Synthesis of Conformationally Liberated Yohimbine Analogues and Evaluation of Cytotoxic Activity

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ABSTRACT: A modular synthetic approach to strategically unique structural analogues of the alkaloid yohimbine is reported. The overall synthetic strategy couples the transition-metal-catalyzed decarboxylative allylation of 2,2-diphenylglycinate imino esters with a scandium triflate-mediated highly endo-selective intramolecular Diels−Alder (IMDA) cycloaddition to generate a small collection of de-rigidified yohimbine analogues lacking the ethylene linkage between the indole and decahydroisoquinoline units. One compound generated in this study contains an unprecedented pentacyclic urea core and appears to demonstrate increased cytotoxicity against the gastric cancer cell line SGC-7901 in comparison to a pancreatic cancer cell line (PATU-8988) and a normal human gastric mucosal cell line (GES-1).

1. INTRODUCTION

Yohimbinoinds are a large family of polycyclic indole alkaloids that have long attracted synthetic and medicinal chemists alike due to the combination of dense functionality and diverse bioactivity.1 The eponymous member of the family, yohimbine (1), is a potent pan-subtype α2-adrenergic receptor (α2-AR) antagonist that is a component used in traditional medicines and is a frequent chemical probe of α2-AR activity for various physiological processes.2 There is a growing body of evidence demonstrating the potent cytotoxic activity of various yohimbinoinds3 and synthetic derivatives of the yohimbine framework.4 For example, Ma and coworkers determined that yohimbine inhibited the proliferation of two different pancreatic cancer cell lines.3b Recent innovative studies by Luesch and Huigens demonstrated that yohimbine can be used as a starting point to generate libraries of complex and selective small molecule modulators of other G-protein-coupled receptors (GPCRs) implicated in the proliferation of various cancers.4 These reports epitomize the unwavering interest in generating novel yohimbine analogues with useful biological activities.

Several racemic5 and asymmetric6 total syntheses of 1 have been reported. Despite the tactical diversity displayed in the previously reported syntheses of 1 and structural derivatives, all these approaches are unified in their use of tryptamine (e.g., 2a) or the corresponding bromide 2b, resulting in a dearth of yohimbine structural derivatives that lack the rigidifying two-carbon linker in the C ring joining the indole and aliphatic amine (bold in Scheme 1A). This ethylene linker enforces coplanarity between the indole and piperidine D-ring units in 1, a factor that is predicted to account for the alkaloid’s lack of increased cytotoxicity against the gastric cancer cell line SGC-7901 in comparison to a pancreatic cancer cell line (PATU-8988) and a normal human gastric mucosal cell line (GES-1).
selectivity in antagonistic activity against the various α2-AR subtypes. To the best of our knowledge, only the aforementioned efforts from Luesch and Huigens have generated and evaluated yohimbine analogues, in which the C-ring ethylene linker has been severed. Specifically, they cleaved the C−N bond linking the C and D rings of (+)-1 with cyanogen bromide and converted the resulting N-cyano primary bromide into a low micromolar inhibitor of CCR8, a GPCR implicated in the cell migration of malignant melanosomes.6

As part of our broader campaign focused on the functionalization of semistabilized 2-azaallyl anions,7−9 we recognized that the transition-metal-catalyzed decarboxylative allylation (DCA) strategy, advanced by our group7 and others,10 could allow for the rapid and modular access to O−functionalizations from Luesch and Huigens have already established.

2. RESULTS AND DISCUSSION

2.1. Synthesis. Our initial studies began with what was expected to be a routine imine condensation between aldehyde 6a and amino ester 7 (Table 1). Surprisingly, this transformation proved to be particularly challenging. The Boc-protecting group was readily hydrolyzed at elevated temperatures, and the electrophilic aldehyde ester was prone to several side reactions. All standard methods for imine condensation were not acceptable means to generate the desired imine 8a. For example, heating to reflux with a Dean−Stark trap equipped with the reaction vessel led to the near-complete decomposition of the starting materials (Table 1, entry 1). Switching the solvent to dichloromethane and adding anhydrous magnesium sulfate as a desiccant to the reaction mixture simply resulted in the deprotection of the Boc carbamate in aldehyde 6a with a negligible imine condensation (entry 2). Similarly, heating the reagents in 1,2-dichloroethane with a buffered mixture of MgSO4 and triethylamine resulted in almost quantitative transfer of the N-Boc moity from 6a to 7.

As part of our broader campaign focused on the functionalization of semistabilized 2-azaallyl anions,7−9 we recognized that the transition-metal-catalyzed decarboxylative allylation (DCA) strategy, advanced by our group7 and others,10 could allow for the rapid and modular access to novel “conformationally liberated” analogues of the yohimbine scaffold lacking the rigidifying C-ring ethylene linker (Scheme 1B). Specifically, subjection of the imine formed by the condensation of indole aldehydes 6 with 2,2-diphenylglycinate ester 7 to our Pd− or Ni-catalyzed DCA conditions, followed by reductive amination with known O-Boc-protected glutaraldehyde (5)6a would quickly afford trienes 4. An endo-selective intramolecular Diels−Alder (IMDA) cycloaddition would then complete the formation of the parent conformationally liberated yohimbine scaffold 3, which could be derivatized further by various functional group transformations. We were confident in the plausibility of this approach given that both Jacobsen (Scheme 2A)6b and Hiemstra

Scheme 2. IMDA Cycloadditions in the Syntheses of Yohimbine from (A) Jacobsen and (B) Hiemstra

A. Jacobsen’s Lewis Acid-Catalyzed IMDA

B. Hiemstra’s Thermal IMDA

(Scheme 2B)6c employed a similar endo-selective IMDA process in their syntheses of (+)-1, albeit with more conformationally restricted precursors in which the C-ring was already established.

| entry | conditions | yielda

Table 1. Imine Condensation Conditions

| entry | conditions | yield
|-------|------------|------|
| 1     | PhCH2, 120 °C, Dean−Stark, 12 h | 99%b
| 2     | MgSO4, CH2Cl2, 70 °C (reflux), 48 h | <10%c
| 3     | MgSO4, NEt3, 1,2-DCE, 100 °C, 48 h, 100 °C | <10%d
| 4     | TiCl4, NEt3, Et2O/hexanes, 0−20 °C, 16 h | 46%
| 5     | air, 70 °C, 2 h | 58%
| 6     | vacuum, 70 °C, 3 h | 81%
| 7     | air, 70 °C, 1 h; vacuum, 70 °C, 2 h | 94%

aIsolated yield. bAmine 7 decomposed. cBoc group in 6a removed. dTransfer of the N-Boc moiety from 6a to 7.
and an additional 2 h under reduced pressure afforded imine 8a in a very high yield and purity (94%, entry 7). Directly heating a mixture of 6a and 7 under vacuum without premixing at atmospheric pressure afforded imine 8a in a reduced yield (81%, entry 6). This high-yielding vacuum-assisted solvent-free imine condensation strategy has proven to be quite general for the synthesis of various 2,2-diphenylglycinate imino esters,\(^7\) including those shown in Figure 1. It should be noted that the condensation does fail, however, to directly construct highly congested imines such as N,O-di-Boc-protected 8c (Figure 1). Imine 8c could be generated in 64% isolated yield, however, by reacting alcohol 8d with Boc\(_2\)O, DMAP, and Et\(_3\)N in THF (see the Experimental Section).

With a collection of imines 8 and 9 in hand, the proposed transition-metal-catalyzed DcA reaction was next investigated beginning with non-stereoselective reaction conditions (Table 2A). Previous studies indicated that the bidentate ligand 1,1'-imine (±)-corresponding homoallylic imine (8d) even imine 10d was converted to DcA product (yield 10% of (MeCN, rt) product (entry 4). This represents, to the best of our knowledge, the first example of a free indole N=H successfully participating in a Pd-catalyzed DcA reaction involving a relatively basic 2-

| Table 2. DcAs Using (A) Achiral or (B) Chiral Ligands |
| --- |
| **A. Racemic** |
| entry | imine | conditions | product (yield)\(^\circ\) |
| 1 | 8a (X = H) | Pd\(_2\)(dba)\(_3\) (5 mol %), dppf (10 mol %), MeCN, rt | 10a (50%) |
| 2 | 8b (X = Cl) | Pd\(_2\)(dba)\(_3\) (5 mol %), dppf (10 mol %), MeCN, rt | 10b (59%) |
| 3 | 8c (X = (CH\(_2\))\(_2\)OH)\(^\circ\) | Pd\(_2\)(dba)\(_3\) (5 mol %), dppf (10 mol %), MeCN, rt | 10c (75%) |
| 4 | 8d (X = (CH\(_2\))\(_2\)OH)\(^\circ\) | Pd\(_2\)(dba)\(_3\) (5 mol %), dppf (10 mol %), MeCN, rt | 10d (30%) |
| 5 | 9a (X = H) | Pd\(_2\)(dba)\(_3\) (10 mol %), dppf (10 mol %), MeCN, rt | 11a (93%) |
| 6 | 9b (X = Cl) | Pd\(_2\)(dba)\(_3\) (5 mol %), dppf (10 mol %), MeCN, rt | 11b (95%) |

| **B. Asymmetric** |
| --- |
| entry | imine | conditions | product (yield)\(^\circ\) |
| 1 | 8a (X = H) | Pd\(_2\)(dba)\(_3\) (5 mol %), 12 (5 mol %), MeCN, rt | 10a (48%, 60:40) |
| 2 | 8a (X = Cl) | Pd\(_2\)(dba)\(_3\) (5 mol %), 12 (5 mol %), DMSO, rt | 10a (64%, 55:45) |
| 3 | 8a (X = N\(_2\)) (2.5 mol %), 12 (2.5 mol %), DMSO, 25 °C | 10a (26%, 55:45) |
| 4 | 9a (X = H) | Pd\(_2\)(dba)\(_3\) (5 mol %), 12 (5 mol %), MeCN, rt | 11a (42%, 66:34) |
| 5 | 9a (X = Cl) | Pd\(_2\)(dba)\(_3\) (5 mol %), 12 (5 mol %), DMSO, rt | 11a (93%, 70:30) |
| 6 | 9a (X = N\(_2\)) (2.5 mol %), 12 (2.5 mol %), DMSO, 60 °C | 11a (31%, 75:25) |
| 7 | 9a (X = N\(_2\)) (2.5 mol %), 12 (2.5 mol %), DMSO, 45 °C | 11a (25%, 50:50) |
| 8 | 9b (X = H) | Pd\(_2\)(dba)\(_3\) (5 mol %), 12 (5 mol %), MeCN, 45 °C | 11b (23%, 56:44) |
| 9 | 9b (X = Cl) | Pd\(_2\)(dba)\(_3\) (5 mol %), 12 (5 mol %), DMSO, 45 °C | 11b (13%, 65:35) |

\(^\circ\)Isolated yield, average of three experiments. \(^\circ\)Possesses a free indole N=H instead of N-Boc. \(^\circ\)Average of two experiments. \(^\circ\)Er determined by chiral stationary phase HPLC and is listed by order of elution. Based on previous studies (refs 7a and 8), the major/first-to-elute enantiomer is presumed to be the (S) configuration.

azallyl anion intermediate. In comparison to acrylates 8, the unsubstituted allyl esters 9 proved to be superior substrates for the racemic Pd-catalyzed DcA reaction conditions. For example, nearly quantitative conversion of 3-chloroindolyl imine 9b into homoallylic imine (±)-11b was observed (95%,
entry 6), marking a significant improvement over the transformation of the corresponding acrylate 8b (entry 2).

We next explored the asymmetric transition-metal-catalyzed DcA using the chiral bisphosphine ligand (S,S)-f-binaphane (12), which was identified in previous studies to impart significant enantioselectivity to related DcA transformations involving allyl 2,2-diphenylglycinate imines.7b,c,8 Unfortunately, the Pd-catalyzed asymmetric DcA of acrylate ester 8a in acetonitrile (Table 2B, entry 1) or dimethylsulfoxide (entry 2) generated the desired homoallylic imine in modest yields (48−64%) and negligible enantiomeric ratios (er). Switching to a Ni(0) catalyst did not improve the er for the DcA of acrylate 8a (entry 4). The yields (42−86%) and er values (up to 68:32 in favor of the S enantiomer) improved somewhat when allyl ester 9a was subjected to the Pd-catalyzed procedures (entries 4 and 5). The highest yield (93%), with an improved er value (70:30), was observed when allyl ester 9a was subjected to our Ni-catalyzed asymmetric DcA reaction conditions using chiral ligand 12 at 60 °C (entry 6).8 Lowering the reaction temperature of the Ni-catalyzed process to 45 °C slightly increased the er to 75:25 but at a significant expense to the yield (entry 7).

Chlorination of the 3-position of the indole moiety (9b) dramatically reduced the isolated yields and observed er values for both the Pd- and Ni-catalyzed DcA transformations (entries 8−10).

Preliminary efforts indicate that homoallylic imine 11a can be converted to the desired acrylate 10a via olefin cross metathesis (see the Supporting Information). The relatively modest er values obtained in these studies, however, highlight the need for more extensive chiral ligand screening for the Pd- and Ni-catalyzed asymmetric DcA of challenging substrates such as imino esters 8 and 9. Nevertheless, these efforts provided sufficient quantities of the desired δ-imino acrylates 10a−c for exploring the remainder of our proposed synthetic

Scheme 3. Synthesis of the Conformationally Liberated Yohimbinoid Framework

entry 6), marking a significant improvement over the transformation of the corresponding acrylate 8b (entry 2).
strategy toward novel racemic conformationally liberated analogues of yohimbine.

Toward this end, we first investigated the critical IMDA cycloaddition, starting with racemic imine 10a (Scheme 3). Selective hydrolysis of the benzophenone imine over the Boc group was achieved with a combination of aqueous HCl in ethyl acetate and careful monitoring of the reaction progress by TLC. Two-step reductive amination between the resulting amine 13a and O-Boc-glutaconaldehyde (5) afforded the IMDA precursor 4a in 56% isolated yield. Heating a solution of 4a in toluene to 70 °C for 24 h led to the near-complete conversion of the triene into a 2:1 mixture of diastereomers in which the endo-chair IMDA cycloadduct endo-14a predominated. The minor diastereomer (exo-14a) was presumed to arise via an exo-chair transition state (Scheme 3, inset). In their synthesis of yohimbine from tryptamine, Hiemstra and coworkers observed a similar endo/exo ratio (3:1 for the free indole; Scheme 2B) for the thermal IMDA cycloadditions of more conformationally restricted triene. 6a Subjecting triene 4a to a combination of scandium trflate (4 equiv) in acetonitrile at ambient temperatures, however, catalyzed the IMDA reaction so as to afford the endo-chair cycloadduct 15a as a single diastereomer with concomitant cleavage of the O-Boc moiety. The relative stereochemistry of 15a was determined by extensive 2D-nuclear magnetic resonance (NMR) spectroscopic analysis. It is currently unknown whether the cleavage of the carbonate occurs prior to, during, or after cycloaddition, but it should be noted that Jacobsen and coworkers also observed outstanding diastereoselectivity for a related Lewis acid-catalyzed IMDA reaction using a more stable terminal O-benzoate group on their diene component (Scheme 2A). 6b Although the Sc(OTf)3-mediated IMDA of triene 4a always proceeded with high diastereoselectivity, it proved particularly challenging to completely remove the sodium triflate formed during the workup of the reaction from the resulting product 15a, thus impacting our ability to accurately determine the yield of the transformation. The removal of the lingering NaOTf could be achieved after acidic hydrolysis of the Boc carbamate on the indole nitrogen, however. Accordingly, the treatment of the IMDA cycloaddition of 4a with trifluoroacetic acid afforded the single cycloadduct 16a in 59% isolated yield over the two steps. Alternatively, Sc(OTf)3-mediated IMDA of unprotected indole 4a′ directly afforded triflate-free cycloadduct 16a as a single diastereomer in 65% isolated yield.

The other IMDA precursors 4b and 4c were obtained following a process similar to the route used to generate 4a in Scheme 3 (see the Supporting Information for more details). Mixing 3-chloroindole 4b with Sc(OTf)3 in acetonitrile afforded the endo-chair cycloadduct 16b as a single diastereomer in 72% yield (Scheme 4). The IMDA cycloaddition of the N,O-di-Boc-protected precursor 4c was more complicated, however. Treatment of 4c with Sc(OTf)3 in acetonitrile at 0 °C and workup with saturated aqueous sodium bicarbonate at this temperature led to the isolation of the IMDA cycloadduct 15b (72%), in which both O-Boc groups in the starting material were removed under the reaction conditions. Quenching the IMDA reaction mixture with NaHCO3 at a slightly elevated temperature (35 °C), however, resulted in the exclusive formation of the cyclic urea 17. As with the IMDA cycloadduct 15a, cyclic urea 17 retained up to 0.5 equiv of sodium triflate, even after extraction and silica gel chromatography, thus complicating the accurate calculation of the yield. This phenomenon proved to be advantageous for structure confirmation, however. A single crystal of 17 cococrystallized with NaOTf (2:1 ratio) and water crashed out of the NMR sample (CDCl3 solvent) and X-ray crystallographic analysis of this crystal verified the presence of the novel pentacyclic core and the relative stereochemistry in the IMDA product (Figure 2, CCDC deposition number: 2082133). It is presumed that the carbonyl group linking the two nitrogens in 17 comes from the indole Boc group on the IMDA precursor 4c, but this was not confirmed definitively.

As detailed in Table 3, the IMDA cycloadducts 15 and 16 were converted to the corresponding decahydroisoquinolines 18 by catalytic hydrogenation. The Boc-protected indoles 15a and 15b and the free indole 16a were readily converted to the corresponding hydrogenated products 18a−c, respectively, in good yields (65−83%) using methanol as the solvent. When chloride 16b was subjected to these conditions, the hydrogenated and dechlorinated product 18c was obtained exclusively (not shown). Simply changing the solvent for the catalytic hydrogenation of 16b from MeOH to EtOAc afforded the corresponding chloride 18d in 70% isolated yield.

Figure 2. ORTEP diagram of (±)-17 cococrystallized with NaO3SCF3 (2:1 ratio) and water (from CDCl3) obtained by single-crystal X-ray crystallography (CCDC-2082133, C = gray, H = white, F = green, N = blue, Na = cyan, O = red, and S = yellow).
Decahydroisoquinoline 18c was further elaborated in two steps to yohimbine analogue 19 (Scheme 5). Specifically, reductive amination between amine 18c and O-TBDBPS-protected hydroxyacetaldehyde, followed by the removal of the silyl-protecting group with tetrabutylammonium fluoride, afforded the tertiary amine 19 in 27% yield over the two steps. It is worth noting that alcohols 19 and 18b both contain all of the carbons and heteroatoms present in yohimbine (1). While our goal in this project was always to generate and evaluate the biological activity of novel conformationally liberated analogues of 1, it is tempting to consider using alcohols 18b or 19 as late-stage intermediates in the total synthesis of this venerable alkaloid. Preliminary attempts to convert either of these two alcohols into racemic 1, however, have not borne fruit.

### 2.2. Biological Activity.

As mentioned in the Introduction, the α2-AR antagonist yohimbine (1) exhibits proapoptotic activity against two different pancreatic cancer cell lines (PC-2 and PC-3). The synthetic strategies discussed above afforded us access to novel structural analogues to 1, and we sought to determine whether these analogues also possessed appreciable cytotoxic activity against similar cancer cells. Toward this goal, an MTT colorimetric assay was employed to determine the cytotoxicity against one pancreatic cancer cell line (PATU-8988) and one gastric cancer cell line (SGC-7901) for four of the novel yohimbine analogues obtained in our study (15a, 16a, 16b, and 17). The general cytotoxicity of these four compounds was evaluated using the same assay against a normal human gastric mucosal cell line (GES-1). The results from these assays are summarized in Table 4. The four compounds all demonstrated modest (sub-millimolar) cytotoxicity against all three cell lines. The Boc-protected indole 15a proved to be an average of 2 times more toxic than the corresponding free indole 16a, but essentially no difference was observed between 16a and the corresponding chloride 16b. While 15a, 16a, and 16b did not display any significant selectivity between the different cell lines, the more conformationally constrained cyclic urea 17 appeared to be more active (potentially 4-fold) against the gastric cancer cell line SGC-7901. To the best of our knowledge, the tetrahydro-6H,8H-pyrrolo[1′,2′:3,4]imidazo[1,5-a]indol-6-one core of 17 is unique to this compound; no other examples of molecules containing this heterotetracyclic core were detected in multiple online database searches. Given the structural novelty of this core and the potential for selective cytotoxicity against cancer cells, future investigations will focus on the synthesis and detailed evaluation of libraries of small molecules inspired by cyclic urea 17.

### 3. CONCLUSIONS

We demonstrated that the transition-metal-catalyzed Dca of 2,2-diphenylglycine imino esters, a process championed by our group, can be combined with a Lewis acid-mediated endo-selective IMDA cycloaddition to afford a relatively rapid and modular strategy for the racemic synthesis of novel conformationally liberated analogues of the alkaloid natural product yohimbine. The synthesis of the necessary imino ester precursors 8 and 9 required employment of a nontraditional solvent-free imine condensation under reduced pressure. Although modest enantioselectivity was observed using chiral bisphosphate 12 in the Pd- and Ni-catalyzed Dca of these indole-containing imino esters, more extensive studies are still required for this strategy to reliably generate the novel yohimbine analogues disclosed herein as single enantiomers. Nevertheless, we demonstrated that four racemic yohimbine analogues disclosed herein as single enantiomers.
analogues (15a, 16a, 16b, and 17) showed modest cytotoxicity against two different gastrointestinal cancer cell lines. Moreover, the structurally unique cyclic urea 17, which was an unexpected product from the IMDA cycloaddition of the corresponding triene 4c, appears to exhibit selectivity in its cytotoxicity against the gastric cancer cell line SGC-7901 versus a pancreatic cancer cell line (PATU-8988) and a normal gastric mucosal cell line (GES-1). We intend to further explore the novel heterocyclic core present in 17 as a scaffold for other potentially selective cytotoxic small molecules.

4. EXPERIMENTAL SECTION

4.1. General Methods. All nonaqueous reactions were performed in oven-dried or flame-dried flasks or vials under an atmosphere of dried and deoxygenated argon with dry solvents and magnetic stirring, unless stated otherwise. All solvents were dried by storing over active 4 Å molecular sieves for at least 48 h and sparged with dried and deoxygenated Ar gas for at least 30 min. Unless noted otherwise, all reagents were purchased from commercial sources and used as received. Triethylamine (Et3N) was distilled and stored over potassium hydroxide before use. Allyl bromide was filtered through basic alumina immediately prior to use. Ester hydroxide before use. Allyl bromide was filtered through basic alumina immediately prior to use. Ester hydroxide before use. Allyl bromide was filtered through basic alumina immediately prior to use. Ester hydroxide before use. Allyl bromide was filtered through basic alumina immediately prior to use. Ester hydroxide before use. Allyl bromide was filtered through basic alumina immediately prior to use.

4.2. Synthetic Procedures. 4.2.1. tert-Butyl-2-((E)-((2-(((E)-4-methoxy-4-oxo-2-but-2-en-1-yl)oxy)-2-oxo-1,1-diphenylethyl)imino)methyl)-1H-indole-1-carboxylate (8a). To a flask equipped with a stir bar were added aldehyde 6a (587 mg, 2.39 mmol) and amine 7 (779 mg, 2.39 mmol). The resulting reaction mixture was stirred under atmospheric pressure at 70 °C for 1 h, followed by reduced pressure (standard laboratory oil diffusion pump) at the same temperature for an additional 2 h to afford, after column chromatography of at least two separate runs at di-flashed, the imine 8a as a thick orange oil that solidifies in a −20 °C freezer (1.308 g, 2.37 mmol, 94%). Rf = 0.26 (10% EtOAc/PE). IR (thin film) ν = 2991.6, 1737.5, 1318.9, 1170.9, 1022.0, 752.3, 687.5. 1H NMR (400 MHz, CDCl3) δ = 8.51 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.44−7.19 (m, 11H), 6.95−6.84 (m, 1H), 5.79−5.86 (m, J = 11.4, 6.7, 1.9 Hz, 1H), 4.93−4.85 (m, 2H), 3.67 (3H, 1H), 1.47 (s, 9H). 13C NMR (101 MHz, CDCl3) δ = 171.6, 166.2, 157.5, 150.0, 142.0, 140.8, 137.6, 137.2, 129.3, 128.7, 128.2, 127.8, 127.6, 125.9, 123.3, 121.9, 121.8, 115.8, 84.7, 80.0, 63.7, 51.6, 28.1. HRMS calcd for C33H33N2O6+ [M + H]+ 587.1943, found 587.1944. To a flamed-dried vial and stirred at 70 °C under air for 1 h and then under reduced pressure (standard laboratory oil diffusion pump) for an additional 2 h at 70 °C. The resulting condensation product was purified by flash chromatography (1% Et3N in 10% EtOAc/PE) to afford the imine 8b as a thick orange oil (1.774 g, 3.02 mmol, 93%). Rf = 0.58 (1% Et3N in 20% EtOAc/PE). IR (thin film) ν = 3062.9, 2981.9, 2362.8, 1735.9, 1444.7, 1321.2, 1163.1, 839.1, 754.2, 700.2. 1H NMR (400 MHz, DMSO) δ = 8.41 (s, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.55−7.47 (m, 1H), 7.43−7.19 (m, 11H), 6.83 (d, J = 15.9, 4.1 Hz, 1H), 5.69 (dt, J = 15.8, 2.0 Hz, 1H), 4.90 (dd, J = 4.1, 2.0 Hz, 1H), 3.51 (3H, 1H), 1.44 (s, 9H). 13C NMR (101 MHz, DMSO) δ = 170.8, 165.8, 155.8, 149.2, 142.5, 142.5, 134.9, 130.7, 129.2, 128.5, 128.13, 128.09, 126.9, 124.5, 120.9, 119.6, 115.8, 114.7, 86.2, 80.5, 64.2, 51.9, 27.9. HRMS calcd for C33H32ClN2O6+ [M + Na]+ 575.2153, found 575.2373 and 575.3588.

4.2.2. tert-Butyl-3-chloro-2-(E)-((2-(((E)-4-methoxy-4-oxo-2-but-2-en-1-yl)oxy)-2-oxo-1,1-diphenylethyl)imino)methyl)-1H-indole-1-carboxylate (8b). 3-Chloro-N-Boc-indole-2-carbaldehyde (909.1 mg, 3.25 mmol) and amine 7 (1.057 g, 3.25 mmol) were combined in a flame-dried vial and stirred at 70 °C under air for 1 h and then under reduced pressure (standard laboratory oil diffusion pump) for an additional 2 h at 70 °C. The resulting condensation product was purified by flash chromatography (1% Et3N in 10% EtOAc/PE) to afford the imine 8b as a thick orange oil (1.774 g, 3.02 mmol, 93%). Rf = 0.58 (1% Et3N in 20% EtOAc/PE). IR (thin film) ν = 3062.9, 2981.9, 2362.8, 1735.9, 1444.7, 1321.2, 1163.1, 839.1, 754.2, 700.2. 1H NMR (400 MHz, DMSO) δ = 8.41 (s, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.55−7.47 (m, 1H), 7.43−7.19 (m, 11H), 6.83 (d, J = 15.9, 4.1 Hz, 1H), 5.69 (dt, J = 15.8, 2.0 Hz, 1H), 4.90 (dd, J = 4.1, 2.0 Hz, 1H), 3.51 (3H, 1H), 1.44 (s, 9H). 13C NMR (101 MHz, DMSO) δ = 170.8, 165.8, 155.8, 149.2, 142.5, 142.5, 134.9, 130.7, 129.2, 128.5, 128.13, 128.09, 126.9, 124.5, 120.9, 119.6, 115.8, 114.7, 86.2, 80.5, 64.2, 51.9, 27.9. HRMS calcd for C33H32ClN2O6+ [M + Na]+ 575.2153, found 575.2373 and 575.3588.
Hz, 1H), 4.86 (dd, J = 4.4, 2.0 Hz, 2H), 3.72 (dd, J = 12.1, 5.9 Hz, 2H), 3.67 (s, 3H), 2.96 (t, J = 6.4 Hz, 2H), 1.96 (s, 2H).

13C NMR (101 MHz, CDCl₃) δ 171.9, 166.2, 153.2, 141.4, 140.7, 137.0, 132.3, 129.1, 128.2, 128.0, 125.2, 121.9, 120.0, 119.8, 118.9, 111.6, 110.0, 79.6, 63.7, 63.0, 51.7, 27.3. HRMS calcd for C₃₀H₂₉N₆O₇⁺ [M + H⁺] 497.2071, found 497.2071.

4.2.4. tert-Butyl-3-2-(tert-butoxycarbonyloxy)ethyl)-2-((E)-1-(diphenylmethylene)imino)-1H-indole-1-carboxylate (8c).

To a stirred solution of imine 8d (5.647 g, 11.7 mmol), and DMAP (428.8 mg, 3.51 mmol), and Et₃N (2.605 g, 25.74 mmol) in THF (60 mL) was added (Boc₂)O (6.380 g, 29.25 mmol) at 0 °C. The reaction was allowed to reach room temperature (rt) and stirred for 5 h, after which the solvent was removed by rotary evaporation. The resulting crude product was purified by flash chromatography (1% EtOAc/PET) to afford imine 8c (5.227 g, 7.65 mmol, 64% as a thick colorless oil. Rf = 0.36 (1% EtOAc in 10% EtOAc/PET).

IR (thin film) ν 3061.0, 2980.0, 2941.4, 1735.9, 1629.8, 1552.7, 1448.5, 1033.8, 744.5, 702.1. 1H NMR (400 MHz, CDCl₃) δ 8.39 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.49–7.17 (m, 12H), 6.89 (dt, J = 15.8, 4.5 Hz, 1H), 5.74 (dt, J = 15.7, 1.9 Hz, 1H), 4.89 (dd, J = 4.5, 2.0 Hz, 2H), 4.43 (t, J = 7.4 Hz, 2H), 3.67 (s, 3H), 3.50 (t, J = 7.4 Hz, 2H), 1.50 (s, 9H), 1.45 (s, 9H). 13C NMR (101 MHz, CDCl₃) δ 171.7, 166.2, 158.0, 153.5, 150.0, 141.6, 140.9, 136.0, 132.7, 130.0, 129.3, 128.1, 127.7, 126.1, 123.0, 121.9, 121.6, 120.0, 115.5, 84.5, 81.7, 86.0, 66.9, 63.7, 51.6, 28.1, 27.8, 24.6. HRMS calcd for C₃₀H₂₈N₆O₇⁺ [M + H⁺] 499.3120, found 499.3121.

4.2.5. tert-Butyl(3-2-((E)-4-methoxy-4-oxobut-2-1-yl)-2-oxo-1,1-diphenylethyl)imino)methyl)-1H-indole-1-carboxylate (9b).

Amine 7 (186 mg, 0.70 mmol) and N-Boc-3-chloroindole-2-carbaldehyde (213 mg, 0.76 mmol) were combined in a flask, and the mixture was stirred at 70 °C under air 1 h, followed by 2 h at 70 °C under reduced pressure (standard laboratory vacuum pump). The resulting mixture was purified by flash chromatography (1% EtOAc in 10% EtOAc/PET) to afford amine 9b (369 mg, 0.70 mmol, 95%). Rf = 0.45 (1% EtOAc in 5% EtOAc/PET).

IR (thin film) ν 2925, 1732, 1447, 1328, 1218, 1164, 1125. 1H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.65–7.61 (m, 1H), 7.51–7.46 (m, 4H), 7.42–7.27 (m, 8H), 5.89 (dd, J = 22.7, 10.8, 5.6 Hz, 1H), 5.24–5.11 (m, 2H), 4.73 (dt, J = 5.6, 1.4 Hz, 2H), 1.53 (d, J = 5.8 Hz, 9H). 13C NMR (101 MHz, CDCl₃) δ 171.4, 156.6, 149.3, 142.2, 135.5, 131.6, 129.5, 127.9, 127.5, 126.9, 123.6, 120.8, 118.4, 115.3, 103.0, 85.2, 66.4, 28.1. HRMS calcd for C₃₁H₃₁ClN₂O₄⁺ [M + H⁺] 533.2045, found 533.2043.

4.2.6. tert-Butyl(3-2-((E)-1-(diphenylmethylene)amino)-5-methoxy-5-oxopent-3-en-1-yl)-1H-indole-1-carboxylate ([±]-10a).

To a flask with a rubber septum and a magnetic stir bar was added imine 8a (2.473 g, 4.86 mmol). The flask was degassed with three consecutive vacuum/argon-fill cycles, and then, inside of an inert atmosphere glovebox, were added Pd₂(dba)₃ (2.5 mol %) and dpff (5 mol %) were added to the mixture inside an inert atmosphere glovebox. MeCN (24 mL) was added to the mixture of solids via a syringe, and the resulting mixture was stirred at 25 °C for 2 h. The solvent was removed by rotary evaporation, and the crude product was purified by flash chromatography (10% EtOAc in 90% MeCN) to afford imine 10a (2.137 g, 2.43 mmol, 50%) as a thick colorless oil. Rf = 0.36 (1% EtOAc in 5% EtOAc/PET).

IR (thin film) ν 1728.2, 1454.3, 1328.9, 1161.2, 1116.8, 1082.0, 852.5, 746.4, 698.2. 1H NMR (400 MHz, CDCl₃) δ 8.17 (d, J = 8.3 Hz, 1H), 7.75–7.70 (m, 2H), 7.50–7.37 (m, 7H), 7.29–7.17 (m, 2H), 7.06–7.01 (m, 2H), 6.95 (dt, J = 15.5, 7.3 Hz, 1H), 6.82 (s, 1H), 5.86–5.80 (m, 1H), 5.29 (dd, J = 5.8, 4.8 Hz, 1H), 3.70 (s, 3H), 2.86–2.76 (m, 2H), 1.41 (s, 9H). 13C NMR (101 MHz, CDCl₃) δ 169.0, 166.8, 150.0, 146.3, 143.0, 139.5, 137.0, 136.7, 130.3, 129.3, 128.7, 128.5, 128.1, 127.4, 123.7, 122.8, 122.7, 120.3, 115.7, 108.3, 84.0, 59.8, 51.4, 40.9, 27.9. HRMS calcd for C₃₂H₃₂ClN₂O₄⁺ [M + H⁺] 509.2435, found 509.2434.
Inside an inert atmosphere glovebox was placed a screw-cap conical vial equipped with a magnetic stir bar and charged with imine 9b (0.25 mmol), followed by addition of Ni(cod)2 (2.5 mol%), (S,S)-binaphane (2.5 mol%), and dimethyl sulfoxide (DMSO) (0.1 mL). The resulting reaction mixture was stirred at 25 °C for 24 h. The product(s) were extracted from the reaction mixture with PE and then purified by flash chromatography (1% Et2N in 3% EtOAc/PE). Rf = 0.71 (1% Et2N in 5% EtOAc/PE). [d]23p = −0.008 (c 2.0 × 10−2 g/mL, CHCl3). IR (thin film) ν 2982, 1735, 1456, 1375, 1334, 1161, 1117. 1H NMR (400 MHz, CDCl3) δ 8.00–7.94 (m, 1H), 7.69 (dd, J = 8.4, 1.3 Hz, 2H), 7.51 (t, J = 8.7 Hz, 1H), 7.32 (ddd, J = 21.1, 13.4, 6.9 Hz, 8H), 6.91 (d, J = 7.1 Hz, 2H), 5.85 (dt, J = 17.2, 7.1 Hz, 1H), 5.45 (dd, J = 8.6, 5.3 Hz, 1H), 5.09 (d, J = 17.3 Hz, 1H), 5.00 (d, J = 10.2 Hz, 1H), 3.10 (dt, J = 15.0, 7.6 Hz, 1H), 2.89 (dt, J = 12.4, 5.6 Hz, 1H), 1.50 (s, 1H). 13C NMR (101 MHz, CDCl3) δ 166.9, 138.8, 134.8, 129.4, 128.7, 128.4, 127.9, 127.2, 124.4, 122.5, 117.4, 116.3, 114.6, 83.3, 50.8, 41.3, 39.2, 28.1. HRMS calc for C25H24N2O2 [M + H]+: 367.1892, found 367.1899. HPLC conditions: Chiral Technologies Daicel OD-H chiral column, eluent: 1:1000 2-propanol/hexane, flow rate: 1 mL/min, average (S)-11b retention time = 7.17 min, average (R)-11b retention time = 8.96 min.

To a solution of imine (±)-10a (821 mg, 1.61 mmol) and EtOAc (70 mL) under an Ar atmosphere chilled to 0 °C in an ice bath was added dropwise HCl (37%, 1.04 mL). After the addition of the acid, the stirred reaction mixture was removed from the ice bath and stirred at rt for 8 h. The reaction was then quenched with sat. aq NaHCO3 and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried (Na2SO4), and concentrated by rotary evaporation. The resulting product was purified by flash chromatography (1% Et2N in 20% → 50% EtOAc/PE) to afford amine (±)-13a (478 mg, 1.39 mmol, 86%) as a thick yellow oil. Rf = 0.37 (1% Et2N in 50% EtOAc/PE). IR (thin film) ν 3385.1, 2978.1, 1732.1, 1654.9, 1452.4, 1327.1, 1159.2, 1080.1, 810.6, 748.4. 1H NMR (400 MHz, CDCl3) δ 8.03 (dd, J = 8.4, 0.7 Hz, 1H), 7.53–7.46 (m, 1H), 7.26 (ddd, J = 8.4, 7.2, 1.5 Hz, 1H), 7.21 (td, J = 7.4, 1.1 Hz, 1H), 7.03 (dt, J = 15.6, 7.2 Hz, 1H), 6.58 (s, 1H), 5.97 (dt, J = 15.7, 1.5 Hz, 1H), 4.74 (dd, J = 7.8, 5.4 Hz, 1H), 3.71 (s, 3H), 2.92–2.79 (m, 1H), 2.69–2.57 (m, 1H), 1.71 (s, 1H). 13C NMR (101 MHz, CDCl3) δ 166.7, 150.6, 146.1, 135.6, 128.6, 128.4, 120.3, 123.3, 122.9, 120.5, 115.8, 106.3, 84.5, 51.5, 48.8, 39.5, 28.2. HRMS calc for C26H22N2O2 [M + H]+: 395.1619, found 395.1613.

To a flask charged with triene (±)-4c (324 mg, 0.48 mmol) and Sc(OTf)3 (3.605 g, 7.28 mmol) under an Ar atmosphere was added dry MeCN (425 mL), and the resulting solution was stirred at rt for 7 h. The resulting mixture was quenched with sat. aq NaHCO3 and extracted with EtOAc (3 × 300 mL). The combined organic layer was washed with brine, dried (Na2SO4), concentrated by rotary evaporation, and purified by flash chromatography (10% MeOH/CH2Cl2) to afford unmodified 9b (696 mg, 1.63 mmol, 90%) as a thick yellow oil. Rf = 0.61 (10% MeOH/CH2Cl2). IR (thin film) ν 3502.7, 2931.8, 1732.1, 1597.1, 1454.3, 1369.5, 1330.9, 1118.7, 1087.9, 1031.9, 846.7, 742.6, 638.4. 1H NMR (400 MHz, CD2OD) δ 8.05 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.27 (dd, J = 11.5, 4.1 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 6.78 (s, 1H), 5.91–5.83 (m, 1H), 5.68 (d, J = 9.9 Hz, 1H), 4.71 (dd, J = 11.6, 1.9 Hz, 1H), 4.36 (t, J = 4.5 Hz, 1H), 3.68 (s, 3H), 3.37 (dd, J = 12.0, 3.5 Hz, 1H), 2.81 (dd, J = 22.7, 10.8 Hz, 1H), 2.64 (dd, J = 11.7, 4.6 Hz, 2H), 2.13–1.97 (m, 2H), 1.73 (s, 9H), 1.55 (dd, J = 24.1, 11.7 Hz, 1H). 13C NMR (101 MHz, CD2OD) δ 171.9, 150.7, 139.2, 136.4, 129.1, 128.9, 126.8, 124.5, 122.8, 120.5, 115.4, 108.3, 85.3, 64.2, 54.6, 50.7, 49.6, 39.1, 33.9, 33.6, 27.1. HRMS calc for C31H25N3O5 [M + H]+: 473.1827, found 473.1827.

To a flask charged with triene (±)-4c (324 mg, 0.48 mmol) and Sc(OTf)3 (957 mg, 2.02 mmol) under an Ar atmosphere was added dry MeCN (110 mL), and the resulting solution was stirred at rt for 7 h. The reaction was cooled to 0 °C, quenched with sat. aq NaHCO3, and extracted with EtOAc (3 × 300 mL). The combined organic layer was washed with brine, dried (Na2SO4), concentrated by rotary evaporation, and purified by flash chromatography (10% MeOH/CH2Cl2) to afford unmodified 9b (90%).

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3H), 3.09 (dd, J = 4.2 Hz, 1H), 3.88 (dd, J = 11.4, 2.4 Hz, 1H), 3.69 (s, 3H), 3.09 (dd, J = 11.8, 2.8 Hz, 1H), 2.53–2.43 (m, 2H), 2.13 (d, J = 12.8 Hz, 1H), 1.94–1.78 (m, 2H), 1.44 (dd, J = 23.9, 11.6 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 173.6, 139.9, 135.9, 131.3, 128.2, 127.9, 121.8, 120.3, 119.7, 111.1, 99.1, 64.5, 55.2, 51.8, 50.8, 50.3, 41.1, 36.0, 34.9. HRMS calcd for C36H39N2O6 [M + H]+ 573.2703, found 573.2701.

4.2.15. rac-Methyl(3S,4aS,5R,6S,8aR)-3-(1-(tert-butoxy- carbonyl)-1H-indol-2-yl)-6-hydroxydecahydroisoquinoline-5-carboxylate ([±]-16b). To a flask charged with triene (±)-4b (650 mg, 1.41 mmol) and Sc(OTf)3 (2.793 g, 5.64 mmol) under an Ar atmosphere was added MeCN (330 mL) and the resulting solution was stirred at rt for 7 h. The reaction was quenched with sat. aq NaHCO3 and extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine, dried (Na2SO4), concentrated by rotary evaporation, and purified by flash chromatography (10% MeOH/CH2Cl2) to afford amide ([±]-16b) (187 mg, 0.50 mmol, 83%) as a thick yellow oil. HRMS calcd for C36H39N2O6 [M + H]+ 573.2701, found 573.2701.

4.2.16. rac-Methyl(8aR,11S,12R,12aS,13aS)-11-hydroxy-14-(2-hydroxyethyl)-6-oxo-8a,11,12,12a,13,13a-hexahydro-6H,8H-indolo[1′,2′:3,4]imidazo[5,1-b]isoquinoline-12-carboxylate ([±]-17). To a flask charged with triene (±)-4c (398 mg, 0.59 mmol) and Sc(OTf)3 (1.176 g, 2.38 mmol) under an Ar atmosphere was added MeCN (200 mL), and the resulting solution was stirred at 35 °C for 7 h. The reaction was quenched with sat. aq NaHCO3 at 35 °C and extracted with EtOAc (3 × 150 mL). The combined organic layer was washed with brine, dried (Na2SO4), concentrated by rotary evaporation, and purified by flash chromatography (5% MeOH/CH2Cl2) to afford cyclic urea (±)-17 (198 mg, 0.50 mmol, ≤84%) as a thick yellow oil. Although not detected by NMR or HRMS spectroscopy, X-ray spectroscopy of a single crystal that formed from the NMR sample (CDCl3) indicated that the resulting product contained up to 0.5 equiv of NaOtBu after chromatography. Rf = 0.43 (5% MeOH/CH2Cl2). IR (thin film) ν 3573.8, 3498.9, 1729.5, 1608.9, 1263.6, 1172.8, 1037.1, 766.9, 644.7. 1H NMR (400 MHz, CDCl3) δ 7.95 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.31–7.25 (m, 1H), 7.24–7.19 (m, 1H), 5.97 (ddd, J = 9.9, 4.8, 2.7 Hz, 1H), 5.69 (d, J = 10.8 Hz, 1H), 4.65 (dd, J = 11.5, 4.0 Hz, 1H), 4.43 (t, J = 4.1 Hz, 1H), 4.27 (dd, J = 13.2, 4.5 Hz, 1H), 3.95–3.80 (m, 2H), 3.76 (s, 3H), 2.94 (t, J = 6.3 Hz, 2H), 2.79–2.70 (m, 1H), 2.60–2.53 (m, 1H), 2.50 (dd, J = 11.8, 3.9 Hz, 1H), 2.10 (ddd, J = 14.3, 11.9, 2.6 Hz, 1H), 1.97 (dt, J = 16.0, 8.8 Hz, 1H), 1.18 (dd, J = 24.4, 11.9 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 173.2, 150.3, 135.9, 132.9, 130.2, 128.9, 123.3, 122.2, 119.1, 112.5, 107.5, 64.6, 62.1, 54.2, 51.9, 49.8, 44.3, 40.9, 34.3, 33.2, 27.7. HRMS calcd for C27H24N3O4 [M + H]+ 439.1758, found 439.1738.
The slurry of alkenne ([±]-16a (148 mg, 1.28 mmol) and Pd/C (105 mg) in MeOH (25 mL) was stirred under an H₂ atmosphere (balloon) for 2 h, after which the mixture was filtered through Celite, the filter cake was washed with EtOAc, and the combined filtrate was concentrated by rotary evaporation. The resulting residue was purified by flash chromatography (10% MeOH/CH₂Cl₂) to afford amine ([±]-18c (305 mg, 0.93 mmol, 73%) as a thick yellow oil. Rₜ = 0.34 (10% MeOH/CH₂Cl₂). IR (thin film) v = 3346.5, 3057.2, 2972.9, 2856.6, 1730.2, 1616.3, 1446.6, 1290.4, 1166.0, 1039.0, 958.6, 852.5, 746.4, 638.4. ¹H NMR (400 MHz, CD₃OD) δ 7.48 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.17–7.06 (m, 1H), 7.01–6.95 (m, 1H), 6.44 (s, 1H), 4.31–4.22 (m, 2H), 3.67 (s, 3H), 3.20 (dd, J = 12.3, 2.9 Hz, 1H), 2.84–2.75 (m, 1H), 2.41–2.28 (m, 2H). 111.4, 111.3, 77.3, 77.2, 77.0, 76.7, 66.2, 52.4, 52.2, 51.9, 51.9, 40.4, 36.9, 36.3, 30.9, 23.1. HRMS calcd for C₂₆H₃₅N₂O₆ [M + H]+ 329.1860, found 329.1856.

4.2.20. rac-Methyl(3S,4aS,5R,6S,8aR)-6-hydroxydecahydoquinoiline-5-carboxylate ([±]-18d). A slurry of alkenne ([±]-16b (66 mg, 0.18 mmol) and Pd/C (17 mg) in EtOAc (4 mL) was stirred under an H₂ atmosphere (balloon) for 1 h, after which the mixture was filtered through Celite, the filter cake was washed with EtOAc, and the combined filtrate was concentrated by rotary evaporation. The resulting residue was purified by flash chromatography (10% MeOH/CH₂Cl₂) to afford amine ([±]-18d (46 mg, 0.13 mmol, 70%) as a thick yellow oil. Rₜ = 0.51 (10% MeOH/CH₂Cl₂). IR (thin film) v = 3261.6, 2927.9, 2854.6, 1732.1, 1582.1, 1424.8, 1311.6, 1215.3, 974.3, 744.5. ¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 7.3 Hz, 1H), 4.22–4.12 (m, 2H), 3.66 (s, 2H), 2.96 (d, J = 11.2 Hz, 1H), 2.59 (t, J = 11.1 Hz, 1H), 2.26 (d, J = 11.7 Hz, 1H), 1.98 (dd, J = 30.2, 12.1 Hz, 3H), 1.70 (d, J = 12.6 Hz, 1H), 1.60–1.19 (m, 7H). ¹³C NMR (100 MHz, CDCl₃) δ 176.0, 134.7, 134.0, 125.5, 125.8, 120.3, 117.8, 111.4, 113.1, 77.3, 77.2, 77.0, 76.7, 66.2, 52.4, 52.2, 51.9, 51.9, 40.4, 36.9, 36.3, 30.9, 23.1. HRMS calcd for C₃₁H₃₇ClNO₆ [M + H]+ 536.1470, found 536.1460.

4.2.21. rac-Methyl(3S,4aS,5R,6S,8aR)-6-hydroxydecahydropseudoquinoline-5-carboxylate ([±]-19). A flask charged with amine 18c (305 mg, 0.93 mmol), O-TBDPS 2-hydroxyacetaldehyde 13 (555 mg, 2.79 mmol) was dissolved in CH₂Cl₂ (6 mL) under an Ar atmosphere and cooled to 0 °C. To this cooled solution was added dropwise TBAF (119 mg, 0.46 mmol). The mixture was stirred at 0 °C for 2 h, then quenched with sat. aq NH₄Cl solution and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried (Na₂SO₄), concentrated by rotary evaporation, and purified by flash chromatography (1% EtOAc/MeOH) to afford alcohol ([±]-19 (92 mg, 0.25 mmol, 81%) as a thick yellow oil. Rₜ = 0.43 (10% MeOH/CH₂Cl₂). IR (thin film) v = 3388.9, 3053.2, 2933.7, 2856.6, 1732.1, 1454.3, 1213.2, 1155.4, 1018.4, 790.8, 742.6. ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 7.4 Hz, 1H), 6.30 (s, 1H), 4.19 (d, J = 2.6 Hz, 1H), 3.59 (s, 3H), 3.57–3.48 (m, 2H), 3.43 (dd, J = 11.0, 6.3, 4.7 Hz, 1H), 1.34 (d, J = 9.5 Hz, 1H), 2.74–2.65 (m, 1H), 2.24 (dd, J = 11.4, 2.6 Hz, 1H), 2.16 (dt, J = 12.9, 5.1 Hz, 1H), 2.05 (t, J = 10.7 Hz, 1H), 1.98–1.83 (m, 3H), 1.69–1.57 (m, 1H), 1.49 (dd, J = 23.7, 11.8 Hz, 1H), 1.38 (dd, J = 14.2, 7.5 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 173.8, 139.9, 136.2, 128.1, 120.7, 119.4, 118.7, 110.5, 99.6, 67.1, 62.5, 59.1, 58.3, 56.3, 52.2, 50.6, 39.6, 38.4, 35.9, 32.0, 22.9. HRMS calcd for C₂₉H₃₇N₃O₆ [M + H]+ 373.2122, found 373.2105.

4.3. In Vivo Cell Viability Assays. A 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay was used to evaluate the cytotoxic effects of synthetic yohimbine analogues 15a, 15b, 16b, and 17 against the pancreatic cancer cell line (PATU-8988) and against the gastric cancer cell line (SGC-7901). The normal human gastric mucosal cell line GES-1 was used to evaluate the general cytotoxicity of the four compounds. Briefly, the cells were counted and then seeded into 96-well plates at a density of 4 × 10⁴ cells per well, followed by incubation in a CO₂ incubator at 37 °C for 24 h. The cells were then treated with the appropriate concentration gradient of each yohimbine analogue and culture for 48 h. Afterward, the contents of the 96-well plates were carefully removed and MTT was added; the reaction was maintained at 37 °C in a 5% CO₂ atmosphere for an additional 4 h, after which the MTT dye was removed. Finally, 150 μL of DMSO was added, and the absorbance of the purple formazan solution was measured by UV at 570 nm. These cytotoxicity assays were performed in three independent assays, and the average IC₅₀ (±SE) were calculated, as reported in Table 4.

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Additional experimental procedures; copies of NMR spectra; raw biological assay data tables; synthesis of tert-butyl-2-formyl-1H-indole-1-carboxylate; synthesis of tert-butyl-3-chloro-2-formyl-1H-indole-1-carboxylate; conversion of 11a into 10a via olefin metathesis; and synthesis of (±)-4b; and synthesis of (±)-4c (PDF)

X-ray structural data for (±)-17 ( cif)

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All syntheses were conducted by H.Y., M.P., and C.L. under the supervision of J.J.C. and X.C. Biological assays were performed by P.X. and L.D. under the direction of S.T. J.J.C., S.T., M.P., and H.Y. contributed to the writing of the manuscript.

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