Liquid crystals carrying stereodefined vicinal difluoro- and trifluoro-alkyl motifs†

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The synthesis of the stereospecifically fluorinated difluoro- and trifluoro- *rac*-3 and *rac*-4 is described where the fluorine atoms are positioned adjacent/vicinal to each other and the physical characteristics of these candidate liquid crystals including negative dielectric anisotropy are measured and rationalised.

Fluorinated compounds have made a significant contribution to materials science.[1] In the main fluorinated polymers and liquid crystals have been developed carrying perfluorinated alkyl motifs, as such motifs confer low viscosity and high thermal stability to particular materials.[2] Partially fluorinated materials are less well understood and of course the unique synthesis of partially fluorinated alkyl chains requires that stereochemical considerations are attended to during assembly. We have begun to explore methods for the synthesis of partially fluorinated alkyl motifs and in particular have investigated the synthesis and properties of compounds with alkyl chains carrying two[3–5] three[6] and four[7,8] vicinal fluorine atoms arranged in a stereospecific manner. The relative stereochemistry of adjacent fluorine atoms (*e.g. erythro* and *threo* difluorotype diastereoisomers) can induce very different preferred conformations in the analogous alkyl chains. We have explored this in fatty acids[4] and peptide mimetics.[5] In this *Communication* we report the synthesis of vicinal difluoro- and trifluoro- liquid crystals with the fluorine atoms positioned stereoselectively along the pendant alkyl chain—the first time that such a tri-fluoro motif has been incorporated into a liquid crystal. Nowadays, all high-resolution, full-colour liquid crystal displays (LCD) are based on active matrix technology, where each pixel is controlled by a separate thin-film transistor (TFT) integrated on the glass substrate. Nematic liquid crystal mixtures for this kind of application have to meet very stringent requirements—not only with regard to physicochemical properties but also in terms of purity and chemical robustness. These requirements can only be met by so-called super-fluorinated materials (SFM),[2] deriving their dielectric anisotropy ($\Delta\varepsilon$) from the dipole moment of the carbon–fluorine bond.[9] Other important characteristics include the mesophase profile and the rotational viscosity (γ_1). Also here, fluorine substitution often serves a very specific function.[10]

LCD television as the fastest growing application of nematic materials is dominated by the vertical alignment (VA) mode. This technology makes use of fluorinated liquid crystals with negative dielectric anisotropy.[11] On the molecular level, in dielectrically negative liquid crystals the dipole moment is oriented perpendicular to the long molecular axis. Whereas there is a large variety of liquid crystalline structures with positive $\Delta\varepsilon$, the design options leading to materials with negative $\Delta\varepsilon$ are quite limited. All such liquid crystals for VA (vertical alignment) applications are based on the 2,3-difluorophenylene substructure (such as **1**),[12] but there have also been some more recent developments (*e.g.*, **2**)[13] (Fig. 1).

However, the design of new basic structures rendering liquid crystals dielectrically negative remains a challenge. A sequence of two or more vicinal fluorine substituents in a terminal alkyl chain of a liquid crystalline offers a rare opportunity to explore the conformational influence exerted by the vicinal fluorine *gauche effect*. For *rac*-**3**, *rac*-**4** a strongly negative $\Delta\varepsilon$ is expected if the fluorinated side chain assumes a linear conformation with the fluorines *gauche* to each other.

In order to combine our recent synthetic developments[3,6] with the preparation of novel liquid crystalline materials with potential in display technology, the racemic compounds **3** and **4** were identified as synthetic targets. The synthesis of **3** (Scheme 1) involved epoxidation of olefin **5** followed by ring opening of epoxide **6** with HF-pyridine. This gave rise to a mixture of the fluorohydrin regioisomers **7a** and **7b**. These fluorohydrins were separated by chromatography and converted individually to the corresponding triflates, **8a** and **8b**. Subsequent fluoride treatment of each regioisomer proceeded with inversion of configuration and gave the unified product *rac*-**3** in each case.

The preparation of liquid crystal *rac*-**4** (Scheme 2) presented a more challenging synthesis. This was achieved following our

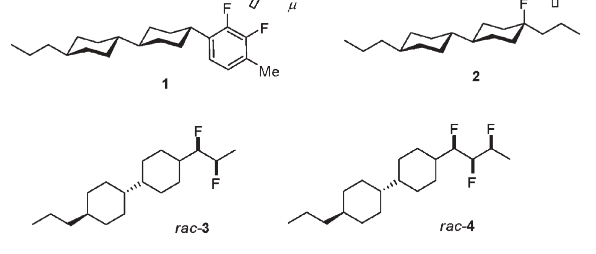

Fig. 1 In liquid crystals with negative dielectric anisotropy ($\Delta\varepsilon$), such as **1** and **2**, the dipole moment (generated by polar C–F bonds) is oriented perpendicular to the long molecular axis. In *rac*-**3** and *rac*-**4** with vicinal di- and tri-fluorinated motifs a linear conformation will have a dipole moment perpendicular to the page and towards the reader.

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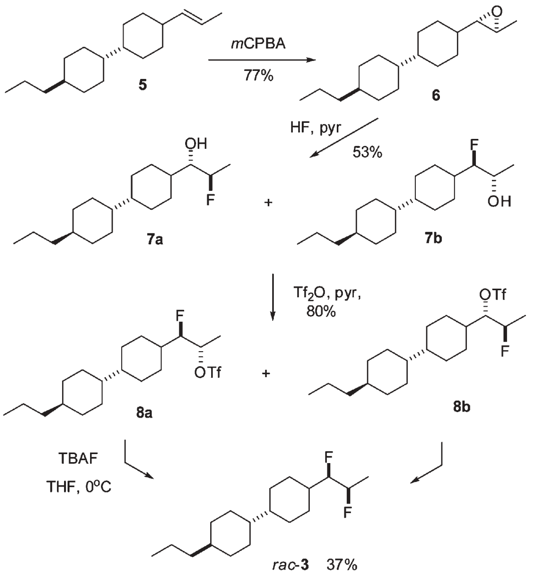
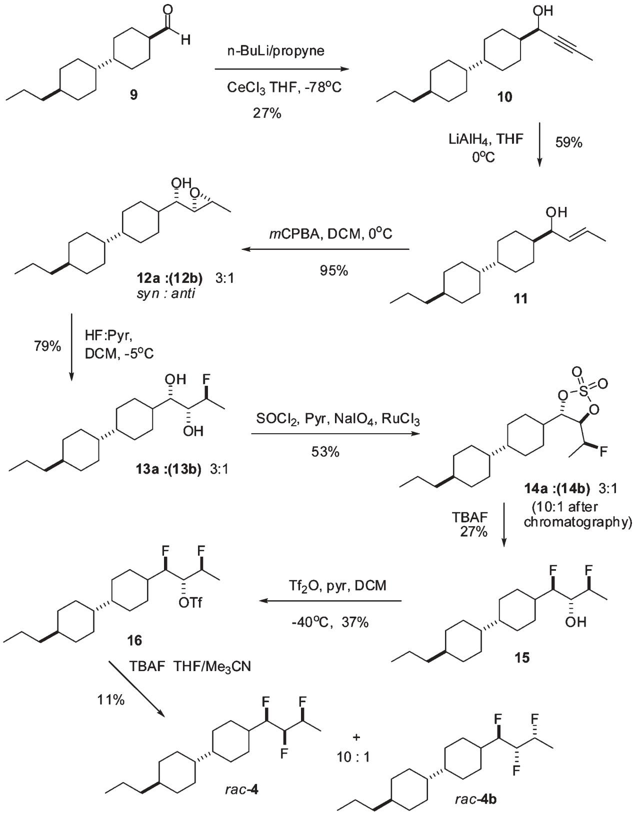


Scheme 1 Synthetic route to liquid crystal *rac*-**3**.

recently described method for the stereospecific synthesis of the vicinal trifluoro motif. Thus propargylic alcohol **10**, which is readily prepared from aldehyde **9**, formed the starting point of the synthesis. Stereospecific reduction[14] with $LiAlH_4$ generated allylic alcohol **11** which was epoxidised with mCPBA to give the diastereoisomeric allylic epoxides **12a** : **12b** (not shown) in a 3 : 1 ratio. In order to retain an efficient synthesis, these diastereoisomers were treated as a mixture until later in the synthesis. Epoxide ring opening with HF–pyridine generated the diastereoisomeric fluorodiols **13a** and **13b** (not shown) and then cyclic sulfatation gave **14a** and **14b** also in a 3 : 1 ratio. These diastereoisomers could be separated by careful chromatography, and for the preparative synthesis a sample of **14a** was used which contained ~10% of **14b**. Treatment then with tetrabutylammonium fluoride (TBAF) resulted in both a stereo- and regio-selective ring opening, to generate fluorohydrin **15**. Finally, triflate formation to give **16** and subsequent TBAF displacement gave *rac*-**4** as the predominant isomer, but containing diastereoisomer *rac*-**4b** (10%) which had carried through from **14b**. Characterization[15] of *rac*-**3** and *rac*-**4** (Table 1) shows in both cases the expected negative dielectric anisotropy. Calculations[16] suggested that the Δε of *rac*-**4** should be about twice as negative as the value of *rac*-**3**. However, the experimental values for the two vicinally fluorinated liquid crystals are practically identical. In general, for liquid crystals based on a bicyclohexyl mesogenic core structure the calculated Δε values tend to be more positive than the experimental ones which are extrapolated from the nematic host mixture ZLI-2857.[15]



Scheme 2 Synthetic route to *rac*-**4**. The material was prepared in a 10 : 1 mix of diastereoisomers with *rac*-**4b** as the minor component.

Table 1 Physical and negative dielectric properties of **1–4**

No.	Mesophase sequence	$T_{\mathrm{NI,virt}}$	$\Delta\varepsilon_{\mathrm{virt}}$
1	Cr 67 N 145.3 Iso	137.1	−2.8
2	Cr 75 SmB 94 Iso	87.3	−2.2
rac-**3**	Cr 83 SmB 100 Iso	69.6	−2.9
rac-**4**	—[a]	36.0[b]	−3.0

[a] Not available due to limited material [b] Extrapolated from ZLI-2857[12]

The prediction of Δε was based on the assumption that the side chains of both compounds prefer a linear conformation, with all fluorines *gauche*. However if the preferred conformation of the side chains deviate from linear, the C–F dipole will not align perpendicular to the molecular axis, and the observed Δε becomes less negative or even positive (Table 1). Therefore the observed Δε is a sensitive indicator of the side chain conformation. In order to obtain a more detailed analysis of the conformer equilibrium of *rac*-**3**, the relative energies of the four major side chain conformations (Fig. 2) were calculated using the simplified, truncated model **17** at the B3LYP/6-311+(2d,p)//B3LYP/6-31G(d)+ZPE level of theory.

The corresponding electrooptical values Δε and Δ*n* were then calculated for the analogous conformers of the whole liquid crystal at the AM1//B3LYP/6-31G(d) level of theory. The electrooptical data for the equilibrium ensemble were obtained by averaging the four conformers, weighted by their respective Boltzmann

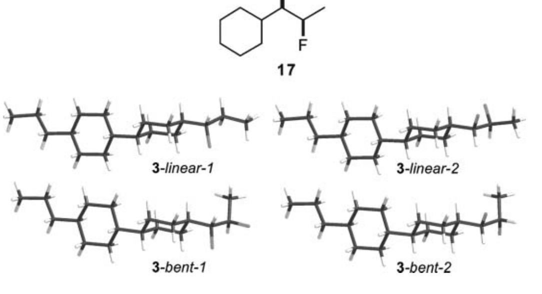


Fig. 2 The four major conformers of *rac*-**3**, and the model compound **17** used for calculation of the relative conformer energies.

Table 2 Side chain conformations, relative gas phase energies E_{rel} and Boltzmann populations of the model compound **17** (B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d)+ZPE level of theory).[17] The electro-optical parameters $\Delta\varepsilon_{\mathrm{calc}}$and Δn_{calc}, were calculated for relevant conformations of the whole liquid crystal **3** at the AM1//B3LYP/6-31G(d) level of theory. The average parameters $\Delta\varepsilon_{\mathrm{ave}}$ and Δn_{ave} were weighted by their relative populations

Conformer **3**	E_{rel} (kcal mol^{-1})	Population (%)	$\Delta\varepsilon_{\mathrm{calc}}$	Δn_{calc}	$\Delta\varepsilon_{\mathrm{ave}}$	Δn_{ave}
linear-1	+1.52	6	−1.7	0.049	−0.8	0.048
linear-2	0	75	−1.5	0.048		
bent-1	+0.98	14	+2.9	0.050		
bent-2	+1.60	5	+0.4	0.045		

populations (Table 2). It is interesting to note that one of the linear conformers (**3**-*linear*-1) is relatively high in energy, which is probably due the repulsive interaction between the side chain α-fluorine substituent and the equatorial hydrogen atoms in the adjoining cyclohexane ring.

Usually this method for the prediction of electrooptical parameters is very reliable.[16] A possible explanation for the discrepancy between the calculated and the observed dielectric anisotropy of *rac*-**3** may be the effect of the condensed, nematic mesophase. The equilibrium properties listed in Table 2 are based on calculations on isolated molecules in a vacuum but it seems reasonable that in an ordered, liquid crystalline system there are additional packing effects.[18]

For *rac*-**4** with its longer trifluorobutyl side chain the number of conformers which have to be taken into account is larger. Accordingly, the error caused by additional effects in the nematic phase becomes large and a property prediction based on a gas phase conformational analysis is not straightforward. However, the relatively low extrapolated clearing point ($T_{\mathrm{NI,virt}}$) of *rac*-**4** in combination with the unexpectedly small (absolute) Δε value, indicates that the preferred conformation of the partially fluorinated side chain is not linear (Table 1). This is in agreement with our recent conclusion[8] that in alkane chains with more than two vicinal fluorines, there are repulsive 1,3-fluorine interactions which destabilize the linear conformation. On a quantitative basis, each *syn*-1,3 interaction destabilizes the linear conformation by ∼3 kcal mol^{-1}, forcing the chain into a non-linear *g*+*g*+ (or *g*−*g*−) conformation with uniform handedness. Thus in *rac*-**3** the linear side chain gains stability from the *gauche* relationship of the fluorine substituents whereas for *rac*-**4**, linearity is strongly destabilized by a repulsive 1,3-difluoro interaction.

In summary, we have demonstrated the diastereoselective synthesis of two novel, selectively fluorinated liquid crystals. Optically pure materials are not required for their function in VA LCD, however, the synthesis of *rac*-**4** is clearly amenable to an enantiopure preparation *via* a Sharpless asymmetric epoxidation of **11**. Both liquid crystals, *rac*-**3** and *rac*-**4** show negative dielectric anisotropy, however the effect for *rac*-**4** is less than predicted as the side chain presumably cannot assume a stable linear conformation due to repulsive *g*+*g*− interactions between 1,3-fluorine substituents.

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Notes and references

1 P. Kirsch and M. Bremer, *Angew. Chem., Int. Ed.*, 2000, **39**, 4216–4235.

2 P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, Germany, 2004.

3 D. O'Hagan, H. S. Rzepa, M. Schüler and A. M. Z. Slawin, *Beilstein J. Org. Chem.*, 2006, **2**, 19.

4 M. Tavasli, D. O'Hagan, C. Pearson and M. C. Petty, *Chem. Commun.*, 2002, 1226–1227.

5 M. Schüler, D. O'Hagan and A. M. Z. Slawin, *Chem. Commun.*, 2005, 4324–4326.

6 M. Nicoletti, D. O'Hagan and A. M. Z. Slawin, *J. Am. Chem. Soc.*, 2005, **127**, 482–483.

7 L. Hunter, A. M. Z. Slawin and D. O'Hagan, *J. Am. Chem. Soc.*, 2006, **128**, 16422–16423.

8 L. Hunter, A. M. Z. Slawin, P. Kirsch and D. O'Hagan, *Angew. Chem., Int. Ed.*, 2007, DOI: 10.1002/anie.200701988.

9 The dielectric anisotropy is defined as $\Delta\varepsilon = \varepsilon_{\parallel} - \varepsilon_{\perp}$ where $_{\parallel}$ stands for parallel and $_{\perp}$ perpendicular to the nematic phase director, which is approximated by the long molecular axis. The correlation between Δε, the dipole moment μ and the angle β between the molecular dipole and the director—approximated by the long molecular axis—is the following: $\Delta\varepsilon \sim \Delta\alpha - F(\mu^2/2kT)\,(1 - 3\cos^2\beta)S$; Δα is the anisotropy of the polarizability, S the order parameter (*a*) W. Maier and G. Meier, *Z. Naturforsch., A: Astrophys. Phys. Phys. Chem.*, 1961, **16**, 262–267; (*b*) D. Demus and G. Pelzl, *Z. Chem. (Stuttgart, Ger.)*, 1981, **21**, 1–9.

10 (*a*) P. Kirsch, M. Bremer, A. Taugerbeck and T. Wallmichrath, *Angew. Chem., Int. Ed.*, 2001, **40**, 1480–1484; (*b*) P. Kirsch, M. Bremer, F. Huber, H. Lannert, A. Ruhl, M. Lieb and T. Wallmichrath, *J. Am. Chem. Soc.*, 2001, **123**, 5414–5417; (*c*) P. Kirsch, F. Huber, M. Lenges and A. Taugerbeck, *J. Fluorine Chem.*, 2001, **112**, 69–72.

11 (*a*) D. Pauluth and K. Tarumi, *J. Mater. Chem.*, 2004, **14**, 1219–1227; (*b*) D. Pauluth and K. Tarumi, *J. SID*, 2005, **13**, 693–702.

12 P. Kirsch, V. Reiffenrath and M. Bremer, *Synlett*, 1999, 389–396.

13 (*a*) P. Kirsch and K. Tarumi, *Angew. Chem., Int. Ed.*, 1998, **37**, 484–489; (*b*) P. Kirsch and K. Tarumi, *Liq. Cryst.*, 1999, **26**, 449–452; (*c*) R. W. Hoffmann, T. Brandl, P. Kirsch and K. Harms, *Synlett*, 2001, **SI**, 960–963; (*d*) M. Bremer and L. Lietzau, *New J. Chem.*, 2005, **29**, 72–74; (*e*) P. Kirsch, A. Hahn, R. Fröhlich and G. Haufe, *Eur. J. Org. Chem.*, 2006, 4819–4824.

14 B. Grant and C. Djerassi, *J. Org. Chem.*, 1974, **39**, 968–970.

15 The "virtual" parameter $T_{\mathrm{NI,virt}}$ was determined by linear extrapolation from a 10% w/w solution in the commercially available Merck mixture ZLI-4792 (T_{NI} = 92.8 °C, Δε = 5.3, Δ*n* = 0.0964). The $\Delta\varepsilon_{\mathrm{virt}}$ values were obtained from ZLI-2857 (T_{NI} = 82.3 °C, Δε = −1.42, Δ*n* = 0.0776). Due to the limited quantity of *rac*-**4**, the extrapolation was carried out in this specific case from a 5% w/w solution on the nematic host mixtures. The extrapolated values are corrected empirically for differences in the order parameter which are induced by the analyte. For the pure substances, the phase transition temperatures were determined by differential scanning calorimetry (DSC), the mesophase types were assigned by optical polarization microscopy.

16 The prediction of the electrooptic properties of nematic liquid crystals is based on the AM1 method: (*a*) M. Bremer and K. Tarumi, *Adv. Mater.*, 1993, **5**, 842–848; (*b*) M. Klasen, M. Bremer, A. Götz, A. Manabe, S. Naemura and K. Tarumi, *Jpn. J. Appl. Phys.*, 1998, **37**, L945–L948.

17 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *GAUSSIAN 03, Revision D.01*: Gaussian, Inc., Wallingford CT, 2004. The minimum geometries were optimized on the B3LYP/6-31G(d) level of theory, and were verified to have only positive eigenfrequencies. The energies were calculated on the B3LYP/6-311+G(2d,p) level of theory, using the B3LYP/6-31G(d) geometries and zero point energies.

18 A. Gavezzotti, *Acc. Chem. Res.*, 1994, **27**, 309–314.