Synthesis of the Pentacyclic Skeleton of the Aspidosperma Alkaloids Using Rhodium Carbenoids as Reactive Intermediates

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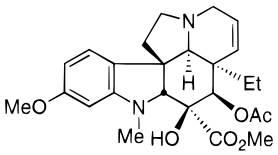
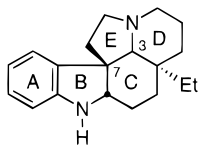
A series of diazo amido keto esters prepared from *N*-alkenyl-substituted 3-carbalkoxy-2-piperidone derivatives was treated with rhodium(II) acetate. Attack of the amido carbonyl oxygen at the resultant rhodium carbenoid center produced a transient push−pull carbonyl ylide dipole which underwent an intramolecular dipolar cycloaddition reaction. A related annulation sequence was used to prepare the pentacyclic skeleton of the aspidosperma family of alkaloids. Synthesis of the required diazo imide was carried out from 3-carboxy-3-ethyl-2-piperidone and *N*-methyl-3-indoleacetic acid. Treatment of the diazo imide with rhodium(II) acetate afforded a transient 1,3-dipole which subsequently underwent cycloaddition across the indole π-bond. The resulting cycloadduct is the consequence of *endo* cycloaddition with respect to the dipole which is fully in accord with the lowest energy transition state. The cycloadduct was converted in three steps into desacetoxy-4-oxo-6,7-dihydrovindorosine. The stereochemistry of the final product was established by a X-ray crystallographic study.

The aspidosperma alkaloids constitute a large family of natural products which have attracted considerable attention over the years due to their diverse and interesting structures.[1] The continuing interest in their synthesis stems in part from the presence of the highly functionalized vindoline nucleus in the clinically useful antineoplastic agents vincristine and vinblastine.[2] Vindoline (**1**)[3] is one of the more heavily oxygenated and complex members of the aspidosperma family and has attracted a great deal of attention owing to its unusual structure and high pharmacological activity.[4] It is the main alkaloidal constituent of *Catharanthus roseus* (vinca rosea) and corresponds to the dihydroindole component present in the potent bis-indole oncolytic agent, vinblastine.[5]



1; vindoline



2; aspidospermidine

The aspidosperma alkaloids share as part of their structure, the [6.5.6.5] ABCE ring system, and a major focus of interest has been in finding efficient routes for the introduction of the B/E spirocyclic junction, shown in aspidospermidine (**2**).[6] The construction of the characteristic 2,3,3-trisubstituted indoline unit by formation of the quaternary stereocenter at C-7 is usually the crucial step of the synthesis.[7] Our synthetic approach toward this class of alkaloids is part of a general approach to the total synthesis of azaspirocyclic natural products based on the *tandem cyclization−cycloaddition reaction* of rhodium carbenoids as the key strategic element.[8] Prompted by our recent work dealing with the internal dipolar cycloaddition reaction of mesoionic oxazolium ylides (**4**),[9] we became interested in the rhodium(II)-catalyzed reactions of diazo ketoamides such as **6**. Attack of the amido oxygen at the rhodium carbenoid produces a carbonyl ylide dipole (i.e., **7**) that is isomeric with the isomünchnone class of mesoionic betaines (**4**).

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(6) For a few of the many references, see: Woodward, R. B.; Cava, M.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98. Thomas, R. *Tetrahedron Lett.* **1961**, 544. Qureshi, A. A.; Scott, A. I. *J. Chem. Soc., Chem. Commun.* **1968**, 945. Battersby, A. R.; Byrne, J. C.; Kapil, R. S.; Martin, J. A.; Payne, T. G.; Arigoni, D.; Loew, P. *J. Chem. Soc., Chem. Commun.* **1968**, 951. Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res* **1984**, *17*, 35. Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403. Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030. Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966. Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293.

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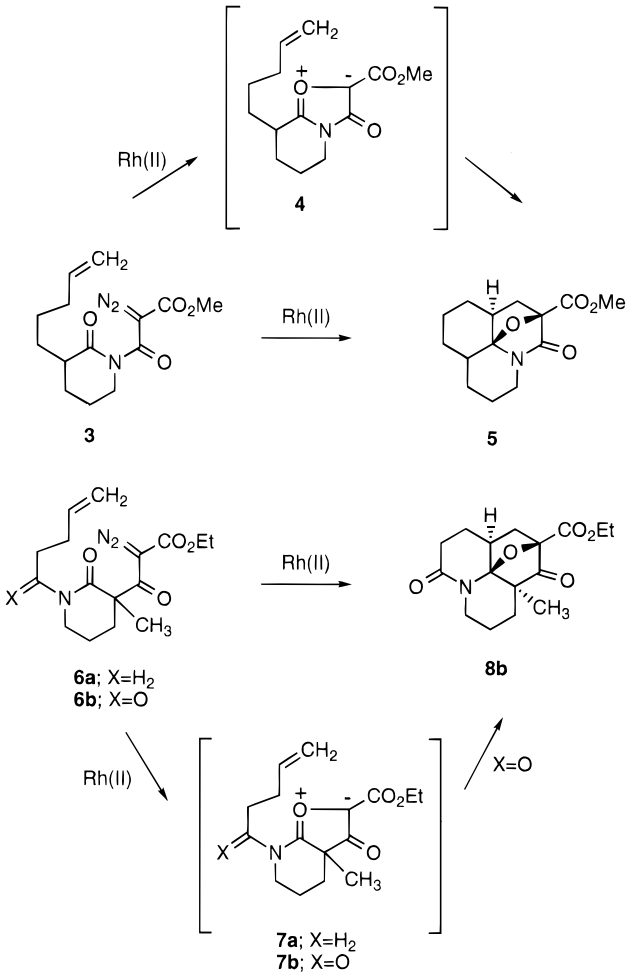
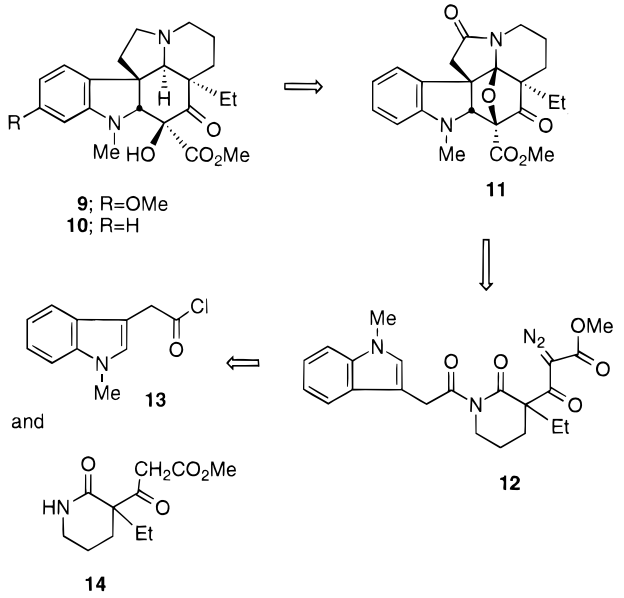


Scheme 1



In an earlier paper, we demonstrated that transient push−pull carbonyl ylide dipoles such as **7b** underwent an intramolecular cycloaddition.[10] As an extension of our studies, we decided to apply the cycloaddition reaction of this class of dipoles to the synthesis of the pentacyclic skeleton of the aspidosperma ring system.[11] Our synthetic plan is shown in antithetic format in Scheme 1 and is centered on the construction of the key oxabicyclic intermediate **11**. We reasoned that desacetoxy-4-oxo-6,7-dihydrovindorosine (**10**) should be accessible by reduction of **11**, which, by analogy with our previous work,[9] should be available by the tandem rhodium(II)-catalyzed cyclization−cycloaddition[12] of diazo imide **12**. This target was selected since the closely related C_{16}-methoxy derivative (**9**) had previously been converted by Kutney and co-workers into vindoline in six steps.[13] Cycloaddition of the initially formed dipole across the pendent indole π-system[14] would be expected to result in simultaneous generation of the CD-rings of the aspidosperma skeleton. The stereospecific nature of the internal cycloaddition reaction should also lead to the correct relative stereochemistry of the four chiral centers about the C-ring. In this paper we describe a synthetic entry to 2,3,3-trisubstituted indole alkaloids embodying the pyrrolo[2,3-*d*]-carbazole skeleton (ABCE rings) based on an intramolecular cycloaddition of a push−pull-stabilized carbonyl ylide. The usefulness of this strategy is exemplified by the synthesis of the dihydrovindorosine derivative **10**.

Results and Discussion

Intramolecular dipolar cycloadditions have been particularly useful in natural product synthesis, as this reaction results in the formation of an additional ring and exhibits increased reactivity due to entropic factors.[15−17] The regiochemistry of the process is complicated by a complex interplay of factors such as the nature of the 1,3-dipole, alkene polarity, ring strain, and nonbonded interactions in the transition state.[15] We have found that the rhodium(II)-catalyzed formation of carbonyl ylide intermediates derived from cyclic diazo amides furnishes tetracycles such as **8b** in good yield, provided that the tether engaged in ring formation carries a carbonyl group (i.e., **6b**, X = O).[10] Without the C=O functionality (i.e., **6a**, X = H), only decomposition products were observed. By performing ab initio transition state geometry optimizations, we learned that a severe cross-ring 1,3-diaxial interaction caused by the bridgehead methyl group promoted a boat or twist-boat conformation in the piperidine ring fused to the newly forming one.[10] The presence of a carbonyl group on the tether helped to relieve the steric congestion by favoring

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(11) For some earlier syntheses, see: Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, 2261. Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685. Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271. Feldman, P. L.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 1603. Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707. Desmaële, D.; d′Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292.

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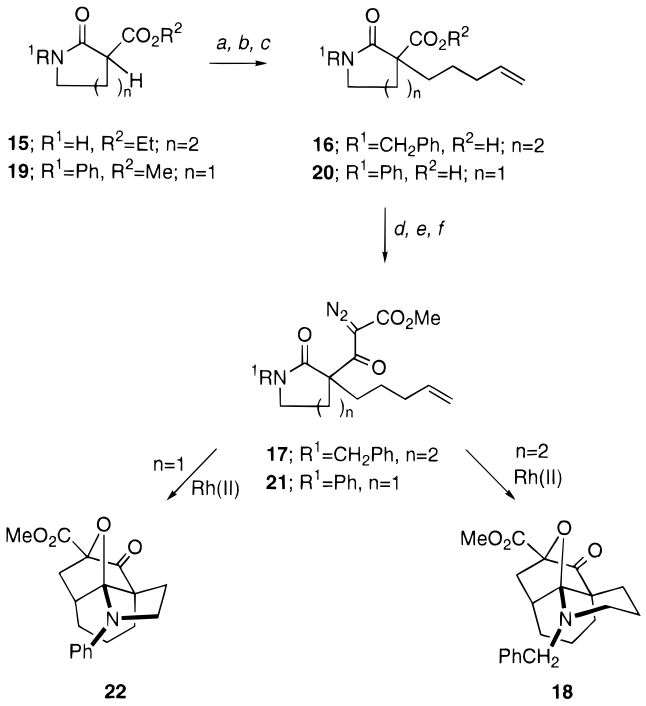
(14) Padwa, A.; Hertzog, D. L.; Nadler, W. R. *J. Org. Chem.* **1994**, *59*, 7072.

(15) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123. Padwa, A.; Schoffstall, A. *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 2−128.

(16) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.

(17) Wade, A. *Intramolecular 1,3-Dipolar Cycloadditions; Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Chapter 4.10, p 111.

Scheme 2[a]

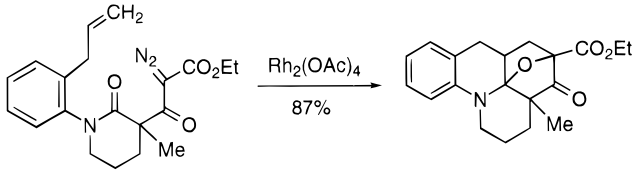


[a] Reagents: (a) *n*-BuLi, THF, $I(CH_2)_3CH{=}CH_2$; (b) NaH, $PhCH_2Br$; (c) KOH (MeOH); (d) $(COCl)_2$; (e) hydrogen methyl malonate, *i*-PrMgCl; (f) mesyl azide, NEt_3.

a second boat conformation in the latter ring. When the side chain is devoid of a carbonyl group, the reaction barrier is much larger, thereby permitting competing processes to intervene. Thus, the reactivity discrepancy between diazo amido esters **6a** *vs* **6b** was attributed to steric effects in the transition states.[10]

To further probe the forces responsible for intramolecular ring formation with these push−pull carbonyl ylides, we examined the Rh(II)-catalyzed behavior of several other cyclic diazo amides containing tethered π-bonds. Our studies began with an investigation of the transition metal catalyzed reaction of diazo amido ester **17** (n = 2). The requisite amide necessary for dipole generation was obtained by alkenylation of 2-oxopiperidine-3-carboxylic acid ethyl ester (**15**) with 5-iodo-1-pentene followed by *N*-benzylation and saponification which furnished carboxylic acid **16** (Scheme 2). Conversion of **16** to the corresponding acid chloride was followed by reaction with the magnesium dianion of hydrogen methyl malonate. The resulting amido ester was treated with mesyl azide in the presence of triethylamine[18] to provide α-diazo amide **17** in 80% as a labile yellow oil. Formation of the push−pull carbonyl ylide dipole proceeded smoothly upon heating a sample of **17** in benzene in the presence of $Rh_2(OAc)_4$. The resultant dipole underwent ready intramolecular dipolar-cycloaddition across the tethered π-bond to produce the tricyclic adduct **18** in 87% yield. Cycloadduct **18** is produced with complete diastereoselectivity and is the result of *exo*-cycloaddition with respect to the dipole. This is in full accord with molecular mechanics calculations which show a large ground state energy difference between the two diastereomers. The stereochemical assignment was unambiguously established by X-ray crystallography.[19] A similar tandem cyclization−cycloaddition sequence also occurred with the pyrrolidinyl-substituted diazo amido ester **21** (n = 1). The only product formed with this system (85% yield) corresponded to cycloadduct **22**. The assignment of the stereochemistry of **22** was based on comparison of NMR signals with those of the related cycloadduct **18**.

In the examples cited above, both the six- and five-ring precursors **17** and **21** deliver cyclized products in high yield even though they do not contain a carbonyl group on the side chain tether. This stands in sharp contrast to the situation encountered with diazo amido ester **6** where the push−pull carbonyl ylide lacking a C=O on the tether (i.e., **6a**, X = H_2) failed to cyclize. The difference in cycloaddition behavior of these systems underscores the complexity of intramolecular cyclization processes that create several fused rings in a single step and simultaneously induce steric effects in the transition state remote from the reaction centers. To further explore the facility of the intramolecular tandem cyclization−cycloaddition reaction, we have investigated the Rh(II)-catalyzed reaction of diazo amido ester **23**. In this case, the tethered π-bond is attached to a phenyl ring, which in turn is connected to the amide nitrogen atom. We found that treatment of **23** with a catalytic quantity of $Rh_2(OAc)_4$ in benzene at 80 °C provided cycloadduct **24** in 87% isolated yield. Thus, an alkenyl π-bond anchored to a phenyl ring emerges as a remote-site promoter of intramolecular cycloaddition yielding a cycloadduct with multiple fused rings.



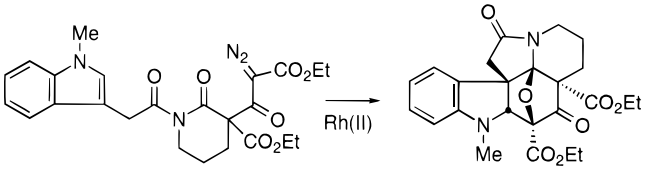
Given the success in forming complex polyheterocyclic systems from the intramolecular cycloaddition reaction of push−pull carbonyl ylides, it seemed to us that selective modification of the starting diazo amido ester would allow application of the method toward the Aspidosperma alkaloid family. In particular, the intramolecular cycloaddition of a push−pull carbonyl ylide derived from the model diazo amido ester **25** across the tethered indolyl π-bond would bode well for the planned Aspidosperma synthesis (vide infra). The key question that needed to be addressed was whether the push−pull carbonyl ylide derived from **25** would undergo cycloaddition across the aromatic π-bond of indole. Heteroaromatic rings such as indole have, despite their aromaticity, frontier orbital energies and shapes similar to those of cyclopentadiene.[20] Although a vast amount of information is available concerning the reactivity of heteroaromatics in cycloadditions where the heteroaromatics enter

(18) Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.

(19) The authors have deposited coordinates for structures **10**, **11**, and **18** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(20) Del Bene, J.; Jaffe, H. H. *J. Chem. Phys.* **1968**, *48*, 4050.

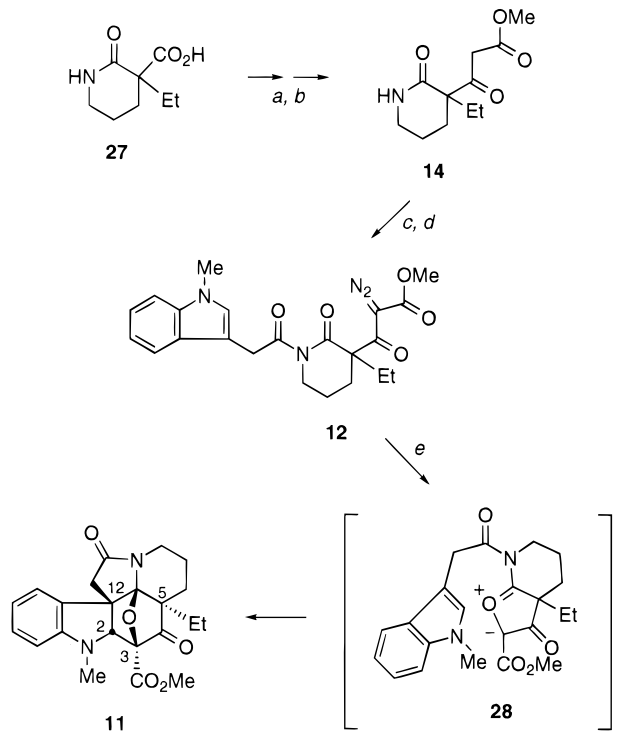
as 4_πs components,[21] a study of their dipolarophilic activities has not been extensively examined to date.[22−25] The dipolarophilic reactivity of the indole π-bond would be expected to be somewhat diminished because of loss of aromaticity in the cycloaddition transition state. Gratifyingly, we found that the Rh(II)-catalyzed reaction of **25** afforded the polyheterocyclic adduct **26** in 90% yield and with complete diastereospecificity. Thus, the conversion of **25** → **26** represents a rare example of dipolar cycloaddition across an indolyl π-bond and opens up this approach as a potentially general strategy for the synthesis of a variety of indolyl alkaloids.



25 **26**

After the successful transformation of diazo amido ester **25** to the desired cycloadduct **26**, we turned our attention to the construction of the pyrrolo[2,3-*d*]carbazole skeleton found in the dihydrovindorosine derivative **10**. Our synthesis of the required diazo imide **12** commences with the easily available 3-carboxy-3-ethyl-2-piperidone (**27**).[26] Treatment of **27** with 1,1-carbonyldiimidazole followed by reaction with the dianion of hydrogen methyl malonate[27] afforded β-keto ester **14** in 60% yield (Scheme 3). *N*-Acylation of **14** with *N*-methylindole-3-acetyl chloride (**13**) using 4 Å molecular sieves as a neutral acid scavenger[28] gave the desired imide (65%) which was readily converted to the requisite diazo imide **12** using standard diazo transfer methodology.[29] When diazo imide **12** was treated with a catalytic quantity of $Rh_2(OAc)_4$ in benzene at 50 °C, cycloadduct **11** was isolated in 95% yield as a single diastereomer. The structure of **11** was firmly established by NMR analysis and by a X-ray crystallographic analysis[19] which revealed that the cycloadduct contains the same relative stereochemical centers (C_2, C_3, C_5, and C_{12}) found in

Scheme 3[a]



[a] Reagents: (a) $(Im)_2CO$; (b) hydrogen methyl malonate, *i*-PrMgCl; (c) indole acid chloride **13**, molecular sieves; (d) MsN_3/NEt_3; (e) Rh(II).

vindoline.[30] The formation of **11** arises by cyclization of the initially formed rhodium carbenoid derived from **12** onto the neighboring piperidone carbonyl oxygen to give dipole **28** which subsequently cycloadds across the indole π-bond. The isolation of **11** is the consequence of *endo* cycloaddition with regard to the dipole, and this is in full accord with the lowest energy transition state. The cycloaddition can also be considered doubly diastereoselective in that the indole moiety approaches the dipole exclusively from the side of the ethyl group and away from the more sterically encumbered piperidone ring.

Having established a viable route to cycloadduct **11**, efforts were next focused on the reduction of the C_{10} lactam carbonyl group and reductive opening of the C_3−C_{19} oxido bridge. Treatment of **11** with Lawesson's reagent[31] furnished the expected thiolactam (85%) which was cleanly reduced (96%) to amine **29** when exposed to Raney nickel in refluxing THF.[32] Reduction of the oxido bridge was achieved by catalytic hydrogenation over PtO_2 using acidic methanol as the solvent to give **10** in 94% yield as a single diastereomer.[33] The C_{19}-stereochemistry was unequivocally established by a single-crystal X-ray analysis.[19] The overall reduction presumably proceeds by an acid-catalyzed ring opening of the *N*,*O*-acetal group to generate a transient iminium ion (i.e., **30**) which reacts further with hydrogen from the least congested face.

After the successful transformation of cycloadduct **11** to the dihydrovindorosine derivative **10**, we decided to

(21) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990.

(22) For an example where a 1,3-dipole undergoes intramolecular 1,3-dipolar cycloaddition across a benzene ring, see: Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056.

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(27) Rapoport, H.; Feldman, P. L.; Mayer, M. P. *J. Org. Chem.* **1985**, *50*, 5223.

(28) Weinstock, L. M.; Karady, S.; Roberts, F. E.; Hoinowski, A. M.; Brenner, G. S.; Lee, T. B. K.; Lumma, W. C.; Sletzinger, M. *Tetrahedron Lett.* **1975**, *11*, 3979.

(29) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733.

(30) Moza, B. K.; Trojánek, J. *Collect. Czech. Chem. Commun.* **1963**, *28*, 1427. Büchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299.

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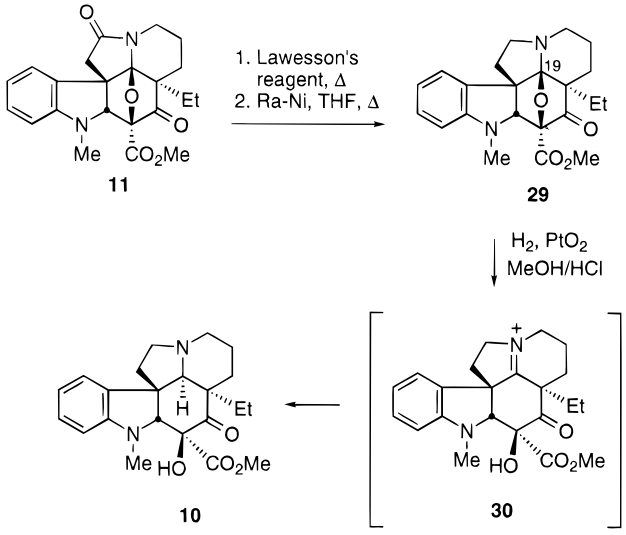
(32) Yde, B.; Yousif, N. M.; Pedersen, U.; Lawesson, S. O. *Tetrahedron* **1984**, *40*, 2047. Laronze, J. Y.; Laronze-Fontaine, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, 491.



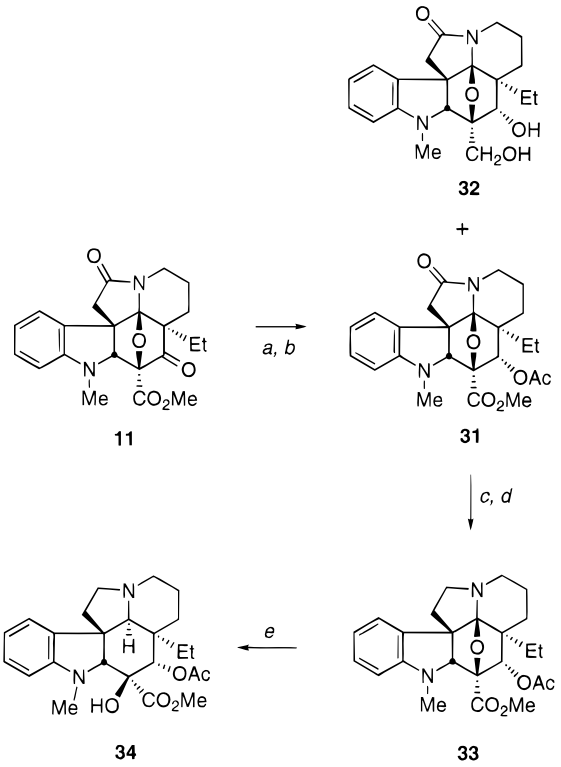
study the reduction chemistry of **11** in further detail. One of the problems with Kutney's synthesis of vindoline was that reduction of the C_4-keto group proceeded in low yield and with poor diastereoselectivity.[13] Our hope was that the oxido bridge present in cycloadduct **11** would offer considerable steric bias and allow reduction of the C_4-carbonyl group to take place with much higher stereospecificity than that encountered by Kutney.[13] To test this possibility, cycloadduct **11** was reduced with $NaBH_4$ in THF/MeOH containing $CeCl_3 \cdot 7H_2O$ which furnished the C_4-alcohol as a single diastereomer in 64% yield. The alcohol was not isolated but instead was immediately converted into the corresponding acetate **31** in quantitative yield (Scheme 4). A small amount of diol **32** (18%) derived from the secondary reduction of the C_3-carbomethoxy group was also obtained. Treatment of **31** with Lawesson's reagent furnished the expected thiolactam which was subsequently reduced to amine **33** in 79% overall yield for both steps. Catalytic reduction of **33** with PtO_2 in methanol afforded the ring-opened compound **34** in 92% yield. The NMR characteristics of **34** clearly indicate that hydride reduction of the C_4-carbonyl group (i.e., **11** → **31**) had occurred from the same side as the oxido bridge. Examination of molecular models shows that the presence of the oxido bridge actually accentuates the cuplike nature of the pyrrolo[2,3-*d*]-carbazole skeleton. To date, our efforts to epimerize the C_4-alcohol at both the oxido bridge (**31**) or ring-opened stage (**34**) have proven unsuccessful. Further work along these lines is currently under investigation.

In conclusion, the successful preparation of desacetoxy-4-oxo-6,7-dihydrovindorosine **10** in seven steps was accomplished in 27% overall yield and establishes the merit of our method as outlined in Scheme 1. The *tandem cyclization−cycloaddition sequence* is particularly attractive as four of the stereocenters are formed in one step with a high degree of stereocontrol. Work to extend these discoveries to the total synthesis of vindoline are in progress, and the results of these investigations will be reported in due course.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate−hexane mixture as the eluent unless specified otherwise.

Scheme 4[a]



[a] Reagents: (a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, THF; (b) CH_3COCl, Ac_2O; (c) Lawesson's regent; (d) Raney Ni; (e) H_3 (MeOH), PtO_2.

General Procedure for the Synthesis of Diazo Amides. A variation of the procedure described by Taber and coworkers[18] was used to prepare the diazo amide system. To a solution containing 2 mmol of the appropriate amido ester and 2.2 mmol of mesyl azide in 5 mL of acetonitrile or CH_2Cl_2 was added 4.0 mmol of NEt_3 under N_2 at rt. After the mixture was stirred for 3 h, the solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography.

2-Oxo-3-pent-4-enylpiperidine-3-carboxylic Acid Ethyl Ester. To a stirred solution of 2.0 g (11.7 mmol) of 2-oxopiperidine-3-carboxylic acid ethyl ester (**15**)[34] in 20 mL of THF at −78 °C was added 7.3 mL (11.7 mmol) of a 1.6 M *n*-butyllithium solution in hexane. The resulting solution was allowed to warm to 0 °C and recooled to −78 °C, and 2.3 g (11.7 mmol) of 5-iodo-1-pentene was added. The solution was heated at 65 °C for 2 h, cooled to rt, and quenched with H_2O. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 2.1 g (75%) of 2-oxo-3-pent-4-enylpiperidine-3-carboxylic acid ethyl ester as a pale yellow oil: IR (neat) 3218, 1723, 1659, 1489, 1446, and 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 3H, J = 7.1 Hz), 1.20−1.50 (m, 2H), 1.70−1.95 (m, 6H), 2.00−2.30 (m, 2H), 3.20−3.40 (m, 2H), 4.17 (qd, 2H, J = 7.1 and 2.4 Hz), 4.89−5.00 (m, 2H), 5.65−5.80 (m, 1H), and 6.32 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 19.7, 23.9, 29.6, 34.0, 35.0, 42.3, 53.8, 61.3, 114.7, 138.3, 171.0, and 172.9. Anal. Calcd. for $C_{13}H_{21}NO_3$: C, 65.23; H, 8.85; N, 5.86. Found: C, 65.09; H, 8.71; N, 5.75.

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1-Benzyl-2-oxo-3-pent-4-enylpiperidine-3-carboxylic Acid (16). To a stirred solution of 1.0 g (4.2 mmol) of the above amido ester in 20 mL of THF at rt was slowly added 0.20 g (5.0 mmol) of NaH (60% in mineral oil). The solution was heated at 65 °C for 1 h and cooled to rt, and 0.89 g (5.2 mmol) of benzyl bromide and 0.78 g (5.2 mmol) of NaI were added. The mixture was heated at 65 °C for 1 h, cooled to rt, and quenched with H_2O. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were concentrated under reduced pressure, the residue was dissolved in 10 mL of methanol, and 5 mL (15 mmol) of a 3 N KOH solution was added. The solution was allowed to stir at rt for 10 h, washed with ether, acidified to pH 2, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 0.80 g (64%) of **16** as a yellow oil: IR (neat) 1728, 1598, 1445, and 1184 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (dt, 2H, J = 16.0 and 7.9 Hz), 1.66−2.03 (m, 7H), 2.25 (ddd, 1H, J = 13.9, 9.7, and 3.9 Hz), 3.24 (t, 2H, J = 6.1 Hz), 4.51 (d, 1H, J = 14.6 Hz), 4.64 (d, 1H, J = 14.6 Hz), 4.90−5.00 (m, 2H), 5.64−5.80 (m, 1H), 7.17−7.35 (m, 5H), and 12.01 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 23.7, 27.5, 33.4, 38.3, 47.9, 51.2, 52.2, 115.3, 127.9, 128.0, 128.9, 135.8, 137.6, 172.8, and 173.5. Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.72; H, 7.70; N, 5.86. Found: C, 71.59; H, 7.63; N, 5.91.

3-(1-Benzyl-2-oxo-3-pent-4-enylpiperidin-3-yl)-3-oxopropionic Acid Methyl Ester. To a stirred solution of 0.25 g (0.8 mmol) of the above carboxylic acid in 5 mL of ether were added 0.23 mL (2.5 mmol) of oxalyl chloride and one drop of DMF. The solution was allowed to stir at rt for 30 min and was concentrated under reduced pressure to remove the excess oxalyl chloride. The residue was taken up in 1 mL of CH_2Cl_2, and this mixture was slowly added to 4 mL of a 0.5 M THF solution of the magnesium dianion of hydrogen methyl malonate at 0 °C. The solution was allowed to stir for 1 h and was quenched with a 1 N HCl solution. The organic layer was separated, and the aqueous layer was extracted with ether. The organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.19 g (63%) of 3-(1-benzyl-2-oxo-3-pent-4-enylpiperidin-3-yl)-3-oxopropionic acid methyl ester as a colorless oil: IR (neat) 1741, 1707, 1643, 1435, and 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19−1.32 (m, 2H), 1.50−1.75 (m, 3H), 1.86 (ddd, 2H, J = 15.6, 9.6, and 3.6 Hz), 1.95−2.05 (m, 2H), 2.37 (dt, 1H, J = 13.6 and 4.1 Hz), 3.16 (t, 2H, J = 6.3 Hz), 3.62 (s, 3H), 3.67 (d, 1H, J = 16.4 Hz), 3.84 (d, 1H, J = 16.4 Hz), 4.49 (d, 1H, J = 14.5 Hz), 4.58 (d, 1H, J = 14.5 Hz), 4.90−5.00 (m, 2H), 5.60−5.80 (m, 1H), and 7.10−7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.0, 23.6, 27.5, 33.8, 36.3, 45.2, 47.6, 51.0, 52.1, 60.5, 115.1, 127.5, 128.0, 128.6, 136.9, 137.9, 168.1, 169.2, and 202.0. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.55; H, 7.62; N, 3.92. Found: C, 70.48; H, 7.44; N, 3.80.

Rhodium(II)-Catalyzed Reaction of 3-(1-Benzyl-2-oxo-3-pent-4-enylpiperidin-3-yl)-2-diazo-3-oxopropionic Acid Ethyl Ester (17). Diazo transfer of the above amido ester according to the general procedure gave **17** (86%) as a yellow oil: IR (neat) 2135, 1714, 1634, 1445, and 1315 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−2.10 (m, 8H), 2.26 (td, 1H, J = 12.8 and 4.4 Hz), 3.15−3.19 (m, 2H), 3.47 (td, 1H, J = 12.2 and 4.4 Hz), 3.69 (s, 3H), 3.91 (d, 1H, J = 14.9 Hz), 4.90−5.01 (m, 2H), 5.05 (d, 1H, J = 14.9 Hz), 5.65−5.90 (m, 1H), and 7.15−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 24.4, 28.7, 34.2, 35.1, 47.0, 49.9, 51.9, 57.6, 114.6, 127.2, 128.4, 128.7, 137.5, 138.6, 161.3, 170.6, and 191.4.

Since diazo amide **17** decomposed on standing, it was immediately subjected to the rhodium(II)-catalyzed reaction. To a mixture of 2 mg of rhodium(II) acetate in 2 mL of benzene at 80 °C was added 40 mg (0.10 mmol) of diazo amide **17** in 0.5 mL of benzene over a period of 5 min. The solution was heated at 80 °C for an additional 1 h and then concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 31 mg (87%) of 5-benzyl-10-oxo-5-aza-6,9-epoxytricyclo[5.3.3.$0^{1,6}$]tridecane-9-carboxylic acid methyl ester (**18**) as a white solid: mp 133−134 °C; IR (KBr) 1771, 1765, 1739, and 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.90 (m, 11H), 2.28 (t, 1H), 2.75−2.95 (m, 3H), 3.57 (d, 1H, J = 15.9 Hz), 3.84 (s, 3H), 4.51 (d, 1H, J = 15.9 Hz), and 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.0, 20.2, 24.9, 28.0, 28.4, 32.7, 35.6, 48.8, 49.5, 52.7, 53.0, 85.4, 100.2, 126.8, 127.4, 128.4, 139.9, 167.3, and 209.5. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.77; H, 7.15; N, 3.92.

1-Phenyl-2-oxo-3-pent-4-enylpyrrolidine-3-carboxylic Acid (20). To a solution containing 0.80 g (3.7 mmol) of 1-phenyl-2-oxopyrrolidine-3-carboxylic acid methyl ester (**19**)[34] in 10 mL of THF at −78 °C was added 2.5 mL (4.0 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. The solution was allowed to warm to rt and recooled to −78 °C, and 1.43 g (7.3 mmol) of 5-iodo-1-pentene was added. The solution was heated at reflux for 2 h and quenched with H_2O, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in 10 mL of methanol, 4 mL of a 3 M KOH solution was added, and the solution was allowed to stir at rt for 12 h. The mixture was washed with ether, acidified to pH 2, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 0.65 g (65%) of **20** as a yellow oil: IR (neat) 3400 (br), 1693, 1498, and 1393 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35−1.55 (m, 2H), 1.75−2.15 (m, 5H), 2.61 (ddd, 1H, J = 13.4, 8.2, and 5.3 Hz), 3.69−3.81 (m, 1H), 3.87 (dt, 1H, J = 8.9 and 6.0 Hz), 4.90−5.01 (m, 2H), 5.60−5.80 (m, 1H), 7.10−7.58 (m, 5H), and 10.01 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.9, 26.9, 33.6, 34.8, 46.2, 56.5, 115.3, 120.4, 125.5, 129.0, 137.7, 138.6, 172.8, and 174.1. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.29; H, 7.01; N, 5.13. Found: C, 70.14; H, 6.89; N, 5.04.

3-(1-Phenyl-2-oxo-3-pent-4-enylpyrrolidin-3-yl)-3-oxopropionic Acid Methyl Ester. To a stirred solution of 0.25 g (1.5 mmol) of carboxylic acid **20** in 10 mL of ether were added 0.40 mL (4.4 mmol) of oxalyl chloride and one drop of DMF. The solution was allowed to stir at rt for 30 min and concentrated under reduced pressure to remove the excess oxalyl chloride. The residue was taken up in 1 mL of CH_2Cl_2, and this mixture was slowly added to 6 mL of a 0.5 M THF solution of the magnesium dianion of hydrogen methyl malonate at 0 °C. The reaction mixture was allowed to stir for 1 h and was then quenched with a 1 N HCl solution. The mixture was extracted with ether, and the ether extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.25 g (52%) of 3-(1-phenyl-2-oxo-3-pent-4-enylpyrrolidin-3-yl)-3-oxopropionic acid methyl ester as a colorless oil: IR (neat) 1743, 1683, 1491, 1392, and 1300 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.41 (m, 2H), 1.75−2.20 (m, 5H), 2.87 (ddd, 1H, J = 12.9, 7.6, and 3.1 Hz), 3.60 (s, 3H), 3.64 (d, 1H, J = 16.6 Hz), 3.64−3.81 (m, 2H), 3.96 (d, 1H, J = 16.6 Hz), 4.95−5.04 (m, 2H), 5.70−5.82 (m, 1H), and 7.12−7.60 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.7, 25.2, 33.6, 34.6, 44.4, 45.8, 52.3, 64.2, 115.6, 120.1, 125.1, 128.9, 137.5, 139.0, 167.7, 171.1, and 200.0. Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.27; H, 7.04; N, 4.25. Found: C, 69.03; H, 6.95; N, 4.17.

Rhodium(II)-Catalyzed Reaction of (1-Phenyl-2-oxo-3-pent-4-enylpyrrolidin-3-yl)-2-diazo-3-oxopropionic Acid Methyl Ester (21). Diazo transfer of the above amido ester according to the general procedure gave **21** (80%) as a pale yellow oil: IR (neat) 2924, 2134, 1739, 1693, 1629, 1434, and 1318 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40−1.60 (m, 2H), 1.85−2.20 (m, 5H), 2.68 (ddd, 1H, J = 12.8, 9.2, and 7.2 Hz), 3.69 (s, 3H), 3.80−4.00 (m, 2H), 4.85−5.10 (m, 2H), 5.68−5.85 (m, 1H), 7.11 (t, 1H, J = 7.3 Hz), 7.33 (t, 2H, J = 8.0 Hz), and 7.59 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.7, 27.5, 34.0, 34.3, 46.6, 52.3, 61.3, 115.0, 120.3, 124.7, 128.8, 138.1, 139.2, 161.2, 172.2, and 189.0.

Since diazo amide **21** decomposed on standing, it was immediately subjected to the rhodium(II)-catalyzed reaction. To a mixture containing 2 mg of rhodium(II) acetate in 1 mL

of benzene at 80 °C was added 0.10 g (0.3 mmol) of **21** in 0.5 mL of benzene over a period of 10 min. The solution was heated at 80 °C for an additional 1 h and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 80 mg (85%) of 5,8-epoxy-9-oxo-4-phenyl-4-azatricyclo[4.3.3.0^{1,5}]dodecane-8-carboxylic acid methyl ester (**22**) as a white solid: mp 139−140 °C; IR (KBr) 2930, 1764, 1744, 1389, and 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.60 (m, 5H), 1.70 (dd, 1H, J = 12.2 and 6.6 Hz), 1.98 (dd, 1H, J = 13.7 and 3.7 Hz), 2.00−2.10 (m, 1H), 2.39−2.50 (m, 2H), 3.15−3.25 (m, 1H), 3.63 (t, 1H, J = 9.3 Hz), 3.84 (s, 3H), 4.05−4.20 (m, 1H), and 6.90−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.3, 24.3, 28.3, 29.7, 30.6, 33.5, 52.7, 53.1, 58.8, 85.8, 104.8, 118.6, 120.9, 128.8, 144.0, 166.9, and 206.6. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.46; N, 4.28. Found: C, 69.64; H, 6.52; N, 4.19.

1-(2-Allylphenyl)-2-oxopiperidine. To a stirred solution of 2.0 g (15 mmol) of *o*-allylaniline[35] in 20 mL of benzene was added 3.0 g (21 mmol) of 5-bromovaleryl chloride, and the solution was heated at 80 °C for 4 h. The mixture was cooled to rt, and the solution was washed sequentially with H_2O, a saturated $NaHCO_3$ solution, a 0.5 N HCl solution, and H_2O. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting oil was dissolved in 10 mL of DMSO, and this solution was added dropwise to a solution of 0.48 g (12 mmol) of NaH (60% in mineral oil) in 10 mL of DMSO. The mixture was allowed to stand at rt for 2 h and was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2, and the extracts were washed sequentially with H_2O, a 0.5 N HCl solution, and a saturated NaCl solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 1.4 g (64%) of 1-(2-allylphenyl)-2-oxopiperidine as a colorless oil: IR (neat) 3068, 1645, 1489, and 1304 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.80−2.05 (m, 4H), 2.51−2.58 (m, 2H), 3.28 (d, 2H, J = 6.7 Hz), 3.36−3.62 (m, 2H), 5.00−5.18 (m, 2H), 5.80−6.00 (m, 1H), and 7.02−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 23.5, 32.7, 35.8, 51.8, 116.2, 127.7, 127.9, 130.1, 130.4, 136.6, 137.1, 141.9, and 169.7. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.09; H, 7.96; N, 6.51. Found: C, 77.96; H, 7.82; N, 6.41.

1-(2-Allylphenyl)-2-oxopiperidine-3-carboxylic Acid Methyl Ester. To a stirred solution of 1.5 g (7 mmol) of the above lactam in 20 mL of THF at −78 °C was added a solution of LDA (8.4 mmol) in 10 mL of THF over a period of 10 min. The solution was allowed to stir for 1 h and was allowed to warm to 0 °C. The mixture was recooled to −78 °C, and 0.71 mL (7 mmol) of HMPA was added. After the solution was stirred for 5 min, 0.90 g (10.5 mmol) of methyl cyanoformate was added.[36] The mixture was allowed to stir for an additional 2 h at rt and was quenched with a 0.1 N HCl solution. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 1.10 g (57%) of 1-(2-allylphenyl)-2-oxopiperidine-3-carboxylic acid methyl ester as a colorless oil: IR (neat) 1743, 1645, 1425, and 1312 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.80−2.40 (m, 4H), 3.20−3.60 (m, 3H), 3.26 (d, 1H, J = 6.5 Hz), 3.73 (s, 3H), 3.77 (d, 1H, J = 6.5 Hz), 5.02−5.10 (m, 2H), 5.80−6.00 (m, 1H), and 7.00−7.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9, 25.4, 35.2, 49.2, 51.7, 52.4, 116.0, 127.0, 127.6, 127.7, 128.1, 130.5, 136.9, 141.2, 165.6, and 171.5. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.29; H, 7.01; N, 5.13. Found: C, 70.09; H, 6.96; N, 5.17.

1-(2-Allylphenyl)-3-methyl-2-oxopiperidine-3-carboxylic Acid. To a stirred solution of 0.6 g (2 mmol) of the above lactam in 10 mL of THF at −78 °C was added 1.5 mL of a 1.6 M *n*-butyllithium solution in hexane. The mixture was allowed to stir for 2 h and recooled to −78 °C, and 0.4 mL (6 mmol) of iodomethane was added. The solution was stirred at rt for 12 h and quenched with H_2O, the aqueous layer was extracted with ether, and the ether extracts were dried over $MgSO_4$. The solution was concentrated under reduced pressure, and the residue was taken up in 5 mL of methanol. To this solution was added 2 mL (6 mmol) of a 3 N KOH solution, and the mixture was allowed to stir at rt for 12 h. The solution was washed with ether, acidified to pH 2, and extracted with CH_2Cl_2, and the CH_2Cl_2 extracts were dried over anhydrous $MgSO_4$. Concentration under reduced pressure gave 0.55 g (92%) of 1-(2-allylphenyl)-3-methyl-2-oxopiperidine-3-carboxylic acid as a yellow oil: IR (neat) 3427 (br), 1729, 1637, and 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.66 (s, 3H), 1.80−2.50 (m, 4H), 3.24 (d, 2H, J = 6.6 Hz), 3.40−3.60 (m, 3H), 5.05−5.20 (m, 2H), 5.80−6.00 (m, 1H), and 7.05−7.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 26.4, 30.4, 35.3, 47.7, 52.5, 116.6, 126.5, 128.0, 128.7, 130.8, 135.9, 136.6, 140.2, 173.9, 174.3. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.29; H, 7.01; N, 5.13. Found: C, 70.08; H, 7.11; N, 5.12.

3-[1-(2-Allylphenyl)-3-methyl-2-oxopiperidin-3-yl]-3-oxopropionic Acid Ethyl Ester. To a stirred solution of 0.55 g (2 mmol) of the above carboxylic acid in 10 mL of ether were added 0.72 mL (6 mmol) of oxalyl chloride and one drop of DMF. The solution was allowed to stir at rt for 30 min and was concentrated under reduced pressure to remove the excess oxalyl chloride. The residue was taken up in 1 mL of CH_2Cl_2, and this mixture was added slowly to 8.8 mL of a 0.5 M THF solution of the magnesium dianion of hydrogen ethyl malonate at 0 °C. The solution was allowed to stir for 1 h and was quenched with a 1 N HCl solution. The reaction was extracted with ether, and the ether extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.40 g (60%) of 3-[1-(2-allylphenyl)-3-methyl-2-oxopiperidin-3-yl]-3-oxopropionic acid ethyl ester as a colorless oil: IR (neat) 1743, 1710, 1635, and 1314 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, 3H, J = 7.1 Hz), 1.52 (s, 3H), 1.60−2.10 (m, 3H), 2.50−2.65 (m, 1H), 3.20−3.65 (m, 4H), 3.59 (d, 1H, J = 16.1 Hz), 3.93 (d, 1H, J = 16.1 Hz), 4.09−4.22 (m, 2H), 5.0−5.17 (m, 2H), 5.80−6.00 (m, 1H), and 7.02−7.18 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 20.2, 23.4, 30.9, 35.2, 45.1, 51.9, 56.5, 61.2, 116.4, 127.2, 127.3, 127.6, 127.8, 130.4, 136.5, 137.0, 167.6, 170.2, and 202.5. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.93; H, 7.34; N, 4.08. Found: C, 69.75; H, 7.24; N, 4.06.

Rhodium(II)-Catalyzed Reaction of 3-[1-(2-Allylphenyl)-3-methyl-2-oxopiperidin-3-yl]-2-diazo-3-oxopropionic Acid Ethyl Ester (23). Diazo transfer of the above amido ester according to the general procedure gave 3-[1-(2-allylphenyl)-3-methyl-2-oxopiperidin-3-yl]-2-diazo-3-oxopropionic acid ethyl ester (**23**) (61%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, 3H, J = 7.1 Hz), 1.65 (s, 3H), 1.65−2.00 (m, 2H), 2.16 (ddt, 1H, J = 13.3, 13.1, and 4.4 Hz), 2.48 (td, 1H, J = 13.1 and 3.9 Hz), 4.07 (td, 1H, J = 12.2 and 3.9 Hz) 4.26 (q, 2H, J = 7.1 Hz), 3.20−3.38 (m, 3H), 4.95−5.10 (m, 2H), 5.80−5.98 (m, 1H), and 7.19−7.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 19.9, 23.1, 31.3, 35.4, 51.4, 54.8, 61.2, 115.8, 126.9, 127.3, 127.5, 130.0, 136.9, 137.0, 142.0, 160.0, 161.3, and 191.9.

Since diazo amide **23** decomposed on standing, it was immediately subjected to the rhodium(II)-catalyzed reaction. To a mixture of 2 mg of rhodium(II) acetate in 1 mL of benzene at 80 °C was added 50 mg (0.14 mmol) of **23** in 0.5 mL of benzene over a period of 10 min. The reaction mixture was heated at reflux for an additional 1 h, cooled to rt, filtered through a pad of silica, and concentrated under reduced pressure to give 41 mg (87%) of 5,12a-epoxy-3a-methyl-4-oxo-1,2,3,3a,4,5,6,6a,7,12a-decahydropyrido[3,2,1-*de*]acridine-5-carboxylic acid ethyl ester (**24**) as a yellow oil: IR (neat) 1732, 1717, 1320, and 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 3H), 1.32 (t, 3H, J = 7.1 Hz), 1.52−2.00 (m, 4H), 2.10−2.35 (m, 3H), 2.54−2.74 (m, 2H), 3.48−3.60 (m, 1H), 3.90 (dt, 1H, J = 8.5 and 4.2 Hz), 4.32 (qd, 2H, J = 7.1 and 1.8 Hz), 6.72 (t, 1H, J = 7.2 Hz), 6.85 (d, 1H, J = 8.2 Hz), 6.99 (d, 1H, J = 7.2 Hz), and 7.13 (t, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz)

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(36) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

δ 14.2, 17.9, 19.4, 30.8, 33.1, 35.1, 36.2, 43.4, 62.0, 84.8, 97.8, 111.9, 118.4, 124.3, 127.5, 127.8, 128.3, 143.3, 166.2, and 209.4; HRMS calcd for $C_{20}H_{23}NO_4$ 341.1628, found 341.1631.

1-[2-(1-Methyl-1*H*-indol-3-yl)acetyl]-2-oxopiperidine-3-carboxylic Acid Ethyl Ester. To a solution of 0.50 g (2.9 mmol) of 2-oxopiperidine-3-carboxylic acid ethyl ester in 10 mL of THF at −78 °C was added 4.0 mL (6.4 mmol) of a 1.6 M *n*-butyllithium solution in hexane, and the mixture was allowed to stir while being warmed to rt. The solution was cooled to −78 °C, and 0.90 g (4.4 mmol) of *N*-methyl-3-indoleacetyl chloride in 2 mL of CH_2Cl_2 was added over 5 min. The solution was allowed to stir for 2 h and was quenched with H_2O. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.45 g (45%) of 1-[2-(1-methyl-1*H*-indol-3-yl)acetyl]-2-oxopiperidine-3-carboxylic acid ethyl ester as a yellow oil: IR (neat) 2947, 1745, 1695, 1645, and 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, 3H, J = 7.1 Hz), 1.65−2.20 (m, 4H), 3.53 (t, 1H, J = 7.6 Hz), 3.60−3.80 (m, 2H), 3.73 (s, 3H), 4.25 (dq, 2H, J = 7.1 and 2.0 Hz), 4.35 (d, 1H, J = 16.9 Hz), 4.43 (d, 1H, J = 16.9 Hz), and 7.00−7.65 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 20.7, 24.2, 32.7, 35.5, 43.9, 51.5, 61.7, 107.2, 109.2, 119.1, 119.2, 121.6, 128.1, 128.4, 136.8, 169.8, 170.0, and 175.1. Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.64; H, 6.48; N, 8.19. Found: C, 66.47; H, 6.41; N, 8.03.

Rhodium(II)-Catalyzed Reaction of 2-Diazo-3-[1-[(1-methyl-1*H*-indol-3-yl)acetyl]-3-carbethoxy-2-oxopiperidin-3-yl]-3-oxopropionic Acid Ethyl Ester (25). To a stirred solution of 0.10 g (0.29 mmol) of the above imide in 5 mL of THF at 0 °C was added 0.18 mL (0.36 mmol) of a 2.0 M solution of *n*-butylmagnesium chloride in THF. The solution was allowed to stir at 0 °C for 1 h, and then 0.10 g (0.55 mmol) of ethyl 2-diazomalonyl chloride was added. The solution was allowed to stir at 0 °C for 2 h and was quenched with H_2O. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give **25** (59%) as a yellow oil: IR (neat) 2143, 1733, 1695, 1646, 1472, and 1320 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 3H, J = 7.0 Hz), 1.29 (t, 3H, J = 7.0 Hz), 1.65−2.26 (m, 4H), 2.41 (ddd, 1H, J = 13.7, 9.5, and 4.3 Hz), 2.66 (dt, 1H, J = 9.5 and 4.3 Hz), 3.73 (s, 3H), 3.76−3.85 (m, 1H), 4.20−4.40 (m, 5H), and 7.00−7.60 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 20.7, 24.2, 28.2, 32.6, 35.5, 43.9, 51.5, 61.7, 70.0, 107.2, 107.6, 109.1, 119.0, 121.5, 128.0, 128.4, 136.8, 160.8, 166.6, 169.8, 175.4, and 187.0.

Since diazo imide **25** decomposed on standing, it was immediately subjected to the rhodium(II)-catalyzed reaction. To 50 mg (0.1 mmol) of **25** in 0.5 mL of benzene was added 2 mg of rhodium(II) acetate. The mixture was heated to 50 °C in an oil bath for 3 h and concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.40 g (90%) of 3,18-dicarbethoxy-3,19-epoxy-4,10-dioxo-1-methylaspidospermidine (**26**) as a white solid: mp 188−189 °C; IR (neat) 2933, 1727, 1697, 1642, 1482, and 1320 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H, J = 7.1 Hz), 1.36 (t, 3H, J = 7.1 Hz), 1.70−1.82 (m, 1H), 1.95 (dt, 1H, J = 13.6 and 3.3 Hz), 2.08 (td, 1H, J = 13.6 and 3.3 Hz), 2.18−2.36 (m, 1H), 2.81 (d, 1H, J = 17.3 Hz) 2.97 (s, 3H), 3.00 (d, 1H, J = 17.3 Hz), 3.15−3.30 (m, 3H), 3.96 (dd, 1H, J = 12.8 and 4.4 Hz), 4.30−4.42 (m, 2H), 4.43 (s, 1H), 6.40 (d, 1H, J = 7.8 Hz), 6.65 (t, 1H, J = 7.3 Hz), 6.91 (d, 1H, J = 7.3 Hz), and 7.12 (t, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 14.1, 18.4, 28.4, 35.2, 38.0, 45.0, 53.9, 59.8, 61.4, 62.7, 80.4, 92.5, 104.9, 107.6, 118.0, 125.1, 125.7, 130.2, 154.2, 165.1, 165.5, 175.6, 195.7. Anal. Calcd for $C_{24}H_{26}N_2O_7$: C, 63.41; H, 5.77; N, 6.17. Found: C, 63.28; H, 5.69; N, 6.04.

3-Carboxy-3-ethyl-2-piperidone (27). To a 68 g (36 mmol) sample of diethyl ethylmalonate in 300 mL of a 1:1 THF:DME solution was added 100 g (72 mmol) of K_2CO_3. The mixture was allowed to stir at rt for 30 min, and 25 g (38 mmol) of acrylonitrile was added. The solution was heated at 65 °C under Ar for 8 h. The mixture was cooled to rt, filtered, and washed with H_2O. The organic layer was separated, washed with a saturated NaCl solution, and dried over $MgSO_4$. Concentration under reduced pressure gave 80 g (92%) of diethyl (2-(2-cyanoethyl)-2-ethyl)malonate as a colorless oil.

To a 75 g (310 mmol) sample of the above nitrile in 1 L of EtOH was added 150 g (620 mmol) of $CoCl_2 \cdot 6H_2O$, and the solution was allowed to stir for 30 min. To this mixture was added 59 g (1.6 mol) of $NaBH_4$ in small portions over 1 h such that the temperature did not rise above 25 °C. The solution was allowed to stir for 1 h, and then 500 mL of 3 N HCl was added to dissolve the black precipitate resulting from the $NaBH_4$ addition. The solution was made basic (pH 10) by the addition of concentrated NH_4OH, and the mixture was extracted with ether. The organic extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was taken up in 200 mL of toluene and heated at reflux under Ar for 24 h. The solution was cooled and concentrated under reduced pressure to give 56 g (90%) of 3-carbethoxy-3-ethyl-2-piperidone as a colorless oil: IR (neat) 1738, 1666, 1239, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, J = 7.4 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.68−2.15 (m, 6H), 3.18−3.40 (m, 2H), 4.00−4.23 (m, 2H), and 6.79 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.9, 14.1, 19.6, 28.4, 28.9, 42.4, 54.1, 61.2, 171.2, and 173.0. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.26; H, 8.60; N, 7.03. Found: C, 60.13; H, 8.45; N, 7.12.

To 56 g (280 mmol) of the above lactam was added 38 g (570 mmol) of 85% KOH pellets in 200 mL of H_2O. The solution was allowed to stir at rt for 12 h. The aqueous solution was washed with ether, acidified to pH 2, and extracted with CH_2Cl_2. The organic extracts were washed with a saturated NaCl solution and dried over $MgSO_4$. Concentration under reduced pressure gave 42 g (87%) of **27** as a white solid: mp 127−128 °C; IR (KBr) 3324, 2940, 1729, 1623, and 905 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H, J = 7.4 Hz), 1.75−2.00 (m, 6H), 3.20−3.45 (m, 2H), 7.12 (brs, 1H), and 10.72 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.9, 19.0, 26.8, 31.3, 42.6, 52.2, 172.9, and 175.5. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.11; H, 7.66; N, 8.18. Found: C, 56.07; H, 7.59; N, 8.13.

3-(3-Ethyl-2-oxopiperidin-3-yl)-3-oxopropionic Acid Methyl Ester (14). To 4.5 g (26 mmol) of the above carboxylic acid in 50 mL of CH_2Cl_2 was added 5.0 g (31 mmol) of 1,1′-carbonyldiimidazole, and the solution was allowed to stir at rt under Ar for 12 h. The crude acylimidizolide was added dropwise to a solution of 4.5 g (39 mmol) of hydrogen methyl malonate and 60 mL (120 mmol) of 2 M isopropyl magnesium chloride in 200 mL THF at rt. The solution was allowed to stir at rt for 12 h, and 50 mL of 1 N HCl was added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3.4 g (58%) of **14** as a white solid: mp 80−81 °C; IR (neat) 1745, 1709, 1652, and 1318 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, 3H, J = 7.4 Hz), 1.43−1.80 (m, 3H), 1.91 (dq, 2H, J = 7.4 and 2.0 Hz), 2.35−2.45 (m, 1H), 3.22−3.33 (m, 2H), 3.67 (s, 3H), 3.69 (d, 1H, J = 16.4 Hz), 3.86 (d, 1H, J = 16.4 Hz), and 6.28 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 19.8, 26.5, 29.4, 42.6, 45.2, 52.2, 60.4, 168.1, 171.5, and 201.6. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.12; H, 7.54; N, 6.17. Found: C, 58.04; H, 7.52; N, 6.09.

3-[3-Ethyl-1-[2-(1-methyl-1H-indol-3-yl)acetyl]-2-oxopiperidin-3-yl]-3-oxopropionic Acid Methyl Ester. To 600 mg (3.2 mmol) of *N*-methyl-3-indoleacetic acid (**13**) in 20 mL of CH_2Cl_2 were added 0.87 mL (10 mmol) of oxalyl chloride and one drop of DMF. The solution was allowed to stir at rt for 4 h and was concentrated under reduced pressure. The residue was taken up in 5 mL of CH_2Cl_2, and this mixture was added to a solution of 0.61 g (2.7 mmol) of lactam **14** and 10 g of 4 Å mesh molecular sieves in 50 mL of CH_2Cl_2. The mixture was allowed to stir at rt for 12 h, filtered, and

concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 690 mg (65%) of 3-[3-ethyl-1-[2-(1-methyl-1*H*-indol-3-yl)acetyl]-2-oxopiperidin-3-yl]-3-oxopropionic acid methyl ester as a yellow oil: IR (neat) 1746, 1691, 1330, and 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 3H, J = 7.4 Hz), 1.50 (ddd, 1H, J = 13.9, 8.7, and 5.6 Hz), 1.65−1.97 (m, 4H), 2.38 (dt, 1H, J = 9.3 and 4.3 Hz), 3.45 (d, 2H, J = 1.6 Hz), 3.56 (s, 3H), 3.62−3.70 (m, 2H), 3.71 (s, 3H), 4.36 (d, 2H, J = 4.4 Hz), 7.02 (s, 1H), 7.09 (t, 1H, J = 7.2 Hz), 7.18 (d, 1H, J = 7.7 Hz), 7.22 (t, 1H, J = 8.0), and 7.57 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 19.8, 26.6, 29.4, 32.6, 36.0, 44.5, 44.6, 52.3, 63.5, 107.1, 109.2, 119.0, 119.2, 121.7, 128.0, 128.3, 136.8, 167.5, 173.4, 175.7, and 200.2. Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.30; H, 6.58; N, 7.03. Found: C, 66.23; H, 6.44; N, 7.15.

Rhodium(II)-Catalyzed Reaction of 2-Diazo-3-[3-ethyl-1-[2-(1-methyl-1*H*-indol-3-yl)acetyl]-2-oxopiperidin-3-yl]-3-oxopropionic Acid Methyl Ester (12). To 500 mg (1.3 mmol) of the above keto ester in 15 mL of CH_3CN was added 0.32 mL (2.3 mmol) of NEt_3. The solution was allowed to stir for 15 min at which time 0.25 mL (2.5 mmol) of mesyl azide was added, and the reaction mixture was allowed to stir for 5 h. The reaction was quenched with H_2O, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 490 mg (90%) of **12** as a yellow oil: IR (neat) 2135, 1717, 1685, 1651, 1616, and 1324 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (t, 3H, J = 7.4 Hz), 1.50−1.84 (m, 5H), 2.21 (td, 1H, J = 12.5 and 4.7 Hz), 3.50−3.70 (m, 1H), 3.62 (s, 3H), 3.65 (s, 3H), 4.11−4.18 (m, 1H), 4.11 (d, 1H, J = 16.7), 4.24 (d, 1H, J = 16.7), 6.90 (s, 1H), 6.97 (t, 1H, J = 7.4 Hz), 7.09 (t, 1H, J = 7.0 Hz), 7.27 (d, 1H, J = 8.3 Hz), and 7.45 (d, 1H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.7, 19.3, 27.9, 29.5, 32.6, 35.7, 44.4, 52.3, 59.9, 107.7, 109.1, 118.9, 119.0, 121.5, 128.0, 128.4, 136.8, 161.6, 173.7, 176.3, and 190.5.

Since diazo imide **12** decomposed on standing, it was immediately subjected to the rhodium(II)-catalyzed reaction. To a solution of 450 mg (1.1 mmol) of **12** in 5 mL of benzene under nitrogen was added 2 mg of rhodium(II) acetate. The mixture was heated in an oil bath at 50 °C for 4 h and concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 410 mg (95%) of 3-carbomethoxy-4,10-dioxo-3,19-epoxy-1-methylaspidospermadine (**11**) as a white solid: mp 207−208 °C; IR (KBr) 1768, 1722, 1605, 1487, and 1350 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.55−0.62 (m, 1H), 0.78 (t, 3H, J = 7.1 Hz), 0.79−0.91 (m, 1H), 1.50−1.98 (m, 4H), 2.68 (d, 1H, J = 17.3 Hz), 2.91 (s, 3H), 2.97 (d, 1H, J = 17.3 Hz), 3.09 (td, 1H, J = 12.7 and 4.3 Hz), 3.60−3.79 (m, 1H), 3.81 (s, 3H), 4.30 (s, 1H), 6.45 (d, 1H, J = 7.7 Hz), 6.67 (t, 1H, J = 7.4 Hz), 6.92 (d, 1H, J = 7.4 Hz), and 7.18 (t, 1H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.0, 17.8, 19.8, 24.7, 34.8, 39.0, 45.5, 51.3, 53.1, 59.5, 80.7, 92.4, 104.5, 107.8, 118.2, 123.5, 127.3, 130.1, 153.0, 166.4, 176.7, and 205.3. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.40; H, 6.18; N, 6.94.

3-Carbomethoxy-4-oxo-3,19-epoxy-10-thioxo-1-methylaspidospermadine. To a 250 mg (0.63 mmol) sample of **11** in 10 mL of toluene was added 260 mg (0.64 mmol) of Lawesson's reagent.[31] The solution was heated at 110 °C under Ar for 5 h and concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 220 mg (85%) of 3-carbomethoxy-4-oxo-3,19-epoxy-10-thio-1-methylaspidospermadine as a yellow solid: mp 170−171 °C; IR (neat) 1773, 1744, 1602, 1368, and 1311 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.56−0.67 (m, 1H), 0.75 (t, 3H, J = 6.8 Hz), 0.80−0.91 (m, 1H), 1.60−2.00 (m, 4H), 2.98 (s, 3H), 3.27 (dt, 1H, J = 13.1 and 4.5 Hz), 3.32−3.47 (m, 2H), 3.88 (s, 3H), 4.30−4.40 (m, 1H), 4.43 (s, 1H), 6.42 (d, 1H, J = 8.0 Hz), 6.60−6.90 (m, 2H), and 7.15−7.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.9, 18.0, 19.7, 24.1, 35.9, 43.5, 51.7, 53.2, 55.6, 57.4, 62.2, 79.9, 93.3, 107.8, 118.4, 123.6, 126.8, 130.2, 152.9, 166.1, 204.6, and 208.2. Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79. Found: C, 63.79; H, 5.93; N, 6.64.

3-Carbomethoxy-4-oxo-3,19-epoxy-1-methylaspidospermadine (29). To a 300 mg (0.73 mmol) sample of the above thiolactam in 15 mL of THF was added an excess of Raney Ni. The solution was heated at 65 °C for 2 h, cooled, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and filtered through a pad of silica gel to give 270 mg (96%) of 3-carbomethoxy-4-oxo-3,19-epoxy-1-methylaspidospermadine (**29**) as a yellow oil: IR (neat) 1760, 1721, 1603, and 908 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.40−0.54 (m, 1H), 0.71 (t, 3H, J = 7.2 Hz), 0.79−0.88 (m, 1H), 1.55−1.85 (m, 4H), 2.14−2.32 (m, 1H), 2.39 (ddd, 1H, J = 14.6, 9.4, and 3.6 Hz), 2.80−3.05 (m, 2H), 2.94 (s, 3H), 3.17 (ddd, 1H, J = 12.3, 7.2, and 3.6 Hz), 3.48−3.56 (m, 1H), 3.84 (s, 3H), 4.25 (s, 1H), 6.36 (d, 1H, J = 7.8 Hz), 6.60 (dt, 1H, J = 7.3 and 0.5 Hz), 6.96 (dd, 1H, J = 7.3 and 0.9 Hz), and 7.10 (dt, 1H, J = 7.8 and 0.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.2, 20.0, 25.2, 34.7, 38.0, 46.3, 50.4, 51.6, 52.8, 52.9, 63.3, 82.2, 91.9, 107.1, 117.6, 124.0, 129.1, 130.4, 130.6, 153.0, 167.9, and 208.5; HRMS calcd for $C_{22}H_{26}N_2O_4$ 382.1892, found 382.1890.

4-Desacetoxy-4-oxo-6,7-dihydrovindorosine (10). To a 250 mg (0.65 mmol) sample of **29** in 10 mL of MeOH were added 5 mg of PtO_2 and one drop of concentrated HCl. The solution was hydrogenated at rt under 40 psi of hydrogen for 2 h. The mixture was filtered through a pad of Celite, diluted with ethyl acetate, washed with a saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash silica gel chromatography gave 230 mg (94%) of 4-desacetoxy-4-oxo-6,7-dihydrovindorosine (**10**) as a white solid: mp 167−168 °C; IR (neat) 1745, 1710, 1604, 1486, and 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.43 (t, 3H, J = 7.4 Hz), 0.98 (dt, 1H, J = 12.7 and 5.5 Hz), 1.13−1.42 (m, 2H), 1.50−1.60 (m, 2H), 2.00 (dt, 1H, J = 11.2 and 4.2 Hz), 2.28−2.50 (m, 5H), 2.64 (s, 3H), 3.05−3.25 (m, 2H), 3.75 (s, 1H), 3.84 (s, 3H), 6.52 (d, 1H, J = 7.9 Hz), 6.75−7.20 (m, 3H), and 8.74 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.2, 21.8, 26.4, 29.8, 40.2, 45.0, 50.8, 52.0, 52.4, 52.5, 53.6, 76.6, 78.9, 85.0, 111.3, 119.9, 122.6, 128.9, 134.8, 153.4, 170.2, and 204.2. Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.71; H, 7.34; N, 7.29. Found: C, 68.52; H, 7.25; N, 7.18.

3-Carbomethoxy-4-acetyl-10-oxo-3,19-epoxy-1-methylaspidospermadine (31). To a 250 mg (0.63 mmol) sample of 3-carbomethoxy-4,10-dioxo-3,19-epoxy-1-methylaspidospermadine (**11**) in 4 mL of THF and 2 mL of MeOH was added 0.47 g of $CeCl_3 \cdot 7H_2O$. To this mixture was added 70 mg (1.88 mmol) of $NaBH_4$, and the solution was allowed to stir at rt for 4 h. The reaction was diluted with ether, washed with H_2O and a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 45 mg (18%) of 3-(hydroxymethyl)-4-hydroxy-10-oxo-3,19-epoxy-1-methylaspidospermadine (**32**) as the minor component of the crude reaction mixture: mp 124−125 °C; IR (neat) 3324, 2950, 1604, and 1441 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.51−0.82 (m, 5H), 1.40−1.55 (m, 3H), 1.87 (d, 1H, J = 11.7 Hz), 2.56 (d, 1H, J = 13.8 Hz), 2.83 (s, 3H), 2.85−3.00 (m, 1H), 3.40−4.00 (m, 5H), 4.18 (s, 1H), 6.02 (d, 1H, J = 10.2 Hz), 6.61 (d, 1H, J = 8.0 Hz), 6.80 (t, 1H, J = 7.4 Hz), 6.92 (d, 1H, J = 7.4 Hz), and 7.15 (t, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.8, 18.7, 18.8, 30.1, 38.5, 39.4, 45.0, 47.6, 60.0, 63.2, 81.1, 82.7, 106.1, 111.3, 121.4, 124.1, 129.4, 131.6, 152.5, and 176.6. Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.18; H, 6.91; N, 7.52.

The major fraction isolated from the silica gel column contained 160 mg (64%) of 3-carbomethoxy-4-hydroxy-10-oxo-3,19-epoxy-1-methylaspidospermadine as a clear oil: IR (neat) 3324, 1703, 1604, 1441, and 1367 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.60−0.98 (m, 5H), 1.45−2.00 (m, 3H), 2.62 (d, 1H, J = 16.9 Hz), 2.93 (d, 1H, J = 16.9 Hz), 3.03 (s, 3H), 3.09 (dd, 1H, J = 12.4 and 4.4 Hz), 3.83 (dd, 1H, J = 12.4 and 4.4 Hz), 3.83 (dd, 1H, J = 12.4 and 5.0 Hz), 3.89 (s, 3H), 4.10 (d, 1H, J = 10.4 Hz), 4.28 (s, 1H), 6.20 (d, 1H, J = 10.4 Hz), 6.70 (d, 1H, J = 7.8 Hz), 6.88 (t, 1H, J = 7.3 Hz), 6.97 (d 1H, J = 7.3

Hz), and 7.23 (t, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.7, 18.7, 18.8, 30.2, 38.3, 39.3, 45.1, 47.3, 52.9, 60.0, 81.4, 83.5, 84.8, 107.4, 111.7, 121.6, 123.0, 129.7, 130.9, 152.5, 170.5, and 175.9.

To a 100 mg (0.25 mmol) sample of the above alcohol was added 2 mL of acetic anhydride, and the solution was allowed to stir at rt for 10 min and then 0.10 g (1.3 mmol) of acetyl chloride was added. The mixture was stirred at rt for 8 h, extracted with ether, and washed with a saturated $NaHCO_3$ solution. The combined ether extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 110 mg (98%) of **31** as a yellow oil: IR (neat) 1745, 1730, 1604, and 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.45 (t, 3H, J = 7.3 Hz), 0.77 (td, 1H, J = 14.6 and 7.0 Hz), 0.93 (td, 1H, J = 14.6 and 7.5 Hz), 1.48−1.70 (m, 3H), 1.77 (dt, 1H, J = 13.4 and 3.0 Hz), 1.93 (s, 3H), 2.65 (d, 1H, J = 17.3 Hz), 2.86 (d, 1H, J = 17.3 Hz), 2.89 (s, 3H), 3.05 (dt, 1H, J = 12.7 and 4.9 Hz), 3.80−3.96 (m, 1H), 3.84 (s, 3H), 4.36 (s, 1H), 4.99 (s, 1H), 6.35 (d, 1H, J = 8.0 Hz), 6.58 (t, 1H, J = 7.3 Hz), 6.86 (d, 1H, J = 7.3 Hz), and 7.10−7.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.3, 18.3, 19.1, 20.6, 29.6, 34.2, 39.2, 45.0, 48.0, 52.9, 59.1, 80.1, 81.4, 83.4, 106.3, 107.6, 117.1, 124.3, 128.2, 129.6, 152.6, 170.0, 170.3, and 176.2; HRMS calcd for $C_{24}H_{28}N_2O_6$ 440.1948, found 440.1949.

3-Carbomethoxy-4-acetyl-10-thioxo-3,19-epoxy-1-methylaspidospermadine. To a 70 mg (0.16 mmol) sample of **31** in 5 mL of toluene was added 75 mg (0.18 mmol) of Lawesson's reagent, and the reaction mixture was heated at 110 °C for 2 h. The solution was cooled and concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 65 mg (89%) of 3-carbomethoxy-4-acetyl-10-thio-3,19-epoxy-1-methylaspidospermadine as a white solid: mp 164−165 °C; IR (neat) 1738, 1604, 1309, and 1231 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.47 (t, 3H, J = 7.3 Hz), 0.76−1.86 (m, 6H), 1.94 (s, 3H), 2.90 (s, 3H), 3.17 (dt, 1H, J = 13.3 and 5.1 Hz), 3.28 (s, 2H), 3.85 (s, 3H), 4.39 (s, 1H), 4.40 (dd, 1H, J = 14.0 and 5.1 Hz), 5.01 (d, 1H, J = 1.1 Hz), 6.36 (d, 1H, J = 8.0 Hz), 6.58 (t, 1H, J = 7.4 Hz), 6.85 (d, 1H, J = 7.4 Hz), and 7.11−7.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.3, 18.4, 19.1, 20.6, 28.8, 34.4, 43.8, 45.7, 53.0, 59.9, 61.7, 79.8, 81.2, 84.3, 106.4, 110.6, 117.3, 124.5, 127.7, 129.7, 152.6, 169.6, 170.2, and 207.2. Anal. Calcd for $C_{24}H_{28}N_2O_5S$: C, 63.14; H, 6.18; N, 6.14. Found: C, 63.05; H, 6.22; N, 6.04.

3-Carbomethoxy-4-acetyl-3,19-epoxy-1-methylaspidospermadine (33). To a 50 mg (0.11 mmol) sample of the above compound in 5 mL of THF was added an excess of Raney Ni, and the mixture was allowed to stir at rt for 2 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and filtered through silica gel to give 41 mg (88%) of 3-carbomethoxy-4-acetyl-3,19-epoxy-1-methylaspidospermadine (**33**) as a yellow oil: IR (neat) 1740, 1602, and 1490, and 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.46 (t, 3H, J = 7.4 Hz), 0.65−1.11 (m, 2H), 1.50−1.90 (m, 5H), 1.90 (s, 3H), 2.18−2.24 (m, 2H), 2.89 (s, 3H), 2.93−3.02 (m, 2H), 3.35 (dt, 1H, J = 8.3 and 5.1 Hz), 3.84 (s, 3H), 4.20 (s, 1H), 4.88 (s, 1H), 6.30 (d, 1H, J = 7.9 Hz), 6.57 (t, 1H, J = 7.4 Hz), 6.96 (d, 1H, J = 7.4 Hz), and 7.10 (dt, 1H, J = 7.9 and 1.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.5, 19.5, 20.5, 20.7, 30.4, 34.3, 41.3, 44.5, 46.6, 50.9, 52.7, 63.0, 68.0, 81.1, 82.1, 83.4, 105.7, 116.4, 125.1, 128.5, 131.6, 152.8, 170.6, and 171.4; HRMS calcd for $C_{24}H_{30}N_2O_5$ 426.2156, found 426.2159.

6,7-Dihydro-4-*epi*-vindorosine (34). To a 45 mg (0.10 mmol) sample of **33** in 10 mL of MeOH was added 5 mg of PtO_2. The solution was hydrogenated at rt under 40 psi of hydrogen for 2 h. The mixture was filtered through a pad of Celite, diluted with ethyl acetate, washed with a saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash silica gel chromatography gave 42 mg (92%) of 6,7-dihydro-4-*epi*-vindorosine (**34**) as a white solid: mp 89−90 °C; IR (neat) 1737, 1602, 1487, and 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.27 (t, 3H, J = 7.4 Hz), 0.80−1.00 (m, 2H), 1.25−2.01 (m, 6H), 2.10 (s, 3H), 2.38−2.40 (m, 3H), 2.75 (s, 3H), 3.05−3.16 (m, 2H), 3.78 (s, 3H), 4.07 (s, 1H), 5.49 (s, 1H), 6.42 (d, 1H, J = 8.0 Hz), 6.69 (t, 1H, J = 8.0 Hz), 7.00−7.19 (m, 2H), and 10.6 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 21.4, 21.5, 27.7, 33.1, 34.3, 39.9, 41.9, 51.3, 52.3, 52.9, 53.4, 72.6, 76.3, 76.5, 78.5, 106.9, 118.0, 122.9, 128.8, 134.4, 152.8, 170.6, and 171.4. Anal. Calcd for $C_{24}H_{32}N_2O_5$: C, 67.25; H, 7.53; N, 6.54. Found: C, 67.13; H, 7.49; N, 6.62.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for new compounds lacking analyses together with an ORTEP drawing for structures **10**, **11**, and **18** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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