Synthesis of *gem*-Difluoro Derivatives of Natural Products by the Reaction of Ketones with Diethylaminosulphur Trifluoride

By **Keith Boulton** and **Brian E. Cross,*** Department of Organic Chemistry, The University, Leeds LS2 9JT

The preparation of *gem*-difluoro compounds, including 12,12-difluoro-octadecanoic acid, 7,7-difluorohexadecanoic acid, *ent*-7,7-difluorokauran-19-ol (8), and 2,2,7-trifluoro-10β-methoxycarbonyl-1β,8-dimethylgibban-1α,4aα-carbolactones (18) and (19), is described. Each synthesis involved fluorination of the appropriate ketone with diethylaminosulphur trifluoride, and the reaction conditions required varied from 6 h at 0 °C for the gibberellin derivatives (14) and (15) to 7 d at 115 °C for methyl 12-oxo-octadecanoate. *gem*-Difluorides are usually stable to alkali, but in the fluorogibberellins (18) and (19) the 2,2-difluoro-groups were readily hydrolysed to the corresponding 2-ketones.

DIETHYLAMINOSULPHUR TRIFLUORIDE (DAST) was introduced [1,2] for the conversion of ketones into *gem*-difluoro compounds. However its use has been limited to simple ketones and more recently to keto- and aldo-sugars.[3]

With the objective of preparing *gem*-difluoro analogues of biologically important natural products some preliminary investigations of the reaction of DAST with polyfunctionalised ketones were made, but the results were unpromising. *gem*-Difluoro-fatty acids, which are structurally simpler than many other natural products and are important compounds for use in the study of the behaviour of lipid bilayers by ^{19}F n.m.r. techniques,[4,5] constituted suitable model compounds. Hitherto their synthesis has been difficult; thus 7,7- and 12,12-difluoro-octadecanoic acids have been reported but not characterised,[4] and no *gem*-difluorohexadecanoic acid has been prepared.

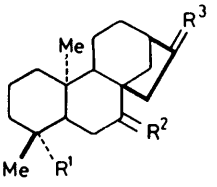
RESULTS AND DISCUSSION

Treatment of methyl 12-oxo-octadecanoate [6] and methyl 7-oxohexadecanoate [7] with DAST afforded the corresponding difluoro-esters in reasonable yield, but the reactions required much higher temperatures and longer reaction times than those used by Middleton [2] for low-molecular-weight ketones. The ^1H and ^{19}F n.m.r. spectra of the crude difluoro-esters showed that they contained small amounts of the unsaturated fluoro-esters, *e.g.* (1). G.l.c. of the methyl difluoro-esters gave in each case two peaks of equal area believed to be due to the isomeric unsaturated esters, *e.g.* (1) and (2), formed by loss of hydrogen fluoride during chromatography. The mass spectra of the difluoro-esters failed to show molecular ions, but contained strong ions at $[M - 40]^+$, *i.e.* $[M - 2HF].^+$ Alkaline hydrolysis of the methyl difluoro-esters gave 12,12-difluoro-octadecanoic and 7,7-difluorohexadecanoic acids which are undergoing tests in model biological systems.

$$CH_3[CH_2]_4CH{=}CF[CH_2]_{10}CO_2Me \quad (1)$$

$$CH_3[CH_2]_5CF{=}CH[CH_2]_9CO_2Me \quad (2)$$

Fluorinated *ent*-kaurene derivatives were required in connection with studies on inhibitors of the biosynthesis of gibberellins, but preliminary results suggested that terminal methylene groups in diterpenes were attacked by DAST.[8] This was confirmed when it was found that treatment of methyl 7-oxo-kaurenoate (3) [9] with DAST in dichloromethane at room temperature gave a gum showing many spots on t.l.c. and no olefinic proton signals in its n.m.r. spectrum. Consequently the



	R^1	R^2	R^3
(3)	CO_2Me	O	CH_2
(4)	CO_2Me	O	α—H β—Me
(5)	CO_2Me	O	α—Me, β—H
(6)	CO_2Me	F_2	α—H, β—Me
(7)	CO_2Me	F_2	α—Me, β—H
(8)	CH_2OH	F_2	α—H β—Me
(9)	CH_2OH	F_2	α—Me, β—H
(10)	CO_2H	F_2	α—H, β—Me
(11)	CHO	F_2	α—H, β—Me

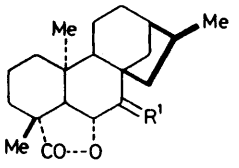
fluorination of some saturated keto-terpenoids has been examined. The model, cholestan-3-one, readily gave 3,3-difluorocholestane [10] under mild treatment with DAST.

Hydrogenation of the terminal methylene group in the ketone (3) gave a mixture of the 16-epimers (4) and (5) which reacted slowly with DAST at 114 °C to give a mixture of the 7,7-difluoro-esters (6) and (7). Reduction of these esters with lithium aluminium hydride afforded a mixture of the difluoro-alcohols (8) and (9).

In contrast to catalytic hydrogenation, di-imide reduction of 7β-hydroxykaurenolide gave, as expected, the almost pure epimer (12) [9] (*cf.* refs. 11—13), which on Jones oxidation afforded the pure keto-lactone (13).[9] The latter was converted by the literature method [9] into the keto-ester (4), which on treatment with DAST gave the 7,7-difluoro-ester (6). Oxidation of the derived alcohol (8) with Jones reagent afforded the difluoro-acid (10), whilst the aldehyde (11) was obtained by oxidation of the alcohol (8) under Ratcliffe conditions.[14]

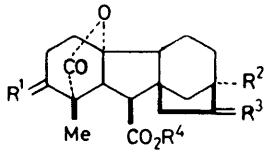
The compounds (8), (10), and (11) are difluoro-

analogues of biosynthetic precursors [15] of the gibberellins. Ring contraction of the kaurene nucleus to form the gibbane ring system proceeds *via* hydroxylation [15] of the former at position 7. Since this position is blocked by fluorine in the analogues they might act as inhibitors of gibberellin biosynthesis and their biological activity is under investigation.



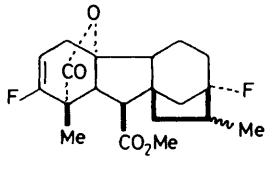
	R^1
(12)	α—H, β—OH
(13)	O

To examine the value of DAST for fluorinating more highly functionalised diterpenoids, the 8-epimeric mixture of gibberellin keto-esters [11] (14) and (15) was treated with the reagent. The reaction proceeded remarkably easily and was nearly complete after 6 h at 0 °C. The 8-epimeric fluoro-ketones (16) and (17) were



	R^1	R^2	R^3	R^4
(14)	O	OH	α—H, β—Me	Me
(15)	O	OH	α—Me, β—H	Me
(16)	O	F	α—H, β—Me	Me
(17)	O	F	α—Me, β—H	Me
(18)	F_2	F	α—H, β—Me	Me
(19)	F_2	F	α—Me, β—H	Me
(20)	O	F	α—H, β—Me	H
(21)	O	F	α—Me, β—H	H

isolated as the more polar products, whilst the faster-running band afforded the epimeric trifluoro-esters (18) and (19). In each case structures were assigned on the basis of ^{1}H and ^{19}F n.m.r. spectroscopy [16] (see Experimental section); a weak signal at ϕ^* 113.29 indicated the presence of a small amount of the vinyl fluoride (22) in the trifluoro-esters.

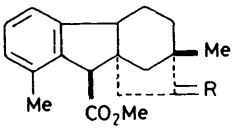


(22)

gem-Difluoro-groups are generally thought to be stable to alkaline hydrolysis,[17] although exceptions have been reported under prolonged treatment with base.[18] The difluoro-groups in the 8-epimeric esters (18) and (19) were particularly unstable to hydrolysis, and with potassium hydroxide in aqueous tetrahydrofuran, the product was a gum which showed no ^{19}F n.m.r. signals assignable to 2-fluorine atoms, but which contained the fluoro-ketones (20) and (21). Further work on the preparation of *gem*-difluorogibberellins is in hand.

As expected, the hindered keto-group in methyl gibberate (23) reacted very slowly with DAST and >50% was recovered after fluorination at 114 °C for 72 h. However, the 8,8-difluoro-ester (24) was isolated.

The results described show that DAST is a convenient reagent for the conversion of keto-groups in complex molecules into the corresponding *gem*-difluoro groups. However the reaction conditions required varied greatly



(23)	R = O
(24)	R = F_2

from several days at 115 °C, for ketones as diverse as methyl 12-oxo-octadecanoate and methyl *ent*-7-oxo-kauran-19-oate (4), to 6 h at 0 °C for the gibberellin ketones (14) and (15).

EXPERIMENTAL

Details of chromatographic materials and conditions used for the determination of physical data, *etc.*, have been reported.[19] G.l.c. was carried out on a Varian 1527B gas chromatograph with a stainless steel column (150 × 0.3 cm o.d.) packed with 5% SE30 on Anakrom and a nitrogen gas flow of 30 ml min^{-1}). Light petroleum had b.p. 60—80 °C unless otherwise stated.

Methyl 12,12-*Difluoro-octadecanoate.*—Methyl 12-oxo-octadecanoate [6] (500 mg) in dry carbon tetrachloride (10 ml) was treated with DAST (1.2 g) at 115 °C in a stainless steel bomb for 7 d. (T.l.c. analysis of samples of the reaction mixture after 1, 2, 3, and 5 d showed the presence of keto-ester). Water was added, the organic layer was separated, and the aqueous layer was extracted with carbon tetrachloride. The combined organic extracts were washed with water, dried over potassium carbonate, and evaporated *in vacuo* to give *methyl* 12,12-*difluoro-octadecanoate* (500 mg) (pure by t.l.c.) which sublimed at 83 °C (bath temperature) and 5 × 10^{-5} mmHg as a crystalline solid (Found: C, 68.4; H, 11.0; F, 11.7. $C_{19}H_{36}F_2O_2$ requires C, 68.2; H, 10.9; F, 11.4%); τ 9.10 (3 H, t, 18-H_3), 8.70br (28 H, 14 × CH_2), 7.68 (2 H, t, J 7 Hz, 2-H_2), 6.33 (3 H, s, OMe), and 5.56 (m, $W_{\frac{1}{2}}$ 55 Hz, C*H*=CF, impurity ≪ 5%); ϕ^* 110.3br (m, CH=C*F*) and 97.8 (quintet, J 16 Hz, 12-F_2); $\nu_{max.}$ 1 747 cm^{-1}. G.l.c. retention times (at a column temperature of 146 °C) were 50 and 56 min.

12,12-*Difluoro-octadecanoic Acid.*—The above ester (162 mg) and potassium hydroxide (1.1 g) in tetrahydrofuran (6 ml) and water (6 ml) were refluxed for 2 h. The solution was washed with chloroform and acidified with 2N-hydrochloric acid. The product was recovered in chloroform, and purified by p.l.c. using benzene for development. The high

R_F band gave 12,12-*difluoro-octadecanoic acid*, which crystallised from light petroleum (b.p. 40—60 °C) as prisms or hexagons (52 mg), m.p. 71—72 °C (Found: C, 67.3; H, 10.35; F, 11.55. $C_{18}H_{34}F_2O_2$ requires C, 67.5; H, 10.7; F, 11.9%); τ 9.13 (3 H, t, 18-H_3), 7.99br ($W_{\frac{1}{2}}$ 12 Hz, 11- and 13-H_2), and 7.65 (2 H, t, *J* 7 Hz, 2-H_2); $\nu_{max.}$ 2 660br and 1 710 cm^{-1}.

7,7-*Difluorohexadecanoic Acid*.—Methyl 7-oxohexadecanoate [7] (139 mg) in dry carbon tetrachloride (5 ml) was treated with DAST (220 mg) at 108 °C in a bomb for 3 d. Recovery and purification (as above) gave methyl 7,7-difluorohexadecanoate as a gum (52 mg); τ 9.10 (3 H, t, 16-H_3), 8.00br (s, 6- and 8-H_2), and 6.32 (3 H, s, OMe); ϕ* 98.0 (quintet, *J* 16 Hz, 7-F_2). The use of toluene as solvent gave black tarry products.

The ester (50 mg) and potassium hydroxide (280 mg) in tetrahydrofuran (5 ml) and water (5 ml) were boiled under reflux for 2 h. Work-up as above afforded 7,7-*difluorohexadecanoic acid* (35 mg) which crystallised from light petroleum (b.p. 40—60 °C) as needles, m.p. 76—77 °C (Found: C, 65.75; H, 10.65; F, 13.15. $C_{16}H_{30}F_2O_2$ requires, C, 65.7; H, 10.35; F, 13.0%); τ 9.14 (t, 16-H_3), 8.0br ($W_{\frac{1}{2}}$ 12 Hz, 6- and 8-H_2), and 7.65 (3 H, t, *J* 7 Hz, 2-H_2); $\nu_{max.}$ 2 660br, 1 710, and 1 690 cm^{-1}; (in $CHCl_3$) 2 670 and 1 708 cm^{-1}.

3,3-*Difluorocholestane*.—Cholestan-3-one (65 mg) in dry dichloromethane (1 ml) was treated with DAST (218 mg) at 20 °C for 84 h. Work-up as in preceding experiments followed by chromatography on silica gel (15 g), and elution with light petroleum gave 3,3-difluorocholestane which crystallised from ethanol as needles (31 mg, 45%), m.p. 108—109 °C (lit.,[10] 109—110 °C) (Found: C, 78.95; H, 11.0; F, 9.1. Calc. for $C_{27}H_{46}F_2$: C, 79.4; H, 11.3; F, 9.3%); ϕ* 126.35 (d, *J* 233 Hz, 3β-F) and 116.14br (dm, *J* 233 Hz, $W_{\frac{1}{2}}$ 110 Hz, 3α-F).

Fluorination of Methyl ent-7-*Oxokaur*-16-*en*-19-*oate* (3).—Treatment of the keto-olefin [9] with DAST in dichloromethane for 25 h at room temperature gave an intractable mixture, shown by t.l.c. to contain at least 6 compounds. The n.m.r. spectrum of the crude product showed no olefinic proton signals.

Hydrogenation of Methyl ent-7-*Oxokaur*-16-*en*-19-*oate*.—The ester (150 mg) in ethyl acetate (10 ml) was hydrogenated in the presence of 10% palladium–charcoal (100 mg) until uptake of hydrogen ceased. Recovery in the usual way gave a mixture of the 16-epimers of *methyl* ent-7-*oxokauran*-19-*oate* (4) and (5) (145 mg) (Found: *m/e* 332.235 6. $C_{21}H_{32}O_3$ requires *M*, 332.235 1); τ 9.01 and 8.95 (3 H, 2 d, *J* 6 Hz, 17-H_3), 8.82 (3 H, s, 20-H_3), 8.72 (3 H, s, 18-H_3), and 6.31 (3 H, s, OMe).

Fluorination of Methyl ent-7-*Oxokauran*-19-*oate* (*Mixture of* 16-*Epimers*).—The keto-esters (130 mg) in dry carbon tetrachloride (5 ml) were treated with DAST (250 mg) in a stainless-steel bomb at 114 °C for 84 h. The mixture was poured into water and extracted with carbon tetrachloride. The organic extracts were washed with water and dried. Removal of the solvent *in vacuo* and purification of the residue by p.l.c. with development in benzene, afforded *methyl* ent-7,7-*difluorokauran*-19-*oate* (mixture of 16-epimers) (6) and (7) as a gum (47 mg) (Found: *m/e* 354.237 5. $C_{21}H_{32}F_2O_2$ requires *M*, 354.237 0); $\nu_{max.}$ ($CHCl_3$) 1 720, 1 150, 1 129, and 970 cm^{-1}; τ 9.16 (3 H, s, 20-H_3), 9.04 and 8.98 (3 H, 2 d, *J* 7 Hz, 17-H), 8.83 (3 H, s, 18-H_3), and 6.38 (3 H, s, OMe); no signal due to C*H*=CF could be detected; ϕ* (on the crude product) 105.26 (m, 7-F_2) and 125.00 (weak, corresponding to <4% C=C*F*). G.l.c. at 180 °C showed only two peaks due to the epimers (6) and (7).

Similarly, fluorination of methyl *ent*-7-oxokauran-19-oate (4) gave methyl *ent*-7,7-difluorokauran-19-oate (6) as a gum.

Preparation of ent-7-*Oxokaurane*-19,6β-*carbolactone* (13).—7β-Hydroxykaurenolide (1.1 g) in alcohol (50 ml) was treated with hydrazine hydrate (3 ml) at 0 °C. Hydrogen peroxide (30%; 3 ml) was added during 1 h, the mixture was stirred at 0 °C for a further 3 h, and then at room temperature for 12 h. Ethanol was removed *in vacuo* and the mixture was acidified with dilute hydrochloric acid. Recovery in ethyl acetate gave nearly pure *ent*-7α-hydroxykaurane-19,6β-carbolactone (12) (1.0 g); τ 9.12 (3 H, s, 20-H_3), 8.99 (3 H, d, *J* 7 Hz, 17-H_3), 8.70 (3 H, s, 18-H_3), 5.70 (1 H, d, *J* 6 Hz, 7-H), and 5.35 (1 H, t, *J* 6 Hz, 6-H), which on oxidation with Jones reagent afforded *ent*-7-oxokauran-19,6β-carbolactone (13), m.p. 263—264 °C (from ethyl acetate–light petroleum) (lit.,[9] m.p. 264 °C).

Reduction of the Difluoro-esters (6) *and* (7) *with Lithium Aluminium Hydride*.—The esters (47 mg) in ether (2 ml) were treated with lithium aluminium hydride (100 mg) at room temperature for 24 h. Isolation of the product in the usual way followed by crystallisation from light petroleum gave a mixture of the 16-epimers of ent-7,7-*difluorokauran*-19-*ol* (8) and (9), as clusters of needles, m.p. 136—139 °C (Found: C, 73.55; H, 9.7; F, 11.95. $C_{20}H_{32}F_2O$ requires C, 73.55; H, 9.9; F, 11.6%); $\nu_{max.}$ 3 470, 1 312, 1 200, and 1 130 cm^{-1}.

Reduction of the difluoro-ester (6) under the same conditions gave ent-7,7-*difluorokauran*-19-*ol* (8) which crystallised from light petroleum as needles, m.p. 124—127 °C (Found: *m/e* 326.242 7. $C_{20}H_{32}F_2O$ requires *M*, 326.242 1); τ 9.0 (3 H, s, 20-H_3), 8.97 (3 H, d, *J* 8 Hz, 17-H_3), 8.74 (3 H, s, 18-H_3), 6.50 (1 H, d, *J* 11 Hz), and 6.31 (1 H, d, *J* 11 Hz) (19-CH_2).

Oxidation of ent-7,7-*Difluorokauran*-19-*ol with Jones Reagent*.—The alcohol (10 mg) in acetone (1 ml) was treated with Jones reagent (0.1 ml) at room temperature for 1 h. Recovery in ethyl acetate and crystallisation from light petroleum (b.p. 40—60 °C) gave needles, m.p. 176—182 °C (decomp.) of ent-7,7-*difluorokauran*-19-*oic acid* (10) (Found: *m/e* 340.221 8. $C_{20}H_{30}F_2O_2$ requires *M*, 340.221 4); $\nu_{max.}$ 3 500—2 400, 1 700, 1 150, 1 068, and 990 cm^{-1}.

Preparation of ent-7,7-*Difluorokauran*-19-*al* (11).—Chromium trioxide (360 mg) in dichloromethane (15 ml) was added to dry pyridine (600 mg) at 0 °C with stirring and then the alcohol (8) (25 mg) in dichloromethane (5 ml) was added, and stirring was continued for 15 min. The organic layer was decanted and the residue was washed with dichloromethane. The combined solutions were washed with dilute sodium hydroxide solution, dilute hydrochloric acid, and water. Recovery *in vacuo* gave ent-7,7-*difluorokauran*-19-*al* (11) as a gummy solid (20 mg) (Found: *m/e* 324.225 8. $C_{20}H_{30}F_2O$ requires *M*, 324.226 5); τ 9.09 (3 H, s, 20-H_3), 8.96 (3 H, d, *J* 6 Hz, 17-H_3), 8.73 (3 H, s, 18-H_3), and 0.26 (1 H, s, 19-CHO).

Fluorination of the 8-*Epimeric Mixture of* 7α-*Hydroxy*-10β-*methoxycarbonyl*-1β,8-*dimethyl*-2-*oxogibbane*-1α,4aα-*carbolactones* (14) *and* (15).—The ketones [11] (145 mg) in dry dichloromethane (1 ml) were treated with DAST (250 mg) at 0 °C for 6 h. Water was added and the products were recovered in dichloromethane. Removal of the solvent *in vacuo* gave a gum which was purified by p.l.c. Development with chloroform–light petroleum (1 : 1) gave two

bands. Elution of the band of lower R_F with acetone afforded a mixture of the 8-epimers, (16) and (17), of 7α-*fluoro*-10β-*methoxycarbonyl*-1β,8-*dimethyl*-2-*oxogibbane*-1α,4aα-*carbolactones* as a semi-solid (20 mg) (Found: *m/e* 364.168 9. $C_{20}H_{25}FO_5$ requires *M*, 364.168 6); $\nu_{max.}$ ($CHCl_3$) 1 770, 1 730, and 1 690 cm^{-1}; τ 9.02 and 8.98 (3 H, 2 d, *J* 8 Hz, 8α- and 8β-Me), 8.80 (3 H, s, 1β-Me), 7.2 (d, *J* 9 Hz, 10a-H), 6.94 (1 H, d, *J* 9 Hz, 10-H), and 6.26 (3 H, s, OMe).

Recovery of the band of higher R_F gave a gum which crystallised from methanol as needles, m.p. 152—158 °C, of the 8-epimeric mixture of 2,2,7-*trifluoro*-10β-*methoxycarbonyl*-1β,8-*dimethylgibbane*-1α,4aα-*carbolactones* (18) and (19) (Found: *m/e* 386.171 8. $C_{20}H_{25}F_3O_4$ requires *M*, 386.170 5); τ 9.03 and 8.98 (3 H, 2 d, *J* 7 Hz, 8α- and 8β-Me), 8.80 (3 H, s, 1β-Me), 7.31 (d, *J* 10 Hz, 10-H), 6.97 (t, *J* 10 and $^4J_{FH}$ 10 Hz, 10a-H), and 6.23 (3 H, s, OMe); $\nu_{max.}$ 1 775 and 1 735 cm^{-1}; ϕ^* 159.40br [s, 7α-F in (18)], 146.95br [s, 7α-F in (19)], 113.29br [vw, s, 2-F in (22)], 109.38 (dm, *J* 238 Hz, 2β-F), and 102.26 (dd, *J* 238 and 10 Hz, 2α-F). Irradiation of the 10α-H signal in (18) and (19) caused the 2α-F signal to collapse to a doublet, *J* 238 Hz.

Hydrolysis of the Fluoro-esters (18) *and* (19).—The esters (30 mg) in water (5 ml) and tetrahydrofuran (5 ml) were refluxed with potassium hydroxide (100 mg) for 1 h. Acidification of the solution with dilute hydrochloric acid and recovery of the product in ethyl acetate followed by purification by p.l.c. [development with benzene–ether (9 : 1)] gave a gum (20 mg) which contained the 7α-fluoro-ketones (20) and (21); $\nu_{max.}$ ($CHCl_3$) 1 765 and 1 710 cm^{-1}; ϕ^* 149.37br and 160.34br (2 s, 7α-F in 8-epimers); no signals were observed corresponding to 2-F atoms (Found: *m/e* 350.151 9. $C_{19}H_{23}FO_5$ requires *M*, 350.152 9). The presence of the fluoro-ketones in the gum was confirmed by methylation, followed by g.l.c. comparison with an authentic sample of the ketones (16) and (17) (from above).

Fluorination of Methyl Gibberate.—The keto-ester (158 mg) in dry carbon tetrachloride (5 ml) was treated with DAST (400 mg) in a stainless-steel bomb at 114 °C for 72 h. Isolation of the products in the usual way followed by p.l.c. [chloroform–light petroleum (1 : 1)] and elution of the band of lower R_F gave, after recrystallisation from methanol, methyl gibberate (85 mg) identical (i.r., g.l.c., and n.m.r.) with an authentic specimen.

Elution of the higher-R_F band gave *methyl* 1,7-*dimethyl*-8,8-*difluoro*-7α-*gibbane*-10β-*carboxylate* (24) as an oil (30 mg) (Found: *m/e* 320.159 1. $C_{19}H_{22}F_2O_2$ requires *M*, 320.158 8); τ 8.95 (3 H, d, $^4J_{FH}$ 2 Hz, 7-H_3), 7.87 (3 H, s, 1-H_3), 6.23 (3 H, s, OMe), 6.00br (1 H, s, 10-H), and 2.85 (3 H, m, aromatic H); ϕ^* 110.58 (dd, *J* 224 and 12 Hz, 8-F) and 94.01 (dm, *J* 224 Hz, 8-F).

We thank Mr. I. S. Nixon [Imperial Chemical Industries (Pharmaceutical Division)] for a gift of chemicals and the S.R.C. for a Research Studentship (to K. B.).

[8/1117 *Received*, 15*th June*, 1978]

REFERENCES

[1] L. N. Markovskij, V. E. Pashinnik, and A. V. Kirsanov, *Synthesis*, 1973, 787.
[2] W. J. Middleton, *J. Org. Chem.*, 1975, **40**, 574.
[3] R. A. Sharma, I. Kavai, Y. L. Fu, and M. Bobek, *Tetrahedron Letters*, 1977, 3433.
[4] F. J. Longmuir and F. W. Dalquist. *Proc. Nat. Acad. Sci. U.S.A.*, 1976, **73**, 2716.
[5] N. Boden, personal communication.
[6] R. Perrotte, *Compt. rend.*, 1935, **200**, 746.
[7] B. E. Cross and P. Hendley, *J.C.S. Perkin I*, 1975, 2523.
[8] B. E. Cross and A. Erasmuson, unpublished work.
[9] B. E. Cross, R. H. B. Galt, and J. R. Hanson, *J. Chem. Soc.*, 1963, 2944.
[10] B.P. 930,888 (*Chem. Abs.*, 1964, **60**, 641).
[11] B. E. Cross, *J. Chem. Soc.*, 1960, 3022.
[12] K. Mori, M. Ohki, A. Sato, and M. Matsui, *Tetrahedron*, 1972, **28**, 3739.
[13] B. E. Cross and I. C. Simpson, unpublished work.
[14] R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 1970, **35**, 4000.
[15] J. MacMillan and R. J. Pryce, in ' Phytochemistry,' ed. L. P. Miller, vol. 3, ch. 11, van Nostrand, New York, 1973.
[16] B. E. Cross and R. E. Banks, *J.C.S. Perkin I*, 1977, 512.
[17] M. Hudlicky, ' Chemistry of Organic Fluorine Compounds,' 2nd edn., Ellis Horwood, New York, 1976, pp. 266—272.
[18] D. R. Strobach, *Tetrahedron Letters*, 1971, 883.
[19] J. H. Bateson and B. E. Cross, *J.C.S. Perkin I*, 1974, 1131.