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THE 1,3-DIPOLAR CYCLOADDITIONS OF 2,2-DIFLUOROMETHYLENECYCLOPROPANE WITH DIAZOALKANES AND THE DEAZETATION OF THE PYRAZOLINE ADDUCTS.

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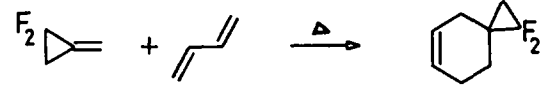
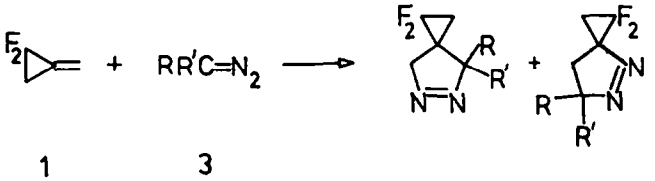
Abstract: 2,2-Difluoromethylenecyclopropane was found to be a reactive dipolarophile in its reactions with three diazoalkanes. The thermal deazetations of the resultant pyrazoline adducts, while feasible, were not able to be carried out efficiently.

Earlier studies in this laboratory demonstrated that 2,2-difluoromethylenecyclopropane(**1**) is an excellent dienophile.[1] It was thus considered likely that **1** would also act as a good dipolaro-



1 **2**

phile in 1,3-dipolar cycloadditions with diazoalkanes. Adducts of the type **4** were of considerable

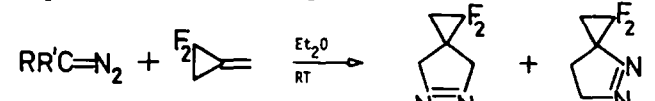


1 **3** **4** **5**

interest to us as potential sources of diradicals through thermal and/or photochemical deazetations.

CYCLOADDITIONS - RESULTS AND DISCUSSION

Indeed, additions of diazomethane, diphenyldiazomethane, and vinyldiazomethane to **1** were virtually immediate and quantitative at room temperature.



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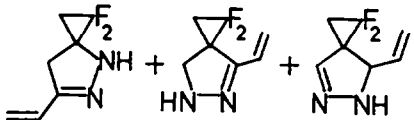
3a: R=R'=H **4a** **5a**

3b: R=R'= Ph **5b**

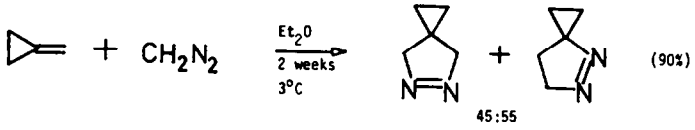
3c R=H, R'= CH=CH$_2$



6 7 8

64.7 : 17.6 : 17.6

1, as expected, proved to be substantially more reactive than its non-fluorine-substituted analog, methylenecyclopropane(9), which apparently required two weeks to complete its reaction with diazomethane.[2] (Note the small difference in regiochemistry observed for 1 and 9 in this reaction.)

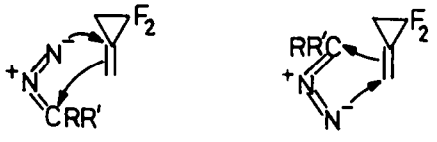


9 10 11

45:55

The enhanced reactivity of 1 is likely due to the expected lowering of the LUMO π^* energy of 1 relative to 9 as a result of the former's allylic fluorine substituents.

The increase in regiochemical preference for regioisomer 5 versus 4 (50% 5 for diazomethane, 65% 5 for vinyldiazomethane and 100% 5 for diphenyldiazomethane) can likely be attributed to

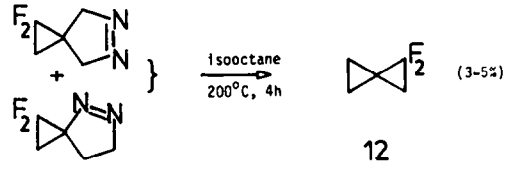


less hindered more hindered

steric considerations wherein the CH_2 end of 1's double bond must be considered the less sterically demanding. A similar variation in regiochemistry due to steric effects was observed for the related addition of diazoalkanes to difluoroallene.[3]

DEAZETATIONS - RESULTS AND DISCUSSION

It was hoped that deazetations of the pyrazoline adducts, particularly those of structure 5, would prove amenable to efficient thermal deazetation so that mechanistic insight might be obtained related to (a) the simultaneity of the two C-N bond cleavages, and (b) the mechanism of methylene cyclobutane product-formation, if any, during deazetation. Unfortunately, other than for the deazetation of **5b**, the thermolyses were <u>not</u> clean, nor did they result in discernable methylene-cyclobutane formation.



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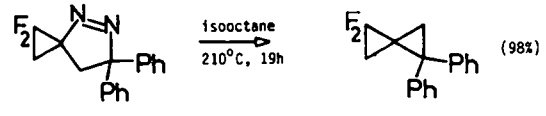
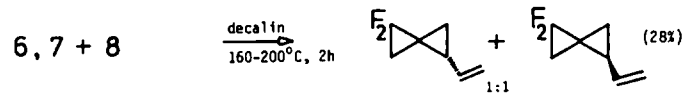


5b 13

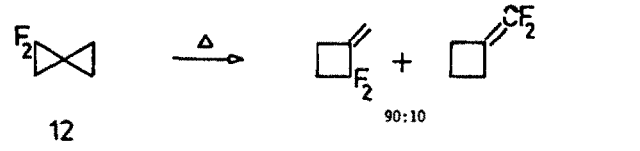


14 15

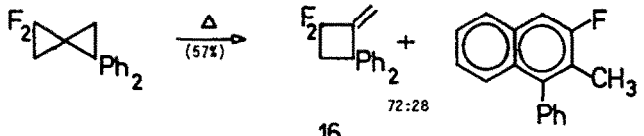
The considerable difference in efficiency of deazetation of the fluorinated pyrazolines **4a**, **5a**, **6**, **7**, and **8** as compared to non-fluorine-substituted analogues **10** and **11** (which deazetated to hydrocarbon products in 97% and 86% yields, respectively) can likely be attributed to the decrease in non-deazetative thermal stability of the fluorine-substituted pyrazolines, which should be more prone to Δ^1 to Δ^2 pyrazoline conversion and subsequent destructive HF-eliminative processes. In the case of **5b** which cannot undergo such an H-shift process, the thermolytic deazetation proved to be very clean.

Thus, 2,2-difluoromethylenecyclopropane(**1**) has been demonstrated to be a good dipolarophile in its reactions with diazoalkanes and should likewise be reactive with other 1,3-dipoles. The thermal deazetations of the resultant pyrazolines, while feasible, were not generally able to be carried out efficiently due to problems of concommitant decomposition of the respective pyrazolines.

The mechanistically diverse thermal rearrangement of spiropentane **12** has already been reported in substantial detail,[4] while the thermolysis of **13** results in the formation, via an interesting minor pathway, of an interesting rearrangement product **17** in addition to the expected[5] product **16**.

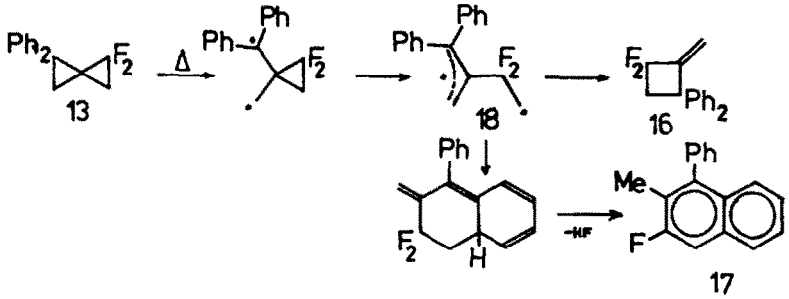


12



13 16 17

The formation of **17** can best be rationalized as deriving from the interception of diradical



13 18 16 17

18, which likely is also the precursor to **16**.[6] Product **16** was found not to rearrange under the reaction conditions to **17**.

EXPERIMENTAL SECTION

Reaction of 2,2-Difluoromethylenecyclopropane(1)

a) with Diazomethane

An ethereal solution of diazomethane (60 ml) was prepared from N-methyl-N-nitroso-p-toluenesulfonylamide (4.75 g, 22.2 mmols) and was pipetted into a large (200 ml) glass ampoule. After degassing and chilling the solution, 2,2-difluoromethylenecyclopropane(**1**) (2.10 g, 23.3 mmols) was condensed into the vessel which was then sealed under vacuum. The tube was set aside and allowed to reach room temperature.

The green solution rapidly turned colorless. The tube was chilled, opened, and the ether removed by bubbling dry N_2 gas through the solution. The product, a pale yellow oil (2.72 g, 91%) was shown to be a mixture (50.0/50.0 by nmr integration) of 1,1-difluoro-5,6-diazaspiro[2.4]hept-5-ene (**4a**) and 1,1-difluoro-4,5-diazaspiro[2.4]hept-4-ene(**5a**). Separation of (**4a**) from (**5a**) by

standard methods was not possible, due to the instability of these compounds.

Spectral data (mixture); Compound (**4a**), ^{1}H NMR δ 1.46 (t, J=8.0 Hz, 2H), 4.55-4.79 (m, 4H); ^{19}F NMR ϕ -137.9 (t, with further fine splitting, J=8.0 Hz); ^{13}C NMR δ 18.2 (t, J_{CF}=11.0 Hz, C_2), 23.6 (t, J_{CF}=9.8 Hz, C_3), 78.4 (s, C_4 + C_7), 111.2 (t, J_{CF}=286.9 Hz, C_1). Compound (**5a**), ^{1}H NMR δ 1.64-1.84 (m, 2H), 2.03-2.15 (m, 1H), 2.58-2.68 (m, 1H), 4.37-4.40 (m, 1H), 4.43-4.47 (m, 1H); ^{19}F NMR ϕ -133.61 and -137.09 (AB with further fine structure, J_{FF}=162.0 Hz); ^{13}C NMR δ 19.8 (s, C_4), 22.4 (t, J_{CF}=11.0 Hz, C_2), 73.9 (t, J_{CF}=11.0 Hz, C_3), 75.5 (s, C_5), 111.8 (t, J_{CF}=288.1 Hz, C_1). IR (film, mixture) 3100, 2965, 1475, 1460, 1258, 1195, 1013, 983, 893 cm^{-1}; mass spectrum, m/z (relative intensity) 133 (M^+ +1, 0.4), 132 (M^+, 2.1), 104 (5.1), 103 (6.6), 77 (7.3), 76 (14.4), 75 (9.7), 64 (16.2), 53 (14), 40 (100), 39 (57).

b) with Diphenyldiazomethane

A purple-colored ethereal solution of diphenyldiazomethane (15 ml) (0.60 g, 3.09 mmols) was pipetted into a large (100 ml) glass ampoule. After chilling and degassing the solution, (**1**) (0.36 g, 4.00 mmols) was condensed into the tube, which was then sealed under vacuum. The tube was allowed to stand in the dark at room temperature for 18 hours with occasional shaking, during which time the reaction mixture became pale amber in color. The tube was chilled and opened and the ether carefully removed on a rotary evaporator. An orange solid (0.86 g, 99%) remained. Recrystalization from n-pentane afforded pale yellow crystals of 1,1-difluoro-6,6-diphenyl-4,5-diazaspiro[2.4]hept-4-ene(**5b**) (0.78 g, 91%), m.p. 91-92°C. ^{1}H NMR δ 1.80-1.89 (m, 1H), 2.39 (dd, J=13.5 and 5.0 Hz, 1H), 2.64-2.79 (m, 2H), 7.28-7.35 (m, 10H); ^{19}F NMR ϕ -132.44 and -136.34 (AB with further splitting, J_{FF}=162.0 Hz); ^{13}C NMR δ 22.7 (t, J_{CF}=9.8 Hz, C_2), 34.0 (s, C_7), 74.3 (t, J_{CF}=11.0 Hz, C_3), 99.1 (s, C_6), 109.8 (t, J_{CF}=292.0 Hz, C_1), 125.5 (s), 125.7 (s), 126.7 (s), 127.7 (s) (all aromatic CH carbons, incompletely resolved), 141.5 (s), 141.9 (s) (aromatic quaternary Cs); IR (CCl_4 soln) 3092, 3064, 3030, 1491, 1468, 1360, 1005, 976, 694 cm^{-1}; mass spectrum gave exact mass (M^+ -28) 256.1062±.0020 (±8.0 ppm), calculated mass for $C_{17}H_{14}F_2$ is 256.1063, dev. -0.0001 (-0.4 ppm).

c) with Vinyldiazomethane

A solution of vinyldiazomethane[8] (6.84 mmols) in ether (75 ml) was pipetted into a large (200 ml) glass ampoule. After chilling and degassing the solution, (**1**) (1.12 g, 12.4 mmols) was condensed into the vessel, which was sealed under vacuum and set aside at room temperature. After about 20 hrs, the tube contents had become colorless. The tube was chilled and opened and the solvent carefully removed on a rotary evaporator. The last traces of ether were removed by blowing dry N_2 through the solution. A viscous orange oil (1.08 g, 98%) remained. This was immediately examined by ^{19}F nmr spectroscopy and shown to consist of three components in the ratio of 64.7:17.6:17.6. These were shown to be the tautomerised Δ^2 pyrazolines 1,1-difluoro-6-vinyl-4,5-diazaspiro[2.4]hept-5-ene(**6**) (major component), 1,1-difluoro-4-vinyl-5,6-diazaspiro[2.4]hept-4-ene(**7**) and 1,1-difluoro-4-vinyl-5,6-diazaspiro[2.4]hept-6-ene(**8**). The mixture was found to be inseparable and the proton nmr spectrum of the mixture was assigned with a 2D ^{1}H-^{1}H COSY experiment. Spectral data (mixture); Compound (**6**); ^{1}H NMR δ 1.32-1.48 (m, 2H), 1.52-1.60 (m, 1H), 2.28-2.36 (m, 1H), 5.15 (br. d, J=7.0 Hz, 1H), 5.41-5.47 (m, 2H), 7.60 (br. s, 1H); ^{19}F NMR ϕ -133.0 and -138.7 (AB with further splitting, J_{FF}=155.4 Hz); Compound (**7**); ^{1}H NMR δ 1.78-2.03 (m, 1H), 2.53-2.63 or 2.65-2.75 (each m, 1H), 4.49 and 4.78 (AB, J_{HH}=18 Hz, 2H), 5.31-5.39 (m, 2H), 5.98-6.07 (m, 1H), 7.60 (br. s, 1H); ^{19}F NMR ϕ -133.0 and -136.4 (AB with further splitting, J_{FF}=160.8 Hz); Compound (**8**); ^{1}H NMR δ 1.78-2.03 (m, 1H), 2.53-2.63 or 2.65-2.75 (each m, 1H), 4.14 (m, 1H), 5.31-5.39 (m, 2H), 5.88-5.97 (m, 1H), 6.32 (t, J=13 Hz, 1H), 7.60 (br. s, 1H); ^{19}F NMR ϕ -133.3 and -137.2 (AB with further splitting, J_{FF}=162.2 Hz); IR (film, mixture) 3280 (broad), 3088, 2987, 1750 (str.), 1470 (str.), 1253 (str.), 1188, 1018, 990 cm^{-1}; mass spectrum gave exact mass M^+=158.0653±0.0014 (9.1 ppm), calculated mass for $C_7H_8N_2F_2$ is 158.0655, dev. -0.0001 (0.8 ppm).

Pyrolysis of Pyrazolines (**4a**) and (**5a**)

Into a small (20 ml) thick-walled glass tube was sealed, under vacuum, degassed decalin (10.0 ml) and a 50/50 mixture of spiropyrazolines (**4a**) and (**5a**) (0.30 g, 2.27 mmols). The tube was heated statically at 190-210°C for 16 hrs. After this time the tube, which now contained a quantity of brown polymeric material, was chilled and opened. After connecting to a vacuum line,

volatile products from the reaction were transferred to a cold finger. A quantity of colorless liquid collected in the trap, and was shown to be mainly decalin together with one volatile component by gc (col.: 8' x 1/4", 20% SE 30, 80°C). The volatile component (0.012 g, 5%) was separated by prep. scale gc and identified as 1,1-difluorospiropentane.

Pyrolysis of 1,1-Difluoro-6,6-diphenyl-4,5-diazaspiro[2.4]hept-4-ene(5b).

Into a large (100 ml) thick-walled glass ampoule was sealed, under vacuum, degassed isooctane (12.0 ml) and (5b) (1.90 g, 6.69 mmols), the tube was heated statically at 210°C for 28 hrs. After chilling, the tube was opened and the contents (a clear yellow liquid) filtered to remove a small quantity of particulate material. Removal of the solvent (rotary evaporator) left a yellow solid (1.73 g). This was purified by flash column chromatography using a 2" column with a sintered glass filter and n-pentane eluant. 1,1-Difluoro-4,4-diphenylspiropentane(13) (1.48 g, 87%) crystalized out from the eluant as a white solid, m.pt. 55-57°C. ^{1}H NMR δ 1.61 (t, with further fine structure, J=9.0 Hz, 1H), 1.72 (t, with further fine structure, J=8.0 Hz, 1H), 1.89-1.95 (m, 2H), 7.14-7.34 (m, 10H); ^{19}F NMR ϕ -130.0 and -133.82 (AB with further splitting, J_{FF}=153.4 Hz); ^{13}C NMR δ 16.8 (t, J_{CF}=11.3 Hz, C_2), 23.6 (s, C_5), 28.0 (t, J_{CF}=11.0 Hz, C_3), 37.5 (s, C_4), 114.1 (t, J_{CF}=286.4 Hz, C_1), 126.5 (s), 126.8 (s), 127.88 (s), 127.91 (s), 128.5 (s), 128.7 (s) (all aromatic CH carbons, incompletely resolved), 141.3 (s), 141.6 (s) (both aromatic quaternary Cs); IR (CCl_4 soln) 3066, 3032, 1718, 1534, 1493, 1446, 1266, 1213, 1180, 1118, 1021, 896, 698 cm^{-1}; mass spectrum gave exact mass M^+=256.1042±0.0023 (9.1 ppm), calculated mass for $C_{17}H_{14}F_2$ is 256.1063, dev. -0.0021 (8.3 ppm).

Pyrolysis of Δ^2 Pyrazolines (6), (7) and (8)

Into a 50 ml capacity thick-walled glass tube was added degassed decalin (8.0 ml) and the pyrazoline mixture (0.65 g, 4.14 mmols). The tube was sealed under vacuum and then heated statically at 160-200°C for 2 hrs. After this time the tube, which contained a quantity of brown polymeric material, was chilled, opened and volatile products transferred under vacuum to a cold finger. A colorless liquid (0.38 g) was collected. This was separated into its two components by preparative scale gc (col: carbowax 20M, 20%, 60°C). The products were identified as syn and anti 1,1-difluoro-4-vinylspiropentanes (14) and (15); however, it was not possible to determine which product was syn and which was anti from the available spectral data. The first eluting product (0.08 g, 14%) had ^{1}H NMR δ 1.04-1.10 (m, 1H), 1.49-1.60 (m, 3H), 2.06-2.14 (m, 1H), 5.05 (dd, J=10.3 and 1.5 Hz, 1H), 5.17 (dd, J=17.2 and 1.5 Hz, 1H), 5.37-5.49 (m, 1H); ^{19}F NMR ϕ -134.4 and -135.1 (AB with further splitting, J_{FF}=152.0 Hz); ^{13}C NMR δ 14.0 (s, C_5), 15.0 (t, J_{CF}=11.4 Hz, C_2), 21.4 (s, C_4), 21.8 (t, J_{CF}=11.1 Hz, C_3), 113.2 (t, J_{CF}=285.4 Hz, C_1), 115.5 (s, -CH=), 137.0, (s, CH_2=); IR (gas) 3098, 3018, 2967, 1563, 1444, 1238 (str.), 1093, 1023, 911 (str.), 802, 748 cm^{-1}; mass spectrum, m/z (relative intensity) 130 (M^+, .17), 129 (1.3), 115 (7.7), 84 (69), 79 (58), 66 (100), 40 (27).

The second eluting product (0.08 g, 14%) was identified as (4S)-1,1-difluoro-4-vinylspiropentane(15), ^{1}H NMR δ 1.17 -1.20 (m, 1H), 1.36-1.43 (m, 1H), 1.56-1.62 (m, 1H), 1.67-1.73 (m, 1H), 2.16-2.19 (m, 1H), 5.00 (dd, J=10.2 and 1.5 Hz, 1H), 5.19 (dd, J=17.1 and 1.5 Hz, 1H), 5.42-5.54 (m, 1H); ^{19}F NMR ϕ -133.3 and -136.1 (AB with further splitting, J_{FF}=152.2 Hz, J_{HF}=8.4 Hz); ^{13}C NMR ϕ 13.9 (s, C_5), 16.8 (t, J_{CF}=11.3 Hz, C_2), 21.0 (t, J_{CF}=11.0 Hz, C_3), 24.9 (s, C_4), 114.5 (s, -CH=), 137.4 (s, CH_2=) (the CF_2 carbon was not observed); IR (gas) 3098, 2964, 1554, 1260, 1237, 1090, 1020, 908 (str.), 796, 740 cm^{-1}; mass spectrum, m/z (relative intensity) 130 (M^+, .17), 129 (.55), 115 (3), 88 (10), 86 (62), 84 (100), 49 (18), 47 (21). The gc ratio of (14) to (15) was 49:51.

Pyrolysis of 1,1-Difluoro-4,4-diphenylspiropentane (13)

The pyrolysis of 13 was carried out in a vacuum-sealed, thick-walled glass ampoule. The solution of 13, in degassed isooctane, was heated in a tube furnace at 210°C for 28h. Products 16 and 17 were isolated by evaporation of solvent, followed by flash chromatography.

16: ^{1}H NMR, δ 3.35 (t, J_{HF}=11.2 Hz, 2H), 5.47 (m, 1H), 5.86 (m, 1H), 7.19-7.33 ppm (m, 10H); ^{19}F, ϕ 94.5 ppm (t, J_{HF}=11.2 Hz); ^{13}C, δ 48.9 (t, J_{CF}=22.0 Hz, C_3), 51.9 (t, J_{CF}=11.0 Hz, C_4), 114.9 (s, =CH_2), 117.6 (t, J_{CF}=280.0 Hz, C_2), 126.7 (s), 127.2 (s), 128.5 (s) (all aromatic CH carbons), 144.7 (s, aromatic quaternary), 152.9 (t, J_{CF}=20.8 Hz, C_1); IR (film) 3080, 3057, 3021,

1594, 1488, 1442, 1288, 1170, 1096, 1077, 1052, 1021, 923, 743 cm^{-1}; MS (exact mass) gave M^+=256.1052 ± 0.0017 (calcd for $C_{17}H_{14}F_2$ is 256.1063).

17: ^1H NMR , δ 2.14 (d, J=2.5 Hz, 3H), 7.15-7.22 (m, 3H), 7.31-7.45 (m, 6H), 7.66-7.69 ppm (m, 1H); ^{19}F, ϕ 117.5 (dq, J_{HF}=10.5 and 2.5 Hz); ^{13}C, δ 13.0 (d, J_{CF}=4.8 Hz, CH_3), 109.9 (d, J_{CF}=22.1 Hz, C_4), 124.0 (d, J_{CF}=19.7 Hz, C_2), 124.8 (d, J_{CF}=2.5 Hz, C_7), 125.8 (s, C_6), 126.4 (d, J_{CF}=1.6 Hz, C_8), 127.1 (d, J_{CF}=5.5 Hz, C_5), 127.4 (s, C_4) 128.4 (s, $C_{2'}$, $C_{6'}$ or $C_{3'}$, $C_{5'}$), 130.0 (s, $C_{2'}$, $C_{6'}$ or $C_{3'}$, $C_{5'}$), 132.5 (s, C_{8a} or $C_{1'}$), 132.6 (s, C_{8a} or $C_{1'}$), 138.6 (d, J_{CF}=2.8 Hz, C_1), 141.1 (d, J_{CF}=5.1 Hz, C_{4a}), 159.7 (d, J_{CF}=246.0 Hz, C_3); a 2D ^1H-^1H COSY experiment (with quadrature detection in both dimensions) revealed no coupling to the methyl group, but further attempts to assign the ^1H spectrum using 2D J-resolved spectroscopy were unsuccessful. The ^{19}F spectrum, with a single resonance (doublet of quartets) was consistent with the F atom being located adjacent both to a proton-bearing C atom and to a carbon bearing a Me group. This was confirmed by a 2D ^{19}F- ^1H COSY experiment. The structure of **17** finally could be proposed as a result of the ^{13}C spectrum. Carbon multiplicity was determined by modified APT and coupled INEPT experiments which showed one methyl carbon, ten C-H carbons and six quaternary carbons. Carbon-fluorine couplings and 2D ^{13}C- ^1H heteronuclear correlation and heteronuclear relayed coherence transfer experiments were also used in making the final assignment of structure to **17**; IR (film), 3057, 3025, 2924, 2857, 1658, 1543, 1493, 1429, 1377, 1337, 1234, 1137, 1094, 933, 868, 841 cm^{-1}; MS (exact mass) gave M^+=236.1001 ± 0.0011 (calcd for $C_{17}H_{13}F$ is 236.1001).

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