Enantioselective Synthesis of *cis*- and *trans*-2(*S*)-Amino-1-*d*-indane: Debrominative [1,2]-Hydride Shift Rearrangement by Reduction of *cis*-2-Azido-1-bromoindane with $LiAlD_4$

Anton A. Mitrochkine,[†] Ingrid Blain,[†] Christelle Bit,[†] Cécile Canlet,[‡] Sébastien Pierre,[†] Jacques Courtieu,[‡] and Marius Réglier*,[†]

Laboratoire de Bioinorganique Structurale, UMR CNRS 6517, Universités d'Aix-Marseille 1 et 3, Faculté des Sciences et Techniques de Saint Jérôme, case 432, avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France, and Institut de Chimie Moléculaire d'Orsay, Bât 410, Laboratoire de Chimie Structurale Organique, URA CNRS 1384, 91405 Orsay Cedex, France

Received February 27, 1997[⊗]

This article describes the synthesis of the racemic and optically pure forms of (1*R*,2*S*)-*cis*- and (1*S*,2*S*)-*trans*-2-Amino-1-*d*-indanes **2** {94% ee} and **3** {83% ee} (ee determined by ^2H NMR in chiral liquid crystal PBLG/CH_2Cl_2, Courtieu, J. *et al. J. Am. Chem. Soc.* **1995**, *117*, 6520) prepared by $LiAlD_4$ reduction of (±)- and (1*S*,2*S*)-*trans*-2-azido-1-bromomoindane (**11**) {87% ee} and (±) and (1*R*,2*S*)-*cis*-2-azido-1-[(methanesulfonyl)oxy]indane (**10**) {83% ee}, respectively. Whereas the $LiAlD_4$ reduction of *trans*-2-azido-1-bromomoindane (**11**) led to *cis*-2-amino-1-*d*-indane **2** by a S_N2 pathway, exclusively, the reduction of *cis*-1-bromo derivative **12** gave only small amounts of the S_N2 product *trans*-2-amino-1-*d*-indane (**3**) (15%) accompanied by 2-amino-2-*d*-indane (**4**) (85%) in which the deuterium atom is incorporated in α position to the amino group. It was established that the primary amine **4** comes from a stereospecific [1,2]-hydride shift rearrangement. We propose that the azido group is reduced first, and the [1,2]-hydride shift rearrangement prevails over the competitive S_N2 substitution. The exclusive formation of *trans*-2-amino-1-*d*-indane (**3**) requires *cis*-2-azido-1-[(methanesulfonyl)oxy]indane (**10**) where the mesylate assisted by electrophilic Li^+ cation switches the deuteride attack to the ester carbon and the direct S_N2 substitution occurs before the azide is reduced.

Introduction

In the course of our studies on the functional models[1] and the topology[2] of the dopamine *β*-hydroxylase active site (DBH; EC 1.14.17.1),[3] a copper-containing monooxygenase which catalyzes the transformation of dopamine into noradrenaline, it became necessary to synthesize 2-aminoindanes **2** and **3** stereoselectively deuterated in one of the benzylic positions. In addition, both racemic and optically pure (2*S*) forms were required. Aluminohydrides which are the reagents commonly used for the C−X bond hydrogenolysis of alkyl halides, react as nucleophilic reagents that donate a hydride ion to the halogenated substrates.[4] Although a variety of mechanisms, including S_N2 and single electron transfer (SET), have been proposed to describe this reduction,[5,6] the pioneering stereochemical studies of Eliel,[7] Mosher,[8] and more recently Ashby[6] have shown that $LiAlH_4$ reacts with secondary benzylic chlorides and bromides according to a S_N2 mechanism devoid of radical species. Therefore, we decided to study the $LiAlD_4$ reduction of *trans*- and *cis*-2-azido-1-bromoindanes (**11** and **12**) in order to prepare selectively *cis*- and *trans*-2-amino-1-*d*-indanes (**2** and **3**). During this work, we found that the reduction of the *cis*-1-bromo derivative **12** did not follow the predicted pathway but gave 2-amino-2-*d*-indane (**4**) in which the deuterium atom is incorporated in the α position of the amino group. Using 2-azido-1-bromoindanes **21** and **22** deuterated in 2 position, we will show that **4** comes from a stereospecific [1,2]-hydride shift rearrangement.

Scheme 1

X = Y = H; **1** (R = H); **5** (R = CF_3CO)
X = H; Y = D; **2** (R = H); **6** (R = CF_3CO)
X = D; Y = H; **3** (R = H); **7** (R = CF_3CO)

4

Results and Discussion

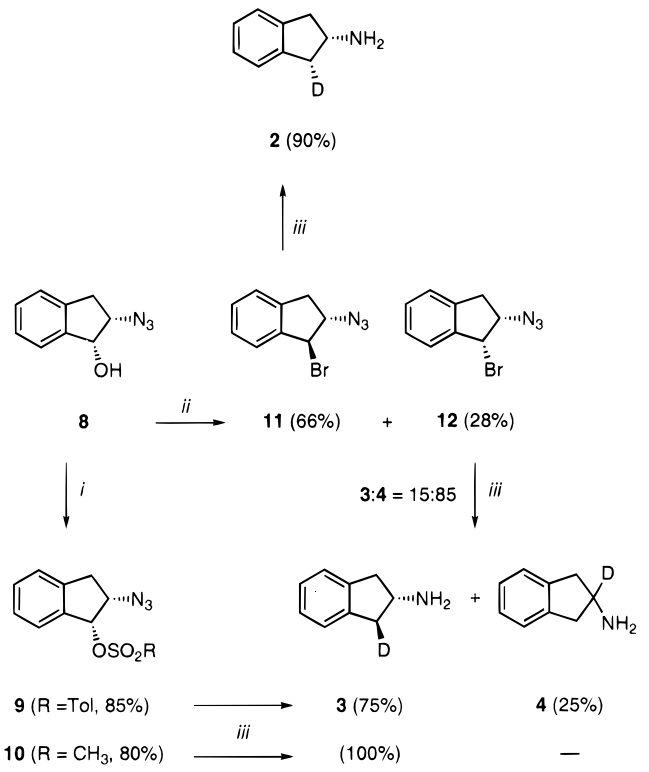
(±)-2-Azido-1-bromoindanes **11** and **12** were obtained as a mixture from (±)-2-azido-1-indanol (**8**)[9] by bromination with PBr_3 in CCl_4. We found that the ratio **11**:**12** depended on the reaction conditions. For example, a **11**:**12** = 99:1 ratio was obtained when PBr_3 was rapidly added (<5 min) at rt to a 0.3 M CCl_4 solution of **8**. Given that both bromides **11** and **12** are necessary for our study

[†] Universités d'Aix-Marseille.
[‡] URA CNRS.
[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) Réglier, M.; Amadéi, E.; Alilou, E. H.; Eydoux, F.; Pierrot, M.; Waegell, B. In *Bioinorganic Chemistry of Copper*; Karlin, K. D., Tiecklar, Z., Eds., Chapman and Hall: New York, 1993; p 348.
(2) Eydoux, F.; Chlenov, M. A.; Réglier, M. *Bioorg. Med. Chem. Lett.* **1995**, *9*, 941.
(3) Stewart, L. C.; Klinmann, J. P. *Annu. Rev. Biochem.* **1988**, *57*, 551. Klinmann, J. P. *Chem. Rev.* **1996**, *96*, 2541.
(4) Seyden-Penne, J. *Reduction by Alumino- and Borohydrides in Organic Synthesis*; VCH: New York, 1991.
(5) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1986**, *51*, 3598. Ashby, E. C.; Pham, T. N.; Amrollah-Madjdabadi, A. *J. Org. Chem.* **1991**, *56*, 1596.
(6) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545.
(7) Eliel, E. L. *J. Am. Chem. Soc.* **1949**, *71*, 3970.
(8) Elsenbaumer, R. L.; Mosher, H. S. *J. Org. Chem.* **1979**, *44*, 600.
(9) Mitrochkine, A.; Eydoux, F.; Martres, M.; Gil, G.; Heumann A.; Réglier, M. *Tetrahedron: Asymmetry* **1995**, *6*, 59. Mitrochkine, A.; Gil, G.; Réglier, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1535.

S0022-3263(97)00378-2 CCC: $14.00

Scheme 2[a]



[a] (i) NaH, THF, then TsCl or nBuLi, THF then MsCl, (ii) PBr_3, CCl_4, (iii) $LiAlD_4$, THF.

and since they are very easily separated by flash chromatography (SiO_2, pentane:CH_2Cl_2 = 7:3, $\Delta R_f = 2$), we chose reaction conditions (addition of PBr_3 to a 0.03 M CCl_4 solution of **8**) which gave a maximum amount of *cis*-bromide **12** (94% yield, **11**:**12** = 2.4:1). In the same way, optically active (1*R*,2*S*)-**8** {83% ee}[9] was converted into (1*S*,2*S*)-**11** {65% yield, 87% ee, $[\alpha]^D_{25} = +5.7$ (*c* 1.4, $CHCl_3$)} and (1*R*,2*S*)-**12** {25% yield, 90% ee, $[\alpha]^D_{25} = -21$ (*c* 1, $CHCl_3$)} both without noticeable loss of enantiomeric purity.[10]

(±)-**11** was transformed with $LiAlD_4$ in THF, into (±)-2-amino-1-*d*-indane (**2**) (90% yield) which showed a broad singlet at 2.64 ppm in the ^{2}H-NMR spectrum. The stereochemistry of **2** was clearly assigned by ^{1}H-NMR. Nondeuterated 2-aminoindane (**1**) shows three characteristic signals at 3.8, 3.1 and 2.6 ppm integrating for 1, 2, and 2 protons and, respectively, assigned to H_α, H_β^{trans}, and H_β^{cis} protons (Figure 1a). Deuterated compound **2** shows the same three resonances but with a ratio of the signal intensity of H_β^{trans}:H_β^{cis} = 2 (Figure 1b). This ratio and the 2.64 ppm chemical shift in ^{2}H-NMR indicate that the deuterium atom in **2** is *cis* with respect to the amino group.

Reduction of the optically active *trans*-bromide (1*S*,2*S*)-**11** {87% ee} afforded (1*R*,2*S*)-**2** at a 66% yield {94% ee}. The enantiomeric excess was measured after transformation of (±)-**2** and (1*R*,2*S*)-**2** into *N*-trifluoroacetamide derivatives (±)-**6** and (1*R*,2*S*)-**6**, respectively, and through ^{2}H-NMR using a chiral liquid crystal (PBLG/CH_2Cl_2) following the technique proposed by Courtieu *et al.*[11] The

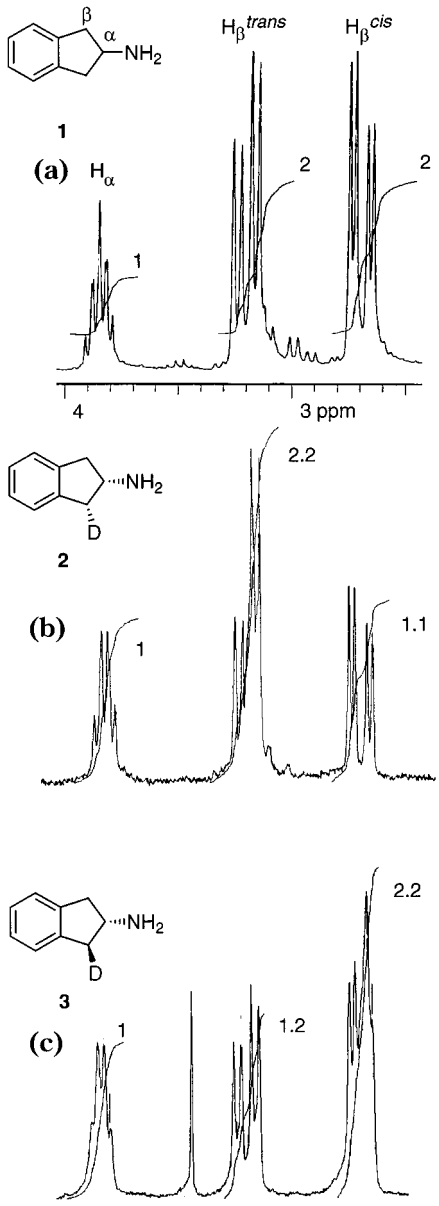


Figure 1. ^{1}H NMR spectra in $CDCl_3$ of 2-aminoindanes **1**−**3**.

^{2}H-NMR spectra of (±)- and (1*R*,2*S*)-**6** are shown in Figure 2. Two different doublets are found for (±)-**6**, one for each enantiomer, with quadrupolar splittings $\Delta\nu_{Q1}$ = 1246 Hz and $\Delta\nu_{Q2}$ = 526 Hz (Figure 2a), whereas (1*R*,2*S*)-**6** shows one doublet with $\Delta\nu_Q$ = 526 Hz (Figure 2b). The large difference in the quadrupolar splittings ($\Delta_{Q1} - \Delta_{Q2}$ = 720 Hz) permits the direct measurement of the enantiomeric excess (94%) by integration of signals.

Reduction of (±)-**12** afforded a mixture which exhibits two broad singlets at 3.75 ppm and 3.10 ppm in the ^{2}H-NMR at a 5.7:1 ratio. This result indicates that the desired compound **3** is obtained as minor product (signal at 3.10 ppm, 15%) accompanied by a new deuterated compound **4** (85%) for which the 3.75 ppm chemical shift in the ^{2}H-NMR suggests a deuterium atom α to the amino group. ^{1}H and ^{13}C-NMR spectra confirm this attribution. Indeed, in ^{1}H-NMR the three characteristic signals of H_α, H_β^{trans}, and H_β^{cis} are in a ratio of 1:8.2:9.6 (Figure 3a). The two doublets of doublets observed for **1** at 3.1 ppm (H_β^{trans}) and 2.6 ppm (H_β^{cis}) are replaced in **4** by two simple doublets with a coupling constant $^2J_{gem}$ = 15.9 Hz. Finally, in the ^{13}C-NMR spectroscopy, the singlet at 53.2

(10) Enantiomeric excesses were determined by HPLC using Chiralcel column OD-H (Daicel) with hexane/isopropyl alcohol (99/1) as eluant.

(11) Canet, I.; Courtieu, J.; Loewenstein, A.; Meddour, A.; Pechiné, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 6520.

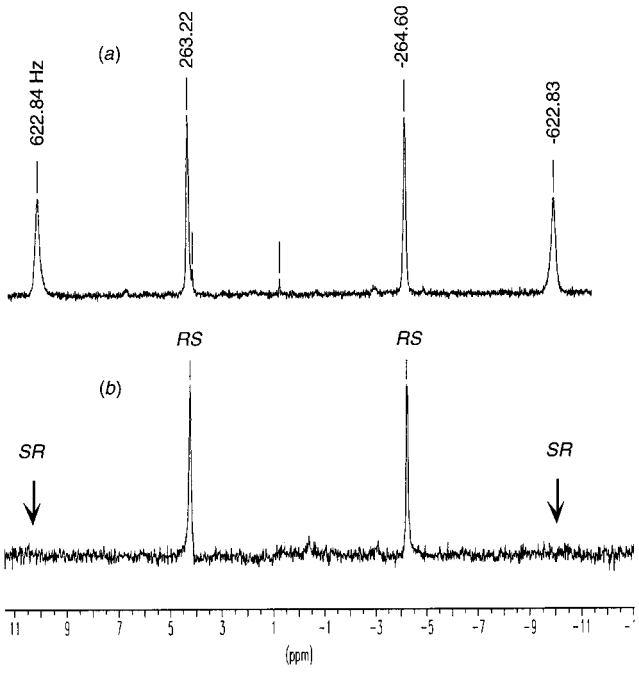


Figure 2. Proton-decoupled ^{2}H NMR spectra in the PBLG/CH_2Cl_2 liquid crystal solvent of *cis* (*a*) (±)-**6** and (*b*) (1*R*,2*S*)-**6**.

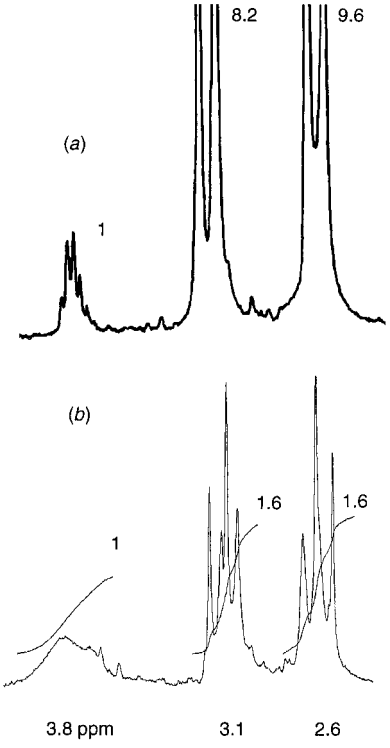


Figure 3. ^{1}H NMR spectra in $CDCl_3$ of 2-aminoindanes obtained by: (a) $LiAlD_4$ reduction of *cis*-2-azido-1-bromoindane (**12**) and (b) $LiAlH_4$ reduction of *cis*-2-azido-1-bromo-2-*d*-indane (**22**).

ppm attributed to the C_α carbon in **1** became a triplet with a coupling constant $^1J_{C-D} = 21$ Hz. All these results confirm that the major product **4** contains a methine deuterium as a result of a transposition.

These complications made us to focus more attention on better leaving groups such as sulfonate derivatives. Compounds (±)-**9** and (±)-**10** were obtained in excellent yields by reaction of the alcoholate anion of (±)-*cis*-2-azido-1-indanol (**8**) with the corresponding sulfonyl chloride. $LiAlD_4$ reduction of tosylate (±)-**9** gave a mixture of compounds **3** and **4** but in a ratio of 3:1, reversed with respect to the reaction of (±)-**12** (determined by ^{2}H-NMR). Finally, (±)-*trans*-2-amino-1-*d*-indane (**3**) could be obtained as the unique product from (±)-**10** when mesylate is the leaving group. For this reduced deuterated compound **3**, ^{2}H-NMR exhibits a single broad singlet at 3.10 ppm and three characteristic proton resonances with a ratio of the signal intensity of H_β^{trans}:$H_\beta^{cis} = 0.57$ (Figure 1c), showing the *trans* stereochemistry of the deuterium atom.

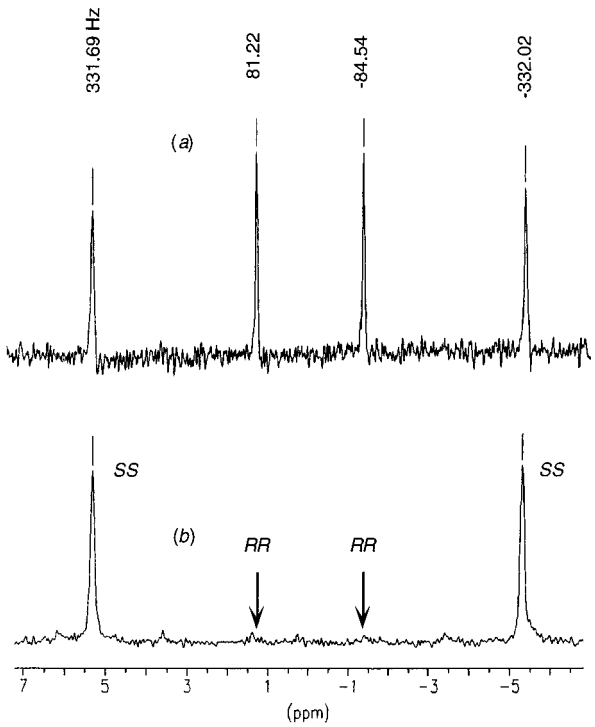


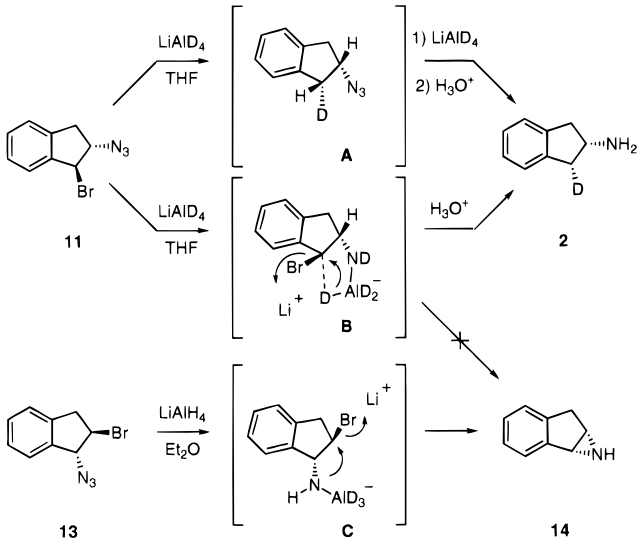
Figure 4. Proton-decoupled ^{2}H NMR spectra in the PBLG/CH_2Cl_2 liquid crystal solvent of *trans* (a) (±)-**7** and (b) (1*S*,2*S*)-**7**.

Reduction of the optically active (1*R*,2*S*)-**10** obtained from (1*R*,2*S*)-**8** {83% ee} afforded (1*S*,2*S*)-**3** at a 35% yield and 89% ee determined after transformation into the *N*-trifluoroacetamide derivatives **7** and ^{2}H-NMR analysis (Figure 4). Similar to (±)-**6**, the ^{2}H-NMR spectrum of (±)-**7** consists of two doublets, one for each enantiomer, with quadrupolar splittings $\Delta\nu_{Q1} = 664$ Hz and $\Delta\nu_{Q2} = 166$ Hz ($\Delta\nu_{Q1} - \Delta\nu_{Q2} = 498$ Hz; Figure 4a), whereas (1*S*,2*S*)-**7** shows only one doublet with $\Delta\nu_Q = 664$ Hz (Figure 4b).

These results show that the $LiAlD_4$ reduction of *trans*-bromide **11** and *cis*-mesylate **10** occur with a high degree of stereolectivity by a S_N2 mechanism leading, exclusively, to *cis*-2-amino-1-*d*-indane (**2**) and *trans*-2-amino-1-*d*-indane (**3**), respectively. However, a question remains: does the azido group reduction occur before or after the hydrogenolysis of the C−Br bond? Hydride reduction of *β*-halo azides is known to lead to aziridines in high yields.[12] For example, reduction of *trans*-1-azido-2-bromoindane (**13**), an isomer of **11**, gives indano[1,2-*b*]aziridine (**14**) quantitatively.[13] In this reaction, reduction of the azido group and the subsequent ring closure

(12) Chen, S.-C. *Synthesis* **1974**, 691.
(13) Chiu, I.-C.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2857. Nguy, N. M.; Chiu, I.-C.; Kohn, H. *J. Org. Chem.* **1987**, *52*, 1649.

Scheme 3. Mechanistic Pathways Proposed for the $LiAlD_4$ Reduction of *trans*-2-Azido-1-bromoindane (11)



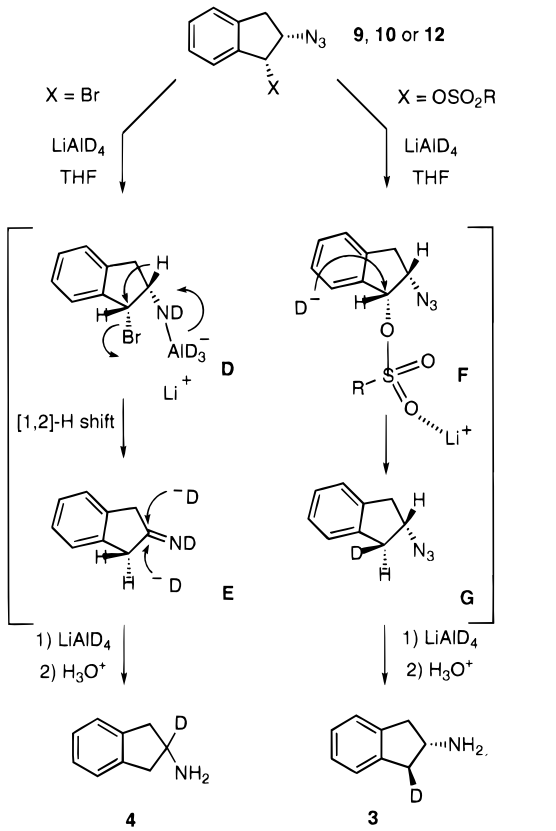
occur prior to the hydrogenolysis of the C−Br bond. Given that, we have never observed the formation of aziridine **14** upon reduction of **11**, one possibility would be to consider that the benzylic C−Br bond hydrogenolysis occurs before azido group reduction. A second possibility takes into account azido group reduction leading to amide **B**, prior to the benzylic C−Br bond hydrogenolysis by a process faster than the ring closure which would have to lead to aziridine **14**. In this case, hydrogenolysis can be accelerated by intramolecular assistance according to a five-membered ring transition state. The results obtained with *cis*-2-azido-1-bromoindane (**12**) support the second possibility (*vide infra*).

The reduction of *cis*-2-azido-1-bromoindane (**12**) and subsequent formation of 2-amino-2-*d*-indane (**4**) needs some comment. This compound was exclusively observed with *cis* derivatives **9** and **12**, and the formation of **4** can be explained: (i) if we assume that the first step of the reaction is the reduction of azido group into amide **D** and (ii) if a [1,2]-hydride shift rearrangement occurs together with the displacement of the bromo group *via* an imine intermediate **E** (Scheme 4). In the final step, imine **E** is reduced to the amine by an excess of $LiAlD_4$. With better leaving groups such as mesylate and assisted by the electrophilic Li^+ cation,[14] the first step is now the hydrogenolysis of C−OMs bound *via* a S_N2 mechanism leading to azido compound **G** which is reduced to the amine **3** in the second step. Finally, with tosylate, which has poorer leaving group properties than mesylate, the two processes are competitive, and a mixture of compounds **3** and **4** is obtained.

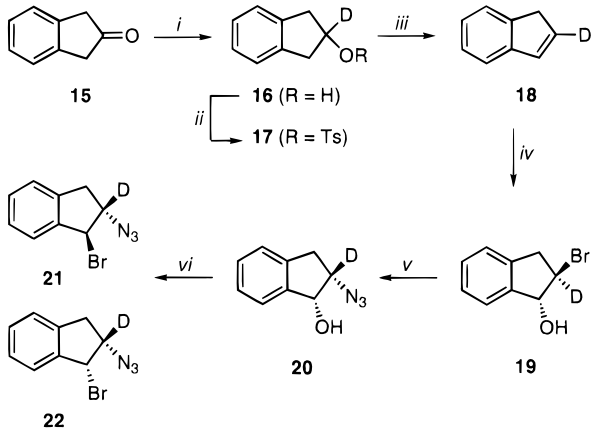
Stereoselective [1,2]-hydride shift rearrangement has been demonstrated with ribonucleoside 2′(or 3′)-monotosylates and lithium triethyl borohydride.[15] In order to show without ambiguities the same type of rearrangement during the reduction of *cis*-2-azido-1-bromoindane (**12**) with $LiAlD_4$, we prepared *cis*- and *trans*-2-azido-1-bromo-2-*d*-indanes (**21** and **22**) and studied their reactivity toward $LiAlH_4$ in THF. In the case of a [1,2]-hydride shift rearrangement, we should expect the formation of a 1:1 mixture of 2-amino-1-*d*-indanes **2** and **3** from the

(14) Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 2250.
(15) Hansske, F.; Robins, M. J. *J. Am. Chem. Soc.* **1983**, *105*, 6736.

Scheme 4. Mechanistic Pathways Proposed for the $LiAlD_4$ Reduction of *cis*-2-Azidoindane Derivatives 9, 10, and 12



Scheme 5[a]

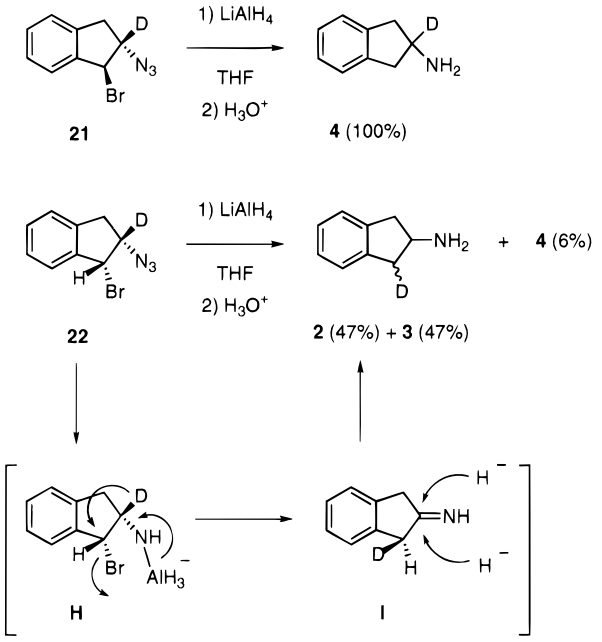


[a] (i) $LiAlD_4$, THF, 73%; (ii) NaH, THF then TsCl, 83%; (iii) MeONa, MeOH, 30%, (iv) NBS, DMSO-H_2O, 98%, (v) NaN_3, DMF, 97%, (vi) PBr_3, CCl_4.

reduction of the *cis*-2-azido-1-bromo-2-*d*-indane (**22**), while *trans*-2-azido-1-bromo-2-*d*-indane (**21**) should give 2-amino-2-*d*-indane (**4**).

2-*d*-Bromides **21** and **22** were obtained in six steps from 2-indanone **15** as described in Scheme 5. As expected, $LiAlH_4$ reduction of *trans*-bromide **21** afforded 2-amino-2-*d*-indane (**4**) as the unique product without any deuterium atom migration. Under the same conditions, *cis*-bromide **22** afforded a mixture of *d*-aminoindanes **2**−**4** which showed the three characteristic NMR signals for H_α, H_β^{trans} and H_β^{cis} in a 1:1.6:1.6 ratio (Figure 3b). From these values we can conclude a ratio **2**:**3**:**4** = 47:47:6.[16] The same ratio was confirmed by ^{2}H-NMR

Scheme 6



where three broad singlets at 3.75 (1 D), 3.10 (8 D), and 2.64 ppm (8 D), corresponding to *d*-aminoindanes **4**, **3** and **2**, were observed. The presence of high quantities (94%) of rearranged 2-amino-1-*d*-indanes **2** and **3** confirms our hypothesis of a [1,2]-hydride shift. Moreover, the presence of 2-amino-1-*d*-indanes **2** and **3** in 1:1 mixture demonstrates the occurrence of an imine intermediate **E** which undergoes a hydride attack by the both faces of the cyclopentane ring.

Conclusion

In conclusion, the results reported in this paper show that it is possible to synthesize all three isomers of selectively (cyclopentane ring) deuterated 2-aminoindanes **2**−**4** from 1,2-disubstituted starting materials and lithium aluminum deuterate as a reducing agent. However, the reactions were less straightforward than initially expected, and the orientation of the deuteration reaction depends on the stereochemistry and/or the nature of the leaving group that is replaced by the deuterium. Whereas the *cis* aminoindane **2** has been obtained by $LiAlD_4$ S_N2 reduction of *trans* bromo derivative **11**, the formation of the *trans* deuterated aminoindane **3** requires a *cis* compound **10** with a better leaving group such as mesylate. During the reduction of the *cis* bromo derivative **12**, a competitive [1,2]-hydride shift becomes the predominant reaction, suppressing the desired direct S_N2 substitution more or less completely leading to compound **4**. It is shown that the azido group is reduced first, and the intramolecular substitution reaction ([1,2]-hydride shift) prevails over the competitive intermolecular one (S_N2 substitution), leading, *via* an imine, to the rearranged primary amine **4**. Better leaving groups such as mesylate assisted by the electrophilic Li^+ cation switches the deuteride attack to the ester carbon, and the direct S_N2 substitution occurs before the azide is reduced.

(16) Ratio **2**:**3**:**4** can be evaluated by resolving the following three equations: $I_{3.8} = [\mathbf{2}] + [\mathbf{3}]$; $I_{3.1} = 2[\mathbf{2}] + [\mathbf{3}] + 2[\mathbf{4}]$ and $I_{2.6} = [\mathbf{2}] + 2[\mathbf{3}] + 2[\mathbf{4}]$ where I are the integration values of signals at 3.8, 3.1, and 2.6 ppm.

Experimental Section

All the reagents were purchased from the Sigma-Aldrich Company and used without purification except 2-aminoindane hydrochloride (**1**) which was used after washing of a CH_2Cl_2 solution by saturated $NaHCO_3$, drying over Na_2SO_4, and evaporation of the solvent. Compound (±)-**8** was obtained by hydroxybromination of indene (NBS/DMSO−H_2O) followed by NaN_3 bromide substitution (NaN_3/DMF) as described in the literature.[9] Optically pure (1*R*,2*S*)-**8** was obtained in 83% ee by enzymatic resolution using lipase as described in the literature.[9] Solvents were freshly distilled under argon: MeOH from magnesium, THF from sodium benzophenone ketyl, DMSO and DMF from calcium hydride, and CCl_4 from P_2O_5. NMR spectra were recorded on Bruker AC-200 (^1H and ^{13}C) or AC-400 (^2H) spectrometers. Chemical shifts are reported in ppm as δ values downfield from an internal standard of TMS (^1H and ^{13}C) or $CDCl_3$ (^2H). Elemental analyses were obtained on a CHN Technicon microanalyser.

1. Standard Conditions for $LiAlD_4$ (or $LiAlH_4$) Reductions. A solution of benzylic bromide (or sulfonate) and $LiAlD_4$ (or $LiAlH_4$) in THF was stirred under Ar until TLC (SiO_2, CH_3OH) showed complete disappearance of the starting material. Then, hydride excess was destroyed by slow addition of 1 N HCl, and the precipitate was separated from the solution by centrifugation. Concentration of the organic layer under reduced pressure gave an acidic aqueous solution (pH = 1) which was washed with CH_2Cl_2 and turned to pH = 9 by addition of 3 M NaOH solution. The basic layer was extracted three times with CH_2Cl_2, and the organic layers were dried over Na_2SO_4. Concentration under reduced pressure gave crude product which was purified by flash chromatography (SiO_2, CH_3OH).

***cis*-2-Amino-1-*d*-indane {2}.** Under standard conditions, the reduction of *trans*-2-azido-1-bromoindane (**11**) (1.23 g, 5.2 mmol) by $LiAlD_4$ (1 g, 24 mmol) in THF (100 mL) at 0 °C gave **2** (624 mg, 90%). ^1H-NMR ($CDCl_3$), δ: 1.5 (br s; 2 H); 2.6 (dd; J = 15.8, 5.0 Hz; 1 H); 3.1 (br dd, J = 15.8, 6.6 Hz; 2 H); 3.8 (td, J = 6.6, 5.0 Hz; 1 H); 7.1−7.4 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 42.7 (t, J_{C-D} = 21 Hz; CDH); 43.1 (CH_2); 53.0 (CH); 124.8 (2 CH); 126.4 (2 CH); 141.8 (2 C). ^2H-NMR (CCl_4), δ: 2.64 (br s).

***trans*-2-Amino-1-*d*-indane {3}.** Under standard conditions, the reduction of *cis*-2-azido-1-[(methanesulfonyl)oxy]indane (**10**) (518 mg, 2.05 mmol) by $LiAlD_4$ (818 mg, 20.5 mmol) in THF (50 mL) at −30 °C gave **3** (96 mg, 35%). ^1H-NMR ($CDCl_3$), δ: 1.5 (br s; 2 H); 2.6 (br dd, J = 15.8, 5.0 Hz; 2 H); 3.1 (dd, J = 15.8, 6.6 Hz; 1 H); 3.8 (dt, J = 6.6, 5.0 Hz; 1 H); 7.1−7.4 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 42.7 (t, J_{C-D} = 21 Hz; CDH); 43.1 (CH_2); 53.0 (CH); 124.8 (2 CH); 126.4 (2 CH); 141.8 (2 C). ^2H-NMR (CCl_4), δ: 3.10 (br s).

2-Amino-2-*d*-indane {4}. Under the standard conditions, the reduction of *trans*-2-azido-1-bromo-2-*d*-indane (**21**) (50 mg, 0.21 mmol) by $LiAlH_4$ (50 mg, 1.3 mmol) in THF (2 mL) at 0 °C gave **4** (20 mg, 72%). ^1H-NMR ($CDCl_3$), δ: 1.7 (br s; 2 H); 2.6 (d, J = 15.9 Hz; 2 H); 3.1 (d, J = 15.9; 2 H); 7.1−7.4 (m; 4 H). ^2H-NMR (CCl_4), δ: 3.75 (br s).

2. Standard Conditions for Trifluoroacetamidation Reactions. A solution of 2-aminoindane was treated with $(CF_3CO)_2NMe$ (1.5 equiv) in EtOAc at 0 °C. The mixture was stirred at rt until TLC (SiO_2, pentane:EtOAc = 70:30) showed complete disappearance of the starting material. The solution was washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave crude product which was purified by flash chromatography (SiO_2, pentane:EtOAc = 70:30).

2-Trifluoroacetamidoindane {5}. Under the standard conditions, the reaction of 2-aminoindane (**1**) (50 mg, 0.38 mmol) with $(CF_3CO)_2NMe$ (90 μL, 0.62 mmol) in EtOAc (1 mL) gave **5** (75 mg, 85%). Anal. Calcd for $C_{11}H_{10}NOF_3$: C 57.64; H 4.40; N 6.11. Found C 57.78; H 4.65; N 6.23. ^1H-NMR (CD_3CN), δ: 2.9 (dd; J = 16.4, 4.1 Hz; 2 H); 3.4 (dd, J = 16.4, 7 Hz; 2 H); 4.8 (m; 1 H) ; 6.6 (br s; 1 H); 7.1−7.3 (m; 4 H).

***cis*-2-Trifluoroacetamido-1-*d*-indane {6}.** Under the standard conditions, the reaction of *cis*-2-amino-1-*d*-indane **2** (72 mg, 0.54 mmol) with $(CF_3CO)_2NMe$ (116 μL, 0.8 mmol) in

EtOAc (2 mL) gave **6** (110 mg, 89%). Anal. Calcd for $C_{11}H_9DNOF_3$: C 57.39; H 4.80; N 6.08. Found C 57.50; H 5.00; N 6.10. ^{1}H-NMR (CD_3CN), δ: 2.9 (dd; J = 16.4, 5.5 Hz; 1 H); 3.3 (br dd, J = 16.4, 7.6 Hz; 2 H); 4.6 (td, J = 7.6, 5.5 Hz; 1 H); 7.1−7.3 (m; 4 H); 7.9 (br s; 1 H).

***trans*-2-Trifluoroacetamido-1-*d*-indane {7}.** Under standard conditions, the reaction of *trans*-2-amino-1-*d*-indane (**3**) (70 mg, 0.53 mmol) with $(CF_3CO)_2NMe$ (116 μL, 0.8 mmol) in EtOAc (1 mL) gave **7** (100 mg, 82%). Anal. Calcd for $C_{11}H_9DNOF_3$: C 57.39; H 4.80; N 6.08. Found C 57.70; H 4.61; N 6.09. ^{1}H-NMR (CD_3CN), δ: 2.9 (dd; J = 16.4, 5.5 Hz; 2 H); 3.3 (br dd, J = 16.4, 7.6 Hz; 1 H); 4.6 (dt, J = 7.6, 5.5 Hz; 1 H); 7.1−7.3 (m; 4 H); 7.9 (br s; 1 H).

3. *cis*-2-Azido-1-(tosyloxy)indane {9}. A solution of *cis*-2-azido-1-indanol (**8**) (591 mg, 3.4 mmol) and NaH (122 mg, 4 mmol) in THF (40 mL) was strirred under Ar at −20 °C for 15 min. Then, TsCl (126 mg, 35 mmol) was slowly added in order to maintain the temperature below −20 °C. The mixture was stirred at −20 °C for 30 min, filtered through Celite, and washed with ether. Evaporation of the solvents under reduced pressure gave **9** (945 mg, 85%) as crude product which for stability reasons was used without further purification. ^{1}H-NMR ($CDCl_3$), δ: 2.5 (s; 3 H); 3.2 (d, J = 6.8 Hz; 2 H); 4.1 (dt, J = 6.6, 5.2 Hz; 1 H); 5.9 (d, J = 5.2 Hz; 1 H); 7.2−7.3 (m; 4 H); 7.4 (d, J = 8.2 Hz; 2 H); 7.9 (d, J = 8.2 Hz; 2 H). ^{13}C-NMR ($CDCl_3$), δ: 21.6 (CH_3); 34.8 (CH_2); 62.2 (CH); 83.1 (CH); 125.0 (CH); 125.8 (CH); 127.6 (CH); 127.9 (CH); 129.8 (CH); 130.0 (CH); 136.3 (C); 140.1 (C); 133.7 (C); 145.1 (C).

4. *cis*-2-Azido-1-(mesyloxy)indane {10}. By the same procedure described for compound **9**, the reaction of *cis*-2-azido-1-indanol (**8**) (464 mg, 2.65 mmol), 2.5 M nBuLi in hexanes (1.16 mL, 2.9 mmol), and MsCl (205 mL, 2.6 mmol) in THF (10 mL) gave compound **10** (518 mg, 85%) as crude product which for stability reasons was used without further purification. ^{1}H-NMR ($CDCl_3$), δ: 3.0 (s; 3 H); 3.1 (d, J = 6.8 Hz; 2 H); 4.15 (dt, J = 6.8, 5.1 Hz; 1 H); 5.9 (d, J = 5.1 Hz; 1 H); 7.0−7.5 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 34.7 (CH_2); 38.7 (CH_3); 61.9 (CH); 82.8 (CH); 125.1 (CH); 126.0 (CH); 127.8 (CH); 130.6 (CH); 136.2 (C); 140.4 (C).

5. 2-Azido-1-bromoindanes {11 and 12}. A solution of *cis*-2-azido-1-indanol (**8**) (1.125 g, 6.4 mmol) and PBr_3 (405 μL, 2.2 mmol) in CCl_4 (200 mL) was strirred at rt until TLC (SiO_2, pentane) showed complete disappearance of compound **8**. The mixture is washed with brine and concentrated under reduced pressure. Flash chromatography (SiO_2, pentane) gave **11** (1 g, 66%) and **12** (426 mg, 28%). ***trans*-2-Azido-1-bromoindane {11}.** Anal. Calcd for $C_9H_8N_3Br$: C 45.40; H 3.39; N 17.65. Found C 42.97; H 3.63; N 17.12. ^{1}H-NMR ($CDCl_3$), δ: 2.9 (dd, J = 16.4, 3.4 Hz; 1 H); 3.4 (dd, J = 16.4, 6.3 Hz; 1 H); 4.5 (dt, J = 3.4, 6.2 Hz; 1 H); 5.3 (d, J = 3.4 Hz; 1 H); 7.1−7.5 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 36.5 (CH_2); 54.6 (CH); 69.8 (CH); 125.0 (CH); 125.7 (CH); 128.0 (CH); 129.6 (CH); 139.8 (C); 140.5 (C). ***cis*-2-Azido-1-bromoindane {12}.** Anal. Calcd for $C_9H_8N_3Br$: C 45.40; H 3.39; N 17.65. Found C 43.57; H 3.53; N 17.29. ^{1}H-NMR ($CDCl_3$), δ: 3.1 (d, J = 7.9; 1 H); 4.05 (dt, J = 7.9, 5.1 Hz; 1 H); 5.5 (d, J = 5.1 Hz; 1 H); 7.1−7.5 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 34.9 (CH_2); 57.2 (CH); 63.4 (CH); 125.0 (CH); 125.2 (CH); 127.9 (CH); 129.7 (CH); 139.0 (C); 140.7 (C).

6. *d*-2-Indanol {16}. A solution of 2-indanone **15** (2.8 g, 21 mmol) and $LiAlD_4$ (1.19 g, 28.6 mmol) in ether (150 mL) was refluxed under Ar for 6 h. Water (20 mL) was carefully added, and the mixture was stirred for 30 min. The suspension was filtered through Celite and concentrated under reduced pressure. Flash chromatography (SiO_2, CH_3OH) gave **16** (2.1 g, 73%). Anal. Calcd for C_9H_9DO: C 79.97; H 8.19. Found C 80.05; H 8.10. ^{1}H-NMR ($CDCl_3$), δ: 1.7 (s; 1 H); 3.0 (d, J = 16.3 Hz; 2 H); 3.3 (d, J = 16.3 Hz; 2 H); 7.2−7.4 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 42.3 (2 CH_2); 72.4 (t, J_{C-D} = 23 Hz; CD); 124.8 (2 CH); 126.5 (2 CH); 140.9 (2 C).

7. 2-(Tosyloxy)-2-*d*-indane {17}. By the same procedure described for compound **9**, the reaction at −5 °C of 2-*d*-2-indanol **16** (2.1 g, 15.5 mmol), NaH (520 mg, 17 mmol), and TsCl (2.96 g, 15.5 mmol) in THF (100 mL) gave **17** (3.74 g, 83%) as crude product which was used without further purification. ^{1}H-NMR ($CDCl_3$), δ: 2.4 (s; 3 H); 3.1 (d, J = 6.5 Hz; 4 H); 7.1−7.3 (m; 4 H); 7.35 (d, J = 8.2 Hz; 2 H); 7.8 (d, J = 8.2 Hz; 2 H). ^{13}C-NMR ($CDCl_3$), δ: 21.5 (CH_3); 39.5 (2 CH_2); 82.1 (t, J_{C-D} = 23 Hz; CD); 124.4 (2 CH); 126.8 (2 CH); 133.9 (C); 138.9 (2 C); 144.7 (C).

8. 2-*d*-Indene {18}. A solution of 2-(tosyloxy)-2-*d*-indane **17** (3.7 g, 13 mmol) and CH_3ONa (700 mg, 13 mmol) in CH_3OH (50 mL) was stirred under Ar at 40 °C for 3 d. Flash chromatography (SiO_2, pentane) gave **18** (495 mg, 30%). Anal. Calcd for C_9H_7D: C 92.27; H 7.73. Found C 92.50; H 7.71. ^{1}H-NMR ($CDCl_3$), δ: 3.4 (s; 2 H); 6.9 (s; 1 H); 7.2−7.5 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 39.0 (CH_2); 121.0 (CH); 123.8 (CH); 124.6 (CH); 126.3 (CH); 132.0 (CH); 134.0 (t, J_{C-D} = 25 Hz; CD); 143.7 (C); 144.9 (C).

9. *trans*-2-Bromo-2-*d*-1-indanol {19}. A solution of 2-*d*-indene **18** (46 μL, 0.4 mmol) and NBS (175 mg, 1 mmol) in DMSO (1 mL) containing water (18 μL) was stirred at rt for 6 h. Water (2 mL) was added, and the mixture was extracted with ether (3 × 5 mL). Organic layer was washed with brine (2 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, CH_2Cl_2) gave **19** (80 mg, 95%). Anal. Calcd for C_9H_8DOBr: C 50.49; H 4.71. Found C 51.11; H 4.63. ^{1}H-NMR ($CDCl_3$), δ: 2.6 (br s; 1 H); 3.2 (d, J = 16.1 Hz; 1 H); 3.5 (d, J = 16.1 Hz; 1 H); 5.3 (s; 1 H); 7.1−7.4 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 40.4 (CH_2); 54.2 (t, J = 24 Hz; CD); 83.4 (CH); 124.1 (CH); 124.6 (CH); 127.7 (CH); 129.0 (CH); 139.8 (C); 141.7 (C).

10. *trans*-2-Azido-2-*d*-1-indanol {20}. A solution of *trans*-2-bromo-2-*d*-1-indanol **19** (80 mg, 0.37 mmol) and NaN_3 (29 mg, 0.44 mmol) in DMF (5 mL) was stirred at 80 °C for 3 h. Water (10 mL) was added, and the mixture was extracted with ether (3 × 5 mL). Organic layer was washed with LiCl saturated solution (2 × 5 mL), dried on Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, CH_3Cl_2) gave **20** (63 mg, 98%). Anal. Calcd for $C_9H_8DON_3$: C 61.35; H 5.72; N 23.85. Found C 61.12; H 5.22; N 23.61. ^{1}H-NMR ($CDCl_3$), δ: 2.4 (br s; 1 H); 3.1 (s; 2 H); 5.1 (s; 1 H); 7.2−7.5 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 35.1 (CH_2); 65.3 (t, J_{C-D} = 24 Hz; CD); 76.4 (CH); 124.7 (CH); 125.1 (CH); 127.6 (CH); 129.0 (CH); 139.1 (C); 141.9 (C).

11. 2-Azido-1-bromo-2-*d*-indanes {21 and 22}. By a procedure analogous to the preparation of compounds **11** and **12**, the reaction of *cis*-2-azido-2-*d*-1-indanol (**20**) (63 mg, 0.36 mmol) with PBr_3 (32.5 μL, 0.18 mmol) in CCl_4 (6 mL) gave **21** (54 mg, 64%) and **22** (21 mg, 25%). ***trans*-2-Azido-1-bromo-2-*d*-indane {21}.** Anal. Calcd for $C_9H_7DN_3Br$: C 45.38; H 3.81; N 17.65. Found C 42.97; H 3.63; N 17.12. ^{1}H-NMR ($CDCl_3$), δ: 2.9 (d, J = 16.1 Hz; 1 H); 3.4 (d, J = 16.1 Hz; 1 H); 5.3 (s; 1 H); 7.2−7.5 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 36.4 (CH_2); 54.5 (CH); 69.9 (t, J_{C-D} = 24 Hz; CD); 125.1 (CH); 125.8 (CH); 128.1 (CH); 129.7 (CH); 139.8 (C); 140.5 (C). ***cis*-2-Azido-1-bromo-2-*d*-indane {22}.** Anal. Calcd for $C_9H_7DN_3Br$: C 45.38; H 3.81; N 17.65. Found C 42.97; H 3.63; N 17.12. ^{1}H-NMR ($CDCl_3$), δ: 3.1 (s; 2 H); 5.5 (s; 1 H); 5.3 (s; 1 H); 7.2−7.45 (m; 4 H). ^{13}C-NMR ($CDCl_3$), δ: 35.0 (CH_2); 57.1 (CH); 63.2 (t, J_{C-D} = 21 Hz; CD); 125.2 (CH); 125.4 (CH); 128.1 (CH); 129.9 (CH); 139.2 (C); 140.9 (C).

Acknowledgment. We are grateful to the French Ministère des Affaires Etrangères and Provence-Alpes-Côte d'Azur country for the scholarship to two of us (A.A.M. and C.B.). We thank Dr. Andreas Heumann for helpful discussions.

JO970378O