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A Model System for the Synthesis of Complanadine Alkaloids by "Diverted Kondrat'eva" Oxazole–Olefin Cycloaddition

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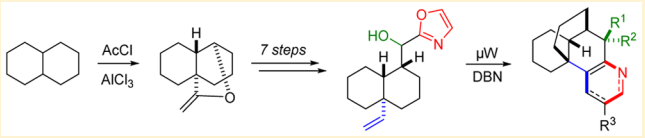
Supporting Information

ABSTRACT: A synthetic approach to complanadine alkaloids is described which employs a Kondrat'eva reaction to construct the pyridine rings. The viability of this approach is demonstrated by its application to a model substrate accessed from unfunctionalized decalin. The key transformation affords the desired tetracyclic architecture with unprecedented incorporation of substituents on the pyridine ring, implicating the oxazole α-hydroxy group as an active participant in the cycloadduct fragmentation process.



INTRODUCTION

The complanadines are a family of lycopodium alkaloids[1−10] isolated from the Japanese club moss *Lycopodium complanatum* by Kobayashi and co-workers.[11−14] The first to be isolated, complanadine A (**1**), is a dimer of the coisolated natural product lycodine (**6**). Notably, it is a nonsymmetrical dimer, incorporating a 2,3′-bipyridyl linkage. This nonsymmetrical linkage is a feature common to all members of the family; complanadines B (**2**), D (**4**), and E (**5**) differ from complanadine A only in oxidation state, whereas complanadine C (**3**) possesses different skeletal connectivity (Figure 1). Biological evaluation of **1** revealed that it is able to induce the secretion of neurotrophic factors from 1321N1 cells, which in turn can promote the differentiation of PC-12 cells.[12] As such, **1** is a promising lead structure for the discovery of neuroregenerative agents. In conjunction with their unusual architecture, this provides a significant impetus to undertake the synthesis of the complanadines.

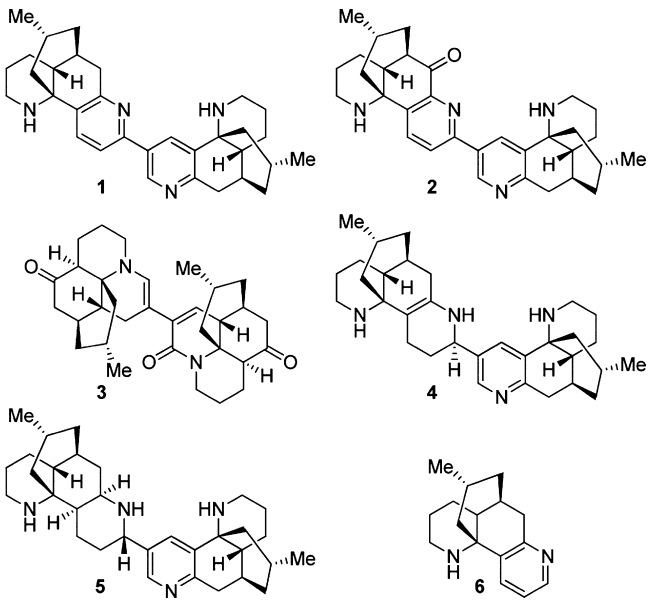


Figure 1. The structures of the complanadines and lycodine.

To date, three groups have completed syntheses of complanadines. In 2010, the Siegel group[15] and the Sarpong group[16] simultaneously disclosed syntheses of **1**. Siegel and co-workers' communication described construction of the 2,3′-bipyridyl motif by means of two sequential [2 + 2 + 2] annulations. For the second of these cyclizations, it was determined that an *N*-formyl protecting group, in conjunction with triphenylphosphine, was required for preferential formation of the desired 2,3′-bipyridyl **12** over the isomeric 2,2′-bipyridyl that would ordinarily be favored (Scheme 1a). In a subsequent full paper,[17] Siegel disclosed a complementary synthesis of **1**, in which careful choice of silylalkyne reactant **13** allowed for reversal of the regioselectivity seen in the first [2 + 2 + 2] annulation, giving rise to the 3-pyridyl subunit **14**. Subsequent functional group manipulation to install a silylalkyne gave **15**, the substrate for a second cyclization to **16** (Scheme 1b). In contrast to the first approach, the absence of a Lewis basic additive or coordinating amine protecting group afforded the second pyridine subunit linked at the 2-position, as desired.

Sarpong and co-workers approached the 2,3′-bipyridyl linkage by means of a divergent synthesis from a common 2-pyridyl triflate **17**. Reduction to *N*-Boc lycodine **18** was followed by iridium-catalyzed C−H borylation[18] at the pyridine 3-position to give the complementary coupling partner **19**. Suzuki−Miyaura coupling of **17** and **19** was followed by deprotection to give **1** (Scheme 1c).

More recently, Sarpong has extended this approach[19] to execute two syntheses of **2**, wherein benzylic oxidation of the 2-pyridyl fragment but not the 3-pyridyl fragment is required.

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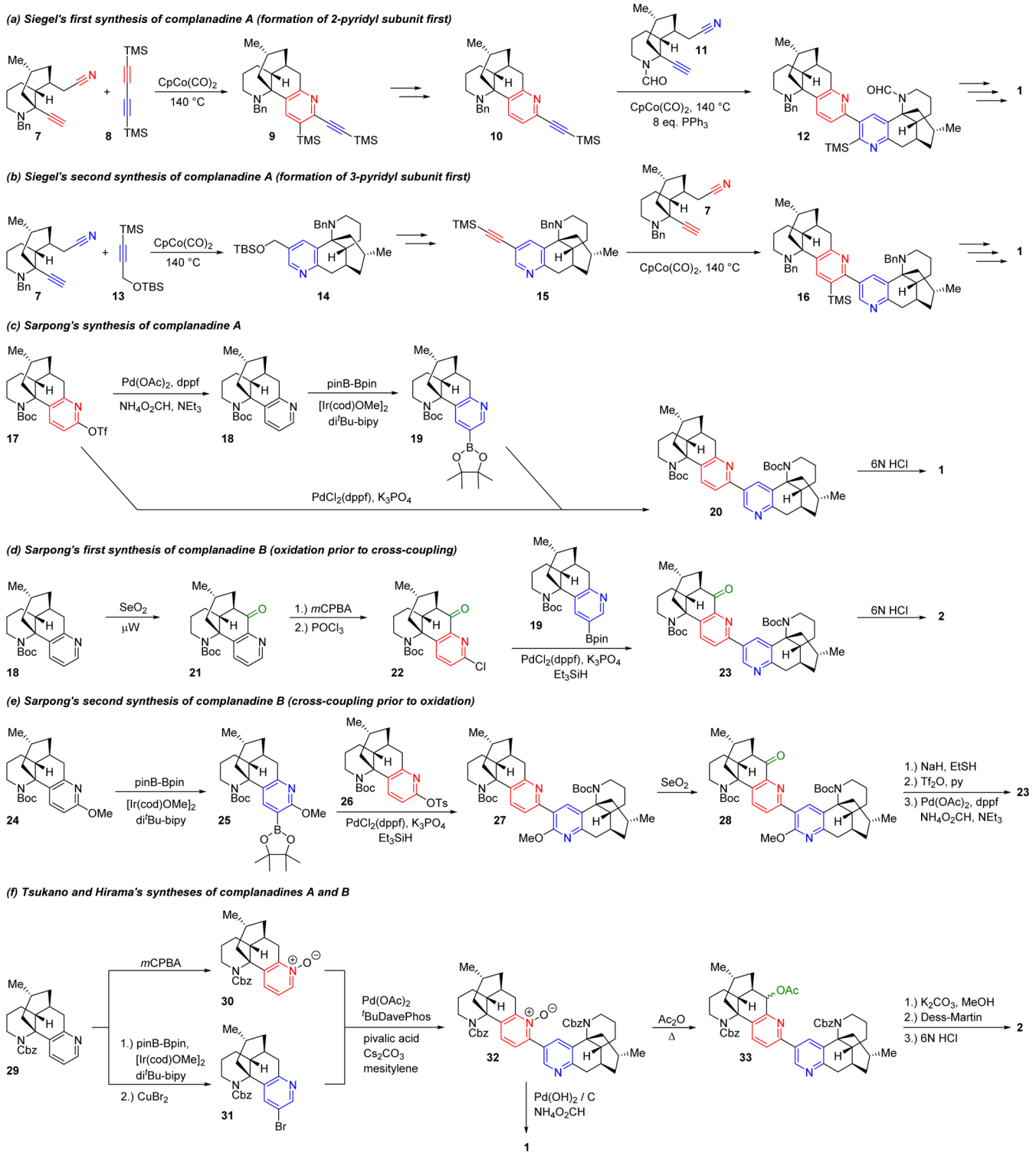
Scheme 1. Different Strategies To Access the 2,3′-Bipyridyl Linkage: Reported Syntheses of 1 and 2 to Date



This distinction was addressed either by effecting the oxidation prior to fragment union (Scheme 1d) or by oxidation after the cross-coupling step, employing a 2-methoxy substituent to deactivate one pyridine ring toward oxidation and so favor selective benzylic oxidation of the other pyridine (Scheme 1e). Concurrently with Sarpong's latest report, Tsukano, Hirama, and co-workers disclosed syntheses of both **1** and **2** that rely on the coupling of highly functionalized pyridine and pyridine *N*-oxide precursors **30** and **31** (Scheme 1f).[20,21] The *N*-oxide serves a dual role, not only facilitating the key biaryl formation giving **32** but also allowing for benzylic functionalization to give **33** and ultimately **2**.

In the present work, we describe a conceptually distinct approach to the 2,3′-bipyridyl linkage of complanadines A (**1**) and B (**2**) and evaluation of its feasibility through a model system for the synthesis of the monomer, lycodine (**6**). A portion of this work has been reported previously in preliminary form.[22]

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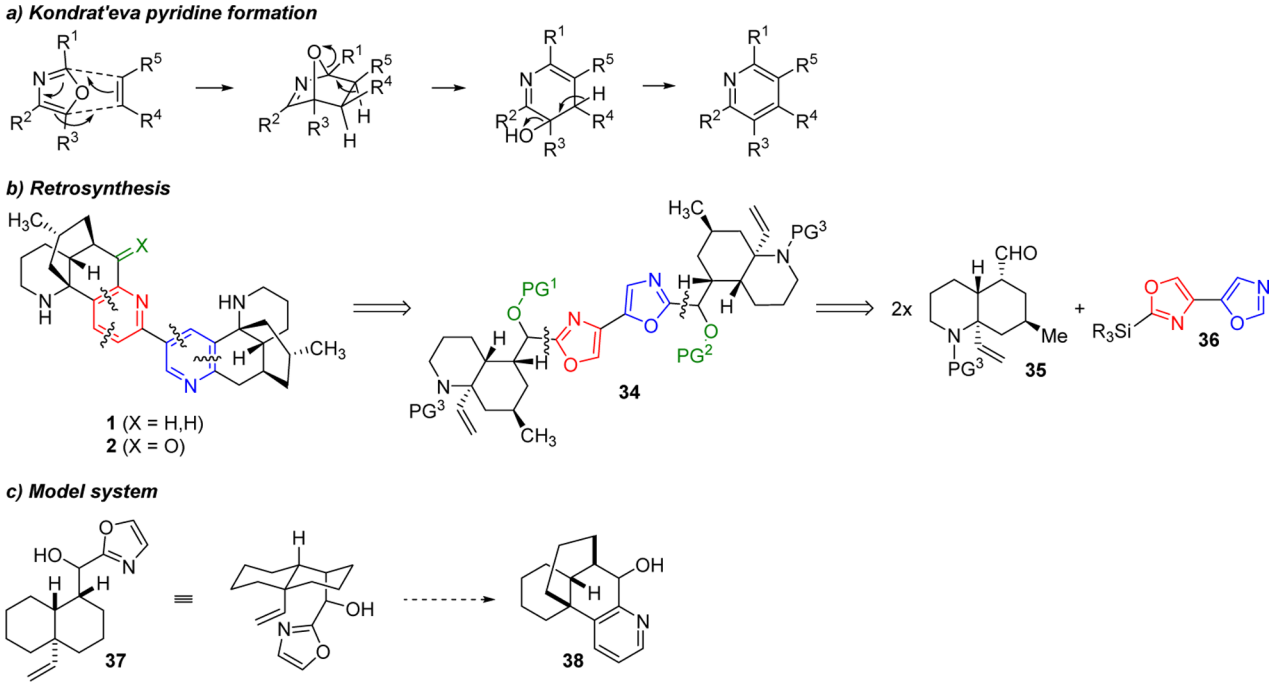
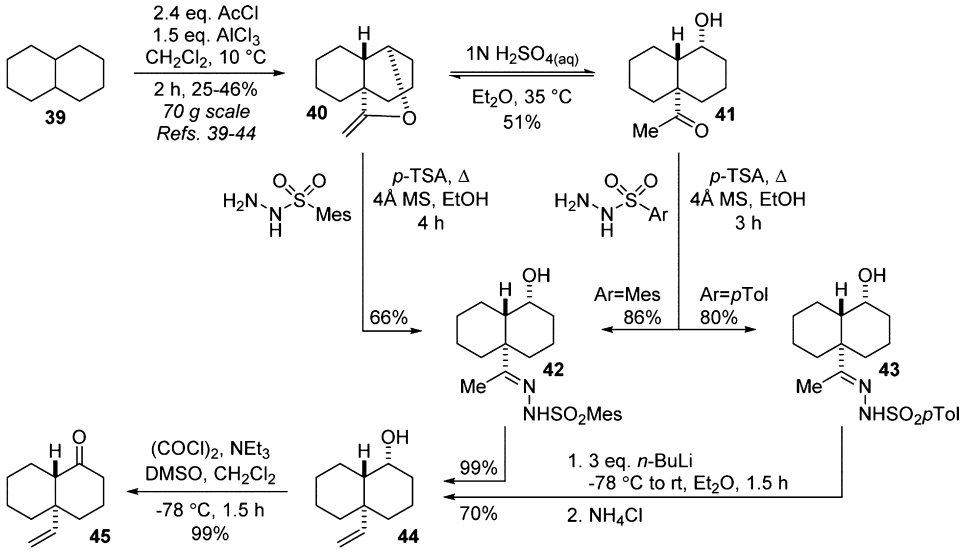
Scheme 2. Proposed Retrosynthesis of Complanadines A and B



Scheme 3. Functionalization of Decalin at C1 and C4a



RESULTS AND DISCUSSION

Our approach to **1** and **2** sought to construct the pyridine rings using an intramolecular Kondrat'eva oxazole−olefin cycloaddition[23−25] (Scheme 2a). In the context of the complanadines, this allows a powerfully simplifying disconnection of each tetracyclic monomer to a bicyclic precursor **34**. The approach requires two identical azadecalins **35** linked by a nonsymmetrical bis(oxazole) motif **36** (Scheme 2b). The presence of oxygenation in the oxazole α-positions would allow ready access to **1** or **2** from the same cyclization product. The Kondrat'eva reaction has seen only limited application in total synthesis to date,[26−38] and because its application in the context of lycopodium connectivity is unknown, we opted to examine a model system to determine the viability of this key late-stage transformation. We expected to access concisely the monomeric cyclization precursor (±)-**37**, which in turn was expected to undergo cycloaddition−fragmentation to afford **38**, a simplified analogue of lycodine **6** (Scheme 2c).

Model substrate **37** is a *trans*-decalin functionalized at C1 and C4a. This substitution pattern may be accessed directly from decalin **39**, via a reported "aliphatic Friedel−Crafts" reaction giving **40**.[39−43] This remarkable transformation, believed to proceed via acylium ion-mediated hydride abstraction, has been studied mechanistically and is also applicable to other substrates.[44] Treatment of **40** with aqueous acid establishes an equilibrium with hydroxy ketone **41**, which may be isolated by crystallization. To install the dienophile, we sought to effect a Shapiro reaction on a corresponding sulfonylhydrazone. Either **42** or **43** are readily formed from **41**; treatment with 3 equiv of butyllithium and subsequent protic quench affords the desired vinyl group. As the Shapiro

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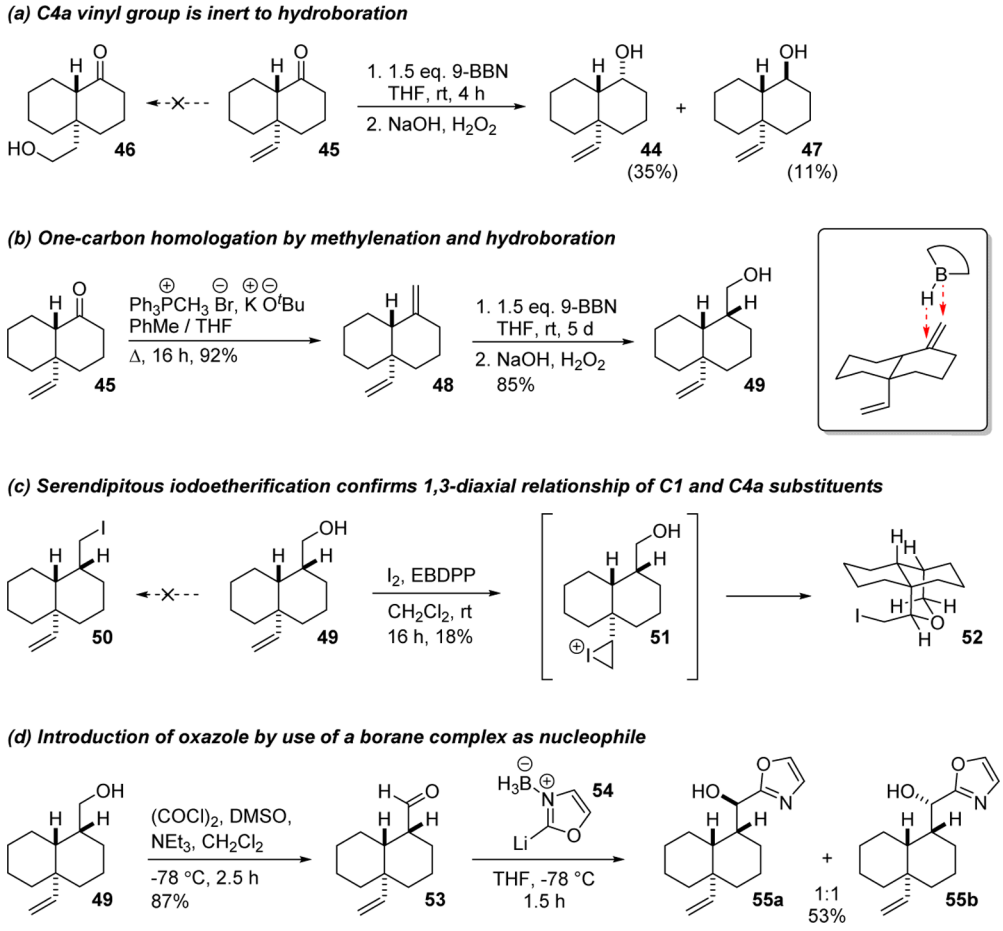
Scheme 4. Access to Kondrat'eva Substrates 55a/b



reaction of **42** is essentially quantitative, we optimized conditions for formation of **42**, establishing that it may be accessed directly from enol ether **40**, in a yield higher than that for the two-step process. Shapiro product **44** underwent Swern oxidation to vinyl ketone **45**, required for one-carbon homologation and oxazole introduction (Scheme 3).

Steric congestion around the vinyl group in **45** is such that it is remarkably inert to hydroboration; in fact, exposure of **45** to 9-BBN followed by basic hydrogen peroxide led not to expected alcohol **46** but instead effected ketone reduction to give **44** and its diastereoisomer **47** (Scheme 4a). This intertness could be exploited to effect the desired one-carbon homologation. Thus, Wittig methylenation of **45** gave bis-(alkene) **48**, which underwent hydroboration in an entirely regio- and diastereoselective fashion to give alcohol **49** as the sole product, in which both the C1 and C4a substituents are axially disposed (Scheme 4b). Evidence for the 1,3-diaxial relationship of the alkene and the hydroxyl group was obtained in the form of a serendipitous iodoetherification upon treatment of **49** with iodine and ethylene-1,2-bis-(diphenylphosphine)[45] to form **52**[46] (Scheme 4c). Swern oxidation of **49** gave aldehyde **53** with negligible epimerization; a clear NOESY interaction between the aldehyde proton and the methine of the vinyl group indicated that the 1,3-diaxial relationship of the C1 and C4a substituents had been maintained. Introduction of the heterodiene was then carried out by direct metalation of oxazole. This lithiates at the 2-position, but use of this nucleophile is hampered by a tautomeric equilibrium with a ring-opened form. Vedejs has reported that precoordination of oxazole to borane before lithiation affords a competent oxazole nucleophile, **54**.[47] By this protocol, diastereoisomeric α-hydroxyoxazoles **55a** and **55b** were accessible from **53** (Scheme 4d) in moderate yield, due to competing reduction of **53** back to **49**.

No diastereoselection was observed in the formation of **55a** and **55b**. Careful chromatography allowed separation of **55a** and **55b** in sufficient quantities for characterization; the structure of **55b** was confirmed by X-ray crystallographic analysis (Figure 2).

As Kondrat'eva substrates **55a/b** possess an unactivated dienophile, we anticipated that forcing conditions would be

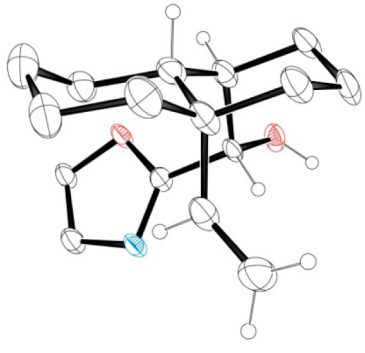


Figure 2. ORTEP plot of **55b**, ellipsoids at 30% probability. Selected H atoms are shown as spheres of arbitrary radius. Only one of two molecules in the asymmetric unit is shown.

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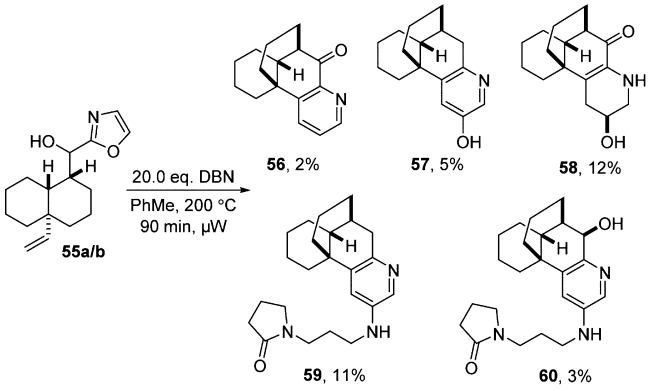
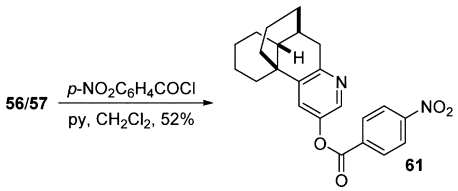
required to effect the desired pyridine formation. Weinreb has introduced the use of DBN as an additive in Kondrat'eva reactions to suppress side-reactions,[26,27] and it is speculated that it exerts its effect by accelerating the dehydration of the initial cycloadduct, thereby minimizing competing oxidative degradation. In the present case, treatment of **55a/b** (1:1 mixture) with 20 equiv of DBN at reflux in *o*-dichlorobenzene led only to very slow conversion, but microwave irradiation (PhMe, 200 °C) led to consumption of starting material in 90 min and formation of cyclization products **56**–**60** (Scheme 5a).

Scheme 5. Products of "Diverted" Kondrat'eva Reaction

(a) Cyclization under conditions of microwave acceleration



(b) Characterization by selective derivatization of a mixture of products



Ketone **56** and hydroxypyridine **57** were isolated and characterized as an inseparable mixture, as were lactones **59** and **60**. Treatment of the mixture of **56**/**57** with *p*-nitrobenzoyl chloride allowed for characterization of a pure derivative of **57**, its ester **61** (Scheme 5b). Of the observed cyclization products, formation of **56** and **60** is oxidative, whereas **57**–**59** must arise by net redox-neutral transformations. Although expected cyclization product **38** was not observed, we ascribe isolation of α-ketopyridine **56** to formation of **38** and its subsequent oxidation. Notably, **57**–**60** all possess functionality meta to the pyridine nitrogen, where no such substitution was present at the corresponding oxazole carbon in precursors **55a/b**. To aid in the rationalization of the formation of **56**–**60**, we undertook DFT calculations on the initial cycloaddition step. These showed that the cycloadduct **62** with the relative stereochemistry shown is the thermodynamic product, for both **55a** and **55b** (Figure 3, see Supporting Information for further details).

Formation of **56**–**60** may be rationalized by considering fragmentation pathways open to this cycloadduct (Scheme 6). Fragmentation of initial cycloadduct **62** to give dihydropyridine **63** can be followed either by the expected dehydration (shown in blue) to give **38** or instead by dehydration through vinylogous elimination of the α-hydroxy group (shown in green) to give **64** which tautomerizes to **57**. An alternative mode of fragmentation of **62** (shown in red) would give

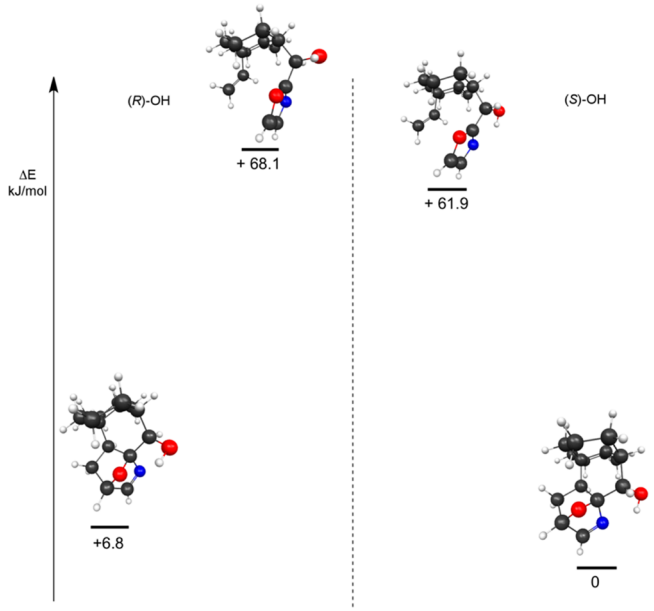


Figure 3. Energy diagram with the calculated (DFT: M06/631G(d)) relative energies of **55a/b** and the corresponding cycloadducts **62a/b**. For the cycloadducts with the opposite relative stereochemistry, see Supporting Information.

azadienol **65**, which would tautomerize first to **66** and subsequently to **58**.

The above mechanistic rationale implies formation of **57** and **58** is only possible due to the presence of the oxazole α-hydroxy group. Formation of a 3-hydroxypyridine by oxazole–olefin cycloaddition and net hydroxy group migration is unprecedented, and we suggest the term "diverted Kondrat'eva reaction" for this transformation.[48] Lactams **59** and **60** are proposed to be formed by incorporation of DBN (Scheme 7).

While DBN was reportedly selected as an additive in preference to triethylamine due to its non-nucleophilic nature,[26,27,49] lactam products arising from nucleophilic attack of DBN and subsequent ring scission have been reported.[50−56] In the case at hand, the configuration of the oxazole α-carbon has an influence on the reaction outcome: whereas the *S** relative configuration in **69b** allows for complete dehydration to **70** (and hence formation **59**), the formation of oxidized product **60** suggests that the corresponding dehydration of *R**-configured alcohol **69a** is less facile.[57]

CONCLUSION

We have demonstrated the fundamental viability of forming a pyridine-containing tetracycle by intramolecular Kondrat'eva oxazole–olefin cycloaddition of a *trans*-decalin bearing an axially disposed diene and dienophile at C1 and C4a, respectively. We expect this approach to be applicable for the synthesis of lycodine and complanadines, although the unexpected participation of the oxazole α-hydroxy group implies that any desired oxygenation at this position would be better introduced postcyclization. Nevertheless, diverted Kondrat'eva products analogous to **58**, bearing a tetrahydropyridine, may be desirable in the context of complanadine D (**4**) and meta-substituted pyridines analogous to **57** would be appropriate coupling partners for constructing the 2,3′-bipyridyl linkage by a union of monomers.[16,19,20] Synthetic efforts in this regard are underway in our laboratory and will be reported in due course.

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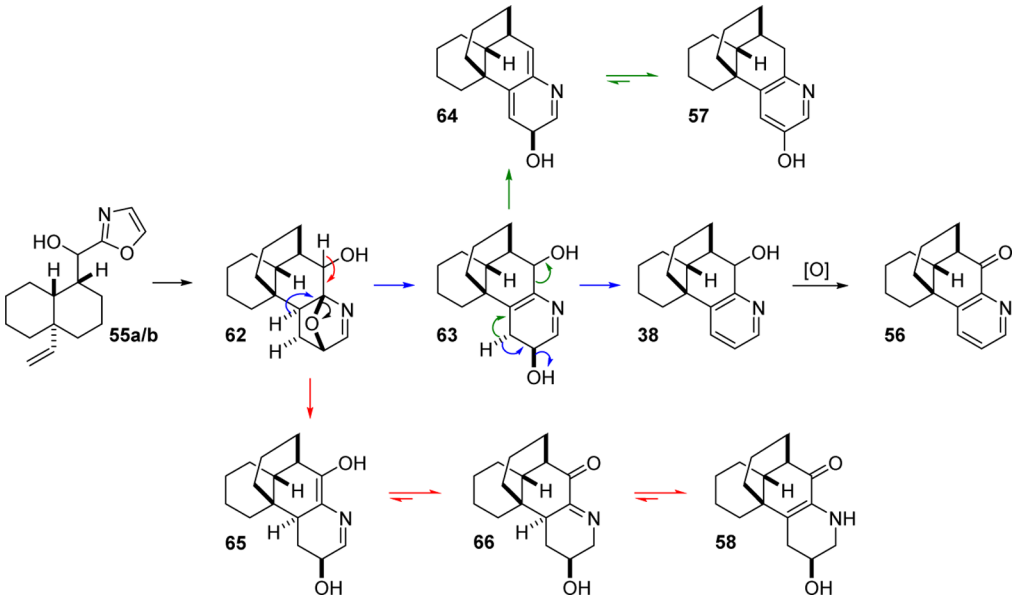
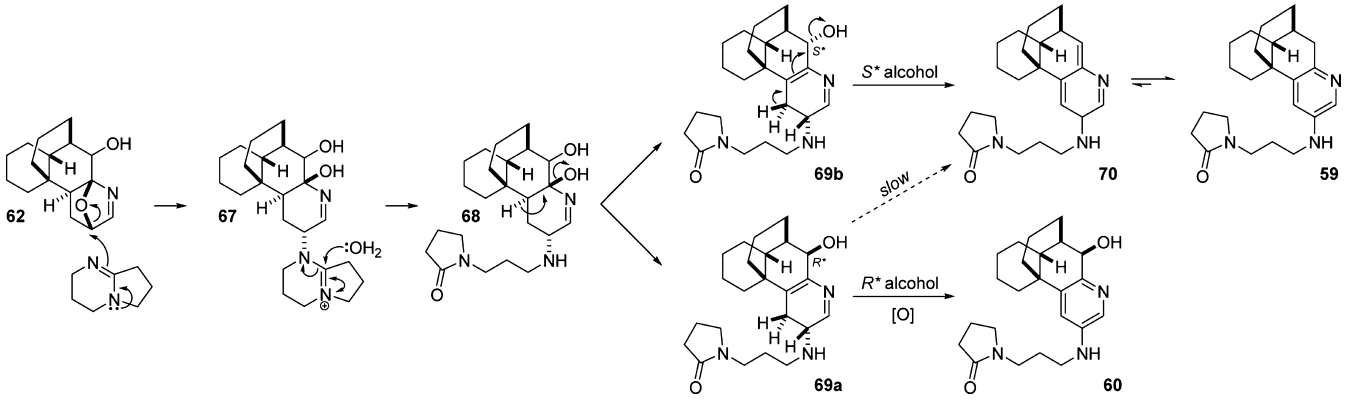
Scheme 6. Divergent Fragmentation Pathways of 62



Scheme 7. Nucleophilic Attack by DBN on Cycloadduct 62



EXPERIMENTAL SECTION

General Procedures. Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen. In most cases, solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system.[58] Petroleum ether, bp 40−60 °C, was used. TLC was carried out using aluminum-backed plates precoated with AlugramSIL G/UV 254 nm. Visualization was accomplished by UV light, $KMnO_4$, DNPH, vanillin, or ceric ammonium molybdate followed by gentle warming. Organic layers were routinely dried with anhydrous $MgSO_4$ and evaporated using a rotary evaporator. When necessary, further drying was facilitated by high vacuum. Flash column chromatography was carried out using Davisil LC 60 Å silica gel (35−70 μm), high purity silica gel (60 Å, 200−400 mesh), or Celite 545. Selected IR absorbances are quoted as ν_{max} in cm^{-1}. NMR spectra were run in $CDCl_3$ on either a 250, 300, 400, or 500 MHz instrument. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; pent, pentet; hept, heptet; dd, doublet of doublets; m, multiplet, and br, broad. For mass spectrometry, micrOTOF electrospray time-of-flight (ESI-TOF) and atmospheric pressure chemical ionization (APCI) mass spectrometers were used; the observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula. Melting point readings were taken from a mercury-in-glass thermometer and were reported uncorrected as the meniscus point. Microwave-assisted reactions were carried out in a Biotage Initiator 2.0 Eight (0−300W at 2.45 GHz) equipped with an external IR probe for measuring reaction temperature.

(±)-(1*R,4a*S**,8a*S**)-9-Methylenedecahydro-1,4a-(epoxymethano)naphthalene (40).** Acetyl chloride (89.4 mL, 1.25 mol, 2.40 equiv) was gradually added with stirring over 15 min to a cooled (<25 °C) mixture of aluminum chloride (104 g, 0.786 mol, 1.50 equiv) in CH_2Cl_2 (225 mL). The resulting yellow-brown solution was decanted into a flask and cooled to <10 °C, and decalin (80.9 mL, 0.524 mol, 1.00 equiv) was gradually added over 30 min with stirring and cooling to keep the temperature of the reaction mixture below 10 °C. After a further 2 h at 10−15 °C, the mixture was gradually added to a vigorously stirred slurry of crushed ice (1 kg) and water. The lower organic layer was separated and, together with CH_2Cl_2 extracts of the aqueous layer, washed several times with ice-cold water, dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure. Fractional distillation of the residual brown oil gave crude product (bp 82−85 °C at 5.8 Torr) which was then further purified by refluxing with $LiAlH_4$ (0.5 g) in dry Et_2O (30 mL) for 30 min. Excess of hydride was destroyed by cautious addition of EtOAc (5 mL), and ice-cold dilute sulfuric acid (50 mL, 0.5 N) was gradually added to the cooled mixture. The ethereal layer was separated and, with further ethereal extracts of aqueous layer, was washed with water (2 × 50 mL), dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure. Further distillation afforded enol ether **40** (22.8 g, 25%) as a pale yellow oil: bp 65 °C at 1.5 Torr; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.22 (1H, dt, J = 1.0, 0.5 Hz, >CHO), 4.03 (1H, d, J = 4.5 Hz, =CH_2), 3.66 (1H, d, J = 1.5 Hz, =CH_2),

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0.86−1.07 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (>C=CH_2), 80.5 (>CHO), 76.9 (=CH_2), 50.0 (3°), 46.2 (4°), 39.5 (2°), 31.3 (2°), 30.2 (2°), 26.5 (2°), 24.9 (2°), 22.1 (2°), 18.9 (2°); IR (film) 2927, 2860, 1679, 1455, 1369, 1198, 1106 cm^{-1}; HRMS (TOF-ESI+) calcd for $[(C_{12}H_{18}O) + H]^+$ 179.1435, found, 179.1422.

(±)-1-((1*R,4a*S**,8a*S**)-1-Hydroxydecahydronaphthalen-4a-yl)ethanone (41).** A mixture of enol ether **40** (20.1 g, 113 mmol, 1.00 equiv) in Et_2O (150 mL) and dilute aqueous sulfuric acid (1.00 N, 290 mL) was refluxed for 2.5 h. The ether layer was separated, and the aqueous layer was washed with ether (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was washed with petroleum ether to give the hydroxy ketone **41** (11.2 g, 51%) as a colorless crystalline solid: mp 60−61 °C; R_f 0.54 (50% EtOAc:petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (1H, dd, J = 8.5, 0.5 Hz, OH), 3.70 (1H, dq, J = 8.5, 3.0 Hz, >CHOH), 2.17 (1H, s, $COCH_3$), 1.96−1.64 (6H, m), 1.53−1.16 (8H, m), 1.21−0.99 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.5 (>$COCH_3$), 68.9 (>CHOH), 56.1 (3°), 48.8 (4°), 39.5 (2°), 36.9 (2°), 35.0 (2°), 26.9 (>$COCH_3$), 26.4 (2°), 25.7 (2°), 24.2 (2°), 17.2 (2°); IR (film), 3751, 3649, 3351, 2927, 2860, 2554, 2350, 2159, 2032, 1977, 1679, 1455, 1369, 1253, 1198, 1177, 1137, 1106, 1066, 1041, 1009, 981, 947, 915, 884, 778, 720, 644, 618 cm^{-1}; HRMS (TOF-ESI+) calcd for $[(C_{12}H_{20}O_2) + H]^+$ 197.1541, found, 197.1514; calcd for $[(C_{12}H_{20}O_2) + Na]^+$ 219.1361, found, 219.1327.

(±)-1-((1*R,4a*S**,8a*S**)-1-Hydroxydecahydronaphthalen-4a-yl)ethanone *N*-(2,4,6-Trimethylbenzenesulfonyl)hydrazone (42).** *From the Hydroxy Ketone.* To a solution of hydroxy ketone **41** (5.00 g, 25.4 mmol, 1.00 equiv) in ethanol (125 mL) were added 2,4,6-trimethylbenzenesulfonohydrazide (5.46 g, 25.4 mmol, 1.00 equiv), *p*-TSA (5 mol %), and 4 Å molecular sieves. The reaction mixture was refluxed for 3 h. The reaction mixture was left to cool over 16 h, during which time the product crystallized. The precipitate was then filtered and washed with cold ethanol (2 × 50 mL), to give the desired hydrazone **42** (8.58 g, 86%) as a white solid.

From the Enol Ether. To a solution of enol ether **39** (6.93 g, 38.9 mmol, 1.00 equiv) in ethanol (125 mL) were added 2,4,6-trimethylbenzenesulfonohydrazide (8.33 g, 38.9 mmol, 1.00 equiv) and *p*-TSA (10 mol %). The reaction mixture was refluxed for 4 h. The reaction mixture was left to cool over 16 h, during which time the product crystallized. The precipitate was then filtered and washed with cold ethanol (3 × 30 mL) to give the desired hydrazone **42** (10.0 g, 66%) as a white solid: mp 173−175 °C; R_f 0.47 (40% EtOAc:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (2H, s, Ar-H), 5.33 (1H, br s, NH), 3.60 (1H, s br, OH), 2.69 (6H, s, Ar-*o*-CH_3), 2.29 (3H, s, Ar-*p*-CH_3), 1.79 (3H, s, CH_3), 1.82−1.76 (3H, m), 1.43−0.99 (12H, m) 0.65−0.52 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2 (CH_3C=N), 143.0 (Ar-C), 139.8 (Ar-C), 132.4 (Ar-C), 131.9 (Ar-C), 69.4 (>COH), 49.6 (3°), 49.0 (4°), 39.4 (2°), 37.5 (2°), 35.4 (2°), 27.3 (2°), 25.2 (2°), 23.0 (2°), 22.6 (C(CH_3)N), 20.9 (2°), 17.2 (1°), 12.6 (1°); IR (film) 3360, 3261, 2938, 2857, 1636, 1604, 1446, 1380, 1338, 1161, 1110, 950, 891 cm^{-1}; HRMS (TOF-ESI +) calcd for $[(C_{21}H_{32}N_2O_3S) + H]^+$ 393.2211, found 393.2205; calcd for $[(C_{21}H_{32}N_2O_3S) + Na]^+$ 415.2031, found 415.2018.

(±)-1-((1*R,4a*S**,8a*S**)-1-Hydroxydecahydronaphthalen-4a-yl)ethanone *N*-(4-Methylbenzenesulfonyl)hydrazone (43).** To a solution of hydroxy ketone **41** (550 mg, 2.80 mmol, 1.00 equiv) in ethanol (15 mL) were added *p*-toluenesulfonyl hydrazide (520 mg, 2.80 mmol, 1.00 equiv), *p*-TSA (5.3 mg, 10 mol %), and 4 Å molecular sieves. The reaction mixture was refluxed for 3 h. The reaction mixture was left to cool overnight, during which time the product crystallized. The precipitate was then filtered and washed with cold ethanol (2 × 10 mL) to give the desired hydrazone **43** (820 mg, 80%) as a white solid: mp 174−176 °C; R_f 0.36 (30% EtOAc:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (1H, br s, NH) 7.93 (2H, d, J = 8.0 Hz, Ar-H), 7.32 (2H, d, J = 8.0 Hz, Ar-H), 5.70 (1H, br s, OH), 3.66−3.64 (1H, m, >C*H*CH(OH)), 2.41 (3H, s, Ar-CH_3), 1.84−1.70 (3H, m), 1.75 (3H, s, C(CH_3)=N), 1.49−1.00 (11H, m) 0.68−0.55 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (C(CH_3)=N), 144.2 (Ar-C), 135.4 (Ar-C), 129.7 (Ar-C), 128.1 (Ar-C), 69.3 (>COH), 49.6 (>CHCH(OH)), 49.1 (4°), 39.7 (2°), 37.2 (2°), 35.4 (2°), 27.1 (2°), 25.5 (2°), 23.0 (2°), 21.5 (C(CH_3)=N), 17.0 (2°), 13.2 (1°); IR (film) 3658, 3270, 2981, 2919, 2855, 1599, 1456, 1342, 1241, 1167, 1094, 994, 951, 812 cm^{-1}; HRMS (TOF-ESI+) calcd for $[(C_{19}H_{28}N_2O_3S) + Na]^+$ 387.1777, found 387.1777.

(±)-(1*R,4a*R**,8a*S**)-4a-Vinyldecahydronaphthalen-1-ol (44).** *From the Mesityl Hydrazone.* To a solution of mesityl hydrazone **42** (2.42 g, 6.17 mmol, 1.00 equiv) in Et_2O (40 mL) was added ^{n}BuLi in hexanes (1.74 M, 10.8 mL, 18.8 mmol, 3.09 equiv), dropwise over 10 min at −78 °C. The bright yellow reaction mixture was warmed to rt and the resulting orange solution then stirred for 1.5 h. The reaction mixture was washed with aq NH_4Cl solution (3 × 20 mL) and then brine (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude product. Purification by column chromatography (10 to 20% EtOAc:petroleum ether) gave the title product **44** (1.10 g, 99%) as a colorless oil.

From the p-Tolyl Hydrazone. To a solution of tosyl hydrazone **43** (0.720 g, 1.99 mmol, 1.00 equiv) in a mixture of Et_2O (20 mL) and THF (5 mL) was added ^{n}BuLi in hexanes (1.39 M, 4.42 mL, 6.15 mmol, 3.09 equiv), dropwise over 5 min at −78 °C. The bright yellow reaction mixture was left to warm to rt, and the resulting orange solution was then stirred for 3.5 h. The reaction mixture was washed with aq NH_4Cl solution (3 × 20 mL) and then brine (20 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude. Purification by column chromatography (10 to 20% EtOAc:petroleum ether) gave the title product **44** (0.25 g, 70%) as a colorless oil: R_f 0.50 (25% EtOAc:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (1H, dd, J = 18.0, 11.0 Hz, C*H*=CH_2), 5.07 (1H, dd, J_{cis} = 11.0, 1.5 Hz, CH=CH_2), 5.01 (1H, dd, J_{trans} = 18.0, 1.5 Hz, CH=CH_2), 3.65 (1H, q, J = 2.5 Hz, OCH), 1.83−1.68 (6H, m), 1.52−1.19 (8H, m), 1.15−1.03 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8 (CH=CH_2), 112.2 (CH=CH_2), 72.0 (>CHOH), 49.6 (2°), 43.1 (>CHCH(OH)), 39.5 (4°), 38.3 (2°), 33.9 (2°), 26.9 (2°), 25.6 (2°), 21.7 (2°), 16.6 (2°); IR (film) 3416, 2925, 2849, 1629, 1450, 1243, 1153, 927, 903 cm^{-1}; HRMS (TOF-ESI+) calcd for $[(C_{12}H_{20}O) + H]^+$ 181.1592, found 181.1583; calcd for $[(C_{12}H_{20}O) + Na]^+$ 203.1411, found 203.1398.

(±)-(4a*R,8a*S**)-4a-Vinyldecahydronaphthalen-1-one (45).** To a stirred solution of oxalyl chloride (1.59 mL, 18.5 mmol, 1.10 equiv) in CH_2Cl_2 (80 mL) at −78 °C was added dimethyl sulfoxide (2.57 mL, 36.2 mmol, 2.15 equiv). The solution was stirred for 10 min, and then vinyl alcohol **44** (3.04 g, 16.8 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) was added. The reaction mixture was stirred for 90 min at −78 °C, and then Et_3N (11.8 mL, 84.3 mmol, 5.00 equiv) was added. After 15 min, the solution was allowed to warm to rt over 30 min, water (100 mL) was added, and the reaction mixture was transferred to a separating funnel. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (10% EtOAc:petroleum ether) to give the title ketone **45** (2.98 g, 99%) as a pale yellow oil: R_f 0.58 (25% EtOAc:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (1H, dd, J = 18.0, 11.0 Hz, C*H*=CH_2), 5.12 (1H, dd, J_{cis} = 11.0, 1.0 Hz, CH=CH_2), 4.93 (1H, dd, J_{trans} = 18.0, 1.0 Hz, CH=CH_2), 2.29−2.23 (2H, m), 2.15 (1H, dd, J = 12.0, 3.0 Hz) 1.87−1.59 (7H, m), 1.47−1.25 (4H, m), 1.25−1.05 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3 (>C=O), 140.6 (*C*H=CH_2), 116.1 (CH=CH_2), 57.0 (>CHCO), 46.1 (4°), 41.2 (2°), 39.9 (2°), 39.8 (2°), 25.5 (2°), 22.1 (2°), 21.4 (2°), 21.0 (2°); IR (film) 2931, 2851, 1708, 1638, 1449, 1366, 1311, 1206, 1089, 999, 918, 838 cm^{-1}; HRMS (TOF-ESI +) calcd for $[(C_{12}H_{18}O) + H]^+$ 179.1435, found 179.1428; calcd for $[(C_{12}H_{18}O) + Na]^+$, 201.1255, found 201.1246.

(±)-(1*S,4a*R**,8a*S**)-4a-Vinyldecahydronaphthalen-1-ol (47).** To a stirred solution of vinyl ketone **45** (0.580 g, 3.25 mmol, 1.00 equiv) in THF (30 mL) was added 9-BBN (0.500 M in THF, 9.76 mL, 4.88 mmol, 1.50 equiv), dropwise at 0 °C, and the resulting mixture was then stirred at rt for 4 h. Water (1 mL) was added,

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followed by aq NaOH (3.00 M, 8.00 mL) and aq 30% H_2O_2 (6.00 mL). The reaction mixture was heated to 60 °C, stirred for 2 h, and then extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with water (2 × 15 mL) and brine (2 × 15 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give the crude product. Purification by column chromatography (25% EtOAc:petroleum ether) gave **44** (210 mg, 35%) as a colorless oil (vide supra) and the title alcohol **47** (61.4 mg, 11%), as a white solid: mp 54−56 °C; R_f 0.46 (30% EtOAc:petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.00 (1H, dd, J = 18.0, 11.5 Hz, C*H*═CH_2), 5.16 (1H, dd, J_{cis} = 11.5, 0.5 Hz, CH═C*H*$_2$), 5.01 (1H, dd, J_{trans} = 18.0, 1.0 Hz, CH═C*H*$_2$), 3.44 (1H, td, J = 10.5, 4.5 Hz, HOC*H*<), 2.01−1.03 (16H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 142.0 (*C*H═CH_2), 114.1 (CH═*C*H$_2$), 70.4 (>CHOH), 52.9 (2°), 41.6 (3°), 41.5 (4°), 40.0 (2°), 36.5 (2°), 26.4 (2°), 22.8 (2°), 21.8 (2°), 20.3 (2°); IR (film) 3416, 2925, 2849, 1629, 1450, 1243, 1153, 927, 903 cm^{-1}; HMRS (TOF-ESI+) calcd for [($C_{12}H_{20}O$) + H]$^+$ 181.1592, found 181.1583; calcd for [($C_{12}H_{20}O$) + Na]$^+$ 203.1411, found 203.1398.

(±)-(4a*R,8a*R**)-1-Methylene-4a-vinyldecahydronaphthalene (48).** A solution of methyltriphenylphosphonium bromide (25.0 g, 70.1 mmol, 2.50 equiv) and potassium *tert*-butoxide (1.00 M in THF, 56.0 mL, 56.0 mmol, 2.00 equiv) in THF (150 mL) was stirred at reflux for 3 h. Vinyl ketone **45** (5.00 g, 28.0 mmol, 1.00 equiv) in toluene (15 mL) was then added dropwise to the above solution, and the resulting mixture was stirred at reflux for 16 h. The reaction was carefully quenched by the addition of acetone (100 mL) and stirred at 60 °C for 30 min. The reaction mixture was then allowed to cool to rt, and water (100 mL) was added. The reaction mixture was extracted with Et_2O (3 × 120 mL), and the combined organic layers were washed with brine (2 × 150 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give the crude product. Purification by column chromatography (100% hexane) gave the title alkene **48** (4.55 g, 92%) as a colorless liquid: bp 233−235 °C at 760 Torr; R_f 0.73 (100% pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (1H, dd, J = 18.0, 11.0 Hz, C*H*═CH_2), 5.13 (1H, dd, J_{cis} = 11.0, 1.0 Hz, CH═C*H*$_2$), 5.01 (1H, dd, J_{trans} = 18.0, 1.5 Hz, CH═C*H*$_2$), 4.76 (1H, q, J = 1.5 Hz, >C═C*H*$_2$), 4.52 (1H, q, J = 1.5 Hz, >C═C*H*$_2$), 2.37−2.28 (1H, m), 2.11−1.99 (1H, m), 1.86−1.74 (3H, m), 1.65−1.18 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6 (>*C*═CH_2), 142.1 (CH═CH_2), 113.6 (CH═*C*H$_2$), 106.1 (>C═*C*H$_2$), 50.2 (4°), 42.7 (2°), 42.6 (3°), 39.6 (2°), 36.9 (2°), 26.7 (2°), 25.1 (2°), 23.5 (2°), 21.9 (2°); IR (film) 2926, 2845, 1644, 1145, 1140, 1230, 1151, 997, 858, 785 cm^{-1}; HRMS (APCI+) calcd for [($C_{13}H_{20}$ + H]$^+$ 177.1638, found, 177.1634.

(±)-((1*R,4a*R**,8a*R**)-4a-Vinyldecahydronaphthalen-1-yl)-methanol (49).** To a stirred solution of bis(alkene) **48** (2.35 g, 13.3 mmol, 1.00 equiv) in THF (75 mL) was added 9-BBN (0.500 M THF solution, 39.9 mL, 20.0 mmol, 1.50 equiv), dropwise at −15 °C, and the resulting mixture was stirred for 15 min. The reaction mixture was allowed to warm to rt and stirred for 120 h. Then aq NaOH (3.00 M, 30 mL) followed by aq 30% H_2O_2 (30 mL) was added (*exothermic!*). The resulting reaction mixture was left to cool to rt with stirring over 3 h. The reaction mixture was then diluted with aq NH_4Cl (50 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (2 × 25 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give the crude. Purification by column chromatography (25% EtOAc:petroleum ether) gave the title alcohol **49** (2.20 g, 85%) as a colorless oil: R_f 0.39 (25% EtOAc:petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.09 (1H, dd, J = 16.5, 10.5 Hz, C*H*═CH_2), 5.05 (1H, dd, J_{cis} = 10.5, 1.5 Hz, CH═C*H*$_2$), 4.99 (1H, dd, J_{trans} = 16.5, 1.5 Hz, CH═C*H*$_2$), 3.66−3.56 (2H, m, C*H*$_2$OH), 1.93−1.01 (17H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 142.6 (*C*H═CH_2), 112.1 (CH═*C*H$_2$), 60.8 (>CHC*H*$_2$OH), 48.2 (>C*H*CH_2OH), 45.0 (>CHC*H*CH_2OH), 43.1 (2°), 40.6 (4°), 38.5 (2°), 28.1 (2°), 27.5 (2°), 26.6 (2°), 22.1 (2°), 17.5 (2°); IR (film) 3311, 2923, 2859, 1631, 1448, 1410, 1223, 1149, 1069, 1020, 995, 974, 847 cm^{-1}; HRMS (TOF-ESI+) calcd for [($C_{13}H_{22}O$) + H]$^+$ 195.1748, found 195.1729.

(±)-(((1*R,4a*S**)-Decahydro-1,4a-methanooxymethanonaphthalen-9-yl)methyl) Iodide (52).** A solution of iodine (261 mg, 1.02 mmol, 2.00 equiv) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of ethylenebis(diphenylphosphine) (256 mg, 0.640 mmol, 1.25 equiv) in CH_2Cl_2 (5 mL) at 0 °C. The reaction temperature was kept below 10 °C for 30 min. A solution of alcohol **49** (100 mg, 0.510 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) was then added dropwise to the reagent mixture. After addition of all the substrate, the resulting reaction mixture was stirred at rt for 16 h. Then solvent was removed under reduced pressure, and the residue was diluted with Et_2O (25 mL) and washed with aq $Na_2S_2O_3$ (2 × 15 mL). The organic phase was washed with brine (25 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (5% to 20% EtOAc:petroleum ether) to afford the title iodide **52** (30.0 mg, 18%) as a colorless oil: R_f 0.36 (5% EtOAc:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (1H, q, J = 6.5 Hz, >C*H*CH_2I), 4.01 (1H, dt, J = 11.5, 2.0 Hz, >CHC*H*$_2$OCH<), 3.57 (1H, d, J = 11.5 Hz, >CHC*H*$_2$OCH<), 2.26 (1H, qt, J = 13.0, 6.0 Hz), 1.99−1.55 (5H, m), 1.50−1.20 (8H, m), 1.08 (2H, d, J = 6.5 Hz, >CHC*H*$_2$I), 0.91 (1H, tdd, J = 13.5, 6.0, 1.5 Hz, decalin C1-H), 0.81−0.78 (1H, td, J = 13.5, 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.4 (>CHCH_2I), 67.9 (>C*H*CH_2OCH<), 44.6, 37.0 (decalin C1), 36.9, 35.8 (decalin C2), 35.0 (decalin C4a), 33.3, 26.8, 25.7, 22.4, 21.7, 15.1 (>CHCH_2I); IR (film) 2924, 2854, 1460, 1377, 1259, 1076, 1017, 798, 752, 606 cm^{-1}; HRMS (APCI+) calcd for [($C_{13}H_{21}IO$) + H]$^+$ 321.0717, found 321.0714.

(±)-(1*R,4a*R**,8a*R**)-4a-Vinyldecahydronaphthalene-1-carbaldehyde (53).** To a stirred solution of oxalyl chloride (1.38 mL, 16.1 mmol, 1.10 equiv) in CH_2Cl_2 (80 mL) at −78 °C was added DMSO (2.23 mL, 31.5 mmol, 2.15 equiv). The solution was stirred for 20 min, and then alcohol **49** (2.85 g, 14.7 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) was added. The reaction mixture was stirred at −78 °C for 2.5 h, and then Et_3N (10.3 mL, 73.3 mmol, 5.00 equiv) was added at the same temperature. After 20 min, the solution was allowed to warm to rt over 30 min, water (100 mL) was added, and the reaction mixture was extracted with Et_2O (2 × 75 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (10% EtOAc:petroleum ether) to give the title aldehyde **53** (2.45 g, 87%) as a pale yellow oil: R_f 0.64 (20% EtOAc:petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (1H, s, CHO), 5.99 (1H, dd, J = 17.5, 11.0 Hz, C*H*═CH_2), 5.14 (1H, d, J_{cis} = 11.0 Hz, C*H*═CH_2), 5.06 (1H, d, J_{trans} = 17.5 Hz, CH═C*H*$_2$), 2.23−2.19 (2H, m), 1.98−0.66 (14H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7 (>CHCHO), 140.2 (*C*H═CH_2), 115.1 (*C*H═CH_2), 51.9 (3°), 48.2 (3°), 43.0 (2°), 40.6 (4°), 38.8 (2°), 27.5 (2°), 26.4 (2°), 26.0 (2°), 21.9 (2°), 18.6 (2°); IR (film) 2923, 2854, 1723, 1448, 1236, 1074, 911 cm^{-1}; HRMS (TOF-ESI+) calcd for [($C_{13}H_{20}O$) + H]$^+$ 193.1593, found 193.1587; [($C_{13}H_{20}O$) + Na]$^+$ 215.1413, found 215.1404.

(±)-(*R)-Oxazol-2-yl((1*R**,4a*R**,8a*R**)-4a-vinyldecahydronaphthalen-1-yl)methanol (55a) and (±)-(*S**)-Oxazol-2-yl-((1*R**,4a*R**,8a*R**)-4a-vinyldecahydronaphthalen-1-yl)methanol (55b).** To a solution of oxazole (355 mg, 338 μL, 5.14 mmol, 1.00 equiv) in anhydrous THF (15 mL), in a flame-dried flask, BH_3·THF complex (1.00 M in THF, 5.40 mL, 5.40 mmol, 1.05 equiv) was added at rt. After being stirred at rt for 1 h, the colorless solution was cooled to −78 °C and ^{n}BuLi in hexanes (1.50 M, 3.60 mL, 5.40 mmol, 1.05 equiv) was added dropwise over 15 min. The resulting yellow solution was stirred at −78 °C for 90 min before a solution of aldehyde **53** (0.990 g, 5.14 mmol, 1.00 equiv) in THF (15 mL) was added dropwise over 30 min. The resulting yellow solution was stirred at −78 °C for 1.5 h and then quenched with 5% AcOH in ethanol (20 mL). The cooling bath was removed, and the reaction mixture was allowed to warm to rt. After being stirred at rt for 16 h, the colorless solution was concentrated under vacuum. The residue was dissolved in Et_2O (20 mL), washed with sat. aq $NaHCO_3$ (2 × 30 mL), and then brine (50 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and then purified by column chromatography (10% to 25% EtOAc:petroleum

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ether) to give the title products **55a** and **55b** (0.704 g, 53%) as a colorless solid mixture of two diastereomers in a ratio of 1:1. Further chromatography allowed sufficient quantities of pure **55a** and **55b** to be isolated for characterization. Crystals of **55b** suitable for X-ray diffraction were grown by slow diffusion of hexane vapor into a solution of **55b** in chloroform. Title product **55a**, a white solid: mp 90−92 °C; R_f 0.55 (40% EtOAc:petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, s, oxazole C*H*═CH), 7.04 (1H, s, oxazole CH═C*H*), 6.61 (1H, dd, J = 18.0, 11.0 Hz, C*H*═CH_2), 5.33 (1H, d, J = 11.0 Hz, >CHO*H*), 5.18 (1H, d, J_{cis} = 12.5 Hz, CH═CH_2), 5.14 (1H, d, J_{trans} = 19.0 Hz, CH═CH_2), 2.35 (1H, br s, >C*H*OH), 2.27 (1H, qd, J = 13.0, 3.5 Hz), 2.13−2.03 (2H, m), 1.86−1.80 (1H, m), 1.67−1.06 (10H, m). 0.99−0.82 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (oxazole 4°), 142.6 (CH═CH_2), 138.1 (oxazole 3°), 126.6 (oxazole 3°), 112.3 (CH═CH_2), 68.8 (>CHOH), 49.5 (3°), 46.3 (2°), 45.1 (3°), 40.6 (4°), 38.1 (2°), 30.3 (2°), 28.8 (2°), 28.4 (2°), 22.4 (2°), 18.4 (2°); IR (film) 3239, 2917, 2849, 1567, 1460, 1238 cm^{-1}; MS (ESI) m/z (%) 262 (M + H$^+$, 100), 198 (3), 132 (2); HRMS (TOF-ESI+) calcd for [($C_{16}H_{23}NO_2$) + H]$^+$ 262.1807, found 262.1788; calcd [($C_{16}H_{23}NO_2$) + Na]$^+$ 284.1626, found 284.1602. Title product **55b**, a white solid: R_f 0.52 (40% EtOAc:petroleum ether), mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, s, oxazole C*H*═CH), 7.01 (1H, s, oxazole CH═C*H*), 6.34 (1H, dd, J = 17.5, 11.0 Hz, C*H*═CH_2), 5.16 (1H, dd, J_{cis} = 11.0, 1.0 Hz, CH═CH_2), 5.08 (1H, d, J = 7.5 Hz, >C*H*OH), 5.04 (1H, dd, J_{trans} = 17.5, 1.5 Hz, CH═CH_2), 3.45 (1H, br s, >CHO*H*), 2.37−2.31 (1H, m), 2.26−2.21 (1H, m), 2.05−1.99 (1H, m), 1.73−1.07 (11H, m), 0.91−0.85 (1H, m), 0.62 (1H, qd, J = 13.0, 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (oxazole 4°), 142.5 (*C*H═CH_2), 138.0 (oxazole 3°), 126.6 (oxazole 3°), 112.4 (CH═CH_2), 64.6 (>CHOH), 48.4 (3°), 45.7 (2°), 43.8 (3°), 40.2 (4°), 38.1 (2°), 28.5 (2°), 27.9 (2°), 25.6 (2°), 21.9 (2°), 17.9 (2°); IR (film) 3239, 2917, 2849, 1567, 1460, 1238, 1071, 916, cm^{-1}; MS (ESI) m/z (%) 262 (M + H$^+$, 100), 244 (10), 147 (1), 116 (2); HRMS (TOF-ESI+) calcd for [($C_{16}H_{23}NO_2$) + H]$^+$ 262.1807, found 262.1787; calcd for [($C_{16}H_{23}NO_2$) + Na]$^+$ 284.1626, found 284.1602.

(±)-(6*R,6a*R**,10a*S**)-6,6a,7,8,9,10-Hexahydro-5*H*-6,10a-propanobenzo[*f*]quinolin-5-one (56), (±)-(6*S**,6a*R**,10a*S**)-6,6a,7,8,9,10-Hexahydro-5*H*-6,10a-propanobenzo[*f*]quinolin-2-ol (57), (±)-(2*S**,6*R**,6a*R**,10a*S**)-2-Hydroxy-1,2,3,4,6,6a,7,8,9,10-decahydro-5*H*-6,10a-propanobenzo[*f*]-quinolin-5-one (58), (±)-1-(3-(((6*S**,6a*R**,10a*S**)-6,6a,7,8,9,10-Hexahydro-5*H*-6,10a-propanobenzo[*f*]quinolin-2-yl)amino)-propyl)pyrrolidin-2-one (59), and (±)-1-(3-(((5*R**,6*R**,6a*R**,10a*S**)-5-Hydroxy-6,6a,7,8,9,10-hexahydro-5*H*-6,10a-propanobenzo[*f*]quinolin-2-yl)amino)propyl)-pyrrolidin-2-one (60).** To a microwave vial charged with a stirring bar were added substrate **55a**/**b** (260 mg, 0.994 mmol, 1.00 equiv, 1:1 ratio of diastereoisomers), toluene (10 mL), and 1,5-diazabicyclo(4.3.0)non-5-ene (2.47 g, 2.45 mL, 19.9 mmol, 20.0 equiv). The reaction mixture was degassed with argon and irradiated in a microwave reactor at 200 °C for 90 min. The reaction solvent was then removed under reduced pressure. The brown residue was diluted with EtOAc (20 mL), washed with water (2 × 15 mL) and brine (30 mL), dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure and then purified by column chromatography (elution gradient 0:0:80:20 to 5:10:100:0 of Et_3N:MeOH:EtOAc:petroleum ether) to give the title products. Ketopyridine **56** was isolated as an inseparable mixture with 3-hydroxypyridine **57**, and lactone **59** was isolated as an inseparable mixture with lactone **60**. In both instances, additional 2D NMR data have allowed discrete ^{1}H and ^{13}C NMR assignments to be made for the individual components of the mixtures. **56** and **57** were isolated as a pale yellow oil, 17 mg (2% yield of **56** and 5% yield of **57** by NMR). For ketopyridine **56**: R_f 0.28 (100% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (1H, d, J = 4.0 Hz, py N═C*H*CH═CH) 7.73 (1H, d, J = 8.0 Hz, py N═CHCH═C*H*), 7.48 (1H, dd, J = 8.0, 4.5 Hz, py N═CHC*H*═CH), 2.36 (1H, d, J = 14.0 Hz), 2.17 (1H, app s), 1.89−1.78 (2H, m), 1.69−0.83 (12 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6 (>C═O), 150.2 (py 4°), 148.1 (py N═CHCH═CH), 142.7 (py 4°), 135.3 (py N═CHCH═CH), 127.9 (py N═CHCH═CH), 50.1 (3°), 47.4 (3°), 40.4 (2°), 40.1 (4°), 36.7 (2°), 30.3 (2°), 29.6 (2°), 26.4 (2°), 21.6 (2°), 18.9 (2°); IR (film) 3423, 2936, 2885, 2831, 1527, 1453, 1343, 1301, 1268, 1204, 1123, 1019, 985, 907 cm^{-1}; HRMS (TOF-ESI+) calcd for [($C_{16}H_{19}NO$) + H]$^+$ 242.1544, found 242.1539. For 3-hydroxypyridine **57**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (1H, d, J = 1.5 Hz, py N═C*H*C(OH)═CH), 7.22 (1H, d, J = 1.5 Hz, py N═CHC(OH)═C*H*), 3.14 (1H, dd, J = 18.0, 7.0 Hz, py C*H*HCH<), 2.72 (1H, d, J = 18.0 Hz, py CH*H*CH<), 2.20 (1H, d, J = 14.0 Hz, py 4° CC*H*H), 2.02−1.96 (2H, m, py CH_2C*H*< and one other alkyl H), 1.78−1.72 (2H, m), 1.68−0.85 (13H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4 (py N═CHC(OH)═CH), 148.9 (py 4°), 138.8 (py 4°), 132.5 (py N═*C*HC(OH)═CH), 122.7 (py N═CHC(OH)═CH), 44.4 (3°), 42.8 (3°), 39.3 (2°), 36.8 (2°), 35.0 (2°), 33.3 (4°), 32.5 (2°), 28.2 (2°), 26.7 (2°), 22.1 (2°), 18.9 (2°); HRMS (TOF-ESI+) calcd for [($C_{16}H_{21}NO$) + Na]$^+$ 266.1516, found 266.1515. For enone **58**, isolated 30 mg (12%) as a colorless oil: R_f 0.40 (100% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) 4.26 (1H, br s, CH_2CH(O*H*)CH_2), 4.20−4.14 (1H, m, CH_2C*H*(OH)CH_2NH) 3.20 (1H, dt, J = 11.0, 3.0 Hz, CH_2CH(OH)C*H*HNH) 2.98 (1H, dt, J = 11.0, 1.5 Hz, CH_2CH(OH)CH*H*NH), 2.57 (1H, br s, CH_2N*H*), 2.37 (1H, ddd, J = 19.0, 4.0, 1.5 Hz, C*H*HCH(OH)CH_2NH), 2.31−2.27 (1H, m), 1.98 (1H, dq, J = 19.5, 2.0 Hz, CH*H*CH(OH)CH_2NH), 1.86−1.77 (2H, m), 1.73−0.83 (13H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 196.4 (>C═O), 138.4 (>*C*═C<), 124.4 (>C═*C*<), 62.7 (>C(OH)<), 48.5 (>C(OH)CH_2NH), 48.1 (3°), 45.9 (3°), 39.6 (4°), 35.7 (2°), 35.0 (2°), 31.6 (2°), 28.3 (2°), 27.8 (2°), 26.0 (2°), 23.1 (2°), 19.1 (2°); IR (film) 3357, 3251, 2947, 2851, 1705, 1552, 1414, 1369, 1284, 1105, 1078, 999, 911, 871 cm^{-1}; MS (ESI) m/z (%) 284 (M + Na$^+$, 17), 263 (17), 262 (M + H$^+$, 100), 260 (7), 245 (8), 244 (42); HRMS (TOF-ESI+) calcd for [($C_{16}H_{23}NO_2$) + Na]$^+$ 284.1626, found 284.1642. **59** and **60** were isolated as a colorless oil, 55 mg (11% yield of **59** and 3% yield of **60** by NMR). For lactone **59**: R_f 0.17 (1:5:100 Et_3N:MeOH:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (1H, d, J = 2.5 Hz, py N═C*H*C(NH)═CH) 6.75 (1H, d, J = 2.5 Hz, py N═CHC(NH)═C*H*), 4.18 (1H, br s, NH), 3.37−3.33 (4H, m, py NHCH_2CH_2CH_2 and C(O)NCH_2CH_2CH_2), 3.14−3.08 (2H, m, py NHCH_2CH_2CH_2), 3.04 (1H, dd, J = 18.0, 7.0 Hz, py C*H*HCH<), 2.58 (1H, d, J = 18.0 Hz, Py-CH*H*CH<), 2.37 (2H, t, J = 8.0 Hz, CH_2CH_2C(O)NCH_2), 2.17−2.14 (1H, m, py C(4°)CH_2), 2.02−1.96 (2H, m, C(O)NCH_2CH_2CH_2), 1.93−1.91 (1H, m, py CH_2C*H*<), 1.79−1.74 (2H, m, py NHCH_2CH_2CH_2), 1.73−0.99 (14H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3 (C(O)N<), 147.5 (py 4°), 142.3 (py N═CHC(NH)═CH), 136.4 (py 4°), 132.0 (py N═CHC-(NH)═CH), 117.4 (py N═CHC(NH)═*C*H), 47.1 (C(O)NCH_2) 44.7 (2°), 42.9 (3°), 40.4 (NHCH_2CH_2CH_2), 39.7 (NHCH_2CH_2CH_2), 39.0 (4°), 36.8 (2°), 35.1 (2°), 34.3 (py CH_2CH<), 32.8 (py CH_2CH<), 30.8 (CH_2CH_2C(O)NCH_2), 28.2 (2°), 26.8 (2°), 25.8 (NHCH_2CH_2CH_2), 22.1 (2°), 19.0 (2°), 17.8 (*C*H_2CH_2C(O)NCH_2); IR (film) 3670, 3321, 2981, 2925, 2854, 1667, 1594, 1494, 1460, 1398, 1350, 1288, 1243, 1164, 1076, 1031, 953 cm^{-1}; HRMS (TOF-ESI+) calcd for [($C_{23}H_{33}N_3O$) + H]$^+$ 368.2796, found 368.2859. For lactone **60**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (1H, d, J = 2.5 Hz, py N═C*H*C(NH)═CH) 6.70 (1H, d, J = 2.5 Hz, py N═CHC(NH)═C*H*), 4.72 (1H, d, J = 7.0 Hz, py C*H*(OH)-CH<), 4.40 (1H, br s, NH), 3.37−0.99 (29H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4 (CONH), 148.5 (py 4°), 143.5 (py N═CHC(NH)═CH), 135.9 (py 4°), 131.9 (py N═CHC(NH)═CH), 116.4 (py N═CHC(NH)═CH), 68.5 (py *C*H(OH)CH<), 46.4, 43.4, 40.1, 39.7, 39.6, 37.3, 36.8, 29.6, 29.5, 29.2, 28.1, 27.0, 26.9, 25.7, 22.3, 18.9; HRMS (TOF-ESI+) calcd for [($C_{23}H_{33}N_3O_2$) + H]$^+$ 384.2646, found 384.2706.

(±)-(6*S,6a*R**,10a*S**)-6,6a,7,8,9,10-Hexahydro-5*H*-6,10a-propanobenzo[*f*]quinolin-2-yl 4-Nitrobenzoate (61).** To a solution of mixture **56**/**57** (24 mg, 0.069 mmol of **57**, 1.00 equiv) in CH_2Cl_2 (3 mL) were added 4-nitrobenzoyl chloride (25.9 mg, 0.139 mmol, 2.00 equiv) and pyridine (27.6 mg, 28 μL, 0.349 mmol, 5.00 equiv). The reaction mixture was stirred at rt for 16 h. The reaction mixture was then quenched by addition of aq NaOH (1.0 M, 5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (15 mL) and brine (30 mL), dried over

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$MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and then purified by column chromatography (40 to 75% EtOAc:petroleum ether) to give the title ester **61** (14 mg, 52%) as pale yellow solid: mp 83−85 °C; R_f 0.47 (40% EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (2H, d, J = 9.0 Hz, Ar-H), 8.36 (2H, d, J = 9.0 Hz, Ar-H), 8.33 (1H, d, J = 2.0 Hz, py N=C*H*C(OH)=CH), 7.43 (1H, d, J = 2.0 Hz, py N=CHC(OH)=C*H*), 3.19 (1H, dd, J = 18.5, 7.0 Hz, py C*H*HCH<), 2.77 (1H, d, J = 18.5 Hz, Py-CH*H*CH<), 2.21−2.16 (1H, m), 2.07−2.03 (1H, m), 1.83−1.77 (1H, m), 1.73−1.65 (2H, m), 1.63−1.58 (1H, m, py CH_2CH<), 1.56−1.50 (1H, m), 1.48−1.03 (9H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 (>C=O), 157.2 (py 4°), 151.0 (Ar-*C*-NO_2), 145.7 (py N=CHC(OPNB)=CH), 139.1 (py N=*C*HC(OPNB)=CH), 137.8 (py 4°), 134.5 (Ar-*C*-NO_2), 131.3 (Ar-CH), 126.2 (py N=CHC(OPNB)=*C*H), 123.7 (Ar-CH), 44.3 (3°), 42.9 (2°), 39.5 (4°), 36.8 (2°), 35.1 (2°), 34.9 (2°), 32.6 (3°), 28.2 (2°), 26.7 (2°), 22.4 (2°), 18.9 (2°); IR (film) 2926, 2855, 1742, 1608, 1528, 1448, 1348, 1258, 1210, 1107, 1014, 907 cm^{-1}; HRMS (TOF-ESI+) calcd for $[(C_{23}H_{24}N_2O_4) + Na]^+$ 415.1633, found 415.1633.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all novel compounds, as well as selected 2D NMR spectra. Details of molecular modeling. X-ray crystallographic data for **55b** (CCDC no. 923516). 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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