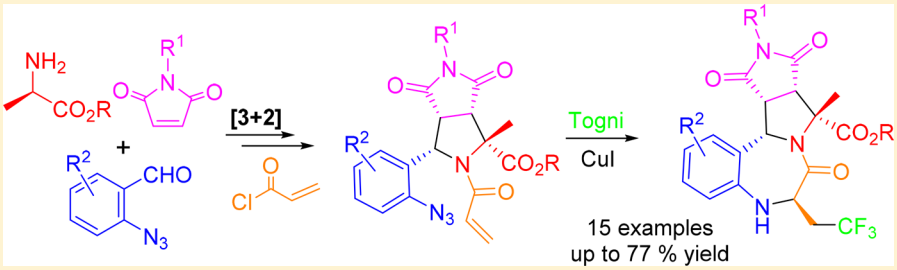
JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. 2019, 84, 5927−5935
Note
pubs.acs.org/joc

[3 + 2] Cycloaddition and Cascade Radical Reactions for the Synthesis of Trifluoromethylated Tetrahydrobenzodiazepin-3-ones

Alex Muthengi, Jon Erickson, Rachel E. Muriph, and Wei Zhang*

Center for Green Chemistry and Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, Massachusetts 02125, United States

Supporting Information



ABSTRACT: A reaction sequence involving three-component [3 + 2] cycloaddition of azomethine ylides followed by CuI-catalyzed cascade trifluoromethyl radical addition and cyclization is developed for diastereoselective synthesis of fused-tetrahydrobenzodiazepin-3-ones.

Incorporation of CF_3 to small molecules gained increasing popularity in the development of biologically interesting compounds to improve their metabolic stability, bioavailability, lipophilicity, protein binding affinity, and blood−brain barrier penetration capability.[1−8] Different from CH_3 group, CF_3 has a high electronegativity of 3.2, and a size of 2.2 Å (van der Waals radius) similar to *i*-Pr.[9] A series of reagents and associated methods for trifluoromethylation have been developed.[10,11] Among them, Togni reagent-based CF_3 radical reactions has been employed for making a series of trifluoromethylated ring systems.[12] For example, the Studer group reported the CF_3 radical reaction with aryl isonitriles for phenanthridines (Scheme 1, A).[12d] The Sodeoka group employed Cu-catalyzed CF_3 radical for the construction of five- and six-membered rings, but the effort for a seven-membered ring was futile (Scheme 1, B).[12e] The Shi group reported Cu- or Fe-catalyzed CF_3 radical reactions for the construction of seven-membered rings (Scheme 1, C).[12f] Introduced in this paper is our effort on the development of CF_3 radical reaction of 2-azidobenzyl acrylamides for the synthesis of tetrahydrobenzodiazepin-3-ones (Scheme 1, D).

Di- and tetrahydrobenzodiazepinones are privileged heterocycles that could be found in numerous biologically active compounds such as diazepam,[13a−c] falcipain-2-inhibitor,[13d] halazepam,[13e] flurazepam,[13f] lotrafiban,[13g,h] and vitamin D receptor (VDR) transcriptional inhibitor[13i] (Figure 1). There are many reports on the synthesis of benzodiazepinones, such as CuI-catalyzed Ullmann type aryl amination,[14a−d] intramolecular nucleophilic substitution[14e] palladium-catalyzed aminocarbonylation,[14f] 1,3-dipolar cycloaddition and decarboxylative rearrangement,[14g] and Ugi four-component reaction.[15] Described in this paper is a radical reaction to construct CF_3-containing benzodiazepinones, which have a structure similarity to halazepam shown in Figure 1. Since organic azides are good radical traps for carbon- and heteroatom-centered radicals,[16] 2-azidobenzyl acrylamides were employed as substrates for CF_3 radical addition to alkene followed by cyclization to azide for the formation of tetrahydrobenzodiazepinones (Scheme 1, D).

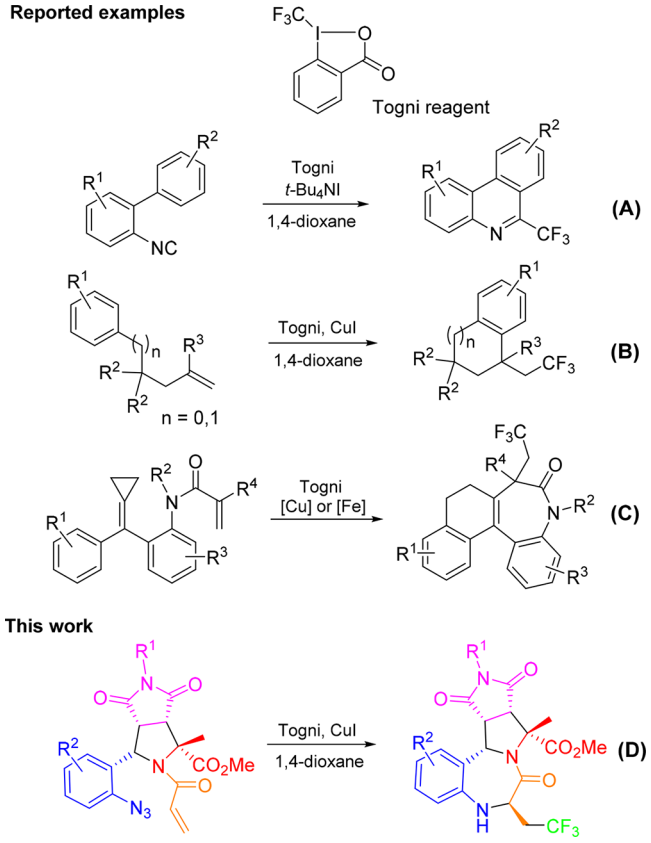
We have recently reported a series of [3 + 2] cycloaddition-based synthesis of diverse heterocyclic structures.[17a−d] Similarly, other groups have reported the [3 + 2] cycloaddition of azomethine ylides and maleimides.[17e−h] In this work, radical precursors **5** were prepared by one-pot [3 + 2] cycloaddition of amino ester **1**, maleimides **2**, and 2-azidobenzaldehydes **3**, followed by *N*-acylation with acryloyl chloride (Table 1). After exploring the reaction conditions, the optimized condition for the [3 + 2] cycloaddition was to use 1.2:1.1:1 of **1a**:**2a**:**3a** and 2 equiv of Et_3N in MeCN under microwave heating at 125 °C for 30 min. After precipitating out from the reaction mixture, **4a** was obtained in 94% isolated yield with a diastereoselectivity of 39:1. The optimized condition for *N*-acylation was to react 1:1.1 of **4a**:acryloyl chloride in the presence of Et_3N at 25 °C for 4 h to give **5a** in 94% isolated yield (Table 1, entry 7). CH_2Cl_2 was also a good solvent (Table 1, entry 6). But MeCN was chosen since it is a greener solvent based on the solvent selection guide.[18] Other than Et_3N, DIPEA and K_2CO_3 could also be used as bases for the acylation reaction (Table 1, entries 9 and 10).

Radical precursor **5a** was used for the development of Togni reagent-based CF_3 radical addition and cyclization for the

Received: February 22, 2019
Published: April 1, 2019

DOI: 10.1021/acs.joc.9b00448
J. Org. Chem. 2019, 84, 5927−5935

Scheme 1. Togni-Based CF_3 Radical Reactions



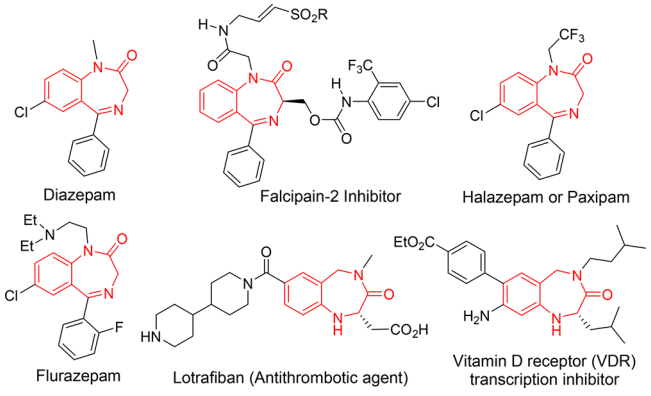
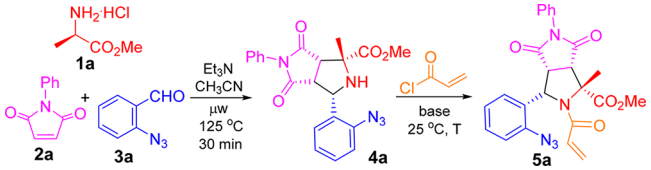


Figure 1. Benzodiazepinone-based biologically active compounds.

synthesis of product **6a** (Table 2).[10,11] The initial reaction using 10 mol % of CuBr as a catalyst in CH_2ClCH_2Cl at 75 °C for 6 h afforded product **6a** in 24% LC yield (Table 2, entry 1), and 29% yield by using CuI as a catalyst (Table 2, entry 2). After screening reaction temperature and solvents including 1,4-dioxane, EtOH, and EtOAc (Table 2, entries 3−11), the best condition was to conduct the reaction using CuI as a catalyst in 1,4-dioxane at 85 °C for 24 h, which gave **6a** in 60% isolated yield and 5:1 dr (Table 2, entry 8). Reduced CuI loading to 5 mol % lowered the yield to 51% (Table 2, entry 12). Replacement of CuI with Bu_4NI[12d,19] or reaction without using a catalyst only resulted in a trace amount of product (Table 2, entries 13 and 14). It is worth noting that N_2 gas generated during the reaction could help to maintain the inert atmosphere necessary for the reaction process.

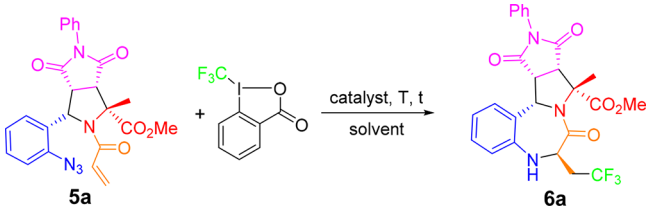
Table 1. Optimization of [3 + 2] Cycloaddition and *N*-Acylation Reactions[a]



entry	solvent	base (2 equiv)	T (h)	**5a** (%)[b]
1	CH_2Cl_2	Et_3N	2	62
2	CH_2Cl_2	Et_3N	3	81
3	CH_2Cl_2	Et_3N	3.5	96
4	MeCN	Et_3N	3	83
5	MeCN	Et_3N	3.5	95
6	CH_2Cl_2	Et_3N	4	98
7	**MeCN**	**Et_3N**	**4**	**98 (94)**[c]
8	EtOAc	TEA	4	79
9	CH_2Cl_2	DIPEA	4	95
10	CH_2Cl_2	K_2CO_3	4	96

[a]Reaction conditions: 1.2:1.1:1 of **1a**:**2a**:**3a**, Et_3N (2 equiv) in MeCN, microwave heating for 30 min for **4a**, then 1:1.1 of **4a**:acryoyl chloride, Et_3N (2 equiv) at 25 °C. [b]Yields based on conversion of **4a**. Detected by LC−MS. [c]Isolated yield in parentheses.

Table 2. Optimization of CF_3Radical Reaction[a]



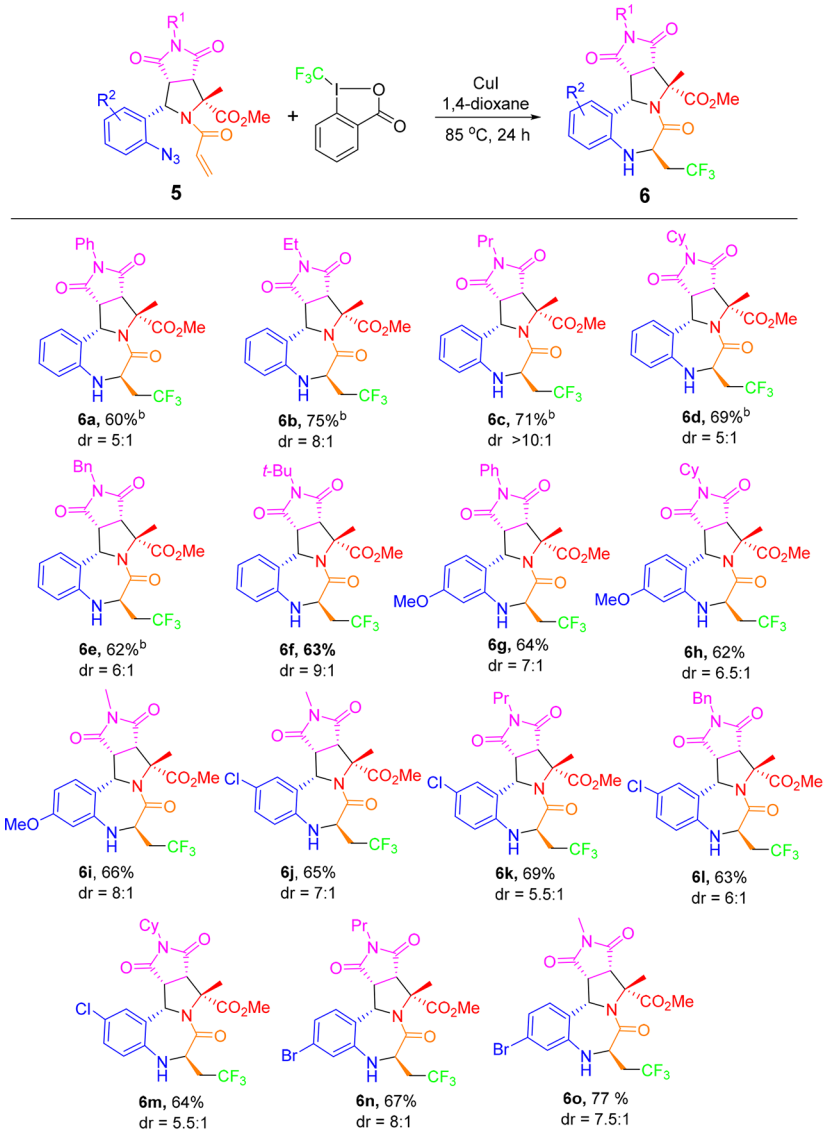
entry	cat	mol %	solvent	T (°C)	t (h)	**6a** (%)[a,b]
1	CuBr	10	CH_2ClCH_2Cl	75	6	24
2	CuI	10	CH_2ClCH_2Cl	80	6	29
3	CuBr	10	CH_2ClCH_2Cl	80	12	59
4	CuBr	10	1,4-dioxane	80	12	61
5	CuI	10	1,4-dioxane	80	12	64
6	CuBr	10	CH_2ClCH_2Cl	80	24	69
7	CuI	10	1,4-dioxane	80	24	70
8	**CuI**	**10**	**1,4-dioxane**	**85**	**24**	**73 (60)**[c]
9	CuI	10	1,4-dioxane	85	28	73
10	CuI	10	EtOH	80	12	15
11	CuI	10	EtOAc	80	12	trace
12	CuI	5	1,4-dioxane	85	24	51
13	–	–	1,4-dioxane	80	24	trace
14	Bu_4NI	–	1,4-dioxane	80	24	trace

[a]Reaction conditions: 1:1.5 of **5a**:Togni and 10 mol % of CuI in 1,4-dioxane. [b]Detected by LC−MS. [c]Isolated yield in parentheses.

A number of radical precursors **5** were prepared and used to evaluate the scope of the CF_3 radical reactions for tetrahydrobenzodiazepinone analogues **6** (Table 3). Under the optimized reaction conditions using CuI or CuBr as a catalyst, substrates **5a**−**o** with different R^1 and R^2 afforded products **6a**−**o** in 60−77% yields. Among them, unsubstituted arenes (R^2 = H) gave **6a**−**f** in 60−75% yields. Substrates with electron donating group (MeO) or withdrawing groups (Cl and Br) at different positions on the aromatic ring did not have significant impact on product yields of **6g**−**o**. Likewise, the substituents on maleimides (R^1 = Me, Et, Pr, *t*-Bu, Ph, Bn and

DOI: 10.1021/acs.joc.9b00448
J. Org. Chem. 2019, 84, 5927−5935

Table 3. Synthesis of Tetrahydrobenzodiazepin-3-ones[a]



[a]Reaction conditions: 1:1.5 of **5**:Togni reagent and CuI (10 mol %) in degassed 1,4-dioxane at 85 °C under Ar, isolated yield, dr determined by ^{19}F NMR of the crude mixture. [b]CuBr (10 mol %) in at 80 °C under N_2.

c-C_6H_{11}) also had limited impact. The results also indicated that the radical trifluoromethylation of 2-azidobenzyl acrylamides are diastereoselective (dr ≥ 5:1). The stereochemistry of radical precursors **5** generated from the [3 + 2] cycloaddition has been well reported.[17c,d] The new stereogenic center on tetrahydrobenzodiazepinone ring established during the radical cyclization was determined on the basis of the NOE experiment of the major diastereomer of **6c** (see SI).

On the basis of literature reports,[12] a mechanism for the formation of tetrahydrobenzodiazepinones is suggested in Scheme 2. The Togni reagent was reduced by Cu(I) to form a CF_3 radical and *ortho*-iodobenzoate ($ArylCO_2^-$).[12d] The CF_3 radical then attacks the terminal alkene of 2-azidobenzyl acrylamide **5** to form acyl group-stabilized radical **A**. Since the azide group is a good radical acceptor,[16] radical **A** cyclized to the azido group to form radical **B**. The N_2-fragmentation of radical **B** generates a *N*-centered radical **C**, which undergoes H-abstraction from the solvent,[16] 1,4-dioxane, forming tetrahydrobenzodiazepinone **6**, and a dioxanyl radical. The dioxanyl radical is oxidized by the Cu(II)-species generated in the initial CF_3-radical formation, hence regenerating the Cu(I)-complex, and an oxy-carbenium ion (3,6-dihydro-2*H*-1,4-dioxin-4-ium).[12g−i] The oxy-carbenium ion is likely trapped by *ortho*-iodobenzoate ($ArylCO_2^-$).[12b−d]

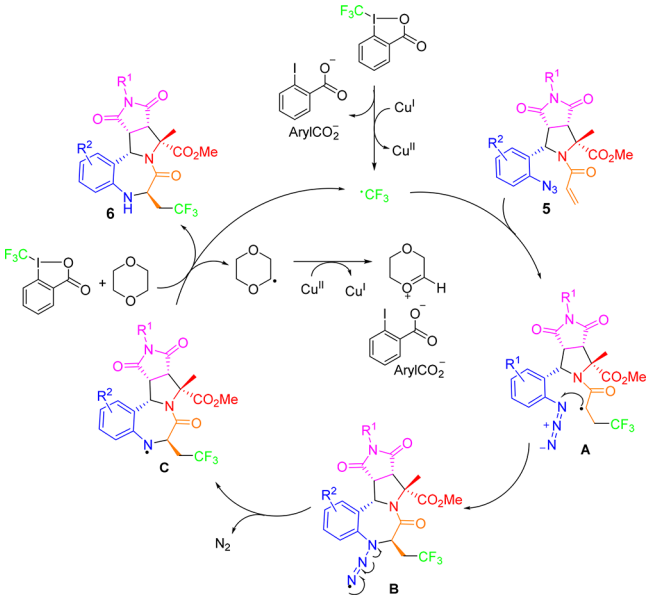
In conclusion, we have developed an efficient synthetic approach to trifluoromethylated tetrahydrobenzodiazepinones through Togni reagent and a Cu^I-catalyzed CF_3 radical reaction of 2-azidobenzyl acrylamides to afford diastereoselective products in good yields. The radical precursors were readily prepared by one-pot and three-component [3 + 2] cycloaddition followed by *N*-acylation. It is a new approach for making biologically interesting tetrahydrobenzodiazepinones bearing CF_3 groups.

EXPERIMENTAL SECTION

General Method. Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), and ^{19}F NMR (376 MHz) spectra were recorded

DOI: 10.1021/acs.joc.9b00448
J. Org. Chem. 2019, 84, 5927−5935

Scheme 2. Proposed Mechanism for CF_3 Radical reaction



on Agilent NMR spectrometers. The chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26) and carbon (chloroform δ 77.0). Multiplicities were indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in hertz (Hz).

LC−MS was performed on an Agilent 2100 LC with a 6130 quadrupole MS spectrometer, and a C18 column (5.0 μm, 6.0 × 50 mm) was used for separation. The mobile phases were MeOH and H_2O; both containing 0.01% trifluoroacetic acid. A linear gradient of 50:50 (v/v) MeOH/H_2O to 100% MeOH was used over 7.0 min at a flow rate of 0.7 mL/min. The chromatograms were detected at UV wavelengths 210, 254, and 365 nm. Low resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization). The microwave reactions were performed on a Biotage Initiator 8 system, equipped with an Infrared (IR) sensor (external surface sensor) to monitor the reaction temperature. The final products were purified on Angela HP-100 pre-LC system with a Venusil PrepG C18 column (10 μm, 120 Å, 21.2 mm × 250 mm).

HRMS was analyzed by RP-LC−MS: 1 μL of each sample was combined and 500 mL of optima grade MeCN (0.1% formic acid) and 500 mL of optima grade H_2O (0.1% formic acid) were added to the mixture. This mixture was then diluted by another factor of 10 with a 75/25 mixture of the optima grade MeCN and H_2O. One mL of this mixture was analyzed by RP-LC−MS. The mass analyzer was Orbitrap.

Representative Procedure for Preparation of 2-Azidobenzaldehydes 3. The 2-azidobenzaldehyde **3** was prepared following the literature procedure.[20] A reaction vessel was charged with HMPA (7.5 mmol) and 2-nitrobenzaldehyde (5.0 mmol). Once 2-nitrobenzaldehyde was dissolved, NaN_3 (10 mmol) was added dropwise. The reaction mixture was run at 25 °C for 24 h. The completion of the reaction was detected using LC−MS. After completion of the reaction, the solvent was removed under reduced pressure and the residue purified using flash chromatography using 80:20 mixture of hexane/EtOAc as eluent, to provide 2-nitrobenzaldehyde **3**.

Representative Procedure for [3 + 2] Cycloaddition. A reaction vial was charged with the corresponding D-alanine methyl ester **1** (1.2 mmol), maleimide **2** (1.1 mmol) and 2-azidobenzaldehyde **3** (1.0 mmol). Then, 2.5 mL of CH_3CN was added and the sealed reaction vial was heated under microwave irradiation at 125 °C for 30 min. The reaction mixture was kept at 25 °C for 2−3 h and a solid product was formed, washed with 1 mL of water, filtered, and dried to obtain intermediate **4** in >95% purity. The intermediate products **4** were used for the next reaction without further purification.

Representative Procedure for *N*-Acylation. To a solution of [3 + 2] cycloaddition adduct **4** (39:1 dr, 1 mmol, 1 equiv), Acryoyl chloride (1.1 mmol, 1.1 equiv) and Et_3N (2.0 mmol, 2.0 equiv) in 2.0 mL of CH_3CN. The reaction mixture in a sealed reaction vial was run at 25 °C for 4 h to obtain intermediate **5**. The completion of the reaction was detected using LC−MS. After completion of the reaction, the solvent was removed under reduced pressure and the residue purified using flash chromatography using a 70:30 mixture of hexane/EtOAc as eluent, to provide the intermediate **5**.

General Procedure for Synthesis of Products 6. (2-Azidobenzyl)acrylamide **5** (0.1 mmol, 1.0 equiv), Togni reagent (1.5 mmol, 1.5 equiv) and CuI (0.01 mmol, 0.1 equiv), were added to a dry reaction vial. The reaction vial was evacuated and backfilled with nitrogen or Argon gas. Then, 1 mL of degassed 1,4-dioxane was added, and the reaction mixture stirred at 85 °C for 24 h as monitored by LC−MS. Upon completion of the reaction, H_2O was added to the reaction mixture and extracted with EtOAc. The organic layer was then washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue purified by Angela HP-100 pre-LC system on (MeOH/H_2O = 70:30) to give the trifluoromethylated product **6a−6o** as a yellow oil.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azidophenyl)-1-methyl-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5a**).* White solid (417.7 mg, 91% yield). mp 253−255 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 6.5 Hz, 1H), 7.37 (td, J = 7.9, 1.5 Hz, 1H), 7.28 (dd, J = 5.4, 3.6 Hz, 2H), 7.26−7.24 (m, 1H), 7.21 (dd, J = 8.0, 0.9 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.65−6.56 (m, 2H), 6.27 (dd, J = 16.5, 1.7 Hz, 1H), 5.97 (d, J = 10.8 Hz, 1H), 5.89−5.77 (m, 1H), 5.47 (d, J = 10.2 Hz, 1H), 4.23−4.15 (m, 1H), 3.89 (s, 3H), 3.54 (d, J = 9.0 Hz, 1H), 1.92 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.4, 171.8, 170.2, 164.5, 137.8, 130.9, 130.0, 129.9, 129.5, 129.0, 128.7, 127.8, 125.9, 125.7, 118.4, 69.2, 58.1, 54.7, 53.0, 49.0, 24.2. HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{24}H_{21}N_5O_5$460.1621, found 460.1607.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azidophenyl)-5-ethyl-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5b**).* Yellow solid (369.9 mg, 90% yield). mp 257−260 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 1H), 7.32 (td, J = 7.9, 1.5 Hz, 1H), 7.18 (dd, J = 8.0, 0.8 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.24 (d, J = 18.3 Hz, 1H), 5.87 (d, J = 10.8 Hz, 1H), 5.78 (dd, J = 16.3, 10.4 Hz, 1H), 5.43 (d, J = 10.3 Hz, 1H), 4.07−3.99 (m, 1H), 3.91 (s, 3H), 3.32 (d, J = 9.1 Hz, 1H), 3.17 (ddd, J = 27.4, 13.4, 6.7 Hz, 2H), 1.87 (s, 3H), 0.74 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.4, 172.6, 170.3, 164.6, 137.7, 129.9, 129.3, 128.4, 127.8, 125.5, 118.1, 69.1, 57.8, 52.9, 48.9, 33.9, 29.7, 24.2, 12.3. HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{20}H_{21}N_5O_5$ 412.1621, found 412.1606.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azidophenyl)-1-methyl-4,6-dioxo-5-propyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5c**).* Yellow solid (395.3 mg, 93% yield). mp 228−231 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.2 Hz, 1H), 7.35−7.30 (m, 1H), 7.18 (dd, J = 8.0, 0.9 Hz, 1H), 7.06 (td, J = 7.6, 0.9 Hz, 1H), 6.23 (d, J = 18.3 Hz, 1H), 5.87 (d, J = 10.9 Hz, 1H), 5.82−5.72 (m, 1H), 5.42 (d, J = 10.3 Hz, 1H), 4.08−4.01 (m, 1H), 3.90 (s, 3H), 3.34 (d, J = 9.1 Hz, 1H), 3.15−3.06 (m, 1H), 3.03−2.93 (m, 1H), 1.87 (s, 3H), 1.20−1.03 (m, 2H), 0.73 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.6, 172.9, 170.3, 164.6, 137.7, 129.9, 129.8, 129.2, 128.3, 127.9, 125.4, 118.1, 69.2, 57.8, 54.5, 52.9, 48.8, 40.6, 24.1, 20.5, 11.3. HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{21}H_{23}N_5O_5$426.1778, found 426.1762.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azidophenyl)-5-cyclohexyl-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5d**).* Light yellow solid (437.1 mg, 94% yield). mp 259−262 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.2 Hz, 1H), 7.32 (td, J = 7.9, 1.5 Hz, 1H), 7.17 (dd, J = 8.0, 0.9 Hz, 1H), 7.07 (td, J = 7.6, 0.9 Hz, 1H), 6.23 (dd, J = 16.5, 1.8 Hz, 1H), 5.84 (d, J = 10.8 Hz, 1H), 5.81−5.71 (m, 1H), 5.42 (d, J = 10.3 Hz, 1H), 4.01−3.94 (m, 1H), 3.91 (s, 3H), 3.57 (tt, J = 12.2, 3.8 Hz, 1H), 3.29 (d, J = 9.2 Hz,

DOI: 10.1021/acs.joc.9b00448
J. Org. Chem. 2019, 84, 5927−5935

1H), 1.86 (s, 3H), 1.65 (dd, J = 18.7, 13.5 Hz, 2H), 1.56−1.48 (m, 2H), 1.26−1.00 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.5, 172.7, 170.3, 164.5, 137.6, 130.0, 129.8, 129.2, 128.6, 127.9, 125.5, 118.1, 69.1, 57.9, 54.4, 52.9, 52.0, 50.9, 48.6, 28.4, 27.5, 25.6, 24.8, 24.2. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{24}H_{27}N_5O_5$466.20907, found 466.2091.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azidophenyl)-5-benzyl-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5e**).* White solid (435.2 mg, 92% yield). mp 237−240 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 6.8 Hz, 1H), 7.21 (dd, J = 8.1, 4.0 Hz, 4H), 7.13 (d, J = 6.6 Hz, 3H), 6.75−6.68 (m, 1H), 6.18 (d, J = 16.6 Hz, 1H), 5.83 (d, J = 12.5 Hz, 1H), 5.78−5.68 (m, 1H), 5.38 (d, J = 10.1 Hz, 1H), 4.27 (dd, J = 13.9, 2.5 Hz, 1H), 4.14 (dd, J = 13.9, 2.4 Hz, 1H), 4.07−3.98 (m, 1H), 3.80 (s, 3H), 3.32 (dd, J = 9.2, 2.5 Hz, 1H), 1.83 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.4, 172.5, 170.1, 164.6, 137.3, 134.8, 129.7, 129.6, 129.2, 129.1, 128.5, 128.0, 127.8, 125.4, 117.9, 69.2, 57.5, 54.4, 52.8, 48.8, 42.6, 24.0. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{25}H_{23}N_5O_5$474.1778, found 474.1760.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azidophenyl)-5-(tert-butyl)-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5f**).* White solid (386.3 mg, 88% yield). mp 257−260 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 6.8 Hz, 1H), 7.34 (t, J = 8.2 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.23 (d, J = 15.2 Hz, 1H), 5.84 (d, J = 10.8 Hz, 1H), 5.74 (d, J = 16.2 Hz, 1H), 5.42 (d, J = 10.0 Hz, 1H), 3.92 (d, J = 9.6 Hz, 1H), 3.89 (s, 3H), 3.22 (d, J = 9.2 Hz, 1H), 1.84 (s, 3H), 1.17 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.2, 173.5, 170.4, 164.5, 137.8, 130.1, 129.8, 129.2, 128.9, 127.9, 125.4, 118.2, 69.8, 58.6, 54.6, 52.8, 49.0, 27.5, 24.1. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{22}H_{25}N_5O_5$440.19342, found 440.1934.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azido-4-methoxyphenyl)-1-methyl-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5g**).* Yellow solid (449.9 mg, 92% yield). mp 258−261 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 1H), 7.33−7.28 (m, 2H), 7.27 (t, J = 3.2 Hz, 1H), 6.72−6.62 (m, 4H), 6.27 (dd, J = 16.6, 1.5 Hz, 1H), 5.87 (dd, J = 18.6, 10.6 Hz, 2H), 5.48 (d, J = 10.4 Hz, 1H), 4.14 (d, J = 10.6 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.52 (d, J = 9.0 Hz, 1H), 1.90 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.5, 172.0, 170.2, 164.5, 160.8, 138.8, 131.0, 129.4, 129.0, 128.7, 127.8, 126.0, 122.2, 111.0, 104.3, 69.1, 60.4, 57.8, 55.5, 53.0, 49.2, 24.1. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{25}H_{23}N_5O_6$490.17269, found 490.1727.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azido-4-methoxyphenyl)-5-cyclohexyl-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]-pyrrole-1-carboxylate (**5h**).* White solid (450.5 mg, 91% yield). mp 251−253 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 1H), 6.68 (s, 1H), 6.60 (d, J = 8.7 Hz, 1H), 6.23 (d, J = 18.0 Hz, 1H), 5.79 (dd, J = 17.5, 10.6 Hz, 2H), 5.43 (d, J = 10.4 Hz, 1H), 3.94 (d, J = 9.6 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 3.64−3.55 (m, 1H), 3.27 (d, J = 9.2 Hz, 1H), 1.84 (s, 3H), 1.72−1.53 (m, 4H), 1.26 (t, J = 7.1 Hz, 2H), 1.10 (q, J = 18.9, 15.5 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.6, 172.9, 170.4, 164.6, 160.7, 138.6, 129.7, 129.1, 127.9, 122.4, 111.0, 104.0, 57.6, 55.5, 54.3, 52.8, 52.0, 48.7, 28.4, 27.6, 25.6, 25.6, 24.8. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{25}H_{29}N_5O_6$496.21964, found 496.2196.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azido-4-methoxyphenyl)-1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate(**5i**).* Light yellow solid (384.3 mg, 90% yield). mp 258−260 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 8.7, 2.4 Hz, 1H), 6.24 (dd, J = 16.6, 1.3 Hz, 1H), 5.83 (dd, J = 23.8, 10.5 Hz, 2H), 5.45 (d, J = 10.4 Hz, 1H), 4.00 (d, J = 10.6 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.32 (d, J = 8.8 Hz, 1H), 2.57 (s, 3H), 1.85 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.6, 173.0, 170.3, 164.5, 160.6, 138.6, 129.3, 127.8, 122.2, 110.9, 103.8, 68.9, 57.4, 55.4, 54.4, 53.0, 49.2, 24.7, 14.2. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{20}H_{21}N_5O_6$428.15708, found 428.1570.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azido-5-chlorophenyl)-1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5j**).* Light yellow solid (379.3 mg, 88% yield). mp 260−262 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.13 (dd, J = 18.5, 8.5 Hz, 1H), 6.28 (d, J = 16.5 Hz, 1H), 5.83 (d, J = 10.5 Hz, 2H), 5.50 (d, J = 9.8 Hz, 1H), 4.04 (d, J = 9.3 Hz, 1H), 3.91 (s, 3H), 3.34 (d, J = 8.7 Hz, 1H), 2.62 (s, 3H), 1.86 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.2, 172.7, 170.0, 164.4, 136.3, 131.8, 130.0, 129.9, 127.5, 127.5, 119.6, 119.4, 57.5, 54.5, 53.0, 49.0, 46.4, 40.3, 24.7. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{19}H_{18}N_5O_5Cl$432.1075, found 432.1077.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azido-5-chlorophenyl)-1-methyl-4,6-dioxo-5-propyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5k**).* White solid (408.5 mg, 89% yield). mp 269−272 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.28 (dd, J = 8.5, 2.4 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.26 (d, J = 16.5 Hz, 1H), 5.85−5.72 (m, 2H), 5.47 (d, J = 10.4 Hz, 1H), 4.01 (t, J = 10.0 Hz, 1H), 3.87 (s, 3H), 3.32 (d, J = 9.2 Hz, 1H), 3.18−3.03 (m, 2H), 1.84 (s, 3H), 1.26−1.13 (m, 2H), 0.77 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.4, 172.7, 164.5, 136.4, 131.7, 131.0, 129.9, 128.4, 127.6, 119.4, 69.3, 57.6, 54.4, 52.8, 48.7, 40.7, 29.7, 20.8, 11.3. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{21}H_{22}N_5O_5Cl$460.1388, found 460.1370.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azido-5-chlorophenyl)-5-benzyl-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5l**).* White solid (456.3 mg, 90% yield). mp 250−253 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.26−7.22 (m, 4H), 7.14 (dd, J = 6.8, 2.8 Hz, 2H), 7.10 (d, J = 8.5 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.81 (d, J = 10.9 Hz, 1H), 5.71 (d, J = 7.7 Hz, 1H), 5.46 (d, J = 10.1 Hz, 1H), 4.13 (s, 2H), 3.76 (d, J = 4.4 Hz, 1H), 3.72 (s, 3H), 3.34 (d, J = 9.3 Hz, 1H), 1.83 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.2, 172.4, 171.1, 164.5, 136.3, 134.6, 131.4, 130.9, 129.1, 128.9, 128.7, 128.5, 128.1, 128.1, 127.6, 119.3, 60.4, 57.7, 52.7, 48.8, 42.8, 21.1, 14.2. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{25}H_{22}N_5O_5Cl$ 508.1388, found 508.1374.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azido-5-chlorophenyl)-5-cyclohexyl-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5m**).* Yellow solid (454.1 mg, 91% yield). mp 277−280 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.29 (dd, J = 8.5, 2.3 Hz, 1H), 7.14 (dd, J = 18.1, 8.5 Hz, 1H), 6.27 (d, J = 17.7 Hz, 1H), 5.81 (d, J = 11.0 Hz, 1H), 5.73 (d, J = 19.6 Hz, 1H), 5.48 (d, J = 9.7 Hz, 1H), 4.01−3.93 (m, 1H), 3.90 (s, 3H), 3.68−3.58 (m, 1H), 3.31 (d, J = 9.3 Hz, 1H), 1.84 (s, 3H), 1.71 (t, J = 11.2 Hz, 2H), 1.57 (t, J = 12.2 Hz, 2H), 1.26−1.07 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.4, 173.4, 172.8, 164.4, 136.3, 131.9, 129.9, 129.8, 127.6, 127.5, 119.6, 119.4, 69.4, 57.4, 52.8, 52.1, 52.0, 50.9, 29.7, 28.3, 27.8, 25.6, 25.6, 24.7. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{24}H_{26}N_5O_5Cl$ 500.1701, found 500.1703.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azido-4-bromophenyl)-1-methyl-4,6-dioxo-5-propyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5n**).* Yellow solid (427.6 mg, 85% yield). mp 135−138 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 9.4 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 7.19−7.15 (m, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.79 (d, J = 10.9 Hz, 1H), 5.72 (d, J = 11.9 Hz, 1H), 5.46 (d, J = 9.5 Hz, 1H), 4.06−3.97 (m, 1H), 3.88 (s, 3H), 3.33 (d, J = 9.4 Hz, 1H), 3.13 (dd, J = 19.3, 8.9 Hz, 2H), 1.85 (s, 3H), 1.14 (dq, J = 16.0, 8.7, 7.7 Hz, 2H), 0.74 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.5, 172.8, 170.1, 164.4, 139.1, 129.8, 127.6, 125.8, 122.7, 121.8, 121.2, 120.0, 61.1, 57.5, 53.1, 53.0, 40.7, 20.6, 17.9, 11.3. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{21}H_{22}N_5O_5Br$ 504.08829, found 504.0887.

*Methyl (1R,3S,3aR,6aS)-2-acryloyl-3-(2-azido-4-bromophenyl)-1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5o**).* Light yellow solid (413.3 mg, 87% yield). mp 281−284 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.30 (d, J = 1.8 Hz, 1H), 7.20 (dd, J = 8.4, 1.7 Hz, 1H), 6.27 (d, J = 16.5 Hz, 1H), 5.81 (d, J = 10.7 Hz, 1H), 5.75 (d, J = 10.4 Hz, 1H), 5.49 (d, J = 10.1 Hz, 1H), 4.04 (t, J = 9.8 Hz, 1H), 3.91 (s, 3H), 3.35 (d, J = 8.9 Hz, 1H), 2.59 (s, 3H), 1.86 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.4, 172.7, 170.3, 164.3, 139.0, 129.9, 129.1, 128.4, 127.5, 123.4, 121.2, 69.3, 57.4, 54.5, 53.1, 48.7, 29.7, 24.8. HRMS (ESI-Orbitrap) m/z $(M + H)^+$ Calcd for $C_{19}H_{18}N_5O_5Br$ 476.05699, found 476.0572.

Methyl (9R,9aS,12aR)-9-methyl-7,10,12-trioxo-11-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo-

DOI: 10.1021/acs.joc.9b00448
J. Org. Chem. 2019, 84, 5927−5935

*[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6a**).* Yellow oil (30 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.50 (m, 2H), 7.48−7.44 (m, 1H), 7.27 (d, J = 1.5 Hz, 1H), 7.25−7.24 (m, 1H), 7.21−7.16 (m, 1H), 7.04 (d, J = 6.5 Hz, 1H), 6.98 (td, J = 7.5, 1.2 Hz, 1H), 6.82 (dd, J = 7.9, 1.1 Hz, 1H), 5.74 (d, J = 9.5 Hz, 1H), 5.22 (s, 1H), 4.23 (t, J = 6.7 Hz, 1H), 3.96−3.90 (m, 1H), 3.53 (s, 3H), 3.38 (d, J = 9.3 Hz, 1H), 3.03−2.85 (m, 2H), 1.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.6, 173.0, 169.0, 143.8, 131.1, 129.5, 129.3, 129.0, 128.3, 126.4, 125.3, 123.0, 120.8, 71.7, 69.8, 52.8, 52.6, 34.5, 34.2, 23.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.38 (t, J = 10.6 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for$C_{25}H_{22}N_3O_5F_3$ 502.1590, found 502.1574.

*Methyl (9R,9aS,12aR)-11-ethyl-9-methyl-7,10,12-trioxo-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo[f]-pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6b**).* Yellow oil (34 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (td, J = 7.6, 1.6 Hz, 1H), 7.03 (d, J = 7.7 Hz, 1H), 6.96 (td, J = 7.5, 1.2 Hz, 1H), 6.82 (dd, J = 7.9, 1.2 Hz, 1H), 5.61 (dd, J = 8.1, 1.4 Hz, 1H), 5.15 (s, 1H), 4.17 (t, J = 6.7 Hz, 1H), 3.76−3.70 (m, 1H), 3.61 (q, J = 7.2 Hz, 2H), 3.52 (s, 3H), 3.18 (d, J = 9.2 Hz, 1H), 2.90 (pd, J = 10.6, 6.6 Hz, 2H), 1.75 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.3, 173.8, 169.1, 169.0, 144.0, 129.0, 128.5, 127.6, 125.3, 122.9, 120.6, 71.5, 69.3, 52.5, 52.4, 47.6, 45.4, 34.5, 34.3, 23.4, 12.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.41 (t, J = 10.6 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for$C_{21}H_{22}N_3O_5F_3$ 454.1590, found 454.1576.

*Methyl (9R,9aS,12aR)-9-methyl-7,10,12-trioxo-11-propyl-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo-[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6c**).* Yellow oil (33 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (td, J = 7.7, 1.6 Hz, 1H), 7.04 (d, J = 9.0 Hz, 1H), 6.97 (td, J = 7.5, 1.2 Hz, 1H), 6.83 (dd, J = 7.9, 1.2 Hz, 1H), 5.54 (d, J = 8.2 Hz, 1H), 5.15 (s, 1H), 4.14 (t, J = 6.7 Hz, 1H), 3.75−3.70 (m, 1H), 3.56 (d, J = 13.0 Hz, 1H), 3.53 (s, 3H), 3.50 (d, J = 10.1 Hz, 1H), 3.17 (d, J = 9.2 Hz, 1H), 2.89 (qd, J = 10.6, 6.8 Hz, 2H), 1.74 (s, 3H), 1.64 (dt, J = 14.4, 7.4 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.6, 174.1, 169.3, 168.9, 144.1, 129.0, 128.9, 125.6, 123.1, 120.7, 71.6, 69.3, 52.5, 52.2, 47.4, 46.0, 41.1, 34.9, 23.2, 20.8, 11.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.42 (t, J = 10.6 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for$C_{22}H_{24}N_3O_5F_3$ 468.1747, found 468.1735.

*Methyl (9R,9aS,12aR)-11-cyclohexyl-9-methyl-7,10,12-trioxo-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo-[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6d**).* Light yellow oil (35 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.15 (m, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.95 (td, J = 7.5, 1.2 Hz, 1H), 6.79 (dd, J = 7.9, 1.2 Hz, 1H), 5.64 (d, J = 8.1 Hz, 1H), 5.14 (s, 1H), 4.18 (t, J = 6.7 Hz, 1H), 3.71−3.66 (m, 1H), 3.49 (s, 3H), 3.14 (d, J = 9.3 Hz, 1H), 2.99−2.80 (m, 2H), 2.18−2.05 (m, 2H), 1.86 (d, J = 13.0 Hz, 2H), 1.74 (s, 3H), 1.70−1.56 (m, 4H), 1.38−1.19 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.6, 174.0, 169.0, 144.0, 128.9, 128.3, 125.0, 122.7, 120.5, 71.5, 69.4, 52.7, 52.4, 52.3, 47.3, 45.1, 34.3, 34.1, 28.7, 28.6, 25.8, 24.9, 23.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.42 (t, J = 10.6 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for$C_{25}H_{28}N_3O_5F_3$ 508.2060, found 508.2049.

*Methyl (9R,9aS,12aR)-11-benzyl-9-methyl-7,10,12-trioxo-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo-[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6e**).* Yellow oil (32 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.35 (m, 2H), 7.34−7.30 (m, 3H), 7.12 (td, J = 7.6, 1.6 Hz, 1H), 7.01 (d, J = 6.4 Hz, 1H), 6.94 (td, J = 7.5, 1.2 Hz, 1H), 6.52 (d, J = 8.9 Hz, 1H), 5.57 (d, J = 9.5 Hz, 1H), 4.93 (s, 1H), 4.11 (t, J = 6.5 Hz, 1H), 3.81−3.74 (m, 1H), 3.49 (s, 2H), 3.21 (d, J = 9.1 Hz, 1H), 3.17 (s, 3H), 2.89−2.77 (m, 2H), 1.72 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.2, 173.5, 169.0, 168.7, 143.9, 134.9, 128.9, 128.8, 128.6, 128.5, 128.3, 125.1, 123.0, 120.8, 71.5, 69.1, 52.4, 52.1, 47.7, 45.8, 43.0, 34.7, 23.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.37 (t, J = 10.6 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for-$C_{26}H_{24}N_3O_5F_3$ 516.1747, found 516.1738.

*Methyl (9R,9aS,12aR)-11-(tert-butyl)-9-methyl-7,10,12-trioxo-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo-[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6f**).* Yellow oil (30 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, J = 7.7, 1.6 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.96 (td, J = 7.5, 1.2 Hz, 1H), 6.82 (dd, J = 7.9, 1.1 Hz, 1H), 5.56 (d, J = 8.0 Hz, 1H), 5.30 (s, 1H), 3.58−3.56 (m, 1H), 3.52 (s, 3H), 3.48 (d, J = 6.9 Hz, 1H), 3.06 (d, J = 9.4 Hz, 1H), 2.96−2.84 (m, 2H), 1.72 (s, 3H), 1.59 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 175.5, 174.9, 169.2, 169.1, 144.1, 128.9, 128.6, 125.3, 122.9, 120.6, 71.9, 69.7, 59.7, 52.5, 52.4, 47.3, 45.6, 28.1, 23.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.44 (t, J = 10.6 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for$C_{23}H_{26}N_3O_5F_3$ 482.1903, found 482.1887.

*Methyl (9R,9aS,12aR,12bS)-3-methoxy-9-methyl-7,10,12-trioxo-11-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6g**).* Yellow oil (34 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.41 (m, 4H), 7.27 (d, J = 1.5 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 6.51 (d, J = 8.5 Hz, 1H), 6.36 (s, 1H), 5.30 (s, 1H), 5.20 (s, 1H), 4.15 (t, J = 6.8 Hz, 1H), 3.90 (d, J = 8.0 Hz, 1H), 3.82 (d, J = 3.7 Hz, 1H), 3.74 (s, 3H), 3.56 (s, 3H), 3.38 (d, J = 9.3 Hz, 1H), 2.95−2.83 (m, 2H), 1.81 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.7, 173.1, 169.4, 160.2, 144.9, 141.6, 133.1, 131.5, 131.1, 129.5, 129.4, 128.0, 126.4, 117.4, 108.4, 106.4, 90.7, 71.6, 69.8, 66.1, 61.9, 55.3, 52.8, 52.5, 47.6, 23.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.27 (t, J = 10.6 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{26}H_{24}N_3O_6F_3$532.1696, found 532.1681.

*Methyl (9R,9aS,12aR,12bS)-11-cyclohexyl-3-methoxy-9-methyl-7,10,12-trioxo-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6h**).* Yellow oil (33.3 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 8.5 Hz, 1H), 6.50 (dd, J = 8.5, 2.5 Hz, 1H), 6.36 (s, 1H), 5.59 (dd, J = 8.1, 1.5 Hz, 1H), 5.30 (d, J = 0.5 Hz, 1H), 4.10 (t, J = 6.7 Hz, 1H), 3.76 (s, 3H), 3.72−3.64 (m, 2H), 3.54 (s, 3H), 3.14 (d, J = 9.3 Hz, 1H), 2.90−2.76 (m, 2H), 2.15−2.05 (m, 2H), 1.86 (d, J = 16.2 Hz, 2H), 1.74 (s, 3H), 1.42−1.16 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.6, 174.0, 169.3, 160.1, 145.1, 129.5, 117.3, 108.0, 106.2, 71.4, 69.3, 55.3, 52.6, 52.5, 52.1, 47.1, 31.0, 28.7, 28.6, 25.7, 24.9, 23.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.31 (t, J = 10.6 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{26}H_{30}N_3O_6F_3$ 538.2165, found 538.2148.

*Methyl (9R,9aS,12aR,12bS)-3-methoxy-9,11-dimethyl-7,10,12-trioxo-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6i**).* Light yellow oil (31 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, J = 8.5 Hz, 1H), 6.52 (dd, J = 8.5, 2.6 Hz, 1H), 6.39 (d, J = 2.5 Hz, 1H), 5.53 (dd, J = 8.1, 1.6 Hz, 1H), 5.19 (s, 1H), 4.08 (t, J = 6.8 Hz, 1H), 3.77 (s, 3H), 3.76−3.71 (m, 1H), 3.59 (s, 3H), 3.21 (d, J = 9.0 Hz, 1H), 3.06 (s, 3H), 2.92−2.79 (m, 2H), 1.75 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.5, 174.1, 169.4, 169.3, 160.2, 145.3, 130.0, 117.6, 108.4, 106.4, 71.5, 69.3, 55.4, 52.8, 52.4, 47.2, 45.3, 35.2, 34.9, 31.0, 25.5, 23.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.21 (t, J = 10.5 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{21}H_{22}N_3O_6F_3$ 470.15392, found 470.1529.

*Methyl (9R,9aS,12aR,12bS)-2-chloro-9,11-dimethyl-7,10,12-trioxo-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6j**).* Yellow oil (31 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J = 8.4, 2.3 Hz, 1H), 6.99 (s, 1H), 6.75 (d, J = 8.4 Hz, 1H), 5.67 (d, J = 9.8 Hz, 1H), 5.24 (s, 1H), 3.81−3.75 (m, 1H), 3.56 (s, 3H), 3.50 (d, J = 7.1 Hz, 1H), 3.25 (d, J = 9.2 Hz, 1H), 3.05 (s, 3H), 2.97−2.79 (m, 2H), 1.77 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.5, 173.8, 169.2, 168.3, 142.4, 128.9, 128.1, 127.7, 127.4, 126.2, 121.8, 71.1, 69.5, 52.8, 52.7, 47.6, 44.5, 25.5, 23.5, 18.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.33 (t, J = 10.4 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{20}H_{19}N_3O_5ClF_3$ 474.10437, found 474.1044.

*Methyl (9R,9aS,12aR,12bS)-2-chloro-9-methyl-7,10,12-trioxo-11-propyl-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (**6k**).* Yellow oil (35 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J = 8.4, 2.4 Hz, 1H), 7.00 (s, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.64 (d, J = 9.7 Hz, 1H), 5.18 (s, 1H), 4.15 (t, J = 6.7

DOI: 10.1021/acs.joc.9b00448
J. Org. Chem. 2019, 84, 5927−5935

Hz, 1H), 3.79−3.73 (m, 1H), 3.54 (s, 3H), 3.51 (d, J = 7.3 Hz, 2H), 3.21 (d, J = 9.3 Hz, 1H), 2.98−2.79 (m, 2H), 1.76 (s, 3H), 1.61 (d, J = 7.2 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.6, 173.9, 169.0, 168.4, 142.4, 128.9, 128.1, 127.7, 127.4, 126.3, 121.7, 71.2, 69.4, 52.6, 52.5, 47.6, 41.2, 34.2, 33.9, 23.4, 20.8, 11.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.41 (t, J = 10.4 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{22}H_{23}N_3O_5ClF_3$502.1357, found 502.1342.

Methyl (9R,9aS,12aR,12bS)-11-benzyl-2-chloro-9-methyl-7,10,12-trioxo-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate ***(6l)***. Yellow oil (35 mg, 63% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 6.8, 3.0 Hz, 2H), 7.35−7.31 (m, 3H), 7.03 (dd, J = 8.4, 2.3 Hz, 1H), 6.94 (s, 1H), 6.28 (d, J = 8.5 Hz, 1H), 5.69 (d, J = 9.7 Hz, 1H), 5.30 (s, 1H), 4.70 (s, 2H), 4.13 (t, J = 6.6 Hz, 1H), 3.88−3.78 (m, 1H), 3.25 (d, J = 9.3 Hz, 1H), 3.20 (s, 3H), 2.97−2.70 (m, 2H), 1.75 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.0, 173.4, 168.7, 168.1, 142.0, 134.9, 128.8, 128.7, 128.6, 128.3, 127.7, 127.5, 125.7, 121.8, 71.0, 69.2, 52.7, 52.3, 48.0, 44.2, 43.0, 33.5, 23.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.41 (t, J = 10.4 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{26}H_{23}N_3O_5ClF_3$ 550.13567, found 550.1352.

Methyl (9R,9aS,12aR,12bS)-2-chloro-11-cyclohexyl-9-methyl-7,10,12-trioxo-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate ***(6m)***. Yellow oil (35 mg, 64% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 10.8 Hz, 1H), 6.97 (s, 1H), 6.70 (d, J = 8.5 Hz, 1H), 5.73 (d, J = 8.1 Hz, 1H), 5.18 (s, 1H), 4.19 (t, J = 6.6 Hz, 1H), 3.80−3.68 (m, 2H), 3.51 (s, 3H), 3.18 (d, J = 9.4 Hz, 1H), 3.02−2.92 (m, 1H), 2.79 (ddd, J = 14.7, 10.4, 5.3 Hz, 1H), 2.12 (d, J = 11.0 Hz, 2H), 1.76 (s, 3H), 1.33 (d, J = 16.3 Hz, 2H), 1.30−1.21 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.5, 173.8, 169.1, 168.2, 142.3, 128.8, 127.6, 127.5, 127.3, 125.7, 121.4, 71.1, 69.6, 52.7, 52.6, 52.5, 47.5, 43.9, 33.7, 28.6, 28.6, 25.7, 24.9, 23.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.44 (t, J = 10.4 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{25}H_{27}N_3O_5ClF_3$ 542.16697, found 542.1672.

Methyl (9R,9aS,12aR,12bS)-3-bromo-9-methyl-7,10,12-trioxo-11-propyl-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate ***(6n)***. Yellow oil (37 mg, 67% yield) ^1H NMR (400 MHz, $CDCl_3$)) δ 7.07 (d, J = 8.2 Hz, 1H), 6.97 (s, 1H), 6.86 (d, J = 8.2 Hz, 1H), 5.67 (d, J = 8.2 Hz, 1H), 5.24 (s, 1H), 4.14 (t, J = 6.6 Hz, 1H), 3.76 (t, J = 8.8 Hz, 1H), 3.53 (s, 3H), 3.52−3.47 (m, 2H), 3.21 (d, J = 9.3 Hz, 1H), 2.99−2.73 (m, 2H), 1.76 (s, 3H), 1.64 (d, J = 7.4 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.6, 173.9, 168.9, 168.7, 144.9, 129.3, 125.5, 123.8, 123.3, 122.2, 71.0, 69.5, 52.6, 52.4, 47.7, 44.3, 41.2, 34.0, 23.5, 20.8, 11.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.39 (t, J = 10.4 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{22}H_{23}N_3O_5BrF_3$546.08516, found 546.0854.

Methyl (9R,9aS,12aR,12bS)-3-bromo-9,11-dimethyl-7,10,12-trioxo-6-(2,2,2-trifluoroethyl)-5,6,7,9,9a,10,11,12,12a,12b-decahydrobenzo[f]pyrrolo[3′,4′:3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate ***(6o)***. Yellow oil (40 mg, 77% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, J = 8.2, 1.9 Hz, 1H), 6.98 (d, J = 1.9 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 5.71 (d, J = 9.7 Hz, 1H), 5.30 (s, 1H), 4.16 (t, J = 6.6 Hz, 1H), 3.78 (t, J = 8.7 Hz, 1H), 3.55 (s, 3H), 3.25 (d, J = 9.3 Hz, 1H), 3.06 (s, 3H), 2.98−2.77 (m, 2H), 1.78 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.5, 173.8, 169.2, 168.4, 145.0, 129.4, 125.5, 123.3, 123.2, 122.3, 70.9, 69.5, 52.8, 52.8, 47.6, 34.1, 33.8, 31.0, 25.6, 23.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.30 (t, J = 10.4 Hz, 3F). HRMS (ESI-Orbitrap) m/z (M + H)$^+$ Calcd for $C_{20}H_{19}N_3O_5BrF_3$518.05386, found 518.0542.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00448.

Copies of ^1H NMR and ^{13}C NMR of **5a−o**, and ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra of compounds **6a−o** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wei2.zhang@umb.edu.

ORCID

Wei Zhang: 0000-0002-6097-2763

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Center for Green Chemistry of University of Massachusetts Boston.

■ REFERENCES

(1) Jeschke, P. The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection. *ChemBioChem* **2004**, *5*, 570.

(2) Muller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking beyond Intuition. *Science* **2007**, *317*, 1881.

(3) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320.

(4) Cheng, L.-J.; Cordier, C. J. Catalytic Nucleophilic Fluorination of Secondary and Tertiary Propargylic Electrophiles with a Copper-N-Heterocyclic Carbene Complex. *Angew. Chem.* **2015**, *127*, 13938.

(5) Ma, J.-A.; Cahard, D. Strategies for Nucleophilic, Electrophilic, and Radical Trifluoromethylations. *J. Fluorine Chem.* **2007**, *128*, 975.

(6) Shimizu, M.; Hiyama, T. Modern Synthetic Methods for Fluorine-Substituted Target Molecules. *Angew. Chem., Int. Ed.* **2005**, *44*, 214.

(7) (a) Shimizu, M.; Hiyama, T. Modern Synthetic Methods for Fluorinated compounds. *Angew. Chem.* **2005**, *117*, 218. (b) Schlosser, M. CF_3-Bearing Aromatic and Heterocyclic Building Blocks. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (c) Salwiczek, M.; Nyakatura, E. K.; Gerling, U. M.; Ye, S.; Koksch, B. Fluorinated amino acids: compatibility with native protein structures and effects on protein−protein interactions. *Chem. Soc. Rev.* **2012**, *41*, 2135. (d) Egli, M. The Steric Hypothesis for DNA Replication and Fluorine Hydrogen Bonding Revisited in Light of Structural Data. *Acc. Chem. Res.* **2012**, *45*, 1237. (e) Wang, J.; Saánchez-Roselloó, M.; Acenña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432. (f) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422.

(8) (a) For special issue on "Role of Fluorine in Medicinal chemistry" see: Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell, 2009. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Isanbor, C.; O'Hagan, D. Fluorine in Medicinal Chemistry: A Review of Anti-Cancer Agents. *J. Fluorine Chem.* **2006**, *127*, 303.

(9) Bott, G.; Field, L. D.; Sternhell, S. Steric Effects. A Study of a Rationally Designed System. *J. Am. Chem. Soc.* **1980**, *102*, 5618.

(10) (a) For selected reports on catalytic C_{sp2}−CF_3 bond-forming reactions, see: Parsons, A. T.; Senecal, T. D.; Buchwald, S. L. Iron(II)-Catalyzed Trifluoromethylation of Potassium Vinyltrifluoroborates. *Angew. Chem.* **2012**, *124*, 3001. (b) Chu, L.; Qing, F.-L. Copper-Catalyzed Direct C−H Oxidative Trifluoromethylation of Heteroarenes. *J. Am. Chem. Soc.* **2012**, *134*, 1298. (c) Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. Pd(II)-Catalyzed Ortho Trifluoromethylation of Arenes and Insights into the Coordination Mode of Acidic Amide

DOI: 10.1021/acs.joc.9b00448
J. Org. Chem. 2019, 84, 5927−5935

Directing Groups. *J. Am. Chem. Soc.* **2012**, *134*, 11948. (d) Fujiwara, Y.; Dixon, J. A.; Hara, F. O.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herl, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. Practical and Innate Carbon−hydrogen Functionalization of Heterocycles. *Nature* **2012**, *492*, 95. (e) Masahiro, O.; Hideaki, K.; Hideki, A. Aromatic Trifluoromethylation Catalytic in Copper. *Chem. Commun.* **2009**, 1909. (f) Cho, E. J.; Cenecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. The Palladium-Catalyzed Trifluoromethylation of Aryl Chlorides. *Science* **2010**, *328*, 1679. (g) Shimizu, R.; Egami, H.; Nagi, T.; Chae, J.; Hamashima, Y.; Sodeoka, M. Direct C2-Trifluoromethylation of Indole Derivatives Catalyzed by Copper Acetate. *Tetrahedron Lett.* **2010**, *51*, 5947. (h) Xu, J.; Luo, D.-F.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Fu, Y.; Liu, L. Copper-Catalyzed Trifluoromethylation of Aryl Boronic Acids Using a CF_3^+ Reagent. *Chem. Commun.* **2011**, *47*, 4300. (i) Mu, X.; Chen, S.; Zhen, X.; Liu, G. *Chem. - Eur. J.* **2011**, *17*, 6039. (j) Nagib, D. A.; MacMillan, D. C. Trifluoromethylation of Arenes and Heteroarenes by Means of Photoredox Catalysis. *Nature* **2011**, *480*, 224.

(11) (a) For selected reports on C_{sp3}−CF_3 bond-forming reactions, see: Nagao, H.; Yamane, Y.; Mukaiyama, T. Asymmetric Trifluoromethylation of Ketones with (Trifluoromethyl)Trimethylsilane Catalyzed by Chiral Quaternary Ammonium Phenoxides. *Chem. Lett.* **2007**, *36*, 666. (b) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. Cinchona Alkaloids/TMAF Combination-Catalyzed Nucleophilic Enantioselective Trifluoromethylation of Aryl Ketones. *Org. Lett.* **2007**, *9*, 3707. (c) Nagib, D. A.; Scott, M. E.; MacMillan, D. C. Enantioselective α-Trifluoromethylation of Aldehydes via Photoredox Organocatalysis. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (d) Allen, A. E.; MacMillan, D. C. The Productive Merger of Iodonium Salts and Organocatalysis: A Non-Photolytic Approach to the Enantioselective α-Trifluoromethylation of Aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 4986. (e) Pham, P. V.; Nagib, D. A.; MacMillan, D. C. Photoredox Catalysis: A Mild, Operationally Simple Approach to the Synthesis of α-Trifluoromethyl Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119. (f) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. Highly Enantioselective Copper-Catalyzed Electrophilic Trifluoromethylation of β-Ketoesters. *J. Am. Chem. Soc.* **2012**, *134*, 10769. (g) Hu, M.; Ni, C.; Hu, J. Copper-Mediated Trifluoromethylation of α-Diazo Esters with $TMSCF_3$: The Important Role of Water as a Promoter. *J. Am. Chem. Soc.* **2012**, *134*, 15257. (h) Novak, P.; Lishchynskyi, A.; Grushin, V. Trifluoromethylation of α-Haloketones. *J. Am. Chem. Soc.* **2012**, *134*, 16167. (i) Prakash, G. K.; Jog, P. V.; Batamack, P. D.; Olah, G. A. Taming of Fluoroform: Direct Nucleophilic Trifluoromethylation of Si, B, S, and C Centers. *Science* **2012**, *338*, 1324.

(12) (a) For selected examples on C_{sp2}−CF_3 reactions: Studer, A. A "Renaissance" in Radical Trifluoromethylation. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (b) Charpentier, J.; Früh, N.; Togni, A. Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. *Chem. Rev.* **2015**, *115*, 650. (c) Tian, Y.; Chen, S.; Gu, Q.-S.; Lin, J.-S.; Liu, X.-Y. Amino and azidotrifluoromethylation of alkenes. *Tetrahedron Lett.* **2018**, *59*, 203. (d) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. 6-Trifluoromethyl-Phenanthridines through Radical-Trifluoromethylation of Isonitriles. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792. (e) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. Alkene Trifluoromethylation Coupled with C−C Bond Formation: Construction of Trifluoromethylated Carbocycles and Heterocycles. *Angew. Chem., Int. Ed.* **2013**, *52*, 4000. (f) Yu, L. Z.; Xu, Q.; Tang, X.-Y.; Shi, S. Iron- or Copper-Catalyzed Trifluoromethylation of Acrylamide-Tethered Alkylidenecyclopropanes: Facile Synthesis of CF_3 -Containing Polycyclic Benzazepine Derivatives. *ACS Catal.* **2016**, *6*, 526. (g) Guifang, H.; Yuxiu, L.; Qingmin, W. Copper-Catalyzed Intramolecular Trifluoromethylation of *N* -Benzylacrylamides Coupled with Dearomatization: Access to CF_3-Containing 2-Azaspiro[4.5]Decanes. *Org. Lett.* **2014**, *16*, 3188. (h) Gao, P.; Yan, X. B.; Tao, T.; Yang, F.; He, T.; Song, X. R.; Liu, X. Y.; Liang, Y. M. Copper-Catalyzed Trifluoromethylation-Cyclization of Enynes: Highly Regioselective Construction of Trifluoromethylated Carbocycles and Heterocycles. *Chem. - Eur. J.* **2013**, *19*, 14420. (i) Zhang, B.; Studer, A. 2-Trifluoromethylated Indoles via Radical Trifluoromethylation of Isonitriles. *Org. Lett.* **2014**, *16*, 1216.

(13) (a) For biological activity of 1,4-benzodiazepin-2-ones and 1,4-benzodiazepin-3-ones: Kopp, C.; Rudolph, U.; Low, K.; Tobler, I. Modulation of Rhythmic Brain Activity by Diazepam: GABAA receptor Subtype and State Specificity. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 3674. (b) Richter, L.; de Graaf, C.; Sieghart, W.; Varagic, Z.; Mörzinger, M.; PdeEsch, I. J.; Ecker, G. F.; Ernst, M. Diazepam-Bound GABAA Receptor Models Identify New Benzodiazepine Binding-Site Ligands. *Nat. Chem. Biol.* **2012**, *8*, 455. (c) Braestrup, C.; Squires, R. F. Specific Benzodiazepine Receptors in Rat Brain Characterized by High-Affinity [3H]Diazepam Binding (Affinity Binding/Diazepam/Anxiolytic Activity/Brain Membranes/Regional Distribution). *Proc. Natl. Acad. Sci. U. S. A.* **1977**, *74*, 3805. (d) Ettari, R.; Micale, N.; Schirmeister, T.; Gelhaus, C.; Leippe, M.; Nizi, E.; Emilia, M.; Francesco, D.; Grasso, S.; Zappala, M. Novel Peptidomimetics Containing a Vinyl Ester Moiety as Highly Potent and Selective Falcipain-2 Inhibitors. *J. Med. Chem.* **2009**, *52*, 2157. (e) Mendels, J.; Wasserman, T. W.; Michals, T. J.; Fine, E. W. Halazepam in the Management of Acute Alcohol Withdrawal Syndrome. *J. Clin. Psych.* **1985**, *46*, 172. (f) Dolly, F. R.; Block, A. J. Effect of Flurazepam on Sleep-Disordered Breathing and Nocturnal Oxygen Desaturation in Asymptomatic Subjects. *Am. J. Med.* **1982**, *73*, 239. (g) Walsgrove, T. C.; Powell, L.; Wells, A. A Practical and Robust Process to Produce SB-214857, Lotrafiban, ((2*S*)-7-(4,4′-Bipiperidinylcarbonyl)-2,3,4,5-Tetrahydro-4-Methyl-3-Oxo-1*H* −1, 4-Benzodiazepine-2-Acetic Acid) Utilising an Enzymic Resolution as the Final Step. *Org. Process Res. Dev.* **2002**, *6*, 488. (h) Pettersson, B.; Rydbeck, A.; Bergman, J. Synthesis of 1,4-Benzodiazepin-3-Ones and 1,5-Benzodiazocin-4-Ones by Addition of Grignard Reagents to Derivatives of o-Aminobenzonitrile. *Org. Biomol. Chem.* **2009**, *7*, 1184. (i) Mita, Y.; Dodo, K.; Noguchi-Yachide, T.; Hashimoto, Y.; Ishikawa, M. Structure−activity Relationship of Benzodiazepine Derivatives as LXXLL Peptide Mimetics That Inhibit the Interaction of Vitamin D Receptor with Coactivators. *Bioorg. Med. Chem.* **2013**, *21*, 993.

(14) (a) For synthesis of 1,4-benzodiazepinones: Spencer, J.; Rathman, P. R.; Chowdhry, B. Z. 1,4-Benzodiazepin-2-Ones in Medicinal Chemistry. *Future Med. Chem.* **2010**, *2*, 1441. (b) Mazimba, O.; Molefe, T. C. 1,5-Benzodiazepines: A Review Update. *Int. J. Chem. Studies* **2015**, *3*, 46. (c) Ma, D.; Xia, C. CuI-Catalyzed Coupling Reaction of β-Amino Acids or Esters with Aryl Halides at Temperature Lower Than That Employed in the Normal Ullmann Reaction. Facile Synthesis of SB-214857. *Org. Lett.* **2001**, *3*, 2583. (d) Rosenstroem, U.; Skoeld, C.; Plouffe, B.; Beaudry, H.; Lindeberg, G.; Botros, M.; Nyberg, F.; Wolf, G.; Karlen, A.; Gallo-Payet, N.; Hallberg, A. New Selective AT $_2$ Receptor Ligands Encompassing a γ-Turn Mimetic Replacing the Amino Acid Residues 4−5 of Angiotensin II Act as Agonists. *J. Med. Chem.* **2005**, *48*, 4009. (e) Clement, E. C.; Carlier, P. R. Simple Route to Tetrahydro-1,4-Benzodiazepin-3-Ones Bearing Diverse N1, N4, and C10 Functionalization. *Tetrahedron Lett.* **2005**, *46*, 3633. (f) Andrews, I. P.; Atkins, R. J.; Badham, N. F.; Bellingham, R. K.; Breen, G. F.; Carey, J. S.; Etridge, S. K.; Hayes, J. F.; Hussain, N.; Morgan, D. O.; Share, A. C.; Smith, S. A.; Walsgrove, T. C.; Wells, A. S. A New Synthesis of the GPIIb/IIIa Receptor Antagonist SB-214857-A. *Tetrahedron Lett.* **2001**, *42*, 4915. (g) D'Souza, A. M.; Spiccia, N.; Basutto, J.; Jokisz, P.; Wong, L.; Meyer, A. G.; Holmes, A. B.; White, J. M.; Ryan, J. H. 1,3-Dipolar Cycloaddition-Decarboxylation Reactions of an Azomethine Ylide with Isatoic Anhydrides: Formation of Novel Benzodiazepinones. *Org. Lett.* **2011**, *13*, 486.

(15) (a) For recent examples of one-pot synthesis of tetrahydro-1*H*-1,5-benzodiazepine-2-carboximides by the Ugi reaction, see: Shaabani, A.; Maleki, A.; Mofakham, H. Novel Multicomponent One-Pot Synthesis of Tetrahydro-1*H*−1,5-Benzodiazepine-2-Carboxamide Derivatives. *J. Comb. Chem.* **2008**, *10*, 595. (b) De Silva, R. A.; Santra, S.; Andreana, P. R. A Tandem One-Pot, Microwave-Assisted Synthesis of Regiochemically Differentiated 1,2,4,5-Tetrahydro-1,4-Benzodiazepin-3-Ones. *Org. Lett.* **2008**, *10*, 4541.

DOI: 10.1021/acs.joc.9b00448
J. Org. Chem. 2019, 84, 5927−5935

(16) (a) For reactions of azides see: Lang, S.; Murphy, J. A. Azide Rearrangements in electron Deficient Systems. *Chem. Soc. Rev.* **2006**, *35*, 146. (b) Minozzi, M.; Nanni, D.; Spagnolo, P. From Azides to Nitrogen-Centered Radicals: Applications of Azide Radical Chemistry to Organic Synthesis. *Chem. - Eur. J.* **2009**, *15*, 7830. (c) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. Radical Reduction of Aromatic Azides to Amines with Triethylsilane. *J. Org. Chem.* **2006**, *71*, 5822. (d) Kizil, M.; Patro, B.; Callaghan, O.; Murphy, J. A.; Hursthouse, M. B.; Hibbs, D. Tandem Radical Cyclizations on IodoarylAzides: Synthesis of the Core Tetracycle of *Aspidosperma* Alkaloids. *J. Org. Chem.* **1999**, *64*, 7856. (e) Lizos, D. E.; Murphy, J. A. Concise synthesis of (±)-horsfiline and (±)-coerulescine by tandemcyclisation of iodoaryl alkenyl azides. *Org. Biomol. Chem.* **2003**, *1*, 117. (f) Lang, S.; Kennedy, A. R.; Murphy, J. A.; Payne, A. H. Amination of Arenes throughElectron-Deficient Reaction Cascades of Aryl Epoxyazides. *Org. Lett.* **2003**, *5*, 3655. (g) Patro, B.; Murphy, J. A. Tandem Radical Cyclizations withIodoarylAzides: Formal Total Synthesisof (±)-Aspidospermidine. *Org. Lett.* **2000**, *2*, 3599.

(17) (a) For [3 + 2] cycloaddition reactions of azomethine ylides and maleimides, see: Zhang, X.; Zhang, W. PASE Synthesis of pyrrolidine-containing heterocycles through [3 + 2]cycloaddition-initiated reactions. *Curr. Opin. Green Sustainable Chem.* **2018**, *11*, 65. (b) Zhang, W. 1,3-Dipolar Cycloaddition-Based Synthesis of Diverse Heterocyclic Scaffolds. *Chem. Lett.* **2013**, *42*, 676. (c) Muthengi, A.; Zhang, X.; Dhawan, G.; Zhang, W.; Corsini, F.; Zhang, W. Sequential (3 + 2) Cycloaddition and (5 + *n*) Annulation for Modular Synthesis of Dihydrobenzoxazines, Tetrahydrobenzoxazepines and Tetrahydrobenzoxazocines. *Green Chem.* **2018**, *20*, 3134. (d) Zhang, X.; Zhi, S.; Wang, W.; Liu, S.; Jasinski, J. P.; Zhang, W. A Pot-Economical and Diastereoselective Synthesis Involving Catalyst-Free Click Reaction for Fused-Triazolobenzodiazepines. *Green Chem.* **2016**, *18*, 2642. (e) Trunkfield, A. E.; Gurcha, S. S.; Besra, G. S.; Bugg, D. H. Inhibition of Escherichia coli glycosyltransferase MurG and Mycobacteriumtuberculosis Gal transferase by uridine-linked transition state mimics. *Bioorg. Med. Chem.* **2010**, *18*, 2651. (f) Kantorowski, E. J.; Kurt, M. J. Dipolar cycloadditions in solid-phase organic synthesis (SPOS). *Mol. Diversity* **1997**, *2*, 207. (g) Nájera, C.; Sansano, J. M. Azomethine ylides in Organic Synthesis. *Curr. Org. Chem.* **2003**, *7*, 1105. (h) Coldham, I.; Hufton, R. Intramolecular dipolar cycloaddition reactions of azomethine ylides. *Chem. Rev.* **2005**, *105*, 2765.

(18) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C. M.; Nagy, A.; Perry, D. A.; Stefaniak, M. Green Chemistry Tools to Influence a Medicinal Chemistry and Research Chemistry Based Organisation. *Green Chem.* **2008**, *10*, 31.

(19) Finkbeiner, P.; Nachtsheim, B. J. Iodine in Modern Oxidation Catalysis. *Synthesis* **2013**, *45*, 979.

(20) (a) For the synthesis of 2-azidobenzalehydes, see: Gribble, G. W.; Pelkey, E. T. Synthesis of 2-nitroindoles via the Sundbery Indole Synthesis. *Tetrahedron Lett.* **1997**, *38*, 5603. (b) Lee, C. H.; Song, Y. S.; Cho, H. I.; Yang, J. W.; Lee, K.-J. Synthesis of 4*H*-Tetrazolo[1,5-*a*][1]benzazepines from the Baylis-Hillman Adducts of 2-Azidobenzaldehyde. *J. Heterocycl. Chem.* **2003**, *40*, 1103.

DOI: 10.1021/acs.joc.9b00448
J. Org. Chem. 2019, 84, 5927−5935