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DAST-mediated preparation of N-substituted 3-alkoxyisoindolinones

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Dedicated to Professor E. J. Corey on the occasion of his 90th birthday

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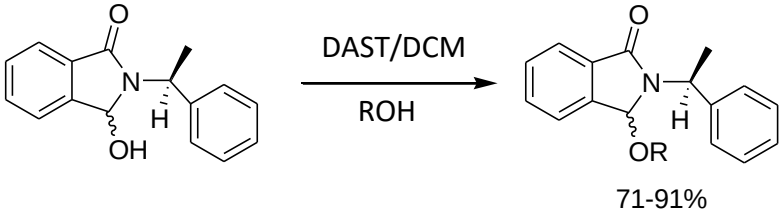
Abstract

3-Alkoxy-2-phenylethylisoindolinones are conveniently prepared by reacting the corresponding hydroxylactams with diethylaminosulfur trifluoride (DAST) in the presence of a range of alcohols. The DAST-mediated reaction did not result in any reactant fluorination but smooth installation of the alkoxy group derived from the reactant alcohol on the benzylic position of the heterocycle. The central starting hydroxylactam substrate was prepared from the corresponding chiral phthalimide, 2-((*S*)-1-phenylethyl)-isoindoline-1,3-dione, by selective reduction using either aluminum amalgam or sodium borohydride. The resultant diasteriomeric mixture of hydroxylactams were used in the DAST alkoxylation reaction and were compared with a more conventional method of alkoxylation using the protic acid camphorsulfonic acid.



Keywords: DAST, imides, iminium ions, isoindolinones

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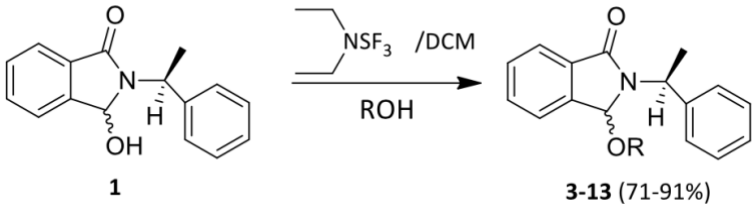
1. Introduction

Isoindolinones form a central heterocyclic scaffold in natural products and medicinal chemistry. A number of compounds bearing the isoindolinone core are of interest as antivirals,[1] inhibitors of protein-protein interaction,[2,3] muscarinic receptor ligands,[4] cytotoxins and cytostatic agents.[5] Substitution on the isoindolinone core, both heteroatom and carbon, may take the form of bonds to the aromatic ring, the heterocyclic nitrogen and the benzylic positions. During the course of our studies of substituted isoindolinones as chiral auxiliaries, we examined methods of mild bond formation to the benzylic position of N-substituted isoindolinones. Normally, nucleophiles such as alcohols or thiols work very well when used in conjunction with a method which generates the corresponding acyliminium ions from the corresponding hydroxylactams.[6-10] In turn, hydroxylactams are easily accessed by selective reduction of the corresponding phthalimides with sodium borohydride, diisobutylaluminum hydride or aluminum amalgam.[11] Given the usual starting materials, which comprise both hydroxylactams and alcohols, the formation of the corresponding alkoxylactams can be accomplished through the agency of acid or metal catalysts.[12-15] While they are harsh and often involve the release of acid, halogenating agents such as thionyl chloride also work well to facilitate the formation of alkoxyisoindolinones from hydroxylactams.[2,3] Diethylaminosulfur trifluoride (DAST) is a mild fluorinating agent which can be used to prepare a distinct array of fluorinated analogues of natural products and medicinal compounds from the corresponding alcohols. While the preparation of the monofluorides and gem-difluorides using DAST has been well-documented, the preparation of ethers with this reagent has been also explored and is the topic of several early reports.[16-18] Inasmuch as ether formation from alcohols using DAST is most notably a consequence of mechanistic variation, the diversion of pathway may be preponderant with some substrates over others. For example, with the use of DAST and some highly reactive substrates such as allylic or benzylic alcohols, fluorination of the alcohols may preclude ether formation. We report herein that hydroxylactam **1** used in conjunction with simple alcohols and DAST leads to the corresponding alkoxylactams (alkoxyisoindolinones) **3-13** (**Scheme 1**) in good to excellent yields.



Scheme 1. DAST-mediated alkoxylation of hydroxylactam **1**.

The yields are comparable to or greater than those which utilize the very commonly-used *p*-toluenesulfonic acid or camphorsulfonic acids, however the reaction does afford diastereomeric mixtures of the corresponding 3-alkoxyisoindolinones. The product distribution of the alkoxylation reaction is not surprising given that the benzylic position which is occupied by the hydroxyl group offers unique reactivity toward the reagent in preference to the substrate alcohols.

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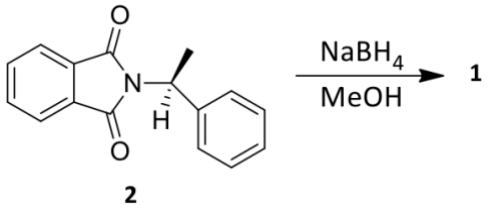
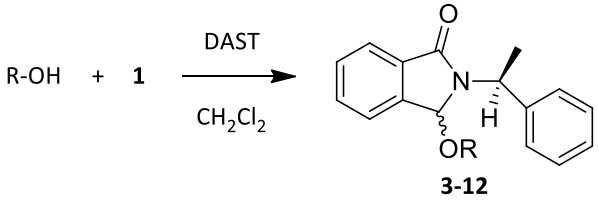
Results and Discussion

Phthaloylation of the chiral amine (*S*)-(-)-α-methylbenzylamine ($[\alpha]_D$ -39°, neat)[19,20] with phthalic anhydride followed by reduction of the resultant chiral phthalimide **2** with sodium borohydride gave the substrate hydroxylactam **1** as a diastereomeric mixture (**Scheme 2**). While the hydroxylactam mixture could be separated by crystallization, the mixture was used directly in the alkoxylation reaction.[7] The alkoxylation entails addition of DAST to a room-temperature solution of the hydroxylactam **1** (CH_2Cl_2), followed by stirring (16 h), then addition of the reactant alcohol followed by stirring (4-8 h). All alkoxylated products were easily purified by flash column chromatography on silica gel, whereby the ratios of diastereomers ranged from 55/45 to 65/35 as determined by ^{1}H NMR (**Table 1**). Although no diastereoselectivity was preferred, the highest ratio (80:20) was derived from using 2,2,2-trichloroethanol as a reactant (See Entry 6, **Table 1**).



Scheme 2. Reduction of phthalimide **2** to hydroxylactam **1**.

Table 1. Reaction of selected alcohols with hydroxylactam **1**



Entry	Substrate alcohol (ROH)/Equivalents	Ratio[a]	Compound/Yield (%)[b]
1	2-propanol/10	60:40	**3**/89
2	cyclopentanol/10	60:40	**4**/88
3	phenylmethanol/5	55:45	**5**/80
4	2-phenylethanol/5	65:35	**6**/91
5	(4-methoxyphenyl)methanol/5	55:45	**7**/60
6	2,2,2-trichloroethanol/5	80:20	**8**/85
7	2-propene-1-ol/5	65:35	**9**/71
8	1,4-butanediol/5	65:35	**10**/77
9	2,2-dimethyl-1-propanediol/5	65:35	**11**/83
10	Anthracen-9-ylmethanol/5	60:40	**12**/79
11	(2-bromophenyl)methanol/5	65:35	**13/**71

[a]Ratios were determined by ^{1}H NMR

[b]Yields are for chromatographically pure products.

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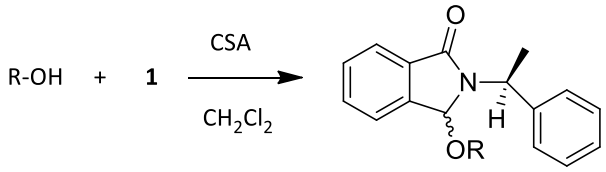
For comparison, a subset of reactions using selected substrate alcohols and catalyzed by camphorsulfonic acid (CSA), were performed with the hydroxylactam **1** and 1,4-butanediol, 2,2-dimethyl-1,3-propanediol and anthracenylmethanol thereby affording products **10**, **11** and **12** respectively after chromatographic purification (**Table 2, Entries 1,2,3**). While acid-mediated alkoxylation of the isoindolinone core may occur through the accepted acyliminium ion mechanism (**Scheme 2**), the DAST-mediated reaction may progress through the same intermediate (**A**) which is enhanced by the benzylic position of the isoindolinone (**Scheme 2**).

Table 2. Reaction of selected alcohols with hydroxylactam **1** mediated by CSA



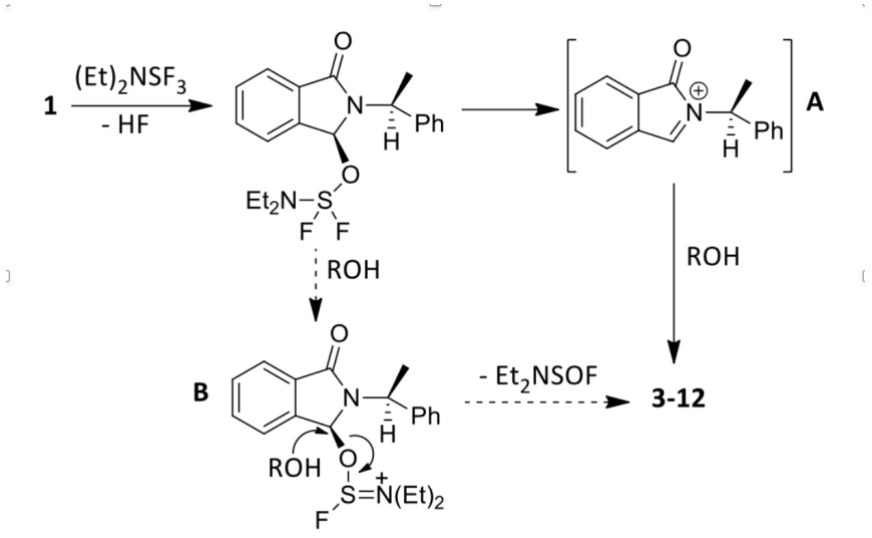
10-12

Entry	Substrate alcohol (ROH)/Equivalents	Ratio[a]	Compound/Yield (%)[b]
1	1,4-butanediol/5	65:35	**10**/80
2	2,2-dimethyl-1-propanediol/5	65:35	**11**/75
3	anthracen-9-ylmethanol/5	60:40	**12**/75

[a]Ratios were determined by ^{1}H NMR

[b]Yields are for chromatographically pure products.

With secondary alcohol substrates, fluorination by DAST gives the corresponding fluorinated compounds with inversion of configuration, quite possibly through displacement of intermediate **B**.[21,22] Consequently, one may argue that if intermediate **B** did indeed exist in the alkoxylation reaction, a high diastereomeric ratio of alkoxyisoindolinones may result, so it is highly likely that the reaction proceeds through intermediate **A**.



Scheme 3. Mechanistic pathways of DAST-mediated alkoxylation.

In theory, one may presume that the inverse sequence whereby the alkoxide of a typical hydroxylactam followed by addition of an alkyl halide will give the desired alkoxyisoindolinones. As reported earlier by other groups, the diastereomeric hydroxylactams **1** could be separated by crystallization after reduction of **2**, and the

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separated diastereomers have been used in several reactions to explore diastereoselectivity.[7] However, generation of the alkoxide of **1** (NaH/THF) from diastereomerically pure **1**, followed by addition of benzyl bromide did not provide the desired benzyloxyisoindolinone, but only an epimeric mixture of hydroxylactams. Presumably, formation of the alkoxide resulted in opening to the corresponding aldamide, which then equlibrates on closing, resulting in epimerization.

Conclusions

We have detailed an efficient route to 3-alkoxyisoindolinones from hydroxylactams and alcohols which does not require the use of acid but utilizes the mediation of the reactive fluorinating reagent DAST. The alkoxylation proceeds by means of an acyliminium ion intermediate which is attacked by the reactant alcohol to yield the product. Despite the fact that the substrate bears a chiral group derived from α-phenethylamine, diastereomeric mixtures result from the reaction.

Experimental Section

General. Solvents and reagents are ACS grade and were used as commercially supplied. Analytical thin-layer chromatography (TLC) utilized 0.25 mm pre-cut glass-backed plates (Merck, Silica Gel 60 F_{254}). Thin-layer chromatograms were visualized during chromatographic and extraction runs by rapidly dipping the plates in anisaldehyde/ethanol/sulfuric acid stain or phosphomolybdic acid/ethanol stain and heating (hot plate). Gravity-column chromatography was carried out using silica gel 60 (E. Merck 7734, 70-230 mesh). Nuclear magnetic resonance (^{1}H and ^{l3}C NMR) spectra were recorded with Varian VNMRS 400 or 500 MHz instruments using $CDCl_3$ as a solvent and TMS as internal standard. Infrared spectra (FTIR) were recorded with a Perkin-Elmer Spectrum 100 instrument and spectral values are reported as cm^{-1}. High resolution mass spectrometry (HRMS) were performed by the Indiana University Mass Spectrometry Facility, Bloomington, Indiana.

General procedure for synthesis of 3-alkoxy-2-((S)-1-phenylethyl)isoindolin-1-ones (3-13). 3-Hydroxy-2-((*S*)-1-phenylethyl)isoindolin-1-one **1** (150 mg, 0.592 mmol, **Entries 1-3, Table 1**) or (100 mg, 0.395 mmol, **(Entries 4-11**, **Table 1**) was dissolved in dichloromethane (3.0 mL) under an inert atmosphere (N_2) while stirring followed by the addition diethylaminosulfur trifluoride (DAST, 240 μL, 1.776 mmol, 3 eq). Stirring was continued overnight (16 hr) and the alcohol (10 or 5 eq) was added and stirring was continued until the reaction was complete as indicated by TLC (4-8 hr). The crude reaction mixture was directly submitted to gravity-column chromatography and the entire series of products were eluted with hexane/ethyl acetate, 4:1. Combination and concentration of the individual fractions gave the pure products detailed in **Table 1**.

General procedure for synthesis of 3-alkoxy-2-((*S*)-phenylethyl)isoindolin-1-ones (10-12). 3-Hydroxy-2-((*S*)-1-phenylethyl)isoindolin-1-one **1** (100 mg, 0.395 mmol, **Entries 1-3, Table 2**) was dissolved in dichloromethane (3.0 mL) with alcohol (1.2 eq) in the presence of camphorsulfonic acid (20% eq). Stirring was continued overnight (4-6 hr) until the reaction was complete as indicated by TLC (4-8 hr). The crude reaction mixture was directly submitted to gravity-column chromatography and the entire series of products were eluted with hexane/ethyl acetate, 4:1. Combination and concentration of the individual fractions gave the pure products detailed in **Table 2**.

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3-Isopropoxy-2-((*S*)-1-phenylethyl)isoindolin-1-one (3). Colorless oil (158 mg, 89%); R_f = 0.44 (hexane/ethyl acetate, 4:1); IR 3029, 2976, 2927, 2886, 1702 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$, major) δ 7.81-7.84 (m, 1H), 7.25-7.55 (m, 8H), 5.68 (q, *J* 7.0 Hz, 1H), 5.53 (s, 1H), 3.66-3.70 (m, 1H), 1.83 (d, *J* 6.5 Hz, 3H), 1.18 (d, *J* 6.0 Hz, 3H), 1.05 (d, *J* 6.0 Hz, 3H). H^1 NMR (500 MHz, $CDCl_3$, minor) δ 7.81-7.84 (m, 1H), 7.25-7.55 (m, 8H), 5.76 (s, 1H), 5.15 (q, *J* 7.0 Hz, 1H), 3.66-3.70 (m, 1H), 1.98 (d, *J* 7.5 Hz, 3H), 1.15 (d, *J* 6.5 Hz, 3H), 0.92 (d, *J* 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 127.7, 143.0, 142.3, 140.5, 132.9, 132.1, 131.9, 131.8, 129.7, 129.5, 128.5, 128.4, 128.2, 127.5, 127.2, 126.6, 123.5, 123.4, 123.3, 85.9 (major), 85.6 (minor), 69.4, 68.7, 52.0, 50.2, 23.9, 23.7, 23.2, 3.0, 18.9, 18.9. HRMS (FTMS + p ESI) *m/z* [M + Na]$^+$; calculated for $C_{19}H_{21}O_2NNa$ 318.1465, Found: 318.1468.

3-(Cyclopentyloxy)-2-((*S*)-1-phenylethyl)isoindolin-1-one (4). Colorless oil (167 mg, 88%); R_f = 0.48 (hexane/ethyl acetate, 4:1); IR 3030, 2999, 2959, 2871, 1697 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$, major) δ 7.81-7.84 (m, 1H), 7.25-7.55 (m, 8H), 5.68 (q, *J* 7.5 Hz, 1H), 5.54 (s, 1H), 3.91-3.93 (m, 1H), 1.81 (d, *J* 7.0 Hz, 3H), 1.31-1.74 (m, 8H). ^{1}H NMR (500 MHz, $CDCl_3$, minor) δ 7.81-7.84 (m, 1H), 7.25-7.55 (m, 8H), 5.81 (s, 1H), 5.17 (q, *J* 7.0 Hz, 1H), 3.78-3.80 (m, 1H), 1.96 (d, *J* 7.0 Hz, 3H) 1.31-1.74 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 167.8, 142.6, 142.2, 140.5, 132.9, 132.3, 131.7, 129.7, 129.6, 128.6, 128.4, 127.7, 127.6, 127.3, 127.2, 126.6, 123.8, 123.8, 123.5, 123.3, 86.0 (major), 85.8 (minor), 51.7, 50.3, 33.7, 33.5, 33.4, 33.3, 23.6, 23.4, 23.2, 18.7, 18.3. HRMS (FTMS + p ESI) *m/z* [M + Na]$^+$; calculated for $C_{21}H_{23}O_2NNa$ 344.1621, Found 344.1624.

3-(Benzyloxy)-2-((*S*)-1-phenylethyl)isoindolin-1-one (5). Colorless oil (108 mg, 80%); R_f = 0.47 (hexane/ethyl acetate, 4:1) IR 3031, 2928, 2886, 2875, 1698 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$, major) δ 7.88-7.89 (m, 1H), 7.21-7.60 (m, 12H), 6.92-6.94 (m, 1H), 5.79 (s, 1H), 5.73 (q, *J* 7.0 Hz, 1H), 4.32 (d, *J* 11.0 Hz, 1H), 3.97 (d, *J* 11.0 Hz, 1H), 1.84 (d, *J* 7.0 Hz, 3H). ^{1}H NMR (500 MHz, $CDCl_3$, minor) δ 7.88-7.89 (m, 1H), 7.21-7.60 (m, 12H), 6.92-6.94 (m, 1H), 6.19 (s, 1H), 5.47 (q, *J* 7.5 Hz, 1H), 3.73 (d, *J* 11.0 Hz, 1H), 3.62 (d, *J* 11.0 Hz, 1H), 1.91 (d, *J* 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 141.7, 141.0, 140.7, 140.3, 137.4, 137.2, 133.1, 132.6, 132.1, 130.0, 129.9, 128.7, 128.4, 127.8, 127.7, 127.6, 127.5, 123.7, 123.6, 123.4, 110.0, 85.8 (major), 85.6 (minor), 64.1, 63.9, 50.7, 50.6, 18.1, 17.5. HRMS (FTMS + p ESI) *m/z* [M + Na]$^+$; calculated for $C_{23}H_{21}O_2NNa$ 366.1465, Found 366.1469.

3-Phenethoxy-2-((*S*)-1-phenylethyl)isoindolin-1-one (6). Colorless oil (193 mg, 91%); R_f = 0.67 (hexane/ethyl acetate, 4:1); IR 3066, 3028, 2937, 2875, 1698 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$, major) δ 7.81-7.82 (m, 1H), 7.11-7.59 (m, 12H), 6.94 (d, *J* 8.0 Hz, 1H), 5.64 (q, *J* 7.0 Hz, 1H), 5.61 (s, 1H) 3.47 (dd, *J* 16.0, 7.0 Hz, 1H), 3.09 (dd, *J* 16.0, 7.0 Hz, 1H), 2.79-2.88 (m, 2H), 1.72 (d, *J* 7.5 Hz, 3H). ^{1}H NMR (500 MHz, $CDCl_3$, minor) δ 7.81-7.82 (m, 1H), 7.11-7.59 (m, 13H), 6.03 (s, 1H), 5.35 (q, *J* 7.5 Hz, 1H), 2,79-2.88 (m, 2H) 2.40-2.46 (m, 1H), 2.28-2.32(m, 1H), 1.85 (d, *J* 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 141.0, 140,4 138.40, 132.6, 131.9, 129.8, 129.7, 129.0, 128.9, 128.6, 128.4, 128.2, 127.8, 127.7, 127.6, 127.4, 126.4, 126.3, 123.6, 123.5, 123.2, 85.7 (major), 85.3 (minor), 62.9, 62.5, 50.7, 50.3, 26.1, 25.5, 17.9, 17.4. HRMS (FTMS + p ESI) *m/z* [M + Na]$^+$; calculated for $C_{24}H_{23}O_2NNa$ 380.1621, Found 380.1624.

3-((4-Methoxybenzyl)oxy)-2-((*S*)-1-phenylethyl)isoindolin-1-one (7). Colorless oil (88 mg, 60%); R_f = 0.37 (hexane/ethyl acetate, 4:1). IR 3063, 2989, 2941, 2843, 1702 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$, major) δ 7.87-7.88 (m, 1H), 7.14-7.60 (m, 8H), 6.77-6.83 (m, 3H), 6.50-6.53 (m, 1H), 5.79 (s, 1H) 5.73 (q, *J* 8.0 Hz, 1H), 4.29 (d, *J* 11.5 Hz, 1H), 3.95 (d, *J* 11.5 Hz, 1H), 3.81 (s, 3H), 1.84 (d, *J* 7.0 Hz, 3H). ^{1}H NMR (500 MHz, $CDCl_3$, minor) δ 7.87-7.88 (m, 1H), 7.14-7.60 (m, 8H), 6.77-6.83 (m, 3H), 6.50-6.53 (m, 1H), 6.19 (s, 1H), 5.47 (q, J 7.0 Hz, 1H), 3.77 (s, 3H), 3.69 (d, J 11.0 Hz, 1H), 3.57 (d, J 11.0 Hz, 1H), 1.91 (d, J 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 159.7, 141.7, 141.0, 140.7, 140.3, 139.0, 138.8, 133.1, 132.6, 132.1 123.0, 129.5, 129.2, 128.7, 128.4, 127.8, 127.7, 127.5, 123.7, 123.6, 123.4, 120.0, 119.8, 113.2, 113.1, 113.0, 85.8 (major), 85.6 (minor), 63.9, 63.8, 55.2, 30.7, 18.1, 17.5. HRMS (FTMS + p ESI) *m/z* [M + Na]$^+$; calculated for $C_{24}H_{23}O_3NNa$ 396.1570, Found 396.1573.

2-((*S*)-1-Phenylethyl)-3-(2,2,2-trichloroethoxy)isoindolin-1-one (8). Colorless oil (129 mg, 85%); R_f = 0.47 (hexane/ethyl acetate, 2:1) IR 3046, 3035, 2980, 2936, 1677 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$, major) δ 7.87-7.88

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(m, 1H), 7.27-7.62 (m, 8H), 5.88 (s, 1H), 5.72 (q, *J* 7.5 Hz, 1H), 3.94 (d, *J* 10.5 Hz, 1H), 3.44 (d, *J* 10.5 Hz, 1H), 1.89 (d, *J* 7.0 Hz, 3H). ^{1}H NMR (500 MHz, $CDCl_3$, minor) δ 7.87-7.88 (m, 1H), 7.27-7.62 (m, 8H), 6.24 (s, 1H), 5.48 (q, *J* 7.5 Hz, 1H), 3.18 (d, *J* 10.5 Hz, 1H), 3.08 (d, *J* 10.5 Hz, 1H), 1.93 (d, *J* 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 141.1, 139.9, 139.5, 139.1, 132.9, 132.7, 132.5 130.6, 130.5, 128.8, 128.7, 128.0, 127.7, 127.6, 124.0, 123.9, 123.7, 95.9, 85.7 (major), 85.5 (minor), 74.2, 73.9, 50.9, 18.0, 17.4. HRMS (FTMS + p ESI) *m/z* [M + Na]$^+$; calculated for $C_{18}H_{16}O_2NCl_3Na$ 406.0139, Found 406.0142.

3-(Allyloxy)-2-((*S*)-1-phenylethyl)isoindolin-1-one (9). Colorless oil (81 mg, 70%); R_f = 0.45 (hexane/ethyl acetate, 9:1) IR 3041, 3010, 2976, 2942, 1700 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$, major) δ 7.84-7.85 (m, 1H), 7.24-7.58 (m, 8H), 5.80-5.84 (m, 1H), 5.70 (q, *J* 7.5 Hz, 1H), 5.67 (s, 1H) 4.94-4.99 (m, 1H), 3.54 (dd, *J* 11.0, 5.5 Hz, 1H), 3.45 (dd, *J* 11.0, 5.5 Hz, 1H), 1.80 (d, *J* 7.0 Hz, 3H). ^{1}H NMR (500 MHz, $CDCl_3$, minor) δ 7.84-7.85 (m, 1H), 7.24-7.58 (m, 8H), 6.09 (s, 1H), 5.44 (q, *J* 7.0 Hz, 1H), 5.37-5.40 (m, 1H), 5.23 (d, *J*=7.0 Hz, 2H), 4.94-4.99 (m, 1H), 3.20 (dd, *J* 13.5, 7.5 Hz, 1H), 3.10 (dd, *J* 13.5, 7.5 Hz, 1H), 1.89 (d, *J* 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 167.6, 141.7, 140.9, 140.6, 140.2, 133.8, 133.6, 133.0, 132.6, 132.0, 129.9, 129.8, 128.6, 128.4, 128.2, 127.9, 127.8, 127.7, 127.4, 126.6, 123.7, 123.5, 123.3, 117.1, 117.0, 85.5 (major), 85.3 (minor), 62.9, 62.8, 50.5, 50.4, 17.9, 17.4. HRMS (FTMS + p ESI) *m/z* [M + Na]$^+$; calculated for $C_{19}H_{19}O_2NNa$ 316.1308, Found 316.1304.

3-(4-Hydroxybutoxy)-2-((*S*)-1-phenylethyl)isoindolin-1-one (10). Colorless oil (103 mg, 80%); R_f = 0.19 (hexane/ethyl acetate, 2:1); IR 3405 br, 2940, 2874, 2836, 1683 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$, major) δ 7.81-7.83 (m, 1H), 7.22-7.24 (m, 8H), 5.65 (q, *J* 6.5 Hz, 1H), 5.62 (s, 1H), 3.86-3.89 (m, 1H), 3.60-3.71 (m, 3H), 3.41-3.46 (m, 1H), 3.28-3.30 (m, 1H) 2.87-2.89 (m, 1H), 1.57-2.0 (4H), 1.23-1.34 (m, 2H). ^{1}H NMR (500 MHz, $CDCl_3$, minor) δ 7.81-7.83 (m, 1H), 7.22-7.24 (m, 8H), 6.03 (s, 1H), 5.43 (q, *J* 6.0 Hz, 1H), 3.60-3.71 (m, 3H), 3.41-3.46 (m, 1H) 2.60-2.68 (m, 2H), 1.57-2.0 (m, 4H), 1.15-1.18 (m, 1H), 1.09-1.10 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 141.8, 141.3, 140.9, 140.5, 133.1, 132.7, 132.2, 130.0, 129.9, 128.8, 128.5, 127.9, 127.8, 127.5, 123.8, 123.7, 123.3, 85.8 (major), 85.4 (minor), 62.7, 62.6, 61.9, 61.7, 50.8, 50.3, 29.7, 29.5, 26.2, 25.7, 18.1, 17.5. HRMS (FTMS + p ESI) *m/z* [M + Na]$^+$; calculated for $C_{20}H_{23}O_3NNa$ 348.1570, Found 348.1573.

3-(3-Hydroxy-2,2-dimethylpropoxy)-2-((*S*)-1-phenylethyl)isoindolin-1-one (11). Colorless oil (101 mg, 75%); R_f = 0.25 (hexane/ethyl acetate, 2:1); IR 3449 br, 3061, 2973, 2870, 1686 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$, major) δ 7.84-7.85 (m, 1H), 7.27-7.58 (m, 8H), 5.66 (q, *J* 7.0 Hz, 1H), 5.64 (s, 1H), 3.36-3.44 (m, 2h) 3.22 (d, *J* 9.0 Hz, 1H), 2.68 (d, *J* 9.0 Hz, 1H), 2.02 (br s, 1H), 1.85 (d, *J* 7.5 Hz, 3H), 0.87 (s, 3H), 0.85 (s, 3H). ^{1}H NMR (500 MHz, $CDCl_3$, minor) δ 7.84-7.85 (m, 1H), 7.27-7.58 (m, 8H), 6.00 (s, 1H), 5.36 (q, *J* 7.0 Hz, 1H), 3.15-3.17 (m, 2H), 2.59 (d, *J* 9.0 Hz, 1H), 2.54 (d, *J* 9.0 Hz, 1H), 1.89 (d, *J* 7.5 Hz, 3H), 1.76 (br s, 1H), 0.70 (s, 3H), 0.63 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 141.7, 141.1, 140.7, 140.3, 133.1, 132.7, 132.2, 132.1, 130.0, 129.9, 128.7, 128.5, 127.8, 127.7, 127.5, 123.7, 123.5, 123.2, 123.0, 85.7 (major), 85.5 (minor), 70.8, 70.5, 69.8, 50.8, 50.7, 35.9, 35.6, 21.8, 21.6, 18.0, 17.8. HRMS (FTMS + p ESI) *m/z* [M + Na]$^+$; calculated for $C_{21}H_{25}O_3NNa$ 362.1727, Found 362.1730.

3-(Anthracen-9-ylmethoxy)-2-((*S*)-1-phenylethyl)isoindolin-1-one (12). Pale yellow solid (138mg, 78%); mp 85-87 °C; R_f = 0.25 (hexane/ethyl acetate, 2:1); IR 3056, 3035, 2927, 2854, 1696 cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$, major) δ 8.43 (s, 1H), 7.95-7.96 (m, 3H), 7.86-7.89 (m, 1H), 7.26-7.72 (m, 12H), 6.98 (d, *J* 7.2 Hz, 1H), 5.86 (s, 1H), 5.80 (q, *J* 7.2 Hz, 1H), 5.34 (d, *J* 12.0 Hz, 1H), 5.12 (d, *J* 12.0 Hz, 1H), 1.90 (d, *J* 7.6 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$, minor) δ 8.39 (s, 1H), 7.95-7.96 (m, 3H), 7.86-7.89 (m, 1H), 7.26-7.72 (m, 12H), 7.18 (d, *J* 7.2 Hz, 1H), 6.10 (s, 1H), 5.40 (q, *J* 7.2 Hz, 1H), 4.85 (q, *J* 7.6 Hz, 2H), 2.04 (d, *J* 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 168.3, 142.0, 141.4, 140.9, 140.7, 133.2, 132.5, 132.0, 131.9, 131.4, 130.5, 130.4, 129.9, 129.8, 129.0, 128.9, 128.8, 128.6, 128.5, 128.3, 127.7, 127.6, 126.5, 126.1, 124.9, 124.9, 124.2, 124.0, 123.8, 123.7, 123.6, 86.3 (major), 86.0 (minor), 58.0, 57.1, 51.6, 51.0, 18.5, 18.3. HRMS (FTMS + p ESI) *m/z* [M + Na]$^+$; calculated for $C_{31}H_{25}O_2NNa$ 466.1778, Found 466.1780.

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3-((2-Bromobenzyl)oxy)-2-((*S*)-1-phenylethyl)isoindolin-1-one (13). Colorless oil (118 mg, 71%); R_f = 0.29 (hexane/ethyl acetate, 9:1) IR 3077, 3035, 2984, 2937, 1686 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$, major) δ 7.88-7.90 (m, 1H), 7.10-7.56 (m, 12H), 5.89 (s, 1H), 5.75 (q, *J* 7.0 Hz, 1H), 4.40 (d, *J* 12.0 Hz, 1H), 4.07 (d, *J* 12.5 Hz, 1H), 1.83 (d, *J* 7.5 Hz, 1H). ^{1}H NMR (500 MHz, $CDCl_3$, minor) δ 7.88-7.90 (m, 1H), 7.10- 7.56 (m, 11H) 5.47 (q, *J* 7.0 Hz, 1H), 4.06 (d, *J* 12.5 Hz, 1H), 3.87 (d, *J* 12.5 Hz, 1H), 1.92 (d, *J* 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.8, 141.6, 140.7, 140.4, 140.3, 136.9, 136.7, 132.9, 132.5, 132.3, 132.2, 132.1, 130.1, 130.0, 129.4, 129.2, 129.1, 128.9, 128.7, 128.4, 127.8, 127.5, 127.4, 127.3, 127.1, 123.8, 123.6, 123.5, 123.4, 122.8, 122.7, 85.7 (major), 85.5 (minor), 63.7, 63.6, 50.7, 50.6, 18.1, 17.6. HRMS (FTMS + p ESI) *m/z* $[M + Na]^+$; calculated for $C_{23}H_{20}O_2NBrNa$ 444.0570, Found 444.0572.

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