7,7a-Hexahydro-3-(2-bromophenyl)-2-(phenylmethyl)-1*H*-isoindol-1-one (Exo) and 2,3,3a,6,7,7a-Hexahydro-3-(2-bromophenyl)-2-(phenylmethyl)-1*H*-isoindol-1-one (3). According to the general method C described above, isoindolone **3** was isolated as a pale yellow oil (0.141 g, 74%) as a mixture of major (exo) and minor diastereomers in a 5:1 ratio (containing trace amount of a third diastereomer detected by GC−MS): R_f = 0.26 (EtOAc/hexane 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (dd, J = 7.9 Hz, 1.2 Hz, 1 H), 7.45−6.90 (m, 8 H), 5.93 (dm, J = 10.0 Hz, 0.83 H), 5.82 (dm, J = 10.0 Hz, 0.17 H), 5.77 (dm, J = 10.0 Hz, 0.83 H), 5.48 (ddt, J = 10.0 Hz, 6.5 Hz, 3.2 Hz, 0.17 H), 5.27 (d, J = 14.8 Hz, 0.83 H), 5.17 (d, J = 14.8 Hz, 0.17 H), 5.02 (d, J = 7.7 Hz, 0.17 H, *H3*), 4.45 (br s, 0.83 H, *H3*), 3.59 (d, J = 14.8 Hz, 1 H), 2.98−2.88 (m, 0.17 H, *H3a*), 2.84 (dt, J = 7.2 Hz, 3.7 Hz, 0.83 H, *H7a*), 2.77−2.70 (m, 0.83 H, *H3a*), 2.47 (td, J = 12.5 Hz, 2.4 Hz, 0.17 H, *H7a*), 2.42−1.96 (m, 3 H), 1.74−1.61 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) and DEPT δ 176.5 (C), **175.9** (C), *175.6* (C), **138.6** (C), 136.4 (C), **135.9** (C), 134.4 (C), **133.7** (CH), 133.2 (CH), 130.2 (CH), **130.0** (CH), 129.6 (CH), 129.6 (CH), 129.5 (CH), **129.2** (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), **128.5** (3 CH), 128.5 (CH), **127.9** (CH), **127.8** (CH), **127.5** (CH), **126.7** (CH), **126.3** (CH), 124.8 (CH), 124.4 (CH), 124.0 (C), **123.3** (C), **64.8** (CH), 62.3 (CH), 60.9 (CH), 49.6 (CH), 46.2 (CH), 44.8 (CH_2), **44.7** (CH_2), 44.0 (CH), 51.5 (CH), **40.9** (CH), **38.1** (CH), 25.9 (CH_2), 22.3 (CH_2), **21.3** (CH_2), **20.2** (CH_2) (peaks of major isomers are printed in bold, and peaks of the third isomers (trace amount) are printed in *italic* if identifiable); IR (neat, cm^{-1}) 1695 (s); HRMS (ES$^+$) calcd for $C_{21}H_{21}BrNO$ (M + H$^+$), 382.0807, found 382.0789.

General Procedure for Two-Step Synthesis of Isoindolones. Method D (One Pot/Two Step). The three-component coupling reaction was run as described in method C, heating the reaction mixture at 45 °C overnight. Solvents were then 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, and 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 the corresponding isoindolones.

(±)-(3*R*,3a*S*,7*R*,7a*S*)-2,3,3a,6,7,7a-Hexahydro-3-(3-bromophenyl)-7-methyl-2-(phenylmethyl)-1*H*-isoindol-1-one (13). According to the general method D, described above, isoindolone **13** was isolated as a white solid (0.136 g, 69%): mp 168−170 °C (CH_2Cl_2/pentane); R_f = 0.42 (EtOAc/hexane 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (ddd, J = 8.0 Hz, 1.9 Hz, 1.0 Hz, 1 H), 7.32−7.25 (m, 5 H), 7.08 (d, J = 7.7 Hz, 1 H), 7.05−7.01 (m, 2 H), 5.81 (dtd, J = 10.0 Hz, 7.8 Hz, 1.7 Hz, 1 H, *H5*), 5.52 (ddt, J = 10.0 Hz, 3.4 Hz, 1.8 Hz, 1 H, *H4*), 5.23 (d, J = 14.9 Hz, 1 H, CH_2Ph), 3.98 (d, J = 4.5 Hz, 1 H, *H3*), 3.53 (d, J = 15.0 Hz, 1 H, CH_2Ph), 2.70−2.63 (m, 1 H, *H3a*), 2.57 (t, J = 7.1 Hz, 1 H, *H7a*), 2.27 (dm, J = 17.6 Hz, 1 H, *H6*α), 2.19 (heptet, J = 6.0 Hz, 1 H, *H7*), 1.80 (dm, J = 17.5 Hz, 1 H, *H6β*), 1.05 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) and DEPT δ 175.9 (C), 142.1 (C), 136.1 (C), 131.2 (CH), 130.6 (CH), 129.6 (CH), 128.5 (2 CH), 128.3 (CH), 128.0 (2 CH), 127.5 (CH), 125.2 (CH), 124.9 (CH), 123.2 (C), 65.8 (CH), 45.3 (CH), 44.3 (CH_2), 41.5 (CH), 30.2 (CH_2), 26.0 (CH), 19.1 (CH_3); IR (neat, cm^{-1}) 1695 (s); HRMS (ES$^+$) calcd for $C_{22}H_{23}BrNO$ (M + H$^+$), 396.0963, found 396.0955.

General Procedure for Suzuki Coupling (Conditions A). To a solution of isoindolone (0.1 mmol) in DMF/H_2O (0.6 mL, 5:1) were added sodium carbonate (0.2 mmol), boronic acid (0.2 mmol), and $PdCl_2(PPh_3)_2$ (0.01 mmol,10 mol %). The flask was flushed with Ar and sealed, and the reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was poured into water (3 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford the crude product, which was purified by flash chromatography over silica eluting with ethyl acetate/hexanes (1:4) to afford the isoindolones **15** or **18**. **(±)-(3*R*,3a*S*,7*R*,7a*S*)-2,3,3a,6,7,7a-Hexahydro-3-(3-*p*-methoxyphenylphenyl)-7-methyl-2-(phenylmethyl)-1*H*-isoindol-1-one (15).** According to conditions A described above, isoindolone **15** was isolated as a colorless oil (0.035 g, 83%): R_f = 0.31 (EtOAc/hexane 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.54 (m, 1 H), 7.53 (d, J = 8.8 Hz, 2 H), 7.45 (t, J = 7.6 Hz, 1 H), 7.33−7.26 (m, 4 H), 7.10 (d, J = 7.6 Hz, 1 H), 7.09−7.05 (m, 2 H), 7.01 (d, J = 8.8 Hz, 2 H), 5.82 (dtd, J = 10.0 Hz, 3.8 Hz, 1.7 Hz, 1 H, *H5*), 5.58 (ddt, J = 10.0 Hz, 3.4 Hz, 1.8 Hz, 1 H, *H4*), 5.25 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.10 (d, J = 4.7 Hz, 1 H, *H3*), 3.89 (s, 3 H, OCH_3), 3.61 (d, J = 14.8 Hz, 1 H, CH_2Ph), 2.79−2.72 (m, 1 H, *H3a*), 2.62 (t, J = 7.2 Hz, 1 H, *H7a*), 2.28 (dm, J = 17.5 Hz, 1 H, *H6*α), 2.21 (hept, J = 6.1 Hz, 1 H, *H7*), 1.81 (dm, J = 17.3 Hz, 1 H, *H6β*), 1.17 (d, J = 6.8 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 159.4, 141.6, 140.0, 136.4, 133.0, 129.4, 128.5 (2 CH), 128.2 (2 CH), 128.0 (2 CH), 128.0, 127.4, 126.4, 125.2, 124.9, 124.8, 114.3 (2 CH), 66.4, 55.4, 45.6, 44.2, 41.7, 30.3, 26.1, 19.2; IR (neat, cm^{-1}) 1690 (s); HRMS (ES$^+$) calcd for $C_{29}H_{30}NO_2$ (M + H$^+$), 424.2277, found 424.2267.

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Supporting Information Available: Description of the synthesis and characterization of all new compounds, including data from NOE experiments, and X-ray data for compounds **11.1** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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