JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX
Article
pubs.acs.org/joc

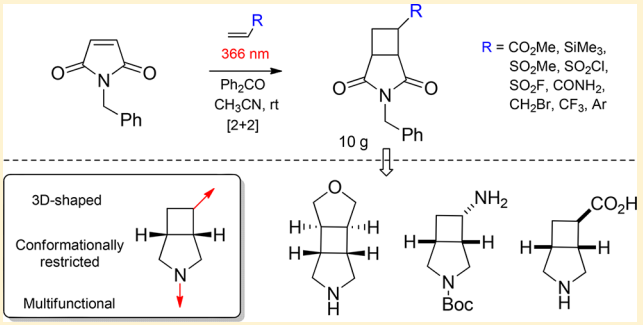
[2+2]-Photocycloaddition of *N*-Benzylmaleimide to Alkenes As an Approach to Functional 3-Azabicyclo[3.2.0]heptanes

Yevhen A. Skalenko,[‡,§] Tetiana V. Druzhenko,[‡,§] Aleksandr V. Denisenko,[†,‡] Maryna V. Samoilenko,[‡] Oleksandr P. Dacenko,[‡] Serhii A. Trofymchuk,[‡] Oleksandr O. Grygorenko,[†,‡] Andrey A. Tolmachev,[†,‡] and Pavel K. Mykhailiuk*[,†,‡]

[‡]Enamine Ltd., Chervonotkatska 78, Kyiv 02094, Ukraine (www.enamine.net, www.mykhailiukchem.org)
[§]Institute of High Technologies, Academician Glushkov av. 4G, Kyiv 03022, Ukraine
[†]Department of Chemistry, Taras Shevchenko National University of Kyiv, Volodymyrska 64, Kyiv 01601, Ukraine

Supporting Information

ABSTRACT: A one-step synthesis of functionalized 3-azabicyclo[3.2.0]heptanes by [2+2]-photochemical intermolecular cycloaddition of *N*-benzylmaleimide to alkenes was elaborated. The obtained compounds were easily transformed into the bi- and tricyclic analogues of piperidine, morpholine, piperazine, and GABA, which are advanced building blocks for drug discovery.



INTRODUCTION

Over the past decade, drug discovery significantly changed with the emerged terms scaffold hopping,[1] escape from flatland,[2] and conformational restriction,[3] which already gained great recognition in the scientific community. In this context, medicinal chemists in pharmaceutical companies use more and more toward saturated mono- and bicyclic building blocks with a high fraction of Fsp^3-carbon atoms.[4,5]

At the beginning of this century, bicyclic pyrrolidines were introduced as conformationally restricted surrogates for the common pyrrolidines and piperidines. This concept was already validated by several bioactive compounds currently under clinical investigation according to the ChEMBL database (Figure 1b).[6] However, compared to the popular compounds in medicinal chemistry, 3-azabicyclo[3.1.0]hexanes (**A**) and 3-azabicyclo[3.3.0]-octanes (**C**) (Figure 1a), 3-azabicyclo[3.2.0]heptanes (**B**) remain somewhat in the shadow. We presume that the main reason is the lack of the practical synthetic approaches to 3-azabicyclo[3.2.0]-heptanes (**B**) from inexpensive starting materials.

Two main approaches to 3-azabicyclo[3.2.0]heptanes were described in the literature: intramolecular[7−9] and intermolecular cyclizations.[10−13] The intramolecular approach usually gives products in high yields due to the preorganization of the conformation of the corresponding substrates. In particular, Bach and coworkers reported on the photochemical [2+2]-intramolecular cyclizations of *N*-substituted bis-allylamines,[7a−c] while Yonn and colleagues performed this reaction under the photoredox catalysis conditions (Scheme 1a).[8a−c] Also, last year, we developed a photochemical intramolecular [2+2]-cyclization

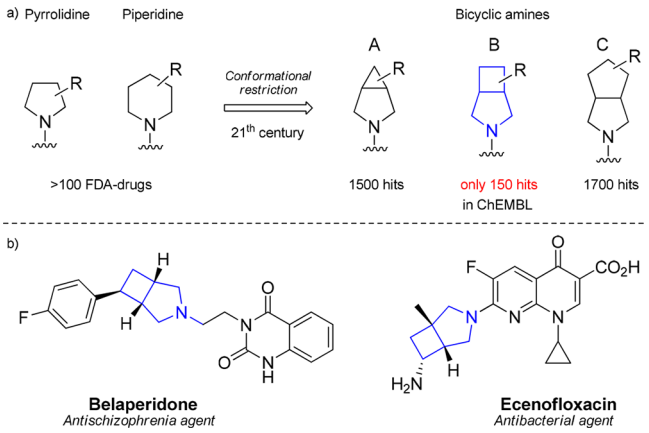


Figure 1. (a) Bioactive bicyclic motifs and the number of the corresponding hits in the ChEMBL database. (b) Representative bioactive compounds.

of allylamides of cinnamic acids. In 2010, Kanger and his team developed a three-component cascade reaction to polysubstituted azabicyclo[3.2.0]heptanes (Scheme 1b).[9]

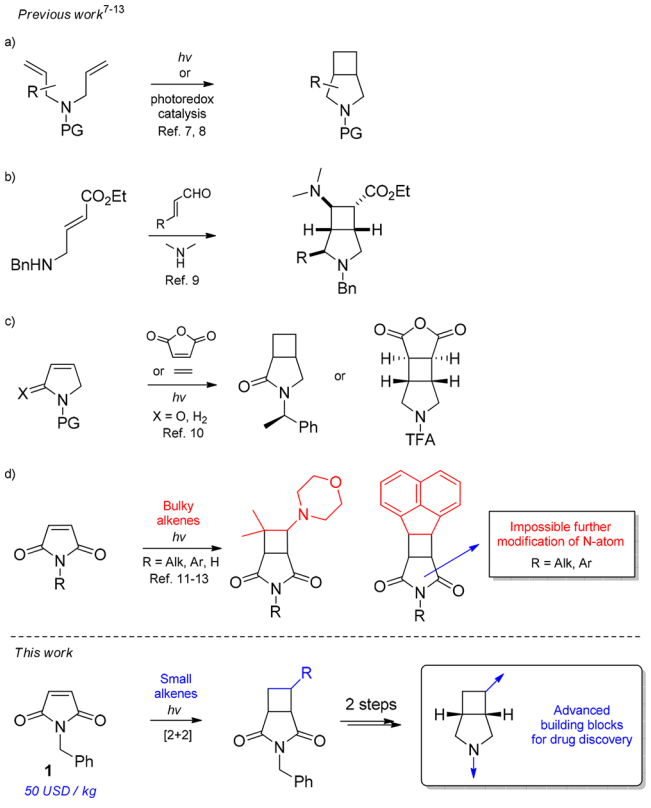
An intermolecular approach to 3-azabicyclo[3.2.0]heptanes usually commences from the commercially available substrates.[10−13] In 2013, Wanner et al. developed the intermolecular [2+2]-photochemical cycloaddition between *N*-trifluoroacetyl 2,5-dihydropyrrole and maleic anhydride (Scheme 1c).[10a]

Received: January 10, 2018

© XXXX American Chemical Society

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. State of the Art



Aitken and colleagues performed the [2+2]-photochemical reaction between *N*-substituted 1,5-dihydropyrrol-2-one and ethylene (Scheme 1c).[10b,c] Many research groups were involved in the development of the intermolecular [2+2]-photochemical reactions of maleimides.[11−13] Most of these transformations, however, were performed on maleimides with *N*-Alk or *N*-Ar substitutents, making the further derivatization of the *N*-atom impossible (Scheme 1d).[11] None-substituted *NH*-maleimides were also shown to participate in [2+2]-cycloadditions by Booker-Milburn, Aitken, and others.[12] In the reaction with simple aliphatic alkenes, however, practical separation of the formed *cis*- and *trans*-isomers was in some cases problematic.

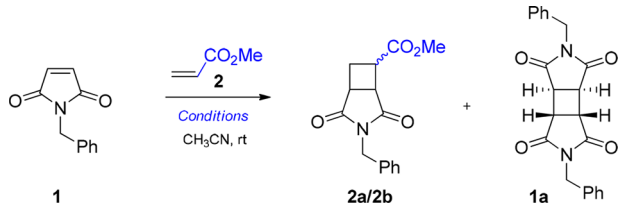
There are only several reports in the literature on the photochemical [2+2]-cycloadditions of *N*-benzyl maleimide (**1**).[13] In 1974, Rynbrandt showed its high potential by reacting maleimide **1** with enamines (Scheme 1).[12a] Subsequently, amide groups were reduced with $LiAlH_4$, followed by a cleavage of the *N*-Bn group by hydrogenolysis. Remarkably, this approach was not extended into other simple alkenes. In 2015, chemists from Roche published a patent on the photochemical dimerization of maleimide **1** into a tricyclic piperazine mimic.[12b] Apart from that, the huge potential of compound **1**(50 USD/kg) for the preparation of the appropriately *N*-protected 3-azabicyclo[3.2.0]heptanes for drug discovery remains not elaborated.[13]

In this context, herein, we have elaborated the [2+2]-photochemical cycloaddition of *N*-benzylmaleimide (**1**) with various simple alkenes toward the preparation of building blocks for drug discovery. In particular, the conformationally restricted bi- and tricyclic analogues of piperidine, morpholine, and GABA were synthesized. The photochemical step was performed in up to a 10 g scale.

RESULTS AND DISCUSSION

Optimization Studies. We started our investigation from the test reaction of maleimide **1** with the simple monosubstituted alkene−methyl acrylate (**2**) (Table 1). All of our attempts to perform [2+2]-photocyclization at 412 and 366 nm failed.[14,15] Only the starting material was recovered from the reaction mixture. At 310 nm, substrate **1** underwent the [2+2]-photocyclization with **2**; however, after 24 h, the conversion reached only ca. 20%. At 255 nm, a formation of the complex mixture was observed (Table 1, entries 1−4). After some experimentation, we found that the addition of benzophenone as a sensitizer, which transfers a triplet excited state to a substrate, significantly facilitated the reaction, and the mixture **2a**/**2b** was formed with no starting material remaining. Furthermore, we reduced the amount of sensitizer to 0.1 equiv, without any significant effect on the reaction outcome (Table 1, entries 5−7).

Table 1. Optimization Studies



entry	λ_{max} (nm)	concentration of **1** (mM)	Ph_2CO (equiv)	**2** (equiv)	conversion[a] (%)
1	412	5		10	0
2	366	5		10	0
3	310	5		10	20
4	255	5		10	compl mix
5	366	5	1.0	10	100
6	366	5	0.5	10	100
7	366	5	0.1	10	100
8	366	5	0.1	5	100
9	366	5	0.1	2	100
10	366	5	0.1	1	100
11	366	10	0.1	1	100
12	366	20	0.1	1	100
13	366	30	0.1	1	100
14	366	50	0.1	1	100
15	366	75	0.1	1	100 (10% of **1a**)

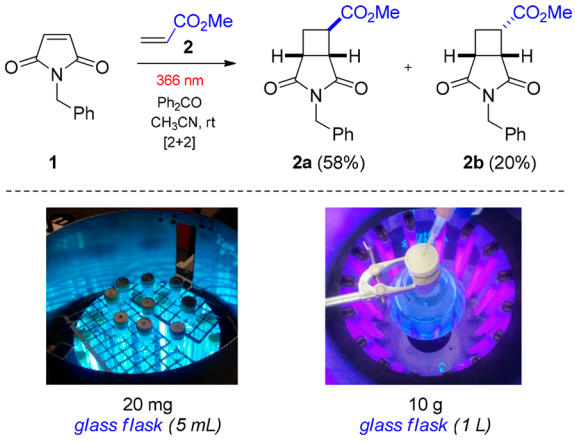
[a]Conversion of the reaction was determined by ^1H NMR of the reaction mixture after 24 h.

It is important to note that, for the potential scale up, we also wanted to minimize the excess of alkene **2** and to maximally increase the concentration of substrate **1**. In fact, an initially used 10 molar excess of alkene **2** was reduced to an equimolar mixture of compounds **1** and **2** (Table 1, entries 7−10). In addition, the concentration of alkene **2** was successfully increased up to 50 mM. At higher concentrations, the formation of dimer **1a** was observed (Table 1, entries 10−15).

Scale Up. With the optimized procedure in hand, we studied the reaction at different scales. The synthesis on a milligram scale was carried out at 5 mM in 5 mL glass vials. The reaction at a 10 g scale was also efficiently performed at a high concentration (50 mM) of **1** using an equimolar mixture of compounds **1** and **2** in a common 1 L glass flask (Scheme 2).[16] Technically, the reaction was very easy to run: a solution of maleimide **1**, alkene **2**, and benzophenone in degassed acetonitrile was

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. Scaled Up Synthesis of Compounds 2a/2b



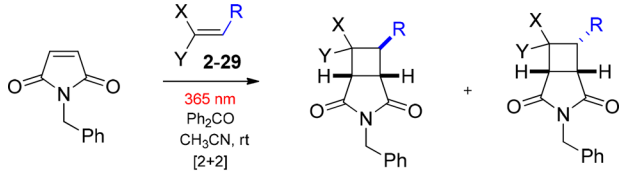
irradiated at room temperature for 48 h. The solvent was evaporated under reduced pressure, and the residue was purified on silica gel to obtain the individual stereoisomers **2a** and **2b**.

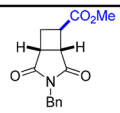
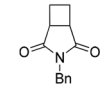
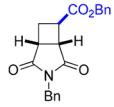
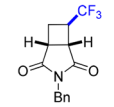
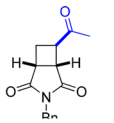
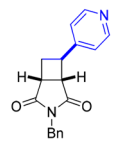
Reaction Scope. Having an established procedure, we next studied the scope of alkenes. In every experiment, an equimolar mixture of **1** and alkene was used. The [2+2]-photocycloaddition of **1** was successfully performed with nonactivated (**3**, **6**, **23**, **24**, **26**, **27**), push–pull (**21**, **29**), electron-poor (**1**, **2**, **4**, **5**, **7**, **8**, **11**–**14**, **16**–**19**, **22**, **28**), and electron-rich (**15**, **20**, **25**) substrates (Table 2). Among them were monosubstituted (**2**, **4**–**15**), 1,1-disubstituted (**16**–**21**), 1,2-disubstituted (**22**–**28**), and 1,1,2-trisubstituted (**29**) alkenes. Predominantly, the major *trans*-cyclobutane isomers were formed. In some cases, however, the minor *cis*-isomers were also isolated by standard column chromatography on SiO_2. The combined yield of products was mainly within 50–90%; however, with electron-withdrawing alkenes **8**, **11**–**13**, and **28**, the yield was poor. With 1 equiv of alkene **13**, an extensive dimerization of maleimide **1** into product **1a** was observed. Therefore, we increased an excess of alkene to 10 times, and the desired product **13a** was isolated in 29% yield. The reaction of alkene **26** at 366 nm led to a significant Paterno–Buchi transformation with benzophenone. The reaction was performed at 310 nm to obtain product **26a** in 47% yield.

The structure of compounds **2a**, **4a**, **5a**, **5b**, **6a**, **7a**, **8a**, **12a**, **14b**, **16a**, **16b**, **19a**, **21a**, **23a-1**, and **23a-2** was confirmed by 1D (NOE) and 2D NMR techniques (COSY, NOESY). The structure of compound **18a** was assigned using the HOESY technique based on H–F correlations. Products of [2+2]-photocycloaddition of 1-substituted alkenes can be also quickly empirically assigned by ^{1}H NMR; the signals of the benzylic protons in *trans*-isomers and *cis*-isomers were singlets and two doublets, respectively (Figure 2). The structure of compounds **6a**, **12a**, **17a**, **23a-1**, **23a-2**, and **24a** was additionally confirmed by X-ray crystallography (Figure 3).

Synthesis of Building Blocks. Quite recently, we showed that 3-azabicyclo[3.2.0]heptanes might be considered as conformationally restricted bicyclic analogues of piperidine.[7h] Therefore, we next wanted to show that the obtained herein compounds could easily be transformed into the appropriate building blocks for the direct use in drug discovery projects. In particular, the reduction of the amide groups in **3a** with $LiAlH_4$, followed by a cleavage of *N*-Bn group via hydrogenolysis over Pd/C accomplished the synthesis of the bicyclic piperidine analogue **30** (Scheme 3).

Table 2. Scope of the Reaction[f]



	Alkene	Product (%)[a,b]
2		 **2a** (58%) **2b** (20%)
3		 **3a** (80%)
4		 **4a** (46%) **4b** (15%)
5		 **5a** (47%) **5b** (11%)
6		 **6a** (40%, *X-Ray*) **6b** (16%)
7		 **7a** (48%)
8		 **8a** (5%)
9		 **9a** (71%) **9b** (21%)
10		 **10a** (62%) **10b** (16%)
11		 **11a** (25%)
12		 **12a** (27%, *X-Ray*)
13		 **13a** (29%)[c]
14		 **14a** (55%) **14b** (15%)

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX–XXX

Table 2. continued

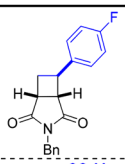
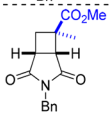
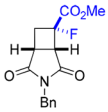
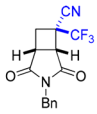
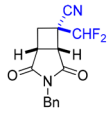
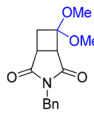
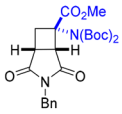
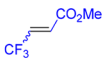
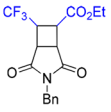
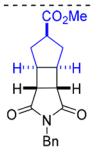
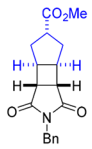
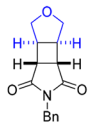
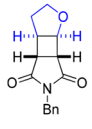
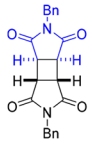
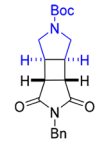
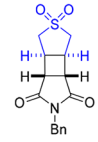
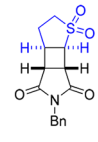
Alkene		Product (%)[a,b]	
15			**15a** (58%) **15b** (15%)
16			**16a** (28%) **16b** (12%)
17			**17a** (26%, *X-Ray*) **17b** (6%)
18			**18a** (42%)
19			**19a** (35%)
20			**20a** (62%)
21			**21a** (21%)
22			**22ab** (67%)[d]
23			**23a-1** (53%, *X-Ray*)
			**23a-2** (17%, *X-Ray*)
24			**24a** (71%, *X-Ray*)
25			**25a** (10%)
1			**1a** (84%)

Table 2. continued

Alkene		Product (%)[a,b]	
26			**26a** (47%)[c]
27			**27a** (63%)
28			**28a** (27%)
29			**29a** (44%)

[a]Structure of only main products (**a**) is shown. [b]Isolated yields. [c]10 times excess of alkene **13a**. [d]Mixture of stereoisomers. [e]The reaction was performed at 310 nm. [f]Reaction conditions: CH_3CN, **1**/alkene = 1:1, rt, 366 nm, 24 h.

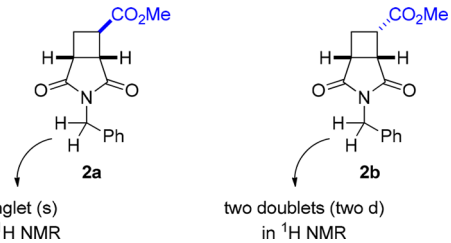
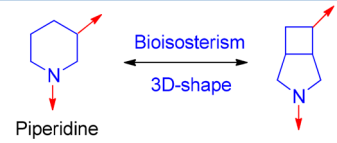


Figure 2. Signals of benzylic protons of compounds **2a** and **2b** in ^{1}H NMR.



Similar transformations of compound **9a/b** gave amino alcohol **31**. The standard *N*-Boc protection and the subsequent oxidation of the alcohol group with the Dess–Martin reagent provided the *N*-protected amino ketone **32**. Finally, the reaction with NH_2OH followed by reduction of the intermediate oxime with the Ni Raney alloy accomplished the synthesis of *N*-Boc diamine **33** as an inseparable mixture (4:1) of diastereomers. Alternatively, the monoprotected *N*-Bn diamine **34** was prepared in one step by reduction of compound **5a** with $LiAlH_4$ in 87% isolated yield (Scheme 4).

The synthesis of bicyclic amino alcohol **36a** was realized by an extensive reaction of amide and ester functions in compound **2a** with $LiAlH_4$ (**35a**), followed by a hydrogenolysis of *N*-Bn bond with Pd/C as a catalyst (Scheme 5). The synthesis of an isomeric compound **36b** was performed analogously from compound **2b** via the intermediate **35b**.

It is worth mentioning that the reduction of the amide group in **15a** with $LiAlH_4$, followed by a cleavage of the *N*-Bn group by hydrogenolysis over Pd/C gave a racemic amine **37**,

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

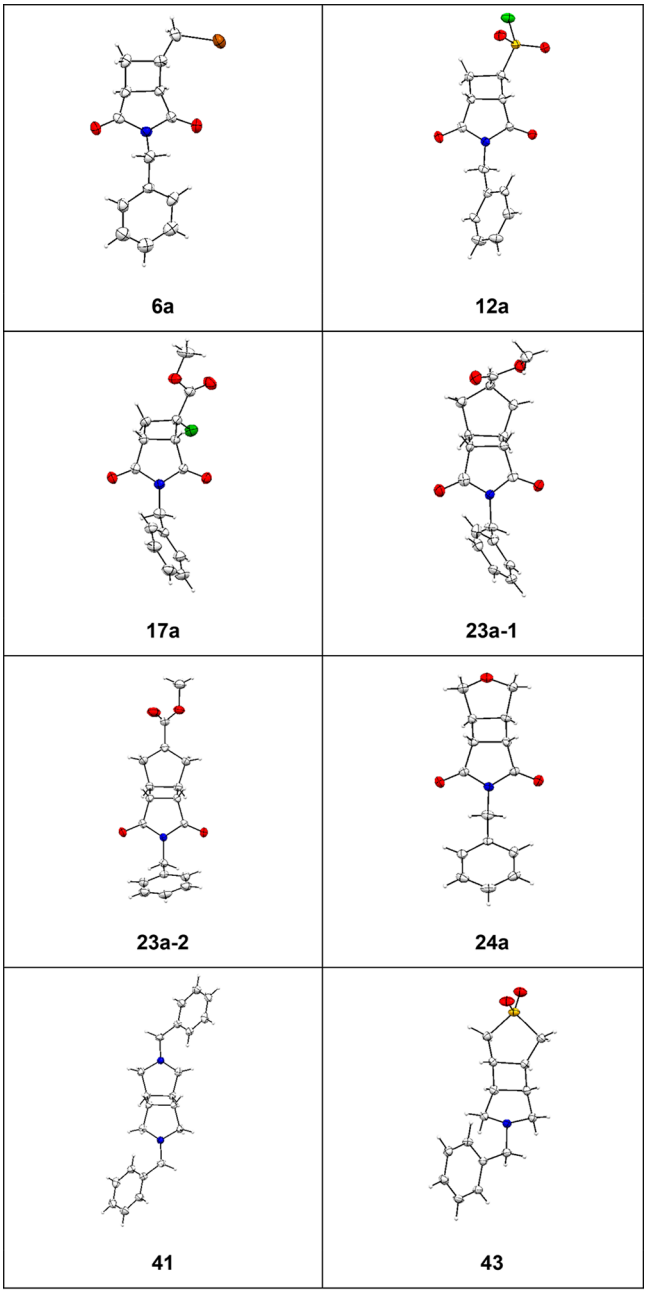
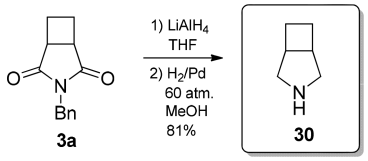


Figure 3. X-ray crystal structure of compounds **6a**, **12a**, **17a**, **23a-1**, **23a-2**, **24a**, **41**, and **43**.

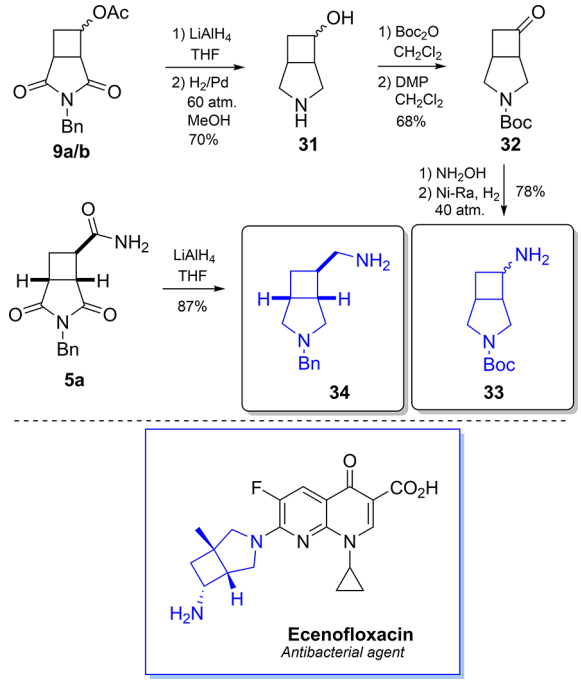
Scheme 3. Synthesis of Bicyclic Amine 30



the component of an antischizophrenia agent, belaperidone (Scheme 6).

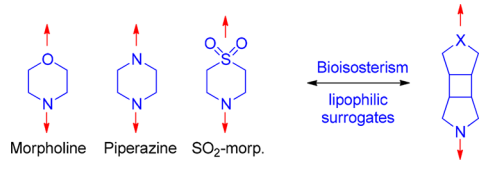
All attempts to replace the hydroxyl group with a fluorine atom in compounds **35a** and **35b** with DAST or Morph-DAST afforded only the complex mixtures. Surprisingly, treatment of both **35a** and **35b** with SF_4/HF selectively provided amine **38** as a sole stereoisomer in 75−78% yield. Presumably, the both

Scheme 4. Synthesis of Bicyclic Diamines 33 and 34



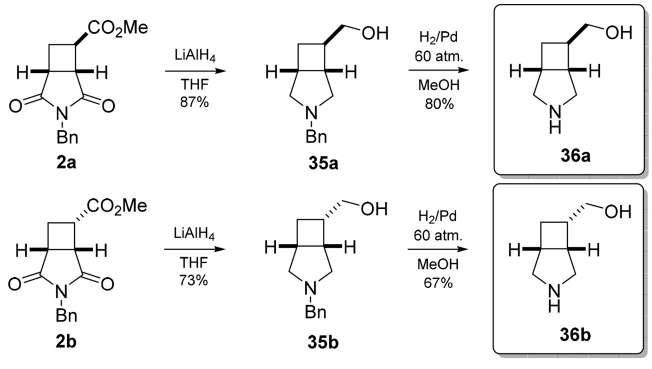
transformations proceeded via the formation of the intermediate carbocation **A** (Scheme 7).

Also, we envisioned that the tricyclic core in compounds **1a** and **23a−28a** might serve as an elongated lipophilic analogue of morpholine, piperazine, and SO_2-morpholine. In this context, we undertook the synthesis of the corresponding building blocks **40**, **42**, and **44** (Scheme 8).



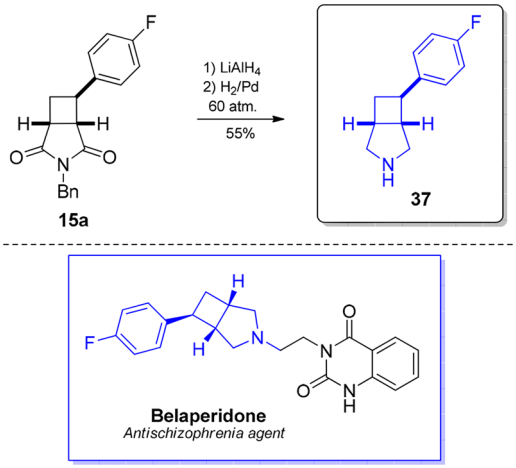
In particular, the reduction of amide groups in **24a** with $LiAlH_4$, followed by a cleavage of the *N*-Bn group by hydrogenolysis over Pd/C as a catalyst gave the tricyclic morpholine analogue **40**. The synthesis of homologues of piperazine (**42**) and SO_2-morpholine (**44**) was carried out alternatively from compounds **1a** and **27a**, correspondingly. The structure of intermediates **41** and **43** was confirmed by X-ray crystallography (Figure 3).

Scheme 5. Synthesis of Bicyclic Aminoalcohols 36a and 36b

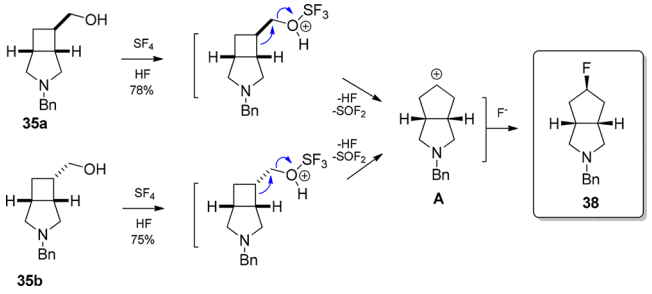


DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

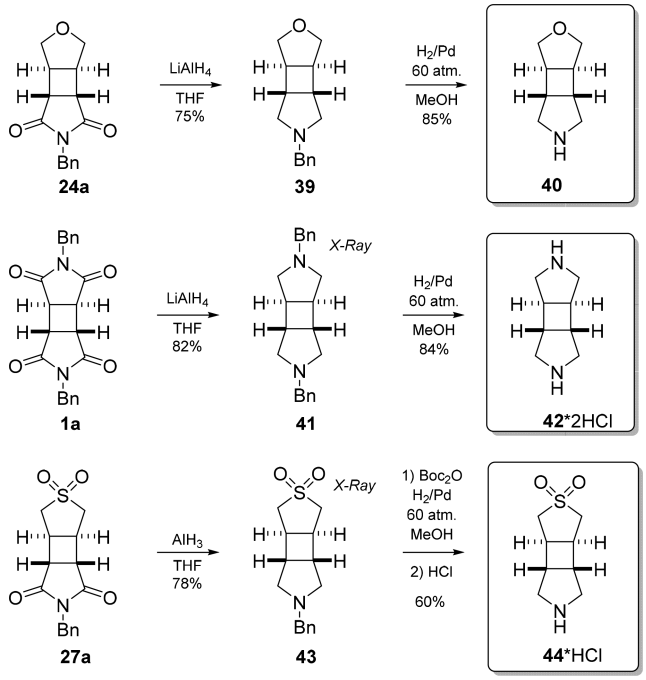
Scheme 6. Synthesis of Bicyclic Amine 37, a Key Component of Belaperidone



Scheme 7. Formation of an Unexpected Fluorinated Amine 38

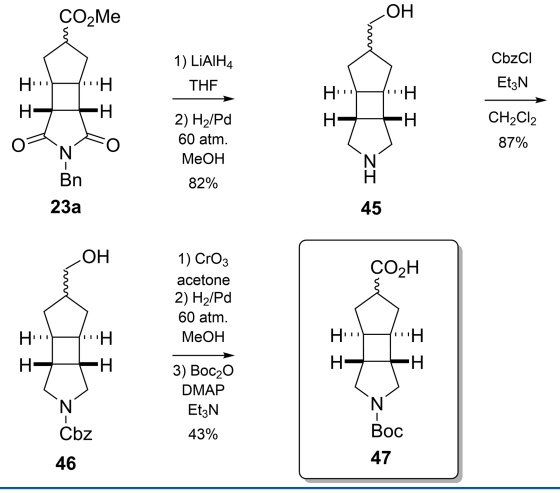


Scheme 8. Synthesis of Tricyclic Amines 40, 42, and 44



The synthesis of the tricyclic analogue **47** of GABA was performed from compound **23a** (Scheme 9). Extensive reduction of the amide and ester functions in **23a** with $LiAlH_4$ (**45**) followed by treatment with CbzCl gave *N*-protected alcohol (**46**). Oxidation of the alcohol group in **46** with CrO_3 and cleavage of the *N*-Cbz moiety followed by *N*-Boc protection

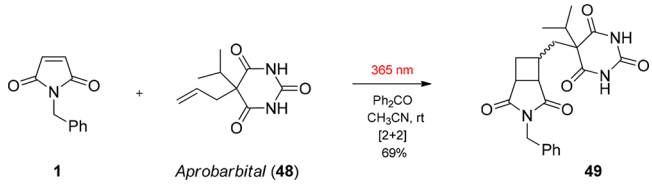
Scheme 9. Synthesis of *N*-Boc Protected Amino Acid 47



furnished the preparation of amino acid **47** as a mixture (1:1) of isomers.

Finally, to show the high potential of this strategy, we performed the photochemical [2+2]-photocycloaddition of maleimide **1** to the sedative drug aprobarbital (**48**). The corresponding product **49** was obtained after the column chromatography in 69% yield as an 70:30 inseparable mixture of stereoisomers (Scheme 10). Given that many FDA-approved

Scheme 10. Synthesis of Cyclobutane 49



drugs contain the double C=C bond,[6] we believe that this strategy could also be used for the late-stage modification of drugs.[17]

3D-Vector Analysis. To compare the three-dimensional structure of the bi- and tricyclic ring systems obtained in this work with that of the corresponding monocyclic scaffolds (piperidine, piperazine, morpholine, and thiomorpholine 1,1-dioxide), we used the exit vector plots (EVP) tool.[18] The key feature of this method is a simulation of the substituents attached to the disubstituted scaffold by so-called exit vectors (n_1 and n_2, Figure 4). To describe a relative spatial arrangement

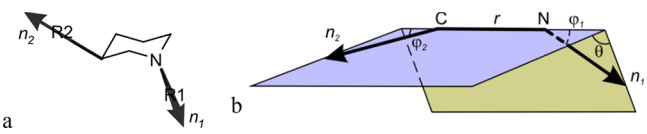
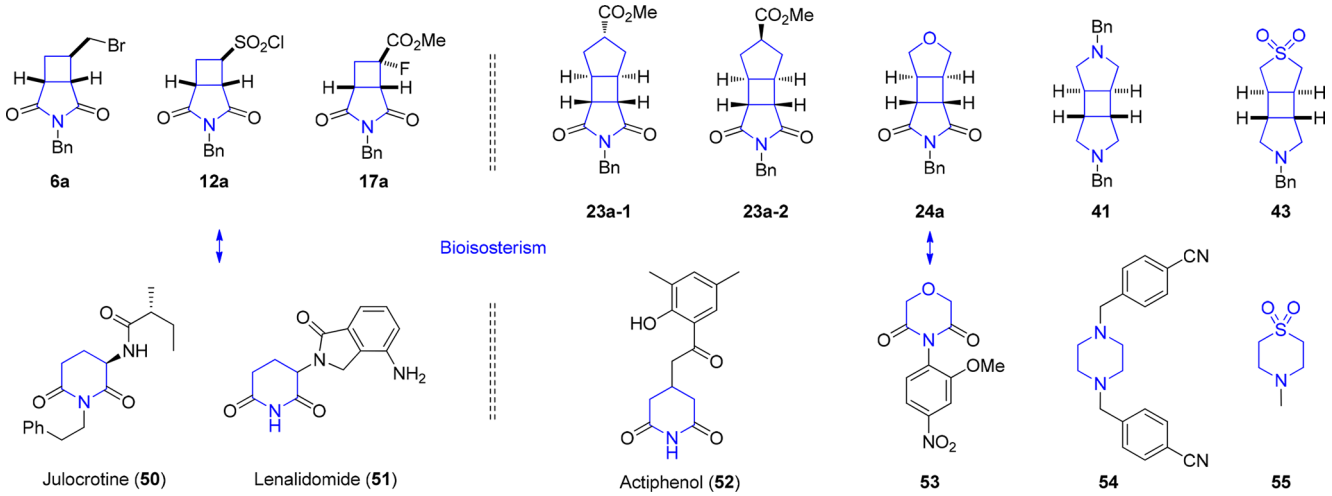


Figure 4. (a) Definition of vectors n_1 and n_2 (1,3-disubstituted piperidine scaffold used as an example). (b) Definition of geometric parameters r, φ_1, φ_2, and θ.

of two exit vectors, four geometric parameters are necessary. These can be the distance between the attachment points **C** and **N** (r), two plane angles, φ_1 (between vectors n_1 and **CN**) and φ_2 (between n_2 and **NC**), and dihedral angle, θ (defined by vectors n_1, **CN** and n_2). When these parameters are shown in $r - \theta$, $\theta - \varphi_1/\varphi_2$, and $\varphi_1 - \varphi_2$ coordinates, exit vector plots (EVP) are obtained. While the r parameter can be considered

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 3. Values of Geometric Parameters r, φ_1, φ_2, and θ for 3-Azabicyclo[3.2.0]heptanes and Piperidine Derivatives



compound	r (Å)	φ_1 (°)	φ_2 (°)	$\lvert\theta\rvert$ (°)[a]	ref
6a	3.221	32.2	23.7	108.8	this work
14a	3.301	28.8	29.1	132.8	this work
17a	3.308	28.3	26.3	125.9	this work
23a-1 (I)[b]	5.147	9.6	4.8	28.2	this work
23a-1 (II)[b]	5.143	10.7	1.9	26.2	this work
23a-2	5.176	14.1	89.3	154.5	this work
24a	5.059	14.9	48.7	166.4	this work
41	4.916	45.4	45.4	180	this work
43	5.464	56.1	21.2	7.4	this work
50	2.492	30.3	49.8	35.2	19
51	2.458	31.2	40.9	39.1	20
52	2.778	14.3	16.9	173	21
53	2.728	16.1	39.8	1.8	22
54	2.873	25	25	180	23
55	3.105	28.7	18.2	178.8	24

[a]Since the signs of θ angle are opposite for different enantiomers, only absolute values of θ are considered. [b]Two different molecules in the crystal cell.

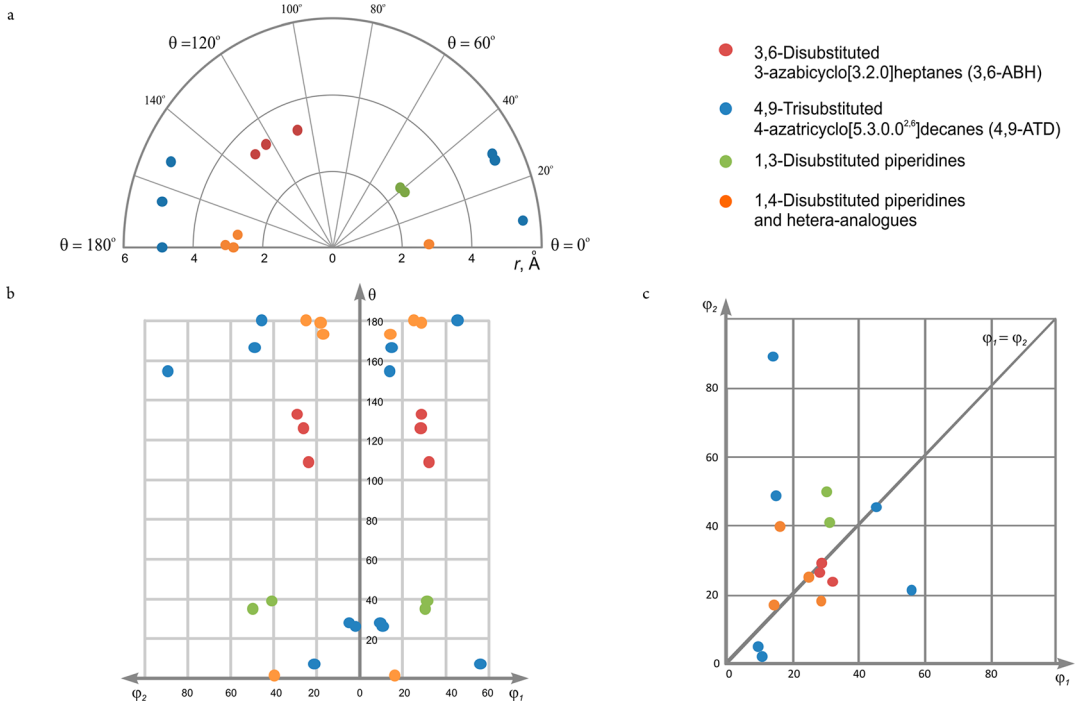


Figure 5. 3,6-Disubstituted 3-azabicyclo[3.2.0]heptanes, 4,9-disubstituted 4-azatricyclo[5.3.0.0^{2,6}]decanes, piperidine derivatives, and their heterocyclic analogues shown in the (a) $r - \theta$ plot (polar coordinates), (b) $\theta - \varphi_1/\varphi_2$ plot, and (c) $\varphi_1 - \varphi_2$ plot.

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

as a measure of the size of a scaffold, the angular parameters correlate with the scaffold's three-dimensionality (as defined by the exit vectors). In particular, for the linear geometry, $\varphi_1/\varphi_2 = 0°$; flat scaffolds have $\theta = 0°$ or 180°.

The values of r, φ_1, φ_2, and θ parameters were calculated from the X-ray data for compounds **6a**, **12a**, **17a**, **23a-1**, **23a-2**, **24a**, **41**, and **43** from this work, as well as derivatives **50**−**55**, which are either close structural analogues thereof or known biologically active compounds[19−24] (Table 3). The exit vector plot analysis (Figure 5) showed that 3,6-disubstituted 3-azabicyclo[3.2.0]heptane-2,4-diones (3,6-ABH, compounds **6a**, **12a**, and **17a**) are slightly larger (r = 3.22−3.31 Å) than both 1,3- and 1,4-disubstituted piperidine derivatives (r = 2.46−2.78 Å). Although the values of φ_1 and (to a lesser extent) φ_2 angles are similar for the 3,6-ABH ($\varphi_1/\varphi_2 \sim 30°$) and 1,3-disubstituted piperidine ($\varphi_1 \sim 30°$and $\varphi_2 \sim 45°$) scaffolds, the absolute values of the θ angle differ significantly. In fact, for the 3,6-ABH core ($|\theta| \sim 120°$), they are intermediate between those for the 1,3- and 1,4-disubstituted piperidines ($|\theta| \sim 40°$ and 180°, respectively). Therefore, while being similar in overall shape, the 3,6-disubstituted 3-azabicyclo[3.2.0]heptane-2,4-dione scaffold occupies a slightly different area of the chemical space as compared to the corresponding piperidine derivatives.

As expected, 4,9-disubstituted 4-azatricyclo[5.3.0.0^{2,6}]decane cores (4,9-ATD, compounds **23a-1**, **23a-2**, **24a**, **41**, and **43**) are significantly (by ca. 2.3 Å) larger than 1,4-disubstituted piperidine or the corresponding heterocyclic analogues. Moreover, while for the monocyclic prototypes, the molecular geometry (as defined by the exit vectors) can be described as flattened ($|\theta|$ is close to 0° or 180°) and even nearly linear (small values of φ_1/φ_2, ca. 20°), the 4,9-ATD-derived scaffolds show more 3D diversity. (This is especially remarkable in the angular EVPs, Figure 5b,c.) In particular, whereas the exit vector disposition in the molecule of **23a-1** is even more linear than for the 1,4-disubstituted piperidines (φ_1/φ_2 = 1.8−10.7°), **23a-2** is the most three-dimensional and dissymmetric among the 4,9-ATD derivatives studied (φ_1 = 14.1°, φ_2 = 89.3°). Meanwhile, the $|\theta|$ values (154.5° for **23a-1**, 26.2−28.2° for **23a-2**) show some distortion of the tricyclic ring system. In our opinion, tricyclic compounds like **23a-1** and **23a-2** can be considered as analogues for 1,4-disubstituted piperidines with an equatorial and axial position of the substituent at the C-4 atom, respectively. 9-Hetera-substituted 4,9-ATD scaffolds (compounds **24a**, **41**, and **43**) also show more three-dimensionality as compared to the corresponding piperazine, SO_2-morpholine, and morpholine derivatives (larger φ_1/φ_2 values), but unlike for **23a**, this is not achieved through the scaffold distortion. ($|\theta|$ does not go far from 0° or 180°.)

CONCLUSIONS

In summary, in this work, we have elaborated an one-step synthesis of 3-azabicyclo[3.2.0]-heptanes by [2+2]-photochemical cyclization of *N*-Bn maleimide (**1**) with alkenes. The photochemical step was performed in up to a 10 g scale. The obtained compounds were easily transformed into bi- and tricyclic analogues of piperidine, morpholine, piperazine, and GABA, which are advanced building blocks ready for the direct use in drug discovery.

The ecenofloxacin and belaperidone examples have demonstrated the potential of 3-azabicyclo[3.2.0]-heptanes in drug discovery. However, the lack of a practical synthetic approach to them from cheap starting materials has constrained their wide use. Taking into account the high efficiency, simplicity, and low costs of our method, we believe that scientists will soon use it, and 3-azabicyclo[3.2.0]-heptanes will soon become very popular in medicinal chemistry.

EXPERIMENTAL SECTION

General Methods. All starting materials were taken at enamine. Column chromatography was performed using Kieselgel Merck 60 (230−400 mesh) as the stationary phase. Reverse phase column chromatography was performed using C_{18}-modified silica gel as a stationary phase, column: SunFire Waters, 5 μm, 19 mm × 100 mm. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded at 500 or 400 MHz, 376 MHz, and 125 or 101 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded on an LC-MS instrument with chemical ionization (CI). LC-MS data were acquired on an Agilent 1200 HPLC system equipped with DAD/ELSD/LCMS-6120 diodematrix and mass-selective detector, column: Poroshell 120 SBC18, 4.6 mm × 30 mm. Eluent, A, acetonitrile−water with 0.1% of FA (99:1); B, water with 0.1% of FA.

For solid and liquid alkenes (**2**, **4**−**6**, **8**−**29**), the 0.05 M solution of **1** (1.0 equiv), the alkene (1.0 equiv), and benzophenone (0.1 equiv) in dry acetonitrile was degassed by bubbling argon for 15 min. No significant evaporation even of volatile alkenes was detected during the bubbling of argon. In case of gaseous alkenes (**3**, **7**), the already degassed solution of **1** (1.0 equiv) and benzophenone (0.1 equiv) was treated with an excess of alkene. The reaction vessel was closed and irradiated with 366 nm UV light. After the accomplishment (indicated by ^{1}H NMR, typical reaction time 24−72 h), the reaction mixture was concentrated under reduced pressure and purified via column chromatography to give the desired product.

(3a*R*,3b*R*,6a*S*,6b*S*)-2,5-Dibenzyldihydrocyclobuta[1,2-*c*:3,4-*c*′]-dipyrrole-1,3,4,6(2*H*,3a*H*,3b*H*,5*H*)-tetraone (1a). The product was filtered from the reaction mixture and washed with acetonitrile to give the product as a white solid, mp above 270 °C; 84% yield (15.7 g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.29 (m, Ph, 10H), 4.63 (s, CH_2Ph, 4H), 3.45 (s, C*H*, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 176.4 (s, C=O), 136.4 (s, C, Ph), 129.1 (s, CH, Ph), 128.1 (s, CH, Ph), 42.7 (s, CH_2Ph), 41.7 (s, CH). LCMS (m/z): 375 (M + H$^+$). Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.27; H, 4.62; N, 7.67.

(1S*,5S*,6S*)-Methyl 3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]-heptane-6-carboxylate (2a). The solution of **1** (10.0 g, 53 mmol, 1.0 equiv), methyl acrylate (4.6 g, 53 mmol, 1.0 equiv), and benzophenone (0.96 g, 5.3 mmol, 0.1 equiv) in dry acetonitrile (1 L) was degassed by the bubbling of argon for 15 min. The reaction flask was closed by a septum and irradiated with 366 nm UV light for 48 h. The reaction mixture was filtered or concentrated under reduced pressure and purified via column chromatography to give the desired products **2a** and **2b**. White solid, mp 71−72 °C; 58% yield (8.4 g). Purified via column chromatography (hexanes/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, Ph, 5H), 4.67 (s, CH_2Ph, 2H), 3.73 (s, OCH_3, 3H), 3.53 (t, C*H*, ^3J(H,H) = 5.4 Hz, 1H), 3.28 (m, C*H*, 1H), 3.12 (m, C*H*, 1H), 2.80 (m, C*H*H, 1H), 2.38 (m, CH*H*, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.9 (s, C=O), 176.6 (s, C=O), 172.6 (s, C=O), 135.3 (s, C, Ph), 128.4 (s, CH, Ph), 128.3 (s, CH, Ph), 127.7 (s, CH, Ph), 52.2 (s, OCH_3), 42.6 (s, CH_2Ph), 41.0 (s, CH), 38.5 (s, CH), 35.8 (s, CH), 26.0 (s, CH_2). LCMS (m/z): 274 (M + H$^+$). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 66.21; H, 5.36; N, 5.38.

(1S*,5S*,6R*)-Methyl 3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]-heptane-6-carboxylate (2b). White solid, mp 82−83 °C; 20% yield (2.9 g). Purified via column chromatography (hexanes/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, Ph, 5H), 4.68 (d, C*H*HPh, ^2J(H,H) = 14.2 Hz, 1H), 4.64 (d, CH*H*Ph, ^2J(H,H) = 14.2 Hz, 1H), 3.59 (q, C*H*, ^3J(H,H) = 9.9 Hz, 1H), 3.52 (s, OCH_3, 3H), 3.48 (m, C*H*, 1H), 3.22 (m, C*H*, 1H), 2.69 (m, C*H*H, 1H), 2.48 (m, CH*H*, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.2 (s, C=O), 176.0 (s, C=O), 171.4 (s, C=O), 135.7 (s, C, Ph), 128.9 (s, CH, Ph), 128.6 (s, CH, Ph), 127.9 (s, CH, Ph), 52.2 (s, OCH_3), 42.7 (s, CH_2Ph), 40.8 (s, CH), 37.2

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

(s, CH), 35.5 (s, CH), 25.5 (s, CH_2). LCMS (m/z): 274 ($M + H^+$). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 65.57; H, 5.81; N, 4.92.

3-Benzyl-3-azabicyclo[3.2.0]heptane-2,4-dione (3a). White solid, mp 134−135 °C; 80% yield (17.2 g). Purified via column chromatography (hexanes/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 5H), 4.70 (s, 2H), 3.27 (s, 2H), 2.64 (s, 2H), 2.12 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 179.5 (s), 136.0 (s), 128.7 (s), 128.6 (s), 127.9 (s), 42.4 (s), 38.4 (s), 22.9 (s). LCMS (m/z): 216 ($M + H^+$).

(1*S,5*S**,6*S**)-Benzyl 3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxylate (4a).** White solid, mp 64−65 °C; 46% yield (1.61 g). Purified via column chromatography twice (hexanes/EtOAc = 2:1, then 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 2 × Ph, 10H), 5.16 (s, OCH_2Ph, 2H), 4.68 (s, NCH_2Ph, 2H), 3.55 (dd, CHC*H*CON, ^3J(H,H) = 6.0, 5.1 Hz, 1H), 3.29 (m, CH_2C*H*CON, 1H), 3.16 (m, C*H*CO_2Bn, 1H), 2.79 (m, C*H*H, 1H), 2.38 (m, CH*H*, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 179.2 (s, CH_2CHCON), 177.8 (s, CHCHCON), 172.8 (s, CO_2Bn), 136.7 (s, *C*, Ph), 136.5 (s, *C*, Ph), 129.2 (s, *C*H, Ph), 129.1 (s, *C*H, Ph), 128.7 (s, *C*H, Ph), 128.6 (s, *C*H, Ph), 128.0 (s, *C*H, Ph), 66.91 (s, OCH_2Ph), 42.3 (s, NCH_2Ph), 41.9 (s, CHCHCON), 38.8 (s, C*H*CO_2Bn), 36.4 (s, CH_2C*H*CON), 25.8 (s, CH_2). LCMS (m/z): 350 ($M + H^+$). Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.45; H, 5.65; N, 3.76.

(1*S,5*S**,6*R**)-Benzyl 3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxylate (4b).** White solid, mp 72−73 °C; 15% yield (0.53 g). Purified via column chromatography twice (hexanes/EtOAc = 2:1, then 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (m, 2 × Ph, 10H), 5.03 (s, OCH_2Ph, 2H), 4.67 (d, NC*H*HPh, ^2J(H,H) = 14.1 Hz, 1H), 4.59 (d, NCH*H*Ph, ^2J(H,H) = 14.1 Hz, 1H), 3.65 (m, C*H*, 1H), 3.52 (m, C*H*, 1H), 3.22 (m, C*H*, 1H), 2.72 (m, C*H*H, 1H), 2.55 (m, CH*H*, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.2 (s, *C*═O), 175.9 (s, *C*═O), 171.0 (s, *C*═O), 135.8 (s, *C*, Ph), 135.4 (s, *C*, Ph), 128.9 (s, *C*H, Ph), 128.8 (s, *C*H, Ph), 128.7 (s, *C*H, Ph), 128.6 (s, *C*H, Ph), 128.0 (s, *C*H, Ph), 67.4 (s, OCH_2Ph), 42.8 (s, NCH_2Ph), 41.0 (s, CH), 37.5 (s, CH), 35.7 (s, CH), 25.7 (s, CH_2). LCMS (m/z): 350 ($M + H^+$). Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.88; H, 5.74; N, 4.29.

(1*S,5*R**,6*S**)-3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxamide (5a).** White solid, mp 163−164 °C; 47% yield (12.1 g). Purified via column chromatography (CH_2Cl_2/methanol/NEt_3 = 1000:50:2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 (s, N*H*H, 1H), 7.27 (m, Ph, 5H), 7.06 (s, NH*H*, 1H), 4.59 (s, CH_2Ph, 2H), 3.41 (dd, CHC*H*CONBn, ^3J(H,H) = 11.2, 5.3 Hz, 1H), 3.26 (m, C*H*, 1H), 3.00 (m, C*H*, 1H), 2.56 (m, C*H*H, 1H), 2.19 (m, CH*H*, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 179.7 (s, C═O), 178.7 (s, C═O), 174.1 (s, C═O), 136.9 (s, *C*, Ph), 129.2 (s, *C*H, Ph), 128.0 (s, *C*H, Ph), 128.0 (s, *C*H, Ph), 42.1 (s, NCH_2Ph), 41.4 (s, CHCHCONBn), 39.7 (s, CH), 36.4 (s, CH), 26.5 (s, CH_2). LCMS (m/z): 259 ($M + H^+$). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.50; H, 5.14; N, 11.18.

(1*S,5*R**,6*R**)-3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxamide (5b).** White solid, mp 169−170 °C; 11% yield (2.8 g). Purified via column chromatography (CH_2Cl_2/methanol/NEt_3 = 1000:50:2). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.46 (s, NH_2, 1H), 7.33 (m, Ph, 5H), 6.97 (s, NH_2, 1H), 4.63 (d, CH_2Ph, ^2J(H,H) = 15.1 Hz, 1H), 4.48 (d, CH_2Ph, ^2J(H,H) = 15.1 Hz, 1H), 3.46 (m, 2 × C*H*, 2H), 3.23 (m, C*H*, 1H), 2.56 (q, C*H*H, ^3J(H,H) = 10.7, 1H), 2.22 (m, CH*H*, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 179.6 (s, *C*═O), 177.4 (s, *C*═O), 172.7 (s, *C*═O), 136.8 (s, *C*, Ph), 128.9 (s, *C*H, Ph), 128.0 (s, *C*H, Ph), 127.7 (s, *C*H, Ph), 42.2 (s, NCH_2Ph), 41.1 (s, CH), 37.9 (s, CH), 35.7 (s, CH), 24.8 (s, CH_2). LCMS (m/z): 259 ($M + H^+$). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.85; H, 5.38; N, 10.69.

(1*S,5*S**,6*S**)-3-Benzyl-6-(bromomethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione (6a).** Yellow oil, 40% yield (124 mg). Purified via column chromatography (hexanes/MTBE = 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (m, Ph, 5H), 4.69 (s, CH_2Ph, 2H), 3.58 (d, CH_2Br, ^3J(H,H) = 6.3 Hz, 2H), 3.22 (m, C*H*, 1H), 3.14 (dd, CHC*H*CON, ^3J(H,H) = 6.9, 4.4, 1H), 2.76 (m, C*H*, 1H), 2.44 (m, C*H*H, 1H), 2.30 (m, CH*H*, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.6 (s, *C*═O), 177.4 (s, *C*═O), 135.8 (s, *C*, Ph), 128.7 (s, *C*H, Ph), 128.6 (s, *C*H, Ph), 128.0 (s, *C*H, Ph), 43.6 (s, CHCHCON), 42.6 (s, NCH_2Ph), 38.4 (s, CH), 36.6 (s, CH_2Br), 35.1 (s, CH), 28.1 (s, CHCH_2CH). LCMS (m/z): 308, 310 ($M + H^+$). Anal. Calcd for $C_{14}H_{14}BrNO_2$: C, 54.56; H, 4.58; N, 4.55. Found: C, 54.85; H, 4.39; N, 4.80.

(1*S,5*S**,6*R**)-3-Benzyl-6-(bromomethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione (6b).** Yellow oil, 16% yield (49 mg). Purified via column chromatography (hexanes/MTBE = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H), 4.70 (d, ^2J(H,H) = 14.0 Hz, 1H), 4.64 (d, ^2J(H,H) = 14.0 Hz, 1H), 3.45 (dd, J(H,H) = 10.0, 5.4, 1H), 3.37 (dd, J(H,H) = 10.0, 6.8, 1H), 3.17 (m, 2H), 2.96 (t, J(H,H) = 10.0, 1H), 2.79 (q, J(H,H) = 10.9, 1H), 1.85 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.8 (s), 175.9 (s), 135.7 (s), 128.9 (s), 128.8 (s), 128.2 (s), 42.6 (s), 42.2 (s), 35.5 (s), 34.3 (s), 33.2 (s), 29.4 (s). LCMS (m/z): 308, 310 ($M + H^+$). Anal. Calcd for $C_{14}H_{14}BrNO_2$: C, 54.56; H, 4.58; N, 4.55. Found: C, 54.88; H, 4.87; N, 4.28.

(1*S,5*S**,6*S**)-3-Benzyl-6-(trifluoromethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione (7a).** White solid, mp 80−81 °C; 48% yield (136 mg). Purified via column chromatography (hexanes/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, Ph, 5H), 4.68 (s, CH_2Ph, 2H), 3.33 (m, 2 × C*H*, 2H), 2.96 (m, C*H*CF_3, 1H), 2.71 (m, C*H*H, 1H), 2.31 (m, CH*H*, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.7 (s, *C*═O), 175.7 (s, *C*═O), 135.5 (s, *C*, Ph), 128.8 (s, *C*H, Ph), 128.7 (s, *C*H, Ph), 128.2 (s, *C*H, Ph), 126.2 (q, ^1J(C,F) = 276.3 Hz, CF_3), 42.8 (s, NCH_2Ph), 39.0 (q, ^3J(C,F) = 3.4 Hz, CHCHCON), 38.5 (q, ^2J(C,F) = 32.0 Hz, *C*HCF_3), 36.0 (s, CH_2CHCON), 23.1 (q, ^3J(C,F) = 3.3 Hz, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.9. LCMS (m/z): 284 ($M + H^+$). Anal. Calcd for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.95. Found: C, 59.02; H, 4.53; N, 4.86.

(1*S,5*S**,6*R**)-6-Acetyl-3-benzyl-3-azabicyclo[3.2.0]heptane-2,4-dione (8a).** White solid, mp 73−74 °C; 5% yield (13 mg). Purified via column chromatography (hexanes/MTBE = 1:3). ^{1}H NMR (500 MHz, CD_3CN): δ 7.35 (m, Ph, 5H), 4.67 (s, CH_2Ph, 2H), 3.54 (t, CHC*H*CON, ^3J(H,H) = 5.8 Hz, 1H), 3.35 (m, C*H*COMe, 1H), 3.16 (m, CH_2C*H*CON, 1H), 2.72 (m, C*H*H, 1H), 2.30 (m, CH*H*, 1H), 2.14 (s, CH_3, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.7 (s, MeC═O), 178.4 (s, *C*═O), 177.5 (s, *C*═O), 135.7 (s, *C*, Ph), 128.8 (s, *C*H, Ph), 128.7 (s, *C*H, Ph), 128.0 (s, *C*H, Ph), 46.3 (s, *C*HCOMe), 42.6 (s, *C*H_2Ph), 40.3 (s, CHCHCON), 35.6 (s, CH_2CHCON), 27.3 (s, CH_3), 25.1 (s, CH_2). LCMS (m/z): 258 ($M + H^+$). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.83; H, 5.75; N, 5.32.

(1*S,5*S**,6*S**)-3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-6-yl acetate (9a).** White solid, mp 66−67 °C; 71% yield (19.4 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31 (m, Ph, 5H), 4.98 (s, C*H*OAc, 1H), 4.58 (s, CH_2Ph, 2H), 3.45 (m, 2 × C*H*, 2H), 2.54 (s, CH_2, 2H), 2.06 (s, CH_3, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 178.8 (s, *C*═O), 175.8 (s, *C*═O), 169.8 (s, OC═O), 136.6 (s, *C*, Ph), 129.0 (s, *C*H, Ph), 127.9 (s, *C*H, Ph), 69.7 (s, CHOAc), 47.4 (s, CH), 42.3 (s, CH_2Ph), 34.6 (s, CH), 31.1 (s, CH_2), 21.1 (s, CH_3). LCMS (m/z): 274 ($M + H^+$). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.58; H, 5.75; N, 5.32.

(1*S,5*S**,6*R**)-3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-6-yl acetate (9b).** White solid, mp 79−80 °C; 21% yield (5.7 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30 (m, Ph, 5H), 5.31 (td, C*H*OAc, ^3J(H,H) = 8.8, 5.8 Hz, 1H), 4.61 (s, CH_2Ph, 2H), 3.72 (t, ^3J(H,H) = 7.2 Hz, C*H*, 1H), 3.13 (m, C*H*, 1H), 3.02 (m, C*H*H, 1H), 2.02 (m, CH*H*, 1H), 1.86 (s, CH_3, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 179.3 (s, C═O), 174.8 (s, C═O), 169.4 (s, OC═O), 136.6 (s, *C*, Ph), 128.9 (s, *C*H, Ph), 127.8 (s, *C*H, Ph), 127.7 (s, *C*H, Ph), 65.1 (s, CHOAc), 45.2 (s, CH), 42. 0 (s, CH_2Ph), 33.6 (s, CH), 31.4 (s, CH_2), 20.8 (s, CH_3). LCMS (m/z): 274 ($M + H^+$). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.65; H, 5.76; N, 5.43.

(1*S,5*R**,6*S**)-3-Benzyl-6-(trimethylsilyl)-3-azabicyclo[3.2.0]heptane-2,4-dione (10a).** Yellow oil, 62% yield (8.9 g). Purified via column chromatography (hexanes/EtOAc = 4:1). ^{1}H NMR

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

(500 MHz, $CDCl_3$): δ 7.39 (m, 5H), 4.70 (s, 2H), 3.16 (s, 1H), 2.97 (m, 1H), 2.39 (q, ^3J(H,H) = 8.9, 1H), 2.19 (t, ^3J(H,H) = 10.5, 1H), 1.80 (m, 1H), 0.08 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 179.9 (s), 179.5 (s), 136.1 (s), 128.7 (s), 128.6 (s), 127.8 (s), 42.4 (s), 39.2 (s), 38.0 (s), 24.0 (s), 23.9 (s), −4.1 (s). LCMS (m/z): 288 (M + H$^+$). Anal. Calcd for $C_{16}H_{21}NO_2Si$: C, 66.86; H, 7.36; N, 4.87. Found: C, 67.21; H, 7.12; N, 5.03.

(1*S,5*R**,6*R**)-3-Benzyl-6-(trimethylsilyl)-3-azabicyclo[3.2.0]-heptane-2,4-dione (10b).** Yellow oil, 16% yield (2.3 g). Purified via column chromatography (hexanes/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 5H), 4.69 (d, ^2J(H,H) = 13.8 Hz, 1H), 4.63 (d, ^2J(H,H) = 13.8 Hz, 1H), 3.41 (m, 1H), 3.29 (dd, J(H,H) = 11.2, 7.0 Hz, 1H), 2.67 (q, J(H,H) = 11.2 Hz, 1H), 2.38 (q, J(H,H) = 10.3 Hz, 1H), 1.98 (m, 1H), −0.10 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 179.6 (s), 179.2 (s), 135.9 (s), 129.2 (s), 128.6 (s), 127.9 (s), 42.5 (s), 40.0 (s), 38.4 (s), 24.2 (s), 23.6 (s), −3.3 (s). LCMS (m/z): 288 (M + H$^+$). Anal. Calcd for $C_{16}H_{21}NO_2Si$: C, 66.86; H, 7.36; N, 4.87. Found: C, 67.23; H, 7.10; N, 5.07.

(1*S,5*R**,6*S**)-3-Benzyl-6-(methylsulfonyl)-3-azabicyclo-[3.2.0]heptane-2,4-dione (11a).** White solid, mp 101−102 °C; 48% yield (140 mg). Purified via column chromatography (hexanes/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, Ph, 5H), 4.68 (s, CH_2Ph, 2H), 3.61 (m, 2 × CH, 2H), 3.37 (m, CH, 1H), 3.12 (m, CHH, 1H), 2.92 (s, CH_3, 3H), 2.44 (m, CHH, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.0 (s), 175.0 (s), 135.3 (s), 128.9 (s), 128.7 (s), 128.3 (s), 55.8 (s), 43.0 (s), 40.6 (s), 38.5 (s), 35.6 (s), 22.9 (s). LCMS (m/z): 294 (M + H$^+$). Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.01; H, 5.01; N, 5.06.

(1*S,5*R**,6*S**)-3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]-heptane-6-sulfonyl chloride (12a).** White solid, mp 109−110 °C; 53% yield (167 mg). Purified via column chromatography (hexanes/EtOAc = 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, Ph, 5H), 4.71 (s, CH_2Ph, 2H), 4.29 (m, CHSO$_2$Cl, 1H), 3.80 (dd, CH, ^3J(H,H) = 7.4, 4.0 Hz, 1H), 3.49 (m, CH, 1H), 3.19 (m, CHH, 1H), 2.66 (m, CHH, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.0 (s, C=O), 173.2 (s, C=O), 135.1 (s, C, Ph), 128.9 (s, CH, Ph), 128.9 (s, CH, Ph), 128.4 (s, CH, Ph), 66.4 (s, CHSO$_2$Cl), 43.2 (s, CH_2Ph), 42.0 (s, CH), 35.2 (s, CH), 26.5 (s, CH_2). LCMS (m/z): 314, 316 (M + H$^+$). Anal. Calcd for $C_{13}H_{12}ClNO_4S$: C, 49.76; H, 3.85; N, 4.46. Found: C, 50.05; H, 3.59; N, 4.71.

(1*S,5*R**,6*S**)-3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]-heptane-6-sulfonyl fluoride (13a).** White solid, mp 124−125 °C, 29% yield (86 mg). Purified via column chromatography (hexanes/EtOAc = 3:1). ^{1}H NMR (500 MHz, CD_3CN): δ 7.36 (m, Ph, 5H), 4.71 (d, ^2J(H,H) = 14.8 Hz, 1H), 4.67 (d, ^2J(H,H) = 14.8 Hz, 1H), 4.45 (s, CHSO$_2$F, 1H), 3.79 (m, CH, 1H), 3.52 (m, CH, 1H), 3.11 (m, CHH, 1H), 2.75 (m, CHH, 1H). ^{13}C NMR (126 MHz, CD_3CN): δ 177.0 (s, C=O), 174.3 (s, C=O), 136.0 (s, C, Ph), 128.8 (s, CH, Ph), 128.2 (s, CH, Ph), 127.9 (s, CH, Ph), 53.53 (d, ^2J(C,F) = 19.2 Hz, CHSO$_2$F), 42.8 (s, CH_2Ph), 41.1 (s, CH), 35.7 (s, CH), 25.1 (s, CH_2). ^{19}F NMR (376 MHz, CD_3CN): δ 44.4 (s). LCMS (m/z): 298 (M + H$^+$). Anal. Calcd for $C_{13}H_{12}FNO_4S$: C, 52.52; H, 4.07; N, 4.71. Found: C, 52.19; H, 4.24; N, 4.62.

(1*S,5*R**,6*S**)-3-Benzyl-6-(pyridin-4-yl)-3-azabicyclo[3.2.0]-heptane-2,4-dione (14a).** White solid, mp 75−76 °C; 55% yield (161 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, Py, ^3J(H,H) = 5.8 Hz, 2H), 7.41 (d, Ar, ^3J(H,H) = 6.8 Hz, 2H), 7.30 (m, Ar, 3H), 7.18 (d, Py, ^3J(H,H) = 5.8 Hz, 2H), 4.73 (s, CH_2Ph, 2H), 3.56 (m, CH, 1H), 3.39 (t, CH, ^3J(H,H) = 5.9 Hz, 1H), 3.32 (m, CH, 1H), 2.74 (m, CHH, 1H), 2.64 (m, CHH, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.5 (s, C=O), 177.5 (s, C=O), 150.8 (s, C, Py), 150.2 (s, CH, Py), 135.7 (s, C, Ph), 128.8 (s, CH, Ph), 128.7 (s, CH, Ph), 128.1 (s, CH, Ph), 121.4 (s, CH, Py), 45.5 (s, CH), 42.7 (s, CH_2Ph), 40.7 (s, CH), 35.8 (s, CH), 28.9 (s, CH_2). LCMS (m/z): 293 (M + H$^+$). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.67; H, 5.37; N, 9.89.

(1*S,5*R**,6*R**)-3-Benzyl-6-(pyridin-4-yl)-3-azabicyclo[3.2.0]-heptane-2,4-dione (14b).** White solid, mp 88−89 °C; 15% yield (44 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (broad s, Py, 2H), 7.27 (m, Ph, 5H), 6.78 (d, ^3J(H,H) = 4.7 Hz, Py, 2H), 4.57 (d, CHHPh, ^2J(H,H) = 13.8 Hz, 1H), 4.52 (d, CHHPh, ^2J(H,H) = 13.8 Hz, 1H), 4.09 (q, CH, ^3J(H,H) = 10.0 Hz, 1H), 3.67 (dd, CH, ^3J(H,H) = 10.6, 6.6 Hz, 1H), 3.34 (s, CH, 1H), 2.98 (dt, CHH, J(H,H) = 13.0, 10.0 Hz, 1H), 2.39 (s, CHH, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.6 (s, C=O), 175.3 (s, C=O), 149.8 (s, CH, Py), 146.6 (s, C, Py), 135.7 (s, C, Ph), 129.2 (s, CH, Ph), 128.7 (s, CH, Ph), 128.1 (s, CH, Ph), 122.4 (s, CH, Py), 43.8 (s, CH), 42.4 (s, CH_2Ph), 38.0 (s, CH), 35.2 (s, CH), 27.3 (s, CH_2). LCMS (m/z): 293 (M + H$^+$). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.03; H, 5.36; N, 9.81.

(1*S,5*R**,6*S**)-3-Benzyl-6-(4-fluorophenyl)-3-azabicyclo-[3.2.0]heptane-2,4-dione (15a).** White solid, mp 58−59 °C; 58% yield (180 mg). Purified via column chromatography (hexanes/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, ^3J(H,H) = 6.7 Hz, Ar, 2H), 7.33 (m, Ar, 3H), 7.22 (dd, ^3J = 8.4, 5.4 Hz, Ar, 2H), 7.03 (t, J = 8.4 Hz, Ar, 2H), 4.73 (s, CH_2Ph, 2H), 3.56 (td, ^3J(H,H) = 8.7, 5.0 Hz, CH, 1H), 3.34 (m, 2 × CH, 2H), 2.70 (m, CHH, 1H), 2.61 (m, CHH, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 179.0 (s, C=O), 178.0 (s, C=O), 162.8 (d, ^1J(C,F) = 245.8 Hz, CF), 137.9 (d, ^4J(C,F) = 3.2 Hz, CCHCHCF), 135.9 (s, C, Ph), 128.8 (s, CH, Ph), 128.7 (s, CH, Ph), 128.0 (s, CH, Ph), 127.9 (d, ^3J(C,F) = 8.0 Hz, CHCHCF), 115.6 (d, ^2J(C,F) = 21.5 Hz, CHCF), 46.6 (s, CH), 42.6 (s, CH_2Ph), 41.2 (s, CH), 35.6 (s, CH), 29.8 (s, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.0 (s). LCMS (m/z): 310 (M + H$^+$). Anal. Calcd for $C_{19}H_{16}FNO_2$: C, 73.77; H, 5.21; N, 4.53. Found: C, 74.01; H, 5.45; N, 4.48.

(1*S,5*R**,6*R**)-3-Benzyl-6-(4-fluorophenyl)-3-azabicyclo-[3.2.0]heptane-2,4-dione (15b).** White solid, mp 64−65 °C; 15% yield (47 mg). Purified via column chromatography (hexanes/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, Ph, 5H), 6.77 (s, Ar, 4H), 4.55 (m, CH_2Ph, 2H), 4.09 (q, ^3J(H,H) = 11.2 Hz, CH, 1H), 3.59 (dd, ^3J(H,H) = 10.5, 6.4 Hz, CH, 1H), 3.27 (dt, ^3J(H,H) = 11.2, 5.7 Hz, CH, 1H), 2.96 (m, CHH, 1H), 2.35 (m, CHH, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.2 (s, C=O), 176.0 (s, C=O), 161.7 (d, ^1J(C,F) = 253.9 Hz, CF), 135.9 (s, C, Ph), 133.7 (d, ^4J(C,F) = 3.2 Hz, CCHCHCF), 129.2 (s, CH, Ph), 128.9 (d, ^3J(C,F) = 8.1 Hz, CHCHCF), 128.6 (s, CH, Ph), 128.0 (s, CH, Ph), 115.2 (d, ^2J(C,F) = 21.4 Hz, CHCF), 44.5 (s, CH), 42.3 (s, CH_2Ph), 38.4 (s, CH), 35.1 (s, CH), 28.5 (s, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.7 (s). LCMS (m/z): 310 (M + H$^+$). Anal. Calcd for $C_{19}H_{16}FNO_2$: C, 73.77; H, 5.21; N, 4.53. Found: C, 73.57; H, 5.50; N, 4.36.

(1*S,5*S**,6*S**)-Methyl 3-Benzyl-6-methyl-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxylate (16a).** White solid, mp 78−79 °C; 28% yield (0.81 g). Purified via column chromatography (hexanes/MTBE = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, Ph, 5H), 4.67 (s, CH_2Ph, 2H), 3.74 (s, OCH_3, 3H), 3.64 (d, ^3J(H,H) = 6.9 Hz, CH, 1H), 3.20 (s, CH, 1H), 2.95 (m, CHH, 1H), 1.92 (dd, ^3J(H,H) = 13.2, 4.8 Hz, CHH, 1H), 1.13 (s, CH_3, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.9 (s, C=O), 175.7 (s, C=O), 175.5 (s, C=O), 135.9 (s, C, Ph), 129.1 (s, CH, Ph), 128.8 (s, CH, Ph), 128.2 (s, CH, Ph), 52.8 (s, OCH$_3$), 45.2 (s, CH), 44.0 (s, C), 42.7 (s, CH_2Ph), 34.0 (s, CH_2), 33.9 (s, CH), 20.8 (s, CH$_3$). LCMS (m/z): 288 (M + H$^+$). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.11; H, 6.15; N, 4.71.

(1*S,5*S**,6*R**)-Methyl 3-Benzyl-6-methyl-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxylate (16b).** White solid, mp 91−92 °C, 12% yield (0.34 g). Purified via column chromatography (hexanes/MTBE = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, Ph, 5H), 4.68 (d, CHHPh, ^2J(H,H) = 14.1 Hz, 1H), 4.63 (d, CHHPh, ^2J(H,H) = 14.1 Hz, 1H), 3.42 (s, OCH_3, 3H), 3.27 (m, CH, 1H), 3.06 (d, ^3J(H,H) = 6.7 Hz, CH, 1H), 2.76 (dd, ^3J(H,H) = 12.9, 5.5 Hz, CHH, 1H), 2.30 (m, CHH, 1H), 1.58 (s, CH_3, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.4 (s, C=O), 175.7 (s, C=O), 172.8 (s, C=O), 135.9 (s, C, Ph), 129.0 (s, CH, Ph), 128.7 (s, CH, Ph), 128.0 (s, CH, Ph), 52.3 (s, OCH$_3$), 48.8 (s, CH), 44.5 (s, C), 42.8 (s, CH_2Ph), 33.5 (s, CH), 33.4 (s, CH_2), 25.1 (s, CH$_3$). LCMS (m/z): 288 (M + H$^+$). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.66; H, 6.26; N, 5.12.

(1*S,5*S**,6*S**)-Methyl 3-Benzyl-6-fluoro-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxylate (17a).** White solid, mp 128−129 °C; 26% yield (0.76 g). Purified via column chromatography

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

(hexanes/MTBE = 1:2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (m, Ph, 5H), 5.18 (d, C*H*HPh, ^2J(H,H) = 14.7 Hz, 1H), 5.12 (d, CH*H*Ph, ^2J(H,H) = 14.7 Hz, 1H), 4.48 (m, CFC*H*, 1H), 4.32 (s, CH_3O, 3H), 3.76 (m, C*H*, C*H*H, 2H), 2.95 (m, CH*H*, 1H). ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ 177.8 (s, CH_2CHCON), 171.7 (d, ^3J(C,F) = 5.3 Hz, CFCHCON), 168.9 (d, ^2J (C,F) = 26.8 Hz, CO_2Me), 136.4 (s, *C*, Ph), 128.7 (s, *C*H, Ph), 128.1 (s, *C*H, Ph), 127.8 (s, *C*H, Ph), 88.8 (d, ^1J(C,F) = 231.5 Hz, *C*F), 52.9 (s, OCH_3), 47.9 (d, ^2J(C,F) = 23.1 Hz, CFC*H*), 42.4 (s, CH_2Ph), 35.0 (d, ^2J(C,F) = 24.8 Hz, CH_2), 31.9 (d, ^3J(C,F) = 5.6 Hz, CH_2C*H*). ^{19}F NMR (376 MHz, DMSO-d_6): δ −155.1 (m). LCMS (*m*/*z*): 292 (M + H$^+$). Anal. Calcd for $C_{15}H_{14}FNO_4$: C, 61.85; H, 4.84; N, 4.81. Found: C, 62.03; H, 4.62; N, 5.08.

(1*S,5*S**,6*R**)-Methyl 3-Benzyl-6-fluoro-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxylate (17b).** White solid, mp 95−96 °C; 6% yield (0.18 g). Purified via column chromatography (hexanes/MTBE = 1:2). ^{1}H NMR (500 MHz, CD_3CN): δ 7.48 (m, Ph, 5H), 4.74 (s, CH_2Ph, 2H), 3.81 (dd, *J* = 20.2, 7.5 Hz, CFC*H*, 1H), 3.61 (m, CH_3O, C*H*, 4H), 2.99 (m, CH_2, 2H). ^{13}C NMR (126 MHz, CD_3CN): δ 177.3 (s, CH_2CHCON), 172.7 (d, ^3J(C,F) = 8.5 Hz, CFCHCON), 167.2 (d, ^2J(C,F) = 27.6 Hz, CO_2Me), 135.8 (s, *C*, Ph), 128.3 (s, *C*H, Ph), 128.1 (s, *C*H, Ph), 127.5 (s, *C*H, Ph), 92.2 (d, ^1J(C,F) = 223.4 Hz, *C*F), 52.1 (s, OCH_3), 50.0 (d, ^2J(C,F) = 28.4 Hz, CFC*H*), 42.2 (s, CH_2Ph), 33.8 (d, ^2J(C,F) = 24.8 Hz, CH_2), 32.7 (d, ^3J(C,F) = 3.1 Hz, CH_2CH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −150.2 (m). LCMS (*m*/*z*): 292 (M + H$^+$). Anal. Calcd for $C_{15}H_{14}FNO_4$: C, 61.85; H, 4.84; N, 4.81. Found: C, 61.52; H, 4.94; N, 4.67.

(1*S,5*S**,6*S**)-3-Benzyl-2,4-dioxo-6-(trifluoromethyl)-3-azabicyclo[3.2.0]heptane-6-carbonitrile (18a).** White solid, mp 105−106 °C; 42% yield (0.13 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, Ph, 5H), 4.81 (d, ^2J(H,H) = 14.0 Hz, C*H*HPh, 1H), 4.71 (d, ^2J(H,H) = 14.0 Hz, CH*H*Ph, 1H), 3.62 (d, ^3J(H,H) = 6.6 Hz, CC*H*, 1H), 3.37 (m, CH_2C*H*, 1H), 3.11 (m, C*H*H, 1H), 2.65 (dd, *J*(H,H) = 14.1, 4.6 Hz, CH*H*, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.3 (s, *C*=O), 171.1 (s, *C*=O), 134.7 (s, *C*, Ph), 129.0 (s, *C*H, Ph), 128.9 (s, *C*H, Ph), 128.5 (s, *C*H, Ph), 123.3 (q, ^1J(C,F) = 280.7 Hz, *C*F_3), 112.7 (s, *C*N), 43.5 (s, *C*CH), 42.6 (s, *C*H_2Ph), 40.3 (q, ^2J(C,F) = 34.1 Hz, *C*CF_3), 34.7 (s, CH_2CH), 29.7 (s, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.5 (s). LCMS (*m*/*z*): 309 (M + H$^+$). Anal. Calcd for $C_{15}H_{11}F_3N_2O_2$: C, 58.45; H, 3.60; N, 9.09. Found: C, 58.80; H, 3.35; N, 9.28.

(1*S,5*S**,6*S**)-3-Benzyl-6-(difluoromethyl)-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carbonitrile (19a).** White solid, mp 97−98 °C; 35% yield (0.10 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, Ph, 5H), 6.09 (t, ^2J(H,F) = 55.4 Hz, C*H*F_2, 1H), 4.80 (d, ^2J(H,H) = 14.0 Hz, C*H*HPh, 1H), 4.71 (d, ^2J(H,H) = 14.0 Hz, CH*H*Ph, 1H), 3.55 (d, ^3J(H,H) = 6.8 Hz, CC*H*, 1H), 3.29 (m, CH_2C*H*, 1H), 3.06 (m, C*H*H, 1H), 2.52 (dd, *J*(H,H) = 13.9, 4.8 Hz, CH*H*, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.0 (s, *C*=O), 172.4 (s, *C*=O), 134.9 (s, *C*, Ph), 128.9 (s, *C*H, Ph), 128.8 (s, *C*H, Ph), 128.4 (s, *C*H, Ph), 114.5 (s, *C*N), 112.4 (t, ^1J(C,F) = 249.9 Hz, *C*HF_2), 43.3 (s, CH_2Ph), 41.6 (s, CCH), 39.2 (t, ^2J(C,F) = 26.4 Hz, C*C*HF_2), 35.0 (s, CH_2CH), 28.2 (s, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ −127.3 (m). LCMS (*m*/*z*): 291 (M + H$^+$). Anal. Calcd for $C_{15}H_{12}F_2N_2O_2$: C, 62.07; H, 4.17; N, 9.65. Found: C, 62.20; H, 4.39; N, 9.34.

3-Benzyl-6,6-dimethoxy-3-azabicyclo[3.2.0]heptane-2,4-dione (20a). White solid, mp 95−96 °C; 62% yield (17.1 g). Purified via column chromatography (hexanes/MTBE = 1:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (m, Ph, 5H), 4.71 (d, ^2J(H,H) = 14.2 Hz, C*H*HPh, 1H), 4.64 (d, ^2J(H,H) = 14.2 Hz, CH*H*Ph, 1H), 3.51 (d, ^3J(H,H) = 6.7 Hz, C*H*, 1H), 3.26 (s, OCH_3, 3H), 3.08 (m, C*H*, OCH_3, 4H), 2.63 (t, *J*(H,H) = 12.0 Hz, C*H*H, 1H), 2.38 (dd, *J*(H,H) = 13.3, 3.6 Hz, CH*H*, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.6 (s), 173.6 (s), 135.9 (s), 128.6 (s), 128.6 (s), 127.9 (s), 100.7 (s), 50.4 (s), 49.4 (s), 49.0 (s), 42.7 (s), 34.9 (s), 30.7 (s). LCMS (*m*/*z*): 276 (M + H$^+$). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.81; H, 6.01; N, 5.20.

(1*S,5*S**,6*R**)-Methyl 3-Benzyl-6-(*N*,*N*-di-*tert*-butylcarbonylimido)-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxylate (21a).** White solid, mp 77−78 °C; 21% yield (0.10 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, Ph, 5H), 4.67 (d, ^2J(H,H) = 14.3 Hz, C*H*HPh, 1H), 4.63 (d, ^2J(H,H) = 14.3 Hz, CH*H*Ph, 1H), 3.90 (q, ^3J(H,H) = 2.3 Hz, CC*H*, 1H), 3.78 (s, CH_3O, 3H), 3.28 (m, CH_2C*H*, 1H), 2.90 (m, C*H*H, 1H), 2.62 (q, *J*(H,H) = 11.0 Hz, CH*H*, 1H), 1.47 (s, 2 × Boc, 18H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.9 (s, *C*=O), 172.9 (s, *C*=O), 172.4 (s, *C*=O), 151.3 (s, $CO_2{}^t$Bu), 135.8 (s, *C*, Ph), 128.6 (s, *C*H, Ph), 128.5 (s, *C*H, Ph), 127.9 (s, *C*H, Ph), 83.6 (s, *C*$(CH_3)_3$), 60.8 (s, CNBoc$_2$), 53.2 (s, OCH_3), 46.7 (s, CCH), 42.5 (s, CH_2Ph), 36.2 (s, CH_2), 34.3 (s, CH_2CH), 27.9 (s, C$(CH_3)_3$). LCMS (*m*/*z*): 489 (M + H$^+$). Anal. Calcd for $C_{25}H_{32}N_2O_8$: C, 61.46; H, 6.60; N, 5.73. Found: 61.78; H, 6.31; N, 5.49.

Ethyl 3-Benzyl-2,4-dioxo-7-(trifluoromethyl)-3-azabicyclo[3.2.0]heptane-6-carboxylate (22ab). Yellow oil, 67% yield (0.24 g). ^{1}H NMR (400 MHz, $CDCl_3$) of both diastereomers δ 7.28 (m, Ph, 5H), 4.66 (m, CH_2Ph, 2H), 4.07 (m, OCH_2, 2H), 3.70−3.21 (m, 2 × C*H*, CH_2, 4H), 1.21 (m, CH_3, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) of both diastereomers δ 175.1 (s), 174.6 (s), 174.1 (s), 173.4 (s), 170.0 (s), 168.6(s), 135.1 (s), 135.0 (s), 129.1 (s), 128.9 (s), 128.7 (s), 128.2 (s), 128.2 (s), 125.2 (q, ^1J(C,F) = 276.6 Hz), 124.1 (q, ^1J(C,F) = 277.9 Hz), 62.4 (s), 62.3 (s), 43.2 (s), 43.1 (s), 41.3 (s), 40.8 (q, ^2J(C,F) = 32.7 Hz), 39.9 (q, ^2J(C,F) = 32.4 Hz), 39.7 (s), 38.4 (s), 38.4 (s), 38.0 (q, ^3J(C,F) = 3.1 Hz), 36.4 (q, ^3J(C,F) = 3.0 Hz), 36.2 (s). ^{19}F NMR (376 MHz, $CDCl_3$) of both diastereomers δ −70.3 (s), −73.8 (s). LCMS (*m*/*z*): 356 (M + H$^+$). Anal. Calcd for $C_{17}H_{16}F_3NO_4$: C, 57.47; H, 4.54; N, 3.94. Found: C, 57.75; H, 4.79; N, 3.83.

(3a*R*,3b*S*,5r,6a*R*,6b*S*)-Methyl 2-Benzyl-1,3-dioxodecahydrocyclopenta[3,4]cyclobuta[1,2-*c*]pyrrole-5-carboxylate (23a-1). White solid, mp 90−91 °C; 53% yield (1.66 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (m, Ph, 5H), 4.67 (s, CH_2Ph, 2H), 3.72 (s, OCH_3, 3H), 3.09 (t, ^3J(H,H) = 8.3 Hz, *CH*CO_2Me, 1H), 2.88 (s, *CH*CON, 2H), 2.84 (d, ^3J(H,H) = 5.3 Hz, CH_2C*H*, 2H), 2.42 (d, ^2J(H,H) = 14.2 Hz, 2 × C*H*H, 2H), 2.05 (m, 2 × CH*H*, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.8 (s, *C*=O), 175.7 (s, *C*=O), 135.9 (s, *C*, Ph), 128.6 (s, *C*H, Ph), 128.4 (s, *C*H, Ph), 127.8 (s, *C*H, Ph), 52.0 (s, OCH_3), 44.8 (s, *CH*CO_2Me), 43.0 (s, CHCON), 42.4 (s, CH_2CH), 42.3 (s, CH_2Ph), 35.2 (s, CH_2). LCMS (*m*/*z*): 314 (M + H$^+$). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.66; H, 6.46; N, 4.30.

(3a*R*,3b*S*,5s,6a*R*,6b*S*)-Methyl 2-Benzyl-1,3-dioxodecahydrocyclopenta[3,4]cyclobuta[1,2-*c*]pyrrole-5-carboxylate (23a-2). White solid, mp 142−143 °C; 17% yield (0.53 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (m, Ph, 5H), 4.68 (s, CH_2Ph, 2H), 3.71 (s, OCH_3, 3H), 3.05 (m, *CH*CO_2Me, 1H), 2.90 (d, ^3J(H,H) = 4.1 Hz, CH_2C*H*, 2H), 2.71 (s, *CH*CON, 2H), 2.12 (m, 2 × C*H*H, 2H), 1.92 (m, 2 × CH*H*, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.4 (s, *C*=O), 174.6 (s, *C*=O), 135.8 (s, *C*, Ph), 128.7 (s, *C*H, Ph), 128.5 (s, *C*H, Ph), 127.9 (s, *C*H, Ph), 52.0 (s, OCH_3), 42.6 (s, *C*H), 42.5 (s, CH_2Ph), 41.8 (s, *C*H), 36.4 (s, CH_2). LCMS (*m*/*z*): 314 (M + H$^+$). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.80; H, 6.01; N, 4.20.

(3a*R*,3b*S*,6a*R*,6b*S*)-5-Benzyltetrahydro-1*H*-furo[3′,4′:3,4]-cyclobuta[1,2-*c*]pyrrole-4,6(3b*H*,5*H*)-dione (24a). White solid, mp 82−83 °C; 71% yield (1.82 g). Purified via column chromatography (hexanes/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H), 4.68 (s, 2H), 4.10 (d, *J*(H,H) = 10.0 Hz, 2H), 3.51 (d, *J*(H,H) = 7.4 Hz, 2H), 2.95 (s, 2H), 2.88 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.4 (s), 135.8 (s), 128.7 (s), 128.6 (s), 128.0 (s), 73.3 (s), 42.5 (s), 42.4 (s), 42.2 (s). LCMS (*m*/*z*): 258 (M + H$^+$). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.30; H, 5.66; N, 5.69.

(3a*S*,3b*S*,6a*S*,6b*S*)-5-Benzyltetrahydro-2*H*-furo[2′,3′:3,4]-cyclobuta[1,2-*c*]pyrrole-4,6(3b*H*,5*H*)-dione (25a). White solid, mp 73−74 °C; 10% yield (0.26 g). Purified via column chromatography (hexanes/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 5H), 4.67 (s, 2H), 4.60 (d, ^3J(H,H) = 5.2 Hz, 1H), 4.26 (t, ^3J(H,H) = 8.3 Hz, 1H), 3.88 (m, 1H), 3.10 (m, 2H), 2.78 (m, 1H), 1.94 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.0 (s), 176.0 (s), 135.8 (s), 128.7 (s), 128.6 (s), 128.0 (s), 79.7 (s), 67.3 (s), 46.9 (s), 44.0 (s), 42.7 (s), 41.0 (s), 31.3 (s). LCMS (*m*/*z*): 258 (M + H$^+$).

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.34; H, 6.07; N, 5.15.

(3a*R*,3b*S*,6a*R*,6b*S*)-*tert*-Butyl 5-Benzyl-4,6-dioxooctahydrocyclobuta[1,2-*c*:3,4-*c*′]dipyrrole-2(3b*H*)-carboxylate (26a). White solid, mp 79−80 °C; 47% yield (0.17 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 5H), 4.69 (s, 2H), 3.88 (s, 2H), 3.22 (d, ^3J(H,H) = 9.6 Hz, 2H), 2.92 (s, 4H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.0 (s), 155.1 (s), 135.7 (s), 128.7 (s), 128.6 (s), 128.0 (s), 80.3 (s), 51.5 (s), 42.7 (s), 42.6 (s), 40.9 (s), 28.4 (s). LCMS (m/z): 357 (M + H$^+$). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.68; H, 6.46; N, 8.02.

(3a*R*,3b*S*,6a*R*,6b*S*)-5-Benzyltetrahydro-1*H*-thieno[3′,4′:3,4]cyclobuta[1,2-*c*]pyrrole-4,6(3b*H*,5*H*)-dione 2,2-Dioxide (27a). White solid, mp 142−143 °C; 63% yield (0.19 g). Purified via column chromatography (MTBE). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H), 4.68 (s, 2H), 3.38 (s, 2H), 3.22 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.8 (s), 135.4 (s), 128.8 (s), 128.6 (s), 128.2 (s), 53.8 (s), 42.8 (s), 42.4 (s), 35.8 (s). LCMS (m/z): 306 (M + H$^+$). Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 59.16; H, 4.83; N, 4.81.

(3a*R*,3b*R*,6a*S*,6b*R*)-5-Benzyltetrahydro-2*H*-thieno[2′,3′:3,4]cyclobuta[1,2-*c*]pyrrole-4,6(3b*H*,5*H*)-dione 1,1-Dioxide (28a). White solid, mp 135−136 °C; 27% yield (82 mg). Purified via column chromatography (MTBE). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H), 4.69 (s, 2H), 3.60 (m, 1H), 3.46 (m, 1H), 3.23 (m, 4H), 2.44 (m, 1H), 2.31 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.1 (s), 174.1 (s), 135.2 (s), 128.9 (s), 128.7 (s), 128.3 (s), 55.9 (s), 47.1 (s), 43.1 (s), 41.5 (s), 40.4 (s), 39.4 (s), 26.4 (s). LCMS (m/z): 306 (M + H$^+$). Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 59.29; H, 4.62; N, 4.42.

2-Benzyl-6a-ethoxyhexahydrocyclopenta[3,4]cyclobuta[1,2-*c*]pyrrole-1,3,4(2*H*)-trione (29a). White solid, mp 120−121 °C; 44% yield (0.14 g). Purified via column chromatography (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 5H), 4.71 (s, 2H), 3.58 (m, 1H), 3.43 (m, 2H), 2.87 (m, 1H), 2.78 (s, 1H), 2.59 (m, 2H), 2.29 (m, 2H), 0.94 (t, ^3J(H,H) = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 211.4 (s), 175.8 (s), 174.2 (s), 135.4 (s), 128.6 (s), 128.5 (s), 127.9 (s), 82.4 (s), 60.0 (s), 51.9 (s), 48.8 (s), 42.9 (s), 37.1 (s), 35.8 (s), 32.1 (s), 15.0 (s). LCMS (m/z): 314 (M + H$^+$). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.68; H, 6.33; N, 4.64.

General Procedure for Reduction with $LiAlH_4$. A suspension of $LiAlH_4$ (3.0 equiv) in THF was cooled to 0−10 °C under an argon atmosphere. A solution of imide (1.0 equiv) in THF was added dropwise, and the reaction mixture was refluxed for 5 h. The reaction mixture was cooled to 0−5 °C under an argon atmosphere and quenched with a mixture of THF/H_2O (3:1). Then, a 30% aqueous solution of NaOH was added, and the formed precipitate was filtered off and washed with hot THF three times. The resulting solution was concentrated under reduced pressure to give the crude product.

General Procedure for Removal of the Benzyl Group. A mixture of benzylamine (1.0 equiv) and 10% palladium on charcoal (0.1 equiv) in methanol was stirred for 12 h under a hydrogen atmosphere (60 atm) at 40 °C. Palladium was filtered off and washed with methanol twice. The solution was acidified with a 10% aqueous hydrochloric acid solution and concentrated under reduced pressure to give the desired product.

3-Azabicyclo[3.2.0]heptane Hydrochloride (30). White solid, mp 196−197 °C; 81% yield (8.5 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (br s, 2H), 3.46 (dd, J = 11.5, 4.7 Hz, 2 × C*H*HN, 2H), 3.35−2.91 (m, 2 × CH*H*N, 2 × C*H*, 4H), 2.29 (m, 2 × C*H*H, 2H), 2.05 (m, 2 × CH*H*, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 52.2 (s, CH_2N), 36.3 (s, CH), 22.3 (s, CH_2). LCMS (m/z): 98 (M − Cl$^-$). Anal. Calcd for $C_6H_{12}ClN$: C, 53.93; H, 9.05; N, 10.48. Found: C, 53.68; H, 9.21; N, 10.19.

3-Azabicyclo[3.2.0]heptan-6-ol (31). White solid, mp 95−96 °C; 70% yield (16.0 g). dr = 81:19 according to the GCMS spectrum. ^{1}H NMR (400 MHz, $CDCl_3$) of both diastereomers: δ 4.36−3.15 (m, 2H), 3.03−2.36 (m, 7H), 2.15−1.24 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) of both diastereomers: δ 69.5 (s), 62.3 (s), 61.2 (s), 53.7 (s), 52.8 (s), 51.9 (s), 50.1 (s), 46.5 (s), 35.7 (s), 35.6 (s), 32.5 (s), 32.3 (s), 29.7 (s). LCMS (m/z): 114 (M + H$^+$). Anal. Calcd for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.35; H, 9.54; N, 12.70.

***tert*-Butyl 6-Oxo-3-azabicyclo[3.2.0]heptane-3-carboxylate (32).** A solution of **31** (6.8 g, 60 mmol, 0.1 equiv) in CH_2Cl_2 (200 mL), DMAP (0.70 g, 6.0 mmol, 0.1 equiv), NEt_3 (6.2 g, 72 mmol, 1.2 equiv), and Boc_2O (15.7 g, 72 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 12 h, then washed with a solution of 10% aqueous citric acid (200 mL), and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (400 mL), and the solution was cooled to 0 °C; then DMP (30.5 g, 72 mmol, 1.2 equiv) was added. The reaction mixture was stirred for 16 h at room temperature and quenched with $NaHCO_3$. The formed precipitate was filtered and washed with CH_2Cl_2 (2 × 200 mL). The solution was washed with a 10% aqueous citric acid solution (200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the desired product as a colorless oil (8.6 g, 68% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (m, 2H), 3.59 (d, J(H,H) = 11.4 Hz, 1H), 3.36 (m, 2H), 3.15 (m, 1H), 3.04 (m, 1H), 2.68 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 211.0 (s), 154.4 (s), 79.3 (s), 63.6 (s), 52.9 (s), 51.7 (s), 48.1 (s), 28.5 (s). LCMS (m/z): 212 (M + H$^+$). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.87; H, 8.37; N, 6.34.

***tert*-Butyl 6-Amino-3-azabicyclo[3.2.0]heptane-3-carboxylate (33).** A mixture of **32** (12.0 g, 57 mmol, 1.0 equiv), NH_2OH·HCl (6.7 g, 96 mmol, 1.7 equiv), and $NaHCO_3$ (8.1 g, 96 mmol, 1.7 equiv) in methanol (250 mL) was stirred for 16 h at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in water (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was dissolved in a methanolic ammonia solution (150 mL), and Raney nickel (2 g) was added. The reaction mixture was stirred for 16 h under a hydrogen atmosphere (40 atm) at room temperature. The catalyst was filtered off, and the solution was concentrated under reduced pressure to afford the desired product as a colorless oil (9.4 g, 78% yield). dr = 81:19 according to the GCMS spectrum. ^{1}H NMR (500 MHz, $CDCl_3$) of all diastereomers and Boc-rotamers: δ 3.91 (s, 1H), 3.68−2.36 (m, 8H), 1.49 (m, 9H), 1.37 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) of all diastereomers and Boc-rotamers: δ 155.0 (s), 154.8 (s), 79.0 (s), 78.9 (s), 51.8 (s), 51.3 (s), 50.7 (s), 44.3 (s), 43.9 (s), 36.7 (s), 35.8 (s), 31.6 (s), 30.9 (s), 28.3 (s), 28.1 (s). LCMS (m/z): 213 (M + H$^+$). Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20. Found: C, 62.04; H, 9.67; N, 13.51.

((1*S,5*R**,6*S**)-3-Benzyl-3-azabicyclo[3.2.0]heptan-6-yl)methanamine (34).** Colorless oil, 87% yield (2.1 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 5H), 3.65 (m, 2H), 2.80 (m, 2H), 2.67 (m, 3H), 2.37 (m, 1H), 2.08 (m, 3H), 1.88 (m, 1H), 1.71 (m, 1H), 1.33 (broad s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.9 (s), 128.6 (s), 128.1 (s), 126.7 (s), 60.4 (s), 60.1 (s), 59.7 (s), 47.9 (s), 41.4 (s), 40.8 (s), 34.2 (s), 28.4 (s). LCMS (m/z): 217 (M + H$^+$). Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.37; H, 9.67; N, 12.67.

((1*S,5*S**,6*S**)-3-Benzyl-3-azabicyclo[3.2.0]heptan-6-yl)methanol (35a).** Colorless oil, 87% yield (17.8 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 5H), 3.69 (m, 4H), 2.81 (d, ^3J(H,H) = 9.4 Hz, 2H), 2.67 (m, 1H), 2.47 (m, 1H), 2.11 (m, 4H), 1.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.8 (s), 128.7 (s), 128.2 (s), 126.7 (s), 67.2 (s), 60.5 (s), 60.0 (s), 59.8 (s), 40.4 (s), 39.6 (s), 34.3 (s), 27.1 (s). LCMS (m/z): 218 (M + H$^+$). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.19; H, 8.93; N, 6.70.

((1*S,5*S**,6*R**)-3-Benzyl-3-azabicyclo[3.2.0]heptan-6-yl)methanol (35b).** Colorless oil, 73% yield (0.32 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m 5H), 6.62 (br s, 1H), 3.89 (d, ^2J(H,H) = 12.6 Hz, 1H), 3.76 (d, J(H,H) = 11.8 Hz, 1H), 3.49 (s, 1H), 3.41 (d, ^2J(H,H) = 12.6 Hz, 1H), 3.19 (d, ^3J(H,H) = 10.3 Hz, 1H), 2.96 (dd, ^3J(H,H) = 7.8, 7.3 Hz, 2H), 2.85 (d, ^3J(H,H) = 9.7 Hz, 1H), 2.71 (m, 1H), 2.60 (s, 1H), 2.12 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.0 (s), 128.9 (s), 128.5 (s), 127.3 (s), 62.0 (s), 60.4 (s), 59.8 (s), 55.8 (s), 39.8 (s), 35.0 (s), 34.5 (s), 25.0 (s). LCMS (m/z): 218

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

(M + H^+). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.07; H, 8.57; N, 6.62.

((1*S,5*S**,6*S**)-3-Azabicyclo[3.2.0]heptan-6-yl)methanol Hydrochloride (36a).** White solid, mp 79−80 °C; 80% yield (10.7 g). ^{1}H NMR (400 MHz, D_2O): δ 3.45 (d, ^3J(H,H) = 7.0 Hz, 2H), 3.32−3.18 (m, 2H), 3.06 (m, 2H), 2.94 (m, 1H), 2.73 (m, 1H), 1.99 (m, 1H), 1.82 (m, 1H), 1.64 (m, 1H). ^{13}C NMR (101 MHz, D_2O): δ 65.0 (s), 51.9 (s), 51.5 (s), 39.3 (s), 37.5 (s), 33.4 (s), 25.0 (s). LCMS (*m*/*z*): 128 (M − Cl^-). Anal. Calcd for $C_7H_{14}ClNO$: C, 51.38; H, 8.62; N, 8.56. Found: C, 51.12; H, 8.84; N, 8.27.

((1*S,5*S**,6*R**)-3-Azabicyclo[3.2.0]heptan-6-yl)methanol (36b).** Colorless oil, 67% yield (85 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (d, *J*(H,H) = 11.6 Hz, 1H), 3.50 (m, 1H), 3.34 (d, *J*(H,H) = 10.5 Hz, 1H), 3.07 (d, *J*(H,H) = 9.1 Hz, 1H), 2.98 (m, 1H), 2.67 (m, 6H), 2.25 (m, 1H), 2.00 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 61.9 (s), 53.3 (s), 47.8 (s), 39.6 (s), 34.7 (s), 34.1 (s), 24.9 (s). LCMS (*m*/*z*): 128 (M + H^+). Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.32; H, 10.63; N, 11.29.

(1*S,5*R**,6*S**)-6-(4-Fluorophenyl)-3-azabicyclo[3.2.0]-heptane Hydrochloride (37).** White solid, mp 147−148 °C; 55% yield (0.52 g). ^{1}H NMR (400 MHz, MeOD): δ 7.29 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.02 (t, *J* = 8.7 Hz, 2H), 3.51 (m, 2H), 3.26 (m, 5H), 2.32 (m, 2H). ^{13}C NMR (101 MHz, MeOD): δ 161.5 (d, ^1J(C,F) = 243.1 Hz), 140.2 (d, ^4J(C,F) = 3.1 Hz), 127.8 (d, ^3J(C,F) = 8.0 Hz), 114.8 (d, ^2J(C,F) = 21.5 Hz), 51.39 (s), 51.37 (s), 45.4 (s), 40.3 (s), 33.4 (s), 30.4 (s). ^{19}F NMR (376 MHz, MeOD): δ −119.3 (s). LCMS (*m*/*z*): 192 (M − Cl^-). Anal. Calcd for $C_{12}H_{15}ClFN$: C, 63.30; H, 6.64; N, 6.15. Found: C, 63.48; H, 6.85; N, 6.47.

(3a*R*,5s,6a*S*)-2-Benzyl-5-fluorooctahydrocyclopenta[*c*]-pyrrole (38). A mixture of **35a** or **35b** (1.6 g, 7.4 mmol, 1.0 equiv), anhydrous HF (2.0 mL), and SF_4 (1.7 g, 15.8 mmol, 2.1 equiv) was kept in a stainless steel autoclave overnight. The gaseous products were removed under an effective fume hood. The reaction mixture was poured into a 10% solution of KOH (150 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product as a colorless oil (1.3 g, 78% yield from **35a**) or (1.2 g, 75% yield from **35b**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, Ph, 5H), 5.08 (d, ^3J(H,F) = 53.5 Hz, C*H*F, 1H), 3.57 (s, CH_2Ph, 2H), 2.87 (m, 2 × C*H*HN, 2H), 2.67 (m, C*HCH*, 2H), 2.26 (m, 2 × CH*H*N, 2H), 1.89 (m, CH_2CHFCH_2, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.7 (s, *C*, Ph), 128.8 (s, CH, Ph), 128.2 (s, CH, Ph), 126.9 (s, CH, Ph), 98.1 (d, ^1J(C,F) = 176.2 Hz, *C*F), 61.3 (s, CH_2NBnCH_2), 60.0 (s, NCH_2Ph), 40.7 (s, *C*HCH), 37.9 (d, ^2J(C,F) = 19.0 Hz, CH_2CHFCH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ −173.3 (s). LCMS (*m*/*z*): 220 (M + H^+). Anal. Calcd for $C_{14}H_{18}FN$: C, 76.68; H, 8.27; N, 6.39. Found: C, 76.97; H, 8.03; N, 6.16.

(3a*R*,3b*S*,6a*R*,6b*S*)-5-Benzyloctahydro-1*H*-furo[3′,4′:3,4]-cyclobuta[1,2-*c*]pyrrole (39). Yellow solid, mp 43−45 °C; 75% yield (2.2 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (m, 5H), 3.88 (d, *J*(H,H) = 9.3 Hz, 2H), 3.68 (s, 2H), 3.45 (m, 2H), 2.89 (d, *J*(H,H) = 9.3 Hz, 2H), 2.58 (s, 2H), 2.33 (s, 2H), 2.08 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.7 (s), 128.6 (s), 128.2 (s), 126.8 (s), 73.9 (s), 59.7 (s), 43.1 (s), 41.3 (s). LCMS (*m*/*z*): 230 (M + H^+). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.25; H, 8.18; N, 6.10.

(3a*R*,3b*S*,6a*R*,6b*S*)-Octahydro-1*H*-furo[3′,4′:3,4]cyclobuta-[1,2-*c*]pyrrole (40). White solid, mp 83−84 °C; 85% yield (0.88 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (d, *J*(H,H) = 9.1 Hz, 2H), 3.45 (d, *J*(H,H) = 8.0 Hz, 2H), 2.97 (d, *J*(H,H) = 11.0 Hz, 2H), 2.66 (d, *J*(H,H) = 11.0 Hz, 2H), 2.34 (d, *J*(H,H) = 15.1 Hz, 4H), 2.23 (broad s, NH, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 73.9 (s), 53.3 (s), 42.2 (s), 42.1 (s). LCMS (*m*/*z*): 140 (M + H^+). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.29; H, 9.74; N, 10.25.

(3a*R*,3b*R*,6a*S*,6b*S*)-2,5-Dibenzyldecahydrocyclobuta[1,2-*c*:3,4-*c*′]dipyrrole (41). White solid, mp 127−128 °C; 82% yield (13.2 g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.34 (m, 2 × Ph, 10H), 3.69 (s, 2 × PhCH_2, 4H), 2.86 (d, *J*(H,H) = 9.1 Hz, 2 × C*H*H, 4H), 2.43 (s, 2 × CH*H*, 4H), 2.10 (m, 4 × C*H*, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.1 (s, *C*, Ph), 128.7 (s, CH, Ph), 128.2 (s, CH, Ph), 126.7 (s, CH, Ph), 60.2 (s, CH_2), 60.0 (s, CH_2), 42.2 (s, CH). LCMS (*m*/*z*): 319 (M + H^+). Anal. Calcd for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.62; H, 8.50; N, 8.56.

(3a*R*,3b*R*,6a*S*,6b*S*)-Decahydrocyclobuta[1,2-*c*:3,4-*c*′]-dipyrrole Dihydrochloride (42). White solid, mp 265−269 °C; 84% yield (7.8 g). ^{1}H NMR (400 MHz, D_2O): δ 2.79 (d, *J*(H,H) = 11.6 Hz, 2 × C*H*H, 4H), 2.45 (m, 2 × C*H*H, 4H), 2.11 (m, 4 × C*H*, 4H). ^{13}C NMR (101 MHz, D_2O): δ 52.1 (s, CH_2), 41.3 (s, CH). LCMS (*m*/*z*): 139 (M − HCl − Cl^-). Anal. Calcd for $C_8H_{16}N_2Cl_2$: C, 45.51; H, 7.64; N, 13.27. Found: C, 45.79; H, 7.56; N, 13.44.

(3a*R*,3b*S*,6a*R*,6b*S*)-5-Benzyloctahydro-1*H*-thieno[3′,4′:3,4]-cyclobuta[1,2-*c*]pyrrole 2,2-Dioxide (43). TMSCl (10.4 g, 96 mmol, 6.0 equiv) was added dropwise to a suspension of $LiAlH_4$ (3.6 g, 96 mmol, 6.0 equiv) in THF at room temperature under an argon atmosphere. The reaction mixture was stirred for 1 h and cooled to 0 °C, and a solution of **27a** (5.0 g, 16 mmol, 1.0 equiv) in THF (20 mL) was added dropwise. The reaction mixture was stirred for 24 h, then cooled to 0 °C under an argon atmosphere, and quenched with a mixture of water/THF (1:3) and then with a 30% aqueous KOH solution. The formed precipitate was filtered off and washed with THF three times. The solution was concentrated under reduced pressure. Diethyl ether was added (100 mL), and the formed precipitate was filtered, washed with diethyl ether (50 mL), and dried to afford the desired product as a white solid, mp 132−133 °C (3.5 g, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 5H), 3.65 (s, 2H), 3.12 (m, 2H), 2.98 (m, 2H), 2.86 (m, 4H), 2.72 (s, 2H), 2.06 (d, ^3J(H,H) = 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.5 (s), 128.5 (s), 128.2 (s), 126.9 (s), 59.3 (s), 59.3 (s), 55.2 (s), 42.0 (s), 37.0 (s). LCMS (*m*/*z*): 278 (M + H^+). Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05. Found: C, 64.63; H, 6.63; N, 5.38.

(3a*R*,3b*S*,6a*R*,6b*S*)-Octahydro-1*H*-thieno[3′,4′:3,4]cyclobuta-[1,2-*c*]pyrrole 2,2-Dioxide Hydrochloride (44). A mixture of **43** (2.8 g, 10 mmol, 1.0 equiv), Boc_2O (2.6 g, 12 mmol, 1.2 equiv), and 10% palladium on charcoal (1.1 g, 1.0 mmol, 0.1 equiv) in methanol (100 mL) was stirred for 12 h under a hydrogen atmosphere (60 atm) at 40 °C. Palladium was filtered off and washed with methanol (2 × 50 mL). The resulting solution was acidified with a 10% aqueous hydrochloric acid solution, stirred for 6 h, and concentrated under reduced pressure to give the product as a white solid (1.3 g, 60% yield), mp 180−181 °C. ^{1}H NMR (400 MHz, D_2O): δ 3.45 (d, *J*(H,H) = 12.4 Hz, 2H), 3.24 (m, 6H), 3.08 (m, 2H), 2.90 (m, 2H). ^{13}C NMR (101 MHz, D_2O): δ 53.8 (s), 51.1 (s), 40.7 (s), 35.5 (s). LCMS (*m*/*z*): 188 (M − Cl^-). Anal. Calcd for $C_8H_{14}ClNO_2S$: C, 42.95; H, 6.31; N, 6.26. Found: C, 42.62; H, 6.52; N, 6.48.

5-(Hydroxymethyl)decahydrocyclopenta[3,4]cyclobuta[1,2-*c*]pyrrole Hydrochloride (45). White solid, mp 151−152 °C; 82% yield (32.5 g). dr = 1:1 according to the ^{1}H NMR spectrum. ^{1}H NMR (500 MHz, D_2O) of both diastereomers: δ 3.59 (m, 2H), 3.39 (m, 2H), 3.13 (m, 2H), 2.71 (m, 1H), 2.55 (m, 1H), 2.31 (m, 2H), 2.09 (m, 2H), 1.71 (m, 1H), 1.41 (m, 1H), 1.22 (m, 1H). ^{13}C NMR (126 MHz, D_2O) of both diastereomers: δ 65.5 (s), 65.4 (s), 51.8 (s), 51.7 (s), 45.2 (s), 42.3 (s), 41.1 (s), 40.9 (s), 40.4 (s), 40.2 (s), 36.3 (s), 35.6 (s). LCMS (*m*/*z*): 168 (M − Cl^-). Anal. Calcd for $C_{10}H_{18}ClNO$: C, 58.96; H, 8.91; N, 6.88. Found: C, 58.61; H, 8.69; N, 6.60.

Benzyl 5-(Hydroxymethyl)octahydrocyclopenta[3,4]-cyclobuta[1,2-*c*]pyrrole-2(3b*H*)-carboxylate (46). A solution of **45** (25.7 g, 0.1 mol, 1.0 equiv) in CH_2Cl_2 (400 mL) was mixed with CbzCl (20.5 g, 0.12 mmol, 1.2 equiv) and NEt_3 (15.2 g, 0.15 mmol, 1.5 equiv). The resulting reaction mixture was stirred at room temperature for 6 h; then the organic phase was separated, washed with a 10% K_2CO_3 aqueous solution (300 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product as a yellow oil (27.2 g, 87% yield). dr = 1:1 according to the ^{1}H NMR spectrum. ^{1}H NMR (400 MHz, $CDCl_3$) of both diastereomers: δ 7.34 (m, 5H), 5.15 (s, 2H), 3.69 (m, 4H), 3.22 (m, 2H), 2.42 (m, 4H), 2.04 (m, 2H), 1.73 (m, 2H), 1.37 (m, 1H), 1.26 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) of both diastereomers: δ 155.6 (s), 136.9 (s), 128.4 (s), 127.9 (s), 127.7 (s), 66.8 (s), 66.4 (s), 66.2 (s), 52.8 (s), 46.5 (s), 42.8 (s), 42.5 (s), 41.7 (s), 36.9 (s), 36.2 (s). LCMS (*m*/*z*): 302

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX

(M + H$^+$). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.41; H, 7.51; N, 4.91.

2-(*tert*-Butoxycarbonyl)decahydrocyclopenta[3,4]cyclobuta-[1,2-*c*]pyrrole-5-carboxylic Acid (47). A mixture of CrO_3 (9.6 g, 96 mmol, 1.6 equiv) and H_2SO_4 (14.1 g, 60 mmol, 2.4 equiv) in water (50 mL) was added to a solution of **46** (18.1 g, 60 mmol, 1.0 equiv) in acetone (300 mL). The reaction mixture was stirred for 12 h, then quenched with isopropanol (20 mL), concentrated under reduced pressure, diluted with water (200 mL), and extracted with ethyl acetate (2 × 200 mL). The combined organic phases were washed with a 10% Na_2SO_4 aqueous solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was dissolved in methanol (200 mL) and 10% palladium on charcoal (5.1 g, 4.8 mmol, 0.05 equiv) in methanol. The mixture was stirred for 12 h under a hydrogen atmosphere (60 atm) at 40 °C. Palladium was filtered off and washed with methanol twice, and the solvent was removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 (200 mL), and then DMAP (0.7 g, 6.0 mmol, 0.1 equiv), NEt_3 (6.2 g, 72 mmol, 1.2 equiv), and Boc_2O (15.7 g, 72 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 12 h, washed with a 10% aqueous citric acid solution (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in hexanes (100 mL), and the formed precipitate was filtered to afford the product as a white solid, mp 68−69 °C (7.2 g, 43% yield). dr = 51:49 according to the LCMS spectrum. ^{1}H NMR (400 MHz, $CDCl_3$) of both diastereomers: δ 10.92 (br s, 1H), 3.61 (m, 2H), 3.03 (m, 3H), 2.10 (m, 8H), 1.46 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) of both diastereomers: δ 181.4 (s), 181.1 (s), 155.5 (s), 155.4 (s), 79.5 (s), 79.4 (s), 52.4 (s), 46.0 (s), 43.3 (s), 42.9 (s), 42.4 (s), 41.4 (s), 36.6 (s), 35.8 (s), 28.5 (s). LCMS (*m*/*z*): 280 (M − H$^+$). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.30; H, 8.46; N, 5.13.

5-((3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-6-yl)-methyl)-5-isopropylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (49). The solution of **48** (100 mg, 0.48 mmol, 1.0 equiv), **1** (90 mg, 0.48 mmol, 1.0 equiv), and benzophenone (20 mg, 0.11 mmol, 0.23 equiv) in dry acetonitrile (25 mL) was degassed by the bubbling of argon for 15 min. The reaction flask was closed by a septum and irradiated with 366 nm UV light for 24 h. With some of **48** left in the reaction mixture after 24 h of irradiation (monitored by ^{1}H NMR), maleimide **1** (90 mg, 0.48 mmol, 1.0 equiv) was added once more and irradiation was continued for another 24 h. The reaction mixture was filtered or concentrated under reduced pressure and purified via reverse-phase column chromatography to get the product as a white solid, mp 192−193 °C; 69% yield (130 mg). dr = 70:30 according to the LCMS spectrum. ^{1}H NMR (500 MHz, DMSO) of both diastereomers: δ 11.52 (broad s, 1H), 11.47 (broad s, 1H), 7.43−7.06 (m, 5H), 4.63−4.43 (m, 2H), 3.20 (m, 1H), 2.95 (dd, J = 6.6, 3.4 Hz, 1H), 2.40−1.99 (m, 6H), 0.94 (d, ^3J(H,H) = 6.6 Hz Hz, 3H), 0.90 (d, ^3J(H,H) = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) of both diastereomers: δ 179.6 (s), 178.7 (s), 172.8 (s), 172.6 (s), 150.3 (s), 136.8 (s), 129.0 (s), 127.8 (s), 127.7 (s), 57.1 (s), 43.8 (s), 41.9 (s), 39.6 (s), 38.5 (s), 35.6 (s), 34.9 (s), 28.6 (s), 18.0 (s), 17.7 (s). LCMS (*m*/*z*): 398 (M + H$^+$). Anal. Calcd for $C_{21}H_{23}N_3O_5$: C, 63.47; H, 5.83; N, 10.57. Found: C, 63.27; H, 5.98; N, 10.23.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00077.

Copies of NMR spectra for all new compounds and X-ray crystallography data (PDF)

Crystal data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Pavel.Mykhailiuk@gmail.com; Pavel.Mykhailiuk@mail.enamine.net.

ORCID

Pavel K. Mykhailiuk: 0000-0003-1821-9011

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are very grateful to Dr. S. Shishkina for X-ray studies, I. Stadnyi for help with UV lamps and reaction vessels, V. Polovinko and A. Kozitskiy for NMR spectra, A. Shukhaev and O. Michurin for alkenes **18**, **19**, and **29**, M. Nechayev for high pressure hydrogenation, and Prof. I. Komarov for incredible ideas and limitless inspiration.

■ REFERENCES

(1) Böhm, H.-J.; Flohr, A.; Stahl, M. *Drug Discovery Today: Technol.* **2004**, *1*, 217.

(2) (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Ritchie, T. J.; Macdonald, S. J. F. *Drug Discovery Today* **2009**, *14*, 1011.

(3) (a) Mann, A. Conformational restriction and/or steric hindrance in medicinal chemistry. In *The Practice of Medicinal Chemistry*, 3rd ed.; Wermuth, C., Ed.; Academic Press/Elsevier: Amsterdam, 2008; 363. (b) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114. (c) Foley, D. J.; Nelson, A.; Marsden, S. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 13650. (d) Goldberg, F. W.; Kettle, J. G.; Kogej, T.; Perry, M. W. D.; Tomkinson, N. P. *Drug Discovery Today* **2015**, *20*, 11. (e) Marson, C. M. *Chem. Soc. Rev.* **2011**, *40*, 5514.

(4) (a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052 (oxetanes). (b) Hsieh, S.-Y.; Bode, J. W. *Org. Lett.* **2016**, *18*, 2098 (piperazines). (c) Wlochal, J.; Davies, R. D. M.; Burton, J. *Org. Lett.* **2014**, *16*, 4094 (cubanes). (d) Chalmers, B. A.; Xing, H.; Houston, S.; Clark, C.; Ghassabian, S.; Kuo, A.; Cao, B.; Reitsma, A.; Murray, C.-E. P.; Stok, J. E.; Boyle, G. M.; Pierce, C. J.; Littler, S. W.; Winkler, D. A.; Bernhardt, P. V.; Pasay, C.; De Voss, J. J.; McCarthy, J.; Parsons, P. G.; Walter, G. H.; Smith, M. T.; Cooper, H. M.; Nilsson, S. K.; Tsanaktsidis, J.; Savage, G. P.; Williams, C. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 3580 (cubanes). (e) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524 (spirocycles). (f) Heugebaert, T.; Hevele, J. V.; Couck, W.; Bruggeman, V.; Van der Jeught, S.; Masschelein, K.; Stevens, C. V. *Eur. J. Org. Chem.* **2010**, *6*, 1017. (g) Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. *Chem. Rev.* **2016**, *116*, 12150.

(5) (a) Druzhenko, T.; Denisenko, O.; Kheylik, Y.; Zozulya, S.; Shishkina, S.; Tolmachev, A.; Mykhailiuk, P. K. *Org. Lett.* **2015**, *17*, 1922. (b) Denisenko, A. V.; Mityuk, A. P.; Grygorenko, O. O.; Volochnyuk, D. M.; Shishkin, O. V.; Tolmachev, A. A.; Mykhailiuk, P. K. *Org. Lett.* **2010**, *12*, 4372. (c) Kirichok, A. A.; Shton, I.; Kliachyna, M.; Pishel, I.; Mykhailiuk, P. K. *Angew. Chem., Int. Ed.* **2017**, *56*, 8865. (d) Chalyk, B.; Isakov, A.; Butko, M.; Hrebeniuk, K.; Savych, O.; Kucher, O.; Gavrilenko, K.; Druzhenko, T.; Yarmolchuk, V.; Zozulya, S.; Mykhailiuk, P. K. *Eur. J. Org. Chem.* **2017**, *31*, 4530. (e) Chalyk, B.; Butko, M.; Yanshyna, O.; Gavrilenko, K.; Druzhenko, T.; Mykhailiuk, P. K. *Chem. - Eur. J.* **2017**, *23*, 16782. (f) Nicolle, S.; Nortcliffe, A.; Bartrum, H.; Lewis, W.; Hayes, C.; Moody, C. J. *Chem. - Eur. J.* **2017**, *23*, 13623. (g) Davis, O. A.; Bull, J. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 14230.

(6) ChEMBL database: www.ebi.ac.uk/chembl.

(7) For intramolecular [2+2]-photochemical into 3-azabicyclo[3.2.0] heptanes, see: (a) Bach, T.; Krüger, C.; Harms, K. *Synthesis* **2000**, *2*, 305. (b) Basler, B.; Schuster, O.; Bach, T. *J. Org. Chem.* **2005**, *70*, 9798. (c) Albrecht, D.; Basler, B.; Bach, T. *J. Org. Chem.* **2008**, *73*, 2345. (d) Fort, D. A.; Woltering, T. J.; Nettekoven, M.; Knust, H.; Bach, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1. (e) Steiner, G.; Munschauer, R.; Klebe, G.; Siggel, L. *Heterocycles* **1995**, *40*, 319. (f) Pedrosa, R.; Andrés, C.; Nieto, J.; del Pozo, S. *J. Org. Chem.* **2003**, *68*, 4923. (g) Oppolzer, W.; Achini, R.; Pfenninger, E.; Weber, H.-P. *Helv. Chim.*

Acta **1976**, *59*, 1186. (h) Denisenko, A. V.; Druzhenko, T.; Skalenko, Y.; Samoilenko, M.; Grygorenko, O. O.; Zozulya, S.; Mykhailiuk, P. K. *J. Org. Chem.* **2017**, *82*, 9627.

(8) For intramolecular [M]-catalyzed cyclizations into 3-azabicyclo[3.2.0]heptanes, see: (a) Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572. (b) Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10329. (c) Hurtley, A. E.; Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 8991. (d) Gonzalez, A.; Benitez, D.; Tkatchouk, E.; Goddard, W.; Toste, D. *J. Am. Chem. Soc.* **2011**, *133*, 5500. (e) Luzung, M.; Mauleon, P.; Toste, D. *J. Am. Chem. Soc.* **2007**, *129*, 12402. (f) Teller, H.; Flugge, S.; Goddard, R.; Furstner, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 1949. (g) Gulias, M.; Collado, A.; Trillo, B.; Lopez, F.; Onate, E.; Esteruelas, M.; Mascarenas, J. *J. Am. Chem. Soc.* **2011**, *133*, 7660. (h) Nakano, S.; Kakugawa, K.; Nemoto, T.; Hamada, Y. *Adv. Synth. Catal.* **2014**, *356*, 2088. (i) Bouwkamp, M. W.; Bowman, A. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 13340. (j) Jiang, X.; Cheng, X.; Ma, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8009. (k) Hong, Y.-H.; Yoon, S.-K.; Kang, S.-K.; Yu, C.-M. *Eur. J. Org. Chem.* **2004**, *22*, 4628.

(9) (a) Kriis, K.; Ausmees, K.; Pehk, T.; Lopp, M.; Kanger, T. *Org. Lett.* **2010**, *12*, 2230. (b) Reinart-Okugbeni, R.; Ausmees, K.; Kriis, K.; Werner, F.; Rinken, A.; Kanger, T. *Eur. J. Med. Chem.* **2012**, *55*, 255. (c) Ausmees, K.; Kriis, K.; Pehk, T.; Werner, F.; Järving, I.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2012**, *77*, 10680.

(10) (a) Petz, S.; Wanner, K. T. *Eur. J. Org. Chem.* **2013**, *19*, 4017. (b) Andre, V.; Gras, M.; Awada, H.; Guillot, R.; Robin, S.; Aitken, D. J. *Tetrahedron* **2013**, *69*, 3571. (c) André, V.; Vidal, A.; Ollivier, J.; Robin, S.; Aitken, D. J. *Tetrahedron Lett.* **2011**, *52*, 1253. (d) Reid, S. T.; De Silva, D. *Tetrahedron Lett.* **1983**, *24*, 1949.

(11) For some examples, see: (a) Elliott, L. D.; Knowles, J. P.; Koovits, P. J.; Maskill, K. G.; Ralph, M. J.; Lejeune, G.; Edwards, L. J.; Robinson, R. I.; Clemens, I. R.; Cox, B.; Pascoe, D. D.; Koch, G.; Eberle, M.; Berry, M. B.; Booker-Milburn, K. I. *Chem. - Eur. J.* **2014**, *20*, 15226. (b) Kumarasamy, E.; Raghunathan, R.; Jockusch, S.; Ugrinov, A.; Sivaguru, J. *J. Am. Chem. Soc.* **2014**, *136*, 8729. (c) Mahendar, V.; Oikawa, H.; Oguri, H. *Chem. Commun.* **2013**, *49*, 2299. (d) Tedaldi, L. M.; Aliev, A. E.; Baker, J. R. *Chem. Commun.* **2012**, *48*, 4725. (e) Horiuchi, S.; Nishioka, Y.; Murase, T.; Fujita, M. *Chem. Commun.* **2010**, *46*, 3460. (f) Nishioka, Y.; Yamaguchi, T.; Kawano, M.; Fujita, M. *J. Am. Chem. Soc.* **2008**, *130*, 8160.

(12) (a) Booker-Milburn, K. I.; Wood, P. M.; Dainty, R. F.; Urquhart, M. W.; White, A. J.; Lyon, H. J.; Charmant, J. P. H. *Org. Lett.* **2002**, *4*, 1487. (b) Booker-Milburn, K. I.; Cowell, J. K.; Jiménez, F. D.; Sharpe, A.; White, A. J. *Tetrahedron* **1999**, *55*, 5875. (c) Booker-Milburn, K. I.; Gulten, S.; Sharpe, A. *Chem. Commun.* **1997**, 1385. (d) Chang, Z.; Boyaud, F.; Guillot, R.; Boddaert, T.; Aitken, D. J. *J. Org. Chem.* **2018**, *83*, 527. (e) Murase, T.; Nishijima, Y.; Fujita, M. *Chem. - Asian J.* **2012**, *7*, 826.

(13) (a) Rynbrandt, R. H. *J. Heterocycl. Chem.* **1974**, *11*, 787. (b) Mattei, P.; Hunziker, D.; Di Giorgio, P.; Hert, J.; Rudolph, M.; Lisha, W. Patent WO 2015078803A1, 2015. (c) Yoshizawa, M.; Takeyama, Y.; Okano, T.; Fujita, M. *J. Am. Chem. Soc.* **2003**, *125*, 3243. Organocatalytic [2+2]-cycloaddition of **1** was reported last year: (d) Zhou, Z.; Wang, Z.-X.; Zhou, Y.-C.; Xiao, W. Q.; Ouyang, W.; Du, W.; Chen, Y.-C. *Nat. Chem.* **2017**, *9*, 590.

(14) Poplata, S.; Troster, A.; Zou, Y.-Q.; Bach, T. *Chem. Rev.* **2016**, *116*, 9748 (review).

(15) For our previous experience in photochemistry, see: (a) Tkachenko, A. N.; Radchenko, D. S.; Mykhailiuk, P. K.; Grygorenko, O. O.; Komarov, I. V. *Org. Lett.* **2009**, *11*, 5674. (b) Mykhailiuk, P. K.; Kubyshkin, V.; Bach, T.; Budisa, N. *J. Org. Chem.* **2017**, *82*, 8831.

(16) We used commercially available photoreactors. Importantly, all reactions up to 10 g scale can also be performed using the simple Shellac UV lamp (366 nm mode) available at any market store for ca. 15 USD.

(17) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546.

(18) (a) Grygorenko, O. O.; Babenko, P.; Volochnyuk, D. M.; Raievskyi, O.; Komarov, I. V. *RSC Adv.* **2016**, *6*, 17595. (b) Grygorenko, O. O.; Prytulyak, R.; Volochnyuk, D. M.; Kudrya, V.; Khavryuchenko, O. V.; Komarov, I. V. *Mol. Diversity* **2012**, *16*, 477.

(19) Abreu, A. S.; Silva, E. O.; Rumjanek, V. M.; Souza Junior, J.; da Silva, A. B. F.; de A.Santos, R. H. *Int. J. Quantum Chem.* **2008**, *108*, 513.

(20) Ravikumar, K.; Sridhar, B. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2009**, *65*, 502.

(21) Onan, K. D.; Rao, H. S. P.; Parry, R. J. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1985**, *41*, 428.

(22) Bhuiyan, M. D. H.; Jensen, P.; Turner, P.; Try, A. C. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2007**, *63*, 1115.

(23) Beeching, L. J.; Hawes, C. S.; Turner, D. R.; Batten, S. R. *CrystEngComm* **2014**, *16*, 6459.

(24) Herdklotz, J.; Sass, R. L. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1969**, *25*, 1614.

DOI: 10.1021/acs.joc.8b00077
J. Org. Chem. XXXX, XXX, XXX−XXX