ELSEVIER

Journal of Fluorine Chemistry 102 (2000) 43–50

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

A simple stereoselective synthesis of biologically important 2-halo-2,3-dideoxy-arabinose derivatives from 1,1,1,2-tetrafluoroethane (134a) and 1-chloro-2,2,2-trifluoroethane (133a)

Paul L. Coe*, James Burdon, Iain B. Haslock

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Received 11 May 1999; received in revised form 28 June 1999; accepted 19 July 1999

Dedicated to Professor Paul Tarrant, to whom organofluorine chemists owe a great deal, on his 85th birthday

Abstract

A simple stereoselective three step synthesis of 2-fluoro- and 2-chloro-2,3-dideoxy arabinose derivatives from the readily available starting materials, (*R*)-glycidol and either 1,1,1,2-tetrafluoroethane (134a) or 1-chloro-2,2,2-trifluroethane (133a), is described. This compares very favourably with the multistep syntheses previously described in the literature. A mechanistic interpretation of the reaction via an unfavourable 5-endo-trig cyclisation is given.

Keywords: Trifluorovinyllithium; Sugar analogues; Stereospecific; De-novo synthesis

1. Introduction

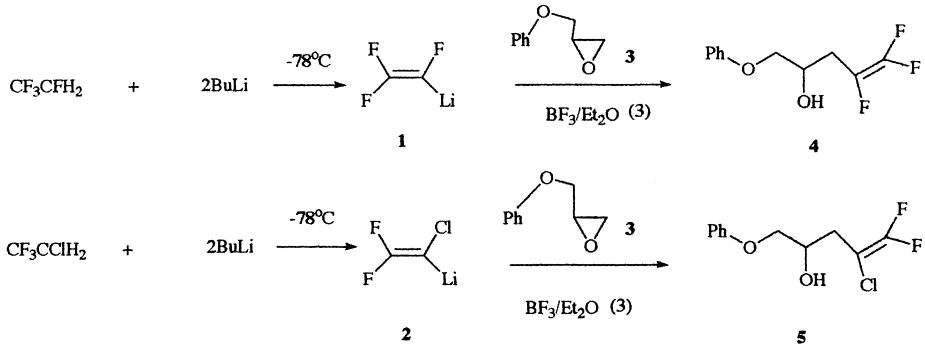
A number of fluorinated di-deoxy nucleosides have shown promise in the treatment of HIV infections but progress on the study of these and related compounds has been hampered by the lack of good de-novo syntheses which in the event of good therapeutic indications could be scaled up. For example, the first ''practical'' de-novo synthesis of 2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl) cytosine (F-ddC) gives a 7.9% yield based on D-xylose [1]. More recently, Patrick [2,3] has reported a better synthesis based on D-mannose as a source of D-glyceraldehyde. To devise a simpler stereoselective synthesis of these interesting molecules provides a challenge to the organofluorine chemist. The use of trifluorovinyllithium (**1**) and trifluorovinylmagnesium bromide as synthetic precursors was recognised by Tarrant, Knunyants and Seyferth almost simultaneously in the 1960s [4–6] but the reactions were at that time very difficult to perform. Subsequently, Normant used chlorotrifluoroethene as starting material to generate **1**, and he also found it important to use rather carefully controlled conditions. Nevertheless, the Normant group showed that a wide range of reactions of **1** could be successfully carried out as reviewed [7]. From the point of view of the present study the ring opening reactions of epoxides catalysed by boron trifluoride etherate were of considerable interest [8]. We have recently shown [9,10] that it is relatively simple, without the use of specialist conditions, to generate **1** from 134a and chlorodifluorovinyllithium **2** from 133a. We now report reactions of these reagents with suitable epoxides to generate precursors of the desired arabinose derivatives.

2. Results and discussion

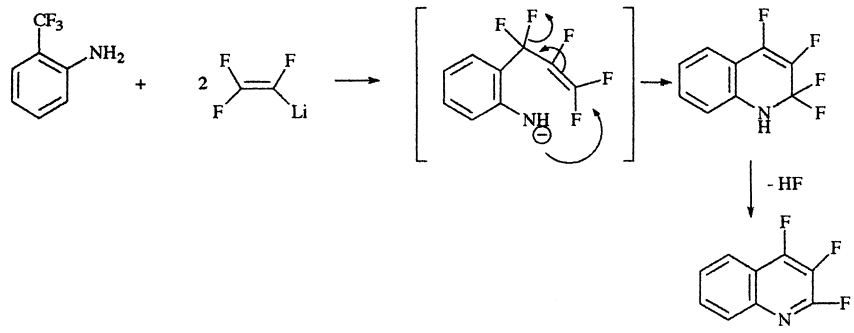
At the outset of this work we believed there were three major problems to be solved to enable us to prepare our desired compounds. Firstly, the opening of a suitable chiral epoxide without epimerisation and without the Payne rearrangement [11] occurring: it is well known that chiral epoxides with acidic hydrogen atoms can readily epimerise and that the Payne rearrangement also readily occurs. Secondly, to cyclise the resulting alcohol to give us the desired tetrahydrofuran structure and thirdly to obtain the fluorine atom in the desired stereochemistry. The synthetic strategy we proposed to use was to investigate the whole reaction sequence using racemic material and when we had obtained optimum conditions to use the appropriate chiral epoxide. The work of Normant [8,12] using both lithium and copper reagents has clearly shown the epoxides open much more readily in the presence of boron trifluoride etherate. Thus,

* Corresponding author. Tel.: +44-121-414-4360; fax: +44-121-414-4403.

0022-1139/00/$ – see front matter
PII: S0022-1139(99)00241-9

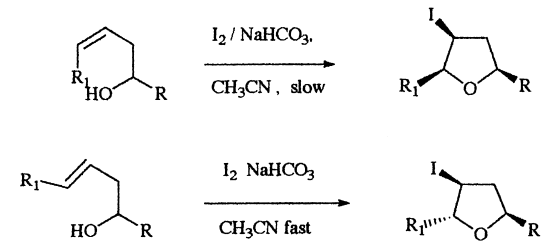


Scheme 1. Reaction of trifluoro and chlorodifluoro-vinyllithium reagents.



Scheme 2. Cyclisation reaction using trifluorovinyllithium.

we first reacted **1** with racemic 1,2-epoxy-3-phenoxy- propane (**3**) in the presence of an equimolar amount of the etherate at −78°C. The product was purified by column chromatography and was identified by physical methods as the expected alcohol, 1,1,2-trifluoro-5-phenoxypent-1-en-4-ol (**4**), in 65% yield. In the same way reaction of **2** afforded 2-chloro-1,1-difluoro-5-phenoxypent-1-en-4-ol (**5**) in 32% yield, identified by standard physical methods. These results are shown in Scheme 1. Thus, we had shown that the first step in our sequence was successful and we now turned our attention to the possible cyclisation step. Our rationale for proceeding along this pathway was based on two observations. Firstly, our reported results [10] that the reaction at the terminal CF_2 group of the introduced trifluorovinyl function with nucleophiles easily leads to the formation of fluoroquinolines (Scheme 2) and secondly to the elegant work of Lipschutz [13] and Knight [14] who studied the use of iodoetherification reactions for the stereoselective formation of substituted five-membered heterocycles as shown in Scheme 3. The latter reactions are thought to proceed via the formation of the iodonium cation which then cyclises to form the corresponding furan derivatives by an unfavourable 5-endo-trig reaction. The reactions can be extremely stereoselective depending on the substituents and are postulated to be controlled by the transition state geometry. We believe that the trifluorovinyl group in **4** is a reasonable mimic for the iodonium cation and this could lead, by a similar process to that proposed by Lipschutz and Knight, to our desired stereoselective cyclisation. An alternative mechanism leading to an unfavourable 5-endo–trig cyclisation has been proposed by Baldwin who showed that reactions leading to dioxolanes can proceed via oxycarbenium ions, in this mode [15], however this mode of reaction it unlikely to be relevant in our case. We thus treated **4** with a large (10-fold) excess of sodium hydride in refluxing THF and obtained a white crystalline solid. The ^{19}F NMR spectrum showed two signals of equal intensity at δ–125 and –192, both of which showed a doublet coupling of 23 Hz in the range for a *cis* FF coupling. The ^{1}H and ^{13}C spectra were consistent with the product being 2,3-difluoro-4,5-dihydro-5-(phenoxymethyl) furan (**6**). This structure was further confirmed by consideration of the mass spectral data and elemental analysis. In the same way, **5** afforded the corresponding chlorofluoroderivative 3-chloro-2-fluoro-4,5-dihydro-5-(phenoxymethyl) furan (**7**), characterised by physical methods as for **6**. When the reaction of **4** was repeated but using only a slight excess of sodium

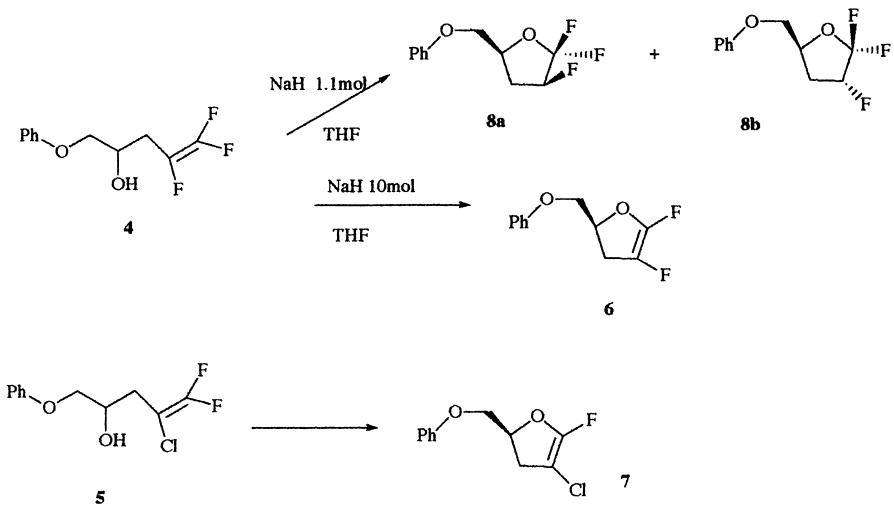


Scheme 3. Iodoetherifications.

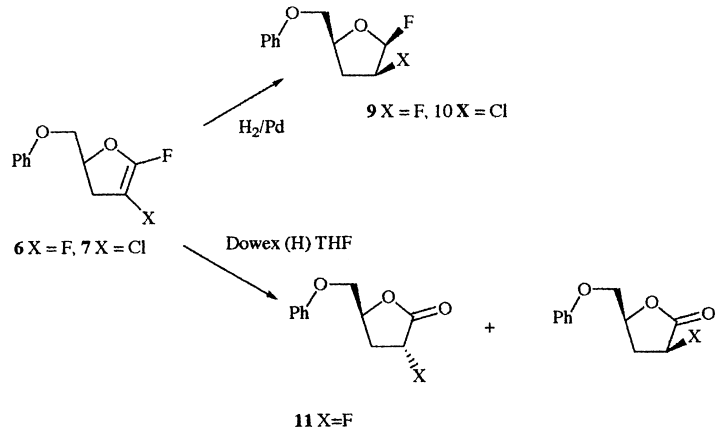
hydride two products were isolated in the ratio of 7:3 and these were readily separated by column chromatography. Both compounds gave a parent ion peak of *m/z* 232 in their mass spectra corresponding to an empirical formula of $C_{11}H_{11}F_3O_2$. ^{19}F NMR spectroscopy showed the presence of a CF_2 group and a CFH group in each compound and the ^1H spectrum showed a series of peaks for highly coupled protons. Significantly there was a complex doublet which showed a coupling constant of 52 Hz attributable to the presence of a CHF group. These data together suggest that the two compounds are two pairs of enantiomers of 2,2,3-trifluoro-4,5-dihydro-5-(phenoxymethyl) furan (**8a, 8b**). This pattern of products can be explained by consideration of the diastereotopicity of the faces of the trifluorovinyl group in the ene-ol (**4**): the oxyanion generated in the reaction can react at either face. The stereoselectivity in this reaction is interesting and potentially useful (see below). We believe, on the basis of comparison of NMR data with literature reports of related compounds [1,3], that the major product pair has the cis structure **8a** and the minor pair the *trans* structure **8b**. We had thus established that our synthetic strategy so far had led to potential precursors of the desired sugar analogue.

These results are shown in Scheme 4. It is now necessary to elaborate **7** or **8** to the final structure. Previously, we had shown that it was possible to catalytically hydrogenate a CF = CH system in a nucleoside stereoselectively to the arabino configuration [16], and recently this has also been shown to occur in sugar analogues [8]. Thus, we hydrogenated **6** under our previously described conditions and obtained the desired 2,3-difluoro-5-(phenoxymethyl)tetrahydrofuran (**9**) in almost quantitative yield. The structure of **9** was readily determined by physical methods as shown in the experimental section. In the same way the hydrogenation of **7** afforded the corresponding 3-chloro-1-fluoro-5-(phenoxymethyl) tetrahydrofuran (**10**) again readily characterised by physical methods. The final experiments we carried out to test our strategy were to consider the hydrolysis of **6** under both acidic and basic conditions. Much to our surprise hydrolysis with a saturated solution of sodium hydroxide in wet THF gave only the starting material. However, hydrolysis with a mixture of aqueous 4 M hydrochloric acid in THF at reflux for 2.5 days afforded a mixture of unreacted starting material and 3-fluoro-5-(phenoxymethyl)-tetrahydrofuran-2-one (**11**) (see below). When **6** was refluxed in THF with Dowex 50 (H) for 2.5 days a mixture of two products in the ratio 13:2 was observed; column chromatography afforded a pure sample of the major product shown to be **11**, as a mixture of enantiomers. The ^{19}F NMR spectrum showed only one band at δ–193 as a multiplet and among the observable couplings was a large doublet of 52 Hz characteristic of a CHF group with a smaller doublet coupling (24.4 Hz) characteristic of a *trans* vicinal HF coupling in a five-membered ring. The ^1H spectrum which was essentially that of the major isomer due to the relatively small amounts of the minor isomer present showed the expected peaks for the proposed structure and in particular the characteristic shift pattern observed in the literature for the 5-methine proton in similar compounds known to have the 3F and the 5-phenoxymethyl groups in the *trans* arrangement [1,8]. From the ^{19}F and ^1H NMR spectra of the crude material we were able to identify the minor isomer as the *cis* product. It is interesting to note that hydrolysis in the presence of Dowex resin appears to proceed more readily than in aqueous hydrochloric acid/THF. This may well be a reflection of the greater acidity of the sulfonic acid moiety in the resin being a stronger acid than HCl under these conditions. This is in line with the greater reactivity of sulfonic acids in electrophilic additions to fluoroalkenes [17]. These reactions are summarised in Scheme 5. Thus, we have been able to show that our strategy worked using racemic materials.

We now turn our attention to using (*R*)-3-(benzyloxy)-1,2-epoxypropane (**12**). We choose to use the benzyl pro-



Scheme 4. Cyclisation of pent-1-en-4-ols (6 and 7) [single enantiomers only shown].



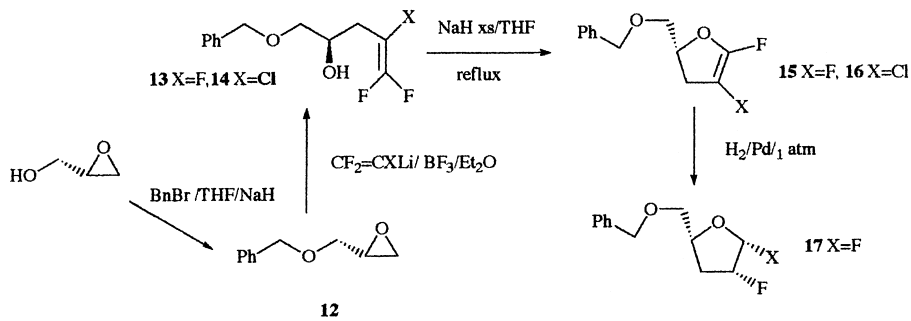
Scheme 5. Reactions of dihydrofurans 6 and 7 [only one enantiomer shown].

Scheme 6. Degenerate Payne rearrangement of glycidol.

tecting group since it is much easier to remove than phenyl group at later stages in a potential nucleoside synthesis. The preparation of the ether (**12**) from the commercially available (*R*)-glycidol was straightforward using the method of Ichikawa [18]. Although this reaction uses sodium hydride to generate the oxyanion which could lead to a Payne rearrangement [11] as shown in Scheme 6 this presents no problem in our case since as can be seen the rearrangement exists as a degenerate equilibrium reforming the (*R*)-epoxide. The epoxide (**12**) was reacted as above with trifluorovinyllithium (**1**) to form the expected chiral alcohol (*R*)-5-(benzyloxy)-1,1,2-trifluropent-1-en-ol (**13**). The alcohol was readily characterised by physical means and had an optical rotation of –6.1°. In the same way the epoxide (**14**) reacted with the vinyllithium (**2**) to give the alcohol (*R*)-5-(benzyloxy)-2-chloro-1,1-difluoro-pent-1-en-4-ol (**14**) again fully characterised by physical methods and with an optical rotation of –3.7°. The alcohol (**13**) was treated as above with a large excess of sodium hydride to form the expected (*R*)-5-(benzyloxymethyl)-2,3-difluoro-4,5-dihydrofuran (**15**) with an optical rotation of +5.4°. Apart from minor differences due to the different group at position 5 the NMR spectra of **4** and **15** were very similar as would be expected. In a similar reaction **12** yielded the dihydrofuran (*R*)-5-(benzyloxymethyl)-3-chloro-2-fluoro-4,5-dihydrofuran (**16**). Catalytic hydrogenation of **16** as above for **6** afforded the desired product, 1(*R*), 2 (R), 3(*R*)-5-(benzyloxymethyl)-2,3-difluorotetrahydrofuran (**17**). The unoptimised overall yield was 29%. The low yielding step in the sequence was reaction of trifluorovinyllithium with the glycidyl ether (**14**) at 43% isolated yield, although GC indicated a yield of ca 75%, and thus it may be possible to increase the overall yield by a better work-up procedure. These reactions are summarised in Scheme 7. Since the condensation of related molecules with pyrimidine and purine bases has been previously reported we have in effect achieved our original objective. We have shown that it is possible by a series of very simple reactions to prepare sugar derivatives directly in good yield from readily available materials in a much smaller number of steps than previously reported.

3. Experimental

The ^{1}H NMR (300 MHz) and the ^{13}C NMR spectra (75 MHz) were measured on a Bruker AC 300 NMR spec-



Scheme 7. Formation of chiral di and tetrahydrofurans.

trometer unless stated otherwise. The ^{1}H NMR spectra (400 MHz) were measured on a Bruker AMX 400 NMR spectrometer. The ^{19}F NMR spectra were carried out either on a Jeol NMR spectrometer, type FX 90 Q (84.26 MHz) or on a Bruker AC 300 NMR spectrometer (282.4 MHz); Tetramethylsilane and fluorotrichloromethane were used as internal references. For the characterisation of the signals the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, "quin" = pseudo quintet etc. *J* values are given in Hz. The mass spectra (CI-MS/EI-MS) were measured on a VG-Prospec-triple focusing mass spectrometer. For GC-MS analysis, a Carlo Erba, 8000 series GC was used with a 50 m column (BPX 5, helium carrier gas).

Thin layer chromatography was performed on TLC plastic sheets (silica gel 60 F_{254}), pre-coated with a layer thickness of 0.2 mm from Merck, Art. 5735. Gas chromatographic analysis was carried out using a Philips PYE Unicam, Series 304 chromatograph with a 50 m CD-SIL-CB 19 column. The data were registered by a JCL 600 chromatography data system.

3.1. Preparation of trifluorovinyllithium (*1*)

Under a dry nitrogen atmosphere *n*-butyllithium (8 cm^3, 2.5 M in hexanes) was added via a syringe pump over 0.5 h to a solution of 1,1,1,2-tetrafluoroethane (134a) (3 cm^3) in ether (40 cm^3) at −78°C. The mixture was allowed to stir for a further 1 h at this temperature and was then used for the other experiments described below.

3.1.1. Preparation of 1-chloro-2,2-difluorovinyllithium *2*

In the same manner as above but using 1-chloro-2,2,2-trifluoroethane (3 cm^3) (133a) a solution of 1-chloro-2,2-difluorovinyllithium was prepared ready for use in the experiments described below.

3.1.2. Preparation of 1,1,2-trifluoro-5-phenoxy-pent-1-en-4-ol (*4*)

1,2-epoxy-3-phenoxypropane (**3**) (1.3 cm^3, 9.6 mmol) and boron trifluoride etherate (1.2 cm^3, 9.8 mmol) were added to a solution of **1** (10 mmol) at –78°C. The reaction mixture was allowed to warm slowly to room temperature over 2 h, saturated $NaHCO_3$ solution (20 cm^3) was added, the aqueous layer extracted with ether (4 × 30 cm^3) and the ether layers combined, dried ($MgSO_4$) and the solvent removed. The residual oil (2.1 g) was purified by column chromatography (Silica, Hexane/ether 4:1) to give 1,1,2-trifluoro-5-phenoxy-pent-1-en-4-ol (**4**) (nc) b.p. 140°C/0.2 mmHg; (Found: C, 56.7; H,4.5% $C_{11}H_{11}F_3O_2$ requires C, 56.9:H, 4.8%); MS *m/z* 232 [M^+], 181 [$M - CHF_2^+$], 137 [$M - C_3H_2F_3^+$] 77 [Ph^+]; d_H 2.5 (s, 1H, exchangeable with D_2O, OH), 2.6 (AB, 2H, $^3J_{HF}$ 24, $^3J_{HF}$ 24, $^3J_{HH}$ 6, $^2J_{HH}$ 4 , $^3J_{HH}$ 2, H 3 and H 3'), 3.9 (dd, 1H, $^2J_{HH}$ 9.5, $^3J_{HH}$, 6.5, H5) 4.1 (dd, 1H, $^2J_{HH}$ 9.5, $^3J_{HH}$ 3.5, H5'), 4.3 (m, H 4), 6.9–7.3 (m, 5H, Ar); δ_F –103 (dd, 1F, $^3J_{FF}$ 33.6, $^2J_{FF}$ 82.5, CF_2 = CF) –122 (dd, 1F, $^3J_{FF}$ 112.7, $^3J_{FF}$ 82.5, CF_2 = CF) –172 (ddt, 1F, $^3J_{FF}$ 112.9, $^3J_{FF}$ 33.6, $^3J_{HF}$ 22.9 CH_2CF=); δ_C 33 (CH_2), 67 (CHOH), 71(CH_2), 115(Ar), 122(Ar), 124 (ddd, $^1J_{CF}$ 234, $^2J_{CF}$ 53.6, $^2J_{CF}$ 16.9, –CF=), 130 (Ar), 150 (ddd, $^1J_{CF}$ 287, $^1J_{CF}$ 274, $^2J_{CF}$ 46.4, =CF_2) 158.3 (Ar).

3.1.3. Preparation of 2-chloro-1,1-difluoro-5-phenoxypent-1-en-4-ol (*5*)

In the same manner as above, reaction of **3** (9.6 mmol) with 1-chloro-2,2-difluorovinyllithium (10 mmol) afforded 2-chloro-2,2-difluoro-5-phenoxy-pent-1-en-4-ol(**5**) (nc) 0.8 g m.p. 31–32°C; (Found: C, 53.3; H, 4.7% $C_{11}H_{11}ClF_20_2$ requires C, 53.1; H4.5%); MS *m/z* 250 [^{37}ClM +], 248[^{35}ClM+], 157 [M-OPh +], 155 [M –Oph^+], 94 [$PhOH^+$]; δ_H 2.6 (m, 2H, $^2J_{HH}$ 14,5, $^3J_{HH}$ 8, $^4J_{HF}$ 4.5, $^4J_{HF}$ 3, $^3J_{HF}$ 1.5, $^3J_{HF}$ 1, H3 and H3'), 4 (dd , 2H, $^2J_{HH}$ 9, $^3J_{HH}$ 5.5, $^3J_{HH}$ 4.5, $^4J_{HH}$, 1, $^4J_{HH}$ 0,5, H 5 and H 5'), 4.2 (m, 1H, CHOH), 4.5 (d, 1H, exchangeable with D_2O, $^3J_{HH}$ 5, OH), 6.9–7.2 (m, Ar); δ_F −89 (d, 1F, $^3J_{FF}$ 48.8, =CF_2), −95 (d, $^3J_{FF}$ 45.8, =CF_2); δ_C 35 (CH_2), 67 (CHOH), 72 (CH_2), 91 (dd, $^2J_{CF}$ 39, $^2J_{CF}$ 19 *C*Cl = CF_2), 115 (Ar), 122(Ar) , 130(Ar), 152 (t, $^1J_{CF}$ 284), 159.9 (Ar).

3.1.4. Preparation of 2,3-difluoro-4,5-dihydro-5(phenoxymethl) lfuran (*6*)

Sodium hydride (0.5 g, 20 mmol) was added to a solution of **4** (0.5 g, 2.2 mmol) in dry THF (30 cm^3) and the mixture was heated under reflux for 2 days. Ice (10 g) was added carefully to the cooled mixture followed by brine (20 cm^3). The organic layer and ether extracts of the aqueous layer (3 × 30 cm^3) were dried ($MgSO_4$) and the solvent removed to yield a white powder. Recrystallisation from chloroform/methanol 9:1 afforded 2,3-difluoro-4,5-dihydro-5-(phenoxymethyl) furan (**6**) (0.31 g) (nc) m.p. 44–46°C; (Found; C, 62.1; H, 4.5% $C_{11}H_{10}F_2O_2$ requires C, 62.3; H, 4.7%), Accurate mass measurement: 212.064986; calc. for $C_{11}H_{10}F_2O_2$212.064984; d_H 2.9 (m, 1H, $^2J_{HH}$ 18.5, $^3J_{HH}$ 8, $^3J_{HF}$ 5.5, $^4J_{HF}$ 2.5, *CH*$_2$–CHF), 3.1 (m, 1H, $^2J_{HH}$ 18.5, $^3J_{HH}$ 10, $^3J_{HF}$ 5, $^4J_{HF}$ 4, *CH*$_2$–CHF), 4.1 (dd, 1H, $^2J_{HH}$ 10, $^3J_{HH}$ 4.5, O*CH*$_2$CH), 4.2 (dd, 1H, $^2J_{HH}$ 10, $^3J_{HH}$ 6, O*CH*$_2$CH), 4.9 (m, 1H CH_2*CH*O), 6.9 (m, Ar), 7(m, Ar), 7.3 (m, Ar); δ_F –125 (d, 1F, $^3J_{FF}$ 23.5, CF=), −192 (d, 1F, $^3J_{FF}$ 23.6, CF=); δ_C 29 (d, $^2J_{CF}$ 18.1, *C*H_2CF=), 69 (s, CH_2), 74 (d, $^3J_{CF}$ 7, *C*HCH_2CF), 114 (dd, $^1J_{CF}$ 239, $^2J_{CF}$ 10), 115(Ar), 122 (Ar), 130 (Ar), 143 (dd, $^1J_{CF}$ 260, $^2J_{CF}$ 20, O*C*F = CF), 158 (Ar).

3.1.5. Preparation of 3-chloro-2-fluoro-4,5-dihydro-5-(phenoxymethyl)furan (*7*)

In the same way as above for the preparation of **6**, the alcohol **5** (0.3 g, 1.2 mmol) and sodium hydride (0.3 g, 15 mmol) afforded 3-chloro-2-fluoro-4,5-dihydro-5-phenoxymethyl-furan (**7**) (nc) (0.26 g) m.p. 61-63°C, (Found:

C, 57.6:H, 4.2% $C_{11}H_{10}ClFO_2$ requires C, 57.8; H, 4.4%); MS *m/z* 230 [$^{37}ClM^+$], 228 [$^{35}ClM^+$]; δ_H 2.9 (ddd, 1H, $^2J_{HH}$ 13, $^3J_{HH}$ 7, $^4J_{HF}$ 4.5, CH_2CCl = CF), 3.1 (ddd, 1H, $^2J_{HH}$ 13, $^3J_{HH}$ 10, $^4J_{HF}$ 4.5, CH_2CCl = CF), 4.25 (m, 2H, OCH_2CH), 5.2 (m, 1H, CH_2CHO), 6.95 (m, Ar), 7.3(m, Ar); δ_F –116 (s, F); δ_C 34 (CH_2), 70 (CH_2CCl=), 79 (CH_2CHO), 116 (Ar), 121 (d, $^2J_{CF}$ 18, *C*Cl = CF), 122 (Ar), 130 (Ar) 154 (d, $^1J_{CF}$ 269, *C*F = CCl), 160 (Ar).

3.1.6. Preparation of 2,2,3-trifluoro-4,5-dihydro-5-(phenoxymethyl) furan (**8**)

The alcohol **4** (2.32 g, 10 mmol) was heated under reflux with sodium hydride (0.4 g, 16 mmol) in dry THF (50 cm^3) for 22 h. Ice was added to the cooled reaction mixture followed by brine (20 cm^3). The separated organic layer and the combined ether extracts of the aqueous layer (3 × 30 cm^3) were dried ($MgSO_4$) and the solvents removed to leave a semi-solid product (1.9 g) m.p. 20–30°C. A portion of this latter was purified by column chromatography(silica, hexane/ethyl acetate 4:1) to give the two pairs of enantiomers of 2,2,3-trifluoro-4,5-dihydro-5-(phenoxymethyl) furan (**8a** and **8b**) (nc) in the ratio 7:3: (Found (for the mixture of isomers): C, 56.6; H, 5.0% $C_{11}H_{11}F_3O_2$ requires C, 56.9; H, 4.8%); δ_H (major isomer) 2.45 (m, 1H, CH_2), 2.55 (m, 1H, CH_2), 4.05 (dd, 1H, $^2J_{HH}$ 10, $^3J_{HH}$ 4.5, CH_2O), 4.15 (dd, 1H, $^2J_{HH}$ 10, $^3J_{HH}$ 3.0, CH_2), 4.95 (m, CH_2CHO), 5.2 (d of m, $^2J_{HF}$ 52, C*H*FCF_2), 6.85(Ar), 6.95 (Ar), 7.25(Ar); (minor isomer) 2.3 (m, 1H CH_2CHF), 2.35 (m, 1H, CH_2CHF), 4.15 (m, 1H, OCH_2), 4.2 (m, 1H, OCH_2), 4.75 (m, 1H, CH_2CHO), 5.1 (m, 1H, C*H*FCF_2), 6.85 (Ar), 7.05 (Ar), 7.35 (Ar); δ_F –71 (major isomer) (d, 1F, $^2J_{FF}$ 149.5, CF_2CFH), −90 (dd, 1F, $^2J_{FF}$ 153, $^3J_{FF}$ 12.2,CF_2CFH), −194 (m, 1F, CH*F*CF_2); (minor isomer) –74 (d, 1F, $^2J_{FF}$ 153, CF_2CFH), −89 (dd, 1F, $^2J_{FF}$ 149.5, $^3J_{FF}$ 12.2 CF_2CFH), −189 (m, 1F, CH*F*CF_2); δ_C (major isomer) 32 (d, $^2J_{CF}$ 21.1, *C*H_2CHF), 69 (CH_2), 78 (CH_2CHO), 90 (ddd, $^1J_{CF}$ 192, $^2J_{CF}$ 46.1, $^2J_{CF}$ 24.2, C*H*FCF_2), 115 (Ar), 122 (Ar), 128 (dt, $^1J_{CF} = {}^1J_{CF}$ 260.5, $^2J_{CF}$ 21.7, *C*F_2CFH), 130 (Ar), 158 (Ar); (minor isomer) 31 (d, $^2J_{CF}$ 20.4), 69 (CH_2), 77(CH_2CHO), 89 (ddd, $^1J_{CF}$ 193.4, $^2J_{CF}$ 46.55, $^2J_{CF}$ 24.5, *C*H*F*CF_2), 115 (Ar), 122 (Ar), 128 (dd, $^1J_{CF} = {}^1J_{CF}$ 262, $^2J_{CF}$ 37.73, CHF*C*F_2), 130 (Ar) 156 (Ar).

3.1.7. Preparation of 2,3-difluoro-5-(phenoxymethyl) tetrahydrofuran (**9**)

The dihydrofuran (0.5 g, 2.3 mmol) in ethyl acetate (20 cm^3) was hydrogenated over palladium on carbon (10%, 0.2 g) at 1 atm for 24 h when no more hydrogen was absorbed. The mixture was filtered through a Celite pad and the filtrate evaporated to dryness to yield 2,3-difluoro-5-(phenoxymethyl) tetrahydrofuran (**9**) as a racemic mixture (0.5 g as an oil) (nc); (Found: C, 61.5; H, 5.4% $C_{11}H_{12}F_2O_2$ requires C, 61.7; H, 5.7%); MS, *m/z* 214 [M^+], 121 [M–PhO^+], δ_H 2.4 (m, 1H, CH_2CHF), 2.6 (m, 1H, CH_2CHF), 4.1 (dd,1H, $^2J_{HH}$ 10, $^3J_{HH}$ 4.3, CH_2), 4.25 (dd, 1H, $^2J_{HH}$ 10, $^3J_{HH}$ 3.0, CH_2), 4.85 (m, 1H, CH C*H*O), 5.3 (d of m, 1H, $^2J_{HF}$ 53.2, CH_2CHF), 5.65, (d of m, 1H, $^2J_{HF}$ 52, CHFC*H*FO), 6.85 (Ar), 6.95 (Ar), 7.3(Ar); δ_F 137 (m, 1F CHFCH*F*O), −193 (m 1F, CH_2CHF), d_C 31 (d, $^2J_{CF}$ 20.9, *C*H_2CF = CF), 68(*C*H_2CHO), 79 (CH_2CHO), 92 (dd, $^1J_{CF}$ 190.5, $^2J_{CF}$ 47.2, CHFCHF), 115 (Ar), 122 (Ar), 129 (dd, $^1J_{CF}$ 246, $^2J_{CF}$ 26.6), 132 (Ar),159 (Ar).

3.1.8. Preparation of 3-chloro-2-fluoro-5-(phenoxymethyl) tetrahydrofuran (**10**)

In the same way as above hydrogenation of **7** (0.25 g, 0.11 mmol) afforded 3-chloro-2-fluoro-5- (phenoxymethyl) tetrahydrofuran (**10**) (nc) as an oil (0.22 g); (Found: C, 57.1:H, 5.1% $C_{11}H_{12}ClFO_2$ requires C, 57.3; H, 5.2%); δ_H 2.4 (m, CH_2CHCl), 2.73 (m, CH_2CHCl), 3.96 (m, 1H, $CH_2CHClCHF$) 4.16 (dd, 1H, $^2J_{HH}$ 10, $^3J_{HH}$ 3.3, CH_2), 4.23 (dd, 1H, $^2J_{HH}$ 10, $^3J_{HH}$ 3.0, CH_2), 4.8 (m, CH_2CHO), 5.3 (d of m, 1H, $^2J_{HF}$ 53.2, CH_2CHF), 6.8(Ar), 6.95 (Ar), 7.3(Ar); δ_F −143 (d of m, $^2J_{HF}$ 53.1 CH*F*O); δ_C 31 (*C*H_2CHCl), 69 (CH_2CHO), 79(CH_2CHO), 91(d, $^2J_{CF}$ 40.5 *C*HClCFH), 115 (Ar), 121 (Ar) 127 (d, $^1J_{CF}$ 263, CHCl*C*FHO), 130 (Ar) 156 (Ar).

3.1.9. Preparation of 3-fluoro-5-(phenoxymethyl) tetrahydrofuran-2-one (**11**)

A solution of **6** (1.06 g 5 mmol) in THF (30 cm^3) was stirred under reflux with Dowex(H) (14 g) for 2.5 days. The mixture was filtered and the solvent removed to give an inseperable mixture in the ratio 13:2 of 3-fluoro-5-(phenoxymethyl) tetrahydrofuran-2-one (**11**) (nc) m.p. 67–71°C; (Found for the mixture: C, 62.6; H, 5.1% $C_{11}H_{11}FO_3$ requires C, 62.9; H, 5.3%); MS, exact mass 210.068728, $C_{11}H_{11}FO_3$requires 210.069223; δ_H 2.5 (m, 1H, CH_2CHF), 2.85 (m, 1H CH_2CHF), 4.1 (dd, 1H, $^2J_{HH}$ 10.5, $^3J_{HH}$ 4.5 CH_2CH), 4.2 (dd,1H, $^2J_{HH}$ 10.5, $^3J_{HH}$ 3.55 CH_2CH), 4.8 (m, 1H, CHO), 5.3 (dt, 1H, $^2J_{HF}$ 51, $^3J_{HH} = {}^3J_{HH}$ 8.5, CH_2CHF), 6.9 (Ar), 7.0 (Ar), 7.3 (Ar); δ_F −193 (d of d of m, 1F, CH_2CHFO); δ_C 31 (d, $^2J_{CF}$ 19.95, *C*H_2CHF), 68 (CH_2), 74 (d, $^3J_{CF}$ 6.3 CH_2CHO), 85 (d, $^1J_{CF}$ 192.1, *C*HF), 115 (Ar), 122 (Ar), 130 (Ar), 158(Ar), 171(d, $^2J_{CF}$ 21.2, CHF*C*O).

3.1.10. Preparation of (R)-3-(benzyloxymethyl)-1,2-epoxyethane (**12**)

A suspension of sodium hydride (1 g, 4.1 mmol) in THF (10 cm^3) was added to a solution of *R*-glycidol (2.2 g, 3 mmol) and benzyl bromide (5.13 g, 3 mmol) in THF (50 cm^3). The reaction stirred at room temperature until the evolution of hydrogen had stopped (1.5 h). The solvent was removed and ether (20 cm^3) and ice (10 g) were added to the residue. The organic layer was separated, combined with the ether extracts (3 × 20 cm^3) of the aqueous layer, dried ($MgSO_4$) and the solvent removed to yield (R)-3-(benzyloxymethyl)-1,2-epoxyethane (**12**), $Na_a^{20} + 2.5°$ with an identical ^1H NMR spectrum to that previously reported [18].

*3.1.11. Preparation of (R)-5-(benzyloxy)-1,1,2-trifluoropent-1-en-4-ol (**13**)*

The epoxide (**12**) (1.25 g, 7.5 mmol) and boron trifluoride/etherate (0.9 cm^3, 7.5 mmol) were reacted as above with a solution of trifluorovinyllithium (7.5 mmol) at –78°C for 2 h whilst the mixture slowly warmed to RT. Work up as described above afforded, after purification by column chromatography (silica, hexane/ether 4:1), (R)-5-(benzyloxy)-1,1,2-trifluoropent-1-en-4-ol (**13**)(nc) as an oil (0.8 g) $Na_a^{20} + 6.1°$; (Found: C, 58.3; H, 5.1% $C_{12}H_{13}F_3O_2$ requires C, 58.5; H, 5.3%); MS 246{M^+], 226 [M–HF^+], 107 [PhCH2O^+]. δ_H 2.6 (m, 2H, $^3J_{HF} = {}^3J_{HF}$ 24, CH_2), 2.85(s, 1H, OH), 3.4 (dd, 1H, $^2J_{HH}$ 9.5, $^3J_{HH}$ 6.5, CH_2CHOH), 3.55 (dd, 1H, $^2J_{HH}$ 9.5, $^3J_{HH}$ 6.5, CH_2CHOH), 4.05 (m, 1H, C*H*OH), 4.55 (s, 2H, PhCH_2), 7.3–7.4 (m, Ph); δ_F −104 (dd, 1F $^3J_{FF}$ 33.6, $^2J_{FF}$ 85.5 CF_2 = CF), −123(dd, 1F, $^3J_{FF}$ −115.9, $^3J_{FF}$ 85.5, CF_2 = CF), −172 (ddt, 1F, $^3J_{FF}$ 115.9, $^3J_{FF}$ 33.6, $^3J_{HF} = {}^3J_{HF}$ 24.4, CF2 = C*F*); δ_C 30 (dd, $^2J_{CF}$ 21.3, $^3J_{CF}$ 2.0 *C*H_2CF = CF_2), 67 (CHOH), 73 (*C*H_2CHOH), 74 (Ph*C*H_2), 124 (ddd, $^1J_{CF}$ 238, $^2J_{CF}$ 51.7, $^2J_{CF}$ 15.6, *C*F = CF_2), 129 (Ar), 138 (Ar), 154 (ddd, $^1J_{CF}$ 320.2, $^1J_{CF}$ 273.6, $^2J_{CF}$ 46.5, CF = *C*F_2).

*3.1.12. Preparation of (R)-5-(benzyloxy)-2-chloro-1,1-difluoropent-1-en-4-ol (**14**)*

In the same way as above but using 1-chloro-2,2-difluorovinyllithium (7.5 mmol) and **12** (1.84 g, 7.5 mmol) we obtained (*R*)-5-(benzyloxy)-2-chloro-1,1-difluoropent-1-en-4-ol (**14**) (nc) 1.66 g) as an oil Na_a^{20} –3.7°; (Found: C, 54.6; H, 5.2% $C_{12}H_{13}ClF_2O$ requires C, 54.9; H, 5%); δ_H 2.4 (m, 1H, $^2J_{HH}$ 15, $^3J_{HH}$ 5, $^4J_{HF} = {}^4J_{HF}$ 3, CH_2CF = CF_2), 2.55(m, 1H, $^2J_{HH}$ 14.5, $^3J_{HH}$ 8, $^4J_{HF}$ 1, $^4J_{HF}$ 3, CH_2CF = CF_2), 3.1 (s, 1H, OH), 3.45 (dd, 1H, $^2J_{HH}$ 9.5, $^3J_{HH}$ 6, CH_2CHOH), 3.55 (dd, 1H, $^2J_{HH}$ 9.5, $^3J_{HH}$ 3.5, CH_2CHOH), 4.1(m, 1H C*H*OH), 7.3−7.4 (m, 5H, Ph); δ_F −88 (d, 1F, $^3J_{FF}$ 42.7, CF_2 = CCl), −94 (d, 1F $^3J_{FF}$ 42.7, CF_2 = CCl); δ_C 34 (s, *C*H_2CCl), 67 (CH_2*C*HOH), 73(*C*H_2CHOH), 74 (*C*H_2Ph), 89 (dd, $^2J_{CF}$ 43.8, $^2J_{CF}$ 19.8, *C*Cl = CF_2), 128 (Ar), 128 (Ar), 129 (Ar),138 (Ar) 154 (t, $^1J_{CF} = {}^1J_{CF}$ 286.2 *C*F_2 = CCl).

*3.1.13. Preparation of (R)-5-(benzyloxymethyl)-2,3-difluoro-4,5-dihydrofuran (**15**)*

The alcohol (**13**) (0.5 g, 2 mmol) in THF (30 cm^3) was heated under reflux with sodium hydride(0.34 g 14 mmol) for 4 h. The reaction mixture was cooled and ice (10 g) was carefully added, the organic layer and the ether extracts (4 × 25 cm^3) of the aqueous layer were combined, dried ($MgSO_4$) and the solvent removed to leave an oil which was purified by column chromatography (silica, hexane/ether 4:1) to give (*R*)-5-(benzyloxymethyl)-2,3-difluoro-4,5-dihydrofuran (**15**) (0.3 g) (nc) $Na_a^{20} + 5.4°$; (Found: C, 63.5; H, 5.5% $C_{12}H_{12}F_2O_2$ requires C, 63.7; H, 5.35%); MS *m/z* 226 [M^+], 107 [PhCH_2O^+]; δ_H 2.8 (m, 1H, $^2J_{HH}$ 13, $^3J_{HH}$ 10.5, $^3J_{HH}$ 5, $^4J_{HF}$ 2.5, CH_2CF = CF), 3 (m, 1H, $^3J_{HH}$ 13, $^3J_{HH}$ 10.5, $^3J_{HF}$ 5, $^4J_{HF}$ 3, CH_2CF = CF_2), 3.6 (dd, 1H, $^2J_{HH}$ 10.5, $^3J_{HH}$ 4.5, CH_2CHO), 3.7(dd, 1H, $^2J_{HH}$ 10.5, $^3J_{HH}$ 6, CH_2CHO), 4.6 (s, 2H CH_2Ph), 4.7 (m, 1H, CH_2C*H*O), 7.3–7.4 (m, 5H, Ph); δ_F −128(d, 1F, $^3J_{HH}$ 24.1, CF = C*F*O), −196 (d of m, 1F, $^3J_{HH}$ 21.4, CH_2C*F* = CF); δ_C 29 (d, $^2J_{CF}$ 17.9, *C*H_2CF = CF), 71 (*C*H_2CHO), 74 (Ph*C*H_2O), 75 (d, $^3J_{CF}$ 8.3, CH_2*C*HO), 115 dd, $^1J_{CF}$ 250, $^2J_{CF}$ 13.1, CH_2*C*F = CF), 128 (Ar), 128 (Ar), 129 (Ar), 138 (Ar), 154 (dd, $^1J_{CF}$ 268, $^2J_{CF}$ 23.7).

*3.1.14. Preparation of (R)-5-(benzyloxymethyl)-3-chloro-4,5-dihydrofuran (**16**)*

In the same manner as above the alcohol (**14**) (0.34 g) and sodium hydride (0.3 g) afforded (R)-5-(benzyloxymethyl)-3-chloro-4,5-dihydrofuran(**16**) (nc) (0.21 g) as an oil $Na_a^{20} + 6.4°$, (Found: C, 59.1; H, 4.7% $C_{12}H_{12}ClFO_2$ requires C, 59.5; H5%); δ_H 2.7 (ddd, 1H, $^2J_{HH}$ 13, $^3J_{HH}$ 7.5, $^4J_{HF}$ 5, CH_2CCl=), 2.9 (ddd, 1H, $^2J_{HH}$ 13, $^3J_{HH}$ 10, $^4J_{HF}$ 4.5, CH_2CCl=), 3.55 (ddd, 1H, $^2J_{HH}$ 10.5, $^4J_{HF}$ 1.5, $^3J_{HH}$ 4, CH_2CHO), 3.65 (ddd, 1H, $^2J_{HH}$ 10.5, $^4J_{HH}$ 1, $^3J_{HH}$ 6.5, CH_2CHO), 4.8 (m, 1H, CH_2C*H*O), 7.3−7.4 (m, 5H, Ar); δ_F −114 (s, 1F, CCl = C*F*); δ_C 34 (s, *C*H_2CCl), 71 (s, *C*H_2CHO), 74 (s, Ph*C*H_2), 121 (d, $^2J_{CF}$ 26, *C*Cl = CF), 128 (Ar), 128 (Ar), 129 (Ar), 138 (Ar) 155 (d, $^1J_{CF}$ 272.5 *C*FO).

*3.1.15. Preparation of 1(R),2(R),3(R)-5-(benzyloxymethyl)-2,3-difluorotetrahydrofuran (**17**)*

The dihydrofuran (**15**) (0.8 g, 0.35 mmol) in ethyl acetate (25 cm^3) was hydrogenated over 10% Pd on C (0.2 g) at room temperature for 24 h. After filtration through a Celite pad the solvent was evaporated to leave an oil which was purified by column chromatography (silica, hexane/ethyl acetate 4:1) to yield 1(*R*),2(*R*),3(*R*)-5-benzyloxymethyl-2,3-difluoro-4,5-dihydrofuran (**17**) (nc) (0.65 g) as an oil; (Found: C, 64.9; H, 6.3% $C_{12}H_{14}F_2O_2$ requires C, 65.2; H, 6.2%); MS *m/z* 228 [M^+], 218 [M–HF^+] 107 [PhCH_2O+]; δ_H 2.5 (m, 1H, CH_2CHF), 2.8 (m, 1H, CH_2CHF), 4.2 (dd, 1H, $^2J_{HH}$ 10.5, $^3J_{HH}$ 4.3, CH_2), 4.3 (dd, 1H, $^2J_{HH}$ 10.5, $^3J_{HH}$ 3.0, CH_2), 4.6 (m, PhCH_2), 4.9 (m, 1H, CH_2C*H*O), 5.3 (d of m, 1H, $^2J_{HF}$ 53.2, CH_2C*H*F), 5.75, (d of m, 1H, $^2J_{HF}$ 52, CHFC*H*FO), 6.9–7.3 (m 5H, Ar); δ_F −137 (m, 1F CHFCH*F*O), −193 (m 1F, CH_2CH*F*); δ_C 31 (d, $^2J_{CF}$ 20.9, *C*H_2CHF), 68 (*C*H_2CHO), 74 (Ph*C*H_2), 79 (CH_2*C*HO), 92 (dd, $^1J_{CF}$ 190.5, $^2J_{CF}$ 47.2, *C*HFCHF), 115 (Ar), 122 (Ar), 129 (dd, $^1J_{CF}$ 246, $^2J_{CF}$ 26.6,CHF*C*HF), 132 (Ar).

References

[1] M. Okabe, R.-C. Sun, G.B. Zenchoff, J. Org. Chem. 56 (1991) 4392.
[2] T.B. Patrick, M.V. Lansham, C. Yang, J.K. Walker, C. Hutchenson, J. Org. Chem. 59 (1994) 1210.
[3] T.B. Patrick, Wei Yei, J. Fluorine Chem. 90 (1998) 53.
[4] P. Tarrant, P. Johncock, J. Savory, J. Org. Chem. 28 (1963) 839.

[5] I.L. Knunyants, R.N. Sterlin, R.D. Yatsenko, L.N. Pinkina, Izv. Akad. Nauk. SSSR Otd. Khim. Nauk. (1958) 1345.
[6] D. Seyferth, T. Wada, G. Raab, Tetrahedron Lett. 22 (1960) 20.
[7] J.F. Normant, J Organomet. Chem. 400 (1990) 19.
[8] J. Gillet, R. Sauvetre, J.F. Normant, Synthesis (1986) 355.
[9] J. Burdon, P.L. Coe, I.B. Haslock, R.L. Powell, J. Chem. Soc. Chem. Commun. (1996) 49.
[10] J. Burdon, P.L. Coe, I.B. Haslockand, R.L. Powell, J. Fluorine Chem. 85 (1997) 151.
[11] G.B. Payne, J. Org. Chem. 27 (1962) 3819.
[12] A. Alexakis, D. Jachiet, J.F. Normant, Tetrahedron 42 (1986) 5607.
[13] B.H. Lipshutz, J.C. Barton, J. Am. Chem. Soc. 114 (1992) 1084.
[14] S.B. Bedford, G. Fenton, D.W. Knight, D. Shaw, Tetrahedron Lett. 33 (1992) 6505.
[15] J.E. Baldwin, in: Ciba Foundation Symposium, Vol. 53, Elsevier, New York, 1978, p. 85ff.
[16] P.L. Coe, R.R. Talekar, R.T. Walker, J. Fluorine Chem. 69 (1994) 19.
[17] V.A. Petrov, V.V. Bardin, in: R.D.Chambers (Ed.), Topics in Current Chemistry, vol. 192, Springer, Berlin, 1997, pp. 39–97.
[18] Y. Ichikawa, M. Isobe, D.L. Bai, T. Goto, Tetrahedron 43 (1987) 4737.