Synthesis of Indolizidines and Pyrrolizidines through the [2 + 2]Cycloaddition of Five-Membered Endocyclic Enecarbamates to Alkyl Ketenes. Unusual Regioselectivity of Baeyer−Villiger Ring Expansions of Alkyl Aza-Bicyclic Cyclobutanones

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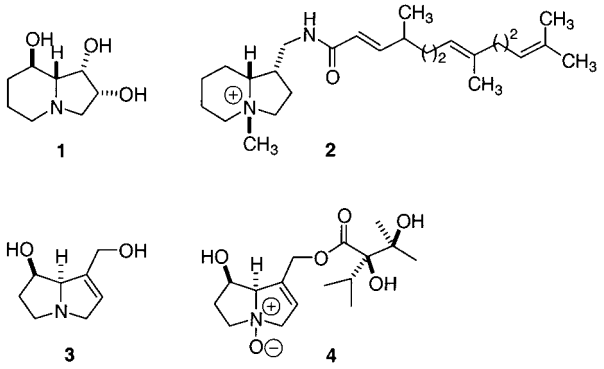
The total syntheses of two indolizidine skeletons and of the necine base (±)-platynecine were accomplished in a concise manner with good overall yields starting from a common five-membered endocyclic enecarbamate. These syntheses feature a [2 + 2]cycloaddition of the five-membered endocyclic enecarbamate **5** to alkylketenes that proceeded in high yields and with high stereoselectivity to provide an *endo* alkyl cycloadduct as the major or only product. The minor *exo* alkyl cycloadducts, which can be observed in some [2 + 2]cycloadditions, seem to derive from the *endo* cycloadduct, the putative kinetic product, by epimerization. An unusual regioselectivity was observed for the Baeyer−Villiger oxidation of 7-alkyl-2-azabicyclic cyclobutanones. *Endo*-7-alkyl cycloadducts ring-expanded exclusively to a γ-lactone in which oxygen is inserted into the C6−C7 bond in preference to the bridgehead C5−C6 bond. With the *exo*-7-alkyl cycloadduct the regioselectivity of the Baeyer−Villiger oxidation is drastically reduced, leading to mixtures of regioisomeric lactones in a ratio of ∼1.5 to 1. It is hypothesized that the steric strain built into the Criegee cyclobutane intermediate is the regioselective controlling factor in these oxidations, overriding any stereoelectronic bias for ring expansion. A rationale for the mechanism of the [2 + 2]cycloaddition involving enecarbamates and ketenes is presented, which seems to involve the participation of an *N*-acyliminium-enolate intermediate.

Introduction

Indolizidine and pyrrolizidine alkaloids are naturally occurring *N*-heterocyclic metabolites encompassing a large number of compounds that display pronounced biological and pharmacological activities with therapeutical potential.[1] For example, swainsonine **1** (Chart 1) exhibits metastasis and tumor growth control besides immunomodulatory activity.[2] Stellettamide A, **2**, a recently discovered indolizidine, has shown antifungal activity and cytotoxicity against K562 epithelium cells.[3] The necine base of pyrrolizidine alkaloids exemplified by retronecine **3** shows acute hepatotoxicity,[4] whereas indicine *N*-oxide **4** has antitumor activity.[5] The increasing need for considerable amounts of indolizidine and pyrrolizidine alkaloids for biological and ecological screening makes these heterocyclic compounds important targets in organic synthesis.[1] As a consequence, new and practical methodologies leading to these classes of substances are not only highly desirable but also necessary.

Chart 1. Biologically Active Indolizidines and Pyrrolizidines



A few years ago we started a program aiming at the synthesis of alkaloids exploiting the moderate reactivity of endocyclic enecarbamate frameworks toward electrophiles. One of the synthetic strategies envisioning the preparation of indolizidines and pyrrolizidines is displayed in Scheme 1. It involves a [2 + 2]cycloaddition of an endocyclic enecarbamate to functionalized ketenes which, by simultaneous C−C bond formation at the α and β positions, could lead to azabicyclic cyclobutanones as potential precursors for the synthesis of alkaloids and *N*-heterocycles. One of the main objectives of such a strategy was the rapid assembly of the carbon skeleton

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(1) (a) For an updated review on the indolizidine alkaloids, see: Michael J. P. *Nat. Prod. Rep.* **2001**, *18*, 520, and references for previous reviews cited therein. For an updated review on pyrrolizidine alkaloids, see: (b) Liddell J. R. *Nat. Prod. Rep.* **2001**, *18*, 441. (c) Harborne, J. B. *Nat. Prod. Rep.* **2001**, *18*, 361, and references therein.

(2) (a) Goss, P. E.; Reid, C. L.; Bailey, D.; Denis, J. W. *Clin. Cancer. Res.* **1997**, *3*, 1077. (b) Goss, P. E.; Baker, M. A.; Carver, J. P.; Denis, J. W. *Clin. Cancer. Res.* **1995**, *1*, 935.

(3) Hirota, H.; Matsunaga, S.; Fusetami, N. *Tetrahedron Lett.* **1990**, *31*, 4163.

(4) Berry, D. L.; Schoofs, G. M.; Molyneux, R. J.; *J. Nat. Toxins* **1996**, *5*, 7.

(5) (a) Kugelman, M.; Liu, W. C.; Axelrod, M.; McBride, T. J.; Rao, K. V.; *Lloydia* **1976**, *39*, 125. (b) Miser, J. S.; Smithson, W. A.; Krivit, W.; Hughes, C. H.; Davis, D.; Krailo, M. D.; Hammond, G. D. *Am. J. Clin. Oncol.-Canc.* **1992**, *15*, 135.

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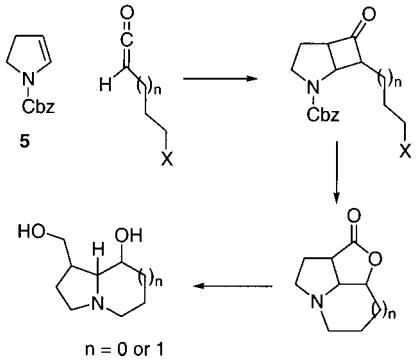
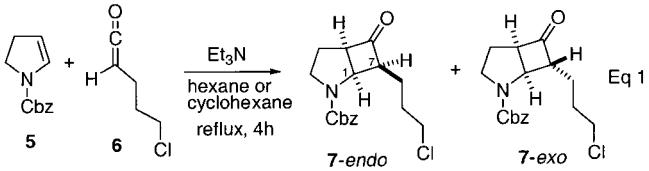
Scheme 1. Strategy for the Synthesis of Indolizidines and Pyrrolizidines from Enecarbamate 5



of indolizidines and pyrrolizidines, thus maximizing the chances for good overall yields of the final products. Studies in our research group have demonstrated for the first time that five-membered endocyclic enecarbamates are indeed suitable substrates for [2 + 2]cycloaddition to ketenes.[6a] Baeyer−Villiger ring expansion of the azabicyclic cyclobutanone adducts can also be performed in a regioselective manner, thus opening the way for the application of this strategy to the synthesis of indolizidine and pyrrolizidine alkaloids.[6b] In this paper we report these findings in detail together with new results which further extend the methodology and provide a rationale for some surprising results encountered during these studies.

Synthesis of Indolizidine Systems. The [2 + 2]-Cycloaddition of Enecarbamate 5 with Alkylketenes. The synthesis was initiated with the preparation of endocyclic enecarbamate **5**, in gram quantities, according to the method of Kraus[7] (∼ 60% yield from pyrrolidine) or by the use of our protocol starting from *N*-acyllactams (two steps, ∼70% yield).[8] [2 + 2]Cycloaddition of endocyclic enecarbamate **5** to alkylketene **6** (generated in situ from commercially available 5-chlorovaleryl chloride) in hexane, at reflux, provided the corresponding 2-azabicyclic cyclobutanones **7**-*endo* and **7**-*exo* in 59% yield (eq 1).[9] Due to the low reactivity of alkylketenes toward cycloaddition, these reactions were performed as rather concentrated mixtures to attain reasonable yields (∼0.62 mol/L).[10] However, changing the solvent to cyclohexane (bp 81 °C) improved yields significantly as well as the ease with which cycloaddition could be conducted. [2 + 2]Cycloaddition in refluxing cyclohexane provided cycloadducts **7**-*endo* and **7**-*exo* in yields of 74% to 76% with high stereoselectivity toward the *endo* cycloadduct (Table 1). Moreover, with cyclohexane as solvent, cycloaddition reactions could be carried out at a much lower concentration, usually at 0.08 mol/L.

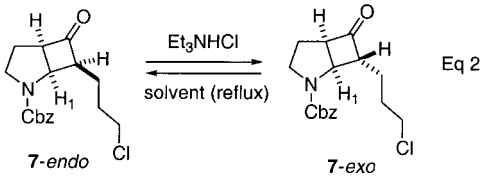
Table 1. Cycloaddition of Ketene 6 to Enecarbamate 5



solvent	yield (%)[a]	*endo*:*exo* ratio[b]
hexane	45−59	95:05
cyclohexane	74−76	>95:05

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude mixture.

Table 2. Epimerization of the 7-*Endo* Cycloadduct



solvent	time (h)	*endo*:*exo* ratio[a,b]
hexane	24	75:25
cyclohexane	24	94:6
THF	20	66:33
CH_2Cl_2	48	50:50

[a] As determined by ^{1}H NMR. [b] >90% recovery of the cycloadducts.

The diastereomeric ratio (dr) for the [2 + 2]cycloadducts was markedly influenced by the solvent employed and by the time of reflux. In cyclohexane the major cycloadduct was the 2-azabicyclic cyclobutanone adduct **7**-*endo* with the 7-*exo* cycloadduct detected only in very minor amounts. Cycloadditions carried out in hexane led to varying amounts of the 7-*exo* cycloadduct (^{1}H NMR analysis) depending on reaction times (12−24 h). This observation suggested that the minor **7**-*exo* cycloadduct was being formed from the major **7**-*endo* cycloadduct, the putative kinetic product of [2 + 2]cycloaddition, by epimerization at C7. Actually, interconvertion of the major 7-*endo* adduct into the minor 7-*exo* adduct can be carried out in the presence of triethylammonium chloride (eq 2). The results of some epimerization experiments are shown in Table 2. Significant epimerization was observed in hexane after 24 h of reflux, but it was only marginal in cyclohexane, in accordance with the results displayed in Table 1.[11] Also noteworthy was the observation that extensive epimerization can be obtained in solvents such as THF and CH_2Cl_2.

The excellent degree of *endo* stereoselectivity observed for the [2 + 2]cycloaddition in cyclohexane was surprising although a higher proportion of the *endo* product was expected based on the accepted mechanism for the cycloaddition, as well as on several precedents in the literature for similar systems.[12] Whether a concerted or

(6) (a) De Faria, A. R.; Matos, C. R. R.; Correia, C. R. D. *Tetrahedron Lett.* **1993**, *34*, 27. (b) Correia, C. R. D.; de Faria, A. R.; Carvalho, E. S. *Tetrahedron Lett.* **1995**, *29*, 5109.

(7) Kraus, G. A.; Neunschwander, K. *J. Org. Chem.* **1981**, *46*, 4791.

(8) Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6646.

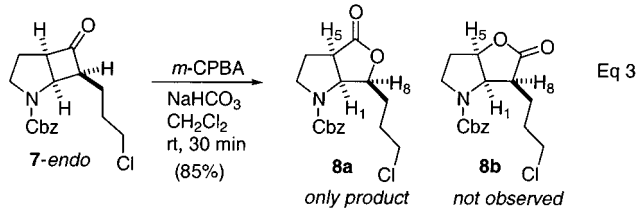
(9) For simplicity, numbering of all heterocycles is based on that of the parent 2-azabicyclo[3.2.0]heptan-6-one throughout this manuscript.

(10) To compensate for the lower reactivity of alkylketenes, a large excess of the olefin is usually employed. However, to avoid using an excess of the olefin, we decided to run the reactions at high concentration. Reactions carried out at lower concentrations in hexane provided lower yields of the cycloadduct, together with ketene dimerization products. According to the literature, precipitation of triethylammonium chloride has a beneficial effect on the cycloaddition since solubilized triethylammonium chloride can catalyze polymerization of ketenes. For more details, see: Brady, W. T.; *Tetrahedron* **1981**, *37*, 2949.

(11) The two cycloadducts could not be separated by column chromatography, but they are easily distinguished by ^{1}H NMR. ^{1}H NMR spectrum for the **7**-*endo* cycloadduct shows duplicated triplets (J = 7.2 Hz) at 4.75 and 4.85 ppm for H1, whereas for the **7**-*exo* cycloadduct H1 appears as duplicated broad doublets at 4.20 and 4.28 ppm. These duplicated signals are due to conformational isomers resulting from restricted rotation along the carbonyl−nitrogen bond of the carbamate moiety. ^{1}H NMR at higher temperatures (60 °C) coalesce these duplicated signals to broad singlets centered at 4.80 and 4.25 ppm, respectively.

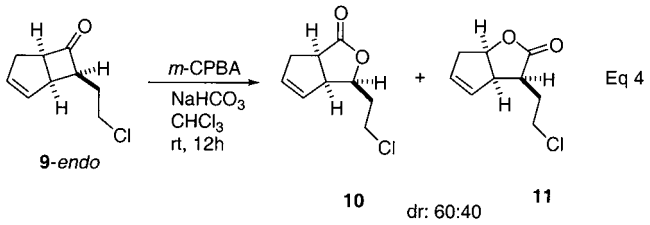
stepwise mechanism is operating in this case is still a matter of controversy although a rationale concerning this type of [2 + 2]cycloaddition is presented later in this paper.

Baeyer−Villiger Oxidation of the Cyclobutanone Adducts. Contrary to the [2 + 2]cycloaddition, which occurred with a predicted high stereoselectivity for the desired *endo* cycloadduct, the planned ring expansion through a Baeyer−Villiger reaction was less predictable in terms of regioselectivity. Moreover, the γ-lactone forming step was a critical one in our synthetic planning since it actually defines the type of indolizidine skeleton to be obtained. Gratifyingly, Baeyer−Villiger ring expansion of the 2-azabicyclic cyclobutanone **7**-*endo* with *m*-CPBA proceeded rapidly with remarkably high regioselectivity to provide the regioisomeric γ-butyrolactone **8a** as the only detectable product in 85% isolated yield. Despite much effort, the regioisomeric γ-butyrolactone **8b** was never isolated, even as a minor product of the Baeyer−Villiger oxidation (eq 3). The reasons for this high regioselectivity based on stereoelectronic grounds has been elusive, but a possible rationale for this unusual regiochemical outcome of the Baeyer−Villiger oxidation is advanced later in this work.



Eq 3

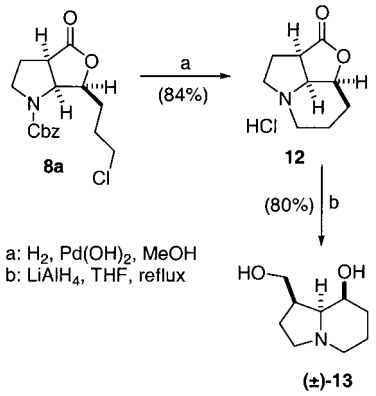
The result depicted in eq 3 is even more remarkable when compared with reports in the literature for the Baeyer−Villiger oxidation of an all-carbon version of a similar bicyclic system, the *endo* bicyclic cyclobutanone **9**. Baeyer−Villiger oxidation of cyclobutanone **9** gave the two possible γ-lactones **10** and **11** in a 60:40 ratio after 12 h (eq 4).[13]



Eq 4

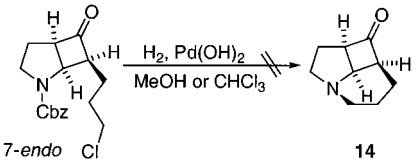
The structure of γ-lactone **8a** was elucidated by ^{1}H and ^{13}C NMR, COSY, and DEPT spectroscopy. Although spectra at room temperature are complex due to the presence of rotamers, some diagnostic signals are present in its ^{1}H NMR spectrum at 60 °C, such as a multiplet at 4.55 ppm for H8, an apparent triplet at 3.36 ppm for H5 (J = 7.9 Hz; implying a dihedral angle of ~90° between H5 and H4$_\beta$), and a broad triplet for H1 at 4.73 ppm.[14]

Scheme 2. Conversion of γ-Lactone 8a into the New Indolizidine 13



Overcoming the critical ring expansion step, conversion of γ-lactone **8a** to the indolizidine **13** was straightforward. Hydrogenolysis of **8a** with $Pd(OH)_2/H_2$ occurred smoothly to remove the Cbz protecting group and to promote an intramolecular ring closure affording the hydrochloride of the aza-tricyclic lactone **12** as a white powder in 84% yield (Scheme 2). It is worth pointing out that an *exo* side chain on γ-lactone **8** would severely restrict closure due to topographic constraints (a trans ring junction). Finally, reduction of the hydrochloride of the aza-tricyclic lactone **12** with lithium aluminum hydride in THF at reflux cleanly provided the indolizidine diol **13** in 80% yield. The 1-hydroxymethyl-8-hydroxyindolizidine **13** embodies the core indolizidine skeleton of the pharmacologically active alkaloid stellettamide A,[15] and is isomeric to that of tashiromine, in which a hydroxymethyl group is found on the six-membered ring.[16] The synthesis of the new indolizidine (±)-**13** was thus accomplished in four steps with an overall yield of 44% from endocyclic enecarbamate **5**.

In principle, γ-lactone **12** could also be generated by a Baeyer−Villiger reaction of the tricyclic cyclobutanone **14**, which in turn could be generated by hydrogenolysis of the 2-azabicyclo cyclobutanone **7**-*endo* (eq 5). This reversal in the order of steps to the indolizidine was also envisioned as another opportunity to probe the regioselectivity of the Baeyer−Villiger ring expansion. Unfortunately, all attempts to obtain cyclobutanone **14** by hydrogenolysis of **7**-*endo* failed, leading to mixtures of compounds that could not be properly identified.



Eq 5

Baeyer−Villiger Oxidations Aiming at Other Isomeric Indolizidines. The indolizidine skeleton resulting from the synthetic methodology presented above is a direct reflection of the regioselectivity of the Baeyer−Villiger reaction on the 2-azabicyclic cyclobutanone **7**-

(12) For a comprehensive review on the [2 + 2]cycloaddition of ketenes to olefins, see: Tidwell, T. T. *Ketenes*; John Wiley: NewYork, 1995.

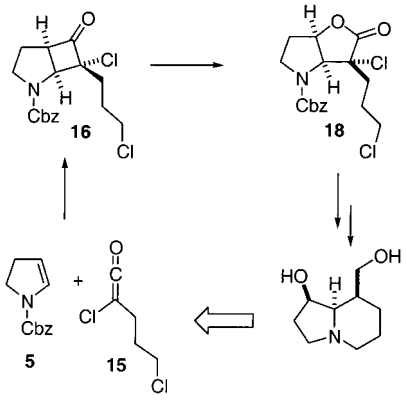
(13) (a) Ali, S. M.; Lee, T. V.; Roberts, S. M.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1979**, 708. (b) Baeyer−Villiger oxidation of **9**-*endo* using hydrogen peroxide−acetic acid led to a 70:30 regiomeric mixture. For details, see: Kelly, D. R.; Knowles, C. J.; Mahdi, J. G.; Wright, M. A.; Taylor, I. N. Hibbs, D. E.; Hursthouse, M. B.; Mish'al, A. K.; Roberts, S. M.; Wan, P. W. H.; Grogan, G.; Willetes, A. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2057.

(14) (a) Wistrand, L. G.; Thanning, M. *J. Org. Chem.* **1990**, *55*, 1406. (b) Takahata, H.; Banba, Y.; Momose, T. *Tetrahedron: Asymmetry* **1991**, *2*, 445.

(15) Shin, J.; Seo, Y.; Cho, K. W.; Rho, J. R.; Sim, C. J. *J. Nat. Prod.* **1997**, *60*, 611. For a synthesis of the *ent*-stellettamide A, see: Whitlock, G. A.; Carreira, E. M. *J. Org. Chem.* **1997**, *62*, 7916.

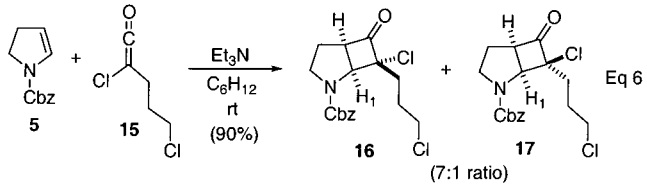
(16) Ohmiya, S.; Kubo, H.; Otomasu, H.; Saito, K.; Murakoshi, I.; *Heterocycles* **1990**, *30*, 537.

Scheme 3. Synthetic Strategy To Obtain an Indolizidine Isomeric to Indolizidine 13



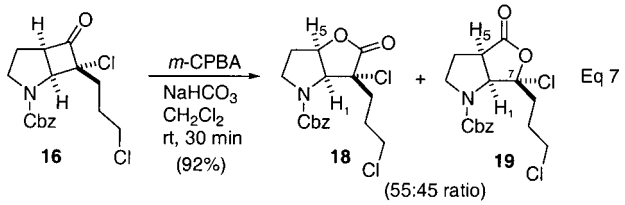
endo. Examples in the literature indicate that the presence of electron-withdrawing groups or atoms next to a carbonyl group decrease the rate of migration of the adjacent C−C bond.[17] Thus, a synthetic strategy to obtain an indolizidine skeleton isomeric to that of **13** should involve a Baeyer−Villiger oxidation of a 2-azabicyclic cyclobutanone bearing a halogen at C7. Incorporation of this halogen could be done in a straightforward manner by a [2 + 2]cycloaddition of enecarbamate **5** with chloro-(3-chloropropyl)ketene, as depicted in Scheme 3. Our interest in the isomeric indolizidine nucleus stems from the existence of a number of indolizidine alkaloids, such as tashiromine, bearing such a framework.[18] The stereochemical and regiochemical outcome of this approach was also of interest since it could provide new insights into the mechanism of the [2 + 2]cycloaddition and of the Baeyer−Villiger ring expansion.

2-Azabicyclic cyclobutanone **16** was obtained from cycloaddition of chloro-(3-chloropropyl)ketene **15** (generated in situ from 2,5-dichlorovaleryl chloride and Et_3N) with endocyclic enecarbamate **5** at room temperature.[19] Cycloaddition provided an easily separable mixture of *endo* alkyl **16** and *exo* alkyl **17** (7:1 ratio) in 90% isolated yield (eq 6). Stereochemical assignments were based on the chemical shift for H1 (doublet at 4.7 ppm for the major *endo* alkyl cycloadduct **16** and a doublet at 4.6 ppm for the minor *exo* alkyl cycloadduct **17**) and on NOE difference between H1 and its neighboring methylene groups.[20] These assignments are also in line with data available in the literature for similar cycloadditions of an all-carbon system.[21]



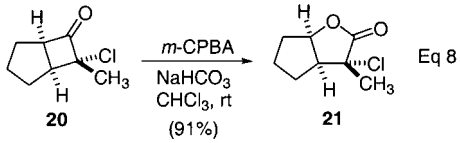
Eq 6

The major *endo* alkyl cycloadduct **16** was easily separated by flash chromatography and submitted to ring expansion with m-CPBA (eq 7). Once again, reaction was fast (30 min) and high yielding (92%) but, contrary to initial expectations, it provided a mixture of the diastereomeric γ-lactones **18** and **19** in a ratio of 55:45, slightly favoring the desired regioisomer resulting from migration of the bridgehead carbon atom.



Eq 7

The diastereomeric ratio between γ-lactones **18** and **19** was surprising in view of precedents in the literature in which the migratory aptitude of a carbon atom bearing an electron-withdrawing chlorine is greatly reduced. For example, Ali and Roberts obtained only the regioisomeric γ-lactone **21** from Baeyer−Villiger oxidation of bicyclic cyclobutanone **20** with m-CPBA (eq 8).[22] The results obtained by Ali and Roberts are in line with several other reports in the literature for all-carbon systems.[23]



Eq 8

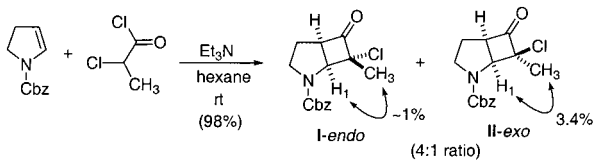
Although Baeyer−Villiger oxidation of azacyclobutanone **16** furnishes a mixture of γ-lactones **18** and **19** in ~1:1 ratio, it should be emphasized that this result represents a significant decrease in the tendency of the system to undergo oxygen insertion into the C6−C7 bond. Nevertheless, it was also clear that the electronegativity

(17) Krow, G. R. *Org. React.* **1993**, *43*, 251.

(18) For previous syntheses of tashiromine, see: (a) Olivier, D.; Bellec, C.; Fargeau-Bellassoued, M. C.; Lhommet, G. *Heterocycles* **2001**, *55*, 1689. (b) Bates, R. B.; Boonsombat, J. *J. Chem. Soc. Perkin Trans. 1* **2001**, 654. (c) Kim, S. H.; Kim, S. I.; Lai, S.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 6771. (d) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M. C.; Haviari, G.; Celerier, J. P.; Lhommet, G.; Gramain, J. C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122. (e) Gage, J. L.; Branchard, B. P. *Tetrahedron Lett.* **1997**, *38*, 7007. (f) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613.

(19) 2,5-Dichlorovaleryl chloride was prepared from commercially available 5-chlorovaleryl chloride according to the method of Harpp in 63−80% yield (NCS, $SOCl_2$, concentrated HCl, reflux). For details, see: Harpp, D. N.; Bao, L. Q.; Black, C. J.; Gleason, J. G.; Smith, R. A. *J. Org. Chem.* **1975**, *40*, 3420.

(20) Values of 6.0% and 9.3% for the NOE diff. involving H1 and the methylene group at C8 were observed for cycloadducts **16** and **17**, respectively. Although a higher NOE value for the *exo* alkyl **17** was expected, the NOE value of 6.0% for the *endo* alkyl cycloadduct **16** was surprising and cast some doubts on the utility of NOE difference as a diagnostic tool for stereochemical assignments in this case. To validate our assignments, we synthesized the simpler cycloadducts **I** and **II** by cycloaddition of enecarbamate **5** to 2-chloropropionyl chloride. A NOE difference of 3.4% was observed for H1 and the methyl group at C7 for the *exo* alkyl cycloadduct **II** against ~1% NOE diff. value for the major *endo* alkyl cycloadduct **I**. These results thus confirmed our previous assumption that a higher NOE diff. value is associated with an *exo* alkyl configuration in the azabicyclic cyclobutanones. The lower stereoselectivity observed in the cycloaddition to produce **I** and **II**, when compared to that displayed in eq 6, can be ascribed to the lower steric bulk of the methyl group when compared to the chloropropyl present in ketene **15**.

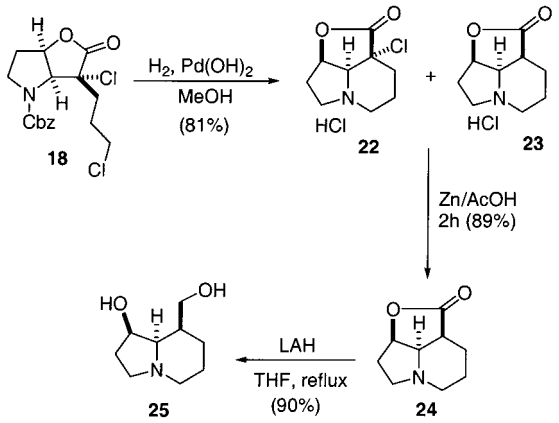


(21) Bradly, W. T.; Rol, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 5922.

(22) Ali, S. M.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1934.

(23) (a) Reference 13a. (b) Hassner, A.; Pinnick, H. W.; Ansell, J. M. *J. Org. Chem.* **1978**, *43*, 1774; and references therein.

Scheme 4. Synthesis of Indolizidine 25 from the α-Chloro-γ-lactone 18



of the chlorine atom at C7 did not suffice to reverse a regioselective trend that seems to be intrinsic to the 2-azabicyclic cyclobutanones bearing an *endo*-alkyl chain at C7.

The main ^{1}H NMR characteristic of γ-lactone **18** is the presence of a broad triplet at 5.3 ppm for the carbinolic hydrogen H5. γ-Lactone **19** displays a doublet at 4.98 ppm for H1 and a triplet at 3.6 ppm for H5 (^{1}H NMR at 60 °C), whereas ^{13}C NMR shows a characteristic quaternary center at 107 ppm for C7.

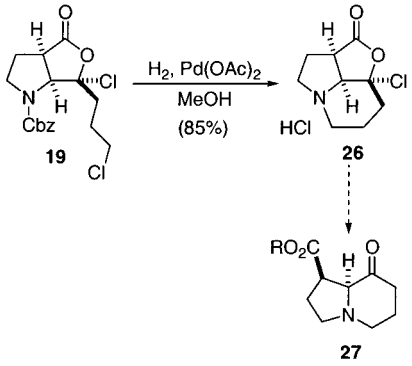
Proceeding with our synthetic scheme, lactones **18** and **19** were separated by flash chromatography and applied to the synthesis of indolizidines. As before, to prepare the desired indolizidine a hydrogenolysis/ring closure procedure was performed in a single step. Thus, hydrogenolysis of lactone **18** in methanol produced the expected tricyclic lactone hydrochloride **22** together with small amounts of a byproduct assigned as the hydrochloride of dechlorinated lactone **23,** resulting from reduction of the labile C−Cl bond (Scheme 4).[24] Since a complete reductive dechlorination under hydrogenolysis conditions can be difficult to achieve, the mixture of lactones **22** and **23** was submitted to dechlorination with Zn in acetic acid to cleanly afford the free base tricyclic lactone **24** in 89% yield (Scheme 4). The dihydroxylated indolizidine alkaloid was finally obtained upon lithium aluminum hydride reduction of lactone **24** in refluxing THF, providing the (±)-1-hydroxyl-8-epitashiromine **25** in 90% yield. The synthesis of indolizidine **25** involved five steps with an overall yield of ∼29%.

The regioisomeric lactone **19**, obtained from the Baeyer−Villiger reaction of azabicyclic cyclobutanone **16**, can also be a useful intermediate for the synthesis of indolizidine compounds. Hydrogenolysis of lactone **19** provided the stable tricyclic lactone **26** in 85% yield. Most probably this compound can be elaborated into indolizidine **27**, although we did not pursue this (Scheme 5).

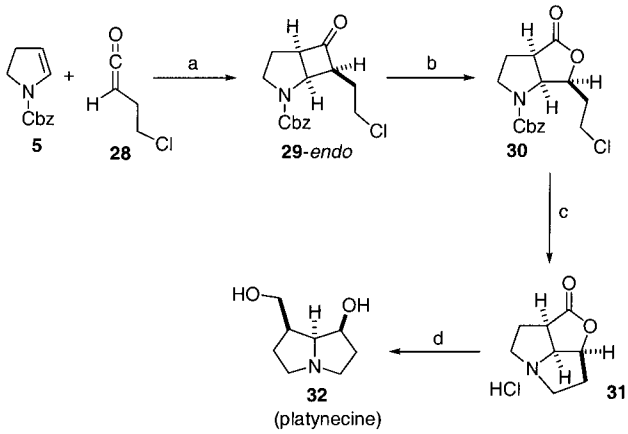
Synthesis of Necine Bases. The Total Synthesis of (±)-Platynecine. The synthetic strategy presented in the previous sections for the synthesis of indolizidines was applied to the synthesis of necine bases. As the necine bases possess a 4-hydroxymethyl-1-azabicyclo-[3.3.0]octane system as the structural core, their synthesis could be achieved by employing an alkylchloroketene

(24) Rylander, R. N. *Hydrogenation Methods*; Academic Press: Orlando, 1985; p 148.

Scheme 5. Approach to the Synthesis of Indolizidine 27 from α-Chloro-γ-lactone 19



Scheme 6. Synthesis of (±)-Platynecine from Enecarbamate 5[a]



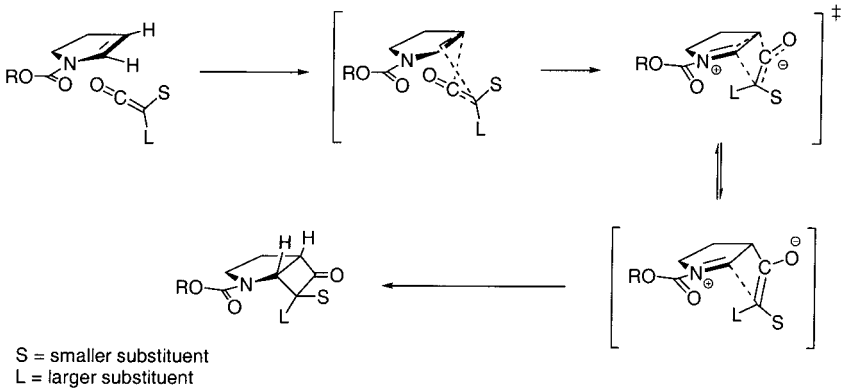
[a] Reagents and conditions: (a) Et_3N, cyclohexane, reflux (72%), (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 30 min (85%), (c) H_2, $Pd(OAc)_2$, MeOH (83%), (d) LAH, THF (85%).

with one less methylene group than alkylchloroketene **6**. Since the synthesis of platynecine was planned to be racemic, the regioselectivity of the Baeyer−Villiger reaction was irrelevant to the overall process as regioisomeric bicyclic lactones lead to enantiomeric tricyclic lactones (see Scheme 1).

The synthesis commenced with a [2 + 2]cycloaddition of endocyclic enecarbamate **5** to 2-chloroethyl ketene **28** (generated in situ from 4-chlorobutyryl chloride in the presence of Et_3N) (Scheme 6). In analogy to results obtained before, the [2 + 2]cycloaddition carried out in cyclohexane provided almost exclusively the expected *endo* cycloadduct **29** in 72% yield.[25] The stereoisomerically pure **29**-*endo* alkyl cycloadduct obtained from the reaction in cyclohexane was crystallized from Et_2O and submitted to X-ray diffraction, which unambiguously established its molecular structure (see Supporting Information).

(25) Ketene−endocyclic enecarbamate [2 + 2]cycloaddition in hexane provided a mixture of **29**-*endo* and **29**-*exo* cycloadducts in 55−59% yield. The ratio between *endo* and *exo* alkyl cycloadducts depends on the time of reaction, reaching a diastereomeric ratio of 56:44 after 12 h. When cycloaddition was quenched after 2.5 h of refluxing, we observed 90% conversion of the endocyclic enecarbamate and a diastereomeric ratio of 75:25 for the **29**-*endo*:**29**-*exo* cycloadducts. **29**-*endo* and **29**-*exo* cycloadducts appear as a single spot on TLC. Diastereomeric ratios were determined by the integration of the signal appearing in the ^{1}H NMR spectra at 4.8 and 4.3 ppm, corresponding to H1 of the **29**-*endo* and **29**-*exo* cycloadducts, respectively ($CDCl_3$, 60 °C).

Scheme 7. [2 + 2]Cycloaddition of Five-Membered Endocyclic Enecarbamates to Ketenes

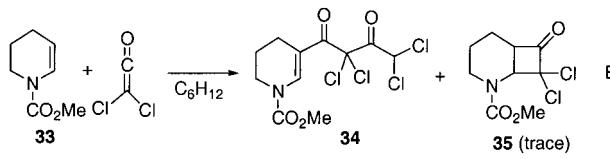


Completion of the synthesis was straightforward and carried out in high yield. Azabicyclic cyclobutanone **29**-*endo* was submitted to Baeyer−Villiger oxidation to yield the γ-lactone **30** in 85% yield (Scheme 6). Once again, a high regioselectivity was observed for the Baeyer−Villiger oxidation of the *endo*-alkyl cycloadduct, and in the same sense as that observed for the oxidation of *endo*-alkyl cycloadduct **7**. Again, the γ-lactone deriving from migration of the bridgehead C5 group could not be detected. Hydrogenolysis of γ-lactone **30** gave an amorphous solid corresponding to the tricyclic lactone **31** (83% yield), which was reduced with lithium aluminum hydride to provide (±)-platynecine **32** in 85% yield. Spectroscopic data (^{1}H NMR, IR, MS) obtained for the synthetic platynecine **32** was identical to those reported in the literature.[26] (±)-Platynecine was obtained in an overall yield of 43% after four steps from endocyclic enecarbamate **5**.[27]

On the Mechanism and Stereoselectivity of the Thermal [2 + 2]Cycloadditions Involving Ketenes and Endocyclic Enecarbamates. The mechanism of the [2 + 2]cycloaddition reaction of ketenes to olefins has been a subject of much interest and controversy. Despite an early emphasis on a concerted [$_\pi 2_a + {}_\pi 2_s$] mechanism, as proposed by Woodward and Hoffmann, it is now widely accepted that a highly asynchronous [$_\pi 2_s + ({}_\pi 2_s + {}_\pi 2_s)$] pathway, involving a dipolar process might be operating in these reactions through a concerted or stepwise mechanism.[28]

Although these cycloadditions involving endocyclic enecarbamates were performed in nonpolar solvents (cyclohexane or hexane), a polar zwitterionic mechanism could not at first be discarded. Actually, the participation of ionic intermediates in a stepwise mechanism or a polar transition structure in a "quasi-pericyclic" mechanism has been proposed as the most probable pathway for the [2 + 2]cycloaddition of ketene to electron-rich (nucleophilic) alkenes.[28a] In the specific case of [2 + 2]-cycloaddition of ketenes to endocyclic enecarbamates, a stepwise mechanism seems likely. Such a mechanism would involve the participation of a zwitterionic enolate-*N*-acylimminium intermediate by virtue of a more extensive C−C bond between the β-carbon of the *N*-acylenamine and the ketene carbonyl moieties (Scheme 7). The internal electrostatic interaction between the enolate and the *N*-acylimminium moiety could help stabilize the transition state and the proposed intermediate in a nonpolar solvent. The observed stereoselectivity for the *endo* cycloadduct is clearly explained by the preferred orthogonal approach of the ketene on the *N*-acylenamine double bond from its least congested side, the S substituent in Scheme 7 (some hydrogens were omitted for clarity).

Interestingly, six-membered endocyclic enecarbamates behave quite differently from five-membered enecarbamates, providing the corresponding cycloadducts in very low yields. The major products isolated from such cycloadditions were the 3-acyl endocyclic enecarbamates (eq 9), exemplified here by the reaction of endocyclic enecarbamate **33** with dichloroketene, producing the acylated enecarbamate **34** in 56% yield with only trace amounts of the putative azabicyclic cyclobutanone **35**.[29]



Eq 9

The Regioselectivity of the Baeyer−Villiger Oxidation of the 7-Alkyl-2-azabicyclic Cyclobutanones. This is certainly the most striking aspect of the synthesis of the indolizidine frameworks and of the necine base platynecine described here. With the reasonable assumption that *m*-CPBA adds to the azabicyclic cyclobutanones from the convex face of the *endo* or *exo* cyclobutanone moieties, the stereoelectronic bias for the preferred migration of either C5 or C7 groups during the concerted rearrangement is not clear and a rationale for the

(26) (a) Viscontini, M.; Buzek, H. *Helv. Chim. Acta* **1972**, *55*, 670. (b) Rueger, H.; Benn, M. *Heterocycles* **1983**, *20*, 1331.

(27) In a previous communication we reported an overall yield of 23% for (±)-platynecine starting from enecarbamate **5**. At that time, [2 + 2]cycloadditions of alkylketenes to endocyclic enecarbamates were being carried out with hexane as solvent, resulting in a 2:1 mixture of the *endo*:*exo* cycloadducts (55−59% yield). See ref 6b for details.

(28) For the mechanism of the [2 + 2]cycloaddition of ketenes to olefins, see: (a) Tidwell, T. T. *Ketenes*; John Wiley: NewYork, 1995; pp 473−513. For recent work dealing with mechanistic aspects of ketene [2 + 2]cycloaddition, see: (b) Yamabe, S.; Kuwata, K.; Minato, T. *Theor. Chem. Acc.* **1999**, *102*, 139. (c) Machiguchi, T.; Hasegawa, T.; Ishiwata, A.; Terashima, S.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **1999**, *121*, 4771. (d) Bachrach, S. M. *J. Org. Chem.* **1996**, *61*, 237. (e) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 1754. (f) Bernardi, F.; Bottoni, A.; Robb, M. A.; Venturini, A. *J. Am. Chem. Soc.* **1990**, *112*, 2106. (g) Valenti, E.; Pericàs, M. A.; Moyano, A. *J. Org. Chem.* **1990**, *55*, 3582.

(29) Formation of both products can be rationalized by the mechanism presented in Scheme 7 in which a more loosely bound enolate-*N*-acylimminium intermediate disproportionates into the [2 + 2]-cycloadduct and the acylated enecarbamate. Cycloadduct **35** was identified by the presence of a strong absorption at 1807 cm^{-1} in the IR spectrum.

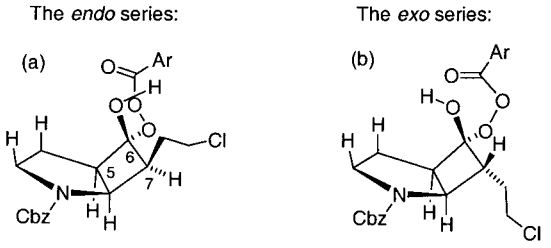
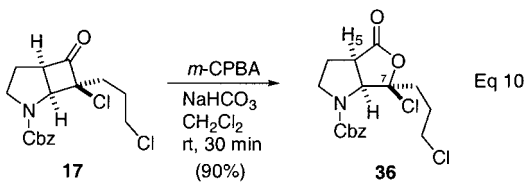


Figure 1. Steric compression in the putative Criegee intermediate.

observed regioselectivity has been elusive (see SI for the graphics displaying the stereoelectronic factors operating at the Criegee intermediates for the *endo* and *exo* alkyl azabicyclic cyclobutanones). On stereoelectronic grounds both the C5 (bridgehead) and the C7 groups could attain the proper stereoelectronic requirements for migration, despite a general preference for bridgehead group migration for similar cyclobutanones reported in the literature.[30] Therefore, the high regioselectivity observed for the *endo* alkyl cycloadduct involving C7 group migration cannot be explained on stereoelectronic grounds alone and is probably associated to other factors.

It is conceivable that the regioselectivity observed in these Baeyer−Villiger oxidations could be related to some localized strain in the Criegee cyclobutane intermediate, overriding some stereoelectronic bias. Although uncommon, steric strain dictating group migration preferences does find precedents in the literature.[31] For the *endo* alkyl series, steric interaction between the alkyl group at C7, the hydroxyl group at C6, and the pyrrolidine ring in an all cis arrangement, probably makes the C6−C7 bond more labile (Figure 1a), thus promoting oxygen insertion at this position. In the less sterically strained *exo* alkyl cyclobutane system (Figure 1b), strain would be less pronounced, thus leading to an expected lower regioselectivity, as is indeed observed in the *exo* alkyl systems (cf. eqs 12 and 13). Substituents other than hydrogen in an *endo* position at C7 in the Criegee azabicyclic intermediate seem to increase steric strain at C6−C7, therefore favoring C7 group migration.

A remarkable example in support of this view was the unusual regioselectivity found for the minor *exo*-alkyl cycloadduct **17** obtained from the cycloaddition of alkylchloroketene **15** to enecarbamate **5** (eq 6). Baeyer−Villiger oxidation of **17** with *m*-CPBA (eq 10) produced the lactone resulting from migration of the more electron deficient C7 group instead of the more electron-rich bridgehead C5 group. Thus, contrary to the prevailing idea that an electron-withdrawing group at C7 would direct oxygen insertion toward the C5−C7 bond, the regioisomer **36** was the only γ-lactone isolated in this case.



(30) (a) Reference 17. (b) Grieco, P. A. *J. Org. Chem.* **1972**, *37*, 2363.
(31) (a) Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611. (b) Dave, V.; Stothers, J. B.; Warnhoff, E. W. *Can. J. Chem.* **1984**, *62*, 1965.

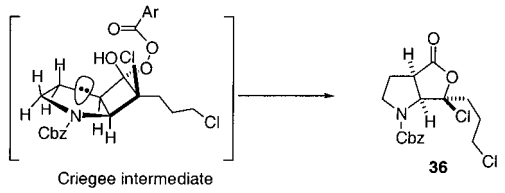
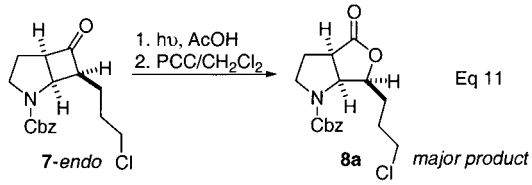


Figure 2. The Criegee intermediate in the conversion of cyclobutanone **17** to lactone **36**.

This result clearly indicates a less pronounced role for stereoelectronic factors in these systems. Analogous to the *endo*-alkyl series, the Criegee intermediate generated by the oxidation of **17** is an all-cis substituted cyclobutane, leading to the same regioselectivity observed for the "*endo*-alkyl model" (Figure 2).[32] Curiously, a C7-*endo*-chloro has a more pronounced effect on the regiochemical outcome of the Baeyer−Villiger oxidation than a C7-*exo*-chloro (cf. eq 7; conversion of cyclobutanone **16** into lactones **18** and **19** in a 55:45 ratio).

An indirect but interesting indication for the enhanced fragility of the C6−C7 bond was obtained by a Norrish I[33] ring opening of 7-*endo*-alkyl azacyclobutanone **7** in acetic acid followed by oxidation of the acyl-acetals with pyridinium chlorochromate (eq 11). The major product obtained (35% yield) was identified as the γ-lactone **8a** (previously prepared by the Baeyer−Villiger oxidation of azacyclobutanone **7**).

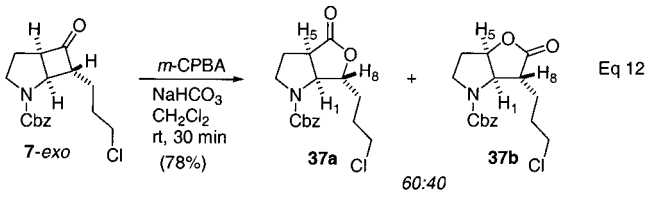


However, it should be noted that the two mechanisms are quite distinct. Therefore, the results obtained with the photochemical ring expansion should be used with caution when compared to those obtained for the Baeyer−Villiger oxidation.

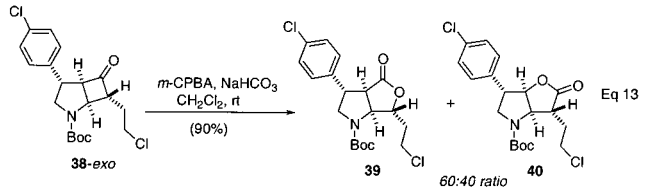
One implication of our rationale is that Baeyer−Villiger ring expansion of *exo*-alkyl cycloadducts should be less regioselective than the *endo* alkyl cycloadducts due to the lack of steric compression in the Criegee intermediate. This was indeed the case observed in the Baeyer−Villiger oxidation of the pure *exo*-alkyl cycloadduct **7**-*exo* (eq 12), in which a mixture of two regioisomeric lactones **37a** and **37b** were detected in a ratio of 60:40. Oxygen insertion at C6−C7 was still the predominant operation in this Baeyer−Villiger oxidation, but to a considerably lesser extent than that observed for the **7**-*endo* stereoisomer (see eq 3). The mixture of lactones **37a** and **37b** could not be separated by chromatography and, despite the complexity of the ^{1}H NMR spectra, the chemical shift for H1, H5, and H8 were quite

(32) Other bicyclic systems are being prepared in our laboratory to confirm these working hypotheses.
(33) For more information on the Norrish I reaction, see: (a) Pirrung, M. C.; Chang, V. K.; DeAmicis, C. V. *J. Am. Chem. Soc.* **1989**, *111*, 5824. (b) Yates, P.; Loutfy, R. O. *Acc. Chem. Res.* **1975**, *8*, 209. (c) Miller, R. D.; Dolce, D. L.; Merritt, V. Y. *Tethahedron Lett.* **1974**, 3347.

characteristic so as to permit distinction between the two isomers.[34]



Similar results regarding the regioselectivity for the *exo* cycloadduct were obtained when the pure *exo* cycloadduct **38** underwent ring expansion with *m*-CPBA to provide lactones **39** and **40** in 90% yield with a regioisomeric ratio of 60:40 (eq 13).[35]



The results shown in eq 12 and eq 13 corroborated the working hypothesis that steric strain seems to be the main factor controlling the Baeyer−Villiger oxidation of 7-*endo*-substituted 2-azabicyclo[3.2.0]heptan-6-ones. In the absence of such steric strain, stereoelectronic factors operate producing the expected mixture of lactones.[36]

Conclusions

[2 + 2]Cycloaddition of ketenes to five-membered endocyclic enecarbamates permitted the construction of two isomeric indolizidine systems and the total synthesis of the necine base (±)-platynecine. [2 + 2]Cycloadditions occurred in good to high yields (72−90%) with high stereoselectivity for the 7-*endo*-alkyl-2-azabicyclic cyclobutanones when the reaction was carried out in cyclohexane. Epimerization experiments suggest that the 7-*endo* alkyl cycloadduct is the kinetic product of the [2 + 2]cycloaddition and the probable precursor of the minor *exo* cycloadduct. Baeyer−Villiger ring expansion of the *endo*-alkyl cycloadducts provided the corresponding γ-lactones in high yields with a remarkable regioselectivity favoring oxygen insertion into the C6−C7 bond, whereas the *exo* alkyl cycloadducts led to a mixture of regioisomeric lactones. The main factor controlling the regioselectivity of the Baeyer−Villiger oxidation seems to be the release of steric strain built into the bicyclic Criegee intermediate, and a rationale for these unusual results has been presented. Two isomeric indolizidines, **13** and **25**, were obtained in four steps from the endocyclic enecarbamate **5** in 42% and ~25% overall yields, respectively. The necine base platynecine was also obtained by the same strategy in four steps with an overall yield of 43%. These results clearly demonstrate the synthetic potential imbedded into the endocyclic enecarbamates as construction frameworks for alkaloids and other *N*-containing heterocyclic targets.

Experimental Section

General Experimental: See Supporting Information.

***Endo*-2-azabicyclic Cyclobutanone 7.** To a solution of the enecarbamate **5** (0.745 g, 3.65 mmol) and triethylamine (0.55 mL, 5.5 mmol) in 30 mL of dry cyclohexane, at reflux, was slowly added a cyclohexane solution of 5-chlorovaleryl chloride (0.81 mL, 5.5 mmol, in 4.2 mL of cyclohexane) using a syringe pump. During addition of 5-chlorovaleryl chloride it was critical to keep the syringe needle tip immersed in the reaction mixture to avoid ketene dimerization at the tip of the needle. After addition of the 5-chlorovaleryl chloride solution a pale yellow suspension was formed, which was kept at reflux for 4 h. Next, the heating was stopped, the reaction vessel was cooled to room temperature, and the mixture was filtered through a short pad of Celite to remove the precipitated triethylammonium chloride. The filtrate was evaporated in vacuo to provide a crude oil that was dissolved in 60 mL of EtOAc/hexane (1:1, v/v), which was then extracted with 10% sodium bicarbonate solution (30 mL) and water (30 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo to give a yellowish oil. Flash chromatography (SiO_2, EtOAc/hexane, 3:7) furnished 0.884 g (75% yield) of cyclobutanone **7** as a slightly yellow oil. TLC: $R_f = 0.4$ (EtOAc/hexane, 3:7). FTIR (neat): 2954, 1776, 1702, 1415, 1361, 1187, 1096, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz, rt) (mixture of rotamers): δ 1.41−1.95 (m, 5H), 2.16 (dd, $J = 13.1$ Hz; $J = 6.6$ Hz; 1H), 3.21 (dt, $J = 11.4$ Hz; $J = 6.6$ Hz, 1H), 3.28−3.48 (m, 3H), 3.84−4.08 (m, 2H), 4.75 and 4.85 (t, $J = 7.2$ Hz, 1H), 5.15 and 5.17 (s, 2H), 7.36 and 7.37 (s, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt) (mixture of rotamers): δ 21.2 (CH_2); 25.8 (CH_2); 30.3 (CH_2); 44.7 (CH_2); 47.0 (CH_2); 52.6 (CH); 62.5 (CH); 62.9 (CH); 67.4 (CH_2); 128.1−128.8 (CH, 5 signals); 136.6 (C); 155.0 (C); 213.2 (C). MS: *m*/*z* (rel intens) 321 ($M^{\bullet+}$), 286, 242, 203, 159, 91(100%), 55. Anal. Calcd for $C_{17}H_{20}NClO_3$ C, 63.53; H, 6.28; N, 4.36. Found: C, 63.88; H, 5.99; N, 4.29.

***Exo*-2-azabicyclic Cyclobutanone 7.** To a solution of cyclobutanone **7**-*endo* (0.025 g, 0.08 mmol) in 1.5 mL of THF was added triethylammonium chloride, and the solution was kept at reflux for ~20 h, when a more apolar spot was clearly visible on TLC. The solvent was evaporated in vacuo, the residue was dissolved in EtOAc/hexane (1:1), and the solution was extracted with 10% $NaHCO_3$ and water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to provide an oil. Careful flash chromatography ($\Delta R_f = 0.05$) using Et_2O/hexane (2.3:1) as eluent allowed the separation of 5 mg of pure **7**-*exo* as an analytical sample. ^1H NMR ($CDCl_3$, 300 MHz, rt) δ 1.70−2.06 (m, 5H), 2.21 (m, 1H), 2.93 (m, 1H), 2.72 (bs, 1H), 3.43−3.62 (m, 3H), 3.79−3.90 (m, 2H), 4.20 and 4.28 (d, $J = 7.1$ Hz, rotamers, 1H), 5.17 (m, 2H), 7.36 (s, 5H). FTIR (neat) 2954, 1779, 1703, 1448, 1413, 1359, 1109, 769, 699 cm^{-1}.

***Endo* Lactone 8a.** To a suspension of cyclobutanone **7**-*endo* (1.83 g, 5.7 mmol) and $NaHCO_3$ (0.72 g, 8.5 mmol) in 50 mL of CH_2Cl_2, at room temperature was added *m*-CPBA portion-

(34) For **37a**, H1 appears as a dd at 4.28 and 4.19 ppm; H8 as duplicated dd at 4.64 and 4.42 ppm. For **37b**, H5 appears at 5.2 ppm underneath the methylene protons of the Cbz group, and H8 appears as a duplicated dd at 4.23 and 4.16 ppm. COSY experiments of the **37a**/**37b** mixture permitted the unambiguous assignment of these hydrogens. Moreover, ^{13}C NMR of the mixture clearly shows it as a mixture of two isomeric compounds. The DEPT ^{13}C NMR spectrum displays six duplicated sets of methinic carbons (three each for compounds **37a** and **37b**).

(35) Like the mixture of lactones **37a** and **37b**, the arylated lactones **39** and **40** could not be separated on column chromatography. The regioisomeric ratio was obtained by converting the lactones into their respective diols ($NaBH_4$, EtOH, 12h, rt), which could be separated by chromatography and analyzed (MSc. thesis of Antonio C. B. M. Oca, 2001, Unicamp).

(36) One interesting question that arises is why Baeyer−Villiger oxidation of compound **9**-*endo* (eq 4) resulted in a 60:40 regiomeric ratio as reported by Roberts and Newton (ref 13). The Criegee intermediate in this case would also be an "all-cis" cyclobutanone like the ones proposed in Figures 1 and 2. The main difference between the results displayed in eq 4 and the ones presented throughout this work is the presence of the C2−C3 double bond and the absence of the *N*-acyl group at position 2 in compound **9**-*endo*. The steric relief provided by the planar molecular fragment at the bicyclic system should significantly decrease any steric compression at the Criegee intermediate, therefore explaining the rather low regioselectivity observed in this case.

wise. After addition of *m*-CPBA, the suspension was left stirring for an additional 30 min, when TLC indicated complete consumption of the starting material. The crude reaction mixture was transferred to a separatory funnel and extracted with saturated Na_2SO_3 (2 × 20 mL) and saturated $NaHCO_3$. The organic extract was dried over $MgSO_4$, filtered, and evaporated in vacuo to give a colorless oil. Flash chromatography (SiO_2, EtOAc/hexane, 1:2.3) gave 1.63 g (85% yield) of lactone **8a**. ^{1}H NMR ($CDCl_3$, 300 MHz, rt.): δ 1.60−2.10 (m, 5H), 2.29 (dd; J = 12.6 Hz and J = 5.6 Hz; 1H), 3.07 (m, 1H), 3.36 (t; J = 7.9 Hz; 1H), 3.43−3.56 (m, 2H), 3.98 and 4.08 (m, rotamers, 1H), 4.50 and 4.57 (m, rotamers, 1H), 4.68 and 4.76 (m, rotamers, 1H), 5.14 (m, 2H), 7.36 (s, 5H).^{1}H NMR ($CDCl_3$, 300 MHz, 60 °C.) coalesced signals δ: 1.62 (m, 1H), 1.86−2.08 (m, 4H), 2.27 (dd; J = 12.7 Hz, J = 5.9 Hz, 1H), 3.07 (dt, J = 11.6 Hz, J = 5.9 Hz, 1H), 3.31 (t; J = 7.7 Hz; 1H), 3.48 (m, 2H), 3.99 (m, 1H), 4.52 (m, 1H), 4.73 (m, 1H), 5.14 (s, 2H), 7.34 (s, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt), (mixture of rotamers): δ 27.2 (CH_2), 28.5 (CH_2), 29.4 (CH_2), 44.4 (CH_2), 45.3 (CH), 46.2 (CH_2), 60.3 (CH), 67.6 (CH_2), 83.1 (CH), 127.9−128.8 (CH, 5 signals), 136.2 (C), 155.4 (C═O carbamate), 177.1 (C═O lactone). FTIR (neat): 2959, 2877, 1773, 1703, 1447, 1413, 1353, 1197, 1113, 970, 699 cm^{-1}. MS: *m*/*z* (rel intens) 41, 91 (100%), 159, 203, 246, 258, 337 (M^+). Anal. Calcd for $C_{17}H_{20}NClO_4$. C, 60.51; H, 5.98; N 4.1. Found C, 60.27; H 5.82; N 3.99.

Tricyclic Lactone Hydrochloride 12. To a solution of lactone **8a** (1.24 g, 3.7 mmol) in 90 mL of methanol was added $Pd(OH)_2$ (0.12 g, 0.8 mmol). The resulting suspension was purged with hydrogen for approximately 10 min and then left stirring with a balloon filled with H_2 for 6 h, when TLC indicated complete consumption of the starting material. The crude reaction mixture was filtered through a short pad of Celite, and the solvent was evaporated in vacuo to provide a white solid. The solid was washed with CH_2Cl_2 to remove some organic impurities, and the remaining solid was freeze-dried in vacuo to give 0.62 g of lactone hydrochloride **12** (84% yield) as a white solid. This compound was pure enough for use in the next step without further purification. ^{1}H NMR (D_2O, 300 MHz, rt): δ 1.62−1.85 (m, 3H), 2.09−2.24 (m, 2H), 2.36 (dd, J = 14.0 Hz, J = 5.6 Hz, 1H), 3.05−3.38 (m, 3H), 3.46 (dd, J = 11.7 Hz, J = 6.6 Hz, 1H), 3.69 (t, J = 7.5 Hz, 1H), 4.47 (dd, J = 6.4 Hz, J = 4.2 Hz, 1H), 4.90 (m, 1H). ^{13}C NMR (D_2O, 75 MHz, rt): δ 11.0 (CH_2), 22.6 (CH_2), 27.1 (CH_2), 46.4 (CH_2), 46.7 (CH), 51.2 (CH_2), 59.5 (CH), 74.7 (CH), 178.8 (C═O). FTIR (neat): 2950, 2411−2567, 1760, 1443, 1368, 1211, 1189, 1171, 984 cm^{-1}. Hydrochloride salt sublimes above 240 °C.

Indolizidine Diol 13. To a suspension of lactone hydrochloride **12** (0.06 g, 0.3 mmol) in 5 mL of THF was slowly added $LiAlH_4$ (1.4 mL of a 1 mol/L solution in Et_2O, dissolved in 7 mL of THF) at room temperature. After addition of $LiAlH_4$ was complete, the reaction mixture was heated at reflux for 4 h, becoming homogeneous. To this solution were added 0.1 mL of H_2O, 0.1 mL of 15% NaOH, and 0.3 mL of H_2O successively. The resulting suspension was filtered through a short pad of Celite, and the solvent was evaporated in vacuo. The resulting residue was dissolved in $CHCl_3$ and dried over $MgSO_4$. Next, it was filtered and evaporated in vacuo to provide a yellowish oil that, after flash chromatography (SiO_2, $CHCl_3$/MeOH/NH_4-OH, 75:21:4), furnished 40 mg (80% yield) of indolizidine diol **13** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.37−1.53 (m, 3H), 1.67 (m, 1H), 1.78−2.11 (m, 5H), 2.35 (m, 1H), 3.04−3.18 (m, 2H), 3.56 (dd, J = 11.7 Hz, J = 4.4 Hz, 1H), 3.67 (m, 1H), 4.18 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt): δ 19.5 (CH_2), 24.8 (CH_2), 31.8 (CH_2), 41.9 (CH), 54.0 (CH_2), 54.1 (CH_2), 63.2 (CH_2), 65.7 (CH), 69.2 (CH). FTIR (neat): 3329, 2937, 2794, 1438, 1384, 1330, 1272, 1218, 1154, 1053, 999, 915 cm^{-1}. MS: *m*/*z* (rel intens) 41, 68, 82, 96 (100%), 114, 127, 140, 153, 171 ($M^{\bullet+}$). HRMS (EI): Calcd for $C_9H_{17}NO_2$: 171.1259; found: 171.1261

Chloro-azabicyclic Cyclobutanones 16 and 17. To a solution of enecarbamate **5** (0.87 g, 4.3 mmol) and Et_3N (0.9 mL, 6.4 mL) in 30 mL of cyclohexane, at room temperature, was slowly added a cyclohexane solution of 2,5-dichlorovaleryl chloride (0.95 g, 5 mmol in 10 mL of cyclohexane) over a period of 1.5 h using a syringe pump (the tip of the needle was kept immersed during addition) and then stirred for 2 h. Next, the brownish suspension was filtered, and the precipitate was washed with 30 mL of EtOAc/hex (1:2, v/v). The organic layer was extracted with saturated $NaHCO_3$ (1 × 20 mL) and saturated NaCl (1 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo to give a yellow oil. Flash chromatography (SiO_2, EtOAc/hexane, 1:3) gave 1.35 g of chloro-azabicyclic cyclobutanone **16** (79% yield) and 0.19 g of chloro-azabicyclic cyclobutanone **17** (11% yield) as colorless oils. **16**: ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.67−2.10 (m, 5H), 2.22 (dd, J = 6.9 Hz, J = 13.4 Hz, 1H), 3.25−3,60 (m, 3H), 4.01 (m, 1H), 4.31 (t, J = 8.2 Hz, 1H), 4.66 e 4.74 (d, J = 7.5 Hz, rotamers, 1H), 5.12−5.29 (m, 2H), 7.37 (s, rotamers, 5H). ^{1}H NMR ($CDCl_3$, 300 MHz, 60 °C), coalesced signals δ: 3.30 (dt, J = 7.0 Hz, J = 11.0 Hz, 1H), 4.00 (t, J = 10 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt) (mixture of rotamers) 25.2 (CH_2), 26.9 (CH_2), 27.3 (CH_2), 44.6 (CH_2), 47.3 (CH_2), 61.5 (CH), 62.2 (CH), 67.5 (CH_2), 80.9 (C), 128.3 (5 CH), 135.9 (C), 154.5 (C═O), 204.2 (C═O). FTIR (neat): 2960, 1791, 1704, 1445, 1409, 1360, 1187, 1105, 756, 698 cm^{-1}. MS: *m*/*z* (rel intens) 65, 91 (100%), 159, 186, 248, 276, 355 ($M^{\bullet+}$). Anal. Calcd for $C_{17}H_{19}NCl_2O_3$ C, 57.45; H, 5.3; N, 3.94; Found: C, 57.16; H, 5.13; N, 3.92. **17**: ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1,73−2.28 (m, 6H), 3.32−3.48 (m, 2H), 3.65 (m, 1H), 3.91−4.02 (m, 2H); 4.48 e 4.63 (d, J = 7.3 Hz; rotamers, 1H), 5.15 (m, 1H), 7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt) (mixture of rotamers) δ 26.7 (CH_2), 27.3 (CH_2), 32.2 (CH_2), 44.3 (CH_2), 46.5 (CH_2), 59.0 (CH), 59.9 (CH), 67.5 (CH_2), 81.4 (C), 128.3 (5 CH), 136.1 (C), 154.5 (C═O), 206.4 (C═O). FTIR (neat): 2959, 1793, 1707, 1415, 1361, 1178, 1112, 755, 698 cm^{-1}. MS: *m*/*z* (rel intens) 65, 91(100%), 159, 186, 248, 276, 355 ($M^{\bullet+}$). Anal. Calcd for $C_{17}H_{19}NCl_2O_3$ C, 57.45; H, 5.39; N, 3.94. Found: C, 57.50; H, 5.14; N, 3.84.

Conversion of Chloro-azabicyclic Cyclobutanone 16 into Lactones 18 and 19. Baeyer−Villiger oxidation was carried out as described for the conversion of aza-cyclobutanone **7**-*endo* to lactone **8a**. Flash chromatography (SiO_2, Et_2O/hexane, 6:4) of the crude oil obtained, after extraction, yielded 0.11 g of lactone **18** (48% yield) and 0.1 g of lactone **19** (44% yield). The less polar lactone **19** was crystallized in hexane/Et_2O (6:4) as fine needles. **18**: ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.86−2,30 (m, 6H), 3.25 (m, 1H), 3.46 (m, 2H), 4.04 (m, 1H), 4.79 (d, J = 4.0 Hz, 1H), 5.17 (m, 2H), 5.32 (t, J = 4.0 Hz, 1H), 7.37 (s, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt) (mixture of rotamers): δ 27.3 (CH_2), 30.3 (CH_2), 31.0 (CH_2), 45.0 (CH_2), 45.8 (CH_2), 68.2 (CH_2), 68.9 (CH), 81.7 (CH), 128.6 (5 CH), 136.1 (C), 156.2 (C═O), 172.4 (C═O). FTIR (neat): 2958, 1785, 1707, 1403, 1350, 1214, 1191, 1098, 993, 736, 699 cm^{-1}. MS: *m*/*z* (rel intens) 65, 91 (100%), 174, 203, 264, 292, 336, 371 ($M^{\bullet+}$). **19**: ^{1}H NMR ($CDCl_3$, 300 MHz, 60 °C): δ 1.99−2.18 (m, 5H), 2.29 (dd, J = 5.6 Hz, J = 12.8 Hz, 1H), 3.05 (dt, J = 5.6 Hz, J = 12.0 Hz, 1H), 3.49 (m, 2H), 3.61 (t, J = 7.4 Hz, 1H), 4.04 (bt, 1H), 4.98 (d, J = 6.7 Hz, 1H), 5.17 (s, 2H), 7.35 (s, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt) (mixture of rotamers): δ 27.1 (CH_2), 28.0 (CH_2), 34.8 (CH_2), 44.3 (CH_2), 44.8 (CH), 46.4 (CH_2), 67.9 (CH_2), 69.5 (CH), 107.4 (C), 128.3 (5 CH), 135.8 (C), 154.9 (C═O), 175.2 (C═O). FTIR (KBr): 2967, 2873, 1798, 1697, 1410, 1346, 1319, 1253, 1186, 1107, 972, 916, 758, 701, 589, 554 cm^{-1}. MS: *m*/*z* (rel intens) 41, 91 (100%), 159, 203, 229, 292, 336, 371 ($M^{\bullet+}$).

Indolizidine 24 from Lactone 18. To a solution of lactone **18** (0.32 g, 0.9 mmol) in 25 mL of methanol was added palladium hydroxide over carbon (0.03 g, 0.05 mmol). The suspension was purged with hydrogen for ∼10 min and attached to a plastic balloon filled with hydrogen for 6 h. The reaction mixture was then filtered through a short pad of Celite, and the solvent was evaporated in vacuo to provide a solid residue which was washed with dichloromethane. The remaining solid was dissolved in water, and the solution was freeze-dried to give 0.17 g (81% yield) of a white solid corresponding to tricyclic lactones **22** and **23**. The mixture of the two lactones were used in the next step without further purification. **22** + **23**: ^{13}C NMR (D_2O, 75 MHz, rt): 21.6 (CH_2), 26.3 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 31.8 (CH_2), 33.5 (CH_2), 36.4

(CH_2), 39.7 (CH), 41.8 (CH), 44.2 (CH_2), 44.7 (CH_2), 45.2 (CH_2), 62.8 (CH), 77.9 (CH), 81.4 (CH), 176.9 (C═O), 182.0 (C═O). FTIR (KBr): 2955, 2741, 1775, 1751, 1525, 1458, 1399, 1360, 1285, 1200, 1182, 1017, 963, 899, 713 cm^{-1}.

Conversion of a Mixture of Lactone Hydrochlorides 22 and 23 into Lactone 24. To a round-bottomed flask containing 1 mL of acetic acid and powdered zinc (0.06 g, 0.9 mmol) was slowly added an acetic acid solution of lactones **22** and **23** (0.03 g), and the reaction mixture was stirred for 2 h at room temperature. The mixture was then filtered through Celite and treated with 20% NH_4OH until pH = 7.[37] After extraction with $CHCl_3$, the organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo to provide 0.015 g (89% yield) of a rather unstable oil corresponding to the tricyclic lactone **24**. **24**: ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.50−2,10 (m, 3H), 2.18 (dd, J = 4.7 Hz, J = 13.3 Hz, 1H), 2.27 (m, 1H), 2.52 (m, 1H), 2.75−3,05 (m, 4H), 3.59 (m, 1H), 3.87 (dd, J = 4.7 Hz, J = 6.7 Hz, 1H), 4.99 (t, J = 4.4 Hz, 1H). FTIR (neat): 2925, 2854, 1766, 1440, 1344, 1145, 1091, 995, 867 cm^{-1}.

Conversion of Azatricyclic Lactone 24 to Indolizidine 25. To a solution of tricyclic lactone **24** (0.04 g, 0.2 mmol) in 4 mL of THF, at room temperature, was slowly added a solution of lithium aluminum hydride (1.6 mL of an ethereal 1 mol/L solution of $LiAlH_4$ dissolved in 7 mL of THF), and the reaction mixture was kept at reflux for 4 h. After this period, the mixture was cooled to room temperature and treated successively with 0.1 mL of water, 0.1 mL of 15% NaOH, and 0.3 mL of water. The resulting suspension was filtered through a short pad of Celite, and the filtrate was evaporated in vacuo. The resulting residue was dissolved in $CHCl_3$, and the solution was dried over anhydrous Na_2SO_4. Next, it was filtered, and the solvent was evaporated in vacuo. Flash chromatography (SiO_2, $CHCl_3$/MeOH/NH_4OH, 75:21:04) provided 0.03 g (90% yield) of a colorless oil corresponding to indolizidine **25**. **25**: ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.29−1.41 (m, 2H), 1.67−1.79 (m, 2H), 2.06−2.29 (m, 4H), 2.57 (dd, J = 3.6 Hz, J = 6.6 Hz, 1H), 2.93 (m, 1H), 3.20 (m, 1H), 3.62−3.71 (m, 2H), 3.80 (dd, J = 6.0 Hz, J = 12.0 Hz), 4.23 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt): δ 21.2 (CH_2), 33.9 (CH_2), 34.0 (CH_2), 37.3 (CH), 50.1 (CH_2), 51.1 (CH_2), 64.4 (CH_2), 72.1 (CH), 73.3 (CH). FTIR (neat): 3330, 2940, 2794, 1440, 1385, 1330, 1270, 1050 cm^{-1}. MS: m/z (rel intens) 58, 68, 114 (100%), 126, 140, 171 ($M^{\bullet+}$). HRMS (EI): Calcd for $C_9H_{17}NO_2$: 171.1259; found: 171.1258.

Conversion of Bicyclic Dichlorolactone 19 to the Tricyclic Chlorolactone 26. This reaction was carried out as described for the conversion of bicyclic lactone **18** to the tricyclic lactones **22** and **23**. Hydrogenolysis of 0.08 g (0.02 mmol) of bicyclic lactone **19** gave 0.04 g (85% yield) of tricyclic lactone **26**. ^{1}H NMR (D_2O, δ, 300 MHz, rt): δ 1.70−1,90 (m, 4H), 2.16 (m, 1H), 2.38−2.50 (m, 2H), 3.40−3.57 (m, 3H), 3.83 (m, 1H), 4.27 (d, J = 7.3 Hz, 1H). ^{13}C NMR (D_2O, 75 MHz, rt): δ 24.8 (CH_2), 24.9 (CH_2), 25.9 (CH_2), 43.8 (CH_2), 43.9 (CH), 47.0 (CH_2), 65.2 (CH), 108.1 (C), 177.7 (C = O). FTIR (KBr): 2948, 2747, 1776, 1451, 1389, 1301, 1180, 1142, 1104, 1069, 970, 927, 651 cm^{-1}.

Preparation of Cyclobutanone 29-*endo*. Synthesis of cyclobutanone **29**-*endo* was carried out as described for the preparation of cyclobutanone **7**-*endo* from enecarbamate **5** and alkylketene **6**. Reaction of enecarbamate **5** (0.66 g, 3.2 mmol) with alkyketene **28** (prepared in situ from 4-chlorobutyryl chloride with Et_3N) provided 0.72 g (72% yield) of alkylcyclobutanone **29**-*endo* as a colorless viscous oil, which crystallizes in ether at 4 °C. **29**: bp 57−59 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.70−1.98 (m, 3H), 2.18 (dd, J = 6.7 Hz, J = 13.0 Hz, 1H), 3.20 (m,1H), 3.46 (m, 1H), 3.59−3.70 (m, 2H), 3.91−4.08 (m, 2H), 4.77 e 4.84 (t, J = 7.2 Hz, rotamers, 1H), 5.16 (s, 2H), 7.35 e 7.37 (s, rotamers, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt) (mixture of rotamers): δ 25.5 (CH_2), 26.8 (CH_2), 42.4 (CH_2), 46.8 (CH_2), 52.4 (CH), 60.4 (CH), 62.5 (CH), 67.3 (CH_2), 128.2 (CH), 136.2 (C), 154.7 (C═O), 212.1 (C═O). FTIR (KBr): 2984, 2864, 1784, 1691, 1447, 1410, 1363, 1317, 1208, 1188, 1093, 924, 758, 707 cm^{-1}. MS: m/z (rel intens) 65, 91 (100%), 113, 159, 203, 214, 272, 307 ($M^{\bullet+}$). Anal. Calcd for $C_{16}H_{18}NClO_3$ C, 62.52; H, 5.91; N, 4.56. found: C, 62.13; H, 5.99; N, 4.49.

Synthesis of Bicyclic Lactone 30 from Cyclobutanone 29. This transformation was carried out as described for the conversion of cyclobutanone **7**-*endo* into lactone **8a**. Cyclobutanone **29**-*endo* (0.46 g, 1.5 mmol) provided 0.41 g (85% yield) of lactone **30**. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.90−2.10 (m, 3H), 2.29 (dd, J = 5.3 Hz J = 12.5 Hz, 1H), 3.06 (m, 1H), 3.38 (t, J = 7.7 Hz, 1H), 3.59−3.74 (m, 2H), 3.94−4.04 (m, 1H), 4.69−4.84 (m. 2H), 5.14 (s, 2H), 7.36 (m, 5H). ^{1}H NMR ($CDCl_3$, 300 MHz, 60 °C) coalesced signals: δ 3.06 ppm (dt, J = 5.9 Hz J = 11.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt) (mixture of rotamers): δ 28.4 (CH_2), 32.7 (CH_2), 41.3 (CH_2), 45.4 (CH), 46.1 (CH_2), 60.4 (CH), 67.6 (CH_2), 80.1 (CH), 136.1 (C), 155.4 (C═O), 176.7 (C═O). FTIR (neat): 2961, 2878, 1776, 1698, 1447, 1412, 1359, 1189, 1100, 991, 735, 699 cm^{-1}. MS: m/z (rel intens) 41, 91 (100%), 159, 203, 232, 288, 323 ($M^{\bullet+}$). Anal. Calcd for $C_{16}H_{18}NClO_4$ C, 59.43; H, 5.61; N, 4.33. Found: C, 59.82; H, 5.51; N, 4.20.

Synthesis of Tricyclic Lactone Hydrochloride 31 from Bicyclic Lactone 30. This reaction was carried out as described for the hydrogenolysis of lactone **8a** to tricyclic lactone hydrochloride **12**. Lactone **30** (0.39 g, 1.2 mmol) gave 0.19 g (83% yield) of tricyclic lactone hydrochloride **31** as a white solid. ^{1}H NMR (D_2O, 300 MHz, rt): δ 2.30−2.56 (m, 4H), 3.17−3.32 (m, 2H), 3.54−3.68 (m, 3H), 4.95 (dd, J = 6.2 Hz, J = 8.8 Hz, 1H), 5.23 (m, 1H). ^{13}C NMR and ^{13}C NMR SFORD (D_2O, 75 MHz, rt): δ 28.5 (CH_2), 31.5 (CH_2), 43.4 (CH), 50.9 (CH_2), 53.2 (CH_2), 72.2 (CH), 81.6 (CH), 178.7 (C═O). FTIR (KBr): 2862, 2533, 2429, 1760, 1417, 1363, 1197, 1156, 1044, 945, 884, 526, 480 cm^{-1}. Hydrochloride salt sublimes above 270 °C.

Synthesis of Platynecine 32 from Tricyclic Lactone Hydrochloride 31. This reaction was carried out as described for the reduction of tricyclic lactone hydrochloride **12** to indolizidine **13**. Lactone **31** (0.06 g, 0.03 mmol) provided 0.04 g (85% yield) of platynecine **32** as colorless crystals after recrystallization in acetone. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.56−1.65 (m, 2H), 1.67−1.72 (m, 2H), 2.23 (m, 1H), 2.53−2.62 (m, 2H), 2.84 (m, 1H), 3.00 (m, 1H), 3.08 (dd, J = 3.4 Hz, J = 8.0 Hz, 1H), 3.74 (m, 1H), 3.74 (dd, J = 2.3 Hz, J = 5.9 Hz, 1H), 4.10 (q, J = 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt): δ 27.3 (CH_2), 35.3 (CH_2), 42.7 (CH), 52.5 (CH_2), 54.0 (CH_2), 60.3 (CH_2), 69.8 (CH), 71.8 (CH). MS: m/z (rel intens) 41, 55, 82 (100%), 99, 113, 126, 138, 157 ($M^{\bullet+}$). Anal. Calcd for $C_8H_{15}NO_2$ C, 61.10; H, 9.62; N, 8.91. Found: C, 61.28; H, 9.27; N, 9.00.

Tetrachloroacyl Enecarbamate 34. To a solution of enecarbamate **33** (0.1 g, 0.7 mmol) and triethylamine (0.25 mL, 1.8 mmol) in 8 mL of dried hexane, at room temperature, was slowly added a hexane solution of dichloroacetyl chloride (0.09 mL, 0.93 mmol, dissolved in 2 mL of hexane), via cannula, over a period of 1 h 45 min. The reaction mixture turned into a dark-brown suspension as addition of dichloroacetyl chloride proceeded. The reaction mixture was then filtered, and the solvent was evaporated in vacuo to provide a dark-brown oil. Flash chromatography (SiO_2, EtOAc/hexane, 1:19) gave 0.095 g (56% yield) of the tetrachloroacyl enecarbamate **34** as a colorless oil that solidified on standing. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.87 (m, 2H), 2.34 (m, 2H), 3.61 (m, 2H), 3.79 (s, 3H), 6.01 (s, 1H), 7.35 and 7.49 (m, rotamers, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, rt): δ 20.8 (CH_2), 23.1 (CH_2), 42.0 (CH_2), 53.4 (CH_3), 63.6 (CH), 108.1(C), 115.0 (C), 129.9 (CH), 143.8 (C), 153.9 (C), 161.0 (C). FTIR (KBr): 3114, 2997, 2949, 1774, 1703, 1610, 1439, 1379, 1327, 1270, 1195, 1121, 968, 887, 764, 672 cm^{-1}. MS: m/z (rel intens) 59, 83, 140, 168 (100%), 216, 251, 326, 363 ($M^{\bullet+}$).

Dichloro Bicyclic Lactone 36. This compound was synthesized as described for the conversion of cyclobutanone **7**-*endo* into lactone **8a**. Cyclobutanone **17** (0.07 g, 0.2 mmol) provided 0.07 g (90% yield) of dichloro lactone **36** as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.95−2.65 (m, 6H), 3.32−3.50 (m, 2H), 3.57−3.90 (m, 3H), 4.63 and 4.75 (d, J = 9.1 hz.

(37) At higher pH (9−10) lactone **24** is easily hydrolyzed to gave an ammonium carboxylate salt.

1H), 5.06−5,23 (m, 2H), 7.37 (s, 5H, rotamers). ^{13}C NMR ($CDCl_3$, 75 MHz, rt) (mixture of rotamers): δ 26.7 (CH_2), 27.2 (CH_2), 41.1 (CH_2), 43.5 (CH), 43.9 (CH_2), 47.5 (CH_2), 66.6 (CH), 67.8 (CH_2), 109.2 (C), 128.5 (5 CH), 135.8 (C), 154.3 (C═O), 172.9 (C═O). FTIR (neat): 2961, 1799, 1706, 1417, 1349, 1266, 1186, 1125, 964, 920, 737, 699 cm^{-1}. MS: *m*/*z* (rel intens) 41, 91 (100%), 159, 203, 244, 292, 299, 371 ($M^{\bullet+}$).

Bicyclic Lactones 37a and 37b. These compounds were prepared as described for the conversion of cyclobutanone **7**-*endo* into lactone **8a**. Cyclobutanone **7**-*exo* (0.017 g, 0.05 mmol) provided 0.014 g (78% yield) of a mixture of lactones **37a** and **37b** as a colorless oil appearing as a single spot on TLC. Copies of the ^{1}H NMR, ^{13}C NMR, COSY, DEPT, and IR spectra are available in the Supporting Information.

Aryl Lactones 39 and **40.** The reaction of 0.10 g of cyclobutanone **38**-*exo* with *m*-chloro perbenzoic acid, as described for the conversion of cyclobutanone **7**-*endo* into lactone **8a**, gave 0.099 g of an unseparable mixture of lactones **39** and **40** (96% yield). Copies of the ^{1}H NMR spectrum and HPLC analysis of the mixture are available in the Supporting Information.

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Supporting Information Available: ^{1}H, ^{13}C NMR, and IR spectra of compounds **7**-*endo*, **7**-*exo*, **8a**, **12**, **13**, **16**, **17**, **18**, **19**, **25**, **29**-*endo*, **30**, **31**, **32**, **34**, **36**, **37a/37b**, and **39/40**, X-ray diffraction analytical data of azabicylic cyclobutanone **29**-*endo*, the HPLC chromatogram of the mixture of aryl lactones **39**/**40**, and a figure describing the stereoelectronic arrangements for the Baeyer−Villiger oxidation of the *endo*- and *exo*-7-alkyl-2-azabicyclic cyclobutanones. This material is available free of charge via the Internet at http://pubs.acs.org.

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