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New synthetic technology for the construction of *N*-hydroxyindoles and synthesis of nocathiacin I model systems

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Abstract—A new synthetic method providing expedient access to a wide range of polyfunctionalized *N*-hydroxyindoles (**IV**) is reported. These unique constructs are assembled by nucleophilic additions to in situ generated α,β-unsaturated nitrones (**III**) through carbon–carbon and carbon–heteroatom bond formation. The new synthetic technology was applied to the synthesis of nocathiacin I (**1**) model systems (**2** and **3a–c**) containing the *N*-hydroxyindole structural motif.

1. Introduction

Nocathiacin I (**1**, Fig. 1), a complex thiopeptide antibiotic isolated from *Nocardia* sp. (ATCC-202099) and the fungus *Amicolaptosis* sp., exhibits remarkably potent in vitro and in vivo activity against Gram-positive bacteria.[1–3] One of the most striking structural motifs within the molecular framework of nocathiacin I (**1**) is the *N*-hydroxyindole moiety that carries the oxygen ether linkage and bridges the 15-membered depsipeptide ring with the 10-membered macrolide system of the molecule.[4] Challenged by the daunting structure of nocathiacin I (**1**) and intrigued by the rarity of its *N*-hydroxyindole structural motif in nature and the relative scarcity of methods for its assembly,[5] we initiated a program directed toward the development of synthetic technologies for the generation of substituted *N*-hydroxyindoles suitable for potential applications to complex molecule construction.

In this article, we describe a detailed account of our investigations in this area that culminated in a general method for the synthesis of highly substituted *N*-hydroxyindoles (**IV**, Scheme 1)[6] from readily available aromatic precursors and a variety of nucleophiles through the trapping of in situ generated α,β-unsaturated nitrones and the application of the developed technology to the construction of certain nocathiacin I (**1**) model systems such as **2** and **3a–c** (Fig. 1).[7]

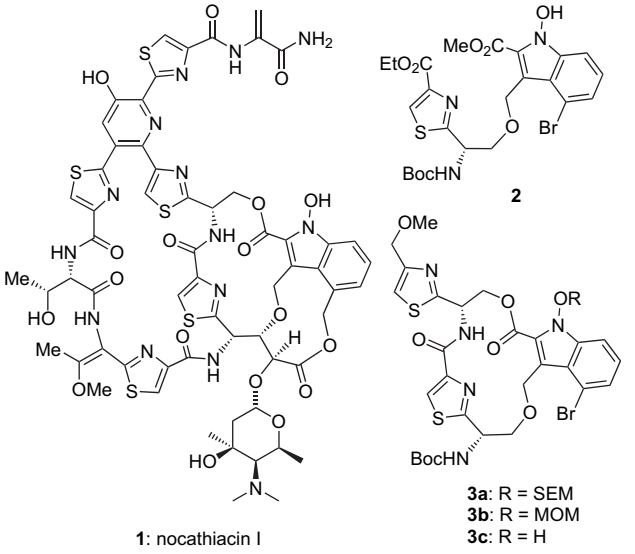

Figure 1. Structures of nocathiacin I (**1**) and *N*-hydroxyindole model systems **2** and **3a–c**. SEM, 2-(trimethylsilyl)ethoxymethyl; MOM, methoxymethyl.

Keywords: *N*-Hydroxyindole; Nitrone; Nocathiacin I; Nucleophilic addition; Synthetic methods.
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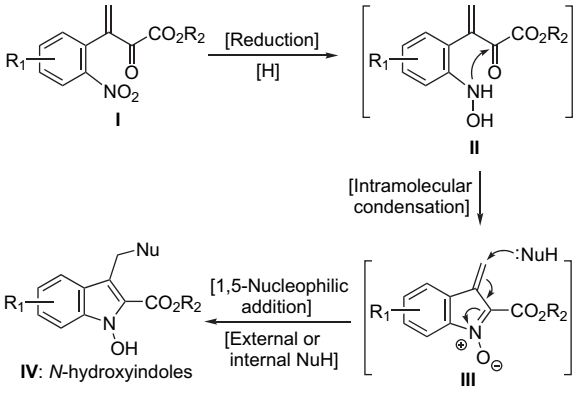


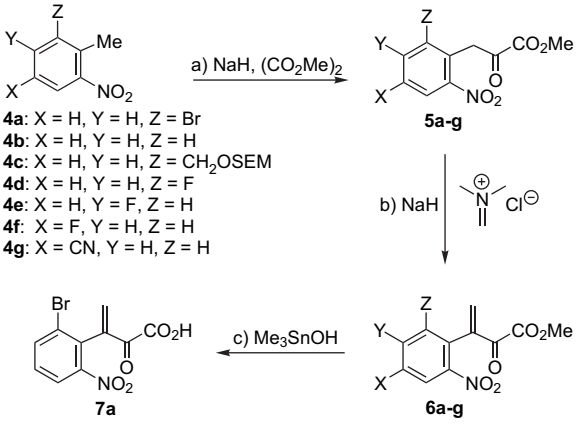
Scheme 1. General route for the construction of 3-substituted *N*-hydroxyindoles (**IV**).

2. Results and discussion

2.1. Synthetic technology development

Based on certain precedents,[5c–g] our general strategy for the construction of *N*-hydroxyindoles, shown in Scheme 1, was devised to take advantage of the ready availability of aromatic nitro compounds as starting materials and the perceived propensity of α,β-unsaturated nitrones to enter into reactions with suitable nucleophiles and give stable adducts. Thus, it was envisioned that reduction of nitro ketoesters **I** under appropriate conditions should produce hydroxylamines **II**, which were expected to undergo facile intramolecular condensation to afford the α,β-unsaturated nitrones **III**, whose existence in the presence of suitable nucleophiles should be transient, leading through 1,5-addition reactions, to *N*-hydroxyindoles **IV**.[8] Having defined the general cascade for the projected synthesis of *N*-hydroxyindoles, the synthesis of the starting nitro ketoesters, the exploration of conditions for their reduction, and the range of capable nucleophiles to be employed in this scheme became the first objectives of the investigation.

Scheme 2 summarizes the synthesis of nitro ketoesters **6a–g** and nitro ketoacid **7a**, which were required for the present

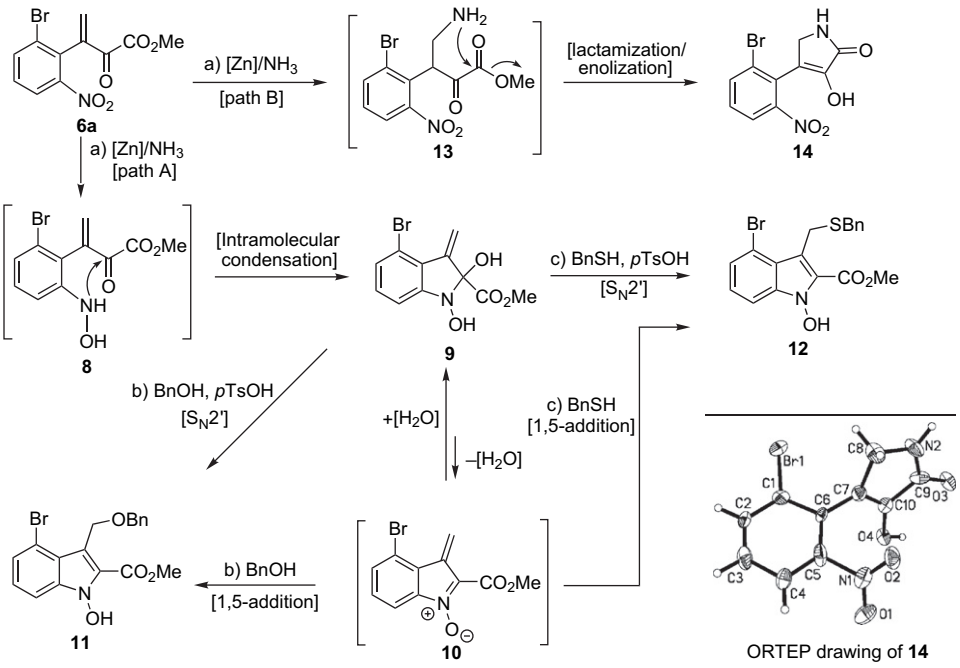


Scheme 2. Synthesis of nitro ketoesters **6a–g** and acid **7a**. Reagents and conditions: (a) NaH (4.0 equiv) $(CO_2Me)_2$ (5.0 equiv), DMF, 0 °C, 1 h; then 25 °C, 12 h, **5a** (60%), **5b** (60%), **5c** (85%), **5d** (80%), **5e** (75%), **5f** (75%), **5g** (65%); (b) NaH (1.1 equiv), THF, 0 °C, 1 h; then $CH_2{=}N^+Me_2Cl^-$ (3.0 equiv), 25 °C, 12 h, **6a** (80%), **6b** (67%), **6c** (98%), **6d** (74%), **6e** (55%), **6f** (75%), **6g** (50%); (c) Me_3SnOH (3.0 equiv), 1,2-DCE, 80 °C, 20 min, 77%. DMF, *N*,*N*-dimethylformamide; DCE, 1,2-dichloroethane.

studies. Thus, reaction of the corresponding nitrotoluene compound with excess dimethyl oxalate in the presence of NaH in DMF at 0–25 °C furnished ketoesters **5a–g** in yields ranging from 60 to 85%.[9] Exposure of each of these compounds to Eschenmoser's salt in the presence of NaH in THF at 0–25 °C then led to the desired α,β-unsaturated ketoesters **6a–g** in 50–98% yield.[10,11] The α,β-unsaturated ketoacid **7a** was prepared from methyl ester **6a** through the action of Me_3SnOH in 1,2-dichloroethane at 70 °C (77% yield), as standard hydrolysis methods resulted in decomposition, as alluded to in a previous communication from our laboratories.[12]

The desired generation and trapping of the α,β-unsaturated nitrones was achieved under two sets of experimental conditions. Scheme 3 depicts the first procedure (method A) for this cascade sequence involving activated zinc [Zn] (prepared from zinc dust, 1,2-dibromoethane and TMSCl) as the reducing agent as demonstrated with nitro ketoester **6a**.[13] Thus, refluxing zinc dust with 1,2-dibromoethane in THF, followed by cooling to 25 °C (refluxing/cooling process repeated three additional times) and subsequent addition of TMSCl, followed by a mixture of aqueous 1 N NH_4Cl and **6a** resulted in the formation of *N*-hydroxyindoline **9** (56% yield) and hydroxylactam **14** (10% yield). The structure of the latter compound was unambiguously proven by X-ray crystallographic analysis (see ORTEP structure, Scheme 3).[14] These results can be rationalized by envisioning ring closure within the structure of the initially formed hydroxylamine (**8**) leading to *N*-hydroxylamine tertiary alcohol **9** (path A, Scheme 3) on one hand, and 1,4-addition of NH_3 to the starting material **6a** followed by a lactamization/enolization sequence within the initially formed aminoketoester **13** to generate compound **14** (path B, Scheme 3) on the other. Tertiary alcohol **9** exhibited high reactivity, especially upon exposure to acidic conditions that resulted in the loss of a molecule of water, generating a reactive species presumed to be the α,β-unsaturated nitrone **10**, whose isolation proved elusive. The presence of the α,β-unsaturated nitrone **10** was supported by its trapping with a variety of nucleophiles. Thus, reaction of **9** with benzyl alcohol (5.0 equiv) or benzyl mercaptan (5.0 equiv) in DME at 40 °C in the presence of *p*TsOH led to the formation of *N*-hydroxyindoles **11** (55% yield) and **12** (90% yield), respectively. These reactions are presumed to proceed either directly from **9** by S_N2'-type displacement, or by 1,5-addition to the initially formed nitrone (**10**), or through both of the potential mechanistic pathways. It is interesting to note that the isolation of *N*-hydroxyindoles **11** and **12** stands in contrast to the observations of Myers and Herzon in which their initially formed products from 1,5-nucleophilic additions to a sterically congested α,β-unsaturated nitrone proved too labile for isolation, rapidly reverting back to their components instead.[5d]

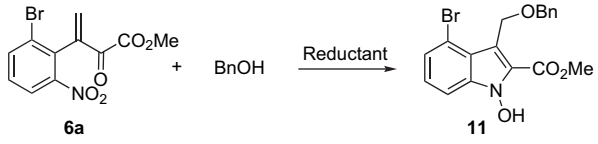
In search of a more direct and convenient access to the desired *N*-hydroxyindoles from the same starting materials, an alternative experimental procedure was explored and optimized as summarized in Scheme 4 and Table 1. According to this method (method B), nitro ketoester **6a** was treated with $SnCl_2\cdot 2H_2O$ (2.2 equiv) in the presence of benzyl alcohol (5.0 equiv) or benzyl mercaptan (5.0 equiv) and 4 Å molecular sieves in DME at 40 °C for 1–1.5 h, conditions that



Scheme 3. Zn/NH_4Cl-induced generation and trapping of isolable tertiary alcohol **9** and in situ generated α,β-unsaturated nitrone **10** to form *N*-hydroxyindoles (method A). Reagents and conditions: (a) Zn dust (4.9 equiv), $BrCH_2CH_2Br$ (0.33 equiv), THF, reflux 5 min, then cool to 25 °C (repeat refluxing/cooling process three times); then TMSCl (0.2 equiv); and then a mixture of aqueous NH_4Cl (1.0 N; 2.2 equiv) and **6a** (1.0 equiv), 25 °C, 15 min, **9** (56%), **14** (10%); (b) **9** (1.0 equiv), *p*TsOH (3.0 equiv), 4 Å molecular sieves (20 wt%), BnOH (5.0 equiv), DME, 40 °C, 3 h, **11** (55%); (c) **9** (1.0 equiv), *p*TsOH (3.0 equiv), 4 Å molecular sieves (20 wt%), BnSH (5.0 equiv), DME, 40 °C, 1 h, **12** (90%). TMS, trimethylsilyl; *p*TsOH, *p*-toluenesulfonic acid; Bn, benzyl; DME, 1,2-dimethoxyethane.

led, through path A_1, to the formation of adducts **11** (60% yield, see ORTEP drawing, Scheme 4)[14] or **12** (55% yield), respectively. The optimum conditions described above were arrived at through a systematic study in which benzyl alcohol (BnOH) was employed as a nucleophile to trap the reactive species reductively generated from nitro ketoester **6a** (see Table 1) whereby the effects of stoichiometry, temperature (entries 1–4), water content (entry 9), molecular sieves (entries 9 and 10), and solvent (entries 11 and 12) were varied. It is interesting to note, in contrast to method A, the absence of the *N*-hydroxy tertiary alcohol **9** as an isolable intermediate in this procedure (method B), presumably due to the fleeting nature of the latter under the prevailing acidic conditions of the reaction medium, which apparently promote its rapid conversion, first to nitrone **10** and subsequently to the observed *N*-hydroxyindole product **11** or **12**.

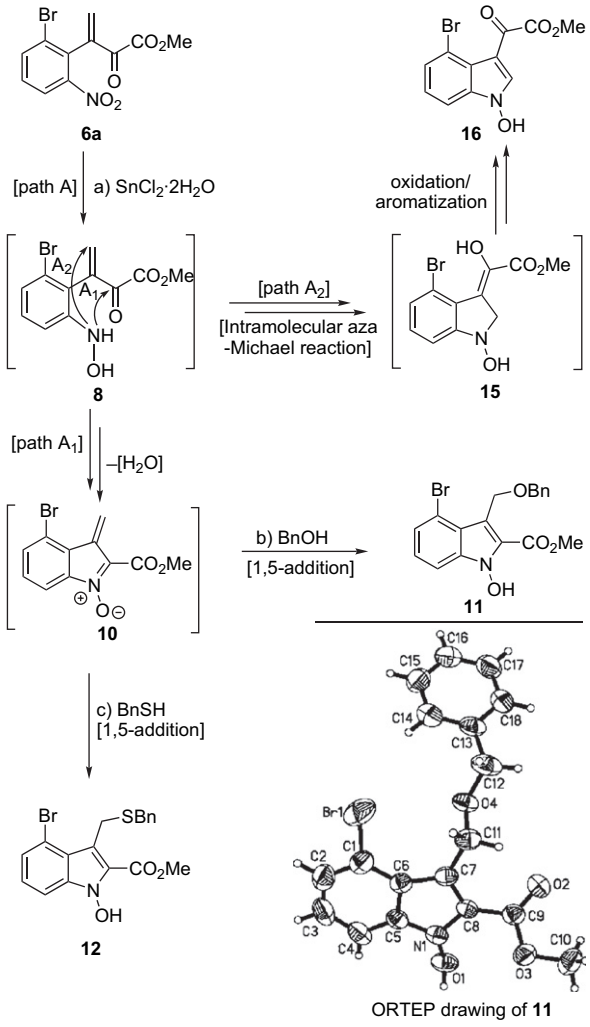
Table 1. Optimization of $SnCl_2\cdot 2H_2O$-induced *N*-hydroxyindole formation reaction conditions using bromonitroaromatic ketoester **6a**[a,b]



Entry	Reductant (equiv)	BnOH (equiv)	H_2O	4 Å MS	Solvent	Temp (°C)	*t* (h)	Yield[c] (%)
1	$SnCl_2\cdot 2H_2O$ (2.2)	10.0	—	+	DME	50	1.0	46
2	$SnCl_2\cdot 2H_2O$ (2.2)	10.0	—	+	DME	25	4.0	56
3	$SnCl_2\cdot 2H_2O$ (2.2)	5.0	—	+	DME	25	4.0	51
4	$SnCl_2\cdot 2H_2O$ (2.2)	5.0	—	+	DME	40	1.5	60
5	$SnCl_2\cdot 2H_2O$ (3.0)	5.0	—	+	DME	40	1.0	51
6	$SnCl_2\cdot 2H_2O$ (5.0)	5.0	—	+	DME	40	0.5	34
7[d]	$SnCl_2\cdot 2H_2O$ (1.2)	5.0	—	+	DME	40	48	34
8	$SnCl_2$ (2.2)	5.0	—	+	DME	40	9.0	43
9	$SnCl_2$ (2.2)	5.0	2.0 equiv	–	DME	40	24	41
10	$SnCl_2\cdot 2H_2O$ (2.2)	5.0	—	–	DME	40	30	36
11	$SnCl_2\cdot 2H_2O$ (2.2)	5.0	—	+	THF	40	2.5	41
12	$SnCl_2\cdot 2H_2O$ (3.2)	5.0	—	+	Et_2O	40	5.0	32

[a] Reactions were carried out on a scale of 0.06–0.10 mmol in anhydrous DME (concentration: 0.12–0.16 M), and the products were purified by PTLC (silica gel).
[b] In each case, an additional compound corresponding to **16** (see Scheme 4) was formed as a minor by-product, not isolated.
[c] Isolated yield.
[d] In addition to the product, 24% yield of unreacted starting material (**6a**) was recovered.

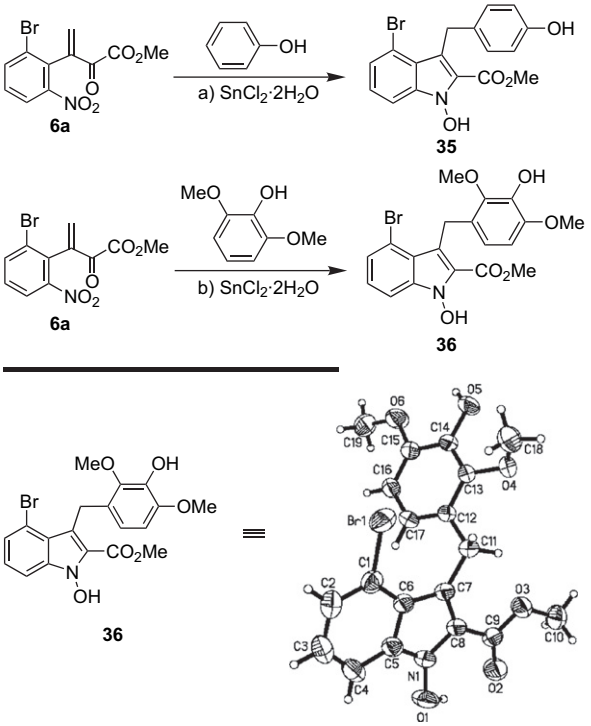
The $SnCl_2 \cdot 2H_2O$-induced process, however, also leads to *N*-hydroxy ketoester **16** (15–17% yield), presumably originating from the initially formed hydroxylamine (**8**) through pathway A_2 (Scheme 4) via an intramolecular aza-Michael addition followed by oxidation/aromatization of the presumed enolic species (**15**). Another possible mechanism for the formation of *N*-hydroxy ketoester **16** may involve the corresponding nitroso compound, generated by partial reduction of **6a** (or its hydrated counterpart), which could similarly undergo, through its nitrogen atom, intramolecular 1,4-addition to the α,β-unsaturated site; such an event may then be followed by rearrangement (or elimination of H_2O) to the observed by-product **16**.



Scheme 4. $SnCl_2 \cdot 2H_2O$-induced generation and trapping of in situ generated α,β-unsaturated nitrone **10** to form *N*-hydroxyindoles (method B). Reagents and conditions: (a,b) $SnCl_2 \cdot 2H_2O$ (2.2 equiv), 4 Å molecular sieves (20 wt %), BnOH (5.0 equiv), **6a** (1.0 equiv), DME, 40 °C, 1.5 h, **11** (60%), **16** (17%); (a,c) $SnCl_2 \cdot 2H_2O$ (2.2 equiv), 4 Å molecular sieves (20 wt%), BnSH (5.0 equiv), **6a** (1.0 equiv), DME, 40 °C, 1 h, **12** (55%), **16** (15%).

Having established the $SnCl_2 \cdot 2H_2O$ procedure (method B) as the preferred method for the generation and trapping of the reactive α,β-unsaturated nitrones such as **10** (or its hydrated form, *N*-hydroxy tertiary alcohol **9**, Scheme 3), we set out to explore its generality and scope. Tables 2 and 3 summarize our initial findings employing various combinations of nitroaromatic ketoesters with oxygen (Table 2), sulfur (Table 3), and nitrogen (Table 3) nucleophiles. As seen in these tables, both primary and secondary alcohols, thiols, and amines participate in these reactions to form the expected *N*-hydroxyindoles in moderate to excellent yields. Aside from by-product **16** (Scheme 4), another probable contributing factor to the moderate yields in certain cases is the possibility of dimerization/polymerization processes, in which the fleeting nitrone (**10**, Scheme 4) can be captured by the *N*-hydroxy group of the desired product.[4b] Benzyl alcohol and benzyl mercaptan were the heteronucleophiles chosen to investigate varying substitutions around the aromatic nuclei of the employed ketoesters. As depicted in Tables 2 and 3, cyano (Table 2, entry 9, Table 3, entry 9), SEM-protected hydroxymethyl (Table 2, entry 5; Table 3, entry 5), and several fluorine-containing (Table 2, entries 6–8; Table 3, entries 6–8) nitro ketoesters successfully enter the reaction.

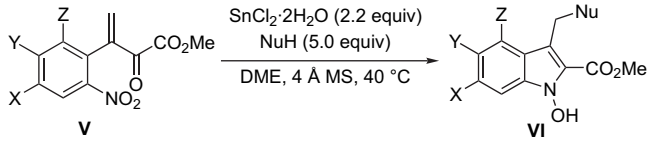
Finally, phenols (Scheme 5) were employed as nucleophiles with the anticipation that they would yield the oxygen–carbon bonded 1,5-addition products that had been observed with the other oxygen nucleophiles. However, we were somewhat surprised to discover that both phenol and 2,6-dimethoxyphenol led to compounds **35** (40% yield) and **36** (31% yield), respectively, which were formed through carbon–carbon bond forming reactions as the major products. An X-ray crystal structure (see ORTEP drawing, Scheme 5) of the latter compound (**36**) further confirmed this outcome.[14]

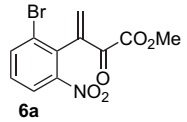
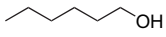
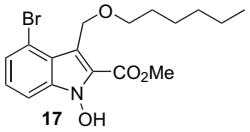
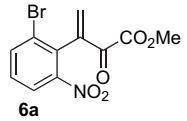
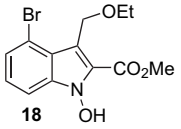
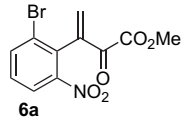
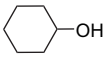
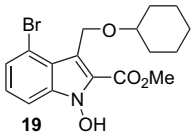
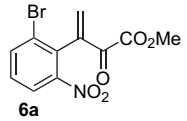
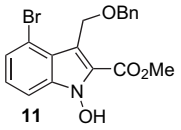
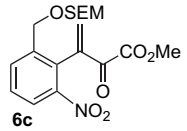
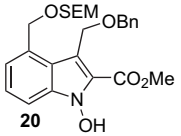
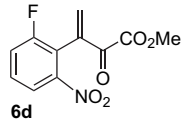
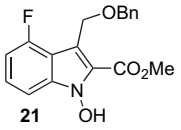
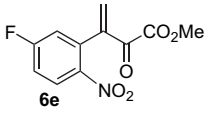
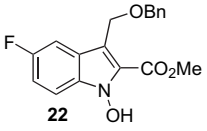
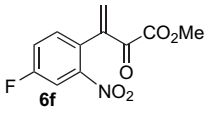
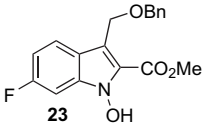
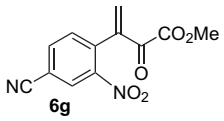
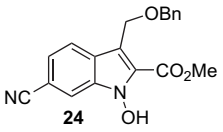


Scheme 5. Initial observations of C–C bond formation via 1,5-addition of phenolic nucleophiles. Reagents and conditions: (a) $SnCl_2 \cdot 2H_2O$ (2.2 equiv), 4 Å molecular sieves (20 wt%), phenol (5.0 equiv), DME, 40 °C, 2.0 h, 40%; (b) $SnCl_2 \cdot 2H_2O$ (2.2 equiv), 4 Å molecular sieves (20 wt%), 2,6-dimethoxyphenol (5.0 equiv), DME, 50 °C, 3.0 h, 31%. ORTEP drawing of **36** drawn at the 50% probability level.

Intrigued by these initial results we then set out to explore the addition of various carbon nucleophiles to

Table 2. Synthesis of 3-substituted-*N*-hydroxyindoles through 1,5-addition of oxygen nucleophiles to substituted α,β-unsaturated nitrones[a,b]

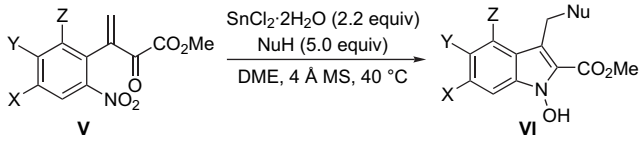


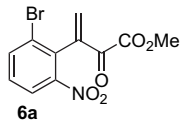
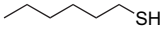
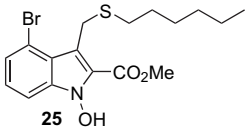
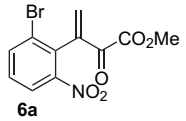
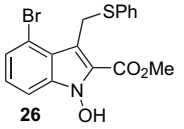
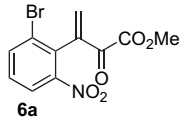
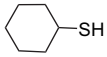
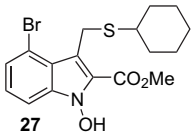
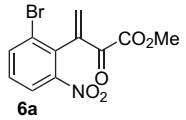
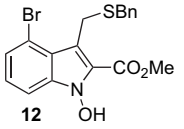
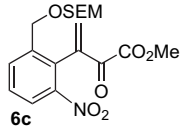
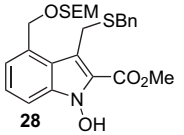
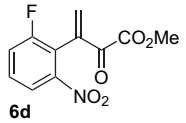
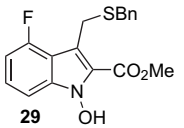
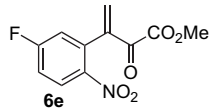
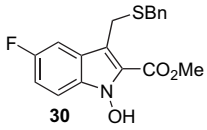
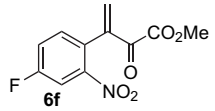
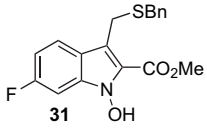
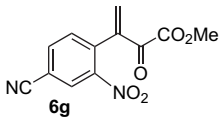
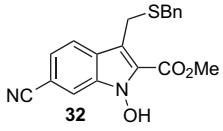
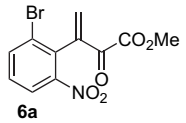
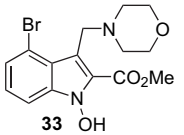
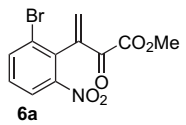
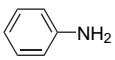
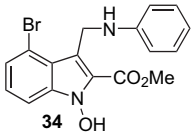
Entry	α,β-Unsaturated nitro ketoester	NuH	*t* (h)	Product **VI**	Yield[c] (%)
1	 **6a**		2.0	 **17**	54
2	 **6a**	EtOH	1.3	 **18**	47
3	 **6a**		3.0	 **19**	41
4	 **6a**	BnOH	1.5	 **11**	60
5	 **6c**	BnOH	1.0	 **20**	37
6	 **6d**	BnOH	1.0	 **21**	87
7	 **6e**	BnOH	1.5	 **22**	56
8	 **6f**	BnOH	1.0	 **23**	55
9	 **6g**	BnOH	1.0	 **24**	47

[a] Reactions were carried out on a scale of 0.06–0.10 mmol in anhydrous DME (concentration: 0.12–0.16 M), and the products were purified by PTLC (silica gel).
[b] In each case, an additional compound corresponding to **16** (see Scheme 4) was formed as a minor by-product, not isolated.
[c] Isolated yield.

α,β-unsaturated nitrones generated from an array of α,β-unsaturated ketoesters employing the $SnCl_2 \cdot 2H_2O$-based reaction (method B). Our studies began with silyl enol ethers as nucleophiles and 2-bromo-substituted ketoester **6a**; the results are shown in Table 4. Thus, in DME at 40 °C and in the presence of $SnCl_2 \cdot 2H_2O$, both cyclic (entries 1–3) and acyclic (entries 4–13) silyl enol ethers, as well as ethyl vinyl ether (entry 14) entered the developed cascade reaction with varying yields, ranging from 30 to 75%. The *N*-hydroxyindoles formed possess substituents at the 3-position containing α-substituted ketones (or an aldehyde as in entry 14) carrying aliphatic, aromatic, and heteroaromatic

Table 3. Synthesis of 3-substituted-*N*-hydroxyindoles through 1,5-addition of sulfur and nitrogen nucleophiles to substituted α,β-unsaturated nitrones[a,b]



Entry	α,β-Unsaturated nitro ketoester	NuH	*t* (h)	Product **VI**	Yield[c] (%)
1	 **6a**		2.0	 **25**	75
2	 **6a**	PhSH	0.7	 **26**	68
3	 **6a**		2.5	 **27**	73
4	 **6a**	BnSH	1.0	 **12**	55
5	 **6c**	BnSH	1.0	 **28**	54
6	 **6d**	BnSH	1.0	 **29**	75
7	 **6e**	BnSH	1.5	 **30**	60
8	 **6f**	BnSH	1.0	 **31**	61
9	 **6g**	BnSH	1.0	 **32**	57
10	 **6a**		6.0	 **33**	27
11	 **6a**		3.0	 **34**	18

[a] Reactions were carried out on a scale of 0.06–0.10 mmol in anhydrous DME (concentration: 0.12–0.16 M), and the products were purified by PTLC (silica gel).
[b] In each case, an additional compound corresponding to **16** (see Scheme 4) was formed as a minor by-product, not isolated.
[c] Isolated yield.

appendages. Of special interest are the fluoro-substituted indoles (entries 8–10), due to their often superior pharmacological properties,[15] and those indoles endowed with synthetically fertile functional groups for further chemical manipulation. The *N*-hydroxy-3-substituted ketoester **16**, whose formation as a by-product has already been discussed above, was also observed in these reactions in small amounts (see Table 4).

Table 5 demonstrates the successful utilization of silanes and related compounds as well as stannanes as nucleophiles in this reaction. Thus, allyl silanes of varying structures serve well as partners with bromo-substituted nitro ketoester **6a**, furnishing novel *N*-hydroxyindoles (entries 1–4) while the allenyl trimethylsilane (entry 8) led to acetylenic compound **57**. Interestingly, the use of allyl trimethoxysilane in this reaction (entry 5) resulted in the formation of the methoxy *N*-hydroxyindole **55** (rather than the allyl substituted product). The same methoxy indole was observed when methoxytrimethylsilane was used (entry 6). X-ray crystallographic analysis of *N*-hydroxyindole **55** confirmed its structure beyond doubt (see ORTEP drawing, Fig. 2). The participation of triethylsilane (entry 7) in this process resulted in the formation of the methyl substituted *N*-hydroxyindole **56**, presumably through 1,5-reduction of the incipient α,β-unsaturated nitrone. The use of allyl stannanes (Table 5, entries 9 and 10) also proved successful, leading to the expected products and demonstrating their potential as partners in this cascade reaction. X-ray crystallographic analysis of the *gem*-dimethyl compound **58** confirmed its structure (see ORTEP drawing, Fig. 2).[14]

In order to explore further the generality and scope of the present methodology we proceeded to vary the nitroaromatic partner and combine the new substrates with a number of nucleophiles. Table 6 shows the results with nitroaromatic substrates **6a**–**g** (whose preparation has already been discussed above, Scheme 2) and silyl enol ethers **59**–**61**. Thus, *N*-hydroxyindoles **37**, **40**, **44**, and **62**–**79** were formed in moderate to good yields as shown in Table 6. It was of interest to observe that the process tolerates various substituents and substitution patterns, although somewhat higher yields were obtained with the *ortho*-substituted nitroaromatic substrates. The survival of the nitrile group under the reductive conditions (see Table 6, entry 7) is also of note and underscores the mildness of the process. Furthermore, the fact that fluoro-substituted nitroaromatic substrates enter the reaction (see Table 6, entries 4–6) bodes well for its potential applications in medicinal chemistry due to the special value of fluorinated compounds in pharmaceutical research.

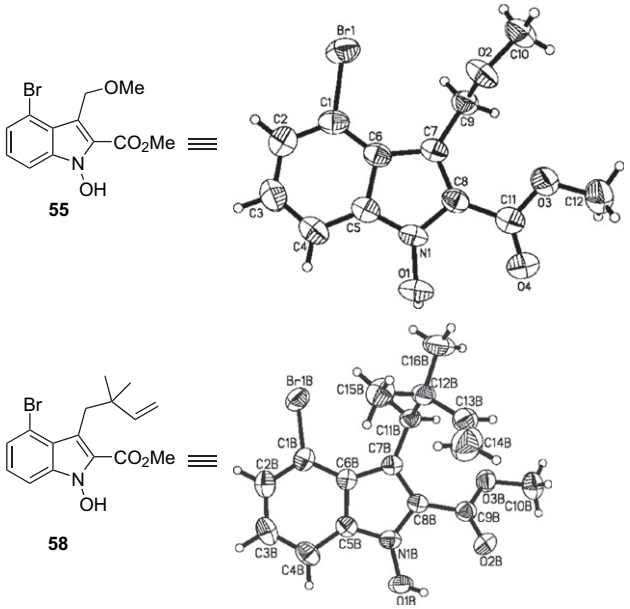
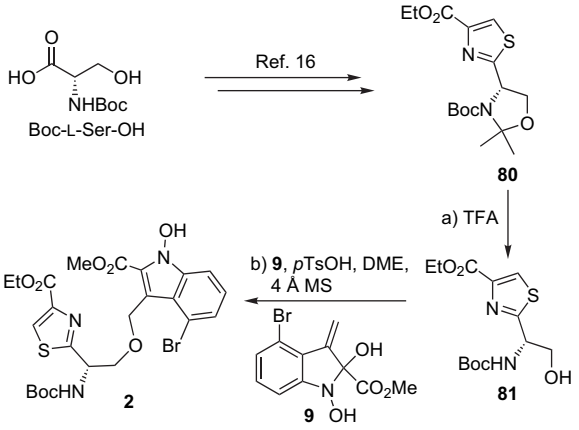


Figure 2. ORTEP drawings of compounds **55** and **58** drawn at the 50% probability level.

Finally, a study was carried out to determine the optimum stoichiometry of the two partners. Table 7 shows the results using the bromo-substituted nitro ketoester **6a** and difluorosilyl enol ether **61** under the standard conditions with $SnCl_2 \cdot 2H_2O$ (method B).[15] As seen from the table, the yields of product **44** increase from 50 to 75% as the number of equivalents of nucleophile increase from 1 to 5, and appear to plateau (74%) as 10 equiv of nucleophile is reached. It is, indeed, reassuring that good yields are still possible with a 1:1 stoichiometry of the two partners, making the process viable in cases where the nucleophile is precious.

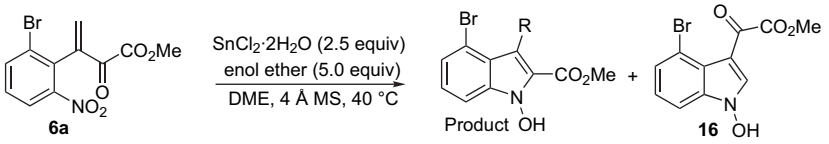
2.2. Application to the synthesis of nocathiacin I model systems

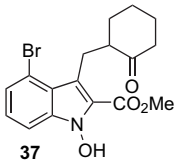
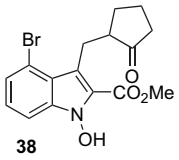
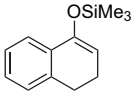
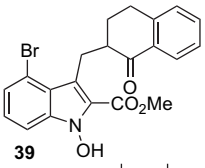
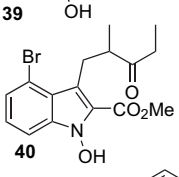
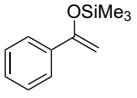
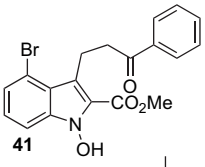
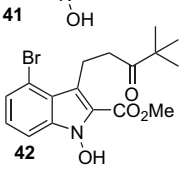
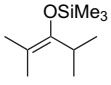
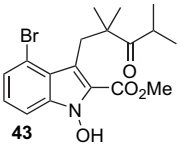
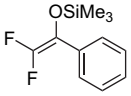
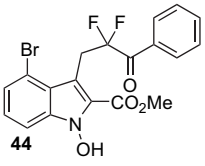
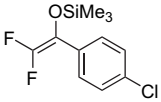
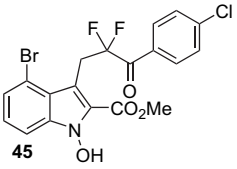
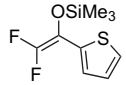
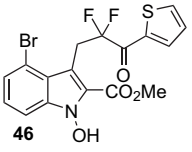
Having developed this synthetic technology to a comfortable level of practicality and scope, we then proceeded to test its applicability to the thiopeptide antibiotic nocathiacin I by targeting suitable model systems. Scheme 6 summarizes the synthesis of the rather simple nocathiacin I model system **2** containing the *N*-hydroxyindole structural motif bridged to a thiazole moiety through an ether linkage. Thus, the *N*-Boc acetonide **80**, prepared as previously described from Boc-L-Ser-OH,[16] was converted to the required *N*-Boc primary alcohol **81** by exposure to TFA (68% yield), a substrate that reacted smoothly with the *N*-hydroxy tertiary alcohol **9** under acidic conditions as prescribed above to afford the targeted *N*-hydroxyindole **2** in 44% yield.



Scheme 6. Construction of *N*-hydroxyindole nocathiacin I model system **2**. Reagents and conditions: (a) TFA/CH_2Cl_2/MeOH (3:2:1), 25 °C, 30 min, 68%; (b) *p*TsOH (3.0 equiv), 4 Å molecular sieves (20 wt%), **81** (4.0 equiv), **9** (1.0 equiv), DME, 25 °C, 10 min; then 40 °C, 2 h, 44%. TFA, trifluoroacetic acid.

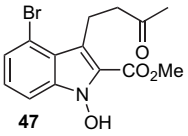
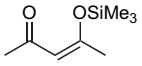
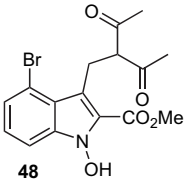
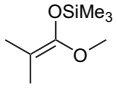
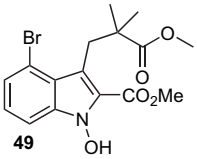
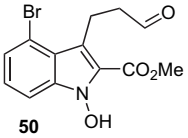
Table 4. Synthesis of 3-alkyl-*N*-hydroxyindoles through 1,5-addition of silyl enol ethers to the α,β-unsaturated nitrone derived from **6a**[a]



Entry	Enol ether	*t* (h)	Product	Yield[b] (%)	Yield (**16**)[b] (%)
1		1.5	 **37**	61	17
2		1.5	 **38**	70	17
3		1.2	 **39**	66	11
4		1	 **40**	73	10
5		1.3	 **41**	60	10
6		2	 **42**	63	10
7		1	 **43**	68	15
8		1.5	 **44**	75	[c]
9		1.5	 **45**	75	[c]
10		1.5	 **46**	63	[c]

(*continued*)

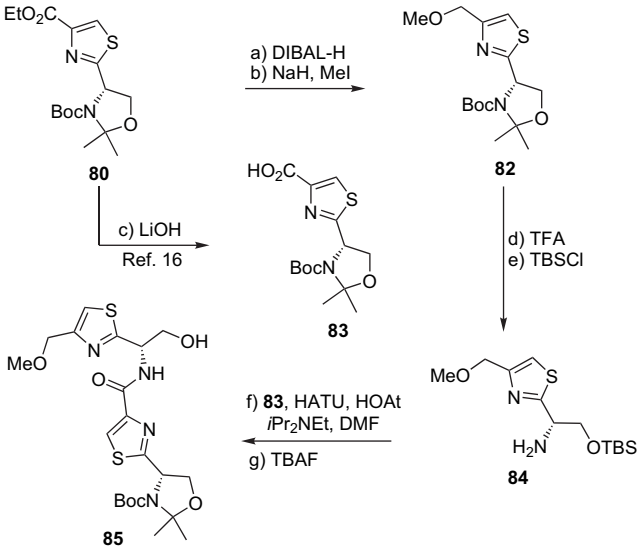
Table 4. (*continued*)

Entry	Enol ether	*t* (h)	Product	Yield[b] (%)	Yield (**16**)[b] (%)
11		1.0	 **47**	51	14
12		14	 **48**	33	20
13		3.0	 **49**	30	19
14		1.5	 **50**	31	10

[a] Reactions were carried out on a scale of 0.06–0.10 mmol in anhydrous DME (concentration: 0.12–0.16 M), and the products were purified by PTLC (silica gel).
[b] Isolated yield.
[c] Trace amount not isolated.

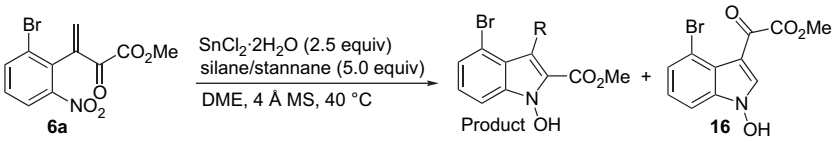
This initial success led us to attempt the next hurdle of synthesizing the more advanced model systems **3a** and **3b** (Fig. 1 and Scheme 8), which contain not only the *N*-hydroxyindole structural motif of nocathiacin I, but also its 15-membered depsipeptide ether ring. The syntheses of these compounds featured a Yamaguchi macrolactonization as the final step of the macrocycle construction,[17] while the ether bridge was formed at an earlier stage through intermolecular nucleophilic addition of a hydroxy component to an in situ generated α,β-unsaturated nitrone. The requisite hydroxy substrate **85** was prepared from *N*-Boc acetonide **80**,[16] as shown in Scheme 7. Thus, exposure of **80** to DIBAL-H followed by treatment with NaH and MeI resulted in the formation of methoxy compound **82** in 74% overall yield. Concomitant removal of the Boc and acetonide groups from the latter compound was achieved by exposure to acid (TFA), leading, upon selective silylation (TBSCl, Et_3N) of the hydroxy group, to the primary amine **84** (85% yield for the two steps). Finally, coupling of this amine (**84**) to carboxylic acid **83** (generated by LiOH hydrolysis of ethyl ester **80**)[16] in the presence of HATU, HOAt, and *i*-Pr_2NEt, furnished, after TBAF-induced desilylation, the targeted hydroxy substrate **85** in 87% over two steps.

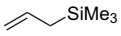
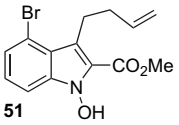
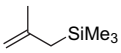
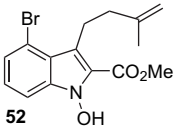
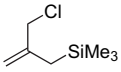
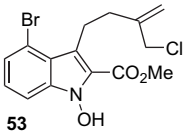
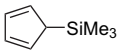
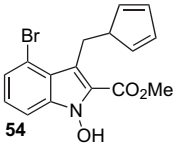
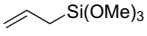
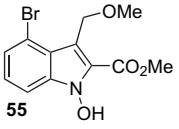
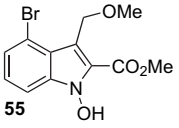
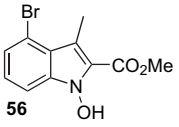
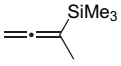
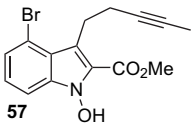
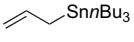
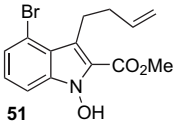
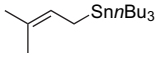
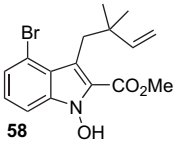
Scheme 8 depicts the final stages of the synthesis of model systems **3a** and **3b** beginning with the preparation of hydroxy acetate **86**, which is poised for the anticipated intermolecular *N*-hydroxyindole formation in partnership with



Scheme 7. Synthesis of complex alcohol **85**. Reagents and conditions: (a) DIBAL-H (2.0 equiv), toluene, 0 °C, 2 h; (b) NaH (2.5 equiv), MeI (7.0 equiv), THF, 0–25 °C, 12 h, 74% (two steps); (c) LiOH (1.5 equiv), THF/EtOH/H_2O (3:1:1), 25 °C, 12 h, 90%; (d) TFA/CH_2Cl_2 (1:1), 0 °C, 10 min; then 25 °C, 1 h; (e) TBSCl (2.2 equiv), Et_3N (3.3 equiv), CH_2Cl_2, 25 °C, 3 h, 85% (two steps); (f) **83** (1.0 equiv), HATU (1.1 equiv), HOAt (1.1 equiv), *i*-Pr_2NEt (2.0 equiv), DMF, 0 °C, 1 h; then 25 °C, 2 h; (g) TBAF (1.2 equiv), THF, 30 min, 0 °C, 87% (two steps). DIBAL-H, diisobutylaluminum hydride; TBSCl, *tert*-butyldimethylsilyl chloride; HATU, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOAt, 1-hydroxy-7-azabenzotriazole; TBAF, tetrabutylammonium fluoride.

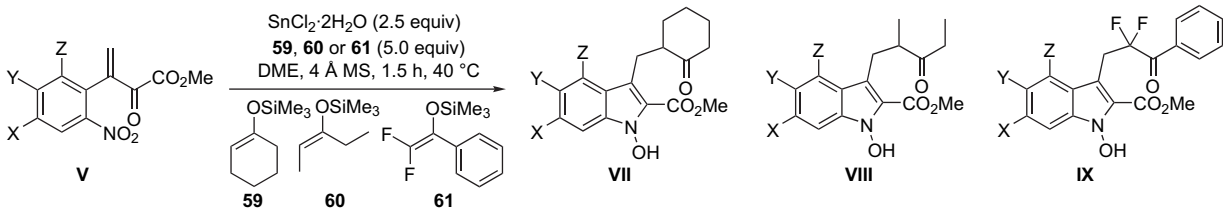
Table 5. Synthesis of 3-alkyl-*N*-hydroxyindoles through 1,5-addition of silanes and stannanes to the α,β-unsaturated nitrone derived from **6a**[a]

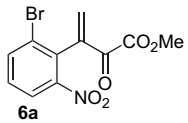
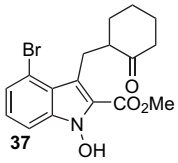
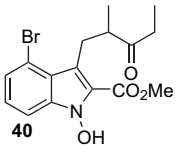
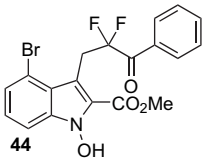
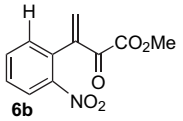
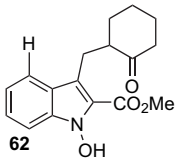
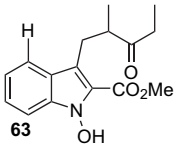
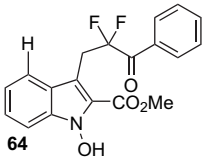
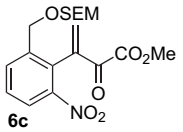
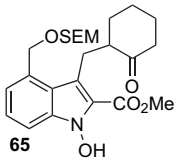
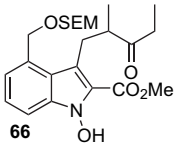
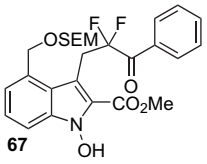
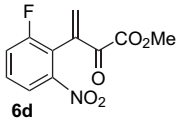
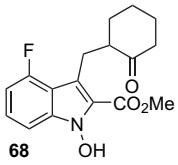
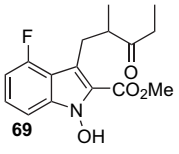
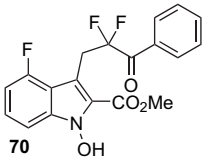
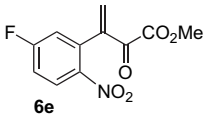
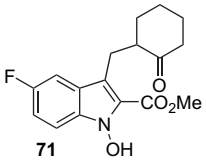
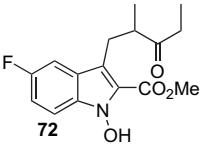
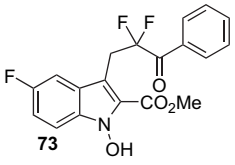
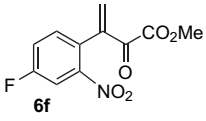
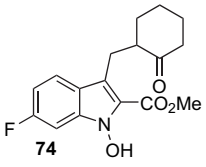
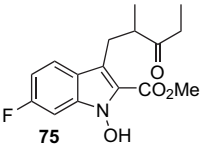
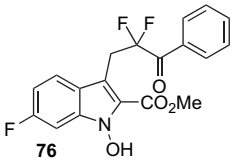
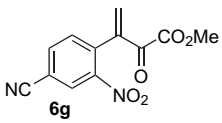
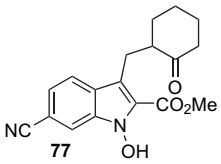
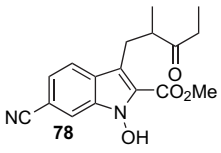
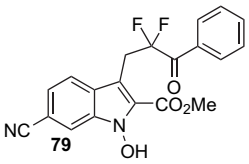


Entry	Silane/stannane	*t* (h)	Product	Yield[b] (%)	Yield (**16**)[b] (%)
1		2.5	 **51**	57	20
2		1.5	 **52**	61	15
3		3.5	 **53**	49	11
4		1.5	 **54**	57	15
5		1.5	 **55**	53	12
6	Me_3SiOMe	2	 **55**	50	15
7	Et_3SiH	3.5	 **56**	50	16
8		28	 **57**	20	[c]
9		30	 **51**	25	15
10		4.5	 **58**	62	14

[a] Reactions were carried out on a scale of 0.06–0.10 mmol in anhydrous DME (concentration: 0.12–0.16 M), and the products were purified by PTLC (silica gel).
[b] Isolated yield.
[c] Trace amount not isolated.

Table 6. Synthesis of 3-alkyl-*N*-hydroxyindoles through 1,5-addition of silyl enol ethers **59**, **60**, and **61** to substituted α,β-unsaturated nitrones[a,b]

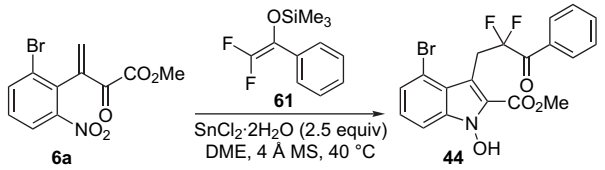


Entry	α,β-Unsaturated nitro ketoester	Product	Yield[c] (%)	Product	Yield[c] (%)	Product	Yield[c] (%)
1	 **6a**	 **37**	61	 **40**	73	 **44**	75
2	 **6b**	 **62**	27	 **63**	33	 **64**	22
3	 **6c**	 **65**	57	 **66**	46	 **67**	50
4	 **6d**	 **68**	44	 **69**	61	 **70**	61
5	 **6e**	 **71**	35	 **72**	44	 **73**	25
6	 **6f**	 **74**	60	 **75**	61	 **76**	34
7	 **6g**	 **77**	43	 **78**	40	 **79**	30

[a] Reactions were carried out on a scale of 0.06–0.10 mmol in anhydrous DME (concentration: 0.12–0.16 M), and the products were purified by PTLC (silica gel).
[b] In each case, an additional compound corresponding to **16** (see Scheme 4) was formed as a minor by-product, not isolated.
[c] Isolated yield.

nitro ketoester **6a** or *N*-hydroxy tertiary alcohol **9**. Thus, acetylation of **85** (Ac_2O, Et_3N, 4-DMAP) followed by TFA treatment furnished the desired hydroxy acetate **86** in 82% overall yield. This substrate performed well as a nucleophile in the crucial coupling with the precursor to the indole structural motif employing either of the two methods (A and B) described above. Thus, reaction of **86** with **6a** in the presence of $SnCl_2\cdot 2H_2O$ according to method B (40 °C, 6 h) led to *N*-hydroxyindole **87** in 40% yield. Subsequent protection (SEMCl, *i*-Pr_2NEt) of the *N*-hydroxy group

Table 7. Effect of varying the stoichiometry in the *N*-hydroxyindole reaction[a]

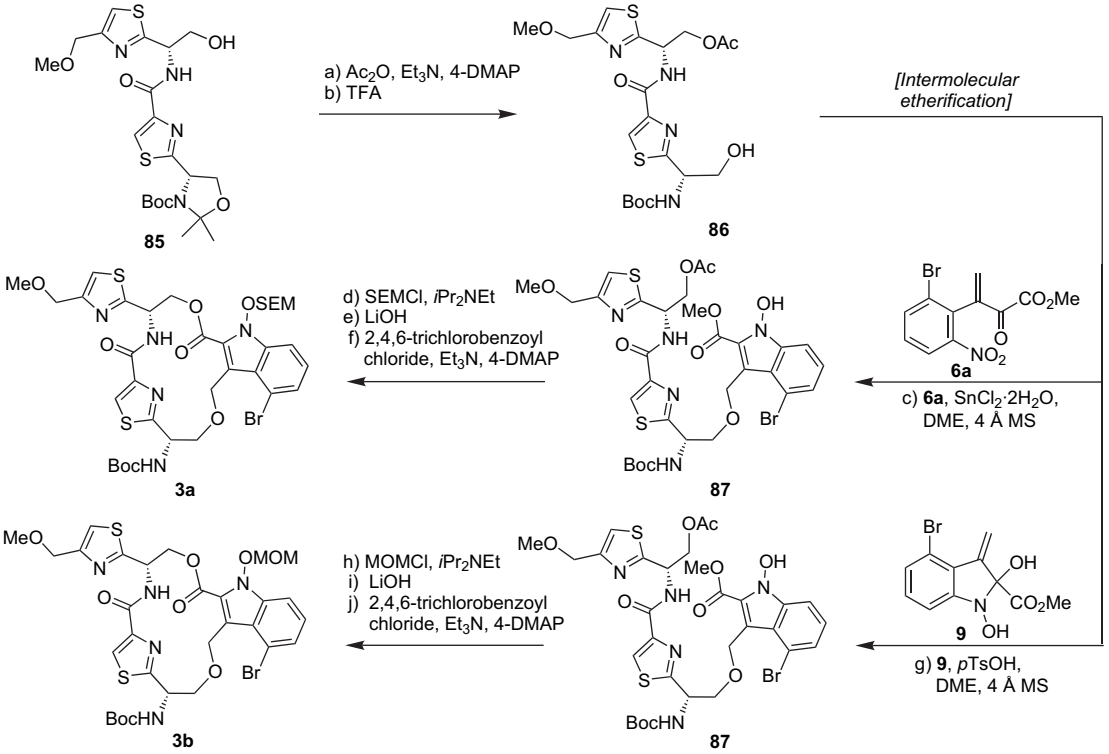


Nucleophile (equiv)	Yield[b] (%)
1	50
3	59
5	75
10	74

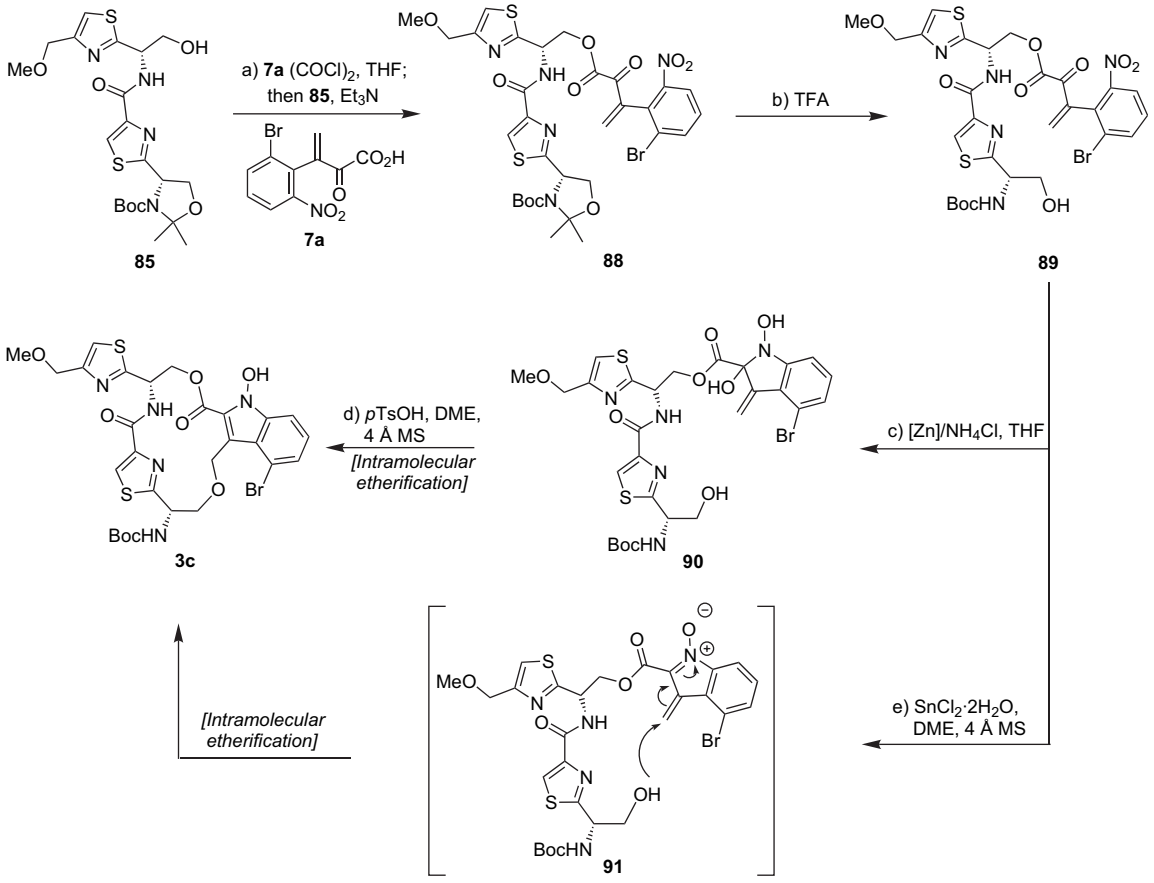
[a] Reactions were carried out on a scale of 0.06–0.10 mmol in anhydrous DME (concentration: 0.12–0.16 M), and the products were purified by PTLC (silica gel).
[b] Isolated yield.

of **87**, followed by exposure to LiOH, afforded the required hydroxy acid for the anticipated macrolactonization, which was brought about through the action of 2,4,6-trichlorobenzoyl chloride in the presence of Et_3N and 4-DMAP, furnishing the *N*-OSEM protected model system **3a** (38% yield for the three steps). The same substrate (**86**) underwent the key *N*-hydroxyindole forming reaction with tertiary alcohol **9**, generated from **6a** through the [Zn]/NH_4Cl protocol (method A), in the presence of *p*TsOH in DME at 40 °C to yield *N*-hydroxyindole **87** in 56% yield. MOM protection (MOMCl, *n*-Bu_4NI cat., *i*-Pr_2NEt) of the latter compound followed by ester hydrolysis (LiOH) and Yamaguchi macrolactonization then led to the MOM-protected nocathiacin I model system **3b** in 44% overall yield for the three steps.

Our final investigation in these studies involved the challenging task of forming the relevant *N*-hydroxyindole ether macrocyclic system through intramolecular, rather than intermolecular, trapping of an incipient α,β-unsaturated nitrone. To this end, and as shown in Scheme 9, the required precursor, hydroxy α,β-unsaturated ketoester **89**, was prepared from alcohol **85** and ketoacid **7a**, which were coupled through the intermediacy of the acid chloride produced from **7a** and oxalyl chloride. Proceeding in the presence of Et_3N, this coupling reaction furnished ester **88** (77% yield), which was then reacted with TFA in CH_2Cl_2/MeOH at 0 °C to afford hydroxy ester **89** in 72% yield. Much to our delight, both methods A and B were found productive in furnishing the desired *N*-hydroxyindole system **3c**. Thus, method A ([Zn]/NH_4Cl) allowed first the generation of tertiary alcohol **90**, and thence, under the influence of *p*TsOH, formation of the nocathiacin I model system **3c** in 40% overall yield from **89**. The same model system **3c** was formed, albeit in lower yield (10%), directly from **89** by method B ($SnCl_2\cdot 2H_2O$), presumably through the fleeting intermediate **91** as shown in Scheme 9.



Scheme 8. Construction of nocathiacin I model systems **3a** (*N*-OSEM) and **3b** (*N*-OMOM) via intermolecular *N*-hydroxyindole formation. Reagents and conditions: (a) Ac_2O (5.0 equiv), Et_3N (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 10 min; (b) TFA/CH_2Cl_2/MeOH (3:2:1), 0 °C, 30 min, 82% (two steps); (c) $SnCl_2\cdot 2H_2O$ (2.2 equiv), 4 Å molecular sieves (20 wt%), **86** (4.0 equiv), **6a** (1.0 equiv), DME, 40 °C, 6 h, 40%; (d) SEMCl (2.0 equiv), *i*-Pr_2NEt (3.0 equiv), *n*-Bu_4NI (0.1 equiv), DMF, 25 °C, 10 min; (e) LiOH (3.0 equiv), THF/MeOH/H_2O (3:1:1), 0–25 °C, 4 h; (f) 2,4,6-trichlorobenzoyl chloride (30 equiv), Et_3N (40 equiv), toluene, 25 °C, 12 h; then 4-DMAP (30 equiv), toluene (0.5 mM), 25 °C, 24 h, 38% (three steps); (g) *p*TsOH (3.0 equiv), 4 Å molecular sieves (20 wt%), **86** (2.0 equiv), **9** (1.0 equiv), DME, 25 °C, 10 min; then 40 °C, 3 h, 56%; (h) MOMCl (2.0 equiv), *i*-Pr_2NEt (3.0 equiv), *n*-Bu_4NI (0.1 equiv), DMF, 25 °C, 10 min; (i) LiOH (3.0 equiv), THF/MeOH/H_2O (3:1:1), 0–25 °C, 4 h; (j) 2,4,6-trichlorobenzoyl chloride (30 equiv), Et_3N (40 equiv), toluene, 25 °C, 12 h; then 4-DMAP (30 equiv), toluene (0.5 mM), 25 °C, 24 h, 44% (three steps). 4-DMAP, 4-dimethylaminopyridine; SEMCl, 2-(trimethylsilyl)ethoxymethyl chloride; MOMCl, chloromethyl methyl ether.



Scheme 9. Construction of nocathiacin I model system **3c** (*N*-OH) via intramolecular *N*-hydroxyindole formation. Reagents and conditions: (a) **7a** (3.0 equiv), oxalyl chloride (2.0 equiv), DMF (cat.), THF, 0 °C, 45 min; then Et_3N (4.0 equiv), **85** (1.0 equiv), 0–25 °C, 2 h, 77%; (b) TFA/CH_2Cl_2/MeOH (3:2:1), 0 °C, 1 h, 72%; (c) Zn dust (4.9 equiv), $BrCH_2CH_2Br$ (0.33 equiv), THF, reflux 5 min, then cool to 25 °C (repeat refluxing/cooling process three times); then TMSCl (0.2 equiv); and then a mixture of aqueous NH_4Cl (1.0 N; 2.2 equiv) and **89** (1.0 equiv), 25 °C, 15 min; (d) *p*TsOH (3.0 equiv), 4 Å molecular sieves (20 wt%), DME (1.0 mM), 25 °C, 10 min; then 40 °C, 12 h, 40% (two steps); (e) $SnCl_2\cdot 2H_2O$ (3.2 equiv), 4 Å molecular sieves (20 wt%), DME (0.05 M), 45 °C, 3 h, 10%.

3. Conclusion

The described chemistry provides a versatile entry into substituted *N*-hydroxyindoles from readily available nitroaromatic systems and suitable partners carrying O–, S–, N– and carbon nucleophilic moieties. Proceeding through a cascade sequence involving trapping of incipient α,β-unsaturated nitrones and/or *N*-hydroxy tertiary alcohol species, these processes tolerate a variety of functionalities and substituents amenable to further chemical manipulations. Furthermore, the model studies performed in the area of nocathiacin I bode well for a potential application of the method to the construction of this natural product's most intriguing and challenging structural motif, its *N*-hydroxyindole moiety. Other applications of the present synthetic technology in chemical synthesis in general, and medicinal chemistry in particular, are also envisioned.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, 1,2-dimethoxyethane (DME), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Difluorosilyl enol ethers were prepared according to the literature procedures.[15] Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, 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 or 0.50 mm E. Merck silica gel plates ($60F_{254}$). Optical rotations were recorded on a Perkin–Elmer 343 polarimeter. NMR spectrum was recorded on Bruker DRX-600, DRX-500, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, ½ABq=½AB quartet, m=multiplet, quin=quintuplet, sext=sextet, sep=septet, hept=heptet, br=broad. IR spectra were recorded on a Perkin–Elmer

1600 or Spectrum 100 series FTIR spectrometer. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin–Elmer SCIEX single quadrupole mass spectrometer at 4000 V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization) or ESI (electrospray ionization).

4.1.1. Trimethyl(2-{[(2-methyl-3-nitrobenzyl)oxy]methoxy}ethyl)silane (4c). To 2-methyl-3-nitrobenzyl alcohol (20 g, 120 mmol) in DMF (600 mL) at 25 °C were added *i*-Pr_2NEt (62.5 mL, 359 mmol), SEMCl (42.2 mL, 239 mmol), and *n*-Bu_4NI (442 mg, 1.20 mmol). After stirring for 12 h, the reaction mixture was diluted with EtOAc (500 mL), washed with H_2O (500 mL), brine (500 mL), and dried (Na_2SO_4). The resulting solution was concentrated and the residue was subjected to flash column chromatography (silica gel, Et_2O/hexanes, 20:80→60:40) to afford **4c** (35 g, 98%) as a yellow oil; R_f=0.60 (silica gel, EtOAc/hexanes, 2:8); IR (film) ν_{max} 2953, 2886, 1527, 1465, 1352, 1248, 1189, 1155, 1105, 1057, 1028, 937, 920, 858, 834, 802, 759, 736, 715, 694, 666 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 7.69 (d, J=8.0 Hz, 1H), 7.62 (d, J=8.0 Hz, 1H), 7.34 (t, J=8.0 Hz, 1H), 4.73 (s, 2H), 4.64 (s, 2H), 3.63 (t, J=8.5 Hz, 2H), 2.39 (s, 3H), 0.91 (t, J=8.5 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN) δ 152.7, 141.2, 134.0, 132.0, 128.0, 124.6, 95.9, 68.5, 66.5, 19.2, 15.1, −0.7 (3C); HRMS (ESI-TOF) calcd for $C_{14}H_{23}NO_4SiNa^+$ [M+Na^+] 320.1288, found 320.1284.

4.2. General procedure for the synthesis of ketoesters 5a–g

To a suspension of NaH (60% dispersion in mineral oil, 4.0 equiv) in DMF (1.67 M) at 0 °C was added a solution of nitrotoluene (3.0–15.0 mmol) in DMF (0.74 M) via cannula. After stirring for 10 min, a solution of dimethyl oxalate (5.0 equiv) in DMF (0.96 M) was added via cannula and after stirring for 1 h at 0 °C, the reaction mixture was allowed to warm to 25 °C and stirring was continued for 12 h. The reaction mixture was then cooled to 0 °C, quenched with saturated aqueous NH_4Cl (5–25 mL) solution, diluted with EtOAc (20–100 mL), washed with H_2O (5–25 mL), and dried (Na_2SO_4). After concentration, the residue was subjected to flash column chromatography to give the ketoesters.

4.2.1. Methyl 3-(2-bromo-6-nitrophenyl)-2-oxopropanoate (5a). R_f=0.78 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3093, 2956, 1735, 1598, 1527, 1436, 1403, 1349, 1274, 1201, 1059, 803, 736, 718 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 8.00–7.97 (m, 2H), 7.46 (t, J=8.3 Hz, 1H), 4.67 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 189.6, 161.4, 151.6, 138.7, 130.9, 129.9, 128.4, 125.3, 53.9, 44.3; HRMS (ESI-TOF) calcd for $C_{10}H_8BrNO_5Na^+$ [M+Na^+] 323.9478, found 323.9475.

4.2.2. Methyl 3-(2-nitrophenyl)-2-oxopropanoate (5b). R_f=0.51 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3441 (br), 2959, 2850, 1732, 1605, 1575, 1514, 1437, 1394, 1346, 1261, 1195, 1057, 966, 858, 786, 725, 664 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 8.10 (d, J=8.1 Hz, 1H), 7.71–7.64 (m, 1H), 7.57–7.51 (m, 1H), 7.42 (d, J=7.7 Hz, 1H), 4.53 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 190.9, 161.7, 149.6, 135.0, 134.8, 130.2, 129.9, 126.1, 53.8, 44.9; HRMS (ESI-TOF) calcd for $C_{10}H_9NO_5Na^+$ [M+Na^+] 246.0373, found 246.0363.

4.2.3. Methyl 3-[2-nitro-6-({[2-(trimethylsilyl)ethoxy]methoxy}methyl)phenyl]-2-oxopropanoate (5c). R_f=0.38 (silica gel, EtOAc/hexanes, 3:7); IR (film) ν_{max} 2953, 2892, 1735, 1612, 1528, 1438, 1349, 1247, 1188, 1155, 1104, 1056, 1031, 991, 858, 833, 804, 767, 734, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J=8.4 Hz, 1H), 7.67 (d, J=7.2 Hz, 1H), 7.46 (t, J=8.0 Hz, 1H), 4.63 (s, 2H), 4.61 (s, 2H), 4.59 (s, 2H), 3.94 (s, 3H), 3.59 (t, J=8.4 Hz, 2H), 0.94 (t, J=8.4 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN) δ 189.1, 161.2, 150.3, 140.1, 135.2, 128.8, 128.7, 125.4, 94.1, 67.4, 66.1, 53.7, 39.6, 18.5, −1.0 (3C); HRMS (ESI-TOF) calcd for $C_{17}H_{25}NO_7SiNa^+$ [M+Na^+] 406.1292, found 406.1291.

4.2.4. Methyl 3-(2-fluoro-6-nitrophenyl)-2-oxopropanoate (5d). R_f=0.29 (silica gel, EtOAc/hexanes, 2:8); IR (film) ν_{max} 3459 (br), 3107, 2950, 1730, 1531, 1466, 1452, 1429, 1401, 1360, 1332, 1281, 1244, 1226, 1189, 1147, 1064, 971, 837, 800, 763, 735 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 7.91 (d, J=7.9 Hz, 1H), 7.58–7.50 (m, 2H), 4.53 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 189.8, 162.0 (d, J=247.3 Hz), 161.3, 150.4, 130.7 (d, J=9.2 Hz), 121.8 (d, J=3.4 Hz), 121.7 (d, J=20.6 Hz), 118.4 (d, J=19.5 Hz), 53.8, 36.6; HRMS (ESI-TOF) calcd for $C_{10}H_8FNO_5Na^+$ [M+Na^+] 264.0279, found 264.0269.

4.2.5. Methyl 3-(5-fluoro-2-nitrophenyl)-2-oxopropanoate (5e). R_f=0.56 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3413 (br), 3083, 2958, 2919, 2849, 1736, 1590, 1525, 1343, 1249, 1062, 840, 751, 613 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 8.20 (dd, J=9.2, 4.1 Hz, 1H), 7.18–7.13 (m, 1H), 7.03 (dd, J=8.7, 4.1 Hz, 1H), 4.51 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 188.4, 164.8 (d, J=256.6 Hz), 160.5, 144.2, 132.5 (d, J=9.1 Hz), 128.3 (d, J=10.3 Hz), 120.5 (d, J=22.8 Hz), 115.8 (d, J=22.8 Hz), 53.5, 44.4; HRMS (ESI-TOF) calcd for $C_{10}H_8FNO_5Na^+$ [M+Na^+] 264.0279, found 264.0276.

4.2.6. Methyl 3-(4-fluoro-2-nitrophenyl)-2-oxopropanoate (5f). R_f=0.45 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3099, 2959, 1734, 1618, 1532, 1499, 1440, 1398, 1349, 1325, 1235, 1133, 1062, 949, 880, 819, 806, 747, 682 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 7.89 (dd, J=8.5, 2.5 Hz, 1H), 7.47–7.45 (m, 2H), 4.53 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 190.7, 162.4 (d, J=247.1 Hz), 161.6, 150.0 (d, J=8.8 Hz), 136.4 (d, J=7.9 Hz), 126.3 (d, J=3.9 Hz), 121.0 (d, J=21.1 Hz), 113.5 (d, J=27.3 Hz), 53.8, 44.3; HRMS (ESI-TOF) calcd for $C_{10}H_8FNO_5Na^+$ [M+Na^+] 264.0279, found 264.0269.

4.2.7. Methyl (2*Z*(*E*))-3-(4-cyano-2-nitrophenyl)-2-hydroxyacrylate (5g). R_f=0.28 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3372 (br), 3088, 2958, 2926, 2237,

1736, 1619, 1535, 1440, 1396, 1352, 1268, 1062, 912, 834, 795, 747, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J=8.0 Hz, 1H), 8.17 (d, J=1.6 Hz, 1H), 7.84 (dd, J=8.0, 1.6 Hz, 1H), 6.96 (d, J=1.4 Hz, 1H), 6.92 (d, J=1.4 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 161.3, 149.8, 137.8, 136.6, 135.9, 135.3, 129.9, 117.5, 113.7, 102.7, 53.9; HRMS (ESI-TOF) calcd for $C_{11}H_7N_2O_5^-$ [M−H$^-$] 247.0360, found 247.0369.

4.3. General procedure for the synthesis of α,β-unsaturated ketoesters 6a–g

To a solution of ketoester (0.5–10 mmol) in THF (0.03 M) at 0 °C was added NaH (60% dispersion in mineral oil, 1.1 equiv) and, after stirring for 1 h, dimethylmethylene ammonium chloride (3.0 equiv) was added and the reaction mixture stirred for 12 h at 25 °C. After cooling to 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (1–20 mL), diluted with EtOAc (5–100 mL), washed with H_2O (1–20 mL), and dried (Na_2SO_4). After concentration, the residue was subjected to flash column chromatography to give the α,β-unsaturated ketoesters.

4.3.1. Methyl 3-(2-bromo-6-nitrophenyl)-2-oxobut-3-enoate (6a). R_f=0.53 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3389 (br), 2954, 2913, 2861, 2355, 1719, 1672, 1526, 1472, 1431, 1349, 1237, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, J=8.4, 1.3 Hz, 1H), 7.94 (dd, J=8.1, 1.3 Hz, 1H), 7.44 (dd, J=8.4, 8.1 Hz, 1H), 6.79 (s, 1H), 6.17 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.1, 162.5, 149.5, 141.8, 137.9, 134.8, 132.5, 130.5, 126.3, 123.8, 53.3; HRMS (ESI-TOF) calcd for $C_{11}H_8BrNO_5Na^+$ [M+Na$^+$] 335.9478, found 335.9477.

4.3.2. Methyl 3-(2-nitrophenyl)-2-oxobut-3-enoate (6b). R_f=0.29 (silica gel, EtOAc/hexanes, 3:7); IR (film) ν_{max} 3474 (br), 3404 (br), 2953, 2906, 2849, 1740, 1688, 1601, 1567, 1531, 1514, 1433, 1410, 1341, 1271, 1236, 1132, 1028, 958, 859, 790, 761 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 8.10 (d, J=8.3 Hz, 1H), 7.77–7.74 (m, 1H), 7.65–7.62 (m, 1H), 7.45 (dd, J=7.5, 1.3 Hz, 1H), 6.55 (s, 1H), 6.51 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 186.5, 164.3, 148.7, 144.1, 135.2, 134.7, 133.4, 131.4, 131.1, 125.4, 53.7; HRMS (ESI-TOF) calcd for $C_{11}H_{10}NO_5^+$ [M+H$^+$] 236.0553, found 236.0550.

4.3.3. Methyl 3-[2-nitro-6-({[2-(trimethylsilyl)ethoxy]-methoxy}methyl)phenyl]-2-oxobut-3-enoate (6c). R_f=0.55 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2954, 2884, 1743, 1690, 1525, 1343, 1243, 1131, 1102, 1061, 1032, 938, 861, 832, 761, 732, 691 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 8.03 (d, J=8.1 Hz, 1H), 7.83 (d, J=7.8 Hz, 1H), 7.60 (dd, J=8.1, 7.8 Hz, 1H), 6.63 (s, 1H), 6.26 (s, 1H), 4.62 (s, 2H), 4.46 (d, J=3.5 Hz, 2H), 3.87 (s, 3H), 3.56 (t, J=8.3 Hz, 2H), 0.88 (t, J=8.3 Hz, 2H), −0.01 (s, 9H); ^{13}C NMR (150 MHz, CD_3CN) δ 186.2, 164.2, 149.7, 140.8, 140.7, 134.9, 134.6, 130.8, 130.4, 124.7, 95.3, 67.3, 66.0, 53.7, 18.5, −1.4 (3C); HRMS (ESI-TOF) calcd for $C_{18}H_{25}NO_7SiNa^+$ [M+Na$^+$] 418.1292, found 418.1297.

4.3.4. Methyl 3-(2-fluoro-6-nitrophenyl)-2-oxobut-3-enoate (6d). R_f=0.54 (silica gel, EtOAc/hexanes, 3:7); IR (film) ν_{max} 3473 (br), 3371 (br), 3096, 3954, 1738, 1687, 1621, 1524, 1447, 1345, 1294, 1248, 1182, 1121, 1065, 1024, 947, 881, 805, 729, 672 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 8.95 (d, J=8.3 Hz, 1H), 7.67–7.63 (m, 1H), 7.59–7.56 (m, 1H), 6.76 (s, 1H), 6.50 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 186.1, 164.1, 160.7 (d, J=247.3 Hz), 149.8, 137.4 (d, J=2.3 Hz), 136.5, 132.1 (d, J=10.3 Hz), 122.4 (d, J=22.9 Hz), 121.5 (d, J=3.4 Hz), 119.9 (d, J=20.6 Hz), 53.9; HRMS (ESI-TOF) calcd for $C_{11}H_9FNO_5^+$ [M+H$^+$] 254.0459, found 254.0452.

4.3.5. Methyl 3-(5-fluoro-2-nitrophenyl)-2-oxobut-3-enoate (6e). R_f=0.52 (silica gel, EtOAc/hexanes, 3:7); IR (film) ν_{max} 3083, 2959, 1743, 1695, 1585, 1526, 1436, 1347, 1218, 1132, 1036, 948, 843, 727, 611 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.24 (dd, J=9.2, 5.3 Hz, 1H), 7.27–7.24 (m, 1H), 7.08 (dd, J=8.3, 2.6 Hz, 1H), 6.64 (s, 1H), 6.29 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.3, 165.4 (d, J=253.2 Hz), 163.5, 144.5, 142.7, 134.6, 134.4 (d, J=10.3 Hz), 128.1 (d, J=10.3 Hz), 120.9 (d, J=25.1 Hz), 117.3 (d, J=22.8 Hz), 53.4; HRMS (ESI-TOF) calcd for $C_{11}H_8FNO_5Na^+$ [M+Na$^+$] 276.0279, found 276.0279.

4.3.6. Methyl 3-(4-fluoro-2-nitrophenyl)-2-oxobut-3-enoate (6f). R_f=0.33 (silica gel, EtOAc/hexanes, 2:8); IR (film) ν_{max} 3097, 2958, 1741, 1690, 1537, 1338, 1349, 1271, 1213, 1132, 1034, 947, 882, 812, 674 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.87 (dd, J=8.3, 2.6 Hz, 1H), 7.43–7.40 (m, 1H), 7.37 (dd, J=8.9, 5.7 Hz, 1H), 6.59 (s, 1H), 6.31 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.9, 162.6, 161.7 (d, J=252.0 Hz), 147.9 (d, J=8.0 Hz), 142.7, 133.8 (d, J=8.0 Hz), 132.5, 127.4 (d, J=3.4 Hz), 121.2 (d, J=20.5 Hz), 112.5 (d, J=27.4 Hz), 52.9; HRMS (ESI-TOF) calcd for $C_{11}H_8FNO_5Na^+$ [M+Na$^+$] 276.0279, found 276.0274.

4.3.7. Methyl 3-(4-cyano-2-nitrophenyl)-2-oxobut-3-enoate (6g). R_f=0.55 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2237, 1742, 1693, 1556, 1537, 1353, 1251, 1140, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J=1.6 Hz, 1H), 7.98 (dd, J=7.8, 1.6 Hz, 1H), 7.54 (d, J=1.6 Hz, 1H), 6.75 (s, 1H), 6.35 (s, 1H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 185.6, 163.8, 148.8, 142.8, 138.4, 136.3, 135.9, 134.7, 129.4, 117.4, 114.8, 53.9; HRMS (ESI-TOF) calcd for $C_{12}H_8N_2O_5Na^+$ [M+Na$^+$] 283.0325, found 283.0325.

4.4. General procedure for the synthesis of *N*-hydroxyindoles (method A)

A stirred suspension of Zn dust (4.9 equiv) and dibromoethane (0.33 equiv) in THF (0.20 M) was heated to reflux (70 °C) for approximately 5 min and then allowed to cool to 25 °C. The refluxing/cooling process was repeated three times. TMSCl (0.2 equiv) was then added and the resulting gray suspension was stirred at 25 °C for 10 min. A separate stirred solution containing a mixture of aqueous 1 N NH_4Cl (2.2 equiv) and nitro ketoester (0.01–0.06 mmol, 1.0 equiv) in THF (0.10 M) was added via cannula to the activated Zn suspension and stirring was continued for 15–30 min in the absence of light at 25 °C. The crude reaction mixture was purified directly by PTLC to afford tertiary alcohol **9**, which

was added to a stirred solution of *p*TsOH (3.0 equiv), nucleophile (5.0 equiv) and 4 Å molecular sieves (20 wt%) in DME (0.05–0.10 M) at 25 °C. After 10 min, the reaction mixture was warmed to 40 °C, stirred for 1–3 h, cooled to room temperature, and purified directly by PTLC to afford the targeted *N*-hydroxyindoles.

4.4.1. Methyl 4-bromo-1,2-dihydroxy-3-methyleneindoline-2-carboxylate (9). R_f=0.53 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3389, 2954, 2849, 1737, 1596, 1566, 1460, 1431, 1290, 1255, 1231, 1184, 1155, 1096, 1026, 885, 802, 749 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 7.64 (s, 1H), 7.14 (t, J=7.9 Hz, 1H), 7.11 (dd, J=7.9, 1.3 Hz, 1H), 6.85 (dd, J=7.9, 1.3 Hz, 1H), 6.32 (s, 1H), 5.40 (s, 1H), 5.08 (br s, 1H), 3.61 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 170.3, 154.8, 144.3, 132.1, 127.3, 123.4, 117.9, 111.8, 111.7, 98.9, 53.6; HRMS (ESI-TOF) calcd for $C_{11}H_{10}BrNO_4Na^+$ [M+Na^+] 321.9685, found 321.9684.

4.4.2. Methyl 3-[(benzyloxy)methyl]-4-bromo-1-hydroxy-1*H*-indole-2-carboxylate (11). *Method A and B*: R_f=0.58 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3194, 2952, 2848, 1710, 1525, 1433, 1353, 1312, 1255, 1226, 1185, 1122, 1047, 1024, 909, 874, 771, 730, 690 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 9.49 (br s, 1H), 7.45 (d, J=8.1 Hz, 1H), 7.39–7.23 (m, 6H), 7.18 (t, J=8.1 Hz, 1H), 5.10 (s, 2H), 4.61 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.2, 139.9, 137.2, 129.2 (2C), 128.9 (2C), 128.3, 127.1, 126.9, 126.8, 121.0, 116.0, 115.9, 110.2, 72.7, 61.8, 52.9; HRMS (ESI-TOF) calcd for $C_{18}H_{16}BrNO_4Na^+$ [M+Na^+] 412.0155, found 412.0155.

4.4.3. Methyl 3-[(benzylthio)methyl]-4-bromo-1-hydroxy-1*H*-indole-2-carboxylate (12). *Method A and B*: R_f=0.57 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3354 (br), 2955, 2908, 2837, 1708, 1672, 1608, 1514, 1484, 1442, 1390, 1255, 1232, 1185, 1120, 738, 692 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 9.30 (br s, 1H), 7.45 (dd, J=8.2, 0.7 Hz, 1H), 7.33–7.23 (m, 5H), 7.22–7.16 (m, 2H), 4.45 (s, 2H), 3.83 (s, 3H), 3.79 (s, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 162.4, 139.9, 137.8, 129.8 (2C), 129.3 (2C), 127.7, 127.4, 126.7, 125.6, 120.1, 117.8, 116.1, 110.4, 52.8, 37.2, 26.7; HRMS (ESI-TOF) calcd for $C_{18}H_{16}BrNO_3SNa^+$ [M+Na^+] 427.9926, found 427.9924.

4.4.4. 4-(2-Bromo-6-nitrophenyl)-3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one (14). R_f=0.20 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3271 (br), 2955, 2919, 1684, 1525, 1455, 1414, 1349, 1220, 1108, 1037, 903, 803, 780 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, J=8.3 Hz, 1H), 7.95 (d, J=8.3 Hz, 1H), 7.49 (t, J=8.3 Hz, 1H), 6.85 (br s, 1H), 4.05 (br s, 2H); ^{13}C NMR (150 MHz, CD_3CN) δ 168.5, 154.2, 151.8, 145.1, 138.2, 131.8, 129.1, 126.7, 124.6, 45.1; HRMS (ESI-TOF) calcd for $C_{10}H_7BrNO_3^-$ [M−H^-] 279.9607, found 279.9615.

4.5. General procedure for the synthesis of *N*-hydroxyindoles (method B)

To a stirred solution of $SnCl_2\cdot 2H_2O$ (2.2–2.5 equiv) and 4 Å molecular sieves (20 wt%) in DME (0.12–0.16 M) were added nucleophile (5.0 equiv) and nitro ketoester (0.03–0.10 mmol, 1.0 equiv) at 25 °C. The reaction mixture was warmed to 40–45 °C and stirring was continued for 1–72 h in the absence of light. Direct purification of the crude reaction mixture by PTLC afforded the desired *N*-hydroxyindoles.

4.5.1. Methyl 4-bromo-1-hydroxy-1*H*-indole-3-carboxylate (16). R_f=0.18 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3149, 2914, 2855, 1722, 1634, 1553, 1370, 1311, 1258, 1199, 1164, 1123, 1070, 976, 841, 753, 729 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 9.54 (br s, 1H), 7.54 (d, J=8.2 Hz, 1H), 7.52 (d, J=7.9 Hz, 1H), 7.25 (dd, J=8.2, 7.9 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 178.7, 165.7, 137.4, 137.0, 129.3, 126.1, 122.9, 114.9, 110.1, 109.0, 53.5; HRMS (ESI-TOF) calcd for $C_{11}H_8BrNO_4^+$ [M+H^+] 297.9709, found 297.9709.

4.5.2. Methyl 4-bromo-3-[(hexyloxy)methyl]-1-hydroxy-1*H*-indole-2-carboxylate (17). R_f=0.60 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3178 (br), 2955, 2920, 2849, 1714, 1531, 1437, 1396, 1355, 1314, 1255, 1226, 1185, 1149, 1120, 1073, 879, 773, 732 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 9.48 (br s, 1H), 7.41 (dd, J=8.2, 0.7 Hz, 1H), 7.32 (dd, J=7.5, 0.7 Hz, 1H), 7.15 (dd, J=8.2, 7.5 Hz, 1H), 5.00 (s, 2H), 3.91 (s, 3H), 3.53 (t, J=6.4 Hz, 2H), 1.57–1.50 (m, 2H), 1.35–1.21 (m, 6H), 0.86–0.82 (m, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 162.2, 137.3, 126.9, 126.8, 126.7, 121.0, 116.3, 116.0, 110.2, 70.7, 61.9, 52.9, 32.4, 30.5, 26.7, 23.4, 14.3; HRMS (ESI-TOF) calcd for $C_{17}H_{22}BrNO_4Na^+$ [M+Na^+] 406.0624, found 406.0618.

4.5.3. Methyl 4-bromo-3-(ethoxymethyl)-1-hydroxy-1*H*-indole-2-carboxylate (18). R_f=0.53 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3166 (br), 2978, 2861, 1713, 1531, 1355, 1249, 1226, 1185, 1126, 1073, 991, 732 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 9.36 (br s, 1H), 7.40 (d, J=8.3 Hz, 1H), 7.32 (d, J=7.5 Hz, 1H), 7.15 (dd, J=8.3, 7.5 Hz, 1H), 5.02 (s, 2H), 3.92 (s, 3H), 3.60 (q, J=7.0 Hz, 2H), 1.17 (t, J=7.0 Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.8, 137.8, 127.7, 127.4, 121.5, 118.9, 116.9, 116.6, 110.7, 66.7, 62.4, 53.5, 16.2; HRMS (ESI-TOF) calcd for $C_{13}H_{14}BrNO_4Na^+$ [M+Na^+] 349.9998, found 349.9996.

4.5.4. Methyl 4-bromo-3-[(cyclohexyloxy)methyl]-1-hydroxy-1*H*-indole-2-carboxylate (19). R_f=0.58 (silica gel, MeOH/CH_2Cl_2, 5:95); IR (film) ν_{max} 3173 (br), 2922, 2853, 1713, 1530, 1433, 1348, 1256, 1228, 1188, 1148, 1125, 1057, 948, 771, 736 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 9.33 (s, 1H), 7.40 (d, J=8.3 Hz, 1H), 7.32 (d, J=7.5 Hz, 1H), 7.14 (t, J=7.9 Hz, 1H), 5.05 (s, 2H), 3.91 (s, 3H), 3.52–3.49 (m, 1H), 1.97–1.93 (m, 1H), 1.73–1.69 (m, 2H), 1.55–1.50 (m, 1H), 1.34–1.21 (m, 6H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.2, 137.1, 127.1, 127.0, 126.7, 120.8, 116.6, 115.9, 110.1, 78.0, 59.3, 52.8, 33.0 (2C), 26.6 (2C), 25.8; HRMS (ESI-TOF) calcd for $C_{17}H_{20}BrNO_4Na^+$ [M+Na^+] 404.0468, found 404.0469.

4.5.5. Methyl 3-[(benzyloxy)methyl]-1-hydroxy-4-({[2-(trimethylsilyl)ethoxy]methoxy}methyl)-1*H*-indole-2-carboxylate (20). R_f=0.69 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 2950, 1718, 1439, 1248, 1057, 835 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 9.24 (s, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.36–7.26 (m, 6H), 7.46 (d, J=7.0 Hz, 1H), 5.05 (s, 2H), 5.02 (s, 2H), 4.71 (s, 2H), 4.56 (s, 2H), 3.88 (s, 3H),

3.61 (t, J=8.5 Hz, 2H), 0.88 (t, J=8.5 Hz, 2H), −0.01 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.7, 139.9, 136.7, 133.6, 130.9, 130.4, 129.2 (2C), 128.6 (2C), 128.3, 126.3, 125.7, 122.9, 110.3, 94.9, 72.1, 68.2, 65.8, 63.2, 52.7, 18.6, −1.4 (3C); HRMS (ESI-TOF) calcd for $C_{25}H_{33}NO_6SiNa^+$ [M+Na$^+$] 494.1969, found 494.1969.

4.5.6. Methyl 3-[(benzyloxy)methyl]-4-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (21). R_f=0.76 (silica gel, MeOH/CH_2Cl_2, 5:95); IR (film) ν_{max} 3194, 2939, 2862, 1711, 1628, 1523, 1434, 1362, 1318, 1263, 1229, 1135, 1097, 1044, 1025, 991, 936, 775, 731, 692 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.30 (br s, 1H), 7.34–7.24 (m, 7H), 6.84 (dd, J=11.4, 7.5 Hz, 1H), 4.97 (s, 2H), 4.55 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.2, 159.2 (d, J=249.1 Hz), 140.6, 138.2 (d, J=10.3 Hz), 129.8 (2C), 129.3 (2C), 128.9, 127.9 (d, J=8.4 Hz), 126.2, 115.2 (d, J=4.0 Hz), 112.3 (d, J=20.6 Hz), 107.5 (d, J=4.0 Hz), 107.4 (d, J=19.3 Hz), 73.7, 64.1, 53.4; HRMS (ESI-TOF) calcd for $C_{18}H_{16}FNO_4Na^+$ [M+Na$^+$] 352.0955, found 352.0952.

4.5.7. Methyl 3-[(benzyloxy)methyl]-5-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (22). R_f=0.78 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3315 (br), 2954, 1708, 1528, 1444, 1259, 1192, 1105 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.22 (s, 1H), 7.49–7.45 (m, 2H), 7.36–7.30 (m, 5H), 7.21–7.15 (m, 1H), 4.96 (s, 2H), 4.54 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.3, 159.0 (d, J=234.0 Hz), 139.8, 133.1, 129.2 (2C), 128.7 (2C), 128.4, 126.0, 123.2 (d, J=16.4 Hz), 116.8 (d, J=2.3 Hz), 115.6 (d, J=27.3 Hz), 112.0 (d, J=9.8 Hz), 106.4 (d, J=24.2 Hz), 72.6, 63.6, 52.6; HRMS (ESI-TOF) calcd for $C_{18}H_{15}FNO_4^-$ [M−H$^-$] 328.0991, found 328.0995.

4.5.8. Methyl 3-[(benzyloxy)methyl]-6-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (23). R_f=0.63 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3205 (br), 3032, 2951, 2860, 1714, 1628, 1529, 1438, 1355, 1177, 1054, 917, 832, 755 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.19 (s, 1H), 7.81 (dd, J=8.4, 4.8 Hz, 1H), 7.36–7.23 (m, 5H), 7.19 (dd, J=9.0, 1.8 Hz, 1H), 6.96 (dt, J=9.3, 2.4 Hz, 1H), 4.98 (s, 2H), 4.54 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.9 (d, J=240.3 Hz), 162.3, 139.7, 136.5 (d, J=13.1 Hz), 129.2 (2C), 129.1, 128.7 (2C), 128.4, 127.6, 124.2 (d, J=10.4 Hz), 119.7, 111.1 (d, J=25.7 Hz), 96.3 (d, J=27.2 Hz), 72.7, 63.6, 52.5; HRMS (ESI-TOF) calcd for $C_{18}H_{16}FNO_4Na^+$ [M+Na$^+$] 352.0955, found 352.0949.

4.5.9. Methyl 3-[(benzyloxy)methyl]-6-cyano-1-hydroxy-1*H*-indole-2-carboxylate (24). R_f=0.71 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2925, 1854, 2225, 1717, 1660, 1573, 1527, 1438, 1416, 1364, 1258, 1144, 1084, 1018, 867, 735, 698 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.38 (br s, 1H), 7.94 (d, J=8.5 Hz, 1H), 7.93–7.91 (m, 1H), 7.39 (dd, J=8.0, 1.5 Hz, 1H), 7.35–7.30 (m, 5H), 4.99 (s, 2H), 4.55 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.4, 139.6, 129.2 (2C), 128.7 (2C), 128.5, 127.7, 125.5, 123.9, 123.5, 120.8, 120.4, 117.0, 115.9, 108.8, 72.8, 63.4, 52.9; HRMS (ESI-TOF) calcd for $C_{19}H_{15}N_2O_4^-$ [M−H$^-$] 335.1037, found 335.1049.

4.5.10. Methyl 4-bromo-3-[(hexylthio)methyl]-1-hydroxy-1*H*-indole-2-carboxylate (25). R_f=0.63 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3349 (br), 2956, 2912, 2847, 1703, 1681, 1517, 1440, 1397, 1342, 1304, 1255, 1195, 1146, 1118, 982, 872, 774, 741 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.18 (s, 1H), 7.46 (d, J=8.5 Hz, 1H), 7.34 (d, J=7.5 Hz, 1H), 7.22 (dd, J=8.5, 7.5 Hz, 1H), 4.44 (s, 2H), 3.93 (s, 3H), 2.48 (t, J=7.3 Hz, 2H), 1.52–1.46 (m, 2H), 1.33–1.19 (m, 6H), 0.84 (t, J=6.6 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.5, 137.9, 127.4, 126.7, 125.6, 120.0, 118.9, 116.2, 110.4, 52.8, 32.2, 32.1, 30.5, 29.3, 25.9, 23.2, 14.3; HRMS (ESI-TOF) calcd for $C_{17}H_{21}BrNO_3S^-$ [M−H$^-$] 398.0431, found 398.0420.

4.5.11. Methyl 4-bromo-1-hydroxy-3-[(phenylthio)methyl]-1*H*-indole-2-carboxylate (26). R_f=0.60 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3342 (br), 2943, 1684, 1514, 1437, 1396, 1343, 1308, 1255, 1191, 1144, 1120, 1020, 979, 873, 773, 738, 691 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.18 (br s, 1H), 7.46 (d, J=8.3 Hz, 1H), 7.35 (d, J=7.4 Hz, 1H), 7.28–7.19 (m, 6H), 4.83 (s, 2H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 162.0, 137.6, 136.4, 132.8 (2C), 129.8 (2C), 128.1, 127.3, 126.7, 125.8, 119.8, 116.6, 116.1, 110.4, 52.6, 30.1; HRMS (ESI-TOF) calcd for $C_{17}H_{14}BrNO_3SNa^+$ [M+Na$^+$] 413.9770, found 413.9761.

4.5.12. Methyl 3-[(cyclohexylthio)methyl]-4-bromo-1-hydroxy-1*H*-indole-2-carboxylate (27). R_f=0.65 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3349 (br), 2956, 2912, 2847, 1703, 1681, 1517, 1440, 1397, 1342, 1304, 1255, 1195, 1146, 1118, 982, 872, 774, 741 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.17 (s, 1H), 7.45 (d, J=9.7 Hz, 1H), 7.33 (d, J=9.0 Hz, 1H), 7.20 (dd, J=9.7, 9.0 Hz, 1H), 4.47 (s, 2H), 3.94 (s, 3H), 2.72–2.64 (m, 1H), 1.95–1.88 (m, 1H), 1.75–1.67 (m, 2H), 1.59–1.54 (m, 1H), 1.33–1.21 (m, 6H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.5, 137.9, 127.3, 126.6, 125.5, 120.0, 119.2, 116.1, 110.3, 52.8, 44.1, 34.7 (2C), 26.9 (2C), 26.5, 24.5; HRMS (ESI-TOF) calcd for $C_{17}H_{21}BrNO_3S^+$ [M+H$^+$] 420.0239, found 420.0236.

4.5.13. Methyl 3-[(benzylthio)methyl]-1-hydroxy-4-({[2-(trimethylsilyl)ethoxy]methoxy}methyl)-1*H*-indole-2-carboxylate (28). R_f=0.65 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 2950, 1709, 1527, 1440, 1248, 1027, 859, 835, 753 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.20 (s, 1H), 7.44 (dd, J=8.4, 1.2 Hz, 1H), 7.34–7.22 (m, 6H), 7.13 (d, J=6.8 Hz, 1H), 4.95 (s, 2H), 4.64 (s, 2H), 4.38 (s, 2H), 3.83 (s, 3H), 3.80 (s, 2H), 3.83 (t, J=7.6 Hz, 2H), 0.87 (t, J=7.6 Hz, 2H), −0.02 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.8, 139.7, 137.1, 133.3, 129.6 (2C), 129.3 (2C), 127.7, 126.5, 124.6, 123.3, 120.6, 117.3, 110.7, 94.8, 68.7, 65.9, 52.5, 37.2, 27.6, 18.6, −1.4 (3C); HRMS (ESI-TOF) calcd for $C_{25}H_{33}NO_5SSiNa^+$ [M+Na$^+$] 510.1741, found 510.1731.

4.5.14. Methyl 3-[(benzylthio)methyl]-4-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (29). R_f=0.65 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3356, 2950, 1700, 1630, 1532, 1451, 1355, 1321, 1262, 1236, 1137, 948, 924 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.22 (s, 1H), 7.33–7.20 (m, 7H), 6.81 (dd, J=10.5, 6.5 Hz, 1H), 4.25 (s, 2H), 3.85 (s, 3H), 3.77 (s, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.3, 158.4 (d, J=248.5 Hz), 139.7, 138.5 (d, J=10.3 Hz), 129.6 (2C), 129.2 (2C), 127.7, 127.5

(d, J=8.0 Hz), 125.2, 116.5 (d, J=4.0 Hz), 111.6 (d, J=20.0 Hz), 106.9 (d, J=4.3 Hz), 106.5 (d, J=19.3 Hz), 52.6, 37.0, 27.9; HRMS (ESI-TOF) calcd for $C_{18}H_{15}FNO_3S^-$ [M−H$^-$] 344.0762, found 344.0765.

4.5.15. Methyl 3-[(benzylthio)methyl]-5-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (30). R_f=0.52 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2956, 1718, 1522, 1442, 1262, 1180 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.13 (br s, 1H), 7.45 (dd, J=8.5, 4.0 Hz, 1H), 7.34–7.22 (m, 6H), 7.17 (dt, J=9.5, 2.5 Hz, 1H), 4.15 (s, 2H), 3.84 (s, 3H), 3.72 (s, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.3, 158.8 (d, J=233.8 Hz), 139.7, 133.4, 129.6 (2C), 129.3 (2C), 127.7, 125.8, 122.9 (d, J=9.9 Hz), 117.5, 115.7 (d, J=27.4 Hz), 112.2 (d, J=9.5 Hz), 106.0 (d, J=24.0 Hz), 52.5, 37.0, 26.3; HRMS (ESI-TOF) calcd for $C_{18}H_{15}FNO_3S^-$ [M−H$^-$] 344.0762, found 344.0769.

4.5.16. Methyl 3-[(benzylthio)methyl]-6-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (31). R_f=0.53 (silica gel, EtOAc/hexanes, 3:7); IR (film) ν_{max} 3315 (br), 2955, 1720, 1530, 1532, 1445, 1399, 1351, 1291, 1266, 1178, 1123 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.19 (br s, 1H), 7.65 (dd, J=8.8, 5.2 Hz, 1H), 7.34–7.23 (m, 5H), 7.16 (dd, J=9.2, 2.4 Hz, 1H), 6.95–6.90 (m, 1H), 4.17 (s, 2H), 3.82 (s, 3H), 3.72 (s, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 163.0 (d, J=240.4 Hz), 162.3, 139.7, 136.8 (d, J=13.3 Hz), 129.7 (2C), 129.4, 128.3 (2C), 128.0, 127.7, 123.8 (d, J=10.4 Hz), 119.5, 110.8 (d, J=25.6 Hz), 96.4 (d, J=27.0 Hz), 52.4, 37.0, 26.3; HRMS (ESI-TOF) calcd for $C_{18}H_{15}FNO_3S^-$ [M−H$^-$] 344.0762, found 344.0769.

4.5.17. Methyl 3-[(benzylthio)methyl]-6-cyano-1-hydroxy-1*H*-indole-2-carboxylate (32). R_f=0.59 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2924, 2360, 2224, 1715, 1523, 1444, 1264, 1116 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.31 (s, 1H), 7.89 (s, 1H), 7.77 (d, J=8.5 Hz, 1H), 7.36 (d, J=8.5 Hz, 1H), 7.28–7.22 (m, 5H), 4.18 (s, 2H), 3.86 (s, 3H), 3.72 (s, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 161.9, 139.5, 134.9, 132.2, 129.6 (2C), 129.3 (2C), 127.7, 125.1, 123.6, 123.0, 120.4, 117.7, 115.9, 109.0, 52.8, 37.0, 26.0; HRMS (ESI-TOF) calcd for $C_{19}H_{15}N_2O_3S^-$ [M−H$^-$] 351.0809, found 351.0813.

4.5.18. Methyl 4-bromo-1-hydroxy-3-(morpholin-4-ylmethyl)-1*H*-indole-2-carboxylate (33). R_f=0.13 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3414 (br), 2923, 2858, 1713, 1642, 1604, 1549, 1517, 1462, 1435, 1353, 1260, 1244, 1221, 1184, 1113, 867, 769, 730 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 7.47 (d, J=8.3 Hz, 1H), 7.35 (d, J=7.5 Hz, 1H), 7.19 (t, J=7.9 Hz, 1H), 4.08 (s, 2H), 3.93 (s, 3H), 3.53 (br s, 4H), 2.48 (br s, 4H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.7, 137.8, 127.7, 126.9, 126.8, 121.3, 116.4, 116.3, 110.2, 67.7 (2C), 54.0 (2C), 52.7, 51.1; HRMS (ESI-TOF) calcd for $C_{15}H_{18}BrN_2O_4^+$ [M+H$^+$] 369.0444, found 369.0446.

4.5.19. Methyl 3-(anilinomethyl)-4-bromo-1-hydroxy-1*H*-indole-2-carboxylate (34). R_f=0.76 (silica gel, MeOH/CH_2Cl_2, 3:97); IR (film) ν_{max} 3385 (br), 2927, 2843, 1706, 1599, 1496, 1435, 1351, 1309, 1253, 1225, 1183, 1127, 1061, 1024, 767, 739 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.24 (br s, 1H), 7.48 (d, J=8.3 Hz, 1H), 7.37 (d, J=7.5 Hz, 1H), 7.22 (dd, J=8.3, 7.5 Hz, 1H), 7.12 (dd, J=8.5, 7.6 Hz, 2H), 6.69 (d, J=7.6 Hz, 2H), 6.65–6.60 (m, 1H), 4.83 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.4, 149.6, 137.6, 130.0 (2C), 127.3, 126.7, 120.8, 117.8, 117.5, 115.9, 115.3, 114.0 (2C), 110.4, 52.9, 38.1; HRMS (ESI-TOF) calcd for $C_{17}H_{16}BrN_2O_3^+$ [M+H$^+$] 375.0339, found 375.0327.

4.5.20. Methyl 4-bromo-1-hydroxy-3-(4-hydroxybenzyl)-1*H*-indole-2-carboxylate (35). R_f=0.41 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3342 (br), 2943, 1690, 1614, 1508, 1443, 1343, 1249, 1173, 1120, 873, 756, 732 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.16 (br s, 1H), 7.49 (d, J=8.3 Hz, 1H), 7.30 (d, J=7.4 Hz, 1H), 7.19 (dd, J=8.3, 7.4 Hz, 1H), 6.92 (d, J=8.5 Hz, 2H), 6.65 (d, J=8.5 Hz, 2H), 4.62 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.5, 155.6, 137.8, 133.5, 129.9 (2C), 127.2, 126.4, 126.0, 120.6, 120.3, 116.0, 115.6 (2C), 110.3, 52.5, 29.3; HRMS (ESI-TOF) calcd for $C_{17}H_{14}BrNO_4Na^+$ [M+Na$^+$] 397.9998, found 397.9987.

4.5.21. Methyl 4-bromo-1-hydroxy-3-(3-hydroxy-2,4-dimethoxybenzyl)-1*H*-indole-2-carboxylate (36). R_f=0.42 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3414, 2934, 2835, 1708, 1675, 1615, 1489, 1440, 1396, 1347, 1287, 1249, 1085, 1030, 894, 746 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.21 (s, 1H), 7.51 (d, J=7.9 Hz, 1H), 7.28 (d, J=7.9 Hz, 1H), 7.21 (t, J=7.9 Hz, 1H), 6.46 (d, J=8.6 Hz, 1H), 6.38 (s, 1H), 5.92 (d, J=8.6 Hz, 1H), 4.62 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.5, 147.5, 146.0, 139.7, 138.0, 128.6, 127.3, 126.5, 126.4, 121.2, 119.2, 118.6, 116.3, 110.4, 107.5, 60.4, 56.7, 52.6, 24.7; HRMS (ESI-TOF) calcd for $C_{19}H_{18}BrNO_6Na^+$ [M+Na$^+$] 458.0210, found 458.0200.

4.5.22. Methyl 4-bromo-1-hydroxy-3-[(2-oxocyclohexyl)-methyl]-1*H*-indole-2-carboxylate (37). R_f=0.38 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3319, 2928, 2855, 1705, 1515, 1436, 1399, 1341, 1304, 1251, 1230, 1120, 882, 756, 729 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.14 (br s, 1H), 7.45 (d, J=8.0 Hz, 1H), 7.30 (d, J=8.0 Hz, 1H), 7.17 (t, J=8.0 Hz, 1H), 3.90 (s, 3H), 3.73 (dd, J=14.2, 4.4 Hz, 1H), 3.18 (dd, J=14.2, 9.2 Hz, 1H), 2.83–2.75 (m, 1H), 2.37–2.26 (m, 2H), 2.02–1.96 (m, 1H), 1.90–1.84 (m, 1H), 1.78–1.71 (m, 1H), 1.68–1.58 (m, 1H), 1.57–1.42 (m, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 212.7, 162.9, 138.1, 127.1, 126.7, 126.5, 120.8, 120.0, 116.2, 110.4, 53.6, 52.6, 42.7, 33.6, 28.8, 25.8, 24.5; HRMS (ESI-TOF) calcd for $C_{17}H_{18}BrNO_4Na^+$ [M+Na$^+$] 402.0311, found 402.0299.

4.5.23. Methyl 4-bromo-1-hydroxy-3-[(2-oxocyclopentyl)methyl]-1*H*-indole-2-carboxylate (38). R_f=0.32 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3318, 2954, 2872, 1713, 1689, 1531, 1437, 1396, 1349, 1307, 1243, 1184, 1143, 1119, 1078, 978, 884, 773, 737 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.29 (br s, 1H), 7.45 (d, J=7.9 Hz, 1H), 7.29 (d, J=7.9 Hz, 1H), 7.17 (t, J=7.9 Hz, 1H), 3.89 (s, 3H), 3.68 (dd, J=13.8, 6.2 Hz, 1H), 3.25 (dd, J=13.8, 9.2 Hz, 1H), 2.63–2.54 (m, 1H), 2.20–2.09 (m, 1H), 1.97–1.91 (m, 2H), 1.90–1.83 (m, 1H), 1.74–1.65 (m, 2H); ^{13}C NMR (150 MHz, CD_3CN) δ 200.0, 162.7, 137.9, 127.1,

126.3, 125.8, 120.4, 120.2, 116.1, 110.3, 52.5, 51.6, 38.5, 29.6, 24.7, 21.0; HRMS (ESI-TOF) calcd for $C_{16}H_{16}BrNO_4Na^+$ [M+Na$^+$] 388.0155, found 388.0148.

4.5.24. Methyl 4-bromo-1-hydroxy-3-[(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]-1*H*-indole-2-carboxylate (39). R_f=0.35 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3310, 2944, 2850, 1708, 1676, 1598, 1519, 1451, 1399, 1352, 1300, 1242, 1221, 1116, 1022, 980, 881, 776, 734 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.27 (br s, 1H), 7.92 (d, J=7.7 Hz, 1H), 7.51–7.43 (m, 2H), 7.31 (t, J=7.7 Hz, 2H), 7.26 (d, J=7.7 Hz, 1H), 7.18 (t, J=7.7 Hz, 1H), 4.06 (br s, 1H), 3.74 (s, 3H), 3.39 (br s, 1H), 3.02–2.92 (m, 2H), 2.91–2.80 (m, 1H), 2.07–1.97 (m, 1H), 1.95 (s, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 199.7, 162.8, 145.4, 138.0, 134.1, 133.4, 129.9, 127.7, 127.4, 127.2, 126.5, 126.2, 120.8, 119.8, 116.2, 110.4, 52.5, 50.6, 29.0, 28.7, 24.9; HRMS (ESI-TOF) calcd for $C_{21}H_{18}BrNO_4Na^+$ [M+Na$^+$] 450.0311, found 450.0297.

4.5.25. Methyl 4-bromo-1-hydroxy-3-(2-methyl-3-oxopentyl)-1*H*-indole-2-carboxylate (40). R_f=0.37 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3300, 2965, 2923, 1708, 1680, 1514, 1441, 1341, 1247, 1184, 1148, 1116, 1090, 1033, 975, 881, 771, 734 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.22 (br s, 1H), 7.45 (d, J=7.9 Hz, 1H), 7.32 (d, J=7.9 Hz, 1H), 7.19 (t, J=7.9 Hz, 1H), 3.91 (s, 3H), 3.49 (br s, 1H), 3.35 (br s, 1H), 3.03–2.97 (m, 1H), 2.51–2.43 (m, 1H), 2.34–2.26 (m, 1H), 0.99 (d, J=7.0 Hz, 3H), 0.89 (d, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 215.2, 162.6, 138.0, 127.2, 126.6, 126.3, 120.6, 119.4, 116.1, 110.4, 52.6, 48.9, 35.3, 27.7, 15.9, 7.9; HRMS (ESI-TOF) calcd for $C_{16}H_{18}BrNO_4Na^+$ [M+Na$^+$] 390.0311, found 390.0307.

4.5.26. Methyl 4-bromo-1-hydroxy-3-(3-oxo-3-phenylpropyl)-1*H*-indole-2-carboxylate (41). R_f=0.35 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3357, 2914, 1708, 1674, 1594, 1520, 1441, 1395, 1310, 1242, 1146, 1117, 771, 737, 686 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.29 (br s, 1H), 7.99–7.94 (m, 2H), 7.60–7.55 (m, 1H), 7.49–7.43 (m, 3H), 7.30 (br s, 1H), 7.18 (t, J=7.7 Hz, 1H), 3.85 (s, 3H), 3.63 (br s, 2H), 3.35 (t, J=7.7 Hz, 2H); ^{13}C NMR (150 MHz, CD_3CN) δ 200.1, 162.5, 137.8, 133.9, 129.5, 128.7, 128.6, 127.1, 126.2, 125.5, 121.0, 120.4, 116.0, 110.3, 52.5, 41.7, 20.2 (3C); HRMS (ESI-TOF) calcd for $C_{19}H_{16}BrNO_4Na^+$ [M+Na$^+$] 424.0155, found 424.0154.

4.5.27. Methyl 4-bromo-3-(4,4-dimethyl-3-oxopentyl)-1-hydroxy-1*H*-indole-2-carboxylate (42). R_f=0.46 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3283, 2942, 2872, 1725, 1707, 1519, 1437, 1396, 1349, 1243, 1178, 1149, 1119, 984, 884, 779, 737 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.34 (br s, 1H), 7.44 (br s, 1H), 7.29 (br s, 1H), 7.17 (t, J=7.4 Hz, 1H), 3.90 (s, 3H), 3.40 (br s, 2H), 2.87 (t, J=7.9 Hz, 2H), 1.09 (s, 9H); ^{13}C NMR (150 MHz, CD_3CN) δ 215.7, 162.6, 138.6, 127.2, 126.3, 124.8, 121.5, 120.5, 116.1, 110.3, 52.7, 44.6, 39.7, 26.6, 20.1 (3C); HRMS (ESI-TOF) calcd for $C_{17}H_{20}BrNO_4Na^+$ [M+Na$^+$] 404.0468, found 404.0456.

4.5.28. Methyl 4-bromo-1-hydroxy-3-(2,2,4-trimethyl-3-oxopentyl)-1*H*-indole-2-carboxylate (43). R_f=0.45 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3309, 2972, 2868, 1712, 1689, 1515, 1464, 1440, 1379, 1346, 1271, 1234, 1182, 1140, 1117, 1042, 1000, 878, 798, 775, 742 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.49 (br s, 1H), 7.49 (br s, 1H), 7.33 (br s, 1H), 7.18 (t, J=7.2 Hz, 1H), 3.90 (s, 3H), 3.67 (br s, 2H), 3.30 (hept, J=6.6 Hz, 1H), 1.04 (d, J=6.6 Hz, 6H), 0.97 (s, 6H); ^{13}C NMR (150 MHz, CD_3CN) δ 220.1, 162.9, 137.6, 128.1, 127.2, 126.6, 121.8, 116.1, 115.6, 110.4, 52.6, 50.6, 35.0, 29.5, 23.0 (2C), 20.4 (2C); HRMS (ESI-TOF) calcd for $C_{18}H_{22}BrNO_4Na^+$ [M+Na$^+$] 418.0624, found 418.0620.

4.5.29. Methyl 4-bromo-3-(2,2-difluoro-3-oxo-3-phenylpropyl)-1-hydroxy-1*H*-indole-2-carboxylate (44). R_f=0.47 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3360, 2955, 2919, 1698, 1520, 1449, 1311, 1264, 1184, 1127, 914, 764, 716 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.24 (br s, 1H), 8.04–8.02 (m, 2H), 7.68 (t, J=7.3 Hz, 1H), 7.53–7.50 (m, 3H), 7.38–7.36 (m, 1H), 7.24–7.21 (m, 1H), 4.46 (t, J=17.7 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 190.5, 162.1, 137.2, 135.4, 133.0, 130.7 (t, J=3.4 Hz, 2C), 129.7 (2C), 127.4, 127.2, 127.1, 121.1, 119.1, 115.9, 110.4, 108.9, 52.7, 29.7 (t, J=23.8 Hz); HRMS (ESI-TOF) calcd for $C_{19}H_{15}BrF_2NO_4^+$ [M+H$^+$] 438.0147, found 438.0145.

4.5.30. Methyl 4-bromo-3-[3-(4-chlorophenyl)-2,2-difluoro-3-oxopropyl]-1-hydroxy-1*H*-indole-2-carboxylate (45). R_f=0.31 (silica gel, EtOAc/hexanes, 2:8); IR (film) ν_{max} 1702, 1588, 1448, 1401, 1265, 1091, 762 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.24 (br s, 1H), 7.96 (d, J=8.8 Hz, 2H), 7.53–7.50 (m, 3H), 7.37 (d, J=7.5 Hz, 1H), 7.23 (t, J=8.8 Hz, 1H), 4.45 (t, J=17.5 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 189.0, 161.6, 140.8, 136.8, 132.0 (t, J=3.6 Hz, 2C), 131.2, 129.5 (2C), 129.4, 128.5, 126.8, 126.7, 120.6, 115.4, 110.0, 108.3, 52.2, 29.3 (t, J=23.8 Hz); HRMS (ESI-TOF) calcd for $C_{19}H_{14}BrClF_2NO_4^+$ [M+H$^+$] 471.9757, found 471.9752.

4.5.31. Methyl 4-bromo-3-(2,2-difluoro-3-oxo-3-thien-2-ylpropyl)-1-hydroxy-1*H*-indole-2-carboxylate (46). R_f=0.25 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3335 (br), 3105, 2954, 1714, 1679, 1614, 1517, 1447, 1411, 1345, 1311, 1266, 1186, 1148, 1127, 1058, 932, 879, 839, 761, 733 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.36 (br s, 1H), 7.95 (dd, J=4.5, 1.3 Hz, 1H), 7.86–7.84 (m, 1H), 7.51 (d, J=8.5 Hz, 1H), 7.38 (d, J=7.0 Hz, 1H), 7.26–7.18 (m, 2H), 4.44 (t, J=17.0 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 183.8, 162.1, 139.3, 138.3, 137.2, 137.1 (t, J=5.4 Hz), 130.1, 127.5, 127.3, 127.1, 121.1, 118.9, 115.9, 110.5, 108.8, 52.7, 30.0 (t, J=23.8 Hz); HRMS (ESI-TOF) calcd for $C_{17}H_{13}BrF_2NO_4S^+$ [M+H$^+$] 443.9711, found 443.9711.

4.5.32. Methyl 4-bromo-1-hydroxy-3-(3-oxobutyl)-1*H*-indole-2-carboxylate (47). R_f=0.37 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3342, 2942, 1707, 1519, 1437, 1396, 1354, 1243, 1184, 1119, 879, 773, 737 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.36 (br s, 1H), 7.45 (d, J=8.2 Hz, 1H), 7.30 (d, J=8.2 Hz, 1H), 7.18 (t, J=8.2 Hz, 1H), 3.91 (s, 3H), 3.44 (t, J=8.0 Hz, 2H), 2.78 (t, J=8.0 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 208.7, 162.5, 137.9, 127.2, 126.3, 125.6, 121.1, 120.4, 116.0, 110.4,

52.7, 46.3, 29.9, 19.8; HRMS (ESI-TOF) calcd for $C_{14}H_{14}BrNO_4Na^+$ [M+Na$^+$] 361.9998, found 361.9990.

4.5.33. Methyl 3-(2-acetyl-3-oxobutyl)-4-bromo-1-hydroxy-1*H*-indole-2-carboxylate (48). R_f=0.23 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3392, 2956, 1710, 1697, 1617, 1519, 1433, 1353, 1243, 1180, 1140, 1117, 870, 773, 733 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.11 (br s, 1H), 7.47 (d, J=7.0 Hz, 1H), 7.35 (d, J=7.0 Hz, 1H), 7.21 (t, J=7.0 Hz, 1H), 4.26 (t, J=6.0 Hz, 1H), 3.90 (s, 3H), 3.71 (d, J=6.0 Hz, 2H), 2.04 (s, 6H); ^{13}C NMR (125 MHz, CD_3CN) δ 205.1 (2C), 162.3, 137.9, 127.3, 126.7, 126.6, 120.4, 117.4, 115.8, 110.5, 69.6, 52.7, 30.7, 23.7 (2C); HRMS (ESI-TOF) calcd for $C_{16}H_{16}BrNO_5Na^+$ [M+Na$^+$] 404.0104, found 404.0100.

4.5.34. Methyl 4-bromo-1-hydroxy-3-(3-methoxy-2,2-dimethyl-3-oxopropyl)-1*H*-indole-2-carboxylate (49). R_f=0.36 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3323, 2944, 1714, 1513, 1433, 1393, 1347, 1249, 1180, 1134, 1025, 985, 865, 773, 733 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.12 (br s, 1H), 7.48 (d, J=7.5 Hz, 1H), 7.33 (d, J=7.5 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 3.89 (s, 3H), 3.72 (s, 2H), 3.51 (s, 3H), 1.11 (s, 6H); ^{13}C NMR (125 MHz, CD_3CN) δ 178.3, 162.8, 137.7, 127.8, 127.2, 126.7, 121.8, 116.6, 116.3, 110.5, 52.7, 52.3, 44.7, 32.7, 25.1 (2C); HRMS (ESI-TOF) calcd for $C_{16}H_{18}BrNO_5Na^+$ [M+Na$^+$] 406.0260, found 406.0243.

4.5.35. Methyl 4-bromo-1-hydroxy-3-(3-oxopropyl)-1*H*-indole-2-carboxylate (50). R_f=0.20 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3471, 1701, 1695, 1537, 1437, 1384, 1237, 1190, 1172, 1149, 1119, 920, 873, 773, 737 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.77 (s, 1H), 9.31 (br s, 1H), 7.46 (d, J=7.9 Hz, 1H), 7.32 (d, J=7.9 Hz, 1H), 7.20 (t, J=7.9 Hz, 1H), 3.91 (s, 3H), 3.56 (t, J=7.7 Hz, 2H), 2.80 (t, J=7.7 Hz, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 203.0, 162.4, 137.9, 127.3, 126.3, 125.5, 120.6, 120.4, 115.9, 110.4, 52.7, 46.7, 18.2; HRMS (ESI-TOF) calcd for $C_{13}H_{11}BrNO_4^-$ [M−H$^-$] 323.9877, found 323.9863.

4.5.36. Methyl 4-bromo-3-but-3-enyl-1-hydroxy-1*H*-indole-2-carboxylate (51). R_f=0.67 (silica gel, MeOH/CH_2Cl_2, 3:97); IR (film) ν_{max} 3360, 2953, 1679, 1638, 1615, 1516, 1440, 1341, 1312, 1254, 1143, 1120, 911, 876, 771, 736 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.23 (br s, 1H), 7.44 (d, J=7.9 Hz, 1H), 7.30 (d, J=7.9 Hz, 1H), 7.18 (t, J=7.9 Hz, 1H), 6.00–5.89 (m, 1H), 5.03 (dd, J=17.2, 1.9 Hz, 1H), 4.95 (d, J=10.2 Hz, 1H), 3.91 (s, 3H), 3.39–3.33 (m, 2H), 2.38 (q, J=7.5 Hz, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.8, 139.2, 137.9, 127.2, 126.4, 125.4, 122.2, 120.5, 116.2, 115.3, 110.3, 52.6, 37.3, 24.7; HRMS (ESI-TOF) calcd for $C_{14}H_{15}BrNO_3^+$ [M+H$^+$] 324.0230, found 324.0234.

4.5.37. Methyl 4-bromo-1-hydroxy-3-(3-methylbut-3-enyl)-1*H*-indole-2-carboxylate (52). R_f=0.69 (silica gel, MeOH/CH_2Cl_2, 1:99); IR (film) ν_{max} 3346, 2960, 2925, 1679, 1511, 1440, 1398, 1342, 1271, 1257, 1239, 1117, 986, 882, 775, 737 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.19 (br s, 1H), 7.44 (d, J=7.9 Hz, 1H), 7.30 (d, J=7.9 Hz, 1H), 7.17 (t, J=7.9 Hz, 1H), 4.75 (s, 2H), 3.92 (s, 3H), 3.41–3.35 (m, 2H), 2.35–2.30 (m, 2H), 1.81 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.7, 146.8, 137.7, 127.1, 126.2, 125.0, 122.4, 120.3, 116.1, 110.6, 110.2, 52.5, 41.2, 24.2, 22.5; HRMS (ESI-TOF) calcd for $C_{15}H_{15}BrNO_3^-$ [M−H$^-$] 336.0241, found 336.0238.

4.5.38. Methyl 4-bromo-3-[3-(chloromethyl)but-3-enyl]-1-hydroxy-1*H*-indole-2-carboxylate (53). R_f=0.70 (silica gel, MeOH/CH_2Cl_2, 1:99); IR (film) ν_{max} 3377, 2954, 2907, 1678, 1513, 1443, 1396, 1343, 1313, 1255, 1119, 908, 879, 787, 732 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.20 (s, 1H), 7.45 (d, J=8.0 Hz, 1H), 7.32 (d, J=8.0 Hz, 1H), 7.19 (t, J=8.0 Hz, 1H), 5.20 (s, 1H), 5.05 (s, 1H), 4.19 (s, 2H), 3.93 (s, 3H), 3.42 (t, J=8.4 Hz, 2H), 2.49 (t, J=8.4 Hz, 2H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.7, 146.5, 137.8, 127.2, 126.3, 125.2, 121.7, 120.3, 116.1, 115.4, 110.3, 52.7, 49.0, 36.0, 24.2; HRMS (ESI-TOF) calcd for $C_{15}H_{14}BrClNO_3^-$ [M−H$^-$] 369.9851, found 369.9852.

4.5.39. Methyl 4-bromo-3-(cyclopenta-2,4-dien-1-ylmethyl)-1-hydroxy-1*H*-indole-2-carboxylate (54). R_f=0.75 (silica gel, MeOH/CH_2Cl_2, 1:99); IR (film) ν_{max} 3356, 2943, 1675, 1614, 1515, 1445, 1398, 1342, 1304, 1257, 1121, 986, 878, 775, 737 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.38 (br s, 1H), 7.47 (d, J=7.9 Hz, 1H), 7.28 (d, J=7.9 Hz, 1H), 7.18 (t, J=7.9 Hz, 1H), 6.34–6.29 (m, 1H), 6.24–6.19 (m, 1H), 5.83 (br s, 1H), 4.43 (br s, 2H), 3.89 (s, 3H), 2.93 (s, 2H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.6, 150.3, 138.0, 133.2, 131.7, 127.7, 127.2, 126.4, 125.7, 120.5, 120.4, 116.3, 110.4, 52.6, 44.1, 26.4; HRMS (ESI-TOF) calcd for $C_{16}H_{13}BrNO_3^-$ [M−H$^-$] 346.0084, found 346.0072.

4.5.40. Methyl 4-bromo-1-hydroxy-3-(methoxymethyl)-1*H*-indole-2-carboxylate (55). R_f=0.32 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3175, 2937, 2887, 1709, 1525, 1436, 1404, 1346, 1311, 1257, 1227, 1187, 1123, 1073, 934, 879, 775, 736, 666 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.38 (br s, 1H), 7.44 (dd, J=8.3, 0.7 Hz, 1H), 7.34 (dd, J=7.6, 0.7 Hz, 1H), 7.18 (dd, J=8.3, 7.6 Hz, 1H), 4.97 (s, 2H), 3.93 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.3, 137.3, 127.1, 127.0, 126.8, 121.0, 116.0, 115.9, 110.2, 63.4, 57.7, 52.9; HRMS (ESI-TOF) calcd for $C_{12}H_{12}BrNO_4Na^+$ [M+Na$^+$] 335.9842, found 335.9834.

4.5.41. Methyl 4-bromo-1-hydroxy-3-methyl-1*H*-indole-2-carboxylate (56). R_f=0.58 (silica gel, MeOH/CH_2Cl_2, 1:99); IR (film) ν_{max} 3436, 2919, 1672, 1613, 1519, 1443, 1272, 1184, 1119, 978, 873, 761, 726, 679, 608, 561 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.09 (s, 1H), 7.43 (d, J=7.9 Hz, 1H), 7.29 (d, J=7.9 Hz, 1H), 7.17 (t, J=7.9 Hz, 1H), 3.92 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.9, 138.2, 127.3, 126.1, 125.7, 121.4, 118.5, 116.7, 110.3, 52.6, 12.0; HRMS (ESI-TOF) calcd for $C_{11}H_9BrNO_3^-$ [M−H$^-$] 281.9771, found 281.9770.

4.5.42. Methyl 4-bromo-1-hydroxy-3-pent-3-ynyl-1*H*-indole-2-carboxylate (57). R_f=0.68 (silica gel, MeOH/CH_2Cl_2, 1:99); IR (film) ν_{max} 3360, 2942, 2907, 2848, 1689, 1513, 1443, 1396, 1255, 1119, 1025, 879, 802, 767,

732, 667 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 9.13 (br s, 1H), 7.46 (d, J=7.9 Hz, 1H), 7.32 (d, J=7.9 Hz, 1H), 7.19 (t, J=7.9 Hz, 1H), 3.93 (s, 3H), 3.48 (t, J=7.4 Hz, 2H), 2.46–2.41 (m, 2H), 1.69 (t, J=2.4 Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.6, 137.8, 127.1, 126.4, 126.2, 120.3, 120.2, 116.0, 110.2, 79.1, 77.3, 52.6, 24.6, 22.2, 3.4; HRMS (ESI-TOF) calcd for $C_{15}H_{13}BrNO_3^-$ [M−H$^-$] 334.0084, found 334.0083.

4.5.43. Methyl 4-bromo-3-(2,2-dimethylbut-3-enyl)-1-hydroxy-1*H*-indole-2-carboxylate (58). R_f=0.53 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3366, 2951, 2917, 1686, 1519, 1439, 1387, 1306, 1254, 1122, 1018, 903, 868, 793, 770, 742, 684 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 9.08 (s, 1H), 7.46 (s, 1H), 7.31 (s, 1H), 7.16 (t, J=7.2 Hz, 1H), 5.87 (dd, J=17.4, 10.8 Hz, 1H), 4.77 (d, J=10.8 Hz, 1H), 4.69 (d, J=17.4 Hz, 1H), 3.88 (s, 3H), 3.49 (br s, 2H), 0.97 (s, 6H); ^{13}C NMR (150 MHz, CD_3CN) δ 163.2, 149.0, 137.7, 128.0, 127.2, 126.6, 121.8, 117.2, 116.4, 110.9, 110.3, 52.5, 40.1, 34.8, 26.5 (2C); HRMS (ESI-TOF) calcd for $C_{16}H_{17}BrNO_3^-$ [M−H$^-$] 350.0397, found 350.0396.

4.5.44. Methyl 1-hydroxy-3-[(2-oxocyclohexyl)methyl]-1*H*-indole-2-carboxylate (62). R_f=0.26 (silica gel, EtOAc/hexanes, 2:8); IR (film) ν_{max} 3020, 1742, 1702, 1528, 1447, 1214 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 9.03 (br s, 1H), 7.68 (d, J=9.6 Hz, 1H), 7.44 (d, J=9.6 Hz, 1H), 7.36 (t, J=9.0 Hz, 1H), 7.12 (t, J=9.0 Hz, 1H), 3.91 (s, 3H), 3.45 (dd, J=16.5, 5.7 Hz, 1H), 2.89 (dd, J=11.1, 5.7 Hz, 1H), 2.75–2.70 (m, 1H), 2.37–2.33 (m, 2H), 2.03–1.97 (m, 1H), 1.86–1.83 (m, 1H), 1.77–1.73 (m, 1H), 1.67–1.63 (m, 1H), 1.54 (ddt, J=30.0, 14.4, 4.2 Hz, 1H), 1.47–1.39 (ddd, J=30.0, 14.4, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 212.7, 163.1, 136.8, 126.8, 124.5, 123.7, 121.9, 121.4, 121.3, 110.5, 52.4, 52.3, 42.5, 34.3, 28.7, 25.5, 25.1; HRMS (ESI-TOF) calcd for $C_{17}H_{20}NO_4^+$ [M+H$^+$] 302.1387, found 302.1387.

4.5.45. Methyl 1-hydroxy-3-(2-methyl-3-oxopentyl)-1*H*-indole-2-carboxylate (63). R_f=0.63 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 2929, 1700, 1540, 1507, 1457, 1259, 119 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 9.06 (br s, 1H), 7.66 (d, J=8.5 Hz, 1H), 7.44 (d, J=8.5 Hz, 1H), 7.38–7.35 (m, 1H), 7.15–7.12 (m, 1H), 3.93 (s, 3H), 3.30–3.26 (m, 1H), 3.01–2.94 (m, 2H), 2.50–2.42 (m, 1H), 2.34–2.26 (m, 1H), 1.01 (d, J=7.0 Hz, 3H), 0.86 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 215.2, 162.3, 126.9, 124.2, 123.4, 122.3, 121.8, 121.5, 120.6, 110.5, 52.3, 47.8, 35.4, 28.8, 16.7, 7.9; HRMS (ESI-TOF) calcd for $C_{16}H_{19}NO_4Na^+$ [M+Na$^+$] 312.1206, found 312.1199.

4.5.46. Methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)-1-hydroxy-1*H*-indole-2-carboxylate (64). R_f=0.52 (silica gel, EtOAc/hexanes, 2:8); IR (film) ν_{max} 3375, 1697, 1598, 1535, 1448, 1264, 1122 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 9.12 (br s, 1H), 8.04–7.99 (m, 2H), 7.72–7.68 (m, 2H), 7.55–7.51 (m, 3H), 7.4 (t, J=3.0 Hz, 1H), 7.2 (t, J=3.0 Hz, 1H), 4.1 (t, J=21.3 Hz, 2H), 3.8 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 190.5 (t, J=28.5 Hz), 162.4, 136.2, 135.4, 135.1, 130.7 (t, J=3.2 Hz), 130.6 (t, J=3.2 Hz), 129.8, 129.7, 126.9, 125.8, 123.8, 122.1, 121.9, 110.5, 52.4, 31.1 (t, J=24.4 Hz); HRMS (ESI-TOF) calcd for $C_{19}H_{16}F_2NO_4^+$ [M+H$^+$] 360.1042, found 360.1039.

4.5.47. Methyl 1-hydroxy-3-[(2-oxocyclohexyl)methyl]-4-({[2-(trimethylsilyl)ethoxy]methoxy}methyl)-1*H*-indole-2-carboxylate (65). R_f=0.25 (silica gel, EtOAc/hexanes, 2:8); IR (film) ν_{max} 3240 (br), 2936, 2860, 1709, 1438, 1396, 1235, 1125, 1037 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 9.11 (br s, 1H), 7.43 (d, J=7.0 Hz, 1H), 7.31–7.30 (m, 1H), 7.11 (d, J=6.5 Hz, 1H), 4.85 (br s, 2H), 4.67 (s, 2H), 3.90 (s, 3H), 3.65–3.56 (m, 3H), 3.12–3.05 (m, 1H), 2.65–2.63 (m, 1H), 2.35–2.30 (m, 2H), 2.05–1.97 (m, 1H), 1.88–1.84 (m, 1H), 1.80–1.73 (m, 1H), 1.65–1.61 (m, 1H), 1.53–1.42 (m, 2H), 0.88 (dd, J=9.0, 8.0 Hz, 2H), −0.01 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN) δ 212.7, 163.3, 137.5, 133.5, 129.6, 126.2, 125.5, 123.2, 120.7, 110.7, 94.7, 68.3, 65.8, 53.3, 52.3, 42.5, 33.7, 28.6, 25.7, 18.6, −1.4 (3C); HRMS (ESI-TOF) calcd for $C_{23}H_{36}NO_6Si^+$ [M+H$^+$] 462.2306, found 462.2304.

4.5.48. Methyl 1-hydroxy-3-(2-methyl-3-oxopentyl)-4-({[2-(trimethylsilyl)ethoxy]methoxy}methyl)-1*H*-indole-2-carboxylate (66). R_f=0.50 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3240 (br), 2950, 1714, 1520, 1456, 1398, 1248, 1128, 1102, 1028, 859, 836 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 9.14 (br s, 1H), 7.44 (d, J=8.0 Hz, 1H), 7.32–7.29 (m, 1H), 7.13 (d, J=6.5 Hz, 1H), 4.94 (d, J=12.0 Hz, 1H), 4.90 (d, J=12.0 Hz, 1H), 4.70 (s, 2H), 3.92 (s, 3H), 3.59 (dd, J=9.0, 8.0 Hz, 2H), 3.42 (dd, J=14.0, 6.0 Hz, 1H), 3.19 (dd, J=14.0, 7.0 Hz, 1H), 2.93 (dd, J=14.0, 7.0 Hz, 1H), 2.47–2.37 (m, 1H), 2.25–2.18 (m, 1H), 1.01 (d, J=7.0 Hz, 3H), 0.90–0.83 (m, 5H), −0.01 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN) δ 215.2, 163.1, 133.4, 126.2, 125.0, 124.5, 123.3, 120.9, 120.0, 110.7, 94.7, 68.4, 65.9, 52.4, 48.6, 35.6, 29.3, 18.6, 16.3, 7.8, −1.4 (3C); HRMS (ESI-TOF) calcd for $C_{23}H_{35}NO_6SiNa^+$ [M+Na$^+$] 472.2126, found 472.2126.

4.5.49. Methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)-1-hydroxy-4-({[2-(trimethylsilyl)ethoxy]methoxy}methyl)-1*H*-indole-2-carboxylate (67). R_f=0.36 (silica gel, EtOAc/hexanes, 1:5); IR (film) ν_{max} 2951, 1700, 1449, 1251, 1096, 1028 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 9.21 (br s, 1H), 8.07–8.03 (m, 2H), 7.71–7.68 (m, 1H), 7.55–7.49 (m, 3H), 7.36–7.33 (m, 1H), 7.16 (d, J=6.5 Hz, 1H), 4.95 (d, J=16.0 Hz, 2H), 4.66 (s, 2H), 4.32 (t, J=18.0 Hz, 2H), 3.79 (s, 3H), 3.54 (t, J=8.0 Hz, 2H), 0.81 (t, J=8.0 Hz, 2H), −0.04 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN) δ 196.2, 159.9, 136.2, 136.1, 133.6, 131.5 (t, J=3.0 Hz, 2C), 130.6, 130.5 (2C), 130.4, 126.9, 126.5, 124.5, 120.7, 114.4, 100.6, 95.3, 69.2, 66.6, 53.2, 32.1, 19.2, −0.8 (3C); HRMS (ESI-TOF) calcd for $C_{26}H_{31}F_2NO_6SiNa^+$ [M+Na$^+$] 542.1781, found 542.1767.

4.5.50. Methyl 4-fluoro-1-hydroxy-3-[(2-oxocyclohexyl)-methyl]-1*H*-indole-2-carboxylate (68). R_f=0.47 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3295 (br), 2931, 2849, 1702, 1631, 1566, 1531, 1443, 1401, 1361, 1314, 1255, 1231, 1131, 937, 785, 732 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 9.19 (br s, 1H), 7.29–7.23 (m, 2H), 6.77 (dd, J=11.4, 7.4 Hz, 1H), 3.92 (s, 3H), 3.50 (dd, J=14.0, 4.8 Hz, 1H), 2.99 (dd, J=14.0, 5.7 Hz, 1H), 2.72–2.66 (m, 1H), 2.35–2.27 (m, 2H), 2.00–1.93 (m, 1H),

1.87–1.85 (m, 1H), 1.75–1.72 (m, 1H), 1.67–1.59 (m, 1H), 1.56–1.49 (m, 1H), 1.46–1.39 (m, 1H); ^{13}C NMR (150 MHz, CD_3CN) δ 212.8, 162.7, 158.8 (d, J=248.4 Hz), 138.8 (d, J=10.3 Hz), 127.3 (d, J=8.0 Hz), 125.0, 118.8 (d, J=3.4 Hz), 112.4 (d, J=19.5 Hz), 106.9 (d, J=3.4 Hz), 106.2 (d, J=20.6 Hz), 52.7, 52.5, 42.5, 33.7, 28.6, 26.3, 25.5; HRMS (ESI-TOF) calcd for $C_{17}H_{18}FNO_4Na^+$ [M+Na$^+$] 342.1112, found 342.1102.

4.5.51. Methyl 4-fluoro-1-hydroxy-3-(2-methyl-3-oxopentyl)-1*H*-indole-2-carboxylate (69). R_f=0.46 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3299 (br), 2970, 1714, 1633, 1538, 1455, 1404, 1361, 1318, 1235, 1137 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.18 (br s, 1H), 7.31–7.26 (m, 2H), 6.80 (dd, J=12.0, 7.5 Hz, 1H), 3.97 (s, 3H), 3.35 (dd, J=13.5, 5.5 Hz, 1H), 3.09 (dd, J=13.5, 9.0 Hz, 1H), 2.97–2.91 (m, 1H), 2.53–2.43 (m, 1H), 2.41–2.35 (m, 1H), 0.99 (d, J=7.0 Hz, 3H), 0.92 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 214.9, 162.6, 158.6 (d, J=248.0 Hz), 138.6, 132.1, 127.3 (d, J=8.3 Hz), 124.8, 112.6, 106.9 (d, J=3.9 Hz), 106.2 (d, J=19.8 Hz), 52.5, 48.1, 34.9, 29.6, 15.8, 7.9; HRMS (ESI-TOF) calcd for $C_{16}H_{18}FNO_4Na^+$ [M+Na$^+$] 330.1112, found 330.1109.

4.5.52. Methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)-4-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (70). R_f=0.52 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3364 (br), 2956, 2926, 2848, 1700, 1636, 1540, 1450, 1323, 1269, 1240, 1142, 1091, 946, 764, 716 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.21 (br s, 1H), 8.02 (d, J=7.8 Hz, 2H), 7.69–7.66 (m, 1H), 7.52 (dd, J=8.0, 7.3 Hz, 2H), 7.33–7.28 (m, 2H), 6.85–6.81 (m, 1H), 4.12 (t, J=17.3 Hz, 2H), 3.97 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 190.4, 161.8, 137.3, 136.4, 135.4, 132.9, 130.6 (t, J=3.8 Hz, 2C), 129.6 (2C), 127.2 (d, J=8.6 Hz), 126.1, 117.3, 113.0, 107.1, 106.8 (d, J=3.8 Hz), 106.6 (d, J=20.0 Hz), 52.4, 32.8 (t, J=26.7 Hz); HRMS (ESI-TOF) calcd for $C_{19}H_{15}F_3NO_4^+$ [M+H$^+$] 378.0948, found 378.0943.

4.5.53. Methyl 5-fluoro-1-hydroxy-3-[(2-oxocyclohexyl)-methyl]-1*H*-indole-2-carboxylate (71). R_f=0.65 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3311 (br), 2937, 2855, 1707, 1577, 1532, 1447, 1403, 1342, 1251, 1192, 1169, 849, 799, 757 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.04 (s, 1H), 7.43 (dd, J=9.0, 4.5 Hz, 1H), 7.40 (dd, J=9.5, 2.5 Hz, 1H), 7.15 (dt, J=9.5, 2.5 Hz, 1H), 3.89 (s, 3H), 3.39 (dd, J=14.0, 5.0 Hz, 1H), 2.85 (dd, J=14.0, 8.5 Hz, 1H), 2.73–2.68 (m, 1H), 2.39–2.27 (m, 2H), 2.04–1.98 (m, 1H), 1.89–1.83 (m, 1H), 1.77–1.73 (m, 1H), 1.68–1.50 (m, 2H), 1.44–1.40 (m, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 212.8, 162.7, 158.8 (d, J=233.1 Hz), 133.6, 126.1, 123.8 (d, J=9.5 Hz), 120.8 (d, J=5.4 Hz), 115.6 (d, J=26.9 Hz), 112.0 (d, J=9.4 Hz), 106.3 (d, J=24.0 Hz), 52.4, 52.3, 42.5, 34.4, 28.7, 25.6, 25.2; HRMS (ESI-TOF) calcd for $C_{17}H_{19}FNO_4^+$ [M+H$^+$] 320.1293, found 320.1289.

4.5.54. Methyl 5-fluoro-1-hydroxy-3-(2-methyl-3-oxopentyl)-1*H*-indole-2-carboxylate (72). R_f=0.58 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3300 (br), 2934, 1699, 1540, 1522, 1456, 1250, 1178, 1110 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.08 (br s, 1H), 7.44 (dd, J=9.0, 4.5 Hz, 1H), 7.36 (dd, J=9.5, 2.5 Hz, 1H), 7.18–7.14 (m, 1H), 3.93 (s, 3H), 3.26–3.21 (m, 1H), 2.97–2.92 (m, 2H), 2.54–2.43 (m, 1H), 2.32–2.26 (m, 1H), 1.02 (d, J=7.5 Hz, 3H), 0.86 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 215.2, 162.6, 158.9 (d, J=233.3 Hz), 133.4, 125.8, 123.5 (d, J=9.6 Hz), 120.1 (d, J=5.1 Hz), 115.6 (d, J=27.5 Hz), 112.1 (d, J=9.5 Hz), 106.2 (d, J=23.8 Hz), 52.4, 47.7, 35.3, 28.7, 16.7, 7.8; HRMS (ESI-TOF) calcd for $C_{16}H_{19}FNO_4^+$ [M+H$^+$] 330.1112, found 330.1104.

4.5.55. Methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)-5-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (73). R_f=0.50 (silica gel, EtOAc/hexanes, 4:6); IR (film) ν_{max} 3383 (br), 2922, 2851, 1700, 1598, 1580, 1528, 1438, 1402, 1379, 1337, 1304, 1251, 1190, 1169, 1108, 1079, 1015, 970, 952, 936, 913, 850, 794, 785, 762, 732, 707, 682 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.11 (s, 1H), 8.00 (d, J=7.8 Hz, 2H), 7.70 (t, J=7.2 Hz, 1H), 7.53 (t, J=7.82 Hz, 2H), 7.48 (dd, J=9.0, 4.2 Hz, 1H), 7.40 (d, J=9.6 Hz, 1H), 7.20 (dt, J=9.6, 2.4 Hz, 1H), 4.04 (t, J=17.4 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 191.1, 162.7, 158.9 (d, J=233.9 Hz), 136.2, 133.7, 131.4 (t, J=3.3 Hz, 2C), 131.2, 130.5 (2C), 127.9, 124.7 (d, J=10.4 Hz), 120.4, 120.2, 116.5 (d, J=27.3 Hz), 112.8 (d, J=9.6 Hz), 106.8 (d, J=24.3 Hz), 53.2, 31.8 (t, J=24.5 Hz); HRMS (ESI-TOF) calcd for $C_{19}H_{15}F_3NO_4^+$ [M+H$^+$] 378.0948, found 378.0943.

4.5.56. Methyl 6-fluoro-1-hydroxy-3-[(2-oxocyclohexyl)-methyl]-1*H*-indole-2-carboxylate (74). R_f=0.44 (silica gel, EtOAc/hexanes, 3:7, eluted two times); IR (film) ν_{max} 3286 (br), 2924, 2854, 1706, 1629, 1537, 1446, 1402, 1352, 1264, 1219, 1177, 1110, 1034, 924, 834, 809 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 9.06 (s, 1H), 7.68 (dd, J=8.8, 4.8 Hz, 1H), 7.13 (dd, J=9.6, 2.2 Hz, 1H), 7.91 (dt, J=9.6, 2.5 Hz, 1H), 3.87 (s, 3H), 3.42 (dd, J=14.0, 4.8 Hz, 1H), 2.86 (dd, J=14.0, 9.2 Hz, 1H), 2.72–2.67 (m, 1H), 2.37–2.23 (m, 2H), 2.01–1.98 (m, 1H), 1.86–1.84 (m, 1H), 1.76–1.72 (m, 1H), 1.65–1.58 (m, 1H), 1.56–1.49 (m, 1H), 1.44–1.37 (m, 1H); ^{13}C NMR (150 MHz, CD_3CN) δ 213.0, 163.2 (d, J=239.5 Hz), 163.0, 135.6, 125.3, 124.2 (d, J=11.4 Hz), 122.0, 120.7, 110.8 (d, J=25.1 Hz), 96.5 (d, J=27.4 Hz), 52.7, 52.6, 42.8, 34.7, 29.0, 25.9, 25.4; HRMS (ESI-TOF) calcd for $C_{17}H_{19}FNO_4^+$ [M+H$^+$] 320.1293, found 320.1282.

4.5.57. Methyl 6-fluoro-1-hydroxy-3-(2-methyl-3-oxopentyl)-1*H*-indole-2-carboxylate (75). R_f=0.56 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 3313, 2924, 2877, 1698, 1539, 1456, 1396, 1260, 1223, 1175, 1110 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 9.10 (br s, 1H), 7.68–7.65 (m, 1H), 7.15 (dd, J=9.5, 2.5 Hz, 1H), 6.95–6.91 (m, 1H), 3.92 (s, 3H), 3.30–3.24 (m, 1H), 3.00–2.93 (m, 2H), 2.51–2.43 (m, 1H), 2.33–2.25 (m, 1H), 1.02 (d, J=6.5 Hz, 3H), 0.86 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 215.2, 163.0 (d, J=239.8 Hz), 162.6, 132.9, 124.9, 123.8 (d, J=10.5 Hz), 121.0, 120.2, 110.7 (d, J=25.6 Hz), 96.3 (d, J=27.1 Hz), 52.4, 47.8, 35.4, 28.7, 16.7, 7.9; HRMS (ESI-TOF) calcd for $C_{16}H_{18}FNO_4Na^+$ [M+Na$^+$] 330.1112, found 330.1110.

4.5.58. Methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)-6-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (76). R_f=0.52 (silica gel, EtOAc/hexanes, 3:7, eluted two times); IR

(film) ν_{max} 3362, 2962, 2923, 2853, 1699, 1632, 1598, 1537, 1449, 1401, 1355, 1264, 1223, 1177, 1112, 1063, 924, 907, 880, 834, 812 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 9.12 (br s, 1H), 7.99 (d, J=7.9 Hz, 2H), 7.71–7.67 (m, 2H), 7.51 (t, J=7.9 Hz, 2H), 7.18 (dd, J=9.1, 1.7 Hz, 1H), 6.98 (dt, J=9.1, 1.7 Hz, 1H), 4.06 (t, J=17.5 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 191.0, 163.3 (d, J=240.6 Hz), 162.5, 136.8 (d, J=14.7 Hz), 135.9, 133.5, 131.1 (t, J=3.4 Hz, 2C), 130.3, 130.2 (2C), 126.9 (d, J=3.4 Hz), 124.4 (d, J=10.3 Hz), 121.0, 120.1, 111.9 (d, J=26.2 Hz), 96.7 (d, J=27.4 Hz), 52.8, 31.5 (t, J=23.9 Hz); HRMS (ESI-TOF) calcd for $C_{19}H_{15}F_3NO_4^+$ [M+H$^+$] 378.0948, found 378.0941.

4.5.59. Methyl 6-cyano-1-hydroxy-3-[(2-oxocyclohexyl)-methyl]-1*H*-indole-2-carboxylate (77). R_f=0.42 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3300 (br), 2930, 2856, 2359, 2221, 1711, 1519, 1446, 1263, 1117 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 9.22 (br s, 1H), 7.88 (s, 1H), 7.85 (d, J=8.5 Hz, 1H), 7.36 (dd, J=8.5, 1.0 Hz, 1H), 3.92 (s, 3H), 3.45 (dd, J=14.0, 5.0 Hz, 1H), 2.88 (dd, J=14.0, 9.0 Hz, 1H), 2.72–2.68 (m, 1H), 2.38–2.26 (m, 2H), 2.03–1.99 (m, 1H), 1.89–1.84 (m, 1H), 1.77–1.73 (m, 1H), 1.67–1.50 (m, 2H), 1.46–1.38 (m, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 212.6, 162.3, 135.0, 127.5, 126.0, 123.3, 123.2, 120.7, 120.5, 115.8, 108.8, 52.7, 52.4, 42.5, 34.5, 28.7, 25.6, 25.0; HRMS (ESI-TOF) calcd for $C_{18}H_{18}N_2O_4Na^+$ [M+Na$^+$] 349.1159, found 349.1149.

4.5.60. Methyl 6-cyano-1-hydroxy-3-(2-methyl-3-oxopentyl)-1*H*-indole-2-carboxylate (78). R_f=0.55 (silica gel, EtOAc/hexanes, 6:4); IR (film) ν_{max} 3242 (br), 2969, 2357, 2224, 1712, 1537, 1445, 1259, 1233, 1117 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 9.31 (br s, 1H), 7.87 (s, 1H), 7.81 (d, J=8.5 Hz, 1H), 7.36 (dd, J=8.5, 1.5 Hz, 1H), 3.95 (s, 3H), 3.28 (m, 1H), 3.00–2.93 (m, 2H), 2.51–2.43 (m, 1H), 2.32–2.24 (m, 1H), 0.86 (d, J=7.0 Hz, 3H), 1.01 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 215.1, 162.2, 134.8, 127.3, 125.7, 123.4, 123.1, 120.4, 120.0, 115.8, 108.8, 52.7, 47.7, 35.4, 28.4, 16.8, 7.9; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O_4^+$ [M+H$^+$] 315.1339, found 315.1331.

4.5.61. Methyl 6-cyano-3-(2,2-difluoro-3-oxo-3-phenylpropyl)-1-hydroxy-1*H*-indole-2-carboxylate (79). R_f=0.47 (silica gel, EtOAc/hexanes, 1:1); IR (film) ν_{max} 2930, 2846, 2358, 2222, 1711, 1560, 1437, 1260, 1117 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 9.38 (br s, 1H), 8.00 (d, J=8.0 Hz, 2H), 7.92 (s, 1H), 7.85 (d, J=8.5 Hz, 1H), 7.71–7.68 (m, 1H), 7.54–7.51 (m, 2H), 7.41 (dd, J=8.5, 1.0 Hz, 1H), 4.08 (t, J=17.5 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 203.1, 170.7, 135.6, 135.3, 133.7, 133.6, 130.8 (t, J=3.1 Hz, 2C), 129.8, 129.7 (2C), 126.0, 123.8, 123.4, 120.8, 114.6, 105.9, 105.6, 54.3, 31.4; HRMS (ESI-TOF) calcd for $C_{20}H_{13}F_2N_2O_4^-$ [M−H$^-$] 383.0849, found 383.0850.

4.6. Synthesis of nocathiacin I model systems 2 and 3a–c

4.6.1. Ethyl 2-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-hydroxyethyl}-1,3-thiazole-4-carboxylate (81). Thiazole ethyl ester **80** (150 mg, 0.42 mmol) was dissolved in CH_2Cl_2 (2.8 mL) and MeOH (1.4 mL) and cooled to 0 °C. Trifluroacetic acid (4.2 mL) was added dropwise over 5 min to the reaction mixture, and after stirring at 0 °C for 2.5 h, toluene (5 mL) was added and the reaction mixture was concentrated. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The solution was then concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc/hexanes, 1:1→80:20) to afford primary alcohol **81** (91 mg, 68%) as a yellow foam; R_f=0.40 (silica gel, MeOH/CH_2Cl_2, 5:95); IR (film) ν_{max} 3354 (br), 2978, 2919, 1707, 1502, 1484, 1390, 1361, 1337, 1231, 1167, 1091, 1055, 1020, 856, 756 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 8.17 (s, 1H), 6.04 (s, 1H), 4.93 (s, 1H), 4.31 (ddd, J=7.8, 3.1, 0.9 Hz, 2H), 3.88 (t, J=6.1 Hz, 2H), 3.22 (t, J=5.7 Hz, 1H), 1.42 (br s, 9H), 1.33 (t, J=6.1 Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 173.9, 162.0, 156.4, 147.8, 129.0, 80.4, 64.5, 62.0, 56.0, 28.5, 14.5 (3C); HRMS (ESI-TOF) calcd for $C_{13}H_{20}N_2O_5SNa^+$ [M+Na$^+$] 339.0985, found 339.0985.

4.6.2. Methyl 4-bromo-3-[({(2*S*)-2-[(*tert*-butoxycarbonyl)-amino]-2-[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]ethyl}-oxy)methyl]-1-hydroxy-1*H*-indole-2-carboxylate (2). Primary alcohol **81** (16.9 mg, 0.05 mmol) was dissolved in DME (350 μL) and to this solution were added 4 Å molecular sieves (20 wt%), *p*TsOH (7.6 mg, 0.04 mmol), and tertiary alcohol **9** (4.0 mg, 0.013 mmol) at 25 °C. After stirring for 10 min, the reaction mixture was heated to 40 °C for 2 h after which the crude reaction mixture was allowed to cool to room temperature and purified directly by PTLC (silica gel, EtOAc/hexanes, 7:3) to afford model system **2** (3.5 mg, 44%) as a yellow oil; R_f=0.43 (silica gel, EtOAc/hexanes, 7:3); $[\alpha]_D^{32}$ −3.0 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 3354, 2978, 2919, 1707, 1490, 1460, 1437, 1390, 1360, 1255, 1231, 1161, 1119, 1090, 1025, 879, 773, 743 cm^{-1}; ^1H NMR (600 MHz, CD_3CN, 66 °C) δ 9.22 (s, 1H), 8.06 (s, 1H), 7.50 (d, J=7.7 Hz, 1H), 7.36 (d, J=7.7 Hz, 1H), 7.22 (t, J=7.7 Hz, 1H), 5.81 (br s, 1H), 5.17 (½ABq, J=11.4 Hz, 1H), 5.14 (½ABq, J=11.4 Hz, 1H), 5.04 (dt, J=7.4, 4.8 Hz, 1H), 4.33 (q, J=7.0 Hz, 2H), 3.97 (s, 3H), 3.96 (dd, J=10.0, 4.8 Hz, 1H), 3.93 (dd, J=10.0, 4.8 Hz, 1H), 1.39 (s, 9H), 1.35 (t, J=7.0 Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 174.0, 162.2, 162.0, 156.2, 147.7, 137.2, 128.9, 127.2, 127.0, 126.9, 120.9, 115.9, 115.2, 110.2, 80.4, 71.2, 62.1, 61.9, 54.2, 53.1, 28.4 (3C), 14.5; HRMS (ESI-TOF) calcd for $C_{24}H_{28}BrN_3O_8SNa^+$ [M+Na$^+$] 620.0673, found 620.0674.

4.6.3. *tert*-Butyl (4*S*)-4-[4-(methoxymethyl)-1,3-thiazol-2-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (82). Thiazole ethyl ester **80** (530 mg, 1.49 mmol) was dissolved in toluene (6.0 mL) and cooled to 0 °C. DIBAL-H (2.0 mL, 3.0 mmol, 1.5 M in toluene) was then added dropwise and the reaction mixture stirred for 2.5 h after which the reaction was slowly quenched at 0 °C with MeOH (2 mL) and the resulting mixture was warmed to 25 °C and stirred for 12 h with saturated aqueous sodium potassium tartrate solution (5 mL). The mixture was extracted with EtOAc (3×20 mL) and the combined organic layers were dried over Na_2SO_4 and the resulting solution was concentrated. The residue was taken up in THF (6.0 mL) and cooled to 0 °C, and to this solution were added NaH (150 mg, 3.7 mmol, 60% dispersion in mineral oil) and MeI (649 μL, 10.43 mmol). The reaction mixture was allowed to warm to room temperature

over 12 h at which time the reaction mixture was poured over ice water (10 mL), extracted with EtOAc (20 mL), washed with brine (10 mL), and dried (Na_2SO_4). The solution was then concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc/hexanes, 60:40→80:20) to afford methyl ether **82** (360 mg, 74% over two steps) as a yellow oil; R_f=0.52 (silica gel, EtOAc/hexanes, 7:3); $[\alpha]_D^{33}$ −24.1 (*c* 0.60, $CHCl_3$); IR (film) ν_{max} 3383 (br), 2971, 1874, 1698, 1455, 1371, 1255, 1164, 1092, 1049 cm^{-1}; ^1H NMR (500 MHz, CD_3CN, 66 °C) δ 7.22 (s, 1H), 5.19 (dd, *J*=6.2, 1.9 Hz, 1H), 4.47 (d, *J*=0.7 Hz, 2H), 4.29 (dd, *J*=9.2, 6.2 Hz, 1H), 4.07 (dd, *J*=9.2, 1.9 Hz, 1H), 3.37 (s, 3H), 1.69 (s, 3H), 1.52 (s, 3H), 1.38 (br s, 9H); ^{13}C NMR (150 MHz, CD_3CN, 66 °C) δ 174.6, 155.2, 147.8, 117.2, 95.3, 81.2, 71.2 (2C), 70.1, 60.7, 58.8 (2C), 28.9 (3C); HRMS (ESI-TOF) calcd for $C_{15}H_{25}N_2O_4S^+$ [M+H$^+$] 329.1529, found 329.1518.

4.6.4. (1*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[4-(methoxymethyl)-1,3-thiazol-2-yl]ethanamine (84). Methyl ether **82** (50 mg, 0.152 mmol) was dissolved in CH_2Cl_2 (761 μL) and cooled to 0 °C. TFA (761 μL) was then added dropwise and the reaction mixture stirred for 10 min at 0 °C and then 1 h at 25 °C at which time the reaction mixture was diluted with toluene (2 mL) and concentrated (three times). After drying under high vacuum for 30 min, the crude amino alcohol was dissolved in CH_2Cl_2 (317 μL) and cooled to 0 °C. Et_3N (70 μL, 0.50 mmol) and TBSCl (50 mg, 0.33 mmol) were then added and the reaction mixture was warmed to 25 °C. After 3 h, the mixture was washed with saturated aqueous $NaHCO_3$ solution (1 mL), brine (1 mL), and then dried over Na_2SO_4. The resulting solution was concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc/hexanes, 80:20→100:0) to afford primary amine **84** (39.0 mg, 85% over two steps) as a yellow oil; R_f=0.57 (silica gel, MeOH/CH_2Cl_2, 5:95); $[\alpha]_D^{31}$ −7.6 (*c* 1.23, CH_2Cl_2); IR (film) ν_{max} 3378 (br), 2931, 2848, 1461, 1255, 1091, 838, 764, 602 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 7.19 (s, 1H), 4.44 (s, 2H), 4.19 (dd, *J*=6.1, 4.3 Hz, 1H), 3.88 (dd, *J*=9.9, 4.3 Hz, 1H), 3.78 (dd, *J*=9.9, 6.1 Hz, 1H), 3.33 (s, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 177.1, 154.9, 117.5, 71.2, 69.1, 58.8, 56.9, 26.3 (3C), 19.0, −4.87, −4.94; HRMS (ESI-TOF) calcd for $C_{13}H_{27}N_2O_2SSi^+$ [M+H$^+$] 303.1484, found 303.1487.

4.6.5. *tert*-Butyl (4*S*)-4-{4-[({(1*S*)-2-hydroxy-1-[4-(methoxymethyl)-1,3-thiazol-2-yl]ethyl}amino)carbonyl]-1,3-thiazol-2-yl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (85). Amine **84** (846 mg, 2.80 mmol) was dissolved in DMF (7 mL), cooled to 0 °C, and then *i*-Pr_2NEt (974 μL, 5.59 mmol) was added followed by cannula addition of thiazole acid **83** (918 mg, 2.80 mmol) dissolved in DMF (7 mL). HATU (1.17 g, 3.08 mmol) and HOAt (419 mg, 3.08 mmol) were then added and the reaction mixture stirred for 1 h at 0 °C and 2 h at 25 °C after which EtOAc (25 mL) was added and the reaction mixture was washed with aqueous 5% HCl solution (10 mL), H_2O (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), brine (10 mL), and dried over Na_2SO_4. The resulting solution was concentrated and the residue was taken up in THF (75 mL) and cooled to 0 °C. TBAF (3.36 mL, 1.0 M in THF) was added dropwise and after 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL), extracted with EtOAc (2×25 mL), washed with brine (20 mL), and dried over Na_2SO_4. The resulting solution was concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc/hexanes, 20:80→90:10) affording complex alcohol **85** (1.21 g, 87% over two steps) as a light yellow foam; R_f=0.42 (silica gel, MeOH/CH_2Cl_2, 5:95); $[\alpha]_D^{32}$ −10.9 (*c* 0.80, CH_2Cl_2); IR (film) ν_{max} 3389 (br), 2966, 2731, 2872, 1696, 1467, 1531, 1472, 1373, 1249, 1167, 1091, 1049, 761 cm^{-1}; ^1H NMR (500 MHz, CD_3CN, 66 °C) δ 8.13 (d, *J*=5.5 Hz, 1H), 8.07 (d, *J*=1.0 Hz, 1H), 7.26 (d, *J*=1.0 Hz, 1H), 5.41–5.37 (m, 1H), 5.24 (d, *J*=6.6 Hz, 1H), 4.51 (s, 2H), 4.34–4.31 (m, 1H), 4.16–4.13 (m, 1H), 4.10–4.04 (m, 2H), 3.97 (dd, *J*=11.4, 4.8 Hz, 1H), 3.39 (s, 3H), 1.72 (s, 3H), 1.57 (s, 3H), 1.39 (br s, 9H); ^{13}C NMR (150 MHz, CD_3CN, 66 °C) δ 175.9, 171.9, 162.3, 155.9, 155.8, 151.0, 125.6, 118.3, 71.6, 70.3, 65.8, 65.7, 61.1, 61.0, 59.4, 55.0 (2C), 29.3 (3C); HRMS (ESI-TOF) calcd for $C_{21}H_{31}N_4O_6S_2^+$ [M+H$^+$] 499.1679, found 499.1670.

4.6.6. (2*S*)-2-{[(2-{(1*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2-hydroxyethyl}-1,3-thiazol-4-yl)carbonyl]amino}-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]EtOAc (86). A solution of complex alcohol **85** (95 mg, 0.19 mmol) in CH_2Cl_2 (1.0 mL) was cooled to 0 °C and Et_3N (80 μL, 0.57 mmol) and 4-DMAP (2.3 mg, 0.02 mmol) were added followed by Ac_2O (90 μL, 0.95 mmol). After 10 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and washed with aqueous 5% HCl solution (3 mL), saturated aqueous $NaHCO_3$ solution (3 mL), brine (3 mL), and dried over Na_2SO_4. The resulting solution was concentrated and the residue was taken up in CH_2Cl_2 (1.26 mL) and MeOH (630 μL) and cooled to 0 °C. TFA (1.88 mL) was then added dropwise and after 30 min the reaction mixture was diluted with toluene (5 mL) and concentrated (three times). The residue was subjected to flash column chromatography (silica gel, EtOAc/hexanes, 1:1→100:0) affording hydroxy acetate **86** (78 mg, 82% over two steps) as a yellow oil; R_f=0.17 (silica gel, EtOAc/hexanes, 8:2); $[\alpha]_D^{31}$ −6.8 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 3309 (br), 2930, 1712, 1661, 1533, 1460, 1382, 1248, 1165, 1059, 797, 679, 590 cm^{-1}; ^1H NMR (600 MHz, CD_3CN, 66 °C) δ 8.16 (d, *J*=4.8 Hz, 1H), 8.10 (s, 1H), 7.30 (s, 1H), 5.41–5.37 (m, 1H), 5.92 (br s, 1H), 5.62–5.64 (m, 1H), 4.99–4.96 (m, 1H), 4.62 (ddd, *J*=11.8, 4.8, 1.3 Hz, 1H), 4.57 (ddd, *J*=11.8, 6.5, 0.8 Hz, 1H), 4.51 (s, 2H), 3.97–3.95 (m, 2H), 3.39 (s, 3H), 2.00 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (150 MHz, CD_3CN) δ 173.7, 171.4, 169.4, 161.6, 156.4, 154.8, 149.8, 125.4, 118.1, 80.3, 70.5, 65.5, 64.4, 58.4, 55.9, 51.3, 28.4 (3C), 20.8; HRMS (ESI-TOF) calcd for $C_{20}H_{29}N_4O_7S_2^+$ [M+H$^+$] 501.1472, found 501.1459.

4.6.7. Methyl 3-[({(2*S*)-2-{4-[({(1*S*)-2-(acetyloxy)-1-[4-(methoxymethyl)-1,3-thiazol-2-yl]ethyl}amino)carbonyl]-1,3-thiazol-2-yl}-2-[(*tert*-butoxycarbonyl)amino]ethyl}oxy)methyl]-4-bromo-1-hydroxy-1*H*-indole-2-carboxylate (87). *Method A*: To a stirred solution of *p*TsOH (13.3 mg, 0.07 mmol) and 4 Å molecular sieves (20 wt%) in DME (470 μL) were added hydroxy acetate **86** (23 mg, 0.046 mmol) and tertiary alcohol **9** (7 mg, 0.023 mmol) at 25 °C. After 10 min, the reaction mixture was warmed to 40 °C, stirred for 3 h, allowed to cool to room temperature

and purified directly by PTLC (silica gel, EtOAc/hexanes, 80:20) to afford *N*-hydroxyindole **87** (10 mg, 56%) as a yellow oil; *Method B*: To a stirred solution of $SnCl_2 \cdot 2H_2O$ (10.4 mg, 0.046 mmol) and 4 Å molecular sieves (20 wt%) in DME (110 μL) were added hydroxy acetate **86** (41 mg, 0.082 mmol) in DME (100 μL) and ketoester **6a** (6.6 mg, 0.021 mmol) at 25 °C. The reaction mixture was warmed immediately to 40 °C and stirring was continued for 6 h in the absence of light at which time the reaction mixture was allowed to cool to room temperature and purified directly by PTLC (silica gel, MeOH/Et_2O, 2:98) to afford *N*-hydroxyindole **87** (6.6 mg, 40%) as a yellow oil; R_f=0.26 (silica gel, EtOAc/hexanes, 7:3); $[\alpha]_D^{31}$ +1.7 (*c* 0.20, CH_2Cl_2); IR (film) ν_{max} 3331 (br), 2919, 2849, 1725, 1708, 1400, 1531, 1449, 1431, 1378, 1249, 1061, 761 cm^{-1}; ^1H NMR (600 MHz, CD_3CN, 66 °C) δ 9.30 (br s, 1H), 8.09–8.05 (m, 1H), 7.97 (d, *J*=9.6 Hz, 1H), 7.48 (d, *J*=8.3 Hz, 1H), 7.34 (d, *J*=7.8 Hz, 1H), 7.31 (d, *J*=6.1 Hz, 1H), 7.20 (t, *J*=7.7 Hz, 1H), 5.84 (br s, 1H), 5.66–5.63 (m, 1H), 5.19–5.14 (m, 2H), 5.07–5.03 (m, 1H), 4.61–4.55 (m, 2H), 4.52 (s, 2H), 4.01 (dd, *J*=10.1, 5.2 Hz, 1H), 3.97–3.94 (m, 4H), 3.39 (s, 3H), 1.99 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CD_3CN) δ 173.8, 171.4, 169.3, 162.0 (2C), 161.5, 156.2, 154.8, 149.7, 137.3, 127.0, 126.8, 126.2, 125.2, 120.7, 115.8, 115.1, 110.1, 80.4, 71.3, 70.4, 65.5, 64.7, 58.4, 54.1, 52.9, 51.3, 28.4 (3C), 20.8; HRMS (ESI-TOF) calcd for $C_{31}H_{36}BrN_5O_{10}S_2Na^+$ [M+Na^+] 804.0979, found 804.0979.

4.6.8. *tert*-Butyl (4*S*,11*S*)-15-bromo-4-[4-(methoxymethyl)-1,3-thiazol-2-yl]-1,6-dioxo-19-{[2-(trimethylsilyl)-ethoxy]methoxy}-3,4,5,6,11,12,14,19-octahydro-1*H*-7,10-epiazeno[1,12,8,4]dioxathiazacyclohexadecino[15,14-*b*]indol-11-ylcarbamate (3a). *N*-Hydroxyindole **87** (34 mg, 0.043 mmol) was dissolved in DMF (1.5 mL) and cooled to 0 °C at which time *i*-Pr_2NEt (23 μL, 0.130 mmol), SEMCl (15 μL, 0.087 mmol), and *n*-Bu_4NI (1.6 mg, 0.004 mmol) were added and the reaction mixture was warmed to 25 °C. After 10 min, the reaction mixture was diluted with EtOAc (5 mL), washed with aqueous 5% HCl solution (3 mL), and dried over Na_2SO_4. The resulting solution was concentrated and the residue was taken up in THF (2.58 mL), MeOH (860 μL), and H_2O (860 μL) and then cooled to 0 °C. LiOH (3 mg, 0.129 mmol) was added and, after warming to 25 °C over 4 h, the reaction mixture was diluted with EtOAc (5 mL), cooled to 0 °C, quenched with aqueous 5% HCl solution, separated, and the organic layer dried with Na_2SO_4. After azeotroping with toluene (3×5 mL), the residue was dissolved in toluene (4.3 mL), and Et_3N (240 μL, 1.72 mmol) and 2,4,6-trichlorobenzoyl chloride (202 μL, 1.29 mmol) were added. After stirring for 12 h at 25 °C, the reaction mixture was added dropwise over the course of 12 h (syringe pump) to a solution of 4-DMAP (158 mg, 1.29 mmol) in toluene (80 mL). After addition was complete, the resulting mixture was stirred at 25 °C for a further 12 h, then cooled to 0 °C and acidified to pH~3 with an aqueous 10 mg/mL solution of $KHSO_4$. The layers were separated and the aqueous layer was re-extracted with EtOAc (2×40 mL). The combined organic layers were then washed with a 1:1 solution of saturated aqueous $NaHCO_3$/brine (40 mL) and the aqueous layer was re-extracted with EtOAc (2×40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by PTLC (silica gel, EtOAc/hexanes, 60:40) to give macrocycle **3a** (14 mg, 38% over three steps) as a yellow oil; R_f=0.37 (silica gel, EtOAc/hexanes, 8:2); $[\alpha]_D^{33}$ −12.3 (*c* 0.72, CH_2Cl_2); IR (film) ν_{max} 3353 (br), 2924, 2854, 2086, 1712, 1536, 1494, 1366, 1214, 1170, 1105, 859, 836, 777 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 8.44 (d, *J*=7.5 Hz, 1H), 8.04 (s, 1H), 7.51 (dd, *J*=8.3, 0.9 Hz, 1H), 7.41 (dd, *J*=7.4, 0.9 Hz, 1H), 7.30 (s, 1H), 7.24 (t, *J*=7.9 Hz, 1H), 6.00 (d, *J*=7.9 Hz, 1H), 5.66–5.62 (m, 1H), 5.34 (d, *J*=3.9 Hz, 1H), 5.21 (d, *J*=10.1 Hz, 1H), 5.18 (dd, *J*=11.4, 3.9 Hz, 1H), 5.14–5.12 (m, 2H), 5.08 (d, *J*=7.5 Hz, 1H), 5.04 (dd, *J*=11.4, 5.7 Hz, 1H), 4.48 (s, 2H), 4.17–4.14 (m, 1H), 3.94 (dd, *J*=9.6, 2.6 Hz, 1H), 3.80–3.70 (m, 2H), 3.36 (s, 3H), 1.40 (br s, 9H), 0.86 (t, *J*=7.0 Hz, 2H), −0.02 (s, 9H); ^{13}C NMR (150 MHz, CD_3CN) δ 170.9, 170.1, 163.0, 162.0, 161.7, 155.3, 149.4, 138.1, 128.0, 127.8, 127.5, 126.7, 122.1, 119.2, 116.3, 113.2, 111.5, 103.3, 72.2, 70.8, 69.6, 65.6, 65.2, 62.7, 58.8, 52.7, 52.6, 28.6 (3C), 18.9, −1.3 (3C); HRMS (ESI-TOF) calcd for $C_{34}H_{45}BrN_5O_9S_2Si^+$ [M+H^+] 838.1606, found 838.1604.

4.6.9. *tert*-Butyl (4*S*,11*S*)-15-bromo-19-(methoxymethoxy)-4-[4-(methoxymethyl)-1,3-thiazol-2-yl]-1,6-dioxo-3,4,5,6,11,12,14,19-octahydro-1*H*-7,10-epiazeno[1,12,8,4]-dioxathiazacyclohexadecino[15,14-*b*]indol-11-ylcarbamate (3b). *N*-Hydroxyindole **87** (30 mg, 0.038 mmol) was dissolved in DMF (1.9 mL) and cooled to 0 °C at which time *i*-Pr_2NEt (20 μL, 0.114 mmol), MOMCl (6 μL, 0.076 mmol), and *n*-Bu_4NI (1.4 mg, 0.004 mmol) were added and the reaction mixture was warmed to 25 °C. After 10 min, the reaction mixture was diluted with EtOAc (5 mL), washed with aqueous 5% HCl solution (3 mL), and dried over Na_2SO_4. The resulting solution was concentrated and the residue was taken up in THF (2.28 mL), MeOH (760 μL), and H_2O (760 μL) and then cooled to 0 °C. LiOH (2.7 mg, 0.114 mmol) was added and after warming to 25 °C over 4 h, the reaction mixture was diluted with EtOAc (5 mL), cooled to 0 °C, quenched with aqueous 5% HCl solution, separated, and the organic layer dried with Na_2SO_4. After azeotroping with toluene (3×5 mL), the residue was dissolved in toluene (4.0 mL), and Et_3N (212 μL, 1.52 mmol) and 2,4,6-trichlorobenzoyl chloride (178 μL, 1.14 mmol) were added. After stirring for 12 h at 25 °C, the reaction mixture was added dropwise over the course of 12 h (syringe pump) to a solution of 4-DMAP (139 mg, 1.14 mmol) in toluene (71 mL). After addition was complete, the resulting mixture was stirred at 25 °C for a further 12 h, then cooled to 0 °C and acidified to pH~3 with an aqueous 10 mg/mL solution of $KHSO_4$. The layers were separated and the aqueous layer was re-extracted with EtOAc (2×40 mL). The combined organic layers were then washed with a 1:1 solution of saturated aqueous $NaHCO_3$/brine (40 mL) and the aqueous layer was re-extracted with EtOAc (2×40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by PTLC (silica gel, EtOAc/hexanes, 80:20) to give macrocycle **3b** (12.7 mg, 44% over three steps) as a yellow oil; R_f=0.36 (silica gel, EtOAc/hexanes, 8:2); $[\alpha]_D^{32}$ −10.5 (*c* 0.68, CH_2Cl_2); IR (film) ν_{max} 3330 (br), 2919, 2849, 1725, 1713, 1608, 1531, 1449, 1384, 1260, 1067, 803 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 8.45 (d, *J*=7.9 Hz, 1H), 8.04 (s, 1H), 7.52 (dd, *J*=8.3, 0.9 Hz, 1H), 7.42 (dd, *J*=7.5, 0.9 Hz, 1H), 7.30 (s, 1H), 7.26 (dd, *J*=8.3, 7.5 Hz, 1H),

6.00 (d, J=8.3 Hz, 1H), 5.66–5.62 (m, 1H), 5.36–5.33 (m, 1H), 5.22–5.18 (m, 2H), 5.13 (d, J=10.1 Hz, 1H), 5.09 (d, J=7.5 Hz, 1H), 5.05 (d, J=7.5 Hz, 1H), 5.02 (dd, J=11.4, 5.2 Hz, 1H), 4.48 (s, 2H), 4.18–4.14 (m, 1H), 3.95 (dd, J=10.1, 3.1 Hz, 1H), 3.52 (s, 3H), 3.36 (s, 3H), 1.40 (br s, 9H); ^{13}C NMR (150 MHz, CD_3CN, 66 °C) δ 171.0, 170.1, 163.0, 162.0, 161.7, 155.3, 149.4, 138.2, 128.2, 127.9, 127.7, 126.8, 122.2, 119.3, 116.3, 113.2, 111.5, 105.3, 80.7, 72.2, 70.8, 65.2, 62.8, 59.0, 58.8, 52.7, 52.6, 28.7 (3C); HRMS (ESI-TOF) calcd for $C_{30}H_{34}BrN_5O_9S_2Na^+$ [M+Na$^+$] 774.0873, found 774.0869.

4.6.10. *tert*-Butyl (4*S*)-4-{4-[({(1*S*)-2-{[3-(2-bromo-6-nitrophenyl)-2-oxobut-3-enoyl]oxy}-1-[4-(methoxymethyl)-1,3-thiazol-2-yl]ethyl}amino)carbonyl]-1,3-thiazol-2-yl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (88). Acid **7a** (18 mg, 0.06 mmol) was dissolved in THF (80 μL), cooled to 0 °C, and oxalyl chloride (3.5 μL, 0.04 mmol) was added followed by DMF (one drop). After 45 min at 0 °C, Et_3N (11 μL, 0.08 mmol) and complex alcohol **85** (10 mg, 0.02 mmol) in THF (80 μL) were added and the reaction mixture was allowed to warm to 25 °C over 2 h. THF was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (5 mL), washed with ice H_2O (5 mL), and dried (Na_2SO_4). The resulting solution was concentrated and the residue was purified by PTLC (silica gel, EtOAc/hexanes, 80:20) to afford α-ketoester **88** (12 mg, 77%) as a yellow oil; R_f=0.71 (silica gel, EtOAc/hexanes, 8:2); $[\alpha]_D^{32}$ −3.5 (*c* 0.34, $CHCl_3$); IR (film) ν_{max} 3377 (br), 3119, 2978, 2919, 1754, 1689, 1666, 1531, 1443, 1372, 1255, 1149, 1091, 1049, 961, 908, 808, 755 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN, 70 °C) δ 8.17 (d, J=8.8 Hz, 1H), 8.10 (d, J=1.7 Hz, 1H), 8.00 (dd, J=8.3, 1.3 Hz, 1H), 7.97 (dd, J=7.8, 0.8 Hz, 1H), 7.50 (t, J=8.3 Hz, 1H), 7.32 (d, J=0.9 Hz, 1H), 6.61 (s, 1H), 6.25 (dd, J=10.1, 0.9 Hz, 1H), 5.84–5.80 (m, 1H), 5.24–5.21 (m, 1H), 4.95–4.87 (m, 2H), 4.50 (s, 2H), 4.32–4.29 (m, 1H), 4.16 (dd, J=9.1, 1.7 Hz, 1H), 3.38 (s, 3H), 1.69 (s, 3H), 1.56 (s, 3H), 1.28 (br s, 9H); ^{13}C NMR (150 MHz, CD_3CN, 66 °C) δ 175.9, 169.2, 163.7, 162.2, 156.1, 150.3, 143.1, 139.1, 137.1, 133.0, 132.5, 126.9, 125.9, 125.2 (2C), 119.0, 96.4, 81.5, 71.3 (2C), 68.1, 60.60, 60.59, 59.2, 51.8 (2C), 29.1 (3C); HRMS (ESI-TOF) calcd for $C_{31}H_{35}BrN_5O_{10}S_2^+$ [M+H$^+$] 780.1003, found 780.1001.

4.6.11. (2*S*)-2-{[(2-{(1*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2-hydroxyethyl}-1,3-thiazol-4-yl)carbonyl]amino}-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]ethyl 3-(2-bromo-6-nitrophenyl)-2-oxobut-3-enoate (89). α-Ketoester **88** (10 mg, 0.013 mmol) was dissolved in CH_2Cl_2 (330 μL) and MeOH (170 μL) and cooled to 0 °C. TFA (500 μL) was added dropwise and, after stirring for 1 h at 0 °C, the reaction mixture was diluted with toluene (3 mL) and concentrated (two times). The residue was purified by PTLC (silica gel, EtOAc/hexanes, 80:20) to afford *N*-Boc amino alcohol **89** (6.8 mg, 72%) as a yellow oil; R_f=0.29 (silica gel, EtOAc/hexanes, 8:2); $[\alpha]_D^{33}$ −0.4 (*c* 0.78, CH_2Cl_2); IR (film) ν_{max} 3383 (br), 3109, 2971, 2923, 2850, 1746, 1698, 1686, 1649, 1528, 1346, 1243, 1158, 1031, 740, 595 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 8.19 (d, J=7.0 Hz, 1H), 8.09 (s, 1H), 8.01–7.98 (m, 1H), 7.98–7.96 (m, 1H), 7.52–7.48 (m, 1H), 7.32 (s, 1H), 6.62 (dd, J=2.2, 0.9 Hz, 1H), 6.25 (dd, J=6.1, 1.3 Hz, 1H), 5.87–5.80 (m, 2H), 4.98–4.90 (m, 3H), 4.51 (s, 2H), 4.95–4.85 (m, 2H), 3.39 (s, 3H), 1.43 (br s, 9H); ^{13}C NMR (150 MHz, CD_3CN) δ 185.3, 174.0, 171.8, 168.9, 163.4, 161.9, 155.5, 151.2, 150.1, 142.6, 138.8, 136.9, 132.5, 132.1, 126.5, 125.8, 124.9, 120.5, 118.6, 80.8, 70.9, 67.6, 64.8, 58.8, 51.3, 28.8 (3C); HRMS (ESI-TOF) calcd for $C_{28}H_{31}BrN_5O_{10}S_2^+$ [M+H$^+$] 740.0690, found 740.0687.

4.6.12. *tert*-Butyl (4*S*,11*S*)-15-bromo-19-hydroxy-4-[4-(methoxymethyl)-1,3-thiazol-2-yl]-1,6-dioxo-3,4,5,6,11,12,14,19-octahydro-1*H*-7,10-epiazeno[1,12,8,4]dioxathiazacyclohexadecino[15,14-*b*]indol-11-ylcarbamate (3c). *Method A*: A stirred suspension of Zn dust (5.0 mg, 0.078 mmol) and dibromoethane (0.46 μL, 0.005 mmol) in THF (79 μL) was heated to reflux (70 °C) for approximately 5 min and then allowed to cool to 25 °C. The refluxing/cooling process was repeated three times. TMSCl (0.41 μL, 0.003 mmol) was then added and the resulting gray suspension was stirred at 25 °C for 10 min. A separate stirred solution containing a mixture of aqueous 1 N NH_4Cl (36 μL, 0.036 mmol) and *N*-Boc amino alcohol **89** (12 mg, 0.016 mmol) in THF (153 μL) was added via cannula to the activated Zn suspension and stirring was continued for 15 min at 25 °C. The crude reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ solution (1 mL) filtered through Celite and dried (Na_2SO_4). The resulting solution was concentrated and the residue was dissolved in DME (16 mL). Molecular sieves (20 wt%, 4 Å) and *p*TsOH (9 mg, 0.048 mmol) were added and, after 10 min at 25 °C and 12 h at 40 °C, the reaction mixture was cooled to room temperature and purified by PTLC (silica gel, MeOH/Et_2O, 5:95) to give *N*-hydroxyindole macrocycle **3c** (4.6 mg, 40%) as a yellow oil; *Method B*: To a stirred solution of $SnCl_2\cdot 2H_2O$ (5.2 mg, 0.022 mmol) and 4 Å molecular sieves (20 wt%) in DME (50 μL) was added *N*-Boc amino alcohol **89** (5.3 mg, 0.007 mmol) in DME (50 μL) at 25 °C. The reaction mixture was warmed immediately to 45 °C and stirring was continued for 3 h in the absence of light at which time the reaction mixture was allowed to cool to room temperature and purified directly by PTLC (silica gel, MeOH/Et_2O, 7:93) to afford *N*-hydroxyindole macrocycle **3c** (0.51 mg, 10%) as a yellow oil; **3c** (+**3c**′) [ca. 1:1 mixture of *N*-Boc rotamers (^{1}H NMR)] R_f=0.63 (silica gel, MeOH/Et_2O, 5:95); $[\alpha]_D^{33}$ +1.0 (*c* 0.23, CH_2Cl_2); IR (film) ν_{max} 3346, 2924, 2850, 1709, 1668, 1534, 1494, 1458, 1365, 1251, 1223, 1185, 1163, 1122, 1100, 778, 743 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN, 67 °C) δ 9.05 (s, 1H), 8.97 (s, 1H), 8.47 (d, J=8.3 Hz, 1H), 8.47 (d, J=6.1 Hz, 1H), 8.01 (s, 1H), 7.97 (s, 1H), 7.48 (dd, J=8.3, 2.6 Hz, 1+1H), 7.39 (dd, J=7.8, 2.1 Hz, 1+1H), 7.34 (s, 1H), 7.32 (s, 1H), 7.23 (dd, J=8.3, 7.8 Hz, 1+1H), 5.85 (br s, 1+1H), 5.68–5.63 (m, 1+1H), 5.43 (d, J=10.5 Hz, 1H), 5.37–5.35 (m, 1+1H), 5.33–5.31 (m, 1+1H), 5.26 (d, J=10.1 Hz, 1H), 5.23 (d, J=10.1 Hz, 1H), 5.18–5.14 (m, 1H), 5.08–5.04 (m, 1H), 5.01 (dd, J=11.8, 4.3 Hz, 1H), 5.01 (dd, J=11.8, 4.9 Hz, 1H), 4.54 (d, J=0.8 Hz, 2H), 4.53 (d, J=0.8 Hz, 2H), 4.37 (dd, J=10.1, 3.5 Hz, 1H), 4.37 (dd, J=10.1, 3.5 Hz, 1H), 4.02 (dd, J=9.6, 3.0 Hz, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, CD_3CN) δ 169.6, 167.6, 162.4, 162.3, 156.3, 149.1, 137.7, 130.9, 127.8, 127.7, 127.2, 125.9, 121.4, 121.3, 116.2, 111.7, 110.6, 70.7, 64.4, 62.6, 62.0, 48.7, 53.1, 52.8, 52.6, 28.6 (3C);

HRMS (ESI-TOF) calcd for $C_{28}H_{31}BrN_5O_8S_2^+$ [M+H$^+$] 708.0792, found 708.0786.

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