EtOAc-HOAc, 45:45:10) and mixed melting point.

Polymer-Dehydrocholate Ketal 2. A mixture of 1.00 g of 1 (1.16 mmol/g, DF = 0.13), 17.8 mmol of ethylene glycol, 50 mg of *p*-toluenesulfonic acid monohydrate, and 50 mL of benzene was slowly distilled over a period of 16 h. After washing and drying (as above), 0.86 g (100%) of white polymer 2 (DF = 0.13) was produced: IR 1740 (ester), 1190-1150 (ketal), 960, 920, 840, 760, 700 cm^{-1}; ^{13}C NMR data, see Figure 2a.

Polymer-Dehydrocholate 2,4-DNP 3. Polymer-dehydrocholate 1, 1.00 g (DF = 0.14) in 50 mL of absolute ethanol was treated with 6.0 mL of 0.25 M (2,4-dinitrophenyl)hydrazine in 51:38:11 (v/v/v) 85% phosphoric acid-95% ethanol-and water. The mixture was stirred at room temperature for 20 h, filtered, washed with 95% ethanol, and Soxhlet extracted with 95% ethanol for 18 h. After drying in a vacuum oven overnight the yellow polymer 3 weighed 1.01 g (28%, DF = 0.04): ^{13}C NMR data, see Figure 2b. Anal.: N, 1.71 (corresponds to 0.31 mmol of p-$CH_3PhSO_2NHN{=}$/g polymer).

Polymer-Spacer-Dehydrocholate 4. A mixture of 2.50 g of Merrifield peptide resin (*p*-alkoxylbenzyl, 1.0 mmol CH_2OH/g, DF = 0.24)[16] was stirred at room temperature with 2.01 g (5.0 mmol) of dehydrocholic acid, 0.61 g (5.0 mmol) of 4-(*N,N*-dimethylamino)pyridine, and 1.20 g (5.8 mmol) of *N,N*-dicyclohexylcarbodimide (DDC) in 35 mL of dichloromethane for 18 h. The resulting mixture was filtered and washed with ethanol, water, methanol, and dichloromethane. Vacuum drying of the polymer at 53 °C for 1.5 h gave 2.68 g (48%) of white polymer (DF = 0.12); IR 3400 (br d, wk), 1740 (shl), 1730 (strong), 1608, 820, 744, 695, 550 cm^{-1}; ^{13}C NMR data, see Figure 1b.

Polymer-Spacer-Dehydrocholate 4 + *p*-Tosylhydrazine. To a solution of 0.93 g (5 mmol) of (*p*-tolylsulfonyl)hydrazine in 10 mL of glacial acetic acid was added 1.00 g of 4 (DF = 0.12). The mixture was placed on a wrist shaker for 37 h at room temperature. The polymer was recovered by filtration, washed with methanol and dichloromethane, and dried in vacuo at 1 Torr at room temperature for 24 h to yield 1.09 g: IR 1390, 1355, 1170, 760, 700 cm^{-1}; ^{13}C NMR showed no resonances due to a steroid or a polymer described by the structure 5. Anal.: N, 2.74; S, 2.70.

Polymer-Cholate 6. To a mixture of 1.00 g (1.16 mmol Cl/g, DF = 0.13) of chloromethylated polystyrene in 50 mL of DMF was added 0.65 g of sodium cholate. The mixture was stirred at 65 °C for 21 h, filtered, washed thoroughly, and dried for 2 h at 1 Torr to give 1.39 g (89%) of 6 (DF = 0.12): IR 3500, 1740 cm^{-1}; ^{13}C NMR data, see Figure 3a.

Polymer-Cholate 6 + 3,5-Dinitrobenzoyl Chloride. A mixture of 6 and 0.93 g (4 mmol) of 3,5-dinitrobenzoyl chloride (recrystallized) in 20 mL of pyridine was stirred at room temperature in a sealed flask for 3 days. The polymer was washed with THF, THF-water (1:1), and THF and dried at 56 °C at 1 Torr overnight to produce 1.16 g (some polymer lost in transfers). Anal.: N, 2.73. DF for monoesterification, 0.12 (100%); diesterification, 0.08 (69%); and triesterification, 0.05 (42%) of hydroxyl groups; ^{13}C NMR data, see Figure 3b.

Swern Oxidation of Polymer-Cholate 6. A solution of 0.5 mL (5.2 mmol) of oxalyl chloride and 6 mL of dichloromethane was cooled to -50 to -60 °C (dry ice-$CHCl_3$). The addition of 0.81 mL (11.4 mmol) of DMSO in 2 mL of dichloromethane proceeded over a period of 2 min via a pressure-equalizing funnel. The reaction flask was then transferred to a salt-ice bath (-10 °C), and the mixture was stirred for 5 min. Polymer 6, 1.50 g (DF = 0.12), in 10 mL of dichloromethane was added to the flask, and stirring was continued for 1.5 h. The mixture was reacted with 1.7 mL of triethylamine and allowed to warm to room temperature over a period of 0.5 h. The polymer was filtered and washed thoroughly with dichloromethane, methanol, water, methanol, and dichloromethane. The polymer was dried overnight at 2 Torr/40 °C, weighed 1.17 g (some loss in transfer), DF = 0.12, and was identical in all spectroscopic respects with polymer 1: ^{13}C NMR data, see Figure 3c and compare to that of Figure 1b.

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Synthesis of Streptazolin: Use of the Aza-Ferrier Reaction in Conjunction with the INOC Process To Deliver a Unique but Sensitive Natural Product

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The total synthesis of the unique alkaloid natural product streptazolin is described. The synthetic route makes use of the Ferrier-like reaction of a Δ^2-piperidinol with allyltrimethylsilane in combination with the INOC reaction to create the ring skeleton of this product. The extension of the aza-Ferrier reaction to other nucleophiles is discussed. The transformation of isoxazolines with peracids to β-hydroxy ketones or diol monoacetates discovered during the course of these studies is also presented.

Streptazolin (1) is a lipophilic, neutral compound first isolated from cultures of *Streptomyces viridochromogenes* strain Tü 1678 by Drautz and Zähner in 1981.[1] The purification of streptazolin was made rather difficult because of its tendency to undergo partial polymerization in concentrated form. In dilute solution, however, streptazolin proved to be stable for several days.

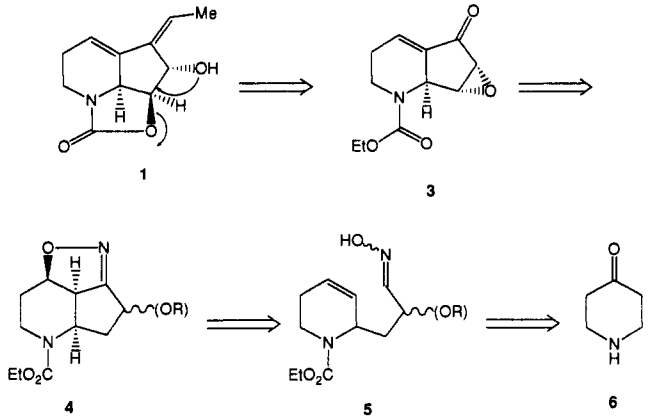
A culmination of spectroscopic investigations, chemical degradation,[1] and an X-ray analysis[2] carried out by Kupfer and Keller-Schierlein established the major features of the streptazolin structure, including its absolute stereochemistry. However, since the X-ray analysis had been carried out on dihydrostreptazolin acetate (2), and due to a lack of suitable reference compounds, the configuration[1] of the C8-C9 exocyclic olefin was not assigned unambiguously.

(1) Drautz, H.; Zähner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752.

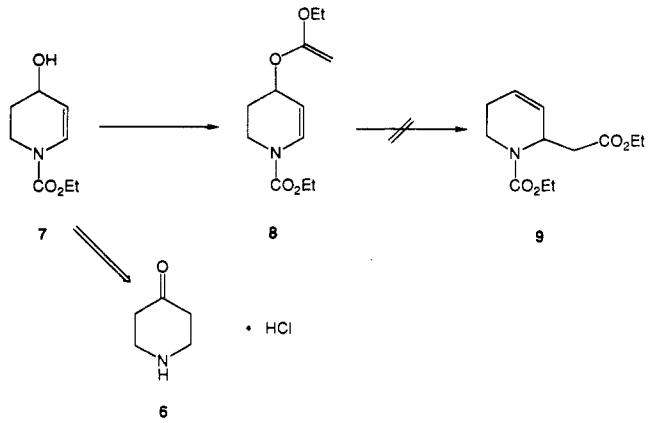
(2) Karrer, A.; Dobler, M. *Helv. Chim. Acta* **1982**, *65*, 1432.

0022-3263/90/1955-4668$02.50/0

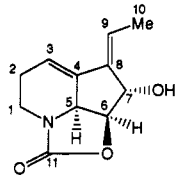
Scheme I



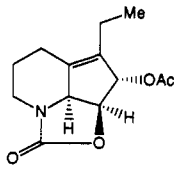
Scheme II



In biological studies, 3,9-dihydrostreptazolin was found to exhibit limited antibacterial and antifungal effects.[1]



Streptazolin (1)



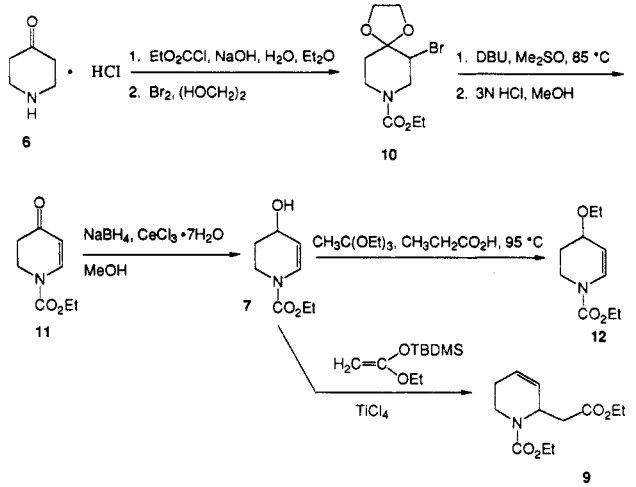
Dihydrostreptazolin acetate (2)

In this paper we describe the total synthesis of racemic streptazolin through the use of the intramolecular nitrile oxide cycloaddition (INOC) reaction.[3,4] Several new methodologies for the functionalization of the piperidine ring system and for the conversion of isoxazolines to β-hydroxy ketones and vicinal diols are also described.

Synthesis of Streptazolin

A retrosynthetic analysis of the tricyclic structure of streptazolin is diagrammed in Scheme I. We imagined that its oxazolidinone ring system could be derived by a Lewis acid initiated attack of a urethane carbonyl group upon a neighboring epoxide, while its ethylidene side chain could be introduced via a Wittig reaction. Such considerations lead to the generation of the enone **3** as one possible intermediate along the synthetic pathway. Observations of the preferential formation of *Z* olefins in the reaction of α-alkoxy ketones with lithium-free Wittig reagents have been reported by W. C. Still, thus providing some support for the anticipated control of stereochemistry in the Wittig step.[5]

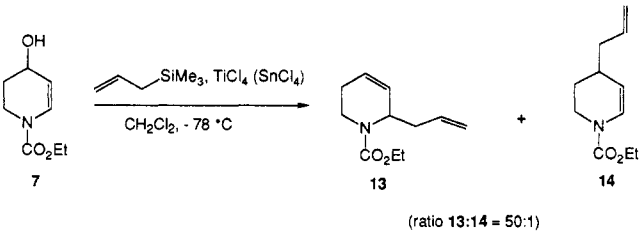
Scheme III



Based upon earlier work[3] in these laboratories, the enone **3** could clearly be generated from the isoxazoline **4**. Lastly, this isoxazoline **4** could be formed by an INOC reaction of the oxime **5**, which can be prepared from the commercially available 4-piperidinone, **6**.

To acquire the oxime **5** required for the elaboration of streptazolin, we initially considered application of the Claisen rearrangement process (Scheme II, **7** → **9**) to the *N*-carbethoxytetrahydropyridine derivative **7**. The tetrahydropyridine **7** needed for this study was best prepared from commercially available 4-piperidone monohydrate hydrochloride **6** by a sequence of reactions commencing with N-carbethoxylation followed by a bromoketalization[6] step (Scheme III). The resulting α-bromo ketal was reacted with DBU in dimethyl sulfoxide at 85 °C and then with 3 N HCl in methanol to provide the enone **11**. Lastly, sodium borohydride reduction of the enone in the presence of cerium trichloride heptahydrate in methanol took place in 95% yield to give **7**.[7]

Scheme IV



Reaction of the allylic alcohol **7** with triethyl orthoacetate in the presence of a catalytic amount of propionic acid at 95 °C failed to furnish the desired Claisen rearrangement product **9**.[8] Instead, the ethyl ether **12** was isolated in 30% yield after chromatography on silica gel.

(3) For recent reviews, see: (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984; Vol. I, pp 368–372, 401–404, and references cited therein. (b) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

(4) Kozikowski, A. P.; Park, P.-u. *J. Am. Chem. Soc.* **1985**, *107*, 1763. For a recent synthesis of streptazolin in optically pure form, see: Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115.

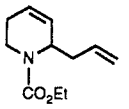
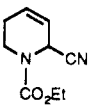
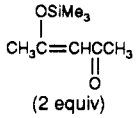
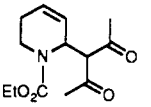
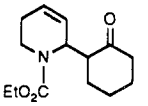
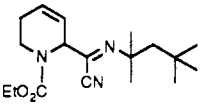
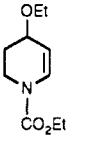
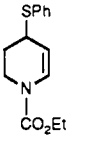
(5) Still, W. C.; Sreekumar, C.; Darst, K. P. *J. Org. Chem.* **1980**, *45*, 4262.

(6) (a) Garbisch, E. W., Jr. *J. Org. Chem.* **1965**, *30*, 2109. (b) Schell, F. M.; Williams, P. R., Jr. *Synth. Commun.* **1982**, *12*, 10.

(7) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J.-L.; Rodrigues-Hahn, L.; Crâbbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. (c) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

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

Table I. Reactions of 7 with Various Carbon and Heteroatom Nucleophiles

nucleophile (amount)	reaction conditions	product (yield, %)
$H_2C{=}CHCH_2SiMe_3$ (2 equiv)	$SnCl_4$ (1.2 equiv), CH_2Cl_2, −78 °C, 30 min	 **13** (90)
$H_2C{=}CHCH_2SiMe_3$ (2 equiv)	$SnCl_4$ (1.2 equiv), CH_3CN, −78 °C then rt,[c] 20 min	**13** (64)
$H_2C{=}CHCH_2SiMe_3$ (2 equiv)	$TiCl_4$ (1.3 equiv), CH_2Cl_2, −78 °C, 30 min	**13** (89)
$H_2C{=}CHCH_2SiMe_3$ (2 equiv)	$BF_3{\cdot}OEt_2$ (1.1 equiv), CH_3CN, 0 °C then rt, 30 min	**13** (43)
$H_2C{=}CHCH_2SiMe_3$ (2 equiv)	Me_3SiOTf (1.3 equiv), CH_2Cl_2, −78 °C, 1 h	**13** (51)
Me_3SiCN (6 equiv)	Me_3SiOTf (1.5 equiv), CH_2Cl_2, −78 °C, 3 h	 **15** (70)
 (2 equiv)	Me_3SiOTf (1.5 equiv), CH_2Cl_2, −78 °C, 2 h	 **16** (47)
$CH_3C(O)CH_2C(O)CH_3$ (solvent)	$BF_3{\cdot}OEt_2$ (1.5 equiv), 0 °C, 1.5 h	**16** (24)
 (2 equiv)	Me_3SiOTf (1.5 equiv), CH_2Cl_2, −78 °C, 2.5 h	 **17** (84)[a]
$(CH_3)_3CCH_2C(CH_3)_2N{\equiv}C$ (2 equiv)	Me_3SiOTf (1.3 equiv), CH_2Cl_2, −78 °C, 1.5 h	 **18** (44)[b]
EtOH (solvent)	PPTS (1 equiv), rt, 1.5 h	 **12** (67)
EtOH (solvent)	Me_3SiOTf (1.1 equiv), −78 °C, 3 h	**12** (54) +  **19** (5)
C_6H_5SH (2 equiv)	PPTS (1.2 equiv), C_6H_6, rt, 1.5 h	 **20** (46)
C_6H_5SH (1 equiv)	Me_3SiOTf (1 equiv), CH_2Cl_2, −78 °C, 3 h	**20** (65)

[a] This compound was contaminated by an unidentified impurity and was thus further characterized by preparing its (2,4-dinitrophenyl)-hydrazone derivative (mp 128–130 °C). [b] The assignment of structure to this product was based on its ^{13}C NMR. Its mechanism of formation is presumably related to that postulated in the Lewis acid catalyzed oligomerization of isocyanides: Saegusa, T.; Taka-ishi, N.; Ito, Y. *J. Org. Chem.* **1969**, *34*, 4040. [c] rt = room temperature.

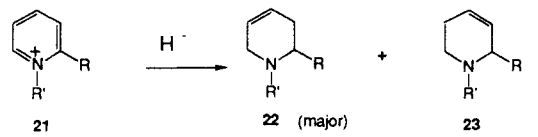
The reaction of **7** with ethyl vinyl ether in the presence of $Hg(OAc)_2$ or other Lewis acid catalysts (e.g., $TiCl_4$, $BF_3{\cdot}OEt_2$, etc.) also failed to provide the corresponding aldehyde.[9] While we were able to obtain **9** by exposure of **7** to *O*-ethyl-*O*-(*tert*-butyldimethylsilyl)ketene acetal[10] employing $TiCl_4$ as catalyst,[11] the yield was only 20%.

The failure to effect the Claisen rearrangement process using this system can most likely be attributed to the instability of the allylic alcohol **7** to Lewis acid conditions. The interaction of the lone pair of the nitrogen atom with the allylic system lies, of course, at the heart of the lability of this alcohol.

The very lability of this alcohol, in fact, suggested a simpler approach to the oxime **5**. Perhaps the iminium ion being formed in the reaction of **7** with a Lewis acid could be trapped at its α-position by a "storable" nucleophile such as allyltrimethylsilane to provide a correctly functionalized tetrahydropyridine derivative.[12]

(9) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *36*, 2526.
(10) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67.
(11) (a) Mukaiyama, T.; Saigo, K.; Osaki, M. *Chem. Lett.* **1975**, 989. (b) For a recent review, see: Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.

Scheme V

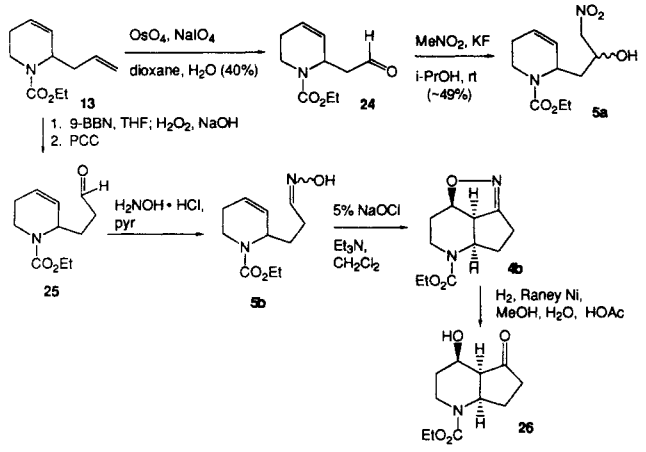


Upon examining a host of Lewis acids, solvents, reaction temperatures, and times, the desired α-substituted compound **13** could, in fact, be produced in this way. Titanium tetrachloride and tin tetrachloride proved to be the most efficacious catalysts when employed in methylene chloride at −78 °C. A 90% yield of the α-allyl substituted tetrahydropyridine was isolated (Scheme IV). A small amount of the γ-substituted isomer **14** was observable in the ^{1}H NMR of the crude reaction product (ratio ~50:1).

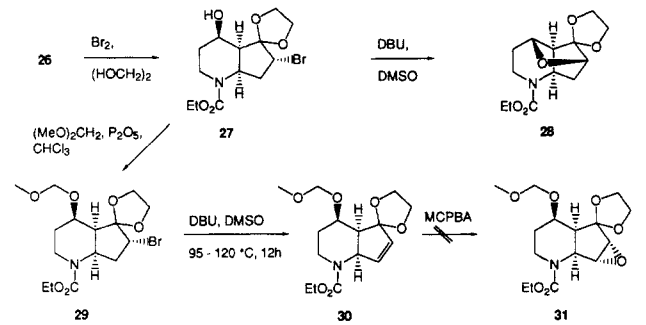
This particular reaction bears close resemblance to the well-known Ferrier rearrangement process.[13] By analogy to the Ferrier rearrangement reaction in which an allylic displacement reaction ensues from a glycal to furnish the product containing a C-1 alkoxy group, the reaction of **7** also proceeds to furnish primarily the product of attack α to the ring heteroatom.[14] This result is general for all of the carbon nucleophiles studied (Table I) and can be rationalized as a consequence of a kinetic preference for attack at the site of lowest electron density in the conjugated iminium ion system. Nucleophilic attack on a pyridinium ion is, for example, known to occur predominantly at the site α to the ring nitrogen.[15] Only with nucleophiles capable of participating reversibly in their reaction with **7** (e.g., thiophenol or ethanol) were the products of γ-substitution isolated. While initial α attack may occur, an anomeric effect[16] weakened by interaction of the nitrogen lone pair with its carbethoxy substituent, the possible nonbonded interactions of the ortho-related substituents, and resonance stabilization of the enamido system resulting from rearrangement may conspire to promote migration of the heteroatom nucleophile to the γ-position.[17]

With trimethylsilyl triflate as catalyst and ethanol as the nucleophile, the γ-addition product **12** was formed in addition to the diaddition product **19** (Table I). The structure of **19** was assigned in analogy to similar 2,4-disubstituted piperidines reported in the literature.[18]

Scheme VI



Scheme VII



While the metal hydride reduction of substituted pyridinium salts represents a well-documented technique for the production of tetrahydropyridines, it has generally been noted that a substituent at the 2-position of the ring system leads to generation of a 2-substituted 1,2,5,6-tetrahydropyridine **22** as the major reaction product rather than the alternative isomer **23** (Scheme V).[15] The Ferrier-like reaction discovered in the context of the streptazolin studies thus provides a useful entry to these alternative reaction products, the 2-substituted Δ^3-piperidines **23**.[19]

Returning to the streptazolin synthesis, an attempt was made to cleave selectively the double bond of the allyl appendage of **13** to provide an aldehyde which might be condensed in turn with the anion of nitromethane (Scheme VI). The desired aldehyde could be obtained in low yield (40%) by the action of osmium tetraoxide (1 mol %) and sodium periodate[20] in water and dioxane. While the reaction of this aldehyde with nitromethane[21] and potassium fluoride in 2-propanol proceeded to afford a diastereomeric mixture of the nitro alcohols **5a** in 49% yield, this mixture was found to be somewhat unstable to chromatographic purification. Due to the low-yielding nature of these two sequential steps, an alternative pathway was devised.

Selective hydration of the monosubstituted olefinic appendage of **13** was accomplished in 90% yield by the use of 9-BBN in THF followed by oxidative workup (3 N

(12) (a) Kozikowski, A. P.; Park, P.-u. *J. Org. Chem.* **1984**, *49*, 1676. The use of silicon reagents for the functionalization of carbohydrates has proven quite popular. (b) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281. (c) Kozikowski, A. P.; Sorgi, K. L.; Wang, B. C.; Xu, Z.-b. *Tetrahedron Lett.* **1983**, *24*, 1563. (d) Hosomi, A.; Sakata, Y.; Sukurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383. (e) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (f) Williams, R. M.; Stewart, A. O. *Tetrahedron Lett.* **1983**, *24*, 2715. (g) Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180. (h) Cupps, T. L.; Wise, D. S.; Townsend, L. B. *J. Org. Chem.* **1982**, *47*, 5115. (i) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803. (j) Sakurai, H.; Sasaki, K.; Hayashi, J.; Hosomi, A. *J. Org. Chem.* **1984**, *49*, 2808. (k) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479. Sparks, M. A.; Panek, J. S. *Tetrahedron Lett.* **1989**, *30*, 407.

(13) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.

(14) For the reaction of some β-dicarbonyl compounds with acetylated glycals, see: Yougai, S.; Miwa, T. *J. Chem. Soc., Chem. Commun.* **1983**, 68.

(15) (a) Ferles, M.; Pliml, J. *Adv. Heterocycl. Chem.* **1970**, *12*, 43. (b) Lyle, R. E.; Anderson, P. S. *Ibid.* **1966**, *6*, 45.

(16) For reviews, see: (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: Berlin, 1983. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.

(17) For some other examples of the trapping of iminium salts by allylsilanes, see: (a) Hart, D. J.; Tsai, Y.-M. *Tetrahedron Lett.* **1981**, *22*, 1567. (b) Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134.

(18) Natsume, M.; Sekine, Y.; Soyagimi, H. *Chem. Pharm. Bull.* **1978**, *26*, 2188.

(19) For a report concerning the use of 2-cyano-Δ^3-piperidines as 5,6-dihydropyridinium salt equivalents, see: Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683 and references cited therein; For the α-allylation of *N*-(alkoxycarbonyl)pyridinium salts by means of allyltin reagents, see: Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawamisi, M. *J. Org. Chem.* **1985**, *50*, 287.

(20) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 418.

(21) (a) Henry, L. *Seances Acad. Sci., Ser.* **1895**, *120*, 1265. (b) Wollenberg, R. H.; Miller, S. J. *Tetrahedron Lett.* **1978**, 3219.

NaOH and 30% H_2O_2).[22] Subsequent PCC oxidation[23] of the alcohol to aldehyde **25** (68–85% yield) and oxime formation with hydroxylamine hydrochloride in pyridine[24] give **5b** in 96% yield. While the cis, trans mixture of oximes could be separated by column chromatography, the individual isomers underwent slow equilibration at room temperature to afford the original isomeric mixture.

The crucial INOC reaction employing the oxime mixture was now tested. Reaction of **5b** with 5% sodium hypochlorite[25] in the presence of triethylamine in methylene chloride as solvent led to the desired isoxazoline **4b** in 90% yield.

Conversion of this isoxazoline to β-hydroxy ketone was best carried out by hydrogenolysis of a 0.05 M solution of **4b** in a 4:1 methanol–water mixture over Raney nickel in the presence of 4 equiv of acetic acid.[26] The desired β-hydroxy ketone **26** was obtained in 88% yield. Use of either $AlCl_3$ or H_3BO_3 as additives in the hydrogenolysis step proved problematic, for various side products including the enone formed by dehydration of **26** were observed.

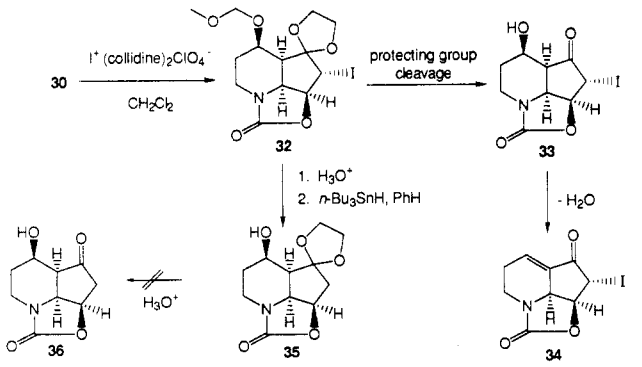
The coupling constants observed for the ring fusion hydrogens in the isoxazoline **4b** and the β-hydroxy ketone **26** were examined in order to check whether epimerization had occurred during the hydrogenolysis step. For the former compound J was 9.3 Hz, while for the latter compound J was 8.5 Hz, thus confirming maintenance of the cis stereochemistry in accordance with the Karplus relationship.

The next requirement to be met in our synthetic efforts became the introduction of a double bond into the five-membered ring. The double bond would, of course, be used to introduce the vicinal diol functionality present in this ring of the natural product. On employing conditions identical to those used in the preparation of **10**, **26** was converted to the α-bromo ketal **27** in 75% yield (Scheme VII).[6] An attempt to dehydrobrominate **27** by the use of DBU in DMSO, however, failed, for the cyclic ether **28** was formed instead. The isolation of **28** in 78% yield is indicative of the α stereochemistry of the bromine atom in **27**. The IR spectrum of **28** showed no alcoholic absorption bands. Clearly, the need to protect the hydroxyl group of **27** became evident.

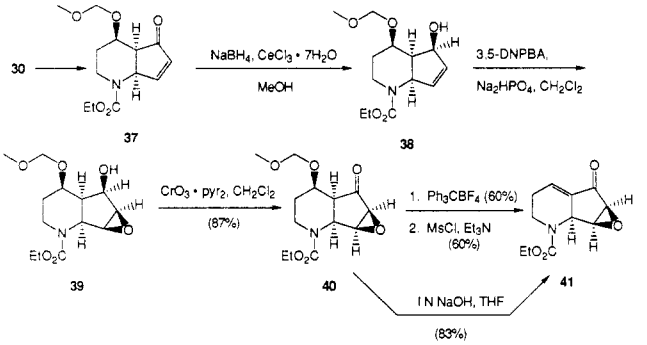
The reaction of **27** with dimethoxymethane and P_2O_5 in chloroform at room temperature for 8 h gave the MOM-protected intermediate **29** in 92% yield.[27] Dehydrobromination of **29** in DBU in DMSO at 95–120 °C for 12 h proceeded well and furnished **30** in 91% yield.

Attempts to epoxidize the double bond of **30** with MCPBA (2 or 10 equiv; buffering with $NaHCO_3$; alkaline biphasic solvent system[28]) failed to provide the desired product, a consequence presumably of the electron-withdrawing inductive effect of the heteroatom appendages. While later on we discovered that 3,5-dinitroperoxybenzoic acid[29] in the presence of Na_2HPO_4 was able to generate the epoxide **31**, we did not pursue this avenue of approach since cleavage of the ketal group was likely to prove troublesome (vide infra).

Scheme VIII



Scheme IX



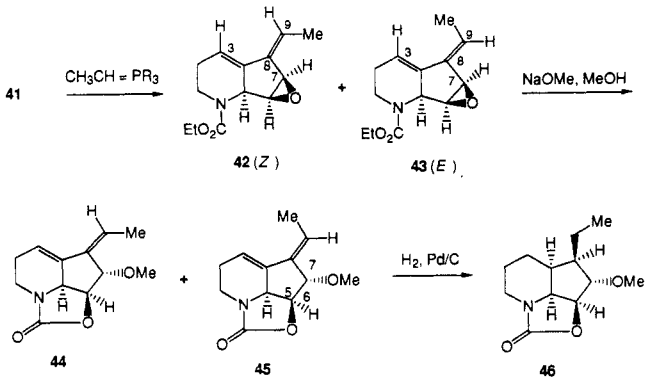
Reaction of **30** with $I^+(collidine)_2ClO_4^-$ in methylene chloride[30] proceeds in accord with literature precedent and led to the oxazolidinone **32** in 78% yield (Scheme VIII).[31] A carbonyl absorption band at 1749 cm^{-1} suggested the presence of the five-membered ring urethane.[32] While attempts were made to replace the iodo group of **32** by a hydroxyl group using various solvolytic methods, all of these failed. Efforts were taken next to cleave the MOM and ketal protecting groups from **32**, for we envisioned that the procurement of **33** would permit us to generate the enone **34**, which could in turn be transformed to a 1,3-diene by Wittig reaction. Lastly, the iodo group of this diene intermediate might then be transformed to alcohol by a solvolysis reaction unimpaired by the inductive effect of the ketal oxygens.[33]

Unfortunately, reaction of **32** under a variety of acidic conditions led only to cleavage of the MOM protecting group. Since we considered that the iodo group might contribute to the stability of the ketal, it was removed from MOM-deprotected **32** by a n-Bu_3SnH reduction.[34] Efforts to cleave the ketal group of **35** also met with failure.[35]

After a host of excursions down other blind alleys, we eventually discovered a workable route to **1**. Hydrolysis of the ketal **30** itself was found to proceed readily in sharp contrast to the results obtained with its more highly

(22) Brown, H. C.; Liotta, R.; Scouten, C. G. *J. Am. Chem. Soc.* **1976**, *98*, 5297.
(23) (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2467. (b) Piancatelli, G.; Scettri, A.; D'Auia, M. *Synthesis* **1982**, 245.
(24) Stevens, R. V.; Christensen, C. G.; Cory, R. M.; Thoursett, E. *J. Am. Chem. Soc.* **1975**, *97*, 5940.
(25) Lee, G. A. *Synthesis* **1982**, 508.
(26) Wollenberg, R. H.,; Goldstein, J. E. *Synthesis* **1980**, 757.
(27) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.
(28) Anderson, W. K.; Veysoglu, T. *J. Org. Chem.* **1976**, *38*, 2267.
(29) Rastetter, W. H.; Richard, T. J., Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.
(30) Lemieu, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190.
(31) For other examples, see: (a) Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956. (b) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 4887.
(32) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654.
(33) Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888.
(34) Kuivila, H. G. *Synthesis* **1970**, 499.
(35) The cleavage methods tried include inter alia: (a) Ph_3CBF_4, CH_2Cl_2, room temperature, 11 h: Barton, D. H. R.; Magnus, P. D.; Smith, G.; Zurr, D. *J. Chem. Soc., Chem. Commun.* **1971**, 861. (b) H_5IO_6, H_2O, dioxane, room temperature, 20 h: Walborsky, H. M.; Davis, R. H.; Howton, D. R. *J. Am. Chem. Soc.* **1951**, *73*, 2590. (c) BF_3·OEt_2, H_2O, 2-butanone, room temperature, 6 h. (d) SiO_2, aqueous 15% $HClO_4$, CH_2Cl_2, room temperature, 20 h: Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63. (e) Concentrated HCl, HOAc, room temperature, 5 h: Zderic, J. A.; Limon, D. C. *J. Am. Chem. Soc.* **1959**, *81*, 4570.

Scheme X



functionalized counterparts (Scheme IX). Since epoxidation of this enone proved difficult, the carbonyl group of **37** was reduced with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ in methanol to provide the alcohol **38**. A number of epoxidizing reagents were then screened before we discovered that 3,5-dinitroperoxybenzoic acid (2 equiv) in the presence of Na_2HPO_4 (4 equiv) in CH_2Cl_2 provided **39** in 90% yield.[29] The β stereochemistry of this epoxide was firmly established by the eventual conversion of **39** to *O*-methyltetrahydrostreptazolin (vide infra).

At this point in the synthesis, we decided to complete the installation of the 1,3-diene unit and lastly to form the oxazolidinone ring. Accordingly, the alcohol **39** was oxidized[36] to ketone **40**, and the MOM group cleaved by the action of trityl fluoroborate.[37] Dehydration of the resulting β-hydroxy ketone was achieved in 60% yield by the use of mesyl chloride and triethylamine. A better route to the enone **41** consisted of treating the MOM-protected β-hydroxy ketone **40** with 1 N NaOH in THF for 7 h; **41** was isolated in 83% yield.

Completion of the streptazolin synthesis required that we execute a Wittig condensation and ring open the epoxide with participation of the urethane carbonyl group to produce the oxazolidinone ring. Since the *E*/*Z* nature of the ethylidene appendage had been assigned arbitrarily by Drautz and Keller-Schierlein, we would not know until the end of the synthesis which stereochemistry corresponded to that of the natural product.[38]

A standard Wittig reaction on the enone **41** employing ethylidenetriphenylphosphorane[39] (from the phosphonium bromide and *n*-BuLi) in ether (sealed tube, 65 °C, 4 h) afforded an 80% yield of a 1:2 mixture of the *Z* olefin **42** and the *E* olefin **43** (Scheme X). Since the structure of these Wittig products could not be rigorously assigned through chemical shift comparisons, NOE difference experiments were carried out using a Bruker WH-600 NMR spectrometer. Irradiation of the C-3 hydrogen of **42** led to a 7% enhancement in the integrated intensity of the C-9 hydrogen and no change for the C-9 methyl group. Irradiation of the C-9 methyl group of **42** led to a 12% enhancement of the C-7 hydrogen. For **43**, irradiation of the C-3 hydrogen gave a 3% enhancement of the integral for the C-9 methyl group and no enhancement in the C-9 hydrogen. A 10% enhancement in the integral of the C-3 hydrogen was observed upon irradiation of the C-9 methyl group of **43**. The accumulated data provide strong support for the assignment of *Z* stereochemistry to **42** and *E* stereochemistry to **43**.

By employing the phosphorane prepared from the corresponding phosphonium iodide and conducting the reaction at room temperature, the *Z*/*E* ratio was found to vary from 1:2 to 6:7. The use of salt-free Wittig conditions[5] led to a 1:10 mixture of **42** and **43**, respectively. The stereochemical preference of this reaction may be rationalized using Schlosser's "leeward approach" model.[40] In an effort to further improve the proportion of *Z* olefin formed in the Wittig reaction, **41** was reacted at −78 °C → room temperature with ethylidenetriethylphosphorane[41] (generated from the addition of *n*-BuLi to tetraethylphosphonium chloride). Unfortunately, **42** and **43** were again formed in the same ratio as observed under the salt-free conditions (i.e., 1:10). While any precise mechanistic explanation of the stereochemical outcome of this Wittig process must take into account the relative rates[42] of dissociation and decomposition of the respective betaine intermediates, we gave up any hopes for further improving the product ratio and continued our synthesis using the Wittig reaction conditions first described. While efforts to thermally or photochemically isomerize the *E*/*Z* mixture were also taken (e.g., PhSH,[43] AIBN, PhH, 65 °C; PhSSPh,[44] $h\nu$, cyclohexane), only polymeric reaction products were formed.

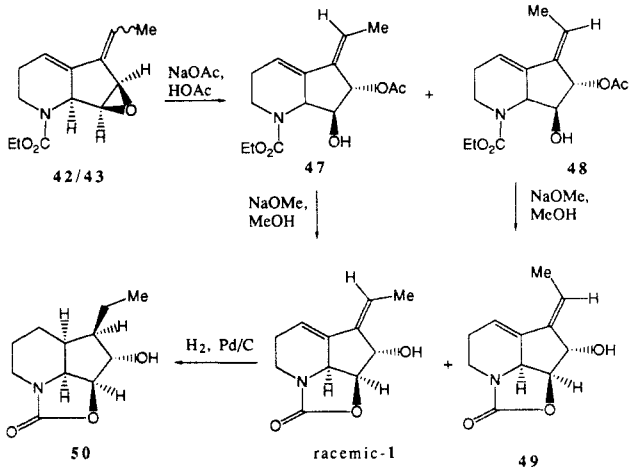
When the 1:2 mixture of **42** and **43** was treated with sodium methoxide in refluxing methanol for 3 h, two more polar products were generated in a 1:2 ratio. The IR spectrum of the mixture clearly revealed the presence of an oxazolidinone ring system (1760 cm^{-1} carbonyl stretch). The IR data in conjunction with the 300-MHz ^1H NMR spectrum of the mixture led us to assign structures **44** and **45** to the reaction products. Clearly the methoxide anion had reacted at the allylically activated epoxide carbon to release a new alkoxide anion which then attacked the urethane carbonyl group, thus delivering the oxazolidinone ring. To rigorously confirm the structures of these moderately stable methyl ether derivatives of streptazolin, especially with regard to the stereochemical relationships among carbon centers 5, 6, and 7, the synthetic material was hydrogenated over palladium on charcoal to provide the tetrahydro derivative **46**.

Authentic dihydrostreptazolin acetate **2**, kindly provided by Professor Drautz, was converted to dihydrostreptazolin by methanolic ammonia treatment,[1] and this intermediate was O-methylated[45] and hydrogenated to furnish nonracemic **46**. The 300-MHz ^1H NMR spectrum of the "naturally derived" material matched precisely that obtained from the total synthesis route. The structural correlation thus firmly establishes the stereochemical course of the epoxidation reaction of **38**.

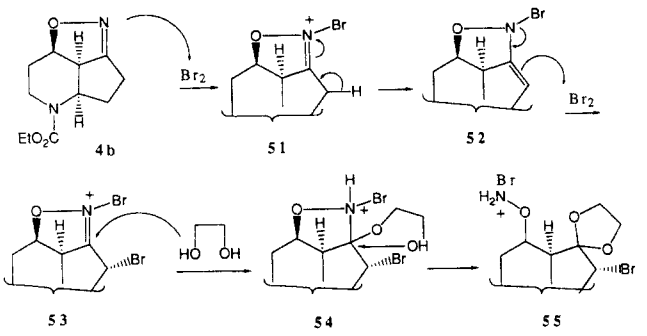
Several attempts were made to cleave the methyl ether of **44**/**45** in order to procure streptazolin itself. Use of $AlCl_3$/EtSH[46] in methylene chloride led to the selective destruction of **44**, while boron tribromide[47] in the presence of sodium iodide led only to recovery of starting material.

(36) Ratcliff, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.
(37) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933.
(38) Professor W. Keller-Schierlein informed us (private communication) that the *Z* configuration shown in their paper for streptazolin was drawn arbitrarily.
(39) Dusza, J. P. *J. Org. Chem.* **1960**, *25*, 93.
(40) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821.
(41) (a) Schmidbaur, H.; Tronich, W. *Chem. Ber.* **1968**, *101*, 595. (b) Köster, R.; Simic, D.; Grassberger, M. A. *Justus Liebigs Ann. Chem.* **1970**, *739*, 211.
(42) Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 1068.
(43) Bhalerao, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 4835.
(44) (a) Moussebois, C.; Dale, J. *J. Chem. Soc. C* **1966**, 260. (b) Corey, E. J.; Hamanaka, E. *J. Am. Chem. Soc.* **1967**, *89*, 2758.
(45) Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.
(46) Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E. *Chem. Lett.* **1979**, 97.
(47) Niwa, H.; Hida, T.; Yamada, K. *Tetrahedron Lett.* **1981**, *22*, 4239.

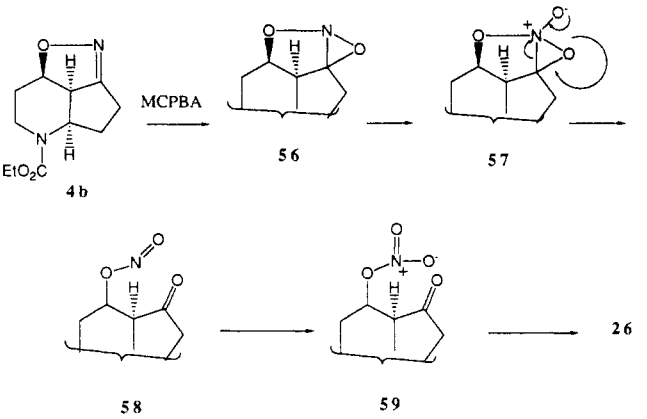
Scheme XI



Scheme XII



Scheme XIII



It thus became clear that a ring-opening reaction of the epoxide mixture (**42/43**) by a more easily deprotected oxygen nucleophile was required. The acetate anion was envisaged to fulfill this role, and indeed reaction of the epoxide mixture with sodium acetate in acetic acid at room temperature led to the hydroxy acetates **47** and **48** (Scheme XI). Fortunately, these poorly stable intermediates could be separated by HPLC and then reacted individually with sodium methoxide in refluxing methanol for 1 h in order to effect both acetate cleavage and oxazolidinone formation. It was found essential to use dilute solutions of **47** and **48** in this step, otherwise immediate polymerization of the reaction products occurred. (*E*)- and (*Z*)-streptazolin were obtained in ~70% yield by this strategy. By keeping the reaction products in dilute form, ^{1}H NMR spectra of both isomers could be readily obtained.[48]

The ^{1}H NMR spectrum of (*Z*)-streptazolin matched nearly perfectly the 100-MHz spectrum of 1 provided to us by Professor Keller-Schierlein. Furthermore, the tetrahydro derivative **50** prepared by hydrogenation of synthetic streptazolin was identical in its spectral properties with a sample prepared from authentic dihydrostreptazolin acetate.

In conclusion, the present synthetic undertaking demonstrates that it is possible to constitute in the laboratory a substance of marginal chemical stability through the judicious selection of the culminating synthetic step. The aza analogue of the Ferrier rearrangement in combination with the INOC reaction is shown to provide an efficient means for crafting ring-fused pyridine structures. The first total synthesis of (±)-streptazolin serves additionally to elucidate the stereochemistry of its exocyclic olefin, a feature that was not rigorously assigned in the pioneering structure work. The overall yield to (*E*)- and (*Z*)-streptazolin from the enone **11** was ~7% for the 18 steps.

An Oxidative Method for the Cleavage of Isoxazolines

During our streptazolin total synthesis efforts, we discovered that the isoxazoline intermediate **4b** could be converted directly to the α-bromo ketal **27** by reaction with bromine in ethylene glycol at 34 °C for 6 h. The structure of this bromo ketal was confirmed by comparison with an authentic sample prepared from the β-hydroxy ketone **26**. A possible mechanism for this transformation involving the initial electrophilic attack of bromine on the isoxazoline nitrogen is provided in Scheme XII.

Spurred by this finding, we decided to examine the reaction of isoxazoline **4b** with a peracid such as MCPBA. Subjection of **4b** to MCPBA in ethylene glycol did in fact produce the β-hydroxy ketone **26**. This finding is notable, for while most cleavage reactions of isoxazolines have been achieved by catalytic hydrogenation[49] or chemical reduction methods,[50] an oxidative means for isoxazoline cleavage might provide a useful synthetic alternative in certain synthetic undertakings. Accordingly, we set out to explore this cleavage process in greater detail.

In the case of **4b** we found that a 47% yield of **26** could be obtained if the reaction was carried out using 4 equiv of MCPBA in methylene chloride as solvent at room temperature for 12 h. Additionally, we found that at least 3 equiv of MCPBA were required to achieve a moderate yield of β-hydroxy ketone from the corresponding isoxazoline. As can be seen from Table II, the peracid reaction can be stopped at the β-hydroxy ketone stage if mild reaction conditions are employed (entries 1 and 8). More vigorous reaction conditions lead to further transformation of the intermediate β-hydroxy ketone to the acetate derivative of the diol formed by a subsequent Baeyer–Villiger oxidation.

In the isoxazoline → diol monoacetate conversion, acyl group transfer was observed. The yields for this one-step reaction range from 40 to 70% and are quite acceptable

(48) The approximate yield was obtained by quickly concentrating and weighing a dilute solution of streptazolin obtained as a homogeneous fraction from silica gel chromatography. The *E* isomer, in contrast to the *Z* isomer, shows a lower tendency toward polymerization.

(49) (a) HOAc as an acid catalyst: Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. (b) $AlCl_3$: Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123. (c) Boric acid: Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826. (d) BF_3·OEt_2: Martin, S. F.; Dupre, B. *Tetrahedron Lett.* **1983**, *24*, 1337.

(50) Anderson, S. H.; Das, N. B.; Jorgensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssel, K. B. G. *Acta Chem. Scand., Ser. B* **1982**, *B36*, 1. (b) Mukerji, S. K.; Sharma, K. K.; Torssell, K. B. G. *Ibid.* **1983**, *39*, 2241. Also see: Torssell, K. B. G., *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH Publishers, Inc.: New York, 1988.

in comparison to the yields obtained in the Baeyer–Villiger oxidation of the isolated β-hydroxy ketones themselves (formed by catalytic hydrogenolysis of the corresponding isoxazolines). In entry 12, the β-hydroxy ester derivative constituted the major product of the Baeyer–Villiger oxidation.

A possible mechanism for this oxidative transformation of isoxazolines which involves formation of an oxaziridine[51] intermediate **56** is presented in Scheme XIII. Futher oxidation of this oxaziridine may be followed by a ring-opening process and then oxidation of the nitrite **58** to a nitrate **59**. Lastly, hydrolytic cleavage of the nitrate **59** would afford the β-hydroxy ketone **26**.

In conclusion, the oxidative transformation of isoxazolines to β-hydroxy ketones and diol monoacetates would appear to further expand the utility of these heterocycles as building blocks for organic synthesis.

Experimental Section

Ethyl 4-Oxo-1-piperidinecarboxylate. To a stirred solution of 4-piperidone monohydrate hydrochloride **6** (20.6 g, 0.130 mol) in 30 mL of water at 0 °C was added a solution of sodium hydroxide (5.40 g, 1.130 mol) in 15 mL of water and then ether (100 mL). Ethyl chloroformate (6.5 mL, 0.66 mol) was added to the reaction mixture dropwise over 10 min at 0 °C. An additional quantity of sodium hydroxide (5.40 g, 0.130 mol) in 15 mL of water and ethyl chloroformate (6.5 mL) were added to the stirred solution simultaneously over 10 min at 0 °C. After an additional 10 min at 0 °C, the organic layer was separated, and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Distillation of the residue afforded 24.4 g (93%) of the title ketone as a colorless liquid: R_f = 0.41 (silica gel, 65% ethyl acetate–hexanes); bp 122–123 °C (3.7 mmHg), 114.5–115.5 °C (2.8 mmHg); IR (thin film) 2991, 2904, 2863, 1726, 1704, 1483, 1430, 1308, 1273, 1235, 1124, 1026, 770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (q, 2 H, J = 7.1 Hz), 3.78 (t, 4 H, J = 6.3 Hz), 2.46 (t, 4 H, J = 6.3 Hz), 1.12 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 171 (M^+), 142 (base), 126, 114, 100, 98, 57, 56, 42, 29.

Ethyl 6-Bromo-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (10). A stirred solution of the above ketone (2.82 g, 16.5 mmol) in 25 mL of dry ethylene glycol was treated with bromine (1.50 mL, 29.3 mmol) in small portions over 3 h at 35–40 °C under a nitrogen-filled balloon. Bromine was added at a rate which was sufficient to maintain a red-orange color. The resulting mixture was stirred for an additional 2 h. Anhydrous potassium carbonate (2.34 g, 16.5 mmol) was added to the reaction mixture, and stirring was continued until bubbling ceased. The mixture was diluted with water (25 mL) and extracted with ether (5 × 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Chromatography of the residue on silica gel with 25% ethyl acetate–hexanes afforded 4.52 g (93%) of the bromide **10**, which solidified on standing: R_f = 0.35 (silica gel, 50% ethyl acetate–hexanes); mp 59–61 °C; IR (thin film) 2974, 2904, 1711, 1683, 1470, 1440, 1430, 1381, 1357, 1330, 1259, 1236, 1213, 1164, 1131, 1060, 1037, 1026, 954, 931, 767, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25–4.10 (m, 5 H), 4.10–3.97 (m, 3 H), 3.78 (dt, 1 H, J = 13.5, 4.4 Hz), 3.57 (br s, 1 H), 3.40 (br s, 1 H), 2.10–1.96 (m, 1 H), 1.68 (ddd, 1 H, J = 13.5, 9.5, 4.4 Hz), 1.27 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 295, 293 (M^+, ^{81}Br), 293 (M^+, ^{79}Br), 266, 264, 214, 200, 142, 128, 99 (base).

Ethyl 3,4-Dihydro-4-oxo-1(2*H*)-pyridinecarboxylate (11). To a stirred solution of the bromo compound **10** (5.03 g, 17.1 mmol) in 100 mL of dimethyl sulfoxide under a nitrogen-filled balloon was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2.90 mL, 19.4 mmol). The reaction mixture was heated at 80 °C for 11 h. Water (20 mL) was added, and the mixture was extracted with ether (5 × 40 mL). The combined organic extracts were washed with water (2 × 5 mL), dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. The residue was dissolved in 30 mL of methanol and treated with 2 mL of 3 N aqueous hydrochloric acid. After 30 min, the methanol was removed in vacuo. The mixture was diluted with water (20 mL) and extracted with ether (4 × 40 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Chromatography of the residue on silica gel with 20% ethyl acetate–hexanes afforded 2.31 g (80%) of the enone **11** as a colorless oil: R_f = 0.38 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 2982, 1741, 1683, 1610, 1465, 1424, 1376, 1344, 1324, 1304, 1216, 1188, 1122, 1022, 972 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (br d, 1 H, J = 6.7 Hz), 5.35 (d, 1 H, J = 8.5 Hz), 4.31 (q, 2 H, J = 7.1 Hz), 4.04 (t, 2 H, J = 7.3 Hz), 2.57 (t, 2 H, J = 7.3 Hz), 1.36 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 169 (M^+, base), 141, 140, 110, 97, 82, 69.

Ethyl 3,4-Dihydro-4-hydroxy-1(2*H*)-pyridinecarboxylate (7). To a stirred solution of **11** (2.97 g, 17.6 mmol) and cerium trichloride heptahydrate (6.24 g, 17.6 mmol) in 44 mL of methanol was added sodium borohydride (678 mg, 17.6 mmol) in small portions at 0 °C over 20 min. The reaction mixture was diluted with 40 mL of water, concentrated in vacuo to ~40 mL, and extracted with ether (4 × 40 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated to afford 2.81 g (93%) of the alcohol **7** as a colorless oil. This compound was used in all subsequent reactions without further purification: R_f = 0.31 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 3439, 3023, 2930, 2884, 1708, 1648, 1462, 1415, 1377, 1344, 1335, 1326, 1296, 1228, 1164, 1059, 997, 948, 878, 859, 834, 770, 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 and 6.92 (two br d, 1 H, J = 8.1 Hz), 5.11 and 5.02 (two br s, 1 H), 4.32–4.15 (m, 1 H), 4.22 (q, 2 H, J = 7.1 Hz), 4.01–3.83 (m, 1 H), 3.40 (td, 1 H, J = 10.5, 3.6 Hz), 1.98–1.70 (m, 2 H), 1.60 (d, 1 H, J = 5.5 Hz), 1.31 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 171 (M^+), 154, 153, 152, 142, 124, 108, 102, 98, 80 (base), 74, 59, 45, 31, 29; exact mass calcd for $C_8H_{13}NO_3$ 171.0895, found 171.0887.

Ethyl 5,6-Dihydro-2-(2-propenyl)-1(2*H*)-pyridinecarboxylate (13). To a stirred solution of the allylic alcohol **7** (2.01 g, 11.8 mmol) and allyltrimethylsilane (3.79 mL, 23.3 mmol) in 20 mL of methylene chloride cooled to −78 °C was added stannic chloride (1.70 mL, 14.5 mmol) dropwise over 5 min. After 30 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate, warmed to room temperature, and extracted with ether (4 × 50 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Chromatography of the residue on 200 g of silica gel with 3% ethyl acetate–hexanes afforded **14** (30 mg) and a mixture of **13** and **14** (21 mg). On further elution, 2.06 g (90%) of **13** was obtained as a colorless liquid: R_f = 0.43 (25% ethyl acetate–hexanes); IR (thin film) 2904, 1695, 1456, 1352, 1326, 1243, 1195, 1103, 1034, 912, 767, 711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93–5.62 (m, 3 H), 5.10–5.02 (m, 2 H), 4.43 (br s, 1 H), 4.28–4.00 (m, 1 H), 4.14 (q, 2 H, J = 7.1 Hz), 2.90 (br s, 1 H), 2.34 (t, 2 H, J = 6.9 Hz), 1.96 (br d, 1 H, J = 16.8 Hz), 1.27 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 196 (M^+ + H), 154 (base), 126, 82, 58, 43; exact mass calcd for $C_8H_{12}NO_2$(M^+ − $CH_2CH{=}CH_2$) 154.0868, found 154.0868.

Ethyl 3,4-Dihydro-4-(2-propenyl)-1(2*H*)-pyridinecarboxylate (14): R_f = 0.52 (silica gel, 25% ethyl acetate–hexanes); IR (thin film) 2947, 1695, 1642, 1450, 1370, 1326, 1291, 1267, 1236, 1168, 1107, 1081, 1031, 962, 912, 837, 809, 767, 728 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 and 6.76 (two br d, 1 H, J = 3.6 Hz), 5.86–5.72 (m, 1 H), 5.11–5.01 (m, 2 H), 4.87 and 4.78 (two br d, 1 H, J = 6.9 Hz), 4.19 (q, 2 H, J = 7.1 Hz), 3.87–3.72 (m, 1 H), 3.40 (ddd, 1 H, J = 13.1, 10.0, 3.4 Hz), 2.31–2.20 (m, 1 H), 2.09 (dd, 2 H, J = 12.8, 7.0 Hz), 1.97–1.81 (m, 1 H), 1.57–1.40 (m, 1 H), 1.29 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 195 (M^+), 154 (base), 149, 134, 126, 119, 111, 105, 94, 82, 77, 69, 65.

Ethyl 2-Cyano-5,6-dihydro-1(2*H*)-pyridinecarboxylate (15). A stirred solution of the allylic alcohol **7** (34.2 mg, 0.200 mmol) and trimethylsilyl cyanide (160 μL, 1.20 mmol) in 8 mL of methylene chloride under a nitrogen atmosphere was cooled to −78 °C and treated with trimethylsilyl triflate (58.0 μL, 0.300 mmol). After 3 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate, warmed to room temperature,

(51) For reviews of preparations and reactions of oxaziridines, see: (a) Schmitz, E. *Adv. Heterocycl. Chem.* **1963**, *2*, 85. (b) Schmitz, E. *Ibid.* **1979**, *24*, 64.

Table II. Oxidations of Isoxazolines and β-Hydroxy Ketones with Peracids

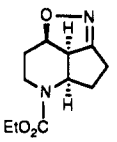
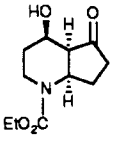
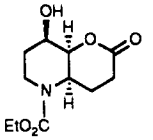
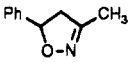
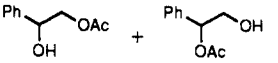
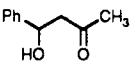
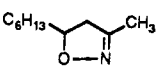
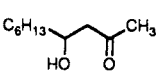
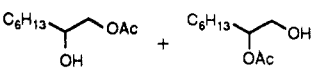
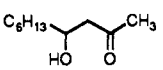
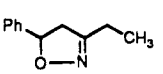
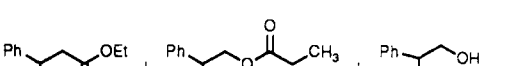
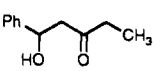
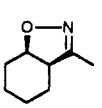
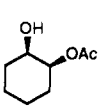
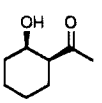
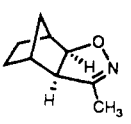
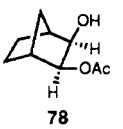
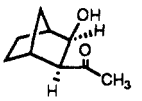
entry no.	substrate	reaction conditions (equiv)	products	yield, %
1	 **4b**	DNPBA[a] (4), CH_2Cl_2, rt,[b] 21 h	 **26**	57
2	**4b**	CF_3CO_3H (10), Na_2HPO_4 (20), CH_2Cl_2, 0 °C, 4 h, then 5 °C, 18 h	 **60**	42
3	**26**	CF_3CO_3H (6), Na_2HPO_4 (12), CH_2Cl_2, 0 °C, 1 h, then rt, 2 h	**60**	50
4	 **61**	DNPBA (20), TBP,[c] $CHCl_3$, reflux, 8 h	 **62** + **63** 3:1	67
5	**61**	CF_3CO_3H (10), Na_2HPO_4 (20), CH_2Cl_2, 0 °C, 1 h then rt, 2 h	**62** + **63** 12:5	45
6	 **64**	DNPBA (5), TBP, dichloroethane, reflux, 3 h	**62** + **63** 3:1	80
7	**64**	CF_3CO_3H (4), Na_2HPO_4 (8), CH_2Cl_2, 0 °C, 1 h then rt, 2 h	**62** + **63** 12:5	50
8	 **65**	DNPBA (5), CH_2Cl_2, rt, 16 h	 **66**	56[d]
9	**65**	DNPBA (20), Na_2HPO_4[e] (20), TBP, dichloroethane, reflux, 3 h	 **67** + **68** 7:3	59
10	 **66**	DNPBA (3), Na_2HPO_4 (3), TBP, dichloroethane, reflux, 3 h	**67** + **68** 7:3	70
11	**66**	CF_3CO_3H (3), Na_2HPO_4 (5), CH_2Cl_2, 0 °C, 1 h then rt, 2 h	**67** + **68** 8:3	50
12[f]	 **69**	DNPBA (20), TBP, dichloroethane, reflux, 3 h	 **70** + **71** 7.5:2.5:1 + **72**	68
13	 **73**	DNPBA (6), TBP, dichloroethane, reflux, 3 h	**70** + **71** + **72** 7.5:2.5:1	83
14	 **74**	DNPBA (4), CH_2Cl_2, rt, 17 h	 **75**	41
15	 **76**	DNPBA (2), CH_2Cl_2, rt, 17 h	**75**	41
16[g]	 **77**	CF_3CO_3H (10), Na_2HPO_4 (20), CH_2Cl_2, 0 °C, 1 h, 5 °C, then 5 °C, 14 h[g]	 **78**	52

Table II (Continued)

entry no.	substrate	reaction conditions (equiv)	products	yield, %
17	 **79**	CF_3CO_3H (3), Na_2HPO_4 (6), CH_2Cl_2, 0 °C, 2 h	78	72

[a] DNPBA = 3,5-dinitroperoxybenzoic acid. [b] rt = room temperature. [c] TBP = 4,4'-thiobis(2-*tert*-butyl-6-methylphenol). [d] A 10% yield of **67** and **68** was also obtained. [e] In the absence of Na_2HPO_4, decomposition occurred. [f] Oxidation occurs very slowly at room temperature. [g] In the reaction of this compound with DNPBA, decomposition was observed.

and extracted with ether (3 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 5% ethyl acetate–hexanes afforded 25.2 mg (70%) of **15** as an oil: R_f = 0.23 (silica gel, 25% ethyl acetate–hexanes); IR (thin film) 2971, 1704, 1461, 1420, 1376, 1335, 1300, 1275, 1259, 1236, 1203, 1168, 1111, 1056, 1037, 987, 899, 770, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (br s, 1 H), 5.70 (br s, 1 H), 5.38 and 5.25 (two br s, 1 H), 4.40–4.10 (m, 1 H), 4.25 (q, 2 H, J = 7.1 Hz) 3.21–2.95 (m, 1 H), 2.40–2.22 (m, 1 H), 2.13 (br d, 1 H, J = 18.2 Hz), 1.31 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 180 (M^+), 152, 151 (base), 135, 125, 108, 107, 81, 80, 68, 42, 29; exact mass calcd for $C_9H_{12}N_2O_2$ 180.0899, found 180.0897.

Ethyl 2-(1-Acetyl-2-oxopropyl)-5,6-dihydro-1(2*H*)-pyridinecarboxylate (16). A stirred solution of **7** (15.0 mg, 0.0876 mmol) and pentane-2,4-dione trimethylsilyl enol ether (42.0 μL, 0.179 mmol, prepared from pentane-2,4-dione and hexamethyldisilazane) in 3 mL of methylene chloride cooled to −78 °C was treated with trimethylsilyl triflate (25.0 μL, 0.129 mmol). After 2 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate, warmed to room temperature, and extracted with ether (3 × 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 25% ethyl acetate–hexanes afforded 10.4 mg (47%) of **16** as a viscous oil: R_f = 0.56 (silica gel, 67% ethyl acetate–hexanes); IR 2965, 2904, 1704, 1467, 1420, 1381, 1353, 1330, 1243, 1199, 1160, 1147, 1110, 1062, 1041, 986, 893, 770, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (br s, 1 H), 5.68 (br s, 1 H), 5.33 and 5.21 (two br s, 1 H) 4.30–3.93 (m, 1 H), 4.14 (q, 2 H, J = 7.1 Hz), 3.98 (d, 1 H, J = 10.1 Hz), 2.40–2.10 (m, 1 H), 2.22 (s, 6 H), 1.95 (two br t, 1 H, J = 17.6, 4.0 Hz), 1.26 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 253 (M^+), 210, 180, 168, 154 (base), 138, 126, 110, 82; exact mass calcd for $C_{13}H_{19}NO_4$ 253.1324, found 253.1310.

Ethyl 5,6-Dihydro-2-(2-oxocyclohexyl)-1(2*H*)-pyridinecarboxylate (17). A stirred solution of **7** (17.0 mg, 0.0993 mmol) and cyclohexanone trimethylsilyl enol ether (34.0 mg, 0.200 mmol) in 4 mL of methylene chloride cooled to −78 °C was treated with trimethylsilyl triflate (29.0 μL, 0.150 mmol). After 2.5 h at −78 °C, the reaction mixture was quenched with saturated aqueous sodium bicarbonate, warmed to room temperature, and extracted with methylene chloride (4 × 10 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 25% ethyl acetate–hexanes afforded 21.0 mg (84%) of **17** as a viscous oil: R_f = 0.19 (silica gel, 25% ethyl acetate–hexanes); IR (thin film) 2947, 1704, 1420, 1381, 1326, 1283, 1240, 1196, 1109, 1083, 1037, 981, 771, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06–5.65 (m, 2 H), 4.99 (br s, 1 H), 4.44–4.00 (m, 1 H), 4.13 (q, 2 H, J = 7.1 Hz), 3.05–1.50 (m, 10 H), 1.34–1.08 (m, 2 H), 1.25 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 251 (M^+), 178, 154 (base), 126, 82; exact mass calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1521.

2,4-Dinitrophenylhydrazone Derivative of 17. A solution of **17** (21.0 mg, 0.0836 mmol) in 0.2 mL of ethanol was treated with 0.6 mL of 2,4-dinitrophenylhydrazine solution, which was taken from the solution of 2,4-dinitrophenylhydrazine (3.00 g, 15.1 mmol) in 15 mL of concentrated sulfuric acid, 20 mL of water, and 70 mL of 95% ethanol. After the mixture was stirred for 5 min, the yellow precipitate was collected by suction filtration and washed with ethanol. The hydrazone (24.1 mg, 67%) was obtained in a first crop as a yellow solid: R_f = 0.23 (silica gel, 25% ethyl acetate–hexanes); mp 128–130 °C (recrystallized from EtOH); IR (Nujol mull) 1690, 1616, 1595, 1514, 1422, 1304, 1199, 1112, 1088, 921, 847, 834, 744, 725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.13 (d, 1 H, J = 2.6 Hz), 8.30 (dd, 1 H, J = 9.5, 2.6 Hz), 7.91 (d, 1 H, J = 9.5 Hz), 5.96 (s, 2 H), 4.98 (s, 1 H), 4.40–3.85 (m, 4 H), 3.28–2.98 (m, 1 H), 2.86–1.03 (m, 14 H); mass spectrum (70 eV), m/z 431 (M^+), 386, 354, 315, 278, 183, 176, 154 (base), 126, 82, 67, 55, 41, 29; exact mass calcd $C_{20}H_{25}N_5O_6$ 431.1805, found 431.1805.

Ethyl 2-[Cyano[(1,1,3,3-tetramethylbutyl)imino]-methyl]-5,6-dihydro-1(2*H*)-pyridinecarboxylate (18). A stirred solution of **7** (30.0 mg, 0.175 mmol) and 1,1,3,3-tetramethylbutyl isocyanide (distilled, 61.0 μL, 0.348 mmol) in 12 mL of methylene chloride cooled to −78 °C was treated with trimethylsilyl triflate (51.0 μL, 0.264 mmol). After 2.5 h at −78 °C, the reaction mixture was quenched with saturated aqueous sodium bicarbonate, warmed to room temperature, and extracted with ether (3 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 5% ethyl acetate–hexanes afforded 24.0 mg (44%) of **18** as a viscous oil: R_f = 0.47 (silica gel, 25% ethyl acetate–hexanes); IR (thin film), 2947, 2213, 1704, 1641, 1461, 1415, 1381, 1362, 1331, 1304, 1283, 1243, 1233, 1200, 1174, 1147, 1110, 1062, 1041, 927, 827, 804, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (br s, 1 H), 5.82 (br s, 1 H), 5.04 and 5.11 (two br s, 1 H), 4.30–3.99 (m, 1 H), 4.17 (q, 2 H, J = 7.1 Hz), 3.14 (br s, 1 H), 2.32–2.17 (m, 1 H), 2.09 (br d, 1 H, J = 17.6 Hz), 1.75 (s, 2 H), 1.43 (s, 6 H), 1.26 (m, 3 H), 0.95 (s, 9 H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 137.33 (s, 1 C), 128.82 (m, 1 C), 122.48 (m, 1 C), 112.03 (s, 2 C), 62.56 (s, 1 C), 61.79 (t, 1 C), 59.23 (d, 1 C), 56.13 (t, 1 C), 38.52 (s, 1 C), 31.80 (qt, 2 C), 29.34 (q, 1 C), 29.24 (t, 1 C), 24.48 (t, 1 C), 14.71 (q, 3 C); mass spectrum (15 eV), m/z 319 (M^+), 304, 262, 248, 207, 154 (base), 126, 118, 103, 97, 82, 57; exact mass calcd for $C_{18}H_{29}N_3O_2$ 319.2260, found 319.2261.

Ethyl 3,4-Dihydro-4-ethoxy-1(2*H*)-pyridinecarboxylate (12). To a stirred solution of **7** (9.0 mg, 0.0526 mmol) in 5 mL of ethanol was added pyridinium *p*-toluenesulfonate (14.0 mg, 0.0546 mmol). After 1.5 h at room temperature, the reaction mixture was quenched with saturated aqueous sodium bicarbonate. Ethanol was removed in vacuo. The mixture was extracted with methylene chloride (4 × 10 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 10% ethyl acetate–hexanes afforded 7.0 mg (67%) of **7** as a viscous oil: R_f = 0.39 (silica gel, 25% ethyl acetate–hexanes); IR (thin film) 2969, 2863, 1704, 1641, 1456, 1371, 1335, 1317, 1295, 1233, 1174, 1112, 1076, 998, 962, 882, 768, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 and 6.92 (two br d, 1 H, J = 8.1 Hz), 5.12 and 5.03 (two br s, 1 H), 4.21 (q, 2 H, J = 7.1 Hz), 3.95–3.76 (m, 1 H), 3.85 (dd, 1 H, J = 4.2, 4.0 Hz), 3.55 (q, 2 H, J = 7.1 Hz), 3.43 (dt, 1 H, J = 11.5, 3.0 Hz), 2.05–1.90 (br s, 1 H), 1.77 (m, 1 H), 1.29 (t, 3 H, J = 7.1 Hz), 1.22 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 199 (M^+), 170, 154 (base), 143, 126, 118, 102, 82, 70, 59, 45, 31, 29; exact mass calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1207.

Ethyl (2β,4α)-2,4-Diethoxy-1-piperidinecarboxylate (19). To a stirred solution of **7** (19.0 mg, 0.111 mmol) in 2 mL of ethanol cooled to −78 °C was added trimethylsilyl triflate (21.0 μL, 0.109 mmol). After 25 min at −78 °C, the mixture was warmed to room temperature and quenched with water. Ethanol was removed in vacuo, and the mixture was extracted with ether (3 × 10 mL).

The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 10% ethyl acetate–hexanes afforded 14.7 mg (54%) of **12** as an oil. Further elution afforded 2.5 mg (5%) of **19** as an oil; R_f = 0.34 (silica gel, 25% ethyl acetate–hexanes); IR (thin film) 2952, 2892, 1706, 1420, 1371, 1321, 1262, 1167, 1106, 991, 951, 884, 810, 770, 724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.64 and 5.54 (two br s, 1 H), 4.14 (q, 2 H, J = 7.1 Hz), 4.08 and 3.96 (two br d, 1 H, J = 12.7 Hz), 3.54 (quint, 2 H, J = 6.9 Hz), 3.48–3.26 (m, 2 H), 2.98 (br q, 1 H, J = 12.7 Hz), 2.26 (br s, 1 H), 2.02 (br s, 1 H), 1.42 (ddd, 1 H, J = 12.7, 11.5, 3.2 Hz), 1.35–1.20 (1 H), 1.27 (t, 3 H, J = 7.1 Hz), 1.19 (t, 3 H, J = 6.9 Hz), 1.17 (t, 3 H, J = 6.9 Hz); mass spectrum (15 eV), m/z 216 ($M^+ - CH_2CH_3$), 200 (base), 188, 172, 170, 156, 154, 144, 128, 112, 110, 102, 98, 92, 72, 56, 29; exact mass calcd for $C_{10}H_{18}NO_4$ (M^+ – Et) 216.1236, found 216.1230.

Ethyl 3,4-Dihydro-4-(phenylthio)-1(2*H*)-pyridinecarboxylate (20). To a stirred solution of **7** (15.6 mg, 0.0911 mmol) in 4 mL of thiophenol was added pyridinium *p*-toluenesulfonate (28.0 mg, 0.109 mmol). After 1.5 h at room temperature, the reaction mixture was quenched with saturated aqueous sodium bicarbonate. The mixture was extracted with methylene chloride (4 × 10 mL), dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 5% ethyl acetate–hexanes afforded 11.0 mg (46%) of **20** as a viscous oil; R_f = 0.45 (silica gel, 25% ethyl acetate–hexanes); IR (thin film) 3060, 2822, 1704, 1641, 1583, 1517, 1404, 1371, 1335, 1306, 1291, 1228, 1178, 1112, 1082, 1029, 996, 962, 889, 831, 792, 767, 743, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.23 (m, 5 H), 7.03 and 6.91 (two br d, 1 H, J = 8.8 Hz), 5.06 and 4.98 (two br s, 1 H), 4.21 (q, 2 H, J = 7.1 Hz), 4.02–3.78 (m, 2 H), 3.70–3.55 (m, 1 H), 2.09–1.82 (m, 2 H), 1.30 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 263 (M^+), 218, 154 (base), 126, 110, 103, 82, 69, 56, 29; exact mass calcd for $C_{15}H_{17}NO_2S$ 263.0980, found 263.0981.

Ethyl 5,6-Dihydro-2-(3-hydroxypropyl)-1(2*H*)-pyridinecarboxylate. To a stirred solution of the diene **13** (1.90 g, 9.73 mmol) in 10 mL of dry tetrahydrofuran under a nitrogen atmosphere was added 9-borabicyclo[3.3.1]nonane (29.3 mL, 14.7 mmol) dropwise over 5 min at room temperature. After 2 h, the reaction mixture was treated sequentially with 3 N aqueous sodium hydroxide (4.90 mL, 14.7 mmol) and 30% hydrogen peroxide (4.90 mL, 44.1 mmol) dropwise at 0 °C. The reaction mixture was heated at 50 °C for 1 h, and the solvent was removed in vacuo. The residue was diluted with water (30 mL) and extracted with ether (4 × 40 mL). The organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Chromatoraphy of the residue on silica gel with 25% ethyl acetate–hexanes afforded 1.87 g (90%) of the title alcohol as a colorless oil: R_f = 0.24 (silical gel, 67% ethyl acetate–hexanes); IR (thin film) 3427, 2926, 1683, 1423, 1327, 1239, 1199, 1112, 1032, 770, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90–5.76 (m, 1 H), 5.68 (br d, 1 H, J = 11.9 Hz), 4.60–4.32 (m, 1 H), 4.28–3.98 (m, 1 H), 4.15 (q, 2 H, J = 7.1 Hz), 3.64 (br s, 2 H), 3.00–2.82 (m, 1 H), 2.32–2.08 (m, 1 H), 1.94 (ddd, 1 H, J = 17.4, 5.3, 4.9 Hz), 1.64 (br s, 4 H), 1.27 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 213 (M^+), 196, 195, 184, 182, 169, 168, 155, 154 (base), 141, 140, 138, 127, 126, 120, 82; exact mass calcd for $C_{11}H_{19}NO_3$ 213.1365, found 213.1365. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.52; H, 8.94; N, 6.45.

Ethyl 5,6-Dihydro-2-(3-oxopropyl)-1(2*H*)-pyridinecarboxylate (25). To a stirred solution of pyridinium chlorochromate (1.98 g, 9.00 mmol) in 12 mL of methylene chloride was added a solution of the above alcohol (1.28 g, 6.00 mmol) in 12 mL of methylene chloride. The reaction mixture was stirred for 8 h and diluted with 30 mL of anhydrous ether. After this dark solution was separated, the residue was further extracted with ether (4 × 30 mL). The combined ether extracts were filtered through Florisil. The Florisil was further eluted with 120 mL of ether, and the combined eluates were concentrated in vacuo. Chromatography of the residue on silica gel with 33% ethyl acetate–hexanes afforded 1.08 g (85%) of the aldehyde **25** as a colorless liquid (the yield varied between 68–85%): R_f = 0.39 (silica gel, 50% ethyl acetate–hexanes); IR (thin film) 2912, 2814, 2715, 1717, 1688, 1461, 1420, 1324, 1271, 1239, 1196, 1107, 1067, 984, 893, 768, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, 1 H, J = 1.2 Hz), 5.90–5.79 (m, 1 H), 5.64 (br d, 1 H, J = 10.5 Hz), 4.46 (br s, 1 H), 4.28–3.96 (m, 1 H), 4.15 and 4.14 (two q, 2 H, J = 7.1 Hz), 2.88 (br s, 1 H), 2.54 (dd, 2 H, J = 7.5, 7.1 Hz), 2.30–2.10 (m, 1 H), 2.01–1.76 (m, 3 H), 1.26 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 211 (M^+), 167, 155, 154 (base), 138, 126, 82; exact mass calcd for $C_9H_{13}NO_2$ ($M^+ - CH_3COH$) 167.0946, found 167.0939.

Ethyl 5,6-Dihydro-2-(3-(hydroxyimino)propyl)-1(2*H*)-pyridinecarboxylate (5b). To a solution of the aldehyde **25** (122 mg, 0.57 mmol) in 2 mL of pyridine was added hydroxylamine hydrochloride (162 mg, 2.32 mmol). After 10 h, the reaction mixture was concentrated in vacuo. The residue was partitioned between ether (30 mL) and water (20 mL). After separation of the organic layer, the aqueous layer was extracted with ether (2 × 50 mL). The combined organic extracts were washed with 1.5 N aqueous hydrochloric acid (2 × 1 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Chromatography of the residue on silica gel with 33% ethyl acetate–hexanes afforded 126 mg (96%) of the oximes **5b** as a colorless liquid: R_f = 0.44 (syn) and 0.36 (anti) (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 3439, 2926, 1671, 1420, 1326, 1267, 1239, 1195, 1109, 1056, 1035, 859, 741, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (br s, 0.5 H), 8.06 (br s, 0.5 H), 7.46 (t, 0.5 H, J = 5.8 Hz), 6.76 (br s, 0.5 H), 5.84 (br s, 1 H), 5.67 (br s, 1 H), 4.58–4.34 (m, 1 H), 4.30–4.00 (m, 1 H), 4.15 (q, 2 H, J = 7.1 Hz), 3.00–2.78 (m, 1 H), 2.57–2.38 (m, 1 H), 2.34–2.13 (m, 2 H), 1.95 (br d, 1 H, J = 16.6 Hz), 1.82–1.68 (m, 2 H), 1.27 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 226 (M^+), 209, 181, 168, 167, 163, 155 (base), 154, 142, 138, 126, 120, 110, 82; exact mass calcd for $C_{11}H_{18}NO_3$ 226.1317, found 226.1316.

Ethyl (4aα,7aα,7bα)-4,4a,6,7,7a,7b-Hexahydro-1-oxa-2,5-diazacyclopent[*cd*]indene-5(3*H*)-carboxylate (4b). To a stirred solution of **5b** (198 mg, 0.875 mmol) in 9 mL of methylene chloride containing triethylamine (120 μL, 0.861 mmol) was added dropwise 5% aqueous sodium hypochlorite (4 mL, 2.69 mmol) over 3 h at 0 °C. After an additional 2 h at room temperature, the organic layer was separated. The aqueous layer was extracted with methylene chloride (3 × 20 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Chromatography of the residue on silica gel with 25% ethyl acetate–hexanes followed by 33% ethyl acetate–hexanes afforded 177 mg (90%) of the isoxazoline **4b** as a colorless oil: R_f = 0.27 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 2965, 1697, 1461, 1410, 1371, 1344, 1308, 1275, 1250, 1204, 1171, 1115, 1062, 1042, 1006, 967, 953, 897, 874, 848, 820, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (br d, 1 H, J = 10.9 Hz), 4.31 (ddd, 1 H, J = 8.7, 6.1, 2.6 Hz), 4.16 and 4.15 (two q, 2 H, J = 7.1 Hz), 3.97 (dd, 1 H, J = 10.5, 9.3 Hz), 4.02–3.88 (m, 1 H), 3.05 (td, 1 H, J = 13.1, 2.0 Hz), 2.70–2.66 (m, 1 H), 2.66–2.34 (m, 2 H), 2.25 (tdd, 1 H, J = 10.9, 5.7, 2.6 Hz), 1.88 (ddt, 1 H, J = 14.8, 4.0, 2.2 Hz), 1.61 (ddt, 1 H, J = 14.8, 12.3, 4.2 Hz), 1.27 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 224 (M^+, base), 196, 195, 179, 170, 168, 167, 154, 151, 142, 135, 123; exact mass calcd for $C_{11}H_{16}N_2O_3$ 224.1161, found 224.1160. Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.92; H, 7.19; N, 12.49. Found: C, 58.99; H, 7.18; N, 12.16.

Ethyl (4β,4aα,7aα)-Octahydro-4-hydroxy-5-oxo-1*H*-1-pyrindinecarboxylate (26). To a stirred solution of the isoxazoline **4b** (4.33 g, 19.3 mmol) in 400 mL of a 4:1 methanol–water mixture was added W-2 Raney nickel (40 mg) and acetic acid (4.40 mL, 76.7 mmol). The reaction mixture was stirred under a hydrogen-filled balloon until 300-MHz ^1H NMR revealed the absence of starting material (11–24 h). The starting material and the reaction product showed nearly identical R_f values (0.27) by TLC analysis with 67% ethyl acetate–hexanes as the developing solvent. The reaction mixture was filtered through Celite, and the Celite was washed with ethyl acetate. The combined eluates were neutralized with saturated aqueous sodium bicarbonate and concentrated in vacuo. A saturated solution of sodium chloride (80 mL) was added, and the mixture was extracted with ethyl acetate (4 × 200 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 50% ethyl acetate–hexanes afforded 3.86 g (88%) of the hydroxy ketone **26** as a colorless oil: R_f = 0.27 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 3457, 2947, 1741, 1683, 1528, 1424,

1371, 1339, 1295, 1270, 1224, 1099, 1047, 1010, 973, 920, 891, 873, 773, 733 cm^{-1}; ^1H NMR (300 MHz) δ 4.74–4.62 (m, 1 H), 4.42 (br s, 1 H), 4.18 (q, 2 H, J = 7.1 Hz), 3.96 (ddd, 1 H, J = 13.1, 4.2, 3.0 Hz), 3.34 (td, 1 H, J = 13.1, 2.6 Hz), 2.58 (d, 1 H, J = 3.8 Hz, this alcoholic signal was absent in most runs), 2.50–2.20 (m, 4 H), 2.30 (dd, 1 H, J = 9.1, 4.4 Hz), 1.81 (ddt, 1 H, J = 13.9, 3.6, 2.8 Hz), 1.63 (ddddd, 1 H, J = 13.9, 13.1, 4.6, 2.4, <1 Hz), 1.29 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 227 (M^+), 209, 198 (base), 183, 181, 169, 154, 152, 142, 136, 122; exact mass calcd for $C_{11}H_{17}NO_4$ 227.1158, found 227.1157. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.29; H, 7.46; N, 6.32.

Ethyl (4′β,4′aα,6′α,7′aα)-6′-Bromohexahydro-4′-hydroxyspiro[1,3-dioxolane-2,5′-5′*H*-[1]pyrindine]-1′(2′*H*)-carboxylate (27). To a stirred solution of the hydroxy ketone **26** (138 mg, 0.607 mmol) in 1.5 mL of dry ethylene glycol was added bromine (40.0 μL, 0.781 mmol) over 30 min at 30–40 °C. The reaction mixture was stirred at this temperature for an additional 3–6 h until TLC analysis revealed the absence of the starting material. Anhydrous potassium carbonate (86.1 mg, 0.607 mmol) was added, and the reaction mixture was stirred for 20 min. Water (20 mL) was added, and the mixture was extracted with methylene chloride (4 × 20 mL). The combined organic extracts were washed with water (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 33% ethyl acetate–hexanes afforded 128 mg (60%) of the bromo ketal **27** as a solid: R_f = 0.32 (silica gel, 67% ethyl acetate–hexanes); mp 144–145 °C dec (recrystallized in ethyl acetate–hexanes); IR ($CHCl_3$) 3427, 2947, 1671, 1420, 1371, 1335, 1330, 1213, 1171, 1100, 1045, 948, 910, 874, 773, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90–4.70 (m, 1 H), 4.64 (dd, 1 H, J = 11.1, 5.1 Hz), 4.32–4.08 (m, 5 H), 4.05–3.82 (m, 3 H), 3.17 (td, 1 H, J = 13.1, 2.0 Hz), 2.52 (dt, 1 H, J = 13.9, 10.7 Hz), 2.43–2.26 (m, 2 H), 2.06 (dd, 1 H, J = 8.1, 4.0 Hz), 1.84 (ddt, J = 13.9, 3.2, 3.0 Hz), 1.57 (tddd, 1 H, J = 13.3, 4.6, 2.4, <1 Hz), 1.26 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 351 (M^+, ^{81}Br), 349 (M^+, ^{79}Br), 334, 332, 305, 303, 270, 242, 142, 100, 99 (base); exact mass calcd for $C_{13}H_{20}{}^{79}BrNO_5$ 349.0525, found 349.0527. Anal. Calcd for $C_{13}H_{20}BrNO_5$: C, 44.58; H, 5.76; N, 4.00; Br, 22.82. Found: C, 44.50; H, 5.86; N, 3.91; Br, 22.92.

Cyclic Ether (28). To a solution of the alcohol **27** (25.0 mg, 0.0714 mmol) in 200 μL of dimethyl sulfoxide was added 1,8-diazabicyclo[5.4.0]undec-7-ene (30.0 μL, 0.193 mmol). After 10 h at 80 °C, the reaction mixture was partitioned between water and ether. The aqueous layer was extracted with ether (3 × 1 mL). The combined organic extracts were washed with water (2 × 5 mL), dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 25% and then 50% ethyl acetate–hexanes afforded 15.0 mg (78%) of **28** as an oil: R_f = 0.29 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 2991, 2904, 1697, 1461, 1420, 1362, 1344, 1300, 1275, 1206, 1181, 1164, 1106, 1085, 1048, 1024, 1001, 948, 910, 882, 836, 770, 717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 and 4.81 (two br s, 1 H), 4.49 (br s, 1 H), 4.14 (q, 2 H, J = 7.1 Hz), 4.09–3.81 (m, 5 H), 3.75 (br s, 1 H), 3.30–3.12 (m, 1 H), 2.30–2.12 (m, 1 H), 1.91 (br d, 1 H, J = 13.3 Hz), 1.85 (br s, 1 H), 1.74 (br d, 1 H, J = 13.5 Hz), 1.69–1.53 (m, 1 H), 1.27 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 269 (M^+), 241, 225, 212, 196, 169, 154 (base), 152, 141, 126, 115, 99, 73; exact mass calcd for $C_{13}H_{19}NO_5$ 269.1263, found 269.1261.

Ethyl (4′β,4′aα,6′α,7′aα)-6′-Bromohexahydro-4′-(methoxymethoxy)spiro[1,3-dioxolane-2,5′-5′*H*-[1]pyrindine]-1′(2′*H*)-carboxylate (29). To a solution of the alcohol **27** (60.0 mg, 0.171 mmol) in 3 mL of chloroform was added dimethoxymethane (1.50 mL, 17.0 mmol) and phosphorus pentoxide (485 mg, 3.42 mmol). The reaction mixture was stirred under a nitrogen-filled balloon for 8 h and was poured into 35 mL of ice-cooled saturated aqueous sodium bicarbonate. The reaction flask was further washed with 5 mL of saturated aqueous sodium bicarbonate. The mixture was extracted with ether (4 × 40 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 50% ethyl acetate–hexanes afforded 62 mg (92%) of the MOM-protected compound **29** as a colorless liquid: R_f = 0.46 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 2926, 1697, 1461, 1420, 1370, 1335, 1304, 1283, 1213, 1171, 1150, 1100, 1037, 931, 876, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (AB q, 2 H, J_{AB} = 7.1 Hz, ν_{AB} = 29.7 Hz), 4.89–4.04 (m, 2 H), 4.26–4.08 (m, 5 H), 4.01–3.85 (m, 3 H), 3.39 (s, 3 H), 2.48–2.26 (m, 2 H), 2.05 (dd, 1 H, J = 7.8, 4.1 Hz), 1.94 (br d, 1 H, J = 14.1 Hz), 1.45 (tdd, 1 H, J = 12.7, 4.7, 1.4 Hz), 1.26 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 395 (M^+, ^{81}Br), 393 (M^+, ^{79}Br), 363, 361, 349, 347, 333, 331, 313, 285, 281, 251, 220, 205, 154, 99 (base); exact mass calcd for $C_{15}H_{24}{}^{81}BrNO_6$ 395.0767, found 395.0764. Anal. Calcd for $C_{15}H_{24}BrNO_6$: C, 45.70; H, 6.13; Br, 20.27; N, 3.55. Found: C, 45.53; H, 6.22; Br, 19.90; N, 3.59.

Ethyl (4′β,4′aα,7′aα)-3′,4′,4′a,7′a-Tetrahydro-4′-(methoxymethoxy)spiro[1,3-dioxolane-2,5′-5′*H*-[1]pyrindine)-1′-(2′*H*)-carboxylate (30). To a stirred solution of the bromide **29** (146 mg, 0.370 mmol) in 4 mL of dimethyl sulfoxide was added 1,8-diazabicyclo[5.4.0]undec-7-ene (280 μL, 1.87 mmol). The reaction mixture was heated at 120 °C for 12 h. Water (10 mL) was added, and the mixture was extracted with ether (4 × 25 mL). The combined organic extracts were washed with water (5 mL), dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 33% ethyl acetate–hexanes afforded 106 mg (91%) of the olefin **30** as a viscous oil: R_f = 0.44 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 2926, 1690, 1470, 1418, 1376, 1317, 1290, 1243, 1222, 1171, 1154, 1000, 1065, 1040, 986, 953, 918, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (br s, 2 H), 5.30–5.03 (m, 1 H), 4.68 (AB q, 2 H, J_{AB} = 6.8 Hz, ν_{AB} = 30.5 Hz), 4.15 (q, 2 H, J = 7.1 Hz), 4.10–3.76 (m, 6 H), 3.37 (s, 3 H), 3.04 (ddd, 1 H, J = 13.7, 10.7, 7.1 Hz), 2.78–2.60 (m, 1 H), 2.17–1.83 (m, 2 H), 1.27 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 312 (M^+ – H), 281, 280, 268, 267, 251, 250 (base), 223, 210, 179, 135, 134, 112, 99; exact mass calcd for $C_{15}H_{22}NO_6$ 312.1447, found 312.1447. Anal. Calcd for $C_{15}H_{22}NO_6$: C, 57.68; H, 7.10; N, 4.48. Found: C, 57.96; H, 7.43; N, 4.27.

(2′aα,3′α,4′aα,5′β,7′bα)-Octahydro-3′-iodo-5′-(methoxymethoxy)spiro[1,3-dioxolane-2,4′-(1′*H*)-2′-oxa-7′a-azacyclopent[*cd*]inden-1′-one] (32). To a solution of the olefin **30** (29.0 mg, 0.0925 mmol) in 6 mL of methylene chloride was added iodonium di-*s*-collidine perchlorate (130 mg, 0.277 mmol). The reaction mixture was heated to reflux for 9 h under a nitrogen atmosphere. The mixture was filtered through Celite. The Celite was washed with ether (75 mL). The combined filtrates were washed with saturated aqueous sodium thiosulfate, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 50% ethyl acetate–hexanes afforded 29.6 mg (78%) of the iodide **32** as an oil: R_f = 0.26 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 2904, 1749, 1455, 1415, 1231, 1150, 1103, 1029, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.23 (d, 1 H, J = 8.1 Hz), 4.71 (AB q, 2 H, J_{AB} = 7.1 Hz, ν_{AB} = 60.2 Hz), 4.30 (dd, 1 H, J = 7.9, 6.7 Hz), 4.27 (s, 1 H), 4.20–4.09 (m, 2 H), 4.03 (ddd, 1 H, J = 13.9, 5.5, 2.0 Hz), 3.98–3.90 (m, 3 H), 3.40 (s, 3 H), 3.22 (t, 1 H, J = 6.2 Hz), 2.92 (ddd, 1 H, J = 13.7, 12.5, 3.6 Hz), 2.18 (qd, 1 H, J = 12.3, 5.5 Hz), 1.66 (br d, 1 H, J = 12.5 Hz); mass spectrum (15 eV), m/z 411 (M^+), 380, 350, 284 (base), 240, 140, 127, 111, 99, 71, 57; exact mass calcd for $C_{13}H_{18}INO_6$, 411.0179; found 411.0180.

(2′aα,3′α,4′aα,5′β,7′bα)-Octahydro-5′-hydroxy-3′-iodospiro[1,3-dioxolane-2,4′-(1′*H*)-2′-oxa-7′a-azacyclopent[*cd*]-inden-1′-one]. To a stirred solution of the MOM ether **32** (21.0 mg, 0.0511 mmol) in 5 mL of methylene chloride was added triphenylcarbenium tetrafluoroborate (50.0 mg, 0.151 mmol). After 23 h at room temperature, the mixture was quenched with water (5 mL) and extracted with methylene chloride (4 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 50% ethyl acetate–hexanes removed triphenylmethane. Further elution with 90% ethyl acetate–hexanes afforded 9.0 mg (48%) of the title alcohol as an oil: R_f = 0.14 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 3517, 2991, 1741, 1414, 1313, 1213, 1137, 1096, 1040, 1021, 991, 948, 935, 844, 820, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24 (d, 1 H, J = 7.9 Hz), 4.32 (s, 1 H), 4.31 (dd, 1 H, J = 7.9, 6.7 Hz), 4.24–4.16 (m, 1 H), 4.15–3.95 (m, 4 H), 3.93–3.83 (m, 1 H), 3.24 (t, 1 H, J = 6.3 Hz), 2.90 (ddd, 1 H, J = 13.9, 12.5, 3.4 Hz), 2.41 (br s, 1 H), 2.14 (qd, 1 H, J = 12.3, 5.5 Hz), 1.72 (br d, 1 H, J = 12.7 Hz); mass spectrum (15 eV), m/z 367 (M^+), 240 (base), 167, 149, 71, 57, 45.

(2′aα,4′aα,5′β,7′bα)-Octahydro-5′-hydroxyspiro[1,3-di-

oxolane-2,4′-(1′*H*)-2′-oxa-7′a-azacyclopent[*cd*]inden-1′-one] (35). To a solution of the above iodide (8.3 mg, 0.0226 mmol) in 4 mL of benzene was added tributyltin hydride (10.0 μL, 0.0372 mmol) and a catalytic amount of AIBN. After 5.5 h at reflux, the mixture was concentrated in vacuo. Flash chromatography of the residue on silica gel with 50% ethyl acetate–hexanes and then ethyl acetate afforded 4.5 mg (83%) of the ketal **35** as an oil: R_f = 0.04 (silica gel, 80% ethyl acetate–hexanes); IR (thin film) 3376, 2960, 1710, 1423, 1142, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (t, 1 H, J = 6.7 Hz), 4.20 (dd, 1 H, J = 7.8, 6.3 Hz), 4.20–4.09 (m, 2 H), 4.08–3.80 (m, 4 H), 2.88 (ddd, 1 H, J = 13.6, 12.8, 3.5 Hz), 2.53 (t, 1 H, J = 6.0 Hz), 2.38 (d, 1 H, J = 4.9 Hz), 2.26 (d, 1 H, J = 14.9 Hz), 2.19 (qd, 1 H, J = 12.4, 5.4 Hz), 1.97 (ddd, 1 H, J = 14.6, 6.4, 0.6 Hz), 1.72 (br d, 1 H, J = 12.5 Hz).

Ethyl (4β,4aα,7aα)-2,3,4,4a,5,7a-Hexahydro-4-(methoxymethoxy)-5-oxo-1*H*-1-pyrindinecarboxylate (37). To a stirred solution of the ketal **30** (1.650 g, 5.27 mmol) in 53 mL of THF was added 390 μL (0.780 mmol) of 2 N aqueous hydrochloric acid. After 1 h at room temperature, the mixture was quenched with saturated aqueous sodium bicarbonate (20 mL). Tetrahydrofuran was removed in vacuo. The mixture was extracted with ether (4 × 40 mL). The organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 33% ethyl acetate–hexanes afforded 1.25 g (88%) of **37** as an oil: R_f = 0.31 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 3549, 2991, 2969, 2909, 2838, 1704, 1690, 1461, 1410, 1366, 1335, 1330, 1277, 1251, 1206, 1167, 1144, 1088, 1053, 1032, 947, 918, 886, 817, 773, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 and 7.53 (two br d, 1 H, J = 4.7 Hz), 6.32 (dd, 1 H, J = 5.9, 2.2 Hz), 5.29 and 5.17 (two br d, 1 H, J = 7.1 Hz), 4.60 (AB q, 2 H, J_{AB} = 6.87 Hz, ν_{AB} = 13.9 Hz), 4.34–4.15 (m, 3 H), 4.10–3.88 (m, 1 H), 3.33 (s, 3 H), 3.30–3.08 (m, 1 H), 2.87 (dd, 1 H, J = 11.9, 6.1 Hz), 1.97–1.80 (m, 1 H), 1.73–1.59 (m, 1 H), 1.31 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 269 (M$^+$), 237, 224, 209, 207, 181 (base), 180, 156, 154, 152, 136, 134, 120, 118, 108, 102, 45; exact mass calcd for $C_{13}H_{19}NO_5$ 269.1263, found 269.1264.

Ethyl (4β,4aα,5β,7aα)-2,3,4,4a,5,7a-Hexahydro-5-hydroxy-4-(methoxymethoxy)-1*H*-1-pyrindinecarboxylate (38). To a stirred solution of the enone **37** (850 mg, 3.16 mmol) and cerium trichloride heptahydrate (1.190 g, 3.16 mmol) in 7.9 mL of methanol was added sodium borohydride (122 mg, 3.16 mmol) in small portions over 5 min. After 5 min, 2 N aqueous hydrochloric acid (1.60 mL, 3.20 mmol) was added. The mixture was diluted with water (20 mL). Methanol was removed in vacuo. The mixture was extracted with ether (4 × 30 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 50% ethyl acetate–hexanes afforded 779 mg (91%) of the alcohol **38** as an oil: R_f = 0.28 (silica gel, 67% ethyl acetate–hexanes); IR ($CHCl_3$) 3517, 2991, 2947, 2904, 1683, 1460, 1426, 1376, 1308, 1251, 1206, 1149, 1112, 1099, 1082, 1032, 937, 914 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (dt, 1 H, J = 5.7, 2.0 Hz), 5.77 (br d, 1 H, J = 4.0 Hz), 5.08–4.87 (m, 1 H), 4.91 (t, 1 H, J = 7.1 Hz), 4.69 (s, 2 H), 4.16 (q, 2 H, J = 7.1 Hz), 4.18–4.08 (m, 1 H), 3.94–3.77 (m, 1 H), 3.40 (s, 3 H), 3.20–3.07 (m, 1 H), 2.80 (q, 1 H, J = 7.2 Hz), 1.97–1.80 (m, 2 H), 1.27 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 271 (M$^+$), 254, 240, 226, 208, 193 (base), 191, 165, 144, 138, 136, 120, 102, 92, 45; exact mass calcd for $C_{13}H_{21}NO_5$ 271.1420, found 271.1418.

Ethyl (1aα,1bα,5β,5aα,6β,6aα)-Octahydro-6-hydroxy-5-(methoxymethoxy)-2*H*-oxireno[4,5]cyclopenta[1,2-*b*]-pyridine-2-carboxylate (39). To a stirred solution–suspension of the olefin **38** (350 mg, 1.29 mmol) and disodium hydrogen phosphate (MCB, 561 mg, 3.87 mmol) in 2 mL of methylene chloride was added 3,5-dinitroperoxybenzoic acid (932 mg, 95% active oxygen, 3.87 mmol active oxygen). After 7 h at room temperature, the mixture was quenched with saturated aqueous sodium bicarbonate (20 mL) and extracted with ether (4 × 40 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 67% ethyl acetate–hexanes afforded 260 mg (70%) of the epoxide **39** as an oil: R_f = 0.13 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 3511, 2947, 1691, 1460, 1417, 1373, 1339, 1267, 1255, 1224, 1146, 1100, 1037, 1021, 940, 914, 901, 857, 844, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (s, 2 H), 4.54–4.30 (m, 2 H), 4.28–4.12 (m, 3 H), 4.11–4.03 (m, 1 H), 4.00–3.88 and 3.87–3.75 (two m, 1 H), 3.68 and 3.55 (two br s, 1 H), 3.50 (br s, 1 H), 3.44 (s, 3 H), 3.42–3.22 (m, 1 H), 2.55–2.39 (m, 1 H), 2.21–2.09 (m, 1 H), 1.58–1.44 (m, 1 H), 1.29 (t, 3 H, J = 7.1 Hz); ^{1}H NMR (300 MHz, $CDCl_3$, 55 °C) 4.71 (s, 2 H), 4.53–4.35 (m, 2 H), 4.24–4.08 (m, 1 H), 4.18 (q, 2 H, J = 7.1 Hz), 4.05 (td, 1 H, J = 6.1, 2.4 Hz), 3.92–3.76 (m, 1 H), 3.61 (br s, 1 H), 3.48 (dd, 1 H, J = 2.8, 1.6 Hz), 3.44 (s, 3 H), 3.43–3.29 (m, 1 H), 2.48 (td, 1 H, J = 9.3, 6.5 Hz), 2.16 (dtd, 1 H, J = 13.9, 5.5, 3.4 Hz), 1.52 (dddd, 1 H, J = 13.8, 10.7, 4.9, 2.8 Hz), 1.28 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 287 (M$^+$), 269, 256, 242, 224 (base), 208, 196, 182, 170, 154, 152, 138, 126, 96, 82, 68, 56, 45; exact mass calcd for $C_{13}H_{19}NO_5$ (M$^+$ − H_2O) 269.1263, found 269.1263.

Ethyl (1aα,1bα,5β,5aα,6aα)-Octahydro-5-(methoxymethoxy)-6-oxo-2*H*-oxireno[4,5]cyclopenta[1,2-*b*]pyridine-2-carboxylate (40). To a stirred solution of a preformed red chromium trioxide dipyridine complex (formed from chromium trioxide (806 mg, 7.09 mmol) and pyridine (1.28 mL, 15.8 mmol)) in 35 mL of methylene chloride was added a solution of the alcohol **39** (227 mg, 0.790 mmol) in 5 mL of methylene chloride. After 0.5 h at room temperature, ethyl acetate (30 mL) was added. The dark solution was filtered through silica gel, which was triturated with ethyl acetate. The filtrate (150 mL) was concentrated in vacuo. Flash chromatography of the residue on silica gel with 33% ethyl acetate–hexanes afforded 196 mg (87%) of the ketone **40** as an oil: R_f = 0.32 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 2969, 2867, 1749, 1690, 1460, 1410, 1370, 1335, 1279, 1255, 1209, 1144, 1094, 1032, 981, 914, 884, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 and 4.62 (two dd, 1 H, J = 10.9, 1.2 Hz), 4.60 (s, 2 H), 4.29–4.14 (m, 1.5 H), 4.21 (q, 2 H, J = 7.1 Hz), 4.06 (br s, J = 0.5 Hz), 3.98 and 3.83 (two dt, 1 H, J = 12.9, 4.5 Hz), 3.47 (ddd, 1 H, J = 13.3, 11.1, 2.6 Hz), 3.41 (d, 1 H, J = 2.4 Hz), 3.34 (s, 3 H), 2.76 (ddd, 1 H, J = 11.1, 7.7, 4.7 Hz), 2.06–1.92 (m, 1 H), 1.57–1.45 (m, 1 H), 1.31 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 254 (M$^+$ − OCH_3), 253, 240 (base), 224, 223, 222, 213, 197, 183, 168, 154, 152, 150, 142, 140, 134, 126, 124, 110, 106, 96, 82, 71, 58, 45; exact mass calcd for $C_{12}H_{16}NO_5$ (M$^+$ − OCH_3) 254.1028, found 254.1025.

Ethyl (1aα,1bα,5β,5aα,6aα)-Octahydro-5-hydroxy-6-oxo-2*H*-oxireno[4,5]cyclopenta[1,2-*b*]pyridine-2-carboxylate. To a stirred solution of the ketone **40** (50.0 mg, 0.175 mmol) in 10 mL of methylene chloride was added triphenylcarbenium tetrafluoroborate (86.8 mg, 0.263 mmol). After 11 h at room temperature, the yellowish red solution was quenched with water (5 mL), stirred for 5 min, and extracted with methylene chloride (4 × 10 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 33% ethyl acetate–hexanes afforded 25.4 mg (60%) of the title alcohol as an oil: R_f = 0.37 (silica gel, 75% ethyl acetate–hexanes); IR ($CHCl_3$) 3613, 2991, 2926, 1764, 1690, 1558, 1462, 1415, 1372, 1339, 1275, 1199, 1184, 1167, 1103, 1076, 1059, 1019, 983, 965, 914, 859 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 and 4.73 (two br d, 1 H, J = 10.3 Hz), 4.34–3.92 (m, 4 H), 3.82–3.66 (m, 1 H), 3.54 (d, 1 H, J = 2.6 Hz), 3.36–3.16 (m, 1 H), 2.69 (dd, 1 H, J = 10.3, 6.7 Hz), 1.95–1.80 (m, 1 H), 1.53–1.44 (m, 1 H), 1.26 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 223 (M$^+$ − H_2O), 194, 169, 142 (base), 125, 111, 97, 83, 71, 57.

Ethyl (1aα,1bα,6aα)-1a,1b,3,4,6,6a-Hexahydro-6-oxo-2*H*-oxireno[4,5]cyclopenta[1,2-*b*]pyridine-2-carboxylate (41). To a stirred solution of the ketone **40** (94.1 mg, 0.330 mmol) in 33 mL of tetrahydrofuran was added 1 N aqueous sodium hydroxide (330 μL, 0.330 mmol). After 7 h at room temperature, the yellow solution was treated with anhydrous potassium carbonate (~1 g), which adsorbed the yellow material. The mixture was gravity filtered, and the filtrate was concentrated in vacuo. Flash chromatography of the residue on silica gel with 25% and then 33% ethyl acetate–hexanes afforded 59.7 mg (81%) of the enone **41** as a viscous oil: R_f = 0.47 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 3037, 2969, 2930, 1740, 1697, 1664, 1460, 1410, 1378, 1344, 1283, 1251, 1228, 1195, 1118, 1091, 1070, 1039, 1011, 962, 891, 878, 827, 796, 770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (dt, 1 H, J = 7.7, 3.0 Hz), 4.53 (br s, 1 H), 4.45–4.26 (m, 1 H), 4.25 (q, 2 H, J = 7.1 Hz), 4.20–3.98 (m, 1 H), 3.48 (d, 1 H, J = 2.8 Hz), 2.88 (td, 1 H, J = 12.6, 2.8 Hz), 2.45 (ddt, 1 H,

J = 17.0, 7.5, 2.6 Hz), 2.20 (dddt, 1 H, J = 17.0, 10.7, 5.1, 3.0 Hz), 1.32 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 223 (M^+, base), 194, 182, 178, 167, 166, 151, 150, 122, 110, 94; exact mass calcd for $C_{11}H_{13}NO_4$ 223.0845, found 223.0840.

Ethyl (1aα,1bα,6Z,6aα)-6-Ethylidene-1a,1b,3,4,6,6a-hexahydro-2H-oxireno[4,5]cyclopenta[1,2-b]pyridine-2-carboxylate (42) and Ethyl (1aα,1bα,6E,6aα)-6-Ethylidene-1a,1b,3,4,6,6a-hexahydro-2H-oxireno[4,5]cyclopenta[1,2-b]-pyridine-2-carboxylate (43). To a stirred suspension of powdered ethyltriphenylphosphonium bromide (43.2 mg, 0.116 mmol) in 2 mL of anhydrous ether at room temperature in a sealed tube was added 1.6 N n-butyllithium (73.0 μL, 0.117 mmol) in hexanes. After 30 min, a solution of the enone **41** (13.0 mg, 0.0582 mmol) in 1 mL of ether was added to the yellow ylide solution. The mixture was heated at 65 °C for 4 h, cooled to room temperature, and quenched with water (5 mL). The mixture was extracted with ether (4 × 5 mL). The combined organic extracts were dried over anhydrous potassium carbonate and concentrated in vacuo. Flash chromatography of the residue on silica gel with 10% ethyl acetate–hexanes afforded 11.7 mg (85%) of a 1:2 mixture of **42** and **43** as an oil which slowly decomposed at room temperature. Since **42** and **43** could not be separated by HPLC or silver nitrate impregnated silica gel chromatography, the following spectral data were obtained for the mixture: R_f = 0.24 (silica gel, 25% ethyl acetate–hexanes); IR (thin film) 3060, 2987, 2926, 1697, 1460, 1410, 1375, 1339, 1279, 1243, 1224, 1194, 1109, 1044, 1013, 981, 948, 889, 870, 827, 807, 771, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, **42**) δ 6.24 (dt, 1 H, J = 7.3, 3.2 Hz), 6.05 (q, 1 H, J = 7.3 Hz), 4.31 (br s, 1 H), 4.23 (q, 2 H, J = 7.1 Hz), 4.20–3.95 (m, 2 H), 3.93 (d, 1 H, J = 3.2 Hz), 2.84 (td, 1 H, J = 11.0, 4.4 Hz), 2.24 (m, 2 H), 1.91 (d, 3 H, J = 7.3 Hz), 1.32 (t, 3 H, J = 7.1 Hz); ^{1}H NMR (300 MHz, $CDCl_3$, **43**) δ 6.29 (dt, 1 H, J = 7.1, 3.2 Hz), 5.89 (q, 1 H, J = 7.1 Hz), 4.31 (br s, 1 H), 4.23 (q, 2 H, J = 7.1 Hz), 2.84 (td, 1 H, J = 11.0, 4.4 Hz), 2.24 (m, 2 H), 1.90 (d, 3 H, J = 7.1 Hz), 1.32 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 235 (M^+, base), 220, 207, 206, 192, 178, 162, 154, 148, 134, 120, 118, 106, 82, 29; exact mass calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1210.

(2aα,3α,4Z,7bα)-4-Ethylidene-2a,3,4,6,7,7b-hexahydro-3-methoxy-1H-2-oxa-7a-azacyclopent[cd]inden-1-one (44) and (2aα,3α,4E,7bα)-4-Ethylidene-2a,3,4,6,7,7b-hexahydro-3-methoxy-1H-2-oxa-7a-azacyclopent[cd]inden-1-one (45). To a stirred solution of a 1:2 mixture of the epoxides **42** and **43** (7.0 mg, 0.0298 mmol) in 1 mL of methanol was added sodium methoxide (160 mg, 2.98 mmol). The mixture was heated to reflux for 3 h and then quenched with water (5 mL). Methanol was removed in vacuo, and the mixture was extracted with ether (3 × 5 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered and concentrated in vacuo. Flash chromatography of the residue on silica gel with 25%, and then 33% ethyl acetate–hexanes afforded 6.2 mg (94%) of a 1:2 mixture of **44** and **45** as an oil. The following spectral data were obtained from the mixture: R_f = 0.50 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 2939, 1760, 1440, 1371, 1199, 1088, 1048, 965, 878, 861, 829, 765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, **44**) δ 6.21 (q, 1 H, J = 7.3 Hz), 6.02 (m, 1 H), 4.78 (d, 1 H, J = 6.9 Hz), 4.40 (br s, 1 H), 4.22 (br d, 1 H, J = 1.6 Hz), 3.48 (s, 3 H), 3.54–3.33 (m, 2 H), 2.62–2.43 (m, 1 H), 2.37–2.13 (m, 1 H), 1.85 (d, 3 H, J = 7.3 Hz); ^{1}H NMR (300 MHz, $CDCl_3$, **45**) δ 6.08 (dt, 1 H, J = 6.9, 2.7 Hz), 5.92 (q, 1 H, J = 7.1 Hz), 4.74 (d, 1 H, J = 7.1 Hz), 4.24 (br s, 1 H), 4.11 (br d, 1 H, J = 1.4 Hz), 3.49 (s, 3 H), 3.54–3.33 (m, 2 H), 2.62–2.43 (m, 1 H) 2.37–2.13 (m, 1 H), 1.91 (d, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 221 (M^+, base), 206, 191, 189, 177, 163, 149, 145, 135, 121; exact mass calcd for $C_{12}H_{15}NO_3$ 221.1052, found 221.1052.

(2aα,3α,4β,4aα,7bα)-4-Ethyloctahydro-3-methoxy-1H-2-oxa-7a-azacyclopent[cd]inden-1-one (46). A solution of a 1:2 mixture of the dienes **44** and **45** (6.0 mg, 0.0269 mmol) in 2 mL of ethanol containing a catalytic amount of 10% palladium on charcoal was stirred under a hydrogen-filled balloon. After 12 h at room temperature, the mixture was filtered through Celite. The filtrate was concentrated in vacuo to afford 6.0 mg (100%) of **46** as an oil. This compound was characterized without further purification. Attempted chromatographic purification (on silica gel or basic alumina) resulted in partial decomposition of the compound: R_f = 0.36 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 2947, 1757, 1458, 1413, 1260, 1199, 1128, 1081, 1034, 976, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (dd, 1 H, J = 8.5, 3.6 Hz), 4.16 (t, 1 H, J = 7.9 Hz), 3.73 (ddd, 1 H, J = 13.1, 8.1, 6.7 Hz), 3.57 (dd, 1 H, J = 7.5, 3.6 Hz), 3.44 (s, 3 H), 3.05 (dt, 1 H, J = 13.1, 6.5 Hz), 2.32 (br dt, 1 H, J = 14.1, 7.9 Hz), 1.94–1.64 (m, 3 H), 1.44 (quint, 2 H, J = 7.5 Hz), 1.50–1.20 (m, 2 H), 0.96 (t, 3 H, J = 7.3 Hz); mass spectrum (15 eV), m/z 225 (M^+), 195, 180, 166, 138 (base), 125, 109, 98; exact mass calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1365.

Authentic Dihydrostreptazolin. To a solution of the acetate **2** (authentic, 30.7 mg, 0.122 mmol) in 2 mL of methanol was added 6 drops of concentrated ammonium hydroxide. After 7 h at room temperature, the mixture was concentrated in vacuo. Flash chromatography of the residue on silica gel with 33% ethyl acetate–hexanes afforded 15.5 mg (100%) of the title alcohol as an oil: R_f = 0.21 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 3404, 2947, 1734, 1440, 1399, 1328, 1218, 1131, 1080, 1032, 979, 893, 794, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (br d, 1 H, J = 5.5 Hz), 4.62 (d, 1 H, J = 6.3 Hz), 4.43 (br d, 1 H, J = 6.3 Hz), 3.86 (br dd, 1 H, J = 14.1, 4.9 Hz), 3.08 (ddd, 1 H, J = 13.9, 12.9, 3.4 Hz), 2.67 (br d, 1 H, J = 13.5 Hz), 2.25–2.11 (m, 2 H), 2.12 (ddd, 1 H, J = 13.5, 13.3, 4.7 Hz), 1.84–1.74 (m, 1 H), 1.43 (qt, 1 H, J = 13.1, 4.6 Hz), 1.05 (t, 3 H, J = 7.7 Hz); mass spectrum (15 eV), m/z 209 (M^+, base), 194, 192, 181, 180, 164, 153, 152, 140, 136, 125, 122, 112, 107, 97, 94, 85, 58, 43; exact mass calcd for $C_{11}H_{15}NO_3$ 209.1052, found 209.1052.

[2aS-(2aα,3α,7bα)]-4-Ethyl-2a,3,5,6,7,7b-hexahydro-3-methoxy-1H-2-oxa-7a-azacyclopent[cd]inden-1-one. To a stirred solution of the above alcohol (11.4 mg, 0.0545 mmol) in 1 mL of dimethyl sulfoxide containing potassium hydroxide (100 mg, 1.51 mmol) was added methyl iodide (10.0 μL, 0.161 mmol). After 30 min, the mixture was diluted with water (5 mL) and extracted with ether (4 × 5 mL). The combined organic extracts were washed with water (2 × 5 mL), dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 50% ethyl acetate–hexanes afforded 11.0 mg (90%) of the title methyl ether as an oil: Rf = 0.36 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 2947, 1757, 1451, 1390, 1353, 1271, 1184, 1137, 1085, 1039, 996, 987, 967, 897, 872, 850, 807, 764, 688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (d, 1 H, J = 6.5 Hz), 4.38 (br d, 1 H, J = 6.3 Hz), 4.23 (br s, 1 H), 3.87 (br dd, 1 H, J = 13.9, 4.9 Hz), 3.46 (s, 3 H), 3.08 (t, 1 H, J = 13.7 Hz), 2.67 (br d, 1 H, J = 13.7 Hz), 2.22–2.20 (m, 3 H), 1.79 (m, 1 H), 1.44 (qt, 1 H, J = 13.1, 4.7 Hz), 1.03 (t, 3 H, J = 7.7 Hz); mass spectrum (15 eV), m/z 223 (M^+, base), 208, 194, 192, 154, 150, 139, 136, 135; exact mass calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1208.

Ethyl (5Z,6aα,7β,7aα)-6-(Acetyloxy)-5-ethylidene-2,3,5,6,7,7a-hexahydro-7-hydroxy-1H-1-pyrindine-1-carboxylate (47) and Ethyl (5E,6aα,7β,7aα)-6-(Acetyloxy)-5-ethylidene-2,3,5,6,7,7a-hexahydro-7-hydroxy-1H-1-pyrindine-1-carboxylate (48). To a stirred 1:2 mixture of the epoxides **42** and **43** (9.0 mg, 0.0383 mmol) and sodium acetate (99%, 63.4 mg, 0.765 mmol) was added acetic acid (1 mL, 17.5 mmol). After 30 min at room temperature, acetic acid was removed in vacuo. The mixture was treated with saturated aqueous sodium bicarbonate (5 mL) and extracted with ether (4 × 5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 33% ethyl acetate–hexanes afforded 8.0 mg (71%) of a 1:2 mixture of **47** and **48** as an oil. The isomers were separated by HPLC (Waters Model 590, 40% ethyl acetate–hexanes, 2 mL/min). NMR spectral data were obtained for the separated isomers, but IR and mass spectral data were obtained from the mixture: R_f = 0.43 (silica gel, 67% ethyl acetate–hexanes); retention time of **47**, 13.2 min (μ-Porasil column, 30% ethyl acetate–hexanes, elution rate 2 mL/min); retention time of **48**, 14.1 min; IR ($CHCl_3$) 3457, 2991, 2947, 2875, 1740, 1690, 1460, 1424, 1371, 1344, 1317, 1267, 1228, 1118, 1021, 967, 918, 882, 842, 828 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, **47**) δ 6.34–6.26 (m, 1 H), 6.27 (q, 1 H, J = 7.3 Hz), 5.61 (br s, 1 H), 4.47–4.33 (m, 2 H), 4.21 and 4.20 (two q, 2 H, J = 7.1 Hz), 4.15–3.99 (m, 1 H), 3.09–2.91 (m, 1 H), 2.34–2.17 (m, 2 H), 2.09 (s, 3 H), 1.78 (d, 3 H, J = 7.3 Hz), 1.30 (t, 3 H, J = 7.1 Hz); ^{1}H NMR (300 MHz, $CDCl_3$, **48**) δ 6.43–6.35 (m, 1 H), 6.05 (q, 1 H, J = 7.3 Hz), 5.32 (br s, 1 H), 4.46–4.33 (m, 2 H), 4.21 and 4.20 (two q, 2 H, J = 7.1 Hz), 4.15–4.00 (m, 1 H), 3.08–2.92 (m, 1 H), 2.34–2.17 (m, 2 H), 2.08 (s, 3 H),

1.96 (d, 3 H, J = 7.3 Hz), 1.30 (t, 3 H, J = 7.1 Hz); mass spectrum (15 eV), m/z 295 (M^+), 277, 235 (base), 218, 206, 189, 162, 146, 134; exact mass calcd for $C_{15}H_{21}NO_5$ 295.1420, found 295.1426.

(2aα,3α,4*Z*,7bα)-4-Ethylidene-2a,3,4,6,7,7b-hexahydro-3-hydroxy-1*H*-2-oxa-7a-azacyclopent[*cd*]inden-1-one (1) and (2aα,3α,4*E*,7bα)-4-Ethylidene-2a,3,4,6,7,7b-hexahydro-3-hydroxy-1*H*-2-oxa-7a-azacyclopent[*cd*]inden-1-one (49). To a vigorously stirred solution of a 1:2 mixture of **47** and **48** (2.0 mg, 0.00680 mmol) in 2 mL of methanol was added sodium methoxide (100 mg, 1.85 mmol). The mixture was heated for 1 h, and the methanol was removed in vacuo. The mixture was diluted with water and extracted with ethyl acetate (4 × 5 mL). The organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated to 0.5 mL. Flash chromatography of the dilute solution on silica gel with 50% ethyl acetate–hexanes afforded a homogeneous fraction which was carefully concentrated. The residual solvent was removed by a dry nitrogen stream to afford 1.4 mg (70%) of a 1:2 mixture of **1** and **49** as an oil, which was immediately diluted with deuterated chloroform. With the pure Z isomer **47** (~0.5 mg, 0.001 70 mmol), the same procedure afforded **1**. With the pure E isomer (2 mg, 0.006 80 mmol), the same procedure afforded **49**: R_f = 0.28 (silica gel, 67% ethyl acetate–hexanes); UV ($CHCl_3$) 296 nm; ^1H NMR (300 MHz, $CDCl_3$, 1) δ 6.17 (q, 1 H, J = 7.5 Hz), 6.10–6.02 (m, 1 H), 4.90 (br s, 1 H), 4.75 (d, 1 H, J = 6.7 Hz), 4.29 (br d, 1 H, J = 6.7 Hz), 3.53–3.33 (m, 2 H), 2.60–2.42 (m, 1 H), 2.40–2.26 (m, 1 H), 1.92 (d, 3 H, J = 7.5 Hz); ^1H NMR (300 MHz, $CDCl_3$, **49**) δ 6.16–6.08 (m, 1 H), 5.97 (q, 1 H, J = 7.3 Hz), 4.70 (d, 1 H, J = 7.5 Hz), 4.59 (br s, 1 H), 4.28 (br d, 1 H, J = 7.5 Hz), 3.50–3.33 (m, 2 H), 2.56 (dtd, 1 H, J = 13.3, 6.7, 4.4 Hz), 2.40–2.16 (m, 1 H), 1.92 (d, 3 H, J = 7.3 Hz); mass spectrum (15 eV, 1), m/z 207 (M^+), 191, 177, 163, 149, 136 (base), 121, 107; exact mass calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0896.

[2a*S*-(2aα,3α,4β,4aα,7bα)]-4-Ethyloctahydro-3-hydroxy-1*H*-2-oxa-7a-azacyclopent[*cd*]inden-1-one (50). A solution of the alcohol prepared from authentic dihydrostreptazolin acetate (6.0 mg, 0.0287 mmol) in 2 mL of ethanol containing a catalytic amount of 10% palladium on charcoal was stirred under a hydrogen-filled balloon. After 12 h at room temperature, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo to afford 6.0 mg (100%) of **50** as an oil. A 1:2 mixture of streptazolins **1** and **49** was also reacted using the same procedure as above, and **50** was obtained. This compound was characterized without further purification. Attempted chromatographic purification (on silica gel or basic alumina) resulted in partial decomposition: R_f = 0.21 (silica gel, 67% ethyl acetate–hexanes); IR (thin film) 3409, 2934, 1729, 1451, 1422, 1255, 1106, 1048, 1026, 910, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (dd, 1 H, J = 8.5, 3.8 Hz), 4.17 (t, 1 H, J = 7.9 Hz), 4.11–4.01 (m, 1 H), 3.71 (dt, 1 H, J = 13.1, 7.3 Hz), 3.07 (dt, 1 H, J = 13.3, 6.3 Hz), 2.40 (br dt, 1 H, J = 14.3, 7.9 Hz), 2.20 (br s, 1 H), 1.90–1.64 (m, 3 H), 1.45 (quint d, 2 H, J = 7.5, 2.4 Hz), 1.50–1.20 (m, 2 H), 0.98 (t, 3 H, J = 7.3 Hz); mass spectrum (15 eV), m/z 211 (M^+, base), 182, 167, 166, 124, 97; exact mass calcd for $C_{11}H_{17}NO_3$ 211.1208, found 211.1209.

General Procedure for the Oxidation of the Isoxazolines Using 3,5-Dinitroperoxybenzoic Acid. To a solution of **61** (71.0 mg, 0.440 mmol) in 25 mL of chloroform containing 4,4′-thiobis(2-*tert*-butyl-6-methylphenol) (20.1 mg, 0.0560 mmol) was added 3,5-dinitroperoxybenzoic acid (2.11 g, 95% active oxygen, 8.80 mmol active oxygen). The mixture was heated to reflux. After 8 h, the reaction mixture was cooled to 0 °C and filtered through sintered glass with a chloroform wash (25 mL). The filtrate was washed with 20% aqueous sodium bisulfite (3 × 10 mL), saturated aqueous sodium bicarbonate (3 × 10 mL), and saturated aqueous sodium chloride (3 × 10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel with 20% ethyl acetate–hexanes afforded 39.8 mg (50%) of **62** as an oil and then 13.3 mg (17%) of **63** as an oil. Acetate **62**: R_f = 0.32 (silica gel, 50% ethyl acetate–hexanes); IR (thin film) 3459, 2947, 1734, 1583, 1546, 1446, 1357, 1313, 1251, 1160, 1134, 1103, 912, 759, 736, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.22 (m, 5 H), 4.98 (dd, 1 H, J = 8.5, 3.2 Hz), 4.30 (A of d AB q, J_{AB} = 11.6 Hz, J_{AX} = 3.2 Hz), 4.17 (B of d AB q, J_{AB} = 11.6 Hz, J_{BX} = 8.5 Hz), 2.50 (br s, 1 H), 2.12 (s, 3 H); mass spectrum (15 eV), m/z 152 ($M^+ - H_2O$), 150, 149, 120, 107 (base), 79, 58, 43. Acetate **63**: R_f = 0.25 (silica gel, 50% ethyl acetate–hexanes); IR (thin film) 3457, 2947, 1734, 1489, 1446, 1366, 1271, 1073, 1040, 942, 857, 758, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.25 (m, 5 H), 5.87 (dd, 1 H, J = 7.4, 4.2 Hz), 3.98–3.72 (m, 2 H), 2.16 (s, 3 H), 1.84 (br s, 1 H); mass spectrum (15 eV), m/z 162 ($M^+ - H_2O$), 150, 149, 134, 120, 107 (base), 74, 59, 45, 31, 29.

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Registry No. (±)-**1**, 95119-35-0; **2**, 80152-10-9; **2** alcohol, 80152-09-6; **2** methyl ether, 127619-65-2; (±)-**4b**, 95019-34-4; (±)-(*E*)-**5b**, 127707-59-9; (±)-(*Z*)-**5b**, 127707-60-2; **6**·HCl, 41979-39-9; (±)-**7**, 127619-50-5; (±)-**10**, 127619-51-6; **11**, 57330-84-4; (±)-**12**, 127619-52-7; (±)-**13**, 95019-32-2; (±)-**14**, 127619-53-8; (±)-**15**, 127619-54-9; (±)-**16**, 127619-55-0; **17**, 89690-69-7; (±)-**18**, 127619-56-1; (±)-**19**, 127645-48-1; (±)-**20**, 127619-57-2; (±)-**25**, 95019-45-7; (±)-**25** alcohol, 95019-44-6; (±)-**26**, 95044-88-5; (±)-**27**, 95019-35-5; (±)-**28**, 127619-58-3; (±)-**29**, 127619-59-4; (±)-**30**, 95019-36-6; (±)-**32**, 127619-60-7; (±)-**32** (5′-alcohol), 127619-61-8; (±)-**35**, 127619-63-0; (±)-**37**, 95019-37-7; (±)-**38**, 95019-38-8; (±)-**39**, 95019-46-8; (±)-**40**, 95019-47-9; (±)-**40** (5′-alcohol), 127619-64-1; (±)-**41**, 95019-39-9; (±)-**42**, 95119-38-3; (±)-**43**, 95019-40-2; (±)-**44**, 95119-39-4; (±)-**45**, 95019-41-3; (±)-**46**, 95019-42-4; (±)-**47**, 95119-40-7; (±)-**48**, 95019-43-5; (±)-**49**, 95119-34-9; (±)-**50**, 95019-48-0; (±)-**60**, 127707-67-9; (±)-**61**, 127619-66-3; (±)-**62**, 127707-63-5; (±)-**63**, 127707-64-6; (±)-**64**, 127707-68-0; (±)-**65**, 127619-67-4; (±)-**66**, 127619-68-5; (±)-**67**, 127619-72-1; (±)-**68**, 127619-73-2; (±)-**69**, 127619-69-6; (±)-**70**, 86286-51-3; (±)-**71**, 127707-61-3; (±)-**72**, 127707-62-4; (±)-**73**, 127619-70-9; (±)-**74**, 73516-75-3; (±)-**75**, 86703-56-2; (±)-**76**, 127619-71-0; (±)-**77**, 127707-65-7; (±)-**78**, 127619-62-9; (±)-**79**, 127707-66-8; ethyl 4-oxo-1-piperidinecarboxylate, 29976-53-2.

Supplementary Material Available: ^1H NMR spectra of **1**, **4b**, **5b**, **7**, **13**, **25–30**, **37**, **38**, **40–45**, and **47–49** (26 pages). Ordering information is given on any current masthead page.