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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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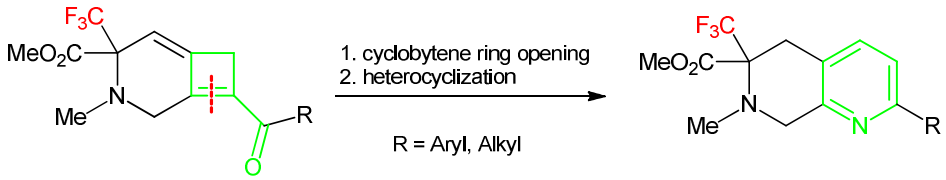
Abstract:



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 depressions,[3] Alzheimer disease,[4] multiple sclerosis,[5] and various skin diseases.[6]

Several synthetic strategies have been developed to access 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 epoxy-tetrahydronaphthyridine 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.

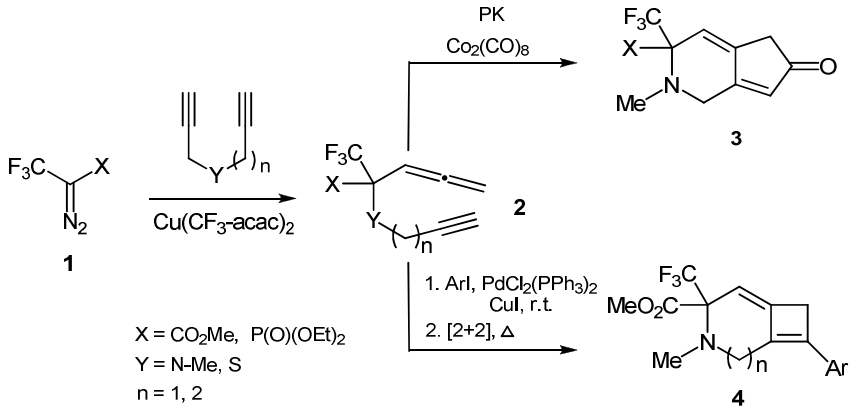
On the other hand, it is well established that the introduction of trifluoromethyl (CF_3) groups into specific positions of organic molecules can substantially alter their chemical and metabolic stability, lipophilicity, and binding selectivity due to the strongly electron withdrawing nature and large 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

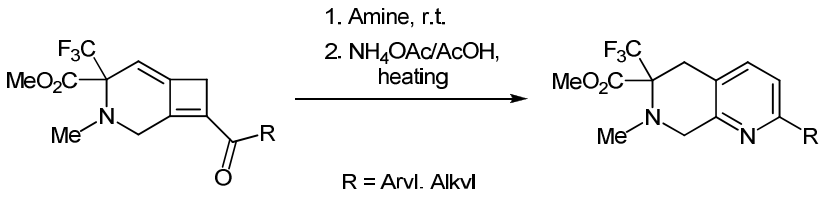
been demonstrated by the intramolecular carbocyclizations such as cobalt-mediated Pauson-Khand reaction and thermal [2+2]-cycloaddition to access the functionally substituted heterocyclic compounds fused with cyclopentenone **3**[15] and cyclobutene **4**[16] rings, respectively (Scheme 1).

Scheme 1. Synthesis and carbocyclizations of CF_3-substituted 1,6-allenynes



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).

Scheme 2. Transformation of bicycloocta-1,6-dienes into tetrahydro-1,7-naphthyridines

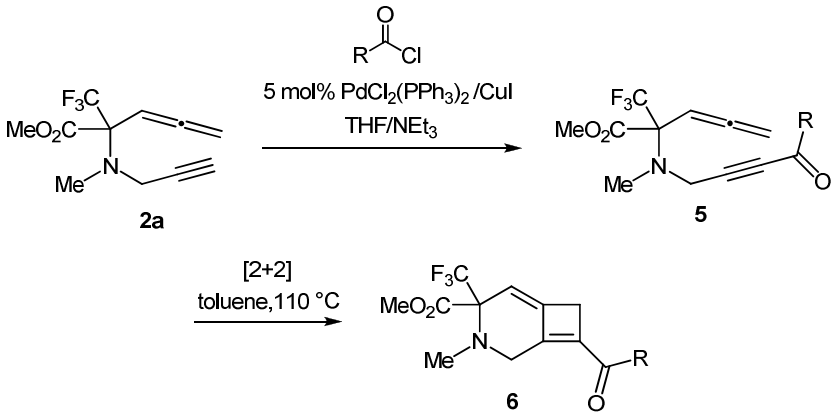


Despite the fact that the compounds containing bicyclo[4.2.0]octa-1,6-diene framework are well documented in the literature[18], to the best of our knowledge, the ring opening of cyclobutene unit was not previously described.

The synthesis of starting bicyclodienes **6** comprising the keto-function on double bond of cyclobutene ring has been accomplished using the same methodology as for their arylated analogues **4**[16] (Scheme 1). First, allenynes **5 a-h** were prepared by means of Pd-catalyzed cross-

coupling of terminal allenyne **2a** with different aromatic and aliphatic acylchlorides. The reactions were performed in THF at room temperature at the presence of 5 mol% of $PdCl_2(PPh_3)_2$/CuI and 1.5-fold excess of NEt_3 to furnish the corresponding allenynes **5 a-h** in good isolated yields. Then we found that intramolecular [2+2]-cycloaddition of **5** smoothly proceeds in toluene at 110 ^oC for 1-2 hours 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).

Table 1. Synthesis of acylated bicyclo[4.2.0]octa-1,6-dienes

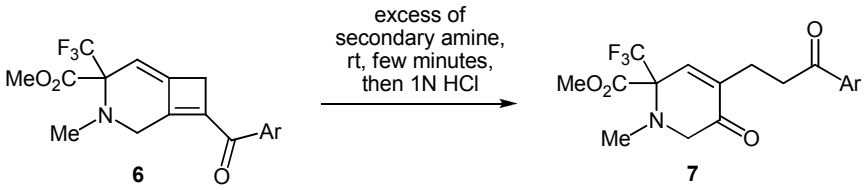


Entry	R	Sonogashira step, Yield, %	[2+2]-Cycloaddition, Yield, %
1	C_6H_5	**5a** - 75	**6a** - 75
2	4-MeO-C_6H_4	**5b** - 78	**6b** - 89
3	2-MeO-C_6H_4	**5c** - 78	**6c** - 91
4	4-Me-C_6H_4	**5d** - 83	**6d** - 91
5	2-Me-C_6H_4	**5e** - 73	**6e** - 88
6	4-NO_2-C_6H_4	**5f** - 64	**6f** - 82
7	Cy	**5g** - 68	**6g** - 78
8	*t*-Bu	**5h** - 57	**6h** – 85

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 double bond of cyclobutene unit, in contrast to their aryl analogues **4**, readily undergo four member ring opening at the presence of piperidine or pyrrolidine to afford the corresponding cyclic 1,5-diketones **7** (Scheme 3).

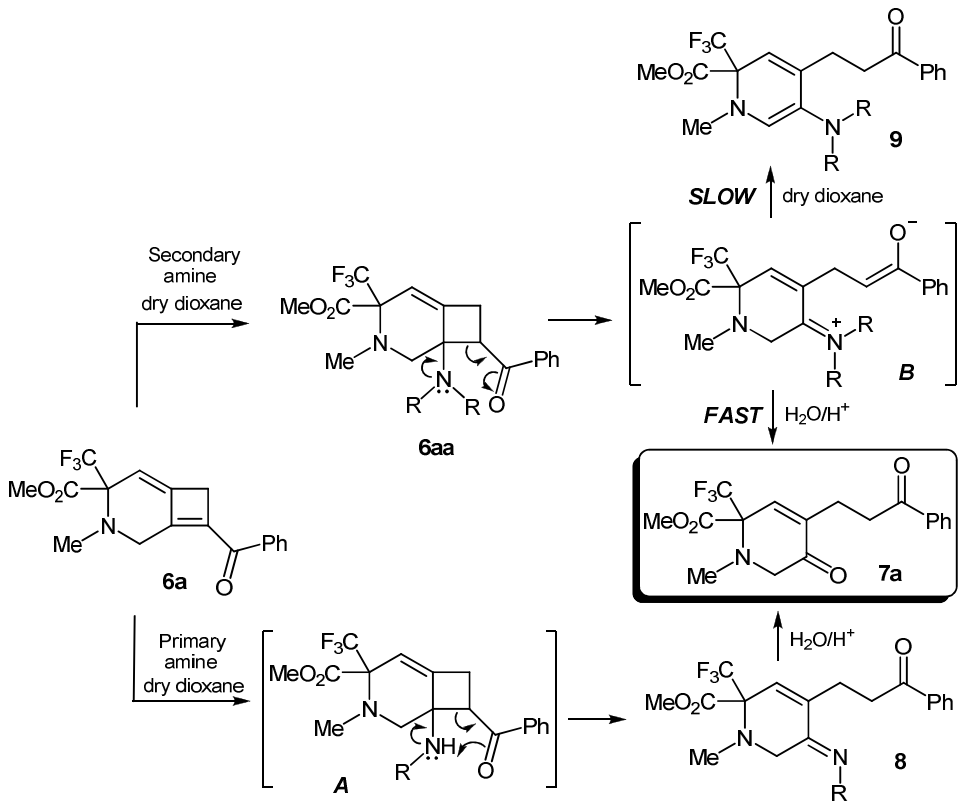
Scheme 3. Cyclobutene ring opening of bicyclo[4.2.0]octa-1,6-dienes



In order to investigate this interesting transformation in details, a number of primary and secondary amines, such as diethyl- and diisopropyl amines, benzyl amine, 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 twofold 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 1N HCl, needed for the removing of the remaining amine, affords **7a** in 68 % yield.

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

Scheme 4. Proposed mechanism of cyclobutene ring opening

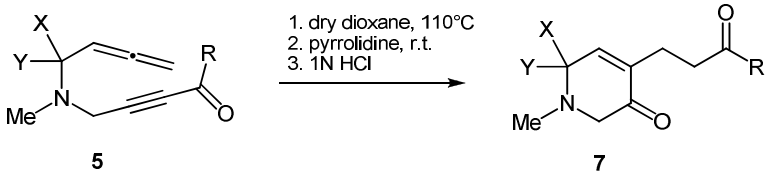


We have succeeded to isolate and characterize the adduct **6aa** (NR_2 = pyrrolidinyl) formed as a mixture of diastereomers in a ratio of 1:2. In the case of primary amines the similar adduct **A** has proved to be unstable; the reaction rapidly leads to the formation of imine **8**. This fact implicitly 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 CH_2N-group in zwitterionic intermediate **B** under exposure of reaction mixture in dry dioxane for 48 hours. 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 Info). 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 ^{o}C until the full conversion of starting material (control by TLC). The reaction usually has gone to completion for 4 hours. Then, after cooling till the room temperature, the resulting solution has been treated with twofold 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-MeO-C_6H_4	**7b**	71
3	CF_3	CO_2Me	2-MeO-C_6H_4	**7c**	73
4	CF_3	CO_2Me	4-Me-C_6H_4	**7d**	70
5	CF_3	CO_2Me	2-Me-C_6H_4	**7e**	74
6	CF_3	CO_2Me	4-NO_2-C_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-MeO-C_6H_4	**7j**	76
11	CO_2Et	CO_2Et	C_6H_5	**7k**	65
12	CO_2Et	CO_2Et	2-MeO-C_6H_4	**7l**	58

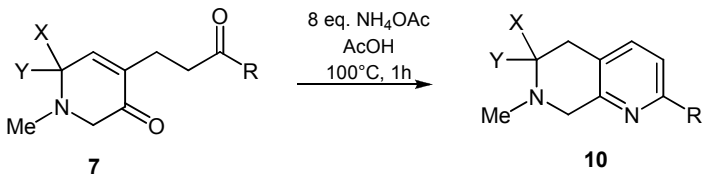
[a] ring opening step was performed under heating at 50°C for 2 hours; there was no conversion of [2+2]-cycloadduct at rt.

To extend a scope of the reaction, terminal 1,6-allenynes **2 b,c** containing two trifluoromethyl- (X = Y = CF_3) and two ethoxycarbonyl - (X = Y = CO_2Et) groups have been specially synthesized from $(CF_3)_2C{=}N_2$ or $(MeO_2C)_2C{=}N_2$ by analogy with **2a**[15] (see Exp. Section). Then, **2b,c** were transformed into **5 i-l** using the same protocol as for 5 **a-h** (Table 1) and directly involved into *one pot* process affording the corresponding diketones **7 i-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**. Low yield of the corresponding diketone **7h** (entry 8) can be addressed to steric effect of 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 **10 a-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-MeO-C_6H_4	**10b**	85
3	CF_3	CO_2Me	2-MeO-C_6H_4	**10c**	89
4	CF_3	CO_2Me	4-Me-C_6H_4	**10d**	90
5	CF_3	CO_2Me	2-Me-C_6H_4	**10e**	84
6	CF_3	CO_2Me	4-NO_2-C_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-MeO-C_6H_4	**10j**	51
11	CO_2Et	CO_2Et	C_6H_5	**10k**	70
12	CO_2Et	CO_2Et	2-MeO-C_6H_4	**10l**	68

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

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 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 Merck 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 Merck 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 MHz, 300 MHz, 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** (0.81mmol) in degassed THF (3 ml) was placed in 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 an argon flow. The resulting mixture was warmed up 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 hours 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-(trifluoro-methyl)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-(trifluoro-methyl)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-(trifluoro-methyl)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-(trifluoro-methyl)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* = 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 dried Schlenk tube. The reaction mixture was heated at 110℃ for 2 hours under argon. Then a resulting solution was cooled to rt, a 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; ^1H 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; ^1H 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, 0.12mmol) was added to solution of **6a** (200 mg, 0.6 mmol) in dry dioxane (4 ml). At that, a color of the reaction mixture was changed from light yellow to red, and the resulting solution was stirred for 20 min (TLC control). Then, the reaction mixture was poured into 50 ml of 1N HCl (water solution), extracted with EtOAc. Combined organic fractions were washed with water, 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-(trifluoro-methyl)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 hours. 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 treating with a mixture of 3N HCl (1.5 ml) / dioxane (0.5 ml) at ambient temperature for 1 hour. The resulting mixture was poured into 20 ml of cold water, extracted twice with EtOAc. Combined organic solution was washed with water, 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 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 rt. The resulting mixture was stirred for 20 min, 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. ^{1}H 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-diketons 7 from 1,6-allenynes 6. A solution of the corresponding allenyne (200 mg) in dry dioxane (4 ml) was refluxed for 4 hours 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 1N HCl, extracted with EtOAc. Combined organic solution was washed with water, dried over anhydrous $MgSO_4$. A solvent was removed under reduced pressure, and the residue was chromatographed with a mixture of hexanes:EtOAc = 6:1 furnishing desired products.

Methyl 1-methyl-5-oxo-4-(3-oxo-3-phenylpropyl)-2-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate, **(7a).** Yield: 148mg, 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). M.p. = 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). M.p. = 74-75C°C; R_f = 0.36; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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), copper trifluoroacetylacetonate (0.4 g, 1,12 mmol, 5 mol %) in dry benzene (30 ml) was placed into preliminarily cooled (0 °C) steel bomb and shuttled at 100 °C for 1 hour. 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 removed under atmospheric pressure and the crude product was re-condensed 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 (15mmol), diethyl diazomalonate 2.8 g (15mmol) and copper trifluoroacetylacetonate 0.55 g (0.15 mmol, 10 mol %) in anhydrous toluene (30 mL) was refluxed for 1.5 h. After the reaction completion (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; ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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(2*H*)-one, **(7i)**. Yield: 147 mg, 70% (yellowish oil). R_f 0.30 (hexanes : EtOAc – 5:1); ^1H 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(2*H*)-one, (**7j**). Yield: 160 mg, 76% (yellowish oil). R_f 0.30 (hexanes : EtOAc – 5:1); ^1H 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-dihydropyridine-2,2(1*H*)-dicarboxylate, (**7k**). Yield: 137 mg, 65% (yellowish oil). R_f 0.35 (hexanes : EtOAc – 3:1); ^1H 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(1*H*)-dicarboxylate, (**7l**). Yield: 122 mg, 58% (yellowish oil). R_f 0.55 (hexanes : EtOAc – 1:1); ^1H 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 corresponding 1,5-diketone (0.5 mmol) in glacial acetic acid (4 ml) was plased into round-bottomed flask, equipped with reflux condenser, magnetic stirrer and tube for argon bubling. Then 0.31 g NH_4OAc (4 mmol) was added and reaction mixtre was heated at 100°C in constant argon flow for 1 hour. The resuling mixture was poured into 50 ml of cold water, extracted with EtOAc. The combinied organic fractions were washed with water and dryed 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). M. p. = 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 $C_{18}H_{17}F_3N_2O_2$ (%): 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). M. p. = 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). M. p. = 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; M. p. = 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) M. p. = 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: 100mg, 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(5*H*)-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(5*H*)-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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Supporting Information for this article (experimental details and NMR-spectra for all new compounds) is available online at http://www.pubs.acs.org

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