# Synthesis of a Mesogenic Compound with a Defined Conformation

Reinhard W. Hoffmann,*[,a] Trixi Brandl,[a] Peer Kirsch,[b] Klaus Harms[a]

[a]Fachbereich Chemie, Philipps-University of Marburg, Hans-Meerwein-Strasse, 35032 Marburg, Germany

[b]Merck KGaA, Liquid Crystals Division, 64271 Darmstadt, Germany

Fax +49 6421 2828917; E-mail: rwho@chemie.uni-marburg.de

*Received 22 January 2001*

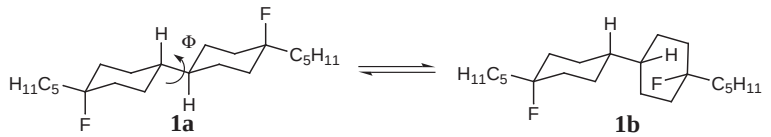
**Abstract:** The synthesis of the bicyclohexyl derivative **2** has been attained in 4 steps by bi-directional elaboration of bicyclohexanone **3**. Due to the specifically placed methyl substituents, **2** populates a single conformation at the inter-ring bond, resulting in improved material properties.

**Key words:** carbocycles, conformation, fluorine, liquid crystals

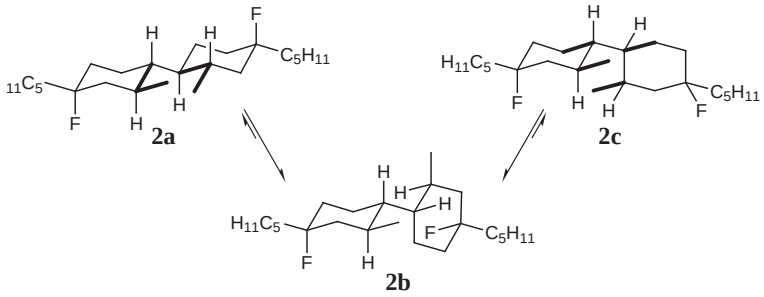
Increased use of liquid crystal displays in electronic devices led to a constantly growing demand of new liquid crystalline materials with optimal properties, such as high clearing temperature, low rotational viscosity or high dielectric anisotropy ($\Delta\varepsilon$).[1] Recent studies on liquid crystalline compounds of the type **1** demonstrated a remarkable dependence of the dielectric anisotropy of these axially fluorinated bicyclohexyl derivatives on the conformation of the molecular backbone.[2] AM1-calculations indicated that the dielectric anisotropy vanishes when the dipole moments of the C-F bonds point in opposite directions and cancel each other, i.e. if the conformation at the bicyclohexyl bond is *trans* ($\Phi$ = dihedral angle H-C-C-H = 180°), cf. Scheme 1. In conformations with smaller dihedral angles the dipoles reinforce each other: the smaller $\Phi$ the more negative will be the dielectric anisotropy $\Delta\varepsilon$. The actual value of $\Delta\varepsilon$ is then the population weighted average over the conformer population.

Compound **1** populates two types of conformation: The *gauche* conformation **1b** (58%, calculated $\Delta\varepsilon = -2.7$)[3-5] and the *trans* conformation **1a** (42%, calculated $\Delta\varepsilon = -0.4$). A Boltzmann distribution over the two conformations **1a** and **1b** predicts an averaged $\Delta\varepsilon$-value of −1.7, which is slightly lower than the experimentally determined value of $\Delta\varepsilon = -2.5$. Obviously, if the conformer equilibrium can be shifted in the direction of **1b**, the compounds should posses larger negative $\Delta\varepsilon$-values. A shift in the conformer population toward **1b** could be attained by rational placement of substituents, i.e. by rational conformation design.[6]

We therefore targeted the $C_2$-symmetric compound **2**, which has two additional methyl groups compared to compound **1**. While maintaining free rotation about the inter-ring bond the two equatorial methyl groups should destabilize both the *trans* conformation **2a** as well as one of the two possible *gauche* conformations (**2c**) by two *syn*-pentane interactions to the point that these arrangements are no longer minima on the rotational energy profile (a comparison of the calculated rotational profiles for **1** and **2** is given in Figure 1).[4,5] The calculations show for **2** only two minima on the rotational energy profile: **2b** ($\Phi$ = −60°) and, substantially (+4.9 kcal mol$^{-1}$) higher, another conformer which reduces *syn*-pentane interactions by increasing[7] the dihedral angle $\Phi$ to 80°. Compound **2** should therefore populate exclusively the strain-free *gauche* conformation **2b** (cf. Scheme 2) which, due to the small dihedral angle at the inter-ring bond should lead to a significantly larger negative $\Delta\varepsilon$-value.




**Scheme 1**




**Scheme 2**

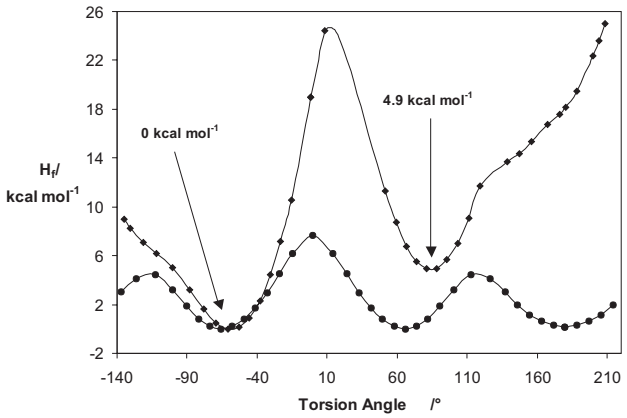
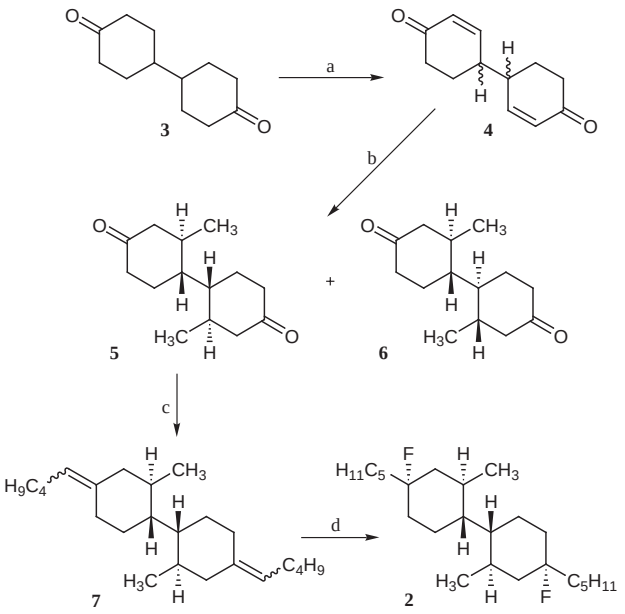



**Figure 1** Influence of the torsion angle Φ on the conformational energy $\Delta H_f$ (MMFF94) • = **1**; ♦ = **2**

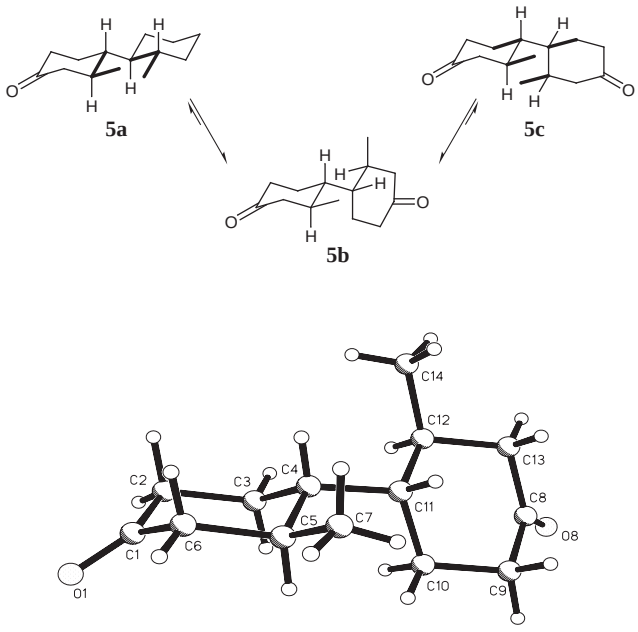
The synthesis of compound **2** originated from 4,4'-dicyclohexanone **3**.[8] In a bi-directional approach, **3** was converted to the bis-silylenolether, which was transformed into the bis-enone **4**[9] using the Saegusa protocol.[10] This led to a 1:1 mixture of the *meso*- and *d/l*-diastereomers. Subsequent addition of $Me_2CuLi$ introduced the two methyl groups selectively *trans* to the cyclohexyl substituent furnishing a mixture of *meso*-**5** and *d/l*-**6**.[11] The diastereomers were both crystalline compounds. X-ray crystal structure analysis[12] of **5** showed that this is the diastereomer which has the proper relative configuration for the synthesis of **2**. Wittig reaction of **5** with pentylidene-phosphorane led to an *E/Z*-mixture of the bisalkene **7**.[13] Following earlier precedent,[2] the bis-alkene was converted with HF/pyridine (Olah's reagent[14]) into the target compound **2**, which was recrystallized to diastereomeric purity.[15]

Conformational analysis of the bicyclohexyl derivatives rests on a determination of the $^3J_{H\text{-}H}$ coupling constant across the inter-ring bond. In the case of compound **2**, this was prevented by severe signal overlap. We therefore turned to conformational analysis of the precursor ketone **5**, which should display a similar conformational behavior to that of **2**. The SELINCOR technique[16,17] without proton decoupling permitted the determination of the $^3J_{H\text{-}H}$ coupling constant across the inter-ring bond to $J$ = 3.0 Hz. This value documents the predominance of a *gauche* conformation but does by itself not differentiate between the two possible *gauche* conformations to **5b** and **5c**. Since the conformation **5b** is the only one free of *syn*-pentane interactions, the latter is likely the predominant conformation. This is indeed the conformation found in the solid state, as the X-ray crystal structure of **5** shows (Scheme 4).

The high conformational preference found for the ketone **5** should also prevail in the difluoro compound **2**, a fact that should be reflected in the dielectric anisotropy of compound **2**: With a Δε-value of −4.2,[18] compound **2** posseses indeed a much improved dielectric anisotropy compared to compound **1**.




**Scheme 3** a) (i) LDA, THF, -78 °C, then TMSCl; (ii) $Pd(OAc)_2$, *p*-benzoquinone, $CH_3CN$, rt, 72%; b) $Me_2CuLi$, THF, -78 °C, separation of *meso* 36% and *d/l* 36%; c) $C_5H_{11}PPh_3Br$, KOtBu, $Et_2O$, 0 °C, 95%; d) 70% HF•pyridine, THF, 28%




**Scheme 4**

We showed in this study that conformation design, i.e. the selective destabilization of undesired conformers by rational placement of substituents, led the way from **1** to compound **2** with an attendant improvement in the conformation-dependent material properties.

## Acknowledgement

This study has been supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie (fellowship to T.B.).

## References and Notes

(1) Kirsch, P.; Bremer, M. *Angew. Chem., Int. Ed.* **2000**, *112*, 4216.
(2) Kirsch, P.; Tarumi, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *110*, 484.
(3) The energy profile for the rotation about the inter-ring bond was calculated using the MMFF94 force field. The structures corresponding to the minima were optimized by AM1-calculations and used as input for the calculations of the Δε-values.
(4) Bremer, M.; Tarumi, K. *Adv. Mater*. **1993**, *5*, 842.
(5) Klasen, M.; Bremer, M.; Götz, A.; Manabe, A.; Naemura, S.; Tarumi, K. *Jpn. J. Appl. Phys.* **1998**, *37*, L945.
(6) Hoffmann, R.W. *Angew. Chem., Int. Ed.* **2000**, *112*, 2054.
(7) Tsuzuki, S.; Schäfer, L.; Goto H.; Jemmis, E.D.; Hosoya, H.; Siam, K.; Tanabe, K.; Osawa, E. *J. Am. Chem. Soc.* **1991**, *113*, 4665.
(8) Pedersen, L.D.; Weiler, L. *Can. J. Chem.* **1977**, *55*, 782.
(9) **Bicyclohexyl-2,2´-diene-4,4´-dione (4)**. *n*-BuLi (1.53 M in hexane, 67.0 mL, 103 mmol) was added at −78 °C into a solution of diisopropylamine (15.1 mL, 108 mmol) in THF (150 mL). The mixture was warmed to 0 °C for 10 min, then cooled to −78 °C prior to addition of a solution of the diketone **3** (4.857 g, 25.00 mmol) in THF (20 mL). After stirring for 2.5 h chlorotrimethylsilane (15.8 mL, 125.0 mmol) was added and the mixture was allowed to warm to 0 °C over a 1 h period. Saturated aqueous $NaHCO_3$ solution (100 mL) was added, the phases were separated and the aqueous phase was extracted with pentane (3 × 70 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated. The resulting crude bis-silylenolether was dissolved in acetonitrile (120 mL) and successively treated with $Pd(OAc)_2$ (5.980 g, 55.00 mmol) and *p*-benzoquinone (12.350 g, 55.00 mmol). The resulting mixture was stirred for 12 h and filtered over a short pad of celite. After removal of the solvent the residue was purified by flash chromatography (pentane/*tert*-butyl methyl ether 1:9) to give dienone **4** (4.384 g, 92%) as a pale yellow solid as a mixture of *d*,*l*- and *meso*-isomers. $R_f$ 0.16 (petroleum ether/*tert*-butyl methyl ether 1:9); mp 40-44 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.84-1.87 (m, 2H), 1.91-1.94 (m, 2H), 2.07-2.13 (m, 4H), 2.41 (ddd, 2H, *J* = 1.3, 5.0, 13.8 Hz), 2.45 (ddd, 2H, *J* = 1.2, 5.0, 13.6 Hz), 2.56 (q, 2H, *J* = 4.3 Hz), 2.60 (q, 2H, *J* = 4.3 Hz), 2.63-2.70 (m, 2H), 2.72-2.78 (m, 2H), 6.09-6.16 ($m_c$, 4H), 6.80-6.83 ($m_c$, 2H), 6.85-6.88 ($m_c$, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 25.8 (2C), 26.1 (2C), 37.1 (2C), 37.2 (2C), 40.0 (2C), 40.1 (2C), 130.8 (2C), 131.2 (2C), 151.2 (2C), 151.6 (2C), 198.7 (2C), 198.8 (2C); HRMS Calcd for $C_{12}H_{14}O_2$: 190.0994; Found: 190.0991.
(10) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(11) **2,2´-Dimethyl-bicyclohexyl-4,4´-dione (5,6)**. Methyllithium (1.3 M in $Et_2O$, 15.5 mL, 20.1 mmol) was added at 0 °C to a suspension of CuI (1.916 g, 10.06 mmol) in $Et_2O$ (50 mL). The solution was cooled to −78 °C and a solution of the dienone **4** (598 mg, 3.14 mmol) in $Et_2O$ (10 mL) was added dropwise. After warming to 0 °C over 5 h saturated aqueous $NH_4Cl$ solution (50 mL) and concd. aqueous $NH_3$ (25 mL) were added. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 40 mL). The combined organic phases were washed with brine (10 mL), dried ($Na_2SO_4$) and concentrated. Purification by flash chromatography (pentane/*tert*-butyl methyl ether 1.5:1) afforded *d*,*l*-diketone **5** (246 mg, 36%) and *meso*-diketone **6** (261 mg, 36%) as colorless solids. **5**: $R_f$ 0.50 (petroleum ether/*tert*-butyl methyl ether 1:9) mp: 92 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.03 (d, 6H, *J* = 6.4 Hz), 1.40 (dq, 2H, $J_d$ = 4.3 Hz, $J_q$ = 13.5 Hz), 1.72-1.78 (m, 2H), 1.87-1.91 (m, 4H), 2.14 (t, 2H, *J* = 13.5 Hz), 2.30 (dd, 2H, *J* = 6.1, 13.5 Hz), 2.39-2.43 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 19.7 (2C), 24.6 (2C), 35.1 (2C), 41.1 (2C), 42.5 (2C), 49.9 (2C), 210.7 (2C); Anal. Calcd for $C_{14}H_{22}O_2$: C 75.63; H 9.97; Found: C 75.50; H 9.88. **6**: $R_f$ 0.44 (petroleum ether/ *tert*-butyl methyl ether 1:9); mp: 90 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.75 (d, 6H, *J* = 6.6 Hz), 1.20-1.24 (m, 2H), 1.27 (dd, 2H, *J* = 4.2, 12.6 Hz), 1.34-1.42 (m, 2H), 1.50-1.59 (m, 2H), 1.78 (ddd, 2H, *J* = 1.0, 10.7, 11.7 Hz), 1.95-2.00 (m, 2H), 2.23 (ddd, 2H, *J* = 2.1, 4.5, 14.1 Hz), 2.27-2.31 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 21.2 (2C), 28.6 (2C), 34.9 (2C), 40.7 (2C), 44.6 (2C), 49.4 (2C), 211.1 (2C); Anal. Calcd for $C_{14}H_{22}O_2$: C 75.63; H 9.97; Found: C 75.92; H 10.06.
(12) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-157219. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.
(13) **(1R*,2R*,1´R*,2´R*)-2,2´-Dimethyl-4,4´-dipentylidene-bicyclohexyl (7).** Potassium *tert*-butoxide (168 mg, 1.50 mmol) was added at 0 °C to a suspension of *n*-pentyltriphenylphosphonium bromide (620 mg, 1.50 mmol) in $Et_2O$ (4 mL). The mixture was stirred for 1.5 h and then diketone **5** (98 mg, 0.44 mmol) was added. After stirring for 8 h at room temperature, silica gel (1.5 g) was added and the solvent was removed in vacuo. The residue was purified by flash chromatography (pentane) to afford an *E*/Z-mixture of the diolefin **7** (139 mg, 95%) as a colorless oil. $R_f$ 0.81 (petroleum ether/ *tert*-butyl methyl ether 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.88-0.95 (m, 26H), 1.29-1.36 (m, 28H), 1.48 (t, 2H, *J* = 12.6 Hz), 1.60-1.66 (m, 6H), 1.80 (t, 2H, *J* = 11.6 Hz), 1.95-2.07 (m, 8H), 2.14-2.20 (m, 4H), 2.57 (d, 2H, *J* = 13.2 Hz), 2.62 (dt, 2H, $J_d$ = 12.6 Hz, $J_t$ = 1.8 Hz), 5.05-5.08 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 14.0 (4C), 19.5 (2C), 19.9 (2C), 20.0 (2C), 22.2 (2C), 26.0 (2C), 26.6 (2C), 28.6 (2C), 32.4 (2C), 34.9 (2C), 35.0 (2C), 35.7 (2C), 35.8 (2C), 37.0 (2C), 38.0 (2C), 44.3 (2C), 44.4 (2C), 44.5 (2C), 46.3 (2C), 121.1 (2C), 121.3 (2C), 138.9 (2C), 139.1 (2C); Anal. Calcd for $C_{24}H_{42}$: C 87.19; H 12.81; Found: C 87.01; H 12.58.
(14) Olah, G.A.; Welch, J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* **1979**, *44*, 3872.
(15) **(1R*,2R*,4S*,1´R*,2´R*,4´S*)-4,4´-Difluoro-2,2´-dimethyl-4,4´dipentyl-bicyclohexyl (2).** A solution of an *E*/*Z*-mixture of the diolefin **7** (165 mg, 0.50 mmol) and HF-pyridine complex (1 mL, 70% w/w) in THF (1 mL) was stirred for 12 h. The mixture was poured on ice and neutralized with solid $NaHCO_3$. The phases were separated and the aqueous phase was extracted with pentane (3 × 3 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated. Purification by flash chromatography (pentane) furnished **2** (59 mg, 32%) along with monofluorinated product (42 mg, 24%) and residual diolefin **7** (46 mg, 28%). Further purification of the obtained product by crystallisation (*n*-heptane) afforded **2** (52 mg, 28%) as a single isomer. $R_f$ 0.11 (pentane); mp: 70 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, 6H, *J* = 6.6 Hz), 0.89 (t, 6H, *J* = 6.6 Hz), 1.01 (dd, 2H, *J* = 12.5, 13.7 Hz), 1.11-1.19 (m, 2H), 1.29-1.58 (m, 22H), 1.74-1.93 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 14.0

(2C), 19.2 (2C), 20.3 (2C), 22.6 (2C), 22.8 (d, 2C, *J* = 4.7 Hz), 28.8 (2C), 32.3 (2C), 35.2 (d, 2C, *J* = 22.9 Hz), 41.1 (d, 2C, *J* = 22.8 Hz), 43.3 (2C), 44.6 (d, 2C, *J* = 22.6 Hz), 96.0 (d, 2C, *J* = 167.2 Hz); $^{19}$F NMR (188 MHz, $CDCl_3$): δ = −157.5; Anal. Calcd for $C_{24}H_{44}F_2$: C 77.78; H 11.97; Found: C 77.79; H 12.26.

(16) Berger, S. *J. Magn. Reson.* **1989**, *81*, 561.

(17) Fäcke, T.; Berger, S. *Magn. Res. Chem.* **1995**, *33*, 144.

(18) The Δε-values were determined by linear extrapolation from a 10% w/w solution in the commercially available Merck mixture ZLI-2857 ($T_{NI}$ = 82.3 °C, Δε = −1.42, Δn = 0.0776) as a standard host.

Article Identifier:
1437-2096,E;2001,0,SI,0960,0963,ftx,en;Y02401ST.pdf