into 100 mL of 0.5 M $Na_2S_2O_3$ and extracted with 100 mL of diethyl ether. After washing (2 × 50 mL of water) and drying, evaporation at aspirator pressure afforded 0.49 g (100%) of 2-phenylethanal, which was homogeneous according to GLC.

Acknowledgment. We thank the Swedish Natural Science Research Council for financial support.

Registry No. **1a**, 111-34-2; **1b**, 935-04-6; **1c**, 3622-76-2; **1d**, 129126-29-0; **1e**, 39565-48-5; **2a**, 591-50-4; **2b**, 108-86-1; **2c**, 624-38-4; **2d**, 696-62-8; **2e**, 624-31-7; **2f**, 636-98-6; **2g**, 766-85-8; **2h**, 90-14-2; **2i**, 10486-61-0; **2j**, 586-78-7; (*E*)-**3a**, 36586-17-1; (*Z*)-**3a**, 36586-16-0; (*E*)-**3b**, 69520-20-3; (*Z*)-**3b**, 78043-55-7; (*E*)-**3c**, 129126-30-3; (*Z*)-**3c**, 129126-31-4; (*E*)-**3d**, 129126-32-5; (*Z*)-**3d**, 129126-33-6; (*E*)-**3e**, 129126-34-7; (*Z*)-**3e**, 129126-35-8; (*E,E*)-**3f**, 129126-36-9; (*E,Z*)-**3f**, 129126-37-0; (*Z,Z*)-**3f**, 129126-38-1; (*E*)-**3g**, 129126-39-2; (*Z*)-**3g**, 129126-40-5; (*E*)-**3h**, 129126-41-6; (*Z*)-**3h**, 129126-42-7; (*E*)-**3i**, 129126-43-8; (*Z*)-**3i**, 129126-44-9; (*E*)-**3j**, 129126-45-0; (*Z*)-**3j**, 129126-46-1; (*E*)-**3k**, 129126-47-2; (*Z*)-**3k**, 129126-48-3; (*E*)-**3l**, 129126-49-4; (*Z*)-**3l**, 129126-50-7; **4a**, 56750-84-6; **4b**, 25109-98-2; **4c**, 129126-51-8; **4d**, 129126-52-9; **4e**, 129126-53-0; **5**, 122-78-1; palladium acetate, 3375-31-3.

Conformational Study of N-Substituted Adenines by Dynamic Proton NMR: Relatively High Barrier to Rotation about C^6–N^6 in N^3,N^6-Disubstituted Adenines

Allen B. Reitz,* David W. Graden, Alfonzo D. Jordan, Jr., and Bruce E. Maryanoff

Chemical Research Department, Janssen Research Foundation, Spring House, Pennsylvania 19477

Received March 8, 1990

Variable-temperature ^1H NMR experiments on six N^6-alkyladenines, additionally substituted at N^3, N^7, or N^9, were conducted in DMSO-d_6, $CDCl_3$, and D_2O. Two distinct conformations (syn and anti) were observed for N^3,N^6-disubstituted adenines in all solvents, resulting from hindered rotation about the C^6–N^6 bond. The free energy of activation ($\Delta G^\ddagger$) for conversion of the minor to the major conformer (39:61 ratio) of N^3-benzyl-N^6-isopropyladenine (**8**) was determined to be 15.8 kcal/mol (320 K, DMSO-d_6) by line-shape analysis (360 MHz). N^6,N^9-Disubstituted adenines displayed conformational nonequivalence (10:90 ratios) in $CDCl_3$, and only one species was seen in DMSO-d_6 (298 K). The analogous barrier to rotation was considerably lower for the N^6,N^9-disubstituted adenines, being 12.8 kcal/mol at 260 K for N^9-benzyl-N^6-isopropyladenine (**11**; $CDCl_3$, 360 MHz). The ratio of conformers for N^3-benzyl-N^6-methyladenine (**9**) was 24:76 (DMSO-d_6, 297 K), which shifted upon protonation to a 3:97 ratio.

Dynamic NMR (DNMR) spectroscopy has been a valuable tool in examining a variety of intramolecular rate processes.[1] For example, the barrier to rotation in *N*-methylaniline was found to be ca. 6–7 kcal/mol (free energy of activation, $\Delta G^\ddagger$).[2,3] In this case, it is unlikely that the aryl N–C atoms are planar, as the nitrogen in aniline itself is pyramidal.[4] Anilines bearing substituents that increase the extent of C–N double bond character, such as in *p*-nitroso-[5] or *p*-acetyl-*N*,*N*-dimethylaniline,[6] exist primarily in an in-plane conformation with a $\Delta G^\ddagger$ of ca. 8–10 kcal/mol. Likewise, *o*-nitro substituents induce planarity in neighboring amino groups due to hydrogen bonding and stabilization of C–N double bond isomers.[7] The aryl N–C atoms are in a planar arrangement in *o*-methyl-*N*-methylaniline because of unfavorable steric interactions between the two methyl groups.[8] A variety of other ortho-substituted and ortho,ortho-disubstituted anilines have relatively high barriers to rotation between the two out-of-plane conformations.[1,9]

Amino heterocycles typically display added stabilization of the in-plane conformers due to enhanced delocalization of the nitrogen lone pair into the π-deficient ring.[1] Fairly high barriers to rotation between two in-plane conformations have been observed. This behavior is analogous to the well-known hindered rotation of amidines and guanidines.[1d,10]

In the course of a medicinal chemistry project, we observed two sets of nonequivalent resonances in the 360-MHz ^1H NMR spectra (DMSO-d_6) of several disubstituted adenines. These resonances, which coalesced at 330 K, were attributed to two in-plane conformations resulting from restricted rotation about the C^6–N^6 bond, designated as syn and anti by virtue of the relative orientation of the N^6 substituent with N^1 (viz. A–D). Hindered rotation in

* Address correspondence to this author at the Medicinal Chemistry Department, R. W. Johnson Pharmaceutical Research Institute, Spring House, PA 19477.

(1) (a) Oki, M. *Application of Dynamic NMR Spectroscopy in Organic Chemistry*; Chemie: New York, 1985. (b) Oki, M. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Interscience: New York, 1983; Vol. 14, p 1. (c) Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic: New York, 1982. (d) Jackman, L. M. In *Dynamic Nuclear Magnetic Resonance Spectroscopy*; Jackman, L. M., Cotton, F. A., Eds.; Academic: New York, 1975; p 203. (e) Sternhell, S. In *Dynamic Nuclear Magnetic Resonance Spectroscopy*; Jackman, L. M., Cotton, F. A., Eds.; Academic: New York, 1975; p 163. (d) Sutherland, I. O. In *Annual Reports in NMR Spectroscopy*; Mooney, E. F., Ed.; Academic: New York, 1971; p 71. (e) Binsch, G. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L.; Eds.; Interscience: New York, 1968; p 97.

(2) (a) Anet, F. A. L.; Ghiaci, M. *J. Am. Chem. Soc.* **1979**, *101*, 6857. (b) Lunazzi, L.; Magagnoli, C.; Guerra, M.; Macciantelli, D. *Tetrahedron Lett.* **1979**, 3031.

(3) Anet, F. A. L.; Ji, X. *Tetrahedron Lett.* **1984**, *25*, 1419.

(4) (a) Evans, J. C. *Spectrochim. Acta* **1966**, 152. (b) Lister, D. G.; Tyler, J. K. *J. Chem. Soc., Chem. Commun.* **1966**, 152.

(5) MacNicol, D. D. *J. Chem. Soc., Chem. Commun.* **1969**, 1516.

(6) Mackenzie, R. K.; MacNicol, D. D. *J. Chem. Soc., Chem. Commun.* **1970**, 1299.

(7) Jouanne, J. von; Heidberg, J. *J. Am. Chem. Soc.* **1973**, *95*, 487.

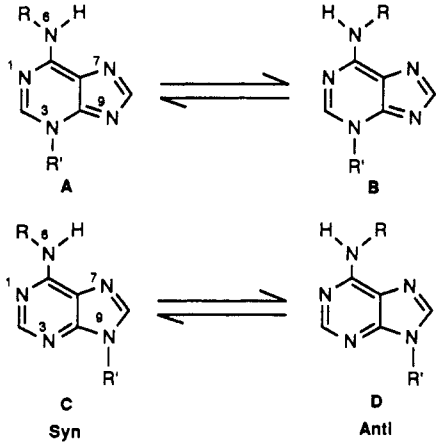
(8) Lunazzi, L.; Magagnoli, C.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1705.

(9) (a) Casarini, D.; Foresti, E.; Lunazzi, L.; Macciantelli, D. *J. Am. Chem. Soc.* **1988**, *110*, 4527 and references cited therein. (b) Schaefer, T.; Penner, G. H.; Marat, K.; Sebastian, R. *Can. J. Chem.* **1984**, *62*, 2686. (c) Brownstein, S.; Horswill, E. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1970**, *92*, 7217. (d) Nagawa, Y.; Honda, K.; Nakanishi, H. *Chem. Lett.* **1989**, 939.

(10) Fodor, G.; Phillips, B. A. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley: New York, 1975; p 85.

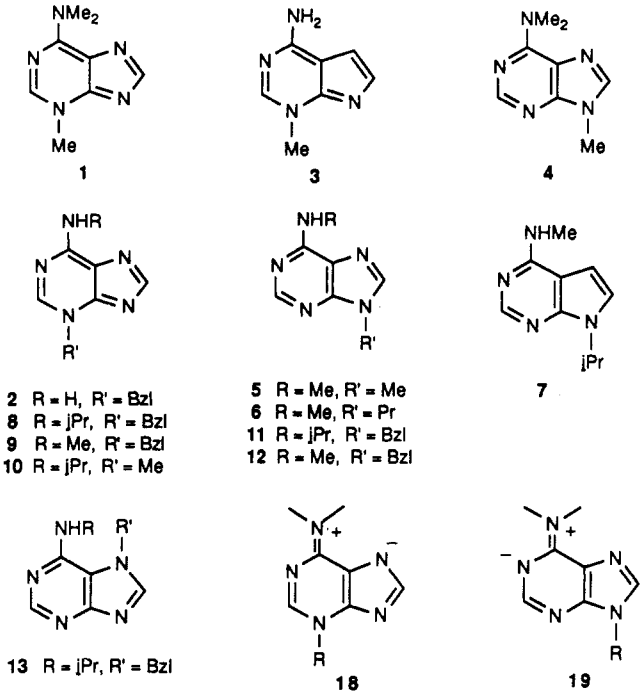
0022-3263/90/1955-5761$02.50/0

adenines is a special case of that in amino heterocycles such as aminopyridines and aminopyrimidines.[11] Dipole moment and UV measurements of adenine derivatives have indicated that N^3-alkyladenines are a mixture of the imine and amine forms.[12] The first observation of hindered rotation by ^1H NMR methods of an adenine was reported by Martin and Reese, who examined N^6,N^6-dimethyl-2′,3′-*O*-isopropylideneadenosine by 100-MHz ^1H NMR.[13]



There have been two reports of hindered rotation about the C^6–N^6 bond among N^3-alkyladenines by NMR, both conducted at 60 MHz.[14,15] In 1968, Neiman and Bergmann described NMR nonequivalence of the N^6-methyl signals of N^3,N^6,N^6-trimethyladenine (**1**) in $CDCl_3$.[14] For the exchange process, the free energy of activation ($\Delta G^{\ddagger}$) at the coalescence temperature was estimated to be 15.3 kcal/mol.[14] Later, Ishino and co-workers examined N^3-benzyladenine (**2**), and its site of protonation, by NMR spectroscopy.[15] Protonation of **2** was found to occur primarily at N^7, increasing the barrier to rotation of the C^6–N^6 bond. The protons on N^6 of the hydrochloride salt of **2** were nonequivalent at 303 K (DMSO-d_6), and coalescence was seen upon warming to ca. 330 K, whereas this signal in the free base was a broad singlet at 303 K.[15] Seela and Bussmann prepared the hydrochloride salt of 7-deaza analogue **3**, which also displayed restricted rotation about the C^6–N^6 bond (90 MHz, DMSO-d_6), with a $\Delta G^{\ddagger}$ value of 16.7 kcal/mol.[16]

N^9-Substituted adenines are the most extensively studied class of adenine derivatives, and this also applies to their conformational behavior as observed by NMR. Engel and von Hippel reported a relatively complete analysis of hindered rotation in this structural type.[17] They found that N^6,N^6,N^9-trimethyladenine (**4**) exhibits nonequivalence of the N^6-methyl groups upon cooling in CD_3OD (T_c = 253 K; 100 MHz). Compound **5** existed as a 96:4 ratio of conformers at the low-temperature limit with a T_c of ca. 273 K (CD_3OD); in $CDCl_3$ **5** displayed a 10:1 ratio of conformers. These authors proposed that the major isomer had the syn configuration.



Dodin and colleagues[18] examined a variety of N^9-substituted adenines in an NMR and IR study. Structure **6** displayed a 9:1 ratio of conformers in $CDCl_3$, whereas **7** revealed a ca. 1:1 ratio. In comparing **6** and **7** there are two changes which are evident. There is no nitrogen at position 7 in **7**, and thus an intramolecular hydrogen bond between N^7 and a proton on N^6 cannot add to the stabilization of the syn isomer. Also, the lone pair of electrons on N^7 of **6** is now replaced with a hydrogen on **7**. This latter change favors the syn isomer because hydrogen is larger than an electron pair.[18] The observed 1:1 ratio in **7** indicates the strong role played by intramolecular hydrogen bonding in stabilization of the syn isomer in **6** and related structures. Methylmercury derivatives of adenines, including some substituted on N^9,[19] as well as the dications of adenine[20] and N^6,N^6-dimethyladenine[21] also display nonequivalence of the N^6 substituents. Watson-Crick and Hoogstein base pairing lowers the rotational barrier of the C^6–N^6 bond.[22]

We investigated hindered rotation among disubstituted adenines systematically because of the keen importance of this structural type. We examined the ^1H NMR properties of adenines **8–13** (360 MHz) at various temperatures and in different solvents (DMSO-d_6, $CDCl_3$, D_2O), measuring the ratio of rotamers where possible. We were able to directly compare the barrier to rotation for several compounds.

Results and Discussion

Preparation of 8–13. Compounds **8–13** were prepared as shown in Scheme I. 6-Chloropurine (**14**) was alkylated

(11) (a) Katritzky, A. R.; Tiddy, G. J. T. *Org. Magn. Reson.* **1969**, *1*, 57. (b) Almong, J.; Meyer, A. Y.; Shanan-Atidi, H. *J. Chem. Soc., Perkin Trans. 2* **1972**, 451. (c) Riand, J.; Chenon, M.-T.; Lumbroso-Bader, N. *Can. J. Chem.* **1980**, *58*, 466. (d) MacNicol, D. D. *J. Chem. Soc., Chem. Commun.* **1969**, 933. (e) Honda, I.; Shimomura, Y. *Fukui Kog. Kenkyu Hok.* **1988**, *36*, 31.

(12) Bergmann, E. D.; Weiler-Feilchenfeld, H.; Neiman, Z. *J. Chem. Soc.* **1970**, 1334.

(13) Martin, D. M. G.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1967**, 1275.

(14) Neiman, Z.; Bergmann, F. *J. Chem. Soc., Chem. Commun.* **1968**, 1002.

(15) Ishino, M.; Sakaguchi, T.; Morimoto, I.; Okitsu, T. *Chem. Pharm. Bull.* **1981**, *29*, 2403.

(16) Seela, F.; Bussmann, W. *Nucleosides Nucleotides* **1984**, *3*, 195.

(17) Engel, J. D.; von Hippel, P. H. *Biochemistry* **1974**, *13*, 4143.

(18) Dodin, G.; Dreyfus, M.; Dubois, J.-E. *J. Chem. Soc., Perkin Trans. 2* **1979**, 438.

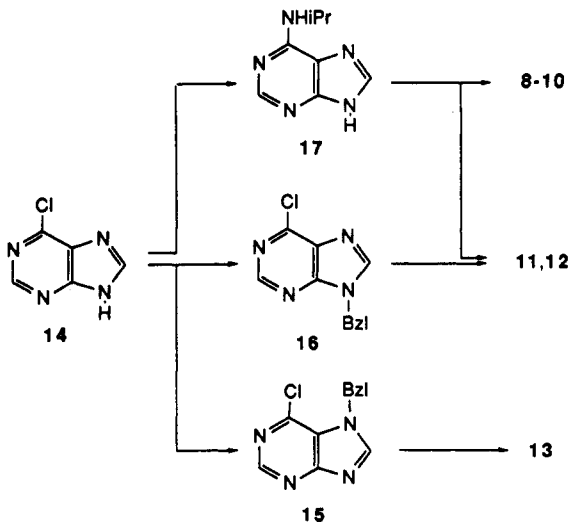
(19) Charland, J.-P.; Viet, M. T. P.; St.-Jauques, M.; Beauchamp, A. L. *J. Am. Chem. Soc.* **1985**, *107*, 8202.

(20) Wagner, R.; von Philipsborn, W. *Helv. Chim. Acta* **1971**, *54*, 1543.

(21) Pitner, T. P.; Sternglanz, H.; Bugg, C. E.; Glickson, J. D. *J. Am. Chem. Soc.* **1975**, *97*, 885.

(22) (a) Iwahashi, H.; Sujeta, H.; Kyogoku, Y. *Biochemistry* **1982**, *21*, 631. (b) Williams, L. D.; Williams, N. G.; Shaw, B. R. *J. Am. Chem. Soc.* **1990**, *112*, 829.

Scheme I



with benzyl chloride to give a mixture of N^7- and N^9-benzylated compounds (**15** and **16**, respectively), identical with those described in the literature.[23] Amination of **15** with isopropylamine led to **13**, and the same reaction with **16** afforded **11**. Alternatively, N^6-isopropyladenine (**17**) and N^6-methyladenine were alkylated with benzyl chloride or methyl iodide in the presence of potassium carbonate to give mixtures of N^9:N^3 substituted products in ratios of ca. 3:1, which were separated by chromatography. The major isomer (**11**) of the reaction of **17** with benzyl chloride was identical with that produced upon amination of **16** with isopropylamine. Additionally, compounds **8–10** were the major products in alkylation reactions of **17** and N^6-methyladenine with the required electrophiles in the *absence* of base, as expected from the work of Leonard and co-workers.[24]

NMR Experiments. Compounds **8** and **9** were dissolved in DMSO-d_6 and examined by 360-MHz ^{1}H NMR. For **8**, there was a 39:61 ratio of isomers observed at 302 K. Spectra were accumulated upon raising the temperature incrementally. Coalescence of most of the nonequivalent protons occurred at ca. 320–330 K. The resonances for H^2 were chosen for further study because they were well isolated, and a reasonable $\Delta\nu$ (ca. 50 Hz) was seen at the low-temperature limit (298 K). The resonance for H^2 was readily assigned, relative to that for H^8, because H^8 was removed upon preparation of the compound in which a bromine is attached to C^8 (see the supplementary material). Iterative line-shape analysis[25] on H^2 was conducted; the calculated and the observed values are plotted in Figure 1. The rates of conversion of the minor to the major conformer were thus estimated, and the $\Delta G^{\ddagger}$ was determined to be 15.8 kcal/mol (value derived for 320 K). The error associated with this $\Delta G^{\ddagger}$ due to uncertainty in the temperature equilibration in the NMR (±1 °C, MeOH standardization method) is ±0.1 kcal/mol. The methyls

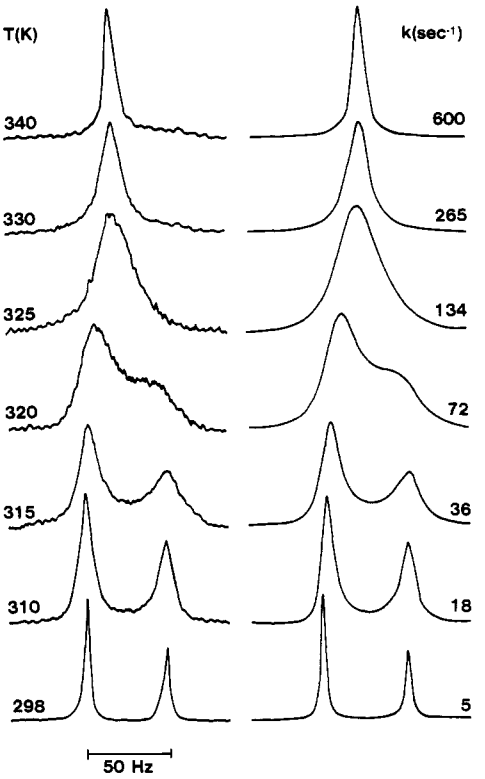


Figure 1. Observed and calculated resonances for H^2 in the ^{1}H NMR spectra of **8** (360 MHz, DMSO-d_6).

of the isopropyl groups were equivalent throughout. Similarly, a 24:76 ratio of two conformers was observed at 298 K for compound **9**.

In $CDCl_3$, **8** existed as a ca. 1:9 mixture of conformers, with a temperature of coalescence of approximately 300 K. Line-shape analysis was attempted for a series of spectra obtained at different temperatures, but minor shoulders in the resonances for H^2 made iterative simulation difficult. At 297 K, the $\Delta G^{\ddagger}$ in $CDCl_3$ for conversion of the minor to major conformer was estimated to be 15.4 kcal/mol. Analysis of the spectra of **8** in DMSO-d_6 (39:61 ratio) and in $CDCl_3$ (1:9 ratio) show that the minor isomer is probably the same in both cases, and that it is present to a relatively larger degree in DMSO-d_6.

The two conformers are also easily observed by ^{13}C NMR spectroscopy (100 MHz, DMSO-d_6). The proton coupling to C^5 was measured for both the major and minor isomers. The coupling between the proton on N^6 and C^5 might provide evidence for the configurational orientation of the two conformers, insofar as the trans H–C arrangement has a larger coupling in simple olefins.[26] There were two observable couplings to C^5 in both isomers: 10.3 and 5.5 Hz for the major one (at 120.8 ppm), and 11.0 and 5.9 Hz for the minor one (at 119.2 ppm). The smaller of the two couplings in both cases arises from interaction with the exchangeable N*H* on N^6, determined by examination of the C^8 brominated derivative (see the supplementary material). The difference between the couplings was too small for a structural assignment. We have tentatively assigned the minor isomer as the anti rotamer.

Molecular mechanics calculations (MM2) were performed on the two conformers of **8**.[27] These conformers

(23) Montgomery, J. A.; Temple, C., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 630.

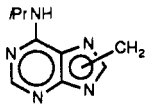
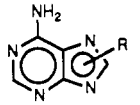
(24) (a) Fujii, T.; Walker, G. C.; Leonard, N. J.; DeLong, D. C.; Gerzon, K. *J. Med. Chem.* **1979**, *22*, 125. Details for the alkylation of **17** and N^6-methyladenine in the absence of base are in the supplementary material. (b) Although the literature suggested that N^3-alkylated products would also be produced upon reaction of adenines under *basic* conditions as minor constituents (Shaw, G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: London, 1984; Vol. 5, pp 530, 552) we performed additional NMR experiments, as described in the supplementary material, to verify our assignments of **8–10**.

(25) Binsch, G.; Kleier, D. A. *The Computation of Complex Exchange-Broadened NMR-Spectra*; Program 140, Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN, 1969.

(26) Marshall, J. L. *Carbon-Carbon and Carbon-Proton NMR Couplings: Applications to Organic Stereochemistry and Conformational Analysis*; Verlag: Deerfield Beach, FL, 1983; pp 11–64.

(27) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph No. 177, Washington, D.C., 1982.

Table I. Comparison of N⁶(H) Chemical Shifts in Variably Substituted Adenines (360 MHz, 0.03–0.05 M)

compound	solvent	N^3	N^9	N^7
	DMSO-d_6	8.22, 8.33	7.47	5.88
	$CDCl_3$	6.7	5.6	4.32
	DMSO-d_6	7.8 (R = Me)	7.2 (R = Et)	6.8 (R = Me)

exhibited relatively equivalent energies, with the syn isomer being favored by only 0.26 kcal/mol.

Compound **9** was converted to its monohydrochloride salt, and this molecule was examined as well, because of the reported increase in $\Delta G^{\ddagger}$ reported upon protonation of **2**.[15] In DMSO-d_6, the spectra at room temperature revealed a 3:97 mixture of conformers with coalescence at ca. 328 K, similar to the results obtained with free base **8**. In D_2O, a 10:90 ratio of conformers was seen, whose spectra coalesce at ca. 310 K. Protonation of N^3-alkyladenines has been reported to occur on N^7.[15] Steric repulsion between the proton on N^7 and the proximal substituent on N^6 would be expected to be greater than that engendered by the nitrogen lone pair of the free base, favoring the syn form for the HCl salt.[28] A nuclear Overhauser experiment (NOE) demonstrated that the N^6 and N^7 protons in the major conformer seen in DMSO-d_6 are close to each other, supporting the syn structural assignment. Correlation of the chemical shifts of this HCl salt and its free base (**9**) indicate that the major conformer of **9** also probably has the syn conformation as well.

Structure **10** was examined in DMSO-d_6. At 298 K, two conformers were observed in a ratio of 24:76. The spectra for **10** and **8** were very similar, indicating that the benzyl group of **8** was not involved as a key facet of the conformational equilibrium process.

The spectra of compounds **11** and **12** revealed only one form in DMSO-d_6 at 298 K. However, upon cooling of **11** and **12** in $CDCl_3$, two forms were observed in a ratio of 11:89. Line-shape analysis on **11** at 240 K resulted in an estimated $\Delta G^{\ddagger}$ of 12.9 kcal/mol for the minor to major conversion. Likewise, similar treatment of the spectrum of **12** at 245 K yielded the same value for $\Delta G^{\ddagger}$. The exchangeable N*H* of **12** was coupled to the adjacent methyl group conclusively showing N_6 to be the primary site of residence for this proton. *The barrier to conversion of the minor to major conformers for 8 (15.8 kcal/mol at 320 K, DMSO-d_6) is thus clearly seen to be higher than that for 11 and 12 (12.9 kcal/mol at 240 K, $CDCl_3$).*

The spectra of N^7-benzyl-N^6-isopropyladenine (**13**) revealed one distinct form in DMSO-d_6 at 298 K, and also in $CDCl_3$ at temperatures as low as 240 K. A severe peri steric interaction for the anti conformer makes it an unlikely contributor. From these data, nothing can be said about the barrier to rotation about C^6–N^6 because the minor isomer cannot be observed.

The chemical shifts of the proton attached to N^6 provide some measure of the relative strengths of intramolecular hydrogen bonds in these molecules. This data is given in Table I, as well as a comparison to data from N^3-, N^7-, and N^9-monosubstituted adenines. The chemical shifts for the N^7-substituted compounds are the farthest upfield, reflective of the diminished opportunity for intramolecular hydrogen bonding. For N^7-methyladenine, intramolecular hydrogen bonding is still conceivable between N^6(*H*) and $N^{1,18}$ whereas this is not the case for **13**. The chemical shift of the exchangeable protons of N^7-methyladenine is further downfield than the exchangeable proton of **13**. Specifically, the difference in this chemical shift between **8** and **13** is ca. 2.4 ppm, and between N^3-methyl- and N^7-methyladenine is 1.0 ppm.

Ours is the first study to afford a direct comparison between the hindered rotation of adenines bearing alkyl groups on N^3, N^7, or N^9. The barriers to rotation in N^9-benzyl molecules **11** and **12** agree qualitatively with those reported in the literature for this structural type. The corresponding barriers for **8**–**10** have been demonstrated to be ca. 3 kcal/mol greater than those for **11** and **12**.

The NMR experiments were conducted at a fixed concentration of 0.04–0.05 M. At this concentration, an IR study in $CHCl_3$ by Lord and co-workers[29] demonstrated that N^9-ethyladenine undergoes some self-association. In DMSO-d_6, less self association would be expected because of solvation. In addition, N^6-substitution on the molecules we studied in either solvent would reduce self-association by a factor of two or more.[29b] Nevertheless, some intermolecular hydrogen-bonding aggregation process may be contributing to the observed barrier to rotation, and also to the observed minor shoulders seen in some of the resonances for the aromatic protons of **1** in $CDCl_3$.

Mechanistic Analysis. What factors increase the barrier to rotation about the C^6–N^6 bond in the N^3-substituted adenine system, relative to other positions of adenine alkylation? Charge-separated limiting structures can be drawn for the N^3,N^6- and N^6,N^9-disubstituted adenines in which there is a formal double bond between C^6 and N^6, such as **18** and **19**. The chemical shift of N^6(*H*) is the furthest downfield in the N^3,N^6- vs the N^6,N^9- or N^6,N^7-disubstituted adenines, perhaps indicating a relatively strong hydrogen bond with a more electronegative N^7 (vide supra and Table I). Quantum mechanics calculations (MNDO)[30] were performed on adenines **1** and **4**; they are included in the supplementary material. They do not provide much insight here as they indicate that there is only slightly greater double bond character (π contribution) for the C^6–N^6 bond in **1** (0.27) vs that in **4** (0.23). Of course, both **1** and **4** lack the capacity to form an intramolecular hydrogen bond between N^7 and a proton bound to N^6.

In DMSO-d_6, relative to $CDCl_3$, the proportion of the minor isomer of **8** and derivatives is greater, as is the barrier to rotation. Both of these effects are probably related to the strong hydrogen bond-accepting properties of DMSO-d_6. It interrupts intramolecular association between N^7 and N^6*H*, and also provides a solvent shield around N^6*H*, lessening the steric advantage of the N^6-alkyl group. Both effects would aid in increasing the proportion of the anti isomer. In the same vein, DMSO-d_6 acts to raise the barrier to rotation by stabilizing charge-separated structures, such as **18**, which may produce the imine character in C^6–N^6.

Conclusions

The barrier to rotation about the exocyclic C^6–N^6 bond of a series of disubstituted adenines was examined by variable-temperature 360-MHz ^{1}H NMR. This barrier was found to be greatest for N^3,N^6-disubstituted adenines, in

(28) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1.

(29) (a) Kyogoku, Y.; Lord, R. C.; Rich, A. *J. Am. Chem. Soc.* **1967**, *89*, 496. (b) Lord, R. C.; Thomas, G. J., Jr. *Develop. Appl. Spect.* **1967**, *6*, 179.

(30) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

which case line-shape analysis revealed a $\Delta G^{\ddagger}$ for conversion of the minor to major conformer of ca. 16 kcal/mol (at 320 K) in DMSO-d_6. The analogous N^6,N^9-disubstituted adenines displayed only one form in DMSO-d_6 at ambient temperature, but resolved into two forms on cooling in $CDCl_3$. From spectra obtained in this way, simulation provided an estimate of ca. 13 kcal/mol for $\Delta G^{\ddagger}$ as defined above at 240 K. An N^6,N^7-disubstituted adenine showed only one form, even on cooling to 240 K.

Since there is only a single non-hydrogen substituent on N^6 in the derivatives studied, the two conformers are nonequivalent and are not equally populated. For **9** in DMSO-d_6 a 76:24 ratio was observed, upon protonation (HCl salt) a 97:3 ratio was seen. The major isomer in the later case was demonstrated to have the syn configuration by an NOE experiment. In $CDCl_3$, both **8**, **11**, and **12** exist as 9:1 mixture of conformers.

Experimental Section

General Procedures. As cited[31] and in the supplementary material.

3-Benzyl-6-(isopropylamino)purine (8). A solution of **17** (500 mg, 2.82 mmol, see the supplementary material) and benzyl chloride (0.65 mL, 5.64 mmol) dissolved in DMF (15 mL) was treated with potassium carbonate (428 mg, 3.1 mmol). The mixture was stirred at room temperature under a drying tube overnight, treated with water, and extracted twice into CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. TLC showed two products which were separated by preparative TLC ($CHCl_3$/MeOH, 97:3). The relatively nonpolar product exhibited TLC behavior and ^1H NMR spectra (DMSO-d_6 and $CDCl_3$) identical with that of **11** prepared by the independent route described below (390 mg, 52%). The more polar material, which was different than either **11** or **13**, was assigned structure **8**, recrystallization of which was conducted in CH_2Cl_2/hexane (150 mg, 23%): mp 108–110.5 °C; IR (KBr) ν_{max} 3382, 3211, 2975, 1634, 1407, 1174 cm^{-1}; CI-MS m/e 267 (M + 1); UV (0.043 M EtOH) λ_{max} (ϵ) 294 (12 704), 220 (15 978), 204 (17 414) nm; ^1H NMR ($CDCl_3$) δ 1.32 (d, 6 H), 4.48 (m, 1 H), 5.57 (s, 2 H), 7.4 (m, 5 H), 7.89 and 8.11 (br s, each ca. 0.1 H, sharpen upon cooling), 7.99 and 8.04 (br s, each ca. 0.9 H, sharpen upon cooling); ^1H NMR (DMSO-d_6) δ 1.21 (d, 6 H), 4.52 (br m, 0.6 H), 5.26 (br m, 0.4 H), 5.49 (br s, ca. 0.8 H), 5.53 (br s, ca. 1.2 H), 7.35 (m, 3 H), 7.48 (m, 2 H), 7.75 (br s, 0.6 H, H^8), 7.76 (br s, 0.4 H, H^8), 8.22 (br d, 0.4 H, exchangeable with D_2O), 8.32 (br d, 0.6 H, exchangeable with D_2O), 8.51 (br s, 0.39 H, H^2), 8.64 (br s, 0.61 H, H^2); ^{13}C NMR (DMSO-d_6) δ 22.5 (q, 1.8 C), 23.4 (q, 0.8 C), 42.1 (d, 0.6 C), 44.1 (d, 0.4 C), 52.0 (t, 0.4 C), 52.1 (t, 0.6 C), 119.7 (dd, J = 5.9, 11.0 Hz, 0.4 C, C^5), 120.8 (dd, J = 5.5, 10.3 Hz, 0.6 C, C^5), 128.2 (m, 5 C), 136.1 (br s, 1 C), 142.9 (ddd, J = 4, 4, 208 Hz, 0.4 C, C^2), 143.4 (ddd, J = 4, 4, 208 Hz, 0.6 C, C^2), 148.8 (br s, 0.6 C, C^6), 150.7 (br s, 0.4 C, C^6), 152.0 (d, J = 199 Hz, 0.6 C, C^8), 152.4 (d, J = 198 Hz, 0.4 C, C^8), 152.6 (br m, C^4); high-resolution MS calcd for $C_{13}H_{13}N_5$ 267.1484, found 267.1474. Anal. Calcd for $C_{15}H_{17}N_5 \cdot 0.2H_2O$: C, 66.50; H, 6.47; N, 25.85. Found: C, 66.58; H, 6.24; N, 25.97.

3-Benzyl-6-(methylamino)purine (9). 6-(Methylamino)-purine (0.545 g, 3.7 mmol) was suspended in DMF (27 mL) and treated with 1.03 g of potassium carbonate (7.36 mmol) and 0.47 mL of benzyl chloride (4.08 mmol). After stirring for 2 days, $CHCl_3$ and water were added. The $CHCl_3$ layer was removed, and the water was washed twice with $CHCl_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a white solid, which was purified by chromatography on silica gel ($CHCl_3$/MeOH/NH_4OH, 93:6:1) to separate the two products of the reaction. The minor, more polar of the two products was collected and recrystallized (MeOH/Et_2O/hexane, 180 mg, 20% yield): mp 256.5–258.5 °C; CI-MS m/e 240 (M + 1), 268 (M + 29); ^1H NMR (DMSO-d_6) δ 3.02 (d, 2.28 H), 3.43 (d, 0.73 H), 5.49 (br s, ca. 0.5 H), 5.54 (br s, 1.5 H), 7.32 (m, 3 H), 7.46 (m, 2 H), 7.74 (br s, ca. 0.76 H, H^8), 7.77 (br s, ca. 0.24 H, H^8), 8.19 (br d, ca. 0.24 H), 8.43 (br d, ca. 0.76 H), 8.49 (s, ca. 0.24 H, H^2), 8.69 (s, ca. 0.76 H, H^2); high-resolution MS calcd for $C_{13}H_{13}N_5$ 239.11710, found 239.11730. Anal. Calcd for $C_{13}H_{13}N_5$: C, 65.25; H, 5.48; N, 29.27. Found: C, 65.47; H, 5.41; N, 29.98.

The hydrochloride salt of **9** was prepared by treating a 180-mg batch of **9** in MeOH/CH_2Cl_2 with saturated HCl/Et_2O. The white precipitate was collected and recrystallized from a mixture of MeOH/Et_2O/hexane. The resulting fine white powder (120 mg) was dried at 60 °C for 6 h under vacuum: mp 239.5–241 °C; CI-MS m/e 240 (M + 1), 268 (M + 29); ^1H NMR (DMSO-d_6) δ 3.16 (d, 3 H), 5.61 (s, 2 H), 7.38 (m, 3 H), 7.46 (s, 2 H), 8.60 (s, 0.97 H, H^8), 8.69 (s, 0.03 H, H^8), 8.96 (s, 0.03 H, H^2), 9.16 (s, 0.97 H, H^2), 10.2 (br s, ca. 1 H, exchangeable with D_2O), 14.2 (br s, ca. 1 H, exchangeable with D_2O). Anal. Calcd for $C_{13}H_{13}N_5 \cdot HCl$: C, 56.63; H, 5.12; Cl, 12.86; N, 25.40. Found: C, 56.67; H, 5.14; Cl, 12.76; N, 25.42.

6-(Isopropylamino)-3-methylpurine (10). A solution of **17** (200 mg, 1.13 mmol) and iodomethane (80 μL, 1.3 mmol) in dimethylacetamide (5 mL) was heated at 45 °C for 7 h. The solvent was removed, the residue was treated with saturated aqueous $NaHCO_3$ and extracted into CH_2Cl_2, and the product was purified by preparative TLC ($CHCl_3$/MeOH/NH_4OH, 92:7:1). The solid that resulted was recrystallized from CH_2Cl_2/hexane (48 mg, 22%): CI-MS m/e 190 (M + 1); ^1H NMR (DMSO-d_6) δ 1.22 (d, 6 H), 3.85 (br s, ca. 1.2 H), 3.90 (br s, ca. 1.8 H), 4.48 (m, 0.6 H), 5.26 (m, 0.4 H), 7.77 (br s, 1 H), 8.1 (br d, ca. 0.6 H, exchangeable with D_2O), 8.2 (br d, ca. 0.4 H, exchangeable with D_2O), 8.24 (br s, ca. 0.4 H), 8.48 (br s, 0.6 H); high-resolution MS calcd for $C_9H_{13}N_5$ 191.1171, found 191.1179.

9-Benzyl-6-(isopropylamino)purine (11). Compound **16** was prepared as described in the literature,[13] mp 86–87.5 °C (lit. mp 86–87 °C). A sample of **16** (1.0 g, 4.1 mmol) was then dissolved in iPrNH$_2$ (70 mL). The solution was added to a Schlenk flask and then heated at 80 °C overnight. The residual solvent was evaporated, the tacky residue was treated with water, and the product was extracted into CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated to give 1.1 g of an oil that was pure by TLC. Crystallization occurred over a period of several weeks while the material was sitting on the benchtop. The substance was recrystallized from CH_2Cl_2/hexane to give a light tan solid: mp 86–88 °C; IR (KBr) ν_{max} 3270, 2970, 1610, 1576, 1476, 1325, 1285 cm^{-1}; UV (0.048 M EtOH) λ_{max} (ϵ) 268 (16 971), 207 (24 357) nm; CI-MS m/e 268 (M + 1), 296 (M + 29); ^1H NMR ($CDCl_3$) δ 1.32 (s, 6 H), 5.37 (s, 2 H), 4.55 (br m, 1 H), 7.3 (m, 5 H), 7.70 (s, 1 H), 8.42 (s, 1 H); ^1H NMR (DMSO-d_6) δ 1.21 (d, 6 H), 4.42 (m, 1 H), 5.39 (s, 2 H), 7.3 (m, 5 H), 7.56 (br d, 1 H), 8.2 (br s, 1 H), 8.27 (s, 1 H). Anal. Calcd for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.24; H, 6.41; N, 26.15.

9-Benzyl-6-(methylamino)purine (12). In the reaction to prepare **9** above, the major, less polar product was recrystallized from CH_2Cl_2/hexane (400 mg, 45%): mp 134.5–137 °C; CI-MS m/e 240 (M + 1), 268 (M + 29); ^1H NMR ($CDCl_3$ at 220 K) δ 3.14 (d, ca. 0.27 H), 3.58 (d, ca. 2.73 H), 5.2 (s, 2 H), 7.01 (br s, 1 H), 7.28 (m, 2 H), 7.38 (m, 3 H), 7.80 (s, ca. 0.9 H), 7.92 (s, ca. 0.1 H), 8.28 (s, ca. 0.1 H), 8.49 (s, ca. 0.9 H). Anal. Calcd for $C_{13}H_{13}N_5$: C, 65.25; H, 5.48; N, 29.27. Found: C, 65.14; H, 5.36; N, 29.46.

7-Benzyl-6-(isopropylamino)purine (13). Compound **15** was prepared by the alkylation of 6-chloropurine with benzyl chloride (mp 151–152 °C; lit.[23] mp 152–153 °C). A solution of **15** (500 mg, 2.0 mmol) in iPrNH$_2$ (25 mL) was heated in a Schlenk flask at 80–85 °C overnight. The solvent was partially removed, water was added, and the solution was cooled. The solid was recrystallized from MeOH/benzene/hexane and dried at 60 °C overnight under vacuum to give 0.27 g (50%) of **6** as a white powder: mp 160–162 °C; CI-MS m/e 268 (M + 1); IR (KBr) ν_{max} 3418, 3342, 2975, 1605, 1559, 1473, 1438, 1373, 1337, 1186 cm^{-1}; UV (0.040 M EtOH) λ_{max} 277.5 (ϵ 12 513), 207.5(ϵ 21 398) nm; ^1H NMR ($CDCl_3$) δ 0.91 (d, 6 H), 4.20 (m, 1 H), 5.50 (s, 2 H), 7.17 (m, 3 H), 7.45 (m, 2 H), 8.01 (s, 1 H), 8.49 (s, 1 H). Upon cooling to 240 K, the signals downfield of δ 5.0 experienced a slight downfield shift: 5.55 (s, 2 H), 7.29 (m, 3 H), 7.50 (m, 2 H), 8.11 (s, 1 H), 8.52 (s, 1 H); ^1H NMR (DMSO-d_6) δ 1.02 (d, 6 H), 4.24 (m, 1 H), 5.76 (s, 2 H), 5.88 (d, 1 H, J = 5 Hz), 7.17 (d, 1 H), 7.35 (m, 4 H), 8.24 (s, 1 H), 8.45 (s, 1 H). Upon warming to 340 K, the N*H* had become a broad singlet at δ 5.5, and the purine protons appeared

(31) Reitz, A. B.; Jordan, A. D., Jr.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4800.

as 1 H singlets at 8.23 and 8.33. Anal. Calcd for $C_{15}H_{17}N_5 \cdot 0.2H_2O$: C, 66.50; H, 6.47; N, 25.85; H_2O, 1.33. Found: C, 66.60; H, 6.30; N, 25.82; H_2O, 1.02.

Acknowledgment. We thank J. Bortiatynski and Prof. L. Jackman (Pennsylvania State University) for the NMR line-shape analysis. In addition, we appreciate the assistance of D. Gauthier, Dr. G. Leo, and, especially, Dr. H. Almond (Janssen Research Foundation); and Prof. D. Liotta (Emory University).

Supplementary Material Available: Additions to the Experimental Section (general procedures, method of ^2H NMR measurements, additional details on the structural assignment of 8, preparation of 17, and alkylation of adenines under neutral conditions), a 360-MHz ^1H NMR spectrum of 10 including D_2O exchange, and MNDO calculations on 1 and 4 (7 pages). Ordering information is given on any current masthead page.

Synthetic Studies on the Mevinic Acids Using the Chiron Approach: Total Synthesis of (+)-Dihydromevinolin

Stephen Hanessian,* Patrick J. Roy, Marino Petrini, Paul J. Hodges, Romano Di Fabio, and Germano Carganico

Department of Chemistry, Université de Montréal, Box 6128, Station A, Montréal, QC, Canada H3C 3J7

Received March 15, 1990

A general strategy for the synthesis of the mevinic acids starting from L-glutamic acid as a chiral template is presented. The octahydronaphthalene ring system of dihydromevinolin and mevinolin is constructed from an intramolecular Diels–Alder cycloaddition involving a butenolide. The lactone portion is elaborated from a cyclopentanone by a Baeyer–Villiger oxidation with bis(trimethylsilyl) peroxide.

In 1975, after testing some 8000 strains of microorganisms for inhibition of in vitro sterol synthesis, Endo and co-workers[1] at the Sankyo laboratories isolated three active compounds from the culture broth of the fungus *Penicillium citrinum*. The main compound, ML-236B, was also isolated as an antifungal agent from *P. brevicompactum* by Brown and co-workers[2] at Beecham Pharmaceuticals and was named compactin (1). A second, more active compound, mevinolin, was later isolated from *Monascus ruber* by Endo[3] and from *Aspergillius terreus* by Alberts and co-workers[4] at Merck, Sharpe & Dohme. Two related compounds, dihydrocompactin (3)[5] and dihydromevinolin (4),[6] were subsequently isolated as minor metabolites from the cultures of these fungi. These four fungal metabolites are part of a family of compounds called the mevinic acids[7] (Figure 1).

Since their discovery, compactin (1) and mevinolin (2) have attracted considerable attention due to their biological activity as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterogenesis in man. Mevinolin, presently marketed under the trade name Mevacor, is one of the most clinically useful hypocholesterolemic agents, and it is manufactured by a fermentation process. Dihydromevinolin (4), which exhibits biological activity similar to mevinolin, is produced in small quantities during the fermentation; hence it has not been developed as a clinical candidate.

The unique structural features of the mevinic acids combined with their important biological action has fostered a large number of studies aimed at their total synthesis as well as the production of structural analogues.[7] To the best of our knowledge there are at present two total syntheses of dihydromevinolin,[8,9] a formal synthesis[10] and a semisynthesis from mevinolin via selective reduction of one of the double bonds.[11] In view of the latter report, the existing syntheses of mevinolin[12] can also be considered as viable approaches to dihydromevinolin.

Examination of the structures of the mevinic acids reveals unique stereochemical and functional features that present certain challenges in stereocontrolled synthesis.[13] The possibility of obtaining enantiomerically pure compounds adds another dimension of complexity to the synthesis plan.

The first total synthesis of dihydromevinolin was accomplished by Falck and Yang in 1984.[8] In this synthesis, a racemic octahydronaphthalene intermediate was con-

(1) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *26*, 1346.
(2) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans.* **1976**, 1165.
(3) Endo, A. *J. Antibiot.* **1979**, *32*, 854.
(4) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C. H.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A. A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schönberg, G.; Hensens, O.; Hirschfield, J.; Hoogsteen, K.; Liesch, J. *Proc. Nat. Acad. Sci. U.S.A.* **1980**, *77*, 3957.
(5) Lam, Y. K. *J. Antibiot.* **1980**, *33*, 334.
(6) Albers-Schönberg, G.; Joshua, M.; Lopez, M. B.; Hensens, O. D.; Springer, J. P.; Chen, J.; Ostrove, S.; Hoffman, C. H.; Alberts, A. W.; Patchett, A. A. *J. Antibiot.* **1981**, *34*, 507.
(7) For a recent review, see: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4209.
(8) Falck, J. R.; Yang, Y. L. *Tetrahedron Lett.* **1984**, *25*, 3563.
(9) Hecker, S. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586.
(10) Davidson, A. H.; Jones, A. J.; Floyd, C. D.; Lewis, C.; Myers, P. L. *J. Chem. Soc., Chem. Commun.* **1987**, 1786. Davidson, A. H.; Floyd, C. D.; Jones, A. J.; Myers, P. L. *J. Chem. Soc., Chem. Commun.* **1985**, 1662.
(11) DeCamp, A. E.; Verhoeven, T. R.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3207.
(12) (a) Wovkulich, P. M.; Tang, P. C.; Chadha, N. K.; Batcho, A. D.; Barrish, J. C.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1989**, *111*, 2596. (b) Clive, D, L. J.; Keshava Murthy, K. S.; Wee, A. G. H.; Siva Prasad, J.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Haugen, R. D.; Heerze, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 6914. (c) Hirama, M.; Iwashita, M. *Tetrahedron Lett.* **1983**, *24*, 1811.
(13) For an excellent monograph, see: Corey, E. J.; Cheng, X.-M. *The Logic of Organic Synthesis*; Wiley: New York, 1989.

0022-3263/90/1955-5766$02.50/0