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Synthesis and Reactivity of Bicyclo[3.2.1]octanoid-Derived Cyclopropanes

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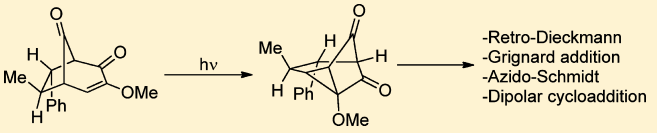
Supporting Information

ABSTRACT: Photochemical oxa-di-π-methane rearrangement of bicyclo[3.2.1]octanoid scaffolds affords multifunctional, donor–acceptor cyclopropanes. A related photochemical reaction of an iminium ether substrate uncovered an unprecedented aza-di-π-methane rearrangement of a β,γ-unsaturated iminium. Donor–acceptor cyclopropanes have been evaluated as substrates for reactions generating several new chemotypes.



INTRODUCTION

The generation of architecturally interesting small molecules for biological screening can be facilitated by synthesis of under-represented scaffold types and by exploring novel reaction pathways.[1] As part of a general program directed toward enhancing molecular diversity, we have reported use of bicyclo[3.2.1]-octanoids as multifunctional scaffolds for the discovery of reactions leading to new chemotypes.[1,2] In this paper, we describe the extension of these efforts to include photochemical rearrangements followed by further transformations that efficiently transform bicyclo[3.2.1]octanoids into new structural types.

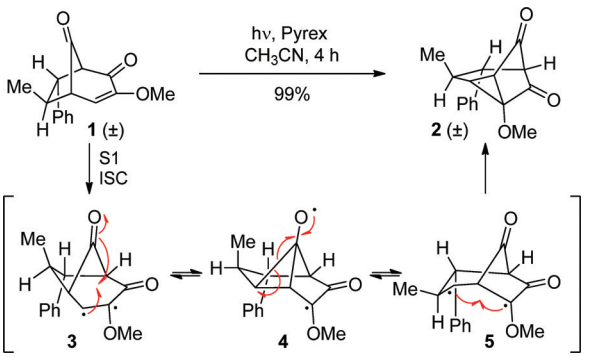
RESULTS AND DISCUSSION

We chose to include scaffold **1** in a photochemical multidimensional reaction screen[3] in anticipation that an oxa-di-π-methane rearrangement[4,5] would be possible because of the presence of a β,γ-unsaturated ketone moiety within the substrate. Accordingly, UV irradiation (>275 nm) of **1** in the absence of a triplet sensitizer afforded cyclopropane **2** in quantitative yield. Although oxa-di-π-methane rearrangements often require triplet sensitization,[3] we believe that in this case the enone functionality of **1** undergoes singlet excitation followed by intersystem crossing (ISC) to the required triplet state (**3**) (*cf.* Scheme 1). In order to access additional cyclopropane scaffolds, we carried out analogous reactions on a series of bicyclo[3.2.1]octanoids (Scheme 2). We found that the oxa-di-π-methane rearrangement was limited to bicyclo[3.2.1]octanoids containing α,β-unsaturated ketones (**6**, **7**, **10**). For example, tertiary alcohol **12**[2a] and the ring-opened cycloheptenone **13**[2a] failed to react under direct irradiation or with triplet sensitization using benzoquinone.

To introduce nitrogen into the skeletal framework, we next investigated the photochemical reactivity of iminium ethers **14** and **15**, compounds derived from bicyclo[3.2.1]octanoid **1** using azido-Schmidt reaction conditions.[2b] Accordingly, photoirradiation of a mixture of **14**/**15** (>275 nm) in acetone afforded cyclopropane **16** (Scheme 3). Structure assignment was confirmed using 1D and 2D NMR analyses of hydrolysis product **17**.[6] The photochemical reaction producing **16** is presumed to proceed through an analogous aza-di-π-methane rearrangement of iminium ether **14**.[7] As isomer **15** lacks a β,γ-unsaturated iminium, it was unable to undergo the equivalent photochemical transformation. To the best of our knowledge, this is the first report of an aza-di-π-methane rearrangement of a β,γ-unsaturated iminium substrate. As previously demonstrated with similar substrates,[2b,8] the rearranged iminium ether **16** could be readily hydrolyzed or undergo nucleophilic ring-opening to afford cyclopropyl amides **17**-**19**.

One reason for our interest in scaffolds derived from oxa-di-π-methane rearrangement was the expectation that the strained cyclopropane would facilitate the discovery of novel transformations. Accordingly, we probed the cyclopropane scaffolds for additional reactivity patterns. For example, addition of *p*-bromobenzylamine to cyclopropane **2** afforded *N*-acyl hemiaminal **20** in good yield (82%) (Scheme 4). This reaction is

Scheme 1. Oxa-di-π-methane Rearrangement of Bicyclo[3.2.1]octanoid Substrate 1



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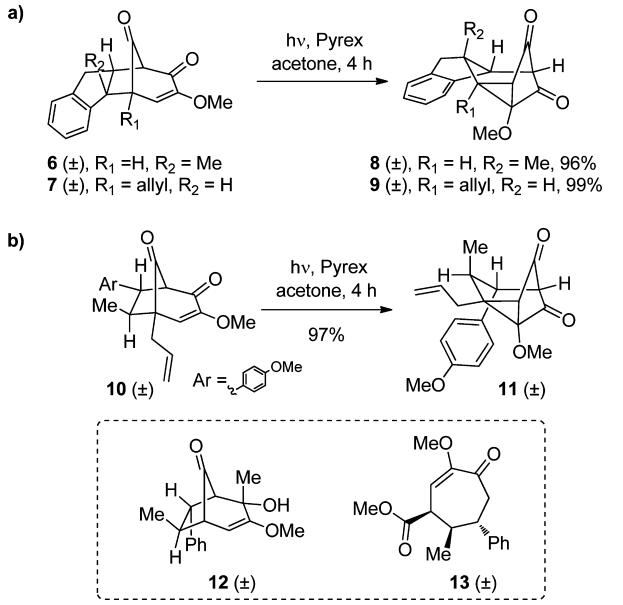
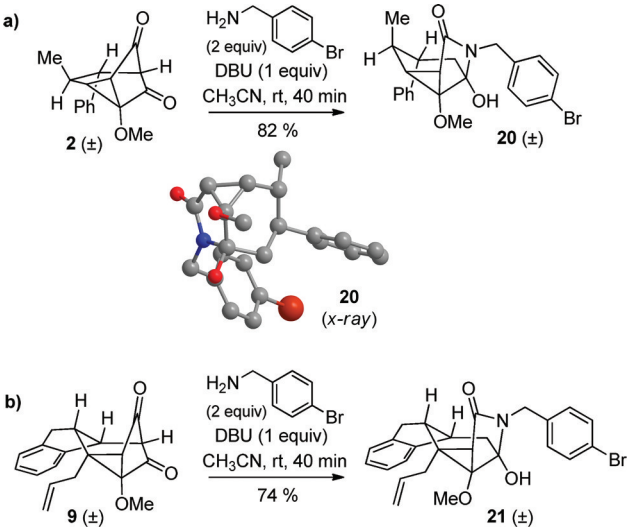
Scheme 2. Scope of the Oxa-di-π-methane Rearrangement



analogous to a previously reported process and occurs through retro-Dieckmann-type fragmentation followed by ring closure.[2a] X-ray crystallographic analysis confirmed the structure of **20**, which also provided further verification of the structure of parent cyclopropane **2**.[6] Similar reactivity was observed when scaffold **9** was subjected to *p*-bromobenzylamine in the presence of DBU, affording *N*-acyl hemiaminal **21** in good yield (74%).

Utilizing Grignard reagents led to the face- and regioselective addition to the β-methoxy ketone of **2**, affording tertiary alcohol **22** as a single diastereomer (Scheme 5a). Diastereoselectivity is derived from selective *si*-face attack likely because of high steric congestion at the *re*-face imparted by the methyl and pseudoaxial hydrogen of the adjacent stereocenter. Regioselectivity of this transformation was in contrast to a similar reaction with the parent bicyclo[3.2.1]octanoid scaffold **1**, which favored selective addition to the diosphenol ether carbonyl.[2a] Interestingly, when the reaction was warmed to room temperature, further rearrangement to dihydrofuran **23** occurred (Scheme 5b). A similar conversion was observed when **2** was treated with 3-methoxyphenylmagnesium bromide, producing dihydrofuran **24**. Alternatively, Grignard additions to cyclopropane **9** afforded exclusively alcohols **25** and **26**

Scheme 4. Retro-Dieckmann-Type Fragmentation/ Annulation

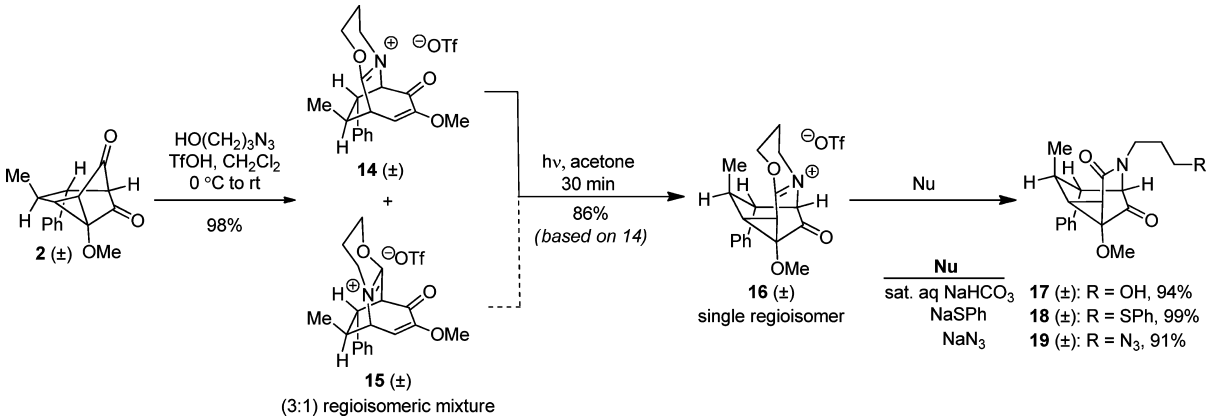


(Scheme 5c and d) without rearrangement. Attempts to access the analogous dihydrofuran product by reaction of **9** with 3-methoxyphenylmagnesium bromide and warming the reaction to room temperature resulted in epimerization of the tertiary alcohol (*epi*-**26**) but no further rearrangement. Reaction of lactam **17** with either methylmagnesium bromide or methyllithium resulted in the production of tertiary alcohol **27** (Scheme 5e).

We propose that the transformation from **2** to **23** proceeds *via* retro-aldol fragmentation of adduct **28** to the intermediate magnesium enolate **29** (Scheme 6). Subsequent cyclopropyl ketone-dihydrofuran rearrangement[8] via oxyallyl cation **30** affords dihydrofuran **23**. The inability of bicyclic scaffold **9** to rearrange to a benzofuran product (Scheme 5c) may be due to a faster rate of recyclization to the tertiary alcohol. It should be noted that cyclopropanes **8** and **11** were also resistant to rearrangement, suggesting that greater structural rigidity and/or functionality of these substrates in comparison to cyclopropane **2** may have an effect on the rate of cyclization versus rearrangement.

Further transformations of tertiary alcohol **22** could also be carried out utilizing azido-Schmidt reaction conditions (Scheme 7). Reaction of **22** in the presence of 3-azido-1-propanol and triflic acid afforded bicyclic imide **31**, albeit in low yield (18%).[9]

Scheme 3. Aza-di-π-methane Rearrangement of an Iminium Ether Substrate



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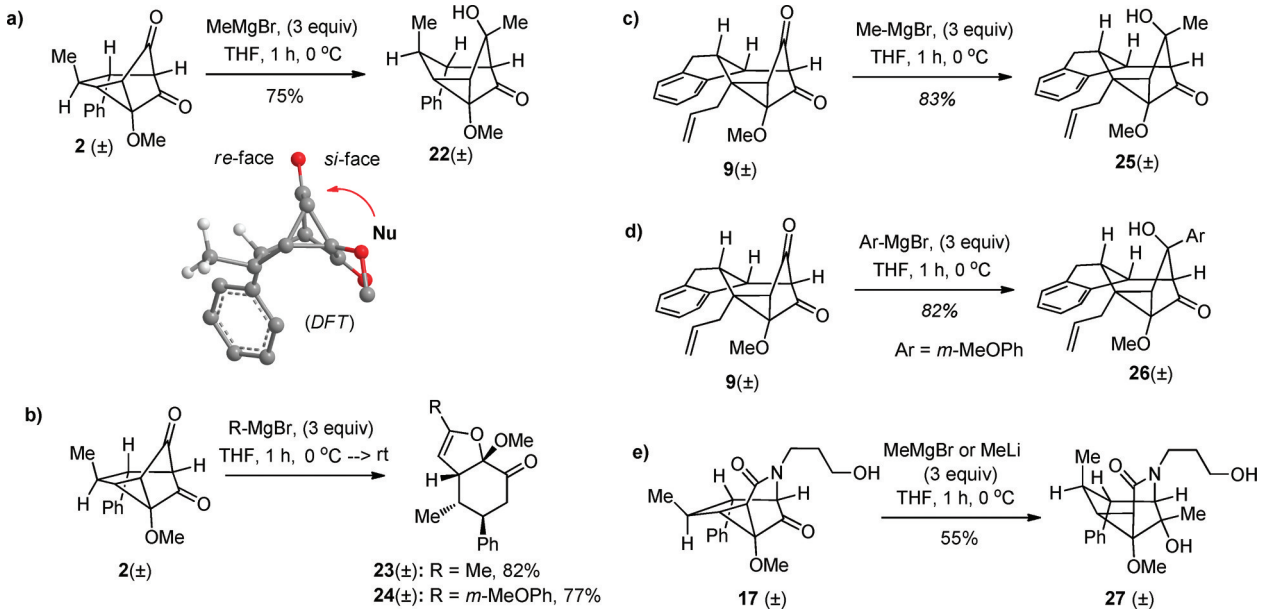
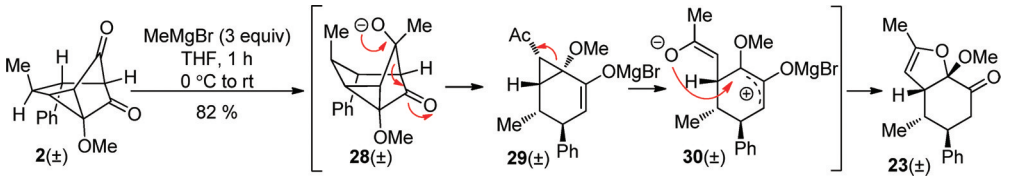
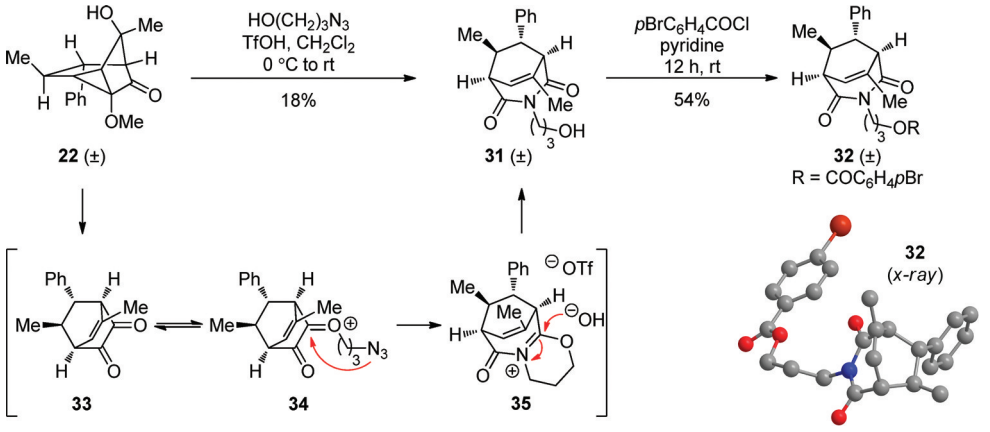
Scheme 5. Grignard Addition to Cyclopropane Scaffolds



Scheme 6. Rearrangement of Cyclopropane 2 to Dihydrofuran 23



Scheme 7. Fragmentation and Azido-Schmidt Ring Expansion



The structure was confirmed by X-ray crystallographic analysis of the derived *p*-bromobenzoate **32**.[6] We believe that, under strong Brønsted acid conditions, Grob-type fragmentation occurs with elimination of water leading to the formation of diketone intermediate **33**.[10] Subsequent azido-Schmidt ring expansion *via* intermediates **34** and **35** produces the corresponding imido alcohol **31**. An alternative mechanism is also possible, proceeding first with the azido-Schmidt reaction followed by fragmentation. On the basis of our current results, we are unable to differentiate between these two possibilities. Moreover, attempts to isolate the putative 1,2-diketone intermediate **33** were unsuccessful. We provisionally favor the former mechanism because previous azido-Schmidt transformations of α-methoxy ketones like **22** favored migration of the unsubstituted carbon, which is opposite to that observed here.[11]

Analogous treatment of alcohols **26** and *epi*-**26** gave a mixture of imide **36** and macrocyclic amide **37** in slightly varying ratios (Scheme 8). In this instance, it is possible that the reaction pathway diverges at the azido-Schmidt aminal intermediate, which may rearrange to afford either imide or amide products (Scheme 8, inset). Previous studies of iminium ethers have revealed a correlation between the nature of the quenching reagent and preferred modes of ring-opening, suggesting that the product ratio between **34** and **35** may be controlled by altering the workup protocol.[12] In addition, the increased skeletal rigidity of **24** induced by the bulky aromatic

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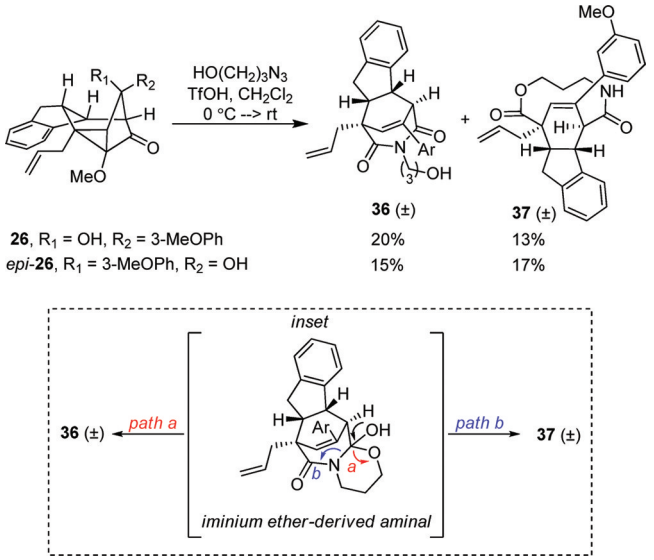
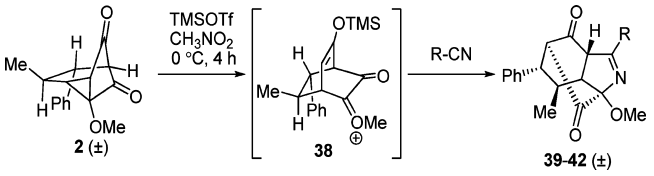
Scheme 8. Fragmentation-Expansion Pathways

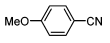


ring may also influence the overall strain of the system leading to the observed mixture of products.

Cyclopropanes with donor−acceptor character can lead to zwitterionic intermediates that may undergo cycloadditions in the presence of dipolarophiles. For example, donor−acceptor cyclopropanes may undergo ionization and further reaction upon treatment with TMSOTf.[13−15] Thus, we treated cyclopropane **2** with TMSOTf in acetonitrile, which afforded polycyclic imine **39** in moderate yield (51%), presumably through a dipole intermediate such as **38** (Table 1, entry 1).

Table 1. Cycloadditions of Donor−Acceptor Cyclopropane Substrates



entry	dipolarophile	product	yield (%)
1	Me−CN	**39**	51
2		**40**	94
3		**41**	80
4		**42**	47

Similar treatment with additional nitriles afforded cycloaddition products in good to excellent yields (Table 1, entries 2−4). X-ray crystallographic analysis confirmed the structure of cyclic imine **41** (Figure 1).[6] Similarly, cycloaddition of cyclopropane **9** and *p*-methoxy benzonitrile under analogous conditions afforded polycyclic imine **43** in moderate yield (54%) (Scheme 9). A number of additional dipolarophiles were investigated but did not participate in analogous cycloadditions. For example, dimethyl acetylenedicarboxylate, indole, maleimide, isonitriles, and enol ethers were all unsuccessful in our hands. Examination of a 3D model of the putative oxonium silyl ether intermediate **38** obtained from DFT calculations[5] reveals

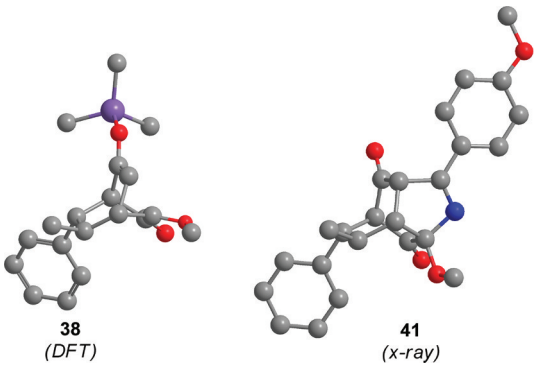
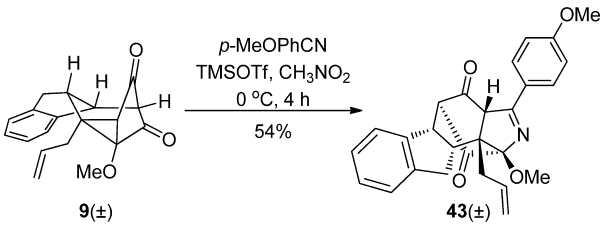


Figure 1. 3D structure of dipole **38** and X-ray crystal structure of **41**.

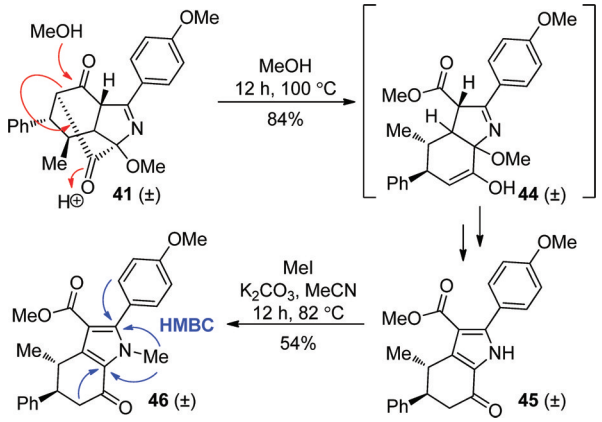
Scheme 9. Cycloaddition of Donor−Acceptor Cyclopropane 9



that this dipole equivalent retains significant cyclopropane character (1.8 Å distance between charged carbons). The dipole is also sterically congested, which may explain limitations of dipolarophiles to sterically non-demanding nitriles.

Polycyclic imine scaffold **41** displayed interesting reactivity when thermolyzed in MeOH (100 °C). The apparent product was the result of a retro-Dieckmann-type fragmentation to afford presumed intermediate (**44**), which may be followed by loss of methanol and aromatization affording pyrrole **45** in 84% yield (Scheme 10). Structural and regiochemical confirmation

Scheme 10. Fragmentation of Polycyclic Imine 41



of this product was achieved by 2D NMR analysis of the corresponding *N*-methylated pyrrole **46**.[6]

Overall, investigation of complex donor−acceptor cyclopropanes derived from oxa-di-π-methane rearrangement of bicyclo[3.2.1]octanoids led to several new and distinctive chemotypes from a single common starting point. The breadth of chemotypes accessed in this study further demonstrates the vast potential of complex and densely functionalized substrates

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for the rapid discovery of new and unique compounds. Further work will focus on expansion of reactions of cyclopropane scaffolds as well as utilization of these pathways for the construction of diverse collections of compounds including polycyclic imines and highly substituted pyrroles.

EXPERIMENTAL SECTION

General Information. All nuclear magnetic resonance spectra were recorded on either a Varian or Bruker spectrometer. ^{1}H NMR spectra were recorded at 400 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. ^{13}C NMR spectra were recorded at 100.0 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ 7.27; ^{13}C, δ 77.0) and acetone-d_6 (^{1}H, δ 2.05; ^{13}C, δ 30.8). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet) and coupling constants are reported as values in hertz. All ^{13}C NMR spectra were recorded with complete proton decoupling. Analytical LC was performed on a 2.1 × 50 mm 1.7 μM C18 column. Analytical thin-layer chromatography was performed using 0.25 mm silica gel 60-F plates. Otherwise, flash chromatography was performed using 200−400 mesh silica gel. Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. Acetonitrile, CH_2Cl_2, THF, and toluene were purified by passing through two packed columns of neutral alumina. All reactions were performed under an argon atmosphere in oven-dried or flame-dried glassware. The stainless steel needles used for handling anhydrous solvents and reagents were oven-dried, cooled in a desiccator, and flushed with dry argon prior to use. Hydroxyalkyl azides were prepared from the corresponding hydroxyalkyl bromides according to previously published procedures.[8c] Photochemical reactions were carried out using a 400 W medium pressure mercury lamp.

General Procedure for Preparation of Cyclopropanes 2, 8, 9, and 11. To a dry Pyrex reaction vessel containing a small magnetic cross stir bar was added bicyclo[3.2.1]octanoid substrate (1.51 mmol) followed by the addition of acetone (10 mL). The reaction vessel was capped with a rubber septum and degassed by bubbling argon via balloon (15 min). The vessel was sealed by wrapping several layers of parafilm around the septa. Next, the reaction vessel was placed in a Hanovia lamp photoreactor with no filter (quartz) and was stirred at approximately 20 °C (rt) for 4 h. A small aliquot was analyzed by UPLC/MS/ELS, which indicated 100% conversion to product. The reaction was concentrated to afford the cyclopropane product, which was used without further purification. Note that cyclopropane products were found to be unstable to purification *via* silica gel chromatography.

(±)-Cyclopropane (2). Bicyclo[3.2.1]octanoid **1** (32 mg, 0.125 mmol) in 5 mL acetone afforded cyclopropane **2** (32 mg, 0.125 mmol, 99%) as a white crystalline solid: mp = 95−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 3 H), 7.14 (d, J = 7.0 Hz, 2 H), 3.61 (s, 3 H), 3.11 (dd, J = 8.9, 1.8 Hz, 1 H), 3.01 (dd, J = 6.4, 2.1 Hz, 1 H), 2.81 (dd, J = 8.9, 1.5 Hz, 1 H), 2.68 (dd, J = 2.1, 1.8 Hz, 1 H), 2.67−2.59 (dquin, J = 6.8, 1.5 Hz, 1 H), 1.25 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 199.7, 140.7, 128.9, 127.7, 127.4, 83.5, 61.2, 59.1, 58.2, 49.5, 47.9, 34.3, 20.5; IR (thin film) ν_{max} 2963, 2935, 1762, 1716, 1456, 1298, 1206, 1162, 1080, 1063, 887, 758, 735, 701 cm^{-1}. HRMS calculated for $C_{32}H_{32}O_6Na$: 535.2097, found 535.2091 (2M + Na).

(±)-Cyclopropane (8). 96% yield. White amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.21 (m, 2 H), 7.18−7.10 (m, 2 H), 3.62 (d, J = 3.5 Hz, 1 H), 3.50 (s, 3 H), 3.31 (d, J = 17.2 Hz, 1 H), 3.10 (dd, J = 9.0, 2.0 Hz, 1 H), 3.05 (d, J = 17.2 Hz, 1 H), 2.91 (ovrlp d, J = 9.0 Hz, 1 H), 2.91(ovrlp dd, J = 3.5, 2.0 Hz, 1H), 1.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 199.0, 140.8, 139.4, 128.6, 127.5, 125.1, 124.1, 82.6, 64.3, 60.8, 58.0, 55.0, 48.4, 46.7, 40.9, 28.7; IR (thin film) ν_{max} 2956, 1764, 1719, 1457, 1302, 1210, 1060, 758, 737 cm^{-1}. HRMS calculated for $C_{34}H_{32}O_6Na$: 559.2097, found 559.2117 (2M + Na).

(±)-Cyclopropane (9). 99% yield. White amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.07 (m, 4 H), 5.91 (ddd, J = 14.1, 8.3, 5.9 Hz, 1 H), 5.30−5.21 (m, 2 H), 4.01 (dd, J = 9.2, 3.0 Hz, 1 H), 3.53 (s, 3 H), 3.40−3.26 (m, 2 H), 3.00−2.92 (ovrlp m, 1 H), 2.94 (ovrlp dd, J = 3.0, 2.0 Hz, 1 H), 2.88 (d, J = 2.0 Hz, 1 H), 2.60 (dd, J = 15.1, 8.3 Hz, 1 H), 2.37 (dd, J = 15.1, 5.9 Hz, 1 H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 199.3, 141.2, 139.7, 133.2, 128.4, 127.4, 124.9, 124.1, 119.1, 85.8, 61.9, 58.2, 57.8, 55.8, 52.1, 37.6, 37.0, 35.1; IR (thin film) ν_{max} 2939, 1761, 1710, 1450, 1284, 1220, 1093, 1010, 879, 762 cm^{-1}. HRMS calculated for $C_{19}H_{18}O_3Na$: 317.1154, found 317.1142 (M + Na).

(±)-Cyclopropane (11). 97% yield. Viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 5.85 (dddd, J = 17.2, 9.9, 9.6, 4.5 Hz, 1 H), 5.23−5.13 (m, 2 H), 3.78 (s, 3 H), 3.60 (s, 3 H), 2.97 (dd, J = 6.3, 2.5 Hz, 1 H), 2.80 (d, J = 2.0 Hz, 1 H), 2.76 (dd, J = 14.7, 9.6 Hz, 1 H), 2.66 (dd, J = 2.5, 2.0 Hz, 1 H), 2.52 (dd, J = 6.6, 6.3 Hz, 1 H), 2.32−2.24 (m, 1 H), 1.18 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 199.8, 159.0, 133.3, 132.7, 128.6, 118.7, 114.2, 86.9, 61.9, 58.2, 57.8, 56.5, 55.2, 51.9, 36.0, 35.0, 18.0; IR (thin film) ν_{max} 2936, 1761, 1713, 1611, 1514, 1250, 1216, 1182, 1034, 838 cm^{-1}. HRMS calculated for $C_{20}H_{23}O_4$: 327.1596, found 327.1597 (M + H).

(±)-Iminium Ether (16). A solution of polycyclic iminium ethers **14**/**15** (5.00 mg, 0.011 mmol) dissolved in acetone-d_6 (1.0 mL) in an NMR tube was placed in a Rayonet photoreactor (>275 nm) for 30 min. The solvent was then removed in vacuo. The isolated product required no additional purification and was found to be unstable to SiO_2. The reaction afforded 4.3 mg (86% corresponding to major isomer **14**) of **16** as a yellow oil: ^{1}H NMR (500 MHz, acetone-d_6) δ 7.35−7.38 (m, 2H), 7.27−7.32 (m, 3H), 5.07 (ddt, J = 2.0, 4.5, 11.0, 1H), 4.83 (ddd, J = 4.0, 10.5, 11.5, 1H), 4.23−4.28 (m, 1H), 4.04 (d, J = 3.0, 1H), 3.98 (ddd, J = 5.5, 10.0, 14.5, 1H), 3.90 (s, 1H), 3.57 (s, 3H), 3.30−3.34 (m, 3H), 2.54−2.66 (m, 2H), 1.47 (d, J = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 195.2, 172.6, 141.6, 130.6 (2), 129.7, 129.6 (2), 72.7, 72.4, 72.2, 58.9 53.9, 48.6, 45.2, 35.7, 34.3, 23.8, 21.4; IR (neat) ν_{max} 1739, 1652, 1274 cm^{-1}; MS (ES+) m/z 312.1 (M+). HRMS calculated for $C_{19}H_{22}NO_3^+$: 312.1600, found 312.1595 (M + H).

General Procedure for 17, 18, 19, and (±)-Amide (17). A solution of polycyclic iminium ether **14**/**15** (400 mg, 0.867 mmol) dissolved in acetone-d_6 (8.0 mL) divided among eight NMR tubes was irradiated in a photoreactor at 300 nm for 1 h. The solutions were combined, and the solvent was removed in vacuo. The residue was taken up in CH_2Cl_2 (10 mL), and saturated aq $NaHCO_3$ (10 mL) was added. The biphasic mixture was vigorously stirred for 3 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine, dried (anhydrous Na_2SO_4), filtered, and concentrated to give pure product. The reaction afforded 268 mg (94% corresponding to major regioisomer **14**) of **17** as a fluffy, yellow solid: mp = 98.0−100.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.5 Hz, 2H), 7.25−7.28 (m, 1H), 7.11 (d, J = 7.0 Hz, 2H), 4.02 (ddd, J = 4.5, 10.0, 14.0 Hz, 1H), 3.57−3.62 (m, 1H), 3.57 (s, 3H), 3.45 (ddd, J = 3.5, 9.5, 12.5 Hz, 1H), 3.36 (d, J = 2.5 Hz, 1H), 3.15 (t, J = 2.5 Hz, 1H), 2.99−3.04 (m, 2H), 2.68 (d, J = 10.5 Hz, 1H), 2.59 (ddd, J = 0.5, 5.5 Hz, 10.5, 1H), 1.74−1.80 (m, 1H), 1.57−1.65 (m, 1H), 1.36 (d, J = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 198.0, 167.8, 140.9, 129.1 (2), 127.7, 127.1 (2), 70.2, 67.7, 58.0, 57.4, 55.2, 42.9, 41.9, 36.8, 33.4, 30.1, 22.3; IR (neat) ν_{max} 3421, 1726, 1648, 1265 cm^{-1}. HRMS calculated for $C_{19}H_{24}NO_4$: 330.1705, found 330.1709 (M + H).

(±)-Cyclopropane (18). Purified by flash chromatography (SiO_2, 7:100, MeOH/CH_2Cl_2). 99% yield according to reaction of the major regioisomer. Yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.34 (m, 7H), 7.16−7.20 (m, 1H), 7.05−7.07 (m, 2H), 3.85 (ddd, J = 7.2, 13.6, 14.4 Hz, 1H), 3.55 (s, 3H), 3.36 (d, J = 2.4 Hz, 1H), 3.14 (dt, J = 6.8, 14.0 Hz, 1H), 3.08 (t, J = 2.4 Hz, 1H), 2.90−3.02 (m, 1H), 2.90 (t, J = 7.2 Hz, 2H), 2.65 (d, I = 10.4 Hz, 1H), 2.55 (ddd, J = 0.8, 5.2, 10.4 Hz, 1H), 1.86 (p, J = 7.2 Hz, 2H), 2.32 (d, J = 7.2 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 198.0, 166.5, 140.9, 136.9, 135.3, 130.6, 129.7, 129.1, 129.0, 127.6, 127.3, 127.0, 126.3, 70.0, 67.9, 57.4, 55.4, 45.6,

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41.7, 36.9, 33.2, 31.0, 27.3, 22.2; IR (neat) ν_{max} 1726, 1662, 1477 cm^{-1}. HRMS calculated for $C_{25}H_{28}NO_3S$: 422.1790, found 422.1777 (M + H).

(±)-Cyclopropane (19). Purified by flash chromatography (SiO_2, 7:100, $MeOH/CH_2Cl_2$). 91% yield according to reaction of the major regioisomer. Yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.22−7.35 (m, 3H), 7.10−7.12 (m, 2H), 3.90 (dt, J = 7.0, 14.0 Hz, 1H), 3.57 (s, 3H), 3.39 (d, J = 2.5 Hz, 1H), 3.32−3.36 (m, 2H), 3.13 (t, J = 2.5 Hz, 1H), 2.95−3.03 (m, 2H), 2.67 (d, J = 10.5 Hz, 1H), 2.57 (ddd, J = 1.0, 5.5, 10.5 Hz, 1H), 1.77−1.84 (m, 2H), 1.34 (d, J = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 198.0, 166.6, 140.9, 129.1 (2), 127.7, 127.0 (2), 70.0, 68.0, 57.4, 55.3, 48.7, 44.2, 41.7, 36.9, 33.3, 27.4, 22.2; IR (neat) ν_{max} 2098, 1726, 1650 1456 cm^{-1}. HRMS calculated for $C_{19}H_{22}N_4O_3Na$: 377.1590, found 377.1653 (M + Na).

(±)-*N*-Acylhemiaminal (20). To a dry vial containing a small magnetic stir bar was added cyclopropane **2** (50 mg, 0.195 mmol) and 1.2 mL DMSO followed by the addition of 4-bromobenzylamine (49.3 μL, 0.390 mmol). DBU (35.0 μL, 0.195 mmol) was added quickly, and the reaction was stirred for 45 min at rt. The reaction was quenched by addition of acetic anhydride (390 μL of 10% by volume in DMSO, ~0.390 mmol) followed by continued stirring for 10 min. DMSO was removed by partitioning the reaction into water and extracting the product with CH_2Cl_2 (10 mL × 3). The organic fractions were combined, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude extract was purified by flash chromatography (SiO_2, 1:1 Hex/EtOAc) to afford *N*-acylhemiaminal **20** as a white solid: mp = 197−198 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.39 (m, 2 H), 7.34−7.30 (m, 2 H), 7.28 (s, 2 H), 7.24−7.18 (m, 1 H), 6.91 (d, J = 6.6 Hz, 2 H), 4.43 (d, J = 14.8 Hz, 1 H), 4.04 (d, J = 14.8 Hz, 1 H), 3.59 (s, 3 H), 3.49 (s, 1 H), 2.33 (ddq, J = 10.6, 6.6, 5.5 Hz, 1 H), 2.24 (d, J = 9.8 Hz, 1 H), 2.16 (dd, J = 9.8, 5.5 Hz, 1 H), 2.08 (ovrlp d, J = 5.1 Hz, 1 H), 2.07 (ovrlp d, J = 11.3 Hz, 1 H), 1.70 (ddd, J = 11.3, 10.6, 5.1 Hz, 1 H), 0.92 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 142.8, 136.9, 131.6, 130.8, 128.6, 127.6, 126.9, 121.4, 87.7, 73.7, 58.4, 44.9, 42.1, 40.6, 36.5, 35.3, 31.4, 18.4; IR (thin film) ν_{max} 3345, 2957, 2929, 1668, 1488, 1453, 1401, 1134, 1070, 1013, 736, 703 cm^{-1}. HRMS calculated for $C_{23}H_{25}BrNO_3$: 442.1018, found 442.1024 (M + H).

(±)-*N*-Acylhemiaminal (21). Purified by flash chromatography (SiO_2, 30:70, CH_2Cl_2/EtOAc). 74% yield. Amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.43 (m, 2 H), 7.43−7.37 (m, 2 H), 7.20 (t, J = 7.4 Hz, 1 H), 7.17−7.10 (m, 2 H), 6.79 (d, J = 6.8 Hz, 1 H), 5.97 (dddd, J = 5.3, 7.9, 10.2, 17.2 Hz, 1 H), 5.28 (d, J = 17.2 Hz, 1 H), 5.19 (d, J = 10.2 Hz, 1 H), 4.48 (d, J = 14.7 Hz, 1 H), 4.22 (d, J = 14.5 Hz, 1 H), 3.61 (s, 1 H), 3.49 (s, 3 H), 3.21 (dd, J = 7.6, 15.1 Hz, 1 H), 2.95 (dd, J = 11.9, 15.1 Hz, 1 H), 2.82 (ddd, J = 6.8, 7.6, 11.9 Hz, 1 H), 2.63 (dd, J = 7.9, 15.0 Hz, 1 H), 2.43 (ddd, J = 4.3, 6.8, 12.9 Hz, 1 H), 2.14 (ovrlp dd, J = 5.3, 15.0 Hz, 1 H), 2.13 (ovrlp s, 1H), 2.05 (dd, J = 4.3, 13.9 Hz, 1 H), 1.62 (dd, J = 12.9, 13.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 145.2, 139.9, 136.9, 134.2, 131.5, 131.0, 127.1, 126.8, 124.4, 123.6, 121.5, 117.9, 88.1, 77.8, 58.9, 43.0, 42.1, 40.2, 38.6, 38.2, 36.9, 36.6, 36.3; IR (thin film) ν_{max} 3354, 2939, 1693, 1487, 1436, 1401, 1291, 1141, 1013, 756, 733 cm^{-1}. HRMS calculated for $C_{26}H_{27}BrNO_3$: 480.1174, found 480.1183 (M + H).

(±)-Tertiary Alcohol (22). To an oven-dried vial was added cyclopropane **2** (40 mg, 0.156 mmol) and anhydrous THF (4.0 mL). The reaction mixture was cooled to 0 °C while under argon. To this mixture was added 3 M methyl magnesium bromide in THF (167 μL, 0.468 mmol) dropwise via syringe over 1 min while at 0 °C. The reaction was held at 0 °C for 1 h with continual stirring. The reaction was quenched while at 0 °C by addition of water (40 μL). This mixture was warmed to rt, diluted with water (20 mL), and extracted with CH_2Cl_2 (20 mL × 3). The organic fractions were combined, washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2/EtOAc) to afford tertiary alcohol **22** (31.9 mg, 0.117 mmol, 75%) as an amorphous white solid (single diastereomer by ^1H NMR): ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 2 H), 7.24−7.18 (m, 1 H), 7.15 (d, J = 7.0 Hz, 2 H), 3.53 (s, 3 H), 3.24 (dd, J = 6.6, 2.3 Hz, 1 H), 2.54−2.45 (m, 2 H), 2.19 (dd, J = 8.2, 2.0 Hz, 1 H), 2.01 (dd, J = 2.3, 2.0 Hz, 1 H), 1.99 (s, 1 H), 1.46 (s, 3 H), 1.28 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 143.6, 128.5, 128.1, 126.8, 75.8, 71.2, 58.7, 57.4, 49.4, 41.8, 41.1, 33.4, 28.4, 20.4; IR (thin film) ν_{max} 3446, 2962, 2930, 1717, 1456, 1375, 1148, 1110, 1053, 701 cm^{-1}. HRMS calculated for $C_{17}H_{21}O_3$: 273.1491, found 273.1503 (M + H).

(±)-(3a*S*,4*R*,5*S*,7a*R*)-7a-Methoxy-2,4-dimethyl-5-phenyl-3a,4,5,6-tetrahydrobenzofuran-7(7a*H*)-one (23). To an oven-dried vial was added cyclopropane **2** (40 mg, 0.156 mmol) and anhydrous THF (4.0 mL). The reaction mixture was cooled to 0 °C while under argon. To this mixture was added 3 M methyl magnesium bromide in THF (167 μL, 0.468 mmol) dropwise via syringe over 1 min while at 0 °C. The reaction was held at 0 °C with continued stirring for 15 min and then warmed to rt for additional 1 h. The reaction was cooled back to 0 °C and then quenched with the addition of water (40 μL). This mixture was warmed to rt, diluted with water (20 mL), and extracted into CH_2Cl_2 (20 mL × 3). The organic fractions were combined, washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2/EtOAc) to afford acetal **23** (34.8 mg, 0.128 mmol, 82%) as an amorphous white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.28 (m, 2 H), 7.25−7.19 (m, 1 H), 7.13 (d, J = 7.0 Hz, 2 H), 4.78−4.72 (m, 1 H), 3.49 (s, 3 H), 3.26−3.18 (m, 1 H), 3.03 (dd, J = 16.4, 8.2 Hz, 1 H), 2.91 (ddd, J = 11.6, 9.0, 8.2 Hz, 1 H), 2.51 (dd, J = 16.4, 9.0 Hz, 1 H), 2.06−1.94 (m, 4 H), 0.62 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 155.1, 143.6, 128.6, 127.7, 126.6, 107.6, 95.5, 56.2, 51.5, 45.8, 43.1, 37.2, 16.2, 13.5; IR (thin film) ν_{max} 3420, 2958, 2926, 1722, 1453, 1373, 1220, 1204, 1131, 1095, 1056, 1037, 1007, 761, 702 cm^{-1}. HRMS calculated for $C_{17}H_{20}O_3Na$: 295.1310, found 295.1314 (M + Na).

(±)-(3a*S*,4*R*,5*S*,7a*R*)-7a-Methoxy-2-(3-methoxyphenyl)-4-methyl-5-phenyl-3a,4,5,6-tetrahydrobenzofuran-7(7a*H*)-one (24). Purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2/EtOAc). 77% yield. Amorphous white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.25 (m, 4 H), 7.24−7.19 (m, 2 H), 7.11 (d, J = 7.0 Hz, 2 H), 6.96−6.91 (m, 1 H), 5.56−5.47 (m, 1 H), 3.87 (s, 3 H), 3.56 (s, 3 H), 3.46−3.37 (m, 1 H), 3.12 (dd, J = 16.9, 8.5 Hz, 1 H), 2.98 (ddd, J = 11.9, 8.9, 8.5 Hz, 1 H), 2.54 (dd, J = 16.9, 8.9 Hz, 1 H), 2.14−2.00 (m, 1 H), 0.71 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 159.7, 155.8, 143.5, 130.9, 129.6, 128.7, 127.7, 126.7, 118.0, 114.8, 110.8, 107.3, 95.8, 56.6, 55.4, 51.7, 45.9, 43.0, 37.6, 16.3; IR (thin film) ν_{max} 2959, 1732, 1601, 1582, 1490, 1454, 1288, 1264, 1208, 1132, 1032, 771, 702 cm^{-1}. HRMS calculated for $C_{23}H_{25}O_4$: 365.1753, found 365.1842 (M + H). Calculated for mass spectrometer hydrolysis: $C_{22}H_{23}O_4$: 351.1596, found 351.1634.

(±)-Tertiary Alcohol (25). Purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2/EtOAc). 83% yield. Amorphous white solid (single diastereomer by ^1H NMR): ^1H NMR (400 MHz, $CDCl_3$) δ 7.19−7.07 (m, 4 H), 5.92 (dddd, J = 17.0, 10.1, 8.1, 5.7 Hz, 1 H), 5.29−5.14 (m, 2 H), 3.97 (dd, J = 9.4, 3.5 Hz, 1 H), 3.44−3.40 (m, 3 H), 3.36 (dd, J = 16.5, 9.8 Hz, 1 H), 3.25−3.17 (m, 1 H), 2.90 (dd, J = 16.5, 6.0 Hz, 1 H), 2.56 (dd, J = 14.9, 8.1 Hz, 1 H), 2.38 (dd, J = 3.5, 1.6 Hz, 1 H), 2.27 (d, J = 1.6 Hz, 1 H), 2.16 (dd, J = 14.9, 5.7 Hz, 1 H), 1.95 (s, 1 H), 1.46 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 142.2, 141.6, 134.7, 127.3, 126.9, 124.6, 123.9, 117.8, 78.7, 71.7, 59.1, 57.6, 48.3, 47.2, 46.5, 38.5, 34.9, 34.8, 27.8; IR (thin film) ν_{max} 3443, 2962, 2929, 1718, 1447, 1377, 1178, 1149, 1102, 1024, 932, 752, 735 cm^{-1}. HRMS calculated for $C_{20}H_{22}O_3Na$: 333.1467, found 333.1462 (M + Na).

(±)-Tertiary Alcohol (26). To an oven-dried vial was added cyclopropane **9** (50.0 mg, 0.170 mmol) and anhydrous THF (4.0 mL). The reaction mixture was cooled to 0 °C while under argon. To this mixture was added 1 M 3-methoxyphenyl magnesium bromide in THF (510 μL, 0.510 mmol) dropwise via syringe over 1 min while at 0 °C. The reaction was held at 0 °C for 1 h with continual stirring. The reaction was quenched while at 0 °C with the addition of water (40 μL). This mixture was warmed to room temperature, diluted with water (20 mL), and extracted into CH_2Cl_2 (20 mL × 3). The organic fractions were combined, washed with brine (20 mL), dried over

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sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2/EtOAc) to afford tertiary alcohol **26** (56.3 mg, 0.140 mmol, 82%) as an amorphous white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.22 (m, 1 H), 7.16−7.13 (m, 4 H), 7.13−7.10 (m, 1 H), 7.09−7.05 (m, 1 H), 6.83 (dd, J = 8.2, 2.3 Hz, 1 H), 5.98 (dddd, J = 17.1, 10.2, 8.0, 5.7 Hz, 1 H), 5.32−5.18 (m, 2 H), 4.20 (dd, J = 9.1, 3.7 Hz, 1 H), 3.79 (s, 3 H), 3.40 (dd, J = 15.8, 9.8 Hz, 1 H), 3.36−3.31 (m, 1 H), 3.31 (s, 3 H), 2.94 (dd, J = 15.8, 5.3 Hz, 1 H), 2.86−2.79 (m, 1 H), 2.63 (dd, J = 15.1, 8.0 Hz, 1 H), 2.55−2.47 (m, 1 H), 2.23 (ovrlp dd, J = 15.1, 5.7 Hz, 1 H), 2.22 (ovrlp s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 160.0, 146.5, 142.0, 141.7, 134.6, 129.9, 127.4, 126.9, 124.6, 124.0, 117.8, 117.2, 113.6, 111.0, 78.8, 75.4, 59.0, 58.0, 55.3, 48.6, 48.2, 46.8, 38.6, 34.9, 34.8; IR (thin film) ν_{max} 3441, 2935, 1730, 1601, 1486, 1292, 1261, 1047, 752, 735, 701 cm^{-1}. HRMS calculated for $C_{26}H_{26}O_4Na$: 425.1729, found 425.1739 (M + Na).

(±)-Tertiary Alcohol (*epi*-26). To an oven-dried vial was added cyclopropane **9** (60.0 mg, 0.204 mmol) and anhydrous THF (6.0 mL). The reaction mixture was cooled to 0 °C while under argon. To this mixture was added 1 M 3-methoxyphenyl magnesium bromide in THF (612 μL, 0.612 mmol) dropwise via syringe over 1 min while at 0 °C. The reaction was stirred for 15 min and then warmed to room temperature with continued stirring for 1 h. The reaction was cooled back down to 0 °C and quenched while at 0 °C with the addition of water (40 μL). This mixture was warmed to room temperature, diluted with water (20 mL), and extracted into CH_2Cl_2 (20 mL × 3). The organic fractions were combined, washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2/EtOAc) to afford tertiary alcohol **26** (9.3 mg, 0.023 mmol, 11%) and tertiary alcohol *epi*-**26** (45.5 mg, 0.113 mmol, 55%) as amorphous white solids. Tertiary alcohol **26**: R_f = 0.37 (30:1, CH_2Cl_2/EtOAc); R_f = 0.58 (20:1 CH_2Cl_2/EtOAc). Tertiary alcohol *epi*-**26**: R_f = 0.08 (30:1, CH_2Cl_2/EtOAc); R_f = 0.19 (20:1 CH_2Cl_2/EtOAc). Characterization data for *epi*-**26**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, J = 8.0 Hz, 1 H), 7.16 (d, J = 7.8 Hz, 1 H), 7.13−7.06 (m, 4 H), 7.02−6.98 (m, 1 H), 6.91 (dd, J = 8.2, 2.3 Hz, 1 H), 6.23−6.09 (m, 1 H), 5.35−5.27 (m, 2 H), 3.86 (s, 3 H), 3.54 (s, 3 H), 3.28 (ddd, J = 16.4, 9.4, 4.7 Hz, 1 H), 3.02−2.96 (m, 2 H), 2.96−2.85 (m, 1 H), 2.64 (dd, J = 14.8, 8.2 Hz, 1 H), 2.62 (s, 1 H), 2.55 (d, J = 2.0 Hz, 1 H), 2.49 (s, 1 H), 2.37 (dd, J = 14.5, 7.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 160.0, 143.5, 141.5, 141.4, 134.3, 130.0, 127.5, 126.9, 124.5, 123.9, 118.7, 118.5, 114.0, 111.9, 79.1, 75.5, 60.4, 57.9, 55.4, 49.3, 49.1, 44.1, 38.3, 35.4, 35.0; IR (thin film) ν_{max} 3365, 2934, 1734, 1487, 1457, 1436, 1262, 1036, 752 cm^{-1}. HRMS calculated for $C_{26}H_{26}O_4Na$: 425.1729, found 425.1742 (M + Na).

(±)-Tertiary Alcohol (27). Methylmagnesium bromide (0.097 mL 3.0 M in Et_2O, 0.291 mmol) was added dropwise to a solution of **17** (32.0 mg, 0.97 mmol) in THF (0.75 mL) at 0 °C. The solution was warmed to rt and stirred for 1 h. The reaction was quenched with water (2.0 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5.0 mL). The organic extracts were collected, washed with brine, dried (anhydrous Na_2SO_4), filtered, and concentrated to afford 18.5 mg (55%, 0.534 mmol) of **27** as a yellow oil. (SiO_2, 5:100 MeOH/CH_2Cl_2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.41 (m, 2H), 7.29−7.33 (m, 2H), 7.20−7.25 (m, 1H), 3.82−3.89 (m, 1H), 3.59−3.66 (m, 1H), 3.50−5.58 (m, 1H), 3.49 (s, 3H), 3.23 (dp, J = 2.8, 6.8 Hz, 1H), 3.04−3.10 (m, 2H), 2.59 (d, J = 7.6 Hz, 1H), 2.17 (d, J = 10.4 Hz, 1H), 1.97 (dd, J = 2.8, 10.4 Hz, 1H), 1.85 (brs, 1H), 1.71−1.80 (m, 1H), 1.53−1.64 (m, 1H), 1.48 (s, 3H), 1.15 (d, J = 7.2 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.1, 143.1, 128.7 (2), 128.5 (2), 126.8, 72.5, 69.2, 68.8, 58.3, 57.0, 52.4, 43.1, 33.1, 32.5, 30.0, 29.8, 24.3, 22.7; IR (neat) ν_{max} 3364, 2921, 1627 cm^{-1}. HRMS calculated for $C_{20}H_{28}NO_4$: 346.2018, found 346.2014 (M+1).

(±)-3-(3-Hydroxypropyl)-6,8-dimethyl-7-phenyl-3-azabicyclo[3.2.2]non-8-ene-2,4-dione (31). 3-Azido-1-propanol (39.3 mg, 0.390 mmol) was added to a solution of **22** (106 mg, 0.390 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C, and the solution was stirred for 5 min. Triflic acid (1.13 M in CH_2Cl_2/MeCN) (1.03 mL, 1.17 mmol) was slowly added dropwise and the solution gradually turned black. The triflic acid stock solution was prepared fresh by the addition of triflic acid (0.20 mL) to a mixture of CH_2Cl_2 (1.45 mL) and MeCN (0.35 mL). The solution was gradually warmed to room temperature and stirred for 12 h. The reaction was diluted with CH_2Cl_2 (5.0 mL) and quenched by the addition of saturated aq $NaHCO_3$ (5.0 mL), and the biphasic solution was stirred at room temperature for 2 h. The layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by SiO_2 preparative TLC (1:10, MeOH/CH_2Cl_2) to afford **31** (21.5 mg, 18%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.27−7.24 (m, 1H), 7.19−7.10 (m, 2H), 5.93 (d, J = 7.0 Hz, 1H), 3.87 (td, J = 6.5, 2.0 Hz, 2H), 3.53 (dd, J = 7.5, 1.0 Hz, 1H), 3.51 (dd, J = 4.0, 1.5 Hz, 1H), 3.48−3.40 (m, 2H), 2.67−2.62 (m, 1H), 2.59 (dd, J = 7.5, 4.0 Hz, 1H), 1.94 (d, J = 1.5 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.2, 172.2, 141.4, 140.2, 128.8 (2), 127.6 (2), 127.5, 120.0, 60.6, 59.0, 53.9, 51.8, 37.8, 37.0, 30.7, 22.5, 21.1; IR (neat) ν_{max} 2962, 1729, 1710, 1656, 726 cm^{-1}. HRMS calculated for $C_{19}H_{24}NO_3$: 314.1756, found 314.1771 (M + H).

(±)-(6,8-Dimethyl-2,4-dioxo-7-phenyl-3-azabicyclo[3.2.2]non-8-en-3-yl)propyl-4-bromobenzoate (32). A solution of **31** (120 mg, 0.383 mmol) in CH_2Cl_2 (4.0 mL) was treated with pyridine (60.6 mg, 0.766 mmol), followed by 4-bromobenzoyl chloride (168 mg, 0.766 mmol). The reaction was stirred overnight at rt. The solution was quenched with brine (5.0 mL) and diluted with CH_2Cl_2 (5.0 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by SiO_2 preparative TLC (1:5, EtOAc/hexane) to afford **32** (140 mg, 73%) as a white solid. The pure material was recrystallized from EtOAc/hexane to give single crystals for X-ray analysis: mp = 99.5−100.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dt, J = 7.2, 1.6 Hz, 2H), 7.56 (dt, J = 7.2, 1.6 Hz, 2H), 7.32−7.29 (m, 2H), 7.27−7.23 (m, 1H), 7.11 (m, 2H), 5.91 (d, J = 5.6 Hz, 2H), 4.28 (t, J = 4.8 Hz, 2H), 3.91 (t, J = 6.0 Hz, 2H), 3.52 (dd, J = 6.0, 0.8 Hz, 1H), 3.49 (dd, J = 3.2, 1.2 Hz, 1H), 2.64 (d, J = 5.6 Hz, 1H), 2.58 (dd, J = 6.0, 3.2 Hz, 1H), 2.00−1.94 (m, 2H), 1.93 (d, J = 1.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.3, 171.3, 165.7, 141.3, 140.3, 131.6 (2), 131.1 (2), 129.1, 128.8 (2), 127.9, 127.7 (2), 127.4, 120.0, 62.9, 60.7, 53.9, 52.0, 38.5, 37.1, 27.1, 22.6, 21.2; IR (neat) ν_{max} 2962, 1717, 1662, 1271 cm^{-1}. HRMS calculated for $C_{26}H_{27}BrNO_4$: 496.1123, found 496.1129 (M + H).

(±)-Imide (36). 3-Azido-1-propanol (17.5 mg, 0.173 mmol) was added to a solution of **26** (69.0 mg, 0.171 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C, and the solution was stirred for 5 min. Triflic acid (1.13 M in CH_2Cl_2/MeCN) (0.455 mL, 0.514 mmol) was slowly added dropwise and the solution gradually turned black. The triflic acid stock solution was prepared fresh by the addition of triflic acid (0.20 mL) to a mixture of CH_2Cl_2 (1.45 mL) and MeCN (0.35 mL). The solution was gradually warmed to room temperature and stirred for 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched by the addition of saturated aq $NaHCO_3$ (5.0 mL), and the biphasic solution was stirred at room temperature for 2 h. The layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by preparative TLC (SiO_2, 1:20 MeOH/CH_2Cl_2) to afford **36** (15.0 mg, 20%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.31 (m, 2H), 7.24−7.16 (m, 3H), 7.12 (ddd, J = 7.5, 1.5, 1.0 Hz, 1H), 7.05 (t, J = 2.5 Hz, 1H), 6.90 (ddd, J = 8.0, 2.5, 0.5 Hz, 1H), 6.40, (d, J = 1.5 Hz, 1H), 6.00−5.91 (m, 1H), 5.32−5.26 (m, 2H), 4.75 (dd, J = 6.5, 2.0 Hz, 1H), 4.03 (dd, J = 10.0, 6.5 Hz, 1H), 3.87 (s, 3H), 3.62−3.57 (m, 1H), 3.55−3.49 (m, 1H), 3.26 (dd, J = 17.5, 10.0 Hz, 1H), 3.01−2.95 (m, 2H), 2.92−2.87 (m, 1H), 2.84 (dd, J = 17.5, 4.0 Hz, 1H), 2.65−2.60 (m, 1H), 2.54 (dd, J = 14.0, 8.5 Hz, 1H), 1.62−1.21 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.4, 172.7, 159.9, 142.5,140.5, 140.5, 139.1, 133.8, 129.8, 129.3, 128.1, 127.1, 125.0, 124.9, 119.7, 117.9, 113.7, 111.3, 58.3, 55.4, 55.3, 54.5,

48.0, 43.4, 40.5, 38.0, 33.2, 30.4; IR (neat) ν_{max} 3487, 1702, 1653 cm^{-1}. HRMS calculated for $C_{28}H_{30}NO_4$: 444.2175, found 444.2151 (M + H).

(±)-Amide (37). 3-Azido-1-propanol (17.5 mg, 0.173 mmol) was added to a solution of *epi*-**26** (69.0 mg, 0.171 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C, and the solution was stirred for 5 min. Triflic acid (1.13 M in CH_2Cl_2/MeCN) (0.455 mL, 0.514 mmol) was slowly added dropwise, and the solution gradually turned black. The triflic acid stock solution was prepared fresh by the addition of triflic acid (0.20 mL) to a mixture of CH_2Cl_2 (1.45 mL) and MeCN (0.35 mL). The solution was gradually warmed to rt and stirred for 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched by the addition of saturated aq $NaHCO_3$ (5.0 mL), and the biphasic solution stirred at rt for 2 h. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by preparative TLC (SiO_2, 1:20 MeOH/CH_2Cl_2) to afford **37** (13.2 mg, 17%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 8.0 Hz, 1H), 7.24−7.14 (m, 6H), 6.92 (dd, J = 8.0, 2.0 Hz, 1H), 6.45 (s, 1H), 6.33, (d, J = 8.0 Hz, NH), 5.86−5.78 (m, 1H), 5.26−5.19 (m, 2H), 4.25 (ddd, J = 11.0, 8.0, 2.5 Hz, 1H), 4.07 (ddd, J = 11.0, 7.5, 3.0 Hz, 1H), 4.00 (d, J = 6.0 Hz, 1H), 3.90−3.83 (m, 1H), 3.86 (s, 3H), 3.51 (dd, J = 10.0 5.5 Hz, 1H), 3.25 (dd, J = 16.5, 9.0 Hz, 1H), 3.05−2.83 (m, 4H), 2.52 (dd, J = 13.5, 9.0 Hz, 1H), 1.89−1.84 (m, 1H), 1.63−1.59 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.3, 169.7, 159.8, 144.4, 142.0, 141.8, 141.4, 133.7, 131.4, 129.7, 127.2, 126.3, 124.4, 123.6, 119.5, 118.4, 113.1, 112.1, 65.5, 55.3, 52.1, 48.8, 48.4, 45.8, 45.3, 40.1, 36.8, 26.4; IR (neat) ν_{max} 3413, 2929, 1726, 1665 cm^{-1}. HRMS calculated for $C_{28}H_{30}NO_4$: 444.2175, found 444.2149 (M + H).

General Preparation of Polycyclic Imines 39−42. To an oven-dried vial was added cyclopropane **2** (30.0 mg, 0.117 mmol) and anhydrous nitromethane (450 μL) followed by the addition of benzonitrile (60 μL, 0.585 mmol). To this mixture was added TMSOTf (21.0 μL, 0.039 mmol) in anhydrous nitromethane (300 μL) while at 0 °C. The reaction was warmed to room temperature and stirred for 4 h. Next, the reaction mixture was cooled to 0 °C and slowly quenched by addition of saturated $NaHCO_3$ (400 uL), diluted with water (5 mL), and extracted into CH_2Cl_2 (5 mL × 3). The organic fractions were combined, washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2).

(±)-Polycyclic Imine (40). Purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2:EtOAc) 94% yield. Amorphous off-white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.0 Hz, 2 H), 7.57−7.51 (m, 1 H), 7.51−7.45 (m, 2 H), 7.38−7.32 (m, 2 H), 7.31−7.25 (m, 1 H), 7.20 (d, J = 7.4 Hz, 2 H), 4.59 (d, J = 5.5 Hz, 1 H), 3.87 (s, 3 H), 3.25−3.18 (m, 3 H), 2.76−2.65 (m, 1 H), 1.25 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 197.4, 169.8, 139.5, 132.5, 131.5, 128.9, 128.8, 128.6, 128.2, 127.9, 105.0, 71.5, 59.9, 57.7, 56.7, 53.0, 30.0, 21.1; IR (thin film) ν_{max} 2959, 1749, 1723, 1568, 1456, 1210, 1147, 1070, 1032, 735, 700 cm^{-1}. HRMS calculated for $C_{23}H_{22}NO_3$: 360.1600, found 360.1593 (M + H).

(±)-Polycyclic Imine (41). Purified by flash chromatography (SiO_2, 100% CH_2Cl_2 to 30:1 CH_2Cl_2/EtOAc). 80% yield. Crystalline solid: mp = 86.6−90.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 9.0 Hz, 2 H), 7.37−7.32 (m, 2 H), 7.30−7.25 (m, 1 H), 7.20 (d, J = 7.4 Hz, 2 H), 6.97 (d, J = 9.0 Hz, 2 H), 4.54 (d, J = 5.1 Hz, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.23−3.21 (m, 1 H), 3.21−3.16 (m, 2 H), 2.76−2.65 (m, 1 H), 1.24 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 197.5, 168.9, 163.1, 139.6, 130.6, 128.9, 128.2, 127.8, 124.2, 114.1, 105.0, 71.3, 59.7, 57.3, 56.7, 55.4, 52.8, 30.0, 21.1; IR (thin film) ν_{max} 2959, 1750, 1723, 1607, 1513, 1256, 1174, 1031, 735, 701 cm^{-1}. HRMS calculated for $C_{24}H_{24}NO_4$: 390.1705, found 390.1717 (M + H).

(±)-Polycyclic Imine (42). Purified by flash chromatography (SiO_2, 100% CH_2Cl_2 to 30:1 CH_2Cl_2/EtOAc). 47% yield. Amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.59−7.55 (m, 2 H), 7.45 (d, J = 16.4 Hz, 1 H), 7.42−7.38 (m, 3 H), 7.38−7.32 (m, 2 H), 7.31−7.26 (m, 1 H), 7.20 (d, J = 7.4 Hz, 2 H), 7.01 (d, J = 16.4 Hz, 1 H), 4.41 (d, J = 5.1 Hz, 1 H), 3.85 (s, 3 H), 3.23 (d, J = 2.0 Hz, 1 H), 3.19−3.12 (m, 2 H), 2.74−2.65 (m, 1 H), 1.24 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 197.4, 169.9, 144.2, 139.5, 134.9, 130.3, 129.0, 128.9, 128.2, 128.0, 127.9, 121.9, 105.0, 71.4, 59.1, 57.4, 56.7, 53.1, 30.0, 21.1; IR (thin film) ν_{max} 2958, 1750, 1724, 1628, 1559, 1578, 1456, 1201, 1143, 754, 735, 700 cm^{-1}. HRMS calculated for $C_{25}H_{24}NO_3$: 386.1756, found 386.1765 (M + H).

(±)-Polycyclic Imine (43). Purified by preparative TLC (SiO_2, 30:1 CH_2Cl_2/EtOAc). 54% yield. Amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 9.0 Hz, 2 H), 7.26−7.21 (m, 3 H), 7.21−7.17 (m, 1 H), 6.97 (d, J = 8.6 Hz, 2 H), 5.78 (dddd, J = 16.8, 10.2, 7.4, 7.4 Hz, 1 H), 5.13 (dd, J = 10.6, 1.6 Hz, 1 H), 5.04 (dd, J = 16.8, 1.2 Hz, 1 H), 4.32 (s, 1 H), 4.08 (dd, J = 9.0, 3.5 Hz, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.70−3.60 (m, 1 H), 3.58 (d, J = 3.5 Hz, 1 H), 3.18−3.14 (m, 2 H), 2.59 (dd, J = 14.5, 7.4 Hz, 1 H), 2.18 (dd, J = 14.5, 7.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 198.9, 168.0, 163.0, 142.3, 139.6, 133.1, 130.5, 128.4, 127.1, 125.2, 124.5, 124.5, 119.4, 114.2, 105.2, 69.2, 67.5, 65.0, 56.4, 55.5, 51.5, 35.3, 33.7, 33.7; IR (thin film) ν_{max} 2943, 1719, 1606, 1513, 1251, 1174, 1027, 739 cm^{-1}. HRMS calculated for $C_{27}H_{26}NO_4$: 428.1862, found 428.1864 (M + H).

(±)-Polycyclic Imine (39). Reaction of cyclopropane **2** (40.0 mg, 0.156 mmol) with anhydrous acetonitrile (neat) was performed according to the general procedure. The product was purified by flash chromatography (SiO_2, 30:1 CH_2Cl_2/EtOAc to 15:1 CH_2Cl_2/EtOAc) to afford polycyclic imine **39** (23.7 mg, 0.080 mmol, 51%) as an amorphous white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.25 (m, 3 H), 7.15 (d, J = 6.6 Hz, 2 H), 3.90 (d, J = 5.1 Hz, 1 H), 3.79 (s, 3 H), 3.21−3.17 (m, 1 H), 3.12−3.07 (m, 2 H), 2.67−2.57 (m, 1 H), 2.18 (s, 3 H), 1.17 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 197.8, 173.9, 139.4, 128.9, 128.1, 127.9, 105.2, 71.1, 64.1, 57.4, 56.1, 53.0, 29.9, 21.0, 20.4; IR (thin film) ν_{max} 2959, 1749, 1718, 1624, 1272, 1142, 1032, 731, 701 cm^{-1}. HRMS calculated for $C_{18}H_{20}NO_3$: 298.1443, found 298.1445 (M + H).

(±)-Methyl-3-(4-methoxyphenyl)-7-methyl-4-oxo-6-phenyl-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (45). A solution of **41** (100 mg, 0.256 mmol) in dry MeOH (5.0 mL) was heated in a sealed tube at 100 °C for 12 h. After cooling, the solvent was removed and the crude material was directly purified by preparative TLC (SiO_2, 2:3, Et_2O/hexanes) to afford **45** (83.5 mg, 84%) as a white amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.53−7.50 (m, 2H), 7.28−7.24 (m, 2H), 7.20−7.17 (m, 3H), 6.93−6.91 (m, 2H), 3.85 (s, 3H), 3.85−3.79 (m, 1H), 3.75 (s, 3H), 3.42 (q, J = 4.0 Hz, 1H), 3.12 (dd, J = 17.2, 2.8 Hz, 1H), 2.78 (dd, J = 17.2, 4.0 Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 187.1, 164.8, 160.2, 144.1, 143.9, 142.4, 130.6 (2), 128.3 (2), 127.4 (2), 126.5, 126.2, 123.0, 113.3 (2), 110.9, 55.2, 50.9, 47.8, 39.4, 34.5, 20.9; IR (neat) ν_{max} 3209, 2953, 1702, 1634 cm^{-1}. HRMS calculated for $C_{24}H_{24}NO_4$: 390.1705, found 390.1678 (M + H).

(±)-Methyl-3-(4-methoxyphenyl)2,7-dimethyl-4-oxo-6-phenyl-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (46). A solution of **45** (100 mg, 0.256 mmol), iodomethane (109 mg, 0.770 mmol), and K_2CO_3 (107 mg, 0.770 mmol) in dry MeCN (5.0 mL) was heated in a sealed tube at 82 °C for 24 h. After cooling, the solvent was removed and the residue was taken up in CH_2Cl_2 (5.0 mL). The solution was washed with water (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5.0 mL). The organic extracts were collected, dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo to afford a light yellow oil. The crude material was purified by flash chromatography (SiO_2, 2:3, Et_2O/hexane) to afford **46** (55.5 mg, 54%) as a white solid: mp = 147−153 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.20 (m, 7H), 7.02 (d, J = 9.0 Hz, 2H), 3.95−3.89 (m, 1H), 3.90 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 3.43−3.40 (m, 1H), 3.20 (dd, J = 17.0, 5.5 Hz, 1H), 2.86 (dd, J = 17.0, 4.0 Hz, 1H), 1.57 (d, J = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 187.6, 164.5, 159.9, 145.7, 144.2, 141.4, 131.3 (2), 128.2 (2), 127.4 (2), 126.1, 126.0, 122.4, 113.4 (2), 111.2, 55.1, 50.7, 46.9, 40.7, 34.3, 34.1 21.3; IR (neat) ν_{max} 1702, 1649, 1456, 1247 cm^{-1}. HRMS calculated for $C_{25}H_{26}NO_4$: 404.1862, found 404.1859 (M + H).

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■ ASSOCIATED CONTENT

Supporting Information

Spectral data for characterized compounds and X-ray crystal structure data for **20**, **32**, and **41**. This material is available free of charge via the Internet at http://pubs.acs.org.

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