Tetrahedron Vol. 35, pp. 815 to 818
© Pergamon Press Ltd., 1979. Printed in Great Britain

CARBOFLUORINATION OF PSEUDOGUAIANOLIDE SESQUITERPENIC LACTONES†

I. SALAZAR and E. DÍAZ
Instituto de Química, Universidad Nacional Autónoma de México, México 20, D.F.

(*Received in UK 23 February 1978*)

Abstract—A novel group of carbofluorinated sesquiterpenic lactones is described. All are generated by difluorocarbene addition to the double bonds of pseudoguaianolide lactones. The various products formed in these reactions are characterized mainly by ^{1}H NMR spectroscopic data.

Interest in the chemistry of halocarbene has continued at high level since dichlorocarbene was reported in 1954.[1] In the area of organic synthesis, carbenes have been utilized very effectively for the construction of cyclopropane ring systems.[2]

Despite the wealth of experimental data accumulated on the later topic during past decade, it is pertinent to note that only a limited number of examples of carbene additions to the double bond of unsaturated carbonyl systems has been observed.

The first examples of the synthesis of α-difluorocyclopropyl ketones by addition of difluorocarbene to steroidal enones and dienones were reported several years ago.[3] Conjugated carbonyl systems appear *a priori* to be relatively poor substrates for attack by the electrophilic difluorocarbene species since the nucleophilic character of the enone double bond is considerably reduced by electron delocalization with the CO group.[4] Nevertheless, Beard *et al.* have reported the reaction of difluorocarbene species with the electron-deficient double bond of some enone and dienone systems.[3]

Our general interest in fluorocarbene chemistry led us to determine the fate of various unsaturated sesquiterpenic lactones upon exposure to a large excess of "difluorocarbene" and to study the nature of the products formed.

The fluorocarbene, generated by pyrolysis of the sodium salt of chlorodifluoroacetic acid[5] in aprotic solvents such as diglyme, has already been utilized to synthetize sesquiterpenic difluorocyclopropane lactones as well as the corresponding bis- and tris-difluorocyclopropane adducts. When peruvinin[6] 1 was reacted with an excess of difluorocarbene, compound 2 was isolated as the main product in approximately 50% yield (Table 1). The addition of difluorocarbene was detected by the absence in the NMR spectrum of the exocyclic methylene signals. Instead, a multiplet assigned to one proton of the cyclopropane methylene appeared at δ 2.1 ppm. Whereas the proton assigned to H-7 shifted from 3.4 in 1 to 2.88 in 2, the proton base of acetate (H-4) shifted from 5.2 to 5.04 ppm, with most other signals remaining similar to those in the starting material.[6] The product 2 exhibits in the mass spectrum the molecular ion peak at *m/e* 356 and the successive loss of fragments CH_3-C^+ (*m/e* 314) and $CH_3-\overset{+}{C}-OH$ (*m/e* 296).

From the thermal treatment of anhydroparthenin[7] 3 with four equivalents of a 4 M solution of sodium chlorodifluoroacetate in anhydrous diglyme for periods

†Contribution No. 486 from the Instituto de Química, U.N.A.M.

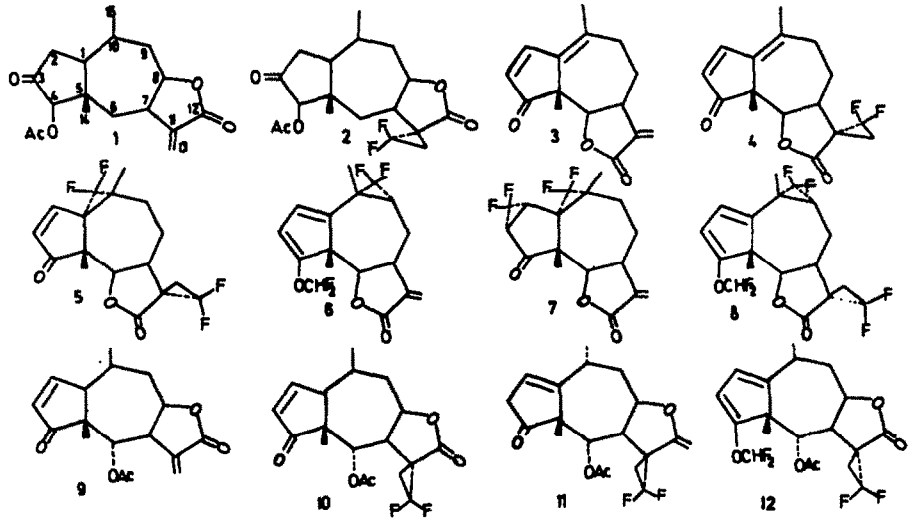


Table 1.

Product	UV λmax EtOH λnm	^{1}H NMR $CDCl_3$	[α]
2	225 ε (2453)	1.00 (s, 14-Me), 1.06 (d, J=6.5, 15-Me), 2.17 (s, OAc), 4.9 (d, d, d, J=4, 7.5, 11, H-8), 5.04 (s, H-4), 2.88 (m, H-7).	- 13.3°
4	297 ε(8415)	1.44 (s, 14-Me), 2.0 (b, s, 15-Me), 2.5 (9-CH_2 and 7-CH), 2.15 (m, H-8, H-13), 4.56 (d, J=6, H-6), 6.04 (d, J=5.5, H-3), 8.1 (d, H-2).	- 163.5°
5	246 ε (3411)	1.38 (t, J=1.5), 15-Me, 1.54 (s, 14-Me), 1.65 (m, H-8 y H-9), 2.14 (m, H-13), 2.38 (m, H-7), 4.94 (d, J=7, H-6), 6.3 (d, H-3), 7.25 (d, J=6.3 H-2).	+ 29.6°
6	270 ε(4435)	1.50 (t, $^4J_{H-F}$=2.5, 15-Me), 1.62 (s, 14-Me), 1.25 (m, H-9), 1.72 (m, H-8), 3.07 (m, H-7), 4.59 (d, J=6, H-6), 5.54 (m, J_{9-3}=2.5, J_{9-F}=1.5 H-2), 5.62 (d, J=1.5, H-13), 6.19 (d, d $^5J_{3-F}$=4.5 H-3), 6.27 (d, J=2 H-13'), 6.42 (d, d J=72.5, 74, $OCHF_2$).	+ 86°
7	219 ε(2471)	1.48 (t, J=2 Hz 15-Me), 1.56 (s, 14-Me), 3.57 (m, H-7), 4.53 (d, J=6, H-6), 5.6 (d, J=1.5 H-13), 6.26 (d, J=2, H-13).	
8	270 ε (4450)	1.53 (t, J=2.5 15-Me), 1.65 (s, 14-Me), 2.16 (m, 13 H), 2.45 (m, H-7), 4.8 (d, J=5.5 H-6) 5.56 (m, $^5J_{H-F}$ = 1.5, H-3), 6.2 (d, d J=2.5 $^5J_{F-H}$= 4.5), 6.45 (d, d, J_{F-H}=72, 73, $OCHF_2$).	+ 70.2°
10	238 ε (3382)	1.06 (s, 14-Me), 1.25 (d, J=6 15-Me), 1.6(d, d, d, J, 2, 3.8, 12 H-9), 1.93 (s, OAc), 2.4 (m, H-13, H-10, H-9'), 3.06 (d, d, d, J=2, 3, 10, H-1), 2.8 (b, d, J=0.5, 7 (H-7), 4.93 (d, d, d, J=2, 6, 7, H-8), 5.06 (d, J=0.5, H-6), 6.05 d, d J=3, 6 H-3), 7.7 (d, d, J=2 H-2).	- 91.5°
11	211 ε (1188)	1.06 (s, 14-Me), 1.3 (d, J=6.5 15-Me), 1.91 (s, OAc), 2.82 (m, H-3, H-10), 4.93 (d, d, d, J=1.5, 6, 8, H-8), 4.93 (d, J=1.5 H-6), 5.87 (q, J=1.2, H-2).	+ 61.5°
12	265 ε(3580)	1.18 (s, 14-Me), 1.30 (d, J=7, 15-Me), 1.94 (s, OAc), 1.85 - 2.45 (m, H-9), 2.90 (m, H-10 J = 4, 9.5, J=2.75), 2.64 (m, H-7), 4.87 (m, J=3, 8.8, H-8), 5.18 (d, J=5.5 H-6), 5.47 (m, J_{9-F}=2.5 $^5J_{3-F}$ = 1.5), 5.87 t, H-2, 6.29 t, $^5J_{F-H}$ = 73, $OCHF_2$)	+ 33.3°

of 15 min we have isolated the following five products, 4 (30%), 5(1%) and traces of 7 and 8.

The yield of products 5, 6 and 8 can be substantially improved by slight modification in the methylenation procedure, namely by adding the reagent, previously dissolved in cold diglyme, to a refluxing diglyme solution of the anhydroparthenin. Unfortunately, such treatment results as well on the reduction of the relative yields of the remaining products.

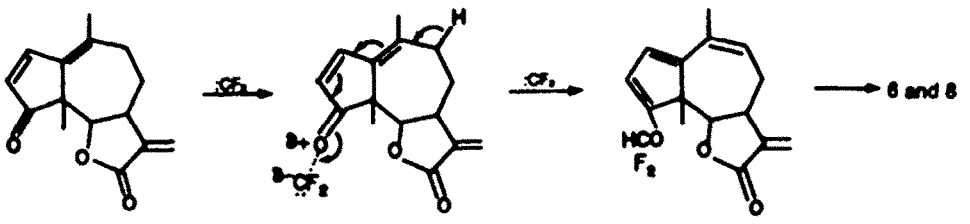
Product 4 shows the molecular ion peak at *m/e* 294 and its ^{1}H NMR spectrum indicates the absence of exocyclic methylene protons, thus suggesting that monocarbofluorination occurs at this double bond.

Amongst the minor constituents we have further characterized adducts 5 and 6. Both compounds exhibit the molecular ion peak at *m/e* 344 but differ in their other physical and spectroscopic properties. In particular, whereas in compound 5 the 15-Me group is seen as a fluorine-coupled triplet ($^4J_{H-F}$ = 1.5 Hz) at δ 1.38 ppm, the vinylic protons H-3 and H-2, appear centered at 6.3 (d, J_{2-3} = 6.3 Hz) and 7.25 ppm, respectively. For isomer 6, however the signals for the exocyclic methylene group remain at 5.62 (d, $^4J_{7-13}$ = 1.5 Hz) with an additional doublet of doublet at 6.42 ppm showing the characteristic coupling constants ($^2J_{H-F}$ = 72.5 Hz and $^2J_{H-F}$ = 74 Hz) for the $-OCHF_2$ grouping.[8,9]

Moreover, in the latter case the two vinylic protons, H-2 and H-3, appear centered at δ 6.19 (dd; J_{2-3} = 2.5 and $^5J_{2-F}$ = 4.5 Hz) and 5.54 ppm (td; J_{2-3} = 2.5 and $^5J_{3-F}$ = 1.5 Hz), respectively, with the 15-Methyl group now showing at 1.50 ppm (t, $^4J_{H-F}$ = 2.5 Hz). The observed multiplicities are in good agreement for structure 6 since the coupling is very similar to that previously reported by Popper *et al.*[10] Its UV spectrum (λ_{max} 270 nm ε 4435) supports as well the proposed structure 6.

We feel that the most probable route to compounds 6 and 8 is as shown in Scheme 1.

Inspection of the ^{1}H NMR spectra of adducts 5 and 6 reveals, in all cases, sharp singlets for the angular 14-Me proton resonances thus suggesting the 1α, 10α stereochemistry in 5 and the 9α, 10α stereochemistry in 6, since for either the 1β, 10β or 9β, 10β configurations we would expect a splitting of the 14-Me signal by long range coupling with fluorine.[11,12] Similar stereochemical considerations can be invoked for compounds 7 and 8 (Table 1).



Scheme 1.

From fluorocarbomethylenation of helenalin acetate[13] 9 three products were isolated, 10 (40%), 11(10%) and 12(1.5%). The ^{1}H-NMR spectrum of derivative 10 clearly shows the absence of the exocyclic methylene signals. Instead, a multiplet at δ 2.35 may be assigned to one proton of the cyclopropane methylene. Whereas the C-6 proton (d, J = 0.5 Hz) appeared shifted −0.32 ppm (Table 1), H-7 shifted by −0.65 ppm (broad doublet, J_{7-8} = 6 and J_{6-7} = 0.5 Hz). No other noticeable differences exist in the spectra of the compounds 9 and 10.

Compound 11 corresponds to an isomer of compound 10, with their ^{1}H-NMR spectra showing differences mainly in the vinylic resonances. While product 10 shows an ABX pattern centered at δ 7.7 (J_{2-3} = 6, J_{1-2} = 2 Hz; H-2) and 6.05 (J_{1-3} = 3 Hz; H-3), adduct 11 shows only one vinylic proton at 5.87 ppm (q, J = 2 Hz), assigned to H-2, coupled with the methylene in C-2 and showing allylic coupling with H-10. Whereas the signals at δ 2.82 belong to H-10 and the methylene protons on C-2, those at 2.25 are assigned to one proton of the cyclopropane methylene and to H-9. The remaining of the spectrum shows no other noticeable differences when compared with 10.

Both products, 10 and 11, exhibit the molecular ion peak at *m/e* 354 and a similar fragmentation pattern, but there are important differences in the carbonyl region of their IR spectra. Whereas 10 shows bands at 1780, 1745 and 1710, 11 exhibits bands at 1780, 1745 and 1740 cm^{-1}.

Product 12, isolated in very low yield, shows in the mass spectrum the molecular ion peak at *m/e* 404 with the usual loss of acetic acid (*m/e* 344). In the UV exhibits a maximum at 265 nm (ϵ, 3580) and in the IR shows carbonyl bands at 1785 and 1745 cm^{-1}.

In its ^{1}H NMR spectrum the signals for both the exocyclic methylene and ABX pattern characteristic of lactone 9 are missing. Instead a triplet signal appear at δ 6.23 ($^2J_{H-F}$ = 73 Hz) showing the large coupling constant typical of the -OCHF$_2$ grouping.[8] The formation of such difluoromethyl ethers has some precedent in the steroid literature.[10]

Moreover, the NMR shows two vinylic protons signals at δ 5.87 (H-2) and 5.47 ppm (H-3). While a former is a triplet and appears coupled with H-3 and H-10 (J = 2.5 Hz), the latter, a quintet, shows the expected coupling with the fluorine atoms of the ether ($^5J_{F-H}$ = 1.5 Hz). Therefore, compound 12 has large structural similarities with adducts 6 and 8 and probably arises accordingly to the mechanism shown in Scheme 2.

Examination of the chemical and spectral evidence available at this stage allows for only a tentative prediction on the stereochemistry of the difluorocarbene addition products to the C_{11}–C_{13} double bond. The formation of the 11α, 13α adducts is clearly favored on steric grounds[3] since perpendicular approach of: CF_2 or related species to the plane of the C_{11-13} double bond from the β-face is markedly restricted by the 14β-Me group. Experimental support for this hypothesis is provided by their known reduction reaction,[14,15] which taking place predominantly from the α-side of the molecule produces the 13α-configuration.

Long range fluorine-hydrogen coupling

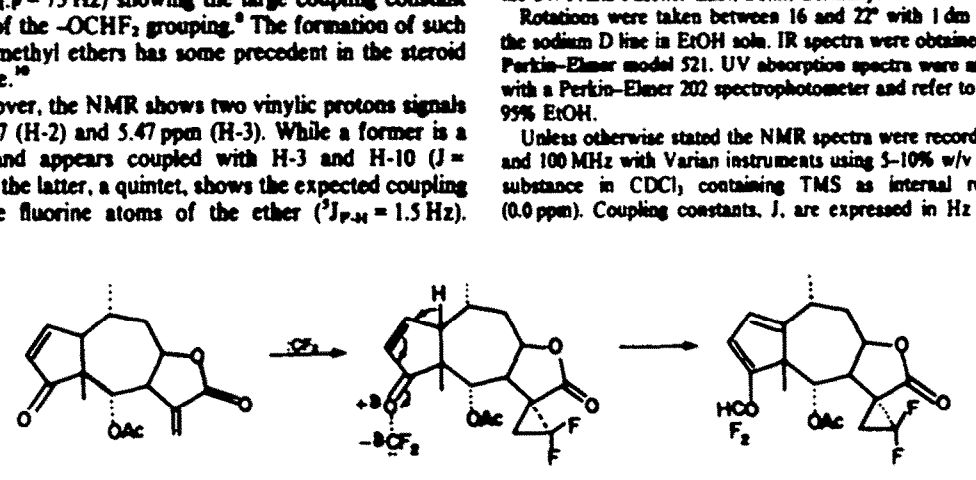
Values of $^nJ_{F-H}$ with n > 3 tend to be larger than the corresponding $^nJ_{H-H}$ values thus exhibiting some useful diagnostic features. Attention should be directed to the significant proton-fluorine coupling over five σ-bonds. Jefford *et al.*[16] describe larger values (8.4–10 Hz) for $^5J_{H-F}$ for molecules bearing the double sig-zag arrangement of fluorine and hydrogen. However, when such an arrangement is absent[17] the J values do not exceed 2.5–3.5 Hz. For many molecules long range F-H coupling is observed only when the two nuclei are close through space.[18] This latter consideration supports the $^5J_{F-H}$ = 4.5 Hz observed for the products 6 and 8, since Dreiding models of these molecules have indicated a close spatial relationship between proton H-2 and one fluorine nucleus of the cyclopropane on C_9–C_{10}.

EXPERIMENTAL

M.ps were determined with Koller hot stage apparatus, and are uncorrected. Microanalytical determinations were performed in the Dr. Franz Pascher Lab., Bonn, Germany.

Rotations were taken between 16 and 22° with 1 dm Tube at the sodium D line in EtOH soln. IR spectra were obtained with a Perkin–Elmer model 521. UV absorption spectra were measured with a Perkin–Elmer 202 spectrophotometer and refer to solns in 95% EtOH.

Unless otherwise stated the NMR spectra were recorded at 60 and 100 MHz with Varian instruments using 5–10% w/v solns of substance in $CDCl_3$ containing TMS as internal reference (0.0 ppm). Coupling constants, J, are expressed in Hz and are



Scheme 2.

accurate to ±0.5 Hz. d, doublet; t, triplet; q, quartet; d,d, doublet of doublet; d,d,d, doublet of doublet of doublet; m, multiplet. The mass spectra were obtained with a Hitachi–Perkin–Elmer model RMU-6D spectrometer. Tlc were performed with silica gel GF-254 (Merck A. G., Germany). We wish to thank to Mr. Noé Rosas and H. Bojórquez, from Instituto de Química, U.N.A.M., for the IR, UV and mass spectral determinations. To Dr. A. Romo de Vivar for supplying us with a sample of helenalin. We are indebted to Dr. I. Sánchez from Facultad de Química, U.N.A.M., for his advice in preparing the manuscript.

General procedures for the addition of difluorocarbene to the sesquiterpenic lactones. The lactones in dry diglyme and a soln (4 M) of sodium chlorodifluoroacetate in the same solvent were heated at reflux for 15 min. The mixture was cooled and in some cases further aliquots of the salt were added. The reaction progress was monitored by tlc.

Attempts to improve the yield by increasing either the amount of reagent or the heating period were unsuccessful. Normally, after addition of a total of twelve equivalents of the sodium salt to the mixture no substantial progress was observed. The resulting mixture was filtered, the solvent evaporated and the brown residue chromatographed on silica gel.

Peruvinin acetate[6] 1, anhydroparthenin[7] 3 and the acetate of helenalin[13] 9 were prepared by literature methods.

Difluoromethylenation of peruvinin acetate (1). The acetate of 1, 223 mg (0.72 mmol) and 5 ml (4 equiv) of sodium difluorochloroacetate in dry diglyme were heated at reflux for 15 min.

The reaction was cooled and tlc monitoring indicated that a further addition of 5 ml of salt was needed.

After work up 111 mg (50%) yield of 2 were obtained, m.p. 110–111°. IR ν_{max} 3060, 1760, 1740, 1730, 1480, 1450, 1200 cm^{-1}. Mass spectrum 356 (M$^+$), 314, 296, 281, 215, 175, 149, 109, 107, 43. $C_{18}H_{22}O_5F_2$ requires: mol wt: 356 (Found: C, 60.59; H, 6.17; O, 22.42; F, 10.82. Calc. C, 60.67: H, 6.19; O, 22.47: F, 10.67%).

Difluorocarbene addition to anhydroparthenin (3). Sodium chlorodifluoroacetate soln (4 M) in anhyd diglyme was added to 1000 mg (4 mmol) of 3 in diglyme. After the usual procedure, the resulting residue was chromatographed on a silica column. Elution with benzene afforded several oily fractions which after purification by preparative chromatography on silica gel yielded 8, 6, 5 and 7, respectively. The most polar fractions afforded product 4 and recovered starting material.

All products were recrystallized using a mixture AcOEt–iPr–ether; 4 shows m.p. = 193–194°, IR ν_{max} 3020, 1770, 1690, 1540, 1445, 1365 cm^{-1}. Mass spectrum 294 (M$^+$), 279, 251, 187, 185, 172, 159, 145, 117, 65, 55. $C_{16}H_{16}O_3F_2$ requires: mol wt: 294 (Found: C, 65.40; H, 5.45; O, 16.15; F, 13.05. Calc.: C, 65.30; H, 5.44; O, 16.32; F, 12.92%).

Compound 5 shows m.p. 220–222° IR ν_{max} 3005, 2980, 2915, 1775, 1712, 1580, 1215. Mass spectrum 344 (M$^+$) 329, 324, 301, 281, 175, 157, 145, 115, 65, 55. $C_{17}H_{16}O_3F_4$ requires mol wt: 344 (Round: C, 59.17; H, 4.85; O, 13.80; F, 22.19. Calc.: C, 59.30; H, 4.65; O, 13.95; F, 22.10%).

Compound 6 gives m.p. 116–118°, IR ν_{max} 3025, 2980, 1765, 1620, 1575 cm^{-1}. Mass spectrum 344 (M$^+$), 329, 315, 294, 265, 223, 197, 171, 147, 109, 77, 65. $C_{17}H_{16}O_3F_4$ requires: mol wt: 344 (Found: C, 59.09; H, 4.21; O, 14.38; F, 22.32. Calc.: C, 59.30; H, 4.65; O, 13.95; F, 22.10%).

Compound 7 shows ν_{max} 3020, 1750, 1220, 750 cm^{-1}. Mass spectrum 344 (M$^+$). $C_{17}H_{16}O_3F_4$ requires: mol wt: 344.

Compound 8 gives m.p. 104–105° from iPr–ether–hexane. IR ν_{max} 3015, 1770, 1610, 1455, 1450, 1440, 750 cm^{-1}. Mass spectrum 394 (M$^+$), 379, 366, 359, 344, 315, 109, 77, 65. $C_{18}H_{18}O_3F_6$ requires mol wt: 394 (Found: C, 54.90; H, 4.16; O, 12.03; F, 28.91. Calc.: C, 54.82; H, 4.07; O, 12.18; F, 28.93%).

Addition of difluorocarbene to helenalin acetate (9). 1297.7 mg (4 mmol) of 9 in 5 ml of anhydrous diglyme was treated with 10 ml of a soln 3.8 M of sodium chlorodifluoroacetate. After usual work up, the resulting brown oil was chromatographed on SiO_2. Elution with benzene yielded several fractions. The mixture was purified using preparative tlc. This fluoromethylenation affords adducts 10, 11 and 12.

Compound 10 shows m.p. 185–187°, IR ν_{max} 3010, 2960, 1780, 1745, 1710, 1380, 1230. Mass spectrum 354 (M$^+$) 312, 294, 279, 235, 221, 173, 135, 124, 95, 65, 43. $C_{18}H_{20}O_5F_2$ requires: mol wt: 354 (Found: C, 61.12; H, 5.57; O, 22.72; F, 10.59. Calc.: C, 61.01; H, 5.65; O, 22.60; F, 10.74%).

The difluoro derivative 11 gives m.p. 161–163°. IR ν_{max} 3100, 2890, 1770, 1750, 1740, 1450, 1370 and 750 cm^{-1}. Mass spectrum 354 (M$^+$) 312, 294, 284, 266, 224, 124, 109, 91, 43. $C_{18}H_{20}O_5F_2$ requires: mol wt: 354 (Found: C, 60.52; H, 5.58; O, 23.09; F, 10.81. Calc.: C, 61.01; H, 5.65; O, 22.60; F, 10.74%).

The tetrafluoro derivative 12 shows m.p. 147–149°. IR ν_{max} 3100, 2990, 1785, 1745, 1450, 1370, 1230. Mass spectrum 404 (M$^+$), 344, 329, 279, 174, 173, 157, 123, 107, 77, 43. $C_{19}H_{20}O_5F_4$ requires: mol wt: 404 (Found: C, 56.30; H, 5.05; O, 19.70; F, 18.95. Calc.: C, 56.43; H, 4.96; O, 19.80; F, 18.81%).

REFERENCES

[1]W. Von Doering and A. K. Hoffmann, *J. Am. Chem. Soc.* **76**, 6162 (1954).

[2a]J. Hine, *Divalent Carbon*. Ronald Press, New York (1964); [b]W. Kirmse, *Carbene Chemistry*. Academic Press, New York (1964).

[3]C. Beard, B. Berkoz, N. H. Dyson, I. T. Harrison, P. Hodge, L. H. Kirkham, G. S. Lewis, D. Giannini, B. Lewis, J. A. Edwars and J. H. Fried, *Tetrahedron* **25**, 1219 (1969).

[4a]R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Ibid.* **2**, 1 (1958).; [b]H. B. Henbest, W. R. Jackson and I. Malunowicz, *J. Chem. Soc.* (C), 2469 (1967).

[5a]W. M. Wagner, *Proc. Chem. Soc.* 229 (1959); [b]J. M. Birchhall, G. W. Cross and R. N. Haszeldine, *Ibid.* 81 (1960).

[6]J. Romo, P. Joseph-Nathan, A. Romo de Vivar y C. Alvarez, *Tetrahedron* **23**, 529 (1967).

[7]W. Herz, H. Watanabe, M. Miyazaki and Y. Kishida, *J. Am. Chem. Soc.* **84**, 2601 (1962).

[8]P. Crabbé, A. Cervantes, A. Cruz, E. Galeazzi, J. Iriarte and E. Verlarde, *Ibid.* **95**, 6655 (1973).

[9]L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis and A. D. Cross, *Ibid.* **85**, 1851 (1963).

[10]T. L. Popper, F. E. Carlon, H. M. Marigliano and M. D. Yudis, *Chem. Commun.* 277 (1968).

[11]A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.* **86**, 4005 (1964).

[12]M. Takahashi, D. R. Davis and J. D. Roberts, *Ibid.* **84**, 2935 (1962).

[13]W. Herz, A. Romo de Vivar, J. Romo and Viswanathan, *Ibid.* **85**, 19 (1963).

[14]J. Romo and A. Romo de Vivar, *Progress in the Chemistry of Organic Natural Products—The Pseudoguaianolides* **25**, 90 (1967).

[15]J. Romo, P. Joseph-Nathan and G. Siade, *Tetrahedron* **22**, 1499 (1966).

[16]C. W. Jefford, J. Mareda, J. C. E. Gehrt, N. T. Kabengele, W. D. Graham and U. Burger, *J. Am. Chem. Soc.* **98**, 2585 (1976).

[17]D. C. F. Law and S. W. Tobey, *Ibid.* **90**, 2376 (1968).

[18]J. W. Emsley, L. Phillips and V. Wray, *Fluorine Coupling Constants—Progress in NMR Spectroscopy* **10**, 111 (1976).