oxyphenyl)-3-methyl-4-(2-phenylethenyl)-2-azetidinone (27) and (*Z*)- and (*E*)-3-Cyano-3,4-dihydro-1-(4-methoxyphenyl)-3-methyl-4-phenyl-2(1*H*)-pyridone (28 and 29). A solution of 120 mg (0.55 mmol) of 2,5-diazido-3,6-dimethyl-1,4-benzoquinone and 237 mg (1.0 mmol) of **11c** in 10 mL of anhydrous chlorobenzene was maintained at 130 °C for 1 h. The solvent was then removed and the dark brown residue subjected to PLC (silica gel, 1:9 ethyl acetate–hexane) to give the purified products **27** and **28**. Compound **29** was detected from the ^{1}H NMR of the mixture.

Compound **27**: yield, 8%; colorless oil; IR (Nujol, cm^{-1}) 2230, 1760; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 7.02 (m, 4 H), 6.87 (d, J = 16 Hz, 1 H), 6.28 (dd, J = 8, 16 Hz, 1 H), 4.40 (d, J = 8 Hz, 1 H), 3.70 (s, 3 H), 1.80 (s, 3 H); mass spectrum (CI), m/e 319 (M + 1).

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.49; H, 5.66. Found: C, 75.72; H, 5.73.

Compound **28**: yield, 46%; white crystals, mp 144–145 °C; IR (Nujol, cm^{-1}) 1690; ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 5 H), 7.05 (m, 4 H), 6.41 (d, J = 8 Hz, 1 H), 5.38 (dd, J = 4, 8 Hz, 1 H), 3.75 (s, 3 H), 3.70 (m, 1 H), 1.61 (s, 3 H).

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.49; H, 5.66. Found: C, 75.72; H, 5.49.

Dechlorination/Methylation of 15c. Preparation of 27. The β-lactam **15c** (45 mg, 0.148 mmol) was reductively dechlorinated (Zn, CH_3CO_2H) and converted to its enolate (NaH, THF, 0 °C) by the procedures previously described. The solution of the enolate was treated with 0.05 mL of CH_3I, and after 30 min the reaction was quenched with 5 mL of water and extracted with CH_2Cl_2. This solution was dried ($MgSO_4$), the solvent was removed, and the light yellow oil was purified by PLC (1:9 ethyl acetate–hexane) to yield 30 mg (64%) of **27**, which was identical with that formed in the cycloaddition of methylcyanoketene to **11c**.

Dechlorination/Methylation of 16c. Preparation of 28. To a solution of 102 mg (0.30 mmol) of **16c** in 14 mL of acetic acid and 5 mL of THF (0 °C) was added 39 mg (0.60 equiv) of powdered Zn. After 1 h the reaction mixture was filtered and washed with brine, then 10% sodium carbonate, and water. After the mixture was dried, the solvent was removed to yield 79 mg (87%) of the dechlorinated lactam: IR (neat, cm^{-1}), 2240, 1690; ^{1}H NMR ($CDCl_3$) δ 7.25 (s, 5 H), 6.90 (m, 4 H), 6.26 (m, 1 H), 5.22 (m, 1 H), 3.94 (m, 2 H), 3.70 (s, 3 H). This product (61 mg, 0.20 mmol) was dissolved in 3 mL of THF (0 °C) and treated with 20 mg of NaH (50:50 dispersion in mineral oil). After 30 min, 0.5 mL (0.80 mmol) of CH_3I was added, and 20 min later the reaction was quenched with 5 mL of water. The mixture was then extracted with $CHCl_3$ and the organic layer dried ($MgSO_4$). The solvent was removed to yield 58 mg of **28**, which was identical with the product obtained in the cycloaddition of methylcyanoketene to **11c**.

Dechlorination/Methylation of 16c. The above enolate anion, generated from 50 mg of the lactam **16c** was treated with 80 mg (0.60 mmol) of *N*-chlorosuccinimide, and after 20 min the reaction was quenched with 5 mL of water and extracted with $CHCl_3$. After the mixture was dried ($MgSO_4$), the solvent was removed to yield 92% of the lactam **16c**, which was identical with the product obtained from the cycloaddition of CCK to **11c**.

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Supplementary Material Available: Full NMR and IR data for compounds **3**, **4**, **6**, **7**, **9**, **10**, and **12–20** and atomic coordinates for **25** (22 pages). Ordering information is given on any current masthead page.

Nicotinic Acid Lariat Ethers: Syntheses, Complexation, and Reduction

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Combination of 2-(hydroxymethyl)-5-oxazolinylpyridine **16a** with lariat ethers **21** and **23** generated chiral 6-methylnicotinic oxazoline lariat ethers **22** and **24**, respectively. Chiral lariat ether **24b** by stereoselective metal-directed addition of methylmagnesium bromide was converted to the corresponding enantiomerically enriched *N*-magnesio-1,4-dihydropyridine **26**. Lariat **26** and the nonlariat analogue **31** both reduced α,α,α-trifluoroacetophenone in a NADH model-like reduction to give the *S* alcohol **32** in low enantiomeric excess.

Metal ion participation in the in vivo stereospecific NADH-mediated hydride reduction of carbonyl substrates has been well established.[1] Likewise, by incorporation of various metal ions into "chiral models", dramatic enhancements in the stereospecificity of carbonyl reductions have been observed.[2] A rationale for the improved selectivity of hydride reduction by chiral NADH models in the presence of magnesium ion was put forward by Ohno et al.,[2,3] in which he proposed the involvement of a three-step mechanism: (1) initial electron transfer, (2) proton transfer, and (3) electron transfer. This overall

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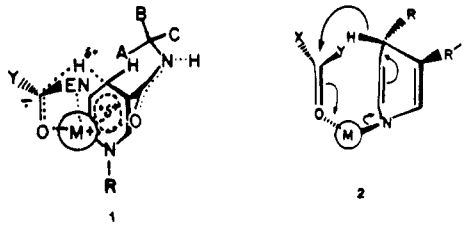
process can be mediated by a metal ion in an intermediate ternary sandwich-type tetradentate charge-transfer complex, as shown in 1. Recently, such a ternary complex was



1 2

spectroscopically (UV) characterized by Fukuzumi et al.[4] by monitoring the reduction of *p*-benzoquinone derivatives with a NADH model. Fukuzumi reported a blue shift (+0.22 eV) in the charge-transfer band upon addition of Mg^{2+}, while Na^+ had no apparent effect. Existence of a ternary complex involving Mg^{2+} was further supported by a +0.2-eV shift in the oxidative peak potential by cyclic voltametry; a similar change was not detected with added Na^+.

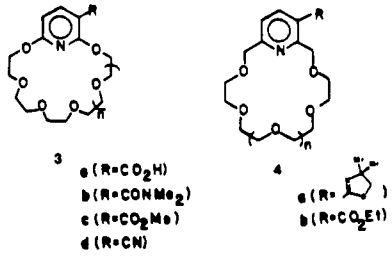
By use of dihydropyridines possessing both a chiral center at the 4-position and a carboxamide moiety, benzoylformates were reduced in excellent (>95%) optical yields depending on the chirality at the 4-position.[3b] The results[3b] strongly support Ohno's proposed mechanism, involving initial electron transfer followed by generation of an electronically and sterically favorable configuration in which the substrate carbonyl oxygen is aligned toward the ring nitrogen with the most electronegative carbonyl substituent facing the carboxamide group, prior to the slow hydrogen-transfer step. Thus, the stereochemical integrity of the reduction is controlled, at least in part, by the thermodynamic stability of the intermediate charge-transfer complex.

Several examples of *N*-metallo-1,4-dihydropyridines capable of transferring hydride to a suitable electrophilic centers, such as carbonyl compounds, have been reported.[5] Like classical "model NADH reactions" (e.g., *N*-alkyl-1,4-dihydropyridines), reductions by *N*-metallo-1,4-dihydropyridines can be envisioned to occur by an analogous mechanism in which the metal mediates the approach and juxtaposition of the C=O substrate, prior to hydrogen transfer. The degree of stereoselectivity should then depend upon the thermodynamic stability of the *N*-metallodihydropyridine–carbonyl complex **2**.

The proposed mechanism involving **2** can be envisioned as a vinylog of the cyclic hydride transfer proposed for the Meerwein–Ponndorf–Verley reduction,[6] the reduction of ketones by Grignard reagents with α-hydrogens,[7] and the addition of Grignard reagents to ketones.[8]

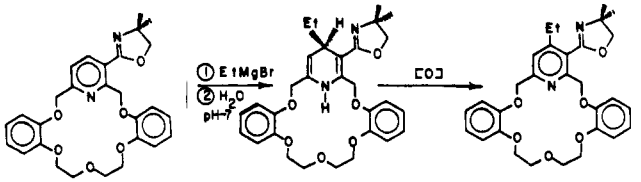
Since the addition of organometallics to ketones is an exothermic process, the stereochemical outcome of the reduction in **2** is most likely "steric approach" controlled[9] and should be predictable, if the model is asymmetric, by evoking Cram's rule.[8c,10] However, the findings of Ohno[3a] suggest the possibility of "anti-Cram" reduction when the ketone's most electronegative group is also the bulkiest. Such a reversal in predictability can be rationalized by the Karabatsos' modification of Cram's rule, which takes into account conformational restrictions due to metal coordination (i.e., coordinative bridging of the model's amide to the ketone's most electronegative group through a metal ion). In reductions by *N*-metallo-1,4-dihydropyridines, such coordinative control of stereoselectivity should be most predominant if a single-electron-transfer (SET) mechanism is operative, as proposed in the Ohno mechanism. Such a SET mechanism has been reported for the eight-center reductions of aryl ketones by unsubstituted *N*-alumino-1,4-dihydropyridines.[11]

With a transition-state model **2** as a guide, we prepared NADH mimics that incorporate a crown ether to stabilize the intermediary *N*-metalated species as well as to favor 1,4- over 1,2-addition of metal hydrides or organometallics to pyridine precursors.[12] Earlier, Newkome and coworkers[13a-h] and others[13i] described the syntheses and reactions of 2,6-bridged nicotinic acid crown ethers, incorporating either ethereal (**3**) or methylene linkages (**4**).



3 a (R=CO_2H) b (R=$CONMe_2$) c (R=CO_2Me) d (R=CN) 4 a (R=) b (R=CO_2Et)

Of these previously studied crowns, only macrocycle **4c** underwent chemical reduction to generate products, which support the *N*-metallodihydropyridine intermediate. Treatment of **4c** with EtMgBr, followed by hydrolysis, gave dihydropyridine **5**, which was readily oxidized to **6**.



4c 5 6

In contrast, under identical conditions the "more flexible", non-benzo crown ether derivatives afforded primarily unchanged macrocycle. The difference in reduction of these related crowns is likely due to steric interactions between the oxazoline and the bridging α-

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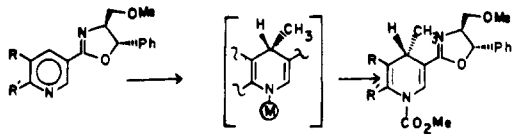
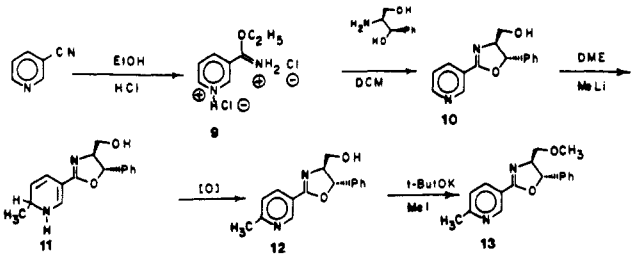
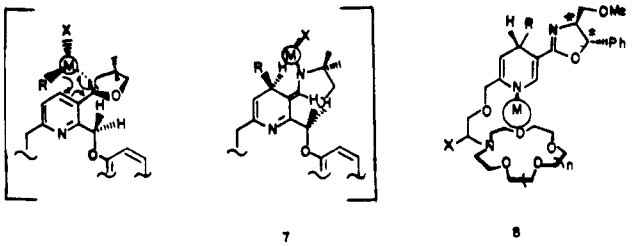
Scheme I



Scheme II



methylene group (see 7), thus inhibiting the oxazoline–pyridine coplanarity necessary for metal directed alkylation.[14,15]



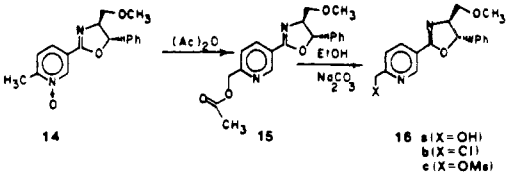
In order to achieve a more effective and representative "NADH model", we now report a new series of "lariat ether" nicotinic acid macrocycles bearing chiral, unhindered oxazoline moieties. This preliminary study describes the synthesis of and reduction with chiral lariat *N*-metallodihydronicotinic acid derivatives (8).

Results and Discussion

Synthesis of Chiral Nicotino Lariat Ether Macrocycles. During the course of our studies, Meyers[14a,16] et al. showed that chiral nicotinic oxazolines (Scheme I) undergo regional, facial-selective ring addition by "metal direction" of selected organometallics. The "trapping" of the intermediate metalated adduct by methyl chloroformate affords *N*-(methoxycarbonyl)-4-alkyl(or aryl)dihydropyridines in *S*/*R* enantiomeric ratios at the dihydropyridine 4-position as high as 97:3! Thus, chiral oxazoline-directing groups would provide a convenient way to produce a chiral center in the dihydropyridine 4-position with a high degree of stereospecificity.

The intermediary chiral metalated adduct (Scheme I) with a single γ-"transferable" hydrogen[3b,17] may provide more detailed information about the credibility of the proposed transition-state **2**, as in Ohno's model which invokes a hydride source possessing a preferred face capable of approach by an electrophile. Thus, Meyers'[16] chiral oxazoline **13** (Scheme II) was an excellent starting point for both proposed synthetic routes. One obvious difference from Meyers' procedures was in the oxidation of 1,2-dihydropyridine **11** to **12**, in that an improved procedure with $KMnO_4$ in acetone was employed.

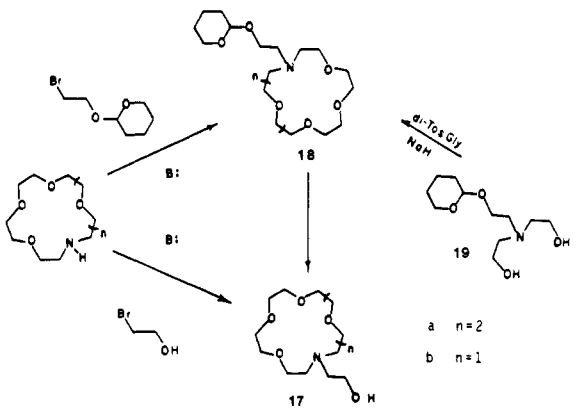
Attempted α-halogenation of **13** via free-radical procedures[21] gave numerous products including worthless halooxazolines; therefore, **13** was selectively N-oxidized[18] with *m*-chloroperoxybenzoic acid[19] in $CHCl_3$ at 0 °C to give **14**, which was substantiated (^1H NMR) by the $\Delta\delta$ 0.25 and 0.38 upfield shifts in the pyridine H-6 and H-4 signals, respectively. *N*-Oxide **14** was treated with refluxing Ac_2O



to give (80%) the desired ester **15**, which was spectroscopically characterized (^1H NMR); however, analytically pure samples were not realized due to its ease of decomposition. Ester **15** was rapidly transesterified in ethanol with anhydrous K_2CO_3[20] to give (69% from **14**) the target molecule **16a**.

Alcohol **16a** was characterized (^1H NMR) by an upfield ($\Delta\delta$ 0.47) shift of the α-methylene singlet to δ 4.81 upon removal of the acetate group and the appearance of a broad (exchangable) singlet at δ 3.9 for the hydroxyl proton. Attempts to generate **16b** by treatment of **16a** with $SOCl_2$ gave a complex mixture of water-soluble decomposition products, presumed to be a quaternary salt.[21] In an attempt to retard quaternization, **16a** was treated with mesyl chloride under mild conditions in order to generate **16c**. Spectral (^1H NMR) data for **16c** showed singlets at δ 3.0 and 5.1 corresponding to mesylmethyl and α-methylene groups, respectively; after a few hours, **16c** underwent similar decomposition. Numerous procedures to create a stable leaving group failed to circumvent the facile degradative problems.

The *N*-2-hydroxyethyl azacrowns **17** were obtained by three procedures. (1) DMF/K_2CO_3 treatment of the azacrown ethers with 2-bromoethanol generated (ca. 40–50%) the desired lariats **17**. (2) Tetrahydropyranyl



ether (THP) of 2-bromoethanol[22] was treated in a similar

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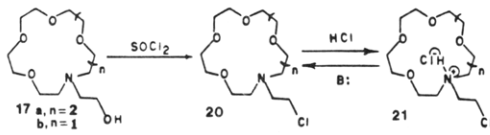
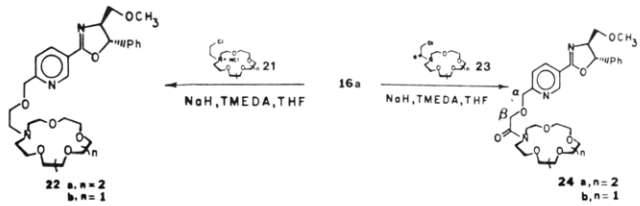
fashion to that of **17** with the azacrown ethers to give (62%) the THP-protected *N*-2-hydroxyethyl azacrown **18**. The tetrahydropyranyl moiety greatly enhanced the ease of purification. Lariat **18** was deprotected by treatment with HCl/MeOH, followed by neutralization and extraction (CH_2Cl_2) to generate (87%) **17**, which required no additional purification. (3) The method of choice entailed a simple three-step process involving nucleophilic substitution of diethanolamine on above THP-protected 2-bromoethanol to give (88%) **19**. Cyclization was accomplished by treatment of the corresponding disodium alkoxide of **19** with a ditosylated polyethylene glycol[23] at 25 °C to give (>45%) the desired **18**.

The ^{1}H NMR spectra of **18** displayed distinct multiplets at δ 1.37–1.70, 3.4–3.9, and 4.58 for the pyranyl methylenes, remaining *O*-methylenes, and methyne protons, respectively, as well as two well-defined triplets for the two nonequivalent *N*-methylenes at δ 2.80 (arm) and 2.84 (crown). Mass spectral data (210 °C, EI, 70 eV, 10KRP) further support monomer **18** by the "typical" *N*-methyl azacrown ether cation (i) as the most abundant fragment; however, neither lariat shows a "parent ion". After deprotection,[24] the hydrophilic nature of **17** is evidenced by reduced spectral resolution (^{1}H NMR) in the presence of a trace of water; thus first-order spectra were only realized under strictly anhydrous conditions.

At the outset of this study, only the 12-crown-4 analogue of **17** was known.[25] Recently, however, two other methods for synthesis of **17** have been reported,[26] in which 2-chloroethanol or ethylene oxide was used to construct the side arm. All physical data herein reported for **17** are in accord.[26] Alcohols **17** were refluxed in freshly purified[27] $SOCl_2$ to give **20**, which was stored as a stable hydrochloride.

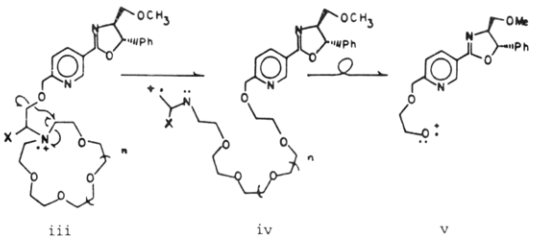


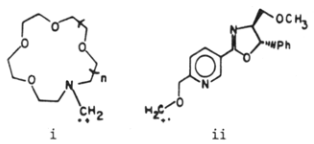
Formation of the lariat targets **22** was accomplished (route II) through the combination of alcohol **16a** and azacrowns **21** (1.5 equiv) in THF at 55-60 °C with NaH.



The low yields (<10%) of **22** were attributed to the diminished nucleophilicity of the alkoxide, in part, due to intramolecular chelative stabilization of the oxygen-metalated species.[28] This complexation can be partially retarded by the introduction of a twofold excess of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) as a competing ligand; yields were improved but were still low. The simultaneous self-quaternization of **20** through facile inter- or intramolecular process diminished the reagent concentration. Lariats **22** were characterized (^{1}H NMR) by the combined appearance of the multiplets at δ 2.41–2.96 and 3.35–3.75 for the *N*- and *O*-methylene protons, respectively, as well as an *up*field shift ($\Delta\delta$ 0.08) of the singlet (δ 4.73) for the pyridine α-methylene and a *down*field shift ($\Delta\delta$ 0.13) in the pyridine H-3 signal. Mass spectral analyses for **22** revealed no parent ion; however, the *N*-methyl azacrown ether cation i was the most abundant fragment in both cases. Further, the anticipated fragment ii was

Scheme III





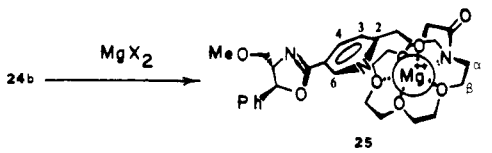
visible (*m/e* 311; **22a** 8.5%, **22b** 9.0%) as well as a predominant fraction with a mass of 339 (**22a** 48.5%, **22b** 49.5%), whose origin will be discussed later.

Attempts to improve the yields of lariats **22** were generally unsuccessful; thus, another method was envisioned for their construction, which utilized an amide linkage. This pivot would diminish the Lewis base character of these azacrowns, therefore circumventing the unwanted quaternization. Synthesis of crowns **23** (**a** 92.5%, **b** 89.9%) was achieved by treatment of an azacrown ether with chloroacetyl chloride in acetone/Na_2CO_3. The ^{1}H NMR spectra of **23** show a broad multiplet (δ 3.50–3.75) for the *O*-α-methylene protons (**23a**, 24 H; **23b**, 20 H) and a two-proton singlet (ca. δ 4.20) for the α-chloromethylene group.

Lariat ethers **24** were synthesized (ca. 80%) by treatment of a mixture of **16a** and **23** with NaH and TMEDA in THF at 55–60 °C for 1 h. The ^{1}H NMR spectra of **24** were nearly superimposable, except for the integrations. In addition, new singlets at δ 4.80 and 4.39 correspond to the α- and β-protons, respectively, and the doublet for the 3-pyridine proton is shifted downfield from that of **22** to δ 7.63. Both amide derivatives exhibited parent ions in their mass spectrum [**24a**, *m/e* 601 (0.7); **24b**, *m/e* 557 (0.6)] and the previously mentioned prominent fragment at *m/e* 339 was observed (**24a**, 100; **24b**, 86) as for **22**. The fragment *m/e* 339 (v) can be envisioned to arise from a five-centered fragmentation process (Scheme III); regardless of the identity of iii fragment v (*m/e* 339) is prevalent.

The magnesium complex **25** was generated by refluxing **24b** and $MgBr_2$ in MeCN followed by concentration in vacuo. The ^{1}H NMR spectra of complex **25** displayed a dramatic *down*field shift ($\Delta\delta$ 0.43 and 0.50) for the α- and β-protons, respectively, indicative of increased rigidity caused by strong encapsulation of the magnesium ion.

(23) Gokel, G. W.; Garcia, B. J. *Tetrahedron Lett.* **1977**, 317.
(24) Amano, M.; Watanabe, M.; Baba, N.; Oda, J.-i.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3672.
(25) (a) Calverley, M. J.; Dale, J. *Acta. Chem. Scand. Ser. B.* **1982**, *B36*, 241; *J. Chem. Soc., Chem. Commun.* **1981**, 684. (b) Usage of these hydroxy lariats were reported, but no experimental data were given: Maeda, H.; Nakatsuji, Y.; Okahara, M. *J. Chem. Commun.* **1981**, 471. *Tetrahedron Lett.* **1981**, *22*, 4105. Masuyama, A.; Nakatsuji, Y.; Ikeda, I.; Okahara, M. *Tetrahedron Lett.* **1981**, *22*, 4665. The related ethereal lariats have recently been reported, see: Schultz, R. A.; Dishong, D. M.; Gokel, G. W. *Tetrahedron Lett.* **1981**, *22*, 2623; *J. Am. Chem. Soc.* **1982**, *104*, 625. Echegoyen, J.; Kaifer, A.; Durst, H.; Schultz, R. A.; Dishong, D. M.; Goli, D. M.; Gokel, G. W. *Ibid.* **1984**, *106*, 5100.
(26) Masuyama, A.; Kug, P.; Ikeda, I.; Okahara, M. *J. Chem. Soc. Jpn. Chem. Ind. Chem.* **1984**, *2*, 249.
(27) Vogel, A. I. "Practical Organic Chemistry"; Longmans: London, 1973; p 189.
(28) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry"; Harper and Row: New York, 1976; p 185.

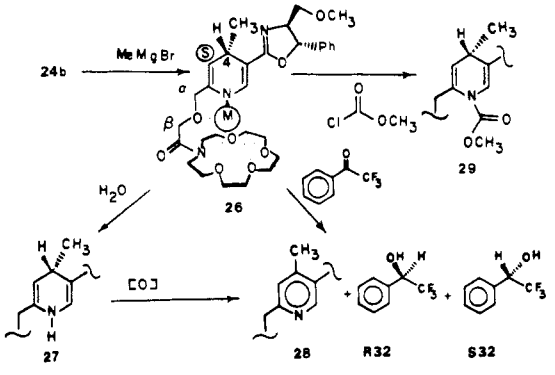


There are, however, only slight up ($\Delta\delta$ 0.04) and down ($\Delta\delta$ 0.14) -field shifts for the 4- and 3-pyridine protons, respectively, and essentially no shift in the 6-proton signal, indicating that there is unfortunately little N-coordination of the pyridine in $CDCl_3$. In addition, the chemical shift values of the oxazoline protons remains invariant, suggesting that Mg^{2+} does *not* coordinate with this moiety in $CDCl_3$.

Similarly, treatment of **24b** with KI did not generate a similar complex according to the ^1H NMR data, which were in all respects indistinguishable from that of **24b** except for a slight signal broadening. These results indicate that the lariat portion of **24b** has a weaker affinity for K^+ than Mg^{2+}, and the oxazoline moiety prefers the alkali metal.

Amide **24b** was converted (55%) to the stable dihydropyridine **29** with stereospecific[14a,16] metal-directed nucleophilic addition of methylmagnesium bromide (2 equiv) at 0 °C in THF. Hence, **24b** was employed in the preliminary reductive studies of carbonyls to evaluate these lariats as possible NADH models. Reduction of the amide **24b** with $LiAlH_4$ afforded the amine **22b** in low yield (ca. 5%); a competitive hydride cleavage reaction is also operative and is currently being evaluated.

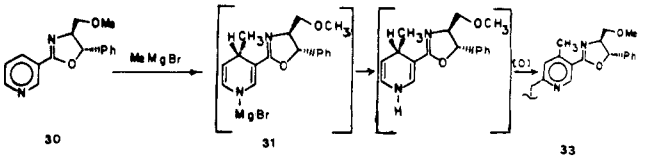
Synthesis of Chiral Lariat *N*-Metallo-1,4-dihydropyridine Derivatives and Their Reductions of α,α,α-Trifluoroacetophenone. Macrocycle **24b** was reacted with 2 equiv of MeMgBr in THF (10^{-2} M) at 0 °C to generate a solution of adduct **26**, which was either hydrolyzed to **27**, trapped with methyl chloroformate to give **29**, or treated with α,α,α-trifluoroacetophenone (TFA) to give **28** along with alcohols **32**.



Hydrolysis of adduct **26** gave dihydropyridine **27** (55%; ^1H NMR), which quickly underwent air oxidation to **28**. The ^1H NMR of freshly prepared **27** exhibited a broad singlet at δ 7.13 and a doublet at δ 1.18 (J = 6.4 Hz) for the 6-dihydropyridine proton and 4-methyl group, respectively, as well as new signals at δ 4.22 and 3.99 for the lariat α- and β-methylenes, respectively. Conversion of **27** to **28** was characterized by loss of the doublet at δ 1.18 and appearance of a singlet at δ 2.65 for the 4-pyridine methyl; also disappearance of the 4-pyridine proton was observed in **24b** (δ 8.31).

Treatment of **26** with methyl chloroformate afforded the "trapped" dihydropyridine **29**, which was characterized (^1H NMR) by (1) a singlet at δ 3.40 for the urethane methyl, (2) an upfield shift ($\Delta\delta$ 0.27) of the oxazoline methoxy ether protons, (3) new lariat bridge methylene signals at δ 4.19 and 3.89 for α- and β-protons, respectively, and (4) a doublet at δ 1.36 corresponding to the dihydropyridine 4-methyl protons. Chromatographic (HPLC, C_6H_{12}/EtOAc, SiO_2) analysis of **29** gave two fractions [MS, m/e 631 (M^+)] in a ratio of 90:10 (area integration), which correspond to the two diastereomers of **29** (90% S, 10% R) as based upon the earlier work of Meyers[14a,16] on the non-lariat oxazoline **30**.

Reduction of TFA was initially tested with simple non-lariat *N*-metallodihydropyridine **31**, as reported by Meyers.[14a,16] Stereoselective addition of MeMgBr (2 equiv) to the corresponding nicotinic oxazoline **30** gave **31** quantitatively (>91:9 S to R diastereomeric ratio with respect to the stereochemistry at the dihydropyridine 4-position).

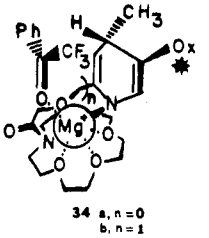


TFA (2 equiv) was allowed to react with **31** (6 h; 55 °C), yielding alcohols **32**, as a mixture of enantiomers [54.5:45.5 ($[\alpha]^{25}_D$ +1.30° (c 1.80, benzene), % ee = 10.4)],[15] which was in agreement with the enantioselective preference predicted by the ternary complex transition-state array.[3] Further, oxazoline **33** was generated in a nearly quantitative yield from **31**.

When 2 equiv of MeMgBr, rather than 1 equiv as reported by Meyers, were utilized, **26** (or **31**) was generated in high yield. Hence 2 equiv of TFA were added; (*S*)- and (*R*)-**32** were isolated in nearly equimolar ratios.

Under identical conditions, reduction of TFA using the lariat *N*-metallodihydropyridine **26** (55% yield, diastereomeric ratio 90:10, HPLC (SiO_2), EtOAc/C_6H_{12}; absolute configuration at py-4 assumed predominantly *S*)[14a,16] gave alcohols **32** with an enantiomeric *S* to *R* ratio of 52.5:47.5 ($[\alpha]^{25}_D$ +0.67° (c 1.54, benzene), % ee = 5). Under these conditions lariat **26** reduced TFA with an enantioselectivity somewhat less than that of the non-lariat **31**. The apparent lack of positive influence on the stereochemical outcome under these conditions by lariat **26** was unexpected and deserves further scrutiny.

It is conceivable that a strongly competing acyclic mechanism may be operative in TFA reduction by **26**, as a result of an extremely strong crown ether complex which might override its coordinating ability toward the carbonyl oxygen of the substrate, as shown in complex **34**.



Work is under way to further refine the lariat concept by employment of various metal hydrides and organometallics in formation of the *N*-metallo reagents, as well as introduction of chiral centers at strategic locus on the lariat appendage.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were determined on an IBM-Bruker NR-80 NMR spectrometer using $CDCl_3$ as solvent, except where noted, with Me_4Si as the internal standard. IR spectra were recorded on a Perkin-Elmer 621 grating-IR spec-

trometer. Mass spectral (MS) data (70 eV) (herein noted as assignment, relative intensity) were determined by D. Patterson on a Hewlett-Packard HP-5985 gas chromatograph/mass spectrometer. High-resolution mass spectral data (210 °C, EI, 70 eV, 10KRP) were determined at the Mass Spectral Laboratory at Florida State University, Tallahassee. CD/ORD measurements were made on Jasco Model J-20 spectropolarimeter. Reported R_f values were ascertained by a standardized TLC procedure: Baker-Flex silica gel IB2-F plates, elution with the stipulated solvent system. For preparative thick-layer chromatography (ThLC), 2-mm silica gel PF-254-366 plates were used. Elemental analyses were performed by MicAnal Laboratories in Tucson, AZ.

Solvents. Anhydrous *N,N*-dimethylformamide (DMF) was purified in order to remove cyanide impurities via refluxing for 4–6 h in the dark over CaH_2 at ca. 29 mm, followed by fractional distillation of which the middle fraction was stored in a dark bottle under argon.[29] Anhyrous tetrahydrofuran (THF) was distilled from benzophenone ketyl under an argon atmosphere, immediately prior to use. Thionyl chloride was purified by distillation sequentially from quinoline and linseed oil and then stored under an inert atmosphere.[27]

Oxazoline 10. Through a stirred solution of 3-cyanopyridine (20 g, 190 mmol), anhydrous EtOH (13 g), and anhydrous CH_2Cl_2 (200 mL) was bubbled anhydrous HCl for 1 h. After 5 h, the solution was evaporated in vacuo (<30 °C) to give the hygroscopic imidate **9**, which was immediately dissolved in a stirred solution of CH_2Cl_2 (150 mL), Et_3N (39 g, 380 mmol), and (1*S*, 2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol[30] (38 g, 190 mmol). After 17 h, the mixture was treated carefully with aqueous $NaHCO_3$ (10%) and extracted with CH_2Cl_2. The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give (48%) **10**: 23.2 g; mp 125 °C (C_6H_{12}) [lit.[16] mp 124–125 °C (Et_2O)].

5-Oxazolinyl-2-methylpyridine 12. To a stirred solution of **10** (10 g, 39.4 mmol) in DME (400 mL) at 0 °C was added MeLi (2 equiv, 2.5 M in ether). After 1 h, H_2O (20 mL) was added, and then the DME was evaporated in vacuo to give a residue, which was dissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ (10%), dried over anhydrous $MgSO_4$, filtered, and concentrated to give dihydropyridine **11**, as an oil: a 4:1 mixture of 1,2- vs. 1,4-dihydro isomers.

The crude isomeric mixture was dissolved in acetone (100 mL), and a saturated $KMnO_4$/acetone solution (ca. 100 mL) was slowly added at 0 °C. Progress was monitored by TLC. Upon completion, the suspension was filtered through a Celite column to give a colorless solution, which was concentrated in vacuo, affording a residue. Recrystallization from C_6H_{12} gave (61%) the desired 2-methyl derivative **12** as colorless crystals: 6.43 g; mp 116–117 °C [lit.[16] mp 117–118 °]; ^1H NMR δ 2.59 (s, 2-pyCH_3), 9.10 (d, 6-py*H*, J = 2 Hz).

Methyl Ether 13. To a stirred solution of **12** (5 g, 18.7 mmol) in THF at 25 °C was added *t*-BuOK (2.5 g, 22.4 mmol), followed by dropwise addition of a THF (20 mL)/MeI (2.9 g) solution. After 6 h, the mixture was concentrated in vacuo and the residue dissolved in CH_2Cl_2. The organic extract was washed with aqueous $NaHCO_3$ (10%), dried over anhydrous $MgSO_4$, evaporated in vacuo, and column chromatographed (silica gel) to give (74%) **13**, as an oil: 3.90 g; R_f 0.6 ($CHCl_3$); ^1H NMR δ 2.64 (s, py 2-CH_3, 3 H), 3.46 (s, OCH_3, 3 H), 3.55–3.75 (m, CH_2OMe, 2 H), 4.16 (m, 4-CH, 1 H), 5.02 (d, 5-CH, J = 7.2 Hz, 1 H), 7.22 (d, py 3-H, J = 8.1 Hz, 1 H), 7.34 (s, Ph H, 5 H), 8.18 (dd, py 4-H, $J_{3,4}$ = 8.1 Hz, $J_{6,4}$ = 2.2 Hz, 1 H) [lit.[14a] δ 8.12 (py 4-H, dd)], 9.12 (d, py 6-H, J = 2.2 Hz, 1 H); MS, m/e 282 (M^+, 4), 119 (100).

Chiral 5-Oxazolinylpyridine *N*-Oxide 14. To a stirred solution of 2-methyl-5-oxazolinylpyridine **13** (3.5 g, 12.4 mmol) in $CHCl_3$ (75 mL) at 0 °C was added MCPBA (80–85%, 3.2 g, ~1.2 equiv) in small portions over 10 min. The stirred solution was warmed to 25 °C and maintained there for 1.5 h. The mixture was washed with 10% aqueous $NaHCO_3$ (50 mL), followed by H_2O, dried over anhydrous $MgSO_4$, filtered, and column chromatographed (SiO_2) by eluting with CH_2Cl_2/5% MeOH to give (94%) *N*-oxide **14**, as a colorless oil: 3.48 g; R_f 0.30; ^1H NMR δ 2.56 (s, py 2-CH_3, 3 H), 3.44 (s, OMe, 3 H), 3.7 (m, CH_2OMe, 2 H), 4.3 (m, 4-CH, 1 H), 5.52 (d, 5-CH, J = 7.1 Hz, 1 H), 7.35 (br s, Ph H, py 3-H, 6 H), 7.78 (dd, py 4-H, $J_{4,3}$ = 8.1 Hz, $J_{6,4}$ = 1.5 Hz, 1 H), 8.85 (d, py 6-H, J = 1.5 Hz, 1 H); IR (neat) 3055, 2985, 1650, 1610, 1375, 1225 cm^{-1}; MS, m/e 298 (M^+, 10.4), 253 (M^+ – OMe, 23.7), 237 (31), 119 (100). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.09; N, 9.39. Found: C, 68.34; H, 6.07; N, 9.15.

Chiral 2-(Hydroxymethyl)-5-oxazolinylpyridine 16a. *N*-Oxide **14** (3 g, 10.1 mmol) was dissolved in Ac_2O (25 mL) at 0 °C, and then the solution was refluxed for 15 min, after which the Ac_2O was evaporated in vacuo. The dark brown residue was dissolved in $CHCl_3$ (50 mL) and washed with aqueous Na_2CO_3 (10%; 40 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give a residue, which was dissolved in ether and passed through a silica gel pad (15 g) to give (>80%; ^1H NMR) **15** (2.8 g). Further attempts to purify **15** resulted in decomposition; thus, transesterification was immediately conducted.

A mixture of crude **15** in absolute EtOH (50 mL) and excess anhydrous K_2CO_3 (5 g, 36.2 mmol) was stirred for 2 h at 25 °C. The suspension was partially dissolved in $CHCl_3$ (50 mL) to precipitate the K_2CO_3 and then filtered through Celite. The filtrate was concentrated in vacuo and chromatographed (ThLC, SiO_2) by eluting with $CHCl_3$/5% MeOH to give (68% from **14**) **16a**, as a colorless oil: 2.37 g; ^1H NMR δ 3.43 (s, OMe, 3 H), 3.7 (m, CH_2OMe, 2 H), 3.9 (br s, OH, 1 H), 4.3 (m, 4-CH, 1 H), 4.81 (s, α-CH_2, 2 H), 5.51 (d, 5-CH, J = 7.1 Hz, 1 H), 7.35 (s, Ph H, 5 H), 7.41 (d, py 3-H, $J_{3,4}$ = 8.1 Hz, 1 H), 8.29 (dd, py 4-H, $J_{4,3}$ = 8.1 Hz, $J_{6,4}$ = 2.0 Hz, 1 H); IR (neat) 3275, 3100, 2905, 1640, 1495, 1380, 750, 705 cm^{-1}; MS, m/e 298 (M^+, 2.5), 253 (M^+ – OMe, 100), 161 (47), 119 (92), 91 (73). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.09; N, 9.39. Found: C, 68.19; H, 6.18; N, 9.21.

Tetrahydropyranyl Ether of 2-Bromoethanol. To a stirred solution of dihydropyran (8.4 g, 100 mmol) at 0 °C was added dropwise a mixture of 2-bromoethanol (6.25 g, 50 mmol) and *p*-toluenesulfonic acid (75 mg). The solution was stirred an additional 12 h, after which aqueous $NaHCO_3$ (10%, 100 mL) was added. The resulting mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give an oil, which was distilled (91%) to give the protected alcohol as an oil: 9.51 g; bp 75 °C (1 mm) [lit.[22b] bp 94 °C (14 mm)]; ^1H NMR δ 1.6 (m, CH_2, 6 H), 3.35–4.1 (m, CH_2, 6 H), 4.6 (br s, CH, 1 H); IR (neat) 1124 cm^{-1}.

***O*-(2-Tetrahydropyranyl)triethanolamine (19).** A mixture of THP-protected bromoethanol (6.0 g, 28.7 mmol), diethanolamine (3.02 g, 28.7 mmol), anhydrous DMF (50 mL), and anhydrous K_2CO_3 (4.76 g, 34.4 mmol) was stirred at 25 °C for 24 h. The solvent was removed in vacuo, affording a solid mass, which was resuspended in CH_2Cl_2, filtered, concentrated in vacuo, and distilled [bp 150 °C (2 mm)] to give (88%) **19**, as a colorless oil: 5.90 g; ^1H NMR δ 1.70 (m, pyran CH_2, 6 H), 2.70 (m, NCH_2, 6 H), 3.6 (m, OH, CH_2, 10 H), 4.50 (m, CH, 1 H); IR (neat) 3400, 2900, 2750, 1735, 1660 cm^{-1}; MS, m/e 132 (M^+ – $C_5H_9O_2$, 6.4), 118 (M^+ – $C_6H_{11}O_2$, 100), 85 (50), 74 (27); exact mass calcd for $C_6H_{14}NO_2$ 132.1025 (M^+ – $C_5H_9O_2$), found 132.1027.

General Preparation of the THP-Protected *N*-2-Hydroxyethyl Azacrown Ethers. Reaction of 19 with Triethylene Glycol Ditosylate. To a stirred suspension of NaH (970 mg, 40.4 mmol) in dry THF (300 mL) at 25 °C under N_2 was added diol **19** (3.9 g, 16.9 mmol), followed in 30 min by triethylene glycol ditosylate[23] (mp 78–79 °C; 7.34 g, 16.9 mmol). The mixture was stirred for 72 h, then neutralized with aqueous NH_4Cl (15%, 20 mL), concentrated in vacuo, dissolved with Et_2O, and washed with water. The combined organic extract was concentrated in vacuo and then column chromatographed (Al_2O_3) by eluting with 5% MeOH/$CHCl_3$ to give (44%) ether **18b**, as a colorless oil: 2.60 g; ^1H NMR δ 1.55 (br m, CH_2, 6 H), 2.80 (t, NCH_2, J = 6.2 Hz, 2 H), 2.84 (t, NCH_2, J = 6.0 Hz, 4 H), 3.4–3.9 (m, OCH_2, 20 H), 4.6 (br m, CH, 1 H); IR (neat) 2915, 2855, 1455, 1355, 1115, 1035 cm^{-1}; MS, m/e 262 (M^+ – C_5H_9O, 0.5), 246 (M^+ – $C_5H_9O_2$, 3.6), 232 (M^+ – $C_6H_{11}O_2$, 100); exact mass calcd for $C_{12}H_{24}NO_4$ 246.1706 (M^+ – $C_5H_9O_2$), found 246.1727.

Reaction of 19 with Tetraethylene Glycol Ditosylate. A mixture of **19** (3.66 g, 15.7 mmol), tetraethylene glycol ditosylate[23] (7.89 g, 15.7 mmol), and NaH (900 mg, 37.5 mmol) in dry THF (300 mL) afforded (57%), after standard workup, **18a** as an oil:

(29) Newkome, G. R.; Robinson, J. M. *Tetrahedron Lett.* **1974**, 691. Trisler, J. C.; Freasier, B. F.; Wu, S.-M. *Ibid.* **1974**, 687.

(30) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.

3.49 g; R_f 0.56 (Al_2O_3, 5% MeOH/$CHCl_3$); ^1H NMR spectrum identical with that of **18b** except for integration ratios; MS, *m/e* 306 ($M^+ - C_5H_9O$, 0.4), 290 ($M^+ - C_5H_9O_2$, 4.3), 276 ($M^+ - C_6H_{11}O_2$, 100); exact mass calcd for $C_{14}H_{28}NO_5$ 290.1973 ($M^+ - C_5H_9O_2$), found 290.1951.

Preparation of 18b. Aza-15-crown-5 with THP-2-Bromoethanol. A mixture of THP-2-bromoethanol (543 mg, 2.6 mmol), aza-15-crown-5[23] (750 mg, 2.6 mmol), and anhydrous K_2CO_3 (1.0 g, 7.2 mmol) in anhydrous DMF (35 mL) was stirred under N_2 for 12 h. The solution was concentrated in vacuo, dissolved in CH_2Cl_2, filtered, concentrated, and chromatographed to yield **18b**, which was previously described (556 mg, 62%).

Acid-Catalyzed Deprotection of 18a. Alcohol 17a. A solution of **18a** (2.9 g, 5 mmol), aqueous HCl (6 M, 4 mL), and MeOH (16 mL) was maintained at 25 °C for 1.5 h, and then solid Na_2CO_3 (10 g) was added *carefully*, followed by concentration in vacuo, dissolution in H_2O, and extraction with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated to give (87%) **17a**, as an oil: 1.33 g; ^1H NMR δ 2.52 (t, NCH_2, J = 4.8 Hz, 2 H), 2.74 (t, NCH_2, J = 5.2 Hz, 4 H), 3.7 (br m, OCH_2, OH, 23 H); IR (neat) 3375, 2910, 2850, 1450, 1110 cm^{-1}; MS, *m/e* 276 ($M^+ - CH_2OH$, 100); exact mass calcd for $C_{13}H_{26}NO_5$ 276.1812 ($M^+ - CH_2OH$), found 276.1812.

Alcohol 17b was prepared in an analogous manner from ether **18b** (2.0 g, 6 mmol): oil; 1.59 g (94%); ^1H NMR spectrum identical with that of **17a** except for proton ratios; IR (neat) 3300, 2900, 1450, 1360, 1110 cm^{-1}; exact mass calcd for $C_{11}H_{22}NO_4$ 232.1550 ($M^+ - CH_2OH$), found 232.1544.

Amine 20a. Reaction of 17a with $SOCl_2$. A solution of **17a** (500 mg, 1.6 mmol) in cold $SOCl_2$ (25 mL) was refluxed for 1 h after which excess $SOCl_2$ was removed in vacuo to give the intermediate hydrochloride **21a** as a very hygroscopic oil (580 mg). A portion of **21a** (100 mg, ~0.3 mmol) was dissolved in H_2O (250 mL), and solid Na_2CO_3 (1.5 g) was *carefully* added. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give (92%) **20a** as an oil, which *rapidly* decomposed on standing: 83 mg; ^1H NMR δ 2.9 (m, NCH_2, 6 H), 3.6 (m, OCH_2, CH_2Cl, 22 H).

Chloride 20b was prepared similarly from **17b** (600 mg, 2.3 mmol); the hygroscopic oil (720 mg) was utilized without additional purification.

Lariat 22a. Reaction of *N*-2-Chloroethyl Azacrown Ether Hydrochloride 21a with Alcohol 16a. Alcohol **16a** (328 mg, 1.1 mmol) was added to a stirred suspension of NaH (75 mg, 3.0 mmol) and TMEDA (250 mg, 2 equiv) in dry THF (50 mL) at 55 °C under N_2, followed by dropwise addition of crude **21a** (637 mg, ca. 1.6 equiv) in THF (20 mL) over 1 h. The mixture was cooled to 25 °C and neutralized with aqueous NH_4Cl (10%) and the THF removed in vacuo. The concentrate was dissolved in aqueous Na_2CO_3 (10%) and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and chromatographed (ThLC, Al_2O_3) by eluting with 5% MeOH/$CHCl_3$ to give (5%) **22a** as an oil: 32 mg; ^1H NMR δ 2.44–2.96 (m, NCH_2, 6 H), 3.45 (s, OMe, 3 H), 3.53–3.75 (m, OCH_2, NCH_2CH_2, 24 H), 4.35 (m, 5-CH, 1 H), 4.73 (s, py CH_2, 2 H), 5.51 (d, 4-CH, J = 7.1 Hz, 1 H), 7.36 (s, Ph H, 5 H), 7.54 (d, py 3-H, J = 8.1 Hz, 1 H), 8.24 (dd, py 4-H, $J_{4,3}$ = 8.1 Hz, $J_{6,4}$ = 2.1 Hz, 1 H), 9.16 (d, py 6-H, J = 2.1 Hz, 1 H); IR (neat) 3050, 2915, 1650, 1590, 1350, 1115 cm^{-1}; MS, *m/e* 339 (48.5), 276 (100). Anal. Calcd for $C_{31}H_{45}N_3O_7$: C, 63.34; H, 7.72; N, 7.15. Found: C, 63.36; H, 7.64; N, 7.22.

Lariat 22b was prepared in an analogous manner from alcohol **16a** (300 mg, 1.0 mmol) and **21b** (579 mg, 1.6 mmol) to give (7%) the lariat ether as an oil: 38 mg; R_f 0.23 (5% MeOH/$CHCl_3$); ^1H NMR spectrum identical with that of **22a** except for δ 3.53–3.75 (m, 28 H); IR (neat) spectrum identical with that of **22a**; MS, *m/e* 339 (49.5), 232 (100). Anal. Calcd for $C_{29}H_{41}N_3O_7$: C, 64.07; H, 7.62; N, 7.23. Found: C, 63.71; H, 7.53; N, 7.01.

Reaction of Aza-18-crown-6 with Chloroacetyl Chloride. Amide 23a. A stirred mixture of aza-18-crown-6[23] (1.56 g, 5.9 mmol), chloroacetyl chloride (780 mg, 7.1 mmol), and Na_2CO_3 (1.8 g, 17.0 mmol) in dry acetone (50 mL) was maintained under N_2 at 25 °C for 8 h, after which MeOH (2 mL) was added. The suspension was stirred for 30 min, and then the solvent was evaporated in vacuo. The solid residue was dissolved in dilute aqueous HCl (50 mL) and then extracted with CH_2Cl_2. The combined organic extract was dried over anhydrous $MgSO_4$, concentrated in vacuo, and chromatographed (Al_2O_3, 5% MeOH/$CHCl_3$) to give (93%) **23a** as an oil: 1.85 g; ^1H NMR δ 3.60 (m, OCH_2, NCH_2, 24 H), 4.19 (s, $ClCH_2CO$, 2 H); IR (neat) 2920, 1720, 1635, 1125 cm^{-1}; MS, *m/e* 304 ($M^+ - Cl$, 7), 262 ($M^+ - COCH_2Cl$, 14.6), 120 (74), 89 (100). Anal. Calcd for $C_{14}H_{26}NO_6Cl$: C, 49.48; H, 7.71; N, 4.12. Found: C, 49.45; H, 7.51; N, 4.10.

Amide 23b was similarly prepared from aza-15-crown-5 (2 g, 9.1 mmol) and chloroacetyl chloride (1.34 g, 11.9 mmol): oil; 2.42 g (90%); R_f 0.42; ^1H NMR spectrum identical with that of **23a** except for δ 3.5–3.75 (20 H); IR (neat) spectrum identical with that of **23a**; MS, *m/e* 295 (M^+, 0.7), 260 ($M^+ - Cl$, 10), 218 ($M^+ - COCH_2Cl$, 16.6), 120 (99), 89 (100). Anal. Calcd for $C_{12}H_{22}NO_5Cl$: C, 48.73; H, 7.50; N, 4.74. Found: C, 48.76; H, 7.46; N, 4.75.

Reaction of 16a with 23a. Lariat 24a. To a stirred suspension of **16a** (250 mg, 0.8 mmol), NaH, (36 mg, 1.5 mmol), and TMEDA (232 mg, 2 mmol) in dry THF (50 mL) at 55–60 °C was added crown ether **22a** (272 mg, 0.8 mmol) in THF (20 mL). The mixture was stirred for 45 min, then cooled to 25 °C, neutralized with a minimum volume of aqueous NH_4Cl (10%), evaporated to dryness, and chromatographed (ThLC, SiO_2) by eluting with 5% MeOH/CH_2Cl_2 to give (8%) **24a** as an oil: 410 mg; ^1H NMR δ 3.44 (s, OMe, 3 H), 3.40–3.70 (m, CH_2O, NCH_2, 26 H), 4.35 (m, 4-CH, 1 H), 4.39 (s, CH_2CO, 2 H), 4.80 (s, α-CH_2, 2 H), 5.50 (d, 5-CH, J = 7.1 Hz, 1 H), 7.35 (s, Ph H, 5 H), 7.63 (d, py 3-H, J = 8.2 Hz, 1 H), 8.31 (dd, py 4-H, $J_{4,3}$ = 8.2 Hz, $J_{4,6}$ = 2.0 Hz, 1 H), 9.15 (d, py 6-H, J = 2.0 Hz, 1 H); IR (neat) 3040, 2890, 1725, 1640, 1120 cm^{-1}; MS, *m/e* 601 (M^+, 0.7), 556 ($M^+ - CH_2OCH_3$, 1), 339 (100). Anal. Calcd for $C_{31}H_{43}N_3O_9$: C, 61.88; H, 7.20; N, 6.98. Found: C, 61.62; H, 7.05; N, 6.86.

Lariat 24b was prepared (80%) under similar conditions as above from **16a** (400 mg, 1.5 mmol) and **23b** (441 mg, 1.5 mmol): oil; 662 mg; ^1H NMR spectrum identical with that of **24a** except for δ 3.40–3.70 (22 H); IR (neat) spectrum identical with that of **24a**; MS, *m/e* 557 (M^+, 0.6), 512 ($M^+ - CH_2COCH_3$, 1), 339 (100). Anal. Calcd for $C_{29}H_{39}N_3O_8$: C, 62.47; H, 7.05; N, 7.54. Found: C, 62.32; H, 6.96; N, 7.50.

Reaction of 24b with Methylmagnesium Bromide. To a stirred solution of **24b** (600 mg, 1.08 mmol) in THF (20 mL) at 0 °C was added MeMgBr (2.16 mmol, 0.75 mL; 2.8 M in ether) in one portion under N_2. Stirring was continued for an additional 30 min, and then the resulting orange solution was used in the following reactions.

A. Hydrolysis of 26. An aliquot of **26** (2 mL) was hydrolyzed by addition of H_2O (5 mL) and then extracted with CH_2Cl_2 (15 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to give a mixture of **24b** (~45%; ^1H NMR), dihydropyridine **27** [~50%; ^1H NMR δ 1.18 (d, py 4-CH_3, J = 6.4 Hz), 3.99 (s, $NCOCH_2$), 4.22 (s, α-CH_2)], and **28** (~5%; ^1H NMR). The dihydropyridine **27** was not isolated pure due to rapid air oxidation to pyridine **28**.

The mixture was oxidizing by bubbling air through the $CHCl_3$ solution; after several hours, only **24b** and **28** were detected (^1H NMR) in 45% and 55% yields, respectively. The 4-methylpyridine **28** was isolated by chromatography (ThLC, SiO_2) eluting with 10% MeOH/$CHCl_3$: oil; 22 mg (~35%); ^1H NMR δ 2.65 (s, $pyCH_3$, 3 H), 3.45 (s, OCH_3 3 H), 3.3–3.8 (m, XCH_2, 22 H), 4.35 (m, 4-CH, 1 H), 4.40 (s, $COCH_2$, 2 H), 4.77 (s, py α-CH_2, 2 H), 5.48 (d, 5-CH, J = 7.2 Hz, 1 H), 7.35 (s, Ph H, 5 H), 7.58 (s, py 3-H, 1 H), 9.0 (s, py 6-H, 1 H); IR (neat) 3045, 2890, 1730 cm^{-1}; MS, *m/e* 571 (M^+, 0.8), 526 ($M^+ - CH_2OCH_3$, 1), 353 (100). Anal. Calcd for $C_{32}H_{45}N_3O_9$: C, 67.72; H, 7.93; N, 7.35. Found: C, 67.51; H, 8.08; N, 7.26.

B. With Methyl Chloroformate. A stirred aliquot (2 mL) of **26** was treated with a solution of methyl chloroformate (100 mg, 1.1 mmol) in dry THF (5 mL) at 25 °C under N_2. After 15 min, volatiles were evaporated in vacuo to give a residue, which was treated with aqueous Na_2CO_3 (10%; 15 mL) and then extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered, evaporated in vacuo, and chromatographed (ThLC, SiO_2) by eluting with 5% MeOH/$CHCl_3$ to give (43%) **29** as an orange oil: 29 mg; ^1H NMR δ 1.36 (d, py 4-CH_3, J = 6.7 Hz, 3 H), 3.40 (s, OMe, 3 H), 3.3–3.75 (m, XCH_2, py 4-H, 23 H), 3.71 (s, CO_2Me, 3 H), 3.89 (s, $COCH_2$, 2 H), 4.19 (s, py α-CH_2, 2 H), 4.20 (m, 4-CH, 1 H), 4.75 (d, py 3-H, J = 6.5 Hz, 1 H), 5.37

(d, 5-CH, J = 5.9 Hz, 1 H), 7.31 (s, Ph H, 5 H), 7.60 (s, py 6-H, 1 H); IR (neat) 1730, 1670, 1635, 1450, 1125 cm^{-1}; MS, m/e 631 (M^+, 0.4), 585 ($M^+ - CH_2OCH_3$, 1), 218 (100). Anal. Calcd for $C_{32}H_{45}H_3O_{10}$: C, 60.84; H, 7.18; N, 6.65. Found: C, 61.06; H, 7.05; N, 6.47.

3-Oxazolinylpyridine 30. As previously reported,[16] to a stirred solution of **10** (5 g, 19.7 mmol) in THF (50 mL) was added t-BuOK (2.43 g, 21.7 mmol), followed by MeI (2.92 g, 19.7 mmol) in THF (10 mL) at 25 °C. The mixture was stirred for 5 h, followed by evaporation in vacuo to give a residue, which was dissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ (10%), dried over anhydrous $MgSO_4$, evaporated in vacuo, and column chromatographed by eluting with EtOAc/C_6H_{12} to give (95%) **30** as an oil: 5.28 g; ^1H NMR δ 3.44 (s, OCH_3, 3 H), 3.67 (m, OCH_2, 2 H), 4.34 (m, 4-CH, 1 H), 5.52 (d, 5-CH, J = 7.0 Hz, 1 H), 7.30–7.44 (m, py 5-H, 1 H), 7.36 (s, Ph H, 5 H), 8.30 (ddd, py 4-H, $J_{4,5}$ = 7.8 Hz, $J_{4,2} = J_{4,6}$ = 2.0 Hz, 1 H), 8.73 (dd, py 6-H, $J_{6,5}$ = 4.6 Hz, $J_{6,4}$ = 2 Hz, 1 H), 9.24 (dd, py 2-H, $J_{2,4}$ = 2.0 Hz, $J_{2,5}$ = 1.4 Hz, 1 H).

Reduction of α,α,α-Trifluoroacetophenone (TFA) with *N*-Metallo-1,4-dihydropyridine 31. As described by Meyers,[14a] to a stirred solution of **30** (268 mg, 1.0 mmol) in THF (10 mL) was added MeMgBr (0.4 mL; 2.5 M in ether, 1.0 mmol), and the mixture was stirred an additional 30 min, to which a second equivalent of MeMgBr (0.40 mL; 2.5 M in ether, 1.0 mmol) was added. A solution TFA (2 equiv, 0.2 mmol) in THF (3 mL) was added in one portion at 0 °C, and then the mixture was slowly warmed to 55 °C. After 5 h, the H_2O (1 mL) was added. The mixture was concentrated in vacuo, dissolved in CH_2Cl_2 (20 mL), washed with aqueous $NaHCO_3$ (10%, 10mL), dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to give a residue, which was column chromatographed (Al_2O_3) by eluting with EtOAc/C_6H_{12} (1:1) to give two major fractions:

Fraction A was a mixture of two components which were separated (ThLC, C_6H_6) to give **32** (93% with respect to **30**) as an oil: 164 mg; bp 93 °C (15 mm) [lit.[31] bp 99–105 °C (17 mm); $[\alpha]^{20}_D$ +13.4° (c 0.91, C_6H_6)]; ^1H NMR δ 2.45 (br s, OH, 1 H), 4.93 (q, CH, $J_{H,F}$ = 6.8 Hz, 1 H), 7.25–7.50 (m, Ph H, 5 H). Alcohol **32** was analyzed by polarimetry:[30] $[\alpha]^{25}_D$ +1.39° (c 1.80, C_6H_6), corresponding to an enantiomeric bias of 54.5:45.5 S/R (% ee = 10.4). The second component was **34**: ^1H NMR δ 1.79 (q, CH_3, $J_{H,F}$ = 1.5 Hz, 3 H), 2.71 (br s, OH), 7.4–7.6 (m, Ph H, 5 H).

Fraction B gave (95%) the 4-methylpyridine **33**[16] as an oil: 268 mg; ^1H NMR δ 2.62 (s, py CH_3, 3 H), 3.42 (s, OCH_3, 3 H), 3.68 (m, OCH_2, 2 H), 4.30 (m, 4-CH, 1 H), 5.48 (d, 5-CH, J = 6.4 Hz, 1 H), 7.16 (d, py 5-H, J = 5.0 Hz, 1 H), 8.91 (d, py 6-H, J = 5.0 Hz, 1 H), 8.98 (s, py 2-H, 1 H).

Reduction of α,α,α-Trifluoroacetophenone with the Lariat 26. To a portion of the THF solution of **26**, described above (16 mL; ~0.475 mmol of **26**), was added TFA (0.86 mmol) in THF (2 mL) in one portion. The reaction was allowed to proceed as above (with **31**), and after standard workup, alcohol **32** (74 mg, ~49%) was recovered along with **34** (243 mg, 1.28 mmol) and lariat **28** (125 mg, ~26% yield). Purified alcohol **32**, as above, was analyzed by polarimetry: $[\alpha]^{25}_D$ +0.67° (c 1.54, C_6H_6), corresponding to an enantiomeric bias of only 52.5:47.5 S/R (% ee = 5).

Reduction of 24b with $LiAlH_4$. To a stirred solution of **24b** (100 mg, 0.18 mmol) in THF at 25 °C was added $LiAlH_4$ (100 mg). The solution was warmed to 60–65 °C and then stirred an additional 24 h. A H_2O/THF (50:50, 10 mL) mixture was added, and then the THF was evaporated in vacuo. The residue was treated with aqueous $NaHCO_3$ (10%, 20 mL), extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, concentrated in vacuo, and chromatographed (ThLC) by eluting with $CHCl_3$/EtOH (1:1) to give the desired product **22b** (5 mg, 5%), unchanged **24b** (25 mg, 26%), and numerous unidentified decomposition products.

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Useful Chemistry of 3-(1-Methylethylidene)-4-acetoxy-2-azetidinone: A Formal Synthesis of (±)-Asparenomycin C

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3-(1-Methylethylidene)-4-acetoxy-2-azetidinone (**5**) was prepared from the addition of chlorosulfonyl isocyanate to 1-acetoxy-3-methylbuta-1,2-diene. Isolated as a stable crystalline solid, this material is a versatile intermediate and is used in a formal synthesis of (±)-asparenomycin C. The double bond can participate in a number of useful reactions including allylic halogenation, hydrogenation, and addition of hypochlorous acid. The 4-acetate can be easily substituted by oxygen, sulfur, and carbon nucleophiles. 3-Alkylidene-4-(phenylthio)-2-azetidinones are easily reduced by $(n\text{-Bu})_3SnH$ in the presence of AIBN.

Some strains of bacteria can defend themselves from conventional β-lactam antibiotics through the use of a defensive enzyme known as β-lactamase.[1] There are, in fact, several types of β-lactamase,[2] and much work has lately focused on determining the mechanism of action of these enzymes as well as on developing effective β-lactamase inhibitors.[3] While clavulanic acid and thienamycin

(1) For a review of β-lactamases, see: Sykes, R. B.; Bush, K. In "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 3.

(2) For a leading reference, see: Knott-Hunziker, V.; Petursson, S.; Waley, S. G.; Jaurin, B.; Grundstrom, T. *Biochem. J.* **1982**, *207*, 315.

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