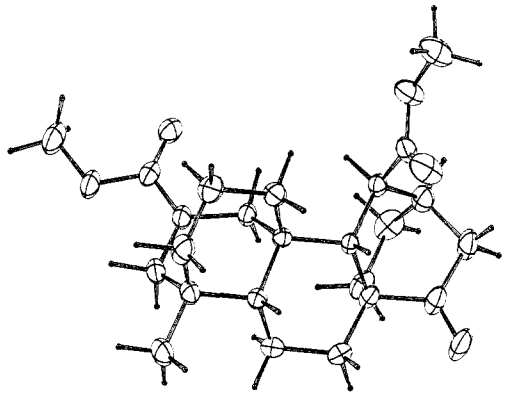


Figure 1. Molecular structure of **2**.

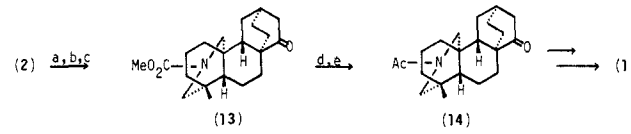
synthesis of (±)-atisine (**1**) according to this strategy as shown in Scheme I.

The azabicyclononane **4** corresponding to the AE part was synthesized in 97% yield by double Mannich reaction from diester **5**[6a] using benzylamine and formaldehyde.[6b] The ketone **4**, mp 121-122 °C, was treated with $Ph_3P{=}CH_2$ to afford methylene **6** in 78% yield. Conversion of **6** into asymmetrical **7** was carried out by two steps: reduction of **6** with $LiAlH_4$ (93%) and monoprotection of the resulting diol with methoxymethyl (MOM) group[7] (see Scheme II). The accompanied di-MOM ether was quantitatively hydrolyzed to the diol, which was recycled to monoether **7**. Thus the diol was transformed into **7** in 61% yield. Conversion of **7** into ether **8** was performed by Swern oxidation (98%) followed by Wolff-Kishner reduction (80%). Stereoselective anti-Markovnikov hydration was achieved by reaction of **8** with $NaBH_4$ in the presence of $BF_3{\cdot}Et_2O$[8] and subsequent oxidation with $Me_3N \rightarrow O$[9] to give primary alcohol **9** in 72% yield along with a stereoisomer (5%). When hydroboration was carried out by using ordinary boranes, two isomers of nearly equal amount formed. Coordination of the amino group with BF_3 hindering the approach of borane would bring about the desired stereoselectivity. The stereochemistry of **9** was ascertained by ^1H NMR NOE experiments. Positive NOE effects were observed between the carbinol CH_2 and $-N(CH_2)_2$ of **9**, while the isomer showed no NOE between those. Since oxidation of **9** to corresponding aldehyde failed because of the amino group existing near the hydroxyl group, **9** was transformed into urethane **10** in 86% overall yield after removal of the *N*-benzyl group.[10] Swern oxidation of **10** (96%), followed by Wittig reaction (98%), hydrogenation of the olefin, and deblocking of the MOM group (82% for two steps) gave the alcohol **11**. Transformation of **11** into the key substrate **3** was accomplished by the following sequence: (1) Birch reduction followed by acidic treatment (65%), (2) Swern oxidation of enone **12** (69%), and (3) Wittig reaction (97%).

Intramolecular double Michael reaction[5] of **3** was conducted by using $LiN(SiMe_3)_2$ in Et_2O-hexane (1:6) at $-78 \sim 0$ °C to furnish the objective pentacyclic ketone **2** in 43% yield together with one stereoisomer[11] (8%). The structure of **2**, mp 172-173 °C, was indicated from spectral data and verified by an X-ray analysis.[12] The molecular structure of **2** is shown in Figure 1.

After hydrolysis of **2** (88%), the decarboxylation was performed in 48% overall yield according to the established method.[13]

Scheme III[a]



[a] (a) KOH; (b) $(COCl)_2$, DMF; (2) 2-mercaptopyridine-*N*-oxide Na, DMAP, toluene, reflux; *n*-Bu_3SnH, AIBN, reflux; (d) Me_3SiI; (e) AcCl, aqueous $NaHCO_3$.

Urethane **13** was transformed into acetamide **14** in 63% overall yield by exposure to Me_3SiI[14] followed by acetylation (see Scheme III). IR data of **14**, mp 191-193 °C, were identical with reported ones,[3b] and the 500 MHz ^1H NMR data well supported structure **14**, although the spectrum was complicated due to rotational isomers. Since **2** has been correlated with atisine by Pelletier and co-workers,[3] the present work represents a stereoselective formal total synthesis of (±)-atisine.

Noteworthy features of the present work form the viewpoint of synthetic methodology include the following: (1) the use of the azabicyclononane **4** readily available by a double Mannich reaction, (2) the stereoselective hydroboration in the presence of $BF_3{\cdot}Et_2O$, and (3) the stereoselective construction of the bicyclo[2.2.2]octane ring by an intramolecular double Michael reaction.

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(10) Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515.
(11) Removal of the methoxycarbonyl group of the minor product gave a ketone different from **13**, and the stereochemistry remained obscure.
(12) Monoclinic, space group $P2_1/c$ with $a = 18.991$ (1) Å, $b = 7.651$ (1) Å, $c = 14.707$ (1) Å, $\beta = 93.73°$ (1), $V = 2132.4$ (3) Å^3, $Z = 4$. Final R value was 0.059 ($R_w = 0.051$) for 3370 reflections with $|F_o| > 3\sigma(|F_o|)$.
(13) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
(14) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315.

Negative Hyperconjugation. The Rotation-Inversion Barrier in α-Fluoramines

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Despite a controversial history,[1] negative hyperconjugation (or the generalized anomeric effect) now rests on a solid foundation, both experimental and theoretical.[2,3] It manifests itself in many ways, among them the anomeric effect per se:[4] the mutual strengthening and shortening of bonds from a carbon to more than one fluorine[5] and the stabilization of anions having β-fluoro substituents.[6] Particularly dramatic recent evidence for negative hyperconjugation is provided by the trifluoromethoxide ion, whose crystal structure reveals an unusually short C-O bond and stretched C-F bonds.[7]

Among neutral species, negative hyperconjugation should be especially important when the excellent lone-pair donor di-

(1) Streitwieser, A., Jr.; Berke, C. M.; Schriver, G. W.; Grier, D.; Collins, J. B. *Tetrahedron Suppl. 1* **1981**, *37*, 345.
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(7) Farnham, W. B.; Smart, B. E.; Middleton, W. J.; Calabrese, J. C.; Dixon, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 4565-7.

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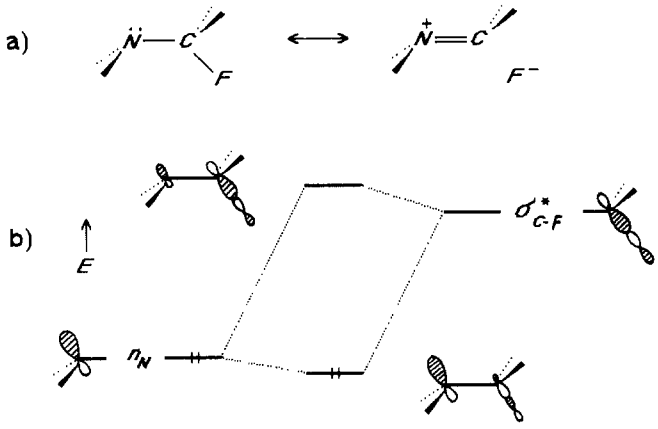


Figure 1. Negative hyperconjugation in an α-fluoramine depicted (a) in resonance terms and (b) with an orbital interaction diagram.

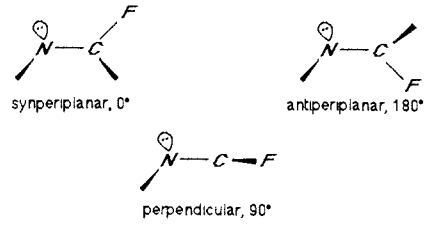
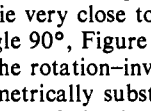


Figure 2. Some conformations of α-fluoramines. The dihedral angles are defined by the N–C–F and lone pair–N–C planes.

alkylamino is attached to the same carbon as a powerfully electronegative substituent X such as fluorine (Figure 1). High electronegativity assures that the C–X σ* orbital be low-lying and have a large coefficient at carbon, features which make it an excellent acceptor.[8] The strength of this stabilizing donor–acceptor interaction can be probed by measuring the rotational barrier about the C–N bond because it is a π-type interaction which vanishes when the axis of the lone pair is perpendicular to the C–X bond. A number of theoretical predictions of the rotational barrier in α-fluoromethylamine have appeared[2,3,9,10] but no experimental measurements of barriers in any α-fluoramines of which we are aware.[11]

Though the nitrogen lone pair is properly aligned for interaction with the C–F σ* orbital in both the synperiplanar and antiperiplanar conformations (dihedral angles 0° and 180°, respectively, Figure 2), the former suffers from both torsional strain and dipole–dipole repulsion.[9] As this geometry is approached the molecule becomes unstable with respect to inversion, which leads to the antiperiplanar form.[2] The top of the rotation–inversion barrier is predicted to lie very close to the perpendicular conformation (dihedral angle 90°, Figure 2).

In order to explore the rotation–inversion process, we have synthesized the unsymmetrically substituted α-fluoramine *N*-benzyl-*N*-methyl-α-fluoromethylamine (**1**) [^{1}H NMR (CCl_3F/$C_6D_5CD_3$, 4:1) 2.4 (s, N-CH_3), 3.8 (s, $PhCH_2$), 4.9 (s, FCH_2), 7.2 ppm (C_6H_5)].[14]



When the proton NMR sample was cooled, the methylene protons geminal to fluorine broadened and then resharpened as a doublet, J = 59.6 Hz, signifying that fluoride exchange was finally slow on the NMR time scale.[11] In this nonpolar solvent the coalescence temperature at 300 MHz was about −30 °C. Further cooling below −100 °C produced no significant change in this doublet, but the singlet for the benzyl methylene protons had metamorphosed into an AB quartet by −80 °C ($\Delta\delta$ = 0.22 ppm, J = 13.0 Hz). The initial decoalescence, producing an apparent doublet, occurred at −61 °C. The inequivalence of the benzylic protons indicates that rotation–inversion was freezing out. At −61 °C the rate constant for this process is 148 ± 8 s^{-1} and $\Delta G^{\ddagger}$ = 10.1 (6) kcal/mol. Our finding is in reasonable agreement with theoretical predictions for the barrier in the parent molecule α-fluoromethylamine, 7.8[3,9] and 9.4[2] kcal/mol, especially when the electron-donating influence of the alkyl substituents on nitrogen is taken into account.

To rule out the possibility that the slowing of inversion *alone* was responsible for the observed spectral changes, we synthesized *N*-benzyl-*N*-(2,2,2-trifluoroethyl)methylamine (**2**).[16] In **2** a

trifluoromethyl group replaces the fluorine of **1**. With respect to inductive electron withdrawal, trifluoromethyl is very similar to fluoro;[17,18] thus, if the high barrier found for **1** represented simple inversion inhibited by a substituent inductive effect, **2** should have as large a barrier as **1**. In fact, no changes occurred in the proton NMR spectrum of **2** down to temperatures below the slow exchange limit for **1**.[19]

We were surprised to find that the methylene protons geminal to fluorine in **1** gave no indication of conformational rigidity, since in this unsymmetrically substituted α-fluoramine they also are anisochronous *in principle* in the antiperiplanar conformation. In order to gain further evidence for the freezing out of rotation–inversion in α-fluoramines, another unsymmetrically substituted derivative, *N*-ethyl-*N*-methyl-α-fluoromethylamine (**3**), was prepared [^{19}F NMR (CCl_3F/$C_6D_5CD_3$, 4:1) 172.0 ppm;[15] ^{1}H NMR (same solvent) 1.1 (t, J = 7.2 Hz, CH_3CH_2), 2.45 (s, CH_3N), 2.75 (q, J = 7.2 Hz, CH_2CH_3), 4.9 ppm (s, CH_2F)].

As the temperature of the proton NMR probe (300 MHz) was lowered, the quartet for the methylene protons of the ethyl group evolved into a complex multiplet, thus signaling the freezing out of rotation–inversion. Changes in the singlet corresponding to the fluoromethylene protons are shown in Figure 3. When the sample was cooled, this signal split into a doublet as fluoride

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(11) In contrast to α-chloramines, which exist in ionic form (as immonium chlorides),[12] α-fluoramines are covalent compounds because of the great strength of the C–F bond. Simple α-fluoramines are quite volatile, pentane-soluble liquids, but they are just barely covalent. These highly reactive, rather unstable compounds suffer fluoride exchange so rapidly at ambient temperature even in nonpolar solvents that no splitting of proton resonances by geminal fluorine is observed in their NMR spectra.[13] One might therefore expect on experimental as well as theoretical grounds to find significant double bond character, i.e., substantial barriers to rotation, for the C–N bonds in these molecules.

(12) Böhme, H.; Hartke, K. *Chem. Ber.* **1960**, *93*, 1305. Böhme, H.; Mundlos, E.; Herboth, O.-E. *Chem. Ber.* **1957**, *90*, 2003.

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(14) ^{19}F NMR of **1** (same solvent) 168.6 ppm (br s);[15] MS, *m/e* 134 (base, $M^+ - F$), 133 ($M^+ - HF$), 120 ($M^+ - CH_2F$), 91 ($C_7H_7^+$). An excellent elemental analysis (C, H, N) was obtained on this compound.

(15) ^{19}F NMR chemical shifts are reported in ppm upfield from internal CCl_3F.

(16) ^{1}H NMR (CCl_3F/$C_6D_5CD_3$, 4:1) 2.95 (s, CH_3), 3.0 (q, J_{HF} = 12.5 Hz, CF_3CH_2), 3.75 (s, $PhCH_2$), 7.3 ppm (C_6H_5). The compound gave a correct analysis (C, H, N).

(17) For trifluoromethyl, σ_I = 0.45; for fluoro, σ_I = 0.50. Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975; pp 97–9.

(18) Apeloig, Y. *J. Chem. Soc., Chem. Commun.* **1981**, 396–8.

(19) In a solvent which permitted operation at lower temperatures (4:1 $CHCl_2F$/$CHClF_2$ plus ~10% $C_6D_5CD_3$), decoalescence occurred at ~−115° for CH_2CF_3 and ~−127° for CH_2Ph, corresponding to a barrier with $\Delta G^{\ddagger}$ ≅ 7.3 kcal/mol (−115°). This barrier is actually *lower* than the inversion barrier for diethylmethylamine ($\Delta G^{\ddagger}$ = 7.9 kcal/mol at −113°),[20] a finding which may reflect stabilization of the inversion transition state in **2** by negative hyperconjugation involving the CF_3 group.[21] [The interaction should be maximal when the lone pair occupies a pure p orbital.] For a discussion of the effect of perfluoroalkyl substituents on inversion barriers, see: Lambert, J. *Top. Stereochem.* **1971**, *6*, 19–105, especially p 44.

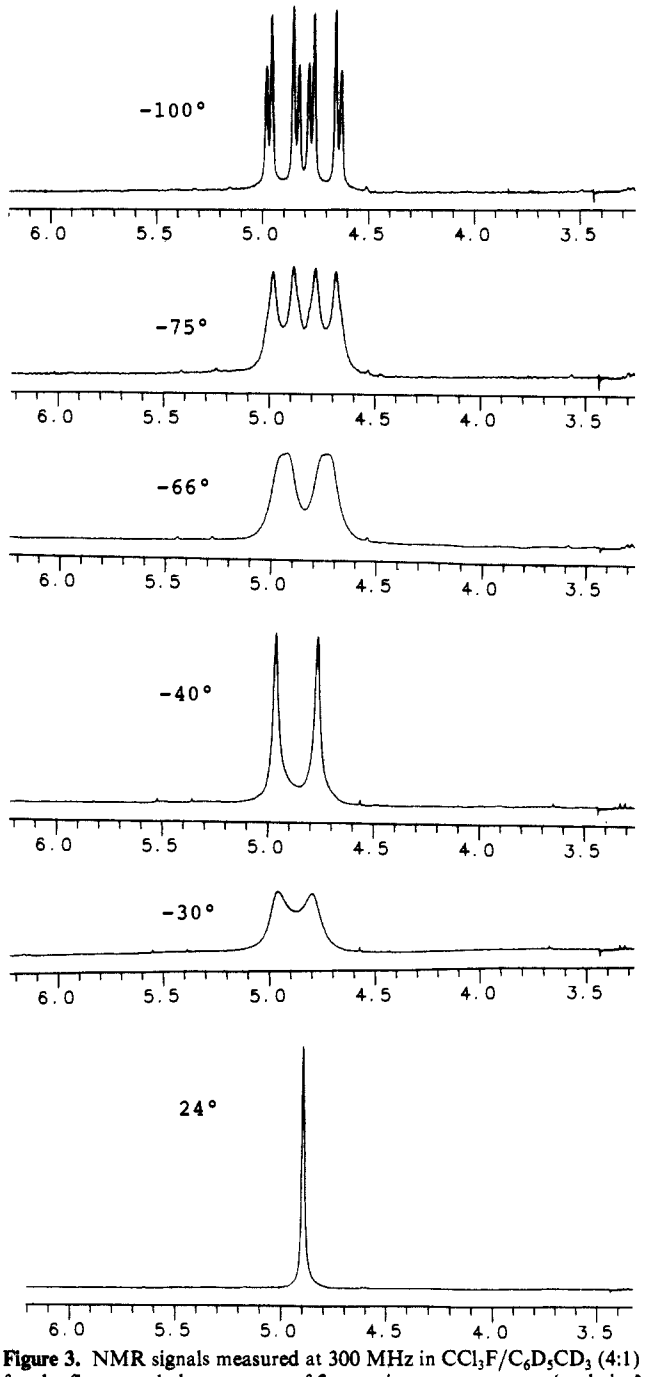

Figure 3. NMR signals measured at 300 MHz in $CCl_3F/C_6D_5CD_3$ (4:1) for the fluoromethylene protons of **3** at various temperatures (scale in δ units).

exchange became slow. Subsequent transformation of the doublet into a doublet of quartets confirmed the message conveyed by the other methylene protons, viz. that conformational mobility had been lost. This result also confirmed that the apparent equivalence of the fluoromethylene protons in **1** had been fortuitous. At the slow exchange limit, $\Delta\delta$ for the fluoromethylene protons of **3** was 0.13 ppm, J_{HH} = 7.8, J_{HF} = 60.1 Hz. Computer simulation[22] of the lineshape changes in the region of the initial decoalescence yielded the rate constant $k = 88 \pm 4$ s^{-1} at −66 °C, $\Delta G^{\ddagger} = 10.1$ (3) kcal/mol for rotation–inversion in **3**.

The barriers found for **1** and **3** are thus identical within experimental error. These remarkably high barriers are not attributable solely to negative hyperconjugation, as there should be contributions from dipole–dipole repulsion and torsional strain as well.[23] If the Pople group's Fourier analysis of the barrier in α-fluoromethylamine[9] is assumed to be correct for **1** and **3**, half of the barrier height we have observed (5 kcal/mol) can be ascribed to negative hyperconjugation.

Acknowledgment. We thank C. H. Bushweller for the use of his modification of the Kleier–Binsch DNMR3 program. This research was supported by the Air Force Office of Scientific Research and the National Science Foundation.

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(21) Ab initio calculations[18] have indicated that trifluoromethyl can engage in negative hyperconjugation, albeit somewhat less effectively than fluoro. A similar study, clearly at odds with our findings, concluded that the two substituents are comparably potent (Stamper, J. G.; Taylor, R. *J. Chem. Res. (S)* **1980**, 128; *(M)*, **1980**, 1930–9).

(22) The DNMR3 program of D. A. Kleier and G. Binsch was used as modified by Bushweller's group (Bushweller, C. H.; Bhat, G.; Letendre, L. J.; Brunelle, J. A.; Bilofsky, H. S.; Ruben, H.; Templeton, D. H.; Zalkin, A. *J. Am. Chem. Soc.* **1975**, *97*, 65).

(23) Note that *inversion makes no contribution to the rotation–inversion barrier height*, as the nitrogen is pyramidal in both the antiperiplanar and perpendicular conformations.

Reactions of MCl_5 (M = Nb or Ta) with Excess PhLi: Structural Characterization of Bisbenzyne/Polyphenyl Derivatives of Niobium and Tantalum

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Reactions between transition-metal halides and an excess of an aryllithium reagent have long been known to give unexpected products with an interesting variety of oxidation states, coordination numbers, and bonding types.[2] A recent example involves the structural characterization of the unusual complex $[Li_4FePh_4{\cdot}4Et_2O]$ in which the lithium ions are thought to play a vital role in stabilization through a coordinative interaction with the transition metal.[3] Earlier work by Kurras[4] and Sarry[5] in the group 5 transition elements had indicated that low valent species such as $[MPh_2(LiPh)_4{\cdot}3.5Et_2O]$ were present in metal halide/excess LiPh reaction mixtures. However, more recent work, based upon ^1H and ^7Li NMR, has indicated the unexpected presence of benzyne complexes in these solutions.[6] Rapid progress in this area has often been hindered by the difficulty in obtaining X-ray data even though many structures are known for closely related complexes that involve various π-acid ligands.[7] Here we provide the first X-ray structural evidence for the presence of benzyne groups in two compounds which are derived from the treatment of $NbCl_5$ or $TaCl_5$ with an excess of PhLi in THF.

The complexes $[Nb(\eta^2\text{-}C_6H_4)_2Ph_3(LiPh{\cdot}THF)(LiTHF)_4]{\cdot}0.5THF0.5C_6H_{14}$, **1**, and $[Ta(\eta^2\text{-}C_6H_4)_2Ph_4(LiTHF)_2]_2[Li_4Cl_2(THF)_{10}]$, **2**, were synthesized as described.[8] Their X-ray crystal

(1) Fellow of the A.P. Sloan Foundation 1985–1987.

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(7) An example of such a compound is $[\{[(LiPh)_3(Et_2O)_{1-1.5}Ni]_2N_2\}_2]$, see: Jonas, K. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 997. See, also: Krüger, C.; Tsay, Y. H. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 998. Jonas, K.; Brauer, D. J.; Krüger, C.; Roberts, P. J.; Tsay, Y. H. *J. Am. Chem. Soc.* **1976**, *98*, 74. For recent reviews which include many such compounds, see: Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353. Jonas, K. *Adv. Organomet. Chem.* **1981**, *19*, 97.

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