N-Acyliminium Ion Rearrangements: Generalities and Application to the Synthesis of Pyrrolizidine Alkaloids

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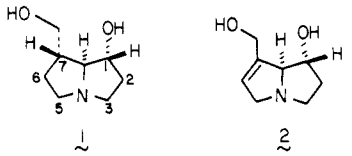
Received August 1, 1984

N-Acyliminium ions of the 2-aza-1,5-hexadienyl type frequently rearrange to isomeric ions by a process which is formally a 2-aza-Cope rearrangement. When *gem*-dimethyl substitution is present at C-4 of the initially formed *N*-acyliminium ion, the rearranged ion cyclizes to afford a substituted pyrrolidine. This rearrangement–cyclization can be used to prepare pyrrolizidinones and indolizidinones and has been applied to enantioselective syntheses of the pyrrolizidine alkaloids hastanecine (**1**) and heliotridine (**2**).

Largely due to the efforts of the Speckamp group, *N*-acyliminium ion cyclizations have been developed to an extent that they now occupy a prominent position in alkaloid synthetic methodology.[1] During the course of our efforts to understand certain stereochemical[2] and mechanistic features of these reactions, we discovered an example where a rapid rearrangement was underlying a typical cyclization.[3,4] In an attempt to further understand the rearrangement process, a substituent effect study was undertaken. This article documents the results of these studies including the development of a useful entry to the pyrrolizidine nucleus and its application to total syntheses of (–)-hastanecine (**1**) and (–)-heliotridine (**2**).[5,6]



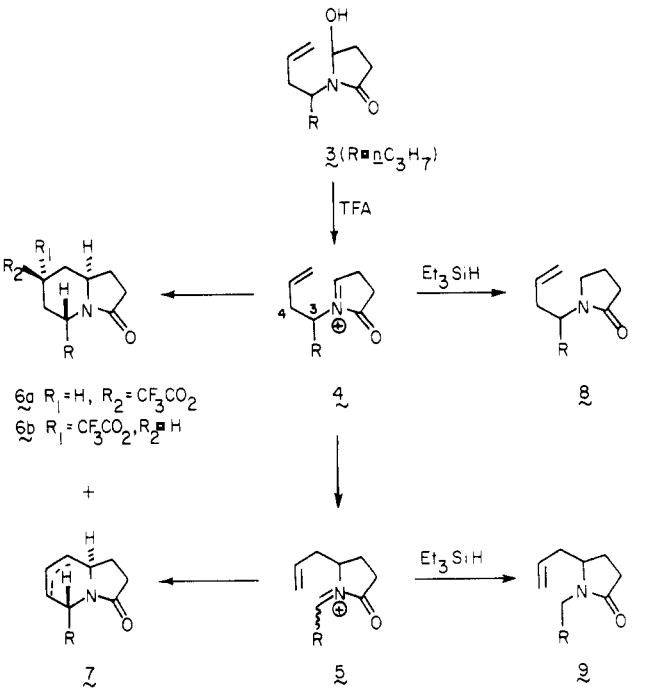
1 **2**

Rearrangement Discovery and Substituents Effects. The rearrangement was discovered while examining the behavior of *N*-acyliminium ions in the presence of triethylsilane (Scheme I).[3] Thus, treatment of carbinol amide **3** with trifluoroacetic acid gave lactams **6a** (49%), **6b** (13%), and **7** (12%) as expected. Treatment of **3** with trifluoroacetic acid–triethylsilane, however, gave no cyclized products. Instead, a separable 3:5 mixture of lactams **8** and **9** was obtained in a 73% yield.[7] Similar results were observed when formic acid was substituted for trifluoroacetic acid. Through a series of control experiments, it was established that the cyclization process was irreversible under the conditions employed. From these results it was concluded that ionization of **3** gives *N*-acyliminium ion **4** which rapidly rearranges to **5**. In the presence of triethylsilane, **4** and **5** are reduced to afford **8** and **9**, respectively. In the absence of triethylsilane, cyclization occurs via a slower secondary process.

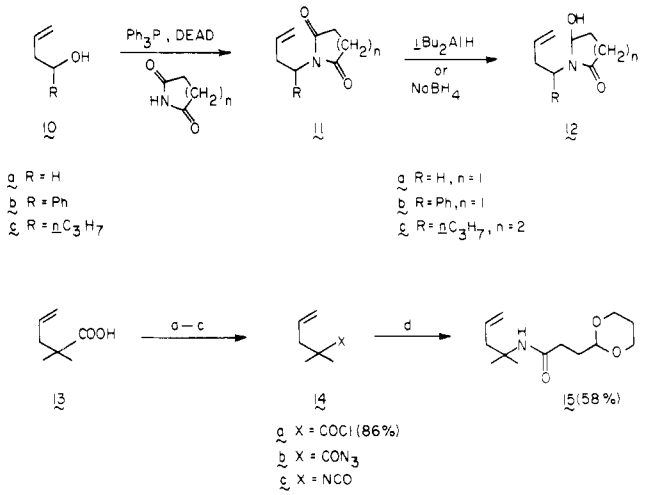
At the time of this discovery, similar rearrangements of iminium ions had been observed and studied in some detail.[8,9] Due to the importance of *N*-acyliminium ion cyclizations in alkaloid synthesis, however, we felt that further studies would be worthwhile. We began by examining the effect of substituents at C-3 of the inititally formed 2-aza-1,5-hexadienyl moiety. Iminium ion precursors **12a–c** and **15** were selected for this study and prepared by using well established procedures as outlined in Scheme II without comment.

Treatment of **12a** with trifluoroacetic acid–triethylsilane gave only *N*-(3-butenyl)-2-pyrrolidone (81%). No evidence for rearrangement of the initially formed *N*-acyliminium ion was obtained in either trifluoroacetic acid or formic acid.

Scheme I



Scheme II[a]



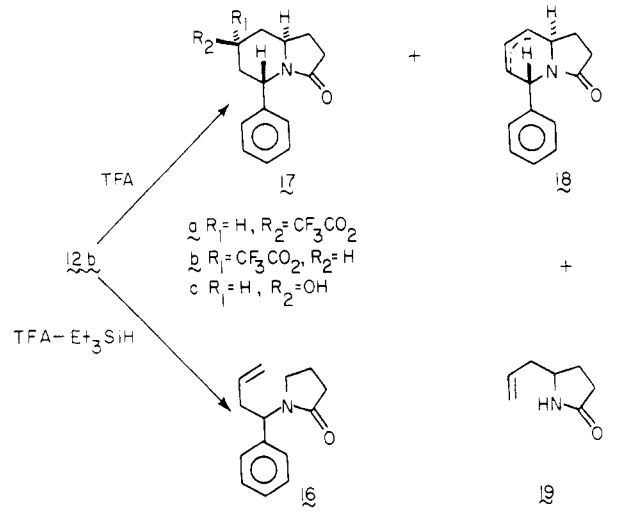
[a] (a) $SOCl_2$; (b) NaN_3, acetone; (c) Δ, PhH; (d) $(OCH_2CH_2CH_2O)CHCH_2CH_2MgBr$, THF.

† Alfred P. Sloan Foundation Fellow, 1983–1985.

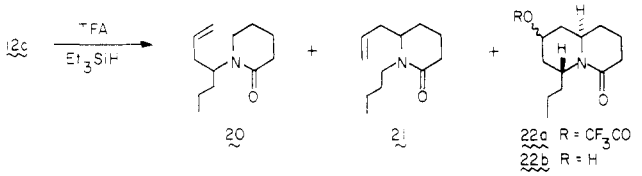
(1) Speckamp, W. N. *Recl. Trav. Chim. Pays-Pas* **1981**, *100*, 345.
(2) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.

0022-3263/85/1950-0235$01.50/0

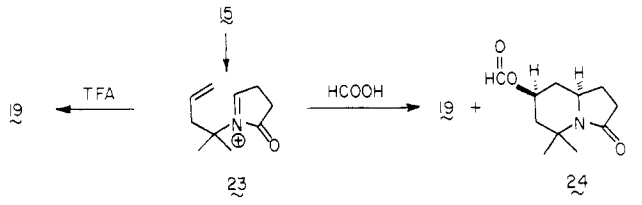
Scheme III



Scheme IV



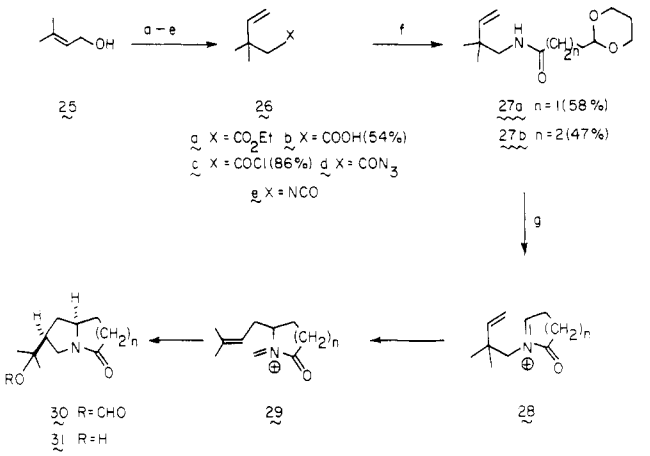
Scheme V



Treatment of **12b** with trifluoroacetic acid–triethylsilane also gave no indication that rearrangement was taking place as only lactam **16** was obtained in an 81% yield. When the triethylsilane was omitted, however, **12b** gave lactam **19** (10%) in addition to cyclized products **17a** (39%), **17b** (9%), **17c** (10%), and **18** (27%) as shown in Scheme III. The formation of **19** presumably is the result of rearrangement of the initially formed *N*-acyliminium ion to an ion analogous to **5**, followed by hydrolysis. Thus, although triethylsilane reduction was not a useful trap in this case, evidence that rearrangement was competing with cyclization was still obtained.

Carbinol amide **12c** behaved as expected upon treatment with trifluoroacetic acid–triethylsilane, affording lactams **20** (39%), **21** (21%) and **22** (19%) as shown in Scheme IV. Thus, there appears to be little difference in the behavior of the five- and six-membered ring iminium ions.

Scheme VI[a]



[a] (a) $CH_3C(OEt)_3$, H^+, Δ; (b) NaOH; (c) $SOCl_2$; (d) NaN_3, acetone; (e) PhH, Δ; (f) $(OCH_2CH_2CH_2O)CHCH_2(CH_2)_nMgBr$; (g) HCOOH.

The effect of *gem*-dimethyl substitution at C-3 of the initially formed *N*-acyliminium ion was examined next (Scheme V). Thus, acetal **15** was treated with trifluoroacetic acid in dichloromethane. Only lactam **19** (80%) was formed, presumably via rearrangement of *N*-acyliminium ion **23** and subsequent hydrolysis. When formic acid was used as the ionization solvent, indolizidinone **24** (25%) was produced in addition to rearrangement product **19** (73%).

In summary, the series of studies described above suggests that 3-substitution encourages rearrangement of *N*-acyl-2-aza-1,5-hexadienes via what is formally a 2-aza-Cope process.[10] Although no experiments which establish the reversibility of the rearrangement were performed, our experiments[3] with **3** and other results emanating from the Speckamp group[11] suggest that this might be the case in several of the systems studied. Finally, the types of products observed depend on the relative rates of cyclization, rearrangement, reduction, and hydrolysis under the reaction conditions employed.

We next examined the effect of C-4 substitution in the initially formed *N*-acyliminium ion. Since studies with **12a** had failed to provide evidence for rearrangement, we moved directly to a system with *gem*-dimethyl substitution. A suitable *N*-acyliminium precursor (**27a**) was prepared as shown in Scheme VI without comment. Treatment of **27a** with formic acid at room temperature gave pyrrolizidinones **30a** (81%) and **31a** (10%), presumably via intermediate ions **28a** and **29a**. The gross structure of **30a** was apparent from spectroscopic data and the stereochemical assignment was confirmed by X-ray crystallography.[12] Although attempts to demonstrate the intermediacy of **29a** met with failure,[13] experiments conducted elsewhere suggest that the pathway shown in Scheme VI is reasonable.[11c]

This rearrangement-cyclization process was also applied to the synthesis of an indolizidinone. Thus, acetal **27b** was prepared as shown in Scheme VI and treated with formic acid to afford **30b** (84%) and **31b** (7%). The relative stereochemistry at C-2 and C-8a in these indolizidinones was assigned by analogy with the behavior of **27a**.

The studies with **27** demonstrate that C-3 substitution is not required to observe *N*-acyliminium ion rearrange-

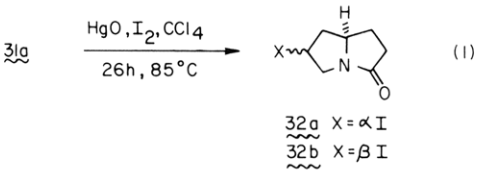
(3) Hart, D. J.; Tsai, Y.-M. *Tetrahedron Lett.* **1981**, *22*, 1567.
(4) For a related rearrangement of a vinylogous *N*-acyliminium ion see: Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367.
(5) Taken from the Ph.D. thesis of T.-K. Yang, Ohio State University, 1983.
(6) For preliminary accounts of a portion of this work see: Hart, D. J.; Yang, T.-K. *Tetrahedron Lett.* **1982**, *23*, 2761. Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135.
(7) For reduction of *N*-acyliminium ions with trifluoroacetic acid–triethylsilane see: Auerbach, J.; Zamose, M.; Weinreb, S. M. *J. Org. Chem.* **1976**, *41*, 725. Drage, J. S.; Earl, R. A.; Vollhardt, K. P. C. *J. Heterocycl. Chem.* **1982**, *19*, 701.
(8) Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579.
(9) For recent studies and other lead references see: Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 1877.
(10) A stepwise rearrangement proceeding through a discrete secondary carbocation intermediate cannot be excluded.
(11) (a) Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, *22*, 3289. (b) Nossin, P. M. M.; Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron Lett.*, **1982**, *23*, 3807. (c) Ent, H.; deKoning, H.; Speckamp, W. N. *Tetrahedron Lett.* **1983**, *24*, 2109.

ment. In fact, the Speckamp group has also observed rearrangement in systems carrying single substituents at C-4 of the initially formed *N*-acyliminium (phenyl, *p*-methoxyphenyl, methoxy).[11c] Finally, we note that the rearrangement–cyclization process described here is related to the directed 2-azonia [3,3]-sigmatropic rearrangements developed by Overman and his co-workers.[8]

Synthesis of Pyrrolizidine Alkaloids. The pyrrolizidine alkaloids are a large class of natural products which have attracted the attention of synthetic organic chemists for over 30 years.[14,15] We felt that the rearrangement–cyclization reaction had features which would be useful in the stereoselective synthesis of several reasonably complex pyrrolizidine bases. Hastanecine (**1**) and heliotridine (**2**) were selected as targets.

To adapt the rearrangement–cyclization reaction for the synthesis of **1** and **2** called for three modifications of the chemistry shown in Scheme VI. First, a hydroxymethyl group had to be placed on C-7. Second, a hydroxyl group had to be installed at C-1. We intended to accomplish these tasks by incorporating appropriate substituents in an *N*-acyliminium ion precursor. Finally, a method for degrading a 2-hydroxy-2-propyl group to either a hydrogen or an olefin had to be developed.

We began by addressing the latter problem as shown in eq 1. Treatment of alcohol **31a** with yellow mercuric oxide and iodine in carbon tetrachloride gave a separable mixture of diastereomeric iodides **32** (38%) and 21% of recovered starting material. Although the efficiency of this alkoxy radical fragmentation[16] was disappointing, it established the first stage of a protocol for accomplishing the required degradations.



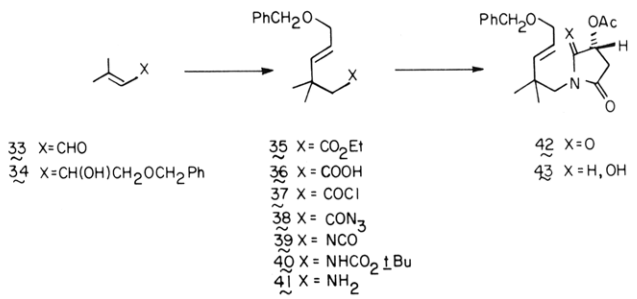
(1)

32a X = αI
32b X = βI

We proceeded with our approach to **1** and **2** by preparing *N*-acyliminium ion precursor **43** as shown in Scheme VII. Treatment of 3,3-dimethylacrolein (**33**)[17] with [(benzyloxy)methyl]lithium[18] gave allylic alcohol **34** (78%). A Johnson orthoester Claisen rearrangement[19] followed by saponification of ester **35** gave carboxylic acid **36** (86%). The acid was converted to acid chloride **37** (83%) which was subjected to a Curtius degradation[20] to afford urethane **40** (87%). The *tert*-butoxycarbonyl group was removed to give amine **41** (86%). Treatment of **41** with (*R*)-2-acetoxysuccinic anhydride[21] gave a mixture of amido acids which were converted to imide **42** (81%) upon warming with acetyl chloride.[22] Reduction of imide **42** with sodium borohydride in methanol under carefully controlled conditions gave the desired *N*-acyliminium ion precursor (**43**) in an 83% yield.[23]

We next turned to the critical rearrangement–cyclization. It was found that stirring **43** with formic acid for a day gave a mixture of formate **46** (60%) and alcohol **47** (17%). Both pyrrolizidinones gave diol **48** upon hydrolysis in aqueous methanol. From an operational standpoint, it was possible to proceed from **43** to **48** in an 89% yield without purification of intermediates. The

Scheme VII

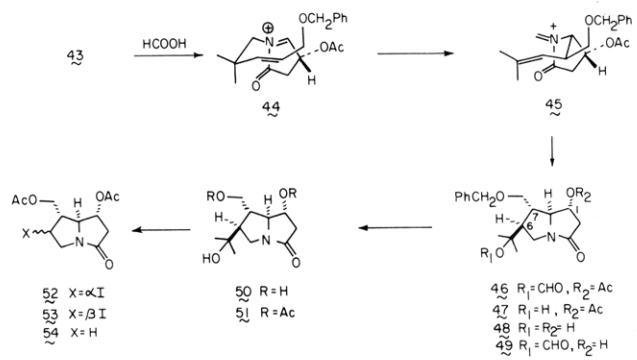


33 X = CHO
34 X = CH(OH)CH2OCH2Ph

35 X = CO_2Et
36 X = COOH
37 X = COCl
38 X = CON_3
39 X = NCO
40 X = $NHCO_2$tBu
41 X = NH_2

42 X = O
43 X = H, OH

Scheme VIII

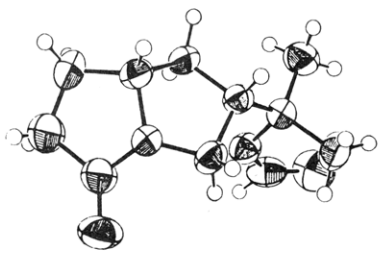


52 X = αI
53 X = βI
54 X = H

50 R = H
51 R = Ac

46 R_1 = CHO, R_2 = Ac
47 R_1 = H, R_2 = Ac
48 R_1 = R_2 = H
49 R_1 = CHO, R_2 = H

(12) We thank Dr. Judith Gallucci for performing the X-ray structure determination of **30a** at The Ohio State University Department of Chemistry Crystallography Facility. Formate **30a** crystallizes in space group $P2_1/c$ with $z = 4$ in a cell dimensions $a = 11.606$ (1) Å, $b = 7.106$ (1) Å, $c = 14.784$ (1) Å, and $\beta = 110.48$ (1)° at 22 °C. The first full-matrix least-squares refinement on F^2 included 2020 unique reflections and 136 variables (non-hydrogen atoms treated anisotropically and hydrogen atoms as fixed contributions) and yielded agreement indices R (on F^2) of 0.080 and R_x (on F^2) of 0.131. The value of R (on F^2) for those 1220 intensities with $F_0^2 > 3\sigma(R_0^2)$ was 0.056.



(13) Treatment of **27a** with trifluoroacetic acid–triethylsilane–dichloromethane gave the trifluoroacetate corresponding to **30a** (37%) and 1-(2,2-dimethyl-3-butenyl)-2-pyrrolidinone (11%). None of the product expected from reduction of **29a** was isolated.

(14) For reviews see: Bull, L. B.; Culvenor, C. C. J.; Dick, A. J. "The Pyrrolizidine Alkaloids"; North-Holland: Amsterdam, 1968. Warren, F. L. *Fortschr. Chem. Org. Naturst.* **1966**, *24*, 329. Warren, F. L. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1970; Vol. 12. Robins, D. J. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1979; Vol. 24, pp 247–291.

(15) For recent syntheses of perhydroxypyrrolizidine bases see: Chamberlain, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. Tatsuta, K.; Takahashi, H.; Amemiya, Y.; Kinoshita, M. *J. Am. Chem. Soc.* **1983**, *105*, 4096. Niwa, H.; Uosaki, T.; Yamada, K. *Tetrahedron Lett.* **1983**, *24*, 5731. Niwa, H. Kuroda, A.; Yamada, K. *Chem. Lett.* **1983**, 125. Ohsawa, T.; Ihara, M.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1983**, *48*, 3644. For earlier syntheses see ref 6 and 14 and citations therein.

(16) Greene, F. D.; Savitz, M. L.; Osterholtz, F. D.; Lau, H. H.; Smith, W. N.; Zanet, P. M. *J. Org. Chem.* **1963**, *28*, 55. Macdonald, T. L.; O'Dell, D. E. *J. Org. Chem.* **1981**, *46*, 1501 and references cited therein.

(17) Prepared by PCC oxidation (Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647) of 3-methyl-2-buten-1-ol.

(18) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(19) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(20) LeBel, N. A.; Cherluck, R. M.; Curtis, E. A. *Synthesis* **1973**, 678 and references cited therin.

(21) Jones, B. *J. Chem. Soc.* **1933**, 788.

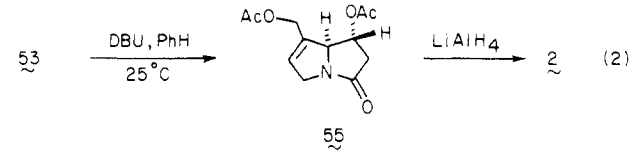
(22) Replacement of the benzyl group with an acetyl group was observed at long reaction times and elevated temperatures.

(23) Substantial amounts of the diol resulting from hydrolysis of **43** was observed when the reaction was allowed to reach 0 °C. For the use of similar conditions for the reduction of imides see ref 15 (Chamberlain).

stereochemistry at C-7 and C-8 was established by completion of the total synthesis of **1** while the stereochemistry at C-6 was assigned by analogy with the behavior of **27a**. One mechanistic rational of this stereoselective conversion is presented in Scheme VIII. We imagine that the initial rearrangement takes place via a transition state which minimizes steric interactions between the (benzyloxy)-methyl and acetoxy groups (**44** → **45**). Subsequent cyclization of **45** affords the observed products. Another possibility is cyclization of **44** to a discrete secondary carbocation followed by a Wagner–Meerwein shift. It is notable that rearrangement–cyclization of the diol derived from hydrolysis of **43** affords **48** and **49** in an excellent yield. Thus it is unnecessary to invoke acetoxonium ion formation as a stereocontrol element in this reaction.[24,25]

The critical C-6 side chain degradation was performed as outlined in Scheme VIII. Hydrogenolysis of the benzyl group followed by selective acetylation of the resulting triol **50** (96%) gave diacetate **51** (94%). Degradation of **51** via the aforementioned alkoxy radical fragmentation[16] gave an equal mixture of iodides **52** and **53** (85%) along with olefin **55** (6%). The efficiency and short reaction time required for the degradation of **51** was unexpected in view of the model studies performed with **31a**. Perhaps the apparent increase in the rate of alkoxy radical fragmentation going from **31a** to **51** is due to steric strain relief.[26] Finally, it is notable that δ-hydrogen atom abstraction, a process which usually competes favorably with fragmentation, is not a problem in the degradation of **51** even though models show that the C-7 acetoxymethyl hydrogens are within reach of the intermediate alkoxy radical. Once again, a fast fragmentation rate could account for this observation. An alternative explanation, however, is based on the suggestion that the optimal geometry for intramolecular δ-hydrogen atom abstraction by an alkoxy radical involves a nearly linear arrangement of the radical and C–H bond undergoing homolysis.[27] If this is the case, such an arrangement in the alkoxy radical derived from **51** would have strain resembling a *trans*-oxabicyclo[3.3.0]-octane. Thus geometric constraints may also be responsible for the lack of complications due to δ-hydrogen atom abstraction.

The synthesis of hastanecine was completed in a straightforward manner. Treatment of iodides **52** and **53** with tri-*n*-butyltin hydride[28] and AIBN gave diacetate **54** (91%). Reduction of **54** with lithium aluminum hydride gave (−)-hastanecine (**1**, 90%), identical with an authentic sample.[29] The synthesis of **2** was accomplished as shown in eq 2. Iodide **52** underwent smooth dehydrohalogenation upon treatment with DBU in benzene to afford **55** in an 81% yield. Iodide **53** gave only intractable materials under similar conditions.[30] Lithium aluminum hydride reduction of **55** gave (−)-heliotridine (**2**) in a 60% yield.



53 → 55 → 2 (2)

Experimental Section

All melting points are uncorrected as are boiling points. ^1H nuclear magnetic resonance spectra are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constants, integration, interpretation]. Mass spectra were recorded at an ionization energy of 70 eV. Samples on which exact masses were measured exhibited no significant peaks at m/e greater than that of the parent. The parent ions of some compounds were either not observed or were too small for exact mass measurements to be obtained. In these cases, fragmentation patterns were in accord with the assigned structures. Combustion analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

Solvents and reagents were purified prior to use. All reactions were carried out under a blanket of either nitrogen or argon in flame-dried flasks unless stated otherwise. Column chromatography was performed over EM Laboratories silica gel (70–230 mesh) or LoBar columns (medium pressure).

Procedures for the experiments described in Schemes I and II and the preparation of **25–27** are described in supplementary material. The experiments appearing in Schemes III–V, VII, VIII, a portion of Scheme VI (**27** → **30** + **31**), and eq 1 and 2 are reported below.

1-(1-Phenyl-3-butenyl)-2-pyrrolidinone (16). To a solution of 0.43 g (1.8 mmol) of **12b** in 0.5 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid–triethylsilane (1:1 by volume) in one portion. The resulting mixture was stirred at room temperature for 15 min, diluted with 10 volumes of dichloromethane, and washed with two equal volumes of water. The combined aqueous layers were extracted with an equal volume of dichloromethane. The organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residual oil was purified by chromatography over 10 g of silica gel (eluted with ethyl acetate–hexane, 1:1) to give 0.32 g (81%) of lactam **16** as a pale yellow oil: IR (CH_2Cl_2) 1685 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.70–3.07 (m, 8 H), 5.00–6.03 (m, 4 H, CH=CH_2 and NCH), 7.33 (s, 5 H, ArH); exact mass calcd for $C_{14}H_{17}NO$ m/e 215.1310, found m/e 215.1314.

Cyclization of Carbinol Lactam 12b: *rel*-(5*R*,7*S*,8a*S*)-5-Phenyl-7-(trifluoroacetoxy)hexahydro-2*H*-indolizin-3-one (17a), *rel*-(5*R*,7*R*,8a*S*)-5-Phenyl-7-(trifluoroacetoxy)hexahydro-2*H*-indolizin-3-one (17b), *rel*-(5*R*,7*S*,8a*S*)-5-Phenyl-7-hydroxyhexahydro-2*H*-indolizin-3-one (17c), 5-Phenyl-1,5,6,8a- and 5-Phenyl-1,5,8,8a-tetrahydro-2*H*-indolizin-3-one (18), and 5-Allyl-2-pyrrolidinone (19). A solution of 1.15 g (5.0 mmol) of **12b** was stirred with 7.5 mL of trifluoroacetic acid and 7.5 mL of dichloromethane at room temperature for 5 min. The mixture was diluted with 75 mL of dichloromethane and washed with two 75-mL portions of water. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The products were separated by chromatography twice over 60 g of silica gel (ethyl acetate–hexane, 1:1 gradually increased to ethyl acetate) to give 141 mg (8%) of trifluoroacetate **17b**, 121 mg (10%) of alcohol **17c**, 60 mg (10%) of lactam **19**, and 1.02 g of a mixture of trifluoroacetate **17a** and olefin **18**.

To 1.0 g of the mixture of trifluoroacetate **17a** and olefin **18** was added 5.5 mL of 0.8 N aqueous methanolic sodium hydroxide (water–methanol, 2.5:13) at room temperature. The resulting mixture was stirred for 1 h, diluted with 60 mL of dichloromethane, and washed with two 30-mL portions of water. The combined washes were extracted twice with 30 mL of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 740 mg of yellow oil which was chromatographed over 50 g of silica gel (ethyl acetate–methanol, 40:1 gradually increased to 80:3) to give 287 mg of olefin **18** and

(24) It is notable that racemization by dehydration and rehydration of **43** did not occur. For relevant studies see: Wijnberg, J. B. P. A.; deBoer, J. J. J.; Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 227.

(25) A related stereoselective cyclization was recently reported by Chamberlain and Chung (ref 15).

(26) We have previously noted that 1-desacetoxy-**51** undergoes degradation with equal efficiency (ref 6).

(27) Stork, G. In "Current Trends in Organic Synthesis"; Nozaki, H., Ed.; Pergamon Press: New York, 1983; pp 359–370.

(28) Kuivila, H. G. *Synthesis* **1970**, 499.

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(30) The differing behavior of **52** and **53** upon attempted dehydrohalogenation was used as a basis for tentative assignments of their stereochemistry. See DePuy et al. [Depuy, C. H.; Morris, G. F.; Smith, J. S.; Smat, R. J. *J. Am. Chem. Soc.* **1965**, *87*, 2421] for a relevant study.

450 mg of alcohol **17c** both as pale yellow oils. The alcohol **17c** was treated with trifluoroacetic anhydride and triethylamine to give an authentic sample of **17a**. Trifluoroacetate **17a**: IR (CH_2Cl_2) 1780, 1685 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.35–2.97 (m, 8 H, CH_2), 3.53–3.87 (m, 1 H, NCH), 5.13 (tt, J = 12, 4 Hz, 1 H, OCH), 5.65 (br d, J = 6 Hz, 1 H, NCHAr), 7.20–7.45 (m, 5 H, ArH); exact mass calcd for $C_{16}H_{16}NO_3F_3$, m/e 327.1082, found m/e 327.1090.

Trifluoroacetate **17b**: IR (CH_2Cl_2) 1780, 1685 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.40–3.00 (m, 8 H), 3.49 (br d, J = 6 Hz, 1 H, NCHPh), 3.95–4.30 (m, 1 H, NCH), 5.30 (m, 1 H, OCH), 5.49 (br d, J = 6 Hz, 1 H, NCHAr), 7.00–7.40 (m, 5 H, ArH); exact mass calcd for $C_{16}H_{16}NO_3F_3$ m/e 327.1082, found m/e 327.1090.

Olefins **18**: IR (CH_2Cl_2) 1675 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.53–2.70 (m, 6 H, CH_2), 3.55–4.00 (m, 1 H, NCH), 5.50–6.17 (m, 3 H, =CH and NCHAr), 7.20–7.50 (m, 5 H, ArH); exact mass calcd for $C_{14}H_{15}NO$ m/e 213.1154, found m/e 213.1159.

Lactam **19**: IR (CH_2Cl_2) 3200 (br), 1690 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.60–2.60 (m, 6 H, CH_2), 3.55–3.97 (m, 1 H, NCH), 4.99–5.30 (m, 2 H, $=CH_2$), 5.50–6.05 (m, 1 H, =CH), 7.13 (br s, 1 H, NH); mass spectrum, m/e (relative intensity) 125 (parent, weak), 84 (strong).

Alcohol **17c**: IR (CH_2Cl_2) 3380(br), 1675 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.95–2.60 (m, 8 H, CH_2), 3.27–3.80 (m, 2 H, NCH and OCH), 4.75 (br d, J = 4 Hz, 1 H, OH), 5.27 (br d, J = 6 Hz, 1 H, NCHAr), 7.05–7.37 (m, 5 H, ArH); exact mass calcd for $C_{14}H_{17}NO_2$ m/e 231.1259, found m/e 231.1264. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.54; H, 7.42.

Rearrangement of Hydroxy Lactam 12c: 6-Allyl-1-butyl-2-piperidinone (21), 1-(1-Propyl-3-butenyl)-2-piperidinone (20), 6-Propyl-8-(trifluoroacetoxy)octahydro-2*H*-quinolizin-4-one (22a), and 6-Propyl-8-hydroxyoctahydro-2*H*-quinolizin-4-one (22b). A sample of 620 mg (2.93 mmol) of hydroxy lactam **46** was treated with a mixture of trifluoroacetic acid (1.0 mL) and triethylsilane (1.0 mL) in 1.0 mL of dichloromethane as described above for **12b**. The crude products were separated by chromatography three times over silica gel at medium pressure (ethyl acetate–hexane, 1:2) to give 225 mg (39%) of lactam **21** and a mixture of lactam **20** (21%) and trifluoroacetate **22a** (19%) (yields were based on separation of lactam **20** and alcohol **22b** after hydrolysis of trifluoroacetate **22a** in aqueous methanolic sodium hydroxide). Lactam **21**: IR (CH_2Cl_2) 1630 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.85–1.02 (m, 3 H, CH_3), 1.15–2.55 (m, 12 H), 2.83 (qu, J = 7 Hz, 1 H, NCH), 3.30–3.60 (m, 1 H, NCH), 3.83 (qu, J = 7 Hz, 1 H, NCH), 4.95–5.25 (m, 2 H, $=CH_2$), 5.50–5.97 (m, 1 H, =CH); mass spectrum, m/e (relative intensity) 154 (100, parent – C_3H_5), 98 (20), 55 (35), 41 (15).

Lactam **20**: IR (CH_2Cl_2) 1630 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.80–1.00 (m, 3 H, CH_3), 1.10–1.60 (m, 4 H), 1.65–1.85 (m, 4 H), 2.15–2.50 (m, 4 H), 3.00–3.20 (m, 2 H, NCH_2), 4.70–5.15 (m, 3 H, $=CH_2$ and NCH), 5.50–6.00 (m, 1 H, =CH); exact mass calcd for $C_{12}H_{21}NO$ m/e 195.1623, found m/e 195.1630.

Alcohol **22b**: IR (CH_2Cl_2) 3350 (br), 1630 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.80–2.20 (m, 15 H), 2.25–2.50 (m, 2 H, CH_2CO), 3.25–3.65 (m, 1 H, NCH), 3.75–4.20 (m, 2 H, OH and NCH), 4.85–5.15 (m, 1 H, NCH).

Formic Acid Cyclization of Acetal Amide 15: 5,5-Dimethyl-7-(formyloxy)hexahydro-2*H*-indolizin-3-one (24) and 5-Allyl-2-pyrrolidinone (19). A solution of 1.04 g (4.3 mmol) of acetal amide **15** in 8.5 mL of 98% formic acid was stirred for 24 h at room temperature. The formic acid was removed in vacuo and products were separated by chromatography over 50 g of silica gel (eluted with ethyl acetate–hexane, 7:3 increased gradually to 1:1) to give 0.23 g (25%) of formate **24** and 0.38 g (73%) of lactam **19** as colorless oils. Formate **24**: IR (CH_2Cl_2) 1720, 1685 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.00–2.50 (m with s at 1.3 and 1.7, 14 H), 3.30–3.80 (m, 1 H, NCH), 4.77–5.30 (tt, J = 12, 4 Hz, 1 H, OCH), 7.99 (s, 1 H, CHO); exact mass calcd for $C_{11}H_{17}NO_3$ m/e 211.1208, found m/e 211.1213.

Similar treatment of 1.0 g (4.1 mmol) of **15** with 6 mL of trifluoroacetic acid–triethylsilane (1:1 by volume) gave 414 mg (80%) of lactam **19**.

Formic Acid Cyclization of Amide 27a and Hydrolysis of Formate 20a: *rel*-(6*R*,7a*S*)-6-[2-(Formyloxy)prop-2-yl]-hexahydro-3*H*-pyrrolizin-3-one (30a) and *rel*-(6*R*,7a*S*)-6-(2-Hydroxyprop-2-yl)hexahydro-3*H*-pyrrolizin-3-one (31a). To 2.40 g (9.9 mmol) of neat acetal amide **27a** was added 20 mL of 98% formic acid in one portion. The resulting mixture was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was dissolved in 50 mL of dichloromethane and washed with 30 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with two 50-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 2.89 g of a mixture of formate **30a** and alcohol **31a**. On one occasion, a pure sample of **30a** was obtained by chromatography over silica gel at medium pressure (ethyl acetate): mp 59–60 °C; IR (CH_2Cl_2) 1720, 1685 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.36 (dt, J = 11.5, 11.5 Hz, 1 H, H_7), 1.53 (s, 6 H, CH_3), 1.73–1.86 (m, 1 H, H_1), 2.05 (ddd, J = 11.6, 6.5, 5.1 Hz, 1 H, H_6), 2.26–2.36 (m, 1 H, H_1), 2.45 (ddd, J = 16.8, 9.9, 2.2 Hz, 1 H, H_2), 2.66–2.75 (m, 1 H, H_2), 2.78–2.87 (m, 1 H, H_6), 3.16 (ddd, J = 10.6, 9.1, 1.5 Hz, 1 H, H_5), 3.50 (dd, J = 11.5, 8.9 Hz, 1 H, H_5), 3.90–4.00 (m, 1 H, H_{7a}); exact mass calcd for $C_{11}H_{17}NO_3$ m/e 211.1208, found m/e 211.1211.

To the mixture of formate **30a** and alcohol **31a** (2.89 g) was added 10 mL of 5% aqueous sodium hydroxide in one portion. The mixture was warmed under reflux for 9 h and cooled to room temperature followed by addition of 50 mL of methanol. The mixture was stirred at room temperature for 3 h and the resulting solution was neutralized with 3 N aqueous hydrochloric acid and extracted with three 150-mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give 2.05 g of residual oil. The residue was chromatographed over 70 g of silica gel (eluted with ethyl acetate–methanol, 6:1) to give 89 mg (4%) of the starting acetal amide **27a** and 1.59 g (89%) of alcohol **31a**: IR (CH_2Cl_2) 3400 (br), 1685 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.10–3.63 (m with singlet at δ 1.21, 16 H), 3.70–4.15 (m, 1 H, NCH); exact mass calcd for $C_{10}H_{17}NO$ m/e 183.1259, found m/e 183.1264.

Cyclization of Acetal Amide 27b: *rel*-(2*R*,8a*S*)-2-[2-(Formyloxy)prop-2-yl]hexahydro-6*H*-indolizin-5-one (30b) and *rel*-(2*R*,8a*S*)-2-(2-Hydroxyprop-2-yl)hexahydro-6*H*-indolizin-5-one (31b). To 280 mg (1.09 mmol) of neat acetal amide **27b** was added 3 mL of 98% of formic acid. The solution was stirred for 9 h at room temperature. Workup and purification by chromatography over 20 g of silica gel (ethyl acetate gradually changed to ethyl acetate–methanol, 5:1) gave 203 mg (83%) of formate **30b** as a pale yellow oil and 15 mg (8%) of alcohol **31b** as pale yellow crystalline solid.

Formate **30b**: IR (CH_2Cl_2) 1720, 1630 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.20–2.65 (m with a singlet at δ 1.59, 15 H), 3.40–3.67 (m, 3 H, NCH_2 and NCH), 8.00 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 21.10 (t), 24.38 (q), 29.08 (t), 30.94 (t), 34.60 (t), 45.76 (t), 46.36 (d), 59.48 (d), 82.77 (s), 160.24 (d), 168.99 (s); exact mass calcd for $C_{12}H_{19}NO_3$ m/e 225.1501, found m/e 225.1432.

Alcohol **31b**: mp 81–82 °C; IR (CH_2Cl_2) 3400 (br), 1630 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.27 (s, 6 H, CH_3), 1.30–2.50 (m, 9 H), 2.67 (br s, 1 H, OH), 3.30–3.67 (m, 3 H, NCH, and NCH_2); exact mass calcd for $C_{11}H_{19}NO_2$ m/e 197.1551, found m/e 197.1438.

***rel*-(6*R*,7a*S*)-6-Iodohexahydro-3*H*-pyrrolizin-3-one (32a) and *rel*-(6*S*,7a*S*)-6-Iodohexahydro-3*H*-pyrrolizin-3-one (32b).** A mixture of 92 mg (0.50 mmol) of alcohol **31a**, 235 mg (1.09 mmol) of mercuric oxide (yellow), and 295 mg (1.16 mmol) of iodine in 34 mL of carbon tetrachloride was heated in an 85 °C oil bath for 26 h. The resulting mixture was cooled to room temperature, filtered, and washed successively with two 10-mL portions of saturated aqueous sodium metabisulfate and 10 mL of brine. The combined washings were extracted with two 20-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 68 mg of an orange oil. The residual oil was chromatographed over silica gel at medium pressure (LoBar size A column, eluted with ethyl acetate) to give 48 mg (38%) of iodoamides **32a** and **32b** and 19 mg (21%) of starting alcohol **31a**. Pure samples of each iodide were obtained upon further chroamtography.

Iodide **32a**: IR (CH_2Cl_2) 1690 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.63–2.10 (m, 2 H), 2.25–3.00 (m, 4 H), 3.47 (dd, J = 12, 3 Hz, 1 H, NCH), 4.17–4.60 (m, 3 H, 2 NCH and CHI); exact mass calcd

for $C_7H_{10}NOI$ m/e 250.9810, found m/e 250.9816.

Iodide **32b**: IR (CH_2Cl_2) 1690 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.80–3.00 (m, 6 H), 3.47 (dd, J = 12, 6 Hz, 1 H, NCH), 3.80–4.10 (m, 2 H, NCH and CHI), 4.20–4.50 (m, 1 H, NCH); exact mass calcd for $C_7H_{10}NOI$ m/e 250.9810, found m/e 250.9816.

1-(Benzyloxy)-4-methyl-3-penten-2-ol (34). To a solution of 27.0 g (65.7 mmol) of [(benzyloxy)methyl]tributylstannane[18] in 250 mL of tetrahydrofuran was added 41 mL (63.5 mmol) of 1.55 M n-butyllithium in hexane with cooling such that the temperature did not exceed −60 °C. The resulting golden yellow solution was stirred at −60 °C for 10 min, followed by addition of 4.4 g (52.5 mmol) of 3,3-dimethylacrolein[17] in 25 mL of tetrahydrofuran at a rate such that the temperature remained at −65 °C. The cooled solution was stirred for 30 min, poured into 500 mL of petroleum ether, and washed with two 200-mL portions of water. The combined aqueous layers were extracted with 200 mL of petroleum ether. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give 36.0 g of pale yellow oil. The crude product was chromatographed over 350 g of silica gel (ethyl acetate) to give 9.6 g (89%) of alcohol **34** as a colorless oil: IR (CH_2Cl_2) 3300 (br) cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.68 (d, J = 3 Hz, 6 H, CH_3), 2.63 (br s, 1 H, OH), 3.48–3.75 (m, 2 H, OCH_2), 4.35–4.50 (m with s at 4.48, 3 H, OCH and $ArCH_2$), 5.06 (br d, J = 8 Hz, 1 H, =CH), 7.30 (s, 5 H, ArH); mass spectrum, m/e (relative intensity) 206 (parent, weak), 188 (1, parent − H_2O), 175 (1), 162 (1), 150 (2), 115 (3), 91 (80), 85 (100), 79 (25), 77 (21), 51 (10).

(*E*)-6-(Benzyloxy)-3,3-dimethyl-4-hexenoic Acid (36). To a 100-mL round-bottom flask fitted with a short distillation column was added 9.6 g (46.6 mmol) of alcohol **34**, 43 g (265 mmol) of triethyl orthoacetate, and 0.2 g (2.7 mmol) of propanoic acid. The mixture was heated with stirring to keep the vapors above the pot at 145 °C. Heating was continued until ethanol no longer distilled from the reaction mixture. The mixture was warmed at 145 °C for another 21 h followed by warming at 180 °C until the residual triethylorthoacetate was removed. The residual 12.9 g of orange oil was crude ester **35**: IR (CH_2Cl_2) 1728 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.17 (s, 6 H, CH_3), 1.21 (t, J = 8 Hz, 3 H, CH_3), 2.27 (s, 2 H, $COCH_2$), 3.98 (d, J = 5 Hz, 2 H, OCH_2C=), 4.09 (q, J = 8 Hz, 3 H, OCH_2), 4.47 (s, 2 H, $ArCH_2O$), 5.36–5.38 (m, 2 H, =CH), 7.30 (s, 5 H, ArH); mass spectrum, m/e (relative intensity) 276 (parent, weak), 170 (24), 141 (5), 139 (3), 111 (6), 92 (15), 91 (100), 83 (17), 82 (15).

To 12.4 g (44.7 mmol) of crude **35** prepared above was added 50 mL of 10% aqueous sodium hydroxide. The mixture was warmed under reflux for 6 h, poured into 200 mL of water, and extracted with two 150-mL portions of ether. The aqueous phase was acidified with 3 N hydrochloric acid solution and extracted with three 200-mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give 9.87 g of brown oil which was distilled (bulb-to-bulb, 145 °C (0.2 mmHg)) to give 9.6 g (87% from alcohol **34**) of acid **36** as a pale yellow oil: IR (CH_2Cl_2) 3350, 1710 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.17 (s, 6 H, CH_3), 2.30 (s, 2 H, $COCH_2$), 4.01 (d, J = 5 Hz, 2 H, OCH_2C=), 4.43 (s, 2 H, $ArCH_2O$), 5.36–5.85 (m, 2 H, =CH), 7.30 (s, 5 H, ArH), 11.13 (br s, 1 H, OH).

6-(Benzyloxy)-3,3-dimethyl-4-hexenoyl Chloride (37). To 9.29 g (37.4 mmol) of acid **36** was added 31.1 g (0.26 mol) of thionyl chloride with cooling in an ice bath. The reaction mixture was heated under reflux for 1 h, cooled to room temperature, and concentrated in vacuo. The dark brown residue was distilled (bulb-to-bulb, 95 °C (0.3 mmHg)) to give 7.09 g (71%, 84% was obtained from a 0.5 g scale run) of acid chloride **37** as a pale yellow oil: IR (CH_2Cl_2) 1808 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.17 (s, 6 H, CH_3), 2.90 (s, 2 H, $COCH_2$), 3.98 (s, 2 H, OCH_2C=), 4.47 (s, 2 H, $ArCH_2O$), 5.40–5.85 (m, 2 H, =CH), 7.30 (s, 5 H, ArH); mass spectrum, m/e (relative intensity) 231 (parent − Cl, weak), 149 (7), 136 (4), 122 (21), 106 (73), 105 (100), 91 (24), 77 (86).

***tert*-Butyl *N*-[5-(Benzyloxy)-2,2-dimethylpent-3(*E*)-en-1-yl]urethane (40).** To a solution of 8.76 g (32.9 mmol) of acid chloride **37** in 60 mL of acetone was added 3.60 g (55.2 mmol) of sodium azide in 25 mL of water at 0 °C. The solution was stirred at 0 °C for 30 min, poured into 100 mL of ice water, and extracted with four 150-mL portions of hexane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give acyl acid **38** (IR 2140 cm^{-1}) as a pale yellow oil. The crude **38** was dissolved in 100 mL of dry benzene, heated under reflux until the rearrangement was completed by IR (about 1 h), and concentrated in vacuo. The residual crude isocyanate **39** (IR 2260 cm^{-1}) was dissolved in 40 mL of *tert*-butyl alcohol and 6.00 g (80.8 mmol) of potassium *tert*-butoxide was added in four equal portions at 0 °C. The reaction mixture was stirred at room temperature for 30 min, poured into 100 mL of water, and extracted with four 150-mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give 9.14 g (87%) of crude urethane **40** as a brown oil. Although this material was used directly in the next reaction, 223 mg of the crude product was purified by chromatography over 25 g of silica gel (ethyl acetate–hexane, 1:9) to give 218 mg (83%) of urethane **40** as a colorless oil: IR (CH_2Cl_2) 3450 (br), 1710 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.00 (s, 6 H, CH_3), 1.40 (s, 9 H, CH_3), 3.00 (d, J = 6 Hz, 2 H, NCH_2), 4.0 (m, 2 H, CH_2O), 4.50 (s with underlying br s, 3 H, NH and $ArCH_2$), 5.53–5.67 (m, 2 H, HC=CH), 7.33 (m, 5 H, ArH); mass spectrum, m/e (relative intensity) 319 (parent, weak), 263 (1), 246 (3), 238 (4), 182 (13), 155 (8), 91 (76), 82 (100), 67 (12), 57 (44).

5-(Benzyloxy)-2,2-dimethylpent-3(*E*)-enamine (41). To 9.01 g (28.2 mmol) of neat urethane **40** cooled in an ice bath was added 12 mL of trifluoroacetic acid. The reaction mixture was stirred for 30 min at room temperature, until TLC analysis (ethyl acetate–hexane, 1:8) showed that no urethane remained. The excess trifluoroacetic acid was removed in vacuo. The residual oil was dissolved in 200 mL of ether and washed with two 80-mL portions of saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 7.02 g of material which was purified via bulb-to-bulb distillation (oven temperature 128–140 °C (0.4–0.55 mmHg)) to give 5.32 g (86%) of amine **41** as a pale yellow oil: IR (CH_2Cl_2) 3480 (br) cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.01 (s, 6 H, CH_3), 1.23 (s, 2 H, NH_2), 2.47 (s, 2 H, NCH_2), 4.0 (m, 2 H, CH_2O), 4.47 (s, 2 H, $ArCH_2$), 5.47–5.60 (m, 2 H, HC=CH), 7.27 (m, 5 H, ArH); mass spectrum, m/e (reltive intensity) 219 (parent, weak), 188 (2), 138 (43), 128 (100), 113 (20), 84 (68).

(+)-4(*R*)-Acetoxy-1-[5-(benzyloxy)-2,2-dimethylpent-3-(*E*)-en-1-yl]-2,5-pyrrolidinedione (42). To a mixture of 8.62 g (18.4 mmol) of (*S*)-2-acetoxysuccinic anhydride[21] in 30 mL of dry dichloromethane in an ice bath was added dropwise 4.03 g (18.4 mmol) of amine **41**. The mixture was stirred at room temperature for 18 h and concentrated in vacuo to give 10.24 g of a brown oil which was chromatographed over 200 g of silica gel (ethyl acetate–hexane–98% formic acid, 100:100:1 gradually increased to 180:100:1) to give 9.36 g of a mixture of amido acids as a pale yellow oil. This material was used directly in the mext reaction: NMR (90 MHz, $CDCl_3$) δ 1.00 (s, 6 H, CH_3), 2.03–2.07 (two s, 3 H, CH_3), 2.90 (d, J = 6 Hz, 2 H, CH_2CO), 3.13 (d, J = 6 Hz, 2 H, NCH_2), 3.93–4.00 (m, 2 H, OCH_2), 4.50 (d, 2 H, $ArCH_2$), 5.48 (t, J = 6 Hz, 1 H, OCH), 5.50–5.60 (m, 2 H, HC=CH), 6.40 (t, J = 6 Hz, 1 H, NH), 7.30 (s, 5 H, ArH), 12.0 (br s, 1 H, OH).

To 9.27 g of the amido acid mixture in 150 mL of dry dichloromethane at 0 °C was added dropwise 25 mL of acetyl chloride in 30 mL of dry dichloromethane. The solution was stirred at 40 °C for 30 h and concentrated in vacuo to give 9.50 g of a brown oil. The oil was chromatographed over 230 g of silica gel (eluted with ethyl acetate–hexane, 1:3 gradually increased to 1:2) to afford 5.25 g (81%) of the desired imide **42** as a pale yellow oil: $[\alpha]^{20}_D$ +15.27° ($CHCl_3$, c 1.5); IR (CH_2Cl_2) 1750, 1720, 1230 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.06 (s, 6 H, CH_3), 2.10 (s, 3 H, CH_3CO), 2.61 (dd, J = 18, 5 Hz, 1 H, CH_2CO), 3.11 (dd, J = 18, 8 Hz, 1 H, CH_2CO), 3.45 (s, 2 H, NCH_2), 3.97 (d, J = 5 Hz, 2 H, CH_2C=), 4.47 (s, 2 H, $ArCH_2$), 5.40 (dd, J = 8, 5 Hz, 1 H, CHOAc), 5.40–5.85 (m, 2 H, HC=CH), 7.30–7.40 (m, 5 H, ArH); mass spectrum, m/e (relative intensity) 268 (4, parent − $PhCH_2$), 252 (10), 170 (70), 158 (38), 118 (38), 110 (36), 105 (20), 104 (20), 100 (33), 91 (100), 82 (67), 77 (16), 71 (31), 67 (13), 55 (89); exact mass calcd for $C_{20}H_{25}NO_5$ − $PhCH_2$ m/e 268.1180, found m/e 268.1086.

4(*R*)-Acetoxy-1-[5-(benzyloxy)-2,2-dimethylpent-3(*E*)-en-1-yl]-5-hydroxy-2-pyrrolidinone (43). To 1.02 g (2.84 mmol) of imide **42** in 25 mL of methanol was added 0.45 g (11.9 mmol) of sodium borohydride in one portion at −25 °C. The reaction mixture was stirred at −25 °C for 20 min and diluted with 50 mL of chloroform. The resulting mixture was poured into 40 mL of water and extracted with four 200-mL portions of chloroform.

The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give 1.03 g of pale yellow solid which was chromatographed over 80 g of silica gel (ethyl acetate–hexane, 4:6 gradually increased to 2:1) to give 40 mg (4%) of the starting imide **42** and 0.85 g (83%) of hydroxy lactam **43** as a white crystalline solid: mp 72–73 °C; IR (CH_2Cl_2) 3400 (br), 1740, 1705, 1240 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.07 (s, 6 H, CH_3), 2.10 (s, 3 H, CH_3), 2.60 (d, J = 6 Hz, 2 H, CH_2CO), 3.07 (d, J = 9 Hz, 1 H, CHN), 3.47 (d, J = 9 Hz, 1 H, CHN), 3.97 (d, J = 5 Hz with underlying signal, 3 H, CH_2C= and OH), 4.50 (s, 2 H, $ArCH_2$), 4.90–5.40 (m, 2 H, NCHO and OCH), 5.50–5.85 (m, 2 H, HC=CH), 7.33 (s, 5 H, ArH); mass spectrum, m/e (relative intensity) 361 (parent, 1), 343 (1, parent – H_2O), 301 (1, parent – HOAc), 283 (7, parent – HOAc and H_2O), 262 (9), 253 (7), 220 (7), 195 (12), 193 (14), 180 (10), 177 (10), 172 (21), 143 (28), 112 (36), 91 (100), 82 (57), 60 (71).

1(*S*)-Acetoxy-6(*R*)-(2-acetoxyprop-2-yl)-7(*S*)-[(benzyloxy)methyl]-7a(*R*)-hexahydro-3*H*-pyrrolizin-3-one (46) and (+)-1(*S*)-Acetoxy-7(*S*)-[(benzyloxy)methyl]-6(*R*)-(2-hydroxyprop-2-yl)-7a(*R*)-hexahydro-3*H*-pyrrolizin-3-one (47). To 1.11 g (3.07 mmol) of hydroxy amide **43** was added 11 mL of 98% of formic acid in one portion at room temperature. The mixture was stirred for 25 h and concentrated in vacuo. To the residual oil was added 50 mL of saturated aqueous sodium bicarbonate and the mixture was extracted with three 100-mL portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give 1.30 g of a pale yellow oil which was chromatographed over 80 g of silica gel (ethyl acetate–hexane, 1:1 gradually increased to 5:1) to give 710 mg (60%) of formate **46** as a colorless oil and 183 mg (17%) of alcohol **47** as a colorless oil. Formate **46**: IR (CH_2Cl_2) 1725, 1695, 1245, 1190 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.49 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.96 (s, 3 H, CH_3), 2.00–2.23 (m, 1 H, OCH_2CH), 2.60–2.73 (m, 2 H, CHCO and CH), 2.86 (dd, J = 17.5, 8.5 Hz, 1 H, CHCO), 3.11 (ddd, J = 11.5, 8.5, 1.2 Hz, 1 H, NCH), 3.49 (dd, J = 9, 6 Hz, 1 H, OCH_2), 3.67 (dd, J = 9, 6 Hz, 1 H, OCH_2), 3.77–3.86 (m, 2 H, NCH), 4.51 (s, 2 H, $ArCH_2O$), 5.22 (ddd, J = 9.6, 6.6, 4.1 Hz, 1 H, OCH), 7.20–7.40 (m, 5 H, ArH), 7.95 (s, 1 H, CHO); mass spectrum, m/e (relative intensity) 343 (1, parent – HCO_2H), 329 (4, parent – HOAc), 283 (24, parent – HCO_2H and HOAc), 192 (26, parent – HCO_2H, HOAc and $PhCH_2$), 177 (49), 162 (51), 146 (59), 91 (100), 77 (30), 68 (16).

Alcohol **47**: $[\alpha]^{20}_D$ +11.0° ($CHCl_3$, c 0.81); IR (CH_2Cl_2) 3300 (br), 1740, 1695, 1245 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.15 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3CO), 2.10–2.40 (m, 3 H, OH, CH and NCCH), 2.65 (ddd, J = 17.5, 6.2, 1.2 Hz, 1 H, CH_2CO), 2.89 (dd, J = 17.5, 6.2 Hz, 1 H, CH_2CO), 3.14 (ddd, J = 12.3, 9, 1.5 Hz, 1 H, NCH_2), 3.53–3.70 (m, 4 H, NCH, NCH_2 and OCH_2), 4.55 (s, 2 H, $ArCH_2O$), 5.22 (ddd, J = 10, 6.2, 3.8 Hz, 1 H, OCH), 7.30–7.40 (m, 5 H, ArH); mass spectrum, m/e (relative intensity) 346 (3, parent – H_2O), 301 (parent – HOAc), 177 (27), 136 (100), 91 (93); exact mass calcd for $C_{20}H_{27}NO_5$ – H_2O m/e 346.1654, found m/e 346.1663.

(+)-7(*S*)-[(Benzyloxy)methyl]-1(*R*)-hydroxy-6(*S*)-(2-hydroxyprop-2-yl)-7a(*R*)-hexahydro-3*H*-pyrrolizin-3-one (48). To a mixture of 580 mg (1.49 mmol) of formate **46** and 249 mg (0.63 mmol) of alcohol **47**, prepared as described above, was added 20 mL of 0.25 N aqueous methanolic sodium hydroxide (methanol–water, 4:1) in one portion at 0 °C. The mixture was allowed to reach room temperature over a period of 2 h, diluted with 150 mL of ether, and washed with 70 mL of brine. The aqueous phase was extracted with two 100-mL portions of chloroform. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 641 mg (95%) of diol **48** as a pale yellow oil: $[\alpha]^{20}_D$ +6.72° (ethanol, c 1.3); IR (CH_2Cl_2) 3400 (br), 1680 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.12 (s, 6 H, CH_3), 2.00–2.30 (m, 2 H, CH), 2.63 (d, J = 7 Hz, 2 H, CH_2CO), 3.00–3.98 (m, 5 H, NCH_2, OCH_2 and NCH), 4.05–4.25 (m, 1 H, OCH), 4.50 (br s, 2 H, $ArCH_2$), 7.30 (s, 5 H, ArH); mass spectrum, m/e (relative intensity) 319 (parent, weak), 301 (10), 177 (20), 136 (68), 106 (32), 105 (34), 91 (100), 77 (32), 59 (20); exact mass calcd for $C_{18}H_{23}NO_3$ – H_2O, m/e 301.1678, found m/e 301.1686.

1(*R*)-Hydroxy-7(*S*)-(hydroxymethyl)-6(*S*)-(2-hydroxyprop-2-yl)-7a(*R*)-hexahydro-3*H*-pyrrolizin-3-one (50). To a suspension of 1.50 g of 5% palladium on activated charcoal in 60 mL of absolute ethanol was added 3.19 g of diol **48** in one portion. The mixture was shaken under 50 psi of hydrogen pressure at room temperature for 42 h, filtered through Celite, and concentrated in vacuo to give 2.26 g of a colorless oil. The oil was charomatographed over 40 g of silica gel (ethyl acetate–methanol, 7:1 gradually increased to 5:1) to give 2.20 g (96%) of triol **50** as a colorless oil: IR (CH_2Cl_2) 3300 (br), 1650 cm^{-1}; NMR (90 MHz, D_2O) δ 1.22 (s, 6 H, CH_3), 2.00–2.50 (m, 2 H), 2.65–2.85 (m, 2 H), 3.00–3.30 (m, 1 H, NCH), 3.40–3.90 (m, 4 H), 4.30–4.55 (m, 1 H, OCH); mass spectrum, m/e (relative intensity) 229 (parent, 34), 211 (86), 180 (58), 140 (77), 127 (43), 110 (43), 97 (43), 95 (43), 91 (43), 81 (56), 68 (100), 59 (69), 57 (69); exact mass calcd for $C_{11}H_{19}NO_4$ – H_2O, m/e 211.1208, found m/e 211.1214.

1(*R*)-Acetoxy-7(*S*)-(acetoxymethyl)-6(*S*)-(2-hydroxyprop-2-yl)-7a(*R*)-hexahydro-3*H*-pyrrolizin-3-one (51). To a solution of 506 mg (2.22 mmol) of triol **50** in 4 mL of anhydrous pyridine was added 1.00 g (9.80 mmol) of acetic anhydride in one portion. The mixture was stirred at room temperature for 2.5 h. The solvent and excess acetic anhydride were removed in vacuo to give 897 mg of a yellow oil which was chromatographed over 35 g of silica gel (ethyl acetate gradually changed to ethyl acetate–methanol, 10:1) to afford 648 mg (94%) of diacetate **51** as a white crystalline solid: mp 103–104.5 °C; IR (CH_2Cl_2) 1740, 1700, 1260 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.23 (s, 6 H, CH_3), 2.00–3.20 (m with two singlets at 2.03 and 2.07, 12 H), 3.50–4.50 (m, 4 H, NCH and CH_2O), 5.00–5.35 (m, 1 H, OCH); mass spectrum, m/e (relative intensity) 298 (4, parent – CH_3), 253 (50, parent – AcOH), 253 (8), 193 (75, parent – 2AcOH), 175 (35), 136 (67), 123 (35), 96 (25), 60 (100). Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.48; H, 7.40. Found: C, 57.10; H, 7.40.

1(*R*)-Acetoxy-7(*S*)-(acetoxymethyl)-7a(*S*)-hexahydro-6-(*R*)-iodo-3*H*-pyrrolizin-3-one (52), 1(*R*)-Acetoxy-7(*S*)-(acetoxymethyl)-7a(*S*)-hexahydro-6(*S*)-iodo-3*H*-pyrrolizin-3-one (53), and 1(*R*)-Acetoxy-7-(acetoxymethyl)-1,2,5,7a(*S*)-tetrahydro-3*H*-pyrrolizin-3-one (55). To 1.37 g (4.37 mmol) of diacetate **51** in 320 mL of carbon tetrachoride was added 2.52 g (11.66 mmol) of yellow mercuric oxide and 3.01 g (11.87 mmol) of iodine. The mixture was warmed in an 85 °C oil bath for 3 h and filtered. The filtrate was washed with two 100-mL portions of saturated aqueous sodium metabisulfate and 100 mL of brine. The aqueous washes were extracted with two 100-mL portions of chloroform. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 1.6 g of an orange oil. The oil was chromatographed over silica gel (ethyl acetate–hexane, 2:3 gradually increased to 2:1) to give 1.41 g (85%) of a mixture of iodo amides **52** and **53** and 65 mg of olefin **55** (6%). Careful chromatography (twice, 80 g and 50 g silica gel, ethyl acetate–hexane, 2:3 gradually increased to 2:1) afforded pure samples of **52** and **53**. Iodoamide **52**: IR (CH_2Cl_2) 1740, 1710, 1240 cm^{-1}; NMR (200 MHz, $CDCl_3$), δ 1.62 (dtd, J = 9.9, 6.6, 6.6 Hz, 1 H, CH), 2.06 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 2.62 (dd, J = 18, 8.3 Hz, 1 H, CH_2CO), 2.96 (dd, J = 18, 8.3 Hz, 1 H, CH_2CO), 3.82 (br d, J = 13 Hz, 1 H, NCH_2), 3.95 (dd, J = 9.5, 4.7 Hz, 1 H, NCH), 4.17 (dd, J = 12, 7 Hz, 1 H, OCH_2), 4.29 (dd, J = 12, 7 Hz, 1 H, OCH_2), 4.48 (dd, J = 14, 6 Hz, 1 H, NCH_2), 4.30 (dt, J = 6, 2.4 Hz, 1 H, CHI), 5.31 (dt, J = 8.3, 4.7 Hz, 1 H, OCH); mass spectrum, m/e (relative intensity) 321 (8, parent – AcOH), 261 (100, parent – 2AcOH), 152 (15), 134 (45), 128 (14), 126 (8), 107 (8), 106 (62), 82 (15), 81 (21), 68 (20); exact mass calcd for $C_{12}H_{16}NO_5I$ – AcOH, m/e 320.9854, found m/e 320.9858.

Iodoamide **53**: mp 75–76 °C; IR (CH_2Cl_2) 1740, 1710, 1240 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.07 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 2.50–3.20 (m, 3 H, CH_2CO and NCCH), 3.50–4.50 (m, 6 H, NCH_2, NCH, OCH_2 and CHI), 5.33 (m, 1 H, OCH); mass spectrum, m/e (relative intensity) 321 (63, parent – AcOH), 261 (100), 254 (26, parent – I), 194 (25), 134 (58), 107 (37), 81 (47); exact mass calcd for $C_{12}H_{16}NO_5I$ – AcOH, m/e 320.9854, found m/e 320.9858.

1(*R*)-Acetoxy-7(*S*)-(acetoxymethyl)-7a(*S*)-hexahydro-3*H*-pyrrolizin-3-one (54). A mixture of 1.77 g (4.64 mmol) of iodoamides **52** and **53**, 2.75 g (9.07 mmol) of tri-*n*-butyltyin hydride, and 10 mg of AIBN in 24 mL of toluene was stirred at 80 °C for 30 min. The resulting mixture was concentrated in vacuo and chromatographed over 140 g of silica gel to give 1.08 g (91%) of diacetate **54** as a pale yellow oil: IR (CH_2Cl_2) 1740, 1700, 1240 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.00 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 1.95–3.25 (m, 6 H, CH_2CO, CH, CH_2, and NCH), 3.50 (m, 2 H, NCH), 4.1 (m, 2 H, CH_2O), 5.00–5.30 (m, 1 H, OCH); mass

spectrum, m/e (relative intensity) 255 (parent, weak), 195 (25), 135 (100), 107 (12), 82 (25).

(-)-Hastanecine (1). To a suspension of 1.00 g (26.3 mmol) of lithium aluminum hydride in 60 mL of tetrahydrofuran was added 1.05 g (4.11 mmol) of diacetate **54** in one portion. The mixture was heated under reflux for 30 min and cooled to room temperature. To the mixture was added sequentially 1.5 mL of tetrahydrofuran, 500 mL of water, 500 μL of 6% aqueous sodium hydroxide, and 500 μL of water. The resulting slurry was stirred for 5 min and filtered through Celite. The filtrate was concentrated in vacuo to give 1.09 g of a white solid which was chromatographed over 50 g of silica gel (methanol–concentrated ammonium hydroxide, 50:1) to give 582 mg (90%) of (-)-hastanecine (1): mp 112.5–113.5 °C (lit.[28] mp 113–114 °C); $[\alpha]^{25}_D$ -9.72° (*c*, 1.15 methanol), $[\alpha]^{25}_D$ -10.0° (*c*, 0.725 ethanol) [lit.[25] $[\alpha]^{20}_D$ -10.0° (*c*, 0.43 ethanol), $[\alpha]_D$ -9.1° (*c*, 0.43 methanol)]; IR (CH_2Cl_2) 3300 (br) cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.58–1.80 (m, 1 H), 1.86–2.05 (m, 2 H), 2.05–2.22 (m, 1 H), 2.45–2.58 (m, 4 H, NCH, OH and CH), 2.60–2.75 (m, 1 H, NCH), 3.19–3.35 (m, 3 H, NCH and NCH_2), 3.59 (dd, J = 10.6, 7.6 Hz, 1 H, OCH_2), 3.86 (dd, J = 10.8, 4.2 Hz, 1 H, OCH_2), 4.08–4.17 (m, 1 H, OCH); mass spectrum, m/e (relative intensity) 157 (parent, 8), 113 (18), 82 (100); exact mass calcd for $C_8H_{15}NO_2$ m/e 157.1103, found, m/e 157.1108. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.11; H, 9.62. Found: C, 61.11; H, 9.47.

1(*R*)-Acetoxy-7-(acetoxymethyl)-1,2,5,7a(*S*)-tetrahydro-3*H*-pyrrolizin-3-one (55). To 370 mg (0.97 mmol) of iodo amide **52** in 30 mL of dry benzene was added 190 mg (1.25 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in one portion. The solution was stirred at room temperature until TLC analysis showed no **52** was left (3.5 h) and diluted with 30 mL of dichloromethane. The mixture was concentrated in vacuo and the residual dark brown oil (598 mg) was chromatographed over 60 g of silica gel (ethyl acetate–hexane, 3:2 gradually increased to 2:1) to give 201 mg (81%) of diacetate **55** as a yellow oil: IR(CH_2Cl_2) 1745, 1705, 1240 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.03 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 2.76 (dd, J = 9, 3 Hz, 2 H, CH_2CO), 3.50–4.23 (m, 1 H, NCH), 4.25–4.90 (m, 4 H, NCH and OCH_2), 5.00–5.40 (m, 1 H, OCH), 5.87 (br s, 1 H, =CH).

(-)-Heliotridine (2). To a solution of 101 mg (0.40 mmol) of diacetate **55** in 6 mL of dry tetrahydrofuran was added 99 mg (2.6 mmol) of lithium aluminum hydride in one portion. The mixture was heated at reflux for 30 min followed by dilution with 15 mL of tetrahydrofuran and sequential addition of 100 μL of water, 70 μL of 6% aqueous sodium hydroxide, and 100 μL of water. The resulting slurry was stirred for 5 min and filtered through Celite. The filtrate was concentrated in vacuo to give 49 mg of a yellow oil which was chromatographed over 15 g of silica gel (methanol–concentrated ammonium hydroxide, 50:1) to give 38 mg (62%) of **2** as a pale yellow crystalline solid: mp 116–117 °C (lit.[28] mp 117.5–118 °C); $[\alpha]^{18}_D$ -31.9° (*c*, 0.35 methanol), $[\alpha]^{18}_D$ -32.1° (*c*, 0.35 ethanol) [lit.[28] $[\alpha]^{18}_D$ +32.0° (*c*, 10.0 methanol)]; IR (CH_2Cl_2) 3300 (br) cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.55–2.00 (m, 2 H, CH_2), 2.50–2.80 (m, 1 H, NCH), 3.05–3.45 (m, 2 H, NCH), 3.55–4.25 (m, 5 H, OCH_2, NCH and OCH), 5.15 (br s, 2 H, OH), 5.45 (br s, 1 H, =CH); mass spectrum, m/e (relative intensity) 155 (20, parent), 110 (55), 93 (16), 79 (100), 67 (15); exact mass calcd for $C_8H_{13}NO_2$ m/e 155.0946, found m/e 155.0950.

Acknowledgment. We thank Richard Weisenberger for recording mass spectra at The Ohio State University Chemical Instrument Center. Financial support from the National Institutes of Health is gratefully acknowledged. We also thank the NIH for a grant (GM-27431) to Ohio State University in support of the acquisition of a Bruker WM-200 MHz NMR spectrometer used during the course of this research.

Supplementary Material Available: Experimental procedures for the preparation of **6a**, **6b**, **7**, **8**, **9**, **11b**, **11c**, **12b**, **12c**, **13**, **14a**, **15**, **26a**, **26b**, **26c**, **27a**, **27b** (11 pages). Ordering information is given on any current masthead page.

2-Siloxy-Substituted Methyl Cyclopropanecarboxylates as Building Blocks in Synthesis: Efficient One-Pot Conversion to γ-Butyrolactones

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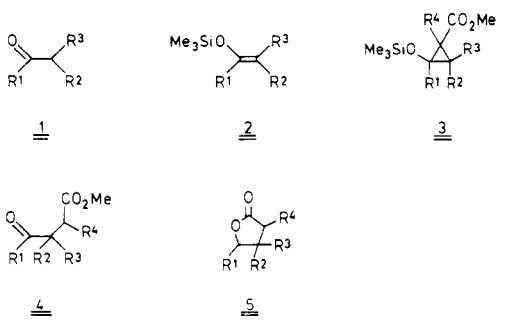
Received June 8, 1984

A high-yield one-pot transformation of the easily available 2-siloxy-substituted methyl cyclopropanecarboxylates **3** to γ-butyrolactones **5** is described. According to the regioselective preparation of **3**, isomeric lactones **5** can be synthesized without problems. Modified procedures delivering α-deuterated or side-chain functionalized lactones are disclosed.

Due to the occurrence in natural products and other biologically active molecules,[1] γ-butyrolactones (dihydro-2(3*H*)-furanones) are highly desirable targets in organic synthesis.[2] In addition, they can be versatile starting materials for other important compound classes (e.g., furans, cyclopentenones, etc.).[3]

Chart I



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