Novel Redox Cyclisation Products Derived from 2-Acylpyrroles and *trans*-3-Bromo-3,4-dihydro-4-hydroxy-2,2-dimethyl-2*H*-chromene-6-carbonitrile

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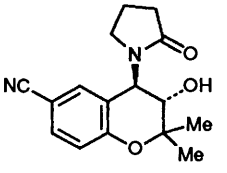
The reaction of 2-(trifluoroacetyl)pyrrole with *trans*-3-bromo-3,4-dihydro-4-hydroxy-2,2-dimethyl-2*H*-chromene-6-carbonitrile under basic conditions has been shown to afford high yields of (4*R**, 5a*S**,11b*S**)-5a-hydroxy-6,6-dimethyl-4-trifluoromethyl-5a,11b-dihydro-4*H*,6*H*-pyrrolo[1′,2′:4,5]-oxazino[2,3-*c*]chromene-10-carbonitrile rather than the anticipated amino alcohol. The unequivocal structural assignment of this unusual tetracyclic product by spectroscopic and X-ray crystallographic techniques is described and possible mechanistic explanations for its formation are discussed. Analogous reactions of pyrroles substituted in the 2-position by formyl, acetyl and benzoyl moieties have been shown to behave in an essentially similar manner, suggesting that the reaction is general for 2-acylpyrroles.

Continued interest in the potassium channel activators, typified by the dihydrochromene cromakalim **1**,† as novel smooth muscle relaxants has identified a large number of structural variants which retain the beneficial properties of this pharmacological class of compound.[1] Although several structurally diverse compounds which share the same mechanism of action as cromakalim have been identified, considerable attention has been focused on the structure of cromakalim itself. This effort has resulted in much detailed knowledge regarding the key structural requirements for biological activity within the cromakalim series,[2–6] although new avenues of research are regularly being opened. One particular approach has been the study of the C-4 pharmacophore, which has highlighted the orthogonal preference of the amide carbonyl such that it is directed to the same face as that of the C-3 hydroxy group.[7] In continuation of our own interest in this area we have investigated the effects of pyrrole substituents at the C-4 position and now describe an unusual redox reaction observed during attempts to prepare 2-acylpyrrole derivatives.

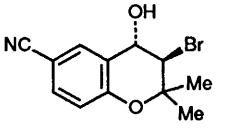
Discussion

The reaction of azide,[2,3] amines[8] and amides[2,3] with *trans*-3-bromo-3,4-dihydro-4-hydroxy-2,2-dimethyl-2*H*-chromene-6-carbonitrile **2** and its derived epoxide **3** generally leads to the formation of the expected dihydrochromenols **4**, accompanied in the latter case by varying quantities of the corresponding alkenes **5**. Similar reactions with the anions derived from substituted pyrroles do not always proceed normally, however, and under the more forcing conditions required for such anions to react with **2**, competitive ring contraction reactions leading to the formation of benzofurans **6** have been reported.[9] The formation of such compounds is believed to reflect the relative ease of pyran ring cleavage and dehydration of the intermediate dihydrochromenols **7**.

As part of our interest in this class of compound, we were anxious to investigate the effects of acyl substitution within the pyrrole nucleus, particularly at the position adjacent to the heteroatom. Accordingly, we have extended our earlier studies[9] to include the reaction of the bromohydrin **2** with selected 2-acylpyrroles. Initial attempts to effect reaction of 2-(trifluoroacetyl)pyrrole with **2** in tetrahydrofuran (THF) in the presence of potassium *tert*-butoxide failed, presumably because of the poor nucleophilicity of the delocalised pyrrole anion. In the presence of TMEDA (tetramethylethylenediamine), however, a high yield (71%) of a new product was obtained, although this was not the expected dihydrochromenol **9** or its alkene **10**, but the novel tetracyclic product **11** (Scheme 1).



1 cromakalim



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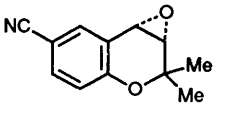

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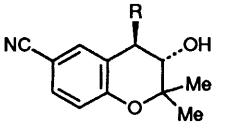
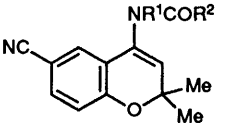


4 R = N_3, NR^1R^2, NR^1COR^2



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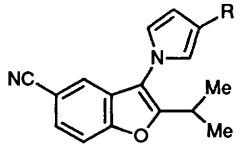
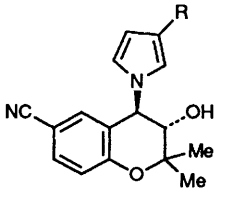
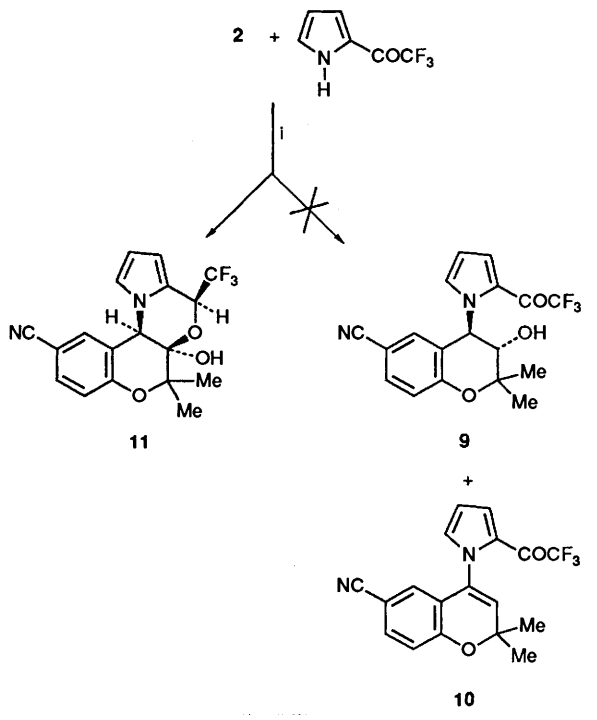


6 R = CN, NO_2



7 R = CN, NO_2
8 R = H

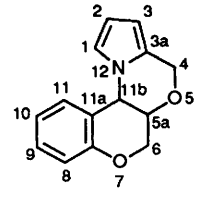
† Only relative stereochemistry shown.

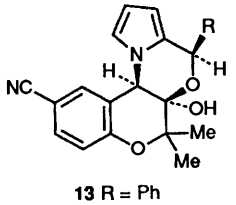


Scheme 1 *Reagents:* i, KOBu^t, TMEDA, THF

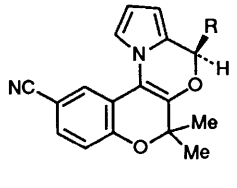
In order to test the generality of this unusual redox reaction, analogous studies were carried out using 2-benzoylpyrrole, 2-formylpyrrole and 2-acetylpyrrole. Thus, the condensation of 2-benzoylpyrrole with the bromohydrin **2** also afforded tetracyclic products, but in this instance the hydroxy compound **13** (17%) was accompanied by the corresponding unsaturated derivative **15** (16%). Whilst it is likely that the formation of the alkene **15** proceeds under the reaction conditions, it was noticed that with time the alcohol **13** gradually eliminated water to generate **15**. A similar transformation of the trifluoromethyl compound **11** with time was not observed.

2-Formylpyrrole also underwent condensation with the bromohydrin **2** to give the unstable tetracyclic alcohol **14** in modest (13%) yield. The poor overall yield in this instance probably reflects the instability of 2-formylpyrrole under the reaction conditions, although no attempt has been made to identify the numerous by-products from this reaction.

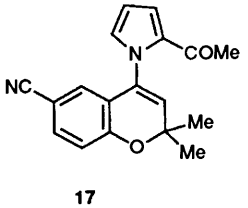




13 R = Ph
14 R = H



15 R = Ph
16 R = Me



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In contrast to the above reactions, in which only tetracyclic products were isolated, 2-acetylpyrrole furnished a 1:1 mixture of the alkene **16** (18%) and the unrearranged chromene **17** (18%) after reaction with the bromohydrin **2**. The formation of **17** suggests that intramolecular cyclisation is disfavoured with less electron deficient acyl substituents to the extent that competitive dehydration becomes a significant alternative reaction.[9] It seems likely that the acetyl group provides a convenient proton source for the intermediate alkoxide which is sufficient to initiate elimination to afford the benzopyran **17**.

Structural Elucidation of Compound **11**.—From the IR spectrum it was evident that the product no longer had a carbonyl stretching frequency at *ca.* 1680 cm^{-1}, although the strong absorbance at 3580 cm^{-1} suggested that a hydroxy moiety had been retained. Since the elemental and MS data confirmed the anticipated molecular formula $C_{18}H_{15}F_3N_2O_3$, it was clear that a stoichiometric combination of the two substrates had taken place. The ^{1}H NMR spectrum was particularly informative in that no vicinally coupled proton resonances characteristic for protons 3-H and 4-H in compound **9**, were evident (Table 1). Furthermore, the NMR spectrum showed the presence of a methine quartet at δ_H 5.48 (J 6.5 Hz) which indicated the attachment of the trifluoromethyl group to a carbon atom bearing one proton which was not coupled to any other proton. A second methine resonating as a singlet at δ_H 5.45 was consistent with that normally observed for 4-H, but lacking the α-hydrogen at C-3.

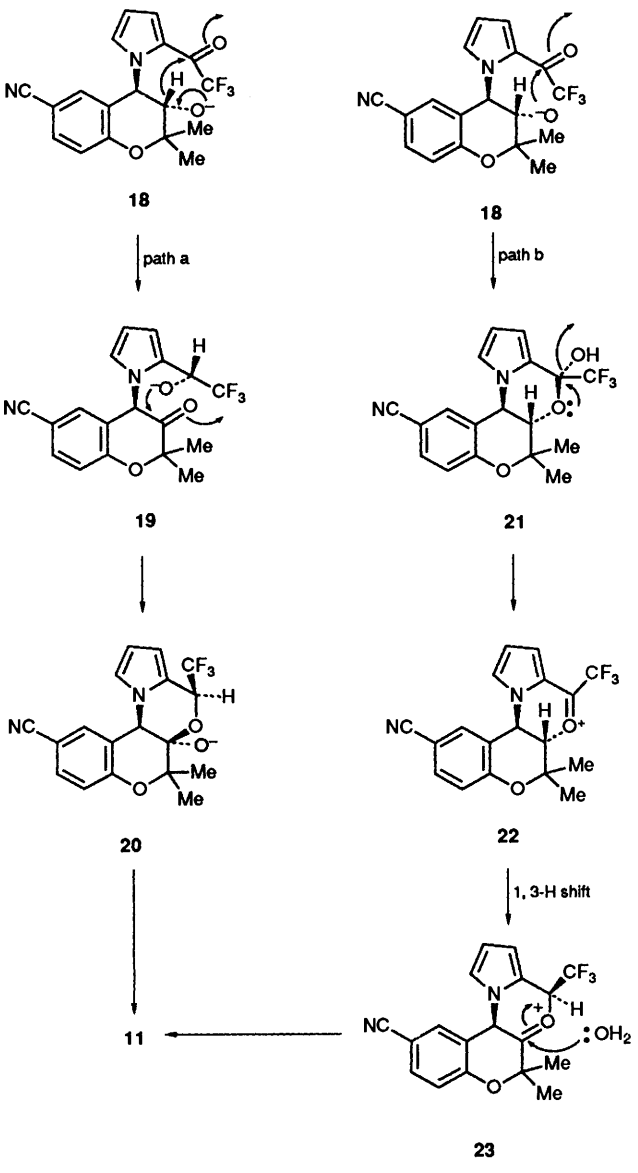
Analysis of the ^{13}C NMR spectroscopic data (Table 1) also showed a number of features inconsistent with the anticipated product **9**; in particular, the absence of the low field carbonyl signal and that expected for the hydroxy bearing carbon atom at C-3. Instead the ^{13}C NMR spectrum contained a methine quartet at δ_C 67.7 ($^3J_{CF}$ 33.4 Hz), indicative of the carbon bearing the trifluoromethyl group, as well as a quaternary resonance at δ_C 92.0, suggesting the presence of a hemiacetal moiety. Analysis of the long-range carbon–proton correlations (usually through 2- or 3- bonds, Table 1), as measured in the ^{1}H, ^{13}C COLOC experiment, completed the structure elucidation and suggested the tetracyclic structure **11** (see **12** for numbering system). In particular, the long-range correlations observed between the carbon resonating at 53.2 ppm and the exchangeable proton at 7.21 ppm, and that 7.48 ppm (11-H), confirmed this carbon as being C-11b whilst at the same time indicating that a hydroxy group must be present at C-5a. From this assignment it followed that the pyrrole nitrogen was attached to C-11b, and this was further supported by the COLOC correlations between 11b-H and the pyrrole carbons C-3a and C-1 and the NOE from 1-H to 11-H, as well as the mutual NOEs between 11b-H and 1-H.

Although these data were consistent with the tetracyclic structure **11**, the morpholine geometry and the relative stereochemistry of its substituents could not be assigned. Single crystal X-ray analysis (Fig. 1; see Tables 2, 3 and 4 for atomic coordinates and bond lengths and angles) confirmed the conclusions derived from the NMR spectroscopic data and unambiguously assigned the relative configuration of the three chiral centres. Thus, the morpholine and pyran rings were shown to be *cis* fused and the 4-trifluoromethyl and 5a-hydroxy groups shown to be orientated *trans* to each other. Subsequent analysis of the NMR spectroscopic data indicated that the solution state conformation of **11** agreed with that of the solid-state X-ray structure. The *syn*-1,3-diaxial relationship of 6-CH_{3ax} and proton 11b-H was confirmed in solution by their mutual NOE and the *syn*-1,3-diaxial relationship of the C-5a hydroxy group and proton 4-H, relative to the morpholine ring, was confirmed by the NOE between 4-H and 5a-OH (Table 1).

Table 1 NMR spectroscopic data for compound **11**

Atom	δ_C[a]	δ_H[a]	COLOC correlations[b]	NOEs observed at
1	122.8	7.40	11b-H[c]	11b-H, 11-H, 2-H
2	108.6	6.28	1-H	
3	105.6	6.09	1-H	2-H, 4-H
3a	115.6	—	11b-H,[c] 3-H, 2-H, 1-H, 4-H	
4	67.7[d]	5.48[d]		3-H, 5a-OH
5a	92.1	—	6-CH_3 ax, 6-CH_3 eq, 11b-H	
6	81.0	—	6-CH_3 ax, 6-CH_3 eq	
7a	154.8	—	11-H	
8	118.0	6.98		
9	133.0	7.63	11-H	
10	102.3	—		
11	132.0	7.48		
11a	122.9	—		
11b	53.2	5.45	5a-OH, 11-H	6-CH_3 ax, 5a-OH, 11-H, 1-H
4-CF_3	123.4[e]	—	4-H	
5a-OH	—	7.21		
6-CH_3 ax	21.7	1.36	6-CH_3 eq	6-CH_3 eq, 5a-OH, 11b-H
6-CH_3 eq	20.6	1.56	6-CH_3 ax	6-CH_3 ax, 5a-OH
10-CN	118.8	—	11-H	

[a] Solvent: $(CD_3)_2SO$, δ_C relative to δ_{TMS} 0; δ_H relative to δ_{TMS} 0. [b] COLOC correlations arising from long range coupling between carbon *n* and the protons tabulated. [c] Additional COLOC correlations measured as a $CDCl_3$–$(CD_3)_2SO$–D_2O solution. [d] $^2J_{CF}$ 33.4 Hz; $^3J_{HF}$ 6.5 Hz. [e] $^1J_{CF}$ 279.7 Hz.



Scheme 2

Mechanistic Considerations.—The initial step in the sequence leading to the tetracyclic product **11** is believed to be dehydrohalogenation of **2** to the epoxide **3**, and this is consistent with the formation of **11** on treatment of 2-(trifluoroacetyl)pyrrole with **3** under essentially similar reaction conditions. Attack of the pyrrole anion in the anticipated manner would then proceed at C-4 to generate the alkoxide **18** (Scheme 2). One possibility (path a) is that the alkoxide **18** is then predisposed for a 1,5-hydride shift from C-3 to the pyrrole acyl group to give **19** which is appropriately orientated for intramolecular cyclisation to the hemiacetal anion **20**. Protonation of **20** on work-up results in the formation of **11**. That compound **18** might undergo such a transformation may be rationalised by the strong tendency of the trifluoroacetyl moiety to assume tetrahedral character, as found in the formation of stable hydrates with electron deficient ketones such as hexafluoroacetone.[10] Alternatively, **18** may undergo intramolecular cyclisation to the isomeric hemiacetal anion of **21** (path b) which then leads to the oxonium ion **22**. A 1,3-hydride shift to **23** and subsequent hydration would again generate compound **11**. Although the alkoxide **18** is the most likely intermediate in the formation of **11**, an authentic sample of **9**, prepared by trifluoroacetylation of **8**, unfortunately failed to yield identifiable products on treatment under conditions approximating those leading to **11**. As found with other

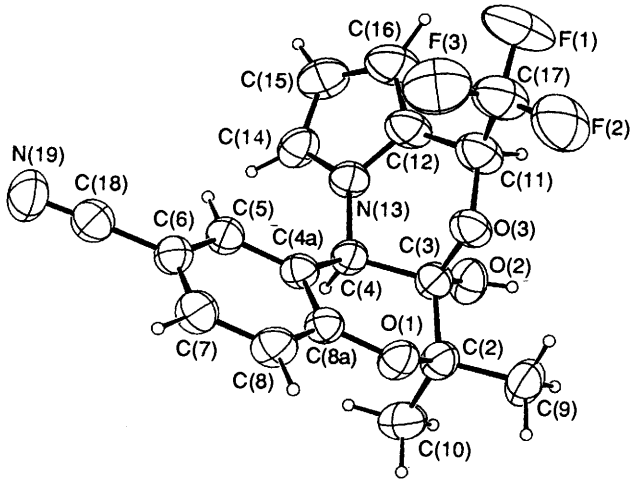
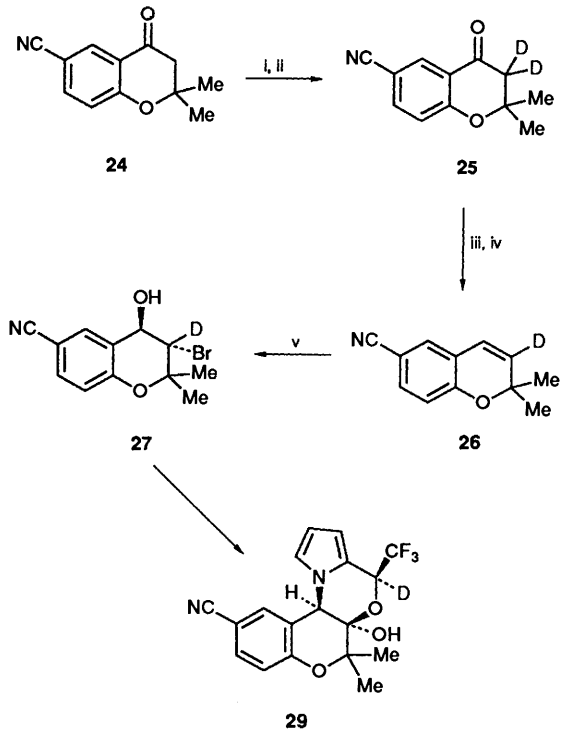


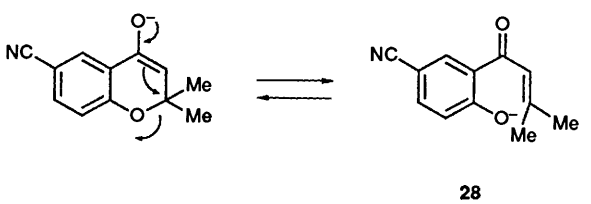
Fig. 1 X-ray molecular structure of compound **11**



Scheme 3 *Reagents:* i, NaH; ii, D_2O, THF; iii, $NaBH_4$, $CeCl_3$; iv, *p*TSA, toluene, reflux; v, NBS, H_2O, DMSO; vi, KOBu^t, TMEDA, THF

compounds of this general type,[9] however, the neopentylic nature of the hydroxy moiety in **9** is likely to hinder deprotonation, thus allowing alternative decomposition pathways to ensue.

In an endeavour to add support to these two possible mechanisms the selectively deuteriated bromohydrin **27** was prepared by the route shown in Scheme 3. Thus, base catalysed deuterium exchange of the ketone **24** afforded **25**, having >95% replacement of the hydrogen atoms at C-3 by deuterium, together with some 62% incorporation of label into the gem-dimethyl group. Deuterium incorporation into the alkyl groups of compound **25** is presumed to occur *via* the reversible retro-Michael reaction shown in Scheme 4 in which the transient formation of the phenoxide **28** is favoured by the stabilising effect of the aromatic nitrile substituent. Reduction of **25** with sodium borohydride and dehydration with toluene-*p*-sulfonic acid in toluene at reflux resulted in the alkene **26** which underwent facile hydrohalogenation to the bromohydrin **27**. Treatment of **27** with 2-(trifluoroacetyl)pyrrole under the conditions described above furnished the tetracyclic compound **29** with 100% retention of deuterium at position 4. This was evident from the total absence of the fluorine-coupled proton signal at δ_H 5.48 in the ^1H NMR spectrum. The quantitative retention of deuterium in compound **28** argues for the transfer of hydrogen from the pyran C-3 position to the acyl carbonyl group, but it is debatable, however, as to whether it serves to favour one of the suggested mechanisms over the other. It does, nonetheless, provide evidence to differentiate these mechanisms from others in which such a transfer does not occur.



Scheme 4

Table 2 Positional parameters and their estimated standard deviations for compound **11**

Atom[a]	*x*	*y*	*z*
F(1)	0.322 6(3)	0.518 3(2)	0.456 95(7)
F(2)	0.355 6(2)	0.734 1(3)	0.449 08(6)
F(3)	0.177 3(2)	0.664 4(3)	0.461 52(7)
O(1)	0.205 3(2)	1.037 4(2)	0.553 88(6)
O(2)	0.409 6(2)	0.759 0(2)	0.593 80(7)
O(3)	0.313 7(2)	0.795 9(2)	0.527 25(6)
N(13)	0.191 8(2)	0.612 5(2)	0.574 26(7)
N(19)	−0.358 4(2)	0.778 4(3)	0.559 7(1)
C(2)	0.311 9(2)	0.979 1(3)	0.576 70(9)
C(3)	0.311 1(2)	0.820 7(3)	0.570 94(9)
C(4)	0.194 8(2)	0.757 1(3)	0.586 34(8)
C(4A)	0.082 9(2)	0.838 9(3)	0.570 15(8)
C(5)	−0.034 5(2)	0.783 6(3)	0.569 88(8)
C(6)	−0.136 7(2)	0.865 4(3)	0.558 60(9)
C(7)	−0.122 6(3)	1.003 2(3)	0.546 93(9)
C(8)	−0.006 3(3)	1.057 3(3)	0.543 3(1)
C(8A)	0.095 6(2)	0.975 8(3)	0.557 45(8)
C(9)	0.419 7(3)	1.045 9(3)	0.557 0(1)
C(10)	0.309 3(3)	1.018 6(3)	0.622 4(1)
C(11)	0.329 7(3)	0.653 5(3)	0.517 2(1)
C(12)	0.254 4(3)	0.559 6(3)	0.542 2(1)
C(14)	0.141 3(3)	0.505 2(3)	0.595 2(1)
C(15)	0.169 9(3)	0.386 5(3)	0.576 5(1)
C(16)	0.241 3(4)	0.418 5(3)	0.542 8(1)
C(17)	0.299 0(4)	0.642 1(4)	0.471 4(1)
C(18)	−0.259 0(3)	0.812 8(3)	0.559 7(1)
F(1′)	0.097 4(2)	1.183 7(2)	0.673 98(9)
F(2′)	−0.040 9(2)	1.184 7(3)	0.717 11(8)
F(3′)	−0.090 2(3)	1.216 8(3)	0.651 96(9)
O(1′)	0.159 8(2)	0.821 5(2)	0.772 01(6)
O(2′)	0.029 4(2)	0.709 9(3)	0.670 48(7)
O(3′)	0.054 6(2)	0.927 0(2)	0.699 38(6)
N(13′)	−0.180 2(2)	0.838 6(3)	0.705 38(8)
N(19′)	−0.324 1(3)	1.064 0(4)	0.864 3(1)
C(2′)	0.144 2(3)	0.733 7(3)	0.735 43(9)
C(3′)	0.034 0(3)	0.874 0(3)	0.707 68(9)
C(4′)	−0.082 4(3)	0.773 6(3)	0.730 78(9)
C(4A′)	−0.060 3(3)	0.841 0(3)	0.773 49(9)
C(5′)	−0.156 9(3)	0.890 1(3)	0.795 17(9)
C(6′)	−0.135 4(3)	0.954 5(3)	0.833 55(9)
C(7′)	−0.016 4(3)	0.968 8(4)	0.851 4(1)
C(8′)	0.079 4(3)	0.919 6(4)	0.830 6(1)
C(8A′)	0.058 2(3)	0.858 5(3)	0.791 66(9)
C(9′)	0.127 7(4)	0.585 3(4)	0.750 1(1)
C(10′)	0.262 6(3)	0.746 4(4)	0.713 4(1)
C(11′)	−0.035 4(3)	0.991 9(4)	0.672 0(1)
C(12′)	−0.163 6(3)	0.947 4(5)	0.679 3(1)
C(14′)	−0.304 9(3)	0.807 8(5)	0.705 3(1)
C(15′)	−0.362 5(4)	0.899 1(7)	0.678 0(1)
C(16′)	−0.276 0(4)	0.985 2(6)	0.661 1(1)
C(17′)	−0.016 4(4)	1.144 9(4)	0.678 7(1)
C(18′)	−0.238 6(3)	1.014 5(4)	0.852 2(1)

[a] Atom numbers are designated in Fig. 1.

Regardless of the mechanism by which the tetracyclic compound **11** is formed, the exclusive formation of the 5a,11b *cis*-fused product is consistent with semi-empirical quantum mechanical calculations based on the AMPAC-AM1 program using the keyword PRECISE.[11] Such calculations indicated that the *cis*-fused ring junction was thermodynamically preferred relative to that of *trans*-fused by approximately 5.4 kcal mol^{-1}.*

Experimental

M.p.s were determined using a Büchi apparatus and are recorded uncorrected. IR spectra were measured as liquid films for oils or as solutions ($CHCl_3$) for solids, using a Perkin–Elmer

* 1 cal = 4.184 J.

Table 3 Bond distances (Å) for compound **11**[a]

Atom 1[b]	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
F(1)	C(17)	1.318(4)	C(6)	C(7)	1.397(4)	N(19′)	C(18′)	1.144(5)
F(2)	C(17)	1.324(4)	C(6)	C(18)	1.435(4)	C(2′)	C(3′)	1.526(4)
F(3)	C(17)	1.365(5)	C(7)	C(8)	1.378(4)	C(2′)	C(9′)	1.527(5)
O(1)	C(2)	1.447(3)	C(8)	C(8A)	1.392(4)	C(2′)	C(10′)	1.526(5)
O(1)	C(8A)	1.354(3)	C(11)	C(12)	1.498(5)	C(3′)	C(4′)	1.522(4)
O(2)	C(3)	1.394(3)	C(11)	C(17)	1.486(5)	C(4′)	C(4A′)	1.519(4)
O(3)	C(3)	1.422(3)	C(12)	C(16)	1.374(4)	C(4A′)	C(5′)	1.390(4)
O(3)	C(11)	1.430(4)	C(14)	C(15)	1.344(4)	C(4A′)	C(8A′)	1.394(4)
N(13)	C(4)	1.453(3)	C(15)	C(16)	1.412(5)	C(5′)	C(6′)	1.384(4)
N(13)	C(12)	1.374(4)	F(1′)	C(17′)	1.320(5)	C(6′)	C(7′)	1.392(5)
N(13)	C(14)	1.374(4)	F(2′)	C(17′)	1.334(5)	C(6′)	C(18′)	1.438(5)
N(19)	C(18)	1.138(4)	F(3′)	C(17′)	1.331(5)	C(7′)	C(8′)	1.368(5)
C(2)	C(3)	1.545(4)	O(1′)	C(2′)	1.448(4)	C(8′)	C(8A′)	1.386(4)
C(2)	C(9)	1.523(4)	O(1′)	C(8A′)	1.365(4)	C(11′)	C(12′)	1.502(5)
C(2)	C(10)	1.514(4)	O(2′)	C(3′)	1.389(4)	C(11′)	C(17′)	1.509(5)
C(3)	C(4)	1.528(4)	O(3′)	C(3′)	1.431(4)	C(12′)	C(16′)	1.372(5)
C(4)	C(4A)	1.519(3)	O(3′)	C(11′)	1.419(4)	C(14′)	C(15′)	1.365(7)
C(4A)	C(5)	1.392(4)	N(13′)	C(4′)	1.443(4)	C(15′)	C(16′)	1.400(7)
C(4A)	C(8A)	1.397(4)	N(13′)	C(12′)	1.366(5)			
C(5)	C(6)	1.397(4)	N(13′)	C(14′)	1.396(4)			

[a] Numbers in parentheses are estimated standard deviations in the least significant digits. [b] Atom numbers are designated in Fig. 1.

Table 4 Bond angles ( ) for compound **11**[a]

Atom 1[b]	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C(2)	O(1)	C(8A)	118.3(2)	C(5)	C(6)	C(18)	121.5(3)	C(4′)	N(13′)	C(12′)	123.8(3)
C(3)	O(3)	C(11)	113.3(2)	C(7)	C(6)	C(18)	117.9(2)	C(4′)	N(13′)	C(14′)	126.4(3)
C(4)	N(13)	C(12)	123.8(2)	C(6)	C(7)	C(8)	119.2(3)	C(12′)	N(13′)	C(14′)	109.7(3)
C(4)	N(13)	C(14)	126.9(2)	C(7)	C(8)	C(8A)	120.3(3)	O(1′)	C(2′)	C(3′)	109.1(2)
C(12)	N(13)	C(14)	108.9(2)	O(1)	C(8A)	C(4A)	123.4(2)	O(1′)	C(2′)	C(9′)	108.2(3)
O(1)	C(2)	C(3)	109.3(2)	O(1)	C(8A)	C(8)	115.3(2)	O(1′)	C(2′)	C(10′)	105.8(2)
O(1)	C(2)	C(9)	104.2(2)	C(4A)	C(8A)	C(8)	121.2(2)	C(3′)	C(2′)	C(9′)	112.0(3)
O(1)	C(2)	C(10)	108.6(2)	O(3)	C(11)	C(12)	112.6(3)	C(3′)	C(2′)	C(10′)	111.5(3)
C(3)	C(2)	C(9)	111.7(2)	O(3)	C(11)	C(17)	105.7(3)	C(9′)	C(2′)	C(10′)	110.0(3)
C(3)	C(2)	C(10)	111.5(2)	C(12)	C(11)	C(17)	112.9(3)	O(2′)	C(3′)	C(3′)	109.7(2)
C(9)	C(2)	C(10)	111.3(2)	N(13)	C(12)	C(11)	119.8(3)	O(2′)	C(3′)	C(2′)	108.3(2)
O(2)	C(3)	O(3)	112.1(2)	N(13)	C(12)	C(16)	107.6(3)	O(2′)	C(3′)	C(4′)	113.8(2)
O(2)	C(3)	C(2)	111.4(2)	C(11)	C(12)	C(16)	132.3(3)	O(3′)	C(3′)	C(2′)	106.8(2)
O(2)	C(3)	C(4)	106.8(2)	N(13)	C(14)	C(15)	108.3(3)	O(3′)	C(3′)	C(4′)	107.6(2)
O(3)	C(3)	C(2)	106.5(2)	C(14)	C(15)	C(16)	108.2(3)	C(2′)	C(3′)	C(4′)	110.5(2)
O(3)	C(3)	C(4)	109.0(2)	C(12)	C(16)	C(15)	107.1(3)	N(13′)	C(4′)	C(3′)	108.1(2)
C(2)	C(3)	C(4)	111.0(2)	F(1)	C(17)	F(2)	108.2(3)	N-(13′)	C(4′)	C(4A′)	112.6(3)
N(13)	C(4)	C(3)	107.8(2)	F(1)	C(17)	F(3)	105.9(3)	C(3′)	C(4′)	C(4A′)	109.0(2)
N(13)	C(4)	C(4A)	114.2(2)	F(1)	C(17)	C(11)	112.2(3)	C(4′)	C(4A′)	C(5′)	121.3(3)
C(3)	C(4)	C(4A)	110.5(2)	F(2)	C(17)	F(3)	104.8(3)	C(4′)	C(4A′)	C(8A′)	120.8(3)
C(4)	C(4A)	C(5)	121.5(2)	F(2)	C(17)	C(11)	113.7(3)	C(5′)	C(4A′)	C(8A′)	117.9(3)
C(4)	C(4A)	C(8A)	120.0(2)	F(3)	C(17)	C(11)	111.4(3)	C(4A′)	C(5′)	C(6′)	120.7(3)
C(5)	C(4A)	C(8A)	118.3(2)	N(19)	C(18)	C(6)	175.9(3)	C(5′)	C(6′)	C(7′)	120.3(3)
C(4A)	C(5)	C(6)	120.4(2)	C(2′)	O(1′)	C(8A′)	118.3(2)	C(5′)	C(6′)	C(18′)	117.5(3)
C(5)	C(6)	C(7)	120.6(2)	C(3′)	O(3′)	C(11′)	115.6(2)	C(7′)	C(6′)	C(18′)	121.9(3)
C(6′)	C(7′)	C(8′)	119.5(3)	C(12′)	C(11′)	C(17′)	112.3(3)	F(1′)	C(17′)	F(2′)	106.1(3)
C(7′)	C(8′)	C(8A′)	120.2(3)	N(13′)	C(12′)	C(11′)	118.9(3)	F(1′)	C(17′)	F(3′)	108.1(3)
O(1′)	C(8A′)	C(4A′)	122.7(3)	N(13′)	C(12′)	C(16′)	108.0(3)	F(1′)	C(17′)	C(11′)	112.6(3)
O(1′)	C(8A′)	C(8′)	116.0(3)	C(11′)	C(12′)	C(16′)	132.6(4)	F(2′)	C(17′)	F(3′)	106.8(3)
C(4A′)	C(8A′)	C(8′)	121.2(3)	N(13′)	C(14′)	C(15′)	105.6(4)	F(2′)	C(17′)	C(11′)	112.4(3)
O(3′)	C(11′)	C(12′)	113.1(3)	C(14′)	C(15′)	C(16′)	109.8(4)	F(3′)	C(17′)	C(11′)	110.5(3)
O(3′)	C(11′)	C(17′)	105.3(3)	C(12′)	C(16′)	C(15′)	106.8(4)	N(19′)	C(18′)	C(6′)	175.3(3)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits. [b] Atom numbers are designated in Fig. 1.

197 spectrometer. ^{1}H and ^{13}C NMR spectra were acquired on a Varian EM 360, EM 390, JEOL GX 270 or Bruker AM 400 spectrometer using $CDCl_3$–TMS solutions unless otherwise noted. *J* Values are given in Hz. All 2D NMR experiments were conducted on a Bruker AM 400 spectrometer using standard Bruker software. The 2D ^{1}H, ^{13}C COSY NMR spectrum [12] was acquired with ^{1}H decoupling in both dimensions and was tuned for $^1J_{CH}$ = 140 Hz with 64 scans for each of 128 × 4K FIDs. The 2D ^{1}H, ^{13}C COLOC experiment [12,13] was tuned for $^nJ_{CH}$ = 8.5 Hz and acquired with 120 scans for each of 256 × 4K FIDs. The sweep widths for all the 2D NMR experiments were optimised prior to acquisition. The NOE difference experiments were conducted using a modification of the method of Hall and Saunders [14] as described previously.[15] Mass spectral data were obtained from a JEOL SX102 instrument. All organic extracts were dried over $MgSO_4$ and samples were chromatographed on silica gel except where stated.

(4R*,5aS*,11bS*)-5a-*Hydroxy*-6,6-*dimethyl*-4-*trifluoromethyl*-5a,11b-*dihydro*-4H,6H-*pyrrolo*[1′,2′:4,5]*oxazino*[2,3-c]-

chromene-10-*carbonitrile* **11**.—Potassium *tert*-butoxide (1.232 g, 11 mmol) was added in one portion to a stirred solution of *trans*-3-bromo-4-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromene-6-carbonitrile **2** (1.4 g, 5.0 mmol) in THF (10 cm^3). After 5 min 2-trifluoroacetylpyrrole[16] (0.897 g, 5.4 mmol) followed by tetramethylethylenediamine (TMEDA) (10 cm^3) was added and the solution was heated under reflux for 18 h. The reaction mixture was cooled, poured into ice-cold dilute hydrochloric acid, extracted with ethyl acetate and the combined organic layers were washed with water and brine. The dried organic phase was concentrated and the residue was chromatographed (2% MeOH–$CHCl_3$) to give the *title compound* as an off-white foam (1.3 g, 71%), m.p. 165–166 °C (EtOAc), ν_{max}/cm^{-1} 3580br, 2230s, 1615s, 1560s, 1480s and 1145s; $\delta_H([CD_3]_2SO)$ 1.36 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 5.45 (1 H, s, 11b-H), 5.48 (1 H, q, *J* 6, 4-H), 6.09 (1 H, m, 3-H), 6.28 (1 H, m, 2-H), 6.98 (1 H, d, *J* 8.5, 8-H), 7.21 (1 H, m, OH), 7.40 (1 H, m, 1-H), 7.48 (1 H, br s, 11-H) and 7.63 (1 H, dd, *J* 8.5, 2, 9-H); $\delta_C([CD_3]_2SO)$ 20.6 (CH_3), 21.7 (CH_3), 53.2 (CH), 67.7 (q, *J* 33, CH), 81.0 (q), 92.0 (q), 102.3 (q), 105.6 (CH), 108.6 (CH), 115.6 (q), 118.0 (CH), 118.8 (q), 122.8 (CH), 122.9 (q), 123.4 (q, *J* 282, CF_3), 132.0 (CH), 133.0 (CH) and 154.8 (q) (Found: C, 59.5; H, 4.0; N, 7.5; M^+, 364.1028. $C_{18}H_{15}F_3N_2O_3$ requires C, 59.3; H, 4.15; N, 7.7%; *M*, 364.1035).

(5a*S**,11b*S**)-5a-*Hydroxy*-6,6-*dimethyl*-5a,11b-*dihydro*-4H,6H-*pyrrolo*[1′,2′:4,5]*oxazino*[2,3-c]*chromene*-10-*carbonitrile***14**. Reaction of 2-formylpyrrole with the bromohydrin **2** in a similar manner to that described above afforded the *title compound*, 13%, m.p. 145–147 °C (MeOH–Et_2O), ν_{max}/cm^{-1} 3500br, 2220s, 1608m and 1580m; $\delta_H(CDCl_3$–$[CD_3]_2SO)$ 1.41 (3 H, s, CH_3), 1.58 (3 H, s, CH_3), 4.61 (1 H, d, *J* 14, 4-H), 5.02 (1 H, d, *J* 14, 4-H), 5.12 (1 H, m, 11b-H), 5.90 (1 H, m, 3-H), 6.29 (1 H, m, 2-H), 6.32 (1 H, s, OH), 6.90 (1 H, d, *J* 8, 8-H), 6.96 (1 H, m, 1-H), 7.43 (1 H, dd, *J* 8.5, 2, 9-H) and 7.52 (1 H, dd, *J* 2, 1, 11-H); $\delta_C([CD_3]_2SO)$ 20.6 (CH_3), 21.8 (CH_3), 53.3 (CH), 58.3 (CH_2), 81.2 (q), 90.9 (q), 101.7 (CH), 102.3 (q), 107.7 (CH), 118.0 (CH), 118.9 (q), 120.7 (CH), 122.7 (q), 123.6 (q), 132.2 (CH), 134.4 (CH) and 155.1 (q) (Found: C, 69.2; H, 5.7; N, 9.65. $C_{17}H_{16}N_2O_3$ requires C, 68.9; H, 5.45; N, 9.45%).

(4*S**,5a*S**,11b*S**)-5a-*Hydroxy*-6,6-*dimethyl*-4-*phenyl*-5a,11b-*dihydro*-4H,6H-*pyrrolo*[1′,2′:4,5]*oxazino*[2,3-c]*chromene*-10-*carbonitrile* **13**. Reaction of 2-benzoylpyrrole[17] with the bromohydrin **2** under similar conditions to the above gave, after chromatography (30–100% EtOAc–hexane) 6,6-*dimethyl*-4-*phenyl*-5a,11b-*dihydro*-4H,6H-*pyrrolo*[1′,2′:4,6]*oxazine*[2,3-c]-*chromene*-10-*carbonitrile* **15** 16%, m.p. 108–110 °C, ν_{max}/cm^{-1} 2220m, 1660m, 1480s and 1130s; δ_H 1.33 (3 H, s, CH_3), 1.51 (3 H, s, CH_3), 5.79 (1 H, m, 3-H), 6.07 (1 H, s, 4-H), 6.34 (1 H, m, 2-H), 6.96 (1 H, d, *J* 8, 8-H), 7.15 (1 H, m, 1-H), 7.41 (5 H, s, Ph), 7.44 (1 H, dd, *J* 8, 2, 9-H) and 7.86 (1 H, d, *J* 2, 11-H) (Found: M^+, 354.1367. $C_{23}H_{18}N_2O_2$ requires *M*, 354.1368) followed by 2-benzoylpyrrole and the *title compound* 17%, m.p. 118–120 °C, ν_{max}/cm^{-1} 3560br, 2220m, 1740m, 1605m, 1485s and 1265s; δ_H 1.49 (3 H, s, CH_3), 1.55 (3 H, s, CH_3), 3.25 (1 H, br s, OH), 5.16 (1 H, s, 11b-H), 5.78 (1 H, m, 3-H), 5.99 (1 H, s, 4-H), 6.29 (1 H, m, 2-H), 6.9–6.96 (4 H, m, Ar), 7.17–7.21 (3 H, m, Ar) and 7.50–7.51 (2 H, m, Ar) [Found: $(MH - H_2O)^+$, 355.1433. $C_{23}H_{20}N_2O_3$ requires $(MH - H_2O)^+$, 355.1447].

4,6,6-*Trimethyl*-5a,11b-*dihydro*-4H,6H-*pyrrolo*[1′,2′:4,5]*oxazino*[2,3-c]*chromene*-10-*carbonitrile* **16**.—Reaction of 2-acetylpyrrole with the bromohydrin **2** under similar conditions to the above gave, after chromatography (10–30% EtOAc–hexane followed by 1% MeOH–$CHCl_3$), the *title compound* 18%, m.p. *126.5–127 °C*, ν_{max}/cm^{-1} 3000m, 2240s, 1665s, 1610m, 1580m and 1500s; δ_H 1.47 (3 H, s, 6-CH_3), 1.58 (3 H, s, 6-CH_3), 1.71 (3 H, d, *J* 6.5, 4-CH_3), 5.07 (1 H, q, *J* 6.5, 4-H), 6.08 (1 H, m, 3-H), 6.33 (1 H, m, 2-H), 6.96 (1 H, d, *J* 8.5, 8-H), 7.07 (1 H, m, 1-H), 7.42 (1 H, dd, *J* 8.5, 2, 9-H) and 7.8 (1 H, d, *J* 2, 11-H); $\delta_C(CDCl_3)$ 18.0 (CH_3), 24.0 (CH_3), 25.2 (CH_3), 71.8 (CH), 79.0 (q), 103.6 (CH), 104.9 (q), 109.4 (q), 109.7 (CH), 117.0 (CH), 118.3 (CH), 119.0 (q), 119.7 (q), 124.9 (CH), 128.6 (q), 131.6 (CH), 144.6 (q) and 154.5 (q) (Found: C, 73.9; H, 5.3; N, 9.55. $C_{18}H_{16}N_2O_2$ requires C, 73.95; H, 5.5; N, 9.6%) followed by 4-(2-*acetylpyrrol*-1-*yl*)-2,2-*dimethyl*-2H-*chromene*-6-*carbonitrile* **17** 18%, m.p. 97–98 °C, ν_{max}/cm^{-1} 3000m, 2240s, 1670s, 1660s, 1615m, 1490s, 1415s and 1290s; δ_H 1.56 (3 H, s, 2-CH_3), 1.61 (3 H, s, 2-CH_3), 2.43 (3 H, s, $COCH_3$), 5.65 (1 H, s, 3-H), 6.35 (1 H, m, 3′-H), 6.59 (1 H, d, *J* 2, 5-H), 6.84 (1 H, m, 4′-H), 6.88 (1 H, d, *J* 8, 8-H), 7.11 (1 H, m, 5′-H) and 7.4 (1 H, dd, *J* 8, 2, 7-H) (Found: C, 73.7; H, 5.4; N, 9.6%; M^+ 292.1212. $C_{18}H_{16}N_2O_2$ requires C, 73.95; H, 5.5; N, 9.6%; *M*, 292.1212).

trans-3-*Hydroxy*-2,2-*dimethyl*-4-(2-*trifluoroacetylpyrrol*-1-*yl*)-3,4-*dihydro*-2H-*chromene*-6-*carbonitrile* **9**.—A mixture of *trans*-3-hydroxy-2,2-dimethyl-4-(pyrrol-1-yl)-3,4-dihydro-2*H*-chromene-6-carbonitrile **8**[18] (0.268 g, 1 mmol) and trifluoroacetic anhydride (141 mm^3, 1 mmol) in chloroform (3 cm^3) was heated under reflux for 1.5 h. The solvent was evaporated and the residue chromatographed. Elution with 0–1% MeOH–$CHCl_3$ gave the *title compound* (0.312 g, 85%), m.p. 146–148 °C (EtOAc–hexane), ν_{max}/cm^{-1} 3605m, 2960br, 2980m, 2220m, 1680s, 1620m, 1550m, 1480s, 1160s, 1145s and 910s; δ_H 1.33 (3 H, s, CH_3), 1.59 (3 H, s, CH_3), 3.03 (1 H, d, *J* 5, OH), 3.94 (1 H, dd, *J* 8, 5, 3-H), 5.03 (1 H, d, *J* 8, 4-H), 6.65 (1 H, m, 3′-H), 6.78 (1 H, m, 4′-H), 6.98 (1 H, d, *J* 9, 8-H), 7.06 (1 H, m, 5′-H), 7.52 (1 H, dd, *J* 9, 2, 7-H) and 7.64 (1 H, br s, 5-H) (Found: C, 59.3; H, 4.0; N, 7.5%; MH^+ 365.1088. $C_{18}H_{15}F_3N_2O_3$ requires C, 59.35; H, 4.15; N, 7.7%; *M*H 365.1113).

trans-3-[^{2}H]-3-*Bromo*-4-*hydroxy*-2,2-*dimethyl*-3,4-*dihydro*-2H-*chromene*-6-*carbonitrile* **27**.—2,2-Dimethyl-4-oxo-3,4-dihydro-2*H*-chromene-6-carbonitrile **24** (1.7 g, 8.5 mmol, prepared by the condensation of 3-acetyl-4-hydroxybenzonitrile with acetone[3]) was added to a stirred suspension of sodium hydride (0.33 g, 8.25 mmol of a 60% dispersion in mineral oil) in THF (20 cm^3) followed by the cautious addition of deuterium oxide (10 cm^3). The resulting solution was stirred for 18 h at ambient temperature and then extracted with ethyl acetate. The extracts were dried and concentrated and the residue was chromatographed to give the labelled ketone **25** (1.09 g, 72%). ^{1}H NMR spectroscopic analysis confirmed the incorporation of deuterium at C-3 and indicated 62% incorporation into the gem-dimethyl group also. To a stirred solution of the labelled ketone **25** (0.80 g, 4 mmol) in THF–MeOH (7.3 cm^3) at 4 °C was added cerium(III) chloride septahydrate (0.3 g, 0.8 mmol) and sodium borohydride (0.15 g, 4 mmol) and after 1 h the reaction mixture was quenched with hydrochloric acid (2 mol dm^{-3}). Extraction of this mixture with ethyl acetate followed by evaporation of the dried extracts then afforded 0.8 g (100%) of the corresponding alcohol, which was converted into the benzopyran **26** (0.645 g, 88%) by dehydration in toluene (40 cm^3) in the presence of toluene-*p*-sulfonic acid (0.15 g, 0.8 mmol) at reflux. Treatment of a stirred solution of the benzopyran **26** (0.645 g, 3.5 mmol) in aqueous dimethyl sulfoxide (10 cm^3) with *N*-bromosuccinimide (0.75 g, 4.2 mmol) at room temperature for 6 h then afforded the title compound as a solid (100%) after the usual work-up.

X-Ray Crystal Analysis of Compound **11**.—*Crystal data.* $C_{18}H_{15}F_3N_2O_3$, M = 364.10. Monoclinic, a = 10.948(8), b = 9.685(5), c = 32.037(13) Å, β = 94.11(5)°, V = 3388 Å^3, space group $P2_1/c$(14), Z = 8, D_c 1.428 g cm^{-3}, colourless, rectangular prisms. Crystal dimensions 0.60 × 0.40 × 0.20 mm, μ(Cu-Kα) = 10.024 cm^{-1}.

Data collection and processing CAD4 diffractometer, $\omega/2\theta$ mode, ω scan speed 2.50–6.70 deg min^{-1}, graphite monochrom-

ated Cu–Kα radiation; 5899 reflections measured ($2° \leqslant 2\theta \leqslant 128°, 0 \leqslant h \leqslant 12, 0 \leqslant k \leqslant 11, -37 \leqslant l \leqslant 37$), 5573 unique, $R_{int} = 0.035$, giving 4351 with $I \geqslant 3\sigma(I)$. There were 478 variables including an extinction coefficient which refined to $1.4(7) \times 10^{-6}$.

Structure analysis and refinement. The structure of compound **11** was solved by direct methods using the SHELXS program series.[19] Atomic positions were initially refined with isotropic temperature factors and subsequently with anisotropic displacement parameters. The function minimised was $\Sigma w(|F_o| - |F_c|)^2$. Weights, w, were assigned to the data as $w = 1/[\sigma^2(I_c) + 0.009\ F_o^2]$. Positions for hydroxy hydrogen atoms were located from Fourier maps and were allowed to refine. Positions for all other hydrogen atoms were calculated and held fixed. Isotropic temperature factors for hydrogen were held fixed at values calculated as 1.3 (B_{eq}) of the attached atom. The large displacement parameters for atoms C(14′), C(15′) and C(16′) suggested the possibility of disorder, however attempts to refine a 2-site occupancy model for these atoms were unsuccessful. The full-matrix least squares refinement converged (max. $\Delta/\sigma = 0.20$) to values of the conventional crystallographic residuals $R = 0.0595$, $R_w = 0.0820$. A final difference Fourier map was featureless with maximum density of $\pm 0.249\ e\ Å^{-3}$. Values of the neutral-atom scattering factors were taken from the International Tables for X-ray Crystallography. Atomic coordinates are found in Table 2 and principal bond distances and angles are found in Tables 3 and 4 respectively.* Thermal parameters and hydrogen atom coordinates have been deposited at the CCDC.†

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* Atom numbers as designated in Fig. 1.

† For full details of the CCDC deposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

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