Efficient Utilization of Tetrabutylammonium Bifluoride in Halofluorination Reactions

F. Camps, E. Chamorro, V. Gasol, and A. Guerrero*

Department of Biological Organic Chemistry, CID (CSIC) Jordi Girona Salgado, 18-26, 08034 Barcelona, Spain

Received October 11, 1988

The halofluorination reaction of a variety of alkenes by using tetrabutylammonium bifluoride (TBABF) in the presence of *N*-halosuccinimide is described. This process occurs stereospecifically to afford anti addition products, and with unsymmetrical olefins a marked Markovnikov-type regioselectivity is observed. In some cases, formation of a remarkable amount of the corresponding dihalo derivatives was found, but this undesirable side reaction can be avoided by using *N*-iodosuccinimide (NIS) as halogenating agent. If *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) is utilized, these dihalo compounds can be easily removed from the halofluorinated compounds by simple column chromatography on silica gel. A mechanism for this side reaction is postulated.

Introduction

Halofluorination reactions of unsaturated compounds are important processes because they lead to useful intermediates for the synthesis of a large variety of fluoroorganic compounds via electrophilic and nucleophilic substitution reactions.

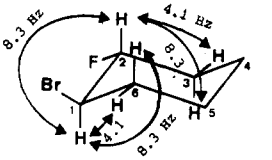
Halofluorination of alkenes can be performed by formal addition of halogen fluorides, either commercially available (ClF) or prepared in situ (BrF and IF). This preparation can be carried out by reaction of positive halogen sources, such as *N*-haloacetamides or *N*-halosuccinimides, and the appropriate fluorination reagents.[1,2] Boron trifluoride promoted reaction of *N*-halo electrophiles with alkenes has been recently reported to give the corresponding halofluorides.[3] Direct reactions of elemental fluorine on bromine and iodine at low temperature have also been described.[4] Likewise, polyhydrogen fluoride solutions either with the combination halogen–silver nitrate[5] or with 1,3-dibromo-5,5-dimethylhydantoin[6] have been successfully utilized to prepare halofluorinated derivatives. Iodofluorination of olefins has been achieved by reaction of alkenes with difluoroiodomethane[7,8] or bis(*s*-collidine)-iodine(I) tetrafluoroborate.[9]

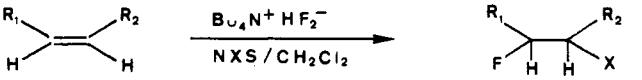
In our search for new applications of tetrabutylammonium bifluoride (TBABF) as new fluorinating agent,[10] we describe herein the effective use of this reagent, in combination with N-halosuccinimides, in halofluorination reactions of various acyclic and alicyclic olefins. This salt is easy to handle, soluble in most organic solvents and the reaction conditions used are mild.

Results and Discussion

Generally, the halofluorination reactions were carried out by using a 3:2.2:1 molar ratio of TBABF:NXS:substrate in methylene chloride at room temperature for 4–41 h. As shown in Table I, the yields of the halofluorinated compounds were dependent on the structure of the substrate and the nature of the positive halogen source.

Chart I





The reaction occurs stereospecifically to yield the anti addition products, as confirmed by the ^{1}H NMR coupling constants found, for example, in 1-bromo-2-fluorocyclohexane ($J_{2,1a} = J_{2,3a} = 8.3$ Hz, $J_{2,3e} = J_{1,6e} = 4.1$ Hz, $J_{1,2a} = J_{1,6a} = 8.3$ Hz) (Chart I). With unsymmetrical olefins the addition proceeds with a marked Markovnikov regioselectivity orientation (entries 1, 7, 8, and 10–12). In some cases the corresponding dihalogenated compound turned out to be an important side product. However, the separation of these compounds from the corresponding halo fluorides is remarkably easy by conventional column chromatography on silica gel.

The reaction is specially advantageous when *N*-iodosuccinimide is used. In this case, the formation of diiodo derivatives was not observed, whereas by using *N*-bromo- or *N*-chlorosuccinimide variable amounts of the corresponding dihalo compounds were found (cf. entries 3–5). Among the olefins tested, trisubstituted olefins such as **9** and **12** afforded better yields of the Markovnikov-oriented products (entries 11 and 14) with practically complete absence of the dibromo derivatives **9c** and **12c**. On the other hand, there was no marked overall difference in the results obtained with mono- or disubstituted olefins.

Reaction with norbornene (**2**) proceeds entirely to the formation of *exo*-3-bromonortricyclane **2d** as the only isolable product according to the ^{1}H NMR spectrum.[11] Compound **2d** has also been isolated in the reactions of **2** with NBS in DMSO,[12] ICl,[13] NBS/HF·Et$_3$N,[14] and NBA/HF,[15] wherein it is accompanied by other com-

(1) Hudlicky, M. *Chemistry of Organic Fluorine Chemistry*, 2nd ed.; Ellis Horwood: Chichester, 1976.
(2) Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 125 and references cited therein.
(3) Heasley, G. E.; Janes, J. M.; Stark, S. R.; Robinson, B. L.; Heasley, V. L.; Shellhamer, D. F. *Tetrahedron Lett.* **1985**, *26*, 1811.
(4) Rozen, S.; Brand, M. *J. Org. Chem.* **1985**, *50*, 3342.
(5) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872.
(6) Chi, D. Y.; Kiesewetter, D. O.; Katzenellenbogen, J. A.; Kilbourn, M. R.; Welch, M. J. *J. Fluorine Chem.* **1986**, *31*, 99.
(7) Zupan, M.; Pollack, A. *J. Org. Chem.* **1976**, *41*, 2179.
(8) Zupan, M. *Synthesis* **1976**, 473.
(9) Evans, R. D.; Schauble, J. H. *Synthesis* **1987**, 551.
(10) Bosch, M. P.; Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *Tetrahedron Lett.* **1987**, *28*, 4733.
(11) *The Aldrich Library of NMR Spectra*; Pouchert, Ch. J., Campbell, J. R., Eds.; Aldrich Chemical Co.: Milwaukee, WI, 1974; Vol. 1.
(12) Dalton, D. R.; Rodenbaugh, R.; Jefford, C. *J. Org. Chem.* **1972**, *37*, 362.
(13) Werstink, N.; Vancas, I.; Warkentin, J.; Clark, F. *Can. J. Chem.* **1972**, *50*, 291.
(14) Alvernhe, G.; Laurent, A.; Haufe, G. *Synthesis* **1987**, 562.
(15) Dean, F. H.; Marshall, D. R.; Warnhoff, E. W.; Pattison, F. L. M. *Can. J. Chem.* **1967**, *45*, 2279.

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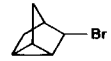
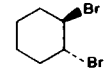
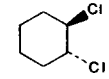
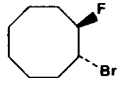
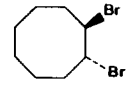
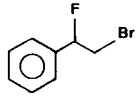
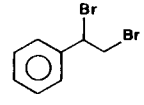
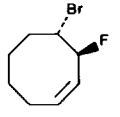
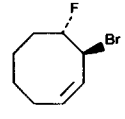
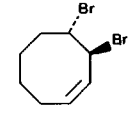
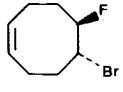
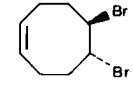
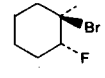
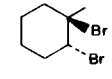
Table I. Halofluorination Reactions of Alkenes with TBABF/NXS Reagent

entry	substrate[a]		NXS, X =	reaction time, h	reaction products (yield, %)[b]					
1	$C_5H_{11}CH{=}CH_2$	**1**	Br	37	$C_5H_{11}CHFCH_2Br$	**1a** (64)	$C_5H_{11}CHBrCH_2F$	**1b** (18)	$C_5H_{11}CHBrCH_2Br$	**1c** (18)
2		**2**	Br	12						**2d** (100)
3		**3**	Br	28		**3a** (65)		**3** (10)		**3c** (25)
4		**3**	Cl	26		**3d** (47)		**3** (15)		**3e** (38)
5		**3**	I	20		**3f** (91)		**3** (9)		
6		**4**	Br	41		**4a** (53)		**4** (18)		**4c** (28)
7		**5**	Br	19		**5a** (56)[c]		–(11)[d]		**5c** (18)[c]
8		**6**	Br	26		**6a** (72)		–[e]		–[e]
9	$CH_2{=}CH(CH_2)_9OH$	**7**	Br	21					$CH_2BrCHBr(CH_2)_9OH$	**7c** (86)[c,f]
10	$CH_2{=}CH(CH_2)_9OAc$	**8**	Br	23	$CH_2BrCHF(CH_2)_9OAc$	**8a** (38)	$CH_2FCHBr(CH_2)_9OAc$	**8b** (10)	$CH_2BrCHBr(CH_2)_9OAc$	**8c** (46)
11	$CH_3C(CH_3){=}CHCH_3$	**9**	Br	4	$CH_3C(CH_3)(F)CH(CH_3)Br$	**9a** (100)				
12		**10**	Br	22		**10a** (40)[g]		**10b** (8)[g,h]		**10c** (47)[g]
13		**11**	Br	23		**11a** (66)[c,g]				**11c** (32)[c,g]
14		**12**	Br	17		**12a** (87) (63)[c]		**12b** (9) (4)[c]		**12c** (4) (2)[c]

[a] Molar ratio of reagents (TBABF:NXS:substrate) was 3:2.2:1 except in entry 2 (2:1.2:1). [b] Based on GLC analysis. [c] Isolated yield. [d] The ^1H NMR spectrum pointed out to a ring-substituted fluorinated compound, whose structure was not pursued further, along with 2-bromo-1-fluoro-2-phenylethane (**5b**), identified by MS. [e] See text. [f] Only a small amount of the expected **7a** was detected by MS and ^{19}F NMR (δ –101.4 ppm). [g] Based on reacted starting material. [h] Tentative assignment.

pounds such as *syn*- and *anti*-7-bromo-2-fluorobicyclo-[2.2.1]heptane. Formation of **2d** can be visualized by the intermediate occurrence of a bromonium ion, or a nonclassical carbonium ion stabilized through carbons C3–C5, followed by deprotonation with fluoride or succinimidyl anion.[9]

Reaction of TBABF with reactive olefins such as styrene proceeded in the desired manner with no tarry byproducts being formed. In addition, contrary to previous reports,[2] there is no need of adding base to increase the fluoride ion concentration since TBABF, as cited above, has been shown to be a good source of "naked" fluoride ion.[10]

In the case of dihydropyran **6** (entry 8), the major compound detected (72% by GLC analysis on a SE-30 fused silica capillary column) was identified as the Markovnikov-oriented stereoisomer **6a**. The compound was too unstable to be isolated, but its structural assignment was mainly based on GC–MS analysis and the ^{1}H NMR spectrum of the crude product, which showed H-1 as a broad doublet of $^3J_{H,F}$ = 51.8 Hz, indicating the predominance of the trans diaxial conformation. This in agreement with the tendency of a polar substituent like fluorine, placed in an α-position to the oxygen atom in a tetrahydropyran ring, to be located in axial position due to the anomeric effect,[16] whereas the trans diequatorial coupling constant $J_{2e,3e}$ is only ca. <1 Hz.[17]

Unexpectedly, the presence of a primary hydroxy group in the olefin, such as in substrate **7**, completely modified the course of the reaction, the corresponding dibromide being the only compound obtained in very good yield (cf. entry 9). However, reaction with the corresponding acetate **8** leads to the formation of the bromofluorinated compounds along with an important amount of the dibromination derivative (cf. entry 10).

In the case of the reaction with a conjugated diene like **10**, only the 1,2-addition products **10a** and **10b** were detected. Although the yield of **10a** was only moderate, the reaction affords a direct entry to 4-bromo-3-fluoro-1-alkenes and, by extension, to 2-fluoro-1,3-dienes, which otherwise might not be easy to prepare (cf. entry 12).

With regard to the formation of the dihalogenated derivatives, we have found only one literature precedent in the bromofluorination of norbornadiene with NBS in the presence of $Et_3N/3HF$, which leads almost quantitatively to a mixture of 3-*exo*-bromo-5-*exo*-fluoro-, 3-*exo*-bromo-5-*endo*-fluoro-, and 3-*exo*,5-*endo*-dibromonortricyclane in a 53:38:5 ratio.[18] In order to explain the formation of these side products through a plausible mechanism, we have run the following series of experiments:

(1) The reaction of 1-bromo-2-fluoro-2-phenylethane (**5a**) with NBS did not yield 1,2-dibromostyrene **5c**, under our standard reaction conditions. Likewise, neither 1,2-dibromoheptane (**1c**) nor 1,2-dibromocyclohexane (**3c**), by reaction of **1** and **3** with TBABF in the presence or absence of NBS, gave any appreciable amount of fluorinated compounds **1a**, **1b**, or **3a**, respectively. These observations would rule out the possibility of formation of these dihaloderivatives from the corresponding halofluorinated compounds.

(2) The reaction of cyclohexene with tetrabutylammonium fluoride (TBAF), thoroughly dried, and NBS in acetonitrile or methylene chloride also afforded the unwanted dibromoderivative **3c** as major compound (50–60%), along with only 10–15% of the desired bromofluoro derivative **3a**. This result is in disagreement with that reported in the bromofluorination of 4-*tert*-butyl-1-methylcyclohexene with NBS and TBAF wherein no formal addition of a bromine molecule was found.[19]

(3) Reaction of cyclohexene with TBABF/NBS in the presence of hydroquinone gave rise to a mixture of **3a** and **3c** in 10% and 46% yields, respectively, in contrast with the results shown in entry 3 (see Table I). This partial inhibition in the formation of **3a** in favor to that of the competing side product **3c** might induce one to consider the concomitant occurrence of a free radical process[20] in this halofluorination reaction, which could compete with the generally accepted ionic mechanism of the electrophilic addition of halogens to olefins.[2] This is not surprising since NBS and NCS can give rise both to free radical chain reactions[21] and to polar mechanism processes.[22]

After a literature search, we have found that Braude and Waight[23] and, more recently, Finkelstein and co-workers[24] reported that complexes from NBS and quaternary ammonium halides could participate as intermediates in the addition of bromine to olefins mediated by NBS. In agreement with this suggestion, we have noticed that whereas the IR spectrum of NBS in $CHCl_3$ presents a strong carbonyl absorption at 1730 cm^{-1}, after admixture of this compound with TBABF in a 3:2 ratio, this band is no longer present and instead a broader and much weaker absorption at 1700 cm^{-1} is observed. On the other hand, the ^{1}H NMR spectrum of NBS in $CDCl_3$ shows a sharp singlet at δ 2.98, whereas after addition of TBABF to this solution this signal moved upfield to δ 2.79. When the alkene is also present in the mixture, this signal is displaced initially to the region of the succinimide absorption at δ 2.75 after 10 min, to finally move to δ 2.58, after 24 h reaction. This progressive displacement may account for the occurrence of a rapid equilibrium between succinimide and succinimidyl anion in agreement with the formation of the above complex.[24] On the other hand, during the workup of the reaction mixture a tarry byproduct, insoluble in hexane and soluble in CH_2Cl_2 or $CHCl_3$, was also obtained. The IR spectrum of this product exhibited significant bands at 3340, 1720, and 1630 cm^{-1}, and the ^{1}H NMR absorptions at δ 0.89 (t, 3 H), 1.45 (m), and 3.3 (t) indicated a tetrabutylammonium moiety. These data along with a CH_2CO absorption at δ 2.6, are consistent with a polymaleimide structure for this material as reported previously.[25]

The above data appear to confirm the mechanism proposed by Finkelstein and co-workers[24] wherein the intermediate formation of a complex between NBS (or NXS) and a tetrabutylammonium salt (TBABF in our case) can account for the formation of an halogenation agent, such as bromine or tetrabutylammonium tribromide. Decomposition of the complex could take place at room temperature in CH_2Cl_2 giving rise via an electron transfer

(16) Cook, M. J.; Howe, T. J.; Woodhouse, A. *Tetrahedron Lett.* **1988**, *29*, 471.

(17) In *trans*-2,3-dibromotetrahydropyran the corresponding coupling constant $J_{2e,3e}$ is lower than 1 Hz (Lemieux, R. V.; Fraser-Reid, B. *Can. J. Chem.* **1965**, *43*, 1460).

(18) Alvernhe, G.; Anker, D.; Laurent, A.; Haufe, G.; Beguin, C. *Tetrahedron* **1988**, *44*, 3551.

(19) Maeda, M.; Abe, M.; Nojima, M. *J. Fluorine Chem.* **1987**, *34*, 337.

(20) Although no direct epr spectrum could be obtained, the use of *N*-nitrosobenzene as spin-trapping agent resulted in a poorly resolved epr signal. This subject will be pursued further with other spin-trapping reagents and the results published elsewhere.

(21) See f.i. Djerassi, C. *Chem. Rev.* **1948**, *43*, 271.

(22) See f.i. (a) Mitchell, R. H.; Lai, Y. H.; Williams, R. V. *J. Org. Chem.* **1979**, *44*, 4733. (b) Caristi, C.; Ferlazzo, A.; Gattuso, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 281.

(23) (a) Braude, E. A.; Waight, E. S. *Nature (London)* **1949**, *164*, 241. (b) *J. Chem. Soc.* **1952**, 1116.

(24) Finkelstein, M.; Hart, S. A.; Moore, M.; Ross, S. O.; Eberson, L. *J. Org. Chem.* **1986**, *51*, 3548 and references cited therein.

(25) Eberson, L.; Barry, J. E.; Finkelstein, M.; Moore, W. M.; Ross, S. D. *Acta Chem. Scand. B* **1985**, *39*, 249.

process to a succinimidyl radical and bromide ion, which would be finally responsible for the formation of the dihalogenated derivatives (Scheme I). In this context, a

Scheme I

$$NBS + HF_2^- \rightleftharpoons NS^- + [BrF] + HF$$

$$NS^- + NBS \rightleftharpoons [NS^- NBS]$$

$$[NS^- NBS] \rightarrow 2NS^\bullet + Br^-$$

$$2NS^\bullet \rightarrow NSH + \text{maleimide}$$

$$\text{maleimide} + NS^\bullet \rightarrow \text{polymer}$$

$$NBS + Br^- \rightleftharpoons NS^- + Br_2$$

recent paper[26] demonstrated the halogen exchange process between *N*-halosuccinimides and quaternary ammonium halides, concluding that the more electronegative halogen atom was associated with the quaternary ammonium ion and the less electronegative halogen atom with the imide nitrogen. In the present case, the high electronegative character of fluorine might preclude this exchange to take place.

Although, as cited above,[2] the halofluorination reaction is expected to proceed through an electrophilic bimolecular mechanism, from our data we cannot conclude whether our reagent (TBABF), in combination with NXS, would give the same product profile as isolated halogen fluoride XF.

In summary, the halofluorination reaction of alkenes carried out with TBABF in the presence of *N*-halosuccinimide is an effective, mild procedure to obtain the corresponding halofluorinated compounds. The process does not require corrosive or toxic reagents and, consequently, it can be carried out in normal glassware apparatus. In addition, the fluoride ion source, TBABF, is easy to prepare and handle, rather stable, and soluble in most organic solvents.[10] The formation of the unwanted dihalo derivatives can be avoided by using NIS instead of NBS or NCS, but in all cases these byproducts can be effectively removed by simple column chromatography on silica gel. The reagent is specially useful with trisubstituted olefins both in cyclic and alicyclic systems.

Experimental Section

Infrared spectra were recorded on a Perkin Elmer Model 457 spectrometer. GLC analyses were performed on a Carlo Erba Model 2350 equipped with a FID detector, using a 30% OV-101 glass column 2 m × $^1/_8$ in. i.d. on Chromosorb W. Mass spectra were run on a HP-5995 mass spectrometer, working at 70 eV in the EI mode, coupled with a gas chromatograph furnished with a SE-30 fused silica capillary column (25 m × 0.2 mm i.d.). ^{1}H NMR and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker WP80SY spectrometer operating at 80 and 75.39 MHz, using tetramethylsilane and trifluoroacetic acid as internal and external standards, respectively.

The alkenes were freed from peroxides by passing through an alumina column (activity I). Anhydrous methylene chloride was prepared by distillation from phosphorus pentoxide. NBS was recrystallized from water. TBABF was prepared by passing an acetonitrile solution of tetrabutylammonium chloride through an Amberlite IRA 410 resin, which has been previously exchanged with a 0.7 M aqueous solution of ammonium bifluoride,[10] or by thermal decomposition of tetrabutylammonium fluoride at 100 °C and 0.1 mm for 4–5 h.[27] The salt was thoroughly dried (4–8 h at 40 °C and 0.1 mm) before use. Halofluorinated compounds were purified by column chromatography on silica gel or alumina (III) except in the case of the reaction with dihydropyran **6**, which resulted in a product too unstable for isolation.

Halofluorination Reaction of Alkenes 1–12 with TBABF/NXS. Typical Procedure: 2-Bromo-1-fluoro-1-methylcyclohexane (12a). In a two-neck round-bottomed flask, previously flamed and under Argon atmosphere was placed 1.7 g (6.1 mmol) of TBABF in 5 mL of anhydrous methylene chloride. A solution of 0.197 g (2.05 mmol) of 1-methylcyclohexene in 1 mL of anhydrous CH_2Cl_2 was added via syringe followed by 800 mg (4.5 mmol) of recrystallized NBS. The reaction mixture was stirred at room temperature for 17 h (GLC analysis). Water was then added, and the organic layer was decanted and extracted with CH_2Cl_2 (3 × 7 mL). The combined organic phases were washed with brine, dried, and concentrated to yield a residue, which was purified by column chromatography on silica gel (80–100 mesh) to afford 257 mg (63%) of **12a**, 14 mg (4%) of **12b**, and 12 mg (2%) of **12c**.

12a: ^{1}H NMR δ 1.25–2.5 (m, 8 H, CH_2), 1.51 (d, 3 H, J_{CH_3-F} = 22.4 Hz, CH_3), 4.20 (dt, 1 H, J = 7.2, 3.9 Hz, CHBr); ^{19}F NMR −60.7 (s); MS m/z (%) 196 (M^+ + 2, 3), 194 (M^+, 3), 134 (4), 132 (4), 115 (25), 95 (100), 73 (39), 67 (10), 55 (12); exact mass m/z 194.0106 (calcd for $C_7H_{12}BrF$ 194.0102).

1-Bromo-2-fluoro-1-methylcyclohexane (12b): ^{1}H NMR δ 1.3–2.6 (m, 8 H, CH_2), 1.83 (d, 3 H, J = 1.6 Hz, CH_3), 4.67 (dm, 1 H, J = 47.1 Hz, CHF); ^{19}F NMR −101.2 (ddd, J = 46.8, 34.4, 12.0 Hz); MS m/z (%) 196 (M^+ + 2, <1), 194 (M^+, <1), 115 (25), 95 (100), 73 (16), 67 (11), 55 (14).

1-Bromo-2-fluoroheptane[28] (1a): ^{1}H NMR δ 0.85 (t, 3 H, J = 7 Hz, CH_3), 1.1–1.9 (m, 8 H, CH_2), 3.45 (dd, 2 H, J = 20.3, 5.3 Hz, CH_2Br), 4.65 (dm, 1 H, J = 46 Hz, CHF); ^{19}F NMR −101.48 (m); MS m/z (%) 155 (34), 153 (39), 97 (81), 81 (32), 73 (24), 57 (23), 55 (100), 43 (61), 41 (96).

2-Bromo-1-fluoroheptane (1b): MS m/z (%) 169 (15), 167 (15), 117 (12), 97 (75), 87 (10), 75 (24), 69 (15), 59 (23), 57 (25), 56 (25), 55 (100). The compound was too unstable for isolation.

3-Bromotricyclo[2.2.1.0^1]heptane[11] (2d): ^{1}H NMR δ 1.15–1.55 (m, 6 H, 2 H_1, H_2, H_5, H_6, H_{7anti}), 2.04 (dm, 1 H, $J_{7syn-7anti}$ = 11.0 Hz, H_{7syn}), 2.10 (m, 1 H, H_4), 3.91 (m, 1 H, H_3); MS m/z (%) 174 (M^+ + 2, 9), 172 (M^+, 7), 94 (9), 93 (100), 91 (65), 77 (40), 66 (12), 65 (15).

***trans*-1-Bromo-2-fluorocyclohexane[14] (3a)**: ^{1}H NMR δ 1.15–2.60 (m, 8 H, CH_2), 4.05 (m, 1 H, $J_{2-3a} = J_{2-1a}$ = 8.2 Hz, J_{2-3e} = 4.2 Hz, CHBr), 4.58 (dm, 1 H, J_{1-F} = 48 Hz, $J_{1-2a} = J_{1-6a}$ = 8.3 Hz, J_{1-6e} = 4.1 Hz, CHF); ^{19}F NMR −91.6 (dm, $^2J_{H-F}$ = 48 Hz); MS m/z (%) 182 (M^+ + 2, 10), 180 (M^+, 9), 101 (36), 81 (100), 79 (14), 59 (23), 55 (16), 41 (25).

***trans*-1-Chloro-2-fluorocyclohexane[14] (3d)**: ^{1}H NMR δ 1.1–2.5 (m, 8 H, CH_2), 3.90 (m, 1 H, CHCl), 4.39 (dm, 1 H, J = 45 Hz, CHF); ^{19}F NMR −96.8 (dm, $^2J_{H-F}$ = 45.1 Hz); MS m/z (%) 138 (M^+ + 2, 20), 136 (M^+, 44), 100 (17), 99 (12), 85 (40), 81 (38), 80 (100), 79 (30), 72 (20), 67 (23), 59 (38), 55 (23), 54 (21), 53 (22), 41 (45).

***trans*-1-Fluoro-2-iodocyclohexane[14,29] (3f)**: ^{1}H NMR δ 1.1–2.6 (m, 8 H, CH_2), 4.05 (m, 1 H, $J_{2-3a} = J_{2-1a}$ = 8.3 Hz, J_{2-3e} = 4.1 Hz, CHI), 4.56 (dm, 1 H, J_{1-F} = 47 Hz, $J_{1-2a} = J_{1-6a}$ = 8.3 Hz, J_{1-6e} = 4.1 Hz, CHF); ^{19}F NMR −83.5 (dm, $^2J_{H-F}$ = 47.0 Hz); MS m/z (%) 228 (M^+, 100), 127 (29), 101 (24), 81 (63), 79 (13), 59 (14), 55 (10), 41 (14).

***trans*-1-Bromo-2-fluorocyclooctane[14] (4a)**: ^{1}H NMR δ 1.25–2.35 (m, 12 H, CH_2), 4.30 (m, 1 H, J = 8.8, 7.2, 3.1 Hz, CHBr), 4.85 (ddt, 1 H, J = 46.8, 8.5, 1.5 Hz, CHF); ^{19}F NMR −78.6 (m); MS m/z (%) 109 (100), 67 (42), 59 (13), 55 (18), 41 (28).

1-Bromo-2-fluoro-2-phenylethane[28] (5a): ^{1}H NMR δ 3.5 (m, 1 H, CH_AH_BBr), 3.78 (d, 1 H, J = 6.0 Hz, CH_AH_BBr), 5.6 (ddd, 1 H, J = 48, 6, 5 Hz, CHF), 3.5 (s, 5 H, C_6H_5); ^{19}F NMR −97.9 (ddd, J = 48, 23.9, 19 Hz); MS m/z (%) 204 (M^+ + 2, 13), 202 (M^+, 15), 109 (100).

2-Bromo-1-fluoro-2-phenylethane[30] (5b). Assignment by mass spectrometry only: MS m/z (%) 184 (M^+ + 2 − HF, 28),

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182 (M^+ - HF, 31), 103 (100), 102 (20), 77 (23).

10,11-Dibromoundecan-1-ol[31] **(7c).** This compound was further confirmed by comparison with an authentic sample prepared by bromination of 10-undecen-1-ol: ^{1}H NMR δ 2.2 (m, 16 H, CH_2), 3.65 (t, 2 H, J = 2.6 Hz, CH_2OH), 3.4-3.7 (m, 1 H, J = 10.2, 5.2 Hz, CH_ABr), 3.84 (dd, 1 H, J = 10.2, 4.4 Hz, CH_BBr), 4.15 (m, 1 H, $CHBrCH_2Br$); MS m/z (%) 244 (14), 242 (33), 240 (19), 229 (14), 205 (21), 203 (26), 177 (40), 175 (40), 163 (23), 161 (25), 151 (96), 149 (27), 147 (20), 123 (63), 109 (70), 95 (100), 83 (56), 81 (87), 69 (68), 67 (55), 55 (97), 41 (85).

11-Bromo-10-fluoroundecan-1-yl acetate (8a): ^{1}H NMR δ 1.1-2.0 (m, 16 H, CH_2), 2.03 (s, 3 H, CH_3CO), 3.45 (dd, 2 H, J = 21, 5.2 Hz, CH_2Br), 4.04 (t, 2 H, J = 6.3 Hz, CH_2O), 4.6 (dm, 1 H, J = 46 Hz, CHF); ^{19}F NMR -101.5 (m); MS m/z (%) 252 (3), 250 (3), 182 (6), 180 (5), 168 (16), 166 (16), 151 (17), 109 (25), 95 (33), 81 (22), 69 (17), 67 (15), 61 (16), 55 (29), 43 (100), 41 (28). Anal. Calcd for $C_{13}H_{24}O_2BrF$: C, 50.16; H, 7.71; Br, 25.72. Found: C, 50.21; H, 7.92; Br, 25.25.

10-Bromo-11-fluoroundecan-1-yl acetate (8b). Assignment by MS only: MS m/z (%) 250 (4), 224 (5), 222 (6), 182 (21), 180 (24), 167 (10), 151 (10), 109 (17), 95 (17), 81 (15), 69 (14), 68 (11), 67 (14), 61 (22), 55 (29), 43 (100), 41 (31).

3-Bromo-2-fluoro-2-methylbutane[32] **(9a):** ^{1}H NMR δ 1.52 (d, 3 H, J_{CH_3F} = 21.6 Hz, CH_3F), 1.48 (d, 3 H, J_{CH_3F} = 21.6 Hz, CH_3F), 1.70 (d, 3 H, J = 6.9 Hz, CH_3CH), 4.13 (dq, 1 H, J = 9.4, 6.9 Hz, CHBr); ^{19}F NMR -62.0 (m); MS m/z (%) 151 (M^+ + 2 - 19, 89), 149 (M^+ - 19, 100), 69 (34), 41 (37).

3-Fluoro-4-bromo-1-cyclooctene (10a): ^{1}H NMR δ 1.25-1.9 (m, 4 H, 2 CH_2), 1.9-2.4 (m, 4 H, CH_2CBr and CH_2C=C), 4.2 (m, 1 H, CHBr), 5.1-6.1 (m, 3 H, CHF and CH=CH); ^{19}F NMR -96.2 (d, J = 48.6 Hz); MS m/z (%) 208 (M^+ + 2, 25), 206 (M^+, 28), 180 (40), 178 (48), 127 (83), 107 (100), 97 (21), 91 (21), 85 (63), 79 (87), 77 (20), 72 (35), 67 (31), 65 (22), 59 (34), 41 (33); exact mass m/z 206.0103 (calcd for $C_8H_{12}BrF$ 206.0106).

5-Bromo-6-fluoro-1-cyclooctene[14] **(11a):** ^{1}H NMR δ 1.8-2.9 (m, 8 H, CH_2), 4.40 (m, 1 H, CHBr), 4.8 (dm, 1 H, J = 47 Hz, CHF), 5.53 (m, 2 H, CH=CH); ^{19}F NMR -86.3 (m); MS m/z (%) 208 (M^+ + 2, 35), 206 (M^+, 36), 180 (13), 178 (13), 127 (17), 107 (100), 91 (22), 85 (36), 79 (92), 67 (32), 59 (19), 53 (21), 41 (26).

Reaction of TBABF/NBS with Dihydropyran 6. The reaction was carried out as described above although the crude reaction mixture could not be purified by column chromatography due to the instability of the resulting compounds. GLC analysis on a SE-30 25 m × 0.25 mm i.d. fused silica capillary column showed a major compound with a 72% estimated purity. The compound was identified as the Markovnikov-oriented stereoisomer ***trans*-3-bromo-2-fluorotetrahydropyran (6a)** in base to the ^{1}H and ^{19}F NMR spectra of the crude product.

6a: ^{1}H NMR δ 1.2-2.7 (m, 4 H, CH_2CH_2CBr), 3.5-4.3 (m, 3 H, CHBr and CH_2O), 5.56 (b d, 1 H, J = 51.8 Hz, CHF); ^{19}F NMR -46.3 (dm, J = 51.9 Hz); MS m/z (%) 184 (M^+ + 2, 30), 182 (M^+, 24), 164 (4), 162 (4), 136 (83), 134 (100), 108 (50), 106 (55), 55 (81), 53 (17).

Acknowledgment. We acknowledge CAICYT (PR 84-0087), CICYT (Pr 87-0290), and CSIC (Pr 263-85) for financial support, CONICET for a fellowship to E.Ch. and MEC for a FPI predoctoral fellowship to V.G.

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Studies on the Synthesis of 1-Azaspiro[5.5]undecanes Related to Histrionicotoxin

John J. Venit,[1] Michael DiPierro, and Philip Magnus*

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Received May 2, 1989

3-Methoxybenzaldehyde was converted into 4-(3-methoxyphenyl)butylamine (**4**), and the derived hydrochloride was reduced with Li/NH_3/EtOH to give the spirocyclic keto amine **6**. The reduction of **6** and urethane derivatives **13** and **14** to give the corresponding cis and trans alcohols **9**/**10**, **15**/**16**, and **17**/**18** was studied. The keto amine **6** upon attempted ketalization underwent rearrangement to give the α,β-unsaturated imine **11**. Treatment of **6** with *N*-chlorosuccinimide, followed by DBU, gave the aziridine **21**. The amide **25** was converted directly into 1-azaspiro[5.5]undecane-2,8-dione (**24**) by Birch reduction and acid hydrolysis. The dione **24** underwent stereospecific reduction with LS-Selectride to give the cis alcohol **30**.

Histrionicotoxin (**1**) has generated an enormous amount of synthetic interest during the last decade or so because of its important inhibitory action on electrogenic membranes and unique molecular structure.[2] Most of the synthetic work has been directed toward perhydrohistrionicotoxin (**3**),[3] and only recently has the first and only total synthesis of histrionicotoxin (**1**) itself been reported by Kishi.[4] The large body of literature associated with this area has been reviewed in detail.[5]

(1) Taken in part from the Ph.D. Thesis of J. J. Venit, Ohio State University, Department of Chemistry, 140 West 18th Avenue, Columbus, Oh 43210.
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