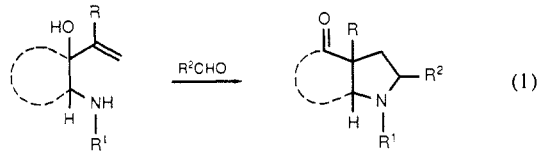
Scope and Mechanism of Tandem Cationic Aza-Cope Rearrangement–Mannich Cyclization Reactions[1]

E. Jon Jacobsen,[2a] Jeremy Levin,[2b] and Larry E. Overman*

Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received September 8, 1987*

Abstract: The first detailed mechanistic studies of the pyrrolidine synthesis of eq 1 are reported. One investigation examined the rearrangement of five unsaturated amino alcohols **11** having internal alkene substituents of widely varying electronic character (R = OEt, SPh, CH_3, H, SO_2Ph). Silver(I)-promoted rearrangement of **11** to afford the *cis*-4-oxocycloheptapyrrolidine products **12** was successfully accomplished in each case. Success of this iminium ion-initiated rearrangement with substrate **11e** containing the strongly electron-withdrawing phenylsulfonyl group is particularly significant. In the case of the vinyl ether containing rearrangement substrate **11d**, the silver(I)-promoted transformation could be controlled to provide either the 4-oxocycloheptapyrrolidine product **16** or *trans*-decahydroquinoline **17**. The second study investigated acid-promoted rearrangement of the optically active oxazolidine **24** which afforded a single racemic 3-acylpyrrolidine product **25**. Extensive control experiments establish that racemization occurred during the conversion of **24** → **25**, which rules out a cyclization–pinacol mechanism (see Scheme I) for the pyrrolidine synthesis. This result and the results of the rearrangements of **11** are consistent with a mechanism involving an initial cationic aza-Cope (2-[azonia]-3,3-sigmatropic) rearrangement followed by an intramolecular Mannich reaction (Scheme I, **3** → **4** → **5**). The synthetic scope of the pyrrolidine synthesis shown in eq 1 is significantly expanded by the observation that alkenes of widely differing electronic properties may be employed. On the other hand, the racemization observed in forming monocyclic products precludes use of this rearrangement for asymmetric synthesis of simple pyrrolidines.

As we first reported in 1979,[3] homoallylic amines containing an allylic hydroxyl group rearrange in the presence of an aldehyde and an acid catalyst to yield 3-acylpyrrolidines (see eq 1). If the

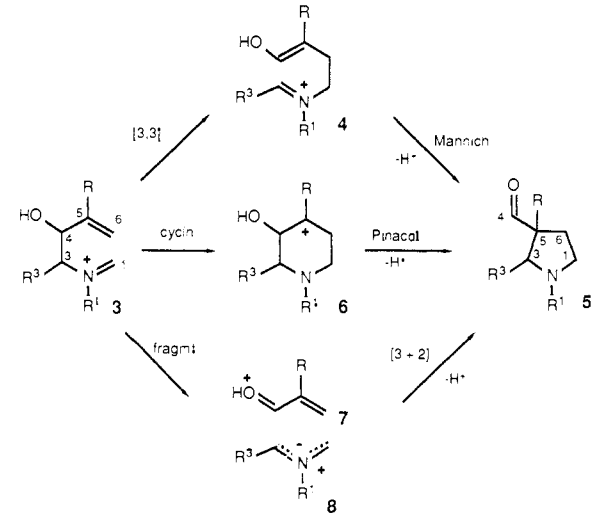


1 2 (1)

starting amino alcohol is cyclic, this transformation provides a pyrrolidine-annulated product, in which the initial ring is expanded by one member.[4] The ready availability of the amino alcohol starting materials and the mild reaction conditions (neutral pH, 20–80 °C) and high efficiency of these transformations combine to make this rearrangement a powerful reaction for heterocyclic synthesis. Thus far, its use for preparing stereochemically complex target systems has been documented in total synthesis of tetracyclic *amaryllidaceae*[4a,5] and pentacyclic *aspidosperma*[6] alkaloids.

In our initial design of this pyrrolidine synthesis we conceptualized the transformation as involving 2-azonia-[3,3]-sigmatropic rearrangement (cationic aza-Cope rearrangement) of the starting iminium ion **3** followed by intramolecular Mannich cyclization of the rearranged cation **4** (see Scheme I). In this plan, the positive charge was envisaged to provide kinetic acceleration for the sigmatropic rearrangement,[7] while the oxygen functionality

Scheme I



was incorporated to provide an irreversible trap for the rearranged iminium cation **4**. Two alternative mechanisms for the conversion of iminium ions **3** to 3-acylpyrrolidines **5** are suggested in Scheme I. One involves initial iminium ion–alkene cyclization[8] to give a 4-piperidinyl cation **6** (or a nucleophile-trapped derivative) followed by a pinacolic rearrangement of this intermediate to afford **5**. This cyclization–pinacol mechanism would be consistent with the stereochemical studies conducted to date,[3-6,9] since both iminium ion cyclization and 2-azonia[3,3]-sigmatropic rearrangement should[9,10] occur preferentially via chair transition states. A third mechanistic possibility suggested in Scheme I is fragmentation of **1** to azomethine ylide **8** and protonated enone **7**,

(1) (1) Part 18 in the series "Synthesis Applications of Cationic Aza-Cope Rearrangements". For part 17 see: Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 685.

(2) Current addresses: (a) Pharmaceutical Research and Development, The Upjohn Company, Kalamazoo, MI 49001. (b) American Cyanamid Company, Medical Research Division, Pearl River, NY 10965.

(3) (a) Overman, L. E.; Kakimoto, M. *J. Am. Chem. Soc.* **1979**, *101*, 1310. (b) Overman, L. E.; Kakimoto, M.; Okazaki, M.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622.

(4) (a) Overman, L. E.; Mendelson, L.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. (b) Overman, L. E.; Jacobsen, E. J.; Doedens, R. J. *J. Org. Chem.* **1983**, *48*, 3393.

(5) Overman, L. E.; Sugai, S. *Helv. Chem. Acta* **1985**, *68*, 745.

(6) Overman, L. E.; Sworin, M.; Burk, R. *J. Org. Chem.* **1983**, *48*, 2685–2690.

(7) A wide variety of formal [3,3]-sigmatropic rearrangements are accelerated by the presence of a charged atom. Several of these are discussed in a recent review: Lutz, R. P. *Chem. Rev.* **1984**, 84.

(8) For a recent mechanistic study of iminium ion–alkene cyclizations and leading references, see: McCann, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6107. See also ref 10.

(9) For a recent study of the transition-state topography of the cationic aza-Cope rearrangement of iminium ions as well as leading references, see ref 1. See, also: Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235. Voegtle, F.; Goldschmitt, E. *Chem. Ber.* **1976**, *109*, 1.

(10) For recent reviews which discuss the topography of iminium ion cyclizations, see: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. E., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 6. Hart, D. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, in press.

0002-7863/88/1510-4329$01.50/0 © 1988 American Chemical Society

Scheme II

followed by 1,3-dipolar cycloaddition of these charged components.[11] A mechanism of this type involving the formation of **7** and **8** as discrete intermediates would appear less attractive since it provides no obvious rationale for the high stereoselectivity observed in these rearrangements, and it might be expected to yield (at least partially) fragmentation products, which have never been observed.[1,3-6]

One possible probe of the first two mechanisms proposed in Scheme I would be to examine the rearrangement of unsaturated amino alcohols having internal alkene substituents R of widely varying abilities for stabilizing an adjacent positive charge. Such stabilization could be critically important in a cyclization–pinacol mechanism, if cation **6** was formed in the rate-determining step of this sequence. In this paper, we report that substrates containing both strongly electron-donating and electron-withdrawing substituents R rearrange under similar conditions to provide 3-acylpyrrolidine products.

We report also in this paper that the rearrangement of an optically active iminium cation **3** (R = Ph, $R^1 = R^3 = CH_3$) affords a racemic acylpyrrolidine product. This rearrangement provides a sensitive mechanistic test, since a cyclization–pinacol sequence should occur with clean retention[12] at the carbon bearing the R^3 substituent, while an aza-Cope–Mannich mechanism would proceed via an intermediate **4** which is devoid of stereogenic centers.

Results

A. Nature of the Vinyl Substituent. We chose for study substrates with the following internal alkene substituents: OEt, SPh, CH_3, H, SO_2Ph. The sulfone substituent was specifically included in this group since it is one of the strongest electron-withdrawing substituents known.[13] For example, recent studies by Creary and co-workers[14] have demonstrated that for solvolyses of substrates of general type p-$CH_3C_6H_4C(CH_3)BrX$, the phenylsulfonyl substituent is extraordinarily deactivating relative to hydrogen (approaching 10^9). Since in this same series[14] the SPh substituent is a powerful activator (7×10^8 relative to H), the substituents included in our study represent extremes of $>10^{17}$ in their abilities to stabilize a developing positive charge.

The required rearrangement substrates were assembled from readily available ketone **9**[4b] and the corresponding 1-(substituted vinyl)lithium reagent (see Scheme II). As we have observed in other cases,[4b] organolithium addition occurred exclusively from the face of the ketone opposite the dialkylamino group (see Table I). The stereochemical assignments for **11a–d** are consistent with the chemical ionization mass spectrum which showed weak peaks for loss of water[15,4b] and with the ^1H NMR spectrum which showed a characteristic doublet of doublets for the axial methine hydrogen H_2 (see Table I). Vinylsulfone **11e** was prepared in 64% yield from the corresponding sulfide by oxidation with 2 equiv of *m*-chloroperoxybenzoic acid. It is noteworthy that the amine substituent did not require protection (e.g., by protonation), which may reflect in part deactivation by the α-cyano substituent.

Table I. Preparation of Cyclohexanols **11**

R	^1H NMR H_2[a]	^1H NMR $J_{H_2-H_3}$[b]	MS, MH^+-H_2O,[c] %	yield,[d,e] %
CH_3	2.49	12.0, 3.8	1	51
H	2.48	12.2, 4.0	7	52
SPh	3.01	12.0, 4.0	2	48
OEt	2.99	12.4, 4.4	0	43

[a] Chemical shifts (δ, ppm). [b] Coupling constant (Hz). [c] Chemical ionization isobutane mass spectrum (relative percent). [d] Yield after column chromatography. [e] None of the other diastereomers could be detected in the ^1H NMR spectrum of the crude material.

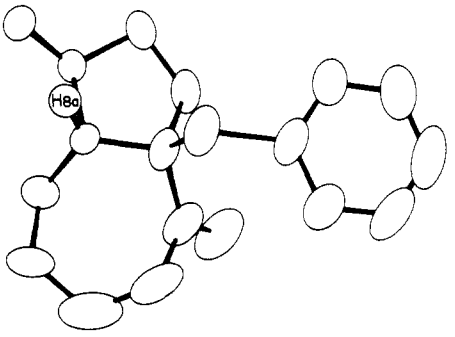


Figure 1. View of the X-ray model of **12c**.

Treatment of aminocyclohexanols **11a** or **11c** with 1.1 equiv of $AgNO_3$ in ethanol at room temperature for 1 h resulted in clean rearrangement to the 4-oxocycloheptapyrrolidine products **12a** (78%) and **12c** (76%). The cis stereochemistry of **12a** was supported by the high field ^1H NMR spectrum which showed a characteristic[4b] doublet (J = 7.1 Hz) at δ 1.98 for the angular hydrogen H_{8a}. Unfortunately, this hydrogen was not clearly resolved in the high field ^1H NMR spectrum of **12c**. The stereostructure of **12c** was established, therefore, by single-crystal X-ray diffraction of the maleic acid salt (see Figure 1).[16] The ^1H NMR spectrum of this salt did show a diagnostic doublet (J = 11.4 Hz) at δ 3.27 for H_{8a} which is rationalized, as in previously studied related cases,[4b] by a favored twist-chair conformation for the cis isomer which has an approximate 90° dihedral angle between the H_{8a} and the cis H_8 hydrogen.[16b]

The rearrangement of **11b** was more complex due to the propensity of the initially formed cis isomer **12b** to epimerize α to the ketone. Exposure of **11b** to 1.1 equiv of $AgNO_3$ in $CHCl_3$ buffered with an excess of pyridine for 19 h at 40 °C afforded a single product **12b** in 64% yield. In contrast, rearrangement of **11b** under standard conditions (1.1 equiv of $AgNO_3$ in EtOH, room temperature, 1 h) gave an inseparable 1.7:1 mixture of **12b** and its trans epimer **13**. That these materials were epimers was confirmed by treatment of this mixture with $NaOCH_3$ in methanol to afford a 5:1 mixture of **13** and **12b**, respectively. Stereochemical

(11) (a) A concerted mechanism in which the aza-allyl fragment "slides across" the carbocyclic allyl fragment to form the new C_3–C_5 σ-bond is a priori also possible. Such a mechanism has no precedent to our knowledge. (b) Cation **6** could be an intermediate in the conversion of **3** → **4**. Whether or not this is so, the unique feature of the aza-Cope–Mannich mechanism is the intervention of the rearranged iminium ion **4**.

(12) For a recent review of pinacol rearrangements, see: Bartok, M.; Molnar, A. In *Chemistry of Ethers, Crown Ethers, Hydroxyl Compounds and Their Sulphur Analogues*; Patai, S., Ed.; Wiley: New York, 1980; Part 2, pp 722–733.

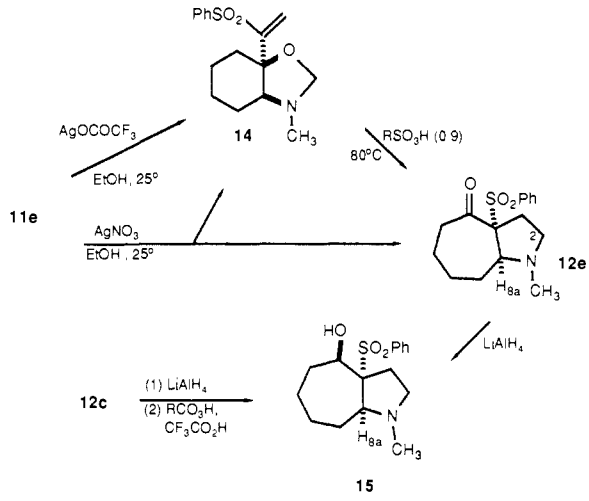
(13) For a recent study and leading references to the general area of carbocations containing electron-withdrawing α substituents, see ref 14.

(14) Creary, X.; Mahrsheikh-Mohammadi, E.; Eggers, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 2435.

(15) (a) Longevialle, P.; Milne, G. W. A.; Fales, H. J. *J. Am. Chem. Soc.* **1973**, *95*, 6666. (b) Longevialle, P.; Girard, J.-P.; Rossi, J.-C.; Tichy, M. *Org. Mass Spectrom.* **1980**, *15*, 268.

(16) (a) The final unweighted and weighted R values were 0.050 and 0.068. Details of the X-ray structure are provided in the Supplementary Material. (b) Ketone **12c** adopts the same twist-chair conformation that is observed for the oxime of 4-oxo-*cis*-perhydroazulene: House, H. O.; Gaa, P. C.; Van Derveer, D. *J. Org. Chem.* **1983**, *48*, 1661.

Scheme III

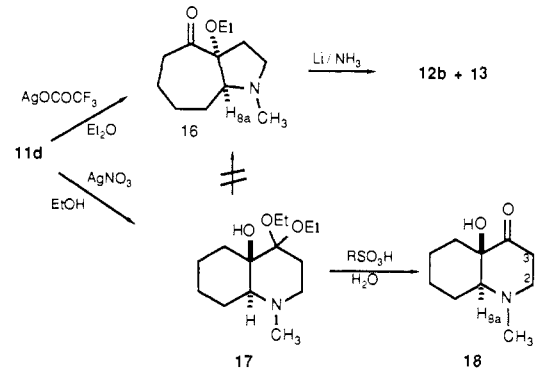


assignments were not readily achieved by spectroscopic means, in part because **12b** adopts a different conformation (H_{8a} is observed as an apparent quartet, J = 8.8 Hz) from that of its **3a**-substituted analogues. Assignment of the cis stereochemistry to the kinetic isomer was thus based solely on analogy. The gross structures of **12b** and **13** were confirmed, however, by their formation by reductive desulfenylation of the α-phenylthio ketone **12c** with Na(Hg).[17]

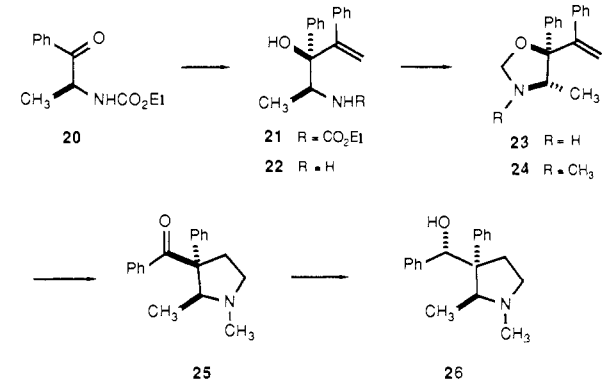
Amino alcohol **11e** was also successfully rearranged to the corresponding cycloheptapyrrolidine containing an angular sulfone substituent (see Scheme III). Thus, treatment of **11e** under standard conditions (1.1 equiv $AgNO_3$, EtOH, room temperature, 1 h) gave cycloheptapyrrolidine **12e** and the unrearranged oxazolidine **14** in 20% and 40% yields, respectively, after chromatographic separation. Cyclohexaoxazolidine **14** showed a diagnostic AB quartet (J = 1.9 Hz) for the NCH_2O group at δ 4.00 in its ^1H NMR spectrum, while the gross structure of the rearranged ketone was confirmed by its reduction with Na(Hg)[17] to provide a mixture of the cis and trans ketones **12b** and **13**. The cis stereochemistry of **12e** was confirmed by chemical correlation with **12c**. Although we were unsuccessful in the direct oxidation of the angular phenylthio group in cycloheptapyrrolidine **12c**, the desired oxidation was possible, after reduction of the carbonyl group, by treatment with *m*-chloroperoxybenzoic acid in the presence of 1 equiv of CF_3COOH. The sulfone alcohol **15**[18] produced in this way was identical with the product of $LiAlH_4$ reduction of **12e**. Cycloheptapyrrolidine **12e** could be obtained in better overall yield by a two-step sequence proceeding via **14**. Thus, treatment of **11e** with $AgOCOCF_3$ (1.1 equiv) for 1 h in EtOH provided oxazolidine **14** in 59% yield, whose subsequent rearrangement with acid (0.9 equiv of camphorsulfonic acid in refluxing benzene)[3] gave **12e** in >50% overall yield from amino alcohol **11e**.

Enol ether **11d** could also be transformed, albeit in low yield, to the corresponding angularly functionalized cycloheptapyrrolidine if the rearrangement was conducted in a nonnucleophilic solvent. For example, treatment of **11d** with 1.1 equiv of $AgOCOCF_3$ in ether for 1.5 h at room temperature provided a complex reaction product from which cycloheptapyrrolidine **16** could be isolated in 37% yield by careful chromatography. The cis stereochemistry of **16** follows from analogy with **12b** and from the fact that the maleic acid salt showed a doublet (J = 8.9 Hz) at δ 3.28 in the ^1H NMR spectrum for the angular hydrogen H_{8a}. Lithium–ammonia reduction of **16** gave a mixture of cycloheptapyrrolidines **13** and **12b**, thus confirming the gross structure of **16**. Rearrangement of **11d** under standard conditions in ethanol did not

Scheme IV

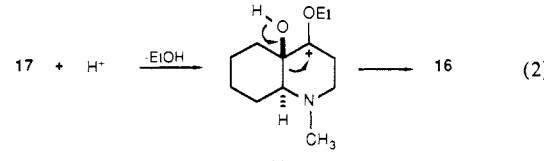


Scheme V



lead to **16** but afforded instead the oxidized perhydroquinoline **17**. The structure of this product was best deduced from the corresponding ketone **18**, which was obtained from **17** in 90% yield upon aqueous hydrolysis. The structure for **18** follows from a detailed analysis of its ^1H NMR spectrum. In particular the ^1H NMR spectrum showed a ddd (J = 11.1, 3.6, and 12.8 Hz) for $H_{2\alpha}$ at δ 2.40 and a ddd (J = 11.1, 1.4, and 7.4 Hz) for $H_{2\beta}$ at δ 3.06, both of which collapsed to doublets (11.4 Hz, geminal coupling) upon dideuteriation of **18** upon exchange with NaOMe/DOMe (see Scheme IV).

Some effort was invested in attempting to convert **17** to cycloheptapyrrolidine **16**. This conversion could, in principle, occur via pinacolic rearrangement of the α-alkoxy carbocation **19** as suggested in eq 2. Attempted rearrangement of **17** in benzene



(2)

in the presence of azeotropically dried camphorsulfonic acid led only to ketone **18**. Hydrolysis by adventitious water plagued attempted rearrangement with other acids also.[19] Ketone **18** also resisted rearrangement under basic conditions:[20] KO-*t*-Bu in refluxing HO-*t*-Bu or NaH in refluxing THF.[21]

B. Rearrangement of a Chiral Enantiomerically Enriched Substrate. Our earlier studies had shown that 5-vinyloxazolidines, which are derived from dehydrative condensation of amino alcohols **1** and aldehydes, can serve also as efficient rearrangement pre-

(17) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *39*, 3477.

(18) The stereochemistry of the alcohol group has not been rigorously established but is assigned on the expectation that reduction would occur from the convex face of the bicyclic ketones **12c** and **12e**.

(19) Possible catalysts for this transformation that were not examined in this study are alkylaluminum halides which have Bronsted base as well as Lewis acid properties see, e.g.: Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, C.; Deutsch, E. A.; Cordova, R.; Price, T. P. *Tetrahedron* **1981**, *37*, 3927.

(20) For a brief review of α-ketol rearrangements, see: Collins, C. J.; Eastham, J. F. In *The Chemistry of the Carbonyl Group*; Patai, S., Ed.; Wiley: New York; 1966; pp 778–783.

(21) This result is not surprising in light of the anticipated thermodynamic stability of **18**.

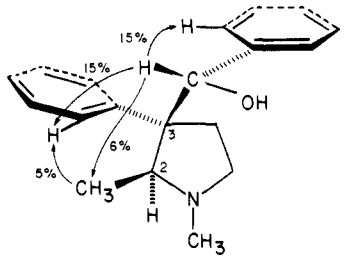


Figure 2. Configuration and conformation of **26** as deduced by ^{1}H NMR difference nuclear Overhauser experiments (DNOE). Diagnostic enhancements are indicated.

cursors.[3b] Thus, optically active 5-vinyloxazolidine **24** was prepared from the known[22] propiophenone **20** which is readily available from L-alanine (see Scheme V). Reaction of this enantiomerically pure intermediate with an excess of (1-phenylvinyl)lithium at −78 °C in THF following the general procedure of Rapoport[22] provided carbamate alcohol **21** in 80% yield as an ca. 20:1 mixture of diastereoisomers. The stereochemical assignment for the major isomer was initially based on the expectation[22,23] that organolithium addition would occur in the sense of the Cram cyclic model and was subsequently confirmed by ^{1}H NMR DNOE experiments with intermediate **24**. Base hydrolysis of **21** followed by reaction of the resulting amino alcohol with paraformaldehyde provided oxazolidine **23** in 73% yield. The 250 MHz ^{1}H NMR spectrum of the Mosher amide derivative of **23** showed signals for only a single diastereomer, which allows us to estimate that the enantiomeric excess of this material is at least 90%. Conversion of oxazolidine **23** to its *N*-methylated derivative was accomplished by the procedure of Borch[25] and provided diastereomerically pure crystalline **24**, $[\alpha]_D$ −159°, in 84% yield. Irradiation of the CH_3 group of **24** resulted in a 4% ^{1}H NMR DNOE enhancement of the ortho hydrogens of the angular phenyl group, while irradiation of the methine hydrogen of the oxazolidine ring resulted in 7% enhancement of the vinylic singlet at δ 5.40.

The desired rearrangement of **24** was readily accomplished in the presence of 1.0 equiv of camphorsulfonic acid in toluene at 60 °C for 1.5 h to provide predominantly a single rearrangement product. Purification on silica gel followed by recrystallization from hexane gave pure pyrrolidine ketone **25** in 79% yield. The lack of optical rotation at 365, 435, 546, 578, and 589 nm demonstrated that this product was racemic. That oxazolidine **24** underwent *no* racemization under the conditions of the rearrangement was established by reisolation of this intermediate from a rearrangement that was allowed to proceed for 20 min (70% completion). The pyrrolidine ketone obtained from this experiment showed a small, but measurable, rotation: $[\alpha]^{23}_{365}$ −1.0° (corresponding, vide infra, to an optical purity of 2%).

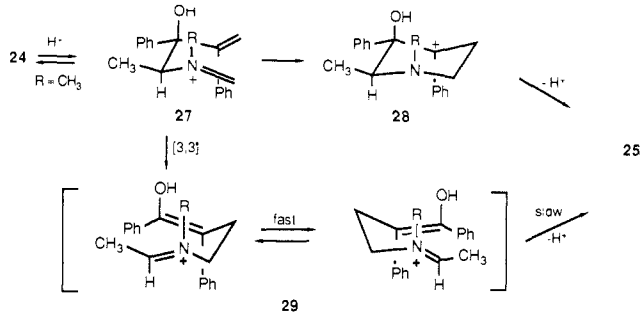
A major concern in this study was to establish that pyrrolidine ketone **25** did not racemize subsequent to its formation. Since **25** is a β-amino ketone it could undergo racemization by a retro-Mannich–Mannich sequence. We initially attempted to obtain a sample of optically active **25** by kinetic resolution. However, reduction of the hindered carbonyl group with a chiral binaphthol-modified $LiAlH_4$[26] or addition of a chiral sulfoximine[27] were not successful. However, reduction of **25** with $LiAlH_4$ at 0 °C proceeded with high diastereoselectivity to yield a single benzylic alcohol product, which could be resolved via its tartrate salt. The optically active alcohol obtained in this way was judged to be >90% enantiomerically pure by ^{1}H NMR analysis of its Mosher[24] ester derivative. Oxidation of this material with MnO_2 followed by rapid flash chromatography on silica gel provided a strongly rotating sample of optically active ketone **25**:[28] $[\alpha]^{23}_{435}$ +424°, $[\alpha]^{23}_{546}$ +216°, $[\alpha]^{23}_{578}$ +185°, $[\alpha]^{23}_{D}$ +177°. Oxidation of this material with MnO_2 followed by rapid flash chromatography on silica gel provided a strongly rotating sample of optically active ketone **25**:[28] $[\alpha]^{23}_{435}$ +424°, $[\alpha]^{23}_{546}$ +216°, $[\alpha]^{23}_{578}$ +185°, $[\alpha]^{23}_{D}$ +177°.

Table II. Stability of Pyrrolidine Ketone **25** to Racemization

condition	% decrease in optical rotation[a]
0.5 equiv RSO_3H, 60 °C, 1 h[b]	13 ± 2 (4)
1.0 equiv RSO_3H, 60 °C, 1 h[b]	6 ± 2 (4)
1.2 equiv RSO_3H, 60 °C, 1 h[b]	6 ± 1 (3)
flash chromatography on silica gel (hexane/EtOAc/Et_3N, 4:1:0.2)	4 ± 1 (2)

[a] at 435 nm; mean ± 1 standard deviation (number of runs). [b] [**25**] = 0.032 M in toluene, see Experimental Section for further details.

Scheme VI



The relative stereochemistry of **26** was assigned on the basis of ^{1}H NMR DNOE studies. These experiments are most consistent with the configuration and conformation that is illustrated in Figure 2. Besides the NOE's shown in Figure 2, the methine hydrogen at C-2 shows a strong NOE with the vicinal phenyl substituent and no enhancement with the methine hydrogen of the C-3-CH(Ph)OH substituent.

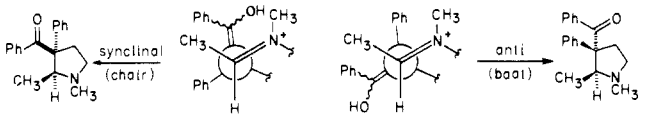
The key control experiments carried out with optically active pyrrolidine ketone **25** are summarized in Table II. Since it was possible that the ratio of amino ketone **25** to camphorsulfonic acid could affect the rate of a retro-Mannich fragmentation, control experiments were carried out in the presence of 0.5, 1.0, and 1.2 equiv of camphorsulfonic acid. Racemization was greatest in the presence of 0.5 equiv of acid, but even under these conditions it proceeded to an extent of only ~13% after 1 h at 60 °C in toluene. Pyrrolidine ketone **25** underwent more rapid racemization on silica gel and was extensively racemized during slow chromatography. However, rapid flash chromatography on silica gel resulted in little racemization. Thus, we conclude that the extensive racemization observed in the rearrangement of **24** occurs *prior* to the formation of the pyrrolidine ketone product **25**.

Discussion

Mechanistic Aspects. The lack of information concerning which step is rate-limiting in the conversion of the cyanomethyl amines **11** to cycloheptapyrrolidines **12** seriously compromises mechanistic interpretation of the rearrangements of these substituted substrates. For example, if formation of the iminium ions from the cyanomethyl amine starting materials was rate-limiting, all of the substituted alkenes **11** would rearrange at comparable rates. The qualitative observation that substrates **11a–e** (R = CH_3, H, SPh, OEt, SO_2Ph) rearrange in EtOH under very similar conditions in the presence of $AgNO_3$ would be consistent with this scenario. Nonetheless, the great instability[14] of α-sulfonyl cations provides at least a qualitative argument against a cyclization–pinacol mechanism for the conversion of vinyl sulfone **11e** to cycloheptapyrrolidine **12e**.

(22) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157.
(23) For a recent summary of diastereoselective additions of α-amino- and α-acylaminoketones, see: Tramontini, M. *Synthesis* **1982**, 605.
(24) Mosher, H. S.; Dale, J. A.; Dull, D. *J. Org. Chem.* **1969**, *34*, 2543.
(25) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Org. Chem.* **1971**, *93*, 2897.
(26) Noyori, R.; Tomino, I.; Nishizawa, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843.
(27) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021.
(28) The absolute stereochemistry of the optically active samples of this material obtained by resolution has not been established.

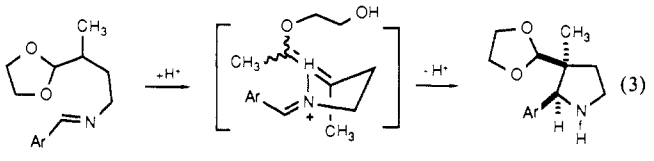
Scheme VII



Mechanistic interpretation of the rearrangement of the chiral, nonracemic substrate **24** is fortunately not clouded by any ambiguity with regard to the kinetic profile of the rearrangement. The observation that the acylpyrrolidine product **25** is produced in racemic (or nearly racemic) form requires the intervention of an achiral or equivalent intermediate. Clearly this result is incompatible with a process involving cyclization of the starting iminium ion to a 4-piperidinyl cation followed by pinacolic rearrangement of the latter intermediate (illustrated in Scheme VI by **27** → **28** → **25**). It should be stressed that this mechanistic test was not biased against the intervention of a 4-piperidinyl cation intermediate, since the intermediate in this case would have been a quite stable tertiary benzylic cation.

Racemization would be expected in a 2-azonia[3,3]sigmatropic rearrangement–Mannich cyclization sequence as long as the initially formed rearranged iminium ion underwent C–C single bond rotation more rapidly than intramolecular Mannich cyclization. This proviso arises from the fact that the initially formed rearrangement product, although devoid of stereogenic centers, would nonetheless be formed in a chiral conformation. Scheme VI illustrates this feature for the specific case of rearrangement of **27** via the more stable of the two possible chair[9,10] topographies. To our knowledge, the racemization observed in the conversion of **24** → **25** provides the first experimental evidence that the barrier for C–C bond formation between two oriented[29] reactive donor (enol) and acceptor (iminium ion) π-bonds has a barrier of at least >4–5 kcal/mol.[30]

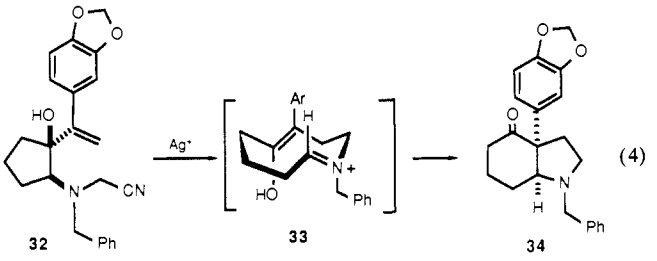
The relative stereochemistry observed for pyrrolidine ketone **25** would be rationalized if Mannich cyclization occurred preferentially via the (*E*)-iminium ion and with an approximate synclinal (or chairlike) geometry as is illustrated in Scheme VII. That the *E* configuration of the iminium ion would be involved seems assured since it is both the iminium geometry initially produced from the lower energy chair rearrangement transition state (see Scheme VI) and the more stable configuration. To our knowledge there is no literature guidance as to the preferred orientation of prochiral enol and iminium groups in Mannich reactions.[31] Our proposal that at least in the intramolecular case this cyclization occurs preferentially via the synclinal orientation shown in Scheme VII would also rationalize the observation[32] that acid-catalyzed Mannich cyclization of imine acetals **30** affords pyrrolidines **31** as the predominant products (see eq 3).



(3)

The isolation of decahydroquinoline **17** (see Scheme IV) from rearrangement of the enol ether substrate **11d** demonstrates, not surprisingly, that iminium ion–alkene cyclization can dominate over [3,3]-sigmatropic rearrangement if the alkene is highly nucleophilic. Our failure to experimentally demonstrate the conversion of **17** to the 4-oxocycloheptapyrrolidine **16** leaves unanswered for the present whether or not rearranged 3-acylpyrrolidines can also arise from unsaturated amino alcohols by a cyclization–pinacol sequence.

Synthetic Aspects. The successful rearrangement of unsaturated amino alcohols **11** containing alkenes of widely differing electronic properties provides an effective demonstration of the unusually broad scope of tandem aza-Cope rearrangement–Mannich cyclizations. The fact that this rearrangement occurs with racemization (even with an electron-rich styrenyl group) effectively precludes use of this chemistry to prepare simple chiral, nonracemic pyrrolidines. This limitation should not extend to the ring-enlarging pyrrolidine annulation version of this rearrangement[4,5] where racemization of the sigmatropic rearrangement product would be much less likely. An excellent example of this fact is provided by the rearrangement of the optically active 1-alkenyl-2-aminocyclopentanol **32** to afford the enantiomerically pure hydroindolone **34**[33] (see eq 4). Racemization of the likely intermediate in this sequence, **33**, by simple C–C single bond rotations is retarded in this case by the conformational constraints of the medium ring.



(4)

Conclusion

The observation that the optically active oxazolidine **24** racemizes during its conversion to the rearranged 3-acylpyrrolidine **25** unambiguously rules out a cyclization–pinacol mechanism (Scheme I, **3** → **6** → **5**) for this conversion. This result is consistent with a mechanism involving tandem cationic aza-Cope rearrangement–Mannich cyclization (Scheme I, **3** → **4** → **5**) as long as C–C bond rotations in **4** occur more rapidly than Mannich cyclization. This latter sequence appears to place few requirements on the electronic nature of the participating alkene group, since successful rearrangements are observed with substrates containing both highly electron-rich and electron-deficient π-bonds.

Experimental Section[34]

***trans*-2-(Methyl(cyanomethyl)amino)-1-((1-phenylthio)ethenyl)-cyclohexanol (11c).** A solution of 1-(phenylthio)ethylene[35] (60 mg, 0.44 mmol) and THF (1.5 mL) was added dropwise over 10 min to a solution of *n*-BuLi (0.32 mL of a 1.4 M solution in hexane, 0.45 mmol), tetramethylethylenediamine (70 μL, 0.46 mmol) and THF (2 mL) at −78 °C under argon. After stirring for 30 min at −78 °C, this solution was added (via double needle) dropwise to a solution of ketone **9**[4b] (72 mg, 0.43 mmol) and THF (2 mL) at −78 °C. The resulting solution was stirred for 30 min, quenched with wet THF, and allowed to warm to room temperature. Aqueous workup (ether, Na_2SO_4/K_2CO_3) and flash chromatography (silica gel, 5:1:0.01 hexane–ethyl acetate–Et_3N) gave 63 mg (48%) of a colorless oil, which solidified upon standing. Recrystallization from hot hexane (twice) gave an analytical sample, mp 108–110 °C: IR (CCl_4) 3607, 3487, 2936, 1601, 1439, 1096, 680 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.25–7.50 (m, PhH), 5.60 (s, C=C*H*H), 4.86 (s, C=CH*H*), 3.76 (ABq, J = 17.3 Hz, $\Delta\nu$ = 16.0 Hz, NCH_2CN), 3.01 (dd, J = 12.0, 4.0 Hz, CHN), 2.53 (s, CH_3N), 2.31 (s, 1 H), 1.45–2.05 (m, 7 H), 1.2–1.4 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) 153.6, 134.0, 133.1, 129.3, 127.9, 117.6, 112.4, 79.2, 65.4, 43.5, 40.4,

(29) By oriented we mean that the chair conformation that the iminium ion and enol groups are initially formed in would appear from Dreiding molecular models to have sufficient overlap between the reactive carbons of these groups for direct Mannich cyclization.

(30) For an introductory discussion of rotational barriers of acyclic molecules, see: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; American Chemical Society: Washington, DC, 1965; Chapter 1.

(31) Seebach has summarized a number of other condensations of donor and acceptor π-systems that occur preferentially via synclinal arrangements of the two prochiral centers and has suggested this arrangement as a general "topological rule": Seeback, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

(32) Bosch, J.; Rubiralta, M. *J. Het. Chem.* **1981**, *18*, 485. Bosch, J.; Rubiralta, M.; Moral, M. *Heterocycles* **1982**, *19*, 473.

(33) Sugai, S., unpublished observations.

(34) General experimental details are described in ref 4b. High resolution electron impact mass spectra determined at Irvine employed a VG-7070 spectrometer, while 500 MHz ^1H NMR spectra were determined with a GN-500 spectrometer.

(35) Pourcelot, G.; Cadiot, P. *Bull. Soc. Chem. Fr.* **1966**, 3024.

39.0, 25.5, 22.8, 21.2; MS (isobutane CI), m/z 303 (MH^+), 276, 111. Anal. Calcd for $C_{17}H_{22}N_2OS$: C, 67.51; H, 7.33; N, 9.26; S, 10.60. Found: C, 67.52; H, 7.35; N, 9.23; S, 10.59.

***trans*-2-(Methyl(cyanomethyl)amino)-1-((1-phenylsulfonyl)ethenyl)-cyclohexanol (11e).** To a solution of sulfide **11c** (182 mg, 0.603 mmol), $NaHCO_3$ (0.127 g, 1.51 mmol), and CH_2Cl_2 (10 mL) at −78 °C under argon was added a solution of 80% *m*-chloroperbenzoic acid (260 mg, 1.20 mmol of peracid) and CH_2Cl_2 (8 mL). The solution was stirred for 30 min at −78 °C and then allowed to warm to room temperature. After 17 h, basic workup (CH_2Cl_2, K_2CO_3) and flash chromatography (silica gel, 40:1:0.5 $CHCl_3$–MeOH–Et_3N) gave 75 mg of pure **11e**. An ca. 1:1 mixture of **11e** (0.103 g) and the corresponding sulfoxide was also obtained. This mixture was resubjected to the oxidation conditions (1.0 equiv of peracid) to give, after chromatography, an additional 53 mg of pure **11e**, combined yield 128 mg (64%): IR (CCl_4) 3501, 2924, 1443, 1299, 1137, 900 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.8–7.9 (m, PhH, 2 H), 7.45–7.65 (m, PhH, 3 H), 6.61 (d, J = 1.5 Hz, C=C*H*H), 5.91 (d, J = 1.5 Hz, C=CH*H*), 3.01 (ABq, J = 17.5 Hz, $\Delta\nu$ = 166 Hz, NCH_2CN), 2.96 (d, J = 1.6 Hz, 1 H), 2.6–2.7 (m, 1 H), 2.17 (s, CH_3N), 1.4–2.1 (m, 7 H), 1.2–1.4 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) 156.5, 141.1, 133.2, 128.9, 128.3, 124.9, 117.7, 79.6, 67.7, 43.1, 42.1, 40.8, 25.7, 21.7, 21.0; MS (isobutane CI), m/z 335 (MH^+), 308, 193, 113; high resolution MS (methane CI), m/z 335.1436 (335.1456 calcd for $C_{17}H_{23}N_2O_3S$).

4-Oxo-1-methyl-*cis*-3a-(phenylthio)decahydrocyclohepta[*b*]pyrrole (12c). To a solution of $AgNO_3$ (87 mg, 0.51 mmol) and absolute EtOH (14 mL) was added a solution of **11c** (0.141 g, 0.467 mmol) and EtOH (7 mL). The resulting mixture was stirred at room temperature under argon for 1 h and then filtered to remove silver cyanide. The residue was partitioned between aqueous K_2CO_3 and $CHCl_3$ (3 × 50 mL), and the combined organic layers were dried (K_2CO_3) and concentrated. The residue was taken up into petroleum ether, filtered, and concentrated to give 98 mg (76%) of **12c** as a clear oil, which was homogeneous by TLC analysis: IR (CCl_4) 2932, 2849, 1695, 1440, 1321, 683 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.1–7.4 (m, PhH), 3.4–3.6 (m, 1 H), 2.9–3.1 (m, 2 H), 2.54 (s, CH_3N), 2.35–2.65 (m, 2 H), 2.24 (ddd, J = 13.7, 10.3, 8.0 Hz, 1 H), 1.15–2.10 (m, 7 H); ^{13}C NMR (63 MHz, $CDCl_3$) 207.6, 135.4, 131.5, 129.4, 72.7, 71.7, 53.2, 41.9, 40.8, 35.0, 30.6, 26.9, 26.8; MS (isobutane CI), m/z 276 (MH^+), 166.

The maleic acid salt was prepared by treating **12c** with 1 equiv of maleic acid in ether. Removal of solvent and recrystallization from CH_2Cl_2–hexane gave transparent thin plates suitable for X-ray analysis: mp 188–189 °C; ^1H NMR (250 MHz, $CDCl_3$) 7.2–7.5 (m, PhH), 6.26 (s, CH=CH, 2 H), 3.9–4.1 (m, 1 H), 3.35–3.60 (m, 2 H), 3.27 (d, J = 11.9 Hz, H_{8a}), 3.09 (s, CH_3), 2.3–2.7 (m, 3 H), 2.0–2.7 (m, 3 H), 2.0–2.2 (m, 2 H), 1.90 (dd, J = 5.0, 15.3 Hz, 1 H), 1.50–1.85 (m, 3 H). Anal. Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58; S, 8.19. Found: C, 61.24; H, 6.45; N, 3.56; S, 8.22.

Reductive Desulfonylation of 12c. A solution of **12c** (13 mg, 0.047 mmol), Na_2HPO_4 (27 mg, 0.19 mmol), methanol (0.5 mL), and 6% Na(Hg) (72 mg)[17] was stirred at 0 °C for 2.5 h and then for 1 h at room temperature. Aqueous workup (ether, K_2CO_3) and flash chromatography (silica gel, 7:1 chloroform–methanol) gave 6.3 mg (48%) of recovered **12c** in early fractions and then 3.3 mg (80%, based on consumed **12c**) of an ~10:1 mixture of **13** and **12b**.

***cis*-4-Oxo-1-methyldecahydrocyclohepta[*b*]pyrrole (12b).** A solution of **11b** (26 mg, 0.134 mmol), $CHCl_3$ (2.5 mL), and $AgNO_3$ (0.15 mL of a 1.0 M solution in pyridine) was heated at 40 °C for 19 h. The resulting mixture was filtered, and the filtrate was partitioned between $CHCl_3$ (3 × 10 mL) and aqueous K_2CO_3 (10 mL). The organic layers were dried (K_2CO_3, Na_2SO_4) and concentrated to give 14.3 mg (64%) of **12b** as a clear oil, which was pure by TLC analysis. Analysis by GLC[36] indicated the presence of only a single isomer: IR (CCl_4) 2938, 2775, 1702, 1450, 1203 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 3.26 (apparent q, J = 8.8 Hz, 1 H), 3.06 (m, 1 H), 2.1–2.6 (m, 5 H), 2.28 (s, CH_3N), 1.5–1.9 (m, 6 H), 1.2–1.4 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) 212.2, 66.0, 56.5, 54.6, 42.2, 40.4, 29.8, 24.4, 24.3; MS (isobutane CI), 168 MH^+), 148, 91. High resolution MS (EI), m/z 167.1301 (167.1310 calcd for $C_{10}H_{17}NO$).

***trans*-4-Oxo-1-methyldecahydrocyclohepta[*b*]pyrrole (13).** A solution of **11b** (48.2 mg, 0.248 mmol) and absolute EtOH (2 mL) was added to a solution of $AgNO_3$ (46 mg, 0.27 mmol) and EtOH (7 mL). Precipitate formation occurred instantly, and the solution was stirred for 70 min at room temperature under argon. After filtration the solvent was removed, and the residue was partitioned between 1 N NaOH (10 mL) and ether (3 × 15 mL). The combined organic extracts were dried (K_2CO_3/Na_2SO_4) and concentrated to give 40 mg (95%) as a clear oil, which was homogeneous by TLC analysis, and a 1.7:1 mixture of trans and cis isomers, respectively, as determined by GLC analysis.[36] Isomerization to a 5:1 mixture of trans and cis isomers was effected by exposure of this oil to a solution of $NaOCH_3$ in MeOH. Spectral data for **13** as determined from this mixture are as follows: IR (CCl_4) 2930, 1708, 1448, 1155 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 3.18 (ddd, J = 10.3, 10.3, 5.3 Hz, 1 H), 3.07 (apparent dt, J = 1.7, 8.8 Hz, 1 H), 2.29 (s, CH_3N), 2.0–2.7 (m, 5 H), 1.2–1.5 (m, 4 H), 1.15–1.5 (m, 3 H); ^{13}C NMR (63 MHz, $CDCl_3$) 211.4, 69.8, 57.0, 56.5, 43.8, 40.4, 34.6, 27.3, 23.5, 22.1; MS (isobutane CI), m/z 168 (MH^+), 149, 137, 107, 91.

***cis*-5-((1-Phenylsulfonyl)ethenyl)-3-methyl-4,5-tetramethyleneoxazolidine (14).** A solution of **11e** (75 mg, 0.22 mmol) and dry Et_2O (4 mL) was added to a solution of $AgOCOCF_3$ (55 mg, 0.25 mmol) and ether (5 mL) causing instantaneous precipitate formation. The resulting mixture was stirred at room temperature under argon for 1 h and filtered, and the filtrate was partitioned between aqueous K_2CO_3 (15 mL) and Et_2O (3 × 15 mL). The combined organic layers were dried (K_2CO_3) and concentrated to give 41 mg (59%) of **14** as a light yellow oil, which was contaminated by a trace impurity by TLC analysis (30:1 $CHCl_3$–MeOH): IR (CCl_4) 2934, 1446, 1316, 1147 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.8–8.0 (m, PhH, 2 H), 7.4–7.7 (m, PhH, 3 H), 6.53 (d, J = 1.0 Hz, C*H*H=C), 6.17 (d, J = 1.0 Hz, CH*H*=C), 4.00 (ABq, J = 1.9 Hz, $\Delta\nu_{AB}$ = 177 Hz, OCH_2N), 2.9–3.0 (m, C*H*N), 2.11 (s, CH_3N), 1.2–2.1 (m, 8 H); ^{13}C NMR (63 MHz, $CDCl_3$) 155.2, 142.1, 132.9, 128.7, 127.9, 126.2, 86.1, 83.5, 64.9, 35.6 (2C), 23.1, 21.5, 20.0; MS (isobutane CI), m/z 309 (MH^+), 308, 296.

***cis*-3a-Phenylsulfonyl-4-oxo-1-methyldecahydrocyclohepta[*b*]pyrrole (12e).** A solution of oxazolidine **14** (37 mg, 0.12 mmol), camphorsulfonic acid (25 mg, 0.11 mmol), and benzene (10 mL) was heated at reflux for 20 h under argon. After having been cooled to room temperature, basic workup ($CHCl_3$, K_2CO_3) gave a quantitative yield of crude **12e**, which was homogeneous by TLC analysis: IR (CCl_4) 2933, 1715, 1447, 1308, 1149; ^1H NMR (250 MHz, $CDCl_3$) 7.9–8.1 (m, PhH, 2 H), 7.4–7.7 (m, PhH, 3 H), 3.36 (d, J = 7.2 Hz, H_{8a}), 3.09 (apparent t, J = 7.1 Hz, 1 H), 2.75–3.0 (m, 1 H), 2.30 (s, CH_3N), 2.20–2.75 (m, 3 H), 1.4–2.0 (m, 7 H); ^{13}C NMR (63 MHz, $CDCl_3$) 205.1, 138.1, 134.0, 131.0, 128.7, 86.2, 65.9, 54.8, 40.8, 39.2, 30.2, 28.8, 27.1, 22.3; MS (isobutane CI), m/z 308 (MH^+), 212, 113, 85, 81, 71; high resolution MS (methane CI), m/z 308.1317 (308.1327 calcd for $C_{16}H_{22}NO_3S$).

Reduction of a sample of this product with Na(Hg),[17] as described for **11c**, gave a 7:1 mixture of **13** and **12b** (~80% yield). Reduction with $LiAlH_4$ (0 °C, THF) gave **15** in 60% yield after chromatographic purification. This latter sample was indistinguishable (TLC and 250 MHz ^1H NMR analysis) from a sample of **15** prepared from **12c**.

Preparation of (3a*R,4*R**,8a*S**)-3a-Phenylsulfonyl-4-hydroxy-1-methyldecahydrocyclohepta[*b*]pyrrole (15) from 12c.** A mixture of $LiAlH_4$ (23 mg, 0.6 mmol) and THF (4 mL) at 0 °C was added to a solution of ketone **12c** (82.1 mg, 0.299 mmol) and THF (4 mL). The resulting mixture was stirred for 25 min at 0 °C and then quenched with 5 N NaOH (5.0 mL). Aqueous workup ($CHCl_3$, K_2CO_3) gave 77 mg (93%) of a single alcohol product as a clear oil, which was homogeneous by TLC analysis: IR (CCl_4) 3477, 2904, 2852, 1441, 1232, 686 cm^{-1}; MS (isobutane CI), m/z 278 (MH^+).

A 60-mg (0.22 mmol) sample of this material, CF_3CO_2H (20 μL, 0.26 mmol) and CH_2Cl_2 (10 mL) at −78 °C was treated with a solution of 80% *m*-chloroperbenzoic acid (93 mg, 0.54 mmol) and CH_2Cl_2 (5 mL). After stirring 15 min at −78 °C, the solution was allowed to warm to room temperature, and after 21 h basic workup (CH_2Cl_2, K_2CO_3) and purification by silica gel chromatography (20:1:0.5 $CHCl_3$–MeOH–Et_3N) gave 55 mg (81%) of **15** as a clear thick oil: IR (CCl_4) 3485, 2912, 2846, 1277, 1127 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.9–8.1 (m, PhH, 2 H), 7.5–7.8 (m, PhH, 3 H), 3.96 (dd, J = 9.1, 7.0 Hz, 1 H), 3.67 (d, J = 7.0 Hz, 1 H), 3.06 (dd, J = 7.4, 3.2 Hz, 1 H), 2.80 (dd, J = 8.6, 7.3 Hz, 1 H), 2.24 (dd, J = 14.7, 5.9 Hz, 1 H), 2.17 (s, CH_3N), 2.1–2.4 (m, 1 H), 1.4–2.1 (m, 9 H); ^{13}C NMR (63 MHz, $CDCl_3$) 137.7, 134.1, 131.0, 129.0, 80.2, 74.5, 67.3, 54.4, 40.1, 33.7, 31.8, 28.7, 24.9, 22.2; MS (isobutane CI), m/z 310 (MH^+), 168.

Rearrangement of Vinyl Sulfone 11e with $AgNO_3$ in Ethanol. A solution of **11e** (94 mg, 0.28 mmol), $AgNO_3$ (51 mg, 0.31 mmol), and absolute EtOH (15 mL) was maintained at room temperature for 1 h and then worked up as described for the preparation of **12c**. Chromatographic purification gave 34 mg (40%) of oxazolidine **14** and 17 mg (20%) of the rearranged ketone **12e**.

***cis*-3a-Ethoxy-4-oxo-1-methyldecahydrocyclohepta[*b*]pyrrole (16).** A solution of **11d** (62 mg, 0.26 mmol) and dry Et_2O (2 mL) was added to a solution of $AgOCOCF_3$ (63 mg, 0.28 mmol) and dry ether (4 mL). The resulting mixture was stirred at room temperature under argon for 1.5 h. Filtration followed by basic workup (ether, K_2CO_3/Na_2SO_4) and flash chromatography (silica gel, 8:1 $CHCl_3$–MeOH) gave 20 mg (37%) of **16** as a light yellow oil: IR (CCl_4) 2930, 1712, 1444, 1053; ^1H NMR (250 MHz, $CDCl_3$) 3.29 (AB_q of q, J = 2.0 Hz, $\Delta\nu$ = 87.3 Hz, J = 7.0 Hz, OCH_2CH_3), 2.80–3.05 (m, 2 H), 2.50 (ddd, J = 12.3, 8.4, 5.1 Hz, CH*H*N), 2.37 (s, CH_3N), 2.1–2.4 (m, 3 H), 1.7–2.1 (m, 4 H), 1.4–1.7

Table III. ^{1}H NMR Spectrum of **18**

	chemical shift (δ)				
J, Hz	$H_{2\alpha}$	$H_{2\beta}$	$H_{3\alpha}$	$H_{3\alpha}$[a]	$H_{3\beta}$[a]
	2.40	3.06	2.23	3.21	1.97
$J_{H_{2\alpha}\text{-}H}$		11.1	3.6	12.8	
$J_{H_{2\beta}\text{-}H}$	11.2		1.3	7.5	
$J_{H_{3\alpha}\text{-}H}$	3.6	1.4		13.8	
$J_{H_{3\beta}\text{-}H}$	12.8	7.4	13.8		
$J_{H_{8a}\text{-}H}$					11.5 and 4.4

[a] Exchanges with NaOMe/DOMe. [b] Is coupled also to hydrogens in upfield multiplet.

(m, 2 H), 1.21 (t, J = 7.0 Hz, CH_3CH_2O), 1.1–1.3 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) 212.8, 95.0, 75.1, 60.1, 54.3, 41.0, 38.8, 31.4, 27.7, 27.4, 25.4, 16.2; MS (isobutane CI), m/z 212 (MH^+), 200, 184, 126; high resolution MS (EI), m/z 211.1567 (211.1572 calcd for $C_{12}H_{21}NO_2$).

The maleic acid salt, mp 148–150 °C (from CH_2Cl_2–hexane), showed the following: ^{1}H NMR (250 MHz, $CDCl_3$) 6.29 (s, HC=CH), 3.88 (dd, J = 7.2, 9.5 Hz, 1 H), 3.35–3.50 (m, 1 H), 3.28 (apparent d, J = 8.9 Hz, 1 H), 2.8–3.2 (m, 3 H), 2.96 (s, CH_3N), 1.9–2.6 (m, 6 H), 1.4–1.7 (m, 3 H), 1.22 (t, J = 7.0 Hz, CH_3CH_2O).

Reduction of a 15-mg sample of **16** with excess Li in refluxing NH_3 gave, in 74% yield, a 2:1 mixture of **13** and **12b**.

***trans*-4,4-Diethoxy-4a-hydroxy-1-methyloctahydroquinoline (17).** To a solution of $AgNO_3$ (31 mg, 0.18 mmol) and absolute EtOH (7 mL) was added a solution of **11d** (40 mg, 0.17 mmol) and absolute EtOH (4 mL). Precipitate formation occurred rapidly, and the solution was stirred for 1 h at room temperature under argon. After filtration and concentration, basic workup (ether, K_2CO_3/Na_2SO_4), followed by purification by flash chromatography (silica gel, 8:1 $CHCl_3$–MeOH) gave 26 mg (61%) of **17** as a light yellow oil: IR (CCl_4) 3465, 2934, 1446, 1109, 1088, 1053 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 3.4–3.8 (m, OCH_2CH_3, 4 H), 2.6–2.9 (m, 2 H), 2.22 (s, CH_3N), 2.1–2.4 (m, 4 H), 1.25–1.90 (m, 8 H), 1.19 (t, J = 7.0 Hz, CH_3CH_2, 3 H), 1.18 (t, J = 7.0 Hz, CH_3CH_2); ^{13}C NMR (63 MHz, $CDCl_3$) 100.8, 74.8, 65.2, 59.9, 56.7, 53.3, 41.6, 27.6, 27.2, 26.0, 24.8, 20.6, 16.2, 15.9; MS (isobutane CI), m/z 258 (MH^+), 228, 212, 140; high resolution MS (EI), m/z 257.1981 (257.1991 calcd for $C_{14}H_{27}NO_3$).

1-Methyl-*trans*-4a-hydroxyoctahydroquinolinone (18). A solution of ketal **17** (21 mg, 0.082 mmol), camphorsulfonic acid (20 mg, 0.086 mmol), water (20 μL, 1.1 mmol), and benzene (5 mL) was heated at reflux for 3 h. After having been cooled to room temperature, basic workup (ether, K_2CO_3/Na_2SO_4) gave 14 mg (90%) of **18** as a gelatinous solid, which was homogeneous by TLC analysis: IR (CCl_4) 3463, 2949, 1729, 1259, 1087, 1009 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 3.5–4.0 (br s, OH), 1.65–1.93 (m, 3 H), 1.35–1.65 (m, 4 H), 1.05–1.35 (m, 1 H) see also Table III; ^{13}C NMR (63 MHz, $CDCl_3$) 209.5, 74.5, 69.1, 56.1, 40.7, 37.9, 27.9, 25.9, 24.5, 20.0; high resolution MS (isobutane CI), m/z (relative intensity) 184.1341 (100, 184.1339 calcd for $C_{10}H_{18}NO_2$), 166 (77), 155 (60).

A 4.5-mg sample of ketone **18** was exposed twice to a solution of MeOD/MeONa. Workup ($CHCl_3/D_2O$) gave a quantitative yield of dideuterio **18**: ^{1}H NMR (250 MHz, $CDCl_3$) 3.06 (d, J = 11.4 Hz, CHHN), 2.40 (d, J = 11.4 Hz, CHHN), 2.31 (s, CH_3N), 1.97 (dd, J = 4.4, 11.3 Hz, CHN), 1.0–1.93 (m, 7 H), 0.80–1.0 (m, 1 H).

(3*S*,4*S*)-4-((Ethoxycarbonyl)amino)-2,3-diphenyl-1-penten-3-ol (21). A solution of (*S*)-2-(ethoxycarbonyl)amino)propiophenone[22] (0.40 g, 1.81 mmol) and 11 mL of dry THF was cooled to −78 °C and added via cannula to a solution of (1-phenylvinyl)lithium (40 mL of a 0.25 M solution in a 4.6:1 mixture of THF and pentane).[4] The resulting solution was maintained at −78 °C for 1.8 h and then quenched with stirring by adding 10 mL of saturated NH_4Cl solution, and the reaction mixture was allowed to warm to room temperature. Aqueous workup (EtOAc, $MgSO_4$) followed by purification on silica gel (6:1 hexane–EtOAc) gave 0.47 g (80%) of an ca. 20:1 mixture (by ^{1}H NMR analysis) of diastereomeric alcohols as a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$ major isomer) 7.1–7.5 (m, 9 H), 6.85 (dd, 1 H, J = 1.4, 7.9 Hz), 5.68 (br s, HC=), 5.28 (d, J = 7.8 Hz, $NHCO_2Et$), 5.27 (br s, HC=), 4.47 (m, CH_3CH), 4.15 (q, J = 6.9 Hz, $CO_2CH_2CH_3$), 2.31 (br s, OH), 1.28 (t, J = 7.0 Hz, CH_2CH_3), 0.91 (d, J = 6.6 Hz, $CHCH_3$, major isomer), 0.84 (d, J = 6.6 Hz, $CHCH_3$, minor isomer); IR (film) 3433, 2985, 1680, 1515, 1449, 1338, 1068 cm^{-1}; MS (EI), m/e (relative intensity) 325 (7), 209 (43), 149 (20), 116 (100).

(3*S*,4*S*)-4-Amino-2,3-diphenyl-1-penten-3-ol (22). A degassed solution of carbamate **21** (0.74 g, 2.3 mmol), KOH (70 g, 1.3 mol), and methanol–water (120 mL, 3:1) was heated at reflux for 12 h. After having been cooled to room temperature, the reaction mixture was extracted with ether (3 × 100 mL), and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. Purification of the residue on silica gel (10:1 $CHCl_3$–MeOH) gave 0.49 g (84%) of a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) 7.4–7.5 (m, 2 H), 7.1–7.35 (m, 6 H), 6.93 (m, 2 H), 5.56 (s, HC=), 5.30 (s, HC=), 3.77 (q, J = 6.3 Hz, CH_3CH), 1.52 (br s, OH), 0.77 (d, J = 6.3 Hz, CH_3); IR (film) 3398, 3025, 2979, 1599, 1492, 1447, 1380, 1140 cm^{-1}; MS (isobutane CI), m/z 254 (MH^+), 236.

(4*S*,5*S*)-4-Methyl-5-phenyl-5-(1-phenylethenyl)oxazolidine (23). A mixture of powdered paraformaldehyde (77 mg, 2.7 mmol), amino alcohol **22** (0.52 g, 2.0 mmol), and dry toluene (15 mL) was stirred at room temperature for 15 h and then concentrated. Purification of the residue on silica gel (10:1 $CHCl_3$–MeOH) gave 0.48 g (87%) of an ca. 16:1 mixture (^{1}H NMR analysis) of diastereomeric oxazolidines **23** as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) 7.2–7.4 (m, 5 H), 7.15 (s, 5 H), 5.56 (s, HC=), 5.41 (s, HC=), 4.87 (d, J = 6.1 Hz, NCHO), 4.53 (d, J = 6.1 Hz, NCHO), 3.79 (q, J = 6.6 Hz, CH_3CH), 2.1 (br s, NH), 0.88 (d, J = 6.6 Hz, $CHCH_3$, major isomer), 0.72 (d, J = 6.6 Hz, $CHCH_3$, minor isomer); IR (film) 3301, 3021, 2971, 2872, 1598, 1489, 1443, 1092 cm^{-1}; MS (CI), m/z 266 (MH^+). ^{1}H NMR analysis of the Mosher amide[24] prepared from (+)-MPTA chloride showed a single methyl doublet at δ 0.85, while this derivative prepared from a racemic sample showed two methyl doublets at δ 0.85 and 0.80.

(4*S*,5*S*)-3,4-Dimethyl-5-phenyl-5-(1-phenylethenyl)oxazolidine (24). Oxazolidine **23** (790 mg, 2.98 mmol) was N-methylated by the general procedure of Borch[25] (formalin and $NaCNBH_3$ in CH_3CN; pH maintained at 6 by periodic addition of 0.1 N HCl, 48 h at room temperature) to afford a solid product. Recrystallization from hexane provided 705 mg (84%) of isomerically pure **24**: mp 94–95 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 7.50 (m, 2 H), 7.2–7.4 (m, 3 H), 7.13 (br s, 5 H), 5.58 (s, HC=), 5.40 (s, HC=), 4.82 (d, J = 2.4 Hz, NCHO), 3.94 (d, J = 2.4 Hz, NCHO), 3.07 (q, J = 6.4 Hz, CH_3CH), 2.29 (s, NCH_3), 0.80 (d, J = 6.5 Hz, $CHCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) 152.6, 141.7, 140.8, 128.2, 127.7, 127.6, 127.3, 127.1, 115.1, 90.3, 87.3, 67.7, 36.4, 15.7; IR ($CHCl_3$) 2972, 1446, 1375, 1144 cm^{-1}; MS (CI), m/z 280 (MH^+); $[\alpha]_{365}^{23}$ −570°, $[\alpha]_{435}^{23}$ −336°, $[\alpha]_{546}^{23}$ −190°, $[\alpha]_{578}^{23}$ −165°, $[\alpha]_{D}^{23}$ −159 (toluene, c 2.2). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.72; H, 7.53; N, 5.02. Found: C, 81.80; H, 7.58; N, 5.02.

(2*S,3*R**)-3-Benzoyl-1,2-dimethyl-3-phenylpyrrolidine (25).** Camphorsulfonic acid (0.21 g, 0.94 mmol) was added in 1 portion to a solution of oxazolidine **24** (264 mg, 0.944 mmol) and toluene (29 mL) at 60 °C. The resulting solution was stirred at 60 °C for 1.5 h and then quenched with an excess of cold 2 N NaOH solution. Aqueous workup (benzene, K_2CO_3) and purification of the residue on silica gel (4:1:0.2 hexane–EtOAc–Et_3N) provided 0.24 g (91%) of chromatographically pure pyrrolidine **25** as a pale yellow solid. Recrystallization from hexane gave 0.208 g (79%) of pure **25**: mp 88–89 °C; ^{1}H NMR (250 MHz, $CDCl_3$), 7.59 (m, 2 H), 7.15–7.4 (m, 8 H), 3.43 (q, J = 6.5 Hz, CH_3CH), 2.9–3.05 (m, 2 H, CH_2NCH_3), 2.4–2.6 (m, 1 H, CH_2CH_2), 2.51 (s, NCH_3), 1.95–2.1 (m, 1 H, CH_2CH_2N), 1.01 (d, J = 6.5 Hz, $CHCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) 199.7, 144.5, 136.9, 131.9, 130.1, 128.9, 128.1, 127.0, 126.7, 96.3, 66.3, 65.8, 52.2, 39.3, 36.7, 14.9; IR (film) 3055, 2964, 2420, 2797, 1674, 1597, 1445, 1251 cm^{-1}; MS (EI), m/z (relative intensity) 279 (64), 202 (22), 158 (22), 105 (63), 71 (100); no measurable optical rotation at 365, 435, 546, 578, and 589 nm. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.72; H, 7.53; N, 5.02. Found: C, 81.69; H, 7.59; N, 5.01.

(2*S,3*R**)-1,2-Dimethyl-3-phenyl-3-((hydroxymethyl)phenyl)-pyrrolidine (26).** Lithium aluminum hydride (11 mg, 0.29 mmol) was added in 1 portion to a solution of ketone **25** (26 mg, 0.093 mmol) and dry THF (1.5 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and 1 h at room temperature. Basic workup ($CHCl_3$, $MgSO_4$) followed by crystallization of the crude product from hexane gave 23 mg (88%) of **26** as white needles: mp 151 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 7.2–7.4 (m, 5 H), 7.0–7.1 (m, 3 H), 6.76 (m, 2 H), 5.03 (s, CHOH), 3.18 (dt, J = 2.4, 9.0 Hz, 1 H, NCHH), 2.85 (q, J = 6.7 Hz, $CHCH_3$), 2.61 (dt, J = 8.0, 12 Hz, 1 H, NCHH), 2.28 (s, NCH_3), 2.1–2.3 (m, 2 H), 1.29 (d, J = 6.6 Hz, $CHCH_3$); IR ($CHCl_3$) 3597, 3200 (br), 2957, 2785, 1600, 1448, 1346, 1173 cm^{-1}; MS (EI), m/e (relative intensity) 281 (11), 174 (17), 160 (15), 71 (100). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.14; H, 8.19; N, 4.98. Found: C, 81.06; H, 8.24; N, 4.96.

Resolution of Pyrrolidine Alcohol 26. D-(−)-Tartaric acid (0.389 g, 2.59 mmol) was dissolved in a minimum volume of hot methanol, and the resulting solution was added to racemic amino alcohol **26** (0.728 g, 2.59 mmol) in 1 portion. The resulting solution was diluted with hot chloroform (40 mL), and the clear, colorless solution was then concentrated by using a steam bath until half of the original volume remained. Additional hot chloroform (20 mL) was then added, and this process was repeated until the solution became turbid. The resulting mixture was allowed to sit at room temperature overnight, and the resulting white crystals were isolated by filtration. This solid was recrystallized in this

way (4×) to a constant mp of 215 °C. Conversion to the free base and crystallization from hexane provided a resolved sample of amino alcohol **26**: $[\alpha]^{23}_{365}$ -43.7°, $[\alpha]^{23}_{435}$ -11.4°, $[\alpha]^{23}_{546}$ -0.37°, $[\alpha]^{23}_{578}$ +0.64°, $[\alpha]^{23}_{D}$ +0.86° (toluene, *c* 2.7). The Mosher ester[24] of this material showed no trace of a diastereomer by ^{1}H NMR analysis at 250 MHz.

Preparation of Optically Active Pyrrolidine Ketone 25 from Resolved 26. A mixture of MnO_2 (200 mg, 2.3 mmol), resolved **26** (20 mg, 0.071 mmol), and dry toluene (4 mL) was rapidly stirred for 5 h at room temperature and then filtered through a pad of Celite. The Celite was washed with benzene (200 mL), the filtrate was concentrated, and the residue was purified by rapid flash chromatography on silica gel (0.5 g; 1:4:0.2 EtOAc-hexane-Et_3N) to give 2.5 mg (13%) of ketone **25** and 12 mg (61%) of recovered alcohol **26**. Pyrrolidine ketone **25** prepared in this way showed the following optical rotations: $[\alpha]^{23}_{435}$ +424°, $[\alpha]^{23}_{546}$ +216°, $[\alpha]^{23}_{578}$ +185°, $[\alpha]^{23}_{D}$ +177° (toluene, *c* 0.66).

Rearrangement of 24 to Partial Completion. A solution of oxazolidine **24** (28.1 mg, 0.101 mmol), camphorsulfonic acid (23 mg, 0.10 mmol), and toluene (3 mL) was heated at 60 °C for 20 min (70% completion by ^{1}H NMR analysis). This crude mixture was reduced with $LiAlH_4$, and the resulting crude product was partially reoxidized with MnO_2. Separation on silica gel gave 2 mg of recovered oxazolidine **24** as an oil: $[\alpha]^{23}_{365}$ -573°, $[\alpha]^{23}_{D}$ -159° (100% optical purity), 6 mg of crystalline alcohol **26** after recrystallization from hexane, $[\alpha]^{23}_{365}$ -1.0° (2.3% optical purity), and 2.5 mg of ketone **25** as an oil, $[\alpha]^{23}_{D}$ +4.4° (2.5% optical purity).

In a similar fashion, **24** (36.1 mg, 0.129 mmol), camphorsulfonic acid (37.6 mg, 0.162 mmol), and toluene (4 mL) were heated for 15 min at 60 °C (83% completion). Pyrrolidine alcohol **26** (11.5 mg, 32%) was then isolated after reduction with $LiAlH_4$, chromatographic purification, and crystallization from hexane: $[\alpha]^{23}_{365}$ -2.1° (4.9% optical purity).

Stability of Pyrrolidine Ketone 25 to Racemization. Camphorsulfonic acid (3.3 mg, 0.014 mmol, 0.5 equiv) was added in 1 portion to a 0.032 M solution of resolved ketone **25** (7.5 mg, 0.027 mmol, $[\alpha]^{23}_{365}$ +343°) in toluene (0.85 mL). The resulting solution was stirred at 60 °C for 1 h and then quenched by adding a cold 2 N NaOH solution (2 mL). Product isolation as described in the preparation of **25** from **24** provided 6.0 mg (80%) of chromatographically pure ketone **25** as a colorless oil. Capillary GC analysis[36] showed the purity of this ketone to be greater than 98%: $[\alpha]^{23}_{365}$ +303°. This experiment was repeated four times, and identical control experiments were performed with 1.0 and 1.2 equiv of camphorsulfonic acid. Results are summarized in Table II.

Acknowledgment. We thank Professor R. J. Doedens for assistance with the X-ray crystallography and M. Fisher for DNOE studies. This research was supported by a Javits Neuroscience Investigator Award from the National Institute of Neurological and Communicative Disorders and Stroke. NMR and mass spectra were determined with spectrometers purchased with the assistance of NSF Shared Instrumentation Grants.

Supplementary Material Available: Experimental details and characterization data for **11a**, **11b**, **11d**, and **12a**, X-ray data for **12c**, tables of atomic and positional parameters, hydrogen atom coordinates, bond angles, and bond distances, and an X-ray model of Figure 2 with full atom labeling (10 pages). Ordering information is given on any current masthead page.

(36) A 30-ft SE-30 quartz capillary column was employed for this analysis.

Structure and Mechanism in the Photo-Retro-Aldol Type Reactions of Nitrobenzyl Derivatives. Photochemical Heterolytic Cleavage of C-C Bonds[1]

Peter Wan*,[2] and S. Muralidharan

Contribution from the Department of Chemistry, University of Victoria, Victoria, British Columbia, Canada V8W 2Y2. *Received September 21, 1987*

Abstract: The photo-retro-aldol type reactions of several nitroaromatic compounds have been studied in aqueous solution over the pH 1-14 range. These reactions are observed only in aqueous or in predominantly aqueous solution. Catalysis of reaction due to hydroxide ion is observed for several derivatives. Quantum yields of reaction and product ratios (of nitrotoluene vs dinitrobibenzyl) are reported as a function of pH. The proposed mechanism of reaction involves heterolytic cleavage of the benzylic C-C bond from the triplet excited state in the primary photochemical step to generate a nitrobenzyl carbanion and a carbocation-equivalent fragment, except for the nitrophenylacetates **24-26**, which eliminate CO_2 in place of such a fragment. Photogenerated nitrobenzyl carbanions are efficiently trapped by molecular oxygen to give isolable hydroperoxides at pH <12. The pH dependence of quantum yield of reaction along with α-deuterium isotope effects indicates that different transition states for benzylic C-C bond heterolysis are operative, depending on the substrate as well as the pH of the solution. Hydroxide ion catalyzed rate constants for the primary photochemical step are estimated for alcohols **8** and **9** to be $\sim 1 \times 10^9$ M^{-1} s^{-1}. The results show that photochemical C-C bond heterolysis requires favorable stabilization of both the carbanion and carbocation-derived fragments. Hydroxide ion catalysis may also facilitate the process. The use of the nitrobenzyl moiety as the carbanion-stabilizing group appears to be generally applicable, as demonstrated by the systems studied.

Studies of C-C bond forming and cleavage reactions play a central role in organic chemistry. Rupture of a C-C bond may proceed via either homolytic or heterolytic pathways. The homolytic pathway has been studied in some detail, and C-C bond dissociation energies have been extensively tabulated.[3] The less common heterolytic process—in which a carbocation and a carbanion are formed—has not been as extensively studied. Recently, however, there has been interest in developing molecular systems for study of kinetics and thermodynamics and structural requirements of C-C bond heterolysis, as well as in carbocation-anion recombination reactions.[4] Heterolytic C-C bond cleavage processes are also not common in photochemical reactions, al-

(1) This work has appeared in preliminary form: Wan, P.; Muralidharan, S. *Can. J. Chem.* **1986**, *64*, 1949.
(2) NSERC Canada University Research Fellow, 1984-1989.
(3) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976.
(4) (a) Arnett, E. M.; Troughton, E. B.; McPhail, A. T.; Molter, K. E. *J. Am. Chem. Soc.* **1983**, *105*, 6172. (b) Troughton, E. B.; Molter, K. E.; Arnett, E. M. *Ibid.* **1984**, *106*, 6726. (c) Arnett, E. M.; Chawla, B.; Molter, K. E.; Amarnath, K.; Healy, M. *Ibid.* **1985**, *107*, 5288. (d) Mitsuhashi, T. *Ibid.* **1986**, *64*, 2239. (e) Arnett, E. M.; Troughton, E. B. *Tetrahedron Lett.* **1983**, 3299. (f) Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Takahashi, K. *J. Chem. Soc., Chem. Commun.* **1985**, 173. (g) Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239.

0002-7863/88/1510-4336$01.50/0 © 1988 American Chemical Society