Tetrahedron: Asymmetry Vol. 4, No. 1, pp. 31-34, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00

Enantiomeric Excess Analysis of Sesquiterpene Precursors through Proton Decoupled Deuterium NMR in Cholesteric Lyotropic Liquid Crystal.[1]

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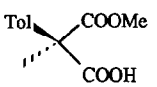
(*Received in UK* 23 *November* 1992)

Key words : Polypeptide (PBLG) lyotropic liquid crystal, Enantiomeric excess analysis, Deuterated sesquiterpene precursors.

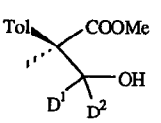
***Abstract** : Poly-γ-benzyl L-glutamate (PBLG) and dichloromethane form a lyotropic liquid crystals which can be used as solvent for enantiomeric excess analysis through proton decoupled ^2H NMR spectroscopy. Deuterated (R) and (S) enantiomers of laurene and epilaurene precursors dissolved in PBLG/CH_2Cl_2 mixtures exhibit different deuterium quadrupolar splittings on their ^2H NMR spectra, which provides a new and accurate method to measure their enantiomeric excesses.*

It has been recently reported that cholesteric binary mixtures which orientate homogeneously their helical axis parallel to a magnetic field, can be used as suitable NMR solvents for the vizualization of enantiomers.[2] This discrimination between the (*R*) and (*S*) molecules has been proven to originate from a difference in the molecular ordering, depending on their asymmetry, giving rise to different dipolar or quadrupolar interactions. Among the polypeptides well known to adopt a helical conformation analogous to cholesteric liquid crystals , the polybenzyl L-glutamate (PBLG) is the most common and has been shown to give separate signals for enantiotopic nuclei.[3] We have recorded high resolution ^2H NMR spectra of mono- and dideuterated chiral molecules dissolved in PBLG/solvent mixtures [4] in order to see if any significant spectral difference could distinguish these enantiomers and consequently allow us to measure accurately their enantiomeric purity.

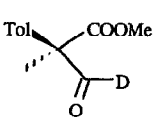
To apply this new analytical method of enantiomeric excess determination, to asymmetric laurene and epilaurene precursors, [1] we have to prepare first their corresponding deuterated products.



(*R*)-(+)- **1**



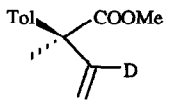
(*R*)-(+)- **d-2**



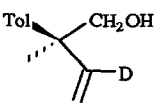
(*R*)-(+)- **d-3**

These syntheses are accomplished from the readily available malonic acid ester (*R*)-**1**.[5,6] Thus, reduction of (*R*)-**1** (ClCOOMe, NEt_3, then $NaBD_4$ in MeOH) provides the dideuterated hydroxy ester

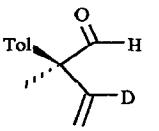
(*R*)-**d-2** [7a] in 81% yield, with a 97% deuterium ratio determined from NMR spectroscopy. This alcohol (*R*)-**d-2** then undergoes Swern oxidation [8] ($(COCl)_2$, DMSO, at -60°C, then NEt_3) to furnish the corresponding aldehyde (*R*)-**d-3** [7b] in 98% yield.



(*S*)-(+)- **d-4**

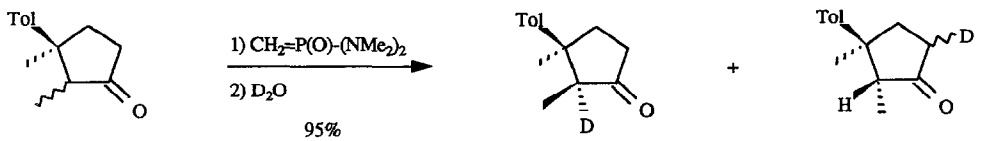


(*S*)-(+)- **d-5**



(*S*)-(+)- **d-6**

Wittig reaction with "salt free" methylenephosphorane (CH_2=PPh_3) [9] gives the olefinic ester (*S*)-**d-4** [7c] in 78% yield. The conversion of ester (*S*)-**d-4** into the alcohol (*S*)-**d-5** [7d] is conveniently achieved by hydride reduction (2 eq. of DIBAH, CH_2Cl_2, -78°C, 98%). Further Swern oxidation [8] leads to the aldehyde (*S*)-**d-6** [7e] in 98% yield. All these products have a deuterium ratio over to 96%, as shown by ^1H NMR spectroscopy.



7 trans/cis 8 : 1

(3*S*)- **d-8** 45% 55% **d-9**

On the other hand, methylenephosphonic bis(dimethylamide) CH_2=$P(O)$-$(NMe_2)_2$ [10] reacts with a trans/cis mixture (8:1 ratio) of cyclopentanone (3*S*)-**7** [1] to provide, after hydrolysis with D_2O, a 45:55 mixture of (3*S*)-**d-8** (cis/trans ratio 10 : 1) and (3*S*)-**d-9** (trans/cis ratio 7 : 1) in 92% yield as determined from ^1H NMR.[7f] This cyclopentanone (3*S*)-**8** constitutes a convenient precursor of laurene and epilaurene.[1] The same sequence is applied to prepare all the corresponding racemic products from the racemic acid ester **1**.

In the figure, entry A shows the proton decoupled deuterium NMR spectrum of 20 mg of **rac-d-2**, dissolved in a mixture of 105 mg of PBLG and 395 mg of CH_2Cl_2. This ^2H spectrum consists of eight signals : a quadrupolar splitting doublet for each deuterium and for each enantiomer. This means that the averaged order parameters of the (*R*) and (*S*) molecules are essentielly different in this chiral lyotropic liquid crystal, leading to different quadrupolar splittings for each optical isomer and for the two diastereotopic geminal deuterium atoms.

On the other hand entry B, the proton decoupled deuterium NMR spectrum of (*R*)-**d-2** in PBLG/CH_2Cl_2 shows a quadrupolar splitting doublet for each deuterium and only traces of doublet (< 1%) corresponding to the enantiomer (*S*)-**d-2**. From their simple relative integration we can conclude that the enantiomeric excess of (*R*)-**d-2** is over than 98%.

In the same way, in entry C the proton decoupled deuterium NMR spectrum of **rac-d-3** in PBLG/CH_2Cl_2 shows two quadrupolar splitting doublets with a small differential ordering effect.

From comparison with the (*R*)-**d-3** spectrum entry D, recorded in the same conditions, we can conclude from signals integration that the enantiomeric excess of (*R*)-**d-3** is also over 98% ee.

Same results are obtained from (*S*)-**d-4** (>98% ee), comparatively to **rac-d-4**.

Entry E displays the proton decoupled deuterium NMR spectrum of **rac-d-5** in PBLG/CH_2Cl_2. The two distinct quadrupolar splitting doublets correspond to each (*R*) and (*S*) enantiomers. The (*S*)-**d-5** spectrum recorded in the same conditions in entry F, exhibits only a doublet with traces of signals (< 1%) attributed to the (*R*)-**d-5** antipode. Therefore the enantiomeric excess of (*S*)-**d-5** is at least 98% ee.

It is worthwhile to note that the proton decoupled deuterium NMR spectrum of **rac-d-6** in PBLG/CH_2Cl_2 does not exhibit distinguished quadrupolar splitting doublets for the two (*R*) and (*S*) enantiomers. This limitation is probably due to comparable van der Waals volumes for the two substituents of the chiral center : CH_2=C(D)- and O=C(H)-. The molecule adopts a meso configuration and differential ordering effect is not effective.

Entry G shows the complex proton decoupled deuterium NMR spectrum of the **rac-d-8** and **rac-d-9** mixture in PBLG/CH_2Cl_2. However, two distinct quadrupolar splitting doublets correspond (for the major cis isomer) to each (3*S*)- and (3*R*)-enantiomers of **rac-d-8**, in which the deuterium is on a carbon in α of the stereogenic center, and two distinct quadrupolar splitting doublets with smaller separation correspond (major isomer) to the (*R*) and (*S*) enantiomers of **rac-d-9** in which the deuterium is in β of the stereogenic center. The others minor isomers of **d-8** and **d-9** are marked by stars. The spectrum of (3*S*)-**d-8** and (3*S*)-**d-9** mixture showed in entry H is simpler. Recorded in the same conditions it exhibits only a doublet corresponding to (3*S*)-**d-8** with traces of signals (< 1%) of the antipode (3*R*)-**d-8** and the (3*S*)-**d-9** doublets. Thus from such a mixture of deuterated products the enantiomeric excess can be also easily determined; for (3*S*)-**d-8** it is over 98% ee.

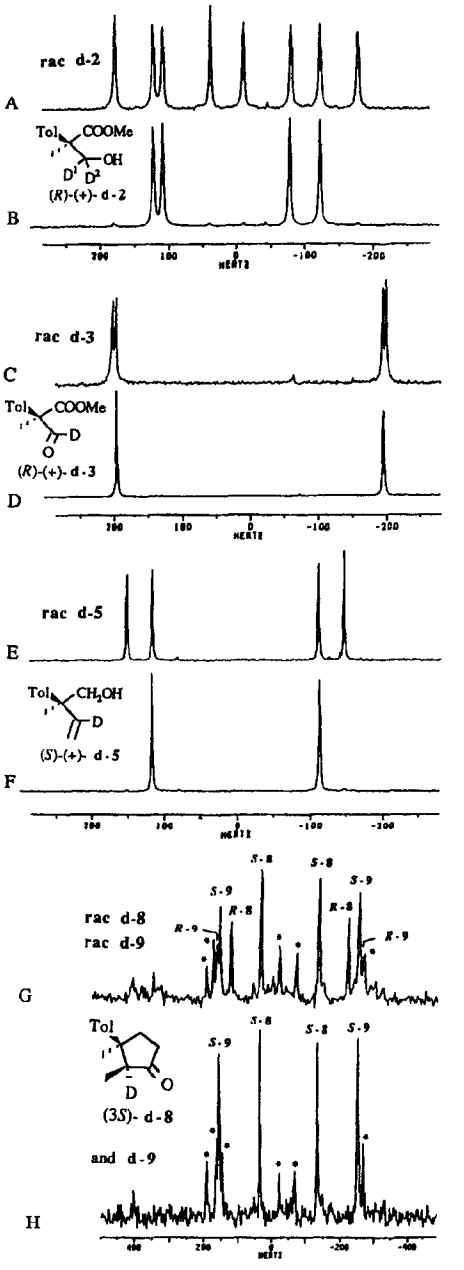


Figure : Selected proton decoupled deuterium NMR spectra of racemic and chiral products in the lyotropic liquid crystal solvent PBLG/CH_2Cl_2, respectively : A and B (rac and (*R*)-**d-2**) ; C and D (rac and (*R*)-**d-3**) ; E and F (rac and (*S*)-**d-5**); G and H (rac **d-8** and rac **d-9** mixture, (3*S*)-**8** and (3*S*)-9 mixture).

We report herein the first examples of enantiomeric excess determination from readily available deuterated molecules where the deuterium atom(s) are located on a carbon vicinal to the stereogenic centers.[11] This new method provides a convenient alternative when the use of chiral shift reagents is not possible, for instance when substrates do not contain a moiety which coordinates efffectively lanthanides.

References and Notes

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7) (a) **(*R*)-(+)-d-2** : $[\alpha]_D$ = +60.0 (c 1, $CHCl_3$). IR (neat) : 3450, 2220, 2100, 1735 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.16 (s, 4H), 3.73 (s, 3H), 2.43 (bs, OH), 2.34 (s, 3H), 1.66 (s, 3H). ^2H NMR (38.4 MHz, PBLG/CH_2Cl_2) $\Delta\nu_Q$ (Hz) for racemic **2-D** : 356.1 (D_1, **(*S*)-2**), 244.9 (D_1, **(*R*)-2**), 188.5 (D_2, **(*S*)-2**), 48.5 (D_2, **(*S*)-2**).

   (b) **(*R*)-(+)-d-3** : $[\alpha]_D$ = +191.0 (c 1, $CHCl_3$). IR (neat) : 2140, 2080, 1755, 1735 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.22 (d, J = 8 Hz, 2H), 7.13 (d, J = 8 Hz, 2H), 3.80 (s, 3H), 2.35 (s, 3H), 1.67 (s, 3H). ^2H NMR (38.4 MHz, PBLG/CH_2Cl_2) $\Delta\nu_Q$ (Hz) for racemic **d-3** : 401.8 (**(*S*)-3**), 392.0 (**(*R*)-3**).

   (c) **(*S*)-(-)-d-4** : $[\alpha]_D$ = -4.5 (c 1, $CHCl_3$). IR (neat) : 2215, 1735, 1635 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.16 (s, 4H), 5.28 (m, 1H), 5.16 (m, 1H), 3.73 (s, 3H), 2.36 (s, 3H), 1.65 (s, 3H). ^2H NMR (38.4 MHz, PBLG/CH_2Cl_2) $\Delta\nu_Q$ (Hz) for racemic **d-4** : 281.5 (**(*S*)-4**), 266.6 (**(*R*)-4**).

   (d) **(*S*)-(+)-d-5** : $[\alpha]_D$ = +13.8 (c 1, $CHCl_3$). IR (neat) : 3400, 2212, 1630 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.28 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 5.29 (m, 1H), 5.18 (m, 1H), 3.81 (s, 2H), 2.37 (s, 3H), 1.45 (s, 3H), 1.43 (bs, OH). ^2H NMR (38.4 MHz, PBLG/CH_2Cl_2) $\Delta\nu_Q$ (Hz) for racemic **d-5** : 299.5 (**(*S*)-5**), 228.4 (**(*R*)-5**).

   (e) **(*S*)-(-)-d-6** : $[\alpha]_D$ = -60.0 (c 1, $CHCl_3$). IR (neat) : 2820, 2720, 2230, 1740, 1625 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 9.57 (s, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.41 (m, 1H), 5.18 (m, 1H), 2.37 (s, 3H), 1.55 (s, 3H). ^2H NMR (38.4 MHz, PBLG/CH_2Cl_2) $\Delta\nu_Q$ (Hz) for racemic **d-6** : 208.6 (for both **(*S*)-6** and **(*R*)-6**).

   (f) Data form a mixture ***(3S)*-d-8** and ***(3S)*-d-9** we can read.
   ***(3S)*-d-8** ^1H NMR ($CDCl_3$) δ : 7.15 (d, J = 8 Hz, 2H), 7.07 (d, J = 8 Hz, 2H), 2.55 - 2.25 (m, $2H_\alpha$), 2.34 (s, CH_3), 2.20 - 2.00 (m, $2H_\beta$), 1.41 (s, 3H), 0.82 (s, 3H). ^2H NMR (38.4 MHz, PBLG/CH_2Cl_2) $\Delta\nu_Q$ (Hz) from a mixture **rac-d-8** and **rac-d-9** : 147.8 (**(*3S*)-8**), 305.4 (**(*3R*)-8**).
   ***(3S)*-d-9** ^1H NMR ($CDCl_3$) δ : 7.34 - 7.15 (m, 4H), 2.60 (q, J = 5,2 Hz), 2.55 - 2.28 (m, 1H), 2.36 (s, 3H), 2.28 - 2.20 (m, $2H_\beta$), 1.21 (s, CH_3), 1.04 ((d, J = 5.2 Hz, 3H). ^2H NMR (38.4 MHz, PBLG/CH_2Cl_2) $\Delta\nu_Q$ (Hz) from a mixture **rac-d-8** and **rac-d-9** : 361.8 (**(*3S*)-9**), 380 (**(*3R*)-9**).

   (g) All new compounds were caracterized by 250 MHz ^1H and ^{13}C NMR, IR, MS and when possible by elemental analysis to ± 0.3%.
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