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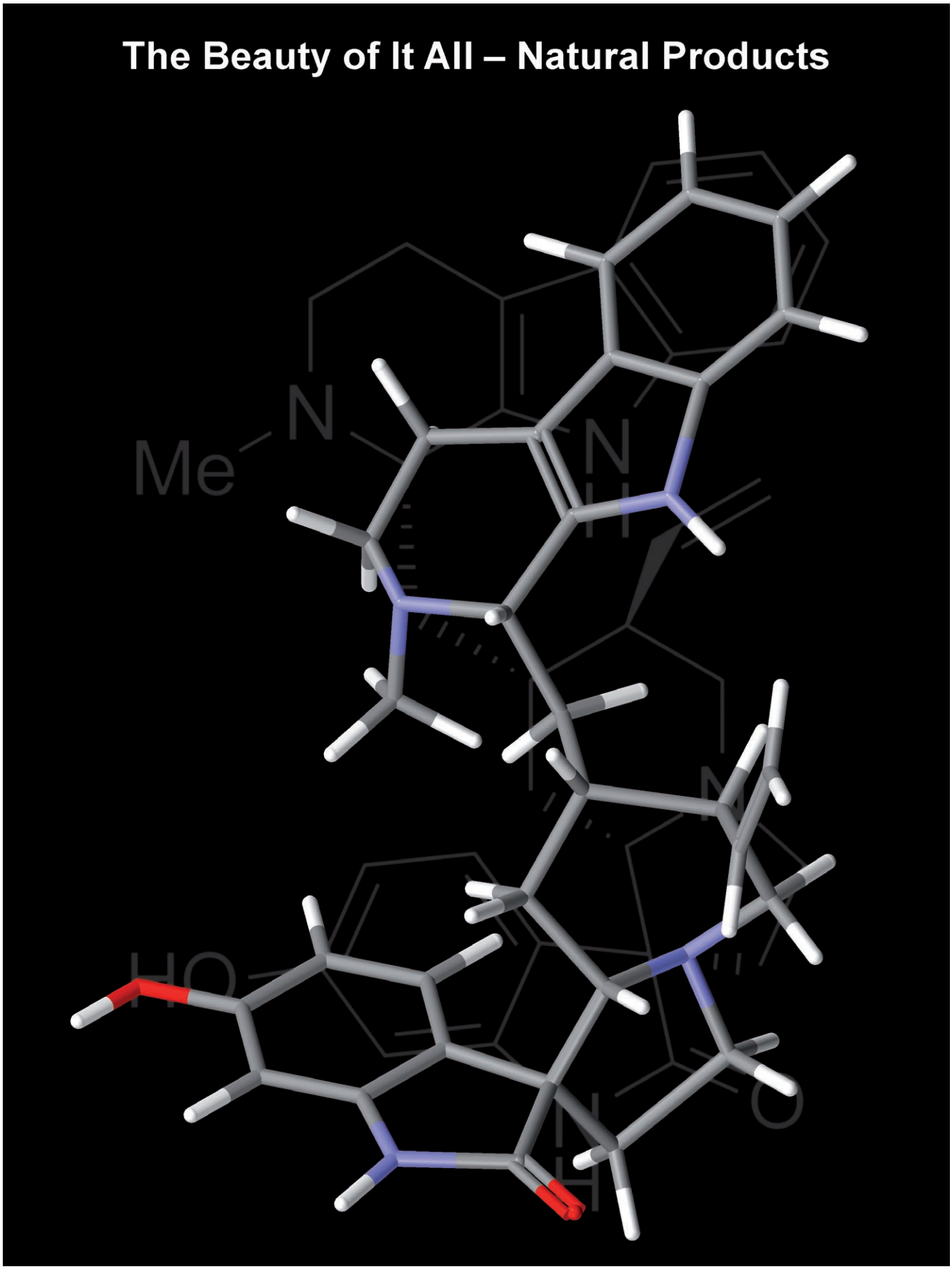
The Beauty of It All – Natural Products



VIP

Synthesis of (±)-Strychnofoline via a Highly Convergent Selective Annulation Reaction

Andreas Lerchner and Erick M. Carreira*[a]

Abstract: Studies aimed at preparing (±)-strychnofoline by total synthesis are detailed. The route described makes use of a recently developed MgI_2-mediated ring-expansion reaction of spiro[cyclopropan-1,3′-oxindole] with a cyclic disubstituted aldimine. The ring-expansion product was formed as a single diastereoisomer in 55% yield, possessing the same stereochemical pattern found in strychnofoline. In addition, our synthetic effort has led to the development of new reaction methodology to access 3,4-disubstituted cyclic aldimines.

Keywords: alkaloids · cyclopropanes · spirocycles · total synthesis

Introduction

In 1978, Angenot and co-workers disclosed the isolation and characterization of strychnofoline (**1**),[1] which belongs to a class of natural products isolated from the leaves of *Strychnos usambarensis*.[2] The compound was shown to inhibit mitosis[3] in a number of cancer cell lines, including mouse melanoma B16, Ehrlich, and Hepatom HW165. A prominent structural feature of the oxindole alkaloids of the *Strychnos* family and related natural products is the presence of a spiro[pyrrolidin-3,3′-oxindole] core (Figure 1). Additional oxindole alkaloids have been isolated from other plant sources, exemplified by spirotryprostatin B (**3**),[4] rhynchophylline (**4**),[5] formosanine (**5**),[6] voachalotine oxindole (**6**),[7] (−)-horsfiline (**7**),[8] and gelsemine (**8**),[9] containing similar structural features.

The biosynthesis of strychnofoline has not been specifically investigated, but the general biosynthetic pathways en route to such alkaloids in the *Corynanthe*/*Strychnos* group have been established[10] and may also be valid for strychnofoline (**1**) (Scheme 1). The biosynthesis of commences with the conversion of geraniol (**9**) to loganin (**10**),[11] and thereafter proceeds from loganin (**10**) to secologanin (**11**).[12] Secologanin is believed to undergo Pictet–Spengler reaction with tryptamine **12**, furnishing strictosidine (**13**).[13] Corynantheal (**14**) is likely to be the last of the *Corynanthe*-type intermediates.[14] Usambaridine Br (**15**) has been isolated from the leaves of *Strychnos usambarensis*, together with strych-

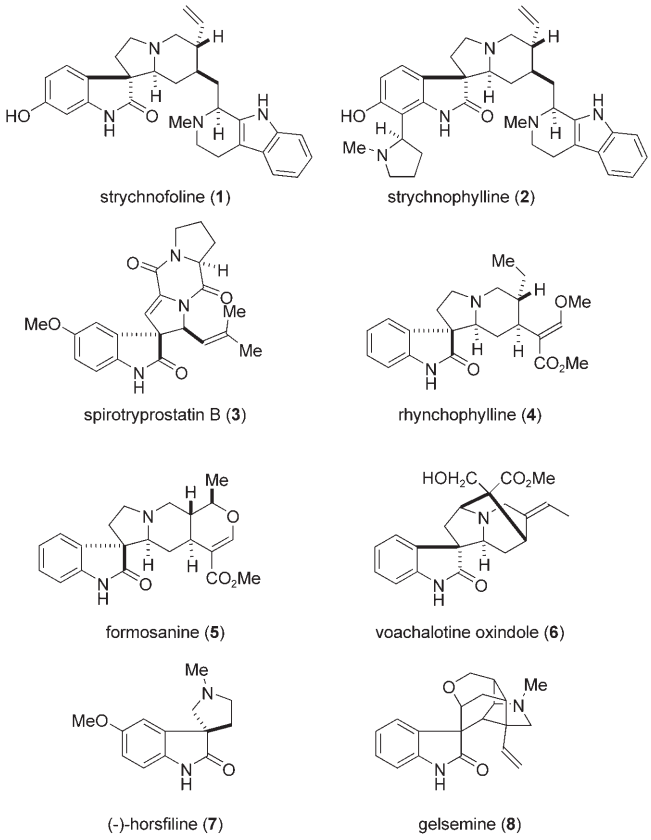


Figure 1. Collection of natural products incorporating the spiro[pyrrolidin-3,3′-oxindole] core.

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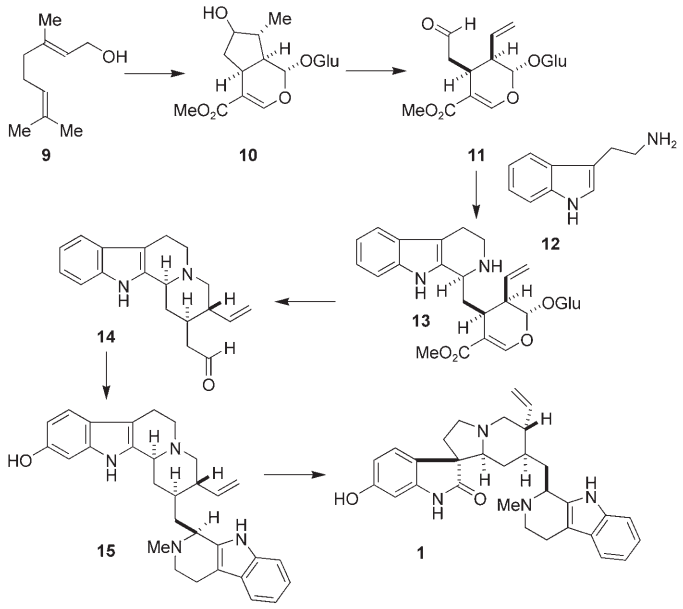


Scheme 1. Putative biosynthetic pathway to strychnofoline.

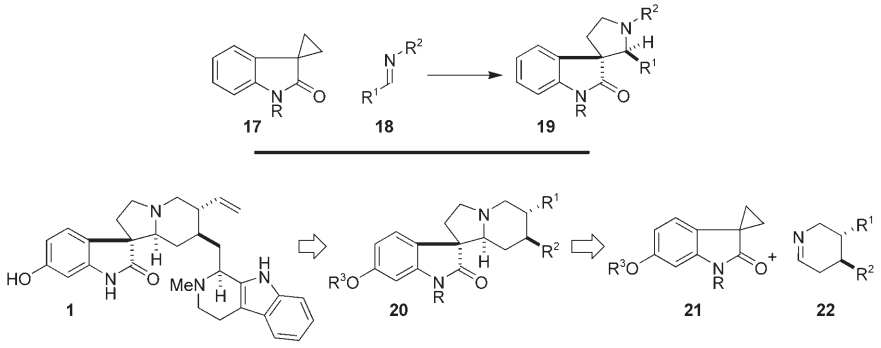
nofoline.[1] Usambaridine Br (**15**) is likely converted to strychnofoline (**1**) by an oxidative rearrangement, a sequence which is probably responsible for the origin of all oxindole alkaloids of the *Strychnos* family.[15]

Within the context of complex molecule syntheses, the successful preparation of spiro[-perhydroindolizine-oxindoles] has been effected following four general strategies. The first was reported for the total synthesis of related antineoplastics,[16] wherein condensation of a 2-oxytryptamine with an aldehyde afforded an intermediate imine that subsequently participated in an intramolecular Mannich reaction. In a second complementary approach, the oxidative rearrangement of yohimbinoids provided access to oxindole alkaloids.[15] The third approach reported to date is exemplified by the elegant total synthesis of pseudotabersonine, wherein the analogous spirofused quinolizidine-oxindole ring system is formed by aza Diels–Alder reaction of an imine and diene.[17] We have recently introduced a fourth method involving the annulation reaction of imines and cyclopropylspirooxindoles described below.[18]

Results and Discussion

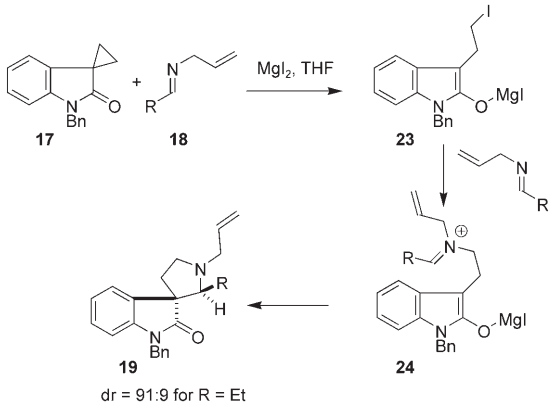
Because of the biological activity of the oxindole alkaloids as well as the synthetic challenges presented by their complex architecture we have embarked on a program that aims at developing and studying efficient strategies toward their preparation. In this context a methodological study was undertaken, leading to the development of a novel ring-expansion reaction of a spiro[cyclopropan-1,3′-oxindole] (**17**) with a range of simple, unfunctionalized imines (**18**) to furnish spiro[pyrrolidin-3,3′-oxindoles] (**19**), whose core structure is identical to the core structure of many oxindole alkaloids (Scheme 2).[19] It was our intention to apply this novel MgI_2-mediated ring-expansion reaction as a key step to the first total synthesis of (±)-strychnofoline (**1**). Within the context of such a target-specific synthesis program, we aimed to address a key issue, namely, whether a cyclic imine could be used in the annulation reaction and whether previously existing stereocenters in such an imine could effect control over the stereochemical course of the annulation process, leading to the formation of the desired relative configuration found in strychnofoline.

Our working hypothesis with respect to the mechanism of the reaction is that the iodide participates in nucleophilic opening of the cyclopropyl ring in the spiro[cyclopropan-1,3′-oxindole] to furnish a putative iodo enolate **23**



Scheme 2. Annulation reaction of imines and cyclopropylspirooxindoles.

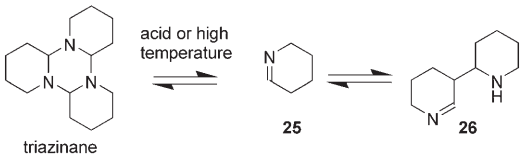
(Scheme 3). A number of several distinct reaction pathways to the end-product are available from this intermediate, which possesses both nucleophilic and electrophilic character. This dual characteristic could also be viewed as a cause



Scheme 3. Working mechanistic model of the annulation process.

of some concern, as the iodo enolate could participate in an intramolecular alkylation forming the corresponding furano-fused indolyl ring system. However, if it was sufficiently long-lived, nucleophilic substitution of the iodide with the aldimine could lead to the formation of a putative aldiminium **24** which could undergo Mannich cyclization to form pyrrolidine **19**. We have circumstantial evidence that lends credence to this pathway; thus when $MgBr_2$ was used as a catalyst, the reaction proceeds at a significantly slower pace, and when $Mg(OTf)_2$ was used, the ring-expansion reaction did not proceed at all.[19] Moreover, the corresponding iodoethyl oxindole could be isolated from the MgI_2-mediated ring-expansion reaction in the absence of added imine.[21]

One key issue that would have to be addressed for the successful execution of the strategy is the preparation of the requisite disubstituted cyclic aldimine. A significant problem was the fact that unsubstituted cyclic aldimines (i.e., **25**) readily suffer self-condensation (Scheme 4). This can be best

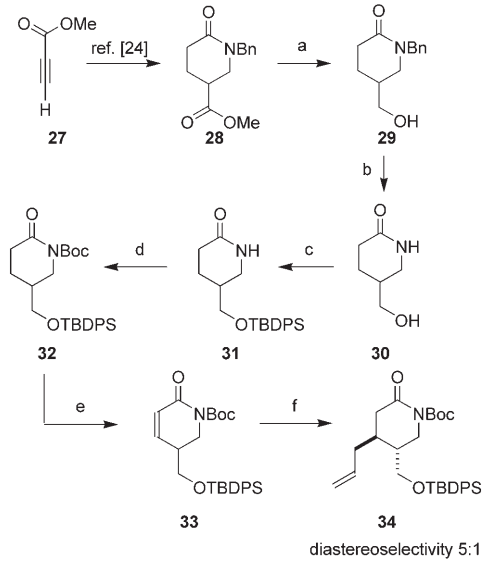


Scheme 4. Formation of tetrahydroanabasin from tetrahydropyridine as reported by Schöpf.

appreciated in the work of Schöpf who investigated the formation of tetrahydroanabasin (**26**) from tetrahydropyridine **25**.[22] In line with these studies, the large number of the stable isolable cyclic imines possess α,α-disubstitution; precluding the formation of the corresponding enamine and subsequent oligomerisation.

The synthesis of strychnofoline commences with the preparation of lactam **34** through a convenient sequence from propiolic acid **27** (Scheme 5).[24] Ester **28** was reduced with $LiBH_4$ in THF at room temperature to give alcohol **29** in a yield of 89%. Debenzylation of **29** (Na in NH_3,THF, *tert*-butanol, −40°C) provided lactam **30** in 75% yield. Deprotection of the *N*-benzyl group by hydrogenation with Pd/C was not found to be a viable option, consistent with findings in literature.[25] The alcohol in **30** was protected with TBDPSCl, (imidazole, DMAP, DMF) to afford **31** (91% yield). Subsequent N-protection was effected by treatment of **31** with Boc_2O (NEt_3, DMAP, CH_2Cl_2/DMF) to afford **32** in 88% yield. Deprotonation of lactam **32** with LHMDS at −78°C in THF was followed by the slow addition of PhSeCl in THF at −78°C via cannula to furnish the α-selenylated derivative. Subsequent treatment of the selenylated product with H_2O_2 in EtOAc afforded unsaturated lactam **33** in 80% yield.

Unsaturated lactam **33** underwent Michael addition with allylMgCl in the presence of $CuBr{\cdot}SMe_2$ and TMSCl (−78°C, THF) to give **34** in 75% yield as a diastereomeric mixture of 5:1 in favor of the desired product. This was con-



Scheme 5. Synthesis of imide intermediate. a) $LiBH_4$, THF, 23°C, 88% yield; b) Na, NH_3, THF, *t*BuOH, −40°C, 10 min, 75% yield; c) imidazole, DMF, TBDPSCl, 23°C, 91% yield; d) DMAP, NEt_3, CH_2Cl_2, Boc_2O, 23°C, 88% yield; e) LHMDS, THF, PhSeCl, −78°C, then EtOAc, H_2O_2, 23°C, 80% yield; f) allylMgCl, $CuBr{\cdot}SMe_2$, THF, −78°C, 75% yield for both diastereoisomers.

veniently assayed by integration of the ^{1}H NMR signals at δ 2.26 (dd, 1H, $J_1=15.8$, $J_2=8.8$ Hz) for the major diastereoisomer and δ 2.34 (dd, 1H, $J_1=17.7$, $J_2=8.1$ Hz) for the minor diastereoisomer. At this stage, it was assumed with a reasonable level of confidence that the major diastereoisomer corresponded to the *trans*-disubstituted product; this could later be confirmed by ^{1}H NMR NOE studies of the ring annulation product **47** as shown in Figure 2. In the course of the studies of this Michael addition reaction, we had observed that reactions in THF gave improved yields over those conducted in Et_2O, and the addition of allylMgCl led to a higher than when allylMgBr was employed.[26,27]

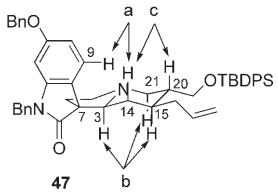
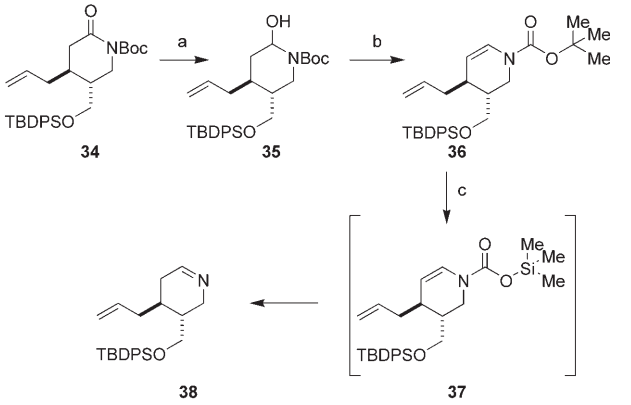
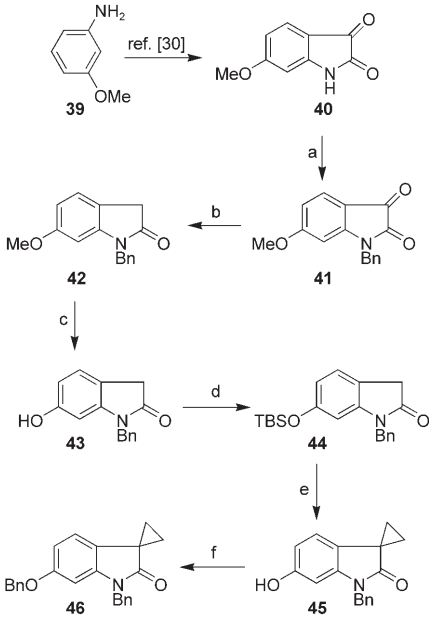


Figure 2. ^{1}H NMR NOE studies of the ring annulation product **47**.

Conversion of disubstituted lactam **34** to the desired imine commenced with reduction of **34** with DIBALH (THF/hexane, −78°C) to afford lactamol **35** (Scheme 6). Treatment of a solution of **35** in CH_2Cl_2 with 1M aq HCl and subsequent stirring of the biphasic reaction mixture at room temperature for 5 min provided the Boc-protected enamine **36** in a yield of 75%.[29] Enamine **36** was treated with TMSOTf and NEt_3 in CH_2Cl_2 at −20°C to afford cyclic aldimine **38**, which was used directly in the ring-expansion reaction.[28] It is worth noting that the selection of N-Boc protection strategy was made, as we were cognizant of the instability of the cyclic imine. Thus, it was particularly appealing that N-Boc deprotection could be carried out under mild conditions and would lead to co-products



Scheme 6. Conversion of imide to the key imine intermediate. a) DIBAL, THF, hexane, −78 °C; b) aqueous HCl in CH_2Cl_2, 23 °C, 75% yield from **34**; c) TMSOTf, NEt_3, then aqueous $NaHCO_3$.



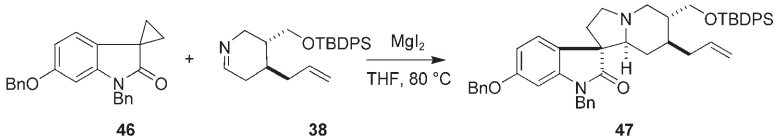
Scheme 7. Synthesis of the spirocyclic cyclopropane. a) NaH, BnBr, DMF, −78 °C to 25 °C, 72% yield; b) hydrazine hydrate, EtOH, 100 °C, 90% yield; c) BBr_3, CH_2Cl_2, 0 °C, 92% yield; d) TBDMSCl, imidazole, DMF, 88% yield; e) dibromoethane, DMF, NaH, 0 °C, then MeOH, −78 to 25 °C, 86% yield; f) BnBr, NaH, DMF, 0 °C, 87% yield.

that were volatile or readily soluble in aqueous media, and thus permit convenient purification and isolation of the imine.

Spiro[cyclopropan-1,3′-oxindole] (**46**), necessary for the synthesis of strychnofoline, was prepared from 6-methoxyisatine (**41**), which itself is conveniently prepared in two steps from *m*-anisidine (**39**) (Scheme 7). Because the cleavage of the *O*-methyl ether would involve the use of harsh conditions that might not be compatible with an advanced intermediate later in the synthetic sequence, the methyl ether was exchanged early on in the synthesis for an *O*-benzyl protecting group. Although isatines **40** and **41** did not withstand the reaction conditions for the removal of the methyl group with BBr_3, oxindole **42** proved sufficiently robust. Thus, oxindole **42** was treated with BBr_3 in CH_2Cl_2 at 0 °C to give **43** in 92% yield. Subsequent attempted *O*-benzylation of **43** by treatment with K_2CO_3 and BnBr in DMF at 60 °C gave a complex mixture including products from *O*-benzylation of the phenol as well as *C*-alkylation of a putative indole enolate. This problem was dealt with at the expense of an additional step in the synthesis of the spiro[cyclopropan-1,3′-oxindole]. In this respect the phenol in **43** was silylated with TBSCl and imidazole in DMF to give silyl ether **44** in a yield of 88%. Oxindole **44** was C-dialkylated using dibromoethane and NaH in DMF at 0 °C to give cyclopropylspirooxindole **45**. Once installation of the cyclopropane was deemed complete by thin layer chromatography, the reaction mixture was cooled to −78 °C and treated with MeOH. Given the slight excess of base employed in the preceding reaction, the residual MeONa effected desilylation of the phenol to provide spiro[cyclopropan-1,3′-oxindole] (**45**) in 86% yield. Spiroindole **45** was treated with BnBr and NaH at 0 °C to afford spiro[cyclopropan-1,3′-oxindole] **46** (87% yield).

With cyclic aldimine **38** and spiro[cyclopropan-1,3′-oxindole] **46** in hand, the MgI_2-mediated ring-expansion reaction could be investigated. Because of the inherent instability of cyclic aldimine **38**, it was employed without purification in the annulation reaction (Scheme 8).

The annulation reaction was carried out by charging a sealable tube with MgI_2 and spiro[cyclopropan-1,3′-oxindole] (**46**) and cyclic aldimine **38** in THF. The sealed tube was placed into a preheated oil bath at 80 °C, and the reaction mixture was heated for 16 h at 80 °C. Upon cooling, spirooxindole **47** was isolated as a single diastereoisomer in a yield of 55% over two reaction steps, namely, imine formation and annulation. The optimal concentration for the annulation proved to be 0.3 M. Moreover, we observed that substoichiometric amounts of MgI_2 could be employed, thus, with 50 mol% of MgI_2 the product could be isolated in roughly similar yield. The assignment of the relative stereochemistry in **47** was effected by ^{1}H NMR NOE studies (Figure 2). Thus, the axial proton at C-14 was shown to be in close proximity to the aromatic proton at C-9: irradiation of the proton at C-9 produces an enhancement at the resonance corresponding to H_{Re}-C(14) of 3%. Irradiation of the



Scheme 8. The critical annulation reaction. a) 1 equiv MgI_2, THF, 80 °C, 55% (combined yield of the imine forming reaction and the ring-expansion reaction).

axial proton at H_{Re}-C-14 resulted in a NOE enhancement at the axial proton at C-20 of 2%. The axial protons at C-3, C-15 and C-21 are also spatially close: the observed ^{1}H NMR NOE enhancement of H-C(15) upon irradiation of H-C(3) is 4% and the ^{1}H NOE enhancement of H-C(15) upon irradiation of H_{Re}-C(21) is 4%. Thus, from these studies it can be concluded that the product possesses the stereochemical pattern commonly found in the pyrrolidinospirooxindole family of natural products and specifically that of strychnofoline.

Because four different diastereoisomers could have been formed in the described MgI_2-mediated ring-expansion reaction, an explanation for the high diastereoselectivity seems called for. In principle, the oxindole alkaloids can exist as mixture of four distinct diastereomers on the basis of the spiro-fusion that are readily interconvertible. These have been classified (Figure 3) into various groups: normal A and

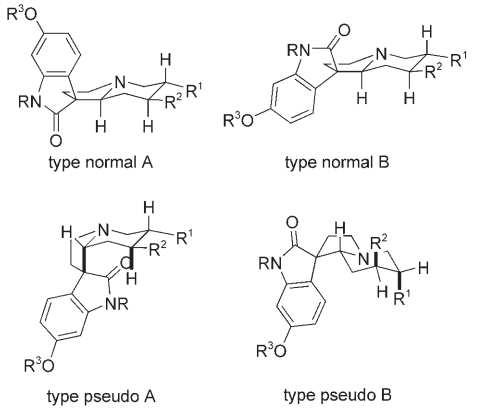


Figure 3. Classification of the diastereomer patterns in pyrrolidinospirooxindole family of natural products.

B along with pseudo A and B.[31] Type pseudo A and pseudo B have not been detected in oxindole alkaloids. It has been suggested that they are thermodynamically less stable than the diastereoisomers of the type normal A and B due to unfavorable diaxial steric interactions between the substituents of the piperidine ring. In the case of the stereoisomers of the type normal A and B, the substituents on the piperidine ring are all equatorially poised. Oxindole alkaloids with the stereochemical pattern of type normal B appear in nature as often as oxindole alkaloids of type normal A. These two types are known to be interconverted via an intramolecular retro-Mannich/Mannich reaction sequence in refluxing pyridine or refluxing acetic acid. Interestingly the position of this equilibrium is correlated to the protonation state of the alkaloid. In acidic medium the stereoisomer of the type normal B dominates; by contrast under alkaline conditions the stereoisomer of the type normal A is predominant (Figure 4). It has been argued that the protonated form of type normal B diastereomer, a stabilizing interaction ensues through the formation of a hydrogen bond to the oxindole carbonyl acceptor. For diastereoisomer of the type normal

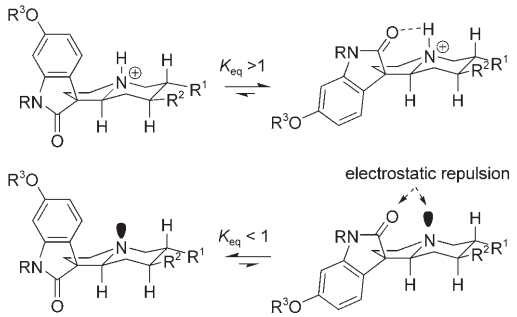
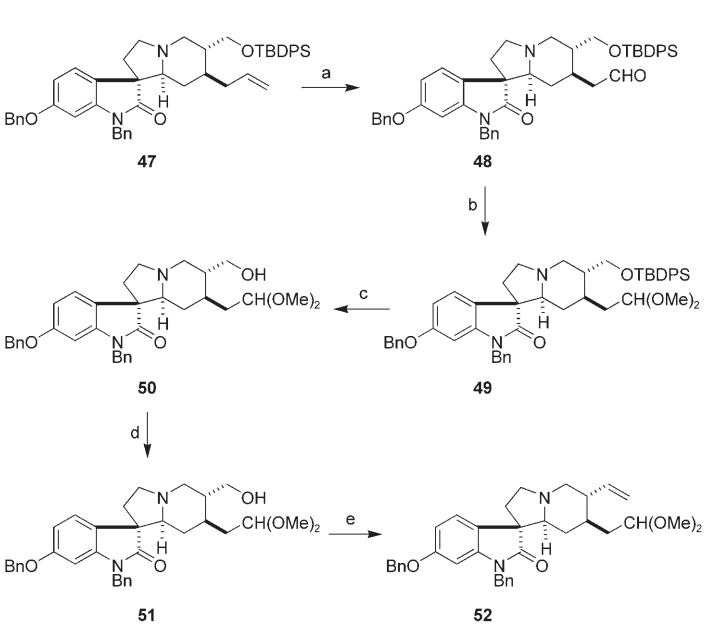


Figure 4. The effect of acidity of the medium on the diastereomer population in the pyrrolidinospirooxindole family of natural products.

A, the formation of a comparable hydrogen bond is precluded. This effect is manifest in the difference of the acidity for the two stereoisomers: the pK_a value for conjugate acid of type normal A are usually by one unit lower than the pK_a value for the conjugate acid of type normal B. It is worth noting that further analysis of these structures reveals an electrostatic repulsion between the nitrogen lone pair and carbonyl lone pairs which is destabilizing. Such a destabilizing interaction is absent in type normal A. In summary, we assume that the product of the MgI_2-mediated ring-expansion reaction is the thermodynamically most stable diastereoisomer in aprotic medium. Thus, the diastereoselectivity of the product isolated from the MgI_2-mediated annulation reaction is at present best accommodated by thermodynamics of the product formed.[32]

Since the MgI_2-mediated ring-expansion reaction had provided access to the core structure of strychnofoline, we could focus on the conversion of the allyl group at C-15 into a carbolinylmethyl group and the conversion of the silyloxymethyl group at C-20 into a vinyl group (Scheme 9).[33] The olefin in spiroindole **47** was oxidized with OsO_4 and NMO (*t*BuOH/water/dioxane) to afford an intermediate diol, which was cleaved directly with $NaIO_4$ to give aldehyde **48** in 86% yield. Aldehyde **48** was treated with *p*-TsOH, MeOH, and $CH(OMe)_3$ to provide acetal **49** (93%). The TBDPS-silyl ether was removed by treatment of **49** with TBAF in THF to provide alcohol **50** (86%). Alcohol **50** was oxidized by IBX in DMSO to afford aldehyde **51** in 88% yield. Aldehyde **51** was subjected to Wittig olefination (PPh_3MeBr, *t*BuOK, THF) at room temperature to provide olefin **52** in a yield of 87%. A crystal structure of **52** could be obtained; analytically useful crystals were formed over two days at −20°C in a solvent mixture of EtOAc and hexane. The crystal structure of **52** confirmed the NOE studies for **47**; the MgI_2-mediated ring-expansion reaction had provided a diastereoisomer of type normal A (Figure 5).[32,33] Acetal **52** was treated with aqueous HCl in acetone to give aldehyde **53** in a yield of 94% (Scheme 10). Aldehyde **53** and *N*-methyltryptamine[35] were stirred in toluene and acetic acid at 80°C for 2 h to provide **54** in 38% yield and desired **55** in 26% yield. The deprotection of the two benzyl groups in **55** by Na in a solvent mixture of ammonia, *t*BuOH, and THF from −78 to −45°C for 10 min provided



Scheme 9. Synthetic elaboration of **47**. a) i) OsO_4, NMO, THF, *t*BuOH, H_2O, 23 °C ii) $NaIO_4$, THF, *t*BuOH, H_2O, 23 °C, 86 % yield over 2 steps; b) *p*-TsOH, MeOH, $CH(OMe)_3$, 23 °C, 93 % yield; c) TBAF, THF, 23 °C, 86 % yield; d) IBX, DMSO, 23 °C, 88 % yield; e) PPh_3MeBr, *t*BuOK, THF, 23 °C, 87 % yield.

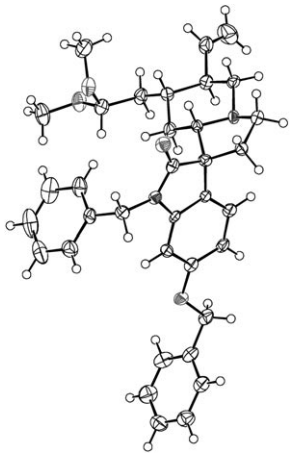
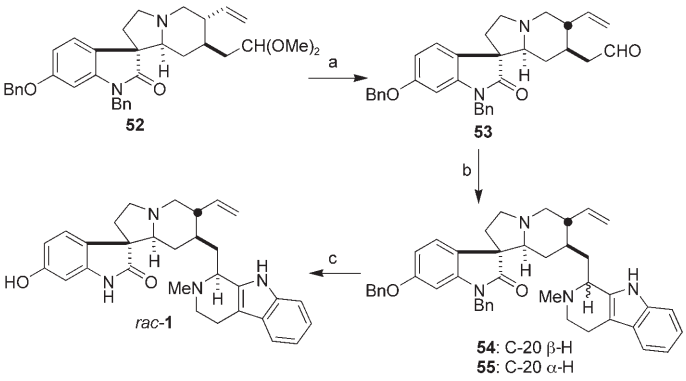


Figure 5. X-ray crystal structure of **52**.

strychnofoline (**1**) in 82 % yield. It could be observed that the benzyl protected aromatic hydroxyl group was deprotected at −78 °C, whereas the benzyl group on the amide moiety was only deprotected at −45 °C. The synthetic material isolated was identical in all respects with the material from natural sources by TLC, mass spectrometry, ^{13}C NMR and ^{1}H NMR spectroscopy.

Conclusion

In summary, we have described the first total synthesis of (±)-strychnofoline with the use of a highly selective MgI_2-mediated annulation reaction, which was shown to effectively work with a spiro[cyclopropan-1,3′-oxindole] and a disubstituted cyclic aldimine to provide the corresponding spiro[perhydroindolizine-oxindole] in good yield over two steps and excellent diastereoselectivity. The stereochemical pattern produced in annulation reaction was identical with the pattern found in strychnofoline. In the context of the total synthesis of strychnofoline, useful, mild method leading to the formation of cyclic aldimines has been established, which may in turn lead to new access to this class of reactive building blocks. The large number of oxindole alkaloids and their promising biological activity makes them an interesting target in academic and industrial chemistry. Thus, the results presented substantively contribute to the development of stereocontrolled synthesis of this important class of natural products.



Scheme 10. End steps. a) HCl (10 % in H_2O), acetone, 23 °C, 94 % yield; b) AcOH, toluene, N^{in}-methyltryptamine, 80 °C, 38 % yield for **55** and 26 % yield for **54**; c) Na in NH_3, *t*BuOH, THF, −78 to −45 °C, 82 % yield.

Experimental Section

All non-aqueous reactions were carried out using glassware that had been dried by heating for 5 min to 300 °C under high vacuum. THF, Et_2O, toluene and CH_2Cl_2 were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H_2O content < 30 ppm, Karl-Fischer titration). Triethylamine and HMDS were distilled prior to use. Radial chromatography was performed with a Cyclo-Graph chromatodron using 1 mm or 2.5 mm $CaSO_4$-bound silica gel plates at a flow rate of 5–7 mL min^{-1}. NMR spectra were recorded on a Bruker DRX500 spectrometer operating at 500 MHz and 125 MHz for ^{1}H and ^{13}C acquisitions, respectively. IR: Perkin Elmer spectrum RXI FT-IR spectrophotometer. Mass spectra (*m*/*z* [amu] (% base peak)): MALDI; IonSpec Ultima Fourier Transform Mass Spectrometer.

***N*-Benzyl-5-hydroxymethyl-2-piperidinone (29)**: $LiBH_4$ (1.23 g, 56.6 mmol, 2.00 equiv) was added in one portion at 0 °C to a solution of ester **28** (7.00 g, 28.3 mmol, 1.00 equiv) in THF (270 mL). The reaction mixture was stirred at room temperature for 24 h and then cooled to 0 °C. The reaction was quenched by H_2O (250 mL), followed by the addition of HCl (10 % in H_2O). The combined organic solvents were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 20:1) provided alcohol **29** (5.53 g, 89 %) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.19–7.32 (m, 5H), 4.60 (d, 1H, J = 14.6 Hz), 4.53 (d, 1H, J = 14.6 Hz), 3.55 (dd, 1H, J_1 = 10.7, J_2 = 5.6 Hz), 3.45 (dd, 1H, J_1 = 10.7, J_2 = 7.1 Hz), 3.31 (ddd, 1H, J_1 = 12.2, J_2 = 5.2, J_3 = 1.7 Hz), 3.00 (dd, 1H, J_1 = 12.2, J_2 = 10.0 Hz), 2.50–2.56 (m, 1H),

2.35–2.46 (m, 1H), 1.95–2.06 (m, 1H), 1.84–1.90 (m, 1H), 1.45–1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 137.0, 128.6, 128.0, 127.4, 64.4, 50.4, 49.8, 36.4, 31.2, 23.8; FTIR (neat): $\tilde{\nu}$ = 3392 (m), 1619 (s, C=O), 1498 (m), 913 (m), 743 cm^{-1} (m); HRMS (MALDI): m/z: calcd for $C_{13}H_{18}NO_2$: 220.1332; found: 220.1333 $[M+H]^+$.

5-Hydroxymethyl-2-piperidinone (30): Alcohol **29** (4.20 g, 19.2 mmol, 1.00 equiv) in THF (5 mL) was added at −45 °C to a homogeneous solution of Na (1.77 g, 76.8 mmol, 4.00 equiv) in NH_3 (70 mL), THF (5 mL), and *t*BuOH (5 mL). The reaction mixture was stirred at −45 °C for 10 min and then cooled to −78 °C. The reaction was quenched by the addition of NH_4Cl (13 g) and diluted with THF (60 mL). NH_3 was allowed to evaporate slowly at −30 °C over 3 h. The slurry was filtered and washed with THF (3×5 mL) and CH_2Cl_2 (20 mL). The filtrate was concentrated under reduced pressure to give lactam **30** (1.85 g, 75 %) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.60 (s, 1H), 3.63 (dd, 1H, J_1=10.7, J_2=5.6 Hz), 3.54 (dd, 1H, J_1=10.7, J_2=7.4 Hz), 3.42–3.46 (m, 1H), 3.09 (dd, 1H, J_1=10.9, J_2=10.3 Hz), 2.42 (ddd, 1H, J_1=18.0, J_2=6.2, J_3=3.8 Hz), 2.33 (ddd, 1H, J_1=18.0, J_2=10.6, J_3=6.6 Hz), 1.98–2.08 (m, 1H), 1.86–1.96 (m, 1H), 1.51–1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8, 64.2, 44.7, 35.7, 30.2, 23.4; FTIR (neat): $\tilde{\nu}$ = 3299 (m), 1644 (m, C=O), 913 (s), 744 cm^{-1} (s); HRMS (MALDI): m/z: calcd for $C_6H_{18}NO_2$: 130.0863; found: 130.0865 $[M+H]^+$.

5-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-2-piperidinone (31): Imidazole (3.27 g, 48.0 mmol, 3.43 equiv) and TBDPSCl (6.60 mL, 25.0 mmol, 1.79 equiv) were added to a solution of alcohol **30** (1.80 g, 14.0 mmol, 1.00 equiv) in DMF (14 mL). The reaction mixture was stirred at room temperature for 12 h and then quenched with saturated aqueous $NaHCO_3$ at 0 °C. The combined organic solvents were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 20:1) provided silyl ether **31** (4.69 g, 91 %) as white crystals. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62–7.65 (m, 4H), 7.37–7.46 (m, 6H), 6.39 (s, 1H), 3.65 (dd, 1H, J_1=10.2, J_2=5.4 Hz), 3.56 (dd, 1H, J_1=10.2, J_2=7.2 Hz), 3.43–3.48 (m, 1H), 3.11 (dd, 1H, J_1=11.0, J_2=10.9 Hz), 2.41 (ddd, 1H, J_1=17.9, J_2=6.2, J_3=3.5 Hz), 2.31 (ddd, 1H, J_1=17.9, J_2=11.0, J_3=6.4 Hz), 2.00–2.11 (m, 1H), 1.80–1.87 (m, 1H), 1.49–1.60 (m, 1H), 1.05 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 135.5, 133.3, 129.8, 127.7, 65.5, 44.8, 35.8, 30.4, 26.8, 23.5, 19.2; FTIR (neat): $\tilde{\nu}$ = 2931 (m), 2858 (m), 1667 (s, C=O), 1427 (m), 1113 (s), 772 (s), 702 cm^{-1} (s); HRMS (MALDI): m/z: calcd for $C_{22}H_{29}NO_2SiNa$: 390.1860, found 390.1859 $[M+Na]^+$.

5-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-2-oxo-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (32): NEt_3 (667 μL, 5.44 mmol, 1.00 equiv) and DMAP (665 mg, 5.44 mmol, 1.00 equiv) were added to a solution of lactam **31** (2.00 g, 5.44 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) and DMF (0.5 mL). Boc_2O (2.37 g, 10.9 mmol, 2.00 equiv) was dissolved in CH_2Cl_2 (5 mL) and added slowly. The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was concentrated to a volume of 5 mL and purified by flash chromatography on silica gel (EtOAc/pentane 1:4) to afford lactam **32** (2.24 g, 88 %) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.65 (m, 4H), 7.36–7.47 (m, 6H), 3.96 (ddd, 1H, J_1=12.8, J_2=5.0, J_3=1.2 Hz), 3.63 (dd, 1H, J_1=10.2, J_2=5.2 Hz), 3.55 (dd, 1H, J_1=10.2, J_2=7.2 Hz), 3.42 (dd, 1H, J_1=12.8, J_2=9.7 Hz), 2.39–2.61 (m, 2H), 2.05–2.17 (m, 1H), 1.80–1.89 (m, 1H), 1.44–1.57 (m, 1H), 1.53 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5, 152.3, 135.5, 133.2, 129.8, 127.7, 82.8, 65.4, 48.0, 36.0, 33.8, 28.0, 26.8, 22.6, 19.2; FTIR (neat): $\tilde{\nu}$ = 1771 (s, C=O), 1717 (s, C=O), 1247 cm^{-1} (s); HRMS (MALDI): m/z: calcd for $C_{27}H_{37}NO_4SiNa$: 490.2384; found: 490.2395 $[M+Na]^+$.

5-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-5,6-dihydro-2-oxo-1(2*H*)-pyridine carboxylic acid 1,1-dimethylethyl ester (33): BuLi (1.60 M in hexane, 10.8 mL, 17.2 mmol, 2.30 equiv) was added at −78 °C to a solution of freshly distilled HMDS (3.75 mL, 18.0 mmol, 2.40 equiv) in THF (30 mL). After stirring the reaction mixture at −78 °C for 1 h, lactam **32** (3.50 g, 7.49 mmol, 1.00 equiv) in THF (30 mL) was added dropwise over 10 min. The reaction mixture was stirred at −78 °C for 1 h. PhSeCl (1.72 g, 8.98 mmol, 1.20 equiv) in THF (40 mL) at −78 °C was transferred via cannula into the reaction mixture within 30 s. The reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched at −78 °C by the addition of saturated aqueous $NaHCO_3$ (20 mL). The combined organic solvents were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide a residue. This residue was dissolved in EtOAc (40 mL), and aqueous H_2O_2 (30 % in H_2O, 8 mL) was added at 0 °C. The ice bath was removed and the reaction mixture was stirred at room temperature for 1 h. The organic layer was separated, washed with brine (2×10 mL) and saturated aqueous $NaHCO_3$ (4×10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide unsaturated lactam **33** (2.79 g, 80 %) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62–7.65 (m, 4H), 7.38–7.47 (m, 6H), 6.60 (dd, 1H, J_1=9.8, J_2=3.7 Hz), 5.95 (dd, 1H, J_1=9.8, J_2=1.9 Hz), 3.98 (ddd, 1H, J_1=12.9, J_2=5.1, J_3=0.6 Hz), 3.84 (dd, 1H, J_1=12.9, J_2=7.9 Hz), 3.61–3.68 (m, 2H), 2.70–2.75 (m, 1H), 1.55 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7, 152.5, 144.2, 135.5, 133.0, 132.9, 130.0, 129.9, 127.9, 126.8, 83.0, 63.3, 45.8, 37.9, 28.1, 26.8, 19.3; FTIR (neat): $\tilde{\nu}$ = 1770 (s, C=O), 1760 (s, C=O), 1714 (m, C=O), 1246 (s), 913 (m), 743 cm^{-1} (m); HRMS (MALDI): m/z: calcd for $C_{27}H_{35}NO_4SiNa$: 488.2228; found: 488.2236 $[M+Na]^+$.

(4*S*,5*R*)-4-Allyl-5-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-2-oxo-1-piperidine carboxylic acid 1,1-dimethylethyl ester (34): Allylmagnesium chloride (2 M in THF, 13.4 mL, 26.9 mmol, 5.00 equiv) was added at −78 °C to a suspension of CuBr·SMe_2 (5.53 g, 26.9 mmol, 5.00 equiv) in THF (50 mL). The reaction mixture was stirred at −78 °C for 1 h. A solution of TMSCl (1.34 mL, 10.8 mmol, 2.01 equiv) and unsaturated lactam **33** (2.50 g, 5.38 mmol, 1.00 equiv) in THF (80 mL) at −78 °C was added via cannula into the reaction mixture over 5 min. After stirring at −78 °C for 1 h, the reaction mixture was quenched by saturated aqueous NH_4Cl (10 mL). NH_3 (25 % in H_2O, 5 mL), H_2O (20 mL), and EtOAc (50 mL) were added. The organic layer was separated, washed with saturated aqueous NH_4Cl (3×10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/hexane 1:5) provided lactam **34** (2.05 g, 75 %) as a thick oil as a diastereomeric mixture in the ratio of 5:1 as determined by integration of δ 2.26 (dd, 1H, J_1=15.8, J_2=8.8 Hz) for the major diastereoisomer and δ 2.34 (dd, 1H, J_1=17.7, J_2=8.1 Hz) for the minor diastereoisomer in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62–7.66 (m, 4H), 7.37–7.46 (m, 6H), 5.53–5.67 (m, 1H), 4.97–5.01 (m, 2H), 3.78–3.87 (m, 2H), 3.62 (dd, 1H, J_1=10.4, J_2=4.6 Hz), 3.55 (dd, 1H, J_1=10.4, J_2=7.9 Hz), 2.52 (dd, 1H, J_1=15.8, J_2=6.0 Hz), 2.26 (dd, 1H, J_1=15.8, J_2=8.8 Hz), 2.06–2.16 (m, 1H), 1.93–1.99 (m, 1H), 1.78–1.85 (m, 1H), 1.67–1.74 (m, 1H), 1.53 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 151.8, 135.5, 134.7, 133.2, 129.8, 127.8, 117.8, 82.9, 64.0, 45.9, 41.0, 39.3, 39.1, 32.6, 28.0, 26.8, 19.2; FTIR (neat): $\tilde{\nu}$ = 1770 (s, C=O), 1759 (s, C=O), 1246 (m), 914 (m), 744 cm^{-1} (m); HRMS (MALDI): m/z: calcd for $C_{30}H_{41}NO_4SiNa$: 530.2697; found: 530.2709 $[M+Na]^+$.

(4*S,5*R**)-4-Allyl-5-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-3,4-dihydro-1(2*H*)-pyridinecarboxylic acid 1,1-dimethylethyl ester (36)**: DIBAL (1.00 M in hexane, 4.73 mL, 4.73 mmol, 2.99 equiv) was added at −78 °C to a solution of lactam **34** (800 mg, 1.58 mmol, 1.00 equiv) in THF (20 mL). The reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched by the addition of saturated aqueous Na/K tartrate (20 mL). The mixture was diluted with Et_2O (40 mL) and stirred over night. The organic layer was separated, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide the lactamol as an oil, which was diluted with CH_2Cl_2 (200 mL). Aqueous HCl (1 M in H_2O, 5 mL) was added and the reaction mixture was stirred for 5 min. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/hexane 1:20) provided enamine **36** (697 mg, 90 %) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.68 (m, 4H), 7.35–7.44 (m, 6H), 6.77 (dd, 1H, J_1=57.4, J_2=7.9 Hz), 5.61–5.80 (m, 1H), 4.95–5.0 (m, 2H), 4.66–4.80 (m, 1H), 3.48–3.73 (m, 4H), 1.90–2.21 (m, 3H), 1.78–1.90 (m, 1H), 1.49 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.1/152.3, 136.0/136.1, 135.6, 133.6, 133.5, 129.7, 127.7, 124.7/124.9, 116.6, 108.3/

108.1, 80.6, 64.1/63.8, 41.6/41.4, 39.4/39.0, 38.5, 32.9/32.6, 28.3, 26.9, 19.3; FTIR (neat): $\tilde{\nu}$ = 1770 (s, C=O), 1759 (s, C=O), 1706 (m, C=O), 1246 cm^{-1} (s); HRMS (MALDI): *m/z*: calcd for $C_{30}H_{41}NO_3SiNa$: 514.2748; found: 514.2763 $[M+Na]^+$. "First number/second number" in the ^{13}C NMR spectrum of **36** means that there are two small peaks belonging to one C, due to a slow equilibrium of rotamers during the measurement because of the Boc-protecting group on the lactam moiety.

1-Benzyl-6-methoxy-1*H*-indole-2,3-dione (41): NaH (1.34 g, 56.0 mmol, 1.99 equiv) was added at −78 °C to a solution of isatine **40** (5.00 g, 28.2 mmol, 1.00 equiv) in DMF (60 mL). After stirring for 5 min, BnBr (4.99 mL, 42.0 mmol, 1.49 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature over 30 min. At −20 °C the reaction mixture turned from orange to black, and gas formation could be observed. The reaction mixture was stirred for 30 min at room temperature and was then cooled to −78 °C. MeOH (15 mL) was added, followed by saturated aqueous $NaHCO_3$ (15 mL). After dilution with Et_2O (150 mL) and H_2O (100 mL), the combined organic solvents were filtered through a plug of silica gel. The filtrate was separated, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/hexane 1:3) provided isatine **41** (5.42 g, 72 %) as orange crystals. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, 1H, J = 8.5 Hz), 7.27–7.39 (m, 5H), 6.52 (dd, 1H, J_1 = 8.1, J_2 = 2.1 Hz), 6.26 (d, 1H, J = 2.1 Hz), 4.89 (s, 2H), 3.82 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.6, 168.2, 159.7, 153.2, 134.7, 129.0, 128.1, 128.0, 127.4, 111.4, 108.0, 98.3, 56.0, 44.0; FTIR (neat): $\tilde{\nu}$ = 1728 (m, C=O), 1612 (m), 1376 (m), 1221 (m), 772 cm^{-1} (s); HRMS (MALDI): *m/z*: calcd for $C_{16}H_{14}NO_3$: 268.0968, found 268.0967 $[M+H]^+$.

1-Benzyl-1,3-dihydro-6-methoxy-2*H*-indol-2-one (42): Isatine **41** (1 g, 3.74 mmol, 1.00 equiv) was dissolved in EtOH (15 mL) and $NH_2NH_2{\cdot}H_2O$ (15 mL). The reaction mixture was refluxed for 12 h. After dilution with brine (30 mL) and Et_2O (100 mL), the combined organic solvents were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (Et_2O/pentane 2:3) provided oxindole **42** (850 mg, 90 %) as yellow crystals. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.30 (m, 5H), 7.05 (ddd, 1H, J_1 = 8.1, J_2 = 1.1, J_3 = 0.8 Hz), 6.50 (dd, 1H, J_1 = 8.1, J_2 = 2.2 Hz), 6.32 (d, 1H, J = 2.2 Hz), 4.88 (s, 2H), 3.72 (s, 3H), 3.55 (d, 2H, J = 1.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9, 158.8, 144.5, 134.8, 127.7, 126.6, 126.3, 123.8, 115.3, 105.1, 96.3, 54.4, 42.8, 34.1; FTIR (neat): $\tilde{\nu}$ = 1714 (s, C=O), 1628 (s), 1503 (s), 1374 (s), 1196 (m), 1162 (m), 1030 (m), 699 (m); HRMS (MALDI): *m/z*: calcd for $C_{16}H_{16}NO_2$: 254.1176, found 254.1178 $[M+H]^+$.

1-Benzyl-1,3-dihydro-6-hydroxy-2*H*-indol-2-one (43): A solution of BBr_3 (0.160 M in CH_2Cl_2, 57.0 mL, 9.12 mmol, 1.92 equiv) was added at −78 °C to a solution of oxindole **42** (1.20 g, 4.74 mmol, 1.00 equiv) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at 0 °C for 5 h and then cooled to −78 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL). After dilution with EtOAc (50 mL), the combined organic solvents were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/hexane 1:2) provided alcohol **43** (1.05 g, 92 %) as slightly yellow crystals. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.30 (m, 5H), 7.05 (ddd, 1H, J_1 = 8.0, J_2 = 1.1, J_3 = 0.8 Hz), 6.45 (dd, 1H, J_1 = 8.0, J_2 = 2.2 Hz), 6.29 (d, 1H, J = 2.2 Hz), 4.86 (s, 2H), 3.53 (d, 2H, J = 1.1 Hz), 1.65 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.3, 156.0, 145.5, 135.7, 128.8, 127.7, 127.3, 125.0, 116.0, 108.8, 98.0, 43.9, 35.2; FTIR (neat): $\tilde{\nu}$ = 3254 (m), 1682 (s, C=O), 1604 (s), 1375 (m), 1220 (s), 773 cm^{-1} (s); HRMS (MALDI): *m/z*: calcd for $C_{15}H_{14}NO_2$: 240.1019, found: 240.1017 $[M+H]^+$.

1-Benzyl-1,3-dihydro-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2*H*-indol-2-one (44): Imidazole (570 mg, 8.37 mmol, 2.00 equiv) and TBDMSCl (941 mg, 6.27 mmol, 1.50 equiv) were added to a solution of alcohol **43** (1.00 g, 4.18 mmol, 1.00 equiv) in DMF (12 mL). The reaction mixture was stirred at room temperature for 3 h and then cooled to 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL). After dilution with Et_2O (50 mL) and H_2O (30 mL), the combined organic solvents were washed with saturated aqueous $NaHCO_3$ (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/hexane 1:4) provided silyl ether **44** (1.30 g, 88 %) as a thick oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.19–7.30 (m, 5H), 7.02 (ddd, 1H, J_1 = 8.0, J_2 = 1.0, J_3 = 0.9 Hz), 6.43 (dd, 1H, J_1 = 8.0, J_2 = 2.2 Hz), 6.19 (d, 1H, J = 2.2 Hz), 4.84 (s, 2H), 3.50 (d, 2H, J = 1.0 Hz), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8, 155.6, 145.1, 135.8, 128.7, 127.5, 127.3, 124.7, 116.7, 113.4, 102.5, 43.7, 35.2, 25.6, 18.1, −4.6; FTIR (neat): $\tilde{\nu}$ = 2930 (m), 2858 (m), 1717 (s, C=O), 1622 (s), 1499 (s), 1373 (s), 1266 (m), 1190 (m), 1163 (m), 955 (m), 839 cm^{-1} (m); HRMS (MALDI): *m/z*: calcd for $C_{21}H_{28}NO_2Si$: 354.1884; found 354.1881 $[M+H]^+$.

1-Benzyl-6-hydroxy-3,3-spirocyclopropyl-1,3-dihydroindol-2-one (45): Dibromoethane (367 μL, 4.26 mmol, 1.51 equiv) was added to a solution of oxindole **44** (1.00 g, 2.83 mmol, 1.00 equiv) in DMF (8 mL). The reaction mixture was cooled to 0 °C. NaH (205 mg, 8.52 mmol, 3.01 equiv) was added portionwise. After stirring for 1 h at 0 °C, the reaction mixture was cooled to −78 °C. MeOH (10 mL) was added to the reaction mixture at −78 °C. After warming to 0 °C, the mixture was diluted with H_2O (15 mL) and Et_2O (50 mL). The combined organic solvents were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/hexane 1:2) provided spiroindole **45** (650 mg, 86 %) as white crystals. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.20–7.30 (m, 5H), 6.65 (d, 1H, J = 8.0 Hz), 6.46 (dd, 1H, J_1 = 8.0, J_2 = 2.2 Hz), 6.29 (d, 1H, J = 2.2 Hz), 5.86 (br s, 1H), 4.92 (s, 2H), 1.73 (dd, 2H, J_1 = 7.9, J_2 = 4.1 Hz), 1.47 (dd, 2H, J_1 = 7.9, J_2 = 4.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.3, 155.5, 143.7, 136.0, 128.8, 127.6, 127.3, 122.3, 119.0, 108.6, 98.1, 44.2, 26.7, 19.0; FTIR (neat): $\tilde{\nu}$ = 3180 (m), 1672 (s, C=O), 1629 (s), 1605 (s), 1479 (m), 1390 (s), 1166 (s), 772 cm^{-1} (s); HRMS (MALDI): *m/z*: calcd for $C_{17}H_{16}NO_2$: 266.1176; found: 266.1175 $[M+H]^+$.

1-Benzyl-6-(phenylmethoxy)-3,3-spirocyclopropyl-3,3-spirocyclopropyl-1,3-dihydroindol-2-one (46): NaH (149 mg, 6.23 mmol, 1.50 equiv) was added in portions at −45 °C to a solution of alcohol **45** (1.10 g, 4.15 mmol, 1.00 equiv) in DMF (7 mL). Benzylbromide (739 μL, 6.23 mmol, 1.50 equiv) was added to the reaction mixture at −45 °C. The reaction mixture was allowed to warm to 0 °C within 30 min and was stirred for 1 h at 0 °C. The reaction was quenched at −45 °C with aqueous saturated $NaHCO_3$ (15 mL).The combined organic solvents were separated, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/hexane 1:3) provided benzyl ether **46** (1.28 g, 87 %) as white crystals. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.37 (m, 10H), 6.72 (d, 1H, J = 8.2 Hz), 6.57 (dd, 1H, J_1 = 8.2, J_2 = 2.2 Hz), 6.48 (d, 1H, J = 2.2 Hz), 4.97 (s, 2H), 4.93 (s, 2H), 1.74 (dd, 2H, J_1 = 7.7, J_2 = 3.9 Hz), 1.47 (dd, 2H, J_1 = 7.7, J_2 = 3.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8, 158.4, 143.8, 136.8, 136.1, 128.7, 128.6, 128.0, 127.5, 127.4, 127.3, 123.0, 118.8, 107.2, 98.2, 70.4, 44.1, 26.6, 18.9; FTIR (neat): $\tilde{\nu}$ = 1710 (s, C=O), 1630 (m), 1501 (m), 1387 (m), 1165 (s), 913 (s), 743 cm^{-1} (s); HRMS (MALDI): *m/z*: calcd for $C_{24}H_{22}NO_2$: 356.1645; found: 356.1648 $[M+H]^+$.

(1′*R,6′*R**,7′*R**,8′a*S**)-7′-Allyl-1-benzyl-6′-(*tert*-butyldiphenylsilyloxymethyl)-2′,3′,6′,7′,8′,8′a-hexahydro-6-phenylmethoxy-spiro[3*H*-indole-3,1′-(5′*H*)-indolizin]-2(1*H*)-one (47)**: NEt_3 (2.00 mL, 14.3 mmol, 10.1 equiv) was added to a solution of enamine **37** (700 mg, 1.42 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL). The reaction mixture was cooled to −78 °C. TMSOTf (1.85 mL, 10.2 mmol, 7.18 equiv) was added slowly. The reaction mixture was allowed to warm to −20 °C and was stirred for 2 h at −20 °C. After cooling to −78 °C, the reaction was quenched by saturated aqueous $NaHCO_3$ (15 mL). After warming to room temperature, the organic layer was separated, washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the cyclic aldimine as a residue. MgI_2 (397 mg, 1.43 mmol, 1.01 equiv) and spiroindole **46** (508 mg, 1.43 mmol, 1.01 equiv) were charged into a sealable tube. The aldimine was dissolved in THF (4 mL) and added into the sealable tube, which was sealed and put into the preheated oil bath at 80 °C. The reaction mixture was refluxed for 16 h at 80 °C. The reaction mixture was allowed to cool to room temperature and was diluted with Et_2O (30 mL) and H_2O (10 mL).

The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/hexane 1:5) provided spiroindole **47** (588 mg, 55%) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.67 (m, 4H), 7.20–7.45 (m, 17H), 6.61 (dd, 1H, J_1=8.2, J_2=2.3 Hz), 6.35 (d, 1H, J=2.3 Hz), 5.47–5.55 (m, 1H), 5.03 (d, 1H, J=15.8 Hz), 4.96 (s, 2H), 4.85 (d, 1H, J=10.1 Hz), 4.76 (d, 1H, J=17.1 Hz), 4.71 (d, 1H, J=15.8 Hz), 3.71 (dd, 1H, J_1=10.3, J_2=3.1 Hz), 3.55 (dd, 1H, J_1=10.3, J_2=6.5 Hz), 3.36 (dd, 1H, J_1=10.8, J_2=3.8 Hz), 3.32 (ddd, 1H, J_1=8.6, J_2=8.6, J_3=2.4 Hz), 2.52 (ddd, 1H, J_1=8.8, J_2=8.6, J_3=8.4 Hz), 2.46 (dd, 1H, J_1=11.2, J_2=2.4 Hz), 2.39–2.44 (m, 1H), 2.07–2.14 (m, 2H), 1.98–2.05 (m, 1H), 1.57–1.63 (m, 1H), 1.46–1.52 (m, 1H), 1.34–1.42 (m, 1H), 1.22–1.30 (m, 1H), 1.06 (s, 9H), 0.64 (ddd, 1H, J_1=11.8, J_2=11.8, J_3=11.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.2, 158.8, 143.3, 136.8, 136.3, 136.0, 135.6, 133.7, 129.6, 128.7, 128.6, 128.1, 127.6, 127.5, 127.0, 125.8, 125.3, 116.1, 107.1, 97.6, 72.0, 70.3, 64.2, 56.7, 56.1, 53.9, 43.8, 42.7, 37.0, 36.2, 35.4, 31.1, 26.9, 19.3; FTIR (neat): $\tilde{\nu}$ = 1770 (s, C=O), 1753 (s, C=O), 1712 (w, C=O), 1246 (s), 913 (m), 743 cm^{-1} (m); HRMS (MALDI): m/z: calcd for $C_{49}H_{55}N_2O_3Si$: 747.3982; found: 747.3977 $[M+H]^+$.

(1′*R,6′*R**,7′*R**,8′a*S**)-1-Benzyl-6′-(*tert*-butyldiphenylsilyloxymethyl)-2′,3′,6′,7′,8′,8′a-hexahydro-6-phenylmethoxy-7′-(2-oxoethyl)-spiro[3*H*-indole-3,1′(5′*H*)-indolizin]-2-(1*H*)-one (48)**: NMO (94.1 mg, 803 μmol, 2.97 equiv) in H_2O (1 mL) was added to a solution of olefin **47** (200 mg, 268 μmol, 1.00 equiv) in *t*BuOH (8 mL), H_2O (9 mL), and dioxane (20 mL). OsO_4 (3% in H_2O, 227 μL, 26.9 μmol, 10.0 mol%) was added dropwise to the homogeneous reaction mixture. After stirring at room temperature for 4 h, the reaction mixture was diluted with H_2O and Et_2O. The organic layer was separated, washed with brine and saturated aqueous $NaHSO_3$ (4×10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the diol as a thick oil. $NaIO_4$ (300 mg, 1.403 mmol, 5.24 equiv) in H_2O (1 mL) was added dropwise to the diol in a mixture of dioxane (10 mL), water (5 mL), and *t*BuOH. The reaction mixture was stirred for 2 h at room temperature and was then diluted with EtOAc (100 mL) and H_2O (20 mL). The organic layer was separated and washed with saturated aqueous NH_4Cl (3×10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give aldehyde **48** (172 mg, 86%) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.46 (dd, 1H, J_1=2.7, J_2=1.1 Hz), 7.58–7.61 (m, 4H), 7.16–7.42 (m, 17H), 6.55 (dd, 1H, J_1=8.2, J_2=2.3 Hz), 6.32 (d, 1H, J=2.3 Hz), 4.92 (d, 1H, J=15.7 Hz), 4.91 (s, 2H), 4.71 (d, 1H, J=15.7 Hz), 3.59 (dd, 1H, J_1=10.6, J_2=3.5 Hz), 3.51 (dd, 1H, J_1=10.6, J_2=5.6 Hz), 3.22–3.26 (m, 2H), 2.46–2.53 (m, 2H), 2.29–2.42 (m, 2H), 2.10 (dd, 1H, J_1=11.0, J_2=10.9 Hz), 1.94–2.01 (m, 1H), 1.84–1.91 (m, 2H), 1.41–1.52 (m, 1H), 1.16–1.26 (m, 1H), 1.03 (s, 9H), 0.68 (ddd, 1H, J_1=11.7, J_2=11.7, J_3=11.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.9, 180.0, 158.9, 143.4, 136.8, 135.9, 135.6, 133.4, 133.3, 129.8, 128.8, 128.6, 128.1, 127.8, 127.7, 127.6, 127.1, 125.4, 125.2, 107.3, 97.7, 71.5, 70.3, 64.2, 56.4, 55.9, 53.9, 47.4, 43.8, 42.8, 35.3, 32.3, 31.7, 26.9, 19.3; FTIR (neat): $\tilde{\nu}$ = 1716 (s, C=O), 1625 (m, C=O), 1499 (m), 1382 (m), 1164 (m), 1112 (m), 913 (m), 745 (s), 701 cm^{-1} (s); HRMS (MALDI): m/z: calcd for $C_{48}H_{53}N_2O_4Si$: 749.3775; found: 749.3773 $[M+H]^+$.

(1′*R,6′*R**,7′*R**,8′a*S**)-1-Benzyl-6′-(*tert*-butyldiphenylsilyloxymethyl)-7′-(2,2-dimethoxyethyl)-2′,3′,6′,7′,8′,8′a-hexahydro-6-phenylmethoxy-spiro[3*H*-indole-3,1′(5′*H*)-indolizin]-2(1*H*)-one (49)**: *p*-TsOH (204 mg, 1.07 mmol, 4.65 equiv) was added to a solution of aldehyde **48** (172 mg, 230 μmol, 1.00 equiv) in MeOH (20 mL) and $CH(OMe)_3$ (20 mL). The reaction mixture was stirred at room temperature for 12 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. After dilution with EtOAc (100 mL) and H_2O (30 mL), the combined organic solvents were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **49** (170 mg, 93%) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64–7.67 (m, 4H), 7.23–7.45 (m, 17H), 6.61 (dd, 1H, J_1=8.2, J_2=2.3 Hz), 6.37 (d, 1H, J=2.3 Hz), 5.01 (d, 1H, J=15.7 Hz), 4.97 (s, 2H), 4.72 (d, 1H, J=15.7 Hz), 4.18 (dd, 1H, J_1=7.7, J_2=4.0 Hz), 3.69 (dd, 1H, J_1=10.4, J_2=3.1 Hz), 3.54 (dd, 1H, J_1=10.4, J_2=6.5 Hz), 3.30–3.35 (m, 2H), 3.13 (s, 3H), 3.10 (s, 3H), 2.39–2.52 (m, 3H), 1.99–2.07 (m, 2H), 1.75–1.80 (m, 1H), 1.35–1.49 (m, 2H), 1.26–1.31 (m, 1H), 1.06 (s, 9H), 0.99–1.05 (m, 1H), 0.66 (ddd, 1H, J_1=12.0, J_2=11.8, J_3=11.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.2, 158.8, 143.3, 136.8, 136.1, 135.7, 135.6, 133.6, 129.6, 128.8, 128.6, 128.1, 127.6, 127.5, 127.2, 125.7, 125.3, 107.1, 102.1, 97.6, 71.7, 70.3, 64.4, 56.8, 56.0, 54.0, 52.6, 51.6, 43.8, 43.4, 35.5, 35.4, 32.7, 31.7, 26.9, 19.3; FTIR (neat): $\tilde{\nu}$ = 1738 (s, C=O), 1723 (s, C=O), 1366 (m), 1217 (m), 913 (m), 744 cm^{-1} (m); HRMS (MALDI): m/z: calcd for $C_{50}H_{59}N_2O_5Si$: 795.4188; found: 795.4159 $[M+H]^+$.

(1′*R,6′*R**,7′*R**,8′a*S**)-1-Benzyl-7′-(2,2-dimethoxyethyl)-2′,3′,6′,7′,8′,8′a-hexahydro-6′-hydroxymethyl-6-phenylmethoxy-spiro[3*H*-indole-3,1′(5′*H*)-indolizin]-2(1*H*)-one (50)**: TBAF (1.00 M in THF, 0.57 mL, 570 μmol, 3.02 equiv) was added at 0°C to a solution of silyl ether **49** (150 mg, 189 μmol, 1.00 equiv) in THF (5 mL). The reaction mixture was stirred for 5 h and was then transferred onto a column with silica gel (diameter 3.5 cm, length 15 cm). Elution with EtOAc/hexane 1:4 followed by CH_2Cl_2/MeOH 15:1 afforded alcohol **50** (90 mg, 86%) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.40 (m, 11H), 6.60 (dd, 1H, J_1=8.2, J_2=2.3 Hz), 6.39 (d, 1H, J=2.3 Hz), 4.98 (d, 1H, J=15.6 Hz), 4.97 (s, 2H), 4.75 (d, 1H, J=15.6 Hz), 4.24 (dd, 1H, J_1=7.7, J_2=3.7 Hz), 3.63–3.65 (m, 2H), 3.24–3.32 (m, 2H), 3.25 (s, 3H), 3.23 (s, 3H), 2.38–2.55 (m, 3H), 1.97–2.12 (m, 3H), 1.85 (ddd, 1H, J_1=14.2, J_2=7.7, J_3=2.7 Hz), 1.33–1.49 (m, 1H), 1.24–1.32 (m, 1H), 1.15–1.24 (m, 1H), 0.74 (ddd, 1H, J_1=11.5, J_2=11.5, J_3=11.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.1, 158.9, 143.4, 136.8, 136.1, 128.8, 128.6, 128.1, 127.6, 127.2, 125.6, 125.3, 107.2, 103.0, 97.6, 71.6, 70.3, 63.3, 56.4, 55.9, 53.8, 52.9, 52.8, 43.9, 43.3, 35.7, 35.4, 32.6, 32.3; FTIR (neat): $\tilde{\nu}$ = 1770 (s, C=O), 1759 (s, C=O), 1246 cm^{-1} (s); HRMS (MALDI): m/z: calcd for $C_{34}H_{41}N_2O_5$: 557.3021; found: 557.3025 $[M+H]^+$.

(1′*R,6′*R**,7′*R**,8′a*S**)-1-Benzyl-7′-(2,2-dimethoxyethyl)-6′-formyl-2′,3′,6′,7′,8′,8′a-hexahydro-6-phenylmethoxy-spiro[3*H*-indole-3,1′(5′*H*)-indolizin]-2(1*H*)-one (51)**: IBX (655 mg, 2.34 mmol, 10.0 equiv) was added to a solution of alcohol **50** (130 mg, 234 μmol, 1.00 equiv) in DMSO (9 mL). The reaction mixture was stirred at room temperature for 12 h. After dilution with Et_2O (100 mL) and H_2O (15 mL), the combined organic solvents were washed with saturated aqueous Na_2CO_3 (4×10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give aldehyde **51** (114 mg, 88%) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.63 (d, 1H, J=3.2 Hz), 7.22–7.40 (m, 11H), 6.61 (dd, 1H, J_1=8.2, J_2=2.3 Hz), 6.39 (d, 1H, J=2.3 Hz), 4.99 (d, 1H, J=15.6 Hz), 4.98 (s, 2H), 4.74 (d, 1H, J=15.6 Hz), 4.24 (dd, 1H, J_1=7.4, J_2=4.2 Hz), 3.48–3.50 (m, 1H), 3.26–3.37 (m, 2H), 3.20 (s, 3H), 3.19 (s, 3H), 2.50–2.63 (m, 2H), 2.40–2.46 (m, 1H), 2.28–2.39 (m, 1H), 2.13 (dd, 1H, J_1=11.1, J_2=11.2 Hz), 1.97–2.07 (m, 1H), 1.79–1.88 (m, 1H), 1.69–1.79 (m, 1H), 1.33–1.37 (m, 1H), 0.70 (ddd, 1H, J_1=11.8, J_2=11.7, J_3=11.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.2, 179.7, 159.0, 143.4, 136.7, 136.0, 128.8, 128.6, 128.1, 127.7, 127.6, 127.2, 125.3, 125.2, 107.3, 101.6, 97.8, 70.8, 70.3, 55.9, 54.3, 53.6, 52.8, 52.2, 51.8, 43.9, 36.5, 35.2, 31.7, 31.2; FTIR (neat): $\tilde{\nu}$ = 1712 (m, C=O), 1625 (m, C=O), 1499 (m), 1381 (m), 1220 (m), 772 cm^{-1} (s); HRMS (MALDI): m/z: calcd for $C_{34}H_{39}N_2O_5$: 555.2854; found: 555.2859 $[M+H]^+$.

(1′*R,6′*R**,7′*R**,8′a*S**)-1-Benzyl-7′-(2,2-dimethoxyethyl)-6′-ethenyl-2′,3′,6′,7′,8′,8′a-hexahydro-6-phenylmethoxy-spiro[3*H*-indole-3,1′(5′*H*)-indolizin]-2(1*H*)-one (52)**: *t*BuOK (97.0 mg, 866 μmol, 3.99 equiv) was added at 0°C to a suspension of Ph_3PMeBr (387 mg, 1.08 mmol, 4.98 equiv) in THF (3 mL). The ice bath was removed and the yellow reaction mixture was stirred at room temperature for 2 h. Aldehyde **51** (120 mg, 217 μmol, 1.00 equiv) in THF (4 mL) and added dropwise. The reaction mixture was stirred at room temperature for 6 h and then cooled to −78°C. The reaction was quenched by the addition of acetone (10 mL). The mixture was warmed to room temperature and stirred for 20 min. After dilution with Et_2O (100 mL) and H_2O (15 mL), the combined organic solvents were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/pentane 2:5) provided olefin **52** (105 mg, 87%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.40 (m, 11H), 6.61 (dd, 1H, J_1=8.2, J_2=2.3 Hz), 6.38 (d, 1H, J=2.3 Hz), 5.51–5.58 (m, 1H), 5.05–5.10 (m, 2H), 5.01 (d, 1H, J=15.6 Hz), 4.97 (s, 2H), 4.73 (d, 1H, J=15.6 Hz), 4.24 (dd, 1H, J_1=8.0,

J_2=4.0 Hz), 3.28 (ddd, 1H, J_1=8.6, J_2=8.5, J_3=2.3 Hz), 3.19 (s, 3H), 3.16 (s, 3H), 3.10 (dd, 1H, J_1=10.7, J_2=3.8 Hz), 2.47–2.52 (m, 2H), 2.38–2.43 (m, 1H), 1.99 (dd, 1H, J_1=10.7, J_2=10.7 Hz), 1.98–2.03 (m, 1H), 1.83–1.95 (m, 2H), 1.22–1.33 (m, 2H), 0.99–1.05 (m, 1H), 0.65 (ddd, 1H, J_1=11.9, J_2=11.5, J_3=11.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.1, 158.9, 143.4, 139.8, 136.8, 136.1, 128.8, 128.6, 128.1, 127.6, 127.2, 125.7, 125.3, 116.9, 107.2, 102.1, 97.7, 71.6, 70.4, 58.8, 56.0, 53.8, 52.8, 51.4, 47.2, 43.9, 36.0, 35.6, 35.3, 31.6; FTIR (neat): $\tilde{\nu}$ = 1770 (s, C=O), 1753 (s, C=O), 1382 (m), 1246 (s), 1056 (m), 913 (m), 744 cm^{-1} (m); HRMS (MALDI): *m/z*: calcd for $C_{35}H_{41}N_2O_4$: 553.3061; found: 553.3064 $[M+H]^+$.

(1′*R,6′*R**,7′*R**,8′a*S**)-1-Benzyl-6′-ethenyl-2′,3′,6′,7′,8′,8′a-hexahydro-7′-(2-oxoethyl)-6-phenylmethoxy-spiro[3*H*-indole-3,1′(5′*H*)-indolizin]-2(1*H*)-one (53)**: Aqueous HCl (10% in H_2O, 15 mL) was added to **52** (100 mg, 181 μmol, 1.00 equiv) in acetone (100 mL). The reaction mixture was stirred at room temperature for 12 h and was then diluted with Et_2O (100 mL) and H_2O (20 mL). The combined organic solvents were washed with saturated aqueous $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was diluted with H_2O (10 mL) and Et_2O (50 mL). The combined organic solvents were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford aldehyde **53** (86 mg, 94%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.59 (dd, 1H, J_1=2.6, J_2=1.1 Hz), 7.20–7.39 (m, 11H), 6.59 (dd, 1H, J_1=8.3, J_2=2.3 Hz), 6.36 (d, 1H, J=2.3 Hz), 5.48–5.57 (m, 1H), 5.08–5.13 (m, 2H), 4.96 (s, 2H), 4.96 (d, 1H, J=15.6 Hz), 4.75 (d, 1H, J=15.6 Hz), 3.29 (ddd, 1H, J_1=8.6, J_2=8.5, J_3=2.3 Hz), 3.14 (dd, 1H, J_1=10.4, J_2=3.3 Hz), 2.50–2.58 (m, 3H), 2.33–2.45 (m, 1H), 1.95–2.08 (m, 4H), 1.75–1.84 (m, 1H), 1.26–1.31 (m, 1H), 0.72 (ddd, 1H, J_1=11.6, J_2=11.6, J_3=11.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.0, 179.9, 159.0, 143.4, 139.1, 136.8, 135.9, 128.8, 128.6, 128.1, 127.6, 127.1, 125.4, 125.2, 117.7, 107.3, 97.7, 71.4, 70.4, 58.4, 55.9, 53.7, 48.1, 46.8, 43.9, 35.2, 34.7, 32.1; FTIR (neat): $\tilde{\nu}$ = 1715 (m, C=O), 1625 (m, C=O), 1276 (s), 1261 (s), 913 (s), 749 cm^{-1} (s); HRMS (MALDI): *m/z*: calcd for $C_{33}H_{35}N_2O_3$: 507.2642; found: 507.2637 $[M+H]^+$.

(1′*R,6′*R**,7′*R**,8′a*S**)-1-Benzyl-6′-ethenyl-2′,3′,6′,7′,8′,8′a-hexahydro-6-phenylmethoxy-7′-[[(1*S*)-2,3,4,9-tetrahydro-2-methyl-1*H*-pyrido[3,4-b]indol-1-yl]methyl]-spiro-[3*H*-indole-3,1′(5′*H*)-indolizin]-2(1*H*)-one (54)**: AcOH (3 mL) was added to a solution of aldehyde **53** (90 mg, 177 μmol, 1.00 equiv) and *N*-methyl tryptamine (80 mg, 460 μmol, 2.6 equiv) in toluene (30 mL). The reaction mixture was heated to 80°C for 2 h and was then diluted with Et_2O (50 mL) and H_2O (10 mL). The organic layer was separated and washed with saturated aqueous Na_2CO_3 (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatotron (isopropanol/hexane 1:4) provided **55** (44 mg, 38%) and **54** (30 mg, 26%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65–7.70 (m, 2H), 7.53–7.57 (m, 1H), 7.32–7.48 (m, 8H), 7.09–7.26 (m, 4H), 6.56 (dd, 1H, J_1=8.2, J_2=2.3 Hz), 6.16 (s, 1H), 5.56–5.63 (m, 1H), 5.13 (dd, 1H, J_1=16.9, J_2=1.9 Hz), 5.08 (dd, 1H, J_1=10.2, J_2=1.9 Hz), 4.95 (s, 2H), 4.74 (d, 1H, J=15.6 Hz), 4.36 (d, 1H, J=15.6 Hz), 3.35–3.41 (m, 1H), 3.25–3.29 (m, 1H), 3.03–3.11 (m, 2H), 2.68–2.76 (m, 2H), 2.61–2.65 (m, 1H), 2.44–2.50 (m, 2H), 2.36–2.41 (m, 1H), 2.33 (s, 3H), 1.96–2.05 (m, 4H), 1.45–1.54 (m, 1H), 1.25–1.35 (m, 1H), 1.05 (d, 1H, J=11.8 Hz), 0.50 (ddd, 1H, J_1=11.5, J_2=11.5, J_3=11.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.9, 158.7, 143.1, 140.5, 136.9, 136.2, 135.7, 135.3, 133.0, 132.2, 132.1, 131.9, 128.7, 128.6, 128.5, 128.1, 127.6, 127.5, 127.2, 124.9, 121.3, 119.2, 117.9, 116.8, 110.9, 107.0, 97.6, 71.9, 70.2, 58.8, 58.0, 56.0, 53.7, 49.0, 48.1, 43.5, 41.8, 37.7, 36.2, 34.5, 31.8, 18.6; FTIR (neat): $\tilde{\nu}$ = 2927 (m), 1711 (s, C=O), 1624 (s), 1500 (s), 1454 (s), 1381 (s), 1167 (s), 737 (m), 698 cm^{-1} (m); HRMS (MALDI): *m/z*: calcd for $C_{44}H_{47}N_4O_2$: 663.3694; found: 663.3699 $[M+H]^+$.

(1′*R,6′*R**,7′*R**,8′a*R**)-1-Benzyl-6′-ethenyl-2′,3′,6′,7′,8′,8′a-hexahydro-6-phenylmethoxy-7′-[[(1*S*)-2,3,4,9-tetrahydro-2-methyl-1*H*-pyrido[3,4-b]indol-1-yl]methyl]-spiro-[3*H*-indole-3,1′(5′*H*)-indolizin]-2(1*H*)-one (55)**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65–7.69 (m, 2H), 7.53–7.56 (m, 1H), 7.33- 7.48 (m, 8H), 7.04–7.27 (m, 4H), 6.66 (dd, 1H, J_1=8.2, J_2=2.3 Hz), 6.44 (d, 1H, J=2.3 Hz), 5.50–5.56 (m, 1H), 5.12 (d, 1H, J=15.6 Hz), 4.97–5.05 (m, 2H), 5.00 (s, 2H), 4.61 (d, 1H, J=15.6 Hz), 3.29–3.35 (m, 2H), 3.02–3.12 (m, 2H), 2.77–2.82 (m, 2H), 2.60 (d, 1H, J=9.4 Hz), 2.50–2.55 (m, 2H), 2.41–2.47 (m, 1H), 2.33 (s, 3H), 1.91–2.06 (m, 4H), 1.54–1.59 (m, 1H), 1.42–1.47 (m, 1H), 1.04–1.09 (m, 1H), 0.67 (ddd, 1H, J_1=11.3, J_2=11.7, J_3=11.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.0, 158.9, 143.5, 140.0, 136.7, 136.2, 135.6, 132.2, 132.1, 132.0, 131.9, 128.7, 128.7, 128.6, 128.5, 128.4, 128.2, 127.7, 127.3, 127.2, 125.5, 121.3, 119.2, 118.0, 116.8, 110.6, 107.1, 97.6, 71.5, 70.4, 58.7, 56.1, 56.0, 53.7, 47.3, 46.0, 43.9, 41.2, 38.4, 36.0, 35.3, 31.5, 16.8; FTIR (neat): $\tilde{\nu}$ = 3405 (w), 2925 (s), 1714 (s, C=O), 1622 (s), 1497(s), 1455 (s), 1380 (s), 1167 (s), 734 (s), 697 cm^{-1} (s); HRMS (MALDI): *m/z*: calcd for $C_{44}H_{47}N_4O_2$: 663.3694; found: 663.3688 $[M+H]^+$.

(+/-)-Strychnofoline (1): Compound **54** (10 mg, 15 μmol, 1.00 equiv) in THF (0.4 mL) was added at −78°C to a solution of Na (40 mg, 1.74 mmol, 11.6 equiv) in a mixture of NH_3 (3 mL), *t*BuOH (0.3 mL) and THF (0.3 mL). The reaction mixture was stirred for 5 min at −78°C and was warmed then to −45°C. After stirring at −45°C for 10 min, the reaction mixture was cooled to −78°C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The mixture was allowed to slowly warm to room temperature, and was then diluted with H_2O (20 mL) and CH_2Cl_2 (100 mL). The combined organic solvents were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel [MeOH/CH_2Cl_2/NH_3 (25% in H_2O) 30:169:1] provided strychnofoline **1** (6 mg, 82%) as an oil. ^{1}H NMR (500 MHz, [D_6]-acetone): δ = 9.60 (s, 1H), 8.90 (s, 1H), 8.17 (br s, 1H), 7.34 (ddd, 1H, J_1=8.0, J_2=0.8, J_3=0.5 Hz), 7.16 (ddd, 1H, J_1=8.0, J_2=1.0, J_3=0.5 Hz), 7.07 (d, 1H, J=7.9 Hz), 7.00 (ddd, 1H, J_1=8.0, J_2=7.2, J_3=1.0 Hz), 6.93 (ddd, 1H, J_1=8.0, J_2=7.2, J_3=0.8 Hz), 6.40 (dd, 1H, J_1=7.9, J_2=2.3 Hz), 6.28 (d, 1H, J=2.3 Hz), 5.63–5.71 (m, 1H), 5.12 (ddd, 1H, J_1=17.2, J_2=2.1, J_3=0.6 Hz), 5.03 (dd, 1H, J_1=10.3, J_2=2.1 Hz), 3.51–3.54 (m, 1H), 3.20–3.26 (m, 1H), 3.00–3.06 (m, 2H), 2.67–2.78 (m, 2H), 2.49–2.54 (m, 1H), 2.32 (s, 3H), 2.19–2.34 (m, 3H), 2.00–2.08 (m, 1H), 1.82–2.00 (m, 3H), 1.58–1.64 (m, 1H), 1.41–1.51 (m, 1H), 1.20–1.23 (m, 1H), 0.69 (ddd, 1H, J_1=11.9, J_2=11.9, J_3=11.9 Hz); ^{13}C NMR (125 MHz, [D_6]-acetone): δ = 181.4, 158.0, 143.3, 142.0, 137.2, 136.7, 128.1, 126.0, 125.4, 121.4, 119.3, 118.2, 116.6, 111.7, 108.7, 107.1, 98.4, 72.5, 59.9, 58.8, 56.9, 54.4, 48.7, 48.6, 41.9, 38.6, 37.5, 35.7, 32.5, 18.8; FTIR (neat): $\tilde{\nu}$ 1738 (s, C=O), 1366 (m), 1229 (m), 1217 cm^{-1} (m); HRMS (MALDI): $\tilde{\nu}$ = calcd for $C_{30}H_{35}N_4O_2$: 483.2755; found: 483.2758 $[M+H]^+$.

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