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Liquid Crystals

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Online publication date: 11 November 2010

To cite this Article Miyazawa, Kazutoshi , Kato, Takashi , Itoh, Maiko and Ushioda, Makoto(2002) 'First synthesis of liquid crystalline 2,3-bis(trifluoromethyl)phenyl derivatives exhibiting large negative dielectric anisotropy', Liquid Crystals, 29: 11, 1483 — 1490

To link to this Article: DOI: 10.1080/02678290260372682

URL: http://dx.doi.org/10.1080/02678290260372682

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LIQUID CRYSTALS, 2002, VOL. 29, NO. 11, 1483–1490

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First synthesis of liquid crystalline 2,3-bis(trifluoromethyl)phenyl derivatives exhibiting large negative dielectric anisotropy

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(*Received 16 June 2002; accepted 25 July 2002*)

A series of liquid crystalline 2,3-bis(trifluoromethyl)phenyl derivatives has been synthesized and their physical properties, namely the dielectric anisotropy, the birefringence, the rotational viscosity and the phase sequences have been measured. This novel class of compound showed an extremely large negative dielectric anisotropy (− 6.1 to − 11.4), exceeding that of currently used 2,3-difluorophenyl derivatives. On the other hand, the compounds synthesized were found to have poorer mesogenic potential and larger viscosities than those of the 2,3-difluorophenyl derivatives. Molecular modelling using molecular orbital calculations has been performed and the calculation results have been compared with experimentally evaluated physical properties.

1. Introduction

Liquid crystalline compounds with large negative dielectric anisotropy ($\Delta\varepsilon$) are essential for recently developed driving modes i.e. the IPS [1–3], and VA [4] modes. These driving modes demonstrate a number of significant advantages at wide viewing angles. The currently applied materials for these modes are mainly 2,3-difluorophenyl derivatives [5]. However, due to their relatively small $\Delta\varepsilon$ (*c.* − 5), their capacity to improve switching speed to any significant degree has been limited. Compounds containing a 2,3-dicyano-1,4-phenylene moiety are known to have a large negative $\Delta\varepsilon$ (*c.* − 23), which is induced by the strong dipole moment values of the C–CN groups directed along the perpendicular axis of the molecules [6]. However, due to the chemically unstable cyano groups, the compounds normally show a low specific resistivity and a low voltage holding ratio, meaning that they cannot be applied to IPS and VA modes. We have now synthesized novel liquid crystalline compounds containing two CF_3 moieties at the 2- and 3-positions of a 1,4-phenylene ring that clearly induce a larger dipole moment in the vertical direction of the molecules; we have also evaluated the potential of this novel series of compounds

2. Results and discussion

2.1. *Synthesis*

The novel liquid crystalline compounds **4** having the 2,3-bis(trifluoromethyl)phenyl moiety and the difluoromethyleneoxy (CF_2O) moiety were synthesized according to the synthetic scheme shown in scheme 1.

The thioester **3** was prepared by the condensation reaction of the phenol **1** and 4-*n*-propylbenzenedithiocarboxylic acid (**2**) in the presence of NaH and iodine giving a 26% yield. The thiocarbonyl moiety of compound **3** was smoothly fluorinated by HF-pyridine complex and NBS to give a 44% yield of compound **4**. Compounds **7a** and **7b**, that have the cyclohexane ring connected directly to the CF_2O moiety, were synthesized by the etherification of the dibromides **5a** and **5b** [7] with phenol **1** at 110°C using K_2CO_3 as base, followed by catalytic hydrogenation on 5% Pd/C. The best result for the etherification was obtained with K_2CO_3 at 110°C with a catalytic amount of tetrabutylammonium bromide (TBABr).

Suzuki cross-coupling reaction of the iodo-compound **8** and 4-(*trans*-4-*n*-propylcyclohexyl)phenylboronic acid [8] gave the three-ring chain system **9** in a yield of 91%. The cyclohexene derivative **10** was synthesized by the lithiation of iodo-compound **8** with *n*-BuLi and reaction with 4-(*trans*-4-*n*-propylcyclohexyl)cyclohexanone, followed by dehydroxylation in acidic conditions to give a 58% yield. The iodide **8** was prepared from 2,3-bis-(trifluoromethyl)-4-iodophenol, synthesized according to the method of Zhu *et al.* [9], by etherification with ethyl iodide and potassium carbonate to give a 63% yield.

The condensation reaction of *trans*-4-(*trans*-4-*n*-propylcyclohexyl)cyclohexanecarboxylic acid [10] and the phenol **1** activated by DCC and DMAP gave a 59% yield of the ester **11**. The methyleneoxy derivative **12** was

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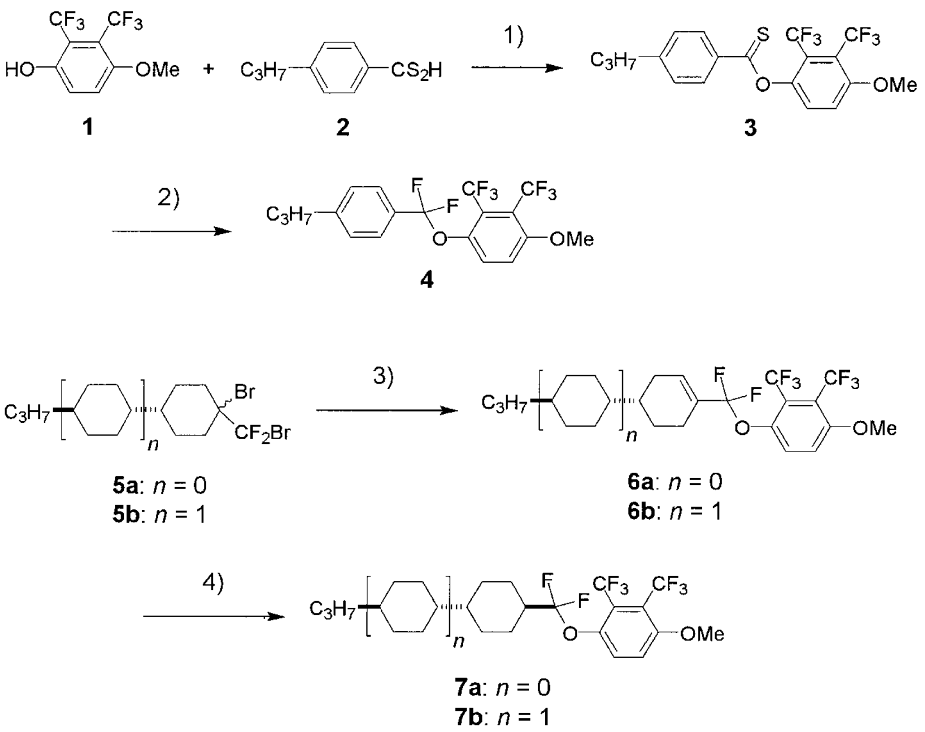
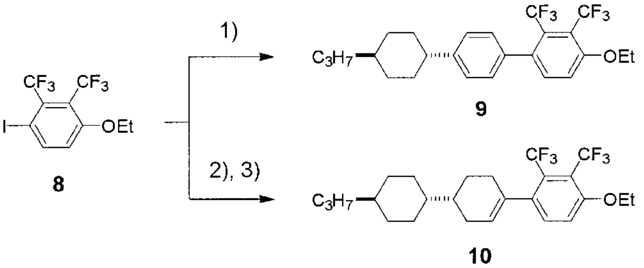
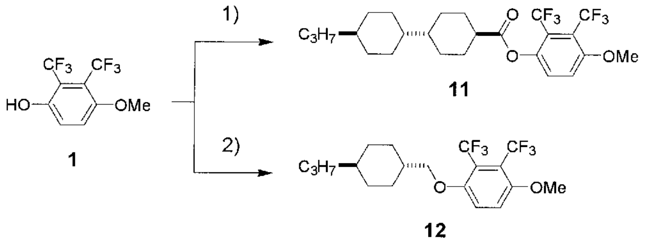
Liquid Crystals ISSN 0267-8292 print/ISSN 1366-5855 online
http://www.tandf.co.uk/journals
DOI: 10.1080/02678290210000031243



Scheme 1. Synthesis of compounds containing the CF_2O moiety. 1) 60% NaH, I_2, THF, 5 °C, 12 h, 26%; 2) NBS, HF Py, CH_2Cl_2, − 68 °C, 1 h, 44%; 3) 2,3-bis(trifluoromethyl)-4-methoxyphenol, K_2CO_3, TBABr, DMF, 110 °C, 1.5 h, 44% (**6a**), 40% (**6b**); 4) H_2, 5% Pd/C, EtOH/Ph–Me (1 : 1), 16 h, 40% (**7a**), 43% (**7b**).



Scheme 2. Synthesis of three-ring chain compounds. 1) 4-(*trans*-4-*n*-Propylcyclohexyl)phenyboronic acid, K_2CO_3, TBABr, 5% Pd/C, EtOH/Ph-me/H_2O (2 : 2 : 1), 70 °C, 4 h, 91%; 2) 4-(*trans*-4-*n*-propylcyclohexyl)cyclohexanone, *n*-BuLi, THF, − 78 °C, 1 h, 100%; 3) *p*-TsOH, Ph-Me, reflux, 9 h, 58% in two steps.



Scheme 3. Synthesis of compounds having CO_2 and CH_2O moieties as the linkage groups. 1) *trans*-4-(*trans*-4-*n*-Propylcyclohexyl)cyclohexanecarboxylic acid, DCC, DMAP, CH_2Cl_2, r.t., 2 h, 59%; 2) *trans*-4-*n*-propylcyclohexylmethyl bromide, K_2CO_3, TBABr, DMF, 110 °C, 7 h, 41%.

obtained in 41% yield by simple etherification at 110 °C of *trans*-4-*n*-propylcyclohexylmethyl bromide [11] and the phenol **1** with K_2CO_3 in the presence of a catalytic amount of TBABr in DMF.

Compound **16** was successfully synthesized by the ring-opening aromatization of the Diels–Alder adduct **14** that had been prepared from the furan derivative **13** [12] and 1,1,1,4,4,4-hexafluorobut-2-yne at a high temperature of 82 °C, followed by ethylation. Since a mixture of *cis*- and *trans*-configured compound **13** was used, the compound **16** obtained was a 1 : 1 mixture of the two isomers. The pure *trans*-configured **16** was obtained in a low yield of 12% by repeated crystallization from EtOH.

2.2. *Physical properties*

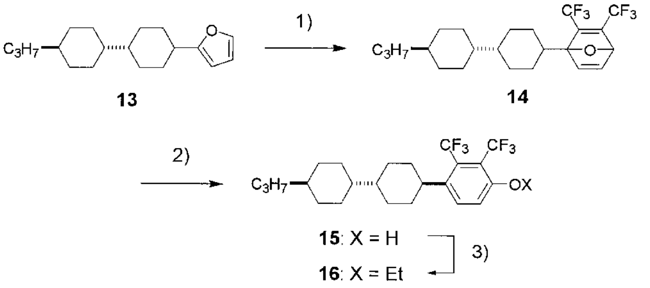
The phase sequences and transition enthalpies of the compounds synthesized are shown in table 1 together with those of the 4-ethoxy-2,3-difluorophenyl derivative **r1** [5] (see figure) as a reference system. Two-ring chain compounds **4**, **7a** and **12** exhibit melting points of 28.2, 41.5 and 73.5 °C, respectively. The melting point

Table 1. Transition temperatures (°C) and enthalpies (kJ mol^{-1}) in parentheses. Data for monotropic transitions are in square brackets.

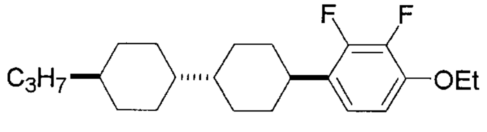
Compound	Cr		SmB		SmA		N		I
4	•	28.2 (21.3)							•
7a	•	41.5 (21.4)							•
7b	•	99.3 (31.8)					•	118.5 (0.75)	•
9	•	82.9 (30.4)							•
10	•	72.3 (13.3)					[•	69.2 (− 0.46)]	•
11	•	129.8 (26.1)			[•	82.0 (− 0.14)]	•	142.6 (0.61)	•
12	•	73. 5(27.6)							•
16	•	97.6 (4.84)[a]					[•	58.5 (− 0.20)]	•
r1[b]	•	76	•	79			•	186	•

[a] Cr–Cr transitions were observed in the first heat at 90.7°C (21.4) and 92.7°C (0.88).

[b] Ref. [5].



Scheme 4. Synthesis of bicyclohexane derivative by Diels–Alder reaction and ring-opening aromatization. 1) 1,1,1,4,4,4-Hexafluorobut-2-yne, Ph-H, 82°C, 5 h, 91%; 2) BF_3 Et_2O, 60°C, 5 h, 95%; 3) EtI, K_2CO_3, 2-butanone, 70°C, 5 h, 12%.



r1

Figure 1. Chemical structure of reference compound **r1** [5].

of compound **12** is 32°C higher than that of compound **7a**, indicating that the fluorine substitution at the methyleneoxy moiety reduces the crystallinity.

Both the three-ring chain compounds **7b** and **11** with the linkage groups CF_2O and CO_2, respectively, show enantiotropic nematic phases with 19.2 and 12.8°C temperature ranges, respectively. Compounds **9**, **10** and **16** without a linkage group show poorer mesogenic potential. Compounds **10** and **16** exhibit monotropic nematic phases, but the biphenyl derivative **9** has a simple melting point of 82.9°C. A smectic phase can be observed only for the ester **11** and it is a monotropic SmA. It is clear that the 2,3-bis(trifluoromethyl)phenyl derivatives tend to show poorer mesogenic potential than the corresponding 2,3-difluorophenyl derivative. For example compound **16** shows only a monotropic nematic phase, while the corresponding 2,3-difluorophenyl derivative **r1** exhibits a nematic phase between 79 and 186°C. The two bulky lateral CF_3 groups increase the width of the molecules, which reduces the length to width ratio (L/D) resulting in a poor mesogenic potential.

The dielectric and optical anisotropies (Δε and Δn, respectively) of the compounds synthesized were estimated by the extrapolation method using a nematic host mixture having small Δε of − 1.3 (see table 2 and the Experimental section). All the synthesized 2,3-bis(trifluoromethyl)phenyl derivatives exhibit extremely large negative Δε ranging from − 6.1 to − 11.4, which is much greater than that of the corresponding 2,3-difluorophenyl compound **r1** (− 5.0). Among the synthesized compounds, compounds **4**, **7a** and **7b** having the CF_2O linking group show smaller Δε. Comparisons of the Δε of compound **7b** (− 7.2) with that of compound **16** (− 9.1), and of compound **7a** (− 6.1) with that of compound **12** (− 11.4) clearly indicate that the CF_2O moiety, more specifically

Table 2. T_{NI} (°C) of mixtures containing 15 wt % of the synthetic compound in a nematic host mixture; Δε and Δn values are extrapolated from a mixture containing the synthetic compound (15 wt %) and a nematic host mixture, see Experimental section.

Compound	T_{NI}	Δε	Δn
4	55.3	− 6.2	0.054
7a	60.0	− 6.1	0.040
7b	76.1	− 7.2	0.080
9	72.3	− 8.5	0.120
10	74.8	− 9.0	0.087
11	77.9[a]	− 9.0[a]	0.087[a]
12	59.7	− 11.4	0.040
16	73.1	− 9.1	0.080
r1[b]	64.1	− 5.0	0.074
host	74.6	− 1.3	0.087

[a] Extrapolated from a mixture containing the synthetic compound (10 wt %) with the nematic host mixture.

[b] Ref. [5].

the fluorine substitution at the linkage group, reduces $\Delta\varepsilon$. The dipole moments of the C–F bonds at the linkage groups are directed along the short axis of the molecules and opposite to the dipole moments of the 2,3-bis(trifluoromethyl)phenyl groups. The combination of the dipole moments of the CF_2O groups and 2,3-bis(trifluoromethyl)-phenyl groups reduces the anisotropy of the polarizability of all of the molecules and induces the smaller $\Delta\varepsilon$ of compounds **4**, **7a**, and **7b**.

The extrapolated Δn values of the compounds synthesized cover a distribution between 0.040 and 0.120. The two-ring chain systems **4**, **7a**, and **12** exhibit relatively small Δn values (0.040–0.054), whereas the Δn of the three-ring chain systems **7b**, **9**, **10**, **11** and **16** exhibit higher values (0.080–0.120). Due to the highly conjugated π-system, biphenyl compound **9** shows the largest Δn value of 0.120.

The bulky lateral CF_3 substituents increase the rotational viscosity (η) as shown in table 3. The extrapolated rotational viscosities of the compounds synthesized lie within the range 80.2–131 mPa s, whereas the reference 2,3-difluorophenyl compound **r1** has an extrapolated rotational viscosity of only 25.1 mPa s. In terms of practical use, this tendency towards a greater viscosity would normally be regarded as a disadvantage. However, since the $\Delta\varepsilon$ of the compounds synthesized are much greater, practical nematic mixtures can be prepared by doping a relatively small amount of the compound synthesized into low viscosity nematic base mixtures.

2.3. *Molecular modelling*

The optimized molecular shapes and the van der Waals volumes of the extended three-ring compounds **9**, **10**, and **16** as well as of the reference **r1** were calculated by the MOPAC ver.6.0/PM3 and the MOL-MOLIS/CRYS ver.2.4R1 methods, respectively, as shown in table 4.

Table 3. Extrapolated viscosity of the synthetic compounds; extrapolated from a mixture containing the compound synthesized (15 wt %) and a nematic host mixture, see experimental section.

Compound	η/mPa s
7a	80.2
7b	96.9
9	110
10	117
11	113[a]
12	98.4
16	131
r1[b]	25.1
host	18.8

[a] Extrapolated from a mixture containing the compound synthesized (10 wt %) and the nematic host mixture.

[b] Ref. [5].

Table 4. L/D ratio and van der Waals molecular volume (V) of the most probable conformation.[a]

Compound	Length L/Å	Width D/Å	L/D	V/Å^3 [b]
9	21.6	10.8	2.00	400.1
10	21.9	10.5	2.08	410.6
16	21.6	11.5	1.88	416.2
r1[c]	21.9	8.40	2.61	365.0

[a] The optimized molecular shapes were obtained by the MOPAC ver.6.0/AM1 method [13].

[b] Van der Waals volume calculated using MOL-MOLIS/CRYS ver.2.4R1 [14].

[c] Ref. [5].

The length L and the width D were obtained for the long and the short axes of the best cylinder containing the molecule in its most extended conformation.

Although the lengths of all four compounds are in the same range of 21.6–21.9 Å, the width of the bis-(trifluoromethyl)phenyl derivatives **9**, **10** and **16** are 10.5–11.5 Å, whereas the compound **r1** has a smaller width of only 8.40 Å. As a result of the difference in width, the L/D ratios of compounds **9**, **10** and **16** are smaller (1.88–2.08) than the L/D ratio for the reference compound **r1** (2.61). A comparison of the optimized L/D ratios clearly demonstrates the poor mesogenic potential for the bis(trifluoromethyl)phenyl derivatives.

The experimental $\Delta\varepsilon$ values for compounds **7a** and **7b** having CF_2O moieties and **11** and **12** containing CO_2 and CH_2O moieties, respectively, have been compared in table 5 with the calculated total dipole moments μ, the angles of the total dipole moments β, the average polarizability α_{ave} and the anisotropy of the polarizability $\Delta\alpha$. β represents the angle formed by the total dipole moment and the moment of inertia of the molecule. The maximum β of 90° would indicate that the dipole moment is directed exactly along the short axis of the molecule. For the two-ring compounds **7a** and **12**, compound **7a** having the CF_2O moiety shows the smaller μ (6.12 D) and the smaller β (69.5°) in comparison with compound **12** containing the CH_2O moiety ($\mu = 7.27$ D, $\beta = 71.4°$). The calculated results show a good fit with

Table 5. Correlation between calculated dipole moment and the experimental value for $\Delta\varepsilon$.[a]

Compound	μ/D	β/°	α_{ave}/A.U.	$\Delta\alpha$/A.U.	$\Delta\varepsilon$[b]
7a	6.12	69.5	157.5	81.2	−6.1
12	7.27	71.4	159.1	85.6	−11.4
7b	6.07	70.9	199.6	98.5	−7.2
11	6.06	73.0	203.5	105.8	9.0

[a] The molecular orbital calculation was performed by the MOPAC ver.6.0/PM3 method [13].

[b] Experimental $\Delta\varepsilon$ (see table 2).

the experimental Δε values for compounds **7a** (− 6.1) and **12** (− 11.4). The structural difference between compounds **7a** and **12** lies only in the fluorine substitutions on the linkage groups, which indicates that the dipole moments induced by the C–F bonds of the CF_2O group and of the 2,3-bis-difluoro-1,4-phenylene moiety are aligned in opposite directions and compensate one another. A similar result was obtained by comparing the three-ring compounds **7b** with the CF_2O group and **11** with the CO_2 group. Both **7b** and **11** show a μ value in the same range (6.07 and 6.06 D, respectively). However, compound **7b** exhibits a β value of 70.9° that is 2.1° smaller than the β value of compound **11** (73.0°), so reducing the effective dipole component in the direction of the short axis of the molecule. This result also clearly explains why there is a difference in Δε for the compounds **7b** (− 7.2) and **11** (− 9.0).

3. Conclusions

A series of liquid crystalline 2,3-bis(trifluoromethyl)-phenyl derivatives has been synthesized. Due to the small L/D ratios that are induced by the bulky lateral CF_3 groups, they show poor mesogenic potential. On the other hand, the compounds exhibit extremely large negative Δε values that are at least 20% larger than the Δε values of the 2,3-difluorophenyl derivatives currently used in the liquid crystal display industry. The results indicate that these novel compounds have the potential to act as dopants capable of inducing quicker response characteristics when they are used in nematic mixtures.

4. Experimental

4.1. *Instrumentation and materials*

The compounds synthesized were characterized using the following conditions and instruments. Phase transition temperatures: Perkin Elmer DSC 7 differential scanning calorimeter and Nikon Optiphot polarization microscope with a Mettler FP82 hot stage. ^{1}H NMR: Bruker DRX 500 (500 MHz); δ (ppm) = 7.26 for chloroform. ^{19}F NMR: Bruker DRX 500 (470 MHz); $CFCl_3$ as reference. MS: JEOL JMS-Automass II-150 (70 eV, EI). The measurements of the physical properties of the liquid crystalline compounds were performed using the following instruments and conditions. Dielectric anisotropy (Δε) measured at 25°C: Hewlett Packard 4284A LCR meter. Optical anisotropy (Δn) measured at 25°C: Atago 4T & 2T Abbé refractometer. Viscosity (μ) measured at 20°C: Lauda Viscoboy viscometer.

The nematic host mixture consisted of phenyl cyclohexanecarboxylates, namely 4-methoxyphenyl *trans*-4-*n*-pentylcyclohexanecarboxylate, 4-ethoxyphenyl *trans*-4-*n*-propylcyclohexanecarboxylate, 4-ethoxyphenyl *trans*-4-*n*-butylcyclohexanecarboxylate, 4-ethoxyphenyl *trans*-4-*n*-pentylcyclohexanecarboxylate and 4-butoxyphenyl *trans*-4-*n*-propylcyclohexanecarboxylate (12:10:12:8:16 by weight). The physical properties of the host mixture are T_{NI} = 74.6°C, Δε = − 1.3, Δn = 0.087, η = 18.8 mPa s.

4.2. *Synthesis*

4.2.1. *2,3-Bis(trifluoromethyl)-4-methoxyphenyl 4-n-propylphenylthiocarboxylate (**3**)*

To a suspension of 60% NaH (865 mg, 21.6 mmol) and THF (5 ml), was added a solution of 4-*n*-propylbenzenedithiocarboxylic acid **2** (1.7 g, 8.65 mmol) in THF (5 ml) at 0°C. The mixture was stirred for 1 h at 0°C. To the resulting mixture was added a solution of 2,3-bis(trifluoromethyl)-4-methoxyphenol **1** (1.5 g, 5.77 mmol) in THF (5 ml) at 5°C, followed by the addition of a solution of I_2 (6.0 g, 23.8 mmol) in THF (20 ml). After 12 h of stirring at ambient temperature, the reaction mixture was shaken with toluene (50 ml) and the separated organic layer washed with 2M HCl (30 ml), sat. $Na_2S_2O_3$ (30 ml) and water (30 ml) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (50 ml) eluting with toluene/heptane (3/7) to yield 640 mg (26%) of **3** as yellow needles. Compound **3** was used for the next reaction without further purification. R_f = 0.44, m.p. 110°C. ^{1}H NMR δ (ppm) = 0.99 (t, J = 7.5 Hz, 3H), 1.69–1.74 (m, 2H), 2.69 (t, J = 7.9 Hz, 2H), 4.00 (s, 3H), 7.30–7.37 (m, 4H), 8.27 (d, J = 8.5 Hz, 2H). ^{19}F NMR δ (ppm) = − 56.1 (q, J = 16.7 Hz, 3F), − 55.2 (q, J = 16.7 Hz, 3F). MS m/z (%) = 422 (2) [M^+], 163 (100).

4.2.2. *2,3-Bis(trifluoromethyl)-4-methoxyphenyl α,α-difluoro-4-n-propylbenzyl ether (**4**)*

To a mixture of NBS (420 mg, 2.36 mmol) and CH_2Cl_2 (5 ml), were added HF-pyridine complex (900 mg, 9.09 mmol) and a solution of compound **3** (500 mg, 1.18 mmol) in CH_2Cl_2 (15 ml) at − 68°C. The reaction mixture was stirred for 1 h at − 68°C, and poured into sat. $NaHCO_3$ (100 ml). The separated organic layer was washed with water (50 ml) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (50 ml) eluting with toluene/heptane (3/7), to yield 221 mg (44%) of **4** as colourless crystals. R_f = 0.46, m.p. 28.2°C. ^{1}H NMR δ (ppm) = 0.98 (t, J = 7.3 Hz, 3H), 1.65–1.73 (m, 2H), 2.67 (t, J = 7.5 Hz, 2H), 4.00 (s, 3H), 7.19–7.32 (m, 4H), 7.66–7.71 (m, 2H). ^{19}F NMR δ (ppm) = − 64.5 (d, J = 4.4 Hz, 2F), − 56.1 (q, J = 16.7 Hz, 3F), − 54.1 (q of triplet, J = 16.7 Hz, J = 4.4 Hz, 3F). MS m/z (%) = 428 (7) [M^+], 409 (7) [M^+ − F], 169 (100).

4.2.3. *2,3-Bis(trifluoromethyl)-4-methoxyphenyl 4-n-propylcyclohexenyl-α,α-difluoromethyl ether (**6a**)*

To a mixture of compound **1** (2.60 g, 10.0 mmol), K_2CO_3 (2.30 g, 16.7 mmol), TBABr (0.13 g, 0.40 mmol) and DMF (20 ml), was added a solution of 1-bromo-1-bromodifluoromethyl-4-*n*-propylcyclohexane **5a** (2.78 g, 8.3 mmol) in DMF (6 ml) at 110°C. The resulting mixture was stirred at 110°C for 1.5 h. The reaction mixture was shaken with toluene, and the organic layer washed with water and dried over anhydrous $MgSO_4$. Purification by column chromatography on silica gel (100 ml), eluting with toluene/heptane (3/7), gave 1.58 g (44%) of **6a** as a colourless oil. ^{1}H NMR δ (ppm) = 0.92 (t, $J = 7.2$ Hz, 3H), 1.22–1.41 (m, 5H), 1.53–1.62 (m, 1H), 1.71–1.81 (m, 1H), 1.84–1.90 (m, 1H), 2.15–2.35 (m, 3H), 3.94 (s, 3H), 6.38–6.40 (m, 1H), 7.22 (d, $J = 9.4$ Hz, 1H), 7.58 (d, $J = 9.4$ Hz, 1H). ^{19}F NMR δ (ppm) = −72.3 (d, $J = 150$ Hz, 1F), −71.8 (d, $J = 150$ Hz, 1F), −56.1 (q, $J = 18.8$ Hz, 3F), −54.3 (triplet of q, $J = 18.8$ Hz, $J = 4.7$ Hz, 3F).

4.2.4. *2,3-Bis(trifluoromethyl)-4-methoxyphenyl trans-4-n-propylcyclohexyl-α,α-difluoromethyl ether (**7a**)*

A mixture of **6a** (1.6 g, 3.7 mmol), 5% Pd/C (0.8 g), toluene (10 ml) and EtOH (10 ml) was stirred under a H_2 atmosphere at ambient temperature for 16 h. The catalyst was removed by filtration and the filtrate concentrated. The residue was purified by column chromatography on silica gel (100 ml), eluting with toluene/heptane (3/7), followed by crystallization (EtOAc), to yield 640 mg (40%) of **7a** as colourless crystals, m.p. 41.5°C. ^{1}H NMR δ (ppm) = 0.87–0.98 (m, 2H), 0.89 (t, $J = 7.3$ Hz, 3H), 1.16–1.43 (m, 7H), 1.83–1.90 (m, 2H), 1.98–2.09 (m, 3H), 3.93 (s, 3H), 7.20 (d, $J = 9.4$ Hz, 1H), 7.54 (d, $J = 9.4$ Hz, 1H). ^{19}F NMR δ (ppm) = −77.7 to −77.9 (m, 2F), −56.1 (q, $J = 16.3$ Hz, 3F), −54.3 (triplet of q, $J = 16.3$ Hz, $J = 3.9$ Hz, 3F). MS m/z (%) = 434 (7) [M^+], 260 (100).

4.2.5. *2,3-Bis(trifluoromethyl)-4-methoxyphenyl 4-(trans-4-n-propylcyclohexyl)cyclohexenyl-α,α-difluoromethyl ether (**6b**)*

Following the method employed for the synthesis of **6a**, 760 mg (40%) of **6b** were obtained as colourless crystals by using **5b** as starting material. ^{1}H NMR δ (ppm) = 0.81–1.06 (m, 4H), 0.88 (t, $J = 7.3$ Hz, 3H), 1.08–1.41 (m, 8H), 1.70–1.93 (m, 6H), 2.12–2.26 (m, 2H), 2.30–2.38 (m, 1H), 3.93 (s, 3H), 6.37–6.46 (m, 1H), 7.22 (d, $J = 9.4$ Hz, 1H), 7.58 (d, $J = 9.4$ Hz, 1H). ^{19}F NMR d (ppm) = −72.3 (d, $J = 150$ Hz, 1F), −71.7 (d, $J = 150$ Hz, 1F), −56.1 (q, $J = 17.3$ Hz, 3F), −54.3 (triplet of q, $J = 17.3$ Hz, $J = 4.7$ Hz, 3F).

4.2.6. *2,3-Bis(trifluoromethyl)-4-methoxyphenyl trans-4-(trans-4-n-propylcyclohexyl)cyclohexyl-α,α-difluoromethyl ether (**7b**)*

Following the same method employed for the synthesis of **7a**, 330 mg (43%) of **7b** were obtained as colourless crystals by using **6b** as starting material, $R_f = 0.56$. Phase transition temperatures (°C): Cr 99.3 N 118.5 I. ^{1}H NMR δ (ppm) = 0.87 (t, $J = 7.4$ Hz, 3H), 0.96–1.16 (m, 11H), 1.25–1.40 (m, 4H), 1.68–1.78 (m, 4H), 1.81–1.87 (m, 2H), 1.99–2.06 (m, 3H), 3.93 (s, 3H), 7.20 (d, $J = 9.4$ Hz, 1H), 7.53 (d, $J = 9.4$ Hz, 1H). ^{19}F NMR δ (ppm) = −77.9 to −77.8 (m, 2F), −56.1 (q, $J = 16.5$ Hz, 3F), −54.3 (q of triplet, $J = 16.5$ Hz, 3.8 Hz, 3F). MS m/z (%) = 516 (9) [M^+], 260 (100).

4.2.7. *2,3-Bis(trifluoromethyl)-4-ethoxyphenyl iodide (**8**)*

A mixture of 2,3-bis(trifluoromethyl)-4-iodophenol (10.0 g, 28.0 mmol), K_2CO_3 (7.77 g, 56.3 mmol) and 2-butanone (250 ml) was stirred at room temperature for 0.5 h. To this mixture was added ethyl iodide (5.70 g, 36.5 mmol), and the resulting mixture was heated under reflux for 10 h. Normal work-up and purification by column chromatography on silica gel, eluting with toluene, and crystallization (EtOH) gave 6.8 g (63%) of **8** as colourless crystals, $R_f = 0.86$, m.p. 53.3°C. ^{1}H NMR δ (ppm) = 1.45 (t, $J = 7.0$ Hz, 3H), 4.13 (q, $J = 7.0$ Hz, 2H), 6.85 (d, $J = 9.0$ Hz, 1H), 8.08 (d, $J = 9.0$ Hz, 1H). ^{19}F NMR δ (ppm) = −56.0 (q, $J = 16.0$ Hz, 3F), −55.3 (q, $J = 16.0$ Hz, 3F). MS m/z (%) = 384 (100) [M^+].

4.2.8. *2,3-Bis(trifluoromethyl)-4-ethoxy-4′-(trans-4-n-propylcyclohexyl)-1,1′-biphenyl (**9**)*

A mixture of **8** (1.5 g, 3.9 mmol), 4-(*trans*-4-*n*-propylcyclohexyl)phenylboronic acid (1.15 g, 4.67 mmol), K_2CO_3 (1.5 g, 10.9 mmol), TBABr (375 mg, 1.16 mmol), 5% Pd/C (105 mg), toluene (37 ml), EtOH (37 ml) and H_2O (15 ml) was stirred at 70°C for 4 h. Normal work-up followed by purification by column chromatography on silica gel, eluting with toluene, and crystallization (EtOH) gave 1.63 g (91%) of **9** as colourless crystals, $R_f = 0.93$, m.p. 82.9°C. ^{1}H NMR δ (ppm) = 0.91 (t, $J = 7.0$ Hz, 3H), 1.05–1.10 (m, 2H), 1.20–1.28 (m, 2H), 1.29–1.39 (m, 3H), 1.43–1.54 (m, 2H), 1.46 (t, $J = 7.0$ Hz, 3H), 1.87–1.94 (m, 4H), 2.47–2.53 (m, 1H), 4.17 (q, $J = 7.0$ Hz, 2H), 7.18–7.25 (m, 4H), 7.42 (d, $J = 8.5$ Hz, 2H). ^{19}F NMR δ (ppm) = −56.3 (q, $J = 15.5$ Hz, 3F), −50.5 (q, $J = 15.5$ Hz, 3F). MS m/z (%) = 458 (100) [M^+].

4.2.9. *1-[2,3-Bis(trifluoromethyl)-4-ethoxyphenyl]-4-(trans-4-n-propylcyclohexyl)cyclohexene (**10**)*

To a mixture of **8** (1.9 g, 4.95 mmol) and THF (20 ml), was added 1.59 M *n*-BuLi in hexane (3.5 ml, 5.57 mmol) at −78°C. The resulting mixture was stirred at −78°C for 1 h, and then a solution of 4-(*trans*-4-*n*-propylcyclohexyl)cyclohexanone (1.0 g, 4.5 mmol) in THF (5 ml) was added. The reaction mixture was stirred at -78°C for 1 h, and the resulting mixture shaken with toluene. The organic layer was washed with 6M HCl and water, and then dried over anhydrous $MgSO_4$. The solvent was removed to yield 2.38 g (100%) of 1-[2,3-bis(trifluoromethyl)-4-ethoxyphenyl]-4-(*trans*-4-*n*-propylcyclohexyl)-cyclohexan-1-ol as brown crystals, which were used for the dehydroxylation without further purification.

A mixture of 1-[2,3-bis(trifluoromethyl)-4-ethoxyphenyl]-4-(*trans*-4-*n*-propylcyclohexyl)cyclohexan-1-ol (2.36 g, 4.9 mmol), *p*-TsOH (144 mg, 0.76 mmol) and toluene (20 ml) was heated at reflux for 9 h and the resulting water was removed. The reaction mixture was washed with water and dried over anhydrous $MgSO_4$. Purification by column chromatography on silica gel, eluting with toluene/heptane (3/7), and crystallization (EtOH) gave 1.31 g (58%) of **10** as colourless crystals, $R_f = 0.63$. Phase transition temperatures (°C): Cr 72.3 (N 69.2) I. ^{1}H NMR δ (ppm) = 0.88 (t, $J = 7.0$ Hz, 3H), 0.95–1.07 (m, 2H), 1.10–1.18 (m, 5H), 1.29–1.40 (m, 4H), 1.44 (t, $J = 7.0$ Hz, 3H), 1.73–1.90 (m, 6H), 2.13–2.33 (m, 4H), 4.12 (q, $J = 7.0$ Hz, 2H), 5.49–5.50 (m, 1H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.27 (d, $J = 8.5$ Hz, 2H). ^{19}F NMR δ (ppm) = -56.2 (q, $J = 16.0$ Hz, 3F), -52.6 (brs, 3F). MS m/z (%) = 462 (18) [M$^+$], 83 (100).

4.2.10. *2,3-Bis(trifluoromethyl)-4-methoxyphenyl trans-4-(trans-4-n-propylcyclohexyl)-cyclohexanecarboxylate (**11**)*

A mixture of compound **1** (1.0 g, 3.84 mmol), *trans*-4-(*trans*-4-*n*-propylcyclohexyl)cyclohexanecarboxylic acid (970 mg, 3.84 mmol), dicyclohexylcarbodiimide (830 mg, 4.0 mmol), 4-*N*,*N*-(dimethylamino)pyridine (47 mg, 0.38 mmol) and CH_2Cl_2 (40 ml) was stirred for 2 h at ambient temperature. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (300 ml), eluting with toluene, to yield 1.13 g (59%) of **11** as colourless crystals, $R_f = 0.68$. Phase transition temperatures (°C): Cr 129.8 (SmA 82.0) N 164.9 I. ^{1}H NMR δ (ppm) = 0.89 (t, $J = 7.1$ Hz, 3H), 0.96–1.17 (m, 11H), 1.30–1.36 (m, 2H), 1.50–1.57 (m, 2H), 1.75 (q, $J = 12.0$ Hz, 4H), 1.87 (d, $J = 10.7$ Hz, 2H), 2.17 (d, $J = 11.1$ Hz, 2H), 2.38–2.54 (m, 1H), 3.95 (s, 3H), 7.24 (d, $J = 11.0$ Hz, 1H), 7.26 (d, $J = 11.0$ Hz, 1H). ^{19}F NMR δ (ppm) = -56.0 (q, $J = 16.5$ Hz, 3F), -55.2 (q, $J = 16.5$ Hz, 3F). MS m/z (%) = 495 (100) [MH$^+$], 494 (85) [M$^+$].

4.2.11. *2,3-Bis(trifluoromethyl)-4-methoxyphenyl trans-4-n-propylcyclohexylmethyl ether (**12**)*

A mixture of compound **1** (100 mg, 0.38 mmol), *trans*-4-*n*-propylcyclohexylmethyl bromide (84.2 mg, 0.38 mmol), K_2CO_3 (52.5 mg, 0.38 mmol), TBABr (12.3 mg, 0.038 mmol) and DMF (1.5 ml) was stirred at 110°C for 7 h in a sealed tube, yielding a brown suspension. The reaction mixture was purified by column chromatography on silica gel (30 ml), eluting with toluene, followed by crystallization (MeOH) to give 64 mg (41%) of **12** as colourless crystals, $R_f = 0.95$, m.p. 73.5°C. ^{1}H NMR δ (ppm) = 1.06–1.14 (m, 5H), 1.18–1.22 (m, 2H), 1.23–1.28 (m, 4H), 1.31–1.38 (m, 2H), 1.75–1.91 (m, 4H), 3.80 (d, $J = 6.1$ Hz, 2H), 3.89 (s, 3H), 7.14–7.21 (m, 2H). ^{19}F NMR δ (ppm) = -55.5 to -55.3 (m, 6F). MS m/z (%) = 398 (2) [M$^+$], 83 (100).

4.2.12. *2,3-Bis(trifluoromethyl)-7-oxa-1-[4-(trans-4-n-propylcyclohexyl)cyclohexyl]bicyclo[2.2.1]-hepta-2,5-diene (**14**)*

A mixture of 2-[4-(*trans*-4-*n*-propylcyclohexyl)cyclohexyl]furan **13** (11.2 g, 0.041 mmol), 1,1,1,4,4,4-hexafluoro-but-2-yne (17.6 g, 0.11 mmol) and benzene (70 ml) was stirred at 82°C in a sealed tube for 5 h. The excess of 1,1,1,4,4,4-hexafluorobut-2-yne was removed and the residue shaken with toluene. The toluene layer was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield 16.4 g (91%) of **14** as a yellow amorphous solid, which was used in the next step without purification. ^{1}H NMR δ (ppm) = 0.80–0.91 (m, 5H), 1.02–1.19 (m, 7H), 1.20–1.37 (m, 6H), 1.39–1.56 (m, 3H), 1.67–1.79 (m, 3H), 1.80–1.89 (m, 2H), 2.18–2.28 (m, 1H), 5.57 (s, 0.5 Hz), 5.60 (s, 0.5 Hz), 7.14–7.18 (m, 1H), 7.23–7.26 (m, 1H). ^{19}F NMR δ (ppm) = -62.6 (q, $J = 8.9$ Hz, 1.5 F), -62.5 (q, $J = 8.9$ Hz, 1.5F), -61.4 (q, $J = 8.9$ Hz, 1.5F), -61.3 (q, $J = 8.9$ Hz, 1.5F).

4.2.13. *2,3-Bis(trifluoromethyl)-4-[4-(trans-4-n-propylcyclohexyl)cyclohexyl]phenol (**15**)*

A mixture of compound **14** (7.26 g, 16.6 mmol) and BF_3 Et_2O (70 ml) was stirred at 60°C for 5 h. At room temperature K_2CO_3 was added to the reaction mixture until the whole became neutral. The reaction mixture was shaken with diethyl ether and the organic layer was washed with water and dried over anhydrous $MgSO_4$. Evaporation gave 6.92 g (95%) of crude **15** as a brown oil, which was used for the next step without purification.

4.2.14. *2,3-Bis(trifluoromethyl)-1-ethoxy-4-[trans-4-(trans-4-n-propylcyclohexyl)cyclohexyl]-benzene (**16**)*

To a mixture of compound **15** (6.92 g, 15.9 mmol), K_2CO_3 (4.62 g, 33.4 mmol) and 2-butanone (40 ml), was added ethyl iodide (3.47 g, 22.2 mmol). The resulting mixture was stirred at 70°C for 5 h. The reaction mixture was added to toluene and the separated organic layer washed with sat. aq. $Na_2S_2O_3$, and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield 6.86 g (93%) of **16** as a crude product. The crude **16** was purified by column chromatography on silica gel, eluting with toluene/heptane (1/1), and repeated crystallization (EtOH) to give 910 mg (12%) of pure **16** as colourless crystals, $R_f = 0.78$. Phase transition temperatures (°C): Cr 97.6 (N 58.5) I. ^{1}H NMR δ (ppm) = 0.87 (t, $J = 7.0$ Hz, 3H), 0.95–1.09 (m, 3H), 1.11–1.20 (m, 5H), 1.27–1.34 (m, 4H), 1.43 (t, $J = 7.0$ Hz, 3H), 1.71–1.83 (m, 10H), 2.84–2.88 (m, 1H), 4.11 (t, $J = 7.0$ Hz, 2H), 7.12 (d, $J = 9.0$ Hz, 2H), 7.48 (d, $J = 9.0$ Hz, 2H). ^{19}F NMR δ (ppm) = − 55.4 (q, $J = 16.5$ Hz, 3F), − 53.4 (q, $J = 16.5$ Hz, 3F). MS m/z (%) = 464 (29) [M^+], 83 (100).

The authors are indebted to Prof. Dr A. de Meijere and Dr V. Belov, Georg-August-Universität Göttingen, Germany for providing the intermediate **1**.

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