Preparation of a Mixture of Equimolar Amounts of 4b and 5b. This was performed in a similar manner as described above using methallyltrimethylsilane (**2c**) instead of **2a**. The molar ratio of **4b**/**5b** was 49.4:50.6 by GLC analysis (Silicone SE-30 25-m capillary column; column temperature, 178 °C; flame ionization detector; t_r, (**4b**) 22.4, (**5b**) 18.4 min).

(*S*)-3-Hydroxy-3-phenyl-5-hexen-2-one (6) from (*S*)-15. To an ether solution of (*S*)-**15**[15] (0.077 g, 0.40 mmol) in an ice bath was added MeLi (0.5 mL, 1.0 mmol) under atmoshere of an argon. After the reaction mixture was stirred for 3 h, a phosphate buffer solution (1.5 mL, pH 7) was added. The aqueous layer was extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4 and was evaporated under reduced pressure. Purification of oily residue on silica gel TLC ($CHCl_3$ as developing solvent) afforded (*S*)-**6** (0.032 g, 41%), $[\alpha]^{27}_D$ +104.4° (*c* 1.01, benzene), 88% ee by NMR analysis using a chiral shift reagent [Eu(hfc)$_3$].

(*R*)-3-Hydroxy-3-phenyl-5-hexen-2-one (6) from (*R*)-15. In a similar manner, from (*R*)-**15**,[15] (*R*)-**6** was obtained in 40% yield, $[\alpha]^{27}_D$ −119.6° (*c* 0.854, benzene).

Condensation of (*S*)-2-Hydroxy-2-phenyl-4-pentenoic Acid (15) and Methyl (*S*)-Prolinate (13). To a solution of (*S*)-**15**[15] (0.115 g, 0.60 mmol) and triethylamine (0.061 g, 0.60 mmol) in CH_2Cl_2 (1 mL) was added Mpt-Cl (**14**, 0.078 g, 0.61 mmol) in 0.3 ml of CH_2Cl_2 under an argon atmosphere. Then the reaction mixture was cooled in an ice bath and was stirred for 30 min. A mixture of (*S*)-methyl prolinate hydrochloride (**13**, 0.109 g, 0.60 mmol) and Et_3N (0.067 g, 0.66 mmol) in 0.4 mL of CH_2Cl_2 was added to the mixture over a period of 2 min. After the reaction mixture was stirred overnight, the solvent was removed in vacuo. Then 10 mL of ethyl acetate was added and was washed with 0.5 M citric acid, water, saturated $NaHCO_3$, water, and brine, successively. The solvent was dried over anhydrous Na_2SO_4 and was evaporated under reduced pressure. GLC analysis (for the conditions, see the preceding paragraphs) showed that the ratio of **4a**/**5a** was 94:6 (corresponding to 88% de).

Condensation of (*R*)-2-Hydroxy-2-phenyl-4-pentenoic Acid (15) and Methyl (*S*)-Prolinate (13). In a similar manner, condensation reaction of (*R*)-**15**[15] and (*S*)-**13** hydrochloride using Mpt-Cl (**14**) afforded mixture of **4a** and **5a**. GLC analysis showed that the ratio of **4a**/**5a** was 1.5:98.5.

Reaction of Allyltrimethylsilane (2a) with Isopropyl (*S*)-*N*-(Benzoylformyl)prolinate (1b). Preparation of (*R*)-(−)-6. **1b** was made to react with **2a** in the presence of $SnCl_4$ in CH_2Cl_2 at 0 °C. The usual workup as described before afforded **3c** + **4c** in 63%. **3c** + **4c**: IR (neat) 3425 (OH), 3080, 3000, 2900, 1750, 1630, 1460, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (br, 6 H), 1.45–2.30 (m, 4 H), 2.67–3.67 (m, 4 H), 3.90 (s, 1 H), 4.08–4.58 (m, 1 H), 4.75–5.40 (m, 3 H), 5.45–6.28 (m, 1 H), 7.12–7.62 (m, 5 H); EIMS, *m*/*e* calcd for $C_{19}H_{25}NO_4$ 331.1785, found 331.1776.

MeLi reacted with **3c** + **4c** in a similar manner as described to afford (*R*)-(−)-**6**, 79% ee by NMR analysis with Eu(hfc)$_3$.

Reaction of Allyltrimethylsilane (2a) with Methyl Pyruvoylprolinate (1c). (8a*S*)-3-Methyl-3-(2-propenyl)-1,4-dioxo-3,4,6,7,8,8a-hexahydro-1*H*-pyrrol[2,1-*c*][1,4]oxazine (16). To a dichloromethane solution (6 mL) of **1c** (0.389 g, 1.95 mmol) under an argon atmosphere was added 5.9 mmol of $TiCl_4$ (6.0 mL of 0.99 M CH_2Cl_2 solution) over 8 min. After the mixture was stirred for 5 min, **2a** (0.376 g, 2.9 mmol) in dichloromethane (3 mL) was added to the mixture. Then the reaction mixture was stirred for 3 h. The reaction was quenched with a pH 7 phosphate buffer solution (5 mL). After the organic layer was separated, the aqueous layer was extracted with dichloromethane (15 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified on silica gel TLC (40:1 CH_2Cl_2/MeOH as developing solvent). The mixture obtained was dissolved in benzene and refluxed with 4A molecular sieves for 5 h. Lactonization occurred to form **16** (0.231 g, 56%): IR (KBr) 3000, 1750, 1690, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.76–2.87 (m, 6 H), 3.45–3.85 (m, 2 H), 4.03–4.42 (m, 1 H), 4.93–5.37 (m, 2 H), 5.47–6.20 (m, 1 H); EIMS, *m*/*e* calcd for $C_{11}H_{15}NO_3$ 209.1053, found 209.1030; mp 113.5–114.5 °C.

3-Hydroxy-3-methyl-5-hexen-2-one (17). To 0.231 g of **16** (1.10 mmol) in 5 mL of THF in an ice–salt bath was added 2.7 mL of methyllithium (4.43 mmol) over 10 min. The reaction mixture was stirred overnight and was quenched with 5 mL of pH 7 phosphate buffer solution. The aqueous layer was extracted with dichloromethane (10 mL × 5). The combined extracts were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The oily residue was purified by preparative silica gel TLC (CH_2Cl_2 as developing solvent), followed by bulb-to-bulb distillation [105 °C (42 mmHg) bath temperature]. Compound **17** was obtained as a clear oil (0.047 g, 33%). NMR analysis using Eu(hfc)$_3$ showed 49% ee: $[\alpha]^{23}_D$ +31.0° (*c* 0.933, benzene); $[\alpha]^{26}_{Hg365}$ +132.9° (*c* 0.933, benzene); IR (neat) 3475, 3100, 3000, 2960, 1720, 1655 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.28 (s, 3 H, CH_3), 2.17 (s, 3 H, $COCH_3$), 2.37 (d, 2 H, CH_2), 3.42 (s, 1 H, OH), 4.78–5.23 (m, 2 H, C=CH_2), 5.28–5.98 (m, 1 H, CH=C).

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Stereochemistry and Conformation of a Nitrogen-Containing, Medium-Sized Ring: Hexahydro-1-phenyl-3-benzazonine Derivatives. High 1,4-Diastereoselectivity in Hydrogenation of an Exocyclic Alkene

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Hydrogenation of olefin **2** or **4** (as a perchlorate salt) over platinum afforded in each case almost exclusively (at least 95%) one diastereomeric, saturated product, **3** or **5**, respectively. The other diastereomer corresponding to **5** was obtained by sodium/ammonia reductive cleavage of **6**. Stereochemical assignments for **5** and **7** were founded on proton NMR data in conjunction with elaborate conformational analysis assisted by empirical force field calculations (MM2). For this, we have explored the conformational space of this medium-sized ring to find all structures that define local energy minima. Base treatment of **5** (in attempted equilibration) produced a mixture of **7** and ring-opened amine **8**, a retro-Michael product. Although equilibrium is violated by (probably) irreversible formation of **8**, this experiment suggests that **7** is more thermodynamically stable than **5**, a point that is supported by the force field calculations. The diastereofacial selectivity of the hydrogenation is rationalized with the aid of computations (MMP1) on **4**.

Stereochemical control in the generation of specific relative configurations at nonadjacent carbon centers has recently attracted a great deal of interest.[1,2] Classically, such remote asymmetric induction has been successfully

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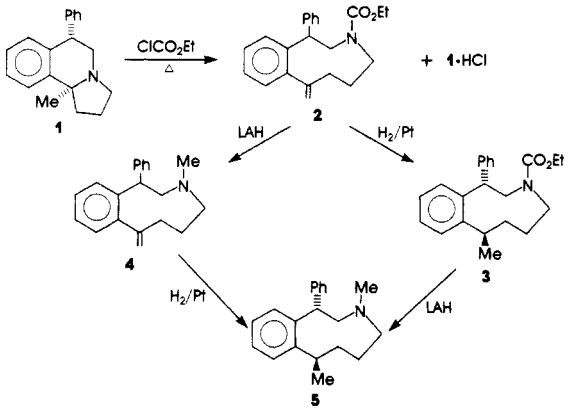
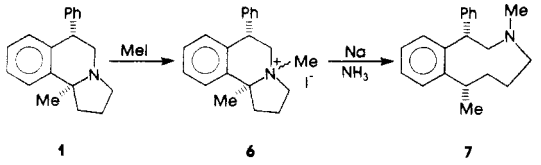
Scheme I



Scheme II



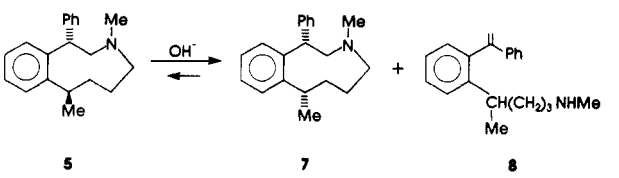
handled by using the steric properties inherent in six-membered rings (in transition states or as intermediate structures). Of course, this is associated with the often marked preference of six-membered rings for a well-defined chair conformation. The situation is more complex in medium-sized rings because of the potential multiplicity of low-energy conformations. However, Still has revealed several inspiring examples of high diastereoselection between distant loci in medium-sized cyclic compounds.[2] His results are closely linked to the conformational behavior of the macrocyclic substrates, indicating that medium- and large-ring molecules can possess intrinsic conformations conducive to high remote stereocontrol.[3]

In this paper we report an interesting example of high 1,4-diastereoselection in a hexahydro-3-benzazonine system, for the hydrogenations of **2** to **3** and **4** to **5**. In addition, we discuss the conformational properties of benzazonines **5** and **7** based on empirical force field (EFF) calculations and proton NMR data. The stereoselective hydrogenation is also rationalized by conformational analysis with the aid of computer calculations.

Results and Discussion

Chemical Transformations. Cleavage of amine **1** with ethyl chloroformate in toluene at 100 °C afforded vinyl carbamate **2**, in addition to the hydrochloride salt of **1** (Scheme I).[4] Hydrogenation of **2** with platinum oxide (3 atm) produced almost exclusively a single (>95% one diastereomer) saturated carbamate, **3**, which was converted to amine **5**. Amine **5** was also synthesized stereoselectively by an alternate route involving lithium aluminum hydride reduction of **2** followed by catalytic hydrogenation of **4**,

Scheme III



as a perchlorate salt (Scheme I). Thus, the highly diastereoselective hydrogenation is independent of whether an amide or protonated amine nitrogen is present in the benzazonine ring.

To be certain that diastereomeric benzazonine **7** could be adequately detected, and to assist the stereochemical assignment, we prepared a sample of **7**. Amine **1** was quaternized with methyl iodide and the crystalline salt (stereochemistry at nitrogen undetermined) was subjected to reduction with sodium in liquid ammonia (Scheme II).[5] Benzazonine compound **7**, which retains the stereochemical relationship of **1**, was produced with high stereoselectivity (<5% of **5**), along with variable amounts of isomeric by-product **8** from base-induced opening of the nine-membered ring (see below; occasionally some amine related to **8**, having the double bond reduced, was also observed). Although it appears that the reductive cleavage of the C–N bond occurred with retention of configuration, the reaction may be subject to thermodynamic control because of the possibility of epimerization in the strongly basic medium.[6] In three different sodium/ammonia reductions the yield of **7** was lower than expected (usually <50%) because of the formation of ring-opened product, presumably via deprotonation of the benzhydryl proton and retro-Michael elimination. Indeed, treatment[6] of **5** with NaOH in aqueous dimethyl sulfoxide yielded amine **7** and elimination product **8**, in a 3:7 ratio, at the expense of **5** (Scheme III). Although we used this type of base-induced equilibration before to obtain thermodynamic ratios,[6] the probably irreversible ring-opening to **8** militates against equilibrium conditions here. Nevertheless, the virtually complete disappearance of **5**, while **7** persisted, suggests a much greater thermodynamic stability for diastereomer **7**. (Extended treatment of **7** with base produced mainly **8**, along with a minor amount of **5**.) The relative stability of **5** and **7** is understandable from the conformational analysis and EFF computations discussed below.

Stereochemical Assignments and Conformational Analysis. Diastereomers **5** and **7** were examined by proton NMR at 270 MHz in order to identify their relative configuration and preferred solution conformation. For **7** there was a 7-Hz doublet for the 7-methyl group at 1.35 ppm, a singlet for the *N*-methyl at 2.40 ppm, a doublet of doublets for H_{2a} at 2.90 ppm with $J(1,2a)$ = 8.5 and $J(2a,2e)$ = 13.5 Hz, a doublet of doublets for H_{2e} at 3.11 ppm with $J(1,2e)$ = ca. 1 and $J(2a,2e)$ = 13.5 Hz, a complex multiplet at 4.27 ppm for H_7, a doublet of doublets at 4.59 ppm for H_1 with $J(1,2e)$ = 0.5–1 and $J(1,2a)$ = 8.5 Hz, a doublet of doublets for aromatic proton H_{11} at 6.66 ppm with J = 1 and 7 Hz, and a doublet of doublet of doublets

(1) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. (b) Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1980**, *102*, 7387.

(2) (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774. (c) Still, W. C.; Novack, V. J. *Ibid.* **1984**, *106*, 1148. (d) Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F.; Rheingold, A. L. *Tetrahedron* **1984**, *40*, 2275.

(3) For examples of stereoselection in medium rings involving additions to alkenes, see: Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058 and ref 3 therein.

(4) (a) It is interesting to note that the carbon–carbon bond is generated exocyclic (Hofmann orientation) rather than endocyclic (Saytzeff orientation), although the exocyclic arrangement is expected to be thermodynamically less stable.[4b] (b) Cope, A. C.; Ambros, D.; Ciganek, E.; Howell, C. F.; Jacura, Z. *J. Am. Chem. Soc.* **1960**, *82*, 1750. Also: Schriesheim, A.; Muller, R. J.; Rowe, C. A., Jr. *Ibid.* **1962**, *84*, 3164.

(5) For information on the cleavage of quaternary heterocyclic amine salts in dissolving-metal reductions, see: (a) Winn, M.; Zaugg, H. E. *J. Org. Chem.* **1968**, *33*, 3779 and ref 14–16 cited therein. (b) Houlihan, W. J.; Manning, R. E. U.S. Patent 3 583 975, 1971. Both ref 5a and 5b report the preparation of hexahydro-3-benzazonines. (c) A photochemical cleavage of quaternary ammonium salts leading to 3-benzazonines has also been reported: Bremner, J. B.; Winzenberg, K. N. *Aust. J. Chem.* **1984**, *37*, 1203.

(6) (a) Sodium hydroxide and potassium carbonate are sufficiently basic to exchange the benzhydryl proton and effect equilibration.[6b] (b) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062.

for aromatic proton H_{10} (presumably) at 6.95 ppm with J = 7, 7, and 1 Hz. The spectrum for **5** contained a 7-Hz doublet for the 7-methyl at 1.17 ppm, a singlet for the N-methyl at 2.33 ppm, a doublet of doublets for H_{2a} at 3.05 ppm with $J(1,2a)$ = 3.5 Hz and $J(2a,2e)$ = 14.0 Hz, a doublet of doublets for H_{2e} at 3.41 ppm with $J(1,2e)$ = 7.5 Hz and $J(2a,2e)$ = 14.0 Hz, a multiplet at 3.64 ppm for H_7, a doublet of doublets for H_1 at 4.33 ppm with J = 3.5 and 7.5 Hz, and no aromatic protons upfield of 7.0 ppm.

Casual inspection reveals that these data readily distinguish the two diastereomers; however, producing a stereochemical assignment is not easy. Since there is a multiplicity of possible low-energy conformations for this medium-ring system, consideration of Dreiding molecular models in conjunction with this NMR data is insufficient to afford a clear impression of the molecular geometries adopted in solution, which is essential in making the stereochemical assignment. In effect, the degrees of freedom for various endocyclic rotamers and substituent placements in these hexahydro-3-benzazonines are so great that any "preferred" conformer arrived at from balancing torsional and transannular steric interactions, in an intuitive fashion, is probably just pure speculation. To help deal with this problem, we resorted to EFF calculations. Thus, we were able to elaborate conformational energy profiles for **5** and **7** to serve as a foundation for analysis of the ^1H NMR data. Details of the methods employed in the EFF calculations for the search of conformational space for minima are furnished in the Experimental Section. Suffice it to say here that energy minimizations were performed by Allinger's MM2 program.[7] Initial geometries were obtained by taking the four stable cyclononane conformers described by Anet,[8] and where any dihedral angle was less than 73°, a benzo moiety was fused onto the cyclononane. The resulting potential conformers (36 structures) were each submitted to MM2 for final minimization. Structures within 10 kcal/mol of the lowest (global) energy conformer were retained for study. By comparison, in calculations with Still's Ringmaker,[2a] a program for producing myriad candidate geometries of ring systems in a systematic manner for minimization, many potential starting geometries were rejected before attachment of the substituents to the rings. The higher energies of the rejected ring conformers could be more than compensated by relief of substitutent interactions. Consequently, not all of the low-energy structures generated by the above MM2 procedure were found by using Still's program. A Boltzmann distribution of the various conformers for each diastereomer at 25 °C was then established (see Experimental Section). This information, for conformations comprising more than 0.1%, is presented in Table I.

The MM2 calculations indicate that there is not just one relatively low-energy conformer for each diastereomer (Table I). Eighty-seven percent of the distribution of conformers for **7** was comprised of the first two conformers, **7A** and **7B**, with the major conformer (**7A**) contributing to the extent of 60%; the next three conformers (**7C–E**) accounted for 12.0%. For **5**, the first two conformers (**5A** and **5B**) amounted to 88%, with the major one (**5A**) populating the mixture to the extent of 68%; the next two conformers (**5C** and **5D**) amounted to 10.1%. The structures that comprise about the top 90% of each diastereomer are depicted in Figure 1, in a stereopair format.

Structures **7A** and **7B** possess three equatorial-like substituents (phenyl and 2 methyls) and a boat-chair type of ring conformation. The dihedral angles between the vicinal protons at C-1 and C-2 in conformer **7A** are 95° and 160°, which would afford coupling constants of ca. 0 and 10 Hz; in conformer **7B** the angles are 60° and 180° (respectively), which would afford coupling constants of ca. 2 and 12 Hz. Given 60% of **7A** and 27% of **7B**, we derive averaged coupling constants of ca. 1 and 11 Hz. These results are reasonably consistent with the observed vicinal couplings of 1 and 8 Hz for **7**, supporting the assignment of relative configuration. Structures **5A** and **5B** differ from one another with respect to the disposition of substituents. Conformer **5A** possesses an axial-like phenyl substituent (with its π surface facing into the benzazonine ring) and equatorial methyl groups, while conformer **5B** possesses equatorial phenyl and N-methyl groups and an axial 7-methyl group; both compounds have a boat-chair type of ring conformation. The dihedral angles between the vicinal protons on C-1 and C-2 in **5A** are 20° and 140°, which would yield coupling values of ca. 10 and 6 Hz; in **5B** the angles are 60° and 180° (respectively), which would yield coupling values of ca. 2 and 12 Hz. Given 68% of **5A** and 20% of **5B**, we derive averaged coupling constants of ca. 8 and 7 Hz, which depart somewhat from the observed values of 7.5 and 3.5 Hz (nevertheless, the comparison is still reasonable).

Additional NMR parameters lend further support to this assignment. For instance, the C-methyl group (on the 7 position) in **7** appeared as a doublet at δ 1.35, compared to the doublet at δ 1.17 for **5** (the chemical shift for the corresponding methyl group in *sec*-butylbenzene is δ 1.18). The 7-methyl group in **7** may be deshielded compared to the one in *sec*-butylbenzene because of its relatively fixed orientation with respect to the fused benzene ring, equatorially disposed near the aromatic deshielding region in the two major conformers (**7A** and **7B**, nearly 90% of conformational space). However, for the 7-methyl in **5** this effect is counteracted by two features: (1) the presence of an axial phenyl ring in a perpendicular orientation relative to the fused benzene ring in the major conformer (**5A**, 68% of conformational space), which results in shielding of the 7-methyl, and (2) the axial orientation of the 7-methyl in the second conformer of **5** (**5B**, 20%), which orients it into the shielding region of the fused benzene ring. Also, H_7 in **7** resonates at δ 4.27, but in **5** it resonates at δ 3.64. This again reflects the cross-ring shielding induced by the axial 1-phenyl group in **5A**. Additional evidence derives from the aromatic protons. Isomer **5** only exhibits aromatic signals downfield of δ 7.0, but **7** does not. Isomer **7** displays a doublet of doublets, with J = 7 and 1 Hz, at δ 6.66 (assigned to H_{11}) and a doublet of doublet of doublets, with J = 7, 7, and 1 Hz,

Table I. Conformational Profiles for 7 and 5[a]

conformer[b]	ΔG^c	% compostn	conformer[b]	ΔG^c	% compostn
7A	24.08	59.76	**5A**	24.71	67.87
7B	24.54	27.49	**5B**	25.42	20.48
7C	25.35	7.82	**5C**	25.99	7.82
7D	25.94	2.59	**5D**	26.71	2.32
7E	25.95	2.54	**5E**	27.66	0.47
7F	27.12	0.35	**5F**	27.93	0.30
7G	27.34	0.24	**5G**	27.97	0.28
			5H	28.16	0.20
			5I	28.17	0.20

[a] Boltzmann distribution at 25 °C. Individual conformers are denoted by capital letters, starting with **A** for the most stable conformer. A zero change in ΔS has been assumed. [b] Sets of endocyclic dihedral angles, which describe each ring geometry, are presented in the Microfilm Supplement (see paragraph at end of paper regarding supplementary material). [c] Energy ascertained from MM2 calculations. Values are in kcal/mol.

(7) Allinger, N. L.; Yuh, Y. H. *QCPE* **1980**, *12*, 395.
(8) Anet, F. A. L.; Krane, J. *Isr. J. Chem.* **1980**, *20*, 72.

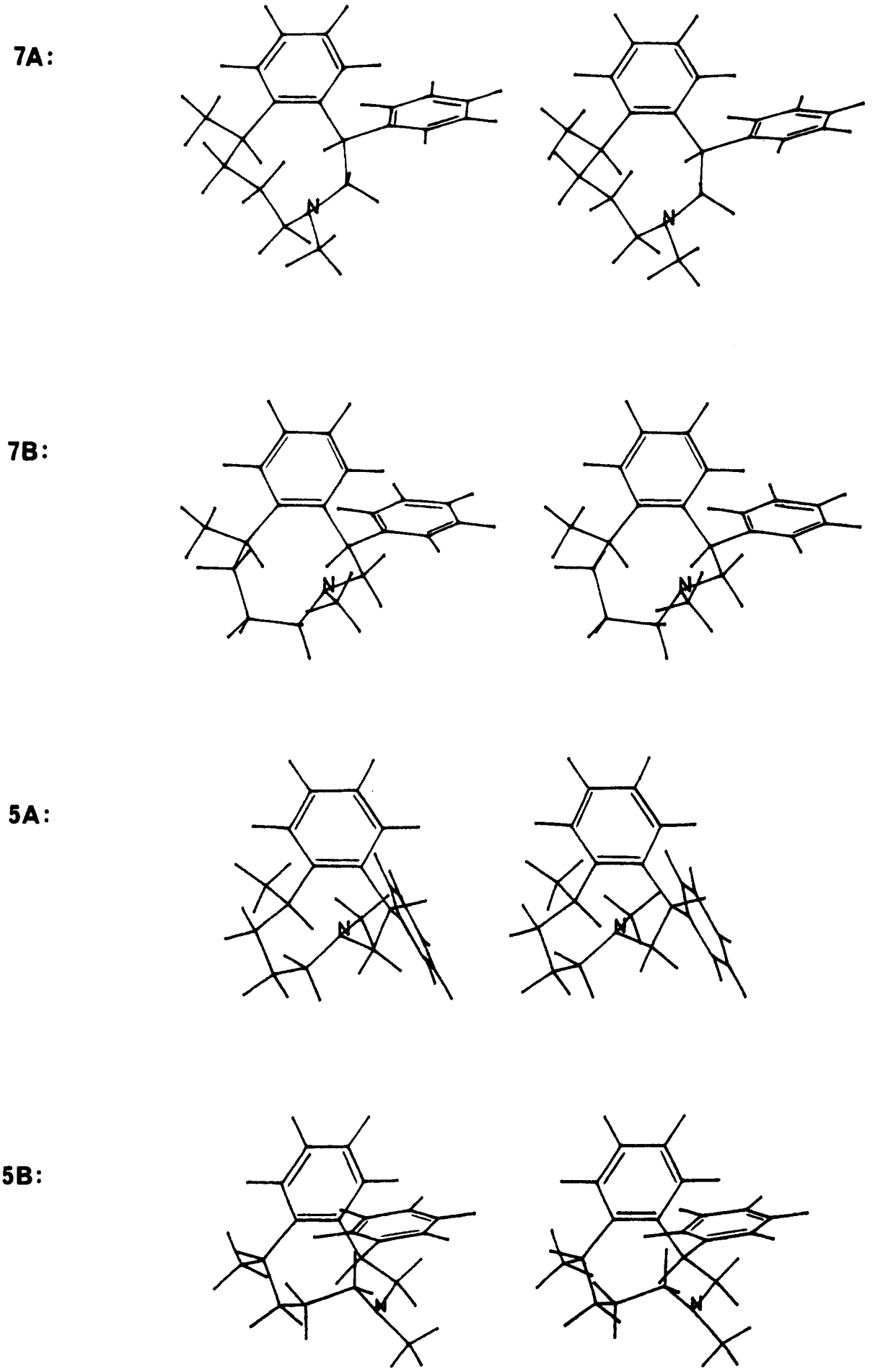


Figure 1. Stereoviews of **7A**, **7B**, **5A**, and **5B**, from EFF calculations.

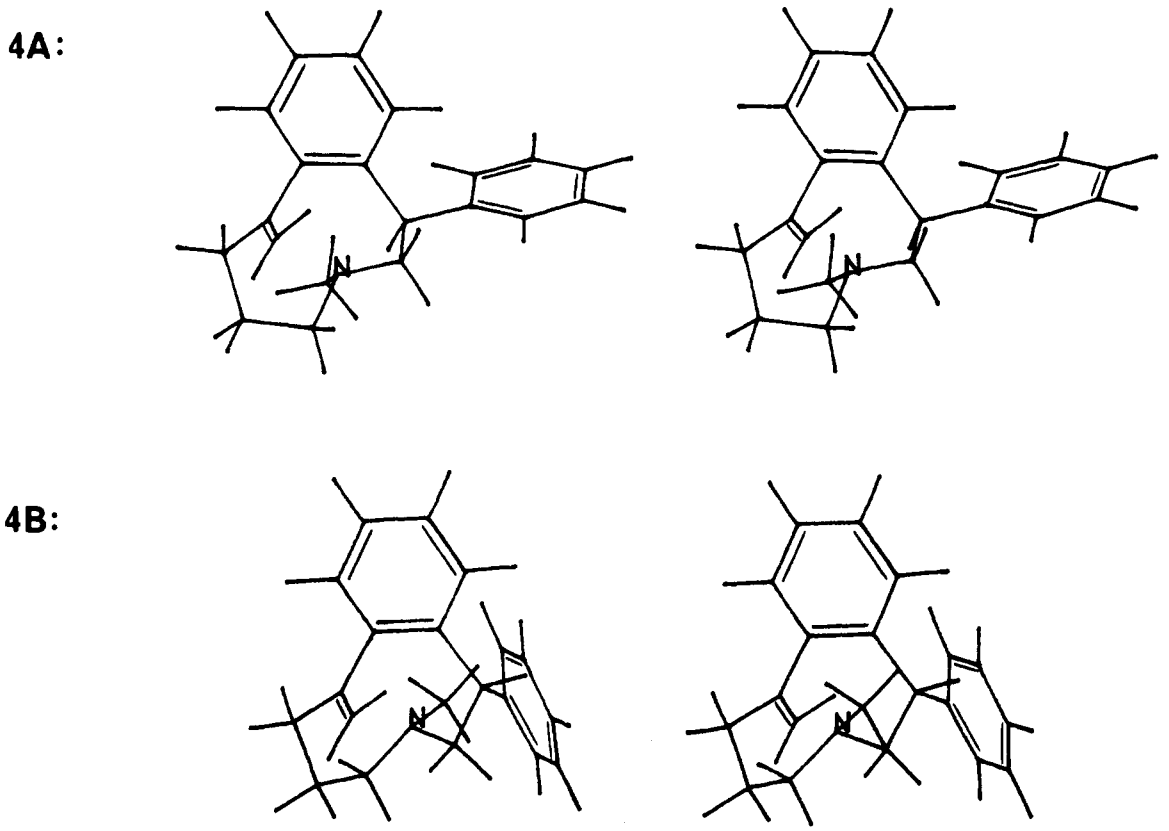


Figure 2. Stereoviews of **4A** and **4B**, from EFF calculations.

at δ 6.95 (assigned to H_{10}). The peri proton at the 11 position is shifted upfield because of the equatorial 1-phenyl group, which, because it is predominantly disposed on average in an orthogonal arrangement relative to the plane of the benzazonine, exerts a strong shielding effect.[9]

Based on the MM2 results for **5** and **7**, a Boltzmann distribution was determined for a combination of **5** and **7**. This procedure permitted evaluation of their relative stability, which is relevant to the outcome of base-catalyzed equilibration. At 25 °C, the computed **7**/**5** ratio was 3.3:1 and at 100 °C it was 2.6:1, supporting the idea that diastereomer **7** is more thermodynamically stable.

Diastereofacial Selectivity in the Hydrogenation. The catalytic hydrogenation of alkenes **2** and **4** occurred highly preferentially from one face of the carbon–carbon double bond. Given the heightened level of interest in remote asymmetric induction in acyclic and large-ring systems, we wanted to discern a reason for the high 1,4-diastereoselectivity in our case. However, since the double bond is contained in a fairly flexible nine-membered ring system, the problem is not straightforward. As a prerequisite, it seemed advisable to search over the conformational space to find the more favorable conformers. Thus, MMP1[10] calculations were performed on **4** in a manner similar to that for **5** and **7** (see Experimental Section for details). A profile of conformers was generated and those comprising more than 0.1% are presented in Table II. Two of the conformers occupy 95.5% of the conformational space: **4A**, 83%, and **4B**, 12.5% (Figure 2). The predominant conformer **4A** possesses a chair-boat ring conformation with an equatorial 1-phenyl and an equatorial-type *N*-methyl. The exocyclic methylene is not coplanar with the fused benzene ring to which it is conjugated; rather, it adopts a bent arrangement that is ca. 35° out of coplanarity. This is consistent with the UV spectrum of **4**·$HClO_4$ (see Experimental Section). The noncoplanarity causes one face of the alkene, the top face in **4A** (as depicted), to be more exposed to reactants; by the same token, the bottom face of **4A** is more sterically hindered to attack. The minor conformer **4B** would lead to the opposite diastereoselectivity, not observed experimentally. Although the calculations here are not definitive in indicating a strong preference for one diastereomer in the hydrogenation, it should be appreciated that solvation and complexation effects may be important. To account for the exclusive diastereoselectivity, we suggest that a conformation like **4A** is strongly favored in solution and that the convex face of the alkene is attacked much more readily.

Table II. Conformational Profile for 4[a]

conformer[b]	ΔG[c]	% compostn	phenyl orientation[d]
4A	39.32	83.06	eq
4B	40.35	12.45	ax
4C	41.51	1.47	eq
4D	41.61	1.22	eq
4E	41.99	0.70	eq
4F	42.05	0.54	eq
4G	42.48	0.25	ax
4H	42.69	0.17	ax

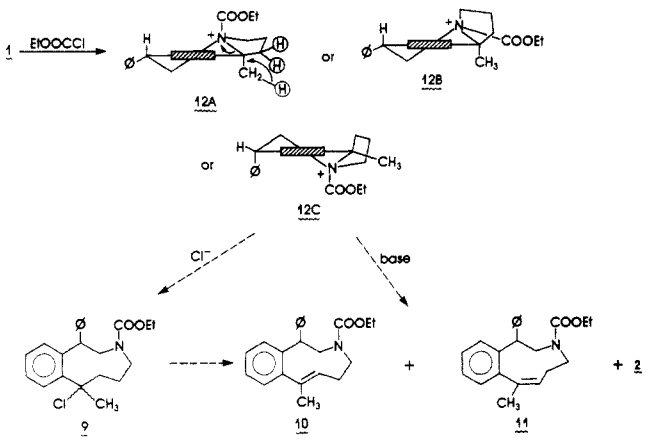
[a] Same as "a" in Table I. [b] Same as "b" in Table I. [c] Energy ascertained from MMP1 calculations. Values are in kcal/mol. [d] Equatorial = eq; axial = ax. Axial refers to a dihedral angle for Ar–CPh of less than 120°.

Exocyclic vs. Endocyclic Alkene Formation in the Cleavage of Amine 1 by Ethyl Chloroformate. In a different vein, it is interesting to note that the reaction of amine **1** with ethyl chloroformate yielded only one frag-

(9) This type of shielding has been observed in related structural situations, see: Weber, H. P.; Petcher, T. J.; Loosli, H. R. *Helv. Chim. Acta* **1977**, *60*, 2886. Oppolzer, W.; Achini, R.; Pfenninger, E.; Wever, H. P. *Ibid.* **1976**, *59*, 1186. Charlton, J. L.; Durst, T. *Tetrahedron Lett.* **1984**, *25*, 5287.

(10) MMP1, a predecessor to MM2, is a program with provision for conjugated π systems, see: Allinger, N. L. *QCPE* **1977**, *10*, 318.

Scheme IV



mentation product, alkene **2**, with the double bond in a presumably thermodynamically less stable exocyclic orientation.[4b,11-13] Of course, other products can readily be conceived for this reaction such as isomeric benzylic chlorides **9** or trans and cis endocyclic alkenes **10** and **11** (Scheme IV). Why is there such a high selectivity for **2**?

As an explanation for the sole production of exocyclic alkene **2**, we suggest the following. Amine **1** is expected to combine with ethyl chloroformate to afford a quaternary intermediate.[14] This salt may exist as three possible half-chair structures, **12A–C** (Scheme IV; one trans and two cis 5-6 ring-fused forms), or the corresponding boat conformations (not shown). *N*-Acylammonium salts **12** could lead by an E1 or E2 process directly to alkenes (**2**, **10** and/or **11**) or by an S_N1 or S_N2 process to chlorides **9**, which then suffer elimination to alkenes. At this point, stereoelectronic and statistical factors in ions **12A–C** probably shape the reaction outcome. [Reference to Dreiding models for visualization purposes will aid in the subsequent discussion.]

In **12A–C** (and the series of boat conformers) one of the three methyl protons is free to align in an antiperiplanar (180°) orientation relative to the departing electron pair in an E2 process (e.g., see arrows in **12A**) that will furnish **2** directly. However, in **12A–C** the other potentially reactive, endocyclic protons (circled in **12A**) are, by comparison, disposed with angles of ca. 90° and 160°. If the proton oriented at ca. 160° in **12A–C** were to eliminate through structural torsion and deformation to give an antiperiplanar arrangement, then alkene **10** or **11** would be produced. However, kinetic factors (stereoelectronics, statistics) do not favor this outcome. If the endocyclic alkenes (**10** and **11**) are actually less stable,[13] then the elimination to form **2** may be under thermodynamic control, in an E1 process. In the alternate route involving chloride **9**, a tremendous preference for **2** over **10** or **11** is not as readily apparent on stereoelectronic grounds, albeit there would be some statistical bias for **2**. Thus, we suggest that the reaction of **1** with ethyl chloroformate proceeds to acylammonium salts **12**, which collapse to alkene **2** without substantial passage through chloride **9**.[15]

Experimental Section

General Information and Procedures. Proton NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz), Varian EM-360 (60 MHz), or Bruker HX-270 (270 MHz) spectrometer with $CDCl_3$ as solvent and $(CH_3)_4Si$ as an internal standard, unless otherwise indicated. NMR abbreviations used are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = d of d of d, m = multiplet, q = quartet, br = broad. Carbon-13 NMR spectra were recorded on a JEOL FX60Q spectrometer (15.00 MHz) in $CDCl_3$ with $(CH_3)_4Si$ as an internal reference. Both proton noise-decoupled and off-resonance-decoupled ^{13}C spectra were determined; only noise-decoupled data are presented. IR spectra were obtained on a Perkin-Elmer 521, 727B, or 283 spectrophotometer in KBr (pellets), unless otherwise noted. Mass spectra (electron impact) were obtained at 70 eV on a Hitachi Perkin-Elmer RMU-6E spectrometer or, for exact mass, an AEI MS-902 instrument equipped with a DEC PDP 8/I computer (at the Pennsylvania State University). GLC analyses were performed on a Perkin-Elmer 3920B instrument (flame-ionization detector) equipped with a Hewlett-Packard Model 3352 data system and 18652A A/D converter, using a glass column (1/8 in. × 6 ft) with 3% SE-30 on Chromasorb Q packing (column A) or with 1.35% OV-17 on Chromosorb W AW/DMS packing (column B). TLC separations were conducted on silica gel plates (1 × 3 in.) with visualization by UV fluorescence and I_2 staining. Melting points are corrected. Chemical microanalyses were determined by Atlantic Microlab, Inc., Atlanta, GA.

Ethyl 2,3,4,5,6,7-Hexahydro-7-methylene-1-phenyl-1*H*-3-benzazonine-3-carboxylate (2).[11,12] Amine 1[5b] (4.5 g, 16 mmol) was dissolved in 35 mL of dry, warm toluene and the solution was treated with ethyl chloroformate (2.0 g, 17.5 mmol). The mixture was heated at reflux for 14 h. On cooling, a solid, the hydrochloride salt of amine **1**, separated (2.40 g, 100%, homogeneous by TLC). Evaporation of the toluene provided 2.60 g (97%) of light brown solid. A portion (1.56 g) was recrystallized from hexane to afford 0.70 g of tan solid, **2**, mp 77–85 °C (homogeneous by TLC): ^1H NMR (90 MHz) δ 1.04 (pair of overlapping t at 1.10 and 1.18, 3, OCH_2CH_3), 1.3–2.0 (m, 2), 2.4–2.7 (m, 2), 2.8–4.2 (m, 6), 4.92 (d, 1, vinyl H trans to phenyl), 4.97 (partially concealed dd, 1, Ph_2CH), 5.24 (br s, 1, vinyl H cis to phenyl), 6.8–7.4 (m, 9, aromatic H). Warming of the NMR sample to 65 °C (from the normal probe temperature of 30 °C) caused a collapse of the methyl signals to a single triplet (J = 7 Hz); changes were also evident elsewhere in the spectrum, e.g., the doublet of doublets at δ 4.97 sharpened (J = 4, 11 Hz), the olefinic proton at δ 4.92 became a broadened singlet at δ 4.93, and the resonance at δ 5.24 sharpened. The variable temperature behavior is attributed to the interconversion of two amide rotamers on the NMR time scale. MS showed a molecular ion at m/e 335.

Synthesis of *trans*-2,3,4,5,6,7-Hexahydro-3,7-dimethyl-1-phenyl-1*H*-3-benzazonine (5) via Ethyl 2,3,4,5,6,7-Hexahydro-7-methyl-1-phenyl-1*H*-3-benzazonine-3-carboxylate (3). Amide **2** (4.9 g, 14.7 mmol) was dissolved in 40 mL of absolute ethanol. The solution was added to a suspension of prereduced PtO_2 in 10 mL of ethanol in a Parr shaking apparatus. The mixture was hydrogenated at 3 atm for 60 min. After filtration, evaporation of solvent gave 4.65 g (95%) of tan syrup, homogeneous by TLC. ^1H NMR showed the absence of olefinic protons and suggested the presence of one major product [60 MHz: δ 0.9–1.9 (m, 10; d for $CHCH_3$ at δ 1.32, J = 7 Hz), 2.2–3.1 (m, 2), 3.4–4.3 (m, 3.5), 4.3–5.1 (m, 1.5, Ph_2CH at δ 4.82), 7.0–7.5 (m, 10)]. Part of this material (4.15 g, 12.4 mmol) in 50 mL of dry ether was reduced with lithium aluminum hydride (1.3 g, 34 mmol) in 25 mL of dry ether. The reduction was over immediately. The reaction was quenched sequentially with 1.3 mL of water, 1.3 mL of 15% NaOH, and 4 mL of water. After filtration, evaporation of solvent furnished 3.1 g (91%) of pale yellow oil, **5**, homogeneous by TLC [R_f 0.24, ethyl acetate/hexane (1:1)] except for a minor

(11) For related cyanogen bromide cleavages leading to 3-benzazonines, see: (a) Browne, E. J. *Aust. J. Chem.* **1984**, *37*, 367. (b) Bremner, J. B.; Winzenberg, K. N. *Chem. Ind. (London)* **1979**, 319. It is interesting that solvolysis, not endocyclic alkene, products were reported in ref 11b. However, ref 11a reports formation of the trans endocyclic alkene, which possibly arises in this case via an E1 process.

(12) Recently, a related chloroformate cleavage of an erythrinane derivative, to give a benzazonine nucleus with an exocyclic (conjugated) olefin, was reported: Bremner, J. B.; Dragar, C. *Heterocycles* **1985**, *23*, 1451.

(13) MMP1 calculations[10] found the endocyclic alkenes **10** and **11** to be less stable than exocyclic alkene **2** by ca. 7 kcal/mol; however, an exhaustive search of conformational space was not made.

(14) Fodor, G.; Abidi, S.; Carpenter, T. C. *J. Org. Chem.* **1974**, *39*, 1507. Paukstelix, J. F.; Kim, M. *Ibid.* **1974**, *39*, 1503.

(15) For a discussion of double bond orientation in elimination reactions, see: March, J. *Advanced Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1977; Chapter 17.

spot due to 7 with R_f 0.51 (a ratio of 5/7 ≥ 95:5 was estimated). GLC analysis showed only one peak; however, 5 and 7 were not separable on column A or B. A perchlorate salt was generated in ethereal methanol with 1.5 mL of 70% perchloric acid. The white crystals, 5·$HClO_4$, which weighed 3.5 g, contained only a trace of 7. Recrystallization of 3.35 g of this solid from ethyl acetate/methanol (5:1) afforded 2.36 g of fluffy white needles, mp 158–160 °C. IR (neat, free base) was nearly identical with that for 7. MS was nearly identical with that for 7: m/e 279 (molecular ion) and 184 (base peak). ^1H NMR of the crude free base showed about 3% of 7, as indicated by small peaks at δ 1.35 and 6.58/6.67. IR (salt) ν_{max} 2950, 2920, 1425, 1090, 750, 704, 622 cm^{-1}. 90-MHz ^1H NMR (salt, with drop of D_2O added) δ 1.1–2.2 (m, 7, d for CH_3CH at δ 1.22), 2.4–3.3 (m, 6, s for NCH_3 at δ 2.96), 3.9–4.4 (m, 2), 4.6–4.9 (m, 1, Ph_2CH), 7.0–7.4 (m, 9). Anal. Calcd for $C_{20}H_{25}N·HClO_4$: C, 63.24; H, 6.90; Cl, 9.33. Found: C, 63.12; H, 6.95; Cl, 9.27. ^1H NMR (free base, 270 MHz) see text. ^{13}C NMR (free base) δ 22.9 (q), 25.6 (t), 35.8 (d, $CHCH_3$), 39.4 (t), 47.8 (q, NCH_3), 53.3 (d, Ar_2CH), 59.2 (t), 60.3 (t), 125.4 (d), 126.0 (d), 127.1 (d), 127.8 (d, 3), 131.7 (d), 141.7 (s), 143.0 (s), 147.6 (s).

Synthesis of *trans*-2,3,4,5,6,7-Hexahydro-3,7-dimethyl-1-phenyl-1*H*-3-benzazonine (5) via 2,3,4,5,6,7-Hexahydro-3-methyl-7-methylene-1-phenyl-1*H*-3-benzazonine (4). Amide 2 (5.0 g, 15 mmol) was reduced with lithium aluminum hydride (1.8 g, 47 mmol) in dry tetrahydrofuran/ether (1:1) at room temperature for 18 h. The mixture was worked up in the usual manner (see above) to give 3.8 g of oil. TLC (ethyl acetate/hexane, 1:1) showed one major substance (R_f 0.33). Most (3.7 g) of this material was converted to a perchlorate salt from ether/methanol (2:1). The tan crystals (2.9 g) were recrystallized from absolute ethanol to afford 2.2 g of tan solid, mp 199–201 °C dec: IR ν_{max} 3130, 1475, 1448, 1095, 915, 751, 695, 618 cm^{-1}; UV (MeOH) λ_{max} (ε) 268 (175), 258 (250, sh) nm,[16] 90-MHz ^1H NMR ($CDCl_3$/Me_2SO-d_6, 2:1; drop of D_2O added) δ 1.5–2.4 (m, 2, CCH_2C), 2.1–2.8 (m, 2, allylic CH_2), 2.88 (s, 3, NCH_3, 3.2–3.5 (m, 2, CH_2N^+), 3.8–4.0 (m, 2, $Ar_2CCH_2N^+$), 4.8–5.1 (m, 1, Ar_2CH), 5.10 (br s, 1, vinyl H trans to phenyl), 5.50 (br s, 1, vinyl H cis to phenyl), 7.0–7.5 (m, 9, Ar H). Anal. Calcd for $C_{20}H_{23}N·HClO_4$: C, 63.57; H, 6.40; Cl, 9.38. Found: C, 63.60; H, 6.44; Cl, 9.34. This salt (100 mg), in 5 mL of 60% aqueous ethanol containing prereduced platinum from 10 mg of PtO_2, was hydrogenated at 3 atm for 5 h. TLC (ethyl acetate/hexane, 1:1) showed one major spot (R_f 0.20) corresponding to 5; no spot for diastereomer 7 was apparent. The identity of this sample of 5·$HClO_4$ was confirmed by ^1H NMR.

***cis*-2,3,4,5,6,7-Hexahydro-3,7-dimethyl-1-phenyl-1*H*-3-benzazonine (7).** Amine 1[5b] (7.5 g, 26.7 mmol) in 75 mL of dry ether was treated with 10 mL of methyl iodide. After 5 h, the mixture was filtered, furnishing 11.4 g of off-white powder, 6. Salt 6 was placed in a flask equipped with a dry ice-acetone condenser and a dry ice bath. Ammonia gas was condensed in the flask (ca. 200 mL) and small pieces of freshly cut sodium metal were added over 20 min (3.0 g of sodium). The reaction was stirred for 30 min at −78 °C, then allowed to warm. The ammonia was evaporated by applying a slow stream of nitrogen while the flask was immersed in a water bath. The solid residue was treated with 25 mL of methanol, followed by 30 mL of water. The mixture was extracted with 120 mL of methylene chloride. The organic phase was separated, rinsed with brine, dried (Na_2SO_4), and concentrated to an oil (6.5 g). TLC (ethyl acetate/hexane, 1:1) showed two spots (R_f 0.45 and 0.60; estimated ratio of ca. 2:1); however, GLC (column B) showed only one peak. MS of the oil displayed a strong molecular ion at m/e 279 for 7. The oil (6.0 g) in ether was treated with 2.0 g of fumaric acid in warm 2-propanol to yield an oily solid, which was recrystallized from ethyl acetate/2-propanol with the assistance of ether to recover as much crystalline material as possible (1.90 g was isolated). TLC indicated that this solid was comprised of only the slower migrating material, 7. The mother liquor afforded a yellow oil (4.5 g) containing 7 and the other product in a ratio of ca. 1:1 (estimated from TLC.[17a] The other constituent, which is isomeric to 7 (MS of a sample separated by preparative TLC; exact mass m/e 279.1985 for $C_{20}H_{25}N$), is believed to be ring-fragmented product 8 (see below). The crystalline fumarate salt was recrystallized from ethyl acetate/methanol (10:1) to give a first crop of 0.55 g and a second crop of 0.49 g. The first white solid was a pure sequifumarate salt of 7, mp 168–171 °C (intumescence, turned orange): IR ν_{max} 2950, 2920, 2600–2300 (NH^+), 1695 (C=O), 1567, 1363, 1262, 1174, 977, 768, 736, 702 cm^{-1}; 90-MHz ^1H NMR ($CDCl_3$/Me_2SO-d_6, 3:1) δ 1.32 (d, 3, J = 7 Hz), 1.1–1.8 (m, 4), 2.38 (s, 3, NCH_3), 2.6–3.3 (m, 3), 4.0–4.4 (m, 1, H_2), 4.62 (dd, 1, J = 1, 8 Hz, H_1), 6.67 (s, 4, vinyl H), 6.7–6.9 (m, 1, H_{11}), 6.9–7.4 (m, 8, Ar), 10.53 (br s, NH^+ and COOH). Anal. Calcd for $C_{20}H_{25}N·1.5C_4H_4O_4$: C, 68.86; H, 6.89. Found: C, 68.74; H, 6.97. ^1H NMR (free base, 270 MHz) see text.

Reaction of 5 with Base in Attempted Equilibration. Amine 5 (45 mg) was dissolved in 1 mL of Me_2SO and 0.6 mL of 10 N NaOH and the mixture was heated at reflux. TLC analysis indicated significant change after only 15 min. Heating was stopped after 30 min, when amine 5 had essentially disappeared. Extraction with CH_2Cl_2 afforded 40 mg of an oil. Two new components were present (TLC) in an ca. 70:30 ratio (^1H NMR; GLC, column B), the lesser of which was 7. ^1H NMR (90 MHz) of the mixture showed vinyl proton doublets for 8 at δ 5.18 and 5.78 (both with J = ca. 2 Hz) in addition to the resonances for 7 and other resonances for 8. A sample of the mixture was treated with benzoyl chloride and triethylamine in ether to give 7 and a benzamide derivative of 8 (M^+· at m/e 383). This was identical with benzamide prepared from product 8 of the sodium–ammonia reduction (see above). The olefinic component 8 was separated from a larger scale experiment by chromatography on silica gel (ethyl acetate/hexane): ^1H NMR (90 MHz) δ 0.99 (d, 3, J = 7 Hz), 0.95–1.4 (m, 5, NH at δ 1.2 exchanged with D_2O), 2.0–2.5 (m, 5, br s for NCH_3 at δ 2.30), 2.6–2.9 (m, 1, CH), 5.16 (d, 1, vinyl H), 5.77 (d, 1, vinyl H), 7.1–7.4 (m, 9, Ar). Hydrogenation of a sample of 8 afforded material with a molecular ion at m/e 281.[17b]

In a similar manner, treatment of 7 with base gave a mixture greatly enriched in 8 (80% of 8 was produced after heating for 30 min). Accurate quantitation of 7 and 8 in a mixture was not possible by TLC or GLC [virtually identical R_f values or retention times (columns A and B)]. The reaction was extracted with CH_2Cl_2 to isolate product, which was assayed by 90-MHz ^1H NMR. A minor amount of 5 (ca. 5%) was evident in addition to the 80% of 8 and 15% of 7.

Conformational Computations. In order to find the low-energy structures of benzazonines 5 and 7, the four stable conformations of cyclononane found by Anet[8] were used as the conformational basis for the cyclononane ring. At each reasonably "flat" dihedral angle (i.e., $\theta \leq 73°$), a benzo moiety was fused to the cyclononane. Thus, the [333] conformation[18] gave two initial geometries by appending benzo groups at the two dihedral angles of 56° on one of the three symmetrical edges of the cyclononane. In a similar manner, the [234] conformation gave rise to six starting geometries, the [225] to 6, and the [144] to 4. The appropriate substituents were then added to the ring. Both the axial and equatorial hydrogens were replaced by the substituents, thus doubling the initial structures. These 36 initial geometries for both diastereomers, 5 and 7, were then submitted to MM2 for minimization. Deliberate rotation of the phenyl substituent was carried out to facilitate the minimization.

Many of the starting structures converged to common minimized conformers. A computer algorithm, which compared structures on the basis their set of dihedral angles, was used to eliminate nonunique structures and any enantiomeric forms. Assuming that the stable conformers found represent all of the significant structures, the familiar Boltzmann relationship,

(16) (a) For reference purposes, cf. data for styrene [292 (600), 282 (600), 244 (10 000)], α-methylstyrene [282 (300), 242 (10 000)], α,2-dimethylstyrene [no maximum], and α,2,4,6-tetramethylstyrene [265 (250)] in ethanol.[16b] (b) Kamlet, M. J. *Org. Electron. Spectr. Data* **1960**, *1*, 183, 256, 274, 328. Also, see: Gillam, A. E.; Stern, S. E. *An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*, 2nd ed.; Edward Arnold: London, 1957, p 277.

(17) (a) In one experiment, two products from reduction of the double bond in the fragmentation product were also observed (diastereomers). This was verified by independent hydrogenation of the amino olefin (8) from an equilibration experiment and comparison of the two mixtures by TLC and GLC/MS (M^+· m/e 281; exact mass m/e 281.2047 for $C_{20}H_{27}N$). (b) See ref 17a for further characterization.

(18) The nomenclature of J. Dale for specifying ring conformation has been used [*Acta Chem. Scand.* **1973**, *27*, 1115, 1130, 1449].

(structures with E_1)/(structures with E_2) = $\exp[(E_1 - E_2)/kT]$, was applied to give the relative proportions shown in Table I.

The 36 starting structures for olefin 4 were generated in a similar manner. However, since the exo methylene group is conjugated to the benzo moiety, the molecules were minimized with MMP1,[10] which has provisions for structures with conjugated π electronic systems. The results for 4 in Table II were obtained as described above.

Acknowledgment. We are grateful to Joan Rogers, Roberta Acchione, and Martin Mutter for spectroscopic data. We also thank R. Rosanske (Florida State University) for 270-MHz ^{1}H NMR spectral data on 5 and 7. Thanks are also due to David McComsey for some technical assistance.

Registry No. 1, 101248-93-5; 1·HCl, 101249-00-7; 2, 101248-94-6; 3, 101248-95-7; 4, 101248-96-8; 4·$HClO_4$, 101315-91-7; 5, 101248-97-9; 5·$HClO_4$, 101399-21-7; 6, 101248-98-0; 7, 101399-20-6; 7·$^3/_2$fumarate, 101468-33-1; 8, 101248-99-1; 8 (benzamide deriv), 101249-01-8; 8 (hydrogenation product), 101249-02-9; EtOCOCl, 541-41-3.

Supplementary Material Available: List of endocyclic dihedral angles for the conformers of 4, 5, and 7 that comprise the top 99th percentile (1 page). Ordering information is given on any current masthead page.

Dramatic Concentration Dependence of Stereochemistry in the Wittig Reaction. Examination of the Lithium Salt Effect

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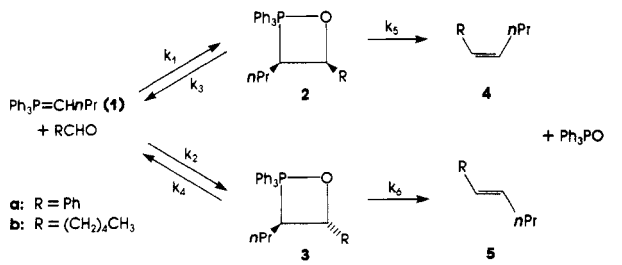
The stereochemistry for Wittig reactions of butylidenetriphenylphosphorane (1) with benzaldehyde and hexanal was examined in detail with regard to concentration effects. For the reaction of 1 and benzaldehyde in the presence of LiBr, the proportion of *trans*-oxaphosphetane (measured by low-temperature ^{31}P NMR) and (*E*)-alkene increased with respect to increasing reaction concentration in THF, approaching limiting values in a hyperbolic manner. Stereochemical drift, i.e., exaggerated production of (*E*)-alkene relative to *trans*-oxaphosphetane intermediate, was also concentration dependent, being more pronounced at higher concentrations. Experiments with varying amounts of lithium cation, and with NaBr instead of LiBr, demonstrated that this phenomenon is associated with the concentration of Li ion, which is increasingly sequestered by the THF solvent at higher dilution. In Me_2SO, the dependence of alkene stereochemistry on concentration was greatly attenuated. In toluene, the concentration effect was inverted to some extent; more (*E*)-alkene was formed at higher dilution (no betaines were observed by ^{31}P NMR at low temperature). The reaction of 1 with hexanal in THF, in the presence of LiBr, exhibited a concentration dependence similar to that observed for the reaction with benzaldehyde (at the oxaphosphetane stage). The rates of the lithium-dependent ("catalyzed") and lithium-independent ("uncatalyzed") reactions in the original carbon–carbon bond-forming step are ranked relative to each other, based on their concentration dependence in THF. For 1 and benzaldehyde in THF (with LiBr present), the catalyzed (k'') and uncatalyzed (k') rate constants have the following *relative* order: $k_1'' = 5.2$ and $k_2'' = 2.5$ mol^{-2}·dm^6·s^{-1}; $k_1' = 1.0$ and $k_2' < 0.02$ mol^{-1}·dm^3·s^{-1} (see Scheme I and Appendix). Thus, at the representative concentrations of 0.05, 0.20, and 0.50 M, the original carbon–carbon bond-forming step of this Wittig reaction is 27%, 61%, and 79% lithium catalyzed, respectively.

Control of stereochemistry in the Wittig olefination reaction has long been an area of intense research.[1,2] Over the 35 years since the reaction's utility was first demonstrated,[3] a variety of factors have been shown to influence the ratio of (*Z*/*E*)-alkenes, including temperature, solvent, choice of aldehyde, type of ylide, and the presence of lithium salts.[1,2a] Nonstabilized phosphorus ylides react with aldehydes to give mainly (*Z*)-alkenes. However, the presence of lithium salts, relative to "salt-free" conditions,

Scheme I



causes the production of (*E*)-alkene, at the expense of (*Z*)-alkene, in reactions of aromatic aldehydes (although the *E* isomer rarely predominates).[4a] Schlosser and Christmann showed that lithium salts affect the original carbon–carbon bond-forming step, by inducing more *threo*-betaine (or, as now accepted, *trans*-oxaphosphetane).[1g] More recently, Vedejs and co-workers, in dem-

(1) (a) Gosney, I.; Rowley, A. G. *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; Chapter 2, and references cited therein. (b) Bergelson, L. D.; Shemyakin, M. M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 250. (c) Bergelson, L. D.; Vauer, V. A.; Varsukov, L. I.; Shemyakin, M. M. *Tetrahedron Lett.* **1964**, 2669. (d) Bergelson, L. D.; Barsukov, L. I.; Shemyakin, M. M. *Tetrahedron* **1967**, *23*, 2709. (e) Le Bigot, Y.; Delmas, M.; Gaset, A. *Inform. Chim.* **1984**, 123. (f) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1. (g) Schlosser, M.; Christmann, D. F. *Liebigs Ann. Chem.* **1967**, *708*, 1. (h) McEwen, W. E.; Beaver, B. D.; Cooney, J. V. *Phosphorus Sulfur* **1985**, *20*, 255. (i) Bestmann, H. J.; Stransky, W.; Vostrowsky, O. *Chem. Ber.* **1976**, *109*, 1694. (j) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.

(2) (a) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823. (b) Also see: Vedejs, E.; Snoble, K. A. *Ibid.* **1973**, *95*, 5778.

(3) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44.

(4) (a) Aliphatic aldehydes do not show as pronounced a shift to the (*E*)-alkene when using a Li base; e.g., see control experiments reported in ref 4b. (b) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217.

0022-3263/86/1951-3302$01.50/0