Pergamon

Tetrahedron 56 (2000) 10057–10066

TETRAHEDRON

Reaction of Benzyl Grignard Reagents with Trifluoroacetyldihydropyrans and Other Cyclic β-Alkoxy-α,β-Unsaturated Trifluoromethylketones

Simon J. Coles,[a] John M. Mellor,[a,*] Afaf H. El-Sagheer,[a] Ezz El-Din M. Salem[b] and Reda N. Metwally[c]

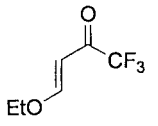
[a]*Department of Chemistry, University of Southampton, Southampton SO17 1BJ, UK*
[b]*Department of Chemistry, Faculty of Science, Suez Canal University, Ismailia, Egypt*
[c]*Department of Science and Maths, Faculty of Petroleum and Mining Engineering, Suez Canal University, Suez, Egypt*

Received 18 July 2000; revised 9 October 2000; accepted 12 October 2000

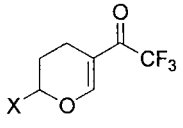
Abstract—Benzyl Grignard reagents react with cyclic β-alkoxy-α,β-unsaturated trifluoromethyl ketones by 1,2-addition to afford unsaturated allylic alcohols in high yield. The factors determining the balance between 1,2- and 1,4-addition to unsaturated ketones are discussed. The structures of major and minor products are established by single crystal X-ray diffraction studies.

Introduction

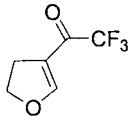
In an earlier paper[1] we have described the reaction of β-dialkylamino-α,β-unsaturated trifluoromethyl ketones and β-alkoxy-α,β-unsaturated trifluoromethyl ketones, such as the acyclic ketone (**1**) with Grignard reagents derived from alkyl and aryl halides. Reaction occurs by 1,4-addition followed by elimination to provide a route to α,β-unsaturated trifluoromethyl ketones. In an accompanying paper[2] we describe similar 1,4-additions to cyclic β-alkoxy-α,β-unsaturated trifluoromethyl ketones, where reaction takes a different course. With the ketones (**2**) and (**3**)[2] the major products are the *cis* adducts, although a minor pathway leads to subsequent ring opening. In the case of the substituted ketones (**4**) and (**5**) initial 1,4-addition at a low temperature permits the isolation of *cis* adducts, but the major pathway at higher temperatures occurs through ring opening to give a variety of products. We recognised that if the reaction of Grignard reagents derived from benzyl and allyl halides were to occur by 1,2-addition a route might be established to trifluoromethylnaphthalenes, based on subsequent dehydration and cyclisation by [3,3]benzannulation.[3] The successful outcome of this strategy is described in this and an accompanying paper,[4] where we report the reactions of a variety of Grignard reagents derived from substituted benzyl halides and the dehydration of the alcohol products to establish a new route to fluorinated substituted naphthalenes. Preliminary details[5] concerning this synthetic strategy have been communicated. In this paper we first review the factors determining the relative importance of 1,2- and 1,4-addition to α,β-unsaturated ketones. Then we describe the outcome of additions of Grignard reagents derived from allyl and benzyl halides to the ketones (**1**–**5**).



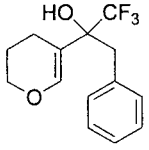
(**1**)



(**2**) X = H
(**4**) X = OMe
(**5**) X = OEt



(**3**)



(**6**)

The factors[6] determining the selectivity in 1,2- and 1,4-additions to a wide range of α,β-unsaturated carbonyl compounds have received much attention and in particular asymmetric conjugate additions[7] have been developed. The hard acid soft base concepts have been used to permit the generalisations[8–10] that among organometallic reagents, organolithiums, which are hard nucleophiles, react by 1,2-addition, and organocopper reagents, which are softer

Keywords: additions; Grignard reagents; trifluoromethylketones.
* Corresponding author. Tel.: +238059-2392; fax: +238059-6805; e-mail: jmm4@soton.ac.uk

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00976-5

Table 1. Crystal data and refinement. (All data were collected on a Nonius KappaCCD equipped with a Nonius FR591 molybdenum ($\lambda_{(Mok\alpha)}$=0.71069 Å) rotating anode. Absorption corrections were performed by comparison of multiply measured and symmetry equivalent reflections, using Sortav.[34] The structures were solved by direct methods (SHELXS-97[35]) and then subjected to full-matrix least squares refinement based on F_o^2 (SHELXL-97[35]). Non-hydrogen atoms were refined anisotropically with hydrogens included in idealised positions (C–H distance=0.97 Å) with isotropic thermal parameters riding on those of the parent atom. The weighting scheme used was $w=1/[\sigma^2(F_o^2)]$. Data have been deposited with the Cambridge Crystallographic Data Centre, deposition numbers: CCDC 146994–146997.)

Compound	(**9**)	(**14**)	(**17**)	(**21**)
Formula	$C_{16}H_{19}F_3O_3$	$C_{19}H_{18}F_6O_4$	$C_{15}H_{17}F_3O_3$	$C_{16}H_{17}F_3O_2$
Formula weight	316.31	424.33	302.29	298.3
T, K	150	150	150	293
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$ (# 2)	$C2/c$ (#15)	$C2/c$ (# 15)	$P2_1/c$ (# 14)
a (Å)	8.2480(7)	21.241(4)	20.426(4)	9.2288(18)
b (Å)	10.7247(9)	16.179(3)	5.5841(11)	20.362(4)
c (Å)	19.0148(18)	10.732(2)	25.536(5)	7.6375(15)
α (°)	80.429(5)	90.0	90.0	90.0
β (°)	88.947(5)	92.64(3)	93.05(3)	91.0(3)
γ, (°)	71.679(5)	90.0	90.0	90.0
V (Å^3)	1573.5(2)	3684.2(12)	2908.6(10)	1435.0(5)
Z	2	8	8	4
μ, mm^{-1}	0.114	0.145	0.12	1.381
Reflections measured	12744	14329	15308	13593
Unique reflections	4495	4175	3306	3244
R_{int}	0.1345	0.0656	0.0734	0.0734
R/wR_2 [$F^2>2\sigma(F^2)$]	0.0566/0.0892	0.0499/0.1236	0.0491/0.1236	0.0571/0.1599
R/wR_2 (F^2), all data	0.1592/0.1165	0.1220/0.1579	0.1169/0.1587	0.0860/0.1774

nucleophiles, react by 1,4-addition. Grignard reagents were seen to lie somewhere between.[11,12] Since then there have been major advances in explaining the selectivity of these additions. In reactions which proceed by kinetic control with organometallic reagents having a highly localised negative charge, a charge controlled 1,2-addition[9] can be expected. In contrast, in additions of nucleophiles having charge delocalisation, where the reaction is frontier orbital controlled, a 1,4-addition[9] is expected. However other factors, notably steric-[6] and solvent-effects and the nature of the nucleophile, disturb these simple generalisations. In particular the nature of the α,β-unsaturated carbonyl compound influences[12–22] the 1,2 to 1,4-ratio, but in the limited known examples[1,22] obtained with acyclic trifluoromethyl ketones having a β-alkoxy substituent or a β-dialkylamino substituent, 1,4-additions have been reported. Early results of additions to β-ionone[23] established that benzyl magnesium chloride and methyl magnesium bromide added by 1,2-addition in 82 and 83% yield, respectively, but there are other examples[24] where benzyl magnesium bromide reacts preferentially by 1,4-addition. The ratio of 1,2- to 1,4-addition by benzyl Grignard reagents is partly determined[16] by the nature of X in $PhCH_2MgX$, but benzyl Grignard reagents are very reactive,[25] prone to self coupling[26] and likely to produce other side-products.[27] Allyl Grignard reagents react[28] relatively cleanly with unsaturated ketones by 1,2-addition. The unusual pattern of reactivity of benzyl and allyl Grignard reagents is also observed[29–32] in additions to dithioesters where allylic and benzylic reagents attack at carbon. Such differences have been attributed by Fukui et al.[31] to the relative importance of a frontier orbital control. In this paper we show that benzyl Grignard reagents add to the ketones (**2**–**5**) by 1,2-addition, a process favoured[31] by charge control. Under the same conditions, alkyl and aryl Grignard reagents add by 1,4-addition, a process favoured by orbital control.

Results and Discussion

The ketone (**2**) was reacted with 4 equiv. of benzyl magnesium bromide in ether to give the product of 1,2-addition (**6**), which was isolated in 93% yield. By contrast, in reaction of ketone (**2**) with phenyl magnesium bromide, we have established that 88% of the products occur from 1,4-addition and very little 1,2-addition is observed. The ketones (**4**) and (**5**) behaved in a similar manner. The former (**4**) gave the two alcohols (**7**) and (**8**) in 34 and 61% yields, respectively, and the latter (**5**) gave the alcohols (**9**) and (**10**) in 33 and 65% yields, respectively. The nature of the products was insensitive to the number of equivalents of Grignard reagent, which were used. Addition to ketone (**3**) was less selective. The alcohol (**11**), the product of 1,2-addition was obtained in 34% yield, and the two products of 1,4-addition, (**12**) and (**13**), were obtained in 31 and 30% yield, respectively. In probing the lack of selectivity in reaction of ketone (**3**), further reactions using 1.2 and 2 equiv. of benzyl magnesium bromide were studied. The former conditions afforded the above three products in lower yields, but produced a fourth product, the spirocycle (**14**) and the same four products were observed using the latter conditions. A single crystal X-ray analysis of the major isomer (**10**) (see Table 1), obtained from the ketone (**5**) confirmed a product of 1,2-addition. The second diastereoisomeric alcohol (**9**) obtained from ketone (**5**) was characterised by spectral comparison with alcohol (**10**). Similarly the assignment of structures of the diastereoisomeric pair (**7**) and (**8**) was made by spectral comparison. As expected the major isomers (**8**) and (**10**) have a common stereochemical relationship. The structures of the products (**6**), obtained from the ketone (**2**), and (**11**), obtained from ketone (**3**), are readily confirmed to be products of 1,2-addition by spectral comparison with the products from the ketones (**4**) and (**5**).

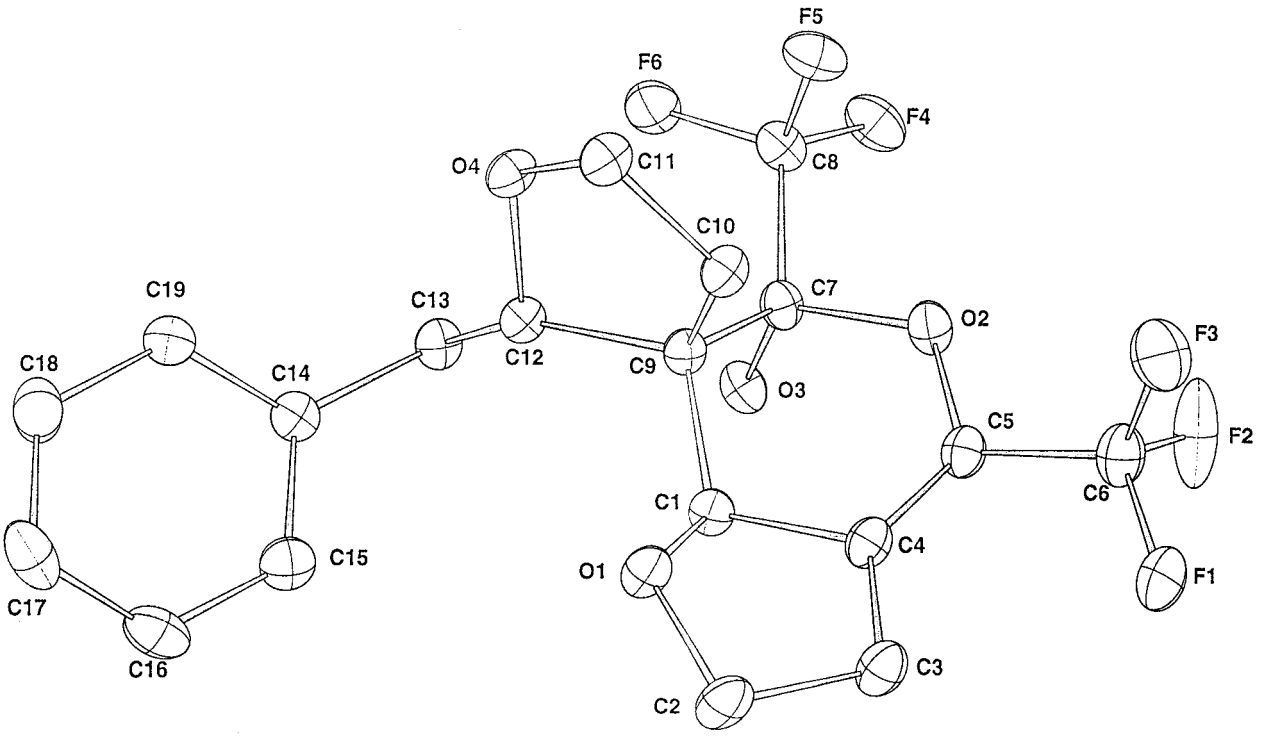
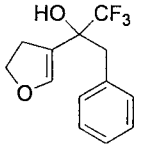


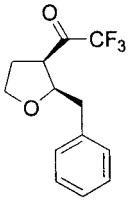
Figure 1.

(**7**) X = OMe
(**9**) X = OEt

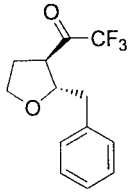
(**8**) X = OMe
(**10**) X = OEt



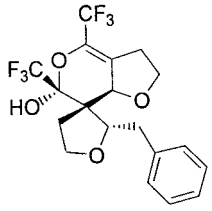
(**11**)



(**12**)



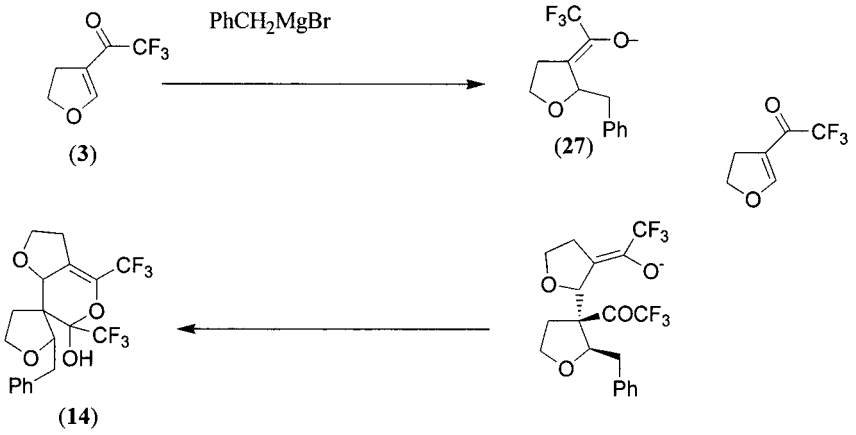
(**13**)



(**14**)

Assignment of the structures to three further products from reaction of ketone (**3**) was less easy. The minor product, the spirocycle (**14**), required a single crystal X-ray analysis (see Fig. 1 and Table 1). The spectra of the two saturated ketones (**12**) and (**13**), the products of 1,4-addition, can be compared with the spectra for other products of 1,4-addition reported[2] in the accompanying paper. Their similarity confirms that products of 1,4-addition are obtained from ketone (**3**), in agreement with the origin of the minor product, the spirocycle (**14**). Assignment of relative stereochemistry, based on coupling constant data in a disubstituted tetrahydrofuran, is less reliable than the assignment in a disubstituted tetrahydropyran. We are unable to assign the stereochemistry of isomers (**12**) and (**13**) based on observation of the 2,3-coupling constants. The two isomers are formed in similar yields reflecting the easy *cis* to *trans* isomerisation of 3-acyl-2-substituted terahydrofurans.[33]

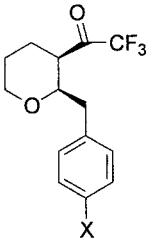
The above results differ from those reported in the accompanying paper[2] in a number of respects. Most notable is the dominance of 1,2-addition with benzyl magnesium bromide. A second feature is the different behaviour of the ketone (**3**) by comparison with the ketones (**2**) and (**4**,**5**). Not only is 1,2-addition the minor pathway from ketone (**3**), but in contrast to the results of 1,4-addition to ketone (**2**), which establish that formation of *cis* products is highly stereoselective, ketone (**3**) affords the two products of 1,4-addition (**12**) and (**13**) unselectively. Finally only from ketone (**3**) is a more complex by-product observed. The 1,2-addition described above has been used with substituted benzyl Grignard reagents to afford, as described in the accompanying paper,[4] a general route to intermediate



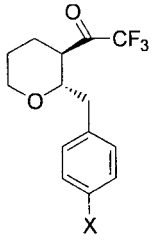
Scheme 1.

1,2-adducts and hence to substituted naphthalenes. However in establishing the generality of the 1,2-addition, we have observed surprising solvent effects.

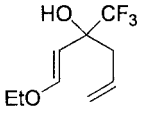
Reaction of benzyl magnesium bromide with the ketone (**2**) in tetrahydrofuran–ether (2:1), rather than ether, afforded mainly the two products of 1,4-addition (**15**) and (**16**) as oils in 46 and 18% yield, respectively; similar results were obtained in neat tetrahydrofuran in the absence of ether. Under the former conditions, *p*-methoxybenzyl magnesium bromide afforded mainly the crystalline 1,4-adducts (**17**) and (**18**) in 50 and 14% yield, respectively. Through a single crystal X-ray analysis of the structure of the adduct (**17**) (see Table 1), we have been able to assign unequivocally the *cis* structure to this adduct. The assignment of the *trans* structure to the second adduct (**18**) is based on spectroscopic comparison. We note that the two major products (**15**) and (**17**) are the *cis*adducts, which can partially epimerise[33] to give the more stable *trans* adducts (**16**) and (**18**). The unequivocal assignment of structures to the 1,4-adducts (**17**) and (**18**), based on X-ray analysis, confirms the structural assignments to the 1,4-adducts reported[2] in the accompanying paper.



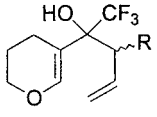
(**15**) X = H
(**17**) X = OMe



(**16**) X = H
(**18**) X = OMe

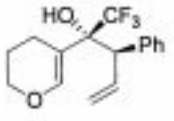


(**19**)

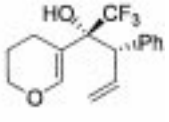


(**20**) R = H
(**23**) R = Me

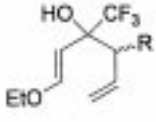
Reaction of allyl Grignard reagents, as expected,[28] occurred by 1,2-addition. Reaction of allyl magnesium bromide with the acyclic ketone (**1**) in ether gave the alcohol (**19**) in 81% yield. Similarly the cyclic ketone (**2**) gave the alcohol (**20**) in 82% yield. It has been well established by Santelli et al.[28] that reaction of allyl Grignard reagents normally occurs at the more substituted site. We find that the Grignard reagents from cinnamyl chloride and crotyl bromide react with ketone (**2**) in such a manner. In the former case the separable adducts (**21**) and (**22**) are obtained, and in the latter case an inseparable mixture of 1,2-adducts (**23**) is obtained. The structure of the minor crystalline adduct (**21**) was determined by a single crystal X-ray analysis (see Table 1). The Grignard reagents from cinnamyl chloride and crotyl bromide react with ketone (**1**) in a similar manner. An unselective addition of cinnamyl magnesium chloride to ketone (**1**) gives the alcohols (**24**) by 1,2-addition. Although one isomer was isolated as a crystalline solid, the relative configurations of the two isomers have not been defined. Crotyl magnesium bromide similarly affords the alcohols (**25**) in an unselective manner. An alternative procedure for allylation is use of indium. We find that the ketone (**3**) can be readily allylated to give the 1,2-adduct (**26**). Hence 1,2-additions with allyl magnesium halides to these fluorinated ketones occurs through a variety of methods.



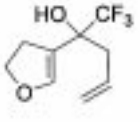
(**22**)



(**21**)



(**24**) R = Ph
(**25**) R = Me



(**26**)

Four aspects of the above results are noteworthy. The most striking observation is the contrast whereby isolation in high yield of 1,4-adducts from the ketone (**2**), as reported in the accompanying paper,[2] with alkyl and aryl Grignard reagents, may be compared with the results in this paper.

Here we observe formation of 1,2-adducts from reaction of ketone (**2**) with benzyl magnesium bromide under identical conditions. The difference can be explained as a spectacular example of frontier orbital control in the former case and charge control in the latter case. However our observation that reactions conducted in tetrahydrofuran follow a different reaction pathway from those in ether suggests that the precise nature of the species responsible for nucleophilic attack is solvent dependent, and hence an interpretation based on charge and frontier orbital controls must be viewed with caution. The difference in behaviour between ketones (**2**) and (**3**) is also noteworthy. The 1,2-pathway is dominant for reaction of ketone (**2**), but the 1,4-pathway is dominant for reaction of ketone (**3**) with benzyl magnesium bromide. Such a difference is not easily explained by an analysis limited to frontier orbital and charge considerations. The observation of the *trans* product (**13**) in the furan series can be attributed to a more favoured equilibration from the kinetically favoured *cis* adduct (**12**) relative to the pyran series. A more rapid equilibration in the five-membered ring is to be expected.[33] Finally the origin of the minor product (**14**) is explained in Scheme 1. 1,4-Addition gives the enolate anion (**27**), which in the presence of the unreacted ketone (**3**) undergoes a further 1,4-addition. In this addition the new carbon–carbon bond is selectively formed on the opposite face to that of the benzyl group. A further cyclisation then affords the spirocyclic hemiketal product (**14**).

The route, by 1,2-addition of benzyl Grignard reagents to ketones (**2**) and (**3**), has been used by us to afford a series of substituted naphthalenes.[4] The addition of benzyl Grignard reagents gives products of 1,2-addition in high yield, in marked contrast to the 1,4-additions of aryl Grignard reagents. These differences might be attributed to the relative importance of charge control and frontier orbital effects. However the observation that a change of solvent from ether to tetrahydrofuran completely alters a reaction pathway emphasises that a more detailed analysis of the factors controlling the pathways of reactions reported in this paper is still required.

Experimental

General procedures are described elsewhere.[1]

2-(3,4-Dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-3-phenyl-2-propanol (6). To a 100 ml round bottomed flask (with an addition funnel, magnetic stirrer bar and reflux condenser carrying a calcium chloride tube), magnesium turnings (0.54 g, 22.22 mmol), dry ether (4.0 ml) and a crystal of iodine were added. A few drops of benzyl bromide (3.80 g, 22.22 mmol) in dry ether (4.0 ml) were added dropwise, and the solution was stirred until the formation of the Grignard reagent. The remainder of the benzyl bromide was diluted with dry ether (8.0 ml) and the solution was added at such a rate to maintain gentle reflux. After the complete addition of the benzyl bromide, the reaction mixture was refluxed with stirring on a warm water bath for 10 min. The reaction mixture was cooled and a solution of the ketone (**2**) (1.00 g, 5.55 mmol) in dry ether (4.0 ml) was added dropwise. The reaction mixture was stirred for 30 min, heated 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), 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 (**6**) as a pale yellow oil (1.40 g, 93%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.32 (3H, m, Ph–H), 7.20 (2H, m, Ph–H), 6.48 (1H, s, H-6), 3.92 (2H, m, H-2), 3.11 (2H, s, CH_2–Ph), 2.12 (2H, m, H-4), 2.02 (1H, s, OH), 1.85 (2H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.6 (C-6), 133.8 (C′-1), 130.8, 128.5 and 127.5 (Ph–C), 125.9 (q, J_{C-F}=287.1 Hz, CF_3), 108.1 (C-5), 76.7 (C–CF_3), 65.5 (C-2), 39.1 (CH_2–Ph), 21.9 (C-3), 20.8 (C-4); ν_{max} (film, cm^{-1}) 3550–3200 (OH), 1658 (C=C); LRMS (Scan AP$^+$): *m*/*z*=255 (M^+−OH, 62%), 203 (M^+−CF_3, 100); HRMS (CI$^+$): (M^++NH_4) found 290.1344, $C_{14}H_{15}F_3O_2$ requires 290.1368.

Reaction of ketone (**2**) was repeated under the above conditions but using benzyl magnesium bromide (2 equiv.) to give the alcohol (**6**) in 79% yield.

Reaction of benzyl magnesium bromide with 2,2,2-trifluoro-1-(2-ethoxy-3,4-dihydro-2*H*-5-pyranyl)-1-ethanone (5). Following the above procedure, ketone (**5**) (1.00 g, 4.46 mmol) was reacted with benzyl magnesium bromide and the two isomeric products (**9**) and (**10**) were separated by flash column chromatography [silica gel, hexane/ethyl acetate (95:5)] to give as the minor product **(2*SR*,2′*SR*)-1,1,1-trifluoro-2-(2-ethoxy-3,4-dihydro-2*H*-5-pyranyl)-3-phenyl-2-propanol (9)** as a pale yellow oil (0.47 g, 33%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.21 (3H, m, Ph–H), 7.12 (2H, m, Ph–H), 6.29 (1H, s, H-6), 4.93 (1H, dd, *J*=3.7, 2.2 Hz, H-2), 3.72 (1H, dq, 11.8, 7.4 Hz, CH_2CH$_3$), 3.49 (1H, dq, 11.8, 7.0 Hz, CH_2CH$_3$), 3.08 (1H, d, *J*=13.8 Hz, CH_2Ph), 2.95 (1H, d, *J*=13.8 Hz, CH_2Ph), 2.24 (1H, m, H-4), 2.04 (1H, m, H-4), 1.90–1.68 (3H, complex, OH, H-3), 1.18 (3H, t, *J*=7.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=141.7 (C-6), 133.35 (C′-1), 130.9, 128.5 and 127.6 (Ph–C), 125.9 (q, J_{C-F}=287.1 Hz, CF_3), 109.0 (C-5), 96.2 (C-2), 76.7 (q, J_{C-F}=28.3 Hz, C–CF_3), 63.7 (CH_2CH_3), 38.4 (CH_2–Ph), 26.4 (C-3), 17.4 (C-4), 15.3 (CH_2CH_3); ν_{max} (CH_2Cl_2, cm^{-1}) 3563 (OH), 1660 (C=C); LRMS (Scan AP$^+$): *m*/*z*=299 (M^+−OH, 100%), 247 (M^+−CF_3, 51); HRMS (CI$^+$): (M^++NH_4) found 334.1635, $C_{16}H_{19}F_3O_3$ requires 334.1630. **(2*SR*,2′*RS*)-1,1,1-Trifluoro-2-(2-ethoxy-3,4-dihydro-2*H*-5-pyranyl)-3-phenyl 2-propanol (10)** was isolated as the major product as a low mp white solid (0.91 g, 65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.22 (3H, m, Ph–H), 7.12 (2H, m, Ph–H), 6.29 (1H, d, *J*=2.2 Hz, H-6), 4.90 (1H, t, *J*=2.9 Hz, H-2), 3.72 (1H, dq, 11.0, 7.0 Hz, CH_2CH$_3$), 3.48 (1H, dq, 11.0, 7.4 Hz, CH_2CH$_3$), 3.04 (2H, s, CH_2Ph), 2.13 (1H, m, H-4), 1.97 (2H, complex, OH, H-4), 1.82 (1H, m, H-3), 1.61 (1H, m, H-3), 1.11 (3H, t, *J*=7.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=141.0 (C-6), 133.8 (C′-1), 130.8, 128.5 and 127.5 (Ph–C), 109.2 (C-5), 95.9 (C-2), 76.9 (C–CF_3), 63.6 (CH_2CH_3), 39.4 (CH_2–Ph), 26.1 (C-3), 16.9 (C-4), 15.3 (CH_3), ν_{max} (film, cm^{-1}) 3500–3200 (OH), 1662 (C=C); LRMS (Scan AP$^+$): *m*/*z*=299 (M^+−OH, 20%), 247 (M^+−CF_3, 37); HRMS (CI$^+$): (M^++NH_4)

found 334.1625, $C_{16}H_{19}F_3O_3$ requires 334.1630. The structure of alcohol (**10**) has been established by an X-ray diffraction study (see Table 1). The reaction of the ethoxy ketone (**5**) was repeated using benzyl magnesium bromide (2 equiv.) to give the alcohol (**9**) (31%) and the alcohol (**10**) (60%).

Reaction of benzyl magnesium bromide with 2,2,2-trifluoro-1-(2-methoxy-3,4-dihydro-2*H*-5-pyranyl)-1-ethanone (4). Following the above procedure the ketone (**4**) (1.0 g, 4.76 mmol) was reacted with benzyl magnesium bromide and the two isomeric products (**7**) and (**8**) were separated by flash column chromatography [silica gel, hexane/ethyl acetate (95:5)] to give as the minor product **(2*SR*,2′*SR*)-1,1,1-trifluoro-2-(2-methoxy-3,4-dihydro-2*H*-5-pyranyl)-3-phenyl-2-propanol (7)** as a white solid (0.49 g, 34%), which was crystallised from petroleum ether to give white crystals mp: 46–47°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.22 (3H, m, Ph–H), 7.13 (2H, m, Ph–H), 6.26 (1H, s, H-6), 4.82 (1H, t, *J*=3.0 Hz, H-2), 3.35 (3H, s, C*H*$_3$), 3.08 (1H, d, *J*=14.0 Hz, C*H*$_2$Ph), 2.93 (1H, d, *J*=14.0 Hz, C*H*$_2$Ph), 2.19 (1H, m, H-4), 2.04 (1H, dt, *J*=16.2, 5.2, 5.2 Hz, H-4), 1.88–1.66 (3H, complex, OH, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=141.4 (C-6), 133.25 (C′-1), 131.0, 128.5 and 127.6(Ph–C), 125.9 (q, J_{C-F}= 287.1 Hz, *C*F$_3$), 109.25 (C-5), 97.3 (C-2), 55.6 (OCH$_3$), 38.55 (*C*H$_2$–Ph), 26.2 (C-3), 17.1 (C-4); ν_{max} (film, cm^{-1}) 3550–3250 (OH), 1664 (C=C); LRMS (Scan AP$^+$): *m*/*z*=285 (M$^+$−OH, 84%), 233 (M$^+$−CF$_3$, 100); HRMS (CI$^+$): (M$^+$+NH$_4$) found 320.1473, $C_{15}H_{17}F_3O_3$ requires 320.1473; Found C, 59.64; H, 5.79. $C_{15}H_{17}F_3O_3$ requires C, 59.60; H, 5.67%. **(2*SR*,2′*RS*)-1,1,1-trifluoro-2-(2-methoxy-3,4-dihydro-2*H*-5-pyranyl)-3-phenyl-2-propanol (8)** was isolated as the major product as a white solid (0.89 g, 61%) and was recrystallised from petroleum ether to give white crystals mp 69–70°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.32 (3H, m, Ph–H), 7.20 (2H, m, Ph–H), 6.36 (1H, d, *J*=2.2 Hz, H-6), 4.89 (1H, t, *J*=2.9 Hz, H-2), 3.45 (3H, s, OC*H*$_3$), 3.13 (2H, s, C*H*$_2$Ph), 2.30–2.11 (2H, complex, OH, H-4), 2.06 (1H, m, H-4), 1.91 (1H, m, H-3), 1.66 (1H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=140.8 (C-6), 133.9 (C′-1), 130.8, 128.5 and 127.5 (Ph–C), 125.8 (q, J_{C-F}= 287.1 Hz, *C*F$_3$), 109.4 (C-5), 97.2 (C-2), 77.1 (C–CF$_3$), 55.7 (O*C*H$_3$), 39.4 (*C*H$_2$–Ph), 25.8 (C-3), 16.65 (C-4); ν_{max} (CH_2Cl_2, cm^{-1}) 3566 (OH), 1661 (C=C); LRMS (Scan AP$^+$): *m*/*z*=285 (M$^+$−OH, 56%), 233 (M$^+$−CF$_3$, 100); HRMS (CI$^+$): (M$^+$+NH$_4$) found 320.1473, $C_{15}H_{17}F_3O_3$ requires 320.1473. Found C, 59.65; H, 5.62. $C_{15}H_{17}F_3O_3$ requires C, 59.60; H, 5.67%. The reaction of the methoxy ketone (**4**) was repeated using benzyl magnesium bromide (2 equiv.) to give the alcohol (**7**) (32%) and the alcohol (**8**) (56%).

Reaction of 1-(4,5-dihydro-3-furanyl)-2,2,2-trifluoro-1-ethanone (3) with benzyl magnesium bromide. Following the above procedure the ketone (**3**) (1.00 g, 6.02 mmol) was reacted with benzyl magnesium bromide and gave a brown oil which was purified by flash column chromatography [silica gel, hexane/ethyl acetate (90:10)] to give an alcohol (**11**) and the two isomeric ketones (**12**) and (**13**). **2-(4,5-Dihydro-3-furanyl)-1,1,1-trifluoro-3-phenyl-2-propanol (11)** was isolated as a white solid (0.53 g, 34%) and was recrystallised from petroleum ether mp 95–96°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.21 (3H, m, Ph–H), 7.14 (2H, m, Ph–H), 6.15 (1H, t, *J*=2.0 Hz, H-2), 4.30 (2H, t, *J*=9.6 Hz, H-5), 3.06 (1H, d, *J*=14.0 Hz, C*H*$_2$–Ph), 2.96 (1H, d, *J*=14.0 Hz, C*H*$_2$–Ph), 2.60 (2H, m, H-4), 2.11 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=146.2 (C-2), 133.7 (C′-1), 130.8, 128.6 and 127.6 (Ph–C), 125.75 (q, J_{C-F}= 287.1 Hz, *C*F$_3$), 111.9 (C-3), 75.35 (*C*–CF$_3$), 71.1 (C-5), 39.6 (*C*H$_2$–Ph), 30.3 (C-4); ν_{max} (CH_2Cl_2, cm^{-1}) 3566 (OH), 1654 (C=C); LRMS (Scan AP$^+$): *m*/*z*=241 (M$^+$− OH, 27%), 189 (M$^+$−CF$_3$, 100); HRMS (CI$^+$): (M$^+$+NH$_4$) found 276.1210, $C_{13}H_{13}F_3O_2$ requires 276.1211. Found C, 60.54; H, 4.92. $C_{13}H_{13}F_3O_2$ requires C, 60.46; H, 5.07%. **2,2,2-Trifluoro-1-(2-benzyltetrahydro-3-furanyl)-1-ethanone (12)** was isolated as a pale yellow oil (0.48 g, 31%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.32–6.97 (5H, complex, Ph), 4.38 (1H, ddd, *J*=9.0, 7.4, 4.4 Hz, H-2), 4.08 (1H, m, H-5), 3.72 (1H, dd, *J*=16.2, 7.4 Hz, H-5), 3.58 (1H, q, *J*=7.4 Hz, H-3), 2.71 (1H, dd, *J*=13.8, 8.8 Hz, C*H*$_2$Ph), 2.58 (1H, dd, J=13.8, 4.4 Hz, C*H*$_2$Ph), 2.19 (2H, m, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.7 (q, J_{C-F}=35.0 Hz, C=O), 137.7 (C′-1), 129.3, 128.7 and 126.9 (Ph–C), 115.5 (q, J_{C-F}=292.2 Hz, *C*F$_3$), 81.7 (C-2), 67.2 (C-5), 48.1 (C-3), 37.5(*C*H$_2$Ph), 29.75 (C-4); ν_{max} (CH_2Cl_2, cm^{-1}) 1755 (C=O); LRMS (Scan AP$^+$): *m*/*z*=258 (M$^+$, 5%), 257 (M$^+$−1, 15), 189 (M$^+$−CF$_3$, 71); HRMS (CI$^+$): (M$^+$+ NH$_4$) found 276.1224, $C_{13}H_{13}F_3O_2$ requires 276.1211. The isomer **2,2,2-trifluoro-1-(2-benzyltetrahydro-3-furanyl)-1-ethanone (13)** was isolated as a pale yellow oil (0.46 g, 30%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.44–7.08 (5H, complex, Ph), 4.46 (1H, dd, *J*=12.5, 6.6 Hz, H-2), 4.02 (1H, m, H-5), 3.88 (1H, dd, *J*=14.7, 7.4 Hz, H-5), 3.28 (1H, dt, *J*=9.6, 6.6, 6.6 Hz, H-3), 3.03 (1H, dd, *J*=14.0, 6.6 Hz, CH$_2$Ph), 2.90 (1H, dd, *J*=14.0, 5.9 Hz, C*H*$_2$Ph), 2.28 (1H, m, H-4), 2.11 (1H, m, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.7 (q, J_{C-F}=35.0 Hz, C=O), 137.0 (C′-1), 129.5, 128.7 and 127.0 (5C, Ph), 115.6 (q, J_{C-F}=292.2 Hz, *C*F$_3$), 81.8 (C-2), 68.00 (C-5), 49.7 (C-3), 40.7 (*C*H$_2$Ph), 30.85 (C-4); ν_{max} (CH_2Cl_2, cm^{-1}) 1757 (C=O); LRMS (Scan AP$^+$): *m*/*z*=258 (M$^+$, 13%), 257 (M$^+$−1, 57), 189 (M$^+$−CF$_3$, 58); HRMS (CI$^+$): (M$^+$+ NH$_4$) found 276.1207, $C_{13}H_{13}F_3O_2$ requires 276.1211.

Spiro[2-benzylfuran-3][furo-(2,3-d)][2,6-ditrifluoromethyl-2-hydroxy-3,4-dihydropyran] (14). The reaction of ketone (**3**) with benzyl magnesium bromide was repeated using benzyl magnesium bromide (1.2 equiv.) and gave the alcohol (**11**) (6%), a further product the spiro compound (**14**) (10%), the ketone (**12**) (7%) and the isomeric ketone (**13**) (10%). The reaction was also repeated using benzyl magnesium bromide (2 equiv.) and gave the alcohol (**11**) (18%), the spiro compound (**14**) (5%), the ketone (**12**) (18%) and the isomeric ketone (**13**) (26%). The title compound (**14**) was isolated as a white solid (0.26 g, 10%) and was recrystallised from petroleum ether to give white crystals mp 151–152°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.38–7.13 (5H, complex, Ph), 4.48 (1H, d, *J*=2.2 Hz, H″-2), 4.19 (1H, dt, *J*=8.1, 8.1, 5.1 Hz, H″-5), 4.10 (1H, t, *J*=6.6 Hz, H-2), 3.95 (2H, m, H-5, H″-5), 3.62 (1H, m, H-5), 3.12 (2H, d, *J*=6.6 Hz, CH$_2$Ph), 2.84 (2H, m, H″-4), 2.12 (1H, m, H-4), 1.97 (1H, m, H-4), 1.77 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=140.0 (C′-1), 129.2, 128.4 and 126.3 (Ph–C), 122.8 (*C*F$_3$), 82.3 (C-2), 73.9 (C″-2), 68.4 (C″-5), 65.2 (C-5), 35.2 (*C*H$_2$–Ph), 28.1 (C″-4), 25.8 (C-4);

ν_{max} (CH_2Cl_2, cm^{-1}) 3595, 3338 (OH); LRMS (Scan AP^+): *m/z*=258 ($M^+-(C_6H_5F_3O_2)$, 27%), 257 [(M^+-1) - ($C_6H_5F_3O_2$), 48], 189 [$M^+-(C_6H_5F_3O_2+CF_3)$, 58]; HRMS (CI^+): (M^++NH_4) found 442.1468, $C_{19}H_{18}F_6O_4$ requires 442.1453. The structure of alcohol (**14**) has been established by X-ray diffraction (see Fig.1 and Table 1).

Reaction of 1-(4,5-dihydro-3-furanyl)-2,2,2-trifluoro-1-ethanone (3) with benzyl lithium. To a mixture of toluene (3.55 g, 38.58 mmol) and TMEDA (1.0 g, 8.61 mmol), a solution of butyl lithium in hexanes (2.5 M/l) (4.35 ml, 10.88 mmol) was added dropwise under nitrogen. The reaction mixture was heated under gentle reflux for about 30 min (until all the gas evolution stopped) and the red solution allowed to cool to room temperature. The benzyl lithium was added dropwise via a syringe to a solution of the ketone (**3**) (0.85 g, 5.0 mmol) in ether (12.5 ml) kept in a liquid nitrogen bath. The reaction mixture was stirred for 30 min, allowed to warm to room temperature, diluted with ether (25.0 ml) and poured into saturated ammonium chloride solution (50 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 to give the alcohol (**11**) (0.39 g, 30%), which is described before.

Reaction of benzyl magnesium bromide with 1-(3,4-dihydro-2*H*-pyranyl)-2,2,2-trifluoro-1-ethanone (2) in tetrahydrofuran. Following the above general procedure for preparation of alcohol (**6**), reaction of benzyl magnesium bromide, in tetrahydrofuran, with ketone (**2**) (1.00 g, 5.55 mmol), in tetrahydrofuran, gave after chromatography [silica gel, hexane/ethyl acetate (90:10)] first the *trans*-2,2,2-trifluoro-1-(2-benzyltetrahydro-2*H*-3-pyranyl)-1-ethanone (**16**) as a colourless oil (0.11 g, 7%), which is described below and then the *cis*-2,2,2-trifluoro-1-(2-benzyltetrahydro-2*H*-3-pyranyl)-1-ethanone (**15**) as a colourless oil (0.56 g, 37%) which also is described below.

Reaction of benzyl magnesium halides in tetrahydrofuran-ether with 1-(3,4-dihydro-2*H*-pyranyl)-2,2,2-trifluoro-1-ethanone (2). To magnesium turnings (0.33 g, 13.58 mmol) in dry ether (34.00 ml) benzyl halide (10.0 mmol) dissolved in dry ether/tetrahydrofuran (1:1, 34 ml) was added dropwise at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 45 min and a solution of the ketone (**2**) (0.90 g, 5.00 mmol) in dry tetrahydrofuran (10.0 ml) was added dropwise at 0°C. The reaction mixture was stirred at room temperature for 1.5 h and was 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 a mixture of two isomeric ketones.

***cis*-2,2,2-Trifluoro-1-[2-(*p*-methoxybenzyl)tetrahydro-2*H*-3-pyranyl)-1-ethanone (17) and *trans*-2,2,2-trifluoro-1-[2-(*p*-methoxybenzyl)tetrahydro-2*H*-3-pyranyl)-1-ethanone (18).** Following the above procedure the ketone (**2**) was reacted with *p*-methoxybenzyl chloride and after chromatography gave first the *trans*-ketone (**18**) as a white solid (0.21 g, 14%) which was recrystallised from petroleum ether to give white crystals mp 41–42°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.12 (2H, d, *J*=8.7 Hz, Ar–H), 6.82 (2H, d, *J*=8.7 Hz, Ar–H), 3.99 (1H, m, H-6), 3.81 (4H, m, H-2, CH_3), 3.38 (1H, m, H-6), 2.93 (1H, m, H-3), 2.68 (1H, d, *J*=14.3 Hz, C*H*$_2$–Ar), 2.59 (1H, d, *J*=14.3 Hz, C*H*$_2$–Ar), 2.21 (1H, m, H-4), 1.73–1.58 (3H, complex, H-4, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=193.8 (C=O), 158.4 (C′-4), 130.45 (Ar–C), 129.9 (C′-1), 115.5 (q, J_{C-F}=292.7 Hz, *C*F_3), 113.8 (Ar–C), 78.65 (C-2), 68.0 (C-6), 55.3 (O*C*H_3), 48.5 (C-3), 39.9 (*C*H_2–Ar), 28.2 (C-4), 24.7 (C-5); ν_{max} (CH_2Cl_2, cm^{-1}) 1754 (C=O); LRMS (Scan AP^+): *m/z*=303 [(M^++1), 12%], 302 (M^+, 100);. Found C, 59.76; H, 5.61. $C_{15}H_{17}F_3O_3$ requires C, 59.60; H, 5.67%. The *cis*-ketone (**17**) was isolated after chromatography as a white solid (0.75 g, 50%) and was recrystallised from petroleum ether to give white crystals mp 55–56°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.09 (2H, d, *J*=8.5 Hz, Ar–H), 6.85 (2H, d, *J*=8.5 Hz, Ar–H), 4.08 (1H, m, H-6), 3.82–3.73 (4H, complex, CH_3 and H-2), 3.48 (1H, dt, *J*=11.0, 11.0, 2.9 Hz, H-6), 3.08 (1H, m, H-3), 2.95 (1H, dd, *J*=14.2, 8.3 Hz, C*H*$_2$–Ar), 2.61 (1H, d, *J*=14.2, 6.0 Hz, C*H*$_2$–Ar), 2.14 (1H, m, H-4), 1.91 (1H, m, H-4), 1.73 (1H, m, H-5), 1.48 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.7 (C=O), 158.5 (C′-4), 129.7 (C′-1), 130.2 (Ar–C), 115.3 (q, J_{C-F}=293.9 Hz, *C*F_3), 114.1 (Ar–C), 78.8 (C-2), 67.7 (C-6), 55.4 (O*C*H_3), 43.3 (C-3), 38.0 (*C*H_2–Ar), 25.05 (C-4), 21.6 (C-5); ν_{max} (CH_2Cl_2, cm^{-1}) 1753 (C=O); LRMS (Scan AP^+): *m/z*=303 [(M^++1), 13%], 302 (M^+, 100), 285 (M^+-OH, 13), 232 [(M^+-1)–CF_3, 9]. Found C, 59.65; H, 5.47. $C_{15}H_{17}F_3O_3$ requires C, 59.60; H, 5.67%. The structure of ketone (**17**) has been established by X-ray diffraction (see Table 1).

***cis*-2,2,2-Trifluoro-1-(2-benzyltetrahydro-2*H*-3-pyranyl)-1-ethanone (15) and *trans*-2,2,2-trifluoro-1-(2-benzyltetrahydro-2*H*-3-pyranyl)-1-ethanone (16).** Following the above procedure the ketone (**2**) was reacted with benzyl bromide and after chromatography gave first the *trans*-ketone (**16**) as a colourless oil (0.24 g, 18%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.38–7.13 (5H, complex, Ph–H), 4.0 (1H, m, H-6), 3.9 (1H, ddd, *J*=10.0, 6.6, 5.2 Hz, H-2), 3.39 (1H, m, H-6), 3.0 (1H, m, H-3), 2.79 (1H, d, *J*=14.0 Hz, C*H*$_2$Ph), 2.69 (1H, d, *J*=14.0 Hz, C*H*$_2$Ph), 2.23 (1H, m, H-4), 1.79–1.57 (3H, complex, H-4, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ=193.7 (q, J_{C-F}=35.0 Hz, C=O), 137.9 (C′-1), 129.5, 128.4 and 126.7 (Ph–C), 115.5 (q, J_{C-F}=292.7 Hz, *C*F_3), 78.5 (C-2), 68.0 (C-6), 48.6 (C-3), 40.8 (*C*H_2Ph), 28.2 (C-4), 24.65 (C-5); ν_{max} (film, cm^{-1}) 1753 (C=O); LRMS (Scan AP^+): *m/z*=272 (M^+, 28%), 271 [(M^+-1), 74], 203 [(M^+-CF_3), 61]; HRMS (CI^+): (M^++1) found 273.1103, $C_{14}H_{15}F_3O_2$ requires 273.1102. The *cis*-ketone (**15**) was isolated as a colourless oil (0.63 g, 46%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.40–7.10 (5H, complex, Ph–H), 4.08 (1H, m, H-6), 3.85 (1H, ddd, *J*=8.1, 5.9, 3.0 Hz, H-2), 3.49 (1H, dt, 11.0, 11.0, 2.9 Hz, H-6), 3.08 (1H, m, H-3), 3.05 (1H, dd, *J*=14.0, 8.1 Hz, C*H*$_2$Ph), 2.69 (1H, dd, *J*=14.0, 5.9 Hz, C*H*$_2$Ph), 2.15 (1H, m, H-4), 1.90 (1H, m, H-4), 1.76 (1H, m, H-5), 1.50 (1H, m, H-5); ^{13}C NMR (75 MHz, $CDCl_3$)

δ=191.6 (C=O), 137.7 (C′-1), 129.2, 128.7 and 126.8 (Ph–C), 115.3 (q, J_{C-F}=293.9 Hz, CF_3), 78.6 (C-2), 67.7 (C-6), 43.35 (C-3), 38.9 (CH_2Ph), 25.1 (C-4), 21.6 (C-5); ν_{max} (film, cm^{-1}) 1755 (C=O); LRMS (Scan AP^+): m/z=272 (M^+, 7%), 271 [(M^+-1), 23%], 255 (M^+-OH, 16), 203 [(M^+-CF_3), 100]; HRMS (CI^+): (M^++1) found 273.1091, $C_{14}H_{15}F_3O_2$ requires 273.1102.

(1*E*)-1-Ethoxy-3-(trifluoromethyl)-1,5-hexadien-3-ol (19). To magnesium turnings (1.0 g, 41.15 mmol) in dry ether (75.0 ml), allyl bromide (2.41 g, 20.0 mmol) 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 (**1**) (0.84 g, 5.00 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 (200 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 (95:5)] to give the title compound (**19**) as a colourless oil (0.85 g, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.68 (1H, d, J=12.5 Hz, H-1), 5.79 (1H, m, H-5), 5.23 (2H, m, H-6), 4.78 (1H, d, J=12.5 Hz, H-2), 3.78 (2H, q, J=7.0 Hz, CH_2CH_3), 2.52 (2H, m, H-4), 2.18 (1H, s, OH), 1.28 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=151.0 (C-1), 130.9 (C-5), 125.5 (q, J_{C-F}=284.8 Hz, CF_3), 121.25 (C-6), 100.2 (C-2), 74.1 (q, J_{C-F}=57.6 Hz, $C-CF_3$), 65.5 (CH_2CH_3), 40.2 (C-4), 14.7 (CH_2CH_3); ν_{max} (film, cm^{-1}): 3443–3350 (OH), 1656 (C=C); LRMS (Scan AP^+): m/z=211 [(M^++1), 36%), 193 [(M^+-OH), 53%], 141 [(M^+-CF_3), 100]; HRMS(CI^+): (M^++1) found 211.0946, $C_9H_{13}F_3O_2$ requires 211.0946.

2-(3,4-Dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-4-penten-2-ol (20). Following the above procedure the ketone (**2**) (0.9 g, 5.0 mmol) was reacted with allyl magnesium bromide to give the title compound (**20**) as a colourless oil (0.91 g, 82%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.71 (1H, s, H-6), 5.72 (1H, m, $CH=CH_2$), 5.25 (2H, m, $CH=CH_2$), 3.96 (2H, m, H-2), 2.65 (1H, dd, J=14.7, 6.6 Hz, $CH-CH_2$), 2.50 (1H, dd, J=14.7, 7.5 Hz, $CH-CH_2$), 2.3 (1H, d, J=4.4 Hz, OH), 2.08 (2H, m, H-4), 1.85 (2H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.7 (C-6), 130.75 ($CH=CH_2$), 125.7 (q, J_{C-F}=287.1 Hz, CF_3), 121.2 ($CH=CH_2$), 108.1 (C-5), 75.6 (q, J_{C-F}=28.3 Hz, $C-CF_3$), 65.5 (C-2), 37.8 (CH_2), 22.0 (C-3), 20.45 (C-4); ν_{max} film, cm^{-1}) 3550–3400 (OH), 1659 (C=C); LRMS (Scan AP^+): m/z=205 [(M^+-OH), 100%], 153 [(M^+-CF_3), 93]; HRMS (CI^+): (M^++NH_4) found 240.1216, $C_{10}H_{13}F_3O_2$ requires 240.1211.

Reaction of ketone (**2**) (1.0 g, 5.55 mmol) with allyl magnesium bromide (4 equiv.) in ether following the general procedure as described above for reaction of benzyl magnesium bromide with ketone (**2**) afforded after flash column chromatography [silica gel, hexane/ethyl acetate (95:5)] the title compound (**20**) in 67% yield.

Reaction of ketone (2) with cinnamyl magnesium chloride. To magnesium turnings (0.44 g, 18.1 mmol) in dry ether (1.5 ml), cinnamyl chloride (0.03 g, 0.20 mmol) was added and the reaction mixture was heated with vigorous stirring to initiate the reaction. A solution of the ketone (**2**) (1.00 g, 5.54 mmol) and the cinnamyl chloride (0.99 g, 6.48 mmol) in dry ether (3.0 ml) was added dropwise to maintain reflux. The reaction mixture was heated under reflux for 3 h, allowed to cool to room temperature and poured into cold saturated aqueous ammonium chloride (50 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 two alcohols (**21**) and (**22**). **2-(3,4-Dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-3-phenyl-4-penten-2-ol (21)** was first isolated as a white solid (0.51 g, 31%) and was recrystallised from petroleum ether, mp 89–90°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.43–7.12 (5H, complex, Ph–H), 6.86 (1H, s, H-6), 6.20 (1H, ddd, J=16.9, 10.2, 10.0 Hz, $CH=CH_2$), 5.12 (1H, d, J=10.2 Hz, $CH=CH_2$), 5.07 (1H, d, J=16.9 Hz, $CH=CH_2$), 3.98 (2H, m, H-2), 3.85 (1H, d, J=10.0 Hz, C*H*–Ph), 2.4 (1H, s, OH), 2.07 (2H, m, H-4), 1.85 (2H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.5 (C-6), 138.9 (C′–Ph), 135.9 ($CH=CH_2$), 129.3, 128.9 and 127.65 (Ph–C), 117.1 ($CH=CH_2$), 107.4 (C-5), 65.5 (C-2), 52.2 (*C*H–Ph), 22.0 (C-3), 20.3 (C-4); ν_{max} (CH_2Cl_2, cm^{-1}) 3564 (OH), 1651 and 1601 (C=C); LRMS (Scan AP^+): m/z=281 [(M^+-OH), 50%], 229 [(M^+-CF_3), 60]; Found C, 64.31; H, 5.62. $C_{16}H_{17}F_3O_2$ requires C, 64.42; H, 5.74%. The structure of alcohol (**21**) has been established by X-ray diffraction (see Table 1). **2-(3,4-Dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-3-phenyl-4-penten-2-ol (22)** was isolated as a colourless oil (0.96 g, 58%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.43–7.13 (5H, complex, Ph–H), 6.48 (1H, s, H-6), 6.31 (1H, m, $CH=CH_2$), 5.29 (1H, d, J=10.3,$CH=CH_2$), 5.13 (1H, d, J=16.9 Hz, $CH=CH_2$), 3.88 (1H, d, J=8.1,C*H*–Ph), 3.72 (2H, m, H-2), 2.48 (1H, s, OH), 1.91 (2H, m, H-4), 1.68 (1H, m, H-3), 1.38 (1H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.5 (C-6), 138.8 (C′–Ph), 135.45 ($CH=CH_2$), 129.4, 128.3 and 127.2 (Ph–C), 119.6 ($CH=CH_2$), 108.2 (C-5), 65.3 (C-2), 52.95 (*C*H–Ph), 21.7 (C-3), 20.5 (C-4); ν_{max} (CH_2Cl_2, cm^{-1}) 3562 (OH), 1650 and 1600 (C=C); LRMS (Scan AP^+): m/z=299 [(M^++1), 9%), 281 [(M^+-OH), 81%], 229 [(M^+-CF_3), 100]; HRMS (CI^+): (M^++1) found 299.1260, $C_{16}H_{17}F_3O_2$ requires 299.1259.

Reaction of ketone (2) with crotyl magnesium bromide. Following the method for the reaction of ketone (**1**) in preparation of alcohol (**19**) using allyl bromide, the ketone (**2**) (0.9 g, 5.0 mmol) was reacted with crotyl bromide (2.7 g, 20.0 mmol) and gave after chromatography [silica gel, hexane/ethyl acetate (95:5)] a mixture of the two isomeric alcohols **2-(3,4-dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-3-methyl-4-penten-2-ol (23)** as a colourless oil (1.12 g, 95%) (obtained as a 38:62% ratio); ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.76 (1H, s, H-6), 6.69 (1H, s, H-6), 5.99 (1H, m, $CH=CH_2$), 5.81 (1H, m, $CH=CH_2$), 5.22 (2H, m, $CH=CH_2$), 5.11 (2H, m, $CH=CH_2$), 3.98 (4H, m, H-2), 2.78 (2H, m, $CHCH_3$), 2.32–1.72 (8H, complex, H-4, H-3), 1.13 (3H, d, J=6, CH_3), 1.01 (3H, d, J=7, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=143.9 (C-6),

138.0 and 137.4 (*C*H=CH_2), 125.5 (CF_3), 117.8 and 116.5 (CH=*C*H_2), 107.8 (C-5), 65.5 (C-2), 40.9 and 39.15 (*C*H–CH_3), 22.1, 20.45 and 20.2 (C-3, C-4), 14.0 and 13.5 (CH_3); ν_{max} (film, cm^{-1}) 3500–3200 (OH), 1658 (C=C); LRMS (Scan AP^+): *m/z*=237 [(M^++1), 8%], 219 [(M^+−OH), 100], 167 [(M^+−CF_3), 99]. HRMS (CI^+) (M^++1) found 237.1095, $C_{11}H_{15}F_3O_2$ requires 237.1102.

Reaction of ketone (1) with cinnamyl magnesium chloride. Following the above procedure for the preparation of alcohols (**21**) and (**22**), the ketone (**1**) (0.93 g, 5.54 mmol) was reacted with cinnamyl magnesium chloride and gave after chromatography [silica gel, hexane/ethyl acetate (90:10)] a mixture of two isomeric alcohols (**24**) (0.95 g, 60%) (obtained as a 42:58% ratio), from which the more polar isomer was separated as a white solid. One isomer of **(1*E*)-1-Ethoxy-4-phenyl-3-(trifluoromethyl)-1,5-hexadien-3-ol (24)** was isolated as a white solid and was recrystallised from petroleum ether mp 65–66°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.43–7.18 (5H, complex, Ph), 6.62 (1H, d, *J*=12.5 Hz, H-1), 6.27 (1H, m, H-5), 5.28 (2H, m, H-6), 4.85 (1H, d, *J*=12.5 Hz, H-2), 3.77 (3H, m, H-4, C*H*$_2$$CH_3$), 2.29 (1H, d, *J*=1.5 Hz, OH), 1.29 (3H, m, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=151.1 (C-1), 138.35 (C′–Ph), 135.6 (C-5), 129.5, 128.4 and 127.4 (Ph–C), 120.0 (C-6), 98.75 (C-2), 65.6 (*C*$H_2$$CH_3$), 55.8 (C-4), 14.75 (*C*H_3); ν_{max} (film, cm^{-1}) 3600–3200(OH); LRMS (Scan AP^+): *m/z*=287 [(M^++1), 5%), 269 [(M^+−OH), 100], 217 [(M^+−CF_3), 100]; HRMS (CI^+): (M^++1) found 287.1266, $C_{15}H_{17}F_3O_2$ requires 287.1259; Found C, 62.65; H, 5.77. $C_{15}H_{17}F_3O_2$ requires C, 62.93; H, 5.99%.

Reaction of ketone (1) with crotyl magnesium bromide. Following the method for the reaction of ketone (**1**) with allyl bromide, the ketone (**1**) (0.84 g, 5.0 mmol) was reacted with crotyl bromide (2.7 g, 20.0 mmol) and gave after chromatography [silica gel, hexane/ethyl acetate (90:10)] a mixture of two isomeric alcohols **(1*E*)-1-ethoxy-4-methyl-3-(trifluoromethyl)-1,5-hexadien-3-ol (25)** as a colourless oil (1.11 g, 99%) (obtained as a 50:50% ratio). ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.56 (2H, m, H-1), 5.70 (2H, m, H-5), 5.05 (4H, m, H-6), 4.77 (2H, m, H-2), 3.70 (4H, m, C*H*$_2$$CH_3$), 2.54 (2H, m, H-4), 2.17 (2H, s, OH), 1.19 (6H, m, CH_3), 0.97 (6H, m, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=151.2 and 150.8 (C-1), 138.05 and 137.9 (C-5), 125.8 (CF_3), 118.5 and 117.3 (C-6), 98.5 and 98.0 (C-2), 65.7 and 65.5 (*C*$H_2$$CH_3$), 44.7 and 43.7 (C-4), 15.2, 14.75 and 14.3 (CH_3); ν_{max} (film, cm^{-1})=3500–3150 (OH), 1655 (C=C); LRMS (Scan AP^+): *m/z*=225 [(M^++1), 11%), 207 [(M^+−OH), 78], 178 [(M^+−C_2H_5OH), 9], 155 [(M^+−CF_3), 100]; HRMS (CI^+): (M^++1) found 225.1103, $C_{10}H_{15}F_3O_2$ requires 225.1102.

Reaction of the ketone (3) with allyl bromide and indium. To a mixture of the ketone (**3**) (0.5 g, 3.01 mmol), water (23 ml) and tetrahydrofuran (7.8 ml), indium powder (0.5 g, 4.36 mmol) and allyl bromide (0.84 g, 6.94 mmol) were added at room temperature. The reaction mixture was stirred for 3 h, filtered through a pad of alumina and washed with dichloromethane, extracted with dichloromethane and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a colourless oil, which was purified by flash column chromatography [silica gel, petroleum ether/ethyl acetate (90:10)] to afford as a colourless oil (0.28 g, 45%) **2-(4,5-dihydro-3-furanyl)-1,1,1-trifluoro-4-penten-2-ol (26)** ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.39 (1H, t, *J*=2.2 Hz, H-2), 5.70 (1H, m, C*H*=CH_2), 5.18 (2H, m, CH=C*H*$_2$), 4.35 (2H, t, *J*=9.6 Hz, H-5), 2.65 (2H, m, H-4), 2.50 (2H, d, *J*=7.4 Hz, CH–C*H*$_2$) 2.35 (1H, s, OH) ^{13}C NMR (75 MHz, $CDCl_3$) δ=146.1 (C-2), 130.6 (*C*H=CH_2), 125.45 (q, J_{C-F}=286.0 Hz, *C*F_3), 121.2 (CH=*C*H_2), 111.7 (C-3), 74.1 (q, J_{C-F}=29.4 Hz, C–CF_3), 71.1 (C-5), 38.3 (CH-*C*H_2), 29.8 (C-4); ν_{max} (film, cm^{-1})= 3500–3200 (OH), 1662 (C=C); LRMS (Scan AP^+): *m/z*=209 [(M^++1), 18%], 191 [(M^+−OH), 98], 139 [(M^+−CF_3), 100]; HRMS (CI^+): (M^++NH_4) found 226.1058, $C_9H_{11}F_3O_2$ requires 226.1055.

Acknowledgements

We thank the Egyptian Government for a research studentship (A. H. El-S.) and EPSRC for X-ray facilities.

References

1. Andrew, R. J.; Mellor, J. M. *Tetrahedron* **2000**, *56*, 7261.
2. Mellor, J. M.; Reid, G.; El-Sagheer, A. H.; El-Tamany, E. H. *Tetrahedron* **2000**, *56*, 10039.
3. Katritzky, A. R.; Li, J.; Xie, L. *Tetrahedron* **1999**, *55*, 8263.
4. Mellor, J. M.; El-Sagheer, A. H.; Metwally, R. N. *Tetrahedron* **2000**, *56*, 10067.
5. Mellor, J. M.; El-Sagheer, A. H.; Salem, E. M. *Tetrahedron Lett.* **2000**, *41*, 7383.
6. Yanovskaya, L. A.; Kryshtal, G. V.; Kul'ganek, V. V. *Russ. Chem. Rev.* **1984**, *53*, 744.
7. Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
8. Kyriakakou, G.; Roux-Schmitt, M. C.; Seyden-Penne, J. *Tetrahedron* **1975**, *31*, 1883.
9. Cossentini, M.; Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron* **1977**, *33*, 409.
10. Lefour, J-M.; Loupy, A. *Tetrahedron* **1978**, *34*, 2597.
11. Posner, G. H. *Org. React.* **1972**, *19*, 1.
12. Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. J. *J. Org. Chem.* **1993**, *58*, 5944.
13. Hunig, S.; Wehner, G. *Chem. Ber.* **1980**, *113*, 302.
14. Cohen, T.; Abraham, W. D.; Myers, M. *J. Am. Chem. Soc.* **1987**, *109*, 7923.
15. Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14; Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Corset, J.; Castella-Ventura, M.; Froment, F. *J. Org. Chem.* **1998**, *63*, 3295.
16. Gustafsson, B. *Acta Chem. Scand.* **1977**, *31B*, 382.
17. Pearson, A. J.; Babu, M. K. M. *Organometallics* **1994**, *13*, 2539.
18. Armstrong, A. In *Comprehensive Organic Functional Group Transformations*, Roberts, S. M., Ed.; Pergamon: Oxford, 1995; Vol. 1, p 293.
19. House, H. O.; Traficante, D. D.; Evans, R. A. *J. Org. Chem.* **1963**, *28*, 348.
20. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
21. Spassky-Pasteur, A.; Riviere, H. *Bull. Soc. Chim. Fr.* **1969**, 811.
22. Nenaidenko, V. G.; Sanin, A. V.; Balenkova, E. S. *Russ. Chem. Rev.* **1999**, *68*, 437.

23. Oroshnik, W.; Karmas, G.; Mallory, R. A. *J. Am. Chem. Soc.* **1954**, *76*, 2325.
24. Gillespie, J. S.; Acharya, S. P.; Shamblee, D. A.; Davis, R. E. *Tetrahedron* **1975**, *31*, 3.
25. Holm, T. *Acta Chem. Scand.* **1983**, *37B*, 567.
26. Gallagher, M. J.; Harvey, S.; Raston, C. L.; Sue, R. E. *J. Chem. Soc. Chem. Commun.* **1988**, 289; Van Campen, M. G.; Meisner, D. F.; Parmerter, S. M. *J. Am. Chem. Soc.* **1948**, *70*, 2296.
27. Danishefsky, S.; Migdalof, B. H. *J. Chem. Soc. Chem. Commun.* **1969**, 1107; Benkeser, R. A.; Snyder, D. C. *J. Org. Chem.* **1982**, *47*, 1243; Bernardon, C.; Deberly, A., *J. Org. Chem.* **1982**, *47*, 463.
28. El Idrissi, M.; Santelli, M. *J. Org. Chem.* **1988**, *53*, 1010; Zair, T.; Santelli-Rouvier, C.; Santelli, M. *J. Org. Chem.* **1993**, *58*, 2686.
29. Masson, S.; Saquet, M.; Thuillier, A. *Tetrahedron* **1977**, *33*, 2949.
30. Leger, L.; Saquet, M. *Bull. Soc. Chim. Fr. B* **1975**, 657.
31. Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054.
32. Boga, C.; Forlani, L.; Todesco, P. F. *Tetrahedron Lett.* **1997**, *38*, 4845.
33. Terlinden, R.; Boland, W.; Jaenicke, L. *Helv. Chim. Acta* **1983**, *66*, 466.
34. Blessing, R. H. *Acta Crystallogr.* **1995**, *A51*, 33; Blessing, R. H. *J. Appl. Crystallogr.* **1997**, *30*, 421.
35. Sheldrick, G. M. *SHELXL 97*. Program for crystal structure refinement, University of Göttingen, 1997.