Studies of the Cyclic Amidoacetal Carbamate Moiety of the Maytansinoids[1]

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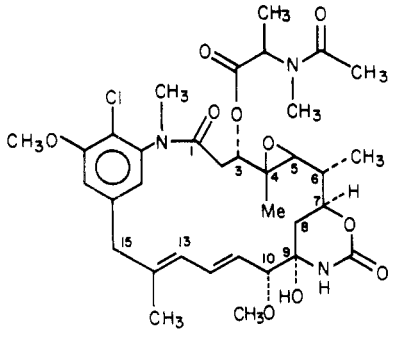
A synthesis of cyclic urethane amidoacetals of the type present in the maytansinoid ansa macrolides is reported both to serve as a synthetic model and to explore the chemistry of the hydroxylated intermediates of structures **5** and **6**. These compounds are prepared by aldol cyclization of the open-chain amidoacetal aldehyde **4e**. Compound **5** is the product of kinetic control, which rearranges to the stable isomeric end products **6** and **7**, the latter of which possesses a five-membered urethane ring. The elucidation of structure, stereochemistry, and conformation of these substances is described. The removal of the secondary hydroxyl group of **5** to form **17a** is accomplished in three steps.

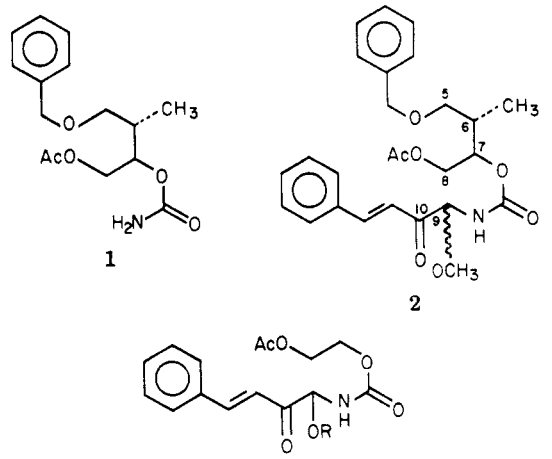
The ansa macrolide maytansine, first described by



maytansine

Kupchan et al.,[2] and related substances[3] have received much attention because of their potent antitumor activity.[3] Synthetic approaches[4] to this potentially important class of chemotherapeutic agents have recently culminated in the synthesis by two groups[5,6] of the maytansinoid (±)-*N*-methylmaysenine, which lacks but the 4,5-epoxide function and the 3-acyloxy substituent of maytansine.

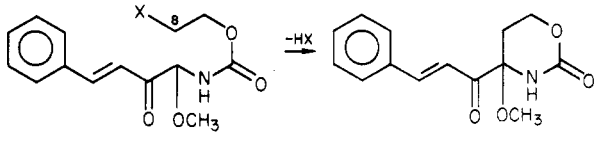
A synthetic approach to the maytansinoids explored in this laboratory involves closure of the macrocycle via the reaction of an α-keto aldehyde which serves as one of the two termini and a urethane grouping which serves as the other. A model reaction of this type was described in a recent publication from this laboratory,[7] involving the preparation of the amido acetal **2** by condensation of styrylglyoxal with the urethane **1**, followed by reaction with methanol. Neither of these reactions required the use of an external catalyst. If this facile condensation reaction was to provide a model for the closure of the macrocycle, bond formation between C-8 and C-9 (maytansine numbering) would have to be effected under the mildest possible conditions to form the six-membered urethane ring. Experiments directed toward this goal and a solution to



3, R = H
3a, R = CH_3

the problem form the subject of this paper. The task turned out to be more complex than anticipated, and further simplification was deemed desirable by deleting the "side chain" composed of carbons 5 and 6 and the attached methyl group.

The immediate objective then was to perform reaction 1. Synthesis of the acyclic precursor **3a** was achieved in



(1)

90% yield by condensation of 2-acetoxyethyl carbamate[8] with styrylglyoxal[9] in ether/chloroform at 25 °C, followed by a brief reaction with 0.003 N HCl in hot methanol. In order to avoid complications when generating the required anion at C-9, the imino nitrogen was methylated in 90% yield with silver oxide and methyl iodide in DMF at 25 °C to form the *N*-methylurethane **4a**. Removal of the acetyl group with 1% KOH in methanol at 25 °C afforded the alcohol **4b**, which formed the starting point for much experimentation aimed at closing the urethane ring. Alkylation reactions involving the tosylate **4c** or the iodide **4d** under a large variety of enolizing conditions, both basic and acidic, were unsuccessful. Success was eventually achieved by an intramolecular aldol reaction via the aldehyde **4e** prepared in 69% yield from the alcohol **4b** by

(1) Dedicated to the memory of S. Morris Kupchan whose discovery of novel and interesting natural products has provided innumerable challenges to organic chemists.

(2) Kupchan, W. M.; Komoda, Y.; Court, W. A.; Thomas, G. J.; Smith, R. M.; Karim, A.; Gilmore, C. J.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 1354.

(3) Kupchan, S. M.; Komoda, Y.; Branfman, A. R.; Dailey, R. G., Jr.; Zimmerly, V. A. *J. Am. Chem. Soc.* **1974**, *96*, 3706.

(4) Meyers, A. I.; Tomioka, K.; Roland, D. M.; Comins, D. *Tetrahedron Lett.* **1978**, 1375. Foy, J. E.; Ganem, B. *Ibid.* **1977**, 775. Corey, E. J.; Bock, M. G.; Kozikowsky, A. P.; Rama Rao, A. V.; Floyd, D.; Lipshutz, B. *Ibid.* **1978**, 1051. Gotschi, E.; Schneider, F.; Wagner, H.; Bernhauer, K. *Helv. Chim. Acta* **1977**, *60*, 1416. Edwards, D. E.; Ho, P. T. *Can. J. Chem.* **1977**, *55*, 371.

(5) Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 2916.

(6) Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 4132.

(7) Elliott, W. J.; Fried, J. *J. Org. Chem.* **1976**, *41*, 2469.

(8) Viard, M. J.; British Patent 689705, April 1, 1953; *Chem. Abstr.* **1953**, *48*, 7055d.

(9) Miyano, M.; Dorn, C. R.; Mueller, R. A. *J. Org. Chem.* **1972**, *37*, 1810.

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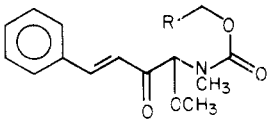
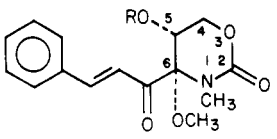
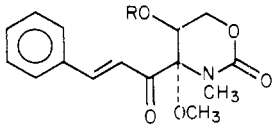
a sodium acetate buffered pyridinium chlorochromate oxidation.[10]



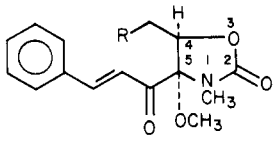
4a, R = CH_2OAc
b, R = CH_2OH
c, R = CH_2OTs
d, R = CH_2I
e, R = CHO



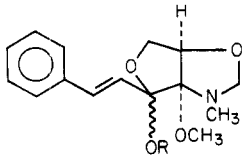
5, R = H
5a, R = Ac
b, R = Ts
c, R = Tf



6, R = H
6a, R = Ac
b, R = Ts
c, R = Tf



7, R = OH
7a, R = OAc
b, R = OMs
c, R = OTs
d, R = I
e, R = OTHP

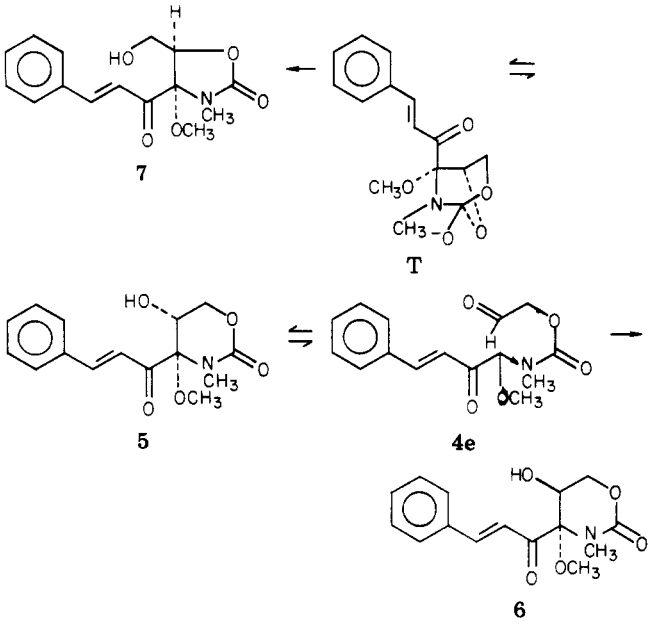


7f, R = H
g, R = CH_3
h, R = THP

The intramolecular aldol reaction of **4e** provided an unanticipated outcome leading not only to the desired six-membered urethanes **5** and **6** but giving rise also to the rearrangement product **7** via a subsequent intramolecular acyl migration. Thus, when the reaction was performed in a saturated solution of K_2CO_3 in methanol for 5 min, all three products, **5**, **6**, and **7**, could be isolated in approximately equal amounts by TLC or column chromatography. The unexpected presence of a five-membered urethane ring in **7** was first inferred from its infrared spectrum which showed a band at 1760 cm^{-1} in contrast to absorption at 1715 cm^{-1} for both **5** and **6**. Such absorption maxima are characteristic of five- and six-membered cyclic urethanes, respectively.[11]

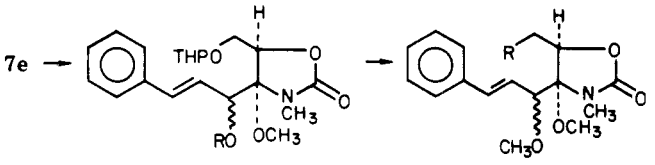
Before considering the stereochemistry of the cyclic urethanes, it is instructive to discuss their relative rates of formation and their interconversions. Such information was gained by performing the reaction in 0.005 M K_2CO_3 in methanol (pH 11.5) at room temperature. Under these conditions the reaction requires 18 to 24 h for completion. Reaction progress was monitored by TLC and occasional workup and isolation of the individual products. The six-membered alcohol **5**, mp 85–86.5 °C, was the first product to appear, followed by the six-membered alcohol **6**, mp 195–196 °C, and finally the five-membered alcohol **7**. Isolation of the products formed after 3.5 h showed 50% **5**, 22% **6**, 9% **7**, and 19% unchanged aldehyde **4e**. On further exposure compound **5** declined at the expense of **6** and **7**, until workup after 24 h revealed only 32% **6** and 68% **7**. In separate experiments using the same conditions, it was shown that **5** was transformed into **6** (25%) and **7** (75%), and that **6** and **7** remained unchanged even after several days of exposure to the base. It may be concluded from these experiments that **5** is the exclusive product of

Scheme I



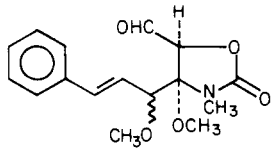
kinetic control, which by two independent competitive routes, namely reversal of the aldol condensation or intramolecular acyl migration, gives rise to the stable end products of the reaction, **6** and **7**, respectively. These relationships are shown in Scheme I. Workup after ca. 4 h represents the optimum condition for obtaining **5**, which turned out to be the intermediate essential for the preparation of the desired deoxyurethane **17a**.

We are now in a position to discuss the stereochemistry of the urethanes **5**, **6**, and **7**. The key to the solution of this problem was the elucidation of the structure of the five-membered rearrangement product **7**. That **7** possesses a hydroxymethyl group was shown by the following sequence of reactions: The alcohol **7** was converted into



8, R = H
8a, R = CH_3

9, R = OH
9a, R = OTs
9b, R = SCH_3
9c, R = H



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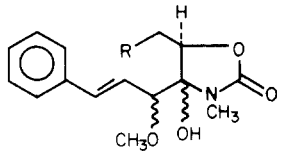
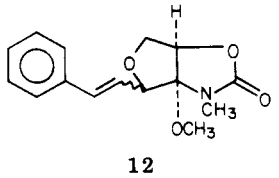


11, R = OH
11a, R = H



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the THP ether **7e**[12] and the keto group reduced with $NaBH_4$ in methanol to furnish a mixture of alcohols **8**,

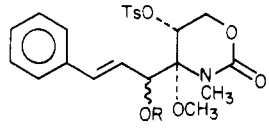
(10) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(11) Hall, H. K., Jr.; Zbinden, R. *J. Am. Chem. Soc.* **1958**, *80*, 6420.
(12) Grieco, P.; Yoshikoshi, A.; Miyashita, N. *J. Org. Chem.* **1977**, *42*, 3772.

which was converted into the methyl ethers **8a** with sodium hydride and methyl iodide.[13] These were hydrolyzed to to the parent alcohols **9** with 0.001 M *p*-TsOH in methanol and the mixture separated by TLC. Both isomers, A and B, yielded tosylates **9a**, neither of which furnished identifiable products on attempted reduction with either $LiAlH_4$ or Superhydride. The two tosylates were therefore converted into the thiomethyl ethers **9b**[14] with sodium methyl mercaptide in DMF at 0 °C and the resulting products desulfurized with Raney nickel in acetone[15] to form the corresponding *C*-methyl-substituted urethanes **9c**. The presence of a *C*-methyl group in these compounds was readily apparent from the 3-proton doublet at δ 1.50 (J = 6 Hz) and the quartet at δ 4.05 for the C-4 methine proton. Additional evidence for the presence of a hydroxymethyl substituent in **9** was obtained by oxidation with pyridinium chlorochromate to the aldehyde **10**. Both **9** and **9c** could be hydrolyzed with 0.2 N HCl in THF/H_2O[2] to the hemiacetals **11** and **11a**.

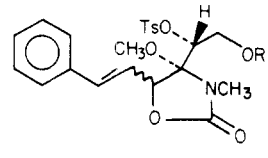
The cis relationship of the hydroxymethyl and cinnamoyl substituents was inferred from the isolation of the hemiketal **7f**, whose proton NMR spectrum in $CDCl_3$ exhibits signals for the two vinyl protons at δ 6.97 and 6.15, approximately 1 ppm upfield from those in all the α,β-unsaturated ketones and near the chemical shifts that these protons exhibit in the corresponding allylic alcohols. Two diastereomers in a 9:1 ratio appeared likely from the presence of satellite doublets for these vinyl protons. Such a cyclic form was also demonstrated by formation of the ketal **7g** by treatment of **7** with dilute HCl in methanol. A similar cyclization took place when the mesylate **7b**, tosylate **7c**, or iodide **7d**, prepared according to standard methods, were reduced with $LiEt_3BH$.[16] In this case the cyclic ether **12** was formed by displacement of the mesylate, tosylate, or iodide by the hydroxylate anion generated in the reduction.

On the basis of the stereochemistry of the rearranged five-membered urethane **7**, the structure of the isomeric six-membered urethanes **5** and **6** can now be derived. According to Scheme I, **7** is formed exclusively from the lower melting faster-moving isomer **5** via the tetrahedral intermediate T by a process which does not involve its two asymmetric centers. In compound **5** the cinnamoyl and hydroxyl substituents must therefore be trans to each other, while in the higher melting isomer **6** they are in a cis relationship. The fully resolved 270-MHz NMR spectra of the *O*-acetyl derivatives of **5** and **6** provide interesting information regarding the conformation of these two compounds. Thus, the methine proton at C-5 in the trans compound **5a** appears as a doublet of doublets coupled to the methylene protons at C-4 with J = 3.0 and 6.0 Hz. In contrast, the coupling constants for the methine proton in the cis compound **6a** are 6.9 and 10.5 Hz. Very similar values were obtained for the coupling constants of the acyl derivatives **5b** and **5c** and **6b** and **6c**, respectively.[17] These data are consistent with a half-chair conformation of the ring, also present in maytansine,[18] with the C-5 substituent in the trans compounds in the axial position, and in the cis compounds in the equatorial position. It furthermore follows that the cinnamoyl group must prefer to be pseudoaxial in both series. The unusual stability of the trans isomer in such a diaxial arrangement persists in more polar solvents such as methanol and dimethyl sulfoxide, since no change in the coupling constants is observed in the proton NMR spectra in these solvents. It is hoped that X-ray crystallographic data now being collected may provide a more precise picture of the conformation of these substances, at least in the solid state. The distinct conformational preference in these compounds serves to explain the facile rearrangement of **5**, in which the axial hydroxyl group is conveniently disposed to form the norbornane-like skeleton of the tetrahedral intermediate T. Apparently, conformational inversion of **6** to achieve axiality for the hydroxyl group is energetically sufficiently unfavorable to prevent rearrangement under the conditions employed. Similarly, the facile formation of the trans isomer **5** in the aldol reaction and the ready reversal of that reaction, in contrast to the stability of the cis isomer, can be related to the close to antiperiplanar arrangement of the hydroxyl and cinnamoyl groups in the former, favored in the transition state.

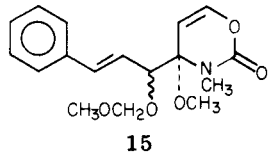
Maytansine does not possess a hydroxyl group in the urethane ring. It became necessary, therefore, to effect its removal. It should be noted, however, that synthetic variants of this antitumor agent may well benefit from its presence, either free or substituted, and a detailed understanding of the chemistry of these hydroxylated urethanes may turn out to be of more than passing interest. The more abundant trans isomer **5** was examined first. A plan utilizing the desulfurization technique, which had proved successful in the deoxygenation of the five-membered urethane **7**, proceeded as follows. The tosylate **5b** was reduced with $NaBH_4$ in methanol at 0 °C to a 1:1 mixture of allylic alcohols **13** which were separated by TLC. It was necessary to terminate the reaction after 11 min since longer reaction times caused yet another rearrangement to form the five-membered urethane **14** by attack of the hydroxylate anion generated in the reduction on the urethane carbonyl and liberation of the hydroxymethyl group. The use of 2-propanol as a solvent yielded **14** even after 11 min, presumably due to its failure to rapidly protonate the hydroxylate anion. In view of this finding methylation of the allylic alcohol with NaH and methyl iodide was out of the question. The alcohol group was therefore protected as the methoxymethyl ether[19] by



13, R = H
13a, R = CH_2OCH_3



14, R = H
14a, R = Ac



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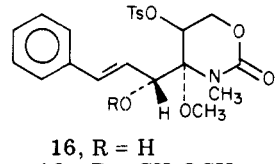
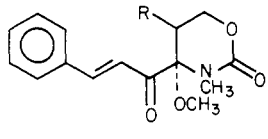
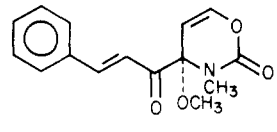


16, R = H
16a, R = CH_2OCH_3



17, R = I
17a, R = H
b, R = H, no C=C



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(13) Diner, U.; Sweet, F.; Brown, R. *Can. J. Chem.* **1966**, *44*, 1591.
(14) Baker, S. B. *Can. J. Chem.* **1955**, *33*, 1102.
(15) Lin, H.; Hung, H.; Mhette, G.; Weinberg, M. *Can. J. Chem.* **1978**, *56*, 1368.
(16) Krishnamurty; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064.
(17) The chemical shifts for the methine proton in the alcohols **5** and **6** are not sufficiently resolved in $CDCl_3$. However, **5** and **6** show coupling constants similar to those of their acyl derivatives in C_5D_5N and CD_3OD, respectively.
(18) Bryan, R. F.; Gilmore, Ch. J.; Haltiwanger, R. C. *J. Chem. Soc., Perkin Trans. 2* **1973**, 897.

using the hindered base diisopropylethylamine. Reaction of the resulting product **13a** (derived from the faster-moving alcohol) with sodium methyl mercaptide led to elimination of *p*-TsOH to form in small yield the unsaturated urethane **15** together with less well-defined products possessing a five-membered urethane ring possibly formed by sulfur–oxygen cleavage, followed by rearrangement. This route was therefore abandoned. Borohydride reduction of the cis tosylate **6b** furnished a *single* allylic alcohol **16**. The stereochemistry as shown is rationalized on the basis of steric interactions between the incoming hydride reagent and the bulky cis-oriented tosyloxy group. The unexpected feature concerning this reduction product was revealed in its proton NMR spectrum, which indicated an *axial* tosyloxy group, whereas in the parent ketone this group was equatorial. This is readily apparent from the coupling constants observed for the C-5 methine proton which are 3.8 and 6.6 Hz. This ring inversion, which must also involve a change in the conformation of the cinnamoyl side chain, is probably the result of some hydrogen-bonding interaction involving the newly formed hydroxyl group. In support of this interpretation may be cited the fact that in the methoxymethyl ether **16a** the tosyloxy group again assumes the equatorial position ($J_{H5,6}$ = 5.9 and 10.9 Hz).

Successful reduction of the hydroxyl group of **5** was achieved via the triflate **5c**. Both **5** and **6** readily form stable triflates in high yield,[20] which can be readily purified by TLC. The triflate **5c** afforded the crystalline iodide **17** with sodium iodide in acetone at 25 °C in 68% yield from **5**. According to its proton NMR spectrum the iodide is equatorial and, since it is most likely formed by a single inversion step, is cis with regard to the cinnamoyl group. The iodide was reduced with tributyltin hydride[21] to the desired deoxyurethane **17a** in 68% yield. An attempt to convert the isomeric cis triflate **6c** into the iodide led instead to the olefin **18** presumably via an intermediate axial iodide. The olefin **18** could be reduced catalytically to the saturated urethane **17b** albeit with concomitant reduction of the styrene double bond. This tetrahydro product was identical with the dihydro derivative prepared by catalytic reduction of **17a**.

Experimental Section[22]

2-Hydroxyethyl Carbamate.[8] To a solution of 17.6 g (0.2 mol) of ethylene carbonate in 5 mL of water was added at 0 °C 30 mL of concentrated NH_3–H_2O (1:1) with stirring. The reaction mixture was maintained at 0 °C for 4 h and then allowed to stir at 25 °C overnight. The solvent was removed in vacuo to leave 21 g (100%) of colorless oil. Crystals formed on long standing at 25 °C: mp 38–41 °C; NMR (60 MHz) δ 6.05 (br s, 2 H, NH_2), 4.15 (t, 2 H, *J* = 5 Hz, OCH_2CH_2OH), 4.0–4.3 (1 H, OH), 3.75 (t, 2 H, *J* = 5 Hz, OCH_2CH_2OH); IR (KBr) 3400–3500 (OH,NH_2), 1725–1740, 1610 (urethane C=O) cm^{-1}.

2-Acetoxyethyl Carbamate.[23] To a solution of 21 g (0.2 mol) of 2-hydroxyethyl carbamate in 40 mL of THF cooled to −78 °C was added with stirring a solution of 20 mL of acetyl chloride in 30 mL of THF which was also cooled to −78 °C. The acetyl chloride solution was added in 1-mL portions over a 2-h period. The resulting mixture was stirred at −78 °C for an additional 3 h, then warmed to 0 °C for 3 h, and stirred at 25 °C overnight. The solvent and the excess acetyl chloride were distilled off under water aspirator pressure and the residue distilled under vacuum. The portion distilling at 135–139 °C (4 mm) was collected to give 25.4 g (86.2%) of colorless crystals: mp 40–42 °C; NMR (60 MHz) δ 5.58 (br s, 2 H, NH_2), 4.28 (s, 4 H, CH_2CH_2), 2.08 (s, 3 H, CH_3CO_2); IR (KBr) 1720–1755 (ester and urethane C=O), 1610 (urethane) cm^{-1}.

Anal. Calcd for $C_5H_9NO_4$: C, 40.81; H, 6.17; N, 9.52. Found: C, 41.05; H, 6.12; N, 9.80.

Condensation of Styrylglyoxal with 2-Acetoxyethyl Carbamate. 2-Acetoxyethyl *N*-(1-Hydroxy-2-oxo-4-phenyl-3-butenyl)carbamate (3). To a solution of 3.5 g (22 mmol) of styrylglyoxal in 20 mL of ether was added 3.3 g (22 mmol) of 2-acetoxyethyl carbamate in 5 mL of $CHCl_3$. The reaction mixture was stirred at 25 °C overnight. On removal of the solvent, a white precipitate formed which was filtered and washed with ether. The yellow solution was concentrated and allowed to stand at 0 °C, when additional precipitation occurred. The process was repeated until 6.5 g (96.3%) of **3** was collected as a white solid: mp 84–86 °C after one recrystallization from ether; NMR δ 7.82 (d, 1 H, *J* = 16 Hz, PhC**H**=CH), 7.69 (d, 2 H, *J* = 6 Hz, ortho Hs of Ph), 7.42 (m, 3 H, meta and para Hs of Ph), 7.06 (d, 1 H, *J* = 16 Hz, PhCH=C**H**), 6.49 (br d, 1 H, *J* = 9 Hz, CHN**H**), 5.80 (br d, 1 H, *J* = 9 Hz, C**H**NH), 5.03 (br s, 1 H, OH), 4.32 (m, 4 H, CH_2CH_2OAc), 2.06 (s, 3 H, CO_2CH_3); IR (KBr) 3350–3400 (OH, NH), 1735 (acetate C=O), 1690 (urethane C=O), 1600 (C=C) cm^{-1}; mass spectrum, *m/e* 176 (2.6%, $M^+ - C_9H_7O$), 131 (86%, C_9H_7O), 103 (37%), 87 (66%, CH_2CH_2OAc), 77 (27%), 43 (100%, CH_3CO).

Anal. Calcd for $C_{15}H_{17}O_6N$: C, 58.63; H, 5.54; N, 4.56. Found: C, 58.35; H, 5.61; N, 4.29.

2-Acetoxyethyl *N*-(1-Methoxy-2-oxo-4-phenyl-3(*E*)-butenyl)carbamate (3a). A solution of 80 mg (0.26 mmol) of 2-acetoxyethyl *N*-(1-hydroxy-2-oxo-4-phenyl-3(*E*)-butenyl)carbamate (**3**) in 0.5 mL of methanol was added to 2.5 mL of boiling methanol containing 0.01 mL of 10% HCl. The reaction mixture was refluxed for 1 min and the solvent removed in vacuo. After purification by TLC ($CHCl_3$), 75 mg (90%) of **3a** was obtained as a white solid: mp 59–60 °C; NMR δ 7.81 (d, 1 H, *J* = 16 Hz, PhC**H**=CH), 7.61 (m, 2 H, Ph), 7.43 (m, 3 H, Ph), 7.00 (d, 1 H, *J* = 16 Hz, PhCH=C**H**), 6.13 (br d, 1 H, *J* = 9 Hz, C**H**NH), 5.63 (br d, 1 H, *J* = 9 Hz, CHN**H**), 4.34 (m, 4 H, CH_2CH_2OAc), 3.50 (s, 3 H, OCH_3), 2.12 (s, 3 H, CO_2CH_3); IR (KBr) 3400 (NH), 1750 (acetate C=O), 1710 (urethane C=O), 1615 (C=C) cm^{-1}; mass spectrum, *m/e* 190 (26%, $M^+ - C_9H_7O$), 131 (22%, C_9H_7O), 103 (20%), 87 (100%), 77 (13%), 43 (50%).

Anal. Calcd for $C_{16}H_{19}O_6N$: C, 59.81; H, 5.92; N, 4.36. Found: C, 60.06; H, 5.84; N, 4.21.

2-Acetoxyethyl *N*-(1-Methoxy-2-oxo-4-phenyl-3(*E*)-butenyl)-*N*-methylcarbamate (4a). To a mixture of 742 mg (2 equiv) of Ag_2O and 840 mg (4 equiv) of CH_3I in 4 mL of dry DMF was added a solution of 460 mg (1.4 mmol) of 2-acetoxyethyl *N*-(1-methoxy-2-oxo-4-phenyl-3(*E*)-butenyl)carbamate (**3a**) in 2 mL of dry DMF. The reaction mixture was stirred at 0 °C for 16 h and poured into 80 mL of $CHCl_3$, and the grey precipitate was filtered and washed with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O (10 × 50 mL) and brine (30 mL) and dried over anhydrous $MgSO_4$. After purification by TLC (1:3 EtOAc/$CHCl_3$), 432 mg (90%) of **4a** was obtained as a yellow oil: NMR δ 7.77 (d, 1 H, *J* = 16 Hz, PhC**H**=CH), 7.59 (m, 2 H, Ph), 7.40 (m, 3 H, Ph), 7.06 (1),[24] 7.01 (5) (2 d, 1 H, *J* = 16 Hz, PhCH=C**H**), 5.90 (5), 5.65 (1) (2 s, 1 H, C**H**NCH$_3$), 4.44–4.27 (m, 4 H, CH_2CH_2OAc), 3.45 (5), 3.43 (1) (2 s, 3 H, OCH_3), 2.78 (1), 2.75 (5) (2 s, 3 H,

(19) An attempt to prepare the methyl thiomethyl ether with Me_2SO and acetic anhydride caused reoxidation to the ketone.

(20) Vedejs, E.; Engles, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.

(21) Kuivila, H. G. *Synthesis* **1970**, *10*, 499.

(22) Infrared (IR) spectra were recorded on a Perkin-Elmer Model 297 spectrophotometer. Samples were run in solution cells at a concentration of ca. 2 mg/mL unless otherwise specified. Proton NMR spectra were recorded on a Bruker HX-270 (270 MHz) spectrometer and were determined as solutions in $CDCl_3$ with Me_4Si as an internal standard. Chemical shifts are reported in δ, coupling constants (*J*) are reported in hertz; the abbreviations s, d, t, q, and m signify singlet, doublet, triplet, quartet, and multiplet, respectively. Low-resolution mass spectra were determined by using a Finnigan 1015 quadrupole mass spectrometer equipped with VPC, gas, and solid probe inlets; the data were recorded and processed by a Systems Industries Computer Interface System/150 and plotted as bar graphs. High-resolution mass spectra were determined by using an AEI Model MS-9 mass spectrometer. Melting points were determined in capillary tubes and are uncorrected. Thin-layer chromatography was carried out by using silica gel analytical plates from Merck. Microanalyses were performed by Baron Consulting Co., Orange, CT. The terms bicarbonate and brine refer to saturated aqueous solutions of $NaHCO_3$ and NaCl respectively.

(23) Prepared by Dr. W. J. Elliott.

(24) These numbers indicate the ratio of the respective signals due to rotational isomerism.

NCH_3), 2.06 (5), 2.03 (1) (2 s, 3 H, CO_2CH_3); IR (neat) 1750 (acetate C=O), 1705 (urethane C=O), 1610 (C=C) cm^{-1}; mass spectrum, *m/e* 204 (1.5%, $M^+ - C_9H_7O$), 131 (9%, C_9H_7O), 103 (9%), 87 (100%), 77 (10%), 43 (52%).

Anal. Calcd for $C_{17}H_{21}O_6N$: C, 60.90; H, 6.27; N, 4.11. Found: C, 60.97; H, 6.18; N, 4.18.

2-Hydroxyethyl *N*-(1-Methoxy-2-oxo-4-phenyl-3(*E*)-butenyl)-*N*-methylcarbamate (4b). To a solution of 133 mg (0.4 mmol) of 2-acetoxyethyl *N*-(1-methoxy-2-oxo-4-phenyl-3(*E*)-butenyl)-*N*-methylcarbamate (**4a**) in 2 mL of methanol was added 0.5 mL of 5% KOH in MeOH. The reaction mixture was stirred at 25 °C for 1 min. The mixture was neutralized with 10% HCl, the solvent removed, the residue taken up in 5 mL of H_2O, and the solution extracted with EtOAc (3 × 20 mL). The extracts were washed with H_2O (10 mL) and brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed, and after purification by TLC (1:1 EtOAc/$CHCl_3$), 106 mg (91%) of **4b** was obtained as a yellow oil: NMR δ 7.78 (d, 1 H, *J* = 16 Hz, PhC**H**=CH), 7.60 (m, 2 H, Ph), 7.41 (m, 3 H, Ph), 7.12, 7.02 (2 d, 1 H, *J* = 16 Hz, PhCH=C**H**), 5.91, 5.65 (2 s, 1 H, C**H**NCH_3), 4.50–4.22 (m, 2 H, CH_2CH_2OH), 3.83–3.73 (m, 2 H, CH_2CH_2OH), 3.46, 3.27 (2 s, 3 H, OCH_3), 2.82, 2.80 (2 s, 3 H, NCH_3); IR (neat) 3500 (OH), 1710 (urethane C=O), 1610 (C=C) cm^{-1}; mass spectrum, *m/e* 162 (100%, $M^+ - C_9H_7O$), 131 (10%, C_9H_7O), 103 (14%), 77 (16%), 74 (63%), 45 (66%, CH_2CH_2OH), 42 (93%).

Anal. Calcd for $C_{15}H_{19}O_5N$: C, 61.43; H, 6.48; N, 4.78. Found: C, 61.16; H, 6.59; N, 4.64.

The tosylate **4c** was prepared from **4b** with tosyl chloride in pyridine at 25 °C, yield 80% of oil.

Anal. Calcd for $C_{22}H_{25}ONS$: C, 59.06; H, 5.89; N, 3.13. Found: C, 59.33; H, 5.86; N, 2.99.

The iodide **4a** was prepared from **4b** with sodium iodide in acetone at 25 °C; yield 85%.

Anal. Calcd for $C_{15}H_{17}O_4NI$: C, 44.67; H, 4.47; N, 3.47; I, 31.51. Found: C, 46.67; H, 4.90; N, 3.33; I, 26.70.

2-Oxoethyl (1-Methoxy-2-oxo-4-phenyl-3(*E*)-butenyl)-*N*-methylcarbamate (4e). To 6 g (6 equiv) of pyridinium chlorochromate and 2.5 g (6 equiv) of sodium acetate refluxing in 300 mL of CH_2Cl_2 under N_2 was added 1.32 g (4.5 mmol) of the alcohol **4b** dissolved in 70 mL of CH_2Cl_2 over a period of 5 min. After addition was complete, the reaction was allowed to reflux for another 5-min period. Ether (300 mL) was then added and the mixture filtered through a column of Florisil (100 g). The column was eluted first with 1.5 L of ether and then with 1.0 L of ethyl acetate. The resulting solution was concentrated to 300 mL, washed with water (2 × 50 mL), and dried over sodium sulfate. The crude product (~1.0 g), consisting of the aldehyde **4e** plus recovered starting material (**4b**), was purified on a 75-g silica gel column by using ethyl acetate/hexane 1:1. There was obtained 657 mg of **4e** and 360 mg of **4b**: yield 69% based on recovered starting material; NMR δ 9.69 (s, 1 H, CHO), 7.84, 7.81 (2 d, 1 H, *J* = 16 Hz, PhC**H**=CH), 7.64 (m, 2 H, Ph), 7.44 (m, 3 H, Ph), 7.20, 7.03 (2 d, 1 H, *J* = 16 Hz, PhCH=C**H**), 5.90, 5.78 (2 s, 1 H, C**H**NCH_3), 4.87 (s), 4.82, 4.79 (2 d, *J* = 16 Hz, 2 H, CH_2CHO), 3.54, 3.52 (2 s, 3 H, OCH_3), 2.87, 2.83 (2 s, 3 H, NCH_3); IR (neat) 3500 (aldehyde hydrate), 1750 (aldehyde C=O), 1700 (urethane C=O), 1610 (C=C) cm^{-1}; mass spectrum, *m/e* 160 (100%, $M^+ - C_9H_7O$), 131 (10%, C_9H_7O), 103 (47%), 77 (20%), 74 (64%), 43 (48%), 42 (47%).

Anal. Calcd for $C_{15}H_{17}O_5N$: C, 61.86; H, 5.84; N, 4.81. Found: C, 61.52; H, 5.66; N, 4.90.

Cyclization of 2-Oxoethyl (1-Methoxy-2-oxo-4-phenyl-3-(*E*)-butenyl)-*N*-methylcarbamate (4e) with K_2CO_3 in Methanol. (5*RS*,6*SR*)-1-Methyl-3-oxa-5-hydroxy-6-cinnamoyl-6-methoxy-2-piperidinone (5, Trans Isomer), (5*SR*,6*SR*)-1-Methyl-3-oxa-5-hydroxy-6-cinnamoyl-6-methoxy-2-piperidinone (6, Cis Isomer), and (4*RS*,5*SR*)-1-Methyl-3-oxa-4-hydroxymethyl-5-cinnamoyl-5-methoxy-2-pyrrolidinone (7). Analytical Experiment. To the aldehyde **4e** (19.0 mg, 0.065 mmol) was added 2 mL of 0.005 M K_2CO_3 in methanol. The mixture was stirred at 25 °C for 3.5 h and carefully neutralized with 10% HCl, and the solvent was removed in vacuo. Ethyl acetate was added, the solution washed with bicarbonate (3 mL) and brine (3 mL), and the extract dried with sodium sulfate. The crude product was chromatographed by TLC (2:1 ethyl acetate/hexane). There was isolated 7.8 mg of **5** (50%), 3.4 mg of **6** (22%), 1.4 mg of **7** (9%), and 3.0 mg of **4e** (19%).

Preparative Experiment Directed at the Isolation of 5 and 6. To the aldehyde **4e** (704 mg, 2.42 mmol) was added 200 mL of 0.005 M K_2CO_3 in methanol. The reaction was stirred at 25 °C for 4.0 h, at which time 10% HCl was added until pH 7 was reached. The solvent was removed in vacuo, EtOAc added (20 mL), and the solution washed with bicarbonate (5 mL) and brine (5 mL) and dried with sodium sulfate. The crude product was purified on a high-pressure LC column packed with 100 g of silica gel. Elution with ethyl acetate/hexane (1:4) produced some of the five-membered urethane **7**. The major product **5** (279 mg, 40%) was eluted with 1700 mL of ethyl acetate–hexane (1:2), followed in the next 450 mL by mixed products. The cis isomer **6** (99.6 mg, 14%) was eluted with ethyl acetate–hexane (1:1).

Preparative Experiment Directed at the Isolation of 7. A solution of the aldehyde **4e** (238 mg, 0.82 mmol) in 75 mL of CH_3OH was added over a 2-h period to a solution of 1.38 g of K_2CO_3 in 400 mL of CH_3OH (0.02 M), and the mixture was stirred at 25 °C for 18 h. The solvent was removed in vacuo, 30 mL of H_2O added, and the mixture acidified with 10% HCl to pH 7.0. The aqueous solution was extracted with EtOAc (3 × 30 mL), and the organic phase washed with brine (20 mL) and dried over sodium sulfate. The crude product was purified on 20 g of silica gel by using ethyl acetate/hexane (2:1). The first 60 mL eluted faster-moving material. The main product **7** was eluted with 330 mL of solvent: total yield 128.5 mg (55%); mp 109–110 °C. The cis isomer **6** could be isolated from subsequent fractions.

Characterization of Products 5, 6, and 7. The trans isomer **5** was recrystallized from Et_2O: mp 85–86.5 °C; NMR δ 7.85 (d, 1 H, *J* = 16.0 Hz, PhC**H**=CH), 7.2 (d, 1 H, *J* = 16.0 Hz, PhCH=C**H**), 7.6–7.4 (br, 5 H, Ph), 4.31–4.2 (m, 3 H, C-4 methylene and C-5 methine), 3.63 (s, 3 H, OCH_3), 2.95 (s, 3 H, NCH_3); in C_5D_5N δ 4.64 (1 H, dd, *J* = 5, 8 Hz, C-5 methine), 4.45 (2 H, m, C-4 methylene), 3.74 (3 H, s, OCH_3), 3.05 (3 H, s, NCH_3); IR 1705 (6-ring urethane C=O), 1605 (C=C) cm^{-1}; low-resolution mass spectrum, *m/e* 291 (0.5%, M^+), 260 (0.5%, M – OCH_3), 160 (100%, M – C_9H_7O), 131 (1.5%, C_9H_7O); high-resolution mass spectrum, *m/e* calcd for $C_{15}H_{17}O_5N$ 291.1106, found 291.1123; $C_{14}H_{14}O_4N$ 260.0922, found 260.0927; $C_6H_{10}O_4N$ 160.0610, found 160.0604; C_9H_7O 131.0497, found 131.0506.

The cis Isomer 6 was recrystallized from EtOAc: mp 195–196 °C; NMR δ 7.6 (d, 1 H, *J* = 15.9 Hz, PhC**H**CH), 7.6–7.2 (br, 5 H, Ph), 4.3–4.25 (m, 3 H, C-4 methylene and C-5 methine), 3.44 (s, 3 H, OCH_3), 2.79 (s, 3 H, NCH_3); in CD_3OD δ 4.42 (dd, 1 H, *J* = 6.0, 10.5 Hz, C-5 methine), 4.12 (m, 2 H, methylene), 3.45 (s, 3 H, OCH_3), 2.69 (s, 3 H, NCH_3); IR 1705 (6-ring urethane C=O), 1605 (C=C) cm^{-1}; low resolution mass spectrum, *m/e* 291 (5%, M^+), 260 (5%, M – OCH_3), 160 (100%, M – C_9H_7O), 131 (10%, C_9H_7O); high-resolution mass spectrum, *m/e* 291.1147, 260.0924, 160.0611.

Anal. Calcd for $C_{15}H_{17}O_5N$: C, 61.86; H, 5.84; N, 4.81. Found: C, 61.58; H, 5.86; N, 5.07.

Rearrangement Product 7: NMR δ 7.68–7.25 (br, 5 H, Ph), 6.91 (d, 1 H, *J* = 16.0 Hz, PhCH=C**H**), 4.92 (d, 1 H, *J* = 4.5 Hz, C-4 methine), 4.41 (dd, 1 H, *J* = 4.5, 10.5 Hz, methylene proton), 4.05 (d, 1 H, *J* = 10.5 Hz, methylene proton), 3.35 (s, 3 H, OCH_3), 2.76 (s, 3 H, NCH_3); IR 3400 (OH), 1760 (5-ring urethane C=O), 1700 (keto C=O), 1610 (C=C) cm^{-1} (the keto band at 1700 cm^{-1} is not present in $CDCl_3$ (acidic)); mass spectrum, *m/e* 290 (0.7%, M – 1), 260 (1%, M – OCH_3), 160 (100%, M – C_9H_7O), 143 (24%, M – C_9H_7O – OH), 142 (20%, M – C_9H_7O – H_2O), 131 (55%, C_9H_7O).

Anal. Calcd for $C_{15}H_{17}O_5N$: C, 61.86; H, 5.84; N, 4.81. Found: C, 61.80; H, 6.02; N, 4.68.

The **acetates** were prepared with acetic anhydride in dry pyridine.

(5*RS*,6*SR*)-1-Methyl-3-oxa-5-acetoxy-6-cinnamoyl-6-methoxy-2-piperidinone. Trans Acetate (5a): NMR δ 7.75 (d, 1 H, *J* = 15 Hz, PhC**H**=CH), 7.6–7.40 (br, 5 H, Ph), 5.25 (dd, 1 H, *J* = 3.0, 6.0 Hz, C-5 methine), 4.40 (dd, 1 H, *J* = 3.0, 12.0 Hz, C-4 methylene), 4.20 (dd, 1 H, *J* = 6.0, 12.0 Hz, C-4 methylene), 3.55 (s, 3 H, OCH_3), 2.85 (s, 3 H, NCH_3), 2.20 (s, 3 H, CO_2CH_3).

(5*SR*,6*SR*)-1-Methyl-3-oxa-5-acetoxy-6-cinnamoyl-6-methoxy-2-piperidinone. Cis Acetate (6a): NMR δ 7.95 (d, 1 H, *J* = 15 Hz, PhC**H**=CH), 7.8–7.40 (br, 5 H, Ph), 5.55 (dd,

1 H, J = 6.9, 10.5 Hz, C-5 methine), 4.35 (t, 1 H, J = 10.5 Hz, C-4 methylene), 4.20 (dd, 1 H, J = 6.0, 10.5 Hz, C-4 methylene), 3.45 (s, 3 H, OCH_3), 2.75 (s, 3 H, NCH_3), 2.0 (s, 3 H, CO_2CH_3); IR 1760 (acetyl C=O), 1710 (6-ring urethane C=O), 1605 (C=O) cm^{-1}; mass spectrum, m/e 202 (100%, M - C_9H_7O).

(4*RS*,5*SR*)-1-Methyl-3-oxa-4-(acetoxymethyl)-5-cinnamoyl-5-methoxy-2-pyrrolidinone (7a): mp 87–87.5 °C; NMR δ 7.80 (d, 1 H, J = 16 Hz, PhCH=CH), 7.64 (m, 2 H, Ph), 7.44 (m, 3 H, Ph), 7.33 (d, 1 H, J = 16 Hz, PhCH=CH), 4.71 (t, 1 H, J = 6.5 Hz, C-4 methine), 4.05, 4.16 (2 q, 2 H, J = 6.5, 13 Hz, CH_2OAc), 3.41 (s, 3 H, OCH_3), 2.82 (s, 3 H, NCH_3), 1.97 (s, 3 H, CO_2CH_3); IR (neat) 1775 (acetyl C=O), 1750 (shoulder urethane C=O), 1700 (keto C=O), 1605 (C=C) cm^{-1}; mass spectrum, m/e 242 (9%, M - OCH_3 - OAc), 202 (83%, M - C_8H_7O), 143 (38%, M - C_8H_7O - OAc), 142 (100%, M - C_8H_7O - HOAc), 131 (60%, C_8H_7O), 103 (55%), 43 (100%).

Anal. Calcd for $C_{17}H_{19}O_6N$: C, 61.26; H, 5.71; N, 4.20. Found: C, 61.23; H, 5.74; N, 4.22.

The **tosylates** were prepared with tosyl chloride and dry pyridine at 25 °C.

Trans Tosylate (5b): NMR δ 7.6–7.4 (br, 9 H, Ph), 4.88 (dd, 1 H, J = 3.9, 7.3 Hz C-5 methine), 4.35 (dd, 1 H, J = 3.9, 11.6 Hz, C-4 methylene), 4.20 (dd, 1 H, J = 7.3, 11.6 Hz, C-4 methylene), 3.56 (s, 3 H, OCH_3), 2.75 (s, 3 H, NCH_3), 2.28 (s, 3 H, $PhCH_3$); IR 1715 (6-ring urethane C=O), 1600 (C=C) cm^{-1}.

Cis Tosylate (6b): NMR δ 7.8–7.40 (br, 9 H, Ph), 5.12 (dd, 1 H, J = 5.3, 10.5 Hz, C-5 methine), 4.37 (t, 1 H, J = 10.5 Hz, C-5 methylene), 4.10 (dd, 1 H, J = 5.5, 10.5 Hz, C-4 methylene), 3.34 (s, 3 H, OCH_3), 2.70 (s, 3 H, NCH_3), 2.36 (s, 3 H, $PhCH_3$).

Rearranged Tosylate (7c): NMR δ 7.97–7.45 (br, 9 H, Ph, $C_6H_4CH_3$), 7.85 (d, 1 H, J = 16.0 Hz, PhCH=CH), 7.46 (d, 1 H, J = 16.0 Hz, PhCH=CH), 4.83 (t, 1 H, J = 6.5 Hz, C-4 methine), 4.10 (dd, 1 H, J = 6.5, 12 Hz, methylene), 3.97 (dd, 1 H, J = 6.5, 12 Hz, methylene), 3.43 (s, 3 H, OCH_3), 2.77 (s, 3 H, NCH_3), 2.43 (s, 3 H, $PhCH_3$); IR 1780 (5-ring urethane C=O), 1600 (C=C) cm^{-1}; mass spectrum, m/e 172 (40%, TsOH), 155 (9%, Ts), 131 (13%, C_9H_7O).

Rearranged Mesylate (7b): NMR δ 7.6–7.35 (br, 5 H, Ph), 7.80 (d, 1 H, J = 16 Hz, PhCH=CH), 7.30 (d, 1 H, J = 16 Hz, PhCH=CH), 4.73 (t, 1 H, J = 6.5 Hz, C-4 methine), 4.23–4.08 (dd, 2 H, J = 6.5 Hz, methylene), 3.38 (s, 3 H, OCH_3), 2.94 (s, 3 H, CH_3SO_2), 2.76 (s, 3 H, NCH_3); IR 1760 (urethane C=O), 1600 (C=C) cm^{-1}; mass spectrum, m/e 273 (30%, M - HOMs), 242 (38%, M - OCH_3 - OMs), 238 (10%, M - C_9H_7O), 142 (32%), 131 (100%, C_9H_7O), 103 (53%), 96 (52%, HOMs), 79 (55%, CH_3SO_2), 77 (58%), 45 (56%).

Anal. Calcd for $C_{16}H_{19}O_7NS$: C, 52.03; H, 5.15; N, 3.79. Found: C, 50.82; H, 5.43; N, 3.49.

The **triflates** were prepared as follows:

Trans Triflate (5c). To the trans alcohol **5** (17.0 mg, 0.058 mmol) in 0.5 mL of methylene chloride cooled to −70 °C was added diisopropylethylamine (0.052 mL, 0.29 mmol), followed by trifluoromethanesulfonic anhydride (0.040 mL, 0.234 mmol). The mixture was stirred at −70 °C for 0.75 h. The cold solution was rapidly added to saturated bicarbonate (3 mL), and the mixture extracted with EtOAc (15 mL), washed with brine (3 mL), and dried over sodium sulfate. The solution was concentrated almost to dryness and passed through a short silica gel column with 1:1 ethyl acetate/hexane. The crude product was purified by TLC (1:1 ethyl acetate/hexane): yield 14.0 mg (57%); NMR δ 7.88 (d, 1 H, J = 16.0 Hz, PhCH=CH), 7.6–7.4 (br, 6 H, Ph + vinyl proton), 5.16 (t, 1 H, J = 3.2 Hz, C-5 methine), 4.52 (dd, 1 H, J = 2.6, 12.7 Hz, C-4 methylene), 4.38 (dd, 1 H, J = 4.1, 12.9 Hz, C-4 methylene), 3.60 (s, 3 H, OCH_3), 2.87 (s, 3 H, NCH_3).

Cis Triflate (6c): NMR δ 7.90 (d, 1 H, J = 15.0 Hz, PhCH=CH), 7.6–7.40 (br, 5 H, Ph), 5.38 (dd, 1 H, J = 5.4, 10.8 Hz, C-5 methine), 4.66 (t, 1 H, J = 10.5 Hz, C-4 methylene), 4.36 (dd, 1 H, J = 5.4, 10.5 Hz, C-4 methylene), 3.54 (s, 3 H, OCH_3), 2.83 (s, 3 H, NCH_3); IR 1710 (urethane C=O), 1415 (RSO_2OR) cm^{-1}.

(4*RS*,5*SR*)-1-Methyl-3-oxa-4[[(tetrahydropyranyl)oxy]-methyl]-5-cinnamoyl-5-methyl-2-pyrrolidinone (7e). To a solution of the rearranged keto alcohol **7** (58.1 mg, 0.199 mmol) in 5 mL of CH_2Cl_2 was added 0.9 mL of dihydropyran (50 equiv), followed by a solution of 5 mg (0.1 equiv) of pyridinium *p*-toluenesulfonate in 0.3 mL of CH_2Cl_2. The mixture was stirred at 25 °C for 18 h and concentrated, and enough ether was added to cause a white precipitate to form. The mixture was washed twice with half-statuated brine and dried over sodium sulfate. The crude product was purified on 10 g of silica gel (1:1 ethyl acetate/hexane) to yield 61.5 mg (82%) of **7e**: NMR δ 7.6–7.25 (br, 5 H, Ph), 7.60 (d, 1 H, J = 16.5 Hz, PhCH=CH), 7.20 (d, 1 H, J = 16.5 Hz, PhCH=CH), 4.70 (dd, J = 6.0, 9.0 Hz, C-4 methine), 4.35 (br s, 1 H, THP acetal proton), 3.35 (s, 3 H, OCH_3), 2.75 (s, 3 H, NCH_3).

In addition to **7e** there was isolated an isomeric product **7h** (16.9 mg), which with 0.01 M *p*-TsOH in methanol was converted into the bicyclic ketal **7g**: NMR δ 7.5–7.20 (br, 5 H, Ph), 6.90 (d, 1 H, J = 16.5 Hz, PhCH=CH), 6.05 (d, 1 H, J = 16.5 Hz, PhCH=CH), 5.95 (m, 1 H, C-4 methine), 4.15 (m, 2 H, methylene), 3.35 (s, 3 H, allylic OCH_3), 3.30 (s, 3 H, $NCOCH_3$), 2.80 (s, 3 H, NCH_3); mass spectrum, m/e 305 (10%, M^+), 290 (40%, M - CH_3), 274 (10%, M - OCH_3), 143 (100%, M - $C_{10}H_{10}O_2$).

(4*RS*,5*RS*)-1-Methyl-3-oxa-4-[[(tetrahydropyranyl)oxy]-methyl]-5-(1′-hydroxycinnamyl)-5-methoxy-2-pyrolidinone (8). To the THP ketone **7e** (61.7 mg, 0.165 mmol) in 1 mL of CH_3OH was added $NaBH_4$ (18.9 mg, 3 equiv) at 0 °C. The mixture was stirred at 0 °C for 1 h, concentrated to a thick paste, EtOAc (15 mL) added, and the organic phase washed with water (5 mL) and brine (5 mL). The solution was then dried over sodium sulfate. The crude product showed a single spot on TLC (2:1 ethyl acetate/hexane); yield 61.5 mg (98.8%). It was used in the next step without further purification: NMR δ 7.4–7.10 (br, 5 H, Ph), 6.80 (d, 1 H, J = 16.5 Hz, PhCH=CH), 6.20 (dd, 1 H, J = 16.5, 6 Hz, PhCH=CH), 4.70 (m, 1 H, C-4 methine), 4.55 (br s, 1 H, THP acetal proton), 4.20–3.35 (m, 3 H, allylic + 2 THP protons), 3.30 (s, 3 H, OCH_3), 2.98 (s, 3 H, NCH_3), 1.9–1.40 (m, 6 H, THP methylenes); IR 3600–3300 (br, OH), 1760 (urethane C=O) cm^{-1}; mass spectrum, m/e 345 (10%, M - CH_3OH), 244 (25%, M - C_9H_9O).

(4*RS*,5*RS*)-1-Methyl-3-oxa-4-[[(tetrahydropyranyl)oxy]-methyl]-5-(1′-methoxycinnamyl)-5-methoxy-2-pyrrolidinone (8a). To the THP alcohol **8** (37.7 mg, 0.1 mmol) in 1.5 mL of DME at 0 °C was added NaH (8.65 mg, 3.5 equiv) as a 50% oil dispersion. After the mixture was stirred for 0.5 h at 0 °C, 0.065 mL of CH_3I (10 equiv) was added and stirring continued for 1 h at 0 °C. The solution was then warmed to 25 °C for 3 h. After the solution was cooled to 0 °C, water was added to decompose excess NaH. The mixture was extracted with EtOAc (15 mL) and the extract washed with brine (5 mL) and dried over sodium sulfate. The crude product was not purified at this stage, but taken on to the next step as a mixture of isomers **8a**. TLC using 2:1 EtOAc/hexane showed two major spots; yield 39.6 mg. The slower-moving isomer A was separated from B to determine their spectra: NMR (isomer A) δ 7.6–7.40 (m, 5 H, Ph), 6.50 (d, 1 H, J = 16.5 Hz, PhCH=CH), 6.35 (dd, 1 H, J = 16.5, 7.5 Hz, PhCH=CH), 6.75–6.55 (m, 2 H, THP acetal proton, C-4 methine), 3.30 (s, 3 H, $CHOCH_3$), 3.20 (s, 3 H, $COCH_3$), 2.80 (s, 3 H, NCH_3), 1.7–1.4 (m, 6 H, THP methylenes); (isomer B) δ 7.6–7.30 (m, 5 H, Ph), 6.70 (d, 1 H, J = 16.5 Hz, PhCH=CH), 6.25 (dd, 1 H, J = 16.5, 7.5 Hz, PhCH=CH), 4.7–4.50 (m, 2 H, THP acetal proton, C-4 methine), 3.40 (s, 3 H, $CHOCH_3$), 3.22 (s, 3 H, $COCH_3$), 2.95 (s, 3 H, NCH_3), 1.9–1.50 (m, 6 H, THP methylenes).

(4*RS*,5*RS*)-1-Methyl-3-oxa-4-(hydroxymethyl)-5-(1′-methoxycinnamyl)-5-methoxy-2-pyrrolidinone (9). A solution of the THP methyl ether **8a** (32.8 mg, 0.084 mmol) in 3 mL of 0.001 M *p*-TsOH in methanol was stirred at 25 °C for 24 h. Then 1 mL of saturated bicarbonate was rapidly added to produce a copious precipitate which dissolved upon addition of 1 mL of water. The mixture was extracted with EtOAc (15 mL) and the extract washed with brine (5 mL) and dried over sodium sulfate. The crude product was separated into its components by TLC (2:1 EtOAc/hexane) to afford 10.1 mg of slower-moving isomer A and 8.1 mg of isomer B; total yield 71%: NMR (isomer A) δ 7.5–7.30 (m, 5 H, Ph), 6.75 (d, 1 H, J = 16.5 Hz, PhCH=CH), 6.00 (dd, 1 H, J = 16.5, 7.5 Hz, PhCH=CH), 4.60 (t, 1 H, J = 6 Hz, C-4 methine), 4.10 (d, 1 H, J = 7.5 Hz, $CHOCH_3$), 4.05–3.90 (m, 2 H, J = 9, 6 Hz, methylene), 3.45 (s, 3 H, $CHOCH_3$), 3.30 s, 3 H, $COCH_3$), 2.90 (s, 3 H, NCH_3); (isomer B) δ 7.5–7.30 (m, 5 H, Ph), 6.75 (d, 1 H, J = 16.5 Hz, PhCH=CH), 6.10 (dd, 1 H, J = 16.5, 7.5 Hz, PhCH=CH), 4.65 (dd, 1 H, J = 7.5, 4.5 Hz, C-4 methine), 3.95 (d, 1 H, J = 7.5 Hz, $CHOCH_3$), 3.95–3.80 (m, 2

H, J = 7.5, 4.5 Hz, methylene), 3.38 (s, 3 H, $CHOCH_3$), 3.23 (s, 3 H, $COCH_3$), 2.88 (s, 3 H, NCH_3). Double irradiation experiment (isomer B): Irradiate dd at δ 6.10, d at δ 3.95 becomes s; irradiate m at δ 3.95–3.80, dd at δ 4.65 becomes s, dd at δ 6.10 becomes d. IR (isomer B) 1760 cm^{-1} (urethane); high-resolution mass spectrum, m/e (isomer B) calcd for $C_6H_{10}O_4N$ 160.0610, found 160.0623 (100%); calcd for $C_{10}H_{11}O$ 147.0810, found 147.0783 (25%).

(4*RS*,5*RS*)-1-Methyl-3-oxa-4-(tosyloxymethyl)-5-(1′-methoxycinnamyl)-5-methoxy-2-pyrrolidinone (9a). Tosyl chloride (72.2 mg, 10 equiv) in 0.6 mL of dry pyridine was added to the alcohol methyl ether **9** (isomer A, 11.4 mg, 0.037 mmol), and the solution stirred for 20 h at 25 °C. The solution, which turned from yellow to brown overnight, was cooled to 0 °C, and upon addition of water (0.5 mL), stirred at 0 °C for an additional 30 min. CH_2Cl_2 (15 mL) was added and the extract washed with 10% HCl (2 × 5 mL) and saturated bicarbonate (5 mL) and then dried over sodium sulfate. The crude product showed a single spot on TLC (2:1 ethyl acetate/hexane) and no further purification was necessary: yield 18.3 mg (100%); NMR (isomer A) δ 7.5–7.30 (br, 9 H, Ph), 6.7 (d, 1 H, J = 16.5 Hz, PhC**H**=CH), 5.95 (dd, 1 H, J = 16.5, 7.5 Hz, PhCH=C**H**), 4.70 (dd, 1 H, J = 9, 3 Hz, C-4 methine), 4.60 (dd, 1 H, J = 12, 3 Hz, methylene), 4.25 (dd, 1 H, J = 12, 9 Hz, methylene), 3.95 (d, 1 H, J = 7.5 Hz, C**H**OCH_3), 3.32 (s, 3 H, $CHOCH_3$), 3.18 (s, 3 H, $COCH_3$), 2.81 (s, 3 H, NCH_3), 2.41 (s, 3 H, PhCH_3).

The same procedure was applied to isomer B. The NMR spectrum of the resulting tosylate showed only slight differences.

(4*SR*,5*RS*)-1-Methyl-3-oxa-4-[(methylthio)methyl]-5-(1′-methoxycinnamyl)-5-methoxy-2-pyrrolidinone (9b). To a solution of **9a** (from isomer A, 62.1 mg, 0.135 mmol) in 3 mL of DMF was added at 0 °C under N_2 atmosphere 0.31 mL (5 equiv) of CH_3SNa in EtOH (2.15 M) and the solution was stirred at 0 °C for 0.5 h. Stirring was continued for 3 h at 25 °C, after which CH_2Cl_2 (15 mL) was added, the resulting mixture washed with water (5 mL) and brine (5 mL), and the CH_2Cl_2 extract dried over sodium sulfate. High vacuum was used to remove traces of DMF. The crude product was purified by TLC (1:1 EtOAc/hexane) by using three developments of the plate. Two related compounds were isolated. The desired slower-moving product **9b** amounted to 23.8 mg: NMR δ 7.5–7.30 (br, 5 H, Ph), 6.70 (d, 1 H, J = 16.5 Hz, PhC**H**=CH), 6.05 (dd, 1 H, J = 16.5, 7.5 Hz, PhCH=C**H**), 4.70 (dd, 1 H, J = 9.0, 3.0 Hz, C-4 methine), 4.00 (d, 1 H, J = 7.5 Hz, C**H**OCH_3), 3.41 (s, 3 H, $CHOCH_3$), 3.31 (s, 3 H, $COCH_3$), 3.05 (dd, 1 H, J = 15.0, 3.0 Hz, methylene), 2.25 (s, 3 H, SCH_3); IR 1760 (urethane C=O) cm^{-1}; low-resolution mass spectrum, m/e 306 (5%, M − OCH_3), 305 (6%, M − CH_3OH), 190 (100%, M − $C_{10}H_{11}O$), 147 (38%, M − $C_7H_{12}O_3N$ S); high-resolution mass spectrum, m/e calcd for $C_{16}H_{19}O_3NS$ 305.1086, found 305.1097 (43.2%); calcd for $C_7H_{12}O_3NS$ 190.0537, found 190.0548 (56.3%).

(4*RS*,5*SR*)-1-Methyl-3-oxa-4-methyl-5-(1′-methoxycinnamyl)-5-methoxy-2-pyrrolidinone (9c). A solution of the thioether **9b** (8.6 mg, 0.025 mmol), derived from isomer A of alcohol **9** in 2 mL of acetone, was added to Raney nickel[25] (T-1, ~100 mg) in 4 mL of acetone which had been deactivated by refluxing for 10 min in acetone. The slurry was stirred vigorously at reflux for 3 h, then filtered through Celite, and washed with 30 mL of EtOH. The crude product was purified by TLC (1:1 EtOAc/benzene) to yield 3.2 mg (43%)[26] of **9c**. In addition, 2.4 mg (32%) of product was obtained in which the double bond had been saturated: NMR δ 7.5–7.30 (m, 5 H, Ph), 6.70 (d, 1 H, J = 16.5 Hz, PhC**H**=CH), 6.05 (dd, 1 H, J = 16.5, 7.5 Hz, PhCH=C**H**), 4.50 (q, 1 H, J = 6 Hz, C-4 methine), 3.95 (d, 1 H, J = 7.5 Hz, C**H**OMe), 3.42 (s, 3 H, $CHOCH_3$), 3.35 (s, 3 H, $CHOCH_3$), 2.98 (s, 3 H, NCH_3), 1.50 (d, 3 H, J = 6 Hz, C-4 methyl). Double-resonance experiment: Irradiation of doublet at δ 1.50 results in singlet at δ 4.50; conversely irradiation of quartet at 4.50 results in singlet at 1.50. IR 1750 (urethane) cm^{-1}; high-resolution mass spectrum, m/e calcd for $C_{10}H_{11}O$ 147.0810, found 147.0811 (36.5%); calcd for $C_6H_{10}O_3N$ 144.0661, found 144.0662 (100%); calcd for C_8H_7 103.0548, found 103.0557 (19.8%).

(25) Dominguez, A.; Lopez, I. C.; Franco, R. *J. Org. Chem.* **1961**, *26*, 1625.

(26) The ratio of **9c** to its dihydro product improved when the nickel was deactivated for 15 min and the reaction was terminated after 30 min.

(4*RS*,5*RS*)-1-Methyl-3-oxa-4-methyl-5-(1′-methoxycinnamyl)-5-hydroxy-2-pyrrolidinone (11a). A solution of the methoxymethyl compound **9c** (3.7 mg, 0.013 mmol) in 1 mL of 0.2 N HCl in THF was stirred at 25 °C for 1.5 h. The mixture was taken up in EtOAc (15 mL), washed with bicarbonate (3 mL) and brine (3 mL), and dried over sodium sulfate. Hemiketal **11a** (3.9 mg) was obtained: NMR δ 7.6–7.20 (br, 5 H, Ph), 6.70 (d, 1 H, J = 16 Hz, PhC**H**=CH), 5.98 (dd, 1 H, J = 16.0, 9.0 Hz, PhCH=C**H**), 4.50 (q, 1 H, J = 6.0 Hz, C-4 methine), 3.95 (d, 1 H, J = 9.0 Hz, C**H**OMe), 3.40 (s, 3 H, $CHOCH_3$), 2.90 (s, 3 H, NCH_3), 1.35 (d, 3 H, J = 6.0 Hz, C-5 methyl); IR 1755 (urethane), 3500–3600 (OH) cm^{-1}.

(4*SR*,5*RS*)-1-Methyl-3-oxa-4-formyl-5-(1′-methoxycinnamyl)-5-methoxy-2-pyrrolidinone (10). The primary alcohol methyl ether **9** (isomer B, 5.9 mg, 0.019 mmol) in 0.5 mL of CH_2Cl_2 was added to pyridinium chlorochromate (20.0 mg, 5 equiv) and sodium acetate (7.9 mg, 5 equiv) in 2 mL of CH_2Cl_2. Addition caused the reaction to turn bright orange as it stirred at 25 °C. After 2 h, ether was added (50 mL) and the mixture was filtered through a short pad of Florisil and Celite: yield 3.1 mg; NMR δ 9.70 (s, 1 H, CHO), 7.5–7.20 (br, 5 H, Ph), 6.75 (d, 1 H, J = 16 Hz, PhC**H**=CH), 6.25 (dd, 1 H, J = 7.5, 16 Hz, PhCH=C**H**), 5.95 (s, 1 H, C-4 methine), 4.05 (d, 1 H, J = 7.5 Hz, C**H**OMe), 3.42 (s, 3 H, $CHOCH_3$), 3.1 (s, 3 H, $CHOCH_3$), 2.9 (s, 3 H, NCH_3); IR 1760 (urethane) cm^{-1}.

(4*RS*,5*RS*)-1-Methyl-3-oxa-5-(1′,4-epoxymethylenocinnamyl)-5-methoxy-2-pyrrolidinone (12). To a solution of the mesylate **7b** (6.1 mg, 0.016 mmol) in 0.5 mL of THF was added at 0 °C 0.05 mL of $LiEt_3BH$ in THF (1 M), and the mixture was stirred at 0 °C for 3 h and then at 25 °C for 2 h. Water (0.5 mL) was added to decompose excess $LiEt_3BH$, followed by 0.05 mL of H_2O_2 (30%) and 0.05 mL of 10% NaOH, and the mixture was stirred for 30 min. CH_2Cl_2 (15 mL) was added and the extract washed with water (5 mL) and brine (5 mL) and then dried over sodium sulfate. The crude product was purified by TLC (1:1 EtOAc/hexane) to yield 3.0 mg of the epoxy urethane **12** (66.5%). The product was recrystallized from EtOAc/hexane: mp 123.5–124 °C; NMR δ 7.5–7.30 (br, 5 H, Ph), 6.80 (d, 1 H, J = 16.5 Hz, PhC**H**=CH), 6.10 (dd, 1 H, J = 16.5, 7.5 Hz, PhCH=C**H**), 4.90 (d, 1 H, J = 4.5 Hz, C-4 methine), 4.30 (d, 1 H, J = 7.5 Hz, CH=CHC**H**), 4.20 (d, 1 H, J = 12 Hz, methylene), 4.00 (dd, 1 H, J = 4.5, 12.0 Hz, methylene), 3.3 (s, 3 H, OCH_3), 2.85 (s, 3 H, NCH_3); IR 1760 (urethane) cm^{-1}; mass spectrum, m/e 275 (3%, M^+), 143 (100%, M − C_9H_8O).

Anal. Calcd for $C_{15}H_{17}O_4N_1$: C, 65.47; H, 6.18; N, 5.09; O, 23.26. Found: C, 64.69; H, 6.46; N, 4.94; O, 23.91.

(5*RS*,6*RS*)-1-Methyl-3-oxa-5-tosyloxy-6-(1′-hydroxycinnamyl)-6-methoxy-2-piperidinone (13). To a solution of the trans keto tosylate **5b** (31.0 mg, 0.07 mmol) in 3 mL of methanol at 0 °C was added $NaBH_4$ (27.3 mg). The mixture was stirred for 11 min at 0 °C, followed by neutralization with 10% HCl (pH 6) and extraction with EtOAc (20 mL). The organic layer was washed with water (3 mL), bicarbonate (3 mL), and brine (3 mL) and dried over sodium sulfate. The crude product was purified by TLC (2:1 EtOAc/hexane). Each of the two possible isomers **13** from the reduction was isolated separately to yield 79% from the keto alcohol **5**. Both isomers showed bands in their IR spectra at 1710 cm^{-1} characteristic of six-membered ring structures. The faster-moving isomer was characterized by its NMR spectrum: δ 7.6–7.40 (br, 5 H, Ph), 6.75 (d, 1 H, J = 15 Hz, PhC**H**=CH), 5.95 (dd, 1 H, J = 4.0, 15.0 Hz, PhCH=C**H**), 5.08 (dd, 1 H, J = 3.4, 4.6 Hz, C-5 methine), 4.60 (d, 1 H, J = 4.0 Hz, CH=CHC**H**), 4.10 (m, 2 H, C-4 methylene), 3.40 (s, 3 H, OCH_3), 2.98 (s, 3 H, NCH_3), 2.47 (s, 3 H, PhCH_3); mass spectrum, m/e 275 (10%, M − TsOH), 243 (90%, M − MeOH − TsOH), 172 (100%, TsOH).

(5*SR*,1′*RS*)-1-Methyl-3-oxa-4ξ-styryl-5-methoxy-5-(1′-tosyloxy-2′-hydroxyethyl)pyrrolidinone (14). The title compound resulted when the borohydride reduction of **5b** was extended to 30 min or longer. A more suitable procedure is the following: to a solution of the trans keto tosylate **5b** (6.0 mg) in 1.5 mL of 2-propanol was added at 0 °C $NaBH_4$ (6.0 mg). The reaction was allowed to proceed for 30 min and worked up as above. The crude product was purified by TLC (2:1 EtOAc/hexane) to yield 2.5 mg: NMR δ 7.8–7.2 (br, 9 H, Ph + OTs), 6.85 (dd, 1 H, J = 16.5 Hz, PhC**H**=CH), 6.25 (dd, 1 H, J = 16.5, 5

Hz, PhCH=CH), 5.70 (d, 1 H, J = 5 Hz, CH=CHCH), 4.80 (t, 1 H, J = 4.5 Hz, CHOTs), 4.10 (m, 1 H, CH_2OH), 3.95 (m, 1 H, CH_2OH), 3.70 (s, 3 H, OCH_3), 2.75 (s, 3 H, NCH_3), 2.45 (s, 3 H, $PhCH_3$); IR 1760 (5-ring urethane) cm^{-1}.

Acetate (14a): NMR δ 7.8–7.2 (br, 9 H, Ph + OTs), 6.90 (d, 1 H, J = 16.5 Hz, PhCH=CH), 6.20 (dd, 1 H, J = 16.5, 6 Hz, PhCH=CH), 5.21 (d, 1 H, J = 6 Hz, CH=CHCH), 5.05 (dd, 1 H, J = 3, 6 Hz, CHOTs), 4.55 (dd, 1 H, J = 3, 12 Hz, CHOAc), 4.30 (dd, 1 H, J = 6, 12 Hz, CHOAc), 3.25 (s, 3 H, OCH_3), 2.80 (s, 3 H, NCH_3), 2.45 (s, 3 H, $PhCH_3$), 2.10 (s, 3 H, $COCH_3$).

(5*RS*,6*RS*)-1-Methyl-3-oxa-5-tosyloxy-6-[1′-[(methoxy)methoxy]cinnamyl]-6-methoxy-2-piperidinone (13a). To a solution of the trans tosylate alcohol (isomer B, 10.9 mg, 0.025 mmol) (**13**) in 0.25 mL of methylene chloride was added diisopropylethylamine (0.21 mL) and chloromethyl methyl ether (0.1 mL). The mixture was stirred at 25 °C for 65 h. The solvent was removed, EtOAc added (15 mL), and the mixture washed with 10% HCl (3 mL) and bicarbonate (3 mL). The EtOAc extract was dried over sodium sulfate and evaporated, and the crude product was purified by TLC (1:1 ethyl acetate/hexane): yield 9.6 mg of **13a** (80%); NMR δ 7.6–7.40 (br, 5 H, Ph), 6.60 (d, 1 H, J = 15.7 Hz, PhCH=CH), 5.95 (dd, 1 H, J = 5.7, 15.9 Hz, PhCH=CH), 5.17 (dd, 1 H, J = 3.3, 7.1 Hz, C-5 methine), 4.58 (d, 1 H, J = 7.5 Hz, $OCHO_2$), 4.43 (d, 1 H, J = 7.5 Hz, OCH_2O), 4.38 (d, 1 H, J = 5.7 Hz, CH=CHCH), 4.25 (dd, 1 H, J = 3.9, 11.5 Hz, C-4 methylene), 4.10 (dd, 1 H, J = 7.2, 11.7 Hz, C-4 methylene), 3.38 (s, 3 H, CH_2OCH_3), 3.32 (s, 3 H, OCH_3), 2.9 (s, 3 H, NCH_3), 2.48 (s, 3 H, $PhCH_3$); IR 1715 (urethane) cm^{-1}.

1-Methyl-3-oxa-6-[1′-[(methoxy)methoxy]cinnamyl]-6-methoxypiperid-4,5-en-2-one (15). To a solution of the trans tosylate methoxymethyl ether (**13a**) (faster-moving isomer B, 9.6 mg, 0.019 mmol) in 0.4 mL of DMF was added CH_3SNa/DMF (0.19 mmol, 0.019 mL), and the resulting mixture was stirred at 25 °C for 18 h. Benzene (15 mL) was then added and the benzene extract washed with water (3 mL) and dried over sodium sulfate. The crude product was purified by TLC (1:1 EtOAc/hexane): yield 1.7 mg of olefin **15**; NMR δ 7.6–7.40 (br, 5 H, Ph), 6.80 (d, 1 H, J = 6.0 Hz, C-4 vinyl), 6.7 (d, 1 H, J = 15.0 Hz, PhCH=CH), 5.95 (dd, 1 H, J = 9.0, 15.0 Hz, PhCH=CH), 5.30 (d, 1 H, J = 6.0 Hz, C-5 vinyl), 4.70 (br, 2 H, OCH_2O), 4.45 (d, 1 H, J = 9 Hz, CH=CHCH), 3.40 (s, 3 H, CH_2OCH_3), 3.20 (s, 3 H, OCH_3), 2.95 (s, 3 H, NCH_3); IR 1715 (urethane) cm^{-1}; mass spectrum, m/e 288 (3%, M - OCH_3), 142 (100%, M - $C_{11}H_{13}O_2$).

(5*SR*,6*RS*,1′*RS*)-1-Methyl-3-oxa-5-tosyloxy-6-(1′-hydroxycinnamyl)-6-methoxy-2-piperidinone (16). The cis keto tosylate **6** (22.3 mg, 0.05 mmol) in 2.5 mL of methanol cooled to 0 °C was reduced with $NaBH_4$ (24.5 mg, 13 equiv) for 8 min as described for the trans isomer **5b** to yield 15.0 mg (67%). Only **16**, one of the two possible isomers, was produced in the reduction; NMR δ 7.5–7.20 (br, 5 H, Ph), 6.70 (d, 1 H, J = 16.0 Hz, PhCH=CH), 6.35 (dd, 1 H, J = 5.5, 16.0 Hz, PhCH=CH), 5.04 (dd, 1 H, J = 3.8, 6.6 Hz, C-5 methine), 4.65 (m, 1 H, J = 5.3, 1.1 Hz, CH=CHCH), 4.42 (dd, 1 H, J = 6.6, 11.6 Hz, C-4 methylene), 4.25 (dd, 1 H, J = 3.7, 11.6 Hz, C-4 methylene), 3.27 (s, 3 H, OCH_3), 3.08 (s, 3 H, NCH_3), 2.40 (s, 3 H, $PhCH_3$).

(5*SR*,6*RS*,1′*RS*)-1-Methyl-3-oxa-5-tosyloxy-6-[1′-[(methoxy)methoxy]cinnamyl]-6-methoxy-2-piperidinone (16a). The cis tosylate **6b** was converted into the methoxymethyl ether **16a** as described above for the trans tosylate. The crude product was purified by TLC (1:1 EtOAc/hexane): yield 9.4 mg of **16a** (68%); NMR δ 7.4–7.10 (br, 5 H, Ph), 6.48 (d, 1 H, J = 16.0 Hz, PhCH=CH), 6.20 (dd, 1 H, J = 7.7 Hz, 16.0 Hz, PhCH=CH), 5.04 (dd, 1 H, J = 5.9, 10.9 Hz, C-5 methine), 4.78 (t, 1 H, J = 10.8 Hz, C-4 methylene), 4.68 (d, 1 H, J = 7.2 Hz, OCH_2O), 4.50 (d, 1 H, J = 7.1 Hz, OCH_2O), 4.39 (d, 1 H, J = 7.7 Hz, CH=CHCH), 4.25 (dd, 1 H, J = 5.9, 10.0 Hz, C-4 methylene), 3.34 (s, 3 H, CH_2OCH_3), 3.02 (s, 3 H, OCH_3), 2.92 (s, 3 H, NCH_3), 2.30 (s, 3 H, $PHCH_3$); IR 1700 (urethane) cm^{-1}.

(5*SR*,6*RS*)-1-Methyl-3-oxa-5-iodo-6-cinnamoyl-6-methoxy-2-piperidinone (17). To a solution of the trans triflate **5c** (70.3 mg, 0.166 mmol) in 3 mL of acetone was added NaI (98.6 mg). The mixture was stirred at 25 °C for 18 h, the solvent removed, and EtOAc (15 mL) added. The resulting solution was washed with saturated sodium thiosulfate (3 mL) and half-saturated brine (3 mL) and dried over sodium sulfate. The crude product (**17**, 80.5 mg) solidified on standing. It was recrystallized from EtOAc/hexane to yield a white crystalline solid, decomposition point 180–182 °C: yield from starting alcohol **7** 38.3 mg (58% for 2 steps); NMR δ 7.75 (d, 1 H, J = 16.0 Hz, PhCH=CH), 7.50 (d, 1 H, J = 16.0 Hz, PhCH=CH), 7.6–7.4 (br, 5 H, Ph), 4.70 (dd, 1 H, J = 10.7, 12.0 Hz, C-4 methylene), 4.44 (dd, 1 H, J = 5.2, 12.0 Hz, C-5 methine), 4.32 (dd, 1 H, J = 5.2, 10.5 Hz, C-4 methylene), 3.40 (s, 3 H, OCH_3), 2.78 (s, 3 H, NCH_3); IR 1708 (urethane C=O), 1605 (C=C) cm^{-1}; low-resolution mass spectrum, m/e 402 (35%, M + 1), 370 (20%, M - OCH_3), 270 (100%, M - C_9H_7O), 131 (100%, M - $C_6H_9O_3NI$); high-resolution mass spectrum, m/e calcd for $C_{14}H_{13}O_3NI$ 369.9940, found 369.9957 (2.2%); calcd for $C_6H_9O_3NI$ 269.9628, found 269.9615 (80.5%).

1-Methyl-3-oxa-6-cinnamoyl-6-methoxy-2-piperidinone (17a). To the cis iodide **17** (6.2 mg, 0.015 mmol) and azobis(isobutyronitrile) (1.4 mg) was added under N_2 0.6 mL of dry benzene (flushed for 20 min with N_2 to remove oxygen), followed by tri-*n*-butyltin hydride (5.0 mL, 1.25 mmol) (strong IR band at 1805 cm^{-1} for SnH). The mixture was stirred at 55 °C for 9 h, the solvent removed, the residue taken up in acetonitrile[27] (15 mL), and the resulting solution washed with hexane (2 × 5 mL). The acetonitrile phase, which contained all of the product free of tin compounds, was evaporated to dryness in vacuo and the residue purified by TLC (2:1 EtOAc/hexane) to yield 2.8 mg (68%) of **17a**. Excess tri-*n*-butyltin hydride caused reduction of the styryl double bond; NMR δ 7.75 (d, 1 H, J = 16 Hz, PhCH=CH), 7.6–7.40 (br, 5 H, Ph), 4.21 (m, 2 H, C-4 methylene), 2.28 (s, 3 H, OCH_3), 2.80 (s, 3 H, NCH_3), 2.46 (septet, 1 H, J = 6, 9, 15 Hz, C-5 methylene), 1.96 (dt, 1 H, J = 3.3, 14.8 Hz, C-5 methylene). Double-irradiation experiment: Irradiation of m at δ 4.21 causes septet at δ 2.46 and dt at δ 1.96 to collapse to d (J = 15 Hz). Irradiation of septet at δ 2.46 causes dt to collapse to t; IR 1700 (6-ring urethane C=O), 1600 (C=C) cm^{-1}; high-resolution mass spectrum, m/e calcd for $C_{14}H_{14}O_3N$ (M - C_9H_7O) 244.0973, found 244.0980 (6.9%); calcd for $C_6H_{10}O_3N$ (M - $C_6H_{10}O_3N$) 144.0660, found 144.0667 (100%).

1-Methyl-3-oxa-6-(1-oxo-3-phenylpropyl)-6-methoxy-2-piperidinone (17b). To the olefin **18** (2.0 mg, 0.007 mmol) in 2.2 mL of EtOH was added 10.1 mg of Pd/C (10%). The suspension was vigorously stirred at 25 °C under an H_2 atmosphere for 3 h. The suspension was then filtered through Celite and washed with 25 mL of EtOAc. The crude product **17b** (1.5 mg), although essentially pure, was purified by TLC (1:1 ethyl acetate/hexane): NMR δ 7.4–7.2 (br, 5 H, Ph), 4.00 (m, 2 H, C-4 methylene), 3.30 (s, 3 H, OCH_3), 3.95 (m, 4 H, $PhCH_2CH_2$), 2.68 (s, 3 H, NCH_3), 2.27 (septet, 1 H, J = 15.0, 10.5, 5.4 Hz, C-5 methylene), 1.55 (dt, 3.2, 15.0 Hz, C-5 methylene); IR 1730 (keto C=O) cm^{-1}.

The NMR and IR spectra of **17b** were identical with those of the product obtained by catalytic reduction of **17a**.

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