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The Pauson–Khand reaction as a new entry to the synthesis of bridged bicyclic heterocycles: application to the enantioselective total synthesis of (−)-alstonerine

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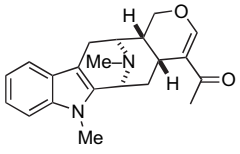
Abstract

The first application of the Pauson–Khand reaction (PKR) to the synthesis of azabridged bicyclic structures is described. Compounds containing azabicyclo[3.3.1]nonane and azabicyclo[3.2.1]octane rings fused to cyclopentenones were efficiently constructed via the PKR of *cis*-2,6-disubstituted *N*-acyl piperidine enyne substrates, many of which can be readily prepared from 4-methoxypyridine in a few steps. Moreover, the PKR of *cis*-2,6-disubstituted piperazine enynes allowed the preparation of diazabicyclo[3.3.1]nonanes fused to cyclopentenones. This new strategy for the synthesis of azabridged bicyclic frameworks was exploited as a key step in a concise, enantioselective total synthesis of the macroline alkaloid (−)-alstonerine.

1. Introduction

The macroline/sarpagine alkaloids comprise a diverse class of biologically active natural products characterized by an azabicyclo[3.3.1]nonane annelated to an indole ring.[1] A variety of methods have been devised to access this structural motif, and these include a sequential Pictet–Spengler reaction and Dieckmann condensation,[2] ring-closing metathesis,[3] phosphine-catalyzed [4+2] annulation/Friedel–Crafts cyclization,[4] and aza Diels–Alder/intramolecular Heck reaction.[5] As a representative member of the macroline family of alkaloids, alstonerine (**1**) has been the subject of a number of synthetic studies culminating in two total syntheses and one formal synthesis.[4,6] In addition to its challenging structural features, **1** has been reported to exhibit cytotoxic activity against two human lung cancer cell lines.[7]

Within the context of an ongoing interest in the synthesis of complex, biologically active alkaloids, we have been interested in designing novel and general strategies for the facile preparation of the representative members of different alkaloid families.[8] While developing new transition metal-catalyzed cascade reaction sequences,[9] we became interested in examining possible applications of the Pauson–Khand reaction (PKR) toward alkaloid synthesis. The intramolecular version of the PKR has been applied to the syntheses of a few alkaloid natural products,[10] but in each case its use has been limited to the preparation of bicyclo[3.3.0]octenones and bicyclo[3.3.0]nonenones.[11]



1

As is apparent from the retrosynthetic strategy outlined in Scheme 1, we expected to obtain **1** by reduction, elimination, and acylation of the lactone **2**, which we envisioned would arise by Baeyer–Villiger oxidation and stereoselective reduction of the enone **3**. A key step in the synthesis of **1** would then be the PKR of the enyne **4**, which had been previously prepared in our group,[3] to give **3**. We anticipated that the PKR approach would represent a particularly efficient strategy for the preparation of **1**, because the PKR of **4** would result in

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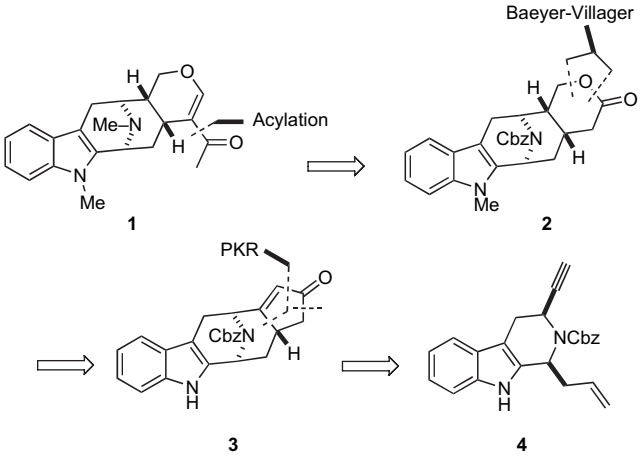
the formation of three new carbon–carbon bonds and the assembly of two rings in a single step. Notably, the enone **3** contains all of the carbons present in the core of **1**.

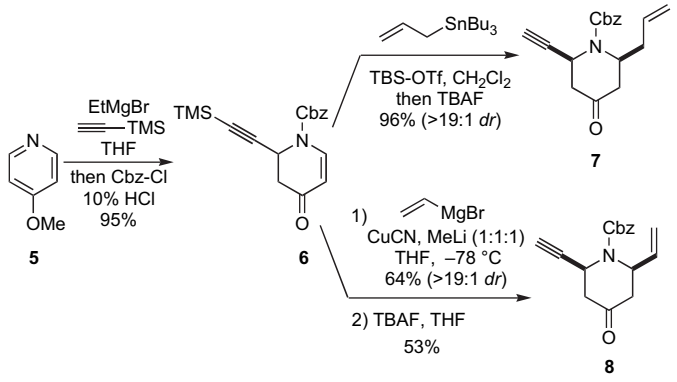


Scheme 1.

2. Results and discussion

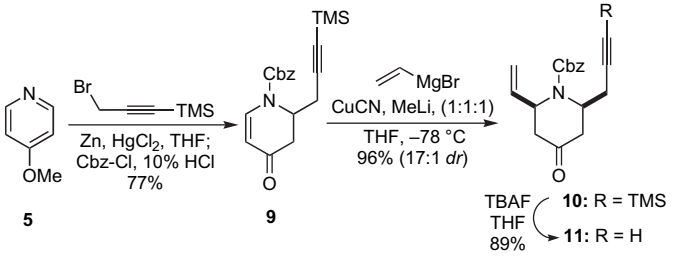
2.1. Model studies

Inasmuch as the pivotal PKR to form azabridged bicyclic frameworks lacked precedent, we undertook the synthesis of a number of *cis*-2,6-disubstituted piperidine enynes that differed in the number of carbons separating the alkene and alkyne moieties from the acylated nitrogen atom. We sought to use these enynes as substrates for PKRs to assemble azabicyclo[3.3.1]nonanes and azabicyclo[3.2.1]octanes. We reasoned that a number of such enynes could be easily prepared from 4-methoxypyridine (**5**) via slight modification of chemistry we had previously developed that was inspired by the work of Comins and coworkers.[3,12] Accordingly, 4-methoxypyridine (**5**) was treated with the acetylide ion derived from TMS–acetylene in the presence of Cbz–Cl, and following an acidic workup, the enone **6** was isolated in 95% yield (Scheme 2). Compound **6** underwent facile conjugate addition of allyltributylstannane in the presence of TBS–OTf as a Lewis acid, and treating the intermediate adduct thus obtained in situ with TBAF furnished the enyne **7** in excellent yield and diastereoselectivity. Similarly, reaction of **6** with a vinyl cuprate followed by removal of the silyl group provided the enyne **8** with excellent diastereoselectivity.



Scheme 2.

Alternatively, treatment of 4-methoxypyridine (**5**) with the zinc reagent derived from 1-trimethylsilyl propargyl bromide in the presence of Cbz–Cl gave enone **9** in 77% yield (Scheme 3). Sequential reaction of **9** with a vinyl cuprate followed by treatment with TBAF gave the enyne **11** with excellent diastereoselectivity.



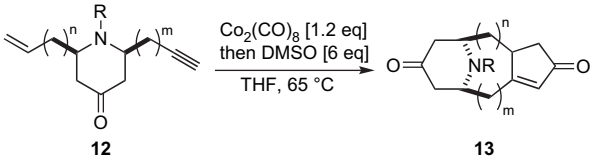
Scheme 3.

With a series of the requisite *cis*-2,6-disubstituted piperidines **7**, **8**, and **11** in hand, the PKR of **7** was investigated utilizing $Co_2(CO)_8$ and a number of common promoters, including NMO,[13] BuSMe,[14] and 4 Å molecular sieves.[15] The conditions that were found to be the most efficient involved reacting **7** with $Co_2(CO)_8$ to give an intermediate cobalt-complex that was then treated with 6 equiv of DMSO and warmed to 65 °C. Using this protocol, the enone **14** was isolated in 89% yield as a single diastereomer (Table 1, entry 1). During the course of optimizing this reaction, we discovered that handling and storage of $Co_2(CO)_8$ under argon gave the best results. We briefly examined several catalytic variants employing either cobalt or rhodium catalysts, but these conditions failed to provide isolable quantities of the enone **14**,[16] and starting enyne **7** was typically recovered. With the optimized PKR conditions in hand, the enyne **11** was then cyclized to provide **15**, again as a single diastereomer (entry 2). On the other hand, the PKR of enyne **8** gave the more strained enone **16** as a mixture (3:1) of diastereomers (entry 3).

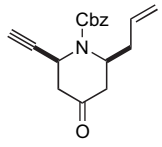
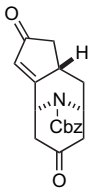
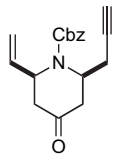
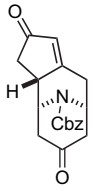
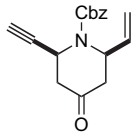
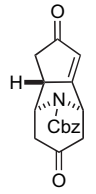
Each of the PKR substrates thus far prepared contained a carbonyl group at C(4) of the piperidine ring, and it was of interest to determine the effect of having an sp^3 carbon atom at this position. Toward this end, the enyne **7** was treated with L-Selectride to deliver the alcohol **17**, which was protected as the corresponding TBS-ether **18** (Scheme 4).

We were also interested in enyne substrates lacking functionality at C(4) such as **23**. However, preliminary attempts to deoxygenate either **7** or **17** under a number of standard conditions to give **23** were unavailing. We therefore developed a different strategy for preparing **23** that was based upon previous work in our group.[3] In the event, alkylation of the known sulphone **19** with the acetylide derived from TMS–acetylene gave the lactam **20**, which was *N*-acylated to provide **21** (Scheme 5). Reduction of the more electrophilic amide carbonyl group in **21** with DIBAL–H gave an intermediate

Table 1
Pauson–Khand reactions of piperidones

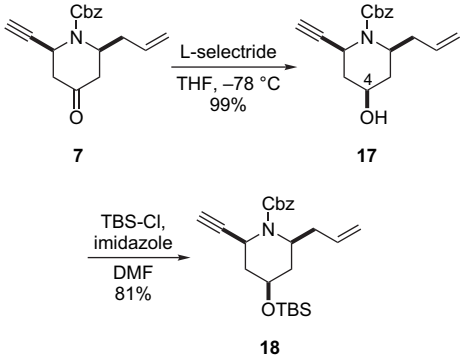


12 13

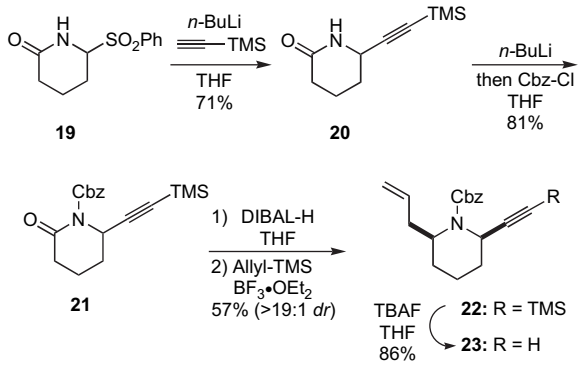
Entry	Substrate	Product	Yield (%)
1	 7	 14	89
2	 11	 15	91
3	 8	 16	33 (3:1 dr)

N,*O*-acetal that was treated sequentially with allyltrimethylsilane TMS in the presence $BF_3 \cdot Et_2O$ and fluoride ion to furnish the desired enyne **23**.

Bicyclic derivatives of piperazine are commonly found in compounds having useful biological activities, so we were intrigued by the possibility of preparing cyclopentenone rings fused to diazabicyclo[3.3.1]nonanes via a PKR. In order to probe the feasibility of such processes we prepared the piperazine derivatives **30** and **31** using chemistry inspired by Beak and coworkers.[17] Accordingly, directed lithiation of the Boc-protected piperazines **24** and **25** followed by transmetalation

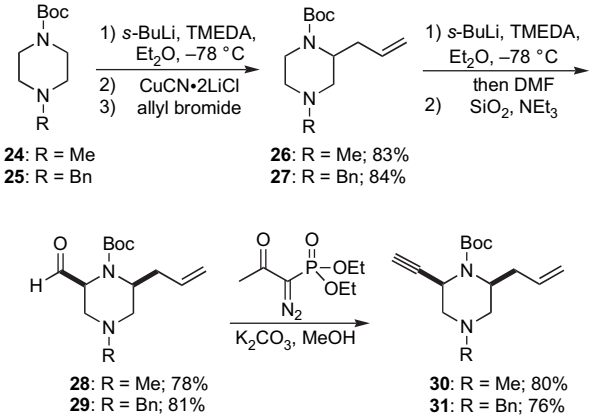


Scheme 4.



Scheme 5.

and alkylation with allyl bromide provided the known allyl piperazines **26** and **27** (Scheme 6).[18] A second directed lithiation of **26** and **27** followed by formylation of the intermediate carbanions with DMF provided a mixture of aldehyde epimers that underwent equilibration on silica gel to provide solely the cis-products **28** and **29**. Subsequent treatment of aldehydes **28** and **29** with the Bestmann–Ohira reagent in methanol containing K_2CO_3 gave the piperazine enynes **30** and **31**.



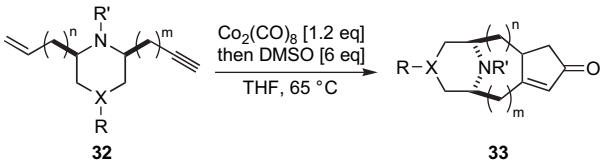
Scheme 6.

We discovered that the substitution at C(4) in **18**, **23**, **30**, and **31** played a role in the diastereoselectivity of the PKR (Table 2). For example, the PKR of the silyl ether **18** gave **34** as a single diastereomer (entry 1), whereas **23**, which bears a methylene group at C(4) underwent a PKR to give a mixture (4:1) of diastereomers favoring **35** as the major product (entry 2). The piperazines **30** and **31** underwent clean PKRs to give the enones **36** and **37** as single diastereomers (entry 3).

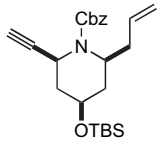
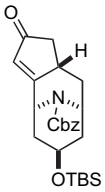
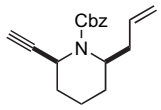
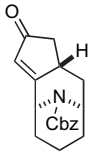
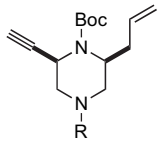
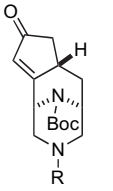
2.2. Total synthesis of (−)-alstonerine (*1*)

As outlined in Scheme 1, our plan for the total synthesis of (−)-alstonerine (**1**) hinged upon the PKR of the enyne **4** to give the azabridged bicyclic cyclopentenone **3**. The precedent established in the PKRs of the model substrates described in the previous section strongly suggested that this retrosynthetic plan was sound. The known enyne **4** was first prepared in four

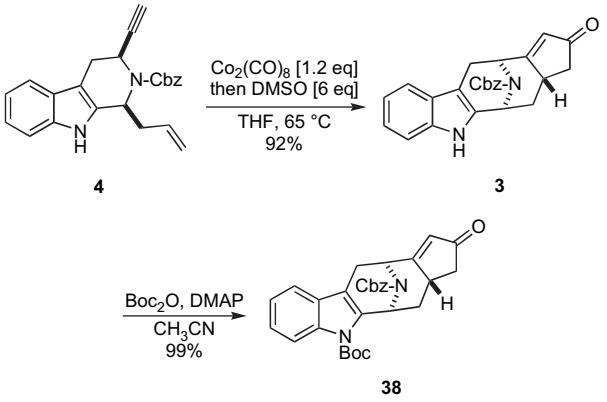
Table 2
Pauson–Khand reactions of piperidines



32 33

Entry	Substrate	Product	Yield (%)
1	 **18**	 **34**	69
2	 **23**	 **35**	74 (4:1 dr)
3	 **30:** R = Me **31:** R = Bn	 **36:** R = Me **37:** R = Bn	R=Me; 85 R=Bn; 81

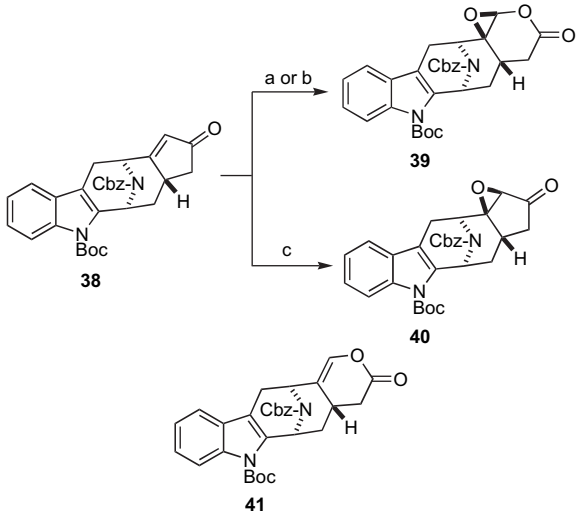
steps from L-tryptophan following a procedure previously developed in our group.[3] The PKR of **4** proceeded smoothly to give the cyclopentenone **3** in excellent yield as a single diastereomer (Scheme 7). At this juncture, it was necessary to establish the relative stereochemistry of the newly established stereocenter on the cyclopentenone ring, but **3** was not crystalline. However, protection of the indole nitrogen atom with a Boc group gave **38**, which was a crystalline compound. The X-ray structure of **38** showed that the hydrogen atom on the newly formed stereocenter was oriented trans to the bridging nitrogen atom, a stereochemical relationship that is identical to that found in (−)-alstonerine (**1**).



4 3 38

Scheme 7.

With the pentacyclic intermediate **3** readily in hand, the next stage of the synthesis required the ring expansion and oxidation of the cyclopentenone ring to give a δ-lactone ring as found in **2**. We had originally envisioned that such a transformation might be induced via a Baeyer–Villiger reaction. Perhaps not unexpectedly in retrospect, initial experiments directed toward conducting a Baeyer–Villiger reaction on **3** gave complicated reaction mixtures. Reasoning competing oxidation of the indole ring in **3** might be a source of difficulty, we also examined the Baeyer–Villiger oxidation of **38** to ascertain whether we might access the unsaturated lactone **41**. While the putative oxidation of the indole ring was thus thwarted, the Baeyer–Villiger reaction of **38** was accompanied by unavoidable double bond oxidation to give the epoxy lactone **39** (Scheme 8), a side reaction we knew was well precedented.[19] As a final attempt, we treated **38** with basic hydrogen peroxide, a reagent that has been reported to induce Baeyer–Villiger reactions of strained ketones,[20] but this reaction afforded only the epoxide **40**.



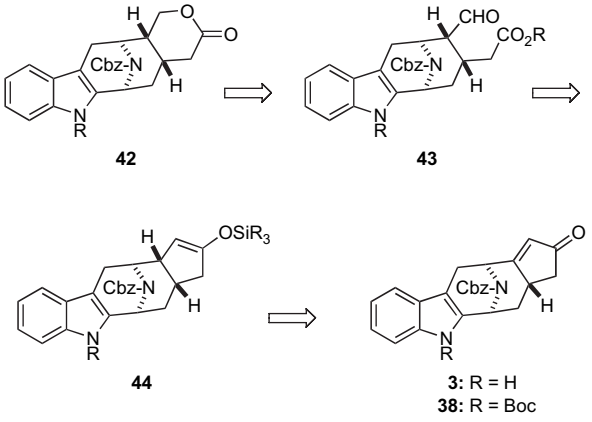
38 39 40 41

(a) MCPBA, CH_2Cl_2, 60%. (b) CF_3CO_3H, Na_2HPO_4, CH_2Cl_2, 99%. (c) H_2O_2, NaOH, THF/MeOH, 78%

Scheme 8.

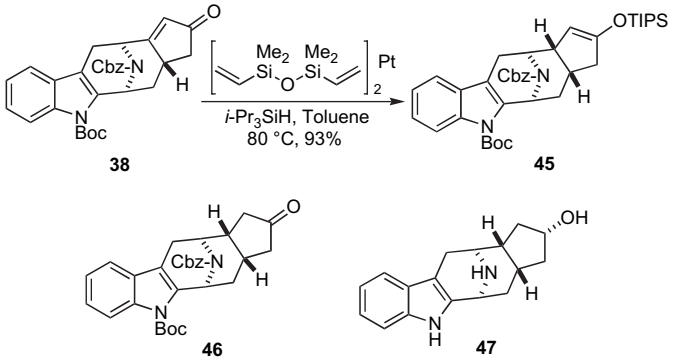
Since we were unable to obtain the unsaturated lactone **41** by a Baeyer–Villiger reaction of **38**, it was necessary to devise an alternate plan for the synthesis of (−)-alstonerine (**1**); this is outlined in retrosynthetic format in Scheme 9. Namely, we envisioned that the saturated lactone **42** would arise from reduction of the aldehyde **43** followed by lactonization. The aldehyde **43** would in turn be prepared by the oxidative cleavage of the silyl enol ether **44**, which in turn would be obtained from either **3** or preferably **38** by stereoselective hydrosilylation of the enone moiety.

In order to minimize any interference from the electron rich indole ring, we initiated our studies with the protected indole **38**. After some experimentation, we discovered that hydrosilylation of **38** was most efficiently induced by treating **38** with 0.5%



Scheme 9.

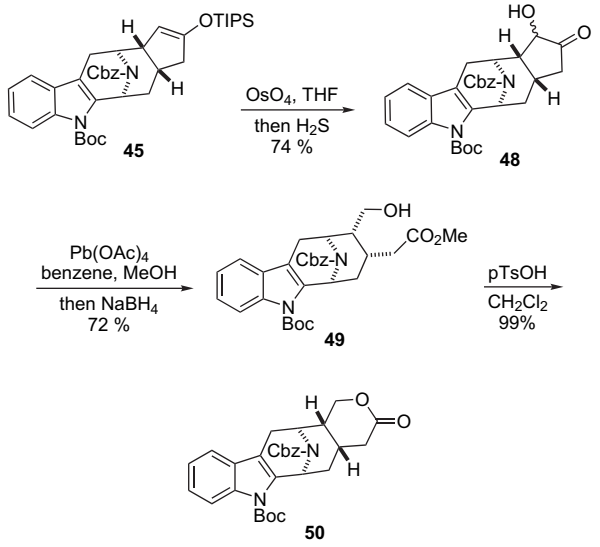
platinum divinyltetramethyl disiloxane complex (Karstedt's catalyst) in the presence of 5 equiv of *i*-Pr_3SiH at elevated temperature to give **45** in excellent yield (Scheme 10).[21] Less bulky silanes such as TES–H and TBS–H led to the formation of significant amounts of the ketone **46** (20–30%), which could have arisen via two different pathways. Silane dimerization would form molecular hydrogen that could then reduce the enone in the presence of the platinum catalyst to give **46**.[22] Alternatively, hydrolysis of the less stable TES- and TBS-enol ethers **44** (R_3=Et_3 or *t*-$BuMe_2$) would also produce **46**. The stereochemistry of the hydrosilylation of **38** was determined by converting the silyl enol ether **45** into the crystalline amino alcohol **47** in four steps [(a) TBAF, THF; (b) $NaBH_4$, THF;



Scheme 10.

(c) silica gel, 100 °C; (d) H_2, Pd/C, EtOAc] in about 50% overall yield. Inasmuch as the X-ray analysis of **47** confirmed that the relative stereochemistry of **47** was identical to that found in **1**, we could further advance our efforts toward the synthesis of **1**.

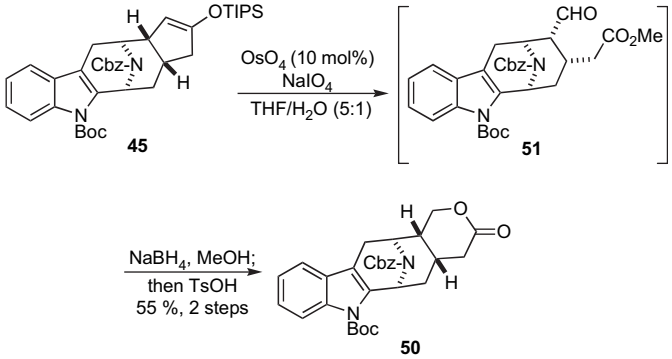
Because ozonolysis of **45** under several different conditions gave complex mixtures, we turned to a two-step procedure to induce oxidative cleavage of the silyl enol ether moiety in **45**. Rubbottom oxidation of **45** using MCPBA or DMDO under a number of conditions was found to be problematic. Similarly, oxidation of **45** using various protocols involving catalytic quantities of OsO_4 led to low conversions. However, treatment of **45** with stoichiometric amounts of OsO_4 led to complete consumption of **45**, and reduction of the intermediate osmate ester using H_2S furnished a mixture of epimeric α-hydroxy ketones **48** (Scheme 11). This mixture of α-hydroxy ketones was treated with $Pb(OAc)_4$ in the presence of MeOH to give an aldehyde/ester intermediate that was reduced in situ to deliver the hydroxy ester **49**. Lactonization of **49** under acidic conditions then gave the lactone **50**, which is a protected derivative of **2**.



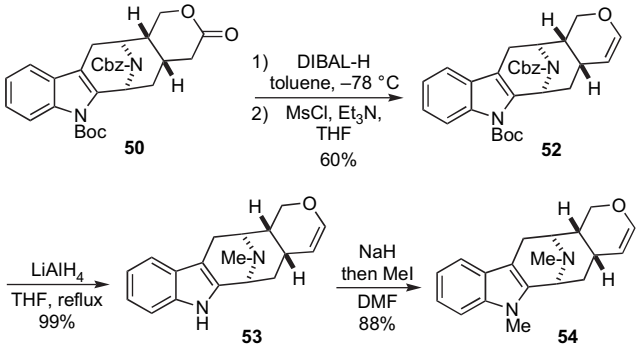
Scheme 11.

Although we had developed an efficient route to access the lactone **50**, the use of stoichiometric amounts of osmium and lead reagents inspired us to pursue an oxidative cleavage strategy that was more environmentally benign. The application of Johnson–Lemieux conditions to the oxidative cleavage of silyl enol ethers is rare.[23] Consequently, we were gratified to find that reaction of **45** with a catalytic amount of OsO_4 (10%) in the presence of $NaIO_4$ gave the intermediate aldehyde/ester **51** that underwent facile lactonization upon sequential treatment with $NaBH_4$ and acid to give **50** (Scheme 12).

Having thus developed an improved route to the intermediate lactone **50**, it was necessary to convert the δ-lactone into a dihydropyran. Toward this objective, **50** was reduced with DIBAL–H to afford an intermediate lactol that was converted to the dihydropyran **52** by a one step process involving O-mesylation and elimination (Scheme 13). Compound **52** was



Scheme 12.

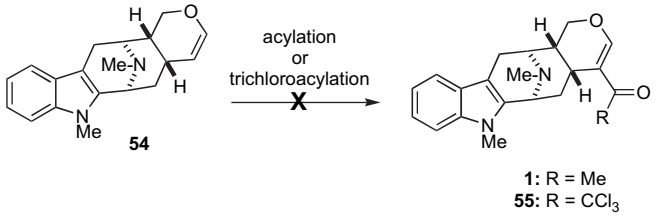


Scheme 13.

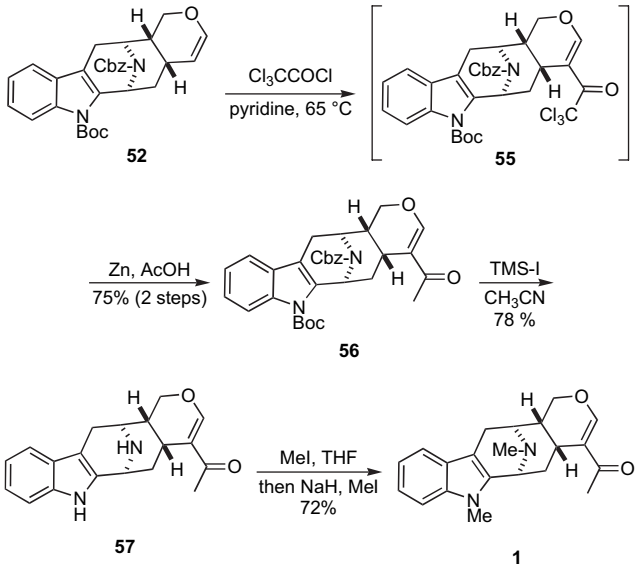
then transformed into the *N*,*N*′-dimethyl derivative **54** by reduction of the Cbz group to a methyl group and removal of the Boc group with $LiAlH_4$ followed by methylation of the indole nitrogen atom of the **53** thus formed.

The final phase of the synthesis of (−)-alstonerine (**1**) required acetylation of the dihydropyran ring of **54**. We therefore examined a number of Friedel–Crafts reaction conditions that had previously been employed to acetylate dihydropyran rings.[24] However, treatment of **54** with acetylating agents such as AcCl and Ac_2O in the presence of different Lewis acids ($AlCl_3$, $BF_3{\cdot}OEt_2$, $FeCl_3$, $ZnCl_2$) led to mixtures of products (Scheme 14). Competitive acylation at C(5) of the indole ring system was observed as a predominant side reaction, and only small quantities of **1** were obtained. In previous work directed toward the syntheses of heteroyohimboid alkaloids,[25] we had discovered that dihydropyrans could be readily trichloroacetylated using trichloroacetyl chloride under less forcing conditions and in the absence of Lewis acid catalysts. If **54** could be converted into **55**, reduction of the trichloroacetyl group would afford **1**. However, treatment of **54** with trichloroacetyl chloride at room temperature led to rapid formation of an intractable mixture of unidentifiable products.

This result did not occasion great surprise as we had previously found that those reactions of pentacyclic indolic dihydropyrans having free amines and/or unprotected indoles could be problematic.[25] Although several attempts to acetylate the protected substrate **52** with AcCl in the presence of Lewis acids were unsuccessful, we discovered that trichloroacetylation of **52** was readily accomplished to give **55** (Scheme 15). Reduction of the trichloroacetyl group using Zn/HOAc gave the protected (−)-alstonerine **56** in good yield over the two steps. This sequence of reactions should prove to be



Scheme 14.



Scheme 15.

generally useful as a method for the synthesis of C(2)-acylated glycals, a functional motif found widely in biologically active natural products.[26]

Removal of both of the carbamate protecting groups from **56** proceeded cleanly upon treatment with TMS–I to give **57**, which was *N*,*N*′-dimethylated **57** by sequential reaction with MeI to methylate the bridging secondary amine followed by NaH and MeI to alkylate the indole nitrogen atom, thereby completing the enantioselective synthesis of (−)-alstonerine (**1**). The spectral data (^1H and ^{13}C NMR) for the synthetic **1** thus obtained were consistent with those previously reported,[6b] and the optical rotation was comparable to the value reported in the literature.[6a]

3. Conclusion

In summary, we have developed the first application of the Pauson–Khand reaction to prepare azabridged bicyclic compounds. A number of *cis*-2,6-disubstituted piperidine and piperazine enynes were efficiently prepared, and these enynes underwent PKR to give cyclopentenone rings fused to aza- and diazabicyclo[3.*n*.1]alkanes (*n*=2, 3), typically in high yields and high diastereoselectivities. The utility of this new entry to bridged nitrogen heterocycles was highlighted by its application to the concise, enantioselective total synthesis of the macroline indole alkaloid (−)-alstonerine (**1**). The total synthesis of **1** required only 15 chemical steps from L-tryptophan and proceeded in a 4.4% overall yield. Other key steps in the synthesis entailed a conjugate hydrosilylation of the cyclopentenone and an oxidative cleavage that led to an intermediate δ-lactone. Moreover, a novel, mild two-step protocol to acetylate cyclic enol ethers such as dihydropyrans to give vinylogous esters, a common structural subunit in many natural products, was developed. Further applications of PKR reactions to the syntheses of other biologically active alkaloid natural products are in progress and will be reported in due course.

4. Experimental

4.1. General

Solvents and reagents were reagent grade and used without purification unless otherwise noted. Dichloromethane (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride and stored under nitrogen. After opening, $Co_2(CO)_8$ was handled and stored under argon. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were passed through a column of neutral alumina and stored under argon. Methanol (MeOH) and dimethylformamide (DMF) were passed though a column of molecular sieves and stored under argon. Toluene was passed through a column of Q5 reactant and stored under argon. All reactions were performed in flame-dried glassware under nitrogen or argon. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained at 500 or 400 MHz. Chemical shifts are reported in parts per million (ppm, δ) and referenced to the solvent. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as: s, singlet; d, doublet; t, triplet; m, multiplet; p, pentuplet; app, apparent; comp, complex; br, broad; and br s, broad singlet. Infrared (IR) spectra were obtained using a Perkin–Elmer FTIR 1600 spectrophotometer on sodium chloride plates and reported as wavenumbers (cm^{-1}). Low-resolution chemical ionization mass spectra were obtained on a Finnigan TSQ-70 instrument, and high-resolution measurements were obtained on a VG Analytical ZAB2-E instrument. Analytical thin layer chromatography was preformed using Merck 250 micron 60F-254 silica plates. The plates were visualized with UV light, *p*-anisaldehyde, and potassium permanganate. Flash column chromatography was performed according to Still's method using ICN Silitech 32-63 D 60A silica gel.[27]

4.2. 4-Oxo-2-trimethylsilanylethynyl-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (**6**)

EtMgBr (2.35 mL, 2 M in THF, 4.7 mmol) was added to a solution of TMS–acetylene (508 mg, 5.17 mmol) in THF (4 mL) at −78 °C, and the cooling bath was removed while stirring was continued for 30 min. The solution was added to a solution of 4-methoxypyridine (430 mg, 3.90 mmol) in THF (4 mL) at −78 °C, and the reaction mixture was stirred for 5 min. Upon warming to −20 °C, Cbz–Cl (1.00 g, 5.90 mmol) was added. The reaction mixture was stirred for an additional 20 min, whereupon 10% HCl (6 mL) was added. The cooling bath was removed, and stirring was continued for 10 min. Et_2O (6 mL) was added, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 678 mg (96%) of **6** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J=7.2 Hz, 1H), 7.39–7.32 (comp, 5H), 5.41–5.22 (comp, 4H), 2.79 (dd, J=16.4, 6.8 Hz, 1H), 2.58 (d, J=16.4 Hz, 1H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 134.8, 128.8, 128.7, 128.6, 128.1, 107.7, 100.3, 89.5, 69.1, 45.6, 41.2, 38.1, −0.39; IR (neat) 2960, 1732, 1677, 1609, 1329, 1307, 1252, 1213, 1188, 845 cm^{-1}; mass spectrum (CI) *m/z* 328.1373 [$C_{18}H_{22}NO_3Si$ (M+H) requires 328.1369], 328 (base), 312, 284.

4.3. 2-Allyl-6-ethynyl-4-oxopiperidine-1-carboxylic acid benzyl ester (**7**)

TBS–OTf (924 mg, 3.50 mmol) was added to a solution of **6** (950 mg, 2.91 mmol) and allyltributylstannane (1.15 g, 3.50 mmol) in CH_2Cl_2 (15 mL) at −78 °C, and the solution was stirred for 15 min. TBAF (2.90 g, 9.00 mmol) was added, and the cooling bath was removed. After 30 min, NH_4Cl (15 mL) was added. The mixture was extracted with CH_2Cl_2 (3×20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 830 mg (96%) of **7** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (comp, 5H), 5.80–5.40 (comp, 2H), 5.20–5.00 (comp, 4H), 4.52 (br s, 1H), 2.80–2.40 (comp, 6H), 2.41 (d, J=2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 154.8, 135.9, 133.9, 128.5, 128.2, 128.0, 118.3, 82.5, 67.9, 53.2, 45.1, 42.9, 42.7, 39.5; IR (neat) 3285, 3067, 3033, 2977, 1693, 1642, 1404, 1322, 1112, 1028, 920, 698 cm^{-1}; mass spectrum (CI) *m/z* 298.1439 [$C_{19}H_{20}NO_3$ (M+H) requires 298.1443].

4.4. 2-Ethynyl-4-oxo-6-vinyl-piperidine-1-carboxylic acid benzyl ester (**8**)

MeLi (0.94 mL, 1.6 M in Et_2O, 1.5 mmol) was added to a suspension of CuCN (134 mg, 1.5 mmol) in THF (4 mL) at −78 °C. The mixture was cooled to 0 °C, stirred for 1 min, and then recooled to −78 °C. A solution of vinyl magnesium bromide (1.5 mL, 1 M in THF, 1.5 mmol) was added dropwise. The reaction mixture was stirred for 20 min, whereupon a solution of **6** (327 mg, 1 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred for 1 h at −78 °C, at which point the reaction mixture was poured into a vigorously stirred mixture (9:1) of satd NH_4Cl/NH_4OH. The mixture was stirred for 30 min until all the solids have dissolved, and the solution was extracted with Et_2O (3×20 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 227 mg (64%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (comp, 5H), 6.07 (ddd, J=16.8, 10.4, 6.4 Hz, 1H), 5.49 (br s, 1H), 5.22–5.10 (comp, 4H), 4.88 (br s, 1H), 2.97 (dd, J=15.6, 7.2 Hz, 1H), 2.69–2.58 (comp, 3H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 154.7, 137.6, 136.0, 128.5, 128.2, 128.0, 116.3, 107.7, 104.0, 90.7, 67.9, 54.7, 45.3, 43.2, −0.49; IR (neat) 2959, 1704, 1403, 1309, 1250, 1224, 1054, 844 cm^{-1}; mass spectrum (CI) *m/z* 356 (M+H) (base), 340, 312, 257, 168. TBAF (400 mg, 1.12 mmol) was added in one portion to a solution of the above oil (200 mg, 0.56 mmol) in THF (5 mL). The reaction mixture was stirred for 30 min and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 83 mg (53%) of

8 as a pale yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.40–7.30 (comp, 5H), 6.07 (ddd, J=17.0, 10.5, 6.0 Hz, 1H), 5.42 (dt, J=7.5, 2.5 Hz, 1H), 5.18 (d, J=17.0 Hz, 1H), 5.17 (s, 2H), 5.10 (d, J=9.0 Hz, 1H), 5.00 (dd, J=13.0, 6.0 Hz, 1H), 3.22 (s, 1H), 2.87 (dd, J=16.0, 7.0 Hz, 1H), 2.80 (dd, J=16.0, 7.0 Hz, 1H), 2.65 (dd, J=16.0, 5.5 Hz, 1H), 2.46 (d, J=2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 154.8, 137.3, 135.8, 128.5, 128.2, 128.0, 116.7, 82.4, 73.8, 68.0, 54.8, 44.9, 43.2, 42.5; IR (neat) 3285, 2957, 1698, 1403, 1310, 1264, 1310, 1264, 1226, 1113, 1027, 698 cm^{-1}; mass spectrum (CI) m/z 284.1291 [$C_{17}H_{18}NO_3$ (M+H) requires 284.1287], 284 (base), 266, 240.

4.5. 4-Oxo-2-(3-trimethylsilanyl-prop-2-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (*9*)

3-Trimethylsilylpropargyl bromide (2.74 g, 14.4 mmol) was added to a mixture of 4-methoxypyridine (752 mg, 7.2 mmol), Zn dust (1.87 g, 28.8 mmol), and $HgCl_2$ (30 mg, 0.1 mmol) in THF (50 mL), and the reaction mixture was heated to reflux for 3 h. Upon cooling to room temperature, Cbz–Cl (2.45 g, 14.4 mmol) was added dropwise, and the reaction mixture was stirred for 10 min. The mixture was filtered through a plug of Celite (1 cm) to remove excess Zn dust by washing with EtOAc (30 mL). The filtrate was washed with 1 N HCl (2×50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (9:1–3:1) to give 1.90 g (77%) of **9** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (br s, 1H), 7.34–7.15 (comp, 5H), 5.25 (br s, 1H), 5.20 (s, 2H), 4.66 (br s, 1H), 2.69 (d, J=6.0 Hz, 2H), 2.50 (d, J=7.6 Hz, 2H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 141.0, 134.6, 128.5, 128.1, 127.1, 126.6, 100.9, 88.2, 68.9, 64.7, 51.6, 38.4, 21.9, −0.4; IR (neat) 2959, 2900, 1731, 1672, 1604, 1328, 1296, 1198, 1107, 1016, 847, 760, 698 cm^{-1}; mass spectrum (CI) m/z 342.1528 [$C_{19}H_{24}NO_3Si$ (M+H) requires 342.1525], 342 (base), 326.

4.6. 4-Oxo-2-(3-trimethylsilanylprop-2-ynyl)-6-vinylpiperidine-1-carboxylic acid benzyl ester (*10*)

A solution of MeLi (2.88 mmol, 1.8 mL, 1.6 M in hexanes) was slowly added to a suspension of flame-dried CuCN (256 mg, 2.88 mmol) at −78 °C. The reaction mixture was warmed to 0 °C for 1 min and then recooled to −78 °C. Vinyl magnesium bromide (2.88 mmol, 2.88 mL, 1 M in THF) was added dropwise over 5 min, and the reaction mixture was stirred for 10 min. A solution of **9** (655 mg, 1.92 mmol) in THF (2 mL) was added, and the mixture, which turned a deep orange/red color was stirred at −78 °C for 1.5 h. The reaction mixture was poured into a solution of NH_4Cl/NH_4OH (9:1, 10 mL), and stirred until all the salts dissolved. The aqueous solution was extracted with Et_2O (3×10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 678 mg (96%) of **10** as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.40–7.29 (comp, 5H), 6.02 (ddd, J=15.5, 10.5, 5.0 Hz, 1H), 5.19–5.10 (comp, 5H), 4.60 (dt, J=7.0, 6.0 Hz, 1H), 2.79 (dd, J=16.0, 7.5 Hz, 1H), 2.71 (dd, J=16.0, 7.5 Hz, 1H), 2.63–2.47 (comp, 5H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 205.2, 154.5, 139.0, 136.1, 127.8, 127.2, 126.9, 115.0, 103.4, 86.8, 66.4, 52.6, 51.0, 41.8, 41.7, 25.9, −0.7; IR (neat) 3089, 3034, 2959, 2900, 1698, 1607, 1403, 1326, 1250, 843 cm^{-1}; mass spectrum (CI) m/z 370.1848 [$C_{21}H_{28}NO_3Si$ (M+H) requires 370.1838].

4.7. 4-Oxo-2-prop-2-ynyl-6-vinylpiperidine-1-carboxylic acid benzyl ester (*11*)

TBAF·H_2O (300 mg, 0.900 mmol) was added in one portion to a stirred solution of **10** (300 mg, 0.813 mmol) in THF (5 mL). The reaction mixture was stirred for 5 min and NH_4Cl (5 mL) was added. The mixture was extracted with Et_2O (3×5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 166 mg (69%) of **11** as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.40–7.29 (comp, 5H), 5.99 (ddd, J=16.0, 10.5, 4.5 Hz, 1H), 5.19–5.12 (comp, 5H), 4.61 (dt, J=6.5, 5.0 Hz, 1H), 2.80 (dd, J=16.0, 7.0 Hz, 1H), 2.74 (dd, J=16.0, 7.0 Hz, 1H), 2.69 (dt, J=3.0, 1.0 Hz, 1H), 2.59 (ddd, J=19.2, 3.0, 1.5 Hz, 1H), 2.53–2.46 (comp, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 205.2, 154.5, 138.8, 136.1, 127.8, 127.2, 127.0, 115.2, 80.3, 72.4, 66.4, 52.7, 51.2, 41.7, 41.6, 24.7; IR (neat) 3307, 3035, 2959, 1694, 1407, 1320, 1271, 1114, 1057 cm^{-1}; mass spectrum (CI) m/z 298.1443 [$C_{18}H_{20}NO_3$ (M+H) requires 298.1443].

4.8. Representative procedure for PKR of cis-2,6-disubstituted piperidines

4.8.1. 4,10-Dioxo-12-azatricyclo[6.3.1.0^{2,6}]dodec-2-ene-12-carboxylic acid benzyl ester (*14*)

$Co_2(CO)_8$ (45 mg, 0.130 mmol) was added to **7** (35 mg, 0.118 mmol) in THF (1 mL) under an Ar atmosphere. The reaction mixture was stirred for 1 h and complete conversion to the alkyne–$Co(CO)_6$ complex observed by TLC. DMSO (55 mg, 0.708 mmol) was added, and the reaction mixture was heated to 50 °C for 14 h. Et_2O (3 mL) was added and the reaction mixture was filtered through Celite by washing with acetone (5 mL). The combined filtrate and washings were concentrated under reduced pressure to give a dark oil that was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 34 mg (89%) of **14** as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.60–7.20 (comp, 5H), 5.98 (s, 1H), 5.57 (d, J=7.0 Hz, 1H), 5.17 (s, 2H), 4.80 (s, 1H), 2.96 (dd, J=16.5, 7.0 Hz, 2H), 2.84 (dd, J=11.0, 7.5 Hz, 2H), 2.54–2.44 (m, 1H), 2.35 (d, J=16.5 Hz, 1H), 2.19 (ddd, J=13.5, 6.5, 2.0 Hz, 1H), 1.92 (dd, J=18.5, 3.0 Hz, 1H), 1.60 (dt, J=13.5, 1.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 205.8, 205.5, 175.5, 153.1, 136.1, 127.9, 127.4, 127.0, 126.5, 66.5, 50.2, 48.0, 44.0, 43.7, 41.1, 38.4, 32.8; IR (neat) 3582, 3408, 3063, 2957, 2919, 1694, 1633, 1416, 1096,

913; mass spectrum (CI) *m/z* 326.1381 [$C_{19}H_{20}NO_4$ (M+H) requires 326.1392].

4.8.2. 4,10-Dioxo-12-azatricyclo[6.3.1.0^{2,6}]dodec-5-ene-12-carboxylic acid benzyl ester (**15**)

The PKR of **11** was performed on a scale of 0.17 mmol according to the representative procedure, and the crude product was purified by flash chromatography eluting with EtOAc to give **15** in a 91% yield as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.42–7.31 (comp, 5H), 5.93 (s, 1H), 5.21 (s, 2H), 4.94 (dt, J=8.0, 1.5 Hz, 1H), 4.85 (t, J=6.5 Hz, 1H), 3.15 (dt, J=6.5, 1.5 Hz, 1H), 2.83 (d, J=14.0 Hz, 1H), 2.74 (dd, J=15.0, 6.0 Hz, 1H), 2.68 (dd, J=16.5, 6.5 Hz, 1H), 2.54 (dd, J=17.0, 7.0 Hz, 1H), 2.41 (dd, J=19.0, 7.0 Hz, 1H), 2.28 (t, J=15.0 Hz, 1H), 2.10 (dd, J=19.5, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 205.0, 204.3, 173.5, 153.3, 136.1, 131.7, 127.9, 127.3, 127.0, 66.5, 50.7, 47.4, 44.8, 43.6, 38.7, 36.7, 34.8; IR (neat) 3035, 2963, 2902, 1706, 1626, 1416, 1335, 1264, 1220, 1100, 1028 cm^{-1}; mass spectrum (CI) *m/z* 326.1392 [$C_{19}H_{20}NO_4$ (M+H) requires 326.1392].

4.8.3. 4,9-Dioxo-11-azatricyclo[5.3.1.0^{2,6}]undec-2-ene-11-carboxylic acid benzyl ester (**16**)

The PKR of **8** was performed on a scale of 0.17 mmol according to the representative procedure, and the crude product was purified by flash chromatography eluting with hexanes/EtOAc (3:1–1:1) to give 14 mg (33%) of **16** as a colorless oil as a mixture (3:1) of diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.42–7.31 (comp, 5H), 6.09 (s, 1H), 5.38 (br s, 1H), 5.20 (s, 2H), 5.24–5.23 (m, 1H), 4.62 (t, J=6.0 Hz, 1H), 3.49–3.45 (m, 1H), 2.91 (dd, J=17.0, 6.0 Hz, 1H), 2.84–2.79 (comp, 1H), 2.60 (dd, J=18.0, 6.0 Hz, 1H), 2.38 (d, J=18.0 Hz, 1H), 2.17 (dd, J=18.0, 3.0 Hz, 1H); mass spectrum (CI) *m/z* 312.1234 [$C_{18}H_{18}NO_4$ (M+H) requires 312.1236], 312 (base), 268.

4.9. 2-Allyl-6-ethynyl-4-hydroxypiperidine-1-carboxylic acid benzyl ester (**17**)

A solution of **7** (750 mg, 2.52 mmol) in THF (20 mL) was cooled to −78 °C and a solution of L-Selectride (3.0 mL, 1 M in THF) was added dropwise. The reaction mixture was stirred at −78 °C whereupon satd NH_4Cl (10 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1–1:1) to give 524 mg (70%) of **17** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (comp, 5H), 5.76 (ddt, J=16.8, 10.0, 7.2 Hz, 1H), 5.28–4.96 (comp, 5H), 4.29–4.22 (m, 1H), 2.83 (t, J=7.2 Hz, 2H), 2.63 (d, J=2.4 Hz, 1H), 2.21–1.98 (comp, 3H), 1.73 (ddd, J=3.2, 7.2, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (rotamers) δ 155.4, 136.4, 135.9, 128.5, 128.0, 127.9, 117.4, 85.5, 71.8, 67.5, 64.6, 50.3, 39.5, 38.2, 36.4, 32.6, 29.7; IR (neat) 3447, 3297, 2953, 1684, 1409, 1324, 1087, 1063, 990, 914 cm^{-1}; mass spectrum (CI) *m/z* 300.1602 [$C_{18}H_{22}NO_3$ (M+H) requires 300.1600], 300 (base), 258, 256, 238, 214.

4.10. 2-Allyl-4-(tert-butyldimethylsilanyloxy)-6-ethynylpiperidine-1-carboxylic acid benzyl ester (**18**)

Compound **17** (250 mg, 0.84 mmol) was dissolved in DMF (5 mL) and imidazole (170 mg, 2.5 mmol) and TBS–Cl (151 mg, 1 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 12 h and NH_4Cl (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (9:1) to give 268 mg (81%) of **18** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (comp, 5H), 5.77 (ddd, J=17.2, 10.0, 7.2 Hz, 1H), 5.15 (s, 2H), 5.07 (d, J=17.2 Hz, 1H), 4.97 (d, J=10.0 Hz, 1H), 4.26–4.20 (m, 1H), 4.08 (app p, J=4.0 Hz, 1H), 3.73 (dt, J=6.8, 4.4 Hz, 1H), 2.92–2.77 (m, 2H), 2.20 (d, J=2.4 Hz, 1H), 2.02–1.67 (comp, 4H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 136.6, 136.5, 128.4, 127.9, 127.8, 116.8, 85.4, 70.6, 67.3, 64.2, 50.7, 39.1, 38.6, 36.6, 33.6, 25.8, 18.1, −4.9, −5.0; IR (neat) 3307, 2953, 2856, 1694, 1640, 1407, 1335, 1312, 1255, 1093, 774 cm^{-1}; mass spectrum (CI) *m/z* 414.2466 [$C_{24}H_{36}NO_3Si$ (M+H) requires 414.2464], 414 (base), 398, 372, 356, 238.

4.11. 6-Trimethylsilanylethynylpiperidin-2-one (**20**)

A solution of TMS–acetylene (3.23 g, 33 mmol) in THF (25 mL) was cooled to −78 °C and *n*-BuLi (13.2 mL, 2.5 M in hexanes, 33 mmol) was added dropwise. The reaction mixture was warmed to 0 °C and stirred for 10 min. The solution was added to a solution of **19** (2.6 g, 10.9 mmol) in THF (25 mL) at −78 °C, and the reaction mixture was stirred for 30 min at −78 °C and 30 min at room temperature. The reaction was quenched with $NaHCO_3$ (30 mL) and the mixture was extracted with EtOAc (3×25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to give 1.52 g (71%) of **20** as a white solid: mp=126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (s, 1H), 4.26–4.23 (m, 1H), 2.37–2.33 (comp, 2H), 2.04–1.95 (comp, 2H), 1.86–1.70 (comp, 2H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 104.4, 88.1, 44.9, 31.1, 28.8, 18.8, −0.3; IR (neat) 3190, 3077, 2956, 1687, 1649, 1405, 1309, 1252, 841, 756 cm^{-1}; mass spectrum (CI) *m/z* 196.1160 [$C_{10}H_{18}NOSi$ (M+H) requires 196.1158], 196 (base), 180.

4.12. 2-Oxo-6-trimethylsilanylethynylpiperidine-1-carboxylic acid benzyl ester (**21**)

A solution of **20** (750 mg, 3.85 mmol) in THF (15 mL) was cooled to −78 °C and a solution of *n*-BuLi (1.86 mL, 2.27 M in hexanes, 4.23 mmol) was added dropwise over 5 min. The

reaction mixture was stirred for 30 min whereupon Cbz–Cl (1.30 g, 7.70 mmol) was added. The cooling bath was removed, and the reaction mixture was stirred for 15 min. The reaction was quenched with satd NH_4Cl (15 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (9:1–3:1) to give 1.02 g (81%) of **21** as a white solid: mp=70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.29 (comp, 5H), 5.32–5.24 (comp, 2H), 5.12–5.10 (m, 1H), 2.75–1.79 (comp, 6H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 152.9, 135.1, 128.3, 128.0, 127.7, 103.1, 88.8, 68.4, 48.3, 34.0, 28.5, 17.5, −0.4; IR (neat) 3065, 2959, 2899, 1778, 1738, 1714, 1498, 1455, 1373, 1250, 1134, 1062, 843 cm^{-1}; mass spectrum (CI) *m/z* 330.1526 [$C_{18}H_{24}NO_3Si$ (M+H) requires 330.1525], 330 (base), 286, 270.

4.13. 2-Allyl-6-ethynylpiperidine-1-carboxylic acid benzyl ester (*23*)

A solution of **21** (830 mg, 2.52 mmol) in THF (25 mL) was cooled to −78 °C and a solution of DIBAL–H (3.03 mL, 1 M in toluene, 3.03 mmol) was added slowly dropwise over 5 min. The reaction mixture was stirred at −78 °C for 30 min and MeOH (0.5 mL) was added. The reaction mixture was warmed to room temperature and satd Rochelle's salt (25 mL) was added with vigorous stirring. The mixture was extracted with EtOAc (3×15 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The pale yellow oil was dissolved in CH_2Cl_2 (25 mL) and cooled to −78 °C whereupon allyl TMS (1.43 g, 12.6 mmol) and $BF_3\cdot Et_2O$ (1.77 g, 12.6 mmol) were added sequentially. The reaction mixture was stirred for 30 min and warmed to room temperature. $NaHCO_3$ (15 mL) was added and the mixture stirred for 15 min. The solution was extracted with CH_2Cl_2 (3×15 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a crude oil (506 mg). A portion of the oil (200 mg) was dissolved in THF (10 mL) and TBAF (220 mg, 0.845 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and NH_4Cl (5 mL) was added. The mixture was extracted with EtOAc (3×10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (9:1) to give 138 mg (52%) of **23** as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.38–7.29 (comp, 5H), 5.73 (ddd, *J*=17.5, 10.0, 7.0 Hz, 1H), 5.12 (s, 2H), 5.05 (d, *J*=17.5 Hz, 1H), 5.04–5.02 (m, 1H), 4.98 (d, *J*=10.0 Hz, 1H), 4.23–4.19 (m, 1H), 2.99 (d, *J*=2.5 Hz, 1H), 2.56–1.48 (comp, 8H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 154.2, 136.3, 135.5, 127.7, 127.2, 126.9, 116.0, 84.5, 72.4, 66.0, 50.6, 40.9, 36.0, 29.8, 26.0, 14.0; IR (neat) 3294, 3248, 2944, 1697, 1406, 1318, 1267, 1098 cm^{-1}; mass spectrum (CI) *m/z* 284.1653 [$C_{18}H_{22}NO_2$ (M+H) requires 284.1651], 284 (base), 242, 198, 176.

4.14. 2-Allyl-4-methyl-piperazine-1-carboxylic acid tert-butyl ester (*26*)

Compound **24** (1 g, 4.99 mmol), *s*-BuLi (20 mL of a 0.6 M solution in *n*-hexane, 11.98 mmol), TMEDA (1.39 g, 11.98 mmol), CuCN (1.07 g, 11.98 mmol), LiCl (1.02 g, 23.97 mmol), and allyl bromide (1.45 g, 11.98 mmol) in Et_2O (150 mL) were reacted as reported in literature.[18] Purification via flash chromatography eluting with CH_2Cl_2/MeOH (20:1) yielded **26** (0.997 g, 83%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 5.65–5.77 (m, 1H), 5.03 (d, *J*=16.8 Hz, 1H), 4.96 (d, *J*=10.0 Hz, 1H), 4.05 (br s, 1H), 3.81 (d, *J*=9.6 Hz, 1H), 2.30 (t, *J*=12.4 Hz, 1H), 2.65 (t, *J*=10.8 Hz, 2H), 2.34–2.47 (m, 2H), 2.18 (s, 3H), 1.97 (d, *J*=11.2 Hz, 1H), 1.86 (t, *J*=12.0 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 154.7, 135.3, 116.9, 79.4, 77.2, 57.1, 55.0, 50.7, 46.4, 39.1, 34.6, 28.3; IR (neat) 2358, 1698, 1458, 1409, 1365, 1247, 1174, 1106 cm^{-1}; mass spectrum (CI) *m/z* 241.1919 [$C_{13}H_{25}N_2O_2$ (M+H) requires 241.1916] 213, 199, 185.

4.15. 2-Allyl-6-formyl-4-methyl-piperazine-1-carboxylic acid tert-butyl ester (*28*)

s-BuLi (0.95 mL of a 1.2 M solution in *n*-hexane, 1.14 mmol) was added to a mixture of **25** (0.210 g, 0.874 mmol) and TMEDA (0.132 g, 1.14 mmol) in Et_2O (20 mL) at −78 °C and the reaction mixture was stirred for 1 h. DMF (0.96 g, 1.31 mL) was quickly added and reaction mixture was stirred for an additional 1 h. The reaction was quenched at −78 °C with satd NH_4Cl, allowed to warm to room temperature, extracted with Et_2O (4×10 mL), dried (K_2CO_3), and concentrated. The crude oil was then dissolved in hexanes/EtOAc/NEt_3 (98:2:1, 20 mL) and SiO_2 (1.4 g) was added. The reaction mixture was allowed to stir until the disappearance of the trans-isomer was observed by TLC (eluting with CH_2Cl_2/MeOH, 20:1). The reaction mixture was filtered, concentrated, and the residue purified via flash chromatography eluting with CH_2Cl_2/MeOH (30:1) to give 183 mg (78%) of **28** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 9.63 (s, 1H), 5.68–5.79 (m, 1H), 5.98–5.04 (comp, 2H), 4.35 (br s, 1H), 4.00 (br s, 1H), 3.30 (d, *J*=11.6 Hz, 1H), 2.65 (d, *J*=10.8 Hz, 1H), 2.21–2.28 (m, 2H), 2.18 (s, 3H), 2.01 (dd, *J*=6.4, 5.2 Hz, 1H), 1.95 (dd, *J*=7.6, 4.0 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 200.4, 154.7, 136.1, 117.1, 79.6, 68.7, 61.2, 54.6, 50.5, 46.5, 39.3, 28.3; IR (neat) 2968, 2790, 1731, 1690, 1455, 1402, 1367, 1331, 1296, 1173, 1049 cm^{-1}; mass spectrum (CI) *m/z* 269.1867 [$C_{14}H_{25}N_2O_3$ (M+H) requires 269.1865], 241, 227, 213, 169, 154.

4.16. 2-Allyl-6-ethynyl-4-methyl-piperazine-1-carboxylic acid tert-butyl ester (*30*)

To a mixture of **28** (0.480 g, 1.79 mmol), K_2CO_3 (0.742 g, 5.37 mmol) in MeOH (20 mL) at 0 °C was added Bestmann–Ohira reagent (0.688 g, 3.58 mmol). The reaction mixture was

warmed to room temperature and stirred under argon for 16 h. The reaction mixture was concentrated, dissolved in EtOAc (30 mL), washed with brine (1×10 mL), satd $NaHCO_3$ (2×10 mL), brine (1×10 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and the residue was purified via flash chromatography eluting with CH_2Cl_2/MeOH (30:1) to give 379 mg (80%) of **30** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 5.74–5.85 (m, 1H), 5.14 (d, J=17.2, 1H), 5.05 (d, J=10.4, 1H), 4.85 (br s, 1H), 4.00–4.04 (m, 1H), 2.93 (dt, J=11.6, 2.0 Hz, 1H), 2.72–2.82 (comp, 2H), 2.60–2.67 (m, 1H), 2.28 (s, 3H), 2.22 (d, J=2.4 Hz, 2H), 2.09 (dd, J=7.2, 4.0 Hz, 1H), 1.95 (dd, J=7.2, 4.0 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 154.7, 136.4, 117.4, 84.7, 80.6, 70.3, 61.5, 59.5, 56.8, 46.9, 37.0, 28.6; IR (neat) 3295, 2978, 2942, 2802, 1696, 1455, 1390, 1337, 1296, 1249, 1179, 1044 cm^{-1}; mass spectrum (CI) m/z 265.1912 [$C_{15}H_{25}N_2O_2$ (M+H) requires 265.1916], 249, 237, 223, 209, 165, 154.

4.17. 2-Allyl-4-benzyl-piperazine-1-carboxylic acid tert-butyl ester (27)

Compound **25** (0.200 g, 0.724 mmol), *s*-BuLi (1.2 mL of a 1.46 M solution in *n*-hexane, 1.74 mmol), TMEDA (0.202 g, 1.74 mmol), CuCN (0.156 g, 1.74 mmol), LiCl (0.148 g, 3.48 mmol), and allyl bromide (0.114 g, 0.941 mmol) in Et_2O (24 mL) were reacted as reported in literature.[18] Purification via flash chromatography eluting with CH_2Cl_2/MeOH (30:1) yielded **27** (0.229 g, 84%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 7.35–7.22 (comp, 5H), 5.74–5.64 (m, 1H), 5.04–4.93 (comp, 2H), 4.06 (br s, 1H), 3.85 (d, J=11.2 Hz, 1H), 3.53 (d, J=13.2 Hz, 1H), 3.38 (d, J=13.2 Hz, 1H), 3.07 (td, J=12.6, 2.8 Hz, 1H), 2.76 (d, J=10.8 Hz, 1H), 2.70 (d, J=11.2 Hz, 1H), 2.53–2.41 (m, 2H), 2.07–1.99 (comp, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 154.8, 138.4, 135.5, 128.8, 128.2, 127.0, 117.0, 79.4, 62.8, 54.7, 53.2, 34.6, 28.4; IR (neat) 3064, 2975, 2807, 1694, 1455, 1410, 1364, 1174 cm^{-1}; mass spectrum (CI) m/z 317.2229 [$C_{19}H_{29}N_2O_2$ (M+H) requires 317.2229], 289, 275, 261, 243, 217, 173.

4.18. 2-Allyl-4-benzyl-6-formyl-piperazine-1-carboxylic acid tert-butyl ester (29)

s-BuLi (0.4 mL of a 1.46 M solution in *n*-hexane, 0.584 mmol) was added to a mixture of **27** (0.123 g, 0.389 mmol) and TMEDA (0.068 g, 0.584 mmol) in Et_2O (13 mL) at −78 °C and the reaction mixture was stirred for 1 h. DMF (0.043 g, 0.05 mL) was quickly added and reaction mixture was stirred for an additional 1 h. The reaction was quenched at −78 °C with satd NH_4Cl, allowed to warm to room temperature, extracted with Et_2O (4×10 mL), dried (K_2CO_3), and concentrated. The crude oil was then dissolved in hexanes/EtOAc/NEt_3 (98:2:1, 13 mL) and SiO_2 (1.0 g) was added. The reaction mixture was allowed to stir until the disappearance of the trans-isomer was observed by TLC (eluting with CH_2Cl_2/MeOH, 20:1). The reaction mixture was filtered, concentrated, and the residue purified via flash chromatography eluting with CH_2Cl_2/MeOH (30:1) to give 0.134 g (81%) of **29** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 9.61 (s, 1H), 7.31–7.20 (comp, 5H), 5.74–5.59 (m, 1H), 5.03–4.83 (comp, 2H), 4.46–4.32 (comp, 1H), 4.02–3.84 (comp, 1H), 3.55 (t, J=12.8 Hz, 2H), 3.37 (d, J=13.2 Hz, 2H), 2.77–2.68 (m, 1H), 2.54–2.42 (m, 1H), 2.35–2.26 (comp, 2H), 2.21 (dd, J=6.4, 4.4 Hz, 1H), 2.06–1.99 (comp, 2H), 1.48–1.45 (comp, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 201.9, 154.7, 137.6, 136.3, 135.4, 135.2, 128.8, 128.7, 128.2, 127.2, 127.0, 117.5, 116.9, 80.6, 79.3, 62.7, 62.4, 54.6, 53.3, 53.1, 28.2; IR (neat) 3072, 2966, 2912, 2801, 2707, 1731, 1690, 1455, 1390, 1367, 1249 cm^{-1}; mass spectrum (CI) m/z 345.2179 [$C_{20}H_{29}N_2O_3$ (M+H) requires 345.2178], 318, 303, 289, 261, 201, 173.

4.19. 2-Allyl-4-benzyl-6-ethynyl-piperazine-1-carboxylic acid tert-butyl ester (31)

To a mixture of **29** (0.094 g, 0.273 mmol), K_2CO_3 (0.113 g, 0.819 mmol) in MeOH (3 mL) at 0 °C was added Bestmann–Ohira reagent (0.105 g, 0.546 mmol). The reaction mixture was warmed to room temperature and stirred under argon for 16 h. The reaction mixture was concentrated, dissolved in EtOAc (10 mL), washed with brine (1×5 mL), satd $NaHCO_3$ (2×5 mL), brine (1×5 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and the residue was purified via flash chromatography eluting with CH_2Cl_2/MeOH (30:1) to give 0.093 g (76%) of **31** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 7.35–7.23 (comp, 5H), 5.74–5.64 (m, 1H), 5.04–4.94 (comp, 2H), 4.07 (br s, 1H), 3.84 (br s, 1H), 3.54 (d, J=13.2 Hz, 1H), 3.38 (d, J=13.2 Hz, 1H), 3.07 (t, J=12.4 Hz, 1H), 2.77 (d, J=10.8 Hz, 1H), 2.70 (d, J=11.6 Hz, 1H), 2.54–2.42 (m, 2H), 2.07–2.00 (comp, 2H), 1.48–1.45 (comp, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 138.6, 135.7, 129.1, 128.4, 127.2, 117.2, 79.7, 63.1, 55.0, 53.4, 51.6, 34.9, 29.9, 28.6; IR (neat) 3304, 3074, 2975, 2811, 2773, 1697, 1640, 1454, 1399, 1367, 1336, 1302, 1255, 1175 cm^{-1}; mass spectrum (CI) m/z 341.2226 [$C_{21}H_{29}N_2O_2$ (M+H) requires 341.2229], 325, 313, 299, 285, 240.

4.20. 10-(tert-Butyldimethylsilanyloxy)-4-oxo-12-azatricyclo[6.3.1.0^{2,6}]dodec-2-ene-12-carboxylic acid benzyl ester (34)

The PKR of **27** was performed on a scale of 0.29 mmol according to the representative procedure, and the crude product was purified by flash chromatography eluting with hexanes/EtOAc (9:1–3:1) to give **39** in a 69% yield as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.37–7.28 (comp, 5H), 5.87 (d, J=2.0 Hz, 1H), 5.17 (d, J=7.5 Hz, 1H), 5.10 (s, 2H), 4.47–4.44 (m, 1H), 4.30–4.24 (m, 1H), 4.09–4.05 (m, 1H), 2.40 (dd, J=18.0, 6.5 Hz, 1H), 2.28 (comp, 2H), 2.00 (ddd, J=13.0, 7.0, 2.0 Hz, 1H), 1.94 (dd, 18.0, 3.0 Hz, 1H), 1.71–1.64 (comp, 2H), 1.53 (dt, J=12.5, 5.0 Hz, 1H), 0.85 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 205.9, 179.0, 153.2,

136.3, 127.8, 127.2, 126.8, 125.6, 66.0, 62.2, 48.0, 45.4, 41.8, 37.1, 35.3, 35.0, 32.6, 25.0, 16.9, −5.6, −5.7; IR (neat) 2928, 2855, 1713, 1623, 1416, 1322, 1278, 1088, 839 cm^{-1}; mass spectrum (CI) *m/z* 442.2411 [$C_{25}H_{36}NO_4Si$ (M+H) requires 442.2414], 442 (base), 308.

*4.21. 4-Oxo-12-azatricyclo[6.3.1.0^{2,6}]dodec-2-ene-12-carboxylic acid benzyl ester (**35**)*

The PKR of **32** was performed on a scale of 0.35 mmol according to the representative procedure, and the crude product was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give **40** in a 74% yield as a colorless oil as a mixture (4:1) of diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.37−7.28 (comp, 5H), 5.89 (br s, 1H), 5.11 (s, 2H), 4.36 (t, *J*=4.4 Hz, 1H), 3.57−3.51 (m, 1H), 2.53 (dd, *J*=18.0, 6.0 Hz, 1H), 2.50−2.48 (m, 1H), 2.15 (dd, *J*=13.5, 7.5 Hz, 1H), 2.08−1.52 (comp, 7H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 205.7, 178.1, 153.2, 136.4, 127.8, 127.2, 126.8, 125.8, 65.9, 49.5, 46.6, 43.2, 37.2, 35.5, 27.6, 18.4, 14.1; IR (neat) 2939, 1694, 1621, 1419, 1321, 1085 cm^{-1}; mass spectrum (ESI) *m/z* 312.1601 [$C_{19}H_{22}NO_3$ (M+H) requires 312.1600], 334 (base), 312.

*4.22. 10-Methyl-4-oxo-10,12-diazatricyclo[6.3.1.0^{2,6}]-dodec-2-ene-12-carboxylic acid tert-butyl ester (**36**)*

The PKR of **30** was performed on a scale of 0.56 mmol according to the representative procedure, and the crude product was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give **36** in a 85% yield as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 5.86 (d, *J*=2.1 Hz, 1H), 4.92 (s, 1H), 4.14 (s, 1H), 3.99−4.05 (m, 1H), 2.92 (d, *J*=11.2 Hz, 1H), 2.87 (d, *J*=11.6 Hz, 1H), 2.48 (dd, *J*=18.2, 6.5 Hz, 1H), 2.32 (dd, *J*=11.5, 3.3 Hz, 1H), 2.26 (dd, *J*=1.8, 1.7 Hz, 1H), 2.24 (dd, *J*=1.8, 1.7 Hz, 1H), 2.19 (s, 3H), 2.17 (m, 1H), 1.79 (dd, *J*=18.2, 3.3 Hz, 1H), 1.87 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 206.1, 178.6, 152.5, 127.6, 125.4, 79.0, 57.9, 56.4, 57.9, 56.4, 44.6, 42.6, 38.0, 37.6, 27.5; IR (neat) 2973, 2920, 2791, 1696, 1623, 1458, 1407, 1322, 1173, 1046 cm^{-1}; mass spectrum (CI) *m/z* 293.1866 [$C_{16}H_{25}N_2O_3$ (M+H) requires 293.1865], 237.

*4.23. 10-Benzyl-4-oxo-10,12-diazatricyclo[6.3.1.0^{2,6}]-dodec-2-ene-12-carboxylic acid tert-butyl ester (**37**)*

The PKR of **31** was performed on a scale of 0.100 mmol according to the representative procedure, and the crude product was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give **37** in a 81% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 7.35−7.24 (comp, 5H), 5.93−5.86 (comp, 1H), 5.07−4.90 (comp, 1H), 4.29 (s, 1H), 4.23 (br s, 1H), 3.51 (d, *J*=12.8 Hz, 1H), 3.46 (d, *J*=13.2 Hz, 1H), 2.95−2.89 (comp, 2H), 2.67 (dd, *J*=12.0, 6.4 Hz, 1H), 2.50 (dd, *J*=8.4, 3.2 Hz, 1H), 2.41 (d, *J*=11.2 Hz, 1H), 2.18−2.12 (m, 1H), 1.90 (dt, *J*=18.4, 2.4 Hz, 1H), 1.75−1.59 (comp, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 208.5, 179.6, 179.0, 153.7, 137.5, 128.7, 128.5, 127.3, 126.4, 80.5, 62.9, 56.7, 55.4, 51.8, 47.6, 43.9, 39.2, 38.7, 28.3; IR (neat) 2967, 2920, 2803, 2768, 1692, 1621, 1451, 1315, 1287, 1246, 1175 cm^{-1}; mass spectrum (CI) *m/z* 369.2175 [$C_{22}H_{29}N_2O_3$ (M+H) requires 369.2178], 341, 313.

*4.24. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-6,13-imino-cyclooct[1,2-b]indole (**3**)*

$Co_2(CO)_8$ (1.77 g, 5.12 mmol) was added to a solution of **4** (1.88 g, 5.08 mmol) in THF (50 mL). The reaction mixture was stirred for 1 h and complete Co−alkyne complex formation was observed by TLC. DMSO (2.20 g, 27.92 mmol) was added and stirred at 60 °C for 8 h. The reaction mixture was cooled to room temperature and Et_2O (30 mL) was added. The purple Co-precipitate was removed via filtration through silica washing with Et_2O (30 mL) and the solution was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1−1:1) to give 1.86 g (92%) of **3** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.73 (s, 1H), 7.39 (d, *J*=7.9 Hz, 1H), 7.35−7.29 (comp, 6H), 7.07 (dt, 7.2, 1.3 Hz, 1H), 6.98 (dt, *J*=7.9, 1.0 Hz, 1H), 6.05 (br s, 1H), 5.64 (d, *J*=6.8 Hz, 1H), 5.50 (br s, 1H), 5.21−5.09 (comp, 2H), 3.33 (dd, *J*=16.4, 6.9 Hz, 1H), 2.75 (d, *J*=16.4 Hz, 1H), 2.79−2.68 (comp, 1H), 2.34 (dd, *J*=18.3, 6.4 Hz, 1H), 2.26 (dq, *J*=6.2, 2.4 Hz, 1H), 1.99 (dd, 18.3, 3.0 Hz, 1H), 1.76 (dt, *J*=12.6, 3.8 Hz, 1H); ^{13}C NMR (125 MHz) δ 205.8, 177.4, 153.4, 136.1, 135.6, 132.3, 127.8, 127.3, 127.0, 126.5, 125.8, 120.6, 118.2, 117.2, 110.8, 105.5, 66.3, 49.3, 47.6, 40.2, 37.1, 34.4, 25.0; IR (neat) 3464, 3052, 2985, 1702, 1623 cm^{-1}; mass spectrum (CI) *m/z* 399.1710 [$C_{25}H_{23}N_2O_3$ (M+H) requires 399.1709].

*4.25. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-14-tert-butoxycarbonyl-6,13-imino-cyclooct[1,2-b]indole (**38**)*

$(Boc)_2O$ (327 mg, 1.22 mmol) was added to a solution of **3** (350 mg, 0.88 mmol) and DMAP (134 mg, 0.88 mmol) in CH_3CN/CH_2Cl_2 (20 mL, 3:1), and the reaction mixture was stirred at room temperature for 1 h. Et_2O (20 mL) was added and the reaction mixture was washed with 0.2 M citric acid (2×10 mL), satd $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 430 mg (99%) of **42** as a white foam. ^{1}H NMR (500 MHz) δ 8.12 (d, *J*=8.2 Hz, 1H), 7.48 (d, *J*=7.8 Hz, 1H), 7.34−7.28 (comp, 6H), 7.24 (t, *J*=6.7 Hz, 1H), 6.08 (br s, 1H), 6.06 (br s, 1H), 5.66 (d, *J*=7.2 Hz, 1H), 5.15 (s, 2H), 3.31 (dd, *J*=17.1, 7.1 Hz, 1H), 2.79−2.76 (comp, 2H), 2.41−2.35 (comp, 1H), 2.38 (dd, *J*=18.4, 6.5 Hz, 1H), 2.01 (dd, *J*=18.5, 3.0 Hz, 1H), 1.76 (dt, *J*=12.7, 4.1 Hz, 1H), 1.62 (s, 9H); ^{13}C NMR (125 MHz) δ 205.9, 176.8, 153.3, 148.8, 136.0, 135.1, 132.3,

127.8, 127.5, 127.4, 127.1, 126.5, 123.9, 122.4, 117.8, 114.9, 114.1, 84.1, 66.5, 54.1, 48.1, 40.3, 36.2, 33.9, 27.2, 24.6; IR (neat) 3400, 2977, 2929, 1771, 1713, 1626 cm^{-1}; mass spectrum (CI) *m/z* 499.2211 [$C_{30}H_{31}N_2O_5$ (M+H) requires 498.2233].

4.26. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-14-tert-butoxycarbonyl-6,13-imino-7,11-[2,7-dioxabicyclo[4.1.0]heptan-3-one]-cyclooct[1,2-b]indole (**39**)

Trifluoroacetic anhydride (15 mg, 0.07 mmol) was added to a mixture of **38** (10 mg, 0.02 mmol), urea·H_2O_2 (19 mg, 0.20 mmol), and Na_2HPO_4 (26 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) at 0 °C, and the reaction mixture was stirred for 3 h. The reaction mixture was filtered through a plug of Celite (1 cm), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1–1:1) to give 10 mg (94%) of **39** as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.80 (d, J=8.0 Hz, 1H), 7.76 (d, J=7.5 Hz, 1H), 7.40 (t, J=8.0 Hz, 1H), 7.37–7.26 (comp, 5H), 7.23 (t, J=7.5 Hz, 1H), 5.88 (br s, 1H), 5.32 (d, J=8.0 Hz, 1H), 5.09 (s, 2H), 4.37 (br s, 1H), 3.70 (br s, 1H), 2.78–2.74 (m, 1H), 2.62 (dd, J=18.0, 6.5 Hz, 1H), 2.32 (d, J=14.0 Hz, 1H), 2.09 (dd, J=13.5, 8.0 Hz, 1H), 1.97 (dd, J=18.0, 3.5 Hz, 1H), 1.70–1.69 (m, 1H), 1.57 (s, 9H); ^{13}C NMR (125 MHz) δ 205.8, 177.4, 151.9, 148.1, 139.4, 136.2, 128.4, 127.7, 127.1, 126.8, 126.7, 125.7, 124.1, 123.1, 123.3, 121.1, 113.8, 109.2, 83.4, 65.9, 60.6, 54.5, 42.3, 33.3, 27.3, 23.1; IR (neat) 2955, 1791, 1764, 1710, 1632, 1421, 1307, 1252, 1150, 739 cm^{-1}; mass spectrum (CI) *m/z* 531 (M+H), 463, 319, 243 (base).

4.27. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-14-tert-butoxycarbonyl-6,13-imino-7,8-epoxycyclopentane-cyclooct[1,2-b]indole (**40**)

A solution of NaOH (10 μL, 100 mg NaOH/1 mL H_2O, 0.024 mmol) and a solution of H_2O_2 (15 μL, 30% in H_2O, 0.1 mmol) were sequentially added to a solution of **38** (10 mg, 0.02 mmol) in THF/MeOH (0.4 mL, 1:1) at −20 °C. The reaction mixture was stirred for 30 min, and the cooling bath was removed. A solution of NaOH (10 μL, 100 mg NaOH/1 mL H_2O, 0.024 mmol) was added, and the reaction mixture was stirred for an additional 1 h. The solution was filtered through a plug of Na_2CO_3/silica (1 cm/1 cm) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (9:1–3:1) to give 7.8 mg (78%) of **40** as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 8.12 (d, J=8.0 Hz, 1H), 7.54 (d, J=5.5 Hz, 1H), 7.35–7.25 (comp, 7H), 5.98 (br s, 1H), 5.14 (s, 2H), 4.51 (d, J=6.5 Hz, 1H), 3.64 (s, 1H), 3.16 (dd, J=17.0, 7.0 Hz, 1H), 2.92 (d, J=17.0 Hz, 1H), 2.44–2.32 (comp, 3H), 1.82–1.73 (comp, 2H), 1.62 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 207.1, 153.4, 148.7, 135.9, 135.2, 132.1, 127.8, 127.5, 127.2, 127.0, 124.0, 122.4, 117.8, 114.8, 114.2, 84.1, 69.6, 66.6, 61.3, 47.7, 47.3, 37.6, 35.1, 29.0, 27.2, 22.8; IR (neat) 2977, 2928, 1750, 1730, 1703, 1455, 1417, 1360, 1326, 1156, 1012, 755 cm^{-1}; mass spectrum (CI) *m/z* 515.2175 [$C_{30}H_{31}N_2O_6$ (M+H) requires 515.2182].

4.28. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-14-tert-butoxycarbonyl-6,13-imino-9-triisopropylsiloxycyclopent-8-ene-cyclooct[1,2-b]indole (**45**)

Solid **38** (1.0 g, 2.0 mmol) was added to a solution of platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex (0.50 mL, 0.1 M in xylenes, 0.05 mmol, 2.5 mol %) and *i*-Pr_3SiH (5 mL, 24 mmol) in toluene (5 mL), and the reaction mixture was heated to 60 °C for 18 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (neutral alumina) eluting with hexanes/EtOAc (1:0–9:1) to give 1.32 g (93%) of **45** as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 8.29–8.25 (m, 1H), 7.42–7.26 (comp, 8H), 6.03 (s, 0.5H), 5.93 (s, 0.5H), 5.22 (s, 1H), 5.17 (s, 1H), 4.91 (d, J=6.6 Hz, 0.5H), 4.83 (d, J=6.6 Hz, 1H), 4.72 (s, 0.5H), 4.61 (s, 0.5H), 3.27–3.12 (m, 1H), 2.78–2.54 (comp, 3H), 2.08–1.80 (comp, 4H), 1.76 (s, 4.5H), 1.61 (s, 4.5H), 1.29–1.13 (comp, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 155.7, 155.4, 154.8, 154.7, 149.7, 136.7, 136.5, 135.9, 133.5, 133.2, 128.7, 128.6, 128.3, 128.2, 127.8, 127.7, 127.4, 124.0, 123.9, 122.6, 122.5, 117.7, 117.6, 115.6, 115.3, 114.7, 104.2, 103.8, 83.8, 83.6, 67.1, 66.8, 48.0, 47.8, 47.6, 47.4, 47.3, 47.1, 40.7, 40.6, 31.3, 30.9, 29.9, 28.0, 27.9, 27.6, 27.0, 17.7, 12.3; IR (neat) 2943, 2865, 1731, 1698, 1634, 1455, 1424, 1366, 1325, 1145, 882 cm^{-1}; mass spectrum (CI) *m/z* 657 (M+H) (base), 601, 556, 405.

4.29. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-14-tert-butoxycarbonyl-6,13-imino-9-oxycyclopentane-cyclooct[1,2-b]indole (**46**)

TBAF·$3H_2O$ (158 mg, 0.5 mmol) was added to a solution of **45** (153 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred at room temperature for 3 h. Satd NH_4Cl (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1–1:1) to give 100 mg (66%) of **46** as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 8.10 (d, J=8.0 Hz, 1H), 7.48 (d, J=7.5 Hz, 1H), 7.32–7.27 (comp, 6H), 7.24 (t, J=7.5 Hz, 1H), 5.94 (s, 1H), 5.12 (s, 2H), 4.64 (d, J=6.5 Hz, 1H), 3.14 (dd, J=16.5, 7.0 Hz, 1H), 2.74 (d, J=17.0 Hz, 1H), 2.50–2.48 (m, 1H), 2.28 (dd, J=18.5, 8.0 Hz, 2H), 2.14–2.08 (comp, 2H), 1.90 (d, J=18.0 Hz, 2H), 1.61 (s, 9H), 1.54 (td, J=13.5, 4.5 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 215.3, 154.2, 148.8, 136.2, 135.1, 132.4, 127.8, 127.2, 127.0, 126.8, 123.7, 122.2, 117.6, 114.8, 110.7, 83.9, 66.2, 46.9, 44.6, 40.2, 38.4, 29.1, 28.3, 27.9, 27.2, 23.1; IR (neat) 2953, 1731, 1701, 1455, 1423, 1368, 1326, 1147, 1016, 747 cm^{-1}; mass spectrum (CI) *m/z* 501 (M+H), 400 (base).

4.30. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-6,13-imino-9R-hydroxycyclopentane-cyclooct[1,2-b]indole (47)

$NaBH_4$ (34 mg, 1.0 mmol) was added in one portion to a solution of **46** (200 mg, 0.4 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred for 1 h and satd $NaHCO_3$ (5 mL) was added. The reaction mixture was extracted with EtOAc (3×5 mL) and the combined organic layers were dried and concentrated under reduced pressure. The crude oil was adsorbed on to silica gel (2.0 g) and heated at 80 °C under vacuum (1 mmHg) for 6 h. The flask was cooled and the silica was washed with EtOAc (5 mL) to which 10% Pd/C (20 mg) was added under an atmosphere of H_2 (1 atm). The reaction mixture was stirred for 3 h and was filtered through Celite (1 cm) and concentrated to give 53 mg (45%) of **47** as a white solid. Slow evaporation from CH_2Cl_2/MeOH (2 mL) gave white needles suitable for X-ray: mp=200–204. ^{1}H NMR (400 MHz, CD3OD) δ 7.26 (d, J=9.5 Hz, 1H), 7.15 (d, J=9.5 Hz, 1H), 6.91 (td, J=8.5, 1.5 Hz, 1H), 6.85 (dt, J=8.5, 1.5 Hz, 1H), 4.17–4.11 (m, 1H), 4.01 (s, 1H), 3.28 (d, J=7.5 Hz, 1H), 3.21–3.19 (m, 1H), 3.09 (dd, J=19.5, 8.0 Hz, 1H), 2.46 (d, J=19.5 Hz, 1H), 2.02–1.43 (comp, 7H), 1.17 (dd, J=18.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 137.6, 135.5, 128.6, 121.7, 119.6, 118.4, 111.8, 108.2, 72.9, 49.7, 45.5, 42.2, 39.4, 35.4, 34.1, 32.3, 30.0; IR (neat) 3394, 2924,1450, 1335, 742 cm^{-1}; mass spectrum (CI) m/z 270 (M+H).

4.31. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-14-tert-butoxycarbonyl-6,13-imino-8-hydroxy-9-oxycyclopentane-cyclooct[1,2-b]-indole (48)

OsO_4 (289 mg, 1.18 mmol) was added in one portion to a solution of **45** (690 mg, 1.12 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h, and then H_2S was bubbled through the reaction mixture for 15 min. The thick black precipitate was removed by filtering through Celite (1 cm), washing with THF (30 mL), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1–1:1) to give 480 mg (71%) of a mixture of epimers **48** as a colorless oil. Major isomer: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 8.10 (d, J=8.0 Hz, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.32–7.22 (comp, 7H), 5.96 (s, 1H), 5.16–5.09 (comp, 2H), 4.86 (d, J=7.0 Hz, 1H), 3.90 (d, J=10.5 Hz, 1H), 3.19 (dd, J=16.5, 7.0 Hz, 1H), 2.69 (d, J=16.5 Hz, 1H), 2.28 (dd, J=19.0, 8.0 Hz, 1H), 2.08–1.98 (comp, 4H), 1.69–1.65 (m, 1H), 1.61 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 215.1, 154.3, 148.8, 136.3, 135.1, 132.5, 127.9, 127.8, 127.2, 126.8, 123.7, 122.3, 117.7, 115.1, 114.8, 83.9, 72.9, 66.2, 47.2, 45.1, 40.5, 39.0, 30.7, 27.2, 25.7, 23.2; IR (neat) 3436, 2976, 1729, 1699, 1456, 1424, 1360, 1328, 1153, 754 cm^{-1}; mass spectrum (CI) m/z 517 (M+H), 473, 461, 417.

4.32. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-14-tert-butoxycarbonyl-6,13-imino-7-hydroxymethyl-11-carboxylic acid methyl ester-cyclooct[1,2-b]indole (49)

$Pb(OAc)_4$ (640 mg, 1.45 mmol) was added to a solution of **48** (375 mg, 0.722 mmol) in MeOH/benzene (10 mL, 1:1) at 0 °C and the reaction mixture was stirred for 15 min at 0 °C. $NaBH_4$ (430 mg, 10 mmol) was added in six portions over 5 min, and the reaction mixture was stirred at 0 °C for 15 min. $NaHCO_3$ (20 mL) was added and the solution was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 291 mg (72%) of **49** as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 8.10 (d, J=8.0 Hz, 1H), 7.47 (d, J=7.0 Hz, 1H), 7.31–7.22 (comp, 7H), 5.93 (br s, 1H), 5.08 (s, 2H), 4.91 (d, J=7.5 Hz, 1H), 3.55 (dd, J=11.0, 5.0 Hz, 1H), 3.49 (s, 3H), 3.50–3.46 (m, 1H), 3.21 (dd, J=17.5, 8.0 Hz, 1H), 2.57 (d, J=17.5 Hz, 1H), 2.37 (dd, J=15.5, 7.0 Hz, 1H), 2.27–2.17 (comp, 2H), 1.88–1.84 (m, 1H), 1.76–1.67 (comp, 2H), 1.60 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 171.6, 154.3, 148.8, 136.4, 134.9, 133.7, 127.7, 127.1, 126.6, 123.6, 122.2, 117.6, 114.7, 83.7, 65.9, 57.6, 50.3, 46.3, 45.3, 36.0, 33.6, 29.6, 27.2, 26.2, 25.0, 23.1; IR (neat) 2931, 1729, 1697, 1454, 1367, 1328, 1155, 1116, 912, 747 cm^{-1}; mass spectrum (CI) m/z 549 (M+H) (base), 493, 449.

4.33. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-14-tert-butoxycarbonyl-6,13-imino-7,11-[tetrahydropyran-2-one]-cyclooct[1,2-b]-indole (50)

OsO_4 (4 mg, 0.015 mmol) was added to a slurry of $NaIO_4$ (130 mg, 4 mmol) and **49** (100 mg, 0.152 mmol) in THF/H_2O (1.5 mL, 5:1). The reaction mixture was stirred at room temperature for 48 h and H_2O (5 mL) was added. The solution was extracted with CH_2Cl_2 (3×3 mL) and the combined organic layers were concentrated to give a crude black oil. The oil was dissolved in MeOH (5 mL) and $NaBH_4$ (6 mg, 0.152 mmol) was added. The reaction mixture stirred at room temperature for 30 min and $TsOH\cdot H_2O$ (48 mg, 0.25 mmol) was added and stirred for an additional 4 h. Satd $NaHCO_3$ (5 mL) was added and the solution was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 43 mg (55%) of **50** as a white foam. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 8.10 (d, J=8.0 Hz, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.31–7.27 (comp, 6H), 7.24 (t, J=7.5 Hz, 1H), 5.98 (br s, 1H), 5.11 (s, 2H), 4.51 (d, J=7.5 Hz, 1H), 4.40 (dd, J=11.5, 5.5 Hz, 1H), 4.32 (t, J=11.5 Hz, 1H), 3.18 (dd, J=17.0, 7.5 Hz, 1H), 2.73 (d, J=17.0 Hz, 1H), 2.60 (dd, J=18.0, 7.5 Hz, 1H), 2.37–2.33 (m, 1H), 2.16–2.09 (dd, J=18.0,

2.0 Hz, 1H), 2.12 (m, 1H), 1.95–1.86 (comp, 2H), 1.61 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 168.9, 153.9, 148.7, 136.2, 135.2, 132.4, 127.8, 127.2, 126.9, 125.9, 122.2, 117.6, 114.9, 110.7, 106.4, 83.9, 67.4, 66.2, 47.4, 46.9, 36.8, 33.6, 30.6, 29.9, 27.2, 23.4; IR (neat) 2976, 1731, 1698, 1455, 1423, 1329, 1141, 912, 733 cm^{-1}; mass spectrum (CI) *m/z* 517 (M+H), 545, 517 (base), 417.

*4.34. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-14-tert-butoxycarbonyl-6,13-imino-7,11-[3,4-dihydro-2H-pyran]-cyclooct[1,2-b]indole (**52**)*

A solution of **50** (235 mg, 0.455 mmol) in toluene (10 mL) was cooled to −78 °C, and a solution of DIBAL−H (0.547 mL, 1 M in toluene, 0.547 mmol) was slowly added dropwise. The reaction mixture was stirred for 1 h at −78 °C and then MeOH (0.5 mL) was added. The reaction mixture was warmed to room temperature and satd Rochelle's salt (20 mL) was added. The solution was extracted with EtOAc (3×10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in THF (5 mL) and cooled to 0 °C. Et_3N (340 mg, 3.36 mmol) and MsCl (121 mg, 1.05 mmol) were sequentially added and the reaction mixture was stirred at 0 °C for 30 min. Satd NH_4Cl (5 mL) was added and the solution was extracted with EtOAc (3×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (9:1) to give 130 mg (61%) of **52** as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 8.10 (d, J=8.5 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.32–7.27 (comp, 6H), 7.23 (t, J=7.0 Hz, 1H), 6.30 (d, J=6.0 Hz, 1H), 5.93 (br s, 1H), 5.11 (s, 2H), 4.61 (t, J=5.5 Hz, 1H), 4.55 (d, J=7.5 Hz, 1H), 4.00 (dd, J=11.0, 2.5 Hz, 1H), 3.76 (t, J=11.0 Hz, 1H), 3.15 (dd, J=17.0, 7.5 Hz, 1H), 2.75 (d, J=17.0 Hz, 1H), 2.12–1.96 (comp, 3H), 1.79–1.73 (m, 1H), 1.61 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 153.8, 148.8, 142.8, 136.2, 135.1, 132.5, 127.7, 127.3, 127.2, 126.9, 123.6, 122.2, 117.6, 114.9, 114.8, 103.6, 83.8, 66.2, 63.7, 47.5, 46.5, 37.9, 32.0, 27.2, 26.0, 23.3; IR (neat) 2976, 1729, 1699, 1455, 1422, 1330, 1142, 747 cm^{-1}; mass spectrum (CI) *m/z* 500 (M+H), 401, 387 (base), 267, 229.

*4.35. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-methyl-6,13-iminopyrano[3′,4′:5,6]cyclooct[1,2-b]indole (**53**)*

$LiAlH_4$ (18 mg, 0.48 mmol) was added in one portion to a solution of **52** (60 mg, 0.12 mmol) in THF (5 mL). The reaction mixture was heated to reflux for 1 h and cooled to room temperature. MeOH was added until bubbling ceased (3 drops) and the reaction mixture was filtered through Celite (1 cm) by washing with EtOAc (5 mL). The solvent was removed under reduced pressure and the residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1–0:1) to give 29 mg (86%) of **53** as a white solid: mp=174–175 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 7.61–7.58 (m, 1H), 7.28–7.24 (comp, 2H), 7.15–7.11 (m, 1H), 6.47 (d, J=6.0 Hz, 1H), 6.23 (br s, 1H), 4.48 (dd, J=11.0, 4.4 Hz, 1H), 4.42 (d, J=11.0 Hz, 1H), 3.91 (d, J=9.2 Hz, 1H), 3.29 (s, 1H), 2.98 (dd, J=16.8, 7.2 Hz, 1H), 2.56 (d, J=6.4 Hz, 1H), 2.14 (s, 3H), 2.11 (s, 1H), 1.99 (td, J=12.0, 3.6 Hz, 1H), 1.87–1.79 (comp, 2H), 1.47 (d, J=12.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 144.1, 136.2, 132.0, 128.5, 121.6, 119.7, 118.5, 111.1, 107.2, 105.0, 66.8, 55.5, 54.9, 41.7, 40.8, 35.8, 24.2, 22.8; IR (neat) 3394, 2927, 2360, 1646, 1457, 1244, 1070, 741, 668 cm^{-1}; mass spectrum (CI) *m/z* 281.1657 [$C_{18}H_{21}N_2O$ (M+H) requires 281.1654].

*4.36. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7,14-dimethyl-6,13-iminopyrano[3′,4′:5,6]cyclooct[1,2-b]indole (**54**)*

NaH (12 mg, 0.311 mmol) was added to a solution of **53** (29 mg, 0.104 mmol) in DMF (1 mL) at −5 °C. The reaction mixture was stirred for 15 min and MeI (22 mg, 0.150 mmol) was added. The reaction mixture was stirred for 1.5 h during which time the temperature had warmed to 5 °C. The reaction was quenched with H_2O/brine (2 mL, 1:1) and extracted with CH_2Cl_2 (4×5 mL). The combined organic layers were washed with H_2O (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The solvent was removed under reduced pressure and the residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 29 mg (86%) of **54** as a white solid: mp=192–193 °C. ^{1}H NMR (400 MHz, C6D6) δ 7.66–7.63 (m, 1H), 7.30–7.28 (comp, 2H), 7.10–7.07 (m, 1H), 6.47 (d, J=6.0 Hz, 1H), 4.49 (t, J=5.6 Hz, 1H), 4.43 (d, J=11.0 Hz, 1H), 3.92 (ddd, J=11.0, 4.0, 1.6 Hz, 1H), 3.48 (t, J=3.2 Hz, 1H), 3.04 (dd, J=16.4, 6.8 Hz, 1H), 2.84 (s, 3H), 2.59 (d, J=6.8 Hz, 1H), 2.20 (d, J=16.4 Hz, 1H), 2.15 (s, 3H), 1.99 (dd, J=12.4, 4.0 Hz, 1H), 1.93–1.83 (m, 2H), 1.48 (dt, J=12.4, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 133.3, 126.5, 120.8, 118.8, 117.9, 109.7, 108.7, 106.3, 104.8, 66.6, 55.2, 53.6, 41.8, 40.5, 37.9, 34.7, 23.7, 22.9; IR (neat) 2925, 2360, 2340, 1644, 1467, 1379, 1070, 895, 738, 668 cm^{-1}; mass spectrum (CI) *m/z* 293.1659 [$C_{19}H_{21}N_2O$ (M−H) requires 293.1654].

*4.37. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7-benzyloxycarbonyl-14-tert-butoxycarbonyl-6,13-imino-7,11-[1-(5,6-dihydro-4H-pyran-3-yl)-ethanone]-cyclooct[1,2-b]indole (**56**)*

Trichloroacetyl chloride (0.4 mL, 3.6 mmol) was added to a solution of **52** (170 mg, 0.34 mmol) in pyridine (2 mL), and the reaction mixture was heated to 65 °C for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL). The solution was washed with NH_4Cl (2×10 mL), filtered through a silica plug (1 cm), and concentrated to give a crude yellow oil. The oil was dissolved in AcOH (2 mL) and added dropwise to a suspension of Zn dust (200 mg, 3.0 mmol) in AcOH (2 mL). The reaction mixture was stirred for 30 min and more Zn dust (200 mg, 3.0 mmol)

was added. The reaction mixture was stirred for an additional 15 min, filtered through Celite (1 cm), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 138 mg (75%) of **56** as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 8.15 (d, J=8.0 Hz, 1H), 7.71 (s, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.33–7.23 (comp, 7H), 5.93 (br s, 1H), 5.12 (s, 2H), 4.62 (d, J=7.5 Hz, 1H), 4.24 (dd, J=11.0, 3.0 Hz, 1H), 3.94 (t, J=11.5 Hz, 1H), 3.20 (dd, J=16.5, 7.5 Hz, 1H), 2.77 (d, J=17.0 Hz, 1H), 2.63 (dt, J=11.5, 4.5 Hz, 1H), 2.22–2.18 (m, 1H), 2.06–2.03 (m, 1H), 2.04 (s, 3H), 1.70–1.65 (m, 1H), 1.60 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 193.9, 156.8, 153.9, 148.8, 136.2, 135.1, 132.7, 127.7, 127.4, 127.3, 126.9, 123.7, 122.3, 119.3, 117.6, 114.8, 110.7, 83.8, 66.2, 64.7, 47.7, 46.0, 35.9, 29.9, 27.2, 25.7, 24.2, 22.3; IR (neat) 2913, 1721, 1691, 1612, 1427, 1318, 1090, 740 cm^{-1}; mass spectrum (CI) *m/z* 543 (M+H), 488, 444 (base), 400.

*4.38. 1-(4aR,6S,13S,13aR)-1,4a,5,6,7,12,13,13a-Hexahydro-7,14-dimethyl-6,13-imino-7,11-[1-(5,6-dihydro-4H-pyran-3-yl)-ethanone]-cyclooct[1,2-b]indole (**57**)*

Freshly distilled TMS–I (19 mg, 0.093 mmol) was added to a solution of **56** (12 mg, 0.022 mmol) in CH_3CN (1 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and 15 min at room temperature. Methanolic HCl (1 mL, 1 M) was added and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in aqueous HCl (5 mL, 1 M) and extracted with CH_2Cl_2 (3×5 mL). The aqueous layer was basified with 30% NH_4OH dropwise until pH ~ 12 and then extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/MeOH (9:1) to give 6 mg (78%) of **57** as a white film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.53 (s, 1H), 7.44 (d, J=7.6 Hz, 1H), 7.28 (d, J=7.6 Hz, 1H), 7.13 (t, J=6.8 Hz, 1H), 7.07 (t, J=7.6 Hz, 1H), 4.43 (t, J=11.6 Hz, 1H), 4.19 (ddd, J=11.2, 4.0, 1.6 Hz, 1H), 4.10 (br s, 1H), 3.44 (d, J=6.8 Hz, 1H), 3.22 (dd, J=16.0, 6.8 Hz, 1H), 2.74–2.67 (m, 1H), 2.66 (d, J=16.4 Hz, 1H), 2.11–2.06 (m, 1H), 2.08 (s, 3H), 1.92–1.70 (comp, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 157.5, 135.6, 135.5, 127.2, 121.5, 121.3, 119.3, 117.7, 111.2, 107.9, 67.4, 48.3, 47.7, 37.4, 32.3, 28.8, 25.0, 23.7; IR (neat) 2921, 1614, 1453, 1321, 1195, 738 cm^{-1}; mass spectrum (CI) *m/z* 309 (M+H) (base).

*4.39. (−)-Alstonerine (**1**)*

Methyl iodide (7 mg, 0.05 mmol) was added to **57** (8 mg, 0.0265 mmol) in THF (0.25 mL) and the reaction mixture was stirred at room temperature for 3 h. NaH (3 mg, 0.075 mmol) was added and the reaction mixture was stirred for 30 min. Methyl iodide (10 mg, 0.075 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h. MeOH/EtOAc (1:9, 1 mL) was added and the reaction mixture was filtered through silica gel. The filtrate was concentrated under reduced pressure and the crude residue dissolved in CH_2Cl_2 (5 mL) and washed with $NaHCO_3$ (5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1–0:1) to give 6 mg (72%) of **1** as a white film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.45 (d, J=8.0 Hz, 1H), 7.29 (d, J=8.0 Hz, 1H), 7.17 (t, J=7.2 Hz, 1H), 7.07 (t, J=8.0 Hz, 1H), 4.39 (t, J=11.2 Hz, 1H), 4.15 (ddd, J=10.8, 4.0, 1.6 Hz, 1H), 3.86 (t, J=3.2 Hz, 1H), 3.63 (s, 3H), 3.31 (dd, J=16.4, 6.8 Hz, 1H), 3.07 (d, J=6.8 Hz, 1H), 2.60 (app dt, J=10.0, 4.4 Hz, 1H), 2.48 (d, J=16.4 Hz, 1H), 2.30 (s, 3H), 2.11 (ddd, J=11.2, 4.6, 4.0 Hz, 1H), 2.07 (s, 3H), 1.89 (m, 1H), 1.80 (dd, J=12.0, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 157.4, 137.2, 133.2, 126.5, 121.1, 120.8, 118.7, 117.8, 109.0, 105.9, 67.8, 54.7, 53.8, 41.8, 38.5, 32.4, 29.1, 25.0, 22.9, 22.8; IR (neat) 2895, 2359, 1617, 1468, 1320, 1276, 1192, 911, 741 cm^{-1}; mass spectrum (CI) *m/z* 337.1914 [$C_{21}H_{25}N_2O_2$ (M+H) requires 337.1916]; $[\alpha]_D^{25}$ −187 (*c* 0.30, EtOH) {lit.[6] $[\alpha]_D^{25}$ −195 (EtOH)}.

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