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Asymmetric Total Synthesis of (+)-Luciduline: Toward a General Approach to Related *Lycopodium* Alkaloids

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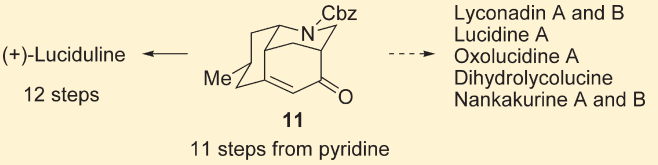
Supporting Information

ABSTRACT: As part of a research program directed toward the synthesis of *Lycopodium* alkaloids, a multigram scale asymmetric synthesis of intermediate **11** was achieved in 11 steps from pyridine (**17**). In addition to our alkene metathesis strategy, a key feature of this synthetic approach consists of a Fukuyama's Diels–Alder cycloaddition between 1,2-dihydropyridine and acrolein using MacMillan's catalyst (**18**) on a 50 g scale. This led to a 12-step catalytic asymmetric synthesis of (+)-luciduline (**1**). A broader subset of *Lycopodium* alkaloids could also be obtained, as demonstrated by the derivatization of **11** into advanced intermediates for the synthesis of some of these natural products.



Since 1881,[1] *Lycopodium* alkaloids have represented an increasing family of structurally diverse natural products.[2] The synthetic challenges associated with these complex molecules have attracted a broad interest in the scientific community.[3] In addition, the biological potential associated with *Lycopodium* alkaloids has motivated notable efforts.[4] However, a thorough investigation of their biological activities is still impaired by their low availability from natural and synthetic sources. Most importantly, this supply limitation has prohibited the chemical synthesis of analogues and the elaboration of a structure–activity relationship.

Recently, we instigated a research program directed toward the synthesis and biological evaluation of natural product analogues, and we became interested in the *Lycopodium* "miscellaneous" subfamily (Scheme 1). More specifically, we examined the possibility for a common synthetic intermediate to allow a late-stage divergence into a broad subset of *Lycopodium* natural products. For its election, a key intermediate would have to be available in its nonracemic form, and the synthetic sequence would have to be flexible and scalable to multigram quantities, requirements that are all necessary for efficient analogues syntheses.

The search for a general strategy to access *Lycopodium* alkaloids has already been discussed in the literature. In his report on the asymmetric total syntheses of nankakurines A (**3**) and B (**4**), Overman suggested that these two natural products could synthetically originate from luciduline (**1**).[5] A few years later, this hypothesis was elegantly validated by Waters through 3- and 4-step syntheses of (±)-nankakurines A (**3**) and B (**4**), respectively, using (±)-luciduline (**1**) as a starting material.[6] Also, as a possible ramification of his total synthesis of lyconadin A (**9**), Sarpong recently suggested that a ring contraction reaction of the seven-membered ring could open the access to the six-membered ring analogues in the family, including luciduline (**1**) and nankakurines (**3** and **4**).[7]

Inspired by Overman's and Sarpong's proposals and by Waters' achievements, we hypothesized that the intermediate **11** could be a common precursor to luciduline (**1**), lucidulinone (**2**), spiroluciduline (**8**), and nankakurines A (**3**) and B (**4**). Obviously, this could be achieved using the ketone functionality as a synthetic handle, as examplified by Waters. In addition, as a variant to Sarpong's suggestion, we also hypothesized that this same ketone functionality could serve as a platform for a 1-carbon ring expansion toward the synthesis of the seven-membered ring analogues such as lucidine A (**6**), oxolucidine A (**7**), dihydrolycolucine (**5**), and lyconadins A (**9**) and B (**10**).

Herein, we describe an asymmetric multigram scale synthesis of **11** and validate its applicability for the synthesis of *Lycopodium* natural products by presenting the first catalytic asymmetric total synthesis of (+)-luciduline (**1**).[8] In addition, we highlight preliminary results on key chemical modifications of **11**, opening the way for a general entry into the *Lycopodium* "miscellaneous" subfamily.

RESULTS AND DISCUSSION

Synthesis of Tandem Alkene Metathesis Precursor 15. Our retrosynthetic analysis of **11** is outlined in Scheme 2. We identified dione **12** as a suitable intermediate for late stage formation of the cyclohexenone ring through an intramolecular aldol condensation. This retrosynthetically exposed the *cis*-fused hydroquinoline core of **11**. For its synthesis, we elected to use our tandem metathesis approach,[9,10] thereby nominating azabicyclo[2.2.2]octene **15** as a key intermediate. Finally, we identified Fukuyama's intermediate **16** as a known starting point for our synthesis.[11]

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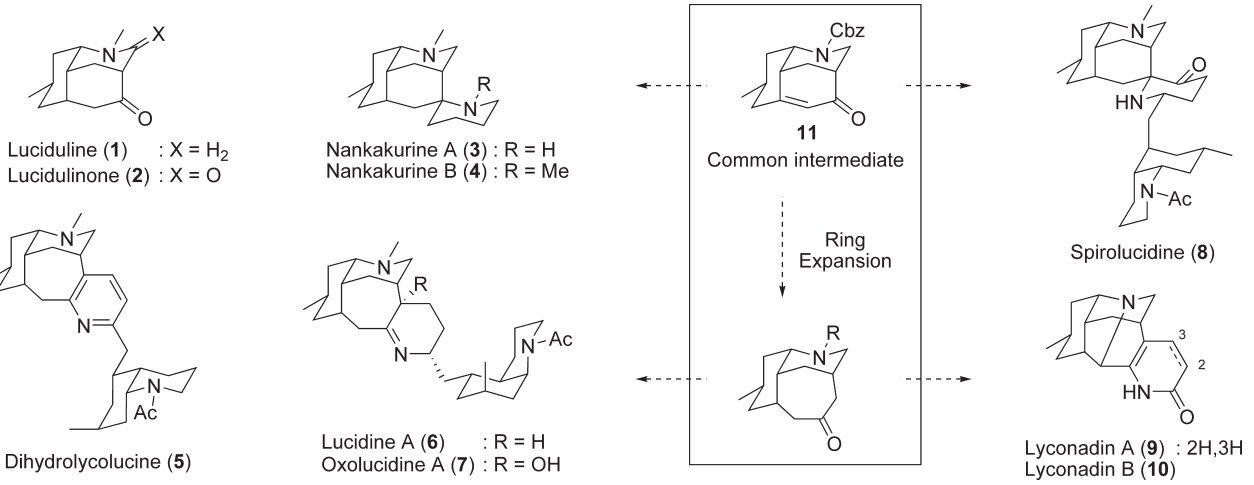
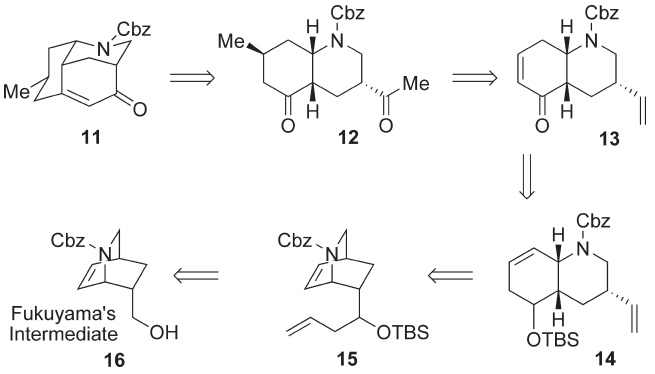
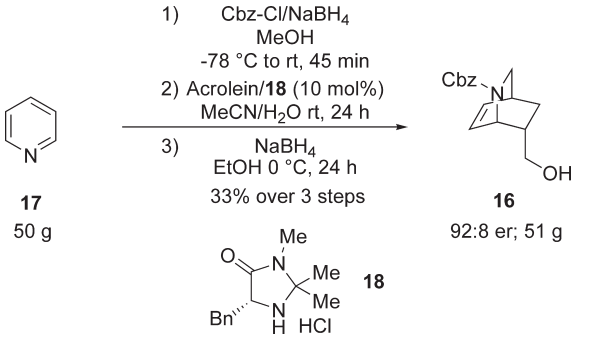
Scheme 1. General Strategy to Selected *Lycopodium* "Miscellaneous" Alkaloids



Scheme 2. Retrosynthetic Analysis of 11



Scheme 3. Synthesis of Fukuyama's Intermediate 16



Upon the initiation of this program, our goal was primarily to identify and synthesize a bench-stable enantioenriched azabicyclo[2.2.2]octene system as a precursor to the ring-closing ring-opening metathesis chemistry. Rapidly, we acknowledged the asymmetric Diels–Alder cycloaddition using 1,2-dihydropyridine as a privileged approach for accessing such a bicyclic system.[12] In this regard, we became interested in a report published by Fukuyama's group on the synthesis of Oseltamivir using MacMillan's asymmetric Diels–Alder methodology.[13] More precisely, a footnote in that report relating to the identification of a byproduct in the Diels–Alder cycloaddition caught our attention. In fact, this footnote directed the reader to the Supporting Information's description of the byproduct identification method, which involved the concomitant synthesis of **16**. Although a modest yield was reported for **16** (28% over three steps), the sequence used could produce multigram quantities using inexpensive commercially available materials. In addition, on the basis of previous observations from our laboratories, we were confident that **16** would fulfill our stability requirement for long-term storage. Finally, although the enantiomeric excess of **16** was not reported and remained to be determined, the context of the report suggested an acceptable outcome. Thus, after minor optimization of the reaction conditions, we were pleased to successfully reproduce Fukuyama's findings by obtaining **16** in 33% yield over three steps starting from 50 g of pyridine (**17**) (Scheme 3). Most importantly, 51 g of **16** was thereby produced with an enantiomeric ratio of 92:8.[14]

With multigram quantities of enantioenriched intermediate **16** in hand, we turned our attention to the elaboration of the tandem metathesis precursor **15**. First, oxidation of the primary alcohol to the aldehyde followed by treatment with allylmagnesium bromide yielded the corresponding homoallylic alcohol as a mixture of diastereoisomers (Scheme 4). Then, as a requirement for the metathesis sequence optimization, the free hydroxyl group was protected as its TBS-ether **15** with an overall yield of 61% for the 3 steps.[9a,15] It is noteworthy that **15** could also be accessed through a 4-step synthesis from pyridine (**17**) by direct allylation of the aldehyde produced through the Diels–Alder cycloaddition. However, although multigram quantities of **15** could still be obtained, the whole process was found to be practically less amenable to large scale synthesis and provided no advantage in terms of overall yield.

Tandem Alkene Metathesis Reaction of 15. With the metathesis precursor **15** in hand, we performed a brief optimization of the conditions for the tandem ring rearrangement reaction. These results are shown in Table 1. Ultimately, we found that submitting diene **15** to 2 mol % of Grubbs second generation catalyst **20**[16] could afford reproducibly the desired hydroquinoline **14** with 81% yield on a multigram scale (entry 9).

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Scheme 4. Synthesis of Metathesis Precursor 15

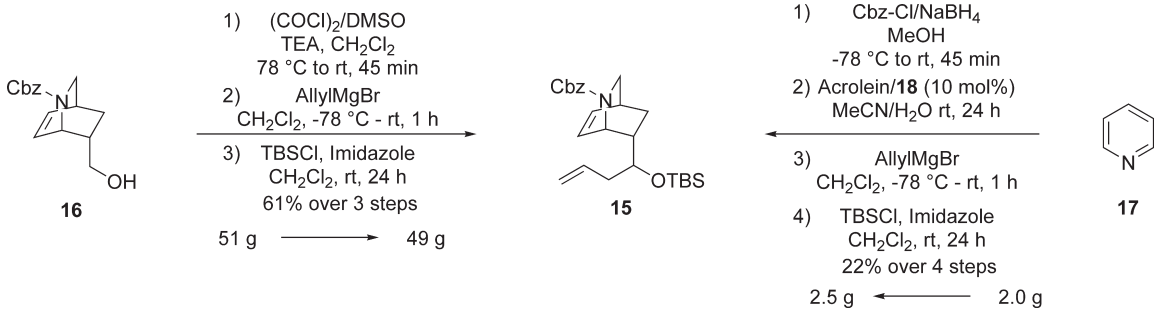
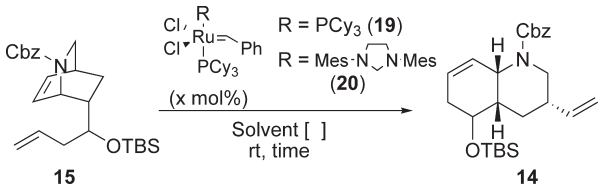


Table 1. Tandem Metathesis Optimization[a]



entry	catalyst	catalyst (mol %)	solvent	[**15**] (M)	time (h)	yield[b] (%)
1	**19**	5.0	CH_2Cl_2	0.01	17	60
2	**20**	5.0	CH_2Cl_2	0.01	17	68
3	**20**	0.5	CH_2Cl_2	0.01	17	69
4	**20**	1.0	CH_2Cl_2	0.01	17	74
5	**20**	2.0	CH_2Cl_2	0.01	17	79
6	**20**	2.0	toluene	0.01	3	61
7	**20**	2.0	CH_2Cl_2	0.10	17	57
8	**20**	2.0	CH_2Cl_2	0.001	17	73
9[c]	**20**	2.0	CH_2Cl_2	0.01	17	81

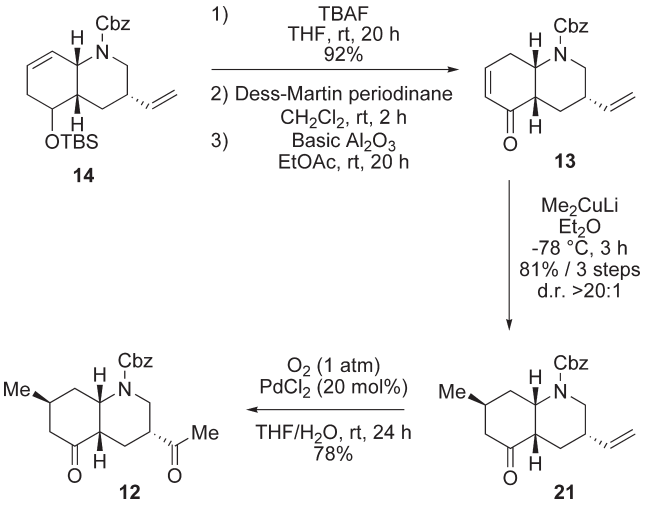
[a] Catalyst is added to a solution of **15** (1 mmol) in commercially available solvent at room temperature under an argon atmosphere. [b] Isolated yield. [c] Reaction performed on a 10 mmol scale.

It is interesting to note that although a much faster reaction was observed in toluene (entry 6), dimerization of the final product became detrimental to the reaction yield. Finally, a decrease in yield was also obtained with higher catalyst loading (entry 2) and increased reaction concentration (entry 8).

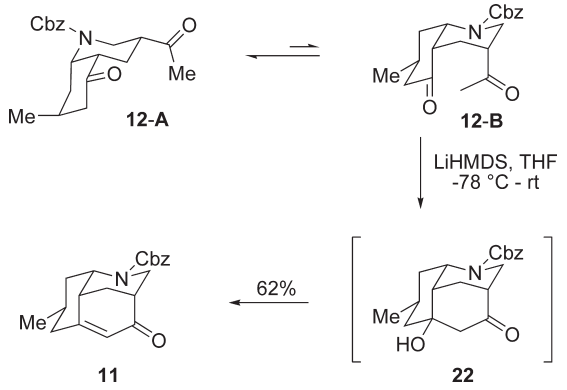
Synthesis of Key Intermediate 11 and (+)-Luciduline 1. We then turned our attention toward the synthesis of dione **12** (Scheme 5). Deprotection of the alcohol followed by a 2-step Dess–Martin oxidation/alumina-induced alkene migration produced the enone **13** as a suitable Michael acceptor for a methylcuprate addition.[17] As anticipated from the *cis*-fused junction of the hydroquinoline, the methyl delivery was observed uniquely on the β-face of the bicyclic system (**21**). This led us to an alkene oxidation distance from our dione target, a transformation that occurred using Wacker oxidation conditions (**12**).[18] This latter result is in sharp contrast with our previous observation that the presence of a methyl group at the 2 position, *cis* to the terminal alkene, completely prohibited the formation of the ketone under the same reaction conditions.[9a,19]

At this point, we became concerned by the well-established preferred conformation for *N*-acyl protected *cis*-fused

Scheme 5. Synthesis of Aldol Precursor 12



Scheme 6. Intramolecular Aldol Condensation and Formation of 11



hydroquinolines. Indeed, in order to minimize the allylic strain between the carbamate moiety and the cyclohexanone ring, the system preferentially adopts a conformation such as **12-A** (Scheme 6). In fact, NMR analysis of compound **12** in d_6-acetone showed that conformer **12-A** was the only one present in solution. Therefore, we anticipated that this would impair our desired intramolecular aldol reaction to efficiently occur.

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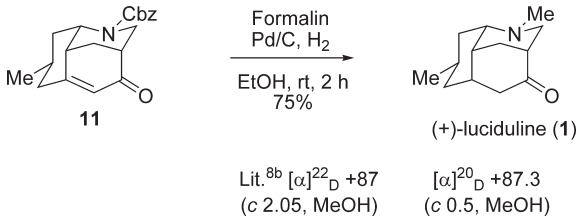
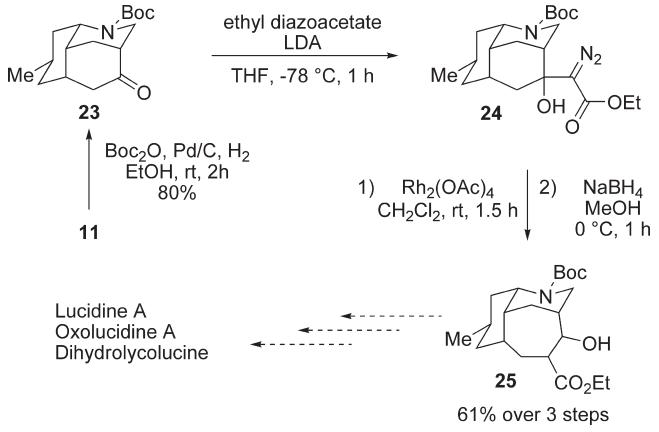
Scheme 7. Synthesis of (+)-Luciduline (1)



Scheme 8. Exploration of the Ring Expansion Strategy



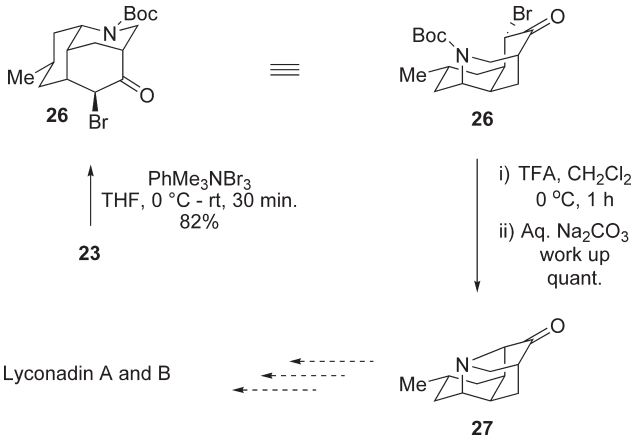
Unfortunately, this concern was supported when dione **12** was submitted to LiHMDS at −78 °C, and only a complex mixture of dimers was observed by LC−MS analysis of the reaction mixture. However, we then found that by simply warming the reaction to room temperature monomers could reform via retroaldol reactions. Most importantly, this temperature also allowed for an equilibrium to occur between the two conformers, thereby enabling the intramolecular process. After 20 h at room temperature, the desired aldol condensation **11** product was obtained in an isolated yield of 62%.

With enone **11** secured, we found ourselves in a suitable position to complete the total synthesis of (+)-luciduline (**1**). Indeed, a concomitant hydrogenation of the enone, hydrogenolysis of the Cbz protecting group, and *in situ* reductive amination with formalin produced (+)-luciduline (**1**) in 75% yield (Scheme 7). Hence, this transformation concluded a 12-step catalytic asymmetric total synthesis of (+)-luciduline from pyridine. In addition, this opened the door to a 15- and 16-step asymmetric formal synthesis of nankakurine A (**3**) and B (**4**), respectively (*vide supra*).[6]

Afterward, we briefly explored the viability of our synthetic approach toward the synthesis of other *Lycopodium* alkaloids. First, we investigated a ring expansion strategy by screening different reaction conditions on various substrates. Ultimately, we found that treating the diazo compound **24** with a catalytic amount of $Rh_2(OAc)_4$ gave a crude, unstable seven-membered β-ketoester (Scheme 8). After reduction of the ketone, the stable compound **25** could be obtained as a single regio- and diastereoisomer in 61% yield over the three steps. Therefore, these results paved the way for the asymmetric synthesis of lucidine A (**6**), oxolucidine A (**7**), and dihydrolycolucine (**5**).

Finally, we probed the formation of the tetracyclic core structures of lyconadins A and B by evaluating the formation

Scheme 9. Synthetic Approach to Lyconadin A and B



of the final nitrogen−carbon bond (Scheme 9).[20] Thus, treatment of ketone **23** with $PhMe_3NBr_3$ expectedly generated the bromide **26** as a single diastereoisomer in good yield. We anticipated this bromide leaving group to be suitably positioned to participate in an intramolecular S_N2 reaction with the amine functionality. Gratifyingly, we found that treating **26** with TFA followed by a basic workup validated this hypothesis by cleanly producing the tetracyclic compound **27** in quantitative yield.

CONCLUSIONS

In conclusion, we achieved an asymmetric multigram scale synthesis of the valuable intermediate **11**. This allowed us to conclude the first catalytic asymmetric synthesis of (+)-luciduline (**1**) in 12 steps from pyridine. In addition, we demonstrated the potential for **11** to enable divergence to a broader subset of *Lycopodium* alkaloids. Our efforts are currently directed toward the optimization of the asymmetric construction of the azabicyclo[2.2.2]octane system and its application to the syntheses of other *Lycopodium* natural products. These results will be reported in due course.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, reactions were run under an argon atmosphere with exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds. Commercial reagents and solvents were used without purification. Analytical thin-layer chromatography was performed on precoated, glass-backed silica gel. Visualization of the developed chromatogram was performed by UV and aqueous potassium permanganate. Flash column chromatography was performed using 230−400 mesh silica. Nuclear magnetic resonance spectra were recorded on 400 and 600 MHz spectrometers (^{1}H and ^{13}C). Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterated solvents as the internal standards. All ^{13}C NMR spectra were obtained with complete proton decoupling. Infrared spectra were taken on NaCl plates (film). High resolution mass spectra (HMRS) were performed on a high resolution magnetic sector mass spectrometer. Optical rotation data were determined with a polarimeter at 589 nm. All spectral data obtained for new compounds are reported here.

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Procedure A: Benzyl Pyridine-1(2*H*)-carboxylate (S-1). To a stirred solution of pyridine (50.0 g, 632 mmol) in methanol (502 mL) at −78 °C was added sodium borohydride (26.4 g, 698 mmol). To this was added benzyl chloroformate (108.1 g, 602 mmol) dropwise using an addition funnel. After stirring 120 min, water and Et_2O were added to the reaction mixture. The resulting mixture was warmed to room temperature, and the layers were separated. The aqueous layer was extracted twice with Et_2O, and the combined organic extracts were washed with 1 N HCl, 1 N NaOH, water, and brine, dried over $MgSO_4$, filtered over Celite, and concentrated under reduced pressure to give dihydropyridine **S-1** as a yellow oil. The crude product was used in the next step without further purification.

Benzyl 7-Formyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (S-2). To a stirred solution of the dihydropyridine (123.7 g, 575 mmol) in acetonitrile (307 mL) and water (77 mL) was added MacMillan's catalyst **18**[13a] (14.64 g, 57.5 mmol) and acrolein (90%, 107 mL, 1725 mmol) after which the mixture turned yellow. After stirring overnight, the reaction mixture was diluted with DCM and washed with water. The layers were separated, and the aqueous layer was extracted twice with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the aldehyde as a green foam. The crude product **S-2** was used in the next step without further purification.

Benzyl 7-(Hydroxymethyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (16). To a stirred solution of the aldehyde (575 mmol) in ethanol (1150 mL) was added sodium borohydride (43.5 g, 575 mmol) at 0 °C at which time the mixture became yellow. After stirring 1 h, the reaction was quenched with 1 N HCl. The reaction mixture was extracted with DCM, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography of the yellow oily residue with EtOAc/hexanes (40/60) afforded 51.4 g of alcohol **16** (33%, 3 steps) as a colorless oil (92:8 er). $[\alpha]^{20}_D$ = +74.8 (*c* 0.500, $CHCl_3$), lit. $[\alpha]^{23}_D$ +70.3 (*c* 1.09, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.43−7.24 (m, 5H), 6.48−6.28 (m, 2H), 5.22−5.08 (m, 2H), 4.92−4.86 (m, 1H), 3.36−3.25 (m, 2H), 3.25−3.12 (m, 1H), 3.08−2.91 (m, 1H), 2.80−2.70 (m, 1H), 2.44−2.31 (m, 1H), 2.06 (br s, 1H), 1.85−1.72 (m, 1H), 0.94−0.77 (m, 1 H); FTIR (cm^{-1}) (neat) 3451 (broad), 3053, 3016, 2946, 2864, 1684, 1432, 1337; HRMS (ESI, Pos) calcd for $C_{16}H_{19}NO_3$ $[M + H]^+$: 274.1438 *m*/*z*, found 274.1440 *m*/*z*.

Procedure B: Benzyl 7-Formyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (S-2). To a stirred solution of oxalyl chloride (26.2 g, 207 mmol) in DCM (611 mL) was slowly added DMSO (33.0 g, 423 mmol) in DCM (50 mL) at −78 °C. After 15 min of stirring, a solution of alcohol **16** (51.4 g, 188 mmol) in DCM (135 mL) was added at −78 °C. After 20 min of stirring, triethylamine (97.0 g, 958 mmol) was added, and the reaction mixture was stirred for 20 min at −78 °C followed by warming to room temperature and stirring an additional 10 min. Saturated NH_4Cl aqueous solution was carefully added to the reaction mixture, the layers were separated, and the aqueous layer was extracted twice with DCM. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure, yielding the aldehyde **S-2** as an orange oil. The crude product was used in the next step without further purification.

Benzyl 7-(1-hydroxybut-3-en-1-yl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (S-3). The crude aldehyde **S-2** (188 mmol) was dissolved in DCM (1880 mL), and the solution was cooled to −78 °C. Allylmagnesium bromide (282 mL of a 1.0 M solution in Et_2O, 282 mmol) was then added dropwise, and the thick reaction mixture was brought to room temperature. The heterogeneous solution was stirred for 2 h, and saturated NH_4Cl aqueous solution was carefully added to the reaction mixture. The solution was transferred into a separation funnel, the layers were separated, and the aqueous layer was extracted twice with DCM. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure yielding a yellow oil. The crude alcohol **S-3** was used in the next step without further purification. **(*R*)-diastereoisomer**: $[\alpha]^{20}_D$ = +69.9 (*c* 0.700, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.47−7.26 (m, 5H), 6.49−6.32 (m, 2H), 5.99−5.86 (m, 1H), 5.20−4.97 (m, 5 H), 3.83−3.74 (m 1H), 3.26 (dd, *J* = 42.0, 10.0 Hz, 1H), 3.03 (br s, 3H), 2.77 (br s, 1H), 2.30 (dd, J = 16.0, 8.0 Hz, 1H), 2.14−1.97 (m, 2H), 1.77 (t, *J* = 12.0 Hz, 1H), 0.96−0.85 (m, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) mixture of rotamers, major δ 154.6, 137.7, 135.9, 134.7, 130.8, 128.3, 127.7, 127.6, 116.1, 73.5, 65.9, 46.9, 46.6, 45.2, 38.7, 31.1, 26.9; FTIR (cm^{-1}) (neat) br 3435, 3065, 2933, 2876, 1694, 1417; HRMS (ESI, Pos) calcd for $C_{19}H_{23}NO_3$ $[M + H]^+$: 314.1751 *m*/*z*, found 314.1766 *m*/*z*. **(*S*)-diastereoisomer**: $[\alpha]^{20}_D$ = +71.5 (*c* 0.990, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.47−7.26 (m, 5 H), 6.51−6.41 (m, 1H), 6.40−6.30 (m, 1H), 6.04−5.87 (m, 1H), 5.23−4.97 (m, 4H), 4.77 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.59 (br s, 1H), 3.27 (ddd, *J* = 30.0, 10.0, 4.0 Hz, 1H). 3.21−3.11 (m, 1H), 2.78 (br s, 1H), 2.46−2.32 (m, 1H), 2.26−2.14 (m, 2H), 1.85−1.74 (m, 1H), 1.50−1.40 (m, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) mixture of rotamers, major δ 154.7, 137.6, 135.4, 135.1, 130.3, 128.4, 127.8, 127.7, 116.5, 73.1, 66.2, 47.5, 46.8, 45.5, 40.0, 31.2, 27.0; FTIR (cm^{-1}) (neat) br 3444, 3065, 2928, 2875, 1700, 1434; HRMS (ESI, Pos) calcd for $C_{19}H_{23}NO_3$ $[M + H]^+$: 314.1751 *m*/*z*, found 314.1752 *m*/*z*.

Benzyl 7-(1-{[*tert*-Butyl(dimethyl)silyl]oxy}but-3-en-1-yl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (15). To a stirred solution of the alcohol **S-3** (188 mmol) in DMF (940 mL) were added imidazole (25.6 g, 376 mmol) and TBS-Cl (42.5 g, 282 mmol). After stirring for 48 h, the reaction mixture was transferred into a separation funnel with Et_2O, and the organic layer was washed with 1 N HCl, water, and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography of the brownish oily residue with EtOAc/hexanes (20/80) afforded 49.0 g of metathesis precursor **5** (61%, 3 steps) as a light yellow oil. **(*R*)-diastereoisomer**: $[\alpha]^{20}_D$ = +17.2 (*c* 0.575, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.06−7.89 (m, 5H), 7.15−7.08 (m, 1H), 7.04−6.92 (m, 1H), 6.63−6.49 (m, 1H), 5.79−5.57 (m, 5H), 3.96−3.79 (m, 2H), 3.65−3.52 (m, 1H), 3.40 (br s, 1H), 2.98−2.88 (m, 1H), 2.88−2.77 (m, 2H), 2.42−2.33 (m, 1H), 1.62−1.52 (m, 10H), 0.74 (dd, *J* = 16.0, 8.0 Hz, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) mixture of rotamers, major δ 154.2, 137.7, 135.4, 134.2, 130.5, 128.3, 127.8, 127.6, 116.9, 74.0, 65.9, 46.7, 46.7, 44.1, 37.7, 31.0, 26.8, 25.5, 17.8, 4.4, −5.4; FTIR (cm^{-1}) (neat) 3064, 2929, 2857, 1712, 1640, 1417; HRMS (ESI, Pos) calcd for $C_{25}H_{37}NO_3Si$ $[M + H]^+$: 428.2616 *m*/*z*, found 428.2617 *m*/*z*. **(*S*)-diastereoisomer**: $[\alpha]^{20}_D$ = +56.7 (*c* 0.580, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.45−7.26 (m, 5H), 6.50−6.42 (m, 1H), 6.40−6.30 (m, 1H), 6.01−5.82 (m, 1H), 5.25−4.96 (m, 4H), 4.77 (dd, *J* = 20.0, 8.0 Hz, 1H), 3.43−3.34 (m, 1H), 3.26 (ddd, *J* = 34.0, 10.0, 2.0 Hz, 1H), 3.01−2.89 (m, 1H), 2.80 (br s, 1H), 2.40−2.18 (m, 3H), 1.84−1.73 (m, 1H), 1.37−1.23 (m, 1H), 0.92 (d, *J* = 4.0 Hz, 9H), 0.08 (t, J = 8.0 Hz, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) mixture of rotamers, major δ 154.5, 137.7, 134.9, 134.1, 130.6, 128.3, 127.9, 127.6, 117.2, 74.5, 66.0, 46.9, 46.5, 44.6, 39.5, 31.2, 27.5, 25.5, 17.8, 4.4, −5.1; FTIR (cm^{-1}) (neat) 3066, 2953, 2857, 1699, 1642, 1416; HRMS (ESI, Pos) calcd for $C_{25}H_{37}NO_3Si$ $[M + H]^+$: 428.2616 *m*/*z*, found 428.2610 *m*/*z*.

Alternative Route for the Synthesis of Metathesis Precursor: Procedure C. The crude aldehyde **S-2** obtained from Procedure A (25.0 mmol) was dissolved in DCM (250 mL), and the solution was cooled to −78 °C. Allylmagnesium bromide (37.5 mL of a 1.0 M solution in Et_2O, 37.5 mmol) was then added dropwise, and the thick reaction mixture was brought to room temperature. The heterogeneous solution was stirred for 2 h, and saturated NH_4Cl aqueous solution was carefully added to the reaction mixture. The solution was transferred into a separation funnel, the layers were separated, and the aqueous layer was extracted twice with DCM. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced

pressure yielding a yellow oil. Crude product was dissolved in Et_2O, and 5% sodium bisulfite aqueous solution was added. After stirring overnight, the layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layer were dried with $MgSO_4$, filtered over Celite, and concentrated under reduced pressure to yield 4.70 g of alcohol **S-3** as a yellowish oil.

To a stirred solution of the alcohol **S-3** (4.70 g, 15.0 mmol) in DMF (75 mL) were added imidazole (2.04 g, 30.0 mmol) and TBS-Cl (3.39 g, 22.5 mmol) at room temperature. After stirring for 48 h, the reaction mixture was transferred into a separation funnel with Et_2O, and the organic layer was washed with 1 N HCl, water, and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography of the brownish oily residue with EtOAc/hexanes (20/80) afforded 2.49 g of metathesis precursor **15** (22%, 4 steps) as a light yellow oil.

Benzyl (3*S*,4a*S*,8a*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-ethenyl-3,4,4a,5,6,8a-hexahydroquinoline-1(2*H*)-carboxylate (14). Metathesis precursor **15** (4.28 g, 10.0 mmol) was dissolved in DCM (1000 mL), and Grubbs' catalyst second generation (**20**) (0.170 g, 0.200 mmol) was added. After stirring 17 h, the reaction mixture was quenched with the addition of ethyl vinyl ether (excess), and the solution was concentrated under reduced pressure. Flash chromatography of the brownish oil with EtOAc/hexane (20/80) afforded 3.48 g of metathesis product **14** (81%) as a colorless oil. **(*R*)-diastereoisomer**: $[\alpha]^{20}_D$ = +56.9 (*c* 0.520, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.45−7.29 (m, 5H), 5.85−5.71 (m, 2H), 5.39−5.29 (m, 1H), 5.23−4.98 (m, 4H), 4.91 (br s, 1H), 4.20−3.98 (m, 2H), 2.53 (dt, *J* = 44.0, 12.0 Hz, 1H), 2.32−2.19 (m, 1H), 2.19−1.98 (m, 3H), 1.88 (d, *J* = 12.0 Hz, 1H), 1.22 (q, *J* = 12.0 Hz, 1H), 0.92 (s, 9H), 0.12 (d, *J* = 8.0 Hz, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) mixture of rotamers, major δ 154.9, 140.3, 137.4, 128.4, 127.8, 127.7, 127.6, 127.3, 114.1, 69.1, 66.5, 51.7, 45.1, 39.8, 39.7, 31.0, 25.4, 24.8, 17.7, −5.4; FTIR (cm^{-1}) (neat) 3029, 2953, 2895, 2857, 1699, 1423, 1272, 1113, 837, 776; HRMS (ESI, Pos) calcd for $C_{25}H_{37}NO_3Si$ $[M + Na]^+$: 450.2435 *m*/*z*, found 450.2455 *m*/*z*. **(*S*)-diastereoisomer**: $[\alpha]^{20}_D$ = +59.8 (*c* 0.660, $CHCl_3$), ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.46−7.29 (m, 5H), 5.80−5.64 (m, 2H), 5.47−5.38 (m, 1H), 5.23−4.97 (m, 5H), 4.16−3.99 (m, 2H), 2.58 (dt, *J* = 41.3, 13.0 Hz, 1H), 2.32 (d, *J* = 20 Hz, 1H), 2.15 (br s, 1H), 1.99 (d, *J* = 12.0 Hz, 2H), 1.62 (d, *J* = 12.0 Hz, 1H), 1.12 (q, *J* = 14.0 Hz, 1H), 0.94−0.88 (m, 9H), 0.14−0.10 (m, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 154.9, 140.0, 137.4, 128.4, 127.7, 127.6, 127.1, 126.2, 114.1, 69.7, 66.5, 48.0, 44.9, 39.9, 39.7, 30.2. 29.5, 25.4, 17.7, −5.4; FTIR (cm^{-1}) (neat) 3028, 2927, 2890, 2856, 1699, 1424, 1259, 1072, 951, 837, 775; HRMS (ESI, Pos) calcd for $C_{25}H_{37}NO_3Si$ $[M + Na]^+$: 450.2435 *m*/*z*, found 450.2442 *m*/*z*.

Benzyl (3*S*,4a*S*,8a*S*)-3-Ethenyl-5-hydroxy-3,4,4a,5,6,8a-hexahydroquinoline-1(2*H*)-carboxylate (S-4). To a stirred solution of metathesis product **14** (5.95 g, 13.9 mmol) in THF (27.8 mL) was added TBAF (27.8 mL of a 1.0 M solution in THF, 27.8 mmol). After stirring overnight, the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography of the brownish oily solid with EtOAc/hexane (40/60) afforded 4.03 g of the alcohol **S-4** (92%) as a brownish oil. **(*R*)-diastereoisomer**: $[\alpha]^{20}_D$ = +49.0 (*c* 0.300, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.45−7.29 (m 5H), 5.85−5.68 (m, 2H), 5.39−5.29 (m, 1H), 5.21−4.97 (m, 4H), 4.90−4.87 (m, 1H), 4.13−3.93 (m, 3H), 2.53 (dt, *J* = 44.0, 12.0 Hz, 1H), 2.34−2.21 (m, 1H), 2.18−1.95 (m, 3H), 1.89 (d, *J* = 16.0 Hz, 1H), 1.24−1.14 (m, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) mixture of rotamers, major δ 155.0, 140.3, 137.4, 128.4, 127.8, 127.8, 127.7, 127.3, 114.0, 67.7, 66.5, 51.9, 45.1, 39.7, 39.5, 30.2, 24.6; FTIR (cm^{-1}) (neat) br 3438, 3029, 2923, 1697, 1427, 1274, 1116, 917; HRMS (ESI, Pos) calcd for $C_{19}H_{23}NO_3$ $[M + Na]^+$: 336.1570 *m*/*z*, found 336.1568 *m*/*z*. **(*S*)-diastereoisomer**: $[\alpha]^{20}_D$ = +58.5 (*c* 0.525, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.47−7.27 (m, 5H), 5.82−5.64 (m, 2H), 5.40 (d, *J* = 8.0 Hz, 1H), 5.25−4.96 (m, 5H), 4.15−3.88 (m, 3H), 2.57 (dt, *J* = 44.0, 12.0 Hz, 1H), 2.30 (d, *J* = 20.0 Hz, 1H), 2.20−1.99 (m, 3H), 1.59 (d, *J* = 12.0 Hz, 1H), 1.12 (q, *J* = 12.0 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) mixture of rotamers, major δ 155.1, 140.1, 137.6, 128.4, 127.7, 127.6, 126.9, 126.6, 114.0, 68.2, 66.4, 47.9, 45.0, 39.8, 39.1, 29.7, 29.6; FTIR (cm^{-1}) (neat) br 3443, 3027, 2923, 1682, 1427, 1261, 1120, 911; HRMS (ESI, Pos) calcd for $C_{19}H_{23}NO_3$ $[M + Na]^+$: 336.1570 *m*/*z*, found 336.1569 *m*/*z*

Benzyl (3*S*,4a*S*,8a*S*)-3-Ethenyl-5-oxo-3,4,4a,5,6,8a-hexahydroquinoline-1(2*H*)-carboxylate (13). To a stirred solution of the alcohol **S-4** (3.98 g, 12.7 mmol) were added Dess−Martin periodinane (8.08 g, 19.1 mmol) and a drop of water. The reaction mixture was stirred for 4 h, diluted with Et_2O, and poured into a saturated $NaHCO_3$ aqueous solution (100 mL) containing $Na_2S_2O_3$ (25 g). This heterogeneous solution was stirred until the solid was completely dissolved. The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ aqueous solution and water, dried over $MgSO_4$, filtered over Celite, and concentrated under reduced pressure. The resulting yellowish oil was dissolved in ethyl acetate (127 mL), and alumina was added (20 g). The mixture was stirred overnight, then filtered over Celite, and concentrated under reduced pressure. The crude enone **13** was used to the next step without any further purification. $[\alpha]^{20}_D$ = −41.1 (*c* 0.730, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.48−7.28 (m, 5H), 7.13−7.01 (m, 1H), 6.03−5.93 (m, 1H), 5.88−5.71 (m, 1H), 5.24−5.02 (m, 4H), 4.82−4.72 (m, 1H), 4.13 (dd, *J* = 20.0, 16.0 Hz, 1H), 2.97−2.69 (m, 2H), 2.60−2.46 (m, 1H), 2.45−2.31 (m, 1H), 2.25 (br s, 1H), 1.79−1.68 (m, 1H), 1.49 (q, *J* = 12.0 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) mixture of rotamers, major δ 199.3, 154.7. 148.4, 139.3, 137.2, 128.5, 128.3, 127.9, 127.8, 115.0, 66.8, 49.4, 47.6, 43.6, 39.3, 28.7, 24.5; FTIR (cm^{-1}) (neat) 3063, 3033, 2930, 1681, 1498, 1417, 1263; HRMS calcd for $C_{19}H_{21}NO_3$ $[M + H]^+$: 312.1594 *m*/*z*, found 312.1586 *m*/*z*.

Benzyl (3*S*,4a*S*,7*S*,8a*S*)-3-Ethenyl-7-methyl-5-oxooctahydroquinoline-1(2*H*)-carboxylate (21). To a stirred suspension of copper iodide (7.26 g, 38.1 mmol) and THF (80 mL) was added methyllithium (47.60 mL of a 1.0 M solution in Et_2O, 47.60 mmol) at 0 °C. After the reaction mixture stirred for 30 min at 0 °C followed by an additional 15 min at room temperature, the solution became colorless. The reaction mixture was cooled to −78 °C and stirred 10 min. A solution of enone **13** (12.7 mmol) in THF (80 mL) was added dropwise, and the reaction mixture was stirred for 3 h at −78 °C. The reaction was quenched at −78 °C by addition of saturated aqueous NH_4Cl, removed from the ice bath, and allowed to warm to room temperature. The heterogeneous solution was diluted with water and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered over Celite, and concentrated under reduced pressure. Flash chromatography of the yellowish oil with EtOAc/hexanes (25/75) afforded 3.38 g of ketone **21** (81%, 3 steps) as a light yellow oil. $[\alpha]^{20}_D$ = −52.2 (*c* 0.720, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.47−7.27 (m, 5H), 5.87−5.70 (m, 1H), 5.28−5.00 (m, 4H), 4.78−4.62 (m, 1H), 4.18−4.00 (m, 1H), 2.76 (dd, *J* = 16.0, 4.0 Hz, 2H), 2.61−2.51 (m 1H), 2.46−2.32 (m, 2H), 2.25−2.12 (m, 1H), 2.01 (d, *J* = 12.0 Hz, 1H), 1.79 (q, *J* = 13.3 Hz, 1H), 1.71−1.61 (m, 1H), 1.50 (d, *J* = 12.0 Hz, 1H), 0.99 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 210.4, 154.5, 139.4, 137.3, 128.4, 127.8, 127.7, 114.9, 66.6, 51.3, 47.7, 43.3, 43.2, 39.4, 29.2, 28.1, 27.1, 18.6; FTIR (cm^{-1}) (neat) 2952, 2929, 2865, 1694, 1420, 1263, 1222; HRMS (ESI, Pos) calcd for $C_{20}H_{25}NO_3$ $[M + H]^+$: 328.1907 *m*/*z*, found 328.1902 *m*/*z*.

Benzyl (3*S*,4a*S*,7*S*,8a*S*)-3-Acetyl-7-methyl-5-oxooctahydroquinoline-1(2*H*)-carboxylate (12). A stirred suspension of ketone **21** (4.83 g, 14.8 mmol), copper(II) chloride (0.146 g, 1.48 mmol), and palladium(II) chloride (0.262 g, 1.48 mmol) in THF (118 mL) and water (29.5 mL) was stirred under an oxygen atmosphere overnight. Additional amounts of copper(II) chloride (0.146 g, 1.48 mmol) and

palladium(II) chloride (0.262 g, 1.48 mmol) were added, and the reaction mixture was stirred an additional 4 h under an oxygen atmosphere. The reaction was quenched with a saturated aqueous NH_4Cl solution, and the mixture was extracted with DCM. The combined organic extracts were dried over $MgSO_4$, filtered over Celite, and concentrated under reduced pressure. Flash chromatography of the brown oil with EtOAc/hexanes (40/60) afforded 3.97 g of diketone **12** (78%) as a white solid, mp 118−120 °C. $[\alpha]^{20}_D$ = +67.5 (*c* 0.810, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.45−7.28 (m, 5H), 5.17 (q, *J* = 13.3 Hz, 2H), 4.77−4.65 (m, 1H), 4.27 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.98−2.93 (m, 1H), 2.75 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.69−2.51 (m, 2H), 2.44−2.31 (m, 2H), 2.19 (s, 3H), 2.09−1.82 (m, 3H), 1.54−1.44 (m, 1H), 0.99 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 210.3, 207.6, 154.6, 137.2, 128.4, 127.9, 127.7, 66.7, 50.7, 48.0, 47.6, 43.5, 39.6, 28.5, 27.6, 27.1, 25.8, 18.6; FTIR (cm^{-1}) (neat) 3028, 2952, 2871, 1717, 1700, 1426, 1350, 1258; HRMS (ESI, Pos) calcd for $C_{20}H_{25}NO_4$ $[M + H]^+$: 344.1856 *m*/*z*, found 344.1846 *m*/*z*.

Benzyl (1*S*,3*R*,7*R*,8a*R*)-3-Methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydro-1,7-(epiminomethano)naphthalene-10-carboxylate (11). To a stirred solution of diketone **12** (3.97 g, 11.6 mmol) in THF (116 mL) at −78 °C was added LiHMDS (12.7 mL of a 1.0 M solution in hexanes, 12.7 mmol) after which the solution became turquoise. After stirring for 1 h at −78 °C, the reaction mixture was warmed to room temperature and stirred overnight. The yellowish reaction mixture was diluted in Et_2O and 1 N HCl. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered over Celite, and concentrated under reduced pressure. Flash chromatography of the colorless oil with EtOAc/hexanes (40/60) afforded 2.25 g of enone **11** (60%) as a colorless oil. $[\alpha]^{20}_D$ = +307.7 (*c* 0.740. $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.42−7.27 (m, 5H), 5.96 (s, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 5.01 (d, *J* = 12.0 Hz, 1H), 4.06 (dt, *J* = 13.3, 2.0 Hz, 1H), 3.77−3.72 (m, 1H), 3.16 (dd, *J* = 16.0, 4.0 Hz, 2H), 2.57−2.53 (m, 1H), 2.46 (ddd, *J* = 10.4, 4.0, 0.8 Hz, 1H), 2.41−2.35 (m, 1H), 2.25−2.18 (m, 1H), 2.07−1.98 (m, 1H), 1.91 (dt, *J* = 13.3, 3.0 Hz, 1H), 1.85−1.69 (m, 1H), 1.38−1.27 (m, 1H), 0.94 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 198.7, 165.8, 156.3, 137.1, 128.4, 127.9, 127.8, 124.8, 66.4, 58.3, 46.9, 44.7, 41.8, 40.3, 39.4, 33.9, 29.6, 21.4; FTIR (cm^{-1}) (neat) 3030, 2956, 2858, 1719, 1672, 1403, 1295, 1209; HRMS (ESI, Pos) calcd for $C_{20}H_{23}NO_3$ $[M + H]^+$: 326.1751 *m*/*z*, found 326.1744 *m*/*z*.

(+)-Luciduline (1): (1*S*,3*R*,4a*S*,7*R*,8a*R*)-3,10-Dimethyloctahydro-1,7-(epiminomethano)naphthalen-6(2*H*)-one. A solution of enone **11** (0.200 g, 0.615 mmol) and 10% palladium on carbon (0.131 g, 0.123 mmol) in ethanol (6.15 mL) was stirred under a hydrogen atmosphere. After 1 h of stirring, formaldehyde (0.229 mL of a solution 37% in water, 3.07 mmol) was added, and the reaction mixture was stirred an additional 3 h under the hydrogen atmosphere. The mixture was filtered and concentrated under reduced pressure. Flash chromatography of the colorless oil with EtOAc/hexanes (25/75) afforded 95 mg (75%) of (+)-luciduline (**1**) as a light yellow oil. $[\alpha]^{20}_D$: +87.3 (*c* 0.495, MeOH), lit.[8b] $[\alpha]^{22}_D$ +87 (*c* 2.05, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.05 (dd, *J* = 16.0, 12.0 Hz, 1H), 2.83 (d, *J* = 8.0 Hz, 1H), 2.42 (br s, 1H), 2.38−2.28 (m, 2H), 2.24 (br s, 1H), 2.21−2.11 (m, 4H), 2.08−2.04 (m, 1H), 2.03−1.92 (m, 1H), 1.91−1.80 (m, 2H), 1.69 (br s, 1H), 1.55−1.51 (m, 1H), 1.25 (td, *J* = 12.0, 4.0 Hz, 1H), 0.99 (t, *J* = 14.0 Hz, 1H), 0.90 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.9, 62.7, 58.8, 46.6, 46.4, 42.3, 39.8, 38.5, 36.6, 35.0, 33.8, 22.3, 20.1; FTIR (cm^{-1}) (neat) 2915, 2861, 2856, 1693, 1458, 1293, 1197, 1133, 909; HRMS (ESI, Pos) calcd for $C_{13}H_{21}NO$ $[M + H]^+$: 208.1696 *m*/*z*, found 208.1690 *m*/*z*.

***tert*-Butyl (1*S*,3*R*,4a*S*,7*R*,8a*R*)-3-Methyl-6-oxodecahydro-1,7-(epiminomethano)naphthalene-10-carboxylate (23).** A solution of enone **11** (1.00 g, 3.07 mmol), 10% palladium on carbon (0.654 g, 0.615 mmol), and Boc_2O (1.01 g, 4.61 mmol) in ethanol (30.7 mL) was stirred under a hydrogen atmosphere. After stirring for 4 h, the mixture was filtered over silica gel eluting with EtOAc, and the solution was concentrated under reduced pressure. Flash chromatography of the colorless oil with EtOAc/hexanes (20/80) afforded 0.785 g (87%) of N-protected ketone **23** as a colorless oil. $[\alpha]^{20}_D$ = +123.3 (*c* 0.520. $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.05 (d, *J* = 16.0 Hz, 1H) 3.48 (s, 1H), 3.20 (d, *J* = 16.0 Hz, 1H), 3.00 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.70 (t, *J* = 14.0 Hz, 1H), 2.49 (s, 1H), 2.29 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.22−2.12 (m, 1H), 1.92 (s, 2H), 1.90−1.79 (m, 1H), 1.76 (s, 1H), 1.54 (d, *J* = 12.0 Hz, 1H), 1.43 (s, 9H), 1.30 (td, *J* = 13.0, 5.3 Hz, 1H), 1.02 (t, *J* = 12.0 Hz, 1H), 0.91 (d, *J* = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 213.5, 156.8, 80.1, 55.9, 48.6, 45.0, 44.9, 39.9, 39.6, 37.0, 35.3, 33.3, 28.4, 22.0, 20.8; FTIR (cm^{-1}) (neat) 2929, 2859, 1717, 1700, 1455, 1152, 1071; HRMS (ESI, Pos) calcd for $C_{17}H_{27}NO_3$ $[M + Na]^+$: 316.1883 *m*/*z*, found 316.1878 *m*/*z*.

***tert*-Butyl (1*S*,3*R*,4a*S*,7*R*,8a*R*)-6-(1-Diazo-2-ethoxy-2-oxoethyl)-6-hydroxy-3-methyldecahydro-1,7-(epiminomethano)-naphthalene-10-carboxylate (24).** To a stirred solution of ketone **23** (0.583 g, 1.987 mmol) in THF (24.84 mL) at −78 °C was added dropwise a cold solution of lithium di-isopropylamide (prepared from the addition of *n*-butyllithium (2.092 mL of a 1.52 M solution in hexanes, 3.18 mmol) to di-isopropylamine (0.481 mL, 3.38 mmol)), and then ethyl diazoacetate (0.309 mL, 2.98 mmol) was added. After stirring for 1 h at −78 °C, the reaction was quenched by the rapid addition of saturated NH_4Cl aqueous solution. The reaction mixture was extracted with Et_2O and washed with a saturated $NaHCO_3$ aqueous solution followed by a brine solution. The combined organic layers were dried over $MgSO_4$, filtered over silica gel eluting with Et_2O, and concentrated under reduced pressure to yield diazo **24** as a yellow oil. The crude product was used in the next step without further purification.

11-*tert*-Butyl 6-Ethyl (1*S*,3*R*,4a*S*,7*R*,8*R*,9a*R*)-3-Methyl-7-oxodecahydro-1H-1,8-(epiminomethano)benzo[7]annulene-6,11-dicarboxylate (S-5). A solution of diazo **24** (0.810 g, 1.987 mmol) and rhodium(II) acetate dimer (8.78 mg, 0.020 mmol) in DCM (39.7 mmol) was stirred at room temperature. After stirring 90 min, the solvent was removed under reduced pressure yielding the β-ketoester **S-5** as a light greenish oil. The crude product was used in the next step without further purification.

11-*tert*-Butyl 6-Ethyl (1*S*,3*R*,4a*S*,7*R*,8*R*,9a*R*)-7-Hydroxy-3-methyldecahydro-1*H*-1,8-(epiminomethano)benzo[7]annulene-6,11-dicarboxylate (25). To a stirred solution of the crude β-ketoester **S-5** (0.754 g, 1.987 mmol) in ethanol (19.9 mL) at 0 °C was added sodium borohydride (0.150 g, 3.97 mmol), and the mixture became yellow. After stirring overnight from 0 °C to room temperature, the reaction was quenched with the slow addition of 1 N HCl. The reaction mixture was extracted with DCM, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography of the yellow oily residue with EtOAc/hexanes (20/80) afforded 0.464 g of alcohol **25** (61%, 3 steps) as a yellowish oil. $[\alpha]^{20}_D$ = +51.7 (*c* 0.755. $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 4.50 (td, *J* = 8.0, 4.0 Hz, 1H), 4.16−4.02 (m, 3H), 3.85 (d, *J* = 8.0 Hz, 1H), 3.60−3.55 (m, 1H), 3.16 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.82 (dd, *J* = 10.0, 3.0 Hz, 1H), 2.58 (br d, *J* = 16.0 Hz, 1H), 2.50−2.41 (m, 1H), 2.11−2.04 (m, 2H), 1.95−1.77 (m, 5H), 1.73−1.61 (m, 2H), 1.47 (s, 9H), 1.34−1.27 (1H), 1.22 (t, *J* = 8.0 Hz, 3H), 1.14−1.04 (m, 1H), 0.88 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 173.7, 154.7, 79.2, 71.7, 59.6, 56.6, 49.6, 45.7, 42.2, 39.8, 39.6, 37.0, 35.5, 29.8, 29.1, 27.8, 23.4, 22.2, 13.7; FTIR (cm^{-1}) (neat) br 3435, 2927, 17.37, 16.44, 1455, 1250, 1160; HRMS (ESI, Pos) calcd for $C_{21}H_{35}NO_5$ $[M + H]^+$: 382.2588 *m*/*z*, found 382.2599 *m*/*z*.

***tert*-Butyl (1*S*,3*R*,4a*S*,5*R*,7*R*,8a*R*)-5-Bromo-3-methyl-6-oxodecahydro-1,7-(epiminomethano)naphthalene-10-carboxylate (26).** To a stirred solution of ketone **23** (0.785 g, 2.68 mmol) in THF (31.5 mL) at 0 °C was slowly added phenyltrimethylammonium

tribromide (1.006 g, 2.68 mmol). The reaction mixture was stirred at 0 °C for 15 min followed by an additional 15 min at room temperature. The solution became white and cloudy. Water and Et_2O were added, the layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered over Celite, and concentrated under reduced pressure. Flash chromatography of the gray solid with EtOAc/hexanes (15/85) afforded 0.820 g of bromoketone **26** (82%) as a white solid, mp 168−171 °C. $[\alpha]^{20}_D$ = +129.9 (*c* 0.535. $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.14 (d, *J* = 12.0 Hz, 1H), 4.10 (dt, *J* = 13.3, 2.0 Hz, 1H), 3.50−3.47 (m, 1H), 3.32−3.26 (m, 1H), 3.02 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.88 (br s, 1H), 2.43−2.36 (m, 1H), 2.29−2.21 (m, 1H), 2.07−1.77 (m, 4H), 1.47 (s, 9H), 1.35−1.26 (m, 1H), 1.13−1.04 (m, 1H), 0.98 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.3, 156.8, 80.8, 60.3, 56.0, 48.2, 48.2, 45.9, 39.9, 38.2, 38.2, 33.3, 28.4, 21.8, 20.7; FTIR (cm^{-1}) (neat) 2929, 2867, 1709, 1366, 1297, 1158; HRMS (ESI, Pos) calcd for $C_{17}H_{26}BrNO_3$ $[M + H]^+$: 372.1169 *m*/*z*, found 372.1182 *m*/*z*.

(3*R*,4a*R*,5*S*,7*R*,8a*R*)-7-Methyloctahydro-1,5,3-(azanetriyl-methano)naphthalen-2(1*H*)-one (27). To a stirred solution of bromoketone **26** (1.42 g, 3.81 mmol) in DCM (9.54 mL) at 0 °C was added trifluoroacetic acid (9.54 mL). The reaction mixture was stirred 1 h at 0 °C and was then slowly added to a 500 mL erlenmeyer flask equipped with a stir bar and containing 150 mL of DCM and 150 mL of 10% Na_2CO_3 aqueous solution. The mixture was stirred for 30 min, the layers were separated, and the aqueous layer was extracted with DCM. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure yielding 0.730 g of tetracycle **27** (99%) as a beige solid, mp 44−47 °C. $[\alpha]^{20}_D$ = +58.4 (*c* 0.640. $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.38 (d, *J* = 4.4 Hz, 1H), 3.30 (d, *J* = 14.0 Hz, 2H), 3.17 (d, *J* = 12.0 Hz, 1H), 2.55 (br s, 1H), 2.29 (d, *J* = 2.4 Hz, 1H), 2.07 (d, *J* = 13.2 Hz, 1H), 2.00 (br s, 1H), 1.98−1.89 (m, 1H), 1.89−1.81 (m, 2H), 1.79−1.65 (m, 1H), 1.11 (t, *J* = 13.2 Hz, 1H), 0.99 (t, *J* = 12.0 Hz, 1H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.7, 71.0, 70.1, 60.2, 55.0, 45.2, 43.7, 40.3, 38.2, 35.7, 25.4, 21.3; FTIR (cm^{-1}) (neat) 2924, 2870, 1756, 1456, 1025, 958, 733; HRMS (ESI, Pos) calcd for $C_{12}H_{17}NO$ $[M + Na]^+$: 214.1202 *m*/*z*, found 214.1213 *m*/*z*.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR, ^{13}C NMR, and HPLC chromatograms for the determination of the enantiomeric ratio **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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