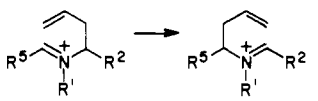
Carbon-Carbon Bond Formation under Mild Conditions via Tandem Cationic Aza-Cope Rearrangement-Mannich Reactions. A Convenient Synthesis of Polysubstituted Pyrrolidines[1a]

Larry E. Overman,* Masa-aki Kakimoto, Mark E. Okazaki, and G. Patrick Meier[1b]

Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received March 21, 1983*

Abstract: The reaction of aldehydes (or ketones) with 2-alkoxy(or hydroxy)-3-alkenamines achieves a general and high-yielding synthesis of polysubstituted 3-acylpyrrolidines (eq 5-9). This tandem cationic aza-Cope rearrangement-Mannich cyclization reaction (eq 1) occurs under mild conditions (temperature and pH), which are compatible with a variety of delicate functionality. Specifically, the reaction of 15 2-alkoxy(or hydroxy)-3-alkenamines with a variety of aldehydes (or ketones) to provide 26 pyrrolidines regioselectively substituted at N-1, C-4, and C-5 with alkyl and aryl moieties and at C-3 with formyl, acetyl, or acetal substituents is described. Three methods for preparing the starting 2-alkoxy(or hydroxy)-3-alkenamines (eq 2-4) are also detailed.

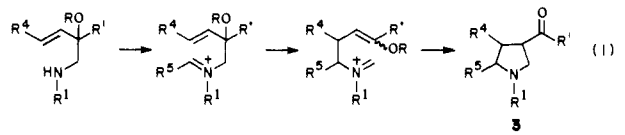
The development of versatile methods for forming carbon-carbon bonds under mild conditions is a central objective of synthetic organic chemistry. Several years ago,[2] the cationic aza-Cope rearrangement (2-azonia[3,3]-sigmatropic rearrangement,[3] e.g., **1** → **2**) attracted our attention as a particularly



1 **2**

appealing vehicle for developing new transformations of this type.[4,5] Three features of this rearrangement were particularly attractive: (a) this reorganization occurs under remarkably mild conditions, typically at (or slightly above) room temperature,[4,5] (b) a variety of methods should be available for preparing the starting iminium ions,[6] and (c) [3,3]-sigmatropic rearrangements typically occur with a high level of stereocontrol.[7,8] To be of use in synthesis, a cationic aza-Cope rearrangement must be essentially irreversible in the desired direction, and prior to our efforts nearly all applications had been in benzoheterocyclic systems[5,9] where the rearrangement was driven by aryl conjugation of the product iminium ion (**1** → **2**, R^2 = aryl).[10]

New methods for controlling the equilibrium position of cationic aza-Cope rearrangements would greatly increase applications of this transformation in synthesis. Thus, our initial objective in this area was the development of new procedures for "directing" this rearrangement such that it would be irreversible in the desired direction. In this paper we present the details of our efforts to elaborate an intramolecular trapping procedure to achieve this aim.[2,11] This procedure allows, for the first time,[12] the "less stable" iminium ion isomer to be captured in good yield. Our strategy has been to incorporate a nucleophilic substituent in such a fashion that it is latent in the starting iminium ion, but upon [3,3]-sigmatropic rearrangement is unleashed and irreversibly captures the desired rearranged iminium ion (eq 1).[12] This tandem cationic



(1)

3

aza-Cope rearrangement-Mannich cyclization sequence provides a variety of substituted 3-acylpyrrolidines **3** from the reaction of 2-alkoxy(or hydroxy)-3-alkenamines with aldehydes or ketones (eq 1).

The preparation of pyrrolidines has received extensive attention from synthesis chemists in recent years,[13-18] in part due to the

(1) (a) Part 11 in the series Synthesis Applications of Aza-Cope Rearrangements. For part 10, see: Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685-2690. (b) Postdoctoral Fellow, National Institute of Health (GM 08155), 1981-1983.

(2) For preliminary reports of portions of the research described in this paper, see: (a) Overman, L. E.; Kakimoto, M. *J. am. Chem. Soc.* **1979**, *101*, 1310-1312. (b) Overman, L. E.; Kakimoto, M.; Okawara, M. *Tetrahedron Lett.* **1979**, 4041-4044.

(3) For this notation of [3,3]-sigmatropic rearrangements, see: Vögtle, F.; Goldschmitt, E. *Chem. Ber.* **1976**, *109*, 1-40.

(4) This reaction was first described in 1950 by Geissman: Horowitz, R. M.; Geissman, T. A. *J. Am. Chem. Soc.* **1950**, *72*, 1518-1522.

(5) Aspects of this rearrangement have been reviewed: Winterfeldt, E. *Fortschr. Chem. Forsch.* **1971**, *16*, 75-102. Heimgartner, H.; Hansen, H.-J.; Schmid, H. In "Iminium Salts in Organic Chemistry"; Böhme, H., Viehe, H. G., Eds.; Wiley: New York, 1979; Part 2, pp 655-732.

(6) For reviews, see: Böhme, H.; Haake, M. In "Iminium Salts in Organic Chemistry"; Böhme, H., Viehe, H. G., Eds.; Wiley: New York, 1976; Part 1, pp 108-149. Paukstelis, J. V. In "Enamines"; Cook, A. G., Ed.; Marcel Dekker: New York, 1969; Chapter 5. Hellman, H.; Opitz, G. "α-Aminoalkylierung"; Verlag-Chemie: Weinheim, 1960.

(7) Cf.: Hansen, H.-J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959-1969.

(8) Stereochemical features of cationic aza-Cope rearrangements have not yet been detailed, although studies of this type are underway in our laboratory. The stereochemistry of some aza- and diaza-Cope rearrangements has been explored: Brombach, D.; Vögtle, F. *Synthesis* **1977**, 800-802. Reference 3.

(9) (a) Knabe, J.; Rupenthal, N. *Arch. Pharm. (Weinheim, Ger.)* **1966**, *299*, 159-165; *Chem. Abstr.* **1966**, *64*, 19553*h*. (b) Winterfeldt, E.; Franzischka, W. *Chem. Ber.* **1967**, *100*, 3801-3807. (c) Winterfeldt, E.; Franzischka, W. *Ibid.* **1968**, *101*, 2938-2946. (d) Knabe, J.; Höltje, H.-D. *Tetrahedron Lett.* **1969**, 2107-2108. (e) Geisel, M.; Grob, C. A.; Wohl, R. A. *Helv. Chim. Acta.* **1969**, *52*, 2206-2215. (f) Marshall, J. A.; Babler, J. H. *J. Org. Chem.* **1969**, *34*, 4186-4188. (g) Rischke; Wilcock, J. D.; Winterfeldt, E. *Chem. Ber.* **1973**, *106*, 3106-3118. (h) Grob, C. A.; Kunz, W.; Marbet, P. R. *Tetrahedron Lett.* **1975**, 2613-2616. (i) Ahmad, V. V.; Feuerherd, K. H.; Winterfeldt, E. *Chem. Ber.* **1977**, *110*, 3624-3635.

(10) For exceptions to this statement, see ref 9e,f,h.

(11) For our preliminary efforts to "direct" this rearrangement via irreversible hydrolysis, see: Overman, L. E.; Yokomatsu, T. *J. Org. Chem.* **1980**, *45*, 5229-5230.

(12) Intramolecular transformations of iminium ions produced in *irreversible* cationic aza-Cope rearrangements have been reported by Winterfeldt and co-workers, see ref 9g.

(13) Aspects of pyrrolidine synthesis have been reviewed, see: (a) Brown, R. C.; Ingall, A. H. In "General and Synthetic Methods"; Pattenden, G., Ed.; Chemical Society: London, 1981; Vol. 5, Chapter 8 pp 336-344, and earlier volumes of this series. (b) Pinder, A. R. In "The Alkaloids"; Grundon, M. F., Ed.; Chemical Society: London, 1982; Vol. 12, Chapter 2 pp 29-35, and earlier volumes of this series. (c) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 776-486.

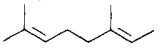
0002-7863/83/1505-6622$01.50/0

Table I. Preparation of 2-Methoxy(or hydroxy)-3-alkenamines

amino alcohol	R	aminolysis conditions: temp, °C	aminolysis conditions: time, h	yield, %	bp, °C (mm)	methyl ether	yield, %	bp, °C (mm)	BF_4 salt mp, °C
4	Pr	48	6	92	78–80 (18)[a]	**12**	86	60–70 (14)	168–170
5	cyclohexyl	110	3[b]	83	109–110 (3)	**13**	87	96–97 (2)	
6	CH_2Ph	110	3[b]	58	103–107 (6)	**14**	87	102–104 (8)	238–240 (dec)
7	H	60	24[c,d]	62	72–75 (17)[e]	**15**	62	80–84 (20)	
8	Me	25	12[d,f]	67	68–70 (18)				
9	Ph	0	24[g]	83	50–75 (0.3)[h]				
10	2-chlorophenyl	67	1[g]	70	100–130 (0.1)[h]				
11	4-fluorophenyl	67	1[g]	73	110–125 (0.1)[h]				

[a] Lit.[21b] bp 82–83 °C (20mm). [b] The reactants were maintained for 6 h at room temperature before being heated in a sealed pressure bottle at the indicated temperature. [c] Aqueous NH_3 (28%) and a sealed pressure bottle were employed. [d] The reaction mixture was saturated with NaOH before extractive workup. [e] Lit.[21a] bp 71–88 °C (62 mm). [f] Aqueous $MeNH_2$ (40%) was employed. [g] The lithium salt (from BuLi) of the amine and THF as solvent were employed. [h] Bulb-to-bulb distillation, not a true boiling point.

Table II. Preparation of 3-Acetylpyrrolidines according to Eq 5

entry	3-acetyl-pyrrolidine	R^1	R^5	OR	reaction conditions[a]: procedure	reaction conditions[a]: temp, °C	reaction conditions[a]: time, h	yield, %
1	**23**	CH_2Ph	H	OH	B	80	10	89
2	**24**	Pr	H	OH	B[b]	79	24	85
3	**25**	Ph	H	OH	B	110	1.5	66
4	**26**	2-chlorophenyl	H	OH	B	110	1	74
5	**27**	Pr	Ph	OMe	A	80	5	87
6	**27**	Pr	Ph	OMe	B	80	24	85
7	**28**	CH_2Ph	Ph	OMe	B	80	24	54
8	**28**	CH_2Ph	Ph	OMe	B	80	72	89
9	**28**	CH_2Ph	Ph	OH	B	24	24	94
10	**29**	Ph	Ph	OH	B	110	28	56
11	**30**	Pr	n-C_6H_{13}	OMe	A	80	24	97
12	**31**	cyclohexyl	n-C_6H_{13}	OMe	A	80	24	95
13	**32**	4-fluorophenyl	n-C_5H_{11}	OH	B	110	19	83
14	**33**	Pr		OMe	A	80	24	90
15	**34**	Pr	cyclohexyl	OMe	A	80	24	95
16	**34**	Pr	cyclohexyl	OMe	B	80	24	84
17	**34**	Pr	cyclohexyl	OMe	B[c]	80	24	90
18	**35**	CH_2Ph		OMe	B	80	24	57
19	**35**	CH_2Ph		OH	B	80	24	95
20	**36**	CH_3		OH	B	80	24	84

[a] Procedure A: A solution of the amine tetrafluoroborate salt (0.6 M) and the aldehyde (1.1 equiv) were heated at reflux in benzene (80 °C) or toluene (110 °C) for the indicated time. Procedure B: The same as A except that the free amine plus 0.9 equiv of camphorsulfonic acid were used. 24 h was often taken as a standard time and many of the reactions were done much sooner. [b] EtOH was the solvent. [c] 0.1 equiv of RSO_3H was employed.

interesting biological activities exhibited by several polysubstituted pyrrolidines.[13b,19] Particularly useful general approaches to these heterocycles are the elegant intramolecular ene strategy pioneered by Oppolzer,[13c,14] 1,3-dipolar cycloaddition reactions of azomethine ylides,[15] and electrophile-promoted cyclizations of unsaturated amine derivatives.[16] The tandem cationic aza-Cope–Mannich cyclization synthesis detailed herein provides a powerful new and general method for the preparation of polysubstituted pyrrolidines.

(14) For recent examples of the pyrrolidine syntheses via intramolecular ene reactions, see: Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978–4979. Oppolzer, W.; Andres, H. *Helv. Chim. Acta* **1979**, *62*, 2282–2284. Oppolzer, W.; Robiano, C.; Bättig, K. *Ibid.* **1980**, *63*, 2015–2018.

(15) For recent examples of pyrrolidine synthesis via 1,3-dipolar cycloaddition reactions, see, inter alia: Livinghouse, T.; Smith, R. *J. Chem. Soc., Chem. Commun.* **1983**, 210–211. Beugelmans, R.; Negron, G.; Roussi, G. *Ibid.* **1983**, 31–32. Grigg, R.; Kemp, J.; Malone, J.; Tangthongkum, A. *Ibid.* **1980**, 648–649. Kraus, G. A.; Nagy, J. O. *Tetrahedron Lett.* **1981**, *22*, 3397–3400. Fouchet, B.; Joucla, M.; Hamelin, J. *Ibid.* **1981**, *22*, 3397–3400.

(16) For recent examples of pyrrolidine synthesis via cyclizations of amino alkenes, see, inter alia: Webb, R. B., II; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 1357–1360. Takano, S.; Kasahara, C.; Ogasawara, K. *Heterocycles* **1982**, *19*, 1443–1447. Danishefsky, S.; Taniyama, E.; Webb, R. R., II. *Tetrahedron Lett.* **1983**, *24*, 11–14. Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920–3922. Clive, D. L. J.; Farina, V.; Singh, A. *J. Org. Chem.* **1980**, *45*, 2120–2126.

(17) An interesting Diels–Alder approach to substituted pyrrolidines was recently exploited to prepare (−)-domoic acid, see: Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511–3513.

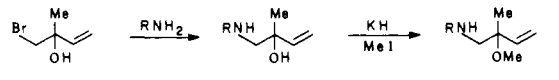
(18) Other recent approaches to pyrrolidines include: (a) Jones, T. H.; Frank, J. B.; Blum, M. S.; Fales, H. M. *Tetrahedron Lett.* **1980**, 789–792. (b) Schmitz, E.; Sonnenschein, H.; Gründemann, C. *J. Prakt. Chem.* **1980**, *322*, 261–265. (c) Labouta, I. M.; Jacobsen, P.; Thorbek, P.; Krogsgaard-Larsen, P.; Hjeds, H. *Acta Chem. Scand., Ser. B* **1982**, *B36*, 2–7. (d) Achini, R. *Helv. Chim. Acta* **1981**, *64*, 2203–2208. (e) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron Lett.* **1979**, 1031–1034. (f) Schumacher, D. P.; Hall, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 6076–6080. (g) Tiner-Harding, T.; Ullrich, J. W.; Chiu, F.-T.; Chen, S.-F.; Mariano, P. S. *J. Org. Chem.* **1982**, *47*, 3362–3364.

(19) For example, α-kainic acid[14a] and domoic acid[17] exhibit potent neurotransmitting activity in the central nervous system. Various 2,5-dialkylpyrrolidines are important ingredients of the poison gland products of several ant species,[18a,b,e] while significant biological activities have been reported for many other "nonnatural" pyrrolidines.[18c,d] Leading references may be found in the referenced synthetic papers.

This synthesis should be of particular significance for the preparation of pyrrolidines with aryl or heteroaryl substitution at N-1 and C-5.

Results and Discussion

Preparation of 2-Methoxy(or hydroxy)-3-alkenamines. The reaction of isoprene oxide (formed in situ from 1-bromo-2-methyl-3-buten-2-ol[20]) with an excess of a primary aliphatic amine (eq 2)[21] provides 2-methyl-1-(alkylamino)-3-buten-2-ols **4–8** in



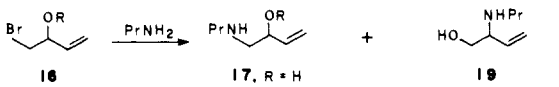
(2)

4, R = Pr; **5**, R = cyclohexyl; **6**, R = CH_2Ph; **7**, R = H; **8**, R = Me; **9**, R = Ph; **10**, R = 2-Cl-phenyl; **11**, R = 4-F-phenyl; **12**, R = Pr; **13**, R = cyclohexyl; **14**, R = CH_2Ph; **15**, R = H

large scale and in good yields (Table I). That a single regioisomer was produced in this reaction was apparent from the ^1H NMR spectrum, which showed diagnostic[22] signals for the C-1 methylene hydrogens at 2.5–2.8 ppm[23] and no signals at 3.4–3.6 ppm for CH_2OH.

Although aniline did not react with isoprene oxide at 110 °C (sealed tube, 16 h), 2 equiv of lithium anilide reacted cleanly with 1-bromo-2-methyl-3-buten-2-ol in tetrahydrofuran (THF, 0 °C → room temperature) to give amino alcohol **9** in 83% yield. The 2-chlorophenyl and 4-fluorophenyl derivatives **10** and **11** were prepared similarly, although this reaction failed with 3- and 4-nitroaniline. Selective O-methylation was achieved by reaction of the potassium salts (from 1 equiv of KH) of **4–7** with 1 equiv of MeI in THF (4 °C → room temperature) to afford amino ethers **12–15** in good yields.

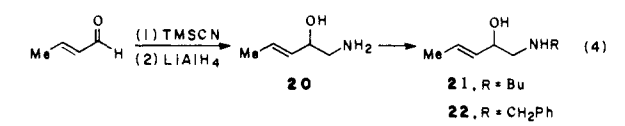
The corresponding 1-amino-3-buten-2-ols could not be cleanly prepared from the aminolysis of butadiene oxide with primary amines. For example, the reaction of propylamine with 1-bromo-3-buten-2-ol (**16**, R = H) at 25 °C gave a 2.6:1 mixture of **17** and **19**.[24-26] However, the reaction of readily available[27] 4-bromo-3-methoxy-1-butene (**16**, R = Me) with propylamine occurred cleanly to give amino ether **18** in 72% yield (eq 3).



(3)

16; **17**, R = H; **18**, R = Me; **19**

Lithium aluminum hydride reduction of vinyl trimethylsilyl cyanohydrins also provides access to 1-amino-3-alken-2-ols. Thus, the general method of Evans[28] was convenient for preparing **20** from *trans*-crotonaldehyde (eq 4). Reductive amination of **20**

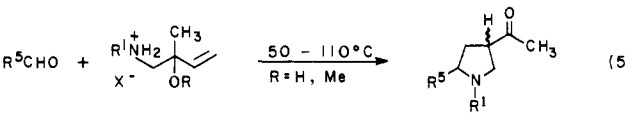


(4)

20; **21**, R = Bu; **22**, R = CH_2Ph

with butanal or hydride reduction of the benzamide derivative gave secondary amines **21** and **22** in good overall yields.[29]

3-Acetylpyrrolidines from the Reaction of 2-Methoxy(or hydroxy)-2-methyl-3-butenamines with Aldehydes. A variety of 1- and 5-substituted 3-acetylpyrrolidines[30] (see Table II) have been prepared, typically in excellent yield, by the one-step reaction illustrated in eq 5. Either the crystalline amine tetrafluoroborate



(5)

23–36

salt (procedure A) or the free amine and 0.9 equiv of camphorsulfonic acid (procedure B) was employed. In one case (entry 17), we demonstrated that the reaction could be successfully conducted with a catalytic amount (0.1 equiv) of acid. A variety of solvents (benzene, toluene, $CHCl_3$, CH_2Cl_2, and ethanol) and reaction temperatures (25–110 °C) have been successfully employed, although most of the reactions summarized in Table II were conducted in refluxing benzene or toluene. The 5-substituted acetylpyrrolidines were always obtained as mixtures of acetyl epimers (typically 1:1 to 3:1 mixtures depending upon reaction conditions).

This pyrrolidine synthesis succeeds with a variety of aliphatic, aromatic, and heteroaromatic aldehydes. The critical oxygen substituent of the homoallylic amine component can be either a methoxyl or hydroxyl group. In cases where a direct comparison can be made (entries 7–9, 18, and 19), the reaction was slightly faster and, in the case of furfural, higher yielding when the amino alcohol was employed. The reaction was slower with aromatic amines (entries 10–13), and the preparation of 3-acetyl-1,5-diphenylpyrrolidine (**29**) from the reaction of aniline **9** and benzaldehyde (a relatively unreactive aldehyde was accomplished in somewhat lower yield (entry 10). Particularly significant are (a) the absence of products resulting from diene cyclization when citral (entry 14) was employed, (b) the high yields obtained with acid-sensitive furfural (entry 19), (c) the convenient preparation of 1-arylpyrrolidines (entries 3, 4, 10, and 13), which are generally difficult to prepare by other pyrrolidine syntheses,[13] and (d) the preparation of 3-acetylnicotine (entry 20) by this procedure.

The structural assignments for acetylpyrrolidines **23–36** followed from a combination of spectroscopic, analytical, and chemical evidence. Particularly diagnostic was ^{13}C NMR data. For example, **23** showed signals at 53.9 (C-2), 50.5 (C-3), 26.6 (C-4), and 55.7 (C-5) ppm, which are at predicted positions using standard shift parameters for an acetyl group[31] and 1-methylpyrrolidine (C-2, 55.7; C-3, 23.7)[32] as a reference. Characteristic signals for C-5 of the 5-substituted acetylpyrrolidines were observed at 60–70 ppm (see Table IV, supplementary material). The mass spectra of the substituted acetylpyrrolidines were also characteristic and showed important fragmentations resulting from α-cleavage.[33] For example, **27** showed prominent ions at *m/e*

(20) Petrov, A. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1943**, *13*, 481–490; *Chem. Abstr.* **1944**, *38*, 3248[3]. Dalton, D. R.; Davis, R. M. *Tetrahedron Lett.* **1972**, 1057–1060.

(21) This general transformation had been described previously, see: (a) Mishra, A.; Rice, S. N.; Lwowski, W. *J. Org. Chem.* **1968**, *33*, 481–486. (b) Al'bitskaya, V. M.; Petrov, A. A. *Zh. Obshch. Khim.* **1958**, *28*, 901–904; *Chem. Abstr.* **1958**, *52*, 17098*f*. (c) Pudovik, A. N.; Aladzheva, I. M. *Ibid.* **1958**, *28*, 2497–2500; *Chem. Abstr.* **1959**, *53*, 3034*i*.

(22) Cf.: Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon: Oxford, 1969.

(23) These hydrogens were observed at 3.3–3.7 ppm in the N-acetylated derivative.

(24) This result is not surprising, since Etlinger[25] many years ago showed that the reaction of ammonia with butadiene oxide gave a mixture of amino alcohol products. Although the similar reaction with primary and secondary amines has been reported to give 1-amino-3-buten-2-ols,[26] these products are surely mixtures of regioisomers.

(25) Etlinger, M. G. *J. Am. Chem. Soc.* **1957**, *79*, 4792–4796.

(26) Petrov, A. A.; Al'bitskaya, V. M. *Zh. Obshch. Khim.* **1956**, *26*, 1907–1909; *Chem. Abstr.* **1957**, *51*, 4943*f*. Blocke, F. F.; Biel, J. H. *J. Am. Chem. Soc.* **1957**, *79*, 5508–5512.

(27) (a) Degraw, J. I.; Goodman, L.; Baker, B. R. *J. Org. Chem.* **1961**, *26*, 1156–1161. (b) Petrov, A. *J. Gen. Chem. USSR (Engl. Transl.)* **1938**, *8*, 208; *Chem. Abstr.* **1938**, *32*, 5370[6].

(28) (a) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55–56. (b) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914–917.

(29) 2-Alkoxy(or hydroxy)-3-alkenamines are also available from the reaction of α-aminoketones and α-aminoaldehydes with vinyl organometallics, see, inter alia: (a) Tiollais, R.; Lattes, H. B.; Bouget, H.; Huet, J.; Bonnic, J. *C. R. Seances Acad. Sci., Ser. C* **1968**, *267*, 1350–1351. (b) Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579–81. (c) The following paper in this issue.

(30) These compounds would be named in *Chemical Abstracts* as 1-(1,5-disubstituted-3-pyrrolidinyl)ethanones.

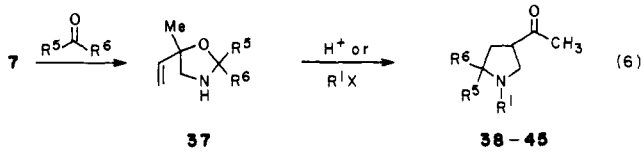
(31) Breitmaier, E.; Voelter, W. "^{13}C NMR Spectroscopy"; Verlag Chemie: Weinheim, 1974; pp 148–154.

(32) Cf.: Wenkert, E.; Bindra, J. S.; Chang, C.-J.; Cochran, D. W.; Schell, F. M. *Acc. Chem. Res.* **1974**, *7*, 46–51.

(33) Cf.: Budzikiewicz, H.; Djerassi, C.; Williams, D. H. "Mass Spectrometry of Organic Compounds"; Holden Day: San Francisco, 1967; pp 309–313.

202 ($M - C_2H_5$) and 154 ($M - C_6H_5$). That the substituent was at C-5 rather than C-2 was unambiguously established for **34** by N-benzylation and base-promoted retro-Michael fragmentation[34] to give a single enone that showed characteristic terminal methylene signals[22] at 5.7 and 6.0 ppm in the ^1H NMR spectra.

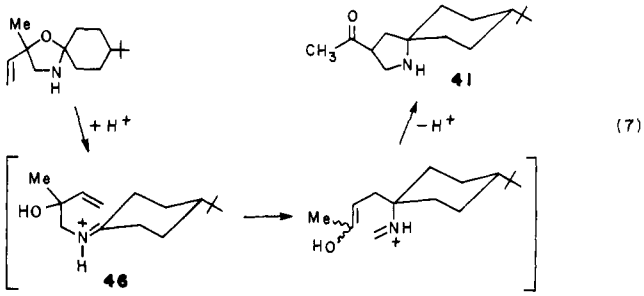
3-Acetylpyrrolidines from Rearrangement of 5-Methyl-5-vinyloxazolidines. The one-step pyrrolidine synthesis of eq 5 is limited, at least in the case of amino ethers, to reactive aldehyde components (formaldehyde or unhindered aldehydes). Thus, the tetrafluoroborate salt of **12** was recovered unchanged when heated in refluxing benzene with pivaldehyde, cyclohexanone, or 3-pentanone. Similarly, the tetrafluoroborate salt of **18** (or **18** and a catalytic amount of the corresponding salt) failed to react with cyclohexanone in refluxing benzene or toluene. In contrast, condensation of amino alcohol **7** with an aldehyde or ketone to give the corresponding oxazolidine **37** followed by acid catalyzed rearrangement in refluxing benzene (eq 6) did yield 3-acetylpyrrolidines **38–45** (Table III).



(6)

This two-step sequence was quite efficient with cyclohexanone and substituted cyclohexanones and gave the 1-azaspiro[4.5]decanes **38**, **41**, and **42** in greater than 50% overall yields. This process was much less successful with other ketones and afforded 1-azaspiro[4.11]hexadecane **43** and acetylpyrrolidine **44** in only very low yields from cyclododecanone and 3-pentanone and gave no recognizable 1-azaspiro[4.4]octane products from cyclopentanone.[35,36b] It is significant that these latter transformations can be accomplished in good yields by a base-promoted reaction, in which the 5-vinyloxazolidine is treated with KH and a crown ether.[36]

Acid-catalyzed rearrangement of the oxazolidines formed from amino alcohol **7** and 4-*tert*-butylcyclohexanone yielded a 92:8 mixture of stereoisomeric 1-azaspiranes (eq 7). Stereochemical

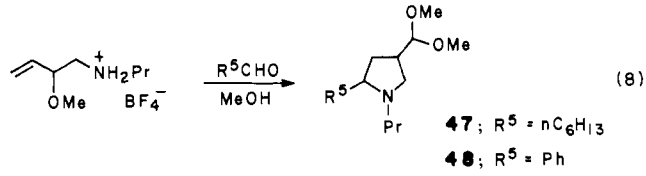


(7)

assignments were made on the basis of (a) lanthanide-induced shift experiments with $Eu(fod)_3$, which showed a smaller induced shift for the acetyl methyl of the major stereoisomer (major, 0.8 ppm mol^{-1} mol^{-1}; minor, 1.3 ppm mol^{-1} mol^{-1}), and (b) N-benzylation studies (benzyl iodide, DBU, MeOH, room temperature),[36b] which showed that the major isomer reacted more slowly. Both results are consistent with the major isomer being **41** (eq 7), since the "axial" nitrogen of **41** should interact less readily with electrophiles than the "equatorial" nitrogen of the stereoisomeric azaspirane.[37] The high stereoselectivity observed in this transformation implies that iminium ion intermediate **46** undergoes rearrangement preferentially from the equatorial direction (see eq 7). It is important to note that the preference for equatorial carbon–carbon bond formation in this cationic aza-Cope rearrangement is higher than that observed in analogous Claisen or ortho-ester Claisen rearrangements.[38]

Several miscellaneous observations also merit mention: (1) Treatment of oxazolidine **37** (R^5,R^6 = $-(CH_2)_5-$) at 80 °C with 1 equiv of methyl or hexyl iodide gave the corresponding 1-alkyl-1-azaspiro[4.5]decans **39** and **40** in moderate yield (Table III). This conversion was complicated by formation of significant amounts of **38**, which likely arises from proton transfer between N-alkylated and nonalkylated oxazolidines. (2) Azaspirane **38** was also produced, but in lower yield (45%), from the direct reaction of amino alcohol **7** with cyclohexanone and camphorsulfonic acid in refluxing benzene. However, **38** was not formed to any significant extent when oxazolidine **37** (R^5,R^6 = $-(CH_2)_5-$) was treated with 0.1 equiv of camphorsulfonic acid in refluxing benzene. (3) The imine produced from cyclohexanone and amino ether **15** did afford **38** (in 57% yield) when heated in refluxing benzene with 1.0 equiv of camphorsulfonic acid.

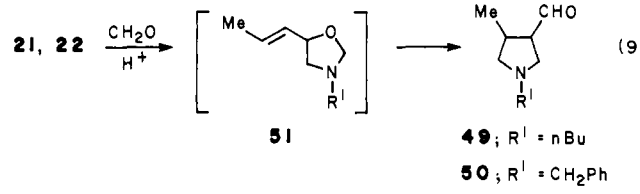
Preparation of 3-Formylpyrrolidines. In extending this chemistry to the preparation of 3-formylpyrrolidines, we initially examined the reaction of aldehydes and the tetrafluoroborate salt of **18**. When this salt was allowed to react with heptanal for 24 h in refluxing benzene, formylpyrrolidine dimethyl acetal **47** was isolated in 21% yield together with considerable high molecular weight material (see eq 8). The corresponding aldehyde was not



(8)

detected. The polymerization reaction, which is an obvious complication in this case, was suppressed when the identical reaction was carried out under acetalizing conditions (3-Å molecular sieves, 1 equiv of methanol) and gave **47** in 81% yield. Benzaldehyde was similarly converted to dimethyl acetal **48** in 69% yield.

An alternate method for minimizing polymerization in the preparation of formylpyrrolidines is to employ a 5-vinyloxazolidine precursor. Thus, condensation of amino alcohols **21** and **22** with formaldehyde and camphorsulfonic acid produced initially oxazolidines **51**, which were subsequently converted in refluxing benzene to formylpyrrolidines **49** and **50** in yields of 79% and 82%, respectively (eq 9). Both formylpyrrolidines were primarily



(9)

(>14:1) a single stereoisomer, which presumably has a trans orientation of the C-3 and C-4 substituents. The clean formation of **49** and **50** is significant, since it demonstrates that a C-4 pyrrolidine substituent can also be introduced via the tandem aza-Cope rearrangement–Mannich cyclization pyrrolidine synthesis.

Conclusion

The intramolecular Mannich trapping procedure detailed herein significantly extends the applicability of cationic aza-Cope rearrangements as a vehicle for carbon–carbon bond formation. In cases where the starting iminium ion was aryl conjugated (i.e., an aromatic aldehyde was employed in iminium ion generation, eq 5, R^5 = aryl), cationic aza-Cope rearrangement would not have been observed[9c] in the absence of the Mannich trap. Clearly, other

(34) Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454–1456.
(35) In these cases low molecular weight, water soluble products were produced.
(36) (a) Kakimoto, M.; Okawara, M. *Chem. Lett.* **1979**, 1171–1174. (b) Kakimoto, M. Ph.D. Thesis, Tokyo Institute of Technology, 1980. (c) Overman, L. E.; Okazaki, M. E., unpublished observations.
(37) Barton, D. H. R. *Experientia* **1950**, *6*, 316–330.
(38) Cf.: House, H. O.; Lubinkowski, J.; Good, J. J. *J. Org. Chem.* **1975**, *40*, 86–92.

methods for manipulating the equilibrium position of this facile transformation will further expand its utility in synthesis.[11]

The tandem cationic aza-Cope–Mannich cyclization reaction allows a variety of polysubstituted pyrrolidines to be assembled in excellent yields from the reaction of aldehydes (or ketones) and allylically oxygenated homoallylic amines. This pyrrolidine synthesis occurs under remarkably mild temperature (25–110 °C) and pH (pH ~8, amine/amine salt buffers) conditions. These conditions allow tertiary allyl ethers and alcohols to be employed as starting components and should also guarantee the survival of other delicate functionality. The preparation of 26 pyrrolidines regioselectively substituted at N-1, C-4, and C-5 with alkyl and aryl moieties and at C-3 with formyl, acetyl, or acetal substituents has been explicitly demonstrated. Clearly, a wide variety of other polysubstituted 3-acyl pyrrolidines should be accessible in this way. This pyrrolidine synthesis would appear to be particularly powerful for preparing pyrrolidines with aryl and heteroaryl substituents at N-1 and C-5.[13] For pyrrolidines of this type, as well as pyrrolidines that contain sensitive substituents, the tandem cationic aza-Cope–Mannich cyclization reaction should be the synthetic method of choice.[13-18] Extensions of this chemistry to the construction of more complex ring systems is described in the accompanying paper[39] as well as other recent publications from our laboratories.[1]

Experimental Section[40]

Preparation of 2-Methoxy(or hydroxy)-3-alkenamines. Typical experimental procedures follow.

1-Bromo-2-methyl-3-buten-2-ol. This bromohydrin has been described previously.[20] A convenient large-scale preparation follows. A mixture of ether (70 mL), water (50 mL), and isoprene (20 g, 0.30 mol) was rapidly stirred and cooled to 0 °C in a flask fitted with a dry-ice condenser. *N*-Bromosuccinimide (53.4 g, 0.30 mol) was added in one portion, the cooling bath was removed, and the mixture was stirred rapidly at room temperature for 6–12 h. The ether layer was separated, the aqueous layer was extracted with ether (3 × 50 mL), and the organic extracts were dried (Na_2SO_4). Rapid distillation through a short Vigreaux column gave 35 g (71%) of pure product: bp 55–56 °C (15 mm) [lit.[20] bp 50 °C (10 mm)]; ^1H NMR (60 MHz, $CDCl_3$) 5.0–6.3 (ABX m, $CH{=}CH_2$), 3.43 (s, CH_2Br), 2.5 (s, OH), 1.40 (s, CH_3).

2-Methyl-1-(propylamino)-3-buten-2-ol (4). 1-Bromo-2-methyl-3-buten-2-ol (14.9 g, 90 mmol) was added dropwise at 0–10 °C to a large excess of freshly distilled propylamine (100 mL, 1.2 mol). This solution was heated at reflux for 6 h and concentrated. The resulting residue was partitioned between ether (50 mL) and 15% NaOH solution (30 mL), the aqueous layer was extracted with additional ether (3 × 20 mL), and the combined organic extracts were dried (Na_2SO_4). Concentration and distillation (short-path still; 78–80 °C, 18 mm) gave 11.8 g (92%) of 4, which was a single peak by GLC analysis:[41] IR (film) 3430, 3340, 1460, 1380, 1120, 990, 920 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 4.8–6.2 (ABX m, $CH{=}CH_2$), 2.2–2.8 (m, NCH_2), 2.3 (s, NH), 1.1–1.6 (m, NCH_2CH_2), 1.17 (s, CH_3), 0.86 (t, J = 7 Hz, CH_2CH_3); MS (isobutane CI), m/z 144 (MH).

2-Methoxy-2-methyl-*N*-propyl-3-butenamine (12). A solution of 4 (5.74 g, 40 mmol) and dry THF (80 mL) was added dropwise at ca. 4 °C over 1 h to a rapidly stirred suspension of potassium hydride (40 mmol, 6.7 g of a 24% dispersion in oil) and dry THF (50 mL). The resulting mixture was stirred for an additional 30 min, and CH_3I (5.68 g, 40 mmol) was added dropwise at ca. 4 °C. After stirring for 24 h at room temperature, the mixture was filtered, the filtrate was concentrated, and the residue was distilled to give 5.40 g (86%) of **12**: bp 69–70 °C (14 mm); IR (film) 3330, 1460, 1130, 1070, 922 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 4.8–6.2 (ABX m, $CH{=}CH_2$), 3.12 (s, OCH_3), 2.2–2.8 (m, NCH_2), 1.1–1.6 (m, NCH_2CH_2), 1.23 (s, CH_3), 0.87 (t, J = 7 Hz, CH_2CH_3); MS (isobutane CI), m/z 158 (MH), 126, 72; ^{13}C NMR (23 MHz, $CDCl_3$) 141.65 (C-3), 115.5 (C-4), 77.5 (C-2), 58.4 (C-1), 52.5 ($CH_2CH_2CH_3$), 50.1 (OCH_3), 23.1 ($CH_2CH_2CH_3$), 20.0 (CH_3), 11.7 (CH_2CH_3).

The tetrafluoroborate salt was prepared by treatment of a solution of **12** (2.28 g, 14.5 mmol) and ethanol (5 mL) at 0 °C with tetrafluoroboric acid (1.57 mL of a 9.2 M aqueous solution, 14.4 mmol). Concentration and recrystallization of the residue from benzene gave 3.18 g (90%) of the pure salt: mp 168–170 °C; ^1H NMR (90 MHz, $CDCl_3$–D_2O) 5.2–6.0 (ABX m, $CH{=}CH_2$), 3.23 (s, OCH_3), 2.9–3.3 (m, NH_2CH_2), 1.5–2.0 (m, $CH_2CH_2CH_3$), 1.40 (s, CH_3), 0.99 (t, J = 7.3 Hz, CH_2CH_3). Anal. Calcd for $C_9H_{20}BF_4NO$: C, 44.10; H, 8.23; N, 5.72. Found: C, 44.19; H, 8.12; N, 5.67.

2-Methyl-1-(phenylamino)-3-buten-2-ol (9). A solution of aniline (3.4 g, 37 mmol) and dry THF (40 mL) was treated dropwise with *n*-BuLi (38 mmol, 21 mL of a 1.79 M solution in hexane) at 0 °C. 1-Bromo-2-methyl-3-buten-2-ol (2.8 g, 17 mmol) was added at 0 °C, and the resulting solution was left at room temperature for 24 h and concentrated. This residue was partitioned between hexane–ethyl acetate (19:1, 25 mL) and H_2O–brine (1:1, 10 mL), the aqueous layer was extracted with hexane–ethyl acetate (19:1, 4 × 25 mL), and the combined organic extracts were dried (K_2CO_3) and concentrated. Excess aniline was removed by distillation (60–100 °C, 30–10 mm) and the resulting oil was bulb-to-bulb distilled (oven temperature 50–75 °C, 0.3 mm) to give 2.8 g (93%) of **9**, which was 89% pure by capillary GC analysis.[42] A sample of comparable material was purified by flash chromatography (silica gel, 4:1 hexane–ethyl acetate) to give an analytical sample of **9**: IR (film) 3200–3600, 1607, 1510, 992, 925 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.1–7.25 (m, 2 H, Ph), 6.6–6.8 (m, 3 H, Ph), 5.94 (dd, J = 17.3, 10.7 Hz, $CH{=}CH_2$), 5.37 (dd, J = 17.3, 1.5 Hz, $CH{=}CHH$), 5.19 (dd, J = 10.7, 1.5 Hz, $CH{=}CHH$), 3.78 (br s, NH), 3.15 (AB q, J = 12.1 Hz, $\Delta\nu$ = 21.4 Hz, CH_2N), 2.2 (br s, OH), 1.36 (s, CH_3); ^{13}C NMR (23 MHz, $CDCl_3$) 148.7, 143.2, 129.5, 118.3, 114.1, 113.8, 73.1, 54.0, 26.1; MS (methane CI), m/z 178.1228 (178.1232 calcd for $C_{11}H_{16}NO$).

4-Bromo-3-methoxy-1-butene (16, R = Me). This material has been described previously.[27] A convenient large-scale preparation follows. A mixture of *N*-bromosuccinimide (178 g, 1 mol) and MeOH (500 mL) was cooled to −78 °C under a nitrogen atmosphere in a round-bottom flask fitted with a dry-ice condenser and a mechanical stirrer. 1,3-Butadiene (54 g, 84 mL, 1 mol, condensed in a graduated cylinder at −78 °C) was added dropwise via cannula, the cooling bath was removed, and the *rapidly stirred* reaction mixture was allowed to warm to room temperature overnight. Water (700 mL) was added and the bromoether was isolated by extraction with ether (4 × 300 mL) and dried (Na_2SO_4). Removal of the ether by distillation at atmospheric pressure followed by vacuum distillation at 65–70 °C (60 mm) gave 84 g (51%) of pure **16** (R = Me): lit.[27a] bp 71–88 °C (62 mm); ^1H NMR (90 MHz, $CDCl_3$) 5.0–6.0 (ABX m, $CH{=}CH_2$), 3.4–3.9 (m, $CHOCH_3$), 3.27 (s, OCH_3), 3.1–3.3 (m, CH_2Br).

2-Methoxy-*N*-propyl-3-butenamine (18). 4-Bromo-3-methoxy-1-butene (**16**, R = Me, 23 g, 0.14 mol) was treated with propylamine (100 mL), following the procedure described for the preparation of **4**, to give 14.4 g (72%) of **18**: bp 80–83 °C (30 mm); IR (film) 3320, 1462, 1102 cm^{-1}; ^1H NMR (60 MHz, CCl_4) 4.9–6.2 (m, $CH{=}CH_2$), 3.6 (apparent q, $J \sim 5$ Hz, $CHOCH_3$), 3.20 (s, OCH_3), 2.1–2.9 (m, NCH_2), 1.1–1.8 (m, NH and $CH_2CH_2CH_3$), 0.88 (unsym t, J = 6 Hz, CH_2CH_3); MS (isobutane CI), m/z 144 (MH), 112, 72. Anal. Calcd (HBF_4 salt) $C_8H_{18}BF_4NO$: C, 41.59; H, 7.85; N, 6.06. Found: C, 41.60; H, 7.92; N, 6.01.

(*E*)-1-Amino-3-penten-2-ol (20). (*E*)-2[(Trimethylsilyl)oxy]-3-pentenenitrile[28b] (10.6 g, 62.5 mmol) was reduced with $LiAlH_4$ (2.38 g, 62.5 mmol) in ether (200 mL), following the general procedure of Evans.[28b] The crude product was distilled (bp 105–110 °C (20 mm)) to give 4.44 g (70%) of **20**[26] as a colorless oil which crystallized (mp 50–55 °C) at room temperature: IR (film) 2500–3600, 1580, 1450, 1380, 1250, 1070, 960 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 5.70 (ddq, J = 15.4, 1.0, 6.4 Hz, $CH_3CH{=}$), 5.43 (ddq, J = 15.4, 6.5, 1.4 Hz, $=CH$), 3.96 (m, $CHOH$), 2.66 (d AB q, J_{AB} = 12.7, J_A = 4.4, J_B = 7.2 Hz, $\Delta\nu_{AB}$ = 23.4 Hz, CH_2N), 2.43 (br s, OH and NH), 1.69 (complex d, J = 6.4 Hz, $CH_3CH{=}$); ^{13}C NMR (63 MHz, $CDCl_3$) 132.2, 126.2, 72.5, 47.2, 17.3.

(*E*)-1-(Butylamino)-3-penten-2-ol (21). A mixture of **20** (790 mg, 7.82 mmol), butanal (freshly distilled, 0.85 mL, 9.8 mmol), Na_2SO_4 (2 g), and dry CH_2Cl_2 (20 mL) was stirred at 0 °C for 0.5 h and then at room temperature for 4 h. Filtration provided the crude oxazolidine (1.17 g) as a yellow oil. A 178-mg sample of this material was dissolved in ethanol (5 mL) and treated at 0 °C with an excess of $NaBH_4$ (44 mg, 1.1 mmol). The resulting mixture was stirred for 3 h at 0 °C and then 3 h at 25 °C. The reaction mixture was acidified (pH 1–2) with 10% HCl, concentrated to ~2 mL, basified with 6 N NaOH, and extracted with ether (4 × 10 mL). The organic extracts were dried (K_2CO_3), concentrated, and distilled (bp 108–110 °C (10 mm)) to give 161 mg (89%) of **21** as a low-melting hygroscopic white solid: mp 30–35 °C; IR (film) 2700–3500, 1680, 1460, 1384, 1120, 1060, 970 cm^{-1}; ^1H NMR

(39) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, following paper in this issue.

(40) General experimental details have been described, see: Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373–5380.

(41) A 6 ft × 1/4 in. 3% SP2100 on 100/120 Supelcoport column was used.

(42) A 12.5-ft silica capillary column coated with SE-30 was employed for this analysis.

Table III. Preparation of 3-Acetylpyrrolidines according to Eq 6[a]

carbonyl compound	oxazolidine 37 bp, °C (mm)	oxazolidine 37 yield	acetylpyrrolidine product	R^1	R^5	R^6	yield, %
cyclohexanone	73–75 (3)	92	**38**	H	$-(CH_2)_5-$		69
			39[b]	CH_3	$-(CH_2)_5-$		54
			40[c]	n-C_8H_{17}	$-(CH_2)_5-$		48
4-*tert*-butylcyclohexanone	140–145 (3)	91	**41**[d]	H	$-(CH_2CH_2)_2CH$-*t*-Bu-		70
2-methylcyclohexanone	84–85 (3)	91	**42**[e]	H	$-CHMe(CH_2)_4-$		55
cyclododecanone	120–130 (0.1)	92	**43**	H	$-(CH_2)_{11}-$		13[f]
3-pentanone	100–103 (5)	94	**44**	H	Et	Et	9[f]
heptanal	84–85 (5)	86	**45**	H	n-C_6H_{13}	H	65

[a] A 1.0 M solution of oxazolidine **37** and camphorsulfonic acid (1.0 equiv) was heated in refluxing benzene for 24 h. 24 h was chosen as a standard time and most rearrangements were done much sooner. [b] MeI (1.0 equiv) was substituted for RSO_3H in this reaction. Azaspirane **38** (17%) was also formed. [c] *n*-Octyl iodide (1.0 equiv) was substituted for RSO_3H, and DMF (80 °C) was employed as the solvent in this reaction. Azaspirane **38** (21%) was also formed. [d] A 92:8 mixture of stereoisomers. [e] A mixture of four stereoisomers. [f] This product was identical with that prepared by base-promoted rearrangement.[36a]

(250 MHz, $CDCl_3$) 5.72 (ddq, J = 16.3, 1.2, 6.3 Hz, =CH), 5.43 (ddq, J = 16.3, 6.9, 1.9 Hz, =CH), 4.09 (m, C*H*OH), 2.60 (m, 4 H), 1.68 (complex d, J = 6.3 Hz, CH_3CH=), 1.40 (m, 4 H), 0.92 (t, J = 7.5 Hz, CH_3CH_2); ^{13}C NMR (63 MHz, $CDCl_3$) 132.7, 126.5, 70.2, 55.4, 49.3, 32.0, 20.3, 17.5, 13.8; MS (isobutane CI), m/z 158 (MH), 140, 86, 74, 71; MS (EI), m/z 157.1467 (157.1467 calcd for $C_9H_{19}NO$).

(*E*)-1-(Benzylamino)-3-penten-2-ol (22). Benzoyl chloride (5 mL, 43 mmol) was added at 0 °C to a solution of **20** (1.98 g, 19.6 mmol) and dry pyridine (25 mL). The resulting solution was maintained at 0 °C for 15 min, at room temperature for 4 h, and then partitioned between saturated aqueous $NaHCO_3$ (25 mL) and ether (25 mL). The aqueous layer was extracted with ether (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated (ultimately for 12 h at 0.1 mm) to give 5.9 g of crude (*E*)-1-(benzoylamino)-3-penten-2-yl benzoate. A solution of this material and dry THF (25 mL) was added at 0 °C to a rapidly stirred slurry of $LiAlH_4$ (1.45 g, 38.4 mmol). The resulting mixture was heated at reflux for 4 h, cooled to 0 °C, and slowly quenched by adding 6 N NaOH (20 mL). The resulting mixture was extracted with THF (4 × 20 mL), the organic extracts were dried (K_2CO_3) and concentrated, and the residue was purified by bulb-to-bulb distillation (oven temperature 110–140 °C, 0.1 mm) to give 3.37 g (90%) of **22** as a colorless oil, which solidified at 0 °C: IR (film) 2700–3500, 1675, 1605, 1450, 1105, 1050, 960 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.37–7.21 (m, Ph), 5.72 (ddq, J = 15.4, 1.0, 6.5 Hz, CH_3CH=), 5.43 (ddq, J = 15.4, 6.6, 1.5 Hz, =CH), 4.1 (m, C*H*OH), 3.80 (AB q, J = 13.2 Hz, $\Delta\nu$ = 8.9 Hz, CH_2Ph), 2.61 (dAB q, J_{AB} = 11.9, J_A = 3.8, J_B = 8.5 Hz, $\Delta\nu_{AB}$ = 35.3 Hz, CH_2N), 2.6–2.1 (br m, NH and OH), 1.68 (ddd, J = 6.5, 1.5, 0.9 Hz, CH_3CH=); ^{13}C NMR (63 MHz, $CDCl_3$) 139.7, 132.3, 128.2, 127.0, 126.8, 70.3, 54.6, 53.4, 17.6; MS (EI), m/z (relative percent) 120.0807 (120.0813 calcd for $C_{12}H_{17}NO - C_4H_7O$) (70) 92 (38), 91 (100).

Preparation of 3-Acetylpyrrolidines from the Reaction of 2-Methoxy-(or hydroxy)-2-methyl-3-alkenamines with Aldehydes. Typical experimental procedures follow.

3-Acetyl-5-phenyl-1-propylpyrrolidine (27) (Procedure A). A mixture of the tetrafluoroborate salt of amino ether **12** (735 mg, 3 mmol), benzaldehyde (350 mg, 3.3 mmol), and dry benzene (5 mL) was heated at reflux for 5 h. After cooling to room temperature, 1 N NaOH (3 mL) was added, the organic layer was separated, and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by bulb-to-bulb distillation (oven temperature 95 °C, 0.01 mm) to give 599 mg (87%) of **27** as a colorless oil, which was a **4**:3 mixture of acetyl epimers: IR (film) 1712 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) 7.2–7.4 (m, Ph), 2.18 and 2.22 (s, CH_3CO), 0.82 (t, J = 7.2 Hz, CH_3CH_2); ^{13}C NMR ($CDCl_3$, signals clearly due to the major isomer are in italics)[37] 208.2 and *208.1* (s, C=O), 143.2 and 142.6 (s, C-h), 128.2, 127.4, 127.3, 127.1, 127.0, 70.3 and *69.2* (d, C-5), 55.8, 55.39, 55.33, and 54.28 (t, CH_2N and C-2), 49.1 (d, C-3), 38.0 and *37.2* (t, C-**4**), *28.9* and 27.1 (q, CH_3CO), 21.6 and 21.5 (t, CH_3CH_2), 11.7 (q, CH_3CH_2); MS (EI), m/z (relative percent) 231.162 (231.162 calcd for $C_{15}H_{21}NO$) (8), 230 (4), 202 (100), 188 (23), 154 (12), 127 (11), 91 (37).

3-Acetyl-1-benzylpyrrolidine (23) (Procedure B). A mixture of amino alcohol **6** (450 mg, 2.35 mmol), paraformaldehyde (78 mg, 2.6 mmol), camphorsulfonic acid (495 mg, 2.13 mmol), and dry benzene (5 mL) was heated at reflux for 10 h. The pyrrolidine product was isolated exactly as described in procedure A to give, after bulb-to-bulb distillation (oven temperature 95–105 °C, 0.4 mm), 425 mg (89%) of **23** as a colorless oil, which was >95% pure by GC analysis.[42] A specimen of comparable material was purified by preparative GC[41] to yield an analytical sample: IR (film) 1712 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.2–7.4 (m, Ph), 3.62 (br s, CH_2Ph), 3.05–3.2 (m, 1 H), 2.75–2.9 (m, 1 H), 2.45–2.75 (m, 3 H), 2.15 (s, CH_3CO), 1.95–2.2 (m, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$)[43] 208.8 (s, C=O), 139.0 (s, C-1 Ph), 128.7 (d, meta Ph), 128.3 (d, ortho Ph), 127.1 (d, para Ph), 60.2 (t, NCH_2Ph), 55.7 (t, C-5), 53.9 (t, C-2), 50.5 (d, C-3), 28.5 (q, CH_3CO), 26.6 (t, C-4); MS (isobutane CI), m/z 204 (MH), 200, 112, 91; MS (methane CI) m/z 204.1380 (204.1388 calcd for $C_{13}H_{18}NO$).

3-Acetyl-1-propylpyrrolidine (24): IR (CCl_4) 1718 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 3.09–3.18 (m, 1 H, CHN), 2.80–2.87 (dd, $J \sim 7$ Hz, 1 H, C-2 H), 2.55–2.72 (m, 2 H, CHN), 2.30–2.49 (m, 3 H, two CHN and C-3 H), 2.18 (s, CH_3CO), 1.98–2.07 (m, CH_2CH_3), 0.92 (t, J = 7.4 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$)[43] 207.0 (C=O), 57.2, 54.8, 53.1, 49.5, 27.4, 25.7, 21.2, 11.2; MS (methane CI), m/z 156.1386 (156.1388 calcd for $C_9H_{18}NO$).

3-Acetyl-1-phenylpyrrolidine (25): IR (film) 1712, 1602 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.15–7.3 (m, meta Ph), 6.68 (apparent t, J = 7 Hz, para Ph), 6.55 (apparent d, J = 8 Hz, ortho Ph), 3.1–3.6 (m, 5 H), 2.20 (s, CH_3CO), 2.0–2.3 (m, 2 H); ^{13}C NMR (63 Hz, $CDCl_3$) 207.9 (s, C=O), 147.7, 129.3, 116.3, 112.1, 51.1 (d, C-3), 49.1 (t, C-5), 47.5 (t, C-2), 28.8 (q, CH_3CO), 28.0 (t, C-4); MS (isobutane CI), m/z 190 (MH), 189. MS (methane CI), m/z 190.1230 (190.1232 calcd for $C_{12}H_{16}NO$).

3-Acetyl-1-(2-chlorophenyl)pyrrolidine (26):[43] IR (film) 1712, 1595 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 6.8–7.4 (m, Ph), 3.4–3.65 (m, 3 H), 3.2–3.35 (m, 2 H), 2.25 (s, CH_3CO), 2.1–2.3 (m, 2 H); MS (EI), m/z (relative percent) 223 (91), 208 (38), 182 (26), 180 (94), 160 (28), 155 (31), 153 (100), 140 (62), 138 (52), 125 (80), 118 (61), 111 (51), 91 (20); MS (methane CI), m/z 224.840 (224.0843 calcd for $C_{12}H_{15}NOCl$).

3-Acetyl-1-benzyl-5-phenylpyrrolidine (28):[43] a 2:1 mixture of acetyl epimers; IR (film) 1712 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 7.1–7.6 (m, Ph), 3.40 (AB q, J = 13 Hz, $\Delta\nu$ = 48 Hz, CH_2Ph), 2.11 and 2.14 (s, CH_3CO); MS (methane CI), m/z 280.1706 (280.1701 calcd for $C_{19}H_{22}NO$).

3-Acetyl-1,5-diphenylpyrrolidine (29): a 3:1 mixture of acetyl epimers; IR (CCl_4) 1719, 1600, 1360 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 6.4–7.4 (m, Ph), 4.86 (apparent d, J = 8 Hz, C-5 H of major isomer) 4.75 (apparent t, J = 6 Hz, C-5 H of minor isomer), 2.19 (s, CH_3CO of major isomer), 2.09 (s, CH_3CO of minor isomer); MS (EI), m/z (relative percent) 265.147 (265.147 calcd for $C_{18}H_{19}NO$) (100), 222 (23), 194 (65), 188 (62), 144 (46).

3-Acetyl-5-hexyl-1-propylpyrrolidine (30): a 4:3 mixture of acetyl epimers; IR (film) 1715 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) 2.16 and 2.17 (CH_3CO); MS (EI), m/z (relative percent) 239.225 (239.225 calcd for $C_{15}H_{29}NO$) (6), 210 (10), 164 (14), 154 (100).

3-Acetyl-1-cyclohexyl-5-hexylpyrrolidine (31):[43] a 2:1 mixture of acetyl epimers; IR (film) 1715 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) 2.16 (s, CH_3CO); MS (isobutane CI), m/z 280 (MH), 194; MS (EI), m/z 279.255 (279.256 calcd for $C_{18}H_{33}NO$).

3-Acetyl-1-(4-fluorophenyl)-5-pentylpyrrolidine (32): a 2:1 mixture of acetyl epimers; IR (film) 1718, 1614 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 6.9–7.0 (m, meta Ph), 6.45–6.55 (m, ortho Ph), 3.1–3.8 (m, 4 H), 2.24 and 2.25 (s, CH_3CO); MS (isobutane CI), m/z 278 (MH), 206; MS (methane CI), m/z 278.1914 (278.1920 calcd for $C_{17}H_{25}NOF$).

3-Acetyl-5-(2,6-dimethyl-1,5-heptadienyl)-1-propylpyrrolidine (33); a mixture of acetyl epimers and double-bond stereoisomers; IR (film) 1712, 1670, 1630, 1440, 1380, 1360 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) 4.9–5.1 (m, 2 H, =CH), 1.73, 1.67, 1.65, 1.64, 1.62, 1.60, and 1.53 (s, 9 H,

(43) Selected ^{13}C NMR data for this compound may be found in Table IV; see supplementary material.

=CHCH_3), 2.17 (br s, CH_3CO), 0.88 (apparent t, J = 6.8 Hz, CH_2CH_3); ^{13}C NMR (23 MHz, $CDCl_3$) 208.5 and 208.4 (C=O), 138.1, 131.6, 131.3, 127.6, 127.5, 126.8, 125.6, 124.2, 123.2 (alkene carbons); MS (EI), m/z (relative percent) 277.240 (M, 277.241 calcd for $C_{18}H_{31}NO$) (2) 248 (14), 234 (20), 208 (13), 154 (100). Catalytic hydrogenation of this material gave 3-acetyl-5-(2,6-dimethylheptyl)-1-propylpyrrolidine: mass spectrum (isobutane CI), m/z 282 (MH), 154, 72; MS (methane CI), m/z 282.2799 (282.2797 calcd for $C_{18}H_{36}NO$).

3-Acetyl-5-cyclohexyl-1-propylpyrrolidine (34):[43] a 1:1 mixture of acetyl epimers; IR (film) 1715 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) 2.15 and 2.16 (s, CH_3CO); MS (EI), m/z (relative percent) 237.210 (237.209 calcd for $C_{15}H_{27}NO$, 1), 154 (100), 110 (11).

3-Acetyl-1-benzyl-5-(2-furanyl)pyrrolidine (35):[43] a 2:1 mixture of acetyl epimers; IR (film) 1712 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 6.8–7.7 (m, Ph and 5-furan H), 6.1–6.4 (m, furan H), 3.42 (AB q, J = 13 Hz, $\Delta\nu$ = 39 Hz, CH_2Ph), 2.07 and 2.12 (s, CH_3CO); MS (EI), m/z (relative percent) 269.140 (269.142 calcd for $C_{17}H_{19}NO_2$) (0.5), 268 (1), 226 (6), 178 (35), 175 (20), 108 (25), 91 (100).

3-Acetyl-1-methyl-5-(3-pyridinyl)pyrrolidine (36):[43] a 1:1 mixture of acetyl epimers; IR (film) 1712, 1580 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 8.47–8.6 (m, 2 H), 7.6–7.8 (m, 1 H), 7.32–7.42 (m, 1 H), 3.0–3.55 (m, 3 H, CHN), 2.24, 2.20, 2.17, and 2.13 (s, CH_3N and CH_3CO); MS (isobutane CI), m/z 205 (MH), 126, 105; MS (methane CI), m/z 205.1334 (205.1341 calcd for $C_{12}H_{17}N_2O$).

3-(Dimethoxymethyl)-5-phenyl-1-propylpyrrolidine (48). A mixture of the tetrafluoroborate salt of amino ether **18** (462 mg, 2.00 mmol), benzaldehyde (212 mg, 2.00 mmol), methanol (96 mg, 3.0 mmol), 3-Å molecular sieves (600 mg), and dry benzene (3 mL) was heated at reflux for 24 h. The pyrrolidine product was isolated exactly as described in procedure A to give, after bulb-to-bulb distillation (oven temperature (105–110 °C, 0.01 mm), 362 mg (69%) of **48** as a colorless oil: a 3:1 mixture of stereoisomers; IR (film) 1600, 1060 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 6.8–7.5 (m, Ph), 4.21 (d, J = 8 Hz, MeOC*H*OMe of minor isomer), 4.10 (d, J = 8 Hz, MeOC*H*OMe of major isomer), 3.20 and 3.16 (s, OMe); ^{13}C NMR (23 MHz, $CDCl_3$) 143.7, 143.5, 128.3, 127.4, 126.9, 107.5, 107.2, 70.6, 69.7, 56.3, 56.0, 55.9, 54.9, 53.2, 52.8, 52.5, 38.6, 38.2, 37.3, 21.7, 11.9; MS (isobutane CI), m/z 264 (MH), 232; MS (methane CI), m/z 264.1961 (264.1963 calcd for $C_{16}H_{26}NO_2$).

3-(Dimethoxymethyl)-5-hexyl-1-propylpyrrolidine (47). Following the exact procedure described for the preparation of **48**, **47** was prepared in 81% yield as a 9:1 mixture of stereoisomers: IR (film) 1160 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, major isomer) 4.17 (d, J = 8 Hz, OCHO), 3.32 and 3.27 (s, OCH_3), 3.23 (m, 1 H, CHN), 2.44–2.8 (m, 2 H, CHN); ^{13}C NMR (23 MHz, $CDCl_3$) 107.2, 107.1, 65.2, 64.5, 56.3, 55.8, 55.3, 52.8, 52.5, 52.4, 37.9, 37.6, 33.9, 33.4, 32.7, 31.7, 29.5, 26.1, 22.4, 21.5, 13.8, 11.9; MS (methane CI), m/z 272.2587 (272.2589 calcd for $C_{16}H_{13}NO_2$).

Preparation of Acetylpyrrolidines from 5-Methyl-5-vinyloxazolidines. The following procedure is typical.

3-Acetyl-1-azaspiro[4.5]decane (38): A solution of amino alcohol **7** (3.03 g, 30 mmol), cyclohexanone (2.94 g, 30 mmol), and dry benzene (30 mL) was heated at reflux for 2 h using a Dean-Stark water separator. After concentration, the residue was distilled (short-path still) to give 5.0 g (92%) of 2-methyl-2-vinyl-1-oxa-4-azaspiro[4.5]decane: IR (film) 3300, 1445, 1369, 1140, 1070, 920 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) 5.84 (dd, J = 10.3, 17.1 Hz, C*H*=CH_2), 5.25 (dd, J = 2.2, 17.1 Hz, CH=C*H*H), 5.01 (dd, J = 2.1, 10.3 Hz, CH=CH*H*), 2.97 (AB q, J = 12 Hz, $\Delta\nu$ = 6.4 Hz, OCH_2N), 2.2 (br s, NH), 1.2–1.7 (m, 10 H), 1.30 (s, CH_3); MS (isobutane CI), m/z 182 (MH), 164, 138, 84.

A 543 mg (3.00 mmol) sample of this material, camphorsulfonic acid (700 mg, 3.0 mmol), and dry benzene (3 mL) were heated at reflux for 24 h. The pyrrolidine product was isolated as described in procedure A, to give, after bulb-to-bulb distillation (oven temperature 80–85 °C, 0.01 mm), 375 mg (69%) of pure **38** as a colorless liquid: IR (film) 3300, 1705, 1448, 1363, 1175, 918 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) 3.1–3.2 (m, CH_2N and 1 H), 2.22 (s, CH_3CO), 1.2–2.1 (m, 10 H); ^{13}C NMR (23 MHz, $CDCl_3$)[43] 209.1 (C=O), 62.9 (C-5), 52.6 (C-2), 47.8 (C-3), 39.7 (C-4), 38.1 and 37.3 (C-6 and C-10), 29.2 (*C*H_3CO), 25.9 (C-8), 23.9 and 23.6 (C-7 and C-9); MS (isobutane CI), m/z 182 (MH), 138; MS (methane CI), m/z 182.1542 (182.1545 calcd for $C_{11}H_{20}NO$).

3-Acetyl-8-*tert*-butyl-1-azaspiro[4.5]decane (41):[43] A 92:8 mixture of stereoisomers (from integration of the CH_3CO hydrogens in the presence of $Eu(fod)_3$); IR (film) 3330, 1705, 1440, 1363, 1170, 1092 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) 3.0–3.2 (m, CH_2N and 1 H), 2.18 (s, CH_3CO), 0.84 (s, Me_3C), 0.8–1.9 (m, 11 H); MS (isobutane CI), m/z 238 (MH), 128; MS (EI), m/z 237.210 (237.209 calcd for $C_{15}H_{27}NO$).

3-Acetyl-6-methyl-1-azaspiro[4.5]decane (42): A mixture of 4 stereoisomers (^{13}C NMR analysis): IR (film) 3350, 1705, 1460, 1365, 1170 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) 3.0–3.3 (m, CH_2N and 1 H), 2.20 (s, CH_3CO), 1.0–2.0 (m, 9 H), 0.92 (d, J = 8 Hz, CH_3CH); MS (isobutane CI), m/z 196 (MH) 182, 152.

3-Acetyl-5,5-diethylpyrrolidine (44).[43] IR (film) 3350, 2950, 1710, 1460, 1362, 1170 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) 3.0–3.3 (m, CH_2N and 1 H), 2.08 (s, CH_3CO), 1.0–1.8 (m, 6 H), 0.86 (t, J = 7 Hz, CH_3CH_2); MS (isobutane CI), m/z 170 (MH), 140; MS (EI), m/z 169.143 (169.147 calcd for $C_{10}H_{19}NO$).

3-Acetyl-5-hexylpyrrolidine (45): IR (film) 3320, 2950, 1710, 1460, 1365, 1175 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) 3.0–3.2 (m, 4 H), 2.18 (s, CH_3CO), 2.10 (br s, NH); MS (isobutane CI), m/z 198 (MH), 112; MS (EI), m/z 197.176 (197.178 calcd for $C_{12}H_{23}NO$).

1-Butyl-3-formyl-4-methylpyrrolidine (49). A mixture of **21** (216 mg, 1.37 mmol), paraformaldehyde (1.0 g, 33 mmol), camphorsulfonic acid (303 mg, 1.31 mmol), and dry benzene was heated at reflux for 24 h. Product isolation as described in procedure A gave, after bulb-to-bulb distillation (oven temperature 24–45 °C, 0.25 mm), 184 mg (79%) of **49** as a 19:1 mixture (250-MHz ^1H NMR analysis) of two formyl epimers: IR (film) 2800, 1735, 1465, 1380, 1265, 1100, 1020 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 9.75 (d, J = 3.1 Hz, CHO of minor isomer), 9.64 (d, J = 2.5 Hz, CHO of major isomer), 3.06 (dd, J = 9.7, 3.9 Hz, CHN), 3.00 (dd, J = 8.8, 6.8 Hz, CHN), 2.6–2.3 (m, 4 H), 2.02 (t, J = 8.8 Hz, CHN), 2.5–2.2 (m, 4 H), 1.13 (d, J = 6.6 Hz, CH_3CH), 0.91 (t, J = 7.2, CH_3CH_2); ^{13}C NMR (63 MHz, $CDCl_3$, major isomer) 202.2, 62.2, 58.0, 56.0, 54.1, 34.1, 31.0, 20.9, 19.3, 14.2; MS (isobutane CI), m/z 170 (MH), 126; MS (EI), m/z 169.146 (169.147 calcd for $C_{10}H_{19}NO$).

1-Benzyl-3-formyl-4-methylpyrrolidine (50): 82% yield; a colorless oil, which is a 14:1 mixture of formyl epimers; IR (film) 2800, 1740, 1450, 1150, 1030 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 9.75 (d, J = 3.2 Hz, CHO of minor isomer), 9.62 (d, J = 2.5 Hz, CHO of major isomer), 7.2–7.4 (m, Ph), 3.60 (AB q, J = 12.5 Hz, $\Delta\nu$ = 13.4 Hz, CH_2Ph), 3.03 (dd, J = 9.9, 4.0 Hz, CHN), 2.96 (dd, J = 8.8, 7.0 Hz, CHN), 2.3–2.7 (m, 3 H), 2.06 (dd, J = 8.8, 7.4 Hz, CHN), 1.13 (d, J = 6.6 Hz, CH_3CH); ^{13}C NMR (63 MHz, $CDCl_3$, major isomer) 202.2, 138.3, 128.6, 128.3, 127.0, 61.6, 59.9, 58.0, 53.7, 33.9, 19.3; MS (EI), m/z (relative percent) 203.1310 (203.1310 calcd for $C_{13}H_{17}NO$) (5), 131 (15), 120 (18), 119 (15), 91 (100).

Acknowledgment. Financial support from the National Institutes of Health (NS-12389), the National Science Foundation (CHE-82-03366), and the Camille and Henry Dreyfus Foundation (teacher-scholar award to L.E.O) is gratefully acknowledged. NMR and mass spectra were determined at Irvine with spectrometers purchased with the assistance of NSF departmental instrumentation grants. High-resolution mass spectra were determined at the NSF-supported MCMS at the University of Nebraska, Lincoln, NE. We particularly thank Professor Makoto Okawara, Research Laboratory of Resources Utilization, Tokyo Institute of Technology, in whose laboratory part of the experiments of M.K. were conducted.

Registry No. 4, 77924-56-2; **5**, 87088-61-7; **6**, 69917-78-8; **7**, 15158-22-2; **8**, 69917-79-9; **9**, 29740-54-3; **10**, 87088-62-8; **11**, 87088-63-9; **12**, 69917-75-5; **12**·HBF_4, 87088-64-0; **13**, 69917-76-6; **13**·HBF_4, 87088-65-1; **14**, 69917-77-7; **14**·HBF_4, 87088-66-2; **15**, 73738-92-8; **16** (R = H), 64341-49-7; **16** (R = M), 22427-00-5; **17**, 85771-10-4; **18**, 87088-67-3; **18**·HBF_4, 87088-68-4; **19**, 87088-69-5; (*E*)-**20**, 87088-70-8; (*E*)-**21**, 87088-71-9; (*E*)-**22**, 87088-72-0; **23**, 87088-73-1; **24**, 87088-74-2; **25**, 87088-75-3; **26**, 87088-76-4; *cis*-**27**, 87088-77-5; *trans*-**27**, 87088-78-6; *cis*-**28**, 87088-79-7; *trans*-**28**, 87088-80-0; *cis*-**29**, 87088-81-1; *trans*-**29**, 87088-82-2; *cis*-**30**, 87088-83-3; *trans*-**30**, 87088-84-4; *cis*-**31**, 87088-85-5; *trans*-**31**, 87088-86-6; *cis*-**32**, 87088-87-7; *trans*-**32**, 87088-88-8; (*E*)-*cis*-**33**, 87088-89-9; (*E*)-*trans*-**33**, 87100-14-9; (*Z*)-*cis*-**33**, 87088-90-2; (*Z*)-*trans*-**33**, 87088-91-3; *cis*-**34**, 87088-92-4; *trans*-**34**, 87088-93-5; *cis*-**35**, 87088-94-6; *trans*-**35**, 87088-95-7; *cis*-**36**, 87088-96-8; *trans*-**36**, 87088-97-9; **37** (R^5 = R^6 = $(CH_2)_5$), 72612-27-2; **37** (R^5 = R^6 = $(CH_2CH_2)_2CH$-*t*-Bu), 72612-28-3; **37** (R^5 = R^6 = $CHMe(CH_2)_4$), 73738-87-1; **37** (R^5 = R^6 = $(CH_2)_{11}$), 72612-35-2; **37** (R^5 = R^6 = Et), 72612-30-7; **37** (R^5 = *n*-C_6H_{13}; R^6 = H), 73738-88-2; **38**, 72612-36-3; **39**, 73738-93-9; **40**, 73756-12-4; **41** (isomer 1), 87088-98-0; **41** (isomer 2), 87088-99-1; **42**, 87144-15-8; **43**, 87089-00-7; **44**, 72612-39-6; **45**, 73738-91-7; *cis*-**47**, 87089-01-8; *trans*-**47**, 87089-02-9; *cis*-**48**, 87089-03-0; *trans*-**48**, 87089-04-1; *cis*-**49**, 87089-05-2; *trans*-**49**, 87089-06-3; *cis*-**50**, 87089-07-4; *trans*-**50**, 87089-08-5; **51** (R′ = *n*-Bu), 87089-09-6; **51** (R′ = CH_2Ph), 87089-10-9; isoprene oxide, 1838-94-4; 1-bromo-2-methyl-3-buten-2-ol, 36219-40-6; lithium anilide, 20732-26-7; lithium *o*-chloroanilide, 87089-11-0; lithium *p*-fluoroanilide, 76085-46-6; aniline,

62-53-3; 3-nitroaniline, 99-09-2; 4-nitroaniline, 100-01-6; formaldehyde, 50-00-0; benzaldehyde, 100-52-7; heptanal, 111-71-7; hexanal, 66-25-1; (*E*)-3,7-dimethyl-2,6-octadienal, 141-27-5; (*Z*)-3,7-dimethyl-2,6-octadienal, 106-26-3; cyclohexanecarboxaldehyde, 2043-61-0; 2-furancarboxaldehyde, 98-01-1; 3-pyridinecarboxaldehyde, 500-22-1; cyclohexanone, 108-94-1; 4-*tert*-butylcyclohexanone, 98-53-3; 2-methylcyclohexanone, 583-60-8; cyclododecanone, 830-13-7; 3-pentanone, 96-22-0; (*E*)-2-[(trimethylsilyl)oxy]-3-pentenenitrile, 87089-12-1.

Supplementary Material Available: Table IV, selected ^{13}C NMR data for 15 substituted 3-acetylpyrrolidines (3 pages). Ordering information is given on any current masthead page.

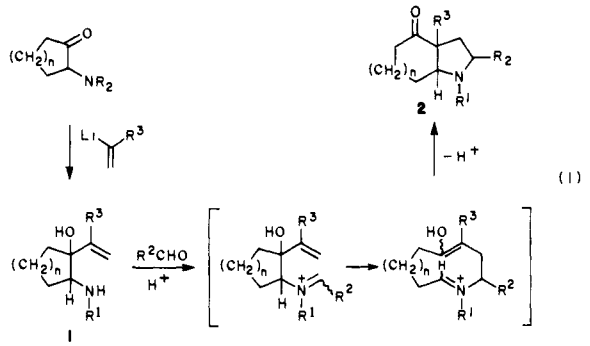
Applications of Cationic Aza-Cope Rearrangements for Alkaloid Synthesis. Stereoselective Preparation of *cis*-3a-Aryloctahydroindoles and a New Short Route to Amaryllidaceae Alkaloids[1]

Larry E. Overman,* Leah T. Mendelson, and E. Jon Jacobsen

Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received March 21, 1983*

Abstract: A new synthesis of *cis*-3a-aryloctahydroindoles is detailed (eq 1). The key step is a "ring-enlarging pyrrolidine annulation" reaction which occurs when 2-amino-1-(1-arylethenyl)cyclopentanols are treated under mild conditions with an aldehyde and acid. Three different methods (Schemes I–III) for assembling the 2-amino(1-arylethenyl)cyclopentanol intermediates are reported. An efficient formal total synthesis of the Amaryllidaceae alkaloid (±)-crinine (Scheme III) is reported, in which key intermediate **26** was assembled with virtually complete stereocontrol in four steps and 44% overall yield from readily available 1,2-bis(trimethylsilyloxy)cyclopentene.

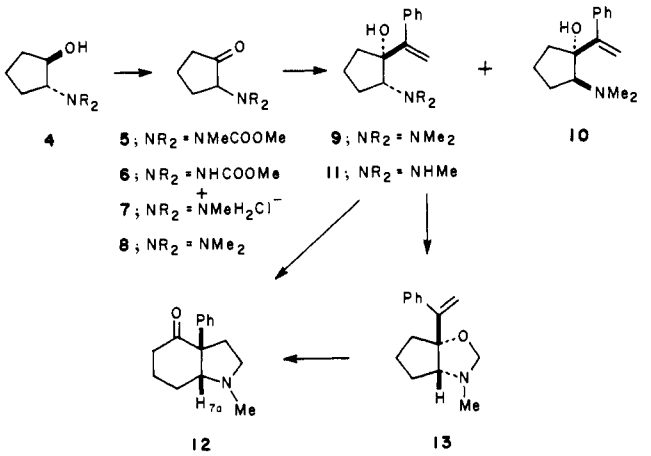
The preceding paper[1] described the development of tandem cationic aza-Cope–Mannich reactions as a new strategem for preparing substituted pyrrolidines under extremely mild conditions. A potentially useful annulation sequence that exploits this chemistry is illustrated in eq 1.[2] This unusual transformation



(1)

would convert an α-amino ketone[3] into a pyrrolidine-annulated product, in which the starting ring is expanded by one member. We chose to initially examine this sequence with cyclopentanol precursors to see if the widely occurring[4] *cis*-3a-aryloctahydroindole ring system (*cis*-**2**, $n = 1$, R^3 = Ar) could be assembled in this fashion.[5,6] If the amine and vinyl groups are oriented trans in cyclopentanol **1** ($n = 1$), this sequence should stereospecifically lead to the formation of only the *cis*-octahydroindole ring system, since rearrangement via only a single "chair-type" transition state is possible for systems of this type (eq 2).[2,7] A *cis*-octahydro-

Scheme I



(1) Part 12 in the series: Synthesis Applications of Aza-Cope Rearrangements. For part 11, see: Overman, L. E.; Kakino, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) We wish to stress that although we have chosen to discuss this sequence as a [3,3]-sigmatropic rearrangement followed by a Mannich cyclization, alternate mechanisms with *similar topographical constraints* are possible with some substrates and are not excluded by data currently available. For example, with electron-rich styrenyl substrates, cyclization to a benzylic cation followed by pinacol rearrangement is a conceivable alternative. Experiments that address these mechanistic issues are in progress and will be reported in due course.

(3) The preparation of α-amino ketones has been reviewed, see: Mayer, D. In "Methoden der Organische Chemie (Houben-Weyl)", 4th ed.; Müller, E., Ed.; Thieme-Verlag: Stuttgart, 1977; Vol. VII/2C, pp 2253–2307.

(4) This ring system is found, inter alia, in alkaloids of the Sceletium, Amaryllidaceae, Aspidosperma, and Strychnos families. Cf.: Dalton, D. R. "The Alkaloids. The Fundamental Chemistry"; Marcel Dekker: New York, 1979.

(5) For recent reviews that cover the preparation of this ring system, see: (a) Jeffs, P. W. In "The Alkaloids"; Manske, R. H. F., Rodrigo, R. G. A., Ed.; Academic Press: New York, 1980; Chapter 1. (b) Tsuda, Y. *Heterocycles* **1978**, *10*, 555–595. (c) Stevens, R. V. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, pp 443–453.

(6) For recent contributions, see inter alia: Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591–7599. Sanchez, I. H.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *Tetrahedron Lett.* **1983**, *24*, 551–554. Keck, G. E.; Webb, R. R., II. *J. Org. Chem.* **1982**, *47*, 1302–1309. Jeffs, P. W.; Cortese, N. A.; Wolfram, J. *J. Org. Chem.* **1982**, *47*, 3881–3886. Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479–4482. Keck, G. E.; Webb, R. E., II. *J. Am. Chem. Soc.* **1981**, *103*, 3173–3177.

(7) This prediction assumes that intramolecular Mannich ring closure of the presumed azacyclononadiene would be more rapid than any loss of stereochemical integrity of this intermediate.

0002-7863/83/1505-6629$01.50/0