Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 465–476

BIOORGANIC & MEDICINAL CHEMISTRY

Novel Strategies for the Solid Phase Synthesis of Substituted Indolines and Indoles

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Received 10 June 2002; accepted 29 July 2002

Abstract—Using a polymer-bound selenenyl bromide resin, *o*-allyl and *o*-prenyl anilines were cycloaded to afford a series of solid-supported indoline and indole scaffolds. These scaffolds were then functionalized and cleaved via four distinct methods, namely traceless reduction, radical cyclization, radical rearrangement, and oxidative elimination, to afford 2-methyl indolines, polycyclic indolines, 2-methyl indoles, and 2-propenyl indolines, respectively. A number of small combinatorial libraries of compounds reminiscent of certain designed ligands of biological interest were constructed demonstrating the potential utility of the developed methodology to chemical biology studies and the drug discovery process.

Introduction

Combinatorial chemistry has become an important tool in both drug discovery and chemical biology studies and its continued success is dependent, in part, on further advances in solid phase organic synthesis (SPOS).[1] Our laboratory has been engaged in the development of novel solid phase linking strategies and chemical technologies aimed at the construction of discovery-oriented, natural product-like libraries.[2] Toward this end, several natural product-like templates have been tethered to a solid support utilizing an intramolecular, selenium-mediated cycloaddition procedure. Encouraged by our success in developing chemistry and technology to produce natural product-like libraries of oxygen-containing heterocycles and carbocyclic frameworks[3] and due to the potential utility of such libraries in chemical biology investigations,[4] we sought to expand the scope of this selenium-based solid phase chemistry to include nitrogen-containing heterocycles. The indoline and indole frameworks are embedded in a wide range of natural products and designed compounds with varied biological activities (see Fig. 1 for selected examples).[5] Four types of indoline and indole templates, namely the 2-methyl indoline, polycyclic indoline, 2-methyl indole, and the 2-propenyl indoline templates, were selected as initial goal structures as it was envisaged that they could be accessed from a common resin-bound indoline intermediate **2** (Fig. 2). Herein, we describe the design and production of combinatorial libraries of substituted indolines and indoles using a novel selenium-based linking strategy.

Results and Discussion

Library design and synthetic strategy to substituted indolines and indoles

Recently, we reported a selenium-based approach for the solid phase combinatorial synthesis of benzopyran-containing natural products and analogues thereof utilizing a practical cycloloading strategy.[3a,b] Given the versatility of this approach, we sought to extend it toward the solid phase synthesis of other heterocycles. It was projected that substituted *o*-allyl anilines (**1**, $R^1 = H$, Fig. 2) might be cycloloaded onto a polystyrene-derived selenenyl bromide resin[6] via a 5-*exo*-trig cyclization to afford resin-bound indoline scaffolds (**2**, $R^1 = H$). Elaboration of **2** ($R^1 = H$) would provide structures such as **3** ($R^1 = H$) that could be tracelessly cleaved providing access to 2-methyl indolines (**5**), a structural class from which several drug candidates have emerged, including antineoplastic sulfonamides,[5c] 5-hydroxytryptamine

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PII: S0968-0896(02)00386-3

receptor antagonists (5-HT3),[7a] and muscarine receptor agonists and antagonists.[7b] Moreover, it was expected that the ability of this selenium tether to generate a carbon-centered radical upon cleavage might be exploited to create additional complexity in the target structure concomitant with release. Specifically, if an intramolecular radical acceptor could be positioned in proximity to this radical (i.e., as in **4**, Fig. 2), then relatively complex polycyclic indolines (**6**) could be constructed in short order.[8] In order to create further diversity during the cleavage operation, it was reasoned that if resin-bound indoline **2** ($R^1 = H$) was functionalized to afford **7** and then treated with a radical initiator in the absence of a quenching agent (i.e., *n*-Bu_3SnH), a radical rearrangement may ensue leading to substituted indoles (**9**).[9] Finally, it was thought that *o*-prenyl anilines (**1**, $R^1 = Me$) could be cyclized in a similar mode to their allyl cousins via 5-*exo*-trig fashion to give indoline scaffolds **2** ($R^1 = Me$). These scaffolds could then be further functionalized to afford **8** and the selenium tether could be cleaved under oxidative conditions to produce the targeted 2-propenyl indoline structure (**10**). Below we describe the implementation of this strategy to the construction of a series of substituted indolines and indoles.

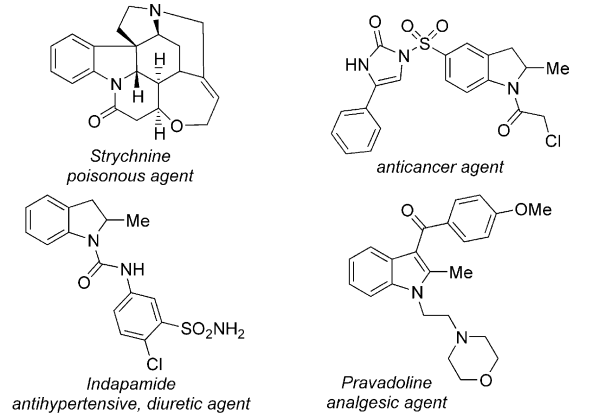


Figure 1. Biologically active polycyclic indolines, 2-methyl indolines and 2-methyl indoles.

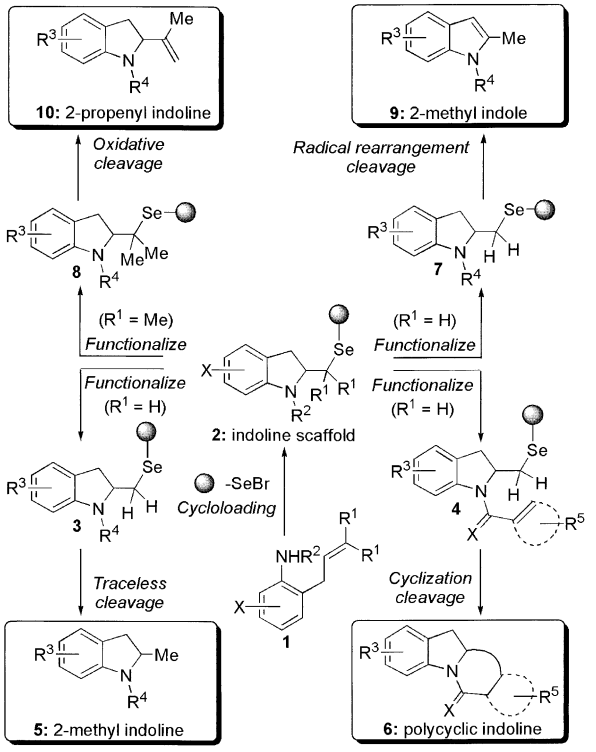
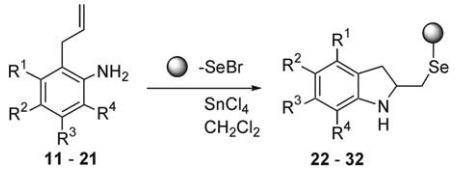


Figure 2. General strategy for the solid phase cycloloading, functionalization, and cleavage of substituted indolines and indoles.

Loading of *o*-allyl anilines onto solid support and process development

In order to efficiently access indoline scaffolds **2**, it was first necessary to define conditions for the cycloloading of *o*-allyl anilines onto the resin.[10] Preliminary solution phase studies with *o*-allyl aniline (**11**, Table 1) revealed that such unprotected anilines could smoothly undergo a selenium-mediated cyclization with PhSeBr in the presence of suitable Lewis acid catalysts such as AgOTf or $SnCl_4$. Encouraged by this result, we attempted the corresponding reaction on solid phase. Hence, treatment of a suspension of the selenenyl bromide resin and aniline **11** (3.0 equiv) in the presence of $SnCl_4$ (3.0 equiv) at −20 °C in CH_2Cl_2 resulted in rapid resin decolorization signaling attachment of the substrate onto the solid support. Subsequent treatment of the resulting resin with *n*-Bu_3SnH (2.5 equiv) and AIBN (0.5 equiv) at 90 °C in toluene followed by polarity-based removal of the reaction by-products[11] afforded indoline **18** in 87% overall yield (for loading and subsequent cleavage) and 89% purity (determined by ^1H NMR). As shown in Table 1, a series of functionalized anilines were then prepared and tested for loading.[12] Substrates **11**–**17**, bearing alkyl substituents or halogens, underwent facile loading under these conditions

Table 1. Selenium-mediated loading of substituted *o*-allyl anilines



Entry	Aniline	R^1	R^2	R^3	R^4	Product	Temp (°C)	Time (h)	Purity (%)[a]
1	**11**	H	H	H	H	**22**	−20	0.5	89
2	**12**	H	Me	H	H	**23**	−20	0.5	85
3	**13**	Me	H	Me	H	**24**	−20	0.5	92
4	**14**	H	*t*-Bu	H	H	**25**	−20	0.5	92
5	**15**	H	F	H	H	**26**	−20	0.5	86
6	**16**	H	Cl	H	H	**27**	−20	0.5	94
7	**17**	H	Br	H	H	**28**	−20	0.5	89
8	**18**	H	CN	H	H	**29**	0	1.0	95
9	**19**	H	CO_2Me	H	H	**30**	0	1.0	95
10	**20**	H	NO_2	H	H	**31**	0	1.0	n/a
11	**21**	H	OMe	H	H	**32**	−20	0.5	n/a

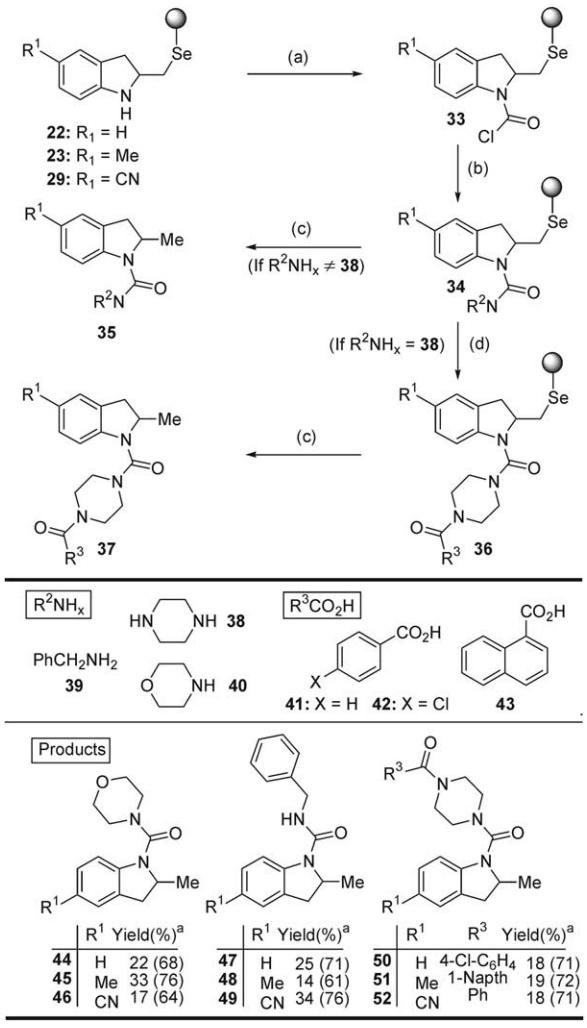
Reagents and reaction conditions: 1.0 equiv of selenenyl bromide resin (0.75 mmol/g), 3.0 equiv of *o*-allyl aniline, 3.0 equiv of $SnCl_4$. AIBN = 2,2′-azobisisobutyronitrile.

[a]Purities estimated by cleavage (*n*-Bu_3SnH, AIBN, 90 °C), polarity-based purification, and ^1H NMR analysis. Loading ranged from 54–87% as determined by weight of cleavage product.

(−20 °C, 0.5 h), whereas those with electron withdrawing groups (**18** and **19**) required slightly modified conditions (0 °C, 1 h). The only substrates from those tested which failed to load were 4-nitro aniline (**20**) and 4-methoxy aniline (**21**).

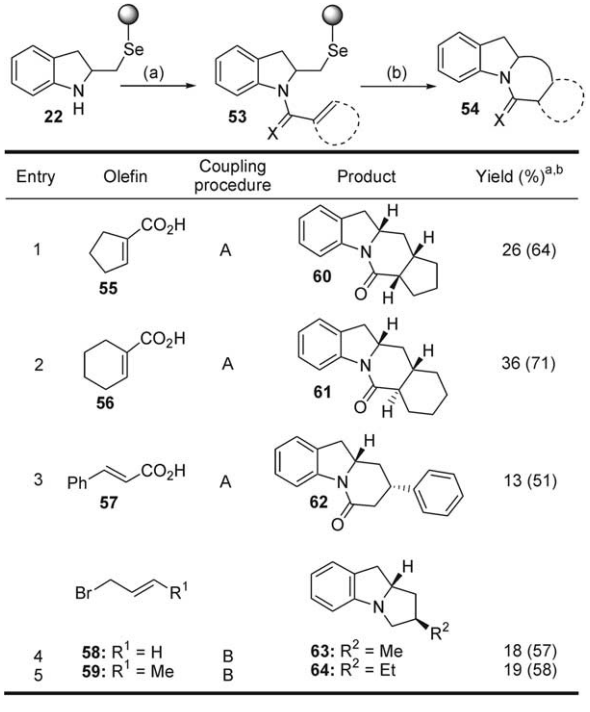
Library construction

With resin-bound indolines **22**–**30** (Table 1) now in hand, we set out to explore their aforementioned applications. First, we undertook the solid phase synthesis of a collection of 2-methyl indolines resembling previously reported 5-HT3 receptor antagonists[7a] in order to demonstrate how the current linking strategy might be employed in combinatorial synthesis. The adopted synthetic strategy is outlined at the top of Scheme 1. Thus, resin-bound indolines were converted to acyl chlorides (**33**, $COCl_2$) which were subsequently reacted with various amines (R^2NH_x) to afford ureas (**34**). When diamines such as piperazine (**38**) were utilized, the resulting secondary amine could be further derivatized by coupling with carboxylic acids (R^3CO_2H). All of the resulting indolines (**34** or **36**) were tracelessly cleaved under reducing conditions to produce compounds of type **35** or **37**. The parallel application of this sequence to indoline scaffolds **22**, **23**, and **29**, amines **38**–**40**, and carboxylic acids **41**–**43** resulted in the formation of a nine-membered library of 2-methyl indolines (**44**–**52**) in reasonable yields and purity (see Scheme 1).



Scheme 1. Parallel synthesis of substituted 2-methyl indolines. Reagents and reaction conditions: (a) 27.0 equiv of $COCl_2$, CH_2Cl_2, 0 °C, 1 h; (b) 10.0 equiv R^2NH_x, 27.0 equiv of Et_3N, CH_2Cl_2, 25 °C, 12 h; (c) 4.0 equiv of *n*-Bu_3SnH, 1.3 equiv of AIBN, toluene, 90 °C, 2 h; (d) 10.0 equiv of R^3CO_2H, 10.0 equiv of DCC, 1.3 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 16 h. DCC = 1,3-dicyclohexylcarbodiimide. 4-DMAP = 4-dimethylaminopyridine. [a]Isolated yields of chromatographically pure material over four or five steps. Yield in parentheses refers to average yield per chemical transformation.

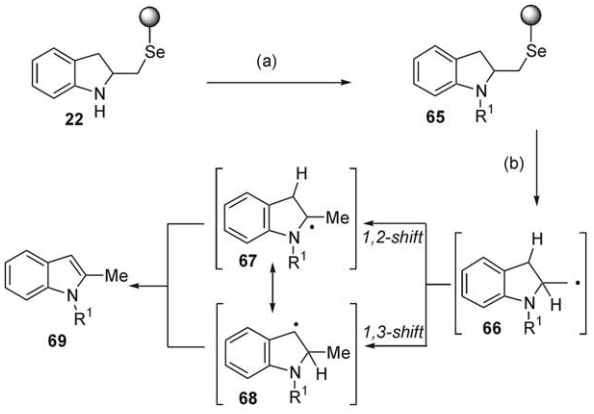
As stated above, our second goal was to develop a diversity-building cleavage protocol whereby the selenium tether would be utilized as a progenitor to a carbon-centered radical which could engage a proximal functionality to afford polycyclic indolines. Hence, the secondary nitrogen of indoline **22** (Scheme 2) was coupled to a series of olefinic radical acceptors via either amide or alkyl linkages to form derivatives of type **53** which could be released with concomitant cyclization to provide polycyclic indolines of type **54**. For example, DCC coupling of indoline **22** with 1-cyclopentene-1-carboxylic acid (**55**) afforded the corresponding amide which was then suspended in toluene at 90 °C and a solution of *n*-Bu_3SnH and AIBN was slowly added over

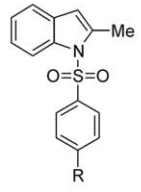
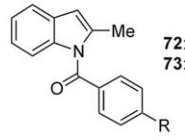
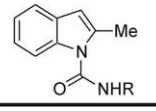


Scheme 2. Radical-based release and cyclization producing polycyclic indolines. Reagents and reaction conditions: (a) Coupling produre A: 10.0 equiv of acid, 10.0 equiv of DCC, 1.3 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 24 h; Coupling procedure B: 10.0 equiv of alkenyl bromide, 20.0 equiv of NaH, DMF, 60 °C, 48 h; (b) 4.0 equiv of *n*-Bu_3SnH, 1.3 equiv of AIBN, toluene, 90 °C, 4 h. [a]Products obtained as single diastereomers with relative stereochemistry shown as determined by ^1H NMR and ROESY analysis unless otherwise noted. [b]Isolated yield of chromatographically pure material over three steps based on an estimated resin loading of 0.75 mmol/g. Yield in parentheses refers to average yield per chemical transformation.

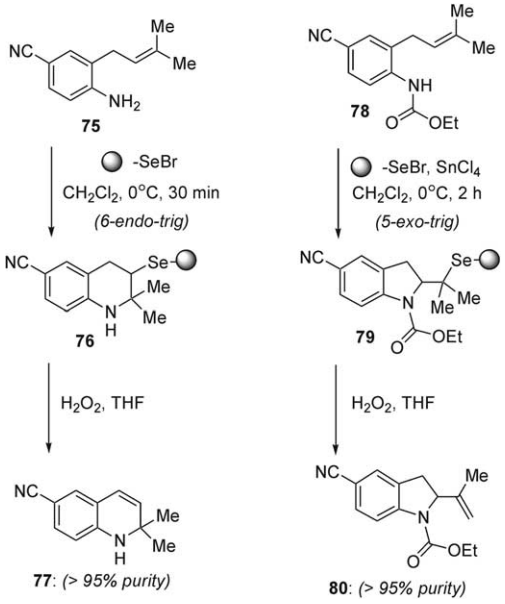
a 4 h interval. To our delight, tetracycle **60** was released as a single diastereomer in 26% yield over three steps. Coupling of **22** with 1-cyclohexene-1-carboxylic acid (**56**) and *trans*-cinnamic acid (**57**) followed by similar cleavage from the solid support afforded tetracycle **61** and tricycle **62** in moderate yields (36 and 13%, respectively) over three steps. In addition, alkylation (NaH, DMF, 60 °C) of indoline **22** with either allyl or crotyl bromide (**58** or **59**) led to the formation of tricycles **63** and **64** in 18 and 19% yields, respectively.

In a final application of the resin-bound indoline scaffold **2** (Fig. 2, $R^1 = H$), the 2-methyl indole was targeted as a template for library design as it represented an important class of biologically relevant ligands, including the analgesic agent pravadoline (Fig. 1).[5b] It was envisioned that exposure of **7** (Fig. 2) to an appropriate radical initiator in the absence of a quenching agent could lead to a radical rearrangement process to produce 2-methyl indoles (**9**). This idea came to fruition upon treatment of polymer-bound indoline **22** (Scheme 3) with various electrophiles to form sulfonamides, amides and ureas (**65**). These functionalized indoline scaffolds were then treated with AIBN (3.0 equiv) in refluxing benzene to afford 2-methyl indoles (**70**–**75**) in satisfactory yields (23–64% over three steps). The formation of the 2-methyl indole presumably arises via a 1,2- or 1,3-hydride shift within the initially formed primary radical **66** (Scheme 3, structures **67** and **68**, respectively) followed by elimination of a hydrogen radical to afford the final product.



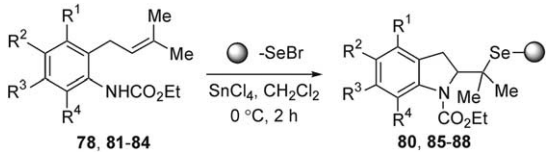
Entry	Electrophile	Acylation procedure	Product	Yield (%)[a,b]
1	TsCl or $PhSO_2Cl$	A		**70**: R = Me: 27 (64) **71**: R = H: 29 (66)
2	BzCl or *p*-OMe-PhC(O)Cl	A		**72**: R = H: 42 (75) **73**: R = OMe: 23 (61)
3	$COCl_2$, $CH_2{=}CHCH_2NH_2$ or $PhCH_2NH_2$	B		**74**: R = allyl: 64 (89) **75**: R = Bn: 39 (79)

Scheme 3. Radical rearrangement cleavage of functionalized indoles. Reagents and reaction conditions: (a) acylation produre A: 10.0 equiv of electrophile, 20.0 equiv of *i*-Pr_2NEt, 1.0 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 48 h; acylation procedure B: 20.0 equiv $COCl_2$, 20.0 equiv Et_3N, CH_2Cl_2, 0 °C, 1 h, filter and wash, then 20.0 equiv amine, 20.0 equiv Et_3N, CH_2Cl_2, 25 °C, 18 h; (b) 3.0 equiv AIBN, benzene, 85 °C, 48 h. [a]Isolated yield of chromatographically pure material based on an estimated resin loading of 0.75 mmol/g. [b]Yield in parentheses refers to average yield per chemical transformation.



Scheme 4. Selective loading of 2,2-dimethyldihydroquinoline or indoline scaffolds via *o*-prenylated anilines. Purities estimated by ^1H NMR spectroscopic analysis after oxidative cleavage (see Experimental for details).

Table 2. Selenium-mediated cycloloading of substituted *o*-prenyl anilines

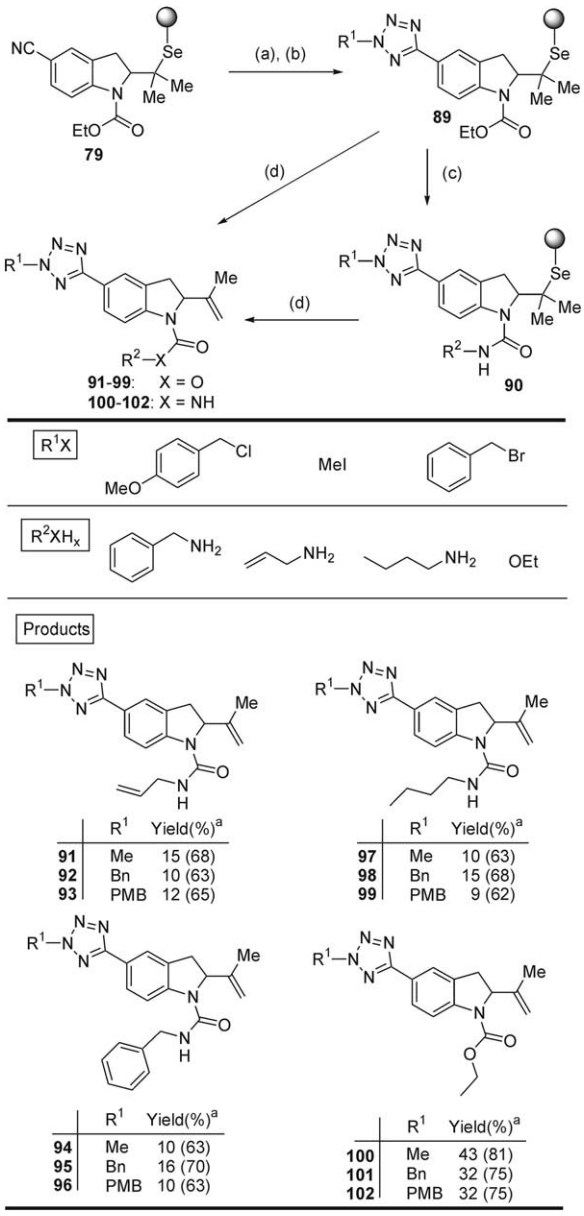


Entry	Urethane	R^1	R^2	R^3	R^4	Product	Purity (%)[a,b]
1	**78**	H	CN	H	H	**80**	95
2	**81**	Me	H	Me	H	**85**	95
3	**82**	H	Br	H	H	**86**	95
4	**83**	H	CO_2Me	H	H	**87**	95
5	**84**	H	NO_2	H	H	**88**	90

Reagents and conditions: 1.0 equiv of selenenyl bromide resin (0.75 mmol/g), 2.0 equiv of *o*-prenyl aniline, 3.0 equiv of $SnCl_4$.
[a]Purities estimated by cleavage (H_2O_2, THF, 25 °C) and ^1H NMR analysis.
[b]Loading ranged from 75–95% as determined by recovery of oxidatively cleaved product.

Cycloloading of *o*-prenyl anilines and library construction

In order to obtain the second indoline scaffold (**2**, Fig. 2, $R^1 = Me$), it was necessary to study the cyclization of *o*-prenyl anilines (**1**, $R^1 = Me$).[13] It was reasoned that if these substrates undergo the cyclization event in a 6-*endo*-trig fashion, this would afford the 2,2-dimethyldihydroquinoline nucleus, a structural class which has received considerable attention from the pharmaceutical industry.[14] On the other hand, if these substrates were to undergo cyclization in a 5-*exo*-trig manner, this would afford the 2-propenyl indoline substructure. However, according to literature precedents, selenium-mediated cyclizations of *o*-prenylated anilines or urethanes produced either mixtures of indoline and quinoline or exclusively the indoline product, depending on the reaction conditions.[10b,15] Gratifyingly, after much experimentation, it was found that the selectivity of this cyclization (5-*exo* *vs.* 6-*endo*) could be modulated through the electronic properties of the aniline ring and proper derivatization of the aniline nitrogen as shown in Scheme 4. Thus, treatment of a suspension of the selenenyl bromide resin in CH_2Cl_2 at 0 °C with 2 equivalents of 4-cyano-2-prenylaniline (**75**) afforded complete conversion to the 2,2-dimethyldihydroquinoline nucleus (**76**) after 30 min, which, after oxidative cleavage, produced quinoline **77** in > 95% purity. Complementary to this result, if the resin was treated with the ethyl carbamate of 4-cyano-2-prenylaniline (**78**) followed immediately by the addition of tin (IV) chloride, smooth conversion to the 2-propenyl indoline nucleus (**79**) was observed after 2 h, which, after oxidative cleavage, gave indoline **80** in > 95% purity. Unfortunately, all attempts to cleanly functionalize the nitrogen center of the 2,2-dimethyldihydroquinoline scaffold (**76**) were hampered by the severe steric encumbrance of this position due to the adjacent *gem*-dimethyl group as well as the diminished nucleophilicity of this group (only electron-deficient, i.e., CN and NO_2, anilines afforded clean conversion to the quinoline nucleus). Unfortunately, derivatization of the aromatic ring was complicated by the presence of the unprotected nitrogen, as most diversity building transformations attempted proved unsuccessful in the presence of a free secondary amine. Hence, the 2-propenyl indoline scaffold was selected for further development as a template for library design.



	R1	Yield(%)a
91	Me	15 (68)
92	Bn	10 (63)
93	PMB	12 (65)

	R1	Yield(%)a
97	Me	10 (63)
98	Bn	15 (68)
99	PMB	9 (62)

	R1	Yield(%)a
94	Me	10 (63)
95	Bn	16 (70)
96	PMB	10 (63)

	R1	Yield(%)a
100	Me	43 (81)
101	Bn	32 (75)
102	PMB	32 (75)

Scheme 5. Solid phase parallel synthesis of 2-propenyl indoline tetrazole library. Reagents and conditions: (a) 10.0 equiv of Me_3SnN_3, PhMe, 100 °C, 12 h, filter and wash, then TFA/CH_2Cl_2 (1:20), 25 °C, 1 h; (b) 20.0 equiv R^1X, 30.0 equiv of *i*-Pr_2NEt, CH_3CN, 80 °C, 12 h; (c) 20.0 equiv $AlMe_3$, 20.0 equiv amine, PhMe, 90 °C, 12 h; (d) 6.0 equiv of H_2O_2, THF, 25 °C, 1 h. TFA = trifluoroacetic acid. [a]Isolated yields of chromatographically pure material based on an estimated resin loading of 0.75 mmol/g. Number in parentheses indicates average yield per chemical transformation.

As shown in Table 2, cyclization of electron-rich (**81**) and electron-deficient (**78** and **82**–**84**) *o*-prenylated urethanes afforded the tethered 2-propenyl indoline nucleus (**79** and **85**–**88**) in good to excellent yields (75–95% after oxidative cleavage) and greater than 90% purity. In order to explore the utility of this application to library construction, we synthesized a 12-membered library of tetrazole-containing 2-propenyl indolines reminiscent of the antihypertensive and diuretic agent, indapamide,[5a] and the anticancer agent, both shown in Fig. 1. As shown in Scheme 5, aryl cyanide **79** was treated with azidotrimethyltin to form, after acidic hydrolysis, a free tetrazole[16] which was then alkylated with three alkyl halides in the presence of diisopropylethylamine to afford functionalized tetrazoles (**89**).[17] These tetrazoles were either cleaved directly to yield carbamates (**100**–**102**) or transformed into ureas (**90**) upon exposure to trimethylaluminum and primary amines[18] followed by oxidative cleavage (**91**–**99**).

Conclusion

In summary, we have described the successful loading, functionalization, and cleavage of four novel classes of natural product-like templates, namely 2-methyl indoline,

polycyclic indoline, 2-methyl indole, and 2-propenyl indoline using selenium-based solid phase chemistry. These technologies may prove useful in the synthesis of further combinatorial libraries of biologically relevant compounds for chemical biology studies and drug discovery purposes.

Experimental

General techniques

Reagents and resins were purchased at highest commercial quality and used without further purification, unless otherwise stated. Anhydrous solvents were obtained by passing them through commercially available alumina column. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Solution phase reactions were monitored by thin layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 mm E. Merck silica gel plates (60F-254). All final products cleaved from solid support were characterized by ^{1}H NMR and HRMS. NMR spectra were recorded on Bruker DRX-600, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under MALDI-FTMS conditions with NBA as the matrix or gas chromatography–mass spectra (GCMS) conditions. Representative procedures for each combinatorial library synthesized are provided below. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, oct = octet, quin = quintuplet, sep = septet, sext = sextet, b = broad.

Preparation of *o*-allyl anilines 11–21

Representative procedure. Preparation of 16.[19] To a solution of 4-chloro aniline (10.0 g, 78.3 mmol, 1.0 equiv) in DMF (40 mL) at 0 °C was added allyl bromide (5.77 mL, 78.3 mmol, 1.0 equiv). The solution was warmed to room temperature and allowed to stir for 12 h. The reaction mixture was then poured into a solution of 10% NaOH (100 mL) and extracted with EtOAc (2×100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated, and the crude product was purified by column chromatography (silica, 5–10% EtOAc in hexanes) to afford *N*-allyl-4-chloro aniline (3.85 g, 29%). To fused $ZnCl_2$ (6.10 g, 44.7 mmol, 3.0 equiv) was added a solution of *N*-allyl-4-chloro aniline (2.5 g, 14.9 mmol, 1.0 equiv) in xylenes (25 mL) and the resulting heterogenous reaction mixture was heated to 145 °C for 5.5 h. After cooling, the reaction mixture was poured into 10% NaOH (10 mL), and extracted with EtOAc (3×10 mL). The combined organic extracts were then washed with brine (30 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica, 5→25% EtOAc in hexanes) to yield 2-allyl-4-chloro aniline (**16**) (0.65 g, 26%). All other *o*-allyl aniline substrates were prepared in an identical fashion with the following exceptions. In order to reduce the amount of *N*,*N*-bisallyl aniline product formed during *N*-allylation of electron rich anilines, a sub-stoichiometric amount (0.65 equiv) of allyl bromide and a shorter reaction time (2 h) were used in the preparation of substrates **12**–**16** and **21**. Also, since $ZnCl_2$ failed to catalyze the amino Claisen rearrangement of electron poor substrates **18**–**20**, $BF_3{\bullet}OEt_2$ (1.0 equiv) was used instead of $ZnCl_2$ and the reaction time was shortened to 2 h. Physical data for previously unreported *o*-allyl anilines **12**–**21** are listed below:

12: $R_f = 0.14$ (silica gel, EtOAc/hexanes 1:9); FT-IR (neat) ν_{max} 3364, 3341, 3076, 2915, 1632, 1504, 1435 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 6.90$–6.87 (m, 2H), 6.62 (d, $J = 7.6$ Hz, 1H), 6.01–5.91 (m, 1H), 5.15–5.08 (m, 2H), 3.54 (s, 2H), 3.29 (d, $J = 6.2$ Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 142.2$, 136.2, 130.9, 128.3, 128.1, 124.3, 116.2, 116.1, 36.6, 20.6; HRMS calcd for $C_{10}H_{13}N$ [M + H$^+$] 148.1121, found 148.1127.

13: $R_f = 0.15$ (silica gel, EtOAc/hexanes 1:9); FT-IR (neat) ν_{max} 3444, 3366, 2917, 1620, 1579, 1457 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 6.54$ (s, 1H), 6.44 (s, 1H), 5.98–5.92 (m, 1H), 5.10–5.03 (m, 2H), 3.62 (s, 2H), 3.35–3.33 (m, 2H), 2.28 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 144.8$, 137.1, 136.4, 135.1, 121.8, 119.4, 114.9, 114.6, 31.4, 20.9, 19.7; HRMS calcd for $C_{11}H_{15}N$ [M + H$^+$] 162.1283, found 162.1280.

14: $R_f = 0.12$ (silica gel, EtOAc:hexanes 1:9); FT-IR (neat) ν_{max} 3446, 3368, 3222, 2959, 1623, 1505, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.13$–7.08 (m, 2H), 6.77–6.71 (m 1H), 6.02–5.92 (m, 1H), 5.15–5.10 (m, 2H), 3.36 (d, $J = 6.4$ Hz, 2H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 152.7$, 151.0, 136.1, 127.2, 124.3, 116.2, 115.6, 36.8, 34.0, 31.5; HRMS calcd for $C_{13}H_{19}N$ [M + H$^+$] 190.1596, found 190.1593.

15: $R_f = 0.65$ (silica gel, EtOAc/hexanes 1:3); FT-IR (neat) ν_{max} 3446, 3370, 3078, 2977, 1634, 1501, 1436 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 6.81$–6.75 (m, 2H), 6.65–6.62 (m, 1H), 5.98–5.88 (m, 1H), 5.18–5.08 (m, 2H), 3.57 (s, 2H), 3.28 (d, $J = 6.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 140.3$, 135.1, 117.0, 116.9, 116.7, 116.5, 114.0, 113.7, 36.4; HRMS calcd for $C_9H_{10}FN$ [M$^+$] 152.0875, found 152.0871.

16: $R_f = 0.64$ (silica gel, EtOAc/hexanes 1:3); FT-IR (neat) ν_{max} 3458, 3379, 3218, 2976, 1622, 1490, 1415 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.04$–7.01 (m, 2H), 6.64 (dd, $J = 9.1$, 3.0 Hz, 1H), 5.97–5.87 (m, 1H), 5.17–5.08 (m, 2H), 3.81 (s, 2H), 3.27 (d, $J = 6.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 135.4$, 130.2, 127.7, 117.6, 117.3, 36.6; HRMS calcd for $C_9H_{10}ClN$ [M$^+$] 168.0580, found 168.0583.

17: $R_f = 0.68$ (silica gel, EtOAc/hexanes 1:3); FT-IR (neat) ν_{max} 3457, 3380, 3078, 2974, 1621, 1488, 1412

cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.18–7.15$ (m, 2H), 6.61 (d, $J = 8.8$ Hz, 1H), 5.97–5.87 (m, 1H), 5.18–5.08 (m, 2H), 4.12 (s, 2H), 3.28 (d, $J = 6.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 134.9$, 132.6, 130.2, 117.7, 116.9, 36.1; HRMS calcd for $C_9H_{10}BrN$ $[M+H^+]$ 210.9997, found 210.9991.

18: $R_f = 0.20$ (silica gel, EtOAc/hexanes 1:3); FT-IR (neat) ν_{max} 3476, 3377, 3235, 2978, 2214, 1635, 1571, 1504, 1432 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.37–7.33$ (m, 2H), 6.70 (d, $J = 8.2$ Hz, 1H), 5.94–5.86 (m, 1H), 5.22–5.10 (m, 2H), 4.60 (s, 2H), 3.29 (d, $J = 6.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 134.4$, 134.3, 132.1, 132.1, 124.9, 124.8, 120.1, 117.7, 116.1, 35.9; ESMS calcd for $C_{10}H_{10}N_2$ $[M+H^+]$ 159, found 159.

19: $R_f = 0.45$ (silica gel, EtOAc/hexanes 1:3); FT-IR (neat) ν_{max} 3475, 3375, 3234, 2948, 1697, 1632, 1436, 1277 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.76$ (d, $J = 7.3$ Hz, 2H), 6.64 (d, $J = 10.6$ Hz, 1H), 5.98–5.88 (m, 1H), 5.17–5.08 (m, 2H), 4.02 (s, 2H), 3.85 (d, $J = 2.0$ Hz, 3H), 3.31 (d, $J = 5.9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 167.3$, 149.3, 135.1, 132.1, 129.8, 122.7, 119.9, 116.7, 114.7, 51.6, 36.3; HRMS calcd for $C_{11}H_{13}NO_2$ $[M+H^+]$ 192.1019, found 192.1028.

20: $R_f = 0.12$ (silica gel, EtOAc/hexanes 1:3); FT-IR (neat) ν_{max} 3486, 3382, 3248, 2979, 2712, 1635, 1488, 1435, 1310 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.99–7.97$ (m, 2H), 6.63 (d, $J = 9.4$ Hz, 1H), 5.98–5.88 (m, 1H), 5.23–5.13 (m, 2H), 4.43 (s, 2H), 3.32 (d, $J = 6.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 151.2$, 139.0, 134.0, 126.5, 124.5, 122.7, 117.7, 114.0, 36.0; ESMS calcd for $C_9H_{10}N_2O_2$ $[M+Na^+]$ 201, found 201.

21: $R_f = 0.22$ (silica gel, EtOAc/hexanes 1:3); FT-IR (neat) ν_{max} 3433, 3359, 2942, 1608, 1503, 1432 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 6.67–6.62$ (m, 3H), 5.99–5.90 (m, 1H), 5.14–5.07 (m, 2H), 3.75 (s, 3H), 3.43 (s, 2H), 3.29 (d, $J = 6.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 153.1$, 138.5, 135.8, 125.9, 117.1, 116.4, 116.1, 112.8, 55.8, 36.8; HRMS calcd for $C_{10}H_{13}NO$ $[M+H^+]$ 163.0997, found 163.0998.

Solid phase loading and cleavage of anilines 11–21

Representative procedure. Preparation of *o*-allyl aniline 11. To a suspension of selenium bromide resin (200 mg of 0.75 mmol/g, 0.150 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at $-20\,^\circ C$ was added a solution of *o*-allyl aniline (**11**) (80 mg, 0.60 mmol, 4.0 equiv) in CH_2Cl_2 (1 mL) followed by addition of $SnCl_4$ (0.825 mL of a 1.0 M solution in CH_2Cl_2, 0.825 mmol, 5.5 equiv). The reaction mixture was slowly stirred at $-20\,^\circ C$ for 30 min and then quenched by addition of Et_3N (0.5 mL). The resulting suspension was poured into a fritted funnel and the resin was washed with CH_2Cl_2 (4×15 mL), MeOH (4×15 mL), and Et_2O (2×15 mL). The resulting resin was then suspended in toluene (2 mL), and *n*-Bu_3SnH (87.3 mg, 0.30 mmol, 2.0 equiv) and AIBN (24.6 mg, 0.150 mmol, 1.0 equiv) were added after which the reaction mixture was heated to $90\,^\circ C$ for 2 h. After cooling, the suspension was poured into a fritted funnel and the resin was washed with CH_2Cl_2 (2×10 mL). The filtrate was then concentrated and 10% HCl (5 mL) was added, and the resulting solution was washed with hexanes (3×10 mL). The aqueous phase was then neutralized with 10% NaOH and extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated to afford **22** (17.4 mg, 87% yield in 89% purity as estimated by ^1H NMR). An identical procedure was used for the cyclization of *o*-allyl anilines **12**–**17**, while for substrates **18** and **19** the reaction time and temperature were increased to 1 h and $0\,^\circ C$, respectively.

Solid phase synthesis of 2-methyl indolines 44–52

Preparation of compounds 44–49. To a suspension of resin (**22**, **23**, or **29**: 200 mg, 0.150 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at $0\,^\circ C$ was added triethylamine (0.558 mL, 4.00 mmol, 26.7 equiv) followed by $COCl_2$ (20 wt% by weight in toluene, 1.98 mL, 4.00 mmol, 26.7 equiv). The resulting mixture was stirred at $0\,^\circ C$ for 1 h and then poured into a fritted funnel where the resin was washed with CH_2Cl_2 (3×10 mL) and Et_2O (3×10 mL). After drying for 5 min, this resin was resuspended in CH_2Cl_2 (3 mL) and appropriate R^2NH_x amine (benzylamine or morpholine, 1.50 mmol, 10.0 equiv) and triethylamine (0.558 mL, 4.00 mmol, 26.7 equiv) were added. The reaction mixture was stirred at $25\,^\circ C$ for 18 h and then poured into a fritted funnel where the resin was washed CH_2Cl_2 (4×10 mL), MeOH (4×10 mL), and Et_2O (4×10 mL) and dried. The resin was then suspended in toluene (2 mL), and *n*-Bu_3SnH (0.162 mL, 0.600 mmol, 4.0 equiv) and AIBN (33 mg, 0.200 mmol, 1.3 equiv) were added, and the reaction mixture was heated to $90\,^\circ C$ and stirred for 2 h. After cooling to $25\,^\circ C$, the resin was removed by filtration, washed with CH_2Cl_2 (4×15 mL) and the resulting filtrate was concentrated to afford the crude products which were purified by column chromatography (5→50% EtOAc in hexanes) to afford pure **44**–**49**.

Preparation of compounds 50–52. To a suspension of resin (**22**, **23**, or **29**: 200 mg, 0.150 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at $0\,^\circ C$ was added triethylamine (0.558 mL, 4.00 mmol, 26.7 equiv) followed by $COCl_2$ (20 wt% in toluene, 1.98 mL, 4.00 mmol, 26.7 equiv). The resulting mixture was stirred at $0\,^\circ C$ for 1 h and then poured into a fritted funnel where the resin was washed with CH_2Cl_2 (3×10 mL) and Et_2O (3×10 mL). After drying for 5 min, the resin was resuspended in CH_2Cl_2 (3 mL), and piperazine (128 mg, 1.5 mmol, 10.0 equiv) and triethylamine (0.558 mL, 4.00 mmol, 26.7 equiv) were added. The mixture was stirred at $25\,^\circ C$ for 18 h and then poured into a fritted funnel where the resin was washed with CH_2Cl_2 (4×10 mL), MeOH (4×10 mL), and Et_2O (4×10 mL) and dried. This resin was then resuspended in CH_2Cl_2 (5 mL) and DCC (310 mg, 1.5 mmol, 10.0 equiv), 4-DMAP (24 mg, 0.200 mmol, 1.3 equiv), and the corresponding carboxylic acid

(**41**–**43**: 1.5 mmol, 10 equiv) were added. The resulting mixture was stirred at 25 °C for 48 h and then poured into a fritted funnel where the resin was washed CH_2Cl_2 (4×10 mL), MeOH (4×10 mL), and Et_2O (4×10 mL) and dried. The resulting resin was then suspended in toluene (2 mL) and *n*-Bu_3SnH (0.162 mL, 0.600 mmol, 4.0 equiv) and AIBN (33 mg, 0.200 mmol, 1.3 equiv) were added, and the reaction mixture was heated to 90 °C for 2 h after which time the resin was removed by filtration and washed with CH_2Cl_2 (2×10 mL). The filtrate was then concentrated and the crude reaction products were purified by column chromatography (5→100% EtOAc in hexanes) to afford pure **50**–**52**.

44: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.15–7.10 (m, 2H), 6.93–6.85 (m, 2H), 4.56–4.47 (m, 1H), 3.79–3.69 (m, 4H), 3.49–3.44 (m, 2H), 3.39–3.33 (m, 2H), 3.20 (dd, *J* = 15.5, 8.8 Hz, 1H), 2.64 (dd, *J* = 15.5, 7.3 Hz, 1H), 1.39 (d, *J* = 6.2 Hz, 3H); HRMS calcd for $C_{14}H_{18}N_2O_2$ [M + H$^+$] 247.1446, found 247.1443.

45: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.97 (s, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.53–4.45 (m, 1H), 3.78–3.69 (m, 4H), 3.45–3.41 (m, 2H), 3.36–3.32 (m, 2H), 3.16 (dd, *J* = 15.4, 8.4 Hz, 1H), 2.60 (dd, *J* = 15.8, 7.4 Hz, 1H), 2.27 (s, 3H), 1.37 (d, *J* = 5.9 Hz, 3H); HRMS calcd for $C_{15}H_{20}N_2O_2$ [M + H$^+$] 261.1603, found 261.1615.

46: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 8.6 Hz, 1H), 7.37 (s, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.61–4.53 (m, 1H), 3.78–3.67 (m, 4H), 3.55–3.49 (m, 2H), 3.38–3.32 (m, 2H), 3.24 (dd, *J* = 15.8, 8.8 Hz, 1H), 2.68 (dd, *J* = 15.8, 7.9 Hz, 1H), 1.39 (d, *J* = 6.2 Hz, 3H); ESMS calcd for $C_{15}H_{17}N_3O_2$ [M + H$^+$] 272, found 272.

47: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 8.5 Hz, 1H), 7.38–7.26 (m, 5H), 7.17 (t, *J* = 7.0 Hz, 2H), 6.93 (t, *J* = 7.6 Hz, 1H), 5.05 (s, 1H), 4.60–4.50 (m, 2H), 4.45–4.38 (m, 1H), 3.39 (dd, *J* = 15.8, 9.1 Hz, 1H), 2.62 (d, *J* = 15.8 Hz, 1H), 1.31 (d, *J* = 6.5 Hz, 3H); HRMS calcd for $C_{17}H_{18}N_2O$ [M + Na$^+$] 289.1317, found 289.1321.

48: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 8.0 Hz, 1H), 7.37–7.26 (m, 6H), 6.97 (d, *J* = 9.5 Hz, 1H), 5.02 (s, 1H), 4.58–4.49 (m, 2H), 4.46–4.37 (m, 1H), 3.35 (dd, *J* = 15.8, 9.2 Hz, 1H), 2.57 (d, *J* = 15.8 Hz, 1H), 2.28 (s, 3H), 1.30 (d, *J* = 6.6 Hz, 3H); HRMS calcd for $C_{18}H_{20}N_2O$ [M + H$^+$] 281.1654, found 281.1645.

49: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 8.5 Hz, 1H), 7.54–7.47 (m, 1H), 7.39–7.29 (m, 6H), 5.03 (s, 1H), 4.54 (d, *J* = 5.6 Hz, 2H), 4.41–4.35 (m, 1H), 3.41 (dd, *J* = 16.1, 9.4 Hz, 1H), 2.70 (d, *J* = 16.1 Hz, 1H), 1.33 (d, *J* = 6.2 Hz, 3H); HRMS calcd for $C_{18}H_{17}N_3O$ [M + H$^+$] 292.1450, found 292.1446.

50: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.41–7.35 (m, 4H), 7.16–7.10 (m, 2H), 6.91–6.87 (m, 2H), 4.55–4.48 (m, 1H), 3.86–3.36 (m, 8H), 3.22 (dd, *J* = 15.8, 8.8 Hz, 1H), 2.65 (dd, *J* = 15.8, 7.4 Hz, 1H), 1.39 (d, *J* = 6.3 Hz, 3H); HRMS calcd for $C_{21}H_{22}ClN_3O_2$ [M + Na$^+$] 406.1298, found 406.1314.

51: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89–7.84 (m, 3H), 7.58–7.42 (m, 4H), 6.96–6.81 (m, 3H), 4.50–4.45 (m, 1H), 3.56–3.51 (m, 4H), 3.30–3.22 (m, 4H), 3.16 (dd, *J* = 15.8, 8.5 Hz, 1H), 2.58 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.26 (s, 3H), 1.36 (d, *J* = 6.2 Hz, 3H); HRMS calcd for $C_{26}H_{27}N_3O_2$ [M + Na$^+$] 436.2001, found 436.2017.

52: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.39 (m, 7H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.63–4.54 (m, 1H), 3.94–3.49 (m, 8H), 3.26 (dd, *J* = 15.8, 8.8 Hz, 1H), 2.70 (dd, *J* = 16.2, 7.9 Hz, 1H), 1.40 (d, *J* = 6.2 Hz, 3H); HRMS calcd for $C_{22}H_{22}N_4O_2$ [M + Na$^+$] 397.1640, found 397.1643.

General procedure for construction and radical release of polycyclic indolines 60–64

Preparation of compounds 60–62. To a suspension of resin **22** (200 mg, 0.150 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at ambient temperature was added DCC (310 mg, 1.5 mmol, 10.0 equiv), 4-DMAP (24 mg, 0.200 mmol, 1.3 equiv), and carboxylic acid **55**, **56** or **57** (1.5 mmol, 10.0 equiv). The resulting mixture was allowed to stir at ambient temperature for 48 h and then poured into a fritted funnel where the resin was washed with CH_2Cl_2 (5×10 mL), MeOH (10×10 mL), and Et_2O (5×10 mL). This resin was then suspended in toluene (4 mL) and warmed to 90 °C. To the reaction mixture was added a solution of *n*-Bu_3SnH (0.162 mL, 0.600 mmol, 4.0 equiv) and AIBN (33 mg, 0.200 mmol, 1.3 equiv) in toluene (1 mL) via syringe pump over a period of 4 h. After addition was completed, the reaction mixture was cooled to 25 °C and the resin was removed by filtration and washed with CH_2Cl_2 (2×10 mL). The filtrate was then concentrated and the crude cyclization product was purified by column chromatography (0→25% EtOAc in hexanes) to afford pure **60**–**62**. In all three cases, only one diastereometric product was isolated.

Preparation of compounds 63 and 64. To a suspension of resin **22** (200 mg, 0.150 mmol, 1.0 equiv) in DMF (4 mL) was added alkenyl bromide **58** or **59** (1.5 mmol, 10.0 equiv) and NaH (60% dispersion in mineral oil, 120 mg, 3.0 mmol, 20.0 equiv). The reaction mixture was heated to 40 °C for 48 h and then cooled to 25 °C and quenched with methanol (5 mL). The resulting suspension was poured into a fritted funnel where the resin was washed with CH_2Cl_2 (4×10 mL), MeOH (4×10 mL), and Et_2O (4×10 mL). After drying the resin was cleaved as described above to provide polycycles **63** and **64**.

60: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.1 Hz, 1H), 7.26–7.17 (m, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.59–4.53 (m, 1H), 3.17 (dd, *J* = 15.4, 8.5 Hz, 1H), 2.85 (dd, *J* = 15.1, 9.9 Hz, 1H), 2.38 (dd, *J* = 12.1, 5.9 Hz, 1H), 2.31–2.26 (m, 1H), 1.91–1.84 (m, 4H), 1.70–1.66 (m, 2H), 1.50–1.45 (m, 1H), 1.36–1.21 (m, 1H); HRMS calcd for $C_{15}H_{17}NO$ [M + H$^+$] 228.1388, found 228.1380.

61: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23–7.17 (m, 3H), 7.04–7.00 (m, 1H), 4.60–4.52 (m, 1H), 3.18 (dd, *J* = 15.5, 8.5 Hz, 1H), 2.84 (dd, *J* = 15.3, 10.0 Hz, 1H), 2.61 (dd, *J* = 12.3, 5.9 Hz, 1H), 1.95–1.88 (m, 1H), 1.80–1.58 (m,

6H), 1.47–1.10 (m, 4H); HRMS calcd for $C_{16}H_{19}NO$ [M + H$^+$] 242.1545, found 242.1541.

62: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, J = 7.7 Hz, 1H), 7.41–7.01 (m, 8H), 4.51–4.43 (m, 1H), 3.40 (dd, J = 14.1, 4.4 Hz, 1H), 3.18–3.10 (m, 2H), 2.83 (dd, J = 15.5, 9.7 Hz, 1H), 2.63 (dd, J = 14.1, 10.3 Hz, 1H), 2.50–2.41 (m, 1H), 1.50–1.43 (m, 1H); HRMS calcd for $C_{18}H_{17}NO$ [M + H$^+$] 264.1388, found 264.1386.

63: ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.12–7.05 (m, 2H), 6.75 (td, J = 7.3, 1.1 Hz, 1H), 6.57 (d, J = 7.7 Hz, 1H), 4.17–4.03 (m, 1H), 3.43 (dd, J = 11.3, 6.9 Hz, 1H), 3.21 (dd, J = 16.1, 9.5 Hz), 2.98–2.85 (m, 2H), 2.19 (oct, J = 6.6 Hz, 1H), 1.60 (dd, J = 7.3, 6.6 Hz, 2H), 1.06 (d, J = 7.0 Hz, 3H); HRMS calcd for $C_{12}H_{15}N$ [M + H$^+$] 174.1277, found 174.1281.

64: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16–7.08 (m, 2H), 6.87–6.75 (m, 2H), 4.25–4.16 (m, 1H), 3.74 (dd, J = 10.3, 7.9 Hz, 1H), 3.45 (dd, J = 11.4, 7.0 Hz, 1H), 3.26 (dd, J = 16.1, 9.1 Hz, 1H), 3.07 (dd, J = 11.4, 7.3 Hz, 1H), 2.90 (dd, J = 16.4, 3.8 Hz, 1H), 2.02 (m, 1H), 1.71 (m, 1H), 1.43 (quint, J = 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H); HRMS calcd for $C_{13}H_{17}N$ [M + H$^+$] 188.1434, found 188.1439.

Procedure for solid phase synthesis of 2-methyl indoles 70–75

Acylation procedure A. To a suspension of resin **22** (200 mg, 0.150 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 25 °C was added diisopropylethylamine (0.52 mL, 3.0 mmol, 20 equiv), 4-DMAP (18 mg, 0.15 mmol, 1.0 equiv), and the appropriate electrophile (1.5 mmol, 10 equiv). The resulting mixture was stirred for 48 h and then poured into a fritted funnel and the resin was washed with CH_2Cl_2 (4×15 mL), MeOH (4×15 mL), and Et_2O (2×15 mL)

Acylation procedure B. To a suspension of resin **33** (200 mg, 0.150 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C was added triethylamine (0.42 mL, 3.0 mmol, 20 equiv) and $COCl_2$ (1.5 mL of a 20% solution by weight in toluene). The reaction mixture was stirred for 1 h and then poured into a fritted funnel and the resin was washed with CH_2Cl_2 (4×15 mL) and Et_2O (2×15 mL). The resin was then resuspended in CH_2Cl_2 (5 mL) at 25 °C, and triethylamine (0.42 mL, 3.0 mmol, 20 equiv) and the appropriate amine (3.0 mmol, 20 equiv) were added. The reaction mixture was stirred for 18 h and then poured into a fritted funnel, and the resin was washed with CH_2Cl_2 (4×15 mL), MeOH (4×15 mL), and Et_2O (2×15 mL). The resin was then resuspended in benzene (10 mL) at 25 °C and treated with AIBN (74 mg, 0.45 mmol, 3.0 equiv). The reaction mixture was then heated at 85 °C and stirred for 48 h. The reaction mixture was then filtered and the filtrate was directly concentrated and purified by PTLC (30% ethyl acetate/hexane) and analyzed by HRMS and ^{1}H NMR spectroscopic methods.

70: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 7.9 Hz, 1H), 7.21–7.17 (m, 4H), 6.73 (s, 1H), 2.59 (d, J = 1.1 Hz, 3H), 2.34 (s, 3H); HRMS calcd for $C_{16}H_{15}NO_2S$ [M + H$^+$] 286.0896, found 286.0901.

71: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 7.9 Hz, 2H), 7.52 (t, J = 7.9 Hz, 1H), 7.44–7.40 (m, 3H), 7.22–7.20 (m, 2H), 6.35 (s, 1H), 2.60 (s, 3H); HRMS calcd for $C_{15}H_{13}NO_2S$ [M + H] 271.06615, found 271.066. **72**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, J = 8.2 Hz, 2H), 7.63 (t, J = 6.7 Hz, 1H), 7.51–7.46 (m, 3H), 7.14–7.12 (m, 1H), 7.01–7.00 (m, 2H), 6.43 (s, 1H), 2.41 (s, 3H); HRMS calcd for $C_{16}H_{13}NO$ [M + H$^+$] 236.1070, found 236.1064.

73: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.71 (d, J = 7.0 Hz, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.14–7.10 (m, 1H), 7.02–6.95 (m, 4H), 6.42 (s, 1H), 3.90 (s, 3H), 2.44 (d, J = 1.1 Hz, 3H); HRMS calcd for $C_{17}H_{15}NO_2$ [M + •] 264.1019, found 264.1010.

74: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.20–7.13 (m, 2H), 6.33–6.30 (m, 1H), 6.03–5.98 (m, 1H), 5.72 (m, 1H), 5.31–5.26 (m, 2H), 2.59 (s, 3H); HRMS calcd for $C_{13}H_{14}N_2O$ [M + H$^+$] 215.1179, found 215.1189.

75: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.60 (dd, J = 1.4, 6.9 Hz, 1H), 7.48–7.47 (m, 1H), 7.40–7.38 (m, 4H), 7.35–7.34 (m, 1H), 7.15–7.11 (m, 2H), 6.32–6.30 (m, 1H), 5.94 (bs, 1H), 4.69 (d, J = 5.8 Hz, 2H), 2.59 (d, J = 1.1 Hz, 3H); HRMS calcd for $C_{17}H_{16}N_2O$ [M + Na$^+$] 287.1155, found 287.1150.

Analytical data for *o*-prenylated carbamates 78, 81–84

78: R_f = 0.25 (silica gel, EtOAc:hexanes 1:3); FT-IR (neat) ν_{max} 2226, 1740, 1584, 1522, 1298, 1215, 1058 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, J = 8.5 Hz, 1H), 7.50 (dd, J = 8.5, 1.7 Hz, 1H), 7.41 (s, 1H), 6.92 (s, 1H), 5.15 (t, J = 7.0 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 3.28 (d, J = 7.0 Hz, 2H), 1.79 (s, 6H), 1.31 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.0, 140.7, 136.1, 133.0, 131.4, 129.6, 119.7, 119.6 119.1, 106.0, 61.6, 30.9, 25.6, 17.7, 14.4; HRMS calcd for $C_{15}H_{18}N_2O_2$ [M + Na$^+$] 281.1260, found 281.1270.

81: R_f = 0.74 (silica gel, EtOAc/hexanes 1:3); FT-IR (neat) ν_{max} 1690, 1527, 1451, 1252, 1236, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (s, 1H), 6.86 (s, 1H), 6.60 (s, 1H) 5.09–5.07 (m, 1H), 4.29 (q, J = 5.9 Hz, 2H), 3.36 (d, J = 5.3 Hz, 2H), 2.36 (s, 6H), 1.91 (s, 3H), 1.81 (s, 3H), 1.38 (t, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.7, 136.7, 136.5, 136.4, 133.6, 127.6, 122.0, 121.0, 116.7 61.4, 27.2, 26.1, 21.5, 20.6, 18.2, 15.0; HRMS calcd for $C_{16}H_{23}NO_2$ [M + H$^+$] 262.1801, found 262.1805.

82: R_f = 0.60 (silica gel, EtOAc:hexanes 1:3); FT-IR (neat) ν_{max} 1688, 1527, 1477, 1398, 1245, 1062 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (bs, 1H), 7.32 (dd, J = 8.4, 2.2 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 6.62 (bs, 1H), 5.17–5.14 (m, 1H), 4.21 (q, J = 7.3 Hz, 2H), 3.24 (d, J = 6.9 Hz, 2H), 1.78 (s, 6H), 1.30 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.6, 135.3, 134.9, 134.8, 132.1, 129.9, 129.8, 120.6, 116.5, 61.2, 31.0, 25.6,

17.7, 14.5; HRMS calcd for $C_{14}H_{18}NBrO_2$ [M + Na^+] 334.0415, found 334.0415.

83: R_f = 0.22 (silica gel, EtOAc/hexanes 1:3); FT-IR (neat) ν_{max} 1736, 1718, 1589, 1524, 1278, 1207, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.5 Hz, 1H), 7.88 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.80 (d, *J* = 2.1 Hz, 1H), 6.93 (s, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 3.30 (d, *J* = 7.0 Hz, 2H), 1.78 (s, 3H), 1.75 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.6, 153.1, 140.7, 134.8, 130.9, 128.9, 128.8, 124.5, 120.7, 119.0, 61.2, 51.7, 31.2, 28.0, 17.6, 14.3; HRMS calcd for $C_{16}H_{21}NO_4$ [M + H^+] 292.1543, found 292.1545.

84: R_f = 0.13 (silica gel, EtOAc:hexanes 1:3); FT-IR (neat) ν_{max} 1734, 1560, 1541, 1508, 1340, 1213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 9.1 Hz, 1H), 8.05 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.99 (d, *J* = 2.6 Hz, 1H), 7.06 (s, 1H), 5.18–5.14 (m, 1H), 4.21 (q, *J* = 7.3 Hz, 2H), 3.34 (d, *J* = 7.0 Hz, 2H), 1.79–1.78 (m, 6H), 1.29 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.8, 142.6, 142.5, 136.1, 129.2, 124.7, 122.9, 119.5, 118.7, 61.7, 31.0, 25.6, 17.7, 14.2; ESI calcd for $C_{14}H_{18}N_2O_4$ [M + Na^+] 301, found 301.

Procedure for the loading of the 2,2-dimethyldihydroquinoline template 77

To a suspension of selenium bromide resin (200 mg of 0.75 mmol/g, 0.150 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at 0 °C was added a solution of 4-cyano-2-prenylaniline (**75**) (56 mg, 0.30 mmol, 2.0 equiv) in CH_2Cl_2 (1 mL). The resulting mixture was slowly stirred at 0 °C for 30 min, and the resulting suspension was poured into a fritted funnel and the resin was washed with CH_2Cl_2 (4×15 mL), MeOH (4×15 mL), and Et_2O (2×15 mL). The resulting resin was then resuspended in THF (5 mL) at 25 °C and treated with H_2O_2 (0.10 mL of a 30 wt.% aqueous solution, 0.90 mmol, 6 equiv). The reaction mixture was then slowly stirred for 1 h, and the resulting suspension was then filtered. The excess H_2O_2 was quenched by the addition of 1.0 M Na_2SO_3 (5 mL). The aqueous phase was then extracted with Et_2O (3×10 mL), and the combined extracts were dried over $MgSO_4$ and concentrated. The crude product (24 mg, 85% yield) was analyzed for purity by ^1H NMR (>95% purity).

77: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.18 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.33 (d, *J* = 8.1 Hz, 1H), 6.19 (d, *J* = 9.9 Hz, 1H), 5.50 (d, *J* = 9.6 Hz, 1H), 4.11 (bs, 1H) 1.34 (s, 6H); HRMS calcd for $C_{12}H_{12}N_2$ [M + H^+] 185.1073, found 185.1067.

General procedure for the loading of the 2-propenyl indoline templates 80, 85–88

To a suspension of selenium bromide resin (200 mg of 0.75 mmol/g, 0.150 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at 0 °C was added a solution of the ethyl carbamate of 4-cyano-2-prenylaniline (**78**, 77 mg, 0.30 mmol, 2.0 equiv) in CH_2Cl_2 (1 mL) followed by addition of $SnCl_4$ (0.450 mL of a 1.0 M solution in CH_2Cl_2, 0.450 mmol, 3.0 equiv). The reaction mixture was slowly stirred at 0 °C for 2 h and then quenched by addition of Et_3N (2.0 mL). The resulting suspension was poured into a fritted funnel and the resin was washed with CH_2Cl_2 (4×15 mL), MeOH (4×15 mL), and Et_2O (2×15 mL). The resulting resin was then resuspended in THF (5 mL) at 25 °C and treated with H_2O_2 (0.10 mL of a 30 wt.% aqueous solution, 0.90 mmol, 60 equiv). The reaction mixture was then slowly stirred for 1 h, and the resulting suspension was then filtered. The excess H_2O_2 was quenched by the addition of 1.0 M Na_2SO_3 (5 mL). The aqueous phase was then extracted with Et_2O (3×10 mL), and the combined extracts were dried over $MgSO_4$ and concentrated. The crude product (35 mg, 90% yield) was analyzed for purity by ^1H NMR (>95% purity).

80: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 8.5 Hz, 1H), 7.38 (s, 1H), 4.90 (dd, *J* = 10.5, 2.9 Hz, 1H), 4.79 (s, 2H), 4.33–4.22 (m, 2H), 3.44 (dd, *J* = 16.7, 10.9 Hz, 1H), 2.85 (dd, *J* = 16.7, 3.2 Hz, 1H), 1.66 (s, 3H), 1.31 (t, *J* = 6.9 Hz, 3H); GCMS calcd for $C_{15}H_{16}N_2O_2$ [M + H] 256, found 256.

85: ^1H NMR (400 MHz, $CDCl_3$) δ = 6.70 (s, 1H), 4.94 (bd, *J* = 7.6 Hz, 1H), 4.85 (d, *J* = 29.4 Hz, 2H), 4.32 (bs, 1H), 3.38–3.32 (m, 1H), 2.76 (d, *J* = 12.9 Hz, 1H), 2.39 (s, 3H), 2.24 (s, 3H), 1.75 (s, 3H), 1.38 (b, 3H); HRMS calcd for $C_{16}H_{21}NO_2$ [M + H +] 260.1645, found 260.1648.

86: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 9.1 Hz, 1H), 7.24 (s, 1H), 4.86 (d, *J* = 9.4 Hz, 1H), 4.79 (d, *J* = 14.7 Hz, 2H), 4.26–4.25 (m, 2H), 3.42 (dd, *J* = 16.4, 10.6 Hz, 1H), 2.80 (dd, *J* = 16.7, 2.6 Hz, 1H), 1.66 (s, 3H), 1.35–1.29 (b, 3H); HRMS calcd for $C_{14}H_{16}BrNO_2$ [M + H^+] 310.0437, found 310.0443.

87: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 7.3 Hz, 1H), 7.80 (s, 1H), 4.90 (dd, *J* = 12.8, 2.6 Hz, 1H), 4.79 (d, *J* = 14.4 Hz, 2H), 4.28–4.21 (m, 2H), 3.87 (s, 3H), 3.45 (dd, *J* = 16.7, 10.8 Hz, 1H), 2.85 (dd, *J* = 13.5, 2.9 Hz, 1H), 1.65 (s, 3H), 1.34 (t, *J* = 14.6 Hz, 3H); HRMS calcd for $C_{16}H_{19}NO_4$ [M + H^+] 290.1387, found 290.1386.

88: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 6.8 Hz, 1H), 8.01 (s, 1H), 4.96 (dd, *J* = 10.3, 2.6 Hz, 1H), 4.81 (s, 2H), 4.31–4.28 (m, 2H), 3.49 (dd, *J* = 16.1, 10.0 Hz, 1H), 2.91 (dd, *J* = 16.7, 2.6 Hz, 1H), 1.68 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H); HRMS calcd for $C_{14}H_{16}N_2O_4$ [M + H^+] 277.1183, found 277.1178.

Representative procedure for solid phase synthesis of 2-propenyl indolines 91–102

To a suspension of resin **79** (200 mg, 0.150 mmol, 1.0 equiv) in toluene (5 mL) at 25 °C was added azidotimethyltin (308 mg, 1.50 mmol, 10 equiv) as a solid. The reaction mixture was then heated to 100 °C and stirred for 12 h, and the resulting suspension was poured into a fritted funnel and the resin was washed with CH_2Cl_2 (4×15 mL), MeOH (4×15 mL), and Et_2O (2×15 mL).

After drying for 30 min, the resulting resin was resuspended in CH_2Cl_2:TFA (20:1, 10 mL) at 25 °C and stirred for 1 h. The reaction mixture was poured into a fritted funnel and the resin was washed with CH_2Cl_2 (4×15 mL), MeOH (4×15 mL), and Et_2O (2×15 mL). The resin was then resuspended in CH_3CN (5 mL), and appropriate alkylating agent (R^1X, 3.0 mmol, 20.0 equiv) and diisopropylethylamine (0.78 mL, 4.5 mmol, 30 equiv) were added. The reaction mixture was heated to 80 °C for 12 h, cooled to 25 °C, and then poured into a fritted funnel and the resin was washed with CH_2Cl_2 (4×15 mL), MeOH (4×15 mL), and Et_2O (2×15 mL). For compounds **100**–**102**, the resulting resin was resuspended in THF (4 mL) at 25 °C and treated with H_2O_2 (0.10 mL of a 30 wt.% aqueous solution, 0.90 mmol, 6.0 equiv), and slowly stirred for 1 h, and the resulting suspension was then filtered. The excess H_2O_2 was quenched by the addition of 1.0 M Na_2SO_3 (5 mL). The aqueous phase was then extracted with Et_2O (3×10 mL), and the combined extracts were dried over $MgSO_4$ and concentrated. The compounds were purified by PTLC (30% ethyl acetate/hexane) and analyzed by HRMS and ^1H NMR spectroscopic methods. For compounds **91**–**99**, the resulting resin was resuspended in toluene (5 mL) and to this was added a pre-mixed solution of amine (R^2NH_2, 3.0 mmol, 20.0 equiv) and trimethylaluminum (0.15 mL of a 2.0 M solution in toluene, 3.0 mmol, 20.0 equiv). The reaction mixture was then heated to 90 °C for 12 h, cooled to 25 °C, and then poured into a fritted funnel and the resin was washed with CH_2Cl_2 (4×15 mL), MeOH (4×15 mL), and Et_2O (2×15 mL). The compounds were then oxidatively cleaved from the solid support and subsequently purified in a manner analogous to that used for compounds **30**–**32**.

91: ^1H NMR (500 MHz, $CDCl_3$) δ = 8.16 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 6.01–5.96 (m, 1H), 5.29–5.22 (m, 3H), 5.15–5.13 (m, 1H), 5.06–5.04 (m, 1H), 4.84 (dd, J = 10.6, 4.4 Hz, 1H), 4.48 (s, 3H), 4.06–3.99 (m, 2H), 3.68 (dd, J = 16.9, 11.0 Hz, 1H), 3.04 (dd, J = 16.5, 4.4 Hz, 1H), 1.77 (s, 3H); HRMS calcd for $C_{17}H_{20}N_6O_2$ [M + H$^+$] 325.1771, found 325.1774.

92: ^1H NMR (500 MHz, $CDCl_3$) δ = 8.14 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.47–7.41 (m, 5H), 6.01–5.94 (m, 1H), 5.85 (s, 2H), 5.28–5.18 (m, 3H), 5.13–5.10 (m, 1H), 5.05–5.03 (m, 1H), 4.84 (dd, J = 10.6, 4.0 Hz, 1H), 4.03–3.99 (m, 2H), 3.66 (dd, J = 16.5, 10.6 Hz, 1H), 3.02 (dd, J = 16.5, 4.0 Hz, 1H), 1.77 (s, 3H); HRMS calcd for $C_{23}H_{24}N_6O$ [M + H$^+$] 401.2084, found 401.2077.

93: ^1H NMR (500 MHz, $CDCl_3$) δ = 8.13 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.94 (s, 1H), 7.44 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.01–5.95 (m, 1H), 5.78 (s, 2H), 5.28–5.19 (m, 3H), 5.14–5.12 (m, 1H), 4.83 (dd, J = 11.0, 4.4 Hz, 1H), 4.06–3.95 (m, 2H), 3.87 (s, 3H), 3.65 (dd, J = 16.9, 11.0 Hz, 1H), 3.01 (dd, J = 16.5, 4.0 Hz, 1H), 1.78 (s, 3H); HRMS calcd for $C_{24}H_{26}N_6O_2$ [M + H$^+$] 431.2190, found 431.2181.

94: ^1H NMR (500 MHz, $CDCl_3$) δ = 8.16 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.95 (s, 1H), 5.19 (s, 1H), 5.05 (s, 1H), 4.81 (dd, J = 10.6, 4.4 Hz, 1H), 4.44 (s, 3H), 3.65 (dd, J = 16.8, 10.6 Hz, 1H), 3.40–3.35 (m, 2H), 3.03 (dd, J = 16.9, 4.4 Hz, 1H), 1.78 (s, 3H), 1.60–1.57 (m, 2H), 1.44–1.42 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); HRMS calcd for $C_{18}H_{24}N_6O$ [M + H$^+$] 341.2084, found 341.2085.

95: ^1H NMR (500 MHz, $CDCl_3$) δ = 8.14 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 7.51–7.42 (m, 5H), 5.85 (s, 2H), 5.18 (s, 1H), 5.06 (t, J = 5.1 Hz, 1H), 5.04 (s, 1H), 4.80 (dd, J = 10.6, 4.1 Hz, 1H), 3.64 (dd, J = 16.5, 11.0 Hz, 1H), 3.38–3.33 (m, 2H), 3.01 (dd, J = 16.8, 4.4 Hz, 1H), 1.76 (s, 3H), 1.60–1.57 (m, 2H), 1.45–1.39 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); HRMS calcd for $C_{24}H_{28}N_6O$ [M + H$^+$] 217.2397, found 417.2385.

96: ^1H NMR (500 MHz, $CDCl_3$) δ = 8.13 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.93 (s, 1H), 7.42 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 5.78 (s, 2H), 5.17 (s, 1H), 5.06 (t, J = 5.2 Hz, 1H), 5.04 (s, 1H), 4.79 (dd, J = 10.6, 4.4 Hz, 1H), 3.89 (s, 3H), 3.63 (dd, J = 16.5, 10.6 Hz, 1H), 3.39–3.33 (m, 2H), 3.00 (dd, J = 16.9, 4.4 Hz, 1H), 1.75 (s, 3H), 1.61–1.56 (m, 2H); HRMS calcd for $C_{25}H_{30}N_6O_2$ [M + H$^+$] 447.2503, found 447.2508.

97: ^1H NMR (500 MHz, $CDCl_3$) δ = 8.18 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.43–7.37 (m, 5H), 5.43 (t, J = 5.5 Hz, 1H), 5.13 (s, 1H), 5.00 (s, 1H), 4.85 (dd, J = 11.0, 4.4 Hz, 1H), 4.58 (d, J = 5.8 Hz, 2H), 4.45 (s, 3H), 3.67 (dd, J = 16.8, 11.0 Hz, 1H), 3.04 (dd, J = 16.8, 4.8 Hz, 1H), 1.76 (s, 3H); HRMS calcd for $C_{21}H_{22}N_6O$ [M + H$^+$] 375.1928, found 375.1925.

98: ^1H NMR (500 MHz, $CDCl_3$) δ = 8.17 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.49–7.38 (m, 10H), 5.85 (s, 2H), 5.40 (t, J = 5.5 Hz, 1H), 5.12 (s, 1H), 4.99 (s, 1H), 4.84 (dd, J = 10.6, 4.4 Hz, 1H), 4.57 (d, J = 5.2 Hz, 2H), 3.65 (dd, J = 16.8, 11.0 Hz, 1H), 3.02 (dd, J = 16.8, 4.4 Hz, 1H), 1.78 (s, 3H); HRMS calcd for $C_{28}H_{28}N_6O_2$ [M + H$^+$] 481.2346, found 481.2346.

99: ^1H NMR (500 MHz, $CDCl_3$) δ = 8.16 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.45–7.38 (m, 6H), 6.97 (d, J = 8.3 Hz, 2H), 5.78 (s, 2H), 5.40 (t, J = 5.1 Hz, 1H), 5.12 (s, 1H), 4.99 (s, 1H), 4.84 (dd, J = 10.6, 4.4 Hz, 1H), 4.58 (d, J = 5.5 Hz, 2H), 3.87 (s, 3H), 3.65 (dd, J = 16.6, 11.0 Hz, 1H), 3.01 (dd, J = 16.8, 4.4 Hz, 1H), 1.74 (s, 3H); HRMS calcd for $C_{27}H_{26}N_6O$ [M + H$^+$] 451.2241, found 451.2235.

100: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, J = 7.6 Hz, 1H), 7.90 (s, 1H), 4.91 (d, J = 8.8 Hz, 1H), 4.83 (s, 1H), 4.78 (s, 1H), 4.37 (s, 3H), 4.29–4.27 (m, 2H), 3.50 (dd, J = 16.4, 11.1 Hz, 1H), 2.89 (dd, J = 16.4, 3.2 Hz, 1H), 1.68 (s, 3H), 1.36–1.30 (m, 3H); HRMS calcd for $C_{16}H_{19}N_5O_2$ [M + H$^+$] 314.1611, found 314.1621.

101: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, J = 8.5 Hz, 1H), 7.89 (s, 1H), 7.41–7.37 (m, 5H), 5.78 (s, 2H), 4.90 (d, J = 10.3 Hz, 1H), 4.82 (s, 1H), 4.76 (s, 1H), 4.28–4.26 (m, 2H), 3.47 (dd, J = 16.1, 10.8 Hz, 1H), 2.87

(dd, $J=16.4$, 2.8 Hz, 1H), 1.66 (s, 3H), 1.33–1.30 (m, 3H); HRMS calcd for $C_{22}H_{23}N_5O_2$ $[M+H^+]$ 390.1924, found 390.1907.

102: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=7.97$ (d, $J=8.2$ Hz, 1H), 7.88 (s, 1H), 7.36 (d, $J=8.8$ Hz, 2H), 6.89 (d, $J=8.8$ Hz, 2H), 5.70 (s, 2H), 4.90 (d, $J=8.8$ Hz, 1H), 4.82 (s, 1H), 4.76 (s, 1H), 4.28–4.26 (m, 2H), 3.79 (s, 3H), 3.47 (dd, $J=16.7$, 10.8 Hz, 1H), 2.87 (dd, $J=16.4$, 2.6 Hz, 1H), 1.66 (s, 3H), 1.33–1.31 (m, 3H); HRMS calcd for $C_{23}H_{25}N_5O_3$ $[M+Na^+]$ 442.1849, found 442.1850.

Acknowledgements

Financial support for this work was provided by the Skaggs Institute for Chemical Biology, The National Institutes of Health (USA), fellowships from the Division of Organic Chemistry of the American Chemical Society (to A.R.), the Division of Medicinal Chemistry of the American Chemical Society (to R.H.), Dr. Saal van Zwanenbergstichting (to R.v.S.), and the Department of Defense (to J.P.), and grants from American BioScience, Amgen, Array Biopharma, Boehringer-Ingelheim, Glaxo, Hoffmann-LaRoche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

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