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Synthesis of Trifluoromethylnaphthalenes

John M. Mellor,[a,*] Afaf H. El-Sagheer,[a] El-Sayed H. El-Tamany[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*

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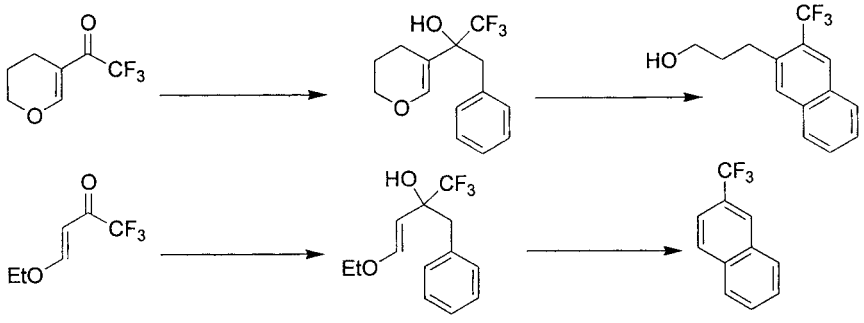
Abstract—Reaction of 1-(3,4-dihydro-2*H*-5-pyranyl)-2,2,2-trifluoro-1-ethanone with benzylic Grignard reagents affords by 1,2-addition unsaturated allylic alcohols. These alcohols readily undergo dehydration and cyclisation to give trifluoromethylnaphthalenes. The generality of this procedure was established by reaction with diverse benzyl and allyl Grignard reagents and by reaction of a number of unsaturated ketones. The resulting trifluoromethylnaphthalenes were oxidised to give substituted acetic- and propionic acids.

Introduction

Acyclic fluorinated building blocks[1] have been used widely in the synthesis of fluorinated heterocyclic compounds. Routes to fluorinated carbocyclic aromatic compounds have relied more on either direct fluorination[2] or the introduction of trifluoromethyl groups from trifluorobromomethane,[3] trifluoroiodomethane,[4] trifluoromethyltrimethylsilane[5] and other silanes,[6] silver trifluoroacetate,[7] sodium trifluoroacetate,[8] *N*-trifluoromethyl-*N*-nitrosotrifluoromethanesulfonamide,[9] or bistrifluoromethylmercury.[10] Introduction of trifluoromethyl side chain substituents into aromatic carbocycles via a building block approach permitting construction of the ring with incorporation of the trifluoromethyl substituent is little developed. The possibility that the [3+3] benzannulation procedures, recently developed by Junjappa et al.[11] and reviewed by Katritzky et al.,[12] might be used to give fluorinated naphthalenes, is attractive. In this methodology an unsaturated ketone is reacted with a benzyl organometallic reagent to afford a 1,2-adduct, which on dehydration affords aromatic products. In order that this procedure might be applied to trifluoromethylketones, thus giving trifluoromethyl substituted aromatic compounds (Scheme 1), it is essential that the benzyl organometallic reagent should undergo 1,2-addition with, for example, a β-alkoxy-α,β-unsaturated ketone, rather than the possible 1,4-addition. Earlier[13,14] we have shown that benzyl magnesium bromide reacts with the ketone (**1**) by 1,2-addition in high yield. There are a number of protocols using organometallic reagents to favour 1,2-addition and minimise 1,4-addition. In the favourable case of allyl derivatives, not only do allyl Grignard reagents preferentially add[15] by 1,2-addition, but direct reaction of an allyl halide with indium metal leads to in situ formation of an indium allyl[16] and hence to selective 1,2-addition. We find that either this protocol, or the related Barbier conditions[17] whereby an allyl Grignard reagent is generated in situ, are effective. In the case of 1,2-addition of benzyl groups, although the



Scheme 1.

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

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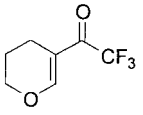
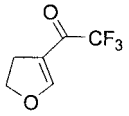
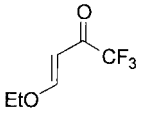
procedures using organocerium intermediates[18] have been well described, we find no advantage relative to the use of Grignard reagents. In this paper we describe the synthesis of a series of 1,2-adducts by reaction of benzyl Grignard reagents with the cyclic ketone (**1**) and related ketones. By subsequent dehydration of the resulting alcohols, and of an alcohol obtained via addition of allyl magnesium bromide, and cyclisation through [3,3] benzannulation, the resulting intermediate 1,2-adducts are transformed to trifluoromethyl substituted aromatics.



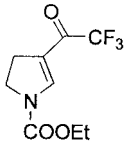
(**1**)



(**2**)



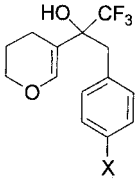
(**3**)



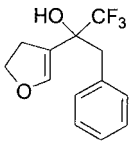
(**4**)

Results and Discussion

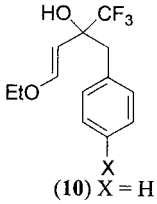
Our study has been based on cyclic ketones (**1**) and (**2**), which are readily prepared[19] by Friedel and Crafts acylation of dihydropyran and dihydrofuran respectively. Similarly the acyclic ketone (**3**) is easily prepared[19,20] by acylation of ethyl vinyl ether. Recently the ketone (**4**) has become available[21] by the reaction of an *N*-protected proline with trifluoroacetic anhydride. In the accompanying paper,[22] we have described the 1,4-addition reactions of phenyl and other aryl Grignard reagents with e.g. the cyclic ketone (**1**). In a further paper[13] we have found that benzyl magnesium bromide afforded by 1,2-addition the alcohol (**5**) in 93% yield. Under similar reaction conditions we found that the Grignard reagent derived from *p*-methoxybenzyl bromide did not add efficiently to ketone (**1**). Self-coupling in the course of attempted reactions of Grignard reagents derived from benzyl halides, and in particular *p*-methoxybenzyl halides, is a serious limitation to their use. We found that attempts to vary the reaction conditions to avoid self-coupling led in ether-tetrahydrofuran to 1,4-additions rather than the desired 1,2-addition. Consequently we have not found conditions permitting efficient 1,2-addition of *p*-methoxybenzyl magnesium bromide to ketone (**1**). Fortunately the behaviour of *p*-methoxybenzyl magnesium bromide proved to be the exception. Reaction of the Grignard reagents derived from *p*-methylbenzyl bromide, *p*-bromobenzyl bromide and *p*-chlorobenzyl chloride with ketone (**1**) give the desired 1,2-adducts (**6**–**8**) in good yield following method A in ether. The structure of alcohol (**7**) was established[14] by a single crystal X-ray diffraction study. We have reported[13] that the addition of benzyl magnesium bromide to the ketone (**2**) is less efficient under the same conditions. The alcohol (**9**) was obtained as a minor product, as, in this case, 1,4-addition was the dominant pathway. In reactions with the acyclic ketone (**3**) the major pathway is via 1,2-addition affording the alcohols (**10**) and (**11**) from benzyl magnesium bromide and *p*-methylbenzyl magnesium bromide respectively.



(**5**) X = H
(**6**) X = Me
(**7**) X = Br
(**8**) X = Cl

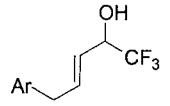


(**9**)

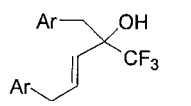


(**10**) X = H
(**11**) X = Me

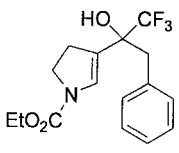
We find that method A by prior preparation of the Grignard reagent in ether followed by addition of the ketone (**3**) is markedly less efficient than method B, using Barbier conditions of in situ preparation and reaction of the Grignard reagent. In these reactions with ketone (**3**) significant amounts of the alcohols (**12**) and (**13**), products derived via 1,4-addition, were observed using method B. In particular using method A in ether reaction of *p*-methylbenzyl magnesium bromide with ketone (**3**) gave, in addition to the alcohol (**11**), the tertiary alcohol (**14**). Analogous observations[23] have been made in addition of other Grignard reagents to the ketone (**3**). From ketone (**4**) the crystalline 1,2-adduct (**15**) was obtained in 25% yield under Barbier conditions (method B), but in lower yield by method A. However by reaction with benzyl lithium the 1,2-adduct (**15**) was obtained in 35% yield. The 1,2-adducts (**16**–**18**) derived by addition of the Grignard reagents from allyl bromide and cinnamyl chloride to ketones (**1**) and (**3**), have been described[13] in the accompanying paper, where we have used Barbier conditions. In the preparation of 1,2-adducts from allyl and benzyl Grignard reagents, whilst recognising the advantages of using Barbier conditions, as described elsewhere,[13] we also note that the nature of the ketone is a factor in the choice of reaction conditions. Thus the acyclic ketone (**3**) and the ketone (**4**) give higher yields under Barbier conditions (method B) and the cyclic ketone (**1**) gives satisfactory yields under the conditions of method A with benzyl Grignard reagents.



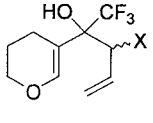
(**12**) Ar = Ph
(**13**) Ar = p-MeC_6H_4



(**14**) Ar = p-MeC_6H_4

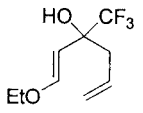


(**15**)

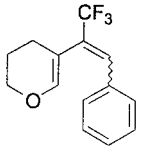


(**16**) X = Ph
(**17**) X = H

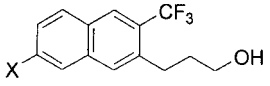
Katritzky et al.[12] have reviewed methods of [3,3] benzannulation. An efficient method of dehydration of alcohols derived from additions of benzyl Grignard reagents to ketones, and subsequent cyclisation, has been developed by Junjappa et al.[11] using boron trifluoride etherate. We have found that this method and a further procedure using *p*-toluenesulfonic acid as the promoter of dehydration and cyclisation, are effective. The course of the reaction pathway is established by the reaction of alcohol (**5**) with *p*-toluenesulfonic acid in toluene at reflux for a short period. The dehydration products, a mixture of the alkenes (**19**) are isolated in 84% yield. Either reaction of these alkenes (**19**) or of the alcohol (**5**) under more vigorous conditions gives the desired naphthalene (**20**) in good yield. Using *p*-toluenesulfonic acid, reaction of the alcohol (**5**) gave the naphthalene (**20**) in 70% yield, alongside two minor products, the ester (**21**) and the ether (**22**). With boron trifluoride etherate the naphthalene (**20**) is obtained in 82% yield. Similarly the naphthalenes (**23**–**25**) are obtained by efficient cyclisations.

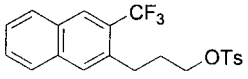


(**18**)



(**19**)

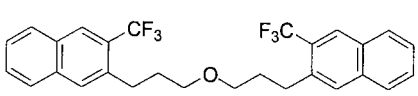




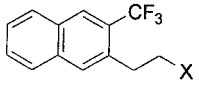
(**21**)

(**20**) X = H
(**23**) X = Me
(**24**) X = Br
(**25**) X = Cl

Using the procedure with *p*-toluenesulfonic acid, the cyclisation of the alcohols (**9**) and (**15**) gave respectively the naphthalenes (**26**) and (**27**) having side-chain alcohol and protected amine functionality. The procedure based on *p*-toluenesulfonic acid is particularly efficient for transforming the alcohols (**10**) and (**11**) derived from the acyclic ketone (**3**) to 2-trifluoromethylnaphthalene (**28**) and 2-methyl-6-trifluoromethylnaphthalene (**29**) respectively. The cyclisation of the alcohol (**17**), obtained by 1,2-allylation of the ketone (**1**) could only be achieved under forcing conditions, which resulted in the formation of the tosylate (**30**) in 60% yield. The cyclisation of the alcohol (**16**) was studied under a variety of conditions without success.

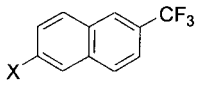


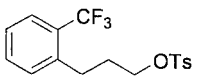
(**22**)



(**26**) X OH
(**27**) X = $NHCO_2Et$

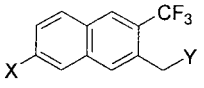
The major significance of these results is the development of a route to 2-trifluoromethyl benzenes and naphthalenes, which defines specifically the position of the fluorinated substituent relative to other substituents. Although 2-trifluoromethylnaphthalene (**28**) is known,[24–27] the preparation from naphthalene is characterised by separation problems[9,28] from 1-trifluoromethylnaphthalene. Other routes require the use of HF,[24] SF_4[26] or XeF_2[29] and have not been shown to be applicable to more substituted naphthalenes. 3,6-Disubstituted 2-trifluoromethyl- naphthalenes have not been prepared prior to our work. The interest in the side-chain alcohols is enhanced by their possible transformation to other substituents, thus offering a wider range of aromatic end-groups, which might be used to modify polarity and hence properties of biologically active molecules. The point is illustrated by oxidation using Jones reagent of the alcohols (**20**) and (**24**–**26**) to the naphthylpropionic acids (**31**–**33**) and the naphthylacetic acid (**34**) in good yield. 3-Substituted-2-trifluoromethylnaphthalenes have already been prepared[30] in a study of candidate drugs to be used against diabetes. Hence our access to a series of trifluoromethyl-substituted naphthalenes carrying additional alcohol, acid and amine endgroups promises much scope for subsequent structural elaboration.





(**28**) X = H
(**29**) X = Me

(**30**)



(**31**) X = H; Y = CH_2CO_2H
(**32**) X = Br; Y = CH_2CO_2H
(**33**) X = Cl; Y = CH_2CO_2H
(**34**) X = H; Y = CO_2H

Experimental

General experimental procedures are described elsewhere.[31]

4-(Ethoxy)-1,1,1-trifluoro-3-butene-2-one (3).[19,20] To a stirred solution of 4-dimethylaminopyridine (12.0 mg, 0.10 mmol) and trifluoro acetic anhydride (3.28 gm, 15.62 mmol) in dichloromethane (20.00 ml), ethyl vinyl ether (1.06 g, 14.70 mmol) was added dropwise at −10°C. The reaction mixture was stirred for 19 h at 0°C, allowed to warm to room temperature and the solvent was evaporated in vacuo. The reaction mixture was poured into sodium bicarbonate solution (the deep violet colour changed to a yellow colour), the two phases were separated and the organic phase was washed with water, dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo to give the crude title compound (**3**) as a yellow oil (2.00 gm, 81%). The crude product was used directly in subsequent Grignard reactions.

Alcohols prepared by 1,2-addition of Grignard reagents

Method A. 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 (4.2 ml) and a crystal of iodine were added. A few drops of benzyl halide (22.22 mmol) in dry ether (4.2 ml) were added dropwise, and the solution was stirred until the formation of the Grignard reagent. The remainder of the benzyl halide was diluted with dry ether (8.4 ml) and the solution was added at such a rate as to maintain gentle reflux. After the complete addition of the benzyl halide, the reaction mixture was heated under reflux with stirring on a warm water bath for 20 min. The reaction mixture was cooled and a solution of the ketone (**1**) (1.00 g, 5.55 mmol) in dry ether (4.2 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), the combined organic phases were collected, washed with water (2×20 ml), dried over $MgSO_4$ and the solvent evaporated in vacuo to afford a crude product.

Method B. To magnesium turnings (0.44 gm, 18.11 mmol) in dry ether (1.5 ml), the benzyl bromide (0.20 mmol) was added, the reaction mixture was heated with vigorous stirring to initiate the reaction. A solution of the ketone (**3**) (0.93 gm, 5.54 mmol) and the benzyl bromide (6.58 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 (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 (2×20 ml), dried over $MgSO_4$ and the solvent evaporated in vacuo to afford a crude product.

(*E*)-2-Benzyl-4-ethoxy-1,1,1-trifluoro-3-buten-2-ol (10). Following method B, reaction of ketone (**3**) with benzyl magnesium bromide afforded after chromatography [silica gel, hexane: ethyl acetate (95:5)] two fractions. The title compound (**10**) was isolated as a pale yellow oil (0.79 g, 55%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.33 (3H, m, Ph), 7.22 (2H, m, Ph), 6.38 (1H, d, J=12.5 Hz, OC*H*), 4.85 (1H, d, J=12.5 Hz, CH=C*H*), 3.70 (2H, q, J=7.0 Hz, OCH_2), 3.15 (1H, d, J=14.0 Hz, CH_2Ph), 2.95 (1H, d, J=14.0 Hz, CH_2Ph), 2.00 (1H, s, OH), 1.24 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=151.05 (–O–*C*H), 133.9 (C′-1), 131.2, 128.4 and 127.45 (Ph-C), 125.6 (q, J_{C-F}=285.9, *C*F_3), 100.5 (CH=*C*H), 75.0 (*C*–CF_3), 65.6 (*C*H_2CH$_3$), 41.5 (*C*H_2–Ph), 14.7 (CH$_2$*C*H$_3$); υ_{max} (film, cm^{-1}) 3500–3100 (OH), 1630, 1590 (C=C); LRMS (Scan AP$^+$): m/z=243 (M$^+$−OH, 60 %), 191 (M$^+$−CF_3, 100); HRMS (CI$^+$): (M$^+$+NH$_4$) found 278.1369; $C_{13}H_{15}F_3O_2$ requires 278.1368.

(*E*)-1,1,1,-Trifluoro-5-phenyl-3-penten-2-ol (12). The compound was isolated as a pale yellow oil (0.30 g, 25%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.30–7.00 (5H, complex, Ph–H), 6.03 (1H, dt, J=14.7, 7.5, 7.5 Hz, C*H*–CH$_2$), 5.49 (1H, dd, J=14.7, 6.6 Hz, CH=C*H*), 4.35 (1H, Pent., J=6.6 Hz, C*H*–CF_3), 3.38 (2H, d, J=6.6 Hz, CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ=139.0 (C′), 137.4 (CH=*C*H), 128.8 and 126.6 (Ph–C), 124.45 (q, J_{C-F}=281.4, *C*F_3), 123.5 (*C*H=CH), 71.5 (q, J=31.65 Hz, *C*H–CF_3), 38.8 (*C*H_2Ph); υ_{max} (film, cm^{-1}) 3550–3100 (OH), 1603 (C=C); LRMS (Scan AP$^+$): m/z=216 (M$^+$, 12%), 199 (M$^+$−OH, 12), 198 (M$^+$−H_2O, 100); HRMS (EI$^+$): M$^+$ found 216.0768; $C_{11}H_{11}F_3O$ requires 216.0762.

Following method A, reaction of ketone (**3**) with benzyl magnesium bromide (2.5 equiv.) afforded the alcohol (**10**) in 40% yield, (analytical data as described above).

(*E*)-4-Ethoxy-1,1,1-trifluoro-2-(*p*-methylbenzyl)-3-buten-2-ol (11). Following method B reaction of ketone (**3**) with *p*-methylbenzyl magnesium bromide afforded after chromatography [silica gel, hexane: ethyl acetate (90:10)] two fractions. The title compound (**11**) was isolated first as a pale yellow oil (0.68 g, 45%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.15 (4H, m, Ar-H), 6.42 (1H, d, J=12.5 Hz, C*H*=CH), 4.88 (1H, d, J=12.5 Hz, CH=C*H*), 3.72 (2H, q, J=7.0 Hz, OCH_2), 3.11 (1H, d, J=13.2 Hz, CH_2-Ar), 2.97 (1H, d, J=13.2 Hz, CH_2-Ar), 2.38 (3H, s, CH_3), 2.12 (1H, s, OH), 1.31 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=151.0 (–O–*C*H), 137.1 (C′), 131.0 and 129.1 (Ar-H), 100.6 (CH=*C*H), 65.5 (*C*H_2CH$_3$), 41.1 (*C*H_2-Ar), 21.2 (CH$_3$), 14.7 (CH$_2$*C*H$_3$); υ_{max} (CH$_2$Cl$_2$, cm^{-1}) 3563 and 3438 (OH), 1653 and 1515 (C=C); LRMS (Scan AP$^+$): m/z=257 (M$^+$−OH, 47%), 228 (M$^+$−C_2H_5OH, 23), 205 (M$^+$−CF_3, 100) HRMS (EI$^+$): M$^+$ found 274.1176, $C_{14}H_{17}F_3O_2$ requires 274.1181. **(*E*)-1,1,1-trifluoro-5-(*p*-methylphenyl)-3-penten-2-ol (13)** was isolated as a pale yellow oil (0.27 g, 21%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.19 (2H, d, J=8.1 Hz, Ar-H), 7.11 (2H, d, J=8.1 Hz, Ar-H), 6.17 (1H, dt, J=14.7, 7.5, 7.5 Hz, C*H*–CH$_2$), 5.60 (1H, dd, J=14.7, 6.6 Hz, CH=C*H*), 4.43 (1H, pent., J=6.6 Hz, C*H*–CF_3), 3.44 (2H, d, J=6.6 Hz, CH_2-Ar), 2.55 (1H, s, O*H*), 2.35 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=137.75 (*C*H=CH), 136.2, 135.9 (C′-Ar), 129.5, 128.7 (Ar-C), 124.5 (q, J_{C-F}=281.4, *C*F_3), 123.25 (*C*H=CH), 71.6 (q, J_{C-F}=31.65, *C*H–CF_3), 38.4 (*C*H$_2$-Ar), 21.2 (*C*H$_3$); υ_{max} (film, cm^{-1}) 3550–3100 (OH); LRMS (Scan AP$^+$): m/z=230 (M$^+$, 60%), 213 (M$^+$−OH, 15), 212 (M$^+$−H_2O, 100), 160 [(M$^+$−1)−CF_3, 13], HRMS (EI$^+$): M$^+$ found 230.0924, $C_{12}H_{13}F_3O$ requires 230.0918.

(*E*)-1,1,1-Trifluoro-2-(*p*-methylbenzyl)-5-(*p*-methylphenyl)-3-penten-2-ol: (14). Following method A reaction of ketone (**3**) with (*p*-methylbenzyl) magnesium bromide afforded after chromatography [silica gel, hexane: ethyl acetate (90:10)] two fractions: (*E*)-4-ethoxy-1,1,1-trifluoro-2-(*p*-methylbenzyl)-3-buten-ol (**11**) which was isolated as a pale yellow oil (0.45 g, 30%) (analytical data as described above); and the title compound (**14**) which was isolated as a pale yellow oil (0.38 g, 20%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.10 (6H, m, Ar-H), 6.90 (2H, d, J=7.4 Hz, Ar-H), 5.82 (1H, dt, J=15.4, 6.6, 6.6 Hz, C*H*–CH$_2$), 5.60 (1H, d, J=15.4 Hz, CH=C*H*), 3.34 (2H, d, J=6.6 Hz, CHCH_2-Ar), 3.12 (1H, d, J=13.5 Hz, CH_2-Ar), 2.95 (1H, d, J=13.5 Hz, CH_2-Ar), 2.35 (3H, s, CH_3), 2.34 (3H, s, CH_3), 2.08 (1H, s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ=137.0, 136.2, 135.9 and 130.6 (C′-Ar), 133.8, 131.05, 129.2, 129.1, 128.65 and 127.2 (Ar-C and *C*H=CH), 125.6 (q, J_{C-F}=286.0, *C*F_3), 76.1 (q, J_{C-F}=55.4 Hz, *C*–CF_3), 40.2 and

38.1 (2C, CH_2-Ar), 21.3 and 21.2 (2C, CH_3); υ_{max} (film, cm^{-1}) 3600–3400 (OH); LRMS (Scan AP^+): m/z=334 (M^+, 61 %), 316 [(M^+-1)−OH, 100%)], 265 (M^+-CF_3, 38), HRMS (EI^+): M^+ found, 334.1547; $C_{20}H_{21}F_3O$ requires, 334.1544.

2-(3,4-Dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-3-(*p*-methylphenyl)-2-propanol (6). Following method A reaction of ketone (**1**) with *p*-methylbenzyl magnesium bromide afforded after chromatography [silica gel, hexane: ethyl acetate (95:5)] the title compound (**6**) as a pale yellow oil (1.54 g, 97%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.18 (2H, d, J=8.5 Hz, Ar-H), 7.09 (2H, d, J=8.5 Hz, Ar-H), 6.51 (1H, s, H-6), 4.00, (1H, m, H-2), 3.91 (1H, m, H-2), 3.08 (2H, s, CH_2-Ar), 2.33 (3H, s, CH_3), 2.13 (2H, m, H-4), 2.00 (1H, s, OH), 1.85 (2H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.6 (C-6), 137.2 and 130.5, (C′-1, C′-4), 130.7 and 129.3 (Ar-C), 125.9 (q, J_{C-F}=287.1, CF_3), 108.2 (C-5), 76.8 (C-CF_3), 65.5 (C-2), 38.6 (CH_2-Ar), 21.95 (C-3), 21.2 (CH_3), 20.8 (C-4); υ_{max} (film, cm^{-1}) 3550–3200 (OH), 1657 (C=C); LRMS (Scan AP^+): m/z=269 (M^+−OH, 64 %), 217 (M^+-CF_3, 100); HRMS (CI^+): (M^++NH_4) found 304.1529, $C_{15}H_{17}F_3O_2$ requires 304.1525.

3-(*p*-Bromophenyl)-2-(3,4-dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-2-propanol (7). Following the method A reaction of ketone (**1**) with *p*-bromobenzyl magnesium bromide afforded after chromatography [silica gel, hexane: ethyl acetate (95:5)] the title compound (**7**) as a white solid (1.45 g, 74%) which was recrystallised from petroleum ether mp 69–70°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.45 (2H, d, J=8.1 Hz, Ar-H), 7.09 (2H, d, J=8.1 Hz, Ar-H), 6.45 (1H, s, H-6), 3.95 (1H, m, H-2), 3.88 (1H, m, H-2), 3.09 (1H, d, J=13.9 Hz, CH_2-Ar), 3.04 (1H, d, J=13.9 Hz, CH_2-Ar), 2.20–2.00 (3H, complex, H-4, OH), 1.80 (2H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.6 (C-6), 133.1 and 121.5, (C′-1, C′-4), 132.7 and 132.5 (Ar-C), 125.8 (q, J_{C-F}=287.1, CF_3), 107.8 (C-5), 65.5 (C-2), 38.4 (CH_2-Ar), 21.8 (C-3), 20.8 (C-4); υ_{max} (CH_2Cl_2, cm^{-1}) 3567 (OH), 1663 (C=C); LRMS (Scan AP^+): m/z=335 [(M^++2)−OH, 22%], 333 (M^+−OH, 20), 283 [(M^++2)−CF_3, 9], 281(M^+-CF_3, 9); HRMS (CI^+): (M^++NH_4) found 368.0474, $C_{14}H_{14}BrF_3O_2$ requires 368.0473. Found C, 47.90; H, 4.03; Br, 22.78. $C_{14}H_{14}F_3O_2Br$ requires C, 47.88; H, 4.02; Br, 22.75%. The structure of alcohol (**7**) has been established[14,32] by X-ray diffraction.

3-(*p*-Chlorophenyl)-2-(3,4-dihydro-2*H*-5-pyranyl)-1,1,1-trifluoro-2-propanol (8). Following method A reaction of ketone (**1**) with *p*-chlorobenzyl magnesium chloride afforded after chromatography [silica gel, hexane: ethyl acetate (95:5)] the title compound (**8**) as a pale yellow oil (1.36 g, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.28 (2H, d, J=8.1 Hz, Ar-H), 7.13 (2H, d, J=8.1 Hz, Ar-H), 6.44 (1H, s, H-6), 3.96 (1H, m, H-2), 3.84 (1H, m, H-2), 3.10 (1H, d, J=14.0 Hz, CH_2-Ar), 3.02 (1H, d, J=14.0 Hz, CH_2-Ar), 2.20–1.98 (3H, complex, H-4, OH), 1.78 (2H, brm, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.6 (C-6), 133.35 and 132.5 (C′-1, C′-4), 132.1, and 128.5 (Ar-C), 125.8 (CF_3), 107.8 (C-5), 65.5 (C-2), 38.4 (CH_2-Ar), 21.8 (C-3), 20.8 (C-4); υ_{max} (film, cm^{-1}) 3500–3150 (OH), 1655 (C=C); LRMS (Scan AP^+): m/z=291 [(M^++2)−OH, 38%], 289 (M^+−OH, 100), 239 [(M^++2)−CF_3, 30], 237 (M^+-CF_3, 94); HRMS (EI^+): M^+ found 306.0634, $C_{14}H_{14}ClF_3O_2$ requires 306.0634.

Ethyl 4-(1-benzyl-2,2,2-trifluoro-1-hydroxyethyl)-2,3-dihydro-1*H*-1-pyrrolecarboxylate (15) prepared by 1,2-addition of benzyl lithium (Method C). To a mixture of toluene (0.930 g, 9.00 mmol) and TMEDA (0.380 g, 3.72 mmol), a solution of butyl lithium in hexanes (1.6 m/l) (1.88 ml, 3.00 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 syringe to a solution of the ketone (**4**) (0.237 g, 1.00 mmol) in tetrahydrofuran (2.5 ml), the reaction mixture was stirred for 30 min, allowed to warm to room temperature, diluted with tetrahydrofuran (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 (2×20 ml), dried over $MgSO_4$ and the solvent evaporated in vacuo. The title compound (**15**) was isolated as a white solid which was recrystallised from petroleum ether to give white crystals (0.120 g, 35%) mp 99–100°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.29 (3H, m, Ph-H), 7.21 (2H, m, Ph-H), 6.66 and 6.50 (1H, s, H-6), 4.11 (2H, m, CH_2CH_3), 3.77 (2H, m, H-2), 3.10 (2H, m, CH_2-Ph), 2.85–2.50 (3H, complex, H-3, OH), 1.23 (3H, m, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=133.5 (C′-1), 130.7, 128.6 and 127.6 (Ph-C), 118.7 (C-4), 75.8 (C–CF_3), 61.8 (CH_2CH_3), 46.1 (C-2), 39.6 (CH_2-Ph), 30.2 and 29.2 (C-3), 14.75(CH_3); υ_{max} (film, cm^{-1}) 3500–3200 (OH), 1681 (C=O), 1600 (C=C); LRMS (Scan AP^+): m/z=330 [(M^++1), 58%], 312 (M^+−OH, 28), 260 (M^+-CF_3, 100); HRMS (CI^+): (M^++NH_4); found, 347.1587 $C_{16}H_{18}F_3NO_3$ requires 347.1583. Found C, 58.35; H, 5.39; N, 4.17. $C_{16}H_{18}F_3O_3N$ requires C, 58.35; H, 5.51; N, 4.25%.

Dehydration of alcohols with *p*-toluene sulfonic acid in toluene

Method C. To a solution of the alcohol (0.385 mmol) in toluene (7.65 ml) was added under nitrogen *p*-toluenesulfonic acid (0.134 mmol). The reaction mixture was heated under reflux for 2 h and poured into sodium bicarbonate solution (30 ml). The two layers were separated and the organic layer was washed with water (2×20 ml), dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo to afford a crude product.

Dehydration of alcohols with BF_3/benzene

Method D. To a solution of the alcohol (0.10 mmol) in dry benzene (0.34 ml), boron trifluoride etherate (0.013 ml) was added and the reaction mixture was refluxed for 50 min. The mixture was poured into sodium bicarbonate solution (50 ml), the two layers were separated and the organic layer was washed with water (2×20 ml), dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo to afford a crude product.

5-[(*E*) and (*Z*)-2-Phenyl-1-(trifluoromethyl)-1-ethenyl]-3,4-dihydro-2*H*-pyran (19). Following the method C alcohol

(**5**) (0.60 g, 2.2 mmol) in toluene (70 ml) was heated under reflux for 20 min and the title compounds (**19**) were isolated after chromatography [silica gel, petroleum ether: ethyl acetate (90:10)] as a pale yellow oil [mixture of the two isomeric dienes (**19**)] (0.47 g, 84%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.44 (2H, m, Ph-H), 7.31–7.14 (8H, complex, Ph-H), [6.91 (1H, s), 6.73 (1H, s), 6.64 (1H, s) and 6.39 (1H, s), vinylic-H], 3.94 (4H, m, H-2), 2.16 (2H, m, H-4), 2.01 (2H, m, H-4), 1.84 (4H, m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=145.7, 144.7, 133.5 and 132.9 (vinylic-c), 135.7, 134.5, 133.5 and 132.9 (*C*–CF_3 and C′-Ar), 129.6, 129.0, 128.7, 128.6, 128.1 and 127.9 (Ph-C), 124.2 (q, J_{C-F}=273.5, *C*F_3) 123.8 (q, J_{C-F}=276.9, *C*F_3), 110.7 and 105.0 (C-5), 65.7 and 65.5 (C-2), 23.3, 23.1, 22.3, and 22.1 (C-3 and C-4); υ_{max} (film, cm^{-1}) 1644 and 1620 (C=C); LRMS (Scan AP$^+$): *m*/*z*=255 [(M^++1), 13%], 254 (M^+, 100) HRMS (EI$^+$): M^+ found 254.0915, $C_{14}H_{13}F_3O$ requires 254.0918.

3-[3-(Trifluoromethyl)-2-naphthyl]-1-propanol (20). Following method D, alcohol (**5**) (0.30 g, 1.1 mmol) afforded after chromatography [silica gel, petroleum ether: ethyl acetate (70:30)] the title compound (**20**) as a white solid (0.23 g, 82%) mp 50–52°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.18 (1H, s, H′-4), [7.88 (1H, d, *J*=8.1 Hz) and 7.81 (1H, d, *J*=8.1 Hz), H′-5 and H′-8], 7.80 (1H, s, H′-1), 7.68–7.42 (2H, complex, H′-6 and H′-7), 3.80 (2H, t, *J*=6.5 Hz, H-1), 3.02 (2H, t, *J*=8.1 Hz, H-3), 2.01 (2H, m, H-2), 1.80 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 136.4, 134.8 and 130.7 (Ar-C′), 129.75, 128.7, 128.4, 127.3, 127.2, 127.1 and 126.6 (Ar-C), 125.05 (*C*F_3), 62.5 (C-1), 34.5 (C-2), 28.8 (C-3); υ_{max} (CH_2Cl_2, cm^{-1}) 3616 (OH), 1637 and 1600 (C=C); LRMS (Scan AP$^+$): *m*/*z*=255 [(M^++1), 11%], 254 (M^+, 100), 236 [(M^+−H_2O), 26]. Found C, 66.15; H, 4.96. $C_{14}H_{13}F_3O$ requires C, 66.14; H, 5.15%.

Following method C, alcohol (**5**) (0.270 g, 0.99 mmol) in toluene (16 ml) was heated under reflux for 8 h and afforded after chromatography [silica gel, petroleum ether:ethyl acetate (90:10)] three fractions. 3-[3-(Trifluoromethyl)-2-naphthyl]-1-propanol (**20**) was isolated as a white solid (0.175 g, 70%) (analytical data as described above). **3-[3-(trifluoromethyl)-2-naphthyl]propyl *p*-methyl-1-benzenesulfonate (21)** was isolated as a white solid (0.06 g, 16%), which was recrystallised from ethyl acetate/petroleum ether to give white crystals mp 91–92°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.18 (1H, s, H′-4), [7.90 (1H, d, *J*=8.1 Hz) and 7.79 (1H, d, *J*=8.8 Hz), H′-5 and H′-8], 7.82 (2H, d, *J*=8.1 Hz, Ar-H), 7.69 (1H, s, H′-1), 7.57 (2H, m, H′-6, H′-7), 7.35 (2H, d, *J*=8.1 Hz, Ar-H), 4.18 (2H, t, *J*= 6.0 Hz, H-1), 2.95 (2H, t, *J*=8.0 Hz, H-3), 2.48 (3H, s, CH_3), 2.06 (2H, m, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=145.0, 134.8, 134.7, 133.2 and 130.8 (Ar-C′), 130.05, 128.7, 128.5, 128.1, 127.4, 127.3 and 127.2 (Ar-C), 124.6 (*C*F_3), 69.8 (C-1), 30.6 and 28.5 (C-2, C-3), 21.8 (*C*H_3); υ_{max} (CH_2Cl_2, cm^{-1}) 1639 and 1599 (C=C); LRMS (Scan AP$^+$): *m*/*z*=409 [(M^++1), 15%], 408 (M^+, 75), 254 [(M^++1)−(CH_3–C_6H_4–SO_2), 12], 236 [M^+−(CH_3–C_6H_4–SO_3H), 53]. Found C, 61.59; H, 4.53. $C_{21}H_{19}F_3O_3S$ requires C, 61.75; H, 4.69%. **Di{3-[3-(trifluoromethyl)-2-naphthyl]propyl} ether (22)** was isolated as a yellow oil (0.03 g, 6%) ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.21 (2H, s, H′-4), [7.90 (2H, d, *J*=8.1 Hz) and 7.86 (2H, d, *J*=8.1 Hz), H′-5 and H′-8], 7.84 (2H, s, H′-1), 7.65−7.48 (4H, complex, H′-6 and H′-7), 3.63 (4H, m, H-1), 3.12 (4H, m, H-3), 2.10 (4H, m, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=136.6, 134.85, 130.7 and 123.2 (Ar-C′), 129.75–126.4 (Ar-C), 125.05 (*C*F_3), 70.3 (C-1), 31.6 and 29.3 (C-2 and C-3); υ_{max} (film, cm^{-1}): 1638 and 1600 (C=C); LRMS (Scan AP$^+$): *m*/*z*=491 [(M^++1), 44%], 490 (M^+, 100), 254 [(M^+−($C_{14}H_{11}F_3$, 21)], 236 [M^+−($C_{14}H_{13}F_3O$), 52]; HRMS (EI$^+$): M^+ found 490.1728, $C_{28}H_{24}F_6O$ requires 490.1731.

Following method C, a mixture of the two isomeric trienes (**19**) (0.050 g, 0.2 mmol) in toluene (1 ml) was heated under reflux for 1.5 h and afforded after chromatography [silica gel, petroleum ether:ethyl acetate (90:10)] the alcohol (**20**) (0.030 g, 65%), the tosylate (**21**) (0.010 g, 13%) and the ether (**22**) (0.019 g, 21%).

3-[7-Methyl-3-(trifluoromethyl)-2-naphthyl]-1-propanol (23). Following method D, alcohol (**6**) (0.20 g, 0.70 mmol), afforded after chromatography [silica gel, hexane: ethyl acetate (70:30)] the title compound (**23**) as a white solid (0.17 g, 90%) which was recrystallised from petroleum ether, mp 40–41°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.12 (1H, s, H′-4), 7.79 (1H, d, *J*=8.1 Hz, H′-5), 7.70 (1H, s, H′-1), 7.59 (1H, brs, H′-8), 7.36 (1H, dd, *J*=8.1, 1.5 Hz, H′-6), 3.81 (2H, t, *J*=6.6 Hz, H-1), 3.02 (2H, t, *J*=8.1 Hz, H-3), 2.55 (3H, s, C*H*$_3$), 2.02 (2H, m, H-2), 1.52 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=138.4, 136.35, 135.05, 126.7 and 123.2 (Ar-C′), 129.1, 128.9, 128.5, 126.8 and 126.3 (Ar-C), 62.6 (C-1), 34.5 (C-2), 28.85 (C-3), 22.0 (CH_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3615 (OH), 1640 and 1600 (C=C); LRMS (Scan AP$^+$): *m*/*z*=269 [(M^++1), 14%], 268 (M^+, 100), 250 [(M^+−H_2O), 7]. Found C, 66.95; H, 5.67. $C_{15}H_{15}F_3O$ requires C, 67.16; H, 5.64%.

3-[7-Bromo-3-(trifluoromethyl)-2-naphthyl]-1-propanol (24). Following method D, alcohol (**7**) (0.300 g, 0.86 mmol), afforded after chromatography [silica gel, hexane: ethyl acetate (70:30)] the title compound (**24**) as a white solid (0.264 g, 92%) which was recrystallised from petroleum ether to give white crystals, mp 81–82°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.98 (1H, s, H′-4), 7.82 (1H, d, *J*=1.5 Hz, H′-8), 7.59 (1H, d, *J*=8.6 Hz, H′-5), 7.53 (1H, s, H′-1), 7.44 (1H, dd, *J*=8.6, 1.5 Hz, H′-6), 3.65 (2H, t, *J*=6.5 Hz, H-1), 2.89 (2H, t, *J*=8.0 Hz, H-3), 1.96 (1H, s, OH), 1.88 (2H, m, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=137.75, 135.7, 129.0, 126.9 and 122.7 (Ar-C′), 130.2, 130.1, 129.4, 128.7, and 126.8 (Ar-C), 124.7 (CF_3), 62.4 (C-1), 34.3 (C-2), 28.8 (C-3); υ_{max} (CH_2Cl_2, cm^{-1}) 3615 and 3466 (OH), 1637 and 1591 (C=C); LRMS (Scan AP$^+$): *m*/*z*=334 [(M^++2), 58%], 332 (M^+, 48), 314 [(M^+−H_2O), 33]. Found C, 50.76; H, 3.47, Br, 24.06. $C_{14}H_{12}F_3OBr$ requires C, 50.47; H, 3.63; Br, 23.98%.

3-[7-Chloro-3-(trifluoromethyl)-2-naphthyl]-1-propanol (25). Following method D, alcohol (**8**) (0.40 g, 1.31 mmol) afforded after chromatography [silica gel, hexane: ethyl acetate (70:30)] the title compound (**25**) as a white solid (0.36 g, 94%) which was recrystallised from petroleum ether to give white crystals mp 67–68°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.13 (1H, s, H′-4), 7.81 (1H, d,

J=8.8 Hz, H′-5), 7.79 (1H, m, H′-1), 7.70 (1H, brs, H′-8), 7.46 (1H, dd, J=8.8, 2.2 Hz, H′-6), 3.79 (2H, t, J=6.5 Hz, H-1), 3.02 (2H, t, J=8.1 Hz, H-3), 2.00 (2H, m, H-2), 1.65 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=137.8, 135.4 and 134.3 (Ar-C′), 130.2, 128.9, 127.6, 126.9, and 126.1 (Ar-C), 124.7 (CF_3), 62.4 (C-1), 34.35 (C-2), 28.8 (C-3); υ_{max} (CH_2Cl_2, cm^{-1}) 3616 (OH), 1640 (C=C); LRMS (Scan AP^+): m/z=290 [(M^++2), 49%], 288 (M^+, 100), 272 [(M^++2)−H_2O, 28], 270 [(M^+−H_2O), 75]. Found C, 58.28; H, 4.11; Cl, 12.40. $C_{14}H_{12}F_3OCl$ requires C, 58.25; H, 4.19; Cl, 12.28%.

2-[3-(Trifluoromethyl)-2-naphthyl]-1-ethanol (26). Following method C, alcohol (**9**) (0.070 g, 0.27 mmol) was heated under reflux for 4 h and the title compound (**26**) was isolated after chromatography [silica gel, petroleum ether: ethyl acetate (70:30)] as a white solid (0.060 g, 92%) which was recrystallised from petroleum ether to give white crystals mp 66–67°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.20 (1H, s, H′-4), [7.90 (1H, d, J=8.1 Hz) and 7.85 (1H, d, J=8.1 Hz), H′-5 and H′-8], 7.89 (1H, s, H′-1), [7.68 (1H, m) and 7.48 (1H, m), H′-6 and H′-7], 3.97 (2H, t, J=6.6 Hz, H-1), 3.20 (2H, t, J=6.6 Hz, H-2), 1.68 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=134.6, 132.6, 130.85 and 127.3 (Ar-C′), 130.85, 128.7, 128.5, 127.4, 127.25 and 126.9 (Ar-C), 124.8 (CF_3), 63.2 (C-1), 36.0 (C-2); υ_{max} (CH_2Cl_2, cm^{-1}) 3611 (OH), 1639 (C=C); LRMS (Scan AP^+): m/z=241 [(M^++1), 6%], 240 (M^+, 43); HRMS (CI^+): (M^++NH_4) found, 258.1109, $C_{13}H_{11}F_3O$ requires 258.1106. Found C, 64.78; H, 4.57. $C_{13}H_{11}F_3O$ requires C, 65.00; H, 4.62%.

Ethyl *N*-{2-[3-(trifluoromethyl)-2-naphthyl]ethyl}carbamate (27). Following method C, alcohol (**15**) (0.12 g, 0.36 mmol) was heated under reflux for 3 h and the title compound (**27**) was isolated after chromatography [silica gel, petroleum ether:ethyl acetate (80:20)] as a white solid (0.07 g, 63%) which was recrystallised from ethyl acetate/petroleum ether to give white crystals mp 56–57°C ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.20 (1H, s, H′-4), [7.90 (1H, d, J=8.1 Hz) and 7.85 (1H, d, J=8.1 Hz), H′-5 and H′-8], 7.83 (1H, s, H′-1), [7.66 (1H, m) and 7.50 (1H, m), H′-6 and H′-7], 4.85 (1H, brs, NH), 4.15 (2H, q, J=7.4 Hz, CH_2CH_3), 3.53 (2H, q, J=7.0 Hz, H-1), 3.19 (2H, t, J=7.0 Hz, H-2), 1.29 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=156.8 (C=O), 134.7, 133.0, 130.9 and 127.2 (Ar-C′), 130.7, 128.7, 128.55, 127.4, 127.3 and 126.9 (Ar-C), 124.8 (CF_3), 61.0 (OCH_2CH_3), 42.1 (C-1), 33.1 (C-2), 14.8 (CH_2CH_3); υ_{max} (CH_2Cl_2, cm^{-1}) 3447(NH), 1716(C=O), 1630 and 1590 (C=C); LRMS (Scan AP^+): m/z=312 [(M^++1), 25%], 265 [(M^+−C_2H_5OH), 6]; HRMS (CI^+): (M^++NH_4) found, 329.1487, $C_{16}H_{16}F_3O_2N$ requires, 329.1477. Found C, 61.75; H, 5.05; N, 4.37%. $C_{16}H_{16}F_3O_2N$ requires C, 61.73; H, 5.18; N, 4.50%.

2-Methyl-6-(trifluoromethyl)naphthalene (29). Following method C, alcohol (**11**) (0.28 g, 1.0 mmol) afforded the title compound (**29**) as a yellowish white solid (0.20 g, 95%), which was recrystallised from ethanol/water to give a yellowish white crystals mp 101–102°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.00 (1H, s, H′-5), [7.75 (1H, d, J=8.1 Hz) and 7.71 (1H, d, J=8.1 Hz), H′-8 and H′-4], 7.58 (1H, s, H′-1), 7.50 (1H, dd, J=8.0, 1.5 Hz, H′-7), 7.32 (1H, dd, J=8.0, 1.5 Hz, H′-3), 2.46 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ=138.25, 135.0 and 130.55 (Ar-C′), 129.6, 128.7, 128.4, 127.0 and 125.5 (Ar-C), 124.1 (CF_3), 22.0 (CH_3); υ_{max} (CH_2Cl_2, cm^{-1}) 1620 and 1600 (C=C); LRMS (Scan AP^+): m/z=211 [(M^++1), 7%], 210 (M^+, 55). Found C, 68.85; H, 4.21; $C_{12}H_9F_3$ requires C, 68.57; H, 4.32%.

2-(Trifluoromethyl)naphthalene (28). Following method C, alcohol (**10**) (0.150 g, 0.58 mmol) afforded the title compound (**28**) as white solid (0.096 g, 84%), which was recrystallised from ethanol/water to give a white crystals mp 64–65°C (lit.[27] mp 63–64°C) ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.08 (1H, s, H′-1), 7.92–7.78 (3H, m, Ar-H), 7.61–7.45 (3H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=134.7.0 and 132.3 (Ar-C′), 129.1, 129.0, 128.3, 128.0, 127.3, 125.8 and 121.6 (Ar-C); υ_{max} (CH_2Cl_2, cm^{-1}) 1640 and 1606 (C=C); LRMS (Scan AP^+): m/z=196 (M^+, 100).

3-[2-(Trifluoromethyl)phenyl]propyl *p*-methyl-1-benzenesulfonate (30). Following method C, alcohol (**17**) (0.30 g, 1.35 mmol) was reacted with *p*-toluene sulfonic acid (0.76 g, 4.0 mmol) in toluene (10 ml) and was heated under reflux for 22 h to afford after chromatography [silica gel, petroleum ether:ethyl acetate (90:10)] the title compound (**30**) as a yellow oil (0.29 g, 60%); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.82 (2H, d, J=8.8 Hz, Ar-H), 7.60 (1H, d, J=7.4 Hz, H′-3), [7.45 (1H, t, J=7.4 Hz) and 7.28 (1H, t, J=7.4 Hz) H′-4 and H′-5], 7.39 (2H, d, J=8.1 Hz, Ar-H), 7.32 (1H, d, J=7.4 Hz, H′-6), 4.09 (2H, t, J=5.9 Hz, H-1), 2.79 (2H, t, J=8.0 Hz, H-3), 2.46 (3H, s, CH_3), 1.95 (2H, m, H-2); ^{13}C NMR (75 MHz, CDCl3) δ=145.0, 139.4 and 133.1 (Ar-C′), 132.0, 131.2, 130.05, 128.0, 126.5 and 126.3 (Ar-C), 124.5 (CF_3), 69.8 (C-1), 30.75 and 28.7 (C-2, C-3), 21.8 (CH_3); υ_{max} (film, cm^{-1}) 1620, 1583 (C=C); LRMS (Scan AP^+): m/z=376 (M^++NH_4, 3%), 186 (M^+−*p*-CH_3–C_6H_4–SO_3H, 100); HRMS (CI^+): (M^++NH_4) found 376.1164,. $C_{17}H_{17}F_3O_3S$ requires 376.1194.

Oxidations using Jones reagent

To a cold solution of the alcohol (**20**) (0.13 g, 0.51 mmol) 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 (20 ml) and extracted with dry ether (3×15 ml). The combined organic phases were collected, washed with water (2×20 ml), dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting solid was purified by flash column chromatography [silica gel, hexane: ethyl acetate (70:30)].

3-[3-(Trifluoromethyl)-2-naphthyl]propanoic acid (31). Oxidation of alcohol (**20**) (0.13 g, 0.51 mmol) gave the title compound (**31**) as a white solid (0.124 g, 90%) which was recrystallised from petroleum ether to give white crystals mp 117–118°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.20 (1H, s, H′-4), [7.92 (1H, d, J=8.1 Hz) and 7.86 (1H, d, J=8.1 Hz), H′-5 and H′-8], 7.83 (1H, s, H′-1), 7.67–7.50 (2H, complex, H′-6 and H′-7), 3.30 (2H, t, J=8.0 Hz, H-3), 2.81 (2H, t, J=8.0 Hz, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=179.0 (C=O), 134.8, 134.5, 130.9 and 127.4 (Ar-C′), 129.8, 128.7, 128.6, 127.4, 127.3 and

127.0 (Ar-C), 124.8 (q, J_{C-F}=273.5, *C*F_3), 35.5 (C-2), 27.4 (C-3); υ_{max} (CH_2Cl_2, cm^{-1}) 3036–2800 (OH), 1712 (C=O), 1640 and 1600 (C=C); LRMS (Scan AP^+): *m/z*=268 (M^+, 36 %), 222 [M^+−(HCOOH), 9], 194 [M^+−(CH_3CH_2COOH), 10]; HRMS (CI^+): (M^++NH_4) found, 286.1060, $C_{14}H_{11}F_3O_2$ requires, 286.1055. Found C, 62.67; H, 4.15%. $C_{14}H_{11}F_3O_2$ requires C, 62.69; H, 4.13%.

2-[3-(Trifluoromethyl)-2-naphthyl]acetic acid (34). Oxidation of alcohol (**26**) (0.24 g, 1.0 mmol) gave the title compound (**34**) as a white solid (0.21 g, 85%) which was recrystallised from ethyl acetate/petroleum ether to give white crystals mp 150–151°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.21 (1H, s, H′-4), [7.92 (1H, d, *J*=8.1 Hz) and 7.88 (1H, d, *J*=8.1 Hz), H′-5 and H′-8], 7.85 (1H, s, H′-1), 7.68–7.53 (2H, complex, H′-6 and H′-7), 4.10 (2H, s, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ=177.2 (C=O), 134.5, 131.4 and 128.7 (Ar-C′), 132.3, 128.8, 127.7, 127.5, 127.4 and 127.3 (Ar-C), 124.4 (*C*F_3), 38.2 (C-1); υ_{max} (CH_2Cl_2, cm^{-1}): 3250–2800 (OH), 1707 (C=O), 1640 and 1600 (C=C); LRMS (Scan AP^+): *m/z*=255 [(M^++1), 8%], 254 (M^+, 65), 236 [(M^+−H_2O), 7], 210 [(M^+−CO_2), 7]. Found C, 61.39; H, 3.35. $C_{13}H_9F_3O_2$ requires C, 61.42; H, 3.57%.

3-[7-Bromo-3-(trifluoromethyl)-2-naphthyl]propanoic acid (32). Oxidation of alcohol (**24**) (0.070 g, 0.21 mmol) gave the title compound (**32**) as a white solid (0.065 g, 88%) which was recrystallised from ethyl acetate/petroleum ether to give white crystals mp 158–159°C; ^{1}H NMR (300 MHz, DMSO) δ=8.42 (1H, s, H′-4), 8.23 (1H, brs, H′-8), 8.08 (1H, d, *J*=8.8 Hz, H′-5), 7.99 (1H, s, H′-1), 7.73 (1H, dd, *J*=8.8, 1.5 Hz, H′-6), 3.10 (2H, t, *J*=8.0 Hz, H-3), 2.68 (2H, t, *J*=8.0 Hz, H-2), 2.5 (1H, s, OH); ^{13}C NMR (75 MHz, DMSO) δ=173.5 (C=O), 135.95, 135.5, 128.85 and 122.4 (Ar-C′), 131.0, 130.1, 129.2, 128.6 and 127.2 (Ar-C), 34.5 (C-2), 26.9 (C-3); υ_{max} (CH_2Cl_2, cm^{-1}): 3200–2900 (OH), 1712 (C=O), 1637 and 1591 (C=C); LRMS (Scan AP^+): *m/z*=348 (M^++2, 72%), 347 (M^++1, 72%), 302 [(M^+−CO_2), 10]; Found C, 48.44; H, 2.93. $C_{14}H_{10}F_3O_2Br$ requires C, 48.44; H, 2.90%.

3-[7-Chloro-3-(trifluoromethyl)-2-naphthyl]propanoic acid (33). Oxidation of alcohol (**25**) (0.10 g, 0.347 mmol) gave the title compound (**33**) as a white solid (0.093 g, 89%) which was recrystallised from ethyl acetate/petroleum ether to give white crystals mp 137–138°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.18 (1H, s, H′-4), 7.83 (1H, d, *J*=8.8 Hz, H′-5), 7.81 (1H, s, H′-1), 7.73 (1H, brs, H′-8), 7.49 (1H, dd, *J*=8.8, 2.2 Hz, H′-6), 3.31 (2H, t, *J*=8.0 Hz, H-3), 2.82 (2H, t, *J*=8.0 Hz, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=178.7 (C=O), 135.9, 135.35, 134.6, 129.2 and 126.8 (Ar-C′), 130.3, 128.9, 128.0, 127.2 and 126.2 (Ar-C), 35.3 (C-2), 27.4 (C-3); υ_{max} (CH_2Cl_2, cm^{-1}): 3300–2900(OH), 1710 (C=O), 1640 (C=C). LRMS (Scan AP^+): *m/z*=304 (M^++2, 10%), 302 (M^+, 33). Found C, 55.42; H, 3.07; Cl, 11.86. $C_{14}H_{10}F_3O_2Cl$ requires C, 55.55; H, 3.33; Cl, 11.71%.

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