a white solid (138 g). To determine the composition of this material, a small quantity (~10 mg) was weighed carefully and suspended in water (~5 mL). Ammonium sulfate solution (0.5 mL, 3.2 M) was added and the mixture was shaken for several minutes. The resulting solution was diluted to 10 mL, and an aliquot was analyzed by HPLC. This analysis indicated that the precipitate contained 106 mmol of dATP corresponding to a yield of 68% and a purity of 60%. Analysis of the solution from which the dATP·Ba_2 had been isolated indicated the following distribution of deoxynucleotide monophosphates (mmol): dAMP (6.5), dCMP (121), dGMP (9), and TMP (115).

Purification of dATP·Ba_2. All steps in this procedure were conducted in a cold room at 4 °C. The crude dATP·Ba_2 obtained as described above (20 g, 15.8 mmol of dATP) was suspended in cold water (200 mL). Ion-exchange resin (Bio-Rex 70, 100–200 mesh, Na^+ form, 60 g) was added and the suspension was stirred vigorously for 30 min. The resin and any undissolved material were removed by centrifugation and the separated solids were washed with water (2 × 75 mL). ^{31}P NMR spectroscopy indicated that the residual combined aqueous solutions (320 mL) contained 1 mmol of inorganic phosphate (calculated from the peak integral ratio and the assumption that all the dATP·Ba_2 had dissolved). After the pH of this solution had been adjusted to 4.8 with 10% aqueous HCl, $BaBr_2$ solution (2.5 mL, 0.5 M, 1.25 mmol) was added slowly with stirring. The resulting precipitate of barium phosphate was removed by centrifugation and discarded. To the clear supernatant was added $BaBr_2$ solution (50 mL, 0.5 M, 25 mmol) with stirring over 10 min. At this point, the solution had a volume of 550 mL. Ethanol (100 mL, 95%, 4 °C) was added over 10 min, and the resulting precipitate was allowed to stand for 2 h. The precipitate was collected by centrifugation and washed with 15% ethanol (150 mL), 50% ethanol (150 mL), 95% ethanol (2 × 150 mL), acetone (150 mL), and anhydrous ether (2 × 100 mL). The resulting solid was dried (0.1 torr, 25 °C, 4 h) to give 9.3 g (78% yield, 95% pure by enzyme assay) of dATP·Ba_2.

Polar Substituent Effects on ^{19}F Chemical Shifts of Aryl and Vinyl Fluorides: A Fluorine-19 Nuclear Magnetic Resonance Study of Some 1,1-Difluoro-2-(4-substituted-bicyclo[2.2.2]oct-1-yl)ethenes

William Adcock* and Gaik B. Kok

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

Received September 14, 1984

An extensive series of 1,1-difluoro-2-(4-substituted-bicyclo[2.2.2]oct-1-yl)ethenes (**2**) covering a diverse range of substituents (X = H, NO_2, CN, CF_3, $COOCH_3$, F, Cl, Br, OCH_3, C_6H_5, C_2H, $C_2Si(CH_3)_3$, CH_3, and $C(CH_3)_3$) have been synthesized and their ^{19}F NMR spectra have been recorded. Most of the compounds (except **2**, X = C_2H) were synthesized by difluoromethylenation of the appropriate carbaldehydes which, in turn, with one exception (**2**, X = $C_2Si(CH_3)_3$), were all prepared from the corresponding carboxylic acids. The ^{19}F chemical shifts of **2** (δ_{F_a} and δ_{F_b}) were found to correlate very well against polar field substituent parameters (σ_F values). Most importantly, the pattern of polar susceptibility parameters ($\rho_F(F_a) > \rho_F(F_b)$) for **2** in cyclohexane was found to be similar to that previously observed for 4-substituted β,β-difluorostyrenes (**1**). Since the analysis of the latter system hinged critically on the dissection of polar and resonance effects by multiple linear least-squares regression analysis (DSP method), the corroboration of the conclusions drawn from **1** concerning direct field effects provides strong support for the validity of this controversial methodology.

Introduction

Although the origin of polar substituent effect contributions (ρ_F effect) to aryl ^{19}F substituent chemical shifts (SCS; sensitive monitors of π electron density perturbations at remote centers of substituted arene ring systems)[1] has been a subject of some debate in the past,[2,3] it is now generally acknowledged that two electronic transmission mechanisms are chiefly responsible, [4-7] viz., field-induced π polarization of the aromatic system ($F_{\pi\leftarrow\pi}$) and a direct electrostatic field effect acting on the π component of the C–F bond (F_π).[8] In general, the former mechanism is predominant[4,7] and, in these circumstances, polar aryl ^{19}F SCS are found to parallel the corresponding ^{13}C SCS of the unfluorinated aryl derivatives, i.e., $\Delta q_\pi^F \propto \Delta q_\pi^C$ (π electron density perturbations at the respective remote probe nuclei, viz., fluorine and carbon). However, in some situations the $F_{\pi\leftarrow\pi}$ effect is fortuitously small (e.g., 1,5 (or 5α) and 2,5 (or 5β) dispositions in 1- and 2-substituted naphthalenes, respectively)[9,10] and, as a consequence, the F_π effect can now dominate. Here there is no longer a simple relationship between polar aryl ^{19}F and ^{13}C SCS.

(1) Hehre, W. J.; Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1976**, *12*, 159 and references cited therein.
(2) Fukunaga, J.; Taft, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 1612.
(3) Adcock, W.; Gupta, B. D. *J. Am. Chem. Soc.* **1975**, *97*, 6871. Adcock, W.; Gupta, B. D.; Khor, T. C. *Aust. J. Chem.* **1976**, *29*, 2571.
(4) Reynolds, W. F.; Hamer, G. K. *J. Am. Chem. Soc.* **1976**, *98*, 7296 and references cited therein.
(5) Adcock, W.; Khor, T. C. *J. Am. Chem. Soc.* **1978**, *100*, 7799 and references cited therein.
(6) Reynolds, W. F.; Gibb, V. G.; Plavac, N. *Can. J. Chem.* **1980**, *58*, 839.
(7) Reynolds, W. F. *Prog. Phys. Org. Chem.* **1983**, *14*, 165 and references cited therein.
(8) In this and future publications we shall adhere to the nomenclature recently suggested by Reynolds[7] to represent various electronic substituent effects. Thus, the symbol σ_F is employed in place of σ_I in view of the overwhelming evidence that σ_I is a manifestation of polar field effects. $F_{\pi\leftarrow\pi}$ and F_π replace F_π and F_D, respectively, to represent field-induced π electron transfer between conjugated groups (e.g., fluorine and field-polarized aromatic groups) and direct π polarization (e.g., π component of the C_{sp^2}–F bond).
(9) Kitching, W.; Bullpitt, M.; Gartshore, D.; Adcock, W.; Khor, T. C.; Doddrell, D.; Rae, I. D. *J. Org. Chem.* **1977**, *42*, 2411.
(10) Adcock, W.; Cox, D. P. *J. Org. Chem.* **1979**, *44*, 3004.

0022-3263/85/1950-1079$01.50/0

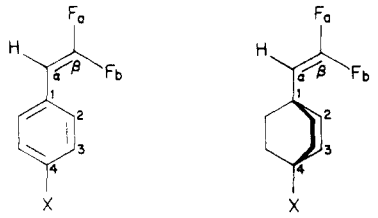
Table I. ^{19}F Chemical Shifts (ppm)[a] of 1,1-Difluoro-2-(4-substituted-bicyclo[2.2.2]oct-1-yl)ethenes (2)

	c-C_6H_{12}					$CDCl_3$				
X	δ_{F_a}[b,e]	δ_{F_b}[b,e]	$\Delta\delta_F$[c]	SCS (F_a)[d]	SCS (F_b)[d]	δ_{F_a}[b,e]	δ_{F_b}[b,e]	$\Delta\delta_F$[c]	SCS (F_a)[d]	SCS (F_b)[d]
H	26.630	27.265	−0.635	0.00	0.00	25.626	26.369	−0.743	0.00	0.00
NO_2	28.517	29.015	−0.498	1.89	1.75	27.723	28.474	−0.751	2.10	2.11
CN	28.267	28.711	−0.444	1.64	1.45	27.415	28.180	−0.761	1.79	1.81
CF_3	27.834	28.510	−0.676	1.20	1.25	26.865	27.719	−0.854	1.24	1.35
$COOCH_3$	27.264	27.898	−0.634	0.63	0.63	26.496	27.261	−0.766	0.89	0.87
F	27.824	28.165	−0.341	1.19	0.90	27.036	27.598	−0.562	1.41	1.23
Cl	27.956	28.239	−0.283	1.33	0.97	27.112	27.624	−0.512	1.49	1.26
Br	28.005	28.262	−0.257	1.38	1.00	27.168	27.648	−0.480	1.54	1.28
OCH_3	27.245	27.688	−0.443	0.62	0.42	26.542	27.134	−0.592	0.92	0.77
C_6H_5	27.113	27.644	−0.531	0.48	0.38	26.217	26.902	−0.685	0.59	0.53
C_2H	27.374	27.818	−0.444	0.74	0.55	26.527	27.184	−0.657	0.90	0.82
$C_2Si(CH_3)_3$	27.289	27.727	−0.438	0.66	0.46	26.398	27.027	−0.629	0.77	0.66
CH_3	26.825	27.344	−0.519	0.20	0.08	25.828	26.476	−0.648	0.20	0.11
$C(CH_3)_3$	26.623	27.371	−0.749	−0.01	0.11	25.664	26.401	−0.737	0.04	0.03

[a] Low-field shifts are positive. Conversely, high-field shifts are negative. [b] Relative to internal 1,1,2,2-tetrachloro-3,3,4,4-tetrafluorocyclobutane (TCTFCB). TCTFCB relative to internal $CFCl_3$: −114.25 (c-C_6H_{12}) and −113.78 ppm ($CDCl_3$). [c] $\Delta\delta_F = \delta F_a - \delta F_b$. [d] Chemical shifts relative to that of the parent compound (X=H), i.e., SCS(F_a) = $(\delta F_a)_X - (\delta F_a)_H$ and SCS(F_b) = $(\delta F_b)_X - (\delta F_b)_H$. [e] Accurate to ±0.005 ppm.

It is worthwhile noting that several other instances of nonlinearity between these electronic probe parameters have been recorded which can be attributed to the importance of the direct field influence on aryl ^{19}F chemical shifts.[1,9-12]

Reynolds and co-workers[4,6] have employed the internal shift differential between the ^{19}F chemical shifts ($\Delta\delta_F \equiv \delta_{F_a} - \delta_{F_b}$) of 4-substituted β,β-difluorostyrenes (1) for the



1 2

quantitative assessment of the aforementioned direct electrostatic field effect. This methodology hinges on the apparently very reasonable premise that field-induced polarization (F_π and $F_{\pi\leftarrow\pi}$ effects)[7,8] and resonance (R_π effect)[7] influences on the carbon π system, which lead to equivalent π electron density perturbations (Δq_π^F) at both fluorine probe centers in 1, are cancelled out in the subtraction process. Hence, the relative internal differential shifts ($\Delta\Delta\delta_F$) of 1 should reflect solely the difference in the electric field components acting along the two C–F bonds ($\Delta E_z \equiv E_z(C\text{–}F_a) - E_z(C\text{–}F_b)$). This shift parameter, therefore, allows the constant, A, in the Buckingham equation (eq 1)[13] to be conveniently and accurately evaluated. However, a multiple linear least-squares regression analysis (DSP) method)[14] of the ^{19}F SCS of 1 ($(\delta F_a)_X - (\delta F_a)_H$) and ($(\delta F_b)_X - (\delta F_b)_H$) vs. polar field ($\sigma_F$ values)[8] and resonance (σ_R° values) parameters reveal that the resonance susceptibility parameters (ρ_R values) for the two fluorines of 1 are *not* exactly equal.[6] Consequently, the $\Delta\delta_F$ values of 1 cannot be considered precise monitors of direct electrostatic field effects. Hence, in order to evaluate A accurately, statistical factorization of the $\Delta\delta_F$ values by the DSP method[14] was essential in order to obtain the direct field component ($\rho_F\sigma_F = AX\Delta E_z$).[6]

$$\Delta\Delta\delta_F = AX\Delta E_z \quad (1)$$

Although the A value ($(3.0 \pm 0.5) \times 10^{-11}$ esu) determined from 1 by Reynolds et al.[6] seems indisputable, particularly in view of the excellent agreement with a value ($(2.5\text{–}3.1) \times 10^{-11}$ esu) independently evaluated by Adcock et al.[5] from entirely different model systems (fluorophenylbicyclo[2.2.2]octanes), we decided to examine the situation further for three main reasons. First, controversy still surrounds the validity of the DSP correlative procedure.[15-18] Thus, the efficacy of disentangling polar (σ_F effect) and resonance (R_π) effects by statistical means is still not universally accepted. Second, since the origin of the σ_R° dependence of the $\Delta\delta_F$ values from 1[6] must lie with the charges induced in the benzene ring by the resonance effect of the substituent (secondary field) and, moreover, since these charges also have a polar component due to field-induced π polarization,[5] the $\rho_F\sigma_F$ values statistically dissected from the $\Delta\delta_F$ values must embody the effect of the primary field of the substituent dipole as well as a contribution from the secondary field emanating from the aromatic ring system. Thus, even if the DSP method is successful in providing an accurate dissection of the $\rho_F\sigma_F$ effect, these values probably lead to a significant overestimation of the A value. Third, skepticism has been expressed in some quarters[19,20] concerning the significance of direct field contributions to aryl ^{19}F SCS. These workers claim that field-induced π polarization can account entirely for the polar contributions.

Since the aforementioned apparent difficulties associated with 1 for probing direct field influences on ^{19}F chemical shifts are due to strong conjugative interactions between the substituent and the aromatic π system and, moreover, since this interfering phenomenon (when investigating polar substituent effects) can be structurally

(11) Adcock, W.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1967**, *89*, 379.
(12) Adcock, W.; Aldous, G. L. *J. Organomet. Chem.* **1980**, *201*, 411.
(13) Buckingham, A. D. *Can. J. Chem.* **1960**, *38*, 300.
(14) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1 and references cited therein.
(15) Reynolds, W. F.; Dais, P.; MacIntyre, D. W.; Hamer, G. K.; Peat, I. R. *J. Magn. Reson.* **1981**, *43*, 81 and references cited therein.
(16) Craik, D. J.; Brownlee, R. T. C.; Sadek, M. *J. Org. Chem.* **1982**, *47*, 657 and references cited therein.
(17) Johnels, D.; Edlund, U.; Grahn, H.; Hellberg, S.; Sjöstrom, Wold, S.; Clementi, S.; Dunn, W. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 863 and references cited therein.
(18) Reynolds, W. F.; Gomes, A.; Maron, A.; MacIntyre, D. G.; Maunder, R. G.; Tanin, A.; Wong, H. E.; Hamer, G. K.; Peat, I. R. *Can. J. Chem.* **1983**, *61*, 2367. We thank professor Reynolds for a preprint prior to publication.
(19) Ewing, D. F.; Toyne, K. J. *J. Chem. Soc., Perkin Trans. 2* **1979**, 243.
(20) Ewing, D. F. *Org. Magn. Reson.* **1979**, *12*, 499.

Table II. ^{19}F–^{19}F and ^{1}H–^{19}F Coupling Constants (Hz) of 1,1-Difluoro-2-(4-substituted-bicyclo[2.2.2]oct-1-yl)ethenes (2)

	c-C_6H_{12}			$CDCl_3$		
X	J_{F-F}[a]	J_{H-F_a}[b]	J_{H-F_b}[b]	J_{F-F}[a]	J_{H-F_a}[b]	J_{H-F_b}[b]
H	50.48	5.26	28.94	52.24	5.55	29.61
NO_2	47.36	4.75	27.84	48.58	4.90	28.79
CN	47.79	4.78	28.54	48.95	4.94	28.99
CF_3	48.47	4.87	28.33	49.93	5.24	28.58
$COOCH_3$	49.50	5.43	28.59	50.84	5.34	29.08
F	48.95	4.97	28.37	49.98	5.30	29.68
Cl	48.53	5.52	28.90	49.86	5.36	28.33
Br	48.40	5.15	28.53	49.68	5.15	28.97
OCH_3	49.74	5.18	28.28	50.90	5.47	29.21
C_6H_5	50.12	4.89	29.79	51.51	5.43	29.25
C_2H	49.62	4.92	28.41	50.78	5.38	29.54
$C_2Si(CH_3)_3$	49.69	5.12	28.46	51.03	5.38	29.41
CH_3	50.47	5.22	28.72	52.24	5.68	29.60
$C(CH_3)_3$	50.35	5.17	29.13	52.25	5.47	29.45

[a] Obtained from proton-decoupled ^{19}F NMR spectra. Accurate to ±0.12 Hz. [b] Obtained from an ABX analysis of proton-coupled ^{19}F NMR spectra (digital resolution ±0.12 Hz.).

precluded by replacing the phenyl substrate with the geometrically rigid bicyclo[2.2.2]octane (BCO) ring system,[21,22] we have accordingly synthesized an extensive series of 1,1-difluoro-2-(4-substituted-bicyclo[2.2.2]oct-1-yl)ethenes (**2**) and measured their ^{19}F chemical shifts in anticipation that their δ_F values would provide a definitive solution to the problem once and for all.

Herein we report the results of our study.

Results and Discussion

The ^{19}F chemical shifts for system **2** in c-C_6H_{12} and $CDCl_3$ as solvents are assembled in Table I. These shifts were determined from an analysis of the AB ^{19}F NMR spectra obtained under proton-decoupled conditions. Assignments followed unambiguously from an ABX analysis of the corresponding proton-coupled spectra. For the sake of completion, the coupling constants obtained from these analyses are listed in Table II.

It can be seen from the regression parameters listed in Table III that the actual shifts (excluding H as a substituent) correlate very well[23] against polar field substituent parameters (σ_F values).[8,24] By contrast, the ^{19}F SCS in 4-substituted-bicyclo[2.2.2]oct-1-yl fluorides depend strongly on both polar field and electronegativity effects.[22] All the correlations (Table III) are significant at the 99.99% confidence level (CL) and most of the variations (>97%) are apparently accounted for. Most importantly, it can be seen that the intercepts of the correlations provide accurate estimates of the ^{19}F chemical shifts of the appropriate fluorine probe (F_a or F_b) in the parent system (**2**, X = H; see Table I). This appears to confirm that there is no significant effect other than polar influences perturbing the shifts when H is replaced by the various dipolar substituents. However, it is always important to bear in mind that small, but real, effects can often be obscured by very good correlation coefficients and high confidence levels. In this regard, a scrutiny of the ^{19}F SCS trends (Table I) is revealing. It can be seen that the values for CH_3, a nonpolar substituent ($\sigma_F = 0$),[22,25,26] are *positive* and display a pattern ($F_a > F_b$) in c-C_6H_{12} superficially similar to the polar electron-withdrawing groups. However, we believe this result is not a manifestation of a weak intrinsic polar effect but is, in fact, an artifact of the methyl-substituted BCO ring system. There is NMR evidence from other model systems[24c,25,26] which indicates that a bridgehead CH_3 substituent weakly perturbs (reduces) the electron-donating resonance effect of the BCO group ($\sigma_R^\circ = -0.17$)[5,27] by an as yet obscure mechanism. Thus, the unusual effect of CH_3 on the ^{19}F chemical shifts of **2** is compatible with this resonance phenomenon (felt equally by F_a and F_b)[28] plus an additional small upfield effect impinging on the proximate F_b probe. The $C(CH_3)_3$ group, which is also nonpolar ($\sigma_F = 0$),[22,25,26] exhibits a small but distinctly anomalous downfield influence on F_b in c-C_6H_{12} but not in $CDCl_3$ (Table I). Notice also that for CF_3 in c-C_6H_{12} (Table I), SCS (F_b) > SCS (F_a), which runs counter to the general trend ($F_a > F_b$) for the polar groups. However, omitting the data for CF_3, CH_3, and $C(CH_3)_3$ did not improve the precision of the statistical fits of the correlations. These minor discrepancies may have a steric origin since distortions may be engendered in the BCO ring by substituents. Available evidence[29] as well as an examination of appropriate molecular models indicates that the BCO skeletal framework is conformationally mobile (staggered (D_3) ⇄ eclipsed (D_{3h}) ⇄ staggered (D_3)). Thus, if a different conformational equilibrium is struck on replacing H at the bridgehead in **2** by another group then the steric environment of F_b, which is cis and proximate to the BCO group, may be perturbed and this may significantly influence their shifts in an unpredictable way. Obviously, a conformational problem of this kind is not encountered in system **1**.

(21) (a) Bridgehead-substituted bicyclo[2.2.2]octanes have played a pivotal role in physical organic studies as "saturated analogues" of the correspondingly substituted benzene ring systems.[21b,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.

(22) Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2957 and references cited therein.

(23) Three statistical tests of the precision of fit of the correlations are given in Table III (SE, *r*, and *F*). The most significant is the *F* test since it involves division by the number of parameters in the correlation equation. A larger value of *F* implies a better overall correlation or a greater significance of an individual regression coefficient.[7]

(24) (a) σ_F values derived from the ^{19}F SCS of 1-X-4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes[22,24b] were employed for the correlations except those for the acetylene groups (C≡CH and C≡CSiMe$_3$). The σ_F values for C≡CH (0.28 ($CDCl_3$) and 0.27 (CCl_4)), which were accurately determined from the ^{13}C SCS of the *para* carbon center of 4-phenylbicyclo[2.2.2]oct-1-ylethyne,[24c] were available from other studies.[24c] For this study, in order to define the σ_F value (0.24) of C≡CSiMe$_3$ in a similar way, a sample of the appropriate acetylene derivative[24c] was converted to 1-(trimethylsilyl)-2-(4-phenylbicyclo[2.2.2]oct-1-yl)ethyne in a standard way (*n*-butyllithium/Me_3SiCl), mp 105.5–106.5 °C. ^{13}C NMR ($CDCl_3$, relative to Me_4Si): δ 27.85 (C1); 32.66 (C2); 31.88 (C3); 33.89 (C4); 149.37 (ipso); 125.40 (ortho); 128.09 (meta); 125.66 (para); 114.57 (Cα); 83.49 (Cβ); 0.35 (Si(CH_3)$_3$). Anal. Calcd for $C_{19}H_{26}Si$: C, 80.78; H, 9.28. Found: C, 80.51; H, 9.06. (b) These polar field parameters parallel, in the main, another recent compilation reported in: Reynolds, W. F.; Gomes, A.; Maron, A.; MacIntyre, D. W.; Tanin, A.; Hamer, G. K.; Peat, I. R. *Can. J. Chem.* **1983**, *61*, 2376. (c) Adcock, W.; Butt, G.; Kok, G. B.; Marriott, S.; Topsom, R. D. *J. Org. Chem.*, in press.

(25) Adcock, W.; Khor, T. C. *J. Org. Chem.* **1978**, *43*, 1272 and references cited therein.

(26) Adcock, W.; Aldous, G. L.; Kitching, W. *J. Organomet. Chem.* **1980**, *202*, 385.

(27) Broxton, T. J.; Cameron, D. G.; Topsom, R. D.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 2* **1974**, 256.

(28) In support of the resonance explanation it is pertinent to note that although ρ_F (*c*-C_6H_{12}, 2.70)[22] for 1-X-4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes is similar to that for F_a of **2** (ρ_F = 2.81, Table III), the ^{19}F SCS for CH_3 in both systems are significantly different (0.09[25,26] and 0.20 ppm, respectively). The larger ^{19}F SCS for **2** is in line with the more efficient transmission of resonance effects across the ethylenic moiety vs. the benzene ring. Further support for this idea comes from the significantly *positive* ^{13}C SCS (0.38 ppm) observed for the β-carbon of the acetylene moiety (ρ_F = 2.72 (β-carbon; $CDCl_3$)) in 4-substituted bicyclo[2.2.2]octyl acetylenes.[24c]

(29) (a) Bruesch, P.; Gunthard, H. H. *Spectrochim. Acta* **1966**, *22*, 877. (b) Cameron, A. F.; Ferguson, G.; Morris, D. G. *Chem. Commun.* **1968**, 316. *J. Chem. Soc. B* **1968**, 1249. (c) Ermer, O.; Dunitz, J. D. *Helv. Chim. Acta* **1969**, *52*, 1861. (d) Yokozeki, A.; Kuchitsu, K.; Marino, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2017. (e) Anderson, J. E.; Lehn, J. M. *Am. Chem. Soc. Meeting Abstr.* **1967**, 079. (f) Hirota, E. *J. Mol. Spectrosc.* **1971**, *38*, 367.

Table III. Results of Correlation Analyses[a] of ^{19}F Chemical Shifts and ^{19}F-^{19}F Coupling Constants of 1,1-Difluoro-2-(4-substituted-bicyclo[2.2.2]oct-1-yl)ethenes (2) vs. Polar Field Parameters (σ_F Values)

solvent	dependent variables	ρ_F[b]	c[c]	r[d]	r^2	SE[e]	F[f]	n[g]
c-C_6H_{12}	δ_{F_a}	2.81 ±0.10	26.67	0.994	0.988	0.07	872[h]	13
c-C_6H_{12}	δ_{F_b}	2.50 ±0.14	27.25	0.983	0.966	0.10	310[h]	13
c-C_6H_{12}	$^2J_{F-F}$	−4.86 ±0.23	50.67	0.988	0.975	0.16	434[h]	13
$DCCl_3$	δ_{F_a}	3.20 ±0.09	25.67	0.996	0.992	0.06	1300[h]	13
$DCCl_3$	δ_{F_b}	3.20 ±0.11	26.33	0.993	0.986	0.07	780[h]	13
$DCCl_3$	$^2J_{F-F}$	−6.06 ±0.11	52.44	0.998	0.996	0.07	2830[h]	13

[a] General form of correlation equations: δ_F or $J_{F-F} = \rho_F\sigma_F + c$. [b] Polar susceptibility parameter ± standard error. [c] Intercept. [d] Multiple correlation coefficient. [e] Standard error or estimate. [f] F test of variance. Superscripts indicate confidence level of test. [g] Number of data points in correlation. [h] 99.99% CL.

Table IV. Results of DSP Correlative Analysis[a,b] of ^{19}F SCS of 4-Substituted β,β-Difluorostyrenes (1)

solvent	dependent variable	ρ_F	ρ_R	r	F
c-C_6H_{12}	δ_{F_a}	5.75 ±0.26	8.21 ±0.27	0.999	1346
c-C_6H_{12}	δ_{F_b}	4.90 ±0.40	7.92 ±0.41	0.997	490
c-C_6H_{12}	$\Delta\delta_F$	0.85 ±0.16	0.29 ±0.17	0.953	34

[a] General form of correlation equation: SCS = $\rho_F\sigma_F + \rho_R\sigma_R^\circ$. [b] Taken from ref 6.

A comparison of the polar susceptibility parameters (ρ_F values; c-C_6H_{12}) of **2** (Table III; ρ_F = 2.81 and 2.50 for δ_{F_a} and δ_{F_b}, respectively) with those of **1**[6] (listed in Table IV in order to facilitate comparisons) is most revealing. First, it can be seen that the values for **1** are at least twice as large as those for **2**. Bearing in mind that the cross ring distance is actually *less* in bicyclo[2.2.2]octane than in benzene, this result strikingly exemplifies the effectiveness of extended π polarization for transmitting polar substituent influences in fully conjugated systems.[7] Second, although different in magnitude the ρ_F values (c-C_6H_{12}) for both systems display a fairly similar pattern, viz., $\rho_F(F_a) > \rho_F(F_b)$. In line with Reynolds and co-workers[6] interpretation of **1** (wide supra), the internal difference in the ρ_F values of **2** is compatible with a differential direct field contribution to the shifts as clearly indicated by classical electrostatic field calculations (Table V).[30] From the estimated electric field component to $\Delta\delta_F$ of **2**, it can be seen (Table V) that the coefficient (A) for the Buckingham equation is calculated to be (0.79–0.83) × 10^{-11} esu. This value is significantly less than the value ((3.0 ± 0.5) × 10^{-11} esu) estimated by Reynolds et al.[6] from **1**. The discrepancy is clearly in line with the notion (vide supra) that the DSP derived $\rho_F\sigma_F$ term of **1** (δ_{F_a} shifts) embodies not only the electric field emanating from the substituent dipole but also a significant contribution from a secondary field as a result of field-induced π polarization of the benzene ring.

Since the electric field component acting along the C–F_b bond is very small (Table V), it is reasonable to assume that ρ_F for the δ_{F_b} shifts is a manifestation of pure π polarization. Thus, on this basis, the ρ_F value for δ_{F_a} indicates that the polar influence for this probe is due to ca. 89% (2.50/2.81) π polarization ($F_{\pi\leftarrow\pi}$) and 11% (0.31/2.81) direct field effect (F_π). This is very similar to the blend of these polar mechanisms determining the corresponding shifts of **1** in c-C_6H_{12} (85% and 15%, respectively).[6] An examination of the results for **2** in $CDCl_3$ as solvent (Table III) indicates that the ρ_F values are substantially enhanced in this polar medium. This probably can be ascribed to the general phenomenon of polar solvents being better able to promote charge separation owing to π polarization. However, the similar ρ_F values for F_a and F_b in $CDCl_3$ is surprising. Thus, in contrast to the results in c-C_6H_{12}, the direct field contribution to the ^{19}F chemical shifts of **2** is not apparent in the polar environment. We can offer no satisfactory explanation for this observation. However, it is of interest to note that the effects of π polarization on differently oriented side-chain π systems (C≡N and C=O; monitored by ^{13}C chemical shifts) has been investigated in model aromatic substrates[31] for polar solvents and similar results have been observed, namely, that polar effects in polar solvents seem independent of the orientation of the side-chain probes with respect to the C–X dipole.

It is significant to note that the ^{19}F chemical shifts of **2** correlate very well ($r > 0.99$) with the Cβ ^{13}C chemical shifts of 4-substituted-bicyclo[2.2.2]oct-1-yl ethenes.[24c] These excellent correlations further confirm that, in the absence of significant direct field effects, $\Delta q_\pi^F \propto \Delta q_\pi^C$ (see Introduction). A similar situation was noted by Reynolds et al.[6] for the δ_{F_b} shifts of **1** vs. $\delta_{C\beta}$ for the corresponding styrene derivatives. The results of the correlations of the ^{13}C SCS vs. σ_F of the difluoroethylene group (Table VII) have been presented elsewhere in connection with another study.[24c]

The regression parameters listed in Table III also shows that $^2J_{F-F}$ of **2** responds sensitively and systematically to the polar electronic effects of remote substituents. Clearly, this NMR parameter is also governed by π polarization effects.

Finally, we draw attention to a conceptual problem posed by the direct field contribution to aryl and vinyl ^{19}F SCS. It stems from the fact that this influence appears to be due to the minor polarization of the π component of the CF bond and not the dominant polarization of the orthogonal σ electrons.[4-6] Thus, since the π electrons on fluorine are generally considered an integral part of the whole π system, it seems artificial (or arbitrary) to dissect the polar field effect into two independent mechanisms ($F_{\pi\leftarrow\pi}$ and F_π)[8] which perturb the same molecular parameter (Δq_π^F). Reynolds[7] has argued that the dissection is probably justifiable where the C–F π bond order is small (e.g., aryl and vinyl fluorides) but indefensible when it is large (e.g., acyl fluorides). However, we would like to suggest that the conceptual problem vanishes if one is prepared to accept that the C–F π bond can be viewed as being due to two separate and independent types of overlap (n_π–π^* and n_π–σ^*).[33] The $F_{\pi\leftarrow\pi}$ effect can be

(30) (a) In order to minimize reaction field effects and bulk dielectric influences, the calculations are restricted to the data for cyclohexane as solvent. Structural and molecular parameters were employed as previously indicated for substituted-BCO derivatives.[5,22] Precise structural information is not available for the 1,1-difluoroethenyl moiety, thus, two sets of calculations were performed: one based on standard bond lengths and angles and the other employing known structural parameters for the 1,1,2-trifluoroethenyl fragment.[30b] (b) Kaz'mina, N. B.; Lavrukhin, B. D.; Antipin, M. Yu.; Akhmedov, A. I.; Struchkov, Yu. T. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, *No. 4*, 851.

(31) Craik, D. J.; Brownlee, R. T. C. *Prog. Phys. Org. Chem.* **1983**, *14*, 1 and references cited therein.

(32) Bromilow, J.; Brownlee, R. T. C.; Lopez, V. O.; Taft, R. W. *J. Org. Chem.* **1979**, *44*, 4766.

Table V. Electric Field Calculations[a-c] for System 2

X	$10^{-4}E_z$(C–F_a), esu	$10^{-4}E_z$(C–F_b), esu	$10^{-4}\Delta E_z$,[d] esu	$\rho_F\sigma_F$[e]	$10^{11}A$,[f] esu
NO_2	2.31 (2.08)	−0.19 (−0.41)	2.50 (2.49)	0.21	0.84 (0.84)
CN	2.04 (2.02)	−0.11 (−0.26)	2.15 (2.28)	0.18	0.84 (0.79)
F	1.46 (1.44)	−0.18 (−0.32)	1.64 (1.76)	0.12	0.73 (0.68)
Cl	1.42 (1.37)	−0.14 (−0.27)	1.56 (1.64)	0.13	0.83 (0.79)
Br	1.43 (1.41)	−0.13 (−0.27)	1.56 (1.68)	0.14	0.90 (0.83)
					av 0.83 (0.79)

[a] $E_z(C\text{–}F) = \mu(2\cos\theta\cos\phi - \sin\theta\sin\phi)/r^3$ (see ref 5) where E_z(C–F) is the electric field component acting along the C–F bond, μ is the dipole moment of the polar C–X bond, r is the distance between the origin of the dipole and the midpoint of the C–F bond, and θ and ϕ are the angles between the CF and CX bond vectors, respectively. [b] Standard bond lengths and bond angles assumed for $CH{=}CF_2$ moiety. ∠Cl C ∝ Cβ = 128.5° (see ref 6). [c] Calculations in parentheses employ actual bond lengths and bond angles of the $CF{=}CF_2$ moiety (see ref 30b). ∠Cl C ∝ Cβ = 129.5°. [d] $\Delta E_z = E_z(C\text{–}F_a) - E_z(C\text{–}F_b)$. [e] Estimated electric field component to $\Delta\delta_F$. $\rho_F = 0.31$ (see Table III). [f] $\rho_F\sigma_F = \Delta E_z A$ (Buckingham eq).

considered to be a consequence of the former while the latter is manifested by F_π.

Conclusions

The results from the study of system 2 corroborate the conclusions derived from 1 concerning the direct field contribution to ^{19}F SCS for fluorine attached to sp^2 carbons. Since the analysis of the latter system hinged critically on a DSP dissection of the appropriate shifts, it follows that compelling credence is given to the validity of this multiparameter statistical procedure. Hopefully then, this study may assist in dispelling further unnecessary criticism of this practically useful correlative methodology.

Experimental Section

General. Analytical vapor-phase chromatographic (vpc) analyses were performed on a Varian 1740 gas chromatograph using a 10-ft column of 5% SE-30 on 100/120 Chromosorb W. Preparative vpc were carried out on a Varian 920 gas chromatograph. All melting and boiling points are uncorrected. Liquid samples were purified by distillation in a Kugelrohr apparatus (Bucki: GKR-50). Hence, the boiling points quoted pertain to the glass oven temperature of the latter equipment.

Synthesis of Compounds. Except for one compound (2, X = C_2H), which was prepared from the silyl derivative (2, X = C_2SiMe_3) by desilylation with potassium fluoride hydrate in DMF,[34] all the difluoroethylene compounds (2, X = H, NO_2, CN, CF_3, $COOCH_3$, F, Cl, Br, OCH_3, C_6H_5, C_2SiMe_3, CH_3, and $C(CH_3)_3$) were obtained directly by treating the corresponding aldehydes with $LiCF_2P(O)(OC_2H_5)_2$ in THF (see below). The required aldehydes, except for 4-[1-(trimethylsilyl)ethynyl]bicyclo-[2.2.2]octane-1-carbaldehyde (see below), were obtained from the corresponding carboxylic acids by reduction and subsequent oxidation of the appropriate alcohol. General procedures for these conversions are given below. 4-Methoxy-, 4-phenyl-, and 4-fluorobicyclo[2.2.2]octane-1-carboxylic acids were obtained as previously described.[5,35,36]

Bicyclo[2.2.2]octane-1-carboxylic Acid. By use of the procedure of Adcock and Khor,[5,37] a solution of 1-methoxybicyclo[2.2.2]octane (2.0 g, 0.013 mol; prepared in the manner previously indicated[35]) in acetic anhydride (14 mL) was cooled to 0 °C and 48% aqueous hydrobromic acid (2 mL) was added dropwise. After the initial exothermic reaction had subsided, additional hydrobromic acid (12 mL) was quickly added to the reaction mixture which was then heated under reflux for 24 h before being poured onto ice (20 g). After stirring at 0 °C for 2 h, the precipitate was collected by vacuum filtration, washed with aqueous sodium metabisulfite and water, and then air-dried. Sublimation of the crude material afforded a colorless solid (2.15 g, 87%), mp 63–64 °C (lit.[38] mp 66–67 °C).

By use of the improved Koch–Haaf carboxylation procedure of Chapman et al.,[39] the bromo compound (2.10 g, 0.011 mol) was converted to bicyclo[2.2.2]octane-1-carboxylic acid which was obtained as a white solid (1.37 g, 81%) after sublimation, mp 136–139 °C (lit.[40] mp 140.8–141.3 °C). This acid was used in subsequent reactions without further purification.

4-Bromobicyclo[2.2.2]octane-1-carboxylic Acid. This compound was prepared from 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid[35] (4.0 g, 0.0217 mol) by treatment with 48% aqueous hydrobromic acid (refluxed for 3 days) in the manner outlined above for the preparation of 1-bromobicyclo[2.2.2]octane. After a similar workup, a white solid (3.35 g, 66%) was obtained after sublimation. Recrystallization from a hexane/benzene mixture afforded colorless needles, mp 262–265 °C (lit.[40] mp 268–270 °C).

4-Iodobicyclo[2.2.2]octane-1-carboxylic Acid. By use of the procedure of Adcock and Khor,[5,37] a solution of 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid[35] (10.0 g, 0.0543 mol) in acetic anhydride (140 mL) at 0 °C under nitrogen was treated carefully with freshly distilled 55% aqueous hydroiodic acid (140 mL). The resulting deep red reaction mixture was then heated under reflux, in the dark, for 5 days. After cooling, the reaction mixture was poured onto ice (200 g) and, after stirring at 0 °C for 2 h, the resulting precipitate was collected by vacuum filtration, washed with 10% aqueous sodium thiosulfate and water, and then air-dried. Sublimation of the crude material afforded a white solid (12.7 g, 83%). Recrystallization from ethanol gave the iodoacid as colorless needles, mp 282–285 °C (lit.[41] mp 275 °C).

Methyl 4-Iodobicyclo[2.2.2]octane-1-carboxylate. By use of the esterification procedure of Clinton et al.,[42] a solution of the carboxylic acid (6.9 g, 0.025 mol) in absolute methanol (3.5 g) and 1,2-dichloroethane (50 mL) containing concentrated sulfuric acid (0.5 mL) was heated under reflux for 24 h. A standard workup followed by sublimation gave the ester as a white solid (6.7 g, 92%). Recrystallization from hexane gave colorless needles, mp 104.5–106 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 35.57 (C1), 31.80 (C2), 39.80 (C3), 42.92 (C4), 177.20 ($COOCH_3$), 51.77 ($COOCH_3$). Anal. Calcd for $C_{10}H_{15}O_2I$: C, 40.84; H, 5.14. Found: C, 41.06; H, 5.34.

Methyl 4-Chlorobicyclo[2.2.2]octane-1-carboxylate. A solution of methyl 4-iodobicyclo[2.2.2]octane-1-carboxylate (6.6 g, 0.022 mol) and iodine monochloride (4.99 g, 0.030 mol; prepared by passing a known volume of dry chlorine gas into iodine)[43] in carbon tetrachloride (35 mL) was stirred in the dark at room temperature[44] for 48 h. The solution was then diluted with carbon

(33) Kirby, A. J. In "Reactivity and Structure Concepts in Organic Chemistry"; Springer-Verlag: New York, 1983; pp 62–64 and references cited therein.
(34) Corey, E. J.; Ruden, R. A. *Tetrahedron Lett.* **1973**, 1495. Corey, E. J.; Fleet, G. W. J.; Kato, M. *Tetrahedron Lett.* **1973**, 3963.
(35) Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2951.
(36) ^{13}C NMR of 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid ($CDCl_3$, relative to Me_4Si): δ 38.08 (C1), 29.07 (C2), 28.61 (C3), 73.75 (C4), 49.07 (CH_3), 183.23 (COOH).
(37) Khor, T. C. Ph.D. Dissertation, The Flinders University of South Australia, 1978.
(38) Kopecky, J.; Semjkal, J. *Tetrahedron Lett.* **1967**, 1931.
(39) Chapman, N. B.; Sotheeswaran, S.; Toyne, K. J. *J. Org. Chem.* **1970**, *35*, 917.
(40) Roberts, J. D.; Moreland, W. T.; Frazer, W. *J. Am. Chem. Soc.* **1953**, *75*, 637.
(41) Abeywickrema, R. S.; Della, E. W. *Aust. J. Chem.* **1981**, *34*, 2331.
(42) Clinton, R. O.; Laskowski, S. C. *J. Am. Chem. Soc.* **1948**, *70*, 3135.
(43) Woollett, G. H.; Johnson, W. W. In "Organic Syntheses"; Wiley: New York, 1943; Collect Vol. 11, p 343.

tetrachloride (40 mL) and washed with a sodium thiosulfate solution. A standard workup followed by sublimation gave the chloroester as a white solid in almost quantitative yields. Recrystallization from hexane afforded colorless leaflets, mp 65–67 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 37.52 (C1), 30.37 (C2), 35.57 (C3), 66.13 (C4), 176.94 ($COOCH_3$), 51.83 ($COOCH_3$). Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.46. Found: C, 59.37; H, 7.59.

4-Chlorobicyclo[2.2.2]octane-1-carboxylic Acid. Methyl 4-chlorobicyclo[2.2.2]octane-1-carboxylate (4.5 g, 0.022 mol) was treated with aqueous ethanolic potassium hydroxide (1.6 g of 85% pellets; 0.024 mol) in the manner previously described for the corresponding fluoroester.[35] A standard workup followed by sublimation afforded a white solid (3.8 g, 91%). Recrystallization from aqueous methanol gave a white microcrystalline solid, mp 253–256 °C (lit.[45] 268–269 °C); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 37.38 (C1), 30.18 (C2), 35.38 (C3), 65.93 (C4), 183.11 (COOH). An elemental analysis was sought because of the discrepancy between the observed and literature melting points. Anal. Calcd for $C_9H_{13}ClO_2$: C, 57.30; H, 6.95. Found: C, 57.54; H, 7.12.

An attempt to prepare the chloroacid directly by treatment of the methoxyacid with acetyl chloride and tin tetrachloride[46] led to a mixture of the chloro and acetoxy acids which proved difficult to separate. The formation of acetates as byproducts is a problem previously encountered with other bridgehead substitution reactions.[35]

1-Fluoro-4-(trifluoromethyl)bicyclo[2.2.2]octane and 1-Methoxy-4-(trifluoromethyl)bicyclo[2.2.2]octane. A mixture of 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid[35] (3.0 g, 0.016 mol) and excess sulfur tetrafluoride[47] (15 g, 0.14 mol) was heated at 150 °C for 48 h in a sealed stainless-steel autoclave without stirring. After a standard workup,[35] vpc and ^{13}C NMR analyses of the crude reaction product indicated a mixture of 1-fluoro- and 1-methoxy-4-(trifluoromethyl)bicyclo[2.2.2]octane (35% and 65%, respectively) which were separated by careful fractional distillation. The *fluoro trifluoromethyl* compound distilled as a colorless liquid (bp 75–80 °C/36 mm). A sample was further purified by preparative vpc. ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 93.26, $^1J_{CF}$ = 185.55 Hz and $^5J_{CCF_3}$ = 1.46 Hz (C1); 29.74, $^2J_{CF}$ = 20.02 Hz (C2), 25.78, $^3J_{CF}$ = 10.25 Hz and $^3J_{CCF_3}$ = 1.95 Hz (C3); 36.90, $^4J_{CF}$ = 3.66 Hz and $^2J_{CCF3}$ = 26.12 Hz (C4); 128.71, $^5J_{CF}$ = 3.66 Hz and $^1J_{CF_3}$ = 279.55 Hz (CF_3). Anal. Calcd for $C_9H_{12}F_4$: C, 55.10; H, 6.16. Found: C, 54.94; H, 6.16.

The *methoxy trifluoromethyl* compound distilled (90–95 °C/18 mm) as a colorless liquid (1.5 g, 44%). A sample was further purified by preparative vpc to afford a colorless solid, mp 22–22.5 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 73.68, $^5J_{CCF_3}$ = 1.47 Hz (C1); 27.95 (C2); 25.26, $^3J_{CCF_3}$ = 1.95 Hz (C3); 36.77, $^2J_{CCF_3}$ = 26.37 Hz (C4); 128.98, $^1J_{CF_3}$ = 279.29 Hz (CF_3); 49.26 (OCH_3). Anal. Calcd for $C_{10}H_{15}F_3O$: C, 57.68, H, 7.26. Found: C, 57.77; H, 7.39.

A repeat of the reaction with a different cylinder of sulfur tetrafluoride led to a product which was predominantly 1-fluoro-4-(trifluoromethyl)bicyclo[2.2.2]octane (61%, isolated yield) with only trace amounts of 1-methoxy-4-(trifluoromethyl)bicyclo[2.2.2]octane. It should be noted that a previous attempt[22] to prepare the fluoro trifluoromethyl compound from 4-fluorobicyclo[2.2.2]octane-1-carboxylic acid led to a only a small amount of the desired compound heavily contaminated with the acyl fluoride. ^{19}F NMR measurements on a pure sample obtained from this study provided ^{19}F SCS in exact agreement with those previously determined from an impure compound.[22]

1-Chloro-4-(trifluoromethyl)bicyclo[2.2.2]octane. 4-Chlorobicyclo[2.2.2]octane-1-carboxylic acid (2.5 g, 0.013 mol) was treated with sulfur tetrafluoride in the manner described above for the methoxy acid. After a standard workup, vpc and ^{13}C NMR analyses of the crude reaction product indicated a mixture of 1-chloro-4-(trifluoromethyl)bicyclo[2.2.2]octane (~55%) and the acyl fluoride of the chloro acid (~45%). Treatment of the crude reaction product with a 10% aqueous solution of potassium hydroxide (10 mL) and benzene (1 mL) under reflux for 4 h led to the isolation, in the usual manner, of the crude chloro trifluoromethyl derivative. Sublimation afforded a white solid, mp 122–130 °C (0.65 g, 44% yield based on consumed acid). Recrystallization from hexane gave a colorless microcrystalline solid, mp 133–135.5 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 65.08, $^5J_{CCF_3}$ = 1.46 Hz (C1); 34.72 (C2); 26.39, $^3J_{CCF_3}$ = 1.95 Hz (C3); 36.30, $^2J_{CCF_3}$ = 26.37 Hz (C4); 128.65, $^1J_{CF_3}$ = 279.30 Hz (CF_3). Anal. Calcd for $C_9H_{12}ClF_3$: C, 50.84; H, 5.69. Found: C, 51.07; H, 5.97.

1-Iodo-4-(trifluoromethyl)bicyclo[2.2.2]octane. By use of the procedure of Olah et al.,[48] a solution of 1-fluoro-4-(trifluoromethyl)bicyclo[2.2.2]octane (3.0 g, 0.0153 mol) in dry methylene chloride (15 mL) was treated with iodotrimethylsilane (0.24 mL, 0.0168 mol). After stirring in the dark at ambient temperature for 15 h, a vpc analysis indicated that approximately 30% of the fluoro trifluoromethyl compound had been converted to the iodide derivative. A further amount of iodotrimethylsilane (0.24 mL, 0.0168 mol) was added and the reaction mixture was then stirred for 5 days before being quenched with water. A standard workup, followed by sublimation (2.25 g, 48%) and recrystallization from aqueous methanol, gave colorless leaflets of the desired iodo compound, mp 150.5–153 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 40.60, $^5J_{CCF_3}$ = 1.47 Hz (C1); 38.95 (C2); 27.78, $^3J_{CCF_3}$ = 1.95 Hz (C3); 34.39, $^2J_{CCF_3}$ = 26.37 Hz (C4); 128.80, $^1J_{CF_3}$ = 279.30 Hz (CF_3).

A sample of 1-iodo-4-(trifluoromethyl)bicyclo[2.2.2]octane was also prepared from 1-methoxy-4-(trifluoromethyl)bicyclo[2.2.2]-octane (2.0 g, 0.0096 mol) by treatment with aqueous HI in the manner described above for the preparation of 4-iodobicyclo-[2.2.2]octane-1-carboxylic acid. After the reaction mixture had been heated under reflux for 14 days, during which time it was carefully monitored by vpc, it was quenched by pouring onto ice and the precipitate collected by vacuum filtration in the usual way. Sublimation afforded the iodide as a white solid (2.4 g, 82%) which was recrystallized from aqueous methanol to afford colorless leaflets, mp 150.5–153 °C.

The filtrate from the reaction mixture was saturated with sodium chloride and then extracted with methylene chloride (4 × 10 mL). The extracts were combined and dried, and the solvent was evaporated. Sublimation of the residue gave a colorless solid (0.4 g) which was further purified by preparative vpc, mp 118.5–120 °C. ^{13}C NMR ($CDCl_3$, relative to Me_4Si) indicated that this product was 4-(trifluoromethyl)bicyclo[2.2.2]octan-1-ol: δ 68.99 (C1); 32.48 (C2); 25.58, $^3J_{CCF_3}$ = 1.83 Hz (C3); 36.92, $^2J_{CCF_3}$ = 25.63 Hz (C4); 129.02, $^1J_{CF_3}$ = 279.54 Hz (CF_3).

4-(Trifluoromethyl)bicyclo[2.2.2]octane-1-carboxylic Acid. A solution of 1-iodo-4-(trifluoromethyl)bicyclo[2.2.2]octane (2.4 g, 0.0079 mol) in dry diethyl ether (30 mL) was cooled to −100 °C and treated with 12.2 mL of 1.3 M *tert*-butyllithium (0.0158 mol) in pentane. The reaction mixture was allowed to warm up to −80 °C within 5 min and then maintained at this temperature for 10 min while stirring. After cooling rapidly again to −100 °C, the reaction mixture was quenched quickly with excess dry CO_2 gas. After a standard workup, the crude acid was sublimed (1.3 g, 75%) and recrystallized from cyclohexane to afford a colorless microcrystalline solid, mp 213.5–214 °C (lit.[49] mp 214–215.5 °C).

An initial attempt to prepare the acid by lithiation of 1-chloro-4-(trifluoromethyl)bicyclo[2.2.2]octane with lithium metal[50] in pentane followed by carboxylation was not successful.

1-*tert*-Butyl-4-iodobicyclo[2.2.2]octane. By use of the procedure of Adcock and Abeywickrema,[35] 1-*tert*-butyl-4-methoxybicyclo[2.2.2]octane was prepared from 4-methoxybicyclo-[2.2.2]octane-1-carboxylic acid. The former compound was obtained as a colorless oil (bp 80–85 °C/2.0 mm) which solidified on standing. A sample was purified by preparative vpc, mp 36–38.5 °C. The *tert*-butyl-methoxy compound (2.0 g, 0.01 mol) was converted to 1-*tert*-butyl-4-iodobicyclo[2.2.2]octane (2.35 g, 79% yield after sublimation) by treatment with aqueous HI (refluxed for 24 h) in the manner described above for the preparation of 4-iodobicyclo[2.2.2]octane-1-carboxylic acid. Recrystallization of the sublimed iodide from hexane afforded colorless

(44) Kauer, J. C. *Prep., Div. Pet. Chem., Am. Chem. Soc.* **1970**, *158* B14–B18.
(45) Stock, L. M.; Holtz, H. D. *J. Am. Chem. Soc.* **1964**, *86*, 5183.
(46) Suzuki, Z.; Morita, K. *J. Org. Chem.* **1967**, *32*, 31.
(47) Boswell, G. A.; Ripka, W. C.; Scribner, R. M.; Tullock, C. W. *Org. React.* **1974**, *21*, 1.
(48) Olah, G. A.; Narang, S. C.; Field, L. D. *J. Org. Chem.* **1981**, *46*, 3727.
(49) Baker, F. W.; Stock, L. M. *J. Am. Chem. Soc.* **1967**, *32*, 3344.
(50) Molle, G.; Bauer, P.; Dubois, J. E. *J. Org. Chem.* **1983**, *48*, 2975.

plates, mp 121–123.5 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si): δ 32.40 (C1), 29.45 (C2), 41.00 (C3), 47.09 (C4), 34.56 ($C(CH_3)_3$), 25.05 ($C(CH_3)_3$). Anal. Calcd for $C_{12}H_{21}I$: C, 49.33; H, 7.24. Found: C, 49.45; H, 7.27.

4-*tert*-Butylbicyclo[2.2.2]octane-1-carboxylic Acid. 1-*tert*-Butyl-4-iodobicyclo[2.2.2]octane (2.0 g, 0.00684 mol) was lithiated and carboxylated in the manner outlined above for the preparation of 4-(trifluoromethyl)bicyclo[2.2.2]octane-1-carboxylic acid. A colorless solid (1.27 g, 88%) was obtained after sublimation which was recrystallized from ethanol to afford plates, mp 270–271.5 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si): δ 38.03 (C1), 28.39 (C2), 24.81 (C3), 35.43 (C4), 34.16 ($C(CH_3)_3$), 25.27 ($C(CH_3)$). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.06; H, 10.60.

4-Methylbicyclo[2.2.2]octane-1-carboxylic Acid. 1-Iodo-4-methylbicyclo[2.2.2]octane (mp 75–76 °C; lit.[51] mp 75.5–76.5 °C), prepared from 1-methoxy-4-methylbicyclo[2.2.2]octane[46,52] by treatment with aqueous HI (refluxed for 24 h) in the manner described above for the preparation of 4-iodobicyclo[2.2.2]octane-1-carboxylic acid, was lithiated and carboxylated in the manner outlined above for 4-(trifluoromethyl)bicyclo[2.2.2]octane-1-carboxylic acid. The methyl acid was sublimed and recrystallized from methanol to afford a microcrystalline solid, mp 186–187 °C (lit.[45] mp 187–188 °C).

4-Nitrobicyclo[2.2.2]octane-1-carboxylic Acid. By use of the procedure of Applequist et al.,[53] 4-phenylbicyclo[2.2.2]octane-1-amine[5,37] (1.0 g, 0.000497 mol) was treated with *m*-chloroperbenzoic acid (4.0 g of 85% activity; 0.0193 mol) to afford 1-nitro-4-phenylbicyclo[2.2.2]octane as a white solid (1.1 g, 96%) after sublimation. Recrystallization from aqueous ethanol gave a microcrystalline solid, mp 103–105.5 °C (lit.[5,37] 105.5–107 °C). By use of the procedure of Carlsen et al.,[54] sodium periodate (10 g, 0.047 mol) and water (12 mol) were added to a solution of 1-nitro-4-phenylbicyclo[2.2.2]octane (1.0 g, 0.00432 mol) in acetonitrile (8 mL) and carbon tetrachloride (8 mL). Ruthenium trichloride hydrate (20 mg) was then added to the vigorously stirred reaction mixture. After stirring for 4 days at room temperature, the reaction mixture was worked up in a standard way. Sublimation of the residue at 120 °C/0.1 mm and then at 170° C/0.1 mm afforded unreacted starting material (275 mg) and 4-nitrobicyclo[2.2.2]octane-1-carboxylic acid (455 mg, 73% yield based on consumed starting material), respectively. Recrystallization of the acid from ethanol gave a colorless microcrystalline solid, mp 241–243 °C (lit.[45] mp 251–253 °C); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 38.57, 28.39 (C2), 29.53 (C3), 84.08 (C4), 182.41 (COOH).

4-Cyanobicyclo[2.2.2]octane-1-carboxylic Acid. By use of the procedures outlined by Adcock et al.,[35] 4-phenylbicyclo[2.2.2]octane-1-carboxylic acid (3.0 g, 0.013 mol)[5,37] was converted via the amide (2.65 g, 0.0116 mol) to 1-cyano-4-phenylbicyclo[2.2.2]octane, which was obtained as a white solid after sublimation (2.35 g, 86.5%), mp 140–144 °C (lit.[5,37] 144.4–145 °C). The nitrile was oxidized to 4-cyanobicyclo[2.2.2]octane-1-carboxylic (80% yield based on consumed starting material) in the same manner indicated above for the corresponding nitro compound. The cyano acid sublimed as a white solid, mp >280 °C (lit.[40] 298–300 °C); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 37.29 (C1), 26.87 (C2), 29.01 (C3), 27.22 (C4), 124.33 (CN), 182.68 (COOH).

4-Carbomethoxybicyclo[2.2.2]octane-1-carboxylic Acid. By use of the esterification procedure of Clinton et al.,[42] methyl 4-phenylbicyclo[2.2.2]octane-1-carboxylate (mp 80–82 °C) was obtained almost quantitatively from 4-phenylbicyclo[2.2.2]octane-1-carboxylic acid.[5,37] The ester was oxidized to 4-carbomethoxybicyclo[2.2.2]octane-1-carboxylic acid (78% yield based on consumed starting material) in the same manner indicated above for the nitro acid. Sublimation afforded a white solid which was recrystallized from methanol to give colorless leaflets, mp 181–183.5 °C (lit.[39] mp 180–182 °C).

General Synthetic Procedures for the Preparation of 4-Substituted Bicyclo[2.2.2]octane-1-carbaldehydes from 4-Substituted Bicyclo[2.2.2]octane-1-carboxylic Acids. By use of the procedure of Brown et al.,[55] a solution of the carboxylic acid (ca. 0.01 mol) in dry tetrahydrofuran (10 mL) was treated dropwise with borane-methyl sulfide (ca. 0.011–0.012 mol), and the resulting mixture was allowed to stir overnight under a nitrogen atmosphere. Methanol (10–11 mL) was then carefully added to the reaction mixture and the resulting solution was then heated under reflux for 1–5 h. The residue obtained after removal of the solvent under vacuum was either distilled or sublimed to yield the alcohol.

Finely powdered pyridinium chlorochromate[56] (0.0153 mol) was added to a well-stirred solution of the alcohol (0.00764 mol) in dry methylene chloride at room temperature. The dark brown reaction mixture was left to stir for 15 h. Ether (20 mL) was then added and the mixture was filtered through a column of Florisil. The column was triturated with ether (3 × 20 mL). The extracts were combined and dried, and the solvent was evaporated. The residue was either distilled or sublimed to provide the desired aldehyde.

Physical properties and ^1H and ^{13}C NMR data for the alcohols and aldehydes are available from the authors.

4-[1-(Trimethylsilyl)ethynyl]bicyclo[2.2.2]octane-1-carbaldehyde. By use of the procedure of Villieras et al.,[57] 4-iodobicyclo[2.2.2]octane-1-carbaldehyde (2.0 g, 0.00757 mol) was treated with $LiCCl_2P(O)(OC_2H_5)_2$ in THF at −100 °C to provide, after workup, 1,1-dichloro-2-(4-iodobicyclo[2.2.2]oct-1-yl)ethene. Sublimation afforded a white solid (2.2 g, 88%) which was recrystallized from pentane, mp 91–92.5 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 30.97 (C1), 33.61 (C2), 40.41 (C3), 43.82 (C4), 136.45 ($CH{=}CCl_2$), 119.81 ($CH{=}CCl_2$). Anal. Calcd for $C_{10}H_{13}Cl_2I$: C, 36.28; H, 3.96. Found: C, 36.04; H, 4.10.

By use of the procedure of Villieras et al.,[57] the 1,1-dichloroethene (3.4 g, 0.0103 mol) in ether (10 mL) and THF (10 mL) at −100 °C was treated with *n*-butyllithium in hexane (14.1 mL of 1.6 M solution; 0.0226 mol) and then with chlorotrimethylsilane (15 mL; 0.124 mol) at 0 °C. After heating the reaction mixture under reflux for 2 h, a standard workup followed by sublimation afforded 1-(trimethylsilyl)-2-(4-iodobicyclo[2.2.2]oct-1-yl)ethyne as a cream solid (3.05 g, 87%). Recrystallization from methanol gave colorless plates, mp 147–149 °C. ^1H NMR ($CDCl_3$): δ 0.08 (9 H, s, $Si(CH_3)_3$), 1.70–2.70 (12 H, m, CH_2CH_2).

A solution of 1-(trimethylsilyl)-2-(4-iodobicyclo[2.2.2]oct-1-yl)ethyne (2.9 g, 0.000847 mol) in dry ether (60 mL) at −100 °C was treated dropwise with *tert*-butyllithium (0.0017 mol; 13.1 mL of a 1.3 M pentane solution). The reaction mixture was allowed to warm up to −80 °C over 10 min and then maintained at that temperature for 5 min. Following the procedure of Olah et al.,[58] a solution of *N*-formylpiperidine (13.5 g, 0.12 mol) in ether (8 mL) was then added dropwise to the reaction mixture at −100 °C. After being allowed to warm to room temperature, the reaction mixture was worked up in the described manner.[58] Sublimation afforded 4-[1-(trimethylsilyl)ethynyl]bicyclo[2.2.2]octane-1-carbaldehyde[59] as a white solid (1.8 g, 89%), mp 48–51.5 °C; ^1H NMR ($CDCl_3$): δ 0.05 (9 H, s, $Si(CH_3)_3$), 1.37–2.00 (12 H, m, CH_2CH_2). The compound was homogeneous to vpc. An elemental analysis was not sought.

General Synthetic Procedure for the Difluoromethylenation of 4-Substituted Bicyclo[2.2.2]octane-1-carbaldehydes. A solution of the appropriate aldehyde (1.78 mmol) in tetrahydrofuran (1 mL) was added over 5 min to a well-stirred THF solution of (diethylphosphinyl)difluoromethyllithium[60] (2.16

(51) Dorn, H. C. Ph.D. Dissertation, University of California, 1974.
(52) (a) Prepared in connection with other studies.[52b] (b) Adcock, W.; Abeywickrema, A. N.; Kok, G. B.; Iyer, V. S. *Org. Magn. Reson.*, submitted for publication.
(53) Applequist, D. E.; Renken, T. L.; Wheeler, J. W. *J. Org. Chem.* **1982**, *47*, 4985.
(54) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(55) Brown, H. C.; Ras, C. G.; Kulkarui, S. U. *Synthesis* **1979**, 704.
(56) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *2647*.
(57) Villieras, J.; Perriot, P.; Normant, J. F. *Synthesis* **1975**, *458*.
(58) Olah, G. A.; Arranaghi, M. *Angew. Chem., Int. Ed. Engl.* **1980**, *20*, 878.
(59) In connection with another study,[24c] 4-[1-(trimethylsilyl)-ethynyl]bicyclo[2.2.2]octane-1-carbaldehyde was also employed for the synthesis of 4-cyanobicyclo[2.2.2]oct-1-yl acetylene. For the same investigation,[24c] all the other aldehydes (except X = I) prepared in this study were employed for the synthesis of the corresponding 4-substituted bicyclo[2.2.2]oct-1-yl acetylenes mainly via the 1,1-dichloroethene derivatives.[57]

Table VI. Physical and Analytical Properties of 1,1-Difluoro-2-(4-substituted-bicyclo[2.2.2]oct-1-yl)ethenes

X	bp or mp, °C	^{1}H NMR Data ($CDCl_3$), δ (Me_4Si)
H	75–80 (760 mm)	1.58 (s, 13 H, CH_2CH_2 and CH), 3.98 (q, 1 H, $CH{=}CF_2$)
NO_2	75–80 (6.2 mm)	1.63–2.43 (m, 12 H, CH_2CH_2), 4.05 (q, 1 H, $CH{=}CF_2$)
CN	120–125 (80 mm)	1.07–2.50 (m, 12 H, CH_2CH_2), 3.93 (q, 1 H, $CH{=}CF_2$)
CF_3[a]	90–100 (40 mm)	1.73 (br s, 12 H, CH_2CH_2), 4.02 (q, 1 H, $CH{=}CF_2$)
F	110–115 (760 mm)	1.83 (d, 12 H, CH_2CH_2), 4.02 (q, 1 H, $CH{=}CF_2$)
Cl	100–105 (175 mm)	1.57–2.33 (m, 12 H, CH_2CH_2), 3.97 (q, 1 H, $CH{=}CF_2$)
Br	90–95 (20 mm) mp 41–43	1.60–2.50 (m, 12 H, CH_2CH_2), 3.97 (q, 1 H, $CH{=}CF_2$)
OCH_3	85–90 (19 mm)	1.73 (s, 12 H, CH_2CH_2), 3.20 (s, 3 H, OCH_3), 3.83 (q, 1 H, $CH{=}CF_2$)
C_6H_5	100–105 (0.7 mm) mp 32–34.5	1.82 (br s, 12 H, CH_2CH_2), 4.08 (q, 1 H, $CH{=}CF_2$), 7.37 (br s, 5 H, aromatic)
C_2H	75–80 (8 mm)	1.71 (m, 12 H, CH_2CH_2), 2.08 (s, 1 H, C≡CH), 3.95 (q, 1 H, $CH{=}CF_2$)
$C_2Si(CH_3)_3$	80–90 (2.7 mm)	0.08 (s, 9 H, $Si(CH_3)_3$), 1.72 (br s, 12 H, CH_2CH_2), 3.97 (q, 1 H, $CH{=}CF_2$)
CH_3[a]	90–95 (760 mm)	0.78 (s, 3 H, CH_3), 1.17–1.83 (m, 12 H, CH_2CH_2), 4.00 (q, 1 H, $CH{=}CF_2$)
$C(CH_3)_3$	100–105 (100 mm)	0.78 (s, 9 H, $C(CH_3)_3$, 1.52 (br s, 12 H, CH_2CH_2), 3.97 (q, 1 H, $CH{=}CF_2$)

[a] Homogeneous with respect to vpc (SE-30 and OV-17). Elemental analyses not sought. All other compounds in this table gave satisfactory C and H analyses.

Table VII. ^{13}C Chemical Shifts[a,b] of 1,1-Difluoro-2-(4-substituted-bicyclo[2.2.2]oct-1-yl)ethenes (2)

X	chemical shift, ppm						
	C1	C2	C3	C4	Cα	Cβ	others
H	28.57	31.51	26.11	23.77	87.51	155.31	
NO_2	29.19	31.62	30.11	84.00	84.98	155.45	
CN	27.62	29.84	29.28	26.66	85.51	155.07	124.33 (CN)
CF_3[c]	28.85	30.17	24.27 (1.95)	36.83	86.03	155.40	129.06 (CF_3) (279.29)
$COOCH_3$	27.26	30.95	28.27	38.21	86.44	155.28	177.86 (CO) 51.64 ($COOCH_3$)
F[d]	28.78	32.73 (9.55)	31.05 (19.05)	93.49	85.30	155.33	
Cl	28.08	33.53	36.15	66.53	85.59	155.33	
Br	27.47	34.37	37.54	62.83	85.82	155.30	
OCH_3	28.74	32.47	29.32	72.94	85.95	155.18	49.04 (OCH_3)
C_6H_5[e]	29.27	32.08	32.27	34.14	86.89	155.29	149.53 (i), 125.45 (o), 128.10 (m), 125.64 (p)
C_2H	28.06	30.90	31.88	26.10	86.39	155.07	91.15 (*C*≡CH), 67.86 (C≡*C*H)
$C_2Si(CH_3)_3$	28.25	31.14	32.10	27.07	86.63	155.23	114.07 (*C*≡CSi), 83.58 (C≡*C*Si), 0.26 (CH_3)
CH_3	28.95	32.04	33.25	25.63	87.05	155.17	28.12 (CH_3)
$C(CH_3)_3$	28.35	31.88	25.43[f]	34.81	87.24	155.23	25.24[f] (CH_3), 34.18 ($C(CH_3)_3$)

[a] Chemical shifts for $CDCl_3$ solution relative to Me_4Si. Accurate to ±0.03 ppm. Low-field shifts are positive. [b] The carbon numbering system is as shown on the structural formula **2** in the Introduction. [c] ^{13}C–^{19}F coupling constants (in hertz) due to CF_3 are given in parentheses. [d] ^{13}C–^{19}F coupling constants (in hertz) due to fluorine substituent are given in parentheses. [e] The aromatic carbons are designated ipso (i), ortho (o), meta (m), and para (p) with respect to the bicyclooctyl group. [f] Assignments may be transposed.

mmol) at −100 °C. After addition was complete, the temperature of the mixture was allowed to rise slowly to room temperature. It was then heated under reflux for 24 h. Upon cooling, the mixture was hydrolyzed with dilute hydrochloric acid (5 mL) and then extracted with fluorotrichloromethane (3 × 20 mL). The combined organic extracts were washed with water (3 × 10 mL), saturated sodium bicarbonate (10 mL), and again with water (10 mL) and dried over sodium sulfate. The solvent was carefully removed by distillation through a short column packed with glass helices, and the resulting residue was then distilled in a Kugelrohr apparatus to provide **2** as a colorless oil. Yields (not optimized) ranged between 30% and 50%. Most of the compounds were then subsequently purified by preparative vpc. The ester (**2**, X = $COOCH_3$) was obtained as a colorless oil which was found to be contaminated with an unidentifiable derivative of **2**. Limited amounts of the mixture precluded attempts at purification. However, the dominant presence of the ester (**2**, X = $COOCH_3$) in the mixture was unequivocally established by ^{13}C NMR (see Table VII).

Physical properties, elemental analyses, and ^{1}H NMR data for the difluoroethylenes are presented in Table VI. The ^{13}C NMR data are listed in Table VII.

Spectra. ^{1}H NMR spectra were measured with a Varian EM-360 (60 MHz). 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 spectra were obtained on $CDCl_3$ solutions (ca. 0.5 M) in 5-mm tubes with Me_4Si as an internal reference (spectral width 4000/5000 Hz, 18K/8K data point, minimum digital resolution of 0.5/0.6 Hz). Assignments for the various compounds followed unambiguously from chemical shift, intensity, and substituent effects[5,35] condiserations. The ^{19}F–^{13}C splittings of Cβ, Cα, C1, and C2 due to the geminal fluorines in the difluoroethylene compounds (**2**), which were helpful in confirming assignments for these compounds, were not analyzed by ABX analysis to provide ^{19}F–^{13}C coupling constants.

The ^{19}F NMR spectra were obtained under proton-decoupled as well as coupled conditions in the pulse Fourier transform mode with a JEOL FX-90Q spectrometer operating at 84.26 MHz. Spectral widths of 3000 and 1000 Hz, respectively, were used, and the data were collected into 16K/8K data points, giving a digital resolution of 0.36 and 0.12 Hz, respectively. Each sample consisted of the compound (**2**; ca. 1 mg) and 1,1,2,2-tetrachloro-3,3,4,4-tetrafluorocyclobutane (TCTFCB; <1 mg) in the appropriate solvent.

Registry No. **2** (X = H), 94993-85-8; **2** (X = NO_2), 94993-86-9; **2** (X = CN), 94993-87-0; **2** (X = CF_3), 94993-88-1; **2** (X = $COOCH_3$), 94993-89-2; **2** (X = F), 94993-90-5; **2** (X = Cl), 94993-91-6; **2** (X = Br), 94993-92-7; **2** (X = OCH_3), 94993-93-8; **2** (X = C_6H_5), 94993-94-9; **2** (X = CH_3), 94993-95-0; **2** (X = $C(CH_3)_3$), 94993-96-1; **2** (X = C_2H), 94993-97-2; **2** (X = $C_2Si(CH_3)_3$), 94993-98-3; $LiCF_2P(O)(OC_2H_5)_2$, 94993-99-4; $LiCCl_2P(O)(OC_2H_5)_2$, 51346-77-1; 4-iodobicyclo[2.2.2]octane-1-carboxylic acid, 80745-61-5; methyl 4-iodobicyclo[2.2.2]octane-1-carboxylate, 94994-00-0; methyl 4-chlorobicyclo[2.2.2]octane-1-carboxylate, 94994-01-1; 1-fluoro-4-(trifluromethyl)bicyclo[2.2.2]octane, 78385-81-6; 1-methoxy-4-(trifluromethyl)bicyclo[2.2.2]octane, 94994-02-2; 1-chloro-4-(trifluoromethyl)bicyclo[2.2.2]octane, 94994-03-3; 1-iodo-4-(trifluromethyl)bicyclo[2.2.2]octane, 94994-04-4; 4-(trifluoromethyl)bicyclo[2.2.2]octane-1-carboxylic acid, 14234-09-4; 1-*tert*-butyl-4-iodobicyclo[2.2.2]octane, 94994-05-5; 4-(*tert*-butyl)bicyclo[2.2.2]octane-1-carboxylic acid, 5605-13-0; 4-carbomethoxybicyclo[2.2.2]octane-1-carboxylic acid, 18720-35-9;

(60) Obayashi, M.; Ito, E.; Matsui, K.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323.

1-bromobicyclo[2.2.2]octane, 7697-09-8; 4-acetoxybicyclo[2.2.2]-octane-1-carboxylic acid, 72963-86-1; 4-chlorobicyclo[2.2.2]octane-1-carbonyl fluoride, 94994-06-6; 4-(trifluromethyl)bicyclo-[2.2.2]octan-1-ol, 94994-07-7; 1-(*tert*-butyl)-4-methoxybicyclo-[2.2.2]octane, 81687-94-7; 1-iodo-4-methylbicyclo[2.2.2]octane, 55044-63-8; 1-methoxy-4-methylbicyclo[2.2.2]octane, 6555-95-9; 4-phenylbicyclo[2.2.2]octane-1-amine, 10206-89-0; 4-phenylbicyclo[2.2.2]octane-1-carboxylic acid, 953-69-5; 4-phenylbicyclo[2.2.2]octane-1-carboxamine, 23744-33-4; 1-cyano-4-phenylbicyclo[2.2.2]octane, 950-22-1; 4-[1-(trimethylsilyl)-ethynyl]bicyclo[2.2.2]octane-1-carboxaldehyde, 94994-08-8; 4-iodobicyclo[2.2.2]octane-1-carboxaldehyde, 94994-09-9; 1,1-dichloro-2-(4-iodobicyclo[2.2.2]oct-1-yl)ethene, 94994-10-2; 1-(trimethylsilyl)-2-(4-iodobicyclo[2.2.2]oct-1-yl)ethyne, 94994-11-3; 4-fluorobicyclo[2.2.2]octane-1-carboxylic acid, 78385-84-9; bicyclo[2.2.2]octane-1-methanol, 2574-42-7; 4-nitrobicyclo[2.2.2]octane-1-methanol, 94994-12-4; 4-cyanobicyclo[2.2.2]octane-1-methanol, 94994-13-5; 4-(trifluoromethyl)bicyclo[2.2.2]octane-1-methanol, 94994-14-6; methyl 4-(hydroxymethyl)bicyclo[2.2.2]-octane-1-carboxylate, 94994-15-7; 4-fluorobicyclo[2.2.2]octane-1-methanol, 94994-16-8; 4-chlorobicyclo[2.2.2]octane-1-methanol, 94994-17-9; 4-bromobicyclo[2.2.2]octane-1-methanol, 94994-18-0; 4-methoxybicyclo[2.2.2]octane-1-methanol, 94994-19-1; 4-phenylbicyclo[2.2.2]octane-1-methanol, 23760-80-7; 4-methylbicyclo[2.2.2]octane-1-methanol, 28305-83-1; 4-*tert*-butylbicyclo[2.2.2]octane-1-methanol, 94994-20-4; 4-iodobicyclo-[2.2.2]octane-1-methanol, 94994-21-5; bicyclo[2.2.2]octane-1-carboxaldehyde, 2064-05-3; 4-nitrobicyclo[2.2.2]octane-1-carboxaldehyde, 94994-22-6; 4-cyanobicyclo[2.2.2]octane-1-carboxaldehyde, 94994-23-7; 4-(trifluromethyl)bicyclo[2.2.2]octane-1-carboxaldehyde, 94994-24-8; 4-carbomethoxybicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-25-9; 4-fluorobicyclo-[2.2.2]octane-1-carboxaldehyde, 78385-82-7; 4-chlorobicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-26-0; 4-bromobicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-27-1; 4-methoxybicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-28-2; 4-phenylbicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-29-3; 4-methylbicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-30-6; 4-*tert*-butylbicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-31-7; 4-ethynylbicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-32-8; 4-ethynylbicyclo-[2.2.2]octane-1-methanol, 94994-33-9; 4-ethynylbicyclo[2.2.2]octane-1-carboxylic acid, 94994-34-0; bicyclo[2.2.2]octane-1-carboxylic acid, 699-55-8; 4-bromobicyclo[2.2.2]octane-1-carboxylic acid, 1989-50-0; 4-chlorobicyclo[2.2.2]octane-1-carboxylic acid, 1007-73-4; 4-methylbicyclo[2.2.2]octane-1-carboxylic acid, 702-67-0; 4-nitrobicyclo[2.2.2]octane-1-carboxylic acid, 775-65-5; 4-cyanobicyclo[2.2.2]octane-1-carboxylic acid, 15941-09-0; 1-methoxybicyclo[2.2.2]octane, 7697-14-5; 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid, 773-34-2; methanol, 67-56-1; iodine monochloride, 7790-99-0; chlorine, 7782-50-5; iodine, 7553-56-2; iodotrimethylsilane, 16029-98-4; 1-nitro-4-phenylbicyclo[2.2.2]octane, 64852-68-2; methyl 4-phenylbicyclo[2.2.2]octane-1-carboxylate, 23062-52-4; chlorotrimethylsilane, 75-77-4; *N*-formylpiperidine, 2591-86-8; carbon monoxide, 630-08-0.

Stereoselective Synthesis of an Analogue of Podophyllotoxin by an Intramolecular Diels–Alder Reaction

Michael E. Jung,*[1] Patrick Yuk-Sun Lam, Muzzamil M. Mansuri, and Laurine M. Speltz

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

Received May 4, 1984

The dihydrobenzocyclobutene **90** having a 4-hydroxycrotonate unit attached via an ester linkage as an internal dienophile can be cyclized to a 3:1 mixture of the trans lactone **92** (an analogue of podophyllotoxin, **1**) and the cis lactone **93**. This stereoselective reaction proceeds via the intermediacy of the *o*-quinodimethane **91** which cyclizes from the endo transition state **91n** in preference to the exo-one **91x**, presumably because of stabilization of the former by secondary orbital overlap. This result provides evidence that a proposed general route to the synthesis of podophyllotoxin, **1**, and its analogues via the internal cycloaddition of the *o*-quinodimethane **8** to **9n** may prove successful. Several possible approaches to the synthesis of the *trans*-2-aryldihydrobenzocyclobutenol **4** are described. The benzyne **11** was prepared and underwent [2 + 4] but no [2 + 2] cycloadditions. Although the 2-bromobenzocyclobutenone **23** could be synthesized in an efficient manner, it proved impossible to convert it into **4** by means of the aryl organometallic reagents **22ab**. The bromo epoxide **52** was prepared and subjected to metal–halogen exchange and Lewis acid catalyzed epoxide rearrangement in an attempt to prepare **4**. The aldehyde **56** was obtained in this reaction, clearly indicating that the desired intermediate **54** had been formed but could not be trapped under these conditions. Two ring contraction routes to **4** are also described, both beginning with the 1-indanone **74** prepared in good yield from piperonal **14**. The diol monomesylate **78**, prepared from **74**, suffered base-catalyzed E2 elimination rather than the desired rearrangement to **80**. The diazo ketone **83** underwent Wolff rearrangement to give the desired ester **84**, but only in 7% yield. Two interesting transformations were observed in these ring contraction schemes, namely the formation of the oxathiole dioxide **77** on mesylation of the ketol **75** and the preparation of the diazirene **86** on photolysis of the diazo ketone **83** at long wavelengths. The ester **84** was then saponified to the acid **87** which was coupled with methyl 4-hydroxycrotonate, **5**, to give **90**. The assignment of the structures of the products of thermolysis of **90** was based on high field ^{1}H NMR and analogy to the spectra of similar compounds in the literature.

Introduction

In the early 1970's several derivatives of podophyllotoxin **1**, the active principle isolated from podophyllin,[2] began to show great promise as cancer chemotherapeutic agents.[3] The results of extensive phase I clinical testing produced two drugs, designated VM-26 (for 4′-demethyl-1-*O*-[4,6-*O*-(2-thienylmethylene)-β-D-glucopyroanosyl]epipodophyllotoxin, NSC-122819) (**2**) and VP-16-213 (for 4′-demethyl-1-*O*-[4,6-*O*-(ethylidene)-β-D-glucopyranosyl]epipodophyllotoxin, NSC 141540) (**3**), which showed acceptable toxicity levels[4] and showed useful therapeutic

(1) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983; Fellow of the Alfred P. Sloan Foundation, 1979–1981.

(2) Hartwell, J.; Shear, M. *Cancer Res.* **1947**, *7*, 716.

(3) (a) Vaitkevicius, R. K.; Reed, M. L. *Cancer Chemother. Rep.* **1966**, *50*, 565. (b) For a recent review of podophyllotoxin **1**, see: Jardin, I. *Med. Chem. (Wiley)* **1980**, *16*, 319.

(4) Muggia, F. M.; Selawry, O. S.; Hansen, F. H. H. *Cancer Chemother. Rep.* **1971**, *55*, 575.

0022-3263/85/1950-1087$01.50/0