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Investigation of SmI_2-mediated cyclisation of δ-iodo-α,β-unsaturated esters by deuterium 2D NMR in oriented solvents

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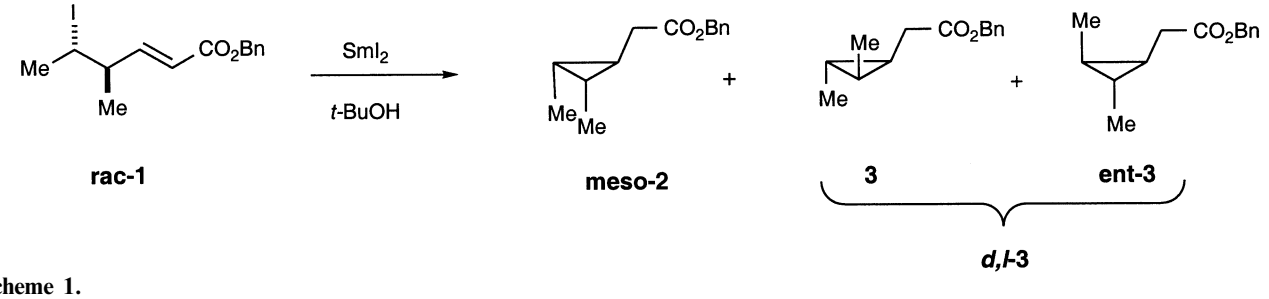
Abstract—We have investigated the mechanism of the SmI_2-mediated cyclisation of δ-iodo-α,β-unsaturated esters using proton-decoupled deuterium 1D and 2D NMR in weakly ordered polypeptide liquid crystal solvents. Analysis of the spectroscopic results demonstrates that the cyclisation reaction takes place with concomitant and extensive racemisation at the γ-position and the reason for this racemisation is discussed. We also report an efficient 2D NMR strategy for distinguishing *meso*- from *d*- and *l*-diastereoisomers based on the introduction of a CD_2 probe in the molecules to be studied. This approach allows determination of the diastereoisomeric and enantiomeric composition of a mixture.

1. Introduction

It was recently reported that δ-iodo- and δ-bromo-α,β-unsaturated esters readily cyclise, according to a 3-*exo*-trig process, to cyclopropane compounds in the presence of samarium diiodide and a proton source.[1] This reaction was shown to be highly tolerant of various substitution patterns in the starting homoallylic halides. However, only racemic compounds were used in this study and the important question—both from a synthetic point of view and for a better understanding of the reaction mechanism—as to whether a homochiral γ-substituted substrate would retain its enantiomeric purity during the cyclisation process has not been addressed. We present herein our investigations using deuterium 1D and 2D NMR spectroscopy in weakly ordered polypeptide liquid crystals as an analytical tool. In the course of this investigation, we have developed an interesting and efficient method for distinguishing *meso*- from *d,l* stereoisomers, and consequently for safely assessing diastereoisomeric and enantiomeric purity based on proton-decoupled deuterium (^2H-{^1H}) 2D NMR in chiral and achiral anisotropic solvents.

2. Results and discussion

We chose the '*anti*'-(*E*)-benzyl 5-iodo-4-methylhex-2-enoate **1** as a model substrate for cyclisation. Its cyclisation has already been studied in racemic form and it was reported that the ratio of *meso* and *d,l*-cyclopropane products **2** and **3** was around 0.5 (Scheme 1).[1]



Scheme 1.

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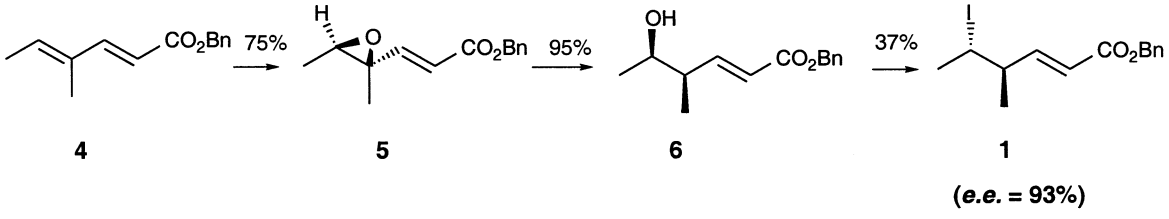
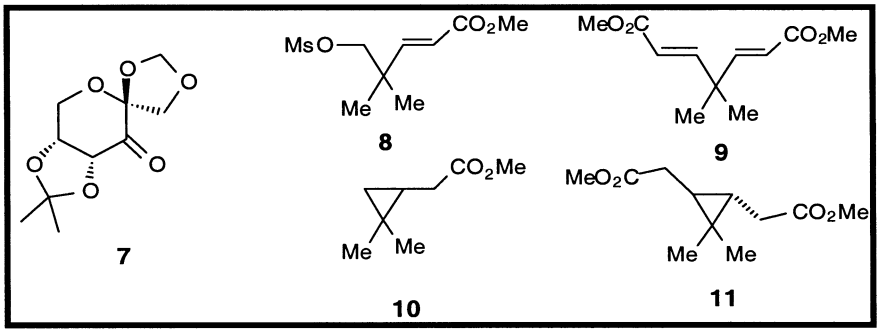
Enantiomerically enriched benzyl (4*R*,5*S*)-5-iodo-4-methylhex-(2*E*)-enoate was synthesised according to Scheme 2. From diene **4**, prepared by Wittig olefination of tiglic aldehyde with carbobenzyloxymethylene phosphorane, (*R*,*R*)-2-[(*E*)-(benzyloxycarbonyl)vinyl]-2,3-dimethyloxirane **5** was obtained in 95% yield and high enantiomeric purity (94% e.e., as determined by HPLC) by chemoselective and enantioselective epoxidation with oxone in the presence of the fructose-derived ketone **7** according to the procedure of Shi and co-workers.[2] Regio- and stereoselective reductive ring opening of epoxide **5** with the ternary system[3] Me_2NH–BH_3/AcOH/$Pd(PPh_3)_4$ (5 mol%) gave homoallylic alcohol **6** without any loss of enantiomeric purity (e.e. = 93% as determined by HPLC). Compound **6** was then converted into enantioenriched (4*R*,5*S*)-5-iodo-4-methylhex-(2*E*)-enoic acid benzyl ester **1** by reaction with I_2/PPh_3/imidazole. The rather low yield obtained in this last step is the result of competitive elimination leading back to diene **4**. Racemic **1** was obtained in a similar way except that the racemic epoxide intermediate was prepared in 95% yield by chemoselective monoepoxidation of **4** with one equivalent of MCPBA. The two enantiomers of the iodo compound could not be separated by chiral HPLC, but the fact that benzyl 5-iodo-4-methylhex-(2*E*)-enoate *was* obtained in diastereoisomerically pure form (within ^{1}H NMR detection limits, d.e. >95%) in the racemic as well as in the enantioenriched series shows that the conversion of alcohol to iodide takes place without any appreciable epimerisation, presumably with clean inversion at the hydroxyl bearing carbon atom.

The cyclisation of **1**, either in racemic or enantiomerically enriched form, was achieved by exposure to samarium diiodide (2.5 equiv.) in the presence of *tert*-butanol (3 equiv.) in THF (no HMPA added) at room temperature for several hours. The reaction was then quenched by adding dilute aqueous HCl and subjected to standard extractive workup. ^{1}H NMR analysis of the crude products confirmed the already observed[1] total conversion of benzyl 5-iodo-4-methylhex-(2*E*)-enoate to a ca. 1:2 mixture of *meso*-**2** and *d*,*l*-**3** cyclopropanes (based on integration of the hydrogen signal next to the carbobenzyloxy group in the isotropic proton spectrum).

If spectral diastereodifferentiation based on the proton resonance anisochrony was obtained in this example, the determination of the enantiomeric composition of **3** was not possible. Note that NMR diastereodifferentiation is not[4] always observed in isotropic solvents even when operating at very high magnetic fields. Experimentally, neither chiral chromatographic approaches nor conventional isotropic NMR methods involving the use of chiral shift reagents or chiral solvents provided successful results[4,5] because **3** does not form diastereoisomeric complexes or short-lived diastereoisomeric adducts in situ which give distinct NMR signals on the basis of an isotropic chemical shift difference. Chemical derivatisation of the molecule could be envisaged, but NMR results are not always guaranteed.

To circumvent these problems we have explored another analytical strategy involving NMR in a weakly ordered chiral polypeptide solvent.[6] In this new approach, the enantiomeric discrimination observed in NMR spectra is due to selective orientational ordering of two enantiomers within the oriented phase. This effect depends both on geometrical and electrostatic factors. Consequently, whatever their chemical functionalities and their topology, two enantiomers will





Scheme 2.

always have different orientational ordering in a chiral liquid crystal (CLC). In almost all cases, this differential molecular ordering effect yields a doubling of the spectra (one for each enantiomer) compared to that observed with an achiral oriented solvent. This fact is an obvious advantage compared to classical NMR methods, which involve chiral solvents or chiral lanthanide chemical shift reagents, both approaches requiring specific chemical functions in the analyte. Notably, this selective ordering enables discrimination between two diastereoisomers that have different molecular 'shapes'.[7] Thus, we have shown that this approach is a powerful and flexible tool, generally providing better spectroscopic results than those achieved using routine techniques.

Earlier investigations have shown that proton-decoupled deuterium (^{2}H-{^{1}H}) NMR of isotopically labelled molecules was a very efficient means of enantiomeric analysis, mainly for two reasons: firstly, the determination of the enantiomeric or diastereoisomeric composition by peak integration is easy and very accurate even for highly enantioenriched mixtures, because we benefit from an abundant spin. Secondly, the ^{2}H-{^{1}H} spectrum of two monodeuterated enantiomers oriented differently in a chiral anisotropic environment are particularly simple to analyse because they usually consist of two independent quadrupolar doublets (spin $I=1$) centred on the corresponding $\delta^{aniso}_{^2H}$ which is very close to $\delta^{iso}_{^1H}$. The separation between the two components is referred to as the quadrupolar splitting and noted $\Delta\nu_Q$ (see Fig. 1).[6,8]

To introduce deuterons into compounds *meso*-**2** and *d,l*-**3** in one step without racemisation, the crude mixture of cyclopropane esters was directly reduced with lithium aluminium deuteride ($LiAlD_4$) to yield a mixture of cyclopropane dideuteroalcohols (Scheme 3). This first mixture is referred to as mixture **I**. It could be argued here that the synthesis of monodeuterated derivatives could simplify subsequent analysis of the ^{2}H-{^{1}H} NMR spectrum in the oriented phase. However, this remark is partly false because the monodeuteration of compounds would be chemically more delicate and would not permit assignment of *meso*- from *d,l*-diastereoisomers in the mixture as we will see below.

The same reasons also preclude the investigation of the mixture using natural abundance deuterium NMR,[8] even if this approach was *a priori* much more attractive because no further step for introducing a deuterium probe was required.

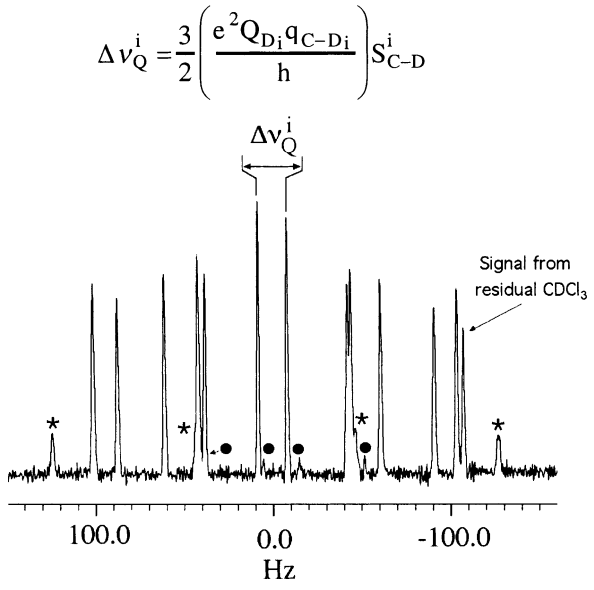
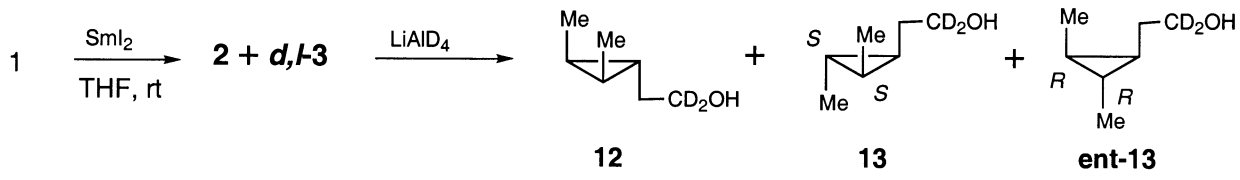


Figure 1. 61.4 MHz proton-decoupled deuterium 1D spectrum of the mixture **I** dissolved in the PBLG/$CHCl_3$ phase (sample 1) at 293 K. Here the *d,l* mixture is racemic. A Gaussian filtering (GB = 50%, LB = −2.5 Hz) was applied to enhance the spectral resolution. $\Delta\nu^i_Q$ is the quadrupolar splitting for corresponding doublet. In the formula given at the top of the figure, Q_{Di} is the deuterium quadrupole moment, eq_{C-Di} is the electric field gradient (EFG) along the C–D_i bond and S_{C-Di} is the order parameter of the C–D_i bond.

Fig. 1a shows the ^{2}H-{^{1}H} spectrum of the mixture **I** issued from cyclisation of racemic **1** and containing the isotopically labelled *meso*-isomer and *d,l*-enantiomers dissolved in the PBLG/$CHCl_3$ phase (sample 1). Disregarding the signal (the most shielded component) from residual $CDCl_3$, twelve intense peaks, corresponding to six quadrupolar doublets approximately centred on the same chemical shift, are visible (note that some weak deuterated impurity peaks are also observed in the spectrum, but do not interfere with the other doublets).

To decipher this spectrum, we must keep three points in mind: firstly, three distinct dideuterated species, a single *meso*-isomer and two enantiomers, exist in the mixture (see Fig. 2); secondly, two deuterons of a CD_2 group in a chiral molecule are diastereotopic, and are thus spectroscopically non-equivalent, as in isotropic solvents. Consequently, we expect to observe two pairs of quadrupolar doublets (if the chiral discrimination of the derivatives **13** and ent-**13** oriented in a CLC occurs), each of them centred on the chemical shift of the corresponding diastereotopic deuteron;[8,9] thirdly, enantiotopic nuclei in C_s symmetry molecules, such as the



Scheme 3.

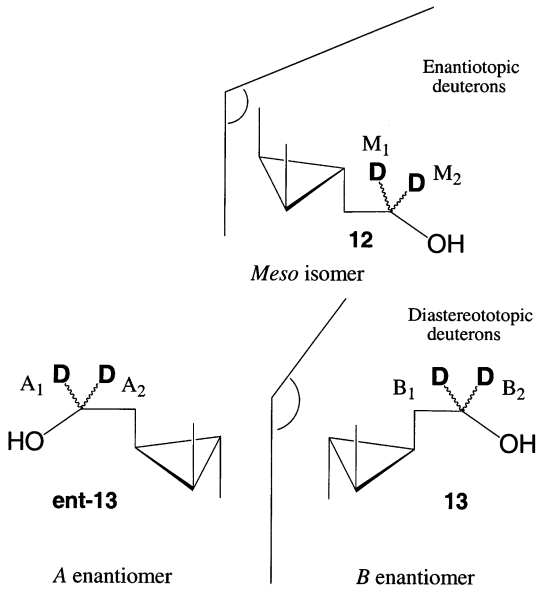


Figure 2. *meso* (**12**) and active forms (**13** and ent-**13**) of isotopically labelled cyclopropane derivatives studied. The enantiotopic deuterons in the *meso* compound are referred to as M_1 and M_2. The diastereotopic deuterons in chiral compounds are referred to as A_1 and A_2 in the A enantiomer, and B_1 and B_2 in the B enantiomer. In this scheme, deuterons A_1 (A_2) and B_2 (B_1) are mirror images. Note that the numbering A,B and 1,2 is chosen arbitrarily.

pro-R/*pro-S* deuterons in the *meso*-compound **12**, are also magnetically non-equivalent in a CLC (see Fig. 2).[10] Consequently, two distinct quadrupolar doublets (one for each enantiotopic deuteron) centred on the same chemical shift are expected to be observed if the spectral separation is large enough. In conclusion, in a CLC, three pairs of quadrupolar doublets should be visible if no overlap occurs fortuitously. Although the diastereotopic and enantiotopic deuterons are theoretically anisochronous, in this example, the chemical shift differences between them are too weak (<3 Hz) to provide an unambiguous assignment of the various quadrupolar splittings.

The very small differences in chemical shifts for the three stereoisomers yield a symmetrical ^{2}H-{^{1}H} spectrum, from which the identification of the two components for each quadrupolar splitting is rather trivial, but the distinction between the *meso*- and *d,l*-diastereoisomers is not.

The relative intensity of each pair of doublets (which depends hopefully on the e.e. and d.e. of the mixture) can afford information to allow the doublet assignment. For instance, if the mixture is only diastereoisomerically enriched in *meso* compound (d.e. >33%), four quadrupolar doublets over six possible of weak and equal intensity (associated with the *d,l* enantiomers) will be visible in the spectrum. In contrast, two small doublets of weak and equal intensity (associated with the *meso* compound) will be observed when the mixture is only diastereoisomerically enriched in *d,l* species (d.e. >66%). In both cases, the *meso*/*d,l* assignment of doublets as well as the d.e. measurement are possible. Other spectral situations exist but they are not so informative compared with the previous ones. Thus the presence of three pairs of quadrupolar doublets with variable area on the ^{2}H-{^{1}H} spectrum implies that d.e. and e.e. are both not null, but neither the assignment of doublets nor the composition of the mixture are possible. When six doublets of equal area are observed, we can deduce that the e.e. is null while the *meso*/*d,l* ratio is 0.5. However, pairing doublets can be extremely difficult if the ^{2}H chemical shift of the *meso* and *d,l* isomers is too small, and in all cases the assignment of the three pairs of doublets to the corresponding isomers is precluded from analysis of the 1D spectrum.

This last situation is observed in the ^{2}H-{^{1}H} spectrum shown in Fig. 1. This result is therefore consistent with the fact that the cyclisation of *rac*-**1** leads to a 1:2 mixture of cyclopropanes **2** and **3** as already estimated using isotropic NMR, but no further information can be extracted from the spectrum. The differences in peak intensity, which could theoretically be expected to be of the same intensity, mainly arises from non resolved ^{2}H–^{2}H dipolar and scalar couplings between *gem*-deuterons participating to the linewidth of resonances. The presence of non-zero ^{2}H–^{2}H geminal couplings leads to the possibility of correlating the two quadrupolar doublets corresponding to the deuterons of the same isomer, as is schematically presented in Fig. 3. This is the reason why natural abundance deuterium NMR could not be successfully used in this respect. Indeed the very low natural abundance of deuterium nuclei (0.015%) excludes the possibility of detecting the ^{2}H–^{2}H scalar and dipolar couplings, and hence the ^{2}H-{^{1}H} spectra consist of a superimposition of independent quadrupolar doublets which cannot be correlated.[8]

In order to detect the correlation peaks between quadrupolar doublets, we recorded the deuterium COSY 2D spectrum of the mixture. Fig. 4a shows the deuterium COSY-45 2D map of the mixture in the PBLG system recorded at 293 K. In this 2D contour plot, we observe three types of deuterium signal: the resonances of the deuterium spectrum appearing on the main diagonal, the autocorrelation peaks appearing displaced from the other diagonal by the chemical shifts[8] and the cross-correlation peaks between quadrupolar doublets sharing the same ^{2}H-^{2}H spin-spin coupling. An important point to emphasise here is that cross-correlation peaks are observable even when the dipolar and scalar couplings are not resolved in the 1D spectrum.[11] We have employed a read pulse of 45° (and not 90°) because for such an angle the autocorrelation peaks are visible,[11] and consequently we can draw correlation squares on the 2D spectrum as for any spin-1/2 homonuclear COSY-90 experiment. The use of a 90° read pulse provides a similar spectrum, but the diagonal peaks are simply no longer visible.[11] The analysis of the spectral information is therefore formally identical to that performed on spin-1/2 COSY spectra because any row or column of the square exhibits the four components belonging to each pair of

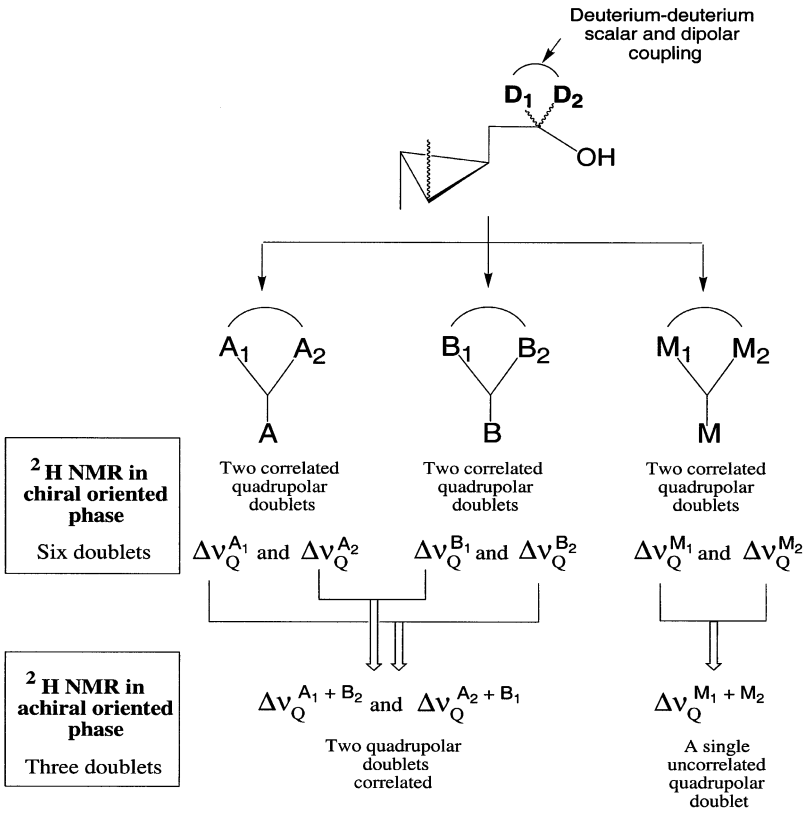


Figure 3. Spectroscopic principle for grouping of the various quadrupolar doublets observed in a mixture made of dideuterated, *meso*-isomer and A,B enantiomeric pair in the chiral and achiral oriented phase. Coupling correlations are only expected to be observed between doublets originating from deuterons belonging to the same stereoisomer. The magnitude of quadrupolar splittings in the achiral phase is equal to $|\Delta\nu_Q^{M_1+M_2}|=|(\Delta\nu_Q^{M_1}+\Delta\nu_Q^{M_2})/2|$ for the *meso*, and $|\Delta\nu_Q^{A_1+B_2}|=|(\Delta\nu_Q^{A_1}+\Delta\nu_Q^{B_2})/2|$ and $|\Delta\nu_Q^{A_2+B_1}|=|(\Delta\nu_Q^{A_2}+\Delta\nu_Q^{B_1})/2|$ for the active forms.

correlated doublets. This allows determination of the pairs of quadrupolar doublets associated with the three isomers. We can note that the doublets associated with the deuterated impurities (labelled by an asterisk) are also correlated by a dipolar coupling, and therefore correspond to a CD_2 probe.

If the information extracted from the COSY spectrum in the CLC allows the differentiation between signals for the three isomers, stereochemical assignment through this method is however impossible and to perform an eventual stereochemical attribution, we need a further property that exists for the *meso* isomer but not for the enantiomers. The answer is schematically given in Fig. 3. Indeed we can see that enantiomeric discrimination involves two different species while enantiotopic discrimination involves a single compound. Thus, it becomes possible to distinguish *meso*- from *d*,*l*-diastereoisomers (but not each enantiomer). For this purpose we used an achiral polypeptide liquid crystal, containing a racemic mixture of PBLG and PBDG (poly-γ-benzyl-D-glutamate). Such solutions denoted PBG in the following are also nematic but not chiral. Consequently, solute molecules exchange rapidly between the PBLG and PBDG vicinities, resulting in identical average magnetic interactions for two enantiomers or two enantiotopic elements.[12] Due to the elimination of both enantiomeric and enantiotopic discriminations, one quadrupolar doublet for the *meso*-compound and two correlated quadrupolar doublets for both enantiomers should be observed in the ^2H-$\{^1H\}$ spectrum if no overlap occurs. Indeed as the two doublets associated with the *d*- and *l*-isomers in the achiral phase originate from two pairs of two correlated doublets in the CLC, a correlation peak between them is also expected to be seen in the 2D spectrum (see Fig. 3). Consequently, the assignment of the *meso*-isomer and the chiral pair becomes possible. This second step is therefore crucial in this respect.

Fig. 4b shows the proton-decoupled deuterium COSY-45 2D map of the mixture in the PBG system at 293 K. The 2D spectrum was recorded using the same experimental conditions as previously. As expected, the six quadrupolar doublets in the CLC collapse now into three doublets in the achiral phase and a unique correlation peak is now observed between the inner and the outer doublets. The *meso*/*d*,*l* enantiomers attribution is therefore trivial in this second 2D spectrum.

The next step of the analysis consists of assigning the pairs of doublets in the 2D spectrum recorded in the chiral phase (see Fig. 4a). For this purpose, we must keep in mind that the magnitude of quadrupolar splittings determined in the achiral phase corresponds in principle to the algebraic average of the splittings mea-

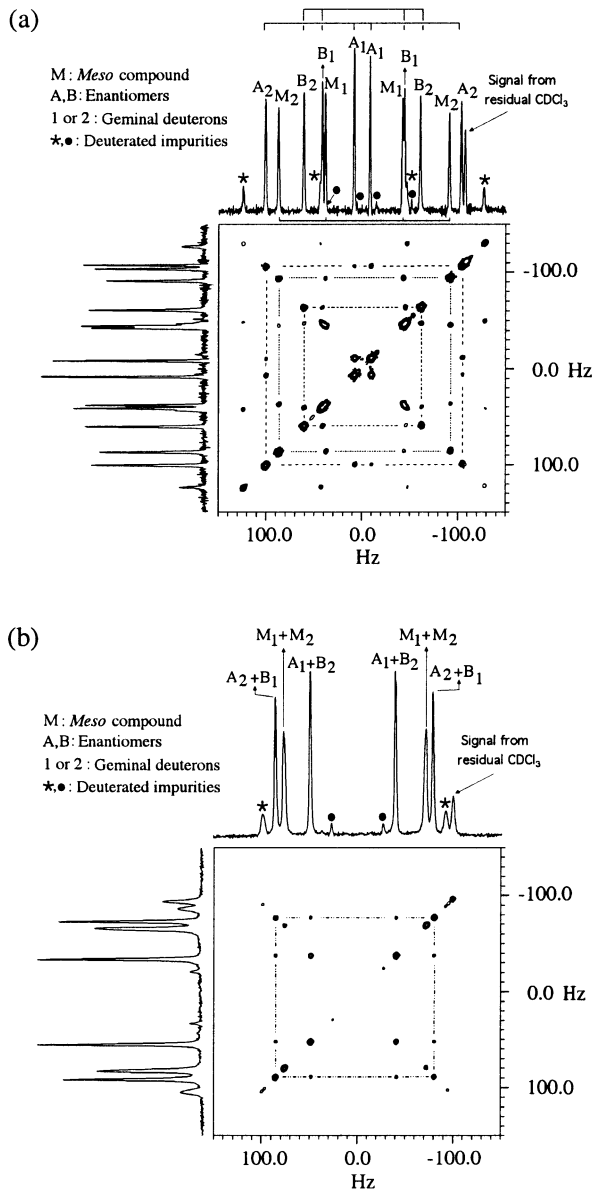


Figure 4. (a) 61.4 MHz proton-decoupled deuterium COSY-45 spectrum of mixture I (sample 1) recorded at 293 K in the PBLG/$CHCl_3$ phase. The 2D spectrum was acquired as a 256 (t_1)×700 (t_2) data matrix with 64 scans per t_1 increments and identical spectral widths in the two dimensions. The matrix was zerofilled to 1 k (t_1)×2 k (t_2) data points prior to the double Fourier transform. Sine-bell and square sine-bell filtering were used in the F_1 and F_2 dimensions to enhance the resolution of the magnitude spectrum. In F_1 and F_2 are displayed the 1D spectrum. (b) Same experiment recorded in the PBG/$CHCl_3$ phase (sample 2). The quadrupolar doublets due to each enantiotopic deuteron in the meso compound are labelled M_1 and M_2. Those due to each diastereotopic deuterons in each of the enantiomers are labelled A_1, A_2 and B_1, B_2. Note that in each case the attribution of 1 and 2 is arbitrary. Only the two quadrupolar doublets associated with diastereotopic deuterons are correlated to each other.

sured in the chiral solvent. The relationship between quadrupolar splittings measured in the chiral and the achiral phase for the *meso*-compound is therefore,

$$\left|\Delta\nu_Q^{M_1+M_2}\right| = \left|(\Delta\nu_Q^{M_1}+\Delta\nu_Q^{M_2})/2\right| \quad (1)$$

where $\Delta\nu_Q^{M_1}$ and $\Delta\nu_Q^{M_2}$ are the quadrupolar splittings of enantiotopic deuterons. Similar relationships exist for the enantiomeric pairs as we can write,

$$\left|\Delta\nu_Q^{A_1+B_2}\right| = \left|(\Delta\nu_Q^{A_1}+\Delta\nu_Q^{B_2})/2\right| \quad (2)$$

and

$$\left|\Delta\nu_Q^{A_2+B_1}\right| = \left|(\Delta\nu_Q^{A_2}+\Delta\nu_Q^{B_1})/2\right| \quad (3)$$

where $\Delta\nu_Q^{A_1}$, $\Delta\nu_Q^{A_2}$, $\Delta\nu_Q^{B_1}$ and $\Delta\nu_Q^{B_2}$ are the quadrupolar splittings of diastereotopic deuterons in the enantiomers noted A and B. Contrary to Eqs. (1)–(3) both involve two quadrupolar splittings associated with each of enantiomers and corresponding with diastereotopic deuterons related by a plane of symmetry (see Fig. 2).

From these relationships we considered and calculated all possible combinations of signs and experimental quadrupolar splittings in the chiral phase, and then retained the best fit, corresponding to the minimum error between the experimental and calculated values. The corresponding results obtained are collected in Table 1 and the final assignment of doublets is shown in Fig. 4a. The differences between the experimental splitting and the best set of calculated values vary between 10 and 17%. Although the relative discrepancies are not negligible, we can safely retain this set because all other solutions provide larger errors, and therefore can be excluded. The discrepancies between experimental and expected values presumably arise from solvent effects in the racemic phase and the non-strictly identical preparation of oriented solvent. Further investigations are currently underway to investigate these factors.

To answer the initial problem addressed at the beginning of this work, we analysed a new sample (referred to as mixture **II**) formed by cyclisation of enantioenriched (e.e. = 93%) (4*R*,5*S*)-iodoester **1**. Note that, in the absence of racemisation, such a mixture is expected to lead to *meso*-**12**, the (*S*,*S*)-enantiomer **13** and its antipode ent-**13** with a 93% e.e. in favour of **13**.

Fig. 5a reports the ^2H-{^1H} spectrum of mixture **II** expected to be enantioenriched. Here the spectrum exhibits five quadrupolars doublets (over six possible). This situation corresponds to the overlapping of two quadrupolar doublets. Some impurities (labelled with an asterisk) are also detected, but they do not interfere with the analysis of other doublets. As before, the analysis of doublets is not straightforward, and we therefore applied the two-step strategy described previously. The peak assignment found is reported in Fig. 5a. As we expected, this assignment is similar to that obtained for the mixture **I** even if the magnitude of some quadrupolar splittings varied slightly. In particular we can note that the doublets associated with the deuterons noted M_1 and B_1 are now fortuitously identical. These variations indicate that the orientational ordering of solutes in the phase have slightly changed compared to that of the mixture **I**. The difference in the sample composition (see Table 2) and the nature of

Table 1. Assignment of quadrupolar doublets of the mixture **I** dissolved in the PBLG phase

Enantiomeric pairs	$\lvert\Delta\nu_Q\rvert$[a] (Hz)	$\lvert\Delta\nu_Q^{A_1+B_2}\rvert$ (Hz)	$\lvert\Delta\nu_Q^{M_1+M_2}\rvert$ (Hz)	$\lvert\Delta\nu_Q^{A_2+B_1}\rvert$ (Hz)	$\lvert\Delta\nu_Q\rvert$[b] (Hz)	Error (%)
A_1/B_2	$17\pm1/122\pm2$	70			85 ± 1	17
M_1/M_2	$81\pm2/179\pm2$		130		144 ± 2	10
A_2/B_1	$86\pm2/205\pm2$			145	161 ± 2	10

[a] Experimental values measured in the PBLG phase.
[b] Experimental values measured in the PBG phase.

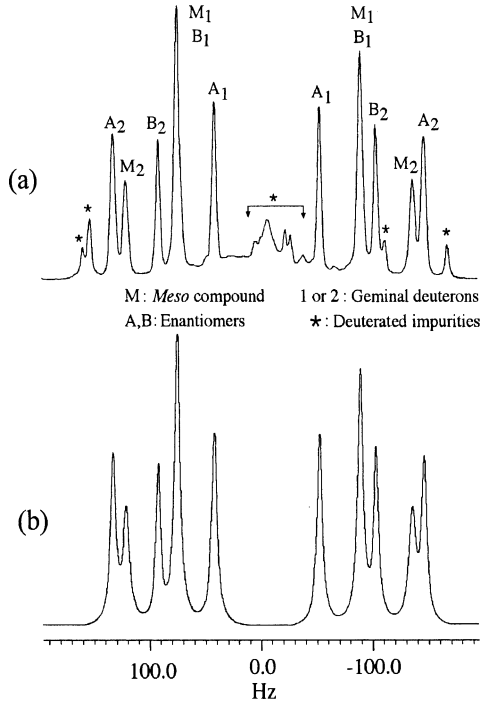


Figure 5. (a) 61.4 MHz proton-decoupled deuterium spectrum of the mixture **II** dissolved in the PBLG/$CHCl_3$ phase (sample 3) at 293 K. No filtering was applied to enhance the spectral appearance. (b) Deconvoluted spectrum. The d.e. and e.e. values are 35%±5% and 20%±5%, respectively.

deuterated impurities, which seems to be different from those contained in the mixture **I**, is responsible for this effect.

The diastereoisomeric and enantiomeric composition can now be determined using either an average for a series of peak integrations in the spectrum or values calculated from deconvoluted 1D spectrum (Fig. 5b). The d.e. and e.e. values have been evaluated to 35%± 5% and 20%±5%. Results from both integration methods are in full agreement. The d.e. value is therefore consistent with that evaluated in the isotropic solvent (*meso*/*d*,*l* ratio = 0.5) and was not expected to change compared to that of the mixture **I**. In contrast, the enantiomeric excess of the mixture **II** is rather low, and indicates a marked loss in enantiopurity.

The results given by the ^2H-{^1H} NMR in oriented solvent unambiguously show that the SmI_2-mediated cyclisation of homochiral γ-substituted δ-halo-α,β-unsaturated esters is not racemisation-free. This now enables us to propose a chemical mechanism explaining the racemisation process. Concerning the mechanism of this SmI_2-mediated ring closure, a radical anionic sequence has already been proposed[1] in which the homoallylic radical **A** formed by an initial monoelectronic reduction of the halide substrate rapidly cyclises according to a 3-*exo*-trig process to the α-carbalkoxy-substituted cyclopropylcarbinyl radical **B** (Scheme 4). A second monoelectronic reduction of this electrophilic radical followed by trapping of the resulting samarium enolate **C** by the proton source ultimately leads to the reaction product **D**. A similar sequence, involving 5- and 6-*exo*-trig cyclisations at the radical stage had previously already been proposed by Molander and Harris[13–15] for the related ring closures of ζ- or η-iodo-α,β-unsaturated esters or amides to cyclopentanes or cyclohexanes.

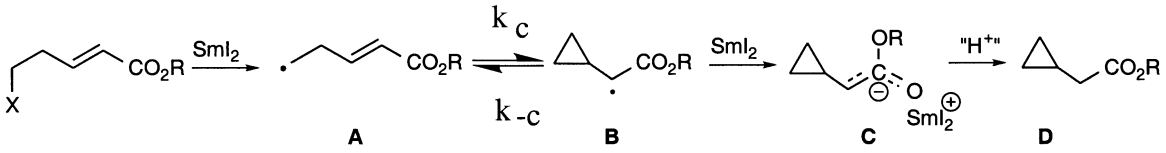
The main difference between these two reactions is that, contrary to 5- and 6-*exo*-trig radical cyclisations, the cyclisation of the homoallylic radical to cyclopropylalkyl radical is a reversible process.[16] According to the kinetic measurements (in hydrocarbon solvents) and the Arrhenius function for ring opening and ring closure of carbalkoxysubstituted radicals species **B** and **A** obtained by Beckwith and Bowry[17] both reactions are very rapid processes ($k_c = 1.6\times10^7$ and $k_{-c} = 1.2\times10^7$ s^{-1} at 353 K). More recent data presented by Newcomb and co-workers[18] obtained in THF reported that the rate of ring-opening had been in fact underestimated, and should be raised by a factor of approximately 50 for which the change of solvent from cyclohexane to THF is only partially responsible. We are well aware that the presence of samarium species could also change these values appreciably. In any case, the extensive racemisation at the γ-carbon centre observed in the present study shows that, under the conditions used (if the reaction does follow the mechanism of Scheme 4), the ring-opening of cyclopropyl radical **B** is more rapid than its reduction to **C** by a second molecule of SmI_2.

As already stated,[1] two carbanionic cyclisation processes, in place of the radical mechanism, may be envisaged to account for the cyclisation (Scheme 5). In the first one, the cyclisation would involve an intramolecular Michael-type addition of an organosamarium intermediate formed at the carbon–iodine bond. In the second, a radical anion formed by one electron reduction of the electron-withdrawn π-system would displace the iodide atom by S_N2 intramolecular attack. In relation to these possibilities, the electrochemically-induced cyclisation of δ-mesyloxy-α,β-enoate **8**[19] and SmI_2-mediated reductive dimerisation of

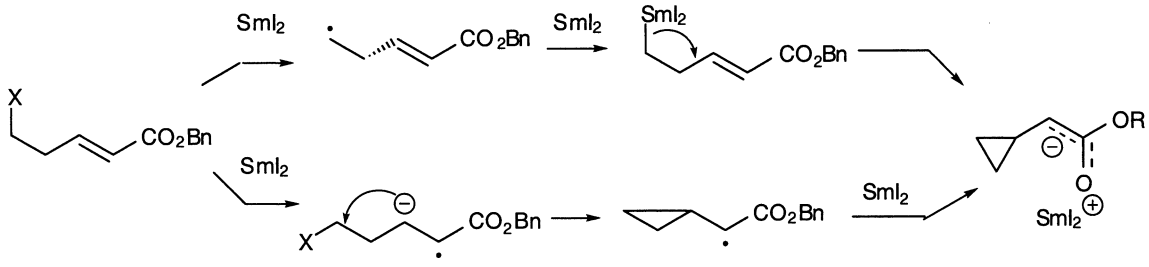
Table 2. Compositions of liquid-crystalline NMR samples investigated

Sample	Solute mixture	Polymeric solvent	DP[a] PBLG/PBDG	Co-solvent	Solute (mg)[b]	Polymer (mg)[b]	Co-solvent (mg)[b]	% of polymer in weight
1	I	PBLG	562	$CHCl_3$	12	100	400	19.5
2	I	PBG	562/914	$CHCl_3$	12	51+51	402	19.7
3	II	PBLG	562	$CHCl_3$	20	99	450	17.4
4	II	PBG	562/914	$CHCl_3$	20	51+50	451	17.5

[a] DP: Degree of polymerisation of polypeptide used.
[b] The accuracy on the weighting is ±1 mg.



Scheme 4.



Scheme 5.

bis-enoate ester **9**[20] leading to cyclopropane compounds **10** and **11**, respectively, have been described in the literature.

Returning to the present study, it should be noted that the racemisation observed does not permit us to rule out these two possibilities. Indeed, since SmI_2 is a one electron reductant, both possibilities entail the transient formation of either an uncyclised (homoallylic) or a cyclopropylcarbinyl radical, and therefore the possibility of an equilibration process between these two species during the course of the reaction. However, following Molander and Harris[13] and Bennett and coworkers,[14a] strong arguments against these carbanionic alternatives have already been given.[1] Moreover, the fact that δ-tosyloxy-α,β-enoates were found to be very poor substrates[21] for cyclisation in comparison with their δ-bromo analogues, would indicate that the radical anion mechanism is strongly disfavoured.

3. Conclusion

We have investigated the mechanism of the SmI_2-mediated cyclisation of δ-halo-α,β-unsaturated esters. From a synthetic point of view and for a better understanding of the reaction mechanism it was of importance to assess whether a homochiral γ-substituted substrate would retain its configuration during the cyclisation process. The analysis of spectroscopic results using proton decoupling deuterium NMR in weakly oriented liquid crystals have clearly demonstrated that the cyclisation reaction is accompanied by extensive racemisation, probably as a result of faster ring reopening of α-carbalkoxy cyclopropylcarbinyl radicals compared to their reduction to a carbanionic species.

In the course of this work, we have developed an efficient 2D NMR strategy for distinguishing *meso*-isomers from *d,l*-diastereoisomers based on the introduction of a CD_2 probe. This work emphasises the value and analytical potential of NMR in weakly oriented chiral media to the determination of enantiomeric and diastereoisomeric compositions and to finding solutions for applied stereochemical problems. The development of such tools is of paramount importance considering the difficulties involved in the control and evaluation of the enantiomeric composition of chiral mixtures.

4. Experimental

4.1. Synthetic procedures

4.1.1. General. Routine ^1H and ^{13}C NMR spectra in isotropic solvents were recorded on a Bruker AC 250 or a Bruker AC 200 apparatus. Chemical shifts are reported in δ (ppm) referenced to the residual $CHCl_3$ ^1H signal at 7.26 ppm and $CDCl_3$ ^{13}C signal at 77.0 ppm. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. HPLC analyses were performed on a Spectra-Physics P100-UV100 HPLC system with

detection at $\lambda = 254$ nm and equipped with a chiral column Chiralcel OD-H from Daicel Chemical Industries Ltd. Mixtures of hexane and isopropanol were used for elution. GC–MS analyses were carried out on a OK1 DP 125 gas chromatograph equipped with a CPSil quartz capillary column and connected to a Riber Mag R10-10 mass detector. High resolution mass spectra (HRMS) and electrospray mass spectra were obtained on a Finnigan-MAT-95-S spectrometer. All solvents used in the reactions were distilled under argon and over a drying agent (P_2O_5 for dichloromethane and benzophenone sodium for THF and diethylether).

4.1.2. 2-[(*E*)-(Benzyloxycarbonyl)vinyl]-2,3-dimethyloxirane. *rac*-2-[(*E*)-(Benzyloxycarbonyl)vinyl]-2,3-dimethyloxirane, *rac*-5. Benzyl (2*E*,4*E*)-4-methylhexa-2,4-dienoate (4.54 g, 21 mmol) and 3-chloroperoxybenzoic acid (25–30% water content, 5.86 g, ca. 1.2 equiv.) were dissolved in chloroform (50 mL). The reaction mixture was stirred for 8 h at room temperature and then extracted with aqueous 1N sodium thiosulfate and 0.5N sodium hydroxide until pH ca. 9. The aqueous phases were extracted with dichloromethane. The organic phases were dried over $MgSO_4$, filtered, evaporated and the residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 80:20) to afford a colourless oil (4.63 g, 95%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.41–7.34 (m, 5H); 6.85–6.79 (d, 1H, $^3J = 16.0$ Hz, 1H); 6.12–6.06 (d, $^3J = 16.0$ Hz, 1H); 5.20 (s, 2H); 3.03–2.96 (q, $^3J = 4.5$ Hz, 1H); 1.44 (s, 3H); 1.39–1.36 (d, $^3J = 5.45$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 165.7; 150.4; 135.9; 128.4; 128.1; 121.0; 66.2; 61.4; 58.2; 14.8; 13.8. HRMS (EI): calcd for $C_{14}H_{16}O_3$ [M^+] 232.1099, found 232.1107.

4.1.3. (*R*,*R*)-2-[(*E*)-(Benzyloxycarbonyl)vinyl]-2,3-dimethyloxirane 5. The epoxidation reaction was carried out as described by Shi and co-workers[2] by simultaneous addition via two syringe pumps of an aqueous solution of oxone (2.3 g, 3.75 mmol) in aqueous EDTA (4×10^{-4} M, 20 mL) and a solution of K_2CO_3 (2.3 g, 16.6 mmol) in water (20 mL) to a magnetically stirred buffered biphasic mixture of 2:1 dimethoxyethane/acetonitrile (50 mL) and 33 mL of aqueous solution containing $Na_2B_2O_4{\cdot}10H_2O$ (0.05 M) and EDTA (4×10^{-4} M), with the diene (721 mg, 3.3 mmol), ketone **7** (215 mg, 0.83 mmol, 0.25 equiv.) and tetrabutylammonium hydrogen sulfate (50 mg, 0.15 mmol). After column chromatography, the epoxide was obtained as an oil (727 mg, 95%). Its enantiomeric purity (e.e. = 94%) was measured by chiral HPLC analysis (Chiralcel ODH, hexane/isopropanol 98:2). $[\alpha]_D^{20} = +17.4$ (*c* 0.41, CH_2Cl_2). HRMS (EI): calcd for $C_{14}H_{16}O_3$ [M^+] 232.1099, found 232.1103.

4.1.4. (*E*)-4-Methyl-5-hydroxyhex-2-enoic acid benzyl ester. (4*R,5*R**)-4-Methyl-5-hydroxyhex-(2*E*)-enoic acid benzyl ester, *rac*-6**. The reaction was completed under an argon atmosphere: dimethylamineborane complex (380 mg, 6.45 mmol) and palladium (tetrakis)triphenylphosphine (5 mol%, 373 mg, 0.325 mmol) were dissolved in dichloromethane (90 mL). A solution of *rac*-2-[*(E)*-(benzyloxycarbonyl)vinyl]-2,3-dimethyloxirane (1.5 g, 6.46 mmol) and acetic acid (1.13 mL, 1.95 mmol) in dichloromethane (10 mL) was then rapidly added by syringe to the Schlenk tube. After 15 min stirring at room temperature, total conversion of the epoxide to homoallylic alcohol was achieved (tlc analysis). The solvent was evaporated and the crude residue was directly submitted to column chromatography (silica gel, 80:20 cyclohexane/ethyl acetate) to give (4*R**,5*R**)-4-methyl-5-hydroxyhex-(2*E*)-enoic acid benzyl ester as a colourless oil (1.36 g, 95%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.42–7.27 (m, 5H); 7.08–6.97 (dd, $^3J = 16.0$ and 8.0 Hz, 1H); 5.98–5.89 (dd, $^3J = 15.5$ and 1.0 Hz, 1H); 5.19 (s, 2H); 3.83–3.71 (app. quint, $^3J = 6.5$ Hz, 1H); 3.37 (broad s, 1H, OH); 2.36–2.25 (m, 1H); 1.18–1.15 (d, $^3J = 6.5$ Hz, 1H); 1.11–1.08 (d, $^3J = 7.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 166.1; 151.3; 135.9; 128.5; 128.2, 121.3; 70.4; 66.1; 43.66; 20.35; 14.32. Electrospray (ESI, positive mode): 234.1 (M^+, 18%); 252.1 ($M+NH_4^+$). Enantioenriched (4*R*,5*R*)-4-methyl-5-hydroxyhex-(2*E*)-enoic acid benzyl ester **6** was obtained in a similar manner, starting from (*R*,*R*)-2-[(*E*)-(benzyloxycarbonyl)vinyl]-2,3-dimethyloxirane. $[\alpha]_D^{20} = +18.7$ (*c* 0.41, CH_2Cl_2). E.e. = 93% (HPLC on Chiralcel ODH, hexane/isopropanol 98:2).

4.1.5. (*E*)-5-Iodo-4-methyl-hex-2-enoic acid benzyl ester. (4*R,5*S**)-5-Iodo-4-methylhex-(2*E*)-enoic acid benzyl ester, *rac*-1**. To a magnetically stirred solution of triphenylphosphine (1.12 g, 4.27 mmol) in dichloromethane (5 mL) were successively added a solution of I_2 (1.1 g, 4.33 mmol) in dichloromethane (2.5 mL) and a solution of imidazole (291 mg, 4.27 mmol) in dichloromethane (2.5 mL). An insoluble salt formed in the medium. A solution of *rac*-(4*R**,5*R**)-5-hydroxy-4-methylhex-(2*E*)-enoic acid benzyl ester *rac*-**6** 1.00 g (4.27 mmol) in dichloromethane (2.5 mL) was then added. The reaction mixture was stirred for a few hours at room temperature while the conversion of the alcohol was monitored by tlc analysis. As soon as the reaction was complete (ca. 3 h), the reaction mixture was concentrated on a Rotovapor and the residue was resolved by column chromatography (to be carried out preferentially in the dark) to afford the iodide *rac*-**1** as an oil (543 mg, 37% yield) and diene **4** (370 mg) (silica gel, 80:20 cyclohexane/ethyl acetate, $R_f = 0.4$ (diene) and 0.5 (iodide)). (4*R**,5*S**)-5-Iodo-4-methylhex-(2*E*)-enoic acid benzyl ester, *rac*-**1**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.42–7.28 (m, 5H); 6.98–6.89 (dd, $^3J = 15.5$ and 8.0 Hz, 1H); 5.98–5.91 (dd, $^3J = 15.5$ Hz, ^{4}J = 1.0 Hz, 1H); 5.22 (s, 2H); 4.26–4.2 (dq, $^3J = 3.0$ and 7 Hz, 1H); 2.22–2.15 (m, 1H); 1.88–1.86 (d, $^3J = 6.5$ Hz, 3H); 1.17–1.14 (d, $^3J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 165.9; 146.9; 135.6; 128.5; 128.1; 123.6; 66.2; 42.7; 22.2; 21.7; 19.0. GC/MS (EI): 216 (M^+–HI, 100%). Similarly, enantiomerically enriched (4*R*,5*S*)-5-iodo-4-methylhex-(2*E*)-enoic acid benzyl ester **1** was prepared from (4*R*,5S)-5-hydroxy-4-methylhex-(2*E*)-enoic acid benzyl ester.

4.1.6. SmI_2-induced cyclisation of racemic (4*R,5*S**) and enantiomerically enriched (4*R*,5*S*)-5-iodo-4-methylhex-(2*E*)-enoic acid benzyl ester. 0.1N solution of SmI_2 in THF**. In a graduated Schlenk tube under an argon atmosphere, 1,2-diiodoethane (2.82 g, 10 mmol) was diluted to a volume of 100 mL in anhydrous and degassed THF. This solution was slowly transferred, through a cannula into a second Schlenk tube containing metallic samarium (1.8 g, 1.19 mmol) and a stirring bar. The yellow suspension was magnetically stirred at room temperature for 2 h to give a deep blue solution. This solution was stored for not more than a week under argon and in the dark.

Cyclisation: Either (4*R**,5*S**)- or enantiomerically enriched (4*R*,5*S*)-5-iodo-4-methylhex-(2*E*)-enoic acid benzyl ester (200 mg, 0.58 mmol) together with *tert*-butanol (165 μL, 1.75 mmol), were diluted with THF (2 mL). The resulting solution was added dropwise over a period of 1 min and under stirring in a Schlenk tube (argon atmosphere) containing a solution of SmI_2 in THF (0.1 M, 14.5 mL, 2.5 equiv.). After 2 h, during which the deep blue colour of the SmI_2 solution progressively discharged, the reaction mixture was quenched with 0.1N HCl and extracted with diethyl ether. The organic phase was washed with aqueous sodium thiosulfate solution and dried over magnesium sulfate.

NMR and HRMS characterisation of cyclised propanes: The crude products were directly purified by column chromatography (silica gel, 80:20 cyclohexane/ethyl acetate) to give 100 mg (80% overall yield) of a ca. 1:2 mixture of unseparated *meso* 2-(*trans*-2-*trans*-3-dimethylcyclopropyl)acetic acid benzyl ester **2** and *d*,*l*-2-(*cis*-2-*trans*-3-dimethylcyclopropyl)acetic acid benzyl ester [**3**+ent-**3**].

^{1}H NMR ($CDCl_3$, 400 MHz): peak assignments to respectively the *d*,*l*- and the *meso*-isomers were established using COSY 2D proton NMR experiments *d*,*l*-2-(*cis*-2-*trans*-3-dimethyl-cyclopropyl)acetic acid benzyl ester **3**: δ 7.33–7.27 (m, 5H); 5.15 (s, 2H); 2.33 (d, ^3J=7.35 Hz, 2H); 1.01–0.96 (two d, ^3J= 6.45 Hz, 3H+3 H); 0.76–0.71 (m, 1H); 0.59–0.54 (m, 1H); 0.20–0.16 (m, 1H). *meso*-2-(*cis*-2-*trans*-3-Dimethylcyclopropyl)acetic acid benzyl ester **2**: 7.33–7.27 (m, 5H); 5.13 (s, 2H); 2.24 (d, ^3J=7.15 Hz, 2H); 0.99 (s, 6H); 0.59-0.54 (m, 2H); 0.39–0.33 (m, 1H). Electrospray (ESI, positive mode) **2** and **3**: 219.3 (23%, MH^+); 236.3 (34%, $M+NH_4^+$); 241.3 (75%, M^++Na); 242.3.

4.1.7. Reduction of esters to deuterated alcohols. The crude (unchromatographed) products of cyclisation (theoretical amount: 0.58 mmol) were dissolved in THF (1 mL) and added to a solution of $LiAlD_4$ (20 mg, 0.48 mmol) in THF (1 mL) at 0°C. After stirring for 1 h the reaction mixture was hydrolysed with 1N aqueous HCl and extracted several times with ethyl acetate. The organic phases were washed with water, dried over $MgSO_4$ and the solvent was evaporated. ^{1}H and ^{2}H NMR analyses were carried out directly on the crude residue.

4.2. NMR spectroscopy in oriented solvents

The chiral and non chiral liquid crystalline NMR samples were prepared using the homopolypeptide (ca. 100 mg, commercially available from Sigma), the deuterated solutes (ca. 10 mg) and organic co-solvent (ca. 400 mg) directly weighed into a 5 mm o.d. NMR tube. The exact compositions of each oriented NMR sample are given in Table 2. All NMR tubes were sealed to avoid solvent evaporation and centrifuged back and forth until an optically homogeneous birefringent phase was obtained. Various experimental details on the method can be found in Ref. 6a. The ^{2}H-{^{1}H} 1D and 2D experiments were performed at 9.4 T on a Bruker DRX 400 high-resolution spectrometer equipped with an inverse multinuclear probe (BBI) operating at 61.4 MHz for deuterium and with a standard variable temperature unit (BVT 3000). In order to remove the proton–deuterium scalar and dipolar couplings, the protons were broadband decoupled using WALTZ-16 composite pulse sequence. Other experimental NMR parameters or details are given in the figure captions.

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