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Solid-phase synthesis of isoindolinones and naturally-occurring benzobutyrolactones (phthalides) using a cyclative-cleavage approach

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Abstract—Starting from Merrifield resin, 2-formylbenzoic acids were immobilized on solid supports. Reactions between immobilized 2-formylbenzoic acids and different organometallic reagents (Grignard reagents, zinc reagents, allyl silanes via Sakurai type reactions) furnished secondary alcohols which cyclized depending on the metal counter ion and reaction conditions, forming benzoannelated lactones. Asymmetric synthesis was possible on the resin using chiral [2.2]paracyclophane ligands. While the reaction of immobilized *ortho*-carboxy benzaldehydes with primary amines at elevated temperatures yielded 3-hydroxyisoindolinones, a reaction at ambient temperature allowed imine formation, which underwent 1,2-addition-cleavage reaction with various nucleophiles, yielding isoindolinones with three points of diversity.
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1. Introduction

Natural products play a pivotal role in modern drug discovery. Therefore, the access to natural product libraries remains one of the foundations in this progress.[1,2]

Among the class of oxygen heterocycles, benzoannelated butyrolactones (phthalides) are present in various natural products.[3]

In particular, the 3-alkylated phthalides are present in some natural products such as Fuscinarin,[4] 3-butylphthalide, (−)-hydrastine ((−)-narcotine),[5] (−)-noscapine,[6] (−)-typhaphthalide,[7] spirolaxine,[8] (+)-monascodilone,[9] isoochracinic acid,[10] cryphonectric acid peracetate methyl ester,[11] vermistatin,[12] (−)-rubiginone-H,[13] alcyopterosin E,[14] and cytosporone E[15] (Fig. 1). Phthalides, such as the aforementioned, possess a wide range of biological activity. They are active at the opiod receptor ((−)-hydrastine), also known as the human CCR5 receptor, an important anti HIV-1 target, which interferes with HIV entry into cells (fuscinarin).[4] Some members of this group are cytotoxic (vermistatin, alcyopterosin E[14]) or antibacterial (e.g., cytosporone E[15] and related compounds[16]). 3-Butylphthalide, a constituent in the Chinese folk medicine extracted from celery seed oil,[17] reduces brain damage in mice.[18] It has been used for seasoning and flavoring purposes, shows anticonvulsant action,[19] increases the duration of anesthesia,[20] and exhibits cerebral antiischemic action.[21] Various naturally occurring phthalides, such as 3-butylphthalide from *Angelica sinensis* roots, or synthetic 3-alkenylphthalides showed muscle relaxant effects on animal tracheal smooth muscle, indicating that the phthalide moiety is the principal antiasthmatic component of phthalide derivatives of *Angelica* extractions.[22] In addition, the class of most of these chiral natural products are found only as one enantiomer. Because biological activity is strongly dependent on their configuration, synthesizing drugs and other biological compounds asymmetrically is highly desirable.

The analogous six-membered lactones are present in the very important class of ochratoxins (Fig. 2).[23]

Another class of potential biologically and pharmacologically active compounds are benzoannelated nitrogen heterocycles.[24] In this case, isoindolinones (phthalimidines) should be specifically mentioned.[25] taliscanine,[26] which occurs in the rhizomes of *Aristolochia taliscanina*, enterocarpam II,[27] isolated from the stem bark of *Orophea enterocarpa* (*Annoniacae*), or velutinam[28] from extracts of leaves and twigs of *Goniothalamus velutinus* belong to the aristolactams. Aristolactams are a minor group of

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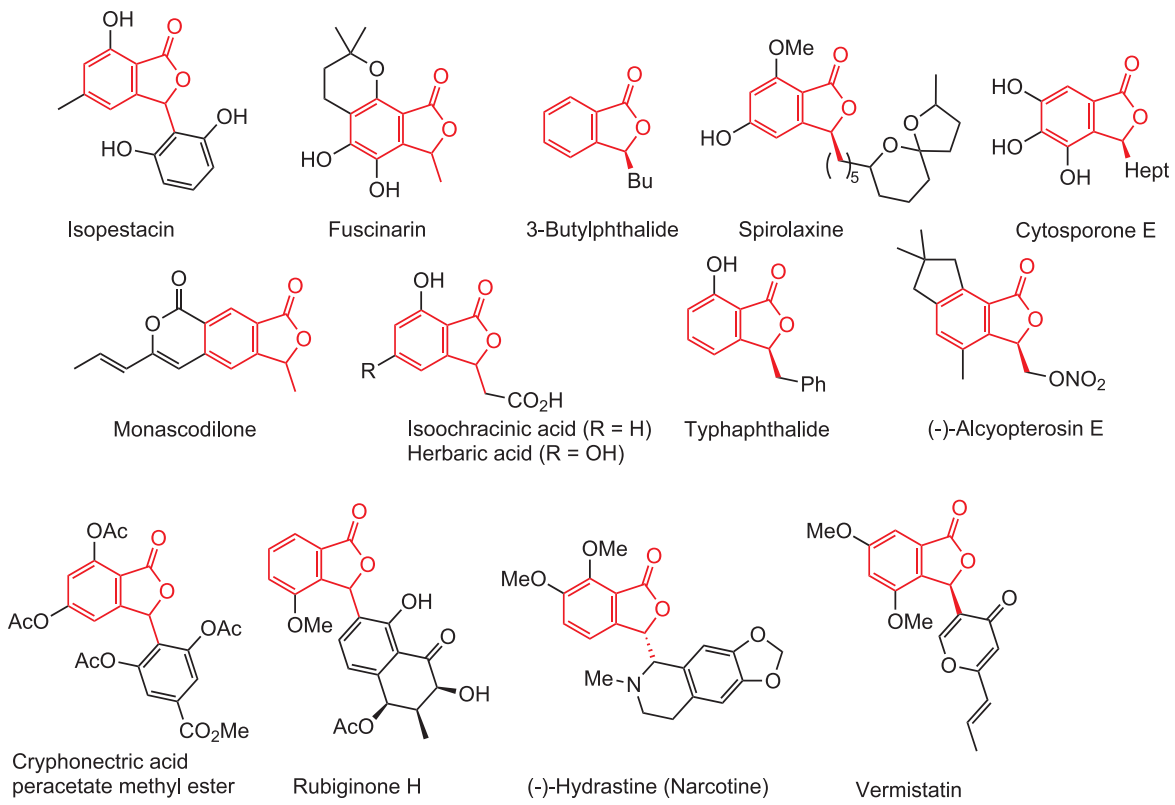


Figure 1. Some naturally occurring 3-alkyl and 3-aryl phthalides.

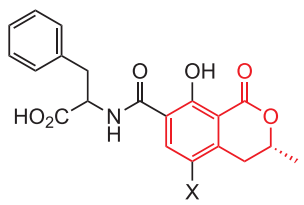


Figure 2. Structure of ochratoxins.

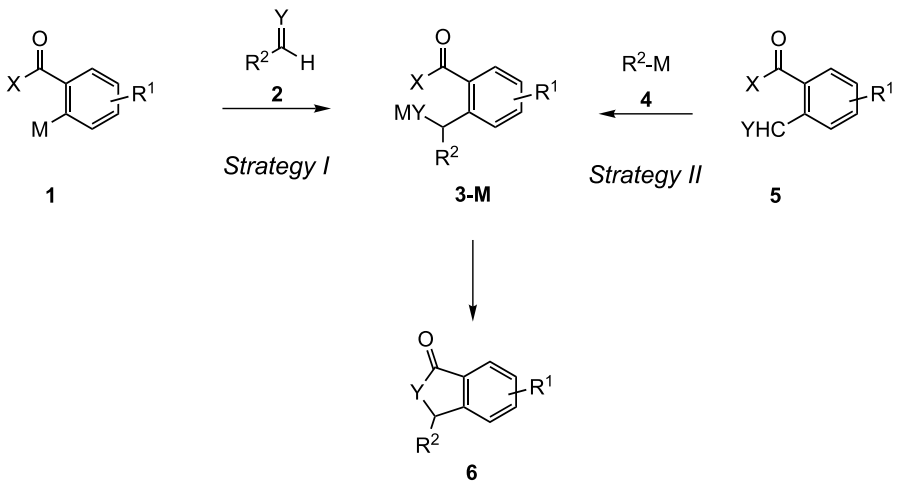
aporphinoid alkaloids biogenetically derived from isoquinolines. Phenanthrene lactams are used in folk medicine[29] as immunostimulant and anticancer agents.[30] The phenylidene derivative AKS 186 and its *O*-methylated analogue have been reported as inhibiting the thromboxane A2 analogue (U-46619)-induced vasoconstriction.[25a,b] Isoindolinone L-709,780 inhibits ADP-induced platelet aggregation with an IC_{50} of 27 nM.[31] In 1996, Egbertson et al. reported two- to three-fold improvement in potency over L-709,780 by introducing its sulfonamide derivatives.[32] Nofedone is an antiarrhythmic agent, it has been reported that in the treatment of ventricular arrhythmias, this drug was effective with quinidine-like action.[33] But one of the most famous representative compounds with a isoindolinone structure is thalidomide (Contergan®),[34] which is still used as a drug for the treatment of painful inflammations associated with leprosy,[35] rheumatoid arthritis,[36] and graft versus host disease (Fig. 3).[37]

For a modular synthesis of naturally occurring 3-substituted phthalides or isoindolinones, two strategies are applicable. The first originates with an *ortho* metallated ester **1** (X=OR), amide **2** ($X=NR_2$), or their synthon. Reaction with an aldehyde (**2**, Y=O) or an imine (**2**, Y=NR) and subsequent cyclization would lead to lactones **6** (Scheme 1, strategy I, Y=O) or isoindolinones **6** (Y=NR), respectively. This strategy has been used for the solid phase synthesis of phthalides.[38]

The other strategy is based on formyl-substituted benzoic acid derivatives **5** (Y=O) or their imines (Y=NR). Treatment with organometallic reagents such as alkyl lithium,[39] alkyl zinc,[40] alkyl sodium,[41] alkyl titanium,[42] or Grignard reagents[43] furnishes during or after acidic treatment the corresponding 3-substituted lactones (Scheme 1, strategy II, Y=O) or isoindolinones **6** (Y=NR), respectively. The second strategy is particularly interesting for an asymmetric variant, since the organometallic species can be purified before use (e.g., removal of salts) and can also be symmetric in the case of divalent metals (e.g., R_2Zn).

Since the required 2-formyl benzoic acids building blocks can be readily immobilized via an ester linkage, we decided to investigate this reaction on solid supports. Our primary intention was to examine the scope and limitation of this cyclization/cleavage approach with different nucleophiles. Simple starting materials were chosen as model compounds.

Therefore, commercially available 2-formyl benzoic acids **8** and **9** were immobilized on Merrifield resin **7** using standard conditions. To our knowledge, these resins have not been prepared before (Scheme 2).



Scheme 1. Strategies for the synthesis of 3-substituted phthalides (Y=O) and isoindolinones (Y=NR).

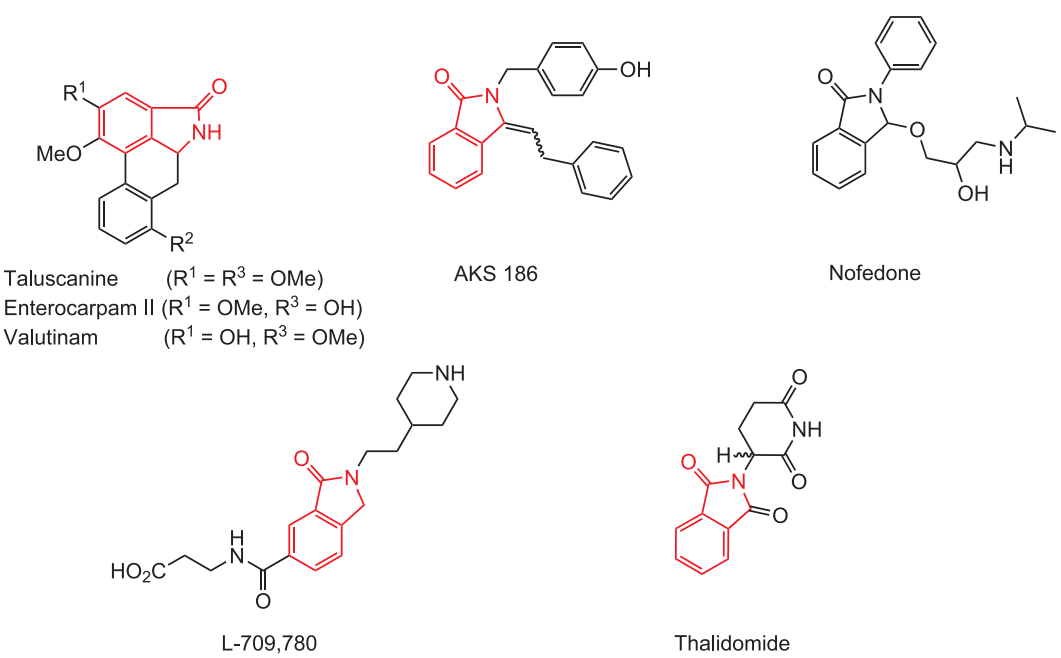
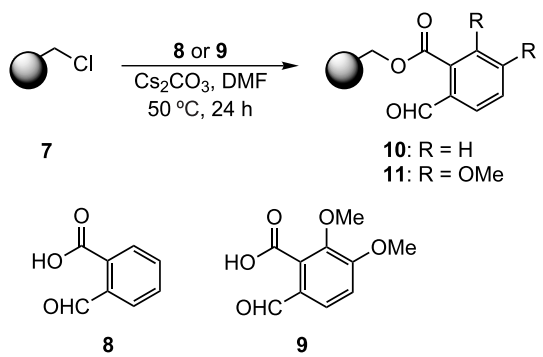


Figure 3. Natural products and biologically and pharmacologically active isoindolinones.

The resin **10** was then reacted with different organometallic reagents under various conditions (Tables 1–4). Reactions with lithium reagents (MeLi, EtLi, BuLi) led to cleavage at low temperature (−70 °C). However, an inseparable mixture of various alcohols was also isolated. In contrast, Grignard reagents react at low temperature (−70 °C) selectively to give the phthalides **13** in good purities, with the exception of ethyl magnesium chloride being not reactive enough for addition/cleavage at this temperature. It is important to note that the reaction at higher temperature with various Grignard reagents results in an addition reaction to the ester, which produces tertiary alcohols **15**. Reduction of the formyl group to a hydroxymethyl group to give benzyl alcohols **14** was also observed for ethyl magnesium chloride (Scheme 3).



Scheme 2. Immobilization of the benzoic acids **8** and **9** on Merrifield resin **7**.

Zinc reagents react at higher temperature in the presence of an amino alcohol such as *N*,*N*-dimethylamino ethanol selectively to give the phthalides **13b–d** in good purities and moderate overall yields. The formation of a reduction product or addition to the carbonyl group was not observed (Scheme 4).

Table 1. Addition of Grignard reagents to resin **10** (see Scheme 3)

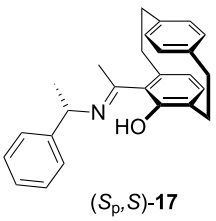
Grignard reagent	Solvent	T (°C)	t (h)	Product	R	Yield (%)[a]	Purity (%)[b]
MeMgCl	THF	−70	20	**13a**	Me	15	89
MeMgCl	THF	−10	20	**15a**	Me	36	n.d.
EtMgCl	THF	−70	20	—[c]	Et	—	—
EtMgCl	THF	−10	20	**14a/15a**	Et	17/11	n.d.
*i*PrMgCl	THF	−70	20	**13c**	*i*Pr	16	87
*i*PrMgCl	THF	−10	20	—[d]	*i*Pr	—	—
*n*BuMgCl	THF	−70	20	**13d**	*n*Bu	23	85
*n*BuMgCl	THF	−10	20	**15d**	*n*Bu	27	n.d.
PhMgCl	THF	−70	20	**13e**	Ph	13	85
(*E*)-$CH_3CH{=}CHMgCl$	THF	−70	20	**13f**[22,27]	$CH{=}CHCH_3$	15	74

[a] Overall isolated yields of purified compounds.
[b] Purity of the crude mixture after cleavage determined by GC.
[c] No conversion was observed.
[d] Inseparable mixture of products.

Table 2. Addition of zinc reagents to resin **10**

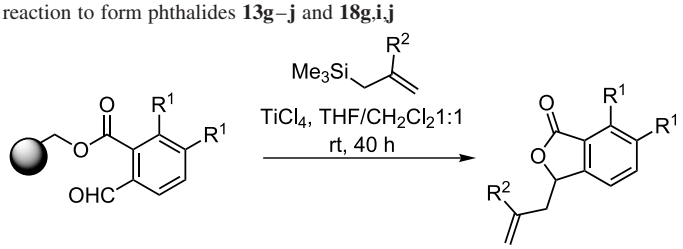
R_2Zn	Ligand	Product	Yield (%)[a]	Purity (%)[b]	ee (%)[c]
Me_2Zn	(S_p,*S*)-**17**	**13a**	—[d]	—	—
Et_2Zn	Dimethylamino ethanol	**13b**	14	80	0
Et_2Zn	(S_p,*S*)-**17**	**13b**	21	85	37
iPr_2Zn	(S_p,*S*)-**17**	**13c**	19	88	60
nBu_2Zn	Dimethylamino ethanol	**13d**	35	82	0
nBu_2Zn	(S_p,*S*)-**17**	**13d**	25	86	35

[a] Overall isolated yields of purified compounds.
[b] Purity of the crude mixture after cleavage determined by GC.
[c] Determined on a chiral stationary phase.
[d] No conversion was observed.



(S_p,*S*)-**17**

Table 3. Sakurai-type reaction to form phthalides **13g–j** and **18g,i,j**



10 (R^1 = H)
11 (R^1 = OMe)

13g-j (R^1 = H, R^2 = H, CH_2OCOCH_3, CH_2Cl, $SiMe_3$)
18g,i,j (R^1 = OMe, R^2 = H, CH_2Cl, $SiMe_3$)

Resin	R^1	R^2	Product	Yield (%)	Purity (%)
10	H	H	**13g**	73	95
10	H	CH_2OCOCH_3	**13h**	67	85
10	H	CH_2Cl	**13i**	69	90
10	H	$SiMe_3$	**13j**	51	86
11	OMe	H	**18g**	51	88
11	OMe	CH_2Cl	**18i**	24	76
11	OMe	$SiMe_3$	**18j**	60	75

At this point, it should be noted that it is important to exclude any air from the system due to the formation of alkoxides, which lead to acetals **16** in 19% yield.[44] However, the main advantage of using zinc reagents is, the possibility of stereoinduction by using chiral ligands. In 2001 and 2002, we introduced the [2.2]paracyclophane ketimine system as an effective ligand system for the asymmetric 1,2-addition of zinc reagents to aldehydes[45] and imines.[46] In the presence of ligand (S_p,*S*)-**17**, scalemic phthalides were isolated in moderate yields. Unfortunately, the enantiomeric excess was quite low compared to solution phase experiments.[45] Further studies are necessary to investigate these results. The introduction of Me_2Zn did not result in the desired product **13a**. To our knowledge, this is the first asymmetric addition of zinc reagents to polymer-bound aldehydes.

The third method involves a Sakurai-type addition of allyl silanes to resin **10**. The Sakurai reaction has seldom been applied to solid-phase synthesis. To our knowledge only

Table 4. Addition of primary amines to resins **10** and **11**

Resin	R^1	R^2	Product	Yield (%)
10	H	Me	**19**	90[a]
10	H	*n*Pr	**20b**	76[a]
10	H	Allyl	**20c**	77[a]
10	H	*c*Pr	**20d**	97[a]
10	H	*c*Hex	**20e**	82[a]
10	H	Bn	**20f**	75[b]
10	H	(*S*)-Phenylethyl	**20g**	22[b]
11	MeO	*n*Pr	**21b**	40[a]
11	MeO	Allyl	**21c**	17[a]
11	MeO	*c*Pr	**21d**	49[a]

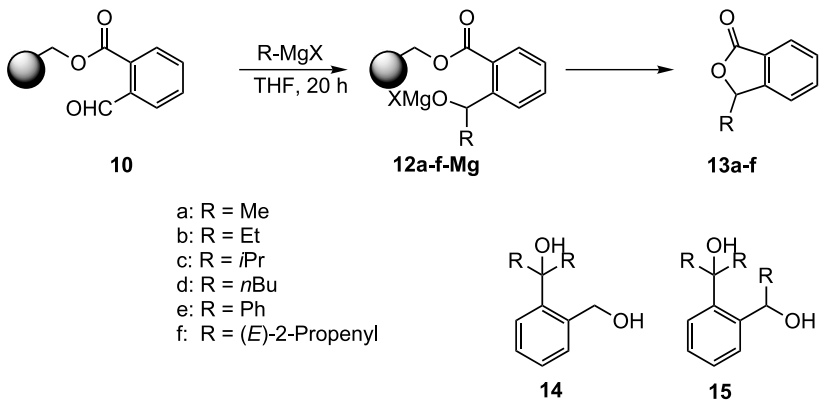
[a] Overall isolated yields of purified compounds. Purity of the crude mixture after cleavage determined by NMR-spectroscopy or GC >95%.
[b] Purity of the crude mixture not determined.

resin-bound allyl silanes have been used in similar studies.[47] Treatment of resin **10** with allyltrimethyl silanes in the presence of five equivalents of titanium tetrachloride the phthalides **13g–j**[48] were obtained in good yields and excellent purity. The Sakurai reaction was also accomplished with allyltrimethyl silanes and immobilized 6-formyl-2,3-dimethoxy benzoic acid (**11**), yielding the corresponding phthalides **18g–j** in good purities and moderate yields.

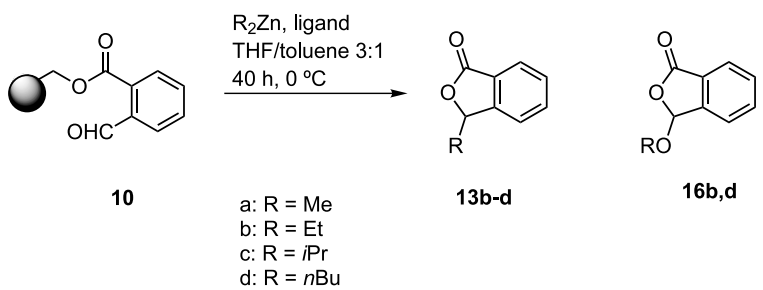
Primary amines were chosen as the next set of nucleophiles. In 2002, Ley and Taylor reported the introduction of *ortho*-carboxy benzaldehyde (**8**) and various primary amines in liquid phase synthesis of isoindolinones.[49] Reactions of resins **10** or **11** with primary amines produce 3-hydroxy-*N*-alkylisoindolinones **19**[50] or 3-alkylamino-*N*-alkylisoindolinones **20b–g** and **21b–d** with branched amines. Presumably, the cyclative cleavage of semiaminal **22** proceeds slower with sterically hindered amines leading to the formation of imines. The isoindoles **20** and **21** are interesting building blocks for further derivatization (Scheme 5).[51]

With these results in hand, we tried to interrupt the reaction on the intermediate immobilized imine **23b** and **23c** stage in order to add different nucleophiles. The addition of the *N*-nucleophile Et_2NH yielded excellent purities but low yields to the isoindolinones **25b** and **25c**. By addition of methanolate as nucleophile an isomerization of the double bond of the allyl moiety after cyclative-cleavage was observed. The isoindolinone **26** was isolated in an *E*/*Z*-ratio of 3:1 and purity higher than 98% was achieved after aqueous workup. However, no *C*-nucleophile reacted with the imine at different temperatures (up to room temperature). The cleavage with NaOMe of imine resins **23** which subsequently treated with Et_2Zn yielded in product (*E*)-**26**. This experiment shows that no reaction with Et_2Zn previously took place. In contrast, no product was found even after cleavage with NaOMe of the resins from the Grignard addition (Table 5).

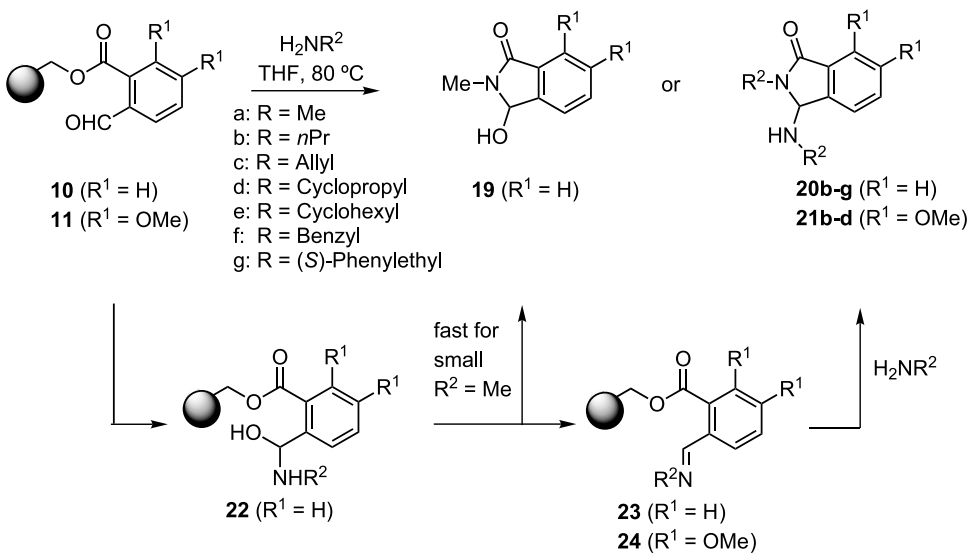
In conclusion, we presented the synthesis of phthalides via reaction of polymer-bound 2-formyl benzoic acids with different organometallic reagents (Grignard reagents, zinc reagents, allyl silanes). We also demonstrated that asymmetric induction was achieved by using chiral ligands. Isoindolinones, which represent an important scaffold for biologically active compounds are accessible from primary amines and different nucleophiles. Future work is dedicated to the application of more complex resins, their transformation on solid supports and the use of acylbenzoic acids.



Scheme 3. Solid-phase synthesis of 3-alkyl, 3-aryl and 3-alkenyl phthalides.

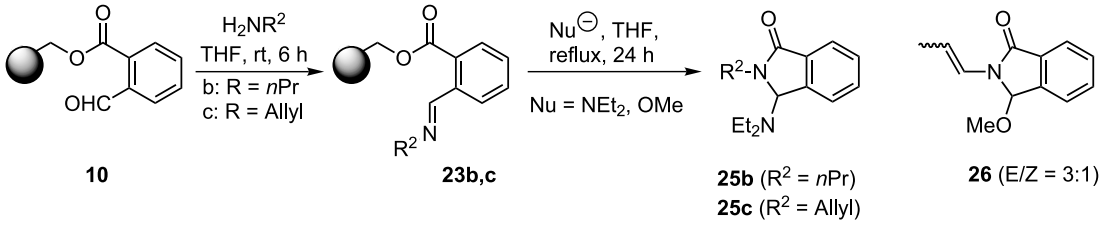


Scheme 4. Synthesis of phthalides using zinc reagents.



Scheme 5. Addition reactions of primary amines to form 3-hydroxy-isoindolinones **19** or 3-alkylamino-isoindolinones **20b–g** and **21b–d**.

Table 5. Addition of different nucleophiles to immobilized imine **23**



R^2NH_2	Nucleophile (NuX)	Product	Purity (%)[a]	Yield (%)[b]
nPrNH$_2$	Et$_2$NH	**25b**	94	10
AllylNH$_2$	Et$_2$NH	**25c**	92	12
AllylNH$_2$	MeONa	**26**	>98[c]	35[d]

[a] Purity of the crude mixture.
[b] After purification.
[c] After aqueous work-up.
[d] Combined yield of the *E*/*Z*-mixture.

2. Experimental

^{1}H NMR: Bruker DP 300 (300 MHz), Bruker DP 400 (400 MHz); δ=2.50 ppm for [D$_5$] dimethylsulfoxide, 3.31 ppm for [D$_3$] methanol, 7.24 ppm for CHCl$_3$. Description of signals: s=singlet, bs=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet, mc=centered multiplet, dd=doublet of doublet, ddd=doublet of dd, dt=doublet of triplets, dq=doublet of quartets, tt=triplet of triplets, ca=complex area. The spectra were analyzed according to first order. All couplings constants are absolute values. Abbreviations for signals: Ar-H=Ar. ^{13}C NMR: Bruker DP 300 (75 MHz), Bruker DP 400 (100 MHz); δ=39.52 ppm for perdeuterodimethylsulfoxide, 77.20 ppm for deuterochloroform, 49.00 for perdeuteromethanol. The signal structure was analyzed by DEPT and described as follows: +=primary or tertiary C-atom (positive signal), −=secondary C-atom (negative signal), and q=quaternary C-atom (no signal). IR (infrared-spectroscopy): Perkin Elmer FT-IR 1750. The substances were dissolved in distilled dichloromethane. The resins were measured as KBr pellets on a Bruker IFS88 IR. ps=polystyrene. MS (mass spectroscopy): EI-HRMS (electronic ionization—high resolution mass spectroscopy): Kratos MS 50 (70 eV) and Thermo Quest Finnigan MAT 95 XL (70 eV). GC (gas chromatography) analytical: Hewlett–Packard HP 5890 Series II 12 m×0.25 mm capillary column HP I (carrier gas N$_2$). HPLC: Varian WCOT fused silica 25 m×0.25 mm, coating CP chiral-dex CB DF=0.25. TLC (thin layer chromatography): Silica gel coated aluminium plates (Merck, silica gel 60, F$_{254}$). Detection under UV-light at 254 nm, displayed with molybdato phosphate (5% phosphor molybdic acid in ethanol, dipping solution), and potassium permanganate (0.45 g potassium permanganate and 2.35 g of sodium carbonate in 90 ml of water, dipping solution). Elemental analysis: elementar vario EL at the Mikroanalytisches Labor des Instituts für Organische Chemie der Universität Bonn. Reaction without nominated temperature were done at room temperature (rt). Solid materials, except resins, were powdered. All Chemicals, solvents, and reagents were purchased from Acros, Aldrich, Fluka, Janssen, or Merck. The Merrifield resin (1–2% cross-linked, 200–400 mesh) was obtained from Polymer-Laboratories with loading=1.06 g mol^{-1}. All resins were

washed sequentially by using a vacuum reservoir connected to a sintered glass frit. Cleavage was conducted using Teflon tubes with a frit connected to a vacuum line, with a glass pipette filled with glass wool, or were simply paper-filtered. Evaporation of the solvent was achieved using a rota-vapor and/or under a high vacuum (ca. 0.1 mbar). All solvents were dried by usual methods and distilled under argon. General washing procedure: (methanol, THF, pentane, dichloromethane) three times; (methanol, DMF, pentane, THF) once and (pentane, dichloromethane, pentane) two times.

2.1. General procedure for the attachment of benzoic acids to the merrifield resin

In a three-necked round bottom flask equipped with a mechanical stirrer, 9.70 g (30.0 mmol) of cesium carbonate was suspended in DMF and stirred for 10 min. Then, *ortho*-carboxybenzaldehyde **8** or **9** (30.0 mmol) was added and the mixture was once again stirred for 10 min. Afterwards, 10.0 g (10.6 mmol, loading 1.06 mmol/g) of Merrifield resin were added, and the mixture was stirred for 24 h at 50 °C. The mixture was allowed to reach room temperature. The resin was filtered off, washed with water, followed by the general washing procedure, and dried under high vacuum.

2.1.1. 2-Formylphenylcarboxymethyl polystyrene (10). IR (KBr): 3575 (m, ps), 3384 (vs), 3082 (m, ps), 3026 (m, ps), 2928 (s, ps), 2849 (m), 2761 (m), 2546 (s), 2254 (m), 1946 (m, ps), 1873 (m, ps), 1804 (m, ps), 1718 (vs, ps), 1596 (m), 1494 (m, ps), 1450 (m, ps), 1374 (m), 1268 (s, ps), 1193 (m, ps), 1132 (m), 1087 (m), 964 (m, ps), 907 (m, ps), 855 (m), 769 (m, ps), 706 (m, ps) cm^{-1}. Elemental analysis: found C: 88.01, H: 7.462.

2.1.2. 2-Formyl-5,6-dimethoxyphenylcarboxymethyl polystyrene (11). IR (KBr): 3573 (m, ps), 3060 (m, ps), 3026 (m, ps), 2926 (s, ps), 2761 (m), 2601 (m), 2337 (m), 1944 (s, ps), 1873 (m, ps), 1803 (m, ps), 1742 (vs, ps), 1600 (s), 1493 (s, ps), 1452 (m, ps), 1425 (m), 1372 (m), 1280 (m, ps), 1181 (m, ps), 1146 (m), 1053 (m), 967 (m, ps), 907 (m, ps), 841 (m), 816 (m), 762 (m, ps), 705 (s, ps) cm^{-1}. Elemental analysis: found C: 86.79, H: 7.478.

2.2. Synthesis of lactones 13a–j, 18 g,j

2.2.1. 1,2-Addition of organo lithium and organo magnesium reagents. The resin **10** was suspended in THF (20 ml/mmol resin), flushed with argon (crucial), and cooled to −70 or −10 °C. Five equivalents of the organo lithium or organo magnesium reagent were added. The reaction vial was occasionally shaken over a period of 20 h at constant temperature. The reaction was then quenched with 1 M HCl (aq.) The organic phase was separated, washed with water, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the product was then purified by flash column chromatography on silica with *n*-pentane/diethyl ether (4:1) as eluent.

2.2.2. 1,2-Addition of organo zinc reagents promoted by achiral and chiral *N,O*-ligands. The resin **10** was suspended in THF (20 ml/mmol resin), flushed with argon, and cooled to 0 °C. Proportional to the amount of resin, 20 mol% of the *N,O*-ligand **17** or *N,N*-dimethylamino ethanol were dissolved in toluene (5 ml/mmol resin). After stirring for a few minutes, 5 equiv (related to the amount of resin) of the zinc reagent were added to the *N,O*-ligand solution. The zinc reagent/ligand-solution was stirred for one hour at room temperature and then added to the resin suspension at 0 °C. The reaction was quenched after 40 h at 0 °C with 1 M HCl (aq.). The organic phase was separated, washed with water, and dried over $MgSO_4$. After removing the solvent under reduced pressure, the product was purified by flash column chromatography on silica with *n*-pentane/diethylether (4:1) as the eluent.

2.3. Sakurai reaction

The resin **10** was suspended in THF (20 ml/mmol resin) and the mixture flushed with argon. Five equivalents of a 1 M solution of $TiCl_4$ in CH_2Cl_2 were added. After shaking for 2 h 5 equiv of allyl silane were added and the reaction mixture was shaken for 40 h at room temperature. Then, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with diethyl-ether. The organic phase was washed with brine and dried with $MgSO_4$. After removing the solvent under reduced pressure, the product was purified by flash column chromatography on silica with *n*-pentane/diethyl-ether (4:1) as the eluent.

2.3.1. 3-Methyl-3*H*-isobenzofuran-1-one (13a). Yellow oil, 15% (from MeMgCl). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.62 (d, ^3J=6.70 Hz, 3H, CH_3), 5.54 (q, ^3J=6.70 Hz, 1H, 3-H), 7.42 (dd, ^3J=7.58 Hz, ^4J=0.76 Hz, 1H, 5-H), 7.42 (tt, ^3J=8.21 Hz, ^4J=0.76 Hz, 1H, 4-H), 7.66 (dt, ^3J=7.46 Hz, ^4J=1.02 Hz, 1H, 6-H), 7.88 (d, ^3J=7.71 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.6 (+, CH_3), 77.9 (+, C-3), 121.7 (+, C-6), 125.9 (+, C-4), 126.0 (q, C-7a), 129.2 (+, C-7), 134.2 (+, C-5), 151.4 (q, C-3a), 170.6 (q, C-1). IR (CH_2Cl_2): ν=1763 (CO), 1608 (arene) cm^{-1}. MS (EI), *m/z* (%)=148 (M^+, 25), 133 (60), 105 (100), 77 (35). HRMS ($C_9H_8O_2$): Calcd 148.0524, found 148.0533.

2.3.2. 3-Ethyl-3*H*-isobenzofuran-1-one (13b). Yellow oil, 21% (37% ee, from Et_2Zn). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.98 (t, ^3J=7.3 Hz, 3H, CH_3), 1.81 (ddq, ^3J=14.6, 7.3, 7.3 Hz, 1H, CH_2), 2.10 (ddq, ^3J=14.6, 7.3, 4.4 Hz, 1H, CH_2), 5.43 (dd, ^3J=7.07, 4.4 Hz, 1H, 3-H), 7.41 (dd, ^3J=7.52 Hz, ^4J=0.82 Hz, 1H, 5-H), 7.50 (tt, ^3J=7.52 Hz, ^4J=0.76 Hz, 1H, 4-H), 7.65 (dt, ^3J=8.53 Hz, ^4J=1.07 Hz, 1H, 6-H), 7.88 (d, ^3J=7.70 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=9.0 (+, CH_3), 27.9 (−, CH_2), 82.5 (+, C-3), 121.9 (+, C-6), 125.9 (+, C-4), 126.7 (q, C-7a), 129.2 (+, C-7), 134.1 (+, C-5), 149.3 (q, C-3a), 170.8 (q, C-1). IR (CH_2Cl_2): ν=1762 (CO), 1616 (arene) cm^{-1}. MS (EI), *m/z* (%)=162 (M^+, 15), 133 (100), 105 (25), 77 (10). HRMS ($C_{10}H_{10}O_2$): Calcd 162.0681, found 162.0672.

2.3.3. 3-Isopropyl-3*H*-isobenzofuran-1-one (13c). Yellow oil, 16% (from *i*PrMgCl), 27% (60% ee, from iPr_2Zn). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.79 (d, ^3J=6.79 Hz, 3H, CH_3), 1.11 (d, ^3J=6.97 Hz, 3H, CH_3), 2.26 (m, 1H, CH), 5.34 (d, ^3J=3.77 Hz, 1H, 3-H), 7.42 (dd, ^3J=7.54 Hz, ^4J=0.76 Hz, 1H, 5-H), 7.50 (t, ^3J=7.54 Hz, 1H, 4-H), 7.64 (dt, ^3J=7.35 Hz, ^4J=1.13 Hz, 1H, 6-H), 7.88 (d,

^3J=7.54 Hz, 1H, 7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.9 (+, CH_3), 18.9 (+, CH_3), 32.6 (+, CH), 85.8 (+, C-3), 122.3 (+, C-6), 125.9 (+, C-4), 127.0 (q, C-7a), 129.2 (+, C-7), 134.0 (+, C-5), 149.1 (q, C-3a), 171.0 (q, C-1). IR (CH_2Cl_2): ν=1762 (CO), 1616 (arene) cm^{-1}. MS (EI), *m*/*z* (%)=176 (M^+, 15), 133 (100), 105 (20), 77 (10), 51 (5). HRMS ($C_{11}H_{12}O_2$): Calcd 176.0837, found 176.0840.

2.3.4. 3-*n*-Butyl-3*H*-isobenzofuran-1-one (13d). Yellow oil, 23% (from *n*BuMgCl, 31% (35% ee, from nBu_2Zn). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.89 (t, ^3J=7.16 Hz, 3H, CH_3), 1.31–2.10 (ca, 6H, 3×CH_2), 5.45 (dd, ^3J=7.71, 7.71, 4.15 Hz, 1H, 3-H), 7.41 (dd, ^3J=7.53 Hz, ^4J=0.75 Hz, 1H, 5-H), 7.50 (t, ^3J=7.53 Hz, 1H, 4-H), 7.64 (dt, ^3J=7.54 Hz, ^4J=1.13 Hz, 1H, 6-H), 7.87 (d, ^3J=7.73 Hz, 1H, 7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (+, CH_3), 22.2 (−, CH_2), 27.1 (−, CH_2), 34.7 (−, CH_2), 81.6 (+, C-3), 121.9 (+, C-6), 125.9 (+, C-4), 126.4 (q, C-7a), 129.2 (+, C-7), 134.1 (+, C-5), 150.3 (q, C-3a), 170.8 (q, C-1). IR (CH_2Cl_2): ν=1773 (CO), 1615 (arene) cm^{-1}. MS (EI), *m*/*z* (%)=190 (M^+, 5), 175 (5), 133 (100), 105 (20), 77 (10). HRMS ($C_{12}H_{14}O_2$): Calcd 190.0994, found 190.0991.

2.3.5. 3-Phenyl-3*H*-isobenzofuran-1-one (13e). Yellow oil, 13% (from PhMgCl). ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.29 (s, 1H, 3-H), 7.18–7.64 (ca, 8H, Ar-H), 7.86 (d, ^3J=7.58 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=82.8 (+, C-3), 123.0 (+, C-6), 129.0 (+, C-4), 126.7 (q, C-7a), 128.5 (+, C-2′, C-6′), 129.1 (+, C-4′), 129.9 (+, C-3′, C-5′), 130.5 (+, C-7), 133.1 (+, C-5), 137.3 (q, C-1′), 149.8 (q, C-3a), 170.6 (q, C-1). IR (CH_2Cl_2): ν=1768 (CO), 1663 (arene) cm^{-1}. MS (EI), *m*/*z* (%)=210 (M^+, 90), 165 (40), 152 (20), 133 (15), 105 (100), 77 (45). HRMS ($C_{14}H_{10}O_2$): Calcd 210.0681, found 210.0688.

2.3.6. 3-Propenyl-3*H*-isobenzofuran-1-one (13f). Yellow oil, 15% (from (*E*)-CH_3CH=$CHMgCl$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.94 (dd, ^3J=7.07 Hz, ^4J=1.70 Hz, 3H, CH_3), 5.33 (m, 1H, CH=C*H*CH_3), 5.94 (m, 1H, C*H*=$CHCH_3$), 6.23 (d, ^3J=9.09 Hz, 1H, 3-H), 7.35 (m, ^3J=7.70, 0.88 Hz, 1H, 4-H), 7.51 (dd, ^3J=7.45, 7.45 Hz, 1H, 5-H), 7.64 (dd, ^3J=7.58 Hz, ^4J=1.14 Hz, 1H, 6-H), 7.89 (d, ^3J=7.71 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9 (+, CH_3), 77.1 (+, C-3), 122.5 (+, C-6), 125.8 (+, C-4), 126.0 (+, *C*H=$CHCH_3$), 126.2 (q, C-7a), 129.4 (+, C-7), 131.8 (+, CH=*C*HCH_3), 134.3 (+, C-5), 149.9 (q, C-3a), 170.8 (q, C-1). IR (CH_2Cl_2): ν=1763 (CO), 1606 (arene) cm^{-1}. MS (EI), *m*/*z* (%)=174 (M^+, 60), 159 (100), 146 (35), 133 (30), 105 (50), 77 (30), 51 (15). $C_{11}H_{10}O_2$ HRMS: Calcd 174.0681, found 174.0683.

2.3.7. 3-Allyl-3*H*-isobenzofuran-1-one (13g). Yellow oil, 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.55–2.77 (ca, 2H, $(CH)_2CH_2$), 5.12 (dd, ^2J=5.46 Hz, ^3J=10.17 Hz, 1H, CH=C*H*H), 5.14 (dd, ^2J=5.46 Hz, ^3J=17.14 Hz, 1H, CH=CH*H*), 5.45 (dd, ^3J=5.93, 5.93 Hz 1H, 3-H), 6.72 (dddd, ^3J=16.95, 10.17, 7.16 Hz, 2H, C*H*=CH_2), 7.47 (m, 2H, 4-H, 5-H), 7.63 (dd, ^3J=7.53 Hz, ^4J=1.00 Hz, 1H, 6-H), 7.85 (d, ^3J=7.53 Hz, 1H, 7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=38.8 (−, $(CH)_2CH_2$), 80.3 (+, C-3), 119.8 (−, CH=*C*H_2), 122.1 (+, C-6), 125.8 (+, C-4), 126.4 (q, C-7a), 129.3 (+, C-7), 131.3 (+, *C*H=CH_2), 134.1 (+, C-5), 149.5 (q, C-3a), 170.4 (q, C-1). IR (CH_2Cl_2): ν=1764 (CO), 1616 (arene), 999 (CH=CH_2) cm^{-1}. MS (EI), *m*/*z* (%)=174 (M^+, 10), 133 (100), 105 (15), 91 (5), 77 (20), 51 (5). HRMS ($C_{11}H_{10}O_2$): Calcd 174.0681, found 174.0685.

2.3.8. 3-(2-Acetoxymethyl)allyl-3*H*-isobenzofuran-1-one (13h). Yellow oil, 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.05 (s, 3H, CH_3), 2.55 (ddd, ^2J=15.03 Hz, ^3J=7.83 Hz, ^4J=0.63 Hz, 1H, CHC*H*H), 2.70 (ddd, ^3J=15.03, 4.99 Hz, ^4J=0.76 Hz, 1H, CHCH*H*), 4.52 (d, ^2J=13.25 Hz, 1H, C*H*HO), 4.58 (d, ^2J=13.25 Hz, 1H, CH*H*O), 5.13 (d, ^2J=0.82 Hz, 1H, C=C*H*H), 5.23 (d, ^2J=0.82 Hz, 1H, C=CH*H*), 5.59 (dd, ^3J=7.90, 4.99 Hz, 1H, C-3), 7.45 (dd, ^3J=7.50 Hz, ^4J=0.82 Hz, 1H, 4-H), 7.50 (ddd, ^3J=7.48, ^4J=0.76, 0.76 HZ, 1H, 5-H), 7.64 (dt, ^3J=7.48 Hz, ^4J=1.05 Hz, 1H, 6-H), 7.86 (d, ^3J=7.70 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.0 (+, CH_3), 38.8 (−, CH*C*H_2), 67.0 (−, CH_2O), 79.4 (+, C-3), 117.7 (−, C=*C*H_2), 122.2 (+, C-6), 125.9 (+, C-4), 126.2 (q, C-7a), 129.5 (+, C-7), 134.1 (+, C-5), 138.4 (q, *C*=CH_2), 149.4 (q, C-3a), 170.2, 170.6 (q, O*C*OCH_3 and C-1). IR (CH_2Cl_2): ν=1765 (CO), 1615 (arene), 100 (CH=CH_2) cm^{-1}. MS (EI), *m*/*z* (%)=246 (M^+, 10), 220 (200), 133 (100), 105 (15), 91 (15), 77 (10), 55 (10).

2.3.9. 3-(2-Chloromethyl)allyl-3*H*-isobenzofuran-1-one (13i). Yellow oil, 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.59 (ddd, ^2J=9.60 Hz, ^3J=6.95 Hz, ^4J=1.01 Hz, 1H, CHC*H*H), 2.90 (ddd, ^2J=9.60 Hz, ^3J=4.60 Hz, ^4J=1.01 Hz, 1H, CHCH*H*), 4.02 (dd, ^2J=11.88 Hz, ^4J=0.88 Hz, 1H, ClC*H*H), 4.13 (dd, ^2J=11.88 Hz, ^4J=0.88 Hz, 1H, ClCH*H*), 5.14 (d, ^2J=0.76 Hz, 1H, C=C*H*H), 5.30 (d, ^2J=0.76 Hz, 1H, C=CH*H*), 5.62 (dd, ^3J=8.40, 4.369 Hz, 1H, C-3), 7.46–7.55 (ca, 2H, 4-H and 5-H), 7.66 (dt, ^3J=7.52 Hz, ^4J=1.09 Hz, 1H, 6-H), 7.87 (d, ^3J=7.71 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=38.4 (−, CH*C*H_2), 48.5 (−, CH_2Cl), 79.5 (+, C-3), 119.2 (−, C=*C*H_2), 122.2 (+, C-6), 126.0 (+, C-4), 126.2 (q, C-7a), 129.6 (+, C-7), 134.2 (+, C-5), 139.7 (q, *C*=CH_2), 149.3 (q, C-3a), 170.2 (q, C-1). IR (CH_2Cl_2): ν=1767 (CO), 1614 (arene), 1003 (CH=CH_2) cm^{-1}. MS (EI), *m*/*z* (%)=222 (M^+, 20), 133 (100), 105 (15), 77 (10). HRMS ($C_{12}H_{11}ClO_2$): Calcd 222.0448, found 222.0452.

2.3.10. 3-(2-Trimethylsilyl-allyl)-3*H*-isobenzofuran-1-one (13j). Yellow oil, 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.12 (s, 9H, $Si(CH_3)_3$), 2.65 (dd, ^3J=7.83 Hz, ^2J=2.27 Hz, 1H, C*H*HCSi), 2.68 (dd, ^3J=7.83 Hz, ^2J=2.27 Hz, 1H, CH*H*CSi), 5.53–5.58 (ca, 2H, C-3 and CH_{cis}=CSi), 5.77 (d, ^2J=2.40 Hz, 1H, CH_{trans}=CSi), 7.44 (dd, ^3J=7.58 Hz, ^4J=0.99 Hz, 1H, 4-H), 7.50 (t, ^3J=7.58, 1H, 5-H), 7.62 (dd, ^3J=7.58 Hz, ^4J=0.99 Hz, 1H, 6-H), 7.87 (d, ^3J=7.58 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=−1.3 (+, $Si(CH_3)_3$), 41,3 (−, CH*C*H_2), 80.3 (+, C-3), 122.4 (+, C-6), 125.9 (+, C-4), 126.4 (q, C-7a), 128.8 (−, C=*C*H_2), 129.3 (+, C-7), 133.9 (+, C-5), 146.5 (q, *C*=CH_2), 150.1 (q, C-3a), 170.5 (q, C-1). IR (CH_2Cl_2): ν=1758 (CO), 1616 (arene), 997 (CH=CH_2) cm^{-1}. MS (EI), *m*/*z* (%)=231 (M^+-CH_3, 100), 201 (10), 189 (10), 133 (80), 105 (20), 91 (10), 77 (15), 75 (30), 51 (15). HRMS ($C_{14}H_{18}O_2Si-CH_3$): Calcd 231.0841, found 231.0843.

2.3.11. 3-Allyl-6,7-dimethoxy-3*H*-isobenzofuran-1-one (18g). Yellow oil, 51%. ^{1}H NMR (400 MHz, $CDCl_3$):

δ=2.56 (ddd,, ^2J=2.40 Hz, ^3J=6.51, 7.45 Hz, 1H, CHC*H*HCH), 2.65 (ddd,, ^2J=2.40 Hz, ^3J=6.44, 6.57 Hz, 1H, CHCH*H*CH), 3.87 (s, 3H, CH_3O), 4.06 (s, 3H, CH_3O), 5.12 (dd, ^2J=4.42 Hz, ^3J=10.11 Hz, 1H, CH=CH*H*), 5.15 (dd, ^2J=4.49 Hz, ^3J=17.05 Hz, 1H, CH=C*H*H), 5.35 (dd, ^3J=6.07, 6.07 Hz 1H, 3-H), 5.72 (dddd, ^3J=6.51, 7.45, 10.11, 17.05 Hz, 1H, C*H*=CH_2), 7.02 (dd, ^3J=8.09 Hz, ^4J=0.76 Hz, 1H, 4-H), 7.18 (d, ^3J=8.15 Hz, 1H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=39.2 (−, CH*C*H_2CH), 57.0, 62.5 (+, 2×CH_3O), 79.1 (+, C-3), 116.6 (+, C-4), 119.5 (+, C-5), 119.6 (−, CH=*C*H_2), 131.6 (+, *C*H=CH_2), 142.6 (q, C-3a), 148.5, 152.7 (q, C-6 and C-7), 167.9 (q, C-1). IR (CH_2Cl_2): ν=1761 (CO), 1599 (arene), 1014 (CH=CH_2) cm^{-1}. MS (EI), *m*/*z* (%)=234 (M^+, 10), 193 (100), 122 (10). HRMS ($C_{13}H_{14}O_4$): Calcd 234.0892, found 234.0897.

2.3.12. 3-(2-Chloromethyl-allyl)-6,7-dimethoxy-3*H*-isobenzofuran-1-one (18i). Yellow oil, 24%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.55 (ddd, ^2J=15.22 Hz, ^3J=8.37 Hz, ^4J=0.89 Hz, 1H, CHC*H*H), 2.84 (ddd, ^2J=15.22 Hz, ^3J=4.20 Hz, ^4J=0.89 Hz, 1H, CHCH*H*), 3.89 (s, 3H, CH_3O), 4.02 (dd, ^2J=11.88 Hz, ^4J=0.89 Hz, 1H, ClC*H*H), 4.08 (s, 3H, CH_3O), 4.13 (dd, ^2J=11.88 Hz, ^4J=0.89 Hz, 1H, ClCH*H*), 5.14 (d, ^2J=0.76 Hz, 1H, C=C*H*H), 5.30 (d, ^2J=0.76 Hz, 1H, C=CH*H*), 5.50 (ddd, ^3J=8.37, 4.20 Hz, ^4J=0.81 Hz, 1H, C-3), 7.06 (dd, ^3J=8.21 Hz, ^4J=0.81 Hz, 1H, 4-H), 7.20 (d, ^3J=8.21 Hz, 1H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=38.8 (−, CH*C*H_2), 48.6 (−, CH_2Cl), 57.1, 62.5 (+, 2×CH_3O), 78.2 (+, C-3), 116.5 (+, C-4), 118.4 (q, C-7a), 119.1 (−, C=*C*H_2), 119.6 (+, C-5), 139.8 (q, *C*=CH_2), 142.4 (q, C-3a), 148.7, 152.9 (q, C-6 and C-7), 167.7 (q, C-1). IR (CH_2Cl_2): ν=1764 (CO), 1600 (arene), 1010 (CH=CH_2) cm^{-1}. MS (EI), *m*/*z* (%)=282 (M^+, 10), 256 (10), 193 (100). HRMS ($C_{14}H_{15}ClO_4$): Calcd 282.0659, found 222.0660.

2.3.13. 6,7-Dimethoxy-3-(2-trimethylsilanyl-allyl)-3*H*-isobenzofuran-1-one (18j). Yellow oil, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.00 (s, 9H, $SiMe_3$), 2.50 (dd, ^3J=8.46 Hz, ^2J=3.16 Hz, 2H, CH_2CSi), 3.77 (s, 3H, CH_3O), 3.97 (s, 3H, CH_3O), 5.31 (t, ^3J=7.79 Hz, 1H, 3-H), 5.43 (dd, ^2J=2.27 Hz, ^4J=1.01 Hz, 1H, CH=CH*H*), 5.64 (dd, ^2J=2.27 Hz, ^4J=1.39 Hz, 1H, CH=C*H*H), 6.90 (dd, ^3J=8.21 Hz, ^4J=0.75 Hz, 1H, 4-H), 7.05 (dd, ^3J=8.21 Hz, 1H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=1.3 (+, $Si(CH_3)_3$), 41.8 (−, $CHCH_2$), 57.2, 62.6 (+, 2×CH_3O), 79.0 (+, C-3), 116.8 (+, C-4), 118.6 (q, C-7a), 119.4 (+, C-5), 128.7 (−, C=*C*H_2), 143.4 (q, C-3a), 146.6 (q, *C*=CH_2), 148.7, 152.8 (q, C-6 and C-7), 167.9 (q, C-1). IR (CH_2Cl_2): ν=1760 (CO), 1601 (arene), 1045 (CH=CH_2) cm^{-1}. MS (EI), *m*/*z* (%)=306 (M^+, 10), 291 (10), 193 (100). HRMS ($C_{16}H_{22}O_4Si$): Calcd 306.1287, found 306.1294.

2.3.14. 3-Ethoxy-3*H*-isobenzofuran-1-one (16b). Yellow oil, 19% (from Et_2Zn). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (t, ^3J=7.07 Hz, 3H, CH_3), 3.85 (m, 1H, CH_2), 3.97 (m, 1H, CH_2), 6.35 (s, 1H, 3-H), 7.57 (ca, 2H, 4-H, 5-H), 7.64 (dt, ^3J=7.46 Hz, ^4J=1.14 Hz, 1H, 6-H), 7.87 (d, ^3J=7.54 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.3 (+, CH_3), 66.1 (−, CH_2), 102.5 (+, C-3), 123.6 (+, C-6), 125.6 (+, C-4), 127.5 (q, C-7a), 130.9 (+, C-7), 134.5 (+, C-5), 145.3 (q, C-3a), 168.9 (q, C-1). IR (CH_2Cl_2): ν=1773 (CO), 1616 (arene) cm^{-1}. MS (EI), *m*/*z* (%)=178 (M^+, 20), 133 (100), 162 (20), 147 (10), 133 (100), 105 (25), 90 (10), 77 (10), 51 (5). HRMS ($C_{10}H_{10}O_3$): Calcd 178.0630, found 178.0634.

2.3.15. 3-Butoxy-3*H*-isobenzofuran-1-one (16d). Yellow oil, 19% (from nBu_2Zn). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (t, ^3J=7.39 Hz, 3H, CH_3), 1.36–1.70 (ca, 4H, 2×CH_2), 3.77 (ddd, ^2J=9.42 Hz, ^3J=6.69 Hz, ^2J=2.72 Hz, 1H, CH_2), 3.90 (ddd, ^2J=9.42 Hz, ^3J=6.50 Hz, ^2J=2.83 Hz, 1H, CH_2), 6.35 (s, 1H, 3-H), 7.56 (ca, 2H, 4-H, 5-H), 7.68 (dt, ^3J=7.48 Hz, ^4J=1.10 Hz, 1H, 6-H), 7.87 (d, ^3J=7.58 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9 (+, CH_3), 19.3 (−, CH_2), 31.7 (−, CH_2), 70.2 (−, CH_2), 102.7 (+, C-3), 123.6 (+, C-6), 125.6 (+, C-4), 127.5 (q, C-7a), 130.9 (+, C-7), 134.5 (+, C-5), 145.3 (q, C-3a), 168.9 (q, C-1). IR (CH_2Cl_2): ν=1763 (CO), 1608 (arene) cm^{-1}. MS (EI), *m*/*z* (%)=206 (M^+, 10), 175 (30), 162 (10), 149 (5), 133 (100), 105 (15), 77 (5). HRMS ($C_{12}H_{14}O_3$): Calcd 206.0943, found 206.0946.

2.3.16. 2-[2-(1-Hydroxy-ethyl)-phenyl]-propan-2-ol (15a). Yellow oil, 19% (from MeMgCl). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.48 (d, ^3J=6.41 Hz, 3H, CHC*H*$_3$), 1.58 (s, 3H, CCH_3), 1.64 (s, 3H, CCH_3), 2.67 (bs, 1H, OH), 5.67 (q, ^3J=6.41 Hz, 3H, C*H*CH_3), 7.11–7.28 (ca, 3H, Ar-H), 7.52 (dd, ^3J=7.72 Hz, ^4J=1.60 Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.9 (+, CH_3), 32.7 (+, CH_3), 32.9 (+, CH_3), 66.6 (+, CH), 125.7, 127.1, 127.3, 127.7 (+, C-Ar), 143.9, 144.8 (q, C-Ar). IR (CH_2Cl_2): ν=3596, 3411 (OH), 1605 (arene) cm^{-1}.

2.3.17. 3-(2-Hydroxymethyl-phenyl)-pentan-3-ol (14b). Yellow oil, 17% (from EtMgCl). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.78 (t, ^3J=7.45 Hz, 6H, 2×CH_3), 1.75–2.00 (m, 4H, 2×C*H*$_2$$CH_3$), 2.75 (s, 2H, 2×OH), 4.77 (s, 2H, CH_2OH), 7.10–7.25 (m, 4H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=8.2 (+, 2×CH_3), 36.7 (−, 2×C*H*$_2$$CH_3$), 66.8 (−, CH_2), 73.5 (q, *C*(CH_2CH_3)$_2$), 126.8, 127.9, 128.1, 132.3 (+, C-Ar), 139.3 (q, *C*-$_{Ar}$$CH_2OH$), 143.5 (q, C_{Ar}C(CH_2CH_3)$_2$). IR (CH_2Cl_2): ν=3598, 3472 (OH), 1602 (arene) cm^{-1}. $C_{12}H_{18}O_2$.

2.3.18. 3-[2-(1-Hydroxy-propyl)-phenyl]-pentan-3-ol (15b). Yellow oil, 11% (from EtMgCl). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.79 (t, ^3J=7.45 Hz, 6H, C(CH_2C*H*$_3$)$_2$), 0.99 (t, ^3J=7.45 Hz, 3H, $CHCH_2$C*H*$_3$), 1.76–2.14 (ca, 6H, 3×CH_2), 5.43 (t, ^3J=7.07 Hz, 1H, 3-H), 7.25–7.67 (ca, 4H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=8.3 (+, C(CH_2*C*H$_3$)$_2$), 9.9 (+, $CHCH_2$*C*H$_3$), 27.9 (−, CH*C*H_2CH_3), 36.8 (−, C(*C*H_2CH_3)$_2$), 66.8 (+, CHOH), 82.5 (q, COH), 121.9, 125.9, 129.2, 132.3 (+, C-Ar), 139.4, 150.0 (q, C-Ar). IR (CH_2Cl_2): ν=3597, 3410 (OH), 1605 (arene) cm^{-1}. MS (EI), *m*/*z* (%)=222 (M^+, 5), 220 (10), 162 (10), 147 (100), 133 (45), 105 (45), 77 (20), 59 (39).

2.3.19. 5-(2-Hydroxymethyl-phenyl)-nonan-5-ol (14d). Yellow oil, 27% (from *n*BuMgCl). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.76 (t, ^3J=7.20 Hz, 6H, 2×CH_3), 0.90–1.30 (ca, 8H C*H*$_2$C*H*$_2$$CH_3$), 1.70, 1.88 (m, 4H, 2×CC*H*2CH2), 3.20 (bs, 1H, OH), 4.71 (s, 2H, C*H*$_2$OH), 7.06–7.21 (ca, 4H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2 (+, 2×CH_3), 23.2 (−, 2×*C*H_2CH_3), 26.0 (−, 2×CH_2*C*H_2CH_2), 44.5 (−,

2×CCH_2CH_2), 66.7 (−, CH_2OH), 80.4 (q, COH), 126.7, 127.8, 128.1, 132.2 (+, C-Ar), 138.9, 144.3 (q, C-Ar). IR (CH_2Cl_2): ν=3591, 3488 (OH), 1602 (arene) cm^{-1}.

2.4. Synthesis of the isoindolinones 19, 20b–g and 21b–c

The resin **10** or **11** was suspended in THF (20 ml/mmol resin) and flushed with argon. Five equivalents of the primary amine were added and the reaction mixture was shaken and refluxed for 48 h. The liquid phase was separated. The solvent and the excess of amine was removed under reduced pressure or high vacuum. The product was purified by flash column chromatography on silica with *n*-pentane/diethylether (1:1 for **19** and **20**, 1:3 for **21** and 9:1 for **20g**) as the eluent.

2.5. Synthesis of the isoindolinones 25b,c and 26

The resin **10** was suspended in THF (20 ml/mmol resin) and flushed with argon. Two equivalents of the primary amines allyl amine or *n*-propyl amine were added and the reaction mixture was shaken for 6 h at room temperature. The resins were filtered off, washed with water, followed by the general washing procedure, and dried under high vacuum. The resin was then suspended again in THF (20 ml/mmol resin) and flushed with argon. Two equivalents of diethyl amine or NaOMe were added, and the reaction mixture was shaken and refluxed for 24 h. The liquid phase was separated. The solvent and the excess of amine was removed under reduced pressure or high vacuum. The products were purified by flash column chromatography on silica with *n*-pentane/diethyl ether (2:1) as the eluent.

2.5.1. 3-Hydroxy-2-methyl-2,3-dihydro-isoindol-1-one (19). Colorless powder, 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.81 (s, 3H, CH_3), 4.55 (bs, 1H, OH), 5.52 (s, 1H, 3-H), 7.28–7.54 (ca, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.2 (+, CH_3), 83.7 (+, CH), 123.0 (+, C-4), 123.3 (+, C-7), 129.6 (+, C-5), 131.5 (q, C-7a), 132.2 (+, C-6), 144.1 (q, C-3a), 167.8 (q, CON). IR (CH_2Cl_2): ν=3333 (OH), 1694 (CON), 1619 (arene) cm^{-1}. MS (EI), *m/z* (%)=162 (M^-, 100), 146 (80), 133 (35), 105 (55), 91 (30), 77 (50). HRMS ($C_9H_9NO_2$): Calcd 163.0633, found 163.0639.

2.5.2. 2-Propyl-3-propylamino-2,3-dihydro-isoindol-1-one (20b). Colorless powder, 76%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.79 (t, ^3J=7.32 Hz, 3H, CH_3), 0.92 (t, ^3J=7.42 Hz, 3H, CH_3), 1.34 (m, 2H, $CH_3CH_2CH_2NH$), 1.62 (m, 2H, $CH_3CH_2CH_2N$), 1.98 (ddd, ^3J=14.31, 7.25 Hz, ^2J=4.52 Hz, 1H, NHC*H*H), 2.21 (ddd, ^3J=13.94, 6.99 Hz, ^2J=4.52 Hz, 1H, NHCH*H*), 3.08 (ddd, ^3J=13.90, 8.28 Hz, ^2J=5.39 Hz, 1H, NC*H*H), 3.76 (ddd, ^3J=13.75, 8.48 Hz, ^2J=5.39 Hz, 1H, NCH*H*), 5.35 (s, 1H, 3-H), 7.38–7.51 (ca, 3H, Ar-H), 7.75 (dd, ^3J=7.54 Hz, ^4J=0.88 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.5, 11.7 (+, 2×CH_3), 21.9, 23.5 (−, 2×CH_2CH_3), 40.6 (−, NCH_2), 43.0 (−, $NHCH_2$), 72.7 (+, C-3), 123.1 (+, C-4), 123.2 (+, C-7), 129.0 (+, C-5), 131.5 (+, C-6), 133.2 (q, C-7a), 143.7 (q, C-3a), 167.8 (q, CON). IR (CH_2Cl_2): ν=3361 (NH), 1694 (CON), 1617 (arene) cm^{-1}. MS (EI), *m/z* (%)=232 (M^+, 20), 220 (25), 205 (50), 174 (100), 132 (40), 104 (5), 77 (5). HRMS ($C_{14}H_{20}N_2O$): Calcd 232.1576, found 232.1580.

2.5.3. 2-Allyl-3-allylamino-2,3-dihydro-isoindol-1-one (20c). Yellow oil, 77%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.00 (bs, 1H, NH), 2.73 (ddt, ^2J=14.15 Hz, ^3J=5.43 Hz, ^4J=3.24 Hz, 1H, NHC*H*H), 2.90 (ddt, ^2J=14.15 Hz, ^3J=6.31 Hz, ^4J=2.80 Hz, 1H, NHCH*H*), 3.76 (ddt, ^2J=15.54 Hz, ^3J=7.07 Hz, ^4J=2.49 Hz, 1H, NC*H*H), 4.49 (ddt, ^2J=15.54 Hz, ^3J=4.93 Hz, ^4J=3.06 Hz, 1H, NCH*H*), 4.98 (ddd, ^3J=10.23 Hz, ^4J=2.80 Hz, ^2J=1.58 Hz, 1H, CH=C*H*H), 5.07 (ddd, ^3J=17.18 Hz, ^4J=3.24 Hz, ^2J=1.58 Hz, 1H, CH=CH*H*), 5.16 (ddd, ^3J=10.10 Hz, ^4J=2.49 Hz, ^2J=1.64 Hz, 1H, CH=C*H*H), 5.20 (ddd, ^3J=17.18 Hz, ^4J=3.06 Hz, ^2J=1.64 Hz, 1H, CH=CH*H*), 5.37 (s, 1H, 3-H), 5.69–5.89 (ca, 2H, 2×CH_2CH=CH_2), 7.42–7.52 (ca, 3H, Ar-H), 7.75 (dd, ^3J=7.33 Hz, ^4J=1.01 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=42.0 (−, NCH_2), 44.2 (−, $NHCH_2$), 72.3 (+, C-3), 116.1, 117.8 (−, 2×CH=CH_2), 123.3 (+, C-4), 123.4 (+, C-7), 129.2 (+, C-5), 131.8 (+, C-6), 132.9 (q, C-7a), 133.5 (+, C*H*=CH_2), 136.3 (+, C*H*=CH_2), 143.4 (q, C-3a), 167.5 (q, CON). IR (CH_2Cl_2): ν=3374 (NH), 1694 (CON), 1617 (arene) cm^{-1}. MS (EI), *m/z* (%)=228 (M^+, 5), 220 (10), 205 (30), 172 (100), 130 (20). HRMS ($C_{14}H_{16}N_2O$): Calcd 228.1263, found 228.1269.

2.5.4. 2-Cyclopropyl-3-cyclopropylamino-2,3-dihydro-isoindol-1-one (20d). Colorless powder, 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.15–0.84 (ca, 8H, 4×CH_2), 2.06 (dd, ^3J=8.97, 4.29 Hz, 1H, C*H*NH), 2.55 (bs, 1H, NH), 2.66 (dd, ^3J=8.59, 4.43 Hz, 1H, C*H*N), 5.17 (s, 1H, 3-H), 7.34–7.47 (ca, 3H, Ar-H), 7.70 (d, ^3J=7.33 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=5.0, 5.4, 7.0, 8.1 (−, 4×CH_2), 22.9, 24.7 (+, 2×CH), 74.7 (+, C-3), 123.1 (+, C-4), 123.6 (+, C-7), 128.9 (+, C-5), 131.5 (+, C-6), 132.9 (q, C-7a), 143.7 (q, C-3a), 168.9 (q, CON). IR (CH_2Cl_2): ν=3356 (NH), 1695 (CON), 1618 (arene) cm^{-1}. MS (EI), *m/z* (%)=172 ($M-C_3H_6N^+$, 100), 145 (20), 132 (15), 115 (10).

2.5.5. 2-Cyclohexyl-3-cyclohexylamino-2,3-dihydro-isoindol-1-one (20e). Colorless powder, 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91–1.95 (ca, 20H, 10×CH_2), 2.62 (m, 1H, C*H*NH), 3.70 (m, 1H, C*H*N), 5.39 (s, 1H, 3-H), 7.38–7.51 (ca, 3H, Ar-H), 7.74 (d, ^3J=7.32 Hz, ^4J=1.01 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.9, 25.2, 25.8, 26.0, 26.5, 26.6 (−, 6×CH_2), 30.8, 31.1 (−, 4×CH_2), 52.0, (+, CHN), 53.2 (+, CHNH), 72.3 (+, C-3), 123.2 (+, C-4), 125.7 (q, C-7a), 128.9 (+, C-7), 131.4 (+, C-6), 133.4 (+, C-5), 145.4 (q, C-3a), 167.8 (q, CON). IR (CH_2Cl_2): ν=3374 (NH), 1685 (CON), 1616 (arene) cm^{-1}. MS (EI), *m/z* (%)=312 (M^+, 10), 220 (10), 214 (100), 205 (30), 133 (15), 132 (70), 105 (10), 77 (5), 55 (5). HRMS ($C_{20}H_{28}N_2O$): calcd 312.2202, found 312.2200.

2.5.6. 2-Benzyl-3-benzylamino-2,3-dihydro-isoindol-1-one (20f). Yellow oil, 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.00 (bs, 1H, NH), 3.18 (d, ^2J=13.01 Hz, 1H, C*H*HNH), 3.29 (d, ^2J=13.01 Hz, 1H, CH*H*NH), 4.27 (d, ^2J=14.97 Hz, 1H, C*H*HN), 5.09 (d, ^2J=14.97 Hz, 1H, CH*H*N), 5.25 (s, 1H, 3-H), 7.06–7.84 (ca, 14H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=43.4 (−, CH_2N), 45.8 (−, CH_2NH), 72.5 (+, C-3), 123.3 (+, C-4), 123.7 (+, C-7), 127.5 (+, CH_{Ar}), 127.8 (+, CH_{Ar}), 128.2 (+, 2×CH_{Ar}), 128.4 (+, 2×CH_{Ar}), 128.6 (+, 2×CH_{Ar}), 129.0 (+, 2×CH_{Ar}), 129.3 (+, C-6), 132.0 (+, C-5), 133.0 (q, C-7a), 137.5 (q, CH_2C_{Ar}), 139.8

(q, CH_2C_{Ar}), 143.5 (q, C-3a), 167.9 (q, CON). IR (CH_2Cl_2): ν=1693 (CON), 1615 (arene), 918 (arene) cm^{-1}. MS (EI), *m/z* (%)=328 (M^+, 15), 237 (15), 222 (95), 193 (10), 132 (10), 106 (30), 91 (100). HRMS ($C_{22}H_{20}N_2O$): Calcd 328.1576, found 328.1569.

2.5.7. (*S*,*S*)-2-(1-Phenyl-ethyl)-3-(1-phenyl-ethylamino)-2,3-dihydro-isoindol-1-one (20g). Colorless oil, 22%, 1:1-mixture of diastereomers. ^1H NMR (300 MHz, $CDCl_3$): δ=0.81, 1.08 (, ^3J=6.59, 6.59 Hz, 3H, NHCHCH_3), 1.79, 1.83 (d, ^3J=7.16, 7.16 Hz, 3H, NCHCH_3), 3.61, 3.72 (q, ^3J=6.59, 6.59 Hz, 3H, NHC*H*CH_3), 5.02, 5.28 (s, 1H, 3-H), 5.33, 5.62 (q, ^3J=7.16, 7.16 Hz, 1H, NC*H*CH_3), 6.93–7.47, 7.67–7.77 (ca, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.1, 18.4 (+, NCH*C*H_3), 23.8, 24.6 (+, NHCH*C*H_3), 50.5, 50.7 (+, NCH), 52.5, 55.2 (+, NHCH), 71.5, 72.0 (+, C-3), 123.0–131.8 (+, CH_{Ar}), 132.1, 132.6, 141.1, 142.3, 144.0, 145.7, 146.0, 146.1 (q, C_{Ar}), 167.6 and 168.2 (q, CON). IR (CH_2Cl_2): ν=2923 (aliphatic), 1686 (CON), 1602 (arene) cm^{-1}. MS (EI), *m/z* (%)=356 (M^+, 15), 341 (15), 236 (20), 225 (15), 172 (100), 132 (25), 105 (20), 77 (10). HRMS ($C_{24}H_{24}N_2O$): Calcd 356.1889, found 356.1886.

2.5.8. 6,7-Dimethoxy-2-propyl-3-propylamino-2,3-dihydro-isoindol-1-one (21b). Yellow oil, 40%. ^1H NMR (300 MHz, $CDCl_3$): δ=0.80 (t, ^3J=7.44 Hz, 3H, CH_3), 0.94 (t, ^3J=7.44 Hz, 3H, CH_3), 1.33 (m, 2H, $CH_3CH_2CH_2NH$), 1.61 (m, 2H, $CH_3CH_2CH_2N$), 1.80 (bs, 1H, NH), 2.01 (ddd, ^3J=14.32, 7.22 Hz, ^2J=4.34 Hz, NHC*H*H), 2.23 (ddd, ^3J=14.04, 7.07 Hz, ^2J=4.43 Hz, 1H, NHCH*H*), 3.05 (ddd, ^3J=13.85, 8.29 Hz, ^2J=5.56 Hz, 1H, NC*H*H), 3.73 (ddd, ^3J=13.85, 8.56 Hz, ^2J=5.18 Hz, 1H, NCH*H*), 3.86 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 5.23 (s, 1H, 3-H), 7.04 (d, ^3J=8.10 Hz, 1H, 4-H), 7.13 (d, ^3J=8.10 Hz, 1H, 5-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.7, 11.9 (+, 2×CH_2CH_3), 21.8, 23.7 (−, 2×CH_2CH_3), 40.8 (−, NCH_2), 42.9 (−, $NHCH_2$), 56.8, 62.6 (+, 2×OCH_3), 71.7 (+, C-3), 116.1 (+, C-4), 118.2 (+, C-5), 125.1 (q, C-7a), 137.1 (q, C-3a), 147.1 (q, C-7), 153.2 (q, C-6), 16708 (q, CON). IR (CH_2Cl_2): ν=2926 (aliphatic), 1687 (CON). 1613 (arene) cm^{-1}. MS (EI), *m/z* (%)=292 (M^+, 5), 234 (10), 220 (25), 205 (100), 145 (5). HRMS ($C_{16}H_{24}N_2O_3$): Calcd 292.1787, found 292.1793.

2.5.9. 2-Allyl-3-allylamino-6,7-dimethoxy-2,3-dihydro-isoindol-1-one (21c). Colorless oil, 49%. ^1H NMR (400 MHz, $CDCl_3$): δ=1.95 (bs, 1H, NH), 2.77 (ddt, ^2J=14.15 Hz, ^3J=5.43 Hz, ^4J=3.16 Hz, 1H, NHC*H*H), 2.90 (ddt, ^2J=14.15 Hz, ^3J=6.44 Hz, ^4J=2.59 Hz, 1H, NHCH*H*), 3.73 (ddt, ^2J=15.60 Hz, ^3J=7.14 Hz, ^4J=2.02 Hz, 1H, NC*H*H), 3.86 (s, 3H, OCH_3), 4.05 (s, 6H, OCH_3), 4.45 (ddt, ^2J=15.60 Hz, ^3J=5.00 Hz, ^4J=3.07 Hz, 1H, NCH*H*), 4.99 (ddd, ^3J=10.24 Hz, ^4J=4.30 Hz, ^2J=1.59 Hz, 1H, CH=C*H*H), 5.08 (ddd, ^3J=17.18 Hz, ^4J=4.93 Hz, ^2J=1.59 Hz, 1H, CH=CH*H*), 5.16 (ddd, ^3J=10.17 Hz, ^4J=3.79 Hz, ^2J=1.40 Hz, 1H, CH=C*H*H), 5.21 (ddd, ^3J=17.18 Hz, ^4J=4.43 Hz, ^2J=1.40 Hz, 1H, CH=CH*H*), 5.27 (s, 1H, 3-H), 5.67–5.89 (ca, 2H, 2×CH_2CH=CH_2), 7.05 (d, ^3J=8.08 Hz, 1H, 4-H), 7.16 (d, ^3J=8.08 Hz, 1H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=42.1 (−, NCH_2), 44.0 (−, $NHCH_2$), 56.8, 62.6 (+, 2×OCH_3), 71.3 (+, C-3), 116.0 (−, CH=CH_2), 116.4 (+, C-4), 117.8 (−, CH=CH_2), 118.5 (+, C-5), 124.8 (q, C-7a), 133.6 (+, C*H*=CH_2), 136.7 (+, C*H*=CH_2), 136.7 (q, C-3a), 147.2 (q, C-7), 153.4 (q, C-6), 167.7 (q, CON). IR (CH_2Cl_2): ν=3373 (NH), 1694 (CON), 1599 (arene), 1045 (CH_2=CH) cm^{-1}. MS (EI), *m/z* (%)=288 (M^+, 15), 247 (10), 232 (100), 205 (5), 190 (10). HRMS ($C_{16}H_{20}N_2O_3$): Calcd 288.1474, found 288.1475.

2.5.10. 2-Cyclopropyl-3-cyclopropylamino-6,7-dimethoxy-2,3-dihydro-isoindol-1-one (21d). Colorless oil, 17%. ^1H NMR (400 MHz, $CDCl_3$): δ=0.15–0.42 (ca, 4H, 2×CH_2), 0.68–1.05 (ca, 5H, 2×CH_2 and NH), 2.08 (dd, ^3J=9.35, 4.92 Hz, 1H, C*H*NH), 2.64 (dd, ^3J=6.95, 4.04 Hz, 1H, C*H*N), 3.85 (s, 3H, OCH_3), 4.05 (s, 6H, OCH_3), 5.12 (s, 1H, 3-H), 7.02 (d, ^3J=8.08 Hz, 1H, 4-H), 7.11 (d, ^3J=8.08 Hz, 1H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=5.1, 5.5, 7.2, 8.0 (−, 4×CH_2), 23.1, 24.7 (+, 2×CH), 56.9, 62.6 (+, 2×OCH_3), 73.6 (+, C-3), 116.3 (+, C-4), 118.9 (+, C-5), 125.0 (q, C-7a), 136.5 (q, C-3a), 147.0 (q, C-7), 153.3 (q, C-6), 167.2 (q, CON). IR (CH_2Cl_2): ν=3357 (NH), 1694 (CON), 1600 (arene) cm^{-1}. MS (EI), *m/z* (%)=232 ($M-C_3H_6N^+$, 100), 190 (10), 84 (30). $C_{16}H_{20}N_2O_3$.

2.5.11. 3-Diethylamino-2-propyl-2,3-dihydro-isoindol-1-one (25b). Colorless oil, 10%. ^1H NMR (400 MHz, $CDCl_3$): δ=0.94 (t, ^3J=7.46 Hz, 3H, CH_3), 1.01–1.12 (ca, 6H, 2×CH_3), 1.57 (m, 2H, $CH_3CH_2CH_2NH$), 2.56 (m, 4H, $N(CH_2CH_3)_2$), 3.21 (ddd, ^3J=12.88, 7.07 Hz, ^2J=6.44 Hz, 1H, NC*H*H), 3.78 (ddd, ^3J=13.13, 7.90 Hz, ^2J=6.44 Hz, 1H, NCH*H*), 5.34 (s, 1H, 3-H), 7.40–7.51 (ca, 3H, Ar-H), 7.80 (d, ^3J=6.94 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.7 (+, $CH_2CH_2CH_3$), 15.0 (+, $N(CH_2CH_3)_2$), 21.9 (−, $CH_2CH_2CH_3$), 38.4, 41.4, 43.7 (−, 3×NCH_2), 76.1 (+, C-3), 123.4 (+, C-4), 123.5 (+, C-7), 128.9 (+, C-5), 131.2 (+, C-6), 133.5 (q, C-7a), 143.9 (q, C-3a), 167.7 (q, CON). IR (CH_2Cl_2): ν=2925 (aliphatic), 1686 (CON), 1615 (arene) cm^{-1}. MS (EI), *m/z* (%)=246 (M^+, 10), 174 (100), 146 (10), 132 (30), 104 (5), 77 (5). $C_{15}H_{22}N_2O$, HRMS: Calcd 246.1732, found 246.1740.

2.5.12. 2-Allyl-3-diethylamino-2,3-dihydro-isoindol-1-one (25c). Colorless oil, 12%. ^1H NMR (400 MHz, $CDCl_3$): δ=0.90–1.10 (ca, 6H, 2×CH_2CH_3), 2.45–2.60 (ca, 4H, 2×CH_2CH_3), 3.75 (dd, ^2J=13.90 Hz, ^3J=6.82 Hz, 1H, NC*H*H), 4.50 (d, ^2J=13.90 Hz, 1H, NCH*H*), 5.30 (s, 1H, 3-H), 5.13 (m, 2H, CH=CH_2), 5.77 (dddd, ^3J=17.37, 10.42, 7.32, 6.82 Hz, 1H, C*H*=CH_2), 7.35–7.49 (ca, 3H, Ar-H), 7.77 (d, ^3J=7.07 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.1 (+, 2×CH_3), 42.3 (−, NCH_2CH), 43.8 (−, 2×CH_2CH_3), 75.9 (+, C-3), 117.3 (−, CH=CH_2), 123.5 (+, C-4), 123.6 (+, C-7), 128.9 (+, C-5), 131.4 (q, C-7a), 133.2 (+, C-6), 133.8 (+, C*H*=CH_2), 143.5 (q, C-3a), 170.0 (q, CON). IR (CH_2Cl_2): ν=2922 (aliphatic), 1693 (CON), 1615 (arene) cm^{-1}. MS (EI), *m/z* (%)=244 (M^+, 10), 172 (100), 152 (15), 132 (15), 77 (5). HRMS ($C_{15}H_{20}N_2O$): Calcd 244.1576, found 244.1579.

2.5.13. 3-Methoxy-2-propenyl-2,3-dihydro-isoindol-1-one ((*E*)-26). Colorless solid, 25%. ^1H NMR (400 MHz, $CDCl_3$): δ=1.78 (dd, ^3J=6.75 Hz, ^4J=1.67 Hz, 2H, CH=CHCH_2), 2.84 (s, 1H, OCH_3), 5.66 (dt, ^3J=14.65, 6.75 Hz, 1H, CH=$CH_{trans}CH_2$), 6.09 (s, 1H, 3-H), 6.92 (dd, ^3J=14.65 Hz, ^4J=1.67 Hz, 1H, NC*H*=CH), 7.53 (d,

^3J=8.35 Hz, 1H, 4-H), 7.54 (d, ^3J=7.39 Hz, 1H, 7-H), 7.59 (dd, ^3J=7.39 Hz, ^4J=1.21 Hz, 1H, 6-H), 7.83 (dd, ^3J=8.35 Hz, ^4J=1.21 Hz, 1H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.0 (+, CH*C*H$_3$), 48.7 (+, OCH$_3$), 86.2 (+, C-3), 109.1 (+, CH$_2$=*C*HCH$_3$), 122.4 (+, N*C*H=CH), 123.6 (+, C-4), 123.9 (+, C-7), 130.4 (+, C-5), 132.6 (q, C-7a), 132.9 (+, C-6), 140.5 (q, C-3a), 165.4 (q, CON). IR (CH_2Cl_2): ν=2920 (aliphatic), 1710 (CON), 1615 (arene) cm^{-1}. MS (EI), *m/z* (%)=203 (M$^+$, 80), 188 (80), 172 (100), 161 (15), 143 (15), 132 (25), 97 (20), 77 (15), 57 (30). HRMS ($C_{12}H_{13}NO_2$): Calcd 203.0946, found 203.0950.

2.5.14. 3-Methoxy-2-(*Z*)-propenyl-2,3-dihydro-isoindol-1-one ((*Z*)-26). Colorless solid, 10%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.84 (dd, ^3J=7.17 Hz, ^4J=1.69 Hz, 2H, CH=CHC*H*$_2$), 2.91 (s, 1H, OCH$_3$), 5.34 (dt, ^3J=9.13, 7.17 Hz, 1H, CH=C*H*$_{cis}$CH$_2$), 6.19 (s, 1H, 3-H), 6.33 (dd, ^3J=9.13 Hz, ^4J=1.69 Hz, 1H, NC*H*=CH), 7.52 (d, ^3J=6.95 Hz, 1H, 4-H), 7.55 (d, ^3J=7.20 Hz, 1H, 7-H), 7.59 (dd, ^3J=8.97, 7.20 Hz, 1H, 6-H), 7.84 (dd, ^3J=8.97, 6.95 Hz, 1H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.5 (+, CH*C*H$_3$), 49.6 (+, OCH$_3$), 87.3 (+, C-3), 117.0 (+, CH$_2$=*C*HCH$_3$), 121.0 (+, N*C*H=CH), 123.7 (+, C-4), 124.0 (+, C-7), 130.4 (+, C-5), 132.6 (q, C-7a), 132.8 (+, C-6), 140.3 (q, C-3a), 166.1 (q, CON). IR (CH_2Cl_2): ν=2922 (aliphatic), 1710 (CON), 1616 (arene) cm^{-1}. MS (EI), *m/z* (%)=203 (M$^+$, 100), 188 (80), 172 (80), 161 (15), 143 (10), 133 (20), 130 (15), 115 (10), 89 (10), 77 (10), 57 (5). HRMS ($C_{12}H_{13}NO_2$): Calcd 203.0946, found 203.0952.

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