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Stereoselective Synthesis and Biological Evaluation of C1-Epimeric and Desmethyl Monomeric Nuphar Analogues

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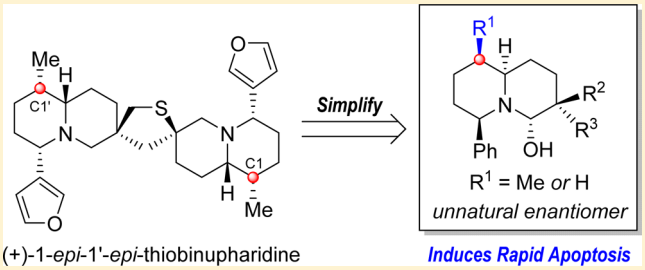
Supporting Information

ABSTRACT: A class of monomeric nuphar analogues that are either epimeric at C1 and C1′ or lack the naturally occurring methyl group at those positions were synthesized and evaluated for biological activity. The syntheses feature enantioselective vinylogous Mukaiyama−Mannich (vM−Mannich) reactions catalyzed by chiral phosphoric acids that proceed with excellent diastereoselectivity. Biological assays reveal that both the desmethyl and C1-epimeric monomeric nuphar analogous are able to induce rapid apoptosis.



INTRODUCTION

The dimeric nuphar alkaloids are a family of structurally complex, sulfur-containing, quinolizidine triterpenoids of which there are approximately a dozen and a half known members.[1−3] They exhibit a diverse set of biological properties including cytotoxic,[4,5] antibacterial,[6] antifungal,[7] and immunosuppressant activities.[8,9] Significantly, (+)-6-hydroxythiobinupharidine (+)-**1b** (Figure 1), induces unprecedented rapid apoptosis in U937 human leukemia cells within 1 h.[5] Epimeric congeners at C1 and/or C1′ (e.g., **4**−**6**) have also been isolated from *Nuphar Luteum* and *Nuphar pumilum*.[10,11] However, Yoshikawa and co-workers have shown that these are apoptotically inactive,[5] which may be due to the absence of either a C6 or C6′ hydroxyl functionality.

Because of their unique structures and potential as anticancer agents, both the monomeric[12−20] and dimeric nuphar alkaloids[21,22] have been the subject of intense synthetic efforts.[23] Despite that they were discovered over half a century ago,[1] the first total synthesis of (−)-neothiobinupharidine (−)-**3c** was not completed until 2013 by Shenvi.[21] Soon afterward, our group published the first total syntheses of both enantiomers of the dimeric hydroxylated nuphar alkaloids **1a**−**b** and **2a**,[22] as well as reported the first apoptosis data for several of these compounds. We then reported the discovery of the first known apoptotically active monomeric nuphar analogues, of which (+)-7 is even more potent than the naturally occurring compound (+)-**1b**.[20] Although the precise biological target and mode of action of the nuphar alkaloids is not known, Yoshikawa has demonstrated a dependence on both caspase **3** and **8**,[5] while Gopas and co-workers report that nuphar extracts appear to inhibit NFκB.[24] More recently, Shenvi proposes that retro-dimerization of certain members of the dimeric nuphar alkaloids, resulting from electrophilic attack at sulfur, generates a reactive intermediate that is ultimately responsible for apoptosis.[25,26]

As part of our ongoing investigations toward comprehensive SAR and identification of the biological target and mechanism of action, we became interested in profiling the apoptotic properties of monomeric quinolizidines that are either epimeric at C1/C1′ or lack the naturally occurring methyl group at those positions. On the basis of our previous finding that enantioenriched quinolizidine (+)-7 (Scheme 1), which corresponds to the absolute configuration of unnatural (−)-**1b**, is more potent than its respective natural antipode (−)-7, we decided to pursue the synthesis and evaluation of the epimeric/desmethyl quinolizidine **8** which corresponds to the unnatural absolute configuration of the dimeric compounds. Since the right-hand portion of (+)-**1b** and (+)-**4a** are identical, we reasoned this extra quinolizidine ring may not be required for biological activity and that it could be excised without compromising potency. Similar to the strategy we successfully adopted for the discovery of (+)-7, we proposed that the presence of a C6 hydroxyl group in the truncated structure **8** would be necessary for apoptotic activity. Because furan moieties are known to readily oxidize in vivo, we decided to replace it with a phenyl group which possesses greater metabolic stability as compared to furan.

RESULTS AND DISCUSSION

Our studies commenced with the construction of C1-desmethyl monomeric nuphar analogues **8** (when R^1 = H). By employing the protocol developed previously by Schneider[27−34] and our group,[20] compound **13** was obtained with high enantioselectivity by means of the chiral phosphoric acid-catalyzed

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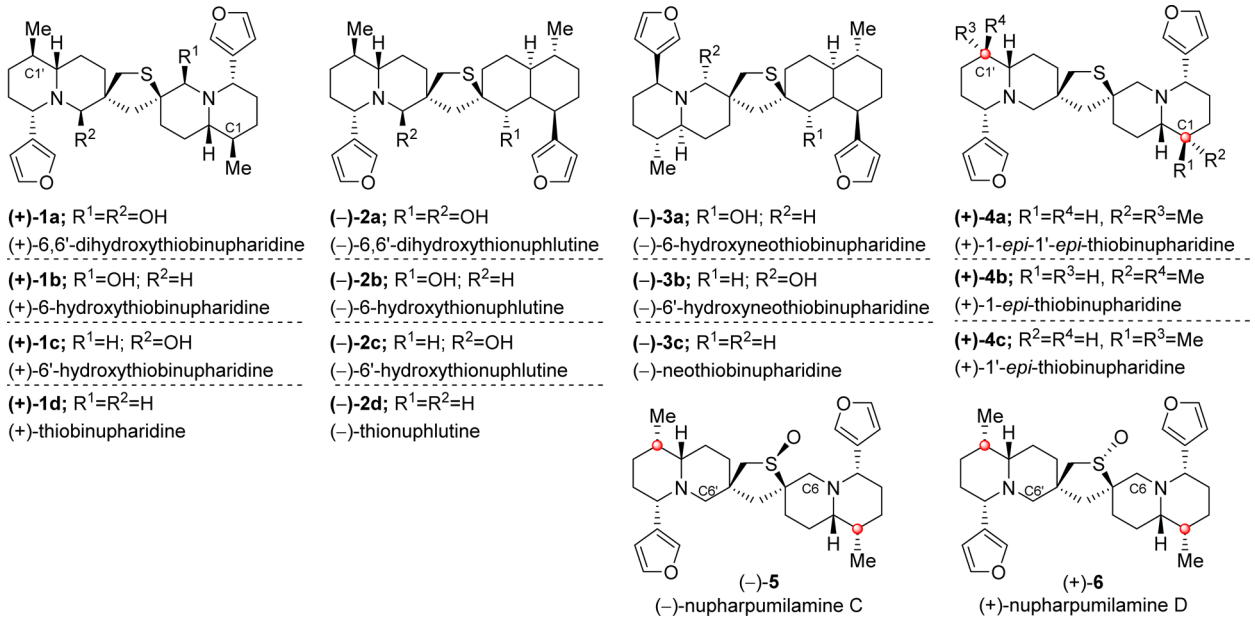
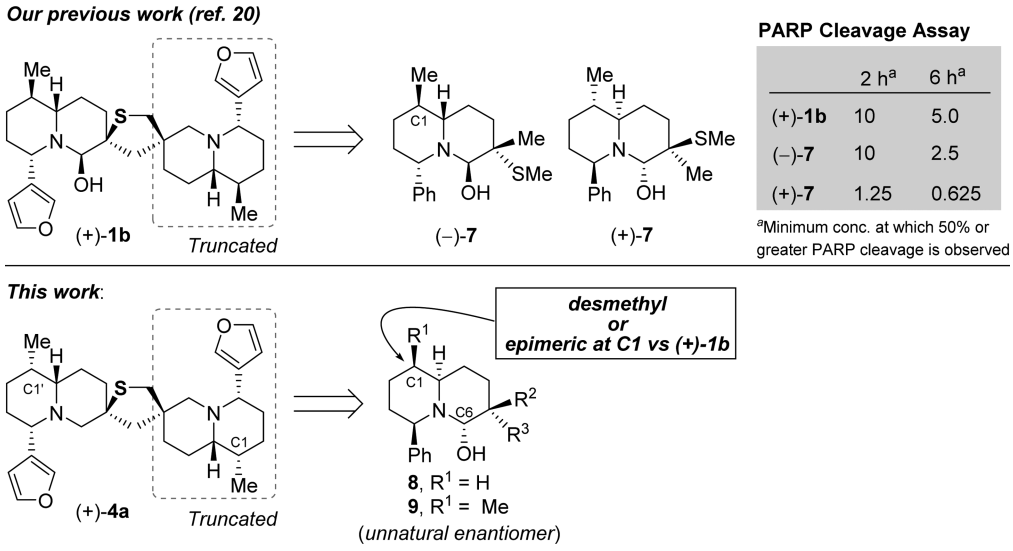


Figure 1. Representative dimeric nuphar alkaloids.

Scheme 1. Simplification of Dimeric Nuphar Alkaloids



vinylogous Mukaiyama–Mannich (vM–Mannich) reaction between aldehyde **10**, *p*-anisidine, and *O*-TBS vinylketene acetal **11** (Scheme 2). Hydrogenation of piperidinone **13** and subsequent Weinreb amide formation yielded **14**. Treatment of **14** with phenylmagnesium bromide provided ketone **15**. This was followed by CAN-promoted deprotection of the PMP group, then *p*-TsOH-catalyzed condensation to give quinolizidine **16**. Diastereoselective hydrogenation gave quinolizidine **17**. The late-stage intermediate **17** was then transformed into three C1-desmethyl monomeric nuphar analogs (+)-**8a–c** via two consecutive operations: (1) LDA-mediated C7 difunctionalization, and (2) DIBAL-H reduction to reveal the C6 hydroxyl group. The relative stereochemical relationship of compounds (+)-**8a–c** were assigned by 1D and 2D-NOESY NMR experiments (see Supporting Information), while the absolute configuration was assigned by analogy to our previous work.[20] The relative stereochemical relationship of **18a** and **18b** was inferred from the assignment of (+)-**8a** and (+)-**8b**, respectively.

In order to establish the 1,10-*syn* relationship found in C1-epimeric monomeric nuphar analogues **9** (when R^1 = Me), we elected to use a different route starting with the cyclic iminium precursor **19** (Scheme 3). In the presense of stoichiometric amounts of TMSOTf, the vM–Mannich reaction between **19** and dienol silane **20** provided compound **21** with complete γ-regioselectivity and good 1,10-*syn* diastereoselectivity. The phenyl group of dienol silane **20** is likely to account for the excellent γ-regioselectivity as it provides additional steric shielding of its α-position, rendering the γ-site relatively more nucleophilic.[35] Further attempts to employ chiral Brønsted acid and Lewis acid complexes to achieve enantiochemical control of the above vM–Mannich reaction have thus far been unsuccessful.

Compound **21** then underwent chemoselective hydrogenation and TFA-mediated deprotection of the PMB group

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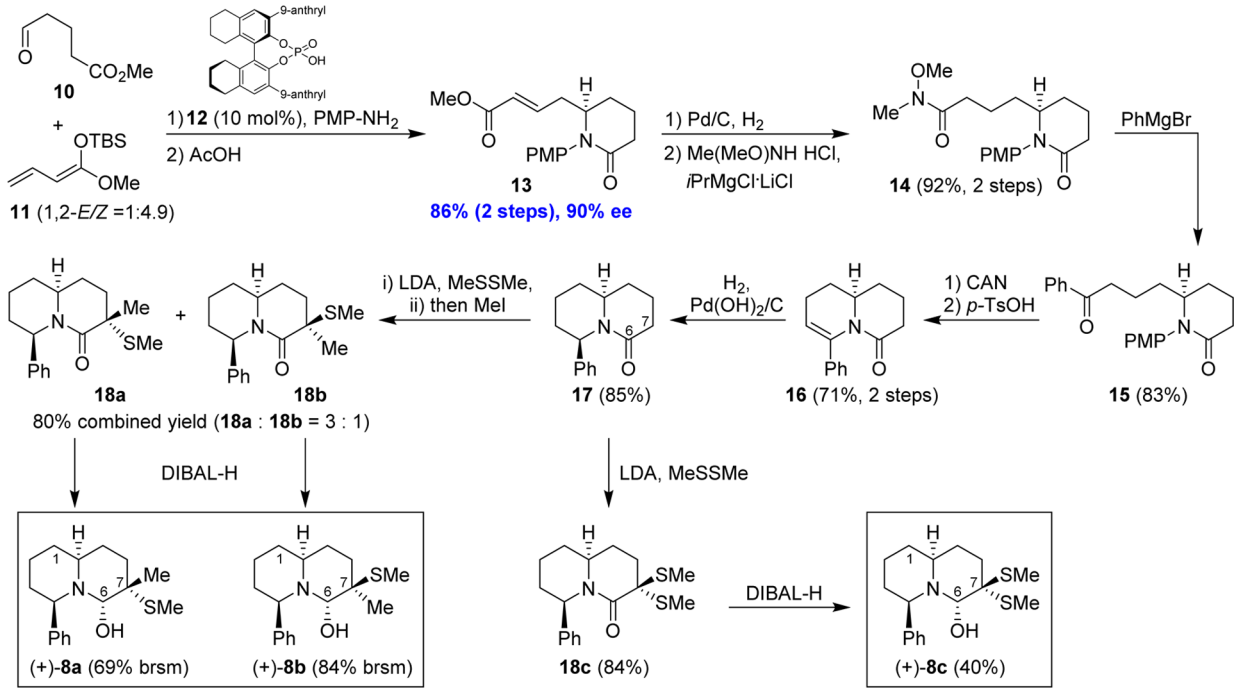
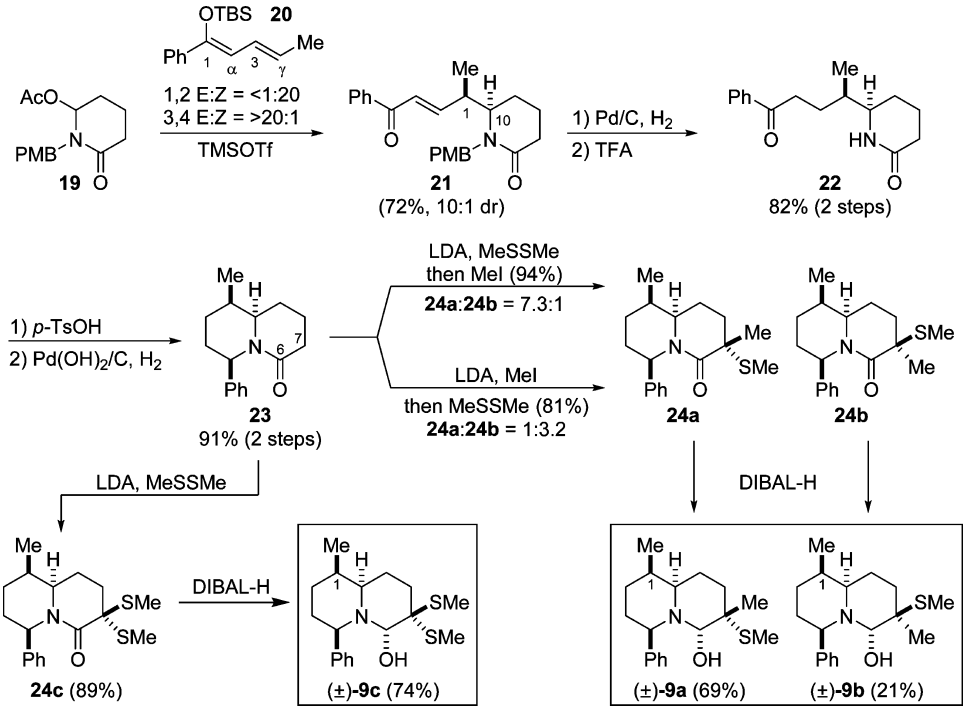
Scheme 2. Synthesis of C1-Desmethyl Monomeric Nuphar Analogues



Scheme 3. Synthesis of C1-Epimeric Monomeric Nuphar Analogues



to give **22** in 82% yield for two steps. Compound **22** was then subjected to a sequence of condensation, hydrogenation, then difunctionalization at C7 to give quinolizidines **24a–c**. It is noteworthy that the diastereochemical outcome of the C7-difunctionalization to obtain **24a** and **24b** may be altered by reversing the order of sulfenylation versus methylation. Subsequent half-reduction of **24a–c** with DIBAL-H successfully provided monomeric quinolizidines **9a–c** in their racemic forms. The relative stereochemical relationship of (±)-**9a–b** was established with 2D-NOESY NMR experiments (see Supporting Information), while that of (±)-**9c** was assigned by analogy. The relative stereochemistry of **24a** and **24b** was inferred from the assignment of (±)-**9a** and (±)-**9b**, respectively.

We then evaluated the apoptotic properties of C1-desmethyl analogues (+)-**8a–c** and C1-epimeric compounds (±)-**9a–c** against the human U937 cell line. The apoptotic assays were carried out by caspase cleavage of poly(ADP-ribose) polymerase (PARP), a marker of apoptosis (Table 1). Rapid apoptosis of U937 cells (within 2 h) was observed with analogues (+)-**8a**,

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Table 1. Apoptosis Assays (PARP Cleavage)

entry	compound	2 h[a]	6 h[a]
1	(+)-**7**	1.25	0.625
2	(+)-**8a**	10	5.0
3	(+)-**8b**	–	5.0
4	(+)-**8c**	10	5.0
5	(±)-**9a**	10	5.0
6	(±)-**9b**	–	–
7	(±)-**9c**	5.0	2.5

[a]Minimum conc. (μM) at which 50% or greater PARP cleavage is observed. "–" indicates that no PARP cleavage was observed up to a concentration of 10 μM at the indicated time.

(+)-**8c**, (±)-**9a**, and (±)-**9c**. Figure 2 shows a representative western blot of the PARP cleavage for compound (+)-**8b**. From this data, we conclude that presence of the methyl group or stereochemical configuration at C1 does not materially affect the apoptotic properties of the compound. Thus, it may be possible to make use of C1 as a point of attachment for photoreactive groups or tags in proteomics experiments designed to clarify the biological target or mechanism of action of the nuphar alkaloids.

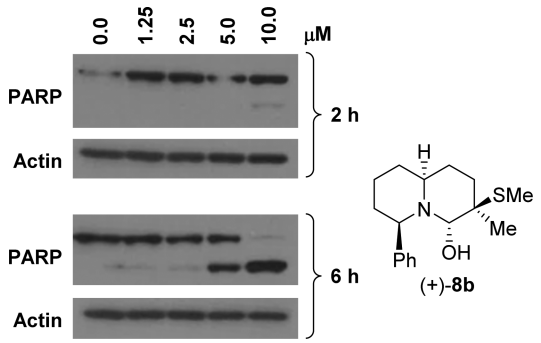

Figure 2. Representative Western blot for PARP cleavage of (+)-**8b**.

In conclusion, we have designed and synthesized several C1-desmethyl and C1-epimeric monomeric nuphar analogues. The syntheses featured stereoselective vM–Mannich reactions to achieve high enantio- or diastereoselectivity. Biological assays indicated that both desmethyl and C1-epimeric monomeric nuphar analogues are apoptotically active.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR data were recorded on a Bruker Avance III 500 MHz spectrometer (TBI probe) and a Bruker Avance III 600 MHz spectrometer (BBFO probe) with calibration of spectra to $CHCl_3$ (7.26 ppm) or CH_2Cl_2 (5.32 ppm). ^{13}C NMR data were recorded at 125 MHz on a Bruker Avance III 500 MHz spectrometer (TBI probe) and at 150 MHz on a Bruker Avance III 600 MHz spectrometer (BBFO probe) at ambient temperature and are expressed in ppm using solvent as the internal standard ($CDCl_3$ at 77.16 ppm, CD_2Cl_2 at 53.84 ppm). Two-dimensional NMR spectra, including COSY, HMQC, HMBC, and NOESY were recorded on a Bruker Avance III 500 MHz spectrometer (TBI probe) and a Bruker Avance III 600 MHz spectrometer (BBFO probe). Infrared spectra were recorded on a JASCO FT/IRM4100 Fourier Transform Infrared Spectrometer. Chemical shift values (δ) are expressed in ppm downfield relative to internal standard (tetramethylsilane at 0 ppm). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br s (broad singlet). Coupling constants are reported in hertz (Hz). Analytical thin layer chromatography (TLC) was performed on SILICYCLE precoated TLC plates (silica gel 60 F-254, 0.25 mm). Visualization was accomplished with UV light and/or with ceric ammonium molybdate (CAM) or $KMnO_4$ staining solutions. Flash column chromatography was performed using Biotage Isolera System on Biotage SNAP Ultra 10 or 25 g columns (part No. FSUL-0442–0010 and FSUL-0442–0025). Preparatory thin layer chromatography (prep TLC) was performed on basic alumina TLC plate from Sigma-Aldrich (catalog# 90066). High-resolution mass spectrometry was carried out by the Mass Spectrometry Laboratory of the University of Illinois (Urbana–Champaign, IL) using a Q-ToF analyzer.

General Procedure of PARP Cleavage and Images of Western Blots. The U937 cell line was obtained from the American Type Culture Collection and maintained in RPMI 1640 media containing 10% fetal bovine serum (FBS). For treatment, 0.5×10^6 cells in 0.5 mL were incubated with a 2-fold dilution of each compound for 1–6 h. Cells were then pelleted by centrifugation, washed once with phosphate buffered saline, lysed with 100 μL of urea lysis buffer [4 mol/L urea, 10% β-mercaptoethanol, 6% SDS, 125 mmol/L Tris (pH 6.8), 0.01% bromophenol blue, and protease/phosphatase inhibitor cocktail], and boiled for 5 min. Proteins were separated by standard SDS-PAGE and transferred to polyvinylidene difluoride membrane (Thermo Scientific, Rockford IL). Membranes were blocked with 5% nonfat milk in Tris-buffered saline and 0.05% Tween 20, and probed with a rabbit anti-PARP antibody (9542) obtained from Cell Signaling Technology, Danvers, MA. Subsequently, membranes were washed in Tris-buffered saline and 0.05% Tween 20, and incubated with secondary antibody conjugated to horseradish peroxidase. Proteins were visualized by enhanced chemiluminescence (Amersham).

*(3S,4S,6R,9aS)-3-Methyl-3-(methylthio)-6-phenyloctahydro-2H-quinolizin-4-ol (**8a**).* To a solution of compound (+)-**18a** (46.6 mg, 0.160 mmol) in CH_2Cl_2 (2 mL) at −78 °C was slowly added DIBAL-H (1.2 M in toluene, 66 μL, 0.080 mmol) along the flask wall. The reaction mixture was stirred at −78 °C for 20 min. Then 1 mL of pivalic acid (0.1 M in CH_2Cl_2) and 0.2 mL of MeOH was added. After 5 min, the dry ice-acetone bath was removed, followed by addition of saturated aqueous Rochelle's salt (0.5 mL) and 2 N NaOH (0.5 mL). After being warmed to rt, the mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer was separated, dried over anhydrous Na_2SO_4, then concentrated in *vacuo*. The residue was purified using preparatory thin layer chromatography on basic alumina TLC plate (20 × 20 cm, 250 μm thickness, Sigma-Aldrich, catalog # 90066). The basic alumina TLC plate was prepared by drawing a pencil line about 2 cm from the bottom and 0.5 cm from the two edges of the plate. The crude residue obtained above was dissolved in 1.5 mL of CH_2Cl_2. The CH_2Cl_2 solution was then delivered evenly onto the drawn line on the TLC plate using a micro glass pipet. After that, the TLC plate was developed in a chamber containing 10% ethyl acetate/hexane until the solvent line reached approximately 1 cm to the top of the plate. The plate was then removed and dried under a gentle stream of nitrogen. The plate was then visualized under UV light and three bands were observed with R_f values of 0.89 (fully reduced product), 0.40 (**8a**) and 0.13 (**18a**). The middle band (R_f = 0.40), which corresponded to compound **8a**, was scraped off with a razor blade. The collected basic alumina was transferred to a short column containing a tight cotton plug and Celite. Compound **8a** was eluted with CH_2Cl_2 into a flask and concentrated to afford 19.6 mg of a clear colorless oil, with a yield of 69% calculated based on the recovered starting material (18.2 mg). $[\alpha]_D^{23}$ = +88.5° (c = 0.1, CH_2Cl_2). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.34 (d, J = 7.1 Hz, 2H), 7.29 (dd, J = 7.9, 7.9 Hz, 2H), 7.21 (dd, J = 7.5, 7.5 Hz, 1H), 3.85 (s, 1H), 3.70 (dd, J = 11.4, 2.6 Hz, 1H), 2.89 (tt, J = 10.9, 3.2 Hz, 1H), 2.77 (d, J = 1.4 Hz, 1H), 1.91–1.81 (m, 1H), 1.75–1.64 (m, 3H), 1.70 (s, 3H), 1.64–1.48 (m, 4H), 1.47–1.38 (m, 2H), 1.38 (s, 3H), 1.33–1.22 (m, 2H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 145.3, 128.6, 128.2, 127.1, 82.3, 64.5, 51.9, 49.9, 37.4, 34.3, 30.8, 30.7, 24.8, 22.0, 9.5. IR (film, cm^{-1}), 2951, 1735, 1648, 1510, 1246, 1105, 1032, 830. HRMS (ESI) calcd. for $C_{17}H_{26}NOS$ (m/z M+H$^+$): 292.1735, found: 292.1729.

*(3R,4S,6R,9aS)-3-Methyl-3-(methylthio)-6-phenyloctahydro-2H-quinolizin-4-ol (**8b**).* By following the procedure of preparing (+)-**8a**,

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compound (+)-**8b** (10.2 mg) was obtained as a clear colorless oil starting from (+)-**18b** (21.1 mg, 0.073 mmol) with a yield of 84% calculated based on recovered starting material (9.1 mg). $[\alpha]_D^{23}$ = +55.2° (c = 0.1, CH_2Cl_2). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.39 (d, J = 7.1 Hz, 2H), 7.30 (dd, J = 7.7, 7.7 Hz, 2H), 7.27−7.19 (m, 1H), 3.95 (d, J = 5.5 Hz, 1H), 3.57 (dd, J = 11.4, 2.7 Hz, 1H), 2.73 (dd, J = 12.4, 9.6 Hz, 1H), 1.97−1.87 (m, 1H), 1.85 (s, 3H), 1.82−1.65 (m, 5H), 1.60−1.50 (m, 5H), 1.50−1.43 (m, 1H), 1.43−1.31 (m, 2H), 1.13 (s, 3H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 144.8, 128.7, 128.3, 127.4, 84.7, 64.2, 52.4, 49.4, 37.4, 34.2, 30.4, 29.3, 25.5, 24.9, 10.9. IR (film, cm-1), 2974, 1830, 1644, 1591, 1360, 1331, 1160, 798. HRMS (ESI) calcd. for $C_{17}H_{26}NOS$ (m/z M+H+): 292.1735, found: 292.1742.

*(4S,6R,9aS)-3,3-Bis(methylthio)-6-phenyloctahydro-2H-quinolizin-4-ol (**8c**).* By following the procedure for preparing (+)-**8a**, but using 1 equiv of DIBAL-H, compound (+)-**8c** (12.0 mg) was obtained as a clear colorless oil starting from (+)-**18c** (30.0 mg, 0.093 mmol) with a isolated yield of 40%. $[\alpha]_D^{23}$ = +79.1° (c = 0.1, CH_2Cl_2). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.37 (d, J = 7.2 Hz, 2H), 7.29 (dd, J = 7.7, 7.7 Hz, 2H), 7.21 (dd, J = 7.3, 7.3 Hz, 1H), 3.95 (s, 1H), 3.70 (dd, J = 11.6, 2.6 Hz, 1H), 2.99−2.90 (m, 1H), 2.85 (d, J = 0.9 Hz, 1H), 2.03 (ddd, J = 13.1, 11.5, 4.3 Hz, 1H), 1.97−1.83 (m, 4H), 1.78−1.60 (m, 7H), 1.54−1.48 (m, 2H), 1.45−1.29 (m, 2H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 144.7, 128.7, 128.5, 127.4, 80.7, 66.6, 64.9, 52.3, 37.3, 34.2, 30.7, 27.9, 24.9, 11.8, 10.2. IR (film, cm^{-1}), 2923, 1684, 1510, 1317, 1230, 1208, 1032. HRMS (ESI) calcd. for $C_{17}H_{26}NOS_2$ (m/z M+H$^+$): 324.1456, found: 324.1447.

*(3S,4S,6R,9R,9aR)-3,9-Dimethyl-3-(methylthio)-6-phenyloctahydro-2H-quinolizin-4-ol ((±)-**9a**).* By following the procedure of preparing (+)-**8a**, but using 1 equiv of DIBAL-H, compound **9a** (15.2 mg) was obtained as a colorless oil starting from **24a** (21.6 mg, 0.071 mmol), with a yield of 69%. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.35 (d, J = 6.6 Hz, 2H), 7.29 (dd, J = 7.6, 7.6 Hz, 2H), 7.21 (d, J = 7.3 Hz, 1H), 3.86 (s, 1H), 3.75 (dd, J = 11.6, 3.5 Hz, 1H), 3.04 (d, J = 11.6 Hz, 1H), 2.73 (d, J = 1.2 Hz, 1H), 1.95−1.82 (m, 2H), 1.82−1.64 (m, 6H), 1.61 (dt, J = 9.4, 2.8 Hz, 1H), 1.51−1.42 (m, 2H), 1.35 (s, 4H), 1.13 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 145.7, 128.6, 128.0, 127.0, 82.6, 64.7, 54.4, 49.8, 32.6, 32.5, 31.3, 30.4, 27.0, 21.6, 13.3, 9.5. IR (film, cm^{-1}), 2918, 2853, 1645, 1144, 1072, 756. HRMS (ESI) calcd. for $C_{18}H_{28}NOS$ (m/z M+H$^+$): 306.1892, found: 306.1881.

*(3R,4S,6R,9R,9aR)-3,9-Dimethyl-3-(methylthio)-6-phenyloctahydro-2H-quinolizin-4-ol ((±)-**9b**).* By following the procedure of preparing (+)-**8a**, but using 1 equiv of DIBAL-H, compound **9b** (2.9 mg) was obtained as a colorless oil starting from **24b** (14.0 mg, 0.046 mmol), with a yield of 21%. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.41 (s, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 3.94 (d, J = 5.7 Hz, 1H), 3.61 (dd, J = 11.6, 3.6 Hz, 1H), 2.86 (dt, J = 12.0, 3.2 Hz, 1H), 2.24−2.14 (m, 1H), 1.84 (s, 3H), 1.81−1.71 (m, 4H), 1.61 (dd, J = 10.5, 8.4 Hz, 2H), 1.50−1.44 (m, 2H), 1.23 (dd, J = 9.7, 6.2 Hz, 1H), 1.15 (d, J = 6.9 Hz, 3H), 1.13 (s, 3H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 128.7, 128.2, 127.3, 85.1, 64.2, 54.9, 32.7, 32.7, 31.5, 30.1, 28.9, 27.0, 25.5, 13.4, 10.7. IR (film, cm^{-1}), 2918, 2853, 1645, 1446, 1058, 704. HRMS (ESI) calcd. for $C_{18}H_{28}NOS$ (m/z M+H$^+$): 306.1892, found: 306.1881.

*(4S,6R,9R,9aR)-9-Methyl-3,3-bis(methylthio)-6-phenyloctahydro-2H-quinolizin-4-ol ((±)-**9c**).* By following the procedure of preparing (+)-**8a**, using 1 equiv of DIBAL-H, compound **9c** (11.1 mg) was obtained as a colorless oil starting from **23c** (15.1 mg, 0.045 mmol), with a yield of 74%. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.38 (d, J = 6.3 Hz, 2H), 7.29 (t, J = 7.7 Hz, 2H), 7.23−7.17 (m, 1H), 3.96 (s, 1H), 3.75 (dd, J = 11.6, 3.6 Hz, 1H), 3.11−3.04 (m, 1H), 2.82 (d, J = 1.2 Hz, 1H), 2.38−2.26 (m, 1H), 1.97−1.86 (m, 4H), 1.80−1.71 (m, 2H), 1.69 (d, J = 3.8 Hz, 3H), 1.68−1.57 (m, 3H), 1.50−1.43 (m, 1H), 1.31 (ddd, J = 13.3, 6.8, 3.7 Hz, 1H), 1.16 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 145.1, 128.5, 128.2, 127.1, 81.0, 66.5, 64.8, 54.7, 32.6, 32.5, 31.3, 27.5, 27.2, 13.3, 11.6, 10.0. IR (film, cm^{-1}), 2916, 2853, 1490, 1437, 1406, 1261, 1135, 1052, 952, 755, 701. HRMS (ESI) calcd. for $C_{18}H_{28}NOS_2$ (m/z M+H$^+$): 338.1612, found: 338.1606.

*Methyl (R,E)-4-(1-(4-Methoxyphenyl)-6-oxopiperidin-2-yl)but-2-enoate (**13**).* In a flame-dried round-bottomed flask, *p*-anisidine (1.18 g, 9.60 mmol) was dissolved in THF (20 mL) and the resulting solution was cooled to −50 °C. A solution of **10**[36] (1.50 g, 11.5 mmol) in 20 mL of THF was added via a syringe and allowed to stir for 30 min. Then, chiral phosphoric acid catalyst **12**[37] (0.543 g, 0.96 mmol) dissolved in 20 mL of THF was added dropwise, followed by dropwise addition of **11**[38] (1,2-*E*/*Z* = 1:4.9; 4.28 g, 19.2 mmol) in 20 mL of THF. The reaction mixture was stirred overnight at −50 °C and subsequently concentrated to give a dark brown oil. The crude product was filtered through a short pad of silica gel (gradually from 20 to 50% EtOAc/Hex) to give 2.77 g of a pale yellow oil. This oil was dissolved in a mixture of toluene (40 mL) and acetic acid (5 mL) and heated to reflux for 20 h. After the reaction was complete, the resulting mixture was concentrated, and the residue was purified by automated silica gel flash chromatography (neat ethyl acetate) to give 2.50 g of the pure product (+)-**13**, with an isolated yield of 86% over two steps. Enantiomeric excess of (+)-**13** was determined by HPLC with Chiracel ODH column, 30% *i*-PrOH/hexane, 1.0 mL/min, 254 nm, t_r (major) = 12.8 min, t_r (minor) = 16.4 min, 90% ee. $[\alpha]_D^{23}$ = +32.8° (c = 1.0, CD_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.80−6.63 (m, 1H), 5.77 (d, J = 15.6 Hz, 1H), 3.99−3.85 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 2.53 (m, 2H), 2.42 (dd, J = 11.7, 7.3 Hz, 1H), 2.31 (dd, J = 15.9, 7.4 Hz, 1H), 2.11−2.00 (m, 1H), 1.93 (m, 5.0 Hz, 1H), 1.85−1.77 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 166.5, 158.6, 144.1, 133.8, 129.0, 123.9, 114.7, 59.2, 55.5, 51.7, 36.5, 32.8, 27.6, 18.2. HRMS (ESI) calcd. for $C_{17}H_{22}NO_4$ (m/z M+H$^+$): 304.1549, found: 304.1556.

*(R)-N-Methoxy-4-(1-(4-methoxyphenyl)-6-oxopiperidin-2-yl)-N-methylbutanamide (**14**).* (+)-**13** (1.21 g, 3.99 mmol) was dissolved in 40 mL of EtOAc/MeOH (v/v = 1:1) and then Pd/C (0.41 g, 0.4 mmol) was added. Hydrogen gas (via balloon) was slowly bubbled through the resulting solution for 2 h through a rubber septa on the reaction flask outfitted with a disposable 21-gauge outlet needle. After the reaction was complete as judged by TLC analysis, the mixture was filtered through a short pad of Celite and concentrated *in vacuo*. The resulting product was used in the next step without further purification. To a solution of the hydrogenated product (1.20 g, 3.93 mmol) and HN(OMe)Me·HCl (0.575 g, 5.89 mmol) in dry THF (10 mL) was added 1.3 M *i*-PrMgCl·LiCl in THF (8.8 mL, 11.4 mmol) at −20 °C. The reaction mixture was stirred at −20 °C for 30 min and then quenched with a saturated solution of aqueous NH_4Cl (30 mL), extracted with CH_2Cl_2 (2 × 30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 1.233 g of (+)-**14** as a light brown solid in 92% yield. This product was carried forward to the next step without a purification. m.p.: 121.5−122.9 °C. $[\alpha]_D^{23}$ = +16.6° (c = 0.9, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) 7.08 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 3.81 (s, 3H), 3.79−3.68 (m, 2H), 3.61 (s, 3H), 3.13 (s, 3H), 2.52 (m, 2H), 2.28 (m, 2H), 2.10−2.01 (m, 1H), 1.96 (m, 1H), 1.93−1.76 (m, 3H), 1.54−1.34 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.8, 158.3, 129.1, 114.5, 61.3, 60.3, 55.5, 33.0, 32.8, 32.2, 31.7, 27.0, 20.7, 18.2. IR (film, cm^{-1}), 3468, 2942, 1650, 1510, 1294, 1179, 1032, 831. HRMS (ESI) calcd. for $C_{18}H_{27}N_2O_4$ (m/z M+H$^+$): 335.1971, found: 335.1966.

*(S)-1-(4-Methoxyphenyl)-6-(4-oxo-4-phenylbutyl)piperidin-2-one (**15**).* To a solution of (+)-**14** (1.230 g, 3.68 mmol) in THF (5 mL) at −78 °C was added 1.6 M PhMgBr (3.45 mL, 5.52 mmol). The mixture was warmed to 0 °C and stirred for 3 h. The reaction was then quenched with a saturated solution of aqueous NH_4Cl (20 mL), extracted with CH_2Cl_2 (2 × 30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting crude product was purified by automated silica gel flash chromatography (50−100% EtOAc/hexanes) to give 1.072 g (83% yield) of (+)-**15** as a white solid. m.p.: 66.1−66.9 °C. $[\alpha]_D^{23}$ = +22.2° (c = 0.2, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.3, 1.1 Hz, 2H), 7.58−7.51 (m, 1H), 7.43 (dd, J = 10.7, 4.8 Hz, 2H), 7.11−7.04 (m, 2H), 6.94−6.86 (m, 2H), 3.80 (s, 3H), 3.75 (m, 1H), 2.84 (t, J = 6.9 Hz, 2H), 2.52 (t, J = 6.5 Hz, 2H), 2.16−2.04 (m, 1H), 2.03−1.95 (m, 1H), 1.93−1.86 (m, 1H), 1.86−1.79 (m, 1H), 1.80−1.71 (m, 1H), 1.63−1.56 (m, 1H), 1.51 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.7, 170.7, 158.4,

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J. Org. Chem. 2017, 82, 2648−2655

137.0, 134.5, 133.2, 129.1, 128.7, 128.1, 114.6, 60.4, 55.5, 38.3, 33.0, 32.9, 27.3, 20.3, 18.3. IR (film, cm^{-1}), 2950, 1880, 1663, 1293, 1139, 1092, 765. HRMS (ESI) calcd. for $C_{22}H_{26}NO_3$ (m/z M+H$^+$): 352.1913, found: 352.1907.

*(R)-6-Phenyl-1,2,3,8,9,9a-hexahydro-4H-quinolizin-4-one (**16**).* A solution of (+)-**15** (912 mg, 2.60 mmol) in 30 mL of CH_3CN/H_2O (v/v = 5:1) was cooled to 0 °C. CAN (3.560 g, 6.50 mmol) was added in small portions over 15 min. After stirring at 0 °C for 2 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (30 mL), extracted with EtOAc (2 × 30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product (640 mg) was used in the next step without further purification. The residue was dissolved in 400 mL of anhydrous toluene followed by the addition of $TsOH·H_2O$ (248 mg, 1.31 mmol). The reaction was refluxed with a Dean−Stark apparatus overnight (16 h). Then, the mixture was condensed under reduced pressure, redissolved in EtOAc, and washed with a saturated solution of aqueous $NaHCO_3$ (30 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude product was purified by automated silica gel flash chromatography (20−100% EtOAc/hexanes) to give 419 mg of **16** as a yellow oil (71%). ^{1}H NMR (600 MHz, CDCl3) 7.40 (2H, d, J = 7.7 Hz), 5.61 (1H, t, J = 3.9 Hz), 3.74−3.69 (1H, m), 3.24 (1H, t, J = 5.0 Hz), 2.56−2.48 (1H, m), 2.39 (2H, dt, J = 3.8, 7.3 Hz), 2.35−2.29 (1H, m), 2.20 (3H, s), 2.00−1.90 (2H, m), 1.87−1.82 (1H, m), 1.72−1.65 (1H, m); ^{13}C NMR (151 MHz, CDCl3) 169.1, 138.6, 128.3, 127.2, 124.5, 118.1, 77.2, 56.7, 46.8, 30.7, 25.7, 25.1, 24.0, 16.3;

*(6R,9aS)-6-Phenyloctahydro-4H-quinolizin-4-one (**17**).* Compound (+)-**16** (120 mg, 0.53 mmol) was dissolved in 10 mL of EtOAc and $Pd(OH)_2/C$ (77 mg, 0.11 mmol) was added to this solution. Hydrogen gas (via balloon) was slowly bubbled through the resulting solution for 3 h through a rubber septa on the reaction flask outfitted with a disposable 21-gauge outlet needle. After the reaction was complete as judged by TLC analysis, the mixture was filtered through a short plug of Celite and concentrated. The residue was then submitted to automated silica gel flash chromatography (40−100% EtOAc/hexanes) to afford 95 mg of (+)-**17** (85% yield) as a pale yellow oil. $[\alpha]_D^{23}$ = +56.1° (c = 0.9, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J = 7.6 Hz, 2H), 7.19 (dd, J = 16.9, 7.6 Hz, 3H), 5.43 (t, J = 3.6 Hz, 1H), 3.63 (m, 1H), 2.59−2.45 (m, 2H), 2.25−2.13 (m, 1H), 2.13−2.05 (m, 1H), 1.95 (ddd, J = 9.0, 5.9, 3.6 Hz, 2H), 1.88−1.76 (m, 1H), 1.76−1.67 (m, 1H), 1.65−1.51 (m, 3H), 1.41−1.30 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 142.4, 128.3, 126.3, 125.6, 54.1, 52.9, 32.6, 31.4, 28.3, 26.6, 20.7, 15.3. IR (film, cm^{-1}), 2946, 1644, 1408, 1342, 173, 922, 840. HRMS (ESI) calcd. for $C_{15}H_{20}NO$ (m/z M+H$^+$): 230.1545, found: 230.1537.

*(3S,6R,9aS)-3-Methyl-3-(methylthio)-6-phenyloctahydro-4H-quinolizin-4-one (**18a**).* To a flame-dried round-bottom flask under an inert N_2 atmosphere, containing a solution of diisopropylamine (0.100 mL, 0.99 mmol) in dry THF (0.75 mL) at −78 °C, was added *n*-BuLi (1.6 M in hexane, 0.60 mL, 0.99 mmol). The reaction was stirred for 5 min at −78 °C before being warmed to 0 °C over 15 min. The mixture was then cooled to −78 °C and a dry THF solution (0.75 mL) of compound (+)-**17** (75 mg, 0.33 mmol) was added dropwise into the reaction. The mixture was stirred at −78 °C for 15 min, warmed to rt, and then stirred at rt for 30 min. The reaction was cooled to −78 °C, followed by dropwise addition of a dry THF (0.75 mL) solution of MeSSMe (31 μL, 0.36 mmol). The reaction mixture was stirred at −78 °C for 30 min and then slowly warmed up to rt and stirred for 30 min. The mixture was recooled to −78 °C and MeI (82 μL, 1.32 mmol) was added. The dry ice-acetone bath was removed and the reaction was warmed to rt and stirred for 30 min. The resulting mixture was quenched with sat. $NaHCO_3$ (4 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, then concentrated in *vacuo*. The diastereomeric ratio of (+)-**18a**:(+)-**18b** of the unpurified product mixture at this point was determined to be 3:1 as judged by ^{1}H NMR spectroscopic analysis prior to column chromatography. The residue was purified by automated silica gel flash chromatography (ethyl acetate/hexane, 5−15%) to afford 46.6 mg (49%) of (+)-**18a**, 21.2 mg (22%) of (+)-**18b**, and 8.4 mg (9%) of a mixture of **18a** and **18b**, for a combined yield of 80%. For compound (+)-**18a**, $[\alpha]_D^{23}$ = +71.4° (c = 0.1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.26 (m, 2H), 7.19 (dd, J = 8.0, 2.9 Hz, 3H), 5.27 (t, J = 4.1 Hz, 1H), 3.85−3.75 (m, 1H), 2.19 (s, 3H), 2.19−2.13 (m, 2H), 2.12−2.03 (m, 1H), 2.03−1.95 (m, 2H), 1.74−1.61 (m, 2H), 1.61 (m, 3H), 1.59−1.39 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.3, 142.4, 128.3, 126.3, 125.4, 55.4, 53.0, 46.7, 34.5, 28.5, 28.3, 26.5, 26.1, 16.3, 13.2. IR (film, cm^{-1}), 2926, 1629, 1406, 1356, 1260, 1055, 866. HRMS (ESI) calcd. for $C_{17}H_{24}NOS$ (m/z M+H$^+$): 290.1579, found: 290.1579.

*(3R,6R,9aS)-3-Methyl-3-(methylthio)-6-phenyloctahydro-4H-quinolizin-4-one (**18b**).* $[\alpha]_D^{23}$ = +61.3° (c = 0.2, CD_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, J = 7.8 Hz, 2H), 7.28 (dd, J = 7.7, 7.7 Hz, 2H), 7.17 (dd, J = 7.3, 7.3 Hz, 1H), 5.32 (t, J = 4.0 Hz, 1H), 3.78−3.62 (m, 1H), 2.31−2.13 (m, 2H), 2.13−1.99 (m, 3H), 2.08 (s, 3H), 1.85−1.76 (m, 1H), 1.76−1.61 (m, 2H), 1.56−1.47 (m, 1H), 1.50 (s, 3H), 1.33 (m, 1H). ^{13}C NMR (151 MHz, CDCl3) δ 170.8, 143.6, 128.2, 126.2, 125.4, 54.4, 53.7, 46.6, 35.3, 28.9, 27.8, 27.5, 25.2, 15.3, 12.9. IR (film, cm-1), 2924, 1632, 1450, 1417, 1318, 1265, 1024. HRMS (ESI) calcd. for $C_{17}H_{24}NOS$ (m/z M+H+): 290.1579, found: 290.1579.

*(6R,9aS)-3,3-Bis(methylthio)-6-phenyloctahydro-4H-quinolizin-4-one (**18c**).* To a flame-dried round-bottom flask under an inert N2 atm, containing a solution of diisopropylamine (46 μL, 0.33 mmol) in dry THF (1 mL) at 0 °C, was added *n*-BuLi (2.5 M in hexane, 132 μL, 0.33 mmol). The reaction mixture was stirred at 0 °C for 5 min before being cooled to −78 °C at which point a dry THF solution (0.3 mL) of compound (+)-**17** (30 mg, 0.13 mmol) was added dropwise. The mixture was stirred at −78 °C for 10 min, then warmed up to rt and stirred at rt for 0.5 h. The reaction mixture was recooled to −78 °C, which was followed by dropwise addition of a THF (0.3 mL) solution of MeSSMe (60 μL, 0.65 mmol). The reaction mixture was stirred at −78 °C for 0.5 h and then slowly warmed up to rt and stirred for 0.5 h. The resulting mixture was quenched with sat. aqueous $NaHCO_3$ (4 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was purified by automated silica gel flash chromatography (ethyl acetate/hexane, 15−30%) to afford 35.0 mg of (+)-**18c**, with a yield of 84%. $[\alpha]_D^{23}$ = +36.1° (c = 0.1, CD_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.26 (m, 4H), 7.18 (dd, J = 7.0, 7.0 Hz, 1H), 5.33 (t, J = 3.9 Hz, 1H), 3.71 (tt, J = 12.0, 3.5 Hz, 1H), 2.42−2.26 (m, 2H), 2.25−2.12 (m, 2H), 2.12−2.01 (m, 7H), 1.88 (dq, J = 13.7, 3.7 Hz, 1H), 1.77−1.67 (m, 1H), 1.67−1.61 (m, 1H), 1.60−1.50 (m, 1H), 1.42−1.29 (m, 1H). ^{13}C NMR (151 MHz, CDCl3) δ 167.6, 142.9, 128.3, 126.3, 125.4, 60.9, 54.8, 53.2, 34.7, 28.5, 28.3, 27.1, 15.3, 13.7, 11.8. HRMS (ESI) calcd. for $C_{17}H_{24}NOS_2$ (m/z M+H+): 322.1299, found: 322.1303. IR (film, cm-1), 2948, 1634, 1414, 1317, 1264, 1223, 1141.

*(R)-1-(4-Methoxyphenyl)-6-((R,E)-5-oxo-5-phenylpent-3-en-2-yl)-piperidin-2-one ((±)-**21**).* To a solution of compound **19** (180 mg, 0.65 mmol) in toluene (5 mL) cooled to −78 °C, was slowly added a solution of **20**[39] (267.6 mg, 0.98 mol) in toluene (2 mL) and TMSOTf (144.5 mg, 0.65 mmol). The reaction mixture was warmed to rt and stirred overnight, then quenched with sat. aqueous $NaHCO_3$. The mixture was diluted with 5 mL of EtOAc. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The d.r. of the unpurified product mixture at this point was determined to be 10:1 as judged by ^{1}H NMR spectroscopic analysis prior to column chromatography. The resulting residue was purified via automated silica gel flash column chromatography (50% ethyl acetate/hexane) to give 176.7 mg of (±)-**21** as a colorless oil, with a yield of 72%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.5 Hz, 2H), 7.57 (dd, J = 7.5, 7.5 Hz, 1H), 7.48 (dd, J = 7.5, 7.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 6.96 (dd, J = 7.0 Hz, 7.5 Hz, 1H), 6.77−6.86 (m, 3H), 5.43 (d, J = 15 Hz, 1H), 4.01 (d, J = 15 Hz, 1H), 3.78 (s, 3H), 3.40 (q, 1H), 3.03 (m, 1H), 2.47−2.56 (m, 1H), 2.34−2.40 (m, 1H), 1.61−1.90 (m, 5H), 1.16 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 190.2, 171.7, 159.2, 150.6, 137.8, 133.2, 129.6, 129.2, 128.9, 128.8, 128.7, 125.8, 114.3, 114.2, 58.3, 55.5, 46.7, 38.7, 32.6, 24.4, 18.6, 13.0; HRMS (ESI) calcd. for $C_{24}H_{28}NO_3$ (m/z M+H$^+$): 378.2069, found: 378.2069.

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J. Org. Chem. 2017, 82, 2648−2655

*(R)-6-((R)-5-oxo-5-Phenylpentan-2-yl)piperidin-2-one ((±)-**22**).* Compound (±)-**21** (100 mg, 0.26 mmol) was dissolved in 12.5 mL of pentane/ethyl acetate (v/v = 85:15). Pd/C (60.1 mg, 0.052 mmol) was added to the reaction mixture and then placed under a hydrogen atmosphere (balloon). The reaction was closely monitored by ^{1}H NMR every 3 to 5 min. Once complete as judged by TLC analysis, the mixture was filtered through a short pad of Celite. Note: significant amounts of over reduced products are obtained if the reaction is allowed to proceed too long. In order to ensure high yields, the reaction must be quenched as soon as it has reached completion. The filtrate was concentrated *in vacuo* to afford a slight yellow oil, which was then dissolved in trifluoroacetic acid (5 mL). The mixture was stirred at 65 °C overnight and then water (20 mL) and DCM (40 mL) were added. The DCM layer was separated and washed sequentially with sat. Na_2CO_3 (20 mL × 2) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The residue was purified via automated silica gel flash column chromatography (3% methanol/DCM) to afford 80.1 mg of (±)-**22** as a colorless solid, with an yield of 82% over two steps. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.97 (d, J = 8.5 Hz, 2H), 7.60 (dd, J = 7.5, 7.5 Hz, 1H), 7.45 (dd, J = 8.0, 8.0 Hz, 2H), 5.65 (brs, 1H), 3.34−3.38 (m, 1H), 3.06−3.12 (m, 1H), 2.97−3.03 (m, 1H), 2.31−2.36 (m, 1H), 2.18−2.26 (m, 1H), 1.82−1.96 (m, 3H), 1.57−1.71 (m, 3H), 1.37−1.45 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) 199.8, 172.1, 133.2, 128.8, 128.1, 57.8, 37.9, 36.3, 31.7, 26.9, 24.3, 20.5, 14.4; HRMS (ESI) calcd. for $C_{16}H_{22}NO_2$ (m/z M+H$^+$): 260.1651, found: 260.1643.

*(6R,9R,9aR)-9-Methyl-6-phenyloctahydro-4H-quinolizin-4-one ((±)-**23**).* To a round-bottomed flask (250 mL) equipped with a Dean−Stark trap and a reflux condenser was added compound (±)-**22** (2.13 g, 8.2 mmol), toluene (150 mL), and TsOH·H2O (156 mg, 0.82 mmol). The mixture was refluxed overnight. Toluene was then removed in vacuo and the crude oil was diluted with EtOAc (60 mL). The mixture was washed with sat. $NaHCO_3$ (30 mL). The organic layer was separated, dried over anhydrous Na2SO$_4$ and concentrated in vacuo to give a brownish oil. To a round-bottomed flask (250 mL) containing the obtained residue was added EtOAc (75 mL) and $Pd(OH)_2$/C (20 wt%, 287 mg, 0.41 mmol). Hydrogen gas was bubbled into the mixture for 15 min. The mixture was stirred under a hydrogen atmosphere (balloon) for another 1.5 h before being filtered through Celite and concentrated in vacuo. The residue was purified by automated silica gel flash column chromatography (ethyl acetate/hexane, 40−60%) to afford 1.81 g of product (±)-**23**, with a yield of 91% over two steps. ^{1}H NMR (600 MHz, CD2Cl2) δ 7.32−7.27 (m, 2H), 7.20 (d, J = 7.4 Hz, 2H), 7.18 (dd, J = 11.4, 4.2 Hz, 1H), 4.88 (t, J = 5.4 Hz, 1H), 3.69 (dt, J = 10.5, 4.2 Hz, 1H), 2.45−2.32 (m, 2H), 2.19−2.08 (m, 1H), 2.08−1.99 (m, 1H), 1.99−1.94 (m, 1H), 1.92−1.71 (m, 5H), 1.19−1.09 (m, 1H), 0.99 (d, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 173.3, 144.7, 128.2, 125.9, 57.5, 57.3, 34.4, 32.0, 28.7, 28.3, 26.5, 21.5, 15.9. IR (film, cm-1), 2957, 2851, 1672, 1487, 1421, 1280, 832. HRMS (ESI) calcd. for $C_{16}H_{22}NO$ (m/z M+H$^+$): 244.1701, found: 244.1703.

*(3S,6R,9R,9aR)-3,9-Dimethyl-3-(methylthio)-6-phenyloctahydro-4H-quinolizin-4-one ((±)-**24a**).* By following the procedure of preparing (+)-**18a** and (+)-**18b**, compounds (±)-**24a** and (±)-**24b** were derived from compound (±)-**23** (145.8 mg, 0.6 mmol) using MeSSMe (80 μL, 0.90 mmol). The d.r. ((±)-**24a**: (±)-**24b**) of the unpurified product mixture was determined to be 7.3:1 as judged by ^{1}H NMR spectroscopic analysis. Automated silica gel flash column chromatography with ethyl acetate/hexane (10−30%) afforded 83.0 mg (46%) of (±)-**24a**, 15.2 mg (8%) of (±)-**24b** and 72.6 mg (40%) of a mixture of (±)-**24a** and (±)-**24b** as colorless oils, for a combined yield of 94%. For compound (±)-**24a**, ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.27 (d, J = 7.3 Hz, 2H), 7.17 (d, J = 7.3 Hz, 3H), 4.73 (t, J = 5.8 Hz, 1H), 3.80 (dt, J = 9.3, 4.8 Hz, 1H), 2.14−2.04 (m, 5H), 2.04−1.91 (m, 4H), 1.90−1.84 (m, 1H), 1.83−1.75 (m, 1H), 1.51 (s, 3H), 1.31−1.20 (m, 1H), 1.00 (d, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 174.9, 144.5, 128.2, 126.0, 125.8, 58.7, 57.1, 48.4, 34.5, 32.9, 27.8, 27.3, 25.7, 24.7, 15.6, 12.7. HRMS (ESI) calcd. for $C_{18}H_{26}NOS$ (m/z M +H$^+$): 304.1735, found: 304.1731.

*(3R,6R,9R,9aR)-3,9-Dimethyl-3-(methylthio)-6-phenyloctahydro-4H-quinolizin-4-one ((±)-**24b**).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.32−7.21 (m, 4H), 7.15 (d, J = 6.6 Hz, 1H), 4.69 (t, J = 6.0 Hz, 1H), 3.64 (dt, J = 11.8, 3.7 Hz, 1H), 2.46 (dd, J = 13.5, 5.7 Hz, 1H), 2.08−1.89 (m, 7H), 1.85−1.68 (m, 2H), 1.58 (dd, J = 13.7, 3.5 Hz, 1H), 1.38 (s, 3H), 1.28−1.17 (m, 1H), 1.05 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, CD2Cl2) δ 174.4, 146.2, 128.3, 125.9, 125.5, 59.2, 57.5, 47.4, 35.8, 32.1, 29.0, 27.3, 25.3, 25.1, 15.4, 12.6. HRMS (ESI) calcd. for $C_{18}H_{26}NOS$ (m/z M+H$^+$): 304.1735, found: 304.1732.

*(6R,9R,9aR)-9-Methyl-3,3-bis(methylthio)-6-phenyloctahydro-4H-quinolizin-4-one ((±)-**24c**).* By following the procedure of preparing (+)-**18c**, compound (±)-**24c** was derived from compound (±)-**23** (84.1 mg, 0.35 mmol) using MeSSMe (123 μL, 1.38 mmol) as the sulfenylation reagent. Automated silica gel flash column chromatography with ethyl acetate/hexane (15−35%) afforded 103.1 mg of (±)-**24c** as a colorless oil, with a yield of 89%. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.31−7.24 (m, 4H), 7.20−7.13 (m, 1H), 4.74 (t, J = 6.0 Hz, 1H), 3.77−3.65 (m, 1H), 2.43−2.29 (m, 3H), 2.09−1.99 (m, 2H), 1.99 (s, 3H), 1.98 (s, 3H), 1.89−1.68 (m, 3H), 1.27−1.18 (m, 1H), 1.05 (d, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 171.3, 145.3, 128.3, 126.1, 125.5, 62.45, 58.5, 57.9, 35.3, 31.9, 28.7, 27.1, 25.6, 15.4, 13.7, 11.3. IR (film, cm^{-1}), 2916, 2869, 1636, 1450, 1311, 1204, 735,701. HRMS (ESI) calcd. for $C_{18}H_{26}NOS_2$ (m/z M+H$^+$): 336.1456, found: 336.1466.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03052.

NMR spectra including ^{1}H, ^{13}C, 2D-NOESY, COSY, HMBC, and HMQC (PDF)

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Notes

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■ REFERENCES

(1) Achmatowicz, O.; Bellen, Z. *Tetrahedron Lett.* **1962**, *3* (24), 1121−1124.

(2) LaLonde, R. T.; Wong, C. *Pure Appl. Chem.* **1977**, *49* (2), 169−181.

(3) Cybulski, J.; Wrobel, J. T. In *The Alkaloids Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press, Inc: London, 1989; Vol. *35*, pp 215−257.

(4) Matsuda, H.; Morikawa, T.; Oda, M.; Asao, Y.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **2003**, *13* (24), 4445−4449.

(5) Matsuda, H.; Yoshida, K.; Miyagawa, K.; Nemoto, Y.; Asao, Y.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **2006**, *16* (6), 1567−1573.

(6) Okamura, S.; Nishiyama, E.; Yamazaki, T.; Otsuka, N.; Taniguchi, S.; Ogawa, W.; Hatano, T.; Tsuchiya, T.; Kuroda, T. *Biochim. Biophys. Acta, Gen. Subj.* **2015**, *1850* (6), 1245−1252.

(7) Cullen, W. P.; LaLonpe, R. T.; Wang, C. J.; Wong, C. F. *J. Pharm. Sci.* **1973**, *62* (5), 826−827.

(8) Yamahara, J.; Shimoda, H.; Matsuda, H.; Yoshikawa, M. *Biol. Pharm. Bull.* **1996**, *19* (9), 1241−1243.

DOI: 10.1021/acs.joc.6b03052
J. Org. Chem. 2017, 82, 2648−2655

(9) Matsuda, H.; Shimoda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2001**, *9* (4), 1031−1035.
(10) LaLonde, R. T.; Wong, C. *Can. J. Chem.* **1975**, *53* (23), 3545−3550.
(11) Yoshikawa, M.; Murakami, T.; Ishikado, A.; Wakao, S.; Murakami, N.; Yamahara, J.; Matsuda, H. *Heterocycles* **1997**, *46* (1), 301.
(12) Bohlmann, F.; Winterfeldt, E.; Laurent, H.; Ude, W. *Tetrahedron* **1963**, *19* (1), 195−208.
(13) Hwang, Y. C.; Fowler, F. W. *J. Org. Chem.* **1985**, *50* (15), 2719−2726.
(14) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1999**, *64* (10), 3736−3740.
(15) Moran, W. J.; Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2003**, *5* (19), 3427−3429.
(16) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70* (1), 207−213.
(17) Katoh, M.; Mizutani, H.; Honda, T. *Tetrahedron Lett.* **2005**, *46* (31), 5161−5163.
(18) Honda, T.; Katoh, M.; Mizutani, H. *Heterocycles* **2006**, *69* (1), 193.
(19) Stoye, A.; Quandt, G.; Brunnhöfer, B.; Kapatsina, E.; Baron, J.; Fischer, A.; Weymann, M.; Kunz, H. *Angew. Chem., Int. Ed.* **2009**, *48* (12), 2228−2230.
(20) Li, H.; Korotkov, A.; Chapman, C. W.; Eastman, A.; Wu, J. *Angew. Chem., Int. Ed.* **2016**, *55* (10), 3509−3513.
(21) Jansen, D. J.; Shenvi, R. A. *J. Am. Chem. Soc.* **2013**, *135* (4), 1209−1212.
(22) Korotkov, A.; Li, H.; Chapman, C. W.; Xue, H.; MacMillan, J. B.; Eastman, A.; Wu, J. *Angew. Chem., Int. Ed.* **2015**, *54* (36), 10604−10607.
(23) Lu, P.; Herrmann, A. T.; Zakarian, A. *J. Org. Chem.* **2015**, *80* (15), 7581−7589.
(24) Ozer, J.; Eisner, N.; Ostrozhenkova, E.; Bacher, A.; Eisenreich, W.; Benharroch, D.; Golan-Goldhirsh, A.; Gopas, J. *Cancer Biol. Ther.* **2009**, *8* (19), 1860−1868.
(25) Tada, N.; Jansen, D. J.; Mower, M. P.; Blewett, M. M.; Umotoy, J. C.; Cravatt, B. F.; Wolan, D. W.; Shenvi, R. A. *ACS Cent. Sci.* **2016**, *2* (6), 401−408.
(26) Marcaurelle, L. A.; Mulvihill, M. J. *ACS Cent. Sci.* **2016**, *2* (6), 367−369.
(27) Sickert, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2008**, *47* (19), 3631−3634.
(28) Giera, D. S.; Sickert, M.; Schneider, C. *Org. Lett.* **2008**, *10* (19), 4259−4262.
(29) Sickert, M.; Abels, F.; Lang, M.; Sieler, J.; Birkemeyer, C.; Schneider, C. *Chem. - Eur. J.* **2010**, *16* (9), 2806−2818.
(30) Abels, F.; Schneider, C. *Synthesis* **2011**, *2011* (24), 4050−4058.
(31) Gupta, V.; Sudhir, S.; Mandal, T.; Schneider, C. *Angew. Chem., Int. Ed.* **2012**, *51* (50), 12609−12612.
(32) Abels, F.; Lindemann, C.; Koch, E.; Schneider, C. *Org. Lett.* **2012**, *14* (23), 5972−5975.
(33) Abels, F.; Lindemann, C.; Schneider, C. *Chem. - Eur. J.* **2014**, *20* (7), 1964−1979.
(34) Lindemann, C.; Schneider, C. *Synthesis* **2016**, *48* (06), 828−844.
(35) Denmark, S. E.; Xie, M. *J. Org. Chem.* **2007**, *72* (18), 7050−7053.
(36) Chen, J.; Chen, J.; Xie, Y.; Zhang, H. *Angew. Chem., Int. Ed.* **2012**, *51* (4), 1024−1027.
(37) Caruana, L.; Fochi, M.; Ranieri, S.; Mazzanti, A.; Bernardi, L. *Chem. Commun.* **2013**, *49* (9), 880−882.
(38) Simsek, S.; Horzella, M.; Kalesse, M. *Org. Lett.* **2007**, *9* (26), 5637−5639.
(39) Matsuya, Y.; Koiwai, A.; Minato, D.; Sugimoto, K.; Toyooka, N. *Tetrahedron Lett.* **2012**, *53* (44), 5955−5957.

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J. Org. Chem. 2017, 82, 2648−2655