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β-Lactams as building blocks in the synthesis of macrocyclic spermine and spermidine alkaloids

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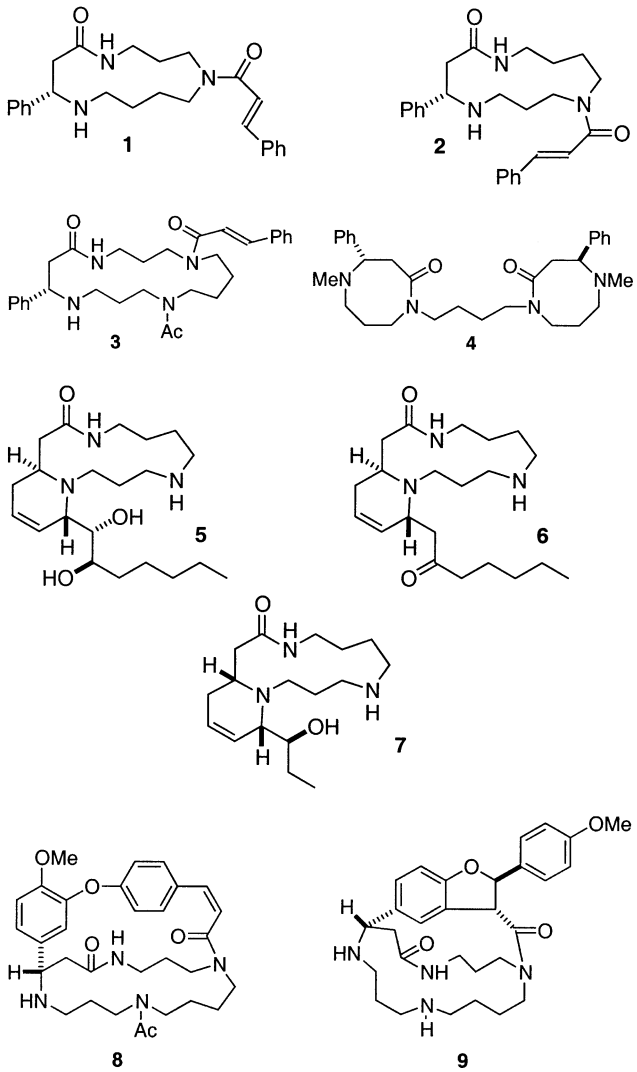
Abstract—Syntheses of the macrocyclic spermidine alkaloids (±)-celacinnine (**1**) and (±)-dihydroperiphylline (**2**) as well as the related spermine alkaloid (±)-verbascenine (**3**) were accomplished by means of sequential ring expansions of smaller lactam rings. Three ring expansion methods were employed: (1) transamidation of *N*-(aminoalkyl)lactams, (2) β-lactam-lactim ether condensation followed by reductive cleavage of the bicyclic 4-oxotetrahydropyrimidine product with $NaBH_3CN$/AcOH and (3) bicyclic acyl hydrazine formation followed by N–N bond cleavage with Na/NH_3. Each synthesis features ring expansion of a 4-phenylazetidin-2-one intermediate that undergoes transamidative ring expansion or lactim ether condensation.

1. Introduction

Alkaloids derived from the polyamines spermine and spermidine comprise a large family of natural products in which there has been sustained interest due to their spectrum of biological activity.[1,2] Representatives of this group, especially those products containing the polyamine unit within the core of a macrocylic ring, present challenging targets for total synthesis.[2,3]

Early work on the synthesis of macrocyclic polyamine alkaloids involved preparation of the large ring by direct cyclization, usually via amide bond formation.[2,3] An alternative strategy for forming the macrocyclic system in these alkaloids was developed in our laboratory as an outgrowth of our interest in the use of β-lactams as reactive sources of β-amino acyl units.[4] We found that ring-opening of these strained entities by intramolecular nucleophilic attack could serve as a general method for incorporation of the four atom fragment. The syntheses of the spermidine alkaloids celacinnine (**1**)[5] and dihydroperiphylline (**2**),[6] and the spermine alkaloids verbascenine (**3**)[7] and homaline (**4**)[8] established the viability of the ring expansion approach. Subsequently, we applied the strategy to the synthesis of more complex targets: the 13-membered spermidine alkaloids cannabisativine (**5**),[9] anhydrocannabisativine (**6**)[10] and dihydropalustrine (**7**),[11] as well as the 17-membered spermine alkaloids chaenorhine (**8**)[12] and *O*-methylorantine (**9**).[13]



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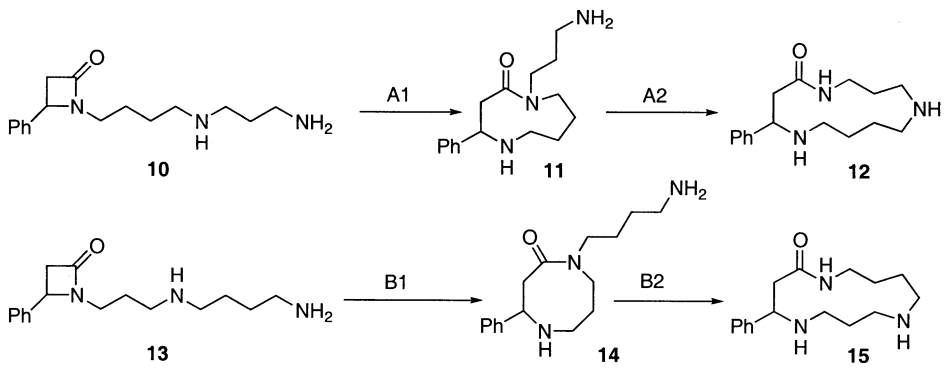


Scheme 1.

More recently, other groups, most notably that of Hesse, have extended the above approach to efficient syntheses of other spermidine alkaloids.[14–16] Asymmetric syntheses of **1** and other spermidine alkaloids have also been reported, employing ring expansion methodology.[15–18] In related work by Crombie, transamidative ring expansion was studied in detail and applied to syntheses of **2**, celabenzine (a close analog of **1**) and alkaloids of the homaline group.[19,20]

In this paper, we report full details of our early work on the synthesis of macrocyclic spermine and spermidine alkaloids, in particular, celacinnine (**1**), dihydroperiphylline (**2**), and verbascenine (**3**). In each case, β-lactam ring expansion was used in one or more key steps. Full details of the syntheses of homaline (**4**) and anhydrocannabisativine (**6**) have previously been disclosed.[21,22]

2. Early approaches to celacinnine(1) and dihydroperiphylline (2) via transamidation

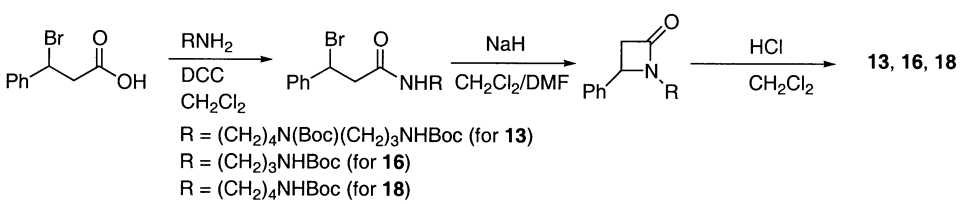
For alkaloids **1** and **2**, we first considered formation of the 13-membered lactam systems by sequential transamidation reactions analogous to the 'zip' reaction of Hesse (Scheme 1).[23] Release of ring strain in the starting β-lactam and medium-ring lactam intermediates would be expected to favor ring expansion. Furthermore, as in the zip reaction, use of a sufficiently strong base would drive formation of the 13-membered lactams by irreversible deprotonation of the secondary amide. Steps A2 and Bl are entirely analogous to the individual steps in the zip reaction for which 6-membered transition states are involved. Steps Al and B2, however, would proceed through 7-membered transition states. Although transamidations of this type were unprecedented, we believed that the β-lactam **10** and perhaps the 8-membered lactam **14** would be sufficiently reactive because of ring strain to overcome the relatively unfavorable 7-membered transition states.

Particularly relevant information regarding the feasibility of steps A1 and B1 arose from ongoing studies of Berger in the synthesis of homaline (**4**).[8,21] In this case, the key step involved intramolecular attack of a secondary amine on the 4-phenylazetidin-2-one ring through a 6-membered transition state. The strong conditions required to carry out this reaction (quinoline, 237°) suggested that the β-lactam was kinetically more stable than anticipated, and that step A1 in Scheme 1, requiring a 7-membered transition state, was unlikely to be successful. Later work by Crombie, confirmed our ideas since he found compound **10** to be resistant to reaction under zip conditions (potassium 3-aminopropylamide, 55°C).[19]

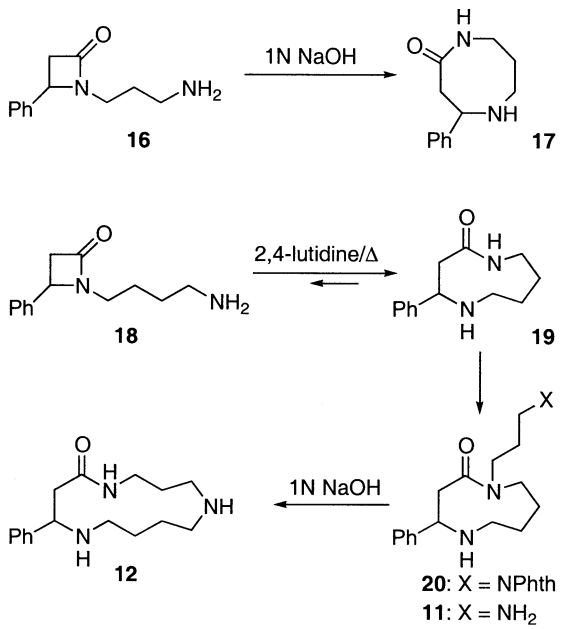
Although we did not prepare **10**, we did prepare its isomer **13**. The synthesis was accomplished in three steps starting from the corresponding di-Boc spermidine derivative (Scheme 2).[24,25] However, all efforts to convert **13** to the 13-membered lactam **15** or even to the 8-membered lactam **14** proved unsuccessful. Crombie has since prepared **14** by a different route and has established that step B2 can be accomplished under relatively mild conditions (potassium hexamethyldisilazide/25°), albeit in low yield (21%).[19]

Considering the relative stability of the 4-phenylazetidin-2-one ring toward intramolecular ring opening by secondary amino groups, we then investigated ring expansion of the simple primary amino β-lactams **16** and **18** (Scheme 3). These were prepared from mono-Boc-1,3-diaminopropane[26] and mono-Boc-1,4-diaminobutane,[26] respectively, by the same sequence used in the preparation of **13** (Scheme 2). Both compounds were of potential interest as precursors to **11** and **14** via an aminoalkylation sequence.

As anticipated, the amino β-lactam **16** underwent facile ring



Scheme 2.



Scheme 3.

expansion under mild conditions (1N NaOH/55°C/12 h)[27] to give the 8-membered azalactam **17** (50% after chromatography). Not surprisingly, more forcing conditions were required to expand the homologous compound **18** via a 7-membered transition state. The compound was inert in warm 1N NaOH, but slowly underwent conversion to the 9-membered azalactam **19** in refluxing 2,4-lutidine. Despite long reaction times of up to 64 h, significant amounts of starting material were invariably recovered; the yield of **19** after 64 h was 57%. This result suggested that equilibrium between **18** and **19** was being approached. To test this possibility, a sample of **19** was subjected to the reaction conditions. After heating to reflux in 2,4-lutidine for 64 h, an IR of the crude product showed the emergence of absorption at 1740 cm^{-1} characteristic of a β-lactam. The TLC showed the appearance of a spot having the same R_f as authentic **18**. The product was isolated by flash chromatography and although the yield was low (3% with 57% of **19** recovered), NMR confirmed the identity of the product as **18**. From this result, it was concluded that **19** is only slightly more stable than **18** (<3 kcal/mol) allowing easily detectable quantities of **18** to be observed at equilibrium. Thus, the strain associated with the 9-membered azalactam ring is comparable in magnitude to that of the β-lactam.[28]

3. Synthesis of (±)-celacinnine (1)

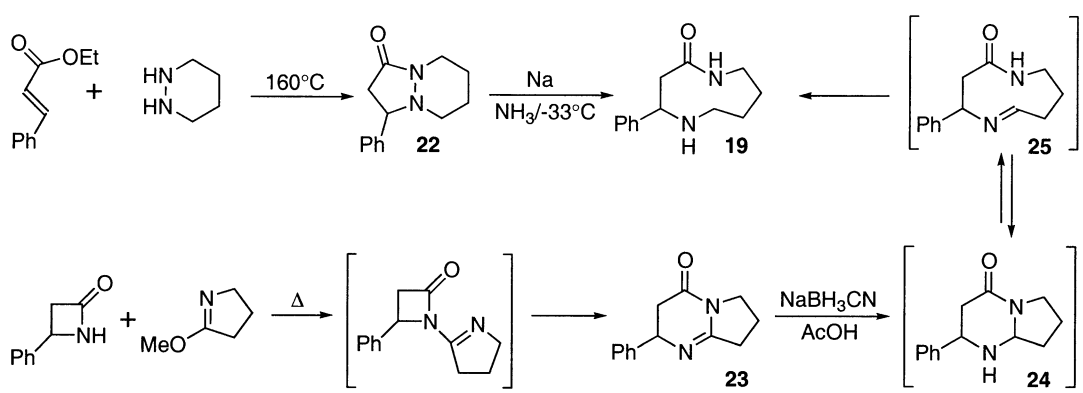
To prepare celacinnine (**1**), our plan involved conversion of **19** to its *N*-aminopropyl derivative **11** and subsequent ring expansion (step A2 in Scheme 1). Alkylation of the sodium salt of **19**, formed in DMF at 50°C by NaH deprotonation, with *N*-(3-iodopropyl)phthalimide gave **20** (23%) (Scheme 3). Several attempts to improve this yield were made without success and, although the hindered secondary amine of **19** could be protected with a Boc group, the product (described in Section 8 as **21**) did not undergo the desired alkylation under the above conditions. Conditions for obtaining **11** and related intermediates in higher overall yield from the corresponding 9-membered azalactams have since appeared in the literature.[14–16]

Treatment of **20** with hydrazine hydrate in refluxing EtOH furnished **11** in high yield. Transamidation to the 13-membered lactam **12** took place slowly under conditions similar to those used for ring expansion of the amino β-lactam **16** (2:1 1N NaOH/MeOH). Complete disappearance of **11** was observed after 50 h at 50–60°C and the yield of **12** was 42% after chromatography. We later noted that the ring expansion also occurs during the phthalimide cleavage step. Thus, when **20** was heated with hydrazine hydrate in refluxing EtOH for an extended period (19 h), a 4:6 mixture of the amino lactams **11** and **12** was obtained. Further conversion to **12** (isolated in 50% yield) was carried out by warming the mixture in 2:1 1N NaOH/dioxane at 50°C for 7 h.

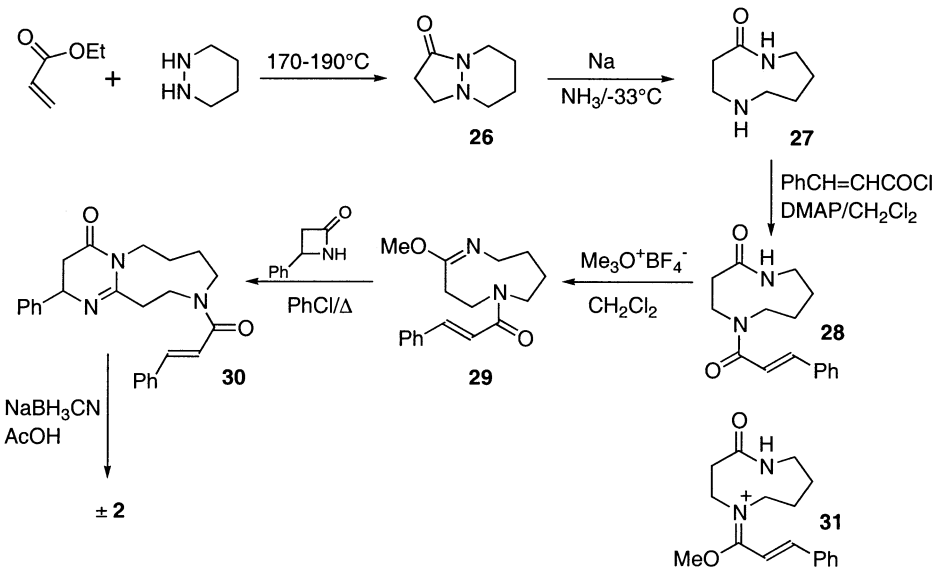
The synthesis of (±)-celacinnine (**1**) was completed by treatment of a solution of **12** and 4-*N*,*N*′-dimethylaminopyridine (DMAP) in CH_2Cl_2 with *trans*-cinnamoyl chloride. At rt, the yield of **1** was 40% (as reported by Ganem[29]) with some diacylated material also being isolated. At −78 to −20°C (conditions described by Yamamoto[30]), the yield of **1** was improved markedly to 85%.

4. Alternative routes to medium ring azalactams

During our investigation of transamidation routes to **1** and **2** we became interested in finding alternative, more efficient methods of accessing the medium-ring azalactams **17** and **19**. As described below, two new routes to **19** were found.[31] These introduced new methodologies that were later



Scheme 4.



Scheme 5.

employed in syntheses of dihydroperiphylline (**2**), the related spermidine alkaloids **5**–**7** and the 17-membered spermine alkaloids **3**, **8** and **9**.

In the first approach to **19**, hexahydropyridazine[32] was condensed with ethyl cinnamate to provide **22** (80%) presumably via initial 1,4-addition to the unsaturated ester followed by amide bond formation (Scheme 4).[33] Subsequent reduction of **22** with Na/NH_3 at −33°C took place smoothly, cleaving the N–N bond to furnish **19** in 80% yield.[34] Although the corresponding 8-membered azalactam **17** could be accessed in a similar way starting from pyrazolidine, the N–N cleavage using Na/NH_3 under similar conditions was accompanied by significant competing hydrogenolysis of the benzylic C–N bond. Matsuyama has since improved the yield of this reduction significantly.[17]

The second alternative route to **19** made use of the β-lactam-lactim ether condensation reaction first reported by Bormann[35] in which 4-phenylazetidin-2-one[21,36] is heated with 2-methoxypyrroline at 130°C to form the 4-oxo-tetrahydropyrimidine **23** (80%, Scheme 4). Reaction of **23** with 4 equiv. of $NaBH_3CN$ in glacial AcOH (25°C/1 h, 50°C/1 h, 25°C/22.5 h) then gave rise to **19** (31%).

The first step in the reductive opening of **23** is undoubtedly C=N bond reduction to form the 4-oxo-hexahydropyrimidine **24**. A reasonable mechanism for the subsequent step involves equilibrium between **24** and its ring-opened form **25** which, upon imine bond reduction, yields **19**. As also noted by Hesse,[15] a major competing side reaction was *N*-ethylation of **24**.

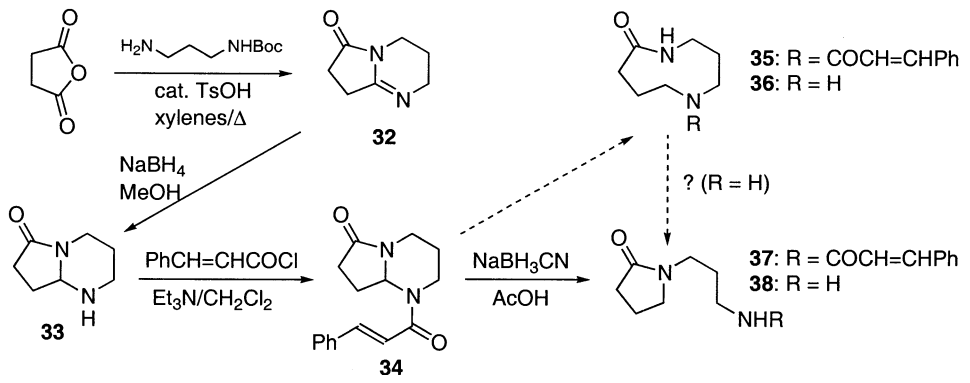
5. Synthesis of (±)-dihydroperiphylline (2)

The development of the two alternative ring expansion methods for accessing the intermediate azalactam **19** in our synthesis of celacinnine (**1**), led us to consider a new approach to dihydroperiphylline (**2**) that would circumvent the transamidation route and a potentially troublesome 7-membered transition state in step B2 (Scheme 1). This would make further use of the N–N cleavage reaction and explore the Bormann condensation for the expansion of medium-ring lactim ethers.

Azalactam **27** was obtained in a manner analogous to the preparation of **22** (Scheme 5). Slow addition of ethyl acrylate to hexahydropyridazine at 0°C led to formation of the Michael adduct which, on heating to 190°C underwent cyclization with loss of EtOH to give **26** (85%). The 9-membered azalactam **27** was then obtained by Na/NH_3 reduction (87%).

Compound **27** was treated with *trans*-cinnamoyl chloride and DMAP to provide the acyl derivative **28** (95%). To prepare for the subsequent incorporation of the 3-amino propionyl unit, **28** was treated with trimethyloxonium tetrafluoroborate to give the crude lactim ether **29** after basic aqueous workup (78%).[37] The compound was normally used without purification in the next reaction because of its instability on silica gel. It is noteworthy that methylation occurred predominantly on the secondary amide oxygen. A small amount of tertiary amide *O*-alkylation was evident from traces of methyl cinnamate, **27**, and **28** in the crude product resulting from hydrolysis of the imidate **31** during workup.

Based upon previous studies of imino ethers, and supporting NMR data, we assigned the *E* configuration to **29**. Using ^1H NMR, Moriarty[38] has studied the geometry of simple cyclic (lactim) and acyclic imino ethers. Under neutral conditions, a high-energy barrier (>23 kcal/mol) exists for interconversion of the geometrical isomers. Lactim ethers derived from simple 4–11-membered lactams exist as the stable *E* isomers. In these cases, the $N-CH_2$ hydrogens absorb at δ 3.40–3.41 ($CDCl_3$). In comparison, acyclic imino ethers and simple 12–16 membered lactim ethers were found to exist as the stable *Z* isomers, with the $N-CH_2$ group at δ 3.20–3.28. Compound **29** showed absorption above baseline between δ 3.8 and 3.25 (6H), only barely into the range



Scheme 6.

for the *Z*-isomer. Although there is the complication of overlapping signals from two other N–CH_2 groups, we believe the data is more consistent with the *E* isomer, the geometry expected based on ring size.

The reaction of **29** with 4-phenylazetidin-2-one provided the first example of the Bormann condensation involving a medium ring lactim ether. After heating the reactants in refluxing chlorobenzene (bp 132°C) for 21 h, the 4-oxo-tetrahydropyrimidine **30** was isolated in 67% yield. The use of chlorobenzene as solvent in the condensation is preferred when performing the reaction on a small scale.[39] Compound **30** could also be obtained by the reaction of **29** with methyl 3-amino-3-phenyl propionate under the same conditions, albeit in lower yield (48%).[40]

The final step in the dihydroperiphylline synthesis was carried out by treatment of **30** with 3 equiv. of $NaBH_3CN$ in AcOH. The yield of (±)-dihydroperiphylline (**2**) in this step (93%) was a significant improvement over that for the analogous conversion of **23** to **19** (31%). It seems reasonable to assume that the increased efficiency of the reductive ring expansion of **30** versus **23** is related to the relative strain energy in the rings broken and formed: in the reduction of **23**, a medium (strained) ring is formed whereas in the reduction of **30**, a medium ring is broken to form a less strained 13-membered ring.

6. Attempted synthesis of (±)-celacinnine (1) via 9-membered lactim ether condensation

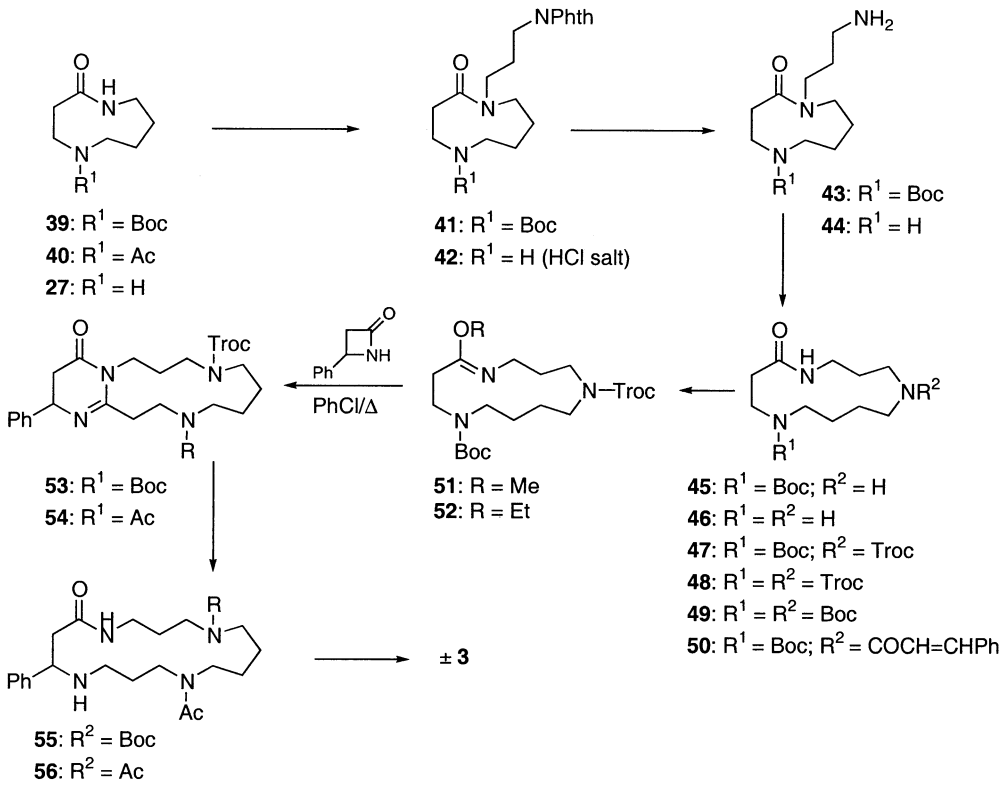
The efficiency of the dihydroperiphylline synthesis, accomplished without need for protecting groups, prompted us to explore an analogous route to celacinnine (**1**). This required the preparation of the 9-membered azalactam **35** (Scheme 6). Condensation of mono-Boc-1,3-diaminopropane with succinic anhydride (catalytic *p*-TsOH/xylenes/reflux) provided **32** (77%).[41] Reduction of **32** with $NaBH_4$ in MeOH yielded **33**, which underwent reaction with cinnamoyl chloride to give **34**. Although $NaBH_3CN$ reduction of **34** (AcOH/50°C) took place smoothly in good yield, the product was not **35** as anticipated but instead the *N*-aminopropylpyrrolidinone derivative **37**. We believe that the outcome of the reaction is related to the relative ring strain energies of **35** and **37** and the likelihood that **37** is far more stable (5-membered versus 9-membered ring). Considering the readiness of the 9-membered azalactam **19** to undergo ring contraction to the aminopropyl β-lactam **18** (Scheme 3), as well as the ease of related ring contractions reported by Hassal[27] and Hesse,[42] we suggest that attempts to prepare the free 9-membered azalactam **36** by reduction ring opening of **32** or **33** would suffer from facile conversion to *N*-(aminopropyl)-pyrrolidinone (**38**).

7. Synthesis of (±)-verbascenine (3)

The synthesis of the spermine-based alkaloid verbascenine (**3**), which was our first attempt to explore 17-membered azalactams, served as a model system for the synthesis of the more complex macrobicyclic alkaloids **8** and **9**. The synthesis required preparation of a suitably protected 13-membered azalactam derivative having the same core structure as **1**. The 17-membered azalactam system of **3** would be accessed via subsequent amide O-alkylation, condensation with 4-phenylazetidin-2-one and reductive ring expansion.

Attachment of a 3-aminopropyl side chain to **39** (the Boc derivative of **27**) was carried out as in the celacinnine synthesis (Scheme 7). Thus, alkylation of **39** using *N*-(3-bromopropyl)phthalimide in NaH/DMF gave **41** (75%) and subsequent phthalimide cleavage under standard conditions took place uneventfully to afford **43** in high yield. The relatively efficient formation of **41** was a welcome result considering the low yields or failures encountered in alkylating other 9-membered azalactam derivatives, e.g. **19**, **21** and the acetyl derivative **40**.

Unlike **11**, the amino azalactam **43** proved to be quite resistant toward transamidative ring expansion. The material was recovered unchanged after prolonged reaction with hydrazine hydrate in refluxing EtOH, or after warming at 55°C in 1:1 NaOH/dioxane for 12 h, and even after exposure to zip reaction conditions (potassium 3-aminopropylamide in 1,3-diaminopropane). Acrylamide signals were evident in the crude product obtained after exposure of **43** to KOtBu in toluene at reflux, indicating that β-elimination had occurred. Fortunately, the desired reaction took place when **43** was heated to reflux in 2,4-lutidine (19 h), the conditions used previously for expansion of the amino β-lactam **18**. The crude product mixture was chromatographed on silica gel to provide a mixture of the desired product **45** and a trace of starting material. This mixture was treated with 2,2,2-trichloroethyl chloroformate to obtain the



Scheme 7.

differentially protected azalactam **47** (40% from **43**), which was separable from the Troc derivative of **43**. It was important that the crude product mixture from the ring expansion reaction be chromatographed prior to the Troc protection. When chromatography was not performed, a small amount of di-Troc compound **48** was obtained which was not easily separable from **47**. The formation of **48** indicates that thermolysis of the Boc group occurs to some extent under the transamidation conditions giving rise to the free azalactam **46**. This result parallels our findings in the synthesis of homaline (**4**).[8,21]

To help establish the structure of **47**, an authentic sample of the di-Boc derivative **49** was prepared. Deprotection of **41** (HCl/CH_2Cl_2) gave the amine hydrochloride **42**, which was then subjected to the phthalimide cleavage conditions (H_2NNH_2/EtOH/reflux). In this instance, transamidation of the initially formed product (**44**) took place very readily under the deprotection conditions to give **46**. Consumption of **44** was complete after continued heating for 12 h (**46** isolated in 58% yield). Ring expansion of **44**, isolated from early workup of the deprotection, was also complete on warming at 50°C in aqueous 1N NaOH solution for 8 h. Spectroscopic characterization of **46** and comparison to an authentic sample[30] confirmed the assigned 13-membered macrocyclic structure. Treatment of **46** with Boc_2O then furnished **49**. The ^1H NMR spectra of the azalactams **47** and **49** were almost identical, except for the singlets assigned to the protecting groups. In addition, the NMR spectrum of **49** was identical to that of a sample prepared via 2,4-lutidine expansion of the amino azalactam **43** to **45**.

Lactim ether formation was carried out by treatment of **47** with trimethyl or triethyloxonium tetrafluoroborate in CH_2Cl_2 at rt. The reaction time was an important factor since after prolonged exposure to the conditions, cleavage of the Boc group occurred. This may have been due to the presence of acid (HBF_4) generated by reaction of the trialkyloxonium ion with traces of water in the reaction mixture. The optimized procedure for the alkylation involved carrying out the reaction in the presence of 4 Å molecular sieves for a period of 4–5 h. Excellent yields of the crude lactim ethers **51** or **52** were obtained after basic workup. The compounds appeared to be very pure by NMR analysis and, because they were unstable to silica gel, were normally used in the next step without chromatographic purification.

The lactim ethers **51** and **52** are believed to have the *Z* configuration as predicted by Moriarty.[38] Direct evidence for the assignment was obtained from the 500 MHz ^1H NMR spectra in which both compounds exhibited a 2H multiplet between δ 3.28 and 3.20.

Condensation of **51** or **52** with 4-phenylazetidin-2-one occurred in refluxing chlorobenzene to give **53**. Remarkably, the yield of **53** using the ethyl lactim ether **52** (59%) was nearly four times higher than in the case of the methyl ether **51** (16%). Although regeneration of **47** was noted in both instances, it was a more serious side reaction in the case of the methyl lactim ether (**51**). We attribute the formation of **47** to competing S_N2 attack by the azetidin-2-one nitrogen on the ether alkyl group, a process that is more facile when the alkyl group is methyl. The fact that very little dealkylation of the methyl lactim ether **29** occurred during its condensation with 4-phenylazetidin-2-one (Scheme 5) may reflect differences in reactivity arising from a change in lactim ether geometry (*E* versus *Z*).

After exchange of the Boc group for an acetyl group (HCl/CH_2Cl_2, followed by treatment with AcCl/DMAP) to obtain **54**, the 17-membered lactam **55** was obtained (88%) by reductive opening with $NaBH_3CN$ in AcOH. Removal of the Troc protecting group was achieved using Zn/AcOH affording the azalactam **56**. The final step, selective cinnamoylation of **56**, was carried out under conditions similar to those for the analogous acylation in the celacinnine synthesis. In this way, racemic verbascenine (**3**) was obtained in 58% yield overall from **55**.

An unsuccessful attempt was made to introduce the *trans*-cinnamoyl group at an earlier stage and thereby shorten the synthesis. Acylation of the Boc-azalactam **45** with cinnamoyl chloride yielded the corresponding Boc/cinnamoyl derivative **50**. From our experience in the synthesis of **2**, there was good reason to believe that selective *O*-alkylation of the secondary amide group could be accomplished. However, the reaction with trimethyloxonium tetrafluoroborate (CH_2Cl_2/25°C, followed by aq. $NaHCO_3$) gave a number of products including a poor yield of the desired lactim ether. Substantial amounts of methyl cinnamate appeared to form from competing *O*-alkylation of the tertiary amide. Based on this result and attempts to *O*-alkylate other 13-membered azalactam amide derivatives chemoselectively, it is now clear that the secondary amino groups must be protected in the form of carbamates (e.g. Boc) to insure lactim ether formation with a minimum of side reactions.

8. Experimental

8.1. General

Melting points were determined on a Thomas-Hoover melting point apparatus and, except where otherwise indicated, open capillary tubes were used. All melting and boiling points are uncorrected. The ^1H NMR spectra were recorded on a Varian EM-390, a Bruker HX-270, or a Bruker WM-500 spectrometer. Unless otherwise noted, all NMR spectra were run in deuterochloroform. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ 0). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br, broad peak. The infrared (IR) spectra were recorded on a Perkin–Elmer 700A spectrophotometer or a Nicolet 7000 spectrophotometer (FT). Except where indicated, all IR spectra were obtained on chloroform solutions ($CHCl_3$ or $CDCl_3$). Mass spectra (MS) were obtained on a Hewlett Packard GC 5840A/MS 5985A system. Peaks are reported as *m/z* (relative percent). Non-volatile compounds were analyzed on this instrument by direct input into the mass spectrometer. High-resolution mass spectra were obtained at the Midwest Center for Mass Spectrometry, the University of Nebraska-Lincoln or at the Mass Spectrometry Facility, Pennsylvania State University. Elemental analyses were performed by Dr Robert Rittner, Olin Laboratories, New Haven, CT, or at Atlantic Microlab, Inc., Atlanta, GA.

Reaction solvents and reagents were prepared for use as follows. Dichloromethane, chlorobenzene and 2,4-lutidine were distilled from calcium hydride. Tetrahydrofuran and 1,4-dioxane were freshly distilled from sodium metal. Pyridine and triethylamine were distilled from anhydrous barium oxide. *N*,*N*-dimethylformamide was purchased from Baker and stored over 4 Å molecular sieves prior to use. Anhydrous diethyl ether was used as supplied by Mallinckrodt. Unless otherwise noted, all other reagents were used as obtained from the manufacturers. Reactions were generally run under nitrogen; those requiring anhydrous conditions were carried out in flame-dried or oven-dried (120°C). Chromatography was performed on silica gel 60 (40–63 μm EM Laboratories) under flash conditions. For thin layer chromatographic analysis throughout this work, Merck precoated (silica gel F-254, 0.25 mm) glass plates were used. Ethyl acetate and dichloromethane were distilled for chromatography; otherwise, reagent grade solvents were used as supplied.

8.1.1. [3-(2-Oxo-4-phenylazetidin-1-yl)propyl]carbamic acid, *tert*-butyl ester. A solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (2.06 g, 10 mmol) in CH_2Cl_2 (10 mL) was added to a suspension of 3-bromo-3-phenylpropionic acid[43] (2.29 g, 10 mmol) in CH_2Cl_2 (50 mL) at 0°C. After stirring the solution for 0.5 h at 0°C, *N*-*tert*-butoxycarbonyl-1,3-diaminopropane[26] (1.74 g, 10 mmol) in CH_2Cl_2 (30 mL) was added dropwise. The mixture was then stirred for 10 h at rt, filtered through Celite and then concentrated. The residue was diluted with Et_2O (100 mL) and filtered to remove the precipitate. Evaporation left the crude amide (3.6 g, 94%) as a white foam. ^1H NMR (90 MHz): δ 7.5–7.2 (m, 5H), 6.7 (br s, 1H), 5.5 (t, J=7 Hz, 1H), 5.0 (br t, J=7 Hz, 1H), 3.40–2.95 (m, 6H), 1.7–1.4 (m, 2H), 1.45 (s, 9H).

A solution of the amide (3.6 g, 9.3 mmol) in CH_2Cl_2 (64 mL) and DMF (16 mL) was added slowly, over a period of 2 h, to a suspension of hexane-washed NaH (0.5 g, 21 mmol) in CH_2Cl_2 (64 mL) and DMF (16 mL) at rt. When addition was complete, the mixture was stirred for 10 h and then poured into saturated aq. NH_4Cl (150 mL). The mixture was extracted twice with Et_2O (1×150, 1×100 mL) and the combined Et_2O fractions washed with H_2O (6×100 mL) and brine (50 mL). The Et_2O solution was dried ($MgSO_4$) and concentrated to leave a pale yellow oil. The title compound (1.88 g, 62%) was obtained by chromatography, eluting with 0.5% MeOH/$CHCl_3$. An analytical sample was prepared by running a second column (33% EtOAc/CH_2Cl_2) and carefully evaporating the solvent with a stream of dry N_2. The last traces of solvent were removed by warming the sample at 50°C under high vacuum. ^1H NMR (90 MHz): δ 7.35 (s, 5H), 5.0 (br s, 1H), 4.55 (dd, J=2.5, 5 Hz, 1H), 3.6–2.7 (m, 6H), 1.8–1.5 (m, 2H), 1.45 (s, 9H). IR: 3440, 1740, 1710, 1515 cm^{-1}. MS (20 eV): M^+ 304 (3), 248 (16), 174 (15), 131 (33), 104 (100), 56 (60). Anal. calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.86; H, 7.97; N, 9.11.

8.1.2. 1-(3-Aminopropyl)-4-phenylazetidin-2-one (16). Gaseous HCl was bubbled through a solution of [3-(2-oxo-4-phenylazetidin-1-yl)propyl]carbamic acid, *tert*-butyl ester (0.44 g, 1.44 mmol) in CH_2Cl_2 (10 mL) for ~10 min at 0°C. The solution was stirred at 0°C for 1 h and then concentrated. The residue was dissolved in saturated aq.

$NaHCO_3$ (30 mL) and then extracted with $CHCl_3$ (3×20 mL). The combined $CHCl_3$ fractions were dried (Na_2SO_4) and evaporated to leave **16** (116 mg, 69%). ^1H NMR (90 MHz): δ 7.25 (s, 5H), 4.45 (dd, J=2.5, 5 Hz 1H), 3.6–3.1 (m, 2H), 3.0–2.5 (m, 4H), 1.8–1.3 (m, 4H). IR: 1740 cm^{-1}.

8.1.3. 4-Phenyl[1,5]diazocan-2-one (17). A solution of **16** (41 mg, 0.2 mmol) in 1N aq. NaOH (5 mL) was warmed at 55°C for 12 h. After the solution was cooled, it was extracted with CH_2Cl_2. The CH_2Cl_2 fractions were combined, dried (Na_2SO_4) and concentrated. The IR spectrum of the product indicated complete disappearance of the starting β-lactam. Chromatography with 1% MeOH/$CHCl_3$ as eluant provided pure **17** (20 mg, 50%) as a white crystalline solid that was recrystallized from CH_2Cl_2/hexanes, mp 130–131°C (lit.[19] mp 128–130°C). ^1H NMR (270 MHz): δ 7.43–7.25 (m, 5H), 5.76 (br s, 1H), 4.04 (dd, J=2, 11 Hz, 1H), 3.98–3.82 (m, 1H), 3.31–3.16 (m, 2H), 2.92 (dd, J=11, 12 Hz, 1H), 2.63–2.51 (m, 1H), 2.47 (dd, J=2, 12 Hz, 1H), 1.84–1.52 (m, 3H). IR: 3650, 3380, 1655, 1470 cm^{-1}. MS (70 eV): M^+ 204 (47), 132 (77), 118 (100), 104 (42), 91 (28), 77 (24). Anal. calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89; N, 13.71. Found: C, 70.50; H, 7.93; N, 13.68.

8.1.4. [4-(2-Oxo-4-phenylazetidin-1-yl)butyl]carbamic acid, *tert*-butyl ester. *N*,*N*′-dicyclohexylcarbodiimide (DCC) (1.3 g, 6.3 mmol) was added to a suspension of 3-bromo-3-phenyl propionic acid (1.37 g, 6.0 mmol) in CH_2Cl_2 (20 mL) at 25°C. After stirring this mixture for 0.5 h, *N*-*tert*-butoxycarbonyl-1,4-diaminobutane[26] (1.13 g, 6.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was then stirred for 1.5 h at rt, filtered through Celite and concentrated to leave the crude amide as a white foam (~100%). ^1H NMR (90 MHz): δ 7.5–7.15 (m, 5H), 6.85 (br t, J=5 Hz, 1H), 5.45 (dd, J=7, 8 Hz, 1H), 5.0–4.7 (br m, 1H), 3.4–2.85 (m, 6H), 2.0–1.0 (br m, 4H), 1.4 (s, 9H).

A solution of the amide (6 mmol) in CH_2Cl_2 (50 mL) and DMF (12 mL) was added slowly over a period of 4 h, to a suspension of hexane-washed NaH (0.36 g, 15 mmol) in CH_2Cl_2 (50 mL) and DMF (12 mL) at rt. When addition was complete, the mixture was stirred for 2 h and quenched with saturated aq. NH_4Cl (100 mL). The mixture was extracted with Et_2O (1×200 mL, 1×100 mL) and the combined Et_2O fractions washed with H_2O (6×100 mL) and brine (100 mL). The Et_2O solution was dried ($MgSO_4$) and evaporated to a pale yellow oil containing some solid. The title compound (1.40 g, 73%) was then obtained by chromatography eluting with 0.5% MeOH/$CHCl_3$. ^1H NMR (90 MHz): δ 7.3 (s, 5H), 4.9–4.6 (br m, 1H), 4.5 (dd, J=2.5, 5 Hz, 1H), 3.5–2.65 (m, 6H), 1.7–1.3 (m, 4H), 1.4 (s, 19H). IR: 3450, 1740, 1710, 1515 cm^{-1}. MS (20 eV): M^+ 318 (l), 262 (14), 149 (24), 114 (17), 104 (48), 70 (100), 1 57 (15). HRMS calcd for $C_{14}N_{18}N_2O_3$ (parent minus C_4H_8): 262.1317. Found: 262.1306.

8.1.5. 1-(4-Aminobutyl)-4-phenylazetidin-2-one (18). Gaseous HCl was bubbled through a solution of [4-(2-oxo-4-phenylazetidin-1-yl)butyl]carbamic acid, *tert*-butyl ester (0.56 g, 1.76 mmol) in CH_2Cl_2 (40 mL) for ~5 min at 0°C. The solution was stirred at 0°C for 2.5 h and concentrated. The residue was dissolved in 1N aq. NaOH (30 mL) and then extracted with CH_2Cl_2 (4×30 mL). The combined CH_2Cl_2 fractions were dried (Na_2SO_4) and evaporated. The pure amino β-lactam (209 mg, 54%) was obtained by chromatography eluting with EtOAc and then 25:1:1 $CHCl_3$/MeOH/*i* $PrNH_2$. ^1H NMR (90 MHz): δ 7.3 (s, 5H), 4.5 (dd, J=2.5, 5 Hz, 1H), 3.6–3.15 (m, 2H), 3.0–2.45 (m, 4H), 1.65–1.3 (m, 4H), 1.3–1.0 (br s, 2H). IR: 1740 cm^{-1}. MS (70 eV): M^+ 218 (l), 118 (18), 104 (93), 91 (23), 78 (14), 70 (100). HRMS calcd for $C_{13}H_{18}N_{20}$: 218.1419. Found: 218.1418.

8.1.6. 4-Phenyl[1,5]diazonan-2-one (19) by transamidation of 18. A solution of **18** (35 mg, 0.16 mmol) in 2,4-lutidine (10 mL) was purged with N_2 for 5 min. and then heated to reflux for 64 h. The lutidine was removed under vacuum to leave a brown oil. Chromatography, eluting successively with EtOAc and 25:1:1 $CHCl_3$/MeOH/*i* $PrNH_2$, gave pure **19** (20 mg, 57%) and unreacted **18** (14 mg, 40%).

8.2. Ring contraction of 19

A solution of the 9-membered azalactam **19** (35 mg, 0.16 mmol) in 2,4-lutidine (10 mL) was purged with N_2 for 5 min and then heated to reflux for 64 h. The lutidine was removed under vacuum to leave a brown oil showing IR absorption at 1740 and 1670 cm^{-1} (neat). Thin layer chromatography (25:1:1 $CHCl_3$/MeOH/*i* $PrNH_2$) clearly showed the presence of the β-lactam **18** and unreacted **19** in the crude product. The oil was chromatographed eluting successively with EtOAc and 25:1:1 $CHCl_3$/MeOH/*i* $PrNH_2$ to obtain **18** (~1 mg, 3%) and recovered **19** (20 mg, 57%).

8.2.1. 3-Phenylhexahydropyrazolo[1,2-a]pyridazin-1-one (22). A mixture of hexahydropyridazine[32] (3 g, 34.8 mmol) and ethyl cinnamate (7.1 g, 40.3 mmol) was heated to reflux in an oil bath at 160°C for 1 h. The condenser was replaced with an 8 cm Vigreux column fitted with a short-path distillation head. Heating of the reaction mixture at 160°C was resumed for 10.5 h and was accompanied by distillation of EtOH. On cooling, the crude product crystallized. Chromatography with EtOAc as eluant provided pure **22** (6.0 g, 80%) as a white crystalline solid. An analytical sample was prepared by two recrystallizations from hot hexanes to give white crystals, mp 65–66°C. ^1H NMR (270 MHz): δ 7.44–7.25 (m, 5H), 4.18 (br d, J=12.4 Hz, 1H), 3.84 (dd, J=8.1, 11.7 Hz, 1H), 3.08–2.98 (m, 2H), 2.88 (dd, J=8.1, 16.8 Hz, 1H), 2.56 (dd, J=11.7, 16.8 Hz, 1H), 2.30–2.21 (m, 1H), 1.77–1.33 (m, 4H). FT IR: 1676 cm^{-1}. MS (70 eV): 217 (14), m 216 (100), 139 (25), 104 (45), 85 (54), 56 (34), 41 (25). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.10; H, 7.29; N, 13.02.

8.2.2. 4-Phenyl[1,5]diazonan-2-one (19) by Na/NH_3 reduction of 22. Sodium metal (0.53 g, 23 mmol) was carefully added in portions to a refluxing mixture of **22** (2.0 g, 9.25 mmol) and liquid NH_3 (50 mL). The resulting blue solution was allowed to reflux (−33°C) for 1.25 h. The reaction was quenched by slow addition of solid NH_4Cl (1.5 g, 28 mmol). After evaporation of NH_3, the residue was

extracted with several portions of CH_2Cl_2 which were combined and concentrated to leave a yellow solid. Chromatography with EtOAc as eluant afforded **19** (1.60 g, 79%) as a white crystalline solid. An analytical sample was obtained by recrystallization from hexanes/CH_2Cl_2 to give white crystals, mp 97–98°C.[44] ^{1}H NMR (270 MHz): δ 7.40–7.22 (m, 5H), 6.98 (br s, 1H), 3.86–3.67 (m, 1H), 3.58 (dd, J=2.2, 12.2 Hz, 1H), 2.90–2.70 (m, 3H), 2.52 (t, J=12.2 Hz, 1H), 2.37 (dd, J=2.2, 12.2 Hz, 1H), 1.98–1.32 (m, 5H). FT IR: 3341, 1670, 1549 cm^{-1}. MS (70 eV): M$^+$ 218 (33), 158 (30), 146 (72), 132 (45), 119 (36), 118 (91), 106 (52), 104 (100), 91 (42), 70 (34). Anal. calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.38; H, 8.23; N, 12.81.

8.2.3. 4-Phenyl[1,5]diazonan-2-one (19) by $NaBH_3CN$ reduction of 23. To a solution of **23**[35] (428 mg, 2 mmol) in glacial AcOH (5 mL) at rt was added $NaBH_3CN$ (504 mg, 8 mmol) in portions. The mixture was stirred at rt for 2 h, warmed at 50°C for 1 h and then stirred overnight at rt (22.5 h). After cooling the mixture to 0°C in an ice bath, H_2O (12 mL) was added and the solution made strongly basic by addition of 50% aq. NaOH. The mixture was extracted with CH_2Cl_2 (3×50 mL). The combined CH_2Cl_2 fractions were washed with brine, dried over K_2CO_3 and concentrated to a yellow oil. Pure **19** (134 mg, 31%) was obtained by chromatography with EtOAc as eluant.

8.2.4. 2-[3-(2-Oxo-4-phenyl[1,5]diazonan-1-yl)propyl]-isoindole-1,3-dione (20). A 60% suspension of NaH in oil (140 mg, 3.5 mmol) was rinsed with hexane. To this was added DMF (6 mL) and **19** (500 mg, 2.3 mmol). The mixture was mechanically stirred while it was warmed in an oil bath at 50–55°C. Evolution of H_2 was observed and when this was complete, the resulting solution was allowed to cool to rt. Solid *N*-(3-iodopropyl)phthalimide[45] (795 mg, 2.5 mmol) was then added in one portion. The reaction mixture was stirred for 2 h at rt and quenched by addition of saturated aq. NH_4Cl (25 mL). The aqueous mixture was extracted with EtOAc (2×50 mL). The combined EtOAc extracts were washed with H_2O (10×50 mL), dried (Na_2SO_4) and concentrated to a yellow oil. Chromatography with EtOAc as eluant gave pure **20** (215 mg, 23%) and unreacted **19** (100 mg, 20%). The material was recrystallized from benzene/hexanes, mp 122–123°C. ^{1}H NMR (270 MHz): δ 7.87–7.80 (m, 2H), 7.75–7.66 (m, 2H), 7.38–7.20 (m, 5H), 4.86–4.75 (m, 1H), 4.00–3.89 (m, 1H), 3.78–3.71 (m, 3H), 3.29 (dd, J=5, 14 Hz, 1H), 3.16 (dd, J=11, 12.5 Hz, 1H), 2.98–2.76 (m, 3H), 2.59 (d, J=12.5 Hz, 1H), 2.05–1.33 (m, 7H). FT IR: 1771, 1713, 1615 cm^{-1}. MS (70 eV): M$^+$ 405 (12), 259 (37), 245 (42), 244 (37), 243 (22), 188 (23), 160 (100), 159 (98), 158 (30), 146 (53), 132 (35), 118 (39), 104 (58), 91 (35), 84 (26), 77 (25), 70 (34). Anal. calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.99; H, 6.90; N, 10.14.

8.2.5. 2-Phenyl-4-oxo-[1,5]diazonane-1-carboxylic acid, *tert*-butyl ester (21). A solution of the azalactam **19** (110 mg, 0.5 mmol) and di-*tert*-butyldicarbonate (130 mg, 0.6 mmol) in dioxane (2 mL) was warmed at 60°C for 22 h. The solvent was evaporated to leave a clear oil that crystallized on standing. Chromatography with EtOAc as eluant provided pure **21** (150 mg, 94%) as a white crystalline solid which was recrystallized from CH_2Cl_2/hexanes, mp 147–148°C. ^{1}H NMR (90 MHz): δ 7.25 (br s, 5H), 6.5, 5.6–5.0 (br s, br m, total 1H), 4.7–4.0 (m, 1H), 4.0–2.4 (series of br m, 6H), 2.2–1.55 (br s, 4H), 1.55–0.9 (3 br s, total 9H). IR: 3430, 3370, 1680, 1520 cm^{-1}. MS (20 eV): M$^+$ 318 (1), 262 (100), 218 (6), 146 (27), 104 (19), 70 (16), 57 (41). Anal. calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 68.03; H, 8.28; N, 8.78.

8.2.6. 1-(3-Aminopropyl)-4-phenyl[1,5]diazonan-2-one (11). A solution of **20** (190 mg, 0.47 mmol) and 85% hydrazine hydrate (0.25 mL) in absolute EtOH was heated for 1 h. A white solid precipitated during this time. After evaporation of EtOH, the residue was dissolved in concd aq. NH_4OH (5 mL). The solution was diluted with H_2O (5 mL), saturated with NaCl, and extracted four times with CH_2Cl_2. The combined CH_2Cl_2 fractions were dried (Na_2SO_4) and concentrated to afford the crude azalactam **11** (130 mg, 100%) as a yellow oil. Except for a trace of the ring-expanded product (**12**), this material was quite pure as determined by ^{1}H NMR and IR. ^{1}H NMR (90 MHz): δ 7.25 (s. 5H), 4.9–4.5 (m, 1H), 4.1–3.65 (m, 2H), 3.4–2.4 (m, 8H), 2.2–1.2 (m, 9H). IR: 1620, 1475 cm^{-1}.

8.2.7. 2-Phenyl-1,5,9-triazacyclotridecan-4-one (12). A solution of **20** (259 mg, 0.64 mmol) and 85% hydrazine hydrate (0.35 mL) in absolute EtOH (7 mL) was heated to reflux for 19 h. After cooling, the EtOH was evaporated to leave a white residue that was dissolved in concd aq. NH_4OH (8 mL). The solution was diluted with H_2O (10 mL), saturated with NaCl and extracted with CH_2Cl_2 (6×20 mL). The combined CH_2Cl_2 fractions were dried and concentrated to leave a partially solid yellow residue. The relative integral intensity of the signals at δ 8.5 (amide NH, 1H) for **12** and δ 4.9–4.5 (m, 1H) for **11** indicated that the ratio of **12** to **11** in this mixture was ~6:4. The material was dissolved in 1N aq. NaOH (4 mL) and dioxane (2 mL). After it was warmed at 50°C for 7 h, the solution was diluted with H_2O (10 mL), saturated with NaCl and extracted with CH_2Cl_2 (6×25 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated to leave the crude product. This was chromatographed eluting with 10:5:1 $CHCl_3$/MeOH/*i* $PrNH_2$ and then 5:5:1 $CHCl_3$/MeOH/*i* $PrNH_2$. The white crystalline azalactam **12** (86 mg, 50%) eluted with the latter solvent system. A small amount of impure **11** was eluted in advance of **12**. Analytically pure white crystals of **12**, mp 128–131°C (lit.[30] mp 132–133°C), were obtained by recrystallization from CH_2Cl_2/hexanes. ^{1}H NMR (500 MHz): δ 8.50 (br s, 1H), 7.40–7.10 (m, 5H), 3.93 (dd, J=5.0, 9.1 Hz, 1H), 3.70–3.61 (m, 1H), 3.30–3.22 (m, 1H), 2.95–2.88 (m, 1H), 2.83–2.77 (m, 1H), 2.77–2.66 (m, 2H), 2.60–2.53 (m, 1H), 2.52–2.47 (m, 2H), 2.42–2.34 (m, 1H), 2.10–1.82 (br s, 2H), 1.82–1.71 (m, 3H), 1.71–1.60 (m, 1H), 1.60–1.50 (m, 1H), 1.48–1.38 (m, 1H). IR: 3650, 3210, 1650 1530 cm^{-1}. MS (70 eV): M$^+$ 275 (7), 259 (16), 258 (100), 191 (9), 160 (17), 146 (31), 126 (17), 118 (19), 104 (28), 84 (17). Anal. calcd for $C_{16}H_{25}N_3O$: C, 69.78; H, 9.15; N, 15.26. Found: C, 69.90; H, 9.21; N, 14.98.

8.2.8. (±)-Celacinnine (1). The title compound was prepared from the azalactam **12** according to the procedure of Yamamoto and Maruoka.[30] A solution of **12** (114 mg, 0.41 mmol) and DMAP (150 mg, 1.23 mmol) in CH_2Cl_2

(20 mL) was cooled to −78°C. A solution of cinnamoyl chloride (103 mg, 0.62 mmol) in CH_2Cl_2 (2mL) was then added dropwise. The reaction was stirred at −78°C for 2.5 h and allowed to stand at −20°C for 8 h. The mixture was poured into 14% aq. NH_4OH (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×25 mL). Evaporation of the combined CH_2Cl_2 fractions (dried over Na_2SO_4) left a clear oil that crystallized on standing. Pure (±)-celacinnine (**1**) (142 mg, 85%) was obtained by chromatography with 6% MeOH/$CHCl_3$ as eluant. White crystals, mp 181–185°C (lit.[30] mp 178–181°C) were obtained by crystallization from CH_2Cl_2/hexanes. ^{1}H NMR (270 MHz): δ 7.71 (d, J=15.4 Hz, 1H), 7.57–6.96 (11H), 6.83 (d, J=15.4 Hz, ~0.5H), 6.81 (d, J=15.7 Hz, ~0.5H), 4.01–3.93 (m, 1H), 3.85–3.06 (m, 6H), 2.75–2.61 (m, 1H), 2.57–2.36 (m, 3H), 2.20–1.31 (m, 7H). FT IR: 3450, 3210, 1656 (sh), 1649, 1598, 1548, 1520, 1496 cm^{-1}. MS (70 eV): M^+ 405 (9), 274 (70), 260 (13), 188 (12), 160 (21), 159 (14), 146 (35), 131 (100), 104 (23), 103 (62), 100 (25), 91 (23), 84 (27), 70 (35), 69 (21), 56 (19), 44 (34), 43 (21).

An excellent correlation was observed between the 270 MHz ^{1}H NMR and FT-IR spectra of synthetic (±)-celacinnine and the corresponding spectra obtained from a sample of authentic (±)-**1** provided by Dr Bruce Ganem, Cornell University. The TLC properties of the synthetic and reference material were identical (acetone: R_f=0.54; 10% MeOH/EtOAc: R_f=0.30).

8.2.9. Hexahydropyrazolo[1,2-*a*]pyridazin-1-one (26). Ethyl acrylate (16.9 g, 0.17 mol) was added slowly to hexahydropyridazine (13.2 g, 0.15 mol) cooled in an ice bath. The mixture was initially heated to reflux in an oil bath at 190°C for 3 h. A short path distillation head was then attached to the flask and heating was continued at 170°C for 10 h with EtOH distilling off. The reaction mixture was then distilled to give **26** as an oil (18.1 g, 85%), bp 78–81°C/0.07 mm Hg. ^{1}H NMR (90 MHz): δ 4.35–2.15 (br m, 8H), 1.95–1.2 (br m, 4H). IR (neat): 1680 cm^{-1}. MS (70 eV): M^+ 140 (55), 84 (38), 56 (100), 41 (72). Elemental analysis was obtained on the HCl salt (HCl/Et_2O; recrystallized from MeOH/Et_2O). Anal. calcd for $C_7H_{13}ClN_2O$: C, 47.59; H, 7.42; N, 15.86; Cl, 20.07. Found: C, 47.61; H, 7.53; N, 15.99; Cl, 20.28.

8.2.10. [1,5]Diazonan-2-one (27). Lactam **26** (2.80 g, 20 mmol) was dissolved in refluxing anhydrous liquid NH_3. Sodium metal (1.38 g, 60 mmol) was then added in small pieces to the solution. During the addition of Na, a permanent blue color developed. The mixture was kept at reflux for 1.75 h and then quenched by addition of an excess of NH_4Cl (4.3 g, 80 mmol). The NH_3 was evaporated under a stream of N_2 to leave a solid residue that was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (K_2CO_3) and concentrated. The crude crystalline product was distilled under vacuum (bp 114–116°C/0.8 mm Hg) to afford pure **27** (2.49 g, 87%) as a white crystalline solid which was recrystallized from hexanes, mp 82–84°C. ^{1}H NMR (90 MHz): δ 6.8, 5.6 (2 br s, total 1H), 3.9–3.6 (m, 1H), 3.6–2.6 (m, 4H), 2.55–2.35 (m, 1H), 2.15 (t, J=6 Hz, 2H), 2.05 (s, 1H), 1.8–1.2 (br m, 4H). IR: 3640, 3370, 1670, 1555 cm^{-1}. MS (70 eV): M^+ 142 (39), 114 (100), 84 (57), 70 (93), 57 (97), 43 (41). Anal. calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.38; H, 10.11; N, 19.94.

8.2.11. (*E*)-5-(3-Phenylacryloyl)[1,5]diazonan-2-one (28). To a solution of the azalactam **27** (1.42 g, 10 mmol) and DMAP (1.22 g, 10 mmol) in CH_2Cl_2 (30 mL) at rt was added cinnamoyl chloride (1.67 g, 10 mmol). The reaction was stirred overnight (10 h) and washed with 0.5N aq. HCl (10 mL) and H_2O (20 mL). The solution was dried (Na_2SO_4) and concentrated to leave **28** (2.57 g, 95%) as a white crystalline solid. This material was recrystallized from CH_2Cl_2/hexanes, mp 147–148°C. ^{1}H NMR (90 MHz): δ 7.9–6.7 (m, 7H), 5.8–5.4 (br s, 1H), 3.9–3.0 (m, 5H), 2.9–2.3 (m, 3H), 2.0–1.4 (m, 4H). IR: 3320, 1650, 1600 cm^{-1}. MS (70 eV): M^+ 272 (17), 131 (100), 103 (38), 77 (23). Anal. calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.40; H, 7.40; N, 10.17.

8.2.12. (*E*)-1-(4-Methoxy-2,3,6,7,8,9-hexahydro[1,5]diazonin-1-yl)-3-phenylprop-2-en-1-one (29). To a solution of the lactam **28** (545 mg, 2.0 mmol) in CH_2Cl_2 (15 mL) was added trimethyloxonium tetrafluoroborate (316 mg, 2.1 mmol). The reaction was stirred at rt for 12 h and then quenched by addition of a solution of K_2CO_3 (0.33 g) in H_2O (0.35 mL). The mixture was diluted with CH_2Cl_2, dried (Na_2SO_4) and concentrated to leave the crude lactim ether **29** (448 mg, 78%). Thin layer chromatography (10% MeOH/$CHCl_3$) and ^{1}H NMR (90 MHz) indicated that only traces of impurities, including starting material and methyl cinnamate were present. Since **29** was found to decompose on silica gel the crude product was normally used directly, without purification, for the subsequent reaction. However, a sample of pure **29** (a colorless oil) could be obtained by chromatography on a short column eluting with EtOAc. ^{1}H NMR (90 MHz): δ 7.7 (d, J=15 Hz, 1H), 7.7–7.3 (m, 5H), 7.0 (d, J=15 Hz, 1H), 3.8–3.25 (m, 6H), 3.65 (s. 3H), 2.8–2.6 (m, 2H), 2.0–1.7 (m, 2H), 1.7–1.4 (m. 2H). IR: 1670, 1650, 1600 cm^{-1}. MS (70 eV): M^+ 286 (11), 271 (9), 155 (48), 131 (100), 113 (21), 103 (48), 82 (31), 77 (23), 70 (18). HRMS calcd for $C_{17}H_{22}N_2O_2$: 286.1682. Found: 286.1685.

8.2.13. (*E*)-2-Phenyl-9-(3-phenylacryloyl)-2,5,6,7,8,9,10,11-octahydro-3*H*-1,4a,9-triaza-benzocyclononen-4-one (30). A solution of crude **29** (448 mg, 1.56 mmol) and 4-phenylazetidin-2-one[21,36] (240 mg, 1.60 mmol) in chlorobenzene (2 mL) was heated to reflux for 21 h. After evaporation, the residue was chromatographed on a short column eluting with EtOAc. The product (**30**) (636 mg, 67%) was recrystallized from CH_2Cl_2/hexanes to obtain an analytical sample, mp 195–197°C. ^{1}H NMR (270 MHz, 50°C): δ 7.72 (d, J=15.4 Hz, 1H), 7.54–7.25 (m, 10H), 6.97 (d, J=15.4 Hz, 1H), 4.65 (dd, J=4.81 13.4 Hz, 1H), 4.34–2.57 (m, 10H), 2.11–1.39 (m, 4H). IR: 1690, 1640, 1600 cm^{-1}. MS (70 eV): 402 (20), M^+ 401 (31), 270 (12), 227 (14), 131 (100), 103 (64), 84 (22), 77 (25). Anal. calcd for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.56; H, 6.62; N, 10.43.

8.2.14. (±)-Dihydroperiphylline (2). A solution of **30** (400 mg, 1.0 mmol) and $NaBH_3CN$ (190 mg, 3.0 mmol) in AcOH (3.5 mL) was stirred for 3 h at rt, 2 h at 50°C and then overnight (12 h) at rt. While it was cooled in an ice bath, the solution was diluted with H_2O (10 mL) and made

alkaline by addition of 50% aq. NaOH (5 mL). The mixture was extracted with CH_2Cl_2 (2×100 mL) and the combined extracts dried (Na_2SO_4) and concentrated to yield (±)-dihydroperiphylline (**2**) (375 mg, 93%) as a white solid. The recrystallized material (CH_2Cl_2/hexanes) displayed anomalous melting behavior, slowly turning from a white solid to a white foam on heating above 35°C. ^{1}H NMR (270 MHz, 50°C): δ 7.67 (d, J=15.4 Hz, 1H), 7.47–7.16 (m, 11H), 6.79 (d, J=15.4 Hz, 1H), 3.91 (m, 1H), 3.89–3.06 (m, 6H), 2.68–2.55 (m, 1H), 2.50–2.32 (m, 3H), 2.01–1.49 (m, 7H). FT IR: 3300, 1648, 1601, 1546, 1523 cm^{-1}. MS (70 eV): M$^+$ 405 (3), 350 (7), 314 (18), 288 (2), 274 (20), 260 (7), 201 (9), 163 (9), 146 (31), 131 (100), 118 (18), 103 (50), 98 (13), 91 (17), 84 (10), 77 (18), 70 (22), 44 (15). TLC (R_f=0.50, 10% MeOH/$CHCl_3$).

The structure of **2** was confirmed by using natural periphylline[46] (kindly provided by Dr H. P. Husson, Institut de Chemie des Substances Naturelles, C.N.R.S., Gif-sur-Yvette, France) as a reference material. Hydrogenation of **2** with PtO_2 in EtOH yielded tetrahydroperiphylline, identical (NMR, IR, TLC) with the product obtained from periphylline by the uptake of 2 mol of hydrogen. Selective reduction of periphylline by using $NaBH_3CN$ in formic acid yielded a dihydro product identical (NMR, MS, TLC) with synthetic (±)-dihydroperiphylline (**2**).

8.2.15. 3,4,7,8-Tetrahydro-2*H*-pyrrolo[1,2-*a*]pyrimidin-6-one (32). A mixture of *N*-*tert*-butoxycarbonyl-1,3-diaminopropane (8.05 g, 46 mmol), succinic anhydride (4.6 g, 46 mmol) and xylenes (20 mL) was heated to reflux for 30 min. After cooling the solution, additional xylenes (50 mL) and *p*-TsOH·H_2O (0.2 g) were added. The mixture was then heated to reflux for 17.5 h, collecting water in a Dean–Stark trap. The apparatus was fitted with a short path distillation head and the solvent was distilled off at 1 atm. The dark residue was transferred to a smaller flask and distilled under vacuum collecting material boiling between ~160 and 180°C at ~4 mm Hg. The crude distillate was again distilled under vacuum to afford **32** as an oil that solidified on cooling (4.6 g, 72%), bp 113–122°C/0.15 mm Hg, mp 44–46°C (lit.[41] mp 23–25°C). IR: 1740, 1675 cm^{-1}. Anal. calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.29; N, 20.27. Found: C, 60.72; H, 7.20; N, 20.34.

8.2.16. Hexahydropyrrolo[1,2-*a*]pyrimidin-6-one (33). To a solution of **32** (3.0 g, 21.7 mmol) in MeOH (50 mL) was added solid $NaBH_4$ (1.6 g, 42 mmol) in portions. After it was stirred at rt for 15 h, the solvent was evaporated. The remaining solid was extracted repeatedly with Et_2O and CH_2Cl_2. The combined organic extracts were dried over K_2CO_3 and concentrated to a white gelatinous solid. This was chromatographed, eluting with 1:2:25 *i*PrNH$_2$/MeOH/$CHCl_3$ to afford **33** as a clear oil (1.30 g, 43%). IR: 1680 cm^{-1}. MS (70 eV): M$^+$ 140 (81), 139 (100). HRMS calcd for $C_7H_{12}N_2O$: 140.0942. Found: 140.0949.

8.2.17. 1-(3-Phenylacryloyl)-hexahydropyrrolo[1,2-*a*]-pyrimidin-6-one (34). To a solution of **33** (1.16 g, 8.3 mmol), Et_3N (1.4 mL, 10.0 mmol) and DMAP (50 mg, 0.41 mmol) in CH_2Cl_2 (50 mL) at rt was added cinnamoyl chloride (1.4 g, 8.4 mmol). The reaction mixture was stirred for 30 min and then washed successively with 1N aq. HCl, H_2O, saturated aq. $NaHCO_3$ and brine (50 mL each). The solution was dried ($MgSO_4$) and concentrated to red oil. Chromatography eluting with EtOAc and then 10% MeOH/EtOAc afforded **34** as a white foam (1.9 g, 85%). IR: 1695, 1650, 1605 cm^{-1}. MS (70 eV): 271 (8), M$^+$ 270 (44), 139 (100), 131 (97), 103 (36), 77 (20).

8.2.18. 4-Oxo-[1,5]diazonane-1-carboxylic acid, *tert*-butyl ester (39). To a solution of the azalactam **27** (2.69 g, 18.9 mmol) in CH_2Cl_2 (30 mL) at rt was added a solution of di-*tert*-butyldicarbonate (4.3 g, 19.7 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred until evolution of CO_2 was complete (~20 min). The solvent was evaporated to leave a clear oil that was chromatographed on a short column eluting with EtOAc. Pure **39** (4.55 g, 99%) was obtained as a colorless oil. Crystallization from CH_2Cl_2/hexanes provided analytically pure white crystals, mp 91–92°C. ^{1}H NMR (90 MHz): δ 6.0, 5.2 (2 br s, total 1H), 3.6–3.0 (m, 6H), 2.8–2.3 (m, 2H), 1.8–1.6 (m, 4H), 1.5 (s, 9H). IR: 1680, 1660, 1520 cm^{-1}. MS (20 eV): M$^+$ 242 (1), 186 (23), 142 (22), 125 (28), 114 (46), 70 (33), 57 (100). Anal. calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.20; H, 8.93; N, 11.44.

8.2.19. 5-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)propyl]-4-oxo[1,5]diazonane-1-carboxylic acid, *tert*-butyl ester (41). A 60% suspension of NaH in oil (1 g, 25 mmol) was rinsed with hexane. To this was added DMF (55 mL) and the azalactam **39** (4.0 g, 16.5 mmol). The mixture was mechanically stirred while it was warmed in an oil bath at 50–55°C. Evolution of H_2 was observed and when this was complete, the resulting solution was allowed to cool to rt. Solid *N*-(3-bromopropyl))phthalimide (6.7 g, 25 mmol) was then added. The reaction was stirred for 3 h at rt and quenched by addition of saturated aq. NH_4Cl (100 mL). The mixture was diluted with H_2O (100 mL) and extracted with Et_2O (2×150 mL). The Et_2O extracts were combined, washed with H_2O (5×120 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated to a yellow oil. Chromatography with EtOAc as eluant provided pure 41 (5.3 g, 75%) as a colorless oil which could be crystallized from hexanes/benzene to give analytically pure white crystals, mp 105–106°C. ^{1}H NMR (500 MHz, 50°C): δ 7.83–7.81 (m, 2H), 7.70–7.68 (m, 2H), 3.70 (t, J=7.1 Hz, 2H), 3.62–2.95 (br m, 8H), 2.85–2.60 (br m, 2H), 1.97 (quin, J=7.1 Hz, 2H), 1.87–1.64 (br m, 2H), 1.48 (s, 3H), 1.64–1.00 (br m, 2H). IR: 1775, 1715, 1690, 1625 cm^{-1}. MS (20 eV): M$^+$ 429 (20), 329 (77), 285 (51), 243 (98), 217 (63), 70 (50), 57 (100). Anal. calcd for $C_{23}H_{31}N_3O_5$: C, 64.32; H, 7.27; N, 9.78. Found: C, 64.10; H, 7.12; N, 9.66.

8.2.20. 5-(3-Aminopropyl)-4-oxo[1,5]diazonane-1-carboxylic acid, *tert*-butyl ester (43). A solution of **41** (4.3 g, 10 mmol) and 85% hydrazine hydrate (5.7 mL) in absolute EtOH (110 mL) was heated to reflux for 1 h. A white solid precipitated shortly after the reaction began. The EtOH was evaporated and the residue dissolved in concd aq. NH_4OH (120 mL). The resulting solution was saturated with NaCl and extracted with CH_2Cl_2 (4×100 mL). The combined CH_2Cl_2 fractions were dried (Na_2SO_4) and concentrated to a yellow oil. Chromatography eluting with 5:2:1 $CHCl_3$/MeOH/*i*PrNH$_2$ gave pure **43** (2.8 g, 93%) as a pale yellow oil. ^{1}H NMR (500 MHz, 50°C): δ 3.85–2.95 (br

m, 8H), 2.85–2.50 (br m, 2H), 2.68 (t, J=6.8 Hz, 2H), 1.85–1.55 (m, 4H), 1.67 (quin, J=6.8 Hz, 2H), 1.55–1.05 (m, 2H), 1.47 (s, 9H). IR: 1685, 1620 cm^{-1}. MS (20 eV): M^+ 299 (24), 281 (9), 226 (24), 213 (41), 199 (36), 182 (34), 156 (43), 141 (28), 125 (40), 113 (45), 84 (60), 70 (38), 57 (100). HRMS calcd for $C_{15}H_{29}N_3O_3$: 299.2209. Found: 299.2214.

8.2.21. 4-Oxo-1,5,9-triazacyclotridecane-1-carboxylic acid, *tert*-butyl ester (45). A solution of the azalactam **43** (1.0 g, 3.3 mmol) in 2,4-lutidine (300 mL) was heated to reflux for 19 h. After cooling the solution, the 2,4-lutidine was removed by distillation under vacuum to leave an orange oil. The crude material was chromatographed with 25:2:1 $CHCl_3$/MeOH/i $PrNH_2$ as eluant to yield partially purified **45** (0.48 g) containing a small amount of the starting material. The oily mixture crystallized on standing. An analytical sample was prepared by two recrystallizations from CH_2Cl_2/hexanes to provide white crystals, mp 112–113°C. The partially purified material was normally used in the subsequent step. ^{1}H NMR (500 MHz, 50°C): δ 7.5 (br s, 1H), 3.64–3.62 (m, 2H), 3.47–3.44 (m, 2H), 3.30 (t, J=6.5 Hz, 2H), 2.78–2.76 (m, 2H), 2.67–2.65 (m, 2H), 2.47–2.45 (m, 2H), 1.73–1.62 (m, 4H), 1.62–1.35 (m, 3H), 1.47 (s, 9H). IR: 1680, 1660 (sh), 1525 cm^{-1}. MS (20 eV): M^+ 299 (27), 198 (100), 156 (22), 141 (28), 129 (42), 112 (21), 100 (23), 84 (34), 70 (24), 57 (40). Anal. calcd for $C_{15}H_{29}N_3O_3$: C, 60.17; H, 9.76; N, 14.03. Found: C, 59.94; H, 9.79; N, 13.97.

8.2.22. 4-Oxo-1,5,9-triazacyclotridecane-1,9-dicarboxylic acid, 1-*tert*-butyl ester, 9-(2,2,2-trichloroethyl) ester (47). To a solution of the partially purified azalactam **45** (0.41 g, 1.37 mmol) and DMAP (250 mg, 2.05 mmol) in CH_2Cl_2 (11 mL) at rt was added 2,2,2-trichloroethylchloroformate (0.23 mL, 1.67 mmol). The reaction was stirred at rt for 45 min and then concentrated. The residue (containing insoluble DMAP hydrochloride) was chromatographed eluting with EtOAc to yield pure **47** (0.56 g, 40% from **43**) as a colorless oil. The less polar 2,2,2-trichloroethyl-carbonyl derivative of **43** eluted separately in advance of **47**. An analytical sample of **47** was prepared by running a second column as above and carefully evaporating the solvent with a stream of dry N_2. The last traces of solvent were removed by warming the sample at 50°C under high vacuum. ^{1}H NMR (500 MHz, 50°C): δ 5.87 (br t, 1H), 4.77 (s, 2H), 3.72–3.60 (br m, 2H), 3.53–3.36 (m, 6H), 3.20 (t, J=6.5 Hz, 2H), 2.45–2.32 (br m, 2H), 2.03–1.93 (m, 2H), 1.68–1.45 (m, 4H), 1.48 (s, 9H). IR: 1710 (sh), 1700 (sh), 1680, 1520 cm^{-1}. MS (20 eV): 477 (3), 475 (8), 473 (10), 376 (32), 375 (46), 374 (77), 373 (54), 372 (77), 338 (36), 334 (43), 332 (44), 270 (40), 208 (46), 141 (44), 127 (32), 115 (35), 114 (44), 84 (41), 69 (50), 57 (100). Anal. calcd for $C_{18}H_{30}Cl_3N_3O_5$: C, 45.53; H, 6.37; Cl, 22.40; N, 8.85. Found: C, 45.62; H, 6.39; Cl, 22.42; N, 8.78.

8.2.23. 1,5,9-Triazacyclotridecan-4-one (46). Gaseous HCl was bubbled for 10 min through a solution of **41** (458 mg, 1.07 mmol) at 0°C. The solution was stirred at 0°C for another 10 min and then concentrated. The HCl salt (**42**) was dissolved in absolute EtOH (10 mL) and to the solution was added 85% hydrazine hydrate (0.8 mL). The mixture was then heated to reflux for 12 h, cooled and then concentrated. The white residue was dissolved in concd aq. NH_4OH (15 mL), diluted with H_2O (10 mL) and saturated with NaCl. This solution was extracted with CH_2Cl_2 (4×50 mL). The combined organic fractions were dried (Na_2SO_4) and evaporated to leave **46** (124 mg, 58%) as a white crystalline solid which was recrystallized from EtOAc/hexanes, mp 115–117°C (lit.[30] mp 113.5–115°C). ^{1}H NMR (90 MHz): δ 8.5 (br s, 1H), 3.5–3.25 (m, 2H), 3.15 (br s, 2H), 3.0–2.55 (m, 8H), 2.5–2.25 (m, 2H), 1.8–1.5 (br m, 6H). IR: 3650, 3250, 1650, 1540 cm^{-1}. MS (70 eV): M^+ 199 (27), 182 (33), 156 (31), 141 (30), 128 (27), 112 (26), 100 (65), 84 (100), 70 (91), 56 (31). The ^{1}H NMR, IR and MS spectra of this material compared well with the corresponding spectra of authentic **46** provided by Dr K. Maruoka, Nagoya University, Japan.[30]

8.2.24. 4-Oxo-1,5,9-triazacyclotridecane-1,9-dicarboxylic acid, di-*tert*-butyl ester (49). To a solution of **46** (50 mg, 0.25 mmol) in CH_2Cl_2 (1 mL) was added a solution of di-*tert*-butyldicarbonate (120 mg, 0.55 mmol) in CH_2Cl_2 (2 mL). After stirring the solution at 25°C for 1 h, the solvent was evaporated to a clear oil. Chromatography with EtOAc as eluant provided pure **49** (90 mg, 90%). ^{1}H NMR (90 MHz): δ 6.25 (br t, J=6 Hz, 1H), 3.8–3.6 (m, 2H), 3.5–3.05 (m, 8H), 2.4–2.2 (m, 2H), 2.0–1.7 (m, 2H), 1.7–1.4 (m, 4H), 1.48 (s, 9H), 1.43 (s, 9H).

8.2.25. 4-Methoxy-1,5,9-triazacyclotridec-4-ene-1,9-dicarboxylic acid, 1-*tert*-butyl ester, 9-(2,2,2-trichloroethyl) ester (51). To a solution of the azalactam **47** (582 mg, 1.23 mmol) in CH_2Cl_2 (6.5 mL) over 4 Å molecular sieves (1.5 g) was added trimethyloxonium tetrafluoroborate (273 mg, 1.84 mmol) under N_2 in a glove bag. The mixture was stirred for 4.5 h at rt. After it was cooled to 0°C, the reaction mixture was quenched by addition of saturated aq. $NaHCO_3$ (4 mL) and stirred for an additional 5 min. The aqueous and organic layers were separated and the aqueous layer washed several times with CH_2Cl_2. The combined CH_2Cl_2 fractions were dried (K_2CO_3) and concentrated to a colorless oil (0.55 g, 91%). Thin layer chromatography (EtOAc) and ^{1}H NMR (90 MHz) indicated that only traces of impurities, including starting material, were present. Since lactim ether **51** was found to decompose on silica gel, the crude material was normally used directly, without purification, in the subsequent coupling step. However, a sample of pure **51** (a colorless oil) was obtained by chromatography on a short column eluting with EtOAc. ^{1}H NMR (500 MHz, 50°C): δ 4.75 (s, 2H), 3.64 (s, 3H), 3.57–3.45 (m, 4H), 3.42–3.31 (m, 4H), 3.28–3.20 (m, 2H), 2.58–2.49 (m, 2H), 1.98–1.89 (m, 2H), 1.72–1.63 (m, 2H), 1.61–1.45 (m, 2H), 1.46 (s, 9H). IR: 1710, 1680, 1480 cm^{-1}. MS (20 eV): 491 (26), 489 (79), M^+ $^{35}Cl_3$ 487 (80), 432 (42), 430 (43), 388 (100), 386 (98), 374 (46), 372 (49), 347 (20), 345 (25), 340 (80), 252 (32), 174 (49), 155 (31), 141 (23), 114 (37), 112 (80), 111 (47), 100 (53), 91 (47), 84 (30), 57 (20). HRMS calcd for $C_{19}H_{32}Cl_3N_3O_5$: 487.1407. Found: 487.1394.

8.2.26. 4-Ethoxy-1,5,9-triazacyclotridec-4-ene-1,9-dicarboxylic acid, 1-*tert*-butyl ester, 9-(2,2,2-trichloroethyl) ester (52). Prepared in the same manner as **51** from **47** (595 mg, 1.25 mmol) and triethyloxonium tetrafluoroborate (400 mg, 2.1 mmol) in CH_2Cl_2 (6.7 mL). After a reaction

time of 1.5 h and workup, crude **52** was isolated (615 mg, 98%). Thin layer chromatography (EtOAc) and ^{1}H NMR (90 MHz) indicated that only traces of impurities including starting material were present. Since **52** was found to decompose on silica gel, the crude material was normally used directly in the next step. A sample of pure **52** (a colorless oil) was obtained via chromatography on a short column eluting with EtOAc. ^{1}H NMR (500 MHz, 50°C): δ 4.74 (s, 2H), 4.06 (q, J=7.1 Hz, 2H), 3.56–3.44 (m, 4H), 3.39–3.29 (m, 4H), 3.27–3.20 (m, 2H), 2.56–2.48 (m, 2H), 1.95–1.88 (m, 2H), 1.71–1.63 (m, 2H), 1.61–1.40 (m, 2H), 1.45 (s, 9H), 1.25 (t, J=7.1 Hz, 3H). IR: 1715, 1680, 1480 cm^{-1}. MS (20 eV): 505 (12), 503 (31), M$^+$ $^{35}Cl_3$ 501 (37), 446 (27), 444 (33), 402 (84), 400 (100), 374 (77), 372 (93), 361 (21), 359 (24), 354 (31), 252 (21), 188 (21), 155 (25), 141 (40), 128 (71), 126 (87), 125 (63), 114 (80), 101 (53), 84 (61), 57 (70). HRMS calcd for $C_{20}H_{34}Cl_3N_3O_5$: 501.1565. Found: 501.1586.

8.2.27. 4-Oxo-2-phenyl-3,4,6,7,9,10,11,12,14,15-decahydro-2*H*,5*H*-1,4a,8,13-tetraazabenzocyclotridecene-8,13-dicarboxylic acid, 13-*tert*-butyl ester, 8-(2,2,2-trichloroethyl) ester (53). A solution of **52** (285 mg, 0.57 mmol) and 4-phenylazetidin-2-one (84 mg, 0.57 mmol) in chlorobenzene (0.5 mL) was heated to reflux in an oil bath for 15 h. The reaction was cooled and concentrated to leave a red oil that was chromatographed eluting with CH_2Cl_2, 20% EtOAc/CH_2Cl_2 and then 33% EtOAc/CH_2Cl_2. A 1.6:1 mixture (235 mg) of **53** and 4-phenylazetidin-2-one was obtained as determined by ^{1}H NMR integration. From this ratio, the mass of **53** was calculated to be 205 mg (59%). The mixture was chromatographed again with 20% EtOAc/CH_2Cl_2 as eluant to achieve partial separation of **53** and the β-lactam. An analytical sample of **53** was prepared by running a third column (20% EtOAc/CH_2Cl_2) on a clean fraction of **53** and carefully evaporating the solvent with a stream of dry N_2. The last traces of solvent were removed by warming the oily sample at 50°C under high vacuum. The less pure fractions of **53** obtained above were combined and used directly in the next step. ^{1}H NMR (500 MHz, 50°C): δ 7.6–7.24 (m, 5H), 4.78 (d, J=12.0 Hz, 1H), 4.75 (d, J=12.0 Hz, 1H), 4.63 (dd, J=4.6, 13.0 Hz, 1H), 4.0–3.88 (m, 1H), 3.88–3.2 (series of br m, 9H), 2.90–2.70 (m, 3H), 2.48 (t, J=13 Hz, 1H), 2.07–1.95 (m, 1H), 1.95–1.84 (m, 1H), 1.84–1.65 (br m, 4H), 1.45 (s, 9H). IR: 1705 (sh), 1690, 1650 (sh) cm^{-1}. Anal. calcd for $C_{27}H_{37}Cl_3N_4O_5$: C, 53.69; H, 6.17; N, 9.28. Found: C, 53.71; H, 6.21; N, 9.18.

8.2.28. 13-Acetyl-4-oxo-2-phenyl-2,3,4,6,7,9,10,11,12,13,14,15-dodecahydro-5*H*-1,4a,8,13-tetraazabenzocyclotridecene-8-carboxylic acid, 2,2,2-trichloroethyl ester (54). A mixture of **53** (~190 mg, 0.32 mmol) and 4-phenylazetidin-2-one (~50 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) was cooled to 0°C in an ice bath. The solution was saturated with HCl gas, stirred at 0°C for 1 h, and concentrated to leave a pale yellow solid. The solid was dissolved in CH_2Cl_2 (3 mL). To the solution at rt was added DMAP (190 mg, 1.56 mmol) and then acetyl chloride (45 μL, 0.63 mmol). The reaction mixture was stirred at rt for 1 h. After quenching with a few drops of iPrNH$_2$, the solvent was evaporated. The residue (containing insoluble DMAP hydrochloride) was chromatographed eluting with EtOAc and then 5% MeOH/EtOAc to provide pure **54** (140 mg, 80%). ^{1}H NMR (500 MHz, 50°C): δ 7.46–7.17 (m, 5H), 4.79 (s, 2H), 4.65 (dd, J=3.9, 12.7 Hz, 1H), 4.03–3.78 (m, 3H), 3.78–3.65 (m, 1H), 3.65–3.32 (m, 6H), 2.95–2.68 (m, 3H), 2.55–2.43 (m, 1H), 2.11 and 2.09 (2s, total 3H), 2.02–1.87 (br m, 2H), 1.87–1.60 (br m, 4H). IR: 1710, 1640 cm^{-1}. MS (20 eV): 546 (22), M$^+$ $^{35}Cl_3$ 544 (27), 503 (14), 501 (17), 397 (17), 314 (20), 287 (35), 244 (24), 227 (53), 216 (45), 215 (100), 202 (42), 201 (65), 131 (11). HRMS calcd for $C_{24}H_{31}Cl_3N_4O_4$: 544.1411. Found: 544.1437.

8.2.29. 13-Acetyl-6-oxo-8-phenyl-1,5,9,13-tetraazacycloheptadecane-1-carboxylic acid, 2,2,2-trichloroethyl ester (55). To a solution of **54** (104 mg, 0.19 mmol) in glacial AcOH (2 mL) at rt was added $NaBH_3CN$ (40 mg, 0.64 mmol). The mixture was stirred for 3 h at rt, warmed at 50°C for 1 h and then stirred at rt overnight (12 h). The solution was diluted with CH_2Cl_2 (70 mL) and washed with H_2O (30 mL) and saturated aq. $NaHCO_3$ (30 mL). After it was dried (Na_2SO_4), the solution was concentrated to leave a clear oil. The pure azalactam **55** (92 mg, 88%) was obtained by chromatography with 8% MeOH/EtOAc as eluant. ^{1}H NMR (500 MHz, 50°C): δ 7.8–6.88 (m, 6H), 4.75 (s, 2H), 4.08–3.93 (m, 1H), 3.8–3.22 (m, 9H), 3.22–3.08 (m, 1H), 2.68–2.33 (m, 4H), 2.26–1.56 (series of br m, 9H), 2.04 and 2.02 (2s, total 3H). IR: 1710, 1660, 1635, 1520 cm^{-1}. MS (20 eV): 550 (2), M$^+$ 35013 548 (3), 507 (2), 505 (3), 401 (9), 374 (8), 333 (8), 331 (9), 291 (7), 289 (9), 245 (10), 214 (34), 189 (31), 176 (31), 163 (11), 155 (15), 146 (100), 145 (33), 132 (21), 112 (15), 100 (13), 98 (10), 84 (17), 56 (16). HRMS calcd for $C_{22}H_{33}N_4O_3$ (parent minus Cl_3CCH_2O): 401.2553. Found: 401.2583.

8.2.30. (±)-Verbascenine (3). A mixture of **55** (64 mg, 0.12 mmol) and powdered Zn (500 mg) in AcOH (2 mL) was stirred at rt for 18.5 h. The reaction mixture was diluted with CH_2Cl_2 (70 mL) and filtered through Celite. The filtrate was washed with H_2O (30 mL) and saturated aq. $NaHCO_3$ (30 mL). The combined aqueous fractions were then made basic with 1N aq. NaOH, saturated with NaCl and extracted with CH_2Cl_2 (8×50 mL). The combined CH_2Cl_2 fractions were dried and concentrated to leave the crude azalactam **56** as an oil (37 mg). The 90 MHz ^{1}H NMR spectrum of this material confirmed the absence of the 2,2,2-trichloroethyloxycarbonyl protecting group (no s at δ 4.8). The azalactam **56** (37 mg, 0.1 mmol), Et_3N (50 μL, 0.36 mmol) and DMAP (6 mg, 0.05 mmol) were dissolved in CH_2Cl_2 (1 mL) and the solution cooled to −78°C. A solution of cinnamoyl chloride (17 mg, 0.1 mmol) in CH_2Cl_2 (0.25 mL) was added dropwise. The reaction was stirred at −78°C for 4 h and then allowed to stand at −20°C overnight (14 h). The reaction was quenched by addition of 14% aq. NH_4OH (10 mL) and the mixture extracted several times with CH_2Cl_2. The combined CH_2Cl_2 fractions were dried (Na_2SO_4) and evaporated to leave the crude oily product. Chromatography with 15% MeOH/EtOAc as eluant provided (±)-verbascenine (**3**) (35 mg, 58% from **55**) as a clear oil. The ^{1}H NMR, IR and mass spectra of the synthetic (±)-verbascenine compared very favorably with the corresponding spectra obtained from natural (−)-verbascenine, a sample of which was kindly supplied by Dr K. Seifert, Institut fur Biochemie de Pflanzen Halle,

DDR.[47] ^{1}H NMR (500 MHz, 50°C): δ 7.9, 6.92 (2 br s, ~0.5H), 7.72 (d, J=15.3 Hz, ~0.6H), 7.71 (d, J=15.3 Hz, ~0.4H), 7.51 (br s, 2H), 7.46–7.17 (m, ~8.5H), 6.84 (d, J=15.3 Hz, ~0.4H), 6.83 (d, J=15.3 Hz, ~0.6H), 4.12–3.93 (br m, 1H), 3.70–3.10 (series of br m, 10H), 2.65–2.30 (m, 4H), 2.15–1.50 (series of br m, 9H), 2.06, 2.01 (2s, total 3H). IR: 1650, 1635 (sh), 1605 (sh), 1430, 1240–1210 (br). MS (20 eV): M^+ 504 (5), 449 (65), 373 (56), 359 (21), 245 (31), 228 (20), 188 (20), 169 (37), 157 (21), 146 (100), 131 (93), 112 (46), 100 (25), 98 (25), 84 (59), 70 (24). The synthetic and natural verbascenine also displayed identical behavior on TLC (R_f=0.45, 20% MeOH/EtOAc).

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