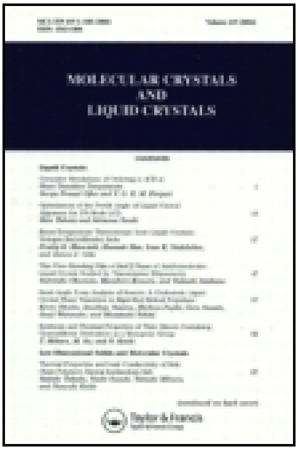

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The Synthesis and Transition Temperatures of Some Fluoro-Substituted 4-Cyanophenyl and 4-Cyanobiphenyl-4′-yl 4-Pentyl- and 4-Butoxy-Benzoates

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The Synthesis and Transition Temperatures of Some Fluoro-Substituted 4-Cyanophenyl and 4-Cyanobiphenyl-4′-yl 4-Pentyl- and 4-Butoxy-Benzoates†

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A series of 4-cyanophenyl 4-X-benzoates and a series of 4-cyanobiphenyl-4′-yl 4-X-benzoates (X = pentyl, butoxy) have been prepared without fluoro-substitution and with mono-fluoro to tetra-fluoro-substitution; all possible combinations of substitution patterns at the positions *ortho*- to the cyano group and *ortho*- to the carboxylate group have been obtained in an attempt to determine the structural features which are responsible for some members of these series showing very large positive values of dielectric anisotropy. The synthesis of novel precursors required for the preparation of these esters is described and the melting points and transition temperatures of the esters are discussed and an explanation is provided for the variation of T_{N-I} values with position and extent of fluoro-substitution.

Keywords: Fluoro-substitution, phenyl and biphenyl benzoates, terminal cyano nematogens.

INTRODUCTION

Fluoro-substitution in mesogens has for many years been used as a useful way of modifying the transition temperatures and/or the mesophase types of the parent systems.[1-6] The fluoro-substituent is ideal in that it combines the properties of large electronegativity and small size so that it significantly affects the physical properties of molecules without eliminating the possibility of mesophase formation. In non-polar systems, such substitution often depresses the mesophase thermal stabilities of smectic phases more than those of nematic phases and so is capable of giving enhanced nematic temperature ranges. For polar mesogens, such as terminal cyano-systems, additional effects on dipole moments or anti-parallel correlation of the molecular dipoles can arise because of the electronic and steric changes caused by fluoro-substitution.[7,8,9]

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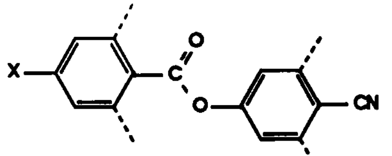
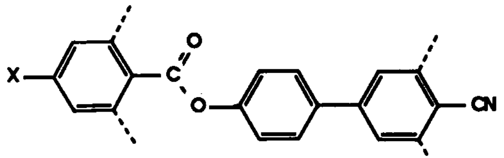
†Presented at The Twelfth International Liquid Crystal Conference, Freiburg, Federal Republic of Germany, 15–19th August 1988.

Some of our previously reported work on fluoro-substitution includes a study of the terminal cyanobiphenyls[8] and the physical properties of these compounds have been reported by our collaborators.[7] Perhaps the most dramatic effect of fluoro-substitution in simple terminal cyano- systems is provided by the work of Schad and Kelly on 3-fluoro-4-cyanophenyl 4-alkylbenzoates[10-14] (see also Reference 15) and the revelation that the very high positive values of dielectric anisotropy which have been obtained may arise, not simply by a destruction of anti-parallel correlations of molecules, but by a positive encouragement of parallel molecular associations. Such an occurrence is extremely important since, if structural reasons for such an effect can be understood, then it may be possible to design molecular systems with greater parallel associations of molecular dipoles which would give much larger values of positive dielectric anisotropy, with the obvious advantage for applications in various electro-optic display devices.

We have therefore decided to prepare a coherent set of 4-cyanopheny 4-alkyl- and 4-alkoxy-benzoates with mono-, di-, tri- and tetra-fluoro-substituents at the positions which should help to increase the dipole moment and to destroy anti-parallel correlation of molecular dipoles.



I



II

a...X = C_5H_{11}
b...X = C_4H_9O

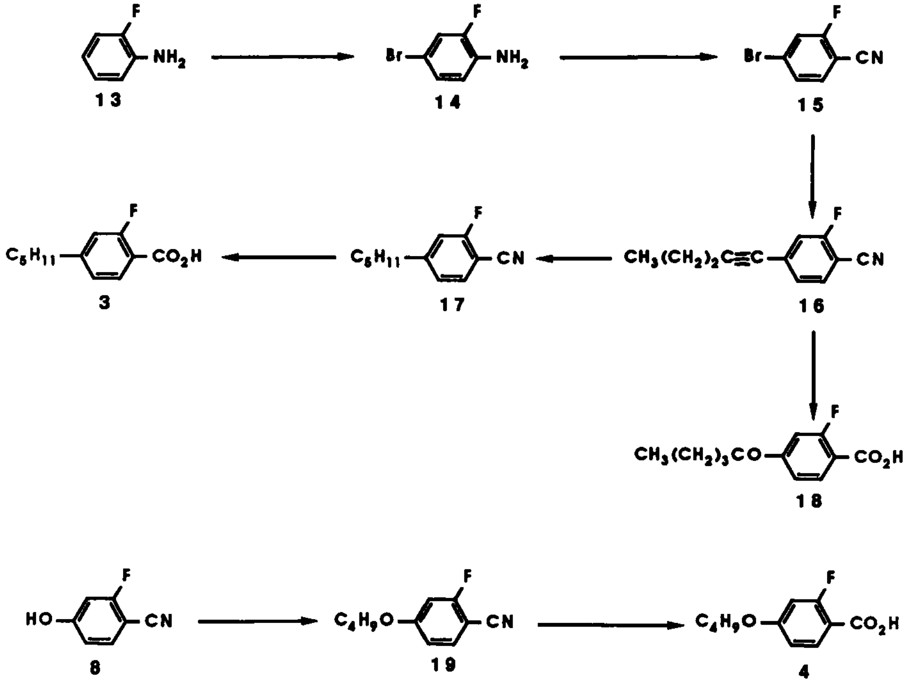
---- Indicates H or F in all the possible combinations

The pentyl and butoxy compounds (Ia and b) were chosen for this work and, because we anticipated that monotropic and virtual *N-I* transitions would arise, we also prepared the related 4-cyanobiphenyl-4′-yl benzoates (IIa and b) in order to determine the effect of fluoro-substitution more accurately from enantiotropic phases. In this paper we describe the preparation of these compounds and we discuss their transition temperatures.

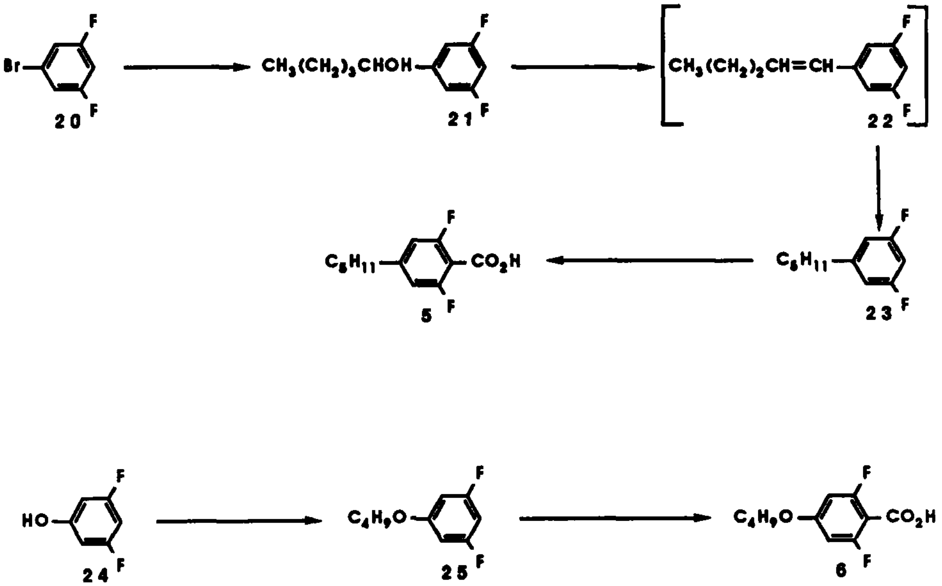
The preparation of the full set of thirty six esters required the availability of six acids (1–6) and six phenols (7–12) (see Schemes and Tables I and II). Of these, four starting materials (1, 7, 8, 10) were supplied to us by our collaborators at BDH Ltd (Poole, England) and the remaining acids and phenols were prepared as described below; the esters were all made by the dicyclohexylcarbodiimide method as given in the Experimental Section.

Compound 2 was prepared by a conventional alkylation of 4-hydroxybenzoic acid. Although we have prepared compound 3 on one occasion by an alternative procedure, the route we prefer is shown in Scheme 1 and starts with 2-fluoroaniline (13). Bromination with *N*-bromosuccinimide (NBS) followed by diazotisation-cyanation in carefully controlled conditions gave 15 which was coupled with pent-1-yn-1-ylzinc chloride. The original plan was to hydrolyse the nitrile (16) and then hydrogenate the triple bond so that there was no risk of reduction of the nitrile group. However, this approach was changed when it was found that the hydrolysis gave a keto-acid (18); reduction of compound 16 was, in fact, achieved efficiently. Compound 4 was obtained by alkylation of 8 followed by hydrolysis.

The preparations of compounds 5 and 6 are outlined in Scheme 2 and have similar features in their final steps which involve carboxylation at a position between two aromatic fluoro-substituents. Preparation of 23 was tried by a variety of methods from 20 but all of these were unsatisfactory and the indirect route *via* the alcohol (21) and alkene (22) was used. Lithiation, by using butyllithium, at the 'acidic position' between the two fluoro-substituents, and subsequent carboxylation gave 5. Similarly, lithiation/carboxylation of 25 gave the required acid 6 and it is interesting that although the position *ortho*- to an alkoxy group or *ortho*- to a fluoro-substituent is activated to metallation,[16-18] the position between the two



SCHEME 1 Synthetic routes to 4-pentyl- and 4-butoxy-2-fluorobenzoic acids.



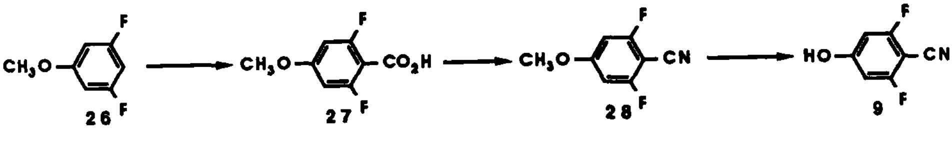
SCHEME 2 Synthetic routes to 4-pentyl- and 4-butoxy-2,6-difluorobenzoic acids.

fluorine substituents is much more activated and no trace of product arising from metallation between alkoxy and fluoro-substituent was detected.

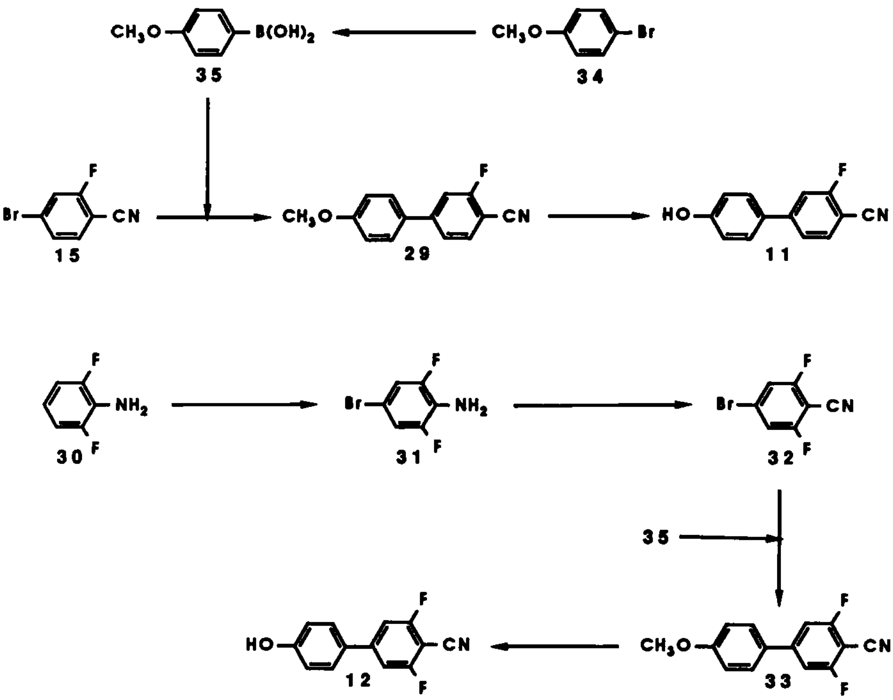
The preparation of compound 9 (Scheme 3) is, similarly, based on carboxylation of 26 to give compound 27, followed by conversion of the carboxylic acid into a nitrile and demethylation of the ether (28). The normally successful procedure of boron tribromide-demethylation failed and the more powerful conditions of fused ($AlCl_3$/NaCl) had to be used.[10]

Scheme 4 shows the two parallel routes to the fluorobiphenyls 11 and 12. Compound 15 was coupled with the boronic acid 35 to give 29 using the tetrakis(triphenylphosphine)palladium(0)-catalysed reaction developed by Suzuki *et al.*[19] and Miller *et al.*[20]

Similarly, coupling of 32 and 35 gave compound 33 (compound 32 was prepared by a related route to that used for 15, but significant practical differences are apparent from the experimental details). Both of the compounds 29 and 33 were demethylated by the boron tribromide procedure to give compounds 11 and 12 respectively.



SCHEME 3 Synthetic route to 2,6-difluoro-4-hydroxybenzonitrile.



SCHEME 4 Synthetic routes to 3-fluoro- and 3,5-difluoro-4-cyano-4′-hydroxybiphenyl.

DISCUSSION OF TRANSITION TEMPERATURES

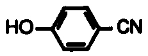
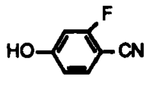
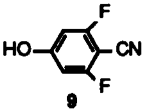
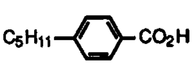
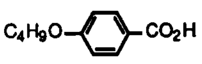
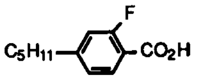
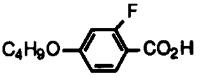
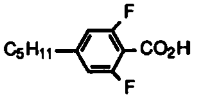
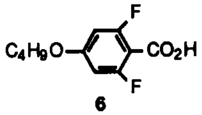
There are many different ways of comparing the transition temperatures shown in Tables I and II, and the following comments are intended to highlight the main generalities. The overall trends are more clearly seen from the plots in Figures 1, 2 and 4, 5 and the general shapes of the lines show the similarities and differences caused by fluoro-substitution from one series to another.

Phenyl benzoates (Table I[24] and Figures 1 and 2)

The effect of fluoro-substitution on the melting points of the esters is variable and is never very great, but only three fluoro-substituted esters have higher melting points than their parent compounds. Some compounds of quite low melting point are obtained by difluoro-substitution (compound 38, mp 29.5°C; compound 43, mp 39.5°C), trifluoro-substitution (compound 49, mp 32°C) and tetrafluoro-substitution (compound 50, mp 36.5°C), but although low mps are achieved, the disadvantage is that the T_{N-I} values (enantiotropic, monotropic or virtual) for multi-fluoro-substituted esters are very much depressed. The melting points and T_{N-I} values for the 4-butoxy esters are always higher than those for the corresponding 4-pentyl esters by approximately 15–40°C and 15–50°C respectively; such differences between alkyl and alkoxy compounds are typical of the differences in other systems.

TABLE I

Transition temperatures (°C) of fluoro-substituted 4-cyanophenyl 4-pentyl- and 4-butoxy-benzoates

PHENOL ACID	 7	 8	 9
 1	K-I 64.5 N-I (55.5) 36	K-I 30.5 N-I (24.5) 37	K-I 29.5 N-I (-8.0) 38
 2	K-N 92.0 N-I 104.0 39	K-I 72.0 N-I (48.5) 40	K-I 71.5 N-I [7.5] 41
 3	K-I 65.5 N-I (32.0) 42	K-I 39.5 N-I (-3.0) 43	K-I 55.0 N-I (-20.5) 44
 4	K-I 90.0 N-I (61.0) 45	K-I 55.0 N-I (21.5) 46	K-I 68.0 N-I [-6.0] 47
 5	K-I 74.5 N-I [-18.0] 48	K-I 32.0 N-I [-45.0] 49	K-I 36.5 N-I [-67.0] 50
 6	K-I 101.0 N-I [25.0] 51	K-I 56.0 N-I (-1.5) 52	K-I 63.0 N-I [-31.5] 53

( )..... monotropic transition
[ ]..... virtual transition

The T_{N-I} values shown in Table I vary even more regularly than mps and three distinct categories of substituent effect are apparent. Firstly, mono-fluoro-substitution in the phenol ring has a greater effect on the T_{N-I} values of esters than mono-fluoro-substitution in the acid ring [e.g. compare compounds 36/37 (31°C difference) and compounds 36/42 (23.5°C difference); compounds 39/40 (55.5°C difference) and compounds 39/45 (43.0°C difference): the equivalent comparison for the biphenyl benzoates shows compounds 54/55 (39.0°C difference) and com-

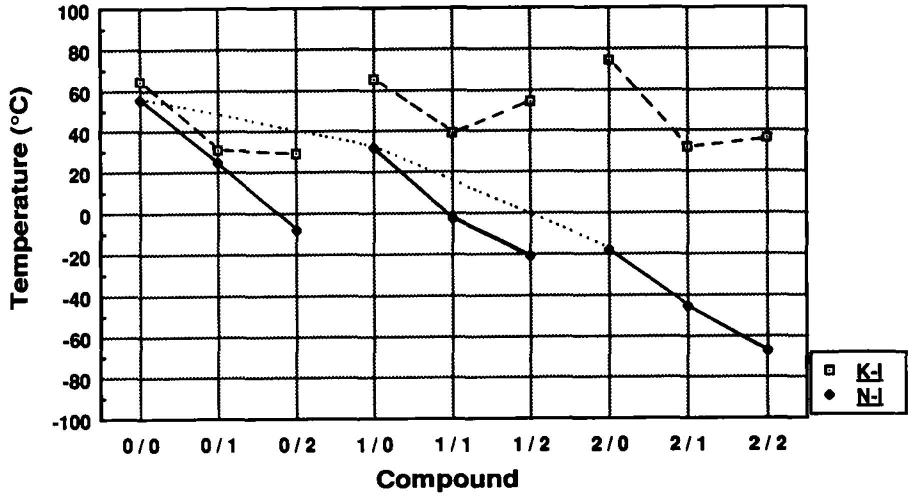


FIGURE 1 Transition temperatures for fluoro-substituted phenyl alkylbenzoates.

pounds 54/60 (12.5°C difference); compounds 57/58 (33.0°C difference) and compounds 57/63 (10.5°C difference)]. Secondly, a second fluoro-substituent in the phenol causes a further depression in T_{N-I} value which is approximately equivalent to that of the first substitution i.e., the effects are approximately additive [e.g. compare compounds 36, 37, 38 (31.0°C and 32.5°C decrease); compounds 39, 40, 41 (55.5°C and 41.0°C decrease): the equivalent comparisons for the biphenyl benzoates are compounds 54, 55, 56 (39.0°C and 48.5°C decrease); compounds 57, 58, 59 (33.0°C and 42.0°C decrease)]. Thirdly, a second fluoro-substituent in the

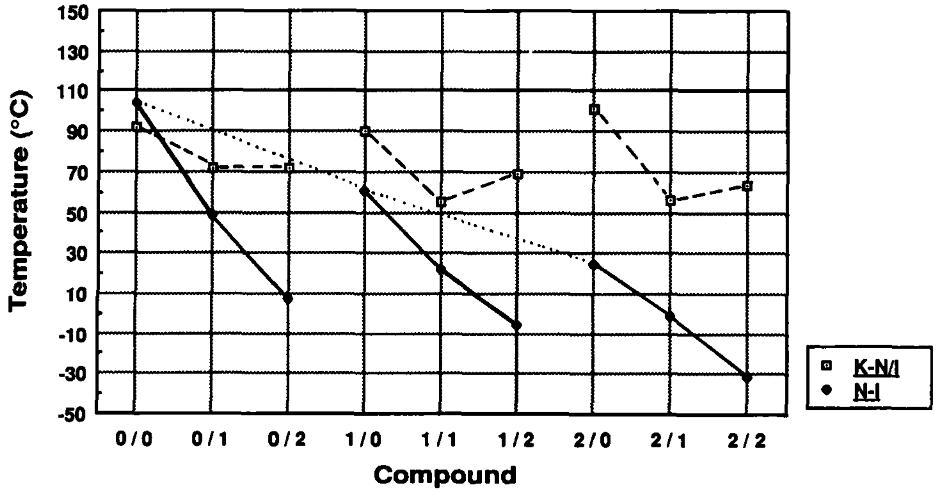
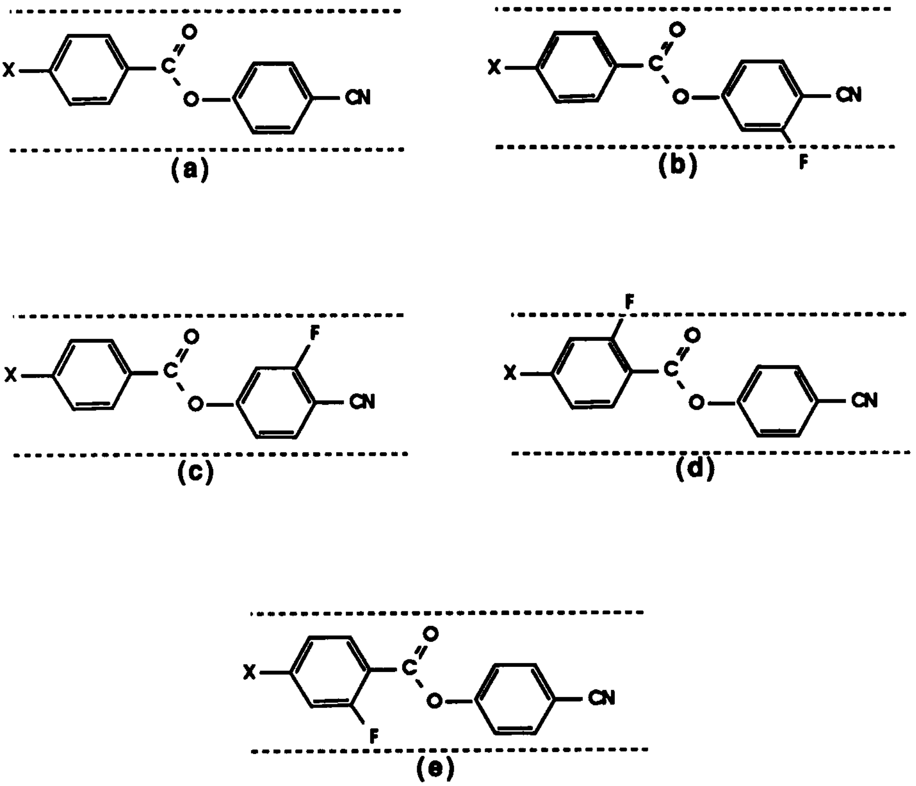


FIGURE 2 Transition temperatures for fluoro-substituted phenyl alkoxybenzoates.

acid causes a larger depression in T_{N-I} than that caused by a single fluoro-substituent in the acid [e.g., compare compounds 42, 48 (50.0°C difference) and compounds 36, 42 (23.5°C difference); compounds 43, 49 (42.0°C difference) and compounds 37, 43 (27.5°C difference): the equivalent comparisons for the biphenyl benzoates are compounds 60, 66 (34.0°C difference) and compounds 54, 60 (12.5°C difference); compounds 61, 67 (29.5°C difference) and compounds 55, 61 (11.0°C difference)]. (There are 12 different examples for which this effect can be considered in Tables I and II and 10 of these comparisons conform to the generalisations made here).

We believe that these effects can be rationalised by considering how fluoro-substitution affects the breadth of the molecule. In Figure 3(a), the natural breadth of the parent molecule is shown by a dotted line. Mono-fluoro-substitution in the phenol can give one extreme planar conformation (b) in which the substituent increases the breadth of the molecule. There is no particular reason why this conformation or the alternative planar conformation (c) produced by rotation about the O-aryl bond would be preferred and about half the number of molecules may therefore have similar dimensions to the parent system. With a second fluoro-substituent in the phenol it is inevitable that every ester molecule is appreciably broader than the parent molecule (a) and these effects may be revealed as an



(a) (b) (c) (d) (e)

FIGURE 3 Conformations of some fluoro-derivatives of phenyl benzoates.

additive effect. For fluoro-substitution in the acid part of the ester, the fluoro-substituent, placed as shown in (d), may suffer electro-static repulsion by the carbonyl oxygen atom and the alternative conformation (e), which does not involve significant molecular broadening, may be favourable. The first fluoro-substituent of this type should therefore have a small effect on the T_{N-I} values, but the second fluoro-substituent will give a marked depression because of the much greater broadening of the molecule.

Biphenyl benzoates (Table II[24] and Figures 4 and 5)

All the T_{N-I} values for these esters are enantiotropic and are about 150–200°C higher than those for the corresponding phenyl esters. Their melting points are also somewhat higher, but still lie within a relatively narrow band, and the lowest value of 89.0°C is for the tetra-fluoro derivative 68. Many of the general points discussed earlier for the phenyl benzoates are also applicable to the biphenyl benzoates.

All of these effects are more easily visualised by reference to Figures 1, 2 and 4, 5, rather than by considering the numerical values in Tables I and II. (The four figures each show the title esters in three separate groups where *x*/*y* on the abscissa refers to *x* fluoro-substituents in the acid and *y* fluoro-substituents in the phenol; e.g., in Figure 1, 2/1 signifies compound 49). Figures 4 and 5, with enantiotropic values more clearly show the following points:

(a) a narrow spread of mps, showing a rise and fall with mono- and di-fluoro-substitution respectively in the phenol (dashed line);

(b) the approximately additive effect in the depression of T_{N-I} values caused by mono-, di-fluoro-substituents in the phenol (the almost linear arrangement of the three points connected by full lines);

(c) the smaller, then larger effect on T_{N-I} values caused by fluoro-substitution in the acid (one example is shown in each figure as a dotted line).

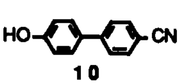
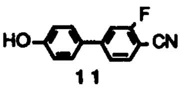
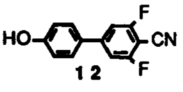
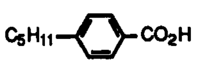
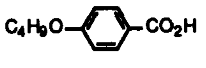
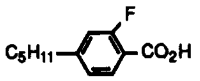
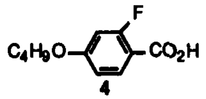
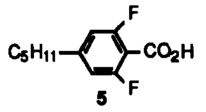
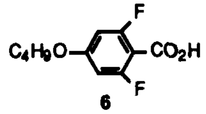
Very similar results are revealed in Figures 1 and 2 for the phenyl benzoates, but here monotropic (and less certain virtual) values are being considered. The pattern of melting points, however, shows a fall and then a rise for fluoro-substitution in the phenol.

Substituted benzoic acids

Four of the six acids used to form the esters are themselves liquid crystals; transition temperatures for the parent 4-pentyl- and 4-butoxy-benzoic acids have been reported previously as K 88°C N 126.5°C I and K 147°C N 160°C I respectively.[25] The transition temperatures for 2-fluoro-4-pentyl- and 2-fluoro-4-butoxy- benzoic acid reported here are K 85°C N 91°C I and K 108°C N 125°C I respectively and the corresponding 2,6-difluoro-compounds, with melting points of 78–79°C and 113–114°C respectively, are not mesogenic. The melting points of the fluoro-substituted acids are always lower than those of the parent acids and the depression in nematic thermal stability is 35.5°C and 35.0°C for the alkyl and alkoxy acids respectively. Such values, which arise for dimerised molecules and therefore could

TABLE II

Transition temperatures (°C) of fluoro-substituted 4-cyanobiphenyl-4'-yl 4-pentyl- and 4-butoxybenzoates

PHENOL / ACID	 10	 11	 12
 1	K-N 109.0 N-I 237.5 54	K-N 123.5 N-I 198.5 55	K-N 96.5 N-I 150.5 56
 2	K-N 120.0 N-I 270.0 57	K-N 135.0 N-I 237.0 58	K-N 114.5 N-I 195.0 59
 3	K-N 103.0 N-I 225.0 60	K-N 112.5 N-I 187.5 61	K-N 98.0 N-I 143.5 62
 4	K-N 94.0 N-I 259.5 63	K-N 115.0 N-I 219.5 64	K-N 104.0 N-I 184.0 65
 5	K-N 109.5 N-I 191.0 66	K-N 116.5 N-I 158.0 67	K-N 89.0 N-I 121.0 68
 6	K-N 94.0 N-I 223.0 69	K-N 103.0 N-I 194.0 70	K-N 102.0 N-I 161.5 71

be regarded as showing the effect of two fluoro-substituents in a 'three-ring' system, are not too dissimilar from the effect of fluoro-substitution as shown in Table I.

EXPERIMENTAL

4-Butoxybenzoic acid (2)

1-Bromobutane (22.6 g, 0.165 mol) was added dropwise at room temperature to a stirred mixture of 4-hydroxybenzoic acid (15.0 g, 0.11 mol) in ethanol (60 ml) and sodium hydroxide (10.60 g) in the minimum amount of water. The stirred

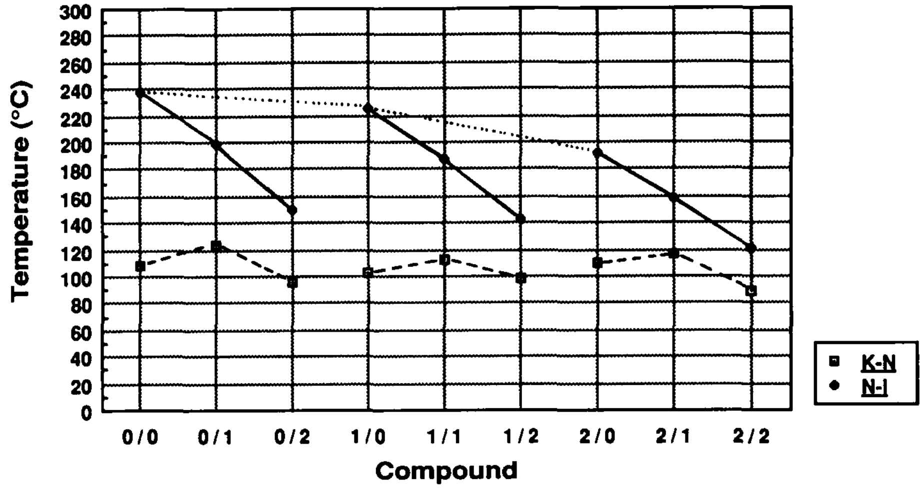


FIGURE 4 Transition temperatures for fluoro-substituted biphenyl alkylbenzoates.

mixture was heated under reflux overnight (tlc analysis revealed a complete reaction), and then the ethanol was distilled off and an equal volume of water was added. The mixture was boiled to give a solution, cooled, washed with ether and acidified with 36% hydrochloric acid. The cooled mixture was filtered, and the product was washed with water to give a colourless solid (13.9 g) which was recrystallised from ethanol to give colourless crystals. Yield 12.1 g, 57%; K 147°C N 160°C I. ^{1}Hnmr ($CDCl_3$)δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.00 (2H, t) 6.80(2H, d), 8.00(2H, d). Ir (KCl) 3300–2500, 2980, 2890, 2670, 2550, 1680, 1610, 1590, 1520, 1300, 1260, 1170 cm^{-1}. Ms *m*/*z* 194(M^+), 138, 121, 65.

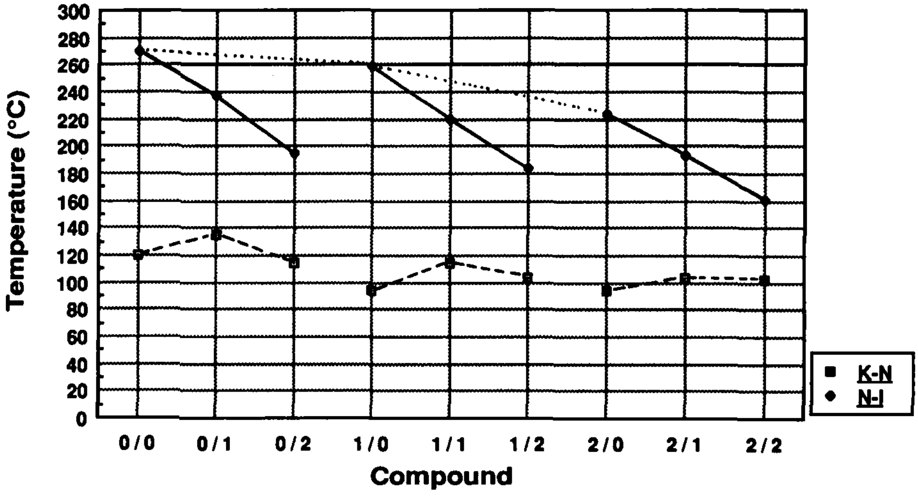


FIGURE 5 Transition temperatures for fluoro-substituted biphenyl alkoxybenzoates.

2-Fluoro-4-pentylbenzoic acid (3)

A mixture of concentrated sulphuric acid (150 ml) and water (150 ml) was added dropwise to a stirred solution of compound 17 (15.0 g, 0.078 mol) in glacial acetic acid (300 ml). The stirred mixture was heated under reflux for 48 h, cooled in a refrigerator overnight and the product was filtered off. The product was dissolved in ether, extracted into 10% sodium hydroxide, which was then acidified with 36% hydrochloric acid, washed with ether (twice), and the combined ethereal phases were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a brown crystalline solid. Yield 11.5 g, 70%; K 85°C N 91°C I. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.30(4H, m), 1.60(2H, quint), 2.65(2H, t), 7.00(2H, q), 7.95(1H, t). Ir (KCl) 3300–2500, 1695, 1670, 1630, 1570, 1500, 1450, 1300, 1210, 1160 cm^{-1}. Ms *m/z* 210(M^+), 193, 175, 167, 154.

4-Butoxy-2-fluorobenzoic acid (4)

A mixture of concentrated sulphuric acid (190 ml) and water (190 ml) was added dropwise to a stirred solution of compound 19 (19.0 g, 0.098 mol) in glacial acetic acid (380 ml). The stirred mixture was heated under reflux for 48 h, cooled in a refrigerator for 24 h and the product was filtered off and dried ($CaCl_2$) *in vacuo* to give pale yellow crystals. Yield 18.7 g, 90%; K 108°C N 125°C I. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.00(2H, t) 6.70(2H, q), 8.00 (1H, t), 11.30(1H, s). Ir (KCl) 3300–2500, 2960, 2880, 1680, 1620, 1575, 1455, 1420, 1400, 1340, 1275, 1245, 1180, 1150, 1040 cm^{-1}. Ms *m/z* 212(M^+), 188, 179, 168, 156, 139.

2,6-Difluoro-4-pentylbenzoic acid (5)

A solution of *n*-butyllithium (10.5 M in hexane; 2.70 ml, 0.028 mol) was added dropwise to a stirred, cooled (−78°C) solution of compound 23 (5.10 g, 0.028 mol) in dry THF (30 ml) under dry nitrogen. The stirred mixture was maintained under these conditions for 2.5 h and then poured onto a slurry of solid carbon dioxide and dry ether. The product was extracted into 10% sodium hydroxide which was then acidified with 36% hydrochloric acid. The acidic mixture was washed with ether (twice), and the combined ethereal layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a colourless solid. Yield 5.8 g, 91%; mp 78-79°C. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.60(2H, quint), 2.65(2H, t), 6.80(2H, d), 7.30(1H, s). Ir (KCl) 3300–2500, 2680, 2550, 1690, 1640, 1570, 1490, 1440, 1410, 1285, 1210 cm^{-1}. Ms *m/z* 228(M^+), 186, 172, 155.

4-Butoxy-2,6-difluorobenzoic acid (6)

A solution of *n*-butyllithium (10.5 M in hexane; 3.60 ml, 0.038 mol) was added dropwise to a stirred, cooled (−78°C) solution of compound 25 (7.00 g, 0.038 mol) in dry THF (35 ml) under dry nitrogen. The stirred solution was maintained under these conditions for 2.5 h and then poured onto a slurry of solid carbon dioxide and dry ether. The product was extracted into 10% sodium hydroxide which was then acidified with 36% hydrochloric acid. The product was filtered off and dried

($CaCl_2$) *in vacuo* to give a colourless solid. Yield 8.3 g, 96%; mp 113–114°C. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.00(2H, t), 6.50(2H, d), 7.30(1H, s), Ir (KCl) 3300–2500, 2980, 2880, 2650, 2550, 1690, 1630, 1570, 1440, 1370, 1270, 1230, 1050 cm^{-1}. Ms *m/z* 230(M$^+$), 226, 213, 187, 174.

2,6-Difluoro-4-hydroxybenzonitrile (9)

A stirred, homogeneous mixture of finely powdered, compound 28 (17.0 g, 0.10 mol), aluminum chloride (29.4 g, 0.22 mol) and sodium chloride (7.1 g, 0.12 mol) was heated to 180°C over 25 min and then at 180°C for 1 h (glc and tlc analyses both revealed a complete reaction). Ice-water was added, and the product was extracted into ether (twice). The combined ethereal extracts were washed with water, and the product was extracted into 10% sodium hydroxide (twice) and the combined basic extracts were acidified with 36% hydrochloric acid. The product was extracted into ether (twice), and the combined ethereal extracts were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a fawn solid. Yield 14.6 g, 94%; mp 119–120°C. ^{1}Hnmr ($CDCl_3$) δ 6.50(2H, d), 10.9 (1H, s). Ir(KCl) 3300, 2250, 1640, 1600, 1510, 1480, 1270, 1160, 1040, 850 cm^{-1}. Ms *m/z* 155(M$^+$), 127, 107, 100.

4-Cyano-3-fluoro-4′-hydroxybiphenyl (11)

A solution of boron tribromide (12.0 ml, 31.8 g, 0.13 mol) in dry dichloromethane (100 ml) was added dropwise to a stirred, cooled (−78°C) solution of compound 29 (14.0 g, 0.06 mol) in dry dichloromethane (250 ml) under dry nitrogen. The stirred mixture was allowed to warm to room temperature over 20 h (i.e., until glc analysis revealed absence of starting material). Water was added and a yellow precipitate was produced. The product was extracted into ether (twice), and the combined ethereal extracts were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford a pale-yellow powder. Yield 13.1 g, 100%; mp 201–202°C. ^{1}Hnmr ($CDCl_3$) δ 6.95(2H, d), 7.40(2H, q), 7.45(2H, d), 7.65(1H, t), 9.45(1H, s). Ir(KCl) 3400–2900, 2240, 1630, 1610, 1560, 1490, 1450, 1410, 1370, 1270, 1180, 820 cm^{-1}. Ms *m/z* 213 (M$^+$), 184, 164, 158.

4-Cyano-3,5-difluoro-4′-hydroxybiphenyl (12)

A solution of boron tribromide (25.0 ml, 61.5 g, 0.25 mol) in dry dichloromethane (140 ml) was added dropwise to a stirred, cooled (−78°C) solution of compound 33 (12.22 g, 0.05 mol) in dry dichloromethane (250 ml) under dry nitrogen. The stirred mixture was allowed to warm to room temperature over 9 h (i.e., until glc analysis revealed absence of starting material). The mixture was cooled to −10°C, water was added slowly (exothermic) and cooled to 2°C. The product was filtered off, washed with water and dried ($CaCl_2$) *in vacuo* to give a pale-yellow powder. Yield 13.3 g, 100%; mp 230–231°C. ^{1}Hnmr ($CDCl_3$) δ 6.60(2H, d), 6.95(2H, d), 7.13(2H, d), 9.20(1H, s). Ir (KCl) 3390, 2250, 1630, 1610, 1590, 1490, 1460, 1420, 1280, 1230 cm^{-1}. Ms *m/z* 231(M$^+$), 211, 202.

4-Bromo-2-fluoroaniline (14)

N-Bromosuccinimide (160.4 g, 0.09 mol) was added in small portions to a stirred, cooled solution of 2-fluoroaniline (13) (100.0 g, 0.90 mol) in dry dichloromethane (400 ml). The stirred mixture was allowed to warm to 0°C over 45 min, washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a red solid (180 g) which was steam distilled to give a colourless solid. Yield 120.0 g, 70%; mp 41–42°C. ^{1}Hnmr ($CDCl_3$) δ 3.70(2H, s), 6.70(1H, t), 7.05(1H, d), 7.20(1H, d). Ir (KCl) 3410, 3320, 1630, 1580, 1500, 1210 cm^{-1}. Ms *m/z* 191(M^+), 189(M^+), 110, 94.

4-Bromo-2-fluorobenzonitrile (15)

Concentrated sulphuric acid (60 ml) was added dropwise to a stirred mixture of compound 14 (75.0 g, 0.39 mol), water (150 ml) and glacial acetic acid (185 ml). The clear solution was cooled to −5°C (a micro-crystalline suspension formed) and a solution of sodium nitrite (30.0 g, 0.44 mol) in water (100 ml) was added dropwise; the stirred mixture was maintained at −5°C for 15 min.

A solution of potassium cyanide (128.3 g, 1.98 mol) in water (300 ml) was added dropwise to a stirred solution of copper(II) sulphate pentahydrate (118.1 g, 0.48 mol) in water (300 ml) and ice (300 g) at 10–20°C. Sodium hydrogen carbonate (265.1 g, 3.16 mol) and cyclohexane (450 ml) were added, the temperature was raised to 50°C and the cold diazonium salt mixture was added in portions with rapid stirring. The mixture was cooled, the organic layer was separated and the aqueous layer was washed with ether (twice). The combined organic phases were washed with water, 10% sodium hydroxide, water and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford a dark brown solid (78.0 g) which was steam distilled to give an off-white solid. Yield 59.2 g, 76%; mp 69–70°C. ^{1}Hnmr ($CDCl_3$) δ 7.40(1H, d), 7.45(1H, d), 7.50(1H, t). Ir (KCl) 2240, 1600, 1570, 1480, 1400, 1230, 1060, 890, 860, 820 cm^{-1}. Ms *m/z* 201(M^+), 199(M^+), 120, 100.

2-Fluoro-4-pent-1′-yn-1′-ylbenzonitrile (16)

A solution of *n*-butyllithium (10.0 M in hexane; 10.0 ml, 0.10 mol) was added dropwise to a stirred, cooled (< 0°C) solution of pent-1-yne (6.80 g, 0.10 mol) in dry THF[†] (51 ml) under dry nitrogen. This mixture was stirred for 10 min and then a solution of zinc chloride[‡] (13.63 g, 0.10 mol) in dry THF (100 ml) was added dropwise at < 0°C. The mixture was stirred at room temperature for 15 min and a solution of compound 15 (20.0 g, 0.10 mol) in dry THF (100 ml) followed by a solution of tetrakis(triphenylphosphine)palladium(0) (2.31 g, 2.0 mmol) in dry THF (25 ml) were added dropwise at < 0°C[21]. The mixture was stirred at room temperature for 20 h (glc analysis revealed absence of starting material; 20 h was probably longer than required for reaction) and poured into 10% hydrochloric acid

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[†] Sodium dried THF was distilled from lithium aluminum hydride and kept over molecular sieves (type 4A).

[‡] Zinc chloride (ACS reagent) was dried overnight at 100°C.

(200 ml). The product was extracted into ether (twice), and the combined ethereal extracts were washed with water, saturated sodium hydrogen carbonate, water and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford an orange liquid which was distilled to yield a pale-yellow oil. Yield 17.6 g, 94%; bp 100–105°C at 0.1 mm Hg. ^{1}Hnmr ($CDCl_3$) δ 1.05(3H, t), 1.65(2H, sex), 2.40(2H, t), 7.20(2H, q), 7.50 (1H, t). Ir (KCl) 2980, 2950, 2880, 2240, 1620, 1550, 1500, 1420, 1180, 1120 cm^{-1}. Ms *m/z* 187 (M^+), 172, 158, 152, 145, 131.

2-Fluoro-4-pentylbenzonitrile (17)

A stirred mixture of compound 16 (16.0 g, 0.085 mol) and 5% palladium-on-charcoal (4.00 g) in ethanol (100 ml) was hydrogenated at atmospheric pressure for 8h (glc analysis revealed absence of starting material). The catalyst was filtered off and the solvent was removed *in vacuo* to yield a pale-orange semi-solid. Yield 15.35 g, 95%; mp not recorded, probably around 20°C. ^{1}Hnmr ($CDCl_3$) δ 0.85 (3H, t), 1.30(4H, m), 1.60(2H, quint), 2.65(2H, t), 7.10(2H, q), 7.60(1H, t). Ir (KCl) 2960, 2880, 2250, 1640, 1570, 1510 cm^{-1}. Ms *m/z* 191 (M^+), 134.

2-Fluoro-4-pentanoylbenzoic acid (18)

A mixture of concentrated sulphuric acid (165 ml) and water (165 ml) was added dropwise to a stirred solution of compound 16 (14.0 g, 0.075 mol) in glacial acetic acid (330 ml) at room temperature. The stirred mixture was heated under reflux for 72 h, cooled and the product was extracted into ether (twice). The combined ethereal extracts were washed with water and the product was extracted into 10% sodium hydroxide. The basic extract was acidified with 36% hydrochloric acid and the product was extracted into ether (twice). The combined ethereal extracts were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an off-white solid. Yield 5.62 g, 33%; mp 114–115°C. ^{1}Hnmr ($CDCl_3$) δ 0.95 (3H, t), 1.45(2H, sex), 1.65(2H, quint), 3.00(2H, t), 7.75(2H, q), 8.10(1H, t). Ir (KCl) 2960, 2940, 2880, 2660, 1700, 1690, 1620, 1570, 1430, 1410, 1290, 1240, 1170, 1080 cm^{-1}. Ms *m/z* 224(M^+), 182, 167, 154.

4-Butoxy-2-fluorobenzonitrile (19)

A solution of 1-bromobutane (18.0 g, 0.13 mol) in acetone (30 ml) was added dropwise to a stirred refluxing mixture of 2-fluoro-4-hydroxybenzonitrile (8) (15.0 g, 0.11 mol) and potassium carbonate (46.0 g, 0.33 mol) in acetone (300 ml). The stirred mixture was heated under reflux for 21 h (glc analysis revealed absence of starting material). The product was extracted into ether (twice), and the combined ethereal extracts were washed with water, 5% sodium hydroxide, water and dried ($MgSO_4$). The solvent and the excess of 1-bromobutane were removed *in vacuo* to yield a pale-orange solid. Yield 19.5 g, 93%; mp 25–26°C. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.00(2H, t), 6.90(2H, q), 7.80(1H, t). Ir (KCl) 2960, 2880, 2250, 1640, 1570, 1510, 1460, 1440, 1340, 1300, 1250 cm^{-1}. Ms *m/z* 193(M^+), 188, 149, 137, 120.

1-(3,5-Difluorophenyl)pentan-1-ol (21)

A solution of pentanal (19.0 g, 0.22 mol) in dry ether (75 ml) was added dropwise to a stirred solution of the Grignard reagent at room temperature, under dry nitrogen, prepared from 1-bromo-3,5-difluorobenzene (20) (50.2 g, 0.26 mol) and magnesium (7.25 g, 0.30 mol) in dry THF (100 ml). The stirred mixture was heated under reflux for 2 h, cooled and a saturated solution of ammonium chloride (300 ml) was added. The product was extracted into ether (twice), and the combined ethereal extracts were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a pale-orange liquid (51.1 g) which was distilled to yield a colourless liquid. Smaller quantities of crude product were purified by column chromatography (silica gel/dichloromethane) to yield a colourless liquid (92%). Yield 35.8 g, 69%; bp 90°C at 0.5 mm Hg. ^{1}Hnmr ($CDCl_3$) δ 0.75(3H, t), 1.25 (4H, m), 2.10(1H, s), 3.65(2H, q), 4.70(1H, t), 6.80–7.10(3H, m). Ms *m/z* 200(M^+), 151, 143, 127.

Attempted preparation of 3,5-difluoro-1-pentylbenzene (23)
Method A

A solution of pentyl tosylate (0.9879 g, 4.08 mmol) was added dropwise to a stirred, cooled (−15°C) mixture of the Grignard reagent prepared from 1-bromo-3,5-difluorobenzene (1.0129 g, 5.25 mmol) and magnesium (0.1414 g, 5.82 mmol) in dry ether (5 ml), and a portion of a catalyst solution (2 ml), prepared from lithium chloride (0.2202 g, 5.00 mmol) and copper(II) chloride (0.3403 g, 2.50 mmol) in dry THF (25 ml). The stirred mixture was allowed to warm to room temperature and was stirred at room temperature for 20 h (glc analysis revealed absence of desired product). This procedure was repeated at −78°C with the same result.

Method B

A solution of the Grignard reagent prepared from 1-bromopentane (1.0105 g, 6.69 mmol) and magnesium (0.1778 g, 7.32 mmol) in dry ether (5 ml) was added dropwise to a stirred, refluxing mixture of 1-bromo-3,5-difluorobenzene (1.0782 g, 5.59 mmol) and Ni(dppp)Cl_2 (0.1908 g, 0.35 mmol) in dry ether (5 ml). The stirred mixture was gently heated under reflux for 24 h (glc analysis revealed absence of desired product).

Method C

Copper(I) chloride (0.1012 g, 1.01 mmol) was added to a solution of the Grignard reagent prepared from 1-bromo-3,5-difluorobenzene (1.2355 g, 6.40 mmol) and magnesium (0.1670 g, 6.87 mmol) in dry THF (5 ml) followed by dropwise addition of a solution of 1-bromopentane (1.1463 g, 7.60 mmol) in dry THF (4 ml). The stirred mixture was heated under reflux for 1.5 h (glc analysis revealed presence of desired product), cooled and poured into 20% hydrochloric acid (45 ml). The mixture was washed with dichloromethane, and the organic layer was washed with water and dried ($MgSO_4$). The residual mixture was distilled at atmospheric pressure, but isolation of the desired product proved impossible.

Method D

Copper(I) chloride (0.1000 g, 1.01 mmol) was added to the solution of the Grignard reagent prepared from 1-bromo-3,5-difluorobenzene (0.0125 g, 0.01 mol) and magnesium (0.2484 g, 0.01 mol) in dry THF (5 ml) followed by dropwise addition of a solution of pentyl tosylate (4.7741 g, 0.02 mol) in dry THF (3 ml). The stirred mixture was heated under reflux for 6 h (glc analysis revealed presence of desired product), cooled and poured onto 36% hydrochloric acid (25 ml) and ice (200 g). The mixture was washed with dichloromethane, and the organic layer was washed with water and dried ($MgSO_4$). The residual mixture was distilled at atmospheric pressure but isolation of the desired product proved impossible.

3,5-Difluoro-1-pent-1′-enylbenzene (22)

Phosphorus(V) oxide (64.5 g, 0.45 mol) was added in portions to a stirred solution of compound 21 (35.0 g, 0.175 mol) in dry pentane (150 ml) at room temperature. The mixture was stirred at room temperature overnight (glc analysis revealed absence of starting material), filtered and this solution was used in the next step.

3,5-Difluoro-1-pentylbenzene (23)

5% Palladium-on-charcoal (4.0 g) was added to the above filtrate [i.e., compound 22 in pentane (150 ml)] at room temperature. The stirred mixture was hydrogenated at atmospheric pressure for 4 h (i.e., until glc analysis revealed absence of starting material) and the mixture was filtered. The majority of the pentane was removed *in vacuo*, and the final amount of pentane was distilled off (760 mm Hg) at 38°C and the residue was then distilled to yield a colourless liquid. Yield 23.4 g, 73%; bp 200°C at 760 mm Hg. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.30(4H, m), 1.60(2H, quint), 2.60(2H, t), 6.60(3H, m). Ir (KCl) 2980, 2930, 2870, 1630, 1600, 1460, 1330, 1140, 1120 cm^{-1}. Ms *m/z* 184(M^+), 168, 151, 141.

1-Butoxy-3,5-difluorobenzene (25)

A solution of 1-bromobutane (11.0 g, 0.08 mol) in acetone (30 ml) was added dropwise to a stirred, refluxing mixture of 3,5-difluorophenol (24) (9.1 g, 0.07 mol) and potassium carbonate (30 g, 0.2 mol) in acetone (200 ml). The stirred mixture was heated under reflux for 24 h (glc analysis revealed absence of starting material). The product was extracted into ether (twice), and the combined ethereal extracts were washed with water, 5% sodium hydroxide, water and dried ($MgSO_4$). Most of the solvent was removed *in vacuo*, and after the removal of the final amount of solvent and the excess of 1-bromobutane at atmospheric pressure, the residue was distilled to yield a colourless liquid. Yield 11.7 g, 90%; bp 204°C at 760 mm Hg. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.75(2H, quint), 3.95(2H, t), 6.40(3H, m). Ir (KCl) 2980, 2880, 1630, 1470, 1350, 1130 cm^{-1}. Ms *m/z* 186(M^+), 138, 130, 112, 100.

2,6-Difluoro-4-methoxybenzoic acid (27)

A solution of *n*-butyllithium (10.0 M in hexane; 25.0 ml, 0.25 mol) was added dropwise to a stirred, cooled (−78°C) solution of 3,5-difluoroanisole (26) (35.9 g, 0.25 mol) in dry THF (200 ml) under dry nitrogen. The stirred mixture was maintained under these conditions for 2.5 h and then poured into a slurry of solid carbon dioxide and dry ether. The product was extracted into 10% sodium hydroxide (twice), the combined basic extracts were acidified with 36% hydrochloric acid, and the product was extracted into ether (twice); the combined ethereal extracts were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a colourless solid. Yield 46.5 g, 99%; mp 184–185°C. ^{1}Hnmr ($CDCl_3$) δ 3.85(3H, s), 6.50(2H, d), 11.00(1H, s). Ir (KCl) 3200–2500, 2680, 2550, 1700, 1630, 1570, 1450, 1420, 1360, 1330, 1290, 1160, 1050, 850 cm^{-1}. Ms *m*/*z* 188(M^+), 171, 141, 126, 97, 84.

2,6-Difluoro-4-methoxybenzoyl chloride

A solution of oxalyl chloride (36.5 g, 0.29 mol) in dry benzene (50 ml) was added dropwise to a stirred solution of compound 27 (25.5 g, 0.14 mol) and dry DMF (40 drops) in dry benzene (500 ml) at room temperature. The mixture was stirred at room temperature overnight and the excess of oxalyl chloride and benzene were removed *in vacuo*.

2,6-Difluoro-4-methoxybenzamide

The crude acid chloride was dissolved in dry diglyme (60 ml) and added dropwise at room temperature with gentle stirring to 35% ammonia (750 ml). The resulting colourless precipitate was filtered off and dried ($CaCl_2$) *in vacuo* to give a colourless solid. Yield 21.2 g, 81%; mp 158–159°C. ^{1}Hnmr ($CDCl_3$) δ 3.85(3H, s), 6.50 (2H, d), 7.25(2H, d). Ir (KCl) 3400, 3200, 1640, 1580, 1440, 1400, 1350, 1200, 1160, 1140, 1050, 1030, 830 cm^{-1}. Ms *m*/*z* 187(M^+), 171, 149, 121, 118.

2,6-Difluoro-4-methoxybenzonitrile (28)

A solution of thionyl chloride (139.0 g, 1.17 mol) in dry DMF (150 ml) was added to a stirred solution of 2,6-difluoro-4-methoxybenzamide (20.0 g, 0.11 mol) in dry DMF (250 ml) at room temperature. The mixture was stirred at room temperature overnight and then poured into ice-water. The product was extracted into ether (twice), and the combined ethereal extracts were washed with water, saturated sodium hydrogen carbonate, and water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give off-white crystals. Yield 17.7 g, 95%; mp 59–60°C. ^{1}Hnmr ($CDCl_3$) δ 3.90(3H, s), 6.55(2H, d). Ir (KCl) 3090, 2250, 1640, 1580, 1500, 1440, 1370, 1210, 1200, 1040, 960 cm^{-1}. Ms *m*/*z* 169(M^+), 139, 132, 126, 120, 112, 106.

4-Cyano-3-fluoro-4′-methoxybiphenyl (29)

A solution of compound 35 (10.64 g, 0.07 mol) in ethanol (90 ml) was added dropwise to a stirred mixture of compound 15 (12.0 g, 0.06 mol) and tetrakis(triphenylphosphine)palladium(0) (2.10 g, 1.82 mmol) in benzene (125 ml) and 2M-sodium carbonate (100 ml) at room temperature under dry nitrogen. The stirred mixture was heated under reflux (90–95°C) for 2.5 h (i.e., until glc analysis revealed absence of starting material). The mixture was cooled and stirred for 1 h at room temperature with 30% hydrogen peroxide (2 ml). The mixture was cooled further to 2°C; the product was filtered off and washed with water. The product was dried ($CaCl_2$) *in vacuo* to give a yellow powder. Yield 11.9 g, 88%; mp 153–154°C. ^{1}Hnmr ($CDCl_3$) δ 3.90(3H, s), 7.00(2H, d), 7.40(2H, q), 7.55(2H, d), 7.65(1H, t). Ir (KCl) 2220, 1610, 1490, 1250, 1170, 820 cm^{-1}. Ms *m/z* 227(M^+), 212, 195, 184, 158.

4-Bromo-2,6-difluoroaniline (31)

A solution of bromine (127.0 g, 0.79 mol) in glacial acetic acid (200 ml) was added slowly, dropwise to a stirred solution of 2,6-difluoroaniline (30) (101.5 g, 0.79 mol) in glacial acetic acid (550 ml) keeping the temperature below 25°C. The mixture was stirred at room temperature for 2 h, and then sodium thiosulphate (50 g), sodium acetate (125 g) and water (700 ml) were added and the mixture was cooled in a refrigerator overnight. The product was filtered off, dissolved in ether, and the ether phase was washed with water, 10% sodium hydroxide, and water and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a pale yellow solid (134 g) which was steam distilled to give a colourless solid. Yield 117.9 g, 72%; mp 67–68°C. ^{1}Hnmr ($CDCl_3$) δ 3.65(2H, s), 7.20(2H, d). Ir (KCl) 3420, 3330, 1640, 1610, 1580, 1500, 1430, cm^{-1}. Ms *m/z* 209(M^+), 207(M^+), 128, 108, 101.

4-Bromo-2,6-difluorobenzonitrile (32)

A stirred mixture of compound 31 (56.0 g, 0.27 mol) and concentrated sulphuric acid-water (1:1, 250 ml) was heated until a solution was obtained. The mixture was cooled to −10°C and a solution of sodium nitrite (30.9 g, 0.45 mol) in water (70 ml) was added dropwise. The mixture was stirred at −5°C for 2.5 h.

A solution of potassium cyanide (97.5 g, 1.50 mol) in water was added dropwise to a stirred solution of copper(II) sulphate pentahydrate (86.5 g, 0.35 mol) in water (200 ml) and ice (130 g). Sodium hydrogen carbonate (300 g), cyclohexane (1200 ml) and glacial acetic acid (130 ml) were added, the temperature was raised to 50°C and the cold diazonium salt mixture was added in portions with rapid stirring. The mixture was cooled, the organic layer was separated and the aqueous layer was washed with ether (twice). The combined organic phases were washed with water, 10% sodium hydroxide, and water and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford a dark-brown solid (58.5 g) which was steam distilled to give a light-orange solid. Yield 31.7 g, 54%; mp 79–80°C. ^{1}Hnmr ($CDCl_3$) δ 7.30(d). Ir (KCl) 3050, 2250, 1610, 1560, 1480, 1430, 1200, 1040 cm^{-1}. Ms *m/z* 219(M^+), 217(M^+), 138, 87.

4-Cyano-3,5-difluoro-4′-methoxybiphenyl (33)

A solution of compound 35 (11.50 g, 0.076 mol) in ethanol (90 ml) was added dropwise to a stirred mixture of compound 32 (15.0 g, 0.069 mol) and tetrakis(triphenylphosphine)palladium(0) (2.38 g, 2.06 mmol) in benzene (130 ml) and 2M-sodium carbonate (100 ml) at room temperature under dry nitrogen. The stirred mixture was heated under reflux (90–95°C) for 4.5 h (i.e., *until* glc analysis revealed absence of starting material). The mixture was cooled and stirred for 1 h at room temperature with 30% hydrogen peroxide (2 ml). The mixture was further cooled to 2°C, and the product was filtered off and washed with water. The product was dried ($CaCl_2$) *in vacuo* to give fawn-coloured needles. Yield 14.1 g, 84%; mp 205–207°C. ^{1}Hnmr ($CDCl_3$) δ 3.90(3H, s), 7.00(2H, d), 7.20(2H, d), 7.50(2H, d). Ir (KCl) 2800, 2240, 1630, 1600, 1560, 1490, 1440, 1410, 1290, 1230 cm^{-1}. Ms *m/z* 245(M^+), 230, 213, 202.

4-Methoxyphenylboronic acid (35)

A solution of the Grignard reagent, prepared from 4-bromoanisole (34) (80.0 g, 0.43 mol) and magnesium (11.96 g, 0.49 mol) in dry THF (300 ml) was added dropwise to a stirred, cooled (−78°C) solution of tri-isopropyl borate (161.7 g, 0.86 mol) in dry THF (50 ml) under dry nitrogen.[22] The stirred mixture was allowed to warm to room temperature overnight and was then stirred at room temperature for 1 h with 10% hydrochloric acid (300 ml). The product was extracted into ether (twice), the combined ethereal extracts were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a cream-coloured solid (58.5 g) which was recrystallised from water to give colourless crystals. Yield 27.7 g, 43%; mp 201–202°C. ^{1}Hnmr ($CDCl_3$) δ 3.90(3H, s) 5.50(2H, s), 6.85(2H, d), 7.80(2H, d). Ir (KCl) 3350, 2990, 2870, 1610, 1360, 1250, 1170, 1110, 1020, 1010 cm^{-1}. Ms *m/z* 152(M^+), 134.

Note

A cream-coloured oil was separated during the above recrystallisation which solidified on cooling to give a cream-coloured solid trimeric anhydride. Yield 17.5 g. ^{1}Hnmr ($CDCl_3$) δ 3.70(3H, s), 6.95(2H, d), 8.10(2H, d). Ir (KCl) 2990, 2870, 1610, 1360, 1250, 1170, 1110, 1020, 1010 cm^{-1}. Ms *m/z* 402(M^+), 201, 134.

Fluoro-substituted 4-cyanophenyl 4-pentyl- and 4-butoxy-benzoates and fluoro-substituted 4-cyanobiphenyl-4′-yl 4-pentyl- and 4-butoxy-benzoates

A solution of dicyclohexylcarbodiimide (DCC) (1.15 mol equiv.) in dry dichloromethane (50 ml) was added dropwise to a stirred solution of the appropriate carboxylic acid (1 mol equiv.), the appropriate phenol (1 mol equiv.) and 4-(*N*-pyrrolidino)pyridine (0.30 mol equiv.) in dry dichloromethane (55 ml) at room temperature.[23] The mixture was stirred at room temperature overnight and the *N*,*N*′-dicyclohexylurea (DCU) was filtered off. The filtrate was washed successively with water, 5% acetic acid, and water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica gel/dichloromethane) to give a solid which was recrystallised from ethanol (with decolourisation by using charcoal where required) to yield colourless crystals. The typical scale of the preparations involved about 1–2 g of the acids and phenols. The transition temperatures for the esters are given in Tables 1 and 2.

4-Cyano-3,5-difluorophenyl 4-pentylbenzoate (38): 33%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.70(2H, t), 7.05(2H, d), 7.35(2H, d), 8.05(2H, d). Ir (KCl) 2980, 2940, 2860, 2240, 1740, 1640, 1610, 1580, 1490, 1450, 1420, 1260, 1180, 1050, 1020 cm^{-1}. Ms *m/z* 329(M$^+$), 272, 175.

4-Cyano-3,5-difluorophenyl 4-butoxybenzoate (41): 79%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.05(2H, t), 6.98(2H, d), 7.05(2H, d), 8.10(2H, d). Ir (KCl) 2960, 2940, 2880, 2240, 1730, 1600, 1450, 1260, 1170, 1140, 1050, 1000 cm^{-1}. Ms *m/z* 331(M$^+$), 288, 274, 177, 121.

4-Cyanophenyl 2-fluoro-4-pentylbenzoate (42): 41%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.65(2H, t), 7.04(1H, q), 7.10(1H, q), 7.38(2H, d), 7.74(2H, d), 8.00(1H, t). Ir (KCl) 2950, 2860, 2230, 1750, 1730, 1630, 1600, 1500, 1220, 1170, 1050 cm^{-1}. Ms *m/z* 311(M$^+$), 282, 268, 254, 242, 226.

4-Cyano-3-fluorophenyl 2-fluoro-4-pentylbenzoate (43): 25%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.65(2H, t), 7.05(1H, q), 7.12(1H, q), 7.18–7.25(2H, m), 7.70(1H, q), 8.00(1H, t). Ir (KCl) 2980, 2940, 2860, 2240, 1750, 1730, 1620, 1590, 1500, 1470, 1290, 1250, 1150, 1040 cm^{-1}. Ms *m/z* 329(M$^+$), 272, 193, 179, 136, 108.

4-Cyano-3,5-difluorophenyl 2-fluoro-4-pentylbenzoate (44): 44%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.30(4H, m), 1.65(2H, quint), 2.65(2H, t), 7.05(1H, q), 7.07(1H, d), 7.12(1H, q), 7.95(1H, t). Ir (KCl) 2960, 2940, 2860, 2240, 1750, 1640, 1620, 1580, 1500, 1470, 1290, 1250, 1040 cm^{-1}. Ms *m/z* 347(M$^+$), 290, 193.

4-Cyanophenyl 4-butoxy-2-fluorobenzoate (45): 54%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.85(2H, quint), 4.05(2H, t), 6.70(1H, q), 6.80(1H, q), 7.38(2H, d), 7.74(2H, d), 8.05(1H, t). Ir (KCl) 2960, 2880, 2240, 1750, 1730, 1620, 1600, 1510, 1280, 1220, 1180, 1130, 1040, 1010 cm^{-1}. Ms *m/z* 313(M$^+$), 270, 256, 231, 195.

4-Cyano-3-fluorophenyl 4-butoxy-2-fluorobenzoate (46): 69%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.85(2H, quint), 4.05(2H, t), 6.70(1H, q), 6.80(1H, q), 7.16–7.26(2H, m), 7.65(1H, t), 8.00(1H, t). Ir (KCl) 2970, 2880, 2240, 1750, 1730, 1620, 1590, 1510, 1440, 1350, 1250, 1150, 1030, 1010 cm^{-1}. Ms *m/z* 331(M$^+$), 287, 274, 246, 218.

4-Cyano-3,5-difluorophenyl 4-butoxy-2-fluorobenzoate (47): 71%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.05(2H, t), 6.70(1H, q), 6.79(1H, q), 7.05(2H, d), 8.00(1H, t). Ir (KCl) 2960, 2880, 2240, 1755, 1620, 1450, 1350, 1240, 1220, 840 cm^{-1}. Ms *m/z* 349(M$^+$), 306, 292.

4-Cyanophenyl 2,6-difluoro-4-pentylbenzoate (48): 80%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.65(2H, t), 6.86(2H, d), 7.38(2H, d), 7.75(2H, d). Ir (KCl) 2940, 2240, 1750, 1635, 1600, 1500, 1440, 1295, 1260, 1140, 1070, 1040 cm^{-1}. Ms *m/z* 329(M$^+$), 272, 211, 195.

4-Cyano-3-fluorophenyl 2,6-difluoro-4-pentylbenzoate (49): 55%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.65(2H, t), 6.86(2H, d), 7.20–7.28(2H, m), 7.70(1H, q). Ir (KCl) 2950, 2880, 2250, 1750, 1640, 1500, 1440, 1430, 1250, 1150, 1070, 1040 cm^{-1}. Ms *m/z* 347(M$^+$), 210, 188, 181, 167, 154.

4-Cyano-3,5-difluorophenyl 2,6-difluoro-4-pentylbenzoate (50): 87% (not recrystallised). ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.30(4H, m), 1.65(2H, quint), 2.65(2H, t), 6.87(2H, d), 7.09(2H, d). Ir (KCl) 2960, 2880, 2240, 1760, 1640, 1580, 1450, 1250, 1130, 1050 cm^{-1}. Ms *m/z* 365(M$^+$), 322, 308, 281.

4-Cyanophenyl 4-butoxy-2,6-difluorobenzoate (51): 61%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.00(2H, t), 6.55(2H, d), 7.35(2H, d), 7.70(2H, d). Ir (KCl) 2950, 2900, 2250, 1750, 1640, 1600, 1580, 1500, 1450, 1360, 1260, 1160, 1080 cm^{-1}. Ms *m/z* 331(M$^+$), 213, 157.

4-Cyano-3-fluorophenyl 4-butoxy-2,6-difluorobenzoate (52): 55%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.00(2H, t), 6.55(2H, d), 7.18–7.24(2H, m), 7.70(1H, q). Ir (KCl) 2980, 2880, 2240, 1750, 1640, 1620, 1580, 1500, 1440, 1360, 1250, 1150, 1050 cm^{-1}. Ms *m/z* 349(M$^+$), 330, 306, 292, 264, 244.

4-Cyano-3,5-difluorophenyl 4-butoxy-2,6-difluorobenzoate (53): 58%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.00(2H, t), 6.55(2H, d), 7.05(2H, d). Ir (KCl) 2960, 2880, 2240, 1735, 1630, 1570, 1450, 1350, 1260, 1170, 1140, 1050 cm^{-1}. Ms *m/z* 367(M$^+$), 324, 310.

4-Cyano-3-fluorobiphenyl-4'-yl 4-pentylbenzoate (55): 77%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.40(4H, m), 1.60(2H, quint), 2.60(2H, t), 7.32(2H, d), 7.35(2H, d), 7.43(1H, q), 7.48(1H, q), 7.64(2H, d), 7.68(1H, q), 8.12(2H, d). Ir (KCl) 2940, 2890, 2250, 1740, 1620, 1560, 1480, 1260, 1210, 1170, 1060, 1030 cm^{-1}. Ms *m/z* 387(M$^+$), 329, 314, 297, 286.

4-Cyano-3,5-difluorobiphenyl-4'-yl 4-pentylbenzoate (56): 61%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.70(2H, quint), 2.70(2H, t), 7.28(2H, d), 7.33(2H, d), 7.37(2H, d), 7.62(2H, d), 8.12(2H, d). Ir (KCl) 2950, 2250, 1735, 1640, 1610, 1560, 1490, 1205, 1175, 1070, 1050 cm^{-1}. Ms *m/z* 405(M$^+$), 391, 373, 361, 348, 333.

4-Cyano-3-fluorobiphenyl-4'-yl 4-butoxybenzoate (58): 74%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.55(2H, sex), 1.85(2H, quint), 4.05(2H, t), 7.00(2H, d), 7.35(2H, d), 7.43(1H, q), 7.48(1H, q), 7.63(2H, d), 7.70(1H, q), 8.15(2H, d). Ir (KCl) 2980, 2880, 2240, 1720, 1600, 1510, 1490, 1270, 1210, 1170, 1060 cm^{-1}. Ms *m/z* 389(M$^+$), 346, 304, 177, 121.

4-Cyano-3,5-difluorobiphenyl-4'-yl 4-butoxybenzoate (59): 88%, ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.55(2H, sex), 1.85(2H, quint), 4.05(2H, t), 7.00(2H, d), 7.28(2H, d), 7.35(2H, d), 7.62(2H, d), 8.15(2H, d). Ir (KCl) 2980, 2940, 2250, 1720, 1630, 1560, 1510, 1490, 1270, 1210, 1170, 1060 cm^{-1}. Ms *m/z* 407(M$^+$), 230, 177, 121.

4-Cyanobiphenyl-4'-yl 2-fluoro-4-pentylbenzoate (60): 79%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.70(2H, t), 7.04(1H, q), 7.11(1H, q), 7.35(2H, d), 7.65(2H, d), 7.70(2H, d), 7.75(2H, d), 8.02(1H, t). Ir (KCl) 2960, 2940, 2860, 2240, 1750, 1730, 1620, 1610, 1490, 1200, 1050 cm^{-1}. Ms *m/z* 387(M^+), 373, 221, 209, 193.

4-Cyano-3-fluorobiphenyl-4'-yl 2-fluoro-4-pentylbenzoate (61): 38%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.70(2H, t), 7.05(1H, q), 7.11(1H, q), 7.37(2H, d), 7.43(1H, q), 7.49(1H, q), 7.64(2H, d), 7.70(1H, q), 8.02(1H, t). Ir (KCl) 2980, 2940, 2860, 2240, 1750, 1730, 1620, 1490, 1200, 1020 cm^{-1}. Ms *m/z* 405(M^+), 348, 212, 193.

4-Cyano-3,5-difluorobiphenyl-4'-yl 2-fluoro-4-pentylbenzoate (62): 89%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.65(2H, t), 7.05(1H, q), 7.11(1H, q), 7.28(2H, d), 7.38(2H, d), 7.63(2H, d), 8.02(1H, t). Ir (KCl) 2960, 2940, 2860, 2240, 1750, 1730, 1630, 1490, 1290, 1200, 1050 cm^{-1}. Ms *m/z* 423(M^+), 366, 352, 338, 322.

4-Cyanobiphenyl-4'-yl 4-butoxy-2-fluorobenzoate (63): 73%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.85(2H, quint), 4.05(2H, t), 6.70(1H, q), 6.80(1H, q), 7.35(2H, d), 7.65(2H, d), 7.70(2H, d), 7.75(2H, d), 8.05(1H, t). Ir (KCl) 2970, 2880, 2240, 1740, 1720, 1620, 1490, 1270, 1240, 1170, 1010 cm^{-1}. Ms *m/z* 389(M^+), 346, 332, 304.

4-Cyano-3-fluorobiphenyl-4'-yl 4-butoxy-2-fluorobenzoate (64): 49%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.85(2H, quint), 4.05(2H, t), 6.72(1H, q), 6.80(1H, q), 7.35(2H, d), 7.42(1H, q), 7.48(1H, q), 7.63(2H, d), 7.70(1H, q), 8.05(1H, t). Ir (KCl) 2980, 2940, 2880, 2240, 1730, 1710, 1620, 1490, 1270, 1210, 1190 cm^{-1}. Ms *m/z* 407(M^+), 364, 322, 212, 195.

4-Cyano-3,5-difluorobiphenyl-4'-yl 4-butoxy-2-fluorobenzoate (65): 69%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.85(2H, quint), 4.05(2H, t), 6.70(1H, q), 6.80(1H, q), 7.28(2H, d), 7.38(2H, d), 7.63(2H, d), 8.05(1H, t). Ir (KCl) 2980, 2880, 2240, 1735, 1710, 1630, 1480, 1280, 1260, 1040 cm^{-1}. Ms *m/z* 425(M^+), 382, 340.

4-Cyanobiphenyl-4'-yl 2,6-difluoro-4-pentylbenzoate (66): 85%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.65(2H, t), 6.85(2H, d), 7.38(2H, d), 7.64(2H, d), 7.68(2H, d), 7.75(2H, d). Ir (KCl) 2960, 2880, 2240, 1740, 1640, 1495, 1260, 1200, 1075, 1040 cm^{-1}. Ms *m/z* 405(M^+), 347, 211, 194.

4-Cyano-3-fluorobiphenyl-4'-yl 2,6-difluoro-4-pentylbenzoate (67): 61%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.65(2H, t), 6.85(2H, d), 7.38(2H, d), 7.43(1H, q), 7.48(1H, q), 7.65(2H, d), 7.70(1H, q). Ir (KCl) 2980, 2940, 2880, 2250, 1740, 1640, 1490, 1260, 1200, 1070, 1040 cm^{-1}. Ms *m/z* 423(M^+), 211, 184, 154.

4-Cyano-3,5-difluorobiphenyl-4'-yl 2,6-difluoro-4-pentylbenzoate (68): 83%. ^{1}Hnmr ($CDCl_3$) δ 0.90(3H, t), 1.35(4H, m), 1.65(2H, quint), 2.65(2H, t), 6.86(2H, d), 7.28(2H, d), 7.40(2H, d), 7.64(2H, d). Ir (KCl) 2950, 2930, 2860, 2250, 1740, 1640, 1490, 1260, 1200, 1070, 1040 cm^{-1}. Ms *m/z* 441(M^+), 384, 340, 211.

4-Cyanobiphenyl-4'-yl 4-butoxy-2,6-difluorobenzoate (69): 54%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.00(2H, t), 6.55(2H, d), 7.35(2H, d), 7.64(2H, d), 7.68(2H, d), 7.75(2H, d). Ir (KCl) 2970, 2900, 2240, 1740, 1640, 1620, 1450, 1260, 1200, 1050 cm^{-1}. Ms *m/z* 407(M^+), 364, 350, 336, 258.

4-Cyano-3-fluorobiphenyl-4'-yl 4-butoxy-2,6-difluorobenzoate (70): 79%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.80(2H, quint), 4.00(2H, t), 6.55(2H, d), 7.38(2H, d), 7.43(1H, q), 7.48(1H, q), 7.65(2H, d), 7.70(1H, q). Ir (KCl) 2980, 2890, 2240, 1740, 1640, 1450, 1260, 1200, 1050 cm^{-1}. Ms *m/z* 425(M^+), 382, 368, 340.

4-Cyano-3,5-difluorobiphenyl-4'-yl 4-butoxy-2,6-difluorobenzoate (71): 63%. ^{1}Hnmr ($CDCl_3$) δ 1.00(3H, t), 1.50(2H, sex), 1.85(2H, quint), 4.05(2H, t), 6.55(2H, d), 7.28(2H, d), 7.40(2H, d), 7.64(2H, d). Ir (KCl) 2980, 2880, 2240, 1735, 1640, 1440, 1260, 1200, 1080, 1040 cm^{-1}. Ms *m/z* 443(M^+), 400, 244, 230, 213.

PHYSICAL MEASUREMENTS

Confirmation of the structures of intermediates and products was obtained by ^{1}Hnmr spectroscopy (JEOL JNM-GX270 spectrometer), infrared spectroscopy (Perkin-Elmer 457 grating spectrometer) and mass spectrometry (Finnigan-MAT 1020 GC/MS spectrometer).

Transition temperatures were measured using a Mettler FP5 hot-stage and control unit in conjunction with an Olympus BHSP 753 polarising microscope.

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