2-Azonia-Cope Rearrangement in *N*-Acyliminium Cyclizations

Hugo Ent, Henk de Koning, and W. Nico Speckamp*

Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Received July 16, 1985

Acid-induced cyclizations of *N*-(2′-aryl-3′-butenyl)-5-hydroxy-2-pyrrolidinones to give indolizidine and pyrrolizidine derivatives were studied. The mechanism of the pyrrolizidine formation, proceeding via 2-azonia-Cope rearrangement of the initially formed secondary *N*-acyliminium ion (type **7**) to a primary *N*-acyliminium ion (type **10**), was proved by trapping the latter ion as (hydroxymethyl)pyrrolidine derivative (type **14**) and its subsequent conversion into indolizidine and pyrrolizidine derivatives. Reaction rate and product distribution depend on the substitution pattern of the 2′-aryl substituent. Certain substituents provoke cyclization onto the benzene ring leading to tetrahydropyrrolo[2,1-*a*]isoquinolinones.

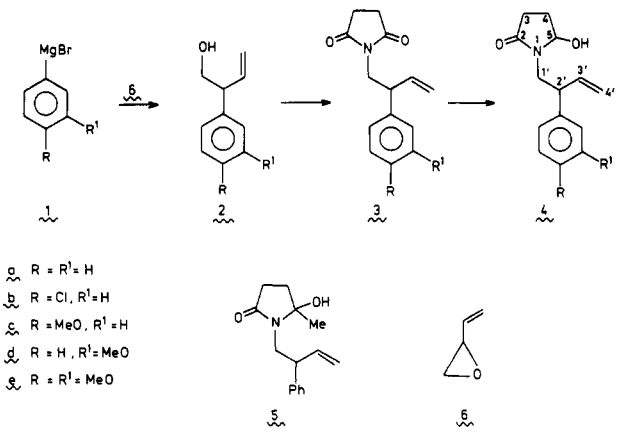
The stereoselective cationic π-cyclization of *N*-acyliminium ions has found wide application in the synthesis of heterocyclic systems.[1] Iminium ions of type **7** (R = H or Me), with a γ,δ-unsaturated side chain as π-nucleophile, generally give rise to the formation of six-membered ring products **8** and **9** (Scheme II). Upon introduction of certain allylic substituents (e.g., R = OMe), however, the reaction outcome may completely change, giving rise to the formation of mainly five-membered ring products **12** and **13**. The latter process presumably proceeds via an initial cationic 2-aza-Cope rearrangement[2] (2-azonia[3,3]sigmatropic rearrangement), followed by cyclization of the newly formed *N*-acyliminium ion **10**.[3]

In connection with our current interest in the synthesis of pyrrolizidines[4] and related ring systems, we decided to study this aza-Cope rearrangement in some detail. Direct proof for the supposed reaction pathway would be obtained if the rearranged *N*-acyliminium ion could be captured and isolated (e.g., as **14**) and subsequently converted into the usual cyclization products.[5] Indeed it was found that a (substituted) phenyl group in the allylic position of the 3-butenyl side chain provoked such behavior. Owing to the moderate rate of the cyclization reaction in this case, the nucleophilic solvent could intercept the intermediate **10**. Moreover, a marked influence of the aromatic substituents on the course of the reaction is reported.[6]

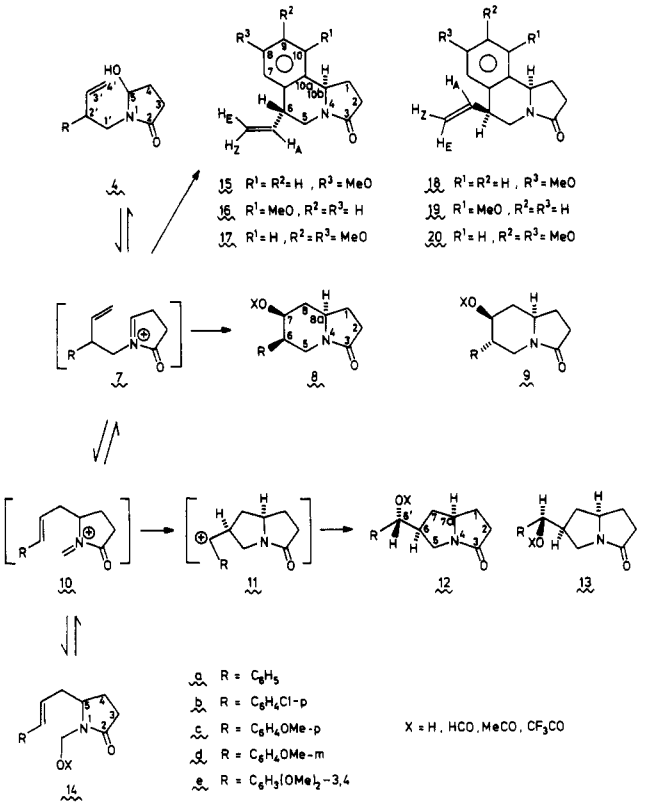
Results and Discussion

The desired *N*-acyliminium ion precursors were prepared in moderate yields as summarized in Scheme I. Reaction[7] of the arylmagnesium bromides **1** with butadiene monoxide **6** afforded the homoallylic alcohols **2**. Oxidation–reduction coupling[8] with succinimide gave the imides **3**. Subsequent reduction[9] with $NaBH_4/H^+$ provided the corresponding hydroxy lactams **4**. The tertiary alcohol **5**

Scheme I



Scheme II. Cyclization Pathway for Aryl-Substituted *N*-Acyliminium Ions



was obtained from the Grignard reaction of imide **3a** with methylmagnesium chloride in THF.

Cyclization experiments on some of the hydroxy lactams, performed under standard conditions in formic acid at 20

(1) For reviews see: Speckamp, W. N. *J. R. Neth. Chem. Soc.* **1981**, *100*, 345. Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
(2) For recent examples, see: Overman, L. E.; Jacobsen, E. J.; Doedens, R. J. *J. Org. Chem.* **1983**, *48*, 3393 and references cited therein.
(3) (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. *Ibid.* **1982**, *23*, 3807. (c) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235 and references of the Hart group cited therein.
(4) For a review see: Robins, D. J. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1979; Vol. 24, p 247.
(5) Though in a similar case with an allenyl side chain the rearranged *N*-acyliminium ion has been captured, its subsequent cyclization could not be effected.[3a]
(6) For a preliminary report of a portion of the research described here, see: Ent, H.; De Koning, H.; Speckamp, W. N. *Tetrahedron Lett.* **1983**, *24*, 2109.
(7) Rose, C. B.; Smith, C. W., Jr. *Chem. Commun.* **1969**, 248.
(8) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(9) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

0022-3263/86/1951-1687$01.50/0

Table I. Cyclization Studies on the Hydroxy Lactams

entry	precursor	reaction[a] medium	reaction[a] time (h)	product ratio 8 + 9	product ratio 12 + 13[b]	product ratio 14	product ratio 15–20
1	**4a**	HCO_2H	4	11	89	0	
2	**4b**	HCO_2H	4	19	81	0	
3	**4c**	HCO_2H	4	0	100	0	
4	**4a**	2:3 HCO_2H/AcOH	18	7[c,d]	77[d]	4[d]	
5	**4a**	TFA/CH_2Cl_2	0.5 (5 °C)	0	44[d]	53[d]	
6	**4b**	2:3 HCO_2H/AcOH	3.5	*e*	*e*	60[d]	
7	**4c**	TFA/CH_2Cl_2	0.5 (5 °C)	0	94[d]	0	
8	**14a** (X = H)	2:3 HCO_2H/AcOH	18	8	84	8	
9	**14b** (X = HCO, MeCO)	HCO_2H	5	10	90	0	
10	**4d**	2:3 HCO_2H/AcOH	18[f]	0	26[d]	0	63[d,g]
11	**4e**	2:3 HCO_2H/AcOH	18	0	0	0	78[d,h]

[a] Room temperature unless otherwise stated. [b] Ratio **12:13** = 1:1. [c] Ratio **8a:9a** = 2:3. [d] Isolated yield. [e] Not determined. [f] In a subsequent experiment the reaction appeared to be completed within 12 min. [g] **15** (37%), **18** (23%), 7:1 mixture of **16** + **19** (3%). [h] **17:20** = 16:9.

Table II. Cyclization of 4a[a] in 2:3 HCO_2H/AcOH at 20 °C

reactn time (h)	product composition[b] (mol %; ±2) **4a**	**8a**[c] + **9a**[c]	**12a**[c] + **13a**[c]	**14a**[c]
0.17	84			16
1	32	<1	12	56
4	4	5	26	65
20		7	66	27
68		10	88	2

[a] 1.3 mmol/6 mL. [b] Determined by ^1H NMR after workup. [c] Mixture: X = HCO, MeCO.

Table III. Cyclization of 4b[a] in 2:3 HCO_2H/AcOH at 21 °C

reactn time (h)	product composition[b] (mol %; ±2) **4b**	**8b**[c] + **9b**[c]	**12b**[c] + **13b**[c]	**14b**[c]
0.25	84			16
1	48	3	2	47
2	22	5	5	68
4	5	9	12	74
7	3	10	19	68
25		12	43	45
47		14	61	25
72		16	70	14

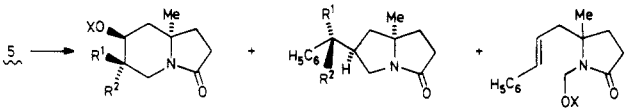
[a] 0.77 mmol/8 mL. [b] Determined by ^1H NMR after workup. [c] Mixture: X = HCO, MeCO.

Table IV. Cyclization of 4c[a] in 2:3 HCO_2H/AcOH at 20 °C

reactn time (h)	product composition[b] (mol %; ±2) **4c**	**12c**[c] + **13c**[c]	**14c**[c]
0.12	65	26	9
1	16	73	11
3.5		99	<1

[a] 0.77 mmol/5 mL. [b] Determined by ^1H NMR after workup. [c] Mixture: X = HCO, MeCO.

Table V. Cyclization of 5[a] in 2:3 HCO_2H/AcOH at 21 °C



21 $R^1 = C_6H_5$, $R^2 = H$ **22** $R^1 = H$, $R^2 = C_6H_5$ **23** $R^1 = OX$, $R^2 = H$ **24** $R^1 = H$, $R^2 = OX$ **25**

X = HCO, MeCO

reactn time (h)	product composition[b] (mol %; ±2) **5**	**21**[d] + **22**[d]	**23**[d] + **24**[d]	**25**[d]
0.20	82	*c*		18
0.50	51	*c*	10	39
1	24	*c*	26	50
2	7	*c*	67	26
4	1	*c*	85	14
7			99	1
25		7	93	

[a] 0.57 mmol/7 mL. [b] Determined by ^1H NMR after workup. [c] Could not be determined because of overlap with absorptions of **5** and **25**. [d] Mixture: X = HCO, MeCO.

°C for 4 h, followed by workup and NMR analysis of the crude products, showed markedly differing results (Table I). Whereas cyclization of the *p*-methoxyphenyl compound **4c** gave a 1:1 mixture of the isomeric pyrrolizidines **12c** and **13c** (X = HCO) (entry 3), the unsubstituted phenyl derivative **4a** produced a 89:11 mixture of pyrrolizidines **12a** and **13a** (X = HCO) and indolizidines **8a** and **9a** (X = HCO) (entry 1). In contrast to the pyrrolizidine formates, the epimeric indolizidine formates **8a** and **9a** (X = HCO) could not be separated by flash chromatography.[10] Upon treatment of the ester mixtures with aqueous ethanolic KOH, however, the pure alcohols **12a** and **13a** (X = H) and **9a** (X = H) could be obtained after flash chromatography. Under these conditions the formate **8a** (X = HCO), in which the ester function is shielded by the cis-phenyl substituent, resists hydrolysis, thereby supporting the assigned structure. Cyclization of the *p*-chlorophenyl derivative **4b** gave even more of the six-membered ring compound; a 81:19 mixture of pyrrolizidines **12b** and **13b** (X = HCO) and indolizidines **8b** and **9b** (X = HCO) was obtained (entry 2).

Cyclization of the unsubstituted phenyl hydroxy lactam **4a** in the milder acidic 2:3 mixture of formic acid and acetic acid[11] for 18 h at room temperature afforded 1:1 mixtures of the C_6-epimeric pyrrolizidine esters **12a** and **13a** (X = HCO, MeCO) in 77% yield, together with 7% of a 2:3 mixture of the C_6-epimeric indolizidine esters **8a** and **9a** (X = CHO, MeCO), and 4% of the primary hydroxy lactam **14** (X = H), the captured aza-Cope intermediate (entry 4).

In view of the marked differences in the above cyclizations of the various hydroxy lactams, the reactions in the 2:3 mixture of formic and acetic acid were followed in time (Tables II–V). The tables show a relatively fast conversion of the starting secondary hydroxy lactam into the primary hydroxy lactam, followed by the slower formation of cyclization products. The most interesting fact from the tables, however, is the continuing formation of indolizidine derivatives, even when the starting hydroxy lactam has disappeared, indicating a dynamic equilibrium between the secondary *N*-acyliminium ion **7** and the primary *N*-acyliminium ion **10**. The faster cyclization of the *p*-

(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(11) In the preliminary publication[6] formic acid was erroneously reported as the cyclization medium, but afterwards we learned that by some mistake the acid we used consisted of a 2:3 mixture of formic and acetic acid.

methoxyphenyl compound **4c** (Table IV), compared to the phenyl compound **4a** (Table II), is apparently due to the rapid ring closure of the primary hydroxy lactam **14c** to the pyrrolizidines **12c** and **13c**. The latter cyclization might be favored because of the relative stability of the intermediary carbenium ion **11c**. In case of less stabilization, like in **11a** and especially **11b** (Table III), the cyclization proceeds slower, and competitive indolizidine formation also occurs. Although the disappearance of the tertiary hydroxy lactam **5** (Table V) proceeds faster than that of the corresponding secondary hydroxy lactam **4a**, indolizidine derivatives **21** and **22** (X = HCO, MeCO) are formed in a comparable amount. This observation may be related to the presence of an unsubstituted phenyl group, thereby accentuating the decisive role of the aryl substituent on the product composition.

Upon treatment of **4a** with trifluoroacetic acid in dichloromethane for 0.5 h at 5 °C the primary hydroxy lactam **14a** (X = H) could be isolated in 53% yield, together with 1:1 mixtures of pyrrolizidine epimers **12a** and **13a** (X = H, 17%; X = CF_3CO, 27%) (Table I, entry 5). Isolation of the primary hydroxy lactams is also possible in case of the slow cyclizations in the formic–acetic acid mixture. Thus, the *p*-chlorophenyl derivative **4b** afforded 60% of a 2:3 mixture of the esters **14b** (R = HCO, MeCO) after 3.5 h at 22 °C (entry 6). On the contrary the *p*-methoxyphenyl compound **4c** gave only pyrrolizidine products upon reaction in trifluoroacetic acid for 0.5 h at 5 °C (entry 7).

When the primary hydroxy lactam **14a** (X = H) was treated with the 2:3 mixture of formic and acetic acid for 18 h at room temperature, according to NMR analysis the crude product consisted of a mixture of the pyrrolizidine esters **12a** and **13a** (X = HCO, MeCO; 84%), the indolizidine esters **8a** and **9a** (X = HCO, MeCO; 8%), and starting material (8%) (entry 8). Upon reaction of the *p*-chlorophenyl lactams **14b** (X = HCO, MeCO) for 5 h at 25 °C in formic acid, a mixture of pyrrolizidines **12b** and **13b** (X = HCO; 90%) and indolizidines **8b** and **9b** (X = HCO; 10%) was produced (entry 9). The results of derivatives of the primary hydroxy lactams, compared with those of the secondary hydroxy lactams, therefore, support the proposed[3] reaction path.

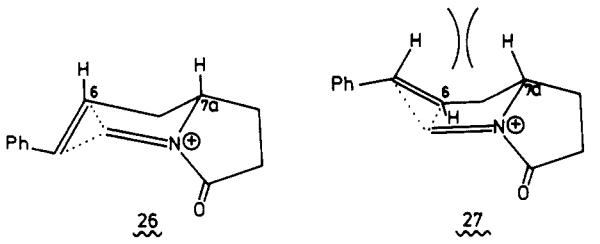
The marked influence of aromatic methoxy substituents is further demonstrated by the cyclization of *m*-methoxyphenyl hydroxy lactam **4d**, which is completed within 12 min in a 2:3 mixture of formic and acetic acid at 20 °C (entry 10). The electron-rich phenyl ring is now in the proper position to act as a π-nucleophile, giving rise to the formation of a considerable amount of isomeric tricyclic products. Upon saponification of the crude product **15** (37%), **18** (23%) and a 7:1 mixture (3%) of **16** and **19** were obtained in addition to a 1:1 mixture (26%) of pyrrolizidines **12d** and **13d** (X = H). Finally, the 3,4-dimethoxyphenyl hydroxy lactam **4e** only afforded a 16:9 mixture (78%) of the stereoisomers **17** and **20**, which could be separated (entry 11).

Stereochemical Assignments

Identification of the diastereomers occurred on the basis of ^{1}H NMR methods, including 2D NMR and 1D multipulse experiments, which allowed unambiguous assignment of the absorptions.

The cis relation between H_6 and H_{7a} in the pyrrolizidines **12a** and **13a** (X = H) was secured by NOE-difference experiments. The relative configuration at $C_{6'}$ followed from Dreiding models, indicating close proximity of the O-atom of the OH group to $H_{7\alpha}$ and $H_{7\beta}$ in the favorable conformation for **12a**, which would cause a downfield shift

Chart I



for these protons.[12] In case of **13a**, on the other hand, the O-atom is in close proximity to $H_{5\alpha}$ and $H_{5\beta}$, which would consequently be deshielded. These predictions are in accordance with the spectral data, which show for **12a** $H_{7\alpha}$ 0.52 ppm and $H_{7\beta}$ 0.26 ppm downfield from the corresponding protons of **13a**, while in the case of **13a** $H_{5\alpha}$ and $H_{5\beta}$ are found at 0.4 and 0.33 ppm downfield from $H_{5\alpha}$ and $H_{5\beta}$ in **12a**. The assignments are supported by NOE-difference spectra of **13a**, which prove interactions of $H_{6'}$ with $H_{5\beta}$ and $H_{7\beta}$, as would be expected from the favorable conformation (Dreiding model). The relative configurations of the indolizidines **8a** (X = HCO) and **9a** (X = H) were also secured by the ^{1}H NMR spectra. In addition for **8a** strong interactions were found in NOE-difference experiments for H_7 with H_{8a} and an aromatic H and for H_{8a} with H_6 and H_7. The relative configurations of the other pyrrolizidines and indolizidines with the substituted phenyl substituents were assigned by analogy with the above results. The configurational assignment of the 6α- and 6β-vinylpyrrolo[2,1-*a*]isoquinoline derivatives **15–20** was based upon the ^{1}H NMR coupling constants $^3J_{5,6}$, compared to those of the corresponding 6α- and 6β-phenyl derivatives recently described by Maryanoff.[13] For the 6α-vinyl compounds (**15–17**) $J_{5\alpha,6\beta}$ = ~10–11.5 and $J_{5\beta,6\beta}$ = ~5.9–6.1 Hz were observed (6α-phenyl[13]: 11 and 6 Hz) and for the 6β-vinyl isomers (**18–20**) $J_{5\alpha,6\alpha}$ = ~4.1–4.2 and $J_{5\beta,6\alpha}$ = ~1.1–2.0 Hz (6β-phenyl[13]: 5 and 2 Hz).

Stereochemistry

The pyrrolizidine derivatives formed upon 5-exo cyclization of the primary *N*-acyliminium ions of type **10** possess a cis relation between H_6 and H_{7a}. The high degree of stereocontrol in this cyclization may be rationalized by chair-like transition state[14] **26** with the sterically more demanding phenyl substituent in an equatorial orientation. The resulting carbenium ion **11** reacts with the nucleophilic solvent to give the 1:1 mixture of $C_{6'}$-epimers. Eventual formation of the isomers with a trans relation between H_6 and H_{7a} would have to proceed via less favorable boat-like transition state **27**.

The high stereoselectivity in the cyclization of the secondary *N*-acyliminium ions of type **7** has been attributed to a chair-like transition state leading to preferential formation of indolizidines with a C_7-equatorial substituent.[1] In case of an allylic methyl substituent (**4**, R = Me), the 6,7-trans-substituted indolizidine is formed with 89% stereoselectivity.[15] However, in the phenyl-substituted **4a**, the stereocontrol is almost lost, leading to a 2:3 mixture of the 6,7-cis- and -trans- substituted indolizidines. The diminished stereoselectivity may be rationalized in terms of a competing indolizidine formation by cyclization of **10a**

(12) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Specroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; p 81.
(13) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062.
(14) Suggested to us by Dr. H. Hiemstra.
(15) Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1991.

in 6-endo fashion. Since concurrent isomerization of **10a** in acid may also be expected to run facile, the stereochemical control is greatly diminished. Conversely, the reactions studied are to our knowledge the first examples of a dual reaction behavior of *N*-acyliminium ions, both forms of **7** and **10** leading to the same products.

The stereochemistry of the cyclization of *N*-acyliminium ions to pyrrolo[2,1-*a*]isoquinolines has extensively been discussed by Maryanoff et al.[13] who found an isomeric ratio $6\alpha/6\beta$ of 93:7 in case of a phenyl substituent at C_6 and 72:28 for a methyl substituent. We observed diminished stereocontrol in case of the 6-vinyl substituent: **15**:**18** = 37:23 and **17**:**20** = 16:9.

Experimental Section

General Methods. Melting points were measured with a Leitz hot-stage microscope and are uncorrected as are boiling points. ^{1}H NMR spectra were recorded on Varian XL-100-12 or Bruker WM-250 spectrometers with $CDCl_3$ as solvent. Data are reported as follows: chemical shift in ppm relative to $(CH_3)_4Si$ as an internal standard [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants in hertz, integration, interpretation]. ^{13}C NMR spectra were recorded on a Bruker WM-250 instrument. IR spectra were taken with a Perkin-Elmer 257 spectrometer with $CHCl_3$ as solvent, unless otherwise noted; absorptions are given in cm^{-1}. Mass spectra [reported as MS, *m/e* (relative intensity)] were obtained with a Varian Mat 711 instrument at 70 eV ionization energy. Samples on which exact masses were measured exhibited no significant peaks at *m/e* greater than those of the parent peak. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ shortly before use. After workup, all organic layers were dried over anhydrous $MgSO_4$. The term "in vacuo" refers to solvent removal via a Büchi rotoevaporator at water aspirator pressure, followed by evacuation at 0.1 torr when deemed necessary. Flash chromatography[10] was performed over silica gel (E. Merck, Kieselgel 80, 230–400 mesh).

Preparation of the Arylbutenols 2a–d. General Procedure. The reaction assembly, already containing the Mg (1.95 g, 80.2 mmol), was flame-dried and cooled under N_2, after which 25 mL of dry ether was added. Then a solution of the aryl bromide **1** (73 mmol) in dry ether (25 mL) was added dropwise over 1 h under reflux. After having been cooled to 25 °C, a solution of butadiene monoxide **6** (5.0 g, 71.4 mmol) in dry ether (10 mL) was added dropwise under gentle reflux. The mixture was stirred for another 20 min under reflux and then poured into 100 mL of 2 M HCl and ice. Following separation the aqueous layer was extracted twice with ether. The combined organic layers were washed 3 times with brine, dried, and concentrated in vacuo, and the residual oil was distilled to afford the butenol **2** as a colorless oil.

2-(3,4-Dimethoxyphenyl)-3-buten-1-ol (2e). More drastic conditions were necessary in this case.[16] Thus a solution of 4-bromo-1,2-dimethoxybenzene (15.6 g, 73 mmol) in 30 mL of THF was added dropwise at 57–59 °C over a period of 6 h to a mixture of Mg (2.25 g, 93 mmol) in 45 mL of THF, containing a catalytic amount of iodine. Then epoxide **6** (4.7 g, 67 mmol) in 10 mL of THF containing 0.03 mL of $BrCH_2CH_2Br$ was added over 1 h, and the mixture was refluxed overnight. The mixture was then cooled, poured into 150 mL of saturated aqueous NH_4Cl and ice, and 2 times extracted with ether. The combined extracts were washed with brine, saturated $Na_2S_2O_3$ solution, and brine, dried, and concentrated in vacuo. Distillation gave 6.48 g of impure **2e**, bp 124–127 °C/0.01 torr, which was used as such in the next step.

General Procedure for the Synthesis of the Imides 3a–e. To a mixture of the alcohol **2** (25 mmol), 2.97 g (30 mmol) of succinimide and 7.86 g (30 mmol) of triphenylphosphine in 100 mL of THF under N_2, cooled in an ice–water bath, was slowly added a solution of 4.38 g (30 mmol) of dimethyl azodicarboxylate in 15 mL of THF. Stirring was continued overnight at room temperature. The mixture was concentrated in vacuo, and the residue was partioned between 100 mL of $CHCl_3$ and 100 mL of 5% aqueous KOH. The aqueous phase was extracted with two 50-mL portions of $CHCl_3$. The combined organic layers were dried, and the solvent was removed in vacuo. The residue was dissolved in a minimum amount of hot EtOAc and then cooled to room temperature to precipitate Ph_3PO. This was filtered off, and the filtrate again was concentrated and treated with EtOAc to remove Ph_3PO for the most part. The imides **3** were then obtained by flash chromatography (EtOAc–hexane, 2:3) or by distillation.

General Procedure for the Synthesis of the Hydroxy Lactams 4. To a solution of the imide **3** (12 mmol) in 100 mL of absolute ethanol cooled in an ice–water bath under N_2 was added 5 g of $NaBH_4$. The mixture was stirred at 0–5 °C for 4 h while a 3 M solution of HCl in ethanol was added at a rate of 2 drops every 1.5 min. The mixture was poured into 0.5 L of water and extracted with five 100-mL portions of CH_2Cl_2. The combined extracts were washed with brine and then dried. The solvent was carefully removed in vacuo. Though the subsequent cyclization may be carried out with this crude product, the pure diastereoisomeric mixture of hydroxy lactams obtained by flash chromatography (AcMe–CH_2Cl_2, 2:9) was preferred.

5-Hydroxy-5-methyl-1-(2-phenyl-3-butenyl)-2-pyrrolidinone (5). To a solution of imide **3a** (917 mg, 4.0 mmol) in 10 mL of dry THF under N_2 was added dropwise at room temperature 2.67 mL of a 3.3 M methylmagnesium chloride solution in THF. After stirring for another 3 h, a saturated aqueous solution of NH_4Cl was added, and the mixture was partitioned between water and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$, and the combined extracts were dried and concentrated in vacuo. Flash chromatography (AcMe–CH_2Cl_2, 1:4) gave 778 mg (79%) of **5** as an oil: IR 3370, 1678; ^{1}H NMR 1.25 (s, 1.5 H, CH_3), 1.26 (s, 1.5 H, CH_3), 4.99–5.22 (m, 2 H, $=CH_2$), 5.90–6.36 (m, 1 H, =CH), 7.19–7.38 (m, 5 H, ArH); exact mass (M – H_2O) calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1297.

Cyclization of Hydroxy Lactams. Example 1. *rel*-(6*R*,7a*S*)-Hexahydro-6-[(*S*)-hydroxyphenylmethyl]-3*H*-pyrrolizin-3-one (12a, X = H) and *rel*-(6*R*,7a*S*)-Hexahydro-6-[(*R*)-hydroxyphenylmethyl]-3*H*-pyrrolizin-3-one (13a, X = H). A solution of 0.60 g (2.6 mmol) of hydroxy lactam **4a** in 10 mL of a 2:3 mixture of formic acid and acetic acid was stirred for 5 days at room temperature and then concentrated in vacuo at about 1 torr. The residue was dissolved in 75 mL of CH_2Cl_2 and washed with aqueous $NaHCO_3$ and with brine. Concentration in vacuo afforded a colorless oil (0.63 g) which was dissolved in 10 mL of ethanol 98%. Then a solution of 177 mg (3.2 mmol) of KOH in 60 mL of ethanol 98% was added dropwise at 0–5 °C, and the mixture was stirred for 80 min. Upon addition of 60 mL of water, the mixture was extracted with three 30-mL portions of CH_2Cl_2. The combined extracts were washed with 25 mL of brine, dried, and concentrated in vacuo. Flash chromatography (AcMe–CH_2Cl_2, 1:3) gave the impure alcohols **12a** (X = H) (232 mg) and **13a** (X = H) (287 mg), which were purified by a second flash chromatographic separation.

Less polar alcohol 12a (X = H): mp 137–138 °C ($(i\text{-Pr})_2O$); IR 3360, 1666; ^{1}H NMR 1.32 (q, J = 11 Hz, 1 H, $H_{7\beta}$), 1.70 (m, 1 H, $H_{1\beta}$), 2.13 (m, 1 H, $H_{7\alpha}$), 2.24 (m, 1 H, $H_{1\alpha}$), 2.35 (ddd, J = 2, 9.5, 16 Hz, 1 H, H_2), 2.58 (m, 1 H, H_2), 2.73–2.88 (m, 2 H, $H_{5\alpha}$, H_6), 3.23 (m, 1 H, $H_{5\beta}$), 3.91 (m, 1 H, $H_{7\alpha}$), 4.53 (d, J = 7 Hz, 1 H, ArCH), 7.24–7.35 (m, 5 H, ArH); exact mass calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1265.

More polar isomer 13a (X = H): mp 131–131.5 °C ($(i\text{-Pr})_2O$); IR 3440, 1673; ^{1}H NMR 1.06 (q, J = 11 Hz, 1 H, $H_{7\beta}$), 1.61 (m, 2 H, $H_{1\beta}$, $H_{7\alpha}$), 2.12 (m, 1 H, $H_{1\alpha}$), 2.31 (ddd, J = 2, 9.5, 16 Hz, 1 H, H_2), 2.56 (m, 1 H, H_2), 2.77 (m, 1 H, H_6), 3.22 (dd, J = 9, 12 Hz, 1 H, $H_{5\alpha}$), 3.55 (dd, J = 8, 12 Hz, 1 H, $H_{5\beta}$), 3.83 (m, 1 H, $H_{7\alpha}$), 4.47 (d, J = 8 Hz, 1 H, ArCH), 7.26–7.33 (m, 5 H, ArH); exact mass calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1265.

Example 2. *rel*-(6*R*,7*S*,8a*R*)-7-(Formyloxy)-6-phenylhexahydro-2*H*-indolizin-3-one (8a, X = HCO), *rel*-(6*R*,7*R*,8a*S*)-7-Hydroxy-6-phenylhexahydro-2*H*-indolizin-3-one (9a, X = H), *rel*-(6*R*,7a*S*)-6-[(*S*)-(Formyloxy)-phenylmethyl]hexahydro-3*H*-pyrrolizin-3-one (12a, X = HCO), and *rel*-(6*R*,7a*S*)-6-[(*R*)-(Formyloxy)phenylmethyl]hexahydro-3*H*-pyrrolizin-3-one (13a, X = HCO). A solution of 0.25 g of **4a** in 15 mL of 98–100% formic acid was stirred for 4 h at 20 °C. Then 50 mL of CH_2Cl_2 was added, and the organic layer was washed with brine, a saturated $NaHCO_3$

(16) Ito, I.; Oda, N.; Ueda, T.; Nagat, S.-I.; Kume, S. *Chem. Pharm. Bull.* **1976**, *24*, 1072.

solution, and brine. The solution was dried and concentrated in vacuo. Repeated flash chromatographic separation (AcMe–CH_2Cl_2, 2:9) afforded with considerable loss the pure pyrrolizidine formates **12a** and **13a** and a mixture of indolizidine formates **8a** and **9a**. Of the latter mixture 19.7 mg (0.076 mmol) was treated with a solution of 5.1 mg (0.091 mmol) of KOH in 5 mL of 97% ethanol at 0–5 °C for 80 min and worked up as described in example 1. Flash chromatography provided 5.4 mg of formate **8a** (X = HCO) and 5.3 mg of alcohol **9a** (X = H).

Formate 8a (X = HCO): mp 142.5–144.5 °C ($CHCl_3$); IR 1729, 1676; ^1H NMR 1.37 (q, J = 11.5 Hz, 1 H, $H_{8\beta}$), 1.62–1.74 (m, 1 H, $H_{1\beta}$), 2.20–2.46 (m, 4 H, $H_{1\alpha}$, $H_{2\alpha}$, $H_{2\beta}$, $H_{8\alpha}$), 2.70–2.83 (m, 2 H, $H_{5\alpha}$, H_6), 3.66–3.80 (m, 1 H, H_{8a}), 4.20–4.32 (m, 1 H, $H_{5\beta}$), 5.15–5.26 (m, 1 H, H_7), 7.13–7.32 (m, 6 H, ArH, O_2CH); exact mass calcd for $C_{15}H_{17}NO_3$ 259.1208, found 259.1215.

Alcohol 9a (X = H); mp 162–163 °C (AcMe–CH_2Cl_2); IR 3390, 1672; ^1H NMR 1.36 (q, J = 11.7 Hz, 1 H, $H_{8\beta}$), 1.68–1.78 (m, 1 H, $H_{1\beta}$), 2.20–2.59 (m, 5 H, $H_{1\alpha}$, $H_{2\alpha}$, $H_{2\beta}$, H_6, $H_{8\alpha}$), 2.74 (t, J = 13.4 Hz, 1 H, $H_{5\alpha}$), 3.62–3.74 (m, 1 H, H_{8a}), 3.95 (dt, J = 4.3 and 10.4 Hz, respectively, 1 H, H_7), 4.22 (dd, J = 4.6, 13.4 Hz, 1 H, $H_{5\beta}$), 7.20–7.38 (m, 5 H, ArH); exact mass calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1265.

Less polar isomer 12a (X = HCO): mp 99–101 °C ($(i\text{-}Pr)_2O$); IR 1723, 1673; ^1H NMR 1.36 (q, J = 11 Hz, 1 H, $H_{7\beta}$), 1.75–1.89 (m, 1 H, $H_{1\beta}$), 2.20–2.38 (m, 2 H, $H_{1\alpha}$, $H_{7\alpha}$), 2.46 (ddd, J = 2.9, 16.5 Hz, 1 H, H_2), 2.65–2.80 (m, 1 H, H_2), 2.92 (dd, J = 9, 11 Hz, 1 H, $H_{5\alpha}$), 2.99–3.14 (m, 1 H, H_6), 3.24 (dd, J = 8, 11 Hz, 1 H, $H_{5\beta}$), 3.92–4.03 (m, 1 H, H_{7a}), 5.80 (d, J = 8 Hz, 1 H, ArCH), 7.32–7.38 (m, 5 H, ArH), 8.11 (s, 1 H, O_2CH); exact mass calcd for $C_{15}H_{17}NO_3$ 259.1208, found 259.1211.

More polar isomer 13a (X = HCO): IR 1726, 1673; ^1H NMR 1.12 (q, J = 11 Hz, 1 H, $H_{7\beta}$), 1.67–1.84 (m, 2 H, $H_{1\beta}$, $H_{7\alpha}$), 2.14–2.29 (m, 1 H, $H_{1\alpha}$), 2.41 (ddd, J = 1.7, 9.5, 16.7 Hz, 1 H, H_2), 2.60–2.71 (m, 1 H, H_2), 2.97–3.08 (m, 1 H, H_6), 3.25 (dd, J = 8.8, 11.6 Hz, 1 H, $H_{5\alpha}$), 3.46 (dd, J = 8.4, 11.6 Hz, 1 H, $H_{5\beta}$), 3.86–3.93 (m, 1 H, H_{7a}), 5.73 (d, J = 8.2 Hz, 1 H, ArCH), 7.22–7.35 (m, 5 H, ArH), 8.04 (s, 1 H, O_2CH); MS, 259. ($M^{+\cdot}$).

Example 3. 1-(Hydroxymethyl)-5-(3-phenyl-2-propenyl)-2-pyrrolidinone (14a, X = H). To a solution of 231 mg (1.0 mmol) of **4a** in 4 mL of CH_2Cl_2 (distilled from P_2O_5) was added 0.4 mL of CF_3CO_2H at 5 °C. After having been stirred for 0.5 h at 5 °C, the mixture was poured into an ice–K_2CO_3 mixture. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organic layers were dried and concentrated in vacuo. Flash chromatography (AcMe–CH_2Cl_2, 2:9) afforded, besides epimeric mixtures of **12a**, **13a** (X = H) (17%) and **12a**, **13a** (X = CF_3CO) (27%), 122 mg (53%) of the primary hydroxy lactam **14a** (X = H): mp 125–128 °C; IR 3360, 1671; ^1H NMR 1.74–1.88 (m, 1 H, H_4); 2.07–2.70 (m, 5 H, $H_{3\alpha}$, $H_{3\beta}$, H_4, $=CCH_2$), 3.87–3.99 (m, 1 H, H_5), 4.78 (d, J = 11 Hz, 1 H, NCHO), 4.99 (d, J = 11 Hz, 1 H, NCHO), 6.15 (dt, J = 16 and 7 Hz, respectively, 1 H, ArC=CH), 6.53 (d, J = 16 Hz, 1 H, ArCH=), 7.19–7.34 (m, 5 H, ArH); exact mass calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1270.

Example 4. *rel*-(6*R*,7*R*,8a*S*)-7-(Formyloxy)-8a-methyl-6-phenylhexahydro-2*H*-indolizin-3-one (22, X = HCO), *rel*-(6*R*,7a*S*)-6-[(*S*)-(Formyloxy)phenylmethyl]-7a-methylhexahydro-3*H*-pyrrolizin-3-one (23, X = HCO), and *rel*-(6*R*,7a*S*)-6-[(*R*)-(Formyloxy)phenylmethyl]-7a-methylhexahydro-3*H*-pyrrolizin-3-one (24, X = HCO). In order to obtain pure compounds for characterization purposes a cyclization was performed with 180 mg (0.73 mmol) of hydroxy lactam **5** in 6 mL of 98–100% formic acid at 21 °C for 4 h and worked up as described in example 2. Flash chromatography (AcMe–CH_2Cl_2, 1:5) gave 10.6 mg (5%) of **22** (X = HCO) and 176.5 mg (88%) of a 1:1 mixture of **23** and **24**. Flash chromatography (AcMe–CH_2Cl_2, 1:6) of the latter mixture afforded 31.4 mg (16%) of **23** and 24.4 mg (12%) of **24** (X = HCO) in this order.

Indolizidine 22 (X = HCO): mp 147–148.5 °C ($(i\text{-}Pr)_2O$); IR 1719, 1674; ^1H NMR 1.44 (s, 3 H, CH_3), 1.55 (t, J = 12 Hz, 1 H, $H_{8\beta}$), 1.85–2.05 (m, 2 H, $H_{1\alpha}$, $H_{1\beta}$), 2.25 (dd, J = 4.4, 12 Hz, 1 H, $H_{8\alpha}$), 2.36–2.55 (m, 2 H, $H_{2\alpha}$, $H_{2\beta}$), 2.72–2.90 (m, 2 H, H_6, $H_{5\alpha}$), 4.20–4.26 (m, 1 H, $H_{5\beta}$), 5.52 (dt, J = 4.3 and 11.0 Hz, respectively, 1 H, H_7), 7.18–7.34 (m, 5 H, ArH), 7.76 (s, 1 H, O_2CH); exact mass calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1355.

Less polar isomer 23 (X = HCO): IR 1723, 1671; ^1H NMR 1.23 (s, 3 H, CH_3), 1.52 (t, J = 11 Hz, 1 H, $H_{7\beta}$), 1.88–2.03 (m, 3 H, $H_{1\alpha}$, $H_{1\beta}$, $H_{7\alpha}$), 2.38 (ddd, J = 5.3, 6.5, 16.8 Hz, 1 H, H_2), 2.72–2.78 (m, 1 H, H_2), 2.89 (ddd, J = 1.1, 8.5, 11.4 Hz, 1 H, $H_{5\alpha}$), 3.11–3.15 (m, 1 H, H_6), 3.25 (dd, J = 7.6, 11.4 Hz, 1 H, $H_{5\beta}$), 5.73 (d, J = 8.1 Hz, 1 H, ArCH), 7.24–7.33 (m, 5 H, ArH), 8.04 (s, 1 H, O_2CH); exact mass calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1382.

More polar isomer 24 (X = HCO): IR 1724, 1670; ^1H NMR 1.20 (s, 3 H, CH_3), 1.29 (t, J = 12.0 Hz, 1 H, $H_{7\beta}$), 1.58 (dd, J = 6.7, 12.0 Hz, 1 H, $H_{7\alpha}$), 1.87–1.97 (m, 2 H, $H_{1\alpha}$, $H_{1\beta}$), 2.39 (ddd, J = 4.7, 7.0, 17.0 Hz, 1 H, H_2), 2.69–2.80 (m, 1 H, H_2), 3.08–3.19 (m, 1 H, H_6), 3.25 (ddd, J = 1.3, 8.8, 11.8 Hz, 1 H, $H_{5\alpha}$), 3.53 (dd, J = 7.4, 11.8 Hz, 1 H, $H_{5\beta}$), 5.67 (d, J = 8.1 Hz, 1 H, ArCH), 7.24–7.33 (m, 5 H, ArH), 8.03 (s, 1 H, O_2CH); exact mass calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1355.

^1H NMR Determination of Product Compositions. The reaction mixture (or a sample in case of reactions followed in time) was worked up as described in example 2. The crude mixture of esters was analyzed by 250-MHz ^1H NMR. The following resonances were monitored: compounds of type **4**, multiplet at δ 5.00–5.13 of $=CH_2$; type **8**, **9**, overlapping multiplets at δ 4.2–4.3 of $H_{5\beta}$ (eq) of the cis and trans isomer; type **12**, **13**, two doublets ($J \sim 8$ Hz) of $H_{6'}$ of the isomeric formates, and two of the acetates at δ 5.6–5.8; type **14**, the doublet ($J \sim 16$ Hz) at δ 6.5 of ArCH=.

Registry No. **2a**, 6052-63-7; **2b**, 101145-07-7; **2c**, 86896-50-6; **2d**, 101145-08-8; **2e**, 101145-09-9; **3a**, 86896-51-7; **3b**, 101145-10-2; **3c**, 86896-52-8; **3d**, 101145-11-3; **3e**, 101145-12-4; **4a** (isomer 1), 101145-13-5; **4a** (isomer 2), 101145-14-6; **4b** (isomer 1), 101145-15-7; **4b** (isomer 2), 101145-16-8; **4c** (isomer 1), 101145-17-9; **4c** (isomer 2), 101145-18-0; **4d** (isomer 1), 101145-19-1; **4d** (isomer 2), 101145-20-4; **4e** (isomer 1), 101145-21-5; **4e** (isomer 2), 101145-22-6; **5**, 101145-23-7; **8a** (X = H), 101145-25-9; **9a** (X = H), 101311-00-6; **9b** (X = H), 101145-41-9; **12a** (X = H), 86941-30-2; **12a** (X = HCO), 86941-29-9; **12a** (X = CF_3CO), 86896-53-9; **12b** (X = H), 101145-30-6; **12c** (X = CF_3CO), 86896-47-1; **12c** (X = H), 86941-33-5; **12d** (X = H), 101145-32-8; **13a** (X = H), 86905-71-7; **13a** (X = HCO), 86905-69-3; **13a** (X = CF_3CO), 86941-31-3; **13b** (X = H), 101145-31-7; **13c** (X = H), 86905-74-0; **13c** (X = CF_3CO), 87679-17-2; **13d** (X = H), 101145-33-9; **14a** (X = H), 101145-26-0; **15**, 101145-34-0; **16**, 101145-35-1; **17**, 101145-38-4; **18**, 101145-36-2; **19**, 101145-37-3; **20**, 101145-39-5; **22** (X = HCO), 101145-27-1; **23** (X = HCO), 101145-28-2; **24** (X = HCO), 101145-29-3; bromobenzene, 108-86-1; 1-bromo-4-chlorobenzene, 106-39-8; 1-bromo-4-methoxybenzene, 104-92-7; 1-bromo-3-methoxybenzene, 2398-37-0; 1-bromo-3,4-dimethoxybenzene, 2859-78-1; butadiene monoxide, 930-22-3; succinimide, 123-56-8; 1-[2-(3,4-dimethoxyphenyl)-3-butenyl]-5-ethoxy-2-pyrrolidinone, 101145-24-8; 5-[3-(4-chlorophenyl)-2-propenyl]-2-pyrrolidinone, 101145-40-8.

Supplementary Material Available: Experimental details and/or spectral data for **2a–d**, **3a–e**, **4a–e**, **9b** (X = H), **12b** (X = H), **12c** (X = H), **12c** (X = CF_3CO), **13b** (X = H), **13c** (X = H), **13c** (X = CF_3CO), **13d** (X = H), and **15–20** (9 pages). Ordering information is given on any current masthead page.