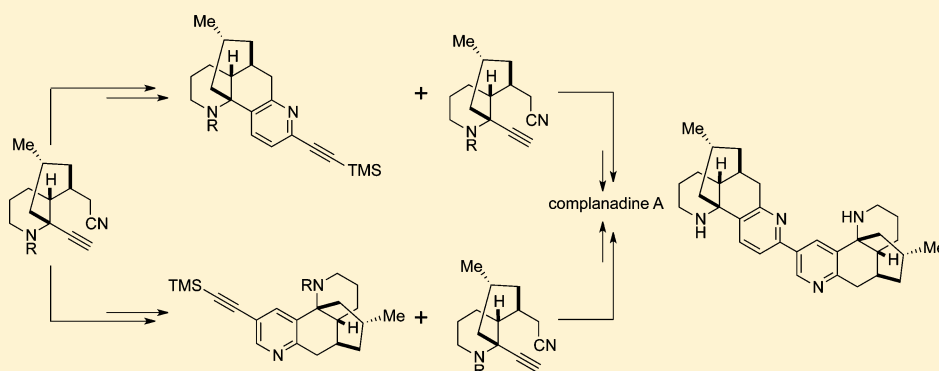


Syntheses of (+)-Complanadine A and Lycodine Derivatives by Regioselective [2 + 2 + 2] Cycloadditions

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S Supporting Information



ABSTRACT: The dimeric alkaloid complanadine A has shown promise in regenerative science, promoting neuronal growth by inducing the secretion of growth factors from glial cells. Through the use of tandem, cobalt-mediated [2 + 2 + 2] cycloaddition reactions, two synthetic routes have been developed with different sequences for the formation of the unsymmetric bipyridyl core. The regioselective formation of each of the pyridines was achieved based on the inherent selectivity of the molecules or by reversing the regioselectivity through the addition of Lewis bases. This strategy has been successfully employed to provide laboratory access to complanadine A as well as structurally related compounds possessing the lycodine core.

INTRODUCTION

Growth factors can significantly enhance the survival and regenerative potential of neurons injured as a result of trauma^{1–3} or disease.^{4–6} These proteins prevent apoptosis, promote the growth and survival of neurons, and aid in the controlled development of progenitor cells.^{2,7} Their effective use as therapeutics, however, has been problematic due to their pharmacokinetic shortcomings:⁸ proteolytic degradation requires continual infusion and their limited ability to cross the blood–brain barrier has meant delivery by intracranial injection, with attendant serious risks to the patient's health. Gene therapy-based approaches to inducing the production of neurotrophic factors, using both direct and ex vivo techniques, have had success in animal models of Parkinson's disease and in regenerating axons after spinal cord injury.² Although promising, gene therapy has yet to overcome the limitations of short-lived effects, undesirable immune responses, intracranial delivery, and challenges involving the use of viral vectors.⁹

Using small molecules provides an alternative approach to regenerative medicine.¹⁰ Able to mimic neurotrophic factors, or to induce neurotrophic factor biosynthesis, small molecules possess a pharmacological advantage. Along these lines it was discovered that the natural product complanadine A (**1**) and complanadine B (**2**), isolated from the club moss *Lycopodium complanatum*, induced the secretion of neurotrophic factors

from 1321N1 cells (human glial cells derived from brain astrocytoma), promoting the differentiation of PC-12 cells.^{11,12} The enhanced expression of NGF mRNA by 1321N1 cells treated with complanadine B was determined by semi-quantitative RT-PCR. In addition to its biological effects complanadine A possesses a unique structure and represented the first dimeric alkaloid containing a lycodine-type C₁₆N₂ skeleton to be characterized. Structurally related natural products to be isolated include complanadine C (**3**) and D (**4**) as well (Figure 1).^{12,13} Synthetic interest in this class of dimeric natural products has led to three successful laboratory preparations of complanadine A (**1**)^{14–16} as well as two synthetic routes to complanadine B (**2**).^{16,17}

RESULTS/DISCUSSION

The synthesis of complanadine A was envisioned through the application of sequential [2 + 2 + 2] cycloaddition reactions between a disubstituted butadiene **7** and two molecules of alkyne nitrile **6** (Figure 2). Two potential sequences for the ordered, regioselective formation of the pyridine rings were possible, both generating complanadine A (Figure 2). Through this approach the corresponding symmetric bipyridyl isomers **9** and **10** bearing 2,2' or 3,3' connectivity, respectively, could

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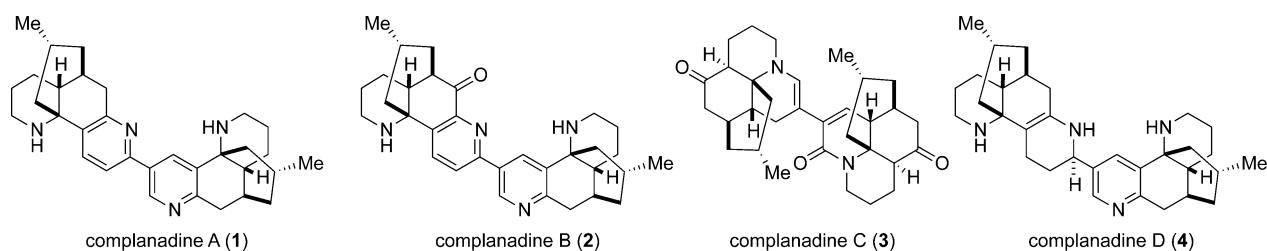


Figure 1. Structures of complanadines A–D.

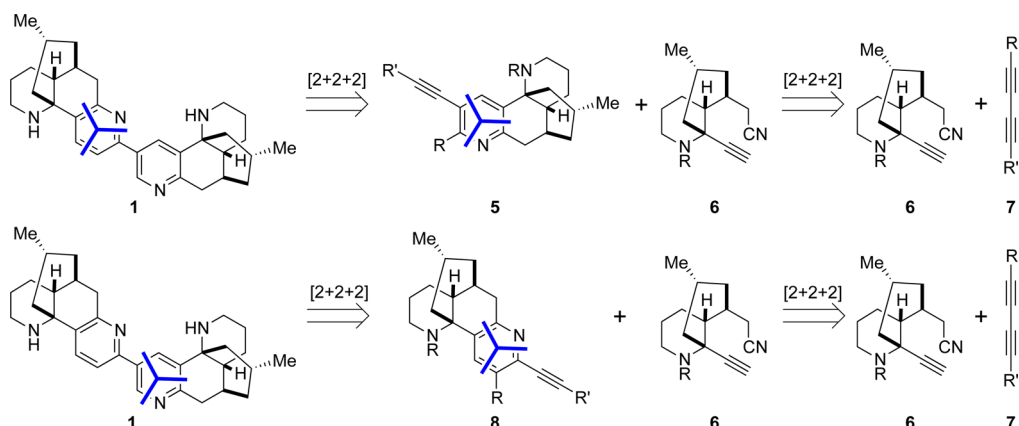


Figure 2. Synthetic disconnections of complanadine A.

potentially be produced as undesirable alternative products arising from the cycloaddition reactions (Figure 3).

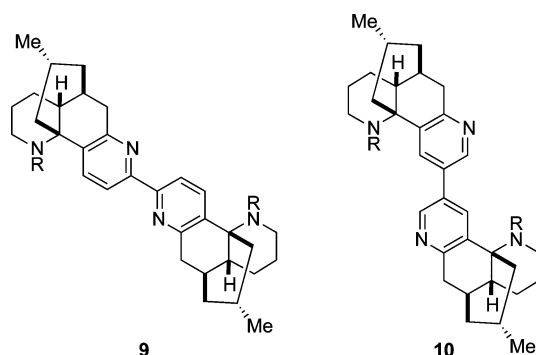
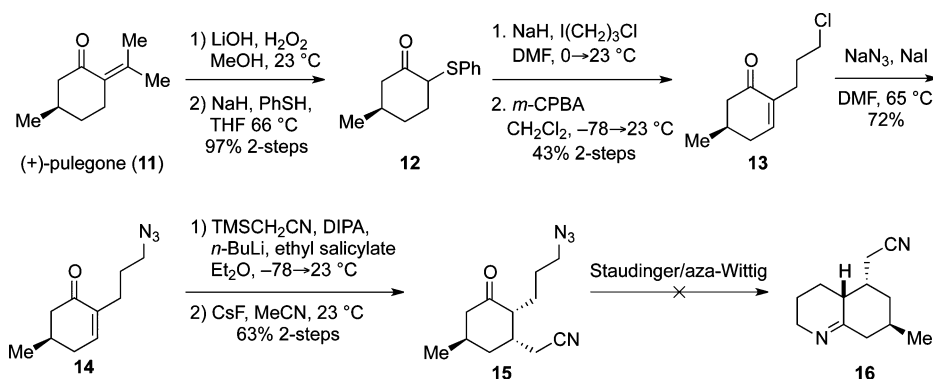


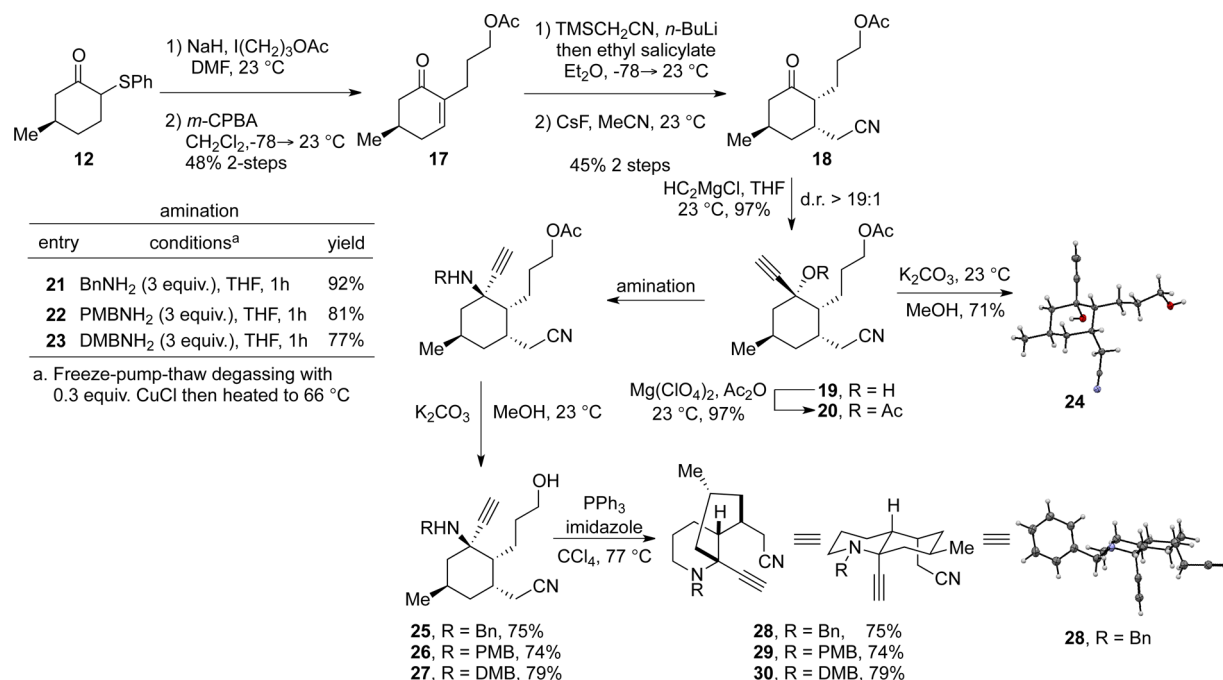
Figure 3. Undesired symmetric isomers.

Alkyne–nitrile **6** represented a pivotal intermediate for these studies and a synthetic route that could generate gram scale quantities was required. The first generation approach toward the synthesis of the alkyne–nitrile fragment was initiated by treatment of (+)-pulegone (**11**) with lithium hydroxide (1.0 equiv) and H_2O_2 (1.0 equiv, 30% aqueous solution) providing pulegone oxide, which was reacted with an excess of the anion of thiophenol (1.3 equiv) to provide thioether **12** as a diastereomeric mixture in 97% yield over two steps (Scheme 1).^{18–20} To a solution of thioether **12** in dimethylformamide at 23 °C solid sodium hydride (1.1 equiv) was added in portions over 10 min with extensive gas evolution. Alkylation of the resulting thermodynamic enolate with 1-chloro-3-iodopropane (1.3 equiv) afforded a mixture of diastereomeric products (1.2:1) along with significant (~30%) amounts of byproduct arising from *O*-alkylation. Oxidation of the mixture of diastereomers with *m*-CPBA (1.1 equiv) at –78 °C generated four diastereomeric sulfoxides that, following warming to 23 °C, underwent a mild *syn*-elimination, generating enone **13**.¹⁹

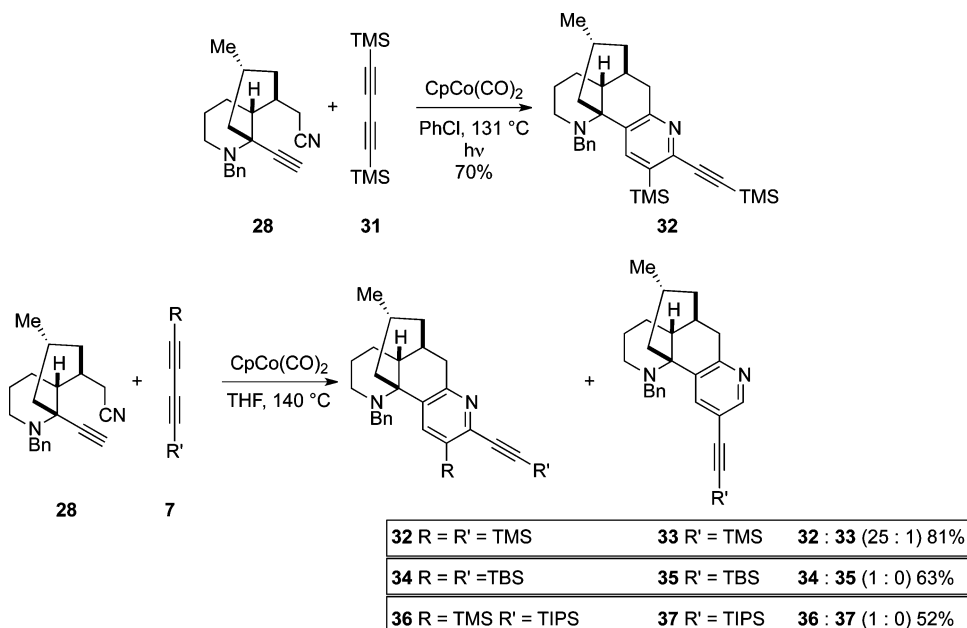
Scheme 1. Synthesis of Azide Precursor 15 and Attempted Staudinger/Aza-Wittig Reaction



Scheme 2. Synthesis of Alkyne–Nitriles 28–30 from Thioether 12



Scheme 3. Regioselective Cobalt-Mediated [2 + 2 + 2] Cycloaddition of Alkyne–Nitrile 28 and Different Butadiynes



Azide **14** was generated by Finkelstein reaction of enone **13** with sodium azide (2.0 equiv) and sodium iodide (2.0 equiv) in DMF (caution should be taken in handling large quantities of azides). Addition of an ether solution of enone **14** to a cooled (−78 °C) solution of the lithium anion of (trimethylsilyl)acetonitrile (1.2 equiv) was followed by transferring the reaction to a −78 °C solution of ethyl salicylate (2.0 equiv).^{21–23} After 30 min this solution was transferred to a solution of acetic acid (5 equiv) in ether at −78 °C and, following complete addition, warmed to 23 °C. After purification, the mixture of diastereomers was subjected to desilylation with cesium fluoride (2.0 equiv) in acetonitrile providing cyclohexanone **15** in 63% yield over two steps. A

major byproduct of this sequence arose from the Peterson olefination of cyclohexenone **14** by the lithium anion of (trimethylsilyl)acetonitrile. Unfortunately, the Staudinger/aza-Wittig reaction of cyclohexenone **15** failed to generate the desired imine **16**, although the corresponding Cbz protected amine of reduced cyclohexenone **15** could be isolated from the reaction providing evidence the Staudinger reaction had occurred.

A second, successful route provided the desired alkyne–nitrile on the multigram scale using related chemistry (Scheme 2). Equatorial delivery of ethynylmagnesium chloride into ketone **18** proceeded with a high degree of diastereoselectivity (>18:1) furnishing propargyl alcohol **19**. The assignment was

corroborated by analysis of the X-ray crystal structure of the corresponding diol **24**. Acylation of the tertiary alcohol using magnesium perchlorate (CAUTION!) in neat acetic anhydride at 23 °C provided the activated propargyl system **20**.²⁴ Copper-mediated amination using propargyl acetate **20** was possible with primary amines providing the desired secondary amines **21–23** in good yields and high diastereoselectivities (>20:1).²⁵ The success of the reaction was dependent on the careful removal of oxygen to prevent an otherwise rapid Glaser dimerization. Removal of the primary acetate and cyclization of the resulting amino alcohols with PPh₃/imidazole/carbon tetrachloride generated alkyne–nitriles **28–30**.^{26,27} Crystals (mp 138.2–138.5 °C) of alkyne nitrile **28** proved suitable for X-ray crystallography helping to further confirm the structural assignment.

With access to alkyne–nitrile **28** [2 + 2 + 2] cyclization reactions were investigated using 1,4-bis(trimethylsilyl)butadiyne (**31**) and CpCo(CO)₂ with or without illumination in different solvents heated to reflux (Scheme 3).^{28–32} The majority of reactions succeeded in generating 2-alkynyl pyridine **32** to some extent. After optimization we found that carrying out the reactions, following freeze–pump–thaw degassing (three cycles), in THF in a sealed tube heated in a 140 °C oil bath proved optimal, forming pyridylalkyne **32** in 78% yield along with 3% of the regioisomeric product pyridylalkyne **33** (loss of the TMS occurred following silica gel chromatography) (Scheme 3).³³ Attempts to achieve a tandem [2 + 2 + 2] + [2 + 2 + 2] cycloaddition sequence, assembling protected complanadine A in a single operation, only succeeded in generating pyridylalkyne **32**. Modifying the stoichiometry of alkyne–nitrile **28**, butadiyne, reaction temperature, and time only led to the formation of pyridylalkynes.

The regioselective formation of pyridylalkyne **32** was anticipated following from the studies of Saá and co-workers where they demonstrated that cobalt catalyzed [2 + 2 + 2] cycloadditions reaction of diynes with tethered alkyne–nitriles form 2-alkynyl pyridines in preference to 3-alkynyl pyridines.^{28,29} In addition to their experimental results computational studies support the formation of the 2-alkynyl metallacycle **38** in preference to the 3-alkynyl metallacycle **39** (Figure 4).

Other alkynes were successfully employed in the [2 + 2 + 2] cycloaddition reaction providing access to N-benzylated lycodine derivatives (Figure 5) as well as the parent natural product lycodine (**60**) (Scheme 4), a natural product that has been previously synthesized.^{34–36} While most substrates demonstrated high levels of regioselectivity we found that the positioning of the alkyne on the pyridine was key as seen in the case of products **49** and **50** formed in a nonselective reaction while the reaction of alkyne–nitrile **28** and 2-(trimethylsilyl)ethynylpyridine gave rise to only the 2,2'-bipyridyl isomer **53**. For the silicon-bearing alkynes the selectivities were determined following desilylation of the pyridine products.

The inability of pyridylalkyne **32** to undergo a second [2 + 2 + 2] cycloaddition was thought to be due to the steric impediment caused by the aryltrimethylsilyl group adjacent to the alkyne (Figure 6). Removal of both trimethylsilyl groups with TBAF in THF generated alkyne **63** which was silylated using LDA and TMSCl to generate silylalkyne **64**. In addition, a series of other pyridylalkynes **65–70** were similarly prepared via deprotonation of **63** with LDA and reaction of the resulting acetylide anion with the appropriate electrophile (Scheme 5).

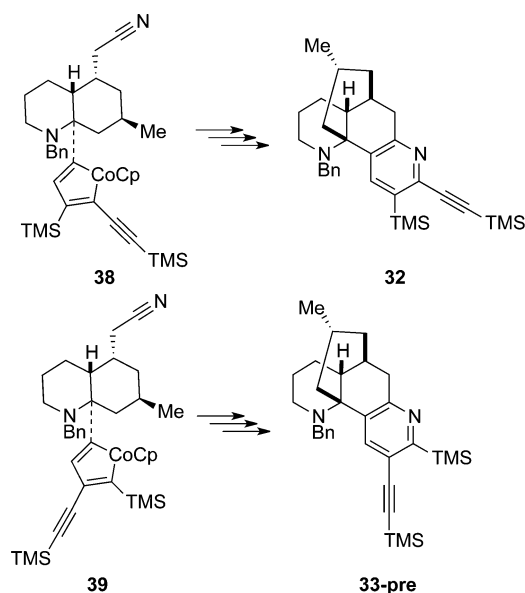


Figure 4. Isomeric metallacycles leading to the formation of the major product **32** and minor product **33-pre** for the cobalt-mediated [2 + 2 + 2] cycloaddition.

These disubstituted alkynes allowed the examination of their propensity to undergo the second [2 + 2 + 2] cycloaddition.

Of the disubstituted alkynes prepared only the silicon bearing alkynes **64**, **65**, **67**, and **70** proved to be competent partners for [2 + 2 + 2] cycloadditions with alkyne–nitrile **28**. Alkyne **64** proved the most effective in generating the corresponding bipyridyl compound. However, in all these reactions the undesired 2,2'-bipyridyl linkage was formed exclusively (as seen in bipyridyls **71** and **72**) (Scheme 6). Other cobalt, nickel, and ruthenium catalysts similarly failed to generate the desired isomer. We propose the selective formation of the metallacycle **75** is responsible for providing the symmetric compound (Figure 7). This selectivity is similar to the reaction generating the lycodine derivative **53** in Figure 5. Verification of the incorrect bipyridyl linkage was readily accomplished by NMR following desilylation, providing the dimer **73** which possessed a simplified ¹H NMR spectrum (Scheme 6). Compound **73** was debenzylated with palladium on carbon and hydrogen to generate the constitutional isomer of complanadine A, bipyridyl **74**.

As the first [2 + 2 + 2] cycloaddition provided a 25:1 ratio the minor 3-alkynylpyridine **33** could be isolated, albeit in small amounts. Under the same conditions used for the formation of the 2,2'-bipyridyl isomer **71**, (Scheme 6) pyridylalkyne **33** cyclized to provide the desired 2,3'-bipyridyl linkage within **77** in 28% yield with ≥20:1 regioselectivity (Scheme 7). Following desilylation and debenzylation complanadine A (**1**) was formed matching the spectroscopic data of the isolated natural product following addition of *d*₄-methanolic DCl solution.³⁷

As the unoptimized reaction proved highly selective for the formation 2,3'-bipyridyl core we required a scalable route to access pyridylalkyne **33**. The diynes investigated consistently provided 2-alkynyl pyridines in the [2 + 2 + 2] cycloaddition reaction therefore a variety of surrogates for diynes were investigated.³⁸ The majority of alkynes examined failed to react with alkyne–nitrile **28** (see the Supporting Information), however, a subset reacted to provide substituted pyridines. The

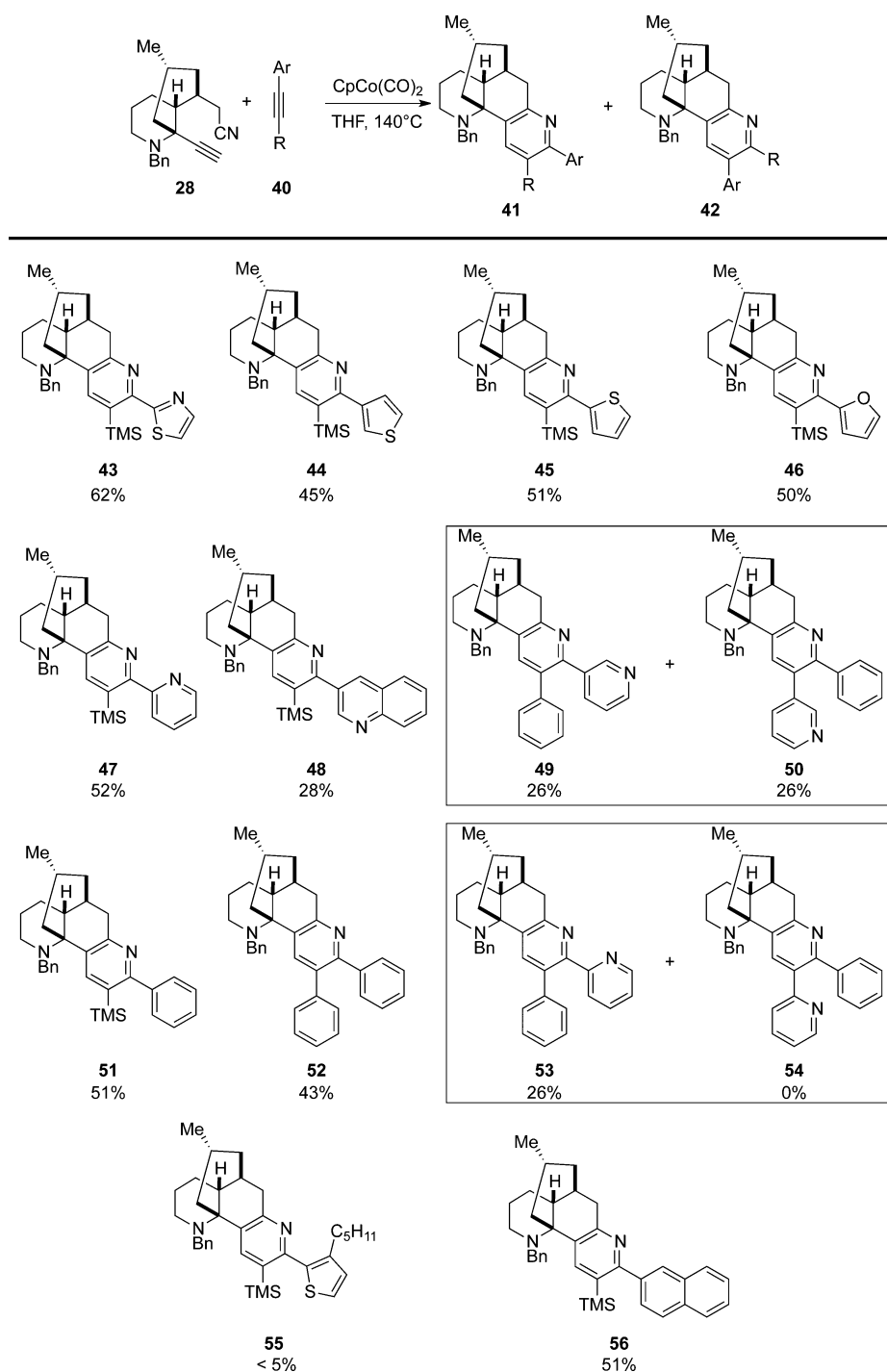
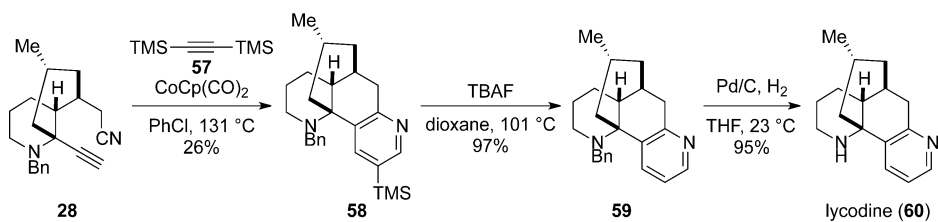


Figure 5. Regioselective formation of N-benzylated lycodine derivatives.

Scheme 4. Synthesis of Lycodine (60)



silyl ether–alkyne **79** reacted to provide the desired regioisomer **81** as the major product (Scheme 8).

This product was converted to the desired pyridylalkyne **33** in four steps (Scheme 8). Cleavage of the TBS ether of pyridine

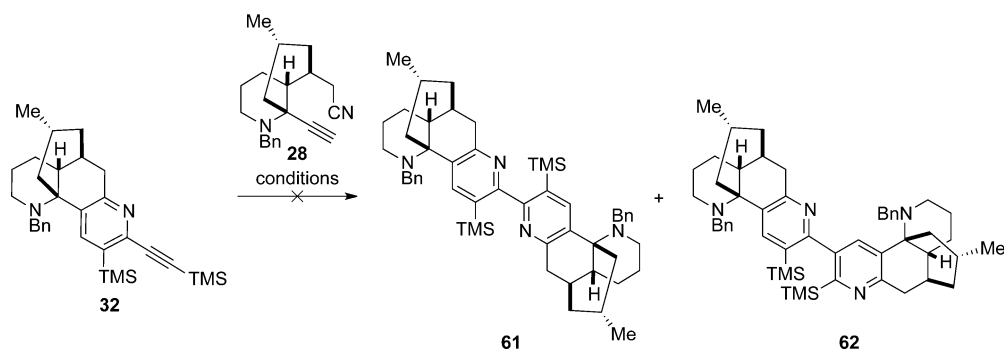
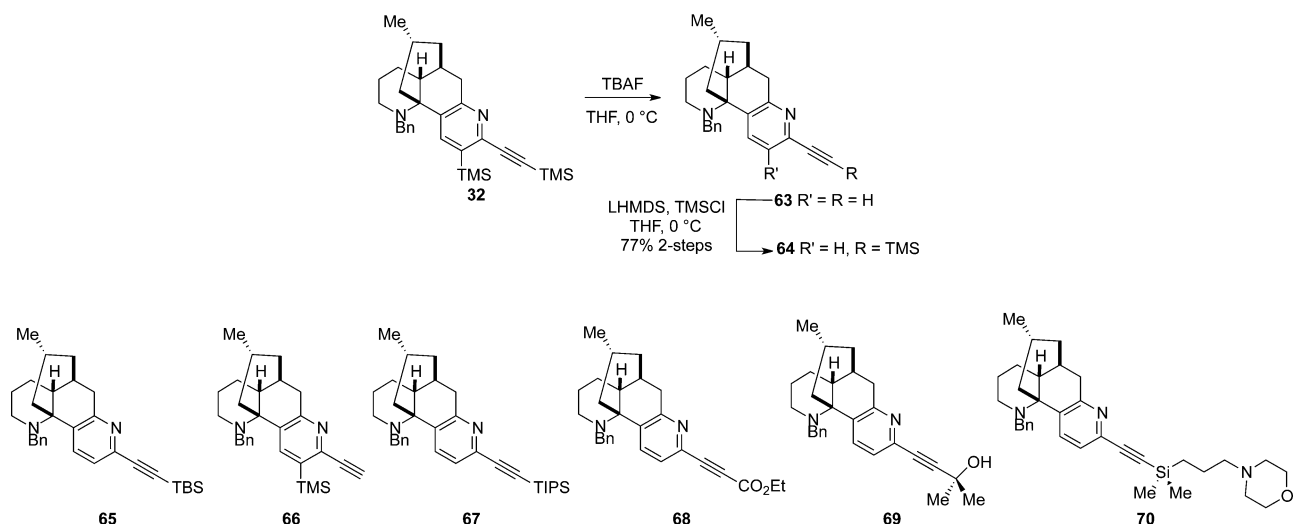
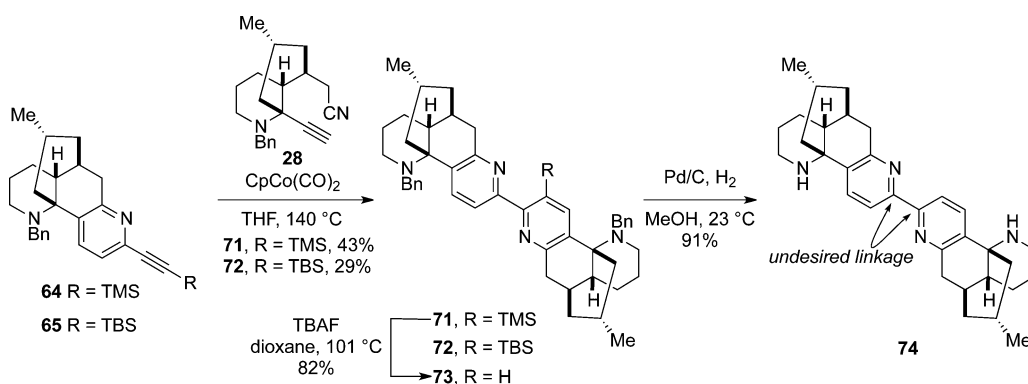


Figure 6. Unsuccessful $[2 + 2 + 2]$ cycloadditions using pyridylalkyne 32.

Scheme 5. Alkynes Prepared for the Second $[2 + 2 + 2]$ Cycloaddition



Scheme 6. Formation of the Symmetric 2,2'-Bipyridyl Isomer 74 of Complanadine A



81 with TBAF and oxidation of the resulting primary alcohol 82 with Dess–Martin periodinane provided aldehyde 83.³⁹ Using the Ohira–Bestmann reagent (84), the aldehyde 83 was converted to the corresponding alkyne 85 in 86% yield.⁴⁰ The alkyne 85 was silylated to generate pyridyl alkyne 33. Cycloaddition reactions were examined, and unfortunately, the best conditions discovered were those initially employed, providing a maximal yield of 77 in 28% yield.

Following the first-generation synthesis of complanadine A, through two low-yielding $[2 + 2 + 2]$ cycloaddition reactions a more efficient sequence was investigated. As the first cycloaddition reaction proved successful generating pyridylalkyne 33 in good yield and high regioselectivity, attempts were made to

control the second $[2 + 2 + 2]$ cycloaddition reaction. Conversion of the benzyl group on nitrogen of alkyne–nitrile 28 to a coordinating functionality was investigated. The removal of the benzyl group of 28 proved challenging; however, the *p*-methoxybenzyl and 2,4-dimethoxybenzyl groups could be introduced in a related manner (Scheme 2). Removal of the methoxy bearing groups from 29 or 30 with CAN provided the secondary amine 86 allowing a variety of groups to be installed providing new substrates such as formamide 87 (Scheme 9). The reactivity of these compounds in the $[2 + 2 + 2]$ cycloaddition reaction was examined (Figure 8). The conversion to coordinating groups provided the first evidence the desired product could be formed starting from the

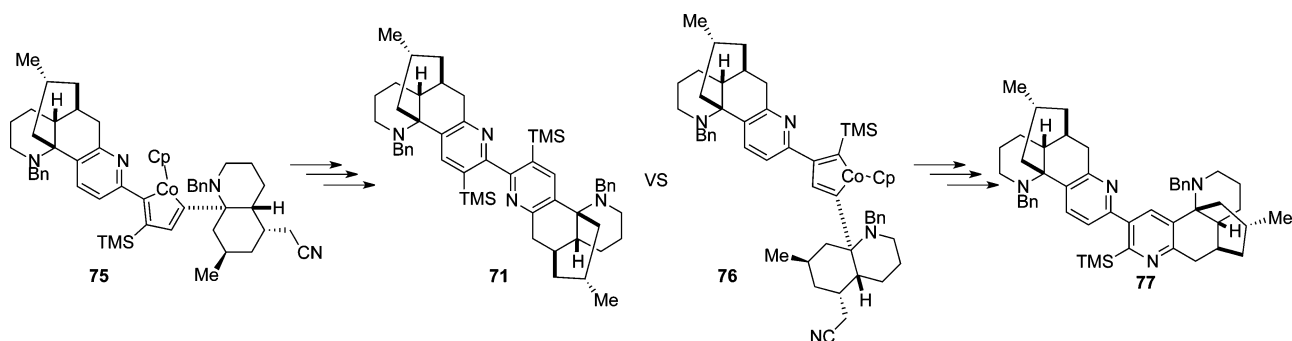
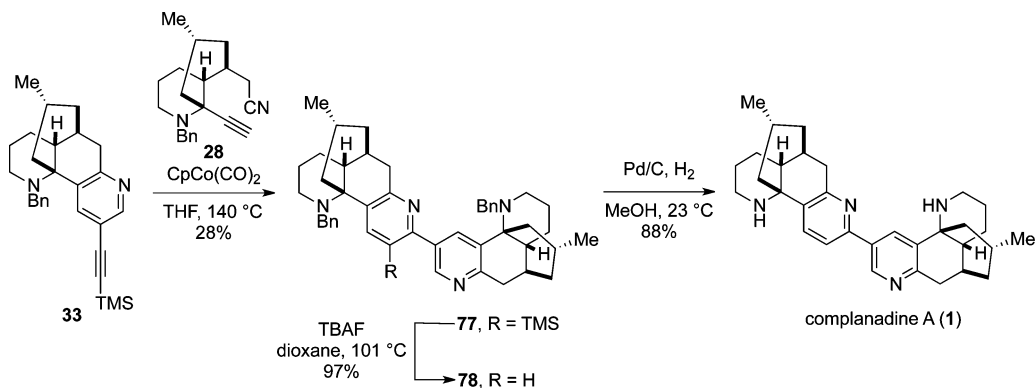
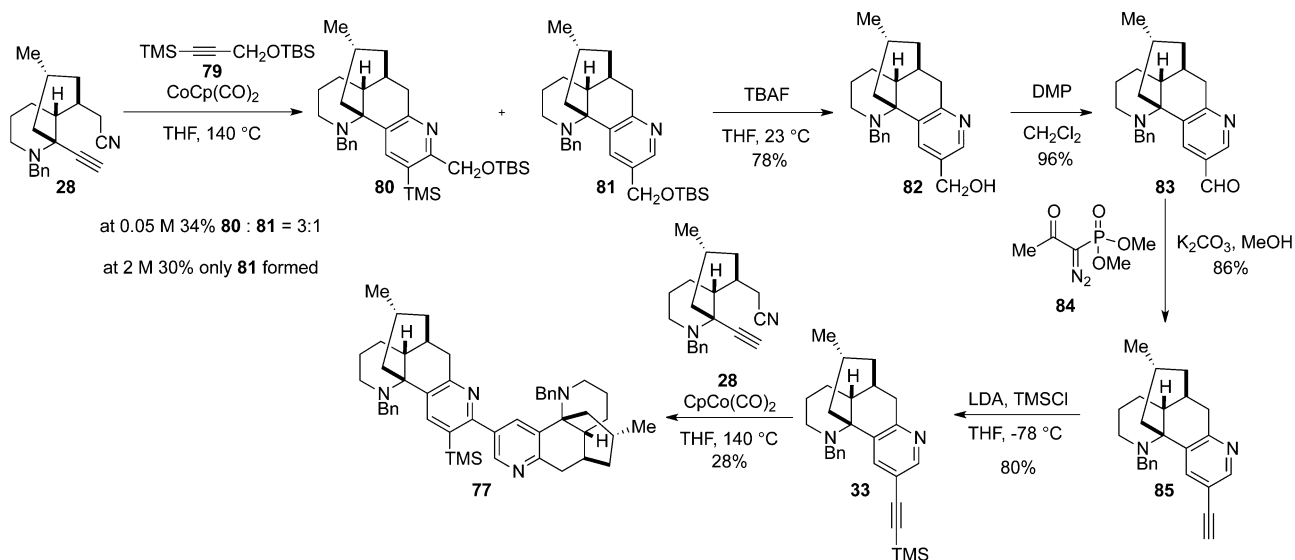


Figure 7. Proposed metallacycles 75 and 76.

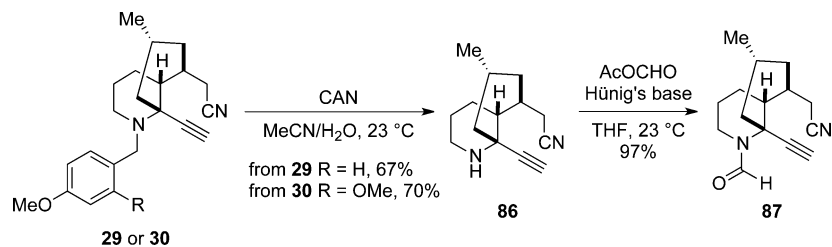
Scheme 7. Regioselective Cobalt-Mediated [2 + 2 + 2] Cycloaddition of Pyridylalkyne 33 and Alkyne–Nitrile 28 Providing, after Deprotection, Complanadine A (1)



Scheme 8. Alternative Synthesis of Pyridylalkyne 33 and Complanadine A in Protected Form 77



Scheme 9. Conversion of Alkyne–Nitriles 29 and 30 to Formamide 87



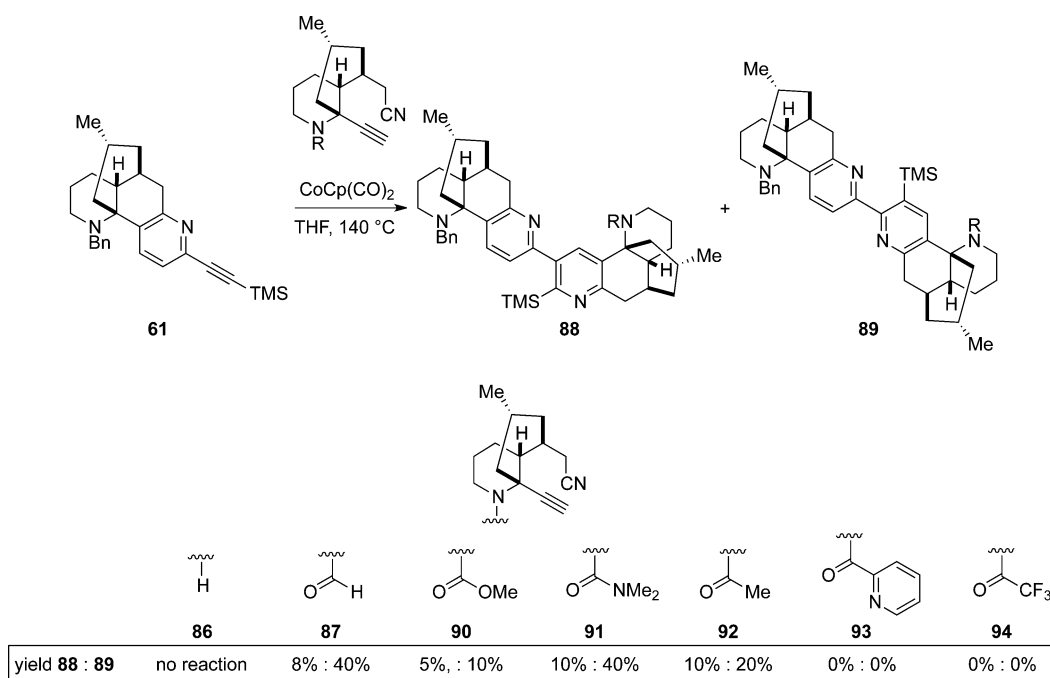


Figure 8. Effects of nitrogen substitution on the regioselectivity of the $[2 + 2 + 2]$ cycloaddition.

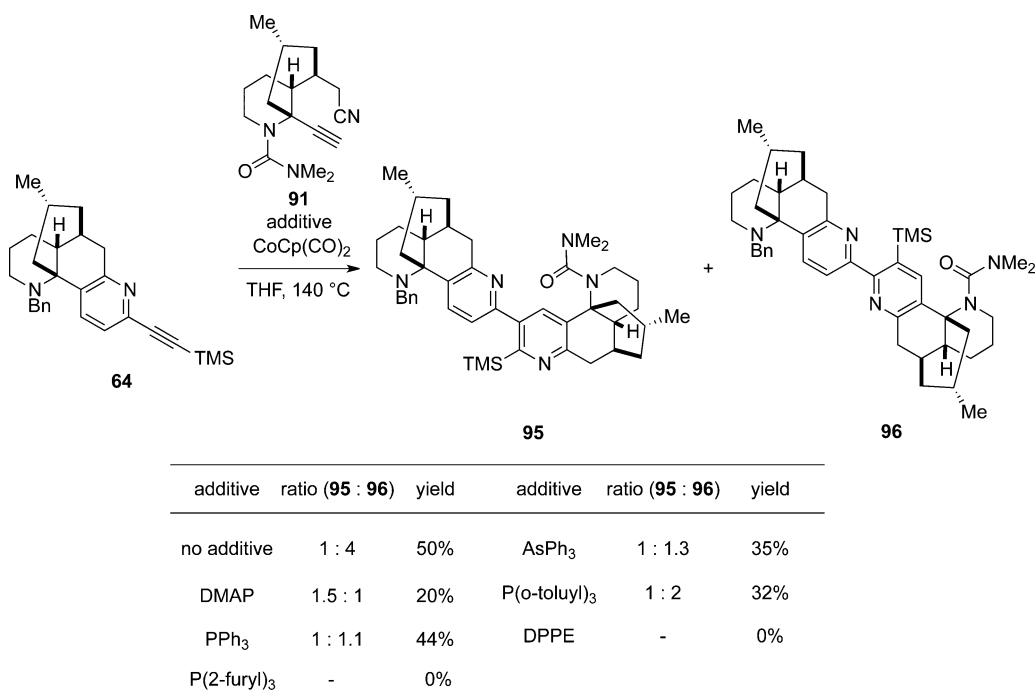


Figure 9. Effect of Lewis basic additives on the regioselectivity of the $[2 + 2 + 2]$ cycloaddition.

pyridylalkyne **61**. The two substrates that showed the best reactivity and selectivity were the formyl and urea derivatives **87** and **91**.

Similar to the goal of adding a coordinating group efforts to reduce the influence of the pyridyl group on the cyclization was achieved by the addition of a variety of Lewis-basic additives and, while some completely suppressed the reaction, it was found that the addition of NMO, DMAP, triphenylphosphine, triphenylarsine, and tri(*o*-tolyl)phosphine improved the selectivity (Figure 9). The use of triphenylphosphine provided the right balance of reactivity and control, providing a nearly

nonselective reaction with a 1:1.1 ratio of products in 44% yield. The use of 1,2-bis(diphenylphosphino)ethane completely inhibited the reaction while the addition of trifurylphosphine led to rapid loss of starting material with no evidence for the formation of either bipyridyl product.

Lastly, a screen of solvents (Figure 10), temperatures, and concentrations (Figure 11) revealed that the use of dioxane (in a sealed tube) at 140 °C with the addition of triphenylphosphine run at 5 mM prove optimal, providing the desired 2,3'-bipyridyl as the major product **97** in 42% yield with 14% of the undesired isomer **98** formed (Scheme 10).

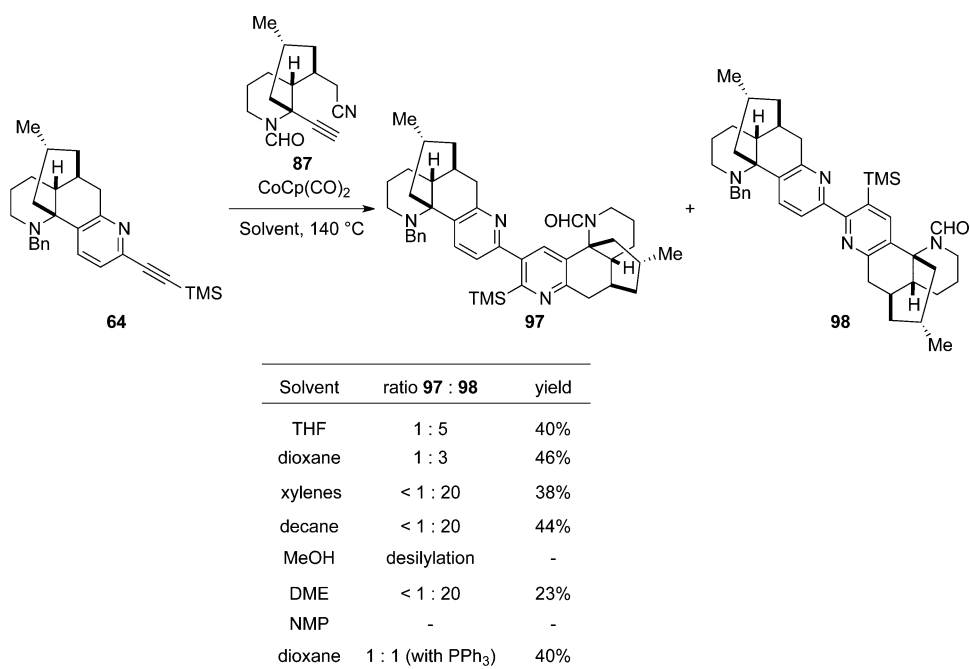


Figure 10. Solvent effects on the on the regioselectivity and yields of the [2 + 2 + 2] cycloaddition.

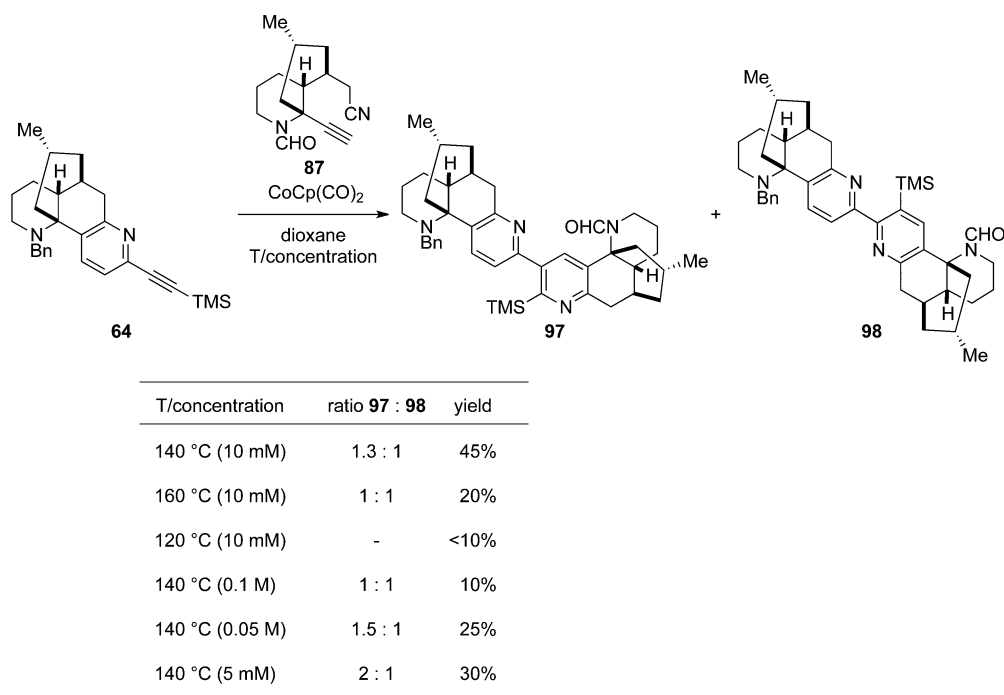


Figure 11. Temperature and concentration effects on the regioselectivity and yields of the [2 + 2 + 2] cycloaddition.

Completion of the synthesis was achieved by first removal of the pyridyl-TMS with TBAF in dioxane heated to reflux to generate bipyridyl **100**. Hydrogenolysis of the benzyl group with palladium on carbon and hydrogen followed by cleavage of the formyl group using hydrochloric acid in methanol provided complanadine A (Scheme 11).

CONCLUSION

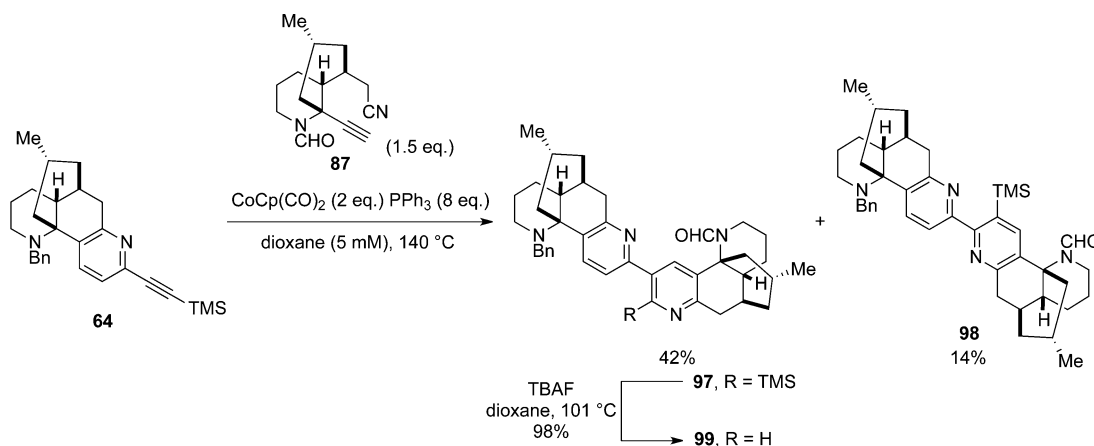
Two routes to complanadine A have been developed utilizing cobalt-mediated [2 + 2 + 2] cycloaddition reactions. In addition, related lycodine derivatives can be accessed through

related cycloadditions using disubstituted alkynes. The controlled formation of the 2,3'-bipyridyl core was achieved through either modifying the partners in the reaction sequence or the use of Lewis-basic additives. With access to complanadine A studies of the compound's effects upon neuronal growth are underway.

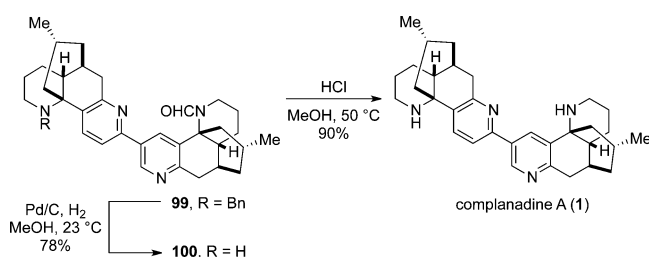
EXPERIMENTAL SECTION

General Information. In addition to characterization data the structures of reaction intermediates (**int-1** to **int-19**) can be found in the Supporting Information.

Scheme 10. Optimized [2 + 2 + 2] Cycloaddition Conditions



Scheme 11. Completion of the Synthesis of Complandine A



(5*R*)-2-(3-Chloropropyl)-5-methyl-2-(phenylthio)cyclohexanone (**int-1**, Precursor for **13**). To a solution of thioether **12** (5.0 g, 22.7 mmol, 1.0 equiv) in DMF (120 mL) at 0 °C was added solid NaH (1.04 g, 60% oil dispersion, 26.0 mmol, 1.2 equiv) in portions over 5 min with extensive gas evolution. After 60 min, neat 1-chloro-3-iodopropane (5.10 g, 25.0 mmol, 1.1 equiv) was added dropwise over 10 min, and the cooling bath was removed and the solution was stirred for 1 h. The reaction mixture was diluted with aqueous saturated NH₄Cl solution (500 mL) and EtOAc (250 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (4 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated. The crude material was purified by silica gel chromatography (5/1 → 2/1 hexanes/Et₂O) to afford **int-1** (3.54 g, 53%) as a yellow oil: *R_f* = 0.45 (silica gel, hexanes/EtOAc = 5/1); ¹H NMR (400 MHz, CDCl₃) **int-1**: *major*: *int-1* *minor* = 0.77:0.23 mixture of diastereomers) δ 0.96 (d, *J* = 6.4 Hz, 3H**), 1.08 (d, *J* = 6.4 Hz, 3H*), 1.42–1.72 (m, 3H), 1.72–2.02 (m, 4H), 2.04–2.15 (m, 2H), 2.28–2.34 (m, 1H), 3.12 (t, *J* = 13.2 Hz, 1H*), 3.30 (dd, *J* = 5.2 and 14.0 Hz, 1H**), 3.44–3.54 (m, 2H), 7.27–7.50 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 19.6, 21.9, 22.2, 27.0, 27.1, 27.8, 29.6, 31.86, 31.91, 32.2, 33.5, 34.5, 35.7, 45.0, 45.1, 45.8, 59.7, 61.4, 128.86, 128.95, 129.0, 129.3, 129.5, 135.3, 136.0, 136.5, 207.2, 207.9; IR *ν* 2955, 2927, 1701, 1438 cm⁻¹; HRMS calcd for C₁₆H₂₁ClOS⁺ [*M*⁺] 296.1002, found 296.1005. H* for minor isomer; H** for major isomer.

(*R*)-2-(3-Chloropropyl)-5-methylcyclohex-2-enone (**13**). To a solution of ketone **int-1** (3.67 g, 12.4 mmol, 1.0 equiv) in CH₂Cl₂ (150 mL) at −78 °C was added a solution of purified *m*-CPBA (2.24 g, 13.0 mmol, 1.1 equiv) in CH₂Cl₂ (50 mL) over 1 h. The mixture was warmed to 23 °C over one hour then stirred 10 h where upon the solution became homogeneous. The reaction was diluted with aqueous NaHSO₃ solution (10% w/w, 50 mL). The mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by silica gel chromatography (10/1 → 2/1 hexanes/Et₂O) to afford **13** as yellow oil (1.9 g, 82%). *R_f* = 0.50 (silica gel, hexanes/EtOAc = 5/1); ¹H NMR (400 MHz, CDCl₃) δ 1.03 (d, *J* = 6.0 Hz, 3H), 1.82–1.89 (m, 2H), 1.99–2.09 (m, 2H), 2.12–2.21 (m,

1H), 2.31 (t, *J* = 7.6 Hz, 2H), 2.37–2.50 (m, 2H), 3.48 (t, *J* = 6.4 Hz, 2H), 6.72–6.74 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.1, 26.9, 30.6, 31.2, 34.3, 44.5, 46.5, 137.8, 145.5, 199.4; IR (neat) *ν* 2957, 1675, 1384 cm⁻¹; HRMS calcd for C₁₀H₁₆ClO⁺ [*M* + H⁺] 187.0890, found 187.0890.

(*R*)-2-(3-Azidopropyl)-5-methylcyclohex-2-enone (**14**). To a solution of enone **13** (231 mg, 1.24 mmol, 1.0 equiv) in DMF (10 mL) at 23 °C solid NaI (403 mg, 2.7 mmol, 2.2 equiv) and NaN₃ (159 mg, 2.5 mmol, 2.0 equiv) were added. The reaction flask was immersed into 65 °C oil bath and stirred for 24 h. The reaction was diluted with aqueous saturated NH₄Cl solution (20 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by silica gel chromatography (10/1 → 2/1 hexanes/EtOAc) to afford **14** as pale yellow oil (171 mg, 72%). *R_f* = 0.50 (silica gel, hexanes/EtOAc = 5/1); ¹H NMR (400 MHz, CDCl₃) δ 1.05 (d, *J* = 6.0 Hz, 3H), 1.66–2.00 (m, 2H), 2.01–2.27 (m, 5H), 2.38–2.45 (m, 1H), 2.45–2.51 (m, 1H), 3.25 (t, *J* = 6.8 Hz, 2H), 6.70–6.73 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.2, 26.9, 27.8, 30.6, 34.3, 46.6, 51.0, 138.2, 145.3, 199.5; IR (neat) *ν* 2956, 2097, 1674 cm⁻¹; HRMS calcd for C₁₀H₁₆N₃O⁺ [*M* + H⁺] 194.1293, found 194.1291.

2-((1*S*,2*R*,5*R*)-2-(3-Azidopropyl)-5-methyl-3-oxocyclohexyl)-acetonitrile (**15**). To a solution of the diisopropylamine (95 μL, 0.67 mmol, 2.0 equiv) in Et₂O (2 mL) was added *n*-BuLi solution (0.35 mL, 2.0 M, 0.67 mmol, 2.0 equiv) at −78 °C. After 5 min, neat trimethylsilylacetonitrile (92 μL, 0.67 mmol, 2.0 equiv) was added. After 30 min, the solution was transferred via cannula to a second flask containing enone **14** (65 mg, 0.34 mmol, 1.0 equiv) in Et₂O (5 mL) cooled to −78 °C. After 25 min, the resulting yellow solution was transferred via cannula to a third flask containing ethyl salicylate (0.15 mL, 1.0 mmol, 3.0 equiv) in Et₂O (2 mL) cooled to −78 °C. The reaction was allowed to slowly warm to 23 °C over 1 h. The lithium phenoxide was quenched by the addition of acetic acid (60 μL, 1.0 mmol, 3 equiv). The reaction was filtered through a pad of Celite. The solution was washed with aqueous saturated NaHCO₃ solution (10 mL) and brine (5 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude material was purified by silica gel chromatography (20/1 → 1/1 hexanes/Et₂O) to afford yellow oil (42 mg, 72%) as a mixture of 4 diastereomers that was used in the next reaction (below). To a solution of the above diastereomers (42 mg, 0.14 mmol, 1.0 equiv) in MeCN (3 mL) solid CsF (5.0 mg, 0.030 mmol, 0.24 equiv) was added. The resulting mixture was stirred at 23 °C for 6 h then diluted with aqueous saturated NH₄Cl solution (5 mL) and extracted with EtOAc (3 × 5 mL). The organic extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The crude material was purified by silica gel chromatography (10/1 → 1/1 hexanes/EtOAc) to afford ketone **15** (27.8 mg, 87%) as a light yellow oil: *R_f* = 0.65 (silica gel, hexanes/EtOAc = 2/1); ¹H NMR (400 MHz, CDCl₃) δ 1.08 (d, *J* = 6.4 Hz,

3H), 1.16–1.25 (m, 1H), 1.40–1.51 (m, 1H), 1.56–1.62 (m, 2H), 1.63–1.84 (m, 2H), 1.96–2.17 (m, 3H), 2.31–2.44 (m, 2H), 2.56–2.61 (m, 2H), 3.24–3.35 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.9, 22.0, 23.7, 27.0, 30.0, 37.3, 38.3, 50.1, 51.3, 52.2, 118.2, 210.0; IR ν 2954, 2098, 1709 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{N}_4\text{ONa}^+ [\text{M} + \text{Na}^+]$ 257.1378, found 257.1373.

3-((4R)-4-Methyl-2-oxo-1-(phenylthio)cyclohexyl)propyl Acetate (int-2, Precursor for 17). To a solution of thioether **12** (30.0 g, 136 mmol, 1.0 equiv) in DMF (1.25 L) at 0 °C solid NaH (5.99 g, 60% oil dispersion, 150 mmol, 1.1 equiv) was added portionwise over 5 min with extensive gas evolution. After 60 min, the iodo ester (37.3 g, 163 mmol, 1.2 equiv) was added neat, dropwise over 10 min, then the cooling bath was removed and the resulting solution was stirred at 23 °C for 1 h. The reaction was diluted with aqueous saturated NH_4Cl solution (2 L) and EtOAc (1 L). The organic phase was collected, and the aqueous phase was extracted with EtOAc (4 \times 500 mL). The combined organic extracts were washed with brine (500 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (5/1 \rightarrow 2/1 hexanes/Et $_2$ O) to afford a diastereomeric mixture of ketones **int-2** as a yellow viscous oil (27.3 g, 63%): R_f = 0.31 (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3 , 7/3 mixture of diastereomers) δ 0.88 (t, J = 6.8 Hz, 0.7 H), 0.96 (d, J = 6.8 Hz, 2.1 H), 1.08 (d, J = 6.0 Hz, 0.9 H), 1.22–1.30 (m, 0.3 H), 1.46–1.94 (m, 5 H), 1.96–2.36 (m, 7 H), 3.14 (t, J = 13.2 Hz, 0.3 H), 3.35 (dd, J = 6.0 and 14.4 Hz, 0.7 H), 3.98–4.04 (m, 2H), 7.26–7.37 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.3, 20.7, 22.0, 22.5, 22.7, 27.5, 29.5, 30.2, 30.6, 31.6, 33.0, 34.3, 35.4, 44.7, 45.6, 59.6, 60.8, 61.2, 64.2, 64.3, 128.6, 128.7, 129.1, 129.2, 129.9, 130.1, 135.8, 136.3, 170.8, 206.9, 207.7; IR ν 1739, 1700, 1043 cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{24}\text{O}_3\text{SNa}^+ [\text{M} + \text{Na}^+]$ 343.13438, found 343.13447.

(R)-3-(4-Methyl-6-oxocyclohex-1-en-1-yl)propyl Acetate (17). The diastereomeric mixture of ketones **int-2** (27.0 g, 84 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 L) was cooled to –78 °C, and a solution of purified *m*-CPBA (15.3 g, 88 mmol, 1.05 equiv) in CH_2Cl_2 (600 mL) was added over 1 h. The cooling bath was removed, and the solution was stirred for 10 h at 23 °C whereupon the solution became homogeneous. The reaction was then diluted with aqueous NaHSO_3 (10% w/w, 200 mL). The mixture was extracted with EtOAc (3 \times 400 mL). The organic extracts were washed with brine (200 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude product was purified by silica gel chromatography (10/1 \rightarrow 2/1 hexanes/Et $_2$ O) to afford enone **17** as yellow oil (13.6 g, 77%): R_f = 0.39 (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 1.05 (d, J = 6.4 Hz, 3H), 1.58–1.77 (m, 2H), 2.04–2.09 (m, 4H), 2.09–2.13 (m, 1H), 2.13–2.19 (m, 1H), 2.25 (t, J = 8.0 Hz, 2H), 2.41 (dt, J = 5.0 and 18.0 Hz, 1H), 2.47–2.52 (m, 1H), 4.04 (t, J = 6.4 Hz, 2H), 6.68–6.70 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.0, 21.2, 26.0, 27.3, 30.6, 34.3, 46.6, 64.0, 138.3, 144.9, 171.2, 199.5; IR (neat) ν 1734, 1717 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{O}_3\text{Na}^+ [\text{M} + \text{Na}^+]$ 233.11536, found 233.11490.

3-((1R,2S,4R)-2-(Cyanomethyl)-4-methyl-6-oxocyclohexyl)propyl Acetate (18). To a solution of trimethylsilyl acetonitrile (0.28 mL, 2.1 mmol, 1.3 equiv) in Et $_2$ O (30 mL) at –78 °C was added a solution of *n*-butyllithium (1.8 M Hexanes, 1.1 mL, 2.0 mmol, 1.2 equiv) over 1 min. After being stirred for 40 min at –78 °C, the pale yellow solution was transferred over 3 min via cannula to a stirred solution of the enone **17** (350 mg, 1.7 mmol, 1.0 equiv) in Et $_2$ O (30 mL) at –78 °C. After 30 min, the bright yellow solution was added over 3 min via cannula to a stirred solution of ethyl salicylate (0.97 mL, 6.6 mmol, 4.0 equiv) at –78 °C in Et $_2$ O (30 mL). After 5 min, the cooling bath was removed, the reaction was allowed to warm to 23 °C over 20 min, and acetic acid (0.10 mL, 1.7 mmol, 1.1 equiv) was added in one portion. The solution was washed with aqueous saturated sodium bicarbonate solution (50 mL). The organic extract was washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (20/1 \rightarrow 5/1 hexanes/EtOAc) to afford a mixture of diastereomers as light yellow oil (300 mg, 56%). To a solution of the above diastereomers (4.50 g, 13.9 mmol, 1.0 equiv) in MeCN (110 mL) at 23 °C was added solid CsF (0.20 g, 1.3 mmol, 0.10 equiv). The resulting mixture was stirred at 23 °C for 6 h.

The reaction was diluted with aqueous saturated NH_4Cl solution (100 mL) and extracted with EtOAc (2 \times 200 mL). The organic extracts were washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (10/1 \rightarrow 1/1 hexanes/Et $_2$ O) to afford ketone **18** (2.80 g, 80%) as yellow oil. The two-step yield is 45%: R_f = 0.45 (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 1.07 (d, J = 6.0 Hz, 3H), 1.15–1.23 (m, 1H), 1.48–1.84 (m, 4H), 1.95–2.17 (m, 7H), 2.31–2.44 (m, 2H), 2.56–2.63 (m, 2H), 3.99–4.09 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.8, 20.9, 22.0, 22.8, 26.5, 30.0, 37.2, 38.1, 50.1, 52.0, 64.0, 118.2, 171.1, 210.1; IR 1735, 1710, 1048 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_3\text{Na}^+ [\text{M} + \text{Na}^+]$ 274.14191, found 274.14169.

3-((1R,2S,4R,6S)-6-(Cyanomethyl)-2-ethynyl-2-hydroxy-4-methylcyclohexyl)propyl Acetate (19). To a solution of ketone **18** (11.5 g, 45.8 mmol, 1.0 equiv) in THF (350 mL) at 23 °C was added dropwise a solution of the ethynylmagnesium chloride (114 mL, 0.60 M in toluene/THF, 69 mmol, 1.5 equiv) over 5 min. After 30 min, the resulting alkoxide was quenched by the addition of aqueous saturated NH_4Cl solution (100 mL) and the mixture was extracted with EtOAc (3 \times 200 mL). The organic extracts were washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude alcohol was purified by silica gel chromatography (5/1 \rightarrow 2/1 hexanes/EtOAc) to afford alcohol **19** (12.3 g, 97%) as a yellow oil. **19**: R_f = 0.41 (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.95 (d, J = 6.8 Hz, 3H), 1.18–1.25 (m, 1H), 1.41–1.66 (m, 3H), 1.70–1.79 (m, 2H), 1.83–1.93 (m, 1H), 1.93–2.04 (m, 2H), 2.06 (s, 3H), 2.20–2.26 (m, 1H), 2.45–2.51 (m, 2H), 2.80 (dd, J = 8.8 and 17.6 Hz, 1H), 2.92 (dd, J = 0.4 and 14.8 Hz, 1H), 4.04–4.16 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.9, 21.0, 21.4, 21.5, 23.2, 25.9, 32.2, 37.6, 45.5, 49.3, 64.2, 70.9, 72.2, 87.5, 120.4, 171.1; IR ν 3462, 1738, 1457, 1024 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Na}^+ [\text{M} + \text{Na}^+]$ 300.15724, found 300.15724.

3-((1R,2S,4R,6S)-2-Acetoxy-6-(cyanomethyl)-2-ethynyl-4-methylcyclohexyl)propyl Acetate (20). To a solution of alcohol **19** (9.0 g, 32 mmol, 1.0 equiv) in acetic anhydride (27.6 mL, 92 mmol, 2.8 equiv) at 23 °C was added solid magnesium perchlorate (0.70 g, 3.1 mmol, 0.1 equiv) in one portion. After 30 min, the mixture was diluted with aqueous saturated NaHCO_3 solution (200 mL), and solid NaHCO_3 was added to adjust the pH to 8. The mixture was extracted with EtOAc (3 \times 100 mL). The organic extracts were washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude acetate was purified by silica gel chromatography (5/1 \rightarrow 2/1 hexanes/EtOAc) to yield diacetate **20** (10.1 g, 97%) as a yellow oil: R_f = 0.45 (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.94 (d, J = 6.4 Hz, 3H), 1.24–1.33 (m, 2H), 1.44–1.64 (m, 4H), 1.69–1.78 (m, 2H), 2.04 (s, 3H), 2.06 (s, 3H), 2.08–2.14 (m, 2H), 2.31–2.34 (m, 1H), 2.52–2.54 (m, 1H), 2.59 (s, 1H), 2.97 (td, J = 2.8 and 14.8 Hz, 1H), 4.05–4.16 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.0, 21.0, 21.3, 21.6, 22.0, 23.0, 25.9, 32.1, 37.3, 43.1, 46.8, 64.0, 74.5, 77.5, 82.7, 119.8, 168.2, 171.1; IR ν 1737, 1727 cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_4\text{Na}^+ [\text{M} + \text{Na}^+]$ 342.16813, found 342.16774.

General Procedure for the $\text{Cu}(\text{OAc})_2$ -Catalyzed Amine Substitution Reaction. A flask containing neat benzylamine and the diacetate substrate was evacuated and backfilled with N_2 three times. By syringe THF was added, and the mixture was degassed via iterative freeze–pump–thaw sequences (three cycles). Solid CuCl was added in one portion with a back flow of N_2 . The reaction flask was placed in an 80 °C oil bath for 30 min, cooled to 23 °C, and diluted with pentane (100 mL). The mixture was filtered through silica gel (EtOAc/hexanes = 1/1) and concentrated to provide amine product.

3-((1R,2R,4R,6S)-2-(Benzylamino)-6-(cyanomethyl)-2-ethynyl-4-methylcyclohexyl)propyl Acetate (21). Following the general procedure, benzylamine (1.2 mL, 11 mmol, 3.5 equiv), diacetate **20** (1.0 g, 3.1 mmol, 1 equiv), THF (24 mL), and CuCl (105 mg, 1.1 mmol, 0.34 equiv) provided amine **21** (1.05 g, 92%) as yellow oil: R_f = 0.35 (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 1.01 (d, J = 6.4 Hz, 3H), 1.10 (t, J = 12.0 Hz, 1H), 1.20–1.27 (m, 1H), 1.43–1.65 (m, 4H), 1.72–1.91 (m, 2H), 2.01 (s, 3H), 2.02–2.06

(m, 1H), 2.22 (m, 1H), 2.30–2.35 (m, 1H), 2.46 (s, 1H), 2.56 (dd, $J = 2.4$ and 17.2 Hz, 1H), 3.00 (dd, $J = 12.4$ and 17.2 Hz, 1H), 3.80 (dd, $J = 12.0$ and 49.6 Hz, 2H), 4.04–4.07 (m, 2H), 7.25–7.33 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.5, 20.8, 21.8, 22.7, 23.8, 25.9, 33.0, 37.7, 46.2, 46.4, 47.0, 55.7, 64.0, 74.7, 86.6, 120.0, 127.0, 128.3, 128.4, 140.3, 171.0; IR ν 2953, 1737 cm^{-1} ; HRMS calcd for $\text{C}_{23}\text{H}_{31}\text{N}_2\text{O}_2^+ [\text{M} + \text{H}^+]$ 367.23855, found 367.23794.

3-((1*R*,2*R*,4*R*,6*S*)-6-(Cyanomethyl)-2-ethynyl-2-((4-methoxybenzyl)amino)-4-methylcyclohexyl)propyl Acetate (22). Following the general procedure, *p*-methoxybenzylamine (2.0 mL, 15.3 mmol, 4.1 equiv), acetate **20** (1.20 g, 3.8 mmol, 1.0 equiv), THF (28 mL), and CuCl (110 mg, 1.08 mmol, 0.29 equiv) provided **22** (1.20 g, 81%) as pale yellow oil: $[\alpha]_D^{24} -38.2$ (c 0.19, CH_2Cl_2); $R_f = 0.30$ (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 1.01 (d, $J = 6.4$ Hz, 3H), 1.09 (t, $J = 12.4$ Hz, 1H), 1.19–1.27 (m, 2H), 1.44–1.64 (m, 3H), 1.72–1.77 (m, 2H), 1.83–1.89 (m, 1H), 2.01–2.06 (m, 4H), 2.17–2.23 (m, 1H), 2.31–2.35 (m, 1H), 2.46 (s, 1H), 2.53–2.58 (m, 1H), 3.0 (dd, $J = 9.0$ and 16.8 Hz, 1H), 3.66 (d, $J = 11.2$ Hz, 1H), 3.78–3.81 (m, 4H), 4.03–4.07 (m, 2H), 6.84–6.88 (m, 2H), 7.23–7.25 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.5, 20.9, 21.9, 22.8, 23.8, 26.0, 33.0, 37.7, 46.2, 46.5, 55.3, 55.7, 64.1, 74.7, 86.8, 113.9, 120.1, 129.6, 132.4, 158.8, 171.1; IR ν 3287, 1735 cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{33}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}^+]$ 397.24912, found 397.24867.

3-((1*R*,2*R*,4*R*,6*S*)-6-(Cyanomethyl)-2-((2,4-dimethoxybenzyl)amino)-2-ethynyl-4-methylcyclohexyl)propyl Acetate (23). Following the general procedure, 3,4-dimethoxybenzylamine (0.22 mL, 1.5 mmol, 2.5 equiv), diacetate **20** (185 mg, 0.58 mmol, 1.0 equiv), THF (6 mL), CuCl (25 mg, 0.25 mmol, 0.44 equiv) provided amine **23** (190 mg, 77%) as a pale yellow oil: $R_f = 0.30$ (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 1.01 (d, $J = 6.8$ Hz, 3H), 1.11 (t, $J = 12.4$ Hz, 1H), 1.18–1.25 (m, 1H), 1.43–1.67 (m, 3H), 1.68–1.79 (m, 4H), 1.83–1.93 (m, 1H), 2.01–2.07 (m, 4H), 2.22 (dt, $J = 2.8$ and 12.8 Hz, 1H), 2.30–2.33 (m, 1H), 2.44 (s, 1H), 2.57 (dd, $J = 2.8$ and 17.2 Hz, 1H), 3.01 (dd, $J = 12.0$ and 17.2 Hz, 1H), 3.61 (d, $J = 12.0$ Hz, 1H), 3.79 (s, 3H), 3.81–3.84 (m, 4H), 4.05–4.08 (m, 2H), 6.42–6.47 (m, 2H), 7.14–7.17 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.5, 20.9, 21.9, 22.7, 23.8, 25.9, 33.1, 37.8, 42.0, 46.0, 46.2, 55.3, 55.4, 55.5, 64.3, 74.7, 86.7, 98.6, 104.1, 120.2, 120.7, 130.4, 158.5, 160.1, 171.1; IR ν 3279, 2953, 2919, 1735 cm^{-1} ; HRMS calcd for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}_4^+ [\text{M} + \text{H}^+]$ 427.25968, found 427.25929.

2-((1*S*,2*R*,3*S*,5*R*)-3-Ethynyl-3-hydroxy-2-(3-hydroxypropyl)-5-methylcyclohexyl)acetonitrile (24). To a solution of acetate **19** (100 mg, 0.36 mmol, 1.0 equiv) in methanol (5 mL) and water (0.1 mL) was added solid potassium carbonate (248 mg, 1.80 mmol, 5.0 equiv). The mixture was stirred for 12 h and then diluted with aqueous saturated NH_4Cl solution (20 mL) and extracted with EtOAc (3 \times 10 mL). The organic extracts were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated to provide **24** as colorless crystals (59.9 mg, 71%, mp 89.0–92.1 $^\circ\text{C}$): $R_f = 0.15$ (silica gel, EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 0.95 (d, $J = 6.4$ Hz, 3H), 1.20–1.26 (m, 1H), 1.41–1.48 (m, 1H), 1.51–1.73 (m, 7H), 1.82–1.92 (m, 1H), 2.02–2.08 (m, 2H), 2.22–2.24 (m, 1H), 2.48 (s, 1H), 2.50–2.55 (m, 1H), 2.77 (dd, $J = 11.6$ and 17.6 Hz, 1H), 3.64–3.75 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.9, 21.4, 21.5, 23.1, 29.9, 32.2, 37.8, 45.7, 49.3, 62.8, 71.1, 72.2, 87.6, 120.6; IR ν 3299, 2918, 2248 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_2^+ [\text{M} + \text{H}^+]$ 236.1651, found 236.1645.

General Procedure for the Deacetoxylation Reaction by K_2CO_3 . To a solution of the propargylamine in methanol was added solid K_2CO_3 in one portion. The heterogeneous solution was stirred vigorously for 7 h at 23 $^\circ\text{C}$ and then diluted with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated to provide alcohol.

2-((1*S*,2*R*,3*R*,5*R*)-3-Ethynyl-2-(3-hydroxypropyl)-3-((4-methoxybenzyl)amino)-5-methylcyclohexyl)acetonitrile (25). Following the general procedure, propargylamine **21** (1.70 g, 4.64 mmol, 1.0 equiv), methanol (25 mL), K_2CO_3 (3.0 g, 21.7 mmol, 4.7 equiv), saturated aqueous NH_4Cl solution (50 mL), EtOAc (3 \times 50

mL), and brine (50 mL) provided alcohol **25** (1.50 g, 99%) as a yellow oil: $R_f = 0.30$ (silica gel, EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 1.01 (d, $J = 6.4$ Hz, 3H), 1.10 (t, $J = 12.0$ Hz, 1H), 1.20–1.27 (m, 1H), 1.41–1.89 (m, 8H), 2.00–2.06 (m, 1H), 2.19–2.25 (m, 1H), 2.31–2.38 (m, 1H), 2.46 (s, 1H), 2.59–2.64 (m, 1H), 2.98 (dd, $J = 12.0$ and 17.2 Hz, 1H), 3.63–3.68 (m, 2H), 3.73 (d, $J = 11.6$ Hz, 1H), 3.84 (d, $J = 11.6$ Hz, 1H), 7.25–7.33 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.5, 21.9, 22.6, 23.8, 29.7, 33.1, 37.8, 46.1, 46.5, 47.2, 55.9, 62.4, 74.8, 86.7, 120.3, 127.1, 128.48, 128.52, 140.2; IR ν 3344, 3063, 2924, 2867, 1454, 733 cm^{-1} ; HRMS calcd for $\text{C}_{42}\text{H}_{56}\text{N}_4\text{O}_2^{2+} [2\text{M}^{2+}]$ 324.22016, found 324.21988.

2-((1*S*,2*R*,3*R*,5*R*)-3-Ethynyl-2-(3-hydroxypropyl)-3-((4-methoxybenzyl)amino)-5-methylcyclohexyl)acetonitrile (26). Following the general procedure, propargylamine **22** (1.20 g, 3.0 mmol, 1.0 equiv), methanol (20 mL), K_2CO_3 (2.0 g, 14.5 mmol, 4.8 equiv), saturated aqueous NH_4Cl solution (60 mL), EtOAc (3 \times 50 mL), and brine (20 mL) provided **26** (1.05 g, 98%) as a yellow oil: $[\alpha]_D^{24} -51.8$ (c 0.55, CH_2Cl_2); $R_f = 0.21$ (silica gel, EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 1.01 (d, $J = 6.4$ Hz, 3H), 1.09 (t, $J = 12.0$ Hz, 1H), 1.21–1.27 (m, 2H), 1.41–1.50 (m, 3H), 1.62–1.75 (m, 3H), 1.81–1.90 (m, 1H), 2.01–2.04 (m, 1H), 2.18–2.22 (m, 1H), 2.31–2.34 (m, 1H), 2.47 (s, 1H), 2.61 (dd, $J = 3.6$ and 17.2 Hz, 1H), 2.97 (dd, $J = 12.0$ and 17.2 Hz, 1H), 3.58–3.67 (m, 3H), 3.78–3.81 (m, 4H), 6.84–6.90 (m, 2H), 7.23–7.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.5, 21.9, 22.6, 23.8, 29.7, 33.0, 37.8, 46.1, 46.4, 46.6, 55.3, 55.8, 62.4, 74.7, 86.8, 113.9, 120.3, 129.6, 132.3, 158.7; IR ν 3406, 1510, 1243, 1033 cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}_2^+ [\text{M} + \text{H}^+]$ 355.23855, found 355.23805.

2-((1*S*,2*R*,3*R*,5*R*)-3-((2,4-Dimethoxybenzyl)amino)-3-ethynyl-2-(3-hydroxypropyl)-5-methylcyclohexyl)acetonitrile (27). Following the general procedure, propargylamine **23** (195 mg, 0.46 mmol, 1.0 equiv), methanol (5.0 mL), water (0.10 mL), K_2CO_3 (300 mg, 2.2 mmol, 4.8 equiv), aqueous saturated NH_4Cl solution (40 mL), EtOAc (3 \times 40 mL), and brine (30 mL) provided the corresponding alcohol **27** (166 mg, 94%) as a yellow oil: $R_f = 0.30$ (silica gel, EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 1.01 (d, $J = 6.8$ Hz, 3H), 1.10 (t, $J = 12.4$ Hz, 1H), 1.20–1.24 (m, 1H), 1.39–1.55 (m, 2H), 1.63–1.72 (m, 2H), 1.77–2.04 (m, 5H), 2.23 (dt, $J = 2.4$ and 12.4 Hz, 1H), 2.30–2.34 (m, 1H), 2.44 (s, 1H), 2.62 (dd, $J = 2.8$ and 17.2 Hz, 1H), 2.99 (dd, $J = 12.0$ and 17.2 Hz, 1H), 3.60–3.67 (m, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.84 (d, $J = 11.6$ Hz, 1H), 6.42–6.45 (m, 2H), 7.15 (dd, $J = 2.0$ and 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.6, 21.9, 22.6, 23.8, 29.8, 33.2, 37.9, 42.1, 45.9, 46.2, 55.3, 55.4, 55.7, 62.4, 74.7, 86.7, 98.7, 104.1, 120.4, 120.5, 130.5, 158.5, 160.2; IR ν 3285, 2921, 1614 cm^{-1} ; HRMS calcd for $\text{C}_{23}\text{H}_{33}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}^+]$ 385.24912, found 385.24852.

General Procedure for the Synthesis of Bicyclic Compound.

The alcohol was dissolved in CCl_4 , and then PPh_3 (2.0 equiv) and imidazole (2.0 equiv) were added sequentially as solids. The reaction was placed in a heated oil bath for 15 h, the oil bath was removed, and the solution was diluted with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 \rightarrow 5/1 hexanes/EtOAc) to afford the bicyclic alkyne–nitrile.

2-((4*aR*,5*R*,7*S*,8*aS*)-1-Benzyl-8*a*-ethynyl-7-methyldecahydroquinolin-5-yl)acetonitrile (28). Following the general procedure, alcohol **25** (750 mg, 2.3 mmol, 1.0 equiv), CCl_4 (20 mL), PPh_3 (1.21 g, 4.6 mmol, 2.0 equiv), imidazole (315 mg, 4.6 mmol, 2.0 equiv), and saturated aqueous NH_4Cl solution (50 mL), extraction with EtOAc (3 \times), and washing with brine (20 mL) afforded alkyne–nitrile **28** (530 mg, 75%, mp 138.2–138.5 $^\circ\text{C}$) as a pale yellow crystalline solid: $[\alpha]_D^{24} -152.7$ (c 1.0, CH_2Cl_2); $R_f = 0.60$ (silica gel, hexanes/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3) δ 0.99 (d, $J = 6.4$ Hz, 3H), 1.12 (t, $J = 12.4$ Hz, 1H), 1.25–1.66 (m, 6H), 1.93–2.01 (m, 2H), 2.11–2.15 (m, 1H), 2.26–2.34 (m, 2H), 2.51 (s, 1H), 2.55–2.63 (m, 2H), 2.93 (d, $J = 13.6$ Hz, 1H), 3.00 (dd, $J = 12.0$ and 18.0 Hz, 1H), 4.06 (d, $J = 13.6$ Hz, 1H), 7.20–7.33 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.3, 22.2, 24.3, 25.9, 26.7, 37.2, 38.1, 45.9, 46.4, 48.5, 53.4, 58.6, 76.6, 83.6, 120.6, 126.6, 128.1, 128.5, 140.3; IR ν 1454, 1068, 701 cm^{-1} ; HRMS calcd for $\text{C}_{21}\text{H}_{27}\text{N}_2^+ [\text{M} + \text{H}^+]$ 307.21742, found 307.21690.

2-((4*aR*,5*R*,7*S*,8*aS*)-8*a*-Ethynyl-1-(4-methoxybenzyl)-7-methyldecahydroquinolin-5-yl)acetonitrile (**29**). Following the general procedure, alcohol **26** (450 mg, 1.3 mmol, 1.0 equiv), CCl₄ (15 mL), PPh₃ (0.67 g, 2.54 mmol, 2.0 equiv), imidazole (172 mg, 2.5 mmol, 2.0 equiv), aqueous saturated NH₄Cl solution (30 mL), EtOAc (3 × 20 mL), and brine (20 mL) afforded **29** (530 mg, 74%) as a pale yellow oil: $[\alpha]_D^{24}$ -70.2 (c 0.69, CH₂Cl₂); R_f = 0.55 (silica gel, hexanes/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃) δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.12 (t, *J* = 12.0 Hz, 1H), 1.28–1.75 (m, 6H), 1.93–2.00 (m, 2H), 2.11–2.15 (m, 1H), 2.22–2.29 (m, 2H), 2.50 (s, 1H), 2.54–2.63 (m, 2H), 2.86 (d, *J* = 13.2 Hz, 1H), 3.00 (dd, *J* = 12.0 and 21.2 Hz, 1H), 3.79 (s, 3H), 3.99 (d, *J* = 13.2 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 17.1, 22.1, 24.2, 25.7, 26.6, 37.1, 40.0, 45.8, 46.2, 48.1, 52.6, 55.1, 58.5, 76.6, 82.5, 113.4, 120.4, 129.4, 132.1, 158.3; IR ν 1512, 1243, 830 cm⁻¹; HRMS calcd for C₂₂H₂₉N₂O⁺ [M + H]⁺ 337.22799, found 337.22731.

2-((4*aR*,5*R*,7*S*,8*aS*)-1-(2,4-Dimethoxybenzyl)-8*a*-ethynyl-7-methyldecahydroquinolin-5-yl)acetonitrile (**30**). Following the general procedure, alcohol **27** (250 mg, 0.65 mmol, 1.0 equiv), CCl₄ (6 mL), PPh₃ (0.34 g, 1.3 mmol, 2.0 equiv), imidazole (89 mg, 1.3 mmol, 2.0 equiv), aqueous saturated NH₄Cl solution (20 mL), EtOAc (3 × 15 mL), and brine (20 mL) afforded the bicyclic compound **30** (189 mg, 79%) as a pale yellow oil: $[\alpha]_D^{23.0}$ -36.0 (c 0.50, CH₂Cl₂); R_f = 0.25 (silica gel, hexanes/EtOAc = 4/1); ¹H NMR (400 MHz, CDCl₃) δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.11 (t, *J* = 4.0 Hz, 1H), 1.29–1.37 (m, 1H), 1.41–1.51 (m, 2H), 1.58–1.66 (m, 2H), 1.71–1.76 (m, 1H), 1.93–2.00 (m, 2H), 2.11–2.15 (m, 1H), 2.23–2.30 (m, 2H), 2.50 (s, 1H), 2.55–2.63 (m, 2H), 2.87 (d, *J* = 17.0 Hz, 1H), 3.00 (dd, *J* = 12.0 and 17.2 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.01 (d, *J* = 13.6 Hz, 1H), 6.77–6.85 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 17.3, 22.2, 24.3, 25.9, 26.7, 37.2, 38.1, 45.8, 46.4, 48.3, 53.0, 55.8, 55.9, 58.6, 76.6, 83.6, 110.8, 111.5, 120.4, 120.5, 132.8, 147.7, 148.8; IR ν 3278, 2921, 1612, 1504 cm⁻¹; HRMS calcd for C₂₃H₃₁N₂O₂⁺ [M + H]⁺ 367.2386, found 367.2380.

(4*aR*,5*S*,10*bR*,12*R*)-1-Benzyl-12-methyl-9-(trimethylsilyl)-8-(trimethylsilyl)ethynyl-2,3,4,4*a*,5,6-hexahydro-1*H*-5,10*b*-propano-1,7-phenanthroline (**32**). To alkyne–nitrile **28** (62 mg, 0.20 mmol, 1.0 equiv) and diyne **31** (50 mg, 0.26 mmol, 1.3 equiv) in degassed chlorobenzene (3 mL) was added a solution of CoCp(CO)₂ (0.049 mL, 0.40 mmol, 2 equiv) in degassed chlorobenzene (2.5 mL) over 90 min. During the addition, the reaction was irradiated with a 600 W slide projector lamp placed 5 cm from the flask. After 4 h, another portion of diyne **31** (50 mg, 0.26 mmol, 1.3 equiv) was added in one portion. Irradiation continued for 4 h. The reaction was loaded on a column and purified by silica gel chromatography (1/0 → 5/1 hexanes/EtOAc) to afford compound **32** (71 mg, 70%); $[\alpha]_D^{24}$ +5.0 (c 0.28, CH₂Cl₂); R_f = 0.60 (silica gel, hexanes/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃) δ 0.26 (s, 9H), 0.42 (s, 9H), 0.74 (d, *J* = 6.0 Hz, 3H), 1.13–1.32 (m, 5H), 1.44–1.46 (m, 2H), 1.53–1.61 (m, 1H), 1.69–1.77 (m, 1H), 1.85–1.90 (m, 1H), 2.07–2.10 (m, 1H), 2.37–2.44 (m, 1H), 2.48–2.53 (m, 1H), 2.68 (d, *J* = 18.8 Hz, 1H), 3.17 (dd, *J* = 14.8 and 18.8 Hz, 1H), 4.14 (dd, *J* = 14.4 and 60.0 Hz, 2H), 7.22–7.26 (m, 1H), 7.32–7.36 (m, 2H), 7.46–7.48 (m, 2H), 8.25 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ -1.4, -0.4, 21.3, 22.3, 26.4, 27.0, 33.9, 35.2, 38.8, 43.7, 46.1, 48.1, 51.0, 60.3, 95.5, 106.0, 126.4, 127.8, 128.2, 134.9, 137.3, 140.2, 142.6, 144.1, 159.2; IR ν 1248, 842 cm⁻¹; HRMS calcd for C₃₁H₄₃N₂Si₂⁺ [M + H]⁺ 501.31213, found 501.31193.

THF Conditions. In a pressure tube, 1,4-(bistrimethylsilyl)-butdiyne **31** (317 mg, 1.6 mmol, 2.0 equiv) and alkyne–nitrile **28** (250 mg, 0.82 mmol, 1.0 equiv) were dissolved in freshly degassed THF (17 mL). Neat CpCo(CO)₂ (100 μL, 0.82 mmol, 1.0 equiv) was added to the solution, and the tube was sealed. The resulting solution was placed in a 140 °C oil bath, and after 20 h the vessel was cooled to 23 °C and the solvent was removed. The crude material was purified by silica gel chromatography (1/0 → 5/1 hexanes/EtOAc) to afford **32** (320 mg, 78%) and **33** (12.3 mg, 3% yield).

(4*aR*,5*S*,10*bR*,12*R*)-1-Benzyl-12-methyl-9-(trimethylsilyl)ethynyl-2,3,4,4*a*,5,6-hexahydro-1*H*-5,10*b*-propano-1,7-phenanthroline (**33**). From the above THF conditions: R_f = 0.55 (silica gel, silica gel,

hexanes/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃) δ 0.29 (s, 9H), 0.75 (d, *J* = 6.4 Hz, 3H), 0.83–0.88 (m, 2H), 0.97 (d, *J* = 6.8 Hz, 1H), 1.14–1.21 (m, 1H), 1.2–1.33 (m, 2H), 1.42–1.61 (m, 2H), 1.72–1.80 (m, 2H), 1.89–1.94 (m, 1H), 2.09–2.12 (m, 1H), 2.4–2.52 (m, 2H), 3.19 (dd, *J* = 6.8 and 19.6 Hz, 1H), 4.14 (dd, *J* = 14.0 and 63.6 Hz, 2H), 7.24–7.33 (m, 1H), 7.34–7.50 (m, 2H), 7.48–7.50 (m, 2H), 8.15 (d, *J* = 2.0 Hz, 1H), 8.46 (d, *J* = 2.0 Hz, 1H); IR ν 2949, 2924, 1451, 1249, 843 cm⁻¹; HRMS calcd for C₂₈H₃₇N₂Si⁺ [M + H]⁺ 429.27260, found 429.27203.

(4*aR*,5*S*,10*bR*,12*R*)-1-Benzyl-9-(tert-butyltrimethylsilyl)-8-(tert-butyltrimethylsilyl)ethynyl-12-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-5,10*b*-propano-1,7-phenanthroline (**34**). In a 30 mL pressure tube, 1,4-(bistrimethylsilyl)butdiyne (455 mg, 1.63 mmol, 2.0 equiv) and nitrile **28** (250 mg, 0.82 mmol, 1 equiv) were dissolved in freshly degassed THF (17 mL). Neat CpCo(CO)₂ (0.2 mL, 1.6 mmol, 2 equiv) was added into the solution, and the tube was sealed. The resulting solution was heated at 140 °C for 20 h. The mixture was cooled to 23 °C, and the solvent was evaporated. The crude material was purified by silica gel chromatography (0/1 to 1/5 EtOAc/Hexanes) to afford compound **34** (300 mg, 63%) as a dark brown foam: $[\alpha]_D^{23.0}$ +4.9 (c 0.23, CH₂Cl₂); R_f = 0.65 (silica gel, hexanes/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃) δ 0.20 (s, 6H), 0.43 (s, 3H), 0.45 (s, 3H), 0.55 (d, *J* = 3.6 Hz, 3H), 0.80–0.99 (m, 20H), 1.12–1.30 (m, 2H), 1.36–1.45 (m, 1H), 1.51–1.75 (m, 2H), 1.86–1.89 (m, 1H), 2.02–2.09 (m, 1H), 2.35–2.50 (m, 2H), 2.66–2.79 (m, 1H), 3.13–3.21 (m, 1H), 4.02 (d, *J* = 14.4 Hz, 1H), 4.21 (d, *J* = 14.4 Hz, 1H), 7.20–7.25 (m, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 8.31 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ -4.5, 14.1, 16.9, 18.2, 21.1, 22.4, 26.4, 26.9, 27.1, 34.0, 35.1, 38.5, 43.6, 46.0, 48.3, 50.9, 60.2, 86.7, 92.7, 107.9, 126.4, 127.8, 128.2, 132.2, 136.7, 141.9, 142.5, 144.5, 159.2; IR ν 2926, 2856, 1507, 901 cm⁻¹; HRMS calcd for C₃₇H₅₇N₂Si₂⁺ [M + H]⁺ 585.4060, found 585.4056.

(4*aR*,5*S*,10*bR*,12*R*)-1-Benzyl-12-methyl-8-(triisopropylsilyl)ethynyl-9-(trimethylsilyl)-2,3,4,4*a*,5,6-hexahydro-1*H*-5,10*b*-propano-1,7-phenanthroline (**36**): $[\alpha]_D^{23.0}$ +6.0 (c 0.33, CH₂Cl₂); R_f = 0.70 (silica gel, hexanes/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃) δ 0.43 (s, 9H), 0.75 (d, *J* = 6.0 Hz, 3H), 1.05–1.32 (m, 23H), 1.44–1.48 (m, 2H), 1.50–1.56 (m, 1H), 1.69–1.80 (m, 2H), 1.84–1.90 (m, 1H), 2.06–2.11 (m, 1H), 2.37–2.52 (m, 2H), 2.70 (d, *J* = 18.8 Hz, 1H), 3.17 (dd, *J* = 7.2 and 18.4 Hz, 1H), 4.07 (d, *J* = 14.4 Hz, 1H), 4.21 (d, *J* = 14.4 Hz, 1H), 7.22–7.26 (m, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 8.24 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ -1.1, 11.6, 18.7, 21.3, 22.4, 26.4, 27.0, 34.0, 35.1, 38.9, 43.7, 46.0, 48.1, 51.0, 60.3, 91.8, 108.0, 126.4, 127.8, 128.2, 134.2, 137.0, 140.2, 142.7, 144.4, 159.3; IR ν 2944, 2865, 1493, 735 cm⁻¹; HRMS calcd for C₃₇H₅₇N₂Si₂⁺ [M + H]⁺ 585.40603, found 585.40510.

General Procedure for the Initial Cobalt-Mediated [2 + 2 + 2] Reaction (for Figure 5). In a pressure tube specific arylalkyne and alkyne–nitrile **28** were dissolved in freshly degassed THF. Neat CpCo(CO)₂ was added to the solution and the tube was sealed. The resulting solution was placed in a 140 °C oil bath. After 24–36 h the vessel was removed from the oil bath, cooled to 23 °C, and the solution was concentrated. The crude material was purified by silica gel chromatography to afford desired compound.

General Procedure for the Desilylation of the TMS Functional Group on the Pyridyl Rings. (for Figure 5 Characterization). To a solution of the TMS pyridyl compound in dioxane at 23 °C was added TBAF solution and the resulting solution was placed in a heated oil bath. After 8–24 h, the mixture was cooled to 23 °C and concentrated. The crude material was purified on silica gel chromatography to afford desired compound.

2-((4*aR*,5*S*,10*bR*,12*R*)-1-Benzyl-12-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-5,10*b*-propano-1,7-phenanthroline-8-yl)thiazole (**int-4**). Following the general procedure 2-(trimethylsilyl)ethynylthiazole **int-3** (18 mg, 98 μmol, 3.0 equiv), alkyne–nitrile **28** (10 mg, 33 μmol, 1.0 equiv), THF (2.0 mL), and neat CpCo(CO)₂ (8 μL, 57 μmol, 1.7 equiv), purified by silica gel chromatography (20/1 → 5/1 hexanes/EtOAc), afforded **43** (9.9 mg, 62%) as a yellow oil; **43** (9.9 mg, 20 μmol, 1.0 equiv), dioxane (1.0 mL) and TBAF solution (81 μL, 1 M in THF, 81 μmol, 4.0 equiv), purified on silica gel chromatography (1/0 to 5/1 hexanes/EtOAc), afforded **int-4** (5.9 mg, 70%) as a light brown

foam: $R_f = 0.31$ (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (600 MHz, CDCl_3) δ 0.75 (d, $J = 6.0$ Hz, 3H), 1.13–1.16 (m, 1H), 1.20–1.34 (m, 4H), 1.47–1.59 (m, 2H), 1.74–1.81 (m, 2H), 1.93 (dt, $J = 3.2$ and 12.7 Hz, 1H), 2.11–2.14 (m, 1H), 2.44–2.60 (m, 2H), 2.74 (d, $J = 18.6$ Hz, 1H), 3.23 (dd, $J = 3.2$ and 18.6 Hz, 1H), 4.07 (d, $J = 14.1$ Hz, 1H), 4.22 (d, $J = 14.1$ Hz, 1H), 7.22–7.24 (m, 1H), 7.33–7.37 (m, 3H), 7.47 (d, $J = 7.1$ Hz, 2H), 7.88 (d, $J = 3.3$ Hz, 1H), 7.99 (d, $J = 8.1$ Hz, 1H), 8.20 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (150.8 MHz, CDCl_3) δ 21.1, 22.4, 26.5, 27.1, 34.0, 35.3, 38.5, 43.7, 45.9, 48.1, 50.9, 60.6, 117.6, 120.6, 126.5, 128.0, 128.3, 135.4, 139.8, 142.2, 143.9, 148.5, 158.7, 170.0; IR ν 2923, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{26}\text{H}_{30}\text{N}_3\text{S}^+ [\text{M} + \text{H}^+]$ 416.21550, found 416.21562.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-8-(thiophene-3-yl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (int-6). Following the general procedure, trimethyl(thiophene-3-ylethynyl)silane **int-5** (17 mg, 98 μmol , 3.0 equiv), alkyne–nitrile **28** (10 mg, 33 μmol , 1.0 equiv), THF (2.0 mL), and $\text{CpCo}(\text{CO})_2$ (8 μL , 57 μmol , 1.7 equiv), purified by silica gel chromatography (20/1 \rightarrow 5/1 hexanes/EtOAc), afforded **44** (7.2 mg, 45%) as pale yellow oil; **44** (6.9 mg, 14 μmol , 1.0 equiv), dioxane (1.0 mL), and TBAF solution (43 μL , 1 M in THF, 43 μmol , 3.0 equiv), purified by silica gel chromatography (1/0 to 10/1 hexanes/EtOAc), afforded **int-6** (5.1 mg, 87%) as a light brown foam: $R_f = 0.35$ (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (600 MHz, CDCl_3) δ 0.74 (d, $J = 5.9$ Hz, 3H), 0.82–0.88 (m, 1H), 1.12–1.16 (m, 1H), 1.23–1.29 (m, 2H), 1.30–1.38 (m, 1H), 1.44–1.57 (m, 2H), 1.72–1.78 (m, 2H), 1.90 (dt, $J = 3.2$ and 12.7 Hz, 1H), 2.09–2.11 (m, 1H), 2.48–2.50 (m, 2H), 2.72 (d, $J = 18.6$ Hz, 1H), 3.20 (dd, $J = 7.0$ and 18.6 Hz, 1H), 4.06 (d, $J = 14.2$ Hz, 1H), 4.22 (d, $J = 14.2$ Hz, 1H), 7.07 (dd, $J = 3.4$ and 5.0 Hz, 1H), 7.22 (d, $J = 7.3$ Hz, 1H), 7.31–7.35 (m, 3H), 7.46 (d, $J = 7.3$ Hz, 2H), 7.49 (d, $J = 8.2$ Hz, 1H), 7.54 (dd, $J = 1.1$ and 3.4 Hz, 1H), 8.09 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (150.8 MHz, CDCl_3) δ 21.1, 22.4, 26.5, 27.1, 34.1, 35.4, 38.6, 43.8, 45.9, 48.2, 50.9, 60.4, 117.0, 124.0, 126.5, 126.7, 127.9, 128.0, 128.2, 135.1, 136.8, 142.4, 145.4, 149.7, 158.5; IR ν 2919, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{27}\text{H}_{31}\text{N}_3\text{S}^+ [\text{M} + \text{H}^+]$ 415.2208, found 415.2208.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-8-(thiophene-2-yl)-9-(trimethylsilyl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (45). Following the general procedure, trimethyl(thiophene-2-ylethynyl)silane **int-7** (16.1 mg, 89 μmol , 3.0 equiv), alkyne–nitrile **28** (9.1 mg, 30 μmol , 1.0 equiv), THF (2.0 mL), and neat $\text{CpCo}(\text{CO})_2$ (8 μL , 57 μmol , 1.8 equiv), purified by silica gel chromatography (20/1 \rightarrow 5/1 hexanes/EtOAc), afforded **45** (8.9 mg, 51%) as a pale yellow oil: $R_f = 0.65$ (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.11 (s, 9H), 0.78 (d, $J = 5.6$ Hz, 3H), 1.18–1.40 (m, 5H), 1.45–1.58 (m, 3H), 1.76–1.81 (m, 2H), 1.91 (dt, $J = 3.6$ and 13.2 Hz, 1H), 2.10–2.12 (m, 1H), 2.53 (d, $J = 6.8$ Hz, 1H), 2.71 (d, $J = 19.2$ Hz, 1H), 3.19 (dd, $J = 6.8$ and 19.2 Hz, 1H), 4.14 (d, $J = 14.4$ Hz, 1H), 4.25 (d, $J = 14.4$ Hz, 1H), 7.23–7.26 (m, 2H), 7.30–7.34 (m, 4H), 7.50 (d, $J = 7.8$ Hz, 2H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 0.22, 21.6, 22.5, 26.4, 27.1, 34.1, 35.3, 39.3, 43.8, 45.9, 48.1, 51.2, 60.2, 124.1, 125.0, 126.4, 127.8, 128.2, 129.1, 130.7, 135.3, 141.5, 142.7, 144.7, 157.5, 158.2; IR ν 2923, 1428 cm^{-1} ; HRMS calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{Si}^+ [\text{M} + \text{H}^+]$ 487.25977, found 487.25969.

(4aR,5S,10bR,12R)-1-Benzyl-8-(furan-2-yl)-12-methyl-9-(trimethylsilyl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (46). Following the general procedure (furan-2-ylethynyl)-trimethylsilane **int-8** (16.2 mg, 99 μmol , 3.0 equiv), alkyne–nitrile **28** (10.1 mg, 33 μmol , 1.0 equiv), THF (2.0 mL), and neat $\text{CpCo}(\text{CO})_2$ (8 μL , 57 μmol , 1.7 equiv), purified by silica gel chromatography (20/1 \rightarrow 5/1 hexanes/EtOAc), afforded compound **46** (7.9 mg, 51%) as a yellow oil: $R_f = 0.60$ (silica gel, Hexanes/EtOAc = 2/1); ^1H NMR (500 MHz, CDCl_3) δ 0.30 (s, 9H), 0.76 (d, $J = 6.0$ Hz, 3H), 1.17–1.37 (m, 4H), 1.44–1.80 (m, 4H), 1.86–1.92 (m, 1H), 2.11–2.13 (m, 1H), 2.47–2.55 (m, 2H), 2.71 (d, $J = 9.5$ Hz, 1H), 3.19 (dd, $J = 7.3$ and 18.8 Hz, 1H), 4.13 (d, $J = 14.4$ Hz, 1H), 4.24 (d, $J = 14.4$ Hz, 1H), 6.53 (dd, $J = 1.7$ and 3.2 Hz, 1H), 6.92 (d, $J = 3.2$ Hz, 1H), 7.24 (d, $J = 7.3$ Hz, 1H), 7.35 (t, $J = 7.3$ Hz, 2H), 7.50 (d, $J = 7.3$ Hz, 3H), 8.38 (s, 1H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 0.38, 21.6, 22.4, 26.4, 27.1, 34.1, 35.3, 39.3, 43.8, 46.0, 48.1, 51.1, 60.3, 109.0, 112.1, 126.4, 127.8,

128.2, 129.0, 135.7, 141.6, 142.1, 142.7, 151.0, 155.8, 158.5; IR ν 3393, 2918, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{OSi}^+ [\text{M} + \text{H}^+]$ 471.28262, found 471.28291.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-8-(pyridin-2-yl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (int-10). Following the general procedure 2-((trimethylsilyl)ethynyl)-pyridine **int-9** (17.2 mg, 98 μmol , 3.0 equiv), alkyne–nitrile **28** (10 mg, 33 μmol , 1.0 equiv), THF (1.5 mL), and neat $\text{CpCo}(\text{CO})_2$ (8 μL , 57 μmol , 1.7 equiv), purified by silica gel chromatography (20/1 \rightarrow 2/1 hexanes/EtOAc), afforded **47** (8.2 mg, 52%) as a yellow oil; **47** (8.2 mg, 17 μmol , 1 equiv), dioxane (1.0 mL), and TBAF solution (49 μL , 1 M in THF, 49 μmol , 3.0 equiv), purified by silica gel chromatography (20/1 to 1/1 hexanes/EtOAc) to afford **int-10** (6.1 mg, 88%) as a light brown foam: $R_f = 0.35$ (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3) δ 0.68 (d, $J = 6.0$ Hz, 3H), 0.78–0.83 (m, 1H), 1.08–1.54 (m, 6H), 1.71–1.75 (m, 2H), 1.89 (d, $J = 3.6$ and 8.8 Hz, 1H), 2.07–2.09 (m, 1H), 2.45–2.47 (m, 2H), 2.72 (d, $J = 18.8$ Hz, 1H), 3.21 (dd, $J = 7.2$ and 18.8 Hz, 1H), 4.05 (d, $J = 14.0$ Hz, 1H), 4.18 (d, $J = 14.0$ Hz, 1H), 7.16–7.22 (m, 2H), 7.30 (t, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 7.6$ Hz, 2H), 7.72 (dt, $J = 1.6$ and 7.6 Hz, 1H), 8.09 (d, $J = 7.6$ Hz, 1H), 8.15 (d, $J = 7.6$ Hz, 1H), 8.27 (dt, $J = 1.2$ and 7.6 Hz, 1H), 8.60–8.63 (m, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 21.3, 22.4, 26.5, 27.2, 34.2, 35.6, 38.8, 43.8, 45.9, 48.2, 51.1, 60.5, 119.1, 121.0, 123.2, 126.5, 128.0, 128.8, 135.3, 136.7, 138.6, 142.4, 149.2, 153.4, 156.8, 158.1; IR ν 2919, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{28}\text{H}_{32}\text{N}_3^+ [\text{M} + \text{H}^+]$ 410.25907, found 410.25875.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-8-(quinolin-3-yl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (int-12). Following the general procedure, 3-((trimethylsilyl)ethynyl)-quinolinetube **int-11** (21.6 mg, 96 μmol , 3.0 equiv), alkyne–nitrile **28** (9.8 mg, 33 μmol , 1.0 equiv), THF (2.0 mL), and neat $\text{CpCo}(\text{CO})_2$ (8 μL , 57 μmol , 1.7 equiv), purified by silica gel chromatography (20/1 \rightarrow 2/1 EtOAc/hexanes), afforded **48** (4.9 mg, 28%) as a yellow oil; **48** (4.9 mg, 9.2 μmol , 1.0 equiv), dioxane (1.0 mL) and TBAF solution (1 M in THF, 37 μL , 37 μmol , 4.0 equiv), purified by silica gel chromatography (20/1 to 1/1 hexanes/EtOAc), afforded **int-12** (4.0 mg, 94%) as a light brown foam: $R_f = 0.43$ (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (500 MHz, CDCl_3) δ 0.79 (d, $J = 5.9$ Hz, 3H), 0.83–0.90 (m, 1H), 1.18–1.44 (m, 4H), 1.52–1.59 (m, 2H), 1.78–1.88 (m, 2H), 1.98 (dt, $J = 3.7$ and 16.1 Hz, 1H), 2.17–2.20 (m, 1H), 2.54–2.57 (m, 2H), 2.84 (d, $J = 18.5$ Hz, 1H), 3.33 (dd, $J = 7.1$ and 18.5 Hz, 1H), 4.11 (d, $J = 14.2$ Hz, 1H), 4.28 (d, $J = 14.2$ Hz, 1H), 7.24–7.27 (m, 1H), 7.36–7.47 (m, 2H), 7.50 (d, $J = 10.0$ Hz, 2H), 7.58–7.59 (m, 1H), 7.71–7.76 (m, 2H), 7.93–7.95 (m, 1H), 8.14 (d, $J = 8.5$ Hz, 1H), 8.27 (d, $J = 8.5$ Hz, 1H), 8.78 (d, $J = 2.1$ Hz, 1H), 9.55 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (150.8 MHz, CDCl_3) δ 21.1, 22.4, 26.6, 27.2, 34.1, 35.6, 38.6, 43.8, 45.9, 48.2, 51.0, 60.5, 118.9, 126.5, 126.8, 128.0, 128.3, 128.5, 129.0, 129.6, 129.7, 132.4, 133.6, 135.5, 137.8, 142.3, 148.0, 149.6, 151.8, 159.3; IR ν 2917, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{32}\text{H}_{34}\text{N}_3^+ [\text{M} + \text{H}^+]$ 460.27472, found 460.27503.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-9-phenyl-8-(pyridin-3-yl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (49). Following the general procedure 3-(phenylethynyl)pyridine **int-13** (23 mg, 0.13 mmol, 2.6 equiv), alkyne–nitrile **28** (15 mg, 49 μmol , 1.0 equiv), THF (2.5 mL), and neat $\text{CpCo}(\text{CO})_2$ (10 μL , 82 μmol , 1.7 equiv), purified by silica gel chromatography (20/1 \rightarrow 1/1 hexanes/EtOAc), afforded **49** (6.9 mg, 26%) and **50** (3.0 mg, 16%): $R_f = 0.31$ (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.81 (d, $J = 5.6$ Hz, 3H), 0.86–0.95 (m, 1H), 1.21–1.60 (m, 6H), 1.81–1.83 (m, 3 H), 1.96–2.00 (m, 2H), 2.17–2.18 (m, 1H), 2.54–2.65 (m, 2H), 2.79 (d, $J = 18.8$ Hz, 1H), 3.30 (dd, $J = 7.6$ and 18.8 Hz, 1H), 4.12 (d, $J = 14.4$ Hz, 1H), 4.22 (d, $J = 14.4$ Hz, 1H), 7.15–7.34 (m, 7H), 7.45 (d, $J = 7.6$ Hz, 2H), 7.69 (dt, $J = 2.0$ and 7.6 Hz, 1H), 8.16 (s, 1H), 8.47 (dd, $J = 2.0$ and 4.8 Hz, 1H), 8.60 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.5, 22.4, 26.5, 27.1, 34.0, 35.3, 38.9, 43.7, 45.9, 48.1, 51.1, 60.4, 122.7, 126.5, 127.2, 128.0, 128.2, 128.3, 128.5, 129.7, 134.4, 136.2, 136.8, 137.2, 137.6, 139.8, 142.2, 148.3, 150.9, 158.0; IR ν 2919, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{34}\text{H}_{36}\text{N}_3^+ [\text{M} + \text{H}^+]$ 486.29037, found 486.29099.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-8-phenyl-9-(pyridin-3-yl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (**50**). Following the above procedure: R_f = 0.69 (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.82 (d, J = 6.0 Hz, 3H), 1.21–1.46 (m, 5H), 1.46–1.62 (m, 2H), 1.81–1.84 (m, 2H), 1.97–2.01 (m, 1H), 2.18–2.19 (m, 1H), 2.59–2.66 (m, 2H), 2.83 (d, J = 18.8 Hz, 1H), 3.32 (dd, J = 7.2 and 18.8 Hz, 1H), 7.13 (d, J = 14.4 Hz, 1H), 4.24 (d, J = 14.4 Hz, 1H), 7.16–7.27 (m, 6H), 7.32–7.35 (m, 4H), 7.42–7.46 (m, 2H), 8.13 (d, J = 2.0 Hz, 1H), 8.50–8.54 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.3, 22.4, 26.5, 27.1, 34.1, 35.3, 38.7, 43.7, 45.9, 48.2, 51.1, 60.4, 122.9, 126.5, 127.8, 128.0, 128.1, 128.3, 130.0, 130.2, 136.4, 136.5, 137.0, 137.0, 139.7, 142.1, 148.0, 150.2, 154.4, 158.4; IR ν 2913, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{34}\text{H}_{36}\text{N}_3^+$ [$\text{M} + \text{H}^+$] 486.29037, found 486.29092.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-8-phenyl-9-(trimethylsilyl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (**51**). Following the general procedure, trimethyl(phenylethynyl)silane **int-14** (8.4 mg, 48 μmol , 4.1 equiv), alkyne–nitrile **28** (3.6 mg, 12 μmol , 1.0 equiv), THF (1 mL), and neat $\text{CpCo}(\text{CO})_2$ (3 μL , 24 μmol , 2.0 equiv), purified by silica gel chromatography (20/1 \rightarrow 10/1 hexanes/EtOAc), afforded **51** (2.3 mg, 51%) as a brown foam: R_f = 0.65 (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.06 (s, 9H), 0.79 (d, J = 5.6 Hz, 3H), 1.19–1.41 (m, 4H), 1.45–1.54 (m, 2H), 1.75–1.79 (m, 2H), 1.90–1.93 (m, 1H), 2.11–2.12 (m, 1H), 1.75–1.78 (m, 1H), 2.54–2.56 (m, 2H), 2.72 (d, J = 18.8 Hz, 1H), 4.12 (d, J = 14.4 Hz, 1H), 4.15 (d, J = 14.4 Hz, 1H), 4.26 (d, J = 14.4 Hz, 1H), 7.25–7.45 (m, 8H), 7.51 (d, J = 8.0 Hz, 2H), 8.34 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 0.2, 21.7, 22.5, 26.4, 27.1, 34.2, 35.4, 39.4, 43.8, 46.0, 48.2, 51.2, 60.2, 126.4, 127.7, 127.8, 127.9, 128.2, 129.1, 130.2, 135.0, 141.6, 142.8, 143.9, 158.0, 162.3; IR ν 2918, 1384, 837 cm^{-1} ; HRMS calcd for $\text{C}_{32}\text{H}_{41}\text{N}_2\text{Si}^+$ [$\text{M} + \text{H}^+$] 481.3039, found 481.3033.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-8,9-diphenyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (**52**). Following the general procedure, 1,2-diphenylethyne **int-15** (25 mg, 0.14 mmol, 3.0 equiv), alkyne–nitrile **28** (14.5 mg, 47 μmol , 1.0 equiv), THF (2.2 mL), and neat $\text{CpCo}(\text{CO})_2$ (10 μL , 82 μmol , 1.7 equiv), purified by silica gel chromatography (20/1 \rightarrow 10/1 hexanes/EtOAc), afforded **52** (9.9 mg, 43%) as a pale yellow foam: R_f = 0.45 (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.81 (d, J = 6.0 Hz, 1H), 1.21–1.25 (m, 1H), 1.33–1.64 (m, 6H), 1.79–1.83 (m, 2H), 1.97 (dt, J = 3.2 and 12.4 Hz, 1H), 2.15–2.17 (m, 1H), 2.53–2.68 (m, 2H), 2.80 (d, J = 18.4 Hz, 1H), 3.30 (dd, J = 7.2 and 18.4 Hz, 1H), 4.16 (d, J = 14.4 Hz, 1H), 4.22 (d, J = 14.4 Hz, 1H), 7.21–7.38 (m, 13H), 7.46 (d, J = 7.2 Hz, 2H), 8.12 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.6, 22.5, 26.5, 27.1, 34.1, 35.3, 39.1, 43.8, 45.9, 48.1, 51.2, 60.3, 126.4, 126.7, 127.4, 127.8, 127.8, 127.9, 128.2, 129.7, 130.0, 133.8, 136.6, 136.6, 140.4, 140.7, 142.4, 154.0, 157.4; IR ν 2922, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{35}\text{H}_{37}\text{N}_2^+$ [$\text{M} + \text{H}^+$] 485.2957, found 485.2959.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-9-phenyl-8-(pyridin-2-yl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (**53**). Following the general procedure, 2-(phenylethynyl)pyridine **int-16** (23 mg, 0.13 mmol, 2.6 equiv), alkyne–nitrile **28** (15 mg, 49 μmol , 1.0 equiv), THF (2.5 mL), and neat $\text{CpCo}(\text{CO})_2$ (10 μL , 82 μmol , 1.7 equiv), purified by silica gel chromatography (20/1 \rightarrow 1/1 hexanes/EtOAc), afforded **53** (6.9 mg, 26%) as a pale foam: R_f = 0.21 (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3) δ 0.79 (d, J = 5.8 Hz, 3H), 1.22–1.60 (m, 6H), 1.73–1.79 (m, 3H), 1.95–1.99 (m, 1H), 2.16–2.17 (m, 1H), 2.53–2.67 (m, 2H), 2.85 (d, J = 15.6 Hz, 1H), 3.26–3.35 (m, 1H), 4.23 (s, 2H), 7.00 (d, J = 7.6 Hz, 1H), 7.15–7.38 (m, 9H), 7.44–7.49 (m, 3H), 8.34 (s, 1H), 8.70 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.9, 22.4, 26.4, 27.1, 34.1, 39.6, 43.8, 46.0, 47.9, 51.3, 60.4, 77.2, 121.6, 125.3, 126.4, 127.9, 128.0, 128.0, 128.1, 128.2, 129.9, 132.5, 135.5, 136.8, 142.4, 149.7, 152.8, 159.8; IR ν 3423, 1918, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{34}\text{H}_{36}\text{N}_3^+$ [$\text{M} + \text{H}^+$] 486.29037, found 486.29031.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-8-(naphthalen-2-yl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (**int-18**). Following the general procedure, trimethyl(naphthalen-2-ylethynyl)silane **int-17** (22 mg, 0.10 mmol, 3.0 equiv), alkyne–nitrile

28 (10 mg, 33 μmol , 1.0 equiv), THF (1.5 mL), and neat $\text{CpCo}(\text{CO})_2$ (8 μL , 57 μmol , 1.9 equiv), purified by silica gel chromatography (20/1 \rightarrow 5/1 hexanes/EtOAc), afforded **56** (8.9 mg, 51%); **56** (8.9 mg, 17 μmol , 1.0 equiv), dioxane (1 mL), and TBAF solution (80 μL , 1 M in THF, 0.080 mmol, 4.8 equiv), purified by silica gel chromatography (1/0 to 20/1 hexanes/EtOAc), afforded **int-18** (7.2 mg, 94%) as a light brown foam: R_f = 0.45 (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.78 (d, J = 5.8 Hz, 3H), 0.86–0.90 (m, 1H), 1.18–1.46 (m, 4H), 1.50–1.63 (m, 3H), 1.79–1.83 (m, 1H), 1.96 (dt, J = 3.6 and 9.5 Hz, 1H), 2.16–2.18 (m, 1H), 2.55–2.59 (m, 2H), 2.82 (d, J = 18.3 Hz, 1H), 3.33 (dd, J = 3.6 and 18.3 Hz, 1H), 4.13 (d, J = 14.1 Hz, 1H), 4.27 (d, J = 14.1 Hz, 1H), 7.25–7.27 (m, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.47–7.52 (m, 3H), 7.73 (d, J = 8.2 Hz, 1H), 7.85–7.96 (m, 3H), 8.16 (dd, J = 1.8 and 8.2 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 21.2, 22.4, 26.6, 27.2, 34.2, 35.7, 38.8, 43.9, 45.9, 48.2, 51.0, 60.4, 118.8, 124.8, 126.0, 126.1, 126.2, 126.5, 127.6, 128.0, 128.2, 128.3, 128.7, 133.4, 133.6, 135.2, 136.9, 137.1, 142.5, 154.3, 158.7; IR ν 2920, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{33}\text{H}_{35}\text{N}_2^+$ [$\text{M} + \text{H}^+$] 459.27948, found 459.27940.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-9-(trimethylsilyl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (**58**). In a pressure tube, **28** (18 mg, 59 μmol , 1.0 equiv) and alkyne **57** (33 mg, 0.19 mmol, 3.3 equiv) were dissolved in freshly degassed chlorobenzene (0.5 mL). A solution of $\text{CpCo}(\text{CO})_2$ (10 μL , 82 μmol , 1.4 equiv) in chlorobenzene (0.5 mL) was added by syringe pump (0.5 mL/h). The reaction was heated to reflux with a projector light for 2 h. The mixture was cooled to 23 $^\circ\text{C}$, and the solvent was removed. The crude material was purified by silica gel chromatography (1/0 \rightarrow 5/1 hexanes/EtOAc) to afford compound **58** (6.1 mg, 26%) as a dark brown oil: $[\alpha]_D^{23.0} +20.0$ (c 0.35, CH_2Cl_2); R_f = 0.32 (silica gel, hexanes/EtOAc = 4/1); ^1H NMR (400 MHz, CDCl_3) δ 0.32 (s, 9H), 0.76 (d, J = 6.0 Hz, 3H), 1.15–1.34 (m, 4H), 1.41–1.58 (m, 3H), 1.74–1.78 (m, 2H), 1.90 (dt, J = 3.2 and 12.4 Hz, 1H), 2.09–2.12 (m, 1H), 2.41–2.53 (m, 2H), 2.67 (d, J = 18.8 Hz, 1H), 3.19 (dd, J = 7.2 and 18.8 Hz, 1H), 4.12 (d, J = 14.4 Hz, 1H), 4.22 (d, J = 14.4 Hz, 1H), 7.23–7.26 (m, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 8.26 (d, J = 2.0 Hz, 1H), 8.44 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 0.0, 22.6, 23.6, 27.5, 28.2, 35.1, 36.4, 40.2, 44.9, 47.0, 49.3, 52.3, 61.3, 127.6, 128.9, 129.3, 133.2, 138.3, 140.7, 143.8, 151.9, 160.0; IR ν 2919, 1360, 837 cm^{-1} ; HRMS calcd for $\text{C}_{26}\text{H}_{37}\text{N}_2\text{Si}^+$ [$\text{M} + \text{H}^+$] 405.2726, found 405.2719.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (**59**). To a solution of **58** (25 mg, 62 μmol , 1.0 equiv) in THF (2 mL) at 23 $^\circ\text{C}$ was added TBAF solution (0.19 mL, 1 M in THF, 0.19 mmol, 3.0 equiv), and the flask was immersed in a heated oil bath. After 12 h, the mixture was cooled to 23 $^\circ\text{C}$, diluted with saturated NH_4Cl solution (5 mL), and extracted with EtOAc (3 \times 5 mL). The organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (5/1 \rightarrow 2/1 hexanes/EtOAc) to afford **59** (20 mg, 97%): $[\alpha]_D^{23.0} +49.2$ (c 0.63, CH_2Cl_2); R_f = 0.23 (silica gel, hexanes/EtOAc = 4/1); ^1H NMR (400 MHz, CDCl_3) δ 0.75 (d, J = 6.0 Hz, 3H), 1.13–1.36 (m, 5H), 1.44–1.50 (m, 1H), 1.55–1.59 (m, 1H), 1.73–1.81 (m, 2H), 1.92 (dt, J = 7.2 and 12.8 Hz, 1H), 2.10–2.13 (m, 1H), 2.43–2.52 (m, 2H), 2.68 (d, J = 18.8 Hz, 1H), 3.21 (dd, J = 7.2 and 18.8 Hz, 1H), 4.07 (d, J = 14.0 Hz, 1H), 4.23 (d, J = 14.0 Hz, 1H), 7.14 (dd, J = 4.8 and 8.0 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.2 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H), 8.12 (dd, J = 1.2 and 8.0 Hz, 1H), 8.38 (dd, J = 1.2 and 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1, 22.4, 26.5, 27.1, 34.0, 35.4, 38.5, 43.8, 45.5, 48.2, 50.9, 60.3, 121.6, 126.5, 128.0, 128.2, 134.4, 138.2, 142.4, 146.8, 158.6; IR ν 2919, 1359, 735 cm^{-1} ; HRMS calcd for $\text{C}_{23}\text{H}_{29}\text{N}_2^+$ [$\text{M} + \text{H}^+$] 333.2331, found 333.2327.

Lycodine (60). Under balloon pressure of H_2 , pyridine **59** (4.2 mg, 0.044 mmol, 1.0 equiv) was dissolved in THF (1.5 mL), and Pd/C (1 mg, 10 wt %, 7%) was added at 23 $^\circ\text{C}$. After 10 h, the same amount of Pd/C was added. After another 10 h, the reaction was diluted with EtOAc (10 mL), filtered, and concentrated to afford lycodine (**60**) (2.9 mg, 95%) as white crystals: mp 95.3–96.3 $^\circ\text{C}$; $[\alpha]_D^{23.0} -69.2$ (c

0.13, MeOH); R_f = 0.22 (silica gel, $\text{CHCl}_3/\text{MeOH}$ = 100/7); ^1H NMR (400 MHz, CDCl_3) δ 0.81 (d, J = 6.4 Hz, 3H), 1.10–1.21 (m, 2H), 1.32 (m, 2H), 1.36–1.43 (m, 1H), 1.49 (ddd, J = 2.0, 3.6, and 12.0 Hz, 1H), 1.56–1.61 (m, 2H), 1.66 (dt, J = 3.6 and 12.8 Hz, 1H), 1.73 (dt, J = 3.6 and 12.8 Hz, 1H), 1.78–1.84 (m, 1H), 2.11–2.15 (m, 1H), 2.45 (dt, J = 3.6 and 12.8 Hz, 1H), 2.68 (d, J = 18.8 Hz, 1H), 2.75–2.80 (m, 1H), 3.15 (dd, J = 7.2 Hz, 1H), 7.29 (dd, J = 4.8 and 8.0 Hz, 1H), 7.89 (dd, J = 1.6 and 8.0 Hz, 1H), 8.31 (dd, J = 1.6 and 4.8 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.3, 27.0, 27.1, 27.4, 34.7, 35.7, 42.0, 44.5, 44.7, 51.5, 58.0, 123.3, 135.3, 137.3, 147.6, 159.6; IR ν 3438, 1635 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{23}\text{N}_2^+$ [$\text{M} + \text{H}^+$] 243.1861, found 243.1856.

(4aR,5S,10bR,12R)-1-Benzyl-8-ethynyl-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (63). To a solution of **32** (700 mg, 1.3 mmol, 1.0 equiv) in THF (15 mL) at 23 °C was added TBAF solution (6.0 mL, 1 M in THF, 6.0 mmol, 4.5 equiv), and the flask was immersed in a heated oil bath. After 13 h, the mixture was cooled to 23 °C, diluted with saturated NH_4Cl solution (20 mL), and extracted with EtOAc (3 \times 30 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 to 5/1 hexanes/EtOAc) to afford **63** (431 mg, 85%) as a light brown foam: $[\alpha]_D^{25} +19.1$ (c 0.29, CH_2Cl_2); R_f = 0.43 (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.75 (d, J = 6.0 Hz, 3H), 1.11–1.32 (m, 4H), 1.47–1.58 (m, 3H), 1.74–1.80 (m, 2H), 1.91–1.94 (m, 1H), 2.05–2.12 (m, 1H), 2.37–2.53 (m, 2H), 2.70 (d, J = 18.8 Hz, 1H), 3.10 (s, 1H), 3.22 (dd, J = 7.2 and 18.8 Hz, 1H), 4.04 (d, J = 14.0 Hz, 1H), 4.21 (d, J = 14.0 Hz, 1H), 7.25–7.47 (m, 6H), 8.11 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.8, 22.4, 26.4, 27.1, 33.9, 35.3, 38.2, 43.7, 45.8, 48.1, 50.8, 60.4, 76.1, 83.2, 125.4, 126.5, 128.0, 128.2, 134.6, 138.9, 139.0, 142.1, 159.3; IR ν 1559, 1451, 734 cm^{-1} ; HRMS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2^+$ [$\text{M} + \text{H}^+$] 357.23307, found 357.23225.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-8-((trimethylsilyl)ethynyl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (64). To a solution of **63** (600 mg, 1.7 mmol, 1.0 equiv) in THF (15 mL) at 0 °C was added a solution of LiHMDS (2.0 mL, 1.0 M in THF, 2.0 mmol, 1.2 equiv) dropwise over 2 min. After 10 min, neat TMSCl (0.30 mL, 2.4 mmol, 1.4 equiv) was added. The resulting solution was stirred for 1 h, diluted with aqueous saturated NH_4Cl solution (20 mL), and extracted with EtOAc (3 \times 30 mL). The organic extracts were washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 to 5/1 hexanes/EtOAc) to afford alkyne **64** (650 mg, 90%) as a light brown foam: $[\alpha]_D^{25} +73.9$ (c 1.9, CH_2Cl_2); R_f = 0.65 (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.26 (s, 9H), 0.73 (d, J = 6.4 Hz, 3H), 1.11–1.32 (m, 4H), 1.43–1.61 (m, 3H), 1.72–1.82 (m, 2H), 1.91 (dt, J = 3.6 and 12.4 Hz, 1H), 2.09–2.11 (m, 1H), 2.36–2.53 (m, 2H), 2.70 (d, J = 18.8 Hz, 1H), 3.18 (dd, J = 7.2 and 18.8 Hz, 1H), 4.3 (d, J = 14.0 Hz, 1H), 4.21 (d, J = 14.0 Hz, 1H), 7.23–7.46 (m, 6H), 8.07 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -0.2, 20.8, 22.3, 26.4, 27.1, 33.9, 35.4, 38.2, 43.7, 45.7, 48.1, 50.8, 60.4, 93.5, 104.2, 125.5, 126.5, 128.0, 128.2, 134.5, 138.5, 139.9, 142.2, 159.2; IR ν 1434, 1249, 843 cm^{-1} ; HRMS calcd for $\text{C}_{28}\text{H}_{37}\text{N}_2\text{Si}^+$ [$\text{M} + \text{H}^+$] 429.27260, found 429.27143.

(4aR,5S,10bR,12R)-1-Benzyl-8-((tert-butylidimethylsilyl)ethynyl)-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (65). To a solution of **63** (9.0 mg, 25 μmol , 1.0 equiv) in THF (1.0 mL) at 0 °C was added LiHMDS solution (80 μL , 1.0 M in THF/toluene, 0.080 mmol, 3.2 equiv) followed by solid TBSCl (6.6 mg, 44 μmol , 1.7 equiv). After 3 h, the reaction was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 to 10/1 hexanes/EtOAc) to afford **65** (10.1 mg, 85%) as clear oil: $[\alpha]_D^{25} +43.3$ (c 0.30, CH_2Cl_2); R_f = 0.75 (silica gel, hexanes/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3) δ 0.20 (s, 6H), 0.74 (d, J = 3.0 Hz, 3H), 1.01 (s, 9H), 1.11–1.32 (m, 4H), 1.43–1.49 (m, 1H), 1.54–1.59 (m, 2H), 1.64 (brs, 1H), 1.72–1.80 (m, 2H), 1.91 (dt, J = 3.6 and 12.8 Hz, 1H),

2.09–2.11 (m, 1H), 2.37–2.53 (m, 2H), 2.70 (d, J = 18.8 Hz, 1H), 3.19 (dd, J = 7.2 and 18.8 Hz, 1H), 4.02 (d, J = 19.2 Hz, 1H), 4.20 (d, J = 19.2 Hz, 1H), 7.22–7.25 (m, 1H), 7.32–7.40 (m, 2H), 7.44–7.47 (m, 2H), 8.08 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -4.68, 16.7, 20.9, 22.3, 26.2, 26.5, 27.1, 33.9, 35.3, 38.2, 43.7, 45.7, 48.1, 50.8, 60.4, 92.0, 105.0, 125.8, 126.5, 128.0, 128.2, 134.4, 138.4, 140.0, 142.2, 159.1; IR ν 2925, 1449, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{31}\text{H}_{43}\text{N}_2\text{Si}^+$ [$\text{M} + \text{H}^+$] 471.3196, found 471.3191.

(4aR,5S,10bR,12R)-1-Benzyl-8-ethynyl-9-(trimethylsilyl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (66). To a solution of **32** (50 mg, 0.10 mmol, 1.0 equiv) in THF (5 mL) at 23 °C was added TBAF solution (0.15 mL, 1.0 M in THF, 0.15 mmol, 1.5 equiv). After 10 min, the mixture was diluted with aqueous saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 to 10/1 hexanes/EtOAc) to afford compound **66** (39 mg, 91%) as a light yellow foam: R_f = 0.55 (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.42 (s, 9H), 0.75 (d, J = 6.4 Hz, 3H), 0.83–0.92 (m, 1H), 1.11–1.32 (m, 4H), 1.46 (s, 1H), 1.52–1.58 (m, 1H), 1.70–1.77 (m, 2H), 1.89 (dt, J = 3.6 and 12.8 Hz, 1H), 2.08–2.12 (m, 1H), 2.37–2.54 (m, 2H), 2.69 (d, J = 18.8 Hz, 1H), 3.14–3.20 (m, 2H), 4.07 (d, J = 14.4 Hz, 1H), 4.22 (d, J = 14.4 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.33–7.36 (m, 2H), 7.46–7.48 (m, 2H), 8.27 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -1.34, 21.3, 22.4, 26.3, 27.0, 33.9, 35.2, 38.8, 43.7, 46.0, 48.1, 51.0, 60.3, 78.1, 84.8, 126.5, 127.8, 128.2, 134.8, 137.6, 140.3, 142.5, 143.3, 159.3; IR ν 2921, 1247, 841 cm^{-1} ; HRMS calcd for $\text{C}_{28}\text{H}_{37}\text{N}_2\text{Si}^+$ [$\text{M} + \text{H}^+$] 429.2726, found 429.2722.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-8-((triisopropylsilyl)ethynyl)-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (67). To a solution of **63** (14.5 mg, 41 μmol , 1.0 equiv) in THF (1 mL) at -78 °C were added LiHMDS solution (61 μL , 1.0 M in THF/toluene, 61 μmol , 1.5 equiv) and neat TIPSOTf (12 μL , 45 μmol , 1.1 equiv). After 1 h, the reaction was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 to 10/1 hexanes/EtOAc) to afford **65** (4.2 mg, 20%) as a clear oil and **67** (4.9 mg, 33%): $[\alpha]_D^{25} +37.5$ (c 0.40, CH_2Cl_2); R_f = 0.72 (silica gel, hexanes/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3) δ 0.74 (d, J = 6.0 Hz, 3H), 0.92 (t, J = 7.2 Hz, 1H), 1.15 (s, 17H), 1.18–1.33 (m, 7H), 1.43–1.49 (m, 1H), 1.52–1.61 (m, 2H), 1.72–1.79 (m, 2H), 1.91 (dt, J = 3.6 and 12.4 Hz, 1H), 2.09–2.12 (m, 1H), 2.39–2.53 (m, 2H), 2.71 (d, J = 18.8 Hz, 1H), 2.19 (dd, J = 7.2 and 18.8 Hz, 1H), 4.04 (d, J = 15.0 Hz, 1H), 4.22 (d, J = 15.0 Hz, 1H), 7.24 (t, J = 6.8 Hz, 1H), 7.33–7.37 (m, 3H), 7.45 (d, J = 6.8 Hz, 2H), 8.09 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 11.3, 18.7, 20.9, 22.3, 26.5, 27.1, 34.0, 35.3, 38.2, 43.7, 45.8, 48.1, 50.8, 60.4, 90.4, 106.6, 126.3, 126.5, 128.0, 128.2, 134.4, 138.3, 140.3, 142.2, 159.0; IR ν 2918, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{34}\text{H}_{49}\text{N}_2\text{Si}^+$ [$\text{M} + \text{H}^+$] 513.36595, found 513.36587.

Ethyl 3-((4aR,5S,10bR,12R)-1-Benzyl-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline-8-yl)propiolate (68). To a solution of **63** (10 mg, 28 μmol , 1.0 equiv) in THF (1 mL) at 0 °C was added LiHMDS solution (0.15 mL, 1.0 M in THF/toluene, 150 μmol , 5.4 equiv) and neat ethyl chloroformate (20 μL , 0.26 mmol, 9.2 equiv). After 2 h, the reaction was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 to 2/1 hexanes/EtOAc) to afford **68** (8.8 mg, 76%) as a clear oil: $[\alpha]_D^{25} +12.0$ (c 0.25, CH_2Cl_2); R_f = 0.68 (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.76 (d, J = 6.0 Hz, 3H), 0.88–0.94 (m, 1H), 1.14–1.36 (m, 5H), 1.40–1.52 (m, 2H), 1.55–1.61 (m, 1H), 1.74–1.80 (m, 2H), 1.92–1.96 (m, 1H), 2.11–2.14 (m, 1H), 2.36–2.42 (m, 1H), 2.51–2.55 (m, 1H), 2.72 (m, d, J = 18.8 Hz, 1H), 3.20 (dd, J = 6.8 and 18.8 Hz, 1H), 4.03 (d, J = 14.0 Hz, 1H), 4.23 (d, J = 14.0 Hz, 1H), 4.12 (dd, J = 14.0 and 80.0 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 7.23–7.27 (m, 1H), 7.35

(t, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 8.18 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 20.8, 22.3, 26.5, 27.1, 33.8, 35.3, 38.1, 43.6, 45.9, 48.2, 50.8, 60.6, 62.2, 78.5, 84.7, 126.6, 126.7, 128.0, 128.3, 134.8, 137.2, 140.7, 142.0, 153.7, 160.1; IR ν 2923, 1710, 1219 cm^{-1} ; HRMS calcd for $\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_2^+ [\text{M} + \text{H}^+]$ 429.2542, found 429.2543.

4-((4aR,5S,10bR,12R)-1-Benzyl-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline-8-yl)-2-methylbut-3-yn-2-ol (69). To a solution of **63** (10 mg, 28 μmol , 1.0 equiv) in THF (1 mL) at 0 °C was added LiHMDS solution (0.15 mL, 1.0 M in THF/toluene, 0.15 mmol, 5.4 equiv), and after 20 min, neat acetone (20 μL , 0.27 mmol, 9.7 equiv) was added. After 10 min, the reaction was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 5 mL). The organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 \rightarrow 2/1 hexanes/EtOAc) to afford **69** (7.9 mg, 68%) as a clear oil: $[\alpha]_D^{23.0} +41.0$ (c 0.56, CH_2Cl_2); $R_f = 0.30$ (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.74 (d, $J = 6.4$ Hz, 3H), 0.94 (t, $J = 7.2$ Hz, 2H), 1.12–1.31 (m, 4H), 1.37–1.49 (m, 1H), 1.52–1.66 (m, 6H), 1.72–1.79 (m, 3H), 1.91 (dt, $J = 3.6$ and 12.8 Hz, 1H), 2.10–2.11 (m, 1H), 2.21–2.23 (m, 1H), 2.36–2.52 (m, 2H), 2.70 (d, $J = 18.8$ Hz, 1H), 3.19 (dd, $J = 7.2$ and 18.8 Hz, 1H), 4.03 (d, $J = 14.0$ Hz, 1H), 4.11 (d, $J = 14.0$ Hz, 1H), 7.25–7.30 (m, 1H), 7.35 (t, $J = 7.2$ Hz, 2H), 7.45 (d, $J = 7.2$ Hz, 2H), 8.10 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.8, 22.3, 26.5, 27.0, 31.2, 33.9, 35.3, 38.1, 43.6, 45.7, 48.1, 50.7, 60.4, 65.5, 81.9, 92.8, 125.3, 126.5, 128.0, 128.2, 134.7, 138.4, 139.6, 142.1, 159.1; IR ν 3500, 1459 cm^{-1} ; HRMS calcd for $\text{C}_{28}\text{H}_{35}\text{N}_2\text{O}^+ [\text{M} + \text{H}^+]$ 415.2749, found 415.2749.

4aR,5S,10bR,12R)-1-Benzyl-8-(((3-chloropropyl)dimethylsilyl)ethynyl)-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (int-19). To a solution of **63** (21.0 mg, 41 μmol , 1.0 equiv) in THF (1.5 mL) at -78 °C were added LiHMDS solution (77 μL , 1.0 M in THF/toluene, 77 μmol , 1.3 equiv) and chloro(3-chloropropyl)dimethylsilane (13 μL , 77 μmol , 1.3 equiv). After 30 min, the reaction was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 \rightarrow 10/1 hexanes/EtOAc) to afford **int-19** (19.0 mg, 66%) as a clear oil: $[\alpha]_D^{23.0} +41.0$ (c 0.56, CH_2Cl_2); $R_f = 0.30$ (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.26 (s, 6H), 0.74 (d, $J = 6.0$ Hz, 3H), 0.82 (dt, $J = 4.4$ and 8.0 Hz, 2H), 1.11–1.32 (m, 4H), 1.43–1.63 (m, 4H), 1.72–1.80 (m, 2H), 1.89–1.97 (m, 3H), 2.09–2.13 (m, 1H), 2.40 (dt, $J = 1.2$ and 13.2 Hz, 1H), 2.48–2.53 (m, 1H), 3.19 (dd, $J = 7.2$ and 18.8 Hz, 1H), 3.57 (t, $J = 8.0$ Hz, 2H), 4.03 (d, $J = 14.4$ Hz, 1H), 4.22 (d, $J = 14.4$ Hz, 1H), 7.24–7.27 (m, 1H), 7.32–7.37 (m, 3H), 7.45 (dd, $J = 0.8$ and 8.0 Hz, 2H), 8.09 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ -1.9 , 13.7, 20.8, 22.3, 26.4, 27.0, 27.5, 33.9, 35.4, 38.1, 43.6, 45.7, 47.7, 48.1, 50.7, 60.5, 91.8, 105.2, 125.7, 126.5, 128.0, 128.2, 134.5, 138.7, 139.7, 142.1, 159.2; IR ν 2920, 1558 cm^{-1} ; HRMS calcd for $\text{C}_{30}\text{H}_{40}\text{N}_2\text{SiCl}^+ [\text{M} + \text{H}^+]$ 491.2649, found 491.2645.

4-(3-(((4aR,5S,10bR,12R)-1-Benzyl-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline-8-yl)ethynyl)dimethylsilyl)propyl)morpholine (70). Pyridine **int-19** (15.0 mg, 31 μmol , 1.0 equiv) was dissolved in acetone (1 mL), and NaI (15 mg, 3.3 mmol, 3.3 equiv), morpholine (13 mL, 0.15 mmol, 5.0 equiv), and K_2CO_3 (10 mg, 2.4 mmol, 2.4 equiv) were added. The heterogeneous reaction was heated to reflux. After 48 h, the reaction was cooled to 23 °C, diluted with saturated NH_4Cl solution (5 mL), and extracted with EtOAc (3 \times 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (10/1 hexanes/EtOAc \rightarrow 10/1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford **70** (13.8 mg, 83%) as a pale yellow oil: $[\alpha]_D^{23.0} +24.4$ (c 0.86, CH_2Cl_2); $R_f = 0.35$ (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); ^1H NMR (400 MHz, CDCl_3) δ 0.24 (s, 6H), 0.67–0.70 (m, 2H), 0.74 (d, $J = 6.4$ Hz, 3H), 0.83–0.97 (m, 1H), 1.11–1.33 (m, 4H), 1.42–1.49 (m, 2H), 1.51–1.68 (m, 3H), 1.72–1.82 (m, 2H), 1.91 (dt, $J = 3.6$ and 12.8 Hz, 2H), 2.09–2.11 (m,

1H), 2.37–2.40 (m, 2H), 2.43–2.59 (m, 4H), 2.70 (d, $J = 18.8$ Hz, 1H), 3.18 (dd, $J = 7.2$ and 15.6 Hz, 1H), 3.72 (t, $J = 4.8$ Hz, 4H), 4.03 (d, $J = 15.6$ Hz, 1H), 4.21 (d, $J = 15.6$ Hz, 1H), 7.25 (t, $J = 7.6$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 7.35 (t, $J = 7.6$ Hz, 2H), 7.45 (d, $J = 7.6$ Hz, 2H), 8.08 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ -1.9 , 13.6, 20.80, 20.83, 22.3, 26.5, 27.1, 33.9, 35.3, 38.2, 43.7, 45.8, 48.1, 50.8, 53.7, 60.5, 62.1, 66.9, 92.5, 104.9, 125.6, 126.5, 128.0, 128.2, 134.5, 138.6, 139.8, 142.1, 159.2; IR ν 2925, 1450 cm^{-1} ; HRMS calcd for $\text{C}_{34}\text{H}_{48}\text{N}_3\text{OSi}^+ [\text{M} + \text{H}^+]$ 542.35666, found 542.35636.

(5R,5'R,6S,6'S,14R,14'R,16R,16'R)-1,1'-Dibenzyl-16,16'-dimethyl-11-(trimethylsilyl)-1,1',2,2',3,3',4,4',5,5',6,6',7,7',15,15',16,16',-17,17'-icosahydro-10,10'-bi(5,10b-propano-1,7-phenanthroline) (71). In a pressure tube, **64** (18.5 mg, 43 μmol , 1.0 equiv) and alkynenitrile **28** (20.0 mg, 65 μmol , 1.5 equiv) were dissolved in degassed THF (4 mL). Neat $\text{CpCo}(\text{CO})_2$ (30 μL , 34 μmol , 0.8 equiv) was added, and the tube was sealed. The resulting solution was placed in an oil bath heated to 140 °C. After 14 h, the mixture was cooled, and the reaction was concentrated. The product was purified by silica gel chromatography (20/1 to 10/1 hexanes/EtOAc) to afford bipyrindyl **71** (13.6 mg, 43%) as a yellow oil: $[\alpha]_D^{24} +26.3$ (c 0.49, CH_2Cl_2); $R_f = 0.65$ (silica gel, hexanes/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3) δ 0.20 (s, 9H), 0.74 (d, $J = 6.4$ Hz, 3H), 0.77 (d, $J = 6.4$ Hz, 3H), 1.10–1.59 (m, 14H), 1.70–1.83 (m, 4H), 1.90–1.96 (m, 2H), 2.13 (bs, 2H), 2.54 (brs, 4H), 2.73–2.78 (m, 2H), 3.19–3.28 (m, 2H), 4.11–4.27 (m, 4H), 7.23–7.27 (m, 1H), 7.36 (t, $J = 7.6$ Hz, 4H), 7.51 (t, $J = 8.0$ Hz, 5H), 7.80 (d, $J = 8.4$ Hz, 1H), 8.20 (d, $J = 8.4$ Hz, 1H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 1.0, 21.4, 21.8, 22.3, 22.4, 26.3, 26.5, 27.1, 27.2, 34.1, 34.2, 35.1, 35.3, 38.8, 39.5, 43.9, 43.9, 45.9, 45.9, 48.1, 48.1, 51.0, 51.2, 60.3, 60.4, 121.0, 126.4, 126.4, 127.8, 128.0, 128.2, 128.2, 130.5, 135.2, 135.9, 137.3, 142.3, 142.5, 142.8, 156.9, 157.0, 158.0, 159.9; IR ν 1453, 1242, 838, 733 cm^{-1} ; HRMS calcd for $\text{C}_{49}\text{H}_{63}\text{N}_4\text{Si}^+ [\text{M} + \text{H}^+]$ 735.48220, found 735.48176.

(5R,5'R,6S,6'S,14R,14'R,16R,16'R)-1,1'-Dibenzyl-11-(tert-butyl(dimethylsilyl)-16,16'-dimethyl-1,1',2,2',3,3',4,4',5,5',6,6',7,7',-15,15',16,16',17,17'-icosahydro-10,10'-bi(5,10b-propano-1,7-phenanthroline) (72). In a pressure tube, alkynenitrile **65** (15 mg, 32 μmol , 1.0 equiv) and **28** (15 mg, 49 μmol , 1.5 equiv) were dissolved in degassed THF (2 mL). Neat $\text{CpCo}(\text{CO})_2$ (5.0 μL , 41 μmol , 1.3 equiv) was added, and the tube was sealed. The resulting solution was placed in an oil bath heated to 140 °C. After 10 h the reaction was cooled and concentrated. The crude was purified by silica gel chromatography (20/1 \rightarrow 10/1 hexanes/EtOAc) to afford **72** (7.2 mg, 29%) as a yellow oil: $[\alpha]_D^{23.0} +26.3$ (c 0.38, CH_2Cl_2); $R_f = 0.62$ (silica gel, hexanes/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3) δ -0.11 (s, 3H), -0.10 (s, 3H), 0.76 (d, $J = 6.0$ Hz, 3H), 0.76 (d, $J = 6.0$ Hz, 3H), 0.83–1.02 (m, 12H), 1.15–1.19 (m, 2H), 1.26–1.43 (m, 5H), 1.47–1.63 (m, 4H), 1.70–1.84 (m, 3H), 1.90–1.95 (m, 2H), 2.11–2.14 (m, 2H), 2.51–2.55 (m, 4H), 2.72 (dd, $J = 3.6$ and 19.2 Hz, 2H), 3.22 (dd, $J = 7.2$ and 19.2 Hz, 2H), 4.8–4.14 (m, 2H), 4.23–4.29 (m, 2H), 7.23–7.27 (m, 2H), 7.33–7.40 (m, 5H), 7.49–7.51 (m, 4H), 8.14 (d, $J = 8.0$ Hz, 2H), 8.45 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -4.0 , -3.8 , 14.1, 17.8, 21.3, 22.3, 22.4, 22.6, 26.38, 26.44, 27.1, 27.4, 34.1, 34.2, 34.7, 35.3, 38.7, 38.8, 43.8, 43.9, 45.6, 46.0, 48.1, 48.3, 50.95, 51.01, 60.2, 60.4, 121.9, 126.4, 126.4, 127.8, 128.0, 128.1, 128.2, 128.2, 134.6, 135.4, 137.1, 142.4, 142.7, 143.1, 157.0, 157.6, 158.1, 161.3; IR ν 2925, 2854, 733 cm^{-1} ; HRMS calcd for $\text{C}_{52}\text{H}_{69}\text{N}_4\text{Si}^+ [\text{M} + \text{H}^+]$ 777.52915, found 777.52834.

Benzyl-Masked Pseudosymmetric Complanadine A (73). To a solution of **71** (21 mg, 29 μmol , 1.0 equiv) in dioxane (1.5 mL) at 23 °C was added TBAF solution (0.15 mL, 1.0 M in THF, 75 μmol , 5.2 equiv). The resulting solution was placed in a heated oil bath. After 10 h, the reaction was concentrated and purified by silica gel chromatography (1/0 \rightarrow 10/1 hexanes/EtOAc) to afford compound **73** (15.5 mg, 82%) as a light yellow foam: $R_f = 0.65$ (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (500 MHz, CDCl_3) δ 0.74 (d, $J = 6.5$ Hz, 6H), 0.86–1.03 (m, 2H), 1.14–1.61 (m, 8H), 1.77–1.80 (m, 4H), 1.94 (dt, $J = 4.5$ and 11.5 Hz, 2H), 2.14 (brs, 2H), 2.52 (d, $J = 9.5$ Hz, 4H), 2.80 (d, $J = 23.5$ Hz, 2H), 3.29 (dd, $J = 9.5$ and 23.5 Hz, 2H), 4.12 (d, $J = 18.0$ Hz, 2H), 4.25 (d, $J = 18.0$ Hz, 2H), 7.23–7.27 (m, 6H), 7.36 (t, $J = 9.5$ Hz, 4H), 7.50 (d, $J = 9.5$ Hz, 4H), 8.10 (d, $J =$

10.0 Hz, 2H), 8.21 (d, J = 10.0 Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 22.4, 26.5, 27.2, 29.7, 34.2, 35.6, 38.8, 34.8, 45.8, 48.2, 51.0, 60.5, 119.2, 126.5, 128.0, 128.2, 135.3, 138.0, 142.5, 154.1, 158.2; IR ν 2965, 1601 cm^{-1} ; HRMS calcd for $\text{C}_{46}\text{H}_{53}\text{N}_4^+$ [$\text{M} + \text{H}^+$] 663.44267, found 663.44200.

(5*R*,5'*R*,6*S*,6'*S*,14*R*,14'*R*,16*R*,16'*R*)-1,1'-Dibenzyl-16,16'-dimethyl-11-(trimethylsilyl)-1,1',2,2',3,3',4,4',5,5',6,6',7,7',15,15',-16,16',17,17'-icosahydro-10,11'-bi(5,10bpropano-1,7-phenanthroline) (**77**). In a pressure tube, **33** (14 mg, 33 μmol , 1.0 equiv) and alkyne–nitrile **28** (14 mg, 46 μmol , 1.4 equiv) were dissolved in degassed THF (2 mL). Neat $\text{CpCo}(\text{CO})_2$ (5 μL , 41 μmol , 1.2 equiv) was added, and the tube was sealed. The resulting solution was placed in an oil bath heated to 140 °C. After 10 h, the mixture was cooled to 23 °C, and the reaction was concentrated. The crude was purified by silica gel chromatography (20/1 \rightarrow 10/1 hexanes/EtOAc) to afford bipyrindyl **77** (6.8 mg, 28%) as a yellow oil: $[\alpha]_D^{23.0} +34.2$ (c 0.30, CH_2Cl_2); R_f = 0.2 (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3) δ 0.10 (s, 9H), 0.79 (d, J = 5.6 Hz, 3H), 0.82 (d, J = 6.0 Hz, 3H), 0.85–0.91 (m, 2H), 1.12–1.43 (m, 7H), 1.49–1.66 (m, 6H), 1.75–1.84 (m, 4H), 1.93–2.00 (m, 2H), 2.12–2.18 (m, 2H), 2.45–2.63 (m, 3H), 2.76 (dd, J = 3.6 and 18.4 Hz, 2H), 3.23 (dt, J = 7.6 and 19.0 Hz, 2H), 4.04–4.29 (m, 4H), 7.22–7.42 (m, 6H), 7.45 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H), 8.18 (d, J = 1.6 Hz, 1H), 8.38 (s, 1H), 8.48 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 0.6, 14.1, 20.7, 21.7, 22.3, 22.6, 24.9, 26.3, 26.6, 27.1, 31.8, 34.0, 34.1, 35.3, 38.3, 39.4, 43.8, 45.4, 45.8, 47.8, 48.0, 50.7, 51.2, 60.2, 60.6, 126.4, 126.5, 127.6, 127.8, 128.1, 128.2, 128.4, 130.8, 134.3, 135.4, 136.9, 137.5, 141.9, 142.0, 142.7, 147.0, 157.9, 158.5, 159.5; IR ν 3390, 2922, 1559, 732 cm^{-1} ; HRMS calcd for $\text{C}_{49}\text{H}_{63}\text{N}_4\text{Si}^+$ [$\text{M} + \text{H}^+$] 735.4822, found 735.4820.

Benzyl-Masked Complanadine A (78). To a solution of **77** (8.1 mg, 11 μmol , 1.0 equiv) in dioxane (1 mL) at 23 °C was added TBAF solution (1.0 M in THF, 50 μL , 50 μmol , 4.6 equiv), and the reaction was placed in a heated oil bath. After 10 h, the mixture was cooled to 23 °C, diluted with saturated NH_4Cl solution (10 mL), and extracted with EtOAc (3 \times 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (5/1 \rightarrow 1/1 hexanes/EtOAc) to afford **78** (7.3 mg, 97%) as a light yellow oil: $[\alpha]_D^{23.0} +36.9$ (c 0.73, CH_2Cl_2); R_f = 0.40 (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3) δ 0.76 (d, J = 6.0 Hz, 3H), 0.77 (d, J = 6.0 Hz, 3H), 1.17–1.21 (m, 2H), 1.23–1.37 (m, 3H), 1.37–1.44 (m, 1H), 1.44–1.55 (m, 2H), 1.55–1.69 (m, 4H), 1.73–1.83 (m, 4H), 1.92–1.99 (m, 2H), 2.13–2.19 (m, 2H), 2.53–2.57 (m, 4H), 2.79 (dd, J = 18.8 and 34.4 Hz, 2H), 3.22–3.35 (m, 2H), 4.10–4.32 (m, 4H), 7.24–7.28 (m, 4H), 7.38 (dt, J = 3.6 and 7.2 Hz, 4H), 7.51 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 7.2 Hz, 2H), 7.61 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.74 (d, J = 2.4 Hz, 1H), 8.98 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1, 21.7, 22.3, 22.4, 26.4, 26.6, 27.2, 34.1, 34.2, 35.3, 35.6, 38.7, 39.3, 43.8, 45.9, 46.0, 48.0, 48.2, 50.9, 51.2, 60.4, 60.5, 118.4, 126.4, 126.5, 128.0, 128.2, 132.7, 133.3, 135.3, 137.1, 137.9, 142.4, 142.6, 145.3, 152.5, 158.7, 158.9; IR ν 3446, 2921, 1447, 732 cm^{-1} ; HRMS calcd for $\text{C}_{46}\text{H}_{53}\text{N}_4^+$ [$\text{M} + \text{H}^+$] 663.4427, found 663.4427.

Complanadine A (1). To protected complanadine (**78**) (8.0 mg, 12 μmol , 1.0 equiv) in THF (1 mL) was added solid 10% palladium on carbon (2.0 mg, 15.6 μmol , 0.16 equiv), and the heterogeneous solution was rapidly stirred under a balloon of H_2 (1 atm) at 23 °C. After 20 h, the solution was filtered through a Celite pad and concentrated to afford the complanadine A (5.1 mg, 88%) as a pale yellow oil. Additional purification was achieved as follows: the above complanadine A (12 mg, 25 μmol , 1.0 equiv) was dissolved in 5% HCl solution (5 mL) and washed with Et_2O (2 \times 5 mL), the aqueous layer was adjusted to a pH of 13 with 10% aqueous NaOH solution, and the white suspension was extracted with EtOAc (3 \times 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated to provide complanadine A (**1**) (5.1 mg, 90%) as a pale yellow oil: $[\alpha]_D^{24} +14.5$ (c 0.30, MeOH); ^1H NMR (400 MHz, MeOH): δ 0.85 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 1.21–1.49 (m, 10H), 1.53–1.64 (m, 5H), 1.68–1.72 (m,

1H), 1.75–1.81 (m, 2H), 1.85–1.89 (m, 2H), 2.18–2.22 (m, 2H), 2.48–2.57 (m, 2H), 2.76–2.85 (m, 4H), 3.20–3.30 (m, 2H), 7.77 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.48 (s, 1H), 8.93 (s, 1H); ^{13}C NMR (100 MHz, MeOH): δ 22.4, 27.1, 27.3, 27.7, 34.8, 34.9, 35.7, 36.2, 42.1, 44.7, 44.8, 44.9, 51.6, 51.7, 57.8, 57.9, 120.4, 133.7, 135.0, 135.9, 136.6, 137.6, 146.1, 153.7, 159.9, 160.5; IR ν 2913, 1575, 1436 cm^{-1} ; HRMS calcd for $\text{C}_{32}\text{H}_{43}\text{N}_4^+$ [$\text{M} + \text{H}^+$] 483.34877, found 483.34828.

(4*aR*,5*S*,10*bR*,12*R*)-1-Benzyl-9-(((tert-butyl)dimethylsilyl)oxy)-methyl-12-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-5,10*b*-propano-1,7-phenanthroline (**81**). In a pressure tube alkyne **79** (218 mg, 0.90 mmol, 2.5 equiv) and alkyne–nitrile **28** (110 mg, 0.36 mmol, 1.0 equiv) were dissolved in freshly degassed THF (2.0 mL). Neat $\text{CpCo}(\text{CO})_2$ (60 μL , 0.48 mmol, 1.4 equiv) was added and the tube was sealed. The resulting solution was placed in an 140 °C oil bath. After 30 h the reaction was cooled to 23 °C and concentrated. The crude material was purified by silica gel chromatography (1/0 \rightarrow 5/1 hexanes/EtOAc) to afford **81** (65 mg, 34%) as a brown oil and unreacted **28** (14 mg, 11%) was recovered. If the reaction was run at 0.05 M, the ratio is 1/3 (**81**/**80**). The undesired product **80** was subjected to desilylation for characterization: $[\alpha]_D^{23.0} +28.5$ (c 0.23, CH_2Cl_2); R_f = 0.41 (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.13 (d, J = 2.0 Hz, 6H), 0.75 (d, J = 6.0 Hz, 3H), 0.95 (s, 9H), 1.11–1.35 (m, 4H), 1.43–1.58 (m, 3H), 1.71–1.80 (m, 2H), 1.93 (dt, J = 3.6 and 12.8 Hz, 1H), 2.09–2.12 (m, 1H), 2.43–2.52 (m, 2H), 3.19 (dd, J = 7.2 and 18.8 Hz, 1H), 4.14 (d, J = 14.4 Hz, 1H), 4.23 (d, J = 14.4 Hz, 1H), 4.77 (s, 2H), 7.22–7.26 (m, 1H), 7.32–7.36 (m, 2H), 7.47–7.49 (m, 2H), 8.10 (d, J = 2.4 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -5.2, -5.1, 18.4, 21.3, 22.4, 25.9, 26.4, 27.1, 34.0, 35.1, 38.7, 43.8, 45.8, 48.1, 51.1, 60.4, 63.0, 126.4, 127.9, 128.2, 132.5, 134.4, 137.7, 142.4, 144.9, 157.3; IR ν 2918, 1653, 1094 cm^{-1} ; HRMS calcd for $\text{C}_{30}\text{H}_{45}\text{N}_2\text{OSi}^+$ [$\text{M} + \text{H}^+$] 477.33012, found 477.32948.

((4*aR*,5*S*,10*bR*,12*R*)-1-Benzyl-12-methyl-9-(trimethylsilyl)-2,3,4,4*a*,5,6-hexahydro-1*H*-5,10*b*-propano-1,7-phenanthroline-8-yl)methanol (**int-20**). To a solution of **80** (61 mg, 0.13 mmol, 1.0 equiv) in THF (5 mL) at 23 °C was added TBAF solution (0.15 mL, 1.0 M in THF, 0.15 mmol, 1.2 equiv). After 30 min, the mixture was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (10/1 \rightarrow 1/1 hexanes/EtOAc) to afford **int-20** (12 mg, 22%) as a light brown foam: $[\alpha]_D^{23.0} +57.1$ (c 0.35, CH_2Cl_2); R_f = 0.35 (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.35 (s, 9H), 0.76 (d, J = 6.0 Hz, 3H), 1.14–1.34 (m, 5H), 1.43–1.57 (m, 3H), 1.71–1.80 (m, 2H), 1.89 (dt, J = 3.6 and 12.8 Hz, 1H), 2.10–2.12 (m, 1H), 2.40–2.53 (m, 2H), 2.65 (d, J = 19.2 Hz, 1H), 3.16 (dd, J = 7.2 and 19.2 Hz, 1H), 4.09 (d, J = 14.0 Hz, 1H), 4.22 (d, J = 14.0 Hz, 1H), 4.73 (d, J = 1.6 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.2 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H), 8.26 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 0.0, 22.0, 23.0, 27.0, 27.6, 34.6, 35.5, 39.6, 44.3, 46.6, 48.6, 51.6, 60.6, 64.1, 127.0, 128.4, 128.8, 136.2, 142.1, 143.2, 157.5, 159.4, 163.5; IR ν 2923, 1068, 839 cm^{-1} ; HRMS calcd for $\text{C}_{27}\text{H}_{39}\text{N}_2\text{OSi}^+$ [$\text{M} + \text{H}^+$] 435.2832, found 435.2826.

((4*aR*,5*S*,10*bR*,12*R*)-1-Benzyl-12-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-5,10*b*-propano-1,7-phenanthroline-9-yl)methanol (**82**). To a solution of **81** (200 mg, 0.42 mmol, 1.0 equiv) in THF (5 mL) at 23 °C was added TBAF solution (0.80 mL, 1.0 M in THF, 0.80 mmol, 1.9 equiv). After 30 min, the reaction was concentrated. The crude material was purified by silica gel chromatography (5/1 \rightarrow 0/1 hexanes/EtOAc) to afford **82** (119 mg, 78%) as light brown oil: $[\alpha]_D^{23.0} +29.0$ (c 0.24, CH_2Cl_2); R_f = 0.32 (silica gel, EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 0.75 (d, J = 6.0 Hz, 3H), 0.91–0.99 (m, 1H), 1.12–1.33 (m, 4H), 1.45–1.58 (m, 3H), 1.74–1.80 (m, 2H), 1.92 (dt, J = 4.0 and 13.2 Hz, 1H), 2.08–2.12 (m, 1H), 2.39–2.53 (m, 2H), 2.69 (d, J = 18.8 Hz, 1H), 3.18 (dd, J = 6.8 and 18.8 Hz, 1H), 4.09 (d, J = 14.4 Hz, 1H), 4.22 (d, J = 14.4 Hz, 1H), 4.73 (s, 2H), 7.23–7.26 (m, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H), 8.11 (d, J = 2.4 Hz, 1H), 8.36 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz,

CDCl_3) δ 21.1, 22.4, 26.4, 27.0, 33.9, 35.0, 38.5, 43.7, 45.8, 48.1, 51.0, 60.4, 63.1, 126.5, 128.0, 128.2, 133.6, 134.1, 138.1, 142.2, 145.7, 157.9; IR ν , 2921, 1453, 732 cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}^+ [\text{M} + \text{H}^+]$ 363.2436, found 363.2433.

(4aR,5S,10bR,12R)-1-Benzyl-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline-9-carbaldehyde (83). To a solution of **82** (46 mg, 0.13 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added solid Dess–Martin periodinane (215 mg, 0.51 mmol, 4.0 equiv) at 23 °C. After 30 min, the heterogeneous solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (20/1 \rightarrow 2/1 hexanes/EtOAc) to afford **83** (44.1 mg, 96%) as a pale yellow oil: $[\alpha]^{23.0}_{\text{D}} +28.5$ (c 0.23, CH_2Cl_2); R_f = 0.20 (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.77 (d, J = 6.0 Hz, 3H), 1.14–1.37 (m, 4H), 1.53–1.63 (m, 3H), 1.75–1.81 (m, 2H), 1.99 (dt, J = 3.2 and 12.4 Hz, 1H), 2.11–2.18 (m, 1H), 2.35–2.42 (m, 1H), 2.53–2.58 (m, 1H), 2.79 (d, J = 19.6 Hz, 1H), 3.27 (dd, J = 7.2 and 19.2 Hz, 1H), 4.18 (dd, J = 14.4 and 64.0 Hz, 2H), 7.24–7.28 (m, 1H), 7.37 (t, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 8.57 (d, J = 2.0 Hz, 1H), 8.47 (d, J = 2.0 Hz, 1H), 10.1 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.0, 22.3, 26.4, 27.1, 33.8, 36.0, 38.2, 43.5, 45.8, 48.1, 51.0, 60.5, 126.7, 128.0, 128.3, 130.3, 134.9, 139.3, 141.8, 149.0, 165.5, 191.3; IR ν 2919, 1698, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}^+ [\text{M} + \text{H}^+]$ 361.2280, found 361.2278.

(4aR,5S,10bR,12R)-1-Benzyl-9-ethynyl-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline (85). To a solution of **83** (50 mg, 0.14 mmol, 1.0 equiv) and K_2CO_3 (47.9 mg, 0.35 mmol, 2.5 equiv) in methanol (2 mL) was added dimethyl 1-diazo-2-oxopropylphosphate **84** (66.6 mg, 0.35 mmol, 2.5 equiv) at 23 °C. After 8 h, the reaction was diluted with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (20/1 \rightarrow 5/1 hexanes/EtOAc) to afford **85** (42.3 mg, 86%) as a white foam: $[\alpha]^{23.0}_{\text{D}} +27.5$ (c 0.29, CH_2Cl_2); R_f = 0.65 (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.76 (d, J = 6.0 Hz, 3H), 1.14–1.33 (m, 4H), 1.48–1.50 (m, 1H), 1.56–1.64 (m, 2H), 1.73–1.83 (m, 2H), 1.93 (dt, J = 3.6 and 12.8 Hz, 1H), 2.10–2.13 (m, 1H), 2.40–2.54 (m, 2H), 2.68 (d, J = 19.2 Hz, 1H), 3.16–3.23 (m, 2H), 4.05 (d, J = 14.0 Hz, 1H), 4.23 (d, J = 14.0 Hz, 1H), 7.25–7.27 (m, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 8.21 (d, J = 2.0 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.9, 22.3, 26.4, 27.0, 33.8, 35.4, 38.2, 43.6, 45.7, 48.1, 50.8, 60.3, 79.2, 81.4, 116.7, 126.6, 128.0, 128.3, 137.5, 137.9, 142.0, 149.8, 158.9; IR ν 2921, 1450, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2^+ [\text{M} + \text{H}^+]$ 357.2331, found 357.2326.

2-((4aR,5R,7S,8aS)-8a-Ethynyl-7-methyldecahydroquinolin-5-yl)-acetonitrile (86). Amine **29** (600 mg, 1.78 mmol, 1.0 equiv) was dissolved in acetonitrile/water (6/1, 15 mL). Solid CAN (4.0 g, 7.3 mmol, 4.1 equiv) was added in one portion, and the solution was placed in a 75 °C oil bath. After 5 h, the mixture was neutralized with aqueous NaOH solution (1.0 M, 15 mL) and filtered through a Celite pad. The mixture was extracted with EtOAc (3 \times 15 mL), washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (the column was neutralized with 1% Et_3N in hexane) (5/1 \rightarrow 0/1 hexanes/EtOAc) to afford the secondary amine **86** (260 mg, 67%, mp 153.8–154.2 °C) as a pale yellow solid. Alternatively, the following procedure was used: Amine **30** (200 mg, 0.55 mmol, 1.0 equiv) was dissolved in acetonitrile/water (6/1, 12 mL) at 23 °C. Solid CAN (500 mg, 0.91 mmol, 1.6 equiv) was added in one portion. After 5 min at 23 °C, the mixture was neutralized with aqueous NaOH solution (1 M, 5 mL) and filtered through a Celite pad. The mixture was extracted with EtOAc (3 \times 10 mL), and the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (column was neutralized with 1% Et_3N in hexane) (5/1 \rightarrow 0/1 hexanes/EtOAc) to afford the secondary amine **86** (81 mg, 70%, mp 153.8–154.2 °C) as a pale yellow solid: $[\alpha]^{24}_{\text{D}} -24.1$ (c 0.27, CH_2Cl_2); R_f =

0.25 (silica gel, neutralized by Et_3N , EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 0.95 (d, J = 6.4 Hz, 3H), 1.13 (t, J = 12.1 Hz, 1H), 1.24–1.32 (m, 1H), 1.43–1.66 (m, 4H), 1.70–1.80 (m, 2H), 1.91–2.08 (m, 3H), 2.44 (s, 1H), 2.50–2.56 (m, 1H), 2.81–2.86 (m, 1H), 2.93 (dd, J = 4.0 and 17.2 Hz, 1H), 3.04–3.11 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.9, 21.8, 24.1, 26.1, 26.4, 36.3, 38.4, 42.3, 45.8, 48.6, 54.1, 75.1, 87.5, 120.5; IR ν 3285, 1457, 1124, 637 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2^+ [\text{M} + \text{H}^+]$ 217.17014, found 217.16996.

2-((4aR,5R,7S,8aS)-8a-Ethynyl-1-formyl-7-methyldecahydroquinolin-5-yl)acetonitrile (87). To a solution of **86** (260 mg, 1.2 mmol, 1.0 equiv) in THF (7 mL) were added neat AcOCHO (200 μL , 1.9 mmol, 1.6 equiv) and Hünig's base (300 μL , 1.6 mmol, 1.4 equiv) at 23 °C. After 30 min, the solution was diluted with aqueous saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated to afford **87** (290 mg, 97%, mp 155.0–155.2 °C) as a pale yellow solid: $[\alpha]^{24}_{\text{D}} +81.8$ (c 1.0, CH_2Cl_2); R_f = 0.28 (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3) δ 1.07 (d, J = 6.8 Hz, 3H), 1.32 (dt, J = 5.2 and 13.6 Hz, 1H), 1.42–1.67 (m, 4H), 1.78–1.85 (m, 2H), 1.98–2.19 (m, 3H), 2.34 (d, J = 11.6 Hz, 1H), 2.59–2.64 (m, 2H), 2.87–2.97 (m, 2H), 4.47–4.51 (m, 1H), 8.36 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.9, 21.9, 24.4, 25.1, 26.5, 36.5, 37.6, 37.7, 44.0, 46.9, 57.4, 76.6, 83.8, 119.8, 158.7; IR 1659, 1385, 1131, 913 cm^{-1} ; HRMS calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}^+ [\text{M} + \text{H}^+]$ 245.16539, found 245.16486.

(4aR,5R,7S,8aS)-Methyl 5-(Cyanomethyl)-8a-ethynyl-7-methyloctahydroquinoline-1(2H)-carboxylate (90). To a solution of **86** (50 mg, 0.23 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) were added Et_3N (0.097 mL, 0.69 mmol, 3.0 equiv) and methyl chloroformate (36 μL , 0.46 mmol, 2.0 equiv) at 23 °C. After 1 h, the resulted solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 10 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (10/1 \rightarrow 5/1 hexanes/EtOAc) to afford carbamate **90** (55 mg, 87%) as a yellow oil: $[\alpha]^{23.0}_{\text{D}} +30.0$ (c 0.20, CH_2Cl_2); R_f = 0.70 (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 1.00 (d, J = 6.4 Hz, 3H), 1.30 (dt, J = 5.2 and 13.2 Hz, 1H), 1.40 (t, J = 13.2 Hz, 1H), 1.51–1.63 (m, 2H), 1.70–1.80 (m, 3H), 1.91–1.99 (m, 2H), 2.14–2.19 (m, 1H), 2.51 (s, 1H), 2.63 (ddd, J = 0.8, 4.0, and 17.2 Hz, 1H), 2.94 (dd, J = 12.0 and 17.2 Hz, 1H), 3.24–3.31 (m, 2H), 3.64 (s, 3H), 3.91–3.96 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.2, 22.0, 24.7, 24.8, 25.9, 37.4, 37.9, 43.8, 45.6, 45.7, 52.3, 58.2, 75.3, 84.6, 120.3, 156.7; IR ν 2924, 1713, 1384, 1268 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_2^+ [\text{M} + \text{H}^+]$ 275.1759, found 275.1753.

(4aR,5R,7S,8aS)-5-(Cyanomethyl)-8a-ethynyl-N,N,7-trimethyloctahydroquinoline-1(2H)-carboxamide (91). To a solution of secondary amine **86** (100 mg, 0.46 mmol, 1.0 equiv) in THF (5 mL) was added solid DMAP (56 mg, 0.46 mmol, 1.0 equiv) following by Et_3N (0.30 mL, 2.3 mmol, 5.0 equiv) and neat dimethylcarbonyl chloride (1.0 mL, 10.2 mmol, 22.0 equiv) at 23 °C. After 12 min, the solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (5/1 \rightarrow 1/1 hexanes/EtOAc) to afford urea **91** (96 mg, 72%) as yellow oil: $[\alpha]^{23.0}_{\text{D}} +54.5$ (c 0.11, CH_2Cl_2); R_f = 0.50 (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3) δ 0.78 (t, J = 12.4 Hz, 1H), 0.89 (d, J = 6.4 Hz, 3H), 1.18–1.25 (m, 2H), 1.42–1.73 (m, 5H), 1.86–1.99 (m, 2H), 2.02–2.08 (m, 1H), 2.50 (s, 1H), 2.55 (ddd, J = 0.8, 4.0, and 17.2 Hz, 1H), 2.73 (td, J = 2.4 and 12.0 Hz, 1H), 2.84 (brs, 6H), 2.88–2.96 (m, 1H), 3.12 (td, J = 2.8 and 12.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.3, 21.9, 24.1, 25.6, 26.4, 37.2, 38.4, 44.0, 46.5, 47.0, 56.3, 85.1, 120.5, 139.8, 163.3; IR ν 2924, 1652, 1385 cm^{-1} ; HRMS calcd for $\text{C}_{17}\text{H}_{26}\text{N}_3\text{O}^+ [\text{M} + \text{H}^+]$ 288.2076, found 288.2068.

2-((4aR,5R,7S,8aS)-1-Acetyl-8a-ethynyl-7-methyldecahydroquinolin-5-yl)acetonitrile (92). To a solution of **86** (200 mg, 0.93 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) were added neat acetyl chloride (0.20 mL, 0.28 mmol, 3.0 equiv) and neat triethylamine (0.28 mL, 0.20

mmol, 2.0 equiv) at 50 °C. After 2 h, the resulting solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated to amide **92** (178 mg, 78%) as a yellow oil: $[\alpha]_D^{25.0} +22.5$ (c 0.80, CH_2Cl_2); $R_f = 0.40$ (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3) δ 0.97 (d, $J = 6.0$ Hz, 3H), 1.24–1.33 (m, 2H), 1.52–1.59 (m, 1H), 1.63–1.71 (m, 1H), 1.76–1.97 (m, 5H), 2.08 (s, 3H), 2.14–2.20 (m, 1H), 2.50 (s, 1H), 2.65 (ddd, $J = 1.2, 4.0$, and 17.2 Hz, 1H), 2.95 (dd, $J = 11.6$ and 17.2 Hz, 1H), 3.34–3.42 (m, 2H), 3.52–3.58 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.3, 21.8, 24.3, 24.6, 25.6, 37.3, 38.0, 43.9, 44.4, 44.8, 58.1, 75.0, 84.5, 120.2, 172.1; IR ν 3216, 1650, 1390 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}^+$ [$\text{M} + \text{H}^+$] 259.1810, found 259.1807.

2-((4aR,5R,7S,8aS)-8a-Ethynyl-7-methyl-1-picolinoyldecahydroquinolin-5-yl)acetonitrile (93). To a solution of **86** (15 mg, 69 μmol , 1.0 equiv) in THF (3 mL) were added pyridine (17 μL , 0.21 mmol, 3.0 equiv) and acid chloride **int-21** (19 μL , 0.14 mmol, 2.0 equiv), and the solution was placed in a 50 °C oil bath. After 3 h, the solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated to afford amide **93** (11 mg, 49%) as a yellow oil: $[\alpha]_D^{25.0} -11.4$ (c 0.35, CH_2Cl_2); $R_f = 0.38$ (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3) δ 1.00 (d, $J = 6.4$ Hz, 3H), 1.35 (dt, $J = 5.2$ and 13.2 Hz, 1H), 1.41 (t, $J = 13.2$ Hz, 1H), 1.59–1.63 (m, 1H), 1.70–1.87 (m, 3H), 1.94–2.09 (m, 3H), 2.20–2.24 (m, 1H), 2.59 (s, 1H), 2.69 (ddd, $J = 0.8, 4.0$, and 17.2 Hz, 1H), 2.99 (dd, $J = 12.0$ and 17.2 Hz, 1H), 3.22–3.29 (m, 1H), 3.50 (dt, $J = 2.4$ and 12.8 Hz, 1H), 3.61–3.66 (m, 1H), 7.34 (ddd, $J = 1.2, 4.8$, and 8.8 Hz, 1H), 7.69 (dt, $J = 1.2$ and 7.6 Hz, 1H), 7.79 (dt, $J = 2.0$ and 7.6 Hz, 1H), 8.59 (dq, $J = 1.2$, and 5.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.3, 21.9, 24.6, 24.7, 25.7, 37.5, 38.0, 44.1, 45.2, 46.4, 58.2, 75.7, 84.2, 120.3, 124.1, 124.9, 137.2, 148.6, 155.0, 171.5; IR ν 2926, 1650, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}^+$ [$\text{M} + \text{H}^+$] 322.1919, found 322.1915.

2-((4aR,5R,7S,8aS)-8a-Ethynyl-7-methyl-1-(2,2,2-trifluoroacetyl)-decahydroquinolin-5-yl)acetonitrile (94). To a solution of **86** (50 mg, 0.23 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) were added trifluoroacetic anhydride (64 μL , 0.46 mmol, 2.0 equiv) and triethylamine (0.097 mL, 0.69 mmol, 3.0 equiv) at 23 °C. After 30 min, the solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated to afford amide **94** (23 mg, 32%) as a white foam: $[\alpha]_D^{25.0} +58.0$ (c 0.50, CH_2Cl_2); $R_f = 0.55$ (silica gel, hexanes/EtOAc = 4/1); ^1H NMR (400 MHz, CDCl_3) δ 1.00 (d, $J = 6.4$ Hz, 3H), 1.28–1.42 (m, 2H), 1.58–1.66 (m, 1H), 1.69–1.77 (m, 1H), 1.81–2.00 (m, 5H), 2.18–2.24 (m, 1H), 2.61 (s, 1H), 2.67 (ddd, $J = 1.2, 4.0$, and 16.8 Hz, 1H), 2.92 (dd, $J = 12.0$ and 16.8 Hz, 1H), 3.25 (dt, $J = 2.8$ and 13.2 Hz, 1H), 3.47–3.54 (m, 1H), 3.65–3.71 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.2, 21.8, 24.0, 24.5, 24.7, 37.2, 37.8, 42.80, 42.84, 43.9, 44.4, 60.1, 82.8, 116.4 (t, $J = 288.7$ Hz), 119.9, 157.0 (t, $J = 34.9$ Hz); IR ν 3265, 2956, 1689, 1184 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{20}\text{N}_3\text{O}_2\text{F}_3^+$ [$\text{M} + \text{H}^+$] 313.1528, found 313.1523.

(5R,5'R,6S,6'S,14R,14'R,16R,16'R)-1-Benzyl-N,N,16,16'-tetramethyl-10'-(trimethylsilyl)-1,2,2',3,3',4,4',5,5',6,6',7,7',15,16,16',17,17'-octadecahydro[10,11'-bi(5,10b)propano-1,7-phenanthroline]-1'-(15'H)carboxamide (95). In a pressure tube, alkynyl nitrile **91** (11 mg, 38 μmol , 1.4 equiv) and pyridylalkyne **61** (12 mg, 28 μmol , 1.0 equiv) were dissolved in degassed THF (2.5 mL). Neat $\text{CpCo}(\text{CO})_2$ (5 μL , 41 μmol , 1.7 equiv) and triphenylphosphine (44 mg, 0.17 mmol, 6.0 equiv) were added, and the tube was sealed. The resulting solution was placed in an oil bath heated to 140 °C for 24 h. The mixture was cooled and the solvent was removed. The product was purified by silica gel chromatography (20/1 to 2/1 hexanes/EtOAc) to afford bipyridyl **95** (4.5 mg, 22%) and bipyridyl **96** (4.1 mg, 20%) both yellow oils: $[\alpha]_D^{25.0} +62.2$ (c 0.45, CH_2Cl_2); $R_f = 0.50$ (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.14 (s, 9H), 0.74 (d, $J = 5.6$ Hz, 3H), 0.79 (d, $J = 5.6$ Hz, 3H), 1.15–1.61 (m, 11 H), 1.72–2.05 (m, 8 H), 2.12 (brs, 2H), 2.21–2.25 (m,

1H), 2.50–2.54 (m, 2H), 2.72–2.88 (m, 3H), 3.02 (s, 6H), 3.05–3.09 (m, 1H), 3.18–3.27 (m, 2H), 4.12 (d, $J = 14.4$ Hz, 1H), 4.24 (d, $J = 14.4$ Hz, 1H), 7.24–7.27 (m, 1H), 7.36 (t, $J = 7.2$ Hz, 2H), 7.50 (d, $J = 7.2$ Hz, 2H), 7.78 (d, $J = 8.0$ Hz, 1H), 8.20 (d, $J = 8.0$ Hz, 1H), 8.38 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 1.0, 14.7, 21.4, 22.2, 22.3, 25.0, 26.1, 26.5, 26.6, 27.2, 28.5, 31.6, 33.9, 34.1, 35.1, 37.7, 38.8, 41.2, 43.6, 43.9, 45.4, 45.9, 46.4, 48.1, 51.1, 60.4, 61.5, 121.1, 126.5, 128.0, 128.2, 130.7, 134.2, 135.2, 137.4, 142.5, 143.3, 156.9, 157.0, 157.9, 160.2, 164.2; IR ν 2919, 1649, 1384 cm^{-1} ; HRMS calcd for $\text{C}_{45}\text{H}_{62}\text{N}_5\text{OSi}^+$ [$\text{M} + \text{H}^+$] 716.4724, found 716.4721.

(5R,5'R,6S,6'S,14R,14'R,16R,16'R)-1-Benzyl-N,N,16,16'-tetramethyl-11-(trimethylsilyl)-1',2,2',3,3',4,4',5,5',6,6',7,7',15,16,16',17,17'-octadecahydro[10,10'-bi(5,10b)propano-1,7-phenanthroline]-1(15H)carboxamide (96). Following the above procedure: $[\alpha]_D^{25.0} +27.4$ (c 0.73, CH_2Cl_2); $R_f = 0.40$ (silica gel, hexanes/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3) δ 0.12 (s, 9H), 0.78 (d, $J = 5.6$ Hz, 3H), 0.80 (d, $J = 5.6$ Hz, 3H), 0.83–0.88 (m, 1H), 0.96 (d, $J = 6.4$ Hz, 1H), 1.18–1.59 (m, 13H), 1.71–1.79 (m, 2H), 1.92–2.01 (m, 2H), 2.13 (brs, 2H), 2.39–2.43 (m, 1H), 2.53–2.55 (m, 2H), 2.76 (t, $J = 18.8$ Hz, 2H), 2.92–3.10 (m, 8H), 3.16–3.29 (m, 2H), 4.11 (d, $J = 14.4$ Hz, 1H), 4.25 (d, $J = 14.4$ Hz, 1H), 7.25–7.27 (m, 1H), 7.34–7.38 (m, 3H), 7.50 (d, $J = 7.2$ Hz, 2H), 8.14–8.17 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 0.26, 14.1, 21.3, 22.3, 22.4, 25.3, 26.0, 26.5, 26.8, 27.2, 31.6, 34.1, 34.2, 34.7, 35.25, 35.30, 38.8, 43.0, 43.6, 43.9, 45.5, 46.0, 46.2, 48.1, 51.1, 60.3, 61.8, 121.1, 126.5, 128.0, 128.2, 133.6, 133.9, 135.1, 136.4, 141.2, 142.6, 156.9, 157.4, 157.6, 163.5, 164.0; IR ν 3446, 2918, 1652, 732 cm^{-1} ; HRMS calcd for $\text{C}_{45}\text{H}_{62}\text{N}_5\text{OSi}^+$ [$\text{M} + \text{H}^+$] 716.4724, found 716.4727.

(5R,5'R,6S,6'S,14R,14'R,16R,16'R)-1-Benzyl-16,16'-dimethyl-10'-(trimethylsilyl)-1,2,2',3,3',4,4',5,5',6,6',7,7',15,16,16',17,17'-octadecahydro[10,11'-bi(5,10b)propano-1,7-phenanthroline]-1'-(15'H)-carbaldehyde (97). In a pressure tube, pyridylalkyne **61** (15.6 mg, 36 μmol , 1.0 equiv), alkynyl nitrile **86** (12.9 mg, 52 μmol , 1.4 equiv), and triphenylphosphine (79 mg, 0.30 mmol, 8.4 equiv) were dissolved in freshly degassed dioxane (8 mL). Neat $\text{CpCo}(\text{CO})_2$ (10 μL , 80 μmol , 2.2 equiv) was added, and the tube was sealed. The resulting solution was placed in a 140 °C oil bath. After 24 h, the reaction was cooled to 23 °C and concentrated. The crude material was purified by silica gel chromatography (20/1 \rightarrow 2/1 hexanes/EtOAc) to afford bipyridyls **97** (10.2 mg, 42%) and **98** (3.4 mg, 14%) both as yellow oils: $[\alpha]_D^{24} +26.6^\circ$ (c 0.50, CH_2Cl_2); $R_f = 0.35$ (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.12 (s, 9H), 0.74 (d, $J = 6.0$ Hz, 3H), 0.90 (d, $J = 6.0$ Hz, 3H), 1.15–1.18 (m, 1H), 1.24–1.32 (m, 4H), 1.35–1.69 (m, 10H), 1.74–1.84 (m, 4H), 1.93–1.96 (m, 2H), 2.05 (s, 1H), 2.11–2.15 (m, 1H), 2.21–2.32 (m, 1H), 2.52–2.54 (m, 1H), 2.76 (d, $J = 40.0$ Hz, 1H), 2.82 (d, $J = 40.4$ Hz, 1H), 3.20–3.31 (m, 2H), 4.18 (dd, $J = 13.6$ and 54.8 Hz, 2H), 4.55–4.59 (m, 1H), 7.36 (t, $J = 7.2$ Hz, 2H), 7.46–7.53 (m, 2H), 7.59 (s, 1H), 7.55–7.70 (m, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 8.23 (d, $J = 8.0$ Hz, 1H), 8.72 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 0.8, 21.2, 22.2, 22.3, 25.4, 25.8, 26.5, 26.7, 27.2, 33.6, 34.0, 35.0, 35.1, 37.2, 38.6, 42.8, 43.8, 44.2, 45.8, 46.5, 48.1, 51.0, 60.4, 61.8, 121.0, 126.5, 128.0, 128.2, 128.5, 131.4, 131.9, 135.3, 137.9, 140.6, 142.3, 156.4, 157.3, 160.5, 161.3; IR ν 1653, 1386, 838 cm^{-1} ; HRMS calcd for $\text{C}_{43}\text{H}_{57}\text{N}_4\text{OSi}^+$ [$\text{M} + \text{H}^+$] 673.43016, found 673.43002.

(5R,5'R,6S,6'S,14R,14'R,16R,16'R)-1-Benzyl-16,16'-dimethyl-11-(trimethylsilyl)-1',2,2',3,3',4,4',5,5',6,6',7,7',15,16,16',17,17'-octadecahydro[10,10'-bi(5,10b)propano-1,7-phenanthroline]-1(15H)-carbaldehyde (98). Following the above procedure: $[\alpha]_D^{24} +35.2$ (c 0.40, CH_2Cl_2); $R_f = 0.28$ (silica gel, hexanes/EtOAc = 2/1); ^1H NMR (400 MHz, CDCl_3) δ 0.09 (s, 9H), 0.79 (d, $J = 6.4$ Hz, 3H), 0.89 (d, $J = 6.4$ Hz, 3H), 1.18–1.65 (m, 11H), 1.71–1.87 (m, 5H), 1.93–1.98 (m, 2H), 2.13–2.16 (m, 1H), 2.22–2.24 (m, 1H), 2.29–2.42 (m, 2H), 2.51–2.55 (m, 2H), 2.73 (d, $J = 18.8$ Hz, 1H), 2.87 (d, $J = 18.8$ Hz, 1H), 2.96–3.12 (m, 1H), 3.21–3.29 (m, 2H), 4.18 (dd, $J = 14.4$ and 64.8 Hz, 2H), 4.50–4.54 (m, 1H), 7.19 (d, $J = 8.0$ Hz, 1H), 7.23–7.27 (m, 1H), 7.34–7.38 (m, 3H), 7.49 (d, $J = 7.6$ Hz, 2H), 8.18 (d, $J = 8.0$ Hz, 1H), 8.66 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -0.1, 0.8, 21.1, 22.2, 22.4, 25.4, 25.8, 26.5, 26.6, 27.2, 33.7, 34.1, 34.9, 35.3, 37.3, 38.5, 42.8, 43.8, 44.2, 45.9, 46.4, 48.2, 50.9, 60.3, 62.0, 121.6, 126.5, 128.0, 128.2, 131.0, 131.4, 135.1, 137.2, 142.1, 142.4,

155.9, 156.6, 157.9, 160.6, 164.8; IR ν 1657, 1652, 1386, 839, 733 cm^{-1} ; HRMS calcd for $\text{C}_{43}\text{H}_{57}\text{N}_4\text{OSi}^+ [\text{M} + \text{H}^+]$ 673.43016, found 673.43030.

(5*R*,5'*R*,6*S*,6'*S*,14*R*,14'*R*,16*R*,16'*R*)-1-Benzyl-16,16'-dimethyl-1,2,2',3,3',4,4',5,5',6,6',7,7',15,16,16',17,17'-octadecahydro[10,11'-bi(5,10*b*-propano1,7-phenanthroline)]-1'(15'*H*)-carbaldehyde (**99**). To a solution of bipyridyl **97** (36 mg, 0.053 mmol, 1.0 equiv) in dioxane (1 mL) was added TBAF solution (1.0 M in THF, 200 μL , 0.20 mmol, 3.8 equiv), and the mixture was placed in a 101 °C oil bath. After 10 h, the solution was cooled to 23 °C, diluted with saturated NH_4Cl solution (10 mL), and extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography (20/1 \rightarrow 1/1 hexanes/EtOAc) to afford amine **99** (32.0 mg, 98%) as a dark yellow oil: $[\alpha]_D^{25} +35.1$ (*c* 0.40, CH_2Cl_2); $R_f = 0.22$ (silica gel, hexanes/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3) δ 0.69 (d, $J = 6.0$ Hz, 3H), 0.82 (d, $J = 6.4$ Hz, 3H), 1.09–1.38 (m, 6H), 1.43–1.80 (m, 12H), 1.88 (td, $J = 3.6$ and 12.8 Hz, 1H), 1.97–2.09 (m, 2H), 2.17–2.27 (m, 2H), 2.41–2.45 (m, 2H), 2.72 (dd, $J = 19.2$ and 30.8 Hz, 2H), 3.18–3.27 (m, 2H), 4.11 (dd, $J = 14.8$ and 68.0 Hz, 2H), 4.48–4.52 (m, 1H), 7.18–7.20 (m, 1H), 7.27–7.31 (m, 2H), 7.41–7.45 (m, 3H), 7.83 (d, $J = 2.4$ Hz, 1H), 8.15 (d, $J = 12.0$ Hz, 1H), 8.68 (s, 1H), 8.89 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.0, 22.1, 22.4, 25.4, 25.9, 26.5, 26.7, 27.1, 33.5, 34.0, 34.9, 35.5, 37.5, 38.5, 42.8, 43.7, 44.1, 45.8, 46.3, 48.2, 50.9, 60.4, 61.9, 118.9, 126.5, 128.0, 128.2, 131.5, 133.4, 134.4, 135.4, 137.7, 142.3, 146.7, 151.7, 157.8, 159.3, 160.5; IR ν 1653, 1443, 1385, 733 cm^{-1} ; HRMS calcd for $\text{C}_{40}\text{H}_{49}\text{N}_4\text{O}^+ [\text{M} + \text{H}^+]$ 601.39064, found 601.39037.

(5*R*,5'*R*,6*S*,6'*S*,14*R*,14'*R*,16*R*,16'*R*)-16,16'-dimethyl-1,2,2',3,3',-4,4',5,5',6,6',7,7',15,16,16',17,17'-octadecahydro[10,11'-bi(5,10*b*-propano1,7-phenanthroline)]-1'(15'*H*)-carbaldehyde (**100**). To a solution of amine **99** (35 mg, 0.058 mmol, 1.0 equiv) in methanol (1 mL) was added solid 5% palladium on carbon (20 mg), and then the solution was rapidly stirred under H_2 (1 atm) at 23 °C. After 8 h, the solution was filtered through a Celite pad and concentrated to afford formamide **100** (22.6 mg, 78%) as pale brown oil: $[\alpha]_D^{25} +25.2$ (*c* 0.40, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 0.81 (d, $J = 6.4$ Hz, 3H), 0.90 (d, $J = 6.4$ Hz, 3H), 1.24–1.45 (m, 7H), 1.53–1.57 (m, 1H), 1.62–1.70 (m, 6H), 1.78–1.86 (m, 4H), 2.04–2.09 (m, 2H), 2.24–2.31 (m, 3H), 2.66–2.73 (m, 1H), 2.80–2.86 (m, 2H), 3.10–3.34 (m, 3H), 4.57 (d, $J = 5.6$ Hz, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.93 (s, 1H), 8.28 (bs, 1H), 8.74 (s, 1H), 8.93 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 22.1, 24.6, 25.4, 25.9 (two peaks very close), 26.7, 32.9, 33.4, 34.9, 35.0, 37.5, 40.7, 41.4, 42.5, 42.7, 44.1, 44.4, 46.3, 47.4, 60.7, 61.9, 119.3, 131.6, 133.7, 134.7, 146.6, 153.4, 158.6, 158.8, 160.5, 170.0, 188.6; IR ν 3419, 1652, 1575, 1262, 910, 731 cm^{-1} ; HRMS calcd for $\text{C}_{33}\text{H}_{43}\text{N}_4\text{O}^+ [\text{M} + \text{H}^+]$ 511.34369, found 511.34377.

Optical Rotation Data. We have found the optical rotation of complanadine A changes as the molecule transitions from the free base form to protonated forms.

Effects of acid addition on rotation:

- 19.0° complanadine A free base
- 9.5° complanadine A free base with 2 equiv of TFA
- 4.7° complanadine A free base with 4 equiv of TFA
- +2.4° complanadine A free base with 6 equiv of TFA
- and +10.5° complanadine A free base with 6 equiv of HCl

■ ASSOCIATED CONTENT

● Supporting Information

Experimental procedures, spectroscopic data, and NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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