Multidimensional Screening and Methodology Development for Condensations Involving Complex 1,2-Diketones

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Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday

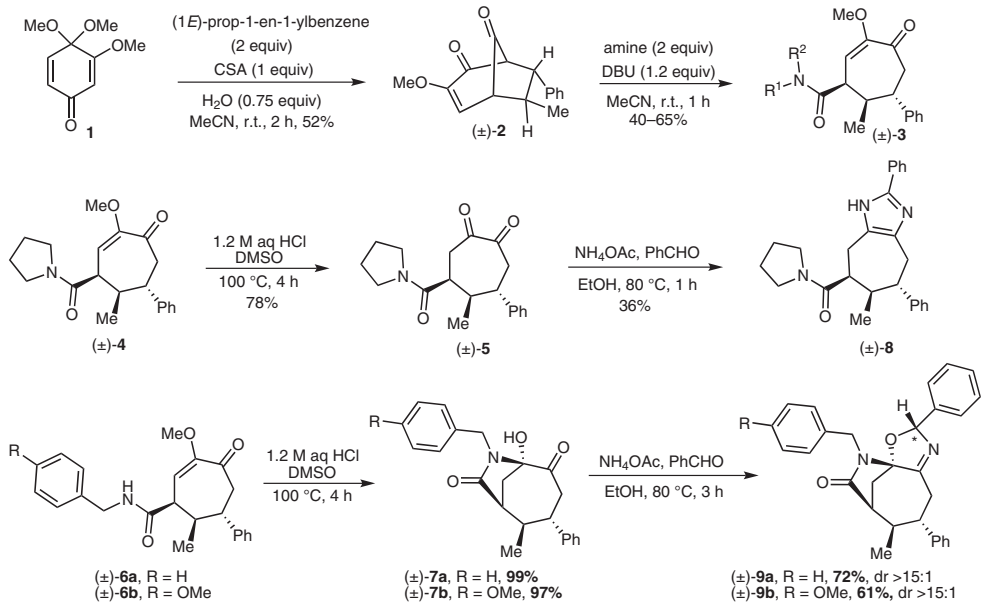
Abstract: Multidimensional reaction screening with complex cycloheptane-1,2-diones is described. The studies resulted in the discovery of regioselective Lewis acid mediated condensation reactions with substituted ureas, and a diastereoselective hydrogenation process that proceeds through an interesting isomerization of allylpalladium hydride.

Key words: reaction discovery, regioselectivity, condensation, diastereoselectivity, hydrogenations

Multidimensional reaction screening[1,2] is an efficient high-throughput approach for the discovery of new synthetic methodologies and complex chemotypes.[3,4] Previous reaction-screening efforts utilizing bicyclo [3.2.1]octanoids led to the discovery of a retro-Dieckmann-type fragmentation that afforded highly functionalized cycloheptenones.[4] We were interested in using the cycloheptenone scaffolds as substrates for additional reaction–discovery projects, with a focus on condensation reactions. Condensation reactions of 1,2-dicarbonyl compounds provide a facile access to heterocyclic or heteropolycyclic compounds, with the generation of highly complex chemotypes. In the current study, we evaluated a wide range of condensation partners[5–14] with complex cycloheptane-1,2-diones. Herein, we report on the results of our initial screening studies and on the subsequent development of regioselective condensation reactions to afford novel heterocyclic frameworks.

As shown in Scheme 1, the synthesis of the target scaffolds for screening began with the [5 + 2] cycloaddition of the quinone monoketal **1** with (1*E*)-prop-1-en-1-ylbenzene to give the bicyclo[3.2.1]octanoid **2**. Retro-Dieckmann-type ring-opening of **2** afforded the corresponding cycloheptenones **3**.[4,15] Subsequent acid-mediated O-demethylation of the α-methoxyenone **4** afforded the 1,2-diketone **5**. Interestingly, O-demethylation of the secondary amides **6** afforded the α-hydroxy ketones **7**.

Preliminary efforts to probe the reactivity of scaffolds **5** and **7** were carried out by using known imidazole-forming conditions. Whereas the reaction with scaffold **5** afforded the desired imidazole **8**, the reaction with scaffold **7** unex-



Scheme 1 Scaffold synthesis and preliminary results

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pectedly gave the oxazoline **9** with a high diastereoselectivity (Scheme 1). The structure of the major diastereomer of oxazoline **9** was confirmed by X-ray crystallographic analysis.[16,17]

Having established preliminary reactivity, we carried out a comprehensive multidimensional reaction screen utilizing scaffolds **5** and **7b** (Figure 1). For this screen, 18 condensation partners were selected using ethanol or acetonitrile as solvent (80 °C, 24 h) in the presence of either pyridinium tosylate (PPTS) or diisopropylethylamine (DIPEA), or without any additive.

Each reaction was performed by using 3 μmol of substrate (approximately a 1 mg scale) with 1.0 equiv of both the reaction partner and the additive (a total reaction volume of 60 μL, 0.05 M). When the reaction partners were used as their hydrochloride salts, 2.0 equivalents of the base were used. Each reaction was prepared in a 1 mL, oven-dried, glass vial, with minimal exposure to air, from stock solutions of the reagents prepared in either ethanol or acetonitrile. The vials were capped with silicone rubber septa and placed in a heated reaction block (80 °C) that was fastened to an orbital shaker and agitated for 24 hours. The mixtures were diluted to 1 mL and analyzed by ultra-performance liquid chromatography/mass spectrometry (UPLC/MS) with an evaporative light-scattering detector (ELSD).[18] Reactions that afforded >20% conversion into major products were subsequently scaled up, and the reaction products were isolated for characterization.

As anticipated, 1,2-diketone scaffold **5** underwent a number of reactions to afford new products (Figure 2). Condensation with benzene-1,2-diamine or (1*S*,2*S*)-(+)-cyclohexane-1,2-diamine afforded pyrazines **10** and **11**, respectively.[6] Reactions with 2-aminobenzenethiol[7] or 2-amino-5-methylphenol[8] also resulted in the formation of adducts, but the products were complex mixtures that were unstable to isolation. The reaction of methyl hydrazonothiocarbamate hydroiodide under acid conditions resulted in the formation of 2:1 mixture of the regioisomeric triazines **12a** and **12b**.[9] Although the two regioisomers were isolated, the structures could not be assigned on the basis of standard NMR analyses. The condensation reaction of 2-aminobenzaldehyde gave a mixture of four quinoline products (**13a–d**). Interestingly, these quinoline products were obtained under acid conditions, in contrast to typical conditions for the Friedländer condensation (potassium hydroxide, ethanol, reflux).[10] Additionally, acid-catalyzed condensations using urea,[11] guanidine hydrochloride,[12] or benzenecarboximidamide hydrochloride[13] afforded the cycloheptadiene products **14**, **15**, and **16a**, respectively. In the case of the reaction with urea, the alkenyl imidazolone **16a** readily oxidized to the corresponding cycloheptatriene **16b** upon exposure to air.

Although screening studies with the α-hydroxy ketone **7b** as a substrate indicated successful conversions into new products, we found that these products were generally unstable to purification. This suggests that, although an imine is formed initially, subsequent cyclization does not occur due to the unexpected stability of the *N*-acylhemiaminal. However, we did observe some reactions of **7b** with isocyanates[14] (DIPEA, MeCN, 80 °C, 24 h) to give

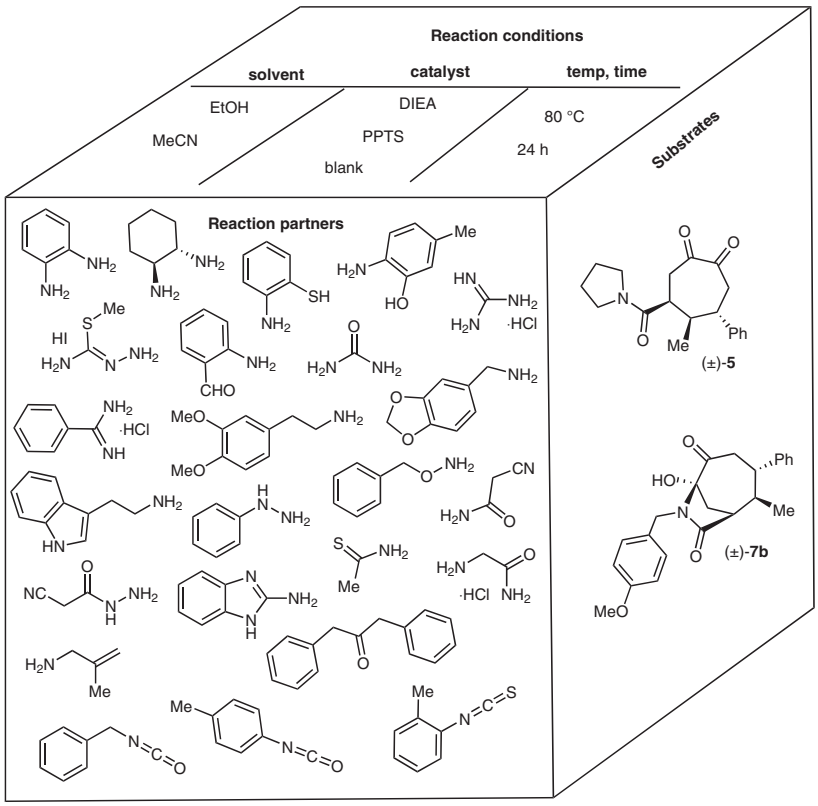


Figure 1 Multidimensional screening parameters

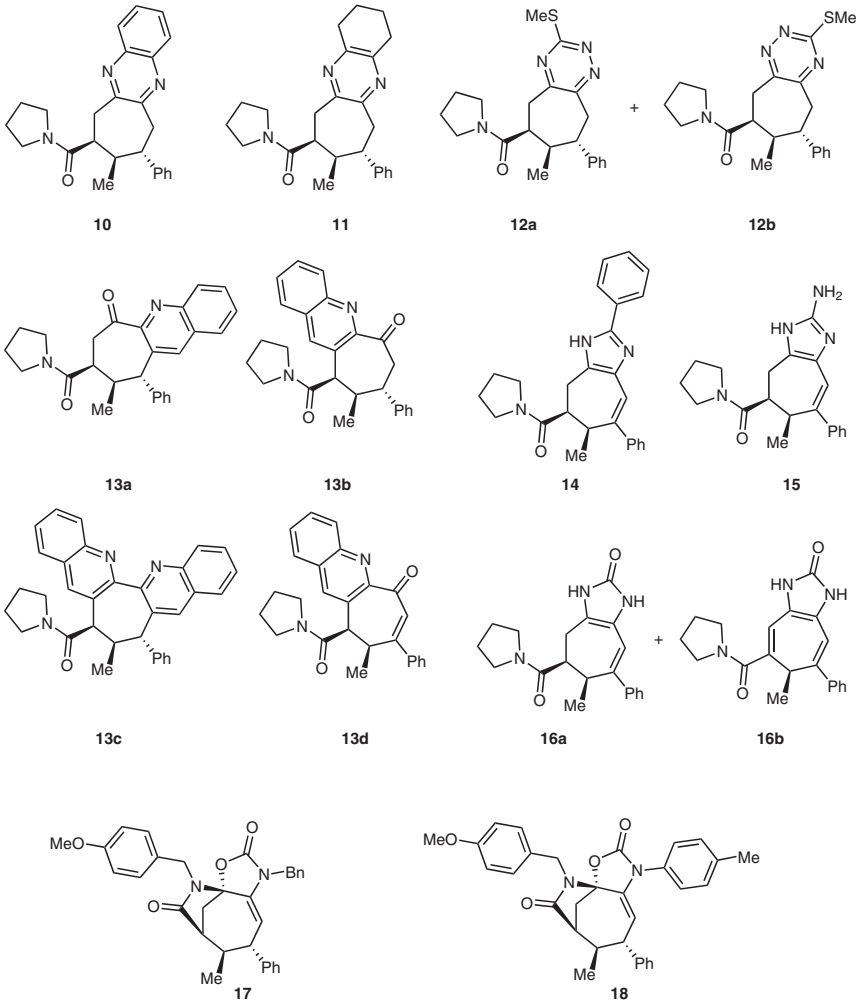


Figure 2 Representative condensation products

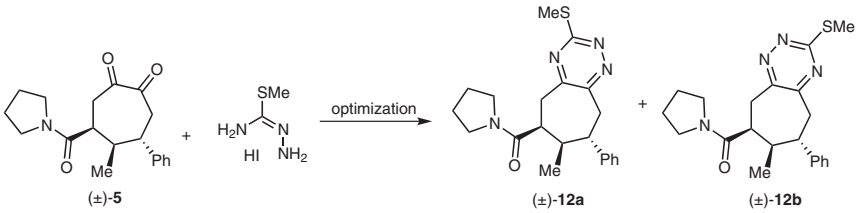
the unusual alkenyl oxazolidinones **17** and **18** (Figure 2). Surprisingly, **17** and **18** were remarkably stable under both acidic and basic conditions.

We next selected the condensation of 1,2-diketone **5** with methyl hydrazonothiocarbamate hydroiodide for initial follow-up, with the goal of developing a regioselective condensation reaction. Although there are numerous reports of reactions with 1,2-dicarbonyl compounds, few studies address the problem of regioselectivity when nonsymmetric substrates were used.[19] In general, regioselectivity is a direct result of the inherent reactivity of the carbonyl compounds.[19c,e] Although some modest advances have been made, achieving regioselectivity with complex scaffolds remains a significant challenge. Accordingly, we conducted a series of triazene-forming reactions using various catalysts and conditions (Table 1).

Generally, the replacement of ethanol by 2,2,2-trifluoroethanol or acetonitrile enhanced the regioselectivity 3-fold. Conversely, the use of tetrahydrofuran–water (9:1) reduced the regioselectivity (Table 1, entry 2). These results suggest that nucleophilic solvents such as ethanol and water react with the slightly more electrophilic ketone to form a hemiketal or a hydrate, respectively, thereby decreasing the regioselectivity of the reaction. Unexpectedly, the addition of scandium(III) triflate resulted in an inversion of the regioselectivity (Table 1, entry 3). Addition of 4 Å molecular sieves resulted in a slight enhancement of the inversion, and additional enhancement was achieved by conducting the reaction at 0 °C for 16 h, and by using extensively dried methyl hydrazonothiocarbamate hydroiodide (Table 1, entry 7). The conversion was ultimately improved by using two equivalents of the hydrazonothiocarbamate (Table 1, entry 11). To the best our knowledge, this study represents the first use of a Lewis acid to invert the regioselectivity of a 1,2-dicarbonyl condensation reaction.

Although two regioisomers were isolated, we were unable to assign the structures of products **12a** and **12b** by standard NMR analysis due to overlapping of key proton resonances. Attempts to grow suitable crystals for X-ray analysis were also unsuccessful. We therefore sought to synthesize an alternative substrate with fewer, more defined, proton resonances. Previous work had shown that the bicyclo[3.2.1]octanoid **2** undergoes a retro-Dieckmann-type ring opening with pyrrolidine in the presence of 1,5,7-triazabicyclo[4.4.0]dec-5-ene.[4] Unfortunately, this methodology is limited in terms of the scope of the

Table 1 Optimization of Triazine Regioselectivity

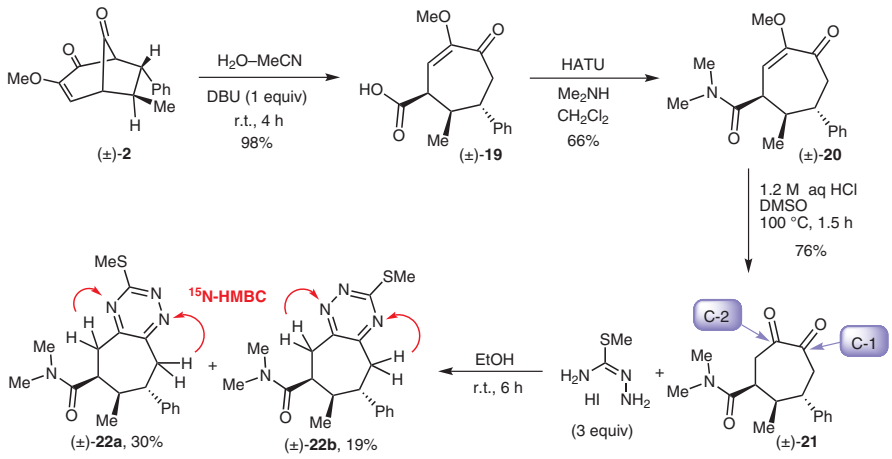


Entry	Solvent	Temp	Time (h)	Catalyst[a]	Additive	Ratio **12a/12b**	Conv. (%)[b]
1	EtOH	r.t.	4	–	–	2:1	100
2	THF–H_2O (9:1)	r.t.	4	–	–	1:1	100
3	THF–H_2O (9:1)	r.t.	2	$Sc(OTf)_3$	–	1:2	100
4	TFE[c]	r.t.	2	–	–	6:1	79
5	TFE	r.t.	2	$Sc(OTf)_3$	–	5:1	51
6	TFE	r.t.	2	$Sc(OTf)_3$	4 Å MS	1:3	30
7	TFE	0 °C	16	$Sc(OTf)_3$	4 Å MS	1:14	68
8	TFE	0 °C	16	$La(OTf)_3$	4 Å MS	1:10	85
9	TFE	0 °C	16	$Zn(OTf)_2$	4 Å MS	1:1	50
10	MeCN	0 °C	16	$Sc(OTf)_3$	4 Å MS	1:17	57
11	MeCN	0 °C	16	$Sc(OTf)_3$	4 Å MS	1:24[d]	70

[a] Lewis acid (1 equiv).
[b] Calculated from UPLC/ELSD percent conversions.
[c] 2,2,2-Trifluoroethanol.
[d] Methyl hydrazonothiocarbamate hydroiodide (2 equiv).

secondary amine reagent. Thus, a revised route to the cycloheptenone scaffold was developed that would allow for greater variability of the tertiary amide. We found that performing the fragmentation reaction with water in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the corresponding carboxylic acid **19** as a viable functional handle (Scheme 2). Coupling of **19** with dimethylamine using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) afforded the desired cycloheptenone **20** in 65% yield over two steps. Subsequent O-demethylation followed by condensation with methyl hydrazonothiocarbamate hydroiodide, afforded triazines **22a** and **22b**.

With triazines **22a** and **22b** in hand, we were able to determine their regiochemistries by means of ^{15}N-heteronuclear multiple-bond coherence (^{15}N-HMBC) NMR analysis[20] (Scheme 2).[17] Based on these experiments, we postulated that the inherently more reactive ketone is in the position *beta* to the phenyl group (C1), and that the

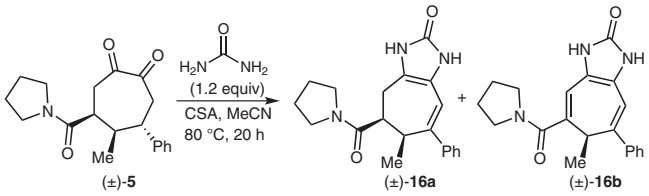


Scheme 2 Synthesis of alternative triazines

Lewis acid may preferentially activate the ketone in the position *beta* to the amide group (C2).

To further understand the mechanism leading to regioselectivity, we turned our attention to condensation with urea, which was also identified in the initial screen. Our first objective, however, was to control the oxidative process that occurred during the reaction. We found that degassing the reaction with argon was effective in preventing the oxidative process (Table 2, entry 2), whereas purging with oxygen increased the degree of oxidation (Table 2, entry 3).

Table 2 Oxidation During Urea Condensation



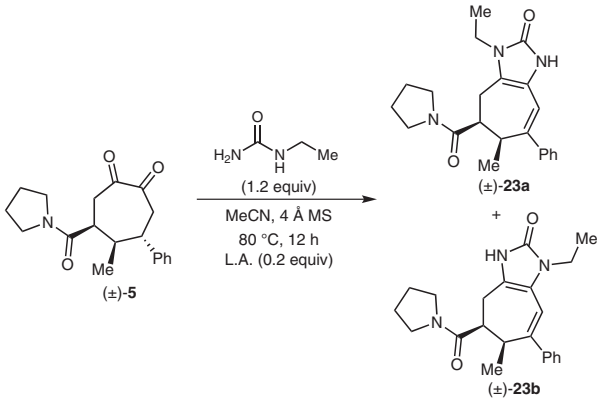
Entry	Atmosphere	Ratio **16a/16b**[a]
1	air	1:1
2	argon	32:1
3	O_2	1:3

[a] Calculated from UPLC/ELSD percentage conversions.

Having developed a viable method for controlling oxidation, our next step was to attempt the condensation reaction of nonsymmetrical *N*-ethylurea. As anticipated, the condensation reaction with 1,2-diketone **5** gave a mixture of the regioisomers **23a** and **23b** (Scheme 3). Regiochemical assignments were confirmed by one-dimensional nuclear Overhauser effect (1D NOE) analysis.[17] As the unsubstituted urea nitrogen is expected to be the more reactive, we predicted that the initial condensation should occur with the slightly more electrophilic C1 ketone group, as observed for condensation with methyl hydrazonothiocarbamate hydroiodide (see Scheme 2).

Next, we conducted a Lewis acid screen to determine if regiochemical control would be possible with substituted ureas. Generally, substituted ureas were found to be substantially less reactive than methyl hydrazonothiocarbamate hydroiodide, which required alternative conditions to achieve regioselectivity. As shown in Table 3, all the Lewis acids that we examined resulted in inversion of regioselectivity, with zinc triflate being the most effective catalyst. Thus, the use of a Lewis acid instead of a Brønsted acid ultimately rendered the C2 ketone more reactive.

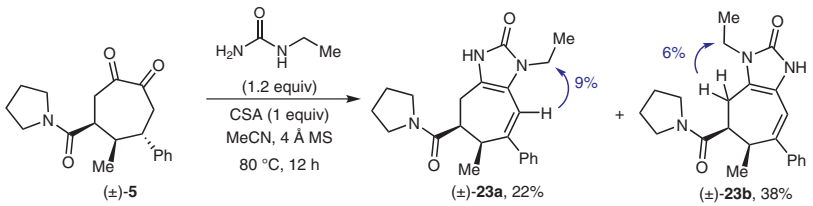
Table 3 Lewis Acid Screening Results



Entry	Catalyst	Ratio **23a/23b**
1	CSA[b]	2:1
2	$Sc(OTf)_3$	1:2
3	$Yb(OTf)_3$	1:2
4	$Y(OTf)_3$	1:2
5	$La(OTf)_3$	1:2
6	$Mg(OTf)_2$	1:4
7	$Fe(OTf)_2$	1:4
8	$Mn(OTf)_2$	1:8
9	$Zn(OTf)_2$	1:9

[a] Calculated from UPLC/ELSD percent conversions.
[b] CSA (1 equiv).

To gain an insight into the role of the Lewis acid, mechanistic studies were initiated by means of ^1H and ^{13}C NMR analyses of substrate **5** in the presence of zinc triflate (Figures 3 and 4). We observed a downfield shift of all the cycloheptane-1,2-dione ring protons except the α-phenylmethine proton (D) which shifted slightly upfield (Figure 3). The addition of zinc triflate did not significantly alter the coupling constants, indicating that the conformation of the cycloheptane-1,2-dione ring was not changed significantly. ^{13}C NMR spectra revealed a selective broadening of the two ketone resonances at 196 ppm and 197 ppm; because zinc(II) is diamagnetic, we did not expect the observed resonance broadening. We propose that iron(II), which is a common impurity (1–20 ppm) in



Scheme 3 The condensation reaction of ethylurea

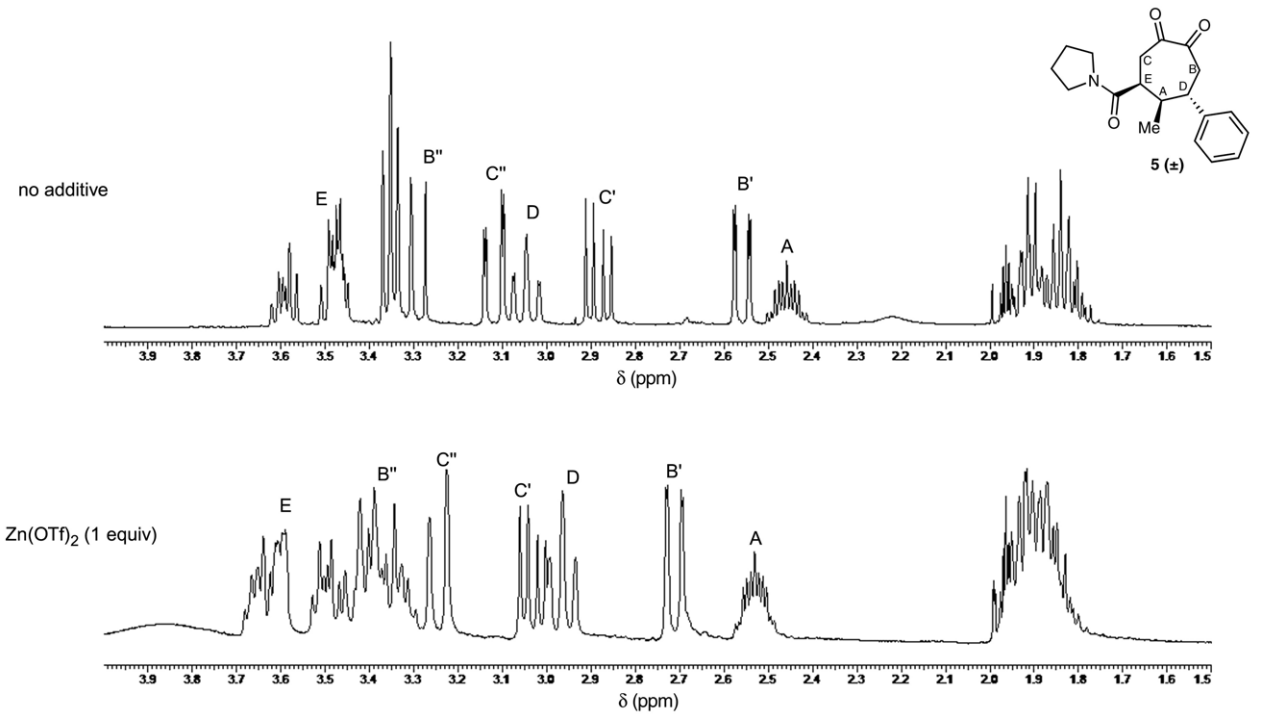


Figure 3 ^{1}H NMR evidence for mechanism (in CD_3CN)

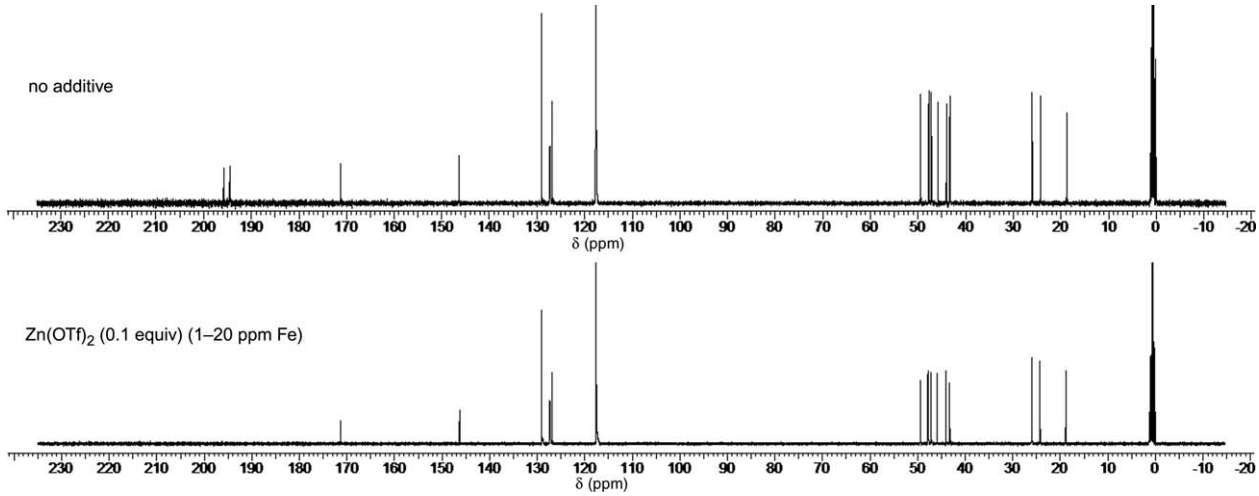


Figure 4 ^{13}C NMR evidence for chelation (in CD_3CN)

zinc triflate, is probably responsible for the resonance broadening, suggesting that iron(II) or zinc(II) may be chelated by the 1,2-diketone and not by the more Lewis basic amide functionality. Since iron(II) triflate also induces a significant inversion in regioselectivity, it is likely that these Lewis acids share a common metal-coordination site.

Primarily on the basis of ^{1}H and ^{13}C NMR studies, we propose a mechanism for the regioselective condensation (Figure 5). By using conformational analysis followed by energy minization,[21] we determined that, in the absence of zinc(II) triflate, the oxygen lone pair on the amide carbonyl is positioned in close proximity to the α-phenylmethine group, altering its electronic environment. We believe that chelation of zinc(II) triflate to the 1,2-dike-

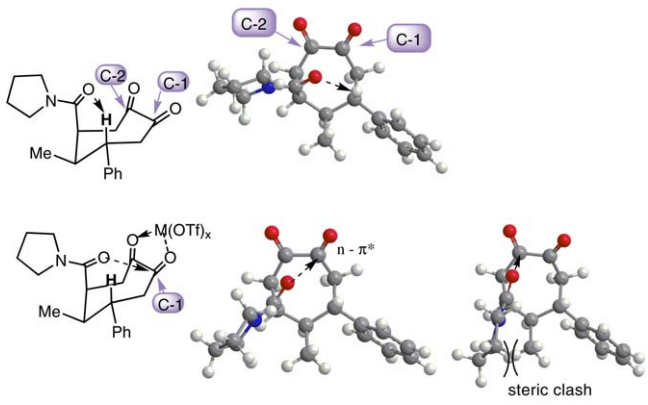


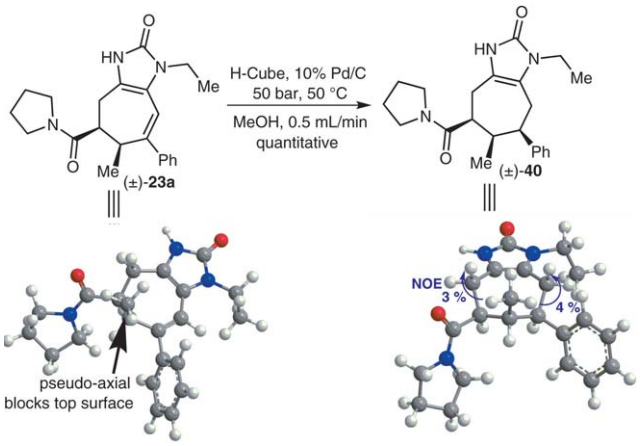
Figure 5 Proposed stereoelectronic effects leading to regioselectivity in the condensation reaction

tone lowers the LUMO for both carbonyl groups, triggering the rotation of the amide carbonyl to form a stabilizing n–π^* interaction with the C1 ketone group. The C2 ketone group cannot undergo a similar n–π^* interaction due to significant steric clash upon further rotation of the amide. It is also noteworthy that replacement of the pyrrolidine with *N*-methylcyclohexylamine resulted in complete loss of regioselectivity, probably as a result of greater steric interactions inhibiting the rotation of the amide.

Next, we probed additional substituted ureas (Table 4). We found that the zinc(II) triflate mediated reaction retained a reasonable degree of regioselectivity over a wide range of functionalities. However, a slight reduction in selectivity was observed on increasing the steric bulk of the substituent on the urea (Table 4, entries 1–4). Additionally, we observed that a greater electron deficiency was accompanied by a slight decrease in yield (Table 4, entries 8–10). In the case of *N*-acetylurea, no reaction was observed. Condensations with 1,3-disubstituted ureas, such as 1-methyl-3-phenylurea or 1-ethyl-3-phenylurea, indicated that the phenyl-substituted nitrogen is the more nucleophilic (Table 4, entries 12 and 13). Reactions with a Brønsted acid catalyst (10-camphorsulfonic acid; CSA) were also carried out in select cases. Whereas both allylurea and (4-chlorophenyl)urea showed a similar regioselectivity to ethylurea, 1-ethyl-3-phenylurea gave similar results to the zinc(II) triflate mediated reaction. The zinc triflate mediated regioselective condensation was also applied to a substituted thiourea, with good results. In this instance, however, a stoichiometric amount of zinc triflate was required to achieve a comparable regioselectivity (Table 4, entry 14).

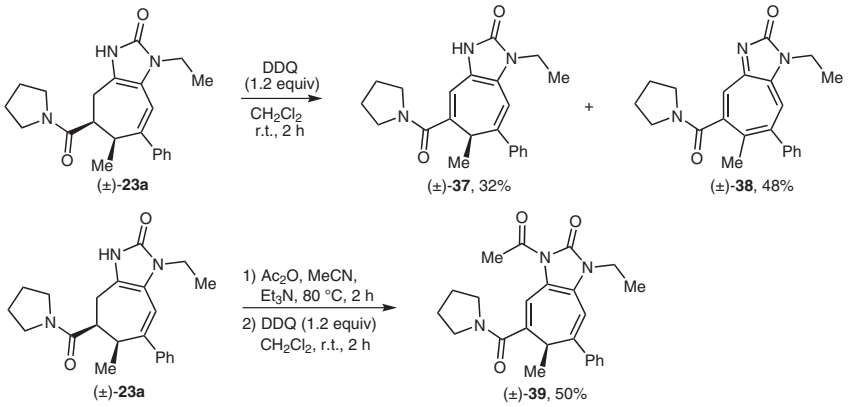
Due to the oxidative instability of alkenyl imidazolones, we sought to determine the oxidation/reduction potential of these interesting ring systems with the intention of increasing their stability. We first oxidized the alkenyl imidazolone **23a** by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 1.2 equiv) to afford the desired cycloheptatriene **37**, along with the pseudo-aromatic cycloheptimidazolone (2-hydroxy-1,3-diazaazulene)[22] **38** (Scheme 4). Acylation of the urea prevented over-oxidation and afforded the cycloheptatriene **39** exclusively in moderate yield over the two steps.

Diastereoselective hydrogenation of the alkenyl imidazolone **23a** with 10% palladium-on-carbon (H-Cube, 50 bar, 50 °C) afforded cycloheptene **40** as a single diastereomer (Scheme 5). The stereochemical assignment was confirmed by 1D NOE analysis.[17] Diastereoselectivity is probably achieved through steric interaction imparted by the pseudo-axial methyl group, which effectively blocks the *re*-face (Scheme 5). Unfortunately, reduction of the styrenyl olefin did not result in an appreciable decrease in oxidative decomposition.



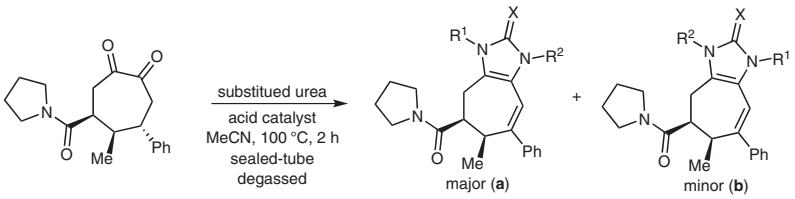
Scheme 5 Diastereoselective reduction of alkenyl imidazolone **23a**[21]

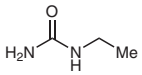
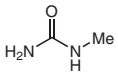
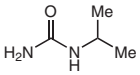
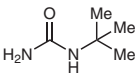
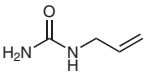
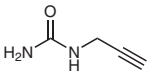
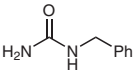
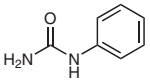
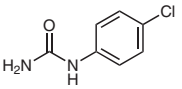
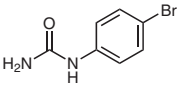
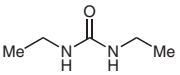
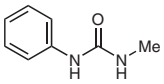
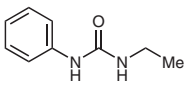
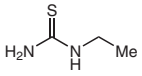
Interestingly, N-acylation of cycloheptene **40** resulted in only a slight increase in stability, which suggests that the electronic structure of the imidazolone ring plays a significant role in the oxidative decomposition. It should be noted that imidazolone rings with a greater electron density, such as the disubstituted urea condensates **33**–**35**, underwent decomposition more readily. Initial attempts to fully reduce alkenyl imidazolone **23a** with 10% palladium-on-carbon under extremely harsh conditions (H-Cube, 90 bar, 80 °C) still afforded the cycloheptene **40** as the major product together with a product derived from the reduction of the phenyl ring. However, full reduction of **23a** was achieved by using Raney Ni (H-Cube, 90 bar, 80 °C) to afford imidazolidinone **41** as a 1:1 mixture of diastereo-



Scheme 4 Further transformations of cycloheptadiene **23a**

Table 4 Scope and Regioselectivity of the Urea Condensation Reaction

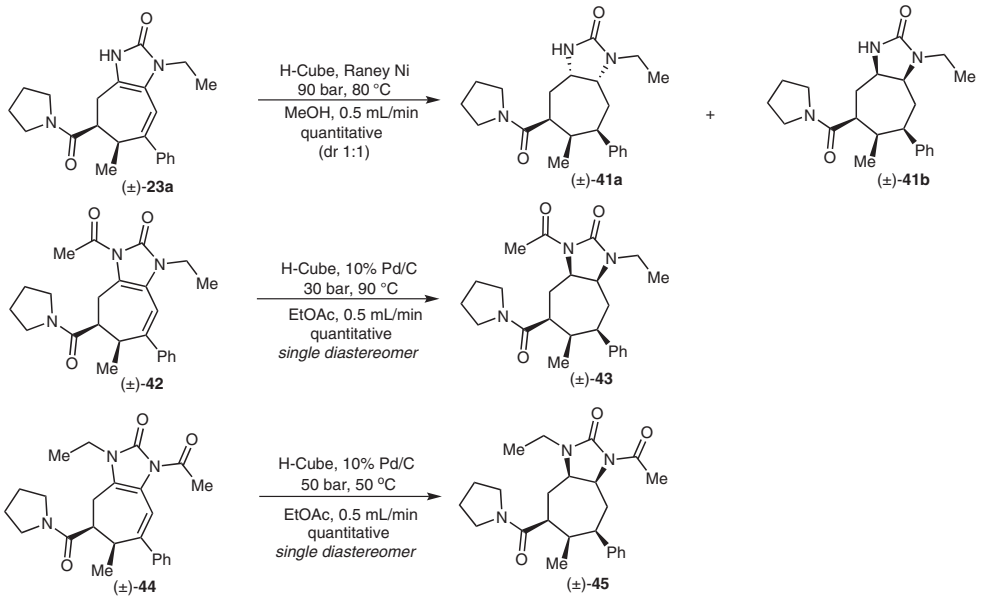


Entry	Urea	X	R^1	R^2	Yield (%)[a,b]	Products	Regioisomeric ratio (**a/b**)
1		O	H	Et	92 (99)[b]	**23a/23b**	77:23 (47:53)[b]
2		O	H	Me	99	**24a/24b**	66:34
3		O	H	*i*-Pr	99	**25a/25b**	71:29
4		O	H	*t*-Bu	88	**26a/26b**	65:35
5		O	H	allyl	98 (96)[b]	**27a/27b**	82:18 (46:54)[b]
6		O	Et	propargyl	91	**28a/28b**	81:19
7		O	H	Bn	98	**29a/29b**	82:18
8		O	H	Ph	99	**30a/30b**	77:23
9		O	H	4-ClC_6H_4	85 (96)[b]	**31a/31b**	85:15 (46:54)[b]
10		O	H	4-BrC_6H_4	80	**32a/32b**	76:24
11		O	Et	Et	93	**33**	–
12		O	Ph	Me	98	**34a/34b**	76:24
13		O	Ph	Et	99 (99)[b]	**35a/35b**	78:22 (64:36)[b]
14		S	H	Et	99	**36a/36b**	80:20[c]

[a] Combined isolated yield when using $Zn(OTf)_2$ (0.2 equiv) and 4 Å MS.
[b] Combined isolated yield when using CSA (1.0 equiv).
[c] Required 1.0 equiv of $Zn(OTf)_2$ and 4 Å MS.

mers (Scheme 6). Hydrogenation of the imidazolone olefin effectively eliminated the occurrence of oxidative decomposition.

Unfortunately, hydrogenation with Raney Ni under harsh H-Cube conditions was highly inconsistent because of variability between batches of the catalyst cartridges. As a result, an alternative more reliable approach for reduc-

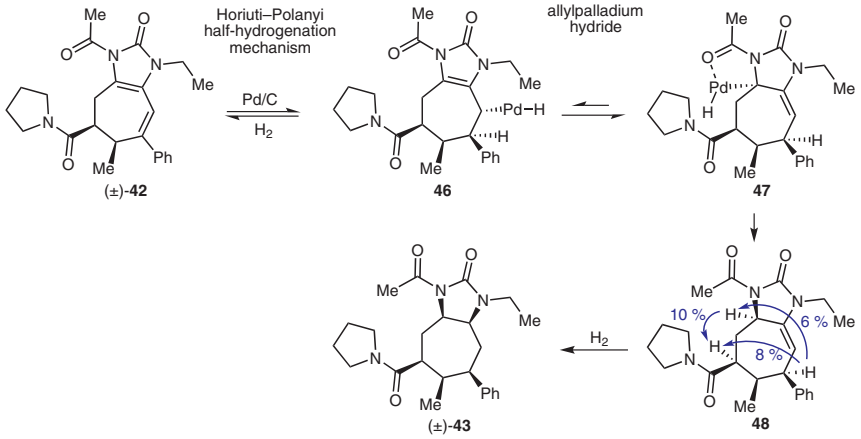


Scheme 6 Hydrogenations of alkenyl imidazolone **23a**

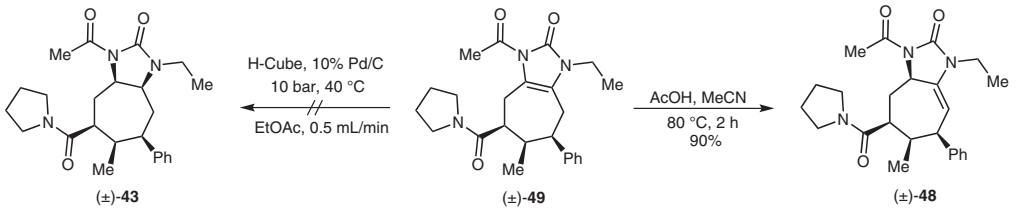
ing the imidazolone olefin was required. Remarkably, we discovered that full reduction of the acetylated alkenyl imidazolone **42** with 10% palladium-on-carbon occurred under considerably milder conditions (H-Cube, 30 bar, 90 °C) to afford imidazolidinone **43** as a single diastereomer (Scheme 6). We also observed full reduction of the acetylated alkenyl imidazolone **44** to afford imidazolidinone **45** as a single diastereomer, albeit under slightly harsher conditions.

As previously described, we propose that the styrenyl olefin initially undergoes diastereoselective hydrogenation by the well-established Horiuti–Polanyi half-hydrogenation mechanism[23] to give the allylpalladium hydride intermediate **46** (Scheme 7). Subsequent isomerization occurs with retention of stereochemistry to afford intermediate **47**, which may, in part, be favored due to stabilization by coordination of the amide acetyl oxygen.[24] Subsequent reductive elimination of palladium provides the net 1,4-addition product **48** as a single diastereomer. We were also able to isolate intermediate **48** under milder conditions (H-Cube, 10 bar, 40 °C). Stereochemical assignments for **48** were confirmed by 1D NOE analysis.[17] Diastereoselective hydrogenation of the resulting enamine afforded the fully reduced product **43**. Diastereoselectivity in the final reduction is the result of blocking of the *re*-face by the flanking phenyl and *N*-acylurea groups. Further evidence for the allylpalladium hydride isomerization mechanism was provided by a failed attempt to reduce the acetylated imidazolone **49** (H-Cube, 10 bar 40 °C) (Scheme 8).

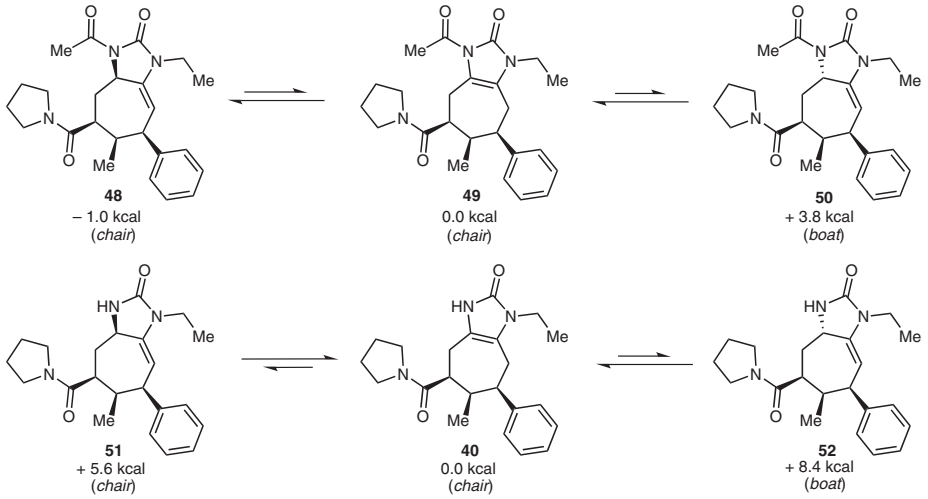
We were also able to isolate enamine **48** by treatment of **49** with acetic acid (Scheme 8). The selectivity of the acid-mediated isomerization suggests that the observed *syn*-diastereomer is thermodynamically favored. Accordingly, we performed computational studies[21] for imidazolone **49** and both the *syn*- and *anti*-diastereomers from isomerization. As shown in Scheme 9, the ground-state energy of the *syn*-diastereomer **48** is 1 kcal lower than that of the parent imidazolone **49** and 4.8 kcal lower than that



Scheme 7 Proposed mechanism for diastereoselective hydrogenation



Scheme 8 Reduction/isomerization of an *N*-acetylimidazolone



Scheme 9 Ground-state energetics of imidazolone isomerizations[21]

of the *anti*-diastereomer **50**. These results confirmed that the *syn*-diastereomer **48** is thermodynamically favored.

Interestingly, similar calculations performed on imidazolone **40**, which lacks the *N*-acetyl group, showed that isomerization to either the *syn*- or the *anti*-diastereomer is not favored, with ground-state energies of +5.6 and +8.4 kcal, respectively (Scheme 9). These findings, in part, help to explain the results obtained for the Raney nickel hydrogenation, in which diastereoselective reduction of imidazolone **40** was not observed. Without isomerization to afford bulky functional groups flanking the olefin, hydrogenation occurs equally from both the *si*- and *re*-faces.

To summarize, multidimensional screening of condensations reactions enabled the discovery of regioselective Lewis acid mediated condensation reactions of a densely functionalized 1,2-diketone scaffold. We determined that regioselective condensations may be conducted by using Lewis acid chelation, with the 1,2-diketone leading to a proposed n–π^* interaction with a pendant amide carbonyl. This unique approach to achieving regioselectivity appears to rely on a presence of a proximal amide group that can undergo a stabilizing n–π^* interaction with the nearest neighboring carbonyl group. Regioselective condensations with substituted ureas led to the discovery of a novel diastereoselective hydrogenation reaction that proceeds through an interesting allylpalladium hydride isomerization. Taken together, these discoveries provide a regioselective and diastereoselective route to a number of densely functionalized cycloheptane urea scaffolds. The application of the developed methodology to the synthesis of a chemical library is currently underway, and will be reported in due course.

^{1}H NMR spectra were recorded at 400 MHz at r.t. unless otherwise stated. ^{13}C NMR spectra were recorded at 100.0 MHz at r.t. unless otherwise stated. Chemical shifts are reported in ppm relative to $CDCl_3$ (^{1}H, δ = 7.27; ^{13}C, δ = 77.0) or CD_3OD (^{1}H, δ = 3.31; ^{13}C, δ = 49.0). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (reported as values in Hz), and integration. IR spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High-resolution mass spectra were recorded at the Boston University Chemical Instrumentation Center by using a Waters Q-TOF mass spectrometer. Analytical LC was performed on a Waters Acquity UPLC with PDA, ELS, and SQ detectors. An Acquity UPLC BEH 2.1 × 50 mm, 1.7 μM C_{18} column was used for analytical LC. Analytical TLC was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200–400 mesh silica gel. Yields refer to chromatographically and spectroscopically pure materials unless otherwise stated. MeCN, THF, and CH_2Cl_2 were purified by passage through two packed columns of neutral alumina. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted. The Arthur™ Suite Reaction Planner was used in planning the experimental procedures.

(4*S,5*R**,6*S**)-5-Methyl-4-phenyl-6-(pyrrolidin-1-ylcarbonyl)cycloheptane-1,2-dione (5); Typical Procedure**

A 20 mL vial was charged with cycloheptenone **4** (170 mg, 0.52 mmol) followed by DMSO (10 mL). When cycloheptenone **4** had fully dissolved, 1.2 M aq HCl (10 mL) was added, and the mixture was heated to 100 °C with stirring for 4 h. The mixture was cooled, diluted with H_2O (25 mL), and extracted with CH_2Cl_2 (20 mL × 3). The organic layer was washed with brine (25 mL), dried (Na_2SO_4),

filtered, and concentrated in vacuo to give a crude product that was purified by flash chromatography [SiO_2, CH_2Cl_2–EtOAc (9:1)]; yield: 124 mg (0.40 mmol; 76%).

IR (thin film): 2973, 1710, 1701, 1653, 1635, 1616, 1559, 1465, 1457, 703 cm^{-1}.

^1H NMR (400 MHz, CD_3CN): δ = 0.73 (d, *J* = 7.0 Hz, 3 H), 1.79–1.87 (m, 2 H), 1.88–1.94 (m, 2 H), 2.40–2.49 (m, 1 H), 2.55 (dd, *J* = 13.3, 1.6 Hz, 1 H), 2.88 (dd, *J* = 16.0, 7.0 Hz, 1 H), 3.00–3.07 (m, 1 H), 3.11 (dd, *J* = 16.0, 2.0 Hz, 1 H), 3.29 (d, *J* = 13.3, 12.0 Hz, 1 H), 3.32–3.38 (m, 2 H), 3.43–3.51 (m, 2 H), 3.54–3.62 (m, 1 H), 7.22–7.28 (m, 3 H), 7.32–7.38 (m, 2 H).

^{13}C NMR (100 MHz, CD_3CN): δ = 19.9, 25.4, 27.2, 44.4, 45.1, 47.0, 48.3, 48.9, 48.9, 50.6, 128.0, 128.4, 130.2, 147.5, 172.4, 195.6, 197.0.

HRMS (ESI): *m/z* $[M + 1]^+$ calcd for $C_{19}H_{24}NO_3$: 314.1756; found: 314.1751.

(1*S,2*R**,3*S**,6*S**)-7-Benzyl-6-hydroxy-2-methyl-3-phenyl-7-azabicyclo[4.2.1]nonane-5,8-dione (7a)**

Yield: 38 mg (0.11 mmol; 99%).

IR (thin film): 3415, 2935, 1690, 1454, 1401, 1380, 1348, 1138, 1117, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 7.0 Hz, 3 H), 2.08–2.17 (m, 1 H), 2.20 (d, *J* = 13.6 Hz, 1 H), 2.33 (d, *J* = 18.2 Hz, 1 H), 2.39 (t, *J* = 11.7 Hz, 1 H), 2.51 (dd, *J* = 13.6, 8.7 Hz, 1 H), 2.75 (dd, *J* = 18.2, 11.7 Hz, 1 H), 2.89 (d, *J* = 8.7 Hz, 1 H), 4.15 (d, *J* = 14.7 Hz, 1 H), 4.72 (d, *J* = 14.7 Hz, 1 H), 4.88 (s, 1 H), 6.88 (d, *J* = 7.8 Hz, 2 H), 7.17–7.22 (m, 1 H), 7.22–7.29 (m, 3 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.36–7.40 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 39.0, 42.0, 43.7, 44.6, 47.0, 47.6, 89.1, 126.6, 126.8, 128.0, 128.5, 128.9, 129.8, 136.4, 144.2, 173.5, 205.9.

HRMS (ESI): *m/z* $[M + 1]^+$ calcd for $C_{22}H_{24}NO_3$: 350.1756; found: 350.1764.

(1*S,2*R**,3*S**,6*S**)-6-Hydroxy-7-(4-methoxybenzyl)-2-methyl-3-phenyl-7-azabicyclo[4.2.1]nonane-5,8-dione (7b)**

Yield: 37 mg (0.098 mmol; 97%).

IR (thin film): 3425, 2935, 1690, 1513, 1247, 1177, 1138, 1112, 1032, 703, 668 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 7.0 Hz, 3 H), 2.08–2.16 (m, 1 H), 2.18 (d, *J* = 13.7 Hz, 1 H), 2.33 (dd, *J* = 18.2, 2.0 Hz, 1 H), 2.37 (td, *J* = 12.0, 2.0 Hz, 1 H), 2.49 (dd, *J* = 13.7, 8.6 Hz, 1 H), 2.74 (dd, *J* = 18.2, 12.0 Hz, 1 H), 2.87 (dd, *J* = 8.6, 2.0 Hz, 1 H), 3.77 (s, 3 H), 4.06 (d, *J* = 14.7 Hz, 1 H), 4.70 (d, *J* = 14.7 Hz, 1 H), 4.90 (s, 1 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 7.0 Hz, 2 H), 7.15–7.21 (m, 1 H), 7.22–7.28 (m, 2 H), 7.30 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 39.0, 41.2, 43.6, 44.4, 46.9, 47.6, 55.2, 89.1, 113.6, 126.6, 126.8, 128.8, 128.5, 131.2, 144.2, 159.2, 173.4, 206.1.

HRMS (ESI): *m/z* $[M + 1]^+$ calcd for $C_{23}H_{26}NO_4$: 380.1862; found: 380.1867.

(1*S,2*R**,3*S**)-*N*,*N*,2-Trimethyl-5,6-dioxo-3-phenylcycloheptanecarboxamide (21)**

Yield: 60 mg (0.21 mmol; 73%).

IR (thin film): 2960, 1709, 1684, 1653, 1635, 1617, 1559, 1506, 1457, 1419, 704 cm^{-1}.

^1H NMR (400 MHz, CD_3CN): δ = 0.71 (d, *J* = 6.6 Hz, 3 H), 2.41–2.50 (m, 1 H), 2.55 (dd, *J* = 13.3, 1.6 Hz, 1 H), 2.83 (dd, *J* = 16.0, 7.4 Hz, 1 H), 2.89 (s, 3 H), 2.95–3.02 (m, 1 H), 3.09 (s, 3 H), 3.10 (dd, *J* = 16.0, 2.0 Hz, 1 H), 3.29 (dd, *J* = 13.3, 12.0 Hz, 1 H), 3.67–3.75 (m, 1 H), 7.21–7.29 (m, 3 H), 7.32–7.38 (m, 2 H).

^{13}C NMR (100 MHz, CD_3CN): δ = 19.7, 36.2, 39.4, 44.5, 45.1, 46.1, 48.2, 50.5, 128.0, 128.4, 130.1, 147.4, 174.1, 195.8, 197.0.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{21}NNaO_3$: 310.1419; found: 310.1407.

(5*S,6*R**,7*S**)-6-Methyl-2,5-diphenyl-7-(pyrrolidin-1-ylcarbonyl)-1,4,5,6,7,8-hexahydrocyclohepta[*d*]imidazole (8); Typical Procedure**

An oven-dried vial was charged sequentially with diketone **5** (40 mg, 0.13 mmol), NH_4OAc (40 mg, 0.52 mmol), anhyd EtOH (1 mL), and PhCHO (15 μL, 0.14 mmol). The vial was sealed with a Teflon-lined cap and heated to 80 °C for 3 h with continuous stirring. The mixture was cooled, concentrated in vacuo, and purified by flash chromatography [SiO_2, CH_2Cl_2–MeOH (gradient 30:1 to 10:1)]; yield: 18 mg (0.046 mmol; 36%).

IR (thin film): 3057, 2971, 2877, 1635, 1493, 1437, 1380, 1265, 773, 734, 702 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 1.12 (d, *J* = 7.0 Hz, 3 H), 1.73–1.82 (m, 4 H), 2.40 (t, *J* = 6.8 Hz, 1 H), 2.76 (d, *J* = 14.5 Hz, 1 H), 2.88–2.98 (m, 1 H), 2.98–3.07 (ovrlp m, 1 H), 3.02–3.10 (ovrlp m, 1 H), 3.05–3.12 (ovrlp m, 1 H), 3.13–3.20 (ovrlp m, 1 H), 3.13–3.23 (ovrlp m, 1 H), 3.17–3.25 (ovrlp m, 1 H), 3.25–3.32 (m, 1 H), 3.32–3.40 (m, 1 H), 7.15–7.22 (m, 1 H), 7.22–7.31 (m, 4 H), 7.35–7.42 (m, 1 H), 7.42–7.49 (m, 2 H), 7.84 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 14.7, 24.0, 25.0, 26.9, 29.3, 41.4, 43.2, 47.1, 47.2, 126.3, 127.6, 129.2, 129.5, 129.9, 130.1, 130.2, 132.0, 133.2, 144.9, 147.0, 175.2.

HRMS (ESI): *m/z* $[M + 1]^+$ calcd for $C_{26}H_{30}N_3O$: 400.2389; found: 400.2389.

(2*R,3a*S**,6*S**,7*R**,8*S**)-4-Benzyl-7-methyl-2,8-diphenyl-6,7,8,9-tetrahydro-2*H*-3a,6-methano[1,3]oxazolo[5,4-*b*]azocin-5-one (9a)**

Purified by flash chromatography [SiO_2, PE–CH_2Cl_2–EtOAc (6:3:1)]; yield: 26 mg (0.058 mmol; 72%).

IR (thin film): 3030, 2965, 2936, 1698, 1494, 1454, 1395, 1153, 1044, 1017, 736, 699, 668 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 3 H), 2.09–2.16 (ddq, *J* = 10.9, 6.6, 1.8 Hz, 1 H), 2.21 (d, *J* = 12.9 Hz, 1 H), 2.40 (ddd, *J* = 12.9, 10.9, 2.3 Hz, 1 H), 2.67 (dd, *J* = 19.0, 2.3 Hz, 1 H), 2.69 (dd, *J* = 12.9, 8.6 Hz, 1 H), 2.80 (ddd, *J* = 19.0, 12.9, 3.1 Hz, 1 H), 2.82 (dd, *J* = 8.6, 1.8 Hz, 1 H), 4.40 (d, *J* = 14.9 Hz, 1 H), 4.60 (d, *J* = 14.9 Hz, 1 H), 6.82 (d, *J* = 3.1 Hz, 1 H), 6.92 (d, *J* = 7.4 Hz, 2 H), 7.14–7.22 (m, 1 H), 7.23–7.29 (m, 3 H), 7.34–7.40 (m, 7 H), 7.49 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 37.4, 39.5, 43.2, 44.2, 44.4, 47.7, 103.1, 105.5, 126.1, 126.7, 126.8, 127.9, 128.5, 128.6, 128.8, 128.9, 129.0, 136.9, 138.4, 144.7, 170.9, 173.1.

HRMS (ESI): *m/z* $[M + 1]^+$ calcd for $C_{29}H_{29}N_2O_2$: 437.2229; found: 437.2236.

(2*R,3a*S**,6*S**,7*R**,8*S**)-4-(4-Methoxybenzyl)-7-methyl-2,8-diphenyl-6,7,8,9-tetrahydro-2*H*-3a,6-methano[1,3]oxazolo[5,4-*b*]azocin-5-one (9b)**

Purified by flash chromatography [SiO_2, PE–CH_2Cl_2–EtOAc (6:3:1)]; yield: 22 mg (0.048 mmol; 61%).

IR (thin film): 3029, 2936, 2836, 1696, 1513, 1395, 1278, 1248, 1178, 1036, 736, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.6 Hz, 3 H), 2.06–2.15 (ddq, *J* = 10.9, 6.6, 1.8 Hz, 1 H), 2.18 (d, *J* = 12.5 Hz, 1 H), 2.35 (ddd, *J* = 12.5, 10.9, 2.3 Hz, 1 H), 2.64 (dd, *J* = 19.0, 2.3 Hz, 1

H), 2.66 (dd, *J* = 12.5, 8.1 Hz, 1 H), 2.78 (ddd, *J* = 19.0, 12.5, 3.3 Hz, 1 H), 2.79 (dd, *J* = 8.1, 1.8 Hz, 1 H), 3.79 (s, 3 H), 4.27 (d, *J* = 14.8 Hz, 1 H), 4.61 (d, *J* = 14.8 Hz, 1 H), 6.82–6.93 (m, 5 H), 7.13–7.21 (m, 1 H), 7.22–7.28 (m, 2 H), 7.34–7.44 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 37.4, 39.5, 42.6, 44.1, 44.4, 47.7, 55.3, 103.1, 105.5, 113.8, 126.1, 126.6, 126.7, 128.6, 128.7, 128.9, 129.1, 130.5, 138.4, 144.8, 159.2, 171.1, 173.0.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{30}H_{31}N_2O_3$: 467.2335; found: 467.2323.

(6*S,7*R**,8*S**)-7-Methyl-3-(methylsulfanyl)-8-phenyl-6-(pyrrolidin-1-ylcarbonyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*e*][1,2,4]triazine (12a) and (6*S**,7*R**,8*S**)-7-Methyl-3-(methylsulfanyl)-6-phenyl-8-(pyrrolidin-1-ylcarbonyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*e*][1,2,4]triazine (12b); Typical Procedure**

An oven-dried vial was charged with diketone **5** (40 mg, 0.13 mmol) followed by anhyd EtOH (1 mL). Next, $H_2NC(SMe)=NNH_2$·HI (91 mg, 0.39 mmol) was added and the mixture was stirred for 6 h at r.t. The mixture was then concentrated in vacuo and the residue was purified by flash chromatography [SiO_2, CH_2Cl_2–EtOAc (gradient 9:1 to 3:1)] to give the regiosomers **12a** and **12b**.

12a

Yield: 19 mg (0.050 mmol; 38%); R_f = 0.55 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2953, 2927, 2873, 1628, 1445, 1376, 1343, 1265, 1165, 734, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (d, *J* = 7.0 Hz, 3 H), 1.72–1.83 (m, 2 H), 1.85–1.94 (m, 2 H), 2.11–2.25 (m, 1 H), 2.58 (s, 3 H), 3.08 (dd, *J* = 15.2, 7.8 Hz, 1 H), 3.18–3.27 (m, 3 H), 3.28–3.44 (m, 6 H), 7.10–7.18 (m, 3 H), 7.21–7.28 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 18.7, 24.3, 26.3, 37.5, 41.0, 43.5, 44.1, 45.0, 45.6, 47.0, 126.4, 128.7, 145.9, 156.6, 160.6, 170.2, 170.6.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{21}H_{27}N_4OS$: 383.1906; found: 383.1893.

12b

Yield: 9 mg (0.025 mmol; 19%); R_f = 0.33 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2972, 2873, 1630, 1443, 1376, 1295, 1262, 734, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (d, *J* = 6.6 Hz, 3 H), 1.76–1.89 (m, 2 H), 1.91–2.02 (m, 2 H), 2.23 (m, 1 H), 2.60 (s, 3 H), 3.07 (dd, *J* = 14.1, 2.0 Hz, 1 H), 3.19–3.29 (m, 2 H), 3.33 (m, 2 H), 3.40 (dd, *J* = 14.9, 2.7 Hz, 1 H), 3.45–3.52 (m, 2 H), 3.53–3.62 (m, 2 H), 7.15–7.23 (m, 3 H), 7.27–7.33 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 19.4, 24.3, 26.3, 35.2, 44.0, 44.2, 44.4, 44.5, 45.5, 46.9, 126.5, 128.7, 145.8, 155.2, 161.4, 170.4, 171.3.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{21}H_{27}N_4OS$: 383.1906; found: 383.1915.

(6*S,7*R**,8*S**)-*N*,*N*,7-Trimethyl-3-(methylsulfanyl)-8-phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*e*][1,2,4]triazine-6-carboxamide (22a)**

Yield: 14 mg (0.039 mmol; 30%); R_f = 0.52 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2928, 1634, 1493, 1376, 1341, 1261, 1132, 734, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68 (d, *J* = 6.9 Hz, 3 H), 2.14–2.24 (m, 1 H), 2.57 (s, 3 H), 2.79 (s, 3 H), 3.01 (s, 3 H), 3.06 (dd, *J* = 15.0, 7.6 Hz, 1 H), 3.20 (dd, *J* = 15.0, 2.8 Hz, 1 H), 3.26–3.33 (m, 2 H), 3.33–3.39 (m, 1 H), 3.39–3.43 (m, 1 H), 7.10–7.17 (m, 3 H), 7.21–7.26 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 18.4, 35.7, 37.3, 37.9, 40.7, 41.3, 43.6, 45.1, 126.5, 128.7, 145.7, 156.5, 160.5, 170.7, 171.9.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{19}H_{25}N_4OS$: 357.1749; found: 357.1757.

(6*S,7*R**,8*S**)-*N*,*N*,7-Trimethyl-3-(methylsulfanyl)-6-phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*e*][1,2,4]triazine-8-carboxamide (22b)**

Yield: 9 mg (0.025 mmol; 19%); R_f = 0.29 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2929, 1635, 1517, 1492, 1375, 1296, 1261, 1155, 1133, 729, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67 (d, *J* = 6.9 Hz, 3 H), 2.16–2.25 (m, 1 H), 2.54 (s, 3 H), 2.77 (s, 3 H), 3.02 (dd, *J* = 14.2, 2.0 Hz, 1 H), 3.07 (s, 3 H), 3.22 (dd, *J* = 14.2, 11.0 Hz, 1 H), 3.36–3.44 (m, 3 H), 3.44–3.50 (m, 1 H), 7.09–7.18 (m, 3 H), 7.21–7.27 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 19.0, 35.7, 37.9, 41.8, 44.1, 44.6, 126.6, 128.7, 145.6, 155.1, 161.6, 171.4, 172.2.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{19}H_{25}N_4OS$: 357.1749; found: 357.1745.

(1*S,2*R**,3*S**)-6-Methoxy-2-methyl-5-oxo-3-phenylcyclohept-2-enecarboxylic Acid (19)**

A vial was charged with bicyclo[3.2.1]octanoid **2** (40 mg, 0.16 mmol) followed by MeCN (1 mL) and H_2O (100 μL). Next, DBU (24 μL, 0.16 mmol) was added, and the mixture was stirred at r.t. for 4 h. The mixture was diluted with H_2O (1 mL), acidified (pH ~3) by addition of 1 M HCl, and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with brine (25 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. The crude material was purified by flash chromatography [SiO_2, CH_2Cl_2–MeOH (20:1)]; yield: 43 mg (0.16 mmol; 98%); R_f = 0.30 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 3063, 2964, 2933, 1734, 1684, 1653, 1456, 1203, 1175, 1145, 735, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.3 Hz, 3 H), 2.53–2.60 (m, 2 H), 2.80 (d, *J* = 17.4 Hz, 1 H), 3.05 (dd, *J* = 17.4, 11.9 Hz, 1 H), 3.71 (s, 3 H), 3.95 (t, *J* = 5.2 Hz, 1 H), 5.97 (d, *J* = 6.1 Hz, 1 H), 7.15–7.20 (m, 2 H), 7.20–7.26 (m, 1 H), 7.27–7.34 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 41.4, 44.2, 45.8, 48.3, 55.5, 106.1, 127.0, 127.7, 128.8, 143.5, 153.1, 178.0, 197.0.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{16}H_{19}O_4$: 275.1283; found: 275.1291.

(1*R,6*S**,7*R**)-3-Methoxy-*N*,*N*,7-trimethyl-4-oxo-6-phenylcyclohept-2-ene-1-carboxamide (20)**

A vial was charged with cycloheptenone **19** (40 mg, 0.15 mmol) followed by CH_2Cl_2 (1 mL). Next, a 2.0 M soln of Me_2NH in THF (0.38 mL, 0.75 mmol), DIPEA (31 μL, 0.18 mmol), and HATU (63 mg, 0.17 mmol) were added, and the mixture was stirred at r.t. for 6 h. The mixture was concentrated in vacuo, and resulting residue was purified by flash chromatography [SiO_2, CH_2Cl_2–MeOH (20:1)]; yield: 30 mg (0.10 mmol; 66%).

IR (thin film): 2962, 2932, 1683, 1646, 1495, 1456, 1399, 1209, 1142, 731, 703 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 0.76 (d, *J* = 6.6 Hz, 3 H), 2.21–2.34 (m, 1 H), 2.53 (dd, *J* = 12.2, 9.2 Hz, 1 H), 2.59 (d, *J* = 17.6 Hz, 1 H), 2.98 (s, 3 H), 3.21 (s, 3 H), 3.42 (dd, *J* = 17.6, 12.2 Hz, 1 H), 3.66 (s, 3 H), 4.39 (t, *J* = 5.5 Hz, 1 H), 6.24 (d, *J* = 5.5 Hz, 1 H), 7.19–7.27 (m, 3 H), 7.29–7.35 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 36.2, 37.4, 40.5, 40.8, 46.0, 48.0, 55.5, 109.4, 126.9, 127.6, 128.8, 144.1, 152.5, 171.4, 197.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{23}NNaO_3$: 324.1576; found: 324.1594.

(5*S,6*S**)-6-Methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (16a) and (6*R**)-6-Methyl-5-phenyl-7-(pyrrolidin-1-ylcarbonyl)-3,6-dihydrocyclohepta[*d*]imidazol-2(1*H*)-one (16b)**

A vial was charged with diketone **5** (40 mg, 0.13 mmol), urea (10 mg, 0.17 mmol), and CSA (30 mg, 0.13 mmol), followed by anhyd EtOH (1 mL). The mixture was heated to 80 °C and stirred for 20 h. The mixture was then concentrated in vacuo and purified by flash chromatography [SiO_2, CH_2Cl_2–acetone (1:1)] to afford diene **16a** and triene **16b**.

16a

Yield: 21 mg (0.062 mmol; 48%); R_f = 0.1 (CH_2Cl_2–acetone, 1:1).

IR (thin film): 2971, 2874, 1700, 1684, 1653, 1635, 1437, 1373, 1040, 734, 698 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.16 (d, *J* = 7.0 Hz, 3 H), 1.78–1.90 (m, 4 H), 2.62 (dd, *J* = 17.5, 2.4 Hz, 1 H), 2.97 (dd, *J* = 12.7, 2.4 Hz, 1 H), 3.09 (dd, *J* = 17.5, 12.7 Hz, 1 H), 3.15–3.25 (m, 2 H), 3.33–3.48 (m, 3 H), 6.31 (s, 1 H), 7.23 (t, *J* = 7.4 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.43 (d, *J* = 7.4 Hz, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 12.8, 24.4, 25.2, 26.9, 40.3, 41.3, 47.2, 47.9, 115.0, 118.5, 121.1, 126.5, 128.3, 129.7, 143.8, 145.0, 155.8, 175.2.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{20}H_{24}N_3O_2$: 338.1869; found: 338.1870.

16b

Yield: 14 mg (0.042 mmol; 32%); R_f = 0.15 (CH_2Cl_2–acetone, 1:1).

IR (thin film): 2970, 1699, 1684, 1653, 1576, 1559, 1436, 1419, 723, 697 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.06 (d, *J* = 7.4 Hz, 3 H), 1.65–1.95 (m, 4 H), 3.17–3.26 (m, 1 H), 3.37–3.48 (m, 3 H), 4.02 (q, *J* = 7.4 Hz, 1 H), 6.61 (s, 1 H), 6.65 (s, 1 H), 7.25–7.32 (m, 1 H), 7.32–7.39 (m, 2 H), 7.54 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 14.2, 24.7, 27.1, 39.4, 47.2, 51.3, 114.3, 118.0, 122.1, 126.3, 126.9, 128.3, 128.9, 129.7, 136.6, 143.5, 155.9, 172.7.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{20}H_{22}N_3O_2$: 336.1712; found: 366.1706.

(5*S,6*S**)-3-Ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (23a) and (5*S**,6*S**)-1-Ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (23b); Typical Procedure**

An oven-dried vial was charged with activated 4 Å MS (approx. 25 mg), diketone **5** (40 mg, 0.13 mmol), $EtNHCONH_2$ (12 mg, 0.14 mmol), and $Zn(OTf)_2$ (10 mg, 0.026 mmol), followed by anhyd MeCN (1 mL). The mixture was then degassed by bubbling argon through the soln for 15 min. Finally, the vial was sealed with a Teflon-lined cap, heated to 100 °C, and stirred for 5 h. The mixture was then cooled and filtered through Celite to remove the MS. The resulting filtrate was concentrated in vacuo and purified by flash chromatography [SiO_2, CH_2Cl_2–MeOH (gradient 50:1 to 20:1)] to afford imidazolinones **23a** and **23b**.

23a

Yield: 33 mg (0.090 mmol; 71%); R_f = 0.20 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 3164, 2973, 2873, 1700, 1697, 1684, 1653, 1635, 1617, 1437, 759, 733, 699 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.17 (d, *J* = 7.2 Hz, 3 H), 1.20 (t, *J* = 7.0 Hz, 3 H), 1.80–1.90 (m, 4 H), 2.64 (dd, *J* = 17.9, 3.5 Hz, 1 H), 2.99 (dd, *J* = 12.9, 3.5 Hz, 1 H), 3.12 (dd, *J* = 17.9, 12.9 Hz, 1 H), 3.18–3.25 (m, 2 H), 3.34–3.49 (m, 3 H), 3.71–3.84 (m, 2 H), 6.36 (s, 1 H), 7.26 (t, *J* = 7.3 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H).

NOESY (400 MHz, CD_3OD): irrad. δ = 6.36 (*beta*-phenyl, CH) 9% enhancement at 3.77 (*alpha*-urea, CH_2).

^{13}C NMR (100 MHz, CD_3OD): δ = 12.5, 15.2, 24.6, 25.1, 26.9, 35.9, 40.5, 41.0, 47.2, 47.9, 113.3, 118.4, 121.0, 126.7, 128.4, 129.8, 144.3, 145.5, 154.5, 175.0.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{22}H_{28}N_3O_2$: 366.2182; found: 366.2189.

23b

Yield: 10 mg (0.027 mmol; 21%); R_f = 0.29 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2973, 2874, 1700, 1696, 1684, 1653, 1635, 1617, 1437, 1374, 765, 732, 698 cm^{-1}.

^{1}H NMR [400 MHz, CD_2Cl_2–CD_3OD (1:5.2)]: δ = 1.17 (d, *J* = 7.0 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.80–1.92 (m, 4 H), 2.69 (dd, *J* = 17.5, 3.2 Hz, 1 H), 2.97 (dd, *J* = 12.7, 3.2 Hz, 1 H), 3.12 (dd, *J* = 17.5, 12.7 Hz, 1 H), 3.17–3.26 (m, 2 H), 3.36–3.51 (m, 3 H), 3.61–3.83 (m, 2 H), 6.31 (s, 1 H), 7.24 (t, *J* = 7.43 Hz, 1 H), 7.33 (t, *J* = 7.24 Hz, 2 H), 7.43 (d, *J* = 8.02 Hz, 2 H).

NOESY (400 MHz, CD_3OD): irrad. δ = 2.69 (*beta*-amide, CH_2) 6% enhancement at 3.72 (*alpha*-urea, CH_2).

^{13}C NMR [100 MHz, CD_2Cl_2–CD_3OD (1:5.2)]: δ = 12.7, 15.1, 23.7, 24.9, 26.7, 36.5, 39.8, 41.2, 46.9, 47.7, 114.7, 117.2, 121.1, 126.2, 128.0, 129.4, 143.3, 144.6, 154.0, 174.7.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{22}H_{28}N_3O_2$: 366.2182; found: 366.2189.

(5*S,6*S**)-3-*tert*-Butyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (26a)**

Yield: 29 mg (0.074 mmol; 57%); R_f = 0.15 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2970, 1675, 1635, 1591, 1430, 1128, 1032, 766, 698 cm^{-1}.

^{1}H NMR (400 MHz, CD_2Cl_2–CD_3OD, 1:9.4): δ = 1.20 (d, *J* = 7.0 Hz, 3 H), 1.67 (s, 9 H), 1.76–1.89 (m, 4 H), 2.59 (dd, *J* = 18.1, 4.0 Hz, 1 H), 2.92 (dd, *J* = 13.1, 4.0 Hz, 1 H), 3.10 (dd, *J* = 18.1, 13.1 Hz, 1 H), 3.13–3.20 (m, 2 H), 3.33–3.48 (m, 3 H), 6.70 (s, 1 H), 7.21–7.30 (m, 1 H), 7.32–7.42 (m, 4 H).

^{13}C NMR [100 MHz, CD_2Cl_2–CD_3OD (1:9.4)]: δ = 11.9, 24.6, 25.0, 26.7, 31.4, 40.0, 40.6, 47.0, 47.7, 58.1, 117.3, 119.3, 122.0, 126.5, 128.0, 129.6, 142.5, 144.9, 154.8, 174.5.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{24}H_{32}N_3O_2$: 394.2495; found: 394.2505.

(5*S,6*S**)-1-*tert*-Butyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (26b)**

Yield: 16 mg (0.040 mmol; 31%); R_f = 0.26 (CH_2Cl_2–MeOH, 20:1).

(5*S,6*S**)-6-Methyl-7-phenyl-3-prop-2-yn-1-yl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (28a)**

Yield: 36 mg (0.096 mmol; 74%); R_f = 0.17 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2971, 2874, 1685, 1635, 1593, 1431, 1387, 734, 700, 633 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.17 (d, *J* = 7.0 Hz, 3 H), 1.78–1.96 (m, 4 H), 2.63 (dd, *J* = 18.1, 3.0 Hz, 1 H), 2.70 (t, *J* = 2.5 Hz,

1 H), 2.98 (dd, *J* = 12.9, 3.0 Hz, 1 H), 3.12 (dd, *J* = 18.1, 12.9 Hz, 1 H), 3.18–3.28 (m, 2 H), 3.38–3.50 (m, 3 H), 4.45 (dd, *J* = 18.4, 2.5 Hz, 1 H), 4.61 (dd, *J* = 18.4, 2.5 Hz, 1 H), 6.53 (s, 1 H), 7.27 (t, *J* = 7.3 Hz, 1 H), 7.36 (t, *J* = 7.8 Hz, 2 H), 7.47 (d, *J* = 7.4 Hz, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 12.6, 24.4, 25.0, 26.8, 30.4, 40.2, 40.8, 47.1, 47.8, 73.5, 79.2, 113.4, 118.4, 121.1, 126.6, 128.3, 129.6, 143.9, 145.2, 154.0, 174.8.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{23}H_{26}N_3O_2$: 376.2025; found: 376.2018.

(5*S,6*S**)-6-Methyl-7-phenyl-1-prop-2-yn-1-yl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (28b)**

Yield: 8 mg (0.022 mmol; 17%); R_f = 0.22 (CH_2Cl_2–MeOH, 20:1).

(5*S,6*S**)-6-Methyl-3,7-diphenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (30a)**

Yield: 41 mg (0.099 mmol; 76%), R_f = 0.17 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2972, 2875, 1700, 1696, 1684, 1635, 1595, 1499, 1437, 1379, 757, 732, 700, 668 cm^{-1}.

^{1}H NMR (400 MHz, CD_2Cl_2–CD_3OD, 1:6.8): δ = 1.23 (d, *J* = 7.03 Hz, 3 H), 1.75–1.94 (m, 4 H), 2.71 (dd, *J* = 18.4, 3.1 Hz, 1 H), 3.00 (dd, *J* = 12.9, 3.1 Hz, 1 H), 3.19–3.24 (m, 2 H), 3.21 (ovrlp dd, *J* = 18.4, 12.9 Hz, 1 H), 3.36–3.50 (m, 3 H), 5.98 (s, 1 H), 7.14–7.22 (m, 1 H), 7.23–7.27 (m, 4 H), 7.31 (d, *J* = 7.42 Hz, 2 H), 7.38–7.43 (m, 1 H), 7.47–7.52 (m, 2 H).

^{13}C NMR (100 MHz, CD_2Cl_2–CD_3OD, 1:6.8): δ = 12.7, 24.4, 25.0, 26.8, 40.1, 40.8, 47.0, 47.8, 113.9, 119.4, 121.2, 126.3, 128.1, 129.2, 129.3, 129.4, 130.3, 135.3, 143.7, 144.7, 154.2, 174.7.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{26}H_{28}N_3O_2$: 414.2182; found: 414.2183.

(5*S,6*S**)-6-Methyl-1,7-diphenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (30b)**

Yield: 12 mg (0.030 mmol; 23%), R_f = 0.24 (CH_2Cl_2–MeOH, 20:1).

(5*S,6*S**)-1-Ethyl-6-methyl-3,7-diphenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (35a)**

Yield: 44 mg (0.10 mmol; 77%), R_f = 0.36 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2972, 2873, 1695, 1636, 1419, 1387, 764, 721, 696 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.22 (d, *J* = 7.0 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.75–1.90 (m, 4 H), 2.36 (d, *J* = 15.2 Hz, 1 H), 2.91–3.07 (m, 2 H), 3.16–3.28 (m, 2 H), 3.32–3.44 (m, 3 H), 3.83–3.95 (m, 2 H), 6.48 (s, 1 H), 7.23–7.32 (m, 1 H), 7.34–7.41 (m, 4 H), 7.47 (d, *J* = 7.4 Hz, 1 H), 7.49–7.58 (m, 4 H).

NOESY (400 MHz, CD_3OD): irrad. δ = 6.48 (*beta*-phenyl, CH) 9% enhancement at 3.90 (*alpha*-urea, CH_2).

^{13}C NMR (100 MHz, CD_3OD): δ = 12.6, 15.2, 25.1, 26.9, 36.6, 40.4, 41.1, 47.1, 47.8, 112.8, 118.4, 122.0, 126.8, 128.6, 129.2, 129.8, 129.8, 130.6, 135.7, 144.1, 146.7, 153.4, 174.9.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{28}H_{32}N_3O_2$: 442.2495; found: 442.2494.

(5*S,6*S**)-3-Ethyl-6-methyl-1,7-diphenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazol-2(1*H*)-one (35b)**

Yield: 13 mg (0.029 mmol; 22%), R_f = 0.29 (CH_2Cl_2–MeOH, 20:1).

(5*S,6*S**)-3-Ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazole-2(1*H*)-thione (36a)**

Yield: 39 mg (0.10 mmol; 79%), R_f = 0.31 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 3174, 3055, 2971, 2933, 2873, 1636, 1608, 1476, 1448, 1414, 1378, 1276, 1210, 1137, 758, 733, 698 cm^{-1}.

^{1}H NMR (400 MHz, CD_2Cl_2–CD_3OD, 1:4.1): δ = 1.16 (d, *J* = 7.0 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.86 (m, 4 H), 2.74 (dd, *J* = 17.9, 3.4 Hz, 1 H), 2.97 (dd, *J* = 13.1, 3.4 Hz, 1 H), 3.19 (ovrlp dd, *J* = 17.9, 13.1 Hz, 1 H), 3.19–3.27 (m, 2 H), 3.34–3.49 (m, 3 H), 4.08–4.29 (m, 2 H), 6.40 (s, 1 H), 7.27–7.33 (m, 1 H), 7.38 (t, *J* = 7.6 Hz, 2 H), 7.46 (d, *J* = 7.4 Hz, 2 H).

^{13}C NMR (100 MHz, CD_2Cl_2–CD_3OD, 1:4.1): δ = 11.9, 13.4, 22.9, 23.9, 25.7, 38.7, 39.3, 45.9, 46.7, 111.9, 123.4, 125.5, 125.6, 127.5, 128.5, 142.7, 146.0, 158.7, 173.2.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{22}H_{28}N_3OS$: 382.1953; found: 382.1947.

(5*S,6*S**)-1-Ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6-tetrahydrocyclohepta[*d*]imidazole-2(1*H*)-thione (36b)**

Yield: 10 mg (0.026 mmol; 20%), R_f = 0.40 (CH_2Cl_2–MeOH, 20:1).

6*R)-1-Ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)-3,6-dihydrocyclohepta[*d*]imidazol-2(1*H*)-one (37) and 1-Ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)cyclohepta[*d*]imidazol-2(1*H*)-one (38); Typical Procedure**

An oven-dried vial was charged with the ethylimidazolone **20a** (40 mg, 0.13 mmol), followed by anhyd CH_2Cl_2 (1 mL). DDQ (36 mg, 0.16 mmol) was added, and the mixture was stirred at r.t. for 2 h. The mixture was diluted with CH_2Cl_2 (10 mL) then washed with sat. aq $NaHCO_3$ (2 × 10 mL) and brine (10 mL). The organic portion was dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography [SiO_2, CH_2Cl_2–MeOH (gradient 50:1 to 20:1)] to give **37** and **38**.

37

Yield: 33 mg (0.090 mmol; 71%).

IR (thin film): 3172, 2974, 2874, 1700, 1596, 1443, 1405, 1378, 750, 732, 698 cm^{-1}.

^{1}H NMR [400 MHz, CD_2Cl_2–CD_3OD (1:6)]: δ = 1.04 (d, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.61–1.94 (m, 4 H), 3.15–3.24 (m, 1 H), 3.33–3.47 (m, 3 H), 3.73–3.95 (m, 2 H), 3.99–4.09 (m, 1 H), 6.64 (s, 1 H), 6.65 (s, 1 H), 7.26–7.33 (m, 1 H), 7.34–7.40 (m, 2 H), 7.56 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR [100 MHz, CD_2Cl_2–CD_3OD (1:6)]: δ = 12.7, 13.7, 24.0, 25.8, 35.4, 38.0, 45.9, 49.5, 111.7, 116.5, 120.1, 125.0, 127.1, 127.3, 127.6, 128.3, 135.2, 142.2, 153.0, 171.1.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{22}H_{26}N_3O$: 364.2025; found: 364.2024.

38

Yield: 10 mg (0.027 mmol; 21%).

IR (thin film): 2958, 2924, 2852, 1701, 1635, 1616, 1653, 1447, 1418, 1078, 731, 703 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 1.96–2.08 (m, 4 H), 2.24 (s, 3 H), 3.15–3.24 (m, 1 H), 3.32–3.41 (m, 1 H), 3.56–3.66 (m, 1 H), 3.66–3.74 (m, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 7.40 (d, *J* = 7.4 Hz, 2 H), 7.47–7.52 (m, 1 H), 7.52–7.59 (m, 2 H), 7.64 (s, 1 H), 7.86 (s, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 13.8, 23.8, 25.3, 26.9, 37.1, 47.0, 49.7, 120.5, 125.8, 129.1, 129.6, 130.1, 139.1, 145.2, 146.5, 151.4, 155.0, 163.7, 167.2, 170.4.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{22}H_{24}N_3O_2$: 362.1869; found: 362.1873.

(6*R)-1-Acetyl-3-ethyl-6-methyl-5-phenyl-7-(pyrrolidin-1-ylcarbonyl)-3,6-dihydrocyclohepta[*d*]imidazol-2(1*H*)-one (39)**
Yield: 22 mg (0.055 mmol; 50%).

IR (thin film): 2973, 2875, 1724, 1621, 1603, 1409, 1372, 1358, 1317, 1276, 749, 731, 700 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.00 (d, *J* = 7.0 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.80–1.98 (m, 4 H), 2.68 (s, 3 H), 3.37–3.57 (m, 3 H), 3.57–3.67 (m, 1 H), 3.77–3.98 (m, 2 H), 4.03–4.10 (m, 1 H), 6.65 (s, 1 H), 7.30–7.36 (m, 1 H), 7.36–7.41 (m, 3 H), 7.68 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 13.1, 14.2, 25.3, 26.0, 27.2, 37.1, 39.4, 47.3, 51.3, 111.6, 120.0, 120.5, 127.4, 128.2, 128.7, 129.2, 129.6, 143.2, 152.4, 172.1, 173.8.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{24}H_{28}N_3O_3$: 406.2131; found: 406.2128.

(5*S,6*R**,7*R**)-1-Ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)-3,4,5,6,7,8-hexahydrocyclohepta[*d*]imidazol-2(1*H*)-one (40)**
A soln of imidazolone **23a** (40 mg, 0.11 mmol) in MeOH (10 mL) was passed at 0.5 mL/min through a 10% Pd/C cartridge at 50 bar and 50 °C in an H-Cube hydrogenator. The collected mixture was concentrated in vacuo and the resulting residue was purified by flash chromatography [SiO_2, CH_2Cl_2–MeOH (gradient 50:1 to 20:1)]; yield: 40 mg (0.11 mmol; 99%).

IR (thin film): 3049, 2973, 1699, 1684, 1653, 1635, 1457, 1437, 1419, 736, 701 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 0.93 (d, *J* = 7.0 Hz, 3 H), 1.15 (t, *J* = 7.2 Hz, 3 H), 1.81–1.93 (m, 2 H), 1.96–2.07 (m, 2 H), 2.11–2.21 (m, 1 H), 2.40 (dd, *J* = 16.4, 3.5 Hz, 1 H), 2.62 (dd, *J* = 15.0, 2.1 Hz, 1 H), 2.93–3.05 (m, 1 H), 3.06–3.25 (m, 3 H), 3.32–3.37 (m, 1 H), 3.45 (dt, *J* = 11.8, 7.2 Hz, 1 H), 3.55 (dt, *J* = 10.2, 7.0 Hz, 1 H), 3.62–3.70 (m, 2 H), 3.76 (dt, *J* = 10.4, 6.5 Hz, 1 H), 7.18–7.28 (m, 1 H), 7.32–7.36 (m, 4 H).

NOESY (400 MHz, CD_3OD): irrad. δ = 0.93 (CH_3) 3% enhancement at 3.00 (β-NH, CH), 4% at 3.14 (β-NEt, CH).

^{13}C NMR (100 MHz, CD_3OD): δ = 6.6, 15.4, 23.7, 25.1, 25.2, 27.1, 36.2, 42.2, 47.2, 48.0, 48.7, 50.0, 117.3, 118.9, 127.7, 128.4, 129.6, 147.0, 154.4, 175.0.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{22}H_{30}N_3O_2$: 368.2338; found: 368.2346.

(3a*S,5*S**,6*R**,7*R**,8a*R**)-1-Ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)octahydrocyclohepta[*d*]imidazol-2(1*H*)-one (41a) and (3a*R**,5*S**,6*R**,7*R**,8a*S**)-1-Ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)octahydrocyclohepta[*d*]imidazol-2(1*H*)-one (41b)**
A soln of imidazolone **23a** (40 mg, 0.11 mmol) in MeOH (10 mL) was passed at 0.5 mL/min through a Raney Ni cartridge at 90 bar and 80 °C in an H-Cube hydrogenator. The collected mixture was concentrated in vacuo and the resulting residue was purified by preparative HPLC to give **41a** and **41b**.

41a
Yield: 20 mg (0.054 mmol; 50%).

IR (thin film): 2971, 2928, 2874, 1700, 1684, 1676, 1653, 1635, 1617, 1457, 1437, 1379, 1276, 731, 703 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 0.76 (d, *J* = 6.6 Hz, 3 H), 0.96 (t, *J* = 7.2 Hz, 3 H), 1.78 (dd, *J* = 16.0, 4.3 Hz, 1 H), 1.86 (dq, *J* = 7.0, 6.5 Hz, 2 H), 1.95–2.05 (m, 3 H), 2.07–2.17 (m, 2 H), 2.38 (ddd, *J* = 15.8, 11.3, 1.8 Hz, 1 H), 2.76 (dq, *J* = 14.0, 7.0 Hz, 1 H), 3.06 (dd, *J* = 11.1, 3.3 Hz, 1 H), 3.12 (dd, *J* = 10.2, 2.7 Hz, 1 H), 3.25–3.35 (m, 1 H), 3.35–3.46 (m, 2 H), 3.55 (dt, *J* = 10.2, 6.8 Hz, 1 H), 3.68 (dt, *J* = 10.2, 6.6 Hz, 1 H), 4.12 (ddd, *J* = 10.9, 3.9, 2.3 Hz, 1 H), 4.20 (ddd, *J* = 10.9, 4.7, 1.6 Hz, 1 H), 7.16–7.22 (m, 3 H), 7.26–7.32 (m, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 7.6, 12.6, 25.2, 27.2, 27.2, 28.3, 36.5, 39.8, 43.6, 45.0, 47.2, 48.0, 53.0, 58.1, 127.3, 129.1, 129.3, 147.2, 163.9, 176.1.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{22}H_{32}N_3O_2$: 370.2495; found: 370.2500.

41b
Yield: 20 mg (0.054 mmol; 49%).

IR (thin film): 2971, 2873, 1689, 1631, 1436, 1375, 1272, 732, 702 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 0.73 (d, *J* = 7.0 Hz, 3 H), 1.06 (t, *J* = 7.2 Hz, 3 H), 1.81 (dd, *J* = 14.8, 3.9 Hz, 1 H), 1.84–1.90 (m, 2 H), 1.94–2.08 (m, 4 H), 2.11–2.26 (m, 2 H), 2.95 (dd, *J* = 10.2, 3.1 Hz, 1 H), 2.99–3.09 (m, 2 H), 3.26–3.34 (m, 1 H), 3.37–3.46 (m, 2 H), 3.53 (dt, *J* = 10.2, 7.0 Hz, 1 H), 3.72 (dt, *J* = 10.5, 6.6 Hz, 1 H), 3.95 (ddd, *J* = 11.3, 9.8, 3.91 Hz, 1 H), 4.02 (ddd, *J* = 11.3, 9.8, 4.3 Hz, 1 H), 7.15–7.25 (m, 3 H), 7.27–7.35 (m, 2 H).

NOESY (400 MHz, CD_3OD): irrad. δ =3.95 (α-NH, CH) 4% enhancement at 2.95 (α-amide, CH), and 1% at 1.81 (β-amide, CH_2); irrad. δ = 4.02 (α-NEt, CH) 6% enhancement at 3.01 (α-phenyl, CH), 2% at 1.06 (CH_3).

^{13}C NMR (100 MHz, CD_3OD): δ = 8.0, 13.2, 25.1, 27.2, 28.2, 28.8, 36.2, 40.1, 47.2, 47.6, 47.9, 48.0, 55.2, 59.9, 127.2, 128.9, 129.3, 147.6, 162.9, 175.6.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{22}H_{32}N_3O_2$: 370.2495; found: 370.2494.

(3a*S,5*R**,6*R**,7*S**,8a*R**)-1-Acetyl-3-ethyl-6-methyl-5-phenyl-7-(pyrrolidin-1-ylcarbonyl)octahydrocyclohepta[*d*]imidazol-2(1*H*)-one (43)**
A soln of imidazolone **42** (40 mg, 0.098 mmol) in EtOAc (10 mL) was passed at 0.5 mL/min through a 10% Pd/C cartridge at 30 bar and 90 °C in an H-Cube hydrogenator. The collected mixture was concentrated in vacuo and the resulting residue was purified by flash chromatography [SiO_2, CH_2Cl_2–MeOH (gradient 50:1 to 20:1)]; yield: 40 mg (0.098 mmol; 99%); R_f = 0.39 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2972, 2875, 1726, 1679, 1634, 1426, 1377, 1351, 1270, 726, 703, 617 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 0.74 (d, *J* = 6.8 Hz, 3 H), 1.10 (t, *J* = 7.2 Hz, 3 H), 1.79–1.92 (m, 2 H), 1.93–2.06 (m, 4 H), 2.12–2.25 (m, 3 H), 2.45 (s, 3 H), 3.00–3.12 (m, 2 H), 3.22 (dq, *J* = 14.5, 7.5 Hz, 1 H), 3.28–3.35 (m, 1 H), 3.40–3.57 (m, 3 H), 3.78 (dt, *J* = 10.2, 6.4 Hz, 1 H), 4.03 (td, *J* = 9.9, 6.3 Hz, 1 H), 4.42–4.54 (m, 1 H), 7.13–7.26 (m, 3 H), 7.27–7.35 (m, 2 H).

NOESY (400 MHz, CD_3OD): irrad. δ = 4.03 (α-NEt, CH) 3% enhancement at 3.01 (α-phenyl/α-amide, CH), 5% at 4.48 (α-NAc, CH); irrad. δ = 4.48 (α-NAc, CH) 6% enhancement at 3.01 (α-amide/α-phenyl, CH), 5% at 4.03 (α-NEt, CH).

^{13}C NMR (100 MHz, CD_3OD): δ = 8.0, 12.6, 24.2, 25.1, 25.4, 27.2, 28.3, 36.8, 39.7, 46.0, 47.2, 47.9, 56.0, 57.4, 127.3, 128.9, 129.3, 147.6, 155.8, 172.2, 175.2.

HRMS (ESI): *m/z* [M + 1]$^+$ calcd for $C_{24}H_{34}N_3O_3$: 412.2600; found: 412.2582.

(3a*R,5*S**,6*R**,7*R**,8a*S**)-1-Acetyl-3-ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)octahydrocyclohepta[*d*]imidazol-2(1*H*)-one (45)**

A soln of imidazolone **44** (40 mg, 0.098 mmol) in EtOAc (10 mL) was passed at 0.5 mL/min through a 10% Pd/C cartridge at 50 bar and 50 °C in an H-Cube hydrogenator. The collected mixture was concentrated in vacuo and the resulting residue was purified by flash chromatography [SiO_2, CH_2Cl_2–MeOH (gradient 50:1 to 20:1)]; yield: 40 mg (0.098 mmol; 99%); R_f = 0.41 (CH_2Cl_2–MeOH, 20:1).

IR (thin film): 2971, 2874, 1727, 1678, 1634, 1426, 1377, 1352, 1323, 1270, 733, 715, 701, 615 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 0.66 (d, *J* = 6.8 Hz, 3 H), 1.14 (t, *J* = 7.1 Hz, 3 H), 1.79–1.92 (m, 3 H), 1.95–2.09 (m, 3 H), 2.16–2.31 (m, 3 H), 2.43 (s, 3 H), 2.94 (dd, *J* = 9.3, 2.0 Hz, 1 H), 3.15 (dd, *J* = 11.1, 3.7 Hz, 1 H), 3.21 (dq, *J* = 14.5, 7.0 Hz, 1 H), 3.34 (s, 1 H), 3.41–3.62 (m, 3 H), 3.73 (dt, *J* = 10.2, 6.5 Hz, 1 H), 4.01 (ddd, *J* = 11.6, 8.80, 6.0 Hz, 1 H), 4.45–4.56 (m, 1 H), 7.13–7.20 (m, 3 H), 7.23–7.31 (m, 2 H).

NOESY (400 MHz, CD_3OD): irrad. δ = 4.01 (α-NEt, CH) 2% enhancement at 1.14 (NEt, CH_3), 3% at 2.22 (CH), 3% at 2.94 (α-amide, CH), 5% at 4.51 (α-NAc, CH); irrad. δ = 4.51 (α-NAc, CH) 7% enhancement at 3.15 (α-phenyl, CH), 5% at 4.01 (α-NEt, CH).

^{13}C NMR (100 MHz, CD_3OD): δ = 8.3, 12.6, 24.2, 25.2, 25.4, 27.2, 27.7, 36.8, 39.9, 45.2, 47.3, 48.0, 49.9, 55.6, 58.2, 127.2, 128.7, 129.2, 146.5, 155.9, 172.0, 175.5.

HRMS (ESI): *m/z* $[M + 1]^+$ calcd for $C_{24}H_{34}N_3O_3$: 412.2600; found: 412.2582.

(3a*R,5*S**,6*R**,7*S**)-3-Acetyl-1-ethyl-6-methyl-7-phenyl-5-(pyrrolidin-1-ylcarbonyl)-3,3a,4,5,6,7-hexahydrocyclohepta[*d*]imidazol-2(1*H*)-one (48)**

A soln of imidazolone **42** (30 mg, 0.074 mmol) in EtOAc (7.5 mL) was passed at 0.5 mL/min through a 10% Pd/C cartridge at 10 bar and 40 °C in an H-Cube hydrogenator. The collected mixture was concentrated in vacuo, and the resulting residue was purified by flash chromatograph [SiO_2, CH_2Cl_2–MeOH (gradient 50:1 to 20:1)]; yield: 24 mg (0.058 mmol; 79%).

IR (thin film): 2971, 2932, 2875, 1740, 1734, 1695, 1684, 1635, 1419, 1374, 1232, 703, 626, 603 cm^{-1}.

^1H NMR (500 MHz, CD_3OD, 45 °C): δ = 0.86 (d, *J* = 6.8 Hz, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 1.72–1.80 (m, 1 H), 1.81–1.93 (m, 2 H), 1.95–2.04 (m, 2 H), 2.06–2.11 (m, 1 H), 2.14 (d, *J* = 13.4 Hz, 1 H), 2.49 (s, 3 H), 3.27–3.31 (m, 1 H), 3.33–3.37 (m, 1 H), 3.41–3.47 (m, 1 H), 3.47–3.54 (m, 1 H), 3.54–3.61 (m, 1 H), 3.61–3.69 (m, 1 H), 3.75–3.84 (m, 1 H), 3.95 (d, *J* = 5.1 Hz, 1 H), 4.97 (d, *J* = 11.2 Hz, 1 H), 5.10 (d, *J* = 5.6 Hz, 1 H), 7.21–7.25 (m, 1 H), 7.32–7.41 (m, 4 H).

NOESY (400 MHz, CD_3OD): irrad. δ = 3.95 (α-phenyl, CH) 8% enhancement at 3.35 (α-amide, CH), 6% at 4.97 (α-NAc, CH); irrad. δ = 4.97 (α-NAc, CH) 7% enhancement at 3.35 (α-amide, CH), 7% at 3.95 (α-phenyl).

^{13}C NMR (125 MHz, CD_3OD, 45 °C): δ = 8.7, 12.0, 24.3, 25.0, 26.1, 27.1, 36.2, 39.9, 47.1, 47.8, 50.6, 57.5, 98.8, 127.6, 128.7, 129.6, 138.7, 145.9, 154.6, 171.7, 174.4.

HRMS (ESI): *m/z* $[M + 1]^+$ calcd for $C_{24}H_{32}N_3O_3$: 410.2444; found: 410.2438.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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