JOC The Journal of Organic Chemistry

Article

Synthesis of 3D-rich heterocycles: Hexahydropyrazolo[1,5-a]pyridin-2(1H)-ones and octahydro-2H-2a,2a1-diazacyclopenta[cd]inden-2-ones.

Eva Pušavec Kirar, Miha Drev, Jona Mirnik, Uroš Grošelj, Amalija Golobi#, Georg Dahmann, Franc Požgan, Bogdan Štefane, and Jurij Svete

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01608 • Publication Date (Web): 14 Sep 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

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[a], Miha Drev[a], Jona Mirnik[a], Uroš Grošelj*[a], Amalija Golobič[a], Georg Dahmann[b], Franc Požgan[a], Bogdan Štefane[a], and Jurij Svete*[a1]

a) Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI-1000 Ljubljana, Slovenia

b) Medicinal Chemistry, Boehringer-Ingelheim Pharma GmbH&Co. KG, 88397 Biberach, Germany

E-mail: jurij.svete@fkkt.uni-lj.si; uros.groselj@fkkt.uni-lj.si

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

[1] Corresponding author. Tel.: +386 1 4798 562; Fax: +386 1 2419 144; e-mail: jurij.svete@fkkt.uni-lj.si

methods. The data obtained were in agreement with the polar concerted cycloaddition mechanism *via* the energetically favorable *syn/endo*-transition states.

Keywords: pyrazolo[1,5-*a*]pyridine; 2a,2a^1-diazacyclopenta[*cd*]indene; azomethine imines; [3+2]-cycloadditions; Grignard reagents; saturated heterocycles.

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 100,000 hits and over 2,500 references according to a SciFinder®[3] substructure search. Derivatives of **1** exhibit different biological activities, such as antiviral,[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]

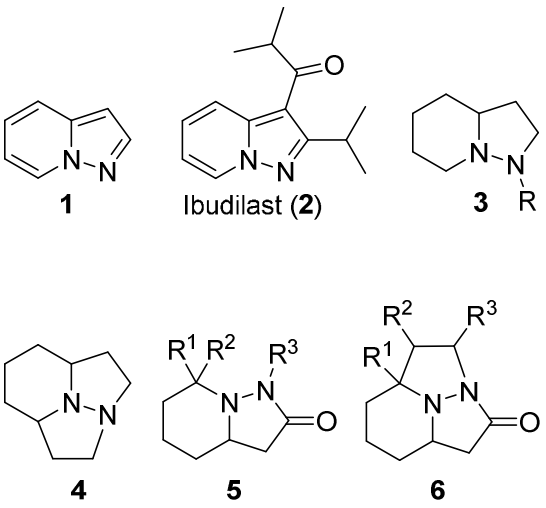


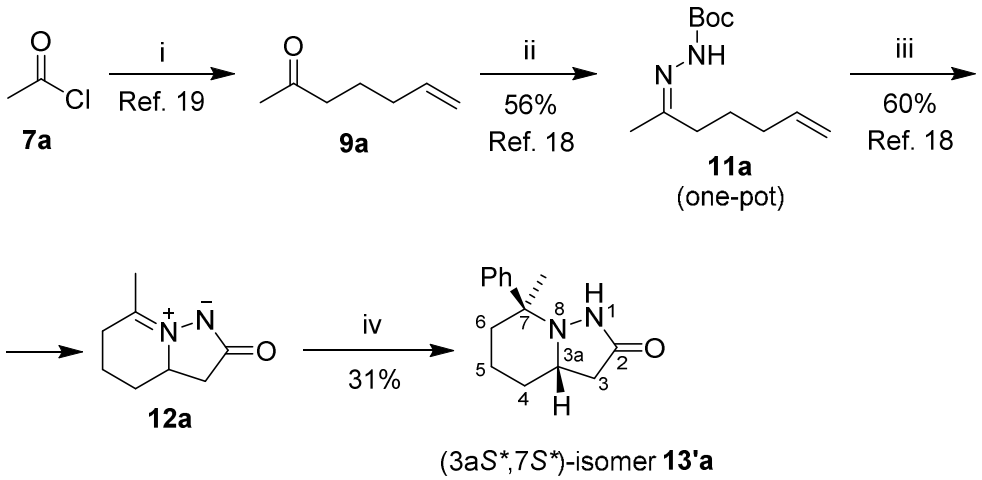
Figure 1. Pyrazolo[1,5-*a*]pyridine (**1**), Ibudilast (**2**), less explored saturated analogues **3**, the unknown saturated tricyclic system **4**, and the target structures **5** and **6**.

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, 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-one) **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, 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, hex-5-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**.

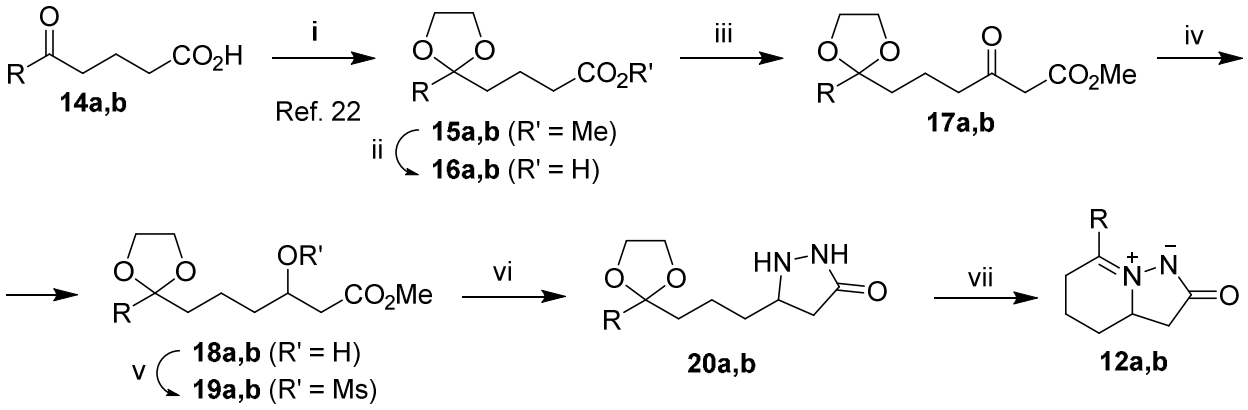


Reaction conditions: (i) pent-4-en-1-ylmagnesium bromide (**8a**), THF, CuI (4 mol%), r.t. (Ref. 19); (ii) $BocNHNH_2$ (**10**), MeOH, AcOH, r.t. (Ref. 18); (iii) μ-waves, 300 W, $C_6H_5CF_3$, 150 °C, 3 h (Ref. 18); and (iv) excess PhMgBr (**8b**), THF, 0→20 °C, followed by column chromatography.

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 similar scale as 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 based on 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).

Scheme 2. Seven-step synthesis of azomethine imines **12a** and **12b**.



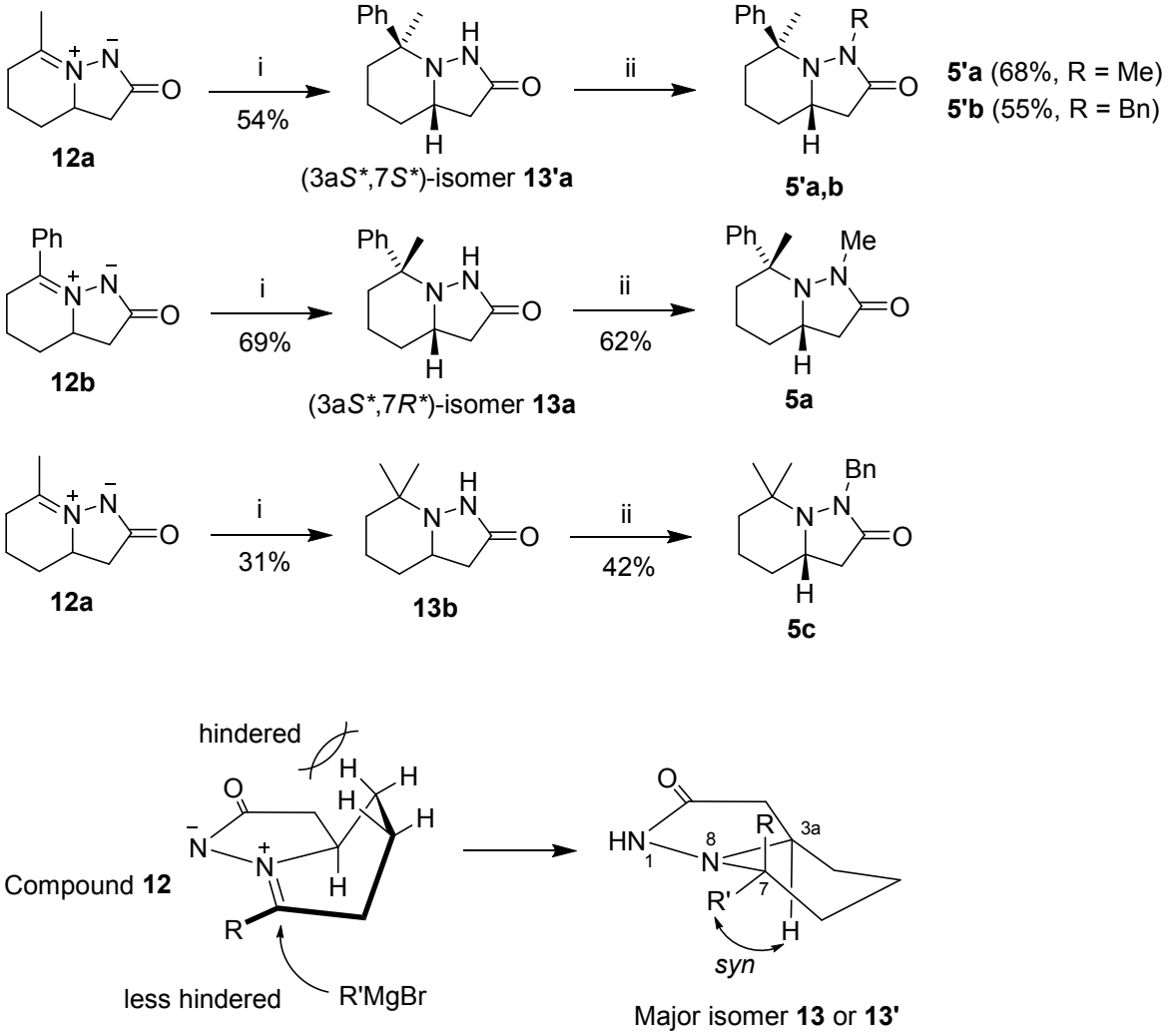
		Yield (%)						
Compound	R	**16**	**17**	**18**	**19**	**20**	**12**	**14→12**
12a, **14a**–**20a**	Me	91	98	85	80	74	80	36
12b, **14b**–**20b**	Ph	98	99	80	95	97	60	43

Reaction conditions: (i) ethylene glycol, TMOF, H_2SO_4 (cat.), r.t. (Ref. 22); (ii) 2 M aq. NaOH, H_2O–MeOH, r.t. (Ref. 22); (iii) CDI, THF, r.t., then $MeO_2CCH_2CO_2K$, $MgCl_2$, r.t.; (iv) $NaBH_4$,

MeOH, 0 °C; (v) MsCl, pyridine, 0 °C; (vi) $N_2H_4 \cdot H_2O$, MeOH, 50 °C; and (vii) EtOH, TFA (cat.), reflux.

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).

Scheme 3. Synthesis of title bicyclic compounds **5**, **5'**, **13**, and **13'** and the proposed stereochemistry of the addition to the C=N bond.

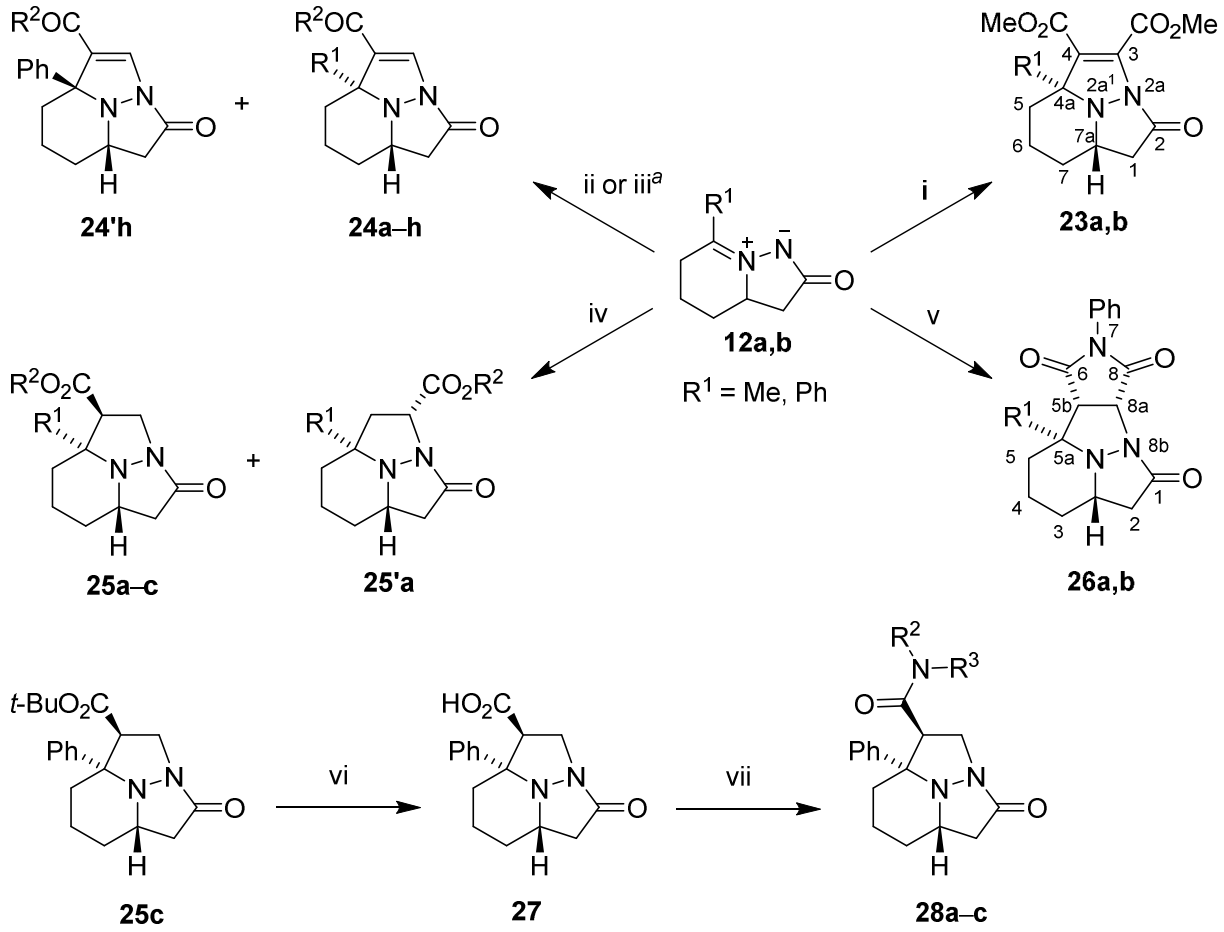


Reaction conditions: (i) excess PhMgBr (**8b**) or MeMgBr (**8c**), THF, –20 °C→ r.t.; (ii) MeI or BnBr, K_2CO_3, DMF, r.t.

The 1,3-dipolar characteristic of azomethine imines **12a** and **12b** was tested in [3+2]-cycloadditions to acetylenic- (**21a**–**d**) 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

acetylenedicarboxylate (DMAD) (**21a**) and terminal ynones **21b**–**d** proceeded at room temperature to give the major (4a*S**,7a*S**)-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 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(pentafluorophenyl) carbonate (BPC) as the activating reagent furnished carboxamides **28a**–**c** in 70–79% yields (Scheme 4, Table 1).

Scheme 4. Synthesis of the title tricyclic compounds **23**–**28**.[a]



Reaction conditions: (i) DMAD (**21a**), toluene or CH_2Cl_2, r.t.; (ii) ynone **21b**–**d** or methyl propiolate (**21e**), CH_2Cl_2, r.t. or 80 °C (pressure vessel); (iii) methyl propiolate (**21e**), CuI (20 mol%), DIPEA (20 mol%), CH_2Cl_2, r.t.; (iv) methyl acrylate (**22a**) or *t*-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), r.t.; and (vii) BPC, Et_3N, DMF, r.t., 1 h followed by RR'NH, Et_3N, r.t., 24 h.

[a]) In the CuI-catalyzed reactions (see iii), by-product **29** was also formed.[24]

Table 1. Experimental data on tricyclic compounds **23**–**28**.

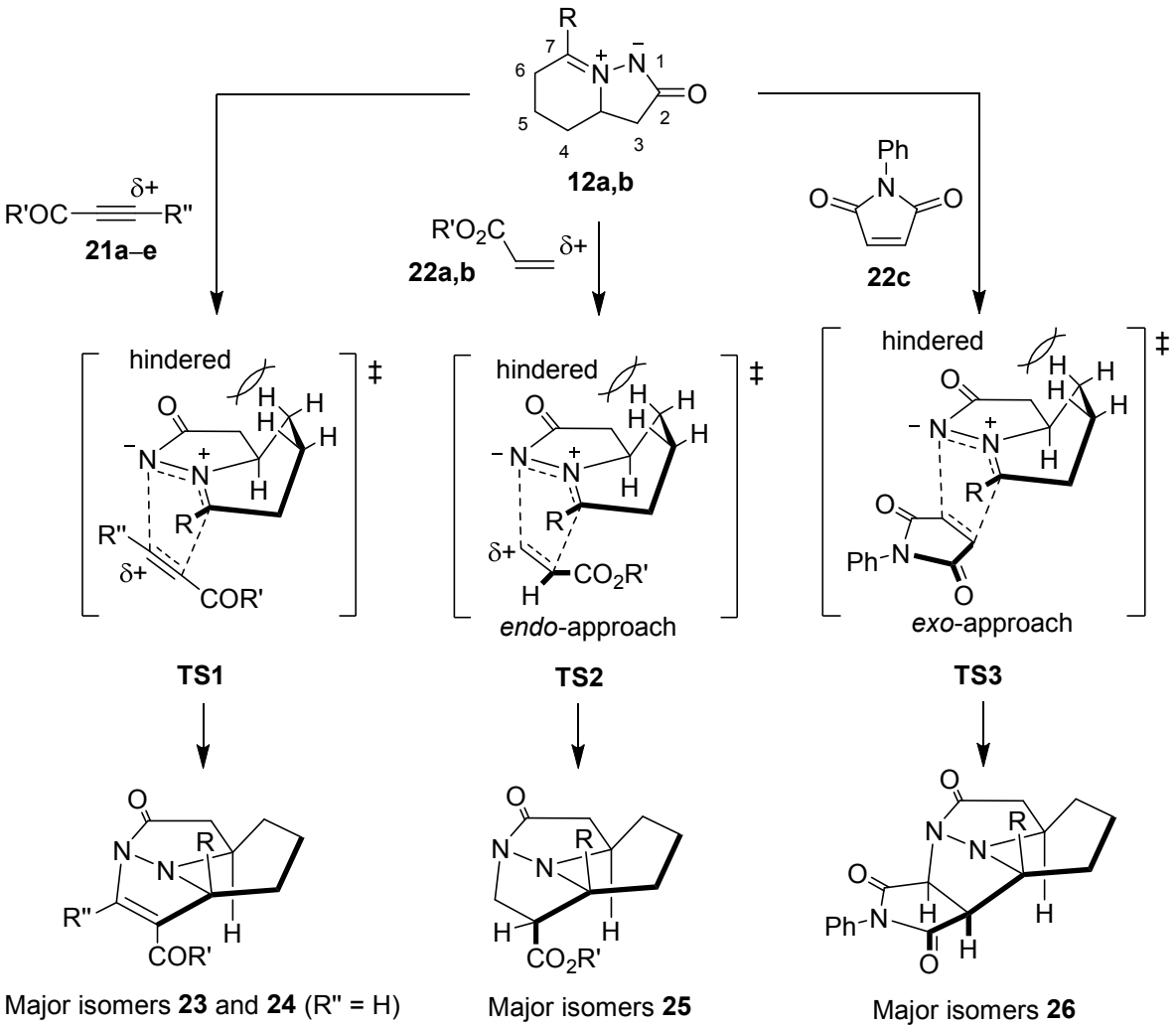
Compound	R^1	R^2	R^3	D.r.[a]	Yield (%)
23a	Me	-	-	94:6	60
23b	Ph	-	-	100:0	56
24a	Me	Me	-	93:7	73
24b	Ph	Me	-	91:9	69
24c	Me	Ph	-	90:10	67
24d	Ph	Ph	-	100:0	71
24e	Me	CH_2NHBoc	-	93:7	42
24f	Ph	CH_2NHBoc	-	89:11	50
24g	Me	OMe	-	93:7 (100:0[b])	56 (47[b])
24h	Ph	OMe	-	85:15 (100:0[b])	60 (59[b])
24'h[c]	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.

The regioselectivity of the cycloadditions to terminal ynones **21b–d** 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).

Scheme 5. Regio- and stereoselectivity of cycloadditions to chiral dipoles **12a** and **12b**.



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.

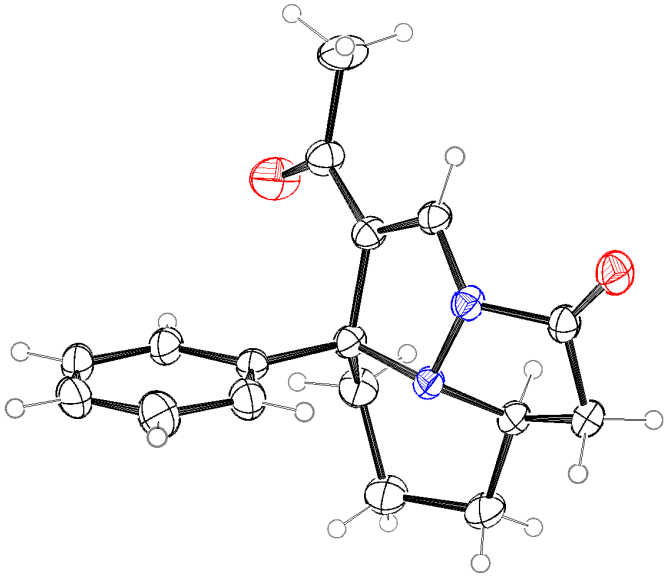


Figure 2. ORTEP drawing of the **24b** molecule showing the atom labelling. The displacement ellipsoids are drawn with a 30% probability level and the hydrogen atoms are shown as small spheres of arbitrary radii.

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 favourable. 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** ($\Delta\Delta G = 6.1^{\ddagger}$ kcal/mol). The calculated parameters given in Table 2 are in agreement with the experimental results in terms of reactivity and selectivity (cf. Scheme 4, Table 1).[28]

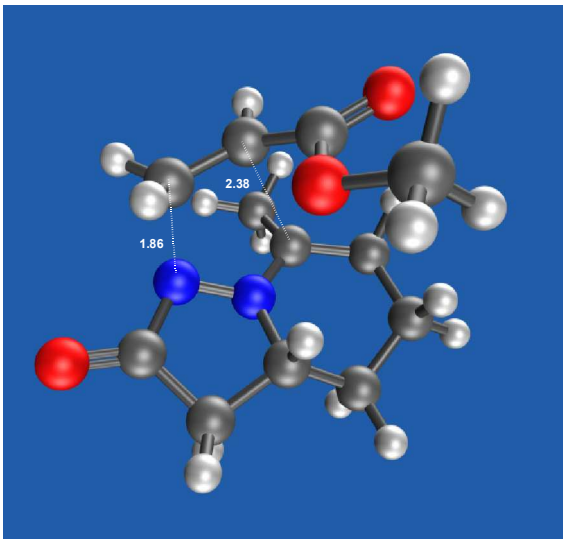
Table 2. B3LYP/6-311+G(d,p) calculated activation energies, distortion energies ($\Delta E_d^{\ddagger}$), interaction energies ($\Delta E_i^{\ddagger}$), and asynchronicity degrees for transition states.

	$TS^{\ddagger}$	B3LYP/6-331+G(d,p)							
		$\Delta G^{\ddagger a}$	$\Delta G^{\ddagger b}$	$\Delta E^{\ddagger c}$	$\Delta E_d^{\ddagger d}$			$\Delta E_i^{\ddagger d}$	$\Delta d_{TS/P}{}^{e}$
					12	**21**/**22**	Total		
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

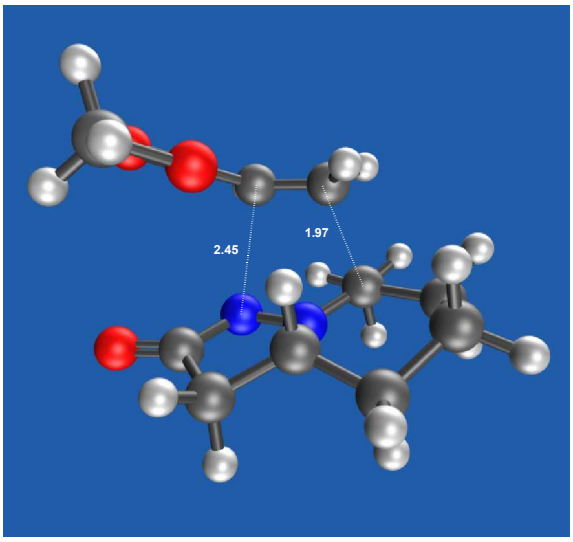
15	**25'a**-*syn*/*exo*	*35,3*	–	*21,5*	–	–	–	–	0.36
16	**25'a**-*syn*/*endo*	*35,3*	–	*21,6*	–	–	–	–	0.37
17	**25b**-*anti*/*exo*	36.0	37.2	22.4	13.5	15.4	28.9	–6.5	0.30
18	**25b**-*anti*/*endo*	34.1	35.1	20.3	10.4	17.0	27.4	–7.2	0.38
19	**25b**-*syn*/*exo*	34.3	35.2	20.1	13.1	15.7	28.8	–8.7	0.30
20	**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] $\Delta d_{TS/P} = |(C–C)_{TS}/(C–C)_P–(C–N)_{TS}/(C–N)_P|$.

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 inversed 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]



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



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

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

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

Table 3. Electrophilicity ω and nucleophilicity *N* of dipoles **12a**,**b** and dipolarophiles.

Entry	Compound	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

The frontier molecular orbital (FMO) analysis 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 favourable FMO interactions,[29] similar HOMO orbital coefficients at N(1) and C(7) in **12a** 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.

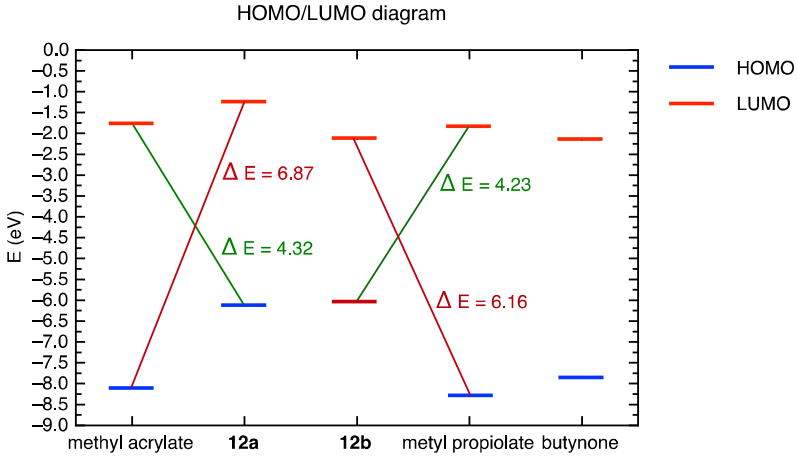


Figure 4. FMO diagram of HOMO-LUMO orbitals calculated by NBO6/6-311+G(d,p) using PCM: toluene.

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 was 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).

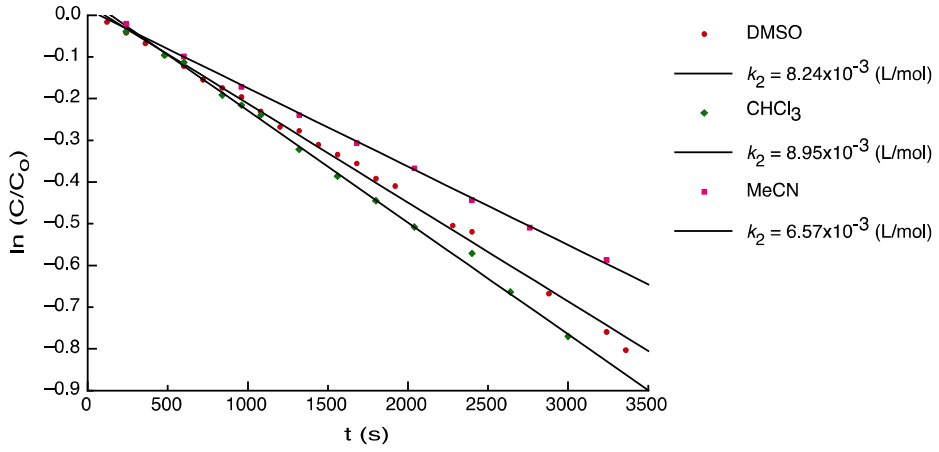


Figure 5. The kinetics of the reaction **12a** + **21b** → **24a** in $CDCl_3$, CD_3CN, and DMSO-d_6.

Next, the reaction kinetics was 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]

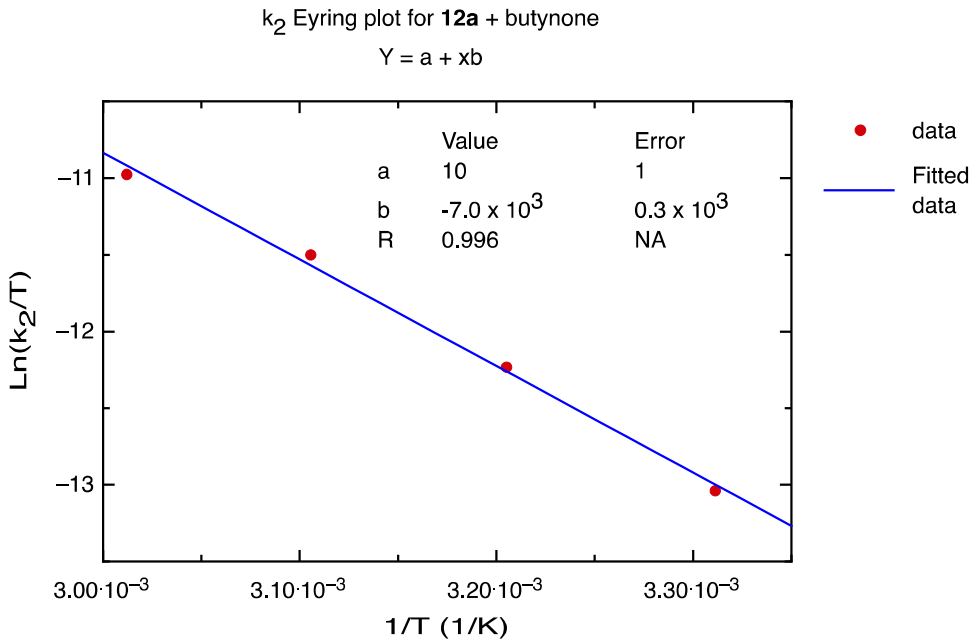


Figure 6. Eyring plot for the cycloaddition between dipole **12a** and butynone **21b**.

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 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, d.r. ≥ 89:11), whereas with olefins **22**, the stereoselectivity was lower (d.r. ≥ 78:22). Interestingly, thermal cycloadditions to terminal acetylenes **21b**–**e** were as regioselective as CuI-catalyzed reactions with methyl propiolate (**21e**). Moreover, the non-catalyzed 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 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 (ΔΔG ~ 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

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 MHz or 500 MHz instrument at 300 and 500 MHz for ^1H and at 75.5 and 126 MHz for ^{13}C nucleus, respectively. Mass spectra were recorded on time-of-flight (TOF) mass spectrometer equipped with a double orthogonal electrospray 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 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. Hex-5-en-2-one (**9a**)[19] and *tert*-butyl 2-(hept-6-en-2-ylidene)hydrazine-1-carboxylate (**11a**)[18] 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 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),

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 non-reacted 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 g (60%) of a beige solid; mp 125–126 °C (decomp.). ^{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. 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. A 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 literature procedure for the synthesis of related compounds.[22] A mixture of carboxylic acid **14** (5 mmol), anh. 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 r.t. for 6 h. Then, $NaHCO_3$ (250 mg) was added and the mixture was stirred at r.t. 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 r.t. for 12 h. The mixture was concentrated to a 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 anh. sodium sulfate, filtered, 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 anh. THF (15 mL) and the mixture was stirred at r.t. for 1 h. Then, a solid well homogenized mixture of anh. $MgCl_2$ (395 mg, 4.8 mmol), and potassium monomethyl malonate (1.130 g, 7.5 mmol) was added, and the suspension was stirred at r.t. 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 anh. sodium sulfate, 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); 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. 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. 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, ice-bath was removed, the mixture was stirred at r.t. for 5 min., and the product was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried over anh. sodium sulfate, 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. 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. ^1H 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 - $C_2H_4O^+$). $C_{14}H_{17}O_3$ requires: *m*/*z* = 233.1178. 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 anh. 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 pH of aqueous phase was around 2. The organic phase was washed again with brine (2×10 mL), dried over anh. sodium sulfate, 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 anh. pyridine (2.5 mL). Yield: 620 mg (80%) of orange oil. ^1H 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. 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); 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. 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**.

*4.7.1. 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. 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. 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 anh. 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 (decomp.). ^{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. (Found: C 71.23, H 6.60, N 12.83. $C_{13}H_{14}N_2O \cdot ¼H_2O$ requires: C 71.37, H 6.68, N 12.81.); 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 anh. 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 r.t. 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 anh. sodium sulfate, 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. (3aS,7S*)-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 anh. 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. ν_{max} (ATR) 3153, 3055, 2953, 2941, 2925, 2866, 1681, 1598, 763, 726, 700 cm^{-1}.

6.9.2. (3aS,7R*)-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 anh. 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^+). $C_{14}H_{19}N_2O$ requires: *m*/*z* = 231.1492. 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 anh. THF (20 mL), flash

column chromatography (EtOAc). Yield: 211 mg (31%) of brownish solid; mp 143–144 °C. ^{1}H 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. 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 anh. DMF (25 mL) and the mixture was stirred at r.t. 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 anh. sodium sulfate, 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 anh. DMF (3 mL), column chromatography (EtOAc–hexanes, 1:1). Yield: 140 mg (68%) of white crystals; mp 131–134 °C. ^{1}H 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. (Found: C

73.88, H 8.35, N 11.16. $C_{15}H_{20}N_2O$ requires: C 73.74, H 8.25, N 11.47.); 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-phenylhexahydropyrazolo[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 anh. DMF (3 mL), column chromatography (EtOAc–hexanes, 1:1). Yield: 150 mg (55%) of white crystals; mp 118–120 °C. ^{1}H 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); 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. (Found: C 78.44, H 7.73, N 8.60. $C_{21}H_{24}N_2O$ requires: C 78.71, H 7.55, N 8.74.); 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 anh. DMF (1.5 mL), column chromatography (EtOAc–hexanes, 1:1). Yield: 50 mg (66%) of orange oil. ^{1}H 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. 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 anh. DMF (2 mL), column chromatography (EtOAc–hexanes, 1:2). Yield: 58 mg (42%) of orange oil. ^{1}H 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. 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), anh. CH_2Cl_2 or toluene (1 mL), and dipolarophile **21** or **22** (0.3 mmol, 1.2 equiv.) was stirred at r.t. 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 cycloadduct **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 anh. CH_2Cl_2 (1 mL), r.t., 72 h, Workup B, column chromatography (CH_2Cl_2–MeOH, 50:1). Yield: 44 mg (60%) of orange oil. ^{1}H 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. 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-diaza-cyclopenta[cd]indene-3,4-dicarboxylate (**23b**).* Prepared from **12b** (43 mg, 0.2 mmol) and DMAD (**21a**) (30 μL, 0.24 mmol) in anh. toluene (2 mL), r.t., 24 h, Workup A. Yield: 42 mg (59%) of brownish oil. ^{1}H 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. 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 anh. DCM (1 mL), r.t., 24 h, Workup B, column chromatography (CH_2Cl_2–MeOH, 100:1). Yield: 40 mg (73%) of beige solid; mp 83–87 °C. ^{1}H 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. 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 **12b** (53 mg, 0.25 mmol) and 3-butyn-2-one (**21b**) (23.5 μL, 0.3 mmol) in anh. DCM (1 mL), r.t., 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. 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 anh. DCM (1 mL), r.t., 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. 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 anh. DCM (1 mL), r.t., 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. 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 anh. DCM (1 mL), r.t., 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. 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 anh. DCM (1 mL), r.t., 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. 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-diaza-cyclopenta[cd]-indene-3-carboxylate (**24g**).* Prepared from **12a** (38 mg, 0.25 mmol) and methyl propiolate (**21e**) (27 µL, 0.3 mmol) in anh. DCM (1 mL), 80 °C (pressure vessel), 24 h, Workup B, column chromatography (CH_2Cl_2–MeOH, 100:1). Yield: 33 mg (56%) of colourless 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. 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-diaza-cyclopenta[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 anh. 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-diaza-cyclopenta[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. 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-diaza-cyclopenta[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. ν_{max} (ATR) 2932, 1690, 1577, 1410, 1310, 1194, 1090, 756, 696 cm^{-1}.

6.11.11. A 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 anh. 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 non-polar 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, 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. 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. ^{1}H 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. 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 anh. CH_2Cl_2 (5 mL), 80 °C, 12 h, Workup B, column chromatography (EtOAc). Yield: 33 mg (44%) of brownish oil. ^{1}H 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. 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 anh. toluene (80 mL), 80 °C, 24 h, Workup B, column chromatography (EtOAc). Yield: 265 mg (77%) of yellow oil. ^{1}H 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. 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. ^{1}H 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. 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. ^{1}H 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. 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), anh. 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 r.t. 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-diaza-cyclopenta[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-diaza-cyclopenta[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 anh. 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 r.t. 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. ^{1}H 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 (4*S,4a*S**,7a*S**)-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 r.t. for 24 h. Volatile component 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. ^{1}H 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. ν_{max} (ATR) 1732, 1723, 1674, 1413, 1205, 757, 702 cm^{-1}.

6.14. Synthesis of (4*S,4a*S**,7a*S**)-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 anh. DMF (2 mL) and the mixture was stirred at r.t. for 10 min. Then, bis(pentafluorophenyl) carbonate (99 mg, 0.25 mmol) was added and the mixture was stirred at r.t. for 1 h. Amine (0.25 mmol) and Et_3N (35 μL, 0.25 mmol) were added and stirring at r.t. 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**.

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. 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-phenyloctahydro-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. 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. ν_{max} (ATR) 2939, 1668, 1580, 1446, 1381, 1288, 702 cm^{-1}.

Supporting Information contains copies of the NMR spectra, data on structure determination by NMR, X-ray diffraction data, computational details, additional Tables and Figures.

Acknowledgements

We thank the Slovenian Research Agency for the financial support through grant P1-0179. We thank the Boehringer-Ingelheim Pharma, Biberach, Germany, for the 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, UK, 2009. (c) Pernerstorfer, J. Molecular Design and Combinatorial Compound Libraries. In *Handbook of Combinatorial Chemistry. Drugs, Catalysts, Materials; Vol. 2*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2002; 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; Vol. 2*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2002; 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, UK, 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, UK, 1996, pp. 249–258.

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

(4) Allen, S. H.; Johns, B. A.; Gudmundsson, K. S.; Freeman, G. A.; Boyd, F. L.; Secxton, 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.; Messner, 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) Csàny, 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. Pharm.* **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.; Schnering, H.-G. *Tetrahedron* **1995**, *51*, 13197–13216. (b) Beck, K.; Hünig, S.; Reinold, P. *Tetrahedron* **1988**, *44*, 3296–3308.

(13) For a recent review see: Grošelj, U.; Svete, J. *Arkivoc* **2015**, *part vi*, 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.; Neves, N. D.; Markiewicz, T.; Toderian, A. B.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 1890–1893.

(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; Vol. 1*; Padwa, A., Ed.; John Wiley & Sons, Inc.: New York, USA, 1984; pp 733–814.

(26) For 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.; Bonongari, T.; Sido, K. S. S.; Keller, M.; Kuhn, P.; Louis, B.; Sommer, J.; Pale, P. *Synthesis* **2010**, 1557–1567. (d)

Mizuno, N.; Kamata, K.; Nakagawa, Y.; Oishi, T.; Yamaguchi, K. *Catalysis 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**, 6443–6448. (h) Pušavec, E.; Mirnik, J.; Šenica, L.; Grošelj, U.; Stanovnik, B.; Svete, J. *Z. Naturforsch.* **2014**, *69b*, 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 Supporting Information.

(29) (a) Huisgen, R. 1,3-Dipolar Cycloadditions – Introduction, Survey, Mechanism. In *1,3-Dipolar Cycloaddition Chemistry; Vol. 1*; Padwa, A., Ed.; John Wiley & Sons, Inc.: New York, USA, 1984; pp 1–176. (b) Houk, K. N.; Yamaguchi, K. Theory of 1,3-Dipolar Cycloadditions. In *1,3-Dipolar Cycloaddition Chemistry*; *Vol. 2*; Padwa, A., Ed.; John Wiley & Sons, Inc.: New York, USA, 1984; 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* **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, NY, 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.; Schleyer, P. V. R. *Organometallics*, **1995**, *14*, 2288–2296. (g) Contini, A.; Leone, S.; Menichetti, S.; Viglianisi, C.; Trimarico, P. *J. Org. Chem.* **2006**, *71*, 5507–5514. (h) Legnani, L.; Lunghi, C.; Marinone Albini F.; Nativi, C.; Richichi, B.; Toma, L. *Eur. J. Org. Chem.* **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.

For Table of Contents Only