JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of 3D-Rich Heterocycles: Hexahydropyrazolo[1,5-*a*]pyridin-2(1*H*)-ones and Octahydro-2*H*-2a,2a^1-diazacyclopenta[*cd*]inden-2-ones

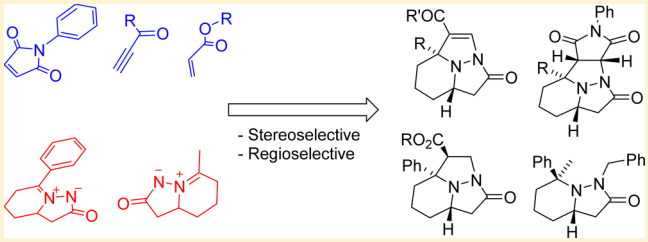
Eva Pušavec Kirar,[†] Miha Drev,[†] Jona Mirnik,[†] Uroš Grošelj,[†] Amalija Golobič,[†] Georg Dahmann,[‡] Franc Požgan,[†] Bogdan Štefane,[†] and Jurij Svete*[,†]

[†]Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI-1000 Ljubljana, Slovenia

[‡]Medicinal Chemistry, Boehringer-Ingelheim Pharma GmbH&Co. KG, 88397 Biberach, Germany

Supporting Information

ABSTRACT: Two cyclic azomethine imines, 7-methyl- and 7-phenyl-2-oxo-Δ^7-hexahydropyrazolo[1,5-*a*]pyridin-8-ium-1-ide, were prepared in seven steps from the respective commercially available δ-keto acids. The addition of Grignard reagents followed by N-alkylation at position 1 afforded the 1,7,7-trisubstituted hexahydropyrazolo[1,5-*a*]pyridin-2(1*H*)-ones, whereas 1,3-dipolar cycloadditions of these dipoles to typical acetylenic and olefinic dipolarophiles gave 4a-substituted 2a,2a^1-diazacyclopenta[*cd*]indene derivatives as the first representatives of a novel heterocyclic system. Regio- and stereoselectivity as well as the mechanism of these [3 + 2]-cycloadditions were evaluated using computational and experimental methods. The data obtained were in agreement with the polar concerted cycloaddition mechanism via the energetically favorable *syn*/*endo*-transition states.



1. INTRODUCTION

Heterocyclic systems are common building blocks for the synthesis of various biologically important and naturally occurring compounds. Consequently, heterocycles are commonly used building blocks for applications in medicinal chemistry, catalysis, and material science.[1] In this context, pyrazolo[1,5-*a*]pyridine (**1**)[2] belongs to a group of well-explored systems with over 100000 hits and over 2500 references according to a SciFinder[3] substructure search. Derivatives of **1** exhibit different biological activities, such as antiviral activity,[4] inhibition of reverse transcriptase,[5] dopamine D3 and D4 antagonist,[6] dopamine D3 agonist,[7] diuretic adenosine A1 antagonist,[8] and intercalating activity.[9] A phosphodiesterase inhibitor, ibudilast (**2**), is an approved anti-inflammatory drug.[10] In contrast to thousands of known derivatives of pyrazolo[1,5-*a*]pyridine (**1**), only ∼120 fully saturated derivatives of **3** are known to date,[3] whereas the tricyclic analogues **4** (2a,2a^1-diazacyclopenta[*cd*]indenes) are unknown to the best of our knowledge. Note that two related examples can be found in the literature. The first example is a theoretical report on **4** as a part of a heterofullerene system,[11] while in the second example **4** was a part of a cage compound (Figure 1).[12]

In the context of our ongoing work on the synthesis of 3-pyrazolidinones and pyrazole analogues of histamine,[13] we recently reported two syntheses of tetrahydropyrazolo[1,5-*c*]pyrimidine-2,7(1*H*,3*H*)-diones as the first representatives of a novel saturated heterocyclic system.[14,15] Subsequently, a library of related tetrahydropyrazolo[1,5-*c*]pyrimidine-3-carboxamides as novel conformationally constrained pyrazole analogues of histamine was also synthesized.[16] In continuation of that work, we focused on 1,7,7-trisubstituted hexahydropyrazolo[1,5-*a*]pyridin-2(1*H*)-ones **5** and their tricyclic analogues (3,4,4a-trisubstituted octahydro-2*H*-2a,2a^1-diazacyclopenta[*cd*]inden-2-ones) **6** (Figure 1). A literature search revealed that scaffolds **5** and **6** were unknown, which prompted us to focus our attention on their synthesis since the availability of this type of template would enable the preparation of compound libraries

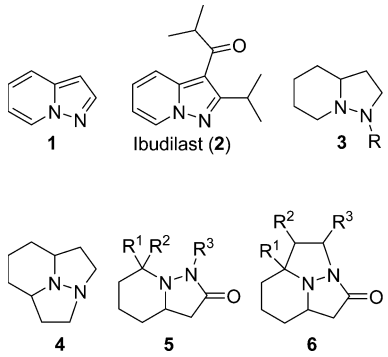


Figure 1. Pyrazolo[1,5-*a*]pyridine (**1**), ibudilast (**2**), less explored saturated analogues **3**, the unknown saturated tricyclic system **4**, and the target structures **5** and **6**.

Received: July 5, 2016
Published: September 14, 2016

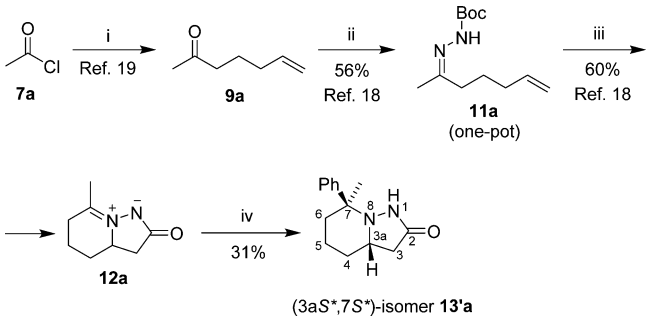
DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

suitable for screening for various activities or applications. The results of this study are reported herein.

2. RESULTS AND DISCUSSION

Initially, we attempted to access the title compounds via 7-substituted 2-oxo-2,3,3a,4,5,6-hexahydropyrazolo[1,5-*a*]pyridin-8-ium-1-ides **12** as key intermediates available by microwave-assisted cyclization of pent-4-en-1-yl *N*-Boc-hydrazones **11**[17] following the procedure described recently by Beauchemin and co-workers.[18] First, hept-6-en-2-one (**9a**) was prepared by Cu(I)-catalyzed treatment of acetyl chloride (**7a**) with pent-4-en-1-ylmagnesium bromide (**8a**).[19] The crude ketone **9a** was, without purification, transformed further with Boc-carbazate (**10**) into the corresponding hydrazone **11a**, which was isolated in 56% yield over two steps. Subsequent cyclization of hydrazone **11a** was performed in trifluoromethylbenzene under microwave irradiation at 150 °C to afford the desired azomethine imine **12a** in 60% yield.[18] Finally, stereoselective reduction of dipole **12a** with excess PhMgBr at 0−20 °C followed by workup using column chromatography furnished the (3a*S**,7*S**)-isomer **13′a** in 31% yield (Scheme 1).

Scheme 1. Four-Step Synthesis of Compound 13′a



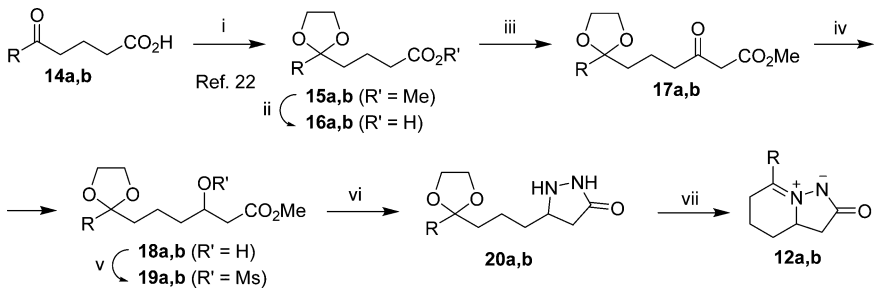
[a]Reaction conditions: (i) pent-4-en-1-ylmagnesium bromide (**8a**), THF, CuI (4 mol %), rt (ref 19); (ii) $BocNHNH_2$ (**10**), MeOH, AcOH, rt (ref 18); (iii) μ-waves, 300 W, $C_6H_5CF_3$, 150 °C, 3 h (ref 18); (iv) excess PhMgBr (**8b**), THF, 0 → 20 °C, followed by column chromatography.

The successful preparation of **13′a** confirmed the viability and simplicity of the original synthetic approach. However, the microwave-assisted cyclization of **11a** into **12a** was the bottleneck of this synthetic sequence because in our hands the reaction was reproducible only on a ∼0.3 mmol scale, i.e., on a scale similar to that reported previously (0.2 mmol).[18] In addition, the incomplete conversion and the formation of by-products required a tedious chromatographic workup to obtain pure **12a**. Thus, despite its simplicity, the original synthetic approach was not suitable to provide sufficient amounts of the key intermediates **12** for further transformations. Consequently, a seven-step synthesis of **12** was developed on the basis of a synthetic method applied previously for the preparation of related pyrazolidinones.[15] The synthesis commenced with an almost quantitative one-pot transformation of commercially available γ-acetyl- (**14a**) and γ-benzoylbutyric acid (**14b**) into the δ-keto acid ketals **16a**[20] and **16b**;[21] these steps were composed of ketalization and esterification with ethylene glycol and trimethyl orthoformate (TMOF) and were followed by hydrolysis of the intermediate ketal-esters **15a,b**.[21,22] Masamune−Claisen condensation of the acids **16** afforded the corresponding β-keto esters **17a,b** in quantitative yields. Then, reduction of ketones **17**, followed by O-mesylation of alcohols **18** and cyclization of O-mesylates **19** with hydrazine hydrate, furnished the pyrazolidinones **20a** and **20b** in good yields over three steps. Finally, acidolytic removal of the ketal protecting group and concomitant cyclization furnished the desired key intermediates **12a**[18] and **12b**[23] in 80 and 60% yield, respectively (Scheme 2).

Next, the addition of Grignard reagents to dipoles **12a** and **12b** was studied. First, we attempted to add excess PhMgBr (**8b**) to the dipole **12a** at a lower temperature; however, at −78 °C, no reaction occurred after several hours. When the reaction was performed at −20 °C for 1 h followed by treatment at room temperature for 12 h, pure (3a*S**,7*S**)-isomer **13′a** was isolated in 54% yield. The other epimer could not be detected in the reaction mixture. As expected, the epimer **13a** was exclusively obtained in 69% yield upon treatment of the 7-phenyl analogue **12b** with excess MeMgBr (**8c**) under the same reaction conditions. However, the addition of MeMgBr (**8c**) to **12a** gave compound **13b** in 31% yield. N-Alkylation of **13a**, **13′a**, and **13b** with methyl iodide or benzyl bromide in DMF in the presence of K_2CO_3 furnished the title compounds **5a**, **5′a**, **5′b**, and **5c** in good yields. The stereoselectivity of the addition reaction is explainable by the preferential attack of the Grignard reagent **8** to the less hindered face of the dipole **12** to give the major isomer with *syn*-oriented R′ and H-3a (Scheme 3).

The 1,3-dipolar characteristics of azomethine imines **12a** and **12b** were tested in [3 + 2]-cycloadditions to acetylenic (**21a−e**) and olefinic dipolarophiles **22a−c**. Most cycloadditions were highly regio- and stereoselective and gave the corresponding cycloadducts **23−26** as single isomers upon workup using flash chromatography. Cycloadditions of **12a,b** to dimethyl

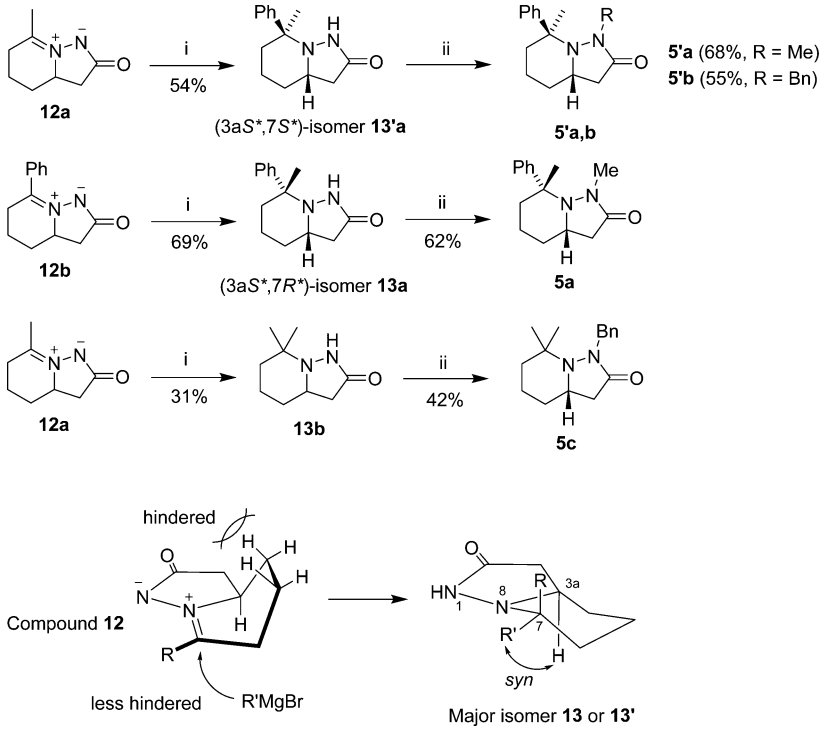
Scheme 2. Seven-Step Synthesis of Azomethine Imines 12a and 12b



[a]Reaction conditions: (i) ethylene glycol, TMOF, H_2SO_4 (cat.), rt (ref 22); (ii) 2 M aq NaOH, H_2O−MeOH, rt (ref 22); (iii) CDI, THF, rt, then $MeO_2CCH_2CO_2K$, $MgCl_2$, rt; (iv) $NaBH_4$, MeOH, 0 °C; (v) MsCl, pyridine, 0 °C; (vi) $N_2H_4{\cdot}H_2O$, MeOH, 50 °C; (vii) EtOH, TFA (cat.), reflux.

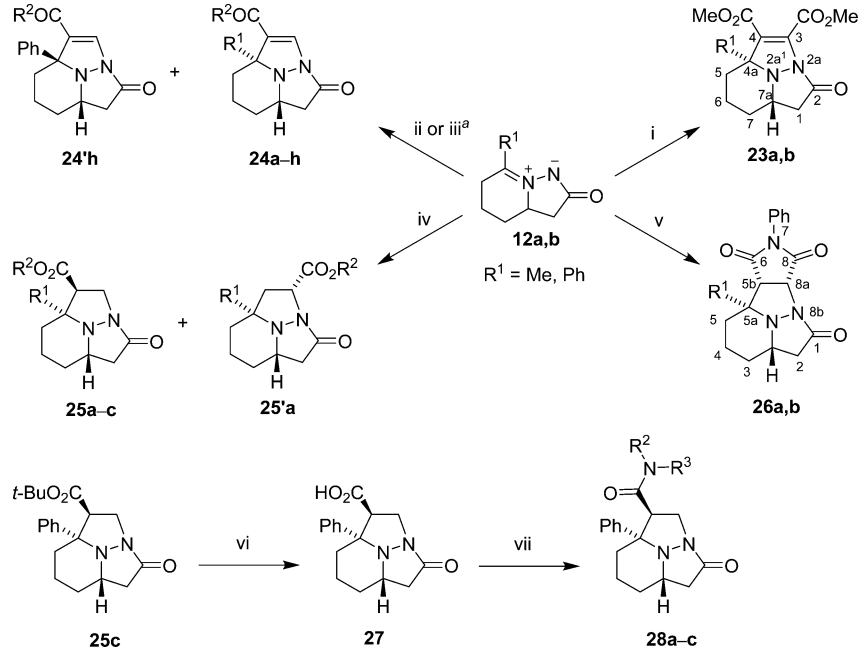
DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

Scheme 3. Synthesis of Title Bicyclic Compounds 5, 5′, 13, and 13′ and the Proposed Stereochemistry of the Addition to the C═N Bond



[a]Reaction conditions: (i) excess PhMgBr (**8b**) or MeMgBr (**8c**), THF, −20 °C→ rt; (ii) MeI or BnBr, K_2CO_3, DMF, rt.

Scheme 4. Synthesis of the Title Tricyclic Compounds 23−28[a]



*Reaction conditions: (i) DMAD (**21a**), toluene or CH_2Cl_2, rt; (ii) ynone **21b−d** or methyl propiolate (**21e**), CH_2Cl_2, rt or 80 °C (pressure vessel); (iii) methyl propiolate (**21e**), CuI (20 mol %), DIPEA (20 mol %), CH_2Cl_2, rt; (iv) methyl acrylate (**22a**) or *tert*-butyl acrylate (**22b**), toluene or CH_2Cl_2 (pressure vessel), 80 °C; (v) *N*-phenylmaleimide (**22c**), toluene, 80 °C followed by column chromatography; (vi) CH_2Cl_2−TFA (2:1), rt; and (vii) BPC, Et_3N, DMF, rt, 1 h followed by R^2R^3NH, Et_3N, rt, 24 h. [a]In the CuI-catalyzed reactions (see (iii)), by-product **29** was also formed.[24]

acetylenedicarboxylate (DMAD) (**21a**) and terminal ynones **21b−d** proceeded at room temperature to give the major (4aS*,7aS*)-isomers **23a,b** and **24a−f** in 42−73% yields. Surprisingly, methyl propiolate (**21e**) did not react at room temperature, and heating at 80 °C was required to obtain cycloadducts **24g** and **24h**. In the reaction of **12b** with **21e**, the minor isomer **24′h** was also isolated. The CuI-catalyzed reactions of **12a,b** with **21e** occurred at room temperature to

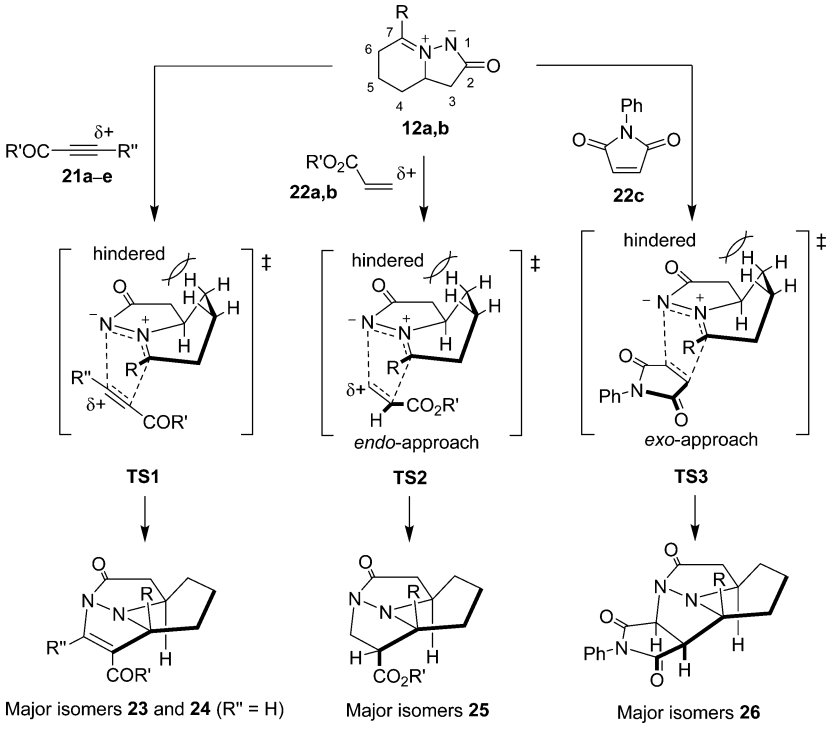
DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

Table 1. Experimental Data on Tricyclic Compounds 23−28

compd	R^1	R^2	R^3	dr[a]	yield (%)
23a	Me			94:6	60
23b	Ph			100:0	56
24a	Me	Me		93:7	73
24b	Ph	Me		91:9	69
24c	Me	Ph		90:10	67
24d	Ph	Ph		100:0	71
24e	Me	CH_2NHBoc		93:7	42
24f	Ph	CH_2NHBoc		89:11	50
24g	Me	OMe		93:7 (100:0[b])	56 (47[b])
24h	Ph	OMe		85:15 (100:0[b])	60 (59[b])
24′h[c]	Ph	OMe		100:0[d]	11
25a	Me	Me		100:0[d]	16
25′a	Me	Me		[d,e]	11
25b	Ph	Me		[e]	44
25c	Ph	*t*-Bu		100:0[e,f]	77
26a	Me			78:22	13
26b	Ph			90:10	40
27	Ph				48
28a		H	Bn		79
28b		H	$(CH_2)_3OH$		76
28c		piperidin-1-yl			70

[a]Determined using ^{1}H NMR. [b]CuI-catalyzed reaction. [c]Minor epimer. [d]Upon separation by column chromatography. [e]The isomer ratio could not be determined due to overlapped signals in the ^{1}H NMR spectrum of the crude product. [f]Upon purification using flash column chromatography.

Scheme 5. Regio- and Stereoselectivity of Cycloadditions to Chiral Dipoles 12a and 12b



give inseparable 85:15 mixtures of cycloadducts **24g,h** and methyl (*E*)-3-[ethyl(isopropyl)amino]acrylate (**29**).[24] The reactions of dipoles **12** with olefinic dipolarophiles **22a−c** required heating at 80 °C to achieve satisfactory conversion into the products. Treatment of **12a** with methyl acrylate (**22a**) produced a mixture of products; upon chromatographic separation, the *endo*-cycloadduct **25a** and the regioisomeric *exo*-adduct **25′a** were isolated in 11% and 16% yield, respectively. The reactions of the 7-phenyl analogue **12b** with methyl (**22a**) and *tert*-butyl acrylate (**22b**) were highly regio- and stereoselective and afforded the major *endo*-isomers **25b** and **25c** as single products. Cycloadditions of **12a** and **12b** to *N*-phenylmaleimide (**22c**) followed by chromatographic separation furnished the major *exo*-isomers **26a** and **26b** in 13% and 40% yield, respectively. To evaluate the further diversification of the core scaffold, the acidolytic deprotection of the carboxy function of cycloadduct **25c** gave the carboxylic acid **27** in 48% yield. Amidation of **27** using bis-

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

(pentafluorophenyl) carbonate (BPC) as the activating reagent furnished carboxamides **28a−c** in 70−79% yields (Scheme 4, Table 1).

The regioselectivity of the cycloadditions to terminal ynones **21b−e** and alkyl acrylates **22** was in agreement with the regioselectivity of closely related thermal[13,25,26] and Cu-catalyzed reactions.[13,26,27] The preferential formation of the regioisomers **24** and **25** is in line with the electrostatically controlled approach of the polarized dipolarophile **21** or **22** to the mesomeric structure **12** via the proposed transition states **TS1** and **TS2** (Scheme 5). Facial selectivity of cycloadditions to **12a,b** is explainable by the preferential attack of the dipolarophile **21** or **22** from the less hindered face of the dipole **12** via the proposed transition states **TS1−TS3**. Accordingly, the *endo*-attack of the acrylate **22** via **TS2** should lead to the major diastereomer **25**, whereas the *exo*-approach of maleimide **22c** via **TS3** should give the major *exo*-isomers **26** (Scheme 5).

3. STRUCTURE DETERMINATION

The structures of novel compounds **5a,c**, **5′a,b**, **13a,b**, **13′a**, **17a,b**, **18a,b**, **19a,b**, **20a,b**, **23a,b**, **24a−h**, **24′h**, **25a−c**, **25′a**, **27**, and **28a−c** were determined using spectroscopic methods (IR, ^{1}H and ^{13}C NMR, COSY, HSQC, HMBC and NOESY spectroscopy, and MS). The structure and purity of compounds **12b**, **5′a**, and **5′b** were additionally determined via elemental analyses for C, H, and N. Crude intermediates **16a,b**, **17a,b**, **18a,b**, **19a,b**, and **20a,b** were used in the following transformation without any purification.

The relative configurations of bicyclic (**5**, **5′**, **13**, and **13′**) and tricyclic compounds **23−26** were determined by ^{1}H NMR and NOESY spectroscopy.[28] The structures of structurally representative compounds **5′b**, **13′a**, **23b**, **24b**, **26b**, and **28a** were unambiguously determined using X-ray diffraction.[28] The crystal structure of cycloadduct **24b** is depicted in Figure 2.

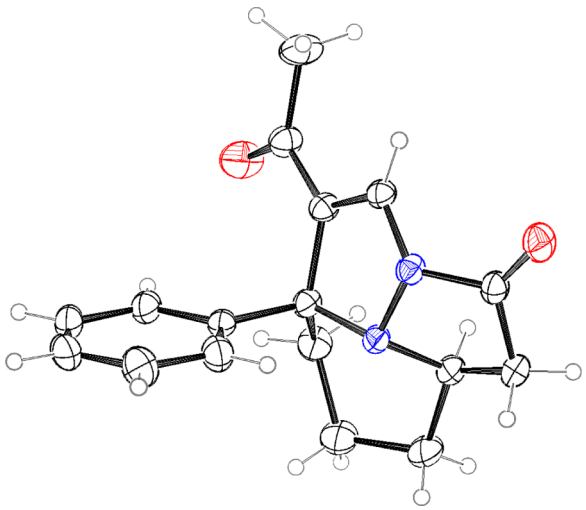


Figure 2. ORTEP drawing of a molecule of **24b** showing the atom labeling. The displacement ellipsoids are drawn with a 30% probability level, and the hydrogen atoms are shown as small spheres of arbitrary radii.

4. COMPUTATIONAL DETERMINATION OF THE MECHANISM AND SELECTIVITY OF [3 + 2]-CYCLOADDITIONS

In contrast to highly regioselective catalyzed reactions,[27] thermal cycloadditions of azomethine imines to terminal acetylenes usually furnish mixtures of regioisomers.[25,26] Intrigued by the high regioselectivity of thermal cycloadditions of dipoles **12** (cf. Scheme 4), we attempted to find a plausible mechanistic explanation[29] using computational methods. Dipoles **12a,b**, 3-butyn-2-one (**21b**), methyl propiolate (**21e**), and methyl acrylate (**22a**) were chosen as model reactants.

All computations were performed using the Gaussian 09 program suite.[30] Geometry optimization of all stationary points was performed using DFT methods at the B3LYP/6-311+G-(d,p) level of theory.[31] First, the ideal gas approximation under the standard conditions was assumed, and then the polarizable continuum model (PCM) for solvation by toluene was used for the computations. The DFT study started with an evaluation of the energetic and structural aspects of possible regio- and stereoisomeric transition states. The *syn*/*anti*-approach refers to facial selectivity with respect to the angular proton H-3a, while for the acetylenic dipolarophiles **21b** and **21e** the *endo*-orientation refers to the orientation of the C═O function in the transition state.[28]

The calculated activation and distortion/interaction parameters[32] as well as asynchronicity parameter ($\Delta d_{TS/P}$)[32g,h] are reported in Table 2. In all reactions, the *syn*-transition states were found to be energetically favorable. The differences of the Gibbs energy of activation values between the *syn* and the *anti* forms in the range of 2.7−4.0 kcal mol^{-1} demonstrate that the reaction channel prefers the *syn*-approach to the dipole **12**. The typical asynchronicity measure value, $\Delta d_{TS/P} \sim 0.3$, suggests that reactions are concerted, although asynchronous. The computed free energy of activation values in toluene as the reaction medium are significantly smaller ($\Delta\Delta G^{\ddagger} \approx 8$ kcal mol^{-1}) for the ynone-derived cycloadducts **24** compared to the acrylate-derived cycloadducts **25**. In the reactions with acrylate **22a**, the 7-phenyl dipole **12b** has a lower energy and more asynchronous transition state than its 7-methyl analogue **12a**. Transition states leading to the minor regioisomers **25′** are higher in energy than those for the major isomers **25**. Finally, the energy difference between the 4a-methyl regioisomers **25a** and **25′a** ($\Delta\Delta G^{\ddagger}$ = 2.8 kcal/mol) is smaller than that for the 4a-phenyl analogs **25b** and **25′b** ($\Delta\Delta G^{\ddagger}$ = 6.1kcal/mol). The calculated parameters given in Table 2 are in agreement with the experimental results in terms of reactivity and selectivity (cf. Scheme 4 and Table 1).[28]

Transition states leading to regioisomers **25a** and **25′a** are shown in Figure 3. In the transition state for the major isomer, TS**25a**-*syn*/*endo*, the C−N bond is shorter than the C−C bond, while these values are inverted in TS**25′a**-*syn*/*endo*. This result suggests that the C−C bond formation is more advanced in TS**25′a,b**-*syn*/*endo*, while the formation of the C−N bond is more advanced in TS**25a**-*syn*/*endo*.[28]

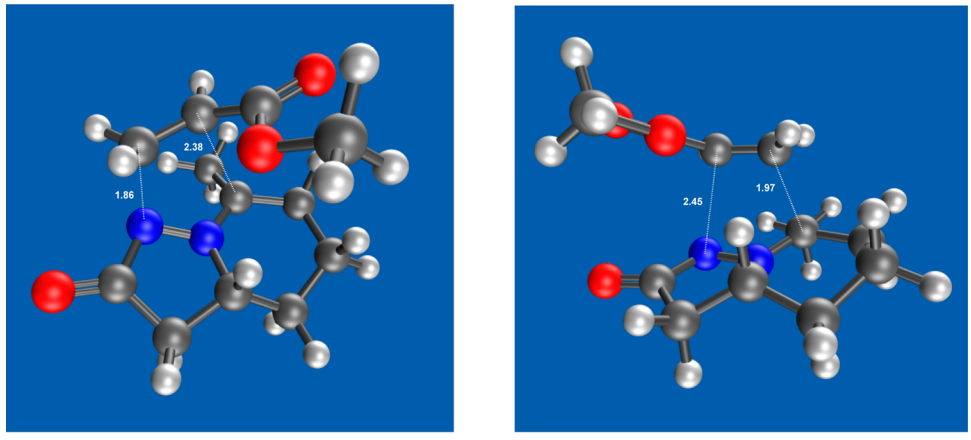
The electrophilicity ω and nucleophilicity N values[33] for the dipoles **12a,b** and dipolarophiles **21b**, **21e**, and **22a** are displayed in Table 3. All dipolarophiles, **21b**, **21e**, and **22a**, have high electrophilicity indices, 1.93, 1.97, and 2.20 eV, respectively, and are classified as strong electrophiles on the electrophilicity scale.[34] However, the dipoles **12a** and **12b** present moderate to strong respective electrophilicity indices of 1.39 and 2.13 eV, respectively, while both are classified as

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

Table 2. B3LYP/6-311+G(d,p)-Calculated Activation Energies, Distortion Energies ($\Delta E_d^{\ddagger}$), Interaction Energies ($\Delta E_i^{\ddagger}$), and Asynchronicity Degrees for Transition States

		B3LYP/6-331+G(d,p)							
					$\Delta E_d^{\ddagger}$[d]				
	TS‡	$\Delta G^{\ddagger}$[a]	$\Delta G^{\ddagger}$[b]	$\Delta E^{\ddagger}$[c]	**12**	**21/22**	total	$\Delta E_i^{\ddagger}$[d]	$\Delta d_{TS/P}$[e]
1	**24a**-*anti/exo*	28.9	32.0	16.2	10.6	14.0	24.6	−8.4	0.30
2	**24a**-*anti/endo*	26.6	31.8	16.0	11.0	13.9	24.9	−8.8	0.28
3	**24a**-*syn/exo*	29.3	28.8	13.6	8.2	14.2	22.4	−8.8	0.40
4	**24a**-*syn/endo*	26.5	27.9	13.7	9.2	13.8	23.0	−9.3	0.33
5	**24g**-*anti/exo*	29.4	31.5	16.2	9.2	18.1	27.3	−11.2	0.53
6	**24g**-*anti/endo*	28.8	31.0	12.3	10.7	14.3	25.0	−12.7	0.53
7	**24g**-*syn/exo*	26.2	27.4	12.3	11.4	20.4	31.8	−19.5	0.57
8	**24g**-*syn/endo*	26.1	27.4	13.5	9.2	14.2	23.5	*−10.0*	0.70
9	**25a**-*anti/exo*	36.8	40.0	23.3	17.1	14.1	31.2	−7.9	0.18
10	**25a**-*anti/endo*	36.2	39.3	22.3	16.6	14.7	31.2	−8.9	0.27
11	**25a**-*syn/exo*	33.6	36.6	19.7	15.5	14.2	29.8	−10.1	0.19
12	**25a**-*syn/endo*	32.5	35.3	18.6	14.7	14.6	29.3	*−10.7*	0.24
13	**25′a**-*anti/exo*	38.3		24.6					0.30
14	**25′a**-*anti/endo*	38.8		25.1					0.37
15	**25′a**-*syn/exo*	35.3		21.5					0.36
16	**25′a**-*syn/endo*	35.3		21.6					0.37
17	**25b**-*anti/exo*	36.0	37.2	22.4	13.5	15.4	28.9	−6.5	0.30
18	**25b**-*anti/endo*	34.1	35.1	20.3	10.4	17.0	27.4	−7.2	0.38
19	**25b**-*syn/exo*	34.3	35.2	20.1	13.1	15.7	28.8	−8.7	0.30
20	**25b**-*syn/endo*	31.2	32.4	17.6	12.1	15.3	27.4	*−9.8*	0.33
21	**25′b**-*anti/exo*	40.0		26.3					0.20
22	**25′b**-*anti/endo*	39.4		25.4					0.24
23	**25′b**-*syn/exo*	38.0		24.0					0.22
24	**25′b**-*syn/endo*	37.3		23.4					0.24

[a] $\Delta G^{\ddagger} = G_{TS} - G_{dipole} - G_{dipolarophile}$ at 298 K in gas. [b] $\Delta G^{\ddagger}$ at 298 K in toluene as a solvent. [c] Zero-point energy corrected values (EZPE) of B3LYP/6-311+G(d,p). [d] $\Delta E_d^{\ddagger}{}_{dipole}$, $\Delta E_d^{\ddagger}{}_{dipolarophile}$, and $\Delta E_d^{\ddagger}{}_{total}$ are the distortion energies of the dipole, dipolarophile, and total distortion energy. $\Delta E_i^{\ddagger}$ indicates the interaction energy between distorted fragments. [e] $\Delta d_{TS/P} = |(C-C)_{TS}/(C-C)_P - (C-N)_{TS}/(C-N)_P|$.



TS**25a**-*syn/endo* TS**25'a** -*syn/endo*

Figure 3. Most favorable transition states for cycloaddition, **12a** + **22a** → **25a** + **25′a**, in the gas phase, calculated at the 6-311+G(d,p) level.

Table 3. Electrophilicity ω and Nucleophilicity N of Dipoles 12a,b and Dipolarophiles

entry	compd	η	μ	ω (eV)	N (eV)
1	7-Me-dipole **12a**	4.87	−3.67	1.39	3.04
2	7-Ph-dipole **12b**	3.92	−4.09	2.13	3.10
3	3-butyn-2-one (**21b**)	5.71	−5.01	2.20	1.27
4	methyl propiolate (**21e**)	6.47	−5.05	1.97	0.85
5	methyl acrylate (**22a**)	6.33	−4.94	1.93	1.03

strong nucleophiles due to their high nucleophilicity index, $N >$ 3 eV.

The frontier molecular orbital (FMO) analyses for the cycloadditions studied show that the main interactions occur between the $HOMO_{dipole}$ of dipoles **12a,b** and the $LUMO_{dipolarophile}$ of the electron-poor dipolarophiles **21b,e** and **22a** due to the very different energy gaps, $\Delta E' - \Delta E > 1.5$ eV (Figure 4). In terms of favorable FMO interactions,[29] similar HOMO orbital coefficients at N(1) and C(7) in **12a**

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

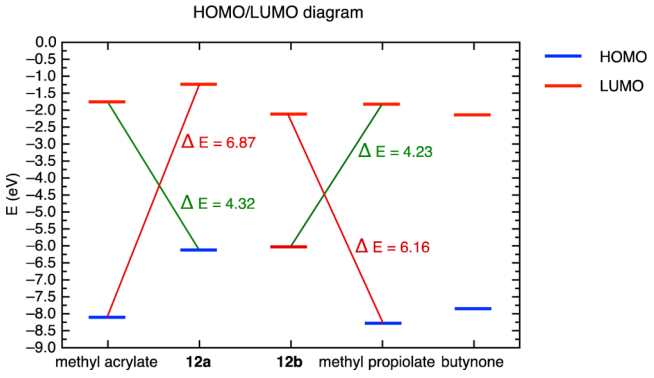


Figure 4. FMO diagram of HOMO−LUMO orbitals calculated by NBO6/6-311+G(d,p) using PCM/toluene.

and larger coefficients at N(1) in the phenyl analogue **12b**[28] indicate a greater regioselectivity for the phenyl analogue **12b**, which was also observed experimentally.

The high asynchronicity of the cycloaddition of dipole **12a** to 3-butyn-2-one (**21b**) that was determined theoretically (cf. Table 2, entry 8) suggested the possibility of a stepwise mechanism.[29] To check this possibility experimentally, the kinetics of this cycloaddition were investigated. The reaction progress was followed using ^{1}H NMR in $CDCl_3$, CD_3CN, and DMSO-d_6 by monitoring the disappearance of the dipole **12a**. The finding of no significant solvent effect on the reaction kinetics was clearly in agreement with the concerted 1,3-dipolar reaction mechanism (Figure 5).

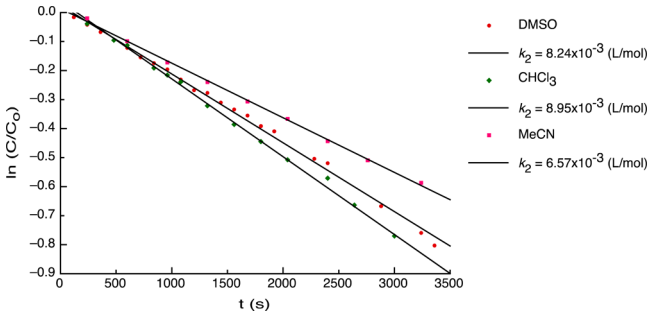


Figure 5. Kinetics of the reaction **12a** + **21b** → **24a** in $CDCl_3$, CD_3CN, and DMSO-d_6.

Next, the reaction kinetics were measured in CD_3CN at different temperatures (302, 312, 322, and 332 K) as a pseudo-first-order reaction with respect to butynone **21b**.[28] Acetonitrile was selected as the solvent of choice due to the appropriate solubility of all reactants within the temperature range needed to construct the Eyring plot (Figure 6).[35] The corresponding experimental activation parameters were determined as $\Delta H^{\ddagger}$ = 13.8 ± 0.1 kcal/mol, $\Delta S^{\ddagger}$ = −27.2 ± 0.2 cal/(mol K), and $\Delta G^{\ddagger}$ = 21.9 ± 0.1 kcal/mol. The experimental results are in fairly good agreement with the computed values (cf. Table 2, entry 8); however, the strong negative entropy value suggests a highly ordered rate-determining transition state, as expected for a polar concerted cycloaddition.[29]

5. CONCLUSION

A seven-step synthesis of C,N,N-cyclic azomethine imines, 7-substituted 2-oxo-Δ^7-hexahydropyrazolo[1,5-*a*]pyridin-8-ium-1-ides **12**, from *δ*-acyl butyric acids **14** was developed as an

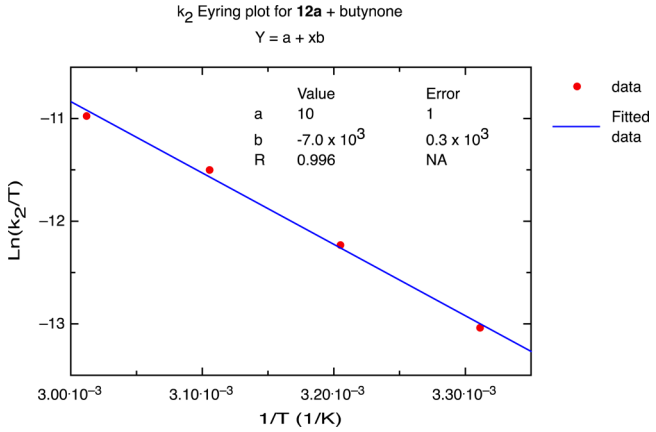


Figure 6. Eyring plot for the cycloaddition between dipole **12a** and butynone **21b**.

alternative to the previously described three-step process starting with acid chlorides **7** and pent-4-en-1-ylmagnesium bromide (**8**).[18] Though requiring a longer synthesis time, the present method allows large-scale preparation of cyclic dipoles **12**, while the shorter and more elegant three-step synthesis[18] has a scale limitation (<0.5 mmol). The stereoselective addition of Grignard reagents to cyclic azomethine imines **12** gave 7,7-disubstituted hexahydropyrazolo[1,5-*a*]pyridin-2(1*H*)-ones **13** or **13′**, which were further *N*-alkylated into the title 1,7,7-trisubstituted compounds **5** and **5′**. [3 + 2]-Cycloadditions of **12** were highly stereoselective, particularly in reactions with acetylenes **21** (one regioisomer, dr ≥ 89:11), whereas with olefins **22**, the stereoselectivity was lower (dr ≥ 78:22). Interestingly, thermal cycloadditions to terminal acetylenes **21b−e** were as regioselective as CuI-catalyzed reactions with methyl propiolate (**21e**). Moreover, the noncatalyzed reactions were even cleaner because they did not lead to the by-product enaminone **29**, which was difficult to separate. Acidolytic deprotection of the carboxy function gave the carboxylic acid **27**, which was amidated into carboxamides **28a−c**. Both reactions, the addition and [3 + 2]-cycloaddition, exhibit the same stereocontrol, leading to the major isomers in which R-C(7) and H-C(3a) from the parent dipole become *anti*-oriented. Regio- and stereoselectivity as well as the mechanism of these [3 + 2]-cycloadditions were evaluated by computational and experimental methods supporting a polar concerted cycloaddition mechanism with the most favorable energetically *syn/endo*-transition states ($\Delta\Delta G$ ∼ 3 kcal/mol). To the best of our knowledge, the title compounds **23−28** are the first known representatives of 2a,2a^1-diazacyclopenta[*cd*]indene, which is an unexplored saturated heterocyclic system. In summary, we developed a viable synthetic protocol for the preparation of cyclic azomethine imines **12** as useful intermediates in the synthesis of 3D-rich saturated heterocycles, which may serve as a starting point in the search for novel lead compounds in medicinal chemistry, chemical biology, and material science.

6. EXPERIMENTAL SECTION

6.1. General Methods. Melting points were determined on a Kofler micro hot stage and on an automated melting point system. The NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as the internal standard on a 300 or 500 MHz instrument at 300 and 500 MHz for ^{1}H and at 75.5 and 126 MHz for ^{13}C nucleus, respectively. Mass spectra were recorded on a time-of-flight (TOF) mass spectrometer equipped with a double-orthogonal electrospray

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

source at athmospheric pressure ionization (ESI) coupled to an HPLC instrument. IR spectra were recorded on a FTIR ATR spectrophotometer. Microanalyses were performed by combustion analysis on a CHN analyzer. Microwave-assisted reactions were performed in a single-mode microwave instrument in pressure reaction vessels. Reaction times refer to hold times at the temperature indicated, not the total irradiation times. The temperature was measured using the IR temperature sensor of the instrument. Column chromatography and flash column chromatography were performed on silica gel (particle size 35−70 μm). Acetyl chloride (**7a**), Grignard reagents **8a−c**, *tert*-butyl carbazate (**10**), γ-acetyl- (**14a**) and γ-benzoyl butyric acid (**14b**), 1,1′-carbonyldiimidazole, bis(pentafluorophenyl) carbonate, potassium monomethyl malonate, benzylamine, 3-amino-1-propanol, piperidine, and dipolarophiles **21a−e** and **22a−c** are commercially available. Hept-6-en-2-one (**9a**),[19] *tert*-butyl 2-(hept-6-en-2-ylidene)hydrazine-1-carboxylate (**11a**),[18] and *tert*-butyl (2-oxobut-3-yn-1-yl)carbamate (**21d**)[27i] were prepared according to the literature procedures.

6.2. Synthesis of 7-Methyl-2-oxo-2,3,3a,4,5,6-hexahydropyrazolo[1,5-*a*]pyridin-8-ium-1-ide (12a) by Microwave-Assisted Cyclization of Hydrazone 11a. Compound **12a** was prepared following a slightly modified literature procedure.[18] A 5 mL Pyrex reaction vessel was charged with hydrazone **9a** (57 mg, 0.25 mmol) and trifluoromethylbenzene (2 mL), and the mixture was heated under microwave irradiation (P = 300 W) at 150 °C for 3 h. Volatile components were evaporated in vacuo, the residue was dissolved in a mixture of MeOH and CH_2Cl_2 (1:5, 10 mL) and silica gel (500 mg), and the suspension was carefully evaporated in vacuo. The so-formed silica gel with adsorbed reaction product(s) was poured into a stabilized chromatographic column (silica gel, 1.5 × 5 cm, EtOAc). First, the nonreacted hydrazine **11a** was eluted with EtOAc, followed by elution of the product **12a** with CH_2Cl_2−MeOH (10:1). Fractions containing the product were combined and evaporated in vacuo to give **12a**. Yield: 22 mg (60%) of a beige solid, Mp: 125−126 °C dec. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.67−1.84 (2H, m); 2.00−2.07 (1H, m); 2.30 (3H, br t, J = 0.8 Hz); 2.33−2.39 (1H, m); 2.57 (1H, dd, J = 15.6, 10.4 Hz); 2.55−2.65 (1H, m); 2.72 (1H, dd, J = 20.5, 6.8 Hz); 2.81 (1H, dd, J = 15.6, 8.4 Hz); 4.17 (1H, br q, J = 10.2 Hz). ^{13}C NMR (126 MHz, DMSO-d_6): δ 18.3, 20.8, 27.3, 30.1, 37.5, 64.5, 148.8, 180.4. m/z (ESI) = 153 (MH^+). m/z (HRMS) found 153.1021 (MH^+), $C_8H_{13}N_2O$ requires m/z = 153.1022. IR ν_{max} (ATR): 3382, 2936, 1674, 1584, 1373, 1337, 1082, 765, 667 cm^{-1}. Physical and spectral data of compound **12a** were in agreement with the literature data.[18]

6.3. Seven-Step Synthesis of 7-Substituted 2-Oxo-2,3,3a,4,5,6-hexahydropyrazolo[1,5-*a*]pyridin-8-ium-1-ides 12a and 12b from γ-Acyl Butyric Acids 14a and 14b. *6.3.1. Synthesis of 4-(2-Substituted 1,3-dioxolan-2-yl)butanoic Acids **16a** and **16b**.* Compounds **16a** and **16b** were prepared following the literature procedure for the synthesis of related compounds.[22] A mixture of carboxylic acid **14** (5 mmol), anhyd CH_2Cl_2 (10 mL), ethylene glycol (1.4 mL, 25 mmol), TMOF (1.6 mL, 15 mmol), and H_2SO_4 (96%, 25 μL) was stirred at rt for 6 h. Then, $NaHCO_3$ (250 mg) was added, and the mixture was stirred at rt for 10 min. Volatile components were evaporated in vacuo (2 mbar, 40 °C), MeOH (7 mL) and 2 M aq NaOH (5 mL) were added, and the mixture was stirred at rt for 12 h. The mixture was concentrated to half of the initial volume by evaporation in vacuo (2 mbar, 40 °C), and aqueous residue was acidified with citric acid to pH ∼2. The product was extracted with EtOAc (3 × 20 mL), the combined organic phases were dried over anhyd sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give **16**.

*6.3.1.1. 4-(2-Methyl-1,3-dioxolan-2-yl)butanoic Acid (**16a**).* Prepared from **14a** (596 μL, 5 mmol). Yield: 800 mg (91%) of pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (3H, s); 1.63−1.79 (4H, m); 2.39 (2H, t, J = 7.1 Hz); 3.88−4.02 (4H, m); 10.42 (1H, br s). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.2, 23.8, 33.8, 38.2, 64.7, 109.7, 178.7. Physical and spectral data of **16a** were in agreement with the literature data.[20]

*6.3.1.2. 4-(2-Phenyl-1,3-dioxolan-2-yl)butanoic Acid (**16b**).* Prepared from **14b** (960 mg, 5 mmol). Yield: 1.180 g (98%) of white solid. Mp: 68−71 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.71 (1H, tt, J = 10.6, 6.3 Hz); 1.89−1.99 (2H, m); 2.35 (2H, t, J = 7.6 Hz); 3.73−3.81 (2H, m); 3.96−4.07 (2H, m); 7.27−7.36 (3H, m), 7.43−7.46 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.9, 33.6, 39.5, 64.5, 110.1, 125.6, 127.9, 128.1, 142.3, 178.2. Physical and spectral data of **16b** were in agreement with the literature data.[21]

6.4. Synthesis of Methyl 3-Oxo-6-(2-substituted 1,3-dioxolan-2-yl)hexanoates 17a and 17b. Under argon, 1,1′-carbonyldiimidazole (815 mg, 5.2 mmol) was added to a solution of carboxylic acid **16** (5 mmol) in anhyd THF (15 mL), and the mixture was stirred at rt for 1 h. Then a solid, well-homogenized mixture of anhyd $MgCl_2$ (395 mg, 4.8 mmol) and potassium monomethyl malonate (1.130 g, 7.5 mmol) was added, and the suspension was stirred at rt for 12 h. Volatile components were evaporated in vacuo, the residue was taken up in EtOAc (20 mL), and the suspension was washed with 1 M $NaHSO_4$ (3 × 20 mL) and brine (3 × 10 mL). The organic phase was dried over anhyd sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give **17**.

*6.4.1. Methyl 6-(2-Methyl-1,3-dioxolan-2-yl)-3-oxohexanoate (**17a**).* Prepared from **16a** (800 mg, 5 mmol). Yield: 977 mg (98%) of brownish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (3H, s); 1.64−1.77 (4H, m); 2.60 (2H, t, J = 7.1 Hz); 3.47 (2H, s); 3.76 (3H, s); 3.90−4.00 (4H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.0, 23.7, 38.0, 42.8, 49.0, 52.4, 64.6, 64.6, 109.8, 167.7, 202.5. m/z (ESI) = 231 (MH^+). m/z (HRMS) found 231.1224 (MH^+), $C_{11}H_{19}O_5$ requires m/z = 231.1227. IR ν_{max} (ATR): 2954, 2883, 2078, 1737, 1713, 1055 cm^{-1}.

*6.4.2. Methyl 6-(2-Phenyl-1,3-dioxolan-2-yl)-3-oxohexanoate (**17b**).* Prepared from **16b** (800 mg, 5 mmol). Yield: 1.100 g (99%) of yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.64−1.70 (2H, m); 1.88−1.91 (2H, m); 2.54 (2H, t, J = 7.4 Hz); 3.41 (2H, s); 3.71 (3H, s); 3.73−3.78 (2H, m); 3.98−4.03 (2H, m); 7.30−7.27 (1H, m); 7.31−7.35 (2H, m); 7.41−7.45 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.7, 39.3, 42.8, 49.0, 52.3, 64.5, 64.5, 110.1, 125.7, 127.9, 128.2, 142.3, 167.7, 202.5. m/z (ESI) = 293 (MH^+), HRMS (ESI) MH^+, found 293.1384, $C_{16}H_{21}O_5$ requires 293.1384. IR ν_{max} (ATR): 2953, 2889, 1966, 1154, 1075, 1039, 949 cm^{-1}.

6.5. Synthesis of Methyl 3-Hydroxy-6-(2-substituted 1,3-dioxolan-2-yl)hexanoates 18a and 18b. Finely ground $NaBH_4$ (188 mg, 5 mmol) was added slowly in several portions to a cold (0 °C, ice bath) solution of β-keto ester **17** (5 mmol) in MeOH (10 mL), and the mixture was stirred at 0 °C for 1.5 h. Then, brine (5 mL) was added, the ice bath was removed, the mixture was stirred at rt for 5 min, and the product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over anhyd sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give **18**.

*6.5.1. Methyl 3-Hydroxy-6-(2-methyl-1,3-dioxolan-2-yl)-hexanoate (**18a**).* Prepared from **17a** (800 mg, 3.5 mmol) and $NaBH_4$ (132 mg, 3.5 mmol) in MeOH (8 mL). Yield: 698 mg (85%) of yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (3H, s); 1.43−1.53 (2H, m); 1.53−1.62 (2H, m); 1.66−1.72 (2H, m); 2.45 (1H, dd, J = 16.5, 9.1 Hz); 2.54 (1H, dd, J = 16.4, 3.1 Hz); 2.94 (1H, d, J = 3.9 Hz); 3.72 (3H, s); 3.92−4.00 (4H, m); 4.04 (1H, ddd, J = 11.3, 7.7, 3.7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.0, 23.8, 36.5, 38.9, 41.1, 51.8, 64.7, 64.7, 67.9, 110.0, 173.5. m/z (ESI) = 171 (MH − H_2O − $C_2H_4O^+$). m/z (HRMS) found 171.1006 (MH − H_2O − $C_2H_4O^+$), $C_9H_{15}O_3$ requires m/z = 171.1021. IR ν_{max} (ATR): 3420, 2951, 1733, 1652, 1118, 1043 cm^{-1}.

*6.5.2. Methyl 3-Hydroxy-6-(2-phenyl-1,3-dioxolan-2-yl)-hexanoate (**18b**).* Prepared from **17b** (800 mg, 2.5 mmol) and $NaBH_4$ (94 mg, 3.5 mmol) in MeOH (5 mL). Yield: 600 mg (85%) of pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35−1.46 (2H, m); 1.46−1.59 (2H, m); 1.87−1.97 (2H, m); 2.38 (1H, dd, J = 16.4, 9.1 Hz); 2.47 (1H, dd, J = 16.4, 3.2 Hz); 2.87 (1H, br s); 3.69 (3H, s); 3.74−3.78 (2H, m); 3.94−3.99 (1H, m); 3.99−4.03 (2H, m); 7.26−7.31 (1H, m); 7.31−7.36 (2H, m); 7.46−7.41 (2H, m). ^{13}C (126 MHz, $CDCl_3$) δ 19.6, 36.4, 40.2, 41.1, 51.8, 64.5, 64.5, 67.9, 110.3, 125.7, 127.8, 128.1, 142.5, 173.4. m/z (ESI) = 233 (MH − H_2O − $C_2H_4O^+$). m/z (HRMS) found 233.1176 (MH − H_2O − $C_2H_4O^+$),

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

$C_{14}H_{17}O_3$ requires m/z = 233.1178. IR ν_{max} (ATR): 3467, 3050, 1731, 1171, 1102, 1072, 1026 cm^{-1}.

6.6. Synthesis of Methyl 3-(Methylsulfonyl)oxy-6-(2-substituted 1,3-dioxolan-2-yl)hexanoates 19a and 19b. Mesyl chloride (450 μL, 5.8 mmol) was added to a cold (0 °C, ice bath) solution of the ester **18** (5 mmol) in anhyd pyridine (5 mL), and the mixture was stirred at 0 °C for 3 h. The reaction mixture was diluted with toluene (30 mL) and washed with 1 M aq $NaHSO_4$ until the pH of the aqueous phase was around 2. The organic phase was washed again with brine (2 × 10 mL), dried over anhyd sodium sulfate, and filtered, and the filtrate was evaporated in vacuo to give **19**.

*6.6.1. Methyl 6-(2-Methyl-1,3-dioxolan-2-yl)-3-((methylsulfonyl)-oxy)hexanoate (**19a**).* Prepared from **18a** (600 mg, 2.5 mmol) and mesyl chloride (225 μL, 2.9 mmol) in anhyd pyridine (2.5 mL). Yield: 620 mg (80%) of orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (3H, s); 1.48−1.59 (2H, m); 1.65−1.76 (2H, m); 1.76−1.91 (2H, m); 2.68 (1H, dd, J = 16.4, 4.8 Hz); 2.81 (1H, dd, J = 16.4, 7.9 Hz); 3.06 (3H, s); 3.74 (3H, s); 3.91−4.02 (4H, m); 5.04−5.09 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.3, 23.9, 34.9, 38.4, 38.5, 39.2, 52.1, 64.7, 64.7, 79.0, 109.7, 170.4. m/z (ESI) = 311 (MH^+). m/z (HRMS) found 311.1154 (MH^+), $C_{12}H_{23}O_7S$ requires m/z = 311.1159. IR ν_{max} (ATR): 3021, 2954, 1734, 1710, 1334, 1167, 968, 902 cm^{-1}.

*6.6.2. Methyl 3-(methylsulfonyl)oxy-6-(2-phenyl-1,3-dioxolan-2-yl)hexanoate (**19b**).* Prepared from **18b** (1.4 g, 5 mmol). Yield: 1.55 g (95%) of pale orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37−1.53 (2H, m); 1.69−1.85 (2H, m); 1.85−2.00 (2H, m); 2.61 (1H, dd, J = 16.4, 4.9 Hz); 2.75 (1H, dd, J = 16.4, 7.9 Hz); 2.97 (3H, s); 3.69 (3H, s); 3.73−3.81 (2H, m); 3.93−4.08 (2H, m); 4.98 (1H, dtd, J = 7.9, 6.2, 4.8 Hz); 7.28−7.31 (1H, m); 7.31−7.36 (2H, m); 7.40−7.46 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.0, 34.7, 38.3, 39.2, 39.7, 52.0, 64.5, 64.5, 79.1, 110.0, 125.7, 127.9, 128.2, 142.3, 170.4. m/z (ESI) = 373 (MH^+). m/z (HRMS) found 373.1312 (MH^+), $C_{17}H_{25}O_7S$ requires m/z = 373.1316. IR ν_{max} (ATR): 2951, 2915, 2884, 1736, 1441, 1355, 1337, 1156, 1111, 910, 887, 702 cm^{-1}.

6.7. Synthesis of 5-(3-(2-Substituted 1,3-dioxolan-2-yl)-propyl)pyrazolidin-3-one 20a and 20b. Hydrazine monohydrate (1.3 mL, 26 mmol) was added to a solution of ester **19** (5 mmol) in MeOH (20 mL), and the mixture was stirred at 50 °C for 3 days. Volatile components were evaporated in vacuo, and the crude product was purified by column chromatography (silica gel, EtOAc−MeOH, 10:1). Fractions containing the product were combined and evaporated in vacuo to give **20**.

*6.7.1. 5-(3-(2-Methyl-1,3-dioxolan-2-yl)propyl)pyrazolidin-3-one (**20a**).* Prepared from **19a** (295 mg, 1 mmol) and hydrazine monohydrate (260 μL, 5 mmol) in MeOH (5 mL). Yield: 160 mg (74%) of yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.82 (1H, dtd, J = 13.6, 11.6, 5.8 Hz); 1.92−2.02 (1H, m); 2.02−2.10 (1H, m); 2.40 (1H, ddt, J = 13.4, 5.8, 3.7 Hz); 2.55 (1H, dd, J = 15.9, 9.3 Hz); 2.80 (1H, dd, J = 15.9, 8.6 Hz); 2.94 (1H, dddd, J = 18.9, 7.4, 4.5, 1.3 Hz); 3.07 (1H, dtd, J = 18.9, 7.8, 1.9 Hz); 4.30−4.40 (1H, m); 7.41−7.45 (3H, m); 8.02−8.07 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.3, 27.4, 28.6, 36.7, 65.9, 128.2, 129.4, 130.9, 132.5, 144.4, 181.8. m/z (ESI) = 215 (MH^+). m/z (HRMS) found 215.1389 (MH^+), $C_{10}H_{19}N_2O_3$ requires m/z = 215.1390. IR ν_{max} (ATR): 3217, 2943, 2877, 1674, 1376, 1219, 1060, 948, 863 cm^{-1}.

*6.7.2. 5-(3-(2-Phenyl-1,3-dioxolan-2-yl)propyl)pyrazolidin-3-one (**20b**).* Prepared from **19b** (7.44 g, 20 mmol) and hydrazine monohydrate (2.5 mL, 50 mmol) in MeOH (100 mL). Yield: 5.40 g (97%) of pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24−1.36 (1H, m); 1.39−1.54 (2H, m); 1.56−1.65 (2H, m); 1.85−1.93 (1H, m); 1.92 (1H, br t, J = 7.6 Hz); 2.16 (1H, dd, J = 16.3, 8.5 Hz); 2.49 (1H, br dd, J = 16.4, 7.0 Hz); 3.61 (1H, br quintet, J = 7.1 Hz); 3.73−3.78 (2H, m); 3.97−4.02 (2H, m); 6.77 (1H, br s); 7.29 (1H, br t, J = 7.2 Hz); 7.34 (2H, t, J = 7.3 Hz); 7.43 (2H, br d, J = 7.2 Hz). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.21−1.47 (4H, m); 1.80 (2H, t, J = 7.7 Hz); 1.86 (1H, dd, J = 15.7, 7.6 Hz); 2.26 (1H, dd, J = 16.0, 7.0); 3.25−3.32 (1H, m); 3.71−3.60 (2H, m); 3.91−3.98 (2H, m); 5.04 (1H, s); 7.24−7.43 (5H, m); 8.88 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6): δ 20.3, 32.9, 38.1, 57.6, 62.8, 64.1, 64.1, 109.6, 125.4, 127.7, 128.0, 142.4, 175.8. m/z (ESI) = 277 (MH^+). m/z (HRMS) found 277.1547 (MH^+), $C_{15}H_{21}N_2O_3$ requires m/z = 277.1547. IR ν_{max} (ATR): 3177, 2947, 2887, 1681, 1171, 1047, 1023, 939, 914, 733, 702 cm^{-1}.

6.8. Synthesis of 7-Substituted 2-Oxo-2,3,3a,4,5,6-hexahydropyrazolo[1,5-*a*]pyridin-8-ium-1-ides 12a and 12b. TFA (3 drops) was added to a solution of pyrazolidinone **20** (1 mmol) in anhyd EtOH (5 mL), and the mixture was stirred under reflux for 6 h. Volatile components were evaporated in vacuo, and the crude product was purified by column chromatography (silica gel, first EtOAc−MeOH, 5:1, then CH_2Cl_2−MeOH, 9:1). Fractions containing the product were combined and evaporated in vacuo to give **12**.

*6.8.1. 7-Methyl-2-oxo-2,3,3a,4,5,6-hexahydropyrazolo[1,5-a]-pyridin-8-ium-1-ide (**12a**).* Prepared from **20a** (214 mg, 1 mmol). Yield: 122 mg (80%) of pale yellow solid. Mp: 106−110 °C. Physical and spectral data for compound **12a** are given in section 6.2. These data are in agreement with the literature data.[18]

*6.8.2. 2-Oxo-7-phenyl-2,3,3a,4,5,6-hexahydropyrazolo[1,5-a]-pyridin-8-ium-1-ide (**12b**).* Prepared from **20b** (230 mg, 1 mmol). Yield: 130 mg (60%) of orange solid. Mp: 110 °C dec. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.84 (1H, dtd, J = 13.7, 11.7, 5.7 Hz); 1.91−2.03 (1H, m); 2.04−2.12 (1H, m); 2.42 (1H, ddt, J = 13.4, 5.5, 3.6 Hz); 2.57 (1H, dd, J = 15.9, 9.3 Hz); 2.84 (1H, dd, J = 15.9, 8.6 Hz); 2.95 (1H, dddd, J = 19.2, 7.6, 4.6, 1.4 Hz); 3.08 (1H, dtd, J = 19.2, 7.8, 2.0 Hz); 4.36 (1H, dddd, J = 9.3, 7.6, 3.6, 1.8 Hz); 7.41−7.46 (3H, m); 8.02−8.06 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.3, 27.4, 28.6, 36.7, 65.9, 128.2, 129.4, 130.9, 132.5, 144.4, 181.8. m/z (ESI) = 215 (MH^+). m/z (HRMS) found 215.0079 (MH^+), $C_{13}H_{15}N_2O$ requires m/z = 215.1179. Anal. Calcd for $C_{13}H_{14}N_2O \cdot {}^1/_4H_2O$: C, 71.37; H, 6.68; N, 12.81. Found: C, 71.23; H, 6.60; N, 12.83. IR ν_{max} (ATR): 2930, 1648, 1572, 1559, 1324, 1299, 901, 753, 691, 668, 635 cm^{-1}. IR data are in agreement with the literature data.[23]

6.9. Synthesis of 7,7-Disubstituted (3a*S,7*R**)-Hexahydropyrazolo[1,5-*a*]pyridin-2(1*H*)-ones 13′a, 13a, and 13b.** Under argon, azomethine imine **12** (5 mmol) was dissolved in anhyd THF (25 mL), and the solution was cooled to −20 °C (ice−salt bath). Then Grignard reagent **8** (1 M, 25 mL, 25 mmol) was added dropwise, and the mixture was stirred at −20 °C for 1 h. The dry ice−salt bath was removed, and the reaction mixture stirred at rt for 12 h. Excess Grignard reagent was quenched by addition of saturated aq NH_4Cl (20 mL), and the product was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over anhyd sodium sulfate, and filtered, and the filtrate was evaporated in vacuo. The crude product was purified by column chromatography (silica gel, EtOAc−hexanes). Fractions containing the product were combined and evaporated in vacuo to give **13′a** or **13a** or **13b**.

*6.9.1. (3a*S**,7*S**)-7-Methyl-7-phenylhexahydropyrazolo[1,5-a]-pyridin-2(1H)-one (**13′a**).* Prepared from **12a** (154 mg, 1 mmol) and PhMgBr (5 mL, 5 mmol) in anhyd THF (5 mL), column chromatography (silica gel, EtOAc−hexanes, 1:1). Yield: 124 mg (54%) of white crystals. Mp: 176−178 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (3H, s); 1.51−1.74 (4H, m); 1.83−1.94 (1H, m); 2.19 (2H, dd, J = 16.0, 5.9 Hz); 2.58 (1H, dd, J = 16.0, 7.4 Hz); 3.41 (1H, br dq, J = 10.6, 6.0 Hz); 7.16−7.28 (1H, m); 7.29−7.39 (2H, m); 7.59 (2H, dd, J = 8.2, 1.4 Hz); 8.76 (1H, br s). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.6, 26.9, 31.2, 31.6, 39.5, 55.5, 61.0, 126.6, 127.0, 128.4, 144.1, 174.9. m/z (ESI) = 231 (MH^+). m/z (HRMS) found 231.1490 (MH^+), $C_{14}H_{19}N_2O$ requires m/z = 231.1492. IR ν_{max} (ATR): 3153, 3055, 2953, 2941, 2925, 2866, 1681, 1598, 763, 726, 700 cm^{-1}.

*6.9.2. (3a*S**,7*R**)-7-Methyl-7-phenylhexahydropyrazolo[1,5-a]-pyridin-2(1H)-one (**13a**).* Prepared from **12b** (214 mg, 1 mmol) and MeMgBr (5 mL, 5 mmol) in anhyd THF (5 mL), column chromatography (silica gel, EtOAc−hexanes, 1:1). Yield: 160 mg (69%) of orange solid. Mp: 112−113 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 (3H, s); 1.58−1.76 (4H, m); 1.79−1.93 (2H, m); 2.28 (1H, dd, J = 15.5, 11.6 Hz); 2.47 (1H, dd, J = 15.5, 6.1 Hz); 3.41 (1H, br s); 5.97 (1H, br s); 7.23−7.28 (1H, m); 7.35 (2H, t, J = 7.8 Hz); 7.57 (2H, d, J = 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 12.7, 21.0, 28.7, 39.1, 56.5, 58.1, 60.7, 125.8, 127.5, 128.9, 146.5, 174.8. m/z (ESI) = 231 (MH^+). m/z (HRMS) found 231.1492 (MH^+), $C_{14}H_{19}N_2O$

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

requires m/z = 231.1492. IR ν_{max} (ATR): 3136, 2936, 2920, 2849, 1680, 1382, 1350, 1237, 1220, 1094, 1069, 757, 729, 695, 670 cm^{-1}.

*6.9.3. (RS)-7,7-Dimethylhexahydropyrazolo[1,5-a]pyridin-2(1H)-one (**13b**).* Prepared from **12a** (608 mg, 4 mmol) and MeMgBr (1 M in Bu_2O, 15 mL, 16 mmol) in anhyd THF (20 mL), flash column chromatography (EtOAc). Yield: 211 mg (31%) of brownish solid. Mp: 143−144 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 1.06 (3H, s); 1.17 (3H, s); 1.46−1.64 (5H, m); 1.79 (1H, brd, J = 11.3 Hz); 2.23 (1H, dd, J = 15.6, 12.6 Hz); 2.39 (1H, dd, J = 15.6, 6.5 Hz); 3.13 (1H, br q, J = 10.8 Hz); 7.62 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.4, 29.0, 30.0, 37.1, 38.9, 55.6, 57.3, 77.4, 175.2. m/z (ESI) = 169 (MH^+). m/z (HRMS) found 169.1336 (MH^+), $C_9H_{16}N_2O$ requires m/z = 169.1335. IR ν_{max} (ATR): 2958, 2842, 1688 (C═O), 1236, 1094, 824, 764, 718, 665 cm^{-1}.

6.10. Synthesis of 7,7-Disubstituted 1-Alkylhexahydropyrazolo[1,5-*a*]pyridin-2(1*H*)-ones 5′a, 5′b, 5a, and 5c. Under argon, K_2CO_3 (688 mg, 5 mmol) and MeI or BnBr (15 mmol) were added to a solution of pyrazolidinone **13a** or **13′a** (5 mmol) in anhyd DMF (25 mL), and the mixture was stirred at rt for 3 days. Volatile components were evaporated in vacuo, and the residue was taken up with EtOAc (30 mL). The organic phase was washed with H_2O (2 × 20 mL) and brine H_2O (2 × 20 mL), dried over anhyd sodium sulfate, and filtered, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc−hexanes). Fractions containing the product were combined and evaporated in vacuo to give **5a**, **5c**, or **5′a**,**b**.

6.10.1. (3aS,7S*)-1,7-Dimethyl-7-phenylhexahydropyrazolo-[1,5-a]pyridin-2(1H)-one (**5′a**).* Prepared from **13′a** (196 mg, 0.85 mmol), K_2CO_3 (117 mg, 0.85 mmol), and MeI (157 μL, 2.55 mmol) in anhyd DMF (3 mL), column chromatography (EtOAc−hexanes, 1:1). Yield: 140 mg (68%) of white crystals. Mp: 131−134 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 1.52−1.61 (1H, m); 1.57 (3H, s); 1.77−1.64 (3H, m); 2.03−1.84 (2H, m); 2.16 (1H, dd, J = 16.2, 7.4 Hz); 2.43 (3H, s); 2.74 (1H, br dd, J = 16.2, 14.3 Hz); 4.10 (1H, dddd, J = 14.1, 7.9, 6.6, 1.9 Hz); 7.22 (1H, t, J = 7.3 Hz); 7.32 (2H, dd, J = 12.9, 5.5 Hz); 7.61 (2H, d, J = 7.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.8, 20.2, 26.4, 32.5, 36.7, 41.8, 57.7, 63.0, 126.1, 126.6, 128.0, 149.8, 173.6. m/z (ESI) = 245 (MH^+). m/z (HRMS) found 245.1646 (MH^+), $C_{15}H_{21}N_2O$ requires m/z = 245.1648. Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.88, H 8.35, N 11.1. IR: ν_{max} (ATR): 2938, 2917, 2861, 1672 (C═O), 1441, 1409, 1180, 950, 691 cm^{-1}.

6.10.2. (3aS,7S*)-1-Benzyl-7-methyl-7-phenylhexahydro-pyrazolo[1,5-a]pyridin-2(1H)-one (**5′b**).* Prepared from **13′a** (196 mg, 0.85 mmol), K_2CO_3 (117 mg, 0.85 mmol), and BnBr (305 μL, 2.55 mmol) in anhyd DMF (3 mL), column chromatography (EtOAc−hexanes, 1:1). Yield: 150 mg (55%) of white crystals. Mp: 118−120 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 1.49−1.56 (1H, m); 1.65 (3H, s); 1.65−1.72 (3H, m); 1.88−1.95 (2H, m); 2.23 (1H, dd, J = 16.3, 7.3 Hz); 2.84 (1H, br dd, J = 16.3, 14.3 Hz); 3.05 (1H, d, J = 15.4); 4.01 (1H, ddt, J = 15.0, 7.7, 4.0 Hz); 4.89 (1H, d, J = 15.4 Hz); 6.76−6.83 (2H, m); 7.21−7.15 (3H, m); 7.21−7.27 (3H, m) 7.44 (2H, t, J = 16.1 Hz) ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.5, 20.3, 26.4, 36.6, 42.2, 46.8, 58.6, 63.1, 126.6, 127.0, 127.7, 127.7, 128.0, 128.1, 137.1, 149.6, 174.8. m/z (ESI) = 321 (MH^+). m/z (HRMS) found 321.1960 (MH^+), $C_{21}H_{25}N_2O$ requires m/z = 321.1961. Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.44; H, 7.73; N, 8.60. IR ν_{max} (ATR): 2932, 2895, 1669 (C═O), 1601, 1494, 1432, 1229, 748, 696, 615 cm^{-1}.

6.10.3. (3aS,7R*)-1,7-Dimethyl-7-phenylhexahydropyrazolo-[1,5-a]pyridin-2(1H)-one (**5a**).* Prepared from **13a** (176 mg, 0.33 mmol), K_2CO_3 (45 mg, 0.33 mmol), and MeI (68 μL, 0.99 mmol) in anhyd DMF (1.5 mL), column chromatography (EtOAc−hexanes, 1:1). Yield: 50 mg (66%) of orange oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.56 (3H, s); 1.57−1.65 (3H, m); 1.65−1.72 (1H, m); 1.84−1.97 (2H, m); 2.22 (1H, t, J = 14.5 Hz); 2.44 (1H, dd, J = 15.2, 6.2 Hz); 2.72 (3H, s); 3.22 (1H, dddd, J = 13.5, 10.7, 6.2, 2.3 Hz); 7.21−7.26 (1H, m); 7.29−7.37 (2H, m); 7.68 (2H, d, J = 8.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.0, 21.5, 29.3, 33.1, 37.7, 43.9, 57.0, 61.6, 126.1, 127.1, 128.1, 149.2, 172.1. m/z (ESI) = 245 (MH^+). m/z (HRMS) found 245.1645 (MH^+), $C_{15}H_{21}N_2O$ requires m/z = 245.1648. IR ν_{max} (ATR): 2944, 2909, 1688, 1373, 1221, 1117, 1035, 1029, 772, 747, 701 cm^{-1}.

*6.10.4. (RS)-1-Benzyl-7,7-dimethylhexahydropyrazolo[1,5-a]-pyridin-2(1H)-one (**5c**).* Prepared from **13b** (90 mg, 0.53 mmol), K_2CO_3 (138 mg, 1 mmol), and BnBr (190 μL, 1.59 mmol) in anhyd DMF (2 mL), column chromatography (EtOAc−hexanes, 1:2). Yield: 58 mg (42%) of orange oil. ^1H NMR (500 MHz, DMSO-d_6): δ 1.15 (3H, s); 1.16 (3H, s); 1.42−1.49 (2H, m); 1.50−1.59 (2H, m); 1.67−1.81 (2H, m); 2.12 (1H, dd, J = 15.9, 6.8 Hz); 2.63 (1H, t, J = 15.2 Hz); 3.52−3.62 (1H, m); 4.33 (1H, d, J = 15.4 Hz); 5.12 (1H, d, J = 15.4 Hz); 7.23−7.34 (5H, m). ^{13}C NMR (126 MHz, DMSO-d_6): δ 16.1, 26.9, 36.7, 36.7, 38.9, 50.8, 50.8, 59.3, 127.4, 128.2, 128.5, 137.4, 176.7. m/z (ESI) = 259 (M^+). m/z (HRMS) found 259.1801 (MH^+), $C_{16}H_{22}N_2O$ requires m/z = 259.1805. IR ν_{max} (ATR): 2935, 1686 (C═O), 1455, 1385, 1250, 1084, 774, 700 cm^{-1}.

6.11. Thermal [3 + 2]-Cycloadditions of Azomethine Imines 12a and 12b. Synthesis of Cycloadducts 23−26. A mixture of azomethine imine **12** (0.25 mmol), anhyd CH_2Cl_2 or toluene (1 mL), and dipolarophile **21** or **22** (0.3 mmol, 1.2 equiv) was stirred at rt or at 80 °C for 24−96 h.

Workup A. The precipitate was collected by filtration to give **23b**.

Workup B. Volatile components were evaporated in vacuo, and the residue was purified by column chromatography (silica gel, EtOAc−hexanes or CH_2Cl_2−MeOH). Fractions containing the product were combined and evaporated in vacuo to give cycloadducts **23−26**.

6.11.1. Dimethyl (4aS,7aS*)-4a-Methyl-2-oxo-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]indene-3,4-dicarboxylate (**23a**).* Prepared from **12a** (38 mg, 0.25 mmol) and DMAD (**21a**) (36 μL, 0.30 mmol) in anhyd CH_2Cl_2 (1 mL), rt, 72 h, workup B, column chromatography (CH_2Cl_2−MeOH, 50:1). Yield: 44 mg (60%) of orange oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.40 (3H, s); 1.66−1.74 (1H, m); 1.76−1.91 (3H, m); 1.94 (1H, dt, J = 14.1, 3.4 Hz); 2.06 (1H, td, J = 13.8, 3.8 Hz); 2.46 (1H, dd, J = 15.2, 4.9 Hz); 2.55 (1H, dd, J = 15.2, 13.0 Hz); 3.50 (1H, ddt, J = 13.0, 11.7, 4.7 Hz); 3.72 (3H, s); 3.94 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$); δ 16.4, 23.2, 25.5, 28.6, 40.7, 51.8, 53.3, 60.3, 66.7, 115.9, 139.8, 161.3, 163.5, 176.5. m/z (ESI) = 295 (MH^+). m/z (HRMS) found 295.1288 (MH^+), $C_{14}H_{19}N_2O_5$ requires m/z = 295.1288. IR ν_{max} (ATR): 2952, 1731, 1706, 1607, 1435, 1368, 1150, 842 cm^{-1}.

*6.11.2. Dimethyl (4aR,7aS)-2-Oxo-4a-phenyl-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]indene-3,4-dicarboxylate (**23b**).* Prepared from **12b** (43 mg, 0.2 mmol) and DMAD (**21a**) (30 μL, 0.24 mmol) in anhyd toluene (2 mL), rt, 24 h, workup A. Yield: 42 mg (59%) of brownish oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.46−1.56 (1H, m); 1.65−1.76 (2H, m); 1.82−1.92 (1H, m); 2.40 (1H, td, J = 14.4, 3.5 Hz); 2.58 (2H, dd, J = 15.2, 4.7 Hz); 2.62 (1H, dt, J = 14.5, 3.6 Hz); 2.70 (1H, dd, J = 15.2, 13.0 Hz); 3.71 (1H, dddd, J = 13.0, 9.8, 4.9, 3.6 Hz); 3.71 (3H, s); 3.88 (3H, s); 7.24−7.29 (1H, m); 7.35 (2H, br t, J = 7.7 Hz); 7.73 (2H, br d, J = 7.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.4, 23.2, 29.3, 40.6, 51.9, 53.2, 59.9, 72.0, 115.9, 126.2, 127.4, 128.4, 138.6, 143.9, 161.1, 164.0, 176.2. m/z (ESI) = 357 (MH^+). m/z (HRMS) found 357.1446 (MH^+), $C_{19}H_{20}N_2O_5$ requires m/z = 357.1445. IR ν_{max} (ATR): 1770, 1742, 1670, 1609, 1437, 1303, 1223, 1146, 754, 704 cm^{-1}.

6.11.3. (4aS,7aS*)-3-Acetyl-4a-methyl-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]inden-2-one (**24a**).* Prepared from **12a** (38 mg, 0.25 mmol) and 3-butyn-2-one (**21b**) (23.5 μL, 0.3 mmol) in anhyd DCM (1 mL), rt, 24 h, workup B, column chromatography (CH_2Cl_2−MeOH, 100:1). Yield: 40 mg (73%) of beige solid. Mp: 83−87 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 1.36 (3H, s); 1.64−1.98 (5H, m); 2.05−2.08 (1H, m); 2.27 (3H, s); 2.44 (1H, dd, J = 15.1, 4.7 Hz); 2.57 (1H, dd, J = 15.1, 13.2 Hz); 3.40 (1H, ddt, J = 13.0, 11.9, 4.5 Hz); 7.30 (1H, s); minor isomer **24′a** 2.82 (1H, dd, J = 17.1, 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.8, 23.1, 25.8, 27.5, 28.2, 40.9, 60.9, 66.6, 128.2, 136.2, 177.2, 193.5. m/z (ESI) = 221 (MH^+). m/z (HRMS) found 221.1284 (MH^+), $C_{12}H_{17}N_2O_2$ requires m/z = 221.1285. IR ν_{max} (ATR): 3068, 2965, 1728, 1648, 1575, 1233, 1186, 660, 612 cm^{-1}.

6.11.4. (4aR,7aS*)-3-Acetyl-4a-phenyl-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]inden-2-one (**24b**).* Prepared from

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

12b (53 mg, 0.25 mmol) and 3-butyn-2-one (**21b**) (23.5 μL, 0.3 mmol) in anhyd DCM (1 mL), rt, 96 h, workup B, column chromatography (EtOAc−hexanes, 1:3). Yield: 49 mg (69%) of pale yellow crystals. Mp: 196−200 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44−1.54 (1H, m); 1.62−1.73 (2H, m); 1.78−1.86 (1H, m); 2.23 (3H, s); 2.29 (1H, td, *J* = 14.5, 3.7 Hz); 2.56 (1H, dd, *J* = 15.1, 4.6 Hz); 2.69 (1H, dt, *J* = 14.4, 3.5 Hz); 2.72 (1H, dd, *J* = 15.1, 13.1 Hz); 3.59 (1H, ddt, *J* = 13.1, 11.6, 4.8 Hz); 7.22−7.25 (1H, m); 7.28 (1H, s); 7.31−7.34 (2H, m); 7.79−7.81 (2H, m); minor isomer **24′b** 3.26 (1H, dd, *J* = 16.5, 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.7, 23.1, 27.9, 29.4, 40.8, 60.3, 71.8, 126.6, 127.1, 127.6, 128.3, 136.2, 145.2, 176.9, 194.1. *m*/*z* (ESI) = 283 (MH^+). *m*/*z* (HRMS) found 283.1441 (MH^+), $C_{17}H_{19}N_2O_2$ requires *m*/*z* = 283.1441. IR ν_{max} (ATR): 3078, 2959, 1742, 1648, 1569, 1296, 1222, 1102, 760, 706 cm^{-1}.

6.11.5. (4aS,7aS*)-4-Benzoyl-4a-methyl-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]inden-2-one (**24c**).* Prepared from **12a** (38 mg, 0.25 mmol) and 1-phenylprop-2-yn-1-one (**21c**) (39 mg, 0.3 mmol) in anhyd DCM (1 mL), rt, 42 h, workup B, column chromatography (EtOAc−hexanes, 1:4). Yield: 47 mg (67%) of brownish solid. Mp: 157−161 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (3H, s); 1.79−1.87 (2H, m); 1.90−1.99 (1H, m); 2.12−2.20 (2H, m); 2.46 (1H, dd, *J* = 15.2, 4.7 Hz); 2.60 (1H, dd, *J* = 15.1, 13.2 Hz); 3.48 (1H, ddt, *J* = 13.2, 12.1, 4.5 Hz); 7.17 (1H, s); 7.41−7.45 (2H, m); 7.50−7.54 (1H, m) 7.61−7.64 (2H, m); minor isomer **24′c** 3.26 (1H, dd, *J* = 16.6, 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.9, 23.2, 26.1, 28.5, 40.9, 61.1, 67.6, 126.6, 128.1, 128.6, 131.8, 138.1, 140.2, 177.0, 191.9. *m*/*z* (ESI) = 283 (MH^+). *m*/*z* (HRMS) found 283.1445 (MH^+), $C_{17}H_{19}N_2O_2$ requires *m*/*z* = 283.1441. IR ν_{max} (ATR): 3077, 2957, 1745, 1619, 1571, 1295, 1237, 1174, 732 cm^{-1}.

6.11.6. (4aR,7aS*)-4-Benzoyl-4a-phenyl-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]inden-2-one (**24d**).* Prepared from **12b** (53 mg, 0.25 mmol) and 1-phenylprop-2-yn-1-one (**21c**) (39 mg, 0.3 mmol) in anhyd DCM (1 mL), rt, 40 h, workup B, column chromatography (EtOAc−hexanes, 1:4). Yield: 61 mg (71%) of orange solid. Mp: 171−174 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52−1.63 (1H, m); 1.68−1.79 (2H, m); 1.83−1.91 (1H, m); 2.55 (1H, dd, *J* = 15.1, 4.6 Hz); 2.60 (1H, dd, *J* = 14.4, 3.7 Hz); 2.73 (1H, dt, *J* = 14.4, 3.5 Hz); 2.74 (1H, dd, *J* = 15.1, 13.0 Hz); 3.65 (1H, ddt, *J* = 13.0, 11.7, 4.8 Hz); 7.09 (1H, s); 7.23−7.27 (1H, m); 7.32−7.39 (2H, m); 7.46−7.50 (1H, m); 7.51−7.54 (2H, m); 7.79−7.82 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.8, 23.3, 30.1, 40.8, 60.6, 73.3, 126.2, 126.4, 127.3, 128.3, 128.51, 128.52, 132.0, 137.6, 140.1, 145.5, 176.6, 193.1. *m*/*z* (ESI) = 345 (MH^+). *m*/*z* (HRMS) found 345.1599 (MH^+), $C_{22}H_{21}N_2O_2$ requires *m*/*z* = 345.1598. IR ν_{max} (ATR): 3059, 2922, 1741, 1612, 1564, 1554, 1294, 1231, 721 cm^{-1}.

6.11.7. tert-Butyl (4aS,7aS*)-(2-(4a-Methyl-2-oxo-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]inden-3-yl)-2-oxoethyl)-carbamate (**24e**).* Prepared from **12a** (38 mg, 0.25 mmol) and *tert*-butyl (2-oxobut-3-yn-1-yl)carbamate (**21d**) (46 mg, 0.3 mmol) in anhyd DCM (1 mL), rt, 48 h, workup B, column chromatography (CH_2Cl_2−MeOH, 100:1). Yield: 35 mg (42%) of yellow resin. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (3H, s); 1.45 (9H, s); 1.65−2.08 (6H, m); 2.46 (1H, dd, *J* = 15.1, 4.7 Hz); 2.57 (1H, dd, *J* = 15.2, 13.1 Hz); 3.38 (1H, tq, *J* = 12.6, 4.5 Hz); 4.15−4.25 (2H, m); 5.29 (1H, br s); 7.40 (1H, s); minor isomer **24′e** 2.81 (1H, dd, *J* = 17.2, 7.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.8, 23.1, 25.8, 28.3, 28.5, 40.8, 47.4, 60.8, 66.8, 79.9, 124.9, 135.9, 155.8, 176.7, 190.5. *m*/*z* (ESI) = 336 (MH^+). *m*/*z* (HRMS) found 336.1923 (MH^+), $C_{17}H_{26}N_3O_4$ requires *m*/*z* = 336.1918. IR ν_{max} (ATR): 3367, 2968, 1751, 1709, 1653, 1577, 1163, 937, 861, 730 cm^{-1}.

6.11.8. tert-Butyl (4aR,7aS*)-(2-Oxo-2-(2-oxo-4a-phenyl-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]inden-3-yl)ethyl)carbamate (**24f**).* Prepared from **12b** (54 mg, 0.25 mmol) and *tert*-butyl (2-oxobut-3-yn-1-yl)carbamate (**21d**) (46 mg, 0.3 mmol) in anhyd DCM (1 mL), rt, 48 h, workup B, column chromatography (EtOAc−hexanes, 1:3). Yield: 50 mg (50%) of brownish resin. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (9H, s); 1.46−1.59 (1H, m); 1.62−1.73 (2H, m); 1.75−1.90 (1H, m); 2.30 (1H, td, *J* = 14.3, 3.6 Hz); 2.57 (1H, dd, 15.1, 4.8 Hz); 2.70 (1H, dt, *J* = 14.3, 3.5 Hz); 2.72 (1H, dd, *J* = 15.2, 12.6 Hz); 3.58 (1H, ddt, *J* = 12.7, 11.3, 5.0 Hz); 3.98 (1H, dd, *J* = 18.3, 4.3 Hz); 4.30 (1H, dd, *J* = 18.2, 5.7 Hz); 5.27 (1H, br s); 7.21−7.26 (1H, m); 7.29−7.35 (2H, m); 7.38 (1H, s); 7.73−7.77 (2H, m); minor isomer **24′f** 3.21 (1H, dd, *J* = 17.2, 7.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.7, 23.2, 28.4, 29.3, 40.8, 47.5, 60.2, 72.1 79.9, 124.5, 126.5, 127.3, 128.4, 135.8, 144.8, 155.7, 176.4, 191.1. *m*/*z* (ESI) = 398 (MH^+). *m*/*z* (HRMS) found 398.2073 (MH^+), $C_{22}H_{28}N_3O_4$ requires *m*/*z* = 398.2074. IR ν_{max} (ATR): 3406, 2938, 1759, 1699, 1676, 1585, 1574, 1522, 1153, 702 cm^{-1}.

6.11.9. Methyl (4aS,7aS*)-4a-Methyl-2-oxo-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]indene-3-carboxylate (**24g**).* Prepared from **12a** (38 mg, 0.25 mmol) and methyl propiolate (**21e**) (27 μL, 0.3 mmol) in anhyd DCM (1 mL), 80 °C (pressure vessel), 24 h, workup B, column chromatography (CH_2Cl_2−MeOH, 100:1). Yield: 33 mg (56%) of colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (3H, s); 1.64−2.02 (6H, m); 2.42 (1H, dd, *J* = 15.1, 4.7 Hz); 2.56 (1H, dd, *J* = 15.0, 13.2 Hz); 3.41 (1H, ddt, *J* = 13.1, 12.1, 4.5 Hz); 3.73 (3H, s); 7.31 (1H, s); minor isomer **24′g** 3.16 (1H, dd, *J* = 16.5, 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.8, 23.2, 26.1, 28.4, 40.9, 51.5, 60.8, 65.9, 118.7, 135.5, 164.6, 176.9. *m*/*z* (ESI) = 237 (MH^+). *m*/*z* (HRMS) found 237.1234 (MH^+). $C_{12}H_{17}N_2O_3$ requires *m*/*z* = 237.1234. IR ν_{max} (ATR): 2952, 1750, 1698, 1595, 1224, 1169, 1076, 765 cm^{-1}.

6.11.10. Methyl (4aR,7aS*)-2-Oxo-4a-phenyl-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]indene-3-carboxylate (**24h**) and Its (4aS*,7aS*)-Epimer **24′h**.* Prepared from **12b** (53 mg, 0.25 mmol) and methyl propiolate (**21e**) (27 μL, 0.3 mmol) in anhyd DCM (1 mL), 80 °C (pressure vessel), 24 h, workup B, column chromatography (EtOAc−hexanes, 1:4).

6.11.10.1. Methyl (4aR,7aS*)-2-Oxo-4a-phenyl-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]indene-3-carboxylate (**24h**).* Yield: 45 mg (60%) of brownish solid. Mp: 140−144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47−1.57 (1H, m); 1.65−1.74 (2H, m); 1.79−1.87 (1H, m); 2.31 (1H, dt. *J* = 14.4, 3.6 Hz); 2.53 (1H, dd, *J* = 15.0, 4.6 Hz); 2.62 (1H, dt, *J* = 14.3, 3.5 Hz); 2.71 (1H, dd, *J* = 15.0, 13.1 Hz); 3.60 (1H, ddt, *J* = 13.2, 11.7, 4.8 Hz); 3.72 (3H, s); 7.23−7.27 (1H, m); 7.29 (1H, s); 7.32−7.36 (2H, m); 7.80−7.82 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.7, 23.2, 29.3, 40.9, 51.5, 60.3, 71.1, 118.2, 126.4, 127.2, 128.4, 135.2, 145.1, 165.1, 176.6. *m*/*z* (ESI) = 299 (MH^+). *m*/*z* (HRMS) found 299.1393 (MH^+), $C_{17}H_{19}N_2O_3$ requires *m*/*z* = 299.1390. IR ν_{max} (ATR): 2932, 1739, 1691, 1604, 1590, 1107, 748, 705 cm^{-1}.

6.11.10.2. Methyl (4aS,7aS*)-2-Oxo-4a-phenyl-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]indene-3-carboxylate (**24′h**).* Yield: 8 mg (11%) of brownish resin. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39−1.49 (1H, m); 1.51−1.62 (3H, m); 1.75−1.86 (2H, m); 2.46 (1H, d, *J* = 16.5 Hz); 2.81−2.88 (1H, m), 3.21 (1H, dd, *J* = 16.5, 7.5 Hz); 3.58 (3H, s); 7.28 (1H, br t, *J* = 7.3 Hz); 7.37 (2H, br t, *J* = 7.7 Hz); 7.41 (1H, s); 7.78 (2H, br d, *J* = 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.3, 27.4, 31.6, 42.9, 51.5, 53.4, 68.8, 125.0, 126.5, 127.5, 128.1, 128.3, 140.8, 163.2, 164.0. *m*/*z* (ESI) = 299 (MH^+). *m*/*z* (HRMS) found 299.1392 (MH^+), $C_{17}H_{19}N_2O_3$ requires *m*/*z* = 299.1390. IR ν_{max} (ATR): 2932, 1690, 1577, 1410, 1310, 1194, 1090, 756, 696 cm^{-1}.

6.11.11. Mixture of Methyl (4S,4aS*,7aS*)-4a-methyl-2-oxo-octahydro-2H-2a,2a1-diazacyclopenta[cd]indene-4-carboxylate (**25a**) and Its Isomers **25′a**.* Prepared from **12a** (152 mg, 1 mmol) and methyl acrylate (**22a**) (450 μL, 5 mmol) in anhyd CH_2Cl_2 (5 mL), 80 °C (pressure vessel), 72 h, workup B, flash column chromatography (EtOAc). Yield: 167 mg (70%) of brownish oil. The isomeric products **25a** and **25′a** were separated by column chromatography (EtOAc−hexanes, 1:3 to elute the nonpolar by-products, then EtOAc−hexanes, 1:1 to elute **25′a**, finally EtOAc to elute **25a**). Fractions containing the products were combined and evaporated in vacuo to give **25a** and **25′a**.

6.11.11.1. Methyl (3R,4aS*,7aS*)-4a-Methyl-2-oxooctahydro-2H-2a,2a1-diazacyclopenta[cd]indene-3-carboxylate (**25′a**).* Yield: 38 mg (16%) of yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (3H, s); 1.63−1.76 (6H, m); 2.20 (1H, dd, *J* = 12.9, 9.6 Hz); 2.31 (1H, dd, *J* = 14.3, 4.8 Hz); 2.55 (1H, d, *J* = 12.9 Hz); 2.60 (1H, t, *J* = 14.2 Hz); 3.07−3.16 (1H, m); 3.77 (3H, s); 4.80 (1H, d, *J* = 9.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.3, 24.2, 26.1, 32.4, 40.1, 41.9, 53.1,

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

59.3, 61.2, 63.2, 171.8, 176.4. *m/z* (ESI) = 239 (MH^+). *m/z* (HRMS) found 239.1394 (MH^+), $C_{12}H_{19}N_2O_3$ requires *m/z* = 239.1390. IR ν_{max} (ATR): 2949, 1728, 1703, 1436, 1349, 1197, 1112, 1016, 638 cm^{-1}.

6.11.11.2. Methyl (4S,4aS*,7aS*)-4a-Methyl-2-oxo-octahydro-2H-2a,2a1-diazacyclopenta[cd]indene-4-carboxylate (**25a**).* Yield: 26 mg (11%) of yellowish oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.34 (3H, s); 1.57−1.66 (2H, m); 1.68−1.92 (4H, m); 2.31 (1H, br dd, *J* = 13.9, 5.7 Hz); 2.46 (1H, t, *J* = 13.9 Hz); 3.00 (1H, d, *J* = 6.7 Hz); 3.40 (1H, br dd, *J* = 12.1, 6.7 Hz); 3.58 (1H, br s); 3.72 (3H, s); 4.42 (1H, br d, *J* = 12.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.5, 24.1, 28.4, 29.1, 39.9, 46.6, 52.1, 55.1, 60.9, 64.5, 173.4, 173.6. *m/z* (ESI) = 239 (MH^+). *m/z* (HRMS) found 239.1392 (MH^+). $C_{12}H_{19}N_2O_3$ requires *m/z* = 239.1390. IR ν_{max} (ATR): 2951, 1728, 1697, 1371, 1194, 1176, 1162, 1111, 635 cm^{-1}.

6.11.12. Methyl (4S,4aS*,7aS*)-2-Oxo-4a-phenyloctahydro-2H-2a,2a1-diazacyclopenta[cd]indene-4-carboxylate (**25b**).* Prepared from **12b** (50 mg, 0.25 mmol) and methyl acrylate (**22a**) (25 μL, 0.4 mmol) in anhyd CH_2Cl_2 (5 mL), 80 °C, 12 h, workup B, column chromatography (EtOAc). Yield: 33 mg (44%) of brownish oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.34−1.45 (1H, m); 1.55−1.80 (3H, m); 2.02−2.08 (2H, m); 2.42 (1H, dd, *J* = 14.1, 5.3 Hz); 2.62 (1H, td, *J* = 14.0, 1.1 Hz); 2.90 (1H, ddd, *J* = 12.0, 6.4, 1.1 Hz); 3.37 (1H, d, *J* = 6.4 Hz); 3.75−3.86 (1H, m); 3.80 (3H, s); 4.32 (1H, d, *J* = 11.9 Hz); 7.27 (1H, d, *J* = 7.3 Hz); 7.37 (2H, br t, *J* = 7.7 Hz); 7.73 (2H, br d, *J* = 7.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.1, 24.4, 30.9, 40.2, 45.6, 52.2, 56.9, 60.1, 70.4, 126.7, 127.4, 128.4, 146.0, 173.0, 173.4. *m/z* (ESI) = 301 (MH^+). *m/z* (HRMS) found 301.1543 (MH^+), $C_{17}H_{21}N_2O_3$ requires *m/z* = 301.1547. IR ν_{max} (ATR): 2949, 1730, 1701, 1491, 1361, 1197, 1177, 1058, 706 cm^{-1}.

6.11.13. tert-Butyl (4S,4aS*,7aS*)-2-Oxo-4a-phenyloctahydro-2H-2a,2a1-diazacyclopenta[cd]indene-4-carboxylate (**25c**).* Prepared from **12a** (214 mg, 1 mmol) and *tert*-butyl acrylate (**22b**) (1.5 mL, 10 mmol) in anhyd toluene (8 mL), 80 °C, 24 h, workup B, column chromatography (EtOAc). Yield: 265 mg (77%) of yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.19−1.25 (1H, m); 1.48 (9H, s); 1.49−1.61 (2H, m), 1.69−1.77 (1H, m); 1.95 (1H, dt, *J* = 13.9, 3.4 Hz); 2.16 (1H, td, *J* = 14.0, 3.2 Hz); 2.29 (1H, dd, *J* = 14.2, 5.3 Hz); 2.53 (1H, m); 2.66 (1H, dd, *J* = 12.0, 6.5 Hz); 3.20 (1H, d, *J* = 6.3 Hz); 3.71 (1H, ddt, *J* = 13.8, 11.7, 5.1 Hz); 4.08 (1H, d, *J* = 12.0 Hz); 7.25−7.30 (1H, m); 7.39 (2H, br t, *J* = 7.7 Hz); 7.60 (2H, dt, *J* = 8.3, 1.7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.6, 23.9, 27.6, 30.0, 39.7, 45.7, 57.5, 59.3, 69.7, 81.4, 126.2, 127.0, 128.1, 146.2, 171.3, 172.3. *m/z* (ESI) = 343 (MH^+). *m/z* (HRMS) found 343.2007 (MH^+), $C_{20}H_{26}N_2O_3$ requires *m/z* = 343.2016. IR ν_{max} (ATR): 1650, 1573, 1557, 1444, 1300, 1087, 774, 692 cm^{-1}.

6.11.14. (2aS,5aS*,5bS*,8aS*)-5a-Methyl-7-phenyloctahydro-2a1,7,8b-triazadicyclopenta[a,cd]indene-1,6,8(7H)-trione (**26a**).* Prepared from **12a** (78 mg, 0.5 mmol) and *N*-phenylmaleimide (**22c**) (104 mg, 0.6 mmol) in toluene (2 mL), 80 °C, 18 h, workup B, column chromatography (CH_2Cl_2−MeOH, 50:1). Yield: 21 mg (13%) of white solid. Mp: 169−172 °C. ^1H NMR (500 MHz, $CDCl_3$): δ major isomer **26a** 1.30 (3H, s); 1.72 (2H, m); 1.81−1.97 (3H, m); 2.09 (1H, m); 2.41 (1H, dd, *J* = 14.5, 4.5 Hz); 2.66 (1H, t, *J* = 14.0 Hz); 3.14 (1H, m); 3.56 (1H, d, *J* = 9.0 Hz); 5.17 (1H, d, *J* = 9.0 Hz); 7.28 (2H, m); 7.41 (1H, m); 7.48 (2H, m); minor isomer **26′a** 5.00 (1H, d, *J* = 7.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.1, 22.8, 24.8, 33.0, 40.4, 53.8, 63.8, 64.8, 65.3, 126.1, 128.9, 129.3, 131.2, 172.4, 172.6, 181.3. *m/z* (ESI) = 326 (MH^+). *m/z* (HRMS) found 326.1503 (MH^+), $C_{18}H_{20}N_3O_3$ requires *m/z* = 326.1499. IR ν_{max} (ATR): 1714, 1499, 1391, 1279, 1181, 1114, 733, 691, 660 cm^{-1}.

6.11.15. (2aS,5aS*,5bS*,8aS*)-5a,7-Diphenyloctahydro-2a1,7,8b-triazadicyclopenta[a,cd]indene-1,6,8(7H)-trione (**26b**).* Prepared from **12b** (108 mg, 0.5 mmol) and *N*-phenylmaleimide (**22c**) (104 mg, 0.6 mmol) in toluene (2 mL), 80 °C, 18 h, workup B, column chromatography (CH_2Cl_2−MeOH, first 50:1, then 25:1). Yield: 77 mg (40%) of white solid. Mp: 195−198 °C. ^1H NMR (500 MHz, $CDCl_3$): δ major isomer **26b** 1.44 (1H, m); 1.70 (2H, m); 1.86 (1H, m); 2.36 (1H, td, *J* = 14.0, 3.5 Hz); 2.50 (1H, dd, *J* = 14.5, 4.5 Hz); 2.63 (1H, dt, *J* = 14.0, 4.0 Hz); 2.76 (1H, t, *J* = 14.0 Hz); 3.51 (1H, m); 3.79 (1H, d, *J* = 8.5 Hz); 5.22 (1H, d, *J* = 8.5 Hz), 6.35 (2H, m), 7.19−7.40 (7H, m); 7.88 (1H, br s); minor isomer **26′b** 3.89 (1H, d, *J* = 6.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.7, 24.5, 33.8, 40.1, 56.9, 62.6, 63.9, 71.4, 126.2, 128.2, 128.4 (br), 128.6, 128.7, 130.7, 139.6, 171.67, 171.69, 179.6. *m/z* (ESI) = 388 (MH^+). *m/z* (HRMS) found 388.1655 (MH^+), $C_{23}H_{22}N_3O_3$ requires *m/z* = 388.1656. IR ν_{max} (ATR): 1716, 1498, 1391, 1283, 1196, 755, 705, 689 cm^{-1}.

6.12. CuI-Catalyzed [3 + 2]-Cycloadditions of Azomethine Imines 12a and 12b to Methyl Propiolate. Synthesis of Cycloadducts 24g and 24h. A mixture of azomethine imine **12** (0.25 mmol), anhyd CH_2Cl_2 (1 mL), methyl propiolate (**21e**) (27 μL, 0.3 mmol), CuI (10 mg, 0.05 mmol), and DIPEA (9 μL, 0.05 mmol) was stirred at rt for 72 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc−hexanes, 1:4). Fractions containing the product were combined and evaporated in vacuo to give cycloadducts **24g** and **24h**.

6.12.1. Methyl (4aS,7aS*)-4a-Methyl-2-oxo-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]indene-3-carboxylate (**24g**) and Methyl (E)-3-(Ethyl(isopropyl)amino)acrylate (**29**).* Prepared from **12a** (38 mg, 0.25 mmol) and methyl propiolate (**21e**). Yield: 28 mg (47%) of brownish oil, **24g**:**29** = 84:16. Characterization data for compound **24g** are given in section 6.11.9.

6.12.2. Methyl (4aR,7aS*)-2-Oxo-4a-phenyl-1,4a,5,6,7,7a-hexahydro-2H-2a,2a1-diazacyclopenta[cd]indene-3-carboxylate (**24h**) and Methyl (E)-3-(Ethyl(isopropyl)amino)acrylate (**29**).* Prepared from **12b** (53 mg, 0.25 mmol) and methyl propiolate (27 μL, 0.3 mmol). Yield: 30 mg (40%) of brownish solid, **24g**/**29** = 84:16. Characterization data for compound **24h** are given in section 6.11.10.

*6.12.3. Methyl (E)-3-(Ethyl(isopropyl)amino)acrylate (**29**).* A mixture of anhyd CH_2Cl_2 (1 mL), methyl propiolate (**21e**) (14 μL, 0.16 mmol), CuI (30 mg, 0.16 mmol), and DIPEA (24 μL, 0.14 mmol) was stirred at rt for 72 h. Volatile components were evaporated in vacuo, and the residue was purified by flash column chromatography (silica gel, EtOAc). Fractions containing the product were combined and evaporated in vacuo to give **29**. Yield: 14 mg (57%) of a brownish oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.15 (3H, t, *J* = 7.2 Hz); 1.21 (6H, d, *J* = 6.7 Hz); 3.13 (2H, q, *J* = 7.2 Hz); 3.47−3.56 (1H, m); 3.66 (s, 3H); 4.58 (1H, d, *J* = 13.0 Hz); 7.51 (1H d, *J* = 13.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 12.7, 21.8, 40.9, 50.5, 56.5, 83.0, 149.5, 170.5. These data were in agreement with the literature data.[24]

6.13. Synthesis of (4S*,4aS*,7aS*)-2-Oxo-4a-phenyloctahydro-2*H*-2a,2a1-diazacyclopenta[*cd*]indene-4-carboxylic Acid (27). A mixture of ester **25c** (0.5 mmol) CH_2Cl_2 (4 mL) and CF_3CO_2H (3 mL) was stirred at rt for 24 h. Volatile components were evaporated in vacuo, and the residue was triturated with Et_2O (10 mL). The precipitate was collected by filtration and washed with Et_2O (2 × 3 mL) to give carboxylic acid **27**. Yield: 69 mg (48%) of white solid. Mp: 175−176 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 1.20 (1H, dtdd, *J* = 16.1, 12.4, 8.4, 4.8 Hz), 1.48−1.61 (2H, m), 1.66−1.77 (1H, m), 1.96 (1H, dt, *J* = 13.9, 3.4 Hz), 2.20 (1H, td, *J* = 14.2, 3.3 Hz), 2.26 (1H, dd, *J* = 14.2, 5.2 Hz), 2.52 (1H, overlapped by the signal for DMSO), 2.66 (1H, dd, *J* = 11.8, 6.5 Hz), 3.25 (1H, d, *J* = 6.3 Hz), 3.71 (1H, ddt, *J* = 13.8, 11.8, 5.1 Hz), 4.09 (1H, d, *J* = 11.8 Hz), 7.23−7.31 (1H, m), 7.38 (2H, t, *J* = 7.7 Hz), 7.61−7.67 (2H, m), 12.99 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6): δ 16.5, 23.8, 30.4, 39.8, 45.8, 56.3, 59.2, 69.1, 126.2, 126.8, 128.0, 146.2, 172.5, 173.9. *m/z* (ESI) = 287 (MH^+). *m/z* (HRMS) found 287.1389 (MH^+), $C_{16}H_{18}N_2O_3$ requires *m/z* = 287.1390. IR ν_{max} (ATR): 1732, 1723, 1674, 1413, 1205, 757, 702 cm^{-1}.

6.14. Synthesis of (4S*,4aS*,7aS*)-2-Oxo-4a-phenyloctahydro-2*H*-2a,2a1-diazacyclopenta[*cd*]indene-4-carboxamides (28a−c). Et_3N (35 μL, 0.25 mmol) was added to a suspension of carboxylic acid **27** (71 mg, 0.25 mmol) in anhyd DMF (2 mL), and the mixture was stirred at rt for 10 min. Then, bis(pentafluorophenyl) carbonate (99 mg, 0.25 mmol) was added, and the mixture was stirred at rt for 1 h. Amine (0.25 mmol) and Et_3N (35 μL, 0.25 mmol) were added, and stirring at rt was continued for 24 h. Volatile components were evaporated in vacuo (50 °C, 2 mbar), and the residue was purified by flash column chromatography (silica gel, CH_2Cl_2−MeOH, 50:1). Fractions containing the product were combined and evaporated in vacuo to give **28**.

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

6.14.1. (4S,4aS*,7aS*)-N-Benzyl-2-oxo-4a-phenyloctahydro-2H-2a,2a1-diazacyclopenta[cd]indene-4-carboxamide (**28a**).* Prepared from **27** (71 mg, 0.25 mmol) and benzylamine (28 μL, 0.25 mmol). Yield: 74 mg (79%) of yellow solid. Mp: 202−203 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (1H, tddd, *J* = 13.9, 10.6, 7.5, 3.3 Hz); 1.56−1.66 (2H, m, overlapped by the signal for H_2O); 1.71 (1H, dddd, *J* = 12.6, 10.5, 7.5, 5.0 Hz); 1.95 (1H, dt, *J* = 13.4, 3.3 Hz); 2.26 (1H, td, *J* = 13.8, 3.4 Hz); 2.40 (1H, dd, *J* = 14.0, 5.3 Hz); 2.60 (1H, t, *J* = 13.9 Hz); 2.91 (1H, br dd, *J* = 11.8, 6.6 Hz); 3.02 (1H, d, *J* = 6.5 Hz), 4.07−4.16 (1H, m); 4.27 (1H, d, *J* = 11.8 Hz); 4.45 (1H, dd, *J* = 14.5, 5.3 Hz); 4.58 (1H, dd, *J* = 14.5, 5.9 Hz); 6.01 (1H,br t, *J* = 5.6 Hz); 7.22−7.28 (1H, m); 7.30−7.40 (7H, m); 7.63 (2H, br d, *J* = 7.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.1, 24.2, 30.0, 40.0, 44.0, 45.7, 58.5, 59.4, 70.2, 126.5, 127.2, 127.9, 128.2, 128.3, 128.9, 137.7, 146.3, 171.5, 173.0. *m*/*z* (ESI) = 376 (MH^+). *m*/*z* (HRMS) found 376.2017 (MH^+), $C_{23}H_{25}N_3O_2$ requires *m*/*z* = 376.2020. IR ν_{max} (ATR): 3354, 1687, 1639, 1523, 1382, 1240, 758, 699 cm^{-1}.

6.14.2. (4S,4aS*,7aS*)-N-(3-Hydroxypropyl)-2-oxo-4a-phenyl-octahydro-2H-2a,2a1-diazacyclopenta[cd]indene-4-carboxamide (**28b**).* Prepared from **27** (71 mg, 0.25 mmol) and 3-hydroxypropylamine (19 μL, 0.25 mmol). Yield: 65 mg (76%) of pinkish resin. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (1H, ddtt, *J* = 14.2, 10.6, 7.2, 3.7 Hz); 1.55−1.66 (2H, m); 1.68−1.84 (3H, m); 1.98 (1H, dt, *J* = 13.5, 3.4 Hz); 2.22 (1H, td, *J* = 13.8, 3.1 Hz); 2.35−2.48 (1H, m); 2.37 (1H, dd, *J* = 14.1, 5.3 Hz); 2.60 (2H, t, *J* = 13.9 Hz); 2.85 (1H, dd, *J* = 11.5, 6.5 Hz); 3.22 (2H, d, *J* = 6.4 Hz); 3.37−3.49 (2H, m); 3.69 (1H, t, *J* = 5.8 Hz); 4.11−4.20 (1H, m); 4.17 (1H, d, *J* = 11.7 Hz); 7.23 (1H, br t, *J* = 7.3 Hz); 7.33 (2H, br t, *J* = 7.7 Hz); 7.73 (2H, br d, *J* = 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.1, 24.3, 30.3, 32.0, 37.3, 40.3, 45.8, 58.2, 59.6, 60.3, 70.0, 126.8, 127.2, 128.3, 146.4, 172.9, 173.0. *m*/*z* (ESI) = 344 (MH^+). *m*/*z* (HRMS) found 344.1966 (MH^+), $C_{19}H_{26}N_3O_3$ requires *m*/*z* = 344.1969. IR ν_{max} (ATR): 1680, 1581, 1395, 1290, 1078, 705 cm^{-1}.

6.14.3. (4S,4aS*,7aS*)-4a-Phenyl-4-(piperidine-1-carbonyl)-octahydro-2H-2a,2a1-diazacyclopenta[cd]inden-2-one (**28c**).* Prepared from **27** (71 mg, 0.25 mmol) and piperidine (25 μL, 0.25 mmol). Yield: 62 mg (70%) of pale orange resin. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (1H, tddd, *J* = 13.8, 10.5, 7.1, 3.2 Hz); 1.56−1.65 (4H, m); 1.67−1.77 (5H, m); 2.03 (1H, dt, *J* = 13.3, 3.3 Hz); 2.18 (1H, td, *J* = 13.8, 3.3 Hz); 2.45 (1H, dd, *J* = 14.2, 5.3 Hz); 2.60 (1H, br t, *J* = 13.9 Hz); 2.91 (1H, ddd, *J* = 11.5, 6.4, 1.2 Hz), 3.46 (1H, d, *J* = 6.3 Hz); 3.58−3.75 (4H, m); 4.14 (1H, ddt, *J* = 13.7, 12.0, 5.2 Hz); 4.29 (1H, d, *J* = 11.5 Hz); 7.29 (1H, br t, *J* = 7.1 Hz); 7.39 (2H, br t, *J* = 7.7 Hz); 7.64 (2H, br d, *J* = 7.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.4, 24.3, 24.6, 25.8, 26.8, 29.8, 40.1, 43.3, 46.9, 47.4, 53.2, 59.3, 70.2, 126.2, 127.4, 128.6, 146.7, 170.7, 173.5. *m*/*z* (ESI) = 354 (MH^+). *m*/*z* (HRMS) found 354.2173 (MH^+), $C_{21}H_{28}N_3O_2$ requires *m*/*z* = 354.2176. IR ν_{max} (ATR): 2939, 1668, 1580, 1446, 1381, 1288, 702 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01608.

X-ray data for **5′b**, **13′a**, **23b**, **24b**, **26b**, and **28a** (ZIP)

NMR spectra, data on structure determination by NMR, X-ray diffraction data, computational details, and additional tables and figures (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +386 1 4798 562. Fax: +386 1 2419 144. E-mail: jurij.svete@fkkt.uni-lj.si.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Slovenian Research Agency for financial support through Grant No. P1-0179. We thank Boehringer-Ingelheim Pharma, Biberach, Germany, for financial support.

■ REFERENCES

(1) (a) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell, 2010. (b) Patrick, G. L. In *An Introduction to Medicinal Chemistry*, 4th ed.; Oxford University Press: Oxford, U.K., 2009. (c) Pernerstorfer, J. Molecular Design and Combinatorial Compound Libraries. In *Handbook of Combinatorial Chemistry. Drugs, Catalysts, Materials*;Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, 2002; Vol. 2, pp 725−742. (d) Dolle, R. E. Solid-Phase Synthesis of Heterocyclic Systems (Heterocycles Containing One Heteroatom). In *Handbook of Combinatorial Chemistry. Drugs, Catalysts, Materials*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, 2002; Vol. 2, pp 643−684.

(2) (a) Couty, F.; Evano, G. Pyrazolo[1,5-a]pyridine in Bicyclic 5−6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: One Extra Heteroatom 1:0. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Vol. *11*; Cossy, J., Ed.; Elsevier: Oxford, U.K., 2008; pp 409−424. (b) Howard, A. S. Pyrazolo[1,5−a]pyridine in Bicyclic 5−6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: One Extra Heteroatom 1:0. In *Comprehensive Heterocyclic Chemistry III*, Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Vol. *8*; Jones, G., Ed.; Elsevier: Oxford, U.K., 1996; pp 249−258.

(3) SciFinder Scholar Substructure search performed on May 18, 2016.

(4) Allen, S. H.; Johns, B. A.; Gudmundsson, K. S.; Freeman, G. A.; Boyd, F. L.; Sexton, C. H.; Selleseth, D. W.; Creech, K. L.; Moniri, K. R. *Bioorg. Med. Chem.* **2006**, *14*, 944−954.

(5) Timári, G.; Soós, T.; Hajós, G.; Messmer, A.; Nacsa, J.; Molnár, J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2831−2836.

(6) (a) Bettinetti, L.; Schlotter, K.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2002**, *45*, 4594−4597. (b) Lôber, S.; Hübner, H.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2001**, *44*, 2691−2694.

(7) Lôber, S.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2377−2380.

(8) Akahane, A.; Katayama, H.; Mitsunaga, T.; Kita, Y.; Kusunoki, T.; Terai, T.; Yoshida, K.; Shiokawa, Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2059−2062.

(9) Csànyi, D.; Hajós, G.; Riedl, Z.; Timári, G.; Bajor, Z.; Cochard, F.; Sapi, J.; Laronze, J.-Y *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1767−1769.

(10) Gibson, L. C. D.; Hastings, S. F.; McPhee, I.; Clayton, R. A.; Darroch, C. E.; MacKenzie, A.; Mackenzie, F. L.; Nagasawa, M.; Stevens, P. A.; Mackenzie, S. J. *Eur. J. Pharmacol.* **2006**, *538*, 39−42.

(11) Xu, X.; Xing, Y.; Shang, Z.; Wang, G.; Cai, Z.; Pan, Y.; Zhao, X. *Chem. Phys.* **2003**, *287*, 317−333.

(12) (a) Hoffman, P.; Hünig, S.; Walz, L.; Peters, K.; von Schnering, H.-G. *Tetrahedron* **1995**, *51*, 13197−13216. (b) Beck, K.; Hünig, S.; Reinold, P. *Tetrahedron* **1988**, *44*, 3295−3308.

(13) For a recent review, see: Grošelj, U.; Svete, J. *ARKIVOC* **2015**, 175−205 and references cited therein.

(14) Grošelj, U.; Podlogar, A.; Novak, A.; Dahmann, G.; Golobič, A.; Stanovnik, B.; Svete, J. *Synthesis* **2013**, *45*, 639−650.

(15) Mirnik, J.; Grošelj, U.; Novak, A.; Dahmann, G.; Golobič, A.; Kasunič, M.; Stanovnik, B.; Svete, J. *Synthesis* **2013**, *45*, 3404−3412.

(16) Lombar, K.; Grošelj, U.; Dahmann, G.; Stanovnik, B.; Svete, J. *Synthesis* **2015**, *47*, 497−506.

(17) (a) Beauchemin, A. M.; Clavette, C.; Gan, W.; Markiewicz, T.; Toderian, A. B. WO2013067646; *Chem. Abstr.* **2013**, *158*, 728238. (b) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686−5687.

(18) Gan, W.; Moon, P. J.; Clavette, C.; Das Neves, N.; Markiewicz, T.; Toderian, A. B.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 1890−1893.

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933

(19) (a) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748−3759. (b) Baggelaar, M. P.; Huang, Y.; Feringa, B. L.; Dekker, F. J.; Minnaard, A. J. *Bioorg. Med. Chem.* **2013**, *21*, 5271−5274.
(20) Duggan, M. E.; Hartman, G. D. WO 9818460; *Chem. Abstr.* **1998**, *128*, 321933.
(21) Marcin, L. R.; Thompson, L. A., III; Boy, K. M.; Guernon, J. M.; Higgins, M. A.; Shi, J.; Wu, Y.-J.; Zhang, Y.; Macor, J. E. WO 2010083141; *Chem. Abstr.* **2010**, *153*, 204359.
(22) Bodi, J.; Janos, E., Szöke, K.; Vukics, K.; Gáti, T.; Temesvári, K., Kiss-Bartos, D. WO 2007/072088; *Chem. Abstr.* 2007, *147*, 95527.
(23) Bongers, A.; Moon, P. J.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 15516−15519.
(24) Compound **29** has been prepared before in the $ZnBr_2$-catalyzed treatment of DIPEA with **21e**: Lee, K. Y.; Lee, C. G.; Na, J. E.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 69−74. Formation of **29** by the same mechanism was confirmed by another experiment, where the enaminone **29** was formed, exclusively, upon treatment of **21e** with DIPEA in the presence of CuI.
(25) Grashey, R. Azomethine Imines. In *1,3-Dipolar Cycloaddition Chemistry*;Padwa, A., Ed.; John Wiley & Sons, Inc.: New York, 1984; Vol. *1*, pp 733−814.
(26) For a recent review on cycloadditions of azomethine imines, see: Nájera, C.; Sansano, J. M.; Yus, M. *Org. Biomol. Chem.* **2015**, *13*, 8596−8636.
(27) For an illustration, see: (a) Pezdirc, L.; Stanovnik, B.; Svete, J. *Aust. J. Chem.* **2009**, *62*, 1661−1666. (b) Keller, M.; Sido, A. S. S.; Pale, P.; Sommer, J. *Chem. - Eur. J.* **2009**, *15*, 2810−2817. (c) Chassaing, S.; Alix, A.; Boningari, T.; Sani souna Sido, K.; Keller, M.; Kuhn, P.; Louis, B.; Sommer, J.; Pale, P. *Synthesis* **2010**, *2010*, 1557−1567. (d) Mizuno, N.; Kamata, K.; Nakagawa, Y.; Oishi, T.; Yamaguchi, K. *Catal. Today* **2010**, *157*, 359−363. (e) Oishi, T.; Yoshimura, K.; Yamaguchi, K.; Mizuno, N. *Chem. Lett.* **2010**, *39*, 1086−1087. (f) Yoshimura, K.; Oshi, T.; Yamaguchi, K.; Mizuno, N. *Chem. - Eur. J.* **2011**, *17*, 3827−3831. (g) Shao, C.; Zhang, Q.; Cheng, G.; Wang, X.; Hu, Y. *Eur. J. Org. Chem.* **2013**, *2013*, 6443−6448. (h) Pušavec, E.; Mirnik, J.; Šenica, L.; Grošelj, U.; Stanovnik, B.; Svete, J. *Z. Naturforsch., B: J. Chem. Sci.* **2014**, *69*, 615−626. (i) Pušavec Kirar, E.; Grošelj, U.; Mirri, G.; Požgan, F.; Strle, G.; Štefane, B.; Jovanovski, V.; Svete, J. *J. Org. Chem.* **2016**, *81*, 5988−5997.
(28) For details, see the Supporting Information.
(29) (a) Huisgen, R. 1,3-Dipolar Cycloadditions − Introduction, Survey, Mechanism. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons, Inc.: New York, 1984; Vol. *1*, pp 1−176. (b) Houk, K. N.; Yamaguchi, K. Theory of 1,3-Dipolar Cycloadditions. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. *2*, pp 407−447.
(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2009.
(31) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789. (c) Hehre, W. J.; Radom, L.; Schleyer, P. V. R.; Pople, J. A. In *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; pp 1−576.
(32) (a) Lopez, S. A.; Munk, M. E.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 1576−1582. (b) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187−10198. (c) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646−10647. (d) Ziegler, T.; Rauk, A. *Theor. Chim. Acta* **1977**, *46*, 1−10. (e) Ziegler, T.; Rauk, A. *Inorg. Chem.* **1979**, *18*, 1755−1759. (f) Bickelhaupt, F. M.; Ziegler, T. *Organometallics* **1995**, *14*, 2288−2296. (g) Contini, A.; Leone, S.; Menichetti, S.; Viglianisi, C.; Trimarco, P. *J. Org. Chem.* **2006**, *71*, 5507−5514. (h) Legnani, L.; Lunghi, C.; Albini, F. M.; Nativi, C.; Richichi, B.; Toma, L. *Eur. J. Org. Chem.* **2007**, *2007*, 3547−3554.
(33) (a) Domingo, L. R.; Pérez, P. *Org. Biomol. Chem.* **2011**, *9*, 7168−7175. (b) Domingo, L. R.; Sáez, J. A. *Org. Biomol. Chem.* **2009**, *7*, 3576−3583. (c) Domingo, L. R.; Chamorro, E.; Pérez, P. *J. Org. Chem.* **2008**, *73*, 4615−4624.
(34) (a) Parr, R. G.; Von Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922−1924. (b) Domingo, L. R.; Aurell, M. J.; Pérez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417−4423.
(35) Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107−115.

DOI: 10.1021/acs.joc.6b01608
J. Org. Chem. 2016, 81, 8920−8933