REACTIVITY OF 2,2-DIFLUORO-3-METHYL-3-BUTENAL TOWARD SOME O-, N- AND C-NUCLEOPHILES*

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Addition of nucleophiles to 2,2-difluoro-3-methyl-3-butenal (*I*) is complicated by its spontaneous polymerization. Compound *I* afforded neither hydrate nor dimethyl acetal but reacted with ethylene glycol to give the cyclic acetal *II*. Reaction with acetyl chloride and acetic anhydride led to the respective acetate *III* and diacetate *IV*.

Satisfactory reaction with N-nucleophiles was observed only in the case of hydroxylamine and dinitrophenylhydrazine. Diethylamine reacted with *I* only at 150°C to give the reduction product *VI* and the ethylaldimine *VII*. The compound *I* added nitromethane and sodium cyanide (giving *X* and *XI*, respectively); the adducts or products of their reduction with lithium aluminium hydride were hydroxylated at the double bond to give analogues of alcoholic sugars with difluoromethylene group in position 3. Hydroxylation of the butenal *I* or the acetate *III* afforded 3,3-difluoro-2,4-dihydroxy-4-methyloxolane (*XIX*) which was prepared also by cleavage of the acetal *XVIII* obtained from *II* by hydroxylation. Addition of bromine to the double bond in *III* and *IV* gave the dibromo derivatives *XV* and *XVI*; the attempted replacement of bromine in *XV* and *XVI* by acetate anion failed. Bromination of *I* in aqueous medium afforded 3-bromo-2,2-difluoro-3-methyl-4-butanolide (*XIV*).

In our previous communication[1] we described the formation of 2,2-difluoro-3-methyl-3-butenal (*I*) in the cleavage of 3,3,4-trifluoro-2,2-dimethyloxetane with mineral acids. Since the product *I* may find synthetic utilization, we investigated its reactivity toward some O-, N- and C-nucleophiles.

The butenal *I* polymerizes very easily, this polymerization being sometimes very vigorous. Whereas other fluorinated aldehydes polymerize only in the presence of catalysts[2], the aldehyde *I* polymerizes already on distillation immediately in the receiver. The polymerization is accompanied by a change of the consistence and a rapid drop of intensity of the C=O absorption band at 1 760 cm^{-1}. In the ^1H NMR spectrum the polymerization can be followed by a gradual disappearance of the CHO signal at δ 9·32, and a simultaneous increase in intensity of the broad —O—CH—O— proton multiplet at δ 4·90–5·55. Heating the polymer above 115°C furnished the monomer as a mobile liquid boiling at 77–80°C.

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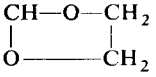
It is probable that this unusually facile polymerization of the butenal *I* may compete with nucleophilic additions to the aldehyde group. The failure of reaction with sodium hydrogen sulfite has been reported by us elsewhere[1]. In the attempted preparation of the hydrate (easily accessible with the structurally similar 2,2-difluoro aldehydes[1,3]) we isolated from the aqueous solution of *I* only its polymer. Similarly, no dimethylacetal or hemiacetal[4] was found when *I* was treated with methanol, even in the presence of sulfuric acid. Dissolution of the butenal *I* in methanol is an exothermic process and the ^{1}H NMR spectrum shows only polymerization. On the other hand, acetalisation with ethylene glycol at 150°C in the presence of traces of sulfuric acid afforded the dioxolane *II* in 43% yield. As expected, compound *II* is hydrolyzed with dilute sulfuric acid at elevated temperature and pressure only with difficulty[5] giving the butenal *I* in low yield. The addition of acetyl chloride[6] and acetic anhydride[7] is relatively easy. The former reagent reacts with the aldehyde in the presence of sulfuric acid to give the already described[1] acetate *III* in 25% yield, reaction with acetic anhydride, catalyzed with zinc chloride, afforded the diacetate *IV* in a yield of 47%. In addition to the acetate *IV*, we isolated substantial amount of the dimer, 2,8-dimethyl-3,3,7,7-tetrafluoro-5-oxanona-1,8-diene-4,6-diol diacetate (*V*). Its two stereoisomers were separated by the GL-MS technique and exhibited very similar mass spectra. We assume that they represent a *meso*-form and a racemic mixture of both enantiomers. Treatment of the butenal *I* with ammonia or diethylamine resulted in its polymerisation. Diethylamine reduced the compound *I* at 150°C, giving rise to a complex reaction mixture from which the butenol *VI* and the aldimine *VII* were isolated by gas–liquid chromatography as the principal products. On the other hand, the 2,4-dinitrophenylhydrazone *VIII* was formed smoothly in the presence of dilute sulfuric acid at room temperature. Also condensation of the butenal *I* with hydroxylamine in boiling methanol presented no problems. Reactions of the butenal *I* with some C-nucleophiles proceed more readily than with O- and N- nucleophiles. Nitromethane in the presence of potassium carbonate[8] in an exothermic reaction affords the corresponding nitropentol *X* in 62% yield. With sodium cyanide, the reaction course depends on temperature: at 0°C (according to ref.[9]) the reaction afforded the cyanohydrin *XI* in a good yield whereas at elevated temperatures (spontaneous warming) the dioxene *XII* was isolated as the principal product. Its formation may be explained by addition of sodium salt of the cyanohydrin to the carbonyl group of another molecule of *I* and subsequent elimination of hydrogen fluoride and cyclization to *XII*.

We investigated also oxidation of the aldehyde group in the butenal *I*. Oxidation with silver oxide[10] is rapid and gives the expected acid *XIII* in low yield. Reaction with bromine in a neutral aqueous medium afforded the butanolide *XIV* arising by bromolactonization of the primarily formed acid *XIII*.

We tried to utilize the butenal *I* for the synthesis of trihydroxy or tetrahydroxy derivatives containing a difluoromethylene group that are analogous to monosac-

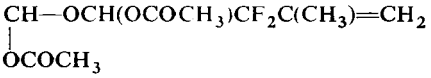
$$CH_2{=}C(CH_3)CF_2{-}X$$

I, X = CHO

II, X = 

III, X = $CH(Cl)OCOCH_3$

IV, X = $CH(OCOCH_3)_2$

V, X = 

VI, X = CH_2OH

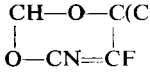
VII, X = $CH{=}NCH_2CH_3$

VIII, X = $CH{=}NNH{-}C_6H_3(NO_2)_2$

IX, X = CH=NOH

X, X = $CH(OH)CH_2NO_2$

XI, X = CH(OH)CN

XII, X = 

XIII, X = COOH

XXIII, X = $CH(OH)CH_2NH_2$

XXV, X = $CH(OH)CH_2OH$

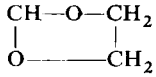
$$CHBr{=}C(CH_3)CF_2CH(OCOCH_3)_2$$

XVII

$$Y{-}CH_2{-}CY(CH_3)CF_2{-}X$$

XV, Y = Br, X = $CH(Cl)OCOCH_3$

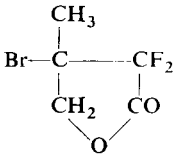
XVI, Y = Br, X = $CH(OCOCH_3)_2$

XVIII, Y = OH, X = 

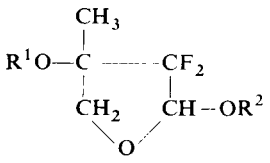
XXII, Y = OH, X = $CH(OH)CH_2NO_2$

XXIV, Y = OH, X = $CH(OH)CH_2NH_2$

XXVI, Y = OH, X = $CH(OH)CH_2OH$



XIV



XIX, R^1 = R^2 = H

XX R^1 = R^2 = $OCOCH_3$

XXI, R^1 = H, R^2 = $OCOCH_3$

charides and might possess biological activity[11,12]. To functionalize the double bond in compound *I*, esters *III* and *IV* were subjected to radical bromination[13] to give the respective dibromo derivatives *XV* and *XVI* in high yields. However, the attempted replacement of halogen atoms in the acetate *XV* with acetoxy groups by treatment with silver or sodium acetate resulted only in substitution of the chlorine atom[14] under formation of the diacetate *XVI*. Further reaction of *XVI* with potassium acetate under more vigorous conditions led to elimination and the obtained complex reaction mixture contained the diacetate *XVII* as the main product. Direct hydroxylation of the double bond proved to be more convenient, the oxidation with catalytic amount of osmium tetroxide in the presence of sodium chlorate[15] being the method of choice. In this manner, we converted the dioxolane *II* into the diol *XVIII* in 66% yield. Acid hydrolysis of the acetal group in the diol *XVIII* is relatively easy as contrasted with the behaviour of *II*, obviously thanks to participation of the primary hydroxyl, leading to the cyclic hemiacetal *XIX*. The same product (*XIX*) was obtained also by direct hydroxylation of the butenal *I* or acetate *III*. Its structure was confirmed by acetylation with acetic anhydride in pyridine which afforded the diastereoisomeric diacetates *XX* as a 1 : 1·5 mixture. The monoacetate *XXI* was obtained by direct hydroxylation of the diacetate *IV* in 67% yield.

Sugar analogs of the pentose series were synthesized starting from the nitro alcohol *X*, the cyanohydrin *XI* or the amino alcohol *XXIII*, prepared by reduction of *X* or *XI* with lithium aluminium hydride. The nitro alcohol *X* was smoothly hydroxylated to give the triol *XXII* as a 1 : 1·2 mixture of diastereoisomers; this ratio (determined by ^{19}F NMR spectrum) illustrated the negligible influence of the original asymmetric center in compound *X* on the stereoselective control of osmium tetroxide. Contrarywise, hydroxylation of the cyanohydrin *XI* afforded a complex reaction mixture. Hydroxylation of the amino alcohol *XXIII* was difficult and the desired amino triol *XIV* was finally isolated by column chromatography in 20% yield as a 1 : 1·8 diastereoisomeric mixture. The amino alcohol *XXIII* proved to be a suitable starting compound for preparation of the tetrol *XXVI*. Treatment of *XIII* with nitrous acid afforded the unsaturated diol *XXV* which was smoothly hydroxylated to give the tetrol *XXVI* in 50% yield. Our attempts to separate the obtained diastereoisomeric mixtures of the hydroxy derivatives *XXII*, *XXIV*, and *XXVI* by thin-layer or column chromatography were unsuccessful.

EXPERIMENTAL

The temperature data are uncorrected. Unless stated otherwise, the IR spectra were taken neat on a Perkin–Elmer 325 spectrometer and are given in cm^{-1}. The NMR spectra were measured on a Varian XL-100 instrument in deuteriochloroform with tetramethylsilane and fluorotrichloromethane as internal standards. Chemical shifts are given in ppm, coupling constants in Hz. Mass spectral measurements were performed on a Gas Chromatograph-Mass Spectrometer LKB 9000 and are described as usual (*m/z*; relative intensity, %, in parentheses). Gas–liquid chromatographic

(GLC) analyses and preparations were carried out on a Chrom 3 instrument (FI detector, carrier gas nitrogen); stationary phase: poly(propylene sebacate) (PPS), poly(1,4-butanediol succinate) (BDS) or silicone elastomer SE-30, on Chromaton N-AW. Thin-layer chromatography (TLC) and liquid–liquid chromatography (LC) were performed on Silpearl. Elemental analyses of the products are given in Table I.

2-(1,1-Difluoro-2-methyl-2-propenyl)-1,3-dioxolane (*II*)

A mixture of the butenal *I* (0·6 g; 5 mmol), ethylene glycol (1 g) and conc. sulfuric acid (0·1 ml) was refluxed at 150—160°C for 5 h. The cold mixture was diluted with ether (2 ml), washed with water and dried over potassium carbonate. Preparative GLC (BDS, 165°C) afforded 352 mg (43%) of the dioxolane *II*, identical (NMR, IR and mass spectra, GLC) with an authentic sample.

Hydrolysis: A stirred mixture of the dioxolane *II* (0·82 g; 5 mmol) and 25% sulfuric acid (3 ml) was heated in a sealed ampoule to 140—150°C for 4 h, cooled, diluted with water (4 ml), neutralized with 15% sodium hydroxide solution and extracted with ether. After drying over magnesium sulfate, ether was evaporated *in vacuo*. According to GLC (PPS, 60—170°C), the remaining oil contained 66% of the starting *II* together with 28% of the butenal *I*.

1-Chloro-2,2-difluoro-3-methyl-3-butenyl Acetate (*III*)

Concentrated sulfuric acid (0·3 ml) was added to a solution of the butenal *I* (0·6 g; 5 mmol) in acetyl chloride (2 g.) After standing overnight at room temperature, the mixture was diluted with ether (10 ml), washed with a solution of sodium hydrogen carbonate and water, dried over magnesium sulfate and taken down. Distillation afforded 0·25 g (25%) of the acetate *III*, identical (GLC, NMR) with an authentic sample.

Reaction of Butenal *I* with Acetic Anhydride

The aldehyde *I* (25·5 g; 210 mmol), acetic anhydride (32 g), and zinc chloride (5·4 g) were mixed together. The mixture warmed spontaneously and was set aside for 48 g at room temperature. After dilution with water (40 ml), the product was taken up in ether (5 × 25 ml), the combined extracts were washed with water, solution of sodium hydrogen carbonate and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* gave 32·8 g of the crude product which was fractionated. After a forerun, containing the starting butenal *I*, the following fractions were collected:

2,2*Difluoro*-3-*methyl*-3-*butenylidene diacetate* (IV), b.p. 114—118°C/2·9 kPa (47%), identical with an authentic sample.

2,8-*Dimethyl*-3,3,7,7-*tetrafluoro*-5-*oxanona*-1,8-*diene*-4,6-*diol diacetate* (V), b.p. 146—151°C/2·5 kPa (4·0 g); IR spectrum: $\nu(CH_2=)$ 3 100 w, $\nu(C=O)$ 1 760 s, $\nu(C=C)$ 1 650 w; ^1H NMR spectrum: 1·86 (s, 3 H, CH_3), 2·22 (s, 3 H, CH_3CO), 5·32 (d, $^2J_{HH}$ = 15, 2 H, $CH_2=$), 6·04 to 6·40 (m, 1 H, CH); ^{19}F NMR spectrum: 113·0 (m, $^3J_{HF}$ = 7, 2 F, CF_2), 113·4 (m, $^3J_{HF}$ = 7, 2 F, CF_2); mass spectrum: *a*) component with shorter retention time: 43 (100), 103 (24), 131 (16), 91 (8·1), 44 (8), 163 (7), 65 (7), 91 (4), $(M - 59)^+$ 283 (1); *b*) component with longer retention time: 43 (100), 103 (16), 131 (11), 61 (6), 44 (6), 65 (4), 91 (4), 183 (3), $(M-59)^+$ 283 (0·1).

Reaction of Butenal *I* with Diethylamine

A mixture of the butenal *I* (2·4 g; 20 mmol) and diethylamine (3·6 g) was heated in a sealed ampoule to 150°C for 3 h and then distilled *in vacuo*. The fraction boiling up to 72°C/2·0 kPa was collected (4·15 g) and freed of diethylamine by distillation on a 15 cm Jansen column. Pre-

TABLE I
Elemental analyses

Compound	Formula Mol.wt.	Calculated/Found				
		% C	% H	% Br	% F	% N
V	$C_{14}H_{18}F_4O_5$	49·13	5·29	—	22·21	—
	(342·3)	49·44	5·11	—	22·54	—
VII	$C_7H_{11}F_2N$	57·10	7·55	—	25·83	9·52
	(147·1)	57·56	7·28	—	26·26	9·63
VIII	$C_{11}H_{10}F_2N_4O_4$	43·99	3·36	—	12·66	18·66
	(300·1)	43·94	3·41	—	12·50	18·71
IX	$C_5H_7F_2NO$	44·41	5·26	—	28·13	10·36
	(135·1)	44·31	5·35	—	27·77	10·68
X	$C_6H_9F_2NO_3$	39·76	5·02	—	20·98	7·73
	(181·1)	39·86	5·94	—	21·29	8·15
XI	$C_6H_7F_2NO$	48·95	4·83	—	25·83	9·52
	(147·1)	48·92	4·91	—	25·42	9·53
XII	$C_{11}H_{12}F_3NO_2$	53·41	4·90	—	23·07	5·66
	(241·1)	53·58	5·00	—	23·25	5·77
XIII	$C_5H_6F_2O_2$	44·08	4·41	—	27·92	—
	(136·1)	44·13	4·88	—	27·71	—
XIV	$C_5H_5BrF_2O_2$	27·91	2·32	37·21	17·37	—
	(215·0)	28·55	2·48	36·56	16·91	—
XV	$C_7H_9Br_2ClF_2O_2$	23·44	2·54	44·58	10·60	—
	(358·3)	23·60	2·58	44·13	10·65	—
XVI	$C_9H_{12}Br_2F_2O_4$	28·30	3·17	41·83	9·95	—
	(382·0)	27·96	3·51	41·88	10·36	—
XVII	$C_9H_{11}BrF_2O_4$	35·90	3·79	—	12·63	—
	(301·0)	36·10	4·11	—	12·13	—
XVIII	$C_7H_{12}F_2O_4$	42·40	6·14	—	19·18	—
	(198·1)	42·65	6·15	—	18·72	—
XIX	$C_5H_8F_2O_3$	38·94	5·26	—	24·66	—
	(154·1)	39·40	5·26	—	24·61	—
XX	$C_9H_{12}F_2O_5$	45·36	5·08	—	15·96	—
	(238·1)	45·66	5·03	—	16·33	—
XXI	$C_7H_{10}F_2O_4$	42·86	5·11	—	19·38	—
	(196·1)	42·60	5·98	—	19·35	—
XXII	$C_6H_{11}F_2NO_5$	33·47	5·16	—	17·67	6·51
	(215·1)	33·22	5·13	—	17·43	6·36

TABLE I
(*Continued*)

Compound	Formula Mol.wt.	Calculated/Found				
		% C	% H	% Br	% F	% N
XXIII	$C_6H_{11}F_2NO$	47·65	7·35	—	25·15	9·27
	(151·1)	47·36	7·30	—	25·40	9·32
XXIV	$C_6H_{13}F_2NO_3$	38·90	7·08	—	20·53	7·56
	(185·1)	39·34	7·43	—	19·82	7·26
XXV	$C_6H_{10}F_2O_2$	47·34	6·64	—	24·98	—
	(152·1)	47·31	7·03	—	25·15	—
XXVI	$C_6H_{12}F_2O_4$	38·69	6·50	—	20·42	—
	(186·1)	38·64	6·40	—	20·59	—

parative GLC (BDS, 140°C) of the remaining oil (1·5 g) afforded 2,2-difluoro-3-methyl-3-butenol (*VI*) (428 mg), identical (GLC, NMR) with an authentic sample, and N-(2,2-difluoro-3-methyl-3-butenylidene)ethylamine (*VII*) (194 mg); IR spectrum: $\nu(CH_3)$ 2 980 s; $\nu(C{=}N)$ 1 675 m; ^1H NMR spectrum: 1·25 (t, 3 H, CH_3), 1·88 (s, 3 H, CH_3), 3·58 (q, 2 H, CH_2), 5·30 (d, $^2J_{HH}$ = = 16, 2 H, $CH_2{=}$), 7·60 (m, 1 H, CH); ^{19}F NMR spectrum: 105·1 (m, 2 F, CF_2); mass spectrum: 56 (100), 58 (18), 65 (14), 91 (14), 41 (12), 133 (6), 148 (3), $(M+1)^+$ 148 (3).

2,2-Difluoro-3-methyl-3-butenal 2,4-Dinitrophenylhydrazone (*VIII*)

Saturated solution of 2,4-dinitrophenylhydrazine in 30% sulfuric acid (3 ml) was added to a solution of the butenal *I* (0·5 g) in ethanol (5 ml). After standing overnight at room temperature, the formed crystalline paste was dissolved in benzene (10 ml), the aqueous phase was separated and the organic one washed with a sodium hydrogen carbonate solution. Evaporation of the solvent afforded a residue (0·4 g) which was purified by column chromatography (Silpearl, cyclohexene–ethyl acetate) to give 0·2 g of the product. Crystallization from cyclohexane–ethyl acetate afforded 155 mg of the hydrazone *VIII*, m.p. 126–128°C.

2,2-Difluoro-3-methyl-3-butenal Oxime (*IX*)

A solution of the butenal *I* (6 g; 50 mmol) in methanol (10 ml) was mixed with a solution of hydroxylamine hydrochloride (3·5 g) and sodium acetate (4·1 g) in water (10 ml). After reflux for 2 h, methanol was evaporated *in vacuo*. The organic portion was extracted with ether (20 ml), washed with sodium hydrogen carbonate solution and dried over magnesium sulfate. Evaporation of the solvent and distillation at 98–101°C/13 kPa gave 3·5 g (52%) of the oxime *IX*. IR spectrum: $\nu(OH)$ 3 550 s, $\nu(C{=}C)$ 1 650 w; ^1H NMR spectrum: 1·86 (s, 3 H, CH_3), 5·32 (d, $^2J_{HH}$ = 15, 2 H, $CH_2{=}$), 7·50 (t, 1 H, CH), 9·08 (bs, 1 H, OH); ^{19}F NMR spectrum 110·7 (dm, 2 F, CF_2); mass spectrum: 39 (100), 65 (93), 41 (87), 118 (67), 91 (64), 44 (53), 120 (47), 77 (37), $(M-1)^+$ 134 (32).

3,3-Difluoro-4-methyl-1-nitro-4-pentene-2-ol (*X*)

A mixture of the butenal *I* (3·6 g; 30 mmol), nitromethane (2 g) and calcined potassium carbonate (0·2 g), which had warmed spontaneously upon mixing the components, was gently boiled for 1 h, cooled, diluted with ether (25 ml), neutralized with dilute (1 : 4) hydrochloric acid, washed with water and dried over magnesium sulfate. After evaporation of ether *in vacuo*, the residue was mixed with a small amount of calcium carbonate and distilled, affording 3·34 g (61%) of the nitro alcohol *X*, b.p. 125–126°C/2·9 kPa. IR spectrum: ν(OH) 3 480 m, ν(C=C) 1 650 w, ν(N—O) 1 565 s; ^{1}H NMR spectrum: 1·92 (m, 3 H, CH_3), 3·18 (bs, 1 H, OH), 4·40–4·90 (m, 3 H, CH, CH_2), 5·40 (d, $^2J_{HH}$ = 10, 2 H, CH_2=); ^{19}F NMR spectrum: 107·8, 111·0 (AB system, $^2J_{FF}$ = 250, 2 F, CF_2; mass spectrum: 91 (100), 65 (67), 39 (27), 41 (24), 51 (17), 77 (15), 92 (12), 71 (10).

3,3-Difluoro-2-hydroxy-4-methyl-4-pentenenitrile (*XI*)

The butenal *I* (12 g; 100 mmol) was added dropwise at 0°C to a stirred and cooled solution of sodium cyanide (5 g) in water (20 ml) so as the temperature did not exceed 4°C. After stirring for 15 min at this temperature, the mixture was acidified with 25% sulfuric acid (17 ml) at 5°C. Stirring was continued at room temperature for 4 h, the product was extracted with ether (4 × × 20 ml) and the combined extracts were washed with sodium hydrogen carbonate solution and dried over magnesium sulfate. Evaporation of the solvent *in vacuo*, followed by distillation of the residue, gave 11·5 g (78%) of the cyanohydrin *XI*, b.p. 107–112°C/2·5 kPa. IR spectrum: ν(OH) 3 400 s, ν(C=C) 1 650 w; ^{1}H NMR spectrum: 1·95 (s, 3 H, CH_3), 3·79 (bs, 1 H, OH), 4·62–4·90 ($^3J_{HF}$ = 7, 1 H, CH), 5·50 (d, $^2J_{HH}$ = 12, 2 H, CH_2=); ^{19}F NMR spectrum: 107·8, 111·0 (AB system, $^2J_{FF}$ = 250, 2 F, CF_2); mass spectrum: 91 (100), 65 (67), 39 (27), 41 (24), 51 (17), 77 (15), 92 (12), 71 (10), M^+ 147 (0·5).

5-Fluoro-2-(1,1-difluoro-2-methyl-2-propenyl)-4-cyano-6-dimethyl-1,3-diox-4-ene (*XII*)

The butenal *I* (5 g; 50 mmol) was added at once to a solution of sodium cyanide (2·5 g) in water (10 ml). The mixture, which spontaneously warmed, was cooled to 0°C during 2 h, acidified with 25% sulfuric acid (8·5 ml) and stirred at room temperature for 2 h. The oily layer was extracted with ether (6 × 10 ml) and the combined extracts were washed with water and dried over magnesium sulfate.

Evaporation of the solvent *in vacuo* and distillation gave 4·65 g (62%) of the dioxene *XII*, b.p. 105–110°C/1·7 kPa. IR spectrum: ν(CF=C) 1 745 s, ν(C=C) 1 660 m, $\nu(CH_3)_{gem}$ 1 385, 1 370 m; ^{1}H NMR spectrum: 1·90 (m, CH, 2 × CH_3), 2·13 (d, $^3J_{HF}$ = 3, 3 H, CH_3), 5·45 (d, $^2J_{HH}$ = 13, 2 H, CH_2=), 5·77 (t, $^3J_{HF}$ = 9, 1 H, CH); ^{19}F NMR spectrum: 106·6, 107·1 (AB system, 2F, CF_2), 130·5 (m, 1 F, CF=); mass spectrum: 101 (100), 91 (69), 53 (30), 117 (29), 100 (22), 47 (22), 39 (21), 41 (20), M^+ 247 (9).

2,2-Difluoro-3-methyl-3-butenoic Acid (*XIII*)

The butenal *I* was added dropwise during 10 min to a stirred suspension of silver oxide (6 g) in 10% aqueous sodium hydroxide, pre-heated to 80°C. After a vigorous reaction, the mixture was stirred at 80°C for 1 h and the silver salts were dissolved by adding 65% nitric acid (5·9 ml) at 70°C during 30 min. The mixture was cooled and extracted with ether (5 × 4 ml). The combined extracts were dried over magnesium sulfate, taken down *in vacuo* and the residue (3·5 g) was distilled, affording 0·45 g (17%) of the acid *XIII*, m.p. 75–80°C/2·00 kPa. IR spectrum: ν(OH) 3 500–2 700 s, ν(C=O) 1 750 s; ^{1}H NMR spectrum: 1·90 (s, 3 H, CH_3), 5·42 (d, $^2J_{HH}$ =

= 19, 2 H, CH_2), 9·75 (bs, 1 H, COOH); ^{19}F NMR spectrum: 108·6 (m, 2 F, CF_2); mass spectrum: 91 (100), 65 (74), 39 (46), 41 (36), 51 (20), 45 (19), 88 (17), 46 (15), M^+ 136 (10).

3-Bromo-2,2-difluoro-3-methyl-4-butanolide (*XIV*)

Bromine (6 ml) was added dropwise to a stirred and cooled mixture of the butenal *I* (6·9 g; 58 mmol), barium carbonate (39·4 g) and water (400 ml). After stirring for 40 h at room temperature, the mixture was acidified with dilute sulfuric acid (1 : 3) to pH 1—2, the precipitated barium sulfate was filtered off, the excess bromine was removed by addition of sodium sulfite and the aqueous solution was extracted with ether. The extract was dried over magnesium sulfate, the solvent removed *in vacuo* and the residue distilled to give 3·8 g (31%) of the butanolide *XIV*, b.p. 85 to 88°C/2·0 kPa. IR spectrum (CCl_4): $\nu(CH_3)$ 2 990 w, ν(C=O) 1 840 s; ^{1}H NMR spectrum: 1·95 (s, 3 H, CH_3), 4·50 (dd, 2 H, CH_2); ^{19}F NMR spectrum: 118·0, 121·2 (AB system, $^2J_{FF}$ = 260, 2 F, CF_2); mass spectrum: 91 (100), 65 (37), 51 (20), 29 (16), 39 (15), 27 (14), 77 (13), 41 (13).

3,4-Dibromo-1-chloro-2,2-difluoro-3-methylbutyl Acetate (*XV*)

Bromine (3·2 g) was added dropwise at room temperature to a solution of the acetate *III* (3·98 g; 20 mmol) in tetrachloromethane (5 ml) with external irradiation with a high-pressure mercury lamp (125 W). After the addition the mixture was irradiated for 7 min more and the excess bromine was removed by washing with sodium sulfite solution. The organic layer was washed with a solution of sodium hydrogen carbonate, dried over calcium chloride and taken down. Distillation gave the acetate *XV* (6·25 g; 87%), b.p. 138—141°C/2·3 kPa. IR spectrum: ν(C=C) 1 775 s, $\delta(CH_3)$ 1 450 s; ^{1}H NMR spectrum: 2·06 (m, 3 H, CH_3), 2·24 (m, 3 H, CH_3CO), 3·90 (m, 2 H, CH_2Br), 6·94—7·17 (m, 1 H, CH); ^{19}F NMR spectrum: 103·2, 114·2 (AB system, $^2J_{FF}$ = 260, $^3J_{HF}$ = 15, 2 F, CF_2), 107·6, 113·0 (AB system, $^2J_{FF}$ = 260, 2 F, CF_2), diastereoisomer ratio 2 : 1; mass spectrum: 43 (100), 91 (36), 39 (9), 65 (9), 44 (8), 92 (7), 41 (5), $(M-35)^+$ 321 (4).

3,4-Dibromo-2,2-difluoro-3-methylbutylidene Diacetate (*XVI*)

A) Bromine (16 g) in tetrachloromethane (50 ml) was aded during 15 min at room temperature to a stirred solution of the diacetate *IV* (22·2 g; 100 mmol) in tetrachloromethane (50 ml) under external irradiation with a high-pressure mercury lamp (125 W). After the addition, the irradiation was continued for 20 min more, the mixture was washed with a sodium sulfite solution and water, dried over magnesium sulfate and taken down. The residue was distilled *in vacuo* to give 33·9 g (89%) of the diacetate *XVI*, b.p. 155—162°/2·0 kPa. IR spectrum: ν(C=O) 1 780 s; ^{1}H NMR spectrum: 2·00 (s, 3 H, CH_3), 2·18 (s, 6 H, 2 × CH_3CO), 3·92 (s, 2 H, CH_2Br), 7·42 (t, $^3J_{HF}$ = 8, 1 H, CH); ^{19}F NMR spectrum: 112·5, 114·5 (AB system, $^2J_{FF}$ = 260, 2 F, CF_2); mass spectrum: 43 (100), 103 (96), 91 (58), 65 (39), 44 (31), 39 (31), 92 (23), 42 (23), $(M-80)^+$ 300 (2·3).

B) A mixture of the acetate *XV* (1·79 g; 5 mmol), silver acetate (2 g) and toluene (3 ml) was refluxed for 50 h. After this time no starting compound was detected. The cold suspension was diluted with ether (10 ml), filtered and the silver salts on the filter were washed with a small amount of ether. Evaporation of the solvents afforded 0·5 g of the diacetate *XVI*, identical (GLC) with an authentic standard.

4-Bromo-2,2-difluoro-3-methyl-3-butenylidene Diacetate (*XVII*)

A mixture of the diacetate *XVI* (1·9 g; 5 mmol), fused potassium acetate (1 g) and acetic acid (5 ml) was refluxed for 25 h, cooled, diluted with ether (20 ml), and neutralized with 15% aqueous

sodium hydroxide. The ethereal layer was separated, the aqueous one was washed repeatedly with ether and the combined organic portions were dried over magnesium sulfate. After evaporation of ether *in vacuo*, the residue (1·23 g) was subjected to preparative GLC (SE-30; 200°C) to afford 160 mg (11%) of the diacetate *XVII*. IR spectrum: $\nu(CH_2=)$ 3 100 w, $\nu(C=O)$ 1 770, 1 790 s; ^1H NMR spectrum: 1·95 (s, 3 H, CH_3), 2·15 (s, 6 H, 2 × CH_3CO), 6·76 (m, 1 H, CHBr=), 7·02 (t, $^3J_{HF}$ = 7, 1 H, CH); ^{19}F NMR spectrum: 112·7 (m, 2 F, CF_2); mass spectrum: 103 (100), 43 (52), 39 (27), 65 (20), 171 (20), 169 (20), 44 (18), 129 (16), $(M-80)^+$ 221 (4).

2-(1,1-Difluoro-2,3-dihydroxy-2-methylpropyl)-1,3-dioxolane (*XVIII*)

A stirred mixture of the dioxolane *II* (1·64 g; 10 mmol), sodium chlorate (1·06), osmium tetroxide (0·1 g) and 50% (vol) aqueous ethanol was heated to 70—80°C for 1 h. Ethanol was evaporated *in vacuo* and the residue was repeatedly extracted with ether. The combined organic portions were dried over magnesium sulfate, ether was removed *in vacuo* and the remaining dioxolane *XVIII* (1·74 g) was distilled at 150—151°C/2·1 kPa; yield 1·3 g (66%). IR spectrum: ν(OH) 3 810 w, 3 590 w, 3 520 m, $\nu(CH_3)$ 2 990 m; ^1H NMR spectrum: 1·32 (s, 3 H, CH_3), 3·18 (bs, 2 H, 2 × OH), 3·36—3·92 (m, 2 H, CH_2), 4·10 (m, 4 H, CH_2CH_2), 5·38 (t, $^3J_{HF}$ = 9, 1 H, CH); ^{19}F NMR spectrum: 127·0 (m, 2 F, CF_2); mass spectrum: 73 (100), 43 (61), 45 (39), 58 (14), 29 (11), 31 (7), 57 (6), 74 (5), $(M-31)^+$ 167(1).

3,3-Difluoro-2,4-dihydroxy-4-methyloxolane (*XIX*)

A) A mixture of the dioxolane *XVIII* (0·99 g; 5 mmol) and 25% sulfuric acid (3 ml) was shaken at 140—150°C in a sealed ampoule for 4 h. After cooling, the content was neutralized with 30% sodium hydroxide solution and repeatedly extracted with ether. The combined extracts were dried over magnesium sulfate, taken down *in vacuo* and the residue (0·6 g) was distilled, affording 0·5 g (65%) of the oxolane *XIX*, b.p. 130—135°C/2·3 kPa. IR spectrum: ν(OH) 3 400 s, $\nu(CH_3)$ 2 950 s; ^1H NMR spectrum: 1·38 (m, 3 H, CH_3), 3·64 (bs, 1 H, OH), 3·70—4·20 (m, 2 H, CH_2), 4·57 (d, 1 H, OH), 5·14 (m, 1 H, OH); ^{19}F NMR spectrum: 121·0, 135·2 (AB system, $^2J_{FF}$ = 235, CF_2), 130·0 (AB system, $^2J_{FF}$ = 230, CF_2), diastereoisomer ratio 1 : 1·3; mass spectrum: 79 (100), 46 (53), 78 (52), 82 (50), 34 (47), 30 (38), 80 (37), 93 (35), M^+ 154 (3·3).

B) A stirred mixture of the butenal *I* (2·4 g; 20 mmol), sodium chlorate (2·12 g), osmium tetroxide (0·02 g) and 50% (vol) aqueous ethanol was kept at 70—80°C for 3 h. Ethanol was evaporated *in vacuo*, the residue was extracted with ether (7 × 10 ml) and the combined extracts were dried over magnesium sulfate. Evaporation of the solvent *in vacuo* furnished 2·8 g (91%) of the oxolane *XIX* whose purity and identity were verified by comparison (GLC, NMR) with an authentic sample.

C) A mixture of the acetate *III* (1·98 g; 10 mmol), sodium chlorate (1·3 g), osmium tetroxide (0·02 g) and 50% (vol) aqueous ethanol (9 ml) was heated to 60—70°C for 5 h. The completely homogeneous mixture was cooled and neutralized with an excess of solid sodium hydrogen carbonate. Ethanol was evaporated *in vacuo* and the residue was extracted with ether (6 × 5 ml). The combined extracts were dried over magnesium sulfate, the solvent was evaporated and the residue distilled to give 0·6 g (39%) of the oxolane *XIX*, identical with an authentic sample.

2,4-Diacetoxy-3,3-difluoro-4-methyloxolane (*XX*)

A mixture of the oxolane *XIX* (0·6 g; 3·9 mmol), acetic anhydride (32 g) and pyridine (0·8 g) was heated to 120—130°C for 6 h, cooled, diluted with ether (20 ml), washed with dilute (1 : 4) hydrochloric acid, sodium hydrogen carbonate solution, and dried over magnesium sulfate.

After evaporation of ether *in vacuo*, the residue (0·89 g) was distilled to give 0·8 g (86%) of the oxolane *XX*, b.p. 105—112°C/1·7 kPa. IR spectrum: $\nu(CH_3)$ 3 000 w, $\nu(C{=}O)$ 1 750 s; ^1H NMR spectrum: 1·70 (m, 3 H, CH_3), 2·10 (s, 3 H, CH_3CO), 2·18 (s, 3 H, CH_3CO), 4·10—4·50 (m, 2 H, CH_2), 6·08—6·24 (m, 1 H, CH); ^1F NMR spectrum: 117·1, 126·1 (AB system, $^2J_{FF} = 245$, 2 F, CF_2), 121·2, 128·3 (AB system, $^2J_{FF} = 240$, 2 F, CF_2), diastereoisomer ratio 1·54 : 1; mass spectrum: 43 (100), 90 (11), 91 (8), 179 (5), 136 (3), 150 (3), 149 (3), 42 (3).

2-Acetoxy-3,3-difluoro-4-hydroxy-4-methyloxolane (*XXI*)

A stirred mixture of compound *IV* (6·66 g; 30 mmol), sodium chlorate (3·3 g), osmium tetroxide (0·045 g) and 50% (vol) aqueous dioxane (33 ml) was heated to 60—70°C for 5 h. Dioxane was evaporated *in vacuo*, the residue was extracted with ether (5 × 15 ml) and the combined extracts were dried over magnesium sulfate. Evaporation of the solvent and distillation of the residue *in vacuo* afforded 3·95 g (67%) of the oxolane *XXI*, b.p. 87—95°C/1·6 kPa. IR spectrum: ν(OH) 3 440 s, $\nu(C{=}O)$ 1 740 s; ^1H NMR spectrum: (hexadeuterioacetone): 1·50 (s, 3 H, CH_3), 2·20 (s, 3 H, CH_3CO), 4·70, 5·90 (bs, bs, 1 H, OH), 5·18 (m, 1 H, CH), diastereoisomer ratio 1·5 : 1; ^{19}F NMR spectrum (hexadeuterioacetone): 124·8—124·9 (m, 2 F, CF_2); mass spectrum: 43 (100), 15 (10), 104 (9), 90 (9), 117 (8), 29 (6), 74 (5), 28 (5).

3,3-Difluoro-2-methyl-5-nitro-1,2,4-pentanetriol (*XXII*)

A stirred mixture of the nitro alcohol *X* (1·8 g; 10 mmol), sodium chlorate (1·08 g), osmium tetroxide (0·01 g) and 60% (vol) aqueous acetic acid (8 ml) was heated to 70—80°C for 5 h. The solvent was removed *in vacuo* and the residue was stirred with saturated solution of sodium hydrogen carbonate (3 ml). After evaporation, the residue was extracted with butanol (3 × 5 ml), the salts were removed by filtration and the filtrate was taken down *in vacuo*. The residue (2·4 g) was chromatographed on a column of Silpearl in chloroform–methanol. The product-containing eluate was taken down *in vacuo*, the residue was dissolved in methanol (5 ml), decolorized with charcoal and filtered. The solvent was evaporated and the residue dried for 3 h at 90—100°C/13 kPa, yielding 0·7 g (32%) of the triol *XXII*. IR spectrum: ν(OH) 3 400 s, ν(N—O) 1 555 s; ^1H NMR spectrum (hexadeuterioacetone): 1·32 (s, 3 H, CH_3), 3·50—4·00 (m, 2 H, CH_2), 4·40—5·25 (m, 5 H, CH_2NO_2, CH_2, 2 × OH); ^{19}F NMR spectrum (hexadeuterioacetone): 115·2, 121·2 (AB system, $^2J_{FF} = 260$, 2 F, CF_2), 118·6, 122·1 (AB system, $^2J_{FF} = 257$, 2 F, CF_2), diastereoisomer ratio 1·22 : 1; mass spectrum: 43 (100), 75 (37), 57 (23), 137 (22), 31 (20), 29 (20), 44 (10), 108 (6), $(M-31)^+$ 184 (2).

1-Amino-3,3-difluoro-4-methyl-4-penten-2-ol (*XXIII*)

A) A solution of the cyanohydrin *XI* (9·4 g; 50 mmol) in tetrahydrofuran (20 ml) was added at −60°C during 30 min to a stirred suspension of lithium aluminium hydride (3·8 g) in tetrahydrofuran (50 ml). The mixture was slowly warmed and then refluxed for 3 h. The excess reagent was decomposed by gradual addition of water (4 ml) and 4% sodium hydroxide (16 ml), the salts were collected on a filter, washed with tetrahydrofuran and the combined filtrates were taken down *in vacuo*. The residue (5·9 g) was dissolved in water (50 ml), the solution was acidified with hydrochloric acid to pH 1, washed with ether (3 × 25 ml), decolorized with charcoal, filtered and the filtrate taken down *in vacuo*. The crude hydrochloride (7 g) was decomposed with 40% potassium hydroxide (8 ml), the liberated base was extracted with ether (4 × 10 ml), the combined extracts were dried over potassium carbonate and the solvent was evaporated *in vacuo*. Distillation of the residue (3·7 g) gave 3·2 g (42%) of the amino alcohol *XIII*, b.p. 95—105°C/1·7

kPa, m.p. 62–66°C. IR spectrum: (KBr): ν(OH, NH_2) 3 380, 3 320 m, $\nu(NH_2)$ 1 595 s; ^{1}H NMR spectrum: 1·90 (s, 3 H, CH_3), 2·50 (b, 3 H, OH, NH_2), 3·94 (d, $^3J_{HH}$ = 6, 2 H, CH_2), 3·60–4·00 (m, 1 H, CH), 5·26 (d, $^2J_{HH}$ = 16, 2 H, CH_2=); ^{19}F NMR spectrum: 110·2, 115·0 (AB system, $^2J_{FF}$ = 250, 2 F, CF_2); mass spectrum: 60 (100), 102 (64), 42 (58), 39 (39), 59 (26), 41 (18), 101 (16), 43 (15), $(M+1)^+$ 152 (14).

B) The nitro alcohol *X* (18·1 g; 100 mmol) in ether (50 ml) was added dropwise at 0°C to a stirred suspension of lithium aluminium hydride (8 g) in ether (250 ml) so as the temperature did not exceed 8°C. After reflux for 8 h, the mixture was cooled, decomposed with 4% sodium hydroxide (32 ml) and set aside overnight. The salts were collected on a filter and extracted with ether in a Soxhlet extractor for 8 h. The filtrate and extract were combined, taken down *in vacuo* and the residue was dissolved in 4% hydrochloric acid (55 ml). The solution was repeatedly washed with ether and taken down *in vacuo* to give a thick paste from which the base was liberated with 40% potassium hydroxide (7·5 ml) and taken up in ether (6 × 15 ml). The combined extracts were dried over potassium carbonate, ether was evaporated and the residue (8·2 g) distilled, yielding 5·96 g (39%) of the amino alcohol *XXIII*, identical (GLC, NMR) with a standard.

5-Amino-3,3-difluoro-2-methyl-1,2,4-pentanetriol (*XXIV*)

A stirred mixture of the amino alcohol *XXIII* (1·51 g; 10 mmol), sodium chlorate (1·08 g), osmium tetroxide (0·01 g), acetic acid (5 ml) and water (5 ml) was heated to 60–70°C for 3 h. The mixture, which still contained the starting compound, was set aside for 1 week at room temperature, the solvent was evaporated *in vacuo* and the residue was extracted with butanol (3 × 10 ml). The salts were filtered off and the solvent was evaporated to give a residue (2·8 g) which was dissolved in water (20 ml), treated with charcoal and filtered. The filtrate was applied on a column of Amberlite IR-120 (H^+-form, 10 g) and after washing with water (150 ml) to neutrality, the product was eluted with 1% ammonia (100 ml). The eluate was taken down and the residue (0·6 g) chromatographed on a column of Silpearl (40 g) in chloroform–2-propanol–ammonia. The pertinent fractions were combined and the solvent was evaporated *in vacuo*; yield 0·38 g (20%) of the triol *XIV*. IR spectrum: ν(OH, NH_2) 3 600–3 000 s; ^{1}H NMR spectrum (hexadeuterioacetone): 1·23 (s, 3 H, CH_3), 2·05 (b, 5 H, NH_2 + 3 × OH), 3·10–3·80 (m, 4 H, CH_2CH_2), 4·05–4·50 (m, 1 H, CH); ^{19}F NMR spectrum (hexadeuterioacetone): 118·7, 124·9 (AB system, $^2J_{FF}$ = 260, 2 F, CF_2), 118·6, 127·1 (AB system, $^2J_{FF}$ = 258, 2 F, CF_2), diastereoisomer ratio 1·76 : 1; mass spectrum: 30 (100), 43 (59), 60 (34), 105 (31), 31 (28), 154 (18), 29 (17), 137 (15), $(M+1)^+$ 186 (1).

3,3-Difluoro-4-methyl-4-pentene-1,2-diol (*XXV*)

A solution of sodium nitrite (1·65 g) in water (3 ml) was slowly added at 0°C to a stirred solution of the amino alcohol *XXIII* (1·2 g; 8 mmol) in 13% perchloric acid (18·5 g). The mixture was kept at 0°C for 5 h, set aside at room temperature overnight, made alkaline with 30% sodium hydroxide (1·5 ml), heated to 60°C for 3 h and concentrated *in vacuo* to one half of the original volume. The residue was extracted with ether (7 × 7 ml), the combined extracts were dried over magnesium sulfate and the solvent was evaporated *in vacuo*. Distillation of the residue (0·8 g) afforded 0·6 g (50%) of the diol *XXV*, b.p. 100–105°C/1·7 kPa. IR spectrum: ν(OH) 3 360 s, ν(C=C) 1 650 w; ^{1}H NMR spectrum: 1·88 (s, 3 H, CH_3), 3·20 (bs, 2 H, 2 × OH), 3·58–4·15 (m, 3 H, CH_2, CH), 5·32 (d, $^2J_{HH}$ = 14, 2 H, CH_2=); ^{19}F NMR spectrum: 111·6, 113·6 (AB system, $^2J_{FF}$ = = 250, CF_2); mass spectrum: 61 (100), 43 (94), 91 (62), 39 (30), 77 (28), 58 (26), 65 (25), 41 (23).

3,3-Difluoro-2-methyl-1,2,4,5-pentanetetrol (*XXVI*)

A solution of the diol *XXV* (0·65 g; 3 mmol), sodium chlorate (0·5 g) and osmium tetroxide (0·01 g) in 50% (vol) aqueous dioxane (5 ml) was heated to 60°C for 5 h. The solvent was evaporated *in vacuo* and the residue was extracted with butanol (2 × 10 ml). Inorganic salts were removed by filtration and the filtrate was taken down *in vacuo*. Chromatography of the residue (0·8 g) on Silpearl (50 g) in chloroform–methanol afforded 0·4 g (50%) of the tetrol *XXVI*. IR spectrum: ν(OH) 3 600–3 030 s; ^{1}H NMR spectrum: (hexadeuterioacetone): 1·28 (m, 3 H, CH_3), 2·80–5·90 (b, 4 × OH), 3·30–3·85 (m, 5 H, CH_2, CH); ^{19}F NMR spectrum (hexadeuterioacetone): 114·4, 122·3 (AB system, $^2J_{FF}$ = 258, 2 F, CF_2); mass spectrum: 43 (100), 75 (43), 137 (40), 95 (36), 31 (29), 29 (20), 89 (13), 61 (10), $(M-31)^+$ 155 (7).

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