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De Novo Synthesis of the DEF-Ring Stereotriad Core of the *Veratrum* Alkaloids

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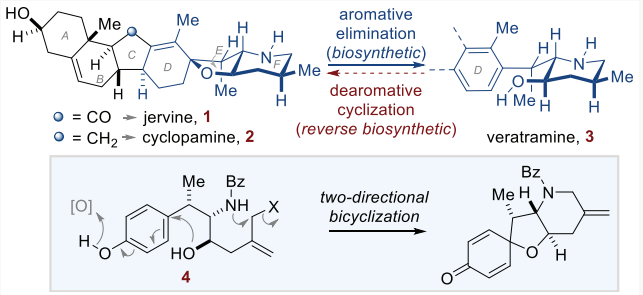
ABSTRACT: The synthesis of the stereotriad core in the eastern portion of the *Veratrum* alkaloids jervine (**1**), cyclopamine (**2**), and veratramine (**3**) is reported. Starting from a known β-methyltyrosine derivative (**8**), the route utilizes a diastereoselective substrate-controlled 1,2-reduction to establish the stereochemistry of the vicinal amino alcohol motif embedded within the targets. Oxidative dearomatization is demonstrated to be a viable approach for the synthesis of the spirocyclic DE ring junction found in jervine and cyclopamine.



The abundance of natural products with unique and desirable biological properties provides chemists with a diverse array of challenges and inspiration for the development of new synthetic strategies and tactics. Jervine (**1**), cyclopamine (**2**), and veratramine (**3**) are representative members of the *Veratrum* steroidal alkaloids,[1] which are most conspicuously known as antagonists of Smoothened (Smo), a Hedgehog (Hh) signaling protein. Dysregulation of this cell signaling pathway is often implicated in rhabdomyosarcoma, medulloblastoma, basal cell carcinoma, and pancreatic, breast, and prostate cancers.[2] Hedgehog signaling inhibition allows improved delivery of chemotherapeutics for pancreatic cancer in a mouse model.[3] A semisynthetic analogue of cyclopamine called IPI-926 (saridegib) is a drug candidate that has been evaluated in clinical trials.[4] Through utilization of a late-stage functionalization of cyclopamine, a kilogram-scale approach to the synthesis of saridegib has been developed.[4d] In addition to these exciting developments, it has been shown that introducing structural modifications to the parent structure of cyclopamine can allow increased stability as well as improved Hh signal inhibition.[5] With these possibilities in mind, a *de novo* synthesis is attractive as it might allow modifications in different regions of the parent structure and potentially provide a more diverse array of analogues. Others[6,7] have taken this approach, although the *de novo* routes have not yet been completed to date, and reliance on the chiral pool has left room for exploration of other tactics.

Early synthetic efforts to access this family of compounds were successful in providing a conceptual framework to obtain these molecules, though the routes began from steroidal starting materials and suffered from high step counts.[8] Subsequent studies expanded on that work and led to completed syntheses of verarine, veratramine, jervine, and veratrobasine.[9] More recent work established a novel skeletal rearrangement for the transformation of 12β-hydroxy steroids (containing a 6−6−6−5 ABCD ring system) into C-*nor*-D-*homo*-steroids (containing a 6−6−5−6 ABCD ring system), allowing a new path to the *Veratrum* alkaloids.[10] After construction of the steroidal portion, installation of a spirocyclic lactone facilitated elaboration to the fused tetrahydrofuran and piperidine rings.

A metathesis-based model study directed toward synthesis of the DEF ring system achieved a high level of efficiency,[11] but several key issues remained: the methyl group of the piperidine was not incorporated, the tetrahydrofuran contained a methyl group in the wrong oxidation state (and with incorrect relative stereochemistry), and the synthesis was racemic. In this Note, we present a route that attempts to address challenges associated with the spirocyclic tetrahydrofuran subunit of the *Veratrum* alkaloids using an oxidative dearomatization to form this challenging motif. In this first installment, we construct the stereogenic triad core of the DEF ring system, suitably functionalized to examine future convergent coupling approaches with an AB fragment to forge the C ring.[12]

Our retrosynthetic analysis of the target molecules placed an emphasis on the construction of the alkaloid core, which possesses several challenging structural features, including a unique fused tetrahydrofuran/piperidine ring system (Scheme 1). It has been proposed that the biosynthesis of veratramine (**3**) proceeds via acid-catalyzed aromatization of the D ring of

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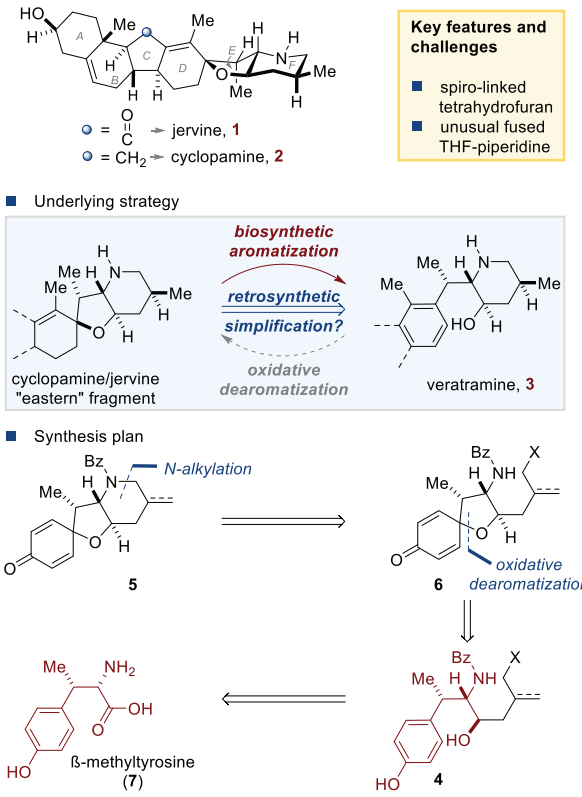
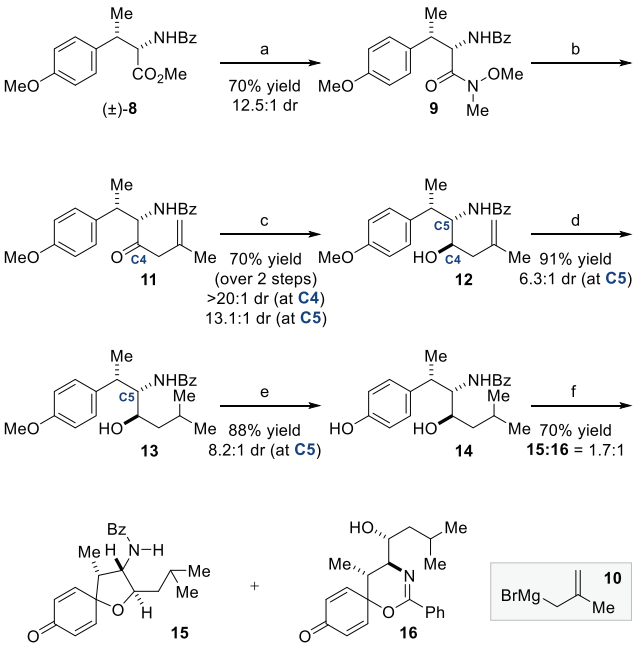
Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Tetrahydrofuran 15[a]



[a]Reagents and conditions: (a) MeNHOMe·HCl, Me_3Al, CH_2Cl_2, rt; (b) **10** (3.8 equiv), THF, 0 °C to rt; (c) $NaBH_4$, MeOH, 0 °C to rt; (d) H_2 (1 atm), Pd/C, MeOH, rt; (e) BBr_3, DCM, −78 to 0 °C; (f) $PhI(OAc)_2$, TFA, DCM, 0 °C to rt.

an intermediate possessing a spirocyclic tetrahydrofuran.[13] Inspired by this knowledge, we considered that it may be possible to take the reverse approach wherein an aromatic precursor could be used to access the tetrahydrofuran scaffold. We envisioned that all three alkaloids might arise from a common intermediate resembling amido alcohol **4**. We considered that by having a synthetic strategy that furnishes a functionalized aromatic D ring, we might be able to access veratramine using a substitution pattern that is well-suited for steroid−alkaloid coupling. Alternatively, for jervine and cyclopamine, we imagined using the phenol in an oxidative dearomatization[14,15] to provide a cyclohexadienone (e.g., **6**). With these considerations in mind, we made it our goal to synthesize the stereochemical array of the common intermediate **4**.

As a first investigation into the feasibility of this synthetic plan, we aimed to study a simplified model system for the intramolecular oxidative dearomatization. We began by synthesizing the known racemic *β*-methyltyrosine derivative **8**,[16] which was obtained in three steps from 4-methoxyacetophenone and hippuric acid (and can be produced on decagram scale in a single batch) (Scheme 2). Weinreb amide formation proceeded smoothly in 70% yield with only minimal epimerization during the reaction, providing amide **9** with a diastereomeric ratio of 12.5:1. Addition of methallylmagnesium bromide **10** furnished enone **11**, which could be diastereoselectively reduced with $NaBH_4$ to afford the secondary alcohol **12** in 70% yield over two steps. The ability of the nitrogen-bearing stereocenter to control the stereochemical outcome at the adjacent carbon is an attractive aspect of this synthetic route.[17] Aiming to minimize the number of reactive functional groups present, we hydrogenated the terminal alkene to obtain the saturated hydroxy benzamide **13** in 91% yield and 6.3:1 dr (major:C5 epimer). Demethylation of anisole **13** using BBr_3 resulted in the target oxidative dearomatization substrate, phenol **14**. Guided by prior studies utilizing $PhI(OAc)_2$ in TFA,[14e] dearomatization of the phenol under these conditions led to the expected spirotetrahydrofuran **15** and the undesired dihydrooxazine **16**[18] in a combined yield of 70%. Unfortunately, the two dearomatization products were inseparable and alternative reaction conditions or efforts to mitigate benzamide participation failed to improve the product distribution.

Given the moderate success of this model system, we next chose to investigate a functionalized methallyl linchpin that would enable the annulation of the piperidine ring (Scheme 3). The reaction of Weinreb amide (±)-**9** with Grignard reagent **17** resulted in the formation of an *β*,*γ*-unsaturated ketone which, upon silica gel chromatography, isomerized to the corresponding *α*,*β*-unsaturated ketone. To prevent the formation of the undesired conjugated system, we elected to treat the unpurified *β*,*γ*-enone with $NaBH_4$ to provide amido alcohol **18** with the requisite stereotriad as a 10.6:1 mixture of diastereomers by way of the illustrated putative hydrogen-bonded intermediate.[17c] Demethylation of anisole **18** could be achieved with BBr_3 with concomitant transformation of the *p*-methoxybenzyl allylic ether to an allylic bromide.[19] Hall and Deslongchamps,[19a] in a related system, propose that conformational restriction about the allylic methylene C−O bond predisposes the substrate for cleavage of the -OPMB group. This procedure enabled the isolation of the functionalized bromoamide **19** as a single diastereomer which was appropriately configured for both projected cyclizations. Oxidative dearomatization with $PhI(OAc)_2$ provided the desired spirocyclic THF **20**, which could be isolated as a single diastereomer. From that point, base-mediated *N*-alkylation using NaH furnished tricycle **21**. An X-ray

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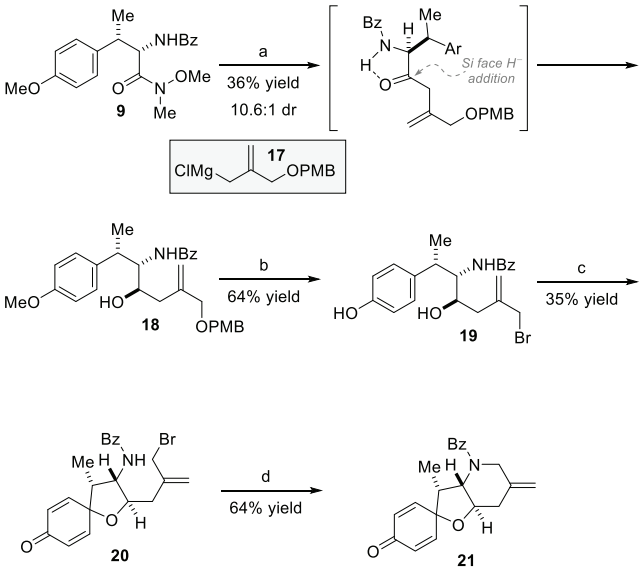
Scheme 3. Completion of Tricycle 21[a]



[a]Reagents and conditions: (a) (i) **17** (3.0 equiv), THF, 0 °C to rt; (ii) $NaBH_4$ (5 equiv), MeOH, rt; (b) BBr_3 (5 equiv), DCM, −78 to 0 °C; (c) PIDA (1.2 equiv), TFA (2 equiv), DCM, 0 °C; (d) NaH (5 equiv), THF, 0−55 °C.

crystallographic study was performed on this compound, confirming the molecule's connectivity and relative stereochemistry.[20]

The stereochemical triad embedded within the alkaloid portions of jervine, cyclopamine, and veratramine was synthesized in a short sequence that uses a simple, easily prepared unnatural amino acid−based building block. The unresolved issues for this synthetic approach, going forward, will be (1) executing a local desymmetrization[21] of the D ring to differentiate the diastereotopic groups after dearomatization, (2) rendering the synthesis asymmetric by employing an enantioselective hydrogenation in the synthesis of amido ester **8**, and (3) addressing inefficient or low-yielding steps in the sequence. We are optimistic that these issues are resolvable and will present exciting opportunities for reaction development and discovery. Studies toward these ends are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Comments. Infrared (IR) spectra were obtained using a Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm or acetone-d_6 at 2.05 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm or acetone-d_6 at 206.26 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, app t = apparent triplet, q = quartet, dd = doublet of doublets, app p = apparent pentet, ddd = doublet of doublet of doublets, app ddt = apparent doublet of doublet of triplets, app td = apparent triplet of doublets, app dt = apparent doublet of triplets, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a mass spectrometer with electrospray introduction and external calibration. All samples were prepared in HPLC-grade methanol. Melting points were obtained using a capillary melting point apparatus. Analytical thin layer chromatography (TLC) was performed on 0.20 mm Silica Gel TLC plates. Visualization was accomplished with UV light, $KMnO_4$, and/or Seebach's stain (2.5 g of phosphomolybdic acid, 1.0 g of $Ce(SO_4)_2$, 6.0 mL of conc. H_2SO_4, 94 mL of H_2O) followed by heating. Purification of the reaction products was carried out by flash column chromatography using silica gel (40−63 μm). Reagents, catalysts, and ligands were purchased and used as received. Solvents were dried by passage through an aluminum oxide column under nitrogen. Methyl ester **8**[16] and 1-(((2-(chloromethyl)allyl)oxy)-methyl)-4-methoxybenzene used to generate Grignard reagent **17**[22] were made according to literature procedures. Unless otherwise noted, all reactions were carried out under an atmosphere of dry nitrogen in flame-dried glassware with magnetic stirring. Yield refers to isolated yield of pure material unless otherwise noted.

*(±)-N-(1-(Methoxy(methyl)amino)-3-(4-methoxyphenyl)-1-oxobutan-2-yl)benzamide (**9**).* A 2 L round-bottomed flask equipped with a magnetic stir bar was charged with *N*,*O*-dimethylhydroxylamine hydrochloride (16.68 g, 171.0 mmol, 3.0 equiv) and DCM (340 mL). The flask was cooled in an ice bath and placed under an atmosphere of N_2. Trimethylaluminum (2.0 M solution in heptane, 85.5 mL, 171.0 mmol, 3.0 equiv) was added in a dropwise fashion. The ice bath was removed and the reaction was stirred for 30 min at ambient temperature. A solution of methyl ester **8** (18.66 g, 57.0 mmol, 1.0 equiv) in DCM (170 mL) was added dropwise. The reaction was allowed to stir for 24 h. Once complete, the reaction was cooled in an ice bath and, while stirring, quenched with saturated sodium potassium tartrate in a dropwise fashion until the reaction stopped bubbling. The quenched reaction was allowed to continue stirring for 1 h. The reaction mixture was filtered through a Celite pad using DCM and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography (30:70 to 60:40 ethyl acetate/hexanes) to obtain the desired product as a white solid (14.20 g, 70%). The product was obtained in 12.5:1 dr, which was determined by comparing the signals at δ 5.51 (minor) and δ 5.46 (major) in the ^{1}H NMR spectrum. Analytical data: mp 128−130 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.49−7.46 (m, 1H), 7.40−7.38 (m, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.86−6.82 (m, 2H), 6.55 (d, *J* = 9.0 Hz, 1H), 5.47−5.45 (m, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 3.34−3.31 (m, 1H), 3.29 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.0, 167.1, 158.6, 134.1, 133.6, 131.6, 128.8, 128.5, 127.0, 113.9, 61.8, 55.2, 53.7, 42.1, 32.1, 18.7; IR (thin film, KBr plate) υ 3310, 2935, 1636, 1509, 1249, 1179, 1036, 987, 912, 834 cm^{-1}; HRMS (ESI) *m*/*z*: [M + Na]$^+$ Calcd for $C_{20}H_{24}N_2NaO_4$379.1628; Found: 379.1623; TLC (60:40 EtOAc/hexanes): R_f = 0.42.

*(±)-N-(2-(4-Methoxyphenyl)-6-methyl-4-oxohept-6-en-3-yl)-benzamide (**11**).* A flame-dried 1 L round-bottomed flask equipped with a magnetic stir bar was cooled under a stream of N_2 and charged with Weinreb amide **9** (14.2 g, 39.8 mmol, 1.0 equiv) and THF (120 mL). The reaction was placed under N_2 and stirred in an ice bath. A solution of 2-methallylmagnesium bromide (0.5 M in THF, 240 mL, 120.0 mmol, 3.0 equiv) was added slowly. The reaction was stirred at room temperature for 16 h, at which point TLC analysis indicated that some starting material remained. The reaction was concentrated *in vacuo* to remove ∼200 mL solvent, then an additional volume of 2-methallylmagnesium bromide (0.5 M in THF, 65 mL, 32.5 mmol, 0.8 equiv) was added slowly at room temperature. After a further 4 h at the same temperature, the reaction was complete. The reaction was cooled to 0 °C and quenched with saturated aqueous ammonium chloride. The solution was transferred to a separatory funnel and extracted three times with diethyl ether. The combined organic phases were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by silica gel chromatography (10:90 to 20:80 ethyl acetate/hexanes) to obtain the desired product as a white solid (70% yield reported over two steps, from **9** to **12**). The product was obtained in 11.9:1 dr, which was determined by integrating the resonances at δ 4.95 (major) and δ 4.88 (minor) in the ^{1}H NMR spectrum. Analytical data: mp 104−106 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.54−7.51 (m, 1H), 7.46−7.43 (m, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 7.7 Hz, 1H), 5.12 (dd, *J* = 7.8 Hz, 5.0 Hz, 1H), 4.95 (s, 1H), 4.73 (s, 1H), 3.82 (s, 3H), 3.57−3.53 (m, 1H), 3.20−3.13 (m, 2H), 1.74 (s, 3H), 1.39 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 206.5, 167.0, 158.8, 138.3, 133.8, 132.8,

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131.8, 128.7, 128.7, 127.0, 115.7, 114.1, 62.7, 55.3, 50.6, 40.5, 22.8, 17.3; IR (thin film, KBr plate) υ 3318, 2969, 1718, 1646, 1514, 1250, 1180, 1035, 833, 711 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}NO_3$ 352.1907; Found: 352.1907; TLC (20:80 EtOAc/hexanes): R_f = 0.22.

*(±)-N-(4-Hydroxy-2-(4-methoxyphenyl)-6-methylhept-6-en-3-yl)benzamide (**12**).* Methallyl ketone **11**, as obtained in the previous procedure, was dissolved in MeOH (290 mL) and cooled in an ice bath. $NaBH_4$ (5.17 g, 137.0 mmol, 3.4 equiv with respect to **11**) was added carefully. The reaction was stirred for 2 h under N_2, slowly allowing it to warm to room temperature. The reaction was then quenched with 1 M HCl and concentrated *in vacuo* to remove MeOH. The crude residue was partitioned between ethyl acetate and 1 M HCl and the layers were separated. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried with sodium sulfate and concentrated *in vacuo* to afford the crude product, which was purified by silica gel chromatography (20:80 to 40:60 ethyl acetate/hexanes) to obtain the title compound as a white solid (8.75 g, 70% over the two steps from **9** to **12**). The product was obtained in 13.1:1 dr, which was determined by comparing the signals at δ 4.85 (major) and δ 4.77 (C5 epimer) in the ^1H NMR spectrum. No C4 epimer was observed. Analytical data: mp 89−90 °C, ^1H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, J = 7.9 Hz, 2H), 7.53−7.51 (m, 1H), 7.44−7.42 (m, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 5.82 (d, J = 9.2 Hz, 1H), 4.92 (s, 1H), 4.85 (s, 1H), 4.32−4.29 (m, 1H), 3.85 (s, 3H), 3.57−3.53 (m, 2H), 2.72 (d, J = 4.0 Hz, 1H), 2.28−2.20 (m, 2H), 1.70 (s, 3H), 1.39 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.7, 158.6, 142.6, 134.1, 133.5, 131.7, 129.3, 128.7, 126.8, 114.1, 114.0, 69.1, 58.8, 55.3, 42.6, 38.0, 22.4, 18.9; IR (thin film, KBr plate) υ 3423, 2965, 1646, 1513, 1249, 1179, 1035, 835, 712, 559 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{28}NO_3$ 354.2064; Found 354.2060; TLC (20:80 EtOAc/hexanes): R_f = 0.07.

*(±)-N-(4-Hydroxy-2-(4-methoxyphenyl)-6-methylheptan-3-yl)-benzamide (**13**).* A flame-dried 300 mL round-bottomed flask equipped with a magnetic stir bar was cooled under a stream of N_2 and charged with alcohol **12** (2.12 g, 6.0 mmol, 1.00 equiv) and 10% Pd/C (424 mg, 20 w/w%). Under an atmosphere of N_2, MeOH (60 mL) was added slowly. The solution was sparged with H_2 for 15 min, then the exit line was removed and the reaction was allowed to stir for 2 h at room temperature under a balloon of H_2. Once complete, the reaction was flowed through a pad of Celite with additional methanol, and the filtrate was concentrated *in vacuo*. The crude product thusly obtained was purified by silica gel chromatography (20:80 to 40:60 ethyl acetate/hexanes) to obtain the desired product as a white solid (1.93 g, 91%); the product was found to be a 6.3:1 dr, which was determined by comparing the signals at δ 3.26 (C5 epimer) and δ 3.16 (major) in the ^1H NMR spectrum. Analytical data: mp 70−72 °C, ^1H NMR (600 MHz, $CDCl_3$): δ 7.50−7.48 (m, 3H), 7.40−7.37 (m, 2H), 7.24 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 5.87 (d, J = 7.9 Hz, 1H), 4.31−4.28 (m, 1H), 3.83 (s, 3H), 3.81−3.80 (m, 1H), 3.34 (d, J = 7.4 Hz, 1H), 3.19−3.14 (m, 1H), 1.93−1.89 (m, 1H), 1.49−1.44 (m, 1H), 1.40 (d, J = 7.1 Hz, 3H), 1.24−1.20 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 168.5, 158.6, 134.6, 134.0, 131.7, 128.8, 128.6, 126.9, 114.4, 70.8, 60.6, 55.4, 41.9, 39.4, 24.4, 24.1, 21.6, 20.0; IR (thin film, KBr plate) υ 3426, 2956, 1644, 1514, 1304, 1285, 1250, 1179, 1038, 733 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{30}NO_3$ 356.2220, Found: 356.2213; TLC (40:60 EtOAc/hexanes): R_f = 0.35.

*(±)-N-(4-Hydroxy-2-(4-hydroxyphenyl)-6-methylheptan-3-yl)-benzamide (**14**).* A flame-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was cooled under a stream of N_2 and charged with anisole **13** (498 mg, 1.40 mmol, 1.0 equiv) and DCM (14 mL). The reaction was cooled in a dry ice/acetone bath and placed under nitrogen before adding BBr_3 (0.41 mL, 4.20 mmol, 3.0 equiv) dropwise. The reaction was placed in an ice water bath and allowed to stir for 1 h. Once complete, the reaction was quenched by adding MeOH dropwise. Water was added, and the layers were separated. The aqueous layer was extracted three times with DCM. The combined organic layers were dried with sodium sulfate and concentrated *in vacuo* to afford the crude product, which was purified by silica gel chromatography (20:80 to 35:65 ethyl acetate/hexanes) to obtain the title compound as a white solid (422 mg, 88%). The product was obtained in 8.2:1 dr, which was determined by comparing the signals at δ 3.19 (C5 epimer) and δ 3.09 (major) in the ^1H NMR spectrum. Analytical data: mp 50−52 °C, ^1H NMR (600 MHz, $CDCl_3$) δ 7.47−7.46 (m, 3H), 7.38−7.36 (m, 2H), 7.15 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.92 (d, J = 7.9 Hz, 1H), 4.32−4.28 (m, 1H), 3.88−3.85 (m, 1H), 3.11−3.06 (m, 1H), 1.94−1.89 (m, 1H), 1.48−1.44 (m, 1H), 1.37 (d, J = 7.0 Hz, 3H), 1.24−1.20 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 168.9, 155.2, 134.2, 133.8, 131.8, 128.8, 128.7, 126.9, 115.9, 70.8, 60.8, 41.6, 39.6, 24.4, 24.1, 21.6, 20.0; IR (thin film, KBr plate) υ 3285, 2957, 1644, 1515, 1488, 1289, 1235, 910, 839, 732 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{28}NO_3$ 342.2064; Found: 342.2059; TLC (35:65 EtOAc/hexanes): R_f = 0.22.

*(±)-N-(2-Isobutyl-4-methyl-8-oxo-1-oxaspiro[4.5]deca-6,9-dien-3-yl)benzamide (**15**) and (±)-4-(1-Hydroxy-3-methylbutyl)-5-methyl-2-phenyl-1-oxa-3-azaspiro[5.5]undeca-2,7,10-trien-9-one (**16**).* $PhI(OAc)_2$ (242 mg, 0.75 mmol, 1.5 equiv) was dissolved in DCM (18 mL) and cooled in an ice bath, and TFA (0.09 mL, 1.2 mmol, 2.3 equiv) was added dropwise. This solution was stirred for 15 min at ambient temperature, before adding it dropwise to a solution of phenol **14** (171 mg, 0.5 mmol, 1.0 equiv) in DCM (18 mL) at 0 °C. The reaction as then allowed to warm to ambient temperature slowly and stir for 3 h. $NaHCO_3$ (210 mg, 2.5 mmol, 5.0 equiv) was added, and the reaction was allowed to continue stirring for 10 min before concentration in vacuo. The crude residue was purified by silica gel chromatography (10:90 to 30:70 ethyl acetate/hexanes) to obtain an inseparable mixture of the two products as a red-brown foam (115 mg, 70%); the composition (by ^1H NMR analysis) was found to be **15**:**16** = 1.7:1. ^1H NMR signals were assigned to **15** and **16**, though assignments were not made for ^{13}C NMR signals. The mixture coeluted under every eluent system evaluated, despite a reasonable R_f difference. Analytical data: ^1H NMR (600 MHz, $CDCl_3$) **15**: δ 7.80 (d, J = 7.9 Hz, 2H), 7.58−7.56 (m, 1H), 7.53−7.48 (m, 2H, overlaps with **16**), 6.89 (dd, J = 10.3, 3.1 Hz, 1H), 6.78−6.76 (m, 1H, overlaps with **16**), 6.31 (d, J J = 7.9 Hz, 1H), 6.27−6.22 (m, 2H), 4.71−4.68 (m, 1H), 4.23−4.20 (m, 1H), 2.74−2.69 (m, 1H), 1.93−1.85 (m, 1H, overlaps with **15**), 1.71−1.67 (m, 1H), 1.61−1.58 (m, 1H), 0.99−0.96 (m, 6H, overlaps with **16**), 0.92−0.90 (m, 3H, overlaps with **15**); **16**: δ 7.98 (d, J = 8.0 Hz, 2H), 7.53−7.48 (m, 1H, overlaps with **15**), 7.45−7.42 (m, 2H), 6.86 (dd, J = 10.3, 3.1 Hz, 1H), 6.78−6.76 (m, 1H, overlaps with **15**), 6.46−6.41 (m, 2H), 4.03−4.00 (m, 1H), 3.58 (dd, J = 11.3, 3.8 Hz, 1H), 2.02−1.98 (m, 1H), 1.93−1.85 (m, 1H, overlaps with **15**), 1.39−1.34 (m, 1H), 0.99−0.96 (m, 6H, overlaps with **15**), 0.92−0.90 (m, 3H, overlaps with **15**); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 185.5, 184.9, 167.6, 155.5, 150.8, 146.8, 146.5, 142.4, 133.9, 132.1, 131.8, 131.6, 131.3, 131.0, 129.1, 128.9, 128.4, 128.3, 127.5, 126.9, 83.0, 81.3, 76.0, 68.7, 60.0, 58.5, 45.8, 44.6, 39.8, 34.3, 25.1, 24.2, 24.1, 23.3, 22.1, 21.4, 11.5, 9.4; IR (thin film, KBr plate) υ 3317, 2956, 1669, 1532, 1490, 1385, 1291, 1178, 862, 732 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{26}NO_3$ 340.1907; Found: 340.1904; TLC (30:70 EtOAc/hexanes): R_f = 0.35, 0.46 (**15** and **16** unassigned on TLC).

*(±)-N-4-Hydroxy-6-(((4-methoxybenzyl)oxy)methyl)-2-(4-methoxyphenyl)hept-6-en-3-yl)benzaimide (**18**).* A flame-dried two-necked 1 L round-bottomed flask equipped with a magnetic stir bar was cooled under a stream of N_2 and charged with magnesium turning (25.34 g, 1.043 mol, 22 equiv) and THF (217 mL). 1,2-Dibromoethane (3.08 mL, 35.6 mmol, 0.75 equiv) was added dropwise and the suspension was stirred at room temperature for 30 min. A few drops of a solution of 1-(((2-(chloromethyl)allyl)oxy)-methyl)-4-methoxybenzene (32.2 g, 142 mmol, 3.0 equiv) in THF (72.4 mL) were added slowly. Once the reaction had initiated, the remaining solution was added slowly to maintain a gentle reflux. The solution was stirred at room temperature for a further 90 min. Weinreb amide **9** was added in two portions and the mixture was stirred at room temperature for 16 h. The reaction was cooled to 0 °C

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and quenched with saturated aqueous ammonium chloride. The biphasic mixture was transferred to a separatory funnel and diluted with EtOAc. The organic layer was collected and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried over sodium sulfated, filtered, and concentrated *in vacuo* to provide the crude *β,γ*-unsaturated ketone as a yellow oil. The crude material thus obtained was dissolved in MeOH (200 mL) and cooled to −10 °C. $NaBH_4$ (8.969 g, 237 mmol, 5.0 equiv) was added in 5 portions, and the reaction was stirred at the same temperature for 2 h. The reaction was quenched with 1 M HCl (aq.) and the biphasic mixture was concentrated *in vacuo* to remove MeOH. The slurry was transferred to a separatory funnel and diluted with EtOAc. The organic layer was collected and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (30:70 to 40:60 to 50:50 ethyl acetate/hexanes) to provide the title compound as a yellow oil (8.34 g, 36% over two steps), existing as a 10.6:1 mixture of diastereomers as determined by the relative integrations of the signals at δ 5.77 (major) and 5.59 (minor) ppm in the ^{1}H NMR spectrum. Analytical data for the major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.49 (tt, J = 7.4, 1.2 Hz, 1H), 7.40 (m, 2H), 7.24 (dd, J = 8.6, 1.6 Hz, 2H), 7.21 (dd, J = 8.5, 1.8 Hz, 2H), 6.89 (dd, J = 8.6, 1.9 Hz, 2H), 6.85 (dd, J = 8.7, 1.0 Hz, 2H), 5.77 (d, J = 9.7 Hz, 1H), 5.12 (d, J = 1.7 Hz, 1H), 5.00 (d, J = 1.8 Hz, 1H), 4.41 (s, 2H), 4.27 (ddd, J = 9.7, 8.1, 3.9 Hz, 1H), 3.95 (d, J = 11.5 Hz, 1H), 3.88 (d, J = 11.5 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.69 (d, J = 4.0 Hz, 1H), 3.57 (qd, J = 7.2, 3.9 Hz, 1H), 3.46 (dddd, J = 9.6, 8.3, 3.7, 2.7 Hz, 1H), 2.43 (dd, J = 14.0, 2.1 Hz, 1H) 2.23 (dd, J = 14.1, 9.6 Hz, 1H), 1.34 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.5, 159.3, 158.5, 142.7, 134.1, 133.3, 131.6, 129.5, 129.5, 129.4, 128.6, 126.8, 117.4, 113.9, 113.8, 73.5, 72.0, 70.8, 58.6, 55.3, 55.2, 39.2, 37.5, 18.6; IR (thin film, KBr plate) υ 3422, 2925, 2853, 1648, 1613, 1513, 1249, 1037, 834, 711, 533 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{30}H_{36}NO_5$ 490.2588; Found: 490.2585; TLC (40:60 EtOAc/hexanes): R_f = 0.23.

*(±)-N-6-(Bromomethyl)-4-hydroxy-2-(4-hydroxyphenyl)hept-6-en-3-yl)benzamide (**19**).* A flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was cooled under N_2 and charged with anisole **18** (1.29 g, 2.63 mmol, 1.0 equiv) and DCM (26.3 mL). The solution was cooled to −78 °C, and BBr_3 (1.27 mL, 13.2 mmol, 5.0 equiv) was added dropwise. The mixture was warmed to 0 °C and stirred for 1 h. The reaction was quenched by careful dropwise addition of methanol then diluted with DCM and water and transferred to a separatory funnel. The organic layer was collected and the aqueous layer was extracted with DCM (2 × 25 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product thus obtained was taken up in acetone and adsorbed onto Celite to make a dry-load then purified by silica gel chromatography (30:70 to 40:60 to 50:50 to 60:40 ethyl acetate/hexanes) to provide the title compound as an amorphous solid (596 mg, 64%). Analytical data: ^{1}H NMR (600 MHz, acetone-d_6) δ 7.75 (m, 2H), 7.48 (tt, J = 7.5, 1.2 Hz, 1H), 7.40 (m, 2H), 7.21 (dt, J = 8.6, 1.9 Hz, 2H), 6.77 (dt, J = 8.5, 2.0 Hz, 2H), 5.25 (d, J = 1.7 Hz, 1H), 5.04 (d, J = 1.3 Hz, 1H), 4.35 (dd, J = 7.3, 5.7 Hz, 1H), 4.17 (d, J = 9.9 Hz, 1H), 4.13 (d, J = 9.9 Hz, 1H), 3.86 (ddd, J = 9.9, 7.3, 2.6 Hz, 1H), 3.47 (qd, J = 7.2, 5.5 Hz, 1H), 2.60 (dd, J = 14.5, 2.6 Hz, 1H), 2.28 (dd, J = 14.5, 9.9 Hz, 1H), 2.07 (m, 1H), 1.32 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3, 156.7, 144.8, 135.8, 134.4, 132.0, 130.1, 129.1, 128.1, 117.8, 115.8, 71.3, 60.1, 39.4, 38.4, 38.0, 19.8; IR (thin film, KBr plate) υ 3424, 2965, 2930, 1693, 1636, 1515, 1452, 1430, 1175, 692, 607 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$Calcd for $C_{21}H_{25}{}^{79}BrNO_3$ 418.1012; Found: 418.1011; [M + H]$^+$Calcd for $C_{21}H_{25}{}^{81}BrNO_3$ 420.0992; Found: 420.0990; TLC (50:50 EtOAc/hexanes): R_f = 0.28.

*(±)-N-(2-(2-(Bromomethyl)allyl)-4-methyl-8-oxo-1-oxaspiro-[4.5]deca-6,9-dien-3-yl)benzamide (**20**).* A flame-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was cooled under a stream of N_2 and charged with $PhI(OAc)_2$ (471.1 mg, 1.463 mmol, 1.2 equiv), DCM (40 mL), and TFA (188 μL,, 2.438 mmol, 2.0 equiv) then cooled to 0 °C and stirred for 10 min. A separate flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was cooled under a stream of N_2 and charged with phenol **19** (509.9 mg, 1.219 mmol, 1 equiv) and DCM (40 mL) then cooled to −10 °C. After stirring for 10 min, the $PhI(OAc)_2$/TFA solution was added slowly to the reaction vessel via cannula. The reaction was stirred for 4 h at the same temperature then quenched with solid sodium bicarbonate (409.6 mg, 4.876 mmol, 4.0 equiv). The mixture was concentrated in vacuo to afford the crude product, which was purified by silica gel chromatography (20:80 to 30:70 to 40:60 ethyl acetate/hexanes) to obtain the title compound as an off-white foam (176.3 mg, 35%). Analytical data: mp 124−125 °C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (dt, J = 7.0, 1.4 Hz, 2H), 7.59 (tt = 7.4, 1.2 Hz, 1H), 7.51 (m, 2H), 6.86 (dd, J = 10.3, 3.1 Hz, 1H), 6.82 (dd, J = 10.0, 3.1 Hz, 1H), 6.29 (dd, J = 10.3, 2.0 Hz, 1H), 6.25 (dd, J = 10.0, 2.0 Hz, 1H), 6.16 (d, J = 7.7 Hz, 1H), 5.35 (s, 1H), 5.19 (s, 1H), 4.75 (ddd, J = 7.6, 7.6, 4.6 Hz, 1H), 4.38 (ddd, J = 8.5, 4.6, 4.3 Hz, 1H), 4.12 (d, J = 10.1 Hz, 1H), 4.08 (d, J = 10.2 Hz, 1H), 2.78 (m, 2H), 2.67 (m, 1H), 0.95 (d, J = 7.3 Hz, d, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 185.2, 167.5, 150.2, 145.8, 141.5, 133.7, 132.2, 129.3, 128.9, 128.6, 126.8, 118.5, 83.2, 81.6, 57.8, 45.4, 39.0, 37.0, 9.5; IR (thin film, KBr plate) υ 3447, 3926, 2362, 1669, 1635, 1540, 644, 629, 609, 596, 546 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{21}H_{23}{}^{79}BrNO_3$ 416.0856; Found: 416.0853; [M + H]$^+$ Calcd for $C_{21}H_{23}{}^{81}BrNO_3$ 418.0835; Found: 418.0830; TLC (40:60 EtOAc/hexanes): R_f = 0.32.40:60 EtOAc/hexanes): R_f = 0.32.

*(±)-4′-Benzoyl-3′-methyl-6′-methylene-3a′,4′,6′,7′,7a′-hexahydro-3′H-spiro[cyclohexane-1,2′-furo[3,2-b]pyridine]-2,5-dien-4-one (**21**).* A flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was cooled under N_2 and charged with cyclohexadienone **20** (526 mg, 1.26 mmol, 1.0 equiv) and THF (25.2 mL). The stirred solution was cooled to 0 °C, and NaH (60% dispersion in oil, 252 mg, 6.30 mmol, 5.0 equiv) was added in one portion. The reaction mixture was warmed to 55 °C and stirred for 3 h. The vessel was cooled to 0 °C and quenched with 1 M HCl. The biphasic solution was transferred to a separatory funnel with EtOAc and the organic layer was collected. The aqueous phase was extracted with EtOAc (2 × 15 mL) and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The thus obtained crude material was purified by silica gel chromatography (15:85 to 20:80 to 30:70 to 40:60 ethyl acetate/hexanes) to obtain the title compound as a white foam (268.6 mg, 64%). Analytical data: mp 145−151 °C,^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (m, 3H), 7.45 (tt, J = 7.0, 1.4 Hz, 2H), 6.93 (dd, J = 15.4, 3.0 Hz, 1H), 6.92 (dd, J = 15.2, 2.9 Hz, 1H), 6.23 (dd, J = 10.0, 2.0 Hz, 1H), 6.11 (dd, J = 10.0, 2.0 Hz, 1H), 5.00 (app. s, 1H), 4.93 (app. s, 1H), 4.38 (td, J = 11.3, 5.9 Hz, 1H), 4.12 (d, J = 14.0 Hz, 1H), 3.84 (d, J = 13.8 Hz, 1H), 3.71 (dd, J = 11.1, 6.8 Hz, 1H), 3.29 (m, 1H), 3.05 (ddt, J = 15.2, 6.0, 2.0 Hz, 1H), 2.39 (ddq, J = 14.9, 11.5, 1.8 Hz, 1H), 1.03 (d, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 185.5, 173.3, 150.1, 146.9, 137.6, 135.0, 131.0, 128.7, 128.1, 128.0, 126.1, 115.3, 80.2, 74.6, 61.8, 53.3, 43.8, 34.9, 11.5; IR (thin film, KBr plate) υ 3057, 2973, 2854, 2361, 2341, 1698, 1633, 1397, 1235, 1097, 1074, 922, 858, 795, 630 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{21}H_{22}NO_3$ 336.1594; Found: 336.1589; TLC (30:70 EtOAc/hexanes): R_f = 0.13.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00685.

Spectral data for all compounds (PDF)

Crystallographic data for **21** (CIF)

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Notes

The authors declare no competing financial interest.

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