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A Synthetic Model for the [4+2] Cycloaddition in the Biosynthesis of the Brevianamides, Paraherquamides, and Related Compounds

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Abstract—The reactivity of model systems for the proposed [4+2] cycloaddition in the biosynthesis of the brevianamides, paraherquamides, and marcfortines is explored. The model for the intermolecular reaction reveals that the cycloaddition takes place under mild conditions only if activated, very reactive dienophiles are used. When relatively unreactive dienophiles such as cyclopentene and cyclohexene are used, harsh reaction conditions and/or a Lewis acid catalyst are necessary for the reaction. In contrast, the model for the intramolecular reaction demonstrates that the cycloaddition takes place within a few hours at room temperature, even in the absence of a Lewis acid catalyst. Conclusions drawn from these results are discussed in relation to the biosynthesis of the aforementioned metabolites.

Introduction

Brevianamide A (**1**) is a fungal metabolite that was first isolated from cultures of the fungus *Penicillium brevicompactum* by Birch and Wright in 1969.[1a] Later, it was also found in cultures of *Penicillium viridicatum* and *Penicillium ochraceum*.[1] This compound was the first known component of a family of fungal metabolites that also includes the paraherquamides[2] (**3**–**12**), marcfortines[3] (**13**, marcfortine A), sclerotamides[4] (**14**), VM55599[5] (**15**), and asperparalines[6] (**16**, asperparaline A) (Fig. 1). Although many of these metabolites show interesting biological activities, the most salient feature of this class of compounds is that their structures formally derive from a [4+2] cycloaddition reaction of an alkene to an azadiene. It is interesting to note that, although the Diels–Alder reaction is a very common procedure for carbon–carbon formation in organic synthesis, the occurrence of this cycloaddition reaction in biological systems is far less frequent. In fact, the existence of the cycloaddition has been postulated or demonstrated in very few systems (Fig. 1).[7,8]

The first significant biosynthetic experiment conducted in this family of compounds was reported by Birch and Wright in 1970, and concerned the biosynthesis of brevianamide A.[1b] The results from feeding experiments with labeled precursors led the authors to conclude that brevianamide A originates from L-Proline, L-Tryptophan and acetate (via dimethylallyl pyrophosphate). Later, Birch and Russell demonstrated that brevianamide F (cyclo-L-Trp-L-Pro) incorporates into brevianamide A in good proportion without degradation.[1c] Later, Williams et al. further showed that deoxybrevianamide E (**17**), the product of reverse prenyl alkylation of brevianamide F in position 2 of the indole ring, is efficiently incorporated into brevianamides A and B, through the use of tritium-labeled precursors.[7c,d] Taking all the previous research into account, the brevianamides, paraherquamides, and marcfortines are most likely the consequence of mixed biogenetic origins, being derived from the oxidative polycyclization of amino acids and isoprene units.[7] Especially interesting in this respect is the accumulating body of experimental evidence that seems to support the notion that the bicyclo [2.2.2] core structural motif common to **1**–**16** is formed by a biosynthetic intramolecular [4+2] cycloaddition of the isoprene-derived olefin across an azadiene moiety derived from a pre-formed, oxidized piperazinedione (**A**→**B**→**C**), as shown in Scheme 1.[7,9] The biosynthetic intramolecular [4+2] cycloaddition reaction for forming the unusual bicyclo[2.2.2] ring system of the brevianamides was first explicitly proposed by Porter and Sammes in 1970.[9a] All subsequent publications regarding the biosynthesis of these alkaloids have supported this idea either at the indole or at the indoxyl stage.[7]

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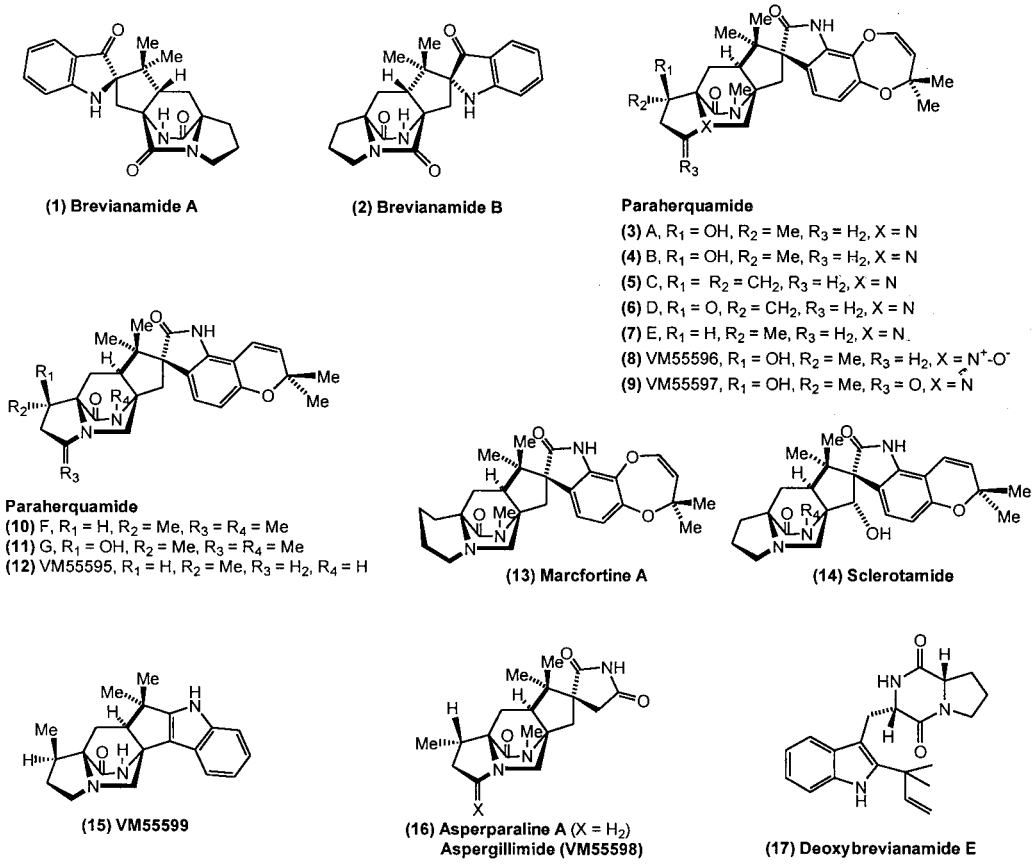
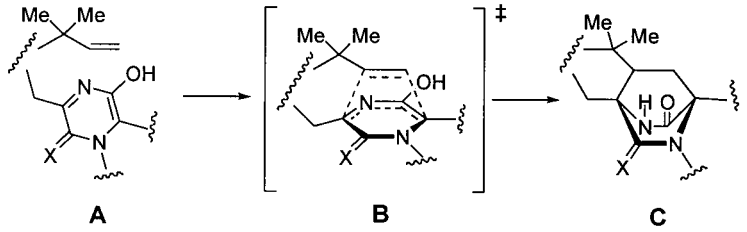


Figure 1. Brevianamides, paraherquamides, and related compounds.

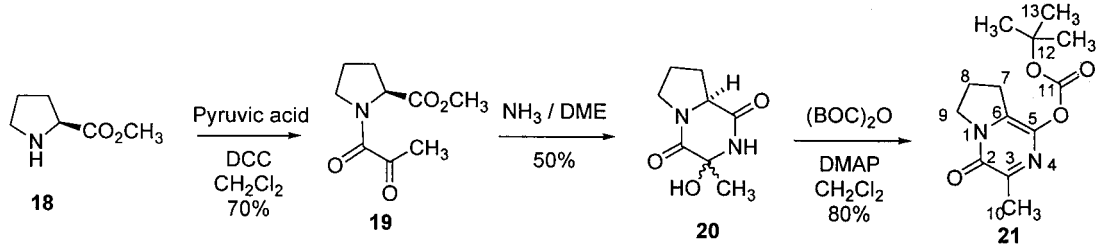
However, the azadienic system that would be operative in these biosynthetic transformations is relatively unknown, and there is almost no published data on the Diels–Alder reactivity of such systems. Porter and Sammes showed that 2,5-dihydroxypyrazines could act as dienophiles in Diels–Alder cycloaddition reactions, even when the diene is not activated.[9a] Sammes and coworkers also proved that the 4,6-dihydroxypyrimidines, a related dienic system, undergo [4+2] cycloaddition reactions with suitable dienophiles, both inter- and intramolecularly.[9b–e] The only other report of the Diels–Alder-type of reactivity of a related azadiene system was published by Fabre et al., who asserted that a dipolar azadiene system was generated and then reacted with 1-chloro-1-cyanoethylene to form a bicyclo[2.2.2] adduct.[9f] In contrast, our work has concentrated on the Diels–Alder reactivity of such systems and we have recently published both experimental and theoretical evidence for the feasibility of the involvement of an intramolecular Diels–Alder cycloaddition in the biosynthesis of this family of alkaloids. We have shown[7] that the intramolecular reaction is not only possible, but also that it proceeds at room temperature in the absence of a catalyst.[7e,f,g] Even though as early as 1973, Machin, Porter, and Sammes examined the reactivity of a related azadienic system towards dimethyl acetylenedicarboxylate and cyclopentene that could serve as a possible model system for the biosynthesis of the brevianamides,[10] we felt that further insight into the reactivity of this kind of system would be of value. The present study thus describes synthetic models for the inter- and intramolecular [4+2] cycloaddition reactions on azadienes pertinent to the biosynthetic systems proposed.

Results and Discussion

As shown in Scheme 2, proline methyl ester (**18**) reacts with pyruvic acid in the presence of DCC to give the *N*-pyruvate



Scheme 1. The proposed [4+2] cycloaddition for the formation of the bicyclo [2.2.2] ring system in the biosynthesis of the brevianamides.



Scheme 2. The preparation of a model for the intermolecular [4+2] cycloaddition reactions.

19.[11] When this compound is treated with ammonia in DME under pressure at room temperature, the diketopiperazine **20** is formed as a mixture of diastereomers.[11] When we tried to protect the secondary amide nitrogen atom in this compound with $(BOC)_2O$ in the presence of DMAP, the result was not the expected *N*-BOC-protected diketopiperazine, but the dehydrated, *O*-BOC-protected enol (**21**) in excellent yield (80%). Yields were considerably lower when crude **19** was used as starting material. This compound showed a very symmetrical ^1H NMR spectrum, as expected due to the loss of the stereogenic center. The resulting molecule has a plane of symmetry and as a result, both H-atoms on each of the methylene groups of the 5-membered ring become equivalent. This serendipitous reaction provided a structure that was suitable as a model for examining [4+2] cycloadditions pertinent to the biosynthesis of the brevianamides, paraherquamides, and marcfortine. Although we tried to remove the BOC group using a variety of methods to prepare a deprotected analog of **21**, the results were invariably negative.

The reactivity of compound **21** towards reactive dienophiles (Table 1) was evident in the reactions with dimethyl acetylenedicarboxylate and diethyl azodicarboxylate. In the first case (Scheme 3), in which an excess of dienophile as solvent was used, the [4+2] cycloadducts did not form at room temperature, but were formed in almost quantitative yield after 48 h of reaction at a temperature of 80°C. The reaction product was the BOC-deprotected cycloadduct **22**. These results indicate that the initially formed *O*-BOC lactim ether is unstable under the reaction conditions. This was indeed the case with the rest of the reactions performed on this model compound, in which all the cycloaddition products are the result of BOC group deprotection.

As expected,[12] the presence of Lewis acids markedly increased the reaction rates for the cycloaddition by lowering the HOMO energy of the azadiene. For instance, the addition of 2 molar equiv. of $AlCl_3$ or $ZnCl_2$ to the reaction mixture made the reaction of **21** with dimethyl acetylenedicarboxylate possible at 25°C in 16 h, in 65 and 75% yields, respectively (Table 1, entries 2 and 4). Decreasing the amount of Lewis acid to 0.65 equiv. did not lower the yield or the reaction rate, and gave the cycloadduct **22** in comparable yield. We also tried other Lewis acids, such as $SnCl_4$ (1 equiv.) in an excess of dienophile as solvent, but in this case the yield was markedly lower (Table 1, entry 6).

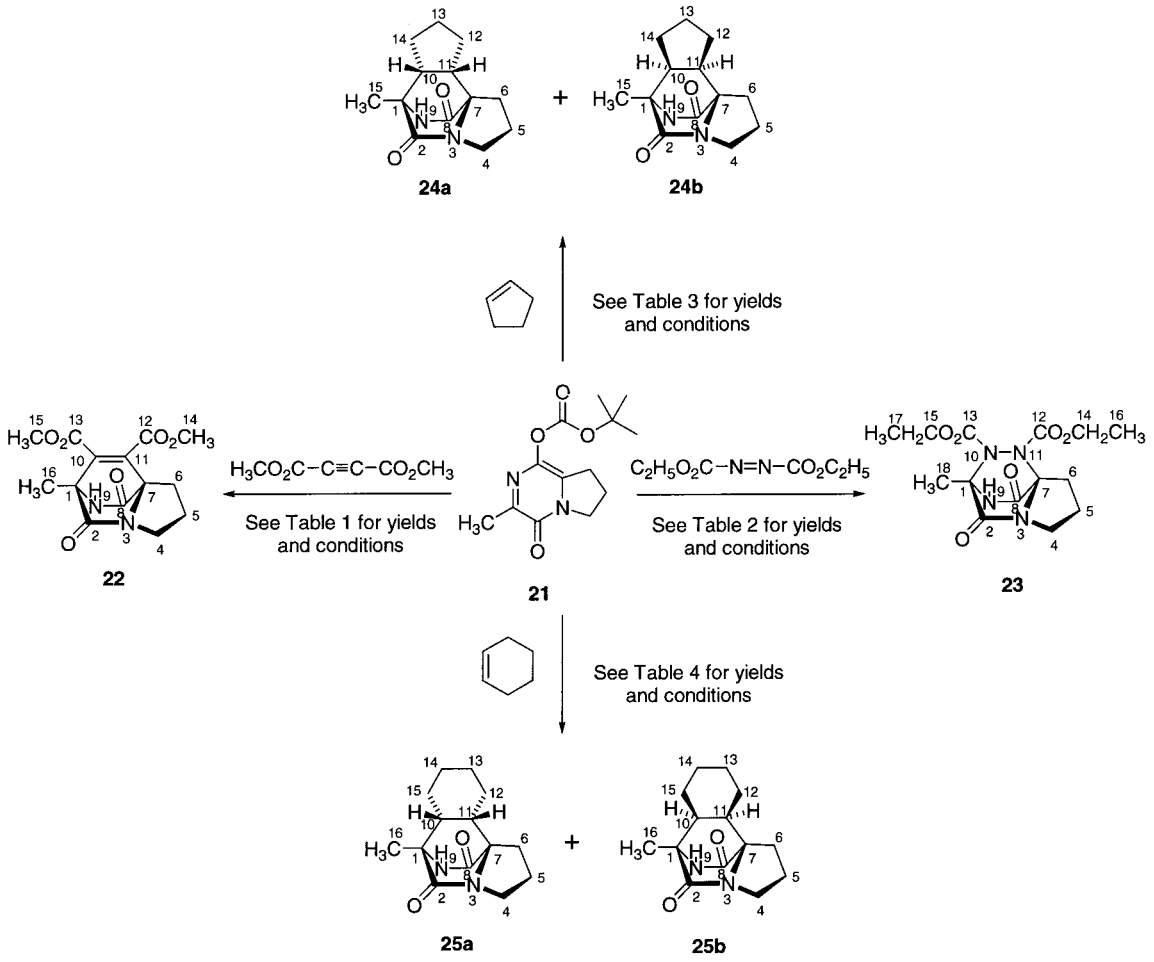
The second dienophile that we examined was diethyl azodicarboxylate (Scheme 3). With an excess of this compound as solvent, substrate **21** reacted readily at room temperature in the absence of a catalyst to give the corresponding cycloadduct **23** in moderate yield (50%) within 18 h (Table 2, entry 1). As before, the presence of Lewis acids accelerated the reaction. For instance, 0.5 equiv. of $AlCl_3$, using an excess of diethyl azodicarboxylate as solvent gave the cycloadduct **23** in 55% yield after only 2 h at 25°C. In this system, $ZnCl_2$ and $SnCl_4$ gave similar results, whereas 1 equiv. of Me_2AlCl in dichloromethane gave an even better yield (77%, Table 2, entry 6). In all these cases, the product was the BOC-deprotected cycloadduct.

We then decided to determine the influence of an aqueous solvent on the reaction rate. That the presence of an aqueous medium dramatically increases the reaction rates for some Diels–Alder reaction is well known.[13] In the present case, diethyl azodicarboxylate is soluble in water, whereas substrate **21** is not; thus, a mixture of water and dioxane was employed. The results of this reaction were somewhat surprising, in that while the aqueous medium did not substantially increase the reaction rate, the yield increased to 86%.

Since the proposed biosynthetic cycloaddition was that of an unactivated dienophile with an azadiene system, we decided to examine the reaction of compound **21** with cyclopentene and cyclohexene. Cyclopentene had been previously used with a somewhat similar system in a reduced model study.[10] In that case, the reaction was done in ethyl acetate under pressure, at 100°C and for prolonged reaction times to give the corresponding Diels–Alder adduct.[10] In the present system (Scheme 3), reaction of **21** with 10 molar equiv. of cyclopentene, and with EtOAc as solvent, no reaction was observed at reflux temperature under atmospheric pressure. However, the reaction at 100°C under pressure for 18 h gave a mixture of cycloadducts **24a** and **24b** as an inseparable mixture in 60% yield. In contrast, when $AlCl_3$ was used as a Lewis acid catalyst, the reaction took place at reflux temperature (approximately 40°C) at atmospheric pressure providing the same ratio of **24a** and **24b** in 62% yield. Other Lewis acids, such as $ZnCl_2$ and $SnCl_4$, gave similar results

Table 1. Results of various cycloaddition conditions for the reaction of **21** with dimethyl acetylenedicarboxylate

Entry	Solvent, temperature, time	Catalyst	Yield of **22** (%)
1	Neat, 80°C, 48 h	No catalyst	98
2	Neat, r.t., 16 h	$AlCl_3$ (2 equiv.)	65
3	Neat, r.t., 16 h	$AlCl_3$ (1.4 equiv.)	65
4	Neat, r.t., 16 h	$ZnCl_2$ (2 equiv.)	75
5	Neat, r.t., 16 h	$ZnCl_2$ (0.65 equiv.)	75
6	Neat, r.t., 16 h	$SnCl_4$ (1 equiv.)	20



Scheme 3. The reaction of model compound **21** with different dienophiles.

(Table 3). However, the use of Me_2AlCl in dichloloromethane at reflux temperature did not furnish the desired products.

The crude reaction products resulting from these cycloaddition reactions were purified by means of silica gel column chromatography, and were obtained as a mixture of diastereomers **24a** and **24b**, (as evidenced by ^1H NMR analysis). The relative intensity of selected ^{13}C NMR signals of the crude mixtures revealed that in all of these reactions, the same mixture of cycloadducts (**24a** and **24b**) was obtained in proportion of approximately 3:1. Unfortunately, it was not possible to separate these two diastereomers by crystallization or any chromatographic means, including HPLC on normal or reverse phase; however, the spectral data for the mixture fully agreed with the structural assignment. A detailed analysis of the spectra of these two compounds was not possible, not only because they could not be separated, but also due to the complexity and accumulation of signals in the ^1H NMR spectrum of the mixture.

Similar results were obtained with cyclohexene. However, the lower reactivity of this dienophile was clearly noticeable. Cyclopentene is more strained than cyclohexene, and therefore should be more reactive in this kind of reaction. No reaction occurred with cyclohexene and **21** under prolonged reflux at atmospheric pressure (Table 4, entry 1). Cycloaddition of **21** and cyclohexene took place in the absence of a catalyst after prolonged heating at 150°C in 38% yield (Table 4, entry 2). The product in this case was also a mixture of diastereomers **25a** and **25b** that could not be separated. When a Lewis acid was used as catalyst, the reaction was faster, but the yield did not increase significantly. This may be due to the fact that even with a

Table 2. Results of various cycloaddition conditions for the reaction of **21** with diethyl azodicarboxylate

Entry	Solvent, temperature, time	Catalyst	Yield of **23** (%)
1	Neat, r.t., 18 h	No catalyst	50
2	Dioxane/H_2O, r.t., 20 h	No catalyst	86
3	Neat, r.t., 2 h	$AlCl_3$ (0.5 equiv.)	55
4	Neat, r.t., 2 h	$ZnCl_2$ (0.5 equiv.)	40
5	Neat, r.t., 2 h	$SnCl_4$ (1 equiv.)	55
6	CH_2Cl_2, r.t., 2 h	Me_2AlCl	77

Table 3. Results of various cycloaddition conditions for the reaction of **21** and cyclopentene

Entry	Solvent, temperature, time	Catalyst	Yield (%)
1	EtOAc, reflux, 18 h	No catalyst	0 (N.R.)
2	EtOAc, reflux, 18 h	$AlCl_3$ (1 equiv.)	62
3	EtOAc, 100°C, 45 h	No catalyst	60
4	EtOAc, reflux, 20 h	$ZnCl_2$ (1 equiv.)	60
5	EtOAc, reflux, 22 h	$SnCl_4$ (1 equiv.)	36

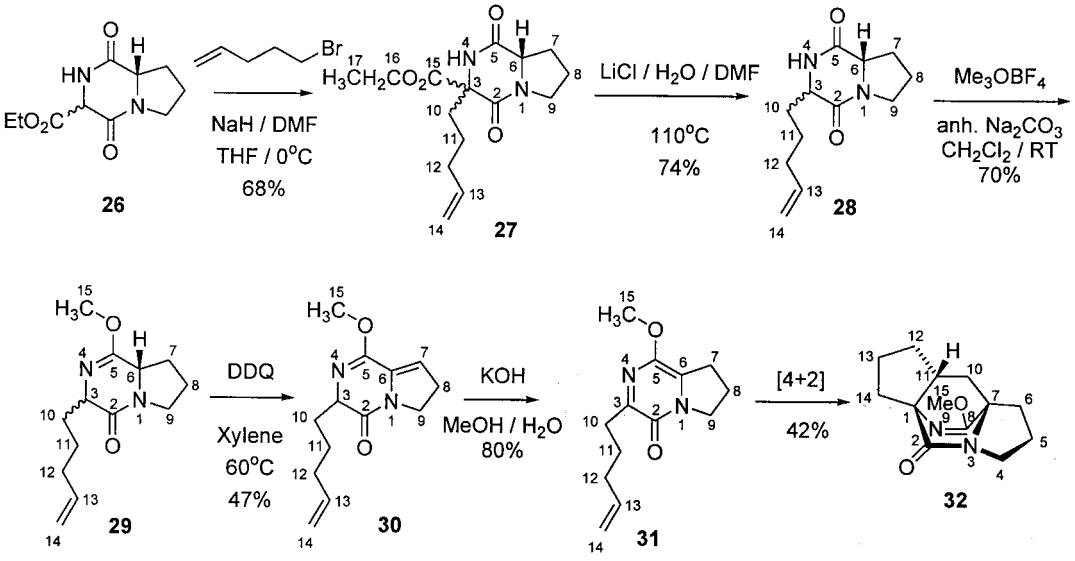
Table 4. Results of various cycloaddition conditions for the reaction of **21** and cyclohexene

Entry	Solvent, temperature, time	Catalyst	Yield (%)
1	EtOAc, reflux, 96 h	No catalyst	0 (N.R.)
2	EtOAc, 150°C, 96 h	No catalyst	38
3	EtOAc, 150°C, 72 h	$AlCl_3$ (2 equiv.)	42
4	EtOAc, 150°C, 72 h	$AlCl_3$ (1 equiv.)	33
5	EtOAc, 150°C, 72 h	$ZnCl_2$ (1 equiv.)	40

catalyst, harsh reaction conditions were required for the cycloaddition to take place, and this may have thermally decomposed some of the starting material.

Having demonstrated that the intermolecular cycloaddition of this type of azadiene system was possible, we next examined a model for the intramolecular reaction (Scheme 4). This was readily achieved starting from the diketopiperazine **26**,[14] which can be easily prepared in four steps and 37% overall yield, starting from Cbz-L-proline and diethylaminomalonate. Treatment of **26** with 2 equiv. of NaH in a mixture of DMF and THF, followed by treatment with 5-bromo-1-pentene at 0°C afforded the desired alkylated diketopiperazine **27** in 68% yield, as a mixture of diastereomers in approximately 2:1 proportion. Once again, the mixture could not be separated, but this was not considered a problem, since the configuration of the newly generated stereogenic center is later sacrificed in the formation of the achiral azadiene intermediate **31**. Thus, **27** was carried on as a diastereomeric mixture.

When the ester **27** was treated with LiCl in wet DMF at 110°C,[15] the hydrolyzed and decarboxylated diketopiperazine **28** was obtained in 74% yield as a mixture of diastereomers. Formation of the lactim ether through reaction of **28** with trimethyloxonium tetrafluoroborate in dichloromethane[16] in the presence of anhydrous Na_2CO_3 afforded **29** in 70% yield. When **29** was treated with DDQ[17] in xylene at 60°C, diene **30** was produced in 47% yield. This diene tautomerized readily in the presence of a base; typical conditions were KOH in aqueous methanol at 0°C, whereby the tautomerization was complete after a few minutes to give compound **31**. This diene reacted spontaneously at room temperature in an intramolecular [4+2] cycloaddition within a few hours, making the isolation, purification, and characterization of this compound difficult. However, the resulting product from the cycloaddition (**32**) was stable and was purified easily. This cycloadduct consisted of one of the two possible diastereoisomers, with no trace of the epimer at C-11. The relative configurations of the three new stereogenic centers at C-1, C-7, and C-11 were deduced from results of 1D and 2D NMR experiments. Due to the accumulation of signals in the ^{1}H NMR spectrum of **32** between δ1.8 and δ 2.0, even at 400 MHz, the only clearly visible signal within the C-10/C-11 segment was that for one of the protons at C-10, either H-10 or H-10′ (this assignment was unequivocal, since only these resonances should appear as a doublet of doublets). The aforementioned hydrogen atom appeared as a doublet of doublets at δ 1.36 with coupling constants of 12.5 and 5.2 Hz. Obviously, the 12.5 Hz coupling corresponded to the geminal coupling with H-10, while the 5.2 Hz corresponded to the coupling with H-11. Furthermore, the same hydrogen atom showed a distinct NOE with the methoxy protons of the lactim ether moiety, a fact which indicates the spatial proximity of those protons. We then performed a molecular mechanics analysis (MacroModel[18]) of the two possible stereoisomers, **32** and C-11-*epi*-**32**, which differ from one another in the configuration at C-11. Our analysis predicted that, for the cycloaddition product displayed in the scheme above, the proton at C-10 proximal to the OMe group should show a vicinal coupling constant with H-11 of 5.7 Hz (*anti* relationship), which is in excellent agreement with the experimental value. In contrast, MacroModel predicted a vicinal coupling constant with H-11 of 10.1 Hz (*syn* relationship) for the same proton in the corresponding C-11 epimer. This analysis was thus useful for assigning the relative configuration of the proton at C-11. Thus, the relative configuration of model cycloadduct **32** appears to be the same as that found in nature for the brevianamides.[1] Azadiene **31** mimics the formation of the five-membered spiro ring fused to the piperazinedione which also takes place in the indoxyl-based



Scheme 4. The preparation of a model for the intramolecular [4+2] cycloaddition reactions.

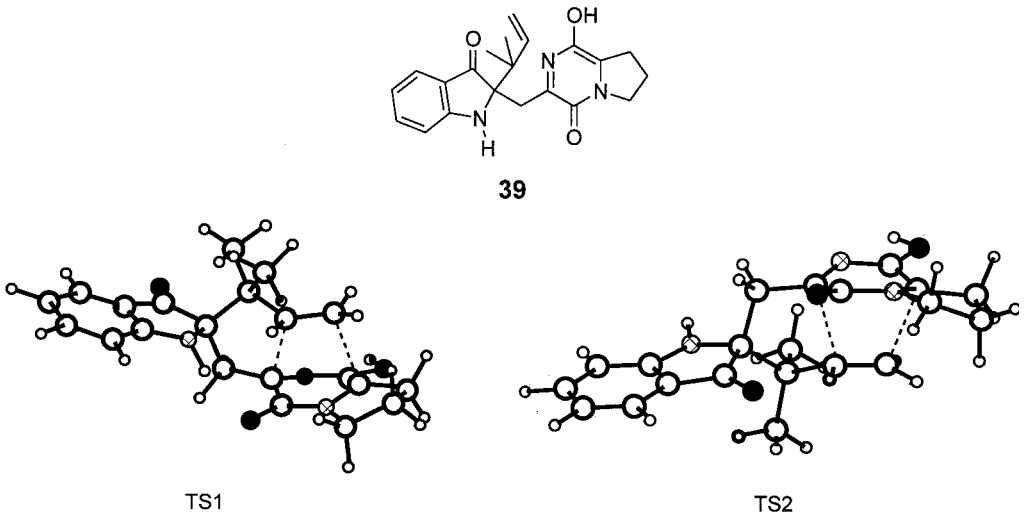
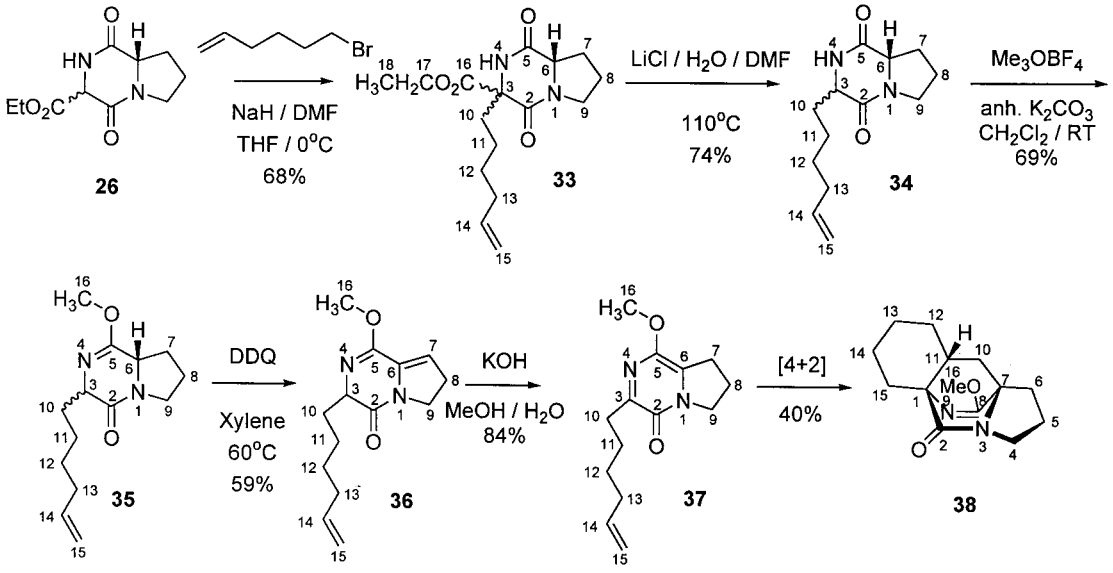


Figure 2. Stereoisomeric transition structures (TS) involved in the intramolecular Diels–Alder cycloaddition of compound **39**. TS1 (left) and TS2 (right) lead to the formation of brevianamides A and B, respectively.[7b]

azadiene substrate that has been hypothesized for the biosynthesis of these compounds. A theoretical calculation that agrees with this result on azadiene **39** (Fig. 2) has been published.[7b] Fig. 2 shows the two transition structures TS1 and TS2 that would lead to brevianamides A and B, respectively; these structures resulted from the above mentioned calculations.

Having shown that the intramolecular reaction is spontaneous and does not require Lewis acid catalysis, we decided to devise a final model system in which the spiro system ring formed in the cycloaddition would be six-membered instead of five-membered (Scheme 5). As mentioned above, the stereochemical result for the formation of the 5-membered spiro ring (*anti*- at C-11) agrees with the observed relative stereochemistry of the brevianamides.[1] However, the paraherquamides,[2] marcfortines[3] and all other known members of this alkaloid family possess the opposite configuration at the stereogenic center corresponding to C-11 in our model system. Thus, we were interested in exploring whether this stereochemical divergence is a manifestation of the intrinsic relative conformational bias for cycloaddition at the indoxyl stage (spiro-5), as proposed for the brevianamides[7c,d] rather than a cycloaddition at the indole stage (spiro-6).[7a]

The analogous model system that would culminate in the formation of the spiro-6 ring fusion was easily prepared by following the same protocol as for **31** (Scheme 5). Thus, treatment of **26** with 2 equiv. of NaH in a mixture of DMF and THF, followed by treatment with 6-bromo-1-hexene at 0°C afforded the desired alkylated diketopiperazine **33** as a mixture of diastereomers in 68% yield. When the ester **33** was treated with LiCl in wet DMF at 110°C,[15] the hydrolyzed, decarboxylated diketopiperazine **34** was obtained in 74% yield. Formation of the lactim ether with trimethyloxonium tetrafluoroborate in dichloromethane[16] in the



Scheme 5. The preparation of a model for the intramolecular [4+2] cycloaddition reactions.

presence of anhydrous K_2CO_3 afforded **35** in 69% yield. Treatment of **35** with DDQ in xylene at 60°C gave compound **36** in 59% yield. As in the previous instance, this diene tautomerized readily in the presence of a base; typical conditions were KOH in aqueous methanol at 0°C, whereby the rearrangement was complete after a few minutes, giving compound **37** with a yield of 80%. This diene was isolated, but it was not possible to purify it completely as it reacted spontaneously at room temperature in an intramolecular [4+2] cycloaddition within a few hours. When compound **37** was dissolved in THF and kept at room temperature for 15 h, it gave the cycloadduct **38** in 42% yield. As was the case for **32**, this cycloadduct also consisted of one of the two possible diastereoisomers, with no trace of the other possible isomer from the cycloaddition.

The relative configurations of the three new stereogenic centers at C-1, C-7, and C-11 in **38** were deduced in a similar manner as for cycloadduct **32**. As in that case, a strong accumulation of signals was visible in the ^{1}H NMR spectrum of **38** in the range between δ 1.8 and δ 2.0. A characteristic signal pattern (dd, J=12.1 and 4.1 Hz) permitted the identification of the signal at δ 1.08 as that for one of the protons at C-10. Obviously, the 12.1 Hz coupling corresponded to the geminal coupling between the protons at C-10, while the 4.1 Hz corresponded to the vicinal coupling with H-11. Furthermore, and as in the previous cycloadduct, an NOE was visible between the methoxy protons of the lactim ether and the aforementioned proton at δ 1.08. In strict analogy to **32**, the two possible configurations for the resulting cycloaddition product were then modeled using MacroModel.[18] Here again, this procedure clearly showed that the 4.1 Hz coupling constant had to come from a hydrogen at C-10, which is spatially proximal to the OMe group and *anti* to H-11 (the predicted value was 4.8 Hz). For the other stereoisomer, the predicted value was 10.2 Hz (*syn* vicinal coupling). These observations lead us to conclude that the configuration at C-11 in both systems (Schemes 4 and 5), parallels that for the brevianamides, but is the opposite to that for the paraherquamides and marcfortines. Therefore, the size of the spiro-ring formed in the cycloaddition step appears to have little influence on the configuration at C-11. We interpret this to mean that the distinct relative configuration at the center corresponding to C-11 in the present model system of the brevianamides on the one hand, and the paraherquamides and marcfortines on the other hand is a consequence of other factors, such as the influence of protein organization of the respective pre-cyclization conformers or the existence of an as yet undefined biosynthetic pathway for these metabolites.

Conclusions

As a result of the studies presented on the synthetic models described in this report, we can now affirm that the intermolecular reaction of an azadiene system structurally homologous to that postulated to be operative in the biosynthetic systems is possible under relatively mild reaction conditions, but only with very activated, electron-deficient dienophiles. With unactivated dienophiles, a Lewis acid catalyst and high temperatures are necessary to obtain the cycloaddition products. In contrast, the intramolecular reaction is spontaneous even at room temperature in the absence of a catalyst and with a non-reactive dienophile such as a monosubstituted alkene. These observations lend credence to the hypothesis that the intramolecular [4+2] cycloaddition that has been postulated as the key ring-forming reaction in the biosynthesis of the paraherquamides, brevianamides, and marcfortines is not only viable, but also spontaneous at room temperature.[7] While these observations imply that a specific protein 'catalyst' may not be necessary for the key bicyclo[2.2.2] ring-forming reaction to occur in nature, the control of the relative configuration of the spiro-ring fusion in each biological vector may be subject to protein organization of the transition state structures. Studies to elucidate these issues are currently in progress in our laboratories.

Experimental

General

^{1}H NMR spectra and ^{13}C NMR spectra were measured in $CDCl_3$ (^{1}H, 7.24 ppm; ^{13}C 77.0 ppm) solution at 22°C on a 200 MHz Bruker, a 400 MHz Varian, or a 500 MHz Varian NMR spectrometer. Mass spectra were measured in electron impact mode (70 eV) on an aVG AutoSpec mass spectrometer. IR spectra were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). IR spectra were recorded on a Perkin–Elmer 1600 Series FTIR spectrometer. EM Science Silica Gel 60 was used for column chromatography while TLC was performed with E. Merck precoated plates (Kieselgel 60, F_{254}, 0.25 mm). Unless otherwise specified, all reactions were carried out under argon atmosphere with magnetic stirring.

***O-tert*-Butoxycarbonyl 1-hydroxy-3-methyl-4,6,7,8-tetrahydroazolo[1,2-*a*]pyrazin-4-one (21).** In a 25 mL round bottom flask, compound **20**[11] (820 mg, 4.5 mmol, 1 equiv.) was dissolved in 10 mL of anh. dichloromethane. 4-Dimethylaminopyridine (4-DMAP) was then added (550 mg, 4.5 mmol, 1 equiv.) and the resulting mixture was stirred for 15 min. at room temp. A solution of $(BOC)_2O$ (4.5 mmol, 1 equiv.) in anh. dichloromethane (3 mL) was then added via syringe. The mixture was stirred for 20 h at room temperature. TLC showed that the reaction was complete after that period of time. The solvent was removed under reduced pressure, and the residue was taken up in ethyl acetate (25 mL) and the resulting solution transferred to a separatory funnel. It was washed with 1 N aq. AcOH soln. (25 mL). The aqueous phases were reextracted with EtOAc (2×25 mL). The organic phases were combined and washed first with 5% aq. $NaHCO_3$ soln. (25 mL) and then brine (25 mL), dried over anh. Na_2SO_4, and filtered. Removal of the solvent under reduced pressure gave a crude reaction product, which was purified by means of column chromatography on grade III neutral alumina, using hexane–EtOAc 1:1 as solvent. This gave 949 mg (80% yield) of pure compound **21**. This substance crystallized from dichloromethane–hexane to give white needles with mp 126–127°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm TMS): 1.5 (9H, s,

H-13), 2.2 (2H, dddd, J=7, 7, 7, 7 Hz, H-8, H-8′), 2.4 (3H, s, H-10), 3.05 (2H, dd, J=7, 7 Hz, H-7, H-7′), 4.15 (2H, dd, J=7, 7 Hz, H-9, H-9′). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm TMS): 19.7 (q, C-13), 21.4 (t, C-8), 27.6 (q, C-10), 28.3 (t, C-7), 49.4 (t, C-9), 84.3 (s, C-12), 131.5 (s, C-6*), 134.6 (s, C-3*), 151.2 (s, C-5†), 152.4 (s, C-2†), 155.5 (s, C-11†). *The assignment for signals with the same superscript may be interchanged. IR (KBr pellet): 2983, 1752, 1667, 1598, 1370, 1273, 1123, 918, 729 cm^{-1}. UV ($CHCl_3$) λ_{max}, nm (ϵ): 230 (13 750), 325 (9000). HREIMS: Calculated for $C_{12}H_{15}N_2O_4$ (M^+-CH_3): 251.1028. Found: 251.1022. EIMS m/z (relative intensity): 251 (2, M^+-CH_3), 207 (5), 167 (15, $M^+-CO_2-CH_2{=}C(CH_3)_2$), 166 (100, $M^+-CO_2-CC(CH_3)_3$), 149 (8), 138 (8), 137 (4), 121 (4), 110 (5), 97 (29), 69 (42), 57 (96), 42 (9), 41 (54). Elemental analysis: Calculated for $C_{13}H_{18}N_2O_4$: 58.64% C, 6.81% H, 10.52% N. Found: 58.81% C, 6.67% H, 10.60% N.

Dimethyl (1*R,7*R**)-7-methyl-6,9-dioxo-5,8-diazatricyclo[5.2.2.0^{1,5}]undec-10-ene-10,11-dicarboxylate (22).** *Without catalyst:* In a 10 mL round bottom flask, compound **21** (100 mg, 0.38 mmol, 1 equiv.) was dissolved in dimethyl acetylenedicarboxylate (1 mL, 8.2 mmol, 21.6 equiv.). The reaction mixture was kept at 80°C for 48 h. The solvent was removed under reduced pressure, and the residue purified by means of column chromatography on silica gel, using dichloromethane–EtOAc 10:1 as solvent. This gave 113.5 mg (98% yield) of pure compound **22**. This substance crystallized from ethyl acetate–hexane to give white needles with mp 143–145°C.

Using $AlCl_3$ as catalyst: In a 10 mL round bottom flask, compound **21** (108.5 mg, 0.41 mmol, 1 equiv.) was dissolved in dimethyl acetylenedicarboxylate (1 mL, 8.2 mmol, 20 equiv.) and $AlCl_3$ (109 mg, 0.82 mmol, 2 equiv.) was added. The reaction mixture was stirred at room temperature for 16 h, upon which TLC results indicated that the reaction was complete. The crude reaction mixture was dissolved in dichloromethane (25 mL); the resulting solution was transferred to a separatory funnel and treated with 5% aq. $NaHCO_3$ soln. (25 mL). The aqueous phase was extracted with dichloromethane (2×25 mL). The organic phases were combined, washed with brine (25 mL), dried over anh. Na_2SO_4, and filtered. Removal of the solvent under reduced pressure gave a residue which was purified by means of column chromatography on silica gel, with dichloromethane–EtOAc 10:1 as solvent. This gave 81.5 mg (65% yield) of pure compound **22**. A similar result was obtained when 1.4 molar equiv. of $AlCl_3$ were used.

Using $ZnCl_2$ as catalyst: A similar procedure as above was followed, using compound **21** (103 mg, 0.39 mmol, 1 equiv.), dimethyl acetylenedicarboxylate (1 mL, 8.2 mmol, 21 equiv.), and $ZnCl_2$ (106 mg, 0.82 mmol, 2 equiv.). This gave 90 mg (75% yield) of pure compound **22** after column chromatography. A similar result was obtained when 0.65 molar equiv. of $ZnCl_2$ were used.

Using $SnCl_4$ as catalyst: A similar procedure as above was followed, using compound **21** (101 mg, 0.38 mmol, 1 equiv.), dimethyl acetylenedicarboxylate (1 mL, 8.2 mmol, 21.6 equiv.), and 1 M solution of $SnCl_4$ in dichloromethane (380 μL, 0.38 mmol, 1 equiv.). This gave 23 mg (20% yield) of pure compound **22** after column chromatography.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm TMS): 1.68 (3H, s, H-16), 1.88–2.00 (1H, m, H-5), 2.02–2.12 (1H, m, H-5′), 2.36 (1H, ddd, J=6.9, 10.0, 13.5 Hz, H-6), 2.82 (1H, ddd, J=4.4, 6.6, 11.0 Hz, H-6′), 3.24 (1H, ddd, J=6.9, 9.1, 11.0 Hz, H-4), 3.53 (1H, ddd, J=3.6, 7.7, 11.0 Hz, H-4′),. 3.20–3.35 (1H, m, H-4), 3.78 (3H, s, H-14), 3.81 (3H, s, H-15). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm TMS): 13.5 (q, C-16), 25.1 (t, C-5), 25.7 (t, C-6), 43.8 (t, C-4), 52.8 (q, C-14, C-15), 62.8 (s, C-1*), 71.2 (s, C-7*), 141.0 (s, C-10†), 148.7 (s, C-11†), 162.6 (s, C-2‡), 163.8 (s, C-8‡), 166.6 (s, C-12§), 171.7 (s, C-13§). *The assignment for signals with the same superscript may be interchanged. IR (KBr pellet): 3237, 2944, 1701, 1424, 1408, 1281, 722 cm^{-1}. HREIMS: Calculated for $C_{14}H_{16}N_2O_6$: 308.1008. Found: 308.1018. EIMS m/z (relative intensity): 308 (2, M^+), 277 (70, M^+-CH_3O), 266 (57, M^+-CON), 265 (35, M^+-CHON), 250 (88), 249 (75, $M^+-CH_3N_2O$), 239 (91), 232 (91), 224 (73), 222 (13), 217 (98), 207 (100), 188 (66), 175 (70), 147 (84). Elemental analysis: Calculated for $C_{14}H_{16}N_2O_6$: 54.54% C, 5.23%H, 9.09%N. Found: 54.22% C, 5.28% H, 9.17% N.

Diethyl (1*R,7*R**)-7-methyl-6,10-dioxo-5,8,9,11-tetraazatricyclo[5.2.2.0^{1,5}]undecane-8,9-dicarboxylate (23).** *Without catalyst:* In a 10 mL round bottom flask, compound **21** (110 mg, 0.41 mmol, 1 equiv.) was dissolved in diethyl azodicarboxylate (1 mL, 6.4 mmol, 15.6 equiv.). The reaction mixture was stirred at room temperature for 18 h. The crude reaction mixture was separated by means of column chromatography on silica gel, with hexane–EtOAc 5:1 as solvent. This gave 70.5 mg (50% yield) of pure compound **23** as a yellowish, viscous oil. This substance could not be crystallized.

Without catalyst, with water as co-solvent: A similar procedure as above was followed, using compound **21** (104 mg, 0.39 mmol, 1 equiv.), dioxane (2 mL), water (1 mL), and diethyl azodicarboxylate (1 mL, 6.4 mmol, 16.4 equiv.). After stirring at room temperature for 20 h, the volatiles were removed under vacuum, and the crude residue was partitioned between water (25 mL) and ethyl acetate (25 mL). The aqueous phase was extracted with ethyl acetate (2×25 mL). The organic phases were combined, washed with brine (25 mL), dried over anh. Na_2SO_4, and filtered. Removal of the solvent under reduced pressure gave a residue which was purified by means of column chromatography on silica gel with hexane–EtOAc 5:1 as eluent to give 114 mg (86% yield) of pure compound **23** as a viscous, yellowish oil.

Using $AlCl_3$ as catalyst: In a 10 mL round bottom flask, compound **21** (98 mg, 0.41 mmol, 1 equiv.) was dissolved in diethyl azodicarboxylate (1 mL, 6.4 mmol, 17.3 equiv.) and then $AlCl_3$ (24 mg, 0.18 mmol, 0.5 equiv.) was added. The reaction mixture was stirred at room temperature for 2 h, after which time TLC results indicated that the reaction was complete. The crude reaction mixture was separated by means of column chromatography on silica gel, with hexane–EtOAc 5:1 as solvent. This gave 69 mg (55% yield) of pure compound **23**.

Using $ZnCl_2$ as catalyst: A similar procedure as above was followed, using compound **21** (103 mg, 0.38 mmol, 1 equiv.), diethyl azodicarboxylate (1 mL, 6.4 mmol, 16.8 equiv.), and $ZnCl_2$ (26 mg, 0.19 mmol, 0.5 equiv.). This gave 52.5 mg (40% yield) of pure compound 23 after column chromatography.

Using $SnCl_4$ as catalyst: A similar procedure as above was followed, using compound **21** (115 mg, 0.43 mmol, 1 equiv.), diethyl azodicarboxylate (1 mL, 6.4 mmol, 15 equiv.), and 1 M solution of $SnCl_4$ in dichloromethane (430 μL, 0.43 mmol, 1 equiv.). This gave 81 mg (55% yield) of pure compound **23** after column chromatography.

Using Me_2AlCl as catalyst: A similar procedure as above was followed, using compound **21** (103 mg, 0.39 mmol, 1 equiv.), diethyl azodicarboxylate (1 mL, 6.4 mmol, 16.4 equiv.), and 1 M solution of $SnCl_4$ in hexane (390 μL, 0.39 mmol, 1 equiv.). This gave 102 mg (77% yield) of pure compound **23** after column chromatography.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm TMS): 1.20 (3H, t, J=7 Hz, H-16*), 1.25 (3H, t, J=7 Hz, H-17*), 1.9–2.1 (2H, m, H-5, H-5′), 2.05 (3H, s, H-18), 2.55–2.65 (1H, m, H-6), 3.0–3.1 (1H, m, H-6′), 3.37–3.44 (1H, m, H-4), 3.58–3.66 (1H, m, H-4′),. 4.05 (2H, q, J=7 Hz, H-14†), 3.84 (2H, q, J=7 Hz, H-15†). Assignments for signals with the same superscript may be interchanged. ^{13}C NMR (50 MHz, $CDCl_3$) δ(ppm TMS): 14.23 (q, C-15$^\$$), 14.26 (q, C-16$^\$$), 17.70 (q, C-18), 24.39 (t, C-5), 30.80 (t, C-6), 44.32 (t, C-4), 63.33 (t, C-14*), 63.44 (s, C-15*), 74.98 (s, C-1†), 81.37 (s, C-7†), 156.80 (s, C-2‡), 156.95 (s, C-18‡), 165.56 (s, C-12§), 167.66 (s, C-13§). *Assignments for signals with the same superscript may be interchanged. IR (neat, NaCl disks): 3267, 2986, 1729, 1445, 1394, 1298, 1213, 1089, 912, 735 cm^{-1}. HREIMS: Calculated for $C_{14}H_{20}N_4O_6$: 340.1383. Found: 340.1377. EIMS *m/z* (relative intensity): 340 (3, M^+), 244 (3), 211 (15), 183 (51), 166 (69, $M^+-C_6H_{10}N_2O_4$, retro Diels–Alder fragmentation), 165 (100, $M^+-C_6H_{11}N_2O_4$), 155 (29), 137 (14), 113 (28), 96 (21), 69 (11), 68 (13). Elemental analysis: Calculated for $C_{14}H_{20}N_4O_6$: 49.41% C, 5.92% H, 16.46% N. Found: 49.17% C, 5.95% H, 16.54% N.

(12*S**,1*R**,7*R**,8*R**)-7-Methyl-5,14-diazatetracyclo-[5.2.2.0^{1,5}.0^{8,12}]tetradecane-6,13-dione (24a) and (8*S**,1*R**, 7*R**,12*R**)-7-methyl-5,14-diazatetracyclo[5.2.2.0^{1,5}.0^{8,12}]-tetradecane-6,13-dione (24b). *Without catalyst, at 100°C:* In a stainless steel high pressure reactor, compound **21** (103 mg, 0.39 mmol, 1 equiv.) was dissolved in ethyl acetate (1 mL). To this solution, cyclopentene (1 mL, 10.6 mmol, 27.2 equiv.) was added. The reactor was sealed and kept at 100°C for 45 h. After that time, the volatiles were removed under reduced pressure to give a residue which was purified by means of column chromatography on silica gel, with dichloromethane–EtOAc 5:1 as eluent. This gave 55 mg (60% yield) of the mixture of diastereomers **24a** and **24b**. This mixture could not be crystallized or separated even though various chromatographic methods were used.

Using $AlCl_3$ as catalyst: In a 10 mL round bottom flask, compound **21** (101.5 mg, 0.38 mmol, 1 equiv.) was dissolved in 1 mL of ethyl acetate. To this solution, cyclopentene (1 mL, 10.6 mmol, 28 equiv.) and $AlCl_3$ (51 mg, 0.38 mmol, 1 equiv.) were added. The reaction was refluxed (at an approximate inner temperature of 40°C) for 18 h, after which time TLC results indicated that the reaction was complete. The crude reaction mixture was poured on 5% aq. $NaHCO_3$ soln. (25 mL). The aqueous phase was extracted with ethyl acetate (3×25 mL). The organic phases were combined, washed with brine (25 mL), dried over anh. Na_2SO_4, and filtered. Removal of the solvent under reduced pressure gave a residue which was purified by means of column chromatography on silica gel, with dichloromethane–EtOAc 5:1 as eluent. This gave 55 mg (62% yield) of the mixture of diastereomers **24a** and **24b**.

Using $ZnCl_2$ as catalyst: A similar procedure as above was followed, using compound **21** (97 mg, 0.37 mmol, 1 equiv.), ethyl acetate (1 mL), cyclopentene (1 mL, 10.6 mmol, 28.6 equiv.), and $ZnCl_2$ (50 mg, 0.37 mmol, 1 equiv.). The reaction was refluxed (at an approximate inner temperature of 40°C) for 20 h. After work-up and purification similar to that described above, 51 mg (60% yield) of the mixture of diastereomers **24a** and **24b** were obtained.

Using $SnCl_4$ as catalyst: A similar procedure as above was followed, using compound **21** (100 mg, 0.37 mmol, 1 equiv.), ethyl acetate (1 mL), cyclopentene (1 mL, 10.6 mmol, 28.6 equiv.), and a 1 M solution of $SnCl_4$ in dichloromethane (370 μL, 0.37 mmol, 1 equiv.). The reaction was refluxed (at an approximate inner temperature of 40°C) for 22 h. After work-up and purification similar to that described above, 32 mg (36% yield) of the mixture of diastereomers **24a** and **24b** were obtained. The following spectroscopic data correspond to the mixture of diastereomers.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm TMS): 1.25 (3H, s, H-15 for one of the diastereomers), 1.30 (3H, s, H-15 for the other diastereomer), 1.00–2.70 (12H, m), 3.20–3.70 (2H, m, H-4, H-4′), 7.62 (br s, H-9). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm TMS) (only for the major diastereomer; some of the signals for the minor isomer did not appear in the spectrum due to low intensity): 15.85 (q, C-15); 24.49 (t, C-5$^\$$), 27.04 (t, C-12$^\$$), 27.98 (t, C-13$^\$$), 28.27 (t, C-14$^\$$), 28.36 (t, C-6$^\$$), 43.86 (t, C-4), 47.92 (d, C-11‡), 49.54 (d, C-10‡); 61.34 (s, C-1*), 70.15 (s, C-7*), 170.88 (s, C-8†), 173.31 (s, C-2†). *The assignment for signals with the same superscript may be interchanged. IR (KBr pellet): 3245, 2920, 1750, 1700 cm^{-1}. HREIMS: Calculated for $C_{13}H_{18}N_2O_2$: 234.1364. Found: 234.1366. EIMS *m/z* (relative intensity): 235 (8, M^++1), 234 (55, M^+), 206 (5), 191 (72, $M^+-CH_2CH_2CH_3$), 166 (100, $M^+-C_5H_8$, retro Diels–Alder fragmentation), 162 (94), 149 (28), 136 (37), 134 (32), 69 (23), 42 (45), 41 (49). Elemental analysis: Calculated for $C_{13}H_{18}N_2O_2$: 66.64% C, 7.74% H, 11.96% N. Found: 66.43% C, 7.79%H, 12.03% N.

(2*S**,1*R**,7*R**,8*R**)-8-Methyl-10,15-diazatetracyclo-[6.5.2.0^{1,10}.0^{2,7}]pentadecane-9,14-dione (25a) and (7*S**,1*R**, 2*R**,8*R**)-8-methyl-10,15-diazatetracyclo[6.5.2.0^{1,10}.0^{2,7}]-pentadecane-9,14-dione (25b). *Without catalyst, at 150°C:* In a stainless steel, high pressure reactor, compound **21** (97 mg, 0.37 mmol, 1 equiv.) was dissolved in ethyl acetate

(1 mL). To this solution, cyclohexene (1 mL, 9.2 mmol, 27.2 equiv.) was added. The reactor was sealed and kept at 150°C for 4 days. The volatiles were removed under reduced pressure and the resulting residue was purified by means of column chromatography on silica gel, with dichloromethane–MeOH 20:1 as eluent. This gave 41 mg (38% yield) of the mixture of diastereomers **25a** and **25b**. This mixture was crystallized from ethyl acetate–hexane to give colorless crystals with mp 213–214°C that were still a mixture (as indicated by ^{1}H NMR spectral data).

Using $AlCl_3$ as catalyst: A similar procedure as above was followed, using compound **21** (97 mg, 0.37 mmol, 1 equiv.), ethyl acetate (1 mL), cyclohexene (1 mL, 9.2 mmol, 25 equiv.) and $AlCl_3$ (99 mg, 0.74 mmol, 2 equiv.). The reactor was kept at 150°C for 3 days. The crude reaction mixture was poured on 5% aq. $NaHCO_3$ soln. (25 mL). The aqueous phase was extracted with ethyl acetate (3×25 mL). The organic phases were combined, washed with brine (25 mL), dried over anh. Na_2SO_4, and filtered. Removal of the solvent under reduced pressure gave a residue which was purified by means of column chromatography on silica gel, with dichloromethane–MeOH 20:1 as eluent. This gave 38 mg (42% yield) of the mixture of diastereomers **25a** and **25b**. A yield of 33% was obtained when only 1 molar equiv. of $AlCl_3$ was used under similar conditions.

Using $ZnCl_2$ as catalyst: A similar procedure as above was followed, using compound **21** (99 mg, 0.37 mmol, 1 equiv.), ethyl acetate (1 mL), cyclohexene (1 mL, 9.2 mmol, 25 equiv.), and $ZnCl_2$ (50 mg, 0.37 mmol, 1 equiv.). The reactor was kept at 150°C for 3 days. After work-up and purification similar to that described above, 37 mg (40% yield) of the mixture of diastereomers **25a** and **25b** were obtained. The diastereomers were present in proportion ~4:1. The following spectroscopic data correspond to this mixture.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm TMS): 1.30 (3H, s, H-16 for one of the diastereomers), 1.40 (3H, s, H-16 for the other diastereomer), 1.0–2.70 (14H, m), 3.35–3.57 (2H, m, H-4, H-4′), 7.60 (br s, H-9). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm TMS) (signals from the major diastereomer only; some of the signals for the minor isomer did not appear in the spectrum due to low intensity): 15.28 (q, C-16); (t, C-5$^{\$}$), 18.66 (t, C-5$^{\$}$), 18.83 (t, C-12$^{\$}$), 20.84 (t, C-15$^{\$}$), 24.61 (t, C-13$^{\$}$), 27.98 (t, C-14$^{\$}$), 28.24 (t, C-6$^{\$}$), 41.28 (d, C-11‡), 42.55 (d, C-10‡), 43.87 (t, C-4), 61.40 (s, C-1*), 69.93 (s, C-7*), 170.26 (s, C-8†), 172.63 (s, C-2†). *The assignment for signals with the same superscript may be interchanged. IR (KBr pellet): 3250, 2920, 2855, 1736, 1680, 1431, 1362, 1254, 1170, 1103, 798, 745 cm^{-1}. HREIMS: Calculated for $C_{14}H_{20}N_2O_2$: 248.1520. Found: 248.1514. EIMS *m/z* (relative intensity): 248 (6, M^+), 220 (2), 205 (9), 203 (13), 190 (28), 177 (70, $M^+-CH_2CH_2CH_2CH_3$), 166 (100, $M^+-C_6H_{10}$), 162 (41), 150 (19), 134 (13), 138 (13), 97 (23), 69 (29), 42 (32), 41 (37). Elemental analysis: Calculated for $C_{14}H_{20}N_2O_2$: 67.72% C, 8.12% H, 11.28% N. Found: 67.46% C, 8.18%H, 11.37% N.

Ethyl (3*RS*,8*aS*)-3-(4-pentenyl)-1,4-dioxoperhydroazolo-[1,2-*a*]pyrazine-3-carboxylate (27). A 60% suspension of sodium hydride in mineral oil (222 mg, 5.5 mmol) was washed three times with dry hexane. Dry DMF (0.5 mL) was then added and the resulting mixture was cooled to −20°C. A solution of compound **26** (626 mg, 2.8 mmol) in DMF (2 mL) was added and the resulting yellow solution was stirred at −20°C for 20 min. 5-Bromo-1-pentene (655 μL, 5.5 mmol) was then added dropwise and the mixture was stirred for 2 h. After this time the reaction mixture was allowed to warm up to room temperature for 6 h. The reaction was quenched with saturated LiCl solution (10 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine, dried over anh. Na_2SO_4, filtered and concentrated to give an oil. Purification on silica gel column with dichloromethane–MeOH 9:1 afforded 547 mg of pure **27** as a colorless, viscous oil (68% yield).

^{1}H NMR (400 MHz) ($CDCl_3$) (a mixture of two diastereomers at C-3 in proportion ~2:1): δ 1.2 (3H, t, *J*=7, H-17); 1.4–2.5 (10H, m, H-7, H-7′, H-8, H-8′, H-10, H-10′, H-11, H-11′, H-12, H-12′); 3.5–3.7 (2H, H-9, H-9′); 4.1 (2H, m, H-6); 4.2–4.4 (1H, m, H-6); 5.0 (2H, dd, H-14, H-14′); 5.7–5.8 (1H, m, H-13), 6.4 (1H, s, H-4, minor diastereomer), 6.7 (1H, s, H-4, major diastereomer). ^{13}C NMR (50 MHz, $CDCl_3$) (a mixture of two diastereomers at C-3 in proportion ~2:1): δ 170.6(s, C-2), 168.7, 168.4, 167.8, 166.0(s, C-5), 162.4, 161.0(s, C-5), 137.5, 137.4, 115.3, 115.0, 73.9, 72.1, 62.4, 62.1, 58.8, 58.6, 45.5, 44.7, 45.3, 43.1, 33.8, 33.4, 33.1, 30.1, 29.9, 28.6, 28.4, 22.8, 22.5, 21.7, 21.6, 13.7, 13.6. IR (neat, NaCl disks) 3058, 2958, 2926, 2855, 1750, 1670, 1460, 1416, 1376, 1263, 1097, 1020, 913, 861, 803, 738, 703 cm^{-1}. HREIMS: Calculated for $C_{15}H_{22}N_2O_4$: 294.1580. Found: 294.1579.

(3*RS*,8*aS*)-3-(4-Pentenyl)perhydroazolo[1,2-*a*]pyrazine-1,4-dione (28). Distilled water (74 μL, 4.1 mmol) and then LiCl (572 mg, 13.5 mmol) were added to a stirred solution of ester **27** (791 mg, 2.7 mmol) in DMF (1.5 mL). The resulting mixture was kept at 92°C for 16 h and after this time cooled to room temperature, poured over brine (10 mL) and extracted with AcOEt (3×8 mL). The organic layers were washed with brine, dried over anh. Na_2SO_4, filtered and concentrated to give an oil. Purification on silica gel with hexane–*tert*-butyl methyl ether–MeOH (5:10:1) afforded 444 mg of pure compound **28** as colorless, viscous oil (74% yield). This compound consisted of a mixture of epimers at C-3 that could not be separated. The following spectra correspond to this mixture.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47 (1H, s, H-4), 5.60–5.84 (1H, m, H-13), 4.87–5.62 (2H, m, H-14, H-14′), 3.80–4.07 (2H, m, H-3, H-6), 3.41–3.63 (2H, m, H-9, H-9′), 1.54–2.32(10H, m).; ^{13}C NMR (50 MHz, $CDCl_3$) 170.7, 169.6, 166.0, 165.6, 137.9, 137.6, 115.1, 114.8, 58.8, 57.9, 57.7, 57.6, 57.5, 55.0, 45.3, 45.1, 33.5, 33.2, 32.9, 29.1, 28.8, 28.0, 24.4, 24.0, 22.4, 21.9. IR (neat, NaCl disks) 3479, 2931, 1655, 1444, 1238, 912 cm^{-1}. HREIMS: Calculated for $C_{12}H_{18}N_2O_2$: 222.1368. Found: 222.1368.

(3*RS*,8*aS*)-3-(4-Pentenyl)-1-methoxy-3,4,6,7,8,8*a*-hexahydroazolo[1,2-*a*]pyrazin-4-one (29). A solution of compound **28** (444 mg, 2.0 mmol) in CH_2Cl_2 (66 mL) at 0°C was sequentially treated first, with potassium carbonate (5.5 g, 40 mmol) and then with trimethyloxonium

tetrafluoroborate (1.5 g, 10 mmol). The resulting mixture was stirred under Ar atmosphere for 20 min. and then warmed up to room temperature and stirred for an additional 4 h. The reaction was then quenched with water (60 mL), poured over brine (30 mL) and extracted with CH_2Cl_2 (2×40 mL). The organic layers were washed with brine, dried over anh. Na_2SO_4, filtered and concentrated to give 345 mg of compound **29** as a viscous, colorless oil (69% yield) which was used in the next step without any further purification. This compound appeared as a mixture of epimers at C-3 in proportion ~7:3 and could not be separated. The following spectroscopic data correspond to the mixture of diastereomers.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.62–5.85 (1H, m, H-13), 4.84–5.00 (2H, m, H-14, H-14′), 3.31–4.15 (4H, m, H-3, H-6, H-9, H-9′), 3.68 (3H, s, H-15), 1.25–2.35 (m, 10H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.3, 168.5, 161.1, 160.9, 138.9, 138.2, 114.6, 114.0, 62.2, 59.5, 56.7, 56.2, 53.1, 52.8, 52.7, 44.3, 44.1, 33.9, 33.6, 33.4, 31.5, 29.5, 28.9, 24.9, 24.7, 22.5, 21.9. IR (neat, NaCl disks) 3665, 3453, 3053, 2983, 2948, 2861, 1740, 1682, 1650, 1459, 1438, 1354, 1337, 1325, 1266, 1181, 1161, 1129, 1029, 998, 915, 704 cm^{-1}. HREIMS: Calculated for $C_{13}H_{20}N_2O_2$: 236.1525. Found: 236.1514.

(3*RS*)-3-(4-Pentenyl)-1-methoxy-3,4,6,7-tetrahydroazolo-[1,2-*a*]pyrazin-4-one (30). A solution of lactim ether **29** (65 mg, 0.27 mmol) in xylene (4 mL) was treated with DDQ (63 mg, 0.27 mmol) and the resulting brown mixture was stirred at 70°C for 2 h. After this time, the mixture was cooled to room temperature, filtered through a neutral alumina pad and washed with dichloromethane–MeOH 50:1 (600 mL). Finally, the solvent was removed and the resulting oil was purified on silica gel with hexane–*tert*-butyl methyl ether–MeOH 5:10:1 as eluent to afford 38 mg of pure compound **30** as dark yellow, viscous oil (59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68–5.88 (1H, ddt, J=16.8, 10.0, and 6.8 Hz, H-13), 5.56 (1H, br t, J=2.9 Hz, H-7), 5.02 (1H, dm, J=16.8 Hz, H-14), 4.92 (1H, dm, J=10.1 Hz, H-14′), 4.33 (1H, br t, J=6.1 Hz, H-3), 3.92 (2H, t, J= 9.1 Hz, H-9, H-9′), 3.76 (3H, s, H-15), 2.73 (2H, br t, J=10.1 Hz, H-8, H-8′), 1.8–2.1 (4H, m, H-10, H-10′, H-12, H-12′), 1.2–1.5 (2H, m, H-11, H-11′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.85 (C-2), 151.75 (C-5), 138.56 (C-13), 139.70 (C-6), 114.55 (C-14), 110.78 (C-7), 62.38 (C-3), 52.83 (C-15), 44.20 (C-9), 34.66 (C-8), 33.51 (C-12), 27.99 (C-10), 24.37 (C-11). IR (neat, NaCl disks) 2940, 2860, 1690, 1630, 1450, 1340, 1250, 1180, 1000, 710 cm^{-1}. HREIMS: Calculated for $C_{13}H_{18}N_2O_2$: 234.1368. Found: 234.1366.

3-(4-Pentenyl)-1-methoxy-4,6,7,8-tetrahydroazolo[1,2-*a*]-pyrazin-4-one (31). Compound **30** (38 mg, 0.16 mmol) was dissolved in MeOH (10 mL) and treated with a 20% aq.KOH solution (2.4 mL). The resulting mixture was stirred for 5 min. at room temperature (24°C) and was then poured over ice-water (20 mL) and extracted with Et_2O (3×20 mL). The organic layers were dried over anh. Na_2SO_4, filtered, and concentrated to give 30 mg of compound **31** as a viscous, yellowish oil (80% yield) which was used in the next step without any further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.67–6.04 (1H, ddt, J=16.8, 10.0, and 6.8Hz, H-13), 5.10 (1H, dm, J=16.8 Hz, H-14), 4.98 (1H, dm, J=10.0 Hz, H-14′), 4.15 (2H, t, J=6.9 Hz, H-9, H-9′) 3.88 (3H, s, H-15), 3.07 (2H, t, J=7.7 Hz, H-7, H-7′), 2.81 (2H, t, J=7.2 Hz, 2H, H-10, H-10′), 1.80–2.26 (4H, m), 1.18–1.25 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.23 (s, C-2*), 152.92 (s, C-5*), 142.50 (s, C-3†), 138.95 (d, C-13), 124.16 (s, C-6†), 114.22 (t, C-14), 54.72 (t, C-9), 49.35 (q, C-15), 33.60 (t, C-12‡), 32.01 (t, C-10‡), 28.82 (t, C-12‡), 27.95 (t, C-11‡), 26.04 (t, C-7‡), 21.53 (t, C-8‡). The IR and MS spectra were not measured because of the lability of this compound.

(1*R**,7*R**,11*R**)-13-Methoxy-5,14-diazatetracyclo-[5.5.2.0^{1,5}.0^{7,11}]tetradec-13-en-6-one (32) Compound **31** (30 mg, 0.4 mmol) was dissolved in THF (2 mL) and stirred for 15 h at room temperature (23°C). The solvent was then removed and the resulting oil was purified on silica gel with hexane–AcOEt (1:3) to afford 13 mg (42% yield) of pure compound **32** as a colorless glass.

^{1}H NMR (400 MHz) ($CDCl_3$) δ 1.12–1.20 (1H, m, H-12); 1.36 (1H, dd, J=12.5, 5.2 Hz, H-10); 1.78–2.00 (7H, m, H-5, H-5′, H-6, H-10′, H-12′, H-13, H-13′); 2.10–2.32 (1H, m, H-11, H-14, H-14′); 2.54 (1H, ddd, J=13, 6.5, 6,5 Hz, H-6′); 3.32–3.38 (2H, m, H-4, H-4′); 3.74 (3H, s, H-15). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 172.55 (s, C-2); 171.65 (s, C-8); 75.67 (s, C-1); 66.24 (s, C-7); 54.41 (q, C-15); 45.27 (d, C-11); 42.96 (t, C-4); 35.81 (t, C-10); 29.90 (t, C-12); 28.72 (t, C-6); 28.38 (t, C-14); 24.98 (t, C-5*) 23.384 (t, C-13*). *Assignments for signals with the same superscript may be interchanged. IR (KBr pellet): 2947, 2869, 1677, 1633, 1442, 1409, 1354, 1253, 1199, 986, 730 cm^{-1}. HRCIMS: Calculated for $C_{13}H_{19}N_2O_2$ $(M+H)^+$: 235.1447. Found: 235.1448. Elemental analysis: Calculated for $C_{13}H_{18}N_2O_2$: 66.64% C, 7.74% H, 11.96% N. Found: 66.22% C, 7.84% H, 12.11% N.

Ethyl (3*RS*,8*aS*)-3-(5-hexenyl)-1,4-dioxoperhydroazolo-[1,2-*a*]pyrazine-3-carboxylate (33). A 60% suspension of sodium hydride in mineral oil (1.16 g, 29 mmol) was washed three times with dry hexane. Dry DMF (7 mL) was then added and the resulting mixture was cooled to −20°C. A solution of compound **26** (3.10 g, 14.5 mmol) in DMF (5 mL) was added and the resulting yellow solution was stirred at −20°C for 20 min. 6-Bromo-1-hexene (3.9 mL, 29 mmol) was then added dropwise and the mixture was stirred for 2 h. After this time the reaction mixture was allowed to warm up to room temperature for 2 h. The reaction was quenched with saturated LiCl solution (50 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine, dried over anh. Na_2SO_4, filtered and concentrated to give an oil. Purification on silica gel column with dichloromethane–MeOH (9:1) afforded 2.50 g of the pure ester **33** as a viscous, colorless oil (62% yield). This compound appeared as a mixture of epimers at C-3 and could not be separated.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (1H, s, H-4, minor diastereomer), 7.85 (1H, s, H-4, major diastereomer),

5.66–5.80 (1H, m, H-14), 4.88–4.98 (2H, dd, H-15, H-15′), 4.15–4.25 (3H, m, H-17, H-6), 3.45–3.62 (2H, m, H-9, H-9′), 1.06–2.35 (m, 15H, H-7, H-8, H-10, H-11, H-12, H-13, H-18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 167.9, 161.9 (C-2, C-5), 138.6, 138.5 (C-14), 114.5 (C-15), 66.7, 66.6 (C-3), 62.7, 62.3 (C-17), 57.6 (C-6), 46.7, 44.4 (C-9), 33.3, 32.1, 28.4, 28.2, 27.5, 24.1, 22.9 (C-7, C-8, C-10, C-11, C-12, C-13), 14.0 (C-18). IR (neat, NaCl disks) 3479, 3077, 2978, 2931, 2859, 1748, 1667, 1456, 1418, 1375, 1333, 1300, 1224, 1159, 1116, 1096, 1022, 994, 968, 912, 858, 733, 647 cm^{-1}. HREIMS $(M)^+$. Calculated for $C_{16}H_{24}N_2O_4$: 308.1736. Found: 308.1733. EIMS *m/z* (relative intensity): 308 (20, M^+), 289 (5), 237 (4), 236 (15), 235 (100, $M^+-CO_2CH_2CH_3$), 226 (18), 225 (8), 208 (5), 207 (36), 184 (4), 180 (3), 170 (4), 126 (10), 125 (6), 110 (10), 99 (42), 98 (60), 70 (65), 69 (6), 68 (8), 55 (5).

(3*RS*,8*aS*)-3-(5-Hexenyl)perhydroazolo[1,2-*a*]pyrazine-1,4-dione (34). Distilled water (81 μL, 4.5 mmol) and then lithium chloride (625 mg, 14.7 mmol) were added to a stirred solution of ester **33** (865 mg, 2.9 mmol) in DMF (1.6 mL). The resulting mixture was kept at 90°C for 16 h and afterwards cooled to room temperature, poured over brine (10 mL) and extracted with AcOEt (3×8 mL). The organic layers were washed with brine, dried over anh. Na_2SO_4, filtered and concentrated to give an oil. Purification on silica gel with hexane–*tert*-butyl methyl ether–MeOH (5:10:1) afforded 484 mg of pure compound **34** as a viscous, colorless oil (74% yield). This compound appeared as a mixture of epimers at C-3 and could not be separated.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (1H, br s, H-4), 5.65–5.85 (1H, m, H-14), 4.90–5.00 (2H, m, H-15, H-15′), 3.43–4.10 (4H, m, H-3, H-6, H-9, H-9′), 2.20–2.35 (2H, m, H-13, H-13′), 1.65–2.10 (m, 6H), 1.25–1.55 (m, 4H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 169.4, 166.1, 165.7, 138.4, 138.3, 114.6, 114.5, 58.9, 58.0, 57.8, 55.2, 45.4, 45.2, 34.0, 33.3, 29.7, 29.3, 29.0, 28.5, 28.3, 24.7, 24.5, 22.5, 22.0. IR (neat, NaCl disks) 3324, 3075, 2931, 2859, 1541, 1458, 1375, 1342, 1297, 1260, 995, 913, 732 cm^{-1}. HRMS $(M)^+$. Calculated for $C_{13}H_{20}N_2O_2$: 236.1525. Found: 236.1519. EIMS *m/z* (relative intensity): 236 (67, M^+), 193 (6), 167 (30), 155 (7), 154 (77), 139 (12), 138 (6), 126 (17), 112 (26), 99 (9), 98 (21), 95 (10), 86 (11), 71 (5), 70 (100), 69 (10), 68 (11), 67 (6), 57 (6), 56 (6), 55 (18).

(3*RS*,8*aS*)-3-(5-Hexenyl)-1-methoxy-3,4,6,7,8,8*a*-hexahydroazolo[1,2-*a*]pyrazin-4-one (35). A solution of compound **34** (468 mg, 2.0 mmol) in CH_2Cl_2 (65 mL) at 0°C was treated first with trimethyloxonium tetrafluoroborate (1.45 g, 9.9 mmol) and then with anh. potassium carbonate (5.5 g, 40 mmol). The resulting mixture was stirred for 20 min. and then warmed to room temperature and stirred for an additional 4 h. Finally, the reaction was quenched with water (60 mL), poured over brine (30 mL) and extracted with CH_2Cl_2 (2×40 mL). The organic layers were washed with brine, dried over anh. Na_2SO_4, filtered and concentrated to give 332 mg of compound **35** as a yellowish, viscous oil (67% yield) which was used in the next step without any further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67–5.85 (1H, m, H-14), 4.85–4.99 (2H, m, H-15, H-15′), 3.32–4.05 (4H, m, H-3, H-6, H-9, H-9′), 3.69 (3H, s, H-16), 2.15–2.29 (m, 2H), 1.55–2.05 (m, 6H), 1.35–1.45 (m, 4H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 168.7, 161.2, 160.9, 139.2, 138.7, 114.3, 114.0, 59.8, 56.9, 62.4, 59.8, 56.9, 56.3, 53.2, 44.5, 44.2, 34.4, 33.7, 33.5, 31.9, 29.6, 29.8, 28.9, 28.7, 25.2, 25.0, 22.6, 22.1. IR (neat, NaCl disks) 3054, 2986, 2984, 2859, 1682, 1650, 1439, 1326, 1265, 1161, 1030, 997, 910, 743, 705, 650 cm^{-1}. HREIMS $(M)^+$. Calculated for $C_{14}H_{22}N_2O_2$: 250.1681. Found: 250.1678. EIMS *m/z* (relative intensity): 250 (63, M^+), 235 (15), 207 (21), 181 (27), 180 (15), 168 (100, $M^+-C_6H_{10}$), 167 (28), 139 (18), 128 (12), 112 (28), 95 (12), 70 (23).

(3*RS*)-3-(5-Hexenyl)-1-methoxy-3,4,6,7-tetrahydroazolo-[1,2-*a*]pyrazin-4-one (36). A solution of lactim methyl ether **35** (332 mg, 1.33 mmol) in xylene (18 mL) was treated with DDQ (302 mg, 1.33 mmol) and the resulting brown mixture was stirred at 70°C for 7 h. After this time, the mixture was cooled to room temperature, filtered through a neutral alumina pad and washed with dichloromethane–MeOH (50:1) (200 mL). Finally, the solvent was removed and the resulting oil was purified on silica gel with hexane–*tert*-butyl methyl ether–MeOH (5:10:1) to afford 267 mg of pure compound **36** as a dark yellow, viscous oil (81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75–5.84 (1H, ddt, J=17.0, 10.2, and 6.8 Hz, H-14), 5.57 (1H, br t, J=2.8 Hz, H-7), 4.99 (1H, dq, J=17.0, 3.5 and 1.7 Hz, H-15), 4.93 (1H, dd, J=10.2 and 1.7 Hz, H-15′), 4.33 (1H, br t, J=5.7 Hz, H-3), 3.93 (1H, t, J=9.0 Hz, H-9), 3.93 (1H, t, J=9.3 Hz, H-9′), 3.79 (3H, s, H-16), 2.75 (2H, br t, J=10.0 Hz, H-8, H-8′), 1.8–2.1 (m, 4H), 1.32–1.45 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 151.8, 138.9, 130.2, 114.3, 110.7, 62.5, 52.8, 44.2, 34.9, 33.6, 28.7, 27.9, 24.5. IR (neat, NaCl disks) 3056, 2986, 1734, 1684, 1655, 1627, 1447, 1374, 1266, 1246, 1097, 1047, 940, 896, 847, 740, 705 cm^{-1}. HREIMS $(M)^+$. Calculated for $C_{14}H_{20}N_2O_2$: 248.1525. Found: 248.1532. EIMS *m/z* (relative intensity): 248 (61, M^+), 235 (8), 233 (25), 205 (13), 18 (10), 181 (11), 180 (6), 179 (54), 178 (10), 177 (12), 169 (5), 168 (50), 167 (16), 166 (100, $C_9H_{12}NO_2$ (from HREIMS)), 165 (25), 163 (5), 139 (8), 138(10), 137 (96), 128 (6), 112 (9), 110 (5), 95 (10), 70 (13), 68 (11), 55 (10).

3-(5-Hexenyl)-1-methoxy-4,6,7,8-tetrahydroazolo[1,2-*a*]-pyrazin-4-one (37). Compound **36** (118 mg, 0.48 mmol) was dissolved in MeOH (34 mL) and treated with a 20% aq. KOH solution (9 mL). The resulting mixture was stirred for 5 min. at room temperature (24°C), after which time it was poured over ice-water (40 mL) and extracted with Et_2O (3×20 mL). The organic layers were dried over anh. Na_2SO_4, filtered and concentrated to give 100 mg of compound **37** as a yellowish oil (84% yield), which was used in the next step without any further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80–5.89 (1H, ddt, J=17.0, 10.3, and 6.8 Hz, H-14), 5.04 (1H, dq, J=17.0, 3.5 and 1.7 Hz, H-15), 4.90 (1H, dd, J=10.3 and 1.7 Hz, H-15′), 4.16 (2H, t, J=7.32 Hz, H-9, H-9′), 3.89 (3H, s, H-16), 3.07 (2H, t, J=7.7 Hz, H-7, H-7′), 2.82 (2H, t, J= 7.5 Hz, H-10, H-10′), 2.20- 2.27 (2H, dt, J=15.2 and 7.7 Hz),

2.10–2.15 (2H, q, J=14.5 and 7.0 Hz), 1.73–1.80 (2H, dt, J=15.2 and 7.5 Hz), 1.47–1.55 (2H,dt, J=15.2 and 7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 152.9, 142.5, 139.0, 124.2, 114.3, 54.8, 49.4, 33.7, 32.2, 28.7, 28.0, 26.2, 21.6. IR (neat, NaCl disks) 3077, 2935, 2857, 1659, 1639, 1582, 1461, 1349, 1295, 1264, 1230, 1174, 1133, 1100, 1048, 995, 909, 734, 646 cm^{-1}. The HRMS for this compound was not measured, because it was labile and reacted too quickly.

(1*R,6*R**,8*R**)-15-Methoxy-12,14-diazatetracyclo-[6.5.2.0^{1,6}.0^{8,12}]pentadec-14-en-13-one (38).** Compound **37** (100 mg, 0.4 mmol) was dissolved in THF (2 mL) and stirred for 15 h at room temperature (23°C). The solvent was then removed and the resulting oil was purified on silica gel with AcOEt–Hexane (3:1) to afford 40 mg (40% yield) of pure compound 38 as a colorless glass.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm TMS):. δ 1.00 (1H, dddd, J=3.6, 12.3, 12.3, 12.3 Hz, H-12); 1.07 (1H, dd, J=12.1, 3.8 Hz, H-10); 1.54 (1H, m, 12); 1.62–1.98 (10H, m, H-5, H-5′, H-6, H-10′, H-11, H-12′, H-13, H-13′, H-14, H-14′); 2.16 (1H, dm, J=13.7 Hz, H-15′), 2.55 (1H, ddd, J=12.6, 6.6, 6,6 Hz, H-6′); 3.33–3.43 (2H, m, H-4, H-4′); 3.77 (3H, s, H-16). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm TMS): 173.20 (s, C-2), 170.52 (s, C-8), 65.51 (s, C-1), 63.80 (s, C-7), 54.20 (q, C-16), 43.17 (t, C-4), 39.20 (t, C-10), 38.63 (d, C-11), 30.27 (t, C-12), 29.79 (t, C-15), 28.84 (t, C-6), 25.56 (t, C-5*), 24.59 (t, C-13*), 21.16 (t, C-14*). *Assignments for signals with the same superscript may be interchanged. IR (neat, NaCl disks): 2927, 2853, 1735, 1655, 1459, 1375, 1263, 1046, 911, 735 cm^{-1}. HREIMS M^+. Calculated for $C_{14}H_{20}N_2O_2$: 248.1525. Found: 248.1525. EIMS *m/z* (relative intensity): 248 (100, M^+), 233 (21), 217 (19), 191 (14), 190 (17), 189 (9), 188 (5), 180 (15), 179 (11), 178 (84, $C_{11}H_{16}NO$ (from HREIMS)), 164 (20), 163 (7), 127 (6), 113 (10), 112 (5), 111 (5), 110 (5), 99 (12), 97 (7), 69 (10). Elemental analysis: Calculated for $C_{14}H_{20}N_2O_2$: 67.72% C, 8.12% H, 11.28% N. Found: 67.30% C, 8.22% H, 11.42% N.

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