Synthesis of the farnesyl ether 2,3,5-trifluoro-6-hydroxy-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]nitrobenzene, and related compounds containing a substituted hydroxytrifluorophenyl residue: novel inhibitors of protein farnesyltransferase, geranylgeranyltransferase I and squalene synthase

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Pentafluoronitrobenzene was converted *via* two successive phase-transfer catalysed S_NAr reactions with (*E*,*E*)-farnesol or geraniol followed by hydroxide ion into the 2,3,6-trifluoro-5-hydroxy-4-nitrophenyl farnesyl ether **3a** and the geranyl ether **3b**. Analogues containing a cyano (**3c**) or carbamoyl (**3d**) group in place of nitro or an epoxygeranyl (**3e**) group as the prenyl (3-methylbut-2-enyl) containing residue were similarly prepared. Those containing a sulfonic acid (**35a**, **35b**) or a methyl sulfone (**41**) group were made by modifications of this approach involving the use of protecting groups. The synthesis of carboxy analogues (**27a**, **27b**) involved the alkylation of a protected fluorinated *ortho*-hydroxybenzoic acid derivative (**25**) with (*E*,*E*)-farnesyl or geranyl bromide. The non-fluorinated compound **18** was analogously prepared *via* compound **17a**. Mitsunobu reactions were used in the synthesis of **15**, a dihydroxylated analogue of **3b**, and of **8**, the non-fluorinated analogue of **3a**. The nitro compounds **3a** and **3b** were moderate inhibitors of both farnesyl transferase and geranylgeranyl transferase I, the geranyl carboxy derivative **27b** of the latter enzyme and the farnesyl sulfonic acid derivative **35a** of squalene synthase.

Introduction

The enzyme protein farnesyl transferase (FTase) plays a pivotal role in the cell-signalling pathway from a cell surface receptor to the nucleus.[1] The enzyme farnesylates the Ras protein, using farnesyl diphosphate as the source of the farnesyl group. This step is a necessary precursor to association of Ras with the cell membrane, where it can interact with its signalling partners. Ras possesses GTPase activity and functions as a molecular switch cycling between the active, GTP-bound and the inactive, GDP bound states. Ras is frequently found mutated or over-expressed in many cancers and so inhibitors of Ras function, *e.g.* of FTase, are attractive targets for novel cancer therapies.[2] Also a potentially important target is the geranylgeranyl diphosphate-utilising enzyme geranylgeranyl transferase I (GGTase I) which can mediate geranylgeranylation and activation of one form of Ras, Ki-Ras, even in the presence of an inhibitor of FTase.[3] GGTase I also mediates the geranylgeranylation of Rho family proteins of potential importance in controlling cell motility and invasion.[4]

After a preliminary modelling study[5] in which certain substituted aryl groups, bearing a hydroxy substituent, were compared with di- or tri-phosphate groups (in relation to selection of possible analogues of guanosine 5′-triphosphate), we synthesised the farnesyl compound 2,3,5-trifluoro-6-hydroxy-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]-nitrobenzene (**3a**), in which the diphosphate group of farnesyl diphosphate is replaced by a 2,3,6-trifluoro-5-hydroxy-4-nitrophenyl group. As previously reported,[6] compound **3a** is an inhibitor of FTase and GGTase I. We subsequently prepared further, related compounds to elucidate effects of structure within the substituted phenyl group on activity against these enzymes. The choice of compounds reflects our interest in the effect of the nature of the group *para* to the isoprenoid-bearing oxygen (a nitro group in compound **3a**). Certain compounds were also prepared to gain information on the effect of the *ortho* hydroxy group and the fluorination within the phenyl group. Compounds containing a geranyl group were also prepared, either in addition to or in place of the corresponding (*E*,*E*)-farnesyl compound. In addition to the syntheses, we report results of inhibition assays for the target enzymes FTase and GGTase I, and also for the enzyme squalene synthase (SqSase), which is critically involved in cholesterol synthesis, and which, like FTase, uses farnesyl diphosphate as a substrate.

The substituted aryl groups in the compounds described here may be compared with those in a series of inhibitors of ATP-dependent EGF-receptor tyrosine kinase reported by Liu *et al.*,[7] which contain a benzene ring with a carboxylic acid, nitro, amide or sulfonic acid group *ortho* to a hydroxy group.

Results and discussion

Synthesis

The target compounds synthesised are listed in Table 1. A general approach which has been used to synthesise several of the target compounds is sequential S_NAr reactions of perfluoroarenes with the appropriate alkoxide ion followed by hydroxide ion (Scheme 1). Thus, pentafluoronitrobenzene (**1a**)

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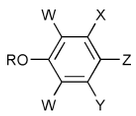
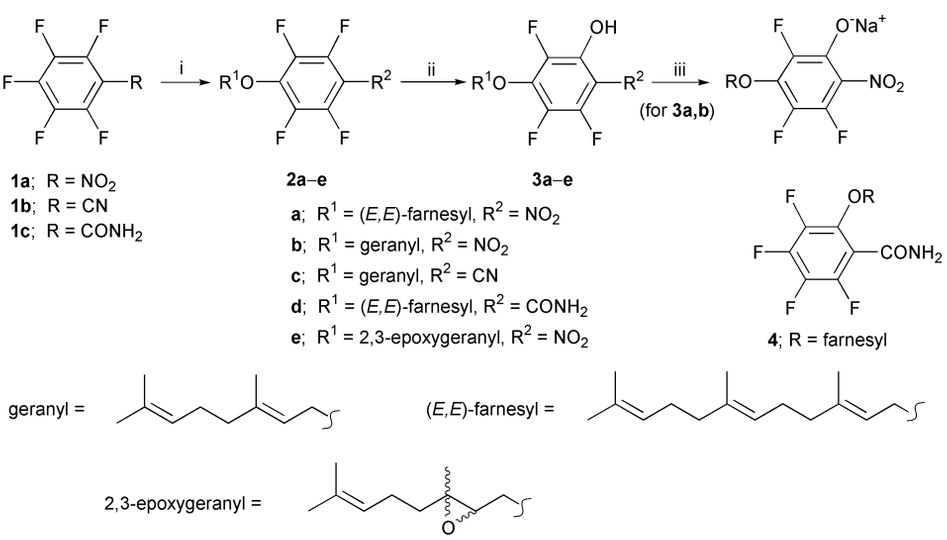
Table 1 Inhibition studies[a]



	R	W	X	Y	Z	FTase[b]	GGTase I[c]	SqSase[d]
2b	Geranyl	F	F	F	NO_2	>100	>100	Nd
3a	Farnesyl[e]	F	F	O^-Na^+	NO_2	6.3 ± 1.11	12.5 ± 2.0	69 ± 7
3b	Geranyl	F	F	O^-Na^+	NO_2	2.9	6.2	>100
3c	Geranyl	F	F	OH	CN^-	64	80	>100
3d	Farnesyl	F	F	OH	$CONH_2$	>100	>100	>100
3e	Epoxygeranyl[f]	F	F	OH	NO_2	>100	7.5 ± 0.8	>100
8	Farnesyl	H	H	OH	NO_2	>100	>100	>100
15	Geranyl	F	OH	OH	NO_2	>100	>100	>100
18	Farnesyl	H	H	OH	CO_2H	>100	>100	90 ± 8
27a	Farnesyl	F	F	OH	$CO_2^-Na^+$	>100	45 ± 12	>100
27b	Geranyl	F	F	OH	$CO_2^-Na^+$	45 ± 12	8.5 ± 1.1	>100
30	Farnesyl	F	F	F	$CO_2^-Na^+$	>100	>100	>100
35a	Farnesyl	F	F	OH	$SO_3^-Na^+$	125	150	12 ± 2
35b	Geranyl	F	F	OH	$SO_3^-Na^+$	>100	114	34 ± 4
41	Geranyl	F	F	OH	SO_2Me	25	30	Nd
	α-Hydroxyfarnesylphosphonic acid					2.6 ± 0.24	25 ± 5	9.2 ± 3.5
	Chaetomellic acid A					2.5 ± 0.5	40 ± 7	100 ± 18

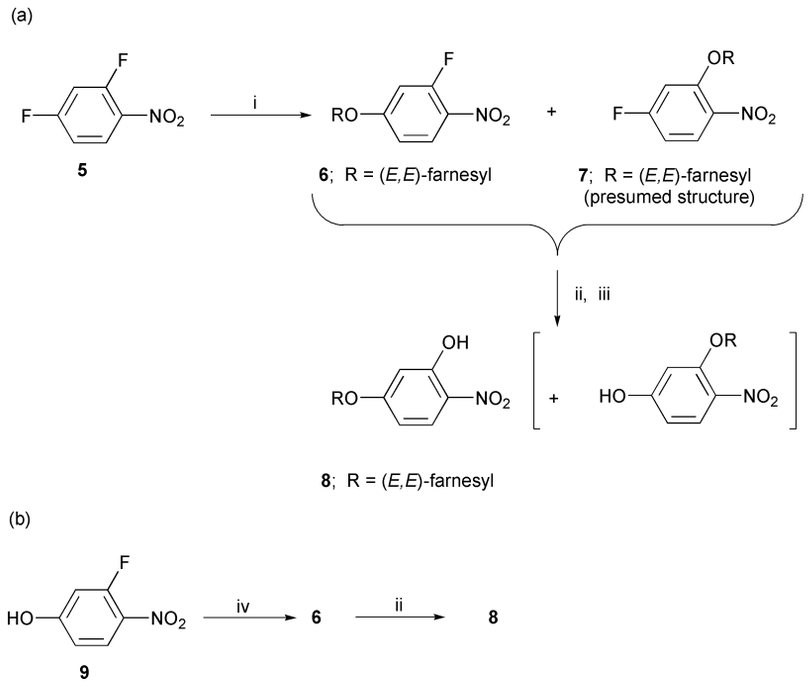
[a] For assay procedures, see ref. 34 (FTase, GGTase I) and ref. 35 (SqSase). [b] Farnesyl transferase. [c] Geranylgeranyl transferase I. [d] Squalene synthase (values are for inhibition of squalene formation). [e] Farnesyl = (*E*,*E*)-farnesyl. [f] Epoxygeranyl = 2,3-epoxygeranyl. Nd = not determined; IC_{50} values are the mean of three independent determinations ±sd, except where no sd is given; >100 means no significant inhibition at highest concentration tested, 100 μM.



Scheme 1 *Reagents and conditions*: i, ROH, 1 M aq. NaOH, $Bu_4N^+HSO_4^-$, CH_2Cl_2; ii, 50% w/w aq. NaOH, $Bu_4N^+HSO_4^-$ (+ $(C_6H_{13})_4N^+HSO_4^-$ for **2d**→**3d**), PhMe; iii, for **3a**: NaOH, Et_2O; for **3b**: Amberlite IRC50 (Na^+ form).

has been reported[8] to undergo mono-substitution by methoxide ion preponderantly at the *para*-position. To generate the corresponding alkoxides from (*E*,*E*)-farnesol or geraniol needed for their analogous reactions with **1a** (Scheme 1), phase-transfer catalysis (PTC) was used. The reaction of a variety of alcohols and phenols with reactive perfluoroarenes was conveniently conducted at ambient temperature in a two-phase system comprising dilute aqueous sodium hydroxide with dichloromethane as the organic phase and tetra-*n*-butylammonium hydrogen sulfate as the phase-transfer catalyst.[9] After purification, solutions in toluene of the intermediate farnesyl and geranyl ethers, respectively **2a** and **2b**, were treated in a second PTC step with 50% aqueous sodium hydroxide and tetra-*n*-butylammonium hydrogen sulfate to introduce the hydroxy group *ortho* to the nitro substituent. Hydroxy derivatives **3a** and **3b** were converted into their respective solid sodium salts since the parent phenols tended to decompose during storage. The choice of phase-transfer conditions for the second step also has literature precedents, including previous work from this laboratory. In concentrated aqueous alkaline solutions (50% NaOH or 60% KOH) hydroxide ions are minimally solvated, and unhydrated anions can be transferred from the aqueous to the organic phase under PTC conditions.[10] It has been proposed[11a] that hydroxide ion itself is extracted from such concentrated alkaline solutions into the organic phase with a limited number of water molecules in its hydration sphere and is thus highly nucleophilic. The formation of phenols from 1,2,3,4-tetrafluorobenzene and hexafluorobenzene under such conditions has been described,[11a,b] and the potential advantage of the phase-transfer methodology over other methods for the synthesis of polyfluorophenols was discussed.[11b] We have also used such conditions to prepare 4,4′-dihydroxyoctafluoroazobenzene from decafluoroazobenzene,[12] whereas the use of potassium hydroxide in *tert*-butyl alcohol had afforded only mono-substitution products.[12,13]

Pentafluorobenzonitrile **1b** has also been shown to react with one equivalent of sodium methoxide in methanol to give predominantly the *para*-substituted product.[14] Analogously, application of the foregoing first PTC reaction conditions to nitrile **1b** (Scheme 1), using geraniol as the alcohol, gave pre-

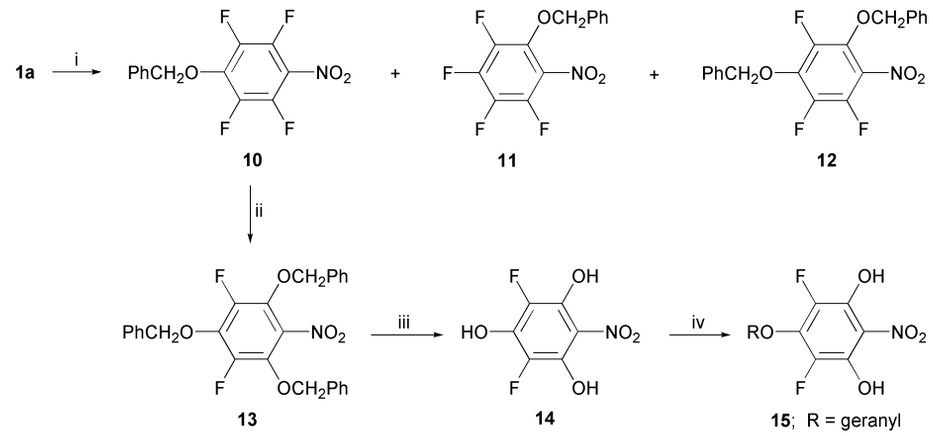


Scheme 2 *Reagents and conditions*: i, (*E*,*E*)-farnesol, 1 M aq. NaOH, $Bu_4N^+HSO_4^-$, CH_2Cl_2; ii, 50% w/w aq. NaOH, $Bu_4N^+HSO_4^-$; iii, chromatography; iv, (*E*,*E*)-farnesol, DEAD, PPh_3, THF.

dominantly geranyl ether **2c**. It is of interest that the nitrile function survived the harsher PTC conditions required to perform the second step, from **2c** to the hydroxy derivative **3c**, given that prolonged treatment of starting nitrile **1b** with aqueous sodium hydroxide is known to hydrolyse the nitrile function to produce tetrafluoro-4-hydroxybenzoic acid.[14] An analogous route from pentafluorobenzamide **1c**, with farnesol as the alcohol, likewise afforded the amide **3d** (Scheme 1), though both steps needed longer reaction times, at elevated temperatures, reflecting the lesser activating effect of the carbamoyl substituent. Also in contrast to the other pentafluoroarene starting materials, which gave product yields of 50% or better in the first PTC step, with strong regioselectivity for *para*-substitution, amide **1c** gave a poor yield of a mixture of the *ortho*-substituted (**4**) and *para*-substituted (**2d**) farnesyl ethers in the first step with preponderance (19% yield) of the former. It is possible that hydrogen bonding between the amide carbonyl function and hydroxide ion directs *ortho*-substitution, by analogy with the observation that a nitro group can direct *ortho*-substitution by an amine.[8] However the carbamoyl function withstood well the conditions of the second PTC step, possibly because of ionisation of the –NH function, and a 50% yield of the hydroxy derivative **3d** was obtained from the intermediate tetrafluoro derivative **2d**.

An unfluorinated analogue of **3a**, compound **8**, was prepared (Scheme 2, (a)) by the general methods described above, using 2,4-difluoronitrobenzene **5** and (*E*,*E*)-farnesol as the starting materials. In contrast to **1a** though, the reaction of **5** with (*E*,*E*)-farnesol was not regioselective, producing an inseparable mixture of the desired intermediate *para*-substituted farnesyl ether **6** and the presumed *ortho*-substituted analogue **7** in *ca.* 1:1 ratio. This lack of regioselectivity is also in contrast to the 5:1 bias in favour of the *para*-substituted product reported for the reaction of 2,4,5-trifluoronitrobenzene with the alkoxide of Boc-piperidin-4-ol.[15] It would appear from these results that it is the additional activating effect of the 5-fluoro substituent which favours 4- over 2-substitution in this trifluoronitrobenzene and the presence of two (as opposed to only one) adjacent fluorine substituents which favours 4-substitution in the case of **1a**. Fortunately the second PTC step, applied to the mixture of **6** and **7**, gave two easily separable products. To confirm which of these products was the desired 2-hydroxy derivative **8**, the second step was repeated on pure 2-fluoro derivative **6** prepared (Scheme 2, (b)) by a Mitsunobu reaction between 3-fluoro-4-nitrophenol **9** and (*E*,*E*)-farnesol, unambiguously producing the correct regioisomer **8**.

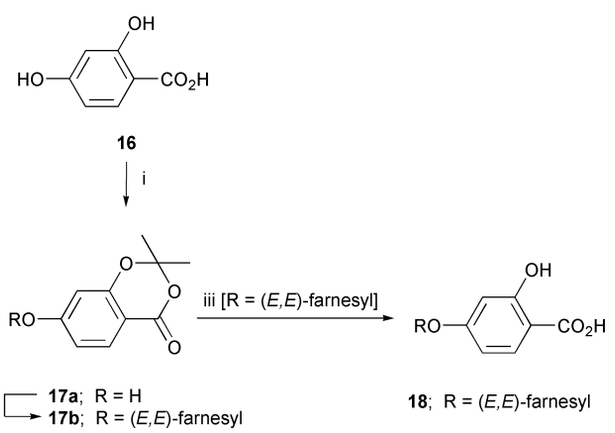
In view of the strongly deactivating influence of the O^- substituent[16] towards further nucleophilic substitution reactions, the direct introduction of a second hydroxy group into **3b** by nucleophilic displacement under strongly basic conditions was not explored as a potential route to the 2,6-dihydroxynitro compound **15**. The alternative approach adopted (Scheme 3) was suggested by the known ready conversion of pentafluoronitrobenzene **1a** into 2,4,6-trialkoxy derivatives by reaction with sodium methoxide[8] or sodium ethoxide.[17] However methoxy or ethoxy derivatives were not precursors of choice for the synthesis of the target intermediate trihydroxy derivative **14** as the strongly deactivating nitro substituent was thought likely to impede cleavage of these alkoxy groups by Lewis acids. Thus 4-methoxytetrafluoronitrobenzene was only partly demethylated[18] by aluminium chloride under conditions known to fully demethylate 2,3,5,6-tetrafluoroanisole.[19] Also, the powerful Lewis acid aluminium triiodide was needed to cleave the strongly deactivated methoxy substituents in 4,4′-dimethoxyoctafluoroazobenzene in one route to the 4,4′-dihydroxy derivative.[12] It was thought that tribenzyl derivative **13** might be cleaved under milder conditions and this compound was therefore targeted as a potential intermediate to **14**. Thus **1a** and benzyl alcohol reacted (Scheme 3) under PTC conditions to give mainly the 4-substituted product **10** in 72% isolated yield, together with minor amounts of the 2-isomer **11** (3%) and the 2,4-disubstituted product **12** (1.5%). The 2- and 6-fluorine substituents in **10** were then displaced by treatment with a solution generated from benzyl alcohol and potassium *tert*-butoxide in THF[15] to give the trisubstituted derivative **13** in 52% isolated yield together with disubstituted derivative **12** (2.6%). The product **13** was debenzylated using TFA–pentamethylbenzene,[20] to give the trihydroxynitro compound **14**. The subsequent reaction of **14** with geraniol under Mitsunobu conditions was sufficiently regioselective to afford the desired regioisomer **15** in moderate (37%) yield. A precedent for such a regioselective Mitsunobu reaction comes from the work of Dushin and Danishefsky,[21] who described the specific benzylation of the



Scheme 3 *Reagents and conditions*: i, BnOH, 1 M aq. NaOH, $Bu_4N^+HSO_4^-$, CH_2Cl_2; ii, BnOH, KOBu^t, THF; iii, pentamethylbenzene, TFA; iv, geraniol, DIAD, PPh_3, THF.

4-hydroxy group of the isopropylidene derivative of 2,4,6-trihydroxybenzoic acid.

Analogues of **3a**, **3b** and **8** which contain a carboxy group in place of nitro are particularly interesting targets. The 2-hydroxybenzoic acid (salicyl) residue is present in several inhibitors of ATP-dependent EGF receptor tyrosine kinase,[7,22,23] where its role may be to compete with ATP for chelation of the Mg^{2+} ion present in the active site of the EGF receptor.[22,23] Magnesium ion is also required by FTase where it probably coordinates to and activates the diphosphate leaving group of farnesyl diphosphate.[24] Analogous inhibition of FTase by compounds containing farnesyl appropriately attached to a salicyl group might therefore be envisaged. The route chosen for the synthesis of the present target compounds was suggested by the aforementioned[21] use of the isopropylidene group to protect simultaneously a carboxy and *ortho*-hydroxy function. Analogously (Scheme 4), protection of these functionalities



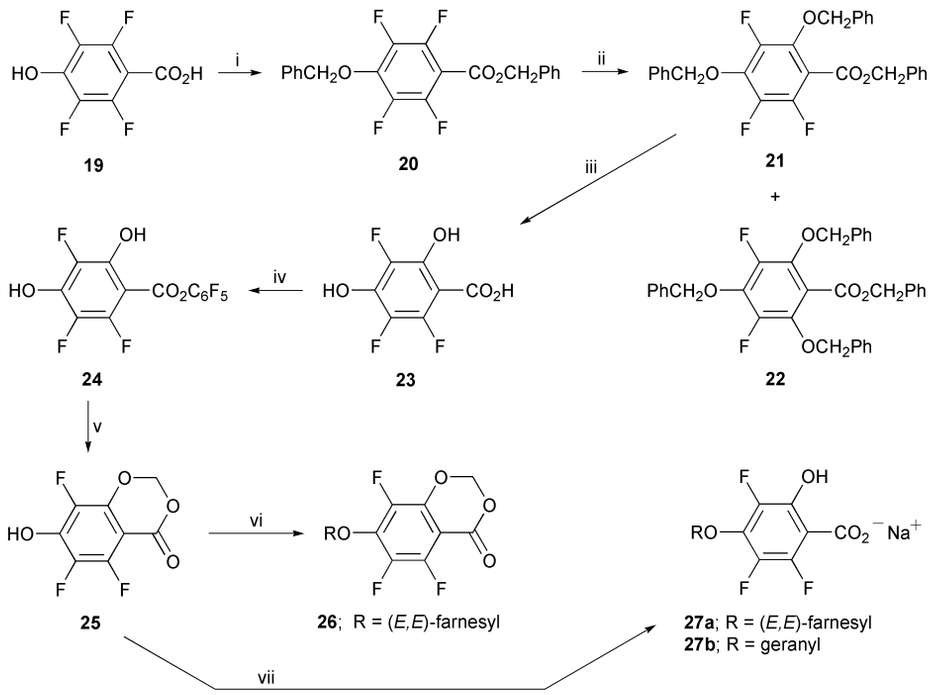
Scheme 4 *Reagents and conditions*: i, Me_2CO, TFAA, TFA; ii, (*E*,*E*)-farnesyl bromide, NaH, THF, 60 °C, 3 h; iii, 48% aq. KOH, DMSO, 60 °C, then 1 M aq. HCl.

in 2,4-dihydroxybenzoic acid **16**, to give the isopropylidene derivative **17a**, then treatment with (*E*,*E*)-farnesyl bromide–sodium hydride, gave farnesyl ether **17b**. Alkaline hydrolysis of **17b** gave the target unfluorinated hydroxy acid **18** in 19% yield overall from **16**.

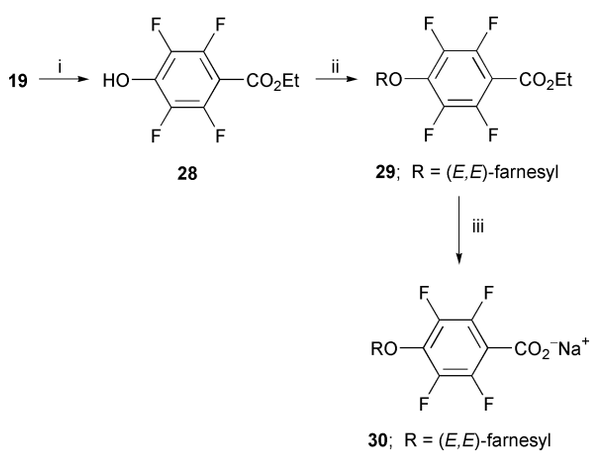
In relation to the preparation of fluorinated analogues of **18**, it was noted that a compound having the desired substitution pattern, namely 3,5,6-trifluoro-2-hydroxy-4-methoxybenzoic acid[25] is known. However, its synthesis involves heating 2,3,4,5-tetrafluorophenol with sodium methoxide in sulfolane at 140 °C, prior to treatment of the resulting 4-methoxy derivative with *n*-butyllithium and carbon dioxide to introduce the carboxy group. It seemed unlikely that the first step could be adapted to introduce the more sensitive farnesyl and geranyl groups, so an alternative synthetic strategy was adopted.

An appropriate dihydroxylated precursor to the target compounds was obtained (Scheme 5) by first dibenzylating commercially available 4-hydroxytetrafluorobenzoic acid **19** using benzyl bromide and caesium carbonate in dimethylformamide,[26] then treating the product benzyl ether **20** with a solution prepared from benzyl alcohol and potassium *tert*-butoxide in THF[15] to give 2,4-bis(benzyloxy) derivative **21** with the 2,4,6-trisubstituted derivative **22** as a minor product. The transformation of **20** into **21** may be regarded as analogous to the reported reaction of methyl 2,3,5,6-tetrafluoro-4-methoxybenzoate with sodium methoxide to give a 2,4-dimethoxy derivative.[25] Catalytic hydrogenation of **21** gave the fluorinated dihydroxy acid **23** in 53% overall yield from monohydroxy acid **19**. Attempts to use the isopropylidene group to protect the carboxy and adjacent hydroxy functions in **23**, as had been successful with the unfluorinated dihydroxy acid **16** (Scheme 4), gave only very low yields of material believed to be the desired product (results not shown). However a base-promoted reaction of phenyl salicylates with a variety of aliphatic aldehydes has been described[27] and from the potential protecting groups exemplified, methylene was chosen. Dihydroxy acid **23** was first converted into its crude pentafluorophenyl ester **24** by reaction with pentafluorophenyl trifluoroacetate.[28] Application of the aforementioned reaction conditions[27] to **24**, using paraformaldehyde, produced the selectively protected derivative **25** albeit in modest yield (24%). Reaction of **25** with (*E*,*E*)-farnesyl bromide–caesium carbonate in dimethylformamide produced protected farnesyl ether **26**. If the time allowed for this step was extended, spontaneous *in situ* cleavage of the methylene protecting group ensued to give the target farnesyl derivative, isolated after passing through an ion-exchange column as its crystalline sodium salt **27a**. Spontaneous deprotection was also observed after geranylation of **25** to give the corresponding geranyl derivative, also isolated as the sodium salt **27b**. To assess the influence of the phenolic function in the trifluorinated carboxylate **27a** on enzyme inhibitory activity, its tetrafluorinated analogue was needed. This was prepared in three steps from hydroxy acid **19** (Scheme 6). Ester **28** had previously been made from ethyl pentafluorobenzoate, using sodium nitrite to introduce the 4-hydroxy group.[29] Alkaline hydrolysis of the product (**29**) of farnesylation of **28** afforded the sodium salt **30** in 33% overall yield from **19**.

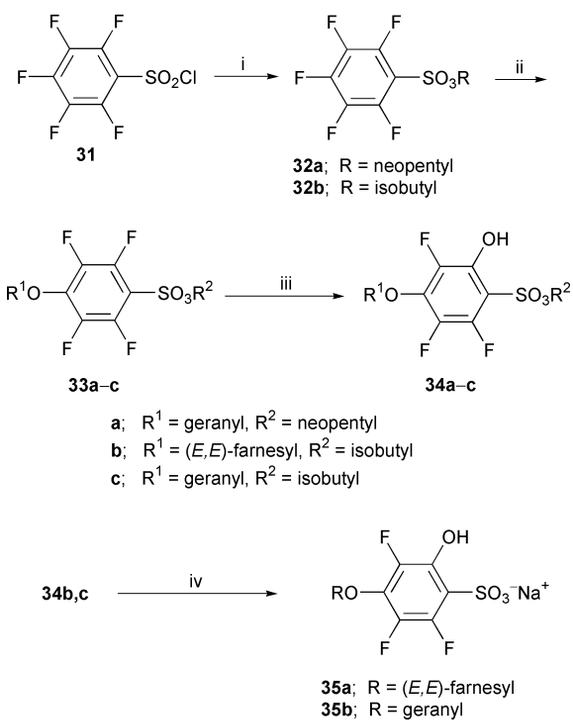
The synthesis of compounds containing the sulfonic acid substituent (Scheme 7) was envisaged as proceeding *via* an ester of pentafluorobenzenesulfonic acid. The ester function needed to be sufficiently base-stable to withstand the conditions of the two PTC reactions used to insert the prenyl containing and hydroxy functions, but labile enough to be removed at the end of the reaction sequence without cleavage of the farnesyl or



Scheme 5 *Reagents and conditions*: i, BnBr, Cs_2CO_3, DMF; ii, BnOH, $KOBu^t$, THF; iii, H_2, Pd–C, MeOH–H_2O; iv, pentafluorophenyl trifluoroacetate, pyridine, CH_2Cl_2; v, paraformaldehyde, DABCO, DMF; vi, (*E*,*E*)-farnesyl bromide, Cs_2CO_3, DMF; vii, RBr, Cs_2CO_3, DMF, then Amberlite IRC50 (Na^+ form).



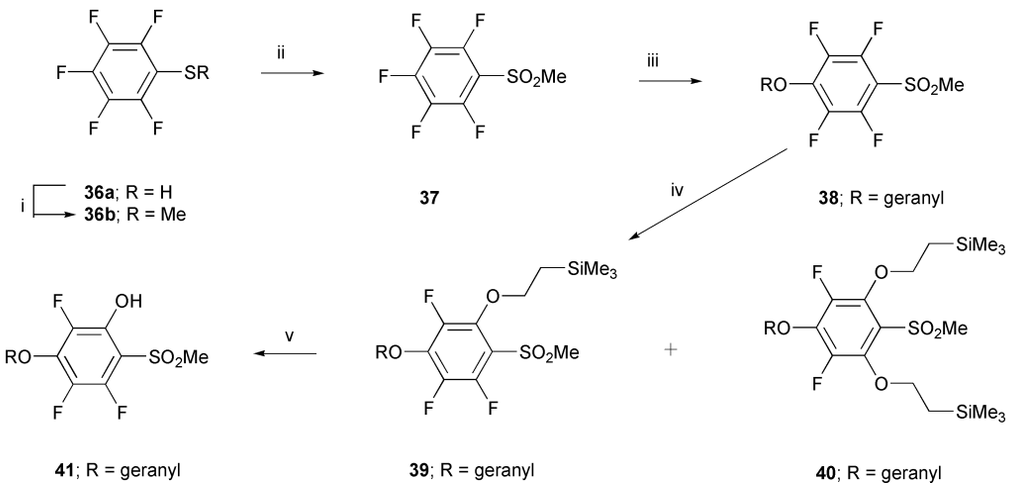
Scheme 6 *Reagents and conditions*: i, EtOH, H_2SO_4; ii, (*E*,*E*)-farnesyl bromide, Cs_2CO_3, DMF; iii, NaOH, EtOH–H_2O.



Scheme 7 *Reagents and conditions*: i, ROH, pyridine, Et_2O; ii, R^1OH, 1 M aq. NaOH, $Bu_4N^+HSO_4^-$, CH_2Cl_2; iii, 50% w/w aq. NaOH, $Bu_4N^+HSO_4^-$, PhMe; iv, for **34b**: NaI, MeCN; for **34c**: $Me_4N^+I^-$, MeCN, then Bio-Rad AG50W X-4 (Na^+ form).

geranyl moiety. The 2,2-dimethylpropan-1-yl (neopentyl) protecting group, developed for arylsulfonic acids,[30] was explored first. Commercially available pentafluorobenzenesulfonyl chloride **31** was converted (Scheme 7) into the neopentyl ester **32a**. Application of the previously described two phase-transfer steps, using geraniol in the first step, produced successively the geranyl ether **33a** and the hydroxy derivative **34a**. However, attempts to remove the neopentyl group selectively from **34a**, by heating with tetramethylammonium iodide in acetonitrile at 40–50 °C or with sodium iodide in $(CD_3)_2SO$ at 50–60 °C appeared to remove the geranyl group (results not shown). We therefore turned to the 2-methylpropan-1-yl (isobutyl) protecting group which has been used[31] in the synthesis of sulfonate-containing nucleosides. Despite the expected greater lability of this group towards hydroxide ion, it withstood the strongly basic conditions of the second phase-transfer step sufficiently to yield the required protected farnesyl derivative (**34b**) in 50% yield from its precursor **33b**. The lower isolated yield of the geranyl derivative **34c** from the corresponding step (19%) reflects at least in part the fact that a portion of the product formed was discarded owing to the presence of a by-product which had been incompletely separated during chromatography. The deprotection of **34b** was carried out with sodium iodide in acetonitrile, which reacted smoothly at room temperature and gave the sodium salt **35a** directly. The isobutyl group was removed from **34c** by warming with tetramethylammonium iodide in acetonitrile; a subsequent ion-exchange step produced the sodium salt **35b**.

The final variable ring-substituent exemplified was the methyl sulfone moiety. The route to the relevant target compound, the sulfone **41**, is shown in Scheme 8. Pentafluorothiophenol (**36a**) was converted into the known thiomethyl derivative (**36b**),



Scheme 8 *Reagents and conditions*: i, methyl toluene-*p*-sulfonate, 1 M aq. NaOH, $Bu_4N^+HSO_4^-$, CH_2Cl_2; ii, 30% w/w aq. H_2O_2, AcOH, 100 °C, 2 h; iii, geraniol, 1 M aq. NaOH, $Bu_4N^+HSO_4^-$, CH_2Cl_2; iv, 2-(trimethylsilyl)ethanol, $KOBu^t$, THF; v, 1 M $Bu_4N^+F^-$, THF then Bio-Rad AG50W-X4 (H^+ form).

using methyl toluene-*p*-sulfonate, thereby avoiding the previously used,[32] potentially hazardous diazomethane. Oxidation to the known sulfone (**37**),[32] followed by the usual phase-transfer catalysed reaction, with geraniol, afforded geranyl ether **38**. However, the second phase-transfer reaction to insert the hydroxy function, which had previously been successful in the presence of nitro, cyano, carbamoyl and sulfonate ester substituents, failed when applied to the methyl sulfone derivative **38**, giving an intractable mixture from which the desired product **41** could not be recovered. An alternative strategy, in which the hydroxy group was introduced in a protected form, was envisaged. The benzyl protecting group had been successfully used for this purpose during syntheses of the dihydroxy nitro derivative **15** and the carboxy derivatives **27a** and **27b**. However, its removal in these cases preceded introduction of the farnesyl or geranyl substituent, which would not be the case in the presently envisaged route to **41**. It seemed unlikely that the geranyl group would survive either the hydrogenolysis or TFA deprotection methods used to remove a benzyl substituent. Therefore, 2-(trimethylsilyl)ethyl, originally developed for the protection of carboxy functions,[33] was chosen as an alternative protecting group, removable under mild conditions that would spare the geranyl function. Tetrafluoro derivative **38** was treated with a solution prepared from 2-(trimethylsilyl)ethanol and potassium *tert*-butoxide in THF to give the (trimethylsilyl)ethyl ether (**39**) (69% yield) together with a minor proportion of the bis[(trimethylsilyl)ethyl] derivative (**40**) (15%). Deprotection of **39** using tetra-*n*-butylammonium fluoride followed by treatment with acidic ion-exchange resin afforded the desired hydroxy derivative **41** in 51% yield from **39** and 26% overall from pentafluorophenyl methyl sulfone **37**.

Enzyme inhibition studies

Compounds were tested for their ability to inhibit the FTase and GGTase I activities of the cytosolic fraction of rat brain (which contains both these activities), using a previously published procedure from this laboratory.[34] Inhibition of the SqSase activity of rat liver microsomes was also determined using a published procedure[35] except that a substrate concentration of 10 μM farnesyl diphosphate with 0.06 μCi [1-^{3}H]farnesyl diphosphate was used, and 2 mM dithiothreitol was added to the assay buffer. Inhibitory activities (see Table 1) were compared with those of standard inhibitors of FTase, namely α-hydroxyfarnesylphosphonic acid and chaetomellic acid A, which have been identified as competitive inhibitors of FTase with respect to farnesyl diphosphate.[36] As had been reported previously,[6] the nitro derivative **3a** inhibited H-Ras farnesylation with IC_{50} 6.3 μM (Table 1). Replacement of the farnesyl group by a geranyl group (**3b**) reduced the FTase IC_{50} to 2.9 μM. Compounds **3a** and **3b** each inhibited GGTase I with about half the potency they displayed against FTase. In the SqSase assay, the (*E*,*E*)-farnesyl compound **3a** had weak activity, while the geranyl compound **3b** was inactive. As a working hypothesis we considered that **3a** acts as an analogue of farnesyl diphosphate, so the greater activity of the geranyl derivative **3b** compared with the farnesyl derivative **3a** in the FTase assay was surprising, and encouraged the synthesis of further geranyl derivatives for evaluation. Attempts to prepare the geranylgeranyl analogue of **3a**, as a potential inhibitor of the geranylgeranyl diphosphate-utilising enzyme GGTase I, were frustrated by the lipophilic character conferred by the geranylgeranyl substituent.[37]

The farnesyl carboxy derivative **27a** had much weaker activity than its nitro analogue **3a** against GGTase I, and did not inhibit FTase. However, as with the nitro compounds, replacement of the (*E*,*E*)-farnesyl group in **27a** with geranyl improved potency against GGTase I, here to such an extent that the geranyl carboxy derivative **27b** was almost as good an inhibitor of this enzyme (IC_{50} 8.5 μM) as the corresponding nitro derivative **3b** (IC_{50} 6.2 μM).

The unfluorinated farnesyl nitro and farnesyl carboxy compounds, respectively **8** and **18**, the geranyl tetrafluoro nitro compound **2a** and the farnesyl tetrafluoro carboxy compound **30** were all inactive against both FTase and GGTase I. Thus, ring fluorination and the presence of the ring –OH group together appear to contribute vitally to activity against these enzymes. Compound **15**, containing two ring –OH groups, was however also inactive in all the assays.

The other substituted phenoxy groups evaluated all had the 2,3,5-trifluoro-6-hydroxy substitution pattern, and exemplified further variations at the ring position *para* to the isoprenoid-bearing O atom. The farnesyl carbamoyl compound **3d** was inactive in all three assays. The geranyl cyano compound **3c** showed slight inhibition of FTase and GGTase I. The geranyl sulfone derivative **41** was a moderate inhibitor but showed little selectivity between FTase and GGTase I. The (*E*,*E*)-farnesyl and geranyl sulfonic acid sodium salts **35a** and **35b** showed very weak or no activity against FTase and GGTase I, but in the SqSase assay they were the two most active among the compounds evaluated. The greater potency towards SqSase of the farnesyl analogue **35a** (IC_{50} 12 μM) compared with the geranyl compound **35b** (IC_{50} 34 μM) is in this case consistent with a compound acting as a substrate analogue.

In the FTase-catalysed reaction, a bond is formed between the sulfur atom of the carboxy terminal cysteine residue of the

protein substrate and C-1 of farnesyl diphosphate and diphosphate ion is released.[38] The 2,3-epoxygeranyl compound **3e** was made with the possibility in mind that, if **3e** could occupy the binding site of farnesyl diphosphate, it might prevent farnesylation of the Ras protein by alkylating its terminal cysteine –SH group. 2,3-Epoxygeraniol is readily obtained by regioselective epoxidation of geraniol using 3-chloroperoxybenzoic acid.[39] The epoxide functionality withstood the conditions of the two PTC reactions starting from pentafluoronitrobenzene **1a** (Scheme 1) to afford successively intermediate **2e** and target epoxygeranyl nitro derivative **3e**. Remarkably, and in marked contrast to its geranyl counterpart **3b** which was the most potent inhibitor of FTase (IC_{50} 2.9 μM) among the compounds described here, epoxygeranyl derivative **3e** did not inhibit FTase, but was a selective inhibitor of GGTase I, with IC_{50} 7.5 μM similar to that of **3b**.

Concluding remarks

In summary, efficient methods have been described for the preparation of compounds containing isoprenoid residues attached to 2,3,6-trifluoro-5-hydroxy-4-X-phenoxy groups, where X represents a variety of substituents. The relative potency of inhibition towards FTase, GGTase I and SqSase varied with the nature of the substituent X and with that of the attached isoprenoid residue. The synthetic methods described should allow the introduction of a wide range of substituents other than farnesyl and geranyl. The chemistry described also extends the variety of methods available for introducing one or even two hydroxy substituents into a polyfluorinated aromatic ring.

Experimental

Melting points were determined with a Reichert micro-hot-stage apparatus, and are uncorrected. NMR spectra were recorded on a Bruker AC250 spectrometer at 250 MHz for ^1H spectra and at 235 MHz for ^{19}F spectra. The residual signal for undeuterated solvent was used as internal standard for ^1H spectra. For ^{19}F spectra, chemical shifts are relative to $FCCl_3$ ($\delta_F = 0$). IR spectra were recorded on a Perkin-Elmer 1720X spectrometer. Elemental analyses were carried out by C.H.N. Analysis Ltd, Leicester, England or Butterworth Laboratories Ltd, Teddington, England. ESI mass spectra were obtained on a Finnigan MAT TSQ700 triple quadrupole mass spectrometer or a Finnigan LCQ ion trap mass spectrometer. FAB mass spectra were obtained at the School of Pharmacy, London University. Dried solvents were used for reactions where appropriate.

4-[(*E*)-3,7-Dimethylocta-2,6-dien-1-yloxy]-2,3,5,6-tetrafluoronitrobenzene 2b. (Phase-transfer catalysed formation of ethers: general procedure A)

Pentafluoronitrobenzene **1a** (3.20 g, 15 mmol), geraniol (2.31 g, 15 mmol), dichloromethane (30 cm^3), 1 M aqueous sodium hydroxide (30 cm^3), and tetra-*n*-butylammonium hydrogen sulfate (0.51 g, 1.5 mmol) were stirred together rapidly at ambient temperature for 1 h. The mixture was cooled in ice and sufficient 1 M sulfuric acid was added dropwise to render the aqueous layer neutral (pH 7). The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (3 × 10 cm^3). The combined dichloromethane solution was washed with water (3 × 25 cm^3), dried ($MgSO_4$) and evaporated. Chromatography (Merck 9385 silica) with hexane–dichloromethane (4:1) as eluant gave the *geranyl derivative* **2b** (2.645 g, 50%) as a yellow oil (Found: C, 55.45; H, 5.0; N, 3.95; F, 21.6; $C_{16}H_{17}F_4NO_3$ requires C, 55.3; H, 4.9; N, 4.0; F, 21.9%); δ_H [$(CD_3)_2SO$] 1.55 (3 H, s), 1.62 (3 H, s), 1.69 (3 H, d, *J* 0.8) (3 × Me), 2.04 (4 H, m, 4,5-H), 4.96 (2 H, d, *J* 7.3, 1-H), 5.02 (1 H, m, 6-H), 5.45 (1 H, t, *J* 7.3, 2-H); δ_F [$(CD_3)_2SO$] −154.56 (2 F, m), −146.99 (2 F, m); *m*/*z* (ESI, −ve ion mode) 346 $(M - H)^-$, 210 $(M - geranyl)^-$.

4-[(*E*)-3,7-Dimethylocta-2,6-dien-1-yloxy]-2,3,5-trifluoro-6-hydroxynitrobenzene 3b. (Phase-transfer catalysed hydrolysis: general procedure B)

A mixture of **2b** (0.695 g, 2.0 mmol), toluene (5.3 cm^3) and 50% w/w aqueous sodium hydroxide (1 cm^3) and tetra-*n*-butylammonium hydrogen sulfate (0.68 g, 2.0 mmol) was stirred rapidly at 50 °C for 1 h. The mixture was cooled and partitioned between toluene (25 cm^3) and water (15 cm^3) with acidification (1 M hydrochloric acid) of the aqueous phase to pH 4–5. The aqueous phase was extracted with diethyl ether (4 × 20 cm^3) and the combined organic phases were washed with water (5 × 10 cm^3), dried ($MgSO_4$) and evaporated. Chromatography [Merck 7729 silica; hexane–dichloromethane (1:1), dichloromethane, and dichloromethane–ethanol (99:1 then 98:2) in succession] gave the *geranyl nitro derivative* **3b** (0.395 g, 57%) (orange oil) (Found: C, 56.0; H, 5.45; N, 3.9; F, 16.2; $C_{16}H_{18}F_3NO_4$ requires C, 55.65; H, 5.25; N, 4.1; F, 16.5%); δ_H [$(CD_3)_2SO$] 1.54 (3 H, s), 1.61 (3 H, s), 1.66 (3 H, d, *J* 0.6) (3 × Me), 2.02 (4 H, m, 4,5-H), 4.82 (2 H, d, *J* 7.3, 1-H), 5.00 (1 H, m, 6-H), 5.42 (1 H, t, *J* 7.3, 2-H), 12.0 (1 H, br, OH); δ_F [$(CD_3)_2SO$] −162.57 (1 F, d, *J* 23.7), −151.86 (1 F, dd, *J* 6.6, 23.7), −151.02 (1 F, d, *J* 8.5).

Sodium salt of 3b

A solution of **3b** (0.282 g, 0.82 mmol) in methanol–water (4:1) was passed through a column (17 cm^3 bed volume) of Amberlite IRC50 ion-exchange resin (Na^+ form). The column was eluted with further methanol–water (4:1) until the eluate was almost colourless, and the eluate was evaporated. The *sodium salt* of **3b** (0.142 g, 47%) gave small yellow needles, mp 130–132 °C (from water: heating should be minimised) (Found: C, 52.05; H, 4.7; N, 3.7; F, 15.3; $C_{16}H_{17}F_3NNaO_4$ requires C, 52.3; H, 4.7; N, 3.8; F, 15.5%); δ_H [$(CD_3)_2SO$] 1.55 (3 H, s), 1.62 (6 H, s) (3 × Me), 2.01 (4 H, m, 4,5-H), 4.59 (2 H, d, *J* 7.1, 1-H), 5.04 (1 H, m, 6-H), 5.39 (1 H, t, *J* 7.1, 2-H); δ_F [$(CD_3)_2SO$] −182.96 (1 F, dd, *J* 8.6, 25.3), −155.98 (1 F, t, *J* 8.4), −154.72 (1 F, dd, *J* 8.5, 25.6); *m*/*z* (ESI, −ve ion mode) 344 $(M - Na)^-$.

2,3,5,6-Tetrafluoro-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]nitrobenzene 2a

From **1a** (1.065 g, 5 mmol) and (*E*,*E*)-farnesol using general procedure A. Chromatography [Merck 15111 silica; hexane–dichloromethane (gradient: 20:1, 10:1, 6:1, 4:1)] gave **2a** (1.16 g, 56%) as a yellow oil (Found: C, 60.7; H, 6.1; N, 3.3; F, 18.2; $C_{21}H_{25}F_4NO_3$ requires C, 60.7; H, 6.1; N, 3.4; F, 18.3%); δ_H ($CDCl_3$) 1.59 (6 H, s), 1.68 (3 H, d, *J* 0.8), 1.74 (3 H, d, *J* 0.8) (4 × Me), 2.09 (8 H, m, 4,5,8,9-H), 4.92 (2 H, d, *J* 7, 1-H), 5.07 (2 H, m, 6, 10-H), 5.46 (1 H, t, *J* 7, 2-H); δ_F ($CDCl_3$) −158.21 (2-F, m), −151.56 (2 F, m); *m*/*z* (FAB) 414.1695 $(M - H)^+$ (calc for $(M - H)^+$, 414.1692).

2,3,5-Trifluoro-6-hydroxy-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]nitrobenzene 3a

From **2a** (0.26 g, 0.626 mmol) using general procedure B. Chromatography [Merck 15111 silica; hexane–ethyl acetate (5:1)] gave the *title compound* **3a** (0.149 g, 57%) as an unstable yellow oil; δ_H ($CDCl_3$) 1.59 (6 H, s), 1.68 (3 H, d, *J* 0.6), 1.75 (3 H, d, *J* 0.6) (4 × Me), 1.93–2.09 (8 H, m, 4,5,8,9-H), 4.98 (2 H, d, *J* 7.2, 1-H), 5.07 (2 H, m, 6,10-H), 5.48 (1 H, t, *J* 7.2, 2-H), 10.5 (1 H, s, OH); δ_F ($CDCl_3$) −165.95 (1 F, d, *J* 22.2), −159.31 (1 F, d, *J* 7.7), −150.52 (1 F, dd, *J* 7.2, 23.1); *m*/*z* (ESI, −ve ion mode) 412 $(M - H)^-$.

Sodium salt of 3a

A solution of **3a** (0.32 g, 0.77 mmol) in dry diethyl ether (4 cm^3)

was added to powdered sodium hydroxide (0.08 g, 2 mmol) and the mixture was stirred under argon for 30 min, then evaporated. The residue was dissolved in the minimum of warm diethyl ether and the insoluble solid removed by filtration. The material that separated from the filtrate on cooling was isolated by centrifugation. Recrystallisation from diethyl ether, and isolation of the solid by centrifugation, gave the *sodium salt* of **3a** (0.120 g, 36%) as an orange powder, mp 132–135 °C; δ_H [$(CD_3)_2SO$] 1.54 (6 H, s), 1.62 (6 H, s) (4 × Me), 1.91–2.08 (8 H, m, 4,5,8,9-H), 4.57 (2 H, d, *J* 7.2, 1-H), 5.06 (2 H, m, 6,10-H), 5.39 (1 H, t, *J* 7.2, 2-H); δ_F [$(CD_3)_2SO$] −183.04 (1 F, dd, *J* 8.7, 25.0), −156.06 (1 F, m), −154.77 (1 F, dd, *J* 8.6, 25.1); *m*/*z* (FAB) 458.1540 (calc for $(M + Na)^+$, 458.1531).

4-[(*E*)-3,7-Dimethylocta-2,6-dien-1-yloxy]-2,3,5,6-tetrafluorobenzonitrile 2c

From pentafluorobenzonitrile **1b** (10 g, 52 mmol) and geraniol using general procedure A. Chromatography [Merck 9385 silica; hexane–dichloromethane (4:1)] gave *nitrile* **2c** (purity 90–95%, by NMR; the remainder being the presumed *ortho*-isomer) (14.09 g, *ca.* 77%) (oil) (Found: C, 62.4; H, 5.2; N, 4.3; F, 23.3; $C_{17}H_{17}F_4NO$ requires C, 62.4; H, 5.2; N, 4.3; F, 23.2%); δ_H [$(CD_3)_2SO$] 1.55 (3 H, s), 1.62 (3 H, s), 1.68 (3 H, s) (3 × Me), 2.04 (4 H, m, 4,5-H), 4.95 (2 H, d, *J* 7.3, 1-H), 5.01 (1 H, m, 6-H), 5.44 (1 H, t, *J* 7.3, 2-H); δ_F [$(CD_3)_2SO$] −154.02 (2 F, m), −135.19 (2 F, m) (minor signals for presumed *ortho*-isomer, all multiplets, *ca.* equal intensity; −161.30, −152.68, −145.59, −133.8); *m*/*z* (FAB) 326 $(M - H)^+$.

4-[(*E*)-3,7-Dimethylocta-2,6-dien-1-yloxy]-2,3,5-trifluoro-6-hydroxybenzonitrile 3c

From **2c** (2.616 g, 8 mmol) using general procedure B. Chromatography [Merck 9385 silica; dichloromethane–ethanol (98:2, 97:3 and 95:5 in succession)] gave *nitrile* **3c** (purity *ca.* 90%, by NMR; 2.117 g, *ca.* 81%) (yellow solid). Further purification of a portion of this material [Merck 9385 silica; hexane–diethyl ether (1:3), diethyl ether, and diethyl ether–methanol (98:2 then 95:5) in succession] gave pure **3c**, mp 62–64 °C (Found: C, 63.1; H, 5.7; N, 4.2; F, 17.05; $C_{17}H_{18}F_3NO_2$ requires C, 62.8; H, 5.6; N, 4.3; F, 17.5%); ν_{max} (film)/cm^{-1} 2250; δ_H [$(CD_3)_2SO$] 1.54 (3 H, s), 1.61 (3 H, s), 1.65 (3 H, s) (3 × Me), 2.01 (4 H, m, 4,5-H), 4.83 (2 H, d, *J* 7.3, 1-H), 4.99 (1 H, br s, 6-H), 5.40 (1 H, t, *J* 7.3, 2-H), 12.07 (1 H, br s, OH); δ_F [$(CD_3)_2SO$] −162.16 (1 F, d, *J* 23.0), −151.88 (1 F, d, *J* 8.0), −137.93 (1 F, dd, *J* 9.8, 23.4); *m*/*z* (ESI, −ve ion mode) 324.5 $(M - H)^-$.

2,3,5,6-Tetrafluoro-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]benzamide 2d and 2,3,4,5-tetrafluoro-6-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]benzamide 4

From pentafluorobenzamide **1c** (3.021 g, 14.3 mmol) and (*E*,*E*)-farnesol using general procedure A, except that the reaction was conducted under argon at room temperature for 26 h and then under reflux for 45 h. Chromatography [Merck 7729 silica; hexane–ethyl acetate (gradient, 100:0 to 5:1)] gave first the *ortho-isomer* **4** (1.129 g, 19%), mp 46–48 °C (from hexane) (Found: C, 63.8; H, 6.6; N, 3.35; $C_{22}H_{27}F_4NO_2$ requires C, 63.9; H, 6.6; N, 3.4%); δ_H [$(CD_3)_2SO$] 1.56 (6 H, s) (2 × Me), 1.63 (6 H, s) (2 × Me), 2.03 (8 H, m, 4,5,8,9-H), 4.63 (2 H, d, *J* 7.1, 1-H), 5.06 (2 H, m, 6,10-H), 5.42 (1 H, t, *J* 7.1, 2-H), 7.91 (1 H, br s, NH), 8.06 (1 H, br s, NH); δ_F [$(CD_3)_2SO$] −162.96 (1 F, t, *J* 23.7), −156.38 (1 F, t, *J* 22.0), −153.77 (1 F, dd, *J* 8.8, 22.0), −143.53 (1 F, dd, *J* 8.6, 25.3); *m*/*z* (FAB) 436 $(M + Na)^+$. An impure fraction eluted (0.406 g) next from which further chromatography [Merck 9385 silica; hexane–ethyl acetate (2:1)] afforded pure *para-isomer* **2d** (0.203 g, 3%), mp 106–108 °C (from hexane) (Found: C, 63.8; H, 6.6; N, 3.4; F, 18.4; $C_{22}H_{27}F_4NO_2$ requires C, 63.9; H, 6.6; N, 3.4; F, 18.4%); δ_H [$(CD_3)_2SO$] 1.55 (6 H, s), 1.63 (3 H, s), 1.66 (3 H, s) (4 × Me), 2.03 (8 H, m, 4,5,8,9-H), 4.78 (2 H, d, *J* 7.2, 1-H), 5.05 (2 H, m, 6,10-H), 5.44 (1 H, t, *J* 7.2, 2-H), 8.01 (1 H, br s, NH), 8.19 (1 H, br s, NH); δ_F [$(CD_3)_2SO$] −155.49 (2 F, m), −143.49 (2 F, m); *m*/*z* (FAB) 436 $(M + Na)^+$.

2,3,5-Trifluoro-6-hydroxy-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]benzamide 3d

From **2d** (0.145 g, 0.35 mmol) using general procedure B, except that the initial reaction was for 24 h, then tetra-*n*-hexylammonium hydrogen sulfate (0.016 g, 0.035 mmol) was added, and the reaction was continued at 50 °C for 2 d and at room temperature for a further 5 d. Chromatography [Merck 15111 silica; hexane–ethyl acetate (9:1 followed by 8:2)] gave *amide* **3d** (0.072 g, 50%), mp 109–110 °C (from ethanol) (Found: C, 64.0; H, 6.8; N, 3.4; F, 13.8; $C_{22}H_{28}F_3NO_3$ requires C, 64.2; H, 6.9; N, 3.4; F, 13.85%); δ_H ($CDCl_3$) 1.56 (3 H, s), 1.59 (3 H, s), 1.68 (3 H, d, *J* 0.8), 1.73 (3 H, s) (4 × Me), 1.96–2.08 (8 H, m, 4,5,8,9-H), 4.85 (2 H, d, *J* 7.1, 1-H), 5.08 (2 H, m, 6,10-H), 5.49 (1 H, t, *J* 7.1, 2-H), 5.80 (1 H, br s, NH), 6.82 (1 H, br s, NH), 12.98 (1 H, s, OH); δ_F ($CDCl_3$) −165.83 (1 F, d, *J* 23.7), −156.91 (1 F, d, *J* 10.1), −143.76 (1 F, m); *m*/*z* (ESI, −ve ion mode) 410 $(M - H)^-$.

4-(3,7-Dimethyl-2,3-epoxyoct-6-en-1-yloxy)-2,3,5,6-tetrafluoronitrobenzene 2e

From **1a** (0.801 g, 3.76 mmol) and 2,3-epoxygeraniol[39] using general procedure A. Chromatography [Merck 15111 silica, hexane–dichloromethane (5:3)] gave *epoxygeranyl derivative* **2e** (0.693 g, 51%) as a yellow oil (Found: C, 52.9; H, 4.7; N, 3.9; F, 21.0; $C_{16}H_{17}F_4NO_4$ requires C, 52.9; H, 4.7; N, 3.9; F, 20.9%); δ_H [$(CD_3)_2SO$] 1.26 (3 H, s, Me), 1.45 (m, 4-H), 1.58 (3 H, s, Me), 1.65 (3 H, s, Me), 2.04 (2 H, m, 5-H), 3.17 (1 H, dd, *J* 3.6, 7.3, 2-H), 4.42 (1 H, dd, *J* 7.3, 11.4, 1-H), 4.73 (1 H, dd, *J* 3.6, 11.4, 1-H), 5.09 (1 H, m, 6-H); δ_F [$(CD_3)_2SO$] −154.74 (2 F, m), −147.07 (2 F, m); *m*/*z* (FAB) 362 $(M - H)^+$.

4-(3,7-Dimethyl-2,3-epoxyoct-6-en-1-yloxy)-2,3,5-trifluoro-6-hydroxynitrobenzene 3e

From **2e** (0.645 g, 1.78 mmol) using general procedure B except that reaction was for 30 min at room temperature. Chromatography [Merck 7729 silica; hexane–dichloromethane, dichloromethane, dichloromethane–ethanol (99:1, 98:2, 97:3) in succession] gave as a yellow oil which solidified on cooling, *epoxygeranyl derivative* **3e** (0.304 g, 48%), mp 72–74 °C (from hexane) (Found: C, 53.35; H, 5.0; N, 3.9; F, 15.8; $C_{16}H_{18}F_3NO_5$ requires C, 53.2; H, 5.0; N, 3.9; F, 15.8%); δ_H [$(CD_3)_2SO$] 1.24 (3 H, s, Me), 1.44 (m, 4-H), 1.57 (3 H, s, Me), 1.64 (3 H, d, *J* 0.9, Me), 2.02 (2 H, m, 5-H), 3.13 (1 H, dd, *J* 3.9, 7.1, 2-H), 4.29 (1 H, dd, *J* 7.1, 11.5, 1-H), 4.55 (1 H, dd, *J* 3.9, 11.5, 1-H), 5.09 (1 H, m, 6-H); δ_F [$(CD_3)_2SO$] −163.07 (1 F, d, *J* 22.2), −151.87 (1 F, dd, *J* 7.4, 23.7), −151.40 (1 F, d, *J* 6.7); *m*/*z* (FAB) 360 $(M - H)^+$.

2-Hydroxy-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]nitrobenzene 8

(a) From 2,4-difluoronitrobenzene (5). The reaction of **5** (1.591 g, 10 mmol) with (*E*,*E*)-farnesol using general procedure A but with overnight reaction, followed by chromatography [Merck 15111 silica; hexane–ethyl acetate (40:1 then 30:1)] gave a 1:1 mixture (shown by the presence of two signals in the ^{19}F NMR spectrum at δ_F ($CDCl_3$) −113.23 (m) and −101.47 (m)), (2.475 g, 68%) (oil) containing *2-fluoro-4-[(E,E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]nitrobenzene* **6** as one component. Using general procedure B, but with reaction time 2 h, this mixture (1.412 g, 3.91 mmol) was converted into *hydroxy nitro derivative* **8** (0.660 g, 47% based on **5**), a yellow solid, mp 38–39 °C (Found: C, 70.12; H, 8.07; N, 3.94; $C_{21}H_{29}NO_4$ requires C, 70.17; H, 8.13; N, 3.9%); δ_H ($CDCl_3$)

1.60 (6 H, s), 1.68 (3 H, d, *J* 0.7), 1.76 (3 H, s) (4 × Me), 1.92–2.20 (8 H, m, 4,5,8,9-H), 4.60 (2 H, d, *J* 6.6, 1-H), 5.10 (2 H, m, 6,10-H), 5.45 (1 H, m, 2-H), 6.53 (2 H, m, Ar-H), 8.02 (1 H, d, *J* 10.1, Ar-H), 11.05 (1H, s, OH); *m*/*z* (ESI, −ve ion mode) 358 $(M - H)^-$.

(b) From 3-fluoro-4-nitrophenol (9). DEAD (0.833 g, 4.8 mmol) was added dropwise during 5 min to a stirred, cooled (ice–water bath) solution of **9** (0.677 g, 4.3 mmol), (*E*,*E*)-farnesol (0.957 g, 4.3 mmol) and triphenylphosphine (1.248 g, 4.8 mmol) in dry THF (8 cm^3) under argon. After a further 5 min the reactants were allowed to warm to room temperature and after 26 h, the mixture was evaporated. Chromatography [Merck 9385 silica; hexane–diethyl ether (15:1)] gave *farnesyl ether* **6** (0.323 g, 21%) as an oil (Found: C, 69.9; H, 7.9; N, 3.8; F, 5.2; $C_{21}H_{28}FNO_3$ requires C, 69.8; H, 7.8; N, 3.9; F, 5.3%); δ_H ($CDCl_3$) 1.59 (6 H, s), 1.67 (3 H, s), 1.76 (3 H, s) (4 × Me), 1.98 (4 H, m), 2.12 (4 H, m) (farnesyl 4,5,8,9-H), 4.61 (2 H, d, *J* 6.6, farnesyl 1-H), 5.08 (2 H, m, farnesyl 6,10-H), 5.44 (1 H, t, *J* 6.6, farnesyl 2-H), 6.73 (2 H, m, Ar-H), 8.08 (1 H, t, *J* 9.3, Ar-H); δ_F ($CDCl_3$) −113.19 (t, *J* 11.7); *m*/*z* (FAB) 384.1940 $(M + Na)^+$ (calc for $(M + Na)^+$ 384.1951). The reaction of **6** (0.142 g, 0.39 mmol) with 50% w/w aqueous sodium hydroxide followed the conditions used to prepare **3b** and gave after chromatography [Merck 9385 silica; hexane–diethyl ether (19:1)] the *hydroxy nitro derivative* **8** (0.117 g, 83%), mp 37–39 °C, with NMR spectrum as for the corresponding product prepared from compound **5**.

4-Benzyloxy-2,3,5,6-tetrafluoronitrobenzene 10, 2-benzyloxy-3,4,5,6-tetrafluoronitrobenzene 11, and 2,4-bis-(benzyloxy)-3,5,6-trifluoronitrobenzene 12

From **1a** (8.52 g, 40 mmol) and benzyl alcohol using general procedure A but with reaction time 3.5 h. Chromatography [Merck 9385 silica; petroleum spirit (bp 60–80 °C)–ethyl acetate (25:1 or 19:1)] gave slightly impure *4-benzyloxy derivative* **10** (6.095 g, from light petroleum (bp 80–100 °C) then from hexane). Chromatography [Merck 15111 silica; petroleum spirit (bp 60–80 °C)–dichloromethane (2:1)] of the concentrated mother liquors gave further **10** (2.567 g, from hexane; total yield 8.662 g, *ca.* 72%), along with *2-benzyloxy derivative* **11** (0.388 g, 3%, from hexane) and *2,4-bis(benzyloxy) derivative* **12** (0.229 g, 1.5%, after re-chromatography). For **10** (sublimed sample): mp 72–74 °C (Found: C, 51.75; H, 2.4; N, 4.6; F, 25.5; $C_{13}H_7F_4NO_3$ requires C, 51.8; H, 2.3; N, 4.65; F, 25.2%); δ_H [$(CD_3)_2SO$] 5.49 (2 H, s, CH_2), 7.46 (5 H, m, Ph); δ_F [$(CD_3)_2SO$] −154.43 (2 F, m), −146.80 (2 F, m); *m*/*z* (FAB) 300 $(M - H)^+$. For **11**: mp 74–75 °C (Found: C, 51.75; H, 2.4; N, 4.6; F, 25.5; $C_{13}H_7F_4NO_3$ requires C, 51.8; H, 2.3; N, 4.65; F, 25.2%); δ_H [$(CD_3)_2SO$] 5.32 (2 H, d, *J* 1.4, CH_2), 7.41 (5 H, s, Ph); δ_F [$(CD_3)_2SO$] −160.06 (1 F, t, *J* 23.6), −151.02 (1 F, dd, *J* 6.9, 21.9), −149.33 (1 F, t, *J* 21.4), −148.47 (1 F, m). For **12**: mp 45–47 °C (Found: C, 61.6; H, 3.7; N, 3.6; F, 14.9; $C_{20}H_{14}F_3NO_4$ requires C, 61.7; H, 3.6; N, 3.6; F, 14.6%); δ_H [$(CD_3)_2SO$] 5.22 (2 H, d, *J* 0.6, CH_2), 5.39 (2 H, s, CH_2), 7.39 (10 H, m, 2 × Ph); δ_F [$(CD_3)_2SO$] −154.21 (1 F, d, *J* 23.7), −149.84 (1 F, dd, *J* 9.0, 23.7), −144.38 (1 F, d, *J* 6.8); *m*/*z* (FAB) 388 $(M - H)^+$.

2,4,6-Tris(benzyloxy)-3,5-difluoronitrobenzene 13

Dry benzyl alcohol (1.7 cm^3, 16 mmol) was added to a stirred, cooled (ice–water bath) suspension of potassium *tert*-butoxide (1.64 g, 14.6 mmol) in dry THF (65 cm^3) under nitrogen. After 30 min a solution of **10** (2.00 g, 6.64 mmol) in THF (7 cm^3) was added rapidly by syringe. After a further 90 min, at room temperature, the mixture was cooled in ice and glacial acetic acid (1.2 cm^3) was added. The mixture was evaporated and the residue partitioned between dichloromethane (60 cm^3) and saturated aqueous $NaHCO_3$ (60 cm^3). The aqueous layer was extracted with dichloromethane (5 × 10 cm^3) and the combined dichloromethane solution washed with brine (40 cm^3), dried ($MgSO_4$) and evaporated. Chromatography [Merck 9385 silica; hexane–dichloromethane (7:4)] gave first **12** (0.068 g, 2.6%) (from hexane; identified by mp and NMR), then *tris-(benzyloxy) derivative* **13** (1.667 g, 52%), mp 77–79 °C (from hexane) (Found: C, 67.9; H, 4.5; N, 2.9; F, 8.0; $C_{27}H_{21}F_2NO_5$ requires C, 67.9; H, 4.4; N, 2.9; F, 8.0%); δ_H [$(CD_3)_2SO$] 5.15 (4 H, s, 2,6-OCH_2), 5.30 (2 H, s, 4-OCH_2), 7.38 (15 H, m, 3 × Ph); δ_F [$(CD_3)_2SO$] −145.28 (s); *m*/*z* (FAB) 476 $(M - H)^+$.

3,5-Difluoro-2,4,6-trihydroxynitrobenzene 14

A mixture of **13** (1.500 g, 3.14 mmol), pentamethylbenzene (7.0 g, 47 mmol), and TFA (75 cm^3) was stirred at room temperature under argon in the dark for 26 h, then evaporated to dryness. The residue was partitioned between 0.1 M aqueous sodium hydroxide (150 cm^3) and dichloromethane (100 cm^3). The aqueous layer was extracted with dichloromethane (3 × 15 cm^3) and the combined dichloromethane solution extracted with 0.1 M aqueous sodium hydroxide (20 cm^3). The combined aqueous phase was acidified with 1 M hydrochloric acid (100 cm^3) and extracted with diethyl ether (6 × 50 cm^3). The combined diethyl ether solution was washed with water (20 cm^3), dried ($MgSO_4$), and evaporated and the residue sublimed *in vacuo* to give *trihydroxy derivative* **14** (0.441 g, 68%) as a deep red solid, mp 162–164 °C (Found: C, 34.7; H, 1.6; N, 6.7; F, 18.3; $C_6H_3F_2NO_5$ requires C, 34.8; H, 1.5; N, 6.8; F, 18.35%); δ_H [$(CD_3)_2SO$] 10.72 (s); δ_F [$(CD_3)_2SO$] −164.52; *m*/*z* (ESI, −ve ion mode) 206 $(M - H)^-$.

4-[(*E*)-3,7-Dimethylocta-2,6-dien-1-yloxy]-3,5-difluoro-2,6-dihydroxynitrobenzene 15

Diisopropyl azodicarboxylate (DIAD) (0.195 g, 0.96 mmol) was added dropwise to a stirred, cooled (ice–water bath) solution of **14** (0.183 g, 0.88 mmol), geraniol (0.150 g, 0.97 mmol), and triphenylphosphine (0.255 g, 0.97 mmol) in THF (4.4 cm^3) under nitrogen. The mixture was allowed to warm to room temperature during 2 h. After a further 3 h, further geraniol (0.053 g, 0.34 mmol), triphenylphosphine (0.073 g, 0.28 mmol) and DIAD (0.071 g, 0.35 mmol) were added. After 23 h (total time) the mixture was partitioned between dichloromethane (50 cm^3) and brine (20 cm^3). The aqueous layer was extracted with dichloromethane (10 cm^3) and the combined dichloromethane solution dried (Na_2SO_4) and evaporated. Chromatography [Merck 9385 silica; hexane–dichloromethane (1:1 then 1:2) then dichloromethane] gave *geranyl derivative* **15** (0.112 g, 37%) as an orange solid (Found: C, 53.9; H, 5.5; N, 4.0; $C_{16}H_{19}F_2NO_5 \cdot 0.75H_2O$ requires C, 53.85; H, 5.8; N, 3.9%). Crystallisation from *n*-pentane without heating above room temperature gave orange flakes (0.081 g), mp 42–45 °C; δ_H [$(CD_3)_2SO$] 1.55 (3 H, s), 1.63 (3 H, s), 1.65 (3 H, s) (3 × Me), 2.01 (4 H, m, 4,5-H), 4.70 (2 H, d, *J* 7.2, 1-H), 5.03 (1 H, br s, 6-H), 5.41 (1 H, t, *J* 7.2, 2-H), 10.95 (2 H, s, 2 × OH); δ_F [$(CD_3)_2SO$] −159.06; *m*/*z* (ESI, −ve ion mode) 342 $(M - H)^-$.

2,2-Dimethyl-7-hydroxy-4*H*-1,3-benzodioxin-4-one 17a

TFAA (6 cm^3) and acetone (1.2 cm^3) were added to a stirred suspension of 2,4-dihydroxybenzoic acid **16** (1.0 g, 6.49 mmol) in TFA (10 cm^3) at 0 °C. After 24 h at room temperature the yellow solution obtained was concentrated. The residue was added to saturated aqueous $NaHCO_3$ (50 cm^3) and the products extracted with ethyl acetate (3 × 50 cm^3). The combined ethyl acetate solution was washed with water (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$) and concentrated. Chromatography [Merck 15111 silica; hexane–ethyl acetate (gradient: 8:2, 7:3, 6:4)] gave *isopropylidene derivative* **17a** (0.592 g, 47%), mp 203–204 °C (from ethyl acetate) (Found: C, 61.8; H, 5.2; $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.2%); ν_{max} (KBr disc)/cm^{-1} 1613, 1694; δ_H [$(CD_3)_2SO$] 1.65 (6 H, s, 2 × Me), 6.37 (1 H, d, *J* 2.3, 8-H),

6.59 (1 H, dd, *J* 2.3, 8.7, 6-H), 7.68 (1 H, d, *J* 8.7, 5-H), 10.85 (1 H, s, OH); *m/z* (FAB) 195 $(M + H)^+$.

2-Hydroxy-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]benzoic acid 18

A solution of **17a** (0.20 g, 1.03 mmol) in THF (3 cm^3) was added to a suspension of sodium hydride (60% dispersion; 0.049 g, 1.23 mmol) in THF (4 cm^3). When effervescence had ceased (after 1 min), (*E*,*E*)-farnesyl bromide (0.28 cm^3, 1.03 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 48 h and at 60 °C for a further 3 h. Water (10 cm^3) was added and the mixture extracted with ethyl acetate (3 × 20 cm^3). The combined ethyl acetate solution was dried ($MgSO_4$) and evaporated. Chromatography [Merck 15111 silica; hexane–ethyl acetate (9:1)] gave *2,2-dimethyl-7-[(E,E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]-4H-1,3-benzodioxin-4-one* **17b** (0.195 g, 47.5%) (oil); δ_H ($CDCl_3$) 1.60, 1.68, 1.72, 1.75 (4 × s, total 18H, 6 × Me), 1.93–2.17 (8 H, m, farnesyl 4,5,8,9-H), 4.57 (2 H, d, *J* 6.6, farnesyl 1-H), 5.10 (2 H, m, farnesyl 6,10-H), 5.46 (1 H, m, farnesyl 2-H), 6.42 (1 H, d, *J* 2.3, 8-H), 6.64 (1 H, dd, *J* 2.3, 8.8, 6-H), 7.85 (1 H, d, *J* 8.8, 5-H). A solution of **17b** (0.192 g, 0.482 mmol) in DMSO (3 cm^3) was treated with 48% w/v aqueous potassium hydroxide (0.7 cm^3) and the mixture was heated at 60 °C for 30 min. The resulting mixture was cooled, acidified (1 M hydrochloric acid) to *ca.* pH 5, and extracted with ethyl acetate (2 × 20 cm^3). The combined ethyl acetate solution was washed successively with water (25 cm^3) and brine (25 cm^3), then evaporated. Chromatography [Merck 15111 silica; hexane–ethyl acetate (4:1)] gave *title compound* **18** (0.153 g, 88%), mp 83–84 °C (from hexane) (Found: C, 73.6; H, 8.4; $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.4); δ_H ($CDCl_3$) 1.60 (6 H, s), 1.68 (3 H, s), 1.75 (3 H, s) (4 × Me), 1.93–2.19 (8 H, m, farnesyl 4,5,8,9-H), 4.58 (2 H, d, *J* 6.6, farnesyl 1-H), 5.10 (2 H, m, farnesyl 6,10-H), 5.47 (1 H, t, *J* 6.6, farnesyl 2-H), 6.46–6.51 (2 H, m, 3,5-H), 7.80 (1 H, d, *J* 8.5, 6-H), 10.66 (1 H, s, OH); *m/z* (ESI, −ve ion mode) 357 $(M - H)^-$; *m/z* (FAB) 381.2050 $(M + Na)^+$; calc for $(M + Na)^+$, 381.2042.

Benzyl 4-benzyloxy-2,3,5,6-tetrafluorobenzoate 20

Caesium carbonate (48.33 g, 0.148 mol) was added to a rapidly stirred, cooled (ice–water bath) mixture of 2,3,5,6-tetrafluoro-4-hydroxybenzoic acid **19** (hydrate, 15.057 g, 0.07 mol), benzyl bromide (18.9 cm^3, 0.159 mol), and DMF (127 cm^3). The mixture was allowed to warm to room temperature. After 3 d the mixture was evaporated and the residue partitioned between ethyl acetate (250 cm^3) and water (125 cm^3). The aqueous layer was extracted with ethyl acetate (3 × 40 cm^3) and the combined ethyl acetate solution washed with half-saturated brine (3 × 40 cm^3), dried ($MgSO_4$) and evaporated to give *benzyl ester* **20** (25.0 g, 91.5%), mp 64–66 °C (from hexane) (Found: C, 64.6; H, 3.7; F, 19.5; $C_{21}H_{14}F_4O_3$ requires C, 64.6; H, 3.6; F, 19.5%); δ_H [$(CD_3)_2SO$] 5.40 (4 H, s, 2 × CH_2), 7.43 (10 H, s, 2 × Ph); δ_F [$(CD_3)_2SO$] −155.12 (2 F, m), −140.30 (2 F, m); *m/z* (FAB) 389 $(M - H)^+$.

Benzyl 2,4-bis(benzyloxy)-3,5,6-trifluorobenzoate 21 and benzyl 2,4,6-tris(benzyloxy)-3,5-difluorobenzoate 22

The procedure, using **20** (24.5 g, 63 mmol), benzyl alcohol (9.74 cm^3, 94 mmol) and potassium *tert*-butoxide (8.77 g, 78 mmol) was essentially that used to prepare compound **13**, except that extraction was with diethyl ether. Chromatography [Merck 7729 silica; *n*-pentane–diethyl ether (stepwise gradient: 99:1, 98.5:1.5, 98:2, 97:3, 95:5)] gave *bis(benzyloxy) derivative* **21** (19.6 g, 65%) (oil) (Found: C, 70.6; H, 4.6; F, 11.6; $C_{28}H_{21}F_3O_4$ requires C, 70.3; H, 4.4; F, 11.9%); δ_H ($CDCl_3$) 5.02 (2 H, s), 5.25 (2 H, s), 5.29 (2 H, s) (3 × CH_2), 7.35 (15 H, m, 3 × Ph); δ_F ($CDCl_3$) −155.86 (1 F, d, *J* 23.1), −147.45 (1 F, d, *J* 9.9), −141.97 (1 F, dd, *J* 10.1, 23.5); *m/z* (FAB) 479 $(M + H)^+$. Samples of the minor product, the more polar *tris(benzyloxy) derivative* **22** (oil) were isolated from other preparations (Found: C, 74.2; H, 5.1; F, 6.75; $C_{35}H_{28}F_2O_5$ requires C, 74.2; H, 5.0; F, 6.7%); δ_H ($CDCl_3$) 5.00 (4 H, s, 2,6-OCH_2), 5.18 (2 H, s), 5.20 (2 H, s) (4-OCH_2, CO_2CH_2), 7.31 (20 H, m, 4 × Ph); δ_F ($CDCl_3$) −147.93 (s); *m/z* (FAB) 565 $(M - H)^+$.

2,3,5-Trifluoro-4,6-dihydroxybenzoic acid 23

A mixture of **21** (13.592 g, 28.4 mmol), methanol (345 cm^3), water (1.4 cm^3), and 10% Pd–C (1.73 g) was degassed and stirred under H_2 at room temperature for 5.5 h. The catalyst was removed by filtration through Celite, the filtrate evaporated, and the residue crystallised from water to give *dihydroxy acid* **23** (5.444 g, 92%, in 2 crops), mp 215–225 °C (sublimes) (Found: C, 40.3; H, 1.35; F, 27.4; $C_7H_3F_3O_4$ requires C, 40.4; H, 1.45; F, 27.4%); δ_H [$(CD_3)_2SO$] 11.8 (br s); δ_F [$(CD_3)_2SO$] −168.83 (1 F, d, *J* 23.5), −161.98 (1 F, d, *J* 10.1), −139.63 (1 F, dd, *J* 10.1, 23.7); *m/z* (FAB) 209 $(M + H)^+$.

Pentafluorophenyl 2,3,5-trifluoro-4,6-dihydroxybenzoate 24

Pentafluorophenyl trifluoroacetate (0.92 cm^3, 5.4 mmol) was added to a stirred mixture of **23** (1.073 g, 5.2 mmol), dry dichloromethane (39 cm^3) and dry pyridine (1.29 cm^3, 15.9 mmol) at room temperature. After 4 h further pentafluorophenyl trifluoroacetate (0.7 cm^3, 4 mmol) was added and after a further 12 h the clear solution was diluted with dichloromethane (100 cm^3), washed successively with 0.1 M hydrochloric acid (3 × 30 cm^3) and water (2 × 30 cm^3), dried ($MgSO_4$) and evaporated to dryness. The residue was triturated with hexane and dried thoroughly (oil pump) to give *pentafluorophenyl ester* **24** (1.813 g, *ca.* 94%) as a white solid which was used without further purification; mp 122–128 °C; δ_F [$(CD_3)_2SO$] −167.20 (1 F, d, *J* 23.2), −161.74 (2 F, t, *J* 21.1), −157.74 (1 F, d, *J* 8.6), −156.95 (1 F, t, *J* 22.6), −152.51 (2 F, d, *J* 21.0), −140.80 (1 F, dd, *J* 9.4, 23.5); *m/z* (FAB) 374.9920 $(M + H)^+$; calc for $(M + H)^+$, 374.9904.

5,6,8-Trifluoro-7-hydroxy-4*H*-1,3-benzodioxin-4-one 25

Paraformaldehyde (0.234 g, equivalent to 7.8 mmol formaldehyde) and DMF (4.5 cm^3) were stirred together at room temperature for 25 min. Compound **24** (0.579 g, 1.5 mmol) and DABCO (0.349 g, 3.1 mmol) were then added successively and stirring continued for 21 h followed by filtration and concentration. A solution of the residue in methanol (5 cm^3) was passed through a column (bed volume 12.5 cm^3) of Bio-Rad AG50W X-4 100–200 mesh cation-exchange resin (H^+ form), which was eluted with methanol and concentrated. Chromatography (Merck 9385 silica; gradient from 0 to 20% ethanol in dichloromethane) followed by concentration of appropriate fractions and passage of a solution in methanol–water (4:1) through another column (6 cm^3 bed volume) of Bio-Rad AG50W X-4 100–200 mesh cation-exchange resin (H^+ form) using further methanol–water (4:1) for elution afforded, on concentration the *methylene derivative* **25**, a white solid (0.083 g, 24%), mp 214 °C (Found: C, 43.5; H, 1.3; F, 25.95; $C_8H_3F_3O_4$ requires C, 43.7; H, 1.4; F, 25.9%); ν_{max} (KBr disc)/cm^{-1} 1647, 1715; δ_H [$(CD_3)_2SO$] 5.84 (s, CH_2); δ_F [$(CD_3)_2SO$] −163.21 (1 F, m), −159.77 (1 F, m), −140.36 (1 F, dd, *J* 10.7, 21.1); *m/z* (FAB) 221 $(M + H)^+$.

5,6,8-Trifluoro-7-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]-4*H*-1,3-benzodioxin-4-one 26

(*E*,*E*)-Farnesyl bromide (0.15 g, 0.53 mmol) was added to a stirred mixture of **25** (0.075 g, 0.34 mmol), caesium carbonate (0.167 g, 0.51 mmol), and dry DMF (0.75 cm^3) under argon at room temperature in the dark. After 2 h the mixture was evaporated and toluene (15 cm^3) was added and evaporated. Chromatography [Merck 7729 silica; hexane–ethyl acetate

(stepwise gradient: 100:0, 99.5:0.5, 99:1, 97:3, 95:5)] gave the *farnesyl derivative* **26** (0.083 g, 57%) (oil) (Found: C, 64.8; H, 6.5; F, 13.3; $C_{23}H_{27}F_3O_4$ requires C, 65.1; H, 6.4; F, 13.4%); δ_H [$(CD_3)_2SO$] 1.55 (6 H, s), 1.63 (3 H, s), 1.68 (3 H, s) (4 × Me), 2.04 (8 H, m, farnesyl 4,5,8,9-H), 4.91 (2 H, d, *J* 7.1, farnesyl 1-H), 5.04 (2 H, m, farnesyl 6,10-H), 5.45 (1 H, t, *J* 7.1, farnesyl 2-H), 5.88 (2 H, s, 2-H); δ_F [$(CD_3)_2SO$] −158.73 (1 F, d, *J* 22.9), −154.51 (1 F, d, *J* 11.2), −139.63 (1 F, dd, *J* 11.9, 22.0); *m*/*z* (FAB) 447 $(M + Na)^+$.

Sodium 2,3,5-trifluoro-6-hydroxy-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]benzoate 27a

The foregoing reaction was set up again, using (*E*,*E*)-farnesyl bromide (0.16 g, 0.56 mmol), **25** (0.100 g, 0.45 mmol), caesium carbonate (0.183 g, 0.56 mmol) and DMF (0.95 cm^3). After 21 h, the mixture was evaporated. Chromatography [Merck 7729 silica; dichloromethane–ethanol (stepwise gradient: 100:0, 98:2, 97:3, 95:5, 90:10, 85:15)], dissolution of the concentrate from pure fractions in ethanol–water (4:1) (TLC with chloroform–methanol–acetic acid, 95:5:3) and passage through a column (10 cm length × 5 mm diameter) of Amberlite IRC50 cation-exchange resin (Na^+ form), using further ethanol–water (4:1) as eluant afforded, on trituration of the concentrates with cold diethyl ether, the *hydroxytrifluoro derivative* **27a** as a white solid (0.064 g, 33%), which gave crystals mp 202–203 °C (from water) (Found: C, 60.55; H, 6.0; F, 13.2; S, 10.7; $C_{22}H_{26}F_3NaO_4$ requires C, 60.8; H, 6.0; F, 13.1; S, 10.5%); δ_H [$(CD_3)_2SO$] 1.55 (6 H, s), 1.63 (6 H, s) (4 × Me), 2.01 (8 H, m, 4,5,8,9-H), 4.64 (2 H, d, *J* 7.2, 1-H), 5.06 (2 H, m, 6,10-H), 5.41 (1 H, t, *J* 7.2, 2-H), 11.47 (s, OH); δ_F [$(CD_3)_2SO$] −172.14 (1 F, d, *J* 22.4), −159.99 (1 F, t, *J* 6.8), −144.90 (1 F, dd, *J* 13.1, 24.0); *m*/*z* (ESI, −ve ion mode) 411 $(M - Na)^-$.

Sodium 4-[(*E*)-3,7-dimethylocta-2,6-dien-1-yloxy]-2,3,5-trifluoro-6-hydroxybenzoate 27b

The procedure, starting from geranyl bromide (0.156 g, 0.72 mmol) and **25** (0.100 g, 0.45 mmol), was essentially that used to prepare the farnesyl analogue **27a**, with the following changes: the reaction time was 7 h; elution with dichloromethane–ethanol was followed by dichloromethane–ethanol–glacial acetic acid (170:30:3); methanol–water (4:1) was the solvent and eluant for ion-exchange column chromatography. The *geranyl derivative* **27b** a white solid (0.084 g, 51%) gave colourless flakes, mp 205 °C (from water) (Found: C, 55.8; H, 5.0; $C_{17}H_{18}F_3NaO_4$ requires C, 55.8; H, 4.95%); δ_H [$(CD_3)_2SO$] 1.54 (3 H, s), 1.62 (6 H, s) (3 × Me), 2.00 (4 H, m, 4,5-H), 4.65 (2 H, d, *J* 7.3, 1-H), 5.03 (1 H, m, 6-H), 5.40 (1 H, t, *J* 7.3, 2-H), 11.47 (1 H, s, OH); δ_F [$(CD_3)_2SO$] −171.98 (1 F, dd, *J* 6.2, 23.8), −159.89 (1 F, d, *J* 6.9), −144.84 (1 F, dd, *J* 13.2, 23.9); *m*/*z* (ESI, −ve ion mode) 343 $(M - Na)^-$.

Ethyl 2,3,5,6-tetrafluoro-4-hydroxybenzoate[29] 28

The preparation from 2,3,5,6-tetrafluoro-4-hydroxybenzoic acid **19** hydrate (2 g, 9 mmol) followed essentially the literature procedure[40] for ethyl 2,3,4,5-tetrafluoro-6-hydroxybenzoate except that chromatography [Merck 15111 silica; dichloromethane–ethanol (stepwise gradient: 100:0, 99:1, 250:6, 250:8, 250:13, 9:1)] was used to give the *ester* **28** (1.473 g, 69%), mp 108–110 °C (lit.[29] mp, 107–109 °C; δ_H ($CDCl_3$) 1.39 (3 H, t, *J* 7.1, CH_3), 4.42 (2 H, q, *J* 7.1, CH_2), 6.3 (1 H, br s, OH); δ_F ($CDCl_3$) −163.12 (2 F, m), −140.54 (2 F, m); *m*/*z* (FAB) 239 $(M + H)^+$.

Ethyl 2,3,5,6-tetrafluoro-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]benzoate 29

The reaction conditions using **28** (0.50 g, 2.1 mmol) and (*E*,*E*)-farnesyl bromide (0.66 g, 2.3 mmol) were essentially those used to prepare **26** except that the reaction time was 16 h. Work-up essentially as for **20** then chromatography [Merck 15111 silica; hexane–dichloromethane (stepwise gradient: 9:1, 3:1, 2:1)] gave the *farnesyl derivative* **29** (0.794 g, 85%) (oil) (Found: C, 65.35; H, 6.9; F, 16.9; $C_{24}H_{30}F_4O_3$ requires C, 65.15; H, 6.8; F, 17.2%); δ_H ($CDCl_3$) 1.39 (3 H, t, *J* 7.1, CH_3CH_2), 1.59 (6 H, s), 1.68 (3 H, s), 1.71 (3 H, s) (4 × farnesyl Me), 2.07 (8 H, m, 4,5,8,9-H), 4.42 (2 H, q, *J* 7.1, CH_3CH_2), 4.84 (2 H, d, *J* 7.2, 1-H), 5.07 (2 H, m, 6,10-H), 5.47 (1 H, t, *J* 7.2, 2-H); δ_F ($CDCl_3$) −156.26 (2 F, m), −141.05 (2 F, m); *m*/*z* (FAB) 442 (M^+).

Sodium 2,3,5,6-tetrafluoro-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]benzoate 30

A 20% aqueous solution of sodium hydroxide (0.1 cm^3) was added to a rapidly stirred solution of **29** (0.115 g, 0.26 mmol) in ethanol (1.1 cm^3) and water (0.1 cm^3) at room temperature with protection from light. After 2.5 h the mixture was diluted with water (6 cm^3), cooled in ice, and centrifuged. The supernatant was pipetted off and the precipitated solid washed with water (2 × 6 cm^3) by resuspension and centrifugation, then crystallised from water (5 cm^3) to give *sodium salt* **30** (0.062 g, 55%), mp 224–226 °C (Found: C, 59.8; H, 5.87; F, 17.3; $C_{22}H_{25}F_4NaO_3 \cdot 0.25H_2O$ requires C, 59.9; H, 5.8; F, 17.2%); δ_H [$(CD_3)_2SO$] 1.56 (6 H, s), 1.62 (3 H, s), 1.63 (3 H, s) (4 × Me), 2.02 (8 H, m, 4,5,8,9-H), 4.64 (2 H, d, *J* 7.2, 1-H), 5.07 (2 H, m, 6,10-H), 5.42 (1 H, t, *J* 7.2, 2-H); δ_F [$(CD_3)_2SO$] −156.76 (2 F, m), −145.37 (2 F, m); *m*/*z* (ESI, −ve ion mode) 413.2 $(M - Na)^-$.

2,2-Dimethylpropan-1-yl pentafluorobenzenesulfonate 32a

A solution of 2,2-dimethylpropan-1-ol (2.498 g, 28.3 mmol) and pyridine (2.3 cm^3, 28 mmol) in dry diethyl ether (2 cm^3) was added to a stirred solution of pentafluorobenzenesulfonyl chloride **31** (5.005 g, 18.8 mmol) in diethyl ether (30 cm^3) at 8 °C under argon. After 30 min at 8 °C then 46 h at room temperature the mixture was filtered and the solids washed with diethyl ether (3 × 20 cm^3). The combined filtrate and washings were washed successively with 2 M hydrochloric acid (2 × 10 cm^3) and saturated aqueous $NaHCO_3$ (10 cm^3), dried ($MgSO_4$) and evaporated. Chromatography [Merck 9385 silica; light petroleum (bp 60–80 °C)–dichloromethane (successively 5:1, 4:1 and 3:1)] gave *ester* **32a** (3.568 g, 60%), mp 85 °C (from hexane) (Found: C, 41.4; H, 3.4; F, 29.8; S, 10.3; $C_{11}H_{11}F_5O_3S$ requires C, 41.5; H, 3.5; F, 29.85; S, 10.1%); δ_H [$(CD_3)_2SO$] 0.91 (9 H, s, CMe_3), 4.00 (2 H, s, OCH_2); δ_F [$(CD_3)_2SO$] −158.76 (2 F, m), −144.50 (1 F, m), −136.02 (2 F, m).

2,2-Dimethylpropan-1-yl 4-[(*E*)-3,7-dimethylocta-2,6-dien-1-yloxy]-2,3,5,6-tetrafluorobenzenesulfonate 33a

From **32a** (0.955 g, 3 mmol) and geraniol using general procedure A. Chromatography [Merck 9385 silica; first with hexane–dichloromethane (2:1), then with hexane–dichloromethane (3:1 and 2:1 in succession)] gave *tetrafluoro derivative* **33a** (0.751 g, 55%) (oil) (Found: C, 55.8; H, 6.25; F, 16.9; S, 7.1; $C_{21}H_{28}F_4O_4S$ requires C, 55.7; H, 6.2; F, 16.8; S, 7.1%); δ_H [$(CD_3)_2SO$] 0.90 (9 H, s, CMe_3), 1.55 (3 H, s), 1.62 (3 H, s), 1.69 (3 H, s) (3 × geranyl Me), 2.04 (4 H, m, 4,5-H), 3.95 (2 H, s, SO_3CH_2), 4.96 (2 H, d, *J* 7.2, 1-H), 5.02 (1 H, m, 6-H), 5.46 (1 H, t, *J* 7.2, 2-H); δ_F [$(CD_3)_2SO$] −154.01 (2 F, m), −138.11 (2 F, m).

2,2-Dimethylpropan-1-yl 4-[(*E*)-3,7-dimethylocta-2,6-dien-1-yloxy]-2,3,5-trifluoro-6-hydroxybenzenesulfonate 34a

From **33a** (0.23 g, 0.5 mmol) using procedure B but with reaction at room temperature. Chromatography [Merck 7729 silica; hexane–dichloromethane (1:1) then dichloromethane, then on Merck 9385 silica with hexane–dichloromethane (1:1)] gave *hydroxytrifluoro derivative* **34a** (0.083 g, 36%) (oil) (Found: C, 56.2; H, 6.5; F, 12.6; S, 7.2; $C_{21}H_{29}F_3O_5S$ requires C, 56.0; H,

6.5; F, 12.65; S, 7.1%); δ_H [$(CD_3)_2SO$] 0.89 (9 H, s, CMe_3), 1.55 (3 H, s), 1.62 (3 H, s), 1.65 (3 H, s) (3 × geranyl Me), 2.01 (4 H, m, 4,5-H), 3.82 (2 H, s, SO_3CH_2), 4.85 (2 H, d, *J* 7.2, 1-H), 5.02 (1 H, m, 6-H), 5.42 (1 H, t, *J* 7.2, 2-H), 11.44 (1 H, br s, OH); δ_F [$(CD_3)_2SO$] −162.69 (1 F, d, *J* 23.5), −151.97 (1 F, d, *J* 8.8), −139.97 (1 F, dd, *J* 9.2, 24.1); *m/z* (ESI, −ve ion mode) 449 $(M - H)^-$.

2-Methylpropan-1-yl pentafluorobenzenesulfonate 32b

The reaction of 2-methylpropan-1-ol (8 cm^3, 87 mmol) with **31** (15 g, 56 mmol) following essentially the method used to prepare **32a** except that the reaction duration, at room temperature, was 17 h. Chromatography [hexane–dichloromethane (stepwise gradient: 5:1, 4:1, 3:1 and 2.5:1)] gave *ester* **32b** (11.0 g, 64%) mp 47–49 °C (from hexane) (Found: C, 39.5; H, 3.0; F, 31.4; S, 10.7; $C_{10}H_9F_5O_3S$ requires C, 39.5; H, 3.0; F, 31.2; S, 10.5%); δ_H [$(CD_3)_2SO$] 0.90 (6 H, d, *J* 6.7, 2 × Me), 1.97 (1 H, m, Me_2CH), 4.12 (d, *J* 6.3, OCH_2); δ_F [$(CD_3)_2SO$] −158.75 (2 F, m), −144.53 (1 F, m), −136.02 (2 F, m). Note: the title compound appears unstable in $(CD_3)_2SO$, since NMR spectra also contain a second set of signals that increase in intensity with time relative to those of **32b**.

2-Methylpropan-1-yl 2,3,5,6-tetrafluoro-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]benzenesulfonate 33b

From **32b** (2.43 g, 8 mmol) and (*E*,*E*)-farnesol using general procedure A, but initiating the reaction at 10 °C. Chromatography [Merck 9385 silica; hexane–dichloromethane (2:1)] gave the slightly impure *title compound* **33b** (2.44 g, 60%) as an oil [Found (for material from the purest fraction of the eluate): C, 59.5; H, 6.8; F, 15.1; S, 6.4; $C_{25}H_{34}F_4O_4S$ requires C, 59.3; H, 6.8; F, 15.0; S, 6.3%]; δ_H [$(CD_3)_2SO$] 0.88 (6 H, dd, *J* 0.7, 6.8, Me_2CH), 1.55 (6 H, s), 1.63 (3 H, s), 1.69 (3 H, s) (4 × farnesyl Me), 2.04 (9 H, m, Me_2CH, 4,5,8,9-H), 4.07 (2H, m, SO_3CH_2), 4.95 (2 H, d, *J* 7.1, 1-H), 5.05 (2 H, m, 6,10-H), 5.46 (1 H, t, *J* 7.1, 2-H); δ_F [$(CD_3)_2SO$] −154.03 (2 F, m), −138.21 (2 F, m); *m/z* (ESI) 529 $(M + Na)^+$.

2-Methylpropan-1-yl 2,3,5-trifluoro-6-hydroxy-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]benzenesulfonate 34b

From slightly impure **33b** (1.55 g, 3.06 mmol) using general procedure B, but at ice-bath temperature initially, then at room temperature. Chromatography [Merck 9385 silica with hexane–dichloromethane (stepwise gradient: 3:2, 1:1) then dichloromethane] gave *farnesyl ether* **34b** (0.77 g, 50%) (oil) (Found: C, 59.1; H, 67.0; F, 11.6; S, 6.3; $C_{25}H_{35}F_3O_5S$ requires C, 59.5; H, 7.0; F, 11.3; S, 6.35%); δ_H [$(CD_3)_2SO$] 0.87 (6 H, d, *J* 6.8, Me_2CH), 1.54 (6 H, s), 1.62 (3 H, s), 1.66 (3 H, s) (4 × farnesyl Me), 1.94 (m), 2.02 (m) (overlapping, total 9H, Me_2CH, 4,5,8,9-H), 3.94 (2 H, d, *J* 6.3, SO_3CH_2), 4.84 (2 H, d, *J* 7.3, 1-H), 5.05 (2 H, m, 6,10-H), 5.42 (1 H, t, *J* 7.3, 2-H), 11.4 (1 H, br s, OH); δ_F [$(CD_3)_2SO$] −162.61 (1 F, d, *J* 24.0), −151.92 (1 F, d, *J* 8.1), −140.02 (1 F, dd, *J* 8.2, 24.6); *m/z* (ESI, −ve ion mode) 503 $(M - H)^-$.

Sodium 2,3,5-trifluoro-6-hydroxy-4-[(*E*,*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]benzenesulfonate 35a

A solution of **34b** (0.303 g, 0.6 mmol) and sodium iodide (0.096 g, 0.64 mmol) in acetonitrile (2.5 cm^3) was stirred under argon at room temperature in the dark. After 20 h the mixture was cooled in ice and the precipitate collected by filtration and washed with the minimum volume of cold acetonitrile to give *title compound* **35a** (0.201 g, 72%), mp 270 °C (decomp.) (from acetonitrile) (Found: C, 52.95; H, 5.5; F, 12.4; S, 7.0; $C_{21}H_{26}F_3NaO_5S \cdot 0.25H_2O$ requires C, 53.1; H, 5.6; F, 12.0; S, 6.75%); δ_H [$(CD_3)_2SO$] 1.54 (6 H, s, 2 × Me), 1.62 (6 H, s, 2 × Me), 2.01 (8 H, m, 4,5,8,9-H), 4.68 (2 H, d, *J* 7.2, 1-H), 5.06 (2 H, m, 6,10-H), 5.41 (1 H, t, *J* 7.2, 2-H), 11.28 (1 H, s, OH); δ_F [$(CD_3)_2SO$] −164.93 (1 F, d, *J* 24.9), −155.88 (1 F, d, *J* 9.9), −141.84 (1 F, dd, *J* 10.1, 27.0); *m/z* (ESI, −ve ion mode) 447 $(M - Na)^-$.

2-Methylpropan-1-yl 4-[(*E*)-3,7-dimethylocta-2,6-dien-1-yloxy]-2,3,5,6-tetrafluorobenzenesulfonate 33c

From recrystallised **32b** (1.217 g, 4 mmol) and geraniol using general procedure A. Chromatography [Merck 9385 silica, hexane–dichloromethane (3:2) then hexane–dichloromethane (2:1)] gave in later fractions pure *geranyl derivative* **33c** (oil) (0.219 g) preceded by impure material (1.119 g) (*ca.* 90% pure by NMR) (total yield *ca.* 1.2 g, 68%) (Found: C, 54.7; H, 6.0; F, 17.5; S, 7.5; $C_{20}H_{26}F_4O_4S$ requires C, 54.8; H, 6.0; F, 17.3; S, 7.3%); δ_H [$(CD_3)_2SO$] 0.88 (6 H, d, *J* 6.8, Me_2CH), 1.55 (3 H, s), 1.62 (3 H, s), 1.68 (3 H, s) (3 × geranyl Me), 1.96 (1 H, m, Me_2CH), 2.03 (4 H, m, 4,5-H), 4.07 (2 H, d, *J* 6.3, SO_3CH_2), 4.95 (2 H, d, *J* 7.2, 1-H), 5.02 (1 H, m, 6-H), 5.45 (1 H, t, 2-H); δ_F [$(CD_3)_2SO$] −154.03 (2 F, m), −138.23 (2 F, m); *m/z* (ESI, −ve ion mode) 436 $(M - H)^-$.

2-Methylpropan-1-yl 4-[(*E*)-3,7-dimethylocta-2,6-dien-1-yloxy]-2,3,5-trifluoro-6-hydroxybenzenesulfonate 34c

From **33c** (purity *ca.* 90%; 0.522 g, 1.2 mmol) using general procedure B but with reaction at room temperature. Chromatography [Merck 9385 silica; hexane–dichloromethane (1:1) then a gradient to neat dichloromethane; next with hexane–dichloromethane (5:4 then 1:3) then neat dichloromethane] gave *title compound* **34c** (0.098 g, 19%) (oil) (Found: C, 55.0; H, 6.2; F, 13.2; S, 7.2; $C_{20}H_{27}F_3O_5S$ requires C, 55.0; H, 6.2; F, 13.1; S, 7.3%); δ_H [$(CD_3)_2SO$] 0.87 (6 H, d, *J* 6.6, Me_2CH), 1.54 (3 H, s), 1.61 (3 H, s), 1.65 (3 H, d, *J* 0.7) (3 × geranyl Me), 1.92 (1 H, m, Me_2CH), 2.01 (4 H, m, 4,5-H), 3.94 (2 H, d, *J* 6.3, SO_3CH_2), 4.84 (2 H, d, *J* 7.2, 1-H), 5.01 (1 H, m, 6-H), 5.42 (1 H, t, *J* 7.2, 2-H), 11.43 (1 H, br s, OH); δ_F [$(CD_3)_2SO$] −162.60 (1 F, d, *J* 24.2), −151.90 (1 F, d, *J* 8.7), −140.02 (1 F, dd, *J* 10.0, 23.7); *m/z* (ESI, −ve ion mode) 435 $(M - H)^-$.

Sodium 4-[(*E*)-3,7-dimethylocta-2,6-dien-1-yloxy]-2,3,5-trifluoro-6-hydroxybenzenesulfonate 35b

Compound **34c** (0.141 g, 0.323 mmol), tetramethylammonium iodide (0.078 g, 0.388 mmol) and acetonitrile (2 cm^3) were stirred together for 3 h at room temperature, then for 66 h at 37 °C. The mixture was evaporated and the residue chromatographed [Merck 7729 silica; dichloromethane then dichloromethane–methanol (stepwise gradient: 95:5 and 90:10) in succession]. A suspension of the product in methanol–water (4:1) was applied to a column (bed volume 8 cm^3) of Bio-Rad AG50W X-4 100–200 mesh cation-exchange resin (Na^+ form) which was eluted with methanol–water (4:1) and the eluate evaporated to dryness. The residue was extracted by trituration with acetonitrile and the extracts concentrated, giving the crystalline *title compound* **35b** as colourless flakes (0.030 g, 23%), mp 260 °C (decomp.) (Found: C, 47.7; H, 4.5; F, 14.2; $C_{16}H_{18}F_3NaO_5S$ requires C, 47.8; H, 4.5; F, 14.2%); δ_H [$(CD_3)_2SO$] 1.54 (3 H, s), 1.62 (6 H, s) (3 × Me), 2.00 (4 H, m, 4,5-CH_2), 4.69 (2 H, d, *J* 7.3, 1-H), 5.03 (1 H, m, 6-H), 5.40 (1 H, t, *J* 7.3, 2-H), 11.28 (1 H, s, OH); δ_F [$(CD_3)_2SO$] −164.92 (1 F, d, *J* 24.7), −155.88 (1 F, d, *J* 9.8), −141.85 (1 F, dd, *J* 9.8, 26.2); *m/z* (ESI, −ve ion mode) 378 $(M - Na)^-$.

Methyl pentafluorophenyl sulfide[32] 36b

Argon was bubbled through a mixture of pentafluorothiophenol **36a** (10.56 g, 52.8 mmol), dichloromethane (105 cm^3), and methyl toluene-*p*-sulfonate (9.89 g, 53.1 mmol). Aqueous sodium hydroxide (1 M; 105 cm^3) and tetra-*n*-butylammonium hydrogen sulfate (1.80 g, 5.3 mmol) were then added successively and the mixture was stirred rapidly under argon with cooling (ice–water bath) for 65 min. The dichloromethane layer was separated and the aqueous layer extracted with dichloro-

methane (3 × 25 cm^3). The combined dichloromethane solution was washed with water (4 × 100 cm^3), dried ($MgSO_4$) and concentrated to leave a liquid. Samples of **36b** were purified by first chromatography (Merck 9385 silica; neat hexane) to separate a by-product more polar than the required product, then distilling under water pump vacuum (bp = 79–82 °C); δ_H ($CDCl_3$) 2.48; δ_F ($CDCl_3$) −161.74 (2 F, m), −154.24 (1 F, t, *J* 20.6), −134.05 (2 F, dd, *J* 6.9, 23.9).

Methyl pentafluorophenyl sulfone[32] 37

This compound was prepared from **36** by the literature procedure; mp 93–95 °C (lit.[32] 85–86 °C); δ_H [$(CD_3)_2SO$] 3.51 (s); δ_F [$(CD_3)_2SO$] −159.42 (2 F, m), −145.51 (1 F, m), −137.56 (2 F, m).

4-[(*E*)-3,7-Dimethylocta-2,6-dien-1-yloxy]-2,3,5,6-tetrafluorophenyl methyl sulfone 38

From **37** (1.50 g, 6.1 mmol) and geraniol, using general procedure A. Chromatography [Merck 9385 silica; hexane–diethyl ether (2:1)] gave the *title compound* **38** (1.738 g, 75%) as an oil which solidified on cooling, mp 36–38 °C (Found: C, 53.7; H, 5.3; F, 19.9; S, 8.5; $C_{17}H_{20}F_4O_3S$ requires C, 53.7; H, 5.3; F, 20.0; S, 8.4%); δ_H [$(CD_3)_2SO$] 1.56, 1.63, 1.69 (3 × s, each 3 H, 3 × geranyl Me), 2.04 (4 H, m, 4,5-H), 3.46 (s, 3 H, SO_2Me), 4.93 (2 H, d, *J* 7.2, 1-H), 5.03 (1 H, m, 6-H), 5.45 (1 H, t, *J* 7.2, 2-H); δ_F [$(CD_3)_2SO$] −154.57 (2 F, m), −139.71 (2 F, m); *m/z* (FAB) 513.0144 $(M + Cs)^+$ (calc for $(M + Cs)^+$, 513.0124).

4-[(*E*)-3,7-Dimethylocta-2,6-dien-1-yloxy]-2,3,5-trifluoro-6-(2-trimethylsilylethoxy)phenyl methyl sulfone 39 and 4-[(*E*)-3,7-dimethylocta-2,6-dien-1-yloxy]-3,5-difluoro-2,6-bis(2-trimethylsilylethoxy)phenyl methyl sulfone 40

The procedure using **38** (0.751 g, 1.97 mmol), 2-(trimethylsilyl)ethanol (0.333 g, 2.82 mmol) and potassium *tert*-butoxide (0.260 g, 2.32 mmol) followed essentially that used to prepare compound **13**. Chromatography [Merck 9385 silica; hexane–diethyl ether (4:1)] gave *bis(trimethylsilylethoxy) derivative* **40** (0.178 g, 15%) and *mono(trimethylsilylethoxy) derivative* **39** (0.652 g, 69%) as colourless oils; for **40** (Found: C, 56.3; H, 8.0; F, 6.6; S, 5.4; $C_{27}H_{46}F_2O_5SSi_2$ requires C, 56.2; H, 8.0; F, 6.6; S, 5.6%); δ_H [$(CD_3)_2SO$] 0.03 (18 H, s, $SiMe_3$), 1.16 (4 H, t, *J* 8.5, CH_2Si), 1.54, 1.61, 1.64 (3 × s, each 3 H, 3 × geranyl Me), 2.00 (4 H, m, 4,5-H), 3.31 (3 H, s, SO_2Me), 4.11 (4 H, t, *J* 8.5, CH_2CH_2Si), 4.80 (2 H, d, *J* 7.2, 1-H), 5.01 (1 H, m, 6-H), 5.40 (1 H, t, *J* 7.2, 2-H); δ_F [$(CD_3)_2SO$] −146.74 (s); *m/z* (FAB) 649.3020 $(M + Me_3Si)^+$ (calc for $(M + Me_3Si)^+$, 649.3046); for **39** (Found: C, 55.0; H, 6.9; F, 11.8; S, 6.8; $C_{22}H_{33}F_3O_4SSi$ requires C, 55.2; H, 6.95; F, 11.9; S, 6.7%); δ_H [$(CD_3)_2SO$] 0.04 (9 H, d, *J* 0.7, $SiMe_3$), 1.19 (2 H, dd, *J* 8.3, 9.0, CH_2Si), 1.54, 1.62, 1.66 (3 × s, each 3 H, 3 × geranyl Me), 2.02 (4 H, m, 4,5-H), 3.38 (3 H, s, SO_2Me), 4.20 (2 H, dd, *J* 8.3, 9.0, CH_2CH_2Si), 4.86 (2 H, d, *J* 7.2, 1-H), 5.01 (1 H, m, 6-H), 5.42 (1 H, t, *J* 7.2, 2-H); δ_F [$(CD_3)_2SO$] −155.58 (1 F, d, *J* 23.7), −146.10 (1 F, d, *J* 9.1), −141.16 (1 F, dd, *J* 10.0, 23.7); *m/z* (FAB) 551.2265 $(M + Me_3Si)^+$ (calc for $(M + Me_3Si)^+$, 551.2294).

4-[(*E*)-3,7-Dimethylocta-2,6-dien-1-yloxy]-2,3,5-trifluoro-6-hydroxyphenyl methyl sulfone 41

Tetra-*n*-butylammonium fluoride (1 M solution in THF; 1.12 cm^3) was added to **39** (0.268 g, 0.56 mmol) and the resulting mixture was stirred at room temperature for 50 min. Methanol–water (4:1) was added and the solution applied to a column (2.5 cm^3) (bed volume 16 cm^3) of Bio-Rad AG50W-X4 100–200 mesh cation-exchange resin (H^+ form). Further methanol–water (4:1) was allowed to percolate through the column and from the eluate was recovered in two crops the crystalline *title compound* **41** (0.109 g, 51%) mp 46–48 °C (Found: C, 54.0; H, 5.6; F, 15.1; S, 8.6; $C_{17}H_{21}F_3O_4S$ requires C, 54.0; H, 5.6; F, 15.1; S, 8.5%); δ_H [$(CD_3)_2SO$] 1.55, 1.62, 1.66 (3 × s, each 3 H, 3 × geranyl Me), 2.02 (4 H, m, 4,5-H), 3.38 (3 H, s, SO_2Me), 4.82 (2 H, d, *J* 7.1, 1-H), 5.03 (1 H, m, 6-H), 5.43 (1 H, t, *J* 7.1, 2-H), 11.4 (br, OH); δ_F [$(CD_3)_2SO$] −162.82 (1 F, d, *J* 22.1), −152.42 (1 F, d, *J* 9.8), −142.83 (1 F, dd, *J* 9.7, 23.8); *m/z* (ESI, −ve ion mode) 377 $[(M - H)^-]$; *m/z* (FAB) 379.1170 $(M + H)^+$ (calc for $(M + H)^+$, 379.1191).

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