N-Benzoyl-5-methyl-1,3-oxathiolan-2-imine (21): IR (neat) 1660 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 1.45 (d, J = 6 Hz, 3 H), 3.00 (dd, J = 9 and 10 Hz, 1 H), 3.35 (dd, J = 6 and 10 Hz, 1 H), 4.40 (s, 2 H), 4.50–4.80 (m, 1 H), 7.20–7.40 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 19.0 (q), 37.7 (t), 57.3 (t), 77.6 (d), 126.6 (d), 127.4 (d), 128.2 (d), 139.5 (s), 162.5 (s); MS, m/e 207 (M^+).

N,3-Diphenyl-5-methyl-1,3-oxazolidin-2-imine (22). To the solution of n-Bu_3SnI (0.42 g, 1 mmol) and Ph_3PO (0.27 g, 1 mmol) in propylene oxide (2.90 g, 50 mmol) was added PhNCNPh (1.94 g, 10 mmol) with stirring under dry nitrogen. The resulting mixture was stirred at 40 °C for 2 h. IR spectra showed the disappearance of characteristic band of PhNCNPh at 2150 cm^{-1}. The yield of **22** was monitored by GLC (2.52 g, 100%). Excess of propylene oxide was removed in vacuo, and the residue was chromatographed, yielding **22** (2.14 g, 85%) as white needles, which were purified by recrystallization from benzene–hexane: mp 72–73 °C (lit.[20] 76–77 °C); IR (KBr) 1670 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 1.45 (d, J = 6 Hz, 3 H), 3.55 (dd, J = 7 and 8 Hz, 1 H), 4.05 (t, J = 8 Hz, 1 H), 4.50–4.90 (m, 1 H), 6.90–7.80 (m, 10 H); MS, m/e 252 (M^+).

N-Butyl-3-phenyl-5-methyl-1,3-oxazolidin-2-imine (23): bp 90 °C (2 mmHg); IR (neat) 1700 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 0.95–1.70 (m, 10 H), 3.30 (t, J = 7 Hz, 2 H), 3.45 (t, J = 7 Hz, 1 H), 3.95 (t, J = 7 Hz, 1 H), 4.50–4.80 (m, 1 H), 6.80–7.80 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 20.1 (q), 20.6 (t), 34.0 (t), 46.5 (t), 52.9 (t), 70.9 (d), 118.0 (d), 121.8 (d), 128.6 (d), 140.7 (s), 149.5 (s); MS, m/e 232 (M^+).

N,3-Dibutyl-5-methyl-1,3-oxazolidin-2-imine (24): bp 68 °C (2 mmHg); IR (neat) 1700 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 0.80–1.70 (m, 17 H), 2.95–3.50 (m, 5 H), 3.65 (t, J = 8 Hz, 1 H), 4.60–4.90 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (q, 2 C), 19.9 (q), 20.2 (t, 2 C), 29.2 (t, 2 C), 33.4 (t), 45.3 (t), 53.2 (t), 73.6 (d), 155.5 (s); MS, m/e 212 (M^+).

β-Iodoisopropyl N,N'-diisopropylcarbamimidate (25): mp 128 °C; IR (KBr) 1680 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 1.20–1.70 (m, 15 H), 3.45 (t, 1 H), 4.00–4.30 (m, 2 H), 4.90–5.10 (m, 1 H), 5.20–5.50 (m, J = 7 and 10 Hz, 1 H), 7.50 (br 1 H). Anal. Calcd for $C_{10}H_{21}ON_2I$: C, 38.47; H, 6.78; N, 8.97. Found: C, 38.15; H, 6.72; N, 8.92.

β-Iodoisopropyl N,N'-dicyclohexylcarbamimidate (26): mp 209–211 °C; IR (KBr) 1670 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 1.00–2.10 (m, 24 H), 3.42 (dd, J = 7 and 9 Hz, 1 H), 3.50–3.90 (m, 1 H), 4.15 (t, J = 9 Hz, 1 H), 4.60–5.00 (m, 1 H), 5.15–5.50 (m, 1 H). Anal. Calcd for $C_{16}H_{29}ON_2I$: C, 48.98; H, 7.45; N, 7.14. Found: C, 48.79; H, 7.29; N, 6.82.

1-Iodo-2-propanol (27a). The solution of n-Bu_3SnI (2.10 g, 5 mmol) and Ph_3PO (1.35 g, 5 mmol) in propylene oxide (2.90 g, 50 mmol) was stirred under dry nitrogen at 40 °C for 1 h. Malonic acid (0.38 g, 2.5 mmol) was added[24b] to the reaction mixture, and the stirring was continued for 2 h. GLC analysis showed the formation of 1-iodo-2-propanol (**27a**, 0.72 g, 77%), which was purified by distillation. Spectral data of **27a** were identical with the authentic sample derived from the iodation of 1-chloro-2-propanol: bp 60 °C (10 mmHg); IR (neat) 3350 (OH), 1050 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 6 Hz, 3 H), 3.20–3.40 (m, 3 H), 3.60–3.90 (m, 1 H).

Acknowledgment. This research was supported by the Grant-in-Aids for Scientific Research (60430022).

Registry No. 1, 708-57-6; 2, 101835-17-0; 3, 711-85-3; 4a, 7426-72-4; 4b, 13606-71-8; 5, 101835-18-1; 6, 100372-80-3; 7, 1226-26-2; 8, 25557-96-4; 9, 101835-19-2; 10, 100371-98-0; 11, 99855-08-0; 12, 101835-20-5; 13, 7007-16-1; 14, 101835-21-6; 15, 15833-10-0; 16, 101835-22-7; 17, 95891-61-5; 18, 101835-23-8; 20, 101835-24-9; 21, 101835-25-0; 22, 13468-06-9; 23, 101835-26-1; 24, 101835-27-2; 25, 101835-28-3; 26, 101835-29-4; 27a, 996-21-4; DBU, 6674-22-2; HMPA, 680-31-9; PhNCO, 103-71-9; BuSnI, 7342-47-4; Ph_3P, 603-35-0; Ph_3PO, 791-28-6; Et_3N, 121-44-8; Bu_3SnCl, 1461-22-9; Bu_3SnBr, 1461-23-0; Bu_2SnI_2, 2865-19-2; Me_2SnI_2, 2767-49-9; 4-MeC_6h_4NCO, 622-58-2; 4-$O_2NC_6H_4NCO$, 100-28-7; PhCONCO, 4461-33-0; MeNCO, 624-83-9; BuNCO, 111-36-4; $PhCH_2NCO$, 3173-56-6; PhNCS, 103-72-0; $PhCH_2NCS$, 622-78-6; MeNCS, 556-61-6; PhN=C=NPh, 622-16-2; BuN=C=NPh, 21848-95-3; BuN=C=NBu, 693-64-1; Me_2CHN=C=$NCHMe_2$, 693-13-0; SnOCH(Me)CH_2I, 101835-30-7; dicyclohexylcarbodiimide, 538-75-0; methyloxirane, 75-56-9; ethyloxirane, 106-88-7; (chloromethyl)oxirane, 106-89-8; phenyloxirane, 96-09-3; (ethoxymethyl)oxirane, 4016-11-9; ((2-propenyloxy)methyl)oxirane, 106-92-3; (phenoxy)oxirane, 79526-11-7; 2,2-dimethyloxirane, 558-30-5; 2-ethenyl-2-methyloxirane, 1838-94-4; 7-oxabicyclo-[4.1.0]heptane, 286-20-4.

Synthesis of Indolizinones and a Pyridoazepinone: A New Method for the Annulation of Pyridinones[1]

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Received November 26, 1985

The synthesis of 2,3-dihydro-5(1*H*)-indolizinone (**1**), 6,7,8,9-tetrahydro-4(4*H*)-quinolizinone (**2**), and 7,8,9,10-tetrahydropyrido[1,2-*a*]azepin-4(6*H*)-one (**3**) is described. Regiospecific addition of a bifunctional organolithium reagent (**8**, **14**, **18**) to the 6-position of 2-methoxypyridine comprises the key bond-forming reaction for the annulation sequence. The resulting lactim is oxidized to a 2,6-disubstituted pyridine (**10**, **16**, and **20**). Under acidic conditions, **10** and **16** afford **1** and **2**, respectively. Compound **20** does not afford **3** under acidic conditions, but **20** is converted to **24**, which under basic conditions cyclizes to **3**. In addition, examples of the synthesis of 3-substituted indolizinones (**29**, **30**) are also presented.

The indolizinone and quinolizinone skeletons comprise the backbone of a number of biologically and structurally interesting molecules,[2] for example, the antitumor agent camptothecin (**4**),[3] and the alkaloid isosophoramine (**5**),[4] respectively. A general and useful route to these types of compounds could be developed by devising a straightforward synthesis of ring-fused pyridinones:[5] indolizinone (**1**), quinolizinone (**2**), and pyridoazepinone (**3**). Wenkert's

(1) Presented in Part at the 190th National Meeting of the American Chemical Society, Chicago, IL, September 9, 1985.

(2) For extensive lead references to indolizidine and quinolizidine alkaloids, see: *The Alkaloids, A Specialist Periodical Report*; The Royal Society of Chemistry: London; Vol. 1–13.

(3) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047–1065.

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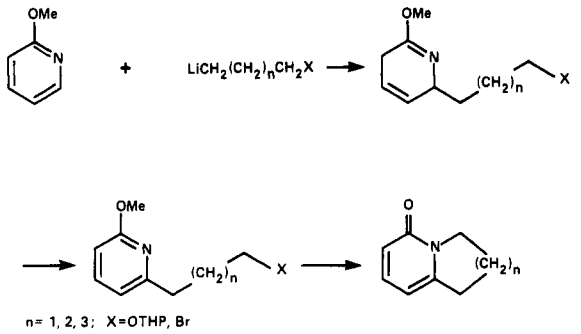
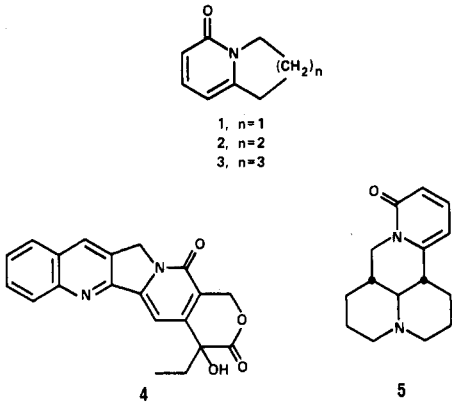
0022-3263/86/1951-2184$01.50/0

Scheme I



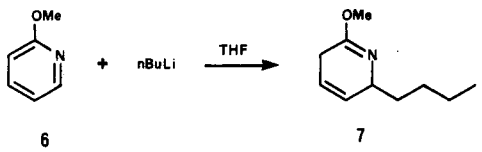
route to **2**[4] and nearly all of the syntheses of camptothecin[3] rely on the construction of the pyridinone ring. We felt a novel route to the simple ring fused pyridinones **1**, **2**, and **3** would be through the annulation of a masked pyridinone ring.



In Scheme I a general method for the formal annulation of pyridone is proposed. The key step in the sequence is the regiospecific addition of a bifunctional nucleophilic reagent[6] to a 2-methoxy substituted pyridine. There are many references to the addition of nucleophiles to pyridine[7] and substituted pyridines.[8] However, there are no references to the addition of nucleophiles to a 2-methoxypyridine. The closest analogy for the addition of nucleophiles to 2-substituted pyridine is the addition of *n*-butyllithium to 2-fluoropyridine.[8a] In this paper, we describe the addition of organolithium reagents to the 6-position of 2-substituted pyridines, which affords substrates amenable to the annulation of pyridinones.

Results and Discussion

The feasibility of adding a nucleophile to the 6-position of 2-methoxypyridine was demonstrated by the addition of 1 equiv of *n*-butyllithium to 2-methoxypyridine (**6**) which afforded the lactim **7** in 75% yield, after distillation.



This method is also a novel way of generating a lactim, a functional group which has found wide use in organic synthesis.[9] By stirring in water, lactim **7** was easily hydrolyzed to lactam **32**. This lactam has been prepared by another route, vida infra.

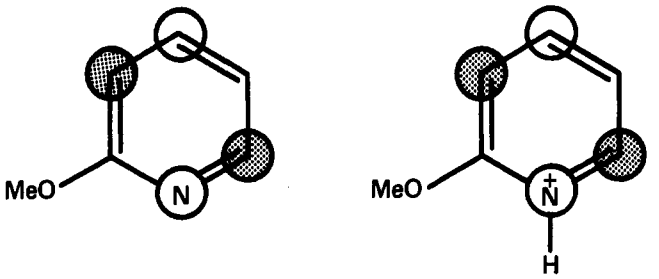
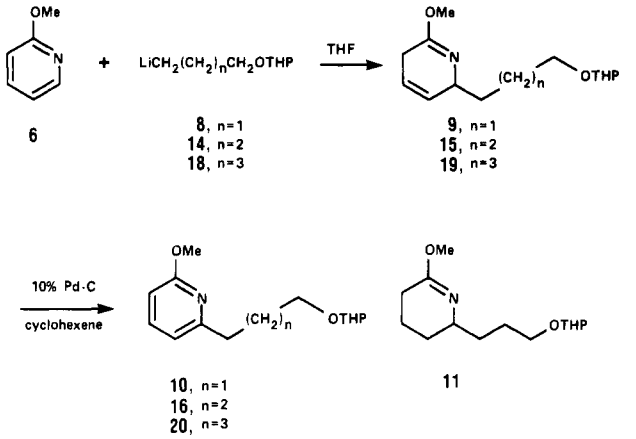


Figure 1. LUMO of 2-methoxypyridine and the pyridinium ion.

Scheme II



In order to understand the regioselectivity of this reaction, ab initio SCF-MO calculations[10] were carried out on 2-methoxypyridine and N-protonated 2-methoxypyridinium cation. The results reveal for both cases a high density in the π orbitals at C-4 and C-6, but not at C-2, Figure 1. However, the LUMO of the cation, where a proton approximates a lithium cation, is a much better electron acceptor than the one in the neutral molecule owing to the marked lowering of its energy by the presence of the positive charge. Since C-6 carries the highest density in the LUMO of the cation and lies near the center of positive charge, it is the favored site for nucleophilic attack. These findings suggest that the reaction of **6** with *n*-butyllithium proceeds by formation of the lithium-pyridinium cation which activates C-6 to attack by the *n*-butyl anion. This mechanism is attractive since it requires minimal separation of the ion pairs during the course of the reaction.

The synthesis of **1** commenced with the reaction of the novel bifunctional organolithium reagent **8**, derived from 2-(3-chloropropoxy)tetrahydro-2*H*-pyran,[11] and 2-methoxypyridine (**6**) produced **9** in 65% yield, Scheme II. Compound **9** was oxidized with 10% Pd–C in cyclohexene[12]

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(8) (a) Marsais, F.; Granger, P.; Queguiner, G. *J. Org. Chem.* **1981**, *46*, 4494–4497. (b) Meyers, A. I.; Gabel, R. A. *J. Org. Chem.* **1982**, *47*, 2633–2637. (c) Abramovitch, R. A.; Notation, A. D. *Can. J. Chem.* **1960**, *38*, 1445–1448. (d) Chavdarian, C. G.; Seeman, J. I. *Tetrahedron Lett.* **1982**, *23*, 2519–2522.
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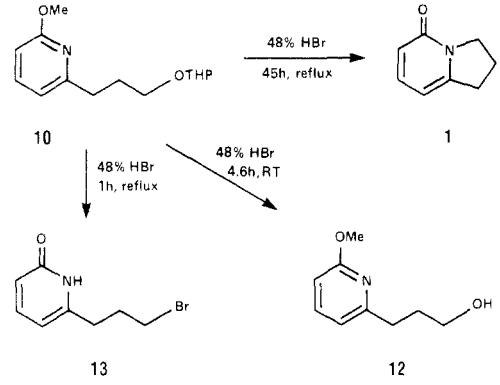
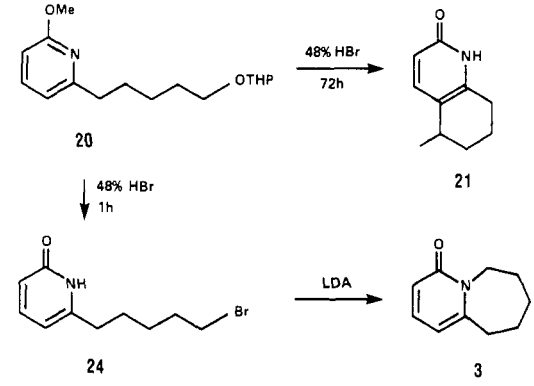
Scheme III



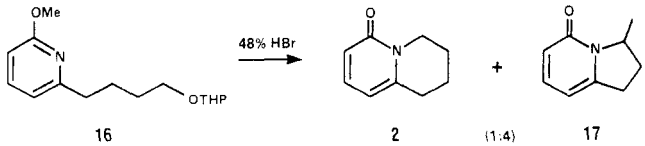
Scheme IV



to yield the desired methoxypyridine **10** (68%), accompanied by the minor component **11** (11%). In order to complete the annulation method, the protecting groups on compound **10** needed to be removed. Refluxing aqueous HBr or HCl is usually employed to hydrolyze methoxypyridines to pyridinones.[13] Aqueous acid hydrolyzes the THP group from alcohols, and aqueous HBr has been employed to convert primary alcohols to primary bromides.[14] In fact, treatment of **10** with 48% HBr afforded **1** in 66% yield. The NMR of compound **1** was practically first order. A triplet at δ 4.15 was present for the methylene group adjacent to the nitrogen and at δ 3.10 for the methylene group adjacent to the pyridinone ring. The chemical shifts and coupling constants for the three pyridinone ring protons are consistent with alkyl groups at the 1- and 6-positions.[15]

The exact order of steps was not known for the conversion of **10** to **1**, and the following experiments shed some light on this area, Scheme III. Compound **10** when treated with 48% HBr for 4.6 h at room temperature afforded **12**. When the reaction was heated at reflux for 1 h, bromide **13** was isolated. One would imagine the alcohol of **12** was converted to the bromide and then cleaved to **13** or the methoxypyridine of **12** was cleaved and the alcohol was then converted to bromide **13**, which is the likely ultimate precursor to **1**.

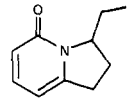
Synthesis of quinolizinone **2** followed the same strategy employed in the synthesis of **1**. Organolithium reagent **14**, derived from 2-(3-chlorobutoxy)tetrahydro-2*H*-pyran,[16] added to methoxypyridine (**6**) affords **15**. This reaction was more capricious in yields (30–70%) on large scale than for the formation of **9**. Although the yields were low for this step, the ease in isolation of **15** through distillation makes this reaction practical on a large scale. Dihydropyridine **15** was smoothly oxidized with 10% Pd–C, on large scale, to methoxypyridine **16**. Treatment of **16** with



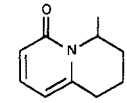
48% HBr at reflux produced two compounds, quinolizinone **2** and indolizinone **17** in a 1:4 ratio, respectively, in 79% overall yield. Although **2** and **17** were inseparable by TLC, careful chromatography of the mixture afforded samples of each. Compound **2** and **17** were separately subjected to the reaction conditions of refluxing 48% HBr for 19 h, and no equilibration was observed as determined by HPLC. Clearly, the ratio of **2** to **17** reflects the kinetic ratio of products.

Employing similar conditions, we attempted to synthesize pyridoazepinone **3**. Lithiation of 2-(3-chloropentoxy)tetrahydro-2*H*-pyran[17] afforded **18**, which added to methoxypyridine (**6**) to yield lactim **19**. Upon scale up, the yields of this step also suffered. Dihydropyridine **19** was oxidized to **20** in excellent yield. Compound **20** was subjected to 48% HBr, and only one compound was isolated **21** (72%). The NMR of compound **21** exhibited only two pyridinone proton resonances at δ 6.44 and δ 7.37, a doublet at δ 1.19 for the ring methyl group, and a broad singlet at δ 13.06 for the N–H.

The expected products from this reaction were structures **3**, **22**, or **23** in which cyclization occurred on the nitrogen. Instead, ring closure occurred on the carbon of the aromatic ring reminiscent of Friedel–Crafts chemistry. Friedel–Crafts chemistry is unusual for pyridine,[18] while pyridinones undergo electrophilic substitution quite readily.[19] The formation of **21** in lieu of **3**, **22**, or **23** is worthy of further investigation.



22



23

Since **21** was formed under acidic conditions, perhaps a precursor such as **24** could cyclize to **3** under basic conditions, Scheme IV. Previously, **10**, a homologue of **20**, had been converted directly into halopyridinone **13**, Scheme III. Similarly, methoxypyridine **20** was converted under acidic conditions to pyridinone **24**. The experimental conditions employed to cyclize **24** were modeled after conditions used by House to form seven-membered rings from ketone enolates and an alkyl halide.[20] Treatment of **24** with LDA afforded the N-alkylated product pyridoazepinone **3** in 49% yield. The structure of **3** was readily determined from its NMR which is similar to that of **1** and **2**.

With compound **3** in hand, it was subjected to the reaction conditions employed to form **21** from **20**. Upon workup, 66% of **3** and 33% of **21** were isolated as deter-

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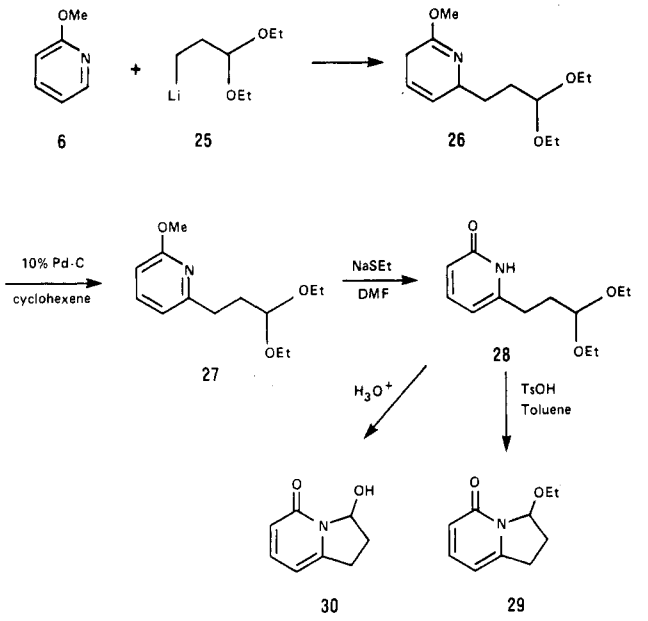
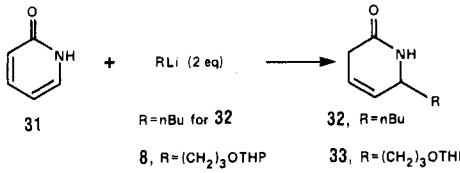
Scheme V



mined by NMR and TLC. Clearly, **3** cannot lie along the major pathway to the formation of **21**, as compound **21** was originally formed in 72% yield from **20**.

Annulation of pyridinone can also be conducted so functionalized rings are introduced such as **29** and **30**, Scheme V. Organolithium reagent **25**, which was generated from commercially available 3-chloro-1,1-diethoxypropane, added smoothly to 2-methoxypyridine (**6**) in the C-6 position to afford lactim **26**. Oxidation of lactim **26** with 10% Pd–C produced pyridine derivative **27**. At this point in the scheme, it was necessary to convert the methoxypyridine functionality into the pyridinone. Conditions normally employed for this transformation are strongly acidic[13] and are not compatible with an acetal. Basic aqueous or methanolic conditions have been used for this transformation,[21] but they proved to be not as facile as employing sodium thioethoxide which previously had been used to cleave methyl ethers.[22] In DMF, NaSEt readily cleaved the methyl ether of **27** to form pyridinone **28** in 80% yield. Pyridinone **28** was cyclized in order to complete the synthesis of ring substituted compounds **29** and **30**. Under anhydrous conditions **28** afforded indolizinone **29**, and under aqueous conditions **28** afforded indolizinone **30**.

One could imagine Scheme I could be simplified further if, instead of employing 2-methoxypyridine as a masked pyridinone, pyridinone **31** itself were employed. Although nucleophiles were found to react in the 6-position of pyridinone **31**,[23] this was not as facile as the reaction with



2-methoxypyridine. For example, 2 equiv of *n*-butyllithium reacted with pyridinone **31** to afford a single product **32**, in 55% yield. However, 2 equiv of organolithium reagent **8** reacted with **31** to form **33** in only 5–15% yield. By varying the reaction solvent, reaction temperature, or alcohol protecting group on **8**, we were unable to improve the yield of **33**.

Conclusions

2-Methoxypyridine (**6**) regiospecifically reacts with nucleophiles in the 6-position, generating lactims which are useful in synthesis. This methodology allows for the formal annulation of five-, six-, and seven-membered rings on the pyridinone ring at the 1,6-position. Pyridinone **31** once deprotonated undergoes nucleophilic attack at the 6-position. This also can be viewed as a nucleophilic addition to a 2-substituted pyridine.

Experimental Section

Infrared spectra were recorded on a Perkin Elmer 297 spectrometer. ^{1}H NMR spectra were recorded on a Varian Associates EM-390 (90-MHz) spectrometer and are reported in δ units from internal tetramethylsilane. ^{13}C NMR were recorded on a Varian CFT-20 spectrometer and are reported in parts per million from tetramethylsilane on the δ scale. Melting points were taken on a Thomas-Hoover capillary melting-point apparatus and are reported uncorrected. Mass spectra were recorded on a Varian MAT-CH5 spectrometer. Combustion analyses were performed by the Upjohn Physical and Analytical Chemistry Laboratory and by the Spang Microanalytical Laboratory. Unless specified all solvents and reagents were used without further purification. THF and Et_2O were dried over 4-Å molecular sieves.[24] The lithium wire was purchased from the Lithium Corporation of America and contains 0.6 % Na. The organolithium reagents were titrated with diphenylacetic acid.[25] All reactions were conducted under an atmosphere of nitrogen.

2-Butyl-2,5-dihydro-6-methoxypyridine (7). *n*-Butyllithium (30 mL, 48 mmol, 1.6 M in hexane) was cooled to −10 °C (ice/acetone bath), and methoxypyridine (**6**) (5.24 g, 48 mmol), dissolved in Et_2O (10 mL), was added. The reaction turned orange, and it was stirred for an additional 1.5 h. The reaction was quenched by pouring it into 20 mL of H_2O. The aqueous portions were extracted with EtOAc (2 × 10 mL), and the organic layers were combined, dried, and evaporated to 7.0 g of crude product. The liquid was distilled at 0.05 mm to afford two fractions: fraction 1, bp 30–40 °C, 1.96 g; fraction 2, bp 40–48 °C, 4.04 g; total yield 6.0 g (74.7%). Fraction 1 was analytically pure, and fraction 2 was not. Their TLC, NMR, IR, and MS were identical. After several weeks fraction 2 developed an orange tint, and fraction 1 remained light amber. Analytical data were obtained on fraction 1 of compound **7**: ^{1}H NMR ($CDCl_3$) δ 0.75–1.04 (m, 3 H, CH_3), 1.10–1.75 (m, 6 H, CH_2), 2.65 (d, 2 H, J = 6.2 Hz, $=CCH_2$), 3.69 (s, 3 H, OCH_3), 3.92–4.30 (m, 1 H, N–CH), 5.75 (s, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$) ppm 160.5 (s), 129.9 (d), 120.4 (d), 57.1 (d), 51.9 (q), 37.4 (t), 27.5 (t), 25.8 (t), 22.9 (t), 14.1 (q); IR (neat) 2957, 2943, 2931, 2860, 1694, 1659, 1437, 1357, 1225, 1017, 891, 698 cm^{-1}; MS, *m/e* (rel intensity) 167 (M^+, 3.9), 152 (4.5), 123(3.8), 111 (9.4), 110 (100.0), 78 (13.5). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.57; H, 10.07; N, 8.29.

2,5-Dihydro-6-methoxy-2-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)propyl)pyridine (9). The organolithium reagent **8** was generated by cooling Li (4.9 g, 0.7 mol) and Et_2O (140 mL) to −10 °C (ice/acetone bath) and adding 2-(3-chloropropoxy)tetrahydro-2*H*-pyran (50.0 g, 0.28 mol) dissolved in Et_2O (70 mL) at a rate of 1 mL min^{-1}. The reaction was stirred for an additional 3 h, then titrated with diphenylacetic acid in THF, and found to be 1 M in Et_2O or 78% yield. In a separate flask methoxypyridine (**6**) (21.8 g, 0.2 mol) and Et_2O (100 mL) were cooled to −10 °C, the organolithium reagent **8** (220 mL, 0.22 mol) was added, and the reaction turned orange. After 2.6 h the reaction was

(21) Zoltewicz, J. A.; Sale, A. A. *J. Org. Chem.* **1970**, *35*, 3462–3467.
(22) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327–1328.
(23) N-alkyl substituted pyridinones react with nucleophiles in the 4-position. For example: (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398. (b) Matsumura, E.; Tohda, Y.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2174–2180.
(24) Burfield, D. R.; Gan, G.; Smithers, R. H. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 23–30.
(25) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879–1880.

poured over 100 mL of ice water. The aqueous fraction was extracted with EtOAc (3 × 50 ml). The organic fractions were combined, extracted with saturated aqueous NaCl (50 mL), dried, and evaporated in vacuo to 57.81 g. Chromatography on a Waters' Prep-500 (SiO_2; hexane/EtOAc, 9/1) afforded 33.73 g of material. This was bulb-to-bulb distilled in a Kugelrohr oven to yield **9** (32.83 g, 64.8%): bp 100–110 °C at 0.01 mm; ^1H NMR ($CDCl_3$) δ 1.40–2.10 (m, 10 H, CH_2), 2.60 (d, 2 H, J = 6.3, =CCH_2), 3.30–4.40 (m, 5 H, OCH_2, NCH), 3.73 (s, 3 H, OCH_3), 4.60–4.70 (m, 1 H, OCHO), 5.84 (s, 2 H, CH=CH); IR (neat) 2945, 2926, 1692, 1658, 1438, 1356, 1224, 1201, 1138, 1121, 1077, 1066, 1033, 1021, 701 cm^{-1}; MS, m/e (rel intensivity) 253 (M^+, 3.2), 169 (52.6), 168 (88.4), 153 (31.2), 152 (65.8), 150 (40.6), 136 (13.2), 123 (23.1), 110 (100.0), 85 (69.9). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.19; H, 9.04; N, 5.40.

2-Methoxy-6-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)-propyl)pyridine (10). Lactim **9** (29.0 g, 0.1 mol) and 10% Pd–C (2.9 g) were mixed, and cyclohexene (200 mL) was added. While adding the cyclohexene, the reaction burst into flames. The flames were extinguished with a CO_2 fire extinguisher, and the hot flask was cooled in an ice bath. (The fire was due to the direct mixing of **9** and 10% Pd–C, which ignited the solvent, cyclohexene. This step has since been modified. In subsequent reactions 10% Pd–C and cyclohexene were premixed and heated to reflux, where upon an exothermic reaction occurs.[26] After the vigorous exotherm subsided, the substrate was added slowly. This step has been successfully run on 40 g of compound with no further accidents.) To the flask was added EtOAc (400 mL), and the contents were filtered. The filtrate was concentrated in vacuo to 29 g of crude material. This was chromatographed on the Waters' Prep-500 (SiO_2; hexane/EtOAc, 9/1). The first compound, **10** (21 g), eluted at 1.5 column volumes, and the second compound, **11**, eluted at 2.8 column volumes. A bulb-to-bulb distillation (78–90 °C at 0.1 mm) of the first component in a Kugelrohr oven provided analytically pure **10** (19.6 g, 68.4%): ^1H NMR ($CDCl_3$) δ 1.36–2.24 (m, 8 H, CH_2), 2.80 (t, 2 H, J = 7.8 Hz, =CCH_2), 3.30–3.97 (m, 4 H, OCH_2), 3.94 (s, 3 H, OCH_3), 4.55–4.70 (m, 1 H, OCHO), 6.60 (d, 1 H, J = 8.4 Hz), 6.78 (d, 1 H, J = 6.6 Hz), 7.50 (dd, 1 H, J = 8.4 Hz, J = 6.6 Hz, OC=CCH); IR (neat) 2948, 2928, 1599, 1579, 1466, 1441, 1414, 1352, 1322, 1286, 1261, 1201, 1148, 1137, 1120, 1060, 1033, 987, 800 cm^{-1}; UV (EtOH), λ_{max} (ϵ) 217 (7700), 274 (5900); MS, m/e (rel intensity) 251 (M^+, 8.0), 222 (1.0), 167 (27.8), 166 (56.9), 150 (100.0), 136 (28.1), 123 (78.1), 85 (40.7). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.00; H, 8.32; N, 5.57. Distillation of the second component in a Kugelrohr oven (89–90 °C at 0.1 mm) afforded **11** (3.09 g, 10.6%): ^1H NMR ($CDCl_3$) δ 1.00–2.30 (m, 16 H, CH_2), 3.16–4.06 (m, 5 H, OCH_2, NCH), 3.64 (s, 3 H, OCH_3), 4.58–4.72 (m, 1 H, OCHO); IR (neat) 2943, 2869, 1679, 1436, 1363, 1353, 1229, 1201, 1181, 1138, 1120, 1078, 1066, 1032 cm^{-1}; MS, m/e (rel intensity) 170 (100.0), 154 (35.3), 138 (6.6), 112 (15.8), 97 (9.2), 85 (21.3). Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 66.08; H, 9.70; N, 5.40.

2,3-Dihydro-5(1*H*)-indolizinone (1). Methoxypyridine **10** (1.0 g, 3.9 mmol) and 48% HBr (25 mL) were heated at reflux for 45 h. The hot liquid was decanted from the tar and filtered through a plug of glass wool. The solvent was removed by distillation at 1 atm, and the residue was made basic (pH 9) with 10% NaOH. The aqueous portion was extracted with CH_2Cl_2 (3 × 25 mL), and the organic layers were combined, dried, and concentrated in vacuo to afford 600 mg of a semisolid. The material was purified on a Waters' Prep-500 (SiO_2, acetone) to yield **1** (430 mg, 81%). By bulb-to-bulb distillation (79–90 °C at 0.1 mm) in a Kugelrohr oven, an analytical sample of **1** (350 mg, 66%) was prepared, which is a low-melting hygroscopic solid: ^1H NMR ($CDCl_3$) δ 2.19 (quintet, 2 H, J = 6.6 Hz, CH_2), 3.10 (t, 2 H, J = 6.6 Hz, =CCH_2), 4.15 (t, 2 H, J = 6.6 Hz, NCH_2), 6.15 (d, 1 H, J = 6.0 Hz, NC=CH), 6.40 (d, 1 H, J = 8.7 Hz, OCCH), 7.34 (dd, 1 H, J = 8.7 Hz, J = 6.0 Hz, OCC=CH); ^{13}C NMR ($CDCl_3$) ppm 162.5, 150.6, 140.0, 117.2, 101.1, 48.7, 31.8, 21.3; IR (neat) 3425, 2964, 1655, 1581, 1548, 1543, 1460, 1439, 1148, 1029, 793, 788 cm^{-1}; MS, m/e (rel intensity) 135 (M^+, 100.0), 134 (73.5), 107 (27.7), 106 (68.0, 93 (6.2), 79 (20.0). Anal. Calcd for $C_8H_9NO \cdot 0.35H_2O$: C, 67.88; H, 6.91; N, 9.89. Found: C, 66.72; H, 6.53; N, 9.60. Anal. Found for H_2O: 4.5%.

3-(2-Methoxypyridin-6-yl)-1-propanol (12). Methoxypyridine **10** (5.0 g, 19.9 mmol) and 48% HBr (100 mL) were stirred at room temperature for 4.7 h. The reaction was quenched by pouring onto ice (100 g) and then treated with aqueous NH_4OH to pH 8. The aqueous layers were extracted with EtOAc (3 × 100 mL), and the organic layers were combined, dried, and concentrated in vacuo to 3.86 g. This was chromatographed on a Waters' Prep-500 (SiO_2; EtOAc/hexane, 3/7) to provide 3.11 g of product. A bulb-to-bulb distillation of this material in a Kugelrohr oven (85–100 °C at 0.4 mm) afforded analytically pure **12** (2.82 g, 84.9%); ^1H NMR ($CDCl_3$) δ 1.98 (quintet, 2 H, J = 6.0 Hz, CH_2), 2.85 (t, 2 H, J = 6.0 Hz, =CCH_2), 3.70 (t, 3 H, J = 6.0 Hz, OCH2, OH), 3.94 (s, 3 H, OCH3), 6.64 (d, 1 H, J = 8.4 Hz), 6.81 (d, 1 H, J = 7.5 Hz), 7.55 (dd, 1 H, J = 7.5 Hz, J = 8.4 Hz, OC=CCH); IR (neat) 3354, 2949, 2932, 1600, 1580, 1467, 1441, 1415, 1292, 1033, 799 cm^{-1}; MS, m/e (rel intensity) 167 (M^+, 23.9), 166 (11.2), 150 (17.4), 137 (37.4), 136 (48.2), 124 (29.8), 123 (100.0), 108 (26.1). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.95; H, 8.13; N, 8.21.

6-(3-Bromopropyl)-2(1*H*)-pyridinone (13). Methoxypyridine **10** (5.0 g, 19.9 mmol) and 48% HBr (100 mL) were heated at reflux for 1 h. The hot reaction was filtered through a plug of glass wool. The solvent was removed by distillation at 1 atm, and the residue was poured over ice (100 g). The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL) and then made basic with aqueous NH_4OH where upon a white solid precipitated from solution. The white solid was filtered and dried to afford 2.2 g of material which was not very soluble in organic solvents. The solid was added to water (not very soluble), 0.1 mL of 10% aqueous HCl was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried, and concentrated in vacuo to afford **13** (2.05 g, 47.7%) as a white solid: mp 98–100 °C; ^1H NMR ($CDCl_3$) δ 2.15–2.47 (m, 2 H, CH_2), 2.83 (t, 2 H, J = 7.5 Hz, =CCH_2), 3.42 (t, 2 H, J = 6.0 Hz, CH_2Br), 6.28 (d, 1 H, J = 6.6 Hz, NC=CH), 6.55 (d, 1 H, J = 9.0 Hz, OCCH), 7.52 (dd, 1 H, J = 9.0 Hz, J = 6.6 Hz, OCC=CH); IR (mull) 2960, 2950, 2927, 2854, 1871, 1670, 1660, 1627, 1550, 971, 803 cm^{-1}; MS, m/e (rel intensity) 217 (M^+, 10.4), 215 (M^+, 10.7), 189 (0.2), 187 (0.2), 136 (11.6), 135 (14.5), 134 (11.7), 109 (100.0). Anal. Calcd for $C_8H_{10}BrNO \cdot 0.06H_2O$: C, 44.26; H, 4.70; Br, 36.81; N, 6.45. Found: C, 44.00; H, 4.48; Br, 37.49; N, 6.47. Anal. Found for H_2O: 0.47%.

2,5-Dihydro-6-methoxy-2-(4-((tetrahydro-2*H*-pyran-2-yl)oxy)butyl)pyridine (15). Organolithium reagent **14** was generated by adding 2-(4-chlorobutoxy)tetrahydro-2*H*-pyran (59.0 g, 306 mmol) in THF (40 mL) over 2.5 h to Li (5.0 g, 710 mmol) in THF (60 mL) at −20 °C. After an additional 3 h, the reaction was titrated with diphenylacetic acid, and the organolithium concentration was 1.0 mol (51%). Solvent (25 mL) was removed under vacuum (0.1 mm), and Et_2O (100 mL) was added to the reaction. In a separate flask 2-methoxypyridine (**6**) (17.01 g, 156 mmol) and Et_2O (200 mL) were cooled to −10 °C. The organolithium reagent **14** was added to the methoxypyridine in 1 portion. After an additional 1 h, the reaction was quenched by pouring into H_2O (200 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL), and the organic layers were combined, dried, and evaporated to 57.9 g of material which consisted of at least six spots by TLC. This material was distilled, and the fraction rich in product was collected (100–140 °C at 0.2 mm). This was chromatographed on the Waters' Prep-500 (SiO_2, Skelly B/EtOAc, 9/1). A bulb-to-bulb distillation (120 °C at 0.1 mm) of the compound in a Kugelrohr oven afforded analytically pure **15** (15.26 g, 36.7%): ^1H NMR ($CDCl_3$) δ 1.20–2.20 (m, 12 H, CH_2), 2.70 (d, 2 H, J = 6.0 Hz, =CCH_2), 3.20–4.30 (m, 5 H, OCH_2, NCH), 3.68 (s, 3 H, OCH_3), 4.64 (brs, 1 H, OCHO), 5.80 (s, 2 H, CH=CH); IR (neat) 2942, 2866, 1692, 1659, 1438, 1356, 1227, 1138, 1121, 1077, 1034, 1022 cm^{-1}; MS, m/e (rel intensity) 267 (M^+, 2.3), 238 (1.5), 183 (28.4), 182 (39.6), 167 (18.1), 166 (51.8), 164 (15.2), 111 (15.3), 110 (100.0), 85 (49.8). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43; N, 5.24. Found: C, 67.36; H, 9.42; N, 5.17.

2-Methoxy-6-(4-((tetrahydro-2*H*-pyran-2-yl)oxy)butyl)-pyridine (16). Cyclohexene (15 mL) and 10% Pd–C (1.2 g) were heated at reflux, and lactim **15** (12.0 g, 44.8 mmol) dissolved in cyclohexene (10 mL) was added slowly. The reaction was con-

(26) Cyclohexene and Pd–C affords benzene and cyclohexane, see: Carra, S.; Ragaini, V. *Tetrahedron Lett.* **1967**, 1079–1082.
(27) Wartski, L.; Wakselman, C. *Bull. Soc. Chim. Fr.* **1967**, 1594–1598.

tinued for 5.75 h. The contents of the flask were filtered and then concentrated in vacuo to 12.5 g of an oil. This was chromatographed on the Waters' Prep-500 (SiO_2, hexane/EtOAc, 9/1), and the product **16** (9.01 g, 75.9%) was eluted at 2 column volumes: ^1H NMR ($CDCl_3$) δ 1.35–2.10 (m, 10 H, CH_2), 2.72 (t, 2 H, J = 7.2 Hz, =CCH_2), 3.30–4.05 (m, 4 H, OCH_2), 3.90 (s, 3 H, OCH_3), 4.57 (brs, 1 H, OCHO), 6.52 (d, 1 H, J = 8.0 Hz), 6.70 (d, 1 H, J = 7.6 Hz), 7.45 (dd, 1 H, J = 7.6 Hz, J = 8.0 Hz, OC=CCH); IR (neat) 2946, 2868, 1600, 1580, 1467, 1440, 1414, 1299, 1284, 1137, 1119, 1077, 1063, 1034, 1022, 797 cm^{-1}; MS, m/e (rel intensity) 265 (M^+, 4.9), 236 (0.7), 181 (46.7), 180 (24.8), 164 (100.0), 150 (7.7), 136 (33.0), 123 (38.5), 85 (73.5). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.29; H, 8.81; N, 5.33.

6,7,8,9-Tetrahydro-4*H*-quinolizin-4-one (2) and 2,3-Dihydro-3-methyl-5(1*H*)-indolizinone (17). Methoxypyridine **16** (29.0 g, 109 mmol) and 48% HBr (750 mL) were heated at reflux for 6.5 h, and the hot mixture was then filtered through glass wool to remove the tar. The filtrate was concentrated by distilling off 600 mL of solvent. The concentrated material was brought to pH 11 with 10% aqueous NaOH. The entire mixture was extracted with CH_2Cl_2 (3 × 250 mL), and the organic portions were combined, dried, and concentrated in vacuo to afford 16.3 g of a dark brown oil. The brown oil was chromatographed (SiO_2, EtOAc) on the Waters' Prep-500 to afford 12.78 g (78.7%) of **2** and **17** in a ratio of 1:4, respectively, as determined by NMR. By TLC, these compounds were indistinguishable (SiO_2: R_f 0.20, EtOAc), but they were separated by HPLC: Whatman Particil 10 column, 60% $CHCl_3$/40% EtOAc, 3 mL min^{-1}, UV at 260 λ, **2** retention volume = 24.3 mL, **17** retention volume = 29.1 mL; Waters' & Bondapak, 60% H_2O/40% MeOH, 2 mL min^{-1}, UV at 260 λ, **17** retention volume = 8.8 mL, **2** retention volume = 10.2 mL. By HPLC **2** (800 mg, 5.4%) was isolated: ^1H NMR ($CDCl_3$) δ 1.45 (d, CH_3, 16% impurity **17**), 1.65–2.15 (m, 4 H), 2.80 (t, 2 H, J = 6.0 Hz, $NCCH_2$), 4.00 (t, 2 H, J = 6.0 Hz, NCH_2), 4.70–5.05 (m, impurity, **17**), 6.05 (d, 1 H, J = 6.9 Hz, NC=CH), 6.45 (d, 1 H, J = 9.0 Hz, OCCH), 7.17–7.46 (m, 1 H, OCC=CH); ^{13}C NMR ($CDCl_3$) ppm 163.5, 147.8, 138.7, 116.6, 105.1, 41.6, 28.8, 22.2, 18.7; IR (neat) 3468, 2950, 1654, 1573, 1546, 1159, 1139, 791 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 233 (6750), 309 (7300); MS, m/e (rel intensity) 149 (M^+, 94.5), 148 (100.0), 134 (49.2), 120 (31.9), 93 (26.3), 91 (48.4); exact mass calcd for $C_9H_{11}NO$ 149.0841, found 149.0852. By HPLC **17** (5.97 g, 36.7%) was isolated: mp 70.5–76.0 °C; ^1H NMR ($CDCl_3$) δ 1.44 (d, 3 H, J = 6.0 Hz, CH_3), 1.68–3.50 (m, 4 H, CH_2), 4.68–5.10 (m, 1 H, NCH), 6.14 (d, 1 H, J = 6.3 Hz, NC=CH), 6.40 (d, 1 H, J = 9.0 Hz, OCCH), 7.19–7.66 (m, 1 H, OCC=CH); ^{13}C NMR ($CDCl_3$) ppm 162.0 (s), 150.0 (s), 140.0 (d), 117.5 (d), 101.1 (d), 57.0 (d), 29.8 (t), 28.8 (t), 18.2 (q); UV (EtOH) λ_{max} (ϵ) 231 (7050), 303 (6450); IR (mull) 2926, 1652, 1580, 1544, 1455, 1448, 1139, 802 cm^{-1}; MS, m/e (rel intensity) 149 (M^+, base), 148 (91.8), 134 (62.1), 122 (13.8), 109 (15.3), 106 (19.4). Anal. Calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.38; H, 7.68; N, 9.33.

2,5-Dihdyro-6-methoxy-2-(5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentyl)pyridine (19). Organolithium reagent **18** was generated by adding 2-(5-chloropentoxy)tetrahydro-2*H*-pyran (62.0 g, 0.3 mol) in THF (40 mL) over 2.5 h to Li (5.25 g, 0.75 mol) in THF (60 mL) at −20 °C. After an additional 2.75 h, the reaction was titrated with diphenylacetic acid, and the organolithium concentration was 1.0 mol (50%). In a separate flask 2-methoxypyridine (**6**) (16.35 g, 0.15 mol) and THF (50 mL) were cooled to −10 °C. The organolithium reagent **18** was added to the methoxypyridine in 1 portion. During the addition step, the internal temperature rose to 20 °C, and the reaction turned brown. After an additional 2 h, the reaction was quenched by pouring into H_2O (100 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, extracted with saturated aqueous NaCl, dried, and evaporated in vacuo to 62.8 g of crude product. This material (6 × 10g) was chromatographed on the Waters' Prep-500 (SiO_2; Skelly B/EtOAc, 9/1), and the product **19** (15.6 g, 37%) eluted at 3.2 column volumes. A bulb-to-bulb distillation (110–120 °C at 0.6 mm) of the compound in a Kugelrohr oven afforded analytically pure **19** (14.77 g, 35.0%): ^1H NMR ($CDCl_3$) δ 1.00–2.00 (m, 14 H, CH_2), 2.65 (d, H, J = 6.3 Hz, $OCCH_2$), 3.21–4.30 (m, 5 H, OCH_2, NCH), 3.68 (s, 3 H, OCH_3), 4.60 (brs, 1 H, OCHO), 5.80 (s, 2 H, CH=CH); IR (neat) 2941, 2859, 1693, 1659, 1438, 1356, 1225, 1201, 1138, 1121, 1078, 1035, 1023, 869, 699 cm^{-1}; MS, m/e (rel intensity) 281 (M^+, 1.4), 252 (1.0), 197 (20.6), 196 (47.1), 180 (34.5), 166 (9.0), 110 (100.0), 85 (60.9). Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.05; H, 9.91; N, 4.84.

2-Methoxy-6-(5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentyl)-pyridine (20). Cyclohexene (10 mL) and 10% Pd–C (1.2 g) were heated to reflux. Lactim **19** (12.0 g, 42.6 mmol), dissolved in cyclohexene (10 mL), was added dropwise over 1 h. After an additional 0.5 h, the reaction was cooled and filtered through Celite, and the Celite pad was washed with EtOAc (100 mL). The filtrate was evaporated to 12.0 g. This was chromatographed on a Waters' Prep-500 (SiO_2; Skelly B/EtOAc, 20/1), and the desired compound **20** (10.44 g) eluted at 2.2 column volumes. By bulb-to-bulb distillation (120–130 °C at 0.5 mm) in a Kugelrohr oven, an analytically pure sample of **20** (10.0 g, 84%) was prepared: ^1H NMR ($CDCl_3$) δ 1.00–2.00 (m, 12 H, CH_2), 2.70 (t, 2 H, J = 6.6 Hz, N=CCH_2), 3.21–4.00 (m, 4 H, OCH_2), 3.94 (s, 3 H, OCH_3), 4.56 (s, 1 H, OCHO), 6.58 (d, 1 H, J = 7.8 Hz), 6.74 (d, 1 H, J = 6.3 Hz), 7.50 (dd, 1 H, J = 6.3 Hz, J = 7.8 Hz, OC=CCH); IR (neat) 2943, 2860, 1599, 1580, 1467, 1441, 1414, 1296, 1271, 1266, 1137, 1120, 1078, 1035, 1023, 798 cm^{-1}; MS, m/e (rel intensity) 279 (M^+, 13.1), 250 (1.3), 224 (1.0), 195 (70.2), 194 (48.3), 179 (22.4), 178 (88.5), 136 (58.4), 123 (100.0), 85 (98.8). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.75; H, 9.12; N, 5.01.

5,6,7,8-Tetrahydro-5-methyl-2(1*H*)-quinolinone (21). Methoxypyridine **20** (5.0 g, 17.9 mmol) and 48% HBr (125 mL) were heated at reflux for 72 h. The reaction was filtered through glass wool to remove the tar, and the solvent was removed by distillation. The pot residue was made basic (pH 9) with 10% NaOH, and a white solid precipitated. The entire mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic portions were combined, dried, and evaporated to 2.8 g. The solid was decolorized with Norite in MeOH and then recrystallized from hexane/CH_2Cl_2 to afford 1.95 g of solid **21**. The mother liquor was passed down a silica gel column (MeOH/acetone), and the solid recrystallized. The solids were recombined to afford **21** (2.11 g, 72%): mp 171–172 °C; ^1H NMR ($CDCl_3$) δ 1.19 (d, 3 H, J = 7.0 Hz, CH_3), 1.20–2.05 (m, 4 H, CH_2), 2.50–2.85 (m, 3 H, $NCCH_2$ and $CHCH_3$), 6.44 (d, 1 H, J = 9.0 Hz, O=CCH), 7.37 (d, 1 H, J = 9.0 Hz, O=CC=CH), 12.85–13.26 (brs, 1 H, NH); ^{13}C NMR ($CDCl_3$) ppm 164.9 (s), 143.2 (s), 142.5 (d), 119.5 (s), 117.1 (d), 30.8 (t), 30.0 (d), 27.3 (t), 21.7 (q), 19.0 (t); IR (mull) 2954, 2913, 2867, 2856, 1866, 1681, 1628, 1556, 1467, 1458, 1378, 842 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 230.5 (8750), 314.0 (7650); MS, m/e (rel intensity) 163 (M^+, 33.5), 149 (11.0), 148 (100.0), 133 (5.6), 130 (6.6), 120 (10.2). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.20; H, 7.83; N, 8.27.

6-(5-Bromopentyl)-2(1*H*)-pyridinone (24). The methoxypyridine **20** (8.2 g, 29.3 mmol) and 48% HBr (160 mL) were heated at reflux for 1 h. The solution was filtered through glass wool to remove the tar, and the solvent (150 mL) was distilled off at 1 atm. The cooled residue was diluted with water (25 mL), and 10% NaOH was added to bring the pH to 6. The aqueous portion was extracted with $CHCl_3$ (3 × 100 mL), dried, and concentrated in vacuo to 6.44 g of an oil. This was further purified by flash chromatography (SiO_2, EtOAc) to yield 4.72 g (66%) of crude material. This was recrystallized from EtOAc to yield **24** (2.29 g), mp 79–80 °C. The mother liquors were chromatographed, and the product was recrystallized from EtOAc to yield an additional 810 mg of **24**, mp 65–75 °C. The overall yield of analytically pure **24** was 3.10 g (43.0%): ^1H NMR ($CDCl_3$) δ 1.25–2.05 (m, 6 H, CH_2), 2.56 (t, 2 H, J = 8.0 Hz, =CCH_2), 3.37 (t, 2 H, J = 7.0 Hz, $BrCH_2$), 6.00 (d, 1 H, J = 7.5 Hz, NC=CH), 6.35 (d, 1 H, J = 8.5 Hz, O=CCH), 7.32 (dd, J = 7.5 Hz, J = 8.5 Hz, O=CC=CH); IR (mull) 2944, 2926, 1649, 1628, 1466, 1157, 1003, 794 cm^{-1}; MS, m/e (rel intensity) 245 (M^+, 11.0), 243 (M^+, 11.3), 164 (33.2), 136 (8.4), 122 (10.0), 109 (100.0). Anal. Calcd for $C_{10}H_{14}BrNO$: C, 49.20; H, 5.78; N, 5.74. Found: C, 49.08; H, 5.95; N, 5.55.

7,8,9,10-Tetrahydropyrido[1,2-*a*]azepin-4(6*H*)-one (3). LDA was generated at room temperature over 25 min from *n*-BuLi (8.6 mL, 12 mmol, 1.4 M in hexane) and diisopropylamine (1.3 g, 13 mmol). THF (100 mL) was added, and the reaction was cooled to −78 °C. Pyridinone **24** (2.46 g, 10.1 mmol) dissolved in THF (40 mL) was added to the reaction over 21 min. The

reaction was warmed to reflux during 24 min and continued at reflux for 4.5 h. The reaction was quenched by pouring into saturated aqueous NH_4Cl. The aqueous portion was extracted with EtOAc (3 × 100 mL), dried, and evaporated in vacuo to give 1.91 g. This material was purified on the Waters' Prep-500 (SiO_2) by eluting with EtOAc/MeOH, 19/1 to yield **3** (800 mg, 49.1%): ^1H NMR ($CDCl_3$) δ 1.34 (dd, 0.5 H, J = 6.1 Hz, impurity), 1.60–2.05 (brs, 6 H, CH_2), 2.69–3.00 (m, 2 H, $=CCH_2$), 4.25–4.55 (m, 2 H, NCH_2), 6.05 (d, 1 H, J = 7.0 Hz, NC=CH), 6.48 (dd, 1 H, J = 9.0 Hz, O=CCH), 7.10–7.50 (m, 1 H, NC=CCH); ^{13}H NMR ($CDCl_3$) ppm 163.5, 152.4, 138.8, 117.7, 105.5, 43.4, 35.0, 28.7, 27.9, 27.2; IR (mull) 3450 (H_2O), 2927, 1656, 1650, 1577, 1550, 1465, 1438, 1429, 1136, 815, 808 cm^{-1}, exact mass calcd for $C_{10}H_{13}NO$ 163.0997, found 163.0993; MS, m/e (rel intensity) 163 (M^+, 100.0), 162 (50.4), 148 (35.6), 134 (94.3), 121 (14.9), 109 (35.4). Anal. Calcd for $C_{10}H_{13}NO \cdot 0.06H_2O$: C, 73.10; H, 8.05; N, 8.53. Found: C, 73.03; H, 8.12; N, 8.47. Anal. Found for H_2O: 0.65%.

2-(3,3-Diethoxypropyl)-2,5-dihydro-6-methoxypyridine (26). Organolithium reagent **25** was generated by cooling Li (7.0 g, 1.0 mol) and Et_2O (300 mL from a fresh can) to −10 °C (ice/acetone bath) and adding 3-chloro-1,1-diethoxypropane (66.0 g, 0.4 mol) dissolved in Et_2O (150 mL) over 3.25 h. The reaction was stirred an additional 1.25 h and then titrated with diphenylacetic acid in THF. The molarity was found to be 0.4 M in Et_2O (50%). In a separate flask, methoxypyridine (**6**) (21.8 g, 0.2 mol) and Et_2O (100 mL) were cooled to −10 °C, and the organolithium reagent **25** was added in 1 portion. The reaction was stirred overnight and then quenched by pouring into H_2O (200 mL). The aqueous fraction was extracted with EtOAc (2 × 100 mL). The organic fractions were combined, dried, and evaporated in vacuo to 62.5 g. Chromatography on a Waters' Prep-500 (SiO_2; Skelly B/EtOAc (5%)) afforded 33.3 g of material. This was bulb-to-bulb distilled in a Kugelrohr oven to yield **26** (31.03 g, 64.4%): bp 100–110 °C at 0.1 mm; ^1H NMR ($CDCl_3$) δ 1.23 (t, 6 H, J = 6.6 Hz, CH_3), 1.45–1.90 (m, 4 H, CH_2), 2.67 (d, 2 H, J = 6.3 Hz, $N=CCH_2$), 3.35–3.84 (m, 4 H, OCH_2), 3.69 (s, 3 H, OCH_3), 4.05–4.35 (m, 1 H, NCH), 4.46–4.65 (m, 1 H, OCHO), 5.80 (s, 2 H, CH=CH); IR (neat) 2975, 2931, 2877, 1693, 1659, 1438, 1357, 1226, 1126, 1064, 1012 cm^{-1}; MS, m/e (rel intensity) 241 (M^+, 0.3), 212 (33.7), 196 (74.8), 195 (37.3), 194 (39.1), 180 (29.9), 123 (54.7), 110 (100.0), 103 (73.9). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.62; H, 9.61; N, 5.79.

2-(3,3-Diethoxypropyl)-6-methoxypyridine (27). Cyclohexene (30 mL) and 10% Pd–C (3.0 g) were heated to reflux. Lactim **26** (25.0 g, 103 mmol) dissolved in cyclohexene (20 mL) was added to the reaction flask over 3.5 h. The reaction was continued overnight. The reaction was filtered through Celite, and the pad was washed with EtOAc (150 mL). The filtrate was concentrated in vacuo to 25.0 g. This was chromatographed on the Waters' Prep-500 (SiO_2; Skelly B/EtOAc (5%)) to afford 16.7 g. This was bulb-to-bulb distilled in a Kugelrohr oven to yield **27** (16.0 g, 65.0%): bp 70–90 °C at 0.1 mm; ^1H NMR ($CDCl_3$) δ 1.22 (t, 6 H, J = 6.3 Hz), 1.94–2.25 (m, 2 H, $OCHCH_2$), 2.76 (t, 2 H, $=CCH_2$), 3.40–3.85 (m, 4 H, OCH_2), 4.94 (s, 3 H, OCH_3), 4.58 (t, 1 H, J = 5.7 Hz, OCHO) 6.59 (d, 1 H, J = 8.7 Hz, NC=CH), 6.75 (d, 1 H, J = 7.5 Hz, OC=CH), 7.50 (m, 1 H, NCCCH); IR (neat) 2975, 2932, 2879, 1600, 1580, 1467, 1442, 1415, 1298, 1288, 1148, 1129, 1062, 1035, 802 cm^{-1}; MS, m/e (rel intensity) 239 (M^+, 5.9), 210 (26.1), 194 (100.0), 166 (27.5), 164 (56.4), 136 (32.0), 123 (41.7), 103 (89.2). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.27; H, 8.91; N, 5.72.

6-(3,3-Diethoxypropyl)-2(1*H*)-pyridinone (28). Sodium hydride (2.88 g, 60 mmol, 50% in oil), washed with hexane, and DMF (35 mL) were cooled in an ice bath, and an ethyl mercaptan/DMF mixture (2:1, v/v; 7.0 mL, 63 mmol) was added. An additional 35 mL of DMF was added to lessen foaming. The reaction was warmed to 40 °C, and the methoxypyridine **27** (12.0 g, 50 mmol) was added. The reaction was heated at reflux for 1 h. Water (25 mL) was added, and the solvents were removed under high vacuum. Additional water (50 mL) was added, and the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). This was dried and concentrated in vacuo to 13.6 g. The aqueous layer was brought to pH 8 with saturated aqueous NH_4Cl. The aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). This was dried and concentrated in vacuo to 4.75 g. Both organic fractions contained DMF. They were combined, and hexane was added where upon the DMF oiled out. The hexane soluble fractions were combined and evaporated to 9.16 g. This was put in a freezer, and 5.70 g of white solid was obtained, mp 67–68 °C. The DMF oiled out fractions were treated with water and then extracted with hexane (8 × 25 mL). Upon cooling, this afforded an additional 1.47 g of white solid, mp 67–68 °C. The total yield of **35** was 9.01 g (80.1%): ^1H NMR ($CDCl_3$) δ 1.21 (t, 6 H, J = 6.3 Hz), 1.85–2.20 (m, 2 H, $OCHCH_2$), 2.70 (t, 2 H, J = 7.2 Hz, $=CCH_2$), 3.32–3.82 (m, 4 H, CH_2O), 4.55 (t, 1 H, J = 6.0 Hz, OCHO), 6.11 (d, 1 H, J = 7.5 Hz, N=CCH), 6.45 (d, 1 H, J = 9.1 Hz, O=CCH), 7.42 (dd, 1 H, J = 9.0 Hz, chloroform obscures other coupling, O=CCH=CH); ^{13}C NMR ($CDCl_3$) ppm 166.0, 149.6, 141.6, 117.0, 105.1, 101.9, 61.4, 32.5, 28.5, 15.3; IR (neat) 2970, 2848, 1654, 1634, 1463, 1379, 1070, 1019, 933, 795 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 228 (7650), 305 (7750); MS, m/e (rel intensity) 225 (M^+, 7.8), 196 (2.6), 180 (9.5), 150 (8.9), 135 (77.7), 134 (100.0), 122 (18.7), 103 (33.6). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 64.09; H, 8.53; N, 6.15. (In subsequent workups, after all the solvent was removed from the reaction, water was added. This was extracted directly with hexane. The aqueous layer was then brought to a pH of 7 or 8 with 10% HCl and extracted with $CHCl_3$. The majority of product was in the $CHCl_3$ extract. Upon removal of solvent, the product was recrystallized from hexane.)

2,3-Dihydro-3-ethoxy-5(1*H*)-indolizinone (29). Pyridinone **28** (4.0 g, 17.7 mmol) was dissolved in toluene (250 mL), and a spatula tip of TsOH was added. The reaction was heated at reflux for 10 min. The reaction was extracted with 10% NaOH (10 mL). The organic layer was dried and concentrated in vacuo to give an oil which looked wet. The material was diluted in Et_2O, dried (Mg_2SO_4) again, and evaporated. The sample still looked wet. The material was distilled to afford **29** (2.24 g, 70.7%): bp 90–95 °C at 0.1 mm; ^1H NMR ($CDCl_3$) δ 1.19 (t, 3 H, J = 6.0 Hz, CH_3), 2.00–2.30 (m, 2 H, CH_2), 2.64–3.65 (m, 2 H, CH_2), 3.90 (q, 2 H, J = 6.0 Hz, OCH_2), 6.00–6.20 (m, 2 H, NCH, NC=CH), 6.41 (d, 1 H, J = 9.0 Hz, OCCH), 7.22–7.46 (m, 1 H, N=CC=CH); IR (neat) 3472, 2975, 1665, 1596, 1545, 1130, 1080, 791 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 231 (6600), 307 (6300); MS, m/e (rel intensity) 179 (17.9), 150 (2.7), 135 (95.7), 134 (100.0), 122 (12.3), 106 (13.4), 104 (11.6). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.96; H, 7.31; N, 7.76.

2,3-Dihydro-3-hydroxy-5(1*H*)-indolizinone (30). Pyridinone **28** (2.07 g, 9.2 mmol) was heated at reflux for 22 h in H_2O (50 mL), and some starting material remained. A spatula tip of Dowex resin 50w-8X was added, and the reaction was heated at reflux for 23 h. The material was filtered and concentrated in vacuo to 1.43 g. This was recrystallized from EtOAc to afford analytically pure **30** (0.95 g), mp 138–139 °C. The mother liquor was concentrated in vacuo to 0.36 g of **30**: mp 133–139 °C. The total yield of the reaction was 1.31 g (94.3%) of **30**: ^1H NMR ($CDCl_3$) δ 1.85–2.55 (m, 4 H, CH_2), 5.35 (brs, 1 H, OH), 5.95–6.25 (m, 2 H, NCH, NC=CH), 6.37 (d, 1 H, J = 9.2 Hz, OCCH), 7.40 (dd, 1 H, J = 9.1 Hz, J = 9.2 Hz, NC=CCH); IR (mull) 3189, 2956, 2925, 1649, 1571, 1564, 1454, 1439, 1172, 1071, 916 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 231 (7300), 305 (7000); MS, m/e (rel intensity) 151 (M^+, 97.6), 150 (18.9), 123 (70.0), 122 (100.0), 104 (20.1), 95 (16.5), 94 (17.7). Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.57; H, 5.99; N, 9.25.

6-Butyl-3,6-dihydro-2(1*H*)-pyridinone (32). Pyridinone (**31**) (3.8 g, 40 mmol) was dissolved in THF (60 mL) and cooled to −10 °C (ice/acetone bath). *n*-Butyllithium (60 mL, 96 mmol, 1.6 M in hexane) was added in 1 portion, and the internal temperature rose to 20 °C. The reaction was brought back to 0 °C and then warmed to room temperature. The reaction was quenched by pouring the mixture over ice (50 g). The aqueous layer was extracted with Et_2O (3 × 50 mL). The organic portions were combined, dried, and evaporated in vacuo to afford 4.78 g of crude material. This was chromatographed on the Waters' Prep-500 (SiO_2; CH_2Cl_2/EtOAc, 1/1) to yield 3.98 g of product. This was purified for an analytical sample by bulb-to-bulb distillation in a Kugelrohr oven affording **32** (3.36 g, 54.8%): bp 90–100 °C at 0.01 mm; ^1H NMR ($CDCl_3$) δ 0.75–1.06 (m, 3 H, CH_3), 1.10–1.70 (m, 6 H, CH_2), 2.80–3.00 (m, 2 H, $OCCH_2$), 3.9–4.2 (m, 1 H, NCH), 5.72 (s, 2 H, CH=CH), 6.98 (brs, 1 H, NH); ^{13}C NMR ($CDCl_3$) ppm 170.1 (s), 125.7 (d), 121.7 (d), 53.9 (d), 36.9 (t), 31.3 (t), 22.6 (t), 14.0 (q); IR (neat) 3209, 2957, 2931, 1681, 1664, 1407, 1336

cm^{-1}; MS, m/e (rel intensity) 153 (M^+, 8.0), 124 (3.3), 111 (11.5), 97 (25.0), 96 (100.0), 95 (22.4). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.54; H, 9.88; N, 9.11.

3,6-Dihydro-6-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)-propyl)-2(1*H*)-pyridinone (33). Organolithium reagent **8** was generated by adding 2-(3-chloropropoxy)tetrahydro-2*H*-pyran (116.74 g, 0.65 mol) in Et_2O (100 mL) over 3.5 h to Li (11.2 g 1.6 mol) in Et_2O (150 mL) at -10 °C. After an additional 1 h, the reaction was titrated with diphenylacetic acid, and the organolithium concentration was 1.25 mol (57%). In a separate flask pyridinone (**31**) (17.8 g, 0.187 mol) and THF (100 mL) were cooled to -78 °C. The organolithium reagent **8** was added to the pyridinone in 1 portion. The reaction was warmed to room temperature and stirred overnight. The deep orange solution was quenched by pouring over ice (400 g). The aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layers were combined, extracted with saturated aqueous NaCl, dried, and evaporated in vacuo to 72.04 g of crude product. Under full vacuum (0.1 mm, 25-30 °C), 2-propoxytetrahydro-2*H*-pyran (33.24 g, 35%) was distilled from the product. The remaining material was chromatographed on the Waters' Prep-500 (SiO_2; CH_2Cl_2/MeOH (5%)) and 4 major fractions were isolated. Fraction 1 eluted at 1.5 column volumes and contained product (4.3 g). Fraction 2 eluted at 2.5 column volumes and contained a THP derivative (11.0 g). Fraction 3 eluted at 4.5 column volumes and contained a THP derivative with nitrogen in the moleucle (4.5 g). Fraction 4 eluted at >9 column volumes, when eluted with methanol, and contained material (16.0 g) which was not identifiable by NMR.

Fraction 1 was rechromatographed under similar conditions and pure **33** (2.09 g, 4.7%) was isolate: ^1H NMR ($CDCl_3$) δ 1.38-2.05 (m, 10 H, CH_2), 2.89-3.05 (m, 2 H, $OCCH_2$), 3.29-4.34 (m, 5 H, OCH_2, NCH), 4.65 (s, 1 H, OCHO), 5.80 (s, 2 H, CH=CH), 6.70 (brs, 1 H, NH); IR (neat) 3211, 3095, 3044, 2942, 1680, 1664, 1136, 1120, 1076, 1064, 1034, 1023 cm^{-1}; MS, m/e (rel intensity) 239 (M^+, 1.2), 191 (2.4), 184 (2.2), 155 (44.3), 154 (15.4), 138 (13.3), 121 (6.1), 96 (100.0), 85 (52.4). Anal. Calcd for $C_{13}H_{21}NO_3$ and 0.6% H_2O: C, 64.85; H, 8.86; N, 5.81. Found: C, 64.81; H, 9.24; N, 5.90.

Fraction 2 was rechromatographed under similar conditions, and 7.37 g of purer material was isolated: ^1H NMR ($CDCl_3$) δ 1.30-2.00 (m, 14 H), 2.68 (s, 1 H), 3.20-4.00 (m, 6 H), 4.60 (s, 1 H); ^{13}C NMR ($CDCl_3$) ppm 99.0 (d), 71.5 (d), 71.4 (d), 67.9 (t), 62.6 (t), 62.5 (t), 37.0 (t), 34.8 (t), 32.6 (t), 30.7 (t), 26.3 (t), 26.1 (t), 25.4 (t), 21.9 (t), 19.6 (t); IR (neat) 3386, 2940, 2867, 1643, 1353, 1200, 1138, 1121, 1077, 1060, 1033, 1024, 989, 974, 907, 869 cm^{-1}; ash, 0.15%; water content, 0.25%. Anal. Found for C and H: C, 62.06; H, 10.21. This material resembles the THP derivative of 1,6-hexanediol, prepared independently,[27] by ^1H NMR, but by ^{13}C NMR and TLC the material is clearly different.

Fraction 3 was rechromatographed under similar conditions, and 640 mg of purer material was isolated: ^1H NMR ($CDCl_3$) δ 1.35-2.20 (m, 10 H), 2.35-2.80 (m, 3 H), 3.40-4.20 (m, 5 H), 4.65 (s, 1 H), 6.00 (d, 1 H, J = 6.6 Hz), 7.21 (d, 1 H, J = 6.6 Hz); IR (neat) 3412, 3276, 3133, 3057, 3025, 2939, 2862, 1642, 1627, 1574, 1154, 1137, 1120, 1074, 1065, 1034, 1021, 1004, 987 cm^{-1}; MS, m/e (rel intensity) 239 (M^+, 21.8), 222 (15.9), 208 (9.9), 195 (34.5), 180 (14.5), 167 (82.5), 148 (28.7), 127 (21.6), 85 (100.0). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 66.56; H. 9.25; N. 4.28. This material was thought to be the α,β-unsaturated isomer of **33** due to MS and IR data. However, the elemental analysis and NMR were not consistent with this structure.

Acknowledgment. We wish to especially thank B. Vernon Cheney, of The Upjohn Company's Computational Chemistry Support Unit, for performing the ab initio calculations and for helpful discussions in this area. We are grateful to The Upjohn Company's Physical and Analytical Chemistry Department for elemental analyses, mass spectra, and IR spectroscopy.

Registry No. **1**, 101773-62-0; **2**, 50720-19-9; **3**, 101773-63-1; **6**, 1628-89-3; **7**, 101773-64-2; **8**, 92785-46-1; **9**, 101773-65-3; **10**, 101773-66-4; **11**, 101773-67-5; **12**, 101773-68-6; **13**, 101773-69-7; **14**, 85560-51-6; **15**, 101773-70-0; **16**, 101773-71-1; **17**, 101773-72-2; **18**, 101773-73-3; **19**, 101773-74-4; **20**, 101773-75-5; **21**, 101773-76-6; **24**, 101773-77-7; **25**, 101773-85-7; **26**, 101773-78-8; **27**, 101773-79-9; **28**, 101773-80-2; **29**, 101773-81-3; **30**, 101773-82-4; **31**, 142-08-5; **32**, 101773-83-5; **33**, 101773-84-6; *n*-BuLi, 109-72-8; 2-(3-chloropropoxy)tetrahydro-2*H*-pyran, 42330-88-1; 2-(5-chloropentoxy)-tetrahydro-2*H*-pyran, 13129-60-7; 3-chloro-1,1-diethoxypropane, 35573-93-4.

2-Benzazepines. 9.[1] Synthesis and Chemistry of 3*H*-2-Benzazepine and Pyrimido[4,5-*d*][2]benzazepine Derivatives

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Received October 15, 1985

The synthesis of 8-chloro-1-phenyl-3*H*-2-benzazepine analogues **6a-c** and their dihydro derivatives **9a-c** from the corresponding alkynes **1a-c** is discussed. The bromination followed by dehydrobromination of **6a-c** led to the formation of the corresponding 5-bromo-1-phenyl-3*H*-2-benzazepines **14a-c** which were useful synthetic intermediates in the synthesis of more complex 2-benzazepine derivatives. An example of the utility for the vinyl bromides **14a-c** in the synthesis of heterocyclic ring systems is presented. The palladium-catalyzed carbalkoxylation of **14a-c** led to a facile synthesis of pyrimido[4,5-*d*][2]benzazepine derivatives.

As part of a program aimed at the discovery of novel agents active on the central nervous system, syntheses of 2-benzazepine derivatives have been investigated in these laboratories[2,3] and elsewhere.[4] Both groups have employed the use of organometallic chemistry as the key step to produce efficient and practical syntheses of the 2-benzazepine ring system. The use of palladium-catalyzed coupling of substituted *o*-iodobenzophenones with *N*-propargylphthalimide provided a facile approach to 2-benzazepin-4-ones and -5-ones[5] by hydration of the aryl-

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