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Electrophilic Carbonyl Activation: Competing Condensative Cyclizations of Tryptamine Derivatives

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Abstract

A series of tryptamine derived bisindole substrates were subject to electrophilic activation of the functional grouping at their alpha-nitrogen in the form of iminium ions to enable cyclization onto the sterically hindered indole substructure. Our observations regarding divergent cyclization outcomes using electronically distinct bisindole substrates are described. Surprising preference for Friedel-Crafts alkylation reaction and evidence for an intriguing reversible spirocyclization are discussed.

Keywords

tryptamine; indole; cyclization; iminium ion; Friedel-Crafts

1. Introduction

Indole alkaloids comprise a family of natural products with a wide range of chemical structures and biological activities.[1] As one of the largest classes of natural products, they are prevalent in Nature and are synthesized by both marine and terrestrial organisms.[2] Many simple indole-containing natural products and synthetic analogs are actively prescribed pharmaceutical agents, exemplified by the serotonin receptor agonist sumatriptan for the treatment of migraine.[3] In addition, terpeneindole alkaloids have been widely exploited in medicine for their anti-cancer, anti-malarial, and anti-arrhythmic properties.[4] More recently, studies have shown possible applications of marine indole alkaloids in the treatment of neurological disorders.[5] Many bisindoles, a subset of indole alkaloids, are generated biosynthetically by the fusion of two molecules of tryptamine. Representative family members include terrequinone A[6] and the DNA-topoisomerase I inhibitor rebeccamycin,[7] which possess fascinating molecular architectures and a spectrum of biological activities that have attracted considerable attention from the scientific community.[8] Our group has continued to pursue programs focused on the syntheses and study of bisindole alkaloids.[9, 10] In our unified strategy to the trigonoliimine natural products (**1–3**), a selective oxidation/stereo controlled cyclization of a bistryptamine heterodimer provided access to all known trigonoliimines.[9] In addition, our program in electrophilic amide activation[11] has provided an entry into the *Aspidosperma* alkaloids.[10] These studies have focused on the oxidation and cyclization of a variety of tryptamine substrates that occur primarily at the C2 and C3

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positions. The combination of our prior strategies for rapid synthesis of 2-(2'-indolyl)-tryptamines,[9] 2-(7'-indolyl)-tryptamines,[12] and our interest in spirocyclization of tryptamines[13] provided a unique opportunity to examine the competing cyclization manifolds available to 2-(4'-indolyl)-tryptamine such as **5** (Scheme 1). Herein we present our studies on the cyclization reactions of bisindoles and detail our results in securing a challenging spirocyclization using a carbamoyl chloride substrate.

As an outgrowth of our studies on the chemistry of cyclotryptamines and indole alkaloids, we chose to undertake an investigation on the possible cyclization modes of 2-(4'-indolyl)-indole nucleophiles in the presence of activated, tethered carbonyl electrophiles (Scheme 1). Due to entropic factors a spirocyclization may be expected to be a favored reaction manifold in these systems (pathway A). The lack of transannular strain in an alternative macrocyclic product could instead lead to attack at the C3' position and macrocyclization (pathway B). In addition, although less nucleophilic than C3, the C4 position could undergo Friedel-Crafts cyclization to provide a seven-membered ring (pathway C).

We chose to investigate the possible cyclization modes of bisindoles outlined above in the context of a demanding cascade reaction: a Pictet-Spengler cyclization of an iminium ion derivative of bisindole **22** followed by reorganization and phenolic trapping would allow for a late-stage cyclization sequence that enables rapid building of molecular complexity.[14] On the other hand, the presence of a second electron-rich indole ring could lead to surprising cyclization pathways (pathway B or C, Scheme 1) over sterically congested, albeit entropically favored Pictet-Spengler cyclization. To evaluate this strategy we envisioned rapid access to the key intermediate **22** via cross-coupling of indoles **10** and **11** (Scheme 2).

2. Cyclization of Bisindole 22

As a continuation of our prior studies on the oxidation, rearrangement[9,12] and cyclization[13] of 2-aryltryptamines, we were intrigued by the possibility of accessing potentially three unique modes of cyclization of 2-heteroaryltryptamine substrates in the presence of activated carbonyl electrophiles (Scheme 1). In our first attempt at evaluating the planned cyclization chemistry, we targeted 4-bromo-5,7-dimethoxyindole **14** and the tryptamine boronic ester **18** as the two coupling partners in the C–C bond-forming cross-coupling reaction (Scheme 3–4). Boronic ester **18** is easily accessed from tryptamine,[9a,12,15] and the indolyl coupling partner can be prepared from the known compound **12** (Scheme 3).[16] While methyl ester hydrolysis followed by decarboxylation[17] gave substrate **14** for exploratory studies,[18] the same synthetic sequence failed to provide **17**, which contained a masked phenol for carbocation trapping under C3-cyclization conditions (pathway A, Scheme 1), owing to the sensitivity of silyl ether **15**[19] to basic hydrolysis conditions. Instead, we decided to pursue a three-step sequence to indole **17**, which involved reduction to the corresponding alcohol and oxidation to the aldehyde, followed by decarbonylation[20] using $RhCOCl(PPh_3)_2$.[21]

The cross-coupling reaction between indole bromide **17** and tryptamine boronic ester **18**[12,15] gave heterodimer **19** in 78% yield (Scheme 4). Bisindole **19** was then converted to the cyclization precursor by first unmasking the primary amine via hydrazinolysis to provide

amine **20**. The primary amine **20** was methylated using a three-step sequence: *N*–sulfonylation, methylation, and desulfonylation. Finally, cleavage of the *tert*-butyldimethylsilyl group furnished the phenol **22**.

We then studied the cyclization of bisindole **22** under a variety of reaction conditions including the most informative cases illustrated in Scheme 5. When 4-nitrobenzaldehyde was employed (Eq. 1), in lieu of Pictet-Spengler cyclization, pentacyclic **23** was isolated as the major product in 24% yield.[22] Formation of compound **23** suggests that aldehyde condensation at the tryptamine α-nitrogen, if occurred, is unproductive towards C3 cyclization under the conditions examined. Similarly, when Eschenmoser's salt[23] was used, amine **24** was isolated in 28% yield (Eq. 2).[24] The propensity for nine-membered ring formation over the kinetically more favorable Pictet-Spengler cyclization is likely a consequence of the geometric constraint in the biaryl system and a lack of transannular strain due to high degree of unsaturation in the resulting product.

3. Cyclization of Bisindoles 34 and 35

Our initial investigations confirmed the complexities present in the cyclization of bisindoles substrates (Scheme 5), and we sought to extend our studies by testing an alternative substrate where the reactivity of the more electron-rich indole is attenuated by introduction of an electron-withdrawing group (Table 1). A variety of conditions were explored to effect selective demethylation of masked indole **26**, where previously developed conditions (Scheme 3) led to the formation of by product **28** (entry 1–3). Under optimal reaction conditions, demethylation at −10 °C in the presence of a basic additive provided exclusively the desired product **27** in 71% yield (entry 4).

The air-sensitive phenol **27** was immediately masked as its corresponding *tert*-butyldimethylsilyl ether **29** (Scheme 6). Subsequent bromination occurred with excellent regioselectivity to provide **30**.[25] Cross-coupling[26] with **18** followed by functional group manipulations using identical conditions (Scheme 4) employed with the des-sulfonyl counterpart furnished **34**.

With access to bisindole **34** we explored its reactivity under a variety of conditions (Table 2). When 4-nitrobenzaldehyde was used cyclization at C3' (Scheme 5) was suppressed owing to the sulfonylation of N1' (Table 2, entry 1). Dissolving substrate **34** in aqueous formaldehyde resulted in the formation of product **36**, which slowly converted back to starting material **34** under acidic conditions (entry 2). Interestingly, Friedel-Crafts alkylation at C4 occurred when acetic acid was employed as the solvent, affording product **38** (entry 3). The preference for formation of the 7-membered ring was intriguing. We reasoned that under the highly acidic environment, the nucleophilic indole is reversibly protonated at C3 to give intermediate **41** (Scheme 7). The iminium ion is stabilized via the intermediacy of orthoquinone **43**. Aniline **43** undergoes Friedel-Crafts alkylation to give the unexpected product **38**. The formation of spirocycle **45** could have also proceeded in a reversible fashion.

Based on this hypothesis we investigated the Friedel-Crafts chemistry of bisindoles through the use of 2-(3',5'-dimethoxy)indole-tryptamine **35**,[27] where formation of the analogous 2-aryltryptamine oxocarbenium intermediate is energetically less unfavorable. However, bisindole **35** behaved similarly to its demethylated substrate **34**: under identical conditions, Friedel-Crafts cyclization products **39** and **40** were isolated while no Pictet-Spengler product was observed (entry 5). The use of aqueous formaldehyde and reducing the amount of acid were similarly ineffective (entry 4 and 6). Interestingly, the structures of Friedel-Crafts products **38–40** map closely onto the clavicipitic[28] and aurantioclavine[29] ergot alkaloids (Figure 2), where the unusual C–C bond between the indole and the isoprene unit is biosynthetically constructed through a Friedel-Crafts alkylation of tryptophan onto dimethylallyl diphosphate.[28,30]

The chemistry of free bisindole substrates **22** and **34** in the presence of activated carbonyl electrophiles underscore the difficulties involved in cyclization around the key C2–C4' bond. Our studies on the free bisindole substrate **22** suggest that although amine condensation occurred (Scheme 5), it did not translate into six-membered ring-forming cyclization. The observed difficulty is likely a result of steric hindrance around the highly congested C2–C4' bond. Next, we set out to design an appropriate substrate that may overcome steric hindrance and the cyclizing propensities of these bisindole substrates.

4. Spirocyclization of Bisindole 47

We envisioned that carbamoyl chloride **47**[31] may act as an ideal substrate for spirocyclization upon activation by a halophilic metal cation (Scheme 8). The intermediate **48** bears minimal steric bulk and its electrophilic nature, similar to that of the activated amide electrophiles in our interrupted Bischler-Napieralski methodology,[13] could be inducible to cyclization.

Treatment of secondary amine **33** with triphosgene at room temperature in pyridine provided tryptamine carbamoyl chloride **52** as an equal mixture of amide rotomers (Scheme 9).[32] Gratifyingly, exposure of carbamoyl chloride **52** to silver trifluoromethanesulfonate in acetonitrile followed by warming led to a quantitative formation of spirolactam **49**.[33] Alternatively, spirolactam **49** can be formed at room temperature, although at a slower rate.

Having accessed the spirocycle **49** successfully, we investigated its 1,2-Wagner-Meerwein Rearrangement reaction under a variety of BrØnsted and Lewis acid catalyzed conditions (Scheme 10). When microwave heating was applied to spirocycle **49** in the presence of trifluoroacetic acid, a small amount of the carbamate **53** was isolated.[34] Similarly, activation of the carbamate **53** with phosphoryl chloride led to its quantitative conversion back to spirolactam **49**. Interestingly, an earlier attempt to cleave the *tert*-butyldimethylsilyl group using a basic fluoride source resulted in a mixture of spirolactam **49** and macrocycle **53** (Scheme 11), a result consistent with our later observations on the thermal rearrangement profile of **49**.[35]

The recalcitrance for spirocycle **49** to undergo structural rearrangement is consistent with observations in the synthesis of spirocyclic indolines via an interrupted Bischler-Napieralski

reaction.[13] The formation of spirocycle **49** supports our hypothesis that the lack of spirocyclization in our prior bisindole substrates was in part due to steric factors. The use of a sterically unencumbered, highly activated iminum ion **48** holds promise for related challenging cyclization chemistry.

5. Conclusion

The mode of cyclization of bisindoles in the presence of a variety of electrophiles was investigated through electronically distinct bisindole substrates. Bisindole substrate **22** preferentially leads to nucleophilic attack at the less sterically hindered C3' position and subsequent cyclizations to afford pentacyclic products such as **23** and **24**. Bisindoles **34** and **35** with attenuated nucleophilicity at C3' afford products through Friedel-Crafts based C4-alkylation. Importantly, activation of carbamoyl chloride **52** to a putative reactive and sterically unencumbered iminum ion **48** provides spirocyclic lactam **49** in quantitative yield. Given the superb reactivity of carbamoyl chloride **52**, its ease of synthesis as described above, and potential for late-stage stereocontrolled introduction of related spirocyclic structures, both the stereocontrolled cyclization of such carbamoyl chlorides and the electrophilic N1-activation of the resulting indolenine products merit further investigation.

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22. To a solution of amine **22** (3.6 mg, 10.7 μmol, 1.00 equiv) at 23 °C in acetonitrile-d_3 (500 μL) was added a solution (0.13 M) of 4-nitrobenzaldehyde in acetonitrile-d_3 (100 μL, 12.9 μmol, 1.20 equiv), followed by trifluoroacetic acid-d_1 (1 μL, 12.9 μmol, 1.20 equiv). The reaction was heated to 50 °C for 4.5 h, at which point ^{1}H NMR analysis indicated complete consumption of the starting material. The reaction was cooled to 23 °C, and diluted with water (5 mL) and ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2×5 mL). Saturated aqueous sodium bicarbonate solution (2 mL) was then added, the layers were separated and the aqueous layer was extracted with ethyl acetate (2×5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 1% NH_4OH and 3% MeOH in chloroform) to provide product **23** (1.2 mg, 24%). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ 8.17 (br-s, 1H), 8.06 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.11–6.99 (m, 2H), 6.94 (d, J = 7.9 Hz, 1H), 6.90 (s, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.44 (s, 1H), 3.92 (s, 3H), 3.15– 3.09 (m, 2H), 3.06–2.93 (m, 2H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ 152.9, 149.7, 147.1, 146.8, 137.0, 132.9, 129.9, 126.1, 124.7, 123.8, 122.1, 120.1, 118.7, 118.4, 117.9, 112.5, 110.2, 106.6, 100.3, 99.7, 57.3, 55.7, 48.6, 35.6, 24.8. FTIR (thin film) cm^{-1}: 3402 (m), 2925 (m), 2852 (m), 1599 (s), 1520 (s), 1464 (s), 1345 (s), 739 (w). HRMS (ESI): calcd for $C_{27}H_{25}N_4O_4$ $[M+H]^+$: 469.1876, found: 469.1880.
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The concentrated fractions were purified again by flash column chromatography on silica gel (eluent: gradient, 1% NH_4OH and 10→15% MeOH in chloroform) to provide product **24** (3.2 mg, 28%). ^{1}H NMR (500 MHz, CD_3CN, 20 °C): δ 9.29 (brs, 1H), 7.68 (ddd, *J* = 7.9, 1.2, 0.7 Hz, 1H), 7.52 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.05 (d, *J* = 1.8 Hz, 1H), 6.52 (s, 1H), 4.54 (d, *J* = 12.9 Hz, 1H), 4.26 (d, *J* = 13.0 Hz, 1H), 3.98 (s, 3H), 3.36–3.25 (m, 2H), 3.12 (d, *J* = 12.7 Hz, 1H), 3.00 (ddd, *J* = 13.7, 11.4, 3.9 Hz, 1H), 2.66–2.60 (m, 1H), 2.55 (dt, *J* = 15.5, 4.0 Hz, 1H), 2.31 (s, 3H), 2.19 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 20 °C): δ 152.4, 148.4, 138.2, 133.6, 129.6, 128.8, 127.2, 122.7, 122.6, 120.4, 119.5, 113.4, 112.2, 110.9, 104.5, 98.6, 65.9, 56.2, 50.3, 49.4, 42.4, 42.1, 22.5. FTIR (thin film) cm^{-1}: 2928 (s), 2860 (w), 2360 (m), 1733 (s), 1581 (m), 1463 (s), 742 (m). HRMS (ESI): calcd for $C_{24}H_{29}N_4O_2$ $[M+H]^+$: 405.2291, found: 405.2278.

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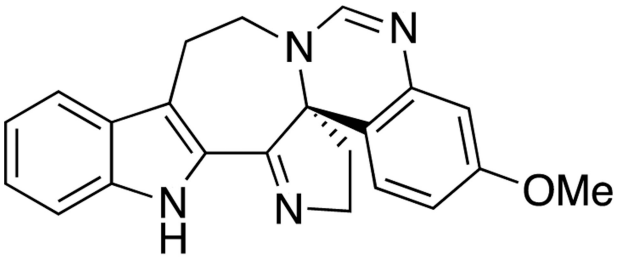
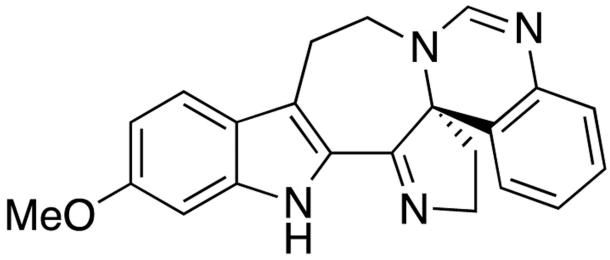
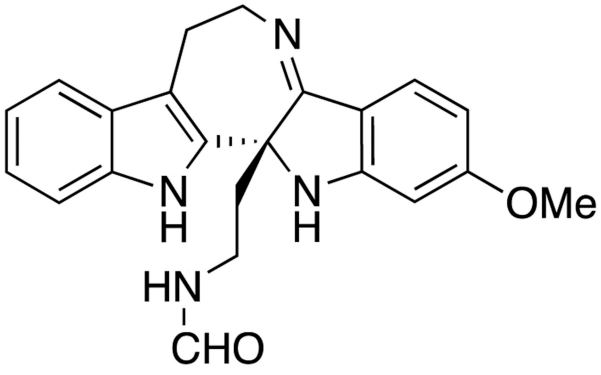
32. Carbamoyl chloride **52** was stable to silica gel column chromatography.
33. To a solution of carbamoyl chloride **52** (20 mg, 30.7 mmol, 1.00 equiv) in acetonitrile (3.1 mL) was added AgOTf (39.4 mg, 15.3 mmol, 5.00 equiv). The reaction mixture was then heated to 75 °C. After 30 min, the reaction was cooled to room temperature, filtered through celite, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (eluent: 2% MeOH in dichloromethane) to provide spirocycle **49** (15.3 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ 7.87 (d, *J* = 3.8 Hz, 1H), 7.79– 7.74 (m, 2H), 7.60–7.54 (m, 1H), 7.53–7.44 (m, 3H), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H), 7.28 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.18 (td, *J* = 7.5, 0.9 Hz, 1H), 6.53 (d, *J* = 3.8 Hz, 1H), 6.39–6.37 (br-s, 1H), 4.03 (ddd, *J* = 10.2, 9.2, 7.9 Hz, 1H), 3.75 (td, *J* = 10.0, 1.3 Hz, 1H), 3.60 (s, 3H), 3.17 (s, 3H), 2.99 (dt, *J* = 13.3, 9.6 Hz, 1H), 2.18 (ddd, *J* = 13.3, 7.9, 1.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ 177.7, 171.9, 164.3, 151.3, 150.6, 140.4, 140.1, 133.6, 131.1, 129.8, 129.4, 129.1, 127.1, 126.1, 120.7, 119.4, 119.3, 106.0, 102.1, 98.5, 66.1, 55.3, 47.6, 30.9, 28.2. FTIR (thin film) cm^{-1}: 2921 (m), 2361 (m), 1700 (s), 1588 (s), 1458 (s), 666 (s). HRMS (ESI): calcd for $C_{27}H_{24}N_3O_5S$ $[M+H]^+$: 502.1437, found: 502.1424.
34. Carbamate **53** could be formed either via direct phenolic attack on the γ-lactam or via intermediate **48**.
35. Macrocycle **53** could be either formed from substrate **52** or via attack of the phenolate onto the amide carbonyl of **49**



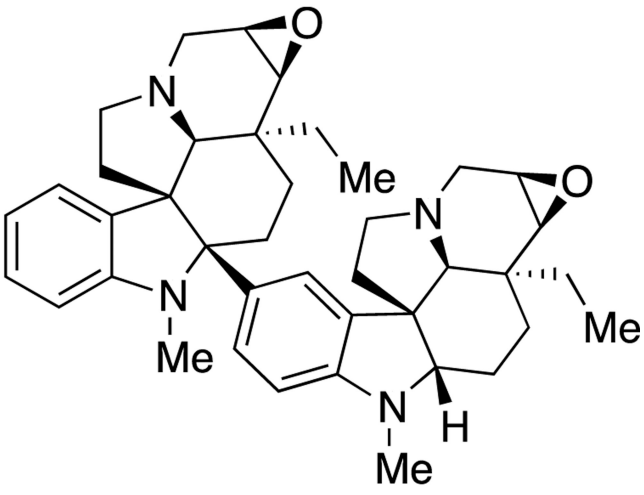
(–)-Trigonoliimine A (**1**)



(–)-Trigonoliimine B (**2**)



(–)-Trigonoliimine C (**3**)



(+)-Tabernaebovine (**4**)

Figure 1.
Representative bisindole natural products.

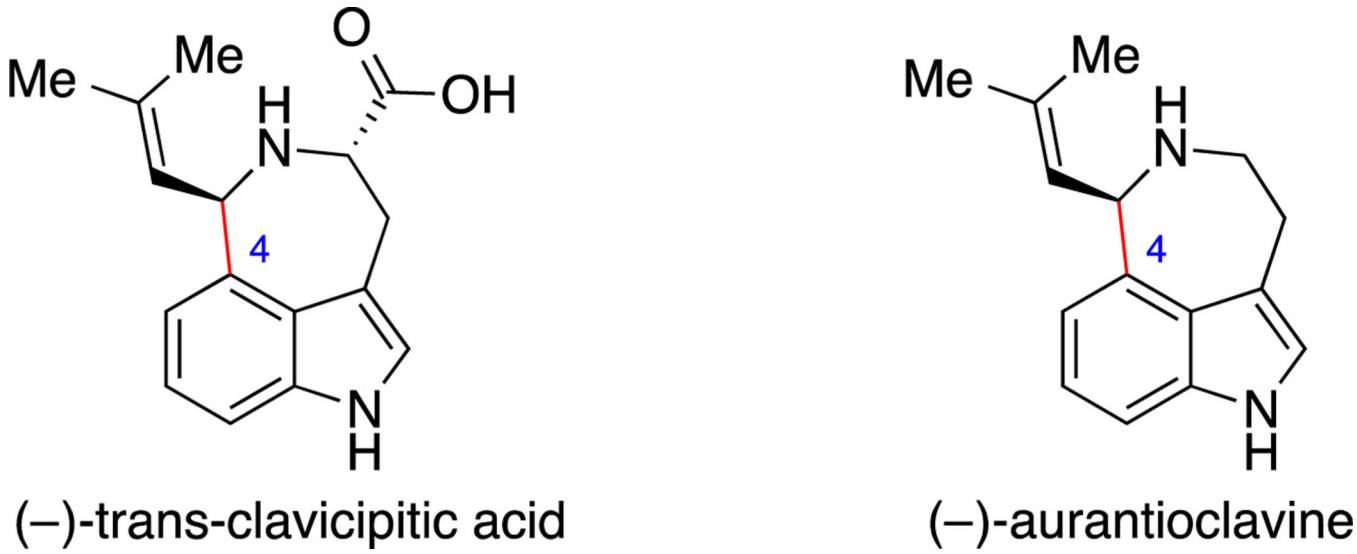
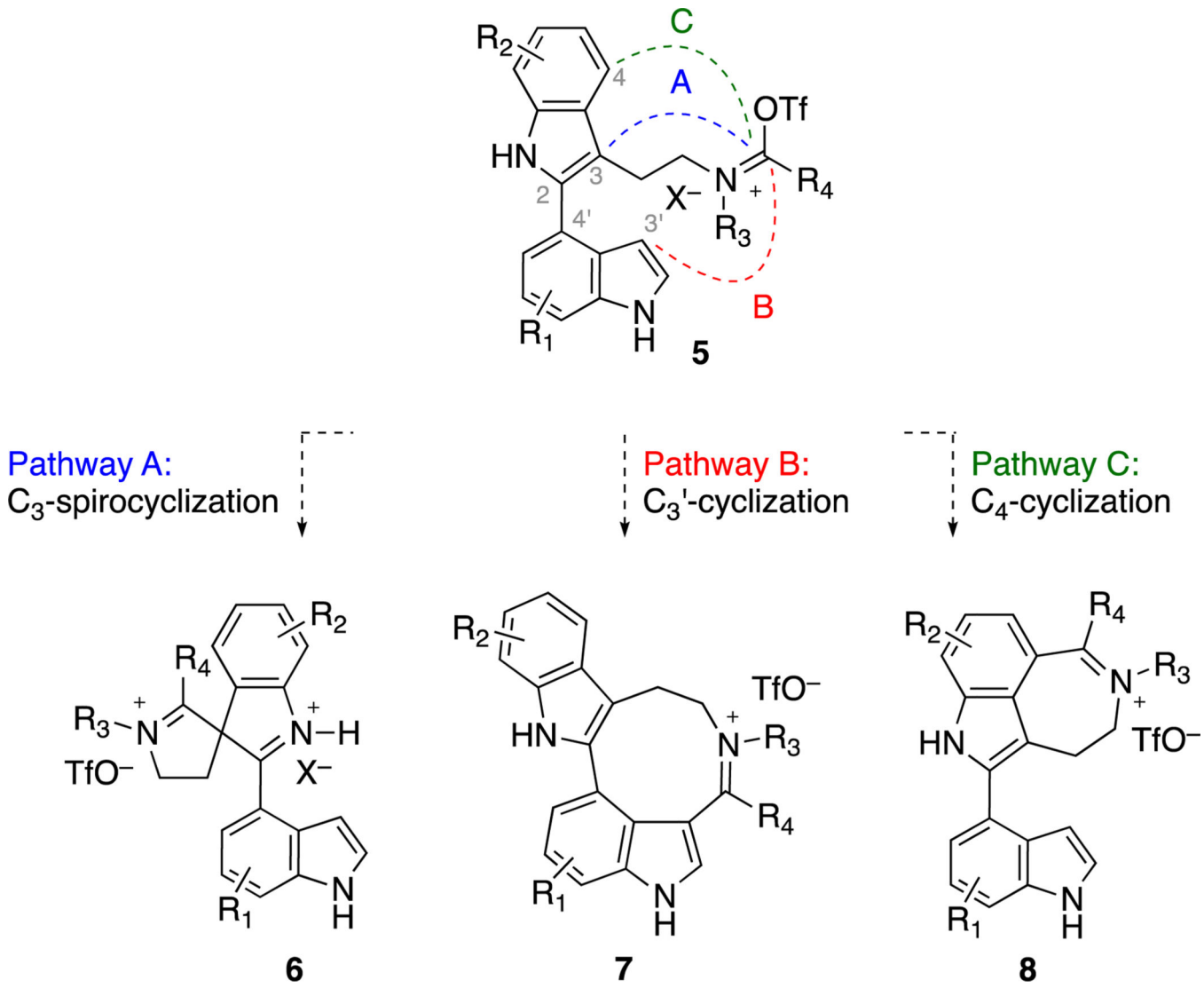
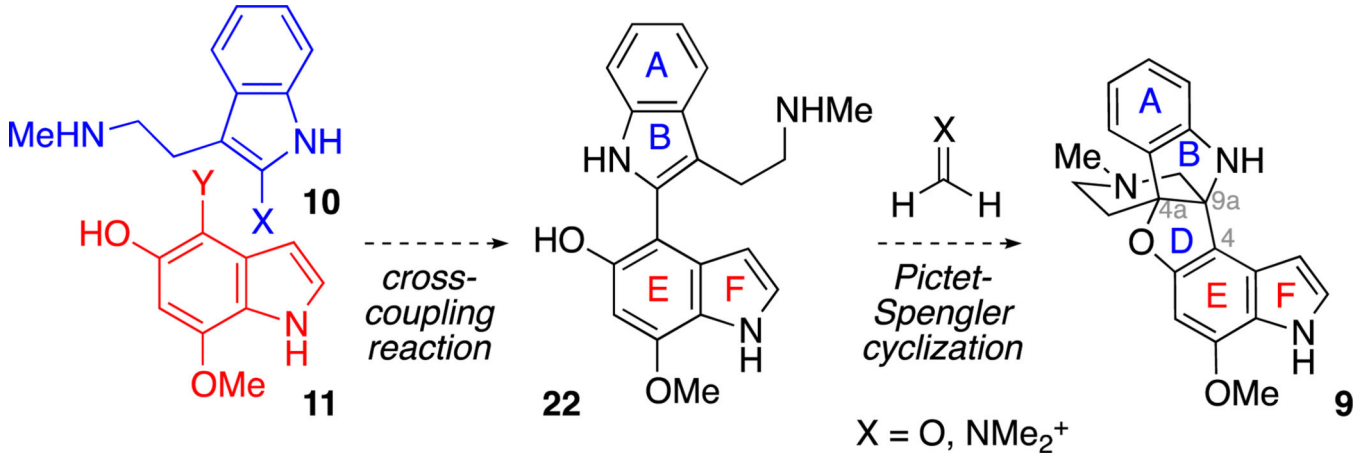


Figure 2.
Representative members of the ergot alkaloids that possess the rare substitution at C4.

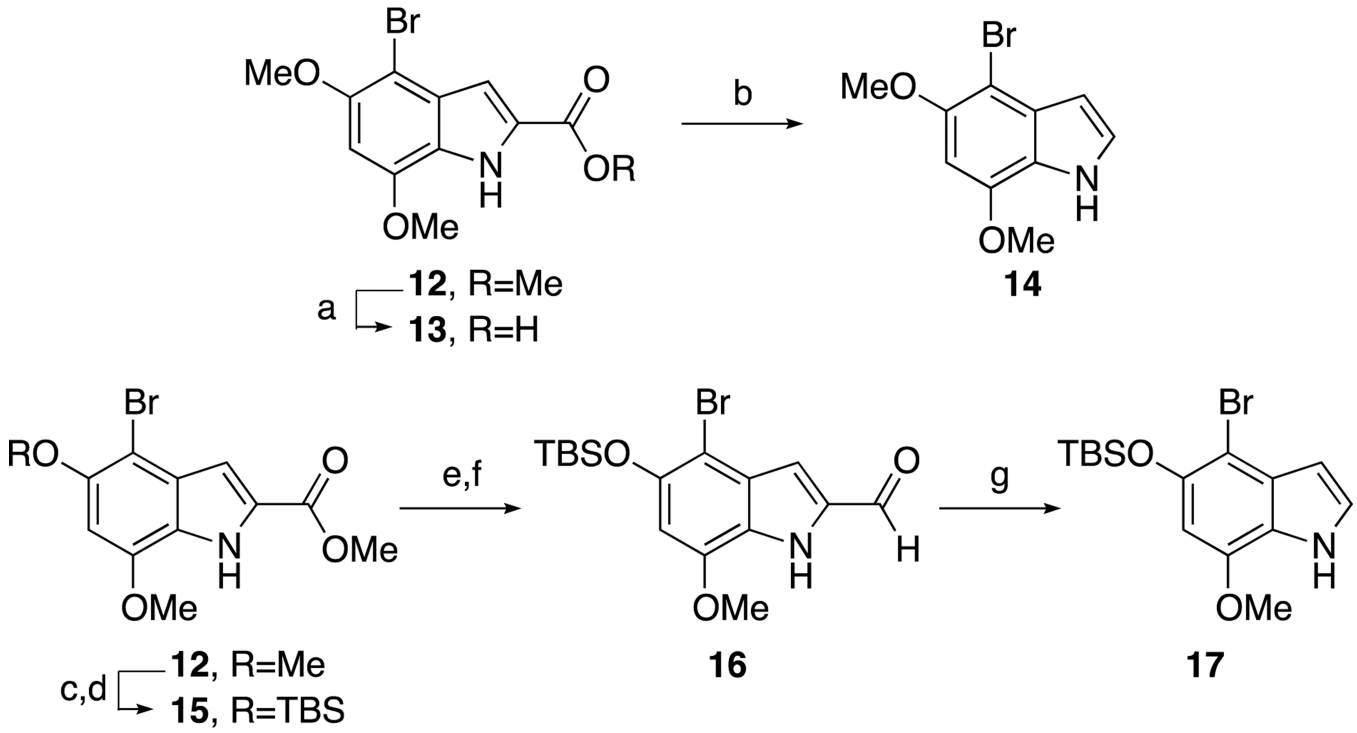


Scheme 1.
Possible cyclization modes of bisindole substrate **5**.



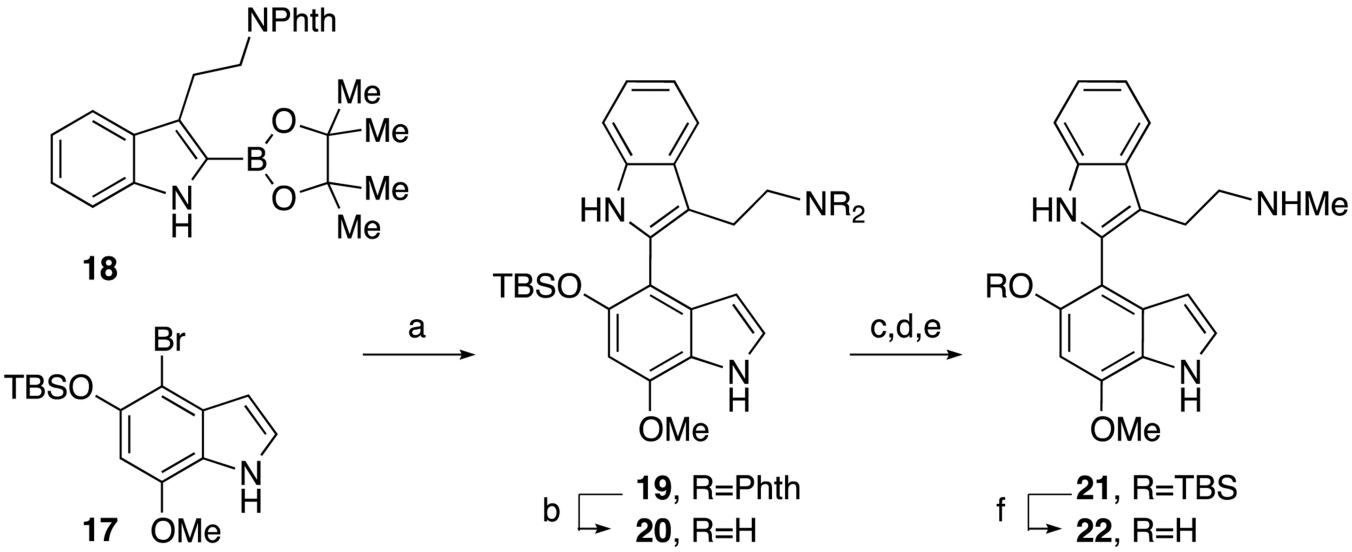
Scheme 2.

Exploring cyclization modes of bisindole substrates via a demanding cascade reaction.



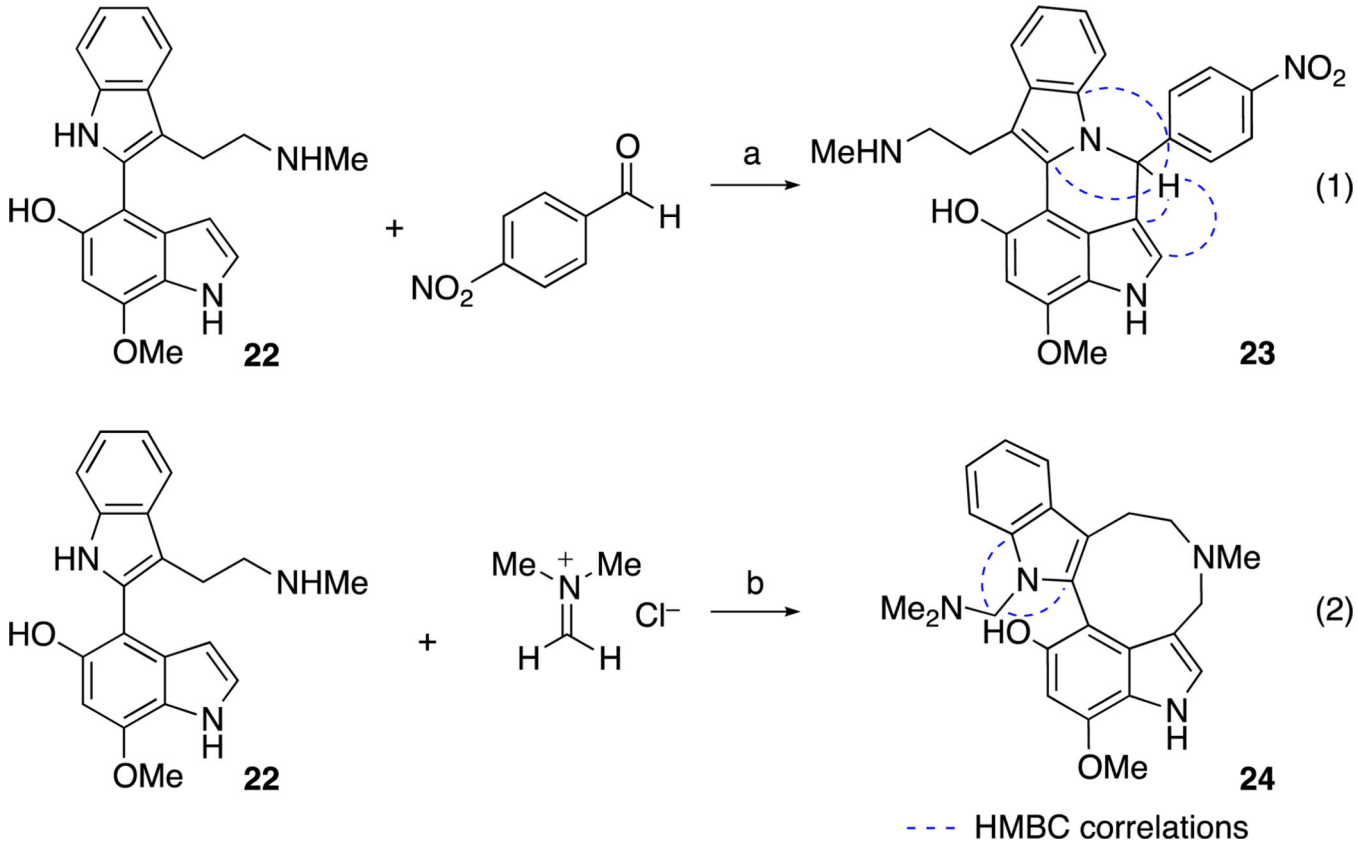
Scheme 3.

Preparation of indoles **14** and **17**. Conditions: (a) LiOH, THF, 23 °C, 99%. (b) Cu, quinoline, 210 °C, 50%. (c) BBr_3, CH_2Cl_2, −78→23 °C, 77%. (d) TBSCl, imidazole, DMF, 23 °C, 71%. (e) $LiAlH_4$, THF, 0 °C, 76%. (f) TPAP, NMO, 4 Å MS, CH_2Cl_2, 23 °C, 55%. (g) $RhCOCl(PPh_3)_2$, dppp, xylene, 140 °C, 80%. dppp = 1,3-bis(diphenylphosphino)propane.



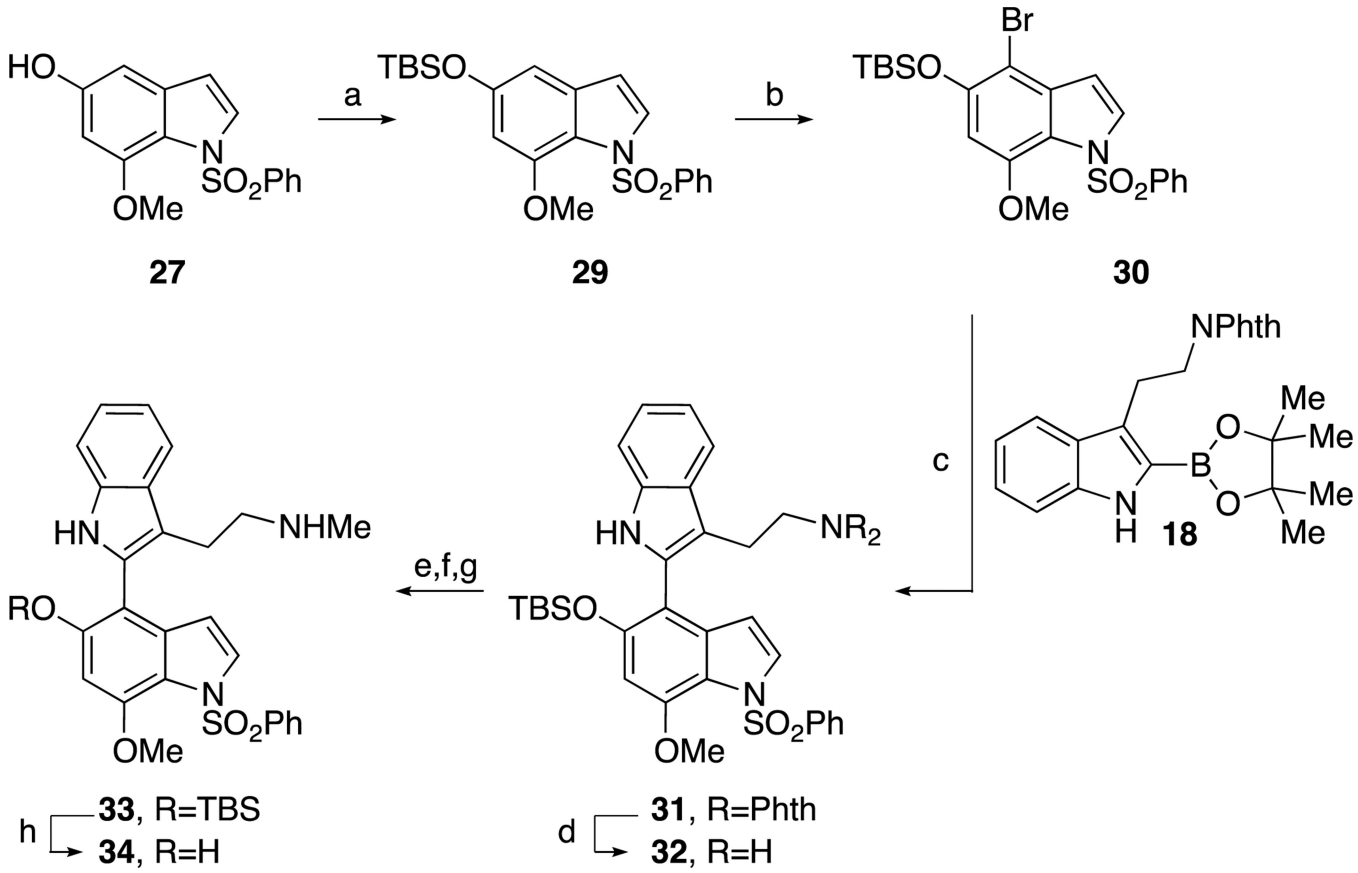
Scheme 4.

Synthesis of bisindole **22**. Conditions: (a) Pd_2dba_3, XPhos, K_3PO_4, toluene, H_2O, 110 °C, 78%. (b) H_2NNH_2, MeOH, CH_2Cl_2, 23 °C, 90%. (c) *o*-$NO_2C_6H_4SO_2Cl$, Et_3N, CH_2Cl_2, 23 °C, 90%. (d) DBU, Me_2SO_4, DMF, 23 °C, 93%. (e) PhSH, K_2CO_3, CH_3CN, 23 °C, 99%. (f) TBAF, THF, 23 °C, 88%. DMF = dimethylformamide. dba = dibenzylideneacetone. DBU = 1,8-diazabicycloundec-7-ene. Phth = phthaloyl. XPhos = 2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl.



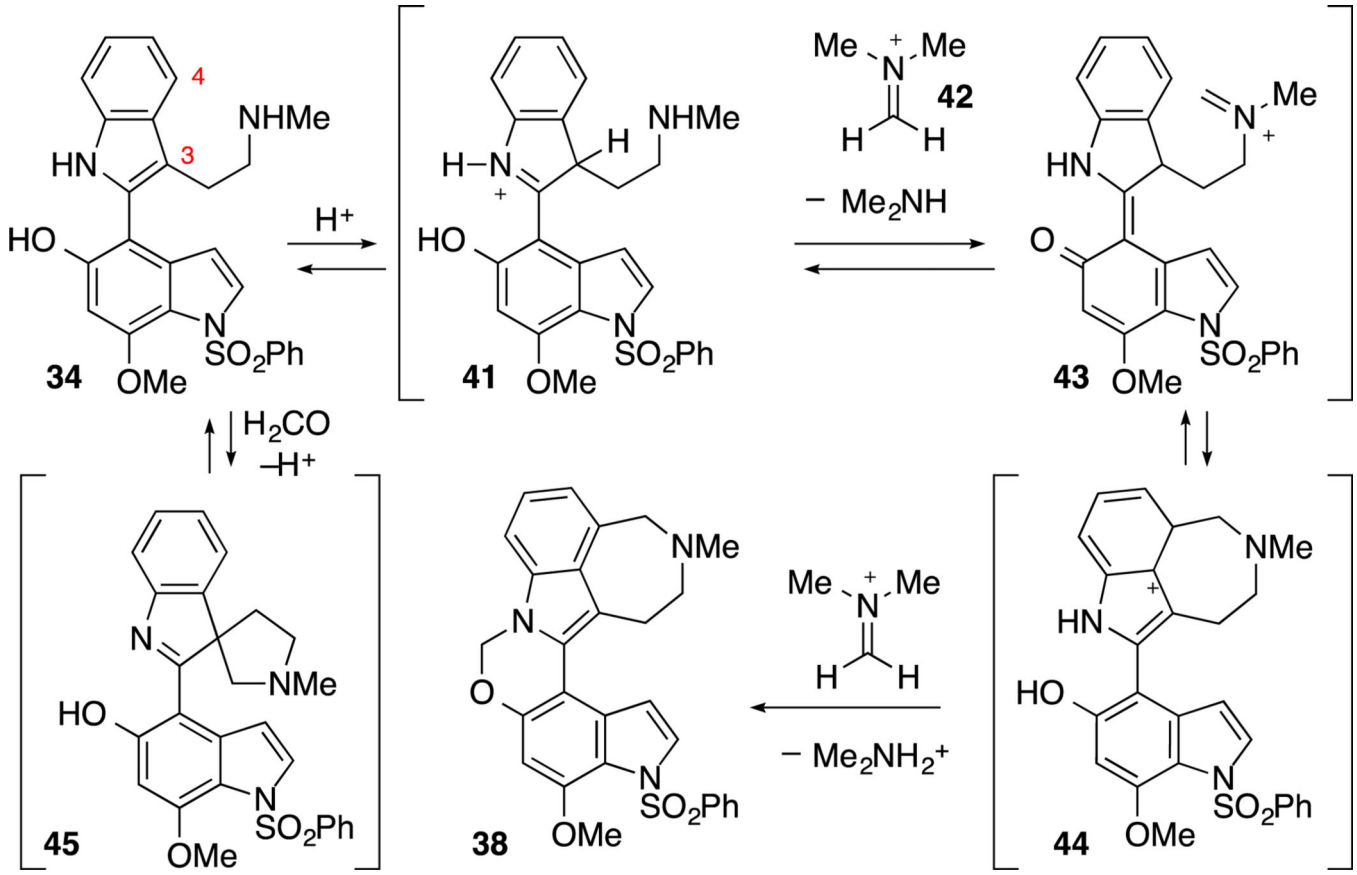
Scheme 5.

Treatment of substrate **22** with carbonyl electrophiles. Conditions: (a) TFA-d_1, CD_3CN, 23 → 50 °C, 24%. (b) CH_3CN, 23 °C, 28%.



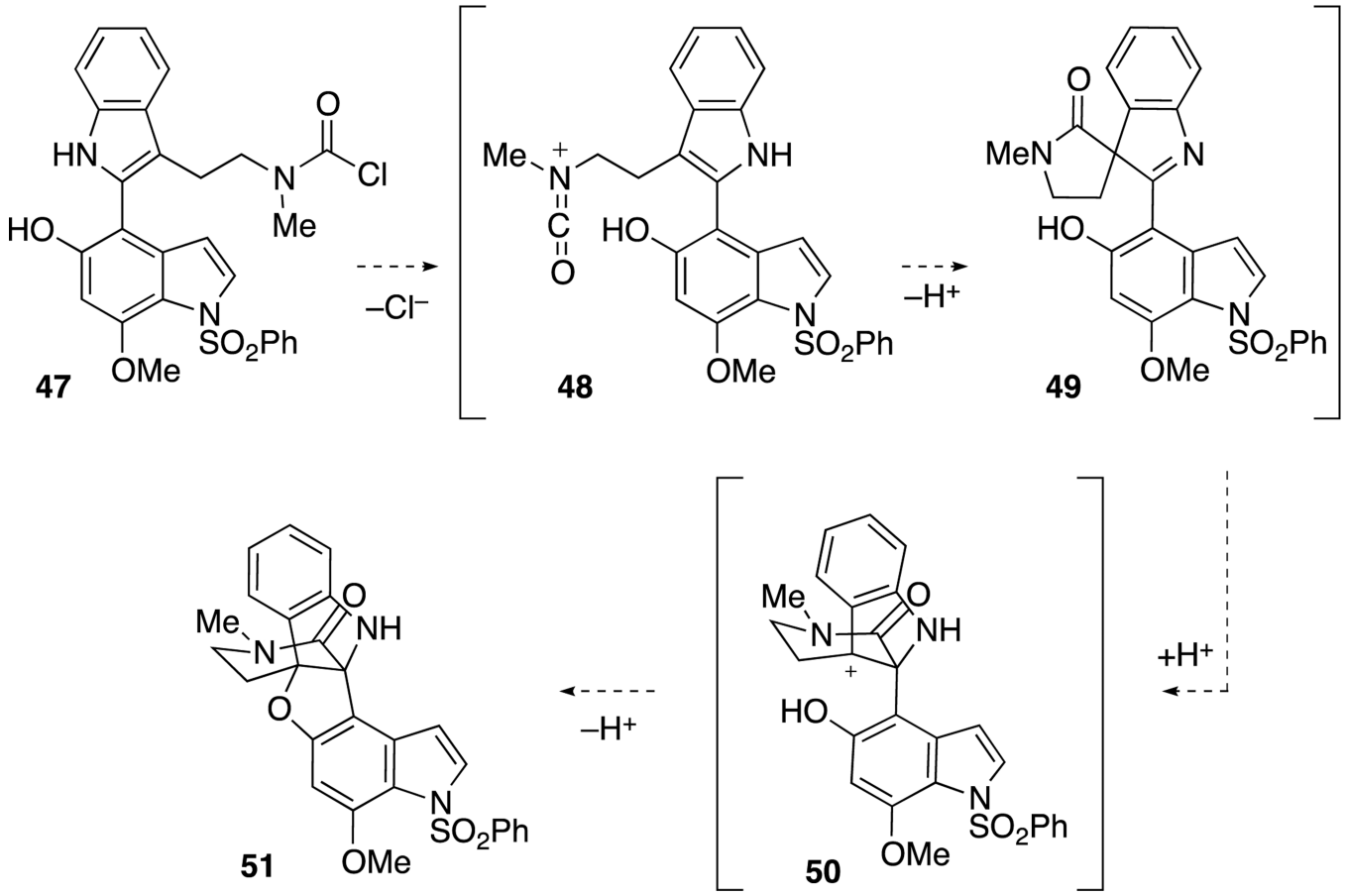
Scheme 6.

Preparation of a new Pictet-Spengler substrate. Conditions: (a) TBSCl, imidazole, DMF, 23 °C, 85%. (b) Br_2, C_5H_5N, DMF, 0 °C, 84%. (c) Pd_2dba_3, XPhos, K_3PO_4, Tl_2CO_3, dioxane, H_2O, 110 °C, 69%. (d) H_2NNH_2, MeOH, CH_2Cl_2, 23 °C, 96%. (e) *o*-$NO_2C_6H_4SO_2Cl$, Et_3N, CH_2Cl_2, 23 °C, 54%. (f) DBU, Me_2SO_4, DMF, 23 °C, 98%. (g) PhSH, K_2CO_3, CH_3CN, 23 °C, 89%. (h) TBAF, THF, 23 °C, 46%. DMF = dimethylformamide. dba = dibenzylideneacetone. XPhos = 2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl. DBU = 1,8-diazabicycloundec-7-ene. Phth = phthaloyl.

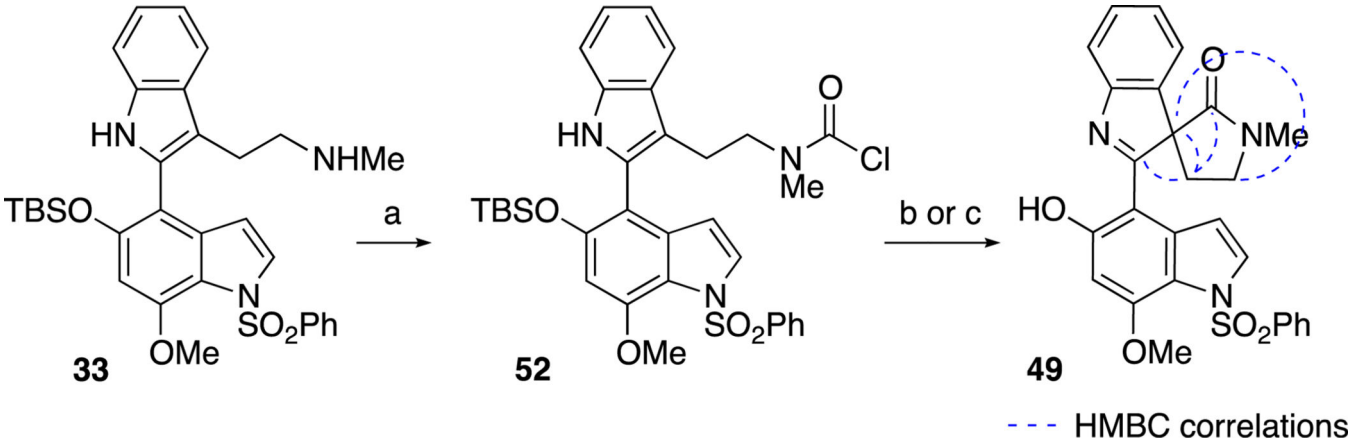


Scheme 7.

A proposed mechanism of formation of cycloheptane **38**.

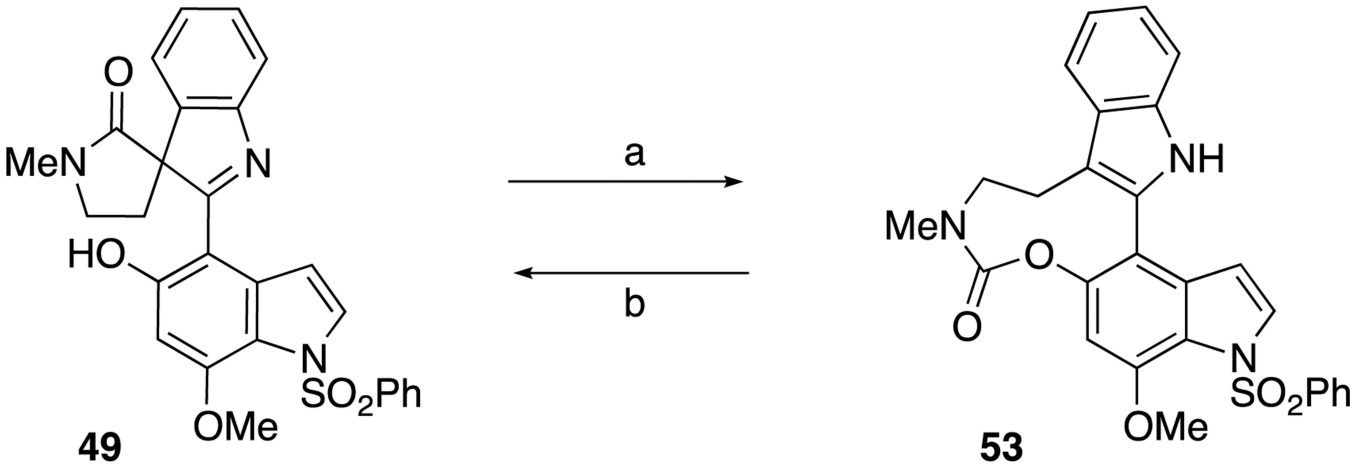


Scheme 8.
Potential use of substrate **47** in spirocyclization.



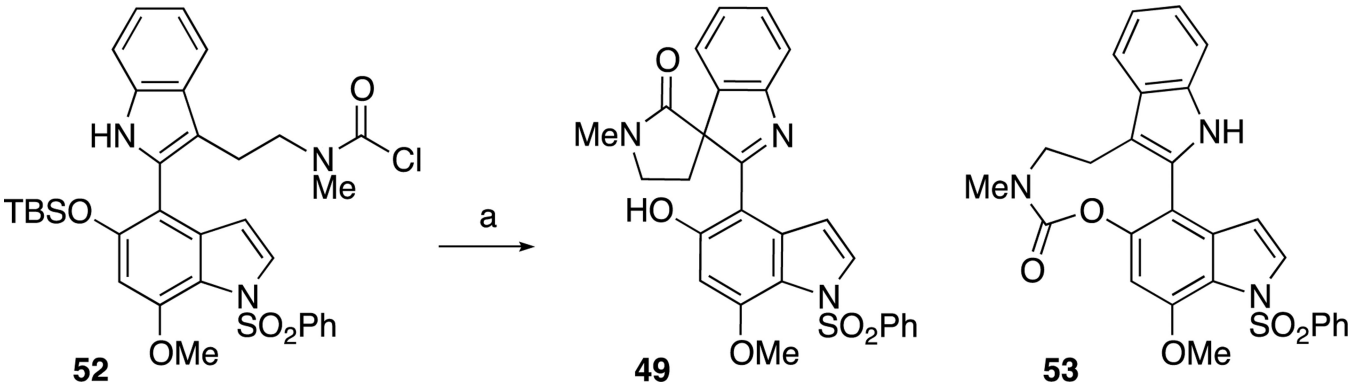
Scheme 9.

Preparation and cyclization of carbamoyl chloride **52**. Conditions: (a) $C_3Cl_6O_3$, C_5H_5N, 23 °C, 75%. (b) AgOTf, CH_3CN, 70 °C, 30 min, 99%. (c) AgOTf, CD_3CN, 23 °C, 5 h, 99%.



Scheme 10.

Thermal rearrangement of spirolactam **49**. Conditions: (a) CF_3CO_2H, μwave, 135 °C, 19%. (b) $POCl_3$, $CDCl_3$, 23 → 60 °C, 100% (NMR yield).

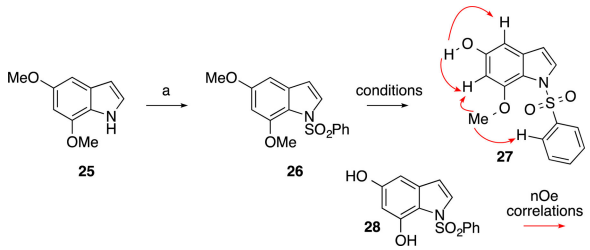


Scheme 11.

Spirocyclization and macrocyclization under basic conditions. Conditions: (a) TBAF, THF, 23 °C, 45% for **49**, 52% for **53**.

Table 1

Regioselective demethylation of **26**.



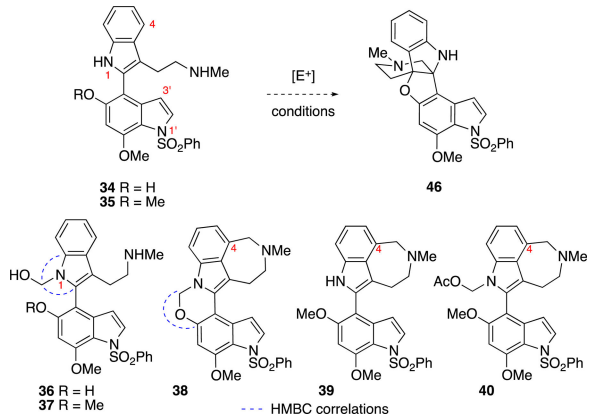
Entry	Reagent (Equiv.)	Additive (Equiv.)	Solvent	Temp (°C)	Time (h)	Product (% yield)
1	BBr_3 (5)	–	CH_2Cl_2	−78 → 0	2.5	**28** (88)
2	BBr_3 (2)	DTBMP (2)	CH_2Cl_2	−78 → 0	2.5	**27** (56) **28** (44)
3	BBr_3 (2)	DTBMP (10)	CH_2Cl_2	−78 → 0	2.5	**27** (60) **28** (40)
4	BBr_3 (1)	DTBMP (10)	CH_2Cl_2	−78 → −10	19	**27** (71)

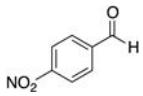
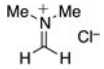
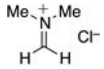
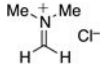
Conditions: (a) NaH, $PhSO_2Cl$, THF, 0 °C, 93%. DTBMP = di-*tert*-butyl-4-methyl-pyridine.

Tetrahedron Lett. Author manuscript; available in PMC 2016 June 03.

Table 2

Use of N1'-masked substrates **34** and **35**.



entry	substrate	[E⁺]	additive	solvent	temp (°C)	product (% yield)
1	**34**		TFA-*d*	CD_3CN	23 → 60	_*a*
2	**34**		TFA	–	23	**36** (50)
3	**34**		–	AcOH	120	**38** (35)
4	**35**		–	–	100	**37** (42)
5	**35**		–	AcOH	120	**39** (52) **40** (25)
6	**35**		AcOH	CH_3CN	85	_*b*

[a] no reaction was observed.

[b] decomposition. TFA = trifluoroacetic acid. DMSO = dimethylsulfoxide.