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Synthesis of Functionalized Indolizidines through Pauson–Khand Cycloaddition of 2-Allylpyrrolidines

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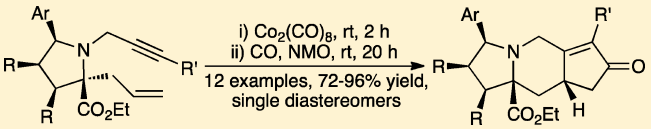
Supporting Information

ABSTRACT: A concise entry to functionalized indolizidine scaffolds through a domino 2-aza-Cope-[3 + 2] dipolar cycloaddition and Pauson–Khand [2 + 2 + 1] cyclization has been accomplished. The process was conducted under mild conditions to afford diverse indolizidine systems as single diastereomers in good overall yields.



INTRODUCTION

New synthetic strategies for the construction of functionally diverse indolizidine scaffolds in a concise and stereoselective fashion are of importance to many areas of pharmaceutical and academic research.[1] Natural products featuring the indolizidine framework often exhibit desirable pharmacological activities such as antibacterial, fungicidal, antihelmintic, and insecticidal properties.[2] Examples of such medicinally relevant indolizidine natural products include asperparaline C (**1**, Figure 1),[3]

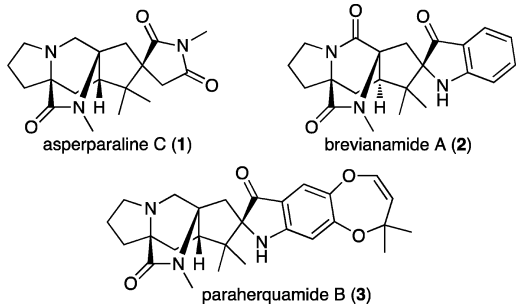
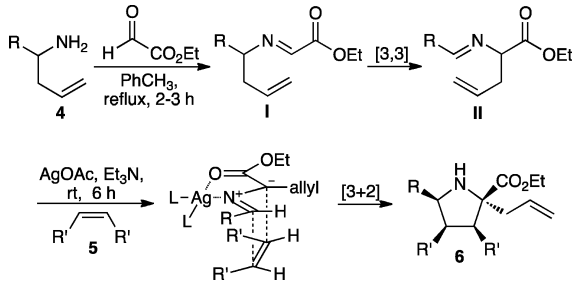


Figure 1. Biologically active indolizidine-containing natural products accessible through Pauson–Khand cycloaddition.

brevianamide A (**2**),[4] and paraherquamide B (**3**).[5] These molecules display a common [5–6–5] tricyclic fused ring system and a bridging lactam function, features which have made them attractive targets for total synthesis.[6] The ability to structurally diversify these heterocyclic systems would offer a means to further explore their biological activities, thereby facilitating the development of more efficacious therapeutics.[7]

Our laboratory has developed a new, one-pot multicomponent procedure for the synthesis of highly functionalized 2-allylpyrrolidine rings through a domino 2-aza-Cope-[3 + 2] dipolar cycloaddition sequence (Scheme 1).[8] Condensation of a homoallylic amine (cf. **4**, Scheme 1) with ethyl glyoxylate affords an imine (**I**) that is positioned to undergo 2-aza-Cope rearrangement[9] to furnish an azomethine ylide precursor (**II**). Addition of AgOAc and Et_3N provides an *N*-metalated

Scheme 1. 2-Aza-Cope-[3 + 2] Dipolar Cycloaddition Process



azomethine ylide[10] that in the presence of a dipolarophile (**5**) undergoes [3 + 2] dipolar cycloaddition to afford a highly substituted pyrrolidine (**6**) as one diastereomer. This process generates up to four stereogenic centers within the proline cycloadduct, is tolerant toward a variety of functional groups, and affords a synthetically versatile 2-allyl appendage for additional structural advancements.

Recognizing the synthetic versatility provided by the 2-allyl function, we are now investigating the merger of the 2-aza-Cope-[3 + 2] dipolar cycloaddition sequence with additional cyclization events to access further *N*-heterocyclic ring systems. Specifically, we envisioned that our 2-allylpyrrolidine cycloadducts could be utilized in the direct syntheses of structurally diverse indolizidines through ring annulation. We have recently reported the stereoselective synthesis of such indolizidine systems through aza-Prins cyclization of our 2-allylpyrrolidine cycloadducts (Scheme 2).[11] The condensation of an aldehyde onto the pyrrolidine nitrogen of **6** furnishes an iminium ion (**10**) that undergoes cationic π-cyclization[12] with the pendant olefin. Capture of the developing secondary carbocation by either the solvent or a tethered nucleophile[13] provides the six-membered ring of the indolizidine (**11**) and two additional stereocenters. With the goal of promoting additional ring

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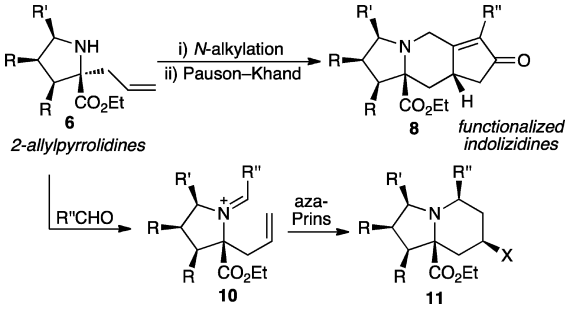
Scheme 2. Elaboration of 2-Allylpyrrolidines to Indolizidines



annulation events for the synthesis of indolizidines in a minimal number of synthetic operations, we have now turned our investigations toward an intramolecular Pauson–Khand [2 + 2 + 1] cycloaddition[14] strategy (Scheme 2). Such a process would afford an indolizidine (**8**) bearing two additional ring fusions, one new stereogenic center, and a versatile enone group. Although the Pauson–Khand reaction has enjoyed some success in alkaloid natural product synthesis,[15] only limited examples utilizing simple 2-allylprolines as substrates have been previously reported,[16] and the process has not been explored in any detail with functionalized 2-allylpyrrolidine systems. Together with our ability to rapidly obtain a variety of 2-allylpyrrolidines in a one-pot process, our synthetic approach would provide a concise entry to indolizidine ring systems that would otherwise require multiple synthetic steps to construct. In this paper, we describe in detail the further elaboration of functionalized 2-allylpyrrolidines, readily obtained through our domino 2-aza-Cope-[3 + 2] dipolar cycloaddition protocol, toward the synthesis of structurally advanced indolizidines through Pauson–Khand cycloaddition.

RESULTS AND DISCUSSION

Our studies commenced with the preparation of a series of 2-allylpyrrolidine cycloadducts, readily obtained in high yields through our multicomponent 2-aza-Cope-[3 + 2] dipolar cycloaddition sequence. For the generation of the *N*-metalated azomethine ylides, homoallylamines (**4a–c**, Figure 2) were

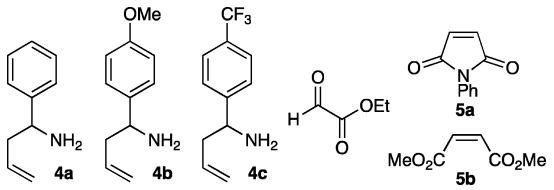
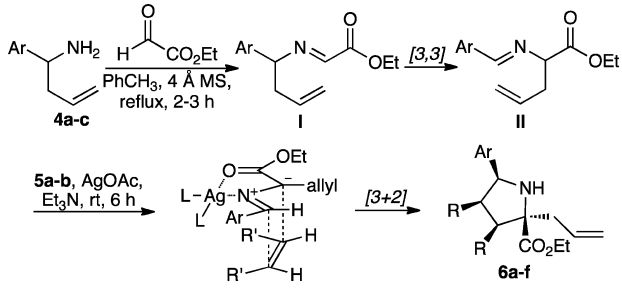


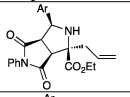
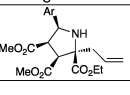
Figure 2. Survey of amine, aldehyde, and alkene components employed in this study.

surveyed as the nucloeophilic component, while ethyl glyoxylate was utilized as the electrophilic component. Phenyl maleimide (**5a**) and dimethyl maleate (**5b**) were employed as the alkenyl dipolarophiles.

Briefly heating a mixture of homoallylamines **4a–c** with ethyl glyoxylate in toluene for 2–3 h afforded an initial imine which underwent clean 2-aza-Cope sigmatropic rearrangement to provide a new imine species that may be viewed as an azomethine ylide precursor (Table 1). Although our original experimental conditions for ylide formation employed a molar excess of AgOAc,[8] we have now observed that the process can be conducted catalytically (10 mol %) with no deleterious effect

Table 1. Preparation of Pauson–Khand Substrates via the Domino 2-Aza-Cope-[3 + 2] Dipolar Cycloaddition Sequence[a]



entry	amine (Ar)	alkene	product		yield (%)[b]
1	**4a** (Ph)	**5a**		**6a**	85
2	**4b** (*p*-MeOPh)			**6b**	81
3	**4c** (*p*-F_3CPh)			**6c**	97
4	**4a** (Ph)	**5b**		**6d**	81
5	**4b** (*p*-MeOPh)			**6e**	85
6	**7f** (*p*-F_3CPh)			**6f**	94

[a]Reaction conditions: homoallylic amine **4a–c** (1.0 equiv), ethyl glyoxylate (1.0 equiv), 4 Å MS, toluene, reflux, 2–3 h; then addition of alkenes **5a,b** (1.5 equiv), AgOAc (0.1 equiv), Et_3N (2.0 equiv), rt, 6 h. [b]Isolated yields after flash column chromatography on silica gel or recrystallization.

on the overall yield. Indeed, the use of Et_3N (2.0 equiv) and AgOAc (0.1 equiv) furnished an *N*-metalated azomethine ylide intermediate that underwent *endo*-selective [3 + 2] dipolar cycloaddition in the presence of dipolarophiles **5a,b**, providing the highly functionalized 2-allylpyrrolidines **6a–f** (Table 1) as single diastereomers in good overall yields. NOE analysis of **6a** revealed that the cycloaddition exhibited *endo*-selectivity, which was unambiguously confirmed via X-ray crystallography. For all cases, the relative stereochemistries of the 2-allylpyrrolidines (**6a–f**) were consistent with a transition state involving a W-shaped azomethine ylide geometry and an *endo* approach of the dipolarophile, as shown in Table 1.

Allylpyrrolidines **6a–f** were *N*-alkylated with propargyl bromide or but-2-ynyl methanesulfonate[17] to furnish enynes **7a–l** (Table 2). Although some substrates were somewhat resistant toward alkylation due to steric encumbrance about the pyrrolidine nitrogen, good yields of enynes **7a–f** could be achieved from **6a–c** in DMF at 130 °C (entries 1–6). Some decomposition of **6d–f** was observed at this temperature but could be minimized at 80 °C in the presence of TBAI (entries 7–12), and any remaining starting material could be readily recovered.

A survey of conditions to promote the Pauson–Khand reaction was investigated using enynes **7a**, **7g**, and **7h** (Table 3). Initially, complexation of $Co_2(CO)_8$ to the alkyne was best achieved in CH_2Cl_2, occurring quantitatively within 1 h at rt, while the cycloaddition could be effected in refluxing toluene within 2 h using NMO as a promotor.[18] Under these conditions, **7a** was converted to indolizidine **8a** in 60% yield with >95:5 diastereoselectivity at the new ring fusion (entry 1). Subjection of **7g** to the same conditions furnished indolizidine **8g**, but an erosion in both yield (48%) and dr (5:1) was observed (entry 2). Lowering the temperature of the cycloaddition to 50–60 °C in toluene led to an increased reaction time (entries 3 and 4) but did not alter the yield or diastereoselectivity. A notable observation for all cases, however, was concomitant 1,7-enyne cycloisomerization to

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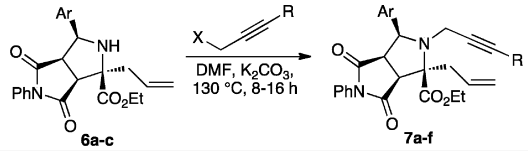
Table 2. *N*-Alkynylation of 2-Allylpyrrolidines[a]



entry	amine	Ar	R	product	yield (brsm)[b]
1	**6a**	Ph	H	**7a**	73 (83)
2	**6b**	*p*-MeOPh	H	**7b**	75 (94)
3	**6c**	*p*-CF_3Ph	H	**7c**	53 (80)
4	**6a**	Ph	Me	**7d**	51 (75)
5	**6b**	*p*-MeOPh	Me	**7e**	62 (98)
6	**6c**	*p*-CF_3Ph	Me	**7f**	58 (77)

entry	amine	Ar	R	product	yield (brsm)[b]
7	**6d**	Ph	H	**7g**	53 (75)
8	**6e**	*p*-MeOPh	H	**7h**	66 (72)
9	**6f**	*p*-CF_3Ph	H	**7i**	65 (75)
10	**6d**	Ph	Me	**7j**	48 (80)
11	**6e**	*p*-MeOPh	Me	**7k**	57 (87)
12	**6f**	*p*-CF_3Ph	Me	**7l**	50 (58)

[a]Reaction conditions: 2-allylpyrrolidine **6a–f** (2.0 mmol), propargyl bromide or but-2-ynyl methanesulfonate (10.0 mmol), K_2CO_3 (10.0 mmol), DMF (0.44 mL), 130 °C or with added TBAI (0.2 mmol) at 80 °C, 8–16 h. [b]Percent isolated yields after flash column chromatography .

afford exocyclic 1,3-diene **9**, presumably arising through an alternative reaction pathway which bypasses migratory insertion of CO from the cobalt complex.[19]

To circumvent these issues, we hypothesized that conducting the process under an atmosphere of CO would promote the Pauson–Khand pathway while suppressing cycloisomerization. We also desired a solvent in which both cobalt complexation and cycloaddition could be achieved at rt, thereby obviating the need for solvent replacement while increasing the prospects for high diastereoselectivity. Gratifyingly, treatment of enyne **7h** with $Co_2(CO)_8$ in CH_2Cl_2 at rt resulted in complete complexation within 2 h (entry 5). Direct addition of NMO and further stirring at rt for 14 h under CO (1 atm) gave indolizidine **8h** in 65% yield as one diastereomer with only trace amounts of diene **9**. The overall yield was further improved when THF was employed as solvent (entry 7), delivering enone **8h** in 82% yield within 20 h at rt.. In this manner, the optimal conditions for a mild, stereoselective, and high-yielding one-pot process were realized.

To establish the configuration of the newly formed stereocenter at the cyclopentenone ring fusion, HMQC, HMBC, and NOE studies were performed on indolizidine **8a** (Figure 3). As the stereochemical assignments for the protons

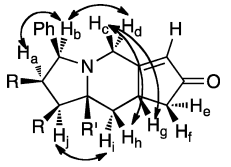
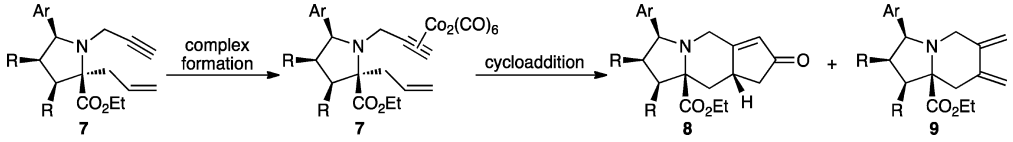


Figure 3. Selected NOE enhancements of cycloadduct **8a**.

on the pyrrolidine ring (H_a, H_b, and H_j) were already established,[3] they could be employed as useful guides for determining the relative relationship of the other protons on the newly formed rings. Proton H_a displayed an NOE enhancement with the benzylic proton H_b, which in turn showed an enhancement with the methylene proton H_d. Proton H_j, known to be syn with vicinal proton H_a, displayed an enhancement with H_i, thereby indicating that these five protons resided on the same face of the indolizidine ring. The methylene proton H_c displayed two significant NOE enhancements with proton H_h and with the methine proton of the newly formed ring fusion (H_g), indicating that these three protons were also on the same face of the indolizidine.

Following the optimized procedure, the application of the method for generating an array of functionalized indolizidines was undertaken (Table 4). Overall, yields were generally good, and the reaction conditions proved to be tolerant toward the diverse functional groups present within the substrates. In general, *N*-butynyl-2-allylpyrrolidines (**7d–f**, **8j–k**) gave slightly higher yields than the *N*-propargyl-2-allylpyrrolidines (**7a–c**, **8g–i**), and no observable epimerization had occurred within substrates or products bearing potentially enolizable centers (e.g., **8g–l**). In all cases, only trace amounts of undesired exocylic diene cycloadducts (e.g., **9**) were observed, and the reactions afforded only one observable diastereomer of

Table 3. Optimization Studies for the Pauson–Khand Reaction of *N*-Propargyl-2-allylpyrrolidines



entry	enyne	conditions for Co complexation	conditions for cycloaddition	enone **8**[a] (%)	dr[b]	diene **9**[a] (%)
1	**7a**	$Co_2(CO)_8$ (1.2 equiv), CH_2Cl_2, rt, 1 h	NMO (6 equiv), $PhCH_3$, reflux, 2 h	60	>95:5	30
2	**7g**	$Co_2(CO)_8$ (1.2 equiv), CH_2Cl_2, rt, 1 h	NMO (6 equiv), $PhCH_3$, reflux, 2 h	48	5:1	31
3	**7g**	$Co_2(CO)_8$ (1.2 equiv), CH_2Cl_2, rt, 1 h	NMO (6 equiv), $PhCH_3$, 50 °C, 19 h	45	5:1	29
4	**7g**	$Co_2(CO)_8$ (1.2 equiv), CH_2Cl_2, rt, 1 h	NMO (6 equiv), $PhCH_3$, 60 °C, 20 h	73	3:1	8
5	**7h**	$Co_2(CO)_8$ (1.2 equiv), CH_2Cl_2, rt, 2 h	NMO (6 equiv), CO (1 atm), CH_2Cl_2, rt, 14 h	65	>95:5	trace
6	**7h**	$Co_2(CO)_8$ (1.2 equiv), THF, rt, 1 h	NMO (6 equiv), CO (1 atm), THF, 50 °C, 20 h	79	>95:5	trace
7	**7h**	$Co_2(CO)_8$ (1.2 equiv), THF, rt, 1 h	NMO (6 equiv), CO (1 atm), THF, rt, 20 h	82	>95:5	trace

[a]Isolated yields after flash column chromatography on silica gel. [b]Diastereomeric ratio determined by ^1H NMR analysis of reaction mixture.

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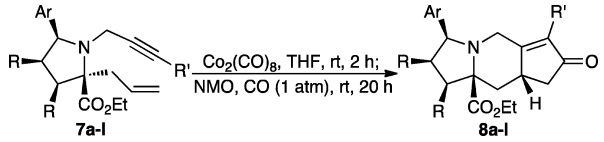
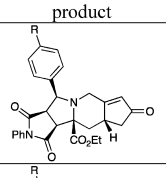
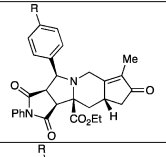
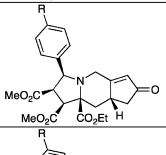
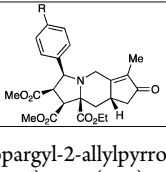
Table 4. Preparation of Functionalized Indolizidines by Pauson–Khand Cycloaddition[a]



entry	enyne (Ar)	product		yield (%)[b]
1	**7a** (Ph)		**8a**	81
2	**7b** (*p*-MeOPh)		**8b**	77
3	**7c** (*p*-F_3CPh)		**8c**	83
4	**7d** (Ph)		**8d**	96
5	**7e** (*p*-MeOPh)		**8e**	95
6	**7f** (*p*-F_3CPh)		**8f**	81
7	**7g** (Ph)		**8g**	78
8	**7h** (*p*-MeOPh)		**8h**	82
9	**7i** (*p*-F_3CPh)		**8i**	73
10	**7j** (Ph)		**8j**	80
11	**7k** (*p*-MeOPh)		**8k**	86
12	**7l** (*p*-F_3CPh)		**8l**	73

[a]Reaction conditions: *N*-propargyl-2-allylpyrrolidine or *N*-butynyl-2-allylpyrrolidine **7a–l** (0.5 mmol), $Co_2(CO)_8$ (0.6 mmol), THF (15 mL), rt, 2 h; then NMO·H_2O (3.0 mmol), CO (1 atm), rt, 20 h. [b]Isolated yields after flash column chromatography on silica gel.

the desired enone. The high levels of diastereoselectivity may be attributed in part to the limited conformational flexibility of the system as well as a favored facial approach of the tethered alkene to the cobalt complex in the transition state. Comparison of selected coupling constants and additional NOE studies in the manner shown for cycloadduct **8a** (Figure 2) was used to assign the relative configuration of the Pauson–Khand cycloadducts prepared.

CONCLUSIONS

In summary, we have demonstrated the synthetic applications of functionalized 2-allylpyrrolidines, readily obtained through our domino 2-aza-Cope-[3 + 2] dipolar cycloaddition protocol, toward the concise preparation of indolizidine scaffolds through intramolecular Pauson–Khand cycloaddition. In a three-step sequence, three rings and five new stereogenic centers are generated in a high-yielding (73–96%) and stereoselective fashion. Though a number of recently described tactics toward indolizidine systems have centered on ring-closing metathesis[20] and other transition-metal-mediated cyclization strategies,[21] the multicomponent and modular nature of our protocol allows for increased amplification of structural diversity in a short number of synthetic steps. The ability to further structurally diversify the indolizidine unit is of particular interest to us, as a number of medicinally promising alkaloid natural products feature a broad range of substitution around this central core.[22] Applications of the Pauson–Khand cycloaddition toward the total synthesis of indolizidine-containing alkaloid natural products are currently being investigated.

EXPERIMENTAL SECTION

General experimental considerations are provided in the Supporting Information.

General Procedure for the Alkylation of 2-Allylpyrrolidines 6a–c. A mixture of propargyl bromide or but-2-ynyl methanesulfonate (10.0 mmol), 2-allylpyrrolidine **6a–c** (2.0 mmol), and K_2CO_3 (10.0 mmol) in DMF (0.44 mL) was heated in a sealed tube at 130 °C for 8–16 h. The reaction mixture was diluted with CH_2Cl_2 and saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated, and the residue was purified as indicated to afford enynes **7a-7f.**

*2-Ethyl 1-Allyl-4,6-dioxo-3,5-diphenyl-2-(prop-2-yn-1-yl)-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**7a**).* Purification by flash chromatography (3:7:0.1 EtOAc/hexanes/Et_3N) afforded **7a** (780 mg, 73% yield) as a white solid: mp 136–137 °C (Et_2O); R_f = 0.5 (3:7 EtOAc/hexanes); IR (neat) 1713, 1497, 1378, 1181, 1027, 910, 849, 754, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, J = 1.5, 8.4 Hz, 2H), 7.24–7.36 (m, 6H), 6.96 (dd, J = 1.4, 8.6 Hz, 2H), 6.27 (dddd, J = 7.5, 10.0, 15.1, 17.4 Hz, 1H), 5.29 (dd, J = 1.4, 17.5 Hz, 1H), 5.26 (dd, J = 1.4, 10.1 Hz, 1H), 4.88 (d, J = 10.3 Hz, 1H), 4.29 (m, 2H), 3.85 (dd, J = 2.4, 18.8, 1H), 3.70 (dd, J = 8.2, 10.3 Hz, 1H), 3.58 (d, J = 8.2 Hz, 1H), 3.47 (dd, J = 2.5, 18.7 Hz, 1H), 2.97 (dd, J = 7.4, 14.1 Hz, 1H), 2.84 (dd, J = 7.6, 14.1 Hz, 1H), 2.22 (app t, J = 2.4 Hz, 1H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 173.7, 171.3, 136.6, 134.4, 131.5, 128.9, 128.7, 128.6, 128.3 (2C), 128.1 (2C), 126.0 (2C), 119.9 (2C), 79.4, 74.1, 73.1, 65.1, 61.6, 52.7, 48.3, 39.0, 35.0, 14.1; high-resolution mass spectrum (ESI) m/z 465.1771 [(M + Na)$^+$; calcd for $C_{27}H_{26}N_2O_4Na^+$: 465.1790].

*2-Ethyl 1-Allyl-3-(4-methoxyphenyl)-4,6-dioxo-5-phenyl-2-(prop-2-yn-1-yl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**7b**).* Purification by flash chromatography (3:7:0.1 EtOAc/hexanes/Et_3N) afforded **7b** (476 mg, 75% yield) as a white solid: mp 153–155 °C (Et_2O); R_f = 0.39 (3:7 EtOAc/hexanes); IR (neat) 1717, 1377, 1245, 1168, 1031, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24–7.37 (m, 5H), 7.04 (d, J = 1.5, 7.3 Hz, 2H), 6.89 (d, J = 1.9, 6.8 Hz, 2H), 6.29 (dddd, J = 7.8, 10.3, 15.1, 17.6 Hz, 1H), 5.30 (dd, J = 1.9, 17.1 Hz, 1H), 5.28 (dd, J = 1.9, 10.3 Hz, 1H), 4.85 (d, J = 10.3 Hz, 1H), 4.31 (m, 2H), 3.86 (dd, J = 2.4, 18.6 Hz, 1H), 3.80 (s, 3H), 3.69 (dd, J = 8.3, 10.3 Hz, 1H), 3.59 (d, J = 8.3, 1H), 3.47 (dd, J = 2.4, 18.6 Hz, 1H), 2.98 (dd, J = 7.3, 14.2 Hz, 1H), 2.85 (dd, J = 7.8, 14.2 Hz, 1H), 2.25 (app t, J = 2.4, 1H), 1.35 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 173.8, 171.4, 159.6, 134.5, 131.6 (2C), 129.1 (2C), 128.9, 128.4, 128.3, 126.0 (2C), 119.8, 114.0 (2C), 79.4, 74.0, 72.9, 64.5, 61.5, 55.1, 52.5, 48.2, 38.8, 34.9, 14.0; high-resolution mass spectrum (ESI) m/z 495.1895 [(M + Na)$^+$; calcd for $C_{28}H_{28}N_2O_5Na^+$ 495.1896].

*2-Ethyl 1-Allyl-4,6-dioxo-5-phenyl-2-(prop-2-yn-1-yl)-3-(4-(trifluoromethyl)phenyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**7c**).* Purification by flash chromatography (2:8:0.1 EtOAc/hexanes/Et_3N) afforded **7c** (268 mg, 53% yield, 80% BRSM) as a white solid: mp 150–152 °C (Et_2O); R_f = 0.35 (2:8 EtOAc/hexanes); IR (neat) 1717, 1378, 1323, 1163, 1124, 1066, 1018, 910, 732, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.24–7.36 (m, 3H), 6.89 (m, 2H), 6.25 (dddd, J = 7.5, 10.0, 15.0, 17.5 Hz, 1H), 5.31 (dd, J = 1.5, 17.0 Hz, 1H), 5.28 (dd, J = 1.7, 10.0 Hz, 1H), 4.93 (d, J = 10.3 Hz, 1H), 4.29 (m, 2H), 3.82 (dd, J = 2.5, 18.8 Hz, 1H), 3.75 (dd, J = 8.3, 10.3 Hz, 1H), 3.60 (d, J = 8.3 Hz, 1H), 3.41 (dd, J = 2.5, 18.8 Hz, 1H), 2.97 (dd, J = 7.6, 14.3 Hz, 1H), 2.83 (dd, J = 7.4, 14.4 Hz, 1H), 2.24 (t, J = 2.4 Hz, 1H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 173.3, 171.1, 141.1, 134.0, 131.3, 130.5 (q, J = 32.3 Hz), 128.9 (2C), 128.4 (2C), 125.7 (2C), 125.5 (2C), 123.9 (q, J = 272 Hz), 120.1, 78.7, 77.2, 74.5, 73.2, 64.6, 61.6, 52.4, 48.1, 38.9, 35.0, 13.9; high-resolution mass spectrum (ESI) m/z 533.1666 [(M + Na)$^+$; calcd for $C_{28}H_{25}N_2O_4F_3Na^+$ 533.1664].

*2-Ethyl 1-Allyl-2-(but-2-yn-1-yl)-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**7d**).* Purification by flash chromatography (2:8:0.1 EtOAc/hexanes/Et_3N) afforded **7d** (429 mg, 51% yield, 74% BRSM) as a white solid: mp 131–132 °C (Et_2O); R_f = 0.53 (3:7 EtOAc:hexanes); IR (neat) 1711,

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1494, 1384, 1298, 1196, 1138, 1025, 930, 752, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 2H), 7.25−7.35 (m, 6H), 6.95 (d, J = 7.7 Hz, 2H), 6.27 (ddd, J = 7.5, 10.0, 17.4 Hz, 1H), 5.28 (d, J = 18.5 Hz, 1H), 5.25 (d, J = 10.4 Hz, 1H), 4.83 (d, J = 10.3 Hz, 1H), 4.26 (m, 2H), 3.72 (dq, J = 2.0, 18.4 Hz, 1H), 3.69 (dd, J = 8.2, 10.2 Hz, 1H), 3.55 (d, J = 8.2 Hz, 1H), 3.39 (dq, J = 2.0, 18.4 Hz, 1H), 2.97 (dd, J = 7.6, 14.1 Hz, 1H), 2.85 (dd, J = 7.4, 14.1 Hz, 1H), 1.76 (t, J = 2.3 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 173.6, 171.4, 137.0, 134.4, 131.5, 128.7 (2C), 128.4 (2C), 128.2, 128.1, 127.9, 125.8 (2C), 119.6 (2C), 81.3, 74.4, 73.0, 65.3, 61.2, 52.6, 48.3, 38.9, 35.3, 13.9, 3.3; high-resolution mass spectrum (ESI) m/z 479.1940 [$(M + Na)^+$, calcd for $C_{28}H_{28}N_2O_4Na^+$: 479.1947].

*2-Ethyl 1-Allyl-2-(but-2-yn-1-yl)-3-(4-methoxyphenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**7e**).* Purification by flash chromatography (3:7:0.1 EtOAc/hexanes/Et_3N) afforded **7e** (600 mg, 62% yield, 98% BRSM) as a white solid: mp 130−131 °C (Et_2O); R_f = 0.47 (3:7 EtOAc/hexanes); IR (neat) 1714, 1511, 1379, 1240, 1181, 1144, 1030, 911, 827, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25−7.35 (m, 5H), 7.00 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.26 (ddd, J = 7.5, 10.0, 17.4 Hz, 1H), 5.27 (d, J = 17.8 Hz, 1H), 5.24 (d, J = 10.4 Hz, 1H), 4.78 (d, J = 10.2 Hz, 1H), 4.26 (m, 2H), 3.76 (s, 3H), 3.70 (dq, J = 2.4, 18.4 Hz, 1H), 3.64 (dd, J = 8.3, 10.2 Hz, 1H), 3.54 (d, J = 8.3 Hz, 1H), 3.36 (dq, J = 2.4, 18.3 Hz, 1H), 2.96 (dd, J = 7.5, 14.1 Hz, 1H), 2.83 (dd, J = 7.5, 14.1 Hz, 1H), 1.76 (t, J = 2.3 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 174.0, 171.6, 159.5, 134.7, 131.6, 129.1, 128.9 (2C), 128.2 (2C), 126.0 (2C), 119.6, 113.9 (2C), 81.4, 74.6, 73.0, 64.9, 61.4, 55.1, 52.6, 48.4, 39.0, 35.3, 14.0, 3.5; high-resolution mass spectrum (ESI) m/z 509.2039 [$(M + Na)^+$; calcd for $C_{29}H_{30}N_2O_5Na^+$ 509.2052].

*2-Ethyl 1-Allyl-2-(but-2-yn-1-yl)-4,6-dioxo-5-phenyl-3-(4-(trifluoromethyl)phenyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**7f**).* Purification by flash chromatography (3:7:0.1 EtOAc/hexanes/Et_3N) afforded **7f** (579 mg, 58% yield, 77% BRSM) as a yellow foam: mp 68−70 °C (Et_2O); R_f = 0.53 (3:7 EtOAc/hexanes); IR (neat) 1714, 1379, 1161, 1120, 1105, 1065, 1017, 871, 829, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.25−7.35 (m, 3H), 6.85 (d, J = 8.0 Hz, 2H), 6.24 (ddd, J = 7.5, 9.8, 17.3 Hz, 1H), 5.30 (d, J = 17.4 Hz, 1H), 5.27 (d, J = 10.3 Hz, 1H), 4.89 (d, J = 10.3 Hz, 1H), 4.27 (m, 2H), 3.73 (dd, J = 8.4, 10.1 Hz, 1H), 3.68 (dd, J = 2.2, 18.4 Hz, 1H), 3.58 (d, J = 8.2 Hz, 1H), 3.35 (dd, J = 2.2, 18.4 Hz, 1H), 2.98 (dd, J = 7.7, 14.2 Hz, 1H), 2.85 (dd, J = 7.3, 14.2 Hz, 1H), 1.76 (t, J = 1.9 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 173.5, 171.4, 141.5, 134.3, 131.4, 130.4 (q, J = 32.6 Hz), 129.0 (2C), 128.5 (2C), 128.4, 125.8 (2C), 125.5 (2C), 124.0 (q, J = 272.0 Hz), 120.0, 81.9, 74.1, 73.4, 65.0, 61.6, 52.6, 48.5, 39.2, 35.5, 14.0, 3.4; high-resolution mass spectrum (ESI) m/z 547.1798 [$(M + Na)^+$; calcd for $C_{29}H_{27}N_2O_4F_3Na^+$ 547.1821].

General Procedure for the Alkylation of 2-Allylpyrrolidines 6d−f. A mixture of propargyl bromide or but-2-ynyl methanesulfonate (10.0 mmol), 2-allylpyrrolidine **6d−f** (2.0 mmol), TBAI (0.2 mmol), and K_2CO_3 (10.0 mmol) in DMF (0.44 mL) was heated in a sealed tube at 80 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2 and saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organics layers were washed with brine, dried (Na_2SO_4), and concentrated, and the residue was purified as indicated to afford enynes **7g-7l.**

*2-Ethyl 3,4-Dimethyl 2-Allyl-5-phenyl-1-(prop-2-yn-1-yl)-pyrrolidine-2,3,4-tricarboxylate (**7g**).* Purification by flash chromatography (2:8:0.1 EtOAc/hexanes/Et_3N) afforded **7g** (542 mg, 53% yield, 75% BRSM) as a colorless oil: R_f = 0.29 (2:8 EtOAc/hexanes); IR (neat) 2950, 1731, 1434, 1198, 1171, 1026, 913, 730, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, J = 1.4, 8.5 Hz, 2H), 7.27 (dd, J = 1.0, 7.9 Hz, 2H), 7.22 (m, 1H), 6.03 (m, 1H), 5.31 (dd, J = 1.9, 17.1 Hz, 1H), 5.20 (dd, J = 1.9, 10.2 Hz, 1H), 4.71 (d, J = 7.5 Hz, 1H), 4.21 (m, 2H), 4.10 (dd, J = 2.4, 19.0 Hz, 1H), 3.71 (s, 3H), 3.54 (dd, J = 2.0, 18.9 Hz, 1H), 3.40 (app t, J = 7.3 Hz, 1H), 3.30 (d, J = 7.2 Hz, 1H), 3.16 (s, 3H), 2.97 (d, J = 7.4 Hz, 2H), 2.16 (t, J = 2.4 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 170.4, 170.1, 137.2, 133.4, 128.2 (2C), 128.0 (2C), 127.8, 119.5, 80.9, 72.9, 72.0, 65.3, 60.6, 52.3, 51.8, 51.0, 49.7, 40.4, 34.8, 14.2/ Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.47; H, 6.616; N, 3.44.

*2-Ethyl 3,4-Dimethyl 2-Allyl-5-(4-methoxyphenyl)-1-(prop-2-yn-1-yl)pyrrolidine-2,3,4-tricarboxylate (**7h**).* Purification by flash chromatography (3:7:0.1 EtOAc/hexanes/Et_3N) afforded **7h** (602 mg, 66% yield) as a white solid: mp 106−107 °C (Et_2O); R_f = 0.41 (3:7 EtOAc/hexanes); IR (neat) 3266, 1730, 1509, 1435, 1304, 1243, 1206, 1027, 849, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.3 Hz, 2H), 6.03 (ddd, J = 7.4, 9.9, 17.2 Hz, 1H), 5.29 (d, J = 17.0 Hz, 1H), 5.19 (d, J = 10.1, 1H), 4.66 (d, J = 7.6 Hz, 1H), 4.20 (m, 2H), 4.09 (dd, J = 2.2, 18.9 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.51 (dd, J = 2.2, 18.9 Hz, 1H), 3.37 (app t, J = 7.4 Hz, 1H), 3.29 (d, J = 7.3 Hz, 1H), 3.21 (s, 3H), 2.95 (d, J = 7.3 Hz, 2H), 2.15 (t, J = 2.3 Hz, 1H), 1.29 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 170.6, 170.3, 159.2, 133.5, 129.4 (2C), 129.0, 119.5, 113.4 (2C), 81.0, 72.8, 71.9, 64.8, 60.7, 55.1, 52.3, 51.8, 51.2, 49.7, 40.0, 34.8, 14.2; high-resolution mass spectrum (ESI) m/z 466.1835 [$(M + Na)^+$; calcd for $C_{24}H_{29}NO_7Na^+$ 466.1842].

*2-Ethyl 3,4-Dimethyl 2-Allyl-1-(prop-2-yn-1-yl)-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2,3,4-tricarboxylate (**7i**).* Purification by flash chromatography (3:7:0.1 EtOAc/hexanes/Et_3N) afforded **7i** (622 mg, 65% yield, 75% BRSM) as a light yellow solid: mp 106−107 °C (Et_2O); R_f = 0.41 (3:7 EtOAc/hexanes); IR (neat) 1732, 1435, 1323, 1200, 1164, 1123, 1066, 911, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 6.01 (ddd, J = 7.3, 10.1, 17.3, 1H), 5.31 (dd, J = 1.4, 17.1 Hz, 1H), 5.21 (dd, J = 1.2, 10.2 Hz, 1H), 4.79 (d, J = 8.0 Hz, 1H), 4.21 (m, 2H), 4.14 (dd, J = 2.3, 19.0 Hz, 1H), 3.71 (s, 3H), 3.49 (app t, 7.7 Hz, 1H), 3.47 (dd, J = 2.3, 19.0 Hz, 1H), 3.33 (d, J = 7.3 Hz, 1H), 3.16 (s, 3H), 2.95 (d, J = 7.3 Hz, 1H), 2.18 (t, J = 2.3 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 170.3, 169.7, 141.8, 133.1, 129.9 (q, J = 32.2 Hz), 128.8 (2C), 124.8 (2C), 124.0 (q, J = 272.0 Hz), 119.7, 80.3, 73.3, 72.2, 64.8, 60.7, 52.2, 51.8, 51.0, 49.4, 40.2, 34.8, 14.1; high-resolution mass spectrum (ESI) m/z 504.1602 [$(M + Na)^+$; calcd for $C_{24}H_{26}NO_6F_3Na^+$ 504.1610].

*2-Ethyl 3,4-Dimethyl 2-Allyl-1-(but-2-yn-1-yl)-5-phenylpyrrolidine-2,3,4-tricarboxylate (**7j**).* Purification by flash chromatography (2:8:0.1 EtOAc/hexanes/Et_3N) afforded **7j** (246 mg, 48% yield, 80% BRSM) as a white solid: mp 244−246 °C (Et_2O); R_f = 0.55 (3:7 EtOAc/hexanes); IR (neat) 2951, 1732, 1434, 1196, 1170, 1026, 918, 731, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 7.6 Hz, 2H), 7.26 (app t, J = 7.2 Hz, 2H), 7.20 (m, 1H), 6.06 (ddd, J = 7.3, 10.0, 17.3 Hz, 1H), 5.28 (dd, J = 0.5, 17.0 Hz, 1H), 5.19 (dd, J = 0.8, 10.1 Hz, 1H), 4.69 (d, J = 7.6 Hz, 1H), 4.20 (m, 2H), 3.99 (dd, J = 2.2, 18.7 Hz, 1H), 3.71 (s, 3H), 3.48 (dd, J = 2.2, 18.7 Hz, 1H), 3.39 (app t, J = 7.4 Hz, 1H), 3.30 (d, J = 7.2 Hz, 1H), 3.16 (s, 3H), 2.96 (d, J = 7.3 Hz, 2H), 1.75 (t, J = 2.0 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 170.4, 170.1, 137.5, 133.7, 128.1, 127.8, 127.5, 119.3, 80.1, 76.0, 72.1, 65.4, 60.5, 52.3, 51.7, 50.9, 49.8, 40.3, 35.0, 14.1, 3.3; high-resolution mass spectrum (ESI) m/z 450.1878 [$(M + Na)^+$; calcd for $C_{24}H_{29}NO_6Na^+$ 450.1893].

*2-Ethyl 3,4-Dimethyl 2-Allyl-1-(but-2-yn-1-yl)-5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate (**7k**).* Purification by flash chromatography (3:7:0.1 EtOAc/hexanes/Et_3N) afforded **7k** (541 mg, 57% yield, 87% BRSM) as a yellow oil: R_f = 0.42 (3:7 EtOAc/hexanes); IR (neat) 2951, 1732, 1511, 1434, 1370, 1243, 1197, 1171, 1031, 922, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.04 (ddd, J = 7.3, 9.8, 17.2 Hz, 1H), 5.26 (d, 17.0 Hz, 1H), 5.17 (d, J = 10.2 Hz, 1H), 4.63 (d, J = 7.6 Hz, 1H), 4.17 (m, 2H), 3.98 (dd, J = 2.2, 18.7 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.43 (dd, J = 1.9, 18.4 Hz, 1H), 3.35 (app t, J = 7.4 Hz, 1H), 3.27 (d, J = 7.3 Hz, 1H), 3.19 (s, 3H), 2.92 (d, J = 7.3 Hz, 2H), 1.74 (t, J = 1.9 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 170.6, 170.3, 159.0, 133.8, 129.5, 129.4 (2C), 119.3, 113.3 (2C), 80.1, 76.1, 72.0, 64.9, 60.5, 55.1, 52.2, 51.7, 51.1, 49.7, 40.4, 35.0, 14.2, 3.4. Anal. Calcd for $C_{25}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06. Found: C, 65.42; H, 6.857; N, 2.88.

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*2-Ethyl 3,4-Dimethyl 2-Allyl-1-(but-2-yn-1-yl)-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2,3,4-tricarboxylate (**7l**).* Purification by flash chromatography (2:8:0.1 EtOAc/hexanes/Et_3N) afforded **7l** (668 mg, 50% yield) as a colorless oil: R_f = 0.62 (3:7 EtOAc/hexanes); IR (neat) 2952, 1737, 1435, 1322, 1198, 1162, 1121, 1108, 1066, 1017, 923, 854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 6.02 (ddd, J = 7.3, 10.1, 17.3 Hz, 1H), 5.28 (dd, J = 1.4, 17.0 Hz, 1H), 5.20 (dd, J = 1.3, 10.2 Hz, 1H), 4.77 (d, J = 8.0 Hz, 1H), 4.19 (m, 2H), 4.02 (dd, J = 2.3, 18.7 Hz, 1H), 3.70 (s, 3H), 3.47 (app t, J = 7.7 Hz, 1H), 3.42 (dd, J = 2.4, 18.6 Hz, 1H), 3.32 (d, J = 7.4 Hz, 1H), 3.16 (s, 3H), 2.93 (d, J = 7.3 Hz, 2H), 1.74 (t, J = 2.2 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 170.5, 169.9, 142.3, 133.5, 129.8 (q, J = 32.2 Hz), 128.8 (2C), 124.8 (2C), 124.2 (q, J = 272.2 Hz), 119.7, 80.8, 75.6, 72.5, 65.1, 60.8, 52.3, 51.9, 51.1, 49.5, 40.3, 35.2, 14.2, 3.4; high-resolution mass spectrum (ESI) m/z 518.1747 [$(M + Na)^+$; calcd for $C_{25}H_{28}NO_6F_3Na^+$ 518.1766].

General Procedure for the Co-Mediated Pauson–Khand Cyclization of Enynes 7a–l. To a solution of the enyne (**7a–l**, 0.5 mmol) in THF (15 mL) under an atmosphere of nitrogen was added $Co_2(CO)_8$ (0.6 mmol). After stirring at rt for 2 h, the solution was purged with carbon monoxide (1 atm), and NMO·H_2O (3.0 mmol) was added. After being stirred at rt for 20 h, the reaction mixture was filtered, the filter cake was rinsed with CH_2Cl_2, the combined organics portions were concentrated, and the residue was purified as indicated to afford enones **8a-8l**.

*Ethyl 1,3,8-Trioxo-2,4-diphenyl-1,2,3,3a,4,6,8,9,9a,10,10a,10b-dodecahydrocyclopenta[f]pyrrolo[3,4-a]indolizine-10a-carboxylate (**8a**).* Purification by flash chromatography (3:1:0.1 EtOAc/hexanes/Et_3N) afforded **8a** (191 mg, 81% yield) as a white solid: mp 218–221 °C (EtOAc); R_f = 0.14 (1:1 EtOAc/hexanes); IR (neat) 1711, 1381, 1201, 1176, 1154, 909, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.38 (m, 8H), 7.05–7.08 (m, 2H), 5.86 (s, 1H), 4.38 (m, 2H), 4.34 (d, J = 9.8 Hz, 1H), 4.03 (d, J = 15.8 Hz, 1H), 3.56 (dd, J = 8.1, 9.9 Hz, 1H), 3.49 (d, J = 15.8 Hz, 1H), 3.39 (d, J = 8.1 Hz, 1H), 2.80–2.90 (m, 2H), 2.65 (dd, J = 6.4, 18.9 Hz, 1H), 2.06 (dd, J = 2.0, 18.4 Hz, 1H), 1.74 (td, J = 3.5, 15.5 Hz, 1H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 174.0, 173.9, 173.1, 170.0, 135.9, 131.4, 130.5 (2C), 128.9 (2C), 128.8, 128.7, 128.4 (2C), 125.9 (2C), 125.8, 69.6, 65.5, 61.9, 53.4, 53.0, 47.4, 45.3, 41.8, 37.5, 37.4, 14.1; high-resolution mass spectrum (ESI) m/z 493.1722 [$(M + Na)^+$; calcd for $C_{28}H_{26}N_2O_5Na^+$: 493.1740].

*Ethyl 4-(4-Methoxyphenyl)-1,3,8-trioxo-2-phenyl-1,2,3,3a,4,6,8,9,9a,10,10a,10b-dodecahydrocyclopenta[f]pyrrolo[3,4-a]indolizine-10a-carboxylate (**8b**).* Purification by flash chromatography (3:1:0.1 EtOAc/hexanes/Et_3N) afforded **8b** (175 mg, 77% yield) as a white solid: mp 252–254 °C (EtOAc); R_f = 0.17 (1:1 EtOAc:hexanes); IR (neat) 1710, 1610, 1509,1377,1296, 1241, 1174, 1099, 1030, 861, 824, 763, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.39 (m, 5H), 7.09 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.85 (s, 1H), 4.37 (m, 2H), 4.28 (d, J = 9.8 Hz, 1H), 3.99 (d, J = 15.8 Hz, 1H), 3.77 (s, 3H), 3.52 (dd, J = 8.1, 9.7 Hz, 1H), 3.47 (d, J = 15.8 Hz, 1H), 3.37 (d, J = 8.1 Hz, 1H), 2.78–2.86 (m, 2H), 2.64 (dd, J = 6.3, 18.8 Hz, 1H), 2.05 (d, J = 18.5 Hz, 1H), 1.72 (app t, J = 12.0 Hz, 1H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 173.9, 173.8, 173.2, 170.0, 159.9, 131.6, 130.4, 128.9 (2C), 128.4, 127.8, 127.4, 126.0 (2C), 114.1, 69.6, 65.1, 61.8, 55.1, 53.0, 47.5, 45.2, 41.9, 37.5, 37.5, 14.1; high-resolution mass spectrum (ESI) m/z 523.1845 [$(M + Na)^+$; calcd for $C_{29}H_{28}N_2O_6Na^+$ 523.1845].

*Ethyl 1,3,8-Trioxo-2-phenyl-4-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,6,8,9,9a,10,10a,10b-dodecahydrocyclopenta[f]pyrrolo[3,4-a]indolizine-10a-carboxylate (**8c**).* Purification by flash chromatography (1:100:0.5 MeOH/CH_2Cl_2/NH_4OH) afforded **8c** (177 mg, 83% yield) as a white solid: mp >260 °C (EtOAc); R_f = 0.23 (1:1 EtOAc/hexanes); IR (neat) 1713, 1382, 1323, 1203, 1158, 1122, 1103, 1066, 727, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.2 Hz, 2H), 7.30–7.40 (m, 5H), 7.03 (d, J = 8.0 Hz, 2H), 5.86 (s, 1H), 4.40 (d, J = 9.5 Hz, 1H), 4.39 (m, 2H), 4.03 (d, J = 15.8 Hz, 1H), 3.62 (dd, J = 8.1, 9.8 Hz, 1H), 3.43 (d, J = 6.7 Hz, 1H), 3.41 (d, J = 8.2 Hz, 1H), 2.86 (dd, J = 5.6, 14.4 Hz, 1H), 2.86 (dd, J = 5.4, 14.4 Hz, 1H), 2.67 (dd, J = 6.3, 18.9 Hz, 1H), 2.07 (dd, J = 2.0, 18.9 Hz, 1H), 1.73 (app t, J = 14.2 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 173.6, 173.3, 172.9, 169.8, 140.2, 131.2 (2C), 130.9 (q, J = 32.5 Hz), 130.7, 129.1 (2C), 128.7 (2C), 125.9 (2C), 125.8 (2C), 123.8 (q, J = 272 Hz), 69.8, 65.1, 62.1, 53.0, 47.4, 45.3, 41.8, 37.6, 37.4, 14.1; high-resolution mass spectrum (ESI) m/z 561.1606 [$(M + Na)^+$; calcd for $C_{29}H_{25}N_2O_5F_3Na^+$ 561.1613].

*Ethyl 7-Methyl-1,3,8-trioxo-2,4-diphenyl-1,2,3,3a,4,6,8,9,9a,10,10a,10b-dodecahydrocyclopenta[f]pyrrolo[3,4-a]indolizine-10a-carboxylate (**8d**).* Purification by flash chromatography (4:6:0.1 EtOAc/hexanes/Et_3N) afforded **8d** (205 mg, 96% yield) as a white solid: mp 250–251 °C (EtOAc); R_f = 0.31 (5:1 CH_2Cl_2/MeOH); IR (neat) 1712, 1658, 1498, 1381, 1296, 1200, 1176, 1153, 1100, 1074, 1031, 910, 726, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (bs, 1H), 7.27–7.39 (m, 7H), 7.09 (d, J = 7.4 Hz, 2H), 4.36 (m, 2H), 4.23 (d, J = 9.8 Hz, 1H), 3.89 (d, J = 15.7 Hz, 1H), 3.53 (dd, J = 8.2, 9.7 Hz, 1H), 3.51 (d, J = 16.0 Hz, 1H), 3.37 (d, J = 8.1 Hz, 1H), 2.81 (dd, J = 5.2, 12.7 Hz, 1H), 2.75 (m, 1H), 2.65 (dd, J = 6.4, 18.8 Hz, 1H), 2.02 (d, J = 18.8 Hz, 1H), 1.64 (app t, J = 12.5 Hz, 1H), 1.44 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 174.0, 173.3, 170.2, 165.2, 137.5, 136.3, 131.5, 129.0 (2C), 128.9, 128.8 (2C), 128.7, 128.4, 126.0 (2C), 69.8, 65.7, 61.9, 53.1, 47.5, 43.4, 40.9, 37.7, 35.8, 14.1, 7.4; high-resolution mass spectrum (ESI) m/z 507.1886 [$(M + Na)^+$; calcd for $C_{29}H_{28}N_2O_5Na^+$ 507.1896].

*Ethyl 4-(4-Methoxyphenyl)-7-methyl-1,3,8-trioxo-2-phenyl-1,2,3,3a,4,6,8,9,9a,10,10a,10b-dodecahydrocyclopenta[f]pyrrolo[3,4-a]indolizine-10a-carboxylate (**8e**).* Purification by flash chromatography (4:6:0.1 EtOAc/hexanes/Et_3N) afforded **8e** (247 mg, 95%) as a white solid: mp 135–138 °C (EtOAc); R_f = 0.34 (1:1 EtOAc:hexanes); IR (neat) 1708, 1688, 1651, 1514, 1291, 1199, 1178, 1154, 1099, 1028, 841, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29–7.45 (m, 5H), 7.13 (d, J = 8.3 Hz, 2H), 6.88 (d, 7.0 Hz, 2H), 4.37 (m, 2H), 4.19 (d, J = 9.8 Hz, 1H), 3.88 (d, J = 15.7 Hz, 1H), 3.78 (s, 3H), 3.51 (d, J = 15.5 Hz, 1H), 3.50 (dd, J = 8.2, 9.7 Hz, 1H), 3.36 (d, J = 8,1 Hz, 1H), 2.81 (dd, J = 5.1, 12.6 Hz, 1H), 2.75 (m, 1H), 2.64 (dd, J = 6.4, 18.8 Hz, 1H), 2.03 (d, J = 18.8 Hz, 1H), 1.63 (app t, J = 12.5 Hz, 1H), 1.45 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 174.1, 173.5, 170.2, 165.4, 159.8, 137.5, 131.5, 130.5, 129.0 (2C), 128.5, 128.0, 126.0 (2C), 114.7, 69.7, 65.2, 61.9, 55.1, 53.0, 47.4, 43.3, 40.9, 37.6, 35.8, 14.1, 7.5; high-resolution mass spectrum (ESI) m/z 537.2014 [$(M + Na)^+$; calcd for $C_{30}H_{30}N_2O_6Na^+$ 537.2001].

*Ethyl 7-Methyl-1,3,8-trioxo-2-phenyl-4-(4-(trifluoromethyl)-phenyl)-1,2,3,3a,4,6,8,9,9a,10,10a,10b-dodecahydrocyclopenta[f]-pyrrolo[3,4-a]indolizine-10a-carboxylate (**8f**).* Purification by flash chromatography (4:6:0.1 EtOAc/hexanes/Et_3N) afforded **8f** (222 mg, 81%) as a white solid: mp 257–258 °C (EtOAc); R_f = 0.59 (8:2 EtOAc:hexanes); IR (neat) 1714, 1660, 1500, 1380, 1324, 1201, 1154, 1101, 1066, 1032, 1017, 871, 832, 752, 730, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.4 Hz, 2H), 7.29–7.40 (m, 5H), 7.05 (d, J = 7.5 Hz, 2H), 4.37 (m, 2H), 4.29 (d, J = 9.7 Hz, 1H), 3.89 (d, J = 15.8 Hz, 1H), 3.58 (app t, J = 9.4 Hz, 1H), 3.43 (d, 15.8 Hz, 1H), 3.37 (d, J = 8.1 Hz, 1H), 2.81 (dd, J = 5.0, 12.8 Hz, 1H), 2.75 (app t, J = 4.7 Hz, 1H), 2.63 (dd, J = 6.4, 18.8 Hz, 1H), 2.00 (d, J = 18.8 Hz, 1H), 1.62 (t, J = 12.6 Hz, 1H), 1.42 (s, 3H), 1.36 (J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 173.7, 173.0, 169.9, 164.5, 140.6, 137.7, 131.3, 130.9 (q, J = 32.3 Hz), 129.1 (2C), 128.7, 125.8 (2C), 125.7 (2C), 123.8 (q, J = 272.2 Hz), 70.0, 65.2, 62.0, 53.1, 47.5, 43.5, 40.8, 37.8, 35.7, 14.1, 7.5; high-resolution mass spectrum (ESI) m/z 575.1758 [$(M + Na)^+$; calcd for $C_{30}H_{27}N_2O_5F_3Na^+$ 575.1770].

*9a-Ethyl 1,2-Dimethyl 7-oxo-3-phenyl-2,3,5,7,8,8a,9,9a-octahydro-1H-cyclopenta[f]indolizine-1,2,9a-tricarboxylate (**8g**).* Purification by flash chromatography (1:1:0.1 EtOAc/hexanes/Et_3N) afforded **8g** (173 mg, 78% yield) as a white solid: mp 187–189 °C (1:1 EtOAc/Et_2O); R_f = 0.44 (1:1 EtOAc:hexanes); IR (neat) 1746, 1695, 1617, 1431, 1293, 1195, 1144, 1097, 1046, 954, 836, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 6.6 Hz, 2H), 7.28 (app t, J = 6.9 Hz, 2H), 7.22–7.26 (m, 1H), 5.89 (s, 1H), 4.44 (d, J = 15.9 Hz, 1H), 4.35 (qd, J = 7.1, 10.8 Hz, 1H), 4.34 (d, J = 10.6 Hz, 1H), 4.24 (qd, 7.1, 10.8 Hz, 1H), 3.75 (dd, J = 9.6, 10.1 Hz, 1H), 3.71 (s, 3H), 3.49 (d, J =

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15.9 Hz, 1H), 3.25 (d, J = 9.4 Hz, 1H), 3.07 (s, 3H), 2.92 (m, 1H), 2.65 (dd, J = 6.5, 18.1 Hz, 1H), 2.52 (dd, J = 5.4, 13.1 Hz, 1H), 2.02 (dd, J = 1.7, 18.8 Hz, 1H), 1.64 (app t, J = 13.1 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 175.4, 171.9, 170.6, 169.3, 137.8, 129.5, 128.9 (2C), 128.0, 128.0 (2C), 69.1, 66.5, 61.2, 53.5, 51.8, 51.3, 48.4, 46.0, 41.8, 40.0, 37.1, 14.1; high-resolution mass spectrum (ESI) m/z 464.1675 [(M + Na)$^+$; calcd for $C_{24}H_{27}NO_7Na^+$ 464.1685].

*9a-Ethyl 1,2-Dimethyl 3-(4-methoxyphenyl)-7-oxo-2,3,5,7,8,8a,9,9a-octahydro-1H-cyclopenta[f]indolizine-1,2,9a-tricarboxylate (**8h**).* Purification by flash chromatography (4:6:0.1 EtOAc/hexanes/Et_3N) afforded **8h** (193 mg, 82% yield) as a brown solid: mp 111−114 °C (EtOAc); R_f = 0.33 (1:1 EtOAc:hexanes); IR (neat) 1740, 1706, 1435, 1356, 1295, 1245, 1200, 1170, 1031, 910, 847, 728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (bs, 2H), 6.82 (d, J = 8.9 Hz, 2H), 5.88 (d, J = 15.8 Hz, 1H), 4.32 (dq, J = 7.1, 10.7 Hz, 1H), 4.26 (d, J = 10.3, 1H), 4.20 (dq, J = 7.1, 10.7 Hz, 1H), 3.77 (s, 3H), 3.69 (app t, J = 9.4, 10.3 Hz, 1H), 3.68 (s, 3H), 3.45 (d, J = 16.0 Hz, 1H), 3.22 (d, J = 9.5 Hz, 1H), 3.09 (s, 3H), 2.88 (m, 1H), 2.61 (dd, J = 6.5, 18.8 Hz, 1H), 2.51 (dd, J = 5.4, 13.1 Hz, 1H), 1.99 (dd, J = 2.0, 18.8 Hz, 1H), 1.61 (t, J = 13.1 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 175.5, 171.9, 170.7, 169.4, 159.4, 130.1 (2C), 129.7, 129.4, 113.3 (2C), 69.0, 66.0, 61.2, 55.1, 53.4, 51.8, 51.4, 48.3, 45.9, 41.8, 39.9, 37.2, 14.1; high-resolution mass spectrum (ESI) m/z 494.1795 [(M + Na)$^+$; calcd for $C_{25}H_{29}NO_8Na^+$ 494.1791].

*9a-Ethyl 1,2-Dimethyl 7-oxo-3-(4-(trifluoromethyl)phenyl)-2,3,5,7,8,8a,9,9a-octahydro-1H-cyclopenta[f]indolizine-1,2,9a-tricarboxylate (**8i**).* Purification by flash chromatography (4:6:0.1 EtOAc/hexanes/Et_3N) afforded **8i** (177 mg, 73% yield) as a brown solid: mp 80−84 °C (EtOAc); R_f = 0.53 (8:2 EtOAc:hexanes); IR (neat) 2954, 1740, 1711, 1622, 1323, 1201, 1163, 1120, 1066, 1018, 912, 855, 729 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7.3 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 5.89 (s, 1H), 4.41 (d, J = 15.9 Hz, 1H), 4.36 (d, J = 10.5 Hz, 1H), 4.25 (m, 2H), 3.75 (app t, J = 9.7, 10.4 Hz, 1H), 3.66 (s, 3H), 3.37 (d, J = 15.9, 1H), 3.24 (d, J = 9.3 Hz, 1H), 3.06 (s, 3H), 2.88 (m, J = 6.3 Hz, 1H), 2.62 (dd, J = 6.6, 18.8 Hz, 1H), 2.53 (dd, J = 1.8, 18.9 Hz, 1H), 1.98 (dd, J = 1.8, 18.9 Hz, 1H), 1.58 (t, J = 13.1 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 174.7, 171.6, 170.5, 169.0, 142.4, 130.3 (q, J = 32.3 Hz), 129.7, 129.5 (2C), 124.9 (2C), 69.4, 66.0, 61.4, 53.6, 52.0, 51.5, 48.2, 46.2, 41.9, 40.0, 37.1, 14.1; high-resolution mass spectrum (ESI) m/z 532.1544 [(M + Na)$^+$; calcd for $C_{25}H_{26}NO_7F_3Na^+$ 532.1559].

*9a-Ethyl 1,2-Dimethyl 6-methyl-7-oxo-3-phenyl-2,3,5,7,8,8a,9,9a-octahydro-1H-cyclopenta[f]indolizine-1,2,9a-tricarboxylate (**8j**).* Purification by flash chromatography (4:6:0.1 EtOAc:hexanes:Et_3N) afforded **8j** (160 mg, 80% yield) as a brown solid: mp 114−116 °C (EtOAc); R_f = 0.30 (3:7 EtOAc:hexanes); IR (neat) 2951, 1740, 1698, 1658, 1434, 1298, 1198, 1168, 1102, 841, 750, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (bs, 2H), 6.82 (d, J = 8.9 Hz, 2H), 4.29 (dq, J = 7.1, 10.7 Hz, 1H), 4.27 (d, J = 17.1, 1H), 4.18 (dq, J = 7.1, 10.8 Hz, 1H), 4.13 (d, J = 10.5 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.65 (app t, J = 9.7, 10.3 Hz, 1H), 3.48 (d, J = 15.8 Hz, 1H), 3.19 (d, J = 9.6 Hz, 1H), 3.06 (s, 3H), 2.76 (m, 1H), 2.59 (dd, J = 6.5, 18.8 Hz, 1H), 2.46 (dd, J = 5.2, 13.1 Hz, 1H), 1.94 (dd, J = 1.7, 18.8 Hz, 1H), 1.55 (s, 3H), 1.50 (t, J = 13.0, 1H), 1.29 (t, J = 7.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 171.9, 170.7, 169.4, 166.8, 138.2, 136.4, 129.0 (2C), 128.0, 128.0 (2C), 69.4, 66.8, 61.1, 53.5, 51.8, 51.3 48.4, 44.2, 40.9, 40.0, 35.5, 14.1, 7.6; high-resolution mass spectrum (ESI) m/z 478.1824 [(M + Na)$^+$; calcd for $C_{25}H_{29}NO_7Na^+$ 478.1842].

*9a-Ethyl 1,2-Dimethyl 3-(4-Methoxyphenyl)-6-methyl-7-oxo-2,3,5,7,8,8a,9,9a-octahydro-1H-cyclopenta[f]indolizine-1,2,9a-tricarboxylate (**8k**).* Purification by flash chromatography (4:6:0.1 EtOAc/hexanes/Et_3N) afforded **8k** (208 mg, 86% yield) as a brown solid: mp 125−129 °C (EtOAc); R_f = 0.31 (1:1 EtOAc/hexanes); IR (neat) 1738, 1695, 1657, 1511, 1434, 1299, 1244, 1198, 1167, 1024, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (bs, 2H), 6.82 (d, J = 8.1 Hz, 2H), 4.27 (d, J = 16.5 Hz, 1H), 4.25 (m, 2H), 4.13 (d, J = 10.5 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.65 (app t, J = 10.1 Hz, 1H), 3.48 (d, J = 15.8 Hz, 1H), 3.19 (d, J = 9.6 Hz, 1H), 3.07 (s, 3H), 2.77 (m, 1H), 2.60 (dd, J = 6.4, 18.8 Hz, 1H), 2.47 (dd, J = 5.1, 13.1 Hz, 1H), 1.94 (d, J = 18.8 Hz, 1H), 1.55 (s, 3H), 1.50 (t, J = 13.1 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 171.9, 170.8, 169.5, 167.1, 159.4, 136.4, 130.2 (2C), 130.1, 113.3 (2C), 69.3, 66.2, 61.1, 55.1, 53.3, 51.8, 51.4, 48.3, 44.1, 40.9, 39.9, 39.5, 14.1, 7.6; high-resolution mass spectrum (ESI) m/z 508.1937 [(M + Na)$^+$; calcd for $C_{26}H_{31}NO_8Na^+$ 508.1947].

*9a-Ethyl 1,2-Dimethyl 6-Methyl-7-oxo-3-(4-(trifluoromethyl)-phenyl)-2,3,5,7,8,8a,9,9a-octahydro-1H-cyclopenta[f]indolizine-1,2,9a-tricarboxylate (**8l**).* Purification by flash chromatography (4:6:0.1 EtOAc/hexanes/Et_3N) afforded **8l** (238 mg, 73% yield) as a brown solid: mp 125−129 °C (EtOAc); R_f = 0.37 (1:1 EtOAc/hexanes); IR (neat) 2952, 1745, 1699, 1658, 1436, 1323, 1200, 1162, 1121, 1066, 1018, 911, 857, 729 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 6.9 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 4.28 (d, J = 14.9 Hz, 1H), 4.24 (d, J = 10.7 Hz, 1H), 4.24 (m, 2H), 3.73 (app t, J = 9.7, 10.0 Hz, 1H), 3.67 (s, 3H), 3.40 (d, J = 15.7 Hz, 1H), 3.22 (d, J = 9.3 Hz, 1H), 3.04 (s, 3H), 2.78 (t, J = 5.8 Hz, 1H), 2.60 (dd, J = 6.5, 18.8 Hz, 1H), 2.50 (dd, J = 5.1, 13.1 Hz, 1H), 1.94 (d, J = 18.8 Hz, 1H), 1.54 (s, 3H), 1.48 (t, J = 13.0 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 171.7, 170.6, 169.0, 166.1, 142.8, 136.6, 130.2 (q, J = 32.0 Hz), 129.5 (2C), 124.9 (2C), 124.0 (q, J = 272.0 Hz), 69.7, 66.2, 61.3, 53.5, 51.9, 51.4, 48.1, 44.3, 40.9, 40.0, 35.3, 14.1, 7.7; high-resolution mass spectrum (ESI) m/z 546.1714 [(M + Na)$^+$; calcd for $C_{26}H_{28}NO_7F_3Na^+$ 546.1716].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for new compounds. X-ray crystallographic information for compound **6a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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