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Synthesis of deuterium-labelled, optically active, ferroelectric liquid crystals

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ABSTRACT

The synthesis of two selectively deuterium-labelled 4-(((*S*)-1-((*S*)-1-((*S*)-2-methylbutoxy)-1-oxopropan-2-yloxy)-1-oxopropan-2-yloxy)carbonyl)phenyl 4′-(heptyloxy)biphenyl-4-carboxylate derivatives is reported. A new preparation strategy was developed in order to optimise the yields as well as the optical purity, this property being of fundamental importance for the optical applications of this ferroelectric liquid crystal.

1. Introduction

Ferroelectric liquid crystals (FLCs)[1] are very promising materials for their technological applications,[2] which are based on high and selective responses to external electric and magnetic fields.[3] The relationship between the molecular properties and the macroscopic physical properties of these liquid crystalline materials can be successfully investigated by means of Nuclear Magnetic Resonance (NMR) methods.[4–6] In particular, Deuterium NMR (DNMR) spectroscopy applied to the study of liquid crystals has been proven to be one of the most powerful tools for the investigation of FLCs mesomorphic properties, molecular and conformational attributes.[6] The complete molecular characterisation of such systems usually necessitates the application of specific DNMR techniques to several species, selectively deuterated in different sites of the molecule. For instance, the availability of samples selectively deuterated on the aromatic core of these FLC systems provides information (i.e., local orientational ordering and molecular dynamics) concerning the rigid moiety of the FLC molecule, which better mimics the whole molecular behaviour of such anisotropic systems.[4]

The development of new and efficient synthetic routes for the labelling of liquid crystals represents an essential and basic step in the DNMR study of these systems. The rod-like ferroelectric liquid crystals, one of the ordered soft materials most studied for their technological applications, derive the property of ferroelectricity directly from molecular chirality.[1] Moreover, the high enantiomeric selectivity is crucial in the appearance of the specific ferroelectric subphases,[7] which are extremely sensitive to both chemical impurities and stereochemistry. In particular, the synthesis of ferroelectric mesogens with more than one chiral centre in one of their terminal chains is very challenging.

New series of ferroelectric liquid crystals, having a flexible core and one or more (up to three) chiral centres derived from (*S*)-lactic acid,[8] have been found to give very interesting properties. Recently, a series of mesogen lactate-derivatives have been found to give twist grain boundary (TGB) phases stable in a very wide temperature range,[9,10] which is a rare phenomenon.

In this work, we have focused our attention on the chiral ferroelectric 4-(((*S*)-1-((*S*)-1-((*S*)-2-methylbutoxy)-1-oxopropan-2-yloxy)-1-oxopropan-2-yloxy)carbonyl)phenyl 4′-(heptyloxy)-biphenyl-4-carboxylate derivative (namely **ZLL 7/***), which shows a rich polymorphism of ferroelectric phases, and the first re-entrant SmC* found in bulk liquid crystal.[11] The structural, orientational ordering and dynamic properties of this material have been characterised thanks to the availability of selectively deuterium-labelled compounds,[12–14] which were in very good agreement with those obtained by means of ^{13}C NMR spectroscopy.[15] Moreover, DNMR investigation on selectively labelled **ZLL 7/*** derivatives revealed peculiar behaviours of the ferroelectric phase in the presence of external magnetic fields of different intensities.[16,17]

2. Results and discussion

In this paper, we report the synthesis of two selectively labelled 4-(((*S*)-1-((*S*)-1-((*S*)-2-methylbutoxy)-1-oxopropan-2-yloxy)-1-oxopropan-2-yloxy)carbonyl)phenyl 4′-(heptyloxy)biphenyl-4-carboxylate derivatives (Fig. 1), namely **ZLL 7/*-phe-D2** (**1**) and **ZLL 7/*-biphe-D2** (**2**), respectively, in very good yields.

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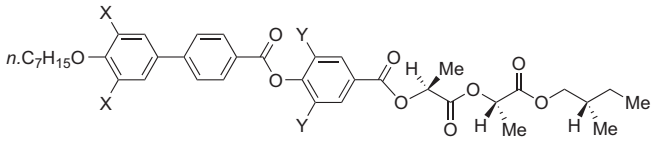


Figure 1. Molecular structure of the two isotopomers **ZLL 7/*-phe-D2** (X=H, Y=D) (**1**) and **ZLL 7/*-biphe-D2** (X=D, Y=H) (**2**).

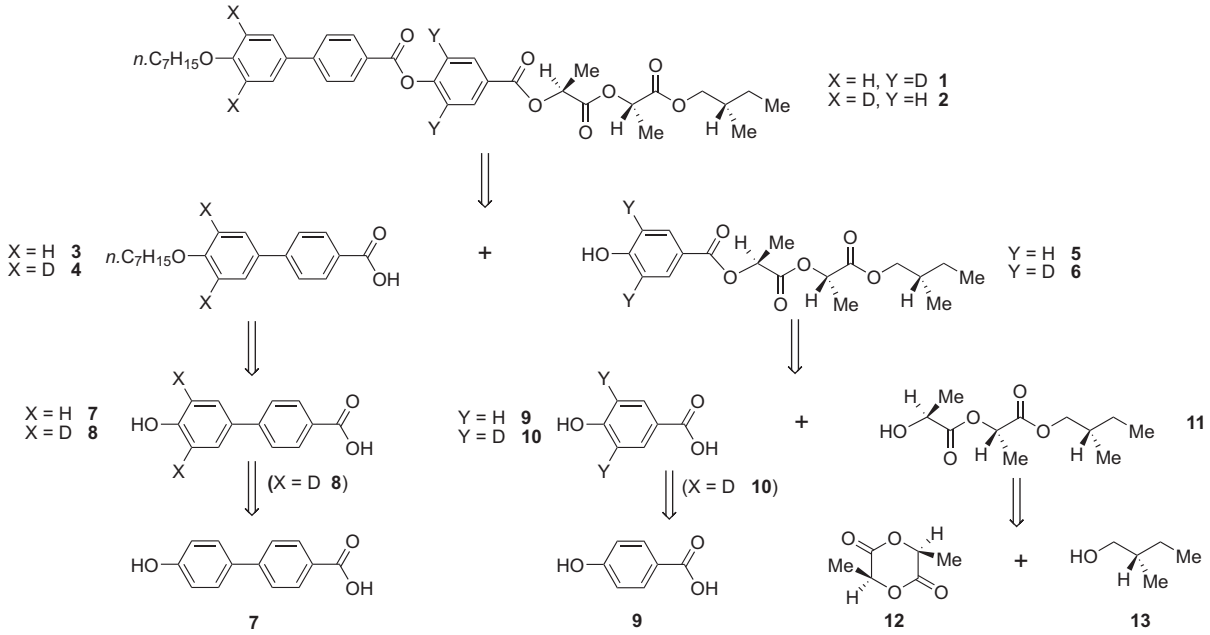
A new synthetic strategy to prepare structural analogues of **1** and **2** was identified by a disconnection approach,[16,17] reported in Scheme 1. This synthetic strategy was followed, in a convergent approach, in order to increase the chemical and isotopic yields, with respect to previously reported procedures.[18]

Table 1
Interconversion of **7** into **8** via deuteration conditions

	Reaction condition	T (°C)	t (h)	Chemical yield[a] (%)	Isotopic yield[b] (%)	Ref.
1	DCl (5%)/D_2O, DMF	130	24	87	16	19
2	DCl (5%)/D_2O, DMSO	130	24	25	12	19
3	$RhCl_3 \cdot 3H_2O$ (10%)/D_2O/DMF	130	24	80	38	20
4	DCl/D_2O (1:1)	100	24	89	51	21
5	CF_3COOD/D_2O (1:1)	165	72	95	85	19

[a] Overall yield.
[b] Evaluated by ^1H and ^2H NMR spectroscopy.

Employing a Carius tube, at elevated temperature allows us to reduce the reaction times, without the use of transition metal catalysts.



Scheme 1. Disconnection approach for the preparation of compounds **1** and **2**.

The regiocontrolled conversion of the commercially available 4-(4′-hydroxyphenyl) benzoic acid, (**7**) into the corresponding **8** (Scheme 1) carried out in acid catalysed conditions,[19] was attempted using different experimental procedures reported in the literature for similar compounds (Table 1). As shown in Table 1 (runs 1–4), even if satisfactory chemical yields (Runs 1, 3, 4) were gained, poor (12/51%) conversions into the deuterated target **8** were obtained.

Compound **8** was obtained in a nearly quantitative chemical and isotopic yield (Table 1, entry 5) when the reaction was carried out in the presence of a 1:1 mixture of deuterotrifluoroacetic acid and deuterium oxide.

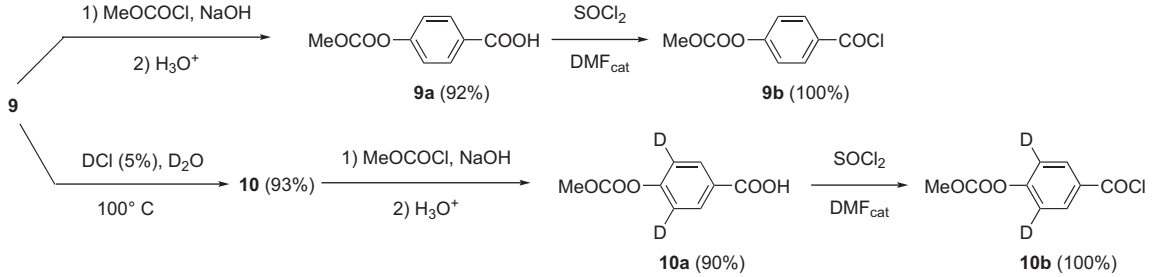
The use of CF_3COOD instead of the DCl, in D_2O, guarantees a higher solubility of the reactants.

Furthermore, this procedure could also be employed on a small scale avoiding the use of cumbersome apparatuses (bench autoclave) ensuring a better recovery of crude reaction mixture.

Compounds **3** and **4** were easily obtained starting from **7** and **8**, respectively, under the experimental condition reported for analogous compounds[18] (Scheme 1).

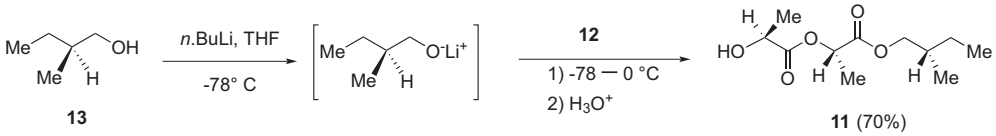
The commercially available **9** was regiochemically dideuterated, in the presence of a 5% solution of DCl in D_2O, to obtain compound **10** (93% yield) (Scheme 2) following the synthetic procedure reported in literature.[22]

Compounds **9** and **10** were successively converted in the corresponding 4-(chlorocarbonyl) phenyl methyl carbonates **9b** and **10b**, respectively (Scheme 2), according to standard procedures.[22]



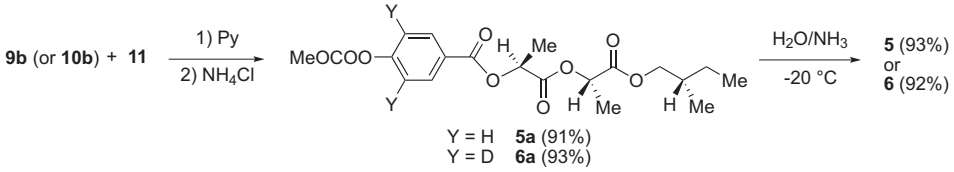
Scheme 2. Preparation of 4-methoxycarbonyloxybenzoyl chloride (**9b**) and the corresponding dideutero derivative (**10b**).

The preparation, in low yields,[8] of the known (3*S*,7*S*,10*S*)10-hydroxy-3,7-dimethyl-5,8-dioxa-6,9-undecandione (**11**) was obtained, in a 70% yield, via a more practical[22] but strongly revised[12] procedure for analogous compounds (see Experimental and Scheme 3).[16]



Scheme 3. Preparation of (3*S*,7*S*,10*S*) 10-hydroxy-3,7-dimethyl-5,8-dioxaundecan-6,9-dione (**11**).

Preparation of **5** and **6**, direct precursors to **1** and **2**, respectively, was carried out reacting **11** (Scheme 1) with the suitable aromatic acyl chloride **9b** or **10b** (Scheme 4). Compounds **5a** and **6a**, recovered in 91 and 93% yields, were converted into **5** and **6** in 93 and 92% yields, respectively, by deacetylation, performed at −20 °C, in the presence of an equimolar amount of a 30% aqueous ammonia solution (Scheme 4).



Scheme 4. Preparation of (3*S*,7*S*,10*S*) 10-(4′-hydroxy)benzoyloxy-3,7-dimethyl-5,8-dioxaundecan-6,9-dione (**5**) and the corresponding 3′,5′-dideutero derivative (**6**).

The coupling of **5** with **4** and **6** with **3**, respectively, was performed in good yields (75%) with dicyclohexylcarbodiimide (2 mol equiv), in the presence of a catalytic amount of di(methylamino)pyridine in a CH_2Cl_2 solution. The optically active *S* precursors used were ≥99% stereochemically pure and the reaction pathways employed were stereospecific. HPLC analyses by means of chiral phases of the compounds synthesised showed a satisfactory and comparable optical purity level for both isotopomers **1** and **2**.

3. Conclusion

This paper describes the first high yield deuterium labelling chiral liquid crystals preparation of the two isotopomers **1** and **2**.

These ferroelectric liquid crystals, having a most fascinating aspect in the Science of Material field, were prepared by a stereo conservative approach with high percentage of deuteration with an almost complete regioselectivity.

4. Experimental

4.1. General procedures and materials

Solvents were purified and dried by standard procedures. GLC analyses were performed on a Perkin–Elmer 8500 instrument [ZB1 column (15 m×0.25 mm), film 0.25 μm] equipped with a flame ionisation detector and a split/splitless injector, with N_2 as carrier gas. Thin layer chromatography (TLC) analyses were performed on silica gel 60 plates (Fluka) and purifications were carried out with silica gel 60 (Fluka, 230–440 mesh). HPLC was carried out with an Ecom High Performance Liquid Chromatography, using the Silica Gel Column Separon 7 μm, 150×3 mm, Tessek with a mixture of toluene and methanol as eluent. The CD (circular dichroism) data registered for compounds **1** and **2** were recorded on a spectropolarimeter Jasco J-40AS instrument, using $CHCl_3$ as solvent.

Mass spectra of **4** and **5** (acquired after derivatization procedure with BSTFA) were carried out by a GC–MS gas chromatography 6890 Agilent, equipped with an HP-5MS fused silica capillary column (stationary phase 5% diphenyl–95% dimethyl-polysiloxane, 30 m×0.25 mm) Hewlett Packard and with a deactivated silica precolumn (2 m×0.32 mm i.d., Agilent J.&W.) and coupled to an Agilent 5975 Mass Selective Detector operating in electron impact mode (EI) at 70 eV. Mass spectra of **1** and **2** were carried out by Applied BioSystems-MDS Sciex API 4000 triple quadrupole mass spectrometer (Concord, Ont., Canada), equipped with a Turbo-V Ion Spry (TIS) source and interfaced to Perkin Elmer Series 200 Micro HIGH Pressure mixing pump and a Series 200 autosampler (Perkin Elmer, Boston, MA, USA), was used for LC/MS/MS analysis.

^1H and ^{13}C NMR (300 and 75 MHz, respectively) characterisation spectra were recorded on a Varian VXR 300 spectrometer; all NMR data were obtained using $CDCl_3$ solutions, if not otherwise stated. Chemical shifts (δ) are referenced to tetramethylsilane (TMS) as internal standard. IR spectra (ν, cm^{-1}) were recorded on a Perkin Elmer FT-IR, 1760X spectrophotometer.

Compounds **7** and **12** (Fluka®) were used without further purifications. (*S*) 2-Methylbutanol (**13**) was accurately distilled to obtain a 97.6% optical purity. 4-Di(methylamino)pyridine (DMAP) and dicyclohexylcarbodiimide (DCCI) (Fluka®) were used as received. The D_2O (99.98 atom% D), and DCl 35 wt % in D_2O, 99.00 atom% D, CF_3COOD 99.5 atom% D were furnished by Aldrich®.

*4.1.1. 4-(3′,5′-Dideutero-4′-hydroxyphenyl)benzoic acid (**8**).* A Carius tube containing 4-(4′-hydroxyphenyl)benzoic acid (**7**) (1.00 g, 4.66 mmol), D_2O (4 mL) and CF_3COOD (4 mL) was warmed at 165 °C, under stirring for 96 h. The reaction mixture was filtered off at room temperature and the solid recovered, washed with a small amount of D_2O and dried at 50 °C/0.05 mmHg. The recovered **8** (0.964 g, 95% yield) having mp 298–299 °C (decomposition at 302 °C) showed a 85% deuteration degree evaluated by ^1H and ^2H NMR spectroscopy. Compound **8** showed:

IR (KBr): 3371, 2965, 1681, 1595, 1426, 1298, 1196, 1003, 830, 771, 715, 575, 490.

^1H NMR (D_2O, 200 MHz): 8.02 (d, 2H, 2-(*CH*)–*o*-COOH, *J*=8.4 Hz), 7.75 (d, 2H, 2-(*CH*)–*m*-COOH, *J*=8.4 Hz), 7.62 (s, 2-(*CH*)–*m*-OH, 2H). δ_D (H_2O, 200 MHz): 6.94 (s, 2D). ^{13}C NMR (D_2O, 50 MHz): 164.7, 153.3, 146.5, 132.2, 131.0 (s, 2C), 128.6 (s, 2C), 127.1, 126.5 (s, 2C), 116.5 (t, $2C_D$).

Anal. Calcd for: $C_{13}H_8D_2O_3$: C, 72.21; H+D, 5.59%. Found: C, 72.19; H+D, 5.53%.

*4.1.2. 4-(3′,5′-Dideutero-4′-n-heptyloxyphenyl)benzoic acid (**4**).* To a two-necked round bottom flask, containing KOH (0.767 g, 10.95 mmol), H_2O (1,5 mL) and absolute ethanol (13.8 mL) under stirring (15 min), **8** (1.00 g, 4.67 mmol) was added. The mixture was

heated at reflux for 1 h. *n*-Heptyl bromide (1.55 mL, 9.86 mmol) and KI (0.015 g) were added and the reaction mixture was heated at reflux for 24 h. After cooling to room temperature, KOH (0.383 g) was added and the mixture heated at reflux for further 12 h until complete conversion of **8** into **4** (TLC analyses). After elimination of the solvent, the crude product was poured into 200 mL of a H_2O/H_2SO_4 1:1 solution and then extracted into Et_2O/PhMe/CH_2Cl_2 (1:3:1, v/v). The organic layer, dried with anhydrous Na_2SO_4, after the removal of solvents at reduced pressure, gave **4** (1.30 g, 91% yield).

Compound **4** showed:

mp 85 °C; mesophases: 132 °C(I)–225÷227 C(II); isotropization temperature 252 °C.

IR (KBr): 3402, 3204, 2935, 2859, 2150, 1678, 1603, 1476, 1293, 1257, 1051, 835, 770, 541, 471. ^{1}H NMR ($CDCl_3$, 200 MHz): 11.55 (s, COO*H*, 1H), 7.81 (d, 2-(C*H*)–*o*-COOH, 2H, *J*=7.8 Hz), 7.64 (s, 2-(C*H*)–*m*-OR, 2H), 6.94 (d, 2H, 2-(C*H*)–*m*-COOH, *J*=7.8 Hz), 3.98 (1t, 2H, O–CH_2–, *J*=6.5 Hz), 1.72 (2t, –O–CH_2–CH_2–, 2H, J_1=6.5 Hz, J_2=7.0 Hz), 1.33–1.28 (m, –(CH_2)$_4$–CH_3, 8H), 0.85 (t, CH_3, 3H, *J*=6.4 Hz). ^{13}C NMR: 164.8, 153.4, 146.5, 132.2, 130.6 (t, 2CD), 128.2, 127.1, 126.5, 116.2, 68.9, 31.9, 29.7, 29.4, 26.0, 22.8, 14.1. Anal. Calcd for: $C_{20}H_{22}D_2O_3$: C, 76.40; H+D, 8.34%. Found: C, 76.41; H+D, 8.30%.

*4.1.3. 4-(4′-n-Heptyloxyphenyl)benzoic acid (**3**).* Compound **3** (91% yield) was obtained starting from 4-(4′-hydroxyphenyl)benzoic acid (**7**) (1.00 g, 4.66 mmol), by using the same procedure employed to prepare **4**. Compound **3** showed:

mp 85 °C; mesophases: 132 °C(I)–225÷227 °C(II); isotropization temperature 252 °C; IR (KBr): 2953, 2935, 2859, 1685, 1604, 1435, 1255, 835, 773, 551, 493.

^{1}H NMR ($CDCl_3$, 200 MHz): 11.42 (s, COO*H*, 1H), 8.05 (d, 2-(C*H*)–*o*-OR, 2H, *J*=8.2 Hz), 7.90 (d, 2-(C*H*)–*o*-COOH, 2H, *J*=7.8 Hz), 7.67 (d, 2-(C*H*)–*m*-OR, 2H, *J*=8.2 Hz), 6.82 (d, 2-(C*H*)–*m*-COOH, 2H, *J*=7.8 Hz), 3.98 (t, O–CH_2–, 2H, *J*=6.5 Hz), 1.72 (2t, –O–CH_2–CH_2–, 2H, J_1=6.5 Hz, J_2=7.0 Hz), 1.33–1.28 (m, –(CH_2)$_4$–CH_3, 8H), 0.85 (t, CH_3, 3H, *J*=6.4 Hz). ^{13}C NMR: 164.8, 153.4, 146.6, 132.1, 130.7, 128.3, 127.2, 126.6, 116.1, 68.9, 31.9, 29.7, 29.4, 26.0, 22.8, 14.1.

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74%. Found: C, 77.00; H, 7.70%.

*4.1.4. 3,5-Dideutero-4-hydroxybenzoic acid (**10**).* To a necked flask containing D_2O (165 mL) and DCl in D_2O (27.36 mL), **9** (22.16 g, 160 mmol) was added. The mixture was heated at reflux for 48 h and, after cooling, compound **10** spontaneously crystallised. The solid was filtered off and washed with D_2O (30 mL), and dried at room temperature at 20 mmHg and successively at 70 °C/0.05 mmHg. The recovered **10** (20.72 g, 93% yield) having mp 219–220 °C showed a 98% deuteration degree, evaluated by ^{1}H and ^{2}H NMR. Compound **10** showed:

IR (KBr): 3285, 2990, 1678, 1596, 1414, 1337, 1269, 1123, 768, 654, 540, 471.

^{1}H NMR (D_2O, 200 MHz): 7.87 (s, 2-(C*H*)–*o*-COOH, 2H), δ_D (H_2O, 200 MHz): 7.12 (s, 2D). ^{13}C NMR (D_2O, 200 MHz): 162.4, 158.3, 131.2, 127.2 (s, 2C), 120.6 (s, 2C), 121.1 (t, 2C*D*, J_{CD}=42 Hz).

Anal. Calcd for $C_7H_4D_2O_3$: C, 59.99; H+D, 5.75%. Found: C, 60.10; H+D, 5.70%.

*4.1.5. 3,5-Dideutero-4-methoxycarbonyloxybenzoic acid (**10a**).* In a 250 mL Erlenmeyer flask cooled at 0 °C, containing water (44 mL) and NaOH (1,75 g, 43.75 mmol), **10** (2.04 g, 14.76 mmol) was added. Methyl chloroformate (2.32 g, 24.56 mmol) was then added over 15 min to the homogeneous solution, under vigorous stirring. After 4 h, a 1:1 solution of HCl/H_2O, was added until pH=4–5. The mixture was filtered off and the recovered **10** was washed with water and then dried at reduced pressure (0.06 mmHg). Compound **10a** (2.59 g, 90% yield) showed:

mp 181–182 °C; IR (KBr): 2963, 1774, 1685, 1426, 1259, 1218, 1043, 1009, 941, 772, 648, 546, 475. ^{1}H NMR ($CDCl_3$, 200 MHz): 12.00 (s, –COOH, 1H), 8.18 (s, 2-(C*H*)–*o*-COOH, 2H), 3.95 (s, –CH_3, 3H). ^{13}C NMR: 171.6, 155.4, 153.7, 132.0, 127.2, 121.2 (t, 2C_D), 120.6 (s, 2C), 55.9. Anal. Calcd for $C_9H_6D_2O_5$: C, 54.54; H+D, 5.09%. Found: C, 54.50; H+D, 5.04%.

*4.1.6. 4-Methoxycarbonyloxybenzoic acid (**9a**).* Compound **9a** (92% yield) was obtained starting from 4-hydroxybenzoic acid (**9**) (1.04 g, 14.78 mmol), by using the same procedure employed to prepare **10a**. Compound **9a** showed:

mp 181–182 °C; IR (KBr): 2962, 1773, 1682, 1619, 1429, 1245, 1224, 1047, 1032, 945, 773, 548. ^{1}H NMR ($CDCl_3$, 200 MHz): 12.00 (s, –COOH, 1H), 8.14 (d, 2-(C*H*)–*o*-COOH, 2H, *J*=8.4 Hz), 7.29 (d, 2-(C*H*)–*o*-O–$COOCH_3$, 2H, *J*=8.4 Hz), 3.92 (s, –CH_3, 3H). ^{13}C NMR: 171.4, 155.5, 153.8, 132.2, 127.3, 121.4, 55.9.

Anal. Calcd for $C_9H_8O_5$: C, 55.10; H, 4.11%. Found: C, 55.00; H, 4.10%.

*4.1.7. (3S,7S,10S) 10-Hydroxy-3,7-dimethyl-5,8-dioxaundecan-6,9-dione (**11**).* A 100 mL three-necked flask, equipped with a magnetic stirrer, a dropping funnel and a reflux condenser, under a nitrogen atmosphere, containing (*S*) 2-methylbutanol ($[\alpha]_D^{25}$ −5.77 o.p.=97.6%) (1.009 g, 12.01 mmol) (**13**) and anhydrous THF (25 mL), was cooled to −78 °C. A 1.6 M hexane solution of BuLi (7.5 mL, 12.0 mmol) was added. The mixture was stirred for 20 min and (3*S*,6*S*)-3,6-dimethyl-1,4-dioxan-2,5-dione (**12**) (1.72 g, 11.96 mmol), dissolved in anhydrous THF (10 mL), rapidly added. The mixture, after 3 min, was siphoned into 150 mL of a 1% aqueous solution of H_2SO_4 and 100 mL of Et_2O, cooled to 0 °C. The organic layer was washed with an aqueous solution of saturated NaCl and dried over anhydrous Na_2SO_4. After elimination of the solvent, the product was purified by an accurate distillation. Chemically pure **11** (1.95 g, 70% yield) showed:

bp 110 °C/2 mmHg; $[\alpha]_D^{20}$ −41.7 (neat); IR (neat): 3477, 2965, 2938, 2879, 1743, 1458, 1380, 1198, 1132, 1098, 1049, 975, 866, 762. ^{1}H NMR: 5.15 (q, –C*H*–OR, 1H, *J*=7.0 Hz), 4.35 (q, –C*H*–OH, 1H, *J*=6.9 Hz), 4.02 (2dd, –CH_2–O–, 2H, J_1=J_2=6.2 Hz), 2.80 (s, –OH, 1H), 1.60 (m, CH_3–C*H*–(CH_2)$_2$–, 1H), 1.52 (d, CH_3–CH–OH, 3H, *J*=7.0 Hz), 1.48 (d, RO–CH–CH_3, 3H, *J*=7.0 Hz), 1.42–1.24 (m, CH_3–CH_2–CH–, 2H), 0.91 (d, CH_3–CH–(CH_2)$_2$–, 3H, *J*=6.6 Hz), 0.88 (t, CH_3–CH_2–, 3H, *J*=6.4 Hz). ^{13}C NMR: 170.6, 170.3, 70.3, 65.7, 65.2, 55.8, 34.3, 26.1, 17.2, 16.5, 11.4.

Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68%. Found: C, 56.77; H, 8.63%.

*4.1.8. (3S,7S,10S) 10-(3′,5′-Dideutero-4′-methoxycarbonyloxy)benzoyloxy-3,7-dimethyl-5,8-dioxaundecan-6,9-dione (**6a**).* A 250 mL three-necked round bottom flask, equipped with a magnetic stirrer, a dropping funnel and a reflux condenser, under a nitrogen atmosphere, containing **11** (3.32 g, 14.31 mmol), pyridine (6 mL) and CH_2Cl_2 (15 mL) was cooled to 0 °C. A solution of 3,5-dideutero-4-methoxycarbonyloxybenzoyl chloride (**10b**)[23] (2.79 g, 12.92 mmol) in CH_2Cl_2 (25 mL) was slowly added and after stirring (24 h), the mixture was hydrolysed with a 5% solution of HCl (100 mL), extracted into CH_2Cl_2 and dried with anhydrous Na_2SO_4. The crude oil, diluted in CH_2Cl_2 was purified by filtration on a short silica gel column eluting with the same solvent (100 mL). Pure **6a** (4.95 g, 93% yield) showed:

IR (KBr): 2963, 2677, 1760, 1686, 1606, 1510, 1437, 1262, 941, 774, 550, 475.

^{1}H NMR ($CDCl_3$, 200 MHz): 8.17 (s, 2-(C*H*)–*o*-COOR, 2H), 5.38 (q, –C*H*–OCOCH–, 1H, *J*=6.9 Hz), 5.17 (q, –C*H*–OCOAr, 1H, *J*=7.0 Hz), 4.02 (2dd, –CH_2–O–, 2H, J_1=J_2=6.2 Hz), 3.95 (s, –CH_3, 3H), 1.60 (m, CH_3–C*H*–(CH_2)$_2$–, 1H), 1.52 (d, CH_3–CH–OCO–Ar, 3H, *J*=7.0 Hz), 1.48 (d, R–COO–CH–CH_3, 3H, *J*=6.9 Hz), 1.42–1.24 (m, CH_3–CH_2–CH–, 2H), 0.91 (d, CH_3–CH–(CH_2)$_2$–, 3H, *J*=6.6 Hz), 0.88 (t, CH_3–CH–-, 3H, *J*=6.4 Hz). ^{13}C NMR: 170.6, 170.3, 165.3, 153.8, 131.9, 127.4, 120.6 (t, 2C_D, J_{CD}=43 Hz), 70.3, 69.6, 65.3, 55.8, 34.3, 26.1, 17.2, 16.5, 11.4.

Anal. Calcd for $C_{20}H_{24}D_2O_9$: C, 58.24; H+D, 6.84%. Found: C, 58.20; H+D, 6.86%.

*4.1.9. (3S,7S,10S) 10-(4′-Methoxycarbonyloxy)benzoyloxy-3,7-dimethyl-5,8-dioxaundecan-6,9-dione (**5a**).* Compound **5a** (91% yield), starting from compounds **9b**[24] and **11**, was obtained by using the same procedure employed to prepare **6a**. Compound **5a** showed:

IR (KBr): 2961, 2676, 1775, 1759, 1687, 1607, 1509, 1435, 1261, 941, 774, 550.

^{1}H NMR ($CDCl_3$, 200 MHz): 8.13 (s, 2-(C*H*)–*o*-O-$COOCH_3$, 2H, *J*=8.2 Hz), 7.24 (d, 2-(C*H*)–*o*-COOR, 2H, *J*=8.2 Hz), 5.38 (q, –C*H*–OCOCH–, 1H, *J*=6.9 Hz), 5.15 (q, –C*H*–OCOAr, 1H, *J*=7.0 Hz), 4.02 (2dd, $–CH_2–O–$, 2H, J_1=J_2=6.2 Hz), 3.95 (s, –O–$COOCH_3$, 3H), 1.60 (m, $CH_3–CH–(CH_2)_2–$, 1H), 1.52 (d, CH_3–CH–OCO–Ar, 3H, *J*=7.0 Hz), 1.48 (d, R–COO–CH–CH_3, 3H, *J*=6.9 Hz), 1.42–1.24 (m, $CH_3–CH_2–CH$, 2H), 0.91 (d, $CH_3–CH–(CH_2)_2–$, 3H, *J*=6.6 Hz), 0.88 (t, $CH_3–CH_2–$, 3H, *J*=6.4 Hz). ^{13}C NMR: 170.6, 170.3, 165.4, 153.8, 131.6, 127.2, 120.4, 70.3, 69.5, 65.2, 55.8, 34.3, 26.1, 17.3, 16.5, 11.6.

Anal. Calcd for $C_{20}H_{26}O_9$: C, 58.53; H+D, 6.39%. Found: C, 58.58; H+D, 6.30%.

*4.1.10. (3S,7S,10S) 10-(3′,5′-Dideutero-4′-hydroxy)benzoyloxy-3,7-dimethyl-5,8-dioxaunde can-6,9-dione (**6**).* A 100 mL Erlenmeyer flask, containing EtOH (30 mL), H_2O (30 mL) and **6a** (1.00 g, 24.3 mmol), was cooled at −20 °C. An equimolar amount of 30% aqueous ammonia (0.25 mL) was added to the reaction mixture and after stirring at room temperature for 18 h, TLC analysis showed the complete conversion of **6a** into **6**. Solvents were removed under reduced pressure and chemically pure **6** (GLC) (0.79 g, 92% yield) was recovered. Compound showed **6**:

IR (neat): 2961, 2878, 1732, 1597, 1496, 1275, 1089, 1056, 928, 862, 772, 625, 476.

^{1}H NMR ($CDCl_3$, 200 MHz): 10.26 (s, –OH, 1H), 7.05 (s, 2-(C*H*)–*m*-OH, 2H), 5.28 (q, –C*H*–OCOCH–, 1H, *J*=6.8 Hz), 5.22 (q, –C*H*–OCOAr, 1H, *J*=7.1 Hz), 4.02 (2dd, $–OCH_2–$, 2H, J_1=J_2=6.3 Hz), 1.61 (m, $CH_3–CH–(CH_2)_2–$, 1H), 1.53 (d, CH_3–CH–OCO–Ar, 3H, *J*=7.1 Hz), 1.48 (d, R–COO–CH–CH_3, 3H, *J*=6.8 Hz), 1.42–1.24 (m, $CH_3–CH_2–CH$–2H), 0.91 (d, $CH_3–CH–(CH_2)_2$, 3H, *J*=6.7 Hz), 0.89 (t, $CH_3–CH_2–$, 3H, *J*=6.4 Hz). ^{13}C NMR: 170.4, 169.7, 155.3, 132.6, 131.9, 127.4, 121.8 (t, $2C_D$, *o*-OH), 70.3, 69.5, 65.3, 34.6, 26.2, 17.3, 16.7, 11.8. *m*/*z* (EI) 426 [M^+−1, +73, (17)], 341 (4), 267 (6),195 (100), 73 (8). Anal. Calcd for $C_{18}H_{22}D_2O_7$: C, 61.00; H+D, 7.40%. Found: C, 61.10; H+D, 7.36%.

*4.1.11. (3S,7S,10S) 10-(4′-Hydroxy)benzoyloxy-3,7-dimethyl-5,8-dioxaundecan-6,9-dione (**5**).* Compound **5** (93% yield) was obtained from (3*S*,7*S*,10*S*) 10-(4′-methoxycarbonyloxy)benzoyloxy-3,7-dimethyl-5,8-dioxaundecan-6,9-dione **5a** (1.01 g, 24.30 mmol) according to the same experimental procedure previously described for compound **6**. Compound **5** showed:

IR (neat): 2965, 2878, 1718, 1609, 1593, 1515, 1454, 1277, 1100, 852, 774, 625, 510.

^{1}H NMR: 10.25 (s, OH, 1H), 7.98 (d, 2-(C*H*)–*o*-OH, 2H, *J*=8.2 Hz), 6.95 (d, 2-(C*H*)–*o*-COOR, 2H, *J*=8.2 Hz), 5.24 (q, –C*H*–OCOCH–, 1H, *J*=6.9 Hz), 5.15 (q, –C*H*–OCOAr, 1H, *J*=7.0 Hz), 4.02 (2dd, $–CH_2–O–$, 2H, J_1=J_2=6.2 Hz), 1.60 (m, $CH_3–CH–(CH_2)_2–$, 1H), 1.52 (d, CH_3–CH–OCO–Ar, 3H, *J*=7.0 Hz), 1.48 (d, R–COO–CH–CH_3, 3H, *J*=6.9 Hz), 1.42–1.24 (m, $CH_3–CH_2–CH$, 2H), 0.91 (d, $CH_3–CH–(CH_2)_2–$, 3H, *J*=6.6 Hz), 0.88 (t, $CH_3–CH_2–$, 3H, *J*=6.4 Hz). ^{13}C NMR: 170.3, 169.5, 155.3, 132.3, 131.8, 127.4, 121.3, 70.3, 69.5, 65.2, 34.3, 26.1, 17.2, 16.5, 11.4. *m*/*z* (EI) 424 [M^+−1, +73, (17)], 339 (5), 265 (6),193 (100), 73 (6). Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86%. Found: C, 61.36; H, 6.90%.

*4.1.12. 2,6-Dideutero-4-(((S)-1-((S)-1-((S)-2-methylbutoxy)-1-oxopropan-2-yloxy)-1-oxopropan-2-yloxy)carbonyl)phenyl 4′-(heptyloxy)biphenyl-4-carboxylate (**1**).* A mixture of **3** (0.75 g, 23.92 mmol), **6** (0.82 g, 23.96 mmol), DMAP (0.29 g, 2.38 mmol) and CH_2Cl_2 (50 mL) were placed, under N_2, into a two-necked flask equipped with a magnetic stirrer and a reflux condenser. The mixture was stirred for 10 min and then DCCI (0.96 g, 46.28 mmol) was added. After 2 h no more traces of **3** and **6** were detected (TLC). After filtration on silica gel and elimination of the solvent by reduced pressure, chemically pure (HPLC, NMR) **1** (1.20 g, 75% yield) was recovered. Compound **1** showed:

$[\alpha]_D^{26.4}$ −4.6 (*c* 0.01085, $CHCl_3$).

CD spectra were recorded and showed a positive absorption with a *g* factor (concentration 0.01674 mol/L in $CHCl_3$) of:

$g(310\ nm)=2.35\times10^{-6}$; $g(285\ nm)=2.66\times10^{-6}$.

IR (KBr): 2935, 2856, 1736, 1603, 1529, 1506, 1414, 1298, 1269, 1195, 1124, 1075, 829, 766, 691, 505. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.31 (d, 2-(C*H*)–*o*-OR, 2H, *J*=7.9 Hz), 7.80 (d, 2-(C*H*)–*o*-COOAr, 2H, *J*=6.4 Hz), 7.67 (d, 2-(C*H*)–*m*-OR, 2H, *J*=7.9 Hz), 7.01 (s, 2-(CH)–*o*-COOR, 2H), 6.94 (d, 2-(CH)–*m*-COOAr, 2H, *J*=6.4 Hz), 5.29 (q, –C*H*–OCOCH–, 1H, *J*=6.9 Hz), 5.15 (q, –C*H*–OCOAr, 1H, *J*=7.0 Hz), 4.02 (2dd, $–OCH_2–$2H, J_1=J_2=6.2 Hz), 3.98 (t, ArO–$CH_2–$, 2H, *J*=6.5 Hz), 1.72 (2t, $–O–CH_2–CH_2–$, 2H, J_1=6.5 Hz, J_2=7.0 Hz), 1.69 (m, 4H), 1.55 (d, CH_3–CH–OCO–Ar, 3H, *J*=6.9 Hz), 1.54–1.23 (m, 10H), 0.91 (d, $CH_3–CH–(CH_2)_2$, 3H, *J*=6.6 Hz), 0.88 (t, $CH_3–CH_2–CH–$, $CH_3–CH_2$, $CH_2–$, 6H, *J*=6.4 Hz). ^{13}C NMR: 170.8, 170.6, 165.4, 164.7, 159.9, 155.3, 146.6, 131.2, 131.1, 128.7, 127.2, 127.2, 126.5, 121.4 (t, $2C_D$ *o*-OH), 115.2, 70.3, 69.5, 65.3, 68.4, 34.3, 32.1, 29.5, 29.3, 26.2, 26.1, 22.5, 17.2, 16.5, 14.3, 11.4. *m*/*z* (TIS) 648 [M^+, (16)], 647 [M^+−1, (92)], 646 [M^+−2, (100)], 414 (7), 296 (27), 218 (6), 89 (7). Anal. Calcd for $C_{38}H_{44}D_2O_9$: C, 70.35; H+D, 7.46%. Found: C, 70.40; H+D, 7.32%.

*4.1.13. 4-(((S)-1-((S)-1-((S)-2-methylbutoxy)-1-oxopropan-2-yloxy)-1-oxopropan-2-yloxy)carbonyl)phenyl 3′,5′-dideutero-4′-(heptyloxy)-biphenyl-4-carboxylate (**2**).* Compound **2** (77% yield) was obtained from compounds (3*S*,7*S*,10*S*) 10-(4′-hydroxy)benzoyloxy-3,7-dimethyl-5,8-dioxaundecan-6,9-dione (**5**) (0.88 g, 23.96 mmol) and 4-(3′,5′-dideutero-4′-*n*-heptyloxyphenyl)benzoic acid (**4**) (0.75 g, 23.92 mmol), by using the same procedure employed to prepare **1**. The compound, chemically pure (HPLC, NMR), **2** showed:

$[\alpha]_D^{30}$ −5.3 (*c* 0.01045, $CHCl_3$).

CD spectra were recorded and showed a positive absorption with a *g* factor (concentration 0.01612 mol/L in $CHCl_3$) of:

$g(310\ nm)=5.12\times10^{-5}$; $g(285\ nm)=5.54\times10^{-5}$.

IR (KBr): 2934, 2855, 1737, 1603, 1529, 1507, 1415, 1269, 1194, 1125, 1074, 829, 766, 691, 504. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.31 (d, 2-(C*H*)–*o*-OCOAr, 2H, *J*=7.8 Hz), 7.78 (d, 2-(C*H*)–*o*-COOR, 2H, *J*=7.8 Hz), 7.57 (d, 2-(C*H*)–*o*-COOAr, 2H, *J*=6.3 Hz), 7.43 (s, 2-(CH)–*m*-OR, 2H), 6.95 (d, 2-(CH)–*m*-COOAr, 2H, *J*=6.3 Hz), 5.32 (q, –C*H*–OCOCH–, 1H, *J*=6.9 Hz), 5.16 (q, –C*H*–OCOAr, 1H, *J*=7.1 Hz), 4.02 (2dd, $–OCH_2–$, 2H, J_1=J_2=6.2 Hz), 3.98 (t, ArO–$CH_2–$, 2H, *J*=6.2 Hz), 1.72 (2t, $–O–CH_2–CH_2–$, 2H, J_1=6.5 Hz, J_2=7.0 Hz), 1.69 (m, 4H), 1.55 (d, CH_3–CH–OCO–Ar, 3H, *J*=6.9 Hz), 1.54–1.23 (m, 10H), 0.91 (d, $CH_3–CH–(CH_2)_2$, 3H, *J*=6.6 Hz), 0.88 (t, $CH_3–CH_2–CH–$, $CH_3–CH_2$, $CH_2–$, 6H, *J*=6.4 Hz). ^{13}C NMR: 170.6, 170.4, 165.4, 164.7, 159.9, 155.3, 146.5, 131.8, 131.0, 128.6, 127.2, 127.1, 126.9, 122.1 (t, $2C_D$ *o*-OH), 115.2, 70.2, 69.4, 65.2, 68.3, 34.3, 32.2, 29.5, 29.3, 26.4, 26.1, 22.8, 17.1, 16.5, 14.3, 11.4. *m*/*z* (TIS) 648 [M^+, (16)], 647 [M^+−1, (92)], 646 [M^+−2, (100)], 414 (7), 296 (27), 218 (6), 89 (7). Anal. Calcd for $C_{38}H_{44}D_2O_9$: C, 70.35; H+D, 7.46%. Found: C, 70.33; H+D, 7.50%.

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23. Previously prepared according to the usual procedure starting from **10a** (2.56 g, 12.92 mmol), freshly distilled thionyl chloride (25 mL, 0.34 mol) and dimethylformamide (DMF) (300 μL).
24. Previously prepared according to the usual procedure starting from **9a** (2.57 g, 12.97 mmol), freshly distilled thionyl chloride (25 mL, 0.34 mol) and dimethylformamide (DMF) (300 μL).