Intermolecular and Intramolecular Diels−Alder Cycloadditions of 3-Ylidenepiperazine-2,5-diones and 5-Acyloxy-2(1*H*)-pyrazinones†

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The 3-ylidenepiperazine-2,5-diones **16** and **39** and 5-acyloxy-2(1*H*)-pyrazinones **17** can serve as starting materials for the Diels−Alder reactions of alkenes and alkynes to the piperazine ring, under acidic conditions or in the presence of acetyl chloride, to afford tricyclic piperazine-2,5-diones **19**, **20**, **23**−**25**, **27**, **44**, and **45**. Intramolecular cycloadditions occur if 3-ylidenepiperazine-2,5-diones **30** and **32** are used as the starting materials. This procedure is a convenient path to bridged bicyclo-[2.2.2]diazaoctane ring systems such as **31** and **33**, the former being found in biologically active secondary mold metabolites, such as VM55599 (**1**) or brevianamide A (**5**), which have been isolated from various fungi. The synthesis of the indole compound **31** provided evidence for the proposed biochemical pathway with a Diels−Alder reaction as key step. Quantum chemical calculations have revealed that piperazinones with a cationic azadiene moiety are the most reactive species in Diels−Alder cycloadditions.

Introduction

Piperazindiones are cyclodimers of α-amino acids. The corresponding dehydrogenated derivatives such as 5-hydroxy-2(1*H*)-pyrazinones represent azadiene systems. The latter can undergo Diels−Alder reactions with alkenes and alkynes regardless of whether they exist as azadienes or in tautomeric structures, i.e., as 3,4-dihydropiperazine-2,5-diones.[1−3] It is possible to fix the azadiene structure of 5-hydroxy-2(1*H*)-pyrazinones by O-alkylation or O-acylation with Boc-anhydride to afford 5-alkoxy-[4a] or 5-*tert*-butyloxycarbonyl-2(1*H*)-pyrazinones,[4b] before the application in Diels−Alder reactions. In a similar manner, substituted 5-chloro-2(1*H*)-pyrazinones were used as azadienes in Diels−Alder reactions.[5−8] The primary bicyclic cycloadducts derived from alkynes as dienophiles can eliminate cyanic acid or isocyanic acid derivatives to yield monocyclic conjugated pyridines. The 1,4-disubstituted piperazine-2,5-diones, bridged by disulfide or trisulfide linkages at position 3 and 6, cannot form tautomeric azadiene structures. Nevertheless, they could also be employed as starting materials in cycloadditions with alkenes such as enol ethers, benzofurans or indoles after reductive removal of the sulfur bridges by triphenylphosphine, probably affording intermediate 1,4-dipoles.[9] Diels−Alder reactions using 5-chloro-2(1*H*)-pyrazinones[10−12] and other piperazine-2,5-dione[13−15] derivatives as azadienes are also possible in an intramolecular fashion if the dienophile is tethered to the piperazine ring giving rise to tricyclic products. The latter cases have gained intensive interest since intramolecular Diels−Alder reactions have been postulated as a potential biosynthetic key step in the formation of pharmacologically active metabolites of fungi such as in VM55599 (**1**), sclerotamide (**2**), marcfortine (**3**), paraherquamide A and B (**4**), and brevianamide A (**5**).[14−20] Thus, the sequence depicted in Scheme 1 was proposed as the biosynthetic pathway to brevianamide A (**5**) but was recently questioned.[14,16,19] Despite all efforts, the 4 + 2 cycloaddition step could not be verified with the deoxybrevianamide E (**6**) or its dehydrogenation product **7**.

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† Dedicated to Prof. Dr. Barry M. Trost on the occasion of his 60th birthday.

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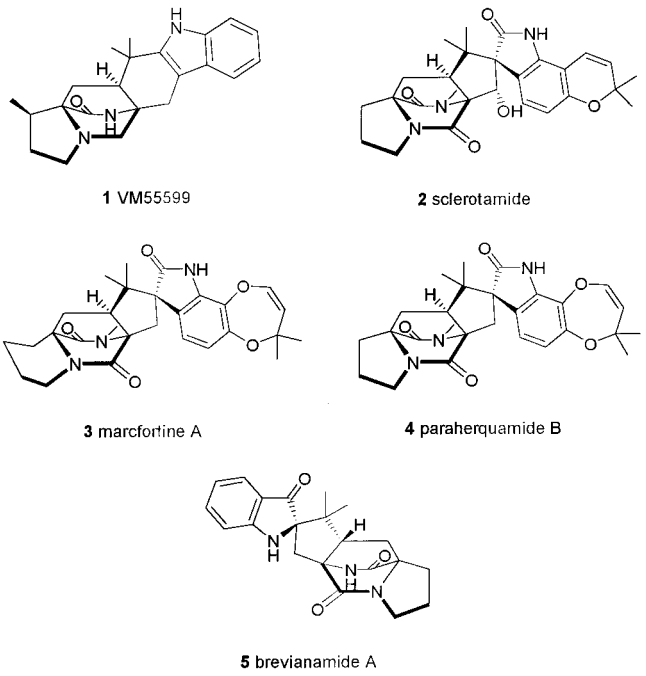
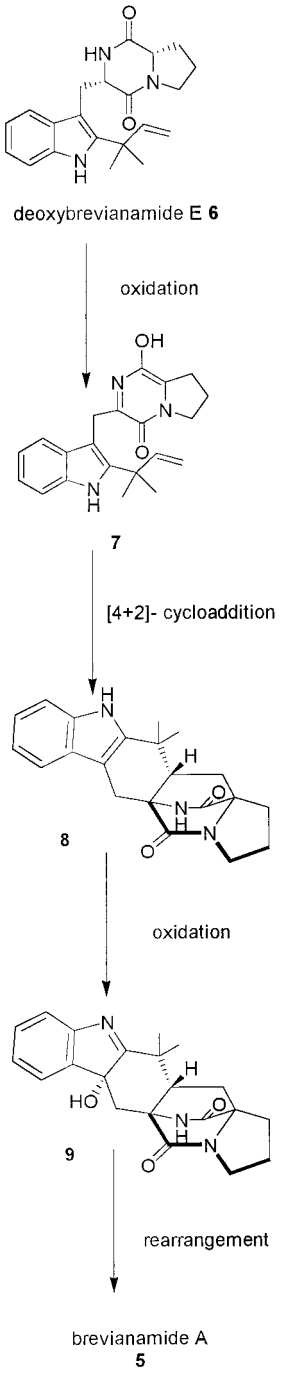


Recently, the Williams' group converted *epi*-deoxybrevianamide E (**10**) and the 3-ylidenepiperazine-2,5-dione **12** into diastereomeric mixtures of Diels−Alder adducts **15** (Scheme 2).[13,14,15a] The latter was utilized in the synthesis of racemic brevianamide B and VM55599. Both syntheses of **15** proceeded via 5-methoxy-2(1*H*)-pyrazinones **13,** which formed the azadiene moieties **14** by rearrangement with KOH. To find alternative and more stereoselective ways for achieving bicyclo[2.2.2]diazaoctane ring moieties as found in natural products **1**−**5** and related compounds, we investigated [4 + 2] cycloadditions starting from 3-ylidenepiperazine-2,5-diones **16** rather than from 5-hydroxy- or 5-alkoxy-2(1*H*)-pyrazinones. Although these compounds have been known to occur naturally for a long time and reveal an impressing synthetic potential, they have not been employed as azadienes in Diels−Alder reactions.[21] We wish to report the successful application of 3-ylidene-piperazines-2,5-diones **16** and **39** in intermolecular Diels−Alder reactions and 3-ylidene-piperazines-2,5-diones **30** and **32** in intramolecular Diels−Alder reactions. Since 5-acyloxy-2(*H*)-pyrazinones **17** may act as intermediates in such Diels−Alder processes, the transformation of **16** into **17** and further into cycloadducts **19**, **20**, and **27** was also investigated.

Scheme 1



Results and Discussion

The 3-ylidenepiperazine-2,5-diones **16** do not possess an azadiene system necessary for the envisaged Diels−Alder reaction. However, they should be able to tautomerize to 5-hydroxy-2(1*H*)-pyrazinones **22** [2,22] or to afford pyrazinium salts[22] with acids similar to 5-hydroxy-2(1*H*)-pyrazinones **22**, with the aza-nitrogen atom being protonated. Both species should be capable of serving as dienes in Diels−Alder reactions (Scheme 3). Since N-unsubstituted 3-ylidenepiperazine-2,5-diones have been reported to tautomerize into 2,5-dihydroxypiperazines in the presence of base,[2,23,24] we evaluated similar reaction conditions for N-monosubstituted compounds **16** in intermolecular cycloadditions. However, even the fairly reactive dieneophile, 1,1-diphenylethene, did not react. Therefore, acidic conditions were investigated. Refluxing the components **16** and 1,1-diphenylethene in formic acid worked reasonably well (see Table 1, entries 4, 6, and 9). Other acidic conditions such as HCl or the application of Lewis acids ($BF_3 \cdot Et_2O$) were not as effective. The use of acetyl chloride as a solvent under high-pressure conditions (10 kbar) was a useful alternative that was more efficient in some cases (compare entry 1 with 4 and 7 with 9). No cycloaddition was achieved with acetyl chloride at atmospheric pressure at room temperature,

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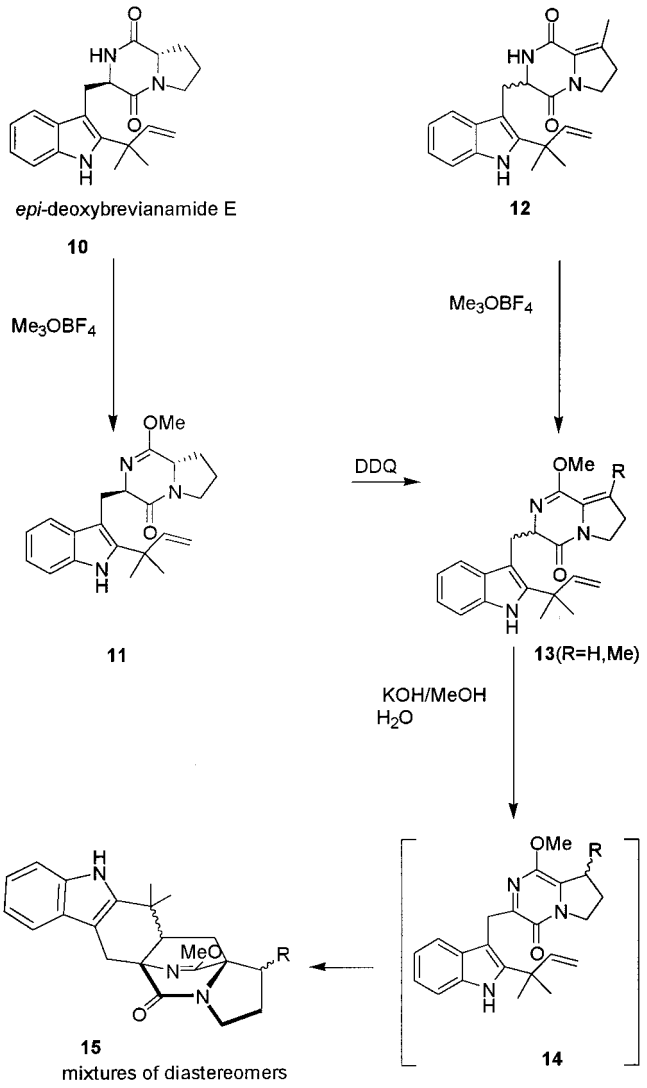
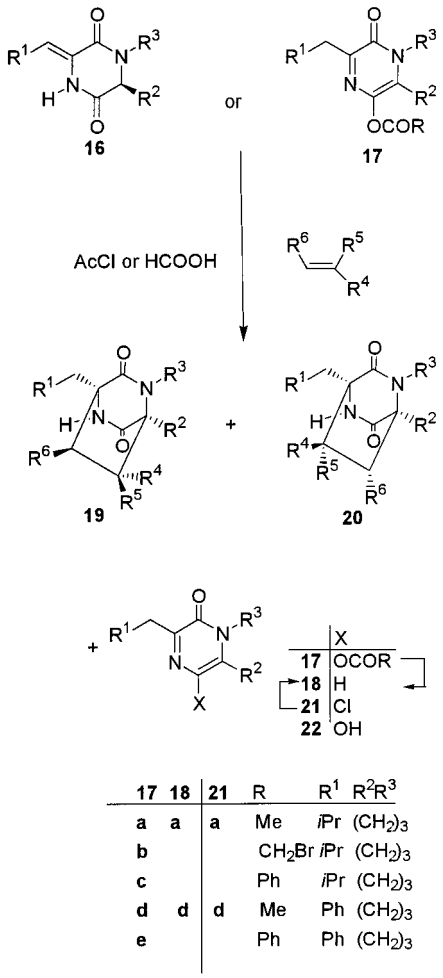
Scheme 2



Scheme 3



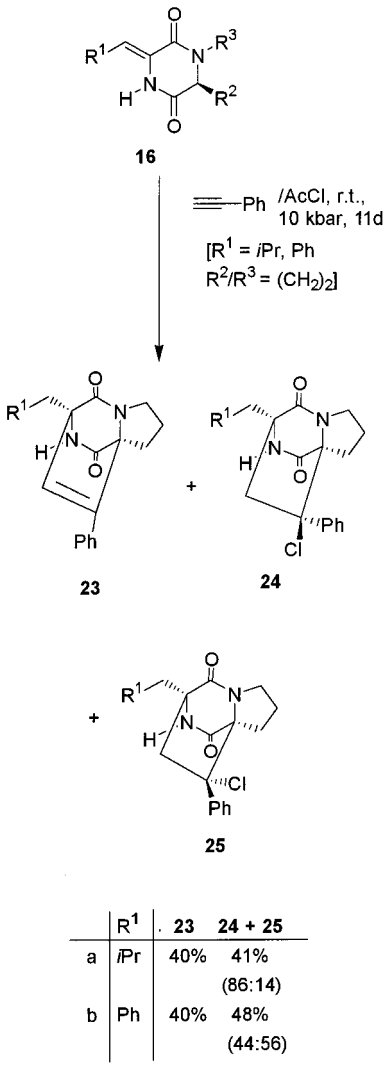
but 5-acetyloxypyrazine-2(1*H*)-ones **17** (R = Me) were formed instead (entries 3 and 8). Since these products possess a locked azadiene moiety, they can be expected as intermediates in the Diels−Alder reaction observed under high pressure. Consequently, we synthesized 5-acyloxy-2(1*H*)-pyrazinones **17** (vide infra) and submitted them to cycloadditions (Table 1, entries 11−15). Indeed, reflux of **17** in formic acid gave a better result than starting with a corresponding **16** (compare entry 9 with 11 and 12). Other alkenes such as cyclohexene (entries 5 and 16) did not react as well as 1,1-diphenylethene with **16** in acetyl chloride at room temperature while phenanthrene totally failed to undergo reaction. In all cases of Diels−Alder reactions of 1,1-diphe-

Table 1. Cycloadditions of 3-Ylidenepiperazine-2,5-diones 16 and 5-Acyloxy-2(1*H*)-pyrazinones 17 with Alkenes

									yield			
entry	R^1	R^2	R3	R^4	R^5	R^6	reactant	conditions	**17**[a]	**19**	**20**	**21**
1	*i*Pr	$(CH_2)_3$		Ph	Ph	H	**16a**	AcCl, rt, 10 kbar, 11 d	**a** (2)	**a** (73)	**a** (17)	**a** (5)
2							**16a**	AcCl, rt, 10 kbar, 6 d	**a** (10)	**a** (68)	**a** (15)	**a** (4)
3							**16a**	AcCl, rt, 6 d	**a** (85)[b]			
4							**16a**	HCO_2H, refl, 6 d		**a** (71)	**a** (28)	
5				H	$(CH_2)_4$		**16a**	AcCl, rt, 10 kbar, 10 d	**a** (70)	**b** (11)[c]		**a** (10)
6		H	H	Ph	Ph	H	**16b**	HCO_2H, refl, 7d		**c** (11)	**c** (12)	*d*
7	Ph	$(CH_2)_3$		Ph	Ph	H	**16c**	AcCl, rt, 10 kbar, 11 d		**d** (93)	**d** (7)	
8							**16c**	AcCl, rt, 6 d	**d** (91)			**d** (8)
9							**16c**	HCO_2H, refl, 5 d		**d** (63)	**d** (36)	
10							**16c**	CH_2Cl_2/BF_3Et_2O, 10 kbar, 6 d		**d** (8)[e]		
11							**17e**[f]	HCO_2H, refl, 18 h		**d** (84)	**d** (14)	
12							**17d**[a]	HCO_2H, refl, 18 h		**d** (89)	**d** (7)	
13							**17d**[a]	HCO_2H, rt, 10 kbar, 6 d		**d** (54)	**d** (9)	
14							**17d**[a]	$AcCl/HCl_{cat.}$, rt, 10 kbar, 6 d	**d** (10)	**d** (86)	**d** (3)	
15							**17e**[f]	HCO_2H, rt, 10 kbar, 6 d		**d** (51)		
16				H	$(CH_2)_4$		**16c**	AcCl, rt, 10 kbar, 11 d	**d** (60)	**e** (10)	**e** (15)[g]	**d** (11)[h]

[a] R = Me). [b] 14% recovered reactant **16**. [c] 11% of nonseparated mixture of **19b** + **20b** (89:11). [d] Low yields due to decomposition of products or starting material. [e] Recovery of 90% **16c**. [f] (R = Ph). [g] Inseparable 1:1 mixture with **19e**. [h] Additionally, 10% of pure **22a** (R^1 = Ph, $R^2/R^3 = (CH_2)_3$) was obtained.

Scheme 4

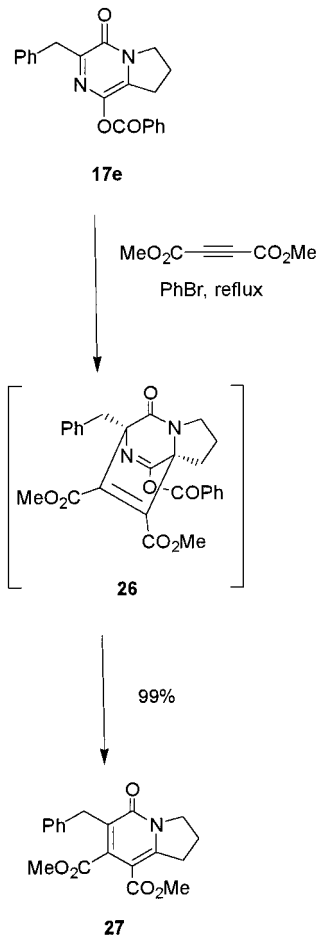


	R^1	23	24 + 25
a	*i*Pr	40%	41% (86:14)
b	Ph	40%	48% (44:56)

nylethene, mixtures of regioisomeric cycloadducts **19** (major isomer) and **20** were obtained. If acetyl chloride was used as the reaction medium partial substitution of the hydroxy group in intermediate **22** occurred to afford 5-chloro-2(1*H*)-pyrazinones **21** as byproducts. Attempts to utilize these compounds **21** in cycloadditions with 1,1-diphenylethene failed although other 5-chloro-2(1*H*)-pyrazinones have been reported to undergo Diels−Alder reactions.[5−8,10−12] Thus **21** does not act as an intermediate in the formation of cycloadducts **19** and **20** in acetyl chloride. The structures of products **19** and **20** were elucidated by X-ray crystal analysis of **19d**,**e** and **20d** (see the Supporting Information) and NMR investigations, such as HMQC and HMBC.

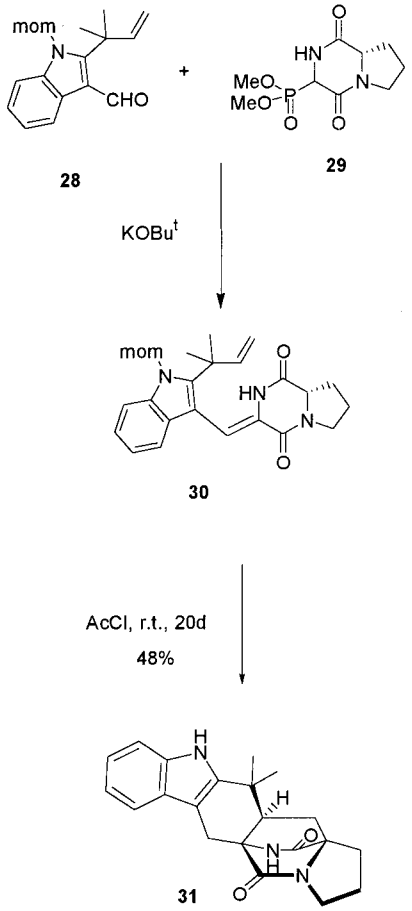
Cycloaddition reactions of 3-ylidenepiperazine-2,5-diones **16** were also possible with phenylacetylene in acetyl chloride under high pressure conditions (10 kbar) (Scheme 4). Only one regioisomer **23** was observed, which was accompanied by nonseparable epimeric mixtures of Markovnikov HCl adducts **24** and **25**. The total yields exceeded 80%. Neither acid catalysis nor high pressure was necessary for the cycloaddition of the 5-benzoyloxy-2(1*H*)-pyrazinone **17e** with dimethyl acetylenedicarboxylate (Scheme 5). The cycloadduct **26** could not be observed but formed the indolizinedicarboxylate in quantitative yield by formal elimination of benzoylcyanate.

Scheme 5

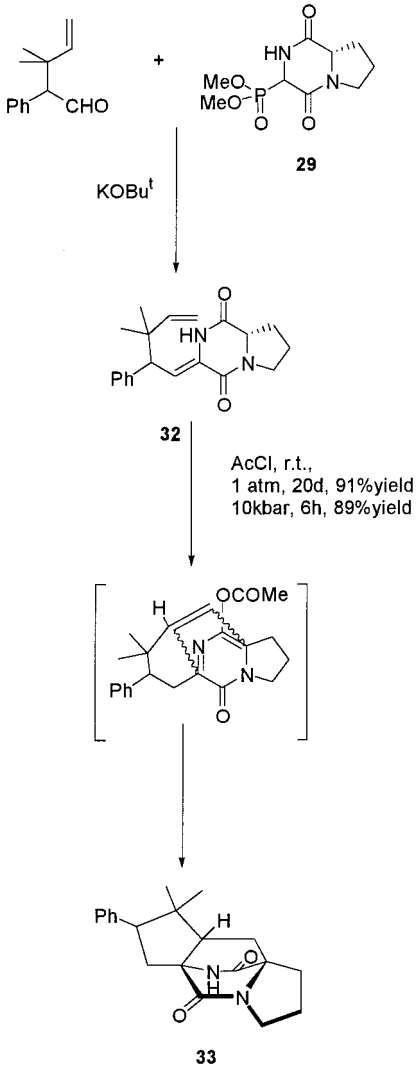


The conditions that proved successful in intermolecular cycloaddition (vide supra) were further applied to intramolecular cases. Remarkably, the MOM-protected 3-indolylmethylidenepiperazine-2,5-dione **30**, which should be able to form tautomeric 5-hydroxy-2(1*H*)-pyrazinone **7** proposed in the biosynthesis of brevianamide A (see Scheme 1) and other natural products **1**−**5**, gave a straightforward intramolecular Diels−Alder reaction to lead to the bicyclo[2.2.2]diazaoctane ring system **31** in 48% yield after merely standing in acetyl chloride at room temperature for 20 days (Scheme 6). The use of refluxing formic acid, $BF_3{\cdot}Et_2O$ in dichloromethane, even under high pressure, or refluxing in DMF/DMAP or aqueous KOH in methanol at room temperature were not successful. As compared with recently published biomimetic synthesis[13,15a] of analogues imidomethyl ethers **15** starting from *epi*-deoxybrevianamide E (**10**) or **12** (Scheme 2), our approach with **28** requires fewer steps. It is worth noting that only one stereoisomer **31** was observed. The stereochemical outcome of this reaction might be due to minimal steric repulsion of the substituents at the C−C double bond and the benzoyloxy group in the transition state, thus favoring the small hydrogen atom to the side of the benzoyloxy group similar to the intermediate shown in Scheme 7. This compound **31** was previously obtained by Williams and co-workers.[15b] The final proof for its structure was obtained by X-ray crystal analysis (see the Supporting Information). The configuration of **31** at the bridgehead carbon atoms is the same as in VM55599 (**1**), sclerotamide (**2**), marcfortine (**3**), and paraherquamides (**4**) but different from brevianamide A

Scheme 6



Scheme 7



(**5**). Our methodology should be particularly useful for the synthesis of these natural products.

As compared with 3-indolylmethylidenepiperazine-2,5-dione **30**, the double bond of 3-ylidenepiperazine-2,5-dione **32,** which could be used for intramolecular Diels–Alder reaction is fixed to the piperazine ring by a shorter tether. This led to the formation of a five membered ring rather than a six-membered ring fused to the bicyclo-[2.2.2]diazaoctane ring system. Excellent yields of the cycloadduct **33** were obtained with acetyl chloride at room temperature (Scheme 7). As previously noted, only one stereoisomer was observed.

The 5-acyloxy-2(*H*)-pyrazinones **17** are precursors or intermediates in the Diels–Alder reactions of piperazines (vide supra). Since only one member of this class of compounds was reported in the literature,[25] we have investigated their formation from 3-ylidenepiperazine-2,5-diones **16** in more detail (Scheme 8, Tables 1 and 2). Acid chlorides, bromides, and anhydrides proved to be useful acylating reagents. Base catalysis was necessary only in exceptional cases (Table 2, entry 8). In other cases (Table 2, entries 3 and 4) the presence of a base biased acylation to the ring nitrogen atom affording 4-acyl-3-ylidenepiperazine-2,5-diones **34**. Analogues **34** can be rearranged to *O*-acyl products **17** ($R^1 = {}^i$Pr, Ph; R = Ph) on being refluxed in toluene with ^{t}BuI[25] or benzoic acid/methanesulfonic acid (Scheme 8). If the 4-benzoyl-3-ylidenepiperazine-2,5-dione **34** was treated with thioacetic acid under radical conditions, a mixture of 5-acetylthio-2(1*H*)-pyrazinone **38a** and 5-benzoylthio-2(1*H*)-pyrazinone **38b** was unexpectedly obtained. The rationalization for this might be that the thioacetate adduct **35** is primarily formed by radical addition to the C–C double bond. The elimination of the mixed thioanhydride derived from benzoic acid and acetic acid forms an N-unsubstituted 3-ylidenepiperazine-2,5-dione **16**. Both products react with each other by acetylation or benzoylation of the oxygen atom at position 5 to produce thiobenzoate and thioacetate, respectively. These two thiocarboxylate anions substitute the acyloxy group of **36** and **37** forming a mixture of the final products **38a** and **38b**, respectively. The 2(1*H*)-pyrazinones with a sulfur functionality at position 5 have rarely been reported in the literature and were obtained by replacement of halo substituents by benzylthiolate.[26]

The 1,4-disubstituted 3-ylidenepiperazine-2,5-diones such as **39** are not able to form tautomers similar to **22** and thus cannot undergo Diels–Alder reactions in the same manner as N-unsubstituted 3-ylidenepiperazine-2,5-diones **16** (see Scheme 3). However, it has been shown that mesoionic isomers **43** possessing azadiene structures can be formed under acid conditions (Scheme 9). Primary

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Scheme 8

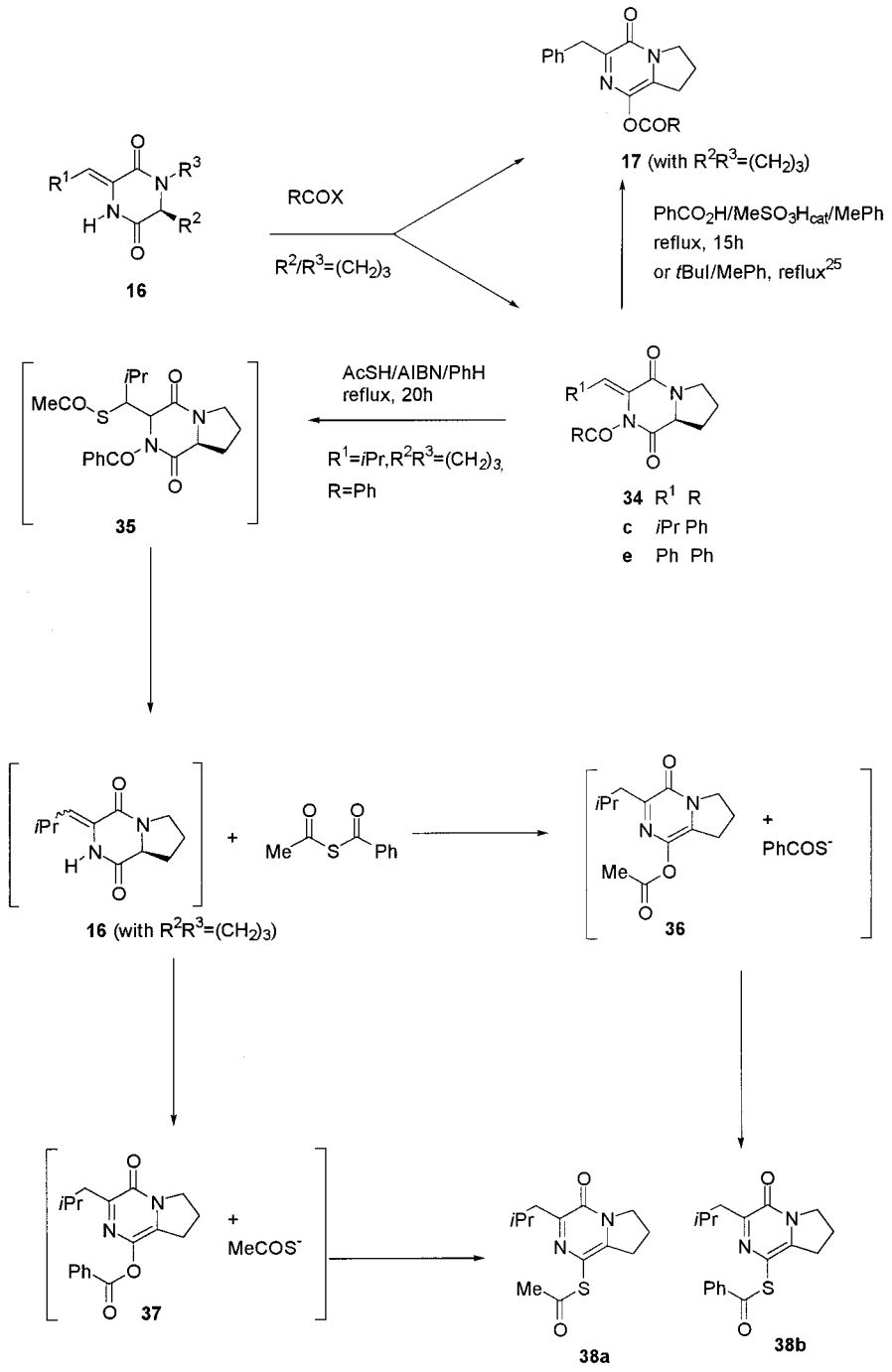


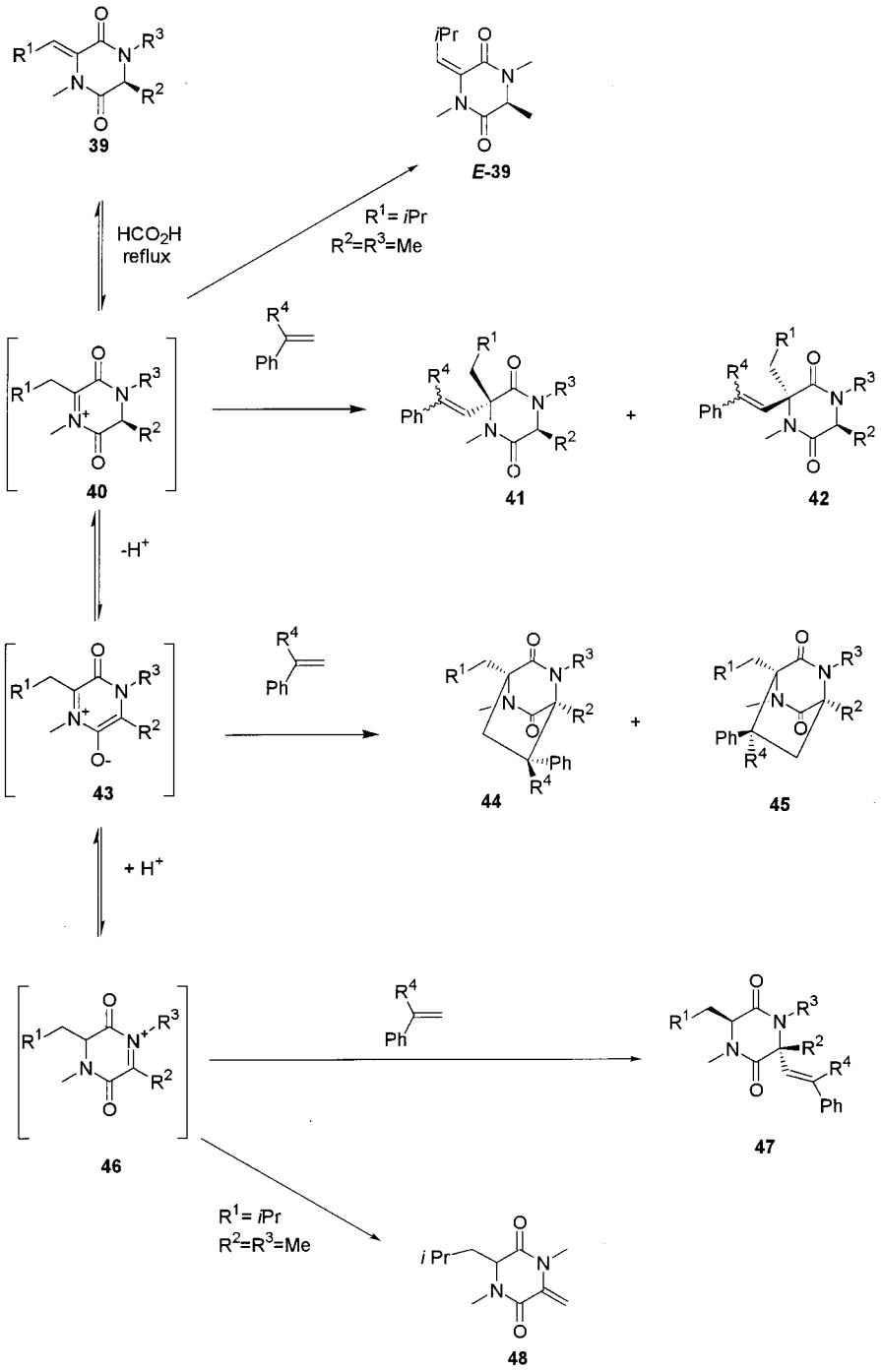
Table 2. Acylation of 3-Ylidenepiperazine-2,5-diones 16

entry	R^1	R	conditions	recovered reactant **16** (%)	**17** $R^2/R^3=(CH_2)_3$ (%)	**34** (%)
1	*i*-Pr	Me	AcCl as solvent, rt, 6 d	(14)	**a** (85)	
2		$BrCH_2$	3 equiv of $BrCH_2COBr$, CH_2Cl_2, rt, 4 d		**b** (80)	
3			3 equiv of $BrCH_2COBr$, DMF, 1 equiv of NaH, rt, 2 h		**b** (23)	**b** (31)
4		Ph	1.5 equiv of PhCOCl, CH_2Cl_2, 2 equiv of NEt_3, rt, 4 d			**c** (63)[a]
5[b]			1.1 equiv of PhCOCl, PhMe, reflux, 44 h	(31)	**c** (54)	**c** (19)[a]
6	Ph	Me	AcCl as solvent, rt, 6 d	(8)	**d** (91)	
7		Me	Ac_2O as solvent, HBr (62%, 0.5 mL), rt, 8 d	(14)	**d** (86)	
8		Ph	1.5 equiv of PhCOCl, CH_2Cl_2, 2 equiv of NEt_3, rt, 69 h		**e** (99)	

[a] Known compound.[29a] [b] See ref 25.

protonation of the enamine moiety of **39** affords piperazinium salts **40** (Scheme 9), which can react with nucleophiles, e.g., heteroaromatics at the iminium group forming 3,3-disubstituted piperazine-2,5-diones[27] or can

Scheme 9



act as intermediates in the rearrangement to 6-ylidenpiperazine-2,5-diones similar to **48**. An intermediate mesoionic compound **43** could be trapped by a Diels–Alder reaction with 1,1-diphenylethene affording a mixture of bicyclo[2.2.2]diazaoctane compounds **44** and **45**.[22] A similar case was observed in the N-unsubstituted series **16**.[22] More details of these reactions are reported here. Upon refluxing 4-methyl-3-ylidenepiperazine-2,5-diones **39** with alkenes in formic acid three types of products were formed, i.e., adducts to position 3 (**41**, **42**), cycloadducts (**44**, **45**), and adducts to position 6 (**47**). Usually mixtures were obtained, which could be separated by flash chromatography (Scheme 9, Table 3). In the case of 1,1-diphenylethene, the cycloaddition is a minor reaction as compared with Mannich-type addition reactions leading to **41** and **42** (Table 3, entries 2–5). Stepwise formation of cycloadducts **44** or **45** via adducts **41**, **42**, or **47** is unlikely since refluxing the adduct **41b** in formic acid did not initiate a cyclization but left the material unchanged. The reaction pathway from **39** (Scheme 9) is likely to start with protonation to piperazinium-2,5-diones **40**, which can electrophilically attack the alkene to afford optically active 3,3-disubstituted piperazine-2,5-diones **41** and **42**. As expected, the attack of the alkene occurs preferably anti with respect to substituent R^2, thus producing **41** as major products (Table 3). Alternatively, piperazinium-2,5-diones **40** can be deprotonated to mesoionic piperazines **43**, which undergo Diels–Alder reaction

(27) Jin. S.; Liebscher, J. *Synlett* **1999**, 459.

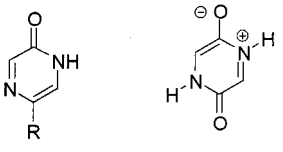
Table 3. Cycloadditions to 4-Methyl-3-ylidenepiperazine-2,5-diones 39

							products (yield, %)				
entry	reactant	R^1	R^2	R3	R^4	reflux	**41**	**42**	**44**	**45**	**47**
1	**39a**	H	$(CH_2)_3$		H	4.5 h	**a** (9)[a]		**a** (15)	**a** (27)[b]	
2	**39a**	H	$(CH_2)_3$		Ph	3 h	**b** (61)			**b** (21)	
3	**39b**	*i*Pr	$(CH_2)_3$		Ph	2 d	**c** (14)	**c** (14)	**c** (22)		
4[c]	**39c**	*i*Pr	Me	Me	Ph	7 d	**d** (52)	**d** (5)			**d** (10)
5	**39d**	Ph	$(CH_2)_3$		Ph	65 h	**e** (42)		**e** (3)	**e** (6)	

[a] Diastereomeric mixture **41a/42a** 87:13. [b] Diastereomeric mixture 73:27. [c] In addition, a mixture (14%) of *E*-isomer *E*-**39** and C=C bonds migration product **48** was produced.

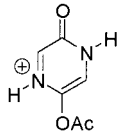
to racemic **44** and **45**. Protonation of **43** affords piperazinium-2,5-diones **46**, which are isomeric to **40,** and can add the alkene to position 6 leading to the formation of racemic 6,6-disubstituted piperazine-2,5-diones **47**. Evidence for intermediates **40**, **43**, and **46** was found in protonation and rearrangement experiments.[22] The stereoselective addition of diphenylethene to a 3-unsubstitued pyrazinium-2,5-dione obtained from a corresponding 3-methoxypiperazine-2,5-dione under acid conditions has been reported in the literature.[28,29] Since piperazine-2,5-diones can be hydrolyzed under acid conditions,[29] the 3,3-disubstituted piperazine-2,5-diones **41** and **42** are promising candidates for acid hydrolysis and lead to novel quaternary α-amino acids.

To shed some light on the nature of Diels−Alder reactions of piperazinones **16, 17**, **30**, **32**, and **39**, quantum chemical calculations (B3LYP[30a] using Gaussian 98[31]) were performed on model compounds **49**−**54**.

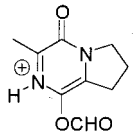


49 (R = OH)
50 (R = Cl)
51 (R = AcO)

52



53



54

Ab initio calculations revealed piperazinone moieties as electronically poor dienes. However, coefficients in the frontier orbitals are sometimes negligible or show unreasonable nodes at the central positions of the 2-azadiene subunit revealing the frontier orbital approach as not useful for these systems. Thus, ab initio calculations were performed to evaluate activation energies and free enthalpies for Diels−Alder reactions of these azadiene systems **49**−**54**(see Table 4). Interestingly, nonprotonated piperazin-2-ones **49**−**51** with an electronegative substituent (OH, Cl, AcO) at position 5 gave activation parameters comparable with those of the parent azadiene. However, the betaine **52** and protonated species **53** and **54** exhibit a remarkably lower activation energy, giving evidence for their suitability in Diels−Alder reactions as found in our practical investigations. As another interest-

Table 4. Calculated Activation Energies (B3LYP/6-31G*// B3LYP/6-31G*) of Diels−Alder Reactions of Azadiene Systems with Ethene

diene	Δ*E* (kcal/mol)	Δ*G* (kcal/mol)
2-azabutadiene[a]	19.5	31.5
pyrazinone, R = OH, **49**	15.0	27.4
pyrazinone, R = Cl, **50**	21.5	33.8
pyrazinone, R = AcO, **51**	22.1	34.4
betaine **52**	8.9	21.0
cation **53**	7.8	19.6

[a] s-cis conformer, for s-trans conformer see ref 30b.

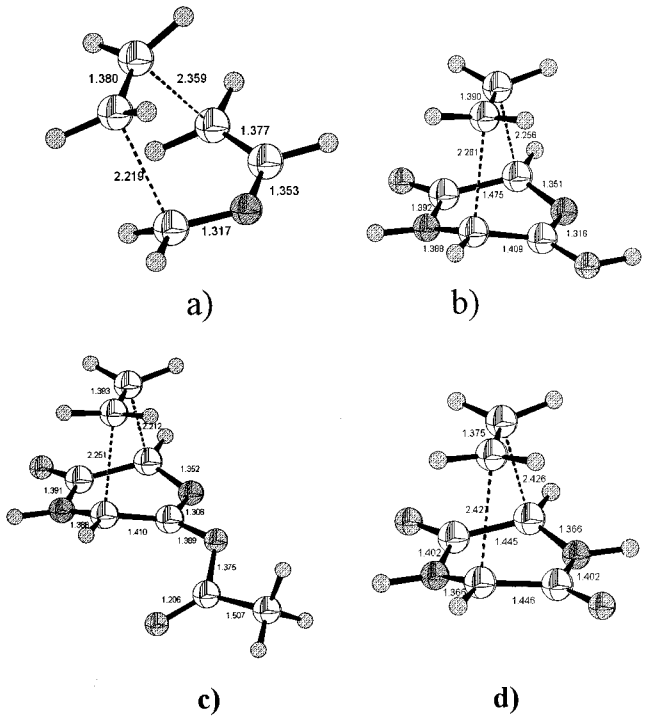


Figure 1. Transition states of Diels−Alder reactions of ethene with (a) 2-azabutadiene, (b) 5-hydroxypyrazinone **49**, (c) 5-acetoxypyrazinone **51**, and (d) betaine **52**.

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(30) (a) Parr, R. G.; Yang, W. *Density-Functional Theory of Atom and Molecules*; Oxford University Press: New York, 1989. (b) Avalos, M.; Babiano, R.; Clemente, F. R.; Cintas, P.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **2000**, *65*, 8251.

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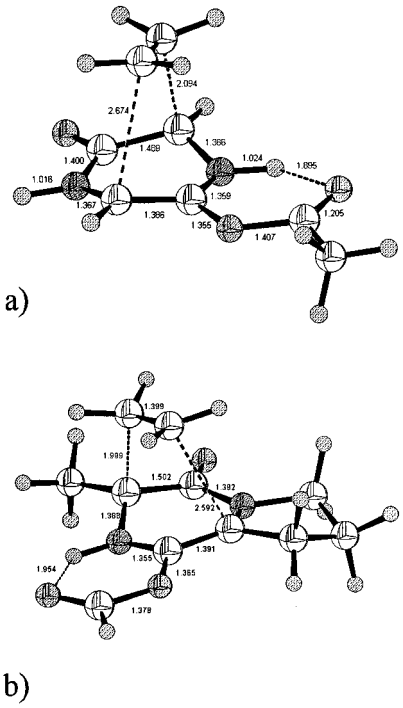

Figure 2. Transition states of Diels−Alder reactions of ethene with (a) 5-acetyloxypyrazinium salt **53** and (b) 5-formyloxypyrazinium salt **54**.

ing aspect of the quantum chemical results, uncharged piperazine-2-ones **49**−**51** show transition states with almost equal lengths of both C−C σ-bonds formed in the course of the Diels−Alder reaction, while protonated species **53** and **54** remarkable differ in these data (compare Figure 1 with Figure 2); i.e., cycloaddition of **53** and **54** tends toward a concerted asynchronous mechanism. Very recently, a DFT study of hetero-Diels−Alder reactions of 1,2-diazadienes was published.[30b]

In summary, we have demonstrated that 3-ylidenepiperazine-2,5-diones **16** and **39**, as well as 5-acyloxy-2(1*H*)-pyrazinones **17**, are useful reactants for Diels−Alder reactions to the piperazine ring. Intramolecular Diels−Alder reactions starting with 3-ylidene-piperazines-2,5-diones are useful for the synthesis of bicyclo-[2.2.2]octane ring systems found in some fungal metabolites such as VM55599 or brevianamide A. In this way, further evidence was found for the biosynthetic pathway to these products via intramolecular cycloaddition. Unlike the biomimetic pathways known so far, pyrazinones of suitable azadiene structure are formed via O-acylation rather than via O-alkylation.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, on a Bruker AC-300 in $CDCl_3$ with TMS as internal standard. 2D NMR experiments include ^{1}H−^{1}H-COSY, HMQC, and HMBC. Optical rotations were determined with a Perkin-Elmer polarimeter 241 (d = 2 mm). For preparative column chromatography silica (0.04−0.063 mm, Merck) was used. High-pressure reactions were performed in a piston-cylinder high-pressure apparatus for pressure up to 14 kbar, manufactured by Andreas Hofer Hochdrucktechnik GmbH, Mülheim/Ruhr, Germany, at room temperature using a 10 mL sealed Teflon tube. Starting materials **16** and **39** were obtained following or adopting literature procedures: **16a**,[29] **16b**,[22] **16c**,[29a] **17c**,[25] **34e**,[29a] **39a**,[32] **39b**,[22] **39c**,[22] **39d**.[29a]

Cycloaddition of 3-Ylidenepiperazine-2,5-diones 16 with 1,1-Diphenylethene in Formic Acid at Atmospheric Pressure Affording Cycloadducts 19 and 20 (See Table 1). General Procedure (Method A). A mixture of 3-ylidene-piperzine-2,5-diones **16** (0.5 mmol), styrene (521 mg, 5.0 mmol) or 1,1-diphenylethene (540 mg, 3.0 mmol), and formic acid (8 mL) was refluxed under argon. After the reaction mixture was evaporated in a vacuum, the residues were chromatographed.

10,10-Diphenyl-7-isobutyl-5,8-diazatricyclo[5.2.2.0^{1,5}]-undecane-6,9-dione (19a) and 11,11-Diphenyl-7-isobutyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undecane-6,9-dione (20a). Reactant: (*S*)-3-[(*Z*)-isobutylidene]-piperazine-2,5-dione **16a** (R_f = 0.09). Reflux, 6 days. EtOAc/hexane (1:1) for chromatography.

19a: yield 138 mg (71%); R_f = 0.48; colorless crystals; mp 246−247 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48 (m, 1H), 0.95 (d, J = 6.2 Hz, 3H), 0.98 (d, J = 6.2 Hz, 3H), 1.50 (m, 1H), 1.76−2.00 (m, 4H), 2.78 (m, 1H), 2.79 (d, J = 14.0 Hz, 1H), 2.91 (m, 1H), 3.01 (d, J = 14.0 Hz, 1H), 3.13 (m, 1H), 6.76 (m, 2H), 7.06 (s, 1H), 7.12−7.22 (m, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.0 (*C*H$_2$), 24.0 (*C*H), 24.3 [(*C*H$_3$)$_2$], 24.9 [(*C*H$_3$)$_2$], 27.2 (*C*H$_2$), 39.2 (*C*H$_2$), 44.1 (*C*H$_2$), 51.1 (*C*H$_2$), 56.7 (*C*), 61.6 (*C*), 72.9 (*C*), 126.5 (*C*H), 127.1 (*C*H), 127.8 (*C*H), 128.3 (*C*H), 128.9 (*C*H), 129.6 (*C*H), 144.8 (*C*), 147.4 (*C*), 170.0 (C=O), 173.4 (C=O); HRMS calcd for $C_{25}H_{29}N_2O_2$ 389.2229, found 389.2225 (M^+ + H). Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.19; H, 7.26; N, 7.16.

20a: yield 55 mg (28%); R_f = 0.37; colorless needles; mp 130 °C dec (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H), 1.34 (dd, J = 5.9, 15.0 Hz, 1H), 1.64−1.78 (m, 2H), 1.93 (m, 2H), 2.41 (dd, J = 6.6, 15.0 Hz, 1H), 2.63 (d, J = 14.2 Hz, 1H), 2.75 (m, 1H), 2.93 (d, J = 14.2 Hz, 1H), 3.40 (m, 1H), 3.51 (m, 1H), 6.15 (s, 1H), 6.92 (m, 2H), 7.10−7.20 (m, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.1 (*C*H$_2$), 24.2 (*C*H), 24.3 [(*C*H$_3$)$_2$], 24.4 [(*C*H$_3$)$_2$], 29.1 (*C*H$_2$), 36.4 (*C*H$_2$), 44.5 (*C*H$_2$), 51.1 (*C*H$_2$), 59.7 (*C*), 66.4 (*C*), 67.4 (*C*), 126.4 (*C*H), 126.8 (*C*H), 127.6 (*C*H), 128.0 (*C*H), 129.1 (*C*H), 130,1 (*C*H), 145.2 (*C*), 147.0 (*C*), 168.3 (C=O), 173.5 (C=O); HRMS calcd for $C_{25}H_{29}N_2O_2$ 389.2229, found 389.2231 (M^+ + H).

7,7-Diphenyl-4-isobutyl-1,2,5-trimethyl-2,5-diazabicyclo-[2.2.2]octane-3,6-dione (19c) and 7,7-Diphenyl-1-isobutyl-2,4,5-trimethyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (20c). Reactant: (*S*)-3-[(*Z*)-isobutylidene]-6-methylpiperazine-2,5-dione **16b** (R_f = 0.01). Reflux, 7 days. The residue was dissolved in DMF (∼1.5 mL) and chromatographed using EtOAc/hexane 1:1 as eluant to afford **19c** and **20c**.

19c: yield 20 mg (11%); R_f = 0.33; colorless needles; mp > 270 °C (EtOAc); ^{1}H NMR (300 MHz, CF_3COOD + $CDCl_3$) δ 0.88 (d, J = 6.0 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H), 1.40 (s, 3H), 1.81 (m, 3H), 2.77 (d, J = 14.6 Hz, 1H), 2.84 (d, J = 14.6 Hz, 1H), 6.83−6.87 (m, 2H), 7.13−7.17 (m, 8H), 7.68 (s), 8.04 (s); ^{13}C NMR (75.5 MHz, CF_3COOD + $CDCl_3$) δ 15.1 (*C*H$_3$), 23.2 [(*C*H$_3$)$_2$], 23.8 (*C*H), 24.1 [(*C*H$_3$)$_2$], 38.0 (*C*H$_2$), 49.9 (*C*H$_2$), 57.2 (*C*), 61.0 (*C*), 64.0 (*C*), 127.0 (*C*H), 127.6 (*C*H), 127.9 (*C*H), 128.3 (*C*H), 128.6 (*C*H), 129.4 (*C*H), 143.1 (*C*), 146.0 (*C*), 176.3 (C=O), 176.6 (C=O); HRMS calcd for $C_{23}H_{27}N_2O_2$ 363.2073, found 363.2075 (M^+ + H). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.91; H, 7.58; N, 7.66.

20c: yield 21 mg (11.6%); R_f = 0.28; colorless needles; mp >270 °C (EtOAc); ^{1}H NMR (300 MHz, CF_3COOD + $CDCl_3$) δ 0.76 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H), 1.49 (s, 3H), 1.73 (dd, J = 5.2, 14.5 Hz, 1H), 1.82 (m, 1H), 2.08 (dd, J = 7.9, 14.5 Hz, 1H), 2.59 (d, J = 14.7 Hz, 1H), 2.94 (d, J = 14.7 Hz, 1H), 6.86−6.89 (m, 2H), 7.09−7.15 (m, 8H), 7.93 (s), 8.13 (s); ^{13}C NMR (75.5 MHz, CF_3COOD + $CDCl_3$) δ 16.4 (*C*H$_3$), 22.7 [*C*H$_3$)$_2$], 23.8 [(*C*H$_3$)$_2$], 24.2 (*C*H), 35.0 (*C*H$_2$), 51.8 (*C*H$_2$), 57.2 (*C*), 58.7 (*C*), 67.1 (*C*), 127.3 (*C*H), 127.4 (*C*H), 128.1 (*C*H), 128.3 (*C*H), 128.9 (*C*H), 129.2 (*C*H), 143.9 (*C*), 144.5 (*C*), 175.2 (C=O), 176.3 (C=O); HRMS calcd for $C_{23}H_{27}N_2O_2$ 363.2073, found 363.2069 (M^+ + H). Anal. Calcd for $C_{23}H_{26}N_2O_2$; C, 76.21; H, 7.23; N, 7.73. Found: C, 75.88; H, 7.55; N, 7.61.

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7-Benzyl-10,10-diphenyl-5,8-diazatricyclo[5.2.2.0^{1,5}]-undecane-6,9-dione (19d) and 7-Benzyl-11,11-diphenyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undecane-6,9-dione (20d). Reactant: (*S*)-3-[(*Z*)-benzylidene]piperazine-2,5-dione **16c** (R_f = 0.24). Reflux, 5 days. Acetone/$CHCl_3$/hexane 1:2:3 as eluant.

19d: yield 133 mg (63%); R_f = 0.47; colorless crystals; mp 260−261 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.50 (m, 1H), 1.50 (m, 1H), 1.97 (m, 1H), 2.75 (d, J = 14.2 Hz, 1H), 2.82 (m, 1H), 2.90 (m, 1H), 2.97 (d, J = 14.3 Hz, 1H), 3.11 (d, J = 14.2 Hz, 1H), 3.15 (m, 1H), 3.55 (d, J = 14.3 Hz, 1H), 6.16 (s, 1H), 6.77 (m, 2H), 7.09−7.30 (m, 13H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.4 (*C*H$_2$), 27.6 (*C*H$_2$), 37.3 (*C*H$_2$), 44.6 (*C*H$_2$), 52.8 (*C*H$_2$), 57.3 (*C*), 61.8 (*C*), 73.8 (*C*), 127.0 (*C*H), 127.6 (*C*H), 127.9 (*C*H), 128.3 (*C*H), 128.8 (*C*H), 129.2 (*C*H), 129.3 (*C*H), 130.0 (*C*H), 131.1 (*C*H), 135.0 (*C*), 144.9 (*C*), 147.6 (*C*), 169.9 (C═O), 173.0 (C═O); HRMS calcd for $C_{28}H_{27}N_2O_2$ 423.2073, found 423.2073 (M^+ + H). Anal. Calcd for $C_{28}H_{27}N_2O_2$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.62; H, 6.21; N, 6.67.

20d: yield 76 mg (36%); R_f = 0.62; colorless crystals; mp 228−230 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (m, 1H), 1.90 (m, 2H), 2.71 (m, 1H), 2.75 (d, J = 14.2 Hz, 1H), 2.93 (d, J = 14.1 Hz, 1H), 2.98 (d, J = 14.2 Hz, 1H), 3.39 (m, 1H), 3.53 (m, 1H), 4.20 (d, J = 14.1 Hz, 1H), 5.23 (s, 1H), 6.62 (m, 2H), 7.04−7.30 (m, 13H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.8 (*C*H$_2$), 29.5 (*C*H$_2$), 33.2 (*C*H$_2$), 45.1 (*C*H$_2$), 51.6 (*C*H$_2$), 60.4 (*C*), 67.2 (*C*), 67.2 (*C*), 127.1 (*C*H), 127.5 (*C*H), 127.8 (*C*H), 128.3 (*C*H), 128.7 (*C*H), 129.4 (*C*H), 129.6 (*C*H), 130.7 (*C*H), 131.0 (*C*H), 135.4 (*C*), 145.7 (*C*), 147.0 (C), 168.7 (C═O), 172.6 (C═O); HRMS calcd for $C_{28}H_{27}N_2O_2$ 423.2073, found 423.2079 (M^+ + H). Anal. Calcd for $C_{28}H_{26}N_2O_2$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.33; H, 6.22; N, 6.60.

Cycloaddition of 3-Ylidenepiperazine-2,5-diones 16 with Dienophiles under High Pressure to Cycloadducts 19, 20, 23, 24, and 25 and Byproducts 17 and 21 (See Table 1). Cycloaddition in the Presence of BF_3·OEt_2 as Catalyst (Method B). A solution of (*S*)-3-(*Z*)-benzylidene-piperazine-2,5-dione **16c** (121 mg, 0.5 mmol) and 1,1-diphenylethene (135 mg, 0.75 mmol) in CH_2Cl_2 (3 mL) was reacted under high pressure (10 kbar) in the presence of BF_3·OEt_2 (70 mg, 0.5 mmol) for 6 days. The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL) after treatment with saturated aqueous $NaHCO_3$ (10 mL) at 0 °C. The organic phases were dried with Na_2SO_4 and then evaporated in a vacuum after removal of the Na_2SO_4. The residue was chromatographed with EtOAc/hexane (9:1) as eluant to afford adduct **19d** (18 mg, 8%) and (*S*)-3-(*Z*)-benzylidenepiperazine-2,5-dione **16c** (109 mg, 90%).

Cycloaddition in Acetyl Chloride (Method C). General Procedure. The mixture of 3-ylidenepiperzine-2,5-diones **16a**,**c** (0.5 mmol), dienophile (1 mmol), and AcCl (3 mL) were performed under high pressure (10 kbar) for a period of time. After removal of solvent and volatile materials under reduced pressure at 40 °C, the products were isolated by chromatography.

17a (see below), 19a, 19d, 20a, 20d. Reaction conditions and yields, see Table 1. For NMR spectra see above.

1-Chloro-3-isobutyl-7,8-dihydro-6*H*-pyrrolo[1,2-a]pyrazine-4-one (21a): R_f = 0.43 (EtOAc/hexane, 9:1) (reactant **16a** R_f = 0.30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.7 Hz), 2.11−2.25 (m, 3H), 2.59 (d, J = 7.2 Hz, 2H), 3.07 (t, J = 7.8 Hz, 2H), 4.10 (pseudo-t, J = 7.4 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9 (*C*H$_2$), 22.5 [(*C*H$_3$)$_2$], 26.9 (*C*H), 30.5 (*C*H$_2$), 41.3 (*C*H$_2$), 50.0 (*C*H$_2$), 121.1 (*C*), 137.5 (*C*), 155.1 (C═O), 157.0 (*C*); HRMS calcd for $C_{11}H_{15}ClN_2O$ 226.0879, found 226.0879.

8-Isobutyl-10,15-diazatetracyclo[6.5.2.0^{1,10}.0^{2,7}]pentadecane-9,14-dione (19b) and 20b. Reactant **16a**, the residue was subjected to column chromatography with (acetone/CH_2Cl_2/hexane 1:2:3) affording 1-chloro-3-isobutyl-7,8-dihydro-6*H*-pyrrolo[1,2-*a*]pyrazine-4-one (**21a**) (11 mg, 10%, R_f = 0.42) and an inseparable mixture (105 mg, R_f = 0.28) of 1-acetyloxy-3-isobutyl-7,8-dihydro-6*H*-pyrrolo[1,2-*a*]pyrazine-4-one (**17a**) (70%) and cycloadducts (**19b** and **20b**) (12%, 89:11). To remove byproduct **17a,** the mixture was hydrogenated in anhyd MeOH (4 mL), K_2CO_3 (75 mg, 0.57 mmol), and 10% Pd/C, 15 mg under atmospheric H_2 for 3 h. After removal of the catalyst by filtration through Celite 545, the filtrate was evaporated in a vacuum, and the residue was dissolved with CH_2Cl_2 (50 mL), washed with water (2 × 25 mL), and dried with Na_2SO_4. All solvent was removed under vacuum, and the residue was submitted to chromatography column with acetone/CH_2Cl_2 1:4. Sixteen milligrams (11%) of cycloadducts (**19b** and **20b**) (89:11, R_f = 0.42) was obtained as an amorphous solid, mp 149−154 °C.

8-Isobutyl-10,15-diazatetracyclo[6.5.2.0.^{1,10}0^{2,7}]pentadecane-9,14-dione (**19b**). Spectra recorded from the mixture of **19b** and **20b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 1.20−1.35 (m, 4H), 1.43 (dd, J =7.3, 14.6 Hz, 1H), 1.47 (m, 2H), 1.63−1.79 (m, 3H), 1.80 (dd, J = 4.7, 14.6 Hz, 1H), 1.89 (m, 2H), 2.05 (m, 1H), 2.63 (m, 1H), 3.34−3.49 (m, 2H), 5.95 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.7 (*C*H$_2$), 18.8 (*C*H$_2$), 20.8 (*C*H$_2$), 24.3 (*C*H$_2$), 24.4 (*C*H), 24.5 (CH$_3$), 24.8 (CH$_3$), 27.8 (*C*H$_2$), 37.3 (*C*H$_2$), 42.1 (*C*H), 42.8 (*C*H), 43.8 (*C*H$_2$), 64.9 (*C*), 69.6 (*C*), 169.7 (C═O), 172.3 (C═O); HRMS calcd for $C_{17}H_{26}N_2O_2$ 290.1994, found 290.1994. Anal. Calcd for $C_{17}H_{26}N_2O_2$ C, 70.31; H, 9.02; N, 9.65. Found: C, 70.22; H, 8.94; N, 9.47.

(2*S*,7*R*)-8-Benzyl-10,15-diazatetracyclo[6.5.2.0.^{1,10}0^{2,7}]-pentadecane-9,14-dione (**19e**), 1-Chloro-3-benzyl-7,8-dihydro-6*H*-pyrrolo[1,2-*a*]pyrazine-4-one (**21d**), and 3-Benzyl-7,8-dihydro-6*H*-pyrrolo[1,2-*a*]pyrazine-4-one (**18a**). Reactant **16c**, column chromatography with acetone/CH_2Cl_2/hexane 1:2:3 afforded 1-acetyloxy-3-benzyl-7,8-dihydro-6*H*-pyrrolo[1,2-*a*]pyrazine-4-one (**17d**) (85 mg, 60%, R_f = 0.26) and an inseparable mixture (56 mg, R_f = 0.39) of **21d** (11%) and cycloadducts (**19e** and **20e**) (26%, 69:31). For removal of the chloropyrazinone **21d** it was transformed into **18a** by hydrogenation of the mixture in anhyd MeOH (4 mL), K_2CO_3 (17 mg, 0.13 mmol), and 10% Pd/C (5 mg) under normal pressure for 3 h. The mixture was filtered through Celite 545, the filtrate was evaporated in a vacuum, and the residue was dissolved in CH_2Cl_2 (50 mL), washed with water (2 × 25 mL), and dried with Na_2SO_4. After evaporation under vacuum, the residue was subjected to a longer chromatography column (70 cm, EtOAc/hexane 7:3) affording pure cycloadduct **19e** (16 mg, 10%, R_f = 0.36), a mixture of cycloadducts (**19e** and **20e**) (25 mg, 15%, 1:1, R_f = 0.32), and **18d** (12 mg, 10%, R_f = 0.26).

18d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (m, 2H), 2.99 (t, J = 7.6 Hz, 2H), 4.03 (m, 4H), 7.11−7.35 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5 (*C*H$_2$), 29.4 (*C*H$_2$), 39.2 (*C*H$_2$), 48.6 (*C*H$_2$), 118.4 (*C*H), 126.4 (*C*H), 128.3 (*C*H), 129.1 (*C*), 129.4 (*C*H), 140.9 (*C*), 155.2 (*C*), 155.5 (C═O); HRMS calcd for $C_{14}H_{14}N_2O$ 226.1106, found 226.1108.

19e: colorless crystals; mp 195−196 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (m, 1H), 1.35 (m, 4H), 1.60−1.82 (m, 4H), 1.83−2.08 (m, 4H), 2.57 (m, 1H), 2.80 (d, J = 14.1 Hz, 1H), 3.33−3.49 (m, 2H), 3.55 (d, J = 14.1 Hz, 1H), 5.49 (s, 1H), 7.12−7.37 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.7 (*C*H$_2$), 18.8 (*C*H$_2$), 19.3 (*C*H$_2$), 21.0 (*C*H$_2$), 24.4 (*C*H$_2$), 27.9 (*C*H$_2$), 33.2 (*C*H$_2$), 41.5 (*C*H), 42.9 (*C*H), 43.9 (*C*H$_2$), 64.8 (*C*), 69.8 (*C*), 127.3 (CH), 128.8 (CH), 130.9 (CH), 135.3 (C), 169.4 (C═O), 171.8 (C═O); HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1835. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H,7.46; N, 8.63. Found: C, 74.00; H, 7.41; N, 8.66.

21d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (m, 2H), 2.97 (t, J = 7.8 Hz, 2H), 3.95 (s, 2H), 4.00 (t, J = 7.5 Hz, 2H), 7.03−7.31 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9 (*C*H$_2$), 30.5 (*C*H$_2$), 39.2 (*C*H$_2$), 50.1 (*C*H$_2$), 121.2 (*C*), 126.6 (*C*H), 128.4 (*C*H), 129.5 (*C*H), 137.1 (*C*), 138.5 (*C*), 154.7 (C═O), 155.4 (*C*); HRMS calcd for $C_{14}H_{13}N_2O$ 260.0716, found 260.0719.

7-Isobutyl-10-phenyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undec-10-ene-6,9-dione (23a) and 10-Chloro-7-isobutyl-10-phenyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undecane-6,9-dione (24a and 25a). Reactant **16a**, chromatography with acetone/CH_2Cl_2 1:8, afforded 62 mg (40%) **23a** (R_f = 0.29) and 71 mg (41%) of a inseparable mixture of **24a** and **25a** (86:14) (R_f = 0.45).

23a: colorless needle crystals; mp 194−196 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 6.3 Hz, 6H), 1.91−2.07 (m, 5H), 2.18 (m, 1H), 2.87 (m, 1H), 3.13 (m, 1H), 3.56 (m, 1H), 6.65 (s, 1H), 7.17 (m, 2H), 7.25 (s, 1H), 7.29−

7.40 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.8 (*C*H_3), 24.0 (*C*H_3), 24.5 (*C*H), 25.1 (*C*H_2), 26.2 (*C*H_2), 37.1 (*C*H_2), 43.3 (*C*H_2), 64.3 (*C*), 73.0 (*C*), 127.2 (2 *C*H), 128.2 (*C*H), 128.6 (2 *C*H), 134.8 (*C*), 135.4 (*C*H), 151.6 (*C*), 169.2 (C=O), 173.5 (C=O); HRMS calcd for $C_{19}H_{22}N_2O_2$ 310.1681, found 310.1680. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.53; H, 7.21; N, 8.98.

24a/**25a.** Amorphous solid, mp 190−200 °C (CH_2Cl_2/hexane). Spectrum recorded from the mixture of **24a** and **25a**.

24a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53 (m, 1H), 1.00 (d, J = 6.3 Hz, 3H), 1.02 (d, J = 6.3 Hz, 3H), 1.51 (m, 1H), 1.65 (m, 1H), 1.79 (dd, J = 6.0, 13.7 Hz, 1H), 1.90 (m, 1H), 1.95 (dd, J = 5.0, 13.7 Hz, 1H), 2.58 (m, 1H), 2.86 (d, J = 15.1 Hz, 1H), 2.99 (m, 1H), 3.00 (d, J = 15.1 Hz, 1H), 3.22 (m, 1H), 6.53 (s, 1H), 7.27−7.41 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.7 (*C*H_2), 24.0 (*C*H_3), 24.1 (*C*H_3), 24.7 (*C*H), 25.3 (*C*H_2), 38.7 (*C*H_2), 45.1 (*C*H_2), 51.4 (*C*H_2), 61.4 (*C*), 71.8 (*C*), 75.5 (*C*), 127.6 (2 *C*H), 128.5 (2 *C*H), 128.8 (*C*H), 138.6 (*C*), 169.1 (C=O), 170.8 (C=O); HRMS calcd for $C_{19}H_{23}ClN_2O_2$ 346.1448, found 346.1441. Anal. Calcd for $C_{19}H_{23}ClN_2O_2$: C, 65.79; H, 6.68; N, 8.08. Found: C, 65.87; H, 6.72; N, 8.00.

7-Benzyl-10-phenyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undec-10-ene-6,9-dione (23b), 10-Chloro-7-benzyl-10-phenyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undecane-6,9-dione (24b), and (±)-10-Chloro-7-benzyl-10-phenyl-5,8-diazatricyclo[5.2.2.0^{1,5}]-undecane-6,9-dione (25b). Reactant **16c**, chromatography acetone/CH_2Cl_2 1:8, afforded 70 mg (40%) of **23b** (R_f = 0.33) and 92 mg (48%) of a nonseparable mixture of **24b**/**25b** (24:56) (R_f = 0.47).

23b: colorless needle crystals; mp 217−219 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (m, 3H), 2.71 (m, 1H), 3.04 (m, 1H), 3.33 (d, J = 14.9 Hz, 1H), 3.38 (d, J = 14.9 Hz, 1H), 3.46 (m, 1H), 6.50 (s, 1H), 6.52 (s, 1H), 6.95−6.99 (m, 2H), 7.10−7.28 (m, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.2 (*C*H_2), 26.3 (*C*H_2), 35.1 (*C*H_2), 43.5 (*C*H_2), 64.2 (*C*), 73.5 (*C*), 127.2 (2 *C*H), 127.5 (*C*H), 128.3 (*C*H), 128.6 (2 *C*H), 129.1 (2 *C*H), 130.2 (2 *C*H), 134.5 (*C*), 134.8 (*C*), 135.3 (*C*H), 151.9 (*C*), 168.8 (C=O), 173.2 (C=O); HRMS calcd for $C_{22}H_{20}N_2O_2$ 344.1525, found 344.1513. Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.44; H, 6.17; N, 8.13.

24b/**25b.** After recrystallization from CH_2Cl_2, the ratio of **24b**/**25b** reached 10:90: amorphous solid; mp 220−230 °C (CH_2Cl_2/hexane). Anal. Calcd for $C_{22}H_{21}ClN_2O_2$ (380.87): C, 69.38; H, 5.56; N, 7.36; Cl, 9.31. Found: C, 69.31; H, 5.59; N, 7.38; Cl, 9.40.

Spectra were taken from the mixture.

24b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53 (m, 1H), 1.52 (m, 1H), 1.64 (m, 1H), 2.56 (m, 1H), 2.85 (d, J = 15.4 Hz, 1H), 2.95 (d, J = 15.4 Hz, 1H), 3.03 (m, 1H), 3.09 (d, J = 14.6 Hz, 1H), 3.21 (m, 1H), 3.44 (d, J = 14.6 Hz, 1H), 6.35 (s, 1H), 7.17−7.40 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.8 (*C*H_2), 25.3 (*C*H_2), 36.5 (*C*H_2), 45.2 (*C*H_2), 52.2 (*C*H_2), 61.1 (*C*), 71.7 (*C*), 75.9 (*C*), 127.6 (2 *C*H), 128.4 (*C*H), 128.5 (2 *C*H), 128.8 (*C*H), 129.0 (2 *C*H), 129.1 (2 *C*H), 134.2 (*C*), 138.5 (*C*), 168.8 (C=O), 169.7 (C=O).

25b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (m, 1H), 2.06 (m, 1H), 2.20 (m, 1H), 2.42 (m, 1H), 2.90 (d, J = 15.0 Hz, 1H), 3.00 (d, J = 14.5 Hz, 1H), 3.13 (d, J = 15.0 Hz, 1H), 3.46 (m, 1H), 3.49 (d, J = 14.5 Hz, 1H), 3.69 (m, 1H), 6.60 (s, 1H), 7.19−7.41 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.5 (*C*H_2), 26.1 (*C*H_2), 36.3 (*C*H_2), 45.6 (*C*H_2), 53.3 (*C*H_2), 59.9 (*C*), 76.8 (*C*), 77.3 (*C*), 126.9 (2 *C*H), 127.8 (*C*H), 128.4 (2 *C*H), 128.6 (*C*H), 129.2 (2 *C*H), 130.5 (2 *C*H), 134.1 (*C*), 139.7 (*C*), 168.8 (C=O), 170.4 (C=O).

Cycloaddition of 5-Acyloxy-2(1*H*)-Pyrazinones 17 with Dienophiles to Cycloadducts 19, 20, and 27 (See Table 1, Scheme 5). Cycloaddition of 5-Acyloxy-2(1*H*)-pyrazinones with 1,1-Diphenylethene. The cycloadditions of 5-acyloxy-2(1*H*)-pyrazinones **17d** or **17e** (0.5 mmol) with 1,1-diphenylethene (540 mg, 3 mmol) were performed under the conditions that are listed in Table 1 following the procedures for cycloadditions of 3-ylidenepiperazine-2,5-diones **16** (vide supra). After the reaction mixture was evaporated in a vacuum, the residue was chromatographed (Me_2CO/$CHCl_3$/hexane 1:2:3).

Cycloaddition of 5-Acyloxy-2(1*H*)-pyrazinone 17e with Dimethyl Acetylenedicarboxylate to 6-Benzyl-7,8-dimethoxycarbonyl-5-oxo-1,2,3,5-tetrahydroindolizine (27). A solution of **17e** (R = Ph) (173 mg, 0.5 mmol) and dimethyl acetylenedicarboxylate (142 mg, 1 mmol) in bromobenzene (12 mL) was refluxed under argon for 2 days and then evaporated in a vacuum. The residue was chromatographed (EtOAc/hexane 2:1, **17e** R_f = 0.21) to yield 169 mg (99%) of **27** (R_f = 0.29): colorless crystals; mp 162−163 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (m, 2H), 3.40 (t, J = 7.9 Hz, 2H), 3.73 (s, 3H), 3.74 (s, 2H), 3.79 (s, 3H), 4.04 (t, J = 7.5 Hz, 2H), 7.06 (m, 1H), 7.14 (m, 2H), 7.24 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5 (*C*H_2), 33.6 (*C*H_2), 34.6 (*C*H_2), 49.7 (*C*H_2), 52.1 (*C*H_3), 52.5 (*C*H_3), 102 (*C*), 126.2 (*C*H), 126.6 (*C*), 128.1 (*C*H), 129.0 (*C*H), 138.6 (*C*), 142.3 (*C*), 155.8 (*C*), 161.1 (*C*=O), 164.6 (*C*O_2Me), 167.8 (*C*O_2Me); HRMS calcd for $C_{19}H_{19}NO_5$ 341.1263, found 341.1264. Anal. Calcd for $C_{19}H_{19}NO_5$ C, 66.84; H, 5.61; N, 4.10. Found: C, 67.04; H, 5.65; N, 4.16.

Intramolecular Cycloaddition of 3-Ylidenepiperazine-2,5-diones 30 and 32 to 31 and 33 (1*S*,13*R*,15*R*)-12,12-dimethyl-10,19,21-triazahexacyclo[13.5.2.0.^{1,13}0.^{3,11}0.^{4,9} 0^{15,19}]-docosa-3(11),4,6,8-tetraene-20,22-dione (31). (*S*)-3-[2-(1,1-Dimethylallyl)-1-methoxymethylindole-3-ylmethylidene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**30**) (393 mg, 1 mmol) was dissolved in acetyl chloride (20 mL) and stirred under argon at room temperature for 20 days during which time some cycloadduct **31** precipitated. The reaction mixture was concentrated under vacuum at 40 °C. The residue was chromatographed (acetone/CH_2Cl_2 1:4) to afford 170 mg (48%) of cycloadduct **31** (R_f = 0.28) as an amorphous solid, mp >270 °C, and 57 mg (16%) of the deprotected starting material **30** (R_f = 0.40). Some cycloadduct **31** was lost during the beginning of chromatography by the formation of deeply colored oxidation products: ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6, 1:1) δ 1.02 (s, 3H), 1.29 (s, 3H), 1.81−2.01 (m, 4H), 2.09 (dd, J = 10.3, 13.3 Hz, 1H), 2.46 (dd, J = 4.7, 10.3 Hz, 1H), 2.61 (m, 1H), 2.72 (d, J = 15.5 Hz, 1H), 3.30 (m, 1H), 3.36 (m, 1H), 3.50 (d, J = 15.5 Hz, 1H), 6.92−7.04 (m, 2H), 7.25 (d, J = 7.7 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 8.67 (s, 1H), 10.56 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$ + DMSO-d_6, 1:1) δ 21.7 (*C*H_3), 23.9 (*C*H_2), 24.2 (*C*H_2), 28.1 (*C*H_3), 28.9 (*C*H_2), 30.5 (*C*H_2), 34.6 (*C*), 43.6 (*C*H_2), 49.3 (*C*H), 59.8 (*C*), 66.0 (*C*), 103.4 (C), 110.7 (CH), 117.6 (CH), 118.2 (CH), 120.6 (CH), 126.5 (C), 136.5 (C), 140.5 (C), 168.6 (C=O), 173.1 (C=O); HRMS calcd for $C_{21}H_{23}N_3O_2$ 349.1790, found 349.1784.

10,10-Dimethyl-11-phenyl-3,13-diazatetracyclo-[5.5.2.0^{1,9}.0^{3,7}]tetradecane-2,14-dione (33). A mixture of (8a*S*)-3(*Z*)-(3,3-dimethyl-2-phenyl-4-pentenylidene)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione **(32)** (162 mg, 0.5 mmol) and acetyl chloride (5 mL) was reacted under high pressure (10 kbar) for 6 h or under atmospheric pressure at room temperature for 20 days. After evaporation of volatile materials at 5mbar and 40 °C, the products were isolated by chromatography with acetone/CH_2Cl_2 1:2 in yields of 90% (high pressure) or 91% (normal pressure): R_f = 0.53 (starting material **32**, R_f = 0.71); colorless needles; mp > 270 °C (DMSO-d_6/CH_2Cl_2/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6, 3:1) δ 0.55 (s, 3H), 0.81 (s, 3H), 1.65 (dd, J = 7.5, 13.0 Hz, 1H), 1.73−1.94 (m, 4H), 2.07 (dd, J = 7.5, 10.2 Hz, 1H), 2.13 (dd, J = 9.4, 13.9 Hz, 1H), 2.58 (m, 1H), 2.83 (dd, J = 10.2, 13.9 Hz, 1H), 2.91 (dd, J = 9.4, 10.2 Hz, 1H), 3.31 (t, J = 6.7 Hz, 2H), 7.11−7.23 (m, 5H), 8.55 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$ + DMSO-d_6, 3:1) δ 16.4 (*C*H_3), 24.4 (*C*H_2), 27.1 (*C*H_3), 28.5 (*C*H_2), 28.6 (*C*H_2), 29.7 (*C*H_2), 43.2 (*C*), 43.5 (*C*H_2), 55.6 (*C*H), 57.4 (*C*H), 66.9 (*C*), 68.5 (*C*), 126.2 (*C*H), 127.4 (2 *C*H), 128.7 (2 *C*H), 138.8 (*C*), 170.2 (C=O), 172.8 (C=O); HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1840. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 74.3; H, 7.42; N, 8.60.

Reactions of 4-Methyl-3-ylidenepiperzine-2,5-diones 39 with Dienophiles to Cycloadducts 44 and 45 and Adducts 41, 42, and 47 (See Table 3). A similar procedure was used as for the cycloadditions of 3-ylidenepiperazine-2,5-diones **16** in HCOOH (method A).

2,3-Dimethyl-3(*E*)-styryl-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (41a), 7,8-Dimethyl-10-phenyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undecane-6,9-dione (44a), and 7,8-Dimethyl-11-phenyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undecane-6,9-dione (45a). Entry 1, reaction of **39a** and styrene gave a mixture of **41a**, **44a**, and **45a** after 4.5 h of reflux, which was separated by 2-fold column chromatography (EtOAc/hexane 9:1, reactant **39a** R_f = 0.23). **41a**: yield 12 mg (8.5%); R_f = 0.42; oil; dr = 87:13, not separable, spectra were recorded from mixture. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (s, 3H), 1.74 (m, 1H), 1.89−2.00 (m, 2H), 2.33 (m, 1H), 2.98 (s, 3H), 3.50 (m, 2H), 3.95 (m, 1H), 6.00 (d, J = 16.0 Hz, 1H), 6.20 (d, J = 16.0 Hz, 1H), 7.09−7.28 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.0 (*C*H$_2$), 23.4 (*C*H$_3$), 29.7 (*C*H$_3$), 30.2 (*C*H$_2$), 46.9 (*C*H$_2$), 59.0 (*C*H), 67.4 (*C*), 127.5 (*C*H), 127.9 (*C*H), 129.1 (*C*H), 129.5 (*C*H), 129.7 (*C*H), 137.5 (*C*), 167.0 (C=O), 170.1 (C=O); HRMS calcd for $C_{17}H_{20}N_2O_2$ 284.1525, found 284.1525. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.42; H, 7.15; N, 9.59.

44a: yield 21 mg (14.8%); R_f = 0.39; colorless crystals; mp 196−197 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (m, 1H, NCH$_2$C*H*$_2$), 1.57 (s, 3H, C*H*$_3$C), 1.45−1.63 (m, 2H, NCH$_2$C*H*$_2$C*H*$_2$), 1.99 (dd, J = 14.1, 4.8 Hz, 1H, PhCHC*H*$_2$), 2.45 (dd, J = 14.1, 10.3 Hz, 1H, PhCHC*H*$_2$), 2.54 (m, 1H, NCH$_2$-CH$_2$C*H*$_2$), 2.90 (s, 3H, C*H*$_3$N), 3.04 (dd, J =10.3, 4.8 Hz, 1H, PhC*H*CH$_2$), 3.13 (m, 1H, NC*H*$_2$), 3.30 (m, 1H, NC*H*$_2$), 7.02 (m, 2H, Ph), 7.24 (m, 3H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.7 (*C*H$_3$C), 23.7 (NCH$_2$*C*H$_2$), 27.0 (NCH$_2$CH$_2$*C*H$_2$), 27.2 (*C*H$_3$N), 42.2 (PhCH*C*H$_2$), 44.8 (N*C*H$_2$), 44.9 (Ph*C*HCH$_2$), 62.3 (CH$_3$*C*), 70.7 (NCH$_2$CH$_2$CH$_2$*C*), 127.7 (CH, Ph), 128.6 (CH, Ph), 128.8 (CH, Ph), 139.5 (C, Ph), 169.4 (C=O), 172.2 (C=O); HRMS calcd for $C_{17}H_{20}N_2O_2$ 284.1525, found 284.1520.

45a: yield 38 mg (26.8%); R_f = 0.37; colorless crystals; mp 167−168 °C (EtOAc/hexane); dr =73:27, not separable, spectra were recorded from the mixture. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.80 (m, 1H), 1.94 (m, 2H), 2.01 (dd, J = 13.8, 4.9 Hz, 1H), 2.33 (dd, J = 13.8, 10.3 Hz, 1H), 2.64 (s, 3H), 2.81 (m, 1H), 2.99 (dd, J = 10.3, 4.9 Hz, 1H), 3.43 (m, 2H), 6.95 (m, 2H), 7.22 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.6 (*C*H$_3$), 24.4 (*C*H$_2$), 28.7 (*C*H$_3$), 29.6 (*C*H$_2$), 39.2 (*C*H$_2$), 44.2 (*C*H$_2$), 48.5 (*C*H), 65.9 (*C*), 66.4 (*C*), 127.5 (*C*H), 128.1 (*C*H), 128.7 (*C*H), 139.4 (*C*), 169.4 (C=O), 171.9 (C=O). Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) (major peaks) δ 1.13 (s, 3H), 1.76 (dd, J = 14.2, 6.5 Hz, 1H), 2.42 (dd, J = 14.2, 10.5 Hz, 1H), 2.87 (s, 3H), 3.09 (dd, J = 10.5, 6.5 Hz, 1H), 3.56 (m, 2H), 6.95 (m, 2H), 7.22 (m, 3H);^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.8 (*C*H$_3$), 24.5 (*C*H$_2$), 27.0 (*C*H$_3$), 29.8 (*C*H$_2$), 40.2 (*C*H$_2$), 44.4 (*C*H$_2$), 51.0 (*C*H), 66.1 (*C*), 66.3 (*C*), 127.7 (*C*H), 128.5 (*C*H), 128.9 (*C*H), 140.0 (*C*), 168.0 (C=O), 172.0 (C=O); HRMS calcd for $C_{17}H_{20}N_2O_2$ 284.1525, found 284.1522. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.92; H, 7.11; N, 9.78.

(3*R*,8a*S*)-2,3-Dimethyl-3-(2,2-diphenylvinyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (41b) and 7,8-Dimethyl-11,11-diphenyl-5,8-diazatricyclo[5.2.2.0^{1,5}]-undecane-6,9-dione (45b). Entry 2, 3 h reflux, chromatography acetone/$CHCl_3$/hexane 1:2 (reactant **39a** R_f = 0.17). **41b**: yield 111 mg (61%); R_f = 0.24; $[\alpha]^{20}_D$ = +75.6° (*c* 0.5, $CHCl_3$); amorphous solid; mp 170−177 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (m, 1H), 1.66 (s, 3H), 1.62−1.80 (m, 2H), 2.13 (m), 2.77 (s, 3H), 3.09 (m, 1H), 3.10 (dd, J = 6.3, 10.1 Hz, 1H), 3.99 (m, 1H), 6.00 (s, 1H), 7.02−7.32 (m, 10H); ^{13}C NMR (75,5 MHz, $CDCl_3$) δ 21.7 (*C*H$_2$), 26.0 (*C*H$_3$), 28.7 (*C*H$_3$), 29.3 (*C*H$_2$), 45.1 (*C*H$_2$), 58.0 (*C*H), 64.5 (*C*), 126.9 (*C*H), 127.8 (*C*), 128.0 (*C*H), 128.2 (*C*H), 129.1 (*C*H), 137.5 (*C*), 141.2 (*C*), 144.8 (*C*), 165.7 (C=O), 167.4 (C=O); HRMS calcd for $C_{23}H_{24}N_2O_2$ 360.1838, found 360.1841.

45b: yield 38 mg (21%); R_f = 0.45; amorphous solid; mp 90 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$)δ 1.50 (s, 3H), 1.69 (m, 1H), 1.98 (m, 2H), 2.24 (s, 3H), 2.32 (d, J = 14.1 Hz, 1H), 2.84 (m, 1H), 3.09 (d, J = 14.1 Hz, 1H), 3.30 (m, 1H), 3.57 (m, 1H), 6.91 (m, 2H), 7.11−7.26 (m, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3 (*C*H$_3$), 24.3 (*C*H$_2$), 28.2 (*C*H$_3$), 29.8 (*C*H$_2$), 44.5 (*C*H$_2$), 49.4 (*C*H$_2$), 58.4 (*C*), 66.2 (*C*), 68.3 (*C*), 126.0 (*C*H), 127.1 (*C*H), 127.5 (2*C*H), 128.3 (2*C*H), 128.4 (2*C*H), 130.3 (2*C*H,), 143.9 (*C*), 148.8 (*C*), 169.7 (C=O), 171.8 (C=O); HRMS calcd for $C_{23}H_{23}N_2O_2$ 359.1760, found 359.1763 (M^+ − H).

(3*R*,8a*S*)-3-(2,2-Diphenylvinyl)-3-isobutyl-2-methylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (41c), (3*S*,8a*S*)-3-(2,2-Diphenylvinyl)-3-isobutyl-2-methylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (42c), and 10,10-Diphenyl-7-isobutyl-8-methyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undecane-6,9-dione (44c). Entry 3, reflux, 2 days. Chromatography EtOAc/hexane, 1:1 (reactant **39b** R_f = 0.11) or EtOAc/hexane, 9:1 (reactant **39b** R_f = 0.29). **41c:** yield 29 mg (14.4%); R_f = 0.43 (EtOAc/hexane, 9:1); oil; $[\alpha]^{20}_D$ = +25.7 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, J = 6.6 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H), 1.28 (m, 1H), 1.50 (m, 2H), 1.77 (m, 1H), 1.90 (dd, J = 4.7, 14.4 Hz, 1H), 2.06 (m, 1H), 2.28 (dd, J = 5.7, 11.0 Hz, 1H), 2.36 (dd, J = 7.1, 14.4 Hz, 1H), 2.77 (s, 3H), 3.07 (m, 1H), 3.55 (m, 1H), 6.04 (s, 1H), 7.04−7.34 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.4 (*C*H$_2$), 23.1 [(*C*H$_3$)$_2$], 24.2 (*C*H), 24.3 [(*C*H$_3$)$_2$], 29.8 (*C*H$_3$), 30.2 (*C*H$_2$), 45.0 (*C*H$_2$), 48.6 (*C*H$_2$), 58.0 (*C*H), 67.5 (*C*), 127.3 (2*C*H), 128.2 (*C*H), 128.4 (*C*H), 128.6 (2*C*H), 128.8 (2*C*H), 129.3 (2*C*H), 130.5 (*C*H), 138.4 (*C*), 141.4 (*C*), 146.1 (*C*), 165.5 (C=O), 166.3 (C=O); HRMS calcd for $C_{26}H_{30}N_2O_2$ 402.2307, found 402.2309. Anal. Calcd for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.11; H, 7.48; N, 7.04.

42c: yield 29 mg (14.4%); R_f = 0.48 (EtOAc/hexane, 9:1); oil; $[\alpha]^{20}_D$ = −55.3 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 3.5 Hz, 3H), 0.84 8d, J = 3.5 Hz, 3H), 0.94 (m, 1H), 1.46 (m, 1H), 1.65 (m, 2H), 1.92 (dd, J = 5.3, 14.5 Hz, 1H), 1.98 (m, 1H), 2.18 (dd, J = 6.0, 14.5 Hz, 1H), 2.80 (s, 3H), 3.23 (m, 1H), 3.36 (m, 1H), 3.72 (dd, J =6.0, 11.5 Hz, 1H), 5.99 (s, 1H), 6.95−7.29 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2 (*C*H$_2$), 24.1 (*C*H), 24.4 [(*C*H$_3$)$_2$], 24.6 [(*C*H$_3$)$_2$], 29.2 (*C*H$_2$), 30.0 (*C*H$_3$), 45.4 (*C*H$_2$), 48.9 (*C*H$_2$), 58.5 (*C*H), 68.0 (*C*), 127.4 (2*C*H), 127.8 (*C*H), 128.3 (*C*H), 128.5 (2*C*H), 128.7 (2*C*H), 129.3 (2*C*H), 131.2 (*C*H), 139.1 (*C*), 141.9 (*C*), 145.4 (*C*), 166.1 (C=O), 166.6 (C=O); HRMS calcd for $C_{26}H_{30}N_2O_2$ 402.2307, found 402.2306. Anal. Calcd for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.30; H, 7.42; N, 6.99.

44c: yield 45 mg (22%); R_f = 0.60 (EtOAc/hexane, 1:1); amorphous solid; mp 60 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.50 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H), 1.50 (m, 1H), 1.66 (dd, J = 4.6, 14.4 Hz, 1H), 1.86 (m, 1H), 1.98 (m, 1H), 2.14 (dd, J = 4.9, 14.4 Hz, 1H), 2.71 (m, 1H), 2.72 (d, J = 14.1 Hz, 1H), 2.79 (s, 3H), 2.99 (m, 1H), 3.13 (m, 1H), 3.18 (d, J =14.Hz, 1H), 6.77 (m, 2H), 7.12−7.23 (m, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.4 (*C*H$_2$), 25.1 (*C*H), 25.7 [(*C*H$_3$)$_2$], 25.8 [(*C*H$_3$)$_2$], 28.2 (*C*H$_2$), 28.4 (*C*H$_3$), 38.8 (*C*H$_2$), 44.4 (*C*H$_2$), 50.2 (*C*H$_2$), 55.7 (*C*), 65.5 (*C*), 72.8 (*C*), 126.8 (*C*H), 127.5 (*C*H), 128.2 (*C*H), 128.7 (*C*H), 129.3 (*C*H), 130.0 (*C*H), 145.5 (*C*), 147.9 (*C*), 170.1 (C=O), 172.7 (C=O); HRMS calcd for $C_{26}H_{31}N_2O_2$ 403.2386, found 403.2388 (M^+ + H).

(3*R*,6*S*)-3-(2,2-Diphenylvinyl)-3-isobutyl-1,4,6-trimethyl-2,5-piperazinedione (41d), (3*S*,6*S*)-3-(2,2-Diphenylvinyl)-3-isobutyl-1,4,6-trimethyl-2,5-piperazinedione (42d), and *trans*-3-(2,2-Diphenylvinyl)-6-isobutyl-1,3,4-trimethyl-2,5-piperazinedione (47d). Entry 4, reflux, 7 days. Chromatography EtOAc/hexane 2:1 (reactant **39c** R_f = 0.20) gave three product fractions. **41d:** 118 mg of a crude product (R_f = 0.37) were obtained, consisting of **41d**, 1,4-dimethyl-6-isobutyl-3-methylidenepiperazine-2,5-dione (**48**) and *E*-isomer (*E*-**39**). Further chromatography with acetone/$CHCl_3$ (1:8) afforded a mixture (15 mg, 14%, R_f = 0.54) of **48** and *E*-**39** and pure **44d** (102 mg, 52%, R_f = 0.63): $[\alpha]^{20}_D$ = +45.1 (*c* 1, $CHCl_3$); colorless crystals, mp 136−138 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, J = 4.9 Hz, 3H), 0.82 (d, J = 4.9 Hz, 3H), 1.26 (d, J = 7.0 Hz, 3H), 1.38 (m, 1H), 1.86 (dd, J = 5.1, 14.4 Hz, 1H), 2.27 (dd, J = 6.1, 14.4 Hz, 1H), 2.61 (s, 3H), 2.73 (s, 3H), 2.76 (q, J = 7.0 Hz, 1H), 6.03 (s, 1H), 6.95 (m, 2H), 7.08−7.31 (m, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.3 (*C*H$_3$), 23.6 [(*C*H$_3$)$_2$], 23.8 [(*C*H$_3$)$_2$], 23.9 (*C*H), 29.6 (*C*H$_3$), 32.1 (*C*H$_3$), 48.1 (*C*H$_2$), 56.1 (*C*H), 65.6 (*C*), 127.0 (*C*H), 127.8 (*C*H), 128.0 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 128.6 (*C*H), 131.0 (*C*H), 138.0 (*C*), 141.1 (*C*), 145.0 (*C*), 165.7 (C=O), 166.5 (C=O); HRMS calcd for $C_{25}H_{30}N_2O_2$ 390.2307, found 390.2312.

42d: yield 9 mg (4.6%); R_f = 0.46; $[\alpha]^{20}_D$ = −52.2 (*c* 0.45, $CHCl_3$); colorless crystals; mp 138 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H), 1.31 (m, 1H), 1.90 (dd, *J* = 4.5, 14.5 Hz, 1H), 2.19 (dd, *J* = 7.0, 14.5 Hz, 1H), 2.72 (s, 3H), 2.78 (s, 3H), 3.68 (q, *J* = 6.9 Hz, 1H), 5.98 (s, 1H), 6.19∼7.02 (m, 2H), 7.19∼7.31 (m, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.5 (CH_3), 22.9 [(CH_3)$_2$], 23.8 (*C*H), 24.2 [(CH_3)$_2$], 30.0 (CH_3), 31.6 (CH_3), 49.2 (CH_2), 55.9 (*C*H), 65.7 (*C*), 127.0 (*C*H), 127.6 (*C*H), 127.9 (*C*H), 128.1 (*C*H), 128.3 (*C*H), 129.1 (*C*H), 130.7 (*C*H), 138.6 (*C*), 141.8 (*C*), 145.1 (*C*), 166.2 (C═O), 167.5 (C═O); HRMS calcd for $C_{25}H_{30}N_2O_2$ 390.2307, found 390.2299. Anal. Calcd for $C_{25}H_{30}N_2O_2$ C, 76.88; H, 7.75; N, 7.18. Found: C, 76.79; H, 7.78; N, 7.20.

47d: yield 19 mg (9.7%); R_f = 0.53; amorphous solid; mp 114−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6.0 Hz, 3H), 0.77 (d, *J* = 6.0 Hz, 3H), 1.44∼1.58 (m, 3H), 1.69 (s, 3H), 2.57 (s, 3H), 2.80 (s, 3H), 2.89 (dd, *J* = 2.8, 6.4 Hz, 1H), 6.11 (s, 1H), 6.96 (m, 2H), 7.11∼7.31 (m, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.5 [(CH_3)$_2$], 23.5 [(*C*H$_3$)$_2$], 24.2 (*C*H), 28.2 (CH_3), 29.6 (CH_3), 32.4 (CH_3), 41.0 (CH_2), 59.7 (*C*H), 62.1 (*C*), 127.0 (*C*H), 127.7 (*C*H), 128.0 (*C*H), 128.1 (*C*H), 128.2 (*C*H), 128.7 (*C*H), 130.0 (*C*H), 137.7 (*C*), 141.0 (*C*), 145.8 (*C*), 164.6 (C═O), 168.2 (C═O); HRMS calcd for $C_{25}H_{30}N_2O_2$ 390.2307, found 390.2297.

(3*R*,8a*S*)-3-Benzyl-3-(2,2-diphenylvinyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (41e), 7-Benzyl-10,10-diphenyl-8-methyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undecane-6,9-dione (44e), and 7-Benzyl-11,11-diphenyl-8-methyl-5,8-diazatricyclo[5.2.2.0^{1,5}]undecane-6,9-dione (45e). Reflux, 65 h. Chromatography with (1) EtOAc/hexane 1:1 (reactant **39d** R_f = 0.015) and (2) EtOAc/hexane, 9:1 (reactant **39d** R_f = 0.35). Starting material **39d (**42 mg, 32.8%) was recovered that was partially racemized: $[\alpha]^{20}_D$ = +181 (*c* 1.3, $CHCl_3$) versus $[\alpha]^{20}_D$ = +541 (*c* 1.1, $CHCl_3$) of pure material.

41e: yield 91 mg (41.7%); dr = 83:17; R_f = 0.52 (EtOAc/hexane, 9:1); colorless crystals; mp 148−149 °C (EtOAc); $[\alpha]^{20}_D$ = +25.8 (*c* 1, $CHCl_3$). Spectra were recorded from the mixture. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (m, 1H), 1.26 (m, 2H), 1.61 (m, 1H), 2.36 (dd, *J* = 5.7, 11.8 Hz, 1H), 2.77 (m, 1H), 3.01 (s, 3H), 3.22 (d, *J* = 13.2 Hz, 1H), 3.35 (m, 1H), 3.56 (d, *J* = 13.2 Hz, 1H), 6.27 (s, 1H), 6.99−7.32 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5 (CH_2), 28.7 (CH_2), 30.0 (CH_3), 43.9 (CH_2), 44.9 (CH_2), 57.5 (*C*H), 69.0 (*C*), 127.0 (*C*H), 127.1 (*C*H), 127.3 (*C*H), 127.8 (*C*H), 127.9 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 128.9 (*C*H), 129.0 (*C*H), 130.0 (*C*H), 134.7 (*C*), 137.9 (*C*), 140.7 (*C*), 147.0 (*C*), 164.4 (C═O), 165.6 (C═O); HRMS calcd for $C_{29}H_{28}N_2O_2$ 436.2151, found 436.2149.

44e: yield 6 mg (2.7%); R_f = 0.62 (EtOAc/hexane, 1:1); colorless crystals; mp 226−227.5 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58 (m, 1H), 1.53 (m, 1H), 1.97 (m, 1H), 2.61 (d, *J* = 14.5 Hz, 1H), 2.72 (m, 1H), 2.82 (d, *J* = 14.5 Hz, 1H), 2.96 (s, 3H), 2.97 (d, *J* = 13.7 Hz, 1H), 3.02 (m, 1H), 3.20 (m, 1H), 3.81 (d, *J* = 13.7 Hz, 1H), 6.55 (m, 2H), 7.02∼7.29 (m, 11H), 7.48 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.1 (CH_2), 27.8 (CH_2), 28.3 (CH_3), 35.9 (CH_2), 44.1 (CH_2), 50.1 (CH_2), 54.9 (*C*), 64.5 (*C*), 72.5 (*C*), 126.4 (*C*H), 126.9 (*C*H), 127.1 (*C*H), 127.7 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 128.8 (*C*H), 129.6 (*C*H), 131.3 (*C*H), 135.5 (*C*), 144.9 (*C*), 147.4 (*C*), 169.5 (C═O), 172.5 (C═O); HRMS calcd for $C_{29}H_{28}N_2O_2$ 436.2151, found 436.2150.

45e: yield 14 mg (6.4%); R_f = 0.48 (EtOAc/hexane, 1:1); colorless crystals; mp 223−224 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (m, 1H), 1.98 (m, 2H), 2.00 (s, 3H), 2.34 (d, *J* = 14.2 Hz, 1H), 2.91 (m, 1H), 3.01 (d, *J* = 17.8 Hz, 1H), 3.13 (d, *J* = 14.2 Hz, 1H), 3.48−3.58 (m, 2H), 4.34 (d, *J* = 17.8 Hz, 1H), 6.99∼7.39 (m, 15H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.0 (CH_2), 29.7 (CH_2), 31.7 (CH_3), 33.5 (CH_2), 44.6 (CH_2), 51.0 (CH_2), 60.6 (*C*), 65.7 (*C*), 72.2 (*C*), 125.7 (*C*H), 126.0 (*C*H), 127.1 (*C*H), 127.3 (*C*H), 128.0 (*C*H), 128.4 (*C*H), 128.6 (*C*H), 128.8 (*C*H), 129.0 (*C*H), 130.8 (*C*H), 137.0 (*C*), 143.9 (*C*), 148.8 (*C*), 167.4 (C═O), 172.7 (C═O); HRMS calcd for $C_{29}H_{27}N_2O_2$ 435.2073, found 435.2075 (M^+ − H). Anal. Calcd for $C_{29}H_{28}N_2O_2$ C, 79.79; H, 6.46; N, 6.42. Found: C, 79.66; H, 6.44; N, 6.48.

Transformation of 3-Ylidenepiperazine-2,5-diones 16 to 5-Acyloxy-2(1*H*)-pyrazinones 17 and 5-Chloro-2(1*H*)-pyrazinones 21 and 4-Acyloxy-3-ylidene-2(1*H*)-pyrazinones 34 (See Table 1, 2). General Procedure. The mixture of 3-ylidenepiperazine-2,5-dione **16** (1 mmol) and acid halide or anhydride was stirred under argon at room temperature in the presence or absence of base or acid for a period of time (see Table 2) and then evaporated under vacuum. The residue was chromatographed with EtOAc/hexane 9:1 or acetone/CH_2Cl_2/hexane 1:2:3 as eluants.

1-Acetyloxy-3-isobutyl-7,8-dihydro-6*H*-pyrrolo[1,2-*a*]pyrazine-4-one (17a): R_f = 0.28 (acetone/CH_2Cl_2/hexane, 1:2:3; starting material **16a** R_f = 0.22); oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.7 Hz, 6H), 2.10−2.20 (m, 3H), 2.24 (s, 3H), 2.58 (d, *J* = 7.2 Hz, 2H), 2.92 (t, *J* = 7.7 Hz, 2H), 4.08 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7 (CH_3), 21.3 (CH_2), 22.6 [(CH_3)$_2$], 26.9 (*C*H), 28.6 (CH_2), 41.3 (CH_2), 49.4 (CH_2), 131.4 (*C*), 134.2 (*C*), 155.2 (*C*), 155.5 (C═O), 168.8 (CH_3*C*O); HRMS calcd for $C_{13}H_{18}N_2O_3$ 250.1317, found 250.1318.

1-Acetyloxy-3-benzyl-7,8-dihydro-6*H*-pyrrolo[1,2-*a*]pyrazine-4-one (17d): R_f = 0.26 (acetone/CH_2Cl_2/hexane, 1:2:3; starting material **16c** R_f = 0.23); colorless crystals, mp 103−109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (m, 2H), 2.20 (s, 3H), 2.85 (t, *J* = 7.7 Hz, 2H), 4.00 (m, 4H), 7.08 (m, 1H), 7.17 (m, 2H), 7.31 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7 (CH_3), 21.3 (CH_2), 28.6 (CH_2), 39.1 (CH_2), 49.5 (CH_2), 126.5 (*C*H), 128.3 (*C*H), 129.4 (*C*H), 132.5 (*C*), 134.2 (*C*), 137.2 (*C*), 153.4 (C═N), 155.0 (C═O), 168.8 (*C*═O); HRMS calcd for $C_{16}H_{16}N_2O_3$ 284.1161, found 284.1164.

1-Benzoyloxy-3-benzyl-7,8-dihydro-6*H*-pyrrolo[1,2-a]pyrazine-4-one (17e): R_f = 0.40 (EtOAc/hexane, 9:1; starting material **16c** R_f = 0.47); colorless amorphous solid; mp 56−61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (m, 2H), 2.86 (t, *J* = 7.7 Hz, 2H), 4.00 (m, 4H), 7.01−7.17 (m, 4H), 7.31−7.53 (m, 4H), 8.06 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.3 (CH_2), 28.7 (CH_2), 39.1 (CH_2), 49.5 (CH_2), 126.5 (*C*H), 128.3 (*C*H), 128.4 (*C*), 128.5 (*C*H), 129.5 (*C*H), 130.4 (*C*H), 132.8 (*C*), 134.1 (*C*H), 134.5 (*C*), 137.3 (*C*), 153.5 (*C*═N), 155.1 (*C*═O), 164.5 (*C*═O); HRMS calcd for $C_{21}H_{18}N_2O_3$ 346.1317, found 346.1316.

(8a*R*)-2-(2-Bromoacetyl)-3-[(*Z*)-isobutylidene]tetrahydropyrrolo[1,2-*a*]pyrazine-1,4(2*H*)-dione (34b): R_f = 0.33 (acetone/CH_2Cl_2/hexane, 1:2:3; starting material **16c** R_f = 0.23); colorless crystals; mp 148−149 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 [d, *J* = 6.5 Hz, 3H, (CH_3)$_2$CH], 1.03 [d, *J* = 6.5 Hz, 3H, (CH_3)$_2$CH], 1.88−2.29 (m, 5H, C*H*CMe$_2$ and NCH$_2$C*H*$_2$C*H*$_2$), 3.38−3.58 (m, 2H, NC*H*$_2$), 4.10 (pseudo-t, *J* = 7.9 Hz, 1H, C*H*CH$_2$), 4.34 (d, *J* = 12.6 Hz, 1H, C*H*$_2$Br), 4.61 (d, *J* = 12.6 Hz, 1H, C*H*$_2$Br), 6.21 (d, *J* = 11.0 Hz, 1H, C═C*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0 [(CH_3)$_2$CH], 22.9 [(CH_3)$_2$CH], 23.7 (NCH$_2$*C*H$_2$), 27.6 (NCH$_2$CH$_2$*C*H$_2$), 28.4 [(CH_3)$_2$*C*H], 32.1 (*C*H$_2$Br), 45.0 (NCH$_2$), 60.5 (*C*HCH$_2$), 126.2 (CH═*C*), 142,4 (*C*H═C), 162,5 (C═O), 166.1 (C═O), 169.7 (C═O); MS (EI) *m/e* 331 (M^+ + 2, 0.4), 330 (M^+ + 1, 2), 329 (M^+, 0.5), 166 (30), 165 (69), 96 (34), 70 (33), 69 (24), 68 (36), 41 (100); HRMS calcd for $C_{13}H_{17}BrN_2O_3$ 328.0423, found 328.0422.

Rearrangement of 4-Benzoyl-3-benzylidenepiperazine-2,5-dione 34e into 1-Benzoyloxy-3-benzyl-7,8-dihydro-6*H*-pyrrolo[1,2-*a*]pyrazin-4-one 17e. Method A. A mixture of 4-benzoyl-3-benzylidene-2,5-piperazinedione **34e**[29a] (346 mg, 1 mmol), benzoic acid (183 mg, 1.5 mmol), $MeSO_3H$ (7 mg, 0.08 mmol), and toluene (10 mL) was stirred under reflux for 15 h. After evaporation of volatile components under vacuum, the remainder was chromatographed with EtOAc/hexane 9:1 as eluant to afford **17e** in 54% yield.

Method B.[25] *tert*-Butyl iodide (0.12 mL, 1 mmol) was added to a mixture of 4-benzoyl-3-benzylidene-2,5-piperazinedione **34e** (346 mg, 1 mmol) and dry toluene (10 mL). The mixture was refluxed under argon for 20 h and then evaporated under vacuum. The residue was chromatographed using EtOAc/hexane (9:1) as eluant to yield **17e** (56.4%).

Thioacylation of 3-Ylidenepiperazine-2,5-diones to *S*-[4,6,7,8-Tetrahydro-3-isobutyl-4-oxopyrrolo[1,2-*a*]pyrazin-1-yl]thioethanoate (38a) and *S*-[4,6,7,8-Tetrahydro-

3-isobutyl-4-oxopyrrolo[1,2-*a*]pyrazin-1-yl] Thiobenzoate (38b). A mixture of 1-benzoyl-3-isobutylidenepiperazine-2,5-dione **34c**[29a] ($R^1 = {}^i$Pr, R^4 = Ph) (156 mg, 0.5 mmol), AcSH (50 μL, 0.7 mmol), and AIBN (33 mg, 0.2 mmol) in dry benzene (15 mL) was refluxed for 20 h under argon. After the reaction mixture was diluted with CH_2Cl_2 (15 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and saturated aqueous NaCl (1 × 20 mL) in the sequence and then dried with Na_2SO_4 and evaporated in a vacuum. The residue was chromatographed using acetone/CH_2Cl_2/hexane (1:2:3) as the eluant to afford oily 2(1*H*)-pyrazinones **38b** (33 mg, 20%, $R_f = 0.46$) and **38a** (70 mg, 52%, $R_f = 0.38$) (starting material **34** $R_f = 0.35$).

38a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 6.6 Hz, 6H), 2.13 (m, 3H), 2.35 (s, 3H), 2.60 (d, J = 7.2 Hz, 2H), 2.99 (t, J = 7.8 Hz, 2H), 4.13 (t, J = 7.4 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (*C*H_2), 22.9 [(*C*H_3)$_2$], 27.3 (*C*H), 30.5 (*C*H_3), 31.7 (*C*H_2), 41.9 (*C*H_2), 50.3 (*C*H_2), 117.4 (*C*), 147.7 (*C*), 155.6 (*C*), 157.9 (*C*), 193.7 (*C*═O). Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52; S, 12.04. Found: C, 58.55; H, 6.89; N, 10.43; S, 11.99.

38b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.6 Hz, 6H), 2.16 (m, 3H), 2.63 (d, J = 7.2 Hz, 2H), 3.04 (t, J = 7.8 Hz, 2H), 4.15 (t, J = 7.4 Hz, 2H), 7.41 (m, 2H), 7.54 (m, 1H), 7.92 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (*C*H_2), 23.0 (2*C*H_3), 27.4 (*C*H), 31.8 (*C*H_2), 41.9 (*C*H_2), 50.4 (*C*H_2), 116.7 (*C*), 128.1 (*C*H), 129.2 (*C*H), 134.4 (*C*H), 136.5 (*C*), 148.4 (*C*), 155.7 (*C*═O), 158.0 (*C*), 189.5 (*C*═O). Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.56; H, 6.08; N, 8.45; S, 9.69.

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Supporting Information Available: X-ray crystal analysis of **19d**,**e**, **20d,** and **31**, experimental procedures and ^{1}H and ^{13}C NMR data of **17b**, **30**, **32**, and precursors, and quantum chemical calculations of **49**−**54**. This material is available free of charge via the Internet at http://pubs.acs.org.

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