Tetrahedron Vol. 48, No. 15, pp. 2993-3000, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

CHIRAL 1-DEUTERIO AZIDES

by

Carolyn Fisher[1], Eric Morse, Blair Romer, Tian-Pa You, Carol W. Mosher and

Harry S. Mosher*

Department of Chemistry, Stanford University

Stanford, California 94305, USA

(*Received in USA* 4 *February* 1992)

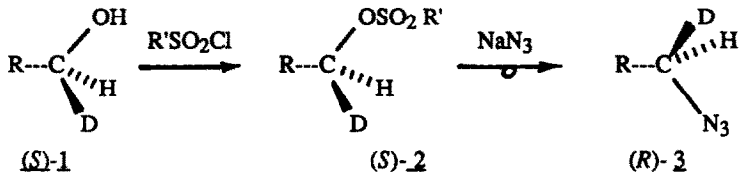
Abstract. Five chiral primary 1-deuterio alcohols (R-CHDOH, R = methyl, n-propyl, tert-butyl, 1-adamantyl, phenyl) were converted (via their tosylate or mesylate) into the corresponding chiral primary 1-deuterio azides ($RCHDN_3$) of opposite configuration. Three of the four non-aromatic, primary, (*R*)-1-deuterio azides have a positive sodium D-line rotation, and a positive circular dichroism (CD) Cotton effect at 286-288 nm attributable to the azide chromophore. However, the first member of the series, (*R*)-(+)-ethyl-1-*d* azide, has a negative CD (287 nm, $[\theta] = 12.5$) and does not conform to the other three which show a positive CD. The chiral azides, $RCHDN_3$, which have an R group possessing C_{3v} symmetry (methyl, tert-butyl and adamantyl), constitute a simple conformational situation for application of the azide octant rule. Since one of these three (methyl) has a CD of opposite sign to the other two, these results cannot be reconciled with the azide octant rule, *per se*.
Ethyl azide detonated upon attempted sealing in a vial.

INTRODUCTION:

The availability of several chiral primary 1-deuterio alcohols[1,2] (R-$\overset{*}{C}$HDOH) presented the opportunity of preparing and studying primary 1-deuterio azides (R-$\overset{*}{C}$HDN_3) for the purpose of observing their circular dichroism (CD) characteristics.[1] The value of such a study was indicated by the prior synthesis of (*R*)-(+)-neopentyl-1-*d* azide.[3,4] The azide group has a long wavelength, low intensity band (λ 286-288 nm, ε = ca. 25),[5] not unlike the $n \rightarrow \pi^*$ transition of carbonyl compounds, which is well suited for studying CD effects.[6] The inherently symmetrical azide group can be asymmetrically perturbed by a chiral environment thus leading to a Cotton effect. Based on the azide octant rule, this Cotton effect has been used for conformational studies and for the correlation of configurations in such diverse structures as steroids[7] and carbohydrates.[8] The chiral primary 1-deuterio azides ($R\overset{*}{C}HDN_3$) can be considered the simplest examples for observing such effects. In those cases where the R group has C_{3v} symmetry, *i.e.*, where R is methyl, tert-butyl and adamantyl, the three rotational conformations are indistinguishable. The general theory of circular dichroism has been reviewed[9-11] including molecules possessing isotopically engendered chirality.[12] Other publications[13,14] emphasize the importance of conformation in CD phenomena due to chirality arising by virtue of deuterium substitution.

DISCUSSION:

The synthesis problem was largely one of obtaining the starting chiral 1-deuterio alcohols (1) in sufficient quantity for conversion (via the tosylate or mesylate 2) into the azides (3).



R = a, methyl; b, n-propyl; c, tert-butyl; d, 1-adamantyl; e, phenyl; R′ = p-$C_6H_4CH_3$ or CH_3.

The *S* chiral alcohols (1b-e) were available from our previous studies,[1,2,15,16] except for the first member of the series (1a, R = CH_3). Enantiomerically pure (*R*)-(+)-ethanol-1-*d* (enantiomer of 1a) was made from ethanol by the equilibration method of Simon and coworkers[17] using yeast alcohol dehydrogenase (ADH), nicotinamide adenine dinucleotide (NAD^+) and diaphorase in D_2O. The absolute configurations of these 1-deuterio alcohols have been established: 1a[17,-21]; 1b[17,21,-23]; 1c[3,4] and 1e[22,23].

Chiral alcohols (1a-e) were converted to either the mesylate or the tosylate (2) which were then treated with sodium azide in either dimethylsulfoxide (DMSO) or hexamethyl-phosphoramide (HMPA) to give the chiral azides (3a-e) of opposite configuration. It has been demonstrated in the case of the toluene sulfonate of neopentyl-1-*d* alcohol (2c → 3c), that no appreciable racemization occurs during this conversion.[4] The benzyl-α-*d* example has the greatest propensity for racemization in this sequence. By the use of the chiral shift reagent it was previously determined[2] that the starting (*S*)-(+)-benzyl-1-*d* alcohol (1e) which had an enantiomeric purity of 30 ± 2% produced (*R*)-(-)-benzyl-1-*d* azide (3e) with an enantiomeric purity of 26 ± 3%. This supports previous research[22] which demonstrated that there is minimum racemization during synthesis of 2e and also with subsequent displacement reactions under proper conditions. Since the configurations of the carbinols 1a-e are known and the S_N2 reaction 2 → 3 proceeds by inversion, the configurations of the azides are also known. We used (+)-ethanol-1-*d* which has been shown[17-21] to have the *R* configuration while the other four starting 1-deuterio alcohols (1b-e) had the *S* configuration. So the ethyl-1-*d* azide formed by inversion is *S* with the properties given in the experimental section, while the other azides in this study are *R*. However, for clarity in presentation we will discuss the chiroptic properties as though all alcohols were *S* and all azides were *R* as shown in 1a-e → 3a-e and as depicted in the CD curves in Figures 3A and 3B.

The subject of CD spectra of molecules with isotopically engendered chirality has been reviewed by Barth and Djerassi.[12] The majority of examples are for carbonyl compounds and the results are interpreted by use of the carbonyl octant rule.[6,11,12] Primary 1-deuterio azides also offer a system for probing the origin of circular dichroism (CD) arising solely by difference in hydrogen *versus* deuterium. The azide octant rule has been developed by Djerassi and coworkers[6] as shown in Figure 1.

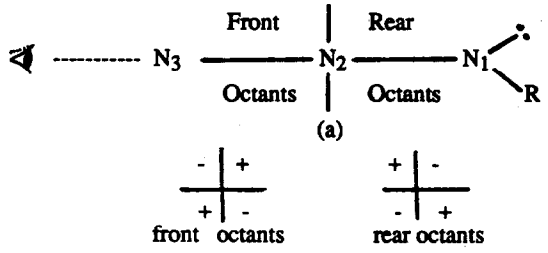


FIGURE 1. Octant diagram of azide chromophore as represented in reference 6.

The azide chromophore at 285-288 nm plays the same role in the azide octant rule as the carbonyl chromophore plays in the carbonyl octant rule.[6] Newman and sawhorse projections are shown in Figure 2. In those cases where the R groups possess C_{3v} symmetry (R = CH_3, 3a; $(CH_3)_3C$, 3c; 1-adamantyl, 3d) the three conformational energy minima resulting from rotation around the C - C bond are indistinguishable; therefore according to this model, conformational contributions to chiroptic properties except those due only to

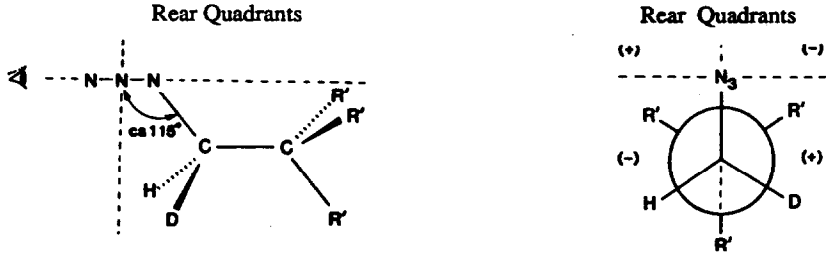
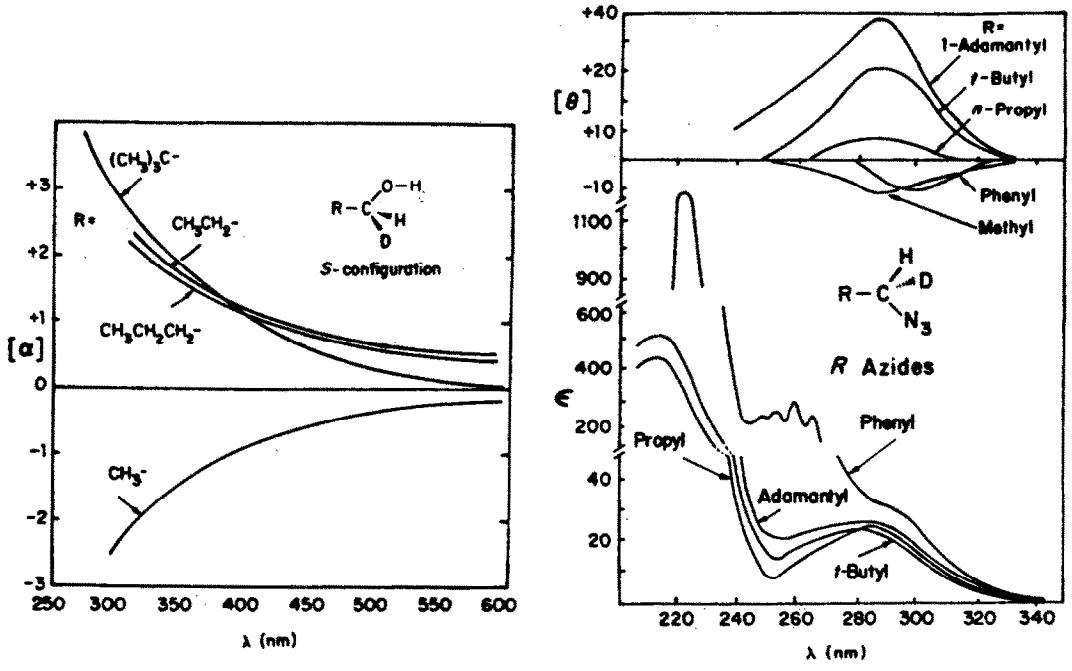


FIGURE 2. Sawhorse and Newman projections of the rear quadrants in the octant rule for R_3CCHDN_3 that depict the symmetrical arrangement of R' in 3a (R' = H), 3c (R = CH_3), 3d (R = adamantyl).

H versus D substitution, should cancel by virtue of symmetry considerations. This assumes, probably incorrectly, that the time average conformational location of the N-N-N group is equidistant between H and D. Three saturated (*R*)-(+)-1-deuterio azides, $RCHDN_3$, (3b, R = n-C_3H_7; 3c R= $(CH_3)_3C$; and 3d, R = 1-adamantyl), show a positive Cotton effect in their CD curves at 286-288 nm (Figure 3B); but (R)-(+)-ethyl-1-*d* azide shows a negative CD at 288 nm. (*R*)-(+)-Benzyl-1-*d* azide also has a negative Cotton effect but at longer wavelength, 296 nm, which results from both the phenyl and azide chromophores; so the lack of correspondence in the CD curves is not unexpected. Application of the azide octant model[6] as shown in Figure 1, in which the molecule is viewed down the N--N--N axis (which is oriented in line with the C – C bond with H and D equally disposed on each side), shows hydrogen occupying a negative and deuterium a positive quadrant for the *R* isomers. All other effects for 3a, 3c, and 3d should cancel based on symmetry considerations. Assuming this model, and the known dissignate contribution of deuterium *versus* hydrogen,[12,26]

(i.e., hydrogen will be determining over deuterium), a negative CD Cotton effect is predicted in the 286-288 wavelength region for these (*R*)-1-deuterio azides. In fact two of the three azides (3c and 3d, R = t-butyl and 1-adamantyl), in which the R group has C_{3v} symmetry, have a positive CD effect, while the third (1a, R = CH_3) has a negative CD effect. The ORD curves for the (*S*)-1-deuterio alcohols (1a-e) are shown in Figure 3A, and the CD and UV curves for the (*R*)-1-deuterio azides (3a-e) are shown in Figure 3B.



A. (*S*)-1-Deuterio alcohols. B. (*R*)-1-Deuterio azides.

FIGURE 3: A, ORD curves for (*S*)-1-deuterio alcohols 1a, 1b, 1c, as neat liquids; solids, 1d and 1e, in hexane. B, CD curves for (R)-1-deuterio azides 3a-3e taken in cyclohexane solvent. Data for CH_3CHDOH (1a) and CH_3CHDN_3 (3a) transposed from that determined for the enantiomer.

As originally stated[6] and re-emphasized,[7,11] the requirement for application of the azide octant rule is a molecule with a rigid skeleton. The $R\overset{*}{C}HDN_3$ examples in this study obviously are **not** rigid. Although the C_{3v} symmetry of the R group in 3a, 3c, and 3d would seem to nullify this restriction, the orientation of the azide group with respect to the remainder of the molecule certainly is not fixed and should have considerable

freedom of rotation around the C - N_3 bond as depicted by the cone in Figure 4, structure C.

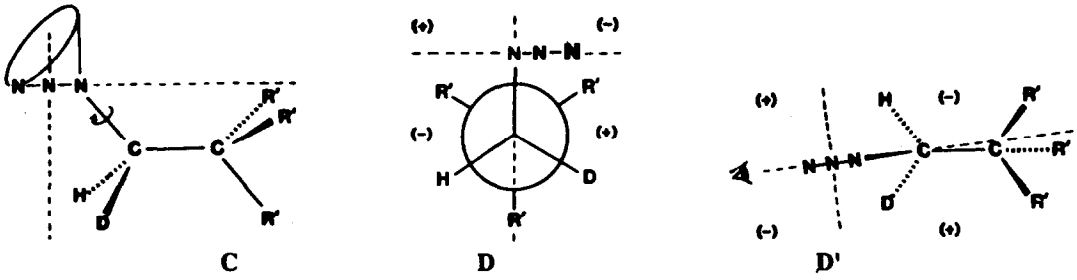


FIGURE 4: C, Sawhorse projection showing rotation around the C-N_3 axis of the azide group.
D, Newman projection indicating (exaggerated) off-center alignment of the N-N-N- group skewed towards deuterium rather than hydrogen.
D', A view as seen from above sawhorse model (D) showing more of the bulk of the remaining molecule in a (+) quadrant.

The equilibrium position for the N-N-N group may **not** be perfectly aligned with the C - C bond. This has been considered in other examples.[6,7,11] The sensitivity of Cotton effects to conformation is well documented[11-13] and is especially evident in the analysis of the CD spectra of cyclopentanone-2-d.[14] We speculate that the conformation shown in D and D', Figure 4, exerts a determining influence on the CD spectra of these azides; but we are not able to reconcile the positive CD for 1b, 1c and 1d with a negative CD for 1a.

The difference in mass between D and H causes anharmonicity in the vibrational potential of these nuclei which affects the average geometry of the molecule, i.e., the equilibrium bond lengths and bond angles and therefore the inherent chirality of the molecule. The average C – H bond length is slightly greater by about 0.008 Å than the C - D bond length,[27] and the atomic diameter of hydrogen is slightly greater than that of deuterium. These effects may allow the azido group to maintain an equilibrium position slightly closer to the deuterium than to the hydrogen. The three linear nitrogens of the azido group are attached to carbon in alkyl azides with a bond angle of about 115°– 135°.[28] Steric and electronic factors govern rotation around this bond which can describe a cone as illustrated in Figure 4C. If the N-N-N group is slightly skewed towards deuterium as shown in an exaggerated way in D and D', then the deuterium in the lower right-hand (+)-quadrant will be closer to the N_3 group than hydrogen in the opposite (-)-quadrant. This might result in deuterium exerting a greater influence on the CD spectrum than hydrogen even though deuterium is dissignate with respect to hydrogen.[12,26] In addition, slightly more of the bulk of the remainder of the molecule, on the average, should occupy the (+)-quadrant, as shown in D'. This model does not rationalize the fact that the sign for the CD for the first member of this series, 3a, is opposite to that predicted, but would fit the unmodified azide octant rule . Since the evidence for the accepted configuration of (*R*)-(+)-ethanol--1-*d* is beyond doubt, we have no satisfactory explanation for this anomaly. A study of the vacuum ultraviolet circular dichroism spectra of these alcohols might shed light on this dilemma.

EXPERIMENTAL:

Optical rotations were taken on either a Rudolph Research Autopol III or on a Perkin-Elmer 141 electronic polarimeter, both of which read to 0.001° and are reproducible with standard solutions to ± 0.002°. Measurements were made in 1.000 dcm, permanent-window, 1-mL capacity, jacketed cells (Perkin-Elmer type) thermostatted to ±0.1°C; concentrations (c) are given in mg/mL. CD measurements were made on a JASCO CD J-40 instrument, UV spectra on a Cary Model 14 spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were taken at 100 MHz (Varian XL-100) or at 300 MHz (superconducting Nicolet, NMC); chemical shifts are reported in parts per million (ppm δ) downfield from internal tetramethylsilane (TMS) in $CDCl_3$ solvent; multiplicity abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Reactions were routinely followed by thin layer chromatography (TLC) using Analtech PGBE silica gel GF plates (250μ) with ethyl acetate:hexane 3:2 as solvent. Melting points were determined between cover glasses on an aluminum block microscope hot-stage.

(*S*)-(+)-Butanol-1-*d*[2,22,23] (1b); (*S*)-(+)-1-Adamantylmethanol-α-*d* [2,24] (1d); (*S*)-(+)-Benzyl-α-*d* alcohol (1e).[2,22,23] These are previously described compounds of known configurations which were prepared by asymmetric reduction of the corresponding aldehyde using the chiral reducing agent $LiAlD_2(OR^*)_2$ [lithium aluminum deuteride: (+)-2*S*,3*R*-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol, 1:2].[2,17] Approximately 5 g of each substrate was reduced[1,2] to give: 1b, 50% yield 13.2 ± 1.5% ee (enantiomer excess); 1d, 88% yield, 29 ± 3% ee; 1e, 72% yield, 30 ± 2% ee; ORD spectra, corrected to 100% ee are given in Figure 3A.

(*S*)-(+)-Neopentyl-1-*d* alcohol, (1c). The sample was made by fermentative reduction of trimethylacetaldehyde-α-*d* and was from the previously described sample[4,16] that was 91% deuteriated and *ca.* 100% ee. (Fig. 3A).

(*R*)-(+)-Ethanol-1-*d*. The enzymic method described by Simon and coworkers[17] was used. A buffer solution of 0.88 g of NaOH, 6.1 g of K_2HPO_4 and 48 mL of D_2O (99.7%) was lyophilized and the residue dissolved in 50 mL of D_2O to which was added EDTA (100 mg., disodium salt), crystalline bovine albumin (200 mg.,Sigma A4378), β-NAD^+ (60 mg., 98%, Sigma, N7004) and β–NADH disodium salt (60 mg., Sigma 98%, N8129). A suspension of porcine heart diaphorase[31] in 3.2 M $(NH_4)_2SO_4$ (40 units, Sigma D3752) was centrifuged and the residue washed twice with an equal volume of 3.2 M solution of $(ND_4)_2SO_4$ in D_2O. The previously deuterium-exchanged reagents, plus crystalline Bakers yeast alcohol dehydrogenase (100 mg., Sigma A7011, 30,000 units) and the diaphorase were added to 300 mL of D_2O, the pH was adjusted with 0.1 M NaOD to 7.5 (pD 5.9). Ethanol-*d* (CH_3CH_2OD, 8.6g, 0.184 mol) was added to the enzyme-coenzyme-buffer mixture and kept at 28°C until NMR analysis indicated that conversion to CH_3CHDOD was complete (148 h). The reaction mixture was fractionated through a 3/32" glass helices-packed column (1 x 25 cm, 28 theoretical plates); the distillate up to 100°C was collected and refractionated to give 8.8 g, b.p. 78-80°C, α_D^{20} +0.179 ± 0.002° (neat, ℓ = 1.000). A 4.0-g portion, after drying over 1.2 g of 3A molecular sieve, contained less than 0.5% D_2O/HOD/H_2O as indicated by GLC analysis (45 m x 0.5 mm Carbowax column). Integration of NMR signals indicated approximately 3 ± 1% CH_3CH_2OH/CH_3CH_2OD; NMR (100 MHz), 1.28 ppm (dt, 3 H, J_H 7.0 Hz, J_D 1.0 Hz); 3.66 ppm (qt, 1 H, J_H 7.0 Hz, J_D 1.0 Hz); α_D^{20} + 0.199°, α_{546}^{20} + 0.240°, α_D^{25} + 0.194°, α_{546}^{25} + 0.236° (neat, ℓ =); $[\alpha]_D^{20}$ + 0.39°, $[\alpha]_{546}^{20}$ + 0.46° (c, 60 cyclopentane); $[\alpha]_{546}^{20}$ +0.69°, $[\alpha]_{546}^{20}$ + 0.79° (c, 30 cyclopentane). The neat specific rotations corrected for 3% CH_3CH_2OH densities[32](d^{20}_4

0.804, d_4^{25} 0.801) are $[\alpha]_D^{20}$ + 0.255°,$[\alpha]_{546}^{20}$ + 0.305°,$[\alpha]_D^{25}$ + 0.245°, $[\alpha]_{546}^{25}$ + 304°, lit. values[33] for the (*S*)-(-)-isomer are: α_D^{28} - 0.22° ± 0.02° (neat, l=1), $[\alpha]_D^{28}$ - 0.28° ± 0.03° (neat);[33] $[\alpha]_D^{25}$ - 0.30 ± 0.025° (neat).[15] The ORD spectrum, transposed for the enantiomer, is given in Figure 3A.

(*S*)-(-)-Ethyl-1-*d* azide. Methanesulfonyl chloride (5.8 g, 50 mmol, in 5 mL CH_2Cl_2) was added at -10 to - 5°C over 20 min. to a stirred solution of (*R*)-(+)-ethanol-1-*d* (1.7 g, 36 mmol) and triethylamine (6.4 g, 63 mmol in CH_2Cl_2, 50 mL). After the mixture warmed to 20°C (2 h), $Et_3N{\cdot}HCl$ was removed by filtration and washed with CH_2Cl_2 (5 mL). The filtrate was washed successively at 5°C with water (2 x 20 mL), 5% HCl (10 mL) and sat'd $NaHCO_3$ (10 mL), dried ($MgSO_4$) and the CH_2Cl_2 evaporated. The residue (4.15 g) was added to a suspension of NaN_3 (2.8 g) in DMSO (15 mL, distilled from CaH_2). The reaction set-up was connected to a trap at -75°C while the mixture was stirred and cautiously heated in an oil bath to 120°C (1.5 h) behind a safety shield. The distillate (1.71 g, 72% crude yield, from CH_3CHDOD) was evaporatively distilled (0.1 torr, 20°) and then vacuum-transferred to a special polarimeter tube[34] with a side arm cooled in liquid N_2: α_D^{25} - 3.94 ± 0.01° (neat, ℓ = 1), $[\alpha]_D^{25}$ - 4.44 ± 0.01° (neat, d^{25} 0.888 calc. from lit. value[35] of d^{25} 0.876, corrected for deuterium content[32]); $n^{20}D$ 1.4002; ^1H NMR, $CDCl_3$: 1.25 ppm (dt, 3 H, J_H = 7.3 Hz, J_D = 1 Hz), 3.29 ppm (qt, 1 H, J_H = 7.0 Hz, J_D = 0.5 Hz). The presence of 1.5% $CH_3CH_2N_3$ was estimated from the downfield-side signal (1.35 ppm) of the triplet centered at 1.25 ppm. Room temperature CD were taken in cyclohexane (Figure 3A gives the CD curve transposed for the enantiomer); UV, λmax 286 nm, ε = 140; CD λ 287 nm, Θ = +12.5 (hexane). While sealing a 263-mg sample of this azide in an ampule behind a safety screen, it detonated, exploding nearby, previously sealed, samples of $CH_3CH_2N_3$ and CH_3CHDN_3.

(*R*)-(+)-*n*-Butyl-1-*d* azide (3b). (*S*)-(+)-Butanol-1-*d*, 1b, (1.89 g, 25 mmol, 13% ee) was treated with toluenesulfonyl chloride (9.57 g, 50 mmol) and pyridine (30 mL) to give 2b, (3.9 g, 70% yield), which had 1.02 ± 0.03 deuterium atoms per molecule by NMR analysis. This tosylate was treated with sodium azide, 2.21 g, in HMPA, 50 mL, at 90°C under 27 mm pressure for 2 h (behind a saftey shield). The distillate was caught in a trap at -78°C and redistilled under vacuum to give 3b, (1.15 g, 67% overall), $\alpha^{20}D$ +7.30° (l = 1, neat, corrected to 100% ee), $n^{20}D$ 1.4194, with properties which correspond closely to those reported for non-deuteriated *n*-butyl azide.[35,36] The UV and CD spectra are given in Figures 3A and 3B.

(*R*)-(+)-Benzyl-α-*d* azide (3e). (*S*)-(+)-Benzyl-α-*d* alcohol[2], 1e, 30% ee, was converted to tosylate 2e by the method of Streitwieser and coworkers.[22] 2e (2.8 g) was treated with sodium azide (1.33 g, in 50 mL DMSO) for 40 h at 45°C to give distilled 3e (1.03 g, 74%), $\alpha^{20}D$ +8.02° (l = 1, neat, corrected to 100% ee) with the properties that correspond closely to those reported[37] for the non-deuteriated compound. The enantiomeric purity (chiral shift reagent,[2]) was 26 ± 3%; NMR integration indicated 0.99 ± 0.03 α-deuterium atoms per molecule. The UV and CD spectra are given in Figure 3A and 3B.

(*R*)-(+)-1-Methylazido-α-*d* adamantane (3d). (*S*)- (+)-1-Adamantylmethanol-α-*d*, 3.72 g, 28% ee, was treated with toluenesulfonyl chloride and pyridine by the procedure of Nordlander and coworkers[38] to give 2d, 6.8 g (95.6%), m.p. 73-76°C, which by NMR integration had 0.97 ± 0.05 α-deuterium atoms per molecule. Tosylate 2d, 6.8 g, was treated with sodium azide, 2.8 g, in HMPA, 50 mL, at 90°C for 12h. Azide 3d was isolated by adding the mixture to water, extracting with ether, drying ($MgSO_4$) and distilling to give 2.87 g (71%, overall yield), b.p. 115°C, 1 mm, $\alpha^{20}D$ +3.34° (neat, l = 1, corrected to 100% ee) with properties corresponding to those of the non-deuteriated parent.[39] The UV and CD spectra are in Figures 3A and3B.

ACKNOWLEDGMENTS:

We dedicate this paper to Dr. Edward Bunnenberg,[40] to whom we are deeply indebted for his advice and for many discussions on chiroptic matters over the years. We also wish to thank Dr. Gunter Barth and Ruth Records for consultations and determinations of the CD spectra and Drs. Lois Durham and Glenn Sullivan for consultation and determinations of NMR spectra.

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