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Reaction of Alkyl and Aryl Grignard Reagents with Trifluoroacetyldihydropyrans and Other Cyclic β-Alkoxy-α,β-unsaturated Trifluoromethylketones

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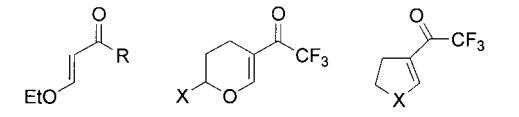
Abstract—Alkyl and aryl Grignard reagents react with cyclic β-alkoxy-α,β-unsaturated trifluoromethylketones by 1,4-addition to give as the major products, for example, *cis*-2,3-disubstituted tetrahydropyrans. In most examples ring opening leads to stereoselective formation of rearranged hemiketals as minor products. Under other conditions with 2,2,2-trifluoro-1-(2-ethoxy-3,4-dihydro-2*H*-5-pyranyl)-1-ethanone stereoselective ring opening leads to acyclic aldehydes, as minor products and, by the major pathway, to a series of diols by addition of further equivalents of the Grignard reagent. In the absence of further Grignard reagent at higher temperatures internal hydride transfer can afford acyclic esters.

Introduction

The elaboration of simple readily available fluorinated heterocyclic building blocks has been inspired by the growing importance[1] of fluorinated heterocycles having useful biological activity. Trifluoromethylketones have become targets of particular synthetic concern, because of this activity. Recently the structure activity relationships have been probed[2] for a wide series of trifluoromethylketone inhibitors of fatty acid amide hydrolase (FAAH). Heteroaromatic trifluoromethylketones show strong inhibitory activity[3] against *Helicobacter pylori*, known to be involved in the pathogenesis of peptic ulceration and gastric carcinogenesis. Trifluoromethylketones inhibit the action of a number of esterases, notably juvenile hormone esterases,[4] serine esterases[5] and other carboxylesterases[6] and chymotrypsin,[7] and can inhibit collagen induced platelet activation.[8]

Using acyclic β-amino-α,β-unsaturated trifluoromethylketones and β-alkoxy-α,β-unsaturated trifluoromethylketones, for example the ketone (**1**), as building blocks, we have recently reported the synthesis of acyclic β-aryl-α,β-unsaturated trifluoromethylketones[9] and alicyclic ketones.[10] The application of these acyclic β-alkoxy-α,β-unsaturated trifluoromethyl ketones in synthesis has been reviewed.[11] In general the use of these ketones as synthons relies upon their electrophilic reactivity with nucleophiles.

Recently the reaction of cyclic β-alkoxy-α,β-unsaturated trifluoromethylketones and β-amino-α,β-unsaturated trifluoromethyl ketones, for example the ketones (**2**) and (**3**), and related ketones, with nucleophiles to afford new heterocyclic systems has been described.[12,13] In these examples there is an addition elimination reaction resulting in the cleavage of the initial heterocycle. In the case of reaction of the ketone (**1**) with Grignard reagents, there is a preference for 1,4-addition, followed by elimination. Whilst the cyclic ketone (**2**) might, by analogy, be expected to react with Grignard reagents by 1,4-addition, there is little satisfactory precedent to establish that 1,4-addition will be observed with fluorinated ketones and there are many examples[14,15] of the differing behaviour of non-fluorinated acyclic and cyclic ketones in the competition between 1,2- and 1,4-addition with Grignard and other organometallic reagents. Aside from this issue of regioselectivity further questions relate to the possibility of ring opening following 1,4-addition and a later ring closure to give hemiketals. In order to resolve these uncertainties we describe in this paper the addition of 11 Grignard reagents to the ketone (**2**), note similar additions to the ketone (**4**), discuss the different course of additions to 2,2,2-trifluoro-1-(2-methoxy-3,4-dihydro-2*H*-5-pyranyl)-1-ethanone (**5**) and 2,2,2-trifluoro-



(**1**) R = CF_3 (**2**) X = H (**3**) X = NCO_2Et
(**5**) X = OMe (**4**) X = O
(**6**) X = OEt

Keywords: additions; A-strain; Grignard reagents; hydride transfer, tetrahydropyrans; trifluoromethylketones.
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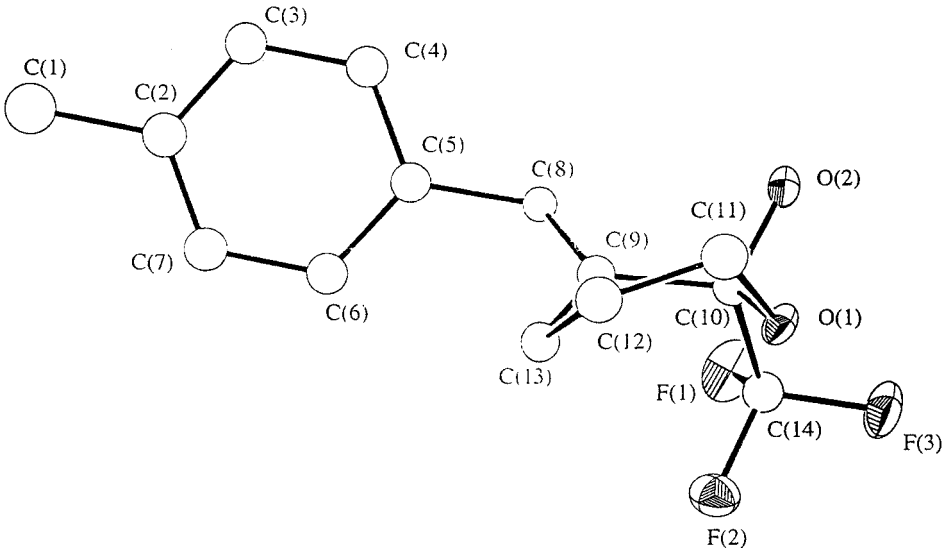
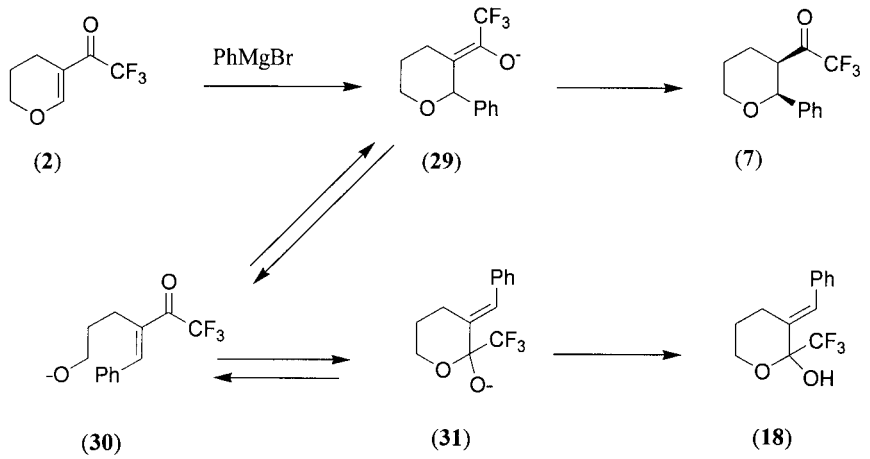


Figure 1.

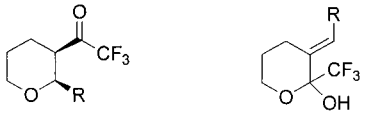


Scheme 1.

1-(2-ethoxy-3,4-dihydro-2*H*-5-pyranyl)-1-ethanone (**6**) and amplify these results with a study of analogous alkyl lithium additions.

Results and Discussion

Reaction of phenyl magnesium bromide (2 equiv.) with the ketone (**2**) in ether, first at room temperature and then under reflux, afforded two products, the saturated ketone (**7**) by 1,4-addition, and the alcohol (**18**) by ring opening and subsequent cyclisation at the ketone centre. Reaction in tetrahydrofuran at an ambient temperature, or in ether at a low temperature, gave the same two products. Under all conditions the ketone (**7**) was the major product and the alcohol (**18**) was the minor product. Under the optimum conditions the ketone (**7**) was obtained in 79% yield with formation of a further 9% of the alcohol (**18**). The general behaviour of aryl Grignard reagents was established by reaction of a further five reagents giving the results reported in the Table. These five additions gave the ketones (**8**–**12**) as the major products and the alcohols (**19**–**23**) were, if observed, the minor products. In all these additions, from the NMR spectra of crude reaction mixtures it was only possible to observe minor amounts (<5%) of further products. Similarly, as discussed below, additions of five Grignard reagents derived from aliphatic halides, afforded the ketones (**13**–**17**) and, again, if observed, the alcohols (**24**–**28**) as minor products.



(**7**) R = Ph
(**8**) R = *o*-MeC_6H_4
(**9**) R = *m*-MeC_6H_4
(**10**) R = *p*-MeC_6H_4
(**11**) R = *p*-$MeOC_6H_4$
(**12**) R = 1-NaphthylCH_2
(**13**) R = *n*-Butyl
(**14**) R = *n*-Pentyl
(**15**) R = *n*-Hexyl
(**16**) R = *n*-Octyl
(**17**) R = $PhCH_2CH_2$

(**18**) R = Ph
(**19**) R = *o*-MeC_6H_4
(**20**) R = *m*-MeC_6H_4
(**21**) R = *p*-MeC_6H_4
(**22**) R = *p*-$MeOC_6H_4$
(**23**) R = 1-NaphthylCH_2
(**24**) R = *n*-Butyl
(**25**) R = *n*-Pentyl
(**26**) R = *n*-Hexyl
(**27**) R = *n*-Octyl
(**28**) R = $PhCH_2CH_2$

The alcohol (**21**) was isolated as good quality needles permitting a single crystal X-ray analysis to be achieved (see Fig. 1). The structures of the other alcohols were established by comparison of their spectra with the spectra of alcohol (**21**). It is evident that these alcohols are formed by the sequence of reactions shown in Scheme 1. Addition of the Grignard reagent, for example phenyl magnesium bromide, gives the enolate anion (**29**) capable of ring opening to afford an alkoxide (**30**), which can then cyclise by a 1,2-addition to afford via the alkoxide (**31**) the unsaturated alcohol (**18**). There are a number of factors, which might control the sequence of possible ring opening and cyclisation reactions. The initial ring opening might be slow and account for the formation of the saturated ketone (**7**) as the major product. However reaction at −65°C still gives the alcohol (**18**) as a product in a comparable yield to that obtained at a higher temperature. Hence it appears probable that ring opening still occurs at a low temperature to release the alkoxide anion (**30**). We do not isolate products of further addition to this new unsaturated ketone (**30**), in contrast to results described below, suggesting that the intermediate (**30**) has a fleeting existence. The subsequent ring closures to give the ketones and alcohols could again be controlled either by kinetic or thermodynamic factors. The analysis of the factors controlling events has been assisted, by our establishing the high stereoselectivity characterising some of the steps. The least helpful information concerns the observed *cis* structure of the saturated ketones, for example (**7**). This stereochemistry is doubtless established by protonation of the enolate anion (**29**) on work up and therefore fails to clarify the prior events. The assigned stereochemistry follows from observation of the coupling constant (J=3.0 Hz) in the signal of the methine protons in ketone (**7**). The coupling is most clearly observed in the signal of the 2-proton. If the two substituents were *trans*, the two protons would have a larger coupling. In *trans*-2,3-substituted tetrahydropyrans values in the range 9.5–12 Hz have been observed.[16,17] In tetrahydropyrans having *cis* substituents the resulting axial and equatorial protons are expected to show coupling in the range 1.5–3 Hz.[16,17] In the ketone (**7**) it is probable that a chair conformation with the phenyl group equatorial and the acyl group axial is adopted; further evidence of the conformation of related compounds is provided in the accompanying paper.[18] In the quenching of the enolate anion (**29**) the kinetic product is expected to arise by a protonation on the face remote from the phenyl group leading to the observed *cis* product (**7**). In the accompanying paper,[18] we describe the addition of *p*-methoxybenzyl magnesium bromide to the ketone (**2**). Benzyl Grignard reagents add mainly by 1,2-addition. However by isolating a crystalline 1,4-adduct from this reaction, we have obtained by X-ray analysis the structural details, which establish a *cis* stereochemistry, and the adoption of a chair conformation having the benzyl group in a pseudo-equatorial position and the trifluoroacetyl group in a pseudo-axial position, confirming the above analysis. As a *trans* 1,4-adduct was also obtained as a minor product in the reaction of *p*-methoxybenzyl magnesium bromide with ketone (**2**), the spectroscopic comparison of these two 1,4-adducts with the *cis* adducts described in this paper, unequivocally confirms the above stereochemical assignments. Zimmerman[19] originally established in a related case that the quenching of a Grignard addition to 1-benzoylcyclohexene afforded a *cis*-product. Our results contrast with a recent study,[20] where reaction of phenyl magnesium bromide with ketone (**2**) is reported to give an acyclic alcohol by protonation of the anion (**30**).

A confirmation that the equilibrium between the enolate anion (**29**) and the open alkoxide (**30**) lies in favour of the enolate anion (**29**) was obtained by quenching the reaction with phenyl magnesium bromide with acetyl chloride. The enol acetate (**32**) was isolated in 90% yield with isolation of a low percentage of the alcohol (**18**). The structure of the ester (**32**) was established by a single crystal X-ray analysis (see Fig. 2). The absence of the acetate of a primary alcohol

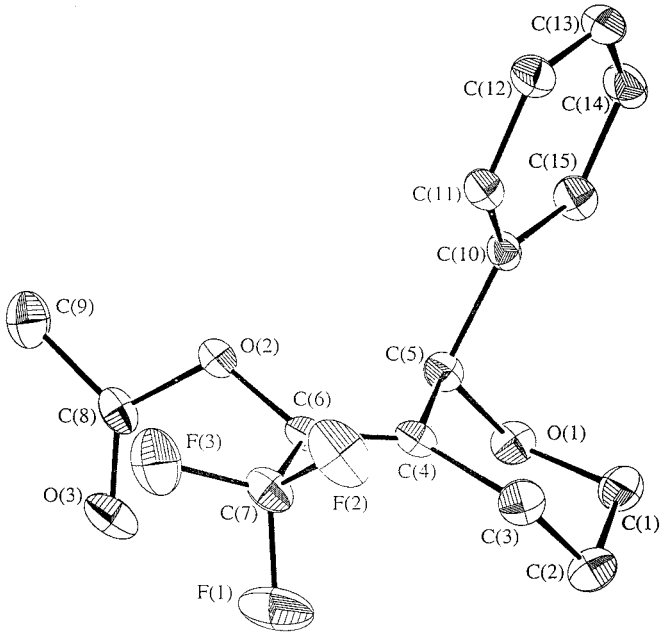


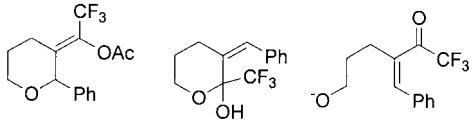
Figure 2.

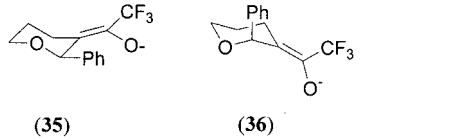
Table 1. Products from additions to ketone (**2**)

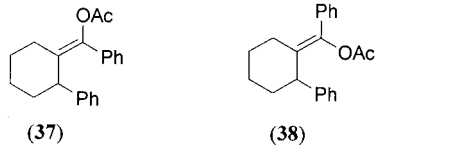
Entry	Organometallic reagent	Ketone product (%)	Alcohol product (%)
1	PhMgBr	(**7**) 79	(**18**) 9
2	PhMgBr[a]	(**7**) 36	(**18**) 8
3	PhMgBr[b]	(**7**) 46	(**18**) 8
4	*o*-$CH_3C_6H_4MgBr$	(**8**) 52	(**19**) 22
5	*m*-$CH_3C_6H_4MgBr$	(**9**) 72	(**20**) 15
6	*p*-$CH_3C_6H_4MgBr$	(**10**) 61	(**21**) 17
7	*p*-$CH_3OC_6H_4MgBr$	(**11**) 50	(**22**) 12
8	1-NaphthylCH_2MgCl	(**12**) 54	(**23**) 0
9	*n*-BuMgBr[c]	(**13**) 55	(**24**) 6
10	*n*-PentMgBr	(**14**) 58	(**25**) 5
11	*n*-HexMgBr[d]	(**15**) 50	(**26**) 3
12	*n*-OctMgBr	(**16**) 67	(**27**) 3
13	$PhCH_2CH_2MgBr$	(**17**) 52	(**28**) 0
14	BuLi[e]	(**13**) 42	(**24**) 0
15	PhMgBr[f]	(**44**) 62	(**45**) 5

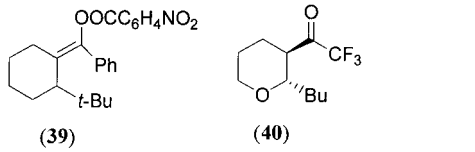
[a] Reaction in tetrahydrofuran.
[b] Reaction at −65°C.
[c] Reaction afforded three further minor products (**40**) (5%); (**41**) (6%); (**42**) (19%).
[d] Reaction afforded a further minor product (**43**) (2%).
[e] Reaction afforded three further products (**40**) (4%); (**41**) (26%); (**42**) (13%).
[f] Reaction with ketone (**4**).

derived from the alkoxide (**30**) establishes that this alkoxide (**30**) can only be a relatively unstable intermediate by comparison with the enolate anion (**29**) and the alkoxide (**31**) of the rearranged alcohol (**18**). Usefully the quenching with acetyl chloride also proves that ring opening from the enolate anion (**29**) gives a single geometrical isomer. There is no evidence of the product (**33**) derived from the alkoxide (**34**). A firm indicator of the stereoselectivity of the reaction pathway is established by the determination of the structure of the alcohol (**21**) by single crystal X-ray diffraction. There is no evidence of a geometrical isomer of (**21**), which might have been formed by a ring opening to give the isomeric alkoxide (**34**), rather than to the alkoxide (**30**), as shown in Scheme 1. With the other Grignard reagents a single rearranged alcohol is also observed and the NMR spectra suggest that in these other alcohols (**19**–**22**) the same olefin stereochemistry is found. Hence there is a significant stereoselectivity occurring as shown in Scheme 1.The origin of this stereoselectivity is clarified by the X-ray structure of the enol acetate (**32**).The elimination to afford the open alkoxides (**34**) and (**30**) might take place from chair conformer (**35**) or chair conformer (**36**), in which the stereochemistry of the alkene product is assigned based on that observed in the enol acetate (**32**). In transition states with optimum overlap of the breaking σ–CO-bond with the π system of the enolate anion, an aryl group could adopt a pseudo-equatorial position as in conformer (**35**), or a pseudo-axial position as in conformer (**36**). In the former case there is a substantial interaction between the aryl group and the oxyanion. This interaction is relieved in the latter case. Elimination from conformer (**35**) would give the enolate (**34**) and elimination from conformer (**36**) would give the enolate (**30**). Clearly isolation of the enol acetate (**32**) and the alcohols (**18**–**22**) proves that elimination occurs from conformer (**36**). The structure of the enol acetate (**32**), as established by the X-ray analysis, features the phenyl group in a pseudo-axial position. Hence the preferential elimination from conformer (**36**) is explained. The adverse 1,3-interaction inhibiting the phenyl group adopting a pseudo-equatorial position in the acetate (**32**) and in conformer (**35**) is an example of allylic $A^{1,3}$-strain.[21] Related enol esters have previously been isolated.[22–25] The structure of the enol acetates[25] (**37**) and (**38**) and the *p*-nitrobenzoate[24] (**39**) have been determined by X-ray analysis showing the 2-substituent to adopt a pseudo-axial position as observed in the enol acetate (**32**) and NMR data[26] establishes the solution conformations are as found in the solid state. An isopropyl group[27] has roughly the same size as a trifluoromethyl group and hence a substantial trifluoromethyl-phenyl 1,3-interaction is to be expected accounting for formation of ester (**32**). The stereoselectivity observed in









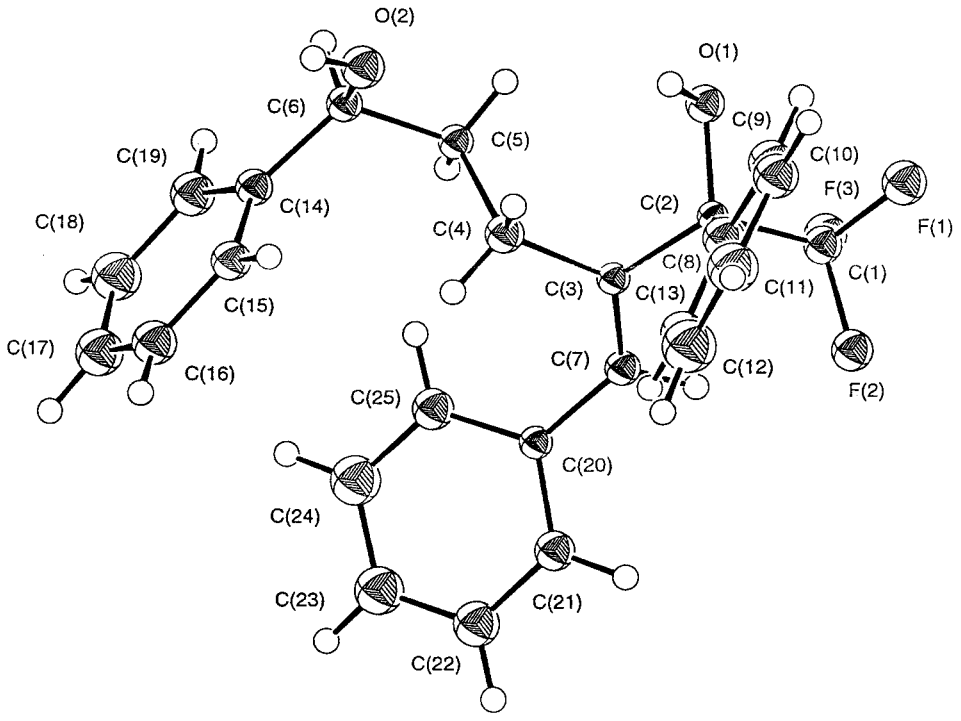


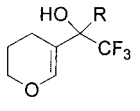
Figure 3.

the ring opening is explained by $A^{1,3}$-strain the control factor in many addition reactions.[21,28] However before our preliminary communication,[29] $A^{1,3}$-strain has not been established as the critical control element in elimination reactions. The stereoselectivity observed in formation of anion (**30**) rather than the isomer (**34**) originates from the requirements of such an elimination reaction. $A^{1,3}$-strain is the key factor determining the geometry of the double bond in the alcohols (**18**–**22**).

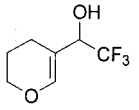
A further consequence of $A^{1,3}$-strain can be seen from the X-ray analysis of the alcohol (**21**). As a result of geminal substitution adjacent to the alkene, if the six-membered ring adopts a chair conformation, then either the trifluoromethyl or the hydroxyl group will be placed in a pseudo-equatorial position and suffer a large amount of steric hindrance through $A^{1,3}$-strain. Fig. 1 shows that the alcohol (**21**) adopts a boat conformation, which we would expect to be also the preferred conformation of the other alcohols (**18**–**28**).

In the case of butyl magnesium bromide (entry in Table 1) exhaustive chromatography permitted minor products to be isolated and characterised. In addition to the major product, the *cis*-ketone (**13**), a second saturated ketone (**40**), observed in low yield, was assigned the *trans* stereochemistry, based[16,17] on coupling constant data. The observation of alcohols (**41**) and (**42**), respectively products of 1,2-addition and reduction, has good precedent[30] in reactions of analogous acyclic β-alkoxy-α,β-unsaturated trifluoromethylketones. In the case of the addition of *n*-hexyl magnesium bromide, in addition to the anticipated products (**15**) and (**26**), the product of 1,2-addition (**43**) was observed as a minor product. The reaction of the ketone (**2**) with butyl lithium led to similar products (see Table 1) but with significant differences in yields. The major product was again the ketone (**13**), the product of 1,4-addition. In keeping with the greater ability of butyl lithium to afford products of 1,2-addition the alcohol (**41**) was isolated in 26% yield. The second product of 1,4-addition, the ketone (**40**) and the reduction product (**42**) were also isolated. The results of additions to the readily available β-alkoxy-α,β-unsaturated trifluoromethylketone (**4**) are also shown in Table 1. In an analogous manner the ketone (**4**) gives with phenyl magnesium bromide the ketone (**44**), by 1,4-addition as the major product, which by analogy with the other results in this paper is tentatively assigned as the *cis* product, and the alcohol (**45**) as the minor product.

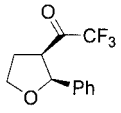
Having established that ring opening is the minor pathway from ketones (**2**) and (**4**) it was interesting to study Grignard additions to ketones (**5**) and (**6**). It was found that when the ketone (**6**) was added to an excess (4 equiv.) of phenyl magnesium bromide in dry ether, two products (**46**) and (**47**) were obtained, following chromatography, in 57 and 35% yields respectively. The molecular weight (412) of the



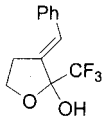
(**41**) R = *n*Bu
(**43**) R = *n*Hex



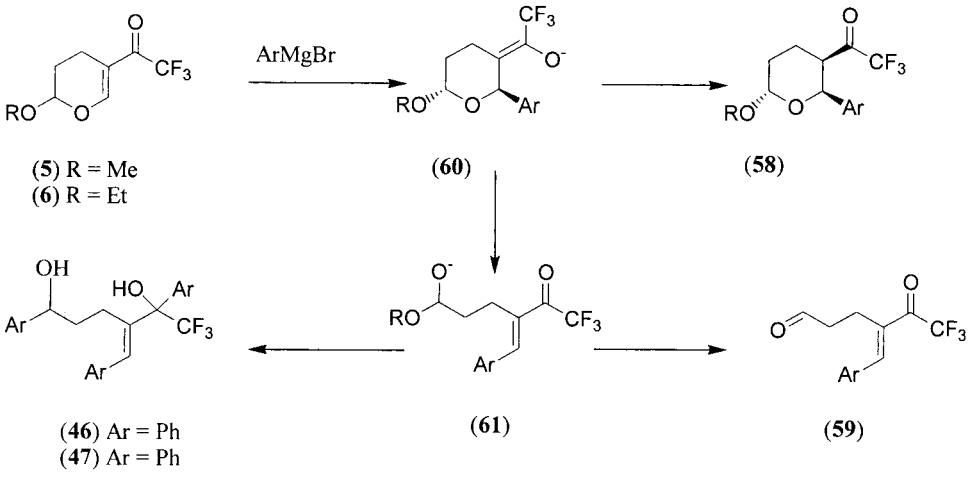
(**42**)



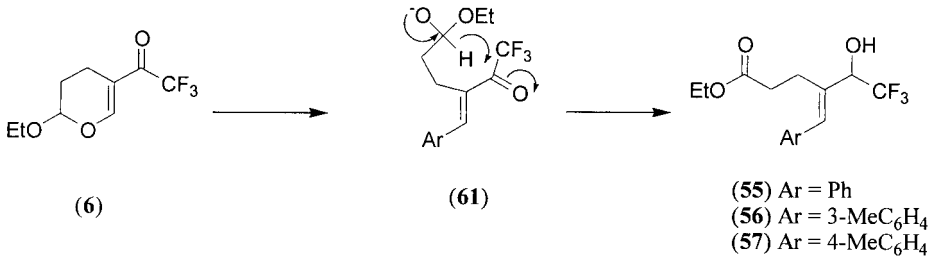
(**44**)



(**45**)



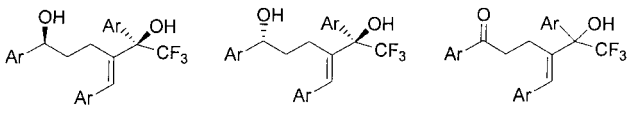
Scheme 2.



Scheme 3.

isomeric products suggested the reaction of the ketone (**6**) with 3 equiv. of phenyl magnesium bromide. The minor isomer (**47**) was crystalline and a single crystal X-ray analysis established the structure of this diol (**47**) (see Fig. 3). The second isomer (**46**) could readily be confirmed to be a diastereoisomer of the diol (**47**). Oxidation using Jones reagent of either diol (**46**) or (**47**) afforded in high yield the ketone (**48**). In a similar manner, the ketone (**5**) afforded the same diols (**46**) and (**47**) in comparable yields. The oxidation of the diols (**46**) and (**47**) to give the same ketone (**48**) proves that the diols (**46**) and (**47**) have the same alkene stereochemistry. Hence the diols (**46**) and (**47**) have an epimeric relationship. The generality of the reaction was established by analogous reaction of the ketone (**6**) with *m*-tolyl magnesium bromide and *p*-tolyl magnesium bromide giving diols (**49**) and (**50**), and (**51**) and (**52**) respectively and then by oxidation hydroxyketones (**53**) and (**54**).

The sequence of events leading to the diols (**46**) and (**47**) and the analogues described above, which sharply contrast with the minor formation of ring opened products from ketone (**2**), was probed by a further series of experiments. When reactions were carried out using only 2 equiv. of Grignard reagent, a different outcome was observed. Under these conditions the diols described above were isolated as minor products (<20%). Reaction of the ketone (**6**) with the three Grignard reagents, phenyl-, *m*-tolyl-and *p*-tolylmagnesium bromide (2 equiv.) afforded respectively the esters (**55**–**57**) in 21–30% yields. The esters are obtained as a result of an initial 1,4-addition, followed by ring opening, and, as a result of the lower concentration of Grignard reagent, a hydride transfer becomes possible leading to the esters (**55**–**57**). At a lower temperature (−35°C) the addition afforded different products. Reaction of the ketone (**5**) with *p*-tolyl magnesium bromide gave the ketone (**58**; R=Me, Ar=*p*-MeC_6H_4)) in 76% yield. A minor product, the aldehyde (**59**; Ar=*p*-MeC_6H_4) was isolated in 4% yield and reaction at 0°C permitted the aldehyde (**59**; Ar=*p*-MeC_6H_4) to be isolated in slightly higher yield (14%).



(**46**) Ar = Ph
(**49**) Ar = 3-MeC_6H_4
(**51**) Ar = 4-MeC_6H_4

(**47**) Ar = Ph
(**50**) Ar = 3-MeC_6H_4
(**52**) Ar = 4-MeC_6H_4

(**48**) Ar = Ph
(**53**) Ar = 3-MeC_6H_4
(**54**) Ar = 4-MeC_6H_4

The likely reaction pathway of the ketones (**5**) and (**6**) with aryl magnesium bromides is shown in Scheme 2. The first attack of the aryl magnesium bromide is by 1,4-addition to afford the enolate (**60**). Of the two possible reaction pathways that of the aryl group entering *trans* to the alkoxy substituent is to be expected and is confirmed below. At a low temperature the enolate anion (**60**) on work up affords the saturated ketone (**58**) in 76% yield, following a similar pathway to that of ketone (**2**) shown in Scheme 1. In confirming the *cis*-relationship of the two vicinal substituents and their *trans* relationship to the alkoxy substituent in the ketone (**58**), coupling constant data from closely related tetrahydropyrans[16] strongly supports the stereochemical assignments. The *cis* stereochemistry

derives from a kinetic protonation from the less hindered face. The same kinetic protonation accounts[19,21,22] for formation of *cis*-products in the quenching of enolate anions arising from 1,4-additions to acylcyclohexenes.

At a higher temperature the enolate anion (**60**) undergoes ring opening to give the alkoxide (**61**). From this alkoxide (**61**), the anion of a hemiacetal, we have observed three reaction pathways. At lower temperatures a minor pathway, in reactions based on less equivalents of a Grignard reagent, leads by collapse of the hemiacetal anion (**61**) to give the aldehyde (**59**) (see Scheme 2), recognised in part, by the proton signal at δ 9.70 ppm. Under all the reaction conditions formation of the aldehyde is a minor pathway. At the higher temperatures in the absence of a large excess of a Grignard reagent, hydride transfer occurs to give the esters (**55**–**57**) (see Scheme 3). However the third pathway from the alkoxide (**61**) affords the diols (**46**) and (**47**) under favourable conditions in the best yields (>90%) (Scheme 2).

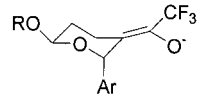
A number of interesting points of comparison may be made between these reactions and, as reported earlier in this paper, those observed with the ketone (**2**) lacking the alkoxy substituent. The first step of 1,4-addition is observed in all cases. Ring opening is not the dominant observed process in the unsubstituted series following 1,4-addition to the ketone (**2**), but the alkoxy substituent will assist the ring opening of intermediates derived by 1,4-addition to the ketones (**5**) and (**6**). Under comparable reaction conditions the diols (**46**) and (**47**) formed by ring opening account for over 90% of the products from addition of phenyl magnesium bromide to ketones (**5**) and (**6**) (Scheme 2), whereas the same reagent via ring opening affords the alcohol (**18**) from ketone (**2**) only by a minor pathway (9%). Once ring opening has occurred there is a divergence of behaviour in the reaction pathways of the unsubstituted and substituted cases. Significantly we observe the same olefin stereochemistry in the alkene moiety in the diols (**46** and **47**), the aldehydes (**59**) and the esters (**55**–**57**). The stereochemistry is firmly established from the X-ray analysis of the diol (**47**) and of the alcohol (**21**) derived via a 1,4-addition to the ketone (**2**) with further ring opening (see Schemes 1–3).

As above, ring opening can occur from conformers (**62**) and (**63**). Preference for elimination from conformer (**62**), to afford anion (**61**), rather than from conformer (**63**) is a further example of control by $A^{1,3}$-strain. It is particularly noteworthy that in the series having the alkoxy substituent, the necessary conformation places this alkoxy substituent in an equatorial position, counter to the influence of an anomeric effect.

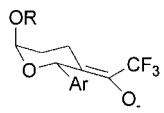
We,[9,10] and others,[11] have shown that whilst addition of phenyl magnesium bromide to β-alkoxy-α,β-unsaturated fluorinated ketones occurs by a 1,4-pathway, additions to β-aryl-α,β-unsaturated fluorinated ketones occur by preferential 1,2-addition. The isolation of the esters (**55**–**57**) is an indicator of the relatively long life of the hemiacetal anion (**61**). A rapid collapse to the aldehyde would preclude formation of the esters (**55**–**57**). As shown in Scheme 3 an internal hydride transfer accounts for the formation of the esters. Either in the presence of excess Grignard reagent, or at low temperatures this pathway is not observed. The unusual combination of a hydride donating moiety, the hemiacetal anion and a trifluoroacetyl group as a powerful hydride acceptor, permits reaction by this new pathway. Hydride transfers from the salts of hemiacetals are the basis of the Tishchenko reaction,[31] which has recently been used in a number of useful synthetic procedures.[32] In such intramolecular hydride transfers involving oxidation of hemiacetal salts non-fluorinated carbonyl compounds, either aldehydes or ketones, have been the hydride acceptors. In view of the greater hydride accepting ability of a trifluoromethyl ketone, particularly under the conditions[33] of Grignard reactions, the formation of esters (**55**–**57**) is unsurprising.

The pathways were further probed by a study of the reaction of the ketone (**5**) with *n*-butyl lithium. Butyl lithium (4 equiv.) gave a diastereoisomeric mixture of diols (**64**) in 15% yield. However, the minor diols (**64**) were accompanied by other products. The major pathway was by 1,2-addition to give a mixture of the diastereoisomeric alcohols (**65**) in 51% yield. Further minor products were the diastereoisomeric mixtures of diols (**66**) obtained by addition and the alcohols (**67**) obtained by reduction. Reaction of ketone (**5**) with *n*-butyl magnesium bromide similarly afforded a complex mixture with formation of the reduction product (**67**) in 28% yield. These results with alkyl organometallics reveal two pathways, which are of greater importance relative to results obtained with the aryl Grignard reagents. Reduction and 1,2-addition are more significant, as observed[11] in related additions. Formation of esters analogous to esters (**55**–**57**) was not observed in these additions.

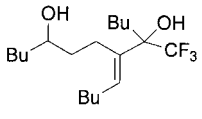
The results presented in this paper clarify the questions raised in the introduction. Addition to trifluoroacetyldihydropyrans by aryl and alkyl Grignard reagents derived from saturated alkyl halides is overwhelmingly by 1,4-attack. With aryl Grignard reagents the 1,2-addition pathway is unimportant. In this respect, the behaviour of the cyclic ketones (**2**) (**4**), (**5**), and (**6**) is comparable to that of analogous acyclic β-alkoxy-α,β-unsaturated trifluoromethyl ketones.[9] However in the following paper,[18] we show that reaction with benzyl and allyl Grignard reagents



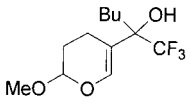
(**62**)



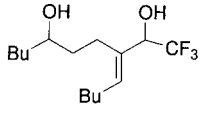
(**63**)



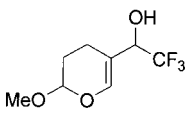
(**64**)



(**65**)



(**66**)



(**67**)

follows a very different course; products of 1,2-addition are observed with yields greater than 90%. Following the 1,4-addition a variety of pathways have been exposed. The quenching of intermediates from the ketones (**2**) and (**4**) by the major pathway leads to *cis* products, a pathway observed at lower temperatures with ketones (**5**) and (**6**). Ring opening is a minor pathway from ketones (**2**) and (**4**), but the major pathway from ketones (**5**) and (**6**). Single crystal X-ray diffraction results have established the stereochemistry of the *cis*-1,4-adducts and have exposed that all the diverse products of ring opening have a stereochemistry, which has been controlled by $A^{1,3}$-strain.

Our comprehensive studies not only clarify the course of organometallic additions to cyclic β-alkoxy-α,β-unsaturated trifluoromethyl ketones, but also establish new routes to heterocyclic trifluoromethylketones, masked trifluoromethylketones and by stereocontrolled ring opening, fluorinated diols.

Experimental

General experimental procedures have been described[10] elsewhere.

General procedure for addition of Grignard reagents to 1-(3,4-dihydro-2*H*-5-pyranyl)-2,2,2-trifluoro-1-ethanone (2)

To a 100 ml round bottomed flask (with an addition funnel, magnetic stirrer bar and reflux condenser carrying a calcium chloride tube), magnesium turnings (0.27 g, 11.1 mmol), dry ether (2.0 ml) and a crystal of iodine were added. A few drops of alkyl (aryl) bromide (11.1 mmol) in dry ether (2.0 ml) were added dropwise, and the solution was stirred until the formation of the Grignard reagent. The remainder of the alkyl (aryl) bromide was diluted with dry ether (4.0 ml) and the solution was added at such a rate to maintain gentle reflux. After the complete addition of the alkyl (aryl) bromide, the reaction mixture was heated under reflux with stirring on a warm water bath for 10 min. The reaction mixture was cooled and a solution of the ketone (1.00 g, 5.55 mmol) in dry ether (2.0 ml) was added dropwise. The reaction mixture was stirred for 30 min., followed by heating under reflux for another 30 min., allowed to cool to room temperature and 2 M hydrochloric acid was added until pH2. The two phases were separated and the aqueous phase extracted with ether (3×15 ml) and the combined organic phases were collected and washed with water, dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting oil was purified by flash column chromatography [silica gel, petroleum ether: ethyl acetate (85:15)] to give two fractions, first the ketones and then the alcohols.

***cis*-2,2,2-Trifluoro-1-(2-phenyltetrahydro-2*H*-3-pyranyl)-1-ethanone (7).** Reaction of the ketone (**2**) with phenyl magnesium bromide afforded the alcohol (**18**) as a minor product and the title ketone (**7**), which was isolated as a pale yellow oil (1.13 g, 79%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.38–7.20 (5H, complex, Ph), 4.68 (1H, d, J=3.0 Hz, H-2), 4.35 (1H, m, H-6), 3.68 (1H, m, H-6), 3.49 (1H, m, H-3), 2.22–1.98 (3H, complex, H-4, H-5), 1.56 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.0 (q, J_{C-F}=33.9 Hz, C=O), 139.6 (C′-1), 128.5, 127.9 and 125.5 (5C, Ph), 114.9 (q, J_{C-F}=293.9 Hz, *C*F_3), 79.2 (C-2), 69.0 (C-6), 45.4 (C-3), 26.1 (C-4), 20.7 (C-5); υ_{max} (film, cm^{-1}) 1755 (C=O), 1055 (CO); LRMS (Scan AP$^+$): m/z=258 (M$^+$, 7%), 257 (M$^+$−1, 43), 189 (M$^+$−CF_3, 100); HRMS (EI$^+$): M$^+$ found 258.0887, $C_{13}H_{13}F_3O_2$ requires 258.0868. **3-[(*E*)-1-Phenylmethylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (18)** was isolated as a white solid (0.13 g, 9%) and was recrystallised (petroleum ether) to give white crystals (0.07 g, 5%) mp 81–82°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.43–7.21 (5H, complex, Ph–H), 7.06 (1H, s, H-vinylic), 3.99 (2H, m, H-6), 3.20 (1H, s, OH), 2.90 (1H, ddd, J=14.7, 7.4, 5.2 Hz, H-4), 2.48 (1H, m, H-4), 1.98 (1H, m, H-5), 1.68 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=136.0 and 131.9 (C-3, C′-1), 131.6 (C-vinylic), 129.2, 128.45 and 127.6 (5C, Ph), 122.9 (q, J_{C-F}=288.2 Hz, *C*F_3), 95.8 (q, J_{C-F}=31.65 Hz, C-2), 61.8 (C-6), 24.3 (C-5), 21.9 (C-4); υ_{max} (CH_2Cl_2, cm^{-1}) 3552 (OH), 1079 (CO); LRMS (Scan AP$^+$): m/z=241(M$^+$−OH, 9%), 189 (M$^+$−CF_3, 100), 171 [(M$^+$−1)−OH−CF_3, 7]; HRMS (CI$^+$): (M$^+$+NH_4) found 276.1212, $C_{13}H_{13}F_3O_2$ requires 276.1212. The reaction of ketone (**2**) with phenyl magnesium bromide (2 equiv.) was repeated using THF as solvent but with heating under reflux for 5 h to give the ketone (**7**) (36%) and the alcohol (**18**) (8%). Reaction in ether with cooling to (−60)–(−65)°C gave the ketone (**7**) (46%) and the alcohol (**18**) (8%).

***cis*-2,2,2-Trifluoro-1-[2-(*o*-methylphenyl)tetrahydro-2*H*-3-pyranyl]-1-ethanone (8).** Reaction of the ketone (**2**) with *o*-methylphenyl magnesium bromide afforded the alcohol (**19**) as a minor product and the title ketone (**8**), which was isolated as a pale yellow oil (0.78 g, 52%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.33 (1H, m, Ar-H), 7.20–7.07 (3H, complex, Ar-H), 4.80 (1H, d, J=2.9 Hz, H-2), 4.36 (1H, dd, J=11.8, 5.0 Hz, H-6), 3.72 (1H, dt, J=11.8, 11.8, 2.2 Hz, H-6), 3.51(1H, m, H-3), 2.35 (3H, s, C*H*$_3$), 2.28–2.00 (3H, complex, H-4, H-5), 1.58 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.3 (q, J_{C-F}=33.9 Hz, C=O), 137.4 and 133.3 (C′-1, C′-2), 130.3, 127.8, 126.45 and 126.3 (4C, Ar), 114.8 (q, J_{C-F}=293.9 Hz, *C*F_3), 76.8 (C-2), 69.35 (C-6), 42.6 (C-3), 26.25 (C-4), 20.75 (C-5), 19.1 (*C*H_3); υ_{max} (film, cm^{-1}) 1755 (C=O), 1055 (CO); LRMS (Scan AP$^+$): m/z=272 (M$^+$, 11%), 271 (M$^+$−1, 30), 203 (M$^+$−CF_3, 100); HRMS (CI$^+$): (M$^+$+NH_4) found 290.1348, $C_{14}H_{15}F_3O_2$ requires 290.1368. **3-[(*E*)-1-(*o*-Methylphenyl)-methylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (19)** was isolated as a white solid (0.33 g, 22%) and was recrystallised (petroleum ether) to give white crystals (0.21 g, 14%) mp 72–73°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.22 (3H, complex, Ar-H), 7.13 (1H, m, Ar-H), 7.07 (1H, s, H-vinylic), 4.00 (2H, m, H-6), 3.12 (1H, s, O*H*), 2.64 (1H, ddd, J=14.7, 7.4, 5.2 Hz, H-4), 2.34 (1H, m, H-4), 2.28 (3H, s, C*H*$_3$), 1.97 (1H, m, H-5), 1.70 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=136.8, 135.4 and 132.2 (C-3, C′-1, C′-2), 130.8, 130.1, 128.8, 127.8 and 125.6 (C-vinylic, 4C–Ar), 123.1 (q, J_{C-F}=288.2 , CF_3), 95.7 (q, J_{C-F}=31.65 Hz, C-2), 61.9 (C-6), 24.5 (C-5), 22.0 (C-4), 19.8 (*C*H_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3552 (OH), 1602 (C=C), 1079 (CO); LRMS (Scan AP$^+$): m/z=203 (M$^+$−CF_3, 100); HRMS (EI$^+$): M$^+$ found 272.1012, $C_{14}H_{15}F_3O_2$ requires 272.1024.

***cis*-2,2,2-Trifluoro-1-[2-(*m*-methylphenyl)tetrahydro-2*H*-3-pyranyl]-1-ethanone (9).** Reaction of the ketone (**2**) with *m*-methylphenyl magnesium bromide afforded the alcohol (**20**) as a minor product and the title ketone (**9**), which was isolated as a pale yellow oil (1.10 g, 72%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.21(1H, t, J=7.4 Hz, H′-5), 7.11 (1H, s, H′-2), 7.04 (2H, m, H′-4, H′-6), 4.62 (1H, d, J=3.0 Hz, H-2), 4.34 (1H, m, H-6), 3.67 (1H, m, H-6), 3.51 (1H, m, H-3), 2.34 (3H, s, CH_3), 2.21–2.00 (3H, complex, H-4, H-5), 1.55 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.1 (q, J_{C-F}=33.9 Hz, C=O), 139.5 and 138.2 (C′-1, C′-3), 128.6, 128.35, 126.1 and 122.5 (4C, Ar), 114.9 (q, J_{C-F}=293.8 Hz, CF$_3$), 79.3 (C-2), 69.0 (C-6), 45.4 (C-3), 26.1 (C-4), 21.55 (CH$_3$), 20.8 (C-5); υ_{max} (film, cm^{-1}) 1755 (C=O), 1055 (CO); LRMS (Scan AP$^+$): m/z=272 (M$^+$, 12%), 271 (M$^+$−1, 35), 203 (M$^+$−CF$_3$, 100); HRMS (EI$^+$): M$^+$ found 272.1010, $C_{14}H_{15}F_3O_2$ requires 272.1024. **3-[(*E*)-1-(*m*-Methylphenyl)methylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (20)** was isolated as a pale yellow oil (0.22 g, 15%) and was rechromatographed [silica gel, petroleum ether: ethyl acetate (85:15)] to give the alcohol (**20**) (0.12 g, 8%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.19 (2H, m, Ar-H), 7.02 (2H, m, Ar-H), 6.98 (1H, s, H-vinylic), 3.89 (2H, m, H-6), 2.87 (1H, s, OH), 2.78 (1H, m, H-4), 2.36 (1H, m, H-4), 2.29 (3H, s, CH_3), 1.90 (1H, m, H-5), 1.62 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=138.1 and 136.2 [C-3, C′–Ar)], 131.7, 129.9, 128.4 and 126.2 [4C, Ar, (C-vinylic)], 123.15 (q, J_{C-F}=288.2 Hz, CF$_3$), 61.8 (C-6), 24.25 (C-5), 22.0 (C-4), 21.6 (CH$_3$); υ_{max} (film, cm^{-1}) 3500–3200 (OH), 1590 (C=C), 1085 (CO); LRMS (Scan AP$^+$): m/z=255 (M$^+$−OH, 7%), 203 (M$^+$−CF$_3$, 100); HRMS (EI$^+$): M$^+$ found 272.1023, $C_{14}H_{15}F_3O_2$ requires 272.1024.

***cis*-2,2,2-Trifluoro-1-[2-(*p*-methylphenyl)tetrahydro-2*H*-3-pyranyl]-1-ethanone (10).** Reaction of the ketone (**2**) with *p*-methylphenyl magnesium bromide afforded the alcohol (**21**) as a minor product and the title ketone (**10**), which was isolated as a pale yellow oil (0.92 g, 61%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.18 (2H, d, J=8.1 Hz, Ar-H), 7.11 (2H, d, J=8.1 Hz, Ar-H), 4.62 (1H, d, J=3.0 Hz, H-2), 4.30 (1H, m, H-6), 3.66 (1H, m, H-6), 3.49 (1H, m, H-3), 2.32 (3H, s, CH_3), 2.18–1.92 (3H, complex, H-4, H-5), 1.52 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.45 (q, J_{C-F}=33.9 Hz, C=O), 137.5 and 136.65 (C′-1, C′-4), 129.15 and 125.4 (4C, Ar), 114.9 (q, J_{C-F}=293.9 Hz, CF$_3$), 79.15 (C-2), 68.95 (C-6), 45.5 (C-3), 26.1 (C-4), 21.25 (CH$_3$), 20.8 (C-5); υ_{max} (film, cm^{-1}) 1748 (C=O), 1054 (CO); LRMS (Scan AP$^+$): m/z=272 (M$^+$, 5%), 271 (M$^+$−1, 22), 203 (M$^+$−CF$_3$, 100); HRMS (EI$^+$): M$^+$ found 272.1017, $C_{14}H_{15}F_3O_2$ requires 272.1024. **3-[(*E*)-1-(*p*-Methylphenyl)methylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (21)** was isolated as a white solid (0.26 g, 17%) and was recrystallised (petroleum ether) to give colourless crystals (0.18 g, 12%) mp 88–89°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.19 (4H, m, Ar-H), 7.02 (1H, s, H-vinylic), 3.96 (2H, m, H-6), 3.05 (1H, s, OH), 2.90 (1H, ddd, J=14.7, 7.4, 5.2 Hz, H-4), 2.45 (1H, m, H-4), 2.38 (3H, s, CH_3), 1.99 (1H, m, H-5), 1.69 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=137.5, 133.1 and 131.1 (C-3, C′-1, C′-4), 131.5 (C-vinylic), 129.1 (C, Ar), 122.55 (q, J_{C-F}=288.2 Hz, CF$_3$), 95.6 (q, J_{C-F}=31.65 Hz, C-2), 61.8 (C-6), 24.2 (C-5), 22.0 (C-4), 21.4 (CH$_3$); υ_{max} (CH_2Cl_2, cm^{-1}) 3545 (OH), 1091(CO); LRMS (Scan AP$^+$): m/z=255 (M$^+$−OH, 41%), 203 (M$^+$−CF$_3$, 100); HRMS (EI$^+$): M$^+$ found 272.1023, $C_{14}H_{15}F_3O_2$ requires 272.1024. The structure of alcohol (**21**) has been established by X-ray diffraction (Fig. 1). A colourless plare crystal (0.57×0.20×0.08) was obtained by recrystallisation from petroleum ether. Crystal data: $C_{14}H_{15}F_3O_2$, M=272.27, monoclinic space group C_2 (#5), a=20.57(1), b=5.888(7), c=15.41(1) Å, β=135.11(2)° V=1317(2) Å^3, Z=4, D_{calc}=1.373 g cm^{-3}, μ=1.12cm^{-1}, F(000)=568. Data collection used a Rigaku AFC7S four-circle diffractometer [$\lambda_{Mo-K\alpha}$=0.71073 Å] operating at 150 K. 1001 unique data were collected (R_{int}=0.037) of which 752 with $I>2\sigma(I)$ were used in all calculations. The structure was solved using SHELXS-86[34] and refined using TEXSAN[35]. The F and O atoms were refined anisotropically and H atoms were included in fixed, calculated positions, R=0.064, R_w=0.081. The Flack parameter[36] confirmed the correct choice of enantiomorph.

***cis*-2,2,2-Trifluoro-1-[2-(*p*-methoxyphenyl)tetrahydro-2*H*-3-pyranyl]-1-ethanone (11).** Reaction of the ketone (**2**) with *p*-methoxyphenyl magnesium bromide afforded the alcohol (**22**) as a minor product and the title ketone (**11**), which was isolated as a pale yellow oil (0.80 g, 50%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.19 (2H, d, J=8.8 Hz, Ar-H), 6.83 (2H, d, J=8.8 Hz, Ar-H), 4.61 (1H, d, J=3.0 Hz, H-2), 4.33 (1H, m, H-6), 3.65 (1H, m, H-6), 3.79 (3H, s, OCH$_3$), 3.46 (1H, m, H-3), 2.20–2.00 (3H, complex, H-4, H-5), 1.52 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.0 (q, J_{C-F}=33.9 Hz, C=O), 159.2 (C′-4), 131.85 (C′-1), 126.7 (C′-3, C′-5), 114.95 (q, J_{C-F}=293.9 Hz, CF$_3$), 113.8 (C′-2, C′-6), 78.9 (C-2), 69.0 (C-6), 55.3 (OCH$_3$) 45.6 (C-3), 26.0 (C-4), 20.7 (C-5); υ_{max} (film, cm^{-1}) 1755 (C=O), 1051 (CO); LRMS (Scan AP$^+$): m/z=289 (M$^+$+1, 48%), 288 (M$^+$, 9), 219 (M$^+$−CF$_3$, 100); HRMS (EI$^+$): M$^+$ found 288.1001, $C_{14}H_{15}F_3O_3$ requires 288.0973. **3-[(*E*)-1-(*p*-Methoxyphenyl)methylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (22)** was isolated as a white solid (0.19 g, 12%) and was recrystallised (petroleum ether) to give colourless crystals (0.11 g, 7%) mp 85–86°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.22 (2H, d, J=8.8 Hz, Ar-H), 7.01 (1H, s, H-vinylic), 6.90 (2H, d, J=8.8 Hz, Ar-H), 3.98 (2H, m, H-6), 3.82 (3H, s, OCH_3), 3.20 (1H, s, OH), 2.91 (1H, ddd, 14.7, 7.4, 5.2, H-4), 2.47 (1H, m, H-4), 1.99 (1H, m, H-5), 1.72 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=159.0 (C′-4), 131.15 (C-vinylic), 130.6 (C′-3, C′-5), 130.3 and 128.5 (C-3, C′-1), 123.1 (q, J_{C-F}=289.35 Hz, CF$_3$), 113.85 (C′-2, C′-6), 95.8 (q, J_{C-F}=31.65 Hz, C-2), 61.8 (C-6), 55.4 (OCH$_3$), 24.2 (C-5), 21.95 (C-4); υ_{max} (CH_2Cl_2, cm^{-1}) 3552 (OH), 1607 (C=C), 1081 (CO); LRMS (Scan AP$^+$): m/z=288 (M$^+$, 14%), 271 (M$^+$−OH, 100), 219 (M$^+$−CF$_3$, 90); HRMS (EI$^+$): M$^+$ found 288.0968, $C_{14}H_{15}F_3O_3$ requires 288.0973.

***cis*-2,2,2-Trifluoro-1-[2-(1-naphthylmethyl)tetrahydro-2*H*-3-pyranyl]-1-ethanone (12).** To magnesium turnings (1.00 g, 41.1 mmol) in dry ether (75.0 ml) (2.41 g, 20.0 mmol), 1-chloromethyl naphthalene dissolved in dry ether (75.0 ml) was added dropwise under nitrogen, the reaction mixture was stirred at room temperature for 1 h and a solution of the ketone (**2**) (0.90 g, 5.0 mmol) in

tetrahydrofuran (60 ml) was added dropwise at 0°C. The reaction mixture was stirred at room temperature for 2 h, poured into saturated ammonium chloride solution (100 ml), the two phases were separated and the aqueous phase extracted with ether (3×15 ml). The combined organic phases were collected, washed with water, dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting oil was purified by flash column chromatography [silica gel, hexane: ethyl acetate (90:10)] to give the title compound (**12**) as a colourless oil (0.87 g, 54%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.0 (1H, d, J=8.1 Hz, Ar-H), 7.89 (1H, m, Ar-H), 7.78 (1H, d, J=8.1 Hz, Ar-H), 7.50 (2H, m, Ar-H), 7.40 (1H, m, Ar-H), 7.25 (1H, d, J=8.1 Hz, Ar-H), 4.1 (1H, m, H-6), 3.99 (1H, dt, J=7.4, 7.0, 2.5 Hz, H-2), 3.49 (2H, m, CH_2Ar, H-6), 3.21 (1H, dd, J=14.0, 7.0 Hz, CH_2Ar), 3.02 (1H, m, H-3), 2.16 (1H, m, H-4), 1.98–1.40 (3H, complex, H-4 and H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.7 (C=O), 134.1, 133.6 and 132.05 (Ar-C′), 129.1, 127.75, 126.3, 125.8, 125.7 and 123.8 (Ar-H), 115.3 (q, J_{C-F}=293.9 Hz, CF_3), 77.8 (C-2), 68.3 (C-6), 43.2 (C-3), 36.5 (CH_2Ar), 25.35 (C-4), 21.5 (C-5); υ_{max} (CH_2Cl_2, cm^{-1}) 1749 (C=O), 1597 and 1550 (C=C); LRMS (Scan AP$^+$): m/z=323 [(M^++1), 18%], 322 (M^+, 100), 252 [(M^+−1)−CF_3, 8]; HRMS (EI$^+$): M^+ found 322.1181, $C_{18}H_{17}F_3O_2$ requires 322.1181.

***cis*-2,2,2-Trifluoro-1-(2-butyltetrahydro-2*H*-3-pyranyl)-1-ethanone (13).** Reaction of the ketone (**2**) with butyl magnesium bromide afforded in successive five fractions, the *trans*-ketone (**40**) as a minor product then the *cis*-ketone (**13**) as the major product in addition to the three alcohols (**41**), (**24**) and (**42**). The title ketone (**13**) was isolated as a pale yellow oil (0.72 g, 55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.92 (1H, m, H-6), 3.54 (1H, dt, J=8.8, 4.0, 3.7 Hz, H-2), 3.42 (1H, m, H-6), 3.12 (1H, dd, J=8.1, 4.0 Hz, H-3), 2.00 (1H, m, H-4), 1.80 (2H, m, H-4, H-5), 1.58 (1H, m, H-side chain), 1.39 [2H, m, (H-5, H-side chain)], 1.22 (4H, m, side chain), 0.84 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.5 (q, J_{C-F}=33.1 Hz, C=O), 115.5 (q, J_{C-F}=293.9 Hz, CF_3), 77.0 (C-2), 66.8 (C-6), 44.2 (C-3), 32.0, and 28.1 (2C, side chain), 24.6 (C-4), 22.5 (1C, side chain), 21.8 (C-5), 14.1 (CH_3); υ_{max} (film, cm^{-1}) 1754(C=O), 1049 (CO); LRMS (Scan AP$^+$): m/z=237 (M^+−1, 5%), 169 (M^+−CF_3, 100); HRMS (CI$^+$): (M^++1) found 239.1263, $C_{11}H_{17}F_3O_2$ requires 239.1259. ***trans*-2,2,2-Trifluoro-1-(2-butyltetrahydro-2*H*-3-pyranyl)-1-ethanone (40)** was isolated as a pale yellow oil (0.07 g, 5%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=4.02 (1H, m, H-6), 3.56 (1H, ddd, J=10.5, 10.3, 2.5 Hz, H-2), 3.45 (1H, m, H-6), 2.92 (1H, ddd, J=10.7, 10.5, 3.5 Hz, H-3), 2.11 (1H, m, H-4), 1.65 (3H, m, H-4, H-5), 1.53–1.18 (6H, m, H-side chain), 0.91 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=193.5 (C=O), 115.5 (q, J_{C-F}=293.9 Hz, CF_3), 77.8 (C-2), 68.0 (C-6), 49.0 (C-3), 34.3 (1C, side chain), 28.2 (C-4), 27.5 (1C, side chain), 24.7 (C-5), 22.6 (1C, side chain), 14.05 (CH_3); υ_{max} (film, cm^{-1}) 1754 (C=O), 1075 (CO); LRMS (Scan AP$^+$): m/z=238 (M^+, 27%), 237 (M^+−1, 45%), 169 (M^+−CF_3, 100); HRMS (CI$^+$): (M^++NH_4) found 256.1529, $C_{11}H_{17}F_3O_2$ requires 256.1524. **2-(3,4-Dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-2-hexanol (41)** was isolated as a pale yellow oil (0.08 g, 6%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.62 (1H, s, H-6), 3.87 (2H, m, H-2), 1.98 (1H, m), 1.92–1.67 (4H, complex), 1.58 (1H, m), 1.39–1.08 (4H, complex), 0.85 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.15 (C-6), 126.1 (q, J_{C-F}=287.09 Hz, CF_3), 107.8 (C-5), 65.5 (C-2), 32.3 (1C-side chain), 24.4, 22.9, 22.1 and 20.45 [4C, (C-3, C-4, C-side chain)], 14.1 (CH_3); υ_{max} (film, cm^{-1}) 3600–3100 (OH), 1658 (C=C); LRMS (Scan AP$^+$): m/z=221 (M^+−OH, 28%), 169 (M^+−CF_3, 100); HRMS (EI$^+$): M^+ found 238.1187, $C_{11}H_{17}F_3O_2$ requires 238.1181. **3-[(*E*)Pentylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (24)** was isolated as a pale yellow oil (0.08 g, 6%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=5.98 (1H, t, J=7.4 Hz, H-vinylic), 3.90 (2H, m, H-6), 2.88 (1H, s, OH), 2.60 (1H, m, H-4), 2.45 (1H, m, H-side chain), 2.26 (1H, m, H-4), 2.13 (1H, m, H-side chain),1.93 (1H, m, H-5), 1.68 (1H, m, H-5), 1.48–1.23 (4H, complex, H-side chain), 0.91 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=132.5 (C-vinylic), 123.2 (q, J_{C-F}=288.2 Hz, CF_3), 61.7 (C-6), 31.4, 27.3, 24.3, 22.4 and 20.9 (C-4, C-5, 3C side chain), 14.05 (CH_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3566 (OH), 1080 (CO); LRMS (Scan AP$^+$): m/z=221 (M^+−OH, 42%), 169 (M^+−CF_3, 99); HRMS (CI$^+$): (M^++NH_4) found 256.1536, $C_{11}H_{17}F_3O_2$ requires 256.1524. **1-(3,4-Dihydro-2*H*-5-pyranyl)-2,2,2-trifluoro-1-ethanol (42)** was isolated as a pale yellow oil (0.25 g, 19%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.58 (1H, s, H-6), 4.22 (1H, q, J=7.4 Hz, CH(OH)–CF_3), 4.08 (1H, m, H-2), 3.93 (1H, ddd, J=11.5, 8.1, 3.7 Hz, H-2), 2.92 (1H, s, OH), 2.22 (1H, dt, J=16.2, 5.2, 5.2 Hz, H-4), 2.08 (1H, m, H-4), 1.88 (2H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=145.8 (C-6), 124.8 (q, J_{C-F}=282.6 Hz, CF_3), 107.15 (C-5), 72.4 (q, J_{C-F}=32.8 Hz, CH(OH)–CF_3), 66.3 (C-2), 21.8 (C-3), 18.65 (C-4); υ_{max} (film, cm^{-1}) 3550–3150 (OH), 1661 (C=C), 1081 (CO); LRMS (Scan AP$^+$): m/z=183 [(M^++1), 6%], 165 (M^+−OH, 100); HRMS (CI$^+$): (M^++NH_4) found 200.0903, $C_7H_9F_3O_2$ requires 200.0898.

***cis*-2,2,2-Trifluoro-1-(2-pentyltetrahydro-2*H*-3-pyranyl)-1-ethanone (14).** Reaction of the ketone (**2**) with *n*-pentyl magnesium bromide afforded the alcohol (**23**) as a minor product and the title ketone (**14**), which was isolated as a pale yellow oil (0.81 g, 58%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.92 (1H, m, H-6), 3.53 (1H, ddd, J=9.6, 4.0, 3.7 Hz, H-2), 3.41 (1H, m, H-6), 3.10 (1H, dd, J=8.0, 4.0 Hz, H-3), 2.01 (1H, m, H-4), 1.40–1.65 (2H, m, H-4, H-5), 1.56 (1H, m, H-side chain), 1.39 [2H, m, (H-5, H-side chain)], 1.31–1.10 (6H, m, side chain), 0.81 (3H, t, J=6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.5 (q, J_{C-F}=33.9 Hz, C=O), 115.5 (q, J_{C-F}=293.9 Hz, CF_3), 77.05 (C-2), 66.85 (C-6), 44.2 (C-3), 32.25, 31.7, 25.6 and 22.6 (4C, side chain), 24.6 (C-5), 21.8 (C-4), 14.1 (CH_3); υ_{max} (film, cm^{-1}) 1754 (C=O), 1044 (CO); LRMS (Scan AP$^+$): m/z=252 (M^+, 7%), 224 [(M^++1)−CH_2CH_3, 87%], 183 (M^+−CF_3, 43), 165 [M^+−(CF_3+H_2O), 100]; HRMS (CI$^+$): (M^++NH_4) found 270.1683, $C_{12}H_{19}F_3O_2$ requires 270.1681. **3-[(*E*)Hexylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (25)** was isolated as a pale yellow oil (0.07 g, 5%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=5.90 (1H, t, J=7.4 Hz, H-vinylic), 3.83 (2H, m, H-6), 2.54 (1H, m, H-4), 2.16 (1H, m, H-4), 2.04 (2H, m, H-side chain), 1.82 (1H, m, H-5), 1.59 (1H, m, H-5), 1.40–1.12 (6H, complex, H-side chain), 0.72 (3H, t, J=6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=132.6 (C-vinylic), 61.7 (C-6), 31.5 and 28.9,

27.6 and 22.6 (4C, side chain), 24.25 (C-5), 20.9 (C-4), 14.2 (CH_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3557 (OH), 1080 (CO); LRMS (Scan AP^+): *m/z*=235 (M^+-OH, 100%), 183 (M^+-CF_3, 40); HRMS (CI^+): (M^++NH_4) found 270.1690, $C_{12}H_{19}F_3O_2$ requires 270.1681.

***cis*-2,2,2-Trifluoro-1-(2-hexyltetrahydro-2*H*-3-pyranyl)-1-ethanone (15).** Reaction of the ketone (**2**) with *n*-hexyl magnesium bromide afforded two alcohols (**26**) and (**43**) as minor products and the title ketone (**15**), which was isolated first as a pale yellow oil (0.74 g, 50%); ^1H NMR (300 MHz, $CDCl_3$) δ=3.99 (1H, m, H-6), 3.60 (1H, m, H-2), 3.50 (1H, m, H-6), 3.15 (1H, m, H-3), 2.08 (1H, m, H-4), 1.85 (2H, m, H-4, H-5), 1.63 (1H, m, H-side chain), 1.46 [2H, m, (H-5, H-side chain)], 1.38–1.10 (8H, complex, side chain), 0.88 (3H, t, *J*=7.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.7 (q, J_{C-F}=33.9 Hz, C=O), 115.4 (q, J_{C-F}=293.9 Hz, CF_3), 77.0 (C-2), 66.8 (C-6), 44.2 (C-3), 32.3, 31.8, 29.1 and 25.9 (4C, side chain), 24.6 (C-4), 22.7 (1C, side chain), 21.8 (C-5), 14.2 (CH_3); υ_{max} (film, cm^{-1}) 1748 (C=O), 1149 (CO); LRMS (Scan AP+): *m/z*=265 (M^+-1, 5%), 197 (M^+-CF_3, 100); HRMS (CI^+): (M^++NH_4), found 284.1819, $C_{13}H_{21}F_3O_2$ requires 284.1837. **3-[(*E*)Heptylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (26)** was isolated as a pale yellow oil (0.04 g, 3%); ^1H NMR (300 MHz, $CDCl_3$) δ=5.98 (1H, t, *J*=7.4 Hz, H-vinylic), 3.90 (2H, m, H-6), 2.61 (1H, m, H-4), 2.21 (1H, m, H-4), 2.13 (2H, m, H-side chain), 1.94 (1H, m, H-5), 1.64 (1H, m, H-5), 1.50–1.19 (8H, complex, H-side chain), 0.79 (3H, m, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ=132.6 (C-vinylic), 129.5 (C-3), 123.3 (q, J_{C-F}=288.2 Hz, *C*F_3), 95.6 (q, J_{C-F}=31.6 Hz, C-2), 61.7 (C-6), 31.8, 29.2, 29.0 and 27.6 (4C, side chain), 24.25 (C-5), 22.7 (1C, side chain), 20.9 (C-4), 14.2 (CH_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3558 (OH), 1080 (CO); LRMS (Scan AP^+): *m/z*=249 (M^+-OH, 19%), 197 (M^+-CF_3, 93); HRMS (CI^+): (M^++NH_4) found 284.1852, $C_{13}H_{21}F_3O_2$ requires 284.1837; **2-(3,4-Dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-2-octanol (43)** was isolated as a pale yellow oil (0.03 g, 2%); ^1H NMR (300 MHz, $CDCl_3$) δ=6.70 (1H, s, H-vinylic), 3.96 (2H, m, H-2), 2.19–1.20 (14H, complex, H-3, H-4, H-side chain), 0.92 (3H, m, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.15 (C-vinylic), 107.7 (C-5), 65.5 (C-2), 32.6, 31.8, 29.5, 22.7, 22.2, 22.1 and 20.45 (C-3, C-4, 5C-side chain), 14.2 (*C*H_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3462 (OH), 1654 (C=C), 1080 (CO); LRMS (Scan AP^+): *m/z*=265 (M^+-1, 19%), 249 (M^+-OH, 100), 197 (M^+-CF_3, 69); HRMS (EI^+): M^+ found 266.1482, $C_{13}H_{21}F_3O_2$ requires 266.1494.

***cis*-2,2,2-Trifluoro-1-(2-octyltetrahydro-2*H*-3-pyranyl)-1-ethanone (16).** Reaction of the ketone (**2**) with *n*-octyl magnesium bromide afforded the alcohol (**27**) as a minor product and the title ketone (**16**), which was isolated as a pale yellow oil (1.09 g, 67%); ^1H NMR (300 MHz, $CDCl_3$) δ=3.99 (1H, m, H-6), 3.59 (1H, ddd, *J*=9.6, 4.0, 3.7 Hz, H-2), 3.47 (1H, m, H-6), 3.18 (1H, dd, *J*=8.1, 4.0 Hz, H-3), 2.07 (1H, m, H-4), 1.84 (2H, m, H-4, H-5), 1.62 (1H, m, H-side chain), 1.48 [2H, m, (H-5, H-side chain)], 1.27 (12H, m, side chain), 0.88 (3H, t, *J*=6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.7 (q, J_{C-F}=33.9 Hz, C=O), 115.4 (q, J_{C-F}=293.9 Hz, *C*F_3), 77.0 (C-2), 66.8 (C-6), 44.2 (C-3), 32.3, 32.0, 29.6, 29.5, 29.3, 25.9, 24.6, 22.8 and 21.8 (C-4, C-5, 7C-side chain), 14.2 (*C*H_3); υ_{max} (film, cm^{-1}) 1748 (C=O), 1049 (CO); LRMS (Scan AP^+): *m/z*=294 (M^+, 13%), 266 ($M^+-C_2H_4$, 100), 225 (M^+-CF_3, 58), 181 [$M^+-(CH_2)_7CH_3$, 16]; HRMS (CI^+): (M^++NH_4), found: 312.2123, $C_{15}H_{25}F_3O_2$ requires: 312.2150. **3-[(*E*)Nonylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (27)** was isolated as a pale yellow oil (0.05 g, 3%); ^1H NMR (300 MHz, $CDCl_3$) δ=5.95 (1H, t, *J*=7.4 Hz, H-vinylic), 3.88 (2H, m, H-6), 2.61 (1H, m, H-4), 2.25 (1H, m, H-4), 2.10 (2H, m, H-side chain), 1.96 (1H, m, H-5), 1.68 (1H, m, H-5), 1.48–1.18 (12H, complex, H-side chain), 0.89 (3H, m,CH_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3566 (OH), 1050 (CO); LRMS (Scan AP^+): *m/z*=293 (M^+-H, 13%), 277 (M^+-OH, 25%), 225 (M^+-CF_3, 100); HRMS (EI^+): M^+ found 294.1816, $C_{15}H_{25}F_3O_2$ requires 294.1807.

***cis*-2,2,2-Trifluoro-1-(2-phenethyltetrahydro-2*H*-3-pyranyl)-1-ethanone (17).** Reaction of the ketone (**2**) with phenylethyl magnesium bromide afforded the title ketone (**17**), which was isolated as a pale yellow oil (0.83 g, 52%); ^1H NMR (300 MHz, $CDCl_3$) δ=7.38–7.12 (5H, complex, Ph–H), 4.10 (1H, m, H-2), 3.58 (1H, dt, *J*=10.5, 3.0, 3.0 Hz, H-6), 3.50 (1H, ddd, *J*=11.0, 10.5, 3.0 Hz, H-6), 3.11 (1H, m, H-3), 2.87 (1H, ddd, *J*=14.0, 9.2, 4.8 Hz, C*H*$_2$Ph), 2.62 (1H, dt, *J*=14.0, 8.1, 8.1 Hz, C*H*$_2$–Ph), 2.11–1.40 (6H, complex, H-4, H-5, C*H*$_2$CH$_2$Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.7 (q, J_{C-F}=33.9 Hz, C=O), 141.35 (C′-1), 128.7, 128.6 and 126.1 (5C-Ph), 115.4 (q, J_{C-F}=293.9 Hz, *C*F_3), 75.9 (C-2), 67.1 (C-6), 44.1 (C-3), 34.1 (C*H*$_2$–Ph), 31.9 (C*H*$_2$CH$_2$–Ph), 24.8 (C-4), 21.6 (C-5); υ_{max} (film, cm^{-1}) 1754 (C=O), 1051 (CO); LRMS (Scan AP^+): *m/z*=286 (M^+, 3%), 285 (M^+-1, 15), 217 (M^+-CF_3, 100), 181 ($M^+-CH_2CH_2Ph$, 3); HRMS (EI^+): M^+ found 286.1162, $C_{15}H_{17}F_3O_2$ requires 286.1180.

2,2,2-Trifluoro-1-(2-phenyltetrahydro-2*H*-3-pyranylidene)ethyl acetate (32) and 3-[(*E*)-1-phenylmethylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (18). Following the above general procedure, the ketone (**2**) (1.00 g, 5.55 mmol) was added to phenyl magnesium bromide, the reaction mixture was stirred for 30 min., heated under reflux for 30 min., allowed to cool to room temperature and acetyl chloride (4.36 g, 55.5 mmol) was added dropwise. The reaction mixture was stirred for 42 h. and cold 2 M hydrochloric acid was added until pH2. The two phases were separated and the aqueous phase extracted with ether (3×15 ml), the combined organic phases were collected, washed with water, dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting oil (2.60 g) was purified by column chromatography [silica gel, petroleum ether: ethyl acetate (85:15)] to give two fractions, first the ester (**32**) and then the alcohol (**18**). 2,2,2-Trifluoro-1-(2-phenyltetrahydro-2*H*-3-pyranylidene)ethyl acetate (**32**) was isolated as colourless crystals (1.51 g, 90%) mp 68–69°C ^1H NMR (300 MHz, $CDCl_3$) δ=7.47–7.30 (5H, complex, Ph), 5.59 (1H, s, *H*-2), 3.70 (2H, m, H-6), 2.86 (1H, m, H-4), 2.30 (1H, m, H-4), 2.11 (3H, s, C*H*$_3$), 1.94 (1H, m, H-5), 1.76 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=168.7 (C=O), 137.2 and 135.6 (C′-1,C-3), 132.5 (q, J_{C-F}=36.2 Hz, *C*–CF_3), 129.0, 128.0 and 127.0 (Ph–C), 120.4 (q, J_{C-F}=275.8 Hz, *C*F_3), 73.1 (C-2), 61.7 (C-6), 26.6 and 22.4 (C-5, C-4), 19.9 (*C*H_3); υ_{max} (Nujol, cm^{-1}) 1789

(C=O), 1050 (CO); LRMS (Scan AP^+): m/z=257 (M^+-COCH_3, 50%), 241 [(M^++1)−CH_3COOH, 39], 230 [(M^+−1)−CF_3, 8], 189 [(M^++1)-(CF_3–$COCH_3$), 100]; HRMS (CI^+): (M^++NH_4) found 318.1315, $C_{15}H_{15}F_3O_3$ requires 318.1317 Found C, 60.00; H, 5.01. $C_{15}H_{15}F_3O_3$ requires C, 60.00; H, 5.04%. 3-[(*E*)-1-phenylmethylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-pyranol (**18**), which is described above was isolated as colourless crystals (0.11 g, 7%).

The structure of ester (**32**) has been established by X-ray diffraction (Fig. 2). A colourless block (0.56×0.55× 0.46 mm) was obtained by recrystallisation from petroleum ether. Crystal data: $C_{15}H_{15}F_3O_3$, M=300.28, triclinic space group *P-1*(#2) a=8.941(5), b=10.719(6), c=7.785(4) Å, α=96.51(4), β=100.06(5), γ=102.18(4), V=709.3(7) Å^3, Z=2, D_{calc}=1.406 g cm^{-3}, μ=1.16cm^{-1}, F(000)=312. Data collection used a Rigaku AFC7S four-circle diffractometer [$\lambda_{Mo-K\alpha}$=0.71073 Å] operating at 150 K. 2509 unique data were collected (R_{int}=0.023) of which 1846 with $I>2\sigma(I)$ were used in all calculations. The structure was solved using SHELXS-86[31] and refined using TEXSAN[32]. All non-H atoms were refined anisotropically and H atoms were included in fixed, calculated positions, R=0.041, R_w=0.055.

Reaction of 1-(3,4-dihydro-2*H*-5-pyranyl)-2,2,2-trifluoro-1-ethanone (2) with *n*-butyl lithium

To a stirred solution of 1.4 M *n*-butyl lithium in hexane (7.93 ml, 11.1 mmol) in dry ether (28 ml) was added dropwise at room temperature under nitrogen, the ketone (**2**) (1 g, 5.55 mmol in 1 ml ether). The reaction mixture was stirred for 30 min., refluxed for another 30 min. and was allowed to cool to room temperature. 2 M Hydrochloric acid was added until pH2, the two phases were separated and the aqueous phase extracted with ether (3×15 ml), the combined organic phases were collected, washed with water, dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting oil (1.32 g) was purified by column chromatography [silica gel, petroleum ether: ethyl acetate (90:10–70:30)] to give in successive four fractions, the trans ketone (**40**), the *cis* ketone (**13**), the alcohol (**41**) by 1,2-addition and the alcohol (**42**) by reduction. *trans*-2,2,2-Trifluoro-1-(2-butyltetrahydro-2*H*-3-pyranyl)-1-ethanone (**40**), which has been described above, was isolated as a pale yellow oil (0.05 g, 4%). *cis*-2,2,2-Trifluoro-1-(2-butyltetrahydro-2*H*-3-pyranyl)-1-ethanone (**13**), which has been described above, was isolated as a pale yellow oil (0.55 g, 42%). 2-(3,4-Dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-2-hexanol (**41**), which has been described above, was isolated as a pale yellow oil (0.34 g, 26%). 1-(3,4-Dihydro-2*H*-5-pyranyl)-2,2,2-trifluoro-1-ethanol (**42**), which has been described above, was isolated as a pale yellow oil (0.17 g, 13%).

***cis*-2,2,2-Trifluoro-1-(2-phenyltetrahydro-3-furanyl)-1-ethanone (44).** Reaction of the ketone (**3**) (1.0 g, 6.02 mmol) with phenyl magnesium bromide afforded the alcohol (**45**) as a minor product and the title ketone (**44**), which was isolated as a pale yellow oil (0.91 g, 62%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.39–7.20 (5H, complex, Ph), 5.25 (1H, d, J=7.4 Hz, H-2), 4.42 (1H, ddd, J=12.5, 8.1, 4.4 Hz, H-5), 4.08–3.90 (2H, m, H-3, H-5), 2.48 (1H, m, H-4), 2.30 (1H, m, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.6 (q, J_{C-F}=35.0 Hz, C=O), 137.0 (C′-1), 128.65, 128.55 and 126.7 (Ph–C), 114.9 (q, J_{C-F}=292.75 Hz, CF_3), 83.1 (C-2), 68.3 (C-5), 50.8 (C-3), 30.1 (C-4); υ_{max} (film, cm^{-1}) 1752 (C=O); LRMS (Scan AP^+): m/z=244 (M^+, 12%), 243 (M^+−1, 92), 175 (M^+-CF_3, 100). HRMS (EI^+): M^+ found 244.0691, $C_{12}H_{11}F_3O_2$ requires 244.0711. **3-[(*E*)-1-Phenylmethylidene]-2-(trifluoromethyl)tetrahydro-2*H*-2-furanol (45)** was isolated as a white solid (0.10 g, 7%) and was recrystallised (petroleum ether) to give white crystals (0.07 g, 5%) mp 122–123°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.45–7.30 (5H, complex, Ph–H), 6.92 (1H, s, H-vinylic), 4.25 (1H, m, H-5), 4.17 (1H, m, H-5), 3.24 (1H, s, OH), 3.03 (2H, m, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ=135.9 (C′-1), 129.0, 128.7 and 128.4 (5C, Ph), 122.8 (q, J_{C-F}=286.0 Hz, CF_3), 101.5 (C-2), 67.9 (C-5), 30.8 (C-4); υ_{max} (CH_2Cl_2, cm^{-1}) 3558 (OH); LRMS (Scan AP^+): m/z=244 (M^+, 16%), 243 (M^+−1, 71), 227 (M^+−OH, 51), 175 (M^+-CF_3, 100); HRMS (EI^+): M^+ found 244.0696, $C_{12}H_{11}F_3O_2$ requires 244.0711.

General procedure for addition of Grignard reagents (4 equiv.) to 2,2,2-trifluoro-1-(2-ethoxy-3,4-dihydro-2*H*-5-pyranyl)-1-ethanone (6) or 2,2,2-trifluoro-1-(2-methoxy-3,4-dihydro-2H-5-pyranyl)-1-ethanone (5)

To a 100 ml round bottomed flask (with an addition funnel, magnetic stirrer bar and reflux condenser carrying a calcium chloride tube), magnesium turnings (0.44 g, 18.10 mmol), dry ether (3.50 ml) and a crystal of iodine were added. A few drops of alkyl (aryl) bromide (18.23 mmol) in dry ether (3.50 ml) were added dropwise, and the solution was stirred until the formation of the Grignard reagent. The remainder of the alkyl (aryl) bromide was diluted with dry ether (7.00 ml) and the solution was added at such a rate to maintain gentle reflux. After the complete addition of the alkyl (aryl) bromide, the reaction mixture was refluxed with stirring on a warm water bath for (10–20) min. The reaction mixture was cooled and a solution of the ketone (**5**) or (**6**) (1.00 g) in dry ether (3.50 ml) was added dropwise. The reaction mixture was stirred for 30 min., followed by heating under reflux for another 30 min., allowed to cool to room temperature and 2 M hydrochloric acid was added until pH2. The two phases were separated and the aqueous phase extracted with ether (3×15 ml) and the combined organic phases were collected and washed with water, dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting oil was purified by flash column chromatography [silica gel, hexane: ethyl acetate (70:30)] to give pure fractions of the isomeric diols described below.

(1*RS*,5*SR*)-6,6,6-Trifluoro-1,5-diphenyl-4-[(*E*)-1-phenylmethylidene]-1,5-hexanediol (47) and (1*RS*,5*RS*)-6,6,6-trifluoro-1,5-diphenyl-4-[(*E*)-1-phenylmethylidene]-1,5-hexanediol (46). Following the above procedure reaction of phenyl magnesium bromide with the ketone (**6**) afforded the title compound (**47**), which was isolated as a white solid (0.65 g, 35%) and was recrystallised from petroleum ether mp 119–120°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.70 (2H, m, Ph), 7.50–7.18 (11H, complex, Ph), 7.10 (2H, m, Ph), 7.04(1H, s, H-vinylic), 4.60 (1H, dd, J=9.0, 4.0 Hz, H-1), 2.59 (1H, m, H-3), 2.12 (1H, dt, J=16.9, 8.0, 8.0 Hz, H-3),

1.71 (1H, m, H-2), 1.58 (1H, m, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.0 (C-4), 138.1, 137.75 and 137.3 (C′-1,C″-1, C‴-1), 130.6 (C-vinylic), 128.7, 128.6, 128.5, 128.4, 127.8, 127.6, 127.5 and 125.7 (Ph–C), 125.45 (q, J_{C-F}= 87.0 Hz, CF_3), 81.2 (C-5), 73.5 (C-1), 36.2 (C-2), 24.15 (C-3); υ_{max} (CH_2Cl_2, cm^{-1}) 3570, 3327(OH); LRMS (Scan AP^+): *m/z*=412 (M^+, 8%), 411 (M^+-1, 100); HRMS (CI^+): (M^++NH_4) found 430.2003, $C_{25}H_{23}F_3O_2$ requires 430.1994. Found C, 72.71; H, 5.47. $C_{25}H_{23}F_3O_2$ requires C, 72.80; H, 5.62%. The structure of alcohol (**47**) has been established by X-ray diffraction (see figure). A colourless lathe crystal (0.60×0.20×0.08) was obtained by recrystallisation from petroleum ether. Crystal data: $C_{25}H_{23}F_3O_2$, *M*=412.45, orthorhombic space group $P2_12_12_1$ (#19), *a*=21.632(6), *b*=25.123(3), *c*=7.622(5) Å, *V*=4142(3) Å^3, *Z*=8, D_{calc}=1.323 g cm^{-3}, μ=0.95 cm^{-1}, *F*(000)=1728. Data collection used a Rigaku AFC7S four-circle diffractometer [$\lambda_{Mo-K\alpha}$=0.71073 Å] operating at 150 K. 4145 data were collected of which 1619 with $I>2\sigma(I)$ were used in all calculations. The structure was solved using SIR88[37] and refined using TEXSAN[35] revealing two crystallographically independent molecules in the asymmetric unit. The F and O atoms were refined anisotropically and H atoms were included in fixed, calculated positions, *R*=0.065, R_w=0.066. The Flack parameter[36] confirmed the correct choice of enantiomorph.

The isomeric title compound (**46**) was isolated as a pale yellow oil (1.04 g, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.58 (2H, m, Ph), 7.35–7.04 (11H, complex, Ph), 7.01 (2H, m, Ph), 6.78 (1H, s, H-vinylic), 4.42 (1H, dd, *J*=8.8, 4.4 Hz, H-1), 2.45 (1H, dt, *J*=15.0, 7.5, 7.5 Hz, H-3), 2.08 (1H, dt, *J*=15.0, 7.5, 7.5 Hz, H-3), 1.62 (2H, m, H-2). ^{13}C NMR (75 MHz, $CDCl_3$) δ=143.9 (C-4), 139.0, 138.15 and 137.1 (C′-1,C″-1, C‴-1, Ph), 130.4 (C-vinylic), 128.7, 128.65, 128.4, 127.9, 127.6, 127.4 and 125.9 (Ph–C), 81.2 (C-5), 75.6 (C-1), 37.7 (C-2), 25.2 (C-3); (CH_2Cl_2, cm^{-1}) υ_{max} 3588, 3318 (OH); LRMS (Scan AP^+): *m/z*=395 (M^+-OH, 14%), 394 [(M^+-1)−OH, 24], 378 (M^+-2OH, 8), 377 [(M^+-1)-2OH, 36], 342 [(M^+-1)−CF_3, 12], 325 [(M^+-1)-(OH+CF_3), 100], 273 [(M^+-1)-(C_6H_5CHOH-CH_2OH), 11]; HRMS (CI^+): (M^++NH_4) found 430.2005, $C_{25}H_{23}F_3O_2$ requires 430.1994.

Similarly ketone (**5**) afforded the alcohols (**46**) and (**47**) in 43 and 39% yields respectively.

Reaction of the ketone (**6**) with phenyl magnesium bromide under the same conditions and using tetrahydrofuran as a solvent instead of ether afforded the alcohol (**46**) in 35% yield and the alcohol (**47**) in 35% yield.

(1*RS*,5*SR*)-6,6,6-Trifluoro-1,5-di(*m*-methylphenyl)-4-[(*E*)-1-(*m*-methylphenyl) methylidene]-1,5-hexanediol (50) and (1*RS*,5*RS*)-6,6,6-trifluoro-1,5-di(*m*-methylphenyl)-4[(*E*)-1-(*m*-methylphenyl)methylidene]-1,5-hexanediol (49). Following the above procedure reaction of *m*-methylphenyl magnesium bromide with the ketone (**6**) afforded the title compound (**50**), which was isolated as a pale yellow oil (0.83 g, 41%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.55 (2H, m, Ar), 7.40–6.90 (11H, complex, H–Ar, H-vinylic), 4.62 (1H, dd, *J*=9.6, 3.7 Hz, H-1), 2.60 (1H, m, H-3), 2.42 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.16 (1H, dt, *J*=15.0, 7.5, 7.5 Hz, H-3), 1.72 (1H, m, H-2), 1.60 (1H, m, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.1 (C-4), 138.3, 138.2, 138.1, 138.0, 137.6 and 137.4 (6C′-Ar), 130.5 (C-vinylic), 129.5, 129.4, 129.3, 128.6, 128.5, 128.2, 126.4, 125.5, 124.8, 122.65 and 121.6 (12C, Ar), 125.5 (q, J_{C-F}=287.1 Hz, CF_3), 81.2 (q, J_{C-F}=27.1 Hz, C-5), 73.5 (C-1), 36.3 (C-2), 24.2 (C-3), 21.8, 21.6 and 21.6 (3C,CH_3); υ_{max} (film, cm^{-1}) 3450–3300 (OH); LRMS (Scan AP^+): *m/z*=454 (M^+,8%), 437 (M^+-OH, 43), 420(M^+-2 OH, 22), 419 [(M^+-1)-2OH, 100], 368 [$M^+-(CF_3+OH)$, 13], 367 [M^+-1-(CF_3+OH), 83], 301 [(M^+-1)-*m*-CH_3–$C_6H_4CHOHCH_2OH$,]; HRMS (CI^+): (M^++NH_4) found 472.2483, $C_{28}H_{29}F_3O_2$ requires 472.2463.

The isomeric title compound (**49**) was isolated as a pale yellow oil (0.87 g, 43%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.50 (1H, s, Ar), 7.45 (1H, d, *J*=8.1 Hz, Ar), 7.33 (1H, d, *J*=8.1 Hz, Ar), 7.30–6.84 (10H, complex, H–Ar, H-vinylic), 4.53 (1H, dd, *J*=9.0, 4.0 Hz, H-1), 2.58 (1H, dt, *J*=14.5, 7.4, 7.4 Hz, H-3), 2.42 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.23 (1H, dt, 14.5, 7.4, 7.4, H-3), 1.78 (2H, m, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.0 (C-4), 138.8, 138.3, 138.2, 138.0 and 137.1 (Ar-C′), 130.25 (C-vinylic), 129.6, 129.5, 128.6, 128.5, 128.2, 128.1 126.5, 125.6, 124.7 and 122.8 (Ar-C), 81.2 (C-5), 75.8 (C-1), 37.7 (C-2), 25.3 (C-3), 21.8, 21.6 (CH_3); υ_{max} (film, cm^{-1}) 3600–3350 (OH); LRMS (Scan AP^+): *m/z*=454 (M^+, 9%), 437 (M^+-OH, 43), 420 (M^+-2OH, 23), 419[(M^+-1)-2OH, 100], 385 (M^+-CF_3, 8), 367 [M^+-1-(CF_3+OH), 52], 301 [(M^+-1)-*m*-CH_3–$C_6H_4CHOHCH_2OH$, 44]; HRMS (CI^+): (M^++NH_4) found 472.2483, $C_{28}H_{29}F_3O_2$ requires 472.2463.

(1*RS*,5*SR*)-6,6,6-Trifluoro-1,5-di(*p*-methylphenyl)-4-[(*E*)-1-(*p*-methylphenyl)methylidene]-1,5-hexanediol (52) and (1*RS*,5*RS*)-6,6,6-trifluoro-1,5-di(*p*-methylphenyl)-4-[(*E*)-1-(*p*-methylphenyl)methylidene]-1,5-hexanediol (51). Following the above procedure reaction of *p*-methylphenyl magnesium bromide with the ketone (**6**) afforded the title compound (**52**), which was isolated as a pale yellow oil (0.60 g, 30%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.59 (2H, d, *J*=8.1 Hz, Ar), 7.30–6.92 (11H, complex, H–Ar, H-vinylic), 4.59 (1H, dd, *J*=9.0, 4.0 Hz, H-1), 2.60 (1H, m, H-3), 2.42 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.18 (1H, dt, *J*=16.0, 8.0, 8.0 Hz, H-3), 1.72 (1H, m, H-2), 1.60 (1H, m, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=141.1 (C-4), 138.4, 137.5, 137.3, 137.2, 135.3 and 134.4 (Ar-C′), 130.3 and 130.2 [2C, (C-vinylic, Ar-C), 129.3, 129.2, 129.1, 128.5, 127.5 and 125.7 (Ar-C), 81.3 (C-5), 73.5 (C-1), 36.3 (C-2), 24.2 (C-3), 21.4, 21.3 and 21.2 (3C, 3CH_3); υ_{max} (film, cm^{-1}) 3600–3350 (OH); LRMS (Scan AP^+): *m/z*=437 (M^+-OH, 21), 420 (M^+-2OH, 11), 419 [(M^+-1)-2OH, 30], 368 [$M^+-(CF_3+OH)$, 17], 367 [(M^+-1)-(CF_3+OH), 42], 301 [(M^+-1)-*p*-CH_3–$C_6H_4CHOHCH_2OH$, 84]; HRMS (CI^+): (M^++NH_4) found 472.2486, $C_{28}H_{29}F_3O_2$ requires 472.2463.

The isomeric title compound (**51**) was isolated as a pale yellow oil (0.71 g, 35%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.48 (2H, d, *J*=8.1 Hz, Ar), 7.11–6.85 (10H, complex, Ar), 6.72 (1H, s, H-vinylic), 4.41 (1H, dd, *J*=8.8, 3.7 Hz, H-1), 2.43 (1H, dt, *J*=14.5, 7.4, 7.4 Hz, H-3), 2.28 (3H, s,

CH_3), 2.22 (3H, s, CH_3), 2.18 (3H, s, CH_3), 2.08 (1H, dt, J=14.5, 7.4, 7.4 Hz, H-3), 1.76–1.50 (2H, m, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=141.0 (C-4), 138.5, 137.5, 137.1, 135.3 and 134.2 (C′-Ar), 130.0, 129.3, 129.1, 128.7, 128.5, 127.5, 125.8 and 125.7 (C-vinylic, Ar), 125.6 (q, J_{C-F}=287.1 Hz, CF_3), 81.35 (q, J_{C-F}=27.1 Hz, C-5), 75.6 (C-1), 37.75 (C-2), 25.3 (C-3), 21.4, 21.3 and 21.3 (3C, 3CH_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3580 (OH), 3314 (OH); LRMS (Scan AP$^+$): m/z=437 (M^+-OH, 20), 420 (M^+-2OH, 10), 419 [(M^+-1)-2OH, 39], 384 [(M^+-1)−CF_3, 8], 301 [(M^+-1)-p-CH_3–C_6H_4CHOH-CH_2OH, 100]; HRMS (CI$^+$): (M^++NH_4) found 472.2500, $C_{28}H_{29}F_3O_2$ requires 472.2463.

General procedure for addition of Grignard reagents (2 equiv.) to 2,2,2-trifluoro-1-(2-ethoxy-3,4-dihydro-2*H*-5-pyranyl)-1-ethanone (6)

Following the above procedure but using Grignard (2 equiv.), the resulting oils were separated by flash column chromatography [silica gel, hexane: ethyl acetate (70:30)] to give first the ethyl pentenoates described below and then the two isomeric diols.

Ethyl (*E*)-5-phenyl-4-(2,2,2-trifluoro-1-hydroxyethyl)-4-pentenoate (55). Using the above procedure the title compound (**55**) was isolated as a yellow oil (0.28 g, 21%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.50–7.21 (5H, complex, Ph), 6.78 (1H, s, H-vinylic), 4.59 (1H, q, J=7.4 Hz, C$H$$CF_3$), 4.09 (2H, q, J=7.4 Hz, C$H_2$$CH_3$), 2.78 (2H, t, J=7 Hz, H-3), 2.47 (2H, t, J=7.0 Hz, H-2), 1.20 (3H, t, J=7.4 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=174.9 (C=O), 136.1 and 134.5 (C′-1, C-4), 134.05 (C-vinylic), 128.75, 128.65 and 127.9 (Ph–C), 124.8 (q, J_{C-F}=282.5 Hz, CF_3),76.0 (q, J_{C-F}=30.5 Hz, CH–CF_3), 61.3 (CH_2CH_3), 32.4 (C-2), 21.5 (C-3), 14.2 (CH_2CH_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3365 (OH), 1713 (C=O), 1602 (C=C); LRMS (Scan AP$^+$): m/z=303 (M^++1, 33%), 285 (M^+-OH, 100), 233 (M^+-CF_3, 10); HRMS (CI$^+$): (M^++NH_4) found 320.1477, $C_{15}H_{17}F_3O_3$ requires 320.1474. The isomeric diols (**46**) and (**47**) were also isolated (28%) and their characterisation has been described above.

Ethyl (*E*)-5-(*m*-methylphenyl)-4-(2,2,2-trifluoro-1-hydroxyethyl)-4-pentenoate (56). The title compound (**56**) was isolated as a pale yellow oil (0.39 g, 28%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.15 (1H, m, Ar), 7.00 (3H, m, Ar), 6.63 (1H, s, H-vinylic), 4.60 (1H, s, OH), 4.48 (1H, q, J=7.4 Hz, C$H$$CF_3$), 4.02 (2H, q, J=7.4 Hz, C$H_2$$CH_3$), 2.68 (2H, m, H-3), 2.42 (2H, m, H-2), 2.28 (3H, s, CH_3), 1.12 (3H, t, J=7.4 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=175.0 (C=O), 138.35 and 136.0 (C′-1, C-4), 134.2 (C-vinylic), 129.4, 128.6 and 125.6 (Ar-C), 124.8 (q, J_{C-F}=283.7 Hz, CF_3), 76.1 (q, J_{C-F}=31.65 Hz, CH–CF_3), 61.3 (CH_2CH_3), 32.4 (C-2), 21.6 (CH_3), 21.5 (C-3), 14.2 (CH_2CH_3); υ_{max} (film, cm^{-1}) 3550–3100 (OH), 1713 (C=O); LRMS (Scan AP$^+$): m/z=317 (M^++1, 59%), 316 (M^+, 8), 315 (M^+-1, 17), 299 (M^+-OH, 100), 247 (M^+-CF_3, 11); HRMS (CI$^+$): (M^++NH_4) found 334.1632, $C_{16}H_{19}F_3O_3$ requires 334.1630. Unreacted ketone (**6**) (40%) and the isomeric diols (**49**) and (**50**) (20%) were also isolated and their characterisation has been described above.

Ethyl (*E*)-5-(*p*-methylphenyl)-4-(2,2,2-trifluoro-1-hydroxyethyl)-4-pentenoate (57). The title compound (**57**) was isolated as a pale yellow oil (0.42 g, 30%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.19 (4H, m, Ar), 6.69 (1H, s, H-vinylic), 4.72 (1H, d, J=2.95 Hz, OH), 4.57 (1H, dq, J=7.4, 2.0 Hz, C$H$$CF_3$), 4.10 (2H, q, J=7.4 Hz, C$H_2$$CH_3$), 2.78 (2H, m, H-3), 2.50 (2H, m, H-2), 2.38 (3H, s, CH_3), 1.21 (3H, t, J=7.4 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=175.0 (C=O), 137.8, 133.7 and 133.1 (C′-1, C-4), 134.0 (C-vinylic), 129.4 and 128.6 (Ar-C), 124.8 (q, J_{C-F}=282.6 Hz, CF_3), 76.2 (q, J_{C-F}=30.5 Hz, $CH$$CF_3$), 61.3 ($CH_2CH_3$), 32.3 (C-2), 21.4 ($CH_3$), 21.3 (C-3), 14.2 ($CH_2CH_3$); υ_{max} (film, cm^{-1}) 3550–3200 (OH), 1712 (C=O); LRMS (Scan AP$^+$): m/z=299 (M^+-OH, 33%), 231 [(M^+ +1)-(CF_3+OH), 29)], 211 [(M^+-1)-(OH–CH_2COOEt), 100]; HRMS (EI$^+$): M^+ found 316.1275, $C_{16}H_{19}F_3O_3$ requires 316.1286. Unreacted ketone (**6**) (39%) and the isomeric diols (**51**) and (**52**) (10%) were also isolated and their characterisation has been described above.

General method of oxidation of (1*RS*,5*SR*)-6,6,6-trifluoro-1,5-(diaryl)-4[(*E*)-1-aryl methylidene]-1,5-hexanediol and (1*RS*,5*RS*)-6,6,6-trifluoro-1,5-diaryl-4-[(*E*)-1-arylmethylidene]-1,5-hexanediol

To a cold solution of a mixture of the triaryl diols (0.2 g) in dry acetone (2 ml), Jones reagent (0.2 ml) was added under nitrogen, the reaction mixture was stirred for 1 h, diluted with water (25 ml) and extracted with dry ether (3×15 ml). The combined organic phases were collected, washed with water, dried over $MgSO_4$ and the solvent evaporated in vacuo to give products (about 99% yield).

(*E*)-1,5-Diphenyl-4-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)-4-penten-1-one (48). The title compound (**48**) was isolated as a pale yellow oil (0.195 g, 98%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.68 (2H, d, J=8.1 Hz, Ph), 7.55 (2H, d, J=7.4 Hz, Ph), 7.41 (1H, t, J=7.4 Hz, Ph), 7.38–7.08 (10H, complex, Ph), 6.88 (1H, s, H-vinylic), 6.06 (1H, s, OH), [2.92 (1H, m), 2.64 (2H, m), 2.38 (1H, m), H-2, H-3]; ^{13}C NMR (75 MHz, $CDCl_3$) δ=201.9 (C=O), 138.0, 137.3 and 136.3 (C′-Ph, C-4), 133.7, 130.1, 128.8, 128.7, 128.4, 128.3, 128.25, 127.7 and 127.6 [(C, Ph)+(1C-vinylic)], 125.5 (q, J_{C-F}=287.1 Hz, CF_3), 80.8 (q, J_{C-F}= 28.3 Hz, C-5), 36.5 (C-2), 21.9 (C-3); υ_{max} (film, cm^{-1}) 3500–3100 (OH), 1681 (C=O); LRMS (Scan AP$^+$): m/z=410 (M^+, 8%), 393 (M^+-OH, 100), 341 (M−CF_3, 67); HRMS (CI$^+$): (M^++NH_4) found 428.1837, $C_{25}H_{21}F_3O_2$ requires 428.1837.

(*E*)-1,5-Di(*m*-methylphenyl)-4-[2,2,2-trifluoro-1-hydroxy-1-(*m*-methyl phenyl)ethyl]-4-penten-1-one (53). The title compound (**53**) was isolated as a yellow oil (0.197 g, 99%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.52 (1H, s, Ar), 7.45 (1H, d, J=7.4 Hz, Ar), 7.38 (1H, s, Ar), 7.32 (1H, d, J=7.4 Hz, Ar), 7.28–6.92 (7H, complex, Ar), [6.88 (1H, s) and 6.83 (1H, s), H–Ar, H-vinylic], 6.02 (1H, s, OH), 2.92 (1H, m), 2.70–2.32 (3H, complex, H-2, H-3), 2.32 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.15 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$)

δ=202.3 (C=O), 138.5, 138.0, 137.9, 137.85, 137.35 and 136.5 (C′-Ar, C-4), 134.4, 130.0, 129.4, 129.1, 128.8, 128.7, 128.5, 128.25, 128.2, 125.5, 125.2 and 124.8 [(C, Ar)+(1C-vinylic)], 125.5 (q, J_{C-F}=287.1 Hz, CF_3), 80.7 (q, J_{C-F}= 28.25 Hz, C-5), 36.5 (C-2), 22.1 (C-3), 21.8 and 21.4 (CH_3); υ_{max} (film, cm^{-1}) 3500–3100 (OH), 1668 (C=O); LRMS (Scan AP^+): *m/z*=452 (M^+, 9%), 435 (M^+-OH, 100), 383 (M^+-CF_3, 27); HRMS (CI^+): ($M^+ + NH_4$) found 470.2344, $C_{26}H_{25}F_3O_2$ requires 470.2307.

(*E*)-1,5-Di(*p*-methylphenyl)-4-[2,2,2-trifluoro-1-hydroxy-1-(*p*-methyl phenyl)ethyl]-4-penten-1-one (54). The title compound (**54**) was isolated as a yellow oil (0.197 g, 99%) ^1H NMR (300 MHz, $CDCl_3$) δ=7.53 (2H, d, *J*=8.1 Hz, Ar), 7.45 (2H, d, *J*=8.1 Hz, Ar), 7.11 (2H, d, *J*=8.1 Hz, Ar), 7.01 (6H, complex, Ar), 6.80 (1H, s, H-vinylic), 5.98 (1H, s, OH), [2.92 (1H, m), 2.75–2.50 (2H, m), 2.32 (1H, m), H-2, H-3], 2.25 (9H, m, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=201.5 (C=O), 144.6, 138.4, 137.6, 137.3, 135.2, 134.3 and 133.9 (C′-Ar, C-4), 129.8, 129.5, 129.3, 129.1, 128.4, 128.3 and 127.7 (C–Ar and C-vinylic), 125.6 (q, J_{C-F}=286.0 Hz, CF_3), 80.7 (q, J_{C-F}=27.1 Hz, C-5), 36.45 (C-2), 22.1 (C-3), 21.8, 21.4 and 21.3 (3C, CH_3); υ_{max} (film, cm^{-1}) 3500–3100 (OH), 1667 (C=O); LRMS (Scan AP^+): *m/z*=452 (M^+, 8%), 435 (M^+-OH, 100), 383 ($M-CF_3$, 24); HRMS (CI^+): ($M^+ + NH_4$) found 470.2333, $C_{26}H_{25}F_3O_2$ requires 470.2307.

Reaction of 2,2,2-trifluoro-1-(2-methoxy-3,4-dihydro-2*H*-5-pyranyl)-1-ethanone (5) with *n*-butyl lithium

To a stirred solution of *n*-butyl lithium in hexane (1.6 M) (13.58 ml, 21.73 mmol) in dry ether (28 ml) was added dropwise at room temperature under nitrogen, the ketone (**5**) (1.00 g, 4.76 mmol) in ether (1 ml). The reaction mixture was stirred for 30 min., heated under reflux for another 30 min. and was allowed to cool to room temperature. 2 M Hydrochloric acid was added until pH2, the two phases were separated and the aqueous phase extracted with ether (3×15 ml). The combined organic phases were collected, washed with water, dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting oil was purified by flash column chromatography [silica gel, petroleum ether: ethyl acetate (90:10)] to give in four successive fractions, by 1,2-addition the isomeric alcohols (**65**), via 1,4-addition the tributyl diols (**64**) and the dibutyl diols (**66**) and finally by reduction the alcohol (**67**).

2-(2-Methoxy-3,4-dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-2-hexanol (65). The fraction representing the 1,2-addition products was isolated as a mixture of the two isomeric alcohols (**65**) (0.65 g, 51%), from which one pure isomer was isolated after further chromatography as a pale yellow oil ^1H NMR (300 MHz, $CDCl_3$) δ=6.48 (1H, d, *J*=2.2 Hz, H-6), 4.84 (1H, t, *J*=2.9 Hz, H-2), 3.39 (3H, s, CH_3), 2.18–1.05 (10H, complex), 0.84 (3H, m, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=140.4 (C-6), 109.0 (C-5), 97.3 (C-2), 55.7 (OCH_3), 32.6, 26.1, 24.4, 22.9 and 16.45 (CH_2), 14.1 (CH_3); υ_{max} (film, cm^{-1}) 3550–3200 (OH); LRMS (Scan AP^+): *m/z*=269 (M^++1, 23%), 268 (M^+, 16), 267 (M^+-1, 12), 251 (M^+-OH, 48), 199 ($M-CF_3$, 100); HRMS (EI^+): M^+ found 268.1299, $C_{12}H_{19}F_3O_3$ requires 268.1286. The stereochemistry of this isomer has not been determined.

6-[(*E*)Pentylidene]-5-(trifluoromethyl)-5,9-tridecanediol (64). The title compounds (**64**) were isolated as a pale yellow oil (0.25 g, 15%) ^1H NMR (300 MHz, $CDCl_3$) δ=5.48 (2H, m, H-vinylic), 3.50 (2H, m, H-1), 2.31–1.11 (44H, complex, CH_2), 0.89–0.80 (18H, complex, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=135.1 and 134.3 (C-4), 132.2 and 131.2 (C-vinylic)], 126.2 (q, J_{C-F}=CF_3), 78.4 (C-5), 72.5 and 71.0 (C-1), 37.3–22.5 (CH_2), 14.2, 14.1 and 14.1 (CH_3); υ_{max} (film, cm^{-1}) 3500–3300 (OH); LRMS (Scan AP^+): *m/z*=335 [(M^++1)−H_2O, 45%), 218 (M^+-2OH, 10%), 283 ($M-CF_3$, 55).

1,1,1-Trifluoro-3-[(*E*)pentylidene]-2,6-decanediol: (66). The diol fraction (**66**) was isolated as a 50:50 mixture of the two isomeric alcohols (0.13 g, 9%), from which one pure isomer was isolated as a white crystalline solid mp 81–82°C ^1H NMR (300 MHz, $CDCl_3$) δ=5.60 (1H, t, *J*=7.4 Hz, H-vinylic), 4.90 (1H, q, *J*=7.4 Hz, C*H*–CF_3), 4.51 (1H, s, O*H*), 3.63 (1H, m, H-1), 2.43–2.00 (4H, complex, CH_2), 1.72–1.18 (12H, complex, CH_2), 0.80 (6H, m, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=135.2 (C-vinylic), 131.55 (C-4), 125.1 (q, J_{C-F}=283.7 Hz, CF_3), 70.4 (C-1), 68.8 (q, J_{C-F}=31.65 Hz, C-5), 37.4, 36.5, 31.8, 27.9, 27.7, 25.4, 22.8 and 22.45 (8C, CH_2), 14.2 and 14.0 (2C, CH_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3594 (OH), 3500–3050 (OH); LRMS (Scan AP^+): *m/z*=295 (M^+-1, 7%); HRMS (CI^+): [($M^+ + NH_4$)−H_2O] found 296.2201, $C_{15}H_{27}F_3O_2$ requires 296.2201. Found C, 60.88; H, 9.30. $C_{15}H_{27}F_3O_2$ requires C, 60.79; H, 9.18%. The stereochemistry of this isomer has not been determined.

1-(2-Methoxy-3,4-dihydro-2*H*-5-pyranyl)-2,2,2-trifluoro-1-ethanol (67). The title compound (**67**) was isolated as a pale yellow oil (0.1 g, 10%) ^1H NMR (300 MHz, $CDCl_3$) δ=6.40 (1H, s, H-6), 4.86 (1H, m, H-2), 4.18 (1H, m, C*H*(OH)–CF_3), 3.35 (3H, s, CH_3), 2.31–1.58 (4H, complex, H-3, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ=142.3 (C-6), 108.15 (C-5), 98.1 (C-2), 72.2 (*C*H(OH)–CF_3), 55.9 (OCH_3), 25.9 (C-3), 14.7 (C-4); υ_{max} (film, cm^{-1}) 3600–3050 (OH), 1668 (C=C); LRMS (Scan AP^+): *m/z*=212 (M^+, 8%), 195 (M^+-OH, 80%), 143 (M^+-CF_3, 38%) HRMS (CI^+): ($M^+ + NH_4$) found 230.1021, $C_8H_{11}F_3O_3$ requires 230.1004.

The ketone (**5**) was reacted with *n*-butyl magnesium bromide (4 equiv.) to afford after chromatography four fractions, first by 1,2-addition the isomeric alcohols (**65**) (8%), by 1,4-addition the tributyl diols (**64**) (11%) and then the dibutyl diols (**66**) (40%) and by reduction the alcohol (**67**) (28%).

Reaction of 2,2,2-trifluoro-1-(2-methoxy-3,4-dihydro-2*H*-5-pyranyl-1-ethanone (5) with *p*-tolyl magnesium bromide (3 equiv.) at −35°C

To a cold solution (−30–−35°C) of *p*-tolyl magnesium bromide prepared, following the above general procedure, from magnesium turnings (0.33 g, 13.58 mmol) in dry ether (2.6 ml) and *p*-bromotoluene (2.3 g, 13.45 mmol) in dry ether (7.8 ml), the ketone (**5**) (0.94 g, 4.48 mmol) in dry

ether (1.6 ml) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h, allowed to warm to 0°C and cold (0°C) hydrochloric acid (2 M) was added until pH2. The two phases were separated and the aqueous phase extracted with dry ether (3×15 ml), the combined organic phases were collected, washed with water, dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting oil was purified by flash column chromatography [silica gel, hexane: ethyl acetate (95:5)] to give the ketone (**58**; R=Me; Ar=*p*-MeC_6H_4) and the aldehyde (**59**; Ar=*p*-MeC_6H_4).

2,2,2-Trifluoro-1-[6-methoxy-2-(4-methylphenyl)tetrahydro-2*H*-3-pyranyl]-1-ethanone (58; R=Me; Ar=*p*-MeC_6H_4). The title compound (**58**) was isolated as a white solid (1.03 g, 76%) and was recrystallised from petroleum ether to give white crystals mp 65–66°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.21 (2H, d, *J*=8.1 Hz, Ar-H), 7.15 (2H, d, *J*=8.1 Hz, Ar-H), 5.10 (1H, d, *J*=2.9 Hz, H-2), 5.02 (1H, d, *J*=3.7 Hz, H-6), 3.47 (1H, m, H-3), 3.38 (3H, s, O*CH*$_3$), 2.48 (1H, m, H-4), 2.32 (3H, s, CH_3), 2.12 (1H, tt, *J*=14.0, 3.7, H-5), 1.91 (1H, dt, *J*=14.0, 2.2, 2.2, H-4), 1.70 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.1 (q, J_{C-F}=33.9 Hz, C=O), 137.6, 136.3 (C′), 129.2 and 125.7 (Ar-C), 114.9 (q, J_{C-F}=293.9 Hz, *C*F_3), 98.6 (C-6), 69.15 (C-2), 55.1 (OCH_3), 44.8 (C-3), 24.4 (C-5), 21.25 (CH_3), 20.8 (C-4); υ_{max} (CH_2Cl_2, cm^{-1}) 1756 (C=O); LRMS (Scan AP$^+$): *m*/*z*=302 (M^+, 5%), 270 [(M^+-CH_3OH), 21], 201[($M^+-CH_3OH+CF_3$), 30]. Found C, 59.63; H, 5.69. $C_{15}H_{17}F_3O_3$ requires C, 59.60; H, 5.67%.

(*E*)-5-(*p*-Methylphenyl)-4-(2,2,2-trifluoroacetyl)-4-pentenal (59; Ar=*p*-MeC_6H_4). The title compound (**61**) was isolated as a pale yellow oil (0.05 g, 4%) ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.70 (1H, t, *J*=1.0 Hz, *H*–C=O), 7.65 (1H, s, H-5), 7.23 (2H, d, *J*=8.2 Hz, Ar-H), 7.15 (2H, d, *J*=8.2 Hz, Ar-H), 2.87 (2H, m, H-3), 2.55 (2H, m, H-2), 2.28 (3H, s, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ=200.7 (H–*C*=*O*), 147.6 (vinylic-C), 141.4, 133.0 and 131.2 (Ar-C′), 130.0 and 129.5 (Ar-C), 116.9 (q, J_{C-F}=291.6 Hz, *C*F_3), 42.3 (C-2), 21.6 (CH_3), 19.7 (*C*-3); υ_{max} (CH_2Cl_2, cm^{-1}) 1728, 1686 (C=O), 1606 (C=C); LRMS (Scan AP$^+$): *m*/*z*=271 [(M^++1), 30%], 270 (M^+, 100), 269 [(M^+−1), 10], 201 [(M^+-CF_3), 53]; HRMS (EI$^+$): M^+ found 270.0877, $C_{14}H_{13}F_3O_2$ requires 270.0868.

Reaction of the ketone (**5**) (1.0 g, 4.46 mmol) with *p*-tolyl magnesium bromide (4 equiv.), following the above procedure, gave the ketone (**58**; R=Me, Ar=*p*-MeC_6H_4) (48%) in addition to mixture of the two diols (**51**), (**52**) (14%) and the aldehyde (**59;** Ar=*p*-MeC_6H_4) (9%).

Reaction of 2,2,2-trifluoro-1-(2-methoxy-3,4-dihydro-2*H*-5-pyranyl-1-ethanone (5) with *p*-tolyl magnesium bromide (2 equiv.) at 0°C

To a cold solution (0°C) of *p*-tolyl magnesium bromide prepared, following the above general procedure, from magnesium turnings (0.22 g, 9.05 mmol) in dry ether (1.7 ml) and *p*-bromo toluene (1.53 g, 8.95 mmol) in dry ether (5.1 ml), the ketone (**5**) (0.94 g, 4.48 mmol) in dry ether (1.7 ml) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h and a cold hydrochloric acid (2 M) was added until pH2. The two phases were separated and the aqueous phase extracted with dry ether (3×15 ml), the combined organic phases were collected, washed with water, dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting oil was purified by flash column chromatography [silica gel, hexane: ethyl acetate (95:5)] to give the starting material (**5**) (30%) in addition to the ketone (**58**) 2,2,2-trifluoro-1-[6-methoxy-2-(*p*-methylphenyl)tetrahydro-2H-3-pyranyl]-1-ethanone, as described above, which was isolated as a white solid (0.31 g, 23%) and (*E*)-5-(*p*-methylphenyl)-4-(2,2,2-trifluoroacetyl)-4-pentenal (**59**), as described above, which was isolated as a pale yellow oil (0.17 g, 14%).

Reaction of the ketone (**5**) (1.0 g, 4.46 mmol) at 0°C was repeated using *p*-tolyl magnesium bromide (4 equiv.) and the ketone (**58**; R=Me, Ar=*p*-MeC_6H_4) (44%), mixture of the two diols (**51**), (**52**) (16%) and the aldehyde (**59**; Ar=*p*-MeC_6H_4) (10%) were isolated.

Reaction of 2,2,2-trifluoro-1-(2-ethoxy-3,4-dihydro-2*H*-5-pyranyl-1-ethanone (6) with *p*-tolyl magnesium bromide (4 equiv.) at 0°C

Following the above procedure the ketone (**6**) (1.00 g, 4.46 mmol) was reacted with *p*-tolyl magnesium bromide (4 equiv.) and gave after flash column chromatography [silica gel, hexane: ethyl acetate (95:5)] **2,2,2-trifluoro-1-[6-ethoxy-2-(*p*-methylphenyl)tetrahydro-2*H*-3-pyranyl]-1-ethanone** (**58**; R=Et, Ar=*p*-MeC_6H_4) as a white solid (0.42 g, 30%) which was recrystallised from petroleum ether to give white crystals, mp 54–55°C^{1}H NMR (300 MHz, $CDCl_3$) δ=7.22 (2H, d, *J*=8.1 Hz, Ar-H), 7.13 (2H, d, *J*=8.1 Hz, Ar-H), 5.20–5.08 (2H, complex, H-2, H-6), 3.71 (1H, m, C*H*$_2$CH$_3$), 3.50 (2H, m, H-3, C*H*$_2$CH$_3$), 2.50 (1H, m, H-4), 2.35 (3H, s, CH_3), 2.10 (1H, tt, *J*=14.0, 4.4 Hz, H-5), 1.91 (1H, m, H-4), 1.69 (1H, m, H-5), 1.22 (3H, t, *J*=7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.2 (q, J_{C-F}=33.9 Hz, C=O), 137.5 and 136.4 (Ar-C′), 129.2 and 125.7 (Ar-C), 114.8 (q, J_{C-F}=293.9 Hz, *C*F_3), 97.1 (C-6), 69.2 (C-2), 63.0 (*C*H$_2$CH$_3$), 44.9 (C-3), 24.6 (C-5), 21.2 (CH_3), 20.9 (C-4), 15.2 (*C*H$_3$); υ_{max} (CH_2Cl_2, cm^{-1})=1756 (C=O); LRMS (Scan AP$^+$): *m*/*z*=317 [(M^++1), 7%], 271 [($M^+-C_2H_5O$), 27], 270 [($M^+-C_2H_5OH$), 21], 201 [($M^+-(C_2H_5OH+CF_3)$, 83], Found C, 61.20; H, 5.96. $C_{16}H_{19}F_3O_3$ requires C, 60.75; H, 6.05%. In addition to the above title compound mixture of the two diols (**51**), (**52**) (13%) and the aldehyde (**59**; Ar=*p*-MeC_6H_4) (4–6%) were isolated.

Reaction of the ketone (**6**) (1.00 g, 4.46 mmol) with *p*-tolyl magnesium bromide (2 equiv.) gave the starting material (30%), the ketone (**58**; R=Et, Ar=*p*-MeC_6H_4) (16%) in addition to the aldehyde (**59**; Ar=*p*-MeC_6H_4) (15%).

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