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Cyclobutene Ring-Opening of Bicyclo[4.2.0]octa-1,6-dienes: Access to CF_3-Substituted 5,6,7,8-Tetrahydro-1,7-naphthyridines

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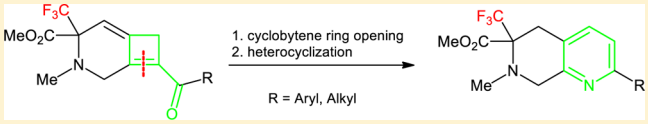
Supporting Information

ABSTRACT: An efficient method for the synthesis of novel CF_3-substituted tetrahydro-1,7-naphthyridines including cyclic α-amino acid derivatives has been developed. The method is based on unusual cyclobutene ring-opening of bicyclo[4.2.0]-octa-1,6-dienes with pyrrolidine to afford the corresponding 1,5-diketones followed by their heterocyclization. A convenient *one-pot* procedure has been also elaborated starting from readily available trifluoromethylated 1,6-allenynes.



INTRODUCTION

Nitrogen heterocycles equipped with diverse functionalities are important structural motifs widely distributed in natural products and pharmaceuticals. Among them, 1,7-naphthyridines represent a special class of dinitrogen-containing heterocycles that are found in the structure of many bioactive compounds.[1] During the past decade, a particular attention has focused on their partially reduced derivatives, the 5,6,7,8-tetrahydro-1,7-naphthyridines (THNs). Being conformationally constrained counterparts of well-known pharmacophore 2-(3-pyridyl)ethylamine,[2] THNs have been shown to function as highly potential agents for the treatment of depression,[3] Alzheimer disease,[4] multiple sclerosis,[5] and various skin diseases.[6]

Several synthetic strategies have been developed to access the 1,7-THN framework due to its medicinal and synthetic usefulness. They include the partial hydrogenation of 1,7-naphthyridine,[7] the conjugative addition of organometallic reagents with chloroformates to C═N-bond of 1,7-naphthyridine,[7c,8] the annulation of a piperidine ring onto a functionalized pyridine,[9] the elaboration of a pyridine core from a preformed piperidine derivative,[10] multicomponent synthesis of epoxytetrahydronaphthyridine with subsequent fragmentation.[11] More recent approach involves the cobalt-catalyzed [2 + 2 + 2]-cycloaddition of orthogonally protected diyne nitriles.[12] These synthetic routes often consist of multistep procedures and have consequently low overall yields. Moreover, most of them are not applicable for the preparation 1,7-THNs with functional groups in the piperidine ring.

On the other hand, it is well established that the introduction of trifluoromethyl (CF_3) groups into specific positions of organic molecules can substantially alter their chemical and metabolic stability, lipophilicity, and binding selectivity due to the strongly electron-withdrawing nature and large hydrophobic domain of trifluoromethyl groups.[13] Indeed, many biologically active compounds, such as the antidepressant Prozac, the anti-inflammatory drug Celebrex, and the anticancer agent Casodex contain the CF_3 group as a key structural motif.[14] Therefore, the development of efficient synthetic methodologies aimed at the rapid construction of new nitrogen-containing heterocyclic systems bearing different functionalities, including CF_3 groups, is of great importance to sustain pharmaceutical innovation.

RESULTS AND DISCUSSION

We have recently elaborated an efficient one-step protocol for the synthesis of functionalized allenynes via [2,3]-sigmatropic rearrangement of propargyl-containing nitrogen and sulfur ylides generated in situ from CF_3-containing diazocompounds **1**.[15] The synthetic potential of allenynes **2** as the unique building blocks for the construction of functionally substituted heterocycles has been demonstrated by the intramolecular carbocyclizations such as cobalt-mediated Pauson−Khand reaction and thermal [2 + 2]-cycloaddition to access the functionally substituted heterocyclic compounds fused with cyclopentenone **3**[15] and cyclobutene **4**[16] rings, respectively (Scheme 1).

In this context, along with our interest in CF_3-containing heterocyclic compounds including cyclic α-amino acid derivatives,[17] we now wish to disclose a convenient route to functionalized 5,6,7,8-tetrahydro-1,7-naphthyridines based on unusual cyclobutene ring-opening of acyl-substituted bicyclo[4.2.0]octa-1,6-dienes with amines followed by intramolecular heterocyclization (Scheme 2).

Despite the fact that the compounds containing the bicyclo[4.2.0]octa-1,6-diene framework are well documented

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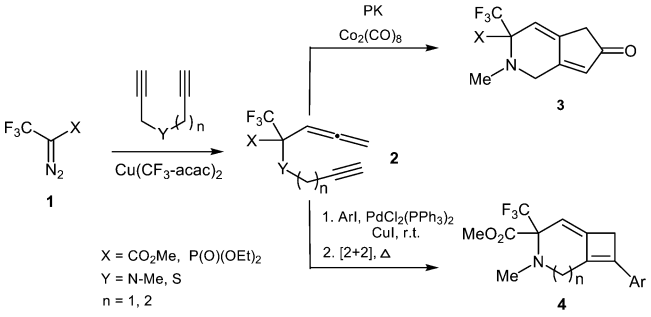
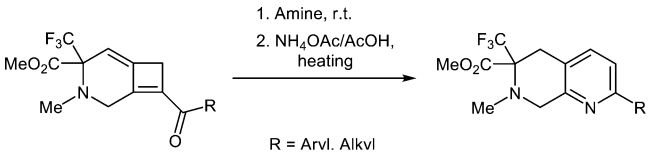
Scheme 1. Synthesis and Carbocyclizations of CF_3-Substituted 1,6-Allenynes



Scheme 2. Transformation of Bicycloocta-1,6-dienes into Tetrahydro-1,7-naphthyridines



in the literature,[18] to the best of our knowledge, the ring-opening of cyclobutene unit was not previously described.

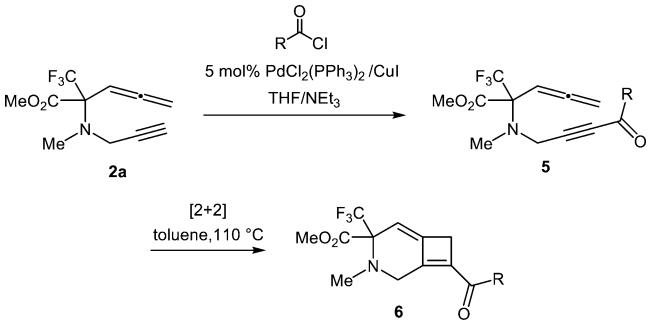
The synthesis of starting bicyclodienes **6** comprising the keto-function on the double bond of the cyclobutene ring has been accomplished using the same methodology as for their arylated analogues **4**[16] (Scheme 1). First, allenynes **5a–h** were prepared by means of Pd-catalyzed cross-coupling of terminal allenyne **2a** with different aromatic and aliphatic acyl chlorides. The reactions were performed in THF at room temperature in the presence of 5 mol % of $PdCl_2(PPh_3)_2$/CuI and a 1.5-fold excess of NEt_3 to furnish the corresponding allenynes **5a–h** in good isolated yields. Then we found that intramolecular [2 + 2]-cycloaddition of **5** smoothly proceeds in toluene at 110 °C for 1–2 h affording the desired bicyclic products **6** in good to excellent yields. It is noteworthy that the formation of cyclobutene ring proceeds upon distal double bond of allene system exclusively (Table 1).

Bicyclo[4.2.0]octa-1,6-dienes **6** contain in their structure the unique combination of constrained cyclobutene ring with carbonyl group coincidently featuring the activated alkene system. Thus, examining their properties, we have unexpectedly found that derivatives **6** comprising aroyl groups on the double bond of the cyclobutene unit, in contrast to their aryl analogues **4**, readily undergo four-membered ring-opening at the presence of piperidine or pyrrolidine to afford the corresponding cyclic 1,5-diketones **7** (Scheme 3).

In order to investigate this interesting transformation in detail, a number of primary and secondary amines, such as diethyl- and diisopropylamines, benzylamine, aniline, piperidine, and pyrrolidine, have been tested using benzoyl-substituted cyclobutene **6a** as a model compound. As a result, we found that the highest yields of cyclic 1,5-diketone **7a** can be achieved on treatment of **6a** with 2-fold excess of pyrrolidine. The full conversion of starting bicycle occurs in dry dioxane at room temperature for 20 min (monitoring by ^{19}F NMR spectroscopy). Subsequent treatment of the reaction mixture with 1 N HCl, needed for the removing of the remaining amine, affords **7a** in 68% yield.

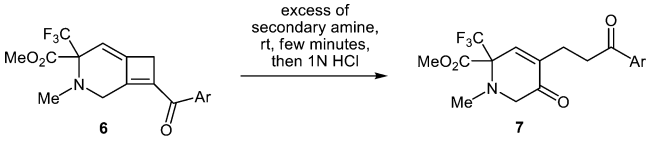
The proposed mechanism of 1,5-diketone formation includes the following: (i) nucleophilic addition of pyrrolidine to the

Table 1. Synthesis of Acylated Bicyclo[4.2.0]octa-1,6-dienes



entry	R	Sonogashira step, yield (%)	[2 + 2] cycloaddition, yield (%)
1	C_6H_5	**5a**, 75	**6a**, 75
2	4-$MeOC_6H_4$	**5b**, 78	**6b**, 89
3	2-$MeOC_6H_4$	**5c**, 78	**6c**, 91
4	4-MeC_6H_4	**5d**, 83	**6d**, 91
5	2-MeC_6H_4	**5e**, 73	**6e**, 88
6	4-$NO_2C_6H_4$	**5f**, 64	**6f**, 82
7	Cy	**5g**, 68	**6g**, 78
8	*t*-Bu	**5h**, 57	**6h**, 85

Scheme 3. Cyclobutene Ring-Opening of Bicyclo[4.2.0]octa-1,6-dienes



activated double bond of cyclobutene ring to give the corresponding Michael adduct **6aa**; (ii) ring-opening of cyclobutene to form zwitterionic intermediate **B**; (iii) hydrolysis of the latter yielding the final product **7a** (Scheme 4).

We have succeeded to isolate and characterize the adduct **6aa** (NR_2 = pyrrolidinyl) formed as a mixture of diastereomers in a ratio of 1:2. In the case of primary amines, the similar adduct **A** has proved to be unstable; the reaction rapidly leads to the formation of imine **8**. This fact implicitly confirms the existence of the intermediate **B**. One more evidence can be considered in favor of the proposed mechanism: the stable dihydropyridine **9** is formed as a result of proton migration of the CH_2N group in zwitterionic intermediate **B** under exposure of reaction mixture in dry dioxane for 48 h. Therefore, the usage of secondary amine, especially pyrrolidine, with subsequent rapid water treatment is a critical point for the successful formation of the desired compound **7a**. At the same time, 1,5-diketone **7a** can be also obtained by acidic hydrolysis of imine **8** when primary amine is utilized.

The found regularities are also implemented for the other bicyclo[4.2.0]octa-1,6-dienes **6** (see the Supporting Information). However, in order to simplify the synthetic procedure and to improve the yields of 1,5-diketones, we have developed a convenient method consisted of thermal [2 + 2]-cycloaddition of allenynes **5** and cyclobutene ring-opening in *one pot*. Thus, the cycloaddition step has been accomplished by heating in dioxane at 110 °C until the full conversion of starting material (control by TLC). The reaction usually has gone to completion for 4 h. Then, after being cooled to room temperature, the

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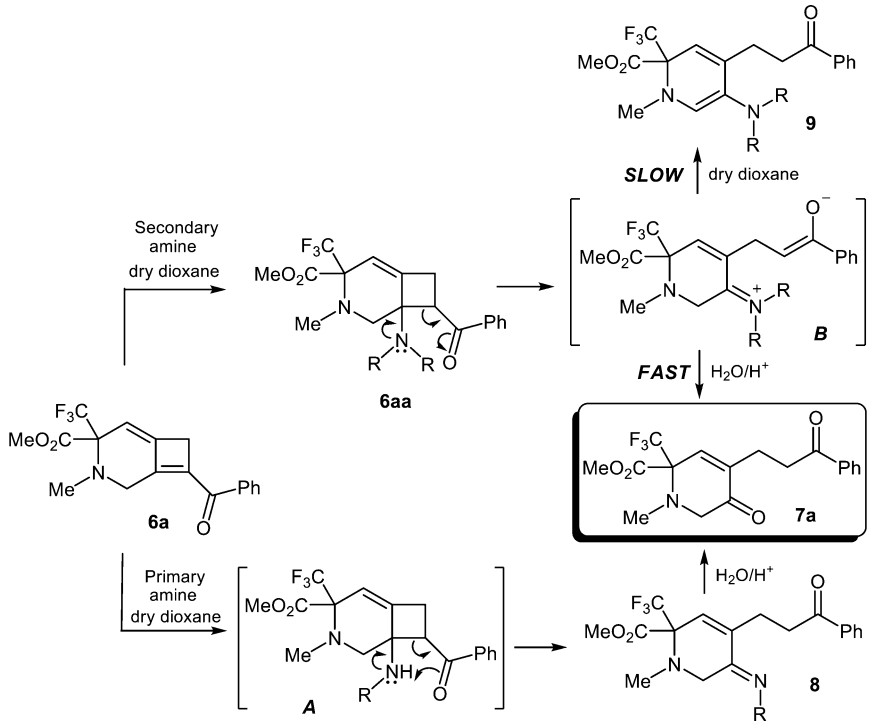
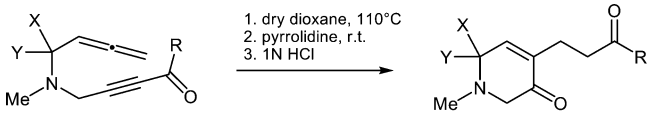
Scheme 4. Proposed Mechanism of Cyclobutene Ring-Opening



resulting solution has been treated with a 2-fold excess of pyrolidine and in 20 min with 1 N HCl to yield **7** (Table 2).

Table 2. One-Pot Synthesis of 1,5-Diketones 7



5 7

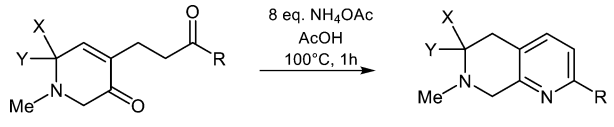
entry	X	Y	R	product	yield (%)
1	CF_3	CO_2Me	C_6H_5	**7a**	70
2	CF_3	CO_2Me	4-$MeOC_6H_4$	**7b**	71
3	CF_3	CO_2Me	2-$MeOC_6H_4$	**7c**	73
4	CF_3	CO_2Me	4-MeC_6H_4	**7d**	70
5	CF_3	CO_2Me	2-MeC_6H_4	**7e**	74
6	CF_3	CO_2Me	4-$NO_2C_6H_4$	**7f**	77
7	CF_3	CO_2Me	Cy	**7g**	87
8	CF_3	CO_2Me	*t*-Bu	**7h**	25[a]
9	CF_3	CF_3	C_6H_5	**7i**	70
10	CF_3	CF_3	2-$MeOC_6H_4$	**7j**	76
11	CO_2Et	CO_2Et	C_6H_5	**7k**	65
12	CO_2Et	CO_2Et	2-$MeOC_6H_4$	**7l**	58

[a]Ring-opening step was performed under heating at 50 °C for 2 h; there was no conversion of [2 + 2]-cycloadduct at rt.

To extend the scope of the reaction, terminal 1,6-allenynes **2b,c** containing two trifluoromethyl- (X = Y = CF_3) and two ethoxycarbonyl- (X = Y = CO_2Et) groups have been synthesized from $(CF_3)_2C{=}N_2$ or $(MeO_2C)_2C{=}N_2$ by analogy with **2a**[15] (see the Experimental Section). Then, **2b,c** were transformed into **5i–l** using the same protocol as for **5a–h** (Table 1) and directly involved in a *one-pot* process affording the corresponding diketones **7i–l** (entries 9–12, Table 2). It should be noted that the nature of substituents (R, X and Y) did not essentially affect the outcome of the process; in all cases, diketones **7** were isolated in good yields after column chromatography on silica gel. The only exception was the case of pivaloyl-containing allenyne **5h**. The low yield of the corresponding diketone **7h** (entry 8) can be attributed to the steric effect of the bulky *t*-Bu group.

The 1,5-diketones obtained have proved to be convenient synthons for the preparation of functional 5,6,7,8-tetrahydro-1,7-naphthyridines **10**. Thus, we found that 1,5-diketones **7** have selectively undergone heterocyclization under heating with excess of ammonia acetate in glacial acetic acid at 100 °C for 1 h to afford the corresponding heterocycles **10a–l** in good to high yields (Table 3).

Table 3. Synthesis of Functional 5,6,7,8-Tetrahydro-1,7-naphthyridines 10



7 10

entry	X	Y	R	product	yield (%)
1	CF_3	CO_2Me	C_6H_5	**10a**	75
2	CF_3	CO_2Me	4-$MeOC_6H_4$	**10b**	85
3	CF_3	CO_2Me	2-$MeOC_6H_4$	**10c**	89
4	CF_3	CO_2Me	4-MeC_6H_4	**10d**	90
5	CF_3	CO_2Me	2-MeC_6H_4	**10e**	84
6	CF_3	CO_2Me	4-$NO_2C_6H_4$	**10f**	86
7	CF_3	CO_2Me	Cy	**10g**	88
8	CF_3	CO_2Me	*t*-Bu	**10h**	93
9	CF_3	CF_3	C_6H_5	**10i**	76
10	CF_3	CF_3	2-$MeOC_6H_4$	**10j**	51
11	CO_2Et	CO_2Et	C_6H_5	**10k**	70
12	CO_2Et	CO_2Et	2-$MeOC_6H_4$	**10l**	68

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The structure of derivative **10i** was confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information).

CONCLUSION

In conclusion, the present study first demonstrated that bicyclo[4.2.0]octa-1,6-dienes derived by thermal [2 + 2]-cycloaddition of functional acylated 1,6-allenynes can regioselectively undergo four member ring-opening by treating with pyrrolidine to afford the corresponding dehydropiperidine-containing 1,5-diketones. A convenient *one-pot* procedure for their preparation involved both of cycloaddition and ring-opening processes has been also performed starting from 1,6-allenynes. The 1,5-diketones obtained were further successfully converted into functionally substituted tetrahydro-1,7-naphthyridines including cyclic α-amino acid derivatives via intramolecular cyclization performed under heating with excess of ammonia acetate in acetic acid. This straightforward method would extend the potential application of novel 1,7-naphthyridine derivatives in synthetic and medicinal chemistry.

EXPERIMENTAL SECTION

General Experimental Methods. All solvents were freshly distilled from the appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. Sonogashira reactions and [2 + 2] cycloaddition reactions were performed under an argon atmosphere. Analytical TLC was performed with silica gel 60 F254 plates. Visualization was accomplished by UV light, spraying by $Ce(SO_4)_2$ solution in 5% H_2SO_4 or $KMnO_4$ solution in water. Column chromatography was carried out using silica gel 60 (230−400 mesh ASTM) and ethyl acetate/hexanes as eluent. NMR spectra were recorded at room temperature on NMR spectrometers operating at 200, 300, 600 MHz, respectively (TMS reference) for ^{1}H; 50, 75, and 151 MHz for ^{13}C; 282 MHz for ^{19}F ($CFCl_3$ reference). 1,6-Allenyne **2a**,[15] 1,1,1,3,3,3-hexafluoromethyl-2-diazopropane,[19] diethyl diazomalonate,[20] and *N*,*N*-dipropargyl-*N*-methylamine[21] were prepared using the literature protocols.

General Procedure for Sonogashira Coupling. A solution of the corresponding acyl chloride (1.05 mmol) and 1,6-allenyne **2** (0.81 mmol) in degassed THF (3 mL) was placed in a dried Schlenk tube. Then $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) and CuI (8 mg, 0.04 mmol) were added sequentially in under an argon flow. The resulting mixture was warmed to room temperature, and dry triethylamine (0.16 mL, 1.13 mmol) was added via septum rubber. The reaction mixture was vigorously stirred for 2−3 h until disappearance of starting 1,6-allenyne (TLC control). The precipitate of triethylamine hydrochloride was filtered off. A solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (hexanes/EtOAc = 8:1) to give pure **5**.

Methyl 2-[methyl(4-oxo-4-phenylbut-2-yn-1-yl)amino]-2-(trifluoromethyl)penta-3,4-dienoate (***5a***): yield 215 mg, 75% (yellowish oil); R_f 0.4; ^{1}H NMR (200 MHz, C_6D_6) δ 8.18 (d, *J* = 6.5 Hz, 2H, H_{arom}), 7.25−6.96 (m, 3H, H_{arom}), 5.22 (t, *J* = 6.8 Hz, 1H, CH_{allene}), 4.60 (d, *J* = 6.8 Hz, 2H, $CH_{2allene}$), 3.65 (s, 2H, CH_2), 3.33 (s, 3H, $COOCH_3$), 2.52 (s, 3H, NCH_3); ^{13}C NMR (50 MHz, C_6D_6) δ 208.2, 175.8, 165.2, 135.9, 132.6, 128.3, 127.4, 124.0 (q, *J* = 290.5 Hz) 89.8, 86.3 (q, *J* = 1.4 Hz), 81.5, 77.9, 72.5 (q, *J* = 25.5 Hz), 50.8, 41.4 (q, *J* = 1.9 Hz), 36.5 (q, *J* = 2.0 Hz); ^{19}F NMR (188 MHz, C_6D_6) δ −68.50 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{16}F_3NO_3$: C, 61.54; H, 4.59; N, 3.99. Found: C, 61.47; H, 4.65; N, 3.81.

Methyl 2-[[4-(4-methoxyphenyl)-4-oxobut-2-yn-1-yl](methyl)-amino]-2-(trifluoromethyl)penta-3,4-dienoate (***5b***): yield 240 mg, 78% (yellowish oil); R_f 0.35; ^{1}H NMR (200 MHz, C_6D_6) δ 8.21 (d, *J* = 8.8 Hz, 2H, H_{arom}), 6.64 (d, *J* = 8.8 Hz, 2H, H_{arom}), 5.25 (t, *J* = 6.8 Hz, 1H, CH_{allene}), 4.60 (d, *J* = 6.8 Hz, 2H, $CH_{2allene}$), 3.67 (s, 2H, CH_2), 3.33 (s, 3H, $COOCH_3$), 3.19 (s, 3H, OCH_3), 2.56 (s, 3H, NCH_3); ^{13}C NMR (50 MHz, C_6D_6) δ 209.9, 176.2, 166.9, 164.9, 132.4, 131.0, 125.6 (q, *J* = 298.3 Hz), 114.4, 90.4, 88.0 (q, *J* = 1.6 Hz), 83.3, 79.5, 74.1 (q, *J* = 25.2 Hz), 55.3, 52.4, 43.0 (q, *J* = 1.7 Hz), 38.1 (q, *J* = 2.1 Hz); ^{19}F NMR (188 MHz, C_6D_6) δ −68.42 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{18}F_3NO_4$: C, 59.84; H, 4.76; N, 3.67. Found: C, 60.05; H, 4.69; N, 3.79.

Methyl 2-[[4-(2-methoxyphenyl)-4-oxobut-2-yn-1-yl](methyl)-amino]-2-(trifluoromethyl)penta-3,4-dienoate (***5c***): yield 240 mg, 78% (yellowish oil); R_f 0.35; ^{1}H NMR (600 MHz, C_6D_6) δ 8.19 (dd, *J* = 7.7, 1.7 Hz, 1H, H_{arom}), 7.21−7.16 (m, 1H, H_{arom}), 6.85−6.80 (m, 1H, H_{arom}), 6.54 (t, *J* = 8.0 Hz, 1H, H_{arom}), 5.34 (t, *J* = 6.8 Hz, 1H, CH_{allene}), 4.68 (d, *J* = 6.8 Hz, 2H, $CH_{2allene}$), 3.77 (s, 2H, NCH_2), 3.46 (s, 3H, OCH_3), 3.41 (s, 3H, $CO2CH_3$), 2.66 (s, 3H, NCH_3); ^{13}C NMR (151 MHz, C_6D_6) δ 209.3, 175.6, 166.4, 159.8, 134.4, 132.1, 127.3, 125.0 (q, *J* = 289.5 Hz), 120.2, 112.2, 89.2, 87.6, 85.3, 79.0, 73.7 (q, *J* = 25.4 Hz), 55.1, 51.8, 42.7, 37.5; ^{19}F NMR (188 MHz, C_6D_6) δ −68.30 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{18}F_3NO_4$: C, 59.84; H, 4.76; N, 3.67. Found: C, 59.72; H, 4.88; N, 3.55.

Methyl 2-[methyl[4-(4-methylphenyl)-4-oxobut-2-yn-1-yl]-amino]-2-(trifluoromethyl)penta-3,4-dienoate, (***5d***): yield 245 mg, 83% (yellowish oil); R_f 0.4; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H, H_{arom}), 7.27 (d, *J* = 8.0 Hz, 2H, H_{arom}), 5.39 (t, *J* = 6.8 Hz, 1H, CH_{allene}), 5.05 (d, *J* = 6.8 Hz, 2H, $CH_{2allene}$), 3.95 (s, 2H, CH_2), 3.81 (s, 3H, $COOCH_3$), 2.71 (s, 3H, NCH_3), 2.41 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.4, 176.4, 165.8, 144.3, 133.3, 128.7, 128.3, 123.5 (q, *J* = 289.7 Hz), 89.8, 86.3 (q, *J* = 1.5 Hz), 81.3, 78.5, 72.5 (d, *J* = 25.3 Hz), 51.7, 41.6 (q, *J* = 1.8 Hz), 36.8 (q, *J* = 2.1 Hz), 20.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ −68.41 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{18}F_3NO_3$: C, 62.46; H, 4.97; N, 3.83. Found: C, 62.40; H, 4.89; N, 3.98.

Methyl 2-[methyl[4-(2-methylphenyl)-4-oxobut-2-yn-1-yl]-amino]-2-(trifluoromethyl)penta-3,4-dienoate, (***5e***): yield 216 mg, 73% (yellowish oil); R_f 0.4; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.5 Hz, 1H, H_{arom}), 7.56−7.12 (m, 3H, H_{arom}), 5.39 (t, *J* = 6.8 Hz, 1H, CH_{allene}), 5.05 (d, *J* = 6.7 Hz, 2H, $CH_{2allene}$), 3.94 (s, 2H, CH_2), 3.82 (s, 3H, $COOCH_3$), 2.71 (s, 3H, NCH_3), 2.62 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.8, 179.7, 167.2, 140.9, 135.7, 133.8, 133.4, 132.5, 126.3, 124.9 (q, *J* = 289.8 Hz), 90.3, 87.7, 84.0, 79.9, 73.9 (q, *J* = 25.3 Hz), 53.1, 43.0 (q, *J* = 1.6 Hz), 38.2 (q, *J* = 1.7 Hz), 22.3; ^{19}F NMR (188 MHz, $CDCl_3$) δ −68.37 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{18}F_3NO_3$: C, 62.46; H, 4.97; N, 3.83. Found: C, 62.53; H, 5.05; N, 3.75.

Methyl 2-[methyl[4-(4-nitrophenyl)-4-oxobut-2-yn-1-yl]amino]-2-(trifluoromethyl)penta-3,4-dienoate (***5f***): Yield: 205 mg, 64% (yellowish oil). R_f 0.45; ^{1}H NMR (200 MHz, C_6D_6) δ 7.86 (d, *J* = 8.7 Hz, 2H, H_{arom}), 7.71 (d, *J* = 8.7 Hz, 2H, H_{arom}), 5.23 (t, *J* = 6.8 Hz, 1H, CH_{allene}), 4.60 (d, *J* = 6.8 Hz, 2H, $CH_{2allene}$), 3.65 (s, 2H, CH_2), 3.31 (s, 3H, $COOCH_3$), 2.53 (s, 3H, NCH_3). ^{13}C NMR (50 MHz, C_6D_6) δ 209.7, 175.4, 166.6, 150.9, 140.7, 130.3, 125.4 (q, *J* = 290.3 Hz), 123.7, 93.4, 87.7 (q, *J* = 2.2 Hz), 82.3, 79.5, 73.9 (q, *J* = 25.6 Hz), 52.3, 42.8, 37.9 (d, *J* = 2.3 Hz). ^{19}F NMR (188 MHz, C_6D_6) δ −68.31 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{15}F_3N_2O_5$: C, 54.55; H, 3.81; N, 7.07. Found: C, 54.70; H, 3.65; N, 6.89.

Methyl 2-[(4-cyclohexyl-4-oxobut-2-yn-1-yl)(methyl)amino]-2-(trifluoromethyl)penta-3,4-dienoate (***5g***): yield 197 mg, 68% (yellowish oil); R_f 0.5; ^{1}H NMR (200 MHz, C_6D_6) δ 5.20 (t, *J* = 6.8 Hz, 1H, CH_{allene}), 4.59 (d, *J* = 6.8 Hz, 2H, $CH_{2allene}$), 3.60 (s, 2H, CH_2), 3.32 (s, 3H, $COOCH_3$), 2.50 (s, 3H, NCH_3), 2.26−2.09 (m, 1H, CH), 1.98−1.73 (m, 2H, CH_2), 1.61−1.25 (m, 6H, $3CH_2$), 1.14−0.91 (m, 2H, CH_2); ^{13}C NMR (50 MHz, C_6D_6) δ 209.6, 189.8, 166.6, 125.4 (q, *J* = 301.9 Hz), 88.8, 87.8 (q, *J* = 1.5 Hz), 83.4, 79.2, 73.9 (d, *J* = 25.4 Hz), 52.3, 52.2, 42.6 (q, *J* = 2.2 Hz), 37.7 (q, *J* = 2.3 Hz), 28.4, 26.1, 25.6; ^{19}F NMR (188 MHz, C_6D_6) δ −68.36 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{22}F_3NO_3$: C, 60.50; H, 6.21; N, 3.92. Found: C, 60.41; H, 6.34; N, 3.81.

Methyl 2-[(5,5-dimethyl-4-oxohex-2-yn-1-yl)(methyl)amino]-2-(trifluoromethyl)penta-3,4-dienoate (***5h***): yield 153 mg, 57% (yellowish oil); R_f 0.5; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.35 (t, *J* = 6.8 Hz, 1H, CH_{allene}), 5.03 (d, *J* = 6.8 Hz, 2H, $CH_{2allene}$), 3.84 (s, 2H, CH_2), 3.81 (s, 3H, $COOCH_3$), 2.64 (s, 3H, NCH_3), 1.20 (s, 9H, $3CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.3, 192.9, 165.8, 123.5 (q, *J*

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= 290.2 Hz), 89.3, 86.3, 80.5, 78.5, 72.5 (q, J = 25.4 Hz), 51.7, 43.7, 41.4 (q, J = 1.6 Hz), 36.6 (q, J = 2.0 Hz), 24.9; ^{19}F NMR (188 MHz, $CDCl_3$) δ −68.36 (s, 3F, CF_3). Anal. Calcd for $C_{16}H_{20}F_3NO_3$: C, 58.00; H, 6.08; N, 4.23. Found: C, 58.11; H, 6.17; N, 4.12.

General Procedure for [2 + 2] Cycloaddition. A solution of the corresponding allenyne (200 mg) in dry toluene (4 mL) was placed in a dried Schlenk tube. The reaction mixture was heated at 110 °C for 2 h under argon. Then a resulting solution was cooled to rt, the solvent was removed under reduced pressure, and the residual oil was chromatographed with mixture of hexanes/EtOAc = 8:1 furnishing the desired bicyclic product **6**.

*Methyl 8-benzoyl-3-methyl-4-(trifluoromethyl)-3-azabicyclo[4.2.0]octa-1(8),5-diene-4-carboxylate (**6a**):* yield 150 mg, 75% (yellowish oil); R_f 0.25; ^{1}H NMR (200 MHz, C_6D_6) δ 7.68 (dd, J = 8.0, 1.5 Hz, 2H, H_{arom}), 7.21−7.00 (m, 3H, H_{arom}), 5.47 (s, 1H, CH), 3.58 (s, 2H, CH_2), 3.29 (s, 3H, $COOCH_3$), 3.15 (t, J = 2.7 Hz, 2H, CH_2), 2.31 (q, J = 1.5 Hz, 3H, NCH_3); ^{13}C NMR (50 MHz, C_6D_6) δ 186.5, 166.3, 148.1, 139.3, 137.0, 134.5, 131.2, 127.4, 127.2, 124.6 (q, J = 292.1 Hz), 110.1 (d, J = 2.3 Hz), 68.7 (q, J = 25.5 Hz), 51.0, 47.8, 38.7 (d, J = 2.1 Hz), 35.9; ^{19}F NMR (188 MHz, C_6D_6) δ −67.23 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{16}F_3NO_3$: C, 61.54; H, 4.59; N, 3.99. Found: C, 61.40; H, 4.71; N, 4.07.

*Methyl 8-(4-methoxybenzoyl)-3-methyl-4-(trifluoromethyl)-3-azabicyclo[4.2.0]octa-1(8),5-diene-4-carboxylate (**6b**):* yield 178 mg, 89% (yellowish oil); R_f 0.23; ^{1}H NMR (200 MHz, C_6D_6) δ 7.76 (d, J = 8.8 Hz, 2H, H_{arom}), 6.65 (d, J = 8.8 Hz, 2H, H_{arom}), 5.49 (s, 1H, CH), 3.69 (s, 2H, CH_2), 3.32 (s, 3H, $COOCH_3$), 3.26 (s, 3H, $COOCH_3$), 3.22 (t, J = 2.6 Hz, 2H, CH_2), 2.36 (q, J = 1.2 Hz, 3H, NCH_3); ^{13}C NMR (50 MHz, C_6D_6) δ 184.9, 166.4, 162.3, 147.6, 139.5, 134.9, 129.8, 129.6, 124.7 (q, J = 292.1 Hz), 112.8, 109.5 (q, J = 2.4 Hz), 68.8 (q, J = 25.3 Hz), 53.6, 51.0, 47.9, 38.8 (q, J = 2.1 Hz), 36.2; ^{19}F NMR (188 MHz, C_6D_6) δ −67.25 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{18}F_3NO_4$:C, 59.84; H, 4.76; N, 3.67. Found: C, 59.93; H, 4.88; N, 3.40.

*Methyl 8-(2-methoxybenzoyl)-3-methyl-4-(trifluoromethyl)-3-azabicyclo[4.2.0]octa-1(8),5-diene-4-carboxylate (**6c**):* yield 182 mg, 91% (yellowish oil); R_f 0.23; ^{1}H NMR (200 MHz, C_6D_6) δ 7.34 (dd, J = 7.5, 1.7 Hz, 1H, H_{arom}), 7.07 (td, J = 7.5, 1.7 Hz, 1H, H_{arom}), 6.73 (t, J = 7.4 Hz, 1H, H_{arom}), 6.44 (d, J = 8.3 Hz, 1H, H_{arom}), 5.46 (s, 1H, CH), 3.45 (s, 2H, CH_2), 3.27 (s, 3H, $COOCH_3$), 3.20−3.14 (m, 5H, OCH_3+CH_2), 2.25 (q, J = 1.4 Hz, 3H, NCH_3); ^{13}C NMR (50 MHz, C_6D_6) δ 187.9, 166.3, 156.1, 147.5, 139.4, 136.0, 131.0, 128.7, 128.3, 124.7 (q, J = 292.1 Hz), 119.5, 110.1, 110.0, 68.8 (q, J = 25.6 Hz), 53.7, 51.0, 47.1, 38.7 (q, J = 1.8 Hz), 35.0; ^{19}F NMR (188 MHz, C_6D_6) δ −67.24 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{18}F_3NO_4$:C, 59.84; H, 4.76; N, 3.67. Found: C, 59.67; H, 4.73; N, 3.80.

*Methyl 3-methyl-8-(4-methylbenzoyl)-4-(trifluoromethyl)-3-azabicyclo[4.2.0]octa-1(8),5-diene-4-carboxylate (**6d**):* yield 182 mg, 91% (yellowish oil); R_f 0.22; ^{1}H NMR (200 MHz, C_6D_6) δ 7.66 (d, J = 7.9 Hz, 2H, H_{arom}), 6.91 (d, J = 7.9 Hz, 2H, H_{arom}), 5.48 (s, 1H, CH), 3.63 (s, 2H, CH_2), 3.32 (s, 3H, $COOCH_3$), 3.19 (s, 2H), 2.33 (s, 3H, NCH_3), 2.03 (s, 3H, CH_3); ^{13}C NMR (50 MHz, C_6D_6) δ 186.1, 166.4, 147.8, 142.0, 139.4, 134.8, 134.5, 128.1, 127.4, 124.6 (q, J = 292.1 Hz), 109.8 (q, J = 2.3 Hz), 68.7 (q, J = 25.3 Hz), 51.0, 47.8, 38.8 (q, J = 1.8 Hz), 36.0, 20.0; ^{19}F NMR (188 MHz, C_6D_6) δ −67.26 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{18}F_3NO_3$: C, 62.46; H, 4.97; N, 3.83. Found: C, 62.33; H, 4.85; N, 3.94.

*Methyl 3-methyl-8-(2-methylbenzoyl)-4-(trifluoromethyl)-3-azabicyclo[4.2.0]octa-1(8),5-diene-4-carboxylate (**6e**):* yield 176 mg, 88% (yellowish oil); R_f 0.22; ^{1}H NMR (200 MHz, C_6D_6) δ 7.21−6.85 (m, 4H, H_{arom}), 5.46 (s, 1H, CH), 3.34 (s, 2H, CH_2), 3.28 (s, 3H, $COOCH_3$), 3.16 (s, 2H, CH_2), 2.37 (s, 3H, NCH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (50 MHz, C_6D_6) δ 189.6, 166.2, 147.7, 139.0, 137.2, 136.2, 135.7, 130.4, 129.6, 127.1, 126.7, 124.6 (q, J = 292.0 Hz), 110.5 (q, J = 2.3 Hz), 68.7 (q, J = 25.3 Hz), 51.0, 47.2, 38.7 (q, J = 2.1 Hz), 35.0, 18.6; ^{19}F NMR (188 MHz, C_6D_6) δ −67.21 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{18}F_3NO_3$: C, 62.46; H, 4.97; N, 3.83. Found: C, 62.58; H, 5.09; N, 3.99.

*Methyl 3-methyl-8-(4-nitrobenzoyl)-4-(trifluoromethyl)-3-azabicyclo[4.2.0]octa-1(8),5-diene-4-carboxylate (**6f**):* yield 164 mg, 82% (yellowish oil); R_f 0.20; ^{1}H NMR (200 MHz, C_6D_6) δ 7.73 (d, J = 8.7 Hz, 2H, H_{arom}), 7.31 (d, J = 8.7 Hz, 2H, H_{arom}), 5.52 (s, 1H, CH), 3.49 (s, 2H, CH_2), 3.30 (s, 3H, $COOCH_3$), 3.07 (t, J = 2.7 Hz, 2H, CH_2), 2.35 (q, J = 1.3 Hz, 3H, NCH_3); ^{13}C NMR (50 MHz, C_6D_6) δ 184.7, 166.1, 149.6, 148.7, 141.0, 138.9, 133.5, 127.6, 124.5 (q, J = 292.0 Hz), 122.4, 111.5 (q, J = 2.6 Hz), 68.7 (q, J = 25.2 Hz), 51.1, 47.6, 38.8 (q, J = 2.1 Hz), 35.7; ^{19}F NMR (188 MHz, C_6D_6) δ −67.17 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{15}F_3N_2O_5$: C, 54.55; H, 3.81; N, 7.07. Found: C, 54.70; H, 3.74; N, 7.19.

*Methyl 8-(cyclohexylcarbonyl)-3-methyl-4-(trifluoromethyl)-3-azabicyclo[4.2.0]octa-1(8),5-diene-4-carboxylate (**6g**):* yield 156 mg, 78% (yellowish oil); R_f 0.35; ^{1}H NMR (200 MHz, C_6D_6) δ 5.44 (s, 1H, CH), 3.60 (s, 2H, CH_2), 3.29 (s, 3H, $COOCH_3$), 2.98 (t, J = 2.8 Hz, 2H. CH_2), 2.39 (q, J = 1.5 Hz, 3H, NCH_3), 2.30−2.13 (m, 1H, H_{Cy}), 1.73−1.23 (m, 8H, H_{cy}), 1.18−0.99 (m, 2H, H_{Cy}); ^{13}C NMR (50 MHz, C_6D_6) δ 197.2, 166.3, 145.6, 138.9, 134.8, 124.6 (q, J = 292.0 Hz), 109.8 (q, J = 2.4 Hz), 68.6 (q, J = 25.6 Hz), 51.0, 47.4, 47.2, 38.9 (q, J = 2.0 Hz), 34.3, 27.3 (d, J = 3.0 Hz), 24.7, 24.6; ^{19}F NMR (188 MHz, C_6D_6) δ −67.30 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{22}F_3NO_3$:C, 60.50; H, 6.21; N, 3.92. Found: C, 60.63; H, 6.35; N, 4.04.

*Methyl 8-(2,2-dimethylpropanoyl)-3-methyl-4-(trifluoromethyl)-3-azabicyclo[4.2.0]octa-1(8),5-diene-4-carboxylate (**6h**):* yield 170 mg, 85% (yellowish oil); R_f 0.35; ^{1}H NMR (200 MHz, C_6D_6) δ 5.47 (s, 1H, CH), 3.78 (s, 2H, CH_2), 3.25 (s, 3H, $COOCH_3$), 3.02 (t, J = 2.8 Hz, 2H, CH_2), 2.36 (q, J = 1.4 Hz, 3H, NCH_3), 0.95 (s, 9H, $3CH_3$); ^{13}C NMR (50 MHz, C_6D_6) δ 200.6, 167.8, 149.5, 140.9, 135.1, 126.1 (q, J = 292.2 Hz), 110.9 (q, J = 2.4 Hz), 70.1 (q, J = 25.8 Hz), 52.3, 49.6, 42.6, 40.2 (q, J = 2.3 Hz), 38.2, 26.0; ^{19}F NMR (188 MHz, C_6D_6) δ −67.34 (s, 3F, CF_3). Anal. Calcd for $C_{16}H_{20}F_3NO_3$: C, 58.00; H, 6.08; N, 4.23. Found: C, 57.89; H, 6.21; N, 4.11.

Typical Procedure for Cyclobutene Ring-Opening of Bicyclo[4.2.0]octa-1,6-diene. Pyrrolidine (81 mg, 0.12 mmol) was added to solution of **6a** (200 mg, 0.6 mmol) in dry dioxane (4 mL). At that, the color of the reaction mixture was changed from light yellow to red, and the resulting solution was stirred for 20 min (TLC control). The reaction mixture was poured into 50 mL of 1 N HCl (water solution) and extracted with EtOAc. Combined organic fractions were washed with water and dried over anhydrous $MgSO_4$. A solvent was removed under reduced pressure, and the residue was chromatographed with a mixture of EtOAc/hexanes = 1:6 furnishing **7a**: yield 143 mg (68%).

*Methyl (5E)-1-Methyl-4-(3-oxo-3-phenylpropyl)-5-(phenylimino)-2-(trifluoromethyl)piperidine-2-carboxylate (**8**):* To solution of compound **7a** (100 mg, 0.28 mmol) in dry dioxane (2 mL) aniline (52 mg, 0.56 mmol) was added and the resulting mixture was vigorously stirred at ambient temperature for 24 h. Then a solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (eluent: EtOAc/hexanes = 1/5) to give compound **8** as yellow oil (purity ∼80% determined by ^{19}F NMR spectroscopy, partially hydrolyzed on column): yield 57 mg (45%); R_f = 0.4; ^{1}H NMR (300 MHz, C_6D_6) δ 7.97 (d, J = 7.2 Hz, 2H, $2CH_{arom}$), 7.29−7.11 (m, 5H, $5CH_{arom}$), 7.04 (t, J = 7.3 Hz, 1H, CH_{arom}), 6.75 (d, J = 7.6 Hz, 2H, $2CH_{arom}$), 6.50 (s, 1H, CH), 3.69 (m, 2H, CH_2), 3.38 (s, 3H, CO_2CH_3), 3.26−3.05 (m, 4H, $2CH_2$), 2.30 (s, 3H, NCH_3); ^{19}F NMR (282 MHz, C_6D_6) δ −67.96 (s, 3F, CF_3).

Transformation of 8 to 7a. Imine **8** (50 mg) was hydrolyzed by treatment with a mixture of 3 N HCl (1.5 mL)/dioxane (0.5 mL) at ambient temperature for 1 h. The resulting mixture was poured into 20 mL of cold water and extracted twice with EtOAc. The combined organic solution was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed with a mixture of EtOAc/hexanes = 1/6 furnishing products **7a**: yield 26 mg (63%).

*Methyl 8-Benzoyl-3-methyl-1-pyrrolidin-1-yl-4-(trifluoromethyl)-3-azabicyclo[4.2.0]oct-5-ene-4-carboxylate **6aa** (Mixture of Diastereomers in a Ratio of 1:2).* Pyrrolidine (40 mg, 0.58 mmol) was added to solution of **6a** (100 mg, 0.29 mmol) in dry dioxane (2 mL) at

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rt. The resulting mixture was stirred for 20 min, and solvent was removed under reduced pressure to give the crude product (purity ~87% determined by ^{19}F NMR spectroscopy). All attempts to purify **6aa** were unsuccessful and led to formation of **9** under column chromatography conditions: ^1H NMR (300 MHz, $CDCl_3$) 7.65 (m, 2H, CH_{arom}), 7.37 (m, 3H, CH_{arom}), 5.90 and 5.86 (1H, =CH), 5.57 (m, 1H, CHC(O)), 3.85 and 3.83 (s, 2H, NCH_2), 3.64 (s, 3H, CO_2CH_3), 3.54 (d, J = 12.9 Hz, 1H, CH_2) and 3.49 (d, J = 12.1 Hz, 1H, CH_2), 3.16−3.27 (m, 1H, CH_2), 3.05−2.85 (m, 4H, $2NCH_2$), 2.64 (q, J = 2.2 Hz, 3H, NCH_3) and 2.60 (s, 3H, NCH_3), 1.77−1.69 (m, 4H, $2CH_2$); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.73 (s, 3F, CF_3), −70.33 (s, 3F, CF_3).

*Methyl 1-Methyl-4-(3-oxo-3-phenylpropyl)-5-pyrrolidin-1-yl-2-(trifluoromethyl)-1,2-dihydropyridine-2-carboxylate (**9**).* Obtained by exposure of **6a** and pyrrolidine (2 equiv) in dry dioxane at room temperature for 48 h and purified by column chromatography: R_f = 0.42 (EtOAc/hexanes =1/6); ^1H NMR (600 MHz, C_6D_6) δ 7.90 (d, J = 7.7 Hz, 2H, H_{arom}), 7.21 (d, J = 6.8 Hz, 1H, H_{arom}), 7.13 (t, J = 7.6 Hz, 2H, H_{arom}), 5.72 (s, 1H, CH), 5.19 (s, 1H, CH), 3.41 (s, 3H, CO_2CH_3), 3.15−3.07 (m, 1H, CH_2), 3.02−2.95 (m, 1H, CH_2), 2.93−2.86 (m, 1H, CH_2), 2.82 (s, 3H, NCH_3), 2.81−2.75 (m, 1H, CH_2), 2.75−2.68 (m, 2H, NCH_2), 2.62−2.53 (m, 2H, NCH_2), 1.66−1.52 (m, 4H, $2CH_2$); ^{13}C NMR (151 MHz, C_6D_6) δ 198.1, 167.3, 141.8, 137.3, 132.3, 128.3, 128.1, 126.8, 125.2 (q, J = 294.5 Hz), 122.3, 104.9, 71.4 (q, J = 27.1 Hz), 53.0, 52.2, 39.1, 38.4, 26.9, 23.8; ^{19}F NMR (282 MHz, C_6D_6) δ −73.23 (s). Anal. Calcd for $C_{22}H_{25}F_3N_2O_3$: C, 62.55; H, 5.96; N, 6.63. Found: C, 62.43; H, 6.12; N, 6.82

General Procedure for *One-Pot* Synthesis of 1,5-Diketones 7 from 1,6-Allenynes 6. A solution of the corresponding allenyne (200 mg) in dry dioxane (4 mL) was refluxed for 4 h under argon atmosphere. After completion of [2 + 2] cycloaddition (TLC control), the reaction mixture was cooled to rt and pirrolidine (2 equiv) was added. The reaction was stirred at rt for 20 min. The resulting red solution was poured into 50 mL of 1 N HCl and extracted with EtOAc. The combined organic solution was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed with a mixture of hexanes/EtOAc = 6:1 furnishing the desired products.

*Methyl 1-methyl-5-oxo-4-(3-oxo-3-phenylpropyl)-2-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate (**7a**):* yield 148 mg, 70% (yellowish oil); R_f = 0.37; ^1H NMR (200 MHz, $CDCl_3$) δ 7.94 (d, J = 7.0 Hz, 2H, H_{arom}), 7.64−7.39 (m, 3H, H_{arom}), 6.71 (s, 1H), 3.84 (s, 3H, $COOCH_3$), 3.60 (s, 2H, CH_2), 3.17 (t, J = 7.5 Hz, 2H, CH_2), 2.76 (t, J = 7.5 Hz, 2H, CH_2), 2.57 (q, J = 0.9 Hz, 3H, NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.9, 193.7, 166.3, 140.9, 137.0, 136.8 (q, J = 2.1 Hz), 133.6, 129.0, 128.4, 124.8 (q, J = 292.1 Hz), 70.5 (q, J = 25.8 Hz), 59.2, 53.7, 40.2 (q, J = 2.1 Hz), 37.1, 24.5; ^{19}F NMR (188 MHz, $CDCl_3$) δ −67.65 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{18}F_3NO_4$: C, 58.54; H, 4.91; N, 3.79. Found: C, 58.41; H, 4.70; N, 3.55.

*Methyl 4-[3-(4-methoxyphenyl)-3-oxopropyl]-1-methyl-5-oxo-2-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate (**7b**):* yield 149 mg, 71% (colorless solid); mp = 86−89 °C; R_f = 0.25; ^1H NMR (200 MHz, $CDCl_3$) δ 7.94 (d, J = 8.8 Hz, 2H, H_{arom}), 6.95 (d, J = 8.8 Hz, 2H, H_{arom}), 6.71 (s, 1H, CH), 3.89 (s, 2H, $COOCH_3$), 3.86 (s, 3H, OCH_3), 3.61 (s, 2H, CH_2), 3.12 (t, J = 7.3 Hz, 2H, CH_2), 2.76 (t, J = 7.2 Hz, 2H, CH_2), 2.59 (s, 3H, NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.0, 192.3, 164.9, 162.5, 139.6, 135.3 (q, J = 2.2 Hz), 129.3, 128.7, 123.4 (q, J = 292.4 Hz), 112.7, 69.1 (q, J = 25.6 Hz), 57.8, 54.4, 52.3, 38.8, 35.4, 23.2; ^{19}F NMR (188 MHz, $CDCl_3$) δ −67.60 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{20}F_3NO_5$: C, 57.14; H, 5.05; N, 3.51. Found: C, 57.01; H, 5.18; N, 3.44.

*Methyl 4-[3-(2-methoxyphenyl)-3-oxopropyl]-1-methyl-5-oxo-2-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate (**7c**):* yield 154 mg, 73% (yellowish oil); R_f = 0.25; ^1H NMR (200 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.6, 1.6 Hz, 1H, H_{arom}), 7.45 (t, J = 7.6 Hz, 1H, H_{arom}), 7.04 - 6.91 (m, 2H, H_{arom}), 6.65 (s, 1H, CH), 3.88 (s, 3H, $COOCH_3$), 3.83 (s, 3H, OCH_3), 3.58 (s, 2H, CH_2), 3.16 (t, J = 7.1 Hz, 2H, CH_2), 2.72 (t, J = 7.1 Hz, 2H, CH_2), 2.56 (s, 3H, NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.7, 192.2, 165.0, 157.5, 139.8, 134.8 (q, J = 2.1 Hz), 132.6, 129.2, 127.0, 123.4 (q, J = 292.3 Hz), 119.6, 110.5, 69.1 (q, J = 25.7 Hz), 57.8, 54.4, 52.3, 40.5, 38.8 (q, J = 2.1 Hz), 22.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ −67.74 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{20}F_3NO_5$: C, 57.14; H, 5.05; N, 3.51. Found: C, 56.99; H, 4.82; N, 3.81.

*Methyl 1-methyl-4-[3-(4-methylphenyl)-3-oxopropyl]-5-oxo-2-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate (**7d**):* yield 147 mg, 70% (colorless solid); mp = 74−75C°C; R_f = 0.36; ^1H NMR (200 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2H, H_{arom}), 7.26 (d, J = 7.7 Hz, 2H, H_{arom}), 6.71 (s, 1H, CH), 3.86 (s, 3H, $COOCH_3$), 3.61 (s, 2H, CH_2), 3.13 (t, J = 7.4 Hz, 2H, CH_2), 2.76 (t, J = 7.3 Hz, 2H, CH_2), 2.59 (s, 3H, NCH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.6, 191.8, 164.4, 142.5, 139.1, 134.8 (q, J = 2.0 Hz), 132.6, 127.8, 126.6, 122.9 (q, J = 292.1 Hz), 68.6 (q, J = 25.7 Hz), 57.3, 51.8, 38.3, 35.1, 22.6, 20.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ −67.61 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{20}F_3NO_4$:C, 59.53; H, 5.26; N, 3.65. Found: C, 59.41; H, 5.35; N, 3.77.

*Methyl 1-methyl-4-[3-(2-methylphenyl)-3-oxopropyl]-5-oxo-2-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate (**7e**):* yield 156 mg, 74% (yellowish oil); R_f = 0.36; ^1H NMR (200 MHz, $CDCl_3$) δ 7.62 (d, J = 7.2 Hz, 1H, H_{arom}), 7.42−7.20 (m, 3H, H_{arom}), 6.71 (s, 1H, CH), 3.85 (s, 3H, $COOCH_3$), 3.59 (s, 2H, CH_2), 3.11 (t, J = 7.2 Hz, 2H, CH_2), 2.74 (t, J = 7.2 Hz, 2H, CH_2), 2.57 (q, J = 1.2 Hz, 3H, NCH_3), 2.48 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.5, 193.7, 166.4, 140.9, 138.6, 137.8, 136.7 (q, J = 2.1 Hz), 132.4, 131.9, 128.9, 126.1, 124.8 (q, J = 292.4 Hz), 70.5 (q, J = 25.6 Hz), 59.2, 53.7, 40.2 (q, J = 2.1 Hz), 39.7, 24.3, 21.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ −67.61 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{20}F_3NO_4$: C, 59.53; H, 5.26; N, 3.65. Found: C, 59.69; H, 5.33; N, 3.77.

*Methyl 1-methyl-4-[3-(4-nitrophenyl)-3-oxopropyl]-5-oxo-2-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate (**7f**):* yield 162 mg, 77% (yellowish oil); R_f = 0.24; ^1H NMR (200 MHz, $CDCl_3$) δ 8.31 (d, J = 8.8 Hz, 2H, H_{arom}), 8.09 (d, J = 8.8 Hz, 2H, H_{arom}), 6.73 (s, 1H, CH), 3.87 (s, 3H, $COOCH_3$), 3.60 (s, 2H, CH_2), 3.22 (t, J = 7.2 Hz, 2H, CH_2), 2.77 (t, J = 7.2 Hz, 2H, CH_2), 2.57 (s, 3H, NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 195.9, 192.4, 164.8, 149.4, 139.9, 139.0, 135.9 (q, J = 2.1 Hz), 128.0, 123.4 (q, J = 292.1 Hz), 122.9, 69.1 (q, J = 25.7 Hz), 57.8, 52.4, 38.8 (q, J = 2.2 Hz), 36.4, 23.0; ^{19}F NMR (188 MHz, $CDCl_3$) δ −67.60 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{17}F_3N_2O_6$: C, 52.18; H, 4.14; N, 6.76. Found: C, 52.33; H, 4.35; N, 6.56.

*Methyl 4-(3-cyclohexyl-3-oxopropyl)-1-methyl-5-oxo-2-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate (**7g**):* yield 184 mg, 87% (yellowish oil); R_f 0.33; ^1H NMR (200 MHz, $CDCl_3$) δ 6.60 (s, 1H, CH), 3.85 (s, 3H, $COOCH_3$), 3.56 (s, 2H, CH_2), 2.67−2.48 (m, 7H, $2CH_2$+ NCH_3), 2.28 (br. s, 1H, H_{Cy}), 2.70 - 2.47 (m, 5H, H_{Cy}), 1.40−1.14 (m, 5H, H_{Cy}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.2, 192.2, 165.0, 139.6, 135.1 (q, J = 2.0 Hz), 123.4 (q, J = 292.0 Hz), 69.1 (q, J = 25.4 Hz), 57.8, 52.3, 49.8, 38.8 (q, J = 1.9 Hz), 37.5, 27.3, 24.8, 24.6, 22.2; ^{19}F NMR (188 MHz, $CDCl_3$) δ −67.73 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{24}F_3NO_4$: C, 57.59; H, 6.44; N, 3.73. Found: C, 57.41; H, 6.12; N, 3.78.

*Methyl 4-(4,4-dimethyl-3-oxopentyl)-1-methyl-5-oxo-2-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate (**7h**):* yield 53 mg, 25% (yellowish oil); R_f 0.34; ^1H NMR (200 MHz, $CDCl_3$) δ 6.62 (s, 1H, CH), 3.87 (s, 3H, $COOCH_3$), 3.56 (s, 2H, CH_2), 2.79−2.48 (m, 7H, $2CH_2$+ NCH_3), 1.09 (s, 9H, $3CH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 214.2, 193.3, 166.0, 140.6, 136.3, 124.4 (q, J = 292.3 Hz), 70.1 (q, J = 26.0 Hz), 58.8, 53.3, 44.1, 39.8, 34.8, 26.2, 23.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ −67.68 (s, 3F, CF_3). Anal. Calcd for $C_{16}H_{22}F_3NO_4$: C, 55.01; H, 6.35; N, 4.01. Found: C, 54.85; H, 6.05; N, 4.23.

*[1,1-Bis(trifluoromethyl)buta-2,3-dien-1-yl]methyl(prop-2-yn-1-yl)amine (**2b**).* A mixture of *N*,*N*-dipropargyl-*N*-methylamine (2.4 g, 22.4 mmol), liquefied 1,1,1,3,3,3-hexafluoromethyl-2-diazopropane (4 g, 22.4 mmol), and copper trifluoroacetylacetonate (0.4 g, 1,12 mmol, 5 mol %) in dry benzene (30 mL) was placed into a preliminarily cooled (0 °C) steel bomb and shuttled at 100 °C for 1 h. Then the bomb was cooled to rt. The reaction mixture was filtered through a short pad of silica gel to remove copper residue. The solvent was

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removed under atmospheric pressure, and the crude product was recondensed under reduced pressure (1 Torr) into cold receiver (−78 °C) to give 2.9 g of colorless liquid: yield 50%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.24 (t, J = 6.9 Hz, 1H, CH_{allene}), 5.14 (d, J = 6.8 Hz, 2H, $CH_{2allene}$), 3.71 (s, 2H, NCH_2), 2.77 (s, 3H, NCH_3), 2.26 (t, J = 2.4 Hz, 1H, CH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.7, 124.6 (q, J = 293.8 Hz), 85.5, 80.08, 80.07, 71.9, 71.0 (sept, J = 26 Hz), 42.1, 36.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.33 (s). Anal. Calcd for $C_{10}H_9F_6N$: C, 46.70; H, 3.53; N, 5.45. Found: C, 46.81; H, 3.43; N, 5.59.

*Diethyl [Methyl(prop-2-yn-1-yl)amino](propa-1,2-dien-1-yl)-malonate (**2c**).* A mixture of *N*,*N*-dipropargyl-*N*-methylamine 1.6 g (15 mmol), diethyl diazomalonate 2.8 g (15 mmol), and copper trifluoroacetylacetonate 0.55 g (0.15 mmol, 10 mol %) in anhydrous toluene (30 mL) was refluxed for 1.5 h. After completion of the reaction (TLC control), the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (hexanes/EtOAc−4:1) to give 2.8 g of yellowish oil: yield 70%; R_f 0.44; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.72 (t, J = 6.8 Hz, 1H, CH_{allene}), 4.93 (d, J = 6.8 Hz, 2H, $CH_{2allene}$), 4.29−4.21 (m, 4H, $2OCH_2$), 3.58 (s, 2H, NCH_2), 2.58 (s, 3H, NCH_3), 2.21 (t, J = 2.4 Hz, 1H, CH), 1.27 (t, J = 7.4 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.7, 167.7, 89.1, 80.0, 78.6, 74.5, 72.5, 61.8, 41.9, 37.3, 14.1. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.28; H, 7.38; N, 5.53.

*4-[[1,1-Bis(trifluoromethyl)buta-2,3-dien-1-yl](methyl)amino]-1-phenylbut-2-yn-1-one (**5i**):* yield 228 mg, 78% (yellowish oil); R_f 0.5 (hexanes/EtOAc = 15:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 7.2 Hz, 2H, H_{arom}), 7.68 (t, J = 7.2 Hz, 1H, H_{arom}), 7.55 (t, J = 7.2 Hz, 2H, H_{arom}), 5.36−5.28 (m, 1H, CH_{allene}), 5.21 (d, J = 6.4 Hz, 2H, H_{allene}), 4.09 (s, 2H, NCH_2), 2.90 (s, 1H, NCH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.9, 177.7, 136.6, 134.3, 129.6, 128.7, 123.8 (q, J = 291.0 Hz), 90.8, 85.2, 82.1, 80.4, 70.9 (sept, J = 26 Hz), 42.7, 37.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.46 (s, 6F, $2CF_3$). Anal. Calcd for $C_{17}H_{13}F_6NO$: C, 56.52; H, 3.63; N, 3.88. Found: C, 56.70; H, 3.55; N, 3.71.

*4-[[1,1-Bis(trifluoromethyl)buta-2,3-dien-1-yl](methyl)amino]-1-(2-methoxyphenyl)but-2-yn-1-one (**5j**):* yield 190 mg, 60% (yellowish oil); R_f 0.45 (hexanes/EtOAc = 15:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 7.8, 1.8 Hz, 1H, H_{arom}), 7.59 (ddd, J = 8.4, 7.8, 1.8 Hz, 1H, H_{arom}), 7.14−7.02 (m, 2H, H_{arom}), 5.38−5.24 (m, 1H, CH_{allene}), 5.23−5.06 (m, 2H, $CH_{2allene}$), 4.03 (s, J = 3.8 Hz, 2H, NCH_2), 3.97 (s, 3H, OCH_3), 2.86 (s, 3H, NCH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.8, 176.5, 159.9, 135.2, 132.8, 126.3, 123.8 (q, J = 291.2 Hz), 120.3, 112.1, 89.4, 85.3, 84.2, 80.4, 70.9 (sept, J = 26 Hz), 55.8, 42.7, 37.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.39 (s, 6F, CF_3). Anal. Calcd for $C_{18}H_{15}F_6NO_2$: C, 55.25; H, 3.86; N, 3.58. Found: C, 55.14; H, 3.99; N, 3.71.

*Diethyl [methyl(4-oxo-4-phenylbut-2-yn-1-yl)amino](propa-1,2-dien-1-yl)malonate (**5k**):* yield 209 mg, 70% (yellowish oil); R_f 0.40 (hexanes/EtOAc = 4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16−8.12 (m, 2H, H_{arom}), 7.61 (t, J = 7.4 Hz, 1H, H_{arom}), 7.48 (t, J = 7.4 Hz, 2H, H_{arom}), 5.78 (t, J = 6.8 Hz, 1H, CH_{allene}), 4.98 (d, J = 6.8 Hz, 2H, $CH_{2allene}$), 4.36−4.22 (m, 4H, $2OCH_2$), 3.96 (s, 2H, NCH_2), 2.68 (s, 3H, NCH_3), 1.29 (t, J = 7.1 Hz, 6H, $2CH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.8, 177.7, 167.7, 136.6, 134.1, 129.6, 128.6, 91.4, 89.0, 82.9, 78.8, 74.4, 62.0, 42.4, 37.7, 14.1 (d, J = 8.1 Hz). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.01; H, 6.53; N, 3.97.

*Diethyl [[4-(2-methoxyphenyl)-4-oxobut-2-yn-1-yl](methyl)-amino](propa-1,2-dien-1-yl)malonate (**5l**):* yield 233 mg, 72% (yellowish oil); R_f 0.40 (hexanes/EtOAc = 4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (dd, J = 7.6, 1.6 Hz, 1H, H_{arom}), 7.54−7.48 (m, 1H, H_{arom}), 7.04−6.96 (m, 2H, H_{arom}), 5.75 (t, J = 6.8 Hz, 1H, CH_{allene}), 4.95 (d, J = 6.8 Hz, 2H, $CH_{2allene}$), 4.35−4.18 (m, 4H, $2OCH_2$), 3.92 (s, J = 3.9 Hz, 3H, OCH_3), 3.90 (s, 2H, NCH_2), 2.65 (s, 3H, NCH_3), 1.28 (t, J = 7.1 Hz, 6H, $2CH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.2, 174.0, 165.1, 157.2, 132.5, 130.5, 123.8, 117.7, 109.5, 87.4, 86.6, 82.4, 76.2, 71.9, 59.4, 53.4, 39.9, 35.1, 11.6. Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.47; H, 6.05; N, 3.19.

*1-Methyl-4-(3-oxo-3-phenylpropyl)-6,6-bis(trifluoromethyl)-1,6-dihydropyridin-3(2H)-one (**7i**):* yield 147 mg, 70% (yellowish oil); R_f 0.30 (hexanes/EtOAc−5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.3 Hz, 2H, H_{arom}), 7.60 (t, J = 7.3 Hz, 1H, H_{arom}), 7.49 (t, J = 7.3 Hz, 2H, H_{arom}), 6.73 (s, 1H, CH), 3.60 (s, 2H, NCH_2), 3.22 (t, J = 7.2 Hz, 2H, CH_2), 2.84 (t, J = 7.2 Hz, 2H, CH_2), 2.75 (s, 3H, NCH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.2, 192.4, 142.7, 136.6, 133.2, 133.1, 128.6, 128.0, 123.6 (q, J = 294.8 Hz), 67.2 (sept, J = 26.2 Hz), 59.1, 39.6, 36.6, 24.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.05 (s, 6F, $2CF_3$). Anal. Calcd for $C_{17}H_{15}F_6NO_2$: C, 53.83; H, 3.99; N, 3.69. Found: C, 53.58; H, 4.21; N, 3.81.

*4-[3-(2-Methoxyphenyl)-3-oxopropyl]-1-methyl-6,6-bis-(trifluoromethyl)-1,6 dihydropyridin-3(2H)-one (**7j**):* yield 160 mg, 76% (yellowish oil); R_f 0.30 (hexanes/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.7, 1.8 Hz, 1H, H_{arom}), 7.51 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H, H_{arom}), 7.10−6.96 (m, 2H, H_{arom}), 6.69 (s, 1H, CH), 3.94 (s, 3H, OCH_3), 3.60 (s, 2H, NCH_2), 3.24 (t, J = 7.1 Hz, 2H, CH_2), 2.82 (t, J = 7.0 Hz, 2H, CH_2), 2.76 (s, 3H, NCH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.5, 192.4, 158.5, 143.0, 133.7, 132.7, 130.3, 127.9, 123.7 (q, J = 294.5 Hz), 120.7, 111.5, 67.1 (sept, J = 26.2 Hz), 59.1, 55.4, 41.4, 39.7, 23.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.06 (s, 6F, $2CF_3$). Anal. Calcd for $C_{18}H_{17}F_6NO_3$: C, 52.82; H, 4.19; N, 3.42. Found: C, 52.89; H, 4.33; N, 3.52.

*Diethyl 1-methyl-5-oxo-4-(3-oxo-3-phenylpropyl)-5,6-dihydro-pyridine-2,2(1H)-dicarboxylate (**7k**):* yield 137 mg, 65% (yellowish oil); R_f 0.35 (hexanes/EtOAc−3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.2 Hz, 2H, H_{arom}), 7.60 (t, J = 7.3 Hz, 1H, H_{arom}), 7.49 (t, J = 7.5 Hz, 2H, H_{arom}), 6.92 (s, 1H, CH), 4.32 (q, J = 7.1 Hz, 4H, $2OCH_2$), 3.56 (s, 2H, NCH_2), 3.20 (t, J = 7.3 Hz, 2H, CH_2), 2.77 (t, J = 7.3 Hz, 2H, CH_2), 2.62 (s, 3H, NCH_3), 1.34 (t, J = 7.1 Hz, 6H, $2CH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.7, 194.3, 166.6, 141.1, 138.0, 136.7, 133.1, 128.6, 128.0, 72.7, 62.4, 59.1, 40.0, 37.1, 24.0, 14.1. Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.00; H, 6.61; N, 3.73.

*Diethyl 4-[3-(2-methoxyphenyl)-3-oxopropyl]-1-methyl-5-oxo-5,6-dihydropyridine-2,2(1H)-dicarboxylate (**7l**):* yield 122 mg, 58% (yellowish oil); R_f 0.55 (hexanes/EtOAc−1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 7.6 Hz, 1H, H_{arom}), 7.48 (t, J = 7.8 Hz, 1H, H_{arom}), 7.06−6.95 (m, 2H, H_{arom}), 6.86 (s, 1H, CH), 4.31 (q, J = 7.1 Hz, 4H, $2OCH_2$), 3.92 (s, 3H, OCH_3), 3.55 (s, 2H, NCH_2), 3.19 (t, J = 7.4 Hz, 2H, CH_2), 2.72 (t, J = 7.4 Hz, 2H, $2CH_2$), 2.61 (s, 3H, NCH_3), 1.33 (t, J = 7.1 Hz, 6H, $2CH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.0, 194.2, 166.7, 158.6, 140.5, 138.4, 133.5, 130.3, 128.0, 120.6, 111.5, 72.7, 62.3, 59.1, 55.5, 41.9, 40.0, 23.8, 14.1. Anal. Calcd for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.11; H, 6.85; N, 3.22.

General Procedure for Synthesis of 5,6,7,8-Tetrahydro-1,7-naphthyridines 10. A solution of the corresponding 1,5-diketone (0.5 mmol) in glacial acetic acid (4 mL) was poured into a round-bottomed flask, equipped with reflux condenser, magnetic stirrer, and tube for argon bubling. Then 0.31 g of NH_4OAc (4 mmol) was added, and reaction mixture was heated at 100 °C in constant argon flow for 1 h. The resulting mixture was poured into 50 mL of cold water and extracted with EtOAc. The combined organic fractions were washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 6/1) to give pure product.

*Methyl 7-methyl-2-phenyl-6-(trifluoromethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-6-carboxylate (**10a**):* yield 131 mg, 75% (white solid); mp = 83−85 °C; R_f 0.50; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (dd, J = 7.8, 1.4 Hz, 2H, H_{arom}), 7.63−7.33 (m, 5H, H_{arom}), 4.21 (s, 2H, CH_2), 3.80 (s, 3H, $COOCH_3$), 3.53 (d, J = 16.3 Hz, 1H, CH_2), 3.28 (d, J = 16.3 Hz, 1H, CH_2), 2.78 (q, J = 0.9 Hz, 3H, NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.6, 156.1, 153.6, 139.5, 136.9, 129.3, 129.1, 127.3, 125.3 (q, J = 288.5 Hz), 124.4, 119.2, 68.9 (q, J = 25.6 Hz), 57.1, 53.3, 40.4 (q, J = 2.0 Hz), 32.5 (q, J = 2.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ −69.78 (s, 3F, CF_3). Anal. Calcd for

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$C_{18}H_{17}F_3N_2O_2$: C, 61.71; H, 4.89; N, 8.00. Found: C, 61.55; H, 4.77; N, 8.25.

*Methyl 2-(4-methoxyphenyl)-7-methyl-6-(trifluoromethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-6-carboxylate (**10b**):* yield 162 mg, 85% (white solid); mp = 94−95 °C; R_f 0.45; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93 (d, J = 8.7 Hz, 2H, H_{arom}), 7.56−7.42 (m, 2H, H_{arom}), 7.00 (d, J = 8.7 Hz, 2H, H_{arom}), 4.29−4.07 (m, 2H, CH_2), 3.88 (s, 3H, $COOCH_3$), 3.80 (s, 3H, OCH_3), 3.51 (d, J = 16.2 Hz, 1H, CH_2), 3.26 (d, J = 16.2 Hz, 1H, CH_2), 2.77 (s, 3H, NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.6, 160.8, 155.8, 153.4, 136.8, 132.2, 128.5, 125.3 (q, J = 288.5 Hz), 123.6, 118.5, 114.5, 68.9 (q, J = 25.3 Hz), 57.1, 55.7, 53.3, 40.3 (q, J = 1.9 Hz), 32.5 (q, J = 2.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ −69.79 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{19}F_3N_2O_3$: C, 60.00; H, 5.03; N, 7.36. Found: C, 60.15; H, 4.74; N, 7.14.

*Methyl 2-(2-methoxyphenyl)-7-methyl-6-(trifluoromethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-6-carboxylate (**10c**):* yield 169 mg, 89% (colorless oil); R_f 0.45; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.5, 1.6 Hz, 1H, H_{arom}), 7.67 (d, J = 8.2 Hz, 1H, H_{arom}), 7.47 (d, J = 8.2 Hz, 1H, H_{arom}), 7.38 (td, J = 8.2, 1.7 Hz, 1H, H_{arom}), 7.08 (t, J = 8.2 Hz, 1H, H_{arom}), 7.00 (d, J = 8.3 Hz, 1H, H_{arom}), 4.34−4.09 (m, 2H, CH_2), 3.86 (s, 3H, $COOCH_3$), 3.81 (s, 3H, OCH_3), 3.53 (d, J = 16.3 Hz, 1H, CH_2), 3.28 (d, J = 16.3 Hz, 1H, CH_2), 2.76 (q, J = 1.0 Hz, 3H, NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.2, 155.9, 153.2, 151.7, 134.3, 130.1, 128.9, 127.7, 123.9 (q, J = 288.4 Hz), 122.4, 122.3, 120.1, 110.3, 67.4 (q, J = 25.4 Hz), 55.6, 54.5, 51.8, 38.9 (q, J = 2.0 Hz), 31.0 (q, J = 2.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ −69.79 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{19}F_3N_2O_3$: C, 60.00; H, 5.03; N, 7.36. Found: C, 60.19; H, 5.21; N, 7.15.

*Methyl 7-methyl-2-(4-methylphenyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-6-carboxylate (**10d**):* yield 164 mg, 90% (white solid); mp = 83−85 °C; R_f 0.50; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 2H, H_{arom}), 7.54 (d, J = 8.1 Hz, 1H, H_{arom}), 7.48 (d, J = 8.1 Hz, 1H, H_{arom}), 7.28 (d, J = 8.1 Hz, 2H, H_{arom}), 4.39−4.02 (m, 2H, CH_2), 3.80 (s, 3H, $COOCH_3$), 3.52 (d, J = 16.3 Hz, 1H, CH_2), 3.27 (d, J = 16.3 Hz, 1H, CH_2), 2.77 (s, 3H, NCH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.6, 156.1, 153.4, 139.3, 136.8, 136.7, 129.9, 127.1, 125.3 (q, J = 288.6 Hz), 124.0, 119.0, 68.9 (q, J = 25.4 Hz), 57.1, 53.3, 40.3 (q, J = 2.0 Hz), 32.5 (q, J = 2.1 Hz), 21.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ −69.79 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{19}F_3N_2O_2$: C, 62.63; H, 5.26; N, 7.69. Found: C, 62.29; H, 5.33; N, 7.55.

*Methyl 7-methyl-2-(2-methylphenyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-6-carboxylate (**10e**):* yield 153 mg, 84% (colorless oil); R_f 0.50; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50 (d, J = 7.9 Hz, 1H, H_{arom}), 7.45−7.18 (m, 5H, H_{arom}), 4.31−4.07 (m, 2H, CH_2), 3.81 (s, 3H, $COOCH_3$), 3.55 (d, J = 16.3 Hz, 1H, CH_2), 3.30 (d, J = 16.3 Hz, 1H, CH_2), 2.77 (s, 3H, NCH_3), 2.36 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.6, 158.5, 153.1, 140.4, 136.3, 136.2, 131.2, 129.9, 128.7, 126.3, 125.3 (q, J = 288.6 Hz), 123.9, 122.7, 68.8 (q, J = 25.4 Hz), 57.0, 53.3, 40.4 (q, J = 1.7 Hz), 32.6 (q, J = 2.2 Hz), 20.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ −69.72 (s, 3F, CF_3). Anal. Calcd for $C_{19}H_{19}F_3N_2O_2$: C, 62.63; H, 5.26; N, 7.69. Found: C, 62.77; H, 5.01; N, 7.32.

*Methyl 7-methyl-2-(4-nitrophenyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-6-carboxylate (**10f**):* yield 170 mg, 86% (yellowish solid); R_f 0.45; mp = 117−119 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.33 (d, J = 8.8 Hz, 2H, H_{arom}), 8.16 (d, J = 8.8 Hz, 2H, H_{arom}), 7.73−7.52 (m, 2H, H_{arom}), 4.34−4.04 (m, 2H, CH_2), 3.82 (s, 3H, $COOCH_3$), 3.56 (d, J = 16.4 Hz, 1H, CH_2), 3.31 (d, J = 16.5 Hz, 1H, CH_2), 2.78 (s, 3H, NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.5, 154.4, 153.3, 148.5, 145.3, 137.2, 128.0, 126.4, 125.2 (q, J = 288.7 Hz), 124.4, 119.8, 68.8 (q, J = 25.3 Hz), 56.9, 53.4, 40.4 (q, J = 2.1 Hz), 32.6 (q, J = 2.3 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ −69.72 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{16}F_3N_3O_4$: C, 54.69; H, 4.08; N, 10.63. Found: C, 54.79; H, 4.15; N, 10.44.

*Methyl 2-cyclohexyl-7-methyl-6-(trifluoromethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-6-carboxylate (**10g**):* yield 157 mg, 88% (colorless oil); R_f 0.55; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32 (d, J = 7.9 Hz, 1H, H_{arom}), 6.95 (d, J = 7.9 Hz, 1H, H_{arom}), 4.18−3.94 (m, 2H, CH_2), 3.74 (s, 3H, $COOCH_3$), 3.40 (d, J = 16.1 Hz, 1H, CH_2), 3.15 (d, J = 16.2 Hz, 1H, CH_2), 2.80−2.46 (m, 4H, NCH_3+CH), 1.99−1.65 (m, 5H, CH_{2cy}), 1.58−1.17 (m, 5H, CH_{2Cy}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.6, 165.1, 152.5, 136.4, 125.3 (q, J = 288.4 Hz), 122.9, 119.2, 68.8 (q, J = 25.3 Hz), 57.0, 53.1, 46.7, 40.2 (q, J = 2.0 Hz), 33.4 (d, J = 7.4 Hz), 32.4 (q, J = 2.2 Hz), 26.9, 26.4; ^{19}F NMR (188 MHz, $CDCl_3$) δ −69.90 (s, 3F, CF_3). Anal. Calcd for $C_{18}H_{23}F_3N_2O_2$: C, 60.66; H, 6.50; N, 7.86. Found: C, 60.88; H, 6.62; N, 7.99.

*Methyl 2-tert-butyl-7-methyl-6-(trifluoromethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-6-carboxylate (**10h**):* yield 153 mg, 93% (colorless oil); R_f 0.55; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 1H, H_{arom}), 7.15 (d, J = 8.1 Hz, 1H, H_{arom}), 4.20−3.98 (m, 2H, CH_2), 3.79 (s, 3H, $COOCH_3$), 3.45 (d, J = 16.2 Hz, 1H, CH_2), 3.19 (d, J = 16.2 Hz, 1H, CH_2), 2.74 (s, 3H, NCH_3), 1.33 (s, 9H, $3CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.3, 166.4, 150.8, 134.6, 123.9 (q, J = 288.6 Hz), 120.8, 116.2, 67.5 (q, J = 25.5 Hz), 55.7, 51.8, 38.9 (q, J = 2.0 Hz), 36.1, 30.9 (q, J = 2.2 Hz), 29.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ −69.89 (s, 3F, CF_3). Anal. Calcd for $C_{16}H_{21}F_3N_2O_2$: C, 58.17; H, 6.41; N, 8.48. Found: C, 58.32; H, 6.35; N, 8.66.

*7-Methyl-2-phenyl-6,6-bis(trifluoromethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine (**10i**):* yield 137 mg, 76% (colorless soid); mp = 115−117 °C; R_f 0.50; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, J = 7.1 Hz, 2H, H_{arom}), 7.61 (d, J = 8.0 Hz, 1H, H_{arom}), 7.55 (d, J = 8.0 Hz, 1H, H_{arom}), 7.49 (t, J = 7.5 Hz, 2H, H_{arom}), 7.43 (t, J = 7.3 Hz, 1H, H_{arom}), 4.17 (s, 2H, NCH_2), 3.26 (s, 1H, CH_2), 2.89 (s, 3H, NCH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.5, 154.3, 139.1, 135.7, 129.0, 128.8, 126.9, 124.9 (q, J = 294.4 Hz), 123.7, 119.2, 66.1 (sept, J = 25.4 Hz), 56.4, 39.6, 30.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.23 (s, 6F, $2CF_3$). Anal. Calcd for $C_{17}H_{14}F_6N_2$: C, 56.67; H, 3.92; N, 7.78. Found: C, 56.82; H, 3.81; N, 7.65.

*2-(2-Methoxyphenyl)-7-methyl-6,6-bis(trifluoromethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine (**10j**):* yield 100 mg, 51% (colorless oil); R_f 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.6, 1.8 Hz, 1H, H_{arom}), 7.76 (d, J = 8.0 Hz, 1H, H_{arom}), 7.54 (d, J = 8.0 Hz, 1H, H_{arom}), 7.48−7.39 (m, 1H, H_{arom}), 7.19−7.11 (m, 1H, H_{arom}), 7.06 (d, J = 8.3 Hz, 1H, H_{arom}), 4.21 (s, 2H, NCH_2), 3.91 (s, 3H, OCH_3), 3.30 (s, 2H, CH_2), 2.92 (s, 3H, NCH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.0, 154.0, 153.9, 134.7, 131.1, 130.0, 128.6, 124.9 (q, J = 294.3 Hz), 123.8, 123.2, 121.1, 111.3, 66.1 (sept, J = 25.4 Hz), 56.4, 55.5, 39.6, 30.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.20 (s, 6F, $2CF_3$). Anal. Calcd for $C_{18}H_{16}F_6N_2O$: C, 55.39; H, 4.13; N, 7.18. Found: C, 55.28; H, 4.28; N, 7.01.

*Diethyl 7-methyl-2-phenyl-7,8-dihydro-1,7-naphthyridine-6,6(5H)-dicarboxylate (**10k**):* yield 129 mg, 70% (colorless oil); R_f 0.50 (hexanes/EtOAc 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, J = 7.1 Hz, 2H, H_{arom}), 7.52 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H, H_{arom}), 7.44 (t, J = 7.5 Hz, 2H, H_{arom}), 7.38 (t, J = 7.3 Hz, 1H, H_{arom}), 4.26 (q, J = 7.1, 4H, $2CH_2$), 4.13 (s, 2H, NCH_2), 3.44 (s, 2H, CH_2), 2.76 (s, 3H, NCH_3), 1.27 (t, J = 7.1 Hz, 6H, $2CH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.2, 155.4, 152.8, 139.3, 136.6, 128.7, 128.7, 126.9, 125.6, 118.7, 71.1, 61.8, 56.3, 40.5, 35.2, 14.1. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.22; H, 6.88; N, 7.88.

*Diethyl 2-(2-methoxyphenyl)-7-methyl-7,8-dihydro-1,7-naphthyridine-6,6(5H)-dicarboxylate (**10l**):* yield 135 mg, 68% (colorless oil); R_f 0.50 (hexanes/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.6, 1.8 Hz, 1H, H_{arom}), 7.66 (d, J = 8.0 Hz, 1H, H_{arom}), 7.47 (d, J = 8.1 Hz, 1H, H_{arom}), 7.38 (ddd, J = 8.1, 7.5, 1.8 Hz, 1H, H_{arom}), 7.09 (td, J = 7.5, 1.0 Hz, 1H, H_{arom}), 7.02 (t, J = 6.2 Hz, 1H, H_{arom}), 4.31 (q, J = 7.1 Hz, 4H, $2OCH_2$), 4.16 (s, 2H, NCH_2), 3.87 (s, 3H, OCH_3), 3.48 (s, 2H, CH_2), 2.78 (s, 3H, NCH_3), 1.32 (t, J = 7.1 Hz, 6H, $2CH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.3, 156.9, 153.9, 152.4, 135.5, 131.1, 129.8, 128.9, 125.0, 123.2, 121.1, 111.4, 71.2, 61.8, 56.2, 55.6, 40.5, 35.0, 14.1. Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.44; H, 6.81; N, 7.15.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR spectra for all new compounds. 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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