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The Synthesis of Deuteriated 4-*n*-Alkyl-4′-Cyanobiphenyls†

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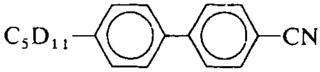
A single synthetic route for chain-deuteriated, totally ring-deuteriated, or per-deuteriated 4-*n*-alkyl-4′-cyanobiphenyls has been developed. This new route gives better yields than the previously reported route for the synthesis of 4-cyano-4′-*n*-pentyl-d_{11}-biphenyl and also eliminates the main "impurity" present in the final product. The synthesis of 4-cyano-4′-*n*-pentyl-d_{11}-2′,3′,5′,6′-tetradeuteriobiphenyl is also reported.

INTRODUCTION

In 1973 a project was initiated to study the structure of various liquid crystal phases by inelastic neutron scattering. Our part in this work was to synthesize the highly deuteriated mesogens that would be required for this study. The obvious choices from compounds which exhibit nematic and smectic A phases were the then recently synthesized 4-cyano-4′-*n*-pentylbiphenyl (5CB) and 4-cyano-4′-*n*-octylbiphenyl respectively. We have already reported the synthesis[1] of 4-cyano-4′-*n*-pentyl-d_{11}-biphenyl (5CB-d_{11}, (I)) and the effect that deuteriation has on the transition temperatures of 4-*n*-alkyl-4′-cyanobiphenyls and other mesogens.[2]



(I)

The synthetic route used to prepare 5CB-d_{11}[1] has two disadvantages: (1) It cannot be readily adapted to the preparation of totally ring-deuteriated or

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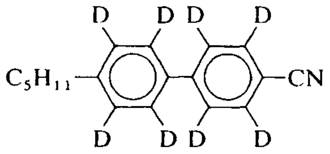
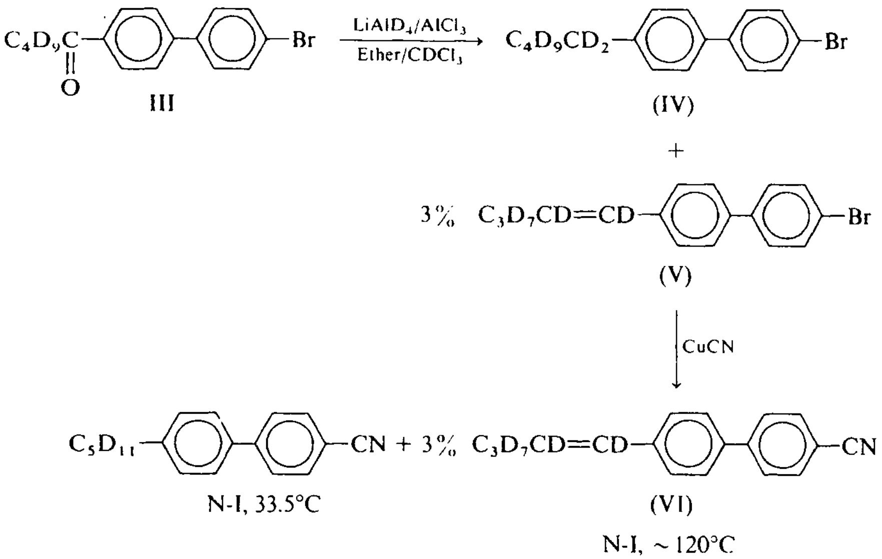
per-deuteriated 4-*n*-alkyl-4′-cyanobiphenyls such as 4-cyano-4′-*n*-pentylbiphenyl-d_8 (5CB-d_8, (II)). (2) The method used to reduce 4-bromo-4′-*n*-



(II)

pentanoyl-d_9-biphenyl (III) to 4-bromo-4′-*n*-pentyl-d_{11}-biphenyl (IV)—see Scheme I—produces approximately 3% of the unsaturated compound 4-bromo-4′-pent-l-enyl-d_9-biphenyl (V). In some cases it was possible to remove (V) by crystallisation,[1] but it was found later that this was not always

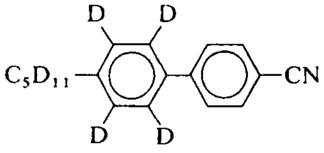


SCHEME I

the case. If a sample of (IV) containing 3% of (V) was cyanated, then ~3% of 4-cyano-4′-*n*-pent-l-enyl-d_9-biphenyl (VI) would also be produced. This compound probably has a N-I transition temperature of 121 °C[2,3] and so was a highly undesirable impurity. The presence of (VI) could be readily detected by g.l.c. and (VI) could be removed by vacuum distillation since it has a higher boiling point than that of 5CB-d_{11}. However, in the preparation of small amounts (~1.5 g) of 5CB-d_{11}, the removal of (VI) leads to a loss of ~25% of the desired product.

Because of these two disadvantages it was decided to seek an alternative synthetic route to deuteriated 4-*n*-alkyl-4'-cyanobiphenyls.

At about this time, a sample of 4-cyano-4'-*n*-pentyl-d_{11}-2', 3', 5', 6'-tetradeuteriobiphenyl (5CB-d_{15}, (VII)) was requested by GR Luckhurst of Southampton University for deuteron magnetic resonance studies. The results of physical studies using this material have been published elsewhere,[4] and it was felt desirable to include the method of preparation in this paper. The route to (VII) involved first the preparation of 4-bromo-2', 3', 4', 5', 6'-pentadeuteriobiphenyl by the Gomberg reaction between 4-bromobenzene diazonium chloride and benzene-d_6.



(VII)

RESULTS AND DISCUSSION

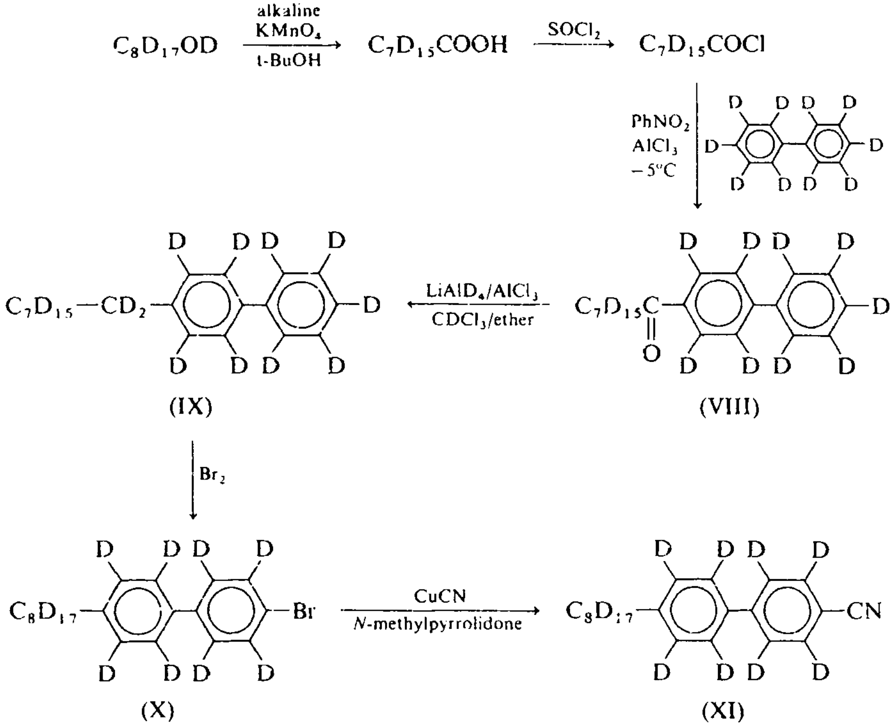
The preparation of chain-, ring- or per-deuteriated 4-*n*-alkyl-4'-cyanobiphenyls

It is apparent that the synthetic route illustrated in Scheme II for the preparation of 4-cyano-4'-*n*-octyl-d_{17}-biphenyl-d_8 (8CB-d_{25}, (XI)) can be readily adapted to prepare chain-deuteriated, ring-deuteriated, or, as shown, per-deuteriated 4-*n*-alkyl-4'-cyanobiphenyls.

The oxidation of octan-l-ol to octanoic acid could not be carried out by the classical method using aqueous alkaline potassium permanganate as reported in the literature. This was presumably due to the extremely low solubility of the octan-l-ol-d_{18} in the aqueous phase, since the addition of t-BuOH produced the desired octanoic acid in 90% yield after stirring the reaction mixture at room temperature for 2 days. This method was used in preference to one involving treatment of the Grignard reagent obtained from l-bromoheptane-d_{15} with carbon dioxide, simply because the octan-l-ol-d_{18} was much cheaper than l-bromoheptane-d_{15}.

The preparation of octanoyl chloride-d_{15} was carried out in the usual manner; the product was not purified after removing the excess of thionyl chloride by rotary evaporation.

If the acid chloride used in the Friedel Crafts reaction to prepare (VIII) contains thionyl chloride and the reaction is carried out at room temperature,



SCHEME II

then the thionyl chloride will react with the biphenyl to form a bis-(biphenylyl) sulphoxide. The removal of this impurity leads to a reduction in the yield of (VIII). This side reaction is not a consideration in the preparation of deuteriated derivatives of 4-cyano-4′-*n*-octylbiphenyl and ring-deuteriated 4-cyano-4′-*n*-pentylbiphenyl. In the former case, the acid chloride can be readily purified without the loss of a valuable deuteriated material, since the high boiling octanoyl chloride-d_{15} allows the ready removal of the more volatile thionyl chloride. In the latter case, purification of pentanoyl chloride does involve loss of the acid chloride, but this is unimportant in the case of a non-deuteriated material.

However, in the case of chain-deuteriated or per-deuteriated 5CB, purification of the acid chloride is not possible without high mechanical losses of material. It was found however that this side reaction could be suppressed by carrying out the acylation reaction at $\sim -5°C$.

The conversion of the ketone (VIII) to 4-*n*-octyl-d_{17}-biphenyl-d_9 (IX) went smoothly, but again approximately 3% of the unsaturated 4-oct-1-enylbiphenyl was produced. However, a simple vacuum distillation of this mixture reduced the level of this impurity to less than 1%, without an undesirable loss of material. The remaining small amount of impurity was subsequently removed by crystallisation of the bromo-compound (X).

A literature method for the preparation of 4-*n*-alkyl-4'-bromobiphenyls by direct bromination of the 4-*n*-alkylbiphenyl did not exist. Several solvents were tried for this reaction, e.g., acetic acid, carbon tetrachloride, and chloroform. Various reaction times were explored, and the effects of the presence or absence of catalytic amounts of pyridine were examined. The progress of the reaction was followed by t.l.c. using hexane fraction (Hopkin and Williams Limited, England) as eluant. The most successful method used chloroform as the solvent, without the presence of a catalyst. The bromine (2 moles) was added in three portions as a 10% solution of bromine in chloroform at 0°C at intervals of 24 hours. This method gave an 85% yield of (X).

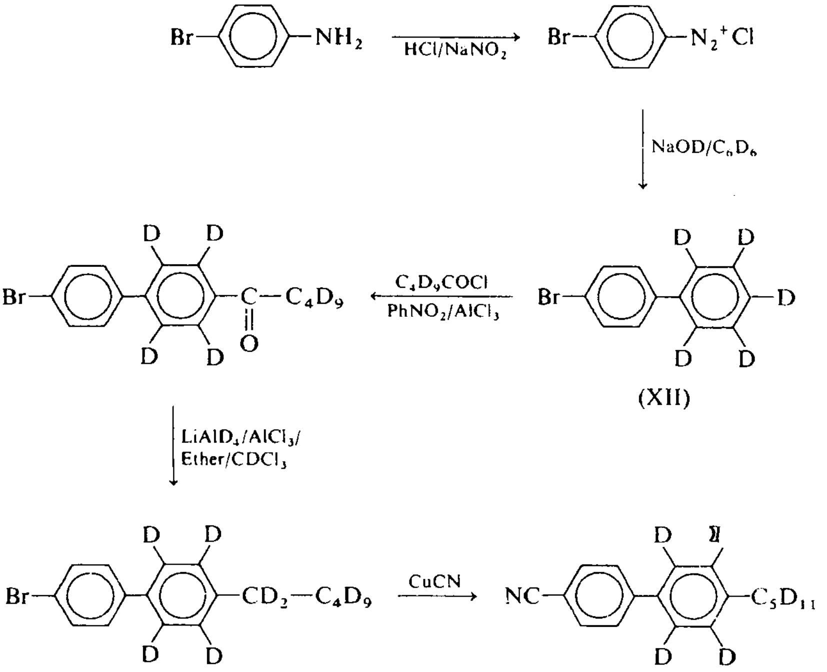
The cyanation of (X) by the normal method[1] and purification of the product by column chromatography (silica gel; chloroform/light petroleum, b.p. 40–60°C 1.5 : 1 as eluant) followed by vacuum distillation gave the required product with a purity of $\geq 99\%$ and an isotopic purity $\geq 98\%$. The isotopic purities of the final products and of the intermediates had not been reduced from those of the starting materials by the chemical reactions illustrated in Scheme II.

The synthesis of 5CB-d_{15}

It was concluded that a sample of 5CB-d_{15} or a suitable starting material could not be prepared by using a hydrogen-deuterium exchange process, because of the high degree of isotopic purity and the selectivity required. Therefore, it was decided to prepare this compound by the route illustrated in Scheme III.

The main problem associated with this synthesis was the preparation of 4-bromo-2', 3', 4', 5', 6'-pentadeuteriobiphenyl (XII). Although Gomberg reactions are well known, they give low yields, and in this case financial considerations limited the excess of deuteriated benzene that could be used. A number of preparations were tried using non-deuteriated benzene, and it was found that the best yields (17%) were obtained by simultaneously adding solutions of the 4-bromobenzene diazonium chloride and 5 M sodium hydroxide to vigourously stirred benzene. The required product was obtained by extraction into petroleum ether (b.p. 40–60°C) followed by vacuum distillation and finally crystallisation from methanol.

When this procedure was used with deuteriated benzene a yield of only 7% was obtained. It is possible that this was due (Scheme IV) to an apparent isotope effect,[5] leading to a larger lifetime for the intermediate cyclohexadienyl radical (XIII) compared with that for the radical (XIV). Thus, radical

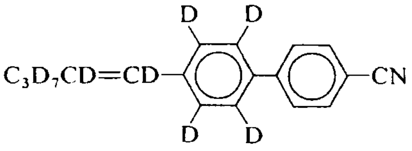


SCHEME III

(XIV) will form 4-bromobiphenyl more readily than radical (XIII), due to the lower energy of the C—H bond compared with the C—D bond. This will lead to the formation of undesirable by-products.

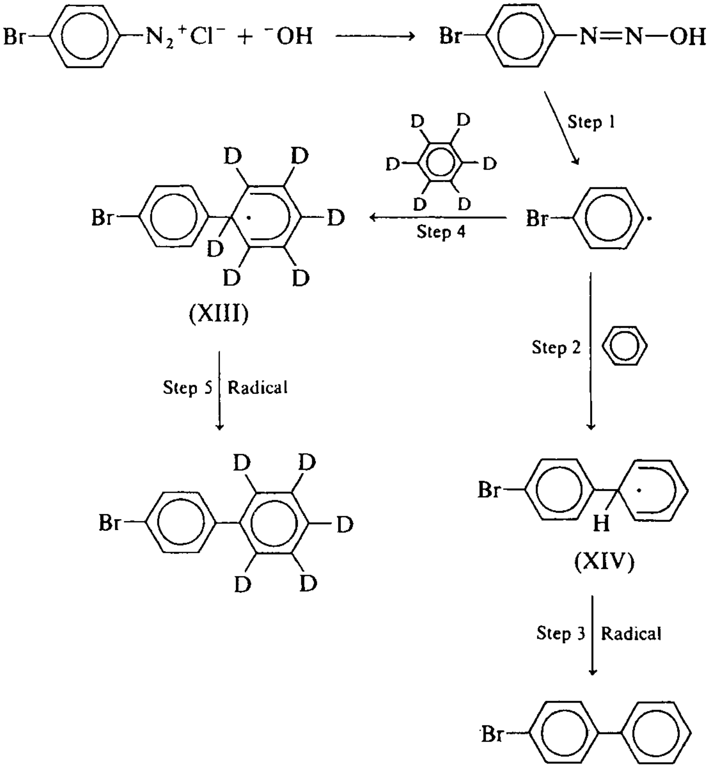
In order to increase the amount of (XII), the unreacted benzene-d_6 was recovered from the reaction mixture and used again.

The remaining part of the synthetic route shown in Scheme III was carried out in the usual manner,[1] with particular emphasis on eliminating any olefin (XV) from the final product.



(XV)

The deuteriated mesogens prepared in our laboratories have been studied by inelastic neutron scattering[6,7] and deuteron magnetic resonance.[4,8,9]



SCHEME IV

EXPERIMENTAL

The preparative methods described in this section were tested at least twice using non-deuteriated materials. In addition the less straightforward reactions e.g., the Gomberg reaction, were repeated several times in order to maximise the yield of the desired product. All deuteriated starting materials and reagents were purchased from Merck, Sharp, and Dohme of Canada and used without purification. The purity of final products was checked by glc and by nmr; infra-red and mass spectrometry provided further checks on structure

The preparation of chain-deuteriated, ring-deuteriated and per-deuteriated 4-*n*-alkyl-4′-cyanobiphenyls is illustrated by the synthesis of 4-cyano-4′-*n*-octyl-d_{17}-biphenyl-d_8.

Octanoic acid-d_{15} To a vigorously stirred mixture of commercial octan-l-ol-d_{18} (5 g) and t-butanol (50 ml) which had been cooled in an ice bath for

15 min was added a mixture of potassium permanganate (8.3 g in 285 ml of water) and sodium hydroxide (1.7 g in 23 ml of water). The reaction mixture was cooled for a further $1\frac{1}{2}$ hours and then allowed to warm up to room temperature. After 24 hours the reaction mixture was cooled in an ice bath and a further portion of alkaline permanganate (2.4 g $KMnO_4$ in 70 ml of water and 0.3 g NaOH in 3 ml of water) was added. After cooling for 1 hour, the reaction mixture was stirred at room temperature for 24 hours. The excess of potassium permanganate was destroyed with sodium metabisulphite (3 g). The reaction mixture was filtered and the residue washed with 2 M NaOH solution (100 ml). The filtrate and washings were combined and then shaken twice with ether (125 ml). The aqueous phase was acidified with concentrated HCl (30 ml). The crude product separated out and was extracted into ether (50 ml and then 2 × 100 ml). The combined ether extracts were washed with water (50 ml), dried (Na_2SO_4) and then rotary evaporated to remove the ether and the t-butanol. The crude acid (4.8 g, 89%) was used in the next stage.

4-n-Octanoyl-d_{15}-biphenyl-d_9 The above octanoic acid-d_{15} (4.7 g, 0.03 mole) was added dropwise to an excess of thionyl chloride (3.0 ml)† and then stirred at room temperature for 15 minutes. The reaction mixture was heated under reflux for 45 minutes, cooled to room temperature, and the excess of thionyl chloride removed by careful rotary evaporation. This unpurified acid chloride was added dropwise to a stirred solution of aluminium chloride (5.0 g, 0.038 mole) and biphenyl-d_{10} (5.1 g, 0.031 mole) in dry nitrobenzene (26 ml) at −5°C. The temperature of the reaction mixture was kept below 0°C during the addition of the octanoyl-d_{15} chloride and for a further 4 hours. The reaction mixture was stirred overnight at room temperature, treated with a mixture of ice (40 g), concentrated HCl (16 ml), and water (8 ml) for 20 minutes, and then steam distilled. The residue was extracted into toluene; this solution was dried (Na_2SO_4), treated with decolourising charcoal, and then evaporated to dryness. The crude product was crystallised from acetone, and dried in a vacuum desiccator. The yield was 5.5 g (62%), mp 99–101°C.

4-n-Octyl-d_{17}-biphenyl-d_9 To a stirred mixture of lithium aluminium deuteride (2.0 g, 0.048 mole) in sodium-dried ether (38 ml) was added dropwise a solution of aluminium chloride (14.0 g, 0.105 mole) in ether (38 ml), followed by the dropwise addition of a solution of 4-*n*-octanoyl-d_{15}-biphenyl-d_9 (5.5 g, 0.018 mole) in chloroform-d_1 (76 ml). The reaction mixture was

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† In the case of pentanoyl-d_9 chloride, only a 10% excess of thionyl chloride was used, and the crude reaction mixture was used in the Friedel Crafts reaction.

stirred and heated under reflux for 21 hours. The excess of reducing agent was destroyed by the *careful* addition of deuterium oxide (34 ml) followed by 36% DCl in D_2O (56 ml). Ether (100 ml) was also added. The organic layer was separated, washed with water (3 × 100 ml), dried (Na_2SO_4), and the solvent removed by evaporation. The crude material was purified by vacuum distillation (188°C at 3 mm Hg) to give 4.5 g (85%) of product with a glc purity of >99% and a mp of 43–44°C.

4-Bromo-4'-n-octyl-d_{17}-biphenyl-d_8 To an ice-cold solution of 4-*n*-octyl-d_{17}-biphenyl-d_9 (4.5 g, 0.015 mole) in chloroform (11 ml) was added a 10% v/v solution of bromine in chloroform (5 ml, equivalent to 0.01 mole of Br_2). The mixture was slowly allowed to warm up to room temperature. After 24 hours, the reaction mixture was again cooled in an ice bath and a second portion (5 ml) of a freshly prepared 10% v/v solution of bromine in chloroform was added. A third addition of bromine solution (5 ml), again to the ice cold reaction mixture, was made 24 hours later. After a further 24 hours, the reaction mixture was poured into aqueous sodium metabisulphite solution in order to destroy the excess of bromine. Ether (100 ml) was then added; the organic layer was separated off, washed with water (3 × 100 ml), dried (Na_2SO_4), and then evaporated to remove the solvent. The residue was crystallised from ethanol and dried in a vacuum desiccator. The yield was 5.0 g (85%), mp 90–92°C.

4-Cyano-4'-n-octyl-d_{17}-biphenyl-d_8 4-Bromo-4'-*n*-octyl-d_{17}-biphenyl-d_8 (5.0 g, 0.014 mole) was dissolved in dry *N*-methylpyrrolidone (50 ml). Anhydrous copper (I) cyanide (2.6 g, 0.028 mole) was added and this mixture stirred and heated at 180°C for 3 hours. The reaction mixture was allowed to cool and then treated with a solution of anhydrous iron (III) chloride (12.5 g) in water (188 ml) and concentrated HCl (7 ml) at 50°C for 20 minutes. The product was extracted into ether (3 × 250 ml). The ether extracts were combined, washed with water (3 × 250 ml), dried (Na_2SO_4), treated with decolourising charcoal, and then evaporated to remove the solvent. The residue was purified by column chromatography (silica gel eluted with a 1.5 : 1 mixture of chloroform and petroleum ether, bp 40–60°C) followed by vacuum distillation (bp 168°C at 0.06 mm Hg). This gave 2.0 g (46%) of product with a glc purity of ≥99% and an isotopic purity of ≥98%. Satisfactory infra-red and mass spectra were also obtained. The transition temperatures of this material were crystal to smectic A, 21°C, smectic A to nematic, 33.0°C, nematic to isotropic liquid, 39.1°C. The transition temperatures of this material and other deuteriated 4-*n*-alkyl-4'-cyanobiphenyls are compared with those of undeuteriated analogues in Ref. 2.

4-Bromo-2′, 3′, 4′, 5′, 6′-pentadeuteriobiphenyl A mixture of water (100 ml) and 4-bromoaniline (57 g, 0.33 mole) was heated to 65°C and vigorously stirred. Concentrated HCl (72 ml, 0.75 mole) was added and the mixture cooled to − 5°C. A solution of sodium nitrite (25 g) in water (100 ml) was added dropwise, at such a rate that the temperature of the reaction mixture was maintained between 0 and 5°C, until there was an excess of nitrous acid present. This excess was then destroyed by the addition of urea. The reaction mixture was then filtered to give a clear, aqueous solution of 4-bromobenzene diazonium chloride, which was then added dropwise, together with a 5 M solution of sodium hydroxide (170 ml), to vigourously stirred benzene-d_6 (100 g). This dual addition took 1 hour, during which time the temperature of the reaction mixture was kept below 10°C. The reaction mixture was then gently stirred overnight at room temperature. The product was extracted into petroleum ether (bp 40–60°C, 4 × 400 ml). The extracts were combined, treated with charcoal, and the organic solvents removed by distillation. The distillate was then fractionated in order to reclaim the unreacted benzene-d_6. The residue was boiled with petroleum ether (bp 40–60°C, 250 ml); this mixture was then cooled, treated with charcoal, and filtered. The filtrate was evaporated to dryness. The residue was then distilled; the fraction boiling at 130–135°C at 3 mm Hg was collected and then crystallised from methanol. This procedure gave 5.8 g (7 %) of the required product, mp 89°C. A further 1.8 g (2 %) of product was obtained by repeating the reaction with the reclaimed benzene-d_6.

A sample of 4-cyano-4′-pentyl-d_{11}-2′, 3′, 5′, 6′-tetradeutriobiphenyl was then prepared by the methods illustrated in Scheme III and described in Ref. 1. The final product had a glc purity of 99 %, an isotopic purity > 98 %, and the following transition temperatures: solid to nematic 22°C, nematic to isotropic liquid 34.3°C.

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