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A new synthetic approach based on (−)-menthone for chiral liquid crystals

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Starting from (−)-menthone, a new chiral building block useful for liquid crystal preparation was synthesized. This chiral moiety was attached to selected phenols under mild conditions by esterification. Rigid cores of tolanebenzoates and phenylbenzoates were prepared using the palladium cross-coupling reaction or by traditional liquid crystal synthesis methods. This convergent approach ended with a second esterification or palladium cross-coupling reaction to furnish new liquid crystal materials with smectic A, smectic C* and N* phases, as well as blue phases (BP). Thermal behavior, and the effect of chiral moiety branches and molecular packing in the smectic phases, have been investigated using differential scanning calorimetry, optical microscopy and X-ray diffraction.

1. Introduction

During the past three decades there has been a growth in the design and synthesis of new chiral liquid crystals, especially with regard to ferroelectric liquid crystals (FLCs) and chiral nematic or cholesteric (N*) liquid crystals. FLCs are interesting materials due to their practical applications in high resolution displays and in photonic technologies for storage and reproduction of information based on non-linear optical (NLO) effects [1]. These compounds have been designed considering aspects related to (i) molecular geometry to obtain smectic C mesomorphism (transverse forces should be larger than longitudinal), and (ii) the presence of a chiral element, usually a centre, to assure symmetry breaking of the smectic C (SmC) phase that gives rise to spontaneous polarization ($\mathbf{P}_S$).

The relationship between molecular chirality and physical properties has been well studied and some models proposed [2]. However, an exact understanding of all the factors significant to the magnitude of $\mathbf{P}_S$ remain unknown. Rigid coupling between the stereo-centre and the rigid core (stereo-polar coupling), and the strength and low intrinsic rotation of dipoles attached to the chiral centre are well established factors that play a role in the $\mathbf{P}_S$ value [3]. On the other hand, chiral nematic LCs (N*) have found applications in twisted nematic displays, medical thermography and imaging, linear and non-linear optics, sensors, and in novel electro- and magneto-optic devices and detectors [4]. The N* helical structure shows constructive interference effects that lead to spectrally selective light reflections [5]. Using this property, N* LCs have been used as media for optical data recording and storage [6] and photonic band gap (PBG) materials for display technology, telecommunications and fibre optics [7].

It is possible to sub-divide N* LCs into three class types, according to the relationship of the chiral moiety and the liquid crystalline core [8]. Type I materials (where the chiral centre or centres are placed at the alkyl chain) are probably the most frequently encountered N* materials. The structural relationship between chiral moiety and core is a very important factor and it has been understood for many years that optical properties, helical twist sense and direction of rotation of plane polarized light depend intimately on the absolute configuration of the chiral centre, its distance from the core, the electronic nature of the substituents attached to the chiral centre and the overall enantiomeric purity of the system in question. In respect to sources of chirality, conventionally natural abundant materials like amino and hydroxy acids, or commercially available alcohols and esters such as (*S*)-2-methylbutanol, (*S*)-2-octanol and (*S*)-ethyl lactate

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have been the most widely employed [9]. But there are also elegant examples where asymmetric synthesis was applied with success to obtain FLCs, N* or dopants for mixtures [10]. (−)-Menthone, despite its use, for instance, as a chiral template and an auxiliary in organic synthesis [11] has been used only as a chiral dopant, to induce ferroelectricity, in SmC liquid crystals or, more recently, in photochromic polymers [12]. In all cases the original cyclic structure of (−)-menthone was kept.

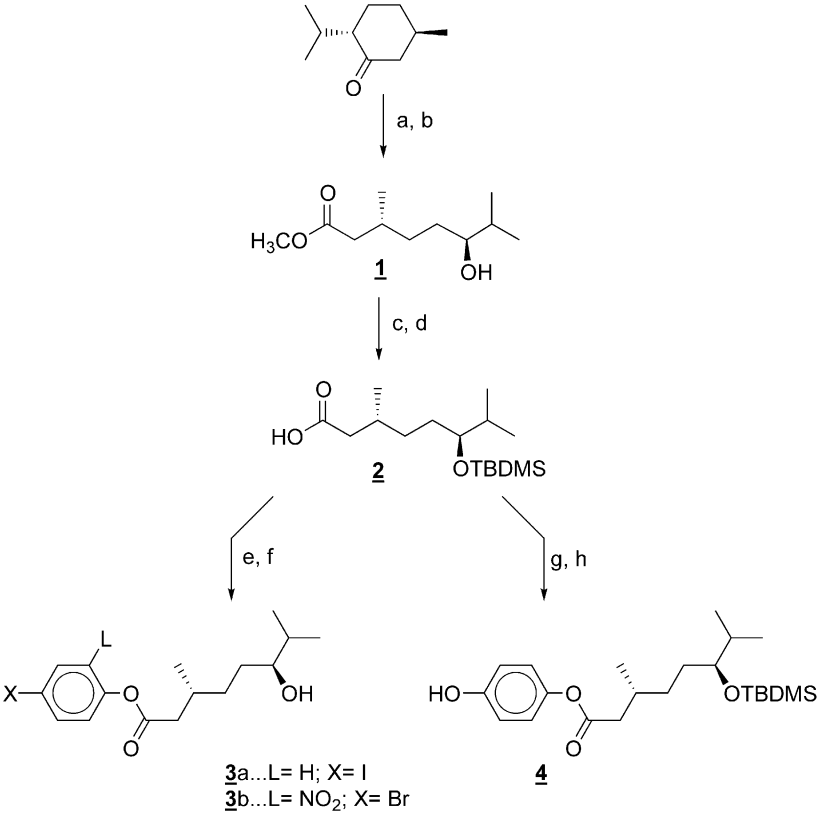
In this context, we recently reported an efficient synthetic route for converting the low cost terperne (−)-menthone to an advanced acyclic fragment useful in the synthesis of LCs [13]. In this paper we present results on the synthesis of several mesogenic and non-mesogenic phenylbenzoates and tolanebenzoates obtained from (−)-menthone. From this study, it is possible to establish the potential and limitations of this new precursor for N* and ferroelectric LC synthesis.

2. Results and discussion

2.1. *Synthesis*

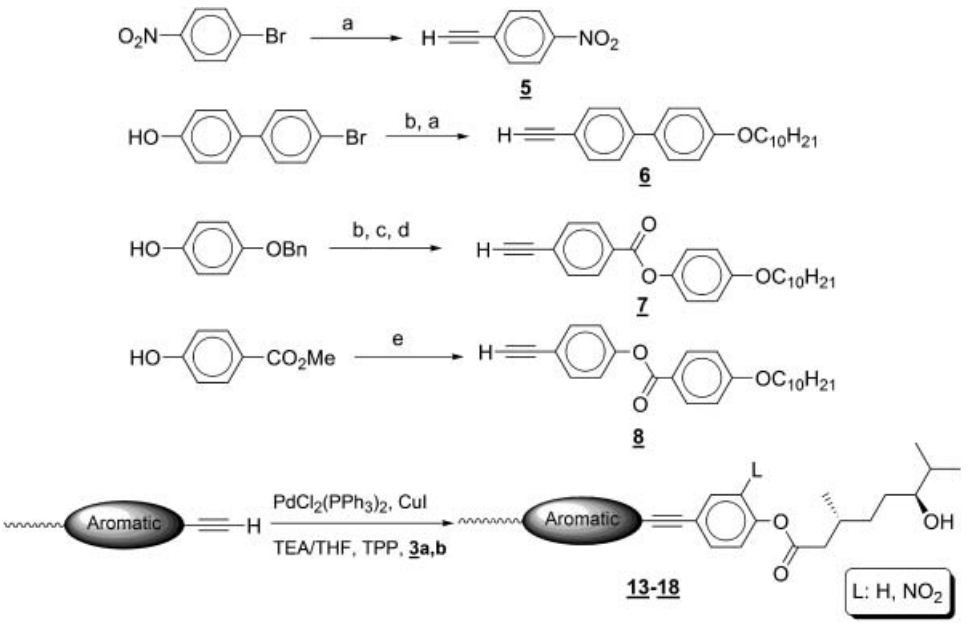
The syntheses were carried out according to schemes 1, 2 and 3. Scheme 1 describes the structural modifications made on (−)-menthone and the corresponding aryl halides and phenol for coupling to the rigid cores.

Baeyer–Villiger oxidation on (−)-menthone and further ring opening of the seven-membered lactone provided the ω-hydroxy methyl ester **1**. Regio- and stereo-control of the Baeyer–Villiger reaction were ensured by NMR experiments (^{1}H, DEPT, COSY ^{1}H-^{1}H and HETCOR), chiral capillary GC and X-ray crystal analysis. The hydroxyl group was protected as silyl ether and the acyclic acid **2** was then obtained by basic hydrolysis. Compound **2** was esterified with selected phenols (e.g. 4-iodophenol, 4-benzyloxyphenol) and then appropriately deprotected to give the compounds **3a, b** and **4**. From these fragments it was possible to construct the chiral tolanebenzoates and



Reagents: a. MCPBA, CF_3CO_2H, CH_2Cl_2; b. MeOH, conc H_2SO_4; c. TBDMSCl, DMF, imidazol; d. MeOH, 2.9M KOH; e. 4-Bromo-2-nitrophenol or 4-iodophenol, DCC, DMAP, CH_2Cl_2; f. CH_3CN, 48% HF; g. 4-benzyloxyphenol, DCC, DMAP, CH_2Cl_2; h. 20% $Pd(OH)_2$/C, cyclohexene, EtOH.

Scheme 1. Synthesis of the chiral moiety from (−)-menthone.



Reagents: a. (i) 2-Methyl-3-butyn-2-ol, $PdCl_2(PPh_3)_2$, CuI, TEA/THF; (ii) NaOH, toluene; b. n-Decylbromide, butanone, K_2CO_3, KI; c. H_2, 5% Pd/C; d. DCC, DMAP, 4-ethynylbenzoic acid [15], CH_2Cl_2; e. (i) n-Decylbromide, butanone, K_2CO_3, KI; (ii) KOH, $MeOH/H_2O$; (iii) conc. HCl; f. DCC, DMAP, 4-ethynylphenol, CH_2Cl_2.

Scheme 2. Synthesis of the terminal acetylenes and final tolanebenzoates.

phenylbenzoates target compounds. Schemes 2 and 3 show the synthetic approach for the rigid cores for tolanebenzoates (scheme 2) and phenylbenzoates (scheme 3). Terminal aryl acetylenes were constructed starting from aryl bromides and the commercially available 2-methyl-3-butyn-2-ol by palladium catalysed cross-coupling (Sonogashira's coupling) [14]. An illustrative example is the compound **6** that derives from 4-bromobiphenol. After the sequence, alkylation (87%), palladium cross-coupling (94%) and protective group elimination as acetone (89%), the desired compound **6** was obtained.

Scheme 3 delineates the synthesis of the carboxylic acids **9**–**12** used in this work.† The reactions applied are the usual in liquid crystals synthesis except for the phenylisoxazole carboxylic acid **12**, a non-linear moiety that has been studied as a potential generator of SmC mesomorphism [16].

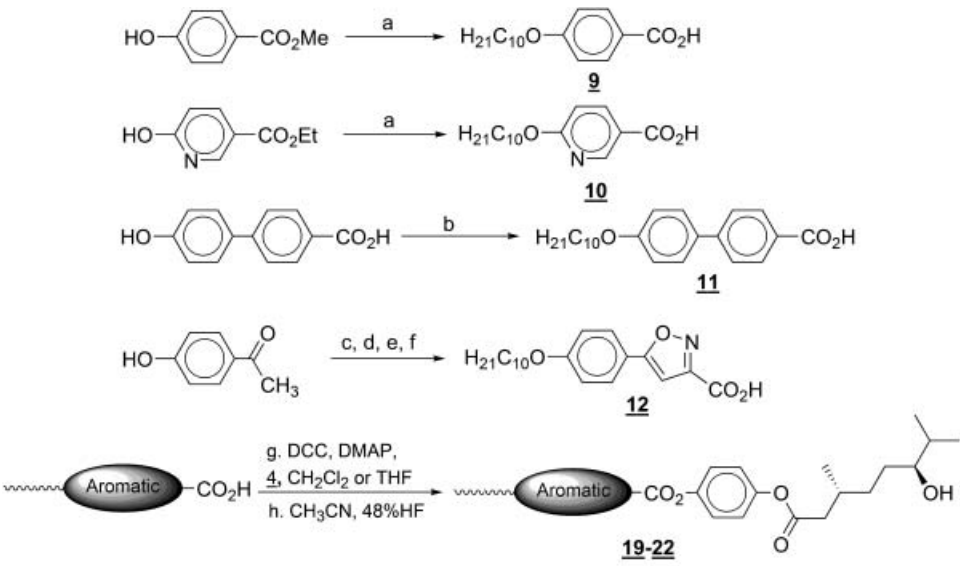
This convergent methodology ended with a second palladium-catalyzed cross-coupling between the terminal acetylenes **5**–**8** and the chiral aryl halides **3a, b**, or with an esterification between acids **9**–**12** and the chiral phenol **4**, followed by hydroxyl deprotection. The products obtained by these reactions were the tolanebenzoates **13**–**19** and phenylbenzoates **20**–**23**, respectively (see schemes 2 and 3 and figure 1).

†Compounds 4-ethynylbenzoic acid and 4-ethynylphenol decompose with light or on heating and were synthesized from 4-bromoethyl benzoate and 4-bromophenyl acetate, respectively, using the procedure described in [15].

2.2. *Liquid crystalline profile of the final compounds*

Mesomorphic properties and transition temperatures of compounds **13**–**22** were determined by polarizing optical microscopy (POM), differential scanning calorimetry (DSC) and X-ray difraction (XRD). The phase behavior of the mesogens studied is summarized in the table.

It is clear from the table that the phases and their transition temperatures are strongly affected by the aromatic core constitution. Short cores (two aromatic rings) are unable to reduce the molecular widening introduced by the chiral chain branches (**13**, **19** and **20**). On the other hand, when a third aromatic ring is present the shape anisotropy is recovered and all compounds present liquid crystalline phases. A short range SmC* phase is present in the tolanebenzoates **15** and **17** and in large one in the isoxazole derivative **22**. Blue phases (BP), indicating great chirality [2 *c*], were observed by POM for compounds **17**, **18**, **21** and **22**. However, all attempts to determine their thermal



Reagents: a. (i) n-Decylbromide, butanone, K_2CO_3, KI; (ii) KOH, MeOH/H_2O; (iii) conc. HCl; b. (i) EtOH, NaOH, n-decylbromide; (ii) NaOH, EtOH/water; (iii) conc HCl; c. DMF/Benzene (1:1), n-decylbromide; d. DME, NaH, diethyloxalate; e. $NH_2OH.HCl$, EtOH, TEA; f. (i) KOH, EtOH/H_2O; (ii) conc HCl.

Scheme 3. Synthesis of the carboxylic acids and final phenylbenzoates.

stability using DSC were frustrated, so we chose to classify them as N*. In order to see if the mesomorphism is changed by the presence of the (−)-menthone chiral moiety, a non-chiral homologue of **22** was prepared using a similar experimental procedure (figure 2).

As can be seen an expected melting and clearing point depression has taken place in **22**, as compared with **23**, but although the thermal stability of the SmC and N phases was affected they still remain in the chiral homologue. Figure 3 shows photomicrographs of selected mesomorphic targets.

2.3. *XRD studies*

X-ray diffraction studies were performed at various temperatures for an aligned sample of **21**. The SmA phase was characterized by a sharp (1 0 0) peak at low angle corresponding to the interlayer reflection. Calculation of the most probable molecular length, by molecular simulation using the AM1 semi-empiral method for the rod-like mesogenic moieties in a totally extended conformation, indicated a molecular length $L = 36.5$ Å. This result is in good agreement with the interlayer distance measured for the SmA phase ($d' = 36.0$ Å). In relation to SmA polymorphism, the relation $d' \approx L$ classifies this phase as SmA_1 [17], the simplest SmA phase. At first we imagined that the hydroxyl group could play some role in molecular packing in the SmA phase (figure 4). However, it is well known that SmA_1 packing is found for systems in which there is little tendency for molecular association, and hence there is complete head–tail disorder. The diffraction patterns for SmA and SmC* phases displayed great similarities, so it has been assumed an analogous packing for the two phases. Since the transition to the SmC* phase occurs from the SmA, it was possible to deduce the tilt angle θ_t using the relation $\theta_t = \cos^{-1}(d/d')$ where $d = 34.0$ Å and $d' = 36.0$ Å are the SmC* and SmA spacings (see the table). The SmC* tilt angle obtained by this procedure was $\theta_{120} = 19.0^\circ$. Gray and Goodby, working with the achiral *p-n*-alkoxyphenyl ester of 4′-*n*-octyloxybiphenyl-4-carboxylic acid, have found values very close to those exhibited by **21** [18]. Generalizing the XRD results, figure 5 shows the proposed probable arrangement in the SmC* for **21**.

3. Conclusions

A new acyclic chiral building block **4** for liquid crystals starting from the terpene (−)-menthone has been prepared. The sequence of reactions is easy and feasible on a preparative scale. A series of derivatives (tolanebenzoates and phenylbenzoates) was synthesized in order to evaluate the mesomorphic influence of **4**.

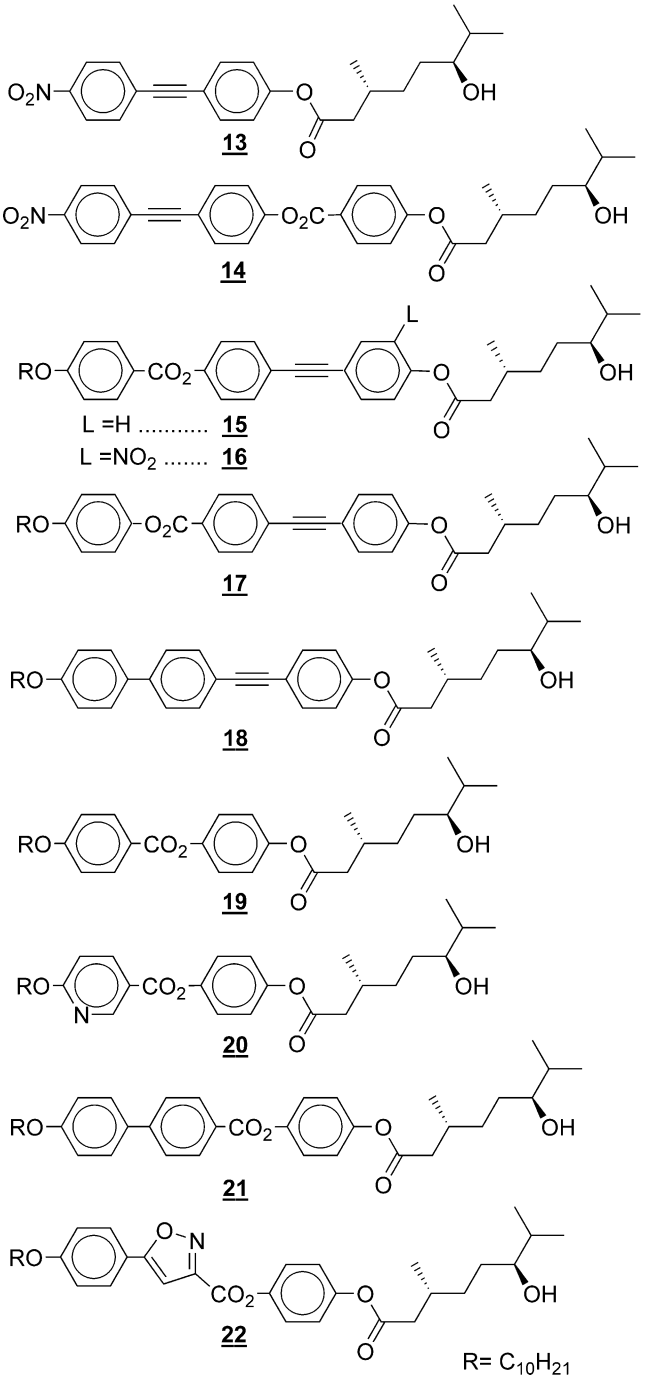


Figure 1. Final compounds synthesized.

The chiral fragment produced chiral LCs when the core was sufficiently large (three aromatic rings), thus reaching the correct anisometry. The mesomorphism observed for the targets was smectic (A, B and C*) as well as N* and BP. Ferroelectric phases had much high temperatures, e.g. **21** and **22**, leading to insignificant $\mathbf{P}_S$ and response time values. XRD experiments were made on compound **21**, the results showing that molecules in the SmA phase are arranged in monolayers and randomly within them. Therefore there is no significant hydrogen bonding association between neighboring molecules. A similar arrangement is proposed for the SmC* with a tilt angle of 19.0°. The high chirality is manifested by the presence of blue phases in **17**, **18**, **21** and **22**, and there is a possibility for the use of these compounds as photonic band gap (PGB) materials [19]. We are presently investigating that application.

4. Experimental

4.1. *Characterization*

^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ with 270 and 50.3 MHz, respectively, Bruker HX spectrometers using TMS as internal standard. IR Spectra were recorded from KBr discs, nujol dispersions or films with a Perkin-Elmer model 283 spectrometer. For elemental analysis, a Perkin Elmer 2400CHN instrument was used. Optical rotations were measured on a Perkin-Elmer 341 polarimeter at the sodium D line. GC analysis was conducted on a Varian 2 instrument equipped with a FID detector using H_2 as carrier gas; the capillary column used β-DEX 120 (30 m × 0.25 mm). Melting points, thermal transitions and mesophase textures were determined using an Olympus BX50 microscope in conjunction with a Mettler Toledo FP-90 heating stage and an exposure control unit PM-30. DSC measures were made with Shimadzu equipment using a DSC-50 module. X-ray diffraction studies were carried out on samples in capillary tubes (5mm internal diameter) with a Siemens generator operating at 40–45 kV, λCuK_α(1.54Å), 20–25 mA, fitted with a Siemens capillary furnace.

4.2. *Synthesis*

All reagents and chemicals were obtained from commercial sources and used without further purification unless otherwise noted. The organic solvents were of commercial grade quality except THF (HPLC grade) and all were dried by traditional methods. Analytical thin layer chromatography (TLC) was conducted on Merck aluminum plates with 0.2 mm of silica gel 60F-254.

4.2.1. *Methyl (3*R*,6*S*)-(−)-6-hydroxy-3,7-dimethyloctanoate, **1***

Baeyer-Villiger reaction: Lactone from (3R,6S)-(−)-6-hydroxy-3,7-dimethyloctanoic acid. CH_2Cl_2 (130 ml), MCPBA (29.09 g, 168.56 mmol) and (−)-menthone (10.00 g, 64.83 mmol) were placed in a 250 ml three-neck flask fitted with dropping funnel, condenser

Table. Thermal behavior of (−)-menthone derivatives determined by optical microscopy, DSC (5°C min^{-1}) and X-ray diffraction[a].

Compound	Transition	T/°C, heating (ΔH/kJ mol^{-1})	T/°C, cooling (ΔH/kJ mol^{-1})	*d*-value/Å (sample T/°C)
13	Cr–I	77.9	51.3	
	Cr–SmA	71.8(23.2)		
	SmA–N*	126.1(0.353)		
14	N*–I	296.3(dec.)		
	Cr–(SmC*)	109.0(39.2)	78.2(−26.5)	
	(SmC*)–N*		108.0(broad)	
15	N*–I	154.9(0.235)	156.8(−0.237)	
	Cr–SmA	78.6(33.7)	<25.0	
	SmA–N*	101.0(0.677)	96.6(−0.733)	
16	N*–I	115.6(0.624)	112.5(−0.674)	
	CrI–CrII	92.7(8.15)	95.5(−21.9)	
	CrII–SmC*	111.5(32.5)	102.5(−11.9)	
	SmC*–N*	119.3(0.608)	115.2(−1.29)	
17	N*–I	160.4(1.46)	157.3(−1.17)	
	Cr–SmB	165.7(8.22)	164.6(−5.15)	
	SmB–N*	173.1(3.41)	169.9(−2.15)	
18	N*–I	179.2(0.88)	175.5(−1.04)	
19	Cr–I	86.7	71.5	
20	Cr–I	72.8	63.2	
	Cr–SmC*	117.3(44.6)	85.5(−26.7)	34.0 (120)
	SmC*–SmA	144.0(0.110)	128.8(−0.124)	36.0 (140)
	SmA–N*	159.4(1.08)	156.3(−1.00)	
21	N*–I	165.4(1.05)	162.7(−1.16)	
	Cr–SmC*	90.4(21.7)	76.7(−18.5)	
	SmC*–N*	107.4(0.578)	104.4(−0.578)	
22	N*–I	122.2(1.36)	119.7(−1.34)	

[a]Compounds **13**, **19** and **20** were investigated only by optical microscopy as they did not exhibit mesomorphic behavior.

and glass stopper. Freshly distilled trifluoroacetic acid (5 ml, 67.31 mmol) was added dropwise to the suspension, magnetically stirred at 0°C. The vessel was protected from light and left at room temperature for 7.5 h. TLC analysis indicated disappearance of the starting material. The resulting white solid was filtered off and washed with CH_2Cl_2 (130 mL). The filtrate was cooled in an ice–water bath and a saturated solution of sodium bisulphite (100 ml) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The combined organic layers were washed with saturated solutions of K_2CO_3 (3 × 100 ml) and NaCl (100 ml) and dried over sodium sulphate. Filtration and evaporation under reduced pressure provided 9.93 g (90%) of the pure lactone as an oil that slowly crystallized to furnish colorless crystals. m.p. 34.0–35.2°C, b.p. 60–63°C at 0.05 mmHg, $[\alpha]_D^{20} = -26.0$(4, $CHCl_3$), $[\alpha]_D^{26}$(Lit. [20]) = −8.5(4, $CHCl_3$). GC: capillary column β-DEX 120, temp. 155°C, R_t 4.67 min., single peak. IR (nujol) ν_{max}/cm^{-1}: 2964, 2938, 1718, 1304, 1278, 1232, 1164, 1020, 1004, 628. ^{1}H NMR ($CDCl_3$) δ: 0.96 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 1.30 (m, 1H), 1.60 (m, 1H), 1.90 (m, 4H), 2.50 (m, 2H), 4.00 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 17.7, 19.0, 24.6, 31.1, 31.6, 34.0, 38.1, 43.2, 85.4, 175.6.

Metanolysis of the lactone. To a magnetically stirred solution of the lactone from (−)-menthone (9.75 g, 51.47 mmol) in MeOH (100 ml) was added concentrated H_2SO_4 (2 ml). The mixture was stirred at room temperature overnight; TLC analysis indicated disappearance of the starting material. Methanol was evaporated under reduced pressure; the residue was dissolved in

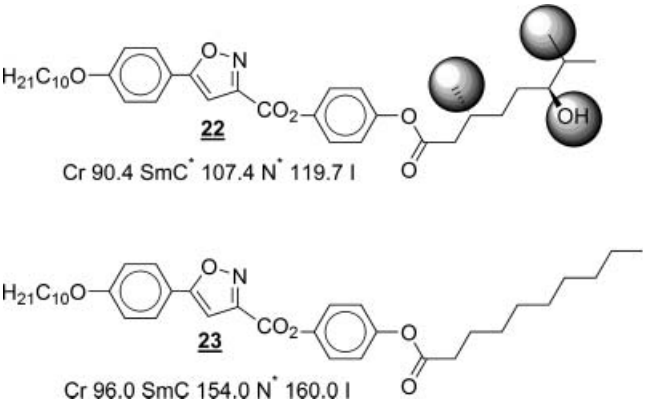


Figure 2. Comparative analysis of the chiral fragment branch on the mesomorphism (transition temperatures in °C).

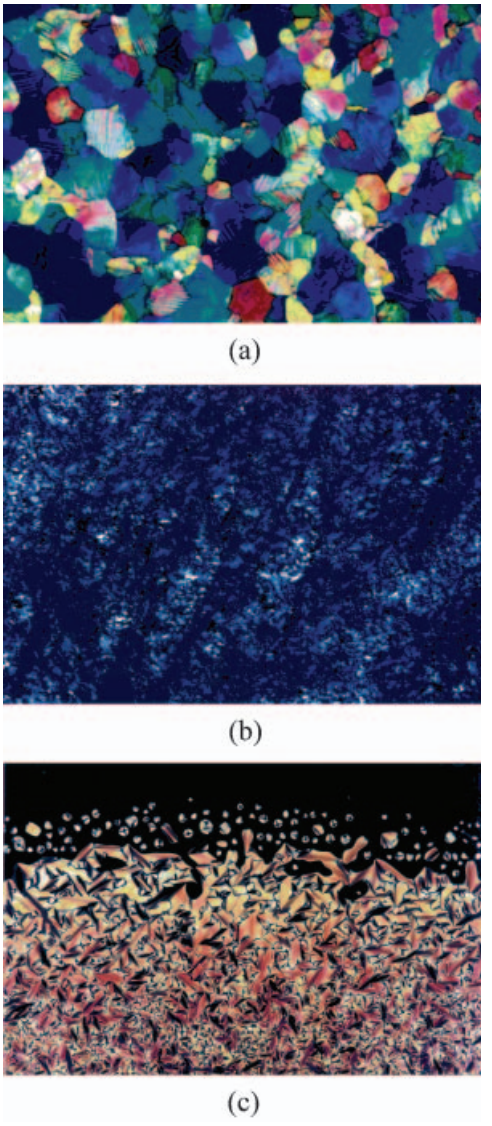


Figure 3. Photomicrographs of (*a*) the N* 'blue' phase platelet texture at 176.5°C of compound **19** (66×), (*b*) SmC* phase aligned (PVA) at 98.7°C of compound **22** (33×), and (*c*) transition isotropic-chiral nematic (N*) focal-conic 'fan-like' texture at 163.5°C of compound **15** (33×). Samples were sandwiched between untreated glass slides, except (*b*), and viewed through crossed polarizers.

ethyl acetate (150 ml) and washed with water (50 ml), saturated $NaHCO_3$ (2 × 50 ml) and saturated NaCl (50 ml), and then dried over sodium sulphate. Filtration, evaporation of the solvent under reduced pressure and vacuum distillation furnished 8.55 g (82%) of **1** as a colorless oil, b.p. 97–103°C at 0.5 mm Hg, $[\alpha]_D^{20} = -11.1$(6.88, $CHCl_3$), $[\alpha]_D^{23}$(Lit. [9]) $= -9.3$(6.88, $CHCl_3$). IR (film) ν_{max}/cm^{-1}: 3434, 2958, 2874, 1736, 1460, 1438, 1260, 1206, 1164, 1006. ^{1}H NMR ($CDCl_3$) δ: 0.90 (d, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 7.0$ Hz, 3H), 0.96 (d, $J = 6.7$ Hz, 3H), 1.25 (m, 2H), 1.50 (m, 2H), 1.70 (m, 1H), 1.90 (m, 1H), 2.10 (dd, $J_{ab} = 15.0$ Hz, $J_{ax} = 7.8$ Hz, 1H), 2.30 (dd, $J_{ab} = 15.0$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.30 (m, 1H), 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 16.9, 18.8, 19.8, 30.4, 31.3, 32.9, 33.3, 41.3, 51.3, 76.7, 173.6.

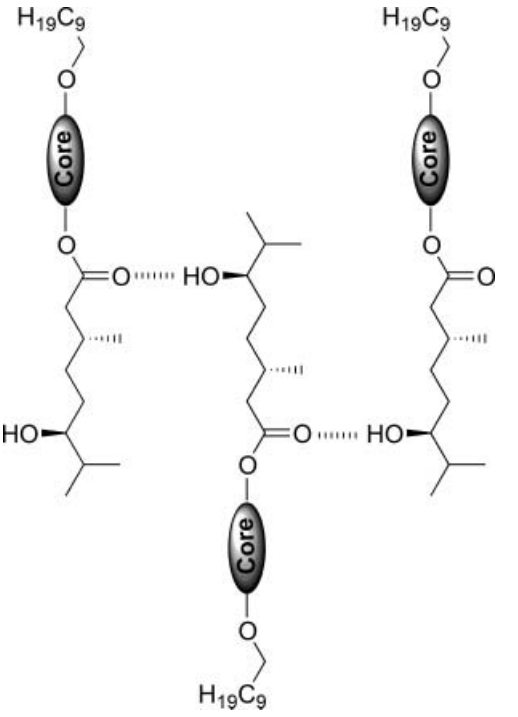


Figure 4. Proposed hydrogen-bonding arrangement in the SmA phase for **21**. In this situation the interlayer spacing would be approximately 1.5 times the molecular length.

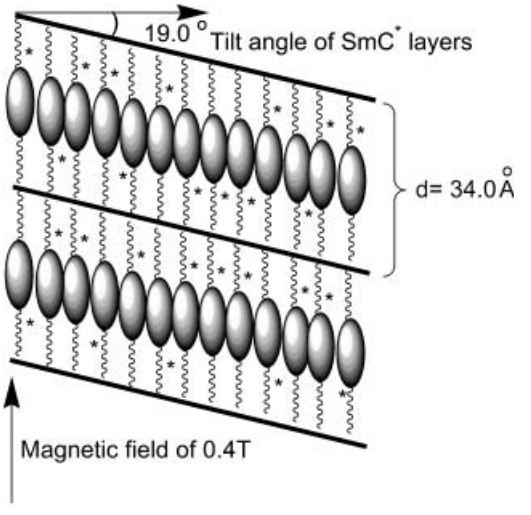


Figure 5. Probable arrangement in the SmC* phase for **21** at 120°C, the chiral tails are disposed in a random fashion without significant molecular association.

4.2.2. *(3R,6S)-(+)-6-tert-Butyldimethylsilyloxy-3,7-dimethyloctanoic acid,* ***2***

Protection with TBDMSCl. To a magnetically stirred solution of **1** (5.05 g, 24.75 mmol) in DMF (10 ml), imidazol (4.21 g, 61.85 mmol) and TBDMSCl (4.48 g, 29.70 mmol) were added. The solution was stirred at room temperature for 24 h, then poured in ice/water (100 ml) and extracted with diethyl ether (4 × 50 ml). The combined organic layers were washed with brine (50 ml), water (50 ml), then dried over magnesium sulphate. Filtration, evaporation under reduced pressure and vacuum distillation provided 6.84 g (87%) of the silyl ether as a colorless oil, b.p. 120–124°C at 1 mm Hg, $[\alpha]_D^{20} = +5.0$(1.84, $CHCl_3$). IR (film) ν_{max}/cm^{-1}: 2956, 2858, 1742, 1466, 1438, 1382, 1364, 1254, 1212, 1166, 1056, 1008, 838, 776. ^{1}H NMR ($CDCl_3$) δ: 0.01 (s, 6H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.82 (d, $J = 6.6$ Hz, 3H), 0.86 (s, 9H), 0.92 (d, $J = 6.6$ Hz, 3H), 1.13 (m, 1H), 1.37 (m, 2H), 1.40 (m, 1H), 1.64 (m, 1H), 1.90 (m, 1H), 2.08 (dd, $J_{ab} = 14.5$ Hz, $J_{ax} = 7.9$ Hz, 1H), 2.29 (dd, $J_{ab} = 14.5$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.35 (m, 1H), 3.68 (s, 3H).

Hydrolysis of methyl ester. To a solution of the silyl ether (6.15 g, 19.45 mmol) in methanol (10 ml), was added, dropwise, a 2.9M solution of KOH was added. The resultant mixture was heated at reflux for 3 h, then cooled to room temperature and poured into ice/water (75 ml). The pH was adjusted to *c.* pH = 3 with concentrated HCl and the mixture was extracted with diethyl ether (4 × 50 ml). The combined organic layers were washed with brine and dried over sodium sulphate. Filtration, evaporation under reduced pressure and vacuum distillation provided 4.25 g (73%) of **2** as a colorless oil, b.p. 133–135°C at 0.5 mm Hg, $[\alpha]_D^{20} = +4.0$(1.82, $CHCl_3$). IR(film) ν_{max}/cm^{-1}: 2958, 2858, 1710, 1466, 1254, 1056, 838, 774. ^{1}H NMR ($CDCl_3$) δ: 0.07 (s, 6H), 0.81 (d, $J = 6.7$ Hz, 3H), 0.83 (d, $J = 7.0$ Hz, 3H), 0.86 (s, 9H), 0.96 (d, $J = 6.7$ Hz, 3H), 1.20 (m, 1H), 1.40 (m, 3H), 1.60 (m, 1H) 1.90 (m, 1H), 2.10 (dd, $J_{ab} = 14.5$ Hz, $J_{ax} = 8.8$ Hz, 1H), 2.30 (dd, $J_{ab} = 14.5$ Hz, $J_{bx} = 5.9$ Hz, 1H), 3.30 (m, 1H). ^{13}C NMR δ: −4.4, −4.3, 17.6, 18.1, 19.8, 25.9, 30.5, 32.4, 32.6, 41.5, 76.8, 179.4.

4.2.3. *4-Iodophenyl (3R,6S)-(−)-6-hydroxy-3,7-dimethyloctanoate,* ***3a***

Esterification with 4-iodophenol. To a solution of **2** (1.09 g, 3.61 mmol) in CH_2Cl_2 (15 ml) was added 4-iodophenol (0.79 g, 3.61 mmol). The solution was cooled in ice–water and then, under magnetic stirring, DCC (0.819 g, 3.97 mmol) and DMAP (0.039 g, 0.36 mmol) were added. After 4 h at 0°C the white solid was filtered off and washed with CH_2Cl_2 (15 ml). The filtrate was washed with 5% HCl (25 ml), saturated $NaHCO_3$ (25 ml) and brine (25 ml); the organic layer was dried over sodium sulphate. The residue after filtration and evaporation of the solvent was purified on a chromatographic column (silica gel, $CHCl_3$) furnishing 1.32 g (73%) of the TBDMS ester as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 0.01 (s, 6H), 0.80 (d, $J = 6.7$ Hz, 3H), 0.82 (d, $J = 6.9$ Hz, 3H), 0.86 (s, 9H), 1.00 (d, $J = 6.7$ Hz, 3H), 1.30 (m, 4H), 1.60 (m, 1H), 2.00 (m, 1H), 2.30 (dd, $J_{ab} = 14.8$ Hz, $J_{ax} = 8.0$ Hz, 1H), 2.50 (dd, $J_{ab} = 14.8$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.30 (m, 1H), 6.80 (d, $J = 8.6$ Hz, 2H), 7.60 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR δ: −4.5, −4.2, 17.6, 18.1, 19.8, 25.9, 30.4, 30.7, 32.3, 32.5, 41.7, 76.8, 89.7, 123.8, 138.4, 150.5, 171.3.

Cleavage of the protective group TBDMS. The TBDMS ester was dissolved in CH_3CN (5 ml), and 40% aqueous HF (0.25 mL) added. After 15 min $CHCl_3$ (25 ml) and water (25 ml) were added, leading to phase separation. The aqueous layer was extracted twice with $CHCl_3$; the combined organic layers were then washed with $NaHCO_3$ and NaCl solutions and dried over sodium sulphate. Filtration and evaporation of the solvent provided compound **3a**, analytically pure in 95% yield, m.p. 59.6–60.1°C, $[\alpha]_D^{20} = -4.0$(1.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.91 (d, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 6.7$ Hz, 3H), 1.07 (d, $J = 6.5$ Hz, 3H), 1.30 (m, 4H), 1.68 (m, 1H), 2.00 (m 1H), 2.38 (dd, $J_{ab} = 14.8$ Hz, $J_{ax} = 8.0$ Hz, 1H), 2.51 (dd, $J_{ab} = 14.8$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.40 (m, 1H), 6.84 (d, $J = 8.0$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 2H).

4.2.4. *4-Bromo-2-nitrophenyl (3R,6S)-(−)-6-hydroxy-3,7-dimethyloctanoate,* ***3b***

This compound was prepared as described for compound **3a**, with 66% yield, in two steps using 4-bromo-3-nitrophenol. Purification was carried out on a chromatographic column (silica gel, *n*-hexane/ethyl acetate 9.5/0.5) giving **3b** as a yellow oil, $[\alpha]_D^{20} = -4.0$(3.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.91 (d, $J = 6.7$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.6$ Hz, 3H), 1.50 (m, 5H), 2.10 (m, 1H), 2.44 (dd, $J_{ab} = 15.8$ Hz, $J_{ax} = 7.8$ Hz, 1H), 2.64 (dd, $J_{ab} = 15.8$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.38 (m, 1H), 7.12 (d, $J = 8.6$ Hz, 1H) 7.75 (dd, $J = 8.6$, 2.4 Hz, 1H), 8.20 (d, $J = 2.4$ Hz, 1H).

4.2.5. *4-Hydroxyphenyl (3R,6S)-(+)-6-tert-butyldimethylsilyloxy-3,7-dimethyloctanoate,* ***4***

Esterification with 4-benzyloxyphenol. 4-Benzyloxyphenol (1.25 g, 6.22 mmol) and the acid **2** (1.88 g, 6.22 mmol) were suspended in dichloromethane (50 ml) under argon. After the addition of DCC (1.35 g, 6.53 mmol) and DMAP (0.067 g, 0.62 mmol) the mixture was stirred for 24 h. The white precipitate

was filtered off and washed with dichloromethane (100 ml). Evaporation of the solvent and column chromatography of the residue (silica gel, *n*-hexane/ethyl acetate 9.5/0.5) produced 2.90 g (96%) of the desired ester as a white powder, m.p. 48.3–51.9°C, $[\alpha]_D^{20} = +2.0(1.01, CHCl_3)$. ^{1}H NMR ($CDCl_3$) δ: 0.04 (s, 6H), 0.86 (m, 15H), 1.03 (d, $J = 6.0$ Hz, 3H), 1.45 (m, 5H), 2.05 (m, 1H), 2.32 (dd, $J_{ab} = 14.8$ Hz, $J_{ax} = 8.0$ Hz, 1H), 2.54 (dd, $J_{ab} = 14.8$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.42 (m, 1H), 5.04 (s, 2H), 6.97 (s, 5H), 7.36 (m, 4H).

Hydrogenolysis of benzyl group. To a refluxing solution of the benzyl ester (1.0 g, 2.06 mmol) in ethanol (15 ml) and cyclohexene (7.5 ml), $Pd(OH)_2/C$ (0.100 g, 20% w/w) was added in small portions. The reflux was held for 24 h then the cold mixture was filtered through celite and washed with ethanol (30 ml). Concentration and column chromatography of the residue (silica gel, *n*-hexane/ethyl acetate 9.5/0.5) produced 0.54 g (66%) of the desired phenol **4** as a yellow oil that crystallized on standing, m.p. 52.8–57.6°C, $[\alpha]_D^{20} = +6.0(1.01, CHCl_3)$. ^{1}H NMR ($CDCl_3$) δ: 0.04 (s, 6H), 0.88 (m, 15H), 1.04 (d, $J = 6.6$ Hz, 3H), 1.35 (m, 4H), 1.69 (m, 1H), 2.04 (m, 1H), 2.33 (dd, $J_{ab} = 14.8$ Hz, $J_{ax} = 8.0$ Hz, 1H), 2.54 (dd, $J_{ab} = 14.8$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.42 (m, 1H), 3.44 (m, 1H), 5.16 (broad, 1H), 6.77 (d, $J = 9.0$ Hz, 2H), 6.90 (d, $J = 9.0$ Hz, 2H).

4.2.6. *1-Ethynyl-4-nitrobenzene,* ***5***

To an oven-dried three-necked flask fitted with condenser, funnel and argon inlet/outlet were transferred 4-nitro-bromobenzene (1.02 g, 4.95 mmol), $PdCl_2(PPh_3)_2$ (10 mg), CuI (5 mg), triphenylphosphine (150 mg) and TEA (20 ml). The mixture was heated under reflux for 15 min then pure 3-methyl-2-butyn-2-ol (0.72 mL, 7.42 mmol) was added. After 5 h of further reflux the cooled mixture was diluted with diethyl ether (50 ml) and filtered through a celite pad. The filtrate was washed with 10% HCl (5×20 ml), $NaHCO_3$ (3×20 ml) and satured NaCl (40 ml); it was then dried over sodium sulphate. After filtration, the solvent was evaporated furnishing a brown solid. This was dissolved in toluene (30 ml) and NaOH powder (50 mg) was added. The reaction mixture was slowly heated and acetone distilled off. The cold mixture was filtered through a celite pad, washing with hexanes (50 ml). Solvents were removed by evaporation, and the residue purified by column chromatography (silica gel, hexanes) to give a pale yellow solid, yield 0.245 g (49%), m.p. 142.6–145.6°C. ^{1}H NMR ($CDCl_3$) δ: 3.30 (s, 1H), 7.60 (d, $J = 8.8$ Hz, 2H), 8.20 (d, $J = 8.8$ Hz, 2H). IR(film) ν_{max}/cm^{-1}: 3252, 1594, 1512, 1344, 1312, 1288, 1104, 854, 750, 678.

4.2.7. *4-Decyloxy-4′-ethynylbiphenyl,* ***6***

Alkylation of 4′-bromobiphenyl-4-ol. A mixture of 4′-bromobiphenyl-4-ol (2.45 g, 9.84 mmol), K_2CO_3 (4.08 g, 29.52 mmol), bromodecane (3.06 ml, 14.76 mmol) and butanone (25 ml) was stirred under reflux for 18 h. Potassium carbonate were filtered off and washed with ethyl ether; the filtrate was concentrated and the residue recrystallized from acetonitrile, yield 3.32 g (87%), m.p. 117.9–118.5°C. ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, 3H), 1.29 (m, 14H), 1.56 (m, 2H), 4.00 (t, 2H), 6.95 (m, 2H), 7.48 (m, 6H).

Coupling with 3-methyl-2-butyn-2-ol. A mixture of 4′-Bromo-4-decyloxybiphenyl (3.90 g, 10.03 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol), CuI (9.5 mg, 0.05 mmol), triphenylphosphine (26.2 mg, 0.10 mmol) and TEA (30 mL)/THF (30 ml) was heated under reflux for 1.5 h. Pure 3-methyl-2-butyn-2-ol (1.65 ml, 15.04 mmol) was then added, and after 12 h of further reflux the cooled mixture was diluted with diethyl ether (150 ml) and filtered through a celite pad. The filtrate was evaporated and the residue recrystallized from heptane; yield 3.70 g (94%), m.p. 125.5–127.2°C. ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, 3H), 1.28 (m, 14H), 1.64 (s, 6H), 1.80 (m, 2H), 2.04 (s, 1H), 3.99 (t, 2H), 6.96 (m, 2H), 7.48 (m, 6H).

Protective group elimination as acetone. The intermediate alkynol (1.45 g, 3.70 mmol) was dissolved in dry toluene (75 ml); sodium hydroxide (0.50 g) was then stirred in, and the mixture was slowly heated and acetone distilled off over 3 h. Toluene was removed under reduced pressure and the crude product recrystallized from methanol; yield 1.10 g (89%), m.p. 104.1–104.5°C. ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, 3H), 1.28 (m, 14H), 1.80 (m, 2H), 3.11 (s, 1H), 4.00 (t, 2H), 6.96 (m, 2H), 7.50 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 14.81, 23.4, 26.7, 30.0, 31.3, 32.6, 68.8, 78.1, 84.4, 115.6, 117.2, 120.8, 127.1, 128.7, 133.2, 141.9, 159.8.

4.2.8. *4-Decyloxyphenyl 4-ethynylbenzoate, 7*

4-Decyloxybenzoic acid (3.11 g, 11.19 mmol) and 4-ethynylphenol (1.32 g, 11.19 mmol) were suspended in dichloromethane (60 ml) under argon. After the addition of DCC (2.54 g, 12.20 mmol) and DMAP (0.120 g, 1.12 mmol) the mixture was stirred for 24 h. The resulting white precipitate was filtered off and washed with dichloromethane (100 ml). The combined filtrate was washed with saturated $NaHCO_3$ (3×50 ml) and water (2×50 ml). The organic layer was dried over sodium sulfate, solvent was evaporated and the residue purified by column chromatography (silica gel, *n*-hexane/ethyl acetate 9/1) to give a white powder; yield 3.47 g (82%), m.p. 70.2–70.5°C. ^{1}H NMR ($CDCl_3$) δ: 0.86 (m, 3H), 1.28 (m, 14H), 1.79 (m, 2H),

3.27 (s, 1H), 3.96 (t, 2H), 6.91 (d, $J=6.8$ Hz, 2H), 7.09 (d, $J=6.8$ Hz, 2H), 7.61 (d, $J=8.4$ Hz, 2H), 8.14 (d, $J=8.4$ Hz, 2H).

4.2.9. *4-Ethynylphenyl 4-decyloxybenzoate,* ***8***

This compound was synthesized as described for **7**, using 4-decyloxyphenol and 4-ethynylbenzoic acid; yield 74% of light yellow crystals, m.p. 93.7–95.3°C. IR(film) ν_{max}/cm^{-1}(KBr): 3287, 2919, 2850, 1743, 1510, 1277, 1213.

4.2.10. *4′-Decyloxy-4-biphenylcarboxylic acid,* ***11***

A mixture of 4′-hydroxy-4-biphenylcaboxylic acid (4.5 g, 21 mmol), potassium hydroxide (2.67 g, 67.2 mmol), potassium iodide (catalytic amount) and ethanol (50 ml) was heated under reflux for 24 h. To the cooled mixture a 10% KOH solution in 70% ethanol was added and reflux was maintained for 3 h. The solid formed was filtered off and suspended in ethanol/water (100 mL, 1/1). Concentrated HCl was added to give pH 2–3 and the resultant suspension was again heated at reflux for 3 h. After cooling, the precipitate was filtered off and washed with water; recrystallization from isopropanol furnished 6.4 g (86%) of **11** as a white powder; m.p. 165–168°C.

4.2.11. *5-(4-Decyloxyphenyl)isoxazole-3-carboxylic acid,* ***12***

Compound prepared according to a previously described procedure [16]. Recrystallization from ethanol gave a white powder, m.p. 155–158°C. ^{1}H NMR (CDCI3) δ: 0.89 (t, 3H), 1.20–1.60 (m, 11H), 1.85 (q, 2H), 4.02 (t, 2H), 6.84 (s, 1H), 6.96 (d, $J=8.7$ Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H).

4.2.12. *4-(4-Nitro-phenylethylnyl)phenyl (3R,6S)-6-hydroxy-3,7-dimethyloctanoate,* ***13***

The iodide **3a** (0.408 g, 1,04 mmol) and the 1-ethynyl-4-nitro-benzene **5** (0.140 g, 0.37 mmol) were added to a nitrogen-filled flask containing Et_3N (15 ml) and THF (3 ml). The catalysts $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (1.9 mg, 0.01 mmol) and triphenylphosphine (5.2 mg, 0.02 mmol) were finally added. The mixture was stirred for 18 h at room temperature and then for 4h at reflux. The cooled mixture was diluted with diethyl ether (70 ml) and filtered through of a celite pad. The filtrate was washed successively with 10% HCl (3×25 ml), satured $NaHCO_3$ (3×25 ml) and brine, and dried over sodium sulphate. The residue from evaporation of the solvent was purified by column chromatography (silica gel, hexanes/ethyl acetate 1/1) and recrystallized twice from aqueous ethanol furnishing 0.149 g (35%) as light yellow crystals, m.p. 77.9°C, $[\alpha]_D^{20}=-2.0$(0.38, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.93 (d, $J=6.7$ Hz, 3H), 0.95 (d, $J=6.8$ Hz, 3H), 1.10 (d, $J=6.5$ Hz, 3H), 1.40 (m, 3H), 1.60 (m, 4H), 2.10 (m, 1H), 2.30 (dd, $J_{ab}=14.9$, $J_{ax}=7.9$ Hz, 1H), 2.60 (dd, $J_{ab}=14.9$, $J_{bx}=5.9$ Hz, 1H), 3.40 (m, 1H), 7.10 (d, $J=8.6$ Hz, 2H), 7.50 (d, $J=8.6$ Hz, 2H), 7.60 (d, $J=8.6$ Hz, 2H), 8,20 (d, $J=8.6$ Hz, 2H).

4.2.13. *4-(4-Nitrophenylethynyl)phenyl (3R,6S)-4-(6-hydroxy-3,7-dimethyloctonoyloxy)benzoate,* ***14***

The TBDMS acid **2** (0.205 g, 0.68 mmol), 4-bromophenyl 4-hydroxybenzoate (0.199 g, 0.68 mmol) and dry THF (5 ml) were placed in a flask fitted with a $CaCl_2$ drying tube. DCC (0.154 g, 0.75 mmol) and DMAP (0.008 g, 0.07 mmol) were added and the mixture stirred for 24 h. The white precipitate was filtered off and washed with THF (20 ml). The solvent was evaporated and the residue purificated by column chromatography (hexanes/acetate 10/2) furnishing the TBDMS ester (0.224 g, 57%) as a white solid, m.p. 34.3–34.5°C, $[\alpha]_D^{20}=+5.2$(4.4, $CHCl_3$).

Cleavage of the protective group TBDMS. The TBDMS ester (0.190 g, 0.33 mmol) was suspended in CH_3CN (5 ml); 48% HF (3 drops) was added and the solution stirred for 2 h. Chloroform (10 ml) and water (5 ml) were added and the phases separated. The organic layer was dried over sodium sulphate, and after solvent evaporation 150 mg (96%) of (3*R*,6*S*)-4-(6-hydroxy-3,7-dimethyloctanoyloxy)benzoic acid as a white solid was obtained, m.p. 76.3–77.6°C, $[\alpha]_D^{20}=-2.5$(3.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.91 (d, $J=6.7$ Hz, 3H), 0.92 (d, $J=6.7$ Hz, 3H), 1.07 (d, $J=6.5$ Hz, 3H), 1.30 (m, 4H), 1.68 (m, 1H), 2.00 (m 1H), 2.38 (dd, $J_{ab}=14.8$ Hz, $J_{ax}=8.0$ Hz, 1H), 2.51 (dd, $J_{ab}=14.8$ Hz, $J_{bx}=6.0$ Hz, 1H), 3.38 (m, 1H), 7.10 (d, $J=8.7$ Hz, 2H), 7.23(d, $J=8.9$ Hz, 2H), 7.54 (d, $J=8.9$ Hz, 2H), 8.21 (d, $J=8.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 17.0, 18.9, 30.7, 31.5, 33.1, 33.5, 41.6, 77.7, 119.1, 122.0, 123.5, 126.6, 131.6, 132.6, 149.8, 155.9, 164.1, 171.1.

Coupling between 4-bromophenyl (3*R*,6*S*)-4-(6-hydroxy-3,7-dimethyloctanoyloxy)benzoate and the acetylene **5** gave compound **14**. It was purified by column chromatography (silica gel, hexanes/ethyl acetate 8/2 then 1/1) and twice recrystallized from ethanol; yield 40%. ^{1}H NMR ($CDCl_3$) δ: 0.92 (d, $J=2.5$ Hz, 3H), 0.95 (d, $J=2.6$ Hz, 3H), 1.00 (d, $J=6.6$ Hz, 3H), 1.40 (m, 2H), 1.60 (m, 3H), 2.15 (m, 1H), 2.42 (dd, $J_{ab}=15.0$ Hz, $J_{ax}=7.9$ Hz, 1H), 2.63 (dd, $J_{ab}=15.0$ Hz, $J_{bx}=6.0$ Hz, 1H), 7.23 (m, 6H), 7.63 (m, 4H), 8.25 (d, 2H). ^{13}C NMR ($CDCl_3$) δ: 17.7, 19.6, 20.6, 31.4, 32.2, 33.8, 34.2, 42.3, 78.3, 88.6, 93.6,

112.2, 116.2, 119.2, 120.7, 122.7, 124.2, 127.3, 128.8, 132.5, 132.7, 133.3, 133.8, 155.8, 164.7, 171.7.

Compounds **15**–**19** were prepared according to the procedure described for **13**.

4.2.14. *(3R,6S)-4-[4-(6-Hydroxy-3,7-dimethyloctonoyloxy)phenylethynyl]phenyl 4-n-decyloxybenzoate, **15***

This was obtained by coupling between **3a** and the acetylene **8**. It was purified by column chromatography (silica gel, hexanes/ethyl acetate 9.5/0.5 then 8/2) and twice recrystallized from *n*-heptane; yield 55% of a white powder, $[\alpha]_D^{20} = -2.0(0.65, CHCl_3)$. ^{1}H NMR ($CDCl_3$) δ: 0.93 (m, 9H), 1.08 (d, $J = 6.5$ Hz, 3H), 1.50 (m, 21H), 2.10 (m, 1H), 2.40 (dd, $J_{ab} = 15.0$ Hz, $J_{ax} = 7.8$ Hz, 1H), 2.60 (dd, $J_{ab} = 15.0$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.35 (m, 1H), 4.05 (t, $J = 6.4$ Hz, 2H), 6.97 (d, $J = 8.7$ Hz, 2H), 7.09 (d, $J = 8.5$ Hz, 2H), 7.21 (d, $J = 8.5$ Hz, 2H), 7.56 (m, 4H), 8.14 (d, $J = 8.7$ Hz, 2H).^{13}C NMR ($CDCl_3$) δ: 17.0, 18.9, 19.9, 22.6, 25.9, 29.3, 29.5, 30.7, 31.5, 31.9, 33.4, 41.6, 68.3, 88.6, 88.7, 114.3, 120.6, 120.7, 121.2, 121.7, 121.9, 132.3, 132.7, 150.5, 150.9, 163.6, 164.6, 171.3. Anal: calcd for $C_{41}H_{52}O_6$ C 76.87, H 8.12; found C 76.23, H 8.12%.

4.2.15. *(3R,6S)-4-[4-(6-Hydroxy-3,7-dimethyloctonoyloxy)-3-nitrophenylethynyl]phenyl 4-n-decyloxybenzoate, **16***

This was obtained by coupling between **3b** and the acetylene **8**. It was purified by column chromatography (silica gel, hexanes/ethyl acetate 9.5/0.5 then 8/2) and twice recrystallized from *n*-heptane to give a light yellow powder; yield 51%, $[\alpha]_D^{20} = -1.0(0.69, CHCl_3)$. ^{1}H NMR ($CDCl_3$) δ: 0.92 (m, 9H), 1.08 (d, $J = 6.6$ Hz, 3H), 1.48 (m, 21H), 2.15 (m, 1H), 2.45 (dd, $J_{ab} = 15.0$ Hz, $J_{ax} = 7.8$ Hz, 1H), 2.7 (dd, $J_{ab} = 15.0$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.38 (m, 1H), 4.05 (t, $J = 6.5$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 8.7$ Hz, 1H), 7.24 (d, $J = 8.5$ Hz, 2H), 7.60 (d, $J = 8.5$ Hz, 2H), 7.75 (dd, $J = 8.7$, 1.9 Hz, 1H), 8.13 (d, $J = 8.8$ Hz, 2H), 8.22 (d, $J = 1.9$ Hz, 1H).^{13}C NMR ($CDCl_3$) δ: 14.2, 17.1, 19.0, 20.0, 22.8, 26.0, 29.2, 29.4, 29.6, 30.3, 31.5, 32.0, 33.0, 33.5, 41.3, 68.4, 86.3, 91.3, 114.4, 119.6, 121.1, 122.3, 125.5, 128.6, 132.4, 133.1, 137.2, 141.8, 143.6, 151.6, 163.8, 164.7, 170.6. Anal: calcd for $C_{41}H_{51}NO_8$ C 71.81, H 7.44, N 2.04; found C 71.21, H 7.45, N 1.95%.

4.2.16. *4-n-Decyloxyphenyl (3R,6S)-4-[4-(6-hydroxy-3,7-dimethyloctonoyloxy)phenylethynyl]benzoate, **17***

This was obtained by coupling between **3a** and the acetylene **7**. It was purified by column chromatography (silica gel, hexanes/ethyl acetate 8/2) and twice recrystallized from *n*-hepane; yield 65%, $[\alpha]_D^{20} = +2.0(1.17, CHCl_3)$. ^{1}H NMR ($CDCl_3$) δ: 0.91 (m, 9H), 1.08 (d, $J = 6.6$ Hz, 3H), 1.53 (m, 21H), 2.39 (dd, $J_{ab} = 14.8$ Hz, $J_{ax} = 7.9$ Hz, 1H), 2.60 (dd, $J_{ab} = 14.8$ Hz, $J_{bx} = 7.9$ Hz, 1H), 3.37 (m, 1H), 3.96 (t, $J = 6.4$ Hz, 2H), 6.92 (d, $J = 8.9$ Hz, 2H), 7.13 (d, $J = 8.9$ Hz, 4H), 7.57 (d, $J = 8.3$ Hz, 2H), 7.64 (d, $J = 8.3$ Hz, 2H), 8.17 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 14.8, 17.7, 19.6, 20.6, 23.4, 26.7, 30.0, 30.2, 31.4, 32.2, 32.6, 33.7, 34.1, 42.3, 69.1, 78.3, 89.3, 92.6, 115.8, 120.9, 122.6, 123.0, 129.1, 129.7, 130.7, 132.3, 133.6, 144.8, 151.6, 157.6, 165.7, 172.0. Anal: calcd for $C_{41}H_{52}O_6$ C 76.84, H 8.18; found C 76.71, H 8.65%.

4.2.17. *4-(4′-n-Decyloxybiphenyl-4-ylethynyl)phenyl (3R,6S)-6-Hydroxy-3,7-dimethyloctanoate, **18***

This was obtained by coupling between **3a** and the acetylene **6**. It was purified by recrystallization (twice) from acetonitrile; yield 60%, $[\alpha]_D^{20} = -4.0(1.07, CHCl_3)$. ^{1}H NMR ($CDCl_3$) δ: 0.92 (m, 9H), 1.08 (d, $J = 6.6$ Hz, 3H), 1.55 (m, 21H), 2.14 (m, 1H), 2.39 (dd, $J_{ab} = 14.8$ Hz, $J_{ax} = 7.9$ Hz, 1H), 2.60 (dd, $J_{ab} = 14.8$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.38 (m, 1H), 4.00 (t, $J = 6.5$ Hz, 2H), 6.97 (d, $J = 8.5$ Hz, 2H), 7.09 (d, $J = 8.5$ Hz, 2H), 7.54 (m, 9H or 8H after D_2O addition). Anal: calcd for $C_{40}H_{52}O_4$ C 80.50, H 8.78; found C 80.81, H 8.81%.

4.2.18. *(3R,6S)-4-(6-hydroxy-3,7-dimethyloctanoyloxy) phenyl 4-n-Decyloxybenzoate, **19***

Phenol **4** (0.20 g, 0.50 mmol) and the acid **9** (0.141 g, 0.50 mmol) were suspended in dichloromethane (10 ml) under argon. After the addition of DCC (0.113 g, 0.55 mmol) and DMAP (0.005 g, 0.05 mmol) the mixture were stirred for 24 h. The resulting white precipitate was filtered off and washed with dichloromethane (50 ml). Solvent was eliminated from the filtrates and the residue redissolved in ethyl acetate (15 ml), followed by the addition of 40% aqueous HF (0.25 ml). When TLC analysis indicated no remaining starting material, $CHCl_3$ (25 ml) and water (25 ml) were added and the phases separated. The aqueous layer was extracted twice with $CHCl_3$ and the $CHCl_3$ solution dried over sodium sulphate. The solvent was evaporated in vacuum and the crude product was purified by recrystallization (twice) from ethanol providing 0.119 g (43%) of **19** as a white powder, m.p. 86.7°C, $[\alpha]_D^{20} = -3.0(0.74, CHCl_3)$. ^{1}H NMR ($CDCl_3$) δ: 0.94 (m, 9H), 1.07 (d, $J = 6.6$ Hz, 3H), 1.60 (m, 21H), 2.11 (m, 1H), 2.36 (dd, $J_{ab} = 14.8$ Hz, $J_{ax} = 7.9$ Hz, 1H), 2.57 (dd, $J_{ab} = 14.8$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.38 (m, 1H), 4.04 (t, $J = 6.5$ Hz, 2H), 6.97 (d, $J = 8.6$ Hz, 2H), 7.19 (m, 5H), 8.23 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR ($CDCl_3$)

δ: 14.8, 17.7, 19.6, 20.6, 23.4, 26.7, 29.8, 30.0, 30.2, 31.4, 32.2, 32.6, 33.7, 34.1, 42.3, 69.0, 78.3, 115.0, 122.0, 123.1, 123.3, 133.0, 148.7, 149.1, 164.3, 165.5, 172.3. Anal: calcd for $C_{33}H_{48}O_6$ C 73.34, H 8.95; found C 72.57, H 9.54%.

Compounds **20**–**22** were prepared according to the procedure described for **19**.

4.2.19. *(3R,6S)-4-(6-Hydroxy-3,7-dimethyloctanoyloxy) phenyl 6-n-decyloxynicotinate,* ***20***

This was obtained by esterification between acid **10** and phenol **4**. It was purified by column chromatography (silica gel, hexanes/ethyl acetate 7/3) and recrystalized from heptane to give a white powder; yield 52%, m.p. 72.8°C, $[\alpha]_D^{20} = -1.0$(1.18, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.94 (m, 9H), 1.07 (d, $J = 6.6$ Hz, 3H), 1.26 (m, 14H), 1.67 (m, 7H), 2.15 (m, 1H), 2.35 (dd, $J_{ab} = 14.8$ Hz, $J_{ax} = 8.0$ Hz, 1H), 2.57 (dd, $J_{ab} = 14.8$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.43 (m, 1H), 4.00 (t, $J = 6.5$ Hz, 2H), 6.68 (d, $J = 9.6$ Hz, 1H), 7.16 (m 4H), 7.94 (dd, $J = 9.6$ Hz, $J = 2.3$ Hz, 1H), 8.32 (d, $J = 2.3$ Hz, 1H). Anal: calcd for $C_{32}H_{47}NO_6$ C 70.95, H 8.74, N 2.59; found C 70.80, H 8.60, N 2.75%.

4.2.20. *(3R,6S)-4-(6-Hydroxy-3,7-dimethyloctanoyloxy) phenyl 4′-n-decyloxybiphenyl-4-carboxylate,* ***21***

This was obtained by esterification between acid **11** and phenol **4**. It was purified by recrystallization (twice) from *n*-heptane to give a white powder; yield 50%, $[\alpha]_D^{20} = -17.0$(0.34, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.92 (m, 9H), 0.95 (d, $J = 4.0$ Hz, 3H), 1.56 (m, 21H), 1.80 (m, 1H), 2.38 (dd, $J_{ab} = 15.0$ Hz, $J_{ax} = 7.8$ Hz, 1H), 2.55 (dd, $J_{ab} = 15.0$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.38 (m, 1H), 4.02 (t, 2H), 6.95 (d, $J = 8.6$ Hz, 2H), 7.19 (m, 4H), 7.59 (d, $J = 8.6$ Hz, 2H), 7.69 (d, $J = 8.3$ Hz, 2H), 8.22 (d, $J = 8.3$ Hz, 2H). ^{1}H NMR ($CDCl_3$) δ: 14.8, 17.7, 19.6, 20.59, 23.4, 26.7, 30.0, 30.1, 30.2, 31.4, 32.2, 32.6, 33.7, 34.1, 42.3, 68.8, 78.3, 115.7, 123.2, 123.3, 127.3, 128.0, 129.1, 131.4, 132.6, 146.8, 148.8, 149.0, 160.3, 165.7, 172.2. Anal: calcd for $C_{39}H_{52}O_6$ C 76.94, H 8.50; found C 76.00, H 8.55%.

4.2.21. *(3R,6S)-4-(6-hydroxy-3,7-dimethyloctanoyloxy) phenyl 5-(4-n-decyloxyphenyl)isoxazole-3-caboxylate,* ***22***

This was obtained by esterification between acid **12** and phenol **4**. It was purified by recrystallization from *n*-heptane, column chromatography (silica gel, hexanes/ethyl acetate 5/1) and again by recrystallization from ethanol to give a slightly yellow powder; yield 35%, $[\alpha]_D^{20} = -8.0$(0.67, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.93 (m, 9H), 1.08 (d, $J = 6.6$ Hz, 3H), 1.58 (m, 21H), 2.12 (m, 1H), 2.39 (dd, $J_{ab} = 14.0$ Hz, $J_{ax} = 8.0$ Hz, 1H), 2.60 (dd, $J_{ab} = 14.8$ Hz, $J_{bx} = 6.0$ Hz, 1H), 3.38 (m, 1H), 4.02 (t, $J = 6.5$ Hz, 2H), 6.91 (s, 1H), 7.00 (d, $J = 8.3$ Hz, 2H), 7.16 (d, $J = 8.7$ Hz, 2H), 7.28 (d, $J = 8.7$ Hz, 2H), 7.75 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 14.7, 17.6, 19.5, 20.5, 23.3, 26.6, 29.8, 30.2, 31.3, 32.1, 32.5, 33.7, 34.1, 42.2, 68.9, 78.3, 99.4, 115.7, 116.7, 119.6, 122.9, 123.3, 128.3, 148.0, 149.3, 156.9, 159.1, 162.0, 172.1, 172.0. Anal: calcd for $C_{36}H_{49}NO_7$ C 71.14, H 8.13, N 2.30; found C 70.55, H 8.52, N 2.44%.

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