Direct Synthesis of Fluoro Bicyclic Compounds with Fluorine

Shlomo Rozen* and Chava Gal

School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel

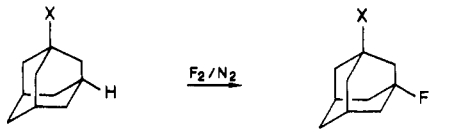
Received December 1, 1987

Elemental fluorine under suitable and simply achieved conditions acts as a strong electrophile able to substitute tertiary, including bridgehead, hydrogens of various bicyclic compounds. The skeleton of the bicyclo molecule was usually unchanged, and the yields, even in the worst cases, represent a great improvement for those extremely few fluoro bicyclic compounds that have previously been prepared. A good correlation between the hybridization of the tertiary C–H bond to its ability to be substituted by fluorine was found. The ^{13}C NMR spectra reveal some similarities to other fluoro compounds as far as the carbons α and β to the halogen are involved, but no firm rules could be detected for the γ or the δ carbons.

Despite the wealth of synthetic fluorinated compounds of almost every conceivable type, only a few fluorinated bicyclic molecules have been described in the literature. The main reason for this discrepancy is the difficulty of their preparation. Most fluorinated compounds, independent of type, are prepared by various nucleophilic reactions, by building a desired molecule from fluorine-containing fragments, or through addition reactions to double bonds.[1] These approaches, however, are of limited use when fluoro bicyclic compounds have to be prepared. Many such derivatives do not have suitable double bonds because of the strain involved, while nucleophilic reactions too often involve carbocations which rearrange easily to compounds with different skeletons. Thus, despite being tedious and difficult, the total synthesis approach has provided up to now the relatively most successful results in this field.[2]

In recent years we have shown that organic chemists do not have to shy away from F_2. This element can be used in an indirect way as a source of electrophilic fluorine[3] and nucleophilic fluorine[4] and, surprisingly, also as a tool for performing difficult organic transformations leading to fluorine-free products.[5] One of the more fundamental and interesting reactions, however, is the direct electrophilic substitution of unactivated tertiary hydrogens by fluorine,[6] which proceeds through a pentacoordinated carbonium ion accompanied by full retention of configuration.[6-9]

We have already shown that a prerequisite for a successful electrophilic substitution of a tertiary hydrogen by fluorine is a relatively high p-orbital contribution (hybridization) to the corresponding C–H bond.[6] From this point of view, adamantane (1) seems to be an ideal substrate since no strain is involved around its tertiary hydrogens, ensuring a quite suitable hybridization for an electrophilic substitution.[10] Indeed, as a result of passing fluorine diluted with nitrogen through a cold (−78 °C) 1:1 $CHCl_3$–$CFCl_3$ solution[11] of 1, 1-fluoroadamantane (2)[12] was obtained in 90% yield. In the methoxy and *p*-nitro-



1: X = H
3: X = OMe
4: X = $OCOC_6H_4NO_2$-*p*
7: X = OH

2: X = H
5: X = OMe
6: X = $OCOC_6H_4NO_2$-*p*
8: X = OH

benzoate derivatives (3 and 4 respectively), the calculated hybridization of the tertiary hydrogens is little changed respective to 1 and the yields of the corresponding 5 and 6 still remained high. The reaction times for the oxygenated compounds, however, were considerably longer, a fact that could be best observed from a series of competitive reactions carried out with mixtures of 1 and 3 and 3 and 4. It could be seen clearly that 3 started to react only after more than 70% conversion of 1 had been achieved. Similar behavior was observed with the mixture of 3 and 4, the latter being the less reactive component. Although the described conditions encourage ionic reactions, there are always some side pathways involving homolytic cleavage of the fluorine molecule resulting in indiscriminate radical reactions. Since F_2 is constantly bubbled through the reaction mixture, the longer the reaction time, the more fluorinated tars are produced. Thus, although, for example, the unprotected adamantanol (7) was successfully

(1) (a) Rozen, S.; Lerman, O. *J. Org. Chem.* **1980**, *45*, 672. (b) Lerman, O.; Rozen, S. *J. Org. Chem.* **1980**, *45*, 4122. (c) Barnett, W. E.; Wheland, R. C.; Middleton, W. J.; Rozen, S. *J. Org. Chem.* **1985**, *50*, 3698. (d) Rozen, S.; Lerman, O.; Kol, M.; Hebel, D. *J. Org. Chem.* **1985**, *50*, 4753.

(2) (a) Della, E. W.; Cotsaris, E.; Hine, P. T. *J. Am. Chem. Soc.* **1981**, *103*, 4131. (b) Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2951.

(3) (a) Rozen, S.; Menahem, Y. *J. Fluorine Chem.* **1980**, *6*, 19. (b) Rozen, S.; Lerman, O.; Kol, M. *J. Chem. Soc., Chem. Commun.* **1981**, 443. (c) Lerman, O.; Rozen, S. *J. Org. Chem.* **1983**, *48*, 724. (d) Lerman, O.; Tor, Y.; Hebel, D.; Rozen, S. *J. Org. Chem.* **1984**, *49*, 806. (e) Rozen, S.; Brand, M. *Synthesis* **1985**, 665. (f) Hebel, D.; Lerman, O.; Rozen, S. *Bull. Soc. Chim. Fr.* **1986**, 861. (g) Hebel, D.; Rozen, S. *J. Org. Chem.* **1987**, *52*, 2588.

(4) (a) Rozen, S.; Brand, M. *J. Org. Chem.* **1985**, *50*, 3342. (b) Rozen, S.; Brand, M. *J. Org. Chem.* **1986**, *51*, 222. (c) Rozen, S.; Zamir, D.; Brand, M.; Hebel, D. *J. Am. Chem. Soc.* **1987**, *109*, 896.

(5) (a) Rozen, S.; Brand, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 554. (b) Rozen, S.; Brand, M. *J. Chem. Soc., Chem. Commun.* **1987**, 752. (c) Rozen, S.; Hebel, D.; Zamir, D. *J. Am. Chem. Soc.* **1987**, *109*, 3789.

(6) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 2769. Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 4928.

(7) Hebel, D.; Rozen, S. *J. Org. Chem.* **1987**, *52*, 2588.

(8) For an excellent book on various types of electrophilic substitutions on a saturated carbon, see: Olah, G. A.; Prakash, G. K. S.; Williams, R. E.; Field, L. D.; Wade, K. *Hypercarbon Chemistry*; Wiley: New York, 1987. Prof. Olah was also one of the first to generally suggest a pentacoordinated carbonium ion as an intermediate for electrophilic substitution on saturated carbon. For detailed references, see the above book.

(9) For preliminary communication, see: Gal, C.; Rozen, S. *Tetrahedron Lett.* **1985**, *26*, 2793.

(10) Most of the C–H bonds in the compounds described in this article were examined by using CNDO and the more advanced PRDDO program (see, for example: Dixon, D. A.; Kleier, D. A.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1978**, *100*, 5681). The coordinates of the calculated molecules were obtained by using Alinger's MM1 and MM2 programs. In most cases the C–H bond with the highest hybridization on p (from the PRDDO calculations) is the one most successfully attacked by fluorine.

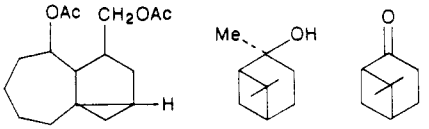
(11) On the importance of the chloroform as a radical scavenger, as a promoter of reactions with ionic character, and as an acceptor for the F^- in the transition state, see ref 6.

(12) See, for example: Rozen, S.; Brand, M. *J. Org. Chem.* **1981**, *46*, 733.

0022-3263/88/1953-2803$01.50/0

fluorinated to 1-hydroxy-3-fluoroadamantane (**8**), solubility problems slowed down the reaction, resulting in a somewhat reduced yield of 70%.

While tertiary hydrogens in adamantane derivatives are easily substituted, ones with very low hybridization are highly resistant to F_2. The tertiary hydrogen located on the cyclopropane ring in the tricyclic molecule **9** and those in *cis*-pinalol (**10**) or nopinone (**11**) have such a low hybridization ($sp^{2.0-2.5}$) that no electrophilic substitution can take place. Even high fluorine concentrations of up to 15% caused in these cases only a very slow deterioration of the starting material as a result of the inevitable fluorine radical reaction.



9 **10** **11**

While the low hybridization of the tertiary hydrogen in **9** is due only to the fact that it is located on the strained cyclopropane ring, the nearby electronegative oxygen atom in **10** and **11** also contributes to the same effect. When this atom is found further away from the tertiary center by one CH_2 unit as in **12**, the electrophilic substitution is already enabled, although in very modest yields. It can

12: R = $OCOC_6H_4NO_2$-*p*; X = Y = H
13: R = $OCOC_6H_4NO_2$-*p*; X = F; Y = H
14: R = $OCOC_6H_4NO_2$-*p*; X = H; Y = F
15: R = CH_2OAc; X = Y = H
16: R = CH_2OAc; X = F; Y = H

17: $R_1 = R_2 = O$; X = H
18: R_1 = H; R_2 = OAc; X = H
19: R_1 = H; R_2 = OAc; X = F

be shown that, in this compound, the C_2 tertiary hydrogen has the highest hybridization ($sp^{2.9}$), and indeed this is the hydrogen replaced by fluorine, forming **13** in 15% yield along with a small amount of the isomeric **14**. The yields of some of the fluorinated bicyclic molecules may look at first sight quite low. However, the yields of most of the fluoro bicyclic compounds totally synthesized by multistep reactions range from a few to a fraction of a percent.[2] The yields in the direct fluorination method thus represent an improvement of at least an order of magnitude.

The ^1H and ^{13}C NMR spectra are of great help in structure elucidation. Thus, for example, the magnitude of $^1J_{(^{13}C-F)}$ in both **13** and **14** is very large (220–225 Hz), characteristic of CF bonding orbitals with a high s contribution[2a] and indicating that no rearrangement took place. Another CH_2 unit inserted between the oxygen-carrying moiety and the tertiary center, as in the case of nopyl acetate (**15**), makes the hydrogen at C_2 much more favorable for electrophilic substitution than the other tertiary hydrogens ($sp^{3.2}$ vs $sp^{2.6}$). Only one monofluoro compound, identified as **16**, was thus formed in a respectable 40% yield.

The same trend was observed with the [2.2.1] bicyclic system. The carbonyl group has a strong deactivating effect toward electrophilic substitutions at the nearby tertiary hydrogens,[6] so camphor (**17**) was fully resistant even to high fluorine concentrations and only the typical slow deterioration was observed. However, in bornyl acetate (**18**), there is a greater p-orbital contribution to the single tertiary C–H bond ($sp^{2.7}$) and one could already observe the formation of 4-fluorobornyl acetate (**19**) in 20% yield.

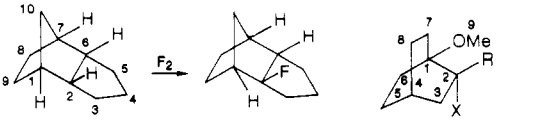
In 2-bicyclo[3.2.1]octyl acetate (**20**), one of the rings of the bicyclic skeleton is enlarged without releasing the strain of the bridgehead C–H bond ($sp^{2.7}$). This does not much change the reactivity toward electrophilic substitution. Again only 20% of the corresponding fluoro derivative **21** was isolated and identified with the help of ^1H, ^{19}F, and ^{13}C NMR spectra. For example, C_2 appears as a slightly shielded singlet, typical of a carbon γ to the fluorine atom, excluding the possibility of the fluorine being attached to C_1.

20: X = H
21: X = F

22: R = $COC_6H_4NO_2$-*p*; X = Y = H
23: R = $COC_6H_4NO_2$-*p*; X = F; Y = H
24: R = $COC_6H_4NO_2$-*p*; X = H; Y = F
25: R = Ac; X = Y = H
26: R = Ac; X = F; Y = H
27: R = Ac; X = H; Y = F

The case of 2-norbornylethyl *p*-nitrobenzoate (**22**) with its additional, nonbridgehead reacting center, resembles the [3.1.1] bicyclic system **12**. In both cases the nonbridgehead tertiary hydrogen has a relatively high hybridization and therefore reacts somewhat better than the hydrogen at C_4. Still the proximity of the electron-withdrawing *p*-nitrobenzoate moiety limits the yields of **23** and **24** to only 20% and 10% correspondingly. Protecting the primary alcohol by acetylation (**25**), rather than *p*-nitrobenzoylation, deactivated the two tertiary hydrogens to a lesser degree; the reaction was faster, and **26** and **27** were isolated in 30% and 15% yields, respectively. The identification of these isomers was based partly on their ^{19}F NMR spectra. In **23** and **26** the fluorine nucleic appeared as a double quintet ($J_{3H(endo)F}$ = 56 Hz; J_{CH-F} = 28 Hz and $J_{3H(exo)F}$ = 9 Hz), in good agreement with the corresponding dihedral angles. The multiplicity of the fluorine atom in **24** and **27** was a heptet, reflecting the fact that the dihedral angle between the fluorine atom and $H_{3(endo)}$ and $H_{5(endo)}$ is very near 90° ($J_{3,5H(exo)F}$ = 42 Hz and J_{CH_2-F} = 21 Hz).

The surprising regioselectivity of this most reactive element can be demonstrated by its reaction with *endo*-tricyclo[5.2.1.$0^{2,6}$]decane (**28**). This molecule has no electron-withdrawing elements which may polarize or deactivate some of the potential reactive centers. PRDDO calculations reveal that there is a small difference in hybridization between the tertiary hydrogens at C_1 and C_2 ($sp^{2.7}$ and $sp^{2.8}$ respectively). This difference seems to be sufficient, and after a relatively fast reaction, only the 2-fluoro derivative **29** was isolated in higher than 75% yield. Here again the ^{19}F and ^{13}C NMR spectra were of major help in determining the structure.



28 **29**

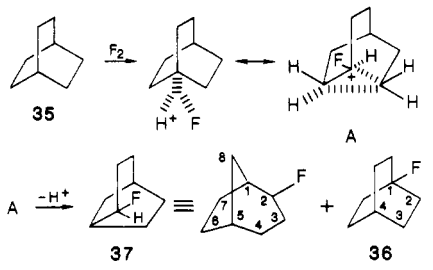
30: R = Et; X = H
31: R = Et; X = F
32: R = CN; X = H
33: R = CH_2OAc; X = H
34: R = $COCH_3$; X = H

The regioselectivity and its dependence on the hybridization can clearly be observed also in the reaction of fluorine with 2-ethyl-1-methoxybicyclo[2.2.2]octane (**30**). Although the tertiary hydrogen on C_2 is closer to the methoxy oxygen, it is not a bridgehead one and its hybridization was calculated to be $sp^{3.1}$ vs $sp^{2.9}$ for the C_4–H bond. The oxygen atom, though, slows down the reaction,

and as a result, only a 25% yield of the 2-ethyl-2-fluoro-1-methoxybicyclo[2.2.2]octane (**31**) was obtained. As in the previous cases, the various NMR spectra did not leave any doubt about the carbon to which the fluorine atom was attached. Thus the CH_3 triplet and the methoxy singlet were shifted to a lower field by 0.1 and 0.17 ppm respectively. The shifts and the coupling constants of the various C-β and C-γ carbons in the ^{13}C NMR spectrum are also in full agreement with the assigned structure.

In compounds **32–34**, the ethyl group in **30** is replaced with electron-withdrawing groups. This caused a total deactivation of the molecule toward electrophilic reactions, and again even high concentrations of fluorine did not react with the starting materials except by the minor radical fluorination pathway which could never be totally suppressed.

As we have previously seen, without electron-withdrawing groups in the [2.2.2] bicyclic system, the reaction proceeds much faster and therefore much more cleanly. Passing fluorine through the parent bicyclo[2.2.2]octane (**35**) resulted in the formation of only two main compounds, which were readily isolated. It was easy to show that the major component was the expected 1-fluorobicyclo[2.2.2]octane (**36**, 50% yield). The second compound, however, possessed a secondary fluorine, and all the spectral evidence pointed toward the formation of 2-fluorobicyclo[3.2.1]octane (**37**, 40% yield).



Although this is the first and only example for a rearrangement process connected with this electrophilic substitution, it can be easily explained by noticing that the pentacoordinated carbonium ion which is formed in the first step[6] is highly stabilized and is in resonance with the nonclassical carbonium ion A keeping eight electrons around each carbon.[8] The fluorine atom even enhances the stability of A compared to the known parent hypercoordinated carbocation. The charged A eventually ejects either the C_1, C_2, or C_6 hydrogen with rearrangement of the relevant C–C bonds, forming **36** and **37** respectively. It may be of interest to note that a somewhat similar remarkably stable nonclassical carbocation was recently described by Schleyer.[13]

^{13}C NMR spectroscopy is usually of great help in the structure determination of fluorinated compounds. As expected, the electronegative fluorine atom introduces an enormous paramagnetic shift on the α carbons of 50–70 ppm along with unique $^1J_{(^{13}C-F)}$ coupling constants of 175–190 Hz. When, however, the fluorine is attached to a carbon with unusually high s character bonding orbitals, $^1J_{(^{13}C-F)}$ increases dramatically[2a] up to 225 Hz (see compounds **13** and **14**). The three β carbons are also deshielded, usually by 0.5–10 ppm, and have a characteristic $^3J_{(^{13}C-F)}$ coupling constant of 15–25 Hz. While these features are common to all tertiary fluorinated compounds, the picture is not so uniform with the carbons in the γ position. When working with strain-free, rigid[14] or configurationally fixed[6a] compounds possessing a tertiary fluorine, we were witness to a consistent pattern for the carbons γ to the halogen. Those gauche to the fluorine atom were always shifted to a higher field, while the ones anti to it were deshielded by 2–4 ppm and usually had ^{13}C–F coupling constants of 0–10 Hz. However, in agreement with Della's findings,[2a] no firm conclusions could be drawn for the γ carbons in the highly constrained bicyclo molecules. Most of these carbons, regardless their C–C–C–F dihedral angle, were shifted to higher field by 0.5–9 ppm although a few were deshielded by up to 5 ppm (see Experimental Section). The large majority of the $^3J_{(^{13}C-F)}$ coupling constants are either 0 or very small, but again a few exceptions were found with no apparent consistent pattern. The δ carbons were usually shifted to a higher field, but here, too, a couple of exceptions were recorded. It is obvious that the way the fluorine atom affects the γ carbons in strained bicyclic molecules has still to be fully evaluated.

In conclusion, it seems that, though it is the most reactive element, F_2 can perform quite selective reactions on sites that are not accessible by any other means. Thus, for the first time, a general way was opened for a direct substitution of bicyclic unactivated hydrogens.

Experimental Section

^1H NMR spectra were recorded with Bruker WH-90 and Bruker WH-360 spectrometers at 90 and 360 MHz respectively using $CDCl_3$ as solvent and Me_4Si as an internal standard. The ^{19}F NMR spectra were measured at 84.67 and 338.8 MHz respectively and are reported in parts per million upfield from $CFCl_3$, which also served as internal standard. The proton broad band decoupled ^{13}C NMR spectra were recorded on Bruker WH-90 and WH-300 spectrometers at 22.63 and 75.46 MHz, respectively. $CDCl_3$ served as a solvent and TMS as internal standard. The ^{13}C NMR spectra of the parent compounds were also recorded, and the δ values were derived by comparing the latter spectra with those of the fluorinated compounds. $\Delta\delta$ is defined as the difference in parts per million between the chemical shift of the relevant carbon atoms in the corresponding unfluorinated and fluorinated derivatives; "+" represents a deshielding effect and "–" a shielding one, both introduced by the fluorine atom. Unless otherwise stated, the signals are singlets and all coupling constants are C–F couplings. In many cases the ^{13}C NMR spectra of the paraffinic parent bicyclic skeletons have been reported in the literature and, after the usual corrections for the various substituents, a full agreement with the ^{13}C NMR spectra of our substituted parent compounds was found. Mass spectra were measured with a Du Pont 21-491B spectrometer. IR spectra were recorded as neat films, in $CHCl_3$ solution, or in KBr pellets on a Perkin-Elmer 177 spectrophotometer.

General Fluorination Procedure. Fluorine is of course a strong oxidizer and a very corrosive material. An appropriate vacuum line made from copper or Monel in a well-ventilated area should be constructed for working with this element. Variations of such vacuum lines are described for example in Matheson Report No. G-115B and in a recent review.[15] The reactions themselves can be carried out in glass vessels. If elementary precautions are taken, work with fluorine is relatively simple, and we have had no accidents. The reactions were usually carried out at –75 °C on scales of 1–6 mmol of substrate dissolved in 400 mL of 1:1 $CFCl_3$–$CHCl_3$. The reactions were monitored by TLC and GC on 20% SE-30 or 10% OV-17 columns. They were usually stopped when the conversion reached about 90–95%. The fluorine concentration varied between 1 and 6% F_2 in N_2 according to the type of the substrate. The gas mixture was prepared in a secondary container[16] before the reaction was started. This mixture

(13) Bremer, M.; Schleyer, P. R.; Schotz, K.; Kausch, M.; Schindler, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 761.

(14) (a) Rozen, S.; Ben-Shushan, G. *Org. Magn. Reson.* **1985**, *23*, 116. (b) Rozen, S.; Ben-Shushan, G. *J. Org. Chem.* **1986**, *51*, 3522.

(15) Vyplel, H. *Chimia* **1985**, *39*, 305.

(16) Various mixtures of fluorine in inert gases such as N_2 or He are commercially available.

was first passed through a dry NaF column serving as a HF scavenger (Matheson) and then in a slow stream of about 15 mL/min through a vigorously stirred solution of the substrate containing NaF. Efficient mixing, which is an especially important factor for obtaining higher yields, is achieved by using a vibromixer (Chemapec), which also ensures a fine dispersion of the gas bubbles. The term "worked up as usual" means stopping the reaction by pouring it into 500 mL of water, washing the organic layer with $NaHCO_3$ solution followed by water until neutral, drying the organic layer over $MgSO_4$, and finally evaporating the solvent preferably at room temperature. The crude product was usually purified by vacuum flash chromatography using silica gel 60-H (Merck) and if needed also by HPLC (Waters) on Merck's Li-Chrosorb Si-100. In general, when no melting point is given, the product is liquid at room temperature.

Preparation of Starting Materials. In general, alcohols were treated with Ac_2O–pyridine for acetate preparation and with freshly prepared *p*-nitrobenzoyl chloride–pyridine for the preparation of the *p*-nitrobenzoates. The crude products were usually purified by short-column chromatography using 2–4% EtOAc in petroleum ether (pe) as eluent.

Fluorination of adamantane (1) was performed on 2.0 g (14.7 mmol) by using 1% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with pe followed by HPLC using cyclohexane as eluent. The pure **2**, identical with an authentic sample.[12] was thus isolated in 90% yield.

Fluorination of 1-methoxyadamantane (3) was performed as described above on 0.65 g (3.9 mmol) by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 10% EtOAc in pe, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure **5** was thus isolated in 90% yield: IR 2815, 1120 cm^{-1}; ^1H NMR 3.25 (3 H, CH_3CO, s), 2.40 (2 H, $CFCH_2CO$, br s), 1.94–1.41 (12 H, m); ^{19}F NMR −131.9 (s); MS, *m/e* 184 (M^+), 153 [$(M - OMe)^+$]. Anal. Calcd for $C_{11}H_{17}FO$: C, 71.74; H, 9.24. Found: C, 71.82; H, 9.35.

Fluorination of 1-adamantyl *p*-nitrobenzoate (4)[17] was performed on 1 g (3.32 mmol) by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in pe followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure **6** was thus isolated in 90% yield: mp 179 °C (from cyclohexane); ^1H NMR 8.24 (4 H, AB, J = 8 Hz), 2.46–1.2 (14 H, m); ^{19}F NMR −133.55 (s); ^{13}C NMR 92.50 (C3[α], d, J = 187 Hz, $\Delta\delta$ = +61.3), 46.78 (C2[β], d, J = 20 Hz, $\Delta\delta$ = +5.2), 41.61 (C4,C7[β], d, J = 18 Hz, $\Delta\delta$ = +5.5), 83.10 (C1[γ], d, J = 12 Hz, $\Delta\delta$ = +0.3), 31.54 (C5,C8[γ] d, J = 10 Hz, $\Delta\delta$ = +0.42), 39.92 (C6,C10[δ], $\Delta\delta$ = −1.6), 34.59 (C9[δ], $\Delta\delta$ = −1.7), 150.5, 137.0, 130.6, 123.3 (C_{arom}); MS, *m/e* 316 (M^+). Anal. Calcd for $C_{17}H_{18}FNO_4$: C, 63.95; H, 5.64. Found: C, 64.94; H, 6.00.

Fluorination of 1-adamantanol (7) was performed on 0.5 g (3.28 mmol) by using 6% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 20% EtOAc in pe, followed by HPLC using 30% EtOAc in cyclohexane as eluent. The pure **8** was thus isolated in 70% yield and was identical with the compound described in the literature.[18]

Fluorination of *cis*-mirtanyl *p*-nitrobenzoate (12, mp 60 °C) was performed on 0.5 g (1.65 mmol) by using 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 10% EtOAc in pe followed by HPLC using 5% EtOAc in cyclohexane as eluent. Two compounds were thus isolated. The less polar one proved to be (*cis*-6,6-dimethyl-2-fluoro-2-bicyclo[3.1.1]heptyl)methyl *p*-nitrobenzoate (**13**): 15% yield; mp 65 °C (hexane); ^1H NMR 8.25 (4 H, AB, J = 8 Hz), ABX system 4.64 (1 H, H_A, dd, J_{HH} = 10.9 Hz, J_{HF} = 5.4 Hz), 4.46 (1 H, H_B, dd, J_{HH} = 10.9 Hz, J_{HF} = 8.9 Hz), 2.88 (1 H, C_1-H, m), 2.57 (1 H, C_5-H, m), 2.22 (2 H, C_3-H, m), 1.85 (4 H, C_4-H, C_7-H, m), 1.24 and 1.14 (6 H, Me, s); ^{19}F NMR −154.8 (narrow m, $W_{h/2}$ = 38 Hz); ^{13}C NMR 96.54; (C2[α], d, J = 225 Hz, $\Delta\delta$ = +53.65), 67.54 (C10[β], d, J = 5 Hz, $\Delta\delta$ = −2.3), 44.00 (C1[β], d, J = 16 Hz, $\Delta\delta$ = +2.9), 39.44 (C3[β], d, J = 18 Hz, $\Delta\delta$ = +14.3), 44.03 (C6[γ], $\Delta\delta$ = +5.7), 24.32 (C7[γ], $\Delta\delta$ = −8.43), 21.42 (C4[γ], $\Delta\delta$ = +2.98), 35.77 (C5[δ], $\Delta\delta$ = −4.37), 22.66 (C8[δ], d, J = 5 Hz, $\Delta\delta$ = −4.37), 22.04 (C9[δ], $\Delta\delta$ = −0.94), 150.2, 135.7, 130.8, 123.6 (C_{arom}), 164.5 (CO); MS, *m/e* 199 [$(M - C_6H_4NO_2)^+$], 171 [$(M - COC_6H_4NO_2)^+$], 155 [$(M - OCOC_6H_4NO_2)^+$]. Anal. Calcd for $C_{17}H_{20}FNO_4$: C, 63.55; H, 6.23. Found: C, 62.93; H, 6.46. The more polar compound was found to be (*cis*-6,6-dimethyl-1-fluoro-2-bicyclo[3.1.1]heptyl)methyl *p*-nitrobenzoate (**14**): 10% yield; mp 55 °C (hexane); ^1H NMR 8.25 (4 H, AB, J = 8 Hz), ABX system (CH_2O) 4.33 and 4.29 (1 H each, both dd, J_{HaHb} = 10.7 Hz, $J_{Ha\ or\ HbHx}$ = 7.8 Hz), 2.63 (1 H, C_5-H, m), 2.39 (2 H, C_2-H, C_7-H_{eq}, m), 2.09 (4 H, C_3-H, C_4-H, m), 1.77 (1 H, C_7-H_{ax}, m), 1.23 and 1.16 (6 H, Me, s); ^{19}F NMR −148.7 (br s, $W_{h/2}$ = 35 Hz); ^{13}C NMR 95.55 (C1[α], d, J = 220 Hz, $\Delta\delta$ = +54.43), 44.30 (C2[β], d, J = 21 Hz, $\Delta\delta$ = +1.4), 39.84 (C6[β], d, J = 19 Hz, $\Delta\delta$ = +1.49), 37.65 (C7[β], d, J = 17 Hz, $\Delta\delta$ = +4.9), 69.38 (C10[γ], $\Delta\delta$ = −0.53), 38.50 (C5[γ], $\Delta\delta$ = −1.64), 29.57 (C8[γ], $\Delta\delta$ = +1.93), 22.63 (C3[γ], $\Delta\delta$ = −2.48), 20.86 (C9[γ], $\Delta\delta$ = −2.12), 20.54 (C4[δ], $\Delta\delta$ = +2.1) 150.7, 135.6, 130.7, 123.5 (C_{arom}), 164.6 (CO); MS, *m/e* 166 $(OCOC_6H_4NO_2)^+$. Anal. Calcd for $C_{17}H_{20}FNO_4$: C, 63.55; H, 6.23. Found: C, 63.31; H, 6.00.

Fluorination of nopyl acetate (15) was performed on 1.0 g (4.76 mmol) by using 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 8% EtOAc in pe followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure (6,6-dimethyl-2-fluoro-2-bicyclo[3.1.1]-heptyl)ethyl acetate (**16**) was thus isolated in 40% yield: ^1H NMR 4.15 (2 H, CH_2O, m), 2.5–1.9 (6 H, CH_2CH_2O, C_3-H, C_5-H, C_1-H, m), 2.05 (3 H, Ac, s), 1.68 (2 H, C_4-H, m), 1.55–1.00 (2 H, C_7-H, m), 0.97 and 0.87 (6 H, Me, s); ^{19}F NMR −179.3 (m, $W_{h/2}$ = 90 Hz); ^{13}C NMR 96.07 (C2[α], d, J = 176 Hz, $\Delta\delta$ = +64.46), 38.95 (C1[β], d, J = 20 Hz, $\Delta\delta$ = +3.03), 32.65 (C10[β], d, J = 10 Hz, $\Delta\delta$ = +1.32), 30.10 (C3[β], d, J = 31 Hz, $\Delta\delta$ = +3.77), 63.03 (C11[γ], $\Delta\delta$ = +0.45), 46.34 (C6[γ], d, J = 4.5 Hz, $\Delta\delta$ = +5.50), 30.28 (C7[γ], $\Delta\delta$ = −7.67), 20.94 (C4[γ], $\Delta\delta$ = −0.15), 36.36 (C5[δ], $\Delta\delta$ = −9.53), 27.86 (C8[δ], $\Delta\delta$ = −3.47), 23.21 (C9[δ], $\Delta\delta$ = −8.4), 20.9 (CH_3CO), 170 (CO); MS, *m/e* 165 [$(M - HF - Ac)^+$]. Anal. Calcd for $C_{13}H_{21}FO_2$: C, 68.42; H, 9.21. Found: C, 67.96; H, 9.11.

Fluorination of bornyl acetate (18) was performed on 0.6 g (3.0 mmol) by using 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in pe followed by HPLC using 5% EtOAc in cyclohexane as eluent. A single product was obtained and identified as 4-fluorobornyl acetate (**19**): 15% yield; ^1H NMR 4.90 (1 H, CHO, ddd, $^4J_{HF}$ = 7.6 Hz, $^3J_{H(exo)H(endo)}$ = 2.6 Hz, $^3J_{H(exo)H(exo)}$ = 11 Hz), 2.04 (3 H, Ac, s), 1.03, 0.92, 0.90 (3 H each, Me-8, 9, and 10), 2.60–0.60 (6 H, m), ^{19}F NMR −158.4 (m, $W_{h/2}$ = 115 Hz); ^{13}C NMR 96.83 (C4[α], d, J = 187 Hz, $\Delta\delta$ = +50.86), 50.46 (C7[β], d, J = 19 Hz, $\Delta\delta$ = +2.63), 37.51 (C3[β], d, J = 18 Hz, $\Delta\delta$ = +0.66), 32.24 (C5[β], d, J = 13 Hz, $\Delta\delta$ = +4.16), 77.66 (C2[γ], $\Delta\delta$ = −2.15), 20.08 (C6[γ], $\Delta\delta$ = −7.08), 20.08 (C9[γ], $\Delta\delta$ = +1.23), 19.37 (C8[δ], $\Delta\delta$ = −0.39), 47.31 (C1[δ], d, $\Delta\delta$ = −1.43), 12.54 (C10[δ], $\Delta\delta$ = +0.34), 21.18 (CH_3CO), 171.18 (CO); MS, *m/e* 214 (M^+), 171 [$(M - Ac)^+$]. Anal. Calcd for $C_{12}H_{19}FO_2$: C, 67.29; H, 8.87. Found: C, 67.00; H, 8.56.

Fluorination of 2-bicyclo[3.2.1]octyl acetate (20) was performed on 0.39 g (2.3 mmol) by using 6% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in pe followed by HPLC using 5% EtOAc in cyclohexane as eluent. A single compound was thus isolated and identified as 5-fluoro-2-bicyclo[3.2.1]octyl acetate (**21**): 20% yield; ^1H NMR 4.70 (1 H, CHO, m, $W_{h/2}$ = 18 Hz), 2.01 (3 H, Ac, s), 2.50–0.90 (11 H, m); ^{19}F NMR −162.7 (m, $W_{h/2}$ = 140 Hz); ^{13}C NMR 97.59 (C5[α], d, J = 175 Hz, $\Delta\delta$ = +64.03), 40.67 (C8[β], d, J = 22 Hz, $\Delta\delta$ = +3.79), 33.90 (C4[β], d, J = 32 Hz, $\Delta\delta$ = +3.65), 32.50 (C6[β], d, J = 22 Hz, $\Delta\delta$ = +8.17), 45.0 (C1[γ], $\Delta\delta$ = +5.65), 29.71 (C3[γ], $\Delta\delta$ = +1.62), 23.0 (C7[γ], $\Delta\delta$ = −0.51), 74.0 (C2[δ], $\Delta\delta$ = −0.77), 21.20 (CH_3CO), 173.50 (CO); MS, *m/e* 143 [$(M - Ac)^+$], 127 [$(M - OAc)^+$]. Anal. Calcd for $C_{10}H_{15}FO_2$: C, 64.52; H, 8.06. Found: C, 64.02; H, 8.28.

Fluorination of 2-norbornylethyl *p*-nitrobenzoate (22, mp 36 °C) was performed on 0.5 g (1.73 mmol) by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 10% EtOAc in pe followed by HPLC using 8% EtOAc in cyclohexane as eluent. Two compounds were thus isolated. The less polar one proved to be (4-fluoro-2-norbornyl)ethyl *p*-nitrobenzoate (**24**): 10% yield; mp 34 °C (hexane);

(17) Fort, R. C.; Schleyer, P. R. *J. Org. Chem.* **1965**, *30*, 789.
(18) Alker, D.; Barton, D. H. R.; Hesse, R. H.; James, J. L.; Markwell, R. E.; Pechet, M. M.; Rozen, S.; Takeshita, T.; Toh, H. T. *Nouv. J. Chim.* **1980**, *4*, 239.

^{1}H NMR 8.24 (4 H, AB, J = 8 Hz), 4.55 (2 H, CH_2O, t, J = 7 Hz), 2.37–1.0 (12 H, m); ^{19}F NMR −159.47 (heptet, $J_{FH(exo)}$ = 43 Hz, J_{FH} = 21 Hz); ^{13}C NMR 101.7 (C4[α], d, J = 183 Hz, $\Delta\delta$ = +62.84), 45.95 (C7[β], d, J = 21 Hz, $\Delta\delta$ = +10.53), 43.28 (C3[β], d, J = 24 Hz, $\Delta\delta$ = +7.66), 38.47 (C5[β], d, J = 27 Hz, $\Delta\delta$ = +9.68), 38.50 (C1[γ], d, J = 4.4 Hz, $\Delta\delta$ = −2.77), 28.00 (C2[γ], $\Delta\delta$ = −8.65), 21.4 (C6[γ], d, J = 13 Hz, $\Delta\delta$ = −8.69), 36.59 (C8[δ], $\Delta\delta$ = −1.76), 61.9 (C9, $\Delta\delta$ = −3.09), 150.5, 136.4, 130.6, 123.4 (C_{arom}), 164.5 (CO); MS, m/e 307 (M^+), 287 [$(M - HF)^+$]. Anal. Calcd for $C_{16}H_{18}FNO_4$: C, 62.54; H, 5.86. Found: C, 62.60; H, 5.46. The more polar compound was found to be (2-fluoro-2-norbornyl)ethyl p-nitrobenzoate (**23**): 20% yield; mp 40 °C (hexane); ^{1}H NMR 8.25 (4 H, AB, J = 8 Hz), 4.39 (2 H, CH_2O, t, J = 6.8 Hz, $^4J_{HF}$ = 1.7 Hz), 2.33–1.0 (12 H, m); ^{19}F NMR −162.57 (d quintet, $J_{FH(endo)}$ = 57 Hz, J_{FH} = 28 Hz, $J_{FH(exo)}$ = 9 Hz); ^{13}C NMR 95.64 (C2[α], d, J = 184 Hz, $\Delta\delta$ = +58.99), 47.10 (C1[β], d, J = 19 Hz, $\Delta\delta$ = +5.83), 39.2 (C8[β], d, J = 20 Hz, $\Delta\delta$ = +0.85), 35.90 (C3[β], d, J = 29 Hz, $\Delta\delta$ = +0.28), 64.54 (C9[γ], $\Delta\delta$ = −0.45), 34.87 (C7[γ], d, J = 13 Hz, $\Delta\delta$ = −0.55), 32.3 (C4[γ], $\Delta\delta$ = −6.56), 29.30 (C6[γ], $\Delta\delta$ = −0.79), 32.11 (C5[δ], $\Delta\delta$ = +3. 32), 150.5, 136.4, 130.7, 123.4 (C_{arom}), 164.5 (CO); MS, m/e 307 (M^+), 287 [$(M - HF)^+$]. Anal. Calcd for $C_{16}H_{18}FNO_4$: C, 62.54; H, 5.86. Found: C, 61.82; H, 5.73. Similarly the acetate of 2-norbornylethanol (**25**) was fluorinated, and after chromatography, two fractions were isolated. The less polar one proved to be the 4-fluoro derivative **27**: 15% yield; ^{1}H NMR 4.24 (2 H, CH_2O, t, J = 7 Hz), 2.04 (3 H, Ac, s), 2.40–1.0 (12 H, m); ^{19}F NMR −159.6 (heptet, $J_{FH(exo)}$ = 44 Hz, J_{FH} = 22 Hz); MS, m/e 200 (M^+), 180 [$(M - HF)^+$], 157 [$(M - Ac)^+$], 137 [$(M - Ac - HF)^+$]. Anal. Calcd for $C_{11}H_{17}FO_2$: C, 66.00; H, 8.50. Found: C, 65.87; H, 8.26. The more polar compound was the corresponding 2-fluoro isomer **26**: 30% yield; ^{1}H NMR 4.06 (2 H, CH_2O, dt, J = 6.5 Hz, $^4J_{FH}$ = 1.5 Hz), 2.05 (3 H, Ac, s), 2.40–0.9 (12 H, m); ^{19}F NMR −162.6 (d, quintet, $J_{FH(endo)}$ = 56 Hz, J_{FH} = 27 Hz, $J_{FH(exo)}$ = 9 Hz); MS, m/e 200 (M^+), 180 [$(M - HF)^+$], 157 [$(M - Ac)^+$], 137 [$(M - Ac - HF)^+$]. Anal. Calcd for $C_{11}H_{17}FO_2$: C, 66.00; H, 8.50. Found: C, 66.21; H, 8.36.

Fluorination of tricyclo[5.2.1.0^{2,6}]decane (28) was performed on 1.0 g (7.35 mmol) by using 1.5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with pe followed by HPLC using cyclohexane as eluent. A single compound was thus isolated in 75% yield and identified as 2-fluorotricyclo[5.2.1.0^{2,6}]decane (**29**), a white solid that sublimes at room temperature: ^{1}H NMR 2.4 (1 H, C_6-H, m), 2.2 (1 H, C_1-H, m), 2.10–1.20 (13 H, m); ^{19}F NMR −126.76 (m, $W_{h/2}$ = 75 Hz); ^{13}C NMR 114.1 (C2[α], d, J = 188 Hz, $\Delta\delta$ = +67.60), 54.20 (C6[β], d, J = 18 Hz, $\Delta\delta$ = +7.70), 45.90 (C1[β], d, J = 26 Hz, $\Delta\delta$ = +3.40), 32.70 (C3[β], d, J = 26 Hz, $\Delta\delta$ = +8.77), 40.5 (C10[γ], $\Delta\delta$ = −3.71), 40.47 (C7[γ], $\Delta\delta$ = −2.03), 28.2 (C4[γ], $\Delta\delta$ = −1.50), 25.26 (C9[γ], d, J = 3.1 Hz, $\Delta\delta$ = −2.56), 23.20 (C5[γ], d, J = 8.9 Hz, $\Delta\delta$ = −0.72), 21.49 (C_8[δ], $\Delta\delta$ = −6.33); MS, m/e 154 (M^+). Anal. Calcd for $C_{10}H_{15}F$: C, 77.92; H, 9.74. Found: C, 77.56; H, 9.44.

Fluorination of 2-ethyl-1-methoxybicyclo[2.2.2]octane (30) was performed on 0.5 g (2.97 mmol) by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in pe followed by HPLC using 5% EtOAc in cyclohexane as eluent. A single compound was thus isolated in 25% yield and identified as 2-ethyl-2-fluoro-1-methoxybicyclo[2.2.2]octane (**31**): ^{1}H NMR 3.29 (3 H, OMe, d, J_{FH} = 1 Hz), 2.20–1.0 (13 H, m), 0.99 (CH_3CH_2, t, J = 7 Hz); ^{19}F NMR −146.18 (q, J_{FH} = 32 Hz); ^{13}C NMR 101.45 (C2[α], d, J = 180 Hz, $\Delta\delta$ = +61.94), 76.91 (C1[β], d, J = 33 Hz, $\Delta\delta$ = +2.13), 40.40 (C3[β], d, J = 23 Hz, $\Delta\delta$ = +6.34), 26.45 (C10[β], d, J = 26 Hz, $\Delta\delta$ = +2.73), 50.78 (C9[γ], $\Delta\delta$ = +2.40), 27.11 (C7[γ], d, J = 6.9 Hz, $\Delta\delta$ = +0.40), 26.45 (C6[γ], $\Delta\delta$ = −2.55), 22.77 (C4[γ], d, J = 7.5 Hz, $\Delta\delta$ = −2.09), 6.26 (C11[γ], d, J = 4.4 Hz, $\Delta\delta$ = −5.42), 25.90 (C5[δ], $\Delta\delta$ = −1.01), 25.08 (C8[δ], $\Delta\delta$ = −0.67); MS, m/e 186 (M^+), 166 [$(M - HF)^+$]. Anal. Calcd for $C_{11}H_{19}FO$: C, 70.97; H, 10.21. Found: C, 70.99; H, 10.18.

Fluorination of bicyclo[2.2.2]octane (35) was performed on 1 g (9.09 mmol) by using 2% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with pe followed by HPLC using cyclohexane as eluent. Two compounds were isolated. The less polar one was proved to be 2-fluorobicyclo[3.2.1]octane (**37**): 40% yield; mp 131 °C (from pentane–methanol); ^{1}H NMR 4.77 (1 H, CHF, br dd, J_{FH} = 53 Hz, J = 9 Hz), 2.05–1.2 (12 H, m); ^{19}F NMR −169.68 (m, $W_{h/2}$ = 140 Hz); ^{13}C NMR 91.08 (C2[α], d, J = 175 Hz, $\Delta\delta$ = +58.28), 35.50 (C1[β], d, J = 20 Hz, $\Delta\delta$ = +0.30), 29.25 (C3[β], d, J = 19 Hz, $\Delta\delta$ = +10.15), 26.89 (C8[γ], d, J = 7 Hz, $\Delta\delta$ = −12.8), 25.90 (C4[γ], $\Delta\delta$ = −6.90), 22.03 (C7[γ], d, J = 8 Hz, $\Delta\delta$ = −6.87), 24.29 (C5[δ], $\Delta\delta$ = −10.9), 18.39 (C4[δ], d, J = 5 Hz, $\Delta\delta$ = −10.5); MS, m/e 128 (M^+). Anal. Calcd for $C_8H_{13}F$: C, 75.00; H, 10.16. Found: C, 74.60; H, 9.85. The more polar compound was the expected known 1-fluorobicyclo[2.2.2]octane (**36**), obtained in 50% yield; mp (sealed tube) 174 °C, identical in all respects with the one reported in the literature.[2a]

Acknowledgment. We thank E. I. du Pont de Nemours and Company for providing us with the opportunity to use the MM1 and PRDDO computational programs.

Reaction of Glyoxal with Acetoacetic Esters: Formation of Furo[3,2-*b*]furan Derivatives†

Earl R. Benson, Michael J. Newlands, and Brian Gregory*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3X7

Jean-Pierre Charland and Eric J. Gabe

Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R9

Received September 23, 1987

The reaction of glyoxal with ethyl or methyl esters of acetoacetic acid in aqueous solution at pH 7 yields furo[3,2-*b*]furan derivatives **6a** and **6b**, respectively. The structures were based on ^{1}H and ^{13}C NMR and mass spectra and confirmed by X-ray analysis of **6b**. Dehydration of **6a** under acidic conditions afforded a mixture of furan **2a** and diethyl *cis*-3a,6a-dihydro-2,5-dimethylfuro[3,2-*b*]furan-3,6-dicarboxylate (**7a**). The corresponding methyl esters were obtained by using **6b**. These results require revision of structures reported by earlier workers for some of these products.

The reaction between glyoxal and β-keto esters has been the subject of several studies. From the reaction of glyoxal with ethyl acetoacetate in concentrated aqueous zinc chloride, Polonowsky[1] obtained a crystalline product, mp 207 °C, identified as 2-methyl-3-carboxyfuran-5-acetic acid, and two isomers, one a crystalline product, mp 139 °C, and

† Issued as NRCC contribution no. 28811.

(1) Polonowsky, M. *Justus Liebigs Ann. Chem.* **1888**, *246*, 1.

0022-3263/88/1953-2807$01.50/0