eluted with methanol. Evaporation of the solvent afforded a white solid (1, X = $^+N(CH_3)_3Cl^-$; 0.48 g, 81%).

1-Fluoro-4-(*p*-methoxyphenyl)bicyclo[2.2.2]octane (1, X = OCH_3). (*p*-Methoxyphenyl)acetone was converted to 1-methoxy-4-(*p*-methoxyphenyl)bicyclo[2.2.2]octan-3-one (a sublimed sample had a melting point of 89.5–91.5 °C) according to procedures previously outlined[6,33] for the synthesis of 1-methoxy-4-phenylbicyclo[2.2.2]octan-3-one from phenylacetone. By use of the general procedure of Aquila,[41] a solution of the ketone (52.0 g, 0.2 mol) and hydrazine hydrate (36.0 g, 0.72 mol) in triethylene glycol (160 mL) was heated under an atmosphere of nitrogen for 2 h at 100 °C. The temperature was then gradually raised to 165 °C during a 15-min period, and then the solution was allowed to cool to 50 °C. Meanwhile, a separate solution of potassium hydroxide (35.8 g, 0.64 mol) in triethylene glycol (100 mL) was also heated to 165 °C and allowed to cool to 50 °C. The two solutions were mixed and gradually heated to 185 °C with stirring under a nitrogen atmosphere, while the distillate was collected. After 4 h at this temperature, the mixture was cooled and poured on to a slurry of ice and water. After combination with the distillate, the solution was neutralized with concentrated hydrochloric acid and extracted with ether (3 × 250 mL). A standard workup followed by sublimation afforded 1-methoxy-4-(*p*-methoxyphenyl)bicyclo[2.2.2]octane as a colorless solid: 43.3 g (88%); mp 63–68 °C. A sample was recrystallized from aqueous methanol to afford colorless leaflets, mp 71–73 °C. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.23; H, 8.95.

A portion of the crude compound was converted, via the acetate (mp 107–109 °C), to 1-hydroxy-4-(*p*-methoxyphenyl)bicyclo-[2.2.2]octane (mp 152–154 °C) by established procedures previously outlined.[6,33] Recrystallization from a hexane/ethanol mixture afforded colorless needles, mp 158–158.5 °C. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.81; H, 8.88.

A mixture of 1-hydroxy-4-(*p*-methoxyphenyl)bicyclo[2.2.2]-octane (1.16 g, 0.005 mol) and anhydrous hydrogen fluoride/pyridine reagent[4,42] (10 mL) was stirred for 48 h at room temperature. The resulting white slurry was poured onto ice and the solid collected by filtration. A VPC analysis of the crude dried product indicated the presence of a significant amount of the starting alcohol (10–15%). The crude product was chromatographed on alumina with pentane as the eluent. A pale yellow solid was obtained which afforded the fluoro derivative (1, X = OCH_3) as colorless plates (0.56 g, 48%) after sublimation and recrystallization from aqueous ethanol and then hexane: mp 86–87 °C; mass spectrum, *m/e* 234 (M^+). Anal. Calcd for $C_{15}H_{19}FO$: C, 76.89; H, 8.17. Found: C, 77.19; H, 8.27.

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(42) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 786.

General Information. Mass spectra were obtained on an AEI MS30 spectrometer using an ionizing energy of 70 eV. Vapor-phase chromatographic analyses were performed on a Varian 1740 gas chromatograph with a 10-ft column of 5% SE-30 on 100/120 Chromosorb W. All melting points are uncorrected.

NMR Spectra. The broad-band proton-decoupled ^{13}C NMR spectra were recorded in the pulse Fourier transform mode on a JEOL FX-90Q spectrometer operating at 22.53 MHz. The probe temperature was 295 ± 2 K. The data listed in Tables VI and IX were obtained from spectra recorded on CF_3CO_2H and $DCCl_3$ solutions (0.3–0.4 M) in 5-mm tubes with Me_4Si as an internal reference (spectral width 4000 Hz, 16K/8K data points, minimum digital resolution of 0.02 ppm). Those listed in Table III were measured on $DCCl_3$ solutions with the central peak of $DCCl_3$ as an internal reference (spectral width 1000 Hz, 16K/8K data points, minimum digital resolution of 0.12 Hz).

The ^{19}F NMR spectral data listed in Tables I, V, and VII were obtained under proton-decoupled conditions in the pulse Fourier transform mode with a JEOL FX-90Q spectrometer operating at 84.26 MHz. A spectral width of 2000 Hz was used, and the data were collected into 8K/4K data points, giving a resolution of better than 0.01 ppm. Each sample consisted of a mixture of the unsubstituted (X = H, 1–2 mg) and substituted (1–2 mg) compounds dissolved in 0.5 mL of the appropriate solvent.

^1H NMR spectra were measured with a Varian A60 spectrometer.

Registry No. 1 (X = COOH), 81688-93-9; 1 (X = Br), 60526-64-9; 1 (X = $COOCH_3$), 81688-94-0; 1 (X = CH_2OH), 81688-95-1; 1 (X = CH_3), 81688-96-2; 1 (X = CH_2Br), 81688-97-3; 1 (X = CH_2CN), 81688-98-4; 1 (X = $C(CN)_3$), 81688-99-5; 1 (X = NH_2), 60526-67-2; 1 (X = $N(CH_3)_2$), 81689-00-1; 1 (X = $^+N(CH_3)_3$) I^-, 81689-01-2; 1 (X = $^+N(CH_3)_3$) Cl^-, 81689-02-3; 1 (X = OCH_3), 81689-03-4; 1 (X = NO_2), 60526-66-1; 1 (X = CN), 60526-65-0; 1 (X = F), 60526-63-8; 1 (X = $^+NH_3$), 81689-04-5; 1 (X = $^+NH(CH_3)_2$), 81689-05-6; 1 (X = H), 22947-58-6; **2** (X = H), 68756-28-5; **2** (X = C_6H_5), 68756-32-1; **2** (X = *p*-$NO_2C_6H_4$), 68756-36-5; **2** (X = F), 60526-63-8; **2** (X = Cl), 61541-33-1; **2** (X = Br), 61541-34-2; **2** (X = I), 61541-35-3; **3** (X = NO_2), 72046-22-1; **3** (X = CN), 72046-23-2; **3** (X = $C(CN)_3$), 79963-25-0; **3** (X = $COOCH_3$), 72046-25-4; **3** (X = $COCH_3$), 72046-24-3; **3** (X = F), 72242-21-8; **3** (X = Br), 72046-26-5; **3** (X = NH_2), 72046-29-8; **3** (X = $NHCOCH_3$), 72046-28-7; **3** (X = CH_3), 72046-27-6; **3** (X = $^+NH_3$) Cl^-, 81689-06-7; **3** (X = H), 74308-36-4; **4** (X = NO_2), 72046-30-1; **4** (X = CN), 72046-31-2; **4** (X = $C(CN)_3$), 79963-24-9; **4** (X = $COOCH_3$), 72046-33-4; **4** (X = $COCH_3$), 72046-32-3; **4** (X = F), 72046-34-5; **4** (X = Br), 72046-35-6; **4** (X = NH_2), 72046-38-9; **4** (X = $NHCOCH_3$), 72046-37-8; **4** (X = CH_3), 72046-36-7; **4** (X = $+NH_3$) Cl^-, 81689-07-8; (*p*-methoxyphenyl)acetone, 122-84-9; 1-methoxy-4-(*p*-methoxyphenyl)bicyclo[2.2.2]octan-3-one, 81689-08-9; 1-methoxy-4-(*p*-methoxyphenyl)bicyclo[2.2.2]octane, 81689-09-0; 1-acetyloxy-4-(*p*-methoxyphenyl)bicyclo[2.2.2]octane, 81689-10-3; 1-hydroxy-4-(*p*-methoxyphenyl)bicyclo[2.2.2]octane, 81689-11-4.

Synthesis of 4-Substituted Bicyclo[2.2.2]oct-1-yl Fluorides

William Adcock* and Anil N. Abeywickrema

School of Physical Sciences, The Flinders University of South Australia, Bedford Park, Australia 5042

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The main details of the synthesis of a series of 4-substituted (X) bicyclo[2.2.2]oct-1-yl fluorides (1), which were required for substituent effect studies, are presented. The synthesis of most of these compounds [1, X = NO_2, CN, $CONH_2$, $COCH_3$, CHO, OCH_3, $OCOCH_3$, OH, F, Cl, Br, I, NH_2, $N(CH_3)_2$, $NHCOCH_3$, C_2H_5, *i*-C_3H_7, and $Sn(CH_3)_3$] has been accomplished from 4-fluorobicyclo[2.2.2]octane-1-carboxylic acid (1, X = COOH) in a straightforward fashion using fairly standard functionalization procedures. The key new precursor compound (1, X = COOH) was prepared from 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid (7) which, in turn, was constructed from 4-acetyl-4-(ethoxycarbonyl)pimelic acid (2) in good yield. 1-*tert*-Butyl-4-fluorobicyclo[2.2.2]octane (1, X = $C(CH_3)_3$) was obtained from 7 via 1-*tert*-butyl-4-methoxybicyclo[2.2.2]octane. 1-Fluorobicyclo[2.2.2]octane (1, X = H), 1-fluoro-4-methylbicyclo[2.2.2]octane (1, X = CH_3), and 1-fluoro-4-phenylbicyclo[2.2.2]octane (1, X = C_6H_5) were prepared by literature procedures.

In this paper we describe the syntheses and physical properties of a large number of 4-substituted bicyclo-[2.2.2]oct-1-yl fluorides (1), most of which were previously unknown, which were required for the reasons indicated

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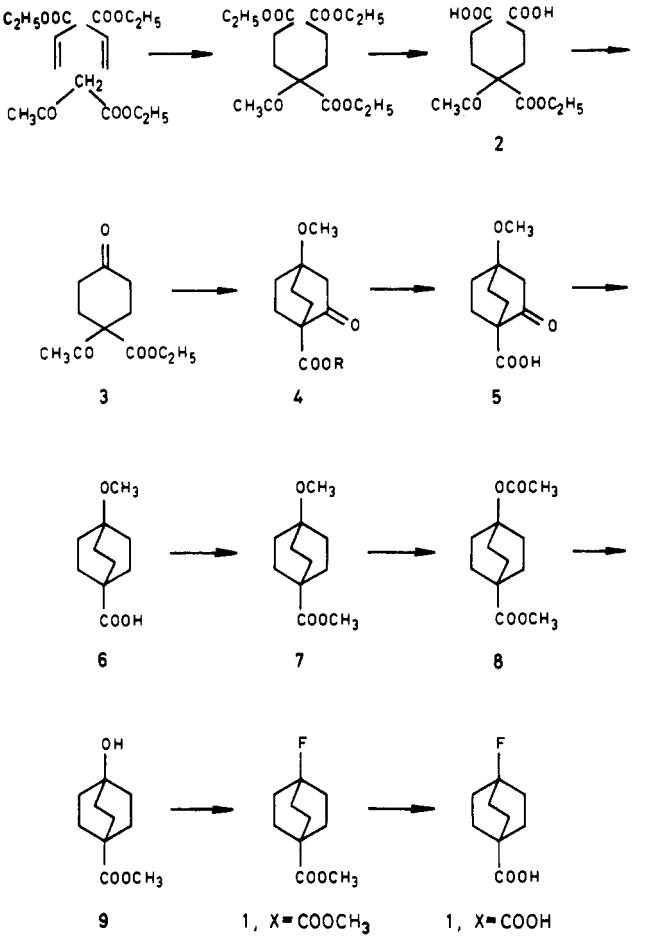
in the following paper[1] and in a recent paper.[2] Except for four of them [1; X = H, CH_3, $C(CH_3)_3$, and C_6H_5], all of these compounds were derived by conventional routes via a common precursor, namely, 4-fluorobicyclo[2.2.2]-octane-1-carboxylic acid (1, X = COOH). The synthetic route adopted for this previously unknown carboxylic acid is as depicted in Scheme I.

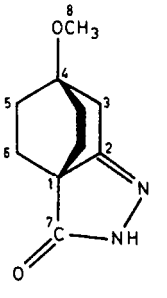
The large-scale synthesis of the dicarboxylic acid **2** proceeded smoothly in high yield by following the procedures recently outlined by Grob and Rich.[3] By the use of the method of these workers,[3] **2** could be converted to the cyclohexanone derivative **3** by refluxing with acetic anhydride in the presence of potassium acetate, removing the excess solvent, and pyrolyzing the residue in a hot evacuated flask. However, although this procedure proved quite adequate for the cyclization of small amounts of **2** (<10 g), it was found to be unsatisfactory for large-scale pyrolyses, which invariably proceeded in greatly diminished yields. The presence of large amounts of reaction mixture in the hot (250–260 °C) flask over extended periods of time led to the formation of high-boiling byproducts, probably polymeric in origin. It was also found that the decrease in the surface area to volume ratio accompanying such large-scale operations compounded the problem by further retarding the rate of pyrolysis. These difficulties were finally overcome by employing a modification similar to that described by Adcock and Khor[4] for the efficient cyclization of 4-acetyl-4-phenylheptane-1,7-dioic acid to 4-acetyl-4-phenylcyclohexanone. In the present work, the reaction mixture was added to a hot evacuated flask at a rate that was approximately equal to the rate of distillation of the resulting pyrolysate. This procedure ensured that the contact time in the hot vessel was minimized and, hence, prevented the buildup of unpyrolyzed material. Good yields of **3** were consistently obtained from reactions 20–30 times larger in scale than those reported by Grob and Rich.[3]

The substituted cyclohexanone **3** was cyclized to a mixture of bicyclo[2.2.2]octanone derivatives (**4**, R = CH_3 and C_2H_5) in excellent yield (>90%) by following an acid-catalyzed ($HCl/(CH_3O)_3CH/CH_3OH$) procedure outlined by Morita and Kobayashi.[5] It should be noted that this procedure to the desired bicyclic skeletal framework is a distinct improvement on the base-catalyzed conditions employed by Grob and Rich.[3] The latter conditions give ethyl 4-hydroxy-2-oxobicyclo[2.2.2]octane-1-carboxylate in only moderate yields (ca. 50%) along with substantial amounts (ca. 25%) of the base-catalyzed cleavage product (ethyl 4-oxocyclohexane-1-carboxylate) of **3**. The esters **4** (R = CH_3 and C_2H_5) were hydrolyzed to the stable[6] β-keto acid **5** by treatment with aqueous

Scheme I



ethanolic potassium hydroxide. The Huang-Minlon[7] modification of the Wolff–Kishner reduction of **5** gave the acid **6** in good yield (80%). Vigorous stirring and prolonged heating (10 h) were essential in order to avoid contamination of **6** with the pyrazolone derivative **10**.



10

However, it was found that if the isolated crude acid **6** is heavily contaminated with **10** (readily identified by ^{13}C NMR),[8] further reflux (6–10 h) of the crude acid under the reaction conditions without hydrazine hydrate readily converts **10** to **6**. It should be noted that since 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid (**6**) possesses appropriate functionality for the synthesis of any number of *unsymmetrically* substituted 1,4-disubstituted bicyclo[2.2.2]octanes by standard procedures, its convenient synthesis outlined herein should assist in making the latter model systems[9] readily available without recourse to te-

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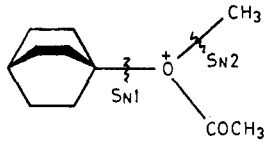
(7) Huang-Minlon J. *Am. Chem. Soc.* **1946**, *68*, 2487.
(8) ^{13}C NMR of **10** ($CDCl_3$, relative to Me_4Si): δ 35.25 (C1), 167.91 (C2), 45.98 (C3), 75.57 (C4), 28.48 (C5), 24.84 (C6), 179.68 (7), 49.94 (C8).

dious syntheses of heavily chlorinated toxic precursors and the concomitant need for expensive high-pressure equipment.[10] In general, other synthetic procedures[11-13] offer only limited access to these important stereochemically well-defined model systems.

Since some bicyclo[2.2.2]oct-1-yl fluorides (1; X = H, CH_3, C_6H_5)[14,15] have been successfully synthesized by treating the corresponding methoxy derivatives with acetyl fluoride in the presence of a catalytic amount of BF_3·H_3PO_4,[15] we initially attempted to obtain the fluorine compounds 1 (X = $COOCH_3$ and COOH) directly from 7 and 6, respectively, in an analogous manner. However, after much experimentation, this approach was abandoned because of low yields due to incomplete reaction and the formation of the corresponding acetate as a byproduct. If one accepts the idea that the fluoride and acetate derivatives are formed in this reaction by competing S_N1 and S_N2 reactions via the oxonium ion 11,[16] these findings



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indicate that the electron-withdrawing polar field effect of the substituents (COOH and $COOCH_3$), which may be enhanced due to complexation with the Lewis acid catalyst, markedly suppresses the desired S_N1 reaction pathway by destabilizing the incipient carbonium ion.

In order to explore alternative synthetic routes to the desired fluorine compound (1, X = COOH), we treated the methoxy derivative 7 with acetic anhydride and a catalytic amount of BF_3·$O(C_2H_5)_2$[16] to obtain the acetoxy compound 8 in excellent yield. Treatment of 8 with sodium methoxide in refluxing methanol afforded the hydroxy ester 9 almost quantitatively. Although only traces of the bridgehead fluoride (1, X = $COOCH_3$) were obtained on treating 9 with anhydrous HF/pyridine[14,17] probably for the same reason outlined above for the failure of acetyl fluoride as the fluorinating agent, a good yield (92%) of 1 (X = $COOCH_3$) was finally obtained by treating the alcohol 9 with excess sulfur tetrafluoride[18] at ambient temperature. The ester (1, X = $COOCH_3$) was hydrolyzed to the acid (1, X = COOH) in virtually quantitative yields by utilizing aqueous ethanolic potassium hydroxide. The successful conversion of 9 to 1 (X = $COOCH_3$), together with the synthesis of 1 (X = F; see Experimental Section and 1-fluoro-4-methyl-1,4-ethano-1,2,3,4-tetrahydronaphthalene[19] from the corresponding alcohols in an analogous manner, exemplifies that for polycyclic hydrocarbons in which poor incipient carbonium ion stability is encountered at the bridgehead, either due to ring strain or the presence of strong electron-withdrawing dipolar substituents, SF_4 is an excellent reagent for efficiently introducing fluorine directly via the corresponding alcohol. Interestingly, in the only report in the literature concerning the use of SF_4 for the synthesis of bridgehead fluorides, it was deemed necessary to employ relatively harsh conditions (125 °C, 4 h) for the preparation of 1,3-difluoro-5,7-dimethyladamantane from the corresponding alcohol.[20] Our experiences suggest otherwise.

An attempt to prepare the *tert*-butyl derivative (1, X = $C(CH_3)_3$) by treatment of the corresponding α-chloroisopropyl compound (1, X = $C(CH_3)_2Cl$; see Experimental Section) with trimethylaluminium at −80 °C[21,22] failed due to the competing replacement of the bridgehead fluorine by methyl.[23] This failure necessitated the synthesis of 1-*tert*-butyl-4-methoxybicyclo[2.2.2]octane from 6 (see Experimental Section). Treatment of this methoxy derivative with CH_3COF/BF_3·H_3PO_4[15] gave the fluoride (1, X = $C(CH_3)_3$) as the major product (ca. 95%) accompanied by small amounts (ca. 5%) of the corresponding acetoxy derivative. It was found that constant monitoring of the reaction by GLC is essential since the fluoride converts to the acetate under the reaction conditions. Interestingly, no such problem was encountered in the synthesis of the known compounds[15] 1, (X = H and CH_3) from the corresponding methoxy precursors.

Experimental Section

General Methods. Melting and boiling points are uncorrected. The former for the fluorides 1 were determined by using sealed capillary tubes. Small liquid samples (up to 5 mL) were usually purified by distillation in a Kugelrohr apparatus (Büchi GKR-50). Hence, the boiling points quoted for these cases pertain to the glass-oven temperatures of the latter equipment. Vapor-phase chromatographic analyses were performed on a Varian 1740 gas chromatograph by using a 10-ft column of 5% SE-30 on 100/120 Chromosorb W. Elemental analyses (C, ±0.3; H, ±0.2) were obtained for all new compounds except 1 (X = $C(CH_3)_3$). All assigned structures were in accord with either their ^1H or ^{13}C NMR spectral data. The latter for all the fluorides 1 are assembled in Table I.

Spectra. Infrared spectra were recorded on a Perkin-Elmer 237 spectrometer while mass spectra were obtained on an AEI MS 30 spectrometer using an ionizing energy of 70 eV. The broad-band proton-decoupled ^{13}C NMR spectral data listed in Table I were recorded in the pulse Fourier transform mode on a JEOL FX-90Q spectrometer operating at 22.53 MHz. The probe temperature was 295 ± 2 K. The spectra were obtained on $CDCl_3$ solutions (ca. 0.1–0.2 M) in 10-mm tubes with Me_4Si as an internal reference (spectral width 2500 Hz, 16K/8K data points, minimum

(9) (a) 4-Substituted bicyclo[2.2.2]octane-1-carboxylic acids have played an important role in physical organic studies as "saturated analogues" of the correspondingly substituted benzene ring systems.[9b,c] (b) Stock, L. M. *J. Chem. Educ.* **1972**, *49*, 400 and references cited therein. (c) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119 and references cited therein.

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(22) Adcock, W.; Khor, T. C. *J. Org. Chem.* **1978**, *43*, 1272.

(23) (a) In general, alkyl fluorides are fairly unreactive substrates with respect to S_N1-type reactions.[23b] However, in the presence of strong Lewis acids such as trivalent aluminum derivatives these cationic-mediated reactions are dramatically facilitated by the stabilization of the transition state and/or the products by formation of the exceptionally strong aluminum–fluorine bond.[23c] Interestingly, we have found[23d] that the order of reactivity of a series of 1-halogen-substituted 4-phenylbicyclo[2.2.2]-octanes with respect to trimethylaluminum is F > Cl > Br > I. It is noteworthy that this order is diametrically opposed to the usual order found for carbonium ion mediated reactions of aliphatic halides.[23b] (b) March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 2nd ed.; McGraw-Hill Kogakusha, Ltd.: Tokyo, 1977. (c) Parker, R. E. *Adv. Fluorine Chem.* **1963**, *3*, 63. (d) Adcock, W.; Khor, T. C., unpublished work.

Table I. ^{13}C Chemical Shifts[a,b] of 4-Substituted Bicyclo[2.2.2]oct-1-yl Fluorides (1)

X	chemical shift, ppm				
	C1	C2	C3	C4	others[c]
H	94.60 (182.5)	31.14 (18.0)	27.31 (9.5)	24.02 (3.4)	
NO_2	91.96 (187.7)	30.72 (21.4)	31.04 (10.7)	82.22 (4.3)	
CN	91.89 (186.5)	30.00 (20.8)	31.06 (10.4)	27.18 (3.7)	
COOH	93.88 (184.6)	30.38 (19.5)	29.50 (10.4)	38.11 (3.7)	
$CONH_2$	93.89 (184.3)	30.57 (19.5)	30.07 (10.4)	38.23 (3.7)	
$COOCH_3$	93.98 (184.0)	30.51 (19.5)	29.69 (10.1)	38.25 (3.7)	51.85 (CH_3)
$COCH_3$	94.06 (184.0)	30.50 (19.5)	29.02 (10.4)	44.12 (3.4)	25.30 (CH_3)
CHO	93.93 (184.3)	30.09 (19.8)	26.86 (10.4)	42.67 (4.0)	
OCH_3	92.39 (185.9)	31.29 (20.5)	29.87 (11.3)	71.66 (4.0)	49.69 (CH_3)
$OCOCH_3$	91.95 (185.8)	31.33 (20.4)	30.30 (10.7)	77.84 (4.3)	22.31 (CH_3)
OH	92.62 (185.5)	31.58 (20.5)	34.42 (11.3)	67.89 (4.0)	
F[d]	91.60 (188.9, 2.1)	31.46 (16.2)	31.46 (16.2)	91.60 (2.1, 188.9)	
Cl	91.50 (186.2)	32.67 (20.4)	37.03 (10.4)	64.13 (4.3)	
Br	90.76 (186.5)	33.68 (20.1)	38.55 (10.1)	59.39 (4.3)	
I	89.60 (185.9)	34.83 (19.8)	41.88 (9.8)	39.81 (4.3)	
NH_2	93.50 (184.0)	31.52 (19.5)	35.80 (11.0)	46.54 (4.0)	
$N(CH_3)_2$	93.03 (184.6)	31.11 (19.5)	27.50 (10.7)	53.28 (4.0)	38.57 (CH_3)
$NHCOCH_3$	92.76 (185.2)	31.00 (20.1)	31.23 (9.8)	49.95 (3.7)	24.41 (CH_3)
CH_3	94.88 (182.4)	31.44 (18.7)	34.42 (10.3)	27.74 (3.3)	26.91 (CH_3) (5.1)[h]
C_2H_5	94.87 (182.5)	31.28 (18.6)	31.63 (10.4)	30.36 (3.4)	32.61 (CH_2), 8.32 (CH_3) (4.9)[h]
i-C_3H_7	94.80 (182.5)	31.20 (18.6)	29.09 (10.1)	32.74 (3.1)	34.77 (CH), 17.46 (CH_3) (4.0)[h]
t-C_4H_9	94.72 (183.1)	31.19 (18.6)	26.91 (9.8)	35.04 (3.4)	33.93 (C), 25.33 (CH_3) (3.4)[h]
C_6H_5[e]	94.77 (183.1)	31.50 (19.2)	33.55 (10.4)	34.27 (3.7)	
$Sn(CH_3)_3$[f,g]	94.36 (181.3) [9.8]	32.42 (16.5) [54.7, 56.1]	31.73 (7.9) [no]	21.48 (1.5) [no]	−12.33 (CH_3) [294.43, 308.11]

[a] Chemical shifts for $CDCl_3$ solutions relative to Me_4Si. Accurate to ±0.02 ppm. Positive shifts indicate decreased shielding. [b] ^{13}C–^{19}F coupling constants (in hertz) are given in parentheses. [c] Because of measuring parameters (see Experimental Section), carbon resonance signals further downfield than ca. 110 ppm from Me_4Si were not observed. [d] The ^{13}C spectrum of C2 (or C3) is a deceptively simple 1:2:1 triplet (see ref 42 for examples). The average of the two coupling constants ($^2J_{CF}$ and $^3J_{CF}$) is given. [e] See ref 4 for the complete spectrum. [f] ^{13}C–$^{117,119}Sn$ coupling constants (in hertz) are given in brackets. [g] no = not observed. [h] $^5J_{CF}$ (in hertz).

digital resolution of 0.31 Hz). Assignments for these compounds followed unambiguously from the characteristic ^{13}C–^{19}F coupling constants in the bicyclo[2.2.2]octane skeletal framework.[4,24] Standard assignment procedures such as chemical shift, intensity, and substituent-effect considerations played a very minor role. It should be noted that some of the very downfield carbon resonances of some functional groups were not observed under the measuring conditions.

^1H NMR spectra were measured with a Varian A60 spectrometer.

Ethyl 1-Acetyl-4-oxocyclohexane-1-carboxylate (3). A solution of 4-acetyl-4-(ethoxycarbonyl)pimelic acid[3] (**2**; 100 g, 0.365 mol) and potassium acetate (0.72 g, 0.0007 mol) in acetic anhydride (250 mL) was refluxed under a nitrogen atmosphere for 2 h after which the excess solvent was quickly removed by distillation under reduced pressure.[3] The residual oil was transferred to a Quickfit "Rotaflo" dropping funnel attached to a well-insulated, two-necked, round-bottomed flask which was equipped for vacuum distillation.[4,25] The flask was then evacuated (10 mm) and heated to 250–260 °C before the reaction mixture was introduced. The rate of addition was adjusted so that it approximately equaled the rate of distillation of the pyrolysis product which was collected in a flask cooled in a dry ice/ethanol bath. After the addition was complete, the distillation was continued for a further 20 min. Redistillation of the crude brownish yellow pyrolysate afforded **3**: 54 g (70%); colorless liquid; bp 96–98 °C (0.1 mm) [lit.[3] bp 89 °C (0.08 mm)].

4-Methoxy-2-oxobicyclo[2.2.2]octane-1-carboxylic Acid (5). A solution of **3** (84.8 g, 0.4 mol) in absolute methanol (800 mL) was treated with trimethyl orthoformate (170 g, 1.6 mol) according to a procedure outlined by Morita and Kobayashi.[5] A workup in the usual manner followed by distillation of the crude product gave **4** [78 g (92%); colorless oil; bp 105–112 °C (0.1 mm)] which solidified on standing: ^1H NMR ($CDCl_3$) δ 1.28 (3 H, t, $COOCH_2CH_3$), 1.88–2.03 (8 H, m, CH_2CH_2), 2.51 (2 H, s, $COCH_2$), 3.23 (3 H, s, OCH_3), 3.75 (3 H, s, $COOCH_3$), 4.23 (2 H, q, $COOCH_2CH_3$).

The ^1H NMR and mass spectral data indicated that **4** was a mixture of esters (R = CH_3 and C_2H_5). The methyl ester was found to be always predominant.

A solution of **4** (85.0 g, 0.4 mol) and potassium hydroxide (29 g of 85% pellets, 0.44 mol) in 50% aqueous ethanol (300 mL) was stirred at ambient temperature for 14–16 h. The resulting solution was concentrated to dryness under reduced pressure. The residue was then dissolved in a minimum quantity of water and extracted with ether to remove nonacidic material. The aqueous layer was carefully acidified with concentrated hydrochloric acid and then thoroughly extracted with methylene chloride (4×). The combined extracts were dried, and the solvent evaporated to give **5** (66.5 g, 84%) as a pale yellow solid. Recrystallization of a sample from hexane/ethanol gave colorless prisms: mp 167–168 °C; mass spectrum, m/e 198 (M^+); ^1H NMR ($CDCl_3$) δ 1.97–2.08 (8 H, m, CH_2CH_2), 2.57 (2 H, s, $COCH_2$), 3.28 (3 H, s, OCH_3), 10.30 (1 H, s, COOH). Anal. ($C_{10}H_{14}O_4$) C, H.

4-Methoxybicyclo[2.2.2]octane-1-carboxylic Acid (6). The keto acid (**5**; 59.4 g, 0.3 mol) was treated with hydrazine hydrate (54.0 g, 1.08 mol) and potassium hydroxide (53.8 g, 0.96 mol) in hot diethylene glycol (540 mL) according to a known procedure.[7] Vigorous stirring and prolonged heating (8–10 h) were essential to obtain the product in high yield (see beginning of paper). A workup in the usual manner afforded the crude product which sublimed as a colorless solid, 44.2 g (80%). A sample was recrystallized from hexane/ethanol to afford **6** as colorless needles, mp 168–169 °C (lit.[11] mp 168–169.5 °C).

Methyl 4-Methoxybicyclo[2.2.2]octane-1-carboxylate (7). By use of the esterification procedure of Clinton et al.,[26] a solution of the carboxylic acid (23.0 g, 0.125 mol) in absolute methanol (12.0 g) and 1,2-dichloroethane (40 mL) containing concentrated sulfuric acid (0.5 mL) was refluxed with stirring for 18–20 h. A standard workup followed by distillation gave **7** as a colorless liquid: 22.5 g (91%); bp 88–90 °C (1.0 mm); mass spectrum; m/e

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198 (M^+); ^1H NMR ($CDCl_3$) δ 1.78–1.85 (12 H, m, CH_2CH_2), 3.20 (3 H, s, OCH_3), 3.67 (3 H, s, $COOCH_3$). Anal. ($C_{11}H_{18}O_3$) C, H.

Methyl 4-Acetoxybicyclo[2.2.2]octane-1-carboxylate (8). By use of the procedure of Suzuki and Morita,[16] a solution of 7 (19.8 g, 0.1 mol) in acetic anhydride (50 mL) was treated with 5–10 drops of boron trifluoride etherate and stirred at room temperature until VPC analysis indicated that all of the starting material had been consumed (48–60 h). The reaction mixture was poured onto ice/water and extracted with ether (3×). The combined extract was washed with saturated sodium bicarbonate solution and dried, and the solvent was removed. Sublimation of the residue afforded 8 as a colorless solid (20.8 g, 92%). Recrystallization of a sample from ethanol/water gave colorless leaflets: mp 67–68 °C; mass spectrum, m/e 226 (M^+); ^1H NMR ($CDCl_3$) δ 1.97–1.99 (15 H, m, CH_2CH_2 and $OCOCH_3$), 3.66 (3 H, s, $COOCH_3$). Anal. ($C_{12}H_{18}O_4$) C, H.

Methyl 4-Hydroxybicyclo[2.2.2]octane-1-carboxylate (9). A mixture of 8 (22.6 g, 0.1 mol), sodium methoxide (10.8 g, 0.2 mol) and absolute methanol (120 mL) was refluxed with stirring for 2 h.[4,25] The resulting white slurry was poured onto ice/water and extracted with ether (3×). The extracts were combined, dried, and the solvent evaporated. Sublimation of the residue gave 9 (17.3 g, 94%) as a colorless solid. Recrystallization from hexane afforded needles, mp 61–62 °C (lit.[12] mp 61–63 °C).

Methyl 4-Fluorobicyclo[2.2.2]octane-1-carboxylate (1, X = $COOCH_3$). A stainless-steel autoclave (300 mL) containing the alcohol (9; 8.1 g, 0.044 mol) was cooled with liquid nitrogen and evacuated to 0.1 mm. Sulfur tetrafluoride (3–4-fold excess) was condensed in, and the sealed autoclave was allowed to warm to ambient temperature. No agitation was required. After the mixture has been allowed to stand for 24 h, the excess sulfur tetrafluoride and hydrogen fluoride were vented, and the residue was extracted with fluorotrichloromethane. The extract was washed with aqueous sodium bicarbonate and dried, and the solvent was removed. Sublimation of the crude product afforded 1 (X = $COOCH_3$) as a colorless solid, 7.5 g (92%). Recrystallization from aqueous methanol gave needles: mp 66.5 °C; mass spectrum, m/e 186 (M^+); ^1H NMR ($CDCl_3$) δ 1.95–1.98 (12 H, m, CH_2CH_2), 3.65 (3 H, s, $COOCH_3$). Anal. ($C_{10}H_{15}O_2F$) C, H.

4-Fluorobicyclo[2.2.2]octane-1-carboxylic Acid (1, X = COOH). The ester (1, X = $COOCH_3$; 6.5 g, 0.035 mol) was treated with aqueous ethanolic potassium hydroxide (2.8 g, 0.05 mol) in the manner described above for the hydrolysis of 4. A similar workup followed by sublimation afforded 1 (X = COOH) as a colorless solid, 5.8 g (96%). Recrystallization from hexane/ethanol gave colorless needles: mp 211.5 °C; mass spectrum, m/e 172 (M^+); ^1H NMR ($CDCl_3$) δ 1.91–1.94 (12 H, m, CH_2CH_2), 10.34 (1 H, s, COOH). Anal. ($C_9H_{13}O_2F$) C, H.

4-Fluorobicyclo[2.2.2]octane-1-carboxamide (1, X = $CONH_2$). The carboxylic acid (1, X = COOH; 1.2 g, 0.007 mol) was treated with thionyl chloride in a standard manner to give the acid chloride (1, X = COCl). A solution of the crude acid chloride in ether (30 mL) was cooled to 0 °C, and dry ammonia gas was bubbled in for 20–30 min. A workup in the usual manner followed by sublimation (1.1 g, 92%) and recrystallization from a hexane/ethanol mixture afforded colorless needles of the amide (1, X = $CONH_2$): mp 179–180 °C; mass spectrum, m/e 171 (M^+). Anal. ($C_9H_{14}ONF$) C, H.

4-Fluorobicyclo[2.2.2]octane-1-carbonitrile (1, X = CN). A solution of the amide (1, X = $CONH_2$; 0.75 g, 0.0044 mol) in dry pyridine (0.72 mL, 0.0088 mol) and dry dioxane (6 Ml) was treated with trifluoroacetic anhydride (0.68 mL), 0.0044 mol) according to a procedure outlined by Campagna et al.[27] A standard workup followed by sublimation (0.55 g, 82%) and recrystallization from hexane gave the nitrile (1, X = CN) as colorless needles: mp 162–163 °C; mass spectrum, m/e 142 (M^+). Anal. ($C_9H_{12}NF$) C, H.

4-Fluorobicyclo[2.2.2]octan-1-amine (1, X = NH_2). To a dry acetone (30 mL) solution of the acid chloride (1, X = COCl), prepared from the acid (1, X = COOH; 3.0 g, 0.0175 mol) as described above, was added with stirring a solution of sodium azide[28] (1.43 g, 0.22 mol) in water (2 mL) while the temperature was maintained at 0–5 °C. After the mixture was stirred at this temperature for a further 1 h, water (60 mL) was added, and the mixture was extracted with methylene chloride (3×). The combined organic layer was washed with water, dried, and concentrated by evaporation to about 15 mL. Benzene (75 mL) was added, and the solution was concentrated again to about 25 mL before being heated under reflux until the evolution of nitrogen had ceased (1–2 h). The resulting solution of the isocyanate (1, X = NCO) was treated with concentrated hydrochloric acid (80 mL) and then heated under reflux for a further 3 h, by which time carbon dioxide evolution had ceased. The cooled mixture was shaken with additional benzene (25 mL) before separation of the aqueous phase. The benzene was washed with water (2×), and the aqueous extracts were combined with the original aqueous phase. These were then carefully basified at 0 °C with 5% aqueous sodium hydroxide, and the free amine (1, X = NH_2) was extracted with trichlorofluoromethane. A standard workup followed by sublimation (1.8 g, 72%) and recrystallization from aqueous ethanol afforded colorless leaflets: mp 155–157 °C; mass spectrum, m/e 143 (M^+). Anal. ($C_8H_{14}FN$) C, H.

***N*-Acetyl-4-fluorobicyclo[2.2.2]octan-1-amine (1, X = $NHCOCH_3$).** A solution of the amine (1, X = NH_2; 0.29 g, 0.002 mol) in acetic anhydride (0.5 mL) and glacial acetic acid (8 mL) was warmed on a steam bath for 1 h. After a standard workup, sublimation (0.24 g, 65%) and recrystallization from hexane/ethanol afforded colorless needles: mp 156–157 °C; mass spectrum, m/e 185 (M^+). Anal. ($C_{10}H_{16}FNO$) C, H.

1-(Dimethylamino)-4-fluorobicyclo[2.2.2]octane (1, X = $N(CH_3)_2$). By use of the procedure of Meiners et al.,[29] the amine (1, X = NH_2; 0.5 g, 0.0035 mol) was added in portions over 20 min to ice-cooled formic acid (0.65 g, 0.014 mol) with stirring. The resulting mixture was then warmed to 90–100 °C before aqueous formaldehyde (0.8 mL of ca. 11 M solution, 0.009 mol) was added in a dropwise fashion. After the mixture was allowed to stir at this temperature for a further 2 h, it was cooled and then carefully basified with 10% aqueous sodium hydroxide. The amine (1, X = $N(CH_3)_3$) was extracted with trichlorofluoromethane and, after the workup, distilled in a Kugelrohr apparatus to afford a colorless liquid: 0.43 g (72%); mass spectrum, m/e 171 (M^+); ^1H NMR ($CDCl_3$) δ 1.81–1.88 (12 H, m, CH_2CH_2), 2.24 (6 H, s, $N(CH_3)_2$). Anal. ($C_{10}H_{18}FN$) C, H.

(4-Fluorobicyclo[2.2.2]oct-1-yl)trimethylammonium Halides (1, X = $^+N(CH_3)_3$). A solution of the dimethylamino compound (1, X = $N(CH_3)_2$; 0.1 g, 0.0006 mol) and methyl iodide (0.34 g, 0.0024 mol) in dry ether (5 mL) was heated under reflux for 2 h. The resulting white precipitate (1, X = $^+N(CH_3)_3I^-$) was collected by vacuum filtration (0.17 g, 91%). A portion of this compound was placed on a column of Amberlite IRA-400 resin (25 g) and eluted with methanol. Evaporation of the solvent afforded a white solid (1, X = $^+N(CH_3)_3Cl^-$).

1-Fluoro-4-nitrobicyclo[2.2.2]octane (1, X = NO_2). By use of the procedure of Kornblum and Jones,[30] a stirred slurry of the amine (1, X = NH_2; 0.5 g, 0.0035 mol), magnesium sulfate (0.53 g), acetone (9 mL), and water (2.5 mL) was treated portionwise with potassium permanganate (3.49 g, 0.021 mol) over a period of 30 min, while the temperature was maintained at 25–30 °C. After the mixture was stirred for a further 48 h at room temperature, the reaction mixture was worked up in a standard manner. Sublimation of the crude residue afforded 1 (X = NO_2) as a colorless solid, 0.35 g (58%). Recrystallization from aqueous ethanol gave leaflets; mp 167–168 °C; mass spectrum (m/e 173 (M^+). Anal. ($C_8H_{12}O_2FN$) C, H.

4-Fluorobicyclo[2.2.2]octane-1-carbaldehyde (1, X = CHO). By use of the procedure of Brown et al.,[31] a solution of the carboxylic acid (1, X = COOH; 0.52 g, 0.003 mol) in dry tetrahydrofuran (4 mL) was treated dropwise with borane–methyl sulfide (0.31 mL, 0.003 mol), and the resulting mixture was refluxed under a nitrogen atmosphere for 1 h. The solvent and dimethyl sulfide were then removed under vaccuum to afford a residue which was dissolved in dry methylene chloride (3 mL) and added dropwise to a well-stirred suspension of pyridinium chlorochromate (0.72 g, 0.0033 mol) in dry methylene chloride

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(5 mL).[31] After the well-stirred reaction mixture was heated under reflux for 1 h, it was cooled and then diluted with ether (10 mL). The supernatant solution was separated by filtration through a column of Florisil. Workup afforded 1 (X = CHO) as a colorless solid (0.30 g, 65%) after sublimation. Recrystallization from aqueous ethanol gave needles: mp 55–58 °C; mass spectrum, *m/e* 156 (M^+). Anal. ($C_9H_{13}FO$) C, H.

1-Acetyl-4-fluorobicyclo[2.2.2]octane (1, X = $COCH_3$). An ethereal solution of methyllithium (46 mL of 1.13 M solution, 0.055 mol) was slowly added to a well-stirred solution of the carboxylic acid (1, X = COOH; 4.3 g, 0.025 mol) in ether (25 mL).[32] The resulting slurry was then refluxed under a nitrogen atmosphere for 2 h. After cooling, the reaction mixture was added to ice–water with vigorous stirring and then worked up in a standard manner. Distillation in a Kugelrohr apparatus afforded the ketone (1, X = $COCH_3$) as a colorless oil: 3.8 g (90%); bp 75–80 °C (5 mm); mass spectrum, *m/e* 170 (M^+); ^1H NMR ($CDCl_3$) δ 1.87–1.92 (12 H, m, CH_2CH_2), 2.10 (3 H, s, $COCH_3$). Anal. ($C_{10}H_{15}OF$) C, H.

1-Acetoxy-4-fluorobicyclo[2.2.2]octane (1, X = $OCOCH_3$). A solution of the acetyl compound (1, X = $COCH_3$; 2.7 g, 0.016 mol) in methylene chloride (100 mL) was stirred with *m*-chloroperbenzoic acid (6.9 g of ca. 80% purity, ca. 0.035 mol) and stirred at room temperature in the dark for 3 days.[3,33] A standard workup followed by sublimation afforded the acetate (1, X = $OCOCH_3$) as a colorless solid (2.3 g, 77%). Recrystallization from aqueous ethanol gave leaflets, mp 60–61 °C (lit.[34] mp 57–58.5 °C).

4-Fluorobicyclo[2.2.2]octan-1-ol (1, X = OH). The acetoxy compound (1, X = $OCOCH_3$; 1.4 g, 0.0075 mol) was treated with sodium methoxide (0.81 g, 0.015 mol) in refluxing methanol (10 mL) as described above for the conversion of **8** to **9**. A standard workup followed by sublimation afforded the alcohol (1, X = OH) as a colorless solid, 1.0 g (93%). Recrystallization from hexane/ethanol gave needles, mp 231–232 °C (lit.[34] mp 235–236 °C).

1-Fluoro-4-methoxybicyclo[2.2.2]octane (1, X = OCH_3). A solution of the alcohol (1, X = OH; 0.3 g, 0.0021 mol) in tetrahydrofuran (2 mL) was added to a suspension of potassium hydride (ca. 0.4 g, ca. 0.01 mol) in tetrahydrofuran (10 mL), and the mixture was refluxed for 30 min. Methyl iodide (0.71 g, 0.005 mol) was then added,[35] and, after the mixture was refluxed for a further 30 min, the liquid phase was separated by centriguation. Removal of the solvent followed by Kugelrohr distillation of the residual liquid into a dry ice/acetone-cooled receiver gave the methoxy compound (1, X = OCH_3) as a colorless oil: 0.25 g (76%); mass spectrum, *m/e* 158 (M^+); ^1H NMR ($CDCl_3$) δ 1.87–1.92 (12 H, m, CH_2CH_2), 3.18 (3 H, s, OCH_3). Anal. ($C_9H_{15}FO$) C, H.

1,4-Difluorobicyclo[2.2.2]octane (1, X = F). The alcohol (1, X = OH; 0.5 g, 0.0035 mol) was treated with a 3–4-fold excess of sulfur tetrafluoride as described above for the conversion of **9** to **1** (X = $COOCH_3$). Sublimation of the crude product afforded a colorless solid (0.41 g, 81%) which recrystallized from aqueous ethanol as leaflets, mp 195–196 °C (lit.[34] mp 193–195 °C).

1-Chloro-4-fluorobicyclo[2.2.2]octane (1, X = Cl). By use of the procedure of Grob et al.,[36] a deoxygenated solution of the carboxylic acid (1, X = COOH; 0.69 g, 0.004 mol) and *N*-chlorosuccinimide (3.08 g, 0.023 mol) in dimethylformamide and glacial acetic acid (1.8 mL of a 5:1 mixture) was treated with lead tetraacetate (2.1 g, ca. 0.004 mol, stabilized by ca. 15% acetic acid). The mixture was warmed to 50 °C and maintained at that temperature until the evolution of carbon dioxide had ceased (20–30 min). After cooling, the mixture was extracted with pentane (3×), and the combined extracts were washed successively with 20% perchloric acid, aqueous potassium carbonate solution, and water. The pentane extract was dried and then evaporated to afford the crude product. Sublimation afforded the chloro compound (1, X = Cl) as a colorless solid: 0.22 g (34%); mp 147–149 °C; mass spectrum, *m/e* 164. Anal. ($C_8H_{12}ClF$) C, H.

1-Bromo-4-fluorobicyclo[2.2.2]octane (1, X = Br). By use of the procedure of Cristol and Firth,[37] a slurry of the carboxylic acid (1, X = COOH; 0.69 g, 0.004 mol), red mercuric oxide (0.9 g, 0.0042 mol), and anhydrous magnesium sulfate (0.4 g) in dry methylene chloride (8 mL) was heated under reflux for 30 min. A solution of bromine (0.8 g, 0.005 mol) in dry methylene chloride (2 mL) was added dropwise and the mixture refluxed for a further 2 h. After the mixture cooled the mercuric salts were filtered off, and the filtrate was washed successively with aqueous sodium metabisulfite and sodium bicarbonate solutions. The solvent was dried and then carefully evaporated to afford the crude product. Sublimation afforded the bromo compound (1, X = Br) as a colorless solid (0.64 g, 77%) which was recrystallized from aqueous ethanol to afford leaflets: mp 154–155 °C; mass spectrum, *m/e* 206, 208 (M^+). Anal. ($C_8H_{12}BrF$) C, H.

1-Fluoro-4-iodobicyclo[2.2.2]octane (1, X = I). By use of the procedure of Abeywickrema and Della,[38] a solution of *tert*-butyl hypoiodite (ca. 0.05 mol) in 1,1,2-trichloro-1,2,2-trifluoroethane (Freon 113; 30 mL) was added to a suspension of the carboxylic acid (1, X = COOH; 1.72 g, 0.01 mol) in Freon 113 (10 mL). The stirred mixture was heated at 40–50 °C while being irradiated with a 200-W tungsten lamp until the evolution of carbon dioxide was ceased. The resulting purple solution was cooled and washed successively with a 10% sodium thiosulfate solution (2×), a saturated sodium bicarbonate solution (2×), and water. The organic layer was dried before the solvent was removed through a short column packed with glass helices. Sublimation of the residue followed by recrystallization of the sublimate (1.58 g, 62%) from aqueous methanol gave 1 (X = I) as colorless needles: mp 115–116 °C; mass spectrum, *m/e* 254 (M^+). Anal. ($C_8H_{12}FI$) C, H.

1-Fluoro-4-(trimethylstannyl)bicyclo[2.2.2]octane (1, X = $Sn(CH_3)_3$). A solution of the iodide (1, X = I; 0.51 g, 0.002 mol) in tetrahydrofuran was treated with trimethyltinlithium in tetrahydrofuran in a standard manner.[39] A workup in the usual fashion followed by Kugelrohr distillation of the crude product afforded the tin compound (1, X = $Sn(CH_3)_3$) as a colorless liquid (0.25 g, 43%) which solidified on standing. Recrystallization from aqueous methanol afforded a colorless solid: mp 63–64 °C; ^1H NMR ($CDCl_3$) δ −0.03 (9 H, s, $SnCH_3$), 1.70–1.85 (12 H, m, CH_2CH_2). Anal. ($C_{11}H_{21}FSn$) C, H.

1-Fluoro-4-methylbicyclo[2.2.2]octane (1, X = CH_3). This compound was prepared from 1-methoxy-4-methylbicyclo[2.2.2]octane[40] as previously described.[15] Distillation afforded a colorless oil: 65% yield; bp 165–170 °C (lit.[15] bp 163–170 °C).

1-Ethyl-4-fluorobicyclo[2.2.2]octane (1, X = CH_2CH_3). The acetyl compound (1, X = $COCH_3$; 0.51 g, 0.003 mol) was treated with hydrazine hydrate (0.54 g, 0.0108 mol) and potassium hydroxide (0.54 g, 0.0096 mol) in hot diethylene glycol according to the modified Wolff–Kishner procedure.[7] A standard workup followed by Kugelrohr distillation of the crude product into a dry ice/acetone-cooled receiver gave the compound (1, X = CH_2CH_3) as a colorless liquid: 0.36 g (77%); mass spectrum, *m/e* 156 (M^+); ^1H NMR ($CDCl_3$) δ 0.58–1.75 (17 H, m, CH_2CH_2, CH_2CH_3). Anal. ($C_{10}H_{17}F$) C, H.

1-Fluoro-4-isopropylbicyclo[2.2.2]octane (1, X = $CH(CH_3)_2$). The acetyl compound (1, X = $COCH_3$; 1.7 g, 0.01 mol) was converted to the tertiary alcohol (1, X = $C(CH_3)_2OH$; 1.7 g, 92%) and then the chloride (1, X = $C(CH_3)_2Cl$) by the same procedures previously indicated for the synthesis of 1-isopropyl-4-(*p*-fluorophenyl)bicyclo[2.2.2]octane.[22] The crude chloride (1, X = $C(CH_3)_2Cl$; 0.61 g, 0.003 mol) was treated with lithium/*tert*-butyl alcohol in tetrahydrofuran[12] and then worked up in the usual manner. Kugelrohr distillation of the crude product into a dry ice/acetone-cooled receiver gave the compound (1, X = $CH(CH_3)_2$) as a colorless liquid: 0.40 g (79%); ^1H NMR

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($CDCl_3$) δ 0.79 (6 H, d, J_{H-H} = 5.5 Hz, CH_3), 1.15–1.73 (13 H, m, CH_2CH_2, CH). Anal. ($C_{11}H_{19}F$) C, H.

1-*tert*-Butyl-4-fluorobicyclo[2.2.2]octane (1, X = $C(CH_3)_3$). 4-Methoxybicyclo[2.2.2]octane-1-carboxylic acid (6) was converted to 1-(α-chloroisopropyl)-4-methoxybicyclo[2.2.2]octane by following the procedures indicated above for the preparation of 1 (X = $C(CH_3)_2Cl$). Treatment of the chloride (1.3 g, 0.006 mol) with trimethylaluminum as previously described for the synthesis of 1-*tert*-butyl-4-(*p*-fluorophenyl)bicyclo[2.2.2]octane[22] afforded 1-*tert*-butyl-4-methoxybicyclo[2.2.21octane as a colorless oil (0.90 g, 77%) after Kugelrohr distillation. The latter compound (0.40 g, 0.002 mol) and acetyl fluoride (0.5 g, 0.008 mol) were treated at −10 °C with BF_3–H_3PO_4[15] (10 drops) and then stirred at 0 °C while being carefully monitored by GLC analyses. As soon as the reaction was complete, the mixture was quenched with ice/water. A workup in the standard manner followed by Kugelrohr distillation afforded 1 (X = $C(CH_3)_3$) as a colorless oil: 0.25 g (68%); bp 55–60 °C (2.0 mm); ^1H NMR ($CDCl_3$) δ 0.79 (9 H, s, CH_3), 1.45–2.18 (12 H, m, CH_2CH_2). The sample was found to be contaminated with 1-acetoxy-4-*tert*-butylbicyclo[2.2.2]octane (ca. 5%). No attempt was made to purify the compound.

1-Fluoro-4-phenylbicyclo[2.2.2]octane (1, X = C_6H_5). This compound was prepared from 1-hydroxy-4-phenylbicyclo-[2.2.2]octane[4] as previously described.[14] Sublimation afforded a white solid, mp 131–132.5 °C (lit.[34] mp 132–133 °C).

1-Fluorobicyclo[2.2.2]octane (1, X = H). 1-Methoxybicyclo[2.2.2]oct-5-en-2-one was prepared as described by Evans et al.[41] The ketone was reduced by the modified Wolff–Kishner procedure[7] to give 1-methoxybicyclo[2.2.2]oct-2-ene: bp 84–86 °C (25 mm); 70%. Catalytic hydrogenation (5% Pd/C, 45 psi of H_2) of an ethanolic solution of the olefin afforded 1-methoxybicyclo[2.2.2]octane as an oil: 95% yield; bp 65–66 °C (10 mm) [lit.[16] bp 185–190 °C (760 mm)]. This latter compound was converted to 1 (X = H) by following a procedure described by Suzuki and Morita.[15] Sublimation afforded a white solid: 62% yield; mp 148–150 °C (lit.[15] mp 152 °C).

Registry No. 1 (X = $COOCH_3$), 78385-85-0; 1 (X = COOH), 78385-84-9; 1 (X = $CONH_2$), 81687-77-6; 1 (X = COCl), 81687-78-7; 1 (X = CN), 78385-80-5; 1 (X = NH_2), 78385-91-8; 1 (X = NCO), 81687-79-8; 1 (X = $NHCOCH_3$), 78385-93-0; 1 (X = $N(CH_3)_2$), 78385-92-9; 1 (X = $N(CH_3)_3^+I^-$), 81687-80-1; 1 (X = $N(CH_3)_3^+Cl^-$), 81687-81-2; 1 (X = NO_2), 32038-89-4; 1 (X = CHO), 78385-82-7; 1 (X = $COCH_3$), 78385-83-8; 1 (X = $OCOCH_3$), 22947-60-0; 1 (X = OH), 22947-61-1; 1 (X = OCH_3), 78385-90-7; 1 (X = F), 20277-40-1; 1 (X = Cl), 78385-86-1; 1 (X = Br), 78385-87-2; 1 (X = I), 78385-89-4; 1 (X = $Sn(CH_3)_3$), 78385-88-3; 1 (X = CH_3), 20417-60-1; 1 (X = CH_2CH_3), 81687-82-3; 1 (X = $CH(CH_3)_2$), 81687-83-4; 1 (X = $C(CH_3)_2OH$), 81687-84-5; 1 (X = $C(CH_3)_2Cl$), 81687-85-6; 1 (X = $C(CH_3)_3$), 81687-86-7; 1 (X = Ph), 22947-58-6; 1 (X = H), 20277-22-9; 2, 72653-14-6; 3, 72653-21-5; 4 (R = Me), 81687-87-8; 4 (R = Et), 81687-88-9; 5, 81687-89-0; 6, 773-34-2; 7, 81687-90-3; 8, 81687-91-4; 9, 23062-53-5; 10, 81687-92-5; 1-(α-chloroisopropyl)-4-methoxybicyclo[2.2.2]octane, 81687-93-6; 1-*tert*-butyl-4-methoxybicyclo-[2.2.2]octane, 81687-94-7; 1-acetoxy-4-*tert*-butylbicyclo[2.2.2]octane, 81687-95-8; 1-methoxybicyclo[2.2.2]oct-5-en-2-one, 38213-08-0; 1-methoxybicyclo[2.2.2]oct-2-ene, 25489-02-5; 1-methoxybicyclo-[2.2.2]octane, 7697-14-5.

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Substituent Effects in the Bicyclo[2.2.2]octane Ring System. A Carbon-13 and Fluorine-19 Nuclear Magnetic Resonance Study of 4-Substituted Bicyclo[2.2.2]oct-1-yl Fluorides[1]

William Adcock* and Anil N. Abeywickrema

School of Physical Sciences, The Flinders University of South Australia, Bedford Park, Australia 5042

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^{19}F and ^{13}C NMR spectra have been recorded for a large number of 4-substituted bicyclo[2.2.2]oct-1-yl fluorides (1) in which the substituents cover a wide range of electronic effects. Correlations of the ^{19}F substituent chemical shifts (SCS) for several solvents with substituent constants (σ_I, ι, and σ_R^0) indicate that these NMR substituent-probe parameters are predominantly manifestations of electric field and electronegativity effects. Moreover, it is also revealed that whereas the former effects are solvent dependent, the latter are essentially independent of the nature of the medium. In addition, the statistical analysis indicates that resonance effects involving orbitals of π symmetry appear not to be transmitted through the bicyclo[2.2.2]octyl skeletal framework. Compelling support for the validity of the overall statistical dissection is provided by an independent measure of the polar susceptibility parameters (ρ_I values) for each solvent. The coefficient (*A*) of the Buckingham equation for linear electric field effects on C_{sp^3}–F bonds is calculated for c-C_6H_{12} as the solvent. A good correlation of solvent-induced changes ($CDCl_3$ to CF_3CO_2H) in the ^{19}F SCS vs. similar differential changes in the corresponding ^{13}C SCS for C1–F confirms the solvent independence of the electronegativity effect. The origin of this latter effect is considered, and some of the possibilities are probed by correlative analysis of the substituent-induced changes in the one-bond carbon–fluorine spin–spin coupling constants (Δ^1J_{CF}). The polar effects of alkyl groups are alluded to in the light of the new results for system 1.

During the course of an attempt to delineate dipolar electrostatic field contributions to the ^{19}F substituent chemical shifts (SCS) of para-substituted fluorobenzenes, Anderson and Stock[2] reported ^{19}F SCS for a limited number of 4-substituted bicyclo[2.2.2]oct-1-yl fluorides (1, X = F and COOEt). Although subsequent studies[3-6] have shown that the investigation was inappropriate for the objective in question, the results obtained for system 1 are of intrinsic interest since the ^{19}F SCS for *fluorine* and *ethoxycarbonyl* were found to be in the *opposite* direction

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