Synthesis of Each Stereoisomer of [3-$^2H_1$]Phenylalanine and Evaluation of the Stereochemical Course of the Reaction of (*R*)-Phenylalanine with (*S*)-Phenylalanine Ammonia-lyase

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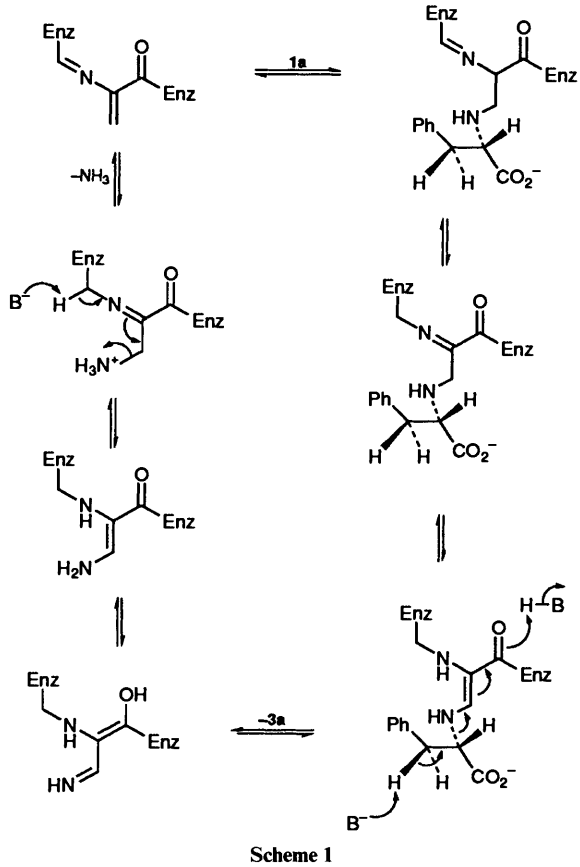
The four stereoisomers of [3-$^2H_1$]phenylalanine have been prepared, each as a single enantiomer in *ca.* 98% diastereoisomeric excess and with *ca.* 99% deuterium incorporation, by side-chain bromination of phenylalanine derivatives, followed by deuteriolysis of each of the diastereoisomeric product bromides with deuterium over 5% palladium-on-carbon. The latter reactions proceeded with retention of configuration. (2*R*,3*S*)-[3-$^2H_1$]Phenylalanine reacted with (*S*)-phenylalanine ammonia-lyase to give [3-$^2H_1$]-*trans*-cinnamic acid, with 92% deuterium incorporation, while the (2*R*,3*R*)-stereoisomer of the deuteriated phenylalanine gave [3-$^2H_1$]-*trans*-cinnamic acid with 27% deuterium incorporation. These results indicate that reaction of (*R*)-phenylalanine with the enzyme involves mainly loss of the 3-*pro*-*R* hydrogen and ammonia, in an antiperiplanar elimination process analogous to that previously reported for (*S*)-phenylalanine, while a minor pathway for reaction of (*R*)-phenylalanine is either isomerization to (*S*)-phenylalanine, before elimination, or synperiplanar elimination.

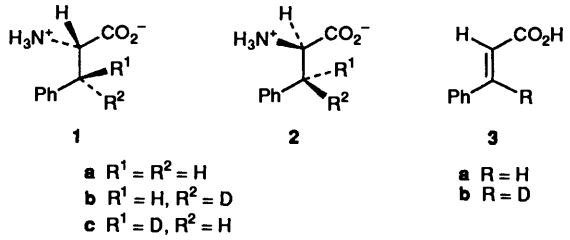
(*S*)-Phenylalanine ammonia-lyase (PAL) catalyses the elimination of ammonia and a proton from (*S*)-phenylalanine **1a**, to give *trans*-cinnamic acid **3a**, in a transformation that has been studied extensively and is thought to occur as shown in Scheme 1.[1-4] Battersby and his co-workers [1] examined the stereoselectivity of the proton transfer from the substrate. They observed that (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b** underwent the enzyme-catalysed reaction to give [3-$^2H_1$]-*trans*-cinnamic acid **3b**, while (2*S*,3*S*)-[3-$^2H_1$]phenylalanine **1c** gave the unlabelled acid **3a**, establishing that PAL removes the 3-*pro*-*S* hydrogen from (*S*)-phenylalanine **1a** in an antiperiplanar elimination process.

(*R*)-Phenylalanine **2a** is a competitive inhibitor of PAL and a poor substrate of the enzyme, being converted into *trans*-cinnamic acid **3a** at a rate $\leqslant$1/5000th of that for reaction of (*S*)-phenylalanine **1a**.[2] No studies of the stereochemical course of the reaction of PAL with (*R*)-phenylalanine **2a** have been reported and we were intrigued to determine how the enzyme catalyses the reaction of this compound having the opposite stereochemistry to that of the natural substrate **1a**. We have, therefore, investigated the interaction of PAL with (2*R*,3*S*)-[3-$^2H_1$]phenylalanine **2b** and the corresponding (2*R*,3*R*)-isomer **2c**.

Although a variety of methods have been reported for the stereoselective synthesis of the [3-$^2H_1$]phenylalanine isomers **1b**, **c** and **2b**, **c**,[1,5] they are indirect and involve the use of enzymes either to introduce chirality or to separate enantiomers. We chose to develop an alternative route for the synthesis of the deuteriated phenylalanine derivatives **1b**, **c** and **2b**, **c**, by direct elaboration of the corresponding phenylalanine enantiomers **1a** and **2a**. The procedure is based on our previous studies of the side-chain halogenation of *N*-phthaloylamino acid derivatives, with retention of chirality at the α-position.[6]



Scheme 1



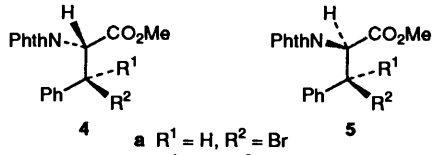
1 2 3

a $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = D$
c $R^1 = D$, $R^2 = H$

a R = H
b R = D

Results and Discussion

The (2*R*,3*S*)-β-bromophenylalanine derivative **4a** and the (2*R*,3*R*)-diastereoisomer **4b** were prepared from (*S*)-phenylalanine **1a** as previously reported.[6] The corresponding (2*S*,3*S*)-bromide **5a** and the (2*S*,3*R*)-isomer **5b** were obtained in an identical fashion from (*R*)-phenylalanine **2a**, and had spectral and physical properties comparable to those of their respective enantiomers **4b** and **4a**.



a $R^1 = H, R^2 = Br$
b $R^1 = Br, R^2 = H$
c $R^1 = H, R^2 = D$
d $R^1 = D, R^2 = H$

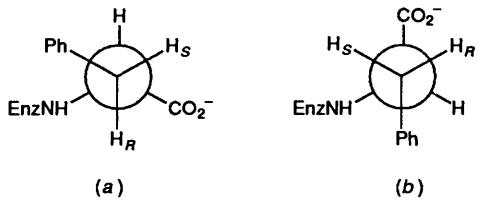


Fig. 1 Newman projections of the preferred conformation of (*a*) (*S*)-phenylalanine **1a** and (*b*) (*R*)-phenylalanine **2a** bound to PAL

A variety of methods for the stereocontrolled synthesis of the deuteriated phenylalanine derivatives **4c**, **d** and **5c**, **d**, from the respective bromides **4a**, **b** and **5a**, **b**, was investigated. Reactions with tributyltin deuteride occurred with only low stereoselectivity. Sodium borodeuteride was found to be an unsuitable reagent for the interconversion because the bromide **4a** reacted with sodium borohydride by reduction of the imide functionality,[7] instead of by substitution of the benzylic halide.[8] The zinc chloride complex of sodium cyanoborohydride is reported[9] to reduce benzylic halides without affecting amides or imides, but the bromide **4a** was inert to treatment with this reagent. Finally, the deuterides **4c**, **d** and **5c**, **d** were prepared in a stereocontrolled manner by deuteriolysis of the corresponding bromides **4a**, **b** and **5a**, **b**, with 5% palladium-on-carbon as the catalyst, under an atmosphere of deuterium. The stereoselectivity of the reduction depended on the reaction conditions. In a mixture of tetrahydrofuran and deuterium oxide, the bromide **4a** gave a 13:1 mixture of the deuteriated phenylalanine derivatives **4c** and **4d** when the reaction was conducted at 25 °C, while the product ratio increased to 27:1 when the reaction was performed at 5 °C. At −20 °C, changing to methan[$^2H_1$]ol as the solvent in order to prevent freezing, the deuteride **4c** was obtained in *ca.* 98% diastereoisomeric excess, and with *ca.* 99% $^2H_1$ incorporation regiospecifically at the β-position. At lower temperatures the bromide **4a** failed to react. These conditions for the stereocontrolled synthesis of the deuteride **4c** from the bromide **4a** were used to prepare the deuteriated phenylalanine derivatives **4d** and **5c**, **d** from the bromides **4b** and **5a**, **b**, respectively, each in *ca.* 98% diastereoisomeric excess and with *ca.* 99% $^2H_1$ incorporation. The extent of deuterium incorporation in each of the phenylalanine derivatives **4c**, **d** and **5c**, **d** was determined using ^{1}H NMR spectroscopy and mass spectrometry. ^{1}H NMR spectroscopy was used to measure the diastereoisomeric excess, with each of the deuterides **4c** and **5d** giving rise to a doublet resonance at δ 3.53 (J 11.7 Hz) due to the β-proton, while the corresponding signal for the stereoisomers **4d** and **5c** appeared at δ 3.59 (J 4.8 Hz).

The deuterides **4c**, **d** and **5c**, **d** were each hydrolysed in a 2:1 mixture of 6 mol dm^{-3} hydrochloric acid and acetic acid, with subsequent treatment with aniline in ethanol giving the corresponding free amino acids **1c**, **b** and **2b**, **c**, without loss of stereochemical integrity or deuterium content. The diastereoisomeric excess of each of the free amino acids **1b**, **c** and **2b**, **c** was determined using ^{1}H NMR spectroscopy. The spectra of the deuterides **1b** and **2b** showed doublet signals at δ 3.92 and 3.21, with a coupling constant of 4.9 Hz, corresponding to the α- and β-protons, respectively. The corresponding signals for the diastereoisomers **1c** and **2c** appeared at δ 3.92 and 3.03, with a coupling constant of 7.9 Hz. By comparison of their ^{1}H NMR spectra with literature data,[1,5] it was possible to assign the relative stereochemistry of the deuterides **1b**, **c** and **2b**, **c**, while their absolute stereochemistry is predetermined by that of the starting phenylalanine enantiomers **1a** and **2a**. From these stereochemical assignments it is clear that deuteriolysis of the bromides **4a**, **b** and **5a**, **b** proceeds with retention of configuration, consistent with other reports of hydrogenolysis of benzylic halides.[10]

With the deuteriated phenylalanine derivatives **1b**, **c** and **2b**, **c** in hand, their interaction with PAL was investigated. In accord with Battersby's studies,[1] the reaction of (2*S*,3*R*)-[3-$^2H_1$]-phenylalanine **1b**, in sodium borate buffer at pH 8.7, gave [3-$^2H_1$]-*trans*-cinnamic acid **3b**, with 98% deuterium incorporation. The deuterium content was determined by integration of the ^{1}H NMR signals at δ 6.47 (J 16.0 Hz) and 7.81 (J 16.0 Hz), corresponding to the α-and β-protons, respectively, of the unlabelled acid **3a**, and the broad singlet signal at δ 6.47, for the α-proton of the deuteriated species **3b**. The outcome of the reaction is consistent with stereospecific loss of the 3-*pro-S* hydrogen in the reaction of (*S*)-phenylalanine **1a**.[1] Production of the 2% unlabelled contaminant **3a** in the deuteriated acid **3b** can be attributed to reaction of the 1% unlabelled (*S*)-phenylalanine **1a** and the 1% (2*S*,3*S*)-[3-$^2H_1$]-phenylalanine **1c** impurities in the (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b**. Thus, this result confirms the stereochemical assignment, diastereoisomeric excess and deuterium content of the deuteride **1b** and, by analogy, the stereoisomers **1c** and **2b**, **c**, since they were prepared using the same procedures.

Treatment of (2*S*,3*S*)-[3-$^2H_1$]phenylalanine **1c** with PAL gave the unlabelled acid **3a**. Again this result is in accord with Battersby's studies and consistent with stereospecific loss of the 3-*pro-S* hydrogen in the reaction of (*S*)-phenylalanine **1a**.[1] A contaminant of *ca.* 1% of the labelled material **3b** would be expected in the acid **3a** produced from the reaction of the phenylalanine derivative **1c**, due to the presence of the 1% impurity of the stereoisomer **1b** in the starting material, but this was not detected in the ^{1}H NMR spectrum, presumably because the signals were masked by those of the dominant product **3a**.

When (2*R*,3*S*)-[3-$^2H_1$]phenylalanine **2b** was treated with PAL, [3-$^2H_1$]-*trans*-cinnamic acid **3b** with 92% deuterium incorporation was obtained, whereas the reaction of (2*R*,3*R*)-[3-$^2H_1$]phenylalanine **2c** with the enzyme gave the labelled acid **3b** with 27% deuterium incorporation. These results establish that while the loss of hydrogen from (*R*)-phenylalanine **2a** in the conversion to *trans*-cinnamic acid **3a** is not stereospecific, the enzyme preferentially abstracts the 3-*pro-R* hydrogen from this substrate. It is thus apparent that the reversal of stereochemistry of the substrate, from (*S*)-phenylalanine **1a** to the (*R*)-enantiomer **2a**, results in a reversal of the stereoselectivity of β-hydrogen abstraction.

This outcome can be explained by considering the likely orientation of the substrates **1a** and **2a** in the enzyme active site. It is reasonable to assume that the conformation of (*S*)-phenylalanine **1a** bound to the enzyme is as shown in Fig. 1a, where the amino, carboxyl and phenyl substituents, and the 3-*pro-S* hydrogen which is abstracted, are coplanar, and the carboxyl and phenyl substituents are antiperiplanar, as are the 3-*pro-S* hydrogen and the amino substituent. The antiperiplanar orientation of the carboxyl and phenyl substituents is consistent with the observation that *trans*-cinnamic acid **3a** binds very effectively to the enzyme active site,[2] while the spatial arrangement of the amino substituent and the 3-*pro-S* hydrogen facilitates their elimination. It is likely that with (*R*)-

phenylalanine **2a**, the phenyl, carboxyl and amino substituents interact with the enzyme *via* the same recognition sites involved in binding (*S*)-phenylalanine **1a**, and therefore adopt a coplanar orientation with the phenyl and carboxyl groups antiperiplanar (Fig. 1b). In this conformation, since the 3-*pro-R* hydrogen is located in the plane of the phenyl, carboxyl and amino substituents, and antiperiplanar to the amino substituent, it is located near that of the 3-*pro-S* hydrogen of bound (*S*)-phenylalanine **1a** and is removed in the enzyme-catalysed elimination.

There are two possible explanations for the lack of stereospecificity in the reactions of the deuteriated phenylalanine derivatives **2b** and **2c**. In a synperiplanar elimination, abstraction of the 3-*pro-S* hydrogen from (*R*)-phenylalanine **2a** may compete with loss of the 3-*pro-R* hydrogen. If the extent of this reaction is *ca.* 15%, a deuterium isotope effect of *ca.* 1.8 would account for the reaction of (2*R*,3*S*)-[3-$^2H_1$]phenylalanine **2b** to give [3-$^2H_1$]-*trans*-cinnamic acid **3b** with 92% deuterium incorporation and of (2*R*,3*R*)-[3-$^2H_1$]phenylalanine **2c** to give the acid **3b** with 27% deuterium incorporation. Alternatively, reversible abstraction of the α-hydrogen from (*R*)-phenylalanine **2a**, and racemization, may compete with loss of the 3-*pro-R* hydrogen. There was no evidence of racemization in partially reacted samples of (*R*)-phenylalanine **2a**, but it is unlikely that the concentration of the product (*S*)-phenylalanine **1a** would build up to detectable levels under these circumstances. Instead, being a better substrate for the enzyme, (*S*)-phenylalanine **1a** would be converted rapidly into *trans*-cinnamic acid **3a**, with loss of the 3-*pro-S* hydrogen. Based on this hypothesis, the reaction of (2*R*,3*S*)-[3-$^2H_1$]phenylalanine **2b** to give [3-$^2H_1$]-*trans*-cinnamic acid **3b** with 92% deuterium incorporation indicates a selectivity of *ca.* 11.5 : 1 for loss of the 3-*pro-R* hydrogen over racemization, while the comparison with the reaction of (2*R*,3*R*)-[3-$^2H_1$]phenylalanine **2c** to give the acid **3b** with 27% deuterium incorporation reflects a deuterium isotope effect of *ca.* 3.4 for loss of the β-hydrogen.

In any event, the primary response of PAL to the change in stereochemistry of the substrate, from (*S*)-phenylalanine **1a** to the (*R*)-enantiomer **2a**, is to reverse the stereoselectivity of β-hydrogen abstraction. Accordingly, the loss of a hydrogen and ammonia from each of the phenylalanine enantiomers **1a** and **2a** involves mainly antiperiplanar elimination.

Experimental

General experimental details have been reported previously.[6] PAL (Grade 1 from *Rhodotorula glutinis*; solution in 60% glycerol, 3 mmol dm^{-3} Tris-HCl, pH 7.5) was purchased from Sigma Chemical Co., and used without further purification. The brominated phenylalanine derivatives **4a**, **b** and **5a**, **b** were synthesized from the corresponding phenylalanine enantiomers **1a** and **2a**, using literature procedures.[6]

(2S,3S)-[3-$^2H_1$]-N-*Phthaloylphenylalanine Methyl Ester* **4c**.—A mixture of the bromide **4a** (1.0 g, 2.6 mmol) and 5% palladium-on-carbon (100 mg) in methan[$^2H_1$]ol (99.5% deuteriated; 20 cm^3) was stirred at −20 °C under an atmosphere of deuterium gas for 72 h, after which it was filtered and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in dichloromethane and the solution was washed with 10% aqueous sodium carbonate, dried and concentrated under reduced pressure. Crystallization of the residual oil from hexane–ethyl acetate gave the deuteride **4c** as colourless prisms (717 mg, 90%), m.p. 125–127 °C; δ($CDCl_3$) 3.53 (d, *J* 11.7, 1 H), 3.77 (s, 3 H), 5.16 (d, *J* 11.7, 1 H), 7.11–7.19 (m, 5 H) and 7.65–7.78 (m, 4 H); *m*/*z* 310 (M^+, 99% $^2H_1$). The ^1H NMR spectrum showed that the deuteride **4c** was contaminated with *ca.* 1% of the diastereoisomer **4d**.

(2S,3R)-[3-$^2H_1$]-N-*Phthaloylphenylalanine Methyl Ester* **4d**.—The deuteride **4d**, prepared in 91% yield from **4b** as described above for the synthesis of the diastereoisomer **4c**, had m.p. 124–126 °C; δ($CDCl_3$) 3.59 (d, *J* 4.8, 1 H), 3.77 (s, 3 H), 5.16 (d, *J* 4.8, 1 H), 7.11–7.19 (m, 5 H) and 7.65–7.78 (m, 4 H); *m*/*z* 310 (M^+, 99% $^2H_1$). The ^1H NMR spectrum showed that the deuteride **4d** was contaminated with *ca.* 1% of the diastereoisomer **4c**.

(2R,3S)-[3-$^2H_1$]-N-*Phthaloylphenylalanine Methyl Ester* **5c** *and* (2R,3R)-[3-$^2H_1$]-N-*Phthaloylphenylalanine Methyl Ester* **5d**.—The deuterides **5c** and **5d**, prepared from the corresponding bromides **5a** and **5b** as described above for the synthesis of the deuteride **4c**, had spectral and physical properties comparable to those of the corresponding enantiomers **4d** and **4c**.

(2S,3R)-[3-$^2H_1$]*Phenylalanine* **1b**.—A solution of the deuteride **4d** (500 mg, 1.6 mmol) in 6 mol dm^{-3} hydrochloric acid–acetic acid (2 : 1; 30 cm^3) was heated at reflux for 6 h, after which it was cooled and concentrated under reduced pressure. Water (30 cm^3) was added to the residual oil and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in a dry mixture of aniline (1.5 cm^3) and ethanol (15 cm^3). The precipitate that formed over 96 h was filtered off and washed with acetone to give (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b** as a colourless powder (223 mg, 83%), m.p. 272–276 °C; δ(D_2O) 3.21 (d, *J* 4.9, 1 H), 3.92 (d, *J* 4.9, 1 H) and 7.24–7.38 (m, 5 H); *m*/*z* 167 (M^+ + 1, 99% $^2H_1$). This spectral data is consistent with that reported.[1,5] The ^1H NMR spectrum showed that the deuteride **1b** was contaminated with *ca.* 1% of the diastereoisomer **1c**.

(2S,3S)-[3-$^2H_1$]*Phenylalanine* **1c**.—The deuteride **1c**, prepared in 85% yield from **4c** as described above for the synthesis of diastereoisomer **1b**, had m.p. 270–275 °C; δ(D_2O) 3.03 (d, *J* 7.9, 1 H), 3.92 (d, *J* 7.9, 1 H) and 7.24–7.38 (m, 5 H); *m*/*z* 167 (M^+ + 1, 99% $^2H_1$). This spectral data is consistent with that reported.[1,5] The ^1H NMR spectrum showed that the deuteride **1c** was contaminated with *ca.* 1% of the diastereoisomer **1b**.

(2R,3S)-[3-$^2H_1$]*Phenylalanine* **2b** *and* (2R,3R)-[3-$^2H_1$]-*Phenylalanine* **2c**.—The free amino acids **2b** and **2c**, prepared from the corresponding protected derivatives **5c** and **5d** as described above for the synthesis of the deuteride **1b**, had spectral and physical properties comparable to those of the corresponding enantiomers **1b** and **1c**.

Reaction of (2S,3R)-[3-$^2H_1$]*Phenylalanine* **1b** *Catalysed by PAL*.—A solution of (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b** (33 mg, 0.20 mmol) and PAL (0.2 cm^3, 0.5 units) in sodium borate buffer (0.04 mol dm^{-3}, pH 8.7; 25 cm^3) was stirred at 30 °C for 20 h, after which it was acidified to pH 1, by adding concentrated hydrochloric acid, and extracted with dichloromethane (2 × 25 cm^3). The combined extracts were dried and concentrated under reduced pressure and crystallization of the residual oil gave [3-$^2H_1$]-*trans*-cinnamic acid **3b** (15.9 mg, 54%), m.p. 135–137 °C; δ($CDCl_3$) 6.47 (br s, 1 H), 7.41–7.44 (m, 3 H) and 7.55–7.58 (m, 2 H). The ^1H NMR spectrum showed that the deuteriated acid **3b** was contaminated with *ca.* 2% of the unlabelled material **3a**.

Reaction of (2S,3S)-[3-$^2H_1$]*Phenylalanine* **1c** *Catalysed by PAL*.—Treatment of (2*S*,3*S*)-[3-$^2H_1$]phenylalanine **1c** with PAL, as described above for the reaction of (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b**, gave *trans*-cinnamic acid **3a** (17.8 mg, 60%), m.p. 134–136 °C (lit.,[11] 132 °C); δ($CDCl_3$) 6.47 (d, *J* 16.0, 1 H), 7.41–7.44 (m, 3 H), 7.55–7.58 (m, 2 H) and 7.81 (d, *J* 16.0, 1 H).

Reaction of (2R,3S)-[3-$^2H_1$]*Phenylalanine* **2b** *and* (2R,3R)-[3-$^2H_1$]*Phenylalanine* **2c** *Catalysed by PAL.*—(2*R*,3*S*)-[3-$^2H_1$]Phenylalanine **2b** and (2*R*,3*R*)-[3-$^2H_1$]phenylalanine **2c** were each treated with PAL, as described above for the reaction of (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b** except that the mixtures were each allowed to react for 8 days, and gave [3-$^2H_1$]-*trans*-cinnamic acid **3b**, in yields of 70% (92% $^2H_1$) and 59% (27% $^2H_1$), respectively, with spectral and physical properties comparable with those of the sample obtained as described above. In each case the deuterium content was determined from the ratio of signals due to the acid **3a** and the labelled species **3b** in the ^1H NMR spectrum.

Acknowledgements

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