Generation of the 7-Azabicyclo[4.3.1]decane Ring System via (4+3) Cycloaddition of Oxidopyridinium Ions

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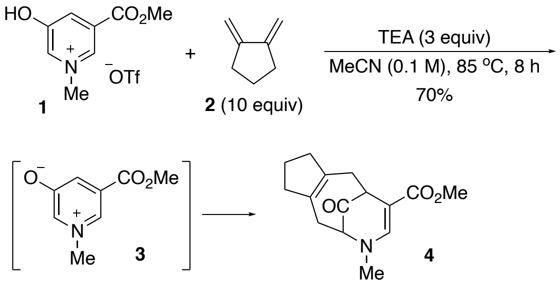
ABSTRACT: Oxidopyridinium ions bearing an ester group at the 5-position undergo (4+3) cycloaddition reaction to afford congeners of 7-azabicyclo[4.3.1]decane. The reaction generally proceeds in high yield, though an excess of diene is often required to achieve such yields. The reaction is highly regioselective, but not *endo*/*exo* selective. It appears the cycloaddition process can be either kinetically or thermodynamically controlled, depending on the nature of the diene used and the reaction time. An intramolecular Heck reaction was used to demonstrate some chemistry possible with the cycloadducts.

INTRODUCTION

The (4+3) cycloaddition reaction of allylic and related cations is a powerful method for the synthesis of both carbocyclic and heterocyclic seven-membered rings.[1] Our interest in this area has a long history.[2] Recently, based on work by Katritzky,[3] we reported the (4+3) cycloaddition of *N*-alkyloxidopyridinium ions having an electron-withdrawing substituent at the 5-position of the pyridinium ring.[4] This made possible the use of an *N*-alkyl rather than an *N*-aryl or *N*-vinylpyridinium ion for the cycloaddition, as the latter had historically been the standard approach for the (4+3) cycloaddition of pyridinium ions (Scheme 1).

Scheme 1. (4+3) Cycloaddition of an *N*-Alkyl Oxidopyridinium Ion with a Diene.



The (4+3) cycloaddition reaction of oxidopyridinium ions produces the 7-azabicyclo[4.3.1] ring system, a substructure of interesting and often biologically active alkaloids including 2-deoxymacropodumine A, alstonlarsine A, and nominine (Figure 1).[5-7] This makes the reaction a potentially powerful method for the synthesis of these and related targets. Understanding this reaction and investigations into its scope and mechanism are thus warranted.

Our initial report on the (4+3) cycloaddition reaction of *N*-alkyloxidopyridinium ions indicated that the reaction often proceeded in high yield.[4] Regioselectivity could be controlled by what we interpreted as steric effects, but *endo*/*exo* selectivity was poor. While most of the reactions appeared to proceed by kinetic control, there was one case in which thermodynamic control was clearly evident. In this article, we report some further studies bearing on the scope of the reaction and its optimization.

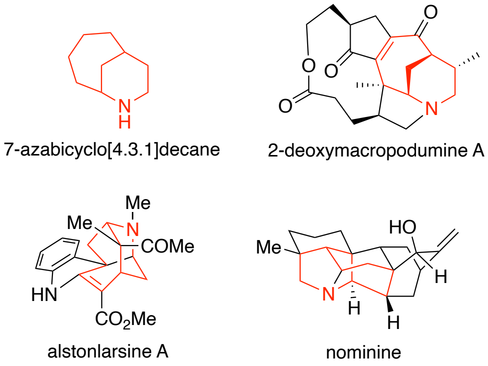


Figure 1. Selected alkaloids possessing the 7-azabicyclo[4.3.1] ring system.

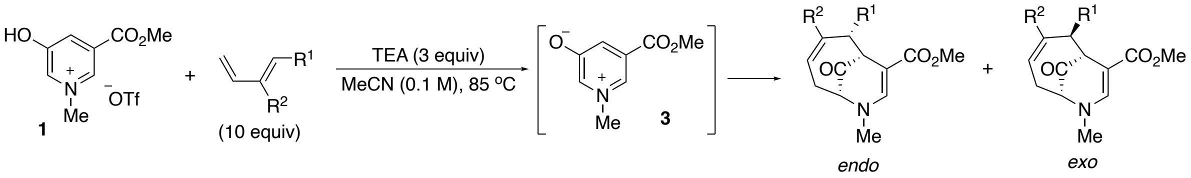
Our efforts focused on 1-substituted dienes because although these reacted with low diastereoselectivity, they exhibited high regioselectivity. Typically, the hydroxypyridinium ion **1** was heated in the presence of 10 equivalents of diene and 3 equivalents of triethylamine at 85 °C in acetonitrile. The reactions were conducted from 7-30 hours in resealable pressure tubes.

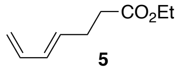
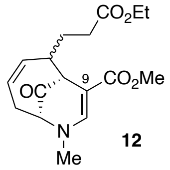
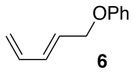
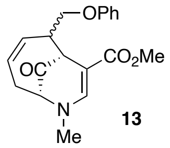
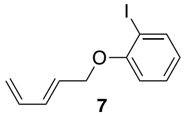
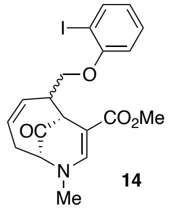
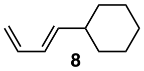
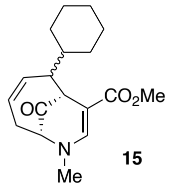
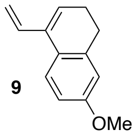
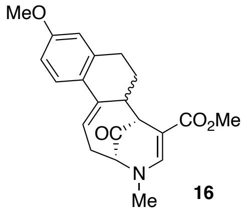
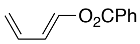
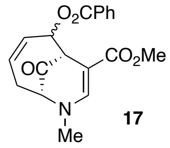
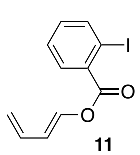
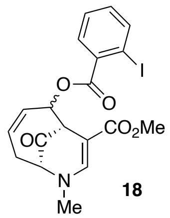
RESULTS AND DISCUSSION

The results of this work are shown in Table 1 and might be described as typical. Cycloadduct **12** was prepared as a 56:44 mixture of diastereomers with apparently complete regioselectivity as determined by ^{1}H NMR analysis of a crude reaction mixture. The cycloadducts were not separable, but after reduction of the ketone functionality in each molecule with sodium borohydride, separation could be achieved. This reduction proceeded with complete diastereoselectivity as far as we could tell (^{1}H

NMR). A crystal grown from the alcohol corresponding to the *exo* cycloadduct confirmed the structure of the molecule. Noteworthy is that the chemical shift for carbon 9 in *exo*-**12** is 93.0 ppm while that of the *endo* isomer is 95.3 ppm. This trend has been noted in other cases

Table 1. (4+3) Cycloadditions of Oxidopyridinium Ion 3.



entry	diene	Time (h)	cycloadduct[a]	dr (endo:exo)[a]	yield (%)
1	 **5**	7	 **12**	56:44	93
2	 **6**	30	 **13**	44:56	97
3	 **7**	22	 **14**	59:41	70
4	 **8**	22	 **15**	38:62	61
5	 **9**	24	 **16**	37:63	94
6	 **10**	17	 **17**	39:61	90
7	 **11**	25	 **18**	50:50	86

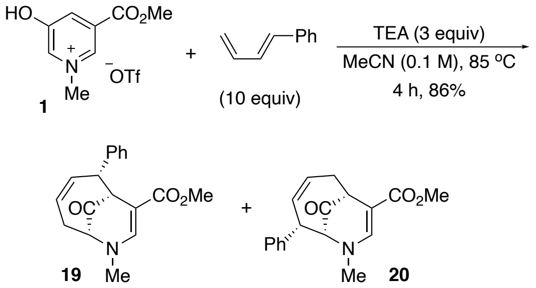
[a]Ratios determined by integration of ^{1}H NMR of crude reaction mixtures.

and serves, we believe, as a general means of assigning *endo* and *exo* cycloadducts. For example, two products were isolated from the reaction of 1-cyclohexyl-1,3-butadiene with **3** (Table1, entry 4). The *exo* isomer's structure was secured on the basis of X-ray analysis. The relevant ^{13}C chemical shifts for the *endo* and *exo* isomers were, 94.2 and 91.8 ppm, respectively. All other structural assignments were made by a combination of X-ray analysis and the use of this chemical shift trend in the ^{13}C NMR., though we are continuing studies to determine the generality of this observation.

The same regiochemical outcome observed in the reaction of 1-substituted butadienes is observed with 1,2-disubstituted butadienes (Table 1, entry 5), as expected. In this case, both isomers were structurally characterized spectroscopically and through X-ray analysis. The chemical shift for carbon 9 of the *endo* isomer of **16** was 96.7 ppm; that for the *exo* isomer was 91.1 ppm.

In our previous work, we found that 1-phenylbutadiene reacted in such a way that the expected regiochemical pattern was drastically altered (Scheme 2).[4] Two *endo* regioisomers were isolated, the only case in which *endo* selectivity was complete, but regiochemical control was poor. This was ultimately determined to be the result of the reversibility of the cycloaddition reaction of this diene, i.e., thermodynamic control.

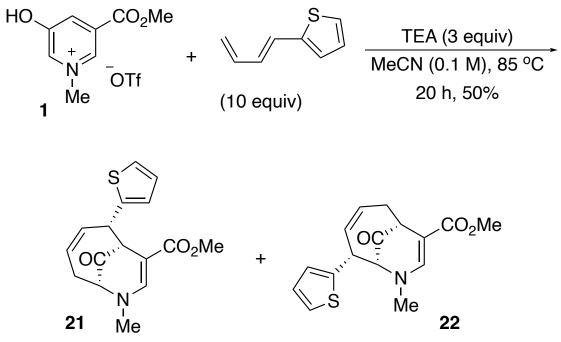
Scheme 2. (4+3) Cycloaddition of 1-Phenyl-1,3-butadiene.[4]



19:**20** = 91:9

The same outcome was observed in the reaction of 1-thienyl-1,3-butadiene, where two *endo* regioisomeric products were isolated in the cycloaddition reaction. Although we have not studied this process in detail, we conclude that this reaction is also under thermodynamic control (Scheme 3). Further, we did not attempt to optimize yield in this case.

Scheme 3. (4+3) Cycloaddition of 1-Thienyl-1,3-butadiene.

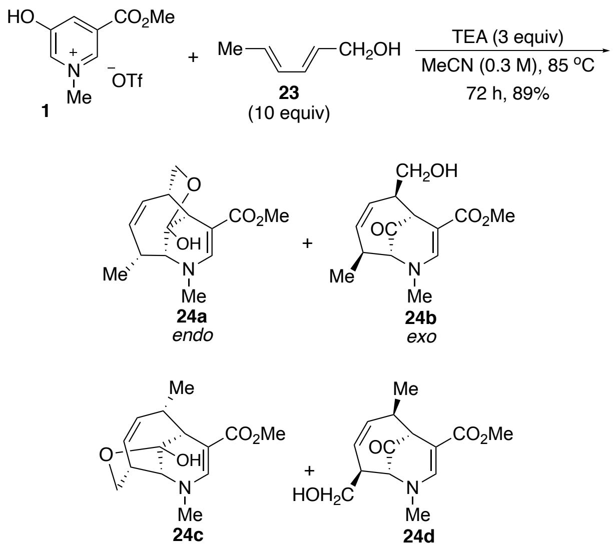


21:**22** = 75:25

While we held no high expectation for any type of stereochemical or regiochemical control, we investigated two 1,4-disubstituted 1,3-butadienes. Indeed, as shown in Schemes 4 and 5, the reaction proceeded well in terms of yield, but without high regio- or diastereoselectivity. Reaction times had to be increased with respect to less substituted dienes as the reaction proceeded more slowly. In the case of sorbyl alcohol (**23**), the *endo* cycloadducts existed as hemiketals. We had hoped that this might serve as a trap had the reaction been reversible and would thus limit the number of cycloadducts to two. However, if the reaction is reversible, it would appear that equilibration is slow, and we did not push this process beyond normal reaction times. Only **24a** and **24d** were isolated as pure substances. The structural assignments and relative ratios of **24b** and **24c** were based on NMR data of reaction mixtures. The acetate of sorbyl alcohol reacted in a similar fashion to give a similar distribution of products. In this case, only **26a** and **26d** could be isolated as pure substances. NMR data were once again used with mixtures to make the other structural assignments.

However, one 1,4-substituted diene did give an interesting result that bears further investigation. The cycloaddition of **27** afforded two *endo* cycloadducts in 41% yield reproducibly (2 runs) in a ratio of 75:25 (Scheme 6). No further data on the reaction is known at this writing, but it is likely a reversible process given that both products are *endo*. Furthermore, it hints at the possible use of thioethers as a regiocontrol element in a direction opposite to simple 1-alkyl-substituted butadienes.

Scheme 4. (4+3) Cycloaddition of Sorbyl Alcohol.

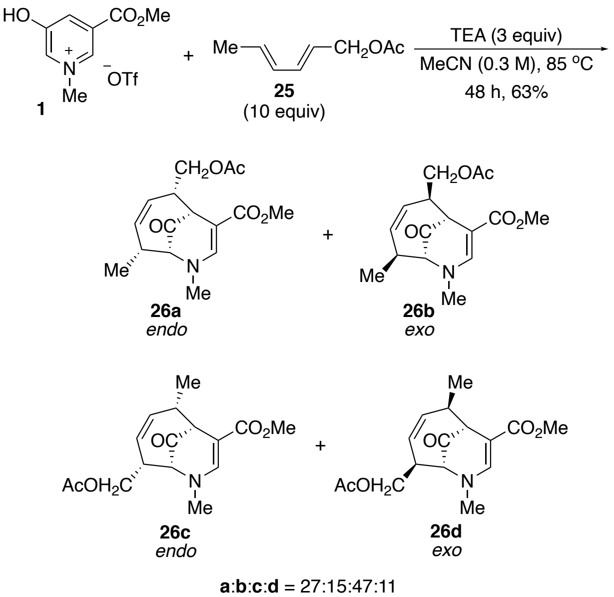


a:**b**:**c**:**d** = 28:12:30:30

Typically, these cycloaddition reactions are run in the presence of a 10-fold excess of diene. For simple dienes, this is of minor consequence, but for dienes of greater value, it can be prohibitive in terms of expense. We thus set out to examine the reaction with respect to the minimum amount of diene needed to effect a successful reaction.

We used **30** as our model diene, as its cycloaddition with **1** had already been studied.[4] The results are summarized in Table 2. The reactions were conducted in such a way that the relative concentration of the diene to the starting salt **1** was always the same with respect to the diene (1 M). This involved increasing the concentration of the salt as the equivalents of the diene dropped. While yields of the cycloadduct **31**[4] were essentially quantitative when 10 or 5 equivalents of diene were used, the yield remained high at 2.5 equivalents. However, the yield declined more dramatically when the amount of diene dropped lower. At this stage, we believe that a per case optimization of the amount individual dienes may be necessary to achieve high yields with less that around 2-2.5 equivalents of diene.

Scheme 5. (4+3)-Cycloaddition of Sorbyl Acetate.



Scheme 6. (4+3) Cycloaddition Reaction of (1*E*,3*E*)-1-(Phenylthio)-1,3-pentadiene.

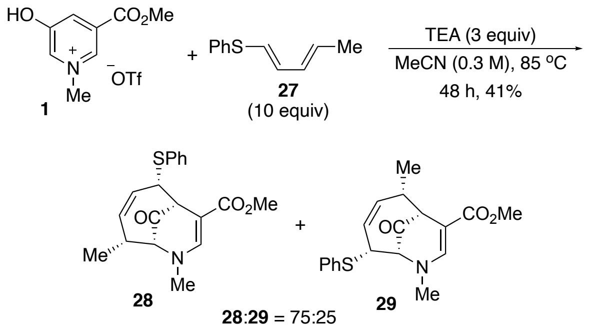
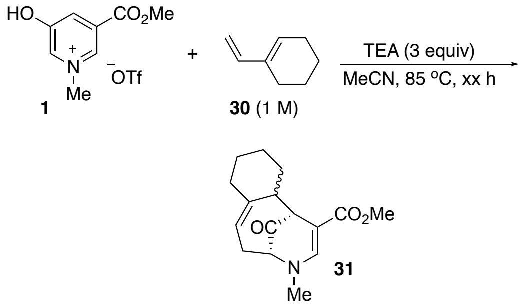


Table 2. Reducing the amount of Diene used in the (4+3) Cycloaddition of 1.

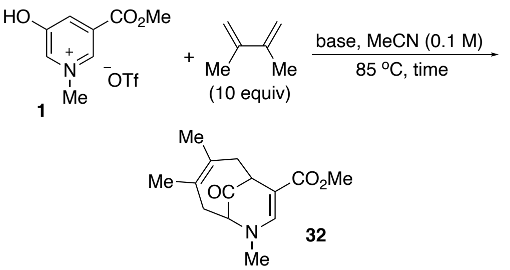


entry	equiv diene	[M] **1**	yield (%)
1	10	0.1	99[a]
2	5	0.2	99[b]
3	2.5	0.4	86[b]
4	1.75	0.57	76[b]
5	1.25	0.8	55[b]

[a]Average of 5 experiments. [b]Average of 2 experiments.

The effect of the base on the reaction was also studied. The results are illustrated in Table 3. Weaker bases such and pyridine and *N*,*N*-dimethylaniline did not perform as well as triethylamine when used at the level of one equivalent relative to **1** (Table 3, entries 1-3). However, even triethylamine required a two equivalent loading to be effective (Table 3, entry 5). Selected carboxylate salts were also investigated. The dibasic sodium succinate performed reasonably well in this reaction, affording **32**[4] in 60% yield (Table 1, entry 6). However, sodium benzoate itself afforded an essentially quantitative yield of the (4+3) cycloadduct at one equivalent, with the yield dropping dramatically at a 0.5 equivalent loading (Table 3, entries 9-10). Finally, inorganic bases in the carbonate and phosphate series at one equivalent loading all afforded **32** in essentially quantitative yield with the exception of sodium bicarbonate, which still afforded a high yield of cycloadduct (Table 3, entries 11-15).

Table 3. Effect of base on the (4+3) Cycloaddition of 1.

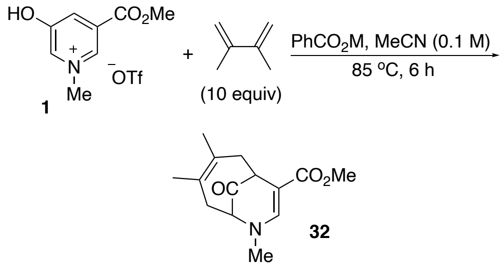


entry	base (equiv)	Time (h)	Yield **32** (%)
1	*N*,*N*-dimethylaniline (1)	6	7
2	pyridine (1)	6	17
3	TEA (1)	6	33
4	DIPA (1)	6	63
5	TEA (2)	6	99
6	sodium succinate (1)	16	60
7	$4\text{-}\mathrm{NO_2C_6H_4CO_2Na}$ (1)	16	2
8	$2\text{-}\mathrm{OHC_6H_4CO_2Na}$ (1)	16	18
9	$\mathrm{PhCO_2Na}$ (1)	16	99
10	$\mathrm{PhCO_2Na}$ (0.5)	16	33
11	$\mathrm{NaHCO_3}$ (1)	16	82
12	$\mathrm{K_2CO_3}$ (1)	16	99
13	$\mathrm{Cs_2CO_3}$ (1)	16	99
14	$\mathrm{K_2HPO_4}$ (1)	16	99
15	$\mathrm{K_3PO_4}$ (1)	16	99

The results using sodium benzoate as base spurred a short study on the effect of cations in the reaction. In this case, the same reaction as shown in Table 3 was conducted, but only for six hours. The reaction was stopped and the yield recorded after that time. As can be seen from Table 4, decreasing the Lewis acidity of the counteraction associated with the benzoate anion appears to increase reactivity. We examined the stability of **32** in the presence of 1 equivalent of lithium benzoate. After 6 hours at 85 ºC, 93% of the starting material was recovered upon chromatographic purification. This supports the idea that the effect seen in Table 4 is kinetic in nature.

Finally, cycloadducts **14** and **18** were used to investigate an intramolecular Heck reaction. The literature suggests that conformational issues with **18** should prevent the Heck cyclization.[8] We indeed found this to be the case. Treatment of both *endo*- and *exo*-**18** under Heck reaction conditions afforded the triene **33** in 38% yield in the case of *endo*-**18**, presumably through the formation of a π-allyl palladium species, followed by elimination (Scheme 7).[9] *Exo*-**18** decomposed to unidentifiable materials under the same reaction conditions. Better results for the intramolecular Heck process were expected with the ether **14** as there is no strong stereoelectronic influence on conformation, making approach of the oxidative addition product to the alkene possible.

Table 4. Effect of countercation change in (4+3) Cycloaddition of 1.

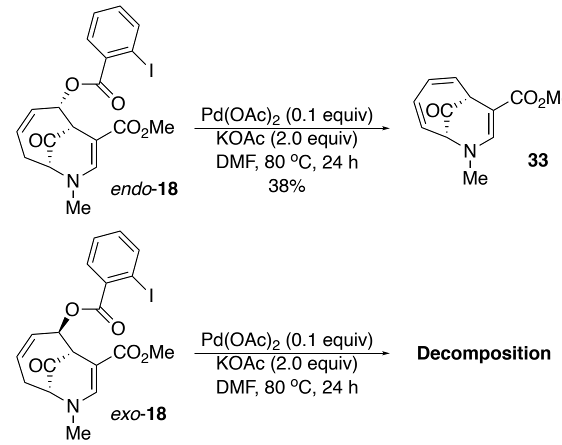


entry	M	yield %[a]
1	Li	41
2	Na	54
3	K	81
4	Cs	95
5	NH_4	38

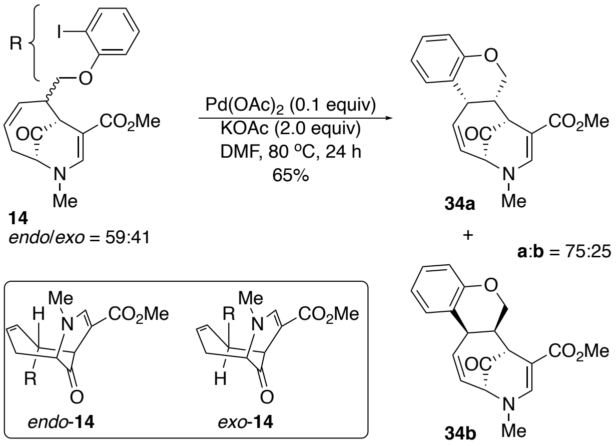
[a]Yield is average of two runs.

Additionally, there is a higher barrier to π-allyl palladium formation, mitigating the elimination reaction seen with **18**, as alkoxides are poorer leaving groups than carboxylates. Thus, treatment of **14** under Heck cyclization conditions led to the polycycle **34** in 65% yield (Scheme 8). However, one isomer may have reacted more efficiently than the other, as the isomer ratio changed from 59:41 in the starting material to 75:25 in the product mixture. An examination of various crystal structures of (4+3) cycloadducts obtained in our studies suggests that the major product of this reaction should arise from the *endo* cycloadduct and should have the stereochemistry depicted by **34a**. *Endo* cycloadducts typically place substituents in a pseudoaxial orientation on a chairlike cycloheptenone ring, poised ideally for an intramolecular Heck reaction (see *endo*-**14**, Scheme 8). However, *exo* cycloadducts possess pseudoequatorial substituents (see *exo*-**14**, Scheme 8) and must undergo a ring flip for such a reaction, slowing the intramolecular Heck reaction for these isomers and giving rising to lower yields. Nevertheless, models suggest that Heck products derived from these species should possess the stereochemistry represented in **34b**.

Scheme 7. Attempted Heck Cyclization of 18.



Scheme 8. Intramolecular Heck Cyclization of 14.



CONCLUSION

In summary, we have further developed the (4+3) cycloaddition chemistry of **1**, including finding conditions amenable to the use of smaller amounts of diene in the process. Further investigations of the cycloaddition process itself and of the chemistry of the cycloadducts are in progress and will be reported in due course.

EXPERIMENTAL SECTION

All reactions were carried out in oven-dried glassware under an argon atmosphere. Tetrahydrofuran was ordered from Sigma Aldrich and was distilled under a nitrogen atmosphere over sodium metal with benzophenone ketyl as an indicator. Dichloromethane was ordered from Sigma Aldrich and was distilled under a nitrogen atmosphere over calcium hydride. Dienes **5**,[10] **6**,[11] **7**,[11,12] **8**,[13] **9**,[14] **10**,[15] **23**,[16] **25**,[16] and **27**[17] are known compounds and were prepared by literature methods. Analytical thin layer chromatography was performed on silica gel plates with UV indicator. Flash chromatography was carried out using 230-400 mesh silica gel with HPLC grade solvents. ^{1}H NMR spectra were recorded on either a Bruker DRX-500 (500

MHz) or a DRX-600 (600 MHz) spectrometer with chemical shifts reported in ppm with tetramethylsilane as an internal reference (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, etc). ^{13}C NMR spectra were obtained on the same instruments at 125 and 150 MHz, respectively, in CDCl$_3$ solution with CDCl$_3$ (77.16 ppm) as an internal reference. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. High-resolution mass spectra were performed by College of Science Major Instrumentation Center, Old Dominion University, on a Bruker 12 Tesla APEX - Qe FTICR-MS with an Apollo II ion source or Charles W Gehrke Proteomics Center, University of Missouri–Columbia, on a Bruker's timsTOF Pro with ESI positive ion source. The raw data were deconvoluted using Bruker's Compass DataAnalysis (v 5.3). Crystal structure data were collected on a Bruker SMART diffractometer (Bruker AXS, Madison, WI, USA) with an Apex II CCD area detector using Mo Kα radiation (λ = 0.71073 Å) from a fine focus source with TRIUMPH optics (structures **12** alcohol, *exo*-**15**, *endo*-**21, 28**), a Bruker X8 Prospector diffractometer (Bruker AXS) with an Apex II detector using Cu Kα radiation (λ = 1.54178 Å) from a microfocus source (structures *endo*-**16, 29** alcohol), or a Bruker D8 Venture diffractometer equipped with a Photon 100 CMOS area detector using Mo Kα radiation from a microfocus source (structures *exo*-**16**, *endo*-**17**, *exo*-**17**, *exo*-**18**, **22**, **24a**, **24d**, **26a**). Crystals were cooled under cold N_2 streams using Cryostream 700 or Cryostream 800 cryostats (Oxford Cryosystems, Oxford, UK). Hemispheres of unique data were collected using strategies of scans about the phi and omega axes with 0.5^{o} frame widths. Unit cell determination, data collection, data reduction, absorption correction and scaling, and space group determination were done using the Bruker Apex3 software suite.[18] Crystal structures were solved by direct methods as implemented in SHELXS[19] (structures **12** alcohol, *exo*-**15**, *exo*-**16**, *exo*-**17**, **22**, **24d**, **28**, **29** alcohol) or an iterative dual-space method as implemented in SHELXT[20] (structures *endo*-**16**, *endo*-**17**, *exo*-**18**, *endo*-**21**, **24a**, **26a**). All structures were refined by full-matrix least squares against F^2 using SHELXL-2017.[20] Olex2 was used for model building and as an interface for refinement.[21] Non-hydrogen atoms were located from the difference map and refined anisotropically. In structures affected by disorder, partial occupancy atoms could also be located from the difference map and refined anisotropically with geometric restraints where necessary to enforce chemical reasonableness. Hydrogen atoms were placed in calculated positions. Hydrogen atom coordinates were refined for structures with sufficient data-to-parameter ratios and were constrained to ride on the carrier atom for all other cases. All hydrogen atom thermal parameters were constrained to ride on the carrier atoms. The structure of **12** contains relatively high residual difference map peaks associated with additional conformations of a disordered ethyl ethanoate group which could not be further modeled.

*Synthesis of methyl 7-methyl-10-oxo-7-azabicyclo[4.3.1]deca-3,8-diene-9-carboxylates **4**, **12-22**, **24**, **26**, **28**, **29**, and **31**: General procedure.* Methyl trifluoromethanesulfonate (1.2 equiv) was added to a suspension of methyl 5-hydroxynicotinate (1 equiv) in dichloromethane (0.1 M), and the mixture was stirred for 3 h at ambient temperature under argon. After completion, the precipitate was filtered off and rinsed with pentane to give **1** as a white solid (94 %). The resulting *N*-methyl hydroxypyridinium salt **1** (100 mg, 0.20 mmol) was dissolved in acetonitrile (0.1-0.3 M) and treated with excess diene (10 equiv), followed by triethylamine (3 equiv). The reaction mixture was heated at 85 ºC in a sealed tube for 4–72 h and quenched with 10% HCl solution. The aqueous solution was extracted with dichloromethane, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (5–50% EtOAc/hexanes) over silica gel to give the final product.

Methyl (1R,2S*,6S*)-2-(3-ethoxy-3-oxopropyl)-10-hydroxy-7-methyl-7-azabicyclo[4.3.1]deca-3,8-diene-9-carboxylate* (corresponding alcohol of *endo*-**12**)and *Methyl (1R*,2R*,6S*)-2-(3-ethoxy-3-oxopropyl)-10-hydroxy-7-methyl-7-azabicyclo[4.3.1]deca-3,8-diene-9-carboxylate* (corresponding alcohol of *exo*-**12**). Following the general procedure, a mixture of **1** (200 mg, 0.631 mmol), **5** (973 mg, 6.31 mmol), triethylamine (191 mg, 1.89 mmol), and acetonitrile (6.3 mL, 0.1 M) was heated at 85 ºC in an oil bath for 14 h, followed by acidic quenching and column chromatography (20–35% EtOAc/hexanes) over silica gel afforded the mixture of *endo*- and *exo*-**12** as colorless oil (188 mg, 93% yield). The mixture of **12** (100 mg, 0.311 mmol) was treated with NaBH$_4$ (13 mg, 0.342 mmol, 1.1 equiv) in methanol (3.1 mL, 0.1 M) and stirred at 0 ºC for 3 h (monitored by TLC). The reaction was quenched with H$_2$O, concentrated under reduced pressure. The crude mixture was extracted with dichloromethane, dried over Na$_2$SO$_4$, and concentrated again under reduced pressure. The result mixture was purified by column chromatography (30–50% EtOAc/hexanes) over silica gel to give the corresponding alcohol of *endo*-**12** and *exo* **12**, each in essentially quantitative yield (57 mg and 43 mg, respectively)

Data for *endo*-**12** alcohol. colorless oil; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29 (s, 1H), 5.58 (ddd, J = 12.0, 8.0, 3.0 Hz, 1H), 5.44 (ddd, J = 12.0, 8.0, 3.0 Hz, 1H), 4.44 (t, J = 5.5 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 3.63 (s, 3H), 3.42-3.40 (m, 1H), 3.26 (s, 3H), 3.09-3.08 (m, 1H), 2.96 (s, 3H), 2.84 (dd, J = 16.5, 3.0 Hz, 1H), 2.59 (qd, J = 8.0, 3.0 Hz, 1H), 2.49 (q, J = 7.0 Hz, 2H), 2.39 (ddd, J = 17.0, 8.5, 5.0 Hz, 1H), 2.18 (ddt, J = 15.0, 8.0, 7.0 Hz, 1H), 1.97 (ddt, J = 14.0, 7.0, 7.0 Hz, 1H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 175.3, 168.1, 147.4, 135.3, 124.2, 95.3, 71.7, 60.5, 58.1, 50.4, 44.2, 40.7, 36.6, 33.6, 29.7, 24.9, 14.2; IR (CH$_2$Cl$_2$) 3417, 3055, 2979, 1724, 1672, 1614, 1415, 1264, 1170, 1065, 986 cm^{-1}; HRMS (ESI-FTICR): *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{25}NO_5H$: 324.1805, found: 324.1804.

Data for *exo*-**12** alcohol. colorless oil; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 (s, 1H), 5.59-5.53 (m, 1H), 5.27 (dt, J = 10.5, 3.0 Hz, 1H), 4.24 (t, J = 5.0 Hz, 1H), 4.14 (q, J = 8.0 Hz, 2H), 3.62 (s, 3H), 3.28 (t, J = 6.0 Hz, 1H), 3.08-3.05 (m, 2H), 2.93 (s, 3H), 2.87 (d, J = 15.5 Hz, 1H), 2.58-2.44 (m, 3H), 2.37 (s, 1H), 1.95 (ddt, J = 15.0, 8.0, 6.0 Hz, 1H), 1.78 (ddt, J = 15.4, 7.9, 6.1 Hz, 1H), 1.66 (s, 1H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 174.3, 168.8, 148.8, 139.4, 125.0, 93.0, 69.5, 60.3, 56.8, 50.4, 40.6, 36.8, 35.3, 32.6, 30.0, 22.9, 14.2; IR (CH$_2$Cl$_2$) 3434, 3049, 2979, 1724, 1666, 1608, 1433, 1404, 1264, 1176, 1059, 896 cm^{-1}; HRMS (ESI-FTICR): *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{25}NO_5H$: 324.1805, found: 324.1804.

Methyl (1S,6S)-7-methyl-10-oxo-2-(phenoxymethyl)-7-azabicyclo [4.3.1]deca-3,8-diene-9-carboxylate (mixture of *endo*- and *exo*-**13**). Following the general procedure, a mixture of **1** (100 mg, 0.315 mmol), **6** (505 mg, 3.15 mmol), triethylamine (96 mg, 0.946 mmol), and acetonitrile (3.2 mL, 0.1 M) was heated at 85 ºC in an oil bath for 30 h, followed by acidic quenching and column chromatography (40–50% EtOAc/hexanes) over silica gel affording an inseparable mixture of *endo*- and *exo*-**13** as yellow solid (100 mg, 97% yield); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40 (s, 1H), 7.39 (s, 1H), 7.29–7.24 (m, 4H), 6.95–6.91 (m, 4H), 6.89-6.87 (m, 1H), 5.93–5.85 (m, 2H), 5.80–5.75 (m, 2H), 4.22 (dd, J = 9.1, 6.5 Hz, 1H), 4.01 (t, J = 9.0 Hz, 1H), 3.90 (dd, J = 9.4, 6.7 Hz, 1H), 3.81 (dd, J = 9.4, 6.6 Hz, 1H), 3.77 (t, J = 2.8 Hz, 1H), 3.75 (t, J = 3.1 Hz, 1H), 3.72–3.71 (m, 2H), 3.65 (s, 3H), 3.49 (s, 3H), 3.30 (ddt, J = 9.6, 6.8, 3.9 Hz, 1H), 2.92 (s, 3H), 2.91–2.88 (m, 4H), 2.87 (dd, J = 9.6, 6.6 Hz, 1H), 2.74 (ddd, J = 16.8, 8.4, 5.4 Hz, 1H), 2.69- 2.66 (m, 1H), 2.24 (ddt, J = 16.7, 2.8, 2.8 Hz, 1H), 2.16-2.12 (m, 1H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 205.8, 205.4, 168.2, 167.5, 158.9, 158.7, 148.5, 147.4, 135.6, 132.9, 129.53, 129.47, 126.0, 125.6, 212.0, 120.9, 114.8, 114.6, 93.2, 90.6, 70.3, 68.7, 66.2, 66.0, 50.93, 50.87, 47.8, 47.1, 43.3, 41.4, 39.82, 39.78, 28.8, 27.7; IR (CH$_2$Cl$_2$) 3056, 2980, 1726, 1681, 1627, 1416, 1249, 903, 679 cm^{-1}. HRMS (ESI-timsTOF): *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}NO_4H$: 328.1540, found: 328.1542.

Methyl (1S,6S*)-2-((2-iodophenoxy)methyl)-7-methyl-10-oxo-7-azabicyclo[4.3.1]deca-3,8-diene-9-carboxylate* (mixture of *endo*- and *exo*-**14**). Following the general procedure, a mixture of **1** (100 mg, 0.315 mmol), **7** (902 mg, 3.15 mmol), triethylamine (96 mg, 0.946 mmol), and acetonitrile (3.2 mL, 0.1 M) was heated at 85 ºC in an oil bath for 22 h, followed by acidic quenching and column chromatography (40–50% EtOAc/hexanes) over silica gel affording an inseparable mixture of *endo*- and *exo*-**14** as off white solid (100 mg, 70% yield); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41 (s, 1H), 7.40 (s, 1H), 7.29–7.24 (m, 4H), 6.95-9.88 (m, 6H), 5.91 (ddd, *J* = 11.6, 8.0, 2.7 Hz, 1H), 5.87 (ddd, *J* = 11.4, 8.4, 2.5 Hz, 1H), 5.80 – 5.75 (m, 2H), 4.22 (dd, *J* = 9.2, 6.5 Hz, 1H), 3.91 (dd, *J* = 9.4, 6.7 Hz, 1H), 3.82 (dd, *J* = 9.4, 6.7 Hz, 1H), 3.77 (t, *J* = 1.9 Hz, 1H), 3.75 (t, *J* = 3.1 Hz, 1H), 3.72–3.71 (m, 2H), 3.66 (s, 3H), 3.49 (s, 3H), 3.30 (ddt, *J* = 10.5, 6.7, 3.8 Hz, 1H), 2.93 (s, 3H), 2.90 (s, 3H), 2.74 (ddd, *J* = 16.8, 8.4, 5.4 Hz,1H), 2.70–2.66 (m, 1H), 2.24 (ddt, *J* = 16.7, 2.8, 2.6 Hz,1H), 2.15 (d, *J* = 15.9 Hz,1H) ; ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 205.6, 205.4, 168.2, 167.6, 157.4, 157.2, 148.7, 147.4, 139.5, 139.4, 135.3, 132.7, 129.6, 129.5, 125.9, 125.5, 122.74, 122.69, 112.32, 112.26, 93.1, 90.4, 86.72, 86.65, 71.5, 69.4, 66.2, 65.9, 51.0, 50.8, 47.6, 46.5, 43.1, 41.2, 39.83, 39.81, 29.8, 28.8, 27.8; IR (CH$_2$Cl$_2$) 3056, 3007, 2993, 1721, 1676, 1622, 1164, 1074, 1016 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{19}H_{20}INO_4Na$: 476.0329, found: 476.0326.

Methyl (1R,2S*,6R*)-2-cyclohexyl-7-methyl-10-oxo-7-azabicyclo [4.3.1]deca-3,8-diene-9- carboxylate* (*endo*-**15**) and *Methyl (1R*,2R*,6R*)-2-cyclohexyl-7-methyl-10-oxo-7-azabicyclo [4.3.1]deca-3,8-diene-9-carboxylate* (*exo*-**15**). Following the general procedure, a mixture of **1** (40 mg, 0.126 mmol), **8** (38 mg, 0.378 mmol), triethylamine (38 mg, 0.378 mmol), and acetonitrile (1.3 mL, 0.1 M) was heated at 85 ºC for 22 h, followed by acidic quenching and column chromatography (20–30% EtOAc/hexanes) over silica gel affording *endo*-**15** and *exo*-**15.**

Data for *endo*-**15**. 9 mg, 24% yield; colorless oil; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (s, 1H), 5.86 (ddd, *J* = 11.6, 8.3, 2.8 Hz, 1H), 5.66 (dddd, *J* = 12.1, 8.6, 3.2, 0.7 Hz, 1H), 3.78 (dd, *J* = 3.6, 3.4 Hz, 1H), 3.66 (s, 3H), 3.62 (ddd, *J* = 4.9, 2.1, 2.1 Hz, 1H), 2.91 (s, 3H), 2.68 (ddd, *J* = 16.3, 8.6, 5.8 Hz, 1H), 2.58 (ddd, *J* = 10.2, 8.5, 4.2 Hz, 1H), 2.23 (d, *J* = 12.7 Hz, 1H), 2.10 (ddt, *J* = 16.3, 3,0, 3.0 Hz, 1H), 1.75–1.72 (m, 2H), 1.66–1.60 (m, 2H), 1.33-1.12 (m, 4H), 1.10–0.94 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 206.3, 167.7, 147.4, 137.5, 123.0, 94.2, 66.2, 50.8, 47.7, 46.3, 40.1, 39.7, 32.2, 31.4, 27.1, 26.6, 26.4, 26.0; IR (CH$_2$Cl$_2$) 3035, 2965, 1694, 1648, 1617, 1263, 945, 899, 740 cm-1; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{18}H_{25}NO_3Na$: 326.1727, found: 326.1727.

Data for *exo*-**15**. 14 mg, 37% yield; colorless solid from EtOAc/hexanes, mp 132–133 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (s, 1H), 5.82 (dddd, *J* = 10.7, 6.8, 4.6, 1.9 Hz, 1H), 5.73 (ddd, *J* = 11.1, 5.1, 2.5 Hz, 1H), 3.84-3.83 (m, 1H), 3.64 (s, 3H), 3.63 (d, *J* = 2.3 Hz, 1H), 2.88 (s, 3H), 2.80 (dddd, *J* = 15.1, 8.4, 6.8, 0.9 Hz, 1H), 2.46 (dpentet, *J* = 12.6, 3.3 Hz, 1H), 2.10-2.07 (m, 1H), 1.85–1.81 (m, 2H), 1.75–1.64 (m, 4H), 1.52 (dtt, *J* = 10.9, 10.8, 3.2 Hz, 1H), 1.34–1.12 (m, 4H), 1.02-0.94 (m, 1H), 0.82-0.74 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 207.2, 168.3, 148.5, 139.6, 124.3, 91.8, 66.6, 50.8, 50.1, 47.4, 39.8, 39.7, 32.6, 31.6, 28.1, 26.7, 26.6, 26.4; IR (CH$_2$Cl$_2$) 3065, 2961, 1708, 1649, 1627, 1273, 1169, 966, 944, 751 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{18}H_{25}NO_3Na$: 326.1727, found: 326.1727.

Methyl (3R,7R*,7aR*)-11-methoxy-4-methyl-14-oxo-3,4,7,7a,8,9-hexahydro-2H-3,7-methanonaphtho[1,2-e]azonine-6-carboxylate* (*endo*-**16**) and *Methyl (3S*,7R*,7aS*)-11-methoxy-4-methyl-14-oxo-3,4,7,7a,8,9-hexahydro-2H-3,7-methanonaphtho[1,2-e]azonine-6-carboxylate (exo*-**16**). Following the general procedure, a mixture of **1** (110 mg, 0.347 mmol), **9** (646 mg, 3.47 mmol), triethylamine (105 mg, 1.04 mmol), and acetonitrile (3.5 mL, 0.1 M) was heated at 85 ºC in an oil bath for 14 h, followed by acidic quenching and column chromatography (2–5% EtOAc/DCM) over silica gel affording *endo*-**16** and *exo*-**16**.

Data for *endo*-**16**. 39 mg, 35%; pale yellow solid from EtOAc/hexanes mp 164–165 ºC; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.40 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.69 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.11 (ddd, *J* = 8.4, 7.2, 2.4 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.60 (ddd, *J* = 10.8, 6.6, 3.4 Hz, 1H), 3.49 (s, 3H), 3.30 (dd, *J* = 6.0, 2.5 Hz, 1H), 2.87-2.83 (m, 2H), 2.57 (ddd, *J* = 15.6, 7.8, 3.6 Hz, 1H), 2.49-2.40 (m, 1H), 2.18-2.11 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$) δ 206.9, 167.6, 158.9, 145.0, 142.0, 139.8, 128.0, 125.2, 117.4, 112.7, 112.6, 96.7, 65.8, 55.2, 50.9, 50.6, 44.5, 40.6, 29.5, 28.8, 28.1; IR (CDCl$_3$) 3049, 2921, 2845, 1730, 1684, 1608, 1491, 1433, 1258 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{21}H_{23}NO_4Na$: 376.1519, found: 376.1516.

Data for *exo*-**16**. 66 mg, 59%; yellow oil; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.34 (s, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.60 (d, *J* = 2.2 Hz, 1H), 6.07 (ddd, *J* = 8.7, 4.1, 2.3 Hz, 1H), 3.67–3.66 (m, 2H), 3.51 (s, 3H), 3.03 (ddd, *J* = 15.8, 8.2, 7.0 Hz, 1H), 2.92 (s, 3H), 2.65 (dd, *J* = 11.5, 6.0 Hz, 1H), 2.61 (dt, *J* = 14.8, 3.4 Hz, 1H), 2.49-2.40 (m, 1H), 2.25 (dd, *J* = 16.0, 4.3 Hz, 1H), 2.18-2.12 (m, 1H), 1.88 (dtd, *J* = 13.3, 13.3, 3.0 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$) δ 205.9, 168.0, 158.8, 148.0, 143.3, 140.7, 130.4, 126.1, 118.0, 112.5, 112.1, 91.1, 65.4, 55.2, 51.3, 50.6, 44.7, 39.6, 30.2, 29.4, 29.2; IR (CH$_2$Cl$_2$) 3052, 2993, 2953, 1721, 1685, 1613, 1425, 903, 741, 710 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{19}H_{19}NO_5Na$: 364.1155, found: 364.1155.

Methyl (1S,2S*,6R*)-2-(benzoyloxy)-7-methyl-10-oxo-7-azabicyclo [4.3.1]deca-3,8-diene-9-carboxylate* (*endo*-**17**) and *Methyl (1S*,2R*,6R*)-2-(benzoyloxy)-7-methyl-10-oxo-7-azabicyclo[4.3.1] deca-3,8-diene-9- carboxylate* (*exo*-**17**). Following the general procedure, a mixture of **1** (330 mg, 1.0 mmol), **10** (1812 mg, 10.4 mmol), triethylamine (316 mg, 3.12 mmol), and acetonitrile (10.4 mL, 0.1 M) was heated at 85 ºC in an oil bath for 17 h, followed by acidic quenching and column chromatography (30–50% EtOAc/hexanes) over silica gel affording *endo*-**17** and *exo*-**17**.

Data for *endo*-**17**. 124 mg, 35%; colorless solid from EtOAc/hexanes, mp 177–178 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.54 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.43 (s, 1H), 7.42 (dd, *J* = 8.0, 7.4 Hz, 2H), 6.22 (ddd, *J* =11.8, 7.4, 3.0 Hz, 1H), 5.98 (ddd, *J* = 11.9, 8.7, 3.4 Hz, 1H), 5.71 (dd, *J* = 7.2, 5.9 Hz, 1H), 3.97 (dd, *J* = 5.6, 2.7, 1H), 3.77–3.76 (m, 1H), 3.71 (s, 3H), 2.99 (s, 3H), 2.81 (ddd, *J* = 16.4, 8.7, 6.1 Hz, 1H), 2.39 (dddd, *J* = 16.4, 3.1, 3.1, 1.7 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 202.6, 167.3, 165.4, 148.8, 133.2, 132.0, 130.0, 129.9, 129.8, 128.6, 89.9, 67.5, 66.7, 51.2, 49.2, 40.0, 27.2; IR (CH$_2$Cl$_2$) 3065, 2953, 1726, 1685, 1631, 1267, 1168, 742, 778 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{19}H_{19}NO_5Na$: 364.1155, found: 364.1153.

Data for *exo*-**17**. 195 mg, 55%; yellow solid from EtOAc/hexanes, mp 135–136 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.07 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.56 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.43 (s, 1H), 7.44 (dd, *J* = 7.9, 7.4 Hz, 2H), 5.88-5.84 (m, 1H), 5.78 (dddd, *J* =12.5, 4.3, 3.4, 2.6 Hz, 1H), 5.51 (dddd, *J* = 11.4, 6.1, 2.5, 2.5 Hz, 1H), 4.23 (ddd, *J* = 4.0, 2.9, 1.5 Hz, 1H), 3.77–3.75 (m, 1H), 3.23 (s, 3H), 2.94 (s, 3H), 2.94 (ddd, *J* = 15.5, 8.3, 6.1 Hz, 1H), 2.21 (dddd, *J* = 16.4, 5.0, 2.7 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 202.5, 168.2, 165.6, 148.4, 135.3, 133.2, 130.2, 129.9, 128.4, 123.6, 90.5, 73.3, 66.4, 50.8, 49.6, 39.8, 29.5; IR (CH$_2$Cl$_2$) 3052, 3002, 1726, 1685, 1609, 1425, 1281, 1263, 1164, 894, 764 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{19}H_{19}NO_5Na$: 364.1155, found: 364.1156.

(E)-buta-1,3-dien-1-yl 2-iodobenzoate (**11**). Crotonaldehyde (1.00 g, 14.3 mmol, 1 equiv) in 10 mL THF was added dropwise to a stirred solution of *t*-BuOK (10 mL of 1.6 M THF solution, 16.7 mmol, 1.17 equiv) at -78 ºC during 10 min. The mixture was stirred for 15 min. Then a solution of 2-iodobenzoyl chloride (4.45 g, 16.7 mmol, 1.17 equiv) in 10 mL THF was added and the reaction was stirred for 1 h. After the reaction was complete (TLC), it was quenched by saturated NH_4Cl solution,

extracted with DCM, and concentrated under vacuum. The product was purified via column chromatography (1–5% EtOAc/hexanes) over silica gel to afford **11** as yellow liquid (2.47 g, 61% yield); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.91, (dd, *J* = 7.8, 1.7 Hz, 1H), 7.63 (dd, *J* = 12.3, 0.4 Hz, 1H), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H), 7.20 (td, *J* = 7.9, 1.7 Hz, 1H), 6.36 (ddd, *J* = 16.8, 10.5 Hz, 1H), 6.24 (t, *J* = 12.3 Hz, 1H), 5.28 (dt, *J* = 16.8, 0.7 Hz, 1H), 5.16 (dt, *J* = 10.2, 0.7 Hz, 1H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 163.1, 141.9, 138.9, 133.5, 132.1, 131.7, 131.6, 128.1, 118.0, 117.3, 94.8; IR (CDCl$_3$) 3061, 2993, 2935, 2858, 1726, 1420, 1285, 1249, 1137, 899, 719, 791 cm^{-1}; HRMS HRMS (ESI-FTICR): *m/z*: [M$_2$ + Na]$^+$ Calcd for ($C_{11}H_9IO_2$)$_2$Na: 622.9187, found: 622.9190.

Methyl (1*S**,2*S**,6*R**)-2-((2-iodobenzoyl)oxy)-7-methyl-10-oxo-7-azabicyclo[4.3.1]deca-3,8-diene-9-carboxylate (*endo*-**18**) and Methyl (1*S*,2*R*,6*R*)-2-((2-iodobenzoyl)oxy)-7-methyl-10-oxo-7-azabicyclo [4.3.1]deca-3,8- diene-9-carboxylate (*exo*-**18**). Following the general procedure, a mixture of **1** (132 mg, 0.416 mmol), **11** (1248 mg, 4.16 mmol), triethylamine (126 mg, 1.25 mmol), and acetonitrile (4.2 mL, 0.1 M) was heated at 85 ºC for 25 h, followed by acidic quenching and column chromatography (30–45% EtOAc/hexanes) over silica gel affording *endo*-**18** and exo-**18**.

Data for *endo*-**18**. 84 mg, 43%; yellow solid from EtOAc/hexanes, mp 208–210 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (dd, J = 8.0, 1.0 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.43 (s, 1H), 7.40 (td, *J* = 7.6, 1.1 Hz, 1H), 7.14 (td, *J* = 7.9, 1.8 Hz, 1H), 6.22 (ddd, *J* = 11.8, 7.4, 3.0 Hz, 1H), 6.01 (ddd, *J* = 11.9, 8.6, 3.2 Hz, 1H), 5.75 (dd, *J* = 7.4, 5.8 Hz, 1H), 3.96 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.75–3.74 (m, 1H), 3.71 (s, 3H), 2.99 (s, 3H), 2.81 (ddd, *J* = 16.5, 8.7, 6.1 Hz, 1H), 2.39 (ddd, *J* = 16.6, 4.7, 3.0 Hz, 1H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 202.5, 167.2, 165.0, 148.8, 141.6, 134.0, 133.0, 131.6, 131.3, 130.5, 128.2, 94.5, 89.7, 68.1, 66.6, 51.2, 49.0, 40.0, 27.2; IR (CH$_2$Cl$_2$) 3061, 2984, 1730, 1699, 1663, 1420, 1272, 894, 760, 728 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{19}H_{18}INO_5Na$: 490.0122, found: 490.0122.

Data for (*exo*-**18**). 84 mg, 43%; yellow solid from EtOAc/hexanes, mp 58–60 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.00 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.50 (s, 1H), 7.42 (td, *J* = 7.8, 1.2 Hz, 1H), 7.17 (td, *J* = 7.7, 1.8 Hz, 1H), 5.92 (dddd, *J* = 12.5, 4.1, 3.2, 2.6 Hz, 1H), 5.80 (dddd, *J* = 15.1, 8.4, 6.0, 2.7 Hz, 1H), 5.52 (ddd, *J* = 8.7, 6.0, 2.6 Hz, 1H), 4.25 (ddd, *J* = 4.9, 3.9, 1.5 Hz, 1H), 3.7–3.76 (m, 1H), 3.37 (s, 3H), 2.98–2.92 (m, 4H), 2.20 (dddd, *J* = 16.1, 7.8, 5.1, 2.3 Hz, 1H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 202.2, 168.0, 164.8, 148.4, 141.8, 135.0, 133.7, 133.1, 132.1, 128.0, 123.7, 94.9, 90.3, 74.2, 66.3, 50.9, 49.6, 39.8, 29.4; IR (CH$_2$Cl$_2$) 3070, 3034, 1703, 1649, 1604, 1258, 746 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{19}H_{18}INO_5Na$: 490.0122, found: 490.0122.

Methyl (1R,2S*,6R*)-7-methyl-10-oxo-2-(thiophen-2-yl)-7-azabicyclo[4.3.1]deca-3,8-diene-9-carboxylate (21) and methyl (1R*,5R*,6S*)-7-methyl-10-oxo-5-(thiophen-2-yl)-7-azabicyclo [4.3.1]deca-3,8-diene-9-carboxylate (22)*. Following the general procedure, a mixture of **1** (200 mg, 0.631 mmol), (*E*)-2-(buta-1,3-dien-1-yl)thiophene (859 mg, 6.31 mmol), triethylamine (191mg, 1.89 mmol), and acetonitrile (6.2 mL, 0.1 M) was heated at 85 ºC in an oil bath for 20 h, followed by acidic quenching and column chromatography afforded **21** and **22**.

Data for **21**. 70 mg, 37%; yellow solid from EtOAc/hexanes, mp = 125–126 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40 (s, 1H), 7.14 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.91 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.88 (dt, *J* = 3.5, 1.2 Hz, 1H), 6.09 (ddd, *J* = 15.01, 8.2, 2.8 Hz, 1H), 5.90 (ddd, *J* = 14.8, 8.5, 2.7 Hz, 1H), 4.44 (dd, *J* = 8.1, 4.1 Hz, 1H), 3.85 (t, *J* = 3.2 Hz, 1H), 3.71 (s, 3H), 3.65 (ddd, *J* = 7.8, 2.5, 2.5 Hz, 1H), 2.93 (s, 3H), 2.76 (ddd, *J* = 16.8, 8.4, 5.6 Hz, 1H), 2.35 (ddt, *J* = 16.8, 2.5, 2.5 Hz, 1H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 203.5, 167.5, 147.5, 142.9, 14.5, 127.0, 126.0, 125.1, 124.2, 93.2, 65.8, 53.4, 51.0, 42.7, 39.8, 27.0; IR (CH$_2$Cl$_2$) 3061, 2989, 1717, 1676, 1627, 1443, 1420, 1272, 1169, 903, 737, 706 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{16}H_{17}NO_3SNa$: 326.0821 found: 326.0821.

Data for **22**. 23 mg, 13%; yellow solid from EtOAc/hexanes, mp = 147–148ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 (s, 1H), 7.19 (dd, *J* = 5.2, 1.1 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.81 (dt, *J* = 3.6, 1.1 Hz, 1H), 6.07–5.95 (m, 2H), 4.38 (dd, *J* = 7.5, 4.9 Hz, 1H), 3.93 (dd, *J* = 4.1, 3.0 Hz, 1H), 3.67 (s, 3H), 3.47 (ddd, *J* = 3.8, 3.8, 3.8 Hz, 1H), 3.08 (s, 3H), 2.78 (ddd, *J* =16.3, 8.4, 4.7 Hz, 1H), 2.35 (ddt, *J* = 16.5, 2.9, 2.9 Hz, 1H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 203.6, 167.3, 146.4, 140.1, 132.0, 129.2, 127.2, 125.8, 125.0, 94.5, 73.3, 50.9, 44.8, 40.6, 39.8, 29.4; IR (CH$_2$Cl$_2$) 3052, 2984, 2948, 1721, 1685, 1636, 1438, 1420, 1272, 1164, 894 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{16}H_{17}NO_3SNa$: 326.0821, found: 326.0821.

Methyl (3R,8S*)-7a-hydroxy-4,8-dimethyl-2,3,3a,4,7,7a-hexahydro-3,7-prop[1]enofuro[3,2-b]pyridine-6-carboxylate* (**24a**) and *Methyl (2R*,5S*)-5-(hydroxymethyl)-2,7-dimethyl-10-oxo-7-azabicyclo[4.3.1] deca-3,8-diene-9-carboxylate* (**24d**). Following the general procedure, a mixture of **1** (760 mg, 2.40 mmol), 23 (2354 mg, 24 mmol), triethylamine (727 mg, 7.19 mmol), and acetonitrile (8.0 ml, 0.3 M) was heated at 85 ℃ in an oil bath for 72 h, followed by acidic quenching and column chromatography affording **24a** and **24d**.

Data for **24a**. 159 mg, 25%; colorless solid from EtOAc/hexanes, mp = 160–161 ℃; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29 (s, 1H), 5.73 (dd, *J* = 12.2, 7.6 Hz, 1H), 5.56 (dd, *J* = 12.2, 8.5 Hz, 1H), 4.25 (dd, *J* = 8.1, 4.8 Hz, 1H), 3.72 (d, *J* = 8.0 Hz, 1H), 3.66 (s, 1H), 3.56 (dd, *J* = 6.1, 1.9 Hz, 1H), 3.50 (s, 1H), 3.02 (ddd, *J* = 8.2, 5.9, 4.9 Hz, 1H), 2.95 (s, 3H), 2.94-2.93 (m, 1H), 2.48 (dpentet, *J* = 7.4, 1.5 Hz, 1H), 1.26 (d, *J* = 7.5 Hz, 3H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 168.6, 145.0, 138.7, 124.3, 104.2, 98.8, 70.7, 66.2, 50.8, 44.8, 41.5, 39.7, 39.6, 22.4; IR (CH$_2$Cl$_2$) 3056, 2989, 1636, 1425, 1254, 921, 773 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{19}NO_4H$: 266.1388, found: 266.1391.

Data for **24d**. 166 mg, 26%; colorless solid from EtOAc/hexanes, mp = 157–158 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (s, 1H), 5.60 (dddd, *J* = 11.3, 4.0, 2.5, 0.7 Hz, 1H), 5.41 (dddd, *J* = 11.4, 4.0, 2.5, 0.7 Hz, 1H), 4.02 (ddd, *J* = 11.1, 7.1, 4.4 Hz, 1H), 3.99 (ddd, *J* = 2.4, 1.2, 1.2 Hz, 1H), 3.79 (ddd, *J* = 10.6, 10.0, 6.8 Hz, 1H), 3.66 (s, 3H), 3.49 (t, *J* = 2.0 Hz, 1H), 3.00 (s, 3H), 2.42-2.40 (m, 2H), 1.78- 1.73 (m, 1H), 1.29 (d, *J* = 7.3 Hz, 3H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 207.2, 168.3, 148.9, 140.3, 127.1, 92.1, 67.2, 64.4, 52.3, 50.9, 45.7, 43.2, 38.6, 21.5; IR (CH$_2$Cl$_2$) 3061, 2984, 1699, 1622, 1429, 1285, 903, 787 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{14}H_{19}NO_4Na$: 288.1206, found: 288.1208.

Methyl (1R,2S*,5R*,6R*)-2-(acetoxymethyl)-5,7-dimethyl-10-oxo-7-azabicyclo[4.3.1]deca-3,8-diene-9-carboxylate* (**26a**) and *Methyl (1R*,2R*,5S*,6R*)-5-(acetoxymethyl)-2,7-dimethyl-10-oxo-7-azabicyclo [4.3.1]deca-3,8-diene-9-carboxylate* (**26d**). Following the general procedure, a mixture of **1** (300 mg, 0.946 mmol), **25** (1326 mg, 9.46 mmol), triethylamine (287 mg, 2.84 mmol), and acetonitrile (3.2 mL, 0.3 M) was heated at 85 ºC for 72 h, followed by acidic quenching and column chromatography (1–3% EtOH/hexanes) over silica gel afforded **26a** and **26d**.

Data for **26a**. 50 mg, 17%; yellow solid from EtOAc/hexanes, mp 77–79 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40 (s, 1H), 5.77 (dd, *J* = 12.9, 7.2 Hz, 1H), 5.58 (dd, *J* = 12.9, 7.4 Hz, 1H), 4.13 (dd, *J* = 11.1, 5.3 Hz, 1H), 3.68 (dd, *J* = 11.1, 9.1 Hz, 1H), 3.66 (s, 3H), 3.61 (dt, *J* = 3.1, 0.7 Hz, 1H), 3.49 (dt, *J* = 3.4, 0.9 Hz, 1H), 3.03–2.99 (m, 1H), 2.99 (s, 3H), 2.81 (dddd, *J* = 14.4, 7.1, 3.9, 3.8 Hz, 1H), 2.10 (s, 3H), 1.03 (d, *J* = 7.3 Hz, 3H); ^{13}C{1H} NMR (125 MHz, CDCl$_3$) δ 203.8, 171.1, 167.4, 146.6, 134.5, 128.0, 93.5, 71.6, 65.0, 50.9, 45.5, 40.7, 40.5, 33.1, 21.1, 19.2; IR (CH$_2$Cl$_2$) 3061, 2984, 1636, 1276, 1258, 760, 733, 701 cm^{-1}; HRMS (ESI-FTICR): *m/z*: [M + Na]$^+$ Calcd for $C_{16}H_{21}NO_5Na$: 330.1312, found: 330.1315.

Data for **26d**. 19 mg, 7% yield; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (s, 1H), 5.62 (dddd, *J* = 11.3, 4.1, 2.5, 0.6 Hz, 1H), 5.45 (dddd, *J* = 11.3, 4.3, 2.6, 0.9 Hz, 1H), 4.42 (dd, *J* = 11.2, 7.4 Hz, 1H), 4.22 (dd, *J* = 11.2, 9.3 Hz, 1H), 3.75-3.74 (m, 1H), 3.66 (s, 3H), 3.49 (t, *J* = 2.3 Hz, 1H), 2.96 (s, 3H), 2.62- 2.59 (m, 1H), 2.44-2.40 (m, 1H), 2.12 (s, 3H), 1.30 (d, *J* = 7.3 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 206.2, 170.0, 168.1, 148.7, 140.7, 126.5, 92.6, 68.1, 65.4, 52.1, 50.9, 43.3, 42.3, 38.4, 21.5, 21.0; IR (CH_2Cl_2) 3052, 2984, 1622, 1272, 1258, 755, 728, 710 cm^{-1}; HRMS (ESI-FTICR): *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{21}NO_5Na$: 330.1312, found: 330.1315.

Methyl (1R,2S*,5R*,6R*)-5,7-dimethyl-10-oxo-2-(phenylthio)-7-azabicyclo[4.3.1]deca-3,8-diene-9-carboxylate* (**28**) and *Methyl (1R*,2S*,5R*,6S)-10-hydroxy-2,7-dimethyl-5-(phenylthio)-7-azabicyclo [4.3.1]deca-3,8- diene-9-carboxylate* (**29**). Following the general procedure, a mixture of **1** (200 mg, 0.631 mmol), **27** (1112 mg, 6.31 mmol), triethylamine (191 mg, 1.89 mmol), and acetonitrile (2.1 mL, 0.3 M) was heated at 85 ℃ in an oil bath for 48 h, followed by acidic quenching and column chromatography (20–30% EtOAc/hexanes) over alumina affording **28** (67 mg, 31% yield) and **29 (**22 mg, 10% yield)**.** Compound **29** (26 mg, 0.076 mmol, 1 equiv.) was treated with $NaBH_4$ (3 mg, 0.083 mmol, 1.1 equiv) in methanol (0.8 mL, 0.1 M) and stirred it at rt for 30 min (monitored by TLC). The reaction was quenched with H_2O, concentrated under reduced pressure. The crude mixture was extracted with dichloromethane, dried over Na_2SO_4, and concentrated again under reduced pressure. The result mixture was purified by column chromatography (40–50% EtOAc/hexanes) over alumina gel to give the corresponding alcohol of **29** (25 mg, 96% yield).

Data for **28**. Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.1 Hz, 2H), 7.37 (s, H), 7.35 (tt, *J* = 7.5, 1.8 Hz, 2H), 7.25 (dt, *J* = 7.1, 1.8 Hz, 1H), 5.87 (dd, *J* = 5.1, 2.6 Hz, 2H), 4.27 (ddd, J = 11.2, 7.1, 3.8 Hz, 1H), 3.59–3.58 (m, 4H), 3.51 (dd, *J* = 4.1, 3.1 Hz, 1H), 2.96 (s, 3H), 2.89- 2.82 (m, 1H), 1.17 (d, *J* = 7.3 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 201.9, 167.1, 147.3, 134.5, 133.4, 131.8, 128.9, 128.0, 127.1, 92.2, 71.4, 50.6, 47.6, 40.3, 32.4, 18.5; IR (CH_2Cl_2) 3065, 2957, 2926, 2876, 1735, 1734.8, 1470, 1371, 1249, 1047, 899, 683 cm^{-1}; HRMS (ESI-FTICR): *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{21}NO_3SNa$: 366.1134, found: 366.1132.

Data for corresponding alcohol of **29**; colorless solid from EtOAc/hexanes, mp = 130–132 ºC; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.39–7.33 (m, 3H), 7.17 (s, 1H), 5.78 (dd, *J* = 12.2, 7.3 Hz, 1H), 5.65 (dd, *J* = 12.2, 6.9 Hz, 1H), 4.54 (ddd, *J* = 10.5, 7.8, 5.3 Hz, 1H), 4.14 (dd, *J* = 6.9, 3.3 Hz, 1H), 3.76 (d, *J* = 7.9 Hz, 1H), 3.64 (s, 3H), 3.63 (dd, *J* = 3.3, 1.8 Hz, 1H), 3.14 (ddd, *J* = 8.0, 5.4, 2.6 Hz, 1H), 2.93 (dpentet, *J* = 7.5, 2.5 Hz, 1H), 2.78 (s, 3H), 1.44 (d, *J* = 7.6 Hz, 3H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 168.0, 145.5, 139.5, 134.1, 132.7, 129.5, 128.4, 122.7, 97.8, 75.4, 59.6, 50.6, 48.4, 40.8, 39.9, 38.7, 23.3; IR (CH_2Cl_2) 3398, 3061, 3011, 2993, 1676, 1627, 921, 733, 652 cm^{-1}; HRMS (ESI- timsTOF): *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{23}NO_3SNa$: 368.1291, found: 368.1288.

Methyl (1S,6S)-7-methyl-10-oxo-7-azabicyclo[4.3.1]deca-2,4,8-triene-9-carboxylate (**33**). A mixture of *endo*-**18** (34 mg, 0.073 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2 mg, 0.0073 mmol, 0.1 equiv), KOAc (14 mg, 0.14 mmol, 2.0 equiv), 4 Å molecular sieves, and DMF (1.5 mL, 0.05 M) was heated at 80 ºC for 24 h (monitored by TLC). When the reaction was complete, the crude mixture was filtered through Celite® and extracted with diethyl ether and water. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting mixture was purified by column chromatography (30–35% EtOAc/hexanes) on silica gel to give **33** as a yellow oil (6 mg, 38% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 6.15 (dd, *J* = 15.0, 10.0 Hz, 1H), 5.88-5.80 (m, 2H), 5.74 (dd, *J* = 15.0, 10.0 Hz, 1H), 4.17 (dd, *J* = 6.5, 3.3 Hz, 1H), 4.01 (dd, *J* = 7.2, 3.3 Hz, 1H), 3.69 (s, 3H), 2.96 (s, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 199.8, 167.2, 147.1, 130.4, 128.1, 122.4, 119.5, 96.9, 66.7, 51.2, 49.8, 39.8; IR (CH_2Cl_2) 3036, 2950, 2938, 2912, 1729, 1680, 1613, 1440, 1323, 1219, 1162, 1066, 761, 707 cm^{-1}; HRMS (ESI- timsTOF): *m/z*: $[M + H]^+$ calcd for $C_{12}H_{13}NO_3H$: 220.0979, found: 220.0978.

Methyl (3S,7S)-4-methyl-14-oxo-3,4,7,7a,8,13b-hexahydro-3,7-methanochromeno[3,4-e]azonine-6-carboxylate (**34**). A mixture of **14** (60 mg, 0.132 mmol, 1.0 equiv), $Pd(OAc)_2$ (3 mg, 0.0132 mmol, 0.1 equiv), KOAc (26 mg, 0.264 mmol, 2.0 equiv), 4 Å molecular sieves, and DMF (3.0 mL, 0.05 M) was heated at 80 ºC for 24 h (monitored by TLC). When the reaction was complete, the crude mixture was filtered through Celite® and extracted with diethyl ether and water. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The result mixture was purified by column chromatography (30–35% EtOAc/hexanes) over silica gel to give the mixture of *endo*- and *exo*-**34** as a colorless oil (28 mg, 65% yield).

Data for **34a/b**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.62 (s, 1H), 7.15-7.09 (m, 2H), 7.15-7.09 (m, 1H), 7.02 (dd, *J* = 7.6, 1.5 Hz, 1H),6.93 (td, *J* = 7.5, 1.2 Hz, 1H), 6.87 (td, *J* = 7.4, 1.1 Hz, 1H), 6.81 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.28 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.97-5.94 (m, 1H), 5.97 (ddd, *J* = 10.7, 7.9, 2.7 Hz, 1H), 5.89 (ddd, *J* = 11.0, 7.8, 3.0 Hz, 1H),4.33 (dt, *J* = 11.0, 3.5 Hz, 1H), 4.30 (ddd, *J* = 11.1, 3.1, 2.1 Hz, 1H), 4.22 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.94 (s, 1H), 3.90-3.84 (m, 1H), 3.90-3.84 (m, 2H), 3.75 (t, *J* = 2.5 Hz, 1H), 3.66 (s, 3H), 3.66 (s, 3H), 3.61 (t, *J* = 11.5 Hz, 1H), 3.61-3.60 (m, 1H), 3.05 (s, 3H), 3.03 (s, 3H), 2.81 (dddd, *J* = 15.5, 11.4, 7.3, 3.5 Hz, 1H), 2.66 (tdd, *J* = 11.4, 3.5, 2.5 Hz, 1H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 201.1, 199.6, 167.9, 167.3, 154.8, 153.7, 149.6, 147.0, 145.7, 143.2, 129.4, 128.9, 128.5, 127.8, 126.8, 125.7, 124.5, 122.7, 121.5, 120.7, 117.1, 117.0, 91.5, 89.1, 69.9, 66.9, 65.7, 65.2, 51.1, 51.1, 49.3, 48.2, 45.4, 40.7, 40.5, 38.9, 37.1, 34.6; IR (CH_2Cl_2): 3011, 2984, 1730, 1685, 1622, 1492, 1280, 912, 777, 724, 656 cm^{-1}; HRMS (ESI-FTICR): *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{19}NO_4Na^+$: 348.1206, found: 348.1206.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 2053228-2053241 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif, or by email-ingdata_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

1. (a) Harmata, M. The (4 + 3)-cycloaddition reaction: simple allylic cations as dienophiles. *Chem. Commun.* **2010**, *46*, 8886-8903. (b) Harmata, M. The (4 + 3)-cycloaddition reaction: heteroatom-substituted allylic cations as dienophiles. *Chem. Commun.* **2010**, *46*, 8904-8922. (c) Mascareñas, J. L.; Gulias, M.; Lopez, F. (4+3) cycloadditions. In *Cycloaddition Reactions in Organic Syntheses*, Nishiwaki, N., Ed.; John Wiley & Sons: Hoboken, 2014, pp 595-655. (d) Lam, S. Y. Y.; Chiu, P. [4+3] Cycloadditions of enol silane derivatives. In *Methods and Applications of Cycloaddition Reactions in Organic Syntheses,* Nishiwaki, N., Ed.; Wiley: New York, 2014; Chapter 18. (e) Jones, D. E.; Harmata, M. Application of the [4+3]-Cycloaddition Reaction to the Synthesis of Natural Products. In *Methods and Applications of Cycloaddition Reactions in Organic Synthesis*; Nishiwaki, N., Ed.; Wiley: New York, 2014; Chapter 19.

2. For selected examples, see: (a) Harmata, M.; Gamlath, C. B. Intramolecular 4 + 3 cycloadditions of 2-alkoxyallylic cations derived from 2-alkoxyallylic sulfones. *J. Org. Chem.* **1988**, *53*, 6154-6156. (b) Harmata, M.; Fletcher, V. R.; Claassen, R. J., II. Alkoxyvinyl thionium ions in intramolecular 4+3 cycloaddition reactions. *J. Am. Chem. Soc.* **1991**, *113*, 9861-9862. (c) Harmata, M.; Elomari, S.; Barnes, C. L. Intramolecular 4 + 3 Cycloadditions. Cycloaddition Reactions of Cyclic Alkoxyallylic and Oxyallylic Cations. *J. Am. Chem. Soc.* **1996**, *118*, 2860-2871. (d) Harmata, M.; Sharma, U. Synthesis and Some Cycloaddition Reactions of 2-(Triisopropylsilyloxy)acrolein. *Org. Lett.* **2000**, *2*, 2703-2705. (e) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. Asymmetric Organocatalysis of [4+3] Cycloaddition Reactions. *J. Am. Chem. Soc.* **2003**, *125*, 2058-2059. (f) Harmata, M.; Huang, C.; Rooshenas, P.; Schreiner, P. R. An Interrupted [4+3] Cycloaddition Reaction: A Hydride Shift (ene reaction) Intervenes. *Angew. Chem., Int. Ed.* **2008**, *47*, 8696-8699. (g) Topinka, M.; Zawatzky, K.; Barnes, C. L.; Welch, C. J.; Harmata, M. An Asymmetric, Catalytic (4 + 3) Cycloaddition Reaction of Cyclopentenyl Oxyallylic Cations. *Org. Lett.* **2017**, *19*, 4106-4109.

3. (a) Dennis, N.; Katritzky, A. R.; Rittner, R. 1,3-Dipolar Character of Six-Membered Aromatic Rings. Part XXV. 5-Aryl-1-methyl-3-oxidopyridiniums. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2329-2334. (b) Katritzky, A. R.; Rahimi-Rastgoo, S.; Sabongi, G. J.; Fischer, G. W. 1,3-Dipolar Character of Six-Membered Aromatic Rings. Part 51. Cycloadditions of 1-(β-Benzoylvinyl)-3-oxidopyridiniums and Subsequent Transformations. *J. Chem. Soc., Perkin Trans. 1* **1980**, 362-371. (c) Katritzky, A. R.; Dennis, N. Cycloaddition Reactions of Heteroaromatic Six-Membered Rings. *Chem. Rev.* **1989**, *89*, 827-861. (d) Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. Facile Synthesis of the Tricyclic Core of Sarain A. 3-Oxidopyridinium Betaine Cycloaddition Approach. *Org. Lett.* **1999**, *1*, 2017-2019. (e) Lee, H. I.; Sung, M. J.; Lee, H. B.; Cha, J. K. Synthetic studies toward sarain A: An improved synthesis of the tricyclic core of sarains by a 3-oxidopyridinium betaine cycloaddition. *Heterocycles* **2004**, *62*, 407-422.

4. Fu, C.; Lora, N.; Kirchhoefer, P. L.; Lee, D. R.; Altenhofer, E.; Barnes, C. L.; Hungerford, N. L.; Krenske, E. H.; Harmata, M. (4+3) Cycloaddition Reactions of *N*-Alkyl Oxidopyridinium Ions. *Angew. Chem., Int. Ed.* **2017**, *56*, 14682-14687.

5. Zhang, J.; Cao, P.; Ma, Y.; Fang, X.; Yang, J.; Zhang, Y.; Chen, D.; Gu, Y.; Di, Y.; Hao, X. Structural Revision of Macropodumine A and Structure of 2-Deoxymacropodumine A, Daphniphyllum Alkaloids with 11-Membered Macrolactone Rings. *J. Nat. Prod.* **2019**, *82*, 427-430.

6. Zhu, X.-X.; Fan, Y.-Y.; Xu, L.; Liu, Q.-F.; Wu, J.-P.; Li, J.-Y.; Li, J.; Gao, K.; Yue, J.-M. Alstonlarsines A–D, Four Rearranged Indole Alkaloids from Alstonia scholaris. *Org. Lett.* **2019**, *21*, 1471-1474.

7. (a) Rinderknecht, B. L.; Wicklow, D. T.; Dowd, P. F. Nominine: a new Insecticidal Indole Diterpene from the Sclerotia of *Aspergillus nomius*. *J. Org. Chem.* **1989**, *54*, 2530-2532. (b) Sakai, S.; Yamamoto, I.; Yamaguchi, K.; Takayama, H.; Ito, M.; Okamoto, T. The Structure of the New Diterpene Alkaloid Nominine and the Absolute Configuration of Kobusine. *Chem. Pharm. Bull.* **1982**, *30*, 4579-4582.

8. Woodcock, S. R.; Branchaud, B. P., Effect of Ether Versus Ester Tethering on Heck Cyclizations. *Tetrahedron Lett.* **2005,** *46*, 7213-7215.

9. Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. Formation of a Terminal Conjugated Diene System by the Palladium Catalyzed Elimination Reactions of Allylic Acetates and Phenyl Ethers. *Tetrahedron Lett.* **1978**, *19*, 2075-2078.

10. Ghosh, A. K.; Gong, G., Total Synthesis and Revision of C6 Stereochemistry of (+)-Amphidinolide W. *J. Org. Chem.* **2006,** *71*, 1085-1093.

11. Maruyama, K.; Nagai, N.; Naruta, Y., Lewis Acid-Mediated Claisen-Type Rearrangement o Aryl Dienyl Ethers. *J. Org. Chem.* **1986,** *51*, 5083-5092.

12. Cooper, I. R.; Grigg, R.; MacLachlan, W. S.; Sridharan, V.; Thornton-Pett, M., Diastereo- and Regioselective Palladium-Indium Bimetallic Cyclisation-Barbier-Type Allylation Cascades. *Tetrahedron Lett.* **2003,** *44*, 403-405.

13. Jing, S. M.; Balasanthiran, V.; Pagar, V.; Gallucci, J. C.; RajanBabu, T. V., Catalytic Enantioselective Hetero-Dimerization of Acrylates And 1,3-Dienes. *J. Am. Chem. Soc.* **2017,** *139*, 18034-18043.

14. Liu, W.; Zhou, J.; Geng, G.; Shi, Q.; Sauriol, F.; Wu, J. H., Antiandrogenic, Maspin Induction, and Antiprostate Cancer Activities of Tanshinone IIA and its Novel Derivatives with Modification in Ting A. *J. Med. Chem.* **2012,** *55*, 971-975.

15. Kawashima, M. Method for Preparation of 1-Acyloxy-1,3-butadiene compounds. JP2018131399A, 2018.

16. Pini, E.; Bertacche, V.; Molinari, F.; Romano, D.; Gandolfi, R., Direct Conversion of Polyconjugated Compounds into Their Corresponding Carboxylic Acids by *Acetobacter aceti*. *Tetrahedron* **2008,** *64*, 8638-8641.

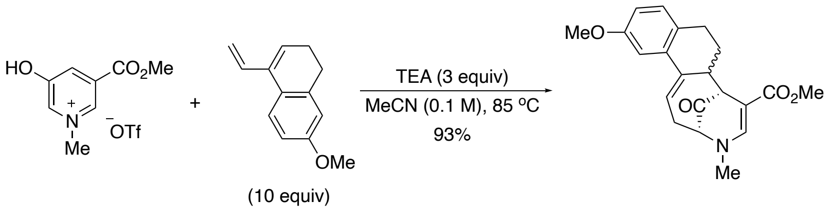
17. Grayson, J. I.; Warren, S.; Zaslona, A. T., Phenylthioallyl and Phenylthiovinyl Phosphine Oxides: Synthesis of 1-Phenylthiobutadienes and a Three-Component Synthesis of Ketones. *J. Chem. Soc., Perkin Trans. 1* **1987**, 967-976.

18. Apex3, AXScale, and SAINT, version 2017.3-0, Bruker AXS, Inc., Madison, WI, 2017.

19. Sheldrick, G. M. SHELXS, v.2013-1, 2013.

20. Sheldrick, G. M. Crystal structure refinement with *SHELXL*. *Acta Cryst. Sect. C. Struct. Chem.* **2015**, *71*, 3-8.

21. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *OLEX2:* A complete structure solution, refinement, and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339-341.


HO
CO2Me
N
Me
OTf
+
(10 equiv)
OMe
TEA (3 equiv)
MeCN (0.1 M), 85 ºC
93%
MeO
OC
CO2Me
N
Me