Neopentyl Displacement Reactions without Rearrangement[1]

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Abstract: (*S*)-Neopentyl-*1-d* tosylate, prepared from the corresponding chiral neopentyl-*1-d* alcohol which is available *via* fermentative reduction, undergoes nucleophilic displacement without rearrangement when treated with various nucleophiles in hexamethylphosphoramide (HMPA) solvent. This constitutes a convenient preparative route for many neopentyl compounds which are not contaminated by rearranged *tert*-amyl products. The neopentyl-*1-d* compounds are formed with configurational inversion and with high stereochemical integrity when the nucleophile is also a poor leaving group (N_3^-, CN^-, Cl^-, $C_2H_5O^-$) but isoracemization may be extensive (Br^-) or complete (I^-) when the nucleophile is also a good leaving group. Thus the use of HMPA solvent makes possible normal SN2 type reactions on the otherwise very refractory neopentyl system. There are now available a series of chiral neopentyl-*1-d* compounds for further mechanistic and optical rotatory studies. Chiral neopentyl-*1-d* bromide was also prepared by the Lee reaction ($CX_4 + Ph_3P$) with net inversion of configuration accompanied by considerable racemization. The synthesis of neopentyl-*1-d* iodide by the Rydon procedure [$(PhO)_3P + CH_3I$] gave racemic product.

We have extended our stereochemical studies[4] using neopentyl systems which are chiral by virtue of deuterium substitution on the primary carbon to include experiments on neopentyl displacements under conditions which should minimize rearrangements. Because of the steric hindrance of the *tert*-butyl group to backside attack, SN2 reactions in the neopentyl system are notoriously slow and rearrangement to the *tert*-amyl system frequently predominates. Nevertheless, substitutions without rearrangement have been observed in the past.

During their studies on neopentyl rearrangements, Whitmore and coworkers[5] observed that a 40–70% yield of neopentyl acetate could be obtained by the treatment of neopentyl iodide with potassium acetate in ethanol (sealed tube, 200°, 20 hr). Dostrovsky and Hughes[6] obtained ethyl neopentyl ether from the reaction of neopentyl bromide and sodium ethoxide (ethanol solvent, sealed tube, 125°, 760 hr). Bordwell, Pitt, and Knell[7] reported that in boiling 2-methoxyethanol solvent (methyl Cellosolve, bp 125°) they obtained unrearranged products by using the more reactive tosyl leaving group and better nucleophiles such as the mercaptide and thiophenoxide ions. For example, treatment of neopentyl tosylate with sodium hydrogen sulfide in refluxing 2-methoxyethanol (2.5 hr) gave a 64% yield of neopentyl mercaptan along with neopentyl sulfide.[8]

Preparations of neopentyl halides from the alcohol by a variety of phosphorus reagents have been studied.[9] The first to be reported was the reaction with phosphorus tribromide in excess refluxing quinoline–bromobenzene mixture (*ca.* 180°, 24 hr, 47% yield).[10] Also triethylneopentoxysilane was treated with phosphorus tribromide in the presence of catalytic amounts of quinoline hydrochloride (*ca.* 170°, 16 hr, 86% yield).[10] According to the method of Landauer and Rydon,[11] neopentyl alcohol is converted into neopentyl iodide (53–57% yield contaminated with 6% *tert*-amyl iodide[12]) by refluxing with triphenyl phosphite and excess methyl iodide. This method has been applied to the synthesis of neopentyl chloride and bromide by using the corresponding benzyl halide instead of methyl iodide.[9] Extensive rearrangement was noted in these cases.[9,11] The method of Lee[13,14] in which an alcohol, triphenylphosphine (or trioctylphosphine[13f]), and carbon tetrachloride or tetrabromide are refluxed together should be applicable to the synthesis of neopentyl chloride and bromide.

In spite of these several reports, the idea persists that substitutions without rearrangement on neopentyl systems are synthetically impractical. We therefore initiated experiments with the purpose of finding suitable conditions for preparing a series of chiral neopentyl compounds from neopentyl-*1-d* alcohol. Initially we studied the reaction of neopentyl tosylate with azide ion; the first experiments in 85% methanol–water solvent according to classical conditions[15] gave only a trace of neopentylamine, after lithium aluminum hydride reduction. When the aprotic, polar solvent dimethylformamide was employed as the solvent (72

(1) Support by the National Science Foundation (NSF Grant GP 27448) is gratefully acknowledged.

(2) Taken in part from the Ph.D. thesis of Betty Winter Stephenson, Stanford, 1970.

(3) NATO Fellow, 1968.

(4) (a) W. A. Sanderson and H. S. Mosher, *J. Amer. Chem. Soc.*, 83, 5033 (1961); (b) *ibid.*, 88, 4185 (1966); (c) G. Solladié, M. Muskatirović, and H. S. Mosher, *Chem. Commun.*, 809 (1968).

(5) F. C. Whitmore, E. L. Wittle, and A. H. Popkin, *J. Amer. Chem. Soc.*, 61, 1586 (1939).

(6) I. Dostrovsky and E. D. Hughes, *J. Chem. Soc.*, 157 (1946).

(7) F. G. Bordwell, B. M. Pitt, and N. Knell, *J. Amer. Chem. Soc.*, 73, 5004 (1951).

(8) After the present work had been completed, we also learned from Professor Nathan Kornblum of the successful displacements on neopentyl and pinacolyl tosylates by thiophenoxide ion in dimethyl sulfoxide solvent: F. Stuckal, Ph.D. Thesis, Purdue University, 1970.

(9) H. R. Hudson, *J. Chem. Soc. B*, 664 (1968), has reviewed these reactions.

(10) L. H. Sommer, H. D. Blankman, and P. C. Miller, *J. Amer. Chem. Soc.*, 76, 803 (1954).

(11) (a) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953); (b) D. G. Coe, S. R. Landauer, and H. N. Rydon, *ibid.*, 2281 (1954).

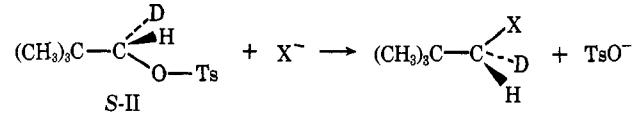
(12) N. Kornblum and D. C. Iffland, *J. Amer. Chem. Soc.*, 77, 6653 (1955).

(13) (a) D. Brett, I. M. Downie, J. B. Lee, and M. F. S. Mataugh, *Chem. Ind. (London)*, 1017 (1969); (b) I. M. Downie, J. B. Holmes, and J. B. Lee, *ibid.*, 900 (1966); (c) J. B. Lee and I. M. Downie, *Tetrahedron*, 23, 359 (1967); (d) J. B. Lee and T. J. Nolan, *ibid.*, 2789 (1967); (e) J. B. Lee, *Chem. Commun.*, 1554 (1968); (f) J. Hooz and S. S. H. Giliani, *Can. J. Chem.*, 46, 86 (1968).

(14) (a) R. G. Weiss and E. I. Snyder, *Chem. Commun.*, 1358 (1968); (b) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, 35, 1627 (1970).

(15) For example, the reaction of 2-butyl brosylate with azide ion: A. Streitwieser, Jr., and W. R. Schaeffer, *J. Amer. Chem. Soc.*, 78, 5597 (1956).

Table I. Optical Rotation and Configuration of Reaction Products from (*S*)-Neopentyl-*1-d* Tosylate[a]



S-II

	X^-	$[\alpha]D°$ (solvent, °C)	Configuration	Yield,[b] %	% ee[c]
III	N_3^- (Na^+)	+2.79 ± 0.05 (neat, 24)	*R*	87[d]	98 ± 2
		+3.21 ± 0.05 (neat, 24)[e]	*R*		
IV	NH_2[f]	+0.224 ± 0.011 (C_6H_{12}, 21)[g]	*R*	87	98 ± 2
V	CN^- (Na^+)	+0.533 ± 0.013 (C_6H_{12}, 22)[g]	*R*	90[h]	
X	Cl^- (Li^+)	−0.250 ± 0.008 (neat, 21)	*R*	62	*i*
XI	Br^- (Li^+)	−0.124 ± 0.003 (neat, 23)	*R*	67[i]	*i*
		−0.143 ± 0.002 (neat, 23)[e]	*R*		
XII	I^- (Na^+)	±0.00 ± 0.02 (neat, 26)	*RS*	42[i]	0
XIII	EtO^- (Na^+)	+0.89 ± 0.02 (neat, 24)[e]	*R*	34	97 ± 3

[a] All results reported on the basis of 1.00 deuterium atom per molecule. The tosylate used in most experiments analyzed for 0.94 deuterium atom and was made from (*S*)-neopentyl-*1-d* alcohol (*S*-I) which, within experimental limits, was enantiomerically pure. [b] These yields could probably be improved with further study. No *tert*-amyl products were observed. [c] % ee refers to enantiomeric excess (enantiomeric purity) and is the excess of one enantiomer over the *dl* pair. [d] The azide was not usually isolated. Since the amine was isolated in 87% yield (as the hydrochloride) from $LiAlH_4$ reduction of the azide, the yield of the azide must be at least 87%. [e] Observed rotation, 1-dm tube, instead of specific rotation. [f] Made by $LiAlH_4$ reduction of the azide (not by attack of NH_2^- ion). [g] C_6H_{12} refers to cyclohexane solvent. [h] Contaminated by a trace of isonitrile as evidenced by odor and by ir spectrum. [i] Presumably enantiomeric purity approaches 100% but no independent check of this could be made. [j] Yield takes into account recovered tosylate.

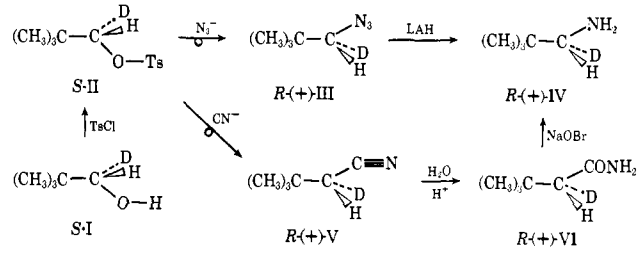
hr, 125°) according to a procedure used in the carbohydrate series,[16] the yield increased but only to about 10%. However, the use of hexamethylphosphoramide (HMPA) as solvent[17] (90°, 24 hr), as applied to azide formation by tosylate displacement in the steroid field by Goutarel and coworkers,[18] led to an overall yield of 87% of neopentylamine (isolated as the hydrochloride) after lithium aluminum hydride reduction of the initially formed azide. The success of this reaction made practical the extension of our previous studies on the stereochemistry of solvolytic neopentyl rearrangements[4] to the stereochemistry of neopentyl displacements using the chiral neopentyl-*1-d* system.

Results

(*S*)-Neopentyl-*1-d* alcohol (I), prepared by fermentative reduction of trimethylacetaldehyde-*1-d*,[19] was converted to the (*S*)-neopentyl-*1-d* tosylate (II) which was then subjected to displacement by azide, cyanide, ethoxide, chloride, bromide, and iodide ions in HMPA solvent. Under typical reaction conditions the temperature was slowly increased to 100–120° with reaction times of 1–7 hr, depending upon the nucleophile, until tlc test samples showed that the tosylate had been consumed. It was advantageous to carry out the reaction under reduced pressure so that the product distilled as formed. This is illustrated for azide and cyanide in Scheme I. A summary of the optical rotations, yields, and stereochemistry of the products is given in Table I.

Interpretation of the stereochemistry of the reactions represented by Scheme I requires that we know both the configuration and enantiomeric purity of the starting

Scheme I



neopentyl-*1-d* alcohol (I) and resulting neopentyl-*1-d*-amine (IV). The neopentyl-*1-d* alcohol used in these experiments was enantiomerically pure and had the *S* configuration.[4] Cram and coworkers[20] previously made chiral neopentyl-*1-d*-amine by a totally different route starting from the aldimine prepared by the reaction of (*S*)-(+)-α-phenylethylamine and trimethylacetaldehyde-*1-d*: a base-catalyzed 1,3-proton shift gave the conjugated aldimine which was subjected to acid hydrolysis. The *R* configuration was assigned by these authors to their (+)-neopentyl-*1-d*-amine based upon Brewster's rules[21a] as applied to 1-deuterio primary alcohols and amines.[21b] It was previously concluded[21] that the *R*-(+) configuration was required by the mechanism of the 1,3-asymmetric induction operating during the 1,3-proton shift. This neopentyl-*1-d*-amine, $\alpha^{25}D$ +0.35 ±0.05° (*l* 1, neat), from either the azide reduction or the Hofmann rearrangement of the amide, therefore, is enantiomerically pure within the experimental limits of these measurements.

Empirical correlation of the relative position of the nmr signals of a selected series of amide (and ester) derivatives from α-methoxy-α-trifluoromethylphenylacetamide (*R*-(+)-MTPA; VII)[22] shows that the signal for the proton α to the amide (or ester) function in the

(16) (a) A. Yamamoto, C. Miyashita, and H. Tsukamoto, *Chem. Pharm. Bull.*, 13, 1036 (1965); (b) R. Carrington, G. Shaw, and D. V. Wilson, *J. Chem. Soc.*, 6864 (1965); (c) H. Shechter, *J. Org. Chem.*, 25, 877 (1960).

(17) J. F. Normant, *Angew. Chem., Int. Ed. Engl.*, 1046 (1967).

(18) (a) M. Leboeuf, A. Cave, R. Goutarel, and G. Normant, *C. R. Acad. Sci.*, 264, 1090 (1967); *Bull. Soc. Chim. Fr.*, 2100 (1967); (b) L. A. Paquette and J. C. Philips, *Tetrahedron Lett.*, 4645 (1967); (c) *J. Chem. Soc. D*, 680 (1969); (d) R. G. Lewis, D. G. Gustafson, and W. F. Erman, *Chem. Commun.*, 401 (1967).

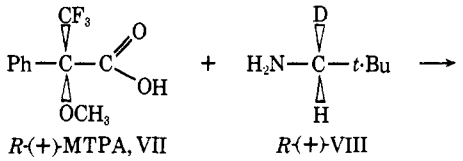
(19) (a) V. E. Althouse, K. Ueda, and H. S. Mosher, *J. Amer. Chem. Soc.*, 82, 5938 (1960); (b) V. E. Althouse, E. Kaufmann, P. Loeffler, K. Ueda, and H. S. Mosher, *ibid.*, 83, 3138 (1961).

(20) (a) R. D. Guthrie, W. Meister, and D. J. Cram, *J. Amer. Chem. Soc.*, 89, 5288 (1967); (b) W. Meister, R. D. Guthrie, J. L. Maxwell, D. A. Jaeger, and D. J. Cram, *ibid.*, 91, 4452 (1969); (c) R. D. Guthrie, *ibid.*, 89, 6718 (1967).

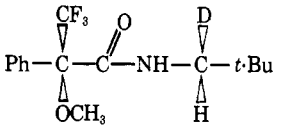
(21) (a) J. Brewster, *J. Amer. Chem. Soc.*, 81, 5475 (1959); (b) *Tetrahedron Lett.*, 20, 23 (1959).

(22) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 34, 2543 (1969).

R,R isomer is downfield from that of the *R,S* diastereomer.[23,24] The analysis is particularly unambiguous for primary alcohols and amines which are chiral by virtue of deuterium substitution.[21,22] Such an analysis for the amide made from *R*-(+)-MTPA and (+)-neopentyl-*1-d*-amine leads to the conclusion that the configuration of the (+)-amine is *R*. This assignment is in accord with that of Cram and coworkers.[20] Furthermore a quantitative study of the nmr spectrum of the MTPA amide permits us to deduce that (+)-neopentyl-*1-d*-amine is more than 96% enantiomerically pure (reported in Table I as 98 ± 2% ee).



R-(+)-MTPA, VII *R*-(+)-VIII



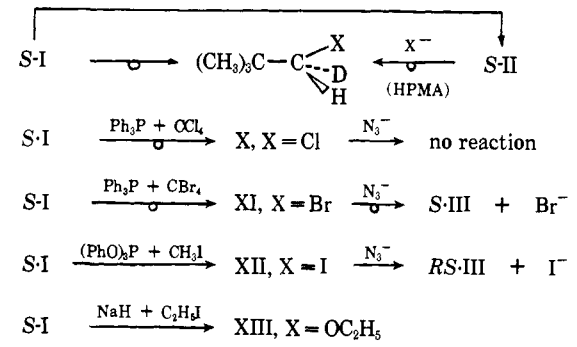
R,R-IX

Since (+)-neopentyl-*1-d*-amine has the *R* configuration, the displacements of azide and cyanide on (*S*)-neopentyl-*1-d* tosylate in HMPA solvent must proceed with configurational inversion in consonance with a typical SN2 reaction mechanism[25] as shown in *S*-II → *R*-V.

(*R*)-Neopentyl-*1-d* chloride (X) was prepared from (*S*)-neopentyl-*1-d* tosylate (II) by treatment with lithium chloride in HMPA solvent. Its configuration is assigned on the basis of the proven SN2 character of the reaction in the analogous azide displacement and on the sign of rotation. According to Brewster's rules,[21] corresponding saturated 1-deuterioalkylamines and halides with the same sign of rotation should have the same configuration. Direct evidence concerning configuration was not available since attempts to displace chloride in X by azide ion (HMPA solvent, 70°, 6 days) failed to give a measurable amount of neopentyl azide when monitored by nmr. We believe that X is essentially enantiomerically pure; since chloride is a rather poor leaving group, there should be no appreciable isoracemization (see Scheme II).

The Lee reaction[13] (CCl_4, $(PhO)_3P$, 70°) was applied to neopentyl alcohol. A vigorous reaction ensued and the distillate contained neopentyl chloride as revealed by nmr measurement; however, separation from carbon tetrachloride proved sufficiently difficult that only impure neopentyl chloride was obtained by this method.[26] Because of the success of the tosylate displacement method, this approach was not studied further.

Scheme II



(*R*)-(−)-Neopentyl-*1-d* bromide (XI) was made by treatment of the (*S*)-tosylate with lithium bromide in HMPA. However, the reaction was complicated by racemization. The product (46% yield) was optically inactive when the reactants were heated together at 120° under nitrogen at atmospheric pressure. However, by conducting the reaction under vacuum so that XI distilled as formed and by interrupting the reaction before all of the tosylate was consumed (100°, 25 mm, 3 hr), a 67% yield of (−)-neopentyl-*1-d* bromide was obtained [$\alpha^{23}D$ −0.143 ± 0.002° (*l* 1, neat)]. The evidence for the *R* configuration parallels that for the corresponding chloride. No independent measure of the stereochemical composition of this material is now available but we infer that it approaches enantiomeric purity because shorter reaction times and greater excess of tosylate gave material with the same rotation within the error limits of the reaction. The racemization observed upon extended reaction times must be the result of inversion by displacement of bromide from the initially formed product by the bromide ion in the reaction mixture (isoracemization). Treatment of the (−)-

$$R\text{-}(-)\text{-XI} \overset{Br^-}{\rightleftharpoons} S\text{-}(+)\text{-XI}$$

bromide XI with sodium azide in HMPA gave III which had 4.7% excess of the (*S*)-(−)-azide. We attribute the low enantiomeric excess (ee) to the ease of isoracemization of unreacted neopentyl-*1-d* bromide by the liberated bromide ion. The azide, *S*-III, from displacement on the bromide *R*-XI, has the opposite rotation from that of *R*-III obtained by the azide displacement on the *S*-tosylate, *S*-II. This is the expected result considering the total of three SN2 reactions involved in the interconnecting reactions.

Subjecting *S*-I to the Lee reaction (Ph_3P + CBr_4) in HMPA gave (−)-neopentyl-*1-d* bromide (XI) which had approximated 22% of the maximum rotation observed for material made by displacement on the tosylate. Since both this reaction and the tosylate displacement gave the same levorotatory isomer in excess, and since the bromide displacement on the tosylate certainly goes with inversion, then this case also must involve net inversion. This substantiates the known strong predilection for inversion[14b] in the Lee reaction.[26] The loss of activity which accompanies the reaction can be rationalized by assuming an isorace-

(23) J. A. Dale, Ph.D. Thesis, Stanford University, 1970.

(24) This oversimplified statement of the empirical correlation is limited to those cases where the configurationally related compounds based upon the nomenclatural sequence rule of Cahn, Ingold, and Prelog correspond to molecules with related preponderant conformations.[23] A detailed analysis will be the subject of a future publication.

(25) (*R*)-(+)-Neopentyl-*1-d*-amine has also been subjected to deamination by treatment with *n*-butyl nitrite[20c] to give (*R*)-(−)-2-methyl-1-butene-*3-d*.[4b] The only reasonable mechanism for this rearrangement requires displacement of the tosyl group with inversion by the migrating methyl group. These results constitute a consistent network of stereochemical correlations which leave no doubt concerning the configurations of the compounds reported in Table I.

(26) Weiss and Snyder[14b] have reported that the Lee reaction on neopentyl-1-*d* alcohol (CCl_4, Ph_3P) gives neopentyl-*1-d* chloride with inversion but the details have not yet been published.

mization mechanism. A similar result was obtained by Wiley, *et al.*,[27] in the preparation of 2-bromobutane from 2-butanol using the mechanistically similar reaction of triphenylphosphine dibromide in dimethylformamide. If the product was removed as formed, inversion was observed, but if chiral 2-bromobutane was left in contact with the reaction mixture, it was racemized. These stereochemical results suggest a mechanism for the Lee reaction in which triphenylphosphine, carbon tetrabromide, and neopentyl alcohol react to give neopentyloxytriphenylphosphonium bromide in which the oxyphosphonium ion serves as a good leaving group for displacement in a typical SN2 reaction by bromide ion.

$$S\text{-}I + Ph_3P + CBr_4 \longrightarrow$$

$$CHBr_3 + \left[(CH_3)_3C-C(D)(H)-\overset{+}{O}PPh_3\right] \xrightarrow{Br^-} XI + Ph_3PO$$

Front side collapse of tight ion pairs to give retention of configuration should be especially favored over backside attack when there is considerably greater steric hindrance at the back side.[28] Certainly the neopentyl system should favor retention if a tight ion pair mechanism were operative. The fact that we observe net inversion strongly discounts the four center mechanism for the Lee reaction (*cf.* ref 14b), at least as carried out in HMPA in this case.

When neopentyl-*1-d* iodide (XII) was prepared from the *S* alcohol by using triphenyl phosphite and excess methyl iodide according to the Rydon procedure, the product was without optical activity.[29] It is possible, although we believe highly unlikely, that XII, even though chiral, happens not to show optical rotation in the accessible region. Therefore this iodide was treated with sodium azide in HMPA (80°, 47 hr) which gave the azide (III) which was racemic.[30] This result could be due to isoracemization either during the Rydon reaction or during the displacement of the iodide by azide (or both). We surmise that it was the former since the iodide should have a higher rotation than either the chloride or bromide. It was also observed that neopentyl-*1-d* iodide prepared from the tosylate by treatment with sodium iodide in HMPA (up to 100°, 3 hr, 42% yield) was without significant optical rotation from 200 to 600 nm.[30] Again we attribute this to isoracemization.

In an attempt to prepare neopentyl fluoride from the tosylate (II) by treatment with sodium fluoride in HMPA (up to 150°) (either anhydrous or in the presence of a trace of water) only unreacted neopentyl-*1-d* tosylate was recovered (86% yield). This tosylate was subsequently converted to the azide which within experimental limits had the maximum observed rotation. From this we conclude that under the reaction conditions for tosylate displacement in HMPA there is no measurable racemization of the tosylate itself.

These results establish that in HMPA solvent, neopentyl tosylate undergoes normal nucleophilic displacements in spite of the backside steric hindrance of the *tert*-butyl group. The role of HMPA must be that ascribed to it by Normant,[17] namely the cation is so strongly solvated that the anion acts as a free nucleophile unencumbered by ion pairing, thereby presenting a minimum of steric hindrance to SN2 attack. These reaction conditions now make available neopentyl derivatives, which were previously difficultly accessible. Futhermore, a series of chiral neopentyl-*1-d* compounds which have the property of four highly symmetrical groups attached to a central carbon (H, D and Cl, Br, or CN with $C_{\infty v}$ symmetry and the *tert*-butyl group with C_{3v} symmetry) are available for optical rotatory dispersion studies. These and related compounds should be of considerable value in determining rotational contributions of various groups and will be the subject of further study.

Experimental Section

(*S*)-Neopentyl-*1-d* Tosylate (II). (*S*)-Neopentyl-*1-d* alcohol (I)[2,19] was converted to the tosylate by treatment with toluenesulfonyl chloride and pyridine by the standard procedure for the nondeuterated compound;[7,31] it was recrystallized after treating with Norit from hexane by dissolving at 35° and cooling to −75°; 85.5% yield, mp 43.4–44.5° (lit.[31] mp 46.0–46.5°), 94.2% deuterium atoms per mol;[32] II shows no observable rotation in methanol solvent between 300 and 589 nm. Except where noted, material with this deuterium content was used in the following experiments.

(*R*)-Neopentyl-*1-d* Azide (III). The (*S*)-tosylate (II, 6.0 g) and NaN_3 (4.5 g) in hexamethylphosphoramide (HMPA, 75 ml) were heated (90°, *ca.* 30 hr) until II could not be detected by tlc (silica gel, ether, I_2). The cold reaction mixture was hydrolyzed (50 ml of water, 200 g of ice) and allowed to stand (3 hr). The upper layer was collected, washed (saturated NaCl, H_2O), and dried ($MgSO_4$) to give a clear liquid (1.0 g, 30%), III: λ_{max} (cyclohexane) 255 and 208 nm; ir 2100 cm^{-1} (N_3); nmr ($CDCl_3$) δ 0.94 (s, 9 H) and 3.05 ppm (unsym t, *ca.* 1 H); $d^{21.5}{}_4$ 0.859; $\alpha^{21.4}D$ +2.62 ± 0.01° (*l* 1, neat), $[\alpha]^{21.4}D$ +3.21 ± 0.05° (neat, corrected to 1.0 deuterium atom per molecule). Extraction of the aqueous layer and washings gave additional azide but in most experiments the azide was extracted and reduced without isolation. A sample of nondeuterated material was analyzed.

Anal. Calcd for $C_5H_{11}N_3$: C, 53.10; H, 9.80; N, 37.13. Found: C, 53.30; H, 9.65; N, 37.45.

(*R*)-(+)-Neopentyl-*1-d*-amine (IV).[20] In an experiment identical with the above, the combined upper layer and benzene–ether extracts of the lower layer were washed, dried, and reduced by adding to lithium aluminum hydride (LiAlH, 5 g) in anhydrous ether (50 ml) with stirring (20°, 12 hr). The reaction mixture was hydrolyzed (5 ml of H_2O, 5 ml of 15% NaOH, 15 ml of H_2O), filtered, dried ($MgSO_4$), and distilled to give a benzene–ether solution of neopentylamine from which the hydrochloride was prepared by passing in a dry HCl gas: 2.9 g, 87% yield, 274–280° dec (lit.[33] 275°).

Anal. Calcd for $C_5H_{13}DClN$: Cl, 28.45. Found: Cl, 28.57.

The free amine *R*-IV was obtained by treating an aqueous solution of the hydrochloride with 50% NaOH, extracting with pentane, drying ($MgSO_4$), and distilling, bp 80° (lit.[20,33] 81–82°, 82–83°). A sample was further purified by glc (Dowfax 9N9, 6.5 ft × 14 in., 80°), $\alpha^{23.4}D$ +0.25 ± 0.01° (*l*, 1, neat), $[\alpha]^{23.4}D$ +0.35 ± 0.01° (neat, corrected for deuterium content and calculated density[34] of $d^{20}{}_4$ 0.754 from that of the nondeuterated compound).[33] This

(27) G. A. Wiley, B. M. Rein, and R. L. Hershkowitz, *Tetrahedron Lett.*, 2509 (1964).

(28) (a) H. L. Goering and S. Chang, *Tetrahedron Lett.*, 3607 (1965); (b) C. W. Schoppee and G. A. R. Johnston, *J. Chem. Soc.*, 3261 (1961).

(29) In one run of the Rydon reaction described by W. A. Sanderson[4a] a rotation of $\alpha^{29}D$ −0.58 ± 0.03° (*l* 1, neat) was reported for XII. This material was used in an unsuccessful solvolysis experiment and its rotation cannot be checked. We have been unable to duplicate this result. It may indicate, however, that conditions for the Rydon reaction which will give chiral neopentyl-*1-d* iodide could be found.

(30) Since the observed rotation of the azide is $\alpha^{24}D$ +2.79° (*l* 1, neat), we can easily detect 1% ee by rotation. The ORD from 600 to 200 nm of iodide from tosylate displacement showed a barely discernible negative trend which may be real.

(31) F. M. Beringer and H. S. Schultz, *J. Amer. Chem. Soc.*, 77, 5533 (1955).

(32) Combustion analysis by J. Nemeth, Urbana, Ill.

(33) (a) M. Freund and F. Lenze, *Ber.*, 24, 2156 (1891); (b) L. Tissier, *Ann. Chim. Phys.*, [6] 29, 373 (1893).

(34) A. McLean and R. Adams, *J. Amer. Chem. Soc.*, 58, 805 (1936).

sample was shown to be 98 ± 2% enantiomerically pure by measuring the nmr of the amide prepared from *R*-(+)-MTPA.[22]

(*S*)-(−)-Neopentyl-*1-d* Azide (III). *R*-(−)-XI (2.0 g), $[\alpha]^{23}D$ −0.124 ± 0.003° (neat), prepared by displacement of tosylate by bromide ion was heated (90 ± 5°, 40 hr) in HMPA solvent (10 ml) with sodium azide (2.3 g). The progress of the reaction was followed by nmr (*tert*-butyl signal from neopentyl bromide 1.03 ppm, from neopentyl azide 0.94 ppm). The cold mixture was extracted with water and the insoluble upper layer separated and dried ($MgSO_4$) to give 1.33 g (87% yield) of (−)-III, $[\alpha]^{22}D$ −0.15 ± 0.03° (neat). Based on $[\alpha]^{24}D_{max}$ of 3.21° (neat) for neopentyl azide, this material has 4.7% excess of (−) enantiomer.

(*R*)-(−)-Neopentyl-*1-d* Chloride (X). *S*-II (6.0 g), lithium chloride hydrate (0.085 g), HMPA (20 ml), and water (25 drops) were heated (up to 90°, 4.5 hr), under vacuum (25 mm). The distillate which was caught in a Dry Ice trap was washed with water and dried to give 1.27 g of X (yield 62%, considering 1 g of recovered II), $\alpha^{21}D$ −0.197 ± 0.002° (*l* 1, neat). A sample was purified by glc (SE-30, 10 ft × 3/8 in., 75°); $[\alpha]^{21}D$ −0.250 ± 0.008° (neat, corrected for 94% deuterium content using d^{20}_4 0.874 as the calculated[33] density of the deuterium compound). The ir (C–Cl, 900 cm^{-1}) and nmr [($CDCl_3$) δ 1.00 (s, 9 H), 3.30 ppm (unsym t, *ca.* 1 H)] were as expected from that of the nondeuterated derivative.

Attempted displacement of chloride from neopentyl chloride with sodium azide in HMPA (70°, 6 days) failed to give detectable amounts of III by nmr.

Neopentyl chloride was also made by treating I (8 g) with triphenylphosphine (26.2 g) and carbon tetrachloride (23 g) according to the conditions of the Lee[13] reaction. A vigorous exothermic reaction occurred when the temperature reached 70°. A white solid formed almost immediately (Ph_3PO). Volatile material was distilled and the distillate twice redistilled to give neopentyl chloride contaminated with CCl_4. Extension to the deuterated derivative was not completed because of the successful reaction of chloride ion on II.

(*R*)-(−)-Neopentyl-*1-d* Bromide (XI). *S*-II (6.0 g), LiBr (2.0 g), HMPA (22 ml), and H_2O (25 drops) were heated (to 100°, 3 hr, 25 mm), and the volatile product was collected (2.21 g after washing and drying, 67% yield considering 0.7 g recovered *S*-II). The ir and nmr were as expected from that of authentic nondeuterated XI: nmr ($CDCl_3$) δ 1.03 (s, 9 H), 3.24 ppm (unsym t, *ca.* 1 H); no *tert*-amyl products were detected by nmr. A sample which was purified by glc [silicone SE-30, 10 ft × 3/8 in., 120°] had $\alpha^{23}D$ −0.143 ± 0.002° (*l* 1, neat), $[\alpha]^{23}D$ −0.124 ± 0.006° (neat, using calculated[34] density of d^{23}_4 1.21 from that of the nondeuterated compound[35] and correcting for 95% deuterium).

A stream of nitrogen was swept through a mixture of *S*-II, excess LiBr, trace of water, all in HMPA solvent, while the temperature was raised to 120°; a 46% yield of optically inactive IV was obtained upon purification of the distillate caught in a cold trap. We plan to investigate further the role of water in this reaction.

A slurry of *S*-I (10 g, 86.4% deuterium), triphenylphosphine (31.4 g), and HMPA (25 ml) was cooled (0–5°) and CBr_4 (39.8 g) in HMPA (100 ml) was added over a 45-min period with cooling. The mixture was heated (nitrogen atmosphere); at 135° neopentyl bromide distilled and at 150° no more volatile material was observed. The distillate was washed (H_2O), dried ($MgSO_4$), and distilled to give 11.8 g (68% yield) of XI [bp 102–104°; $n^{20}D$ 1.4419; nmr ($CDCl_3$) δ 1.03 (s, 9 H) and 3.24 ppm (unsym t, *ca.* 1 H); 86 ± 2% deuterium in α position; ir 2170 (C–D), and 900 cm^{-1} (C–Br); $[\alpha]^{21}D$ −0.024 ± 0.008°, $[\alpha]^{21}_{528}$ −0.020 ± 0.008°, $[\alpha]^{21}_{546}$ −0.036 ± 0.008°, $[\alpha]^{21}_{436}$ −0.060 ± 0.008°, and $[\alpha]^{21}_{365}$ −0.097 ± 0.007° (*c* 28.8, cyclohexane).

An azide displacement on this bromide gave a product which showed no significant rotation (*l* 1/2, neat).

(*RS*)-Neopentyl-*1-d* Iodide (XII). A mixture of *S*-II (4.0 g), NaI (2.2 g), HMPA (15 ml), and H_2O (25 drops) was heated (100°, 4 hr) under vacuum (25 mm) to give a distillate which was washed with water and dried ($MgSO_4$) yielding XII (1.1 g); nmr ($CDCl_3$) δ 3.13 (unsym t, *ca.* 1 H), 1.06 ppm (s, 9 H); lit.[36] nondeuterated compound δ 3.07 (2 H) and 1.03 (9 H). This material showed almost no observable rotation from 200 to 600 nm (cyclohexane) although a very slight negative trend may have been real. Dilution of the HMPA residual reaction mixture gave recovered *S*-II (0.8 g).

Using the method described for the nondeuterated compound,[11,12] triphenyl phosphite, methyl iodide, and *S*-I were refluxed (75–95°) for 23 hr to give, after isolation, a 65% crude yield of XII, $\alpha^{30}D$ +0.01 ± 0.02° (*l* 1/2, neat).[29] This sample was converted to III which also had no observable rotation.

(*R*)-Neopentyl-*1-d* Cyanide (V). *S*-II (10 g), NaCN (2.9 g), HMPA (20 ml), and H_2O (25 drops) were heated (under reduced pressure (26 mm)) for 7 hr so that the nitrile V distilled into a Dry Ice trap as formed; crude yield 90%. The dried product gave ir and nmr spectra which were as expected, based on those of the nondeuterated compound: nmr ($CDCl_3$) δ 1,07 (s, 9 H) and 2.20 ppm (unsym t, *ca* 1 H); 96% deuterium by nmr; $\alpha^{21}D$ +0.070 ± 0.002° (*l* 1, *c* 12.59, cyclohexane), $[\alpha]^{21}D$ +0.585 ± 0.017° (cyclohexane). This material had a strong isonitrile odor and showed a slight peak at 2140 cm^{-1} in accord with this type of impurity. Earlier attempted displacements without added water failed. A glc purified (Carbowax 20 M, 5 ft × 0.25 in., 70°) sample (mp 31–32°, lit.[37] 32.5°) had $\alpha^{22}D$ +0.084 ± 0.002° (*l* 1, *c* 16.6, cyclohexane), $[\alpha]^{22}D$ +0.533 ± 0.013° (*c* 16.6, cyclohexane).

Hydrolysis and Hofmann Rearrangement of (*R*)-Neopentyl-*1-d* Cyanide (V). A mixture of *R*-V (3 g) and 98% sulfuric acid (12 ml) was heated for 5 min on the steam bath and the product isolated by pouring onto ice (60 g), extracting with ether, washing the ether layer (H_2O), and drying ($MgSO_4$) to give crude *tert*-butylacetamide-α-*d* (VI) whose properties were compatible with those of the nondeuterated authentic sample: mp 125–130° (lit.[38] 131–131.5°); nmr ($CDCl_3$) δ 2.10 (broad unsym t, *ca.* 1 H) 1.07 ppm (s, 9 H). This crude amide (0.73 g) was treated with bromine (0.8 ml) and sodium hydroxide (2.4 g in 20 ml of H_2O) according to Whitmore and Homeyer[37] to give IV (95% crude yield from amide) which was purified by glc (silicone SE-30, 10 ft × 3/8 in., 105°), $[\alpha]^{21}D$ +0.238 ± 0.011° (*c* 18.568, cyclohexane, corrected for 94% D).

(*S*)-(−)-Ethyl Neopentyl-*1-d* Ether (XIII). A solution of *S*-I (2.2 g, 86.4% deuterium) in HMPA (3 ml) was slowly added to a suspension of sodium hydride (1.2 g, 50% dispersion in paraffin oil) in HMPA (5 ml) and the mixture stirred for 4 hr. Ethyl iodide (5 g) was added, the mixture heated (70°, 24 hr), the product distilled from the reaction mixture and the crude product (XIII, 0.92 g) purified by glc (Carbowax 20M, 20 ft × 3/8 in., 100°) to give a product whose properties were in accord with the nondeuterated compound: ir (neat) 2100 (C–D) and 1125 cm^{-1} (C–OC); nmr ($CDCl_3$) δ 0.88 (s, 9 H), 1.18 (t, 3 H, J = 7 Hz); $\alpha^{27}D$ −0.93 ± 0.01° (*l* 1, neat, uncorrected for per cent deuterium), $[\alpha]^{21.7}D$ −1.25 ± 0.025° (*c* 8.609, cyclopentane, corrected to 1.0 atom of deuterium per molecule).

(*R*)-(+)-Ethyl Neopentyl-*1-d* Ether (XIII). *S*-II (5.0 g) was added to a solution of sodium ethoxide (20 g in absolute ethanol) in HMPA (25 ml) and the mixture heated to 130° with a stream of nitrogen passing through it. The distillate which was collected in a Dry Ice trap was washed (H_2O) and dried ($MgSO_4$) to give XIII (0.82 g) whose identity was confirmed by glc purification as above: $\alpha^{24}D$ +0.42 ± 0.01° (*l* 1/2, neat), $\alpha^{24}D$ +0.89 ± 0.02° (*l* 1, neat, corrected for 94% D, but uncorrected for density).

Attempted Preparation of Neopentyl Fluoride. A mixture of *S*-II (5.0 g), NaF (1.0 g), HMPA (20 ml), and water (15 drops) was heated to 150° without any product distilling. Dilution of the reaction mixture precipitated starting material (4.3 g, 86%). This recovered tosylate was converted to (*R*)-(+)-neopentyl-*1-d* azide as previously described: nmr indicated 5% impurity of HMPA; $\alpha^{23.5}D$ +1.18 ± 0.02° (*l* 1/2, neat), $[\alpha]^{23.5}D$ +3.08 ± 0.1 (neat correcting for 94% D, 5% HMPA, and using d^{23}_4 0.859 obtained experimentally from sample of azide prepared from the tosylate previously).

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