STUDIES DIRECTED TOWARDS TOTAL SYNTHESES OF THE
COMMUNESINS AND PEROPHORAMIDINE

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ABSTRACT

In work directed toward total syntheses of the communesins (1-9) and perophoramidine (10), several strategies have been investigated to construct the unique ring systems of these alkaloids, including their vicinal quaternary carbon centers with control of the relative stereochemistry.

For perophoramidine, the formation of the reductive Heck product 78 from the nitro substrate 76 in the tandem Heck/carbonylation step was successfully achieved after extensive optimization efforts. Based on X-ray data, the relative stereochemistry of the two quaternary carbon centers of the allyl lactones 82 and 156 was revised to be cis, opposite to the assignment made in the previous work from our group. This revision of stereochemistry led us to discontinue further work on the synthesis of perophoramidine (10) via this strategy.

For the communesins, a similar strategy utilizing a tandem Heck/carbonylation and an intramolecular lactone enolate C-alkylation was first investigated. In spite of the successful synthesis of tricyclic lactones 219 and 226, further manipulation of the hydroxyethyl group to form an alkylation precursor was unsuccessful due to the instability of the highly strained tricyclic ring structures.

A second generation strategy utilizing an alkylation of spirolactones 228 and 262 provided allyl lactones 231 and 264 with moderate diastereoselectivities. These alkylations proceed through initial O-allylation and subsequent thermal Claisen rearrangement of the resulting O-allylketene acetal intermediates 230 and 263.
In a third generation strategy, the Heck/carbonylation step was replaced by an intramolecular Heck reaction of a tetrasubstituted alkene substrate, which efficiently led to the oxindole intermediate 307. However, all efforts to manipulate the exo-olefin moiety of 307 were unsuccessful.

A fourth generation strategy featured an intramolecular Heck reaction of the tetrahydropyridine substrates 339 and 386, followed by reductive cyclization to provide pentacycles 364 and 390. Subsequent metalloenamine alkylation of pentacycles 364 and 390 afforded allyl pentacycles 371 and 391. These products have the communesin relative stereochemistry at the two contiguous quaternary carbon centers. However, manipulation of the allyl group of 371 and 391 was problematic, with the unexpected formation of the rearranged aldehyde 378.

To eliminate the possibility of this undesired rearrangement, a bromo substituent was used at the C12a position. The bromide substrate underwent a similar intramolecular Heck reaction, reductive cyclization and metalloenamine alkylation to afford the allylic pentacycle 412, which was transformed to the hexacyclic hemiacetal 418. Using advanced intermediate 418, a total synthesis of the communesins might be completed through “northern” aminal formation and azepine ring installation, followed by several functional group transformations.
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Chapter 1. INTRODUCTION AND BACKGROUND

1.1. Isolation and Biological Activity of the Communesins and Perophoramidine

Microorganisms in the ocean are a relatively new source of unique natural products, compared to terrestrial metabolites, which have been studied extensively for decades. In 1993 Numata and coworkers reported two structurally unique polycyclic alkaloids, communesins A (1) and B (2), which were isolated from a Penicillium marine fungus growing on the marine alga Enteromorpha intestinalis (Figure 1). Communesins A (1) and B (2) show cytotoxicity against P-388 lymphocytic leukemia cells with moderate to potent activity (ED$_{50}$ = 3.5 µg/mL and 0.45 µg/mL, respectively). The structures of these alkaloids were elucidated by extensive spectroscopic analysis. Thus, the communesins have a novel heptacyclic skeleton bearing two aminal functional groups (C6, C9), two vicinal quaternary carbon centers (C7, C8) and an epoxide moiety on the isobutyl branch. The relative stereochemistry of the communesins (except for C21) was determined by NMR nOe studies. The absolute configuration of 1 and 2, however, could not be established at that time.

Figure 1. Structures of communesins A and B and nomofungin.
In 2003, Hemscheidt and coworkers described an alkaloid, nomofungin (3), which was isolated from the fermentation broth of an unidentified fungus derived from the bark of *Ficus microcarpa* L., growing on the Manoa campus of the University of Hawaii. The name, nomofungin, was chosen because the fungus producing this alkaloid was lost after isolation of the metabolite. Although nomofungin (3) and communesin B (2) have almost identical $^1$H and $^{13}$C NMR spectral data, the metabolite was initially proposed to have structure 3, which has an $\text{N.O}$-acetal rather than the aminal of communesin B (2). However, it was later found that this assignment was in error, and that nomofungin is actually communesin B (2). It should be noted, however, that the Hemscheidt work did serve to establish both the configuration at C21 of 2 using Murata’s $J$-based method, as well as the absolute configuration of the molecule using the exciton chirality method ($6R$, $7R$, $8R$, $9S$, $11S$, $21R$). Hemscheidt also found that communesin B (2) has cytotoxic activity against LoVo and KB cells (MIC 2.0 µg/mL, 4.5 µg/mL, respectively), which was shown to be due to the ability of the metabolite to cause microfilament disruption.

Recently, several other communesin congeners have been isolated, including communesin C (4), D (5), E (6), F (9), G (7) and H (8) (Figure 2). All of these

**Figure 2.** Structures of new communesins
communesins differ only in the substituents at N15 and N16, except for communesin F, which has a double bond instead of an epoxide between C21 and C22. Communesins C and D, along with communesin B, were isolated from a *Penicillium* species isolated from the sponge *Axinella verrucosa*. All three compounds exhibit moderate antiproliferative activity against a series of leukemia cell lines. Communesins A, B, D, E and F were also isolated from the fermentation broth of okara (the insoluble residue of whole soybeans) with *Penicillium expansum* Link MK-57. These communesins show insecticidal activity against the third instar larvae of silkworms (LD$_{50}$ = 150, 5, 80, 300 and 80 µg/g for communesins A, B, D, E and F, respectively). The most recent communesin congeners reported to date are communesin G and H, which were isolated from *Penicillium rivulum* Frisvad. Interestingly these two metabolites were found to be inactive in antimicrobial, antiviral, and anticancer assays.

In 2002, Ireland reported the isolation of a congeneric compound, perophoramidine (10) (Figure 3), from the tropical colonial ascidian *Perophora namei* collected in the Philippines. Extensive spectroscopic analysis showed that the metabolite has a hexacyclic ring system (one less ring than the heptacyclic skeleton of the communesins due to the absence of the azepine ring). Perophoramidine has bis-amidine rather than the bis-aminal functionality seen in the communesins and three halogen atoms.

**Figure 3.** Structure of perophoramidine
around the aromatic rings. The halogen substitution pattern was confirmed by comparing $^{13}$C chemical shifts predicted by ChemNMR software and literature values of structurally similar compounds with the observed values. Perophoramididine also has adjacent quaternary carbon centers (C4, C20) similar to the communesins. However, the relative stereochemistry of these two stereogenic centers was assigned as trans based on a ROESY study. This assignment was supported by a computer modeling study (Chem3D Pro, MM2), in which the trans and cis isomers have steric energy values of 36 and 80 kcal/mol, respectively. These results suggested that the communesins and perophoramididine have opposite relative stereochemistry at the respective vicinal quaternary centers in spite of the overall structural similarity between the two metabolites. The absolute stereochemistry of 10 has not yet been assigned. Perophoramididine has cytotoxicity against the HCT116 colon carcinoma cell line (IC$_{50}$, 60 µM) due to induction of apoptosis by poly(adenosine-5’-diphosphateribose)polymerase (PARP) cleavage.
1.2. Studies on the Biosynthesis of Communesins and Perophoramidine

1.2.1. Tryptamine Dimerization Pathway

Several decades before the actual isolation of the communesins and perophoramidine, the core structure of these alkaloids had been proposed in the literature.\(^5\) During structural elucidation studies of the calycanthaceous alkaloids, Robinson\(^5a\) and Woodward\(^5b\) independently proposed a biogenetic pathway for these alkaloids (Scheme 1). Thus, it was suggested that \(N\)-methyltryptamine (11) undergoes oxidative dimerization and hydrolysis of a resulting bis-indolenine 12a to give a bis-amino bis-aldehyde 12b, which could possibly form five different bis-aminal isomers 13-17. Based on spectroscopic analysis and its acid stability, bis-aminal 14 was proposed as the structure of calycanthine, which was later confirmed by X-ray analysis.\(^6\) Except for isomer 13, the other bis-aminal isomers 15-17 have since been found in Nature having the exact ring structure (chimonanthines (19, 20)\(^7\) and \(iso\)-calycanthine (21)\(^8\)), or a partial skeleton (communesins and perophoramidine). The common intermediate 12 can exist as two possible diastereomers, one of which has \(C_2\)-symmetry and the other which is a \(meso\)-diastereomer. The former diastereomer would give the stereochemistry found in 18, 19 and the communesins, and the latter would afford 20, 21 and perophoramidine (10).
(+)-calycanthine (18)

(-)-chimonanthine (19)

meso-chemonanthine (20)

iso-calycanthine (21)

communesin A (1)

perophoramidine (10)
Recently Mantle and coworkers reported a more definitive experimental study involving feeding isotopically labeled materials to communesin-producing fungi, which showed that tryptophan, methionine, mevalonate and tryptamine are involved in the biosynthetic pathway of the communesin alkaloids (Scheme 2). More precisely, tryptophan and methionine participate in the biosynthesis of the communesins at an early stage and mevalonate is incorporated later to provide the isoprene unit. Lack of incorporation of indole-N-\(^{13}\)C-methyl)tryptophan implies that N-methylation of tryptophan is not an early step in the communesin biosynthetic pathway. Thus, biosynthesis of the communesins probably commences with decarboxylation of tryptophan (22) to give tryptamine (23), which would undergo methylation and oxidative dimerization. The resulting bis-aminal 24 could then be transformed to the communesins through subsequent acylation, prenylation and epoxidation.

Based on the putative biogenetic pathway of the calycanthaceous alkaloids, several biomimetic syntheses of racemic and/or meso-chimonanthines have been reported,
featuring an oxidative homo-dimerization of tryptamine derivatives as a key step. This remarkably simple and short approach, however, is limited by low yields and lack of stereoselectivity. In particular, this method is not applicable for the syntheses of communesins and perophormidine, which require dimerization of two different tryptamine derivatives.

1.2.2. Hetero Diels-Alder Pathway

In 2003 Stoltz and coworkers proposed an alternative pathway for biosynthesis of the communesins in which a hetero Diels-Alder reaction replaces the oxidative dimerization of tryptamine derivatives as a key transformation (Scheme 3). Thus, a biological oxidation of tryptamine (23) would give a reactive hetero diene, N-acyl-aza-ortho-xyylene (26), which could react with the known alkaloid N-methylaurantioclovine (25) via a hetero Diels-Alder cycloaddition to generate the strained bridged lactam 27. This highly strained lactam 27 could then be transformed into the spirolactam 28, which

![Scheme 3](image-url)
would undergo several additional biosynthetic steps to finally afford the communesins (1-9).

This new hypothesis gives synthetic chemists a more viable route to the complex communesin skeleton than does the oxidative dimerization pathway, as was illustrated by Stoltz’ biomimetic synthesis of a model communesin ring system (Scheme 4). Thus, an intermolecular \([4+2]\)-cycloaddition of an \(N\)-acyl-aza-ortho-xylylene 32 derived from precursor 29 and \(N\)-Boc-protected \(N\)-methylaurantioclavine (30) gave aminal 32, which has the core skeleton of the communesins in high yield, but with no diastereoselectivity with regard to C11 (dr = 1:1).

**Scheme 4**

Furthermore, Funk and Crawley have synthesized more complex hexacyclic ring systems of the communesins and nomofungin utilizing an intramolecular version of the hetero Diels-Alder cycloaddition (Scheme 5).\(^{12,13}\) For example, under thermal cycloaddition conditions, benzazepine-tethered ortho-quinone methide precursor 32 was transformed to the hexacyclic \(N,O\)-acetal 33 bearing the postulated nomofungin skeleton.
through *endo* transition state 34. The communesin core ring system was also available through the similar intramolecular cycloaddition of aza-ortho-xylylene precursor 34.

Stoltz and Funk’s biomimetic approaches to communesin skeletons afforded not only efficient synthetic pathways to these complex molecules, but also provided good spectral evidence for revision of the structure of nomofungin (3).

**Scheme 5**

![Diagram of chemical reactions involving compounds 33, 34, 35, 36, 37, and 38, showing the reaction conditions and product yields.](image-url)
1.3. Synthetic Approaches to the Communesins and Perophoramidine

The unprecedented structures of the communesins and perophoramidine, as well as the promising biological activity of these alkaloids, have caught the attention of synthetic chemists. Up to now, however, few successful total syntheses of these complex metabolites have been reported, perhaps due part in part to difficulties in the stereoselective formation of adjacent quaternary carbon centers, which is one of the common features of these natural products.\(^{14,15}\)

Funk and Fuchs made the first breakthrough in synthesis of these molecules by completing a total synthesis of racemic perophoramidine utilizing a biomimetic hetero Diels-Alder reaction as a key step.\(^{16}\) Dehaloperophoramidine has also been synthesized by Rainier and coworkers through a quite different strategy.\(^{17}\) More recently Qin and coworkers published the first total synthesis of communesin F.\(^{18}\) In addition a few other preliminary synthetic approaches to the core ring system of the communesins have been reported.\(^{19}\)

1.3.1. Funk Total Synthesis of Racemic Perophoramidine

In 2004 Funk and Fuchs reported the first, and thus far only, total synthesis of perophoramidine (10).\(^{16}\) The adjacent quaternary carbon centers of the alkaloid were constructed through a key intermolecular hetero Diels-Alder reaction (Scheme 6). Using Corey’s conditions,\(^{20}\) 3-bromo-2-oxindole 39 was transformed \textit{in situ} to intermediate \textit{N}-
acyl-aza-ortho-xyylene 41, which reacted with 3-alkylindole 40 to give indolenine 44 in high yield and with excellent diastereoselectivity (89%, dr > 20:1). The high stereoselectivity presumably results from a preference for an endo transition state in the cycloaddition step, affording strained lactam cycloadduct 42, which is then rapidly transformed into 44 via 43 (path a). A direct conjugate addition of 40 to 41, however, was also considered as a possible route (path b). Pentacyclic aminal 46 then was obtained.
through Boc protection of the lactam and reduction of the azido group, followed by subsequent transamidation to give an intermediate 45, which then cyclized to the aminal. Direct introduction of the “northern” amidine functionality from the γ-spirolactam 46 proved to be problematic. To solve this problem, Funk and Fuchs prepared a pentacyclic imidate 47, which was synthesized from the γ-spiro lactam 46 in several steps, including introduction of the requisite two F-ring chlorines. Using Fukuyama’s nosyl deprotection conditions,21 imidate 47 was converted to the aminal amidine 48, which was oxidized to yield perophoramidine (10).

1.3.2. Rainier Synthesis of Dehaloperophoramidine

In 2006 Rainier and coworkers devised a new strategy for the construction of the vicinal quaternary carbon centers of perophoramidine, which was successfully used in a synthesis of unnatural dehaloperophoramidine (53) (Scheme 7).17 Pentacyclic lactam 51, bearing one of the quaternary carbon centers, was first synthesized from readily prepared 2-thioindole 49. Reduction of 49 to the corresponding α-hydroxy ketone, followed by treatment with methansulfonyl chloride and pyridine, gave spirolactam 50 as a 1:1 mixture of diastereomers. Under basic conditions, equilibration between the two isomers occurred and one diastereomer was smoothly transformed into the pentacyclic lactam 51 in 79% overall yield from 49. The second quaternary center was then introduced by allylation of the enolate of lactam 51 to afford allyl lactam 52 as a single diastereomer in 89% yield. The stereochemistry of 52 was confirmed by X-ray chrystallographic analysis.
The synthesis of dehaloperophoramidine (53) was completed by formation of the “northern” amidine through a route like that Funk and Fuchs had developed.

1.3.3. Qin Total Synthesis of Racemic Communesin F

Recently, Qin and coworkers completed the first total synthesis of communesin F (9), which has olefin functionality at C21/22, rather than the epoxide found in the other communesins.\(^{18}\) The two adjacent quaternary carbon centers of this molecule were installed through a stereoselective allylation of pentacyclic lactone 57 (Scheme 8). The pentacyclic ring system was efficiently constructed from \(\alpha\)-diazoo ester 54 through cyclopropanation followed by azido group reduction of the resulting product 55, which caused concomitant cyclopropane ring opening and cyclization to give a pentacyclic lactam 56 in 83% yield. After amine protection, \(trans\) lactone 57a was converted quantitatively to the more stable \(cis\) epimer 57b under basic conditions. Both epimers 57a
and 57b, however, could be alkylated to give allyl lactone 59 as a single diastereomer via initial O-allylation followed by [3,3]-sigmatropic rearrangement, which was proven by isolation of ketene acetal intermediate 58. The relative stereochemistry of the two quaternary centers turned out to be cis as required, which was confirmed by NMR nOe experiments. The exclusive formation of one isomer might be explained by a facially selective [3,3]-sigmatropic rearrangement in which the α face of the dihydropyran ring is blocked by the bromophenyl unit.

To complete the total synthesis of communesin F, the “northern” aminal and azepine ring systems of the alkaloid were then built (Scheme 9). After several functional group transformations, spiro γ-lactam 60 could be obtained from 59. Introduction of the isoprene unit and azepine ring formation were achieved by a Heck reaction and acid catalyzed S_N2’cyclization, respectively, to afford hexacycle 61. The F ring was installed through imidate formation, Boc-removal and acid catalyzed cyclization on silica gel to
give heptacycle 62. Finally communesin F (9) was synthesized by one-pot reduction and N-acetylation of 62.
1.4. Previous Synthetic Studies on Perophoramidine in the Weinreb Group

In 2003, our group described a concise and efficient approach to stereoselectively construct the two quaternary carbon centers of perophoramidine (10). As shown in Scheme 10, our retrosynthesis for perophoramidine (10) relied on a halogen selective tandem Heck reaction/carbonylation and a diastereoselective C-allylation to introduce the two vicinal quaternary carbon centers. Thus, a total synthesis of perophoramidine (10) would be completed through sequential formation of the two amidine units from α-allyl δ-lactone 63. The allyl group would be introduced by a diastereoselective allylation of lactone 64, which would be formed by Heck reaction/carbonylation of amide 66 to give 65, followed by lactonization. Amide 66 would be prepared from commercially available aniline 67 and easily accessible γ-lactone 68.
The intramolecular Heck reaction is a powerful method for building quaternary carbon centers.\textsuperscript{23} Moreover, the reaction can be performed enantioselectively by using chiral phosphine ligands.\textsuperscript{24} In addition, tandem Heck reactions make it possible subsequently to introduce functional groups if the palladium intermediate is prevented from undergoing a $\beta$-hydride-elimination.\textsuperscript{25} Utilizing this tandem Heck/carbonylation strategy, the C20 quaternary center of perophoramidine (10) was efficiently constructed (Scheme 11). Thus, halogen-selective oxidative addition of palladium(0) into the carbon-iodine bond of amide 69 gave intermediate 70a, which underwent migratory insertion to yield oxindole intermediate 70b. The absence of $\beta$-hydrogens in 70b allowed further reaction \textit{in situ} with CO and MeOH to afford methyl ester 71 in good yield.

\textbf{Scheme 11}

To investigate the compatibility of a C-ring \textit{ortho} substituent in this Heck/carbonylation reaction, \textit{o}-methoxy-substituted substrate 72 was also exposed to the
optimized Heck/carbonylation conditions to give oxindole 73 in high yield (Scheme 12). Installation of the second quaternary center was then explored with lactone 74, which was easily formed from oxindole 73 via desilylation and lactonization. After investigation of various alkylation conditions, it was found that treatment of 74 with NaH and allyl bromide in DMF at 70 °C overnight gave the product 75 as a single diastereomer. At that time the relative stereochemistry of 75 was assigned as shown in Scheme 12 based on NOESY NMR experiments. Subsequent studies, however, revealed that this assignment was in error, and the actual relative stereochemistry of 75 is opposite to the depiction in Scheme 12 (vide infra).

At this stage, we also investigated use of substrate 76, which has all the requisite halogens of 10 and an ortho nitro group as the precursor of the requisite C-ring amino functionality. However, exposure of easily accessible Heck substrate 76 to the previously optimized Heck/carbonylation conditions afforded the desired ester 77 only in low yield.
with reduced (non-carbonylated) compound 78 being the major product (Scheme 13). All efforts to increase the yield of the desired carbonylated product 77 were fruitless.

**Scheme 13**

One of possible reason for the formation of reduced product 78 is the electron-withdrawing character of the nitro group, which would make the carbon-palladium bond of the alkyl-palladium intermediate more polarized and more susceptible to hydride transfer or protonolysis (*vide infra*). Thus, the nitro group of 76 was reduced and the resulting amine was protected as various derivatives including phthalimide, sulfonamide, carbamate, amide and triazene. Unfortunately, these protecting groups were either incompatible with the Heck/carbonylation conditions or gave the desired carbonylated product in very low yields.
Chapter 2. SYNTHETIC STUDIES ON PEROPHORAMIDINE

2.1. Revised Strategy Utilizing a Curtius Rearrangement

The unsuccessful results with nitro substrate 76 described above led us to revise the strategy for introducing the amine functionality into the C ring. We expected that the amino group could be introduced at a late stage of the synthesis through a Curtius rearrangement\textsuperscript{27} of the corresponding carboxylic acid functionality, which would be available from the methoxy substituent of 75 through several functional group transformations.

2.1.1. Retrosynthetic Analysis

Retrosynthetically, we believed that perophoramidine (10) could be synthesized from amino lactam 79 through “southern” amidine formation (Scheme 14). The amine functionality of 79 could be introduced by hydrolysis and Curtius rearrangement of ester 80, which in turn would be formed from anisole 81 through demethylation, triflation, and palladium-catalyzed carbonylation, followed by bromination at the position \textit{meta} to the resulting ester group. Finally, anisole 81 would be obtained from the spiro lactone 75\textsuperscript{22} via several functional group transformations and “northern” amidine formation.
2.1.2. Northern Amidine Formation

As noted above, the stereochemistry of 75 was originally assigned incorrectly. Until it was eventually corrected by later studies (see Section 2.2.4.), all synthetic efforts for perophoramidine discussed in Chapter 2 were based on the assumption that we installed the correct stereochemistry of perophoramidine at the two vicinal quaternary carbon centers. For the sake of clarity, however, from this point on, the correct stereochemistry will be depicted in the structures of all compounds (75 to 82) which we prepared.

2.1.2.1. Spirolactam Route
To pursue this revised strategy, the installation of the “northern” amidine moiety was first investigated. Oxidative cleavage of the terminal olefin of alkylated spirolactone 82, followed by reductive work-up with borane dimethyl sulfide complex, afforded rearranged hydroxy γ-lactone 83 rather than the expected δ-lactone (Scheme 15). The structure of γ-lactone 83 was confirmed by HMQC and HMBC NMR analysis. The hydroxyl group of 83 was activated as its methanesulfonate 84 and then converted into azide 85 in 96% yield for 2 steps. A one-step approach to azide 85 from alcohol 83 was also tested by a Mitsunobu type reaction but this attempt did not give the desired product. Staudinger reduction of azide 85 by treatment with PPh3 in THF/H2O generated the free amine, which was slowly transformed into hydroxy δ-lactam 86 at high temperature in 74% yield.

Scheme 15
With hydroxy spirolactam 86 in hand, the introduction of a second amine function was explored (Scheme 16). Treatment of 86 with mesyl chloride, however, did not afford the desired mesylate 87, but rather the cyclic imidate 88. Direct formation of sulfonamide 89 using Mitsunobu conditions was also unsuccessful.

Scheme 16

To prevent the formation of the cyclic imidate, N-protection of the lactam 86 was explored (Scheme 17). Interestingly, upon treatment with Boc₂O, spirolactam 86 was also converted to cyclic imidate 88. Therefore, the hydroxyl group of 86 was first protected as a TBDMS ether. Boc-protection of the silyl-protected hydroxy lactam 91 was then possible, giving the desired N-Boc-imide 92 in good yield. However, exposure of 92 to TBAF caused not only desilylation, but also lactam ring opening to afford the undesired γ-lactone 93. This result prompted us to test the lactam ring opening with an amine nucleophile to investigate alternative ways to introduce the requisite amine functionality. Treatment of 92 with methylamine, however, provided only the deprotected lactam 91, via attack of the amine on the Boc-carbonyl group rather than the lactam, which
possesses a sterically hindered neopentyl carbonyl group. However, clean desilylation of 92 could be achieved under acidic conditions to give hydroxy lactam 95, which was then converted to chloro lactam 96 by treatment with mesyl chloride and triethylamine. Unfortunately, under azide forming conditions, chloro lactam 96 was again converted to the cyclic imidate 88.
2.1.2.2. γ-Lactam Route

Since introduction of the second amine functionality into the hydroxy spiro-δ-lactam substrates proved to be difficult, we therefore decided to construct the 5-membered lactam first, which we believed might avoid the imidate formation during the installation of the second amino group (Scheme 18). To pursue this strategy, amide 98 was obtained from spirolactone 82 by treatment with the dimethylaluminum amide reagent prepared from ammonia in accordance with our previously described method,32 followed by silyl protection of the resulting hydroxyl group of amide 97. γ-Lactam 99 was accessed in moderate yield from 98 through Lemieux-Johnson oxidation33 of the

Scheme 18

![Scheme 18](image-url)
terminal olefin and reductive amination/cyclization with NaCNBH$_3$ under acidic conditions.\textsuperscript{34} After $N$-methylation of $\gamma$-lactam 99, the silyl-protected hydroxyl group of 100 could be converted into the azide through desilylation, mesylation and azide formation in high yield. Amidine formation from azido lactam 103 was attempted using Shibasaki’s protocol\textsuperscript{35} with oxalyl bromide to form the desired amidine 104, but demethylated phenol 105 instead was obtained as the sole product. An intramolecular aza-Wittig reaction of 103 under Staudinger conditions was also unsuccessful in forming amidine 104. It should be noted that Funk found in the total synthesis of perophoramidine (10) that all attempts to convert a similar azido $N$-methyl-$\gamma$-lactam into the corresponding amidine through a Staudinger reaction were fruitless.\textsuperscript{16}

The formation of demethylated phenol 105 under Shibasaki’s conditions can be rationalized by a proximity interaction between the methoxy group and the $\gamma$-lactam carbonyl carbon (Scheme 19). Thus, based on the mechanism proposed by Shibasaki, the first step would be activation of the lactam by oxalyl bromide affording bromoiminium ion intermediate 106. For amidine formation an intermediate like 106 would be transformed to a cyclic intermediate 109 through either 1,2-addition of the azido group followed by a 1,2-shift of bromine and extrusion of N$_2$ (path a) or a [2+3]-cycloaddition of the azido group to the double bond of the iminium ion and a subsequent retro [2+3]-cycloaddition with a 1,2-shift of bromine (path b). The resulting cyclic intermediate 109 would then be converted to the desired amidine product 104 through a reductive work-up with anisole. However, in our case, before the intramolecular addition of the azido group (path a or b) occurs, we believe that the highly electrophilic bromoiminium carbon center
is attacked by the oxygen of the methoxy group to give a cyclic $N,O$-acetal intermediate 107, which would be subject to subsequent demethylation and hydrolysis to give the phenol lactam 105 via bromide 108.
2.1.2.3. Application of Funk’s Strategy for “Northern” Amidine Formation

At this point, we decided to follow Funk’s synthetic approach toward construction of the “northern” amidine of perophoramidine (10), which started from a similar γ-lactam structure (Scheme 20). Therefore after N-nosylation of γ-lactam 99, the silyloxy group of 110 was converted into the azide 112 via desilylation and Mitsunobu azidation of alcohol 111 in good yields. Exposure of azide 112 to trimethylphosphine produced lactam 113 via amine formation and concomitant transamidation in 98% yield. The nosylamide group in 113 could then be selectively N-methylated in the presence of the δ-lactam by treatment with Cs$_2$CO$_3$ and MeI at room temperature in quantitative yield.

Scheme 20

![Scheme 20](image-url)
Treatment of lactam 114 with Meerwein’s reagent produced cyclic methyl imidate 115 in 78% yield, which was converted into amidine 104 through the removal of the nosyl group using Fukuyama’s protocol in good yield.

However, although using Funk’s approach to the “northern” amidine was successful and proceeded overall in good yields, all efforts of demethylation of 104 were unsuccessful, yielding only recovered starting material or unidentifiable products (Scheme 21).
2.2. Reinvestigation of the Heck/Carbonylation of Nitro Aryl Substrates

While we were investigating the above Curtius rearrangement strategy, we also opted to reexamine the Heck/carbonylation of nitro group-containing substrates, which do not need the above multi-step functional group transformations to install the amine functionality in the C ring.

2.2.1. Reductive Heck Reactions and Protonolysis

As mentioned above, the main problem with the nitro-substituted Heck/carbonylation substrate is the formation of the reductive Heck compound 78 as a major product (see Section 1.4). The reductive Heck reaction is usually facilitated by addition of various reductants (hydride donors) such as HCO$_2$Na, HCO$_2$NH$_4$ and HCO$_2$H.
For example, in a Heck reaction of aryl halide 117 and olefin 118, the first two steps of catalytic cycle are oxidative addition and a subsequent migratory insertion, which give alkylpalladium intermediate 119. Next, the formate 120 adds to the palladium center to yield alkyl formate palladium species 121, which is transformed to alkylpalladium hydride 122 via extrusion of carbon dioxide (path a). Reductive elimination of 122 results in the reductive Heck product 123 and regeneration of Pd (0).

Other possible hydride donors are trialkylamine bases, such as NEt₃, i-Pr₂NEt, i-Pr₂NH, 1,2,2,6,6-pentamethylpiperidine, and proton sponge. In the catalytic cycle with these reductants, the trialkylamine 124 coordinates to alkylpalladium intermediate 119 to form an amine palladium species 125, which can undergo β-hydride elimination to provide common intermediate 122 and imine/enamine 126.

In the work described above, we speculated that the triethylamine possibly acts as a hydride donor under our Heck/carbonylation conditions (Scheme 13). As a possible solution to this problem, we substituted DBACO for triethylamine, which is unable to undergo a β-hydride elimination due to Bredt’s rule. However, DABCO did not provide any significant difference in the ratio of products in the Heck/carbonylation sequence, which suggests the presence of other hydride sources under our reaction conditions.

Reductive Heck products also have been formed in intra- or intermolecular Heck reactions of α,β-unsaturated carbonyl substrates. For instance, the palladium-catalyzed aryl-enone cyclization of 127 provided a mixture of Heck product 128 and reductive Heck product 129 (Scheme 23). The ratio of the two products can vary substantially depending upon the additives and/or solvents employed. Thus, AgNO₃,
which is known to generate cationic palladium species, caused the non-reductive Heck adduct 128 to be the predominant product. In stark contrast, the reductive Heck product 129 was formed almost exclusively in the absence of AgNO₃ and when THF was used as the solvent.

**Scheme 23**

<table>
<thead>
<tr>
<th>additive</th>
<th>solvent</th>
<th>128 : 129</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>CD₃CN</td>
<td>55:45</td>
</tr>
<tr>
<td>Et₃N·HCl (2 eq)</td>
<td>CD₃CN</td>
<td>32:68</td>
</tr>
<tr>
<td>Et₃N·HO₂CH (2 eq)</td>
<td>CD₃CN</td>
<td>28:72</td>
</tr>
<tr>
<td>AgNO₃ (1 eq)</td>
<td>CD₃CN</td>
<td>91:9</td>
</tr>
<tr>
<td>none</td>
<td>THF-d₈</td>
<td>8:92</td>
</tr>
</tbody>
</table>

The formation of the reductive Heck product 129 can be explained by the mechanism discussed above, which involves hydride donors. However, another mechanism, which is more generally accepted for the reductive Heck reaction of α,β-unsaturated carbonyl substrates, has been proposed (Scheme 24). As in the previous reductive Heck reaction of simple alkenes (Cf. Scheme 22), aryl halide 117 first undergoes oxidative addition to Pd (0) and a migratory insertion into enone 130 to give alkylpalladium intermediate 131. This species is the keto-form of palladium enolate 133. Both forms are interconvertible via either a 1,3-shift or a palladotropic shift. β-Hydride elimination from the C-palladium intermediate 131 would then give β-substituted enone product 132 (normal Heck product). However, the saturated ketone 134 (reductive Heck
product) can also result from either hydrolytic cleavage of the C-Pd bond of 131 or protonolysis of the O-palladium species 133, followed by subsequent tautomerization. The proton source for this step could be adventitious acid, H₂O, or a proton produced from thermal Hoffmann elimination of the n-Bu₄NCl. To complete the catalytic cycle, the Pd (II) from protonolysis is reduced to the catalytically active Pd (0) species by a reductant, such as one of the hydride donors mentioned in the previous reductive Heck mechanism. Additionally, carbon monoxide can also act as a reductant, being oxidized to carbon dioxide.⁴¹
In a system similar to our Heck/carbonylation substrate 76, Denmark has studied palladium-promoted intramolecular addition of an aryl iodide to a nitro alkene 135, which gave a mixture of normal Heck adduct 136 and reductive Heck product 137 in 43% and 40% yields, respectively (Scheme 25).

The mechanism proposed by Denmark for this transformation is similar to the general “protonolysis” mechanism shown in Scheme 24. The role of the silver salt is presumably to form the more electrophilic cationic palladium species 138 by abstraction of iodide ion, which allows palladium to form a tighter complex with the less electron-rich nitro olefin (Scheme 26). Cationic alkylpalladium intermediate 139 then undergoes a β-hydride elimination to afford Heck product 136. Alternatively, heterolytic cleavage (path a) or 1,3-shift to a pallado nitronate (path b), followed by protonolysis would give reductive Heck product 137.
Denmark’s study supports the thesis that a nitro group could act like a carbonyl group in a reductive Heck or protonolysis reaction. Given these precedents, we can formulate a mechanistic hypothesis about the Heck/carbonylation reaction of nitro substrate 76 (Scheme 27). Thus, following the straightforward formation of alkylpalladium intermediate 142, methoxycarbonylation would lead to ester 77. For the protonolysis product 78, we can consider two possible intermediates. One is a carbanion intermediate 143, which results from heterolytic cleavage of the Pd-C bond of 142, and the other is pallado nitronate 144, which might be less likely due to the destabilization resulting from C-ring dearomatization. Both 143 and 144 could be converted to reductive...
Heck product 78 along with the catalytically inactive Pd (II) species, which would subsequently be reduced to Pd (0) by carbon monoxide.

**Scheme 27**

2.2.2. Model Study of Heck/Carbonylation Sequence

To reduce the amount of the reductive Heck product formed in our cyclization, we decided to try to remove possible proton sources from the reaction mixtures. One of the possible proton sources is acetic acid generated from Pd(OAc)$_2$ and P(o-Tol)$_3$ when
forming the active palladacycle catalyst 145 (Herrmann’s palladacycle)\textsuperscript{[42]} \textit{in situ} (Scheme 28). To avoid this problem, a commercially available preformed Herrmann’s palladacycle could be used instead.

\textbf{Scheme 28}

\[ 2 \text{Pd(OAc)}_2 + 2 \text{P(o-Tol)}_3 \rightarrow \text{Herrmann's palladacycle (145)} + 2 \text{AcOH} \]

Methanol is also a possible proton source for the protonolysis. In previous work, we had tested alternative alcohol solvents, such as \(t\)-BuOH or \(i\)-PrOH, all of which were ineffective in increasing the ratio of the desired ester to the protonolysis side product.\textsuperscript{[22b]}

Thus, we decided to run the Heck/carbonylation step without MeOH, expecting formation of acyl chloride 146, which could then be converted to the methyl ester by addition of MeOH in a work-up step (Scheme 29).

\textbf{Scheme 29}

To examine these hypotheses, we synthesized the model Heck/carbonylation substrate 150, which is readily accessible from the known \(\gamma\)-lactone 147\textsuperscript{[43]} (Scheme 30). Thus, aminolysis of \(\gamma\)-lactone 147 with the aluminum amide of commercially available
aniline 67 afforded amide 148 in 79% yield. The model substrate 150 was obtained through protection of the hydroxyl group of 148 as the TBDMS silyl ether 149, followed by MOM protection of the amide nitrogen.

Scheme 30

With the amide 150 in hand, the Heck/carbonylation reaction with Herrmann’s palladacycle (145) was investigated (Scheme 31). Under the previously optimized conditions with 145 as catalyst, amide 150 was converted to the desired ester 151 along with uncyclized methoxycarbonylated product 152 in 54 and 18% yields, respectively. Interestingly, the reductive Heck compound, which was the major product of Heck/carbonylation of the nitro substrate 76, could not be detected in the reaction mixture. This quite different result might be due to using Herrmann’s palladacycle or to the substrate itself. To test these possibilities, amide 150 was exposed to the same exact conditions used in previous work with 76 (i.e. Pd(OAc)$_2$ and P(o-tol)$_3$ as palladium catalyst and ligand), which provided 151 and 152 in 63 and 20% yield, respectively. These similar results from the two experiments show that Heck/carbonylation step is very substrate dependent. These promising results with the model substrate led us to reinvestigate the Heck/carbonylation of the real substrate (see Section 2.2.3.). As an
alternative, bromination at the meta position of ester 151 was also attempted under several sets of conditions, but all attempts were unsuccessful.

Another question to be tested was the effect on the Heck/carbonylation step of MeOH. Interestingly, when the reaction was run in DMA without MeOH, reductive Heck compound 153 was the sole product in 53% yield, which is the opposite to what we had expected. One of the reasons for this unexpected result might be that MeOH is a good solvent for dissolving carbon monoxide, whose concentration is important for the carbonylation step.

Scheme 31

2.2.3. Optimization of the Heck/Carbonylation Conditions

Based on the promising results with the model system (see Section 2.2.2.), we decided to reinvestigate the Heck/carbonylation of the actual nitro substrate 76. To
initiate this work, amide 76 was first exposed to the original conditions which were previously used. Surprisingly, the desired ester 77 was now obtained as the major product, along with reductive Heck product 78 and unicyclized ester 154 as minor side products (Table 1, Entry 1). We do not currently have a satisfactory explanation for this lack of reproducibility. However, encouraged by this result, we next screened several palladium catalysts (Entry 2-7). Herrmann’s palladacycle and PdCl₂(PPh₃)₃ showed results similar to that with Pd(OAc)₂. The best result was provided by Pd₂(dba)₃ as catalyst which gave 77 in 68% crude yield (entry 7). This observation led us to use Pd₂(dba)₃ as the catalyst for further optimization studies. Control experiments revealed that both the phosphine ligand (P(o-Tol)₃) and additive (n-Bu₄NBr) are important for full consumption of the starting material (Entry 8, 9). Other bases, such as EtN(i-Pr)₂ or NaOAc, did not lead to total consumption of the starting iodide (Entry 10, 11). Interestingly, when NaOAc was used as the base, the unicyclized carbonylated product 154 was obtained as the major product. Reactions run in other polar solvents (DMF, NMP) provided a lower conversion than in DMA (Entry 12, 13). Finally, we examined the ratio of the solvents used (Entry 14-16). Interestingly, when the ratio of MeOH was increased, the production of the reductive Heck product 78 increased dramatically (Entry 14). This result strongly suggests that MeOH is one of the major proton sources for formation of 78. Using a very low ratio of MeOH to DMA led to an incomplete reaction (Entry 15). The best result was obtained when the ratio of DMA:MeOH is 5:1, affording ester 77 in 73% crude yield with no ester 154 and only a small amount of reductive Heck product 78 (Entry 16).
Table 1. Selected Results of Heck/carbonylation of Nitro Substrate 76

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Catalyst</th>
<th>Phosphine Ligand</th>
<th>Base</th>
<th>Solvents (ratio)</th>
<th>Additive</th>
<th>Product ratio (%)</th>
<th>77</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SM</td>
</tr>
<tr>
<td>1</td>
<td>Pd(OAc)₂</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Herrmann’s</td>
<td></td>
<td></td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>-</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>PdCl₂(PPh₃)₂</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>-</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>Complex mixture</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Pd₂Cl(allyl)²</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>71</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>Pd₃(dba)₂CHCl</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>Pd₃(dba)₃</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>Pd₃(dba)₃</td>
<td></td>
<td>NEt₃</td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>Pd₃(dba)₃</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (2/1)</td>
<td>-</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>Pd₃(dba)₃</td>
<td>P(o-Tol)</td>
<td>EtN(i-Pr)</td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>11</td>
<td>Pd₃(dba)₃</td>
<td>P(o-Tol)</td>
<td>NaOAc</td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>12</td>
<td>Pd₃(dba)₃</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>13</td>
<td>Pd₃(dba)₃</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>NMP/MEOH (2/1)</td>
<td>n-Bu₄NBr</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>14</td>
<td>Pd₃(dba)₃</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (1/2)</td>
<td>n-Bu₄NBr</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>Pd₃(dba)₃</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (10/1)</td>
<td>n-Bu₄NBr</td>
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<td>26</td>
</tr>
<tr>
<td>16</td>
<td>Pd₃(dba)₃</td>
<td>P(o-Tol)</td>
<td>NEt₃</td>
<td>DMA/MEOH (5/1)</td>
<td>n-Bu₄NBr</td>
<td>-</td>
<td>29</td>
</tr>
</tbody>
</table>

a) All reactions were run under a CO atmosphere (1 atm) at 78 °C for 18-22h.
b) Ratios were determined by integration of the crude ¹H NMR spectra.
2.2.4. Alkylation of the Spirolactam

With the Heck/carbonylation product 77 in hand, we next investigated the installation of the second quaternary carbon center (Scheme 32). The substrate for the alkylation, spirolactone 155, was obtained by treatment of the crude mixture of Heck/carbonylation products 77a/77b with TBAF in 51% overall yield from 76 as a mixture of diastereomers (dr = 4:1). Under the previously optimized alkylation conditions, allylation of spirolactone 155 afforded allyl lactone 156 in 86% yield as a single diastereomer. The relative stereochemistry of 156 was confirmed by X-ray crystallography (Figure 4), which surprisingly showed a cis configuration rather than trans, which we had expected, based on the results of our previous model studies (Cf. Scheme 12).

Scheme 32

To clarify these seemingly contradictory results, we attempted to obtain an X-ray structure for a compound derived from allyl lactone 75, the stereochemistry of which had previously been assigned as cis by NMR NOESY studies. Fortunately, amide 97, the aminolysis product of allyl lactone 75, provided crystals suitable for X-ray analysis (Figure 5), which revealed a cis-relationship between the two vicinal quaternary centers.
Furthermore, a careful reexamination of the NOESY data for 75 revealed that one of the key correlations had been misinterpreted due to peak overlap. This evidence proved that allyl lactones 75 and 156 in fact have the *cis* configuration at the vicinal quaternary carbon centers, which corresponds to the relative stereochemistry of the communesins, not of perophoramidine. This result led us to explore this C-alkylation strategy for synthesis of the communesins (see Section 3.3.2.)
Figure 4. ORTEP Structure of allyl lactone 156
Figure 5. ORTEP Structure of amide 97
Before this revised stereochemistry of allyl lactone 156 was established, however, several chemical modifications of 156 were explored (Scheme 33). Based on the previous successful work for “northern” amidine formation (Cf. Schemes 18, 19), aminolysis of lactone 156 was first attempted using a dimethylaluminum amide reagent, but was unsuccessful. In an alternative route, reduction of the nitro group of 156 with iron in acetic acid gave bis-oxindole 158, which resulted from intramolecular aminolysis of the corresponding aniline. After protection of the hydroxyl group of 158 as the TBDMS ether, the “northern” amide of 159 was transformed to \( N \)-Boc imide 160 in good yield. Oxidative cleavage of the terminal olefin and reductive work-up provided hydroxy imide 161 in 81% yield. We envisioned that amidine 162 could be formed from 161 via several functional group transformations. However, when the stereochemistry of these
intermediates was revised, as noted above, we discontinued this study.

2.3. Conclusion and Future Work

In conclusion, we have explored a revised strategy for the synthesis of perophoramidine (10) utilizing a Curtius rearrangement to introduce a C-ring amino group. Using this approach, we have successfully synthesized amidine 104 from one of our advanced intermediates from previous work, spirolactone 82. However, all efforts at cleavage of the methyl ether of 104 were fruitless. We have also solved the problem of formation of reductive Heck product with nitro substrate 76 through mechanistic considerations and optimization efforts. Finally we have proven that the relative stereochemistry of allyl lactones 82 and 156 is cis rather than trans, which had been previously assigned. This revision of stereochemistry led us to discontinue further work on the synthesis of perophoramidine (10) via this strategy.
Chapter 3. SYNTHETIC STUDIES ON THE COMMUNESINS

The structural similarities between the perophoramidine (10) and the communesins (1-9) prompted us to investigate a similar tandem Heck/carbonylation strategy leading to the latter compounds. However, the communesins and perophoramidine have the opposite relative stereochemistry at the two vicinal quaternary carbon centers, which led us to devise a different strategy for the installation of the second quaternary carbon center. Although it was eventually found that the spirolactone alkylation strategy intended for the perophoramidine synthesis produces the relative stereochemistry of the communesins (see Section 2.2.4.), we initially investigated a different type of alkylation strategy for the communesins.

3.1. Intramolecular Alkylation Strategy

3.1.1. Retrosynthetic Analysis

From a retrosynthetic viewpoint, we believed that total syntheses of the communesins might be accomplished as shown in Scheme 34. For the sake of simplicity, the discussion here is focused on communesins A (1) and B (2). However, considering the similarities between all of the communesin congeners, the other metabolites are potentially accessible utilizing a similar strategy. Communesins A (1) and B (2) would be derived from olefin 163 through epoxidation, aminal deprotection and N-acylation of the
upper aminal. The stereoselectivity of the epoxidation will be controlled by the tertiary amine of the upper aminal by using CF$_3$CO$_2$H/CF$_3$CO$_2$H, which would both protect the amine from oxidation by salt formation and allow the salt to act as a directing group by hydrogen-bond formation with the peracid.$^{44}$ The azepine ring of 163 would be formed by a palladium-catalyzed substitution$^{45}$ of an allylic alcohol derivative 164, which will be obtained by a substrate-controlled diastereoselective reduction of unsaturated ketone 165.
A palladium catalyzed carbonylation/Stille coupling of triflate 166 would afford unsaturated ketone 165. The two aminal units of 166 could be installed from cis-fused tetracyclic lactone 167 through several functional group transformations. The cis-stereochemistry of lactone 167 would be secured by an intramolecular ester enolate alkylation of bromoacetal 168. The nearly planar structure of the enolate intermediate should prevent the bromoacetal chain from approaching from the face which would lead to the undesired trans fused system. Tricyclic bromoacetal 168 would be accessed from oxindole 169, which could be formed via a tandem Heck reaction/carbonylation strategy similar to that which was previously developed in our work on perophoramidine (10) (see Sections 1.4 and 2.2). The Heck precursor 170 would be obtained through ring opening of lactone 147 by iodoaniline 171. The C12a substituent of iodoaniline 171 would be an important functional handle for future manipulations.

3.1.2. Model Studies of Heck/Carbonylation Reaction

3.1.2.1. Chloride Substrate

Prior to undertaking a total synthesis of the communesins (1-9), we initiated some model studies on the key Heck/carbonylation reaction. Our first choice for a C12a substituent was a chlorine atom, which had previously been utilized as a substituent in the Heck substrate in our synthetic approach to perophoramidine (10) (see Sections 1.4 and 2.2). The desired chloro-substituted Heck precursor was obtained via the sequence shown in Scheme 35. Known iodonitrobenzene 172 was reduced to iodoaniline 173 using
iron in glacial acetic acid in 86\% yield.\textsuperscript{50} Synthesis of model Heck substrate 175 was accomplished through acylation of aniline 173 with readily accessible $\alpha$-methylcinnamic acid chloride (174) and subsequent $N$-methylation of the resulting amide 174 in good yield.

**Scheme 35**

Studies of the Heck/carbonylation reaction with the model chloro substrate 176 were examined extensively (Table 2). Unfortunately, the previously optimized conditions\textsuperscript{22b} that were used in the perophoramidine synthesis gave a slow reaction rate and low yield of product (entry 1). Different sets of conditions therefore were explored (entry 2-5). With Pd(OAc)$_2$ as catalyst, P($\alpha$-Tol)$_3$ as the ligand, NaOAc as base, DMA/MeOH (2/1) as solvent, under a CO atmosphere (1 atm) (entry 5) the desired oxindole 177 was obtained in 84 \% yield. Further optimization studies of the Heck/carbonylation reaction using different amounts of palladium catalyst and ligand were carried out (entries 6, 7). Reducing the amount of palladium catalyst from 20 mol\% to 10 mol\% decreased the product yield substantially (entry 6). Slightly better yields (85 \%) could be obtained using a 1:3 ratio of catalyst to ligand with 10 mol\% of Pd catalyst (entry 7).
The effect of varying the base in this reaction was also studied (entries 8, 9). These variations had a significant affect upon the product yield, and revealed that NaOAc is a better base than triethylamine or sodium carbonate. The use of additives, such as tetrabutylammonium bromide or tetrabutylammonium chloride, decreased the yield (entries 3, 4 and 10). Replacement of P(o-Tol)$_3$ with PPh$_3$ gave a slightly lower product yield (entry 11). Finally, a set of conditions using Pd(OAc)$_2$ (10 mol%), P(o-Tol)$_3$ (30 mol%), NaOAc (2.0 eq), DMA/MeOH (2/1), under a CO atmosphere (1 atm) (entry 7) was selected for the Heck/carbonylation reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(OAc)$_2$ (mol%)</th>
<th>Ligand (mol%)</th>
<th>Solvent</th>
<th>Additive (eq)</th>
<th>Base (eq)</th>
<th>Rx Time (h)</th>
<th>Recovered S.M. (%)$^a$</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>P(o-Tol)$_3$ (30)</td>
<td>DMA / MeOH (2 / 1)</td>
<td>n-Bu$_2$NBr (2.0)</td>
<td>NEt$_3$ (5.0)</td>
<td>66</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>P(o-Tol)$_3$ (30)</td>
<td>NMP / MeOH (2 / 1)</td>
<td>none</td>
<td>NaOAc (2.0)</td>
<td>48</td>
<td>trace</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>P(o-Tol)$_3$ (30)</td>
<td>NMP / MeOH (2 / 1)</td>
<td>n-Bu$_2$NBr (1.0)</td>
<td>NaOAc (2.0)</td>
<td>52</td>
<td>18</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>P(o-Tol)$_3$ (30)</td>
<td>NMP / MeOH (2 / 1)</td>
<td>n-Bu$_2$NCl (1.5)</td>
<td>NaOAc (2.0)</td>
<td>86</td>
<td>48</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
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<td>DMA / MeOH (2 / 1)</td>
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<td>NaOAc (2.0)</td>
<td>22</td>
<td>trace</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>P(o-Tol)$_3$ (30)</td>
<td>DMA / MeOH (2 / 1)</td>
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<td>NaOAc (2.0)</td>
<td>22</td>
<td>21</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>P(o-Tol)$_3$ (30)</td>
<td>DMA / MeOH (2 / 1)</td>
<td>none</td>
<td>NaOAc (2.0)</td>
<td>22</td>
<td>trace</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>P(o-Tol)$_3$ (30)</td>
<td>DMA / MeOH (2 / 1)</td>
<td>none</td>
<td>NEt$_3$ (5.0)</td>
<td>22</td>
<td>36</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>P(o-Tol)$_3$ (30)</td>
<td>DMA / MeOH (2 / 1)</td>
<td>none</td>
<td>Na$_2$CO$_3$ (2.0)</td>
<td>22</td>
<td>41</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>P(o-Tol)$_3$ (30)</td>
<td>DMA / MeOH (2 / 1)</td>
<td>n-Bu$_2$NBr (2.0)</td>
<td>NaOAc (2.0)</td>
<td>22</td>
<td>29</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>PPh$_3$ (30)</td>
<td>DMA / MeOH (2 / 1)</td>
<td>none</td>
<td>NaOAc (2.0)</td>
<td>22</td>
<td>14</td>
<td>77</td>
</tr>
</tbody>
</table>

$^a$ isolated yield.
3.1.2.2. Protected Phenolic Substrate

Based on the optimized Heck/carbonylation conditions, a study of C12a oxygen-substituted substrates was also conducted (Scheme 36). The synthesis of phenolic precursors started with protection of known iodophenol 178 as MOM ether 179, followed by reduction to yield iodoaniline 180 in good yield. Acylation of iodoaniline 180 with E-α-methylcinnamoyl chloride gave amide 181 in 77% yield, which on N-methylation using NaH and MeI gave the desired O-MOM N-methylamide 182 in 93% yield. However, under the Heck/carbonylation conditions which were optimized for the chloro substituted system, O-MOM protected amide 182 was converted to oxindole 185 in only 27% yield. The low yield obtained from this substrate might be due to the
electron donating nature of the O-MOM group, which is known to slow oxidative addition of palladium(0) into the aryl halide bond. We therefore decided to explore alternative systems having electron withdrawing O-protecting groups. Thus, the MOM group of 182 was removed under acidic conditions to give the phenol 183, and the hydroxyl group was treated with acetyl chloride, mesyl chloride and N,N-dimethylcarbamoyl chloride to give ester 184a, mesylate 184b and carbamate 184c, respectively, in high yields. Exposure of these C12a oxygen-substituted precursors (183-184) to the Heck/carbonylation conditions resulted in the desired oxindole products (185-189) in varied yields. Unprotected phenol 183 gave a very promising result, providing the desired product 186 in 57% yield as a mixture of diastereomers (dr 1:1). The diastereomeric mixture might result from epimerization by an intramolecular proton transfer between the phenol and the ester, since no epimerized product was detected for the other O-protected substrates. The acetyl protecting group of ester 184a was found to be incompatible with the Heck/carbonylation conditions, and gave a complex mixture including deprotected products. Mesylate 184b provided the Heck product only in very low yield. Finally, the carbamoyl-protected Heck substrate 184c gave the oxindole 189 in good yield (75%). This result might be due to both the stability and electron withdrawing character of the carbamoyl protecting group.

3.1.3. Heck/Carbonylation of Nitro Substrates
While we were examining model system for the Heck/carbonylation step and working on the optimization of the C12a substituent, we also investigated a Heck/carbonylation of C4a nitro substrates, which we had previously found to be problematic in related systems due to formation of reductive Heck products.

As the substituents at the C12a position, a chlorine and a MOM-protected hydroxyl group were first chosen because of their availability. The requisite Heck/carbonylation substrates 192 with a nitro substituent at C4a were formed in a straightforward manner from the lactone 147 (Scheme 37). Lactone ring opening with the aluminum amide of anilines 173 and 180 provided amides 190a and 190b in 95% and

**Scheme 37**

![Scheme 37 Diagram](image-url)
80% yield, respectively. Silyl protection of the hydroxyl group of 190, followed by N-methylation of the resulting amides 191, provided the Heck/carbonylation substrates 192 in good yields. Upon exposure to the optimized Heck/carbonylation conditions, the chloro substrate 192a gave the reductive Heck product 194a as the major product in 44% yield, along with the desired oxindole ester 193a in only 22% yield as a mixture of diastereomers (dr = 2.7:1). The Heck/carbonylation of the O-MOM-protected substrate did not go to completion and afforded a mixture of starting material and the two expected products (192b:193b:194b = 0.5:1:0.8).

3.1.4. Heck/Carbonylation of C4a-Protected Anilines

The disappointing results in the Heck/carbonylation reactions of the nitro substrates prompted us to examine same protected aniline substrates. In previous work in our group,\textsuperscript{22b} amide, carbamate or phthalimide protected amines had been tested in some related systems. However, the Heck/carbonylation reaction of these protected aniline substrates resulted in very low yields of the desired products or decomposition of the starting materials. Therefore, we decided to use aniline protecting groups such as triazenes\textsuperscript{52} and triazinones,\textsuperscript{53} which are known to be stable in palladium catalyzed coupling reactions.

Preparation of the protected aniline substrates commenced with reduction of the nitro lactone 147 under mild conditions to aniline 195 (Scheme 38). A triazene protecting group was introduced via diazotization with NaNO\textsubscript{2} and H\textsubscript{2}SO\textsubscript{4} in DMSO, followed by
reaction of the resulting diazonium salt with pyrrolidine to give aryl triazene 196a in 89% yield. Triazinone 196b could also be obtained from 195 using mild acid catalyzed dehydration conditions with $N,N'$-dimethylurea, HCHO and PPTS in 86% yield.

Scheme 38

An aniline counterpart was prepared from phenol 178, based on the previous protecting group study (Scheme 39). Thus, a $N,N$-dimethylcarbamate protecting group was introduced to give nitrobenzene 197, which was reduced with iron and acetic acid to afford carbamate aniline 198 in 93% yield.

Scheme 39
With both the aniline 198 and the lactones 196a/b in hand, we could access the desired Heck/carbonylation substrates 201 through the previously optimized synthetic sequences (Scheme 40). Thus, lactone ring opening with the aluminum amide of aniline 198 provided amides 199a/b, which were converted to the desired substrates 201a/b through TBDMS protection of the hydroxyl group and N-methylation of the amide in good overall yields. Unfortunately, upon the exposure of protected aniline substrates 201 to the optimum Heck/carbonylation conditions, only complex mixtures were produced including unreacted starting materials and compounds bearing deprotected aniline moieties, which suggested that these protecting groups are incompatible with our

**Scheme 40**

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \quad \text{N} \\
&\text{R} \\
&\text{Me}_2\text{N} \\
&\text{I} \\
&\text{NH}_2 \\
&\text{Me}_2\text{N} \\
&\text{O}
\end{align*}
\]
Heck/carbonylation conditions.

3.1.5. Hydroxymethyl Substrates for Curtius Rearrangement Strategy

The above disappointing results led us to next examine a Curtius rearrangement strategy, which had proven to be a promising solution for the reductive Heck problem encountered during our synthetic studies on perophoramidine (see Section 2.1.). However, we needed to devise a new functional handle at the C4a position in place of the methoxy group used in the perophoramidine study, which was discovered to be problematic in the late-stage demethylation step (see Section 2.1.3). We envisioned that solution might be to use a protected hydroxymethyl group, which could be transformed to an amine derivative through deprotection, oxidation to the carboxylic acid and Curtius rearrangement at a late stage. The protecting group for the hydroxymethyl functionality needed to be compatible with various reaction conditions prior to the deprotection step.

3.1.5.1. TBDMS-Protected Hydroxymethyl Derivatives

A TBDMS group was initially chosen as a protecting group for the hydroxymethyl functionality. The synthesis commenced with a Wittig reaction of known lactol 203\textsuperscript{51} and phosphonium ylide 204,\textsuperscript{55} affording \(\alpha\)-benzylidene lactone 205 in 89% yield (Scheme 41). The hydroxyl group of 205 was protected as the TBDMS ether 206, followed by opening of the lactone ring with the aluminum amide of aniline 198 to provide unsaturated amide 207 in good yield. The hydroxyl group of the resulting amide
207 was protected as the MOM ether 208, which was converted to Heck/carbonylation substrate 209 by N-methylation of the amide in 96% yield.

As we hoped, using the previously optimized Heck/carbonylation conditions allowed conversion of N-methyl amide 209 to the desired oxindole 210 in moderate yield (Scheme 43). To continue the synthesis of tricyclic lactone intermediate 167 (Cf. Scheme 34), hydrolytic cleavage of the N,N-dimethylcarbamoyl group of 210 was first attempted by treatment with 1 N NaOH in refluxing alcoholic solvent. However, this reaction provided a complex mixture, in which the major product was identified as desilylated acid 212 instead of the desired phenol acid 211.
3.1.5.2. PMP-Protected Hydroxymethyl Derivatives

The instability of the TBDMS group in the carbamoyl removal step led us to look for another protecting group that would be compatible with the basic hydrolysis conditions. Thus, the hydroxyl group of lactone 205 was protected as the PMP ether 213 using Mitsunobu conditions in 97% yield (Scheme 43). PMP-protected Heck/carbonylation substrate 216 was then synthesized from lactone 213 via the same synthetic sequence used previously (i.e. aminolysis, O-MOM protection and N-methylation) in good overall yield. Under the optimized Heck/carbonylation conditions, amide 216 was converted oxindole 217 in 79% yield.
Alcoholysis of the carbamoyl group of 217 with several alkoxydes was explored next, which provided phenolic esters 218 (Scheme 44). However, under acid catalysis, no tricyclic lactone product 219 was formed from phenolic esters 218. However, the desired tricyclic lactone 219 could be obtained through ester hydrolysis and EDC coupling of the resulting hydroxy acid (84% yield for 2 steps, dr = 3:1).

After successful formation of the desired tricyclic ring system 219, we next tried to manipulate the MOM-protected hydroxyl group to form the requisite bromoacetal functionality needed for the internal lactone alkylation (Cf. 167, Scheme 34). Toward this end, the MOM group of tricyclic lactone 219 was removed with HCl in MeOH at 50 °C, but rather than provide the desired alcohol afforded the undesired spiro lactone 221 and dihydroxy methyl ester 222 in 44 and 40% yields respectively.
This instability of the tricyclic δ-lactone under the acidic conditions required for deprotection led us to replace the MOM protecting group with a benzyl group, which should be removable under neutral hydrogenolysis conditions. Thus, O-benzylation of amide 214 was achieved using benzyl 2,2,2-trichloroacetimidate under acidic conditions in moderate yield. After N-methylation of amide 223, the resulting N-methyl amide 224 was exposed to the Heck/carbonylation conditions to afford oxindole 225 in good yield, which was converted to tricyclic δ-lactone 226 through a two-step sequence in 74% yield. Debenzylation of 226 under neutral catalytic hydrogenolysis conditions, however, again
provided undesired spirolactone 221 as the sole product in 66% yield as a mixture of diastereomers (dr = 1:1) rather than the desired hydroxy tricyclic lactone 220.

**Scheme 45**

3.1.5.3. Intermolecular Alkylation Strategy

Since we were unable to access the intramolecular alkylation substrate 167 (Cf. Scheme 34), we decided to investigate intermolecular alkylation of some of our intermediates. Alkylation of tricyclic lactone 219 was first attempted under various conditions (Scheme 46) but, unfortunately, only led to a mixture of unidentifiable decomposition products.
We next decided to test the intermolecular alkylation of spirolactone 228, which could be prepared from ester 217 via MOM-deprotection under acidic conditions, followed by subsequent lactonization, in 70% yield, along with uncyclized hydroxy ester 229 as a minor product (Scheme 47). Surprisingly, upon treatment of 228 with NaH and allyl iodide at room temperature, O-allyl ketene acetal 230 was obtained in 63% yield, rather than the expected C-allyl lactone 231. However, thermal Claisen rearrangement of 230 gave C-allylated products 231a/b in good yield as a mixture of diastereomers. Interestingly, a solvent effect on the ratio of the two diastereomers was observed in this reaction. The rearrangement reaction in polar solvent (DMF) gave a lower selectivity (dr = 2.3:1) compared to that of the reaction in nonpolar solvent (toluene) (dr = 9.8:1) at the same temperature. We do not have a good explanation for this solvent effect at this time. In addition, the relative stereochemistry of the two diastereomers 231a/b could not be established. However, based on analogy with later studies on other related allyl spirolactones (see Section 3.3.2.), we believe that the relative stereochemistry of the major diastereomer is 231a as shown in Scheme 47. Even though the stereochemistry of
allyl lactones 231 was uncertain, we decided to further explore this spirolactone alkylation strategy for the installation of the second quaternary carbon center (*vide infra*).

**Scheme 47**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
<th>Diastereomeric ratio (231a : 231b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>110</td>
<td>84</td>
<td>2.3 : 1</td>
</tr>
<tr>
<td>toluene</td>
<td>reflux</td>
<td>84</td>
<td>9.8 : 1</td>
</tr>
</tbody>
</table>
3.2. Second Generation Synthetic Strategy

Since the intramolecular alkylation strategy turned out to be unsuccessful, we needed to devise a new strategy for the installation of the second quaternary carbon center. At that time, we determined that alkylation of spirolactone 155 in fact provided the allyl lactone 156 having the cis communesin relative stereochemistry at the vicinal quaternary carbon centers (Cf. Scheme 32). In addition, as discussed above, O-alkylation and subsequent thermal Claisen rearrangement of spirolactone 228 afforded C-allyl lactones 231 with promising levels of diastereoselectivity (Cf. Scheme 47). Based on these results, we decided to utilize the spirolactone alkylation strategy for introduction of the second quaternary center of the communesins.

The functional handle at the C12a position was also reconsidered. In our initial plan, an isoprenyl unit was to be introduced at a late stage of the synthesis, which we felt might be hampered by the congested nature of the polycyclic system (Cf. Scheme 34). Thus, we decided to use a hydroxymethyl group as a new functional handle, which would give us more flexibility in manipulating the C12a substituent.

3.2.1 Revised Retrosynthetic Analysis

Retrosynthetically, communesins A (1) and B (2) would be formed from bis-aminal 232 by a Michael type addition of an amino group of the “northern” aminal moiety to an α,β-unsaturated ester, followed by manipulation of the resulting ester side
chain (Scheme 48). Bis-aminal 232 would be obtained from allyl lactone 233 through several functional group transformations, including bis-aminal formation. Allyl lactone 233 might be prepared from ester 234 via spirolactone formation and C-alkylation. The relative stereochemistry of 233 was expected to be as shown based on the stereochemical outcome of alkylations with similar substrates in our previous study (see Section 2.2.4.). Ester 234 would be accessible via a Heck/carbonylation of unsaturated amide 235, which could be prepared from aniline 236 and γ-lactone 237. The precursor of the amine functionality at C4a in 236 would be a nitro group, which would be the most efficient substituent for transformation to the requisite amine functionality later in the synthesis, but is also prone to inducing formation of the undesired reductive Heck product in the key Heck/carbonylation step. An alternative C4a substituent might be a protected
hydroxymethyl substituent, which could be transformed to an amine via a straightforward synthetic sequence including a Curtius rearrangement.

3.2.2. Reinvestigation of the Heck/Carbonylation Reaction of Nitroaryl Substrates

Since a successful optimization of the Heck/carbonylation step in nitro group-containing substrates 76 had been achieved in the previous synthetic studies on perophoramidine (see Section 2.2.3.), we decided to investigate the same approach in the communesin series.

The second generation synthetic approach to the communesins commenced with the synthesis of protected hydroxymethyl aniline 240, which was prepared from known benzyl alcohol 238 through PMP protection and reduction of the nitro group of the resulting O-PMP ether 239 in good yield (Scheme 49). Aminolysis of lactone 147 with the aluminum amide reagent from aniline 240 afforded amide 241 in 67% yield. The hydroxyl group of 241 was protected as the TBDMS ether 242 in 98% yield, followed by N-methylation of the amide to give Heck/carbonylation substrate 243 in 89% yield.

To find the optimal Heck/carbonylation conditions for the nitro-containing communesin substrate 243, we tested various reaction conditions with combinations of palladium catalysts (Pd(OAc)$_2$, Pd$_2$(dba)$_3$, Pd(dba)$_2$), phosphine ligands (P(o-Tol)$_3$, P(t-Bu)$_3$, biphénylPCy$_2$), bases (NEt$_3$, NaOAc, KOAc, Ag$_2$CO$_3$, MeNCy$_2$, Cs$_2$CO$_3$, K$_3$PO$_4$), additives ($n$-Bu$_4$NBr, $n$-Bu$_4$NCl, AgNO$_3$), cosolvents with MeOH (DMA, DMF, dioxane, toluene, acetonitrile) and different pressures of CO (1 atm, 500 psi). Unfortunately, none
of these conditions gave promising results. In most cases, the reaction did not go to completion and/or provided significant amounts of the reductive Heck product 245 and uncyclized ester 246 along with the desired product 244 as a mixture of diastereomers. The best result was achieved with Pd(dba)$_2$, NaOAc, biphenylPCy$_2$, DMA/MeOH and CO (1 atm) to give the desired ester 244 but in only 28% crude yield.
In an effort to increase the reactivity of Heck/carbonylation substrate, we decided to introduce an ester functionality instead of a hydroxymethyl group at the C12a position, since electron withdrawing substituents on the aryl halide are known to facilitate the oxidative addition of palladium(0). Thus, benzyl alcohol 238 was first protected as the TBDMS ether 245 in quantitative yield (Scheme 50). Reduction of the nitro group and aminolysis of 147 with the resulting aluminum amide of aniline 246 gave amide 247 in good yield. The hydroxyl group of amide 247 was protected as the benzyl ether 248 in
unoptimized 35% yield, followed by amide N-methylation to give N-methyl amide 249. After desilylation of 249, the resulting benzyl alcohol 250 was oxidized to methyl ester 251 via a two-step oxidation procedure with MnO₂. However, under several Heck/carbonylation reaction conditions, ester 251 was converted to desired diester 252 in less than 10% yield.

3.2.3. Attempted Intramolecular C-Acylation of Reductive Heck Product 245

As mentioned above, despite extensive optimization efforts, the Heck/carbonylation reaction of nitro substrate 243 provided a mixture of the desired product 244 and reductive Heck product 245 (Cf. Scheme 49). We envisioned that the reductive Heck product 245 might be utilized for synthesis of the key intermediate spirolactone 255 via an intramolecular acylation at the benzylic methylene carbon ortho to the nitro group (Scheme 51). During optimization of the Heck/carbonylation of 243, reductive Heck product 245 was formed as the sole product in 76% yield, thus making this compound efficiently accessible (condition A). Moreover under traditional reductive Heck conditions with sodium formate as a hydride donor, N-methyl amide 243 was also converted to 245 in good yield (condition B). After removal of the TBDMS group from 245, the resulting hydroxyl group of 253 was activated in situ with CDI to the corresponding imidazolo carbonate, which was then treated with NaH to effect intramolecular acylation at the benzylic position. However, only starting material or decomposition products were isolated. Alternatively, alcohol 253 was transformed to
ethyl carbonate 254a and phenyl carbonate 254b in 84 and 94% yields, respectively. However, all efforts to cyclize these carbonates 254 to spirolactone 255 with various bases were fruitless.

3.2.4. Hydroxymethyl Substrates for Curtius Rearrangement Strategy

The above disappointing results with substrates bearing a nitro group at C4a led us to investigate a hydroxymethyl substituent, which could be transformed to an amine functionality utilizing a Curtius rearrangement. Thus, benzyl alcohol 238 was first protected as the benzyl ether 256, followed by nitro group reduction to afford aniline 257
in good yield (Scheme 52). Ring opening of lactone 213 with the aluminum amide of aniline 257 provide amide 258, which was protected as the TBDMS ether 259, followed by N-methylation of amide 259 to give N-methyl amide 260. After some effort to find optimal conditions for the Heck/carbonylation of 260, the desired oxindole ester 261 was obtained in 71% yield.

Scheme 52
Upon treatment of ester 261 with TBAF, desilylation and concomitant lactonization occurred to afford spirolactone 262 in 85% yield as a mixture of diastereomers (dr = 2:1) (Scheme 53). Allylation of 262 at room temperature with NaH and allyl iodide afforded O-allyl ketene acetal 263 in 57% yield (71% based on recovered starting material). Upon thermolysis, C-allyl spirolactones 264a and 264b were formed via Claisen rearrangement from O-allyl ketene acetal 263 with moderate diastereoselectivity. As before (Cf. Scheme 47), solvent effects on the diastereoselectivity of the rearrangement were observed. Thus, in DMF a 3.3:1 of diastereomeric ratio was observed and in toluene a similar but lower diastereomeric ratio (2.2:1) was obtained. The relative stereochemistry of the minor diastereomer 264b was confirmed by a NOESY study, which showed a strong nOe correlation between the two methylene protons shown.

**Scheme 53**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Diastereomeric Ratio 264a : 264b</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>130</td>
<td>15</td>
<td>77</td>
<td>3.3 : 1</td>
</tr>
<tr>
<td>toluene</td>
<td>130(^a)</td>
<td>15</td>
<td>74</td>
<td>2.2 : 1</td>
</tr>
</tbody>
</table>

\(^a\) sealed tube
Since alkylation of spirolactone 263 showed just moderate diastereoselectivity, we decided to explore the alkylation of other easily accessible related lactones with the hope of achieving better selectivity. We decided to prepare tricyclic lactone 266, which is similar to previously synthesized tricyclic lactone 219 (Cf. Scheme 46), the compound that was not stable to base-promoted alkylation. We expected that lactone 266, however, would be compatible with the alkylation conditions because it contains a less strained ring system than 219. Thus, the benzyl group of ester 261 was removed by catalytic hydrogenolysis and the resulting hydroxy ester 265 was converted to the desired tricyclic lactone 266 through hydrolysis with LiOH and intramolecular EDC coupling of the resulting hydroxy acid (60% yield for the two steps) (Scheme 54). As we expected, in
This case we were able to isolate O-allyl ketene acetal 267 from the alkylation of tricyclic lactone 266, albeit in low yield. However, thermal Claisen rearrangement of O-allyl ketene acetal 267 provided C-allyl lactone 268 in 59% yield but with only moderate diastereoselectivity (dr = 2:1).

Another lactone 269 was prepared in 62% overall yield by removal of the PMP group of 262, followed by translactonization under basic conditions (Scheme 55). After TBDMS protection of the hydroxyl group of 269, the resulting lactone 270 was exposed to the standard alkylation conditions, but gave none of the desired O-allyl ketene acetal 271 or C-allyl lactone 272.

**Scheme 55**

3.2.6. Exploration of C4a Brominated Substrates
Another alternative substituent at the C4a position which we examined was bromine, with the hope that the halogen could be eventually transformed to an amine functionality via a palladium- or copper-catalyzed N-arylation of an amine, amide or sulfonamide.\textsuperscript{61} Thus, Wittig reaction of commercially available 2-bromobenzaldehyde (273) with phosphonium ylide 204 provided \(\gamma\)-lactone 274, which underwent aminolysis with the aluminum amide reagent from aniline 257 to give unsaturated amide 275 in 78% yield. Protection of the hydroxyl group of 275 as the TBDMS ether 276, followed by N-methylation afforded the Heck/carbonylation substrate 277. Under the previously optimized conditions, \(N\)-methyl amide 277 was converted to a mixture of the desired
oxindole ester 278 and the unwanted diester 279 in 49 and 10% yields, respectively.

Desilylation of ester 278 gave spirolactone 280 via lactonization of the corresponding hydroxy ester. Unfortunately, bromo spirolactone 280 could not be allylated under the alkylation conditions previously used.

3.2.7. Rationale for the Diastereoselectivity of Spirolactone Alkylations

As discussed above, we have investigated alkylation of several spirolactone substrates, some of which provided the desired C-allyl δ-lactones with various degrees of diastereoselectivity (Figure 6). Thus, allyl lactones 82 and 156 were obtained as single diastereomers, but allyl lactones 231 and 264 were formed as mixtures of diastereomers with moderate diastereoselectivities.

Figure 6. Summary of spirolactone alkylation stereochemistry

To rationalize the differences in diastereoselectivity among the various lactones, we first considered the alkylation mechanism, which we believe in all cases involve initial O-alkylations followed by Claisen rearrangements. Although in the cases of the former two allyl lactones (82, 156), the corresponding ketene acetals have not actually been
isolated, careful monitoring of the alkylation reactions by TLC, which showed transient formation of these ketene intermediates, suggested that these compounds, like 231 and 264, are also formed through an initial O-allylation and subsequent thermal Claisen rearrangement.

We have considered four possible half-chair transition state conformations for the Claisen rearrangement of the ketene acetal intermediates (Figure 7), where the carbonyl group of the oxindole moiety can occupy either pseudoaxial (A) or pseudoequatorial (E) positions. In addition, each transition state has two possible atropisomers (α and β) derived from the position of the substituent (R) at C10 in the C-ring aryl moiety. It seems reasonable that the allyl group approaches the ketene acetal double bond from the face opposite this substituent in order to avoid severe steric interactions. Since axial attack of the allyl group is stereoelectronically more favorable, transition state A-β and E-α are expected to be preferable to conformations A-α and E-β. In addition, it appears from inspection of molecular models that the aryl group of the oxindole moiety blocks attack of the allyl substituent more effectively than does the carbonyl group, and therefore transition state E-α would seem to be favored over A-β. Steric interactions and/or electronic repulsions between the carbonyl group and the substituent R (OMe or NO₂)

Figure 7. Transition states of Claisen rearrangement for 82 and 156
may additionally destabilize conformation A-β.

For the other two allyl lactones 231 and 264, we propose four similar transition state conformations. For the same reasons discussed above, A-α and E-β can be ruled out as preferable conformations. One of the striking differences between 231 and 264, and the other two systems 82 and 156 is that latter two compounds have substituents R” at C12a. As shown in Figure 8, this R” substituent causes substantial steric interactions not only with substituent R in E-α, but also with the O-allyl group in A-β. These steric interactions presumably slow the thermal Claisen rearrangements of the latter two ketene acetals, making these species more easily isolable, and also lead to generally low stereoselectivities. At this point, however, we are unable to explain the solvent differences observed with DMF and toluene.

**Figure 8.** Transition states of Claisen rearrangement for 231 and 264

![Transition states](image)

R = CH₂OPMP
R’ = O₂CNMe₂, CH₂OBn
3.3. Third Generation Synthetic Strategy

As discussed above, allylation of various spirolactones provided the products as mixtures of diastereomers with only moderate selectivities. These results led us to devise a potentially more selective alkylation strategy for installation of the second quaternary carbon center of the communesins. We also required a solution for the incompatibility of the nitro substituent at C4a in the D ring to the tandem Heck/carbonylation reaction conditions, although the Curtius rearrangement strategy, using a hydroxymethyl substituent at C4a has proven to be an alternative. Our efforts to solve these two problems are reflected in a third generation synthetic strategy for the communesins.

3.3.1. Revised Retrosynthetic Analysis

Retrosynthetically, communesins A (1) and B (2) would be obtained from bis-aminal 282 through manipulation of a C12a substituent, azepine ring formation and several functional group transformations (Scheme 57). The bis-aminal 282 would be synthesized from pentacyclic allyl lactone 283 via introduction of two amine functionalities needed for rings E and F, and subsequent cyclization. Allylation of pentacyclic lactone 285 would provide allyl lactone 283, presumably via initial O-allylation and subsequent thermal Claisen rearrangement as discussed above (see Section 3.2.7.). The stereochemistry of 283 would be secured by the facial selectivity of the rearrangement of O-allylketene acetal intermediate 284. The cup shape of the molecule
should force this thermal [3,3]-sigmatropic rearrangement of 284 to occur from the convex face of the pentacyclic ring system. A similar alkylation strategy was subsequently reported in Qin’s total synthesis of communesin F (9).[^9] Pentacycle 285 would be formed from oxindole 286 through “southern” aminal formation, followed by installation of the “northern” lactone functionality. The oxindole 286 would be formed from amide 287 utilizing a standard Heck reaction instead of the tandem Heck/carbonylation sequence which had been used for oxindole formation in our previous studies. We believe that avoiding the carbonylation step might solve the
problem of formation of the reductive Heck products from the nitro substrates. This substrate has C9, which becomes the carbonyl carbon of the lactone, built into the molecule. However, this strategy requires that the Heck precursors have a tetrasubstituted alkene moiety, which is rarely found in substrates for intramolecular Heck reactions due to the inherent steric strain in such alkenes. Heck substrate 287 would be obtained through ring opening of lactone 288 by iodoaniline 236. Acetophenone derivative 289 would be a possible precursor for the desired olefinic γ-lactone 288.

3.3.2. Intramolecular Heck Reaction of a Tetrasubstituted Alkene

The new synthetic strategy commenced with a Rubottom oxidation of commercially available o-nitroacetophenone (290) to give α-hydroxyketone 291 in moderate yield (Scheme 58). The hydroxyl group of 291 was protected as the benzyl ether 292 by treatment with a benzyl 2,2,2,-trichloroacetimidate under acidic conditions in 71% yield. Unfortunately, all efforts to form tetrasubstituted alkenyl γ-lactone 294 from ketone 292 using phosphonium ylide 204 or phosphonate 293 under various conditions failed.

![Scheme 58]

290 291 292 294 293 204
Thus, we decided to explore the formation of a tetrasubstituted olefin from \( o \)-nitroacetophenone (290) prior to the introduction of the \( \alpha \)-hydroxyl group. After some effort, it was found that treatment of the ketone 290 with excess phosphonate 293 and NaH in refluxing THF provided the desired \( \gamma \)-lactone 295 in 40% yield (89% based on recovered starting material) as a 3:1 mixture of Z/E isomers (Scheme 59). The stereochemistry of the major isomer was confirmed as Z based on a NOESY study, which showed a nOe correlation between the methyl and methylene protons at the \( \beta \)-position of the \( \gamma \)-lactone moiety. In an effort to introduce an oxygen into the methyl group, allylic oxidation of \( \gamma \)-lactone 295 utilizing selenium dioxide was investigated. However, none of
the desired alcohol 296 was produced. We therefore decided to continue the synthesis with the tetrasubstituted alkenyl γ-lactone 295 with the hope that installation of a heteroatom at C9 would be possible at a later stage of the synthesis.

Thus, lactone ring opening of 295 with the dimethylaluminum amide reagent prepared from aniline 240 provided amide 297 in 94% yield. The hydroxyl group of 297 was protected as the TBDMS ether 298, followed by N-methylation to give N-methyl amide 299 in good yield. After some effort to find the optimal conditions for the Heck reaction of 299, the desired oxindole 300 could be obtained in 69% yield. However, reduction of the nitro group of 300 with iron in glacial acetic acid at 60 °C to form aniline 301 did not go to completion. Additionally, exposure of nitroarene 300 to reduction conditions involving strong acid or high temperatures gave a significant amount of desilylated side products.

The instability of the TBDMS group under the harsh reduction conditions led us to replace this group with a more acid-stable benzyl ether moiety (Scheme 60). Thus, from the amide 297, O-benzyl protected Heck substrate 302 was prepared through silver oxide-mediated O-benzylation, followed by N-methylation of the resulting amide benzyl ether 302. Using the previously optimized Heck reaction conditions, α,β-unsaturated N-methyl amide 303 was then converted to oxindole 304 in 84% yield. The nitro group of 304 was successfully reduced by treatment with iron in refluxing methanolic HCl to give aniline 305 in 86% yield. The aniline 305 was also produced in quantitative yield under mild reduction conditions using Cu(acac)₂ and NaBH₄.
3.3.3. Formation of the “Southern” Aminal

With the aniline 305 in hand, we next investigated formation of the “southern” aminal functional group through a reductive cyclization using various reducing agents (Scheme 61). Interestingly, upon exposure of the aniline lactam 305 to LiAlH₄ or Red-Al,
amidine 306, rather than a desired aminal 307, was isolated as the sole product in 46 and 74% yields, respectively. Reductive cyclization of 305 by treatment with alane (AlH₃), which was either prepared in situ (LiAlH₄/AlCl₃) or was obtained as the commercially available complex AlH₃·MeNEt₂, provided mixtures of the amidine 306 and the aminal 307 in ratios of 3:2 and 3:1, respectively. Treatment of 305 with DIBALH at low temperature (-78 °C) provided 1:1 mixture of the amidine 306 and the aminal 307. Finally, DIBALH reduction of 305 at 0 °C afforded the desired aminal 307 in 54% yield along with over-reduced indoline 308 in 40% yield.

In an attempt to solve the above reduction problem, aniline 305 was first converted to carbamate 309 in 74% yield (Scheme 62). Upon exposure of lactam carbamate 309 to Red-Al at room temperature, however, N-methylaniline 310 and N,N’-dimethylaminal 311 were formed in 44 and 33% yields, respectively. The incompatibility of the carbamate group to the reductive cyclization conditions with Red-Al led us to next

Scheme 62
explore the N-benzyl aniline 312, which was prepared in good yield utilizing a reductive alkylation with benzaldehyde.\textsuperscript{70} To our delight, treatment of 312 with LiAlH\textsubscript{4} afforded the desired N-benzyl aminal 313 in 57\% yield.

In an effort to find an even more efficient route for the formation of the “southern” aminal, an alternative two-step approach to aminal 307 was developed (Scheme 63). Thus, under acid-catalyzed dehydration conditions, aniline 305 was first converted to the amidine 306 in good yield, which was quantitatively reduced to the aminal 307 by treatment with DIBALH at 0 °C. The structure of 307 was confirmed by 2D NMR studies (HMQC, HMBC, NOESY). In particular, the stereochemistry at the ring junction was established as \textit{cis} based on a NOESY study, which showed a correlation between the aminal and methylene protons of the benzyloxyethyl substituent as shown in 307a. The free amino group of aminal 307 was subsequently protected as the carbamate 314 in 95\% yield.

\begin{center}
\textbf{Scheme 63}
\end{center}
3.3.4. Attempted Functionalization of the Exo-Olefin Moiety

After successful syntheses of the two tetracyclic aminals 313 and 314, we next explored the oxidation of the *exo*-methylene carbon in order to form the requisite pentacyclic lactone 285 (Cf. Scheme 57). Therefore, the *N*-benzyl aminal 313 was first treated with various borane reagents, followed by oxidative work-up with hydrogen peroxide. Unfortunately, none of these borane reagents afforded the desired alcohol 315, resulting only in recovery of the unreacted *exo*-methylene aminal 313. We believe this disappointing result might be due to the tertiary amine functionality in *N*-benzyl aminal 313, which may be forming unreactive complexes with the borane reagents.

Thus, carbamate-protected aminal 314 was next tested. Under the hydroboration conditions, the carbamate 314 was indeed converted to the desired alcohol 316, but this compound rapidly rearranged to tricyclic *N*,*O*-acetal 317 upon silica-gel column chromatography, or upon standing in dichloromethane at room temperature overnight. Interestingly, attempted hydrolytic removal of the carbamate group of 317 provided the desired rearranged hydroxymethyl aminal 318 in good yield.
Oxidation of the hydroxyl group of 318 was next attempted with several reagents, but these experiments provided none of the desired aldehyde 319. A one pot conversion of olefin 314 to aldehyde 320 utilizing hydroboration/NMO-TPAP oxidation\textsuperscript{71} was also tried, but was unsuccessful. In addition, oxidation of the crude hydroxymethyl aminal 316 did not provide the desired aldehyde 320. Other oxidation reactions, such as epoxidation or dihydroxylation, were also investigated with \textit{exo}-methylene aminal 314, but all of these efforts were fruitless.

\textbf{Scheme 65}
3.4. Fourth Generation Tetrahydropyridine Strategy

3.4.1. Revised Retrosynthetic Analysis

Since the manipulation of the \textit{exo}-methylene carbon of tetracyclic aminal 314 to the corresponding carbonyl compound proved to be problematic, we therefore decided to devise a new Heck substrate in which a requisite heteroatom at C9 is already installed (Scheme 66). First, tetrahydropyran intermediate 321 was deduced from the previously planned substrate 287 (Cf. Scheme 57) with the hope that such a cyclic substrate might be synthetically more accessible than acyclic system 287, whose synthesis was unsuccessful (see Section 3.3.2.). Further considerations of synthetic ease and efficiency led us replace the oxygen of 321 by a nitrogen atom. Thus, a tetrahydropyridine intermediate like 322 was selected as the new Heck substrate.

\textbf{Scheme 66}

\begin{center}
\includegraphics[width=\textwidth]{scheme66.png}
\end{center}

The revised retrosynthetic plan utilizing the Heck substrate 322 is shown in Scheme 67. As discussed in the previous retrosynthetic analysis, communesins A (1) and B (2) would be formed from bis-aminal 282 (Cf. Scheme 57). The advanced intermediate
282 would be obtained from pentacyclic allyl imine 323 through manipulation of the olefin moiety and “northern” aminal formation. The allyl group of 323 would be introduced into pentacycle 324 via an enamine alkylation. The stereoselectivity of this alkylation step would be controlled by the cup-shape of the pentacyclic ring system (see 324a), which would allow the electrophile to approach only from the convex face. The “southern” aminal of pentacycle 324 would be installed from oxindole 325 via reduction of the nitro group, followed by reductive cyclization onto the lactam. Oxindole 325 would be provided by the Heck reaction of the tetrahydropyridine substrate 322, which would be accessible by coupling aniline 236 with carboxylic acid derivative 326.
3.4.2. Synthesis of Tetrahydropyridine Heck Substrates

Synthesis of a Heck substrate bearing a tetrahydropyridine ring system started with the Suzuki coupling \(^{72}\) of known triflate 327\(^{73}\) with commercially available 2-nitrobenzeneboronic acid (328) to provide ester 329 in 94% yield (Scheme 68). However, attempted aminolysis of 329 with the dimethylaluminum or sodium amide of the aniline 240 was unsuccessful. Thus, we decided to explore amide formation by coupling of the corresponding carboxylic acid and aniline 240. Unfortunately, basic hydrolysis of ester 329 afforded a mixture of olefin isomers 331a and 331b with the major isomer being the undesired \(\gamma,\delta\)-unsaturated ester 331a. We believed that the electron withdrawing character of the \(N\)-Boc group acidifies the protons at the \(\gamma\)-position of the \(\alpha,\beta\)-unsaturated ester, which would facilitate base-induced olefin migration. Thus, we decided to replace the Boc group with a benzyl protecting group.

Towards this end, under the same Suzuki coupling conditions, known \(N\)-benzyl
triflate 332 was converted to aryl ester 333 in 100% yield (Scheme 69). Aminolysis of ester 333 with the dimethylaluminum or sodium amide of aniline 240 was again unsuccessful. However, in this case, hydrolysis of ester 333 using LiOH in MeOH/H2O at 50 °C provided the desired α,β-unsaturated carboxylic acid 334 in excellent yield. Coupling reagents such as EDC and the Mukaiyama reagent were not effective for the formation of amide 335 from acid 334 and aniline 240. It was finally found that the desired amide 335 could be obtained in 79% yield by treatment of aniline 240 with the acid chloride derived from acid 334. N-Methylation of amide 335 then afforded the N-benzyl Heck substrate 336 in 96% yield. In addition, upon treatment with ethyl chloroformate in CH2Cl2, N-benzyl substrate 336 was converted quantitatively to the carbamate-protected Heck substrate 337.

3.4.3. Heck Reactions of Tetrahydropyridine Substrates

Scheme 69
With the two substrates 336 and 337 in hand, we next explored the intramolecular Heck reactions of these compounds. After some effort to find the optimal experimental conditions, substrates 336 and 337 could be converted to the desired oxindoles 338 and 339 in 64 and 78% yields, respectively, as shown in Scheme 70.

**Scheme 70**

![Scheme 70 diagram]

3.4.4. Reduction of the C4a Nitro Group

We next investigated the reduction of nitroenamide 339, which was selected as the preferred intermediate for further study because of its higher yield of formation in the Heck reaction and potentially better compatibility to various reduction conditions than N-benzyl enamine 338. Thus, upon treatment of enamide 339 with Cu(acac)\(_2\) and NaBH\(_4\) in EtOH, which was found to be the best conditions for reducing the previous substrate 304 (Cf. Scheme 60), the desired aniline 340 was formed in only 19% yield, along with N-hydroxyindole 341 as the major product in 49% yield (Scheme 71). Alternative reduction conditions (SnCl\(_4\)/NaBH\(_4\)) provided the desired aniline 340 and by-product 341 in 41 and 44% yields, respectively. Interestingly, under catalytic hydrogenation conditions with
Pd/C in EtOH, N-ethylaniline 342 was obtained from 339 as the sole product in good yield. This compound probably results from a reductive alkylation of aniline 340 with adventitiously formed acetaldehyde.\textsuperscript{77} To avoid the formation of the N-ethylaniline 342, the catalytic hydrogenation was instead conducted in THF, which did provide the desired aniline 340 in 82\% yield.

\textbf{Scheme 71}

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(acac)\textsubscript{2}, NaBH\textsubscript{4}, EtOH</td>
<td>19</td>
</tr>
<tr>
<td>SnCl\textsubscript{2}, NaBH\textsubscript{4}, THF/EtOH</td>
<td>41</td>
</tr>
<tr>
<td>Pd/C, H\textsubscript{2}, EtOH</td>
<td>82</td>
</tr>
<tr>
<td>Pd/C, H\textsubscript{2}, THF</td>
<td>44</td>
</tr>
</tbody>
</table>

The unexpected formation of an N-hydroxyindole product during the reduction of a nitro group has previously been observed.\textsuperscript{78} For example, Kuzmich and Mulrooney reported that treatment of nitropyridine 343 with SnCl\textsubscript{2} provided hydroxylamine 344 and N-hydroxyazaindole 345 in 77 and 17\% yields, respectively (Scheme 72). The mechanism for the formation of 345 proposed by the authors involves partial reduction of the nitro group of 343 to give aryl nitroso intermediate 346, which cyclizes to give N-hydroxyiminium compound 347. Finally, rearomatization of 347 would give N-
hydroxyazaindole 345. This mechanism is supported by an alternative approach to N-hydroxyazaindole 345 from arylhydroxylamine 344. Thus, upon exposure of 344 to mild oxidation conditions with DDQ, N-hydroxyazaindole 345 was produced in 93% yield, which can also be explained by formation of the arylnitroso intermediate 346.

3.4.5. Formation of the “Southern” Aminal

3.4.5.1. Amidine Pathway

With aniline 340 available, formation of the “southern” aminal was next investigated. As we learned from the previous study, the “southern” aminal should be accessible by reduction of the corresponding amidine, which was prepared from the corresponding lactam aniline under acid-catalyzed dehydration conditions (Cf. Scheme 63). However, upon exposure of aniline 340 to these same dehydration conditions, rearranged indole 348 was produced instead of the expected amidine 349 (Scheme 73).
Another known approach to forming a cyclic amidine is to utilize a Boc-protected amine tethered to a thiolactam. To pursue this route, aniline \(340\) was first protected as the \(N\)-Boc aniline \(350\) (Scheme 74). Unfortunately, all efforts at thionation of the oxindole moiety of \(N\)-Boc aniline \(350\) failed to give thiolactam \(351\). Had we been able to form this intermediate, it would subsequently have been activated as \(S\)-methylthioimidinium ion intermediate \(352\), followed by cyclization to afford amidine \(349\).

### 3.4.5.2. Imide Reduction Approach to the “Southern” Aminal

Since lower amidine formation turned out to be problematic, we decided to
explore the direct formation of the aminal moiety from the oxindole. Govek and Overman have reported efficient aminal formation utilizing an imide partial reduction (Scheme 75). Thus, the \( N \)-Boc imide group of \( 353 \) was reduced with \( \text{LiEt}_3\text{BH} \) and the resulting hemiaminal cyclized under the acidic work-up conditions. Selective Boc-removal then provided aminal \( 354 \) in 79% yield for the two steps.

Scheme 75

![Scheme 75](image)

To utilize this tactic, amide \( 335 \) was first converted to \( N \)-Boc imide \( 355 \) which was exposed to ethyl chloroformate to give carbamate-protected Heck substrate \( 356 \) in good overall yield (Scheme 76). However, under the previously optimized Heck cyclization conditions, amide \( 356 \) only produced a complex mixture rather than the desired oxindole \( 357 \). One of the compounds isolated from the reaction mixture was aniline \( 358 \), which probably results from hydrolysis of the \( N \)-Boc imide moiety, followed by a palladium catalyzed C-H insertion of the aryl iodide (or \textit{vice versa}).
Due to the incompatibility of the Boc group to the Heck conditions, we decided to install a more stable protecting group on the amide, which would be replaced by a Boc group after the Heck reaction. Thus amide 335 was first protected as the N-SEM amide 359 in low yield (Scheme 77). The N-benzyl group of the tetrahydropyridine moiety was then replaced with a carbamate moiety to give the desired Heck substrate 361 in good yield. Improvement of the yield of the SEM protection was achieved by changing the order of the steps. Thus, after replacement of the benzyl group with a carbamate moiety, amide 360 was converted to N-SEM amide 361 in 75% yield. Upon exposure of the N-SEM amide 361 to the previously optimized Heck conditions, the desired oxindole 362 was produced in 62% yield. However, all efforts to remove the SEM group from 362 to give lactam 363 were unsuccessful.
3.4.5.3. Direct Reductive Cyclization

We next explored a direct reductive cyclization of the oxindole to generate the “southern” aminal group. However, most of the reducing reagents initially used produced complex mixtures. For example, treatment of oxindole 350 with DIBALH at -78 °C provided the desired aminal 364 in 33% yield, along with the unreacted starting material and over-reduced indoline 365 in 36 and 18% yields, respectively (Scheme 78). It was
finally found that exposure of 350 to alane afforded the desired pentacyclic aminal 364 in 84% yield.

Scheme 78

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIBALH, CH₂Cl₂, -78 °C, 1h</td>
<td>36%</td>
</tr>
<tr>
<td>Al⁺⁺Me₂Et, THF, 0 °C, 1h</td>
<td>33%</td>
</tr>
</tbody>
</table>

3.4.6. Introduction of the Second Quaternary Carbon Center

After the successful synthesis of the pentacyclic aminal 364, we then investigated several approaches to introduce the second quaternary carbon center. We first decided to utilize a precededented cyclopropanation of the enamide double bond of 364 with ethyl diazoacetate using a Rh or Cu catalyst (Scheme 79). However, all such efforts failed to provide the desired cyclopropyl ester 366. Treatment of pentacycle 364 with dichlorocarbene to give dichlorocyclopropane compound 367 was also unsuccessful. In addition, oxidative transformation of the cyclic enamide functional group of 364 to the corresponding lactam moiety using NBS produced none of the desired product 368.
At this stage, we decided to explore a metalloenamine C-alkylation strategy for installation of the second quaternary carbon center. Thus, the carbamate group of 364 was removed under basic hydrolysis conditions to produce cyclic enamine 369, the structure of which was confirmed by 2D NMR studies (HMQC, HMBC, NOESY) (Scheme 80). Upon exposure of enamine 369 to various bases such as LiHMDS, NaH, and n-BuLi, followed by allyl iodide, the desired allyl imine 371 was produced, but only in low yield. A more efficient way to effect the alkylation involved in situ formation of metalloenamine intermediate 370 by deacylation with excess n-BuLi, followed by addition of allyl iodide, which provided the desired allyl imine 371 in 79% yield, along with a small amount of N-allyl product 372 (11% yield). The structure and stereochemistry of 371 was established by 2D NMR studies. The relative configuration of the two quaternary carbon centers was confirmed by a NOESY study, which showed correlations between the “southern” aminal proton and the protons shown in 371a.
To have a better understanding of the mechanism of the metalloenamine allylation, we decided to investigate whether the two allylation products 371 and 372 are interconvertible. Thus, both allyl pentacycles were first reexposed to the allylation conditions, but no change was detected. We next tested the thermal interconversion of the two products. However, in refluxing toluene (bp 110 °C) both compounds are stable and no change was detected. At a higher temperature in refluxing o-xylene (bp 143-145 °C), N-allyl pentacycle 372 begins to decompose but none of the C-allyl compound 371 was detected in the mixture (Scheme 81). However, at this same temperature the C-allyl
pentacycle 371 was converted to N-allyl product 372, and after heating for 17 h, the ratio of 371:372 in the mixture was found to be 1:0.6. This unexpected conversion can be rationalized by invoking a 1-aza-Cope rearrangement, which is usually unfavorable relative to its counterpart, a 3-aza-Cope rearrangement (i.e. 372→371). However, in this specific case, relief of ring strain or of unfavorable steric interactions could be the driving force for the 1-aza-Cope rearrangement.85

Encouraged by the success of the C-allylation of enamide 364 utilizing the in situ-formed metalloenamine intermediate 370, we decided to explore this method further with other electrophiles which would afford intermediates better functionalized for “northern” aminal formation. Thus, metalloenamine 370 was formed from 364 and was treated in situ with several electrophiles including ethyl iodoacetate, iodoacetamide,86 as well as N-tosyl87 and N-nosylaziridine88 (Scheme 82). The alkylation reaction using ethyl iodoacetate produced a desired ester 373 but in only 10% yield. The reactions with iodoacetamide or the aziridines did not afford any alkylation products 374 and 375.

3.4.7. Imine Protection

Scheme 82
The failure of the alkylation of 370 with other electrophiles led us to continue the synthesis with allyl pentacycle 371. However, before the terminal olefin moiety of 371 could be functionalized for “northern” aminal formation, the reactive imine functional group of 371 had to be protected. Thus, imine 371 was treated with diethyl pyrocarbonate in EtOH, which provided the desired N,O-acetal 376 as a mixture of diastereomers (Scheme 83). However, N,O-acetal 376 proved to be unstable and on standing slowly decomposed to aldehyde 378, which was also formed by the PTSA catalyzed rearrangement of N,O-acetal 376 (85% yield from 371). The structure of 378 was confirmed by 2D NMR studies (HMOC, HMBC). To minimize this undesired rearrangement, crude N,O-acetal olefin 376 was immediately exposed to several oxidative cleavage conditions, none of which, however, afforded aldehyde 377.

Scheme 83
Formation of the aldehyde 378 from the \(N,O\)-acetal 376 can be rationalized by a proximity interaction between the PMP ether group and the imine carbon (Scheme 84). Mechanistically, \(N,O\)-acetal 376 can be formed through \(N\)-acyliminium ion intermediate 379 via intramolecular hydride transfer\(^9\) of a benzylic hydrogen, which spatially is very close to the iminium ion carbon due to the cup-shaped conformation of the pentacyclic ring system. This hydride migration would lead to oxonium ion intermediate 380, which could be hydrolyzed to aldehyde 378 (path a). Alternatively, it is possible that the oxygen of the PMP ether attacks the highly reactive \(N\)-acyliminium ion to provide oxonium ion intermediate 381 (path b). Subsequent attack of adventitious water at the benzylic position of intermediate 381 would provide alcohol 382a, which could then be converted to \(N\)-acyliminium ion 383. Similar intramolecular hydride transfer of a benzylic hydrogen
would provide aldehyde 378. Evidence for path b is provided by isolation of a small amount of ethyl ether 382b from the reaction mixture. Although compound 382b could not be fully characterized due to its instability, ¹H NMR and MS data support the assignment. This material would result from attack of EtOH at the benzylic position of oxonium ion 381 in path b.

3.4.8. TBDMS-Protected Hydroxymethyl Substrates

3.4.8.1. Synthesis of TBDMS-Protected Allyl Pentacycle

The unexpected formation of aldehyde 378 led us to consider replacement of the PMP protecting group with a bulkier TBDMS group, which for steric reasons would be less likely than the PMP-protected compound to form an oxonium ion intermediate like 381. Towards this end, we first investigated the removal of the PMP group from various intermediates which had been prepared. However, all of these attempts provided complex mixtures rather than the corresponding free alcohol products. Consequently, it became necessary to perform the TBDMS protection at an early stage of the synthetic sequence.

Thus, carboxylic acid 334 was activated as the corresponding acid chloride, which was then treated with aniline 246 to give amide 384 in 68% yield (Scheme 85). Heck substrate 386 was then obtained via a two-step sequence: replacement of the N-benzyl group with a carbamate moiety to form 385, and N-methylation of the resulting amide 385 in good yield. Under the previously optimized Heck conditions, N-methylamide 386
was converted to oxindole 387 in 88% yield. Nitro group reduction and Boc-protection of the resulting aniline 388 provided N-Boc aniline 389, which was smoothly converted to pentacycle 390 under reductive cyclization conditions with alane. Upon treatment of carbamate 390 with n-BuLi, followed by allyl iodide, C-allyl pentacycle 391 and N-allyl product 392 were formed in 80 and 9% yields, respectively. At this point, we also investigated alkylation of 390 with other electrophiles such as nitroethylene91 and 2-azidoiodoethane.92 However, all these efforts failed to give alkylated products 393a or
3.4.8.2. Functionalization of the Terminal Olefin

With allylic pentacycle 391 in hand, we next explored the protection of the cyclic imine functional group. When imine 391 was treated with diethyl pyrocarbonate in EtOH, N,O-acetal 394 was produced as the major product along with some rearranged aldehyde 378 (Scheme 86). In an attempt to decrease the formation of aldehyde 378 we varied several reaction conditions, but neither low temperature (-78 °C) nor addition of bases (NEt₃, K₂CO₃) caused any significant reduction in the formation of the aldehyde. However, TBDMS protected N,O-acetal 394 did seem to be more stable than the PMP-protected product 376 (Cf. Scheme 83). Thus, we proceeded to explore manipulating the terminal olefin moiety of crude product 394. It was found that by three sequential reactions (i.e. dihydroxylation, oxidative cleavage and reduction), the desired alcohol

Scheme 86
395 could be obtained as a 2:1 mixture of diastereomers in 45% yield from the allylic pentacycle 391, along with diol 396 in 30% yield, which results from reduction of rearranged aldehyde 378.

To continue the synthesis, alcohol 395 was converted to azide 396 under Mitsunobu conditions, which was then reduced and the resulting amine was protected with a Boc group in a one-pot reaction to afford N-Boc amine 398 in good yield (Scheme 87). We next explored the formation of the “northern” aminal from 398. Unfortunately, under acidic conditions, only rearranged aldehyde 400 was obtained from 398 as the sole product rather than desired bis-aminal 399.

Scheme 87
3.4.9. Use of C12a Bromo Substrates

To eliminate the possibility of the undesired rearrangement of the intermediate N-acyliminium ion, we considered replacement of the hydroxymethyl group at C12a with a substituent unable to undergo this process. Since a bromine substituent was used as a good functional handle at the C12a position in Qin’s total synthesis of communesin F (see Section 1.3.3.), we therefore decided to utilize such a substituent in our system.

3.4.9.1. Halogen-Selective Intramolecular Heck Reaction

Synthesis of a C12a bromide substrate for the Heck reaction commenced with the coupling of known bromoaniline 401 and the acid chloride derivative of carboxylic acid 334 to afford amide 402 in 79% yield (Scheme 88). The benzyl group of amide 402 was replaced with an ethoxycarbonyl moiety to give carbamate 403, which was then alkylated with MeI to produce Heck substrate 404 in good yield. The Heck reaction of bromo iodo substrate 404 is potentially problematic since there are two halogens which can possibly react with the Pd(0) catalyst. However, we were encouraged by the previous work from our group in which a halogen-selective tandem Heck/carbonylation reaction was successfully developed (see Section 1.4). Initial exposure of bromo iodo substrate 404 to the previously optimized Heck conditions for the tetrahydropyridine Heck substrates provided a 1:1 mixture of desired oxindole 405 and pentacycle 406, which results from a second palladium catalyzed reaction of the aryl bromide moiety. However, at a lower reaction temperature, a better product ratio could be achieved, although a long reaction
time was needed for completion of the cyclization and the overall product yield was low. This result implied that decomposition of the products might be occurring under these conditions. Therefore, to reduce the decomposition of the products, the reaction time needed to be shortened. However, to in order for the reaction to go to completion in a reasonable time period, the cyclization must be run at a high temperature, which increases the amount of pentacycle 406 formed. Although we have not yet found the best solution to this problem, the optimum result achieved to date is when the Heck reaction of 404 is run at 100 °C for 1 h, which provides a 1:0.15 mixture of 405 and 406 in 51% total yield along with unreacted N-methyl amide 404 in 40% yield, which can be recycled.

**Scheme 88**

<table>
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<th>Temp (°C)</th>
<th>Pd(OAc)$_2$ (mol%)</th>
<th>Time (h)</th>
<th>SM (%)</th>
<th>Yield (%) 405+406</th>
<th>Ratio (405 : 406)</th>
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<td>1</td>
<td>40</td>
<td>51</td>
<td>1 : 0.15</td>
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3.4.9.2. Synthesis of Brominated Allyl Pentacycle

To continue the synthesis, the nitro group of oxindole 405 was reduced by catalytic hydrogenation to afford aniline 407 in 76% yield as well as hydrodebrorninated aniline 408 in 11% yield (Scheme 89). Boc protection of aniline 409 and reductive cyclization of the resulting N-Boc aniline 409 provided pentacyclic aminal 410 in 67% yield. However upon exposure of enam ide 410 to the previously optimized allylation conditions, a complex mixture of products was formed. One of identifiable major products was hydrodebrorninated allyl pentacycle 414, which results from halogen-metal exchange of bromide 410 by n-BuLi, followed by protonation. Thus, we decided to use a two-step approach for the allylation. Removal of the ethoxycarbonyl group was achieved

Scheme 89
under basic hydrolysis conditions and after isolation the resulting cyclic enamine 411 was then treated with LDA and allyl iodide to provide the desired C-allyl pentacycle 412 and N-allyl product 413 in 58 and 29% yields, respectively.

3.4.9.3. Functionalization of the Terminal Olefin

With allyl pentacycle 412 in hand, we subsequently investigated manipulation of the allyl group. Upon exposure of 412 to diethyl pyrocarbonate, N,O-acetal 415 was formed cleanly (Scheme 90). However, to our surprise dihydroxylation of 415 and oxidative cleavage of the resulting diol gave cyclic acetal 416 (42% yield for three steps) as a mixture of epimers instead of the desired aldehyde 417. The structure of the cyclic acetal 416 was confirmed by 2D NMR studies (HMQC, HMBC, and NOESY). Presently we do not know why this substrate acts differently from the previous TBDMS protected hydroxymethyl compound in the oxidative cleavage step (Cf. Scheme 86). Cyclic acetal
could then be converted to hemiacetal 418 in good yield, and this compound might be used as an advanced intermediate for further synthetic studies toward the total synthesis of the communesins (*vide infra*).
3.5. Conclusions and Future Work

In conclusion, we have explored several synthetic strategies for the synthesis of the communesins (1-9). It was found after extensive optimization studies that tandem Heck/carbonylation reactions, which were utilized in previous studies by our group, are useful for the formation of oxindole intermediate for synthesis of the communesins. However, it was found that a nitro substituent at C4a in the communesin D ring facilitates the formation of undesired reductive Heck products. Therefore, a hydroxymethyl group was used as a replacement for the nitro substituent in subsequent investigations. The first attempted strategy for the installation of the second quaternary carbon center of C8 was to utilize an intramolecular α-alkylation of tricyclic lactone 168, but unfortunately could not be accessible, probably due to its highly strained structure. A second strategy utilizing the C-alkylation of spirolactones 228 and 262 provided allyl lactones 231 and 264 with moderate diastereoselectivity. These alkylations proceed via initial lactone O-allylation and subsequent thermal Claisen rearrangement of the resulting O-allylketene acetal intermediates 230 and 263.

To avoid the formation of reductive Heck products from substrates containing a nitro group, we devised a new approach involving Heck reactions of tetrasubstituted alkenes 299 and 303, which provided C4a nitro-substituted oxindole intermediates 300 and 304. The “southern” aminal moiety was then formed by reduction of amidine 306 to give the tetracyclic advanced intermediate 307. However, all efforts to manipulate the exo-olefin moiety of 307 were unsuccessful.
To solve the above problems, a revised strategy using tetrahydropyridine substrates 339 and 386 was devised. From these intermediates, pentacyclic advanced intermediates 364 and 390 were easily accessed through Heck reactions and reductive cyclizations. Metalloenamine allylations then provided allyl pentacycles 371 and 391, which have the correct communesin relative stereochemistry at the two vicinal quaternary carbon centers. However, manipulation of the allyl group to the “northern” aminal has been problematic with the unexpected formation of the rearranged aldehyde 378.

To eliminate the possibility of this undesired rearrangement, a bromo substituent was installed at the C12a position rather than a hydroxymethyl group. The bromide substrate underwent a similar sequence involving a Heck reaction, reductive cyclization and metalloenamine allylation to afford the allylic pentacycle 412, which could be transformed to the hexacyclic hemiacetal 418.

To complete the total synthesis of the communesins, first the “northern” aminal will be formed from the advanced intermediate 418 to provide bis-aminal 419 (Scheme 91). Two possible routes to introduce the azepine ring system seem possible. One route will start with a Heck reaction of bis-aminal 419 with 2-methyl-3-buten-2-ol to provide allylic alcohol 420, which can be transformed to heptacyclic intermediate 421 via deprotection and acid catalyzed cyclization. The stereochemical outcome of the cyclization step is expected to be as shown in 421. In the transition state for the cyclization step, the allylic alcohol substituent should be oriented outside of the cup-shaped ring systems to avoid severe steric interactions which will occur if the allyl chain
is located underneath the ring system. It should be noted that a similar Heck reaction/acid catalyzed cyclization route was utilized in Qin’s total synthesis of communesin F.\textsuperscript{18}

Another possible route would commence with removal of the ethoxycarbonyl group of bis-aminal 419, followed by conjugate addition of the corresponding amine to ethyl propiolate to give vinylogous carbamate 422. Cyclization of 422 could be effected using various methods, such as a radical reaction\textsuperscript{94} or Heck cyclization to give the ester 423. The stereochemistry at C11 in 423 would be secured by the same rationale offered

\textbf{Scheme 91}
for 421. This compound could then be transformed to alkene 421 by addition of MeLi and dehydration of the corresponding tertiary alcohol. Finally, total syntheses of communesin A (1) and B (2) would be accomplished from 421 through a stereoselective epoxidation as discussed in Section 3.1.1., followed by removal of the benzyl group and N-acylation of the “northern” aminal with the corresponding carboxylic acid derivative.
**Experimental Section**

5,7-Dichloro-3-(2-hydroxyethyl)-1-methoxymethyl-3-[3-(2-methoxyphenyl)-2-oxotetrahydrofuran-3-yl]-1,3-dihydroindol-2-one (83). A stream of ozone was passed through a solution of allyl lactone 82 (39.0 mg, 0.082 mmol) in CH₂Cl₂ (5 mL) at −78 °C for 10 min. Excess ozone was removed with a stream of nitrogen until the blue color disappeared. The ozonide solution was quenched with BH₃•Me₂S (0.32 mL, 2.0 M in Et₂O, 0.64 mmol), warmed to rt and stirred overnight. To the mixture was carefully added 1N aqueous HCl (10 mL). After 1 h of vigorous stirring, the aqueous layer was extracted with CH₂Cl₂ (2×10 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ solution (10 mL) and brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the γ-lactone 83 (28.0 mg, 71%). 

**1H NMR (400 MHz, CDCl₃)** δ 7.92 (s, 1H), 7.18 (dd, J = 1.5, 7.9 Hz, 1H), 7.15-7.11 (m, 1H), 7.02 (d, J = 2.1 Hz, 1H), 6.76 (ddd, J = 0.9, 7.7, 7.7 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.31, 5.27 (ABq, J = 9.9 Hz, 2H), 4.34 (t, J = 8.1 Hz, 1H), 3.91-3.84 (m, 1H), 3.60 (s, 3H), 3.43 (s, 3H), 3.41-3.25 (m, 3H), 3.14 (dd, J = 4.6, 14.0 Hz, 1H), 2.66 (ddd, J = 6.3, 6.3, 12.5 Hz, 1H), 2.53 (ddd, J = 6.9, 6.9, 13.9 Hz, 1H); 

**13C NMR (75 MHz, CDCl₃)** δ 179.3, 177.1, 157.6, 137.0, 134.0, 130.3, 130.1, 128.4, 126.8, 122.3, 120.7, 115.5, 111.5, 72.2, 66.8, 59.4, 58.1, 56.9, 54.7, 54.4, 37.5, 31.6.
Methanesulfonic Acid 2-{5,7-Dichloro-1-methoxymethyl-3-[3-(2-methoxyphenyl)-2-oxotetrahydrofuran-3-yl]-2-oxo-2,3-dihydro-1H-indol-3-yl}ethyl Ester (84). To a solution of γ-lactone 83 (271 mg, 0.565 mmol) and NEt$_3$ (0.118 mL, 0.847 mmol) in CH$_2$Cl$_2$ (10 mL) was added MsCl (0.065 mL, 0.678 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h and diluted with CH$_2$Cl$_2$ (80 mL). The organic solution was washed with saturated aqueous NaHCO$_3$ solution (10 mL), dried over MgSO$_4$ and concentrated in vacuo to afford the desired mesylate 84 (320 mg), which was used for next step without further purification. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.89 (br s, 1H), 7.16-7.12 (m, 2H), 7.02 (d, $J$ = 2.0 Hz, 1H), 6.74 (t, $J$ = 7.5 Hz, 1H), 6.63 (d, $J$ = 8.1 Hz, 1H), 5.25, 5.23 (ABq, $J$ = 10.0 Hz, 2H), 4.33-4.27 (m, 1H), 3.97-3.80 (m, 3H), 3.58 (s, 3H), 3.40 (s, 3H), 3.22 (m, 2H), 2.83 (ddd, $J$ = 6.6, 6.6, 13.1 Hz, 1H), 2.75 (s, 3H), 2.64 (ddd, $J$ = 6.8, 6.8, 13.6 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 178.1, 177.0, 157.6, 137.2, 132.9, 130.6, 130.5, 128.5, 127.0, 121.8, 120.8, 115.8, 111.6, 72.4, 66.8, 65.9, 58.2, 57.0, 54.8, 53.9, 37.5, 33.6, 31.6.

3-(2-Azidoethyl)-5,7-dichloro-1-methoxymethyl-3-[3-(2-methoxyphenyl)-2-oxotetrahydrofuran-3-yl]-1,3-dihydroindol-2-one (85). To a solution of the above crude mesylate 84 in DMF (5 mL) was added NaN$_3$ (184 mg, 2.82 mmol). The reaction mixture was heated at 60 °C overnight, cooled to rt and diluted with EtOAc (150 mL). The organic solution was washed with water (3×20 mL) and brine (20 mL), dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes).
to give the desired azide 85 (274 mg, 96% for two steps). IR (neat) 2099, 1760, 1732 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.91 (br s, 1H), 7.14-7.07 (m, 2H), 7.01 (d, \(J = 2.1\) Hz, 1H), 6.72 (ddd, \(J = 0.9, 7.6, 7.6\) Hz, 1H), 6.62 (d, \(J = 8.1\) Hz, 1H), 5.27, 5.24 (ABq, \(J = 10.0\) Hz, 2H), 4.30 (t, \(J = 7.8\) Hz, 1H), 3.84 (ddd, \(J = 5.6, 8.8, 11.1\) Hz, 1H), 3.58 (s, 3H), 3.23 (s, 3H), 3.31-3.09 (m, 2H), 3.02-2.97 (m, 1H), 2.91-2.82 (m, 1H), 2.21-2.13 (m, 1H), 2.48-2.39 (m, 1H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 178.2, 176.9, 157.6, 137.1, 133.1, 130.5, 128.6, 126.8, 122.0, 120.8, 115.7, 111.5, 72.3, 66.8, 58.2, 56.9, 54.8, 54.4, 47.7, 33.5, 31.5.

**Synthesis of Spiro Lactam 86.** A solution of azide 85 (155 mg, 0.307 mmol) and PPh\(_3\) (161 mg, 0.614 mmol) in THF (10 mL) and water (1 mL) was refluxed for 2 d. The reaction mixture was diluted with CH\(_2\)Cl\(_2\) (40 mL) and water (10 mL). The organic layer was dried over MgSO\(_4\) and concentrated *in vacuo*. The residue was purified by flash column chromatography (10:5:1 CH\(_2\)Cl\(_2\)::EtOAc::MeOH) to give the desired lactam 86 (109 mg, 74%). \(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 7.52-7.42 (m, 2H), 7.25 (br s, 1H), 7.10 (m, 1H), 6.86 (m, 1H), 6.58 (br s, 1H), 5.87 (br s, 1H), 5.45 (br s, 2H), 3.98-3.92 (m, 1H), 3.85 (br s, 1H), 3.53-3.46 (m, 2H), 3.42 (s, 3H), 3.31 (s, 3H), 2.35 (m, 2H), 1.98 (m, 1H), 1.60 (m, 1H); \(^1\)C NMR (75 MHz, CDCl\(_3\)+CD\(_3\)OD) \(\delta\) 177.0, 175.1, 158.3, 136.1, 133.6, 132.3, 130.0, 129.6, 127.6, 124.1, 122.3, 120.6, 115.7, 111.1, 71.4, 60.0, 57.6, 56.4, 53.7, 53.5, 36.9, 35.5, 26.6; LRMS-APCI: [M+H]\(^+\) calcd for C\(_{23}\)H\(_{25}\)Cl\(_2\)N\(_2\)O\(_5\), 479.1; found, 479.1.
Formation of Cyclic Imidate 88 During Mesylation of Spiro Lactam 86. To a solution of lactam 86 (5.1 mg, 0.011 mmol) and NEt₃ (7.4 μL, 0.052 mmol) in CH₂Cl₂ (1 mL) was added MsCl (1.2 μL, 0.016 mmol) at 0 °C. The reaction mixture was stirred at rt for 1 h and diluted with CH₂Cl₂ (10 mL). The solution was washed with saturated aqueous NaHCO₃ solution (5 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by preparative TLC (10:5:1 CH₂Cl₂:EtOAc:MeOH) to give the cyclic imidate 7 (5.3 mg, ~100%). ¹H NMR (400 MHz, CDCl₃) δ 7.38 (m, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 5.88 (d, J = 1.8 Hz, 1H), 5.48 (s, 2H), 4.09 (t, J = 8.0 Hz, 1H), 3.97 (ddd, J = 5.4, 8.9, 16.7 Hz, 1H), 3.85 (ddd, J = 3.6, 5.6, 16.7 Hz, 1H), 3.56 (m, 1H), 3.43 (s, 3H), 3.30 (s, 3H), 3.14 (dd, J = 4.3, 12.2 Hz, 1H), 2.40 (ddd, J = 7.9, 12.0, 12.0 Hz, 1H), 1.88 (ddd, J = 5.7, 8.7, 14.4 Hz, 1H), 1.60 (ddd, J = 4.4, 4.4, 14.2 Hz, 1H); LRMS-APCI: [M+H]⁺ calcd for C₂₃H₂₂Cl₂N₂O₅, 461.1; found, 461.1.

TBS Protection of Spiro Lactam 86 To a solution of the lactam 86 (53.7 mg, 0.112 mmol) and imidazole (19.0 mg, 0.279 mmol) in DMF (1.5 mL) was added TBDMSCl (25.3 mg, 0.168 mmol) in a single portion. The reaction mixture was stirred at rt overnight and then diluted with EtOAc (50 mL). The organic solution was washed with water (3×10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (3:1 EtOAc:hexanes) to give the TBDMS ether 91 (63.4 mg, 95%). ¹H
NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.33 (t, $J = 8.5$ Hz, 1H), 7.20 (d, $J = 2.0$ Hz, 1H), 6.93 (br s, 1H), 6.85 (br s, 1H), 6.62 (br s, 1H), 6.01 (br s, 1H), 5.43 (br s, 2H), 3.89-3.85 (m, 1H), 3.59 (br s, 1H), 3.48 (br s, 2H) 3.28 (br s, 6H), 2.38 (br s, 1H), 2.21 (br s, 2H), 1.82 (br s, 1H), 0.84 (s, 9H), -0.03 (d, $J = 2.3$ Hz, 6H)

**Boc Protection of Lactam 91.** To a stirred solution of lactam 91 (9.7 mg, 0.016 mmol) in CH$_2$Cl$_2$ (1 mL) were added NEt$_3$ (0.011 mL, 0.079 mmol), DMAP (1.0 mg) and (Boc)$_2$O (0.007 mL, 0.033 mmol). The reaction mixture was stirred at rt overnight and diluted with CH$_2$Cl$_2$ (20 mL). The solution was washed with saturated aqueous NaHCO$_3$ (5 mL), dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the N-Boc lactam 92 (10.1 mg, 89%). $^1$H NMR (360 MHz, acetone-$d_6$) $\delta$ 7.42 (t, $J = 8.3$ Hz, 1H), 7.34 (d, $J = 2.0$ Hz, 1H), 7.13 (br s, 1H), 6.97 (t, $J = 7.0$ Hz, 2H), 5.73 (br s, 1H), 5.47 (s, 2H), 4.09 (m, 2H), 3.85 (br s, 1H), 3.71 (br s, 3H), 3.55 (br s, 1H), 3.43 (s, 3H), 2.47 (m, 2H), 2.11 (m, 1H), 2.01-1.92 (m, 1H), 1.62 (s, 9H), 0.87 (s, 9H), -0.01 (s, 6H).

(2-{5,7-Dichloro-1-methoxymethyl-3-[3-(2-methoxyphenyl)-2-oxotetrahydrofuran-3-yl]-2-oxo-2,3-dihydro-1H-indol-3-yl}-ethyl)carbamic Acid tert-Butyl Ester (93). To a stirred solution of TBS ether 92 (9.8 mg, 0.014 mmol) in THF (1 mL) was added TBAF (0.017 mL, 1.0 M in THF, 0.017 mmol) at 0 °C. The reaction mixture was warmed to rt
and stirred overnight. The mixture was diluted with EtOAc (30 mL) and saturated aqueous NH₄Cl (10 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the γ-lactone 93 (6.3 mg, 73%). ¹H NMR (300 MHz, CDCl₃) δ 7.90 (br s, 1H), 7.18-7.09 (m, 2H), 7.01 (d, ̈J = 2.0 Hz, 1H), 6.75 (t, ̈J = 7.2 Hz, 1H), 6.63 (d, ̈J = 8.1 Hz, 1H), 5.31, 5.27 (ABq, ̈J = 9.7 Hz, 2H), 4.52 (br s, 1H), 4.33 (t, ̈J = 8.3 Hz, 1H), 3.90-3.81 (m, 1H), 3.59 (s, 3H), 3.43 (s, 3H), 3.37-3.29 (m, 1H), 3.09 (dd, ̈J = 4.8, 13.9 Hz, 1H), 2.83-2.72 (m, 2H), 2.65-2.57 (m, 1H), 2.45-2.36 (m, 1H), 1.39 (s, 9H).

Desilylation of Lactam 92 under Acidic Conditions. To a stirred solution of TBS ether 92 (2.2 mg, 0.003 mmol) in EtOH (1 mL) was added a catalytic amount of PPTS (0.3 mg). The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 EtOAc:hexanes) to give the hydroxy lactam 95 (1.4 mg, 78%). ¹H NMR (300 MHz, acetone-d₆) δ 7.43 (t, ̈J = 7.3 Hz, 1H), 7.33 (d, ̈J = 2.1 Hz, 1H), 7.19-7.03 (m, 2H), 6.95 (t, ̈J = 7.1 Hz, 1H), 5.67 (m, 1H), 5.46, 5.43 (ABq, ̈J = 10.7 Hz, 2H), 4.10-4.02 (m, 1H), 3.90-3.77 (m, 1H), 3.68 (br s, 3H), 3.45 (br s, 2H), 3.39 (s, 3H), 2.51 (m, 1H), 2.34 (m, 1H), 1.91 (dd, ̈J = 6.7, 14.6 Hz, 1H), 1.59 (s, 9H), 1.34 (d, ̈J = 15.8 Hz, 1H).

Chlorination of Boc-Protected Lactam 95. To a solution of N-Boc lactam 95 (2.8 mg, 0.005 mmol) and NEt₃ (3.3 μL, 0.023
mmol) in CH₂Cl₂ (1 mL) was added MsCl (0.7 μL, 0.009 mmol) at 0 °C. The reaction mixture was stirred at rt for 30 min and diluted with CH₂Cl₂ (10 mL). The organic solution was washed with saturated aqueous NaHCO₃ solution (5 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by preparative TLC (1:2 EtOAc:hexanes) to give the chloro lactam 96 (2.1 mg, 73%). ¹H NMR (360 MHz, acetone-d₆) δ 7.47 (t, J = 8.6 Hz, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.13 (m, 1H), 7.04 (t, J = 7.6 Hz, 1H), 5.87 (br s, 1H), 5.50 (s, 2H), 4.13 (m, 2H), 3.86 (m, 1H), 3.63 (br s, 3H), 3.44 (s, 3H), 3.36 (m, 1H), 2.62 (m, 1H), 2.49 (br s, 1H), 2.03-1.95 (m, 2H), 1.62 (s, 9H).

2-[5,7-Dichloro-3-(2-hydroxyethyl)-1-methoxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-2-(2-methoxyphenyl)-pent-4-enoic Acid Amide (97). To a stirred suspension of NH₄Cl (229 mg, 4.28 mmol) in toluene (5 mL) was slowly added Me₃Al (2.30 mL, 2.0 M in hexanes, 4.60 mmol) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to rt and was stirred for 1.5 h. To a solution of lactone 82 (291 mg, 0.61 mmol) in toluene (15 mL) was added the above aluminum amide reagent at rt, and the mixture was heated at 80 °C overnight. The reaction mixture was cooled to rt and was carefully quenched with 1N HCl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2×20 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (10:10:1 CH₂Cl₂:EtOAc:MeOH) to give the amide 97 (286 mg, 95%) as a yellow solid (mp 179-180 °C). Recrystallization from EtOAc provided X-ray quality crystals of 16. IR
(film) 3342, 1708, 1672, 1461 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)+CD\(_3\)OD) \(\delta\) 7.85 (br s, 1H), 7.14 (t, \(J = 7.7\) Hz, 1H), 7.06 (d, \(J = 1.6\) Hz, 1H), 6.78 (t, \(J = 7.6\) Hz, 1H), 6.54 (br s, 1H), 5.87 (m, 1H), 5.51 (br s, 1H), 5.17 (d, \(J = 16.8\) Hz, 1H), 5.03 (d, \(J = 10.0\) Hz, 1H), 4.65 (br s, 2H), 3.55-2.89 (m, 10H), 2.42 (br s, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)+CD\(_3\)OD) \(\delta\) 180.2, 174.7, 156.9, 136.9, 134.6, 134.0, 131.1, 129.6, 129.1, 128.2, 127.3, 124.7, 119.4, 118.4, 114.6, 110.7, 71.3, 58.8, 58.4, 57.0, 56.3, 54.1, 37.3, 34.7; HRMS-ES [M+H]\(^+\) calcd for C\(_{24}\)H\(_{27}\)Cl\(_2\)N\(_2\)O\(_5\), 493.1297; found, 493.1285.

2-{3-[2-(tert-Butyldimethylsilanyloxy)-ethyl]-5,7-dichloro-1-methoxymethyl-2-oxo-2,3-dihydro-1\(H\)-indol-3-yl}-2-(2-methoxyphenyl)-pent-4-enoic Acid Amide (98). To a solution of the lactam 97 (1.01 g, 2.38 mmol) and imidazole (194 mg, 2.85 mmol) in DMF (5 mL) was added TBDMSCl (376 mg, 2.49 mmol) in one portion. The reaction mixture was stirred at rt overnight and then diluted with EtOAc (150 mL). The organic solution was washed with water (3×20 mL) and brine (20 mL), dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the TBDMS ether 98 (1.22 g, 99%) as a white foamy solid (mp 69-71 °C). IR (film) 2943, 1719, 1678, 1461, 1255 cm\(^{-1}\); \(^1\)H NMR (300 MHz, toluene-\(d_8\), 90 °C) \(\delta\) 7.94 (br s, 1H), 7.09 (d, \(J = 8.1\) Hz, 1H), 6.97 (d, \(J = 2.1\) Hz, 1H), 6.90 (t, \(J = 8.6\) Hz, 1H), 6.62 (t, \(J = 8.2\) Hz, 1H), 6.25 (d, \(J = 8.2\) Hz, 1H), 5.98-5.84 (m, 1H), 5.12 (d, \(J = 17.0\) Hz, 1H), 4.96 (d, \(J = 10.2\) Hz, 1H), 4.86, 4.77 (ABq, \(J = 11.3\) Hz, 2H), 4.75 (br s, 2H), 3.55-3.24 (m, 5H), 3.09 (s, 3H), 3.01 (s, 3H), 2.81-2.75 (m, 1H), 0.78 (s, 9H), -0.13
(s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 180.1, 174.9, 157.7, 137.5, 135.5, 135.0, 132.0, 130.0, 129.5, 128.8, 127.7, 125.8, 120.1, 118.7, 115.1, 111.5, 72.1, 60.6, 58.9, 58.1, 56.9, 54.8, 38.0, 35.7, 26.2, 18.6, -5.50, -5.54; HRMS-ES [M+H]$^+$ calcd for C$_{30}$H$_{41}$Cl$_2$N$_2$O$_5$Si, 607.2162; found, 607.2185.

3-[2-(tert-Butyldimethylsilyloxy)-ethyl]-5,7-dichloro-1-methoxymethyl-3-[3-(2-methoxyphenyl)-2-oxopyrrolidin-3-yl]-1,3-dihydroindol-2-one (99). To a stirred solution of allyl amide 98 (37.6 mg, 0.062 mmol) in THF (3 mL) and water (1 mL) were added NaIO$_4$ (33.1 mg, 0.155 mmol) and OsO$_4$ (0.036 mL, 4 wt% in water, 0.006 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and was stirred for 2 h. The mixture was diluted with CH$_2$Cl$_2$ (40 mL) and saturated aqueous NH$_4$Cl (15 mL). The organic layer was separated, dried over Na$_2$SO$_4$ and concentrated in vacuo. The oily residue was dissolved in CH$_2$Cl$_2$ (5 mL) and then NaCNBH$_4$ (15.6 mg, 0.245 mmol) and AcOH (0.1 mL) were added. The mixture was stirred at rt overnight and then diluted with CH$_2$Cl$_2$ (20 mL) and 1N aqueous NaOH (10 mL). The organic layer was washed with saturated aqueous NH$_4$Cl (15 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the $\gamma$-lactam 99 (22.0 mg, 60%) as a white solid (mp 151.5-152 °C). IR (film) 3307, 2931, 2860, 1725, 1696, 1578, 1455, 1255 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.99 (d, $J = 2.1$ Hz, 1H), 7.40 (dd, $J = 1.6$, 7.4 Hz, 1H), 7.06 (ddd, $J = 1.5$, 7.4, 7.4 Hz, 1H), 6.94 (d, $J = 2.1$ Hz, 1H), 6.70 (t, $J = 7.6$ Hz, 1H), 6.62 (d, $J = 8.2$ Hz, 1H), 6.14 (br s, 1H), 5.33, 5.29
(ABq, $J = 10.0$ Hz, 2H), 3.59 (s, 3H), 3.49-3.42 (m, 1H), 3.41 (s, 3H), 3.30 (m, 2H), 3.19 (m, 1H), 2.98 (m, 2H), 2.76 (ddd, $J = 4.8$, 8.0, 15.1 Hz, 1H), 2.43 (ddd, $J = 4.7$, 8.2, 14.2 Hz, 1H), 0.76 (s, 9H), -0.11 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.6, 177.7, 157.3, 136.5, 134.9, 130.9, 128.9, 127.6, 126.9, 124.5, 120.0, 114.5, 110.5, 71.7, 59.6, 58.2, 56.3, 53.9, 53.7, 39.7, 37.4, 29.6, 25.8, 18.1, -5.5; HRMS-ES [M+H]$^+$ calcd for C$_{29}$H$_{39}$Cl$_2$N$_2$O$_5$Si, 593.2005; found, 593.2003.

3-[2-(tert-Butyldimethylsilanyloxy)-ethyl]-5,7-
dichloro-1-methoxymethyl-3-[3-(2-methoxyphenyl)-1-
methyl-2-oxopyrrolidin-3-yl]-1,3-dihydroindol-2-one (100).

To a stirred solution of bis-$\gamma$-lactam 99 (113 mg, 0.190 mmol) in THF (5 mL) was added NaHMDS (0.25 mL, 1.0 M in THF, 0.25 mmol) at - 78 °C. The reaction mixture was stirred at this temperature for 30 min, and MeI (0.017 mL, 0.273 mmol) was added dropwise. The mixture was allowed to gradually warm to rt. After 1 h the mixture was diluted with CH$_2$Cl$_2$ (30 mL) and saturated aqueous NH$_4$Cl (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the N-methyl $\gamma$-lactam 100 (112 mg, 97%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.05 (d, $J = 2.1$ Hz, 1H), 7.30 (dd, $J = 1.6$, 7.9 Hz, 1H), 7.03 (t, $J = 7.8$ Hz, 1H), 6.92 (d, $J = 2.1$ Hz, 1H), 6.69 (t, $J = 7.6$ Hz, 1H), 6.60 (dd, $J = 0.8$, 8.2 Hz, 1H), 5.32, 5.28 (ABq, $J = 10.0$ Hz, 2H), 3.56 (s, 3H), 3.48-3.41 (m, 1H), 3.39 (s, 3H), 3.48-3.41 (m, 1H), 3.39 (s, 3H), 3.28-3.11 (m, 1H), 2.93 (s, 3H), 2.86-2.77 (m, 1H), 2.72-2.63 (m, 1H), 2.39-2.30 (m, 1H), 0.75 (s, 9H), -0.13 (s, 6H); $^{13}$C NMR
(75 MHz, CDCl$_3$) $\delta$ 179.1, 174.7, 157.6, 136.9, 135.4, 131.2, 129.3, 129.2, 128.1,
127.5, 125.6, 120.5, 114.9, 110.9, 72.1, 60.1, 59.5, 56.8, 54.4, 54.3, 47.4, 38.0, 30.8, 27.2,
26.2, 18.6, -5.1.

5,7-Dichloro-3-(2-hydroxyethyl)-1-methoxymethyl-3-[3-(2-methoxyphenyl)-1-methyl-2-oxopyrrolidin-3-yl]-1,3-
dihydroindol-2-one (101). To a stirred solution of $N$-methyl $\gamma$-lactam 100 (24.1 mg, 0.040 mmol) in THF (5 mL) was added TBAF (0.06 mL, 1.0 M in THF, 0.06 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The mixture was diluted with EtOAc (20 mL) and saturated aqueous NH$_4$Cl (5 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo to give the hydroxy $\gamma$-lactam 101 (20.5 mg), which was used for the next step without further purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J = 2.1$ Hz, 1H), 7.26 (dd, $J = 1.5$, 7.8 Hz, 1H), 7.04 (t, $J = 7.8$ Hz, 1H), 6.94 (d, $J = 2.0$ Hz, 1H), 6.68 (t, $J = 7.6$ Hz, 1H), 6.59 (d, $J = 8.2$ Hz, 1H), 5.32 (s, 2H), 3.55 (s, 3H), 3.40 (s, 3H), 3.33 (m, 2H), 3.28-3.18 (m, 2H), 3.04-2.97 (m, 1H), 2.94 (s, 3H), 2.81-2.76 (m, 1H), 2.69 (ddd, $J = 6.5$, 6.5, 12.9 Hz, 1H), 2.47 (ddd, $J = 6.9$, 6.9, 13.7 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.9, 174.9, 157.5, 136.8, 135.2, 131.0, 129.5, 129.3, 128.3, 127.4, 125.7, 120.5, 115.1, 110.9, 72.1, 59.6, 56.8, 54.5, 54.2, 47.5, 38.6, 30.8, 27.3.

Methanesulfonic Acid 2-{5,7-Dichloro-1-methoxymethyl-3-[3-(2-methoxyphenyl)-1-methyl-2-oxopyrrolidin-3-yl]-2-oxo-
2,3-dihydro-1H-indol-3-yl}ethyl Ester (102). To a solution of the above crude hydroxy lactam 101 and NEt$_3$ (0.028 mL, 0.201 mmol) in CH$_2$Cl$_2$ (5 mL) was added MsCl (0.06 mL, 0.079 mmol) at 0 °C. The reaction mixture was stirred at rt for 30 min and diluted with CH$_2$Cl$_2$ (30 mL). The organic solution was washed with saturated aqueous NH$_4$Cl (10 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo to afford the desired mesylate 102, which was used for the next step without further purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.01 (d, $J = 2.1$ Hz, 1H), 7.27 (dd, $J = 1.5$, 7.9 Hz, 1H), 7.06 (t, $J = 7.8$ Hz, 1H), 6.98 (d, $J = 2.1$ Hz, 1H), 6.71 (t, $J = 7.6$ Hz, 1H), 6.62 (d, $J = 8.2$ Hz, 1H), 5.30 (s, 2H), 3.98 (ddd, $J = 7.0$, 7.0, 10.1 Hz, 1H), 3.82 (ddd, $J = 6.8$, 6.8, 10.0 Hz, 1H), 3.57 (s, 3H), 3.42 (s, 3H), 3.28-3.23 (m, 1H), 3.18-3.01 (m, 2H), 2.96 (s, 3H), 2.94-2.78 (m, 2H), 2.77 (s, 3H), 2.62 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.6, 174.7, 157.6, 137.0, 134.0, 131.0, 130.0, 129.5, 128.4, 127.6, 125.0, 120.6, 115.4, 111.0, 72.3, 66.3, 59.6, 56.8, 54.4, 53.9, 47.4, 37.5, 34.5, 30.8, 27.3.

3-(2-Azidoethyl)-5,7-dichloro-1-methoxymethyl-3-[3-(2-methoxyphenyl)-1-methyl-2-oxypyrrolidin-3-yl]-1,3-dihydroindol-2-one (103). To a solution of the above crude mesylate 102 in DMF (1 mL) was add NaN$_3$ (12.9 mg, 0.198 mmol). The reaction mixture was heated at 60 °C overnight, cooled to rt and diluted with EtOAc (30 mL). The solution was washed with water (3×5 mL) and brine (5 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the desired azido γ-lactam 103 (16.0 mg,
78% over 3 steps) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 2.1$ Hz, 1H), 7.26 (dd, $J = 1.5$, 7.6 Hz, 1H), 7.05 (t, $J = 7.8$ Hz, 1H), 6.97 (d, $J = 2.1$ Hz, 1H), 6.70 (t, $J = 7.6$ Hz, 1H), 6.61 (d, $J = 8.2$ Hz, 1H), 5.31 (s, 2H), 3.57 (s, 3H), 3.42 (s, 3H), 3.26 (t, $J = 8.5$ Hz, 1H), 3.16 (ddd, $J = 8.8$, 8.8, 13.4 Hz, 1H), 3.06-2.98 (m, 2H), 2.96 (s, 3H), 2.84-2.70 (m, 3H), 2.41 (ddd, $J = 6.6$, 10.5, 14.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.7, 174.6, 157.6, 136.9, 134.2, 131.0, 129.9, 129.4, 128.5, 127.4, 125.3, 120.6, 115.3, 111.0, 72.2, 59.6, 56.8, 54.4, 54.3, 47.8, 47.4, 34.4, 30.8, 27.2.

**Formation of Phenol 105 from Methyl Ether Azide 103.**

To a solution of azido $\gamma$-lactam 103 (11.3 mg, 0.022 mmol) in ClCH$_2$CH$_2$Cl (1 mL) was added (COBr)$_2$ (0.055 mL, 2.0 M in CH$_2$Cl$_2$, 0.110 mmol) dropwise at 0 $^\circ$C. The reaction mixture was stirred at 0 $^\circ$C for 1 h, warmed to rt and stirred overnight. To the mixture was added anisole (0.005 mL, 0.046 mmol) and MeOH (0.01 mL) at 0 $^\circ$C, and the resulting mixture was stirred for 30 min at rt. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1 EtOAc:hexanes) to give the starting azido $\gamma$-lactam 103 (4.3 mg) and phenol 105 (3.4 mg, 50% BRSM). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.09 (d, $J = 2.0$ Hz, 1H), 7.26 (m, 1H), 7.07 (t, $J = 7.8$ Hz, 1H), 7.01 (d, $J = 2.1$ Hz, 1H), 6.72 (t, $J = 7.2$ Hz, 1H), 6.63 (d, $J = 8.1$ Hz, 1H), 5.60 (dd, $J = 7.0$, 11.0 Hz, 1H), 5.50 (dd, $J = 8.9$, 10.9 Hz, 1H), 3.60 (s, 3H), 3.33-3.13 (m, 3H), 3.08-2.95 (m, 1H), 2.97 (s, 3H), 2.89-2.74 (m, 3H), 2.42 (ddd, $J = 7.6$, 7.6, 13.0 Hz, 1H).
3-[2-(tert-Butyldimethylsilanyloxy)ethyl]-5,7-dichloro-1-methoxymethyl-3-[3-(2-methoxyphenyl)-1-(4-nitro benzenesulfonyl)-2-oxopyrrolidin-3-yl]-1,3-dihydroindol-2-one (110).

To a stirred solution of γ-lactam 99 (359 mg, 0.605 mmol) in THF (10 mL) was added NaHMDS (0.79 mL, 1.0 M in THF, 0.79 mmol) at -78 °C. The reaction mixture was stirred at this temperature for 30 min and a solution of 4-nitrobenzenesulfonyl chloride (201 mg, 0.907 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm to rt gradually, then was diluted with EtOAc (150 mL) and saturated aqueous NH₄Cl (10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the N-Ns γ-lactam 110 (442 mg, 94%) as a white foamy solid (mp 91-93 °C). IR (film) 2931, 1725, 1537, 1461, 1179 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.42 (ddd, J = 2.1, 2.1, 9.2 Hz, 2H), 8.27 (ddd, J = 2.1, 2.1, 8.3 Hz, 2H), 7.66 (br s, 1H), 7.08 (ddd, J = 1.6, 7.1, 8.7 Hz, 1H), 6.97 (d, J = 2.1 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 6.54 (t, J = 7.6 Hz, 1H), 5.20 (s, 2H), 3.88 (t, J = 8.2 Hz, 1H), 3.50 (s, 3H), 3.43-3.34 (m, 1H), 3.37 (s, 3H), 3.31-3.25 (m, 1H), 3.16-3.10 (m, 2H), 2.91 (m, 1H), 2.42 (m, 1H), 2.24 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.7, 173.5, 157.3, 150.9, 143.4, 136.6, 133.4, 130.0, 129.6, 129.5, 127.7, 126.3, 124.2, 121.2, 120.0, 115.0, 111.1, 71.8, 60.4, 59.6, 59.4, 56.4, 54.3, 54.2, 44.8, 36.1, 25.6, 18.0, -5.7; HRMS-ES [M+H]⁺ calcd for C₃₅H₄₂Cl₂N₃O₉SSi, 778.1788; found, 778.1800.
5,7-Dichloro-3-(2-hydroxyethyl)-1-methoxymethyl-3-[3-(2-methoxyphenyl)-1-(4-nitrobenzenesulfonyl)-2-oxopyrrolidin-3-yl]-1,3-dihydroindol-2-one (111). To a stirred solution of $N$-Ns $\gamma$-lactam 110 (442 mg, 0.568 mmol) in EtOH (20 mL) was added PPTS (10.8 mg, 0.057 mmol) and the reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (150 mL). The organic solution was washed with saturated aqueous NaHCO$_3$ (30 mL), dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (2:1 EtOAc:hexanes) to give the hydroxy $\gamma$-lactam 111 (369 mg, 95%) as a white solid (mp 175-176 °C). IR (film) 2929, 1714, 1530, 1456, 1181 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.43 (ddd, $J = 2.0, 2.0, 8.9$ Hz, 2H), 8.27 (ddd, $J = 2.0, 2.0, 8.9$ Hz, 2H), 7.69 (br s, 1H), 7.09 (ddd, $J = 1.5, 7.2, 8.7$ Hz, 1H), 7.00 (d, $J = 2.1$ Hz, 1H), 6.76 (d, $J = 7.8$ Hz, 1H), 6.59 (d, $J = 8.3$ Hz, 1H), 6.53 (t, $J = 7.6$ Hz, 1H), 5.25, 5.20 (ABq, $J = 9.9$ Hz, 2H), 3.91 (t, $J = 8.6$ Hz, 1H), 3.50 (s, 3H), 3.45-3.22 (m, 3H), 3.38 (s, 3H), 3.13 (dd, $J = 4.7, 13.6$ Hz, 1H), 2.99 (m, 1H), 2.39 (m, 2H); $^{13}$C NMR (75 MHz, THF-$d_8$) $\delta$ 176.0, 172.3, 156.1, 149.7, 142.2, 136.0, 132.6, 128.3, 128.0, 127.5, 125.3, 124.8, 122.6, 120.9, 118.1, 113.2, 109.6, 70.2, 58.4, 56.3, 56.2, 54.0, 52.5, 52.2, 43.2, 35.2; HRMS-ES [M+Na]$^+$ calcd for C$_{29}$H$_{27}$Cl$_2$N$_3$NaO$_9$S, 686.0743; found, 686.0743.

3-(2-Azidoethyl)-5,7-dichloro-1-methoxymethyl-3-[3-(2-methoxyphenyl)-1-(4-nitrobenzenesulfonyl)-2-oxopyrrolidin-3-yl]-1,3-dihydroindol-2-one (112). To a solution of hydroxy $\gamma$-
lactam 111 (359 mg, 0.539 mmol), PPh₃ (283 mg, 1.078 mmol) and DPPA (0.23 mL, 1.067 mmol) in THF (30 mL) was added DEAD (0.17 mL, 1.083 mmol) at 0 °C. After 2 h, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10:1 CH₂Cl₂:EtOAc) to give the azido γ-lactam 112 (297 mg, 80%) as a white solid. IR (film) 2918, 2855, 2094, 1725, 1535, 1456, 1176 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.44 (ddd, J = 2.2, 2.2, 9.2 Hz, 2H), 8.27 (ddd, J = 2.1, 2.1, 9.2 Hz, 2H), 7.68 (br s, 1H), 7.09 (ddd, J = 1.5, 7.2, 8.7 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), 6.76 (d, J = 6.0 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 6.54 (t, J = 7.4 Hz, 1H), 5.22, 5.20 (ABq, J = 9.9 Hz, 2H), 3.91 (t, J = 8.5 Hz, 1H), 3.51 (s, 3H), 3.41-3.35 (m, 1H), 3.39 (s, 3H), 3.17-3.09 (m, 1H), 2.91 (m, 1H), 2.81 (m, 1H), 2.42 (m, 2H), 2.30 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.5, 173.7, 157.4, 151.1, 143.4, 136.8, 132.3, 130.4, 130.3, 130.2, 129.8, 128.2, 126.4, 124.4, 121.2, 120.3, 115.6, 111.4, 72.0, 60.6, 59.9, 56.6, 54.6, 54.4, 47.2, 45.0, 32.6; HRMS-ES [M+Na]⁺ calcd for C₂₉H₂₆Cl₂N₆NaO₈S, 711.0808; found, 711.0805.

**Transamidation of Azido Lactam 112.** To a stirred solution of azido γ-lactam 112 (297 mg, 0.431 mmol) in THF (20 mL) was added PMe₃ (1.08 mL, 1.0 M in THF, 1.08 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and was stirred for 3 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (3:1 EtOAc:hexanes) to give the N-Ns amine 113 (282 mg, 98%) as a white solid (mp 133-135 °C). IR (film) 2942, 1723, 1653, 1532, 1462, 1346 cm⁻¹; ¹H
NMR (400 MHz, CDCl₃) δ 8.16 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.21 (s, 1H), 7.01 (m, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.45 (br s, 1H), 5.77 (br s, 1H), 5.41, 5.35 (ABq, J = 12.3 Hz, 2H), 3.93 (ddd, J = 5.5, 11.8, 11.8 Hz, 1H), 3.40 (s, 4H), 3.24 (s, 3H), 3.16 (br s, 1H), 2.71 (br s, 1H), 2.28 (m, 2H), 1.91 (m, 1H), 1.58 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.2, 175.2, 158.5, 149.9, 146.7, 136.7, 134.1, 133.0, 130.7, 130.3, 128.5, 128.2, 124.6, 124.5, 122.6, 121.4, 116.5, 111.6, 72.1, 57.5, 57.1, 54.5, 54.0, 42.0, 37.6, 33.3, 27.5; HRMS-ES [M+H]^+ calcd for C₂₉H₂₉Cl₂N₄O₈S, 663.1083; found, 663.1112.

Methylation of N-Ns Amine 113. To a solution of N-Ns amine 113 (939 mg, 1.42 mmol) in CH₃CN (30 mL) was added Cs₂CO₃ (553 mg, 1.70 mmol) at 0 °C. The resulting suspension was allowed to warm to rt and was stirred for 1 h. To the yellow mixture was added MeI (0.44 mL, 7.07 mmol) dropwise at 0 °C. After vigorously stirring the mixture for 11 h at rt, the solvent was removed under reduced pressure and the residue was diluted with EtOAc (100 mL) and saturated aqueous NaHCO₃ (20 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (3:1 EtOAc:hexanes) to give the N-methyl N-Ns amine 114 (957 mg, 100%) as a white solid (mp 118-121 °C). IR (film) 2942, 1722, 1662, 1527, 1346 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.7 Hz, 2H), 7.32 (m, 2H), 7.18 (d, J = 1.7 Hz, 1H), 7.11 (br s, 1H), 6.96 (br s, 1H), 6.80 (br s, 1H), 6.91 (br s, 1H), 5.45 (m, 2H), 3.86 (m, 1H), 3.81-3.79 (m, 1H), 3.39 (s, 7H), 3.08 (m, 1H), 2.71 (br s,
3H), 2.41 (br s, 1H), 2.19 (br s, 2H), 1.59 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$
177.4, 174.3, 158.8, 150.2, 144.3, 136.7, 134.6, 133.1, 130.5, 130.2, 128.8, 128.0, 124.6,
123.0, 121.0, 116.4, 111.3, 72.1, 57.0, 56.0, 54.5, 54.1, 49.7, 37.6, 35.4, 31.0, 27.7;
HRMS-ES [M+H]$^+$ calcd for C$_{30}$H$_{31}$Cl$_2$N$_4$O$_8$S, 677.1240; found, 677.1215.

**Synthesis of Imidate 115.** To a solution of N-methyl N-Ns amine 114 (957 mg, 1.41 mmol) in CH$_2$Cl$_2$ (50 mL) was added (Me$_3$O)BF$_4$ (460 mg, 3.11 mmol) at 0 °C, followed by (i-Pr)$_2$NEt (0.27 mL, 1.55 mmol). The reaction mixture was warmed to rt and stirred overnight. The mixture was diluted with CH$_2$Cl$_2$ (100 mL) and saturated aqueous NaHCO$_3$ (30 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the imidate 115 (757 mg, 78%) as a pale yellow oil. IR (film) 2946, 1724, 1676, 1528, 1460, 1349, 1164 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.29 (d, $J = 8.5$ Hz, 2H), 7.83 (d, $J = 8.4$ Hz, 2H), 7.32 (m,
2H), 7.14 (br s, 1H), 7.09-6.94 (m, 2H), 6.75 (d, $J = 8.1$ Hz, 1H), 5.71 (br s, 1H), 5.45,
5.40 (ABq, $J = 10.3$ Hz, 2H), 4.07-3.98 (m, 1H), 3.76-3.62 (m, 1H), 3.71 (s, 3H), 3.39 (s,
3H), 3.32 (s, 3H), 3.06 (m, 1H), 2.83 (br s, 1H), 2.70 (s, 3H), 2.33 (m, 1H), 2.24 (m, 1H),
1.85 (m, 1H), 1.50 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.7, 162.2, 158.5, 150.3,
144.6, 136.6, 135.2, 132.7, 130.3, 129.8, 128.7, 127.8, 124.8, 124.6, 123.7, 120.8, 116.1,
111.4, 72.0, 56.9, 54.5, 54.0, 53.0, 52.4, 49.8, 42.1, 35.2, 32.5, 29.4; HRMS-ES [M+H]$^+$ calcd for C$_{31}$H$_{33}$Cl$_2$N$_4$O$_8$S, 691.1396; found, 691.1415.
Synthesis of Amidine 104. To a solution of imidate 115 (757 mg, 1.10 mmol) in DMF (10 mL) was added Cs$_2$CO$_3$ (357 mg, 1.10 mmol), followed by benzenethiol (0.90 mL, 8.76 mmol) and the reaction mixture was heated at 50 °C for 2.5 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (100:10:1 CH$_2$Cl$_2$:MeOH:NH$_4$OH) to give the amidine 104 (469 mg, 90%) as a white solid (mp 164-166 °C). IR (film) 2935, 2849, 1725, 1665, 1644, 1461, 1246 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30 (m, 2H), 7.12 (d, $J$ = 2.0 Hz, 1H), 6.96 (t, $J$ = 7.8 Hz, 1H), 6.68 (d, $J$ = 8.0 Hz, 1H), 5.93 (d, $J$ = 1.9 Hz, 1H), 5.47 (s, 2H), 3.80 (m, 2H), 3.42 (s, 3H), 3.26 (s, 3H), 2.94-2.86 (m, 2H), 2.92 (s, 3H), 2.77 (ddd, $J$ = 5.0, 10.5, 10.5 Hz, 1H), 2.30 (ddd, $J$ = 8.0, 8.0, 11.0 Hz, 1H), 1.77 (ddd, $J$ = 5.8, 7.8, 13.6 Hz, 1H), 1.64 (ddd, $J$ = 5.2, 5.2, 13.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 178.4, 163.1, 158.6, 137.3, 136.5, 131.8, 130.0, 129.2, 127.5, 124.6, 124.2, 120.9, 115.8, 111.4, 72.0, 57.0, 54.5, 52.5, 52.3, 48.0, 43.3, 32.1, 31.6, 29.8; HRMS-ES [M+H]$^+$ calcd for C$_{24}$H$_{26}$Cl$_2$N$_3$O$_3$, 474.1351; found, 474.1382.

$N$-(2,4-Dichloro-6-iodophenyl)-4-hydroxy-2-(2-nitrobenzylidene)-butyramide (148). To a stirred solution of 2,4-dichloro-6-iodoaniline (67, 774 mg, 2.69 mmol) and lactone 147 (589 mg, 2.69 mmol) in CH$_2$Cl$_2$ (15 mL) was added AlMe$_3$ (1.48 mL, 2.0 M in hexane, 2.96 mmol) at 0 °C. The mixture was warmed to rt, stirred overnight and then poured into an iced aqueous 1N HCl (20 mL). The organic layer was washed with saturated aqueous
NaHCO₃ (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the amide 148 (1.08 g, 79%). ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, J = 7.5 Hz, 1H), 8.08 (s, 1H), 7.81 (d, J = 2.2 Hz, 1H), 7.79 (s, 1H), 7.71 (t, J = 7.1 Hz, 1H), 7.56 (t, J = 7.3 Hz, 1H), 7.52 (d, 8.0 Hz, 1H), 7.50 (d, J = 2.2 Hz, 1H), 3.77 (t, J = 5.8 Hz, 2H), 2.66 (t, J = 5.8 Hz, 2H), 2.41 (bs, 1H).

4-(tert-Butyldimethylsilanyloxy)-N-(2,4-dichloro-6-iodophenyl)-2-(2-nitrobenzylidene)-butyramide (149). To a solution of the amide 148 (1.08 g, 2.13 mmol) and imidazole (174 mg, 2.56 mmol) in DMF (10 mL) was added TBDMSCl (354 mg, 2.34 mmol) in a single portion. The reaction mixture was stirred at rt for 2 h and then diluted with EtOAc (200 mL). The solution was washed with water (3×20 mL) and brine (20 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to give the TBDMS ether 149 (1.06 g, 80%). ¹H NMR (300 MHz, CDCl₃) δ 8.88 (s, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.75 (s, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.60-7.44 (m, 3H), 7.33 (d, J = 2.2 Hz, 1H), 3.68 (t, J = 5.6 Hz, 1H), 2.62 (t, J = 5.5 Hz, 1H), 0.79 (s, 9H), -0.03 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 167.7, 147.9, 137.5, 136.7, 136.2, 134.3, 134.1, 133.9, 133.7, 132.0, 131.9, 130.2, 129.4, 125.2, 101.0, 62.8, 31.7, 26.3, 18.7, -5.0.
4-(tert-Butyldimethylsilylanyloxy)-N-(2,4-dichloro-6-iodophenyl)-N-methoxymethyl-2-(2-nitrobenzylidene)-butyramide (150). To a stirred suspension of NaH (20 mg, 60% dispersion in mineral oil, 0.508 mmol) in THF (15 mL) was added a solution of lactam 149 (263 mg, 0.423 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at rt for 30 min and recooled to 0 °C. To the mixture was added MOMCl (0.048 mL, 0.635 mmol) and the reaction mixture was warmed to rt and stirred for 1.5 h. The reaction mixture was diluted with saturated aqueous NH₄Cl (10 mL) and extracted with EtOAc (150 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the N-MOM amide 150 (156 mg, 55%). ¹H NMR (360 MHz, CDCl₃) (5:1 atropisomeric mixture) δ 8.16 (d, J = 8.2 Hz, 1H, major), 8.01 (d, J = 8.3 Hz, 1H, minor), 7.86 (s, 1H, major), 7.78-7.63 (m, 3H, major), 7.54-7.50 (m, 2H, major, 3H, minor) 7.13 (d, J = 7.8 Hz, 1H, minor), 6.90 (s, 1H, minor), 5.32, 4.96 (ABq, J = 9.1 Hz, 2H, minor), 5.20, 5.06 (ABq, J = 10.3 Hz, 2H, major), 3.83-3.80 (m, 2H, major), 3.74-3.66 (m, 2H, minor), 3.57 (s, 3H, minor), 3.28 (s, 3H, major), 2.72-2.68 (m, 2H, major), 2.53-2.42 (m, 2H, minor), 0.89 (s, 9H, major), 0.79 (s, 9H, minor), 0.05 (s, 6H, major), -0.07 (s, 6H, minor).

3-[2-(tert-Butyldimethylsilylanyloxy)ethyl]-5,7-dichloro-1-methoxymethyl-3-(2-nitrobenzyl)-1,3-dihydroindol-2-one (153). To a solution of N-MOM amide 150 (26.2 mg, 39.4 μmol) in DMA (1.5 mL) was added Herrmann’s palladacyle (7.4 mg, 7.9 μmol), n-Bu₄NBr
(25.4 mg, 78.8 μmol) and NaOAc (6.5 mg, 79.2 μmol). The mixture was stirred at 90 °C under a CO atmosphere (1 atm) for 5 h. The reaction mixture was cooled to rt and MeOH (1 mL) was added. The mixture was stirred at rt for 1 h and diluted with EtOAc (60 mL). The solution was washed with water (3×15 mL) and brine (15 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:10 EtOAc:hexanes) to give protonolysis adduct 36 (15.0 mg, 71%).

1H NMR (360 MHz, CDCl₃) δ 7.82 (dd, J = 1.3, 8.1 Hz, 1H), 7.53 (ddd, J = 1.4, 7.5, 7.5 Hz, 1H), 7.43 (ddd, J = 1.4, 7.4, 7.4 Hz, 1H), 7.39 (s, 1H), 7.35 (dd, J = 1.3, 7.7 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 5.33, 5.29 (ABq, J = 10.6 Hz, 2H), 3.98, 3.58 (ABq, J = 13.7 Hz, 2H), 3.50 (m, 2H), 3.28 (s, 3H), 2.47 (ddd, J = 6.9, 6.9, 13.8 Hz, 1H), 2.22 (ddd, J = 5.7, 5.7, 13.7 Hz, 1H), 0.87 (s, 9H), 0.01 (d, J = 0.7 Hz, 6H); LRMS-ES: [M+Na]⁺ calcd for C₂₅H₃₂Cl₂N₂NaO₅Si, 561.1; found, 561.0.

**Heck/Carbonylation of N-MOM Amide 150.** Method A: To a solution of N-MOM amide 150 (31.5 mg, 47.3 μmol) in DMA (1.6 mL) and MeOH (0.8 mL) was added Herrmann’s palladacyle (4.4 mg, 4.7 μmol), n-Bu₄NBr (30.5 mg, 94.6 μmol) and NEt₃ (30 μL, 0.215 mmol). The mixture was stirred at 90 °C under a CO atmosphere (1 atm) for 22 h. The reaction mixture was cooled to rt and diluted with EtOAc (80 mL). The solution was washed with water (3×20 mL) and brine (20 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:10 EtOAc:hexanes) to give methyl ester 151 (15.4 mg, 54%) and direct carbonylated adduct 152 (5.2 mg, 18%).
Method B: To a solution of \(N\)-MOM amide 150 (29.0 mg, 43.6 \(\mu\)mol) in DMA (1.6 mL) and MeOH (0.8 mL) was added Pd(OAc)_2 (2.0 mg, 8.9 \(\mu\)mol), P(o-Tol)_3
(8.0 mg, 26.3 \(\mu\)mol), \(n\)-Bu_4NBr (28.1 mg, 87.2 \(\mu\)mol) and NEt_3 (30 \(\mu\)L, 0.215 mmol). The mixture was stirred at 90 °C under a CO atmosphere (1 atm) for 22 h. The reaction mixture was cooled to rt and diluted with EtOAc (80 mL). The solution was washed with water (3×20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (1:10 EtOAc:hexanes) to give methyl ester 151 (16.4 mg, 63%) and direct carbonylated adduct 152 (5.2 mg, 20%).

\[
\begin{align*}
\text{3-[2-\(\text{tert}\)-Butyldimethylsilanyloxy)-ethyl]-5,7-} \\
\text{dichloro-1-methoxymethyl-2-oxo-2,3-dihydro-1\text{H}-indol-3-yl]-} \\
\text{(2-nitrophenyl)-acetic Acid Methyl Ester (151):} \quad \text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3) \quad \delta 7.93 \text{(dd, } J = 1.5, 7.9 \text{ Hz, 1H}), 7.59-7.44 \text{(m, 3H), 7.24 \text{(d, } J = 2.0 \text{ Hz, 1H)}, 6.61 \text{(d, } J = 2.0 \text{ Hz, 1H}), 5.39, 5.33 \text{(ABq, } J = 10.7 \text{ Hz, 2H), 5.24 \text{(s, 1H), 3.64 \text{(s, 3H), 3.43 \text{(s, 3H), 3.21 \text{(m, 2H), 2.24 \text{(m 1H), 2.13 \text{(m, 1H), 0.72 \text{(s, 9H), -0.16 \text{(s, 6H);}}} \\
\text{13C NMR (75 MHz, CDCl}_3) \quad \delta 178.76, 170.60, 151.06, 138.46, 133.10, 132.51, 132.37, 130.74, 129.83, 128.18, 127.83, 125.50, 124.16, 116.96, 72, 63, 59.32, 57.23, 53.03, 52.86, 51.02, 37.78, 26.14, 18.56; LRMS-ES: [M+Na]^+ \text{ calcd for C}_{27}H_{34}Cl_2N_2O_7Si, 619.1; found, 619.0.}
\end{align*}
\]

\[
\begin{align*}
2-\{4-\(\text{tert}\)-Butyldimethylsilanyloxy)-2-(2-\text{nitrobenzylidene})-butyryl\}-\text{methoxymethylamino}\}-3,5- \\
\text{dichlorobenzoic Acid Methyl Ester (152):} \quad \text{\textsuperscript{1}H NMR (360 MHz, CDCl}_3) \quad \delta 8.16 \text{(d, } J = 8.1 \text{ Hz, 1H, \textit{major}), 7.96 \text{(d, } J = 8.2}
\end{align*}
\]
Hz, 1H, minor), 7.88 (d, J = 2.3 Hz, 1H, major), 7.86 (m, 1H, minor) 7.75 (d, J = 7.6 Hz, 1H, major), 7.70 (d, J = 2.3 Hz, 1H, major), 7.68 (m, 1H, minor), 7.65 (t, J = 7.8 Hz, 1H, major), 7.53-7.50 (m, 2H, major, 1H, minor), 7.41 (t, J = 8.1 Hz, 1H, minor), 7.22 (d, J = 8.0 Hz, 1H, minor), 7.08 (s, 1H, minor), 5.26, 4.79 (ABq, J = 10.1 Hz, 2H, major), 5.23, 4.88 (ABq, J = 10.4 Hz, 2H, minor), 3.92 (s, 3H, minor), 3.90 (s, 3H, major), 3.83 (t, J = 6.1 Hz, 2H, major), 3.70-3.64 (m, 2H, minor), 3.47 (s, 3H, minor), 3.23 (s, 3H, major), 2.67 (m, 2H, major), 2.49 (m, 2H, minor), 0.88 (s, 9H, major), 0.80 (s, 9H, minor), 0.04 (s, 6H, major), -0.06 (s, 6H, minor); LRMS-ES: [M+Na]^+ calcd for C_{27}H_{34}Cl_{2}N_{2}NaO_{7}Si, 619.1; found, 619.0.

(4-Bromo-2-nitrophenyl)-{3-[2-(tert-butyldimethyl silanyloxy)-ethyl]-5,7-dichloro-1-methoxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl}-acetic Acid Methyl Ester (77). To a solution of N-MOM amide 76 (27.4 mg, 0.037 mmol) in DMA (2.0 mL) and MeOH (0.4 mL) were added Pd_{2}(dba)_{3} (3.4 mg, 0.004 mmol), P(o-Tol)_{3} (4.5 mg, 0.015 mmol), n-Bu_{4}NBr (23.7 mg, 0.074 mmol) and NEt_{3} (26 μL, 0.187 mmol). The mixture was stirred at 85 °C under a CO atmosphere (1 atm) for 21 h. The remaining catalyst was removed by filtration and washed with EtOAc. The filtrate was washed with water (3×10 mL) and brine (10 mL), dried over Na_{2}SO_{4} and concentrated in vacuo. The crude mixture was used for the next step without further purification. For analytical purposes the compounds were separated by preparative TLC (1:5 EtOAc:hexanes). More polar major diastereomeric of 77a (pale yellow oil): IR (film) 2946, 2860, 1735, 1536, 1461, 1095 cm⁻¹; ¹H NMR
(400 MHz, CDCl₃) δ 8.05 (d, J = 2.1 Hz, 1H), 7.70 (dd, J = 2.1, 8.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 5.37, 5.30 (ABq, J = 10.5 Hz, 2H), 5.09 (s, 1H), 3.65 (s, 3H), 3.42 (s, 3H), 3.24 (ddd, J = 2.6, 6.2, 6.2 Hz, 2H), 2.25 (ddd, J = 3.7, 6.2, 6.2 Hz, 2H), 0.72 (s, 9H), -0.17 (d, J = 2.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 178.4, 170.2, 151.3, 138.3, 135.6, 133.5, 133.0, 130.9, 128.5, 128.4, 126.8, 124.0, 123.2, 117.2, 72.6, 59.4, 57.1, 53.1, 52.8, 50.4, 37.2, 26.1, 18.6, -5.3, -5.4; HRMS-ES [M+H]+ calcd for C₂₇H₃₄BrCl₂N₂O₇Si, 675.0696; found, 675.0712. Less polar minor diastereomer of 77b (pale yellow oil): IR (film) 2946, 2860, 1735, 1536, 1461 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, J = 2.1 Hz, 1H), 7.56 (dd, J = 2.1, 8.5 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 5.24, 5.19 (ABq, J = 10.5 Hz, 2H), 5.16 (s, 1H), 3.64 (s, 3H), 3.29 (t, J = 6.2 Hz, 2H), 3.22 (s, 3H), 2.22-2.12 (m, 2H), 0.72 (s, 9H), -0.17 (d, J = 2.2 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 178.6, 170.4, 151.4, 138.3, 135.7, 133.7, 133.5, 131.2, 129.0, 128.1, 127.0, 124.3, 123.0, 116.9, 72.3, 59.3, 56.8, 53.3, 53.2, 51.0, 39.3, 26.1, 18.6, -5.3, -5.4; HRMS-ES [M+H]+ calcd for C₂₇H₃₄BrCl₂N₂O₇Si, 675.0696; found, 675.0672.

3-(4-Benzoyl-2-nitrobenzyl)-3-[2-(tert-butyldimethylsilanyloxy)-ethyl]-5,7-dichloro-1-methoxymethyl-1,3-dihydroindol-2-one (78). Pale yellow oil. IR (film) 2935, 2860, 1730, 1536, 1461, 1348 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 2.0 Hz, 1H), 7.52 (dd, J = 2.0, 8.3 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 5.19 (s, 2H), 3.80, 3.41 (ABq, J = 13.7 Hz, 2H), 3.37 (m, 2H), 3.32 (s, 3H), 2.32 (ddd, J = 6.9, 6.9, 13.8 Hz, 1H), 2.08 (ddd, J = 5.5, 5.5, 13.8 Hz, 1H), 0.75 (s,
9H), -0.14 (d, J = 3.4 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 179.4, 150.8, 137.3, 135.7, 135.1, 133.8, 130.6, 129.3, 128.9, 128.1, 123.4, 121.8, 116.9, 72.0, 59.5, 56.5, 52.8, 40.3, 39.6, 26.1, 18.5, -5.36, -5.37; HRMS-ES [M+H]$^+$ calcd for C$_{25}$H$_{32}$BrCl$_2$N$_2$O$_5$Si, 617.0641; found, 617.0659.

2-{{[2-(4-Bromo-2-nitrobenzylidene)-4-(tert-butyldimethylsilanyloxy)-butyryl]-methoxymethylamino}-3,5-dichlorobenzoic Acid Methyl Ester (154). Yellow solid (mp 125-126 °C). IR (film) 2946, 2860, 1730, 1665, 1531, 1278 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$, 5:1 atropisomeric mixture) δ 8.30 (d, J = 1.8 Hz, 1H, major), 8.09 (d, J = 1.7 Hz, 1H, minor), 7.89 (d, J = 2.4 Hz, 1H, major), 7.85 (d, J = 2.4 Hz, 1H, minor), 7.77 (d, J = 1.8 Hz, 1H, minor), 7.75-7.69 (m, 3H, major), 7.67 (m, 1H, minor), 7.46 (s, 1H, major), 7.22 (d, J = 8.2 Hz, 1H, minor), 7.00 (s, 1H, minor), 5.23, 4.85 (ABq, J = 10.5 Hz, 2H, minor), 5.20, 4.79 (ABq, J = 10.2 Hz, 2H, major), 3.92 (s, 3H, minor), 3.89 (s, 3H, major), 3.84 (t, J = 6.0 Hz, 2H, major), 3.74 (m, 2H, minor), 3.46 (s, 3H, minor), 3.21 (s, 3H, major), 2.68 (m, 2H, major), 2.41 (m, 2H, minor), 0.90 (s, 9H, major), 0.83 (s, 9H, minor), 0.07 (s, 6H, major), -0.02 (s, 6H, minor); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.7, 164.7, 148.5, 137.6, 136.6, 136.4, 136.2, 134.9, 134.1, 133.8, 133.1, 130.9, 130.5, 129.4, 128.2, 122.4, 83.3, 61.0, 56.8, 53.3, 33.4, 26.3, 18.7, -5.0; HRMS-ES [M+H]$^+$ calcd for C$_{27}$H$_{34}$BrCl$_2$N$_2$O$_7$Si, 675.0696; found, 675.0665.

**Synthesis of Spiro Lactone 155.** To a stirred solution of the above crude mixture of Heck/carbonylation adducts in THF...
(3.0 mL) was added TBAF (0.072 mL, 1.0 M in THF, 0.072 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The mixture was diluted with EtOAc (50 mL) and saturated aqueous NH₄Cl (10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to give the spiro lactone 155 (9.9 mg, 51% over 2 steps) as a pale yellow oil. IR (film) 2924, 1725, 1531, 1455, 1348 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (4:1 diastereomeric mixture) δ 7.95 (s, 1H, minor), 7.79 (d, J = 1.9 Hz, 1H, major), 7.61 (dd, J = 1.9, 8.5 Hz, 1H, major), 7.45 (dd, J = 1.8, 8.6 Hz, 1H, minor), 7.41 (d, J = 8.5 Hz, 1H, major), 7.34 (s, 1H, minor), 7.25 (d, J = 1.8 Hz, 1H, major), 7.22 (s, 1H, minor), 7.12 (d, J = 1.7 Hz, 1H, major), 6.68 (d, J = 8.5 Hz, 1H, minor), 5.50 (bs, 1H, minor), 5.44 (s, 1H, major), 5.30 (s, 1H, minor), 5.21, 5.18 (ABq, J = 10.3 Hz, 2H, major), 5.13 (s, 1H, minor), 5.06 (ddd, J = 4.2, 4.2, 11.5 Hz, 1H, major), 4.85 (m, 1H, minor), 4.72 (m, 1H, minor), 4.64 (ddd, J = 4.7, 4.7, 11.7 Hz, 1H, major), 3.23 (s, 3H, major), 2.99 (s, 3H, minor), 2.59-2.52 (m, 1H, major and minor), 2.26 (m, 1H, minor), 2.19 (ddd, J = 4.0, 4.0, 14.6 Hz, 1H, major); ¹³C NMR (75 MHz, CDCl₃) δ 177.4, 168.8, 150.6, 136.3, 136.2, 134.5, 132.5, 131.8, 130.5, 127.9, 126.6, 123.1, 122.7, 117.6, 72.0, 65.2, 56.8, 52.7, 46.8, 33.2; HRMS-ES [M+Na]⁺ calcd for C₂₀H₁₅BrCl₂N₂NaO₆, 550.9388; found, 550.9388.

**Allylation of Spiro Lactone 155.** To a stirred suspension of spiro lactone 155 (102 mg, 0.191 mmol) and NaH (9.2 mg, 60% dispersion in mineral oil, 0.230 mmol) in DMF (2.0 mL)
was added allyl iodide (0.026 mL, 0.287 mmol) at 0 °C. The mixture was stirred at rt for 1 h and heated to 90 °C for 7 h. The reaction mixture was cooled to rt, diluted with saturated aqueous NH₄Cl (10 mL) and extracted with EtOAc (70 mL). The organic layer was washed with water (3×20 mL) and brine (20 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the allyl lactone 156 (95 mg, 87%) as a yellow solid (mp 157-158 °C). Recrystallization from EtOAc provided X-ray quality crystals of 156. IR (film) 2924, 1725, 1536, 1359 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, J = 2.0 Hz, 1H), 7.33 (dd, J = 2.0, 8.6 Hz, 1H), 7.10 (d, J = 1.9 Hz, 1H), 6.81 (d, J = 1.8 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 5.51-5.34 (m, 4H), 4.99 (d, J = 17.2 Hz, 1H), 4.94 (d, J = 10.4 Hz, 1H), 4.61 (dd, J = 4.0, 4.0, 11.6 Hz, 1H), 3.44 (s, 3H), 3.35 (dd, J = 6.3, 15.2 Hz, 1H), 2.99 (ddd, J = 4.3, 10.9, 15.2 Hz, 1H), 2.86 (dd, J = 7.1, 15.4 Hz, 1H), 2.16 (ddd, J = 3.0, 3.0, 14.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 178.3, 168.0, 150.8, 136.1, 134.8, 134.3, 132.7, 132.6, 132.4, 131.1, 129.0, 128.0, 125.1, 122.1, 120.3, 116.9, 72.3, 65.0, 57.1, 54.4, 54.2, 44.1, 31.5; HRMS-ES [M+Na]⁺ calcd for C₂₃H₁₉BrCl₂N₂NaO₆, 590.9701; found, 590.9697.

3'-Allyl-6'-bromo-5,7-dichloro-3-(2-hydroxyethyl)-1-methoxymethyl-1,3,1',3'-tetrahydro-[3,3']biindolyl-2,2'-dione (158). To a solution of the allyl lactone 156 (93.2 mg, 0.163 mmol) in EtOH (2.0 mL) and glacial acetic acid (1.0 mL) was added iron powder (36.4 mg, 0.652 mmol). The mixture was heated at 60 °C for 1 h and
then cooled to rt. The mixture was diluted with water (20 mL) and carefully neutralized with solid Na$_2$CO$_3$. The resulting solution was extracted with EtOAc (2×40 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2:0.1 EtOAc:hexanes:NEt$_3$) to give the bis-oxyindole 158 (73.7 mg, 84%). $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 10.79 (bs, 0.3H), 9.83 (bs, 0.7H), 7.17 (d, $J$ = 2.1 Hz, 1H), 7.14 (d, $J$ = 2.1 Hz, 1H), 7.05 (dd, $J$ = 1.8, 8.1 Hz, 1H), 6.95 (d, $J$ = 8.1 Hz, 1H), 6.80 (d, $J$ = 1.8 Hz, 1H), 5.31, 5.23 (ABq, $J$ = 10.7 Hz, 2H), 5.16-5.03 (m, 1H), 4.96 (dd, $J$ = 2.2, 17.2 Hz, 1H), 4.80 (dd, $J$ = 2.5, 9.7 Hz, 1H), 3.53-3.44 (m, 2H), 3.37 (s, 3H), 3.33 (m, 1H), 3.20-3.07 (m, 2H), 2.92 (m, 1H), 2.54 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$+CD$_3$OD) $\delta$ 179.2, 178.9, 142.8, 137.5, 131.8, 131.7, 130.8, 128.5, 126.9, 125.6, 125.0, 123.4, 122.6, 120.0, 116.3, 113.3, 72.1, 58.7, 57.1, 57.0, 53.9, 33.8, 31.9.

3'-Allyl-6'-bromo-3-[2-(tert-butyldimethylsilanyl oxy)-ethyl]-5,7-dichloro-1-methoxymethyl-1,3,1',3'-tetrahydro-[3,3']biindolyl-2,2'-dione (159). To a solution of the bis-oxyindole 158 (6.8 mg, 13 µmol) and imidazole (1.7 mg, 25 µmol) in DMF (0.5 mL) was added TBDMSCl (2.8 mg, 19 µmol) in a single portion. The reaction mixture was stirred at rt for 1 h and then diluted with EtOAc (15 mL). The solution was washed with water (3×5 mL) and brine (5 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by preparative TLC (1:4 EtOAc:hexanes) to give the TBDMS ether 159 (7.0 mg, 85%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.57 (s, 1H), 7.14 (d, $J$ = 2.0 Hz,
1H), 7.00 (dd, J = 1.6, 8.1 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.74 (d, J = 1.6 Hz, 1H), 5.29 (s, 2H), 5.11-5.01 (m, 2H), 4.83 (dd, J = 3.8, 8.2 Hz, 1H), 3.50 (dd, J = 5.2, 13.0 Hz, 1H), 3.43 (s, 3H), 3.36 (m, 1H), 3.25-3.11 (m, 2H), 2.95 (m, 1H), 2.56 (m, 1H), 0.75 (s, 9H), -0.14 (s, 6H).

**Boc Protection of γ-Lactam 159.** To a stirred solution of γ-lactam 159 (7.0 mg, 11 μmol) in CH₂Cl₂ (1 mL) was added NEt₃ (3.0 μL, 22 μmol), DMAP (1.3 mg, 11 μmol) and (Boc)₂O (4.9 μL, 21 μmol). The reaction mixture was stirred at rt for 2 h and diluted with CH₂Cl₂ (15 mL). The solution was washed with saturated aqueous NH₄Cl (5 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the N-Boc γ-lactam 160 (7.1 mg, 88%) as white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, J = 1.7 Hz, 1H), 7.13 (dd, J = 1.8, 8.2 Hz, 1H), 7.10 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 5.24 (s, 2H), 5.04-4.96 (m, 2H), 4.83 (m, 1H), 3.51 (m, 1H), 3.41 (s, 3H), 3.35 (m, 1H), 3.23 (m, 1H), 3.01 (m, 2H), 2.57 (m, 1H), 1.67 (s, 9H), 0.74 (s, 9H), -0.15 (s, 6H).

**Ozonolysis and Reductive Work-up of N-Boc γ-Lactam 160.** A stream of ozone was passed through a solution of N-Boc γ-lactam 160 (2.1 mg, 2.8 μmol) in CH₂Cl₂ (1 mL) at −78 °C for 1 min. Excess ozone was removed with a stream of nitrogen until the blue color disappeared. The ozonide solution was quenched with excess BH₃•Me₂S (2.0 M in
Et₂O), warmed to rt and stirred overnight. To the mixture was carefully added 1N aqueous HCl (1 mL). After 1 h of vigorous stirring, the aqueous layer was extracted with CH₂Cl₂ (2×5 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ solution (5 mL) and brine (5 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by preparative TLC (1:2 EtOAc:hexanes) to give hydroxy bis-oxyindole 161 (1.7 mg, 81%). ¹H NMR (300 MHz, CDCl₃) δ 7.77 (d, J = 1.7 Hz, 1H), 7.14-7.10 (m, 3H), 6.95 (d, J = 8.1 Hz, 1H), 5.23, 5.21 (ABq, J = 10.2 Hz, 2H), 3.54 (m, 1H), 3.40 (s, 3H), 3.35 (m, 1H), 3.26-3.00 (m, 4H), 2.67-2.48 (m, 2H), 1.67 (s, 9H), 0.74 (s, 9H), -0.15 (s, 6H).

3-Chloro-2-iodophenylamine (173). To a solution of 1-chloro-2-ido-3-nitrobenzene⁴⁸ (172, 1.26 g, 4.46 mmol) in EtOH (7 mL) and glacial acetic acid (7 mL) was added iron powder (0.995 g, 17.8 mmol). The mixture was heated at 60 °C for 2 h and then cooled to rt. The mixture was diluted with water (100 mL) and carefully neutralized with solid Na₂CO₃. The resulting solution was extracted with CH₂Cl₂ (2×100 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo to yield a brown oil, which was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the aniline 173 (0.97 g, 86%) as a yellow solid. ¹H NMR (360 MHz, CDCl₃) δ 7.03 (t, J = 7.9 Hz, 1H), 6.84 (dd, J = 1.4, 7.8 Hz, 1H), 6.59 (dd, J = 1.4, 8.0 Hz, 1H), 4.31 (br s, 2H); ¹³C NMR (90 MHz, CDCl₃) δ 149.5, 139.5, 129.3, 119.2, 112.5, 88.7.
**N-(3-Chloro-2-iodophenyl)-2-methyl-3-phenylacrylamide (175).** A mixture of α-methylcinnamic acid (714 mg, 4.40 mmol) and SOCl₂ (6.5 mL) was heated at reflux for 3 h. Excess SOCl₂ was removed under reduced pressure and the residue was diluted with CH₂Cl₂ (2.2 mL). To a stirred solution of the aniline 173 (970 mg, 3.83 mmol) and (i-Pr)₂NEt (2.0 mL, 11.5 mmol) in CH₂Cl₂ (20 mL) was added the acid chloride dropwise at rt. After 2 h the reaction mixture was diluted with CH₂Cl₂ (50 mL). The solution was washed with 1N aqueous HCl (10 mL), dried over K₂CO₃ and concentrated in vacuo. The residue was purified by flash column chromatography (1:10 EtOAc:hexanes) to give the amide 175 (1.39 g, 91%) as a white solid.¹H NMR (360 MHz, CDCl₃) δ 8.31 (dd, J = 1.6, 8.1 Hz, 1H), 8.24 (br s, 1H), 7.61 (d, J = 1.2 Hz, 1H), 7.42-7.39 (m, 4H), 7.36-7.32 (m, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.24 (dd, J = 1.5, 8.0 Hz, 1H), 2.28 (d, J = 1.3 Hz, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 167.8, 141.1, 139.3, 136.3, 136.1, 132.5, 130.3, 129.9, 128.9, 128.7, 125.3, 119.7, 95.7, 14.9.

**N-(3-Chloro-2-iodophenyl)-2,N-dimethyl-3-phenylacrylamide (176).** To a stirred suspension of NaH (56 mg, 60% dispersion in mineral oil, 1.40 mmol) in THF (25 mL) was added a solution of amide 175 (483 mg, 1.21 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at rt for 30 min and recooled to 0 °C. To the mixture was added MeI (91 μL, 1.46 mmol) and the reaction mixture was warmed to rt and stirred for 6 h. The reaction mixture was diluted with saturated aqueous NH₄Cl (5 mL) and water (25 mL) and extracted with EtOAc (2×50 mL). The combined organic layers were dried over MgSO₄
and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes, to give the N-methyl amide 176 (449 mg, 90%) as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38 (dd, $J = 1.3, 8.0$ Hz, 1H), 7.31-7.21 (m, 4H), 7.10 (d, $J = 7.5$ Hz, 1H), 7.04 (br s, 2H), 6.71 (br s, 1H), 3.30 (s, 3H), 1.92 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.4, 149.9, 141.0, 136.2, 133.6, 133.1, 130.3, 129.3, 128.7, 128.6, 127.9, 127.7, 104.9, 37.6, 16.6.

(4-Chloro-1,3-dimethyl-2-oxo-2,3-dihydro-$1H$-indol-3-yl)-phenylacetic Acid Methyl Ester (177). To a solution of N-methyl amide 176 (37.3 mg, 0.091 mmol) in DMA (2 mL) and MeOH (1 mL) was added Pd(OAc)$_2$ (2.0 mg, 0.0089 mmol), P(o-Tol)$_3$ (8.3 mg, 0.027 mmol) and NaOAc (14.9 mg, 0.18 mmol). The mixture was stirred at 90 °C under a CO atmosphere (1 atm) for 22 h. The reaction mixture was cooled to rt and diluted with EtOAc (60 mL). The solution was washed with water (3×20 mL), dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to give the ester 177 (26.4 mg, 85%) as a white solid. $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.16-7.14 (m, 2H), 7.06-7.01 (m, 3H), 6.99 (d, $J = 7.9$ Hz, 1H), 6.85 (dd, $J = 0.8, 8.2$ Hz, 1H), 6.40 (dd, $J = 0.7, 7.8$ Hz, 1H), 4.56 (s, 1H), 3.79 (s, 3H), 3.05 (s, 3H), 1.82 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 177.0, 170.5, 144.6, 134.5, 130.2, 129.2, 128.7, 128.6, 127.44, 127.36, 123.4, 106.1, 54.1, 52.7, 52.1, 26.2, 19.7.
2-Iodo-1-methoxymethoxy-3-nitrobenzene (179). To a stirred suspension of NaH (1.67 g, 60% dispersion in mineral oil, 41.8 mmol) in THF (70 mL) was added a solution of 2-iodo-3-nitrophenol (178)\textsuperscript{51} (10.1 g, 38.0 mmol) in THF (30 mL) at 0 °C. The mixture was stirred at rt for 30 min and recooled to 0 °C. To the solution was added MOMCl (3.32 mL, 43.7 mmol) and the reaction mixture was warmed to rt and stirred for 4 h. The reaction mixture was diluted with saturated aqueous NH\textsubscript{4}Cl (2 mL) and water (20 mL) and extracted with EtOAc (2×150 mL). The combined organic layers were dried over MgSO\textsubscript{4} and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the MOM ether 179 (11.8 g, 97%) as a yellow solid. \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) δ 7.41 (t, J = 8.1 Hz, 1H), 7.32 (dd, J = 1.4, 8.0 Hz, 1H), 7.25 (dd, J = 1.3, 8.2 Hz, 1H), 5.32 (s, 2H), 3.52 (s, 3H); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) δ 158.0, 155.8, 130.5, 118.2, 117.8, 95.8, 81.3, 57.2.

2-Iodo-3-methoxymethoxyphenylamine (180). To a solution of the MOM ether 179 (442 mg, 1.43 mmol) in EtOH (3 mL) and glacial acetic acid (3 mL) was added iron powder (281 mg, 5.02 mmol). The mixture was heated at 60 °C for 4 h and then cooled to rt. The mixture was diluted with water (20 mL) and carefully neutralized with solid Na\textsubscript{2}CO\textsubscript{3}. The resulting solution was extracted with EtOAc (2×50 mL). The combined organic layers were dried over MgSO\textsubscript{4} and concentrated in vacuo to yield a brown oil which was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the aniline 180 (379 mg, 95%) as an oil. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.02 (t, J = 8.1 Hz, 1H), 6.41 (d, J = 8.0 Hz, 2H), 5.20 (s, 2H), 4.23 (br s, 2H),
3.49 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 157.0, 148.9, 130.0, 109.0, 104.4, 95.3, 77.9, 56.9.

$N$-(2-Iodo-3-methoxymethoxyphenyl)-2-methyl-3-phenylacrylamide (181). A mixture of $\alpha$-methylcinnamic acid (1.18 g, 7.30 mmol) and SOCl$_2$ (10 mL) was heated at reflux for 2 h. Excess SOCl$_2$ was removed under reduced pressure and the residue was diluted with CH$_2$Cl$_2$ (5 mL). To a stirred solution of the aniline 180 (1.94 g, 6.95 mmol) and ($i$-Pr)$_2$NEt (2.5 mL, 14.3 mmol) in CH$_2$Cl$_2$ (25 mL) was added the acid chloride dropwise at rt. After 4 h the reaction mixture was diluted with CH$_2$Cl$_2$ (80 mL). The solution was washed with 1N aqueous HCl (10 mL), dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the amide 181 (2.68 g, 91%) as a yellow oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.26 (br s, 1H), 8.12 (dd, $J$ = 1.2, 8.2 Hz, 1H), 7.61 (d, $J$ = 1.3 Hz, 1H), 7.41-7.27 (m, 6H), 6.84 (dd, $J$ = 1.2, 8.3 Hz, 1H), 5.25 (s, 2H), 3.50 (s, 3H), 2.29 (d, $J$ = 1.4 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.5, 155.3, 138.9, 135.0, 134.7, 131.4, 129.0, 128.6, 127.6, 127.3, 114.3, 109.4, 94.2, 83.0, 55.7, 13.6.

$N$-(2-Iodo-3-methoxymethoxyphenyl)-2,N-dimethyl-3-phenylacrylamide (182). To a stirred suspension of NaH (43 mg, 60% dispersion in mineral oil, 1.07 mmol) in THF (4 mL) was added a solution of the amide 181 (377 mg, 0.89 mmol) in THF (4 mL) at 0 °C. The mixture was
stirred at rt for 1 h and recooled to 0 °C. To the solution was added MeI (80 μL, 1.29 mmol) and the reaction mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with saturated aqueous NH₄Cl (0.5 mL) and water (5 mL) and extracted with EtOAc (2×20 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the N-methyl amide 182 (363 mg, 93%) as a white solid. ¹H NMR (360 MHz, CDCl₃) δ 7.29-7.18 (m, 4H), 7.02 (br s, 2H), 6.97 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.71 (br s, 1H), 5.25 (s, 2H), 3.49 (s, 3H), 3.30 (s, 3H), 1.91 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 173.4, 158.0, 149.1, 136.5, 133.4, 133.1, 130.3, 130.0, 128.5, 127.7, 123.2, 113.8, 95.5, 93.3, 56.9, 37.5, 16.6.

*N-(3-Hydroxy-2-iodophenyl)-2,N-dimethyl-3-phenylacrylamide* (183). To a stirred solution of the MOM ether 182 (66 mg, 0.15 mmol) in MeOH (10 mL) was added concentrated HCl (5 drops) at rt. The reaction mixture was stirred at 40 °C for 10 h. The solvent was removed under reduced pressure. To the residue was added EtOAc (80 mL) and water (10 mL). The organic layer was separated, dried over MgSO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography (20:1 CH₂Cl₂:MeOH) to give the phenol 183 (60 mg, 100%) as a white solid. ¹H NMR (360 MHz, CDCl₃+CD₃OD) δ 7.28-7.15 (m, 4H), 7.03 (d, J = 7.2 Hz, 2H), 6.81-6.72 (m, 3H), 3.29 (s, 3H), 1.91 (s, 3H).
Acetic Acid 2-Iodo-3-[methyl-(2-methyl-3-phenylacryloyl)-amino]-phenyl Ester (184a). To a stirred solution of the phenol 183 (68 mg, 0.17 mmol), NEt₃ (29 μl, 0.21 mmol) and DMAP (2.1 mg, 0.02 mmol) in CH₂Cl₂ (5 mL) was added AcCl (15 μl, 0.21 mmol) at 0 °C. The mixture was warmed to rt and stirred for 1 h. The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with water (10 mL) and brine (10 mL), dried over MgSO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the acetyl phenol 184a (74 mg, 98%) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.35 (t, J = 7.9 Hz, 1H), 7.29-7.17 (m, 3H), 7.11-7.01 (m, 4H), 6.69 (br s, 1H), 3.31 (s, 3H), 2.37 (s, 3H), 1.89 (s, 3H).

Methanesulfonic Acid 2-Iodo-3-[methyl-(2-methyl-3-phenylacryloyl)-amino]-phenyl Ester (184b). To a stirred solution of the phenol 183 (136 mg, 0.34 mmol), NEt₃ (96 μl, 0.69 mmol) and DMAP (4.2 mg, 0.03 mmol) in CH₂Cl₂ (10 mL) was added MsCl (40 μL, 0.52 mmol) at 0 °C. The mixture was warmed to rt and stirred for 4 h. The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with water (10 mL) and brine (10 mL), dried over MgSO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the mesylate 184b (163 mg, 100%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.36 (m, 2H), 7.27-7.19 (m, 4H), 7.02 (br s, 2H), 6.68 (br s, 1H), 3.32 (s, 3H), 3.25 (s, 3H), 1.91 (br s, 3H); ¹³C NMR (75 MHz,
Dimethylcarbamic Acid 2-Iodo-3-[methyl(2-methyl-3-phenylacryloyl)amino]-phenyl Ester (184c). To a stirred solution of the phenol 183 (158 mg, 0.40 mmol), NEt₃ (67 μl, 0.48 mmol) and DMAP (4.9 mg, 0.04 mmol) in CH₂Cl₂ (20 mL) was added N,N-dimethylcarbamyl chloride (44 μL, 0.48 mmol) at 0 °C. The mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with water (10 mL) and brine (10 mL), dried over MgSO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography (20:1 CH₂Cl₂:MeOH) to give the carbamoyl-protected phenol 184c (186 mg, 100%) as a white solid.¹H NMR (300 MHz, CDCl₃) δ 7.34-7.19 (m, 4H) 7.13-7.06 (m, 4H), 6.73 (br s, 1H), 3.31 (s, 3H), 3.20 (s, 3H), 3.04 (s, 3H), 1.88 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 153.8, 153.7, 148.8, 136.4, 133.8, 133.4, 130.0, 129.4, 128.6, 127.8, 126.7, 122.8, 97.3, 37.6, 37.4, 37.2, 16.6.

(4-Dimethylcarbamoyloxy-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)phenylacetic Acid Methyl Ester (189). To a solution of the carbamoyl protected phenol 184c (113 mg, 0.244 mmol) in DMA (2 mL) and MeOH (1 mL) were added Pd(OAc)₂ (5.5 mg, 0.025 mmol), P(o-Tol)₃ (22.3 mg, 0.073 mmol) and NaOAc (40.0 mg, 0.488 mmol). The
mixture was stirred at 90 °C under a CO atmosphere (1 atm) for 42 h. The reaction mixture was cooled to rt and diluted with EtOAc (60 mL). The solution was washed with water (3×10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the desired ester 189 (70 mg, 75%). ¹H NMR (300 MHz, CDCl₃) δ 7.20-7.17 (m, 2H), 7.14-7.11 (m, 4H), 6.81 (dd, J = 0.8, 8.5 Hz, 1H), 6.44 (dd, J = 0.7, 7.8 Hz, 1H), 4.27 (s, 1H), 3.69 (s, 3H), 3.07 (s, 3H), 3.00 (s, 3H), 2.94 (s, 3H), 1.62 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 178.2, 171.3, 154.1, 148.2, 145.1, 134.9, 129.9, 129.4, 128.1, 127.8, 122.4, 117.2, 105.0, 57.2, 52.5, 52.0, 37.3, 36.9, 26.8, 20.9.

(4-Hydroxy-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)phenylacetic Acid Methyl Ester (186). To a solution of the phenol 183 (22.9 mg, 0.058 mmol) in DMA (2 mL) and MeOH (1 mL) were added Pd(OAc)₂ (1.3 mg, 0.006 mmol), P(o-Tol)₃ (5.3 mg, 0.017 mmol) and NaOAc (9.5 mg, 0.12 mmol). The mixture was stirred at 90 °C under a CO atmosphere (1 atm) for 18 h. The reaction mixture was cooled to rt and diluted with EtOAc (40 mL). The solution was washed with water (3×10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the desired ester 186 (major diastereomer, 5.6 mg, 30%; minor diastereomer, 5.1 mg, 27%). Major diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.20 (m, 5H), 7.05 (t, J = 8.0 Hz, 1H), 6.38 (d, J = 8.3 Hz, 1H), 6.32 (d, J = 7.8 Hz, 1H), 4.74 (s, 1H), 4.34 (s, 1H), 3.68 (s, 3H), 3.13 (s, 3H), 1.64 (s, 3H); LRMS-APCI [M+H]⁺ calcd for C₁₀H₂₀NO₄, 326.1; found,
Minor diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.05 (s, 1H), 7.10-7.04 (m, 4H), 6.96 (dd, $J = 1.4$, 8.1 Hz, 2H), 6.64 (dd, $J = 0.4$, 8.3 Hz, 1H), 6.08 (d, $J = 7.4$ Hz, 1H), 4.48 (s, 1H), 3.80 (s, 3H), 2.91 (s, 3H), 1.57 (s, 3H); LRMS-APCI [M+H]$^+$ calcd for C$_{19}$H$_{20}$NO$_4$, 326.1; found 326.1.

**N-(3-Chloro-2-iodophenyl)-4-hydroxy-2-(2-nitrobenzylidene)-butyramide (190a).** To a stirred solution of 3-chloro-2-iodophenylamine (173) (5.24 g, 20.7 mmol) in CH$_2$Cl$_2$ (30
mL) was added AlMe₃ (11.3 mL, 2.0 M in hexane, 22.6 mmol) at 0 °C. The mixture was warmed to rt, stirred for 30 min and then cooled to 0 °C again. A solution of 3-(2-nitrobenzylidene)-dihydrofuran-2-one (147) (4.12 g, 18.8 mmol) in CH₂Cl₂ (12 mL) was added to the mixture. The reaction mixture was stirred at rt for 8 h and then carefully diluted with 6 N aqueous HCl (5 mL) at 0 °C, followed by CH₂Cl₂ (200 mL) and water (100 mL). The aqueous phase was extracted with CH₂Cl₂ (2×100 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (10:1 CH₂Cl₂:MeOH) to give the amide 190a (8.45 g, 95%) as a white solid. ¹H NMR (300 MHz, CDCl₃+CD₃OD) δ 8.21 (dd, J = 1.0, 8.2 Hz, 1H), 7.94 (dd, J = 2.9, 6.7 Hz, 1H), 7.80 (s, 1H), 7.75 (ddd, J = 1.0, 7.6, 7.6 Hz, 1H), 7.62-7.55 (m, 2H), 7.39-7.32 (m, 2H), 3.69 (t, J = 6.3 Hz, 2H), 2.66 (t, J = 6.3 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃+CD₃OD) δ 168.2, 147.5, 140.4, 139.2, 136.6, 133.8, 133.3, 131.3, 129.3, 125.8, 125.0, 121.1, 97.1, 60.7, 31.2.

4-( tert-Butyldimethylsilanyloxy)-N-(3-chloro-2-iodophenyl)-2-(2-nitrobenzylidene)butyramide (191a). To a solution of the amide 190a (8.36 g, 17.7 mmol) and imidazole (2.53 g, 37.1 mmol) in DMF (35 mL) was added TBDMSCl (2.93 g, 19.5 mmol) in a single portion. The reaction mixture was stirred at rt for 1 h and then diluted with EtOAc (300 mL). The solution was washed with water (4×50 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:10 EtOAc:hexanes) to give the TBS ether 191a (8.54 g, 82%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃+CD₃OD) δ...
MHz, CDCl$_3$) $\delta$ 8.56 (s, 1H), 8.26 (dd, $J = 1.8, 7.9$ Hz, 1H), 8.22 (dd, $J = 1.0, 8.0$ Hz, 1H), 7.79 (s, 1H), 7.73-7.66 (m, 2H), 7.59-7.54 (m, 1H), 7.35 (t, $J = 7.8$ Hz, 1H), 7.29 (dd, $J = 1.8, 8.0$ Hz, 1H), 3.76 (t, $J = 6.1$ Hz, 2H), 2.73 (t, $J = 6.1$ Hz, 2H), 0.84 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 167.5, 148.0, 141.0, 139.4, 137.8, 134.0, 132.8, 132.1, 131.9, 130.1, 129.6, 125.5, 125.4, 120.1, 96.2, 62.1, 31.8, 26.3, 18.7, -5.1.

4-(tert-Butyldimethylsilyloxy)-N-(3-chloro-2-iodophenyl)-N-methyl-2-(2-nitrobenzylidene)-butyramide (192a). To a stirred suspension of NaH (17.2 mg, 60% dispersion in mineral oil, 0.43 mmol) in THF (4 mL) was added a solution of the TBS ether 191a (229 mg, 0.39 mmol) in THF (4 mL) at 0 °C. The mixture was stirred at rt for 30 min and recooled to 0 °C. To the solution was added MeI (29 $\mu$L, 0.47 mmol) and the reaction mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with saturated aqueous NH$_4$Cl (0.5 mL) and water (5 mL) and extracted with EtOAc (2×20 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the N-methyl amide 192a (203 mg, 87%) as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.14-7.95 (m, 1H), 7.65-7.10 (m, 6.5H), 6.93 (br s, 0.5H), 3.81-3.70 (m, 2H), 3.51 (br s, 1H), 3.28 (br s, 2H), 2.68 (br s, 0.7H), 2.35-2.23 (m, 1H), 1.77 (br s, 0.3H), 0.84 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.0, 149.2, 148.1, 141.0, 136.8, 133.4, 132.0, 131.7, 131.4, 130.5, 129.1, 128.9, 128.4, 126.9, 124.9, 104.6, 62.1, 61.5, 40.4, 38.0, 33.4, 30.1, 26.3, 26.1, 18.7, -4.9, -5.0.
3-[2-(tert-Butyldimethylsilanyloxy)ethyl]-4-chloro-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-(2-nitrophenyl)acetic Acid Methyl Ester (193a). To a solution of N-methyl amide 192a (63.0 mg, 0.105 mmol) in DMA (2 mL) and MeOH (1 mL) were added Pd(OAc)$_2$ (2.4 mg, 0.011 mmol), P(o-Tol)$_3$ (9.6 mg, 0.032 mmol) and NaOAc (17.2 mg, 0.210 mmol). The mixture was stirred at 90 °C under a CO atmosphere (1 atm) for 20 h. The reaction mixture was cooled to rt and diluted with EtOAc (60 mL). The solution was washed with water (3×10 mL), dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to give the two diastereomers of the desired ester 193a (major diastereomer, 8.9 mg, 16%; minor diastereomer, 3.4 mg, 6%) and protonolysis product 14 (22.1 mg, 44%). Major diastereomer: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.58 (dd, $J$ = 1.5, 8.0 Hz, 1H), 7.45 (dd, $J$ = 1.4, 7.9 Hz, 1H), 7.29 (ddd, $J$ = 1.5, 7.5, 7.5 Hz, 1H), 7.21 (ddd, $J$ = 1.5, 7.9, 7.9 Hz, 1H), 7.05 (t, $J$ = 8.0 Hz, 1H), 6.81 (d, $J$ = 7.6 Hz, 1H), 6.46 (d, $J$ = 7.3 Hz, 1H), 3.88 (s, 3H), 3.44 (m, 1H), 3.42-3.17 (m, 1H), 3.11 (s, 3H), 2.85 (m, 1H), 2.74-2.68 (m, 1H), 0.71 (s, 9H), 0.18 (s, 3H), -0.21 (s, 3H); LRMS-APCI [M+H]$^+$ calcd for C$_{26}$H$_{34}$ClN$_2$O$_6$Si, 533.2; found, 533.1. Minor diastereomer: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.97 (dd, $J$ = 1.3, 8.0 Hz, 1H), 7.81 (dd, $J$ = 1.4, 8.0 Hz, 1H), 7.59 (ddd, $J$ = 1.4, 7.5, 7.5 Hz, 1H), 7.49 (ddd, $J$ = 1.5, 7.9, 7.9 Hz, 1H), 7.26 (t, $J$ = 8.0 Hz, 1H), 7.02 (d, $J$ = 8.1 Hz, 1H), 6.73 (d, $J$ = 7.7 Hz, 1H), 5.70 (s, 1H), 3.46 (s, 3H), 3.32 (m, 1H), 3.23 (s, 3H), 3.20 (m, 1H), 2.38 (m, 1H), 1.86 (m, 1H) 0.69 (s,
9H), -0.21 (s, 3H), -0.24 (s, 3H); LRMS-APCI [M+H]+ calcd for C_{26}H_{33}ClN_{2}O_{6}Si, 533.2; found, 533.1.

3-[2-(tert-Butyldimethylsilyloxy)ethyl]-4-chloro-1-methyl-3-(2-nitrobenzyl)-1,3-dihydroindol-2-one (194a). \[\text{^1}H\text{ NMR (300 MHz, CDCl}_3\text{) }\delta 7.59 (dd, J = 1.2, 7.9 Hz, 1H), 7.33-7.15 (m, 4H), 7.01 (d, J = 8.2 Hz, 1H), 6.46 (d, J = 7.7 Hz, 1H), 3.97 (d, J = 13.4 Hz, 1H), 3.55-3.47 (m, 2H), 3.31 (ddd, J = 5.1, 9.7, 9.7 Hz, 1H), 2.84 (s, 3H), 2.60-2.49 (m, 2H), 0.71 (s, 9H), -0.18 (s, 3H), -0.25 (s, 3H); LRMS-APCI [M+H]+ calcd for C_{24}H_{32}ClN_{2}O_{4}Si, 475.2; found, 475.1.

4-Hydroxy-N-(2-iodo-3-methoxymethoxyphenyl)-2-(2-nitrobenzylidene)butyramide (190b). To a stirred solution of the aniline 180 (907 mg, 3.25 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (30 mL) was added AlMe\textsubscript{3} (1.92 mL, 2.0 M in hexane, 3.84 mmol) at 0 °C. The mixture was warmed to rt, stirred for 30 min and then recooled to 0 °C. A solution of 3-(2-nitrobenzylidene)dihydrofuran-2-one (147)\textsuperscript{43} (647 mg, 2.95 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (5 mL) was added to the solution. The reaction mixture was stirred at rt overnight and then carefully diluted with saturated aqueous NH\textsubscript{4}Cl (5 mL) at 0 °C, followed by CH\textsubscript{2}Cl\textsubscript{2} (50 mL) and water (20 mL). The aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2×10 mL). The combined organic layers were dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the amide 190b (1.17 g, 80%) as a white solid. \[\text{^1}H\text{ NMR (300 MHz, CDCl}_3\text{) }\delta 8.51 (br s, 1H), 8.20 (dd, J}
= 1.1, 8.2 Hz, 1H), 7.99 (dd, J = 1.2, 8.2 Hz, 1H), 7.73 (s, 1H), 7.69 (dd, J = 1.1, 7.5 Hz, 1H), 7.55 (m, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 8.2 Hz, 1H), 6.88 (dd, J = 1.2, 8.3 Hz, 1H), 5.27 (s, 2H), 3.75 (t, J = 5.9 Hz, 2H), 3.52 (s, 3H), 2.96 (br s, 1H), 2.63 (t, J = 5.9 Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 168.5, 156.8, 148.0, 139.8, 137.7, 134.2, 133.0, 131.8, 131.7, 130.2, 129.7, 125.6, 116.1, 111.3, 95.5, 85.0, 61.9, 57.0, 32.0.

4-(tert-Butyldimethylsilyloxy)-N-(2-iodo-3-methoxymethoxyphenyl)-2-(2-nitrobenzylidene)butyramide (191b). To a solution of the amide 190b (1.17 g, 2.35 mmol) and imidazole (337 mg, 4.95 mmol) in DMF (10 mL) was added TBDMSCl (391 mg, 2.59 mmol) in a single portion. The reaction mixture was stirred at rt for 1 h and then diluted with EtOAc (100 mL). The solution was washed with water (3×30 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the TBS ether 191b (1.45 g, 100%) as a yellow oil. \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.50 (br s, 1H), 8.23-8.20 (m, 1H), 8.09 (dd, J = 1.2, 8.2 Hz, 1H), 7.78 (s, 1H), 7.71-7.69 (m, 2H), 7.59-7.54 (m, 1H), 7.34 (t, J = 8.3 Hz, 1H), 6.90 (dd, J = 1.3, 8.3 Hz, 1H), 5.30 (s, 2H), 3.77 (t, J = 6.2 Hz, 2H), 3.55 (s, 3H), 2.73 (t, J = 6.2 Hz, 2H), 0.84 (s, 9H), -0.01 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 167.5, 156.7, 148.1, 140.1, 138.1, 133.9, 132.34, 132.31, 132.0, 130.2, 129.5, 125.4, 115.9, 111.0, 95.5, 84.7, 62.0, 56.9, 31.9, 26.4, 18.7, -5.1.
4-(tert-Butyldimethylsilanyloxy)-N-(2-iodo-3-methoxymethoxyphenyl)-N-methyl-2-(2-nitrobenzylidene)butyramide (192b). To a stirred suspension of NaH (102 mg, 60% dispersion in mineral oil, 2.55 mmol) in THF (10 mL) was added a solution of the TBS ether 191b (1.42 g, 2.32 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at rt for 30 min and recooled to 0 °C. To the solution was added MeI (29 μL, 0.47 mmol) and the reaction mixture was warmed to rt and stirred for 6 h. The reaction mixture was diluted with saturated aqueous NH₄Cl (1 mL) and water (20 mL) and extracted with EtOAc (2×50 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the N-methyl amide 192b (1.22 g, 84%) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 8.13 (br s, 0.3H), 7.93-7.91 (m, 0.7H), 7.66-7.10 (m, 4.3H), 7.01-6.94 (m, 2.7H), 5.28-5.22 (m, 2H), 3.83-3.70 (m, 2H), 3.49 (br s, 4H), 3.29 (br s, 2H), 2.69-2.26 (m, 2H), 0.84 (s, 9H), 0.00 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 171.1, 158.2, 148.4, 148.2, 136.9, 133.2, 132.0, 131.8, 130.9, 130.4, 128.9, 124.8, 123.7, 114.1, 95.7, 93.0, 62.2, 56.9, 37.9, 33.5, 26.3, 18.7, -4.9, -5.0.

Dimethylcarbamic Acid 2-Iodo-3-nitrophenyl Ester (197). To a stirred solution of 2-iodo-3-nitrophenol (178, 422 mg, 1.59 mmol), NEt₃ (0.33 ml, 2.35 mmol) and DMAP (19.4 mg, 0.16 mmol) in CH₂Cl₂ (20 mL) was added N,N-dimethylcarbamyl chloride (0.18 mL, 1.96 mmol) at 0 °C. The mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with
CH$_2$Cl$_2$ (100 mL), washed with water (20 mL) and brine (20 mL), dried over MgSO$_4$ and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the carbamoyl-protected phenol 197 (505 mg, 94%) as a white solid (mp 125-126 °C). IR (film) 1713, 1531, 1386, 1359, 1246, 1165 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.75 (dd, $J = 1.4$, 7.9 Hz, 1H), 7.60, (t, $J = 8.0$ Hz, 1H), 7.53 (dd, $J = 1.4$, 8.1 Hz, 1H), 3.35 (s, 3H), 3.19 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 155.1, 153.9, 153.4, 130.0, 127.3, 122.4, 86.1, 37.5, 37.3; HRMS-ES [M+Na]$^+$ calcd for C$_9$H$_9$IN$_2$O$_4$, 358.9505; found, 358.9513.

Dimethylcarbamic Acid 3-Amino-2-iodophenyl Ester (198).

To a solution of the nitrobenzene 197 (446 mg, 1.33 mmol) in EtOH (10 mL) and glacial acetic acid (5 mL) was added iron powder (296 mg, 5.30 mmol). The mixture was heated at 60 °C for 4 h and then cooled to rt. The mixture was diluted with water (30 mL) and carefully neutralized with solid Na$_2$CO$_3$. The resulting solution was extracted with EtOAc (2×100 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the aniline 198 (375 mg, 93%) as a white solid (mp 113-114 °C). IR (film) 3333, 1714, 1617, 1466, 1386, 1170 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.33 (t, $J = 7.9$ Hz, 1H), 6.80 (dd, $J = 2.9$, 8.0 Hz, 2H), 4.50 (br s, 2H), 3.42 (s, 3H), 3.28 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 154.3, 152.7, 149.0, 129.8, 113.0, 112.2, 82.0, 37.3, 37.2; HRMS-ES [M+H]$^+$ calcd for C$_9$H$_{12}$IN$_2$O$_2$, 306.9944; found, 306.9949.
3-(2-Aminobenzylidene)-dihydrofuran-2-one (195). To a solution of the nitrolactone 147 (1.09 g, 4.98 mmol) in EtOH (15 mL) and glacial acetic acid (10 mL) was added iron powder (1.11 g, 19.91 mmol). The mixture was heated at 60 °C for 3 h and then cooled to rt. The mixture was diluted with water (80 mL) and carefully neutralized with solid Na₂CO₃. The resulting solution was extracted with EtOAc (2×100 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the aniline 195 (0.88 g, 93%) as a yellow solid. $^1$H NMR (360 MHz, CDCl₃) δ 7.46 (t, $J$ = 2.7 Hz, 1H), 7.12 (d, $J$ = 7.4 Hz, 1H), 7.03 (t, $J$ = 8.3 Hz, 1H), 6.63 (t, $J$ = 7.6 Hz, 1H), 6.59 (d, $J$ = 8.1 Hz, 1H), 4.27 (t, $J$ = 7.2 Hz, 2H), 3.85 (br s, 2H), 3.02 (dt, $J$ = 2.8, 7.2 Hz, 2H); $^{13}$C NMR (90 MHz, CDCl₃) δ 172.9, 146.5, 131.7, 131.4, 129.0, 124.3, 120.1, 118.8, 116.8, 66.0, 27.8.

3-[2-(Pyrrolidin-1-ylazo)-benzylidene]-dihydrofuran-2-one (196a). To a stirred solution of the aniline 195 (245 mg, 1.29 mmol) in DMSO (1 mL) and 30% H₂SO₄ (1 mL) was added dropwise a solution of NaNO₂ (107 mg, 1.55 mmol) in water (1 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h and recooled to 0 °C. Pyrrolidine (0.13 mL, 1.56 mmol) was added dropwise, followed by saturated aqueous NaHCO₃ to basify the reaction mixture. After 30 min the solution was diluted with EtOAc (70 mL) and washed with water (3×10 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified
by flash column chromatography (1:1 EtOAc:hexanes) to give the triazine 196a (312 mg, 89%) as a yellow solid. $^1$H NMR (360 MHz, CDCl$_3$) δ 8.23 (t, $J = 2.9$ Hz, 1H), 7.33-7.29 (m, 2H), 7.18 (ddd, $J = 1.3$, 7.3, 7.3 Hz, 1H), 7.01 (t, $J = 8.0$ Hz, 1H), 4.27 (t, $J = 7.3$ Hz, 2H), 3.79 (br s, 2H), 3.58 (br s, 2H), 3.07 (dt, $J = 2.9$, 7.3 Hz, 2H), 1.89 (br s, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.1, 150.8, 134.3, 130.9, 128.9, 128.7, 125.2, 123.0, 117.8, 65.9, 51.6, 47.3, 28.0, 24.4, 24.0.

1,3-Dimethyl-5-[2-(2-oxodihydrofuran-3-ylidenemethyl)-phenyl]-[1,3,5]triazinan-2-one (196b). To a solution of the aniline 195 (55.0 mg, 0.291 mmol) and 1,3-dimethylurea (51.3 mg, 0.582 mmol) in toluene (50 mL) was added formaldehyde (0.3 ml, 37% aqueous solution, 4.03 mmol) and (i-Pr)$_2$NEt (0.1 ml, 0.574 mmol). The mixture was refluxed for 1 h until most of the water has been removed using a Dean-Stark apparatus. To the hot solution was added PPTS (7.3 mg, 0.029 mmol) and the mixture was refluxed for 4 h. After removing the volatile organics at reduced pressure, the residue was purified by flash column chromatography (10:10:1 CH$_2$Cl$_2$:EtOAc:MeOH) to give the triazinone 196b (75.5 mg, 86%) as a yellow solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.85 (t, $J = 2.9$ Hz, 1H), 7.50 (dd, $J = 1.1$, 7.7 Hz, 1H), 7.38-7.34 (m, 1H), 7.26-7.20 (m, 2H), 4.49 (s, 4H), 4.48 (t, $J = 7.2$ Hz, 2H), 3.25 (ddd, $J = 2.9$, 7.2, 7.2 Hz, 2H), 2.85 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.9, 156.6, 149.7, 133.0, 131.5, 129.3, 129.1, 125.2, 124.6, 122.6, 69.0, 66.0, 32.6, 27.8.
Dimethylcarbamic Acid 3-{4-Hydroxy-2-[2-(pyrrolidin-1-ylazo)benzylidene]butyrylamino}-2-iodophenyl Ester (199a). To a stirred solution of the aniline 198 (38.6 mg, 0.126 mmol) in CH$_2$Cl$_2$ (3 mL) was added AlMe$_3$ (75 μL, 2.0 M in hexane, 0.150 mmol) at 0 °C. The mixture was warmed to rt, stirred for 30 min and then recooled down to 0 °C. A solution of the triazine 196a (31.1 mg, 0.115 mmol) in CH$_2$Cl$_2$ (1 mL) was added to the solution. The reaction mixture was stirred at rt overnight and then carefully diluted with saturated aqueous NH$_4$Cl (0.5 mL) at 0 °C, followed by CH$_2$Cl$_2$ (20 mL) and water (5 mL). The aqueous phase was washed with CH$_2$Cl$_2$ (2×10 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (3:1 EtOAc:hexanes) to give the amide 199a (64.7 mg, 97%) as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.28 (s, 1H), 8.09 (d, $J$ = 8.1 Hz, 1H), 7.80 (s, 1H), 7.38-7.21 (m, 4H), 7.07 (t, $J$ = 7.4 Hz, 1H), 6.90 (d, $J$ = 7.6 Hz, 1H), 3.74 (t, $J$ = 5.8 Hz, 2H), 3.69 (br s, 4H), 3.11 (s, 3H), 2.97 (s, 3H), 2.75 (t, $J$ = 5.8 Hz, 2H), 1.93 (br s, 4H).

Dimethylcarbamic Acid 3-{4-(tert-Butyl dimethylsilyloxy)-2-[2-(pyrrolidin-1-ylazo)benzylidene]butyrylamino}-2-iodophenyl Ester (200a). To a solution of the amide 199a (221 mg, 0.383 mmol) and imidazole (54.8 mg, 0.805 mmol) in DMF (5 mL) was added TBDMSCl (63.5 mg, 0.421 mmol) in a single portion. The reaction mixture was stirred at rt for 1 h and then diluted
with EtOAc (150 mL). The solution was washed with water (3×30 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the TBDMS ether 200a (225 mg, 85%) as a yellow oil. ¹H NMR (360 MHz, CDCl₃) δ 8.32 (s, 1H), 8.22 (dd, J = 1.3, 8.3 Hz, 1H), 7.98 (s, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.41 (dd, J = 1.0, 8.1 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.31-7.26 (m, 1H), 7.12 (dt, J = 0.9, 7.5 Hz, 1H), 6.95 (dd, J = 1.3, 8.1 Hz, 1H), 3.86 (t, J = 6.3 Hz, 2H), 3.74 (br s, 4H), 3.18 (s, 3H), 3.03 (s, 3H), 2.89 (t, J = 6.2 Hz, 2H), 1.98 (m, 4H), 0.84 (s, 9H), 0.00 (s, 6H).

**Dimethylcarbamic Acid 3-{{4-{{tert-Butil dimethylsilanyloxy}-2-[2-(pyrrolidin-1-ylazo)benzylidene]-butyryl}methylamino)-2-iodophenyl Ester (201a).** To a stirred suspension of NaH (28.7 mg, 60% dispersion in mineral oil, 0.718 mmol) in THF (5 mL) was added a solution of the TBS ether 200a (414 mg, 0.598 mmol) in THF (3 mL) at 0 °C. The mixture was stirred at rt for 30 min and recooled to 0 °C. To the solution was added MeI (48.0 μL, 0.777 mmol) and the reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was diluted with saturated aqueous NH₄Cl (1 mL) and water (10 mL) and extracted with EtOAc (2×50 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the N-methyl amide 201a (394 mg, 93%) as a white foamy solid.
$^{1}$H NMR (300 MHz, CDCl$_3$) δ 7.30-7.05 (m, 8H), 3.78 (br s, 6H), 3.37 (br s, 3H), 3.14 (s, 3H), 3.00 (s, 3H), 2.9-2.3 (m, 2H), 1.92 (m, 4H), 0.84 (s, 9H), 0.00 (s, 6H).

**Dimethylcarbamic Acid 3-[2-[2-(3,5-Dimethyl-4-oxo-[1,3,5]triazinan-1-yl)benzylidene]-4-hydroxybutyrylamino]-2-iodophenyl Ester (199b).** To a stirred solution of the aniline 198 (561 mg, 1.83 mmol) and triazinone 196b (547 mg, 1.81 mmol) in CH$_2$Cl$_2$ (30 mL) was added AlMe$_3$ (1.1 mL, 2.0 M in hexane, 2.20 mmol) at 0 °C. The mixture was warmed to rt, stirred overnight and then carefully diluted with saturated aqueous NH$_4$Cl (2.0 mL) at 0 °C, followed by CH$_2$Cl$_2$ (100 mL) and water (20 mL). The aqueous phase was washed with CH$_2$Cl$_2$ (2×10 mL). The combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10:10:1 CH$_2$Cl$_2$:EtOAc:MeOH) to give the amide 199b (1.08 g, 98%) as a white solid. $^{1}$H NMR (300 MHz, CDCl$_3$) δ 8.46 (s, 1H), 8.18 (dd, $J = 1.3$, 8.3 Hz, 1H), 7.57 (s, 1H), 7.44 (d, $J = 7.6$ Hz, 1H), 7.37 (t, $J = 8.2$ Hz, 1H), 7.30 (dd, $J = 1.4$, 7.7 Hz, 1H), 7.20-7.14 (m, 2H), 6.98 (dd, $J = 1.4$, 8.1 Hz, 1H), 4.51 (s, 4H), 3.83 (t, $J = 5.8$ Hz, 2H), 3.19 (s, 3H), 3.04 (s, 3H), 2.92 (t, $J = 5.8$ Hz, 2H), 2.83 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.9, 156.6, 154.0, 152.4, 148.4, 140.1, 136.7, 134.1, 130.5, 130.3, 130.1, 130.0, 124.9, 121.7, 119.7, 119.4, 89.0, 68.5, 61.8, 37.4, 37.2, 32.6, 31.5.
Dimethylcarbamic Acid 3-\{4-(\textit{tert}-Butyldimethylsilanyloxy)-2-[2-(3,5-dimethyl-4-oxo-[1,3,5]triazinan-1-yl)-benzylidene]butyryl]amino]-2-iodophenyl Ester (200b). To a solution of the amide 199b (1.04 g, 1.70 mmol) and imidazole (0.13 g, 1.87 mmol) in DMF (5 mL) was added TBDMSCl (0.27 g, 1.79 mmol) in a single portion. The reaction mixture was stirred at rt for 30 min and then diluted with EtOAc (120 mL). The solution was washed with water (3×15 mL), dried over MgSO$_4$ and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (10:10:1 CH$_2$Cl$_2$:EtOAc:MeOH) to give the TBDMS ether 200b (1.13 g, 92%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.35 (s, 1H), 8.25 (dd, $J = 1.3, 8.3$ Hz, 1H), 7.74 (d, $J = 7.4$ Hz, 1H), 7.60 (s, 1H), 7.38 (t, $J = 8.2$ Hz, 1H), 7.34-7.27 (m, 1H), 7.17 (t, $J = 7.3$ Hz, 2H), 6.97 (dd, $J = 1.3, 8.1$ Hz, 1H), 4.47 (s, 4H), 3.92 (t, $J = 6.0$ Hz, 2H), 3.19 (s, 3H), 3.04 (s, 3H), 2.92 (t, $J = 6.0$ Hz, 2H), 2.84 (s, 6H), 0.86 (s, 9H), 0.03 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.1, 156.5, 153.9, 152.4, 148.5, 140.3, 136.9, 133.7, 131.2, 130.3, 130.1, 130.0, 124.8, 121.6, 119.4, 118.9, 88.6, 68.6, 62.1, 37.3, 37.2, 32.7, 31.7, 26.4, 18.8, -4.9.

Dimethylcarbamic Acid 3-\{4-(\textit{tert}-Butyldimethylsilanyloxy)-2-[2-(3,5-dimethyl-4-oxo-[1,3,5]triazinan-1-yl)benzylidene]butyryl]methylamino\}-2-iodophenyl Ester (201b). To a stirred suspension of NaH (64.4 mg, 60% dispersion in mineral oil, 1.61 mmol) in THF (12.0 mL) was added a
solution of the TBDMS ether 200b (1.11 g, 1.53 mmol) in THF (8.0 mL) at 0 °C. The mixture was stirred at rt for 0.5 h and recooled to 0 °C. To the solution was added MeI (110 μL, 1.77 mmol) and the reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was diluted with saturated aqueous NH₄Cl (5 mL) and extracted with CH₂Cl₂ (100 mL). The organic layers was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (10:10:1 CH₂Cl₂:EtOAc:MeOH) to give the N-methyl amide 201b (1.03 g, 91%) as a white solid.

$^1$H NMR (300 MHz, CDCl₃) δ 7.35-7.00 (m, 7H), 6.74 (br s, 1H), 4.49 (br s, 1H), 4.22 (br s, 3H), 3.81 (br s, 2H), 3.29 (br s, 3H), 3.03 (s, 3H), 2.78 (br s, 7H), 2.55 (br s, 1H), 0.89 (s, 9H), 0.06 (s, 6H).

3-(2-Hydroxymethylbenzylidene)dihydrofuran-2-one (205). A mixture of 1,3-dihydroisobenzofuran-1-ol (203)$^{54}$ (1.42 g, 10.4 mmol) and 3-(triphenylphosphanyliden)e-dihydrofuran-2-one (204)$^{55}$ (3.62 g, 10.5 mmol) in toluene (100 mL) was heated at 70 °C for 2 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:1 to 3:1 EtOAc:hexanes) to give the lactone 205 (1.89 g, 89%) as a white solid (mp 89-89.5 °C).

IR (film) 3430, 1741, 1649, 1208, 1181, 1024 cm⁻¹; $^1$H NMR (360 MHz, CDCl₃) δ 7.86 (t, J = 2.9 Hz, 1H), 7.54-7.36 (m, 4H), 4.85 (s, 2H), 4.45 (t, J = 7.2 Hz, 2H), 3.21 (dt, J = 2.9, 7.2 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl₃) δ 173.1, 141.1, 133.9, 133.2, 130.2, 129.2, 128.6, 128.2, 125.7, 66.2, 63.0, 27.8; HRMS-ES [M+H]$^+$ calcd for C₁₂H₁₃O₃, 205.0865; found, 205.0846.
3-[2-\textit{tert-}Butyldimethylsilanyloxymethyl]benzylidene\textit{dihydrofuran -2-one} (206). To a solution of the lactone 205 (378 mg, 1.85 mmol) and imidazole (139 mg, 2.04 mmol) in DMF (3.0 mL) was added TBDMSCl (293 mg, 1.95 mmol) in a single portion. The reaction mixture was stirred at rt overnight and then diluted with EtOAc (100 mL). The solution was washed with water (3×20 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to give the TBDMS ether 206 (548 mg, 93%) as a colorless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.75 (t, \(J = 2.9\) Hz, 1H), 7.58-7.55 (m, 1H), 7.43-7.30 (m, 3H), 4.84 (s, 2H), 4.43 (t, \(J = 7.2\) Hz, 2H), 3.18 (ddd, \(J = 2.9, 7.2, 7.2\) Hz, 2H); 0.94 (s, 9H), 0.13 (s, 6H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 172.5, 141.5, 133.8, 132.6, 130.0, 128.3, 127.8, 127.5, 125.5, 66.0, 63.3, 27.9, 26.3, 18.7, -4.9.

\textbf{Dimethylcarbamic Acid 3-[2-\textit{tert-}Butyldimethylsilanyloxymethyl]benzylidene]-4-hydroxybutyryl-amino}-2-iodophenyl Ester (207). To a stirred solution of the aniline 198 (54.3 mg, 0.177 mmol) and lactone 206 (53.7 mg, 0.169 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added AlMe\(_3\) (0.17 mL, 2.0 M in hexane, 0.340 mmol) at 0 °C. The mixture was warmed to rt, stirred for 3 h and then carefully diluted with saturated aqueous NH\(_4\)Cl (0.5 mL) at 0 °C, followed by CH\(_2\)Cl\(_2\) (70 mL). The organic layer was washed with water (15 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography
(1:1 EtOAc:hexanes) to give the amide 207 (97.4 mg, 93%) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.46 (br s, 1H), 8.19 (dd, $J = 1.3, 8.3$ Hz, 1H), 7.59-7.55 (m, 2H), 7.43-7.29 (m, 4H), 7.02 (dd, $J = 1.3, 8.1$ Hz, 1H), 4.76 (s, 2H), 3.79 (t, $J = 5.9$ Hz, 2H), 3.23 (s, 3H), 3.07 (s, 3H), 2.76 (t, $J = 5.9$ Hz, 2H), 0.95 (s, 9H), 0.13 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.8, 154.0, 152.4, 140.0, 139.8, 137.9, 134.8, 133.4, 130.1, 129.0, 128.9, 127.5, 127.3, 119.8, 119.5, 89.0, 63.6, 62.5, 37.4, 37.2, 31.8, 26.4, 18.8, -4.7.

**Dimethylcarbamic Acid 3-[[2-[2-[(tert-Butyldimethylsilyloxymethyl)benzylidene]-4-methoxymethoxy-butyrylamino]-2-iodophenyl Ester**

(208). To a mixture of amide 207 (836 mg, 1.34 mmol), (i-Pr)$_2$NEt (0.47 mL, 2.70 mmol) and NaI (401 mg, 2.68 mmol) in CH$_2$Cl$_2$ (20 mL) was added MOMCl (0.15 mL, 1.97 mmol) at 0 $^\circ$C. The mixture was warmed to rt, stirred overnight and then diluted with saturated aqueous NaHCO$_3$ (20 mL) and CH$_2$Cl$_2$ (100 mL). The organic layer was separated, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the MOM ether 208 (750 mg, 84%) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.38 (br s, 1H), 8.23 (dd, $J = 1.2, 8.3$ Hz, 1H), 7.59-7.56 (m, 2H), 7.42-7.30 (m, 4H), 7.00 (dd, $J = 1.3, 8.1$ Hz, 1H), 4.73 (s, 2H), 4.59 (s, 2H), 3.70 (t, $J = 6.4$ Hz, 2H), 3.31 (s, 3H), 3.21 (s, 3H), 3.05 (s, 3H), 2.83 (t, $J = 6.4$ Hz, 2H), 0.94 (s, 9H), 0.11 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 167.7, 153.9,
Dimethylcarbamic Acid 3-({2-[2-(tert-Butyldimethyl-silanyloxymethyl)benzylidene]-4-methoxymethoxy-butyl}methylamino)-2-iodophenyl Ester (209). To a stirred suspension of NaH (41.4 mg, 60% dispersion in mineral oil, 1.04 mmol) in THF (20 mL) was added a solution of the lactam 208 (628 mg, 0.94 mmol) in THF (8 mL) at 0 °C. The mixture was stirred at rt for 30 min and recooled to 0 °C. To the solution was added MeI (70 μL, 1.12 mmol) and the reaction mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with saturated aqueous NH₄Cl (1 mL) and water (10 mL) and extracted with CH₂Cl₂ (100 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the N-methyl amide 209 (618 mg, 96%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.51-7.37 (m, 2H), 7.29-7.08 (m, 4H), 6.94 (br s, 1H), 6.83 (br s, 1H), 4.75-4.45 (m, 4H), 3.66 (br s, 2H), 3.34 (br s, 6H), 3.21 (br s, 3H), 3.06 (br s, 3H), 2.58 (br s, 1H), 2.42-2.38 (m, 1H), 0.97 (s, 9H), 0.12 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 171.8, 153.8, 153.7, 149.0, 139.9, 135.9, 133.6, 133.1, 130.0, 128.6, 128.2, 127.1, 126.8, 126.1, 122.8, 97.2, 96.6, 66.3, 62.8, 55.7, 37.9, 37.3, 37.2, 30.2, 26.4, 18.8, -4.7.
[2-(tert-Butyldimethylsilanyloxymethyl)phenyl]-[4-dimethylcarbamoyloxy-3-(2-methoxymethoxyethyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]acetic Acid Methyl Ester (210). To a solution of N-methyl amide 209 (135 mg, 0.197 mmol) in DMA (2 mL) and MeOH (1 mL) was added Pd(OAc)$_2$ (4.4 mg, 0.019 mmol), P(o-Tol)$_3$ (18.0 mg, 0.059 mmol), Bu$_4$NBr (110 mg, 0.394 mmol) and NEt$_3$ (0.14 mL, 1.00 mmol). The mixture was stirred at 90 °C under a CO atmosphere (1 atm) for 24 h. The reaction mixture was cooled to rt and diluted with EtOAc (60 mL). The solution was washed with water (3×20 mL), dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the ester 210 (60 mg, 50%) as a colorless oil. $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.40 (dd, $J$ = 1.3, 7.7 Hz, 1H), 7.29 (d, $J$ = 7.5 Hz, 1H), 7.24-7.09 (m, 4H), 6.96 (dd, $J$ = 0.6, 8.5 Hz, 1H), 6.53 (d, $J$ = 7.2 Hz, 1H), 4.94, 4.61 (ABq, $J$ = 2.9 Hz, 2H), 4.62 (s, 1H), 4.32, 4.20 (ABq, $J$ = 6.5 Hz, 2H), 3.56 (s, 3H), 3.20-3.02 (m, 2H), 3.13 (s, 3H), 3.09 (s, 3H), 2.91 (s, 3H), 2.69 (s, 3H), 2.61-2.53 (m, 1H), 2.42-2.35 (m, 1H), 0.91 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H).

3-[2-(4-Methoxyphenoxy)methyl]benzylidene)dihydrofuran-2-one (213). To a stirred solution of lactone 205 (1.65 g, 8.08 mmol), PPh$_3$ (2.23 g, 8.49 mmol) and 4-methoxyphenol (1.05 g, 8.49 mmol) in CH$_2$Cl$_2$ (50 mL) was added DEAD (1.51 mL, 9.30 mmol) dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. The solvent was removed under reduced pressure.
and the residue was purified by flash column chromatography (1:10 EtOAc:CH₂Cl₂) to give the PMP-protected lactone 213 (2.44 g, 97%) as a white solid (mp 111-112 °C). IR (film) 2924, 1752, 1649, 1509, 1224 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.84 (t, J = 2.9 Hz, 1H), 7.60-7.57 (m, 1H), 7.50-7.40 (m, 3H), 6.94-6.90 (m, 2H), 6.87-6.82 (m, 2H), 5.12 (s, 2H), 4.44 (t, J = 7.2 Hz, 2H), 3.78 (s, 3H), 3.18 (ddd, J = 2.9, 7.2, 7.2 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 172.4, 154.8, 153.0, 137.3, 133.7, 133.6, 130.1, 129.7, 128.7, 126.3, 116.8, 115.1, 69.4, 66.0, 56.1, 27.8; HRMS-ES [M+H]+ calcd for C₁₉H₁₉O₄, 311.1283; found, 311.1303.

Dimethylcarbamic Acid 3-{4-Hydroxy-2-[2-(4-methoxyphenoxy)methyl]benzylidene}butyrylamino]-2-iodophenyl Ester (214). To a stirred solution of aniline 30 (111 mg, 0.362 mmol) and lactone 213 (107 mg, 0.345 mmol) in CH₂Cl₂ (10 mL) was added AlMe₃ (0.19 mL, 2.0 M in hexane, 0.380 mmol) at 0 °C. The mixture was warmed to rt, stirred overnight and then carefully diluted with saturated aqueous NH₄Cl (0.5 mL) at 0 °C, followed by CH₂Cl₂ (60 mL). The organic layer was washed with water (15 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (10:1 CH₂Cl₂:MeOH) to give the amide 214 (207 mg, 97%) as a white solid (mp 110-111 °C). IR (film) 3387, 2934, 1725, 1665, 1509, 1229 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.37 (s, 1H), 8.06 (dd, J = 1.4, 8.2 Hz, 1H), 7.64 (s, 1H), 7.53-7.51 (m, 1H), 7.40-7.31 (m, 4H), 6.97 (dd, J = 1.4, 8.1 Hz, 1H), 6.92-6.79 (m, 4H), 5.01 (s, 2H), 3.75 (t, J = 5.9 Hz, 2H), 3.74 (s, 3H), 3.18 (s, 3H),
3.03 (s, 3H), 2.74 (t, J = 5.8 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.7, 154.6, 154.0, 153.2, 152.4, 140.0, 138.5, 135.6, 135.2, 129.9, 129.7, 129.6, 129.0, 128.8, 119.82, 119.76, 116.4, 115.2, 89.4, 69.6, 62.3, 56.2, 37.3, 37.2, 31.8; HRMS-ES [M+H]$^+$ calcd for C$_{28}$H$_{30}$IN$_2$O$_6$, 617.1149; found, 617.1139.

**Dimethylcarbamic Acid 2-Iodo-3-{4-methoxymethoxy-2-[2-(4-methoxyphenoxymethyl)benzylidene]butyrylamino}phenyl Ester (215).** To a mixture of amide 214 (961 mg, 1.56 mmol), (i-Pr)$_2$NEt (0.54 mL, 3.10 mmol) and NaI (467 mg, 3.12 mmol) in CH$_2$Cl$_2$ (30 mL) was added MOMCl (0.18 mL, 2.37 mmol) at 0 °C. The mixture was warmed to rt, stirred overnight and then diluted with saturated aqueous NaHCO$_3$ (20 mL) and CH$_2$Cl$_2$ (50 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the MOM ether 215 (914 mg, 89%) as a white solid (mp 107-108 °C). IR (film) 3389, 2937, 1729, 1673, 1509, 1385, 1232 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.32 (s, 1H), 8.17 (dd, J = 1.3, 8.3 Hz, 1H), 7.67 (s, 1H), 7.57-7.54 (m, 1H), 7.43-7.34 (m, 4H), 6.98 (dd, J = 1.3, 8.3 Hz, 1H), 6.93-6.80 (m, 4H), 5.02 (s, 2H), 4.58 (s, 2H), 3.75 (s, 3H), 3.70 (t, J = 6.3 Hz, 2H), 3.29 (s, 3H), 3.19 (s, 3H), 3.05 (s, 3H), 2.84 (t, J = 6.3 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 167.6, 154.6, 153.9, 153.2, 152.3, 140.2, 138.1, 135.8, 135.1, 134.4, 130.0, 129.5, 129.3, 128.9, 128.6, 119.5, 119.4, 116.4, 115.2, 96.7, 88.8, 69.4, 66.5, 56.2, 55.8, 37.3, 37.2, 29.0; HRMS-ES [M+H]$^+$ calcd for C$_{30}$H$_{34}$IN$_2$O$_7$, 661.1411; found, 661.1397.
Dimethylcarbamic Acid 2-Iodo-3-({4-methoxymethoxy-2-[2-(4-methoxyphenoxymethyl)benzylidene]butyryl}methyl-amino)phenyl Ester (216).

To a stirred suspension of NaH (11.1 mg, 60% dispersion in mineral oil, 0.278 mmol) in THF (6 mL) was added a solution of lactam 215 (167 mg, 0.253 mmol) in THF (4 mL) at 0 °C. The mixture was stirred at rt for 1 h and recooled to 0 °C. To the solution was added MeI (0.019 mL, 0.305 mmol) and the reaction mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with saturated aqueous NH₄Cl (10 mL) and water (10 mL) and extracted with CH₂Cl₂ (100 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (10:10:1 CH₂Cl₂:EtOAc:MeOH) to give the N-methyl amide 216 (167 mg, 98%) as a colorless oil. IR (film) 2926, 1723, 1616, 1503, 1227, 1164 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.38-6.96 (m, 8H), 6.81 (br s, 4H), 4.68-4.48 (m, 4H), 3.77 (s, 3H), 3.67 (br s, 2H), 3.36 (s, 6H), 3.11 (s, 3H), 3.02 (s, 3H), 2.59 (br s, 1H), 2.43 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 171.6, 154.4, 153.8, 153.1, 148.8, 136.5, 135.9, 134.4, 133.2, 130.2, 129.1, 128.4, 127.8, 127.0, 122.8, 116.5, 114.9, 97.3, 96.6, 68.5, 66.2, 56.1, 55.7, 37.8, 37.3, 37.1, 30.3; HRMS-ES [M+H]⁺ calcd for C₃₁H₃₆IN₂O₇, 675.1567; found, 675.1562.
methoxyphenoxymethyl)phenyl]acetic Acid Methyl Ester (217). To a solution of
N-methyl amide 216 (280 mg, 0.415 mmol) in DMA (2.6 mL) and MeOH (1.3 mL) were
added Pd(OAc)$_2$ (18.6 mg, 0.083 mmol), P(o-Tol)$_3$ (75.7 mg, 0.249 mmol) and NaOAc
(68.0 mg, 0.829 mmol). The mixture was stirred at 90 °C under a CO atmosphere (1 atm)
for 24 h. The reaction mixture was cooled to rt and diluted with EtOAc (150 mL). The
solution was washed with water (3×20 mL) and brine (20 mL), dried over MgSO$_4$ and
concentrated in vacuo. The residue was purified by flash column chromatography (1:2
EtOAc:hexanes) to give the ester 217 (199 mg, 79%) as a colorless oil. IR (film) 2938,
1729, 1616, 1549, 1509, 1226 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.53-7.50 (m, 1H), 7.32-
7.16 (m, 4H), 6.97 (d, $J = 8.4$ Hz, 1H), 6.88-6.80 (m, 4H), 6.51 (d, $J = 7.6$ Hz, 1H), 5.08,
4.85 (ABq, $J = 11.6$ Hz, 2H), 4.68 (s, 1H), 4.32, 4.21 (ABq, $J = 6.5$ Hz, 2H), 3.78 (s, 3H),
3.61 (s, 3H), 3.19-3.03 (m, 2H), 3.12 (s, 3H), 3.09 (s, 3H), 2.88 (s, 3H), 2.64 (s, 3H),
2.63-2.55 (m, 1H), 2.47-2.40 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 177.9, 171.2, 154.5,
153.4, 153.1, 148.7, 146.3, 136.5, 133.5, 130.6, 129.9, 129.6, 128.3, 127.9, 118.6, 116.8,
116.3, 115.0, 104.9, 96.7, 69.2, 64.4, 56.2, 55.4, 54.5, 52.6, 37.2, 36.4, 34.2, 26.9;
HRMS-ES [M+H]$^+$ calcd for C$_{33}$H$_{39}$N$_2$O$_9$, 607.2656; found, 607.2645.

**General Procedure for Alcoholysis of 217.** To a solution of ester 217 (60.6 mg, 0.100
mmol) in alcohol solvent (10 mL) at rt was added a freshly prepared alkoxide solution
(0.3 mL, 0.5 N in ROH, 0.150 mmol). The mixture was refluxed overnight and then
diluted with saturated aqueous NH$_4$Cl (10 mL) and CH$_2$Cl$_2$ (100 mL). The organic layer
was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give phenol esters 218a-c.

[4-Hydroxy-3-(2-methoxymethoxyethyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-[2-(4-methoxyphenoxymethyl)phenyl] acetic Acid Methyl Ester (2183a). (Yield 47%): ¹H NMR (400 MHz, CDCl₃) δ 9.92 (s, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.17-7.12 (m, 2H), 7.01-6.97 (m, 2H), 6.89-6.79 (m, 4H), 6.73 (d, J = 8.1 Hz, 1H), 6.13 (d, J = 7.5 Hz, 1H), 5.37, 5.09 (ABq, J = 12.4 Hz, 2H), 4.78 (s, 1H), 4.32, 4.21 (ABq, J = 6.5 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.31-3.23 (m, 2H), 3.11 (s, 3H), 2.81 (s, 3H), 2.57 (ddd, J = 4.3, 5.9, 13.7 Hz, 1H), 2.44 (ddd, J = 6.2, 7.7, 15.9 Hz, 1H).

[4-Hydroxy-3-(2-methoxymethoxyethyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-[2-(4-methoxyphenoxymethyl)phenyl] acetic Acid Ethyl Ester (218b). (Yield 55%): ¹H NMR (300 MHz, CDCl₃) δ 10.03 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.18-7.10 (m, 2H), 7.00-6.95 (m, 2H), 6.89-6.80 (m, 4H), 6.72 (d, J = 8.3 Hz, 1H), 6.12 (d, J = 7.7 Hz, 1H), 5.36, 5.13 (ABq, J = 12.7 Hz, 2H), 4.76 (s, 1H), 4.32, 4.22 (ABq, J = 6.5 Hz, 2H), 4.33-4.22 (m, 1H), 4.17-4.09 (m, 1H), 3.79 (s, 3H), 3.28-3.23 (m, 2H), 3.12 (s, 3H), 2.82 (s, 3H), 2.59 (ddd, J = 4.5, 6.2, 13.7 Hz, 1H), 2.49-2.40 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H).

[4-Hydroxy-3-(2-methoxymethoxyethyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-[2-(4-methoxyphenoxymethyl)phenyl] acetic Acid Propyl Ester (218c). (Yield 22%): ¹H NMR (300 MHz,
OPMP

\[ \text{3a-(2-Methoxymethoxyethyl)-3-[2-(4-methoxyphenoxy methyl)phenyl]-5-methyl-3a,5-dihydro-3H-pyrano[4,3,2-c]indole-2,4-dione (219).} \]

To a stirred solution of ester 217 (487 mg, 0.803 mmol) in EtOH (4 mL) was added 2 N aqueous KOH (4 mL) and the mixture was refluxed overnight. The solvent was removed under reduced pressure and the residue was acidified with 1 N aqueous HCl. The resulting white solid was filtered and dried \textit{in vacuo}. To a suspension of the solid residue in CH$_2$Cl$_2$ (10 mL) were added EDC (169 mg, 0.882 mmol) and DMAP (9.8 mg, 0.080 mmol). The mixture was stirred at rt for 4 h and then diluted with saturated aqueous NH$_4$Cl (10 mL) and CH$_2$Cl$_2$ (50 mL). The organic layer was dried over MgSO$_4$ and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give two diastereomers of tricyclic lactone 219 (major diastereomer, 256 mg, 64%; minor diastereomer, 82 mg, 20%). Less polar minor diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 (t, $J = 8.1$ Hz, 1H), 7.37 (dd, $J = 1.0$, 7.7 Hz, 1H), 7.15 (ddd, $J = 1.1$, 7.5, 7.5 Hz, 1H), 7.09-7.04 (m, 2H), 6.92 (d, $J = 8.3$ Hz, 1H), 6.90-6.84 (m, 3H), 6.62 (d, $J = 7.7$ Hz, 1H), 5.95 (d, $J = 2$H), 6.88-6.78 (m, 4H), 6.72 (dd, $J = 0.8$, 8.3 Hz, 1H), 6.13 (dd, $J = 0.7$, 7.7 Hz, 1H), 5.39, 5.15 (ABq, $J = 12.8$ Hz, 2H), 4.76 (s, 1H), 4.32, 4.22 (ABq, $J = 6.5$ Hz, 2H), 4.16-4.05 (m, 2H) 3.79 (s, 3H), 3.28-3.21 (m, 2H), 3.12 (s, 3H), 2.83 (s, 3H), 2.60 (ddd, $J = 4.3$, 6.0, 13.7 Hz, 1H), 2.44 (ddd, $J = 6.2$, 7.5, 15.9 Hz, 1H), 1.62-1.50 (m, 2H), 0.75 (t, $J = 7.4$ Hz, 3H).
MOM Deprotection of Tricyclic Lactone 219. To a stirred solution of lactone 219 (22.5 mg, 0.045 mmol) in MeOH (5.0 mL) was added concentrated HCl (1 drop) at rt. The mixture was warmed to 50 °C and stirred overnight. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give spiro lactone 221 (9.1 mg, 44%) and methyl ester 222 (8.3 mg, 40%). Spiro lactone 55: \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.27-7.19 (m, 1H), 7.16-6.98 (m, 5H), 6.91-6.85 (m, 3H), 7.1 Hz, 1H), 5.52 (d, \(J = 11.8\) Hz, 1H), 5.15 (d, \(J = 11.8\) Hz, 1H), 4.98 (s, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.73-3.50 (m, 1H), 3.48-3.43 (m, 1H), 3.23 (s, 3H), 2.95 (s, 3H), 2.41 (ddd, \(J = 6.3\), 7.7, 14.0 Hz, 1H), 2.22 (ddd, \(J = 5.8\), 5.8, 14.2 Hz, 1H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 177.1, 168.3, 154.6, 153.3, 150.3, 145.2, 136.7, 132.7, 132.0, 130.7, 128.9, 125.7, 116.7, 115.1, 114.5, 110.3, 105.2, 96.8, 69.9, 63.6, 56.2, 55.8, 50.4, 48.7, 38.5, 27.0; LRMS-APCI [M+H]\(^+\) calcd for C\(_{29}\)H\(_{30}\)NO\(_7\), 504.2; found, 504.3. More polar major diastereomer: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.63 (d, \(J = 7.8\) Hz, 1H), 7.48 (ddd, \(J = 1.4\), 7.5, 7.5 Hz, 1H), 7.41-7.34 (m, 3H), 6.83 (d, \(J = 8.3\) Hz, 1H), 6.74-6.66 (m, 5H), 4.92, 4.81 (ABq, \(J = 12.1\) Hz, 2H), 4.56 (s, 1H), 4.39 (s, 2H), 3.74 (s, 3H), 3.33-3.27 (m, 2H), 3.22 (s, 3H), 3.14 (s, 3H), 2.39 (ddd, \(J = 6.7\), 6.7, 13.4 Hz, 1H), 2.29 (ddd, \(J = 6.6\), 6.6, 13.2 Hz, 1H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 176.8, 168.6, 154.7, 152.8, 149.3, 143.7, 137.0, 132.3, 131.5, 130.8, 130.4, 128.8, 128.4, 117.2, 114.9, 110.5, 105.0, 96.8, 71.6, 63.9, 56.1, 55.7, 48.7, 47.0, 33.8, 27.1; LRMS-APCI [M+H]\(^+\) calcd for C\(_{29}\)H\(_{30}\)NO\(_7\), 504.2; found, 504.3.
6.63 (d, J = 8.3 Hz, 1H), 6.18 (d, J = 7.6 Hz, 1H), 5.48 (d, J = 11.4 Hz, 1H), 4.95 (s, 1H), 4.86 (d, J = 11.4 Hz, 1H), 4.71 (m, 2H), 3.79 (s, 3H), 2.74 (s, 3H), 2.53 (ddd, J = 5.5, 9.0, 14.5 Hz, 1H), 2.35 (ddd, J = 4.5, 4.5, 14.5 Hz, 1H).

[4-Hydroxy-3-(2-hydroxyethyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-[2-(4-methoxyphenoxy)methyl]phenyl]acetic Acid Methyl Ester (222). $^1$H NMR (360 MHz, CDCl$_3$) δ 9.81 (s, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.19 (s, 1H), 7.08 (q, J = 8.0 Hz, 2H), 6.94-6.88 (m, 2H), 6.82-6.77 (m, 2H), 6.73 (d, J = 6.9 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.07 (d, J = 7.2 Hz, 2H), 5.27, 5.00 (ABq, J = 12.4 Hz, 2H), 4.74 (s, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.43 (ddd, J = 5.5, 5.5, 11.1 Hz, 1H), 3.29 (m, 1H), 2.75 (s, 3H), 2.48 (ddd, J = 5.3, 5.3, 14.0 Hz, 1H), 2.32 (ddd, J = 5.9, 8.2, 14.1 Hz, 1H).

Dimethylcarbamic Acid 3-{4-Benzxyloxy-2-[2-(4-methoxyphenoxy)methyl]benzylidene|butyrylamino]-2-iodophenyl Ester (223). To a stirred solution of amide 214 (592 mg, 0.961 mmol) in CH$_2$Cl$_2$ (6 mL) and cyclohexane (6 mL) was added benzyl 2,2,2-trichloroacetimidate (0.36 mL, 1.940 mmol), followed by one drop of TfOH. The mixture was stirred overnight at rt and then diluted with saturated aqueous NaHCO$_3$ (20 mL) and CH$_2$Cl$_2$ (100 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give benzyl ether 223 (413 mg, 61%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.34 (s, 1H), 8.10 (dd, J = 1.2, 8.3 Hz, 1H), 7.64 (s, 1H), 7.54-7.52
Dimethylcarbamic Acid 3-({4-Benzyloxy-2-[2-(4-methoxyphenoxymethyl)benzylidene]butyryl}methylaminomethyl)-2-iodophenyl Ester (224). To a stirred suspension of NaH (28.1 mg, 60% dispersion in mineral oil, 0.703 mmol) in THF (10 mL) was added a solution of the lactam 223 (413 mg, 0.584 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at rt for 1 h and recooled to 0 °C. To the solution was added MeI (0.055 mL, 0.883 mmol) and the reaction mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with saturated aqueous NH₄Cl (10 mL) and extracted with CH₂Cl₂ (100 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the N-methyl amide 224 (273 mg, 65%).

$^1$H NMR (360 MHz, CDCl₃) δ 7.46-6.88 (m, 12H), 6.71-6.67 (m, 5H), 4.44-4.38 (m, 4H), 3.68 (s, 3H), 3.63-3.54 (m, 2H), 3.18 (s, 3H), 3.01 (s, 3H), 2.92 (s, 3H), 2.61 (br s, 1H), 2.40 (br s, 1H).
[3-(2-Benzylloxyethyl)-4-dimethylcarbamoyloxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-[2-(4-methoxyphenoxy)methyl]-phenyl]acetic Acid Methyl Ester (225). To a solution of N-methyl amide 224 (273 mg, 0.378 mmol) in DMA (2 mL) and MeOH (1 mL) was added Pd(OAc)$_2$ (17.0 mg, 0.076 mmol), P(o-Tol)$_3$ (69.1 mg, 0.227 mmol) and NaOAc (62.1 mg, 0.757 mmol). The mixture was stirred at 90 °C under a CO atmosphere (1 atm) for 24 h. The reaction mixture was cooled to rt and diluted with EtOAc (150 mL). The solution was washed with water (3×20 mL) and brine (20 mL), dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the ester 225 (169 mg, 69%) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.54-7.51 (m, 1H), 7.47-7.41 (m, 1H), 7.34-7.13 (m, 6H), 7.11-7.06 (m, 2H), 6.97 (d, $J$ = 8.4 Hz, 1H), 6.87-6.80 (m, 4H), 6.45 (d, $J$ = 7.7 Hz, 1H), 5.07, 4.86 (ABq, $J$ = 11.6 Hz, 2H), 4.67 (s, 1H), 4.21, 3.96 (ABq, $J$ = 11.6 Hz, 2H), 3.78 (s, 3H), 3.61 (s, 3H), 3.28 (m, 1H), 3.11 (m, 1H), 2.89 (s, 6H), 2.77-2.67 (m, 1H), 2.62 (s, 2H), 2.51 (s,3H), 2.44-2.37 (m, 1H).

3a-(2-Benzylloxyethyl)-3-[2-(4-methoxyphenoxy)methyl]phenyl]-5-methyl-3a,5-dihydro-3H-pyran[4,3,2-c]indole-2,4-dione (226). To a stirred solution of ester 225 (25.1 mg, 0.039 mmol) in EtOH (4 mL) was added a solution of KOH (2 mL, 2.0 M in water, 8.00 mmol) and the mixture was refluxed overnight. The solvent was removed under reduced pressure and the residue was acidified with 1N HCl. The resulting white solid
was filtered and dried \textit{in vacuo}. To a suspension of the solid residue in CH$_2$Cl$_2$ (10 mL) was added EDC (7.4 mg, 0.039 mmol) and a catalytic amount of DMAP. The mixture was stirred at rt for 30 min and then diluted with saturated aqueous NH$_4$Cl (5 mL) and CH$_2$Cl$_2$ (20 mL). The organic layer was dried over MgSO$_4$ and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give lactone 226 (15.6 mg, 74%) as a mixture of two diastereomers (1: 0.8). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.62 (d, $J$ = 7.5 Hz, 1H, major), 7.49-7.01 (m, 10H, major and minor), 6.93-6.84 (m, 2H, major and minor), 6.73-6.57 (m, 3H, major and minor), 5.96 (d, $J$ = 7.9 Hz, 1H, minor), 5.53 (d, $J$ = 11.8 Hz, 1H, minor), 5.16 (d, $J$ = 11.8 Hz, 1H, minor), 5.00 (s, 1H, minor), 4.91 (d, $J$ = 12.1 Hz, 1H, major), 4.79 (d, $J$ = 12.0 Hz, 1H, major), 4.54 (s, 1H, major), 4.39-4.09 (m, 3H, major and minor), 3.80 (s, 3H, minor), 3.74 (s, 3H, major), 3.57-3.42 (m, 1H, major and minor), 2.99 (s, 3H, major), 2.83 (s, 3H, minor), 2.51-2.40 (m, 1H, major and minor), 2.33-2.29 (m, 1H, major and minor).

**Debenzylation of Benzyl Ether 226.** To a solution of benzyl ether 226 (15.6 mg, 0.028 mmol) in THF (5 mL) was added 10% Pd/C (3.0 mg). The mixture was stirred at rt under a H$_2$ atmosphere (1 atm) overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the two diastereomers of spiro lactone 221 (less polar diastereomer, 4.3 mg, 33%; more polar diastereomer, 4.3 mg, 33%). The less polar diastereomer is the same as the product from MOM-deprotection of tricyclic lactone 219. More polar diastereomer: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.46 (d, $J$
Synthesis of Spiro Lactone 228. To a stirred solution of ester 217 (61.1 mg, 0.101 mmol) in MeOH (5.0 mL) was added concentrated HCl (1 drop) at rt. The mixture was warmed to 60 °C and stirred for 4 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (3:1 EtOAc:hexanes) to give spiro lactone 228 (37.5 mg, 70%) and hydroxy ester 229 (9.5 mg, 17%).

Spiro lactone 228: IR (film) 1729, 1712, 1622, 1509, 1226, 1158 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.47 (dd, J = 1.1, 7.5 Hz, 1H), 7.27-7.19 (m, 2H), 7.12 (ddd, J = 1.3, 7.6, 7.6 Hz, 1H), 7.04 (dd, J = 1.4, 7.6 Hz, 1H), 6.82 (dd, J = 0.6, 8.4 Hz, 1H), 6.78-6.70 (m, 4H), 6.42 (d, J = 7.8 Hz, 1H), 5.01 (ddd, J = 4.7, 6.8, 11.4 Hz, 1H), 4.97 (s, 1H), 4.94 (d, J = 11.9 Hz, 1H), 4.56 (ddd, J = 4.2, 7.5, 11.7 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 3.75 (s, 3H), 3.00 (s, 3H), 2.95 (s, 3H), 2.94 (s, 3H), 2.55 (ddd, J = 4.4, 6.7, 14.8 Hz, 1H), 2.42 (ddd, J = 4.7, 7.7, 14.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.5, 170.8, 154.6, 154.3, 152.9, 148.2, 144.9, 136.5, 132.2, 131.4, 130.6, 129.5, 128.3, 128.0, 121.9, 118.0, 116.7, 115.0, 106.0, 69.8, 65.0, 56.1, 52.1, 46.6, 37.6, 36.8, 30.4, 26.7; HRMS-ES [M+Na]⁺ calcd for C₃₀H₃₀N₂NaO₇, 553.1951; found, 553.1963.
Hydroxy ester 229: IR (film) 3470, 2927, 1735, 1712, 1616, 1509, 1226, 1152 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.54-7.52 (m, 1H), 7.28-7.17 (m, 4H), 6.86-6.80 (m, 5H), 6.53 (d, \(J = 7.7\) Hz, 1H), 5.07, 4.83 (ABq, \(J = 12.9\) Hz, 2H), 4.70 (s, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 3.34 (t, \(J = 6.3\) Hz, 2H), 3.12 (s, 3H), 2.92 (s, 3H), 2.72 (s, 3H), 2.56 (ddd, \(J = 6.9, 6.9, 13.8\) Hz, 1H), 2.34 (ddd, \(J = 6.4, 6.4, 12.7\) Hz, 1H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 177.9, 171.2, 154.5, 154.4, 153.0, 148.3, 146.2, 136.4, 133.4, 130.6, 130.0, 129.6, 128.2, 128.0, 120.3, 117.2, 116.2, 115.0, 105.5, 69.2, 59.6, 56.2, 54.6, 52.7, 37.4, 37.2, 36.6, 27.0; HRMS-ES [M+H]\(^+\) calcd for C\(_{31}\)H\(_{35}\)N\(_2\)O\(_8\), 563.2393; found, 563.2392.

**O- Allylation of Spiro Lactone 228.** To a stirred suspension of spiro lactone 228 (69.1 mg, 0.130 mmol) and NaH (6.2 mg, 60% dispersion in mineral oil, 0.155 mmol) in DMF (2 mL) was added allyl iodide (0.024 mL, 0.262 mmol) at rt. The mixture was stirred at rt overnight. The reaction mixture was diluted with saturated aqueous NH\(_4\)Cl (10 mL) and extracted with EtOAc (100 mL). The organic layer was washed with water (3×20 mL) and brine (20 mL), dried over MgSO\(_4\) and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the O-allyl ketene acetal 230 (46.6 mg, 63%) as a colorless oil. IR (film) 2916, 1712, 1616, 1509, 1226 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\), 2:1 atropisomeric mixture) \(\delta\) 7.40 (d, \(J = 7.3\) Hz, 1H), 7.26-6.95 (m, 7.5H), 6.90-6.77 (m, 4.5 H), 6.73 (s, 2H), 6.46 (d, \(J = 7.7\) Hz, 1H), 6.43 (d, \(J = 7.8\) Hz, 0.5H), 5.80-5.64 (m, 1.5H),
5.24-4.86 (m, 7.5H), 4.38-4.27 (m, 4.5H), 3.78 (s, 3H), 3.76 (s, 1.5H), 3.18 (s, 3H), 3.76 (s, 1.5H), 3.18 (s, 3H), 3.073 (s, 3H), 3.067 (s, 3H), 2.99 (s, 1.5H), 2.95 (s, 3H), 2.49-2.39 (m, 1.5H), 2.08-1.99 (m, 1.5H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 180.0, 179.0, 157.1, 156.2, 154.5, 154.3, 153.9, 153.8, 153.5, 148.2, 148.0, 145.1, 145.0, 138.6, 138.1, 134.0, 133.7, 132.9, 132.5, 131.5, 131.1, 129.6, 129.5, 127.5, 127.2, 126.7, 126.4, 126.2, 123.0, 122.5, 118.3, 118.2, 117.9, 117.7, 116.3, 116.2, 115.0, 114.8, 105.5, 105.3, 88.0, 84.6, 69.5, 69.4, 68.5, 68.3, 65.1, 65.0, 56.2, 50.15, 37.5, 37.4, 36.9, 31.6, 29.8, 26.9, 26.8; HRMS-ES [M+H]$^+$ calcd for C$_{33}$H$_{35}$N$_2$O$_7$, 571.2444; found, 571.2429.

**General Method for Claisen Rearrangement of Ketene Acetal 230.** A solution of ketene acetal 230 in the solvent indicated in the table was heated at 110 °C and stirred overnight. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the two diastereomers of allyl lactone 231. More polar major diastereomer 231a (pale yellow oil): IR (film) 2927, 1729, 1712, 1616, 1502, 1226, 1158 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 (br s, 1H), 7.23 (t, $J$ = 8.0 Hz, 2H), 7.17 (t, $J$ = 7.0 Hz, 1H), 6.83 (d, $J$ = 8.7 Hz, 2H), 6.77 (br s, 2H), 6.60-6.56 (m, 2H), 5.64 (m, 1H), 5.04-4.87 (m, 3H), 4.66 (br s, 1H), 4.47 (br s, 1H), 3.79 (s, 3H), 3.22 (br s, 1H), 3.10 (s, 3H), 2.92-2.87 (m, 4H), 2.78-2.70 (m, 4H), 2.29 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.8, 171.9, 154.0, 153.7, 153.0, 149.3, 145.0, 137.0, 134.9, 134.3, 131.7, 131.4, 130.1, 127.5, 126.8, 120.1, 118.3, 116.9, 115.0, 114.5, 105.2, 68.7, 65.4, 55.7, 55.4, 38.4, 36.9, 36.5, 29.7, 29.4, 24.6; HRMS-ES [M+Na]$^+$ calcd for
C$_{33}$H$_{34}$N$_2$NaO$_7$, 593.2264; found, 593.2263. Less polar minor diastereomer 231b (pale yellow oil): IR (film) 2927, 1729, 1712, 1616, 1509, 1226, 1164 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.71 (br s, 1H), 7.30 (t, $J = 8.1$ Hz, 2H), 7.17 (t, $J = 7.5$ Hz, 1H), 7.02-7.00 (m, 2H), 6.90-6.83 (m, 4H), 6.54 (br s, 1H), 6.34 (d, $J = 7.7$ Hz, 1H), 5.63-5.56 (m, 2H), 5.06-4.96 (m, 3H), 4.79 (br s, 1H), 4.55 (dd, $J = 6.4$, 11.3 Hz, 1H), 3.81 (s, 3H), 3.61 (dd, $J = 5.9$, 15.2 Hz, 1H), 3.23 (s, 3H), 3.18-3.02 (m, 2H), 3.11 (s, 3H), 2.58 (s, 3H), 2.01 (dd, $J = 3.8$, 14.9 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.8, 171.1, 154.6, 154.1, 154.0, 149.4, 146.4, 138.3, 133.8, 132.4, 130.8, 129.9, 127.8, 125.9, 119.4, 118.4, 118.2, 116.4, 115.0, 113.7, 105.7, 71.1, 65.5, 56.7, 56.2 41.9, 37.5, 37.1, 30.1, 26.1, 24.9; HRMS-ES [M+Na]$^+$ calcd for C$_{33}$H$_{34}$N$_2$NaO$_7$, 593.2264; found, 593.2274.

2-Iodo-1-(4-methoxyphenoxy)methyl)-3-nitrobenzene (239). To a stirred solution of (2-iodo-3-nitrophenyl)-methanol$^{57}$ (238, 1.62 g, 5.83 mmol), PPh$_3$ (1.61 g, 6.14 mmol) and 4-methoxyphenol (0.76 g, 6.12 mmol) in CH$_2$Cl$_2$ (25 mL) was added DEAD (1.00 mL, 6.35 mmol) dropwise at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the O-PMP nitrobenzene 239 (1.99 g, 89%) as a yellow solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.73 (dd, $J = 0.7$, 7.7 Hz, 1H), 7.60 (dd, $J = 1.4$, 7.9 Hz, 1H), 7.48 (t, $J = 7.8$ Hz, 1H), 6.94-6.85 (m, 4H), 5.06 (s, 2H), 3.79 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.2, 154.9, 152.4, 143.5, 131.5, 129.5, 124.1, 116.3, 115.2, 88.7, 75.6, 56.1.
2-Iodo-3-(4-methoxyphenoxy)methyl)-phenylamine (240). To a solution of the nitrobenzene 239 (1.99 g, 7.02 mmol) in EtOH (30 mL) and glacial acetic acid (20 mL) was added iron powder (1.15 g, 20.59 mmol). The mixture was heated at 60 °C for 3 h and then cooled to rt. The mixture was diluted with water (150 mL) and carefully neutralized with solid Na₂CO₃. The resulting solution was extracted with EtOAc (2×50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to give the aniline 240 (1.80 g, 98%) as a white solid. ¹H NMR (400 MHz, CDCl₃+CD₃OD) δ 7.10 (t, J = 7.7 Hz, 1H), 6.90-6.80 (m, 5H), 6.71 (d, J = 7.9 Hz, 1H), 4.94 (s, 2H), 3.74 (s, 3H); ¹³C NMR (100 MHz, CDCl₃+CD₃OD) δ 154.4, 153.1, 147.4, 140.5, 129.3, 119.1, 116.3, 115.0, 114.7, 87.7, 75.8, 56.1.

4-Hydroxy-N-[2-iodo-3-(4-methoxyphenoxy)methyl]-phenyl]-2-(2-nitrobenzylidene)-butyramide (241). To a stirred solution of the aniline 240 (63.0 mg, 0.177 mmol) and lactone 147 (38.3 mg, 0.175 mmol) in CH₂Cl₂ (5 mL) was added AlMe₃ (0.11 mL, 2.0 M in hexane, 0.220 mmol) at 0 °C. The mixture was warmed to rt, stirred overnight and then poured into an iced aqueous NH₄Cl (20 mL). The aqueous layer was extracted with EtOAc (50 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1:1 EtOAc:hexanes:CH₂Cl₂) to give the amide 241 (68.7 mg, 67%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.51 (s, 1H), 8.19 (m, 2H), 7.75 (s, 1H), 7.70 (t, J = 7.5 Hz,
1H, 7.55 (t, J = 7.8 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.94-6.84 (m, 2H), 5.02 (s, 2H), 3.78 (s, 3H), 3.76 (t, J = 5.8 Hz, 1H), 2.64 (t, J = 5.8 Hz, 1H).

4-(tert-Butyldimethylsilanyloxy)-N-[2-iodo-3-(4-methoxyphenoxy)methyl]-2-(2-nitrobenzylidene)butyramide (242). To a solution of the amide 241 (68.7 g, 0.120 mmol) and imidazole (24.4 mg, 0.358 mmol) in DMF (2 mL) was added TBDMSCl (43.4 mg, 0.288 mmol) in a single portion. The reaction mixture was stirred at rt overnight and then diluted with EtOAc (30 mL). The solution was washed with water (3×10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the TBDMS ether 242 (81.0 mg, 98%) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 8.51 (s, 1H), 8.25 (dd, J = 1.6, 8.0 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.70-7.68 (m, 2H), 7.55 (m, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.32 (dd, J = 1.7, 7.6 Hz, 1H), 6.95-6.84 (m, 4H), 5.04 (s, 2H), 3.79 (s, 3H), 3.76 (t, J = 6.2 Hz, 1H), 2.73 (t, J = 6.1 Hz, 1H), 0.83 (s, 9H), -0.01 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 167.5, 154.6, 152.9, 148.1, 140.8, 138.9, 138.0, 134.0, 132.6, 132.2, 132.0, 129.5, 129.4, 125.0, 124.2, 122.4, 116.4, 115.1, 94.9, 75.8, 62.1, 56.1, 31.9, 26.4, 18.7, -5.0.
benzylidene)-butyramide (243). To a stirred suspension of NaH (0.077 g, 60% dispersion in mineral oil, 1.93 mmol) in THF (35 mL) was added a solution of the amide 242 (1.210 g, 1.76 mmol) in THF (15 mL) at 0 °C. The mixture was stirred at rt for 30 min and recooled to 0 °C. To the solution was added MeI (0.13 mL, 2.09 mmol) and the reaction mixture was warmed to rt and stirred for 6 h. The reaction mixture was diluted with saturated aqueous NH₄Cl (20 mL) and extracted with EtOAc (100 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the N-methyl amide 243 (1.094 g, 89%). ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.57 (dd, J = 1.0, 8.2 Hz, 1H), 7.36 (m, 1H), 7.15-7.00 (m, 5H), 6.87-6.80 (m, 2H), 6.74-6.69 (m, 2H), 4.97 (s, 2H), 3.85 (ddd, J = 1.8, 6.7, 6.7 Hz, 2H), 3.46 (s, 3H), 3.27 (s, 3H), 2.53 (m, 1H), 2.44 (m, 1H), 0.92 (s, 9H), 0.05 (s, 6H); ¹³C NMR (75 MHz, toluene-d₈, 90 °C) δ 170.1, 155.3, 153.3, 148.9, 147.6, 143.2, 137.8, 132.2, 131.7, 131.6, 129.4, 128.8, 128.2, 127.7, 124.2, 116.6, 115.4, 102.6, 76.0, 62.2, 55.4, 37.9, 33.9, 26.1, 18.5, -5.2.

[3-[2-(tert-Butyldimethylsilanyloxyl)-ethyl]-4-(4-methoxyphenoxy)methyl]-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-2-nitrophenyl-acetic Acid Methyl Ester (244).

To a solution of N-methyl amide 243 (29.3 mg, 0.042 mmol) in DMA (2.0 mL) and MeOH (1.0 mL) were added Pd(dba)₂ (7.6 mg, 0.013 mmol), biphenyldicyclohexylphosphine (11.7 mg, 0.033 mmol) and NaOAc (6.8 mg, 0.083 mmol). The mixture was stirred at 85 °C under a CO atmosphere (1 atm) for 18 h. The
remaining catalyst was removed by filtration and washed with EtOAc. The filtrate was washed with water (3×10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The percent yields of each compound was calculated by integration of the crude ¹H NMR spectrum. For analytical purposes, the compounds were separated by preparative TLC (1:5 EtOAc:hexanes). Major more polar diastereomer of 244: ¹H NMR (300 MHz, CDCl₃) δ 7.89 (dd, J = 1.4, 8.0 Hz, 1H), 7.82 (dd, J = 1.4, 8.0 Hz, 1H), 7.55 (ddd, J = 1.4, 7.5, 7.5 Hz, 1H), 7.45 (ddd, J = 1.5, 8.0, 8.0 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.6 (m, 1H), 7.06-7.00 (m, 2H), 6.93-6.86 (m, 2H), 6.78 (dd, J = 0.9, 7.7 Hz, 1H), 5.47 (s, 1H), 5.19, 5.08 (ABq, J = 11.7 Hz, 2H), 3.80 (s, 3H), 3.40 (s, 3H), 3.22-3.18 (m, 5H), 2.23 (ddd, J = 5.4, 5.4, 13.7 Hz, 1H), 1.99 (ddd, J = 7.0, 7.0, 14.1 Hz, 1H), 0.66 (s, 9H), -0.28 (d, J = 2.3 Hz, 1H).

3-[2-(tert-Butyldimethylsilyloxy)-ethyl]-4-(4-methoxyphenoxymethyl)-1-methyl-3-(2-nitrobenzyl)-1,3-dihydroindol-2-one (245). ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, J = 8.0 Hz, 1H), 7.31-7.20 (m, 4H), 7.15 (d, J = 7.7 Hz, 1H), 6.99-6.96 (m, 2H), 6.90-6.87 (m, 2H), 6.53 (d, J = 7.4 Hz, 1H), 5.03, 4.96 (ABq, J = 10.7 Hz, 2H), 3.96 (d, J = 13.3 Hz, 1H), 3.81 (s, 3H), 3.45-3.36 (m, 3H), 2.83 (s, 3H), 2.53 (ddd, J = 6.0, 8.0, 14.1 Hz, 1H), 2.19 (ddd, J = 4.5, 4.5, 14.0 Hz, 1H), 0.71 (s, 9H), -0.23 (d, J = 12.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 178.4, 154.6, 153.2, 150.4, 144.6, 134.1, 133.8, 131.9, 130.4, 129.2, 128.0, 127.4, 124.9, 124.6, 116.1, 115.2, 108.1, 68.2, 60.1, 56.2, 54.2, 39.8, 38.9, 26.4, 26.2, 18.6, -5.4.
2-[(4-(tert-Butyldimethylsilanyloxy)-2-(2-nitrobenzylidene)-butyryl]-methylamino]-6-(4-methoxyphenoxy)methyl)-benzoic Acid Methyl Ester (246). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.98 (bs, 1H), 7.75-7.26 (m, 6H), 7.06 (bs, 1H), 6.85-6.65 (m, 4H), 5.12 (bs, 2H), 3.88 (bs, 3H), 3.75 (bs, 5.5H), 3.60 (bs, 1H), 3.31 (bs, 2H), 2.62-2.49 (m, 1.5H), 2.27 (bs, 1H), 0.88 (s, 9H), 0.04 (s, 6H).

$^{tert}$-Butyl-(2-iodo-3-nitrobenzyloxy)-dimethylsilane (245). To a solution of alcohol 238 (507 mg, 1.82 mmol) and imidazole (247 mg, 3.63 mmol) in DMF (5 mL) was added TBDMSCl (329 mg, 2.18 mmol) in a single portion. The reaction mixture was stirred at rt for 3 h and then diluted with EtOAc (150 mL). The solution was washed with water (3×30 mL) and brine (30 mL), dried over Na$_2$SO$_4$ and concentrated $\textit{in vacuo}$. The residue was purified by flash column chromatography (1:10 EtOAc:hexanes) to give the TBDMS ether 245 (714 mg, 100%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.73 (d, $J = 7.6$ Hz, 1H), 7.56 (d, $J = 7.2$ Hz, 1H), 7.48 (t, $J = 7.8$ Hz, 1H), 4.68 (s, 2H), 0.98 (s, 9H), 0.17 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 154.8, 146.9, 130.5, 129.3, 123.5, 87.4, 70.7, 26.4, 18.8, -4.9.

3-(tert-Butyldimethylsilanyloxymethyl)-2-iodophenylamine (246). To a solution of the nitrobenzene 245 (714 mg, 1.82 mmol) in EtOH (7 mL) and glacial acetic acid (7 mL) was added iron powder (507 mg, 9.08 mmol). The mixture was heated at 60 °C for 4 h and then cooled to rt. The mixture was diluted
with water (150 mL) and carefully neutralized with solid Na₂CO₃. The resulting solution was extracted with EtOAc (150 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the aniline 246 (2.36 g, 95%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.16 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 4.63 (s, 2H), 4.18 (bs, 2H), 1.00 (s, 9H), 0.17 (s, 6H).

N-[3-(tert-Butyldimethylsilyloxy)methyl]-2-iodophenyl]-4-hydroxy-2-[2-(4-methoxyphenoxymethyl)-benzylidene]-butyramide (247). To a stirred solution of the aniline 246 (428 mg, 1.18 mmol) and lactone 147 (235 mg, 1.07 mmol) in CH₂Cl₂ (10 mL) was added AlMe₃ (0.64 mL, 2.0 M in hexane, 1.28 mmol) at 0 °C. The mixture was warmed to rt, stirred overnight and then poured into an iced aqueous NH₄Cl (100 mL). The aqueous layer was extracted with CH₂Cl₂ (100 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:10 EtOAc:CH₂Cl₂) to give the amide 247 (572 mg, 92%) as a pale yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 8.45 (s, 1H), 8.21 (dd, J = 1.1, 8.1 Hz, 1H), 8.13 (dd, J = 1.8, 7.8 Hz, 1H), 7.73 (s, 1H), 7.69 (dd, J = 1.2, 7.5 Hz, 1H), 7.56 (t, J = 8.3 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.35 (ddd, J = 0.9, 0.9, 7.6 Hz, 1H), 4.65 (s, 2H), 3.75 (m, 2H), 2.95 (bs, 1H), 2.63 (t, J = 5.8 Hz, 2H), 0.98 (s, 9H), 0.16 (s, 6H).
4-Benzylamino-N-[3-(tert-butyldimethylsilyl)oxymethyl]-2-iodophenyl]-2-[2-(4-methoxyphenoxymethyl)-benzylidene]-N-methylbutyramide (248). To a stirred solution of amide 247 (297 mg, 0.510 mmol) in CH₂Cl₂ (4 mL) and cyclohexane (8 mL) was added benzyl 2,2,2-trichloroacetimidate (0.19 mL, 1.022 mmol), followed by one drop of TfOH. The mixture was stirred overnight at rt and then diluted with saturated aqueous NaHCO₃ (20 mL) and EtOAc (100 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give benzyl ether 248 (121 mg, 35%). ¹H NMR (300 MHz, CDCl₃) δ 8.44 (s, 1H), 8.18 (d, J = 8.3 Hz, 1H), 8.12 (dd, J = 1.7, 7.7 Hz, 1H), 7.76 (s, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.56-7.50 (m, 2H), 7.40 (t, J = 7.7 Hz, 1H), 7.35 (dd, J = 1.7, 7.5 Hz, 1H), 7.28-7.19 (m, 5H), 4.67 (s, 2H), 4.45 (s, 2H), 3.57 (t, J = 6.1 Hz, 2H), 2.75 (t, J = 6.1 Hz, 2H), 1.01 (s, 9H), 0.18 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 167.6, 148.2, 144.3, 138.4, 138.3, 138.3, 137.8, 134.0, 132.4, 132.1, 131.9, 129.4, 129.1, 128.7, 128.1, 128.0, 125.4, 124.3, 121.7, 93.6, 73.6, 70.7, 68.6, 29.3, 26.4, 18.9, -4.8.

4-Benzylamino-N-[3-(tert-butyldimethylsilyl)oxymethyl]-2-iodophenyl]-2-[2-(4-methoxyphenoxymethyl)-benzylidene]-N-methylbutyramide (249). To a stirred suspension of NaH (8.6 mg, 60% dispersion in mineral oil, 0.22 mmol) in THF (3 mL) was added a solution of the lactam 248 (121 mg, 0.18 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at rt for 15 min and recooled to 0 °C. To the solution was added MeI
(22 μL, 0.35 mmol) and the reaction mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with saturated aqueous NH₄Cl (10 mL) and extracted with EtOAc (30 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the N-methyl amide 249 (91 mg, 77%). ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.49 (d, J = 8.2 Hz, 1H), 7.41 (ddd, J = 0.8, 0.8, 7.6 Hz, 1H), 7.19-6.96 (m, 9H), 6.90 (t, J = 7.0 Hz, 1H), 6.73 (ddd, J = 0.8, 8.1, 8.1 Hz, 1H), 4.72 (d, J = 2.4 Hz, 2H), 4.29 (d, J = 2.6 Hz, 2H), 3.58 (m, 2H), 3.21 (s, 3H), 2.52 (m, 1H), 2.42 (m, 1H), 0.94 (s, 9H), 0.07 (s, 6H).

4-Benzylxoy-N-(3-hydroxymethyl-2-iodophenyl)-2-[2-(4-methoxyphenoxy)methyl]-benzylidene]-N-methylbutyramide (250). To a stirred solution of TBDMS ether 249 (95.1 mg, 0.14 mmol) in THF (3 mL) was added TBAF (0.15 mL, 1.0 M in THF, 0.15 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 1.5 h. The mixture was diluted with EtOAc (60 mL) and saturated aqueous NH₄Cl (10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the alcohol 250 (67.3 mg, 85%) as a yellow oil. ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.49 (d, J = 8.2 Hz, 1H), 7.22-6.89 (m, 11H), 6.74 (t, J = 7.7 Hz, 1H), 4.45 (d, J = 6.5 Hz, 1H), 4.28 (s, 2H), 3.56 (m, 2H), 3.19 (s, 3H), 2.51 (m, 1H), 2.43 (m, 1H).
3-({4-Benzyl oxy-2-[2-(4-methoxypheno xomethyl)-benzylidene]-butyryl}-methylamino)-2-iodobenzoic Acid M ethyl Ester (251). To a stirred solution of alcohol 250 (39.8 mg, 0.070 mmol) in CH₂Cl₂ (4 mL) was added MnO₂ (121 mg, 1.392 mmol). The mixture was stirred at rt for 48 h. The solid was removed by filtration and washed with ether (30 mL). The filtrate was concentrated in vacuo, and the crude residue was dissolved in MeOH (5 mL). To the solution were added NaCN (17.0 mg, 0.347 mmol) and MnO₂ (121 mg, 1.392 mmol), followed by 2 drops of AcOH, and the mixture was stirred at rt overnight. The solid was removed by filtration, washed with ether (20 mL), and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the methyl ester 251 (31.2 mg, 75%) as a yellow oil. ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.51 (d, J = 8.1 Hz, 1H), 7.27 (dd, J = 1.7, 7.6 Hz, 1H), 7.18-6.86 (m, 8H), 6.72 (t, J = 7.8 Hz, 1H), 4.26 (s, 2H), 3.56 (br s, 5H), 3.16 (s, 3H), 2.44 (m, 2H).

3-[2-(tert-Butyldimethylsilanyloxy)-ethyl]-4-(4-methoxypheno xomethyl)-1-methyl-3-(2-nitrobenzyl)-1,3-dihy droindol-2-one (245). Method A: To a solution of N-methyl amide 243 (27.0 mg, 0.038 mmol) in toluene (2.0 mL) and MeOH (1.0 mL) were added Pd(dba)₂ (7.0 mg, 0.012 mmol), biphenyldicyclohexylphosphine (10.8 mg, 0.031 mmol) and K₂PO₄ (16.3 mg, 0.077 mmol). The mixture was stirred at 85 °C under a CO atmosphere (1 atm) for 18 h. The remaining catalyst was removed by filtration and
washed with EtOAc. The filtrate was washed with water (3×10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the protonolysis product 245 (16.8 mg, 76%). Method B: To a solution of N-methyl amide 243 (100.6 mg, 0.143 mmol) in DMA (3.0 mL) were added Pd(OAc)₂ (3.2 mg, 0.014 mmol), PPh₃ (11.3 mg, 0.043 mmol), NaO₂CH (19.5 mg, 0.287 mmol) and NaOAc (23.5 mg, 0.286 mmol). The mixture was stirred at 85 °C for 18 h. The catalyst was removed by filtration and washed with EtOAc (80 mL). The combined filtrate was washed with water (3×15 mL) and brine (15 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the protonolysis product 245 (60.8 mg, 74%).

3-(2-Hydroxyethyl)-4-(4-methoxyphenoxy)methyl)-1-methyl-3-(2-nitrobenzyl)-1,3-dihydroindol-2-one (253). To a stirred solution of the protonolysis product 245 (33.9 mg, 0.059 mmol) in THF (1.0 mL) was added TBAF (0.070 mL, 1.0 M in THF, 0.070 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 3 h. The mixture was diluted with EtOAc (40 mL) and saturated aqueous NH₄Cl (10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the alcohol 253 (27.2 mg, 100%). ¹H NMR (300 MHz, CDCl₃) δ 7.55 (d, J = 8.3 Hz, 1H), 7.38-7.20 (m, 4H), 7.12 (d, J = 7.8 Hz, 1H), 7.00-6.88 (m, 4H), 6.58 (d, J = 7.8 Hz, 1H), 5.02, 4.97 (ABq, J = 10.4 Hz, 2H), 4.07
(d, J = 13.4 Hz, 1H), 3.81 (s, 3H), 3.55-3.39 (m, 3H), 2.88 (s, 3H), 2.48 (dd, J = 6.2, 7.8, 14.0 Hz, 1H), 2.27 (ddd, J = 5.5, 5.5, 14.2 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 179.0, 154.8, 152.9, 150.3, 144.3, 133.7, 132.2, 130.3, 129.6, 128.2, 127.9, 125.9, 124.7, 116.0, 115.3, 108.7, 68.3, 60.1, 56.2, 54.3, 39.6, 39.4, 26.5.

**Carbonic Acid Ethyl Ester 2-[4-(4-Methoxyphenoxy)methyl]-1-methyl-3-(2-nitrobenzyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-ethyl Ester (254a).** To a stirred solution of alcohol 253 (2.7 mg, 5.8 $\mu$mol) and pyridine (30 $\mu$L, 37.1 $\mu$mol) in CH$_2$Cl$_2$ (1 mL) was added ClCO$_2$Et (10 $\mu$L, 10.5 $\mu$mol) at 0 °C. The reaction mixture was warmed to rt and stirred for 30 min. The mixture was diluted with CH$_2$Cl$_2$ and saturated aqueous NH$_4$Cl. The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by preparative TLC (1:3 EtOAc:hexanes) to give the ethyl carbonate 254a (2.6 mg, 84%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.56 (d, J = 8.0 Hz, 1H), 7.37-7.20 (m, 4H), 7.13 (d, J = 7.2 Hz, 1H), 6.97-6.93 (m, 2H), 6.91-6.87 (m, 2H), 6.59 (d, J = 7.1 Hz, 1H), 5.00 (s, 2H), 4.10-4.01 (m, 4H), 3.81 (s, 3H), 3.80-3.76 (m, 1H), 3.43 (d, J = 13.4 Hz, 1H), 2.89 (s, 3H), 2.66 (ddd, J = 7.0, 7.0, 15.7 Hz, 1H), 2.32 (ddd, J = 4.2, 6.6, 13.9 Hz, 1H), 1.24 (t, J = 8.1 Hz, 1H).

**Carbonic Acid 2-[4-(4-Methoxyphenoxy)methyl]-1-methyl-3-(2-nitrobenzyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-ethyl Ester Phenyl Ester (254b).** To a stirred solution of
alcohol 253 (10.4 mg, 0.023 mmol) and pyridine (9 μL, 0.111 mmol) in CH₂Cl₂ (2 mL) was added ClCO₂Ph (4 μL, 0.032 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 2 h. The mixture was diluted with CH₂Cl₂ (20 mL) and saturated aqueous NH₄Cl (15 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the phenyl carbonate 254b (12.1 mg, 92%). ¹H NMR (300 MHz, CD₂Cl₂) δ 7.62 (dd, J = 1.4, 8.0 Hz, 1H), 7.44-7.19 (m, 8H), 7.16-7.13 (m, 2H), 7.03-6.98 (m, 2H), 6.95-6.91 (m, 2H), 6.69 (d, J = 7.8 Hz, 1H), 5.07 (s, 2H), 4.16 (m, 1H), 4.02, 3.55 (ABq, J = 13.4 Hz, 1H), 3.92 (m, 1H), 3.82 (s, 3H), 2.93 (s, 3H), 2.76 (ddd, J = 5.8, 8.3, 15.7 Hz, 1H), 2.40 (ddd, J = 2.4, 4.0, 5.9 Hz, 1H).

1-Benzylxymethyl-2-iodo-3-nitrobenzene (256). To a stirred solution of (2-iodo-3-nitrophenyl)-methanol (238) (0.86 g, 3.08 mmol) in CH₂Cl₂ (6 mL) and cyclohexane (10 mL) was added benzyl 2,2,2-trichloroacetimidate (1.14 mL, 6.13 mmol), followed by TfOH (0.03 mL, 0.34 mmol). The mixture was stirred at rt for 9 h and then diluted with saturated aqueous NaHCO₃ (20 mL) and EtOAc (60 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:15 EtOAc:hexanes) to give benzyl ether 256 (1.06 g, 93%) as a yellow oil. IR (film) 2871, 1712, 1526, 1350 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, J = 7.6 Hz, 1H), 7.58 (dd, J = 1.4, 7.9 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.44-7.32 (m, 5H), 4.71 (s, 2H), 4.63 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ
To a solution of the nitrobenzene 256 (1.05 g, 2.83 mmol) in EtOH (10 mL) and glacial acetic acid (10 mL) was added iron powder (0.79 g, 14.15 mmol). The mixture was heated at 60 °C for 3 h and then cooled to rt. The mixture was diluted with iced water (50 mL) and carefully neutralized with solid Na₂CO₃. The resulting solution was extracted with EtOAc (2×60 mL). The organic extract was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the aniline 257 (0.83 g, 97%) as a colorless oil. IR (film) 3447, 3357, 2859, 1610, 1463 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.45-7.29 (m, 5H), 7.14 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 6.9 Hz, 1H), 6.72 (dd, J = 0.9, 7.9 Hz, 1H), 4.65 (s, 2H), 4.56 (s, 2H), 4.00 (bs, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 147.4, 141.75, 138.6, 129.2, 128.9, 128.3, 128.1, 119.4, 114.5, 88.6, 77.2, 73.0; HRMS-ES [M+H]⁺ calcd for C₁₄H₁₅INO, 340.0198; found, 340.0195.

To a stirred solution of the aniline 257 (0.69 g, 2.03 mmol) and lactone 213 (0.57 g, 1.84 mmol) in CH₂Cl₂ (30 mL) was added AlMe₃ (1.80 mL, 2.0 M in hexane, 3.60 mmol) at 0 °C. The mixture was warmed to rt, stirred overnight and then poured into ice-cold aqueous NH₄Cl (80 mL). The aqueous layer was
extracted with CH$_2$Cl$_2$ (2×80 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the amide 258 (1.16 g, 97%) as a white solid (mp 126.5-127 °C).

IR (film) 3368, 2859, 1661, 1509, 1226 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.35 (s, 1H), 8.11 (dd, $J$ = 1.5, 8.0 Hz, 1H), 7.68 (s, 1H), 7.54 (m, 1H), 7.51-7.28 (m, 10H), 6.94-6.89 (m, 2H), 6.84-6.80 (m, 2H), 5.03 (s, 2H), 4.64 (s, 2H), 4.55 (s, 2H), 3.79 (t, $J$ = 5.8 Hz, 2H), 3.74 (s, 3H), 2.77 (t, $J$ = 5.8 Hz, 2H), 2.70 (bs, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.9, 154.6, 153.1, 141.9, 138.64, 138.61, 138.3, 135.5, 135.3, 134.3, 129.9, 129.6, 129.3, 129.00, 128.95, 128.9, 128.3, 125.9, 122.5, 116.3, 115.2, 96.0, 77.1, 73.1, 69.7, 62.5, 56.2, 31.9; HRMS-ES [M+H]$^+$ calcd for C$_{33}$H$_{33}$INO$_5$, 650.1404; found, 650.1404.

$N$-(3-Benzylxoymethyl-2-iodo-phenyl)-4-(tert-butyldimethylsilanyloxy)-2-[2-(4-methoxyphenoxy methy]-benzylidene]-butyramide (259). To a solution of the amide 258 (568 mg, 0.87 mmol) and imidazole (178 mg, 2.62 mmol) in DMF (8.7 mL) was added TBDMSCl (316 mg, 2.09 mmol). The reaction mixture was stirred at rt overnight and then diluted with EtOAc (180 mL). The solution was washed with water (3×40 mL) and brine (40 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the TBDMS ether 259 (641 mg, 96%) as a colorless oil. IR (film) 2950, 2848, 1678, 1509, 1226, 1090 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.44 (s, 1H), 8.2 (dd, $J$ = 1.4, 8.0 Hz, 1H), 7.74 (s, 1H), 7.56 (m, 1H), 7.44-7.29 (m, 9H), 6.94-6.91 (m, 2H), 6.85-6.82 (m, 2H), 5.03 (s, 2H),
4.65 (s, 2H), 4.59 (s, 2H), 3.9 (t, J = 6.1 Hz, 2H), 3.76 (s, 3H), 2.84 (t, J = 6.1 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.7, 154.5, 153.3, 141.8, 139.0, 138.5, 138.3, 135.7, 135.2, 134.1, 129.9, 129.3, 129.2, 128.9, 128.8, 128.5, 128.23, 128.21, 125.6, 122.4, 116.4, 115.1, 95.9, 77.2, 73.1, 69.4, 62.5, 56.1, 31.8, 26.4, 18.8, -4.9; HRMS-ES [M+H]$^+$ calcd for C$_{39}$H$_{47}$INO$_5$Si, 764.2268; found, 764.2271.

_N-(3-Benzylkoxyethyl-2-iodophenyl)-4-(tert-butyldimethylsilanyloxy)-2-[2-(4-methoxyphenoxy)methyl]-benzylidene]-N-methyl-butyramide (260)._ To a stirred suspension of NaH (40 mg, 60% dispersion in mineral oil, 1.01 mmol) in THF (8 mL) was added a solution of the amide 259 (641 mg, 0.84 mmol) in THF (3 mL) at 0 °C. The mixture was stirred at rt for 30 min and recooled to 0 °C. To the solution was added MeI (0.08 mL, 1.29 mmol) and the reaction mixture was warmed to rt and stirred for 12 h. The reaction mixture was diluted with saturated aqueous NH$_4$Cl (20 mL) and extracted with EtOAc (100 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated _in vacuo_. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the N-methyl amide 260 (630 mg, 96%) as a colorless oil. IR (film) 2950, 2860, 1650, 1509, 1226, 1090 cm$^{-1}$; $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) $\delta$ 7.38 (m, 1H), 7.28-7.01 (m, 12H), 6.78 (ddd, J = 3.8, 3.8, 12.8 Hz, 2H), 6.72 (ddd, J = 3.8, 3.8, 12.8 Hz, 2H), 4.59 (d, J = 5.5 Hz, 2H), 4.42 (d, J = 7.1 Hz, 2H), 4.38 (s, 2H), 3.94 (m, 2H), 3.45 (s, 3H), 3.22 (s, 3H), 2.75 (m, 1H), 2.57 (m, 1H), 0.95 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (75 MHz, toluene-$d_8$, 90 °C) $\delta$ 170.7, 155.1, 153.6, 148.3, 144.3, 137.5, 129.2, 136.3, 135.1,
131.9, 129.2, 129.1, 128.7, 128.5, 128.1, 127.84, 127.78, 127.7, 127.53, 127.48, 116.9, 115.3, 103.3, 77.1, 73.1, 69.1, 62.5, 55.4, 37.6, 34.0, 26.2, 18.5, -5.2; HRMS-ES [M+H]$^+$ calcd for C$_{40}$H$_{49}$INO$_5$Si, 778.2425; found, 778.2397.

{4-Benzzyloxymethyl-3-[2-(tert-butyldimethylsilanyl oxy)-ethyl]-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl}-[2-(4-methoxyphenoxy methyl)-phenyl]-acetic Acid Methyl Ester (261). To a solution of N-methyl amide 260 (222 mg, 0.286 mmol) in DMA (3.0 mL) and MeOH (1.5 mL) were added Pd(OAc)$_2$ (6.4 mg, 0.029 mmol), biphenyldicyclohexylphosphine (30.1 mg, 0.086 mmol) and NaOAc (46.9 mg, 0.572 mmol). The mixture was stirred at 85 °C under a CO atmosphere (1 atm) for 24 h. The catalyst was removed by filtration and washed with EtOAc (100mL). The filtrate was washed with water (3×20 mL) and brine (20 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the methyl ester 261 (145 mg, 71%) as a colorless oil. IR (film) 2950, 2859, 1740, 1712, 1509, 1226 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35-7.17 (m, 9H), 7.12 (dd, $J = 7.5, 14.8$ Hz, 1H), 7.07 (d, $J = 7.9$ Hz, 1H), 6.87 (d, $J = 9.1$ Hz, 2H), 6.82 (d, $J = 9.2$ Hz, 2H), 6.65 (d, $J = 7.7$ Hz, 1H), 4.93, 4.69 (ABq, $J = 11.6$ Hz, 2H), 4.63 (s, 1H), 4.41, 4.29 (ABq, $J = 11.9$ Hz, 2H), 3.89, 3.77 (ABq, $J = 11.1$ Hz, 2H), 3.78 (s, 3H), 3.59 (s, 3H), 3.19 (m, 2H), 3.10 (s, 3H), 2.56 (ddd, $J = 7.2, 7.2, 14.4$ Hz, 1H), 2.13 (ddd, $J = 4.9, 4.9, 13.4$ Hz, 1H), $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.2, 171.6, 154.5, 153.1, 145.4, 138.2, 136.5, 136.0, 133.4, 130.6, 129.7, 129.0, 128.8, 128.4, 128.3, 128.2, 128.1, 126.1, 126.1, 123.5, 123.4, 133.4, 130.6, 129.7, 129.0, 128.8, 128.4, 128.3, 128.2, 128.1, 126.1, 126.1, 123.5,
Synthesis of Spiro Lactone 262. To a stirred solution of methyl ester 261 (172 mg, 0.24 mmol) in THF (10 mL) was added TBAF (0.27 mL, 1.0 M in THF, 0.27 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 4 h. The mixture was diluted with EtOAc (30 mL) and saturated aqueous NH₄Cl (5 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the lactone 262 (116 mg, 85%) as a separable mixture of diastereomers (2:1). For analytical purposes the diastereomers were separated via preparative TLC (1:1 EtOAc:hexanes). More polar major diastereomer of 262 (colorless oil): IR (film) 2927, 1752, 1712, 1605, 1509, 1226 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.01 (m, 11H), 6.83-6.74 (m, 4H), 6.54 (d, J = 7.7 Hz, 1H), 5.03 (s, 1H), 4.83 (ddd, J = 4.9, 6.7, 11.7 Hz, 1H), 4.67-4.43 (m, 6H), 4.30 (ddd, J = 4.6, 7.2, 11.8 Hz, 1H), 3.77 (s, 3H), 2.96 (s, 3H), 2.61 (ddd, J = 4.8, 6.8, 14.7 Hz, 1H), 2.27 (ddd, J = 5.1, 7.4, 14.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 178.2, 171.1, 154.5, 153.0, 144.1, 137.3, 136.5, 134.4, 132.3, 130.8, 129.7, 129.2, 129.1, 128.79, 128.75, 128.7, 128.2, 127.8, 125.1, 116.3, 115.1, 108.6, 73.8, 70.0, 69.7, 64.8, 56.2, 52.6, 47.2, 30.3, 26.5; HRMS-ES [M+H]⁺ calcd for C₄₂H₄₂NO₇Si, 710.3513; found, 710.3521. Less polar minor diastereomer of 262 (colorless oil): IR (film) 2916, 1746, 1706, 1610, 1509, 1232 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.30 (m, 5H), 7.27-7.23 (m, 3H), 7.09 (t, J = 7.6 Hz,
O-Allylation of Spiro Lactone 262. To a stirred suspension of spiro lactone 262 (20.6 mg, 0.037 mmol) and NaH (2.0 mg, 60% dispersion in mineral oil, 0.050 mmol) in DMF (2 mL) was added allyl iodide (0.010 mL, 0.109 mmol) at 0 °C. The mixture was stirred for 1 h at rt. The reaction mixture was diluted with saturated aqueous NH₄Cl (5 mL) and extracted with EtOAc (60 mL). The organic layer was washed with water (3×10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the O-allyl ketene acetal 263 (12.7 mg, 57%, 71% based on recovered starting material) as a colorless oil and unreacted spiro lactone 262 (3.9 mg). IR (film) 3470, 2927, 1706, 1509, 1226 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 2:1 atropisomeric mixture) δ 7.44-7.22 (m, 7H, major and minor), 7.13 (t, J = 7.7 Hz, 1H, minor), 7.08-7.01 (m, 1H, major and minor), 6.98-6.96 (m, 2H, major and minor), 6.91 (d, J = 6.7 Hz, 1H, minor), 6.86-6.82 (m, 3H, major and minor), 6.77 (t, J = 7.6 Hz, 1H, major), 6.58 (d, J = 8.1 Hz, 1H, major and
Claisen Rearrangement of Ketene Acetal 263. A solution of ketene acetal 263 (3.9 mg, 6.5 μmol) in the solvent (0.5 mL) indicated in the table was heated at 130 °C and stirred for 15 h. The solvent was removed under reduced pressure. The residue was purified by preparative TLC (1:1 EtOAc:hexanes) to give the two diastereomers of allyl lactone 264. More polar major diastereomer 264a (oil): IR (film) 2929, 1704, 1508, 1228 cm⁻¹; ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.56 (d, J = 7.9 Hz, 1H), 7.26-6.98 (m, 9H), 6.90 (t, J = 7.2 Hz, 1H), 6.80-6.67 (m, 4H), 6.38 (d, J = 6.8 Hz, 1H), 6.10 (m, 1H), 5.21 (br s, 1H), 5.13 (ddd, J = 4.4, 12.1, 12.1 Hz, 1H), 4.77 (s, 1H), 4.72 (d, J = 8.8 Hz, 1H), 4.52 (br s, 1H), 4.20, 4.13 (ABq, J = 12.1 Hz, 2H), 4.06 (dd, J = 7.0, 11.0 Hz, 1H), 3.47 (s,
3H), 3.16 (m, 1H), 3.15 (s, 2H), 2.85 (m, 1H), 2.81 (s, 3H), 2.53 (dd, J = 6.8, 15.4 Hz, 1H), 1.35 (dd, J = 4.6, 14.7 Hz, 1H); 13C NMR (75 MHz, toluene-d8, 90 °C) δ 176.5, 172.4, 155.3, 154.0, 145.1, 139.6, 139.1, 138.6, 137.8, 137.3, 134.1, 132.3, 129.4, 128.7, 128.2, 127.9, 127.5, 126.7, 127.5, 126.7, 125.8, 116.1, 115.7, 107.5, 73.0, 69.6, 69.0, 64.6, 59.1, 57.0, 55.7, 41.2, 27.2, 25.7; HRMS-ES [M+H]+ calcd for C38H38NO6, 604.2699; found, 604.2714. Less polar minor diastereomer 264b (oil): IR (film) 2918, 1704, 1508, 1228 cm⁻¹; 1H NMR (300 MHz, toluene-d8, 90 °C) δ 7.83 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 2H), 7.22–6.96 (m, 8H), 6.77 (d, J = 8.8 Hz, 2H), 6.60 (t, J = 7.8 Hz, 1H), 6.36 (bs, 1H), 5.99 (d, J = 7.7 Hz, 1H), 5.77 (m, 1H), 5.52 (ddd, J = 4.1, 12.3, 12.3 Hz, 1H), 5.33 (d, J = 11.8 Hz, 1H), 4.98–4.85 (m, 3H), 4.60, 4.57 (ABq, J = 10.3 Hz, 2H), 4.50, 4.44 (ABq, J = 11.9 Hz, 2H), 4.0 (dd, J = 6.9, 11.1 Hz, 1H), 3.47 (s, 3H), 3.39 (dd, J = 5.6, 14.7 Hz, 1H), 2.95 (dd, J = 6.7, 14.3 Hz, 1H), 2.74 (ddd, J = 6.9, 14.4, 14.4 Hz, 1H), 2.32 (s, 3H), 1.42 (dd, J = 3.7, 14.7 Hz, 1H); 13C NMR (75 MHz, toluene-d8, 90 °C) δ 177.2, 169.9, 155.1, 154.8, 145.9, 139.7, 138.1, 137.4, 137.2, 134.5, 133.9, 129.5, 129.4, 129.3, 128.9, 128.4, 127.5, 127.3, 125.9, 125.6, 117.7, 117.1, 115.6, 107.8, 73.6, 71.2, 70.4, 64.7, 57.9, 57.8, 55.7, 42.0, 26.9, 25.4; HRMS-ES [M+H]+ calcd for C38H38NO6, 604.2699; found, 604.2722.

{3-[2-(tert-Butyldimethylsilanyloxy)-ethyl]-4-hydroxymethyl-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl}-[2-(4-methoxyphenoxymethyl)-phenyl]-acetic Acid Methyl Ester (265). To a solution of methyl ester 261 (145 mg, 0.204 mmol) in
THF (4 mL) and EtOAc (1 mL) was added 10% Pd/C (30 mg). The mixture was stirred at rt under a H₂ atmosphere (1 atm) overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the hydroxy ester 265 (96 mg, 76%). ¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, J = 7.6 Hz, 1H), 7.24-7.19 (m, 3H), 7.13 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.88-6.84 (m, 4H), 6.65 (d, J = 7.7 Hz, 1H), 4.85, 4.76 (ABq, J = 10.9 Hz, 2H), 4.72 (s, 1H), 4.14 (m, 1H), 4.03 (m, 1H), 3.79 (s, 3H), 3.64 (s, 3H), 3.57 (ddd, J = 5.1, 5.1, 10.3 Hz, 1H), 3.31 (ddd, J = 3.3, 8.2, 14.5 Hz, 1H), 3.15 (s, 3H), 3.06 (dd, J = 3.3, 7.9 Hz, 1H), 2.63 (ddd, J = 4.6, 4.6, 14.4 Hz, 1H), 2.52 (ddd, J = 4.1, 8.5, 13.0 Hz, 1H), 0.66 (s, 9H), -0.26 (s, 3H), -0.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 177.3, 171.0, 154.1, 152.4, 144.3, 137.7, 135.6, 133.2, 129.6, 128.8, 127.9, 127.6, 126.7, 124.4, 115.8, 114.6, 107.3, 68.9, 61.7, 60.6, 55.7, 55.0, 52.1, 38.4, 26.3, 25.7, 18.2, -6.0, -6.3.

9a-[2-(tert-Butyldimethylsilanyloxy)-ethyl]-9-[2-(4-methoxyphenoxymethyl)-phenyl]-2-methyl-9,9a-dihydro-2H,6H-7-oxa-2-azabenzo[cd]azulene-1,8-dione (266). To a stirred solution of hydroxy ester 265 (26.9 mg, 0.043 mmol) in THF (1 mL) and water (1 mL) was added LiOH·H₂O (9.1 mg, 0.217 mmol) and the mixture was stirred overnight at rt. The THF was removed under reduced pressure. The aqueous layer was acidified with 1 N aqueous HCl and extracted with EtOAc (2×20 mL). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo. To a solution
of the crude residue in CH$_2$Cl$_2$ (5 mL) were added EDC·MeI (15.5 mg, 0.052 mmol) and DMAP (0.5 mg, 0.004 mmol). The mixture was stirred at rt for 1 h and then diluted with saturated aqueous NH$_4$Cl (10 mL) and CH$_2$Cl$_2$ (15 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the lactone 266 (15.2 mg, 60% over 2 steps) as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40 (t, $J$ = 7.8 Hz, 1H), 7.35 (d, $J$ = 7.1 Hz, 1H), 7.09 (t, $J$ = 7.6 Hz, 1H), 7.05 (d, $J$ = 7.7 Hz, 1H), 7.01 (ddd, $J$ = 3.0, 3.0, 10.6 Hz, 2H), 6.85 (ddd, $J$ = 3.0, 3.0, 10.6 Hz, 2H), 6.77 (t, $J$ = 7.1 Hz, 1H), 6.72 (d, $J$ = 7.8 Hz, 1H), 5.96 (d, $J$ = 7.3 Hz, 1H), 5.70, 5.32 (ABq, $J$ = 13.9 Hz, 2H), 5.46, 5.16 (ABq, $J$ = 12.3 Hz, 2H), 4.79 (s, 1H), 3.78 (s, 3H), 3.39 (m, 2H), 2.78 (s, 3H), 2.64 (m, 2H), 0.71 (s, 9H), -0.20 (s, 3H), -0.23 (s, 3H), $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 176.6, 172.9, 153.9, 152.8, 144.6, 136.4, 133.5, 132.8, 129.4, 128.8, 128.2, 127.9, 127.1, 126.7, 120.8, 116.1, 114.6, 108.3, 71.2, 69.0, 59.5, 55.7, 55.0, 52.6, 38.8, 26.1, 25.7, 18.1, -5.9.

8-Allyloxy-9a-[2-(tert-butyldimethylsilyloxy)-ethyl]-9-[2-(4-methoxyphenoxyethyl)-phenyl]-2-methyl-6,9a-dihydro-2H-7-oxa-2-azabeno[cd]azulen-1-one (267). To a stirred suspension of lactone 266 (15.2 mg, 0.026 mmol) and NaH (1.2 mg, 60% dispersion in mineral oil, 0.030 mmol) in DMF (1 mL) was added allyl iodide (0.004 mL, 0.039 mmol) at 0 °C. The mixture was stirred for 1.5 h at rt. The reaction mixture was diluted with saturated aqueous NH$_4$Cl (5 mL) and extracted with EtOAc (25 mL). The organic layer was washed with water (3×5 mL) and brine (5 mL), dried over
Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by preparative TLC (1:2 EtOAc:hexanes) to give the O-allyl ketene acetal 267 (6.1 mg, 37%).

9-Allyl-9a-[2-(tert-butyldimethylsilyloxy)-ethyl]-9-[2-(4-methoxyphenoxymethyl)-phenyl]-2-methyl-9,9a-dihydro-2H,6H-7-oxa-2-azabenzo[cd]azulene-1,8-dione (268). A solution of ketene acetal 267 (6.1 mg, 9.7 μmol) in DMF (1.0 mL) indicated in the table was heated at 110 °C and stirred for 5 h. The solvent was removed under reduced pressure. The residue was purified by preparative TLC (1:5 EtOAc:hexanes) to give the two diastereomers of allyl lactone 268 (major diastereomer, 2.4 mg, 39%, minor diastereomer, 1.2 mg, 20%). Major less polar diastereomer of 268: $^1$H NMR (400 MHz, CDCl$_3$) δ 9.09 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.31 (m, 2H), 6.83 (m, 5H), 6.72 (d, J = 7.7 Hz, 1H), 5.70 (d, J = 14.1 Hz, 1H), 5.65 (m, 1H), 5.23 (t, J = 13.2 Hz, 1H), 5.05 (d, J = 13.1 Hz, 1H), 4.77-4.73 (m, 2H), 3.77 (s, 3H), 3.21 (s, 3H), 3.09-2.98 (m, 2H), 2.78 (dd, J = 6.6, 13.6 Hz, 1H), 2.52 (m, 1H), 2.46 (dd, J = 7.1, 13.6 Hz, 1H), 2.35 (m, 1H), 0.68 (s, 9H), -0.22 (s, 3H), -0.24 (s, 3H); LRMS-APCI [M+H]$^+$ calcd for C$_{37}$H$_{46}$NO$_6$Si, 628.31; found 628.31. Minor more polar diastereomer of 268: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, J = 7.7 Hz, 1H), 7.14 (ddd, J = 4.7, 9.0, 9.0 Hz, 2H), 6.95-6.83 (m, 5H), 6.72 (d, J = 7.7 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 6.47 (d, J = 8.2 Hz, 1H), 5.82 (m, 1H), 5.11 (s, 1H), 4.94-4.69 (m, 4H), 3.80 (s, 3H), 3.41-3.29 (m, 3H), 3.25 (s, 3H), 3.16 (m, 1H), 2.60 (ddd, J = 8.2, 8.2, 16.4 Hz, 1H), 2.28 (m, 1H), 0.74
4-Benzylxoymethy1-3-(2-hydroxyethyl)-1-methyl-3-(3-oxo-isochroman-4-yl)-1,3-dihydroindol-2-one (269). To a stirred solution of spiro lactone 262 (71.1 mg, 0.126 mmol) in CH₃CN (2 mL) was added a solution of ceric ammonium nitrate (CAN) (82.9 mg, 0.151 mmol) in water (1 mL) dropwise at 0 °C over 5 min and then the mixture was stirred at that temperature. After 1.5 h additional solution of CAN (82.9 mg, 0.151 mmol) in water (1 mL) was added. After 1.5 h the mixture was diluted with EtOAc (20 mL) and saturated aqueous Na₂SO₃ (5 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude residue was dissolved in CH₃CN (3 mL) and K₂CO₃ (4.3 mg, 0.031 mmol) was added to the solution. The mixture was heated at 70 °C and stirred for 24 h. The K₂CO₃ was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (3:1 EtOAc:hexanes) to give hydroxy lactone 269 (major diastereomer, 30.3 mg, 53%, minor diastereomer, 5.2 mg, 0%). Major more polar diastereomer of 269: ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.29 (m, 6H), 7.22-7.13 (m, 2H), 7.03 (d, J = 7.5 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 6.57 (d, J = 7.1 Hz, 1H), 6.33 (d, J = 7.7 Hz, 1H), 5.70 (d, J = 14.7 Hz, 1H), 5.03 (d, J = 14.6 Hz, 1H), 4.70, 4.66 (ABq, J = 11.8 Hz, 2H), 4.59, 4.47 (ABq, J = 10.9 Hz, 2H), 4.41 (s, 1H), 3.42 (m, 1H), 3.25 (m, 1H), 2.74 (s, 3H), 2.74-2.62 (m, 2H). Minor less polar diastereomer of 269: ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.30 (m, 5H), 7.25-7.14 (m, 5H), 6.83 (d, J =
5.5 Hz, 1H), 6.50 (d, J = 5.8 Hz, 1H), 4.82-4.53 (m, 6H), 4.11 (s, 1H), 3.43 (m, 1H), 3.23 (m, 1H), 2.84 (s, 3H), 2.63-2.57 (m, 2H).

4-Benzylxoxymethyl-3-[2-(tert-butyldimethylsilyloxy)ethyl]-1-methyl-3-(3-oxoisochroman-4-yl)-1,3-dihydroindol-2-one (270). To a solution of the hydroxy lactone 269 (35.5 mg, 0.078 mmol) and imidazole (13.2 mg, 0.194 mmol) in DMF (2.2 mL) was added TBDMSCl (17.5 mg, 0.116 mmol) in a single portion. The reaction mixture was stirred at rt overnight and then diluted with EtOAc (60 mL). The solution was washed with water (3×10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the TBDMS ether 270 (major diastereomer, 33.3 mg, 75%, minor diastereomer, 4.2 mg, 9%). Major more polar diastereomer of 270: ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.29 (m, 6H), 7.19 (d, J = 7.9 Hz, 1H), 7.12 (ddd, J = 1.0, 7.5, 7.5 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.81 (t, J = 7.4 Hz, 1H), 6.50 (dd, J = 0.9, 7.7 Hz, 1H), 6.24 (d, J = 7.7 Hz, 1H), 5.82 (d, J = 14.5 Hz, 1H), 5.03 (d, J = 14.6 Hz, 1H), 4.73, 4.67 (ABq, J = 11.2 Hz, 2H), 4.69, 4.50 (ABq, J = 11.0 Hz, 2H), 3.42 (m, 1H), 3.23 (m, 1H), 2.71 (s, 3H), 2.68-2.64 (m, 2H), 0.67 (s, 9H), -0.25 (s, 3H), -0.29 (s, 3H). Minor less polar diastereomer of 270: ¹H NMR (300 MHz, CDCl₃) δ 7.45-7.30 (m, 5H), 7.24-7.17 (m, 5H), 6.82 (d, J = 6.6 Hz, 1H), 6.43 (t, J = 4.4 Hz, 1H), 4.80-4.52 (m, 6H), 4.04 (s, 1H), 3.40 (ddd, J = 4.1, 5.9, 10.0 Hz, 1H), 3.30 (m, 1H), 2.77 (s, 3H), 2.68-2.62 (m, 2H), 0.67 (s, 9H), -0.27 (s, 3H), -0.32 (s, 3H).
3-(2-Bromobenzylidene)-dihydrofuran-2-one (274). A mixture of 2-bromobenzaldehyde (273) (2.0 mL, 17.3 mmol) and 3-(triphenylphosphanylidene) dihydrofuran-2-one (204, 6.59 g, 19.0 mmol) in toluene (50 mL) was heated at 70 °C for 5 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the lactone 274 (3.81 g, 87%) as a white solid. \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.88 (t, \(J = 2.9\) Hz, 1H), 7.68 (dd, \(J = 1.1, 8.0\) Hz, 1H), 7.47 (dd, \(J = 1.5, 7.8\) Hz, 1H), 7.38 (ddd, \(J = 0.8, 7.4, 7.4\) Hz, 1H), 7.25 (ddd, \(J = 1.6, 7.6, 7.6\) Hz, 1H), 4.46 (t, \(J = 7.2\) Hz, 1H), 3.18 (ddd, \(J = 3.0, 7.2, 7.2\) Hz, 1H).

N-(3-Benzylxymethyl-2-iodophenyl)-2-(2-bromobenzylidene)-4-hydroxybutyramide (275). To a stirred solution of the aniline 257 (398 mg, 1.17 mmol) and lactone 274 (248 mg, 0.98 mmol) in CH\(_2\)Cl\(_2\) (20 mL) was added AlMe\(_3\) (0.68 mL, 2.0 M in hexane, 1.36 mmol) at 0 °C. The mixture was warmed to rt, stirred overnight and then poured into an iced aqueous NH\(_4\)Cl (20 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (100 mL). The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the amide 275 (451 mg, 78%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.56 (s, 1H), 8.16 (dd, \(J = 1.6, 7.8\) Hz, 1H), 7.64 (dd, \(J = 0.8, 8.0\) Hz, 1H), 7.51 (s, 1H), 7.44-7.27 (m, 9H), 7.21 (ddd, \(J = 1.5, 7.6, 7.6\) Hz, 1H), 4.66 (s, 2H), 4.59 (s, 2H), 3.82 (t, \(J = 5.9\) Hz, 2H), 3.37 (bs, 1H), 2.75 (t, \(J = 5.9\) Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 168.2, 141.4, 138.1, 137.7, 135.4, 135.0,
To a solution of the amide 275 (774 mg, 1.31 mmol) and imidazole (134 mg, 1.96 mmol) in DMF (10 mL) was added TBDMS-Cl (217 mg, 1.44 mmol) in a single portion. The reaction mixture was stirred at rt overnight and then diluted with EtOAc (300 mL). The solution was washed with water (3×50 mL) and brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the TBDMS ether 276 (898 mg, 97%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 8.50 (s, 1H), 8.23 (dd, J = 1.6, 8.0 Hz, 1H), 7.68-7.64 (m, 2H), 7.55 (s, 1H), 7.43-7.22 (m, 9H), 4.67 (s, 2H), 4.60 (s, 2H), 3.86 (t, J = 6.1 Hz, 2H), 2.84 (t, J = 6.1 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 168.7, 141.8, 139.0, 138.32, 138.29, 136.3, 135.4, 133.1, 131.2, 130.0, 129.3, 128.9, 128.3, 128.2, 127.6, 125.6, 124.7, 122.1, 95.6, 77.2, 73.1, 62.3, 31.7, 26.4, 18.8, -4.9.

To a stirred suspension of NaH (55.9 mg, 60% dispersion in mineral oil, 1.40 mmol) in THF (40 mL) was added a solution of
amide 276 (898 mg, 1.27 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at rt for 1 h and recooled to 0 °C. To the solution was added MeI (0.10 mL, 1.61 mmol) and the reaction mixture was warmed to rt and stirred for 6 h. The reaction mixture was diluted with saturated aqueous NH₄Cl (50 mL) and extracted with EtOAc (200 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the N-methyl amide 277 (881 mg, 96%) as a colorless oil. ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.31-6.95 (m, 10H), 6.86 (ddd, J = 0.7, 7.5, 7.5 Hz, 1H), 6.79 (s, 1H), 6.67 (ddd, J = 1.4, 7.7, 7.7 Hz, 1H), 4.45 (s, 2H), 4.39 (s, 2H), 3.86 (m, 2H), 3.21 (s, 3H), 2.63 (m, 1H), 2.50 (m, 1H), 0.88 (s, 9H), 0.00 (s, 6H); ¹³C NMR (75 MHz, toluene-d₈, 90 °C) δ 170.6, 148.2, 144.3, 138.8, 137.5, 137.3, 133.1, 132.9, 130.8, 129.4, 129.1, 128.9, 128.6, 128.0, 127.9, 127.6, 127.1, 124.2, 103.6, 77.3, 73.3, 62.5, 38.1, 34.0, 26.3, 18.6, -5.0.

{4-Benzylxoxymethyl-3-[2-(tert-butyldimethylsilyl oxy)-ethyl]-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl}-(2-bromophenyl)-acetic Acid Methyl Ester (278). To a solution of N-methyl amide 277 (37.6 mg, 0.052 mmol) in DMA (1.0 mL) and MeOH (0.5 mL) were added Pd(OAc)₂ (2.3 mg, 0.010 mmol), biphenyldicyclohexylphosphine (11.0 mg, 0.031 mmol) and NaOAc (8.6 mg, 0.104 mmol). The mixture was stirred at 85 °C under a CO atmosphere (1 atm) for 22 h. The catalyst was removed by filtration and washed with EtOAc (50mL). The filtrate was washed with water (3×10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column
chromatography (1:5 EtOAc:hexanes) to give the methyl ester 278 (16.6 mg, 49%) and diester 279 (3.4 mg, 10%). Heck/carbonylation adduct 278: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42 (dd, $J = 1.6, 7.4$ Hz, 1H), 7.36-7.28 (m, 5H), 7.22 (t, $J = 7.8$ Hz, 1H), 7.08-6.99 (m, 4H), 6.65 (d, $J = 7.5$ Hz, 1H), 4.86 (s, 1H), 4.49, 4.42 (ABq, $J = 11.8$ Hz, 2H), 4.06, 4.02 (ABq, $J = 12.3$ Hz, 2H), 3.66 (s, 3H), 3.24 (m, 1H), 3.18 (m, 1H), 3.16 (s, 3H), 2.74 (ddd, $J = 6.2, 7.9, 14.2$ Hz, 1H), 2.25 (ddd, $J = 4.8, 13.9, 13.9$ Hz, 1H), 0.73 (s, 9H), -0.20 (s, 3H), -0.21 (s, 3H); LRMS-ES [M+Na]$^+$ calcd for C$_{34}$H$_{42}$BrNNaO$_5$Si, 674.2; found, 674.2.

2-({4-Benzylmethoxymethyl-3-[2-({tert-butylidimethylsilyl oxy})-ethyl]-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-methoxycarbonylmethyl}-benzoic Acid Methyl Ester (279). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, $J = 7.8$ Hz, 1H), 7.43-6.96 (m, 10H), 6.52 (d, $J = 7.6$ Hz, 1H), 5.60 (s, 1H), 4.51, 4.48 (ABq, $J = 8.4$ Hz, 2H), 4.14, 4.11 (ABq, $J = 7.6$ Hz, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.23 (m, 1H), 3.18 (m, 1H), 3.05 (s, 3H), 2.73 (m, 1H), 2.22 (m, 1H), 0.71 (s, 9H), -0.23 (s, 3H), -0.24 (s, 3H); LRMS-ES [M+Na]$^+$ calcd for C$_{35}$H$_{45}$BrN$_2$NaO$_7$Si, 654.3; found 654.3.

**Synthesis of Spiro Lactone 280.** To a stirred solution of methyl ester 278 (35.3 mg, 0.054 mmol) in THF (2.5 mL) was added TBAF (0.065 mL, 1.0 M in THF, 0.065 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 11 h. The mixture was diluted with EtOAc (20 mL) and saturated aqueous NH$_4$Cl (5 mL). The organic layer was dried over Na$_2$SO$_4$ and
concentrated in vacuo. The residue was purified by flash column chromatography (2:1 EtOAc:hexanes) to give the lactone 280 (16.0 mg, 58%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.45-7.36 (m, 5H), 7.30 (dd, $J = 1.6$, 8.0 Hz, 1H), 7.24-7.10 (m, 3H), 7.07 (d, $J = 7.8$ Hz, 1H), 6.97 (ddd, $J = 1.6$, 1.6 7.4 Hz, 1H), 6.52 (dd, $J = 0.8$, 7.7 Hz, 1H), 5.00 (s, 1H), 4.92 (d, $J = 11.0$ Hz, 1H), 4.75-4.58 (m, 4H), 4.37 (ddd, $J = 4.0$, 7.9, 13.2 Hz, 1H), 3.02 (s, 3H), 2.69 (ddd, $J = 5.2$, 5.2, 14.8 Hz, 1H), 2.36 (ddd, $J = 5.6$, 8.7, 14.3 Hz, 1H).

2-Hydroxy-1-(2-nitrophenyl)ethanone (291). To a stirred solution of 2'-nitroacetophenone (290) (2.50 mL, 18.7 mmol) and NEt$_3$ (5.21 mL, 37.3 mmol) in benzene (20 mL) was added TMSOTf (5.08 mL, 28.1 mmol) dropwise at 0 °C. The mixture was warmed to rt and stirred for 4 h. Additional NEt$_3$ (1.04 mL, 7.46 mmol) and TMSOTf (1.00 mL, 5.52 mmol) were added and the reaction mixture was stirred at rt overnight, and then diluted with EtOAc (100 mL) and saturated aqueous NaHCO$_3$ (30 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was dissolved in CH$_2$Cl$_2$ (20 mL). To the solution was added m-chloroperbenzoic acid (77%, 6.92 g, 30.9 mmol) portionwise at 0 °C. The mixture was stirred at rt for 4 h and then diluted with saturated aqueous Na$_2$S$_2$O$_3$ (10 mL). The organic layer was washed with saturated aqueous NaHCO$_3$ (10 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was dissolved in ether (50 mL) and 2 N aqueous HCl (10 mL). After 30 min the organic layer was washed with saturated aqueous NaHCO$_3$ (10 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give α-hydroxyketone
191 (1.47 g, 43%) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.16 (d, $J = 8.1$ Hz, 1H), 7.77 (t, $J = 7.5$ Hz, 1H), 7.68 (t, $J = 7.8$ Hz, 1H), 7.44 (dd, $J = 1.5$, 7.5 Hz, 1H), 4.61 (s, 2H), 3.20 (br s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.2, 146.4, 134.6, 134.4, 131.6, 128.0, 124.7, 68.4.

2-Benzyloxy-1-(2-nitrophenyl)ethanone (292). To a stirred solution of $\alpha$-hydroxyketone 291 (27.8 mg, 0.153 mmol) in CH$_2$Cl$_2$ (2 mL) and cyclohexane (4 mL) was added benzyl 2,2,2-trichloroacetimidate (0.057 mL, 0.307 mmol), followed by one drop of TfOH. The mixture was stirred overnight at rt and then diluted with saturated aqueous NaHCO$_3$ (5 mL) and EtOAc (30 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to give benzyl ether 292 (29.6 mg, 71%) as a colorless solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.12 (dd, $J = 1.0$, 8.1 Hz, 1H), 7.74 (ddd, $J = 1.1$, 7.5, 7.5 Hz, 1H), 7.63 (ddd, $J = 1.5$, 8.0, 8.0 Hz, 1H), 7.42 (dd, $J = 1.4$, 7.5 Hz, 1H), 7.38-7.25 (m, 3H), 7.21-7.18 (m, 2H), 4.51 (s, 2H), 4.38 (s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 201.3, 147.4, 136.9, 135.1, 134.5, 131.3, 128.6, 128.2, 128.0, 123.9, 74.4, 73.7.

3-[1-(2-Nitrophenyl)ethyldene]dihydropyran-2-one (295). To a stirred suspension of NaH (1.04 g, 60% dispersion in mineral oil, 26.1 mmol) in THF (60 mL) was added diethyl (2-oxotetrahydrofuran-3-yl)phosphonate (293) (5.0 mL, 26.9 mmol) dropwise at 0 °C. The mixture was stirred at rt for 30 min
and then refluxed. To the refluxing mixture was added 2'-nitroacetophenone (290, 0.60 mL, 4.5 mmol) dropwise. After 5 h the reaction mixture was cooled to rt and then diluted with saturated aqueous NH₄Cl (50 mL) and EtOAc (300 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give a separable diastereomeric mixture (E/Z = 1/3) of lactone 295 (0.42 g, 40%, 89% based on recovered starting material) as a yellow solid and unreacted ketone 290 (0.41 g). More polar major (Z)-isomer of 295: ¹H NMR (300 MHz, CDCl₃) δ 8.14 (dd, J = 1.2, 8.3 Hz, 1H), 7.63 (dd, J = 1.3, 7.5, 7.5 Hz, 1H), 7.48 (dd, J = 1.4, 7.5, 8.2 Hz, 1H), 7.19 (dd, J = 1.4, 7.6 Hz, 1H), 4.36, (m, 2H), 3.09 (m, 2H), 2.22 (t, J = 1.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.2, 147.0, 146.9, 137.2, 134.1, 129.7, 129.0, 125.0, 121.4, 64.9, 27.7, 24.4. Less polar minor (E)-isomer of 295: ¹H NMR (300 MHz, CDCl₃) δ 8.13 (dd, J = 1.1, 8.3 Hz, 1H), 7.71 (dd, J = 1.2, 7.5, 7.5 Hz, 1H), 7.54 (dd, J = 1.4, 7.5, 8.2 Hz, 1H), 7.26 (dd, J = 1.4, 7.6 Hz, 1H), 4.24, (t, J = 7.4 Hz, 2H), 2.53 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 170.3, 149.2, 146.5, 138.4, 134.8, 129.5, 129.3, 125.5, 121.6, 65.0, 28.8, 20.1.

4-Hydroxy-N-[2-iodo-3-(4-methoxyphenoxymethyl)phenyl]-2-(2-nitrobenzylidene)-butyramide (297). To a stirred solution of aniline 240 (36.7 mg, 0.103 mmol) and lactone 295 (18.8 mg, 0.081 mmol) in CH₂Cl₂ (3 mL) was added AlMe₃ (0.052 mL, 2.0 M in hexane, 0.104 mmol) at 0 °C. The mixture was warmed to rt, stirred overnight and then poured into ice-cold aqueous NH₄Cl (100 mL). The aqueous layer was extracted
with CH$_2$Cl$_2$ (50 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the amide 297 (44.4 mg, 94%) as a pale yellow foam. (Z)-Isomer of 297: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.00 (m, 2H), 7.61-7.54 (m, 2H), 7.44-7.37 (m, 2H), 7.22-7.17 (m, 2H), 6.88-6.80 (m, 4H), 4.89 (s, 2H), 3.96 (m, 2H), 3.76 (s, 3H), 3.34 (br s, 1H), 2.91 (ddd, $J = 4.9$, 4.9, 14.4 Hz, 1H), 2.74 (ddd, $J = 5.6$, 8.0, 13.6 Hz, 1H), 2.06 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.9, 154.7, 152.8, 147.8, 140.8, 138.7, 138.5, 138.4, 134.5, 133.9, 131.4, 129.4, 129.1, 125.8, 125.4, 122.8, 116.3, 115.1, 94.5, 75.7, 61.7, 56.1, 33.8, 20.4. (E)-Isomer of 297: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.28 (s, 1H), 8.23 (d, $J = 6.8$ Hz, 1H), 8.14 (dd, $J = 1.0$, 8.2 Hz, 1H), 7.69 (ddd, $J = 1.2$, 7.5, 7.5 Hz, 1H), 7.52 (ddd, $J = 1.3$, 8.2, 8.2 Hz, 1H), 7.43-7.32 (m, 3H), 6.96-6.83 (m, 4H), 5.03 (s, 2H), 3.78 (s, 3H), 3.61 (t, $J = 3.6$ Hz, 2H), 2.69 (br s, 1H), 2.39-2.16 (m, 5H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.5, 154.6, 152.9, 147.7, 141.0, 138.4, 137.5, 137.3, 134.5, 132.7, 130.9, 129.4, 129.1, 125.7, 125.5, 122.2, 116.3, 115.1, 94.4, 75.8, 61.0, 56.1, 34.8, 23.3.

2-[(2-tert-Butyldimethylsilyloxy)ethyl]-3-(2-nitrophenyl)but-2-enoic Acid [2-Iodo-3-(4-methoxyphenoxy methyl)phenyl]amide (298). To a solution of the amide 297 (7.3 mg, 0.012 mmol) and imidazole (2.5 mg, 0.037 mmol) in DMF (0.5 mL) was added TBDMSCl (2.8 mg, 0.019 mmol). The reaction mixture was stirred at rt overnight and then diluted with EtOAc (20 mL). The solution was washed with water (3×10 mL) and brine (10 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by...
flash column chromatography (1:5 EtOAc:hexanes) to give the TBDMS ether
(7.3 mg, 84%). (Z)-Isomer of 298: $^1$H NMR (300 MHz, CDCl$_3$) δ 8.00 (dd, $J = 0.9, 8.0$
Hz, 1H), 7.98 (s, 1H), 7.60 (t, $J = 4.9$ Hz, 1H), 7.55 (ddd, $J = 1.3, 7.5, 7.5$ Hz, 1H), 7.42-
7.34 (m, 2H), 7.23-7.18 (m, 2H), 6.88-6.80 (m, 4H), 4.90 (s, 2H), 3.98 (t, $J = 6.6$ Hz, 2H),
3.77 (s, 3H), 2.89 (dd, $J = 6.8, 13.4$ Hz, 1H), 2.79 (dd, $J = 6.9, 13.6$ Hz, 1H), 2.07 (s, 3H),
0.91 (s, 9H), 0.10 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.0, 154.6, 152.9, 147.9,
140.7, 139.1, 138.9, 137.9, 134.2, 133.7, 131.2, 129.05, 129.02, 125.4, 125.3, 123.0,
116.3, 115.1, 94.7, 75.8, 62.3, 56.1, 34.3, 26.4, 20.6, 18.8, -4.8. (E)-Isomer of 298: $^1$H
NMR (300 MHz, CDCl$_3$) δ 8.25 (d, $J = 7.0$ Hz, 1H), 8.20 (s, 1H), 8.16 (dd, $J = 1.0, 8.3$
Hz, 1H), 7.69 (ddd, $J = 1.2, 7.5, 7.5$ Hz, 1H), 7.69 (ddd, $J = 1.4, 8.6, 8.6$ Hz, 1H), 7.43-
7.31 (m, 3H), 6.96-6.84 (m, 4H), 5.05 (s, 2H), 3.79 (s, 3H), 3.58 (m, 2H), 2.38 (m, 1H),
2.28 (s, 3H), 2.17 (m, 1H), 0.78 (s, 9H), -0.07 (s, 6H).

2-[2-(tert-Butyldimethylsilanyloxy)ethyl]-3-(2-
nitrophenyl)but-2-enoic Acid [2-Iodo-3-(4-methoxyphenoxy
methyl)phenyl]methylamide (299). To a stirred suspension of
NaH (2.6 mg, 60% dispersion in mineral oil, 0.065 mmol) in THF (1.0 mL) was added a
solution of the amide 298 (38.0 mg, 0.054 mmol) in THF (2 mL) at 0 °C. The mixture
was stirred at rt for 15 min and recooled to 0 °C. To the solution was added MeI (0.01
mL, 0.161 mmol) and the reaction mixture was warmed to rt and stirred for 3 h. The
reaction mixture was diluted with saturated aqueous NH$_4$Cl (10 mL) and extracted with
EtOAc (30 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated $\text{in vacuo}$. 
The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the N-methyl amide 299 (36.1 mg, 93%). (Z)-Isomer of 299: \(^1\)H NMR (300 MHz, toluene-\(d_8\), 90 °C) \(\delta\) 7.74 (dd, \(J = 1.1, 8.2\) Hz, 1H), 7.42 (dd, \(J = 1.3, 7.7\) Hz, 1H), 7.24 (d, \(J = 7.5\) Hz, 1H), 7.04 (m, 1H), 6.93 (t, \(J = 7.7\) Hz, 1H), 6.87 (ddd, \(J = 1.4, 7.5, 8.2\) Hz, 1H), 6.84-6.65 (m, 4H), 6.36 (br s, 1H), 4.80 (m, 2H), 4.06 (m, 2H), 3.41 (s, 3H), 2.97 (s, 3H), 2.76 (m, 2H), 2.00 (s, 3H), 1.00 (s, 9H), 0.15 (s, 6H); \(^{13}\)C NMR (75 MHz, toluene-\(d_8\), 90 °C) \(\delta\) 169.7, 155.2, 153.3, 148.4, 146.6, 142.5, 138.3, 133.2, 132.8, 132.6, 129.1, 128.0, 127.5, 124.7, 116.5, 115.3, 101.5, 75.8, 61.9, 55.4, 37.7, 34.8, 26.2, 18.5, 14.1, -5.1. (E)-Isomer of 299: \(^1\)H NMR (300 MHz, toluene-\(d_8\), 90 °C) \(\delta\) 7.63-7.34 (m, 2H), 7.16-6.93 (m, 4H), 6.86-6.83 (m, 3H), 6.74-6.69 (m, 2H), 4.91 (m, 2H), 3.93-3.60 (m, 2H), 3.41 (s, 3H), 3.28 (br s, 3H), 2.45-2.32 (m, 2H), 2.15 (m, 3H), 0.90 (s, 9H), 0.02 (s, 6H).

3-[2-(tert-Butyldimethylsilanyloxy)-ethyl]-4-(4-methoxyphenoxymethyl)-1-methyl-3-[1-(2-nitrophenyl)vinyl]-1,3-dihydroindol-2-one (300). To a solution of N-methyl amide 299 (10.6 mg, 0.015 mmol) in DMA (1.0 mL) were added Pd(OAc)\(_2\) (0.7 mg, 0.003 mmol), PPh\(_3\) (2.6 mg, 0.009 mmol) and NaOAc (2.4 mg, 0.029 mmol). The mixture was stirred at 90 °C for 4 h. The catalyst was removed by filtration and washed with EtOAc (50 mL). The filtrate was washed with water (3×10 mL) and brine (10 mL), dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to give the Heck adduct 300 (6.0 mg, 69%).
NMR (400 MHz, CDCl₃) δ 7.65 (d, J = 7.4 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.45 (ddd, J = 1.1, 7.4, 7.4 Hz, 1H), 7.35 (t, J = 7.8 Hz, 2H), 7.25 (t, J = 7.8 Hz, 1H), 6.98-6.95 (m, 2H), 6.89-6.86 (m, 2H), 6.70 (d, J = 7.6 Hz, 1H), 5.45 (s, 1H), 5.28 (s, 1H), 4.99, 4.89 (ABq, J = 11.4 Hz, 2H), 3.80 (s, 3H), 3.42-3.33 (m, 2H), 3.05 (s, 3H), 2.55 (ddd, J = 5.9, 7.8, 13.7 Hz, 1H), 2.37 (ddd, J = 4.8, 4.8, 13.6 Hz, 1H), 0.71 (s, 9H), -0.20 (d, J = 6.7 Hz, 6H); LRMS-ES [M+H]⁺ calcd for C₃₃H₄₁N₂O₆Si, 589.3; found, 589.4.

2-(2-Benzyloxyethyl)-3-(2-nitrophenyl)-but-2-enoic Acid [2-Iodo-3-(4-methoxyphenoxymethyl)phenyl]amide (302). To a stirred solution of amide 297 (105 mg, 0.179 mmol) and BnBr (0.11 mL, 0.925 mmol) in CH₂Cl₂ (6.0 mL) was added anhydrous CaSO₄ (100 mg), followed by Ag₂O (83 mg, 0.358 mmol). The mixture was stirred at rt overnight in the dark and then filtered through Celite. The filtrate was washed with 1 N aqueous NaOH, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the benzyl ether 302 (96 mg, 79%) as an oil. (Z)-Isomer of 122: ¹H NMR (300 MHz, CDCl₃) δ 8.04-7.98 (m, 2H), 7.62-7.52 (m, 2H), 7.39-7.15 (m, 10H), 6.90-6.82 (m, 4H), 4.90 (s, 2H), 4.65 (s, 2H), 3.86 (t, J = 6.3 Hz, 1H), 3.77 (s, 3H), 2.93 (br s, 2H), 2.09 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 168.9, 154.8, 153.1, 148.0, 140.7, 139.1, 139.0, 138.6, 137.7, 134.1, 133.9, 131.3, 128.9, 128.7, 128.1, 127.9, 125.3, 125.2, 122.9, 116.5, 115.3, 94.5, 76.0, 73.8, 69.1, 56.2, 34.1, 20.5. (E)-Isomer of 122: ¹H NMR (300 MHz, CDCl₃) δ 8.23 (s, 1H), 8.16 (dd, J = 1.0, 8.2 Hz, 2H), 7.64 (ddd, J = 1.2, 7.5, 7.5 Hz, 1H), 7.51 (m, 1H), 7.40-7.16 (m, 8H), 6.97-
(m, 2H), 2.50 (ddd, \( J = 6.5, 6.5, 13.0 \) Hz, 1H), 2.31 (s, 3H), 2.22 (ddd, \( J = 6.8, 6.8, 13.7 \) Hz, 1H); \( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 168.8, 154.9, 153.1, 148.0, 141.0, 138.9, 138.4, 137.8, 136.9, 134.1, 133.0, 130.9, 129.3, 128.8, 128.6, 128.2, 127.8, 125.3, 122.3, 116.5, 115.3, 94.4, 76.1, 73.6, 68.2, 56.2, 32.6, 23.2.

2-(2-Benzoyloxyethyl)-3-(2-nitrophenyl)-but-2-enoic Acid [2-Iodo-3-(4-methoxyphenoxymethyl)phenyl]methylamide (303). To a stirred suspension of NaH (6.0 mg, 60% dispersion in mineral oil, 0.150 mmol) in THF (4.0 mL) was added a solution of the amide 302 (84.6 mg, 0.125 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at rt for 15 min and recooled to 0 °C. To the solution was added MeI (0.016 mL, 0.257 mmol) and the reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was diluted with saturated aqueous NH\(_4\)Cl (10 mL) and extracted with EtOAc (30 mL). The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the \( N \)-methyl amide 303 (67.8 mg, 79%) as an oil. (Z)-Isomer of 303: \(^1\)H NMR (300 MHz, toluene-\( d_8\), 90 °C) \( \delta \) 7.74 (d, \( J = 0.9, 8.2 \) Hz, 1H), 7.35 (d, \( J = 1.2, 7.7 \) Hz, 1H), 7.30 (d, \( J = 7.1 \) Hz, 2H), 7.21 (d, \( J = 7.6 \) Hz, 1H), 7.16 (t, \( J = 7.4 \) Hz, 1H), 7.08-6.83 (m, 4H), 6.77-6.63 (m, 4H), 6.34 (br s, 1H), 4.79 (d, \( J = 4.5 \) Hz, 2H), 4.46 (s, 2H), 3.84 (m, 2H), 3.39 (s, 3H), 2.93 (s, 3H), 2.78 (br s, 2H), 2.09 (m, 1H), 1.94 (s, 3H); \(^{13}\)C NMR (75 MHz, toluene-\( d_8\), 90 °C) \( \delta \) 169.7, 155.2, 153.4, 148.4, 146.7, 142.4, 139.5, 138.4, 133.1, 132.9, 132.6, 129.1, 128.4,
128.1, 127.9, 127.52, 127.46, 124.7, 116.6, 115.4, 101.6, 75.9, 73.4, 68.9, 55.4, 37.7, 31.9, 19.6. (E)-Isomer of 303: $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) $\delta$ 7.63 (br s, 1H), 7.34 (d, $J = 6.8$ Hz, 1H), 7.22-7.03 (m, 9H), 6.83-6.80 (m, 3H), 6.71-6.65 (m, 2H), 4.89 (s, 2H), 4.29 (s, 2H), 3.54 (br s, 2H), 3.41 (s, 3H), 3.25 (s, 3H), 2.43 (br s, 1H), 2.15 (br s, 3H), 1.96 (br s, 1H).

3-(2-Benzyloxyethyl)-4-(4-methoxyphenoxy)methyl-1-methyl-3-[1-(2-nitrophenyl)-vinyl]-1,3-dihydroindol-2-one (304). To a solution of N-methyl amide 303 (201 mg, 0.290 mmol) in DMA (3 mL) were added Pd(OAc)$_2$ (7 mg, 0.031 mmol), PPh$_3$ (27 mg, 0.089 mmol) and NaOAc (48 mg, 0.585 mmol). The mixture was stirred at 90 °C for 24 h. The catalyst was removed by filtration and washed with EtOAc (150 mL). The filtrate was washed with water (3×20 mL) and brine (20 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the Heck product 304 (142 mg, 87%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.65 (d, $J = 8.0$ Hz, 1H), 7.56 (d, $J = 2.9$ Hz, 1H), 7.45 (t, $J = 7.1$ Hz, 1H), 7.38-7.33 (m, 2H), 7.27-7.19 (m, 4H), 7.08 (d, $J = 6.6$ Hz, 2H), 6.97-6.95 (m, 2H), 6.88-6.85 (m, 2H), 6.66 (d, $J = 7.7$ Hz, 1H), 5.46 (s, 1H), 5.29 (s, 1H), 5.03, 4.89 (ABq, $J = 11.3$ Hz, 2H), 4.23, 3.99 (ABq, $J = 11.6$ Hz, 2H), 3.79 (s, 3H), 3.32 (ddd, $J = 3.5$, 6.5, 9.8 Hz, 1H), 3.22 (ddd, $J = 5.6$, 9.4, 9.4 Hz, 1H), 2.84 (s, 3H), 2.71 (ddd, $J = 2.7$, 6.8, 13.9 Hz, 1H), 2.43 (ddd, $J = 3.9$, 5.2, 13.7 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 177.4, 154.5, 153.3, 149.8, 144.9, 143.4,
3-[1-(2-Aminophenyl)vinyl]-3-(2-benzyloxyethyl)-4-(4-methoxyphenoxymethyl)-1-methyl-1,3-dihydroindol-2-one

(305). To a stirred suspension of Cu(acac)$_2$ (4.6 mg, 0.018 mmol) in EtOH (1.0 mL) was added NaBH$_4$ (9.0 mg, 0.238 mmol). After 5 min a black precipitate formed. To the suspension was added a solution of nitro compound 304 (33.4 mg, 0.059 mmol) in EtOH (2.0 mL). The mixture was stirred at rt for 2 h and then carefully quenched with saturated aqueous NH$_4$Cl (5.0 mL). The resulting suspension was diluted with EtOAc (40 mL) and saturated aqueous NaHCO$_3$ (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the aniline 305 (31.2 mg, 99%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.37-7.20 (m, 5H), 7.12-7.02 (m, 2H), 6.96-6.83 (m, 5H), 6.66 (d, $J = 7.5$ Hz, 1H), 6.59 (d, $J = 8.0$ Hz, 1H), 6.35 (m, 1H), 5.54 (br s, 1H), 5.36 (s, 1H), 5.10, 5.07 (ABq, $J = 11.6$ Hz, 2H), 4.25, 4.08 (ABq, $J = 11.6$ Hz, 2H), 4.23 (br s, 2H), 3.78 (s, 3H), 3.30 (ddd, $J = 3.7$, 6.1, 9.8 Hz, 1H), 3.20 (ddd, $J = 5.7$, 9.1, 9.1 Hz, 1H), 2.84 (s, 3H), 2.78 (m, 1H), 2.49 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 179.1, 154.5, 153.1, 145.19, 145.16, 138.6, 134.5, 129.9, 129.2, 128.8, 128.6, 127.9, 127.8, 125.5, 123.4, 120.1, 117.1, 116.1, 116.0, 115.1, 108.3, 73.4, 67.5, 67.2, 57.6, 56.2, 33.8, 26.7; LRMS-ES [M+H]$^+$ calcd for C$_{34}$H$_{35}$N$_2$O$_4$, 535.3; found, 535.2.
4b-(2-Benzyloxyethyl)-4-(4-methoxyphenoxy)methyl)-11-methyl-5-methylene-5,11-dihydro-4bH-10,11-diazabenzo[b]fluorine (306). To a solution of aniline 305 (204 mg, 0.382 mmol) in toluene (10 mL) was added PTSA·H₂O (7 mg, 0.037 mmol). The mixture was refluxed using a Dean-Stark apparatus for 5 h and then diluted with EtOAc (50 mL). The organic layer was washed with saturated aqueous NaHCO₃ (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the amidine 306 (170 mg, 86%). ¹H NMR (300 MHz, CDCl₃) δ 7.41 (t; J = 7.8 Hz, 1H), 7.39 (dd, J=1.2, 7.5 Hz, 1H), 7.33-7.22 (m, 6H), 7.15-7.11 (m, 2H), 7.02 (ddd, J = 1.5, 7.3, 7.3 Hz, 1H), 6.95-6.78 (m, 5H), 5.51 (s, 1H), 5.26 (s, 1H), 5.03, 4.98 (ABq, J = 10.4 Hz, 2H), 3.79 (s, 3H), 3.29 (s, 3H), 3.18-3.03 (m, 2H), 2.58 (ddd, J = 7.1, 14.2, 14.2 Hz, 1H), 1.93 (ddd, J = 5.3, 7.0, 14.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 168.9, 154.7, 153.3, 147.2, 145.6, 145.4, 138.5, 135.0, 130.1, 129.7, 128.6, 127.9, 127.8, 126.6, 125.7, 125.0, 124.4, 124.0, 123.5, 116.4, 115.1, 110.8, 108.0, 73.2, 68.8, 67.5, 56.2, 51.9, 36.4, 28.2; LRMS-ES [M+H]⁺ calcd for C₃₄H₃₃N₂O₃, 517.3; found, 517.2.

4b-(2-Benzyloxyethyl)-4-(4-methoxyphenoxy)methyl)-11-methyl-5-methylene-5,10,10a,11-tetrahydro-4bH-10,11-diazabenzo[b]fluorine (307). To a stirred solution of amidine 306 (126 mg, 0.243 mmol) in toluene (8.0 mL) was added DIBALH (0.49 mL, 1.0 M in CH₂Cl₂, 0.49 mmol) dropwise at 0 °C. The mixture was stirred at the same temperature
for 2 h and then quenched with saturated aqueous Na₂SO₄ (1.0 mL). The resulting suspension was stirred at rt overnight and diluted with EtOAc (30 mL). The mixture was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the aminal 307 (126 mg, 100%) as a yellow foam. ¹H NMR (400 MHz, CDCl₃) δ 7.40 (d, J = 7.8 Hz, 1H), 7.3-7.2 (m, 2H), 7.16 (d, J = 6.6 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.95 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 6.72 (t, J = 7.4 Hz, 1H), 6.59 (d, J = 7.5 Hz, 2H), 5.42 (s, 1H), 5.14, 5.02 (ABq, J = 11.0 Hz, 2H), 4.81 (s, 1H), 4.68 (br s, 1H), 4.46 (s, 1H), 4.34 (s, 2H), 3.79 (s, 3H), 3.67 (m, 1H), 3.61 (m, 1H), 2.73 (s, 3H), 2.19 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 154.4, 153.4, 150.6, 144.7, 140.5, 138.7, 134.4, 129.6, 129.5, 129.0, 128.7, 128.0, 127.9, 126.5, 121.4, 120.5, 118.7, 116.0, 115.1, 114.5, 111.3, 110.4, 109.7, 80.8, 73.3, 68.5, 68.1, 56.2, 49.1, 34.4, 33.3; LRMS-ES [M+H]⁺ calcd for C₃₄H₃₅N₂O₃, 519.3; found, 519.2.

2-{1-[3-(2-Benzylxyethyl)-4-(4-methoxyphenoxy methyl)-1-methyl-2,3-dihydro-1H-indol-3-yl]vinyl}phenyl amine (308). To a stirred solution of aniline 305 (23.7 mg, 0.044 mmol) in CH₂Cl₂ (1.0 mL) was added DIBALH (0.22 mL, 1.0 M in CH₂Cl₂, 0.22 mmol) dropwise at -78 °C and the temperature was gradually raised to 0 °C. The mixture was stirred at the same temperature for 2 h and then additional DIBALH (0.09 mL, 1.0 M in CH₂Cl₂, 0.09 mmol) was added at 0 °C. After another 2 h the reaction mixture was carefully quenched with saturated aqueous Na₂SO₄ (1.0 mL). The resulting suspension
was stirred at rt overnight and diluted with EtOAc (50 mL). The mixture was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the aminal 307 (12.4 mg, 54%) and over-reduced indoline 308 (9.1 mg, 40%). ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.19 (m, 6H), 7.06 (ddd, J = 1.5, 7.5, 8.1 Hz, 1H), 6.95-6.80 (m, 6H), 6.67-6.61 (m, 2H), 6.49 (d, J = 7.6 Hz, 1H), 5.22 (s, 1H), 5.09 (d, J = 1.3 Hz, 1H), 4.96, 4.85 (ABq, J = 11.3 Hz, 2H), 4.35 (s, 2H), 3.78 (s, 3H), 3.72 (br s, 2H), 3.57 (ddd, J = 5.9, 9.1, 9.1 Hz, 1H), 3.49, 3.24 (ABq, J = 9.3 Hz, 2H), 3.44 (ddd, J = 5.6, 9.2, 9.2 Hz, 1H), 2.70 (s, 3H), 2.42 (ddd, J = 5.6, 8.8, 14.3 Hz, 1H), 2.23 (ddd, J = 5.8, 8.6, 14.4 Hz, 1H); LRMS-ES [M+H]+ calcd for C₃₄H₃₇N₂O₃, 521.3; found, 521.2.

(2-{1-[3-(2-Benzylxyethyl)-4-(4-methoxyphenoxy methyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]vinyl} phenyl)-carbamic Acid Ethyl Ester (309). To a stirred solution of aniline 305 (5.7 mg, 0.011 mmol) and NEt₃ (8 μL, 0.057 mmol) in CH₂Cl₂ (1.0 mL) was added ClCO₂Et (2 μL, 0.021 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The mixture was diluted with EtOAc (20 mL) and saturated aqueous NH₄Cl (5 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the carbamate 309 (4.8 mg, 74%). ¹H NMR (300 MHz, CDCl₃) δ 7.82 (br s, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.28-7.19 (m, 5H), 7.11-7.09 (m, 3H), 6.91-6.82 (m, 4H), 6.63 (m, 2H), 6.13 (br s, 1H), 5.78 (br s, 1H), 5.31 (br s, 1H), 5.08 (m, 2H),
4.33-4.06 (m, 4H), 3.78 (s, 3H), 3.36-3.22 (m, 2H), 2.75 (br s, 3H), 2.58 (br s, 2H), 1.31 (t, $J = 7.1$ Hz, 3H); LRMS-ES [M+H]$^+$ calcd for C$_{37}$H$_{39}$N$_2$O$_6$, 607.3; found, 607.1.

**Reductive Aminal Formation from Carbamate-Protected Aniline 309.** To a stirred solution of carbamate 309 (4.8 mg, 0.008 mmol) in toluene (0.8 mL) was added Red-Al (0.01 mL, 0.033 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The mixture was diluted with saturated aqueous NaHCO$_3$ (5 mL) and EtOAc (15 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by preparative TLC (1:2 EtOAc:hexanes) to give $N$-methylaniline 310 (1.4 mg, 33%) and $N,N'$-dimethylaminal 311 (1.9 mg, 44%).

**3-(2-Benzylxoyethyl)-4-(4-methoxyphenoxymethyl)-1-methyl-3-[1-(2-methylaminophenyl)vinyl]-1,3-dihydroindol-2-one (310).** $^1$H NMR (300 MHz, CDCl$_3$) δ 7.39-7.19 (m, 7H), 7.10-7.07 (m, 3H), 6.92-6.84 (m, 4H), 6.67-6.64 (m, 1H), 6.52 (d, $J = 8.1$ Hz, 1H), 6.34 (br s, 1H), 5.31 (br s, 1H), 5.04 (s, 2H), 4.22, 4.05 (ABq, $J = 11.4$ Hz, 2H), 3.78 (s, 3H), 3.29 (m, 1H), 3.17 (m, 1H), 2.86-2.69 (m, 7H), 2.39 (br s, 1H); LRMS-ES [M+H]$^+$ calcd for C$_{35}$H$_{36}$N$_2$O$_4$, 549.3; found, 549.2.

**4b-(2-Benzylxoyethyl)-4-(4-methoxyphenoxyxymethyl)-10,11-dimethyl-5-methylene-5,10,10a,11-tetrahydro-4bH-10,11-diazabenzo[b]fluorine (311).** $^1$H NMR (300 MHz, CDCl$_3$) δ 7.42 (dd, $J = 7.7$, 1.5 Hz, 1H), 7.31-7.17 (m, 7H), 6.95-6.89 (m, 3H), 6.86-6.82 (m, 2H), 6.72 (t, $J = 6.9$ Hz, 1H), 6.66 (d, $J = 8.1$ Hz, 1H), 6.53 (d, $J = 7.7$ Hz, 1H), 5.42 (s, 1H),...
5.1, 5.0 (ABq, \(J = 11.0 \text{ Hz}, 2\text{H}\)), 4.81 (s, 1H), 4.48 (s, 1H), 4.34 (s, 2H), 3.78 (s, 3H), 3.68-3.52 (m, 2H), 3.15 (s, 3H), 2.77 (s, 3H), 2.26-2.04 (m, 2H); LRMS-ES [M+H]\(^+\) calcd for C\(_{35}\)H\(_{37}\)N\(_2\)O\(_3\), 533.3; found, 533.2.

3-\{1-(2-Benzylaminophenyl)-vinyl\}-3-(2-benzyloxyethyl)-4-(4-methoxyphenoxymethyl)-1-methyl-1,3-dihydroindol-2-one (312). To a stirred solution of aniline 305 (28.7 mg, 0.054 mmol), benzaldehyde (8 \(\mu\)L, 0.080 mmol) and ZnCl\(_2\) (14.6 mg, 0.107 mmol) in MeOH (3.0 mL) was added NaBH\(_3\)CN (6.7 mg, 0.107 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 3 h. The mixture was diluted with 1 N aqueous NaOH (10 mL) and EtOAc (20 mL). The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to give \(N\)-benzylaniline 312 (23.5 mg, 70%). \(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 7.44-7.27 (m, 11H), 7.37-7.33 (m, 2H), 6.98 (t, \(J = 7.7 \text{ Hz}, 1\text{H}\)), 6.91-6.85 (m, 4H), 6.76-6.73 (m, 1H), 6.46 (d, \(J = 8.1 \text{ Hz}, 1\text{H}\)), 6.35 (br s, 1H), 5.61 (br s, 1H), 5.39 (s, 1H), 5.06 (m, 2H), 4.32 (s, 2H), 4.27, 4.11 (ABq, \(J = 11.6 \text{ Hz}, 2\text{H}\)), 3.80 (s, 3H), 3.31 (m, 1H), 3.21 (m, 1H), 2.93 (s, 3H), 2.77 (ddd, \(J = 5.9, 7.9, 13.9 \text{ Hz}, 1\text{H}\)), 2.50 (br s, 1H); LRMS-ES [M+H]\(^+\) calcd for C\(_{41}\)H\(_{41}\)N\(_2\)O\(_4\), 625.3; found, 625.3.

10-Benzyl-4b-(2-benzyloxyethyl)-4-(4-methoxyphenoxy)methyl)-11-methyl-5-methylene-5,10,10a,11-tetrahydro-4bH-10,11-diaza[b]fluorine (313). To a stirred
solution of N-benzylaniline 312 (6.5 mg, 0.010 mmol) was added excess LiAlH₄ at 0 °C, and the temperature was raised gradually to rt. After 2 h the reaction mixture was cooled to 0 °C and carefully quenched with water (2 drops), 15% aqueous NaOH (2 drops) and water (6 drops). The resulting suspension was stirred for 1 h and filtered through Celite. The filtrate was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by preparative TLC (1:2 EtOAc:hexanes) to give aminal 313 (3.6 mg, 57%). ¹H NMR (400 MHz, CDCl₃) δ 7.40 (d, J = 7.6 Hz, 1H), 7.32-7.22 (m, 7H), 7.19-7.14 (m, 4H), 7.06 (t, J = 7.7 Hz, 1H), 6.94-6.92 (m, 3H), 6.86-6.82 (m, 2H), 6.71 (t, J = 7.4 Hz, 1H), 6.58 (d, J = 8.2 Hz, 1H), 6.48 (d, J = 7.8 Hz, 1H), 5.43 (s, 1H), 5.13, 5.02 (ABq, J = 11.2 Hz, 2H), 4.90 (s, 1H), 4.80, 4.64 (ABq, J = 15.8 Hz, 2H), 4.61 (s, 1H), 4.27 (s, 2H), 3.79 (s, 3H), 3.51 (t, J = 6.6 Hz, 2H), 2.72 (s, 3H), 2.35-2.19 (m, 2H); LRMS-ES [M+H]⁺ calcd for C₄₁H₄₁N₂O₃, 609.3; found, 609.4.

4b-(2-Benzylxoyethyl)-4-(4-methoxyphenoxymethyl)-11-methyl-5-methylene-4b,5,10a,11-tetrahydro-10,11-diazabenzo[b]fluorene-10-carboxylic Acid Ethyl Ester (314).

To a stirred suspension of NaH (12 mg, 60% dispersion in mineral oil, 0.293 mmol) in THF (3 mL) was added a solution of the aminal 307 (126 mg, 0.243 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at rt for 15 min and recooled to 0 °C. To the solution was added ClCO₂Et (0.05 mL, 0.523 mmol) and the reaction mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with saturated aqueous NH₄Cl (10 mL) and extracted with EtOAc (30 mL). The organic layer was dried
over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the carbamate protected aminal 314 (136 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.24 (m, 6H), 7.18-7.13 (m, 2H), 7.02 (t, J = 7.8 Hz, 1H), 6.95 (t, J = 7.8 Hz, 1H), 6.89-6.83 (m, 4H), 6.58 (d, J = 7.6 Hz, 1H), 6.15 (s, 1H), 6.13 (d, J = 7.8 Hz, 1H), 5.41 (d, J = 4.7 Hz, 2H), 5.06, 4.88 (ABq, J = 11.4 Hz, 2H), 4.42 (s, 2H), 4.29 (m, 1H), 4.19 (br s, 1H), 3.79 (s, 3H), 3.67 (m, 1H), 3.42 (m, 1H), 2.84 (s, 3H), 2.71 (ddd, J = 4.8, 8.3, 13.1 Hz, 1H), 2.49 (ddd, J = 6.2, 8.1, 14.3 Hz, 1H), 1.29 (t, J = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.2, 154.3, 153.3, 151.9, 144.8, 138.8, 136.4, 136.0, 134.1, 129.2, 128.8, 128.3, 128.0, 127.9, 127.0, 126.23, 126.19, 125.6, 118.3, 115.9, 115.1, 112.9, 104.8, 82.0, 73.6, 67.7, 66.7, 62.5, 58.0, 56.2, 36.8, 30.7, 14.9; LRMS-ES [M+H]+ calcd for C₃₇H₃₉N₂O₅, 591.3; found, 591.2.

**4b-(2-Benzyl oxyethyl)-5-hydroxymethyl-4-(4-methoxyphenoxy methyl)-11-methyl-4b,5,10a,11-tetrahydro-10,11-diaza benzo[b]fluorene-10-carboxylic Acid Ethyl Ester (316).** To a stirred solution of carbamate-protected aminal 315 (6.1 mg, 0.010 mmol) in THF (1.0 mL) was added BH₃·THF (0.08 mL, 1.0 M in THF, 0.08 mmol) at 0 °C. The mixture was stirred at rt for 4.5 h and recooled to 0 °C. To the solution was added 3 N aqueous NaOH (0.1 mL) and 30% H₂O₂ (0.1 mL). The mixture was warmed to rt and stirred for 2 h. The reaction mixture was diluted with saturated aqueous NaHSO₃ (5 mL) and extracted with EtOAc (20 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by preparative TLC (1:3
EtOAc:hexanes) to give the alcohol 316 (3.6 mg, 57%). $^1$H NMR (400 MHz, CDCl$_3$)

$\delta$ 7.43 (d, $J = 8.0$ Hz, 1H), 7.32-7.17 (m, 5H), 7.11-6.97 (m, 5H, 6.91-6.86 (m, 3H), 6.76 (d, $J = 7.5$ Hz, 1H), 6.16 (d, $J = 7.6$ Hz, 1H), 5.96 (s, 1H), 5.06 (s, 2H), 4.41 (s, 2H), 4.26 (m, 2H), 4.04 (t, $J = 5.8$ Hz, 2H), 3.80 (s, 3H), 3.77 (m, 1H), 3.59 (m, 1H), 3.17 (t, $J = 6.0$ Hz, 1H), 2.88 (m, 1H), 2.78 (t, $J = 5.2$ Hz, 1H), 2.62 (s, 3H), 2.59 (m, 1H), 2.44 (ddd, $J = 5.2$, 5.2, 15.3 Hz, 1H), 1.31 (t, $J = 7.1$ Hz); LRMS-ES [M+H]$^+$ calcd for C$_{37}$H$_{41}$N$_2$O$_6$, 609.3; found, 609.5.

{2-[3a-(2-Benzyl oxyethyl)-4-(4-methoxyphenoxy methyl)-8-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b] indol-3-yl]phenyl}-carbamic Acid Ethyl Ester (317). The alcohol 136 is unstable to silica gel column chromatography or to standing in CH$_2$Cl$_2$ at rt overnight, is easily transformed into the N,O-acetal 317 quantitatively under these conditions. $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) $\delta$ 8.17 (br s, 1H), 7.25 (m, 1H), 7.09-6.84 (m, 12H), 6.77-6.74 (m, 2H), 6.22 (d, $J = 7.6$ Hz, 1H), 5.65 (s, 1H), 5.10, 5.00 (ABq, $J = 11.6$ Hz, 2H), 4.09 (m, 2H), 4.00-3.74 (m, 5H), 3.44 (s, 3H), 3.09 (m, 2H), 2.71 (s, 3H), 2.04 (m, 1H), 1.85 (m, 1H), 1.10 (t, $J = 7.0$ Hz, 3H); LRMS-ES [M+H]$^+$ calcd for C$_{37}$H$_{41}$N$_2$O$_6$, 609.3; found, 609.3.

[4b-(2-Benzyl oxyethyl)-4-(4-methoxyphenoxy methyl)-11-methyl-5,10,10a,11-tetrahydro-4bH-10,11-diazabenzo[b] fluoren-5-yl]methanol (318). A solution of the N,O-acetal 317
(4.2 mg, 0.007 mmol) in EtOH (1.0 mL) and 1 N aqueous KOH (0.5 mL) was refluxed for 4 h. The mixture was diluted with EtOAc (20 mL) and saturated aqueous NaHCO₃ (5 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo.

The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the hydroxy aminal 318 (3.2 mg, 87%). ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.23 (m, 4H), 7.13-7.06 (m, 3H), 7.03 (d, J = 6.5 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.91-6.84 (m, 4H), 6.74 (t, J = 7.4 Hz, 1H), 6.70 (d, J = 7.9 Hz, 1H), 6.61 (d, J = 7.7 Hz, 1H), 5.04, 4.91 (ABq, J = 11.3 Hz, 2H), 4.56 (d, J = 5.6 Hz, 1H), 4.48 (d, J = 6.0 Hz, 1H), 4.30 (s, 2H), 3.79 (s, 3H), 3.71 (d, J = 12.0 Hz, 1H), 3.54-3.45 (m, 2H), 3.36 (m, 1H), 3.28 (d, J = 11.7 Hz, 1H), 3.07 (s, 1H), 2.77 (s, 3H), 2.16 (ddd, J = 6.1, 6.1, 15.4 Hz, 1H), 1.94 (ddd, J = 7.3, 7.3, 14.7 Hz, 1H); LRMS-ES [M+H]⁺ calcd for C₃₄H₅₇N₂O₄, 537.3; found, 537.3.

5-(2-Nitrophenyl)-3,6-dihydro-2H-pyridine-1,4-dicarboxylic Acid 1-tert-Butyl Ester 4-Ethyl Ester (329). To a solution of triflate 327 (522 mg, 1.29 mmol) and 2-nitrobenezeneboronic acid (234 mg, 1.43 mmol, Alfa Aesar) in DME (9.0 mL) and water (3.0 mL) were added Pd(PPh₃)₄ (30 mg, 0.03 mmol) and Na₂CO₃ (412 mg, 3.89 mmol). The reaction mixture was stirred at 80 °C for 1 h and then cooled to rt. The mixture was diluted with saturated aqueous NaHCO₃ (30 mL) and EtOAc (150 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the ester 329 (459 mg, 94%). ¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, J = 7.5 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.23 (d, J = 7.2 Hz,
1H), 4.35-4.23 (m, 1.5H), 4.04 (br s, 0.5H), 3.87 (q, \( J = 7.1 \) Hz, 2H), 3.69 (br s, 1.5H), 3.44 (br s, 0.5H), 2.53 (m, 2H), 0.89 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 166.3, 154.8, 148.4, 144.0, 136.1, 133.7, 130.1, 128.9, 125.7, 124.7, 80.6, 60.9, 49.4, 41.0, 39.8, 28.8, 25.9, 13.9; LRMS-ES [M+H]+ calcd for C\(_{19}\)H\(_{24}\)N\(_2\)O\(_6\), 377.2; found, 377.2.

1-Benzyl-5-(2-nitrophenyl)-1,2,3,6-tetrahydropyridine-4-carboxylic Acid Ethyl Ester (333). To a solution of triflate 332\(^2\) (2.15 g, 5.47 mmol) and 2-nitrobenzeneboronic acid (958 mg, 5.74 mmol) in DME (30 mL) and water (10 mL) were added Pd(PPh\(_3\))\(_4\) (126 mg, 0.11 mmol) and Na\(_2\)CO\(_3\) (1.74 g, 16.42 mmol). The reaction mixture was stirred at 80 °C for 3 h and then cooled to rt. The mixture was diluted with saturated aqueous NaHCO\(_3\) (50 mL) and EtOAc (150 mL). The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give ester 333 (2.00 g, 100%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.03 (dd, \( J = 1.2, 8.2 \) Hz, 1H), 7.57 (ddd, 0.8, 7.6, 7.6 Hz, 1H), 7.46-7.39 (m, 3H), 7.36-7.26 (m, 3H), 7.19 (dd, \( J = 1.3, 7.6 \) Hz, 1H), 3.87 (q, \( J = 7.2 \) Hz, 2H), 3.73 (q, \( J = 12.7 \) Hz, 2H), 3.48, 3.22 (ABq, \( J = 17.9 \) Hz, 2H), 2.83 (t, \( J = 5.8 \) Hz, 2H), 2.60 (m, 2H), 0.88 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 166.6, 148.3, 144.7, 138.2, 137.1, 133.5, 130.1, 129.4, 128.8, 128.4, 127.7, 125.1, 124.6, 61.8, 60.7, 58.6, 49.2, 26.0, 14.0.

1-Benzyl-5-(2-nitrophenyl)-1,2,3,6-tetrahydropyridine-4-carboxylic Acid (334). To a solution of the ester 333 (3.07 g, 8.39
mmol) in MeOH (30 mL) and water (12 mL) was added LiOH·H₂O (1.76 g, 41.94 mmol). The reaction mixture was stirred at 50 °C overnight and MeOH was removed under reduced pressure. The residue was acidified with dilute HCl to pH 5-6 and then extracted with EtOAc (3×100 mL). The combined organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:10 MeOH:CH₂Cl₂) to give acid 334 (2.83 g, 100%). ¹H NMR (300 MHz, CDCl₃) δ 12.6 (br s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.1 Hz, 1H), 7.33-7.26 (m, 6H), 7.13 (d, J = 7.2 Hz, 1H), 4.03-3.90 (m, 2H), 3.73-3.51 (m, 2H), 3.00 (br s, 1H), 2.78 (br s, 1H), 2.47 (br s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 169.4, 148.5, 136.6, 135.6, 133.8, 131.8, 130.9, 130.7, 129.4, 129.3, 128.7, 127.3, 124.2, 58.6, 54.5, 46.6, 23.3; LRMS-ES [M+H]+ calcd for C₂₁H₂₃N₂O₄, 367.2; found, 367.2.

**1-Benzyl-5-(2-nitrophenyl)-1,2,3,6-tetrahydro pyridine-4-carboxylic Acid [2-Iodo-3-(4-methoxyphenoxy methyl)phenyl]amide (335).** A mixture of acid 334 (597 mg, 1.77 mmol) and SOCl₂ (5.0 mL) was refluxed for 4 h. Excess SOCl₂ was removed under reduced pressure and the residue was diluted with CH₂Cl₂ (3.0 mL). To a stirred solution of aniline 240 (482 mg, 1.36 mmol) and (i-Pr)₂NEt (1.0 mL, 5.74 mmol) in CH₂Cl₂ (15 mL) was added the above solution of the acid chloride dropwise at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The mixture was diluted with CH₂Cl₂ (60 mL) and saturated aqueous NaHCO₃ (30 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography
(1:1:2 EtOAc:CH$_2$Cl$_2$:hexanes) to give the amide 335 (723 mg, 79%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J = 8.2$ Hz, 1H), 7.81 (br s, 1H), 7.77 (br s, 1H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.47-7.33 (m, 7H), 7.24-7.19 (m, 2H), 6.88-6.81 (m, 4H), 4.91 (s, 2H), 3.87 (br s, 2H), 3.77 (s, 3H), 3.42 (br s, 2H), 3.01 (br s, 3H), 2.74 (br s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.7, 153.5, 151.7, 147.3, 139.5, 137.5, 136.8, 136.1, 134.2, 133.2, 130.4, 129.1, 128.5, 128.3, 128.1, 127.8, 126.9, 124.3, 124.1, 121.3, 115.2, 114.0, 93.0, 74.6, 60.7, 56.0, 55.0, 47.9, 25.7; LRMS-ES [M+H]$^+$ calcd for C$_{33}$H$_{31}$IN$_3$O$_5$, 676.1; found, 676.1.

1-Benzyl-5-(2-nitrophenyl)-1,2,3,6-tetrahydro pyridine-4-carboxylic Acid [2-Iodo-3-(4-methoxyphenoxymethyl)phenyl]methylamide (336). To a stirred suspension of NaH (51 mg, 60% dispersion in mineral oil, 1.26 mmol) in THF (15 mL) was added a solution of amide 335 (711 mg, 1.05 mmol) in THF (5 mL) at 0 °C and the mixture was stirred at 0 °C for 30 min. To the solution was added MeI (0.08 mL, 1.29 mmol) and the reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was diluted with saturated aqueous NaHCO$_3$ (20 mL) and extracted with EtOAc (100 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1:1 EtOAc:CH$_2$Cl$_2$:hexanes) to give N-methyl amide 336 (697 mg, 96%). $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) $\delta$ 7.67 (dd, $J = 0.9$, 8.2 Hz, 1H), 7.34-7.26 (m, 4H), 7.14 (t, $J = 7.4$ Hz, 2H), 7.05-6.96 (m, 3H), 6.85-6.76 (m, 3H), 6.69-6.65 (m, 2H), 6.58 (br s, 1H), 4.81 (s, 2H), 3.47 (br s, 2H), 3.39 (s,
Heck Cyclization of Amide 336. To a solution of N-methyl amide 336 (54.2 mg, 0.079 mmol) in DMA (2.6 mL) were added Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), PPh$_3$ (6.2 mg, 0.024 mmol), $n$-Bu$_4$NBr (50.7 mg, 0.157 mmol) and K$_2$CO$_3$ (21.7 mg, 0.157 mmol). The mixture was stirred at 150 °C for 1.5 h. The catalyst was removed by filtration and washed with EtOAc (100 mL). The filtrate was washed with water (3×20 mL) and brine (20 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the Heck adduct 338 (28.4 mg, 64%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.40 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.32-7.22 (m, 6H), 7.09 (d, $J = 7.7$ Hz, 1H), 7.03 (ddd, $J = 1.5$, 7.5, 7.5 Hz, 1H), 6.98-6.84 (m, 6H), 6.70 (s, 1H), 6.43 (dd, $J = 1.3$, 7.9 Hz, 1H), 5.26 (d, $J = 11.4$ Hz, 1H), 4.73 (d, $J = 11.4$ Hz, 1H), 4.30 (s, 2H), 3.86-3.74 (m, 4H), 3.36 (s, 3H), 3.02-2.92 (m, 1H), 2.50 (ddd, $J = 4.9$, 13.3, 13.3 Hz, 1H), 1.79 (ddd, $J = 2.1$, 3.6, 13.6 Hz, 1H); LRMS-ES [M+H]$^+$ calcd for C$_{34}$H$_{32}$N$_3$O$_5$, 562.2; found, 562.2.
4-[(2-Iodo-3-(4-methoxyphenoxymethyl)phenyl)methylcarbamoyl]-5-(2-nitrophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic Acid Ethyl Ester (337). To a stirred solution of N-methyl amide 336 (219 mg, 0.318 mmol) in CH₂Cl₂ (6 mL) was added ClCO₂Et (0.08 mL, 0.836 mmol) dropwise at rt. After 1 h the reaction mixture was diluted with saturated aqueous NaHCO₃ (20 mL) and CH₂Cl₂ (30 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the carbamate-protected amide 337 (212 mg, 100%). ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.71 (d, J = 7.9 Hz, 1H), 7.25 (t, J = 7.2 Hz, 2H), 7.07-6.77 (m, 5H), 6.71-6.68 (m, 2H), 6.54 (br s, 1H), 4.81 (s, 2H), 4.15 (br s, 2H), 4.07 (m, 2H), 3.55 (br s, 2H), 3.42 (s, 3H), 2.88 (s, 3H), 2.31 (br s, 2H), 1.08 (m, 3H); LRMS-ES [M+Na]⁺ calcd for C₃₀H₃₀IN₃NaO₇, 694.1; found, 694.1.

Heck Cyclization of Carbamate-Protected Amide 337. To a solution of carbamate protected amide 337 (121 mg, 0.181 mmol) in DMA (6.0 mL) were added Pd(OAc)₂ (4 mg, 0.018 mmol), PPh₃ (14 mg, 0.054 mmol), n-Bu₄NBr (117 mg, 0.363 mmol) and K₂CO₃ (50 mg, 0.362 mmol). The mixture was stirred at 150 °C for 1.5 h. The catalyst was removed by filtration and washed with EtOAc (200 mL). The filtrate was washed with water (3×30 mL) and brine (30 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the Heck adduct 339 (76 mg, 78%). ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.64 (s, 1H), 7.04 (dd, J =
1.3, 8.0 Hz, 1H), 7.02-6.93 (m, 2H), 6.89-6.86 (m, 2H), 6.79 (dd, \( J = 1.3, 7.9 \) Hz, 1H),
6.71-6.66 (m, 3H), 6.55 (ddd, \( J = 1.2, 7.7, 7.7 \) Hz, 1H), 6.32 (dd, \( J = 1.5, 7.2 \) Hz, 1H),
5.09, 4.80 (ABq, \( J = 11.5, \) Hz, 2H), 4.14 (ddd, \( J = 3.9, 12.7, 12.7 \) Hz, 1H), 4.02-3.86 (m,
3H), 3.40 (s, 3H), 2.87 (s, 3H), 2.39 (ddd, \( J = 4.9, 12.3, 14.0 \) Hz, 1H), 1.69 (ddd, \( J = 3.5, 3.5, 14.0 \) Hz, 1H), 1.00 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, toluene-\( d_8 \), 90 °C) \( \delta \)
177.6, 155.2, 153.8, 150.5, 144.2, 135.2, 132.4, 131.9, 131.8, 130.5, 128.91, 128.89,
127.0, 124.5, 124.1, 116.5, 115.4, 108.9, 107.5, 67.6, 62.3, 55.4, 50.0, 38.2, 31.3, 26.2,
14.2; LRMS-ES [M+H]\(^+\) calcd for C\(_{30}\)H\(_{30}\)N\(_3\)O\(_7\), 544.2; found, 544.2.

**Preparation of Aniline 340.** To a solution of nitro
compound 339 (125 mg, 0.231 mmol) in THF (10 mL) was added
10% Pd/C (20 mg). The mixture was stirred at rt under a H\(_2\)
atmosphere (1 atm). Additional catalyst (20 mg × 2) was added after 3 and 21 h. After 33
h the catalyst was removed by filtration through Celite and the filtrate was concentrated
in vacuo. The residue was purified by flash column chromatography (1:1
EtOAc:hexanes) to give aniline 340 (97 mg, 82%). \(^1\)H NMR (300 MHz, toluene-\( d_8 \),
90 °C) \( \delta \) 7.48 (s, 1H), 7.06 (d, \( J = 7.7 \) Hz, 1H), 6.94 (t, \( J = 7.8 \) Hz, 1H), 6.84-6.81 (m,
2H), 6.75-6.68 (m, 3H), 6.62 (dd, \( J = 1.4, 7.8 \) Hz, 1H), 6.30-6.18 (m, 3H), 5.10, 4.94
(ABq, \( J = 11.4 \) Hz, 2H), 4.16 (ddd, \( J = 3.5, 12.8, 12.8 \) Hz, 1H), 4.02-3.89 (m, 3H), 3.63
(br s, 2H), 3.41 (s, 3H), 2.74 (s, 3H), 2.36 (ddd, \( J = 4.6, 11.9, 14.0 \) Hz, 1H), 1.77 (ddd, \( J = 3.5, 3.5, 14.0 \) Hz, 1H), 0.97 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, toluene-\( d_8 \), 90 °C)
\( \delta \) 179.2, 155.3, 153.8, 153.2, 146.2, 144.4, 134.7, 130.8, 130.7, 129.9, 128.4, 128.3,
Cyclized \textit{N}-Hydroxyindole 341. Method A: To a stirred suspension of Cu\((\text{acac})_2\) (0.9 mg, 0.003 mmol) in EtOH (0.5 mL) was added \(\text{NaBH}_4\) (5.3 mg, 0.140 mmol). After 5 min a black precipitate formed. To the suspension was added a solution of nitro compound 339 (3.8 mg, 0.007 mmol) in EtOH (1.0 mL). The mixture was stirred at rt for 3 h and then carefully quenched with saturated aqueous \(\text{NH}_4\text{Cl}\) (1.0 mL). The resulting suspension was diluted with \(\text{EtOAc}\) (20 mL) and saturated aqueous \(\text{NaHCO}_3\) (10 mL). The organic layer was dried over \(\text{Na}_2\text{SO}_4\) and concentrated \textit{in vacuo}. The residue was purified by preparative TLC (1:1 \(\text{EtOAc}\):hexanes) to give the aniline 340 (0.7 mg, 19%) and cyclized \(\text{N}\)-hydroxyindole 341 (1.8 mg, 49%).

Method B: To a stirred solution of nitro compound 339 (26.7 mg, 0.049 mmol) in \(\text{THF}\) (2.0 mL) and EtOH (1.0 mL) were added SnCl\(_2\) (46.6 mg, 0.246 mmol) and \(\text{NaBH}_4\) (18.6 mg, 0.492 mmol). The mixture was stirred at rt for 2 h and then diluted with saturated aqueous \(\text{NH}_4\text{Cl}\) (10 mL) and \(\text{EtOAc}\) (30 mL). The organic layer was dried over \(\text{Na}_2\text{SO}_4\) and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:1 to 3:1 \(\text{EtOAc}\):hexanes) to give the aniline 340 (10.3 mg, 41%) and cyclized \(\text{N}\)-hydroxyindole 341 (11.4 mg, 44%). IR (film) 2924, 2853, 1713, 1508, 1236 cm\(^{-1}\); \textsuperscript{1}H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.25 (s, 1H), 7.46 (d, \(J = 7.2\) Hz, 1H), 7.40 (t, \(J = 7.5\) Hz, 1H), 7.11 (m, 2H), 7.01 (m, 1H), 6.80 (m, 1H), 6.65 (d, \(J = 8.6\) Hz, 2H), 6.50 (d, \(J = 8.6\) Hz, 2H), 6.50 (d, \(J = 7.2\) Hz, 1H), 6.46 (d, \(J = 8.6\) Hz, 2H), 6.36 (d, \(J = 8.6\) Hz, 2H), 6.25 (d, \(J = 8.6\) Hz, 2H), 6.15 (d, \(J = 8.6\) Hz, 2H), 6.05 (d, \(J = 8.6\) Hz, 2H), 5.95 (d, \(J = 8.6\) Hz, 2H), 5.85 (d, \(J = 8.6\) Hz, 2H), 5.75 (d, \(J = 8.6\) Hz, 2H), 5.65 (d, \(J = 8.6\) Hz, 2H), 5.55 (d, \(J = 8.6\) Hz, 2H), 5.45 (d, \(J = 8.6\) Hz, 2H), 5.35 (d, \(J = 8.6\) Hz, 2H), 5.25 (d, \(J = 8.6\) Hz, 2H), 5.15 (d, \(J = 8.6\) Hz, 2H), 5.05 (d, \(J = 8.6\) Hz, 2H), 4.95 (d, \(J = 8.6\) Hz, 2H), 4.85 (d, \(J = 8.6\) Hz, 2H), 4.75 (d, \(J = 8.6\) Hz, 2H), 4.65 (d, \(J = 8.6\) Hz, 2H), 4.55 (d, \(J = 8.6\) Hz, 2H), 4.45 (d, \(J = 8.6\) Hz, 2H), 4.35 (d, \(J = 8.6\) Hz, 2H), 4.25 (d, \(J = 8.6\) Hz, 2H), 4.15 (d, \(J = 8.6\) Hz, 2H), 4.05 (d, \(J = 8.6\) Hz, 2H), 3.95 (d, \(J = 8.6\) Hz, 2H), 3.85 (d, \(J = 8.6\) Hz, 2H), 3.75 (d, \(J = 8.6\) Hz, 2H), 3.65 (d, \(J = 8.6\) Hz, 2H), 3.55 (d, \(J = 8.6\) Hz, 2H), 3.45 (d, \(J = 8.6\) Hz, 2H), 3.35 (d, \(J = 8.6\) Hz, 2H), 3.25 (d, \(J = 8.6\) Hz, 2H), 3.15 (d, \(J = 8.6\) Hz, 2H), 3.05 (d, \(J = 8.6\) Hz, 2H), 2.95 (d, \(J = 8.6\) Hz, 2H), 2.85 (d, \(J = 8.6\) Hz, 2H), 2.75 (d, \(J = 8.6\) Hz, 2H), 2.65 (d, \(J = 8.6\) Hz, 2H), 2.55 (d, \(J = 8.6\) Hz, 2H), 2.45 (d, \(J = 8.6\) Hz, 2H), 2.35 (d, \(J = 8.6\) Hz, 2H), 2.25 (d, \(J = 8.6\) Hz, 2H), 2.15 (d, \(J = 8.6\) Hz, 2H), 2.05 (d, \(J = 8.6\) Hz, 2H), 1.95 (d, \(J = 8.6\) Hz, 2H), 1.85 (d, \(J = 8.6\) Hz, 2H), 1.75 (d, \(J = 8.6\) Hz, 2H), 1.65 (d, \(J = 8.6\) Hz, 2H), 1.55 (d, \(J = 8.6\) Hz, 2H), 1.45 (d, \(J = 8.6\) Hz, 2H), 1.35 (d, \(J = 8.6\) Hz, 2H), 1.25 (d, \(J = 8.6\) Hz, 2H), 1.15 (d, \(J = 8.6\) Hz, 2H), 1.05 (d, \(J = 8.6\) Hz, 2H), 0.95 (d, \(J = 8.6\) Hz, 2H), 0.85 (d, \(J = 8.6\) Hz, 2H), 0.75 (d, \(J = 8.6\) Hz, 2H), 0.65 (d, \(J = 8.6\) Hz, 2H), 0.55 (d, \(J = 8.6\) Hz, 2H), 0.45 (d, \(J = 8.6\) Hz, 2H), 0.35 (d, \(J = 8.6\) Hz, 2H), 0.25 (d, \(J = 8.6\) Hz, 2H), 0.15 (d, \(J = 8.6\) Hz, 2H), 0.05 (d, \(J = 8.6\) Hz, 2H).
8.7 Hz, 2H), 6.29 (d, $J = 6.7$ Hz, 1H), 4.61 (d, $J = 10.4$ Hz, 1H), 4.37-4.18 (m, 3H), 4.09 (m, 1H), 3.72 (s, 3H), 3.34 (s, 3H), 2.56 (t, $J = 11.6$ Hz, 1H), 2.11 (d, $J = 13.8$ Hz, 1H), 1.25 (m, 3H); LRMS-ES [M+H]$^+$ calcd for C$_{30}$H$_{30}$N$_3$O$_6$, 528.2; found, 528.2.

**Synthesis of N-Ethylaniline 342.** To a solution of nitro compound 339 (25.8 mg, 0.048 mmol) in EtOH (5 mL) was added 10% Pd/C (10.0 mg). The mixture was stirred at rt under a H$_2$ atmosphere (1 atm) overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give N-ethylaniline 342 (21.4 mg, 83%). $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$ 7.34 (d, $J = 20.4$ Hz, 1H), 7.27 (t, $J = 7.8$ Hz, 1H), 7.12 (d, $J = 7.3$ Hz, 1H), 6.99-6.85 (m, 5H), 6.76 (d, $J = 7.7$ Hz, 1H), 6.59 (d, $J = 7.0$ Hz, 1H), 6.45 (d, $J = 8.1$ Hz, 1H), 6.34 (t, $J = 7.4$ Hz, 1H), 5.98 (d, $J = 10.8$ Hz, 1H), 4.92 (t, $J = 11.5$ Hz, 1H), 4.32 (br s, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 4.14-4.03 (m, 2H), 3.79 (s, 3H), 3.19 (s, 3H), 2.99 (m, 2H), 2.44 (m, 1H), 1.98 (m, 1H), 1.30 (t, $J = 7.0$ Hz, 3H), 1.21 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$ 179.4, 153.7 (d, $J = 45.0$ Hz), 153.2, 147.4, 144.1, 134.0, 130/7, 130/4, 129.6, 128.9, 128.7, 124.0 (d, $J = 14.1$ Hz), 123.5 (d, $J = 14.0$ Hz), 116.2, 115.8, 115.0, 111.6 (d, $J = 49.3$ Hz), 110.6, 108.3, 67.4, 62.7, 56.0, 50.5 (d, $J = 11.8$ Hz), 38.8, 38.0 (d, $J = 16.2$ Hz), 31.4, 26.9, 14.7, 14.6.

**{2-[4-(4-Methoxyphenoxy)methyl]-1-methyl-2-oxo-1,2-dihydro-1'H-[3,3']biindolyl-3-yl]-ethyl}carbamic Acid**
**Ethyl Ester (348).** To a solution of aniline 340 (46.5 mg, 0.091 mmol) in toluene (5.0 mL) was added PTSA·H₂O (3.4 mg, 0.018 mmol). The mixture was stirred at 80 °C overnight and then diluted with EtOAc (50 mL). The organic layer was washed with saturated aqueous NaHCO₃ (10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (3:1 EtOAc:hexanes) to give indole 348 (35.6 mg, 77%). ¹H NMR (400 MHz, CDCl₃) δ 8.99 (s, 1H), 7.38 (t, J = 6.9 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.82-6.78 (m, 2H), 6.52 (d, J = 9.0 Hz, 2H), 6.47 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 9.1 Hz, 2H), 4.79-4.76 (m, 2H), 4.52 (d, J = 12.3 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.68 (s, 3H), 3.38 (s, 3H), 3.05 (m, 2H), 2.82 (ddd, J = 6.7, 6.7, 13.5 Hz, 1H), 2.56 (ddd, J = 6.8, 6.8, 13.5 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 179.3, 156.8, 154.1, 152.4, 144.2, 137.2, 135.2, 129.4 125.4, 124.0, 123.7, 122.5, 120.2, 119.2 115.7, 114.9, 113.2, 112.2, 108.5, 66.3, 61.1, 56.0, 51.7, 37.4, 35.5, 27.2, 15.1; LRMS-ES [M+H]⁺ calcd for C₃₀H₃₂N₃O₅ 514.2; found, 514.2.

**Boc-Protection of Aniline 340.** To a stirred solution of aniline 340 (45 mg, 0.088 mmol) in THF (4.0 mL) and H₂O (2.0 mL) were added K₂CO₃ (182 mg, 1.317 mmol) and (Boc)₂O (192 mg, 0.880 mmol). The reaction mixture was stirred at 60 °C for 12 h and diluted with EtOAc (120 mL). The organic layer was washed with saturated aqueous NaHCO₃ (40 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the N-Boc aniline 350 (49 mg,
91%). $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) $\delta$ 8.06 (d, $J = 8.3$ Hz, 1H), 7.47 (br s, 1H), 7.35 (s, 1H), 7.09-7.06 (m, 1H), 6.98-6.83 (m, 4H), 6.72-6.69 (m, 3H), 6.49 (t, $J =$ 8.1 Hz, 1H), 6.18 (d, $J = 7.7$ Hz, 1H), 5.08, 4.98 (ABq, $J = 11.1$ Hz, 2H), 4.09 (ddd, $J =$ 3.5, 12.9 12.9 Hz, 1H), 3.98-3.91 (m, 3H), 3.42 (s, 3H), 2.64 (s, 3H), 2.28 (m, 1H), 1.83 (ddd, $J =$ 3.9, 3.9, 14.1 Hz, 1H), 1.46 (s, 9H), .095 (t, $J =$ 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, toluene-$d_8$, 90 °C) $\delta$ 178.8, 155.4, 153.6, 153.4, 153.1, 144.4, 138.6, 134.5, 131.4, 130.7, 129.6, 128.7, 128.3, 128.0, 124.1, 122.1, 121.7, 116.7, 115.5, 111.7, 107.9, 79.4, 68.1, 62.1, 55.4, 51.2, 38.8, 31.7, 28.5, 25.9, 14.3; LRMS-ES [M+H]$^+$ calcd for C$_{35}$H$_{40}$N$_3$O$_7$, 614.3; found, 614.3.

[1-Benzyl-5-(2-nitrophenyl)-1,2,3,6-tetrahydro pyridine-4-carbonyl]-[2-iodo-3-(4-methoxyphenoxy)methyl] phenyl]carbamic Acid tert-Butyl Ester (355). To a stirred solution of amide 335 (194 mg, 0.287 mmol) in CH$_2$Cl$_2$ (20 mL) were added DMAP (11 mg, 0.090 mmol) and (Boc)$_2$O (81 mg, 0.371 mmol). The reaction mixture was stirred at rt overnight and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the N-Boc amide 355 (196 mg, 88%). $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) $\delta$ 7.65 (dd, $J = 1.1$, 8.2 Hz, 1H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.30 (dd, $J = 1.4$, 7.6 Hz, 1H), 7.22-7.15 (m, 3H), 7.09-7.04 (m, 2H), 6.91-6.85 (m, 2H), 6.74-6.71 (m, 2H), 6.65-6.61 (m, 2H), 6.30 (d, $J = 7.6$ Hz, 1H), 4.82, 4.73 (ABq, $J = 13.1$ Hz, 2H), 3.66 (s, 2H), 3.47-3.33 (m, 5H), 2.87 (m, 2H), 2.71-2.67 (m, 1H), 2.64-2.60 (m, 1H), 1.30 (s, 9H); $^{13}$C NMR (75 MHz, toluene-$d_8$,}
90 °C) δ 169.6, 155.2, 153.2, 151.1, 149.8, 142.2, 142.0, 139.4, 137.5, 135.1, 132.8, 132.3, 129.1, 128.7, 128.5, 128.3, 127.8, 127.2, 124.4, 116.6, 115.3, 103.1, 83.2, 75.7, 61.4, 56.9, 55.4, 48.8, 27.9, 26.7.

4-{tert-Butoxycarbonyl-[2-iodo-3-(4-methoxyphenoxy)methyl]-phenyl-aminocarbonyl}-5-(2-nitrophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic Acid

Ethyl Ester (356). To a stirred solution of N-Boc amide 355 (108 mg, 0.140 mmol) in CH₂Cl₂ (5.0 mL) was added ClCO₂Et (0.04 mL, 0.418 mmol) dropwise at 0 °C and the temperature was gradually raised to rt. After 3 h the reaction mixture was diluted with saturated aqueous NaHCO₃ (10 mL) and CH₂Cl₂ (40 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the carbamate protected amide 356 (104 mg, 99%). ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.67 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 7.1 Hz, 1H), 7.05 (m, 1H), 6.96-6.84 (m, 2H), 6.73-6.62 (m, 4H), 6.27 (d, J = 7.1 Hz, 1H), 4.81, 4.72 (ABq, J = 13.2 Hz, 2H), 4.36 (s, 2H), 4.1 (q, J = 7.1 Hz, 2H), 3.79 (m, 2H), 3.39 (s, 3H), 2.68-2.49 (m, 2H), 1.24 (s, 9H), 1.12 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, toluene-d₈, 90 °C) δ 169.0, 155.4, 155.2, 153.2, 151.0, 149.8, 142.1, 141.8, 134.0, 133.3, 132.4, 132.2, 131.7, 128.6, 128.1, 127.9, 124.5, 116.6, 115.3, 103.0, 83.4, 75.6, 61.3, 55.4, 47.9, 40.5, 27.8, 27.0, 14.7.
2-Methoxy-6H-benzo[c]chromen-10-ylamine (358). To a solution of carbamate protected amide 356 (14.2 mg, 0.019 mmol) in DMA (0.6 mL) were added Pd(OAc)$_2$ (0.8 mg, 0.004 mmol), PPh$_3$ (3.0 mg, 0.011 mmol), n-Bu$_4$NBr (12.2 mg, 0.038 mmol) and K$_2$CO$_3$ (5.2 mg, 0.038 mmol). The mixture was stirred at 120 °C for 5 h. The catalyst was removed by filtration and washed with EtOAc (30 mL). The filtrate was washed with water (3×10 mL) and saturated aqueous NaHCO$_3$ (10 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by preparative TLC (1:2 EtOAc:hexanes) to give tricyclic compound 358 (1.9 mg, 44%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, $J$ = 2.8 Hz, 1H), 7.10 (t, $J$ = 7.7 Hz, 1H), 7.02 (d, $J$ = 8.8 Hz, 1H), 6.78 (dd, $J$ = 2.8, 8.7 Hz, 1H), 6.75 (d, $J$ = 8.1 Hz, 1H), 6.65 (d, $J$ = 7.3 Hz, 1H), 4.89 (s, 2H), 4.09 (br s, 2H), 3.83 (s, 3H).

1-Benzyl-5-(2-nitrophenyl)-1,2,3,6-tetrahydropyridine-4-carboxylic Acid [2-Iodo-3-(4-methoxyphenoxy)methyl]-phenyl)-(2-trimethylsilanylethoxymethyl)-amide (359). To a stirred solution of amide 335 (19.8 mg, 0.029 mmol) in THF (1.0 mL) was added LHMDS (0.035 mL, 1.0 M in THF, 0.035 mmol) at - 78 °C. The reaction mixture was stirred at this temperature for 15 min, and SEMCl (0.02 mL, 0.113 mmol) was added dropwise. The mixture was allowed to gradually warm to rt. After 15 min the mixture was diluted with EtOAc (25 mL) and saturated aqueous NH$_4$Cl (5 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified
by flash column chromatography (1:1 EtOAc:hexanes) to give the N-SEM amide (8.8 mg, 37%) \(^1\)H NMR (300 MHz, toluene-\(d_8\), 90 °C) \(\delta\) 7.72 (d, \(J = 8.1\) Hz, 1H), 7.39 (d, \(J = 7.9\) Hz, 1H), 7.28 (m, 3H), 7.14 (t, \(J = 7.3\) Hz, 2H), 7.06-6.96 (m, 4H), 6.82 (t, \(J = 7.2\) Hz, 1H), 6.76 (d, \(J = 9.1\) Hz, 2H), 6.65 (d, \(J = 9.1\) Hz, 2H), 5.48 (d, \(J = 9.4\) Hz, 1H), 4.80 (s, 2H), 4.50 (d, \(J = 10.0\) Hz, 1H), 3.47 (s, 2H), 3.38 (s, 3H), 3.37-3.15 (m, 2H), 2.78-2.45 (m, 4H), 0.77 (t, \(J = 7.8\) Hz, 2H), -0.09 (s, 9H); LRMS-ES [M+H]⁺ calcd for C\(_{39}\)H\(_{45}\)I\(_3\)N\(_3\)O\(_6\)Si, 806.2; found, 806.2.

4-[2-Iodo-3-(4-methoxyphenoxymethyl)-phenyl carbamoyl]-5-(2-nitrophenyl)-3,6-dihydro-2\(H\)-pyridine-1-carboxylic Acid Ethyl Ester (360). To a stirred solution of amide (8.5 mg, 0.013 mmol) in CH\(_2\)Cl\(_2\) (1.0 mL) was added ClCO\(_2\)Et (0.01 mL, 0.105 mmol) dropwise at 0 °C and the temperature was gradually raised to rt. After 4 h the reaction mixture was diluted with saturated aqueous NaHCO\(_3\) (5 mL) and CH\(_2\)Cl\(_2\) (10 mL). The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the carbamate protected amide (8.1 mg, 98%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.08 (d, \(J = 8.2\) Hz, 1H), 7.81 (dd, \(J = 2.0, 7.2\) Hz, 1H), 7.69 (s, 1H), 7.63 (t, \(J = 7.5\) Hz, 1H), 7.49 (t, \(J = 7.8\) Hz, 1H), 7.40 (d, \(J = 7.5\) Hz, 1H), 7.25-7.20 (m, 2H), 6.88-6.82 (m, 4H), 4.91 (s, 2H), 4.24-4.19 (m, 4H), 3.95 (m, 1H), 3.77 (s, 3H), 3.75 (m, 1H), 2.80 (m, 1H), 2.66 (m, 1H), 1.28 (m, 3H).
4-[[2-Iodo-3-(4-methoxyphenoxy)methyl]-phenyl]-
(2-trimethylsilanylethoxymethyl)-carbamoyl]-5-(2-
nitrophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic  Acid

**Ethyl Ester (361).** Method A (from 359): To a stirred solution of $N$-SEM amide 359 (8.6 mg, 0.011 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added ClCO$_2$Et (0.01 mL, 0.105 mmol) dropwise at 0 °C and the temperature was gradually raised to rt. After 4 h the reaction mixture was diluted with saturated aqueous NaHCO$_3$ (5 mL) and CH$_2$Cl$_2$ (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the Heck substrate 361 (7.8 mg, 93%).

Method B (from 360): To a stirred solution of amide 360 (8.1 mg, 0.012 mmol) in THF (1.0 mL) was added LHMDS (0.015 mL, 1.0 M in THF, 0.015 mmol) at - 78 °C. The reaction mixture was stirred at this temperature for 15 min, and SEMCl (4.3 μL, 0.024 mmol) was added dropwise. The mixture was allowed to gradually warm to rt. After 20 min the mixture was diluted with EtOAc (20 mL) and saturated aqueous NaHCO$_3$ (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the Heck substrate 361 (7.3 mg, 75%). $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) $\delta$ 7.75 (dd, $J = 1.1$, 8.2 Hz, 1H), 7.31 (d, $J = 7.5$ Hz, 1H), 7.24 (d, $J = 9.2$ Hz, 1H), 7.3-6.82 (m, 4H), 6.77-6.65 (m, 4H), 5.33 (m, 1H), 4.78 (s, 2H), 4.42 (d, $J = 10.2$ Hz, 1H), 4.25-4.02 (m, 4H), 3.60 (br m, 2H), 3.40 (s, 3H), 3.33-3.20 (m, 2H), 2.46 (br s, 2H), 1.07 (t, $J = 7.0$ Hz,
Heck Cyclization of N-SEM Amide 361. To a solution of N-SEM amide 361 (7.8 mg, 9.9 μmol) in DMA (0.4 mL) were added Pd(OAc)$_2$ (0.5 mg, 2.2 μmol), PPh$_3$ (1.6 mg, 6.1 μmol), n-Bu$_4$NBr (6.4 mg, 19.9 μmol) and K$_2$CO$_3$ (2.8 mg, 20.3 mmol). The mixture was stirred at 150 °C for 45 min. The catalyst was removed by filtration and washed with EtOAc (20 mL). The filtrate was washed with saturated aqueous NaHCO$_3$ (5 mL), water (3×5 mL) and brine (5 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by preparative TLC (1:2 EtOAc:hexanes) to give Heck product 362 (4.0 mg, 62%). $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) $\delta$ 7.69 (s, 1H), 7.04-7.01 (m, 1H), 6.90-6.78 (m, 5H), 6.74-6.67 (m, 4H), 6.53 (m, 1H), 5.13 (d, $J = 11.6$ Hz, 1H), 5.00, 4.98 (ABq, $J = 10.7$ Hz, 2H), 4.83 (d, $J = 11.6$ Hz, 1H), 4.12 (ddd, $J = 4.0$, 13.0, 13.0 Hz, 1H), 4.01-3.86 (m, 3H), 3.58 (t, $J = 7.8$ Hz, 2H), 3.39 (s, 3H), 2.43 (ddd, $J = 4.9$, 12.2, 14.0 Hz, 1H), 1.76 (ddd, $J = 3.6$, 3.6, 14.0 Hz, 1H), 0.98 (t, $J = 7.1$ Hz, 3H), 0.88 (ddd, $J = 2.5$, 7.7, 7.7 Hz, 2H), -0.05 (s, 9H); LRMS-ES [M+H]$^+$ calcd for C$_{35}$H$_{42}$N$_3$O$_8$Si, 660.3; found, 660.3.

Preparation of Pentacyclic Aminal 364. To a stirred solution of N-Boc aniline 350 (25.2 mg, 0.041 mmol) in THF (4.0 mL) was added AlH$_3$·Me$_2$NET (0.12 mL, 0.5 M in toluene, 0.060 mmol) dropwise at 0 °C. After 1 h the mixture was quenched with saturated aqueous
Na$_2$SO$_4$ (0.2 mL) and the mixture was stirred for 6 h at rt. The mixture was diluted with EtOAc (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give aminal 364 (19.8 mg, 81%). $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) $\delta$ 7.25 (s, 1H), 7.13 (dd, $J = 1.1$, 7.9 Hz, 1H), 6.84-6.67 (m, 8H), 6.63 (d, $J = 8.0$ Hz, 1H), 6.06 (d, $J = 7.7$ Hz, 1H), 5.89 (s, 1H), 5.04 (d, $J = 11.3$ Hz, 1H), 4.73 (d, $J = 11.3$ Hz, 1H), 4.02-3.95 (m, 3H), 3.43 (s, 3H), 3.19 (dd, $J = 3.3$, 11.1, 13.0 Hz, 1H), 2.93 (s, 3H), 2.27 (ddd, $J = 3.8$, 10.6, 14.4 Hz, 1H), 2.04 (m, 1H), 1.33 (s, 9H), 0.98 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, toluene-$d_8$, 90 °C) $\delta$ 154.9, 154.5, 154.1, 153.2, 151.7, 139.2, 133.9, 133.4, 130.5, 128.8, 126.6, 126.4, 125.4, 125.2, 124.3, 119.4, 116.6, 116.3, 115.4, 105.3, 85.9, 80.7, 67.4, 61.9, 55.4, 52.0, 40.3, 35.0, 30.7, 28.2, 14.3; LRMS-ES [M+H]$^+$ calcd for C$_{35}$H$_{40}$N$_3$O$_6$, 598.3; found, 598.3.

**Preparation of Indoline 365.** To a stirred solution of N-Boc aniline 350 (6.9 mg, 0.011 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added DIBALH (0.03 mL, 1.0 M in CH$_2$Cl$_2$, 0.03 mmol) dropwise at 0 °C. The mixture was stirred at the same temperature for 1 h and then quenched with saturated aqueous Na$_2$SO$_4$ (0.1 mL). The resulting suspension was stirred at rt overnight and diluted with CH$_2$Cl$_2$ (10 mL). The organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by preparative TLC (1:3 EtOAc:hexanes) to give the aminal 364 (2.2 mg, 33%), indoline 365 (1.2 mg, 18%) and unreacted N-Boc aniline 350 (2.5 mg, 36%). $^1$H NMR of indoline 365 (300 MHz,
toluene-$d_8$, 90 °C) δ 8.05 (d, $J = 8.2$ Hz, 1H), 7.17 (s, 1H), 7.04-6.92 (m, 5H), 6.83-6.78 (m, 2H), 6.69-6.61 (m, 3H), 6.22 (d, $J = 7.8$ Hz, 1H), 5.10, 5.02 (ABq, $J = 10.5$ Hz, 2H), 3.93 (q, $J = 6.9$ Hz, 2H), 3.69 (m, 1H), 3.57 (m, 1H), 3.39 (s, 3H), 3.16 (d, $J = 8.7$ Hz, 1H), 2.81 (d, $J = 8.7$ Hz 1H), 2.33 (s 3H), 2.23 (ddd, $J = 4.2$, 6.5, 13.6 Hz, 1H), 1.73 (ddd, $J = 4.4$, 9.4, 13.7 Hz, 1H), 1.39 (s, 9H), 0.95 (t, $J = 7.1$ Hz, 3H); LRMS-ES [M+H]$^+$ calcd for C$_{35}$H$_{42}$N$_3$O$_6$, 600.3; found, 600.3.

**Synthesis of Enamine 369.** To a solution of aminal 364 (9.7 mg, 0.016 mmol) in EtOH (1.0 mL) was added 1 N aqueous NaOH (1.0 mL). The mixture was refluxed for 2 h, then cooled to rt and diluted with EtOAc (30 mL) and saturated aqueous NaHCO$_3$ (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was used for the next step without further purification. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.13 (s, 1H), 6.99-6.84 (m, 8H), 6.69 (s, 1H), 6.62 (d, $J = 7.7$ Hz, 1H), 6.20 (d, $J = 7.7$ Hz, 1H), 5.76 (br s, 1H), 5.14 (d, $J = 9.0$ Hz, 1H), 4.91 (d $J = 9.0$ Hz, 1H), 3.80 (s, 3H), 3.66 (br s, 1H), 3.31 (m, 1H), 3.21 (m, 1H), 2.96 (s, 3H), 2.30 (m, 2H), 1.50 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.1, 153.8, 151.5, 138.3, 135.1, 133.1, 132.2, 131.5, 128.5, 126.5, 125.5, 125.3, 123.9, 117.7, 116.1, 115.0, 107.7, 104.8, 87.4, 81.3, 66.6, 56.1, 51.0, 40.2, 35.7, 31.0, 28.7; LRMS-ES [M+H]$^+$ calcd for C$_{32}$H$_{36}$N$_3$O$_4$, 526.3; found, 526.2.

**Allylation of Aminal 364.** To a stirred solution of aminal 64 (42.8 mg, 0.072 mmol) in THF (3.0 mL) was added $n$-BuLi (0.11 mL, 2.0 M in hexanes, 0.220 mmol)
dropwise at -78 °C. After stirring the mixture for 10 min at the same temperature, allyl iodide (0.21 mL, 1.0 M in THF, 0.210 mmol) was added. The mixture was slowly warmed to rt. After 15 min the mixture was diluted with saturated aqueous NaHCO₃ (10 mL) and EtOAc (50 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the C-allyl product 371 (31.8 mg, 79%) and N-allyl enamine 372 (4.5 mg, 11%).

**C- Allyl Product 371:** ¹H NMR (400 MHz, CD₂Cl₂) δ 8.81 (s, 1H), 7.35 (dd, J = 1.1, 7.6 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.08 (ddd, J = 1.2, 7.4, 7.4 Hz, 1H), 7.00 (i, J = 7.8 Hz, 1H), 6.97 (ddd, J = 1.3, 7.5, 7.5 Hz, 1H), 6.86-6.82 (m, 2H), 6.71-6.68 (m, 2H), 6.64 (d, J = 7.7 Hz, 1H), 6.37 (d, J = 7.5 Hz, 1H), 5.70 (m, 1H), 5.05 (d, J = 10.0 Hz, 1H), 4.97 (d, J = 16.9 Hz, 1H), 4.67 (d, J = 12.4 Hz, 1H), 4.43 (d, J = 12.4 Hz, 1H), 4.03 (m, 1H), 3.80 (s, 3H), 3.63 (m, 1H), 3.05 (s, 3H), 2.78 (dd, J = 8.3, 13.2 Hz, 1H), 2.68 (dd, J = 6.6, 13.2 Hz, 1H), 2.46 (ddd, J = 6.0, 13.0, 13.0 Hz, 1H), 1.89 (m, 1H), 1.50 (s, 9H); ¹³C NMR (100 MHz, CD₂Cl₂) δ 165.0, 154.7, 154.2, 153.3, 151.4, 140.3, 133.6, 133.4, 133.2, 133.0, 129.6, 128.5, 127.9, 126.3, 124.2, 123.0, 119.1, 118.4, 115.8, 114.9, 106.7, 83.9, 81.8, 69.1, 56.0, 55.1, 47.6, 43.0, 41.7, 31.9, 29.1, 28.3; LRMS-ES [M+H]⁺ calcd for C₃5H₄₀N₃O₄, 566.3; found, 566.2.

**N-Allyl Product 372:** ¹H NMR (400 MHz, CDCl₃) δ 7.13 (br s, 1H), 7.01-6.98 (m, 1H), 6.94-6.90 (m, 3H), 6.86-6.83 (m, 4H), 6.59 (d, J = 7.6 Hz, 1H), 6.47 (s, 1H), 6.20 (d, J = 7.8 Hz, 1H), 5.77 (m, 1H), 5.22-5.10 (m, 3H), 4.86 (d, J = 11.9 Hz, 1H), 3.80 (s, 3H), 3.52 (m,
2H), 3.12 (m, 1H), 2.96 (s, 3H), 2.90 (m, 1H), 2.34-2.28 (m, 2H), 1.49 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.2, 153.7, 151.5, 138.3, 135.7, 135.2, 134.9, 133.0, 131.7, 128.6, 126.6, 125.6, 125.3, 123.8, 118.3, 118.0, 116.1, 115.0, 107.4, 104.9, 87.5, 81.4, 66.6, 58.7, 56.2, 50.7, 45.8, 35.6, 31.0, 28.7; LRMS-ES [M+H]$^+$ calcd for C$_{35}$H$_{40}$N$_3$O$_4$, 566.3; found, 566.2.

**Alkylation of Aminal 364 with Ethyl Iodoacetate.** To a stirred solution of aminal 364 (5.9 mg, 0.010 mmol) in THF (1.0 mL) and HMPA (0.1 mL) was added $n$-BuLi (0.025 mL, 1.6 M in hexanes, 0.040 mmol) dropwise at -78 °C. After stirring the mixture at the same temperature for 15 min, ethyl iodoacetate (0.03 mL, 1.0 M in THF, 0.030 mmol) was added, and the mixture was slowly warmed to rt. After 15 min, the mixture was diluted with saturated aqueous NaHCO$_3$ (5 mL) and EtOAc (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC (1:2 EtOAc:hexanes, 3 elutions) to give the alkylated product 373 (0.6 mg, 10%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.23 (s, 1H), 7.44 (d, $J = 7.8$ Hz, 1H), 7.10 (d, $J = 8.2$ Hz, 1H), 7.03-6.96 (m, 2H), 6.90 (t, $J = 7.5$ Hz, 1H), 6.81-6.77 (m, 2H), 6.69-6.65 (m, 3H), 6.32 (d, $J = 7.7$ Hz, 1H), 5.55 (s, 1H), 4.68 (d, $J = 12.7$ Hz, 1H), 4.46 (d, $J = 12.7$ Hz, 1H), 4.08 (dd, $J = 5.8$, 19.6 Hz, 1H), 3.98-3.88 (m, 2H), 3.79 (s, 3H), 3.67-3.60 (m, 1H), 3.01 (s, 3H), 2.97 (s, 2H), 2.27 (ddd, $J = 6.6$, 13.4, 13.4 Hz, 1H), 1.96 (dd, $J = 7.6$, 11.6 Hz, 1H), 1.48 (s, 9H), 1.00 (t, $J = 7.1$ Hz, 3H); LRMS-ES [M+H]$^+$ calcd for C$_{36}$H$_{42}$N$_3$O$_6$, 612.3; found, 612.3.
**Formation of Aldehyde 378.** To a stirred solution of imine 371 (6.9 mg, 0.012 mmol) in EtOH (1.0 mL) was added diethyl pyrocarbonate (2.2 μL, 0.015 mmol) at rt. After 15 min the solvent was removed under reduced pressure. The residue was dissolved in toluene (1.0 mL) and PTSA (1.0 mg) was added. The mixture was stirred at rt for 30 min and then diluted with saturated aqueous NaHCO₃ (5 mL) and EtOAc (10 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by preparative TLC (1:3 EtOAc:hexanes) to give the rearranged aldehyde 378 (5.5 mg, 85%). ¹H NMR (400 MHz, CDCl₃) δ 10.37 (s, 1H), 7.05-6.92 (m, 4H), 6.76 (br s, 1H), 6.56 (d, J = 7.6 Hz, 1H), 6.49 (d, J = 7.8 Hz, 1H), 5.63 (s, 1H), 5.27 (br s, 1H), 4.96-4.90 (m, 2H), 4.76-4.59 (m, 1H), 4.39-4.18 (m, 3H), 3.49 (m, 1H), 3.08 (m, 1H), 3.02 (s, 3H), 2.69 (m, 1H), 2.43 (m, 1H), 2.32 (ddd, J = 5.0, 13.5, 13.5 Hz, 1H), 1.82 (m, 1H), 1.45 (s, 9H), 1.33 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 196.5, 156.7, 154.8, 152.0 138.8, 136.9, 135.2, 133.9, 130.3, 129.0, 127.5, 126.7, 125.1, 123.4, 119.4, 118.2, 110.8, 84.3, 82.0, 62.3, 59.6, 45.4, 41.5, 39.8, 35.4, 32.4, 31.9, 28.6, 15.1; LRMS-ES [M+H]⁺ calcd for C₃₁H₃₈N₃O₅, 532.3; found, 532.2.

1-Benzyl-5-(2-nitrophenyl)-1,2,3,6-tetrahydropyridine-4-carboxylic Acid [3-(tert-Butyldimethyl silanyloxymethyl)-2-iodophenyl]-amide (384). A mixture of the acid 334 (3.72 g, 11.0 mmol) and SOCl₂ (16 mL) was refluxed for 3 h. Excess SOCl₂
was removed under reduced pressure and the residue was diluted with CH$_2$Cl$_2$ (20 mL) to give a stock solution of acid chloride (0.55 M). To a stirred solution of the aniline 246 (2.54 g, 7.0 mmol) and (i-Pr)$_2$NEt (4.9 mL, 28.1 mmol) in CH$_2$Cl$_2$ (50 mL) was added the above solution of the acid chloride (16.5 mL, 0.55 M in CH$_2$Cl$_2$, 9.1 mmol) dropwise at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The mixture was diluted with CH$_2$Cl$_2$ (100 mL) and saturated aqueous NaHCO$_3$ (50 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1:2 EtOAc:CH$_2$Cl$_2$:hexanes) to give amide 384 (3.24 g, 68%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.00 (d, $J = 8.1$ Hz, 1H), 7.79 (d, $J = 6.9$ Hz, 1H), 7.71 (s, 1H), 7.55 (t, $J = 7.5$ Hz, 1H), 7.43-7.33 (m, 6H), 7.29-7.20 (m, 3H), 4.53 (s, 2H), 3.71 (d, $J = 6.2$ Hz, 2H), 3.27, 3.07 (ABq, $J = 16.5$ Hz, 2H), 2.93-2.70 (m, 4H), .095 (s, 9H), 0.11 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 167.0, 148.3, 144.0, 138.2, 138.1, 137.9, 135.6, 134.3, 131.5, 130.4, 129.4, 129.3, 129.0, 128.8, 127.7, 125.2, 124.1, 121.4, 92.4, 70.5, 61.9, 57.3, 49.2, 26.9, 26.3, 18.8, -4.9.

4-[3-(tert-Butyldimethylsilanyloxyethyl)-2-iodophenylcarbamoyl]-5-(2-nitrophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic Acid Ethyl Ester (385). To a stirred solution of amide 384 (503 mg, 0.735 mmol) in CH$_2$Cl$_2$ (10 mL) was added ClCO$_2$Et (0.084 mL, 0.879 mmol) dropwise at 0 °C and then the temperature was gradually raised to rt. The mixture was stirred at rt overnight and diluted with saturated aqueous NaHCO$_3$ (30 mL) and CH$_2$Cl$_2$ (80 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated
in vacuo. The residue was purified by flash column chromatography (1:2:2 EtOAc:CH₂Cl₂:hexanes) to give the carbamate protected amide 385 (464 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, J = 8.1 Hz, 1H), 7.76 (dd, J = 2.9, 6.5 Hz, 1H), 7.63-7.69 (m, 2H), 7.47 (t, J = 7.7 Hz, 1H), 7.39 (d, J = 7.1 Hz, 1H), 7.25-7.20 (m, 2H), 4.52 (d, 2H), 4.24-3.72 (m, 6H), 2.79 (m, 1H), 2.65 (m, 1H), 1.30 (br m, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 166.4, 155.6, 148.4, 144.1, 137.7, 137.0, 134.5, 134.4, 131.5, 130.8, 129.8, 129.0, 125.3, 124.4, 121.7, 92.8, 70.5, 62.1, 47.8, 40.3, 26.9, 26.4, 18.8, 15.1.

4-[[3-(tert-Butyldimethylsilanyloxymethyl)-2-iodophenyl]-methylcarbamoyl]-5-(2-nitrophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic Acid Ethyl Ester (386).

To a stirred suspension of NaH (183 mg, 60% dispersion in mineral oil, 4.57 mmol) in THF (50 mL) was added a solution of amide 385 (2.76 g, 4.15 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and at rt for 30 min. To the solution was added MeI (0.31 mL, 4.98 mmol) at 0 °C and the mixture was stirred at rt overnight. The reaction mixture was diluted with saturated aqueous NaHCO₃ (50 mL) and extracted with EtOAc (150 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the N-methyl amide 386 (2.46 g, 87%). ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.84 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.20-7.09 (m, 2H), 7.00 (t, 7.8 Hz, 1H), 6.65 (br s, 1H), 4.72 (s, 2H), 4.26-4.17 (m, 4H), 3.64 (br s, 2H), 2.98
(s, 3H), 2.44 (br m, 2H), 1.19 (m, 3H), 1.06 (s, 9H), 0.18 (s, 6H); $^{13}$C NMR (75 MHz, toluene-$d_8$, 90 °C) δ 168.5, 155.3, 149.4, 146.1, 146.0, 134.3, 133.0, 131.9, 129.3, 128.9, 127.6, 127.1, 124.9, 101.1, 70.7, 61.4, 47.9, 40.5, 37.6, 27.5, 26.2, 18.7, 14.9, -5.10, -5.13.

**Heck Cyclization of Amide 386.** To a solution of $N$-methyl amide 386 (199 mg, 0.293 mmol) in DMA (4.0 mL) were added Pd(OAc)$_2$ (6.6 mg, 0.029 mmol), PPh$_3$ (23 mg, 0.088 mmol), $n$-Bu$_4$NBr (189 mg, 0.586 mmol) and K$_2$CO$_3$ (81 mg, 0.586 mmol). The mixture was stirred at 150 °C for 30 min. The catalyst was removed by filtration and washed with EtOAc (200 mL). The filtrate was washed with water (4×30 mL) and brine (30 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the Heck product 387 (142 mg, 88%). $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) δ 7.79 (s, 1H), 7.19-7.06 (m, 3H), 6.91 (d, $J = 7.9$ Hz, 1H), 6.76 (t, $J = 7.6$ Hz, 1H), 6.61 (t, $J = 7.7$ Hz, 1H), 6.37 (d, $J = 7.6$ Hz, 1H), 4.98, 4.71 (ABq, $J = 12.5$ Hz, 2H), 4.32 (ddd, $J = 3.8$, 12.9, 12.9 Hz, 1H), 4.22-4.06 (m, 3H), 2.95 (s, 3H), 2.64 (ddd, $J = 4.9$, 13.9, 13.9 Hz, 1H), 1.79 (ddd, $J = 3.5$, 3.5, 14.1 Hz, 1H), 1.17 (t, $J = 7.1$ Hz, 3H), 1.06 (s, 9H), 0.26 (s, 3H), 0.21 (s, 3H); $^{13}$C NMR (75 MHz, toluene-$d_8$, 90 °C) δ 177.9, 153.3, 150.8, 144.1, 139.0, 137.7, 132.5, 131.4, 130.5, 129.0, 128.2, 127.1, 124.2, 123.7, 109.1, 107.1, 62.5, 62.0, 50.2, 38.5, 31.3, 26.33, 26.28, 18.7, 14.5, -5.0, -5.1.
Preparation of Aniline 388. To a solution of Heck product 387 (1.29 g, 2.33 mmol) in THF (60 mL) was added 10% Pd/C (500 mg). The mixture was stirred at rt under a H₂ atmosphere (1 atm) for 9 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give aniline 388 (1.16 g, 95%). ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.47 (s, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.00-6.97 (m, 1H), 6.68 (ddd, J = 1.6, 8.0, 8.0 Hz, 1H), 6.60 (dd, J = 1.5, 7.7 Hz, 1H), 6.27 (ddd, J = 1.2, 7.6, 7.6 Hz, 1H), 6.22-6.16 (m, 2H), 4.90, 4.85 (ABq, J = 12.2 Hz, 2H), 4.22-3.98 (m, 4H), 3.51 (br s, 2H), 2.68 (s, 3H), 2.36 (ddd, J = 5.1, 11.3, 14.0 Hz, 1H), 1.80 (ddd, J = 3.7, 3.7, 14.1 Hz, 1H), 1.02 (t, J = 7.1 Hz, 3H), 0.96 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ¹³C NMR (75 MHz, toluene-d₈, 90 °C) δ 179.5, 153.5, 146.8, 144.3, 138.4, 131.3, 131.1, 129.1, 128.7, 128.6, 123.7, 123.1, 117.5, 116.1, 112.7 107.3, 62.2, 62.0, 51.1, 38.9, 32.1, 26.3, 26.2, 18.7, 14.6, -5.0; LRMS-ES [M+H]⁺ calcd for C₂₉H₄₀N₃O₄Si, 522.3; found, 522.2.

Preparation of N-Boc Aniline 389. To a stirred solution of aniline 388 (1.16 g, 2.22 mmol) in THF (50 mL) and H₂O (25 mL) were added K₂CO₃ (4.61 g, 33.36 mmol) and (Boc)₂O (4.85 g, 22.22 mmol). The reaction mixture was stirred at 60 °C for 20 h and diluted with EtOAc (200 mL). The organic layer was washed with brine (20 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the N-Boc aniline 389 (1.22 g, 89%). ¹H NMR (300 MHz,
toluene-$d_8$, 90 °C) δ 8.06 (dd, $J = 1.1$, 8.3 Hz, 1H), 7.52 (br s, 1H), 7.35 (s, 1H), 7.17 (d, $J = 7.9$ Hz, 1H), 6.98 (t, $J = 7.8$ Hz, 1H), 6.87 (m, 1H), 6.66 (dd, $J = 1.6$, 7.8 Hz, 1H), 6.48 (ddd, $J = 1.2$, 7.7, 7.7 Hz, 1H), 6.14 (d, $J = 7.7$ Hz, 1H), 4.87 (s, 2H), 4.16-3.87 (m, 4H), 2.61 (s, 3H), 2.27 (ddd, $J = 4.5$, 9.7, 15.7 Hz, 1H), 1.84 (ddd, $J = 4.0$, 4.0, 14.2 Hz, 1H), 1.49 (s, 9H), 1.01 (t, $J = 7.1$ Hz, 3H), 0.95 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); $^{13}$C NMR (75 MHz, toluene-$d_8$, 90 °C) δ 179.2, 153.7, 153.4, 144.3, 138.9, 138.4 131.7, 131.0, 128.6, 128.2, 123.4, 122.2, 122.1, 111.6, 107.5, 79.5, 62.3, 61.8, 51.3, 39.1, 32.2, 28.7, 26.3 26.1, 18.7, 14.6, -5.0, -5.1.

**Synthesis of Penatacyclic Aminal 390.** To a stirred solution of $N$-Boc aniline 389 (124 mg, 0.199 mmol) in THF (10 mL) was added AlH$_3$·Me$_2$NEt (0.60 mL, 0.5 M in toluene, 0.300 mmol) dropwise at 0 °C. After 1 h the mixture was quenched with saturated aqueous Na$_2$SO$_4$ (0.6 mL) and then stirred at rt overnight. The mixture was diluted with EtOAc (50 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give aminal 390 (101 mg, 83%) and unreacted $N$-Boc aniline 389 (10 mg, 8%). $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) δ 7.27 (s, 1H), 7.12 (dd, $J = 1.3$, 7.8 Hz, 1H), 7.00 (dd, $J = 1.7$, 7.4 Hz, 1H), 6.81 (t, $J = 7.7$ Hz, 1H), 6.77 (ddd, $J = 1.7$, 7.6, 7.6 Hz, 1H), 6.72-6.68 (m, 2H), 6.02 (d, $J = 7.7$ Hz, 1H), 5.88 (s, 1H), 4.84, 4.56 (ABq, $J = 12.7$ Hz, 2H), 4.13-4.01 (m, 3H), 3.22 (ddd, $J = 3.4$, 11.1, 13.1 Hz, 1H), 2.92 (s, 3H), 2.24 (ddd, $J = 3.8$, 10.7, 14.5 Hz, 1H), 2.01 (ddd, $J = 3.4$, 5.0 14.3 Hz, 1H), 1.34 (s, 9H), 1.10 (t, $J = 7.1$ Hz, 3H), 0.96 (s, 9H), 0.12 (s, 3H), 0.10 (s,
Allylation of Aminal 390. To a stirred solution of aminal 390 (81 mg, 0.134 mmol) in THF (5.0 mL) was added \( n \)-BuLi (0.26 mL, 1.6 M in hexanes, 0.416 mmol) dropwise at -78 °C. After stirring the mixture for 10 min at the same temperature, allyl iodide (0.043 ml, 0.470 mmol) was added. The mixture was warmed gradually to rt gradually. After 15 min at rt, the mixture was diluted with saturated aqueous NaHCO₃ (10 mL) and EtOAc (30 mL). The organic layer was dried over Na₂SO₄ and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:10 to 1:3 EtOAc:hexanes) to give the C-allyl product 391 (61 mg, 80%) and \( N \)-allyl enamine 392 (7 mg, 9%).

\textbf{C-allyl product 391}: \(^1\)H NMR (400 MHz, CDCl₃) \( \delta 8.75 \) (s, 1H), 7.32 (d, \( J = 8.3 \) Hz, 1H), 7.06-6.94 (m, 4H), 6.74 (d, \( J = 7.8 \) Hz, 1H), 6.27 (d, \( J = 7.7 \) Hz, 1H), 5.64 (m, 1H), 5.51 (s, 1H), 5.0 (d, \( J = 10.0 \) Hz, 1H), 4.94 (d, \( J = 16.9 \) Hz, 1H), 4.34 (d, \( J = 13.8 \) Hz, 1H), 4.09-4.00 (m, 2H), 3.55 (m, 1H), 2.99 (s, 3H), 2.70 (dd, \( J = 8.5, 13.1 \) Hz, 1H), 2.62 (dd, \( J = 6.5, 13.1 \) Hz, 1H), 2.38 (ddd, \( J = 4.7, 9.8, 9.8 \) Hz, 1H), 1.87 (dd, \( J = 5.8, 13.7 \) Hz, 1H), 1.46 (s, 9H), 0.93 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta 165.5, 154.9, 150.9, 140.1, 137.8, 133.0, 132.7, 128.4, 128.3, 127.8, 126.6, 124.0, 122.8, 119.5, 117.1, 106.2, 84.1, 81.8, 63.7, 54.8, 47.7, 43.1, 41.9, 32.1, 29.0, 28.6, 26.4, 18.8, -4.77, -4.82.
**N- Allyl Product 392.** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.11 (br s, 1H), 7.05-6.87 (m, 4H), 6.65 (d, $J$ = 7.7 Hz, 1H), 6.47 (s, 1H), 6.14 (d, $J$ = 7.7 Hz, 1H), 5.91 (m, 1H), 5.67 (br s, 1H), 5.28 (dd, $J$ = 1.2, 17.1 Hz, 1H), 5.22 (d, $J$ = 10.1 Hz, 1H), 4.84, 4.57 (ABq, $J$ = 13.8 Hz, 2H), 3.60 (d, $J$ = 6.1 Hz, 2H), 3.15 (ddd, $J$ = 3.9, 3.9, 11.2 Hz, 1H), 2.93 (s, 3H), 2.90 (m, 1H), 2.25 (m, 2H), 1.50 (s, 9H), 0.97 (s, 9H), 0.12 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.9, 151.1, 138.5, 137.1, 135.5, 135.3, 135.1, 130.1, 128.2, 126.5, 125.2, 123.4, 118.3, 116.2, 108.1, 104.1, 87.6, 81.3, 60.9, 58.9, 50.5, 46.2, 34.9, 31.1, 28.8, 26.5, 19.0, -4.8.

**Formation of N,O-Acetal 394.** To a stirred solution of imine 391 (28.9 mg, 0.050 mmol) in EtOH (3.0 mL) was added diethyl pyrocarbonate (8.9 µL, 0.060 mmol) at rt. After 10 min the solvent was removed under reduced pressure. The crude residue was used for the next step without further purification due to the instability of the compound on column chromatography. For analytical purposes the two diastereomers of N,O-acetal 394 were isolated by preparative TLC (1:5 EtOAc:hexanes). More polar major diastereomer of 394: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.11–6.94 (m, 6H), 6.35 (d, $J$ = 7.4 Hz, 1H), 5.61 (s, 1H), 5.44 (d, $J$ = 7.0 Hz, 1H), 5.48-5.31 (m, 1H), 4.94 (m, 1H), 4.83 (d, $J$ = 19.1 Hz, 1H), 4.71 (d, $J$ = 12.4 Hz, 0.5H), 4.56 (d, $J$ = 13.5 Hz, 0.5H), 4.25 (q, $J$ = 7.2 Hz, 2H), 3.95 (d, $J$ = 15.8 Hz, 0.5H), 3.83 (d, $J$ = 13.0 Hz, 0.5H), 3.71 (d, $J$ = 12.9 Hz, 0.5H) 3.61-3.36 (m, 3.5H), 3.05 (s, 3H), 2.76 (m, 1H), 2.40–2.14 (m, 2H), 1.66 (m, 1H), 1.45 (s, 9H), 0.86 (s, 9H), 0.07 (d, $J$ = 3.8 Hz, 3H), -0.56 (d, $J$ = 19.2 Hz, 3H); LRMS-ES [M+H]$^+$ calcd for
C₃₉H₅₈N₃O₆Si, 692.4; found, 692.4. Less polar minor diastereomer of 203: ¹H NMR (400 MHz, CDCl₃) δ 7.05–6.93 (m, 6H), 6.30 (dd, J = 3.2, 5.8 Hz, 1H), 5.82 (d, J = 4.9 Hz, 1H), 5.53 (d, J = 8.7 Hz, 1H), 5.37-5.24 (m, 1H), 4.95-4.85 (m, 2H), 4.69 (d, J = 21.3 Hz, 0.5H), 4.54 (d, J = 13.7 Hz, 0.5H), 4.28-3.95 (m, 4H), 3.36-3.21 (m, 1H) 3.01 (s, 3H), 2.80-2.70 (m, 2H), 2.54-2.35 (m, 2H), 2.27 (ddd, J = 4.9, 13.1, 13.1 Hz, 1H), 1.73 (t, J = 11.7 Hz, 1H), 1.45 (s, 9H), 1.32 (ddd, J = 6.9, 6.9, 13.9 Hz, 3H), 0.98 (t, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.11 (d, J = 4.7 Hz, 3H), 0.06 (d, J = 3.5 Hz, 3H); LRMS-ES [M+H]⁺ calcd for C₃₉H₅₈N₃O₆Si, 692.4; found, 692.4.

Synthesis of Hydroxy N,O-Acetal 395. To a solution of the above crude N,O-acetal 394 in dioxane (2.0 mL) and H₂O (1.0 mL) was added NMO (59 mg, 0.504 mmol) at 0 °C, followed by OsO₄ (0.01 mL, 4 wt% in H₂O). The mixture was gradually warmed to rt. The mixture was stirred at rt for 6 h and then diluted with saturated aqueous NaHCO₃ (10 mL) and EtOAc (20 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude residue was dissolved in THF (2.0 mL) and H₂O (1.0 mL), and NaIO₄ (108 mg, 0.505 mmol) was added. The mixture was stirred at rt for 2 h and then diluted with saturated aqueous NaHCO₃ (10 mL) and EtOAc (20 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude residue was dissolved in EtOH (2.0 mL) and NaBH₄ (9.5 mg, 0.251 mmol) was added at 0 °C. After 10 min the mixture was quenched with saturated aqueous NH₄Cl (0.5 mL) and then diluted with saturated aqueous NaHCO₃ (10 mL) and EtOAc (20 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash
column chromatography (1:1:0.01 EtOAc:hexanes:NEt$_3$) to give hydroxy N,O-acetal 395 (15.7 mg, 45% for 4 steps) as a mixture of diastereomers (2:1) and rearranged diol 396 (8.0 mg, 30%).

**N,O-Acetal 395:** $^1$H NMR (300 MHz, benzene-$d_6$, 65 °C, 2:1 mixture of diastereomers) $\delta$ 7.32 (d, $J = 7.8$ Hz, 1H, major), 7.22 (d, $J = 8.0$ Hz, 1H, minor), 7.01-6.71 (m, 5H, major and minor), 6.22 (d, $J = 7.7$ Hz, 1H, major), 6.18 (d, $J = 6.8$ Hz, 1H, minor), 5.99 (br s, 1H, minor), 5.80 (s, 1H, major), 5.60 (s, 1H, minor), 5.53 (s, 1H, major), 5.06 (br s, 1H, major and minor), 4.27-3.91 (m, 4H, major and minor), 3.58-3.35 (m, 4H, major and minor), 3.04 (s, 3H, major), 3.01 (s, 3H, minor), 2.82 (m, 1H, minor), 2.63 (m, 1H, minor), 2.29-2.19 (m, 2H, major), 2.01-1.88 (m, 2H, major and minor), 1.56-1.49 (m, 1H, major and minor), 1.35 (s, 9H, major and minor), 1.15 (t, $J = 7.1$ Hz, 3H, major), 1.11 (t, $J = 7.2$ Hz, 3H, minor), 1.02 (s, 9H, minor), 0.98-0.94 (m, 3H, major and minor), 0.96 (s, 9H, major), 0.26 (s, 3H, minor), 0.25 (s, 3H, minor), 0.08 (s, 3H, major), -0.37 (br s, 3H, major); LRMS-ES [M+H]$^+$ calcd for C$_{38}$H$_{58}$N$_3$O$_7$Si, 696.4; found, 696.7.

**Diol 396:** $^1$H NMR (300 MHz, toluene-$d_8$, 90 °C) $\delta$ 6.90-6.86 (m, 1H), 6.84-6.81 (m, 1H), 6.77 (t, $J = 7.7$ Hz, 1H), 6.70-6.65 (m, 2H), 6.35 (d, $J = 7.7$ Hz, 1H), 6.13 (d, $J = 7.5$ Hz, 1H), 5.50 (s, 1H), 4.84 (d, $J = 14.2$ Hz, 1H), 4.32, 4.21 (ABq, $J = 12.0$ Hz, 2H), 4.20-4.05 (m, 4H), 3.45 (ddd, $J = 6.1$, 6.1, 12.2 Hz, 1H), 3.31 (ddd, $J = 5.9$, 5.9, 11.7 Hz, 1H), 3.15 (ddd, $J = 6.8$, 6.8, 16.8 Hz, 1H), 2.95 (s, 3H), 2.17-2.10 (m, 1H), 2.00-1.84 (m, 2H), 1.47 (ddd, $J = 2.6$, 2.6, 13.5 Hz,
1H), 1.32 (s, 9H), 1.14 (t, J = 7.1 Hz, 3H); LRMS-ES [M+Na]+ calcd for C₃₀H₃₉N₃NaO₆, 560.3; found, 560.5.

Synthesis of Azido N,O-Acetal 397. To a solution of hydroxy N,O-acetal 395 (15.7 mg, 0.023 mmol), PPh₃ (48 mg, 0.183 mmol) and DPPA (0.04 mL, 0.186 mmol) in THF (1.0 mL) was added DEAD (28 μL, 0.178 mmol) at rt. After 30 min the solvent was removed under reduced pressure and the residue was purified by preparative TLC (1:1:0.01 EtOAc:hexanes:NEt₃) to give the azido N,O-acetal 397 (9.8 mg, 60%) as a mixture of diastereomers (1:0.6). ¹H NMR (300 MHz, benzene-d₆, 65 °C, 1:0.6 mixture of diastereomers) δ 7.30 (d, J = 7.7 Hz, 1H, major), 7.22 (dd, J = 1.2, 8.0 Hz, 1H, minor), 7.06-6.90 (m, 2H, major and minor), 6.82-6.68 (m, 3H, major and minor), 6.20 (dd, J = 1.0, 7.7 Hz, 1H, major), 6.16 (dd, J = 1.1, 7.7 Hz, 1H, minor), 5.99 (br s, 1H, minor), 5.76 (s, 1H, major), 5.53 (s, 1H, minor), 5.45 (s, 1H, major), 4.76 (br s, 1H, major and minor), 4.28-3.89 (m, 4H, major and minor), 3.67-3.35 (m, 3H, major and minor), 3.02 (s, 3H, major), 2.99 (s, 3H, minor), 2.91 (m, 1H, minor), 2.75-2.59 (m, 2H, major, 1H, minor), 2.32-2.18 (m, 2H, major), 1.99-1.78 (m, 2H, major and minor), 1.48-1.41 (m, 1H, major and minor), 1.38 (s, 9H, major and minor), 1.20-1.11 (m, 3H, major and minor), 1.01 (s, 9H, minor), 1.00-0.75 (m, 12H, major, 3H, minor), 0.25 (s, 3H, minor), 0.24 (s, 3H, minor), 0.09 (s, 3H, major), -0.33 (br s, 3H, major); LRMS-ES [M+Na]+ calcd for C₃₈H₅₆N₆NaO₆Si, 743.4; found, 743.6.
**Preparation of N-Boc Amino N,O-Acetal 398.** To a solution of azido N,O-acetal 397 (4.6 mg, 6.4 μmol) in EtOAc (2.0 mL) were added 10% Pd/C (3.0 mg) and Boc₂O (7.0 mg, 32.0 μmol). The mixture was stirred at rt under a H₂ atmosphere (1 atm) for 1 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (1:3:0.01 EtOAc:hexanes:NEt₃) to give two separable diastereomers of N-Boc amino N,O-acetal 398 (2.5 mg / 1.1 mg, 49% / 22%; total yield 71%). More polar major diastereomer of 398: ¹H NMR (300 MHz, benzene-ᴅ₆, 65 °C) δ 7.31 (d, J = 8.1 Hz, 1H), 7.02-6.93 (m, 2H), 6.84-6.72 (m, 3H), 6.22 (d, J = 7.7 Hz, 1H), 5.76 (s, 1H), 5.46 (s, 1H), 4.83 (br s, 1H), 4.28-3.89 (m, 5H), 3.71-3.43 (m, 3H), 3.21 (m, 1H), 3.05 (s, 3H), 3.01 (m, 1H), 2.07 (m, 1H), 1.94 (m, 1H), 1.49 (m, 1H), 1.41 (s, 18H), 1.17-1.12 (m, 6H), 0.96 (s, 9H), 0.07 (s, 3H), -0.37 (s, 3H); LRMS-ES [M+Na]⁺ calcd for C₄₃H₆₆N₄NaO₈Si, 817.5; found, 817.7. Less polar minor diastereomer of 398: ¹H NMR (300 MHz, benzene-ᴅ₆, 65 °C) δ 7.22 (d, J = 8.0 Hz, 1H), 7.00-6.91 (m, 2H), 6.77-6.65 (m, 3H), 6.17 (dd, J = 1.0, 7.7 Hz, 1H), 5.97 (br s, 1H), 5.53 (s, 1H), 4.83 (br m, 1H), 4.42-3.95 (m, 5H), 3.43 (t, J = 13.6 Hz, 1H), 3.18 (m, 1H), 3.02 (s, 3H), 2.94-2.79 (m, 2H), 2.66-2.57 (m, 1H), 2.08 (m, 1H), 1.93 (m, 1H), 1.50 (m, 1H), 1.41 (s, 18H), 1.19 (m, 3H), 1.02 (s, 9H), 0.95 (t, J = 7.0 Hz, 3H), 0.26 (s, 3H), 0.25 (s, 3H); LRMS-ES [M+Na]⁺ calcd for C₄₃H₆₆N₄NaO₈Si, 817.5; found, 817.7.

**Formation of Aldehyde 400.** To a solution of N-Boc amino N,O-acetal 398 (1.1 mg, 1.4 μmol) in CH₂Cl₂ (0.5 mL)
was added PTSA (1.0 mg). The mixture was stirred at rt for 3 h and the solvent was removed under reduced pressure. The residue was purified by preparative TLC (1:1 EtOAc:hexanes) to give aldehyde 400 (0.9 mg, 100%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.37 (s, 1H), 7.11-6.95 (m, 4H), 6.85 (m, 1H), 6.53 (d, \(J = 7.6\) Hz, 1H), 6.48 (d, \(J = 7.8\) Hz, 1H), 5.60 (s, 1H), 4.74-4.64 (m, 1H), 4.44-3.93 (m, 5H), 3.66-3.52 (m, 2H), 3.10 (m, 2H), 3.01 (s, 3H), 2.27 (m, 1H), 1.82 (m, 1H), 1.46 (s, 9H), 1.35 (s, 9H), 1.26 (s, 3H); LRMS-ES [M+H]\(^+\) calcd for C\(_{35}\)H\(_{47}\)N\(_4\)O\(_7\), 635.3; found, 635.7.

1-Benzyl-5-(2-nitrophenyl)-1,2,3,6-tetrahydropyridine-4-carboxylic Acid (3-Bromo-2-iodophenyl)-amide (402). A mixture of the acid 334 (3.72 g, 11.0 mmol) and SOCl\(_2\) (16 mL) was refluxed for 3 h. Excess SOCl\(_2\) was removed under reduced pressure and the residue was diluted with CH\(_2\)Cl\(_2\) (20 mL) to give a stock solution of acid chloride (0.55M). To a stirred solution of aniline 401\(^{93}\) (435 mg, 1.46 mmol) and \((i\text{-Pr})\text{NEt}\) (1.0 mL, 5.74 mmol) in CH\(_2\)Cl\(_2\) (25 mL) was added the above solution of acid chloride (3.45 mL, 0.55 M in CH\(_2\)Cl\(_2\), 1.90 mmol) dropwise at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The mixture was diluted with CH\(_2\)Cl\(_2\) (150 mL) and saturated aqueous NaHCO\(_3\) (30 mL). The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes to 1:2:2 EtOAc:CH\(_2\)Cl\(_2\):hexanes) to give the amide 402 (717 mg, 79%, 91% based on recovered aniline 401) and unreacted aniline 401 (54 mg, 12%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.01 (dd, \(J = 1.1\), 8.2 Hz, 1H), 7.91 (dd, \(J = 1.3\), 8.2 Hz, 1H), 7.78 (s, 1H), 7.56 (ddd, \(J = 1.2\),
7.5, 7.5 Hz, 1H), 7.45-7.26 (m, 8H), 7.10 (t, \( J = 8.1 \) Hz, 1H), 3.74, 3.69 (ABq, \( J = 13.5 \) Hz, 2H), 3.28, 3.08 (ABq, \( J = 16.4 \) Hz, 2H), 2.92 (m, 1H), 2.81-2.78 (m 2H), 2.68 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 166.8, 148.3, 140.8, 139.3, 138.1 135.5, 134.3, 131.3, 130.6, 130.2, 129.7, 129.4, 128.9, 127.8, 125.2, 120.6, 98.4, 61.9, 57.5, 49.2, 27.0.

**4-(3-Bromo-2-iodophenylcarbamoyl)-5-(2-nitrophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic Acid Ethyl Ester (403).**

To a stirred solution of amide 402 (700 mg, 1.13 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added ClCO\(_2\)Et (0.12 mL, 1.26 mmol) dropwise at 0 °C and after 30 min the temperature was gradually raised to rt. The mixture was stirred at rt for 9 h and diluted with saturated aqueous NaHCO\(_3\) (10 mL) and CH\(_2\)Cl\(_2\) (20 mL). The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The residue was purified by flash column chromatography (1:3:3 EtOAc:CH\(_2\)Cl\(_2\):hexanes) to give the carbamate protected amide 403 (666 mg, 98%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.04 (dd, \( J = 0.9, 8.2 \) Hz, 1H), 7.80 (dd, \( J = 1.4, 8.2 \) Hz, 1H), 7.70 (s, 1H), 7.58 (ddd, \( J = 1.2, 7.5, 7.5 \) Hz, 1H), 7.45 (t, \( J = 7.8 \) Hz, 1H), 7.35-7.27 (m, 2H), 7.05 (t, \( J = 8.1 \) Hz, 1H), 4.21-4.10 (m, 4H), 3.83-3.73 (m, 2H), 2.76, 2.60 (ABq, \( J = 16.8 \) Hz, 2H), 1.22 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 166.4, 155.6, 148.3, 140.5, 138.2, 137.7, 134.6, 134.3, 131.4, 130.6, 130.2, 129.9, 129.1, 125.4, 120.6, 98.5, 62.2, 47.9, 40.2, 26.5, 15.1.

**4-[(3-Bromo-2-iodophenyl)-methylcarbamoyl]-5-(2-nitrophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic Acid Ethyl**
Ester (404). To a stirred suspension of NaH (16 mg, 60% dispersion in mineral oil, 0.400 mmol) in THF (10 mL) was added a solution of amide 403 (220 mg, 0.366 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and at rt for 30 min. To the solution was added MeI (0.027 mL, 0.434 mmol) at 0 °C and the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with saturated aqueous NaHCO₃ (30 mL) and extracted with EtOAc (100 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (2:1 EtOAc:hexanes) to give the N-methyl amide 404 (213 mg, 95%).

¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.72 (d, J = 8.2 Hz 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.14-7.08 (m, 2H), 6.98 (m, 1H), 6.68 (m, 1H), 6.43 (br s, 1H), 4.13-4.04 (m, 4H), 2.79 (s, 3H), 2.30 (br s, 2H), 1.07 (t, J = 7.0 Hz 3H); ¹³C NMR (75 MHz, toluene-d₈, 90 °C) δ 168.2, 155.2, 149.2, 148.2 133.8, 133.1, 132.0, 131.7, 131.4, 130.2, 129.0, 127.3, 124.8, 106.9, 61.4, 47.7, 40.3, 37.3, 27.0, 14.7.

Heck Cyclization of Amide 404. To a solution of N-methyl amide 404 (213 mg, 0.347 mmol) in DMA (7.0 mL) were added Pd(OAc)₂ (7.8 mg, 0.035 mmol), PPh₃ (27 mg, 0.104 mmol), n-Bu₄NBr (224 mg, 0.694 mmol) and K₂CO₃ (96 mg, 0.694 mmol). The mixture was stirred at 100 °C for 1 h. The catalyst was removed by filtration and washed with EtOAc (200 mL). The filtrate was washed with water (3×20 mL) and brine (20 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 to 3:1 EtOAc:hexanes) to give a mixture of Heck product 405 and pentacyclic Heck product 406 (86 mg, 51%, 405:406 = 1:0.15, 85% based on
recovered starting material) and unreacted amide 404 (86 mg, 40%). For analytical purposes further purification of 405 and 406 was achieved by careful flash column chromatography (1:10 EtOAc: CH₂Cl₂).

**Heck Product 405:** ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.71 (s, 1H), 7.09 (dd, J = 1.3, 8.0 Hz, 1H), 7.05 (dd, J = 1.3, 7.9 Hz, 1H), 6.79 (ddd, J = 1.4, 7.5, 7.5 Hz, 1H), 6.75 (dd, J = 1.0, 8.2 Hz, 1H), 6.69-6.61 (m, 2H), 6.23 (dd, J = 0.9, 7.7 Hz, 1H), 4.24 (ddd, J = 3.9, 12.8, 12.8 Hz, 1H), 4.03 (q, J = 7.0 Hz, 2H), 4.01 (m, 1H), 2.84 (s, 3H), 2.82-2.74 (m, 1H), 1.46 (ddd, J = 3.1, 3.7, 13.7 Hz, 1H), 1.04 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, toluene-d₈, 90 °C) δ 176.7, 153.3, 150.8, 146.3, 133.0, 132.6, 132.2, 130.7, 130.1, 129.2, 127.5, 126.9, 123.9, 119.7, 108.5, 107.1, 62.4, 51.1, 38.0, 28.2, 26.3, 14.3; LRMS-ES [M+H]⁺ calcd for C₂₂H₂₁BrN₃O₅, 486.1; found, 486.2.

**Pentacyclic Heck Adduct 406:** ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.48 (s, 1H), 7.42 (dd, J = 1.2, 7.9 Hz, 1H), 7.08 (dd, J = 1.3, 9.5 Hz, 1H), 6.99-6.89 m, 2H), 6.64 (t, J = 7.9 Hz, 1H), 6.16 (d, J = 7.2 Hz, 1H), 4.04-3.89 (m, 2H), 3.79 (ddd, J = 5.3, 13.3, 13.3 Hz, 1H), 3.40 (dd, J = 5.2, 13.1 Hz, 1H), 2.59 (s, 3H), 1.59 (ddd, J = 1.2, 5.3, 12.8 Hz, 1H), 1.36 (ddd, J = 5.7, 13.5, 13.5 Hz, 1H), 1.06 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CD₂Cl₂) δ 180.6, 153.2, 148.9, 144.3, 133.3, 131.1, 130.1, 129.9, 129.6, 128.1, 126.1, 126.0, 125.0, 117.1, 108.7, 107.9, 63.2, 48.6, 38.4 (d, J = 27.4 Hz), 38.0, 26.7, 14.5; LRMS-ES [M+H]⁺ calcd for C₂₂H₂₀N₃O₅, 406.1; found, 406.1.
**Preparation of Aniline 407.** To a solution of Heck product 405 (286 mg, 0.589 mmol) in CH₂Cl₂ (60 mL) was added 10% Pd/C (140 mg). The mixture was stirred at rt under a H₂ atmosphere (1 atm). After 12 h additional catalyst (70 mg) was added. After another 10 h the catalyst was removed by filtration through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (1:5 EtOAc:CH₂Cl₂) to give aniline 407 (205 mg, 76%) and hydrodebrominated aniline 408 (24 mg, 11%).

**Aniline 407:** ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.53 (s, 1H), 6.98-6.96 (m, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 6.55 (t, J = 7.6 Hz, 1H), 6.32 (t, J = 7.4 Hz, 1H), 6.17 (d, J = 8.0 Hz, 1H), 6.02 (d, J = 7.8 Hz, 1H), 4.23-4.18 (m, 2H), 4.02 (q, J = 7.1 Hz, 2H), 3.63 (br s, 2H), 2.90-2.79 (m, 1H), 2.64 (s, 3H), 1.54 (ddd, J = 3.3, 3.3, 13.9 Hz, 1H), 0.99 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CD₂Cl₂) δ 179.1, 154.0, 146.0, 131.0, 130.7, 130.11, 130.06, 128.3, 127.2, 123.3, 119.7, 117.5, 115.8, 109.6, 107.7, 62.7, 51.8, 37.7, 28.2, 27.0, 14.8; LRMS-ES [M+H]+ calcd for C₂₂H₂₃BrN₃O₃, 456.2; found, 456.2.

**Hydrodebrominated Aniline 408:** ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.37 (s, 1H), 6.98-6.96 (m, 1H), 6.91 (ddd, J = 1.3, 7.7, 7.7 Hz, 1H), 6.77 (ddd, J = 1.0, 7.5, 7.5 Hz, 1H), 6.69 (ddd, J = 1.6, 7.4, 8.0 Hz, 1H), 6.52 (dd, J = 1.4, 7.6 Hz, 1H), 6.27 (ddd, J = 1.1, 7.4, 7.4 Hz, 1H), 6.21 (t, J = 8.3 Hz, 2H), 4.21 (ddd, J = 4.3, 8.7, 12.9 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.75 (ddd, J = 4.0, 8.1, 12.1 Hz, 1H), 3.59 (br s, 2H), 2.65 (s, 3H), 2.01 (ddd, J = 3.9, 8.0, 13.5 Hz, 1H), 1.69 (ddd, J = 3.9, 8.2, 13.5 Hz, 1H), 1.02 (t, J = 7.1 Hz, 3H); ¹³C NMR
Synthesis of N-Boc Aniline 409. To a stirred solution of aniline 407 (7.5 mg, 0.016 mmol) in THF (1.0 mL) and H₂O (0.5 mL) were added K₂CO₃ (34.0 mg, 0.246 mmol) and (Boc)₂O (35.8 mg, 0.164 mmol). The reaction mixture was stirred at 60 °C. After 12 h, additional (Boc)₂O (16.8 mg, 0.077 mmol) was added. After another 12 h, the mixture was diluted with EtOAc (30 mL). The organic layer was washed with saturated aqueous NaHCO₃ (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:10 EtOAc:CH₂Cl₂) to give N-Boc aniline 409 (8.2 mg, 90%).

¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 8.14 (dd, J = 1.1, 8.3 Hz, 1H), 7.42 (br s, 2H), 7.06-7.03 (m, 1H), 6.90-6.83 (m, 2H), 6.58-6.49 (m, 2H), 6.00 (d, J = 7.8 Hz, 1H), 4.16 (dd, J = 3.5, 8.6 Hz, 2H), 4.00 (q, J = 7.1 Hz, 2H), 2.78 (ddd, J = 8.3, 8.3, 13.8 Hz, 1H), 2.59 (s, 3H), 1.57 (ddd, J = 3.6, 3.6, 13.9 Hz, 1H), 1.48 (s, 9H), 0.97 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CD₂Cl₂, peaks of major atropisomer) δ 178.8, 153.8, 153.6, 145.7, 137.5, 131.7, 130.7, 130.4, 129.4, 128.5, 127.7, 127.3, 122.5, 120.8, 119.7, 108.7, 107.9, 80.3, 62.9, 52.2, 38.1, 28.8, 28.4, 27.0, 15.0; LRMS-ES [M+H]⁺ calcd for C₁₇H₁₃BrN₃O₅, 556.1; found, 556.2.
Synthesis of Pentacyclic Aminal 410. To a stirred solution of N-Boc aniline 409 (177 mg, 0.319 mmol) in THF (8 mL) was added AlH₃·Me₂NEt (0.77 mL, 0.5 M in toluene, 0.385 mmol) dropwise at 0 °C. After 30 min, the temperature was raised to rt. After 2 h, the mixture was quenched with saturated aqueous Na₂SO₄ (0.3 mL) and stirred at rt for 2 h. The mixture was diluted with EtOAc (20 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 to 1:1 EtOAc:hexanes) to give pentacyclic aminal 410 (116 mg, 67%). ¹H NMR (300 MHz, toluene-d₈, 90 °C) δ 7.37 (s, 1H), 7.19 (dd, J = 1.6, 7.4 Hz, 1H), 7.10 (dd, J = 1.1, 7.8 Hz, 1H), 6.79 (ddd, J = 1.7, 7.5, 7.5 Hz, 1H), 6.72 (ddd, J = 1.4, 7.3, 7.3 Hz, 1H), 6.46-6.39 (m, 2H), 5.90-5.86 (m, 2H), 4.11 (m, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.32 (ddd, J = 3.4, 10.0, 13.4 Hz, 1H), 2.84 (s, 3H), 2.28 (ddd, J = 4.1, 10.1, 14.1 Hz, 1H), 1.92 (ddd, J = 3.5, 6.1, 14.0 Hz, 1H), 1.32 (s, 9H), 1.03 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, toluene-d₈, 90 °C) δ 154.5, 153.5, 153.0, 138.7, 134.2, 130.6, 129.8, 126.4, 126.3, 126.2, 125.8, 125.1, 122.6, 118.9, 114.3, 85.5, 80.8, 62.0, 53.0, 40.5, 33.8, 30.4, 28.2, 14.4; LRMS-ES [M+H]⁺ calcd for C₂₇H₃₁BrN₃O₄, 540.2; found, 540.3.

Preparation of Enamine 411. Pentacyclic aminal 410 (38.2 mg, 0.071 mmol) was dissolved in EtOH (2.0 mL) and 1 N aqueous KOH (2.0 mL) and the mixture was refluxed for 2 h. EtOH was removed under reduced pressure. The residue was diluted with EtOAc (20 mL) and saturated aqueous NaHCO₃ (10 mL). The organic layer was dried over Na₂SO₄ and
concentrated \textit{in vacuo}. The residue was used for the next step without further purification. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.21-7.16 (m, 2H), 7.01-6.96 (m, 2H), 6.77 (t, $J = 7.9$ Hz, 1H), 6.74 (s, 1H), 6.55 (d, $J = 7.5$ Hz, 1H), 6.19 (d, $J = 7.7$ Hz, 1H), 5.80 (s, 1H), 3.89 (br s, 1H), 3.47 (dd, $J = 4.6$, 4.6, 11.4 Hz, 1H), 3.24 (ddd, $J = 3.1$, 11.0, 11.0 Hz, 1H), 2.95 (s, 3H), 2.39 (ddd, $J = 3.9$, 10.3, 13.8 Hz, 1H), 2.22 (ddd, $J = 3.2$, 4.8, 13.6 Hz, 1H), 1.51 (s, 9H); LRMS-ES [M+H]$^+$ calcd for C$_{24}$H$_{27}$BrN$_3$O$_2$, 468.1; found, 468.2.

**Allylation of Enamine 411.** The above crude enamine 411 was dissolved in THF (3.0 mL). To the solution was added LDA (0.35 mL, 0.3 M in THF, 0.105 mmol) at -78 $^\circ$C. After 20 min allyl iodide (0.01 mL, 0.109 mmol) was added, and the mixture was gradually warmed to rt. The mixture was diluted with saturated aqueous NaHCO$_3$ (10 mL) and EtOAc (25 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (1:3 to 1:1 EtOAc:hexanes) to give C-allyl product 412 (20.7 mg, 58%) and N-allyl enamine 413 (10.5 mg, 29%).

**C-allyl product 412:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.83 (s, 1H), 7.53 (dd, $J = 3.0$, 5.8 Hz, 1H), 7.02-6.96 (m, 3H), 6.73 (t, $J = 7.9$ Hz, 1H), 6.57 (d, $J = 8.0$ Hz, 1H), 6.26 (d, $J = 7.8$ Hz, 1H), 5.71-5.61 (m, 1H), 5.53 (s, 1H), 5.03-4.93 (m, 2H), 4.04 (dd, $J = 5.3$, 18.7 Hz, 1H), 3.61 (ddd, $J = 4.5$, 4.5, 12.5 Hz, 1H), 2.98 (s, 3H), 2.67-2.62 (m, 2H), 2.42 (ddd, $J = 6.0$, 13.3, 13.3 Hz, 1H), 1.93 (dd, $J = 5.4$, 13.7 Hz, 1H), 1.46 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.1, 154.9, 153.2, 139.6, 133.0, 132.5, 129.7, 127.2, 126.5, 125.0, 124.9, 123.9, 119.5, 118.9,
N-Allyl Product 413. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.19-7.15 (m, 2H), 7.00-6.96 (m, 2H), 6.76 (t, $J = 7.9$ Hz, 1H), 6.55 (s, 1H), 6.54 (d, $J = 8.7$ Hz, 1H), 6.19 (d, $J = 7.7$ Hz, 1H), 6.00-5.91 (m, 1H), 5.77 (s, 1H), 5.36-5.22 (m, 2H), 3.69 (d, $J = 6.0$ Hz, 2H), 3.33 (ddd, $J = 4.5$, 4.5, 11.4 Hz, 1H), 2.99 (ddd, $J = 3.1$, 11.2, 11.2 Hz, 1H), 2.95 (s, 3H), 2.43 (ddd, $J = 3.5$, 10.4, 13.9 Hz, 1H), 2.23 (ddd, $J = 3.2$, 4.7, 13.6 Hz, 1H), 1.51 (s, 9H); LRMS-ES [M+H]$^+$ calcd for C$_{27}$H$_{31}$BrN$_3$O$_2$, 508.2; found, 508.3.

Formation of Debrominated C-allyl product 414. To a stirred solution of aminal 410 (9.6 mg, 0.018 mmol) in THF (2.0 mL) was added $n$-BuLi (0.028 mL, 1.6 M in hexanes, 0.045 mmol) dropwise at -78 °C. After stirring the mixture for 15 min at the same temperature, allyl iodide (0.053 ml, 1.0 M in THF, 0.053 mmol) was added, and the mixture was gradually warmed to rt. After 15 min at rt the mixture was diluted with saturated aqueous NaHCO$_3$ (5 mL) and EtOAc (20 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by preparative TLC (1:2 EtOAc:hexanes) to give the C-allyl product 412 (1.3 mg, 14%) and debrominated C-allyl product 414 (1.1 mg, 12%).

414: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.85 (br s, 1H), 7.27-7.24 (m, 1H), 7.04-6.92 (m, 3H), 6.85 (t, $J = 7.6$ Hz, 1H), 6.55 (d, $J = 7.2$ Hz, 1H), 6.32 (t, $J = 7.1$ Hz, 1H), 6.24 (d, $J = 7.7$ Hz, 1H), 5.67 (s, 1H), 5.63-5.53 (m, 1H), 5.00-4.93 (m, 2H), 4.11 (m, 1H), 3.76-3.60 (m,
1H), 2.94 (s, 3H), 2.69 (d, $J = 6.8$ Hz, 2H), 2.45 (m, 1H), 1.83 (m, 1H), 1.47 (s, 9H); LRMS-ES [M+H]$^+$ calcd for C$_{27}$H$_{31}$N$_3$O$_2$, 430.3; found, 430.4.

**Formation of $N,O$-Acetal 415.** To a stirred solution of imine 412 (20.7 mg, 0.041 mmol) in EtOH (1.0 mL) was added diethyl pyrocarbonate (7.2 μL, 0.049 mmol) at rt. After 10 min the solvent was removed under reduced pressure. The crude residue was used for the next step without further purification. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.44-7.42 (m, 1H), 7.11 (s, 1H), 7.09 (s, 1H), 7.06-7.00 (m, 2H), 6.72 (t, $J = 7.8$ Hz, 1H), 6.60 (d, $J = 8.0$ Hz, 1H), 6.23 (d, $J = 7.3$ Hz, 1H), 5.75 (s, 1H), 5.61-5.51 (m, 1H), 4.80 (d, $J = 17.0$ Hz, 1H), 4.67 (d, $J = 10.0$ Hz, 1H), 4.27-4.15 (m, 3H), 3.98-3.92 (m, 2H), 3.73 (ddd, $J = 5.3$, 8.2, 13.5 Hz, 1H), 3.24 (dd, $J = 5.5$, 15.0 Hz 1H), 2.95 (s, 3H), 2.65 (dd, $J = 7.5$, 14.9 Hz, 1H), 2.37 (ddd, $J = 5.3$, 8.6 13.9 Hz, 1H), 1.88 (ddd, $J = 5.2$, 6.8, 14.1 Hz, 1H), 1.51 (s, 9H), 1.33 (t, $J = 7.1$ Hz, 3H), 1.26 (t, $J = 7.0$ Hz, 3H); LRMS-ES [M+H]$^+$ calcd for C$_{32}$H$_{41}$BrN$_3$O$_5$, 626.2; found, 626.4.

**Synthesis of Hexacyclic Acetal 416.** To a solution of the above crude $N,O$-acetal 415 in dioxane (2.0 mL) and H$_2$O (1.0 mL) was added NMO (47.7 mg, 0.407 mmol) at 0 °C, followed by OsO$_4$ (0.01 mL, 4 wt% in H$_2$O). The mixture was gradually warmed to rt. The mixture was stirred at rt for 3 h and then diluted with saturated aqueous Na$_2$S$_2$O$_3$ (10 mL) and EtOAc (20 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude
residue was dissolved in THF (2.0 mL) and H₂O (1.0 mL) and NaIO₄ (87.0 mg, 0.407 mmol) was added. The mixture was stirred at rt for 1 h and then diluted with saturated aqueous NaHCO₃ (10 mL) and EtOAc (20 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give two separable diastereomers of hexacyclic acetal 416 (7.7 mg and 2.9 mg, 42% for 3 steps). More polar major diastereomer of 416:

₁H NMR (400 MHz, CD₂Cl₂) δ 7.59 (dd, J = 3.6, 5.6 Hz, 1H), 7.05-7.02 (m, 3H), 6.99 (s, 1H), 6.77 (t, J = 7.9 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.30 (d, J = 7.4 Hz, 1H), 5.55 (s, 1H), 5.26 (dd, J = 1.1, 5.3 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.73 (ddd, J = 7.1, 9.7, 14.2 Hz, 1H), 3.60 (dd, J = 4.4, 6.1, 13.0 Hz, 1H), 3.48-3.41 (m, 2H), 2.99 (s, 3H), 2.88 (dd, J = 5.4, 13.0 Hz, 1H), 2.46 (ddd, J = 4.9, 9.4, 16.9 Hz, 1H), 2.06 (ddd, J = 4.3, 6.1, 14.2 Hz, 1H), 1.98 (dd, J = 1.2, 13.0 Hz, 1H), 1.51 (s, 9H), 1.33 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 157.4, 154.8, 153.5, 138.8, 137.3, 131.1, 129.8, 126.9, 126.2, 124.8, 124.3, 124.2, 118.7, 106.2, 101.5, 85.6, 84.4, 82.0, 62.9, 62.2, 57.1, 48.1, 44.4, 39.8, 32.1, 29.5, 28.6, 15.6, 15.3; LRMS-ES [M+H]⁺ calcd for C₃₁H₃₉BrN₃O₆, 628.2; found, 628.4. Less polar minor diastereomer of 416: ¹H NMR (300 MHz, CD₂Cl₂) δ 7.48 (dd, J = 3.9, 5.3 Hz, 1H), 7.04 (s, 1H), 7.03-6.99 (m, 3H), 6.70 (t, J = 7.9 Hz, 1H), 6.56 (d, J = 7.3 Hz, 1H), 6.20 (d, J = 7.6 Hz, 1H), 5.61 (br s, 1H), 5.17 (dd, J = 1.8, 6.2 Hz, 1H), 4.38-4.24 (m, 2H), 3.86-3.71 (m, 2H), 3.60-3.42 (m, 2H), 2.95 (s, 3H), 2.84-2.71 (m, 2H), 2.35-2.31 (m, 1H), 2.04 (ddd, J = 5.6, 5.6, 14.1 Hz, 1H), 1.48 (s, 9H), 1.33 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); LRMS-ES [M+H]⁺ calcd for C₃₁H₃₉BrN₃O₆, 628.2; found, 628.4.
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