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STEREOCHEMISTRY OF NEOPENTYL SYSTEMS

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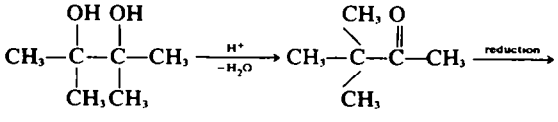
Methods for the synthesis, determination of enantiomeric purity and absolute configuration of primary 1-deuterio alcohols (RCHDOH) are outlined and tabulated. Studies on the rearrangements, solvolyses and S_N2 reactions of chiral neopentyl-1-*d* derivatives are reviewed. Finally, the optical rotatory properties of the $(CH_3)_3C$-CHDX compounds, with their unique symmetry properties, are summarized and discussed.

Recent stereochemical developments utilizing chiral neopentyl-1-*d* alcohol and its derivatives have altered two of the long-established perceptions of the neopentyl system and its reactions. These two ideas, which for many years were universally accepted and essentially unquestioned, are: (1) that replacement of the OH group in a neopentyl system leads to rearrangement *via* a neopentyl cation or cation-type intermediate; and (2) that bimolecular nucleophilic displacement (S_N2) reactions on neopentyl systems are impractical because of excessive hindrance by bulky t-Bu groups to backside attack.

The historical background of these concepts is extremely interesting but can only be incompletely summarized here. The pinacol–pinacolone rearrangement (**1** → **2**) had been reported by Fittig[1] in 1860 and its structural requirements well established by 1901 when Zelinsky[2] dehydrated pinacolyl alcohol **3** with the intent of producing t-butylethylene **5**. However, the product isolated was tetramethylethylene **4**. This dehydration accomplishes a carbon skeleton rearrangement which is the reverse of the pinacol–pinacolone rearrangement. This and many other acid catalyzed rearrangements of terpene alcohols were investigated by Wagner and on a wider structural basis by Meerwein during the period 1899–1922. To our knowledge, the first mention of the rearrangement of neopentyl alcohol itself was by Ingold in a footnote to a paper published in 1923[3] in which he reported a private communication from R. Robinson and M. Tadman in which they obtained a mixture of 2-methyl-1-butene (**7**) and 2-methyl-2-butene (**8**) from its dehydration.



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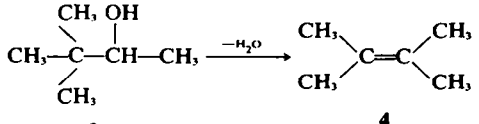

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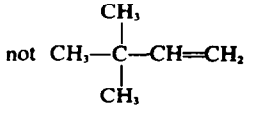

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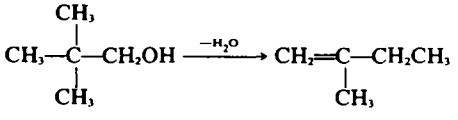

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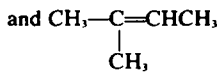
and 

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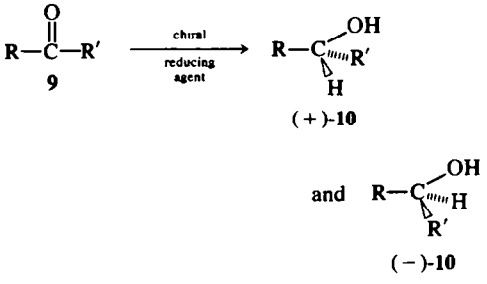
The essential elements of the Wagner–Meerwein rearrangement and other diverse rearrangements were brought together by Whitmore in his classic paper, "A Common Basis for Molecular Rearrangements"[4] in 1932. Thus, in spite of the fact that neopentyl alcohol itself is the simplest carbinol bearing the minimum complete structural requirement for this rearrangement (**3** → **5**), its chemistry was not studied thoroughly until the series of papers by Whitmore and his students from 1932–1939.[5] These studies established the proclivity to rearrangement of the neopentyl system and the extreme resistence of neopentyl halides to displacement

reactions without rearrangement. The results of these studies led to such statements[6] as: "This (neopentyl) chloride cannot be made from the corresponding alcohol"; and "Primary halides of the type R'R'R"CCH_2X cannot be made from the corresponding alcohols except in very small yields, the main product being the (rearranged) tertiary halide formed by shift of one of the alkyl groups." These statements are generally correct but must now be modified in view of the new phosphorus reagents exemplified by the Landauer–Rydon[7] and Lee[8] reactions and methyl-triphenoxyphosphonium iodide[9] and the advent of hexamethylphosphoramide (HMPA) as a powerful solvent for S_N2 reactions.[10]

Our work on neopentyl alcohol and its derivatives did not develop from a desire to investigate this system *per se*. Rather, we were involved in studies on asymmetric reductions[11] which suggested that this was a system that could be profitably studied. In reductions of carbonyl compounds represented by **9** we had assumed that the greater the difference in steric bulk, other factors being equivalent, the greater the asymmetric bias in the reduction. The logical aliphatic substrate which

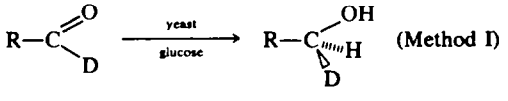


would maximize this steric difference was trimethylacetaldehyde-1-*d* where R was t-Bu and R' was deuterium. Before a meaningful stereochemical study of this substrate could be made it was necessary to develop means of determining both the enantiomeric purity of the resulting neopentyl-1-*d* alcohol and its absolute configuration. This also involved the development of ways of preparing this and other chiral primary 1-deuterio alcohols. It seems appropriate first to review these methods before developing the details of the neopentyl-1-*d* rearrangements and substitution reactions.

Synthesis of chiral 1-deuterio primary alcohols

Enzymatic processes. In the period between 1915 and 1930, Neuberg and Nord[12] pioneered the investigations on actively fermenting yeast as a means of achieving the reduction of various aldehyde and ketone substrates. In general, it was found that yeast cells which were actively engaged in the anaerobic fermentation of dextrose were able to reduce a wide variety of unnatural carbonyl substrates which were added to the fermenting mixture. The chemical yields from the reduction of the lower ketones were often quite satisfactory but with higher members, which were not particularly water soluble, only small amounts were isolated. The products were optically active (when $R \neq R'$) but not optically pure.[13] Lower aldehydes are reduced in a satisfactory manner, but of course there is no chirality at the primary carbinol carbon atom. The pioneering experiment by Westheimer, Vennesland *et al.*[14] showing the stereospecific reduction of acetaldehyde-1-*d* to give (−)-ethanol-1-*d* by the isolated enzyme system, yeast alcohol dehydrogenase and reduced diphosphopyridine nucleotide (ADH–DPNH system), clearly indicated the potential of the enzymatic reduction as a means of obtaining chiral 1-deuterio primary alcohols. This enzymatic asymmetric synthesis was soon followed by the chemical asymmetric reductions of butanal-1-*d* to (+)-butanol-1-*d* first realized by Streitwieser and students.[15]

We found that the purified ADH–DPNH enzyme system would not reduce trimethylacetaldehyde at an appreciable rate; however, by using actively fermenting yeast we have prepared approximately 200 g. of neopentyl-1-*d* alcohol (50% isolated yield).[16] This material did not show appreciable optical rotation down to 300 nm in 80% acetone solution but gave a plain positive ORD curve in cyclohexane.[17] The acid phthalate had a substantial rotation for a compound which owes its chirality to the difference between hydrogen and deuterium: $[\alpha]^{25}D - 1{\cdot}15 \pm 0{\cdot}03°$ (*c* 20, acetone). In addition to neopentyl-1-*d* alcohol, the following have been made on a preparative scale by yeast reductions



(Method I): butanol-1-*d*[18] ($[\alpha]^{27}D + 0{\cdot}45°$, neat), 2-methyl-1-propanol-1-*d*[19] ($[\alpha]^{25}D + 0{\cdot}61°$, neat), benzyl-α-*d* alcohol[18] ($[\alpha]^{24}D + 1{\cdot}58°$, neat), and 1-adamantyl-carbinol-α-*d*[20] (97 ± 3% enantiomerically pure by NMR analysis of the O-methylmandelate ester, rotation not reported). It has now been shown that these 1-deuterio primary alcohols produced by fermentation are enantiomerically pure. Since acetaldehyde is the natural substrate for the yeast ADH–DPNH system, it is expected that reduction by it would yield only one isomer. However, it is not obvious that the reduction of unnatural aldehyde substrates by this system should be stereospecific. The fact that such diverse compounds as n-butanol, trimethylacetaldehyde and benzaldehyde are reduced to give only the *S*-enantiomer of the RCHDOH compound shows that the stereoselectivity of this enzyme system is not

dependent upon the R group. This is compatible with an enzyme reactive site, which is not embedded very deeply in the body of the enzyme molecule. Thus the chiral, reactive site can accommodate the prochiral functional CHO group in only one stereochemical sense so that the hydrogen is transferred to only one face of the CO function. At the same time the R group either is located within a hydrophobic region on the surface or in a very readily expandable hydrophobic cleft on or near the surface of the enzyme molecule. Apparently this reactive site also accepts many ketones,[12] but when it does the stereoselectivity of the reduction is reduced.[13] In these yeast mediated CO reductions it is logical to assume that the ADH–DPNH enzyme system is responsible although we have no proof that this is indeed the case.

Ethanol-1-*d*,[21] propanol-1-*d*,[22] geraniol-1-*d*,[22] 3-methyl-2-butene-1-ol-1-*d*,[22] and benzyl-α-*d* alcohol[22] also have been made on a preparative scale enzymatically by a process (Method II) whereby one of the pro-chiral hydrogens on the primary alcohol carbon is stereoselectively exchanged for deuterium by incubation in the presence of D_2O, ADH–DPNH, diaphorase and either yeast or liver alcohol dehydrogenase.[21,22] Yeast alcohol dehydrogenase exchanges the pro-*S* while liver alcohol dehydrogenase exchanges the pro-*R* hydrogen. By using 1,1-dideuterio alcohol in H_2O, the enantiomer is formed.

$$RCH_2OH + D_2O(\text{excess}) \xrightarrow[\text{Diaphorase}]{\text{DPN-DPNH+ADH}} RCHDOH + HOD \quad \text{(Method II)}$$

Non-enzymatic processes. Although the reduction of butanol-1-*d* (**13**, R = *n*-C_3H_7) by the chiral aluminum alkoxide from (−)-2-octanol[23a] was the first "chemical" asymmetric reduction to produce a chiral primary alcohol, it was subsequently shown that the modification using the magnesium bromo alkoxide **11** (produced by treating isoborneol with CH_3MgBr) was much preferable.[15,23] Benzyl-α-*d* alcohol (**14**, R = Ph) made by reduction of benzaldehyde-α-*d* by this process (Method III) has been shown to have a 41–45% excess of the *R*-(−) isomer. The enantiomer of **14** is produced by using isotopically normal aldehyde and α-deuteriated reagent **11**. Other asymmetric syntheses of chiral 1-deuterio primary alcohols by this method are summarized in Table 1.

Another chemical procedure for the synthesis of 1-deuterio primary alcohols involves reduction by asymmetric Grignard reagents (Method IV).[11] Although this is of considerable mechanistic importance, it is of little preparative value because the chiral Grignard reagents are difficult to obtain. Four examples of this reaction are given in Table 1.

Asymmetric hydroborations, using chiral di-3-camphanylborane (diisopinocampheylborane, Ipc_2BH, **16**) from either (+) or (−) α-pinene (Method V)[31] have provided effective routes to several partially optically active 1-deuterio primary alcohols. Thus (*S*)-(+)-1-hexanol-1-*d* (**18**) was synthesized with a stereochemical purity of 86% starting with *trans*-1-hexene-1-*d* (**15**) and the reagent prepared from (−)-α-pinene.[28] Other examples are given in Table 1. It is important to note that the age of the reagent may affect the stereoselectivity of the reaction.[32] The wide differences in asymmetric synthesis recorded for the reaction starting with either *cis*-1-hexene-1-*d* (42% e.e.) or *trans*-1-hexene-1-*d* (86% e.e.) may be due to this since it is difficult to account for it by any other logical scheme.

Certainly the most convenient method for production of partially active 1-deuterio primary alcohols is the reduction of the corresponding aldehyde with a chirally modified lithium aluminum deuteride reagent. The reagent we have studied to date is prepared by adding two molar equivalents of an ether solution of the commercially available chiral amino alcohol (+)-(2*S*,3*R*)-4-dimethylamino-

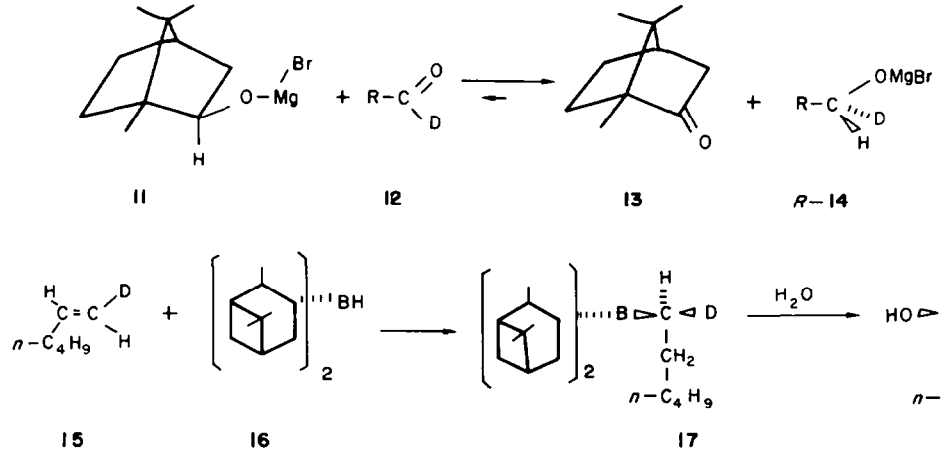


Table 3. "Chemical" synthesis of chiral primary 1-deuterio alcohols

No.	Method[a]	Chiral reagent	Substrate	RCHDOH Product Config.	%e.e.	Ref
1		(*S*)-(+)-2-Octanol-2-*d*	$(CH_3)_2CHCHO$	*R*-(−)	8–15	23*a*
2		(*R*)-(−)-2-Octanol-2-*d*	$(CH_3)_2CHCHO$	*S*-(+)	6	23*a*
3		(*R*)-(−)-2-Octanol	$(CH_3)_2CHCDO$	*R*-(−)	10	23*b*
4		(−)-Isoborneol-2-*d*	CH_3CHO	*S*-(−)	44	23*d*
5	III[c]	(−)-Isoborneol-2-*d*	$(CH_3)_2CHCHO$	*S*-(+)	19	15
6		(−)-Isoborneol	$(CH_3)_2CHCDO$	*R*-(−)	45–50	8
7		(−)-Isoborneol	PhCDO	*R*-(−)	41–45	23*c*, 8
8		(−)-Isoborneol-2-*d*	(*Z*)-4-$CH_3C_6H_{10}CHO$	*S*-(+)	—[d]	24
9		(−)-Isoborneol-2-*d*	(*E*)-4-$CH_3C_6H_{10}CHO$	*S*-(+)	—[d]	24
10		(−)-Isoborneol-2-*d*	*p*-AnisylCH_2CH_2CHO	*S*-(+)	—[d]	25
11		(S)-$EtCHCH_3CH_2MgCl$	$(CH_3)_3CCDO$	*S*-(+)	12	16*a*
12	IV[e]	(*S*)-$EtCHCH_3CH_2MgCl$	C_6H_5CDO	*S*-(+)	19	18
13		(*S*)-$C_6H_5CHEtCH_2MgCl$	$(CH_3)_3CCDO$	*S*-(+)	29	26
14		(*S*)-$C_6H_5CHEtCH_2MgCl$	C_6H_5CDO	*S*-(+)	67	26
15		(−)P_2^*BH	(*Z*)-EtCH=CHD	*R*-(−)	56	27
16		(−)P_2^*BH	(*Z*)-*n*-C_4H_9CH=CHD	*R*-(−)	42	28
17	V[f]	(−)P_2^*BH	(*E*)-*n*-C_4H_9CH=CHD	*S*-(+)	86	28, 29
18		(−)P_2^*BH	$(CH_3)_2C$=CHD	*R*-(−)	28	19
19		(+)P_2^*BH	$(CH_3)_2C$=CHD	*S*-(+)	27	19
20		$LiAl(OR^*)_2D_2$	$CH_3CH_2CH_2CHO$	*S*-(+)	17[h]	30
21		$LiAl(OR^*)_2D_2$	$(CH_3)_2CHCHO$	*S*-(+)	26	30
22		$LiAl(OR^*)_2D_2$	$(CH_3)_3CCHO$	*S*-(+)	42	30
23	VI[g]	$LiAl(OR^*)_2D_2$	C_6H_5CHO	*S*-(+)	40	30
24		$LiAl(OR^*)_2D_2$	$(C_6H_5)_3CCHO$	(−)[i,j]	66	30
25		$LiAl(OR^*)_2D_2$	Cl_3CCHO		27	30
26		$LiAl(OR^*)_2D_2$	Adamantyl	*S*-(+)	31	30

[a] See text for further description and references to the Methods.

[b] %e.e. refers to percent enantiomeric excess.

[c] Method III: Meerwein–Ponndorf–Verley reduction with chiral aluminum alkoxide in entries 1-3 and with isobornyloxy-magnesium bromide (**11**) in entries 4–10.

[d] Enantiomeric purity of product not determined.

[e] Method IV: Asymmetric Grignard reduction.

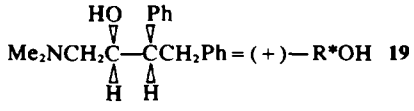
[f] Method V: Hydroboration with di-3-pinanylborane (P_2^*BH, **16**) followed by hydrogen peroxide oxidation. (−)-P_2^*BH stands for the reagent prepared by adding diborane to (+)-α-pinene; (+)-P_2^*BH for the adduct from (−)-α-pinene.

[g] Method VI: Reduction with the chiral $LiAl(OR^*)_2D_2$ reagent **20**, prepared by adding 2 moles of (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (R*OH, **19**) to one mole of $LiAlD_4$.

[h] These stereoselectivities are the average for two runs which were generally within ± 3% of each other.

[i] Configuration not independently established but presumably *S*.

[j] No appreciable sodium D-line rotation.



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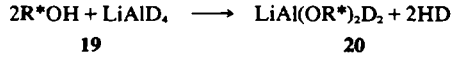
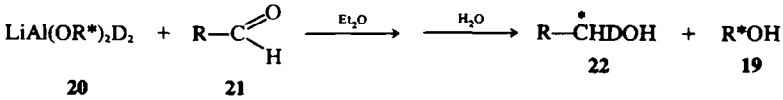


19 **20**

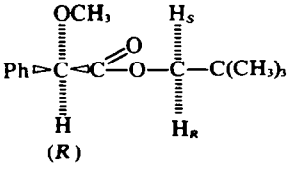


20 **21** **22** **19**

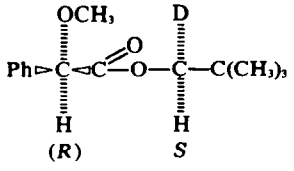
3-methyl-1,2-diphenyl-3-butanol (R*OH, **19**) to one molar equivalent of lithium aluminum deuteride in ether.[30] This reagent, which can be represented by $LiAl(OR^*)_2D_2$ (**20**), is used by adding the substrate aldehyde **21** to it within three minutes of its preparation (Method VI). After 1/2 h of stirring, the primary 1-deuterio alcohol (**22**) is isolated with stereoselectivities varying from 15 to 66% as shown in Table 1. Since the reagent is basic, it can be quantitatively recovered without contaminating the neutral alcohol.

Enantiomeric purity of RĊHDOH *carbinols*

The determination of the enantiomeric purity of chiral RCHDOH alcohols now has been rendered routine by the development of methods based upon the NMR non-equivalence of diastereomers. Raban and Mislow[33] showed that the diastereotopic α-protons, H_S and H_R in neopentyl (*R*)-O-methylmandelate **23A** were distinguishable by NMR. This makes possible the determination of enantiomeric



23A



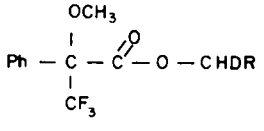
(*R*,*S*)-23*B*

purity of neopentyl-1-*d* alcohol by quantitative conversion to its O-methylmandelate ester, **23B**. Neopentyl-1-*d* alcohol prepared by fermentation was shown, within experimental limits, to consist of one pure isomer by this NMR method, which has been discussed in detail.[34] The α-methoxy-α-trifluoromethylphenylacetyl esters[35] (**24**, MTPA esters) have proven to be equally useful in demonstrating NMR diastereomeric non-equivalence in primary 1-deuterio alcohols. This reagent has the practical advantage of being immune to racemization at the quaternary α-carbon atom. In addition, the ^{19}F diastereomer resonances, which occur in a completely uncluttered region of the NMR spectrum, may also be used, especially in those cases where the relevant proton region is complicated by extraneous signals. These NMR non-equivalences can be enhanced by the use of a lanthanide shift reagent.[22,30]

Gerlach and Zagalak[22] have found that the camphanic acid esters (**25**) of primary 1-deuterio alcohols are especially effective in bringing about substantial NMR non-equivalence of diastereotopic protons in the presence of an ordinary (non-chiral) lanthanide shift reagent such as $Eu(dpm)_3$. Still another technique of equal or greater convenience is the use of a chiral lanthanide shift reagent to separate the signals for the enantiotopic α-hydrogens of the primary 1-deuterio alcohol itself.[30] We found that $Eu(HFC)_3$ caused a chemical shift difference in the α-protons sufficient to permit quantitative determination of enantiomeric purity in six out of seven cases. Several other chiral shift reagents have been described; if one is not effective another very likely will be.[36]

Configuration of RĊHDOH *carbinols*

Several chemical correlation methods have been used for establishing the absolute configuration of RĊHDOH alcohols.[37,38] As the configurations of a reasonable number of these alcohols have been established with certainty, it becomes possible to develop empirical correlations which can be used to predict the configuration of new members of the series.[29,30] The use of asymmetric reduction should be especially reliable in this case. If one establishes that a particular chiral reducing agent such as **20** produces a preponderance of the *S* carbinols when R is n-Pr, tert-Bu and phenyl (by preferentially attacking the pro-*S* face of R—C(=O)H) then it seems completely logical that reasonable changes in R will not reverse the direction of stereoselectivity of the reactions. This reasoning was used by Horeau and Nouaille[29] in their application of the method of kinetic resolution to the correlation of configuration of 1-deuteric primary alcohols (RCHDOH, R = n-Pr, n-pentyl, t-Bu, phenyl). This same general concept was applied successfully to correlate the extent of NMR chemical shift induced in seven



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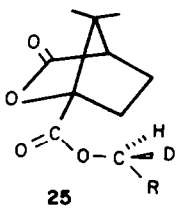

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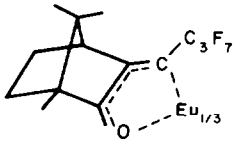
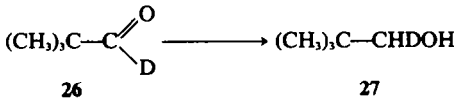


$Eu(HFC)_3$

RCHDOH carbinols in the presence of Eu(HFC)$_3$[30] and with four comphanic acid esters (**25**) in the presence of the achiral shift reagent Eu(dpm)$_3$.[22]

Configuration and enantiomeric purity of neopentyl-1-d alcohol

After this general discussion on the synthesis and determination of enantiomeric purity of chiral RCHDOH alcohols, we will return to our specific problem on the asymmetric reduction of trimethylacetaldehyde-1-*d* and the necessity of establishing the enantiomeric purity and the configuration of the resulting neopentyl-1-*d* alcohols (**26**→**27**). By use of actively fermenting yeast and the Grignard reag-



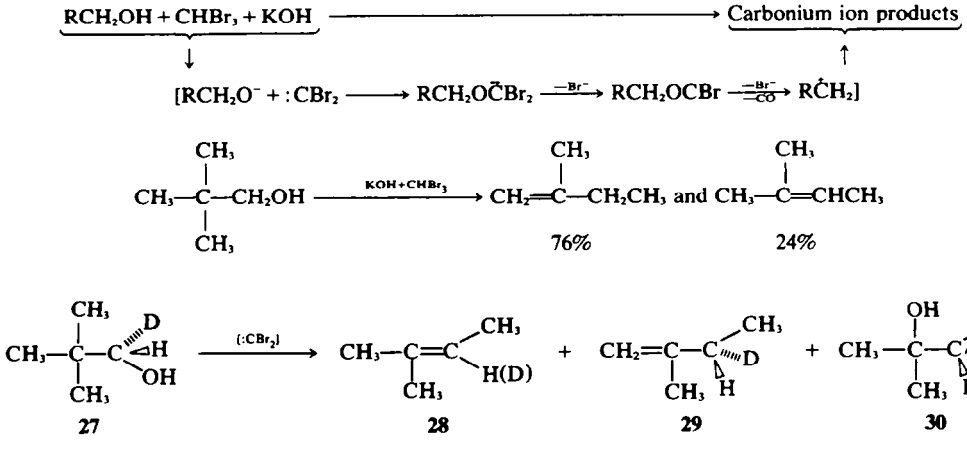
26 **27**

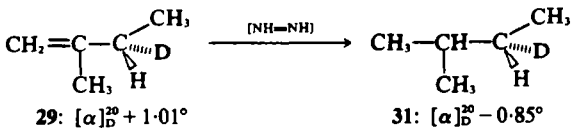
ent, $CH_3\dot{C}H_2CH(CH_3)CH_2MgCl$, we prepared samples of neopentyl-1-*d* alcohol which gave acid phthalate derivatives with $[\alpha]^{24}D$ of $-1{\cdot}14°$ and $-0{\cdot}14°$ ($c \simeq 20$, acetone) respectively. These two reduction products obviously have the same configuration and the Grignard reduction product has 12% of the optical activity of the enzymatically produced alcohol. If we make the assumption that the former is enantiomerically pure and has the same configuration as the ethanol-1-*d* obtained from the ADH–DPNH reduction reported by Westheimer, Vennesland, *et al.*, then the Grignard product represents a 12% asymmetric synthesis of the (*S*)-neopentyl-1-*d* alcohol. These are very reasonable assumptions; however, they are ones which we felt had to be verified. On the other hand, the known chemistry of neopentyl systems made it doubtful that the direct determination of configuration and enantiomeric purity would be possible.

The deoxidation reaction. Since there seemed to be no other alternative, we were forced to consider the possibility that under non-acidic conditions the neopentyl rearrangement might proceed with at least partial stereoselectivity thereby giving us an entry to compounds whose configuration could be established. Fortunately, the carbenoid reaction of alcohols with bromoform and potassium hydroxide (the deoxidation reaction) had just been studied by Hine,[39] Skell[40] and their students. Even though this reaction had been postulated to proceed *via* a cation intermediate we chose to study it because of the basic conditions employed. The reaction of neopentyl alcohol had been reported[40] to give a 76 to 24% mixture of 2-methyl-1-butene and 2-methyl-2-butene. The fact that this ratio is almost the reverse of the known thermodynamic ratio of these olefins indicated that the reaction might be kinetically controlled and encouraged us to try the experiment with chiral starting material. The stereochemical result was more significant than we had anticipated.[41,42]

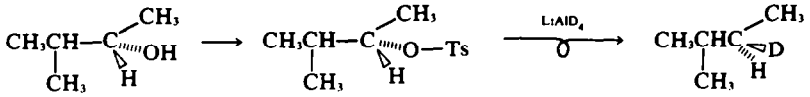
Treatment of neopentyl-1-*d* alcohol (**27**) from yeast reduction with bromoform in boiling 60% potassium hydroxide resulted in formation, in 17% yield, of 2-methyl-2-butene (**28**) and, in 39% yield, of optically active 2-methyl-1-butene-3*d* (**29**), along with a 58% recovery of neopentyl-1-*d* alcohol and a small amount of 2-methyl-2-butanol-3-*d* (**30**). The (+)-2-methyl-1-butene-3-*d* was purified by vapor phase chromatography and subjected to diimide reduction ($H_2NNH_2 + H_2O_2$) to give (−)-2-methylbutane-3-*d* (**31**). This proved to have the opposite sign and slightly higher optical rotation than that of the product prepared from (*S*)-(+)-3-methyl-2-butanol (**32**) of known configuration by the steps shown. It is apparent that the neopentyl rearrangement has proceeded to give a product of high stereochemical purity.* Furthermore, there is no

*The unequivocal statement is that there is less racemization in the sequence involving yeast reduction, rearrangement and diimide reduction (**26**→**27**→**29**→**31**) than in the two step process involving tosylate formation and *lithium aluminum deuteride* displacement (**32**→**31**).





29: $[\alpha]_D^{20} + 1{\cdot}01°$ **31**: $[\alpha]_D^{20} - 0{\cdot}85°$



(*S*)-(+)-**32** $[\alpha]_D^{20} + 0{\cdot}76°$

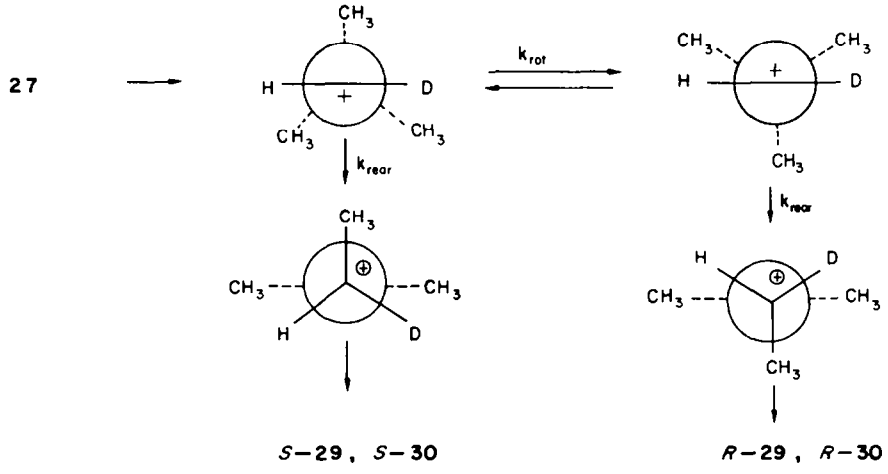
logical mechanistic route which would predict that the methyl migration proceeded by retention of configuration at the migration terminus. Thus the only viable conclusion is that the neopentyl rearrangement proceeded with essentially complete inversion of configuration at the neopentyl carbon as shown in **27** → **29**. Such a conclusion is in complete accord with all the additional stereochemical data that we have collected.

The question of timing with respect to the leaving group and methyl migration in the neopentyl rearrangement has been considered from many viewpoints.[20,43-45] Since we have observed that the product in this rearrangement is enantiomerically pure within experimental limits, the only condition under which a free carbonium ion can be an intermediate in the process is if the rate of rearrangement (k_{rear}) is fast with respect to the rate of rotation ($k_{rot.}$) around the carbon–carbon bond[43] between the potential cation and the t-Bu group; *i.e.*, $k_{rear.} \gg k_{rot.}$. Arguments have been developed, based upon reasonable estimates for the maximum energy barrier to rotation in the free neopentyl cation,[42] which lead to the conclusion that there is no neopentyl cation intermediate, not even one in which k_{rot} is small with respect to k_{rear}. We interpret these results to mean that the free, primary, neopentyl cation is energetically inaccessible in comparison with the very low energy barrier of the rearrangement to the t-amyl cation or its equivalent.

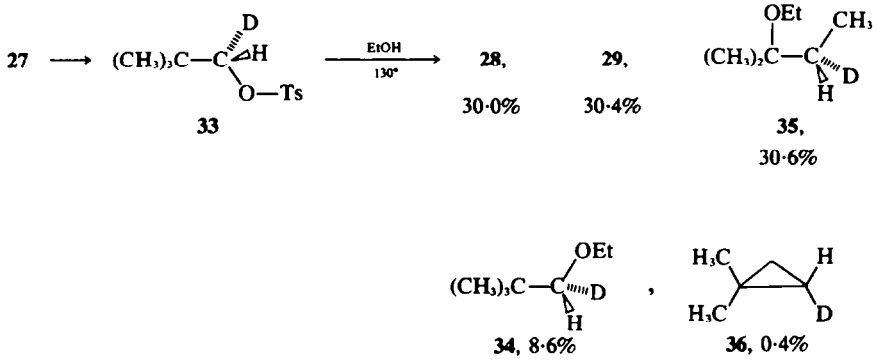
It is worthwhile to note that the recovered neopentyl-1-*d* alcohol in this reaction (**27** → **28** + **29** + **30**) was of the same enantiomeric purity as the starting material, again indicating no free neopentyl cation in the reaction mixture. If there are "cationoid" species involved they must be so closely associated with their anions that they never lose their stereochemical integrity. There has been considerable discussion and controversy over the involvement of "cationoid" species[44-47] variously termed intimate ion pairs, contact ion pairs or dipole assemblages in S_N2 reactions. If such ionic or partial ionic species retain their stereochemical identity during reaction, and if they undergo internal return in the solvent cage with complete retention of their configuration, then stereochemical studies *per se* cannot answer questions concerning the extent of participation of such species.

Neopentyl-1-d *solvolyses*

Ethanolysis. When we realized that the rearrangement of neopentyl-1-*d* alcohol in the presence of bromoform and potassium hydroxide was highly stereoselective in spite of the fact that the products were those associated with carbonium ion reactions, it became of great interest to see if this was



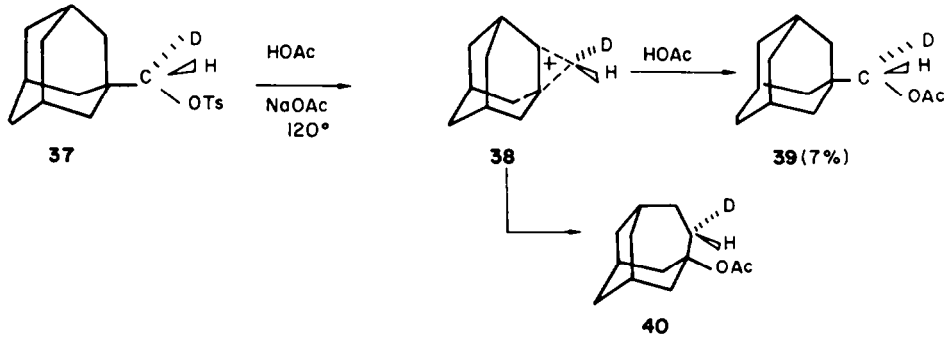
also true for neopentyl solvolyses reactions in general. We chose to study the ethanolysis of (*S*)-neopentyl-1-*d* tosylate[48,49] under conditions used by Fraser and Hoffmann[50] in a kinetic study of the isotopically normal substrate (sealed tube, 130°, 24 h, 2,6-dimethylpyridine). The results are summarized in the following equation. (**33** → **28**, **29**, **34**, **35**, **36**).



These products were analyzed by gas chromatography; with the exception of the cyclopropane **36**, they were also isolated by preparative gas chromatography and their rotations determined. The product of major interest, (+)-2-methyl-1-butene-3-*d*, (**29**) $[\alpha]^{20}D + 0{\cdot}98° \pm 0{\cdot}03°$ (neat) was the *S* isomer corresponding to 97 ± 3% enantiomeric purity.* It is thus apparent that the solvolysis with rearrangement, within experimental limits, also is a stereospecific process.

A product of very special interest was the unrearranged ether **34**. Was it formed with racemization (indication of a free cation intermediate), with retention of configuration (indication of a protonated cyclopropane intermediate), or with inversion (the expected product from an S_N2 displacement)? It was found to be optically active, $[\alpha]^{21}D + 1{\cdot}19 \pm 0{\cdot}06°$ (*c* 3·3, cyclopentane) and, by comparison with a synthetic sample made by a Williamson synthesis from (*S*)-neopentyl-1-*d* alcohol and ethyl iodide, it was shown to be the (*S*)-(+)-ether, formed by inversion with an enantiomeric purity of 95 ± 5%.[49] The logical conclusion is that this ether was formed by a normal S_N2 process in spite of the severe hindrance presented by the t-Bu group to back-side attack. The finding that the unrearranged neopentyl ethanolysis product was formed by inversion is in contrast to the finding by Schleyer *et al.*[20] on the acetolysis of (1-adamantyl)carbinyl-α-*d* tosylate.[37] They found that the unrearranged acetate **39** (7% yield) was enantiomerically pure but of retained configuration. In this case, it seems, the bridged ion **38** is clearly implicated as an intermediate in the reaction. The reason for the stereochemical disparity in the adamantyl *vs* neopentyl cases must lie in the nature of the adamantyl-homoadamantyl system as contrasted to the neopentyl-t-amyl system. Apparently the adamantyl and homoadamantyl systems are readily interconvertible; although the latter represents a tertiary cation, its stability is counteracted to a large extent by the added ring strain. On the other hand the energy difference between the potential primary neopentyl cation and the t-amyl cation is so large that the reaction is essentially irreversible. Thus although one may view the bridged ion as an intermediate in the adamantyl sys-

*The published figure in Ref 51 is 93 ± 7% enantiomeric purity. The 97 ± 3% is a more recent value.[49] Obtaining the required quantity of material and taking the rotation of a neat substance boiling at 31° was a constant problem in this work.

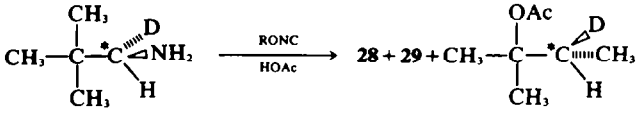


tem, in the neopentyl system it should be considered as a transition state in a concerted process along the reaction path between the starting neopentyl tosylate and the resulting t-amyl cation or its equivalent.

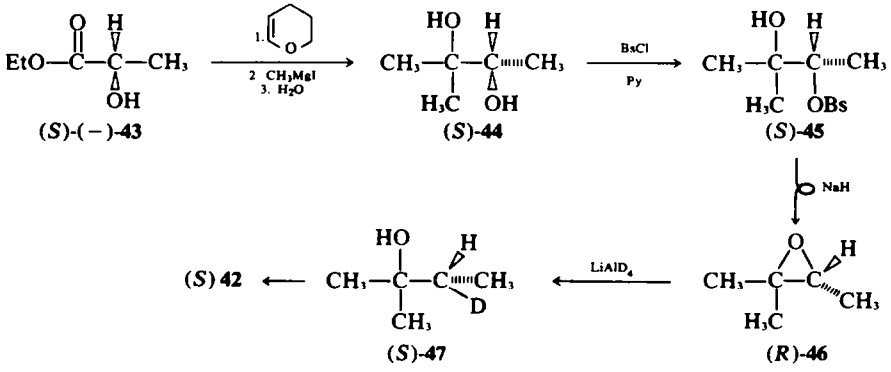
Deamination. That the high stereoselectivity of the rearrangement reaction is not confined to the deoxidation and ethanolysis reactions is shown by investigations on the deamination of chiral neopentyl-1-*d* amine by Guthrie[51] whose findings are in accord with the neopentyl-1-*d* tosylate solvolysis studies. The major product of neopentyl-1-*d* amine deamination with n-butyl nitrite in acetic acid is 3-acetoxy-2-methylbutane-3-*d*, **42**, 47% yield $\alpha^{25}D - 0{\cdot}25°$ (*l* 1, neat). By pyrolysis to 2-methyl-1-butene-3-*d* (**29**) Guthrie demonstrated that this acetate was formed with *at least* 85% inversion at the migrating terminus. We have also studied this deamination[52] and have expended considerable effort on establishing the configuration and enantiomeric purity of the t-amyl acetate derivative **42**. however, the results indicate that the acetate is $90 \pm 10\%$ enantiomerically pure. Thus, in this deamination reaction, methyl migration proceeds with substantial and possibly complete inversion, a fact which mitigates against any stereochemically significant participation of a carbonium ion intermediate.

Neopentyl displacement without rearrangements

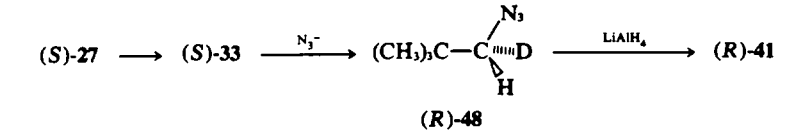
The observation that the ethanolysis of neopentyl-1-*d* tosylate produced the unrearranged neopentyl-1-*d* ethyl ether (8% yield) with inversion at the primary carbon prompted us to re-examine the S_N2 reactions of neopentyl tosylate.[53] In spite of the persistent idea that substitution without rearrangement in neopentyl systems is synthetically impractical,[5] there are several reports which indicate this is not entirely so. We will mention here only the most relevant examples. Bordwell *et al.*[54] reported that neopentyl tosylate reacted with several nucleophiles in boiling 2-methoxyethanol solvent



Its enantiomer was synthesized by the following route from (*S*)-(−)-ethyl lactate, a route which leaves no doubt concerning its configuration.[49] Assuming no racemization in the synthetic steps it also establishes the enantiomeric purity of **42**. The optical rotation of **42** ($[\alpha]^{20}D + 0{\cdot}27 \pm 0{\cdot}03°$ (*c* 6, cyclopentane)) prepared in this manner was of opposite sign to that obtained from the deamination reaction (namely, $\alpha^{20}D - 0{\cdot}26 \pm 0{\cdot}01°$ (neat), $[\alpha]^{21}D - 0{\cdot}35 \pm 0{\cdot}05°$ (*c* 17, cyclopentane)). Since **42** is formed in this synthetic scheme by two inversions it must have the *S* configuration; therefore the deamination product is *R*-**42**. The low optical rotation of **42** renders imprecise the quantitative determination of stereoselectivity for this rearrangement based upon the $[\alpha]D$ value of this product; (methyl cellosolve) to give unrearranged neopentyl products. The best described example was the formation of neopentyl mercaptan in 64% yield (2·5 h at 125°). Furthermore, neopentyl halides have been prepared without rearrangement from neopentyl alcohol by the use of several phosphorus reagents;[7-9,55] notably, neopentyl iodide has been formed in 53–57% yield by refluxing neopentyl alcohol with triphenylphosphite and excess methyl iodide. We chose to study the reaction of neopentyl tosylate (**33**) with azide ion. Not only is the azide ion a powerful nucleophile but its cylindrical symmetry and small size should minimize steric hindrance with the t-Bu group during back-side attack in the S_N2 displacement. If successful, this reaction would give a ready entry to (*R*)-neopentyl-1-*d* amine (**41**)



via (*R*)-neopentyl-1-*d* azide ((*R*)-**48**) from (*S*)-**33**. We experienced very limited but increasing success in progressing from methanol-water solvent to dimethyl sulfoxide to dimethyl formamide (10% yield in DMF, after 72 h at 125°). However, in hexamethylphosphoramide (HMPA) solvent[10] (90°, 24 h) azide **28** was formed in nearly quantitative yield.



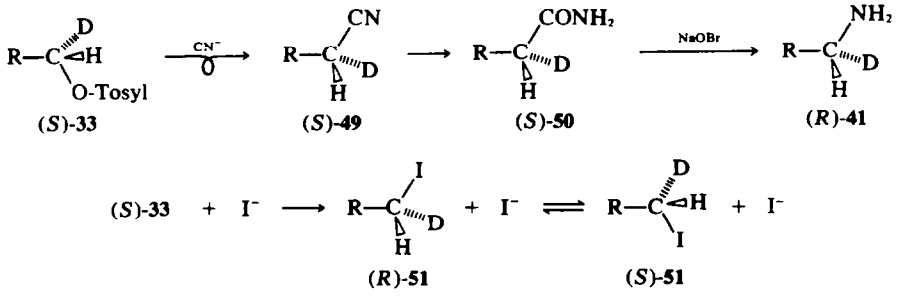
Presumably the success of HMPA solvent is due to its effectiveness in solvating the cation so that the bare azide anion, unsolvated and unassociated with its cation, can act with a minimum of steric interference with the t-Bu group as it approaches the back side of the primary carbinyl center. The question of the enantiomeric purity of the neopentyl-1-*d* azide was readily answered, since (*R*)-(+)-neopentyl-1-*d* amine had been prepared previously[5b] and its optical purity and configuration established by independent means. The neopentyl-1-*d* azide (**48**) was reduced to the amine (**41**) and found to have the *R* configuration and to be enantiomerically pure.

Based upon our success using azide ion in HMPA solvent we proceeded to investigate other S_N2 reactions involving neopentyl-1-*d* tosylate. The purpose of these studies was to determine the limitations of this reaction with other nucleophiles and also to prepare a set of chiral neopentyl-1-*d* derivatives for study of their optical rotatory powers. We have successfully accomplished displacements in HMPA solvent on (*S*)-neopentyl-1-*d* tosylate ((*S*)-**33**) with CN^-, F^-, Cl^-, Br^-, I^-, HS^-, $C_2H_5O^-$ and CH_3^- as well as N_3^-. All of the reactions, except that with iodide ion, proceeded to give optically active products. Cyanide ion attack proceeded by complete configuration inversion to give (*R*)-neopentyl-1-*d* cyanide **49** as proven by conversion to (*R*)-neopentyl-1-*d* amine ((*R*)-**41**) of known configuration and enantiomeric purity using the following reaction sequence whose stereochemical course is well known. Since it has thus been demonstrated that the azide, ethoxide and cyanide displacements proceed by inversion, we are confident that all of these substitutions in HMPA proceed in a typical S_N2 manner with inversion at the primary center. We ascribe the fact that the product from iodide ion attack was racemic to "isoracemization" resulting from subsequent displacement of iodide in the initial product, (*R*)-**51**, by iodide ion to give (*S*)-**51**. Although we were unable to obtain optically active neopentyl-1-*d* iodide by this route, we were able to synthesize it *via* the reaction of methyltriphenoxyphosphonium iodide[9] with neopentyl-1-*d* alcohol itself. This optically active material was shown to racemize rapidly in HMPA solvent in the presence of iodide ion. We strongly suspect that the neopentyl-1-*d* bromide made *via* the tosylate displacement was partially racemic. It is difficult to determine in any definitive manner the enantiomeric purity of the resulting neopentyl-1-*d* halides since these products cannot be derivatized by any reaction which clearly maintains the stereochemistry at the chiral primary carbon atom. Methods such as the use of a chiral solvent or a chiral lanthanide shift reagent were tried and found to be ineffective, as suspected. However, the independent synthesis of neopentyl-1-*d* chloride, *via* the reaction of triphenylphosphine and carbon tetrachloride with neopentyl-1-*d* alcohol,* has given a product with an optical rotation which is the same, within the rather broad limits imposed by the experimental details, as that from the S_N2 displacement. We are therefore confident that isoracemization is not a problem in those examples where the substituent is a poor leaving group.

Optical rotation of neopentyl-1-d compounds

Neopentyl-1-*d* compounds of the type $(CH_3)_3CHDX$ display an unusually simple conformational symmetry which renders them of special

*This Lee reaction was not completely satisfactory because of difficulties associated with separating neopentyl chloride and carbon tetrachloride.[8,49a]

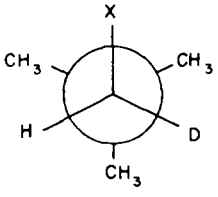


interest for theoretical and experimental studies of their optical rotation properties. The hydrogen, deuterium and X substituents (F, Cl, Br, I and CN) possess $C_{\infty v}$ symmetry while the CH_3 and $C(CH_3)_3$ groups, when considered separately and viewed along the bond axis, possess C_{3v} symmetry. If dynamic displacements of bond angles and bond distances are not considered conformational variables then the only such conformational degrees of freedom are the equivalent and indistinguishable staggered forms obtained by rotation about each of the four C—C bonds over three equivalent eclipsed conformational barriers as shown in **52A** and **52B**. Unquestionably the staggered forms in each case represent the lower energy conformations. As a consequence, conformation *per se* cannot be a variable factor in the determination of the optical rotation of these molecules. The chirality is solely the result of the isotopic difference associated with the substitution of hydrogen by deuterium. The *average* C—D bond distance is approximately 0·008 Å less than the corresponding C—H bond.[57] Thus, these molecules should be excellent models for testing theories of optical rotation based on atomic asymmetry. Only a few other examples of chiral molecules which approximate this conformational situation have been reported previously, *e.g.*, $CH_3CHBrCN$,[58] $CH_3CH(\tilde{N}H_3)CN$,[59] $ClCHISO_3^-$,[60] $CHBrClF$[61] (partially active), the special example of 3-methyl-5-bromo-1-cyanoadamantane,[58] and, of course, ethanol-1-*d*.[14]

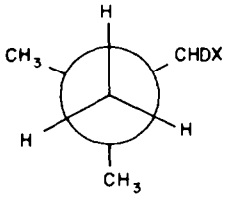
Practical applications of semi-empirical correlations of optical rotation *vs* structure have been thoroughly reviewed.[62] The most fruitful analyses have been based on considerations of the optical rotation in the neighborhood of an absorption band under conditions which give rise to a Cotton effect. Generally, the observed optical rotation of molecules which are saturated and therefore do not have the possibility of $\pi \rightarrow \pi^*$ or $n \rightarrow \pi^*$ transitions is the result of residual effects of some electronically excited state in the far ultraviolet region. Considerable success has been achieved in the empirical interpretation of rotations at the sodium D-line, for many simple aliphatic compounds.[63] The neopentyl-1-*d* halides constitute excellent models which fit Brewster's atomic asymmetry rules[63] based on the established relative atomic polarizabilities, namely that I, Br and Cl have the highest polarizabilities (13·95, 8·74, 5·84), that the central carbon atom of the t-Bu group is next (2·59) but greater than hydrogen (1·028), which in turn is slightly higher than deuterium (1·004). Since the polarizability of fluorine (0·81) is below deuterium, the model predicts that the fluoride will have the same sign of rotation as the other analogous halogen compounds, as is in fact observed. The hydrocarbon, (*R*)-(+)-2,2-dimethylbutane-3-*d*, is an interesting example[17] in which the chirally substituted carbon atom bears two $C_{\infty v}$ symmetry groups (hydrogen and deuterium) and two C_{3v} symmetry groups (methyl and t-Bu). There are no nonbonding electrons in the molecule. The simple atomic polarizability rules would predict zero rotation for this compound. The rotation is indeed low but this saturated aliphatic hydrocarbon does have a plain negative ORD curve similar to but lower in intensity than those of the corresponding halides (halogen replacing methyl group). To reconcile the optical rotation with Brewster's rules one must assume that the polarizability of the Me group as a whole is greater than that of the t-Bu group. This does not seem altogether reasonable but it is consistent with the same assumption which must be made to reconcile Brewster's rules with the rotation and configuration of methyl-t-butylcarbinol,[67] methyl-t-butylcarbinylamine[68] and 1-methyl-3-t-butylallene.[69]

In contrast to the (*R*)-neopentyl halides the rotations of the (*R*)-neopentyl-1-*d* azide, cyanide, mercaptide and sulfonic acid are all positive at the sodium D-line. Of these, only the azide shows a Cotton effect; the others have plain positive ORD curves. The sodium D-line rotations of these (*R*)-(+)-neopentyl-1-*d* compounds are not in accord with Brewster's rule. It is undoubtedly significant that in three of these (RCN, RSH, RN_3) the substituent is known to give rise to Cotton effects in other systems.

Of considerably greater importance than the sodium D-line value is the shape of the ORD curve. (*R*)-Neopentyl-1-*d* halides (X = F, Cl, Br and I) uniformly gave plain negative curves. Alkyl iodides have an absorption maximum near 250 nm and alkyl bromides near 207 nm attributed to an $n \rightarrow \sigma^*$ electronic transition.[65] Presumably the fluorides and chlorides have similar photoexcited states at lower wave lengths. (*R*)-Neopentyl-1-*d* iodide has a UV maximum at 253 nm but we were unable to observe any Cotton effect in this region. Thus it would appear that the differences due to hydrogen *vs*



52A



52B

deuterium are insufficient to cause a dissymmetric perturbation of the inherently symmetrical halogen chromophore *via* an $n \rightarrow \sigma^*$ transition. (*R*)-Neopentyl-1-*d* ammonium chloride and trimethylneopentyl-1-*d* ammonium chloride have no nonbonding electrons on the nitrogen yet they also have a plain negative ORD curve like the corresponding halides. It is thus reasonable that the observed plain negative ORD curves for all of these (*R*)-$(CH_3)_3C$—CHDX compounds are due to a $\sigma \rightarrow \sigma^*$ transition in the far ultraviolet.

The azide shows a well defined positive ORD maximum at 305 nm ($[\phi]^{20}_{305} + 41°$ (cyclohexane)), a trough at 270 nm, and a CD maximum at 288 nm. This Cotton effect must be due to an asymmetric perturbation of the inherently symmetric azide chromophore, which can only be brought about by the isotopic difference in hydrogen *vs* deuterium. An azide octant rule[70] has been developed from the known configurations and ORD spectra of a series of steroidal azides. If primary 1-deuterio azides prove generally to have such a Cotton effect, this may be usable in correlations of configurations of R—$CHDN_3$ compounds. It is of interest to note that application of this octant rule to neopentyl-1-*d* azide leads to the conclusion that deuterium is the Cotton effect-determining group rather than hydrogen, contrary to our expectations based on the relative atomic polarizabilities of hydrogen *vs* deuterium. These observations warrant further study and suggest the preparation of additional chiral analogs to establish the generality of this observation and its utility for configuration determination of 1-deuterio primary alcohols.

The foregoing account of our investigations in the neopentyl system has shown how a stereochemical study, initiated to test a proposal in connection with our asymmetric reduction research, has branched out in several profitable directions. The first work led to practical synthetic methods for the preparation of chiral 1-deuterio primary alcohols. This was followed by the development of methods for determining enantiomeric purity and for correlation of configurations of RCHDOH alcohols. Observations along the way ultimately led into studies on solvolyses, rearrangements, S_N2 reactions, and optical rotatory dispersion studies on chiral $(CH_3)_3CCHDX$ compounds. For us it has been fruitful and enjoyable endeavor and we hope the results will be of value to others.

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