p-Nitrobenzoates.—The p-nitrobenzoates were obtained by heating the corresponding alcohols on a steam-bath with 20% excess p-nitrobenzoyl chloride in pyridine for a few minutes and pouring the product into water. The crude p-nitrobenzoates were isolated by filtration and were recrystallized from pentane.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY, NEW YORK 53, N. Y.]

Stereochemistry of (+)-(S)-2-Propanol-1-d_3. Partial Asymmetric Reduction of 4′,1″-Dimethyl-1,2,3,4-dibenzcyclohepta-1,3-diene-6-one[1]

BY KURT MISLOW, ROBERT E. O'BRIEN AND HANS SCHAEFER

RECEIVED AUGUST 17, 1961

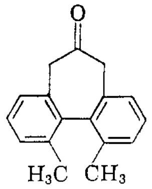
The synthesis of (+)-(S)-2-propanol-1-d_3 from (+)-(S)-lactic acid is described. The asymmetric Meerwein–Ponndorf–Verley reductions by a number of (S)-alkylmethylcarbinols of ketone I demonstrate the utility of this system as a device for estimating relative kinetic size. Use of (+)-2-propanol-1-d_3 in this asymmetric reduction does not reveal the operation of an isotope effect: methyl and trideuteriomethyl appear to have indistinguishable kinetic sizes by this particular criterion.

By virtue of the higher zero-point energy of the lighter isotope, X–H bonds are expected to have higher vibrational amplitudes than the corresponding X–D bonds; the difference in amplitudes, corresponding to the respective van der Waals radii, is estimated[2] at 0.01–0.02 Å.

It might thus be foreseen that protium and deuterium differ in non-bonded potential; evidence exists for corresponding effects in the ground state.[3] A classification of the source of secondary deuterium isotope effects[4] recognizes the possibility that effects may originate in changes in non-bonded interaction which accompany the change of reagents from the ground to the transition state of a reaction[5]; calculations[6] indicate that such effects need not be negligible. Indeed, a number of secondary deuterium isotope effect have recently been uncovered which may conceivably be regarded as reflecting, at least in part, the incursion of kinetic size factors.[7]

The present paper describes an attempt to isolate such factors from effects arising out of differences in ground state energies, by resorting to comparisons of suitable *diastereomeric transition states* in the following experimental approach.

The partial asymmetric reduction of (±)-4′,1″-dimethyl-1,2,3,4-dibenzcyclohepta-1,3-diene-6-one (I)[8] by the method described earlier for analogous ketones[9] affords $\Delta\Delta F^{\ddagger}$ values which show the expected[9] response to increasing differences in kinetic bulk between methyl and alkyl (Table I).



I

TABLE I

RESULT OF PARTIAL ASYMMETRIC REDUCTION OF I BY (+)-(S)-ALKYLMETHYLCARBINOLS AT 63° IN DIOXANE

Alkyl group	k_R/k_S	$\Delta\Delta F^{\ddagger}$, cal./mole	Alkyl group	k_R/k_S	$\Delta\Delta F^{\ddagger}$, cal./mole
CH_3	1.00	0 (std.)	n-C_6H_{13}	1.59	310
C_2H_5	1.29	170	Neo-C_5H_{11}	1.87	420
n-C_3H_7	1.31	180	i-C_3H_7	1.92	440
i-C_4H_9	1.58	310	t-C_4H_9	2.91	720

The use of I as a sensitive reagent had been indicated by the fortuitous circumstance that specific rotations of I are very high in the near ultraviolet and visible region in which the ketone is virtually non-absorbent.[8] This makes possible the measurement of extremely high rotations under conditions

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(1) Communicated in preliminary form: *J. Am. Chem. Soc.*, **82**, 5512 (1960). A Fulbright travel grant (H. S.) and fellowship support by the Alfred P. Sloan Foundation (K.M.) and by the Trubek Laboratories (R.E.O. and H.S.) are gratefully acknowledged.

(2) A. R. Ubbelohde, *Trans. Faraday Soc.*, **32**, 525 (1936). The simple harmonic oscillator approximation is employed; the results satisfy conditions for C–H, N–H and O–H bonds with $\bar{\nu}$ *ca.* 3000–3500 cm.$^{-1}$ and are in harmony with recent electron diffraction data on CH_4 and CD_4 (L. S. Bartell, K. Kuchitou and R. J. DeNeui, *J. Chem. Phys.*, **33**, 1254 (1960)).

(3) (a) The ratio of molal volumes of C_6H_6 and C_6D_6 is 1.008 at 17.2° (G. R. Clemo and A. McQuillen, *J. Chem. Soc.*, 1220 (1935)). (b) The ratio of molal volumes of H_2 and D_2 is 1.13 at T < 18°K. (K. Clusius and E. Bartholomé, *Z. physik. Chem.*, **B30**, 237 (1935); E. Bartholomé, *ibid.*, **B33**, 387 (1936)) and 1.08 for benzene solutions at 25° and 1 atm. (J. Walkley and J. H. Hildebrand, *J. Am. Chem. Soc.*, **81**, 4439 (1959)). (c) The edge of the cubic lattice of LiH diminishes from 4.080 to 4.060 on substitution of deuterium (E. Zintl and A. Harder, *Z. physik. Chem.*, **B28**, 478 (1935); J. M. Robertson, "Organic Crystals and Molecules," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 235).

(4) V. Shiner, *Tetrahedron*, **5**, 243 (1959).

(5) Qualitatively, increased crowding in the transition state is expected to result in a negative, and relief from crowding in a positive, isotope effect k_H/k_D if the kinetic size of X–H significantly exceeds that of X–D. The assignment of van der Waals radii depends on the method of measurement. Kinetic studies (as of the ratio of rates in a competitive reaction system) often give evidence of differential steric effects: since, however, these effects may reflect factors not included in crystallographic parameters, it is advisable to specify kinetic "size" as such.

(6) L. S. Bartell, *Tetrahedron Letters*, **No. 6**, 13 (1960); *J. Am. Chem. Soc.*, **83**, 3567 (1961).

(7) (a) K. T. Leffek, J. A. Llewellyn and R. E. Robertson, *Chemistry & Industry*, 588 (1960); *J. Am. Chem. Soc.*, **82**, 6315 (1960); *Can. J. Chem.*, **38**, 1505, 2171 (1960); K. T. Leffek, R. E. Robertson and S. E Sugamori, *Chemistry & Industry*, 259 (1961); (b) V. Prelog, *Bull soc. chim. France*, 1433 (1960); (c) P. L. Love, R. W. Taft, Jr., and T. Wartik, *Tetrahedron*, **5**, 116 (1959); (d) J. M. Jones and M. L. Bender, *J. Am. Chem. Soc.*, **82**, 6322 (1960); M. L. Bender and M. S. Feng, *ibid.*, **82**, 6318 (1960).

(8) Synthesis and stereochemistry of I and of the derived alcohol (6-ol) have been described by K. Mislow, M. A. W. Glass, R. E. O'Brien, P. Rutkin, D. H. Steinberg and C. Djerassi, *ibid.*, **82**, 4740 (1960); K. Mislow, M. A. W. Glass, R. E. O'Brien, P. Rutkin, D. H. Steinberg, J. Weiss and C. Djerassi, *ibid.*, **84**, 1455 (1962).

(9) P. Newman, P. Rutkin and K. Mislow, *ibid.*, **80**, 465 (1958); K. Mislow and F. A. McGinn, *ibid.*, **80**, 6036 (1958).

TABLE II

OPTICAL ROTATION (365 mμ) OF I IN BENZENE AT 27°

C, g./100 ml.	*l*, dm.	Observed α (lowest value)	Calculated Actual α	Calculated [α]
0.103	0.5	−2.7°	−2.7°	−5240°
.103	1	−5.4	−5.4	−5240
.103	2	−10.9	−10.9	−5290
1.04	2	+69.8	−110.2	−5293
4.26	2	+80.3	−459.7	−5396
6.09	2	+76.4	−643.6	−5284
8.26	2	+19.7	−880.3	−5328
9.99	2	+23.8	−1056.2	−5284

of high concentration (Table II)[10,11] and the detection of optical purities at least as low as 0.01% (corresponding to α_{365} 0.1 ± 0.01° (*c* 10, *l* 2)), a consideration of importance for the identification of the very slight deviations of k_R/k_S from unity which are to be expected in the crucial asymmetric reduction. This experiment involves the use of enantiomerically homogeneous 2-propanol-1-d_3: any isotope effect could with assurance be ascribed to differences in free energies of the diastereomeric transition states,[9] and thus to difference in kinetic size of methyl and trideuteriomethyl groups.

The desired carbinol was secured as separately described below. Two partial reductions of (±)-I with (*S*)-2-propanol-1-d_3 were carried out in dioxane containing aluminum *t*-butoxide. One was taken to 28.6%, the other to 55.6% completion. Each yielded residual I with α^{25}_{435} 0.00 ± 0.01° (*c* 8.8, *l* 2, C_6H_6). The possibility that the optical inactivity was the result of racemization of 2-propanol-1-d_3[12] through oxidation–reduction equilibria involving acetone was eliminated by the following observations: (a) The acid phthalate of 2-propanol-1-d_3 recovered from the reaction mixture had retained the original deuterium content; (b) in partial reductions of I by various (+)-alkylmethylcarbinols, carried out under similar conditions, the recovered carbinols had almost completely retained their optical integrity (Table III).[13]

The observed maximum rotation (0.01°) of recovered I corresponds to a maximum optical purity (ω) of 0.003% since optically pure I has α^{25}_{435} 340° under the conditions of measurement (*c* 8.8, *l* 2, C_6H_6). Since the function expressing the calculated ratio of rates

$$\frac{k_R}{k_S} = \frac{\log\,[n(1-\omega)]}{\log\,[n(1+\omega)]}$$

is quite insensitive to errors in the fraction *n* of residual ketone for small values of ω,[14] the ratio 1.0003 may be taken as an upper limit for k_R/k_S. This corresponds to a difference in energies for diastereomeric transition states involving compression of CH_3– and CD_3– groups not in excess of 0.1 cal./mole.[15]

TABLE III

FATE OF UNREACTED ALCOHOLS IN THE COURSE OF PARTIAL ASYMMETRIC REDUCTIONS OF I

Alkylmethylcarbinol	Acid phthalate of alkylmethylcarbinol Original [α]D (chf.)	Recovered [α]D (chf.)	Recovered % retn.	Reduction % compltn.	Reduction Time, hr.
2-Butanol	+37.4°	+35.5°	95.0	67.4	0.67
4-Methyl-2-pentanol	+53.5	+52.6°	98.4	38.8	.67
4,4-Dimethyl-2-pentanol	+85.4	+82.7°	96.9	5.8	.67
3-Methyl-2-butanol	+52.6	+50.2°	95.4	41.0	2.02

It is possible to account for this result if it is assumed that the sensitivity of the molecular probe (I) is lost when differential compressional effects become sufficiently small—as signalized by the relatively small difference in $\Delta\Delta F^{\ddagger}$ (720 cal./mole) for methyl and *t*-butyl groups. More highly crowded transition states may be required for the exhibition of the steric isotope effect.

In connection with the asymmetric reductions, we note that (+)-neopentylmethylcarbinol has been resolved for the first time; since all of the (+)-alkylmethylcarbinols used in the present work give residual (−)-I on partial reduction, and since all of the other (+)-carbinols are known to have the (*S*)-configuration,[9,16a] that configuration may now be assigned to (+)-neopentylmethylcarbinol.[16b] Furthermore, (−)-I may now be assigned the (*S*)-configuration according to the transition state picture developed for this system.[9] This conclusion is in harmony with previous configurational assignments[8,17] and offers the first *direct* vindication of the expectation[9] that the direction of asymmetric synthesis is independent of the nature of the blocking substituents.[18]

(+)-(S)-**2-Propanol-1-d_3** was synthesized in *ca.* 20% over-all yield from the methyl ester of (+)-

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(10) The choice of benzene as solvent was arbitrary; the long-wave length rotations are essentially solvent independent. Thus $[\alpha]_{365}$ of 1% solutions of I are: −5293° (benzene), −5240° (hexane), −5263° (chloroform), −5225° (dioxane), −4680° (methanol), −4940° (acetone); corresponding values of $[\alpha]_D$: −628°, −644°, −675°, −650°, −607°, −624°.

(11) This circumstance does not obtain in the dibenzo- and dinitro-analogs[9] of I. A further advantage in the use of I is its greater synthetic accessibility and its superior solubility in a variety of solvents.

(12) The possibility that optically active I might racemize is remote. Only two hydride transfer equilibria between *biphenyls* are possible; symbolized[9]

$$K_R + A_S \rightleftarrows A_R + K_S$$
$$K_S + A_S \rightleftarrows A_S + K_S$$

Of these, only the former is stereochemically significant. Under conditions considerably more unfavorable than those employed for the reaction with 2-propanol-1-d_3, it was found that (±)-I suffered only 5% enrichment in the (−)-(*S*)-isomer when reduced with the corresponding (*S*)-alcohol (Experimental Part).

(13) This finding is in harmony with prior related observations.[9]

(14) For $\omega = 3 \times 10^{-5}$, k_R/k_S varies from 1.00012 at $n = 60\%$ to 1.00027 at $n = 80\%$; found $n = 71\%$ for one of the runs. Minor errors in weighing thus can not affect seriously the calculated ratio k_R/k_S.

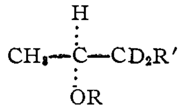
(15) This conclusion is valid only providing that strict adherence to pseudo-first-order kinetics is obeyed. This premise has been indirectly[9] and directly tested (J. Weiss, unpublished results).

(16) (a) P. A. Levene and A. Rothen, *J. Org. Chem.*, **1**, 76 (1936); K. B. Wiberg, *J. Am. Chem. Soc.*, **74**, 3891 (1952). (b) Recent work by Mosher and Brown (R. MacLeod, F. J. Welch and H. S. Mosher, *ibid.*, **82**, 876 (1960); E. P. Burrows, F. J. Welch and H. S. Mosher, *ibid.*, **82**, 880 (1960); H. C. Brown and D. B. Bigley, *ibid.*, **83**, 3166 (1961)) suggests that the group interactions in the present case are far more complex than previously realized. This particular assignment must therefore be regarded as tentative.

(17) K. Mislow and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5247 (1960).

(18) The value (1.6) of k_R/k_S observed in the partial reduction of I with (+)-2-octanol is comparable with those reported for the analogs.

(*S*)-lactic acid[19] by the following sequence of reactions. Benzylation with benzyl bromide in the presence of silver oxide[20] gave the (−)-benzyl ether



$$\begin{array}{c} H \\ \vdots \\ CH_3\text{—}C\text{—}CD_2R' \\ \vdots \\ OR \end{array}$$

(+)-IIa, R = $CH_2C_6H_5$, R′ = OH
(−)-IIb, R = $CH_2C_6H_5$, R′ = Bs
(+)-IIc, R = $CH_2C_6H_5$, R′ = D
(+)-IId, R = H, R′ = D

in 60–70% yield. Reduction with $LiAlD_4$ gave (+)-IIa in 90% yield. Brosylation (80–90%) to the (−)-brosylate (IIb), followed by $LiAlD_4$ reduction (70–80%), gave (+)-IIc; the identity of this product was confirmed by analogy through the comparison of samples of benzyl isopropyl ether prepared (a) by $LiAlH_4$ reduction of IIb and (b) by reaction of isopropyl alcohol, benzyl bromide and silver oxide. Catalytic hydrogenolysis of (+)-IIc afforded (+)-IId, purified *via* the acid phthalate, in 60% over-all yield. In the course of this work, the optically active and racemic *undeuterated* modifications of the above intermediates were also obtained.

The product contained 2.9 atoms of deuterium per molecule and, according to a mass-spectrometric estimate, consisted of a mixture of 2-propanol-1-d_3 and 2-propanol-1-d_2 containing *no less* than 94% of the former.[21] Compound (+)-IId, which has an appreciable optical activity (α^{25}_{563} +0.98° (*l* 1, neat)), is the second compound reported to owe its optical activity to isotopically different substituents not directly attached to the asymmetric carbon,[22] and the first of its type[23] whose absolute configuration is directly and unequivocally relatable to the primary absolute standard.[19] It is interesting to note that the atomic asymmetry rule[24] applies in this case: a dextrorotation in the visible is predicted for (S)-IId if deuterium is taken to be less polarizable than hydrogen.

Since no bonds to the asymmetric carbon are broken in any step of the above sequence, the optical purity of IId may be taken as equal to that of the starting methyl lactate, unless the hydrogenolysis step (IIc → IId) is accompanied by exchange of hydrogen on the asymmetric carbon[25] and concomitant racemization.[26] This eventuality was ruled out in the present instance on the following grounds: (a) the deuteriogenolysis of isopropyl benzyl ether under identical conditions gives no detectable quantities of 2-propanol-2-*d* (within the limits of mass-spectrometric measurement); (b) under very similar conditions, hydrogenolysis of methyl lactate O-benzyl ether gives methyl lactate of unimpaired optical purity.[27]

Experimental Part[28]

(−)-Methyl Lactate.—The method of Lorette and Brown[29] proved most satisfactory. A mixture of 50 g. of zinc lactate dihydrate, $[\alpha]^{25}D$ (anhydrous salt) −9 ± 0.5° (*c* 3, H_2O) (from (+)-(*S*)- lactic acid), 69 g. of *p*-toluenesulfonic acid hydrate, 102.3 g. of 2,2-dimethoxypropane and 125 ml. of methanol was stored at room temperature for 2 days, brought to *p*H 6 through the addition of 25 g. of potassium carbonate and filtered. The filtrate was concentrated at a bath temperature of 100°, the residue was treated with 750 ml. of absolute ether and after the successive removal of crops of crystals the filtrates were distilled to give 26.6 g. (72%) of the desired ester, b.p. 50° (19 mm.), $[\alpha]^{26}D$ −8.4° (neat),[30] $n^{25}D$ 1.4114.

(−)-Methyl and (±)-Ethyl O-Benzyl Lactate.—Dry powdered silver oxide (133 g.) was added to a solution of 60 g. of (−)-methyl lactate and 148 g. of benzyl bromide in 350 ml. of absolute ether over a period of 40 min., with stirring. At this rate of addition, refluxing was maintained without recourse to external heating; the reaction had to be initiated by external heating at the beginning of the addition. The mixture was then stirred for 1.5 hours at room temperature and filtered. Distillation of the filtrate yielded a main cut (81.2 g., b.p. 85–104° (1.7 mm.)) redistillation of which gave 71.1 g. (63%) of the desired product, b.p. 98.5–100° (1.5 mm.), $n^{25}D$ 1.4918, $\alpha^{26}D$ −78.4° (*l* 1, neat).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.03; H, 7.25.

The racemic ethyl ester, similarly prepared from racemic ethyl lactate, had b.p. 105.5–106° (1.5 mm.), $n^{25}D$ 1.4853.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.78; H, 7.77.

Hydrogenolysis of (−)-Methyl O-Benzyl Lactate.—A solution of 4.507 g. of the ester in 35 ml. of methanol containing 0.17 ml. of concd. aq. hydrochloric acid was

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[19] Absolute configuration: A. Wohl and F. Momber, *Ber.*, **50**, 455 (1917); M. L. Wolfrom, R. U. Lemieux, S. M. Olin and D. I. Weisblat, *J. Am. Chem. Soc.*, **71**, 4057 (1949); J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature*, **168**, 271 (1951).

[20] This method of etherification is particularly suitable for optically labile alcohols (K. Mislow, *J. Am. Chem. Soc.*, **73**, 4043 (1951)).

[21] The mass spectrum of IId reveals a ratio 1.1 of peak heights 48 (CD_3CHOH^+) to 45 (CH_3CHOH^+), corresponding to an isotope effect of 1.1 for the fragmentation of C–CH_3 and C–CD_3 bonds in IId on electron impact.

[22] C. Martius and G. Schorre, *Ann.*, **570**, 140, 143 (1950), synthesized citric acid-2-d_2, $[\alpha]^{20}_{546}$ + 1.03 ±0.06° (*c* 12.6, H_2O). Subsequent to our work, further examples were furnished by Y. Pocker, *Proc. Chem. Soc.*, 140 (1961).

[23] Many compounds are known which are optically active solely by virtue of deuterium substitution; *cf.* A. Streitwieser, Jr., J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 338 (1959), for a recent review.

[24] J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959); *Tetrahedron Letters*, No. **20**, 23 (1959).

[25] The tertiary (only) hydrogen of isopropyl alcohol exchanges readily under some conditions (A. Farkas and L. Farkas, *J. Am. Chem. Soc.*, **61**, 1336 (1939); J. R. Anderson and C. Kemball, *Trans. Faraday Soc.*, **51**, 966 (1955); C. Kemball and C. T. H. Stoddard, *Proc. Roy. Soc. (London)*, **A241**, 208 (1957)) but not under others (L. C. Anderson and N. W. MacNaughton, *J. Am. Chem. Soc.*, **64**, 1456 (1942); L. Friedman and J. Turkevich, *ibid.*, **74**, 1669 (1952)). Aliphatic ethers are known to exchange deuterium over metal films (J. M. Forrest, R. L. Burwell, Jr., and B. K. C. Shim, *J. Phys. Chem.*, **63**, 1017 (1959); J. K. Clark and C. Kimball, *Trans. Faraday Soc.*, **55**, 98 (1959)).

[26] Racemization of alcohols may occur on contact with hydrogenation catalysts (R. L. Burwell, Jr., *J. Am. Chem. Soc.*, **59**, 1609 (1937); **70**, 2865 (1948); E. G. Pepiatt and R. J. Wicker, *Chemistry & Industry*, 747 (1955)) and in the case of (+)-3-methylhexane it has been shown that racemization may accompany exchange (R. L. Burwell, Jr., and W. S. Briggs, *J. Am. Chem. Soc.*, **74**, 5096 (1952); H. C. Rowlinson, R. L. Burwell, Jr., and R. H. Tuxworth, *J. Phys. Chem.*, **59**, 225 (1955); R. L. Burwell, Jr., and R. H. Tuxworth, *ibid.*, **60**, 1043 (1956); R. L. Burwell, Jr., B. K. C. Shim and H. C. Rowlinson, *J. Am. Chem. Soc.*, **79**, 5142 (1957); M. Cardew and R. L. Burwell, Jr., *ibid.*, **82**, 6289 (1960)).

[27] In related cases, catalytic hydrogenolysis of benzyl ethers does not affect the optical integrity of the precursor alcohols (W. H. Hartung and R. Simonoff, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, Chapter 5).

[28] Melting points are corrected and boiling points are uncorrected. Deuterium analyses indicating the atom percentage deuterium per molecule were determined by J. Nemeth, Urbana, Ill., using the falling drop method. Mass spectra were determined with a C.E.C. type 21-103C instrument at an ionization potential of 70 v. Sensitivity and reproducibility of mass spectrometric measurements were tested with samples of *n*-butane. We are indebted to Mr. S. Zolty for assistance with these determinations. Elemental analysis were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

[29] N. B. Lorette and J. H. Brown, Jr., *J. Org. Chem.*, **24**, 1261 (1959).

[30] Corresponding to $\alpha^{25}D$ −4.54° (*l* 0.5, neat); *cf.* C. E. Wood, J. E. Such and F. Scarf, *J. Chem. Soc.*, 600 (1923); Th. Purdie and J. C. Irvine, *ibid.*, 483 (1899).

hydrogenated over 5% Pd–C (0.90 g.) at 22° and 749 mm. The uptake (581 ml., theory demands 668 ml.) was complete after 95 min. Filtration, neutralization (potassium carbonate), renewed filtration and distillation of the filtrate yielded 0.86 g. (35%) of methyl lactate, $n^{25}\mathrm{D}$ 1.4113, $\alpha^{25}\mathrm{D}$ −4.44° (*l* 0.5, neat), infrared spectrum identical with that of authentic material.

(+)-2-Benzyloxy-1-propanol-1-d_2 (IIa) and Derivatives.—Reduction of (−)-methyl O-benzyl lactate (45 g.) with 5.84 g. of lithium aluminum deuteride (contg. 99+% deuterium) in 150 ml. of abs. ether and workup in the usual manner gave 35.5 g. (91%) of product, b.p. 88–89° (0.8 mm.), $n^{25}\mathrm{D}$ 1.5106, $\alpha^{28}\mathrm{D}$ +28.6° (*l* 1, neat).

Anal.[31] Calcd. for $C_{10}H_{12}D_2O_2$: 14.29 at. % excess D [2.00]. Found: 14.09, 14.15 [1.98].

The 3,5-dinitrobenzoate was obtained in the usual manner; needles from hexane, m.p. 72–73°, $[\alpha]^{26}\mathrm{D}$ +36° (*c* 2.2, benzene).

Anal. Calcd. for $C_{17}H_{14}D_2N_2O_7$: 12.50 at. % excess D [2.00]. Found: 12.20, 12.11 [1.94].

The *p*-bromobenzenesulfonate IIb was prepared in yields up to 90% by the slow addition of *p*-bromobenzenesulfonyl chloride to the alcohol in pyridine at −15°, followed by the usual[32] workup procedure. Two crystallization from ether–ligroin at −20° gave a colorless product, m.p. 59–60°, $[\alpha]^{26}\mathrm{D}$ −4.2° (*c* 2.3, benzene).

Anal. Calcd. for $C_{16}H_{15}D_2O_4SBr$: 11.76 at. % excess D [2.00]. Found: 11.70, 11.52 [1.98].

(+)- and (±)-2-Benzyloxy-1-propanol and Derivatives.—Reduction of (−)-methyl O-benzyl lactate with lithium aluminum hydride gave the optically active product, b.p. 96.5–97° (1.2 mm.), $n^{25}\mathrm{D}$ 1.5112, $\alpha^{27}\mathrm{D}$ +28.1° (*l* 1, neat).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.45; H, 8.41.

The 3,5-dinitrobenzoate (from hexane) had m.p. 70–71.5°, $[\alpha]^{29}\mathrm{D}$ +35° (*c* 2.0, benzene).

Anal. Calcd. for $C_{17}H_{16}N_2O_7$: C, 56.67; H, 4.47; N, 7.78. Found: C, 56.32; H, 4.58; N, 7.79.

The *p*-bromobenzenesulfonate had m.p. 59–60° after crystallization from ether–ligroin; $[\alpha]^{27}\mathrm{D}$ −4.6° (*c* 2.0, benzene).

Anal. Calcd. for $C_{16}H_{17}O_4SBr$: C, 49.87; H, 4.45; S, 8.32; Br, 20.74. Found: C, 49.70; H, 4.33; S, 8.03; Br, 20.92.

The racemic alcohol, similarly prepared from (±)-ethyl O-benzyl lactate, had b.p. 101–101.5° (1.5 mm.), $n^{25}\mathrm{D}$ 1.5117, infrared spectrum identical with that of the (+)-modification.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.40; H, 8.44.

The racemic ***p*-bromobenzenesulfonate** had m.p. 42–44.5°.

Anal. Calcd. for $C_{16}H_{17}O_4SBr$: C, 49.87; H, 4.45; S, 8.32; Br, 20.74. Found: C, 49.82; H, 4.43; S, 8.58; Br, 20.90.

(+)-2-Benzyloxypropane-1-d_3 (IIc).—A solution of 40.0 g. of (+)-2-benzyloxy-1-propanol-1-d_2 *p*-bromobenzenesulfonate in 400 ml. of absolute ether was added to a solution of 4.44 g. of lithium aluminum deuteride in 100 ml. of ether at 0° over a period of 1 hour. The product, worked up as usual, had b.p. 76.5–78.5° (16 mm.), $n^{25}\mathrm{D}$ 1.4840. Treatment with hot concd. aq. potassium hydroxide, a procedure designed to rid product of sulfur-containing by-products,[33] gave 13.0 g. (82%) of a liquid, b.p. 79–79.5° (16 mm.), $n^{25}\mathrm{D}$ 1.4829; α^{26} (*l* 1, neat): +3.7°, +2.4°, +1.4°, +1.2° and +1.2° at 365, 435, 546, 578 and 589 mμ, respectively.

Anal. Calcd. for $C_{10}H_{11}D_3O$: 21.43 at. % excess D [3.00]. Found: 20.65, 20.50 [2.88].

Benzyl Isopropyl Ether. A.—Silver oxide (46.2 g.) was added to a solution of isopropyl alcohol (12 g.) and benzyl bromide (51.2 g.) in 250 ml. of absolute ether at such a rate that refluxing was maintained without recourse to external heating; the reaction had to be initiated by external heating. The mixture was then refluxed (external heating) 1 hour with stirring, an additional 25.6 g. of benzyl bromide and 24 g. of silver oxide was added and refluxing was continued for 2.25 hours. Filtration from solids and workup of filtrates yielded 19.5 g. of a mixture, b.p. 78–82.5° (17 mm.), $n^{26}\mathrm{D}$ 1.4916. Heating of this liquid under reflux with pyridine (11 ml.) and benzoyl chloride (8 ml.) in benzene (55 ml.) followed by the usual workup gave 13.4 g. (44%) of product, b.p. 78–79° (15 mm.) (lit.[34] b.p. 193.5° (744 mm.), $n^{25}\mathrm{D}$ 1.4831).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.02; H, 9.39.

B.—Reduction of the *p*-bromobenzenesulfonate of (+)-2-benzyloxy-1-propanol with lithium aluminum hydride as described above for the lithium aluminum deuteride reduction gave benzyl isopropyl ether, b.p. 80° (16 mm.), $n^{25}\mathrm{D}$ 1.4832, whose infrared spectrum was identical with material prepared by procedure A.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.09; H, 9.40; S, 0.08.

Propanol-2-*d* was prepared by the lithium aluminum deuteride reduction of acetone[35]; the product had b.p. 82–82.2°, $n^{23}\mathrm{D}$ 1.3760.

Anal. Calcd. for C_3H_7DO: 12.50 at. % excess D [1.00]. Found: 12.43, 12.51 [1.00].

Hydrogenolysis of (+)-2-Benzyloxypropane-1-d_3.—A mixture of (+)-2-benzyloxypropane-1-d_3 (8.0 g.), toluene (30 ml.), concd. aq. hydrochloric acid (0.5 ml.) and 5% Pd–C (1.6 g.) was agitated (Vibromischer) under hydrogen at 23.5° and atmospheric pressure; 94% of the theoretical volume was absorbed in 23 minutes. After addition of 30 ml. of pyridine, the catalyst was filtered, the filtrate was dried (potassium carbonate), treated with phthalic anhydride (16.8 g.) and pyridine (15 ml.), and heated under reflux for 9 hours. The usual workup gave an acid fraction of 9.3 g. (87%) of **2-propanol-1-d_3 acid phthalate**, m.p. 79–81.5° after crystallization from cyclohexane, $[\alpha]^{27}$ (*c* 4.0, $CHCl_3$) +1.2°, +0.8°, +0.6°, +0.5° and +0.2° at 365, 435, 546, 578 and 589 mμ, respectively.

Anal. Calcd. for $C_{11}H_9D_3O_4$: 25.00 at. % excess D [3.00]. Found: 23.97, 24.18, 24.30, 24.21 [2.89].

Hydrogenolysis and Deuteriogenolysis of Benzyl Isopropyl Ether.—A hydrogenolysis performed on the ether by the procedure described for (+)-2-benzyloxypropane-1-d_2 yielded isopropyl phthalate whose m.p. (77–79.5°) was not depressed by admixture of authentic material (from isopropyl alcohol and phthalic anhydride). A similar deuteriogenolysis, using 99.5+% deuterium gas, gave isopropyl acid phthalate (m.p. 78–81°) in 82.6% yield, saponification of which afforded 2-propanol. This material was analyzed mass spectrometrically as follows. The composition of two synthetic mixtures containing 2-propanol and 2-propanol-1-*d* was determined by comparing relative peak heights at *m/e* 45 and *m/e* 46 to the corresponding relative peak heights of the pure components. The result (Table IV) showed that the analytical method was sound and that the deuteriogenolysis product was free of 2-propanol-1-*d*.

TABLE IV

PERCENTAGES OF COMPONENTS IN MIXTURE

Mixture	2-Propanol Calcd.	2-Propanol Found	2-Propanol-1-*d* Calcd.	2-Propanol-1-*d* Found
Synthetic 1	90.0	89.7	10.0	10.3
Synthetic 2	99.0	98.9	1.0	1.1
Deuteriogenolysis Prod.		99.9_5		0.0_5

(+)-2-Propanol-1-d_3 (IId).—A solution of (+)-2-propanol-1-d_3 acid phthalate in 20% aq. sodium hydroxide was refluxed for 3 hours. The water–2-propanol azeotrope was isolated by distillation, dried (ethereal solution over potassium carbonate) and distilled to give a 67% yield of product, b.p. 82–82.5°, $n^{25}\mathrm{D}$ 1.3737 (isopropyl alcohol had $n^{25}\mathrm{D}$ 1.3744), α^{25} (*l* 1, neat) +0.98°, +0.58°, +0.31°, +0.28°, +0.27° at 365, 435, 546, 578 and 589 mμ, resp.

Anal. Calcd. for $C_3H_5D_3O$: 37.50 at. % excess D [3.00]. Found: 36.00, 36.22 [2.89].

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[31] Deuterium analyses here and elsewhere are given as at. % D (= 100D/(D + H)); found values in duplicate. The figures in square brackets are calculated and found (ave.) atoms of D per molecule.

[32] *Cf. e.g.*, R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

[33] *Cf.* K. Mislow, *J. Am. Chem. Soc.*, **73**, 3954 (1951).

[34] J. B. Senderens, *Compt. rend.*, **178**, 1412 (1924).

[35] V. J. Shiner, *J. Am. Chem. Soc.*, **74**, 5285 (1952).

TABLE V

PHYSICAL CONSTANTS OF ALKYLMETHYLCARBINOLS $RCHOHCH_3$

R	B.p.,[a] °C.		n^t_D (t, °C.)		$[\alpha]^t_D$ (t, °C.), neat	
	Found	Repd.	Found	Repd.	Found	Repd.
C_2H_5[b]	98–98.5	98–99.5	1.3952(23)	1.3954(23)	+13.1(28)	13.5(27)
n-C_3H_7[b]	118–118.5	118–119.5	1.4042(23)	1.4053(20)	+13.4(25)	13.4(27.5)
i-C_3H_7[d]	110	113–114	1.4058(25.5)	1.4053(26)	+ 5.0(27)	5.0(28)
i-C_4H_9[b,e]	130–131.5	63–64(45 mm.)	1.4082(25)	1.4103(20)	+20.0(27)	20.0(19.5)
t-C_4H_9[f]	118.5–120.5	119–120	1.4131(24)	1.4130(25)	+ 8.2(26)	8.1(25)
Neo-C_5H_{11}[g]	134.5–138	137–137.5	1.4165(22)	1.4188(20)	+24.8(27)	....
n-C_6H_{13}[c]	55–56(3 mm.)	86(20 mm.)	1.4250(22)	1.4256(20)	+ 9.6(26)	9.5(26)
n-C_6H_{13}	63–64.5(5 mm.)	86(20 mm.)	1.4250(22)	1.4256(20)	− 9.7(24)	9.5(26)

[a] At atmospheric pressure unless otherwise specified. [b] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 45 (1911). [c] R. H. Pickard and J. Kenyon, *ibid.*, 2058 (1907); M. K. Hargreaves, *ibid.*, 2953 (1953). [d] R. H. Pickard and J. Kenyon, *ibid.*, 620 (1912); E. T. Losin, Ph.D. Dissertation, Columbia University, 1955. [e] J. Kenyon and H. E. Strauss, *J. Chem. Soc.*, 2153 (1949). [f] P. Newman, P. Rutkin and K. Mislow, ref. 9. [g] Racemic alcohol: F. C. Whitmore and A. H. Homeyer, *J. Am. Chem. Soc.*, **55**, 4194 (1933).

Mass spectrometric analysis of the product was rendered difficult by the low intensity of the parent peak of isopropyl alcohol. The calculation was therefore based on the peaks resulting from loss of methyl on electron impact[36]

$$CD_3CHOHCH_3\ (63) \longrightarrow CD_3CHOH^+\ (48) + CH_3$$

$$CHD_2CHOHCH_3\ (62) \longrightarrow CHD_2CHOH^+\ (47) + CH_3$$

under the assumption (a) that the 2-propanol-1-*d* and 2-propanol contents are negligible, (b) that the loss of methyl *and* tertiary hydrogen from 2-propanol-1-d_3 contribute negligibly to the peak at *m/e* 47[37] and (c) that no significant difference exists in the ease with which methyl is lost from 2-propanol-1-d_3 and 2-propanol-1-d_2. After the customary correction[38] for the natural abundance of C^{13}, H^2, O^{18} and O^{17}, the *upper limit* of 2-propanol-1-d_2 was calculated to be 5.8%, corresponding to an average of 2.9_4 atoms of D per molecule of product, in excellent agreement with the value (2.89) found by combustion (above).

Alkylmethylcarbinols Used in Asymmetric Reductions.—The carbinols were prepared and resolved *via* the acid phthalate brucine salts as described in the literature; physical constants are summarized in Table V. The resolution of methylneopentylcarbinol has not been previously described. The racemic alcohol[39] was converted (phthalic anhydride and pyridine) to the acid phthalate, m.p. 55–59°. A solution of the acid phthalate (300 g.) and brucine (500 g.) in a mixture of acetone (3 l.) and water (225 ml.) was allowed to stand overnight. The precipitated solid (339 g.) was recrystallized four times to give a brucine salt, m.p. 176–178.5°, $[\alpha]^{32.5}_D$ −1.7° (*c* 2.7, 95% ethanol). A sample was decomposed to the active acid phthalate, an oil which could not be induced to crystallize, $[\alpha]^{32.5}_D$ +84.5° (*c* 5.5, 95% ethanol).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.14; H, 7.67.

Liberation of the carbinol in the usual manner gave a product having the properties listed in Table V.

Anal. Calcd. for $C_7H_{16}O$: C, 72.35; H, 13.88. Found: C, 72.43; H, 13.59.

Asymmetric Reductions.—The feasibility of separating ketone I and the derived alcohol (6-ol) was established in the following manner. A mixture of 97.2 mg. of (−)-I[8] and 87.7 mg. of (±)-6-ol[8] dissolved in 10 ml. of 1:4 benzene–hexane was chromatographed on 30 g. of neutral alumina, activity grade III. Elution with 150 ml. of 1:1 benzene–hexane yielded 103 mg. of eluate, m.p. 61.5–63°, m.m.p. with authentic (−)-I, 61.5–63°, $[\alpha]^{27}_{365}$ −5348° (*c* 1.1, benzene). The eluent was changed to benzene and 96.9 mg. of eluate was collected in 150 ml. of solution. The material had m.p. 120–122°, m.m.p. with authentic (±)-6-ol, 120–122.5°, α^{27}_{365} −0.03° (*c* 1.9, *l* 1, benzene).

Asymmetric reductions were carried out in the manner described as follows for 2-octanol. A solution of aluminum *t*-butoxide (0.268 g., 1.09 mmoles) in dioxane (3.5 ml.) was added to a mixture of (±)-I (0.251 g., 1.06 mmoles), 2-octanol (5.53 g., 42.5 mmoles, $[\alpha]^{24}_D$ + 9.07° (neat), 94.5% optically pure) and dioxane (7.25 ml.) at 63.0°. The resulting solution was kept at 63.0° for 16 minutes. The reaction mixture was quenched in ice, 7 ml. of 2 *M* hydrochloric acid was added and the mixture was taken to dryness at 2 mm. (bath temperature 70°). The residual oily solid was leached with benzene, the benzene extracts were evaporated to dryness and the residue, dissolved in 1:4 benzene–hexane, was chromatographed on 50 g. of neutral alumina, activity grade III, as described in the preceding section. There was obtained 54.6 mg. of I as an oil ($[\alpha]^{26}_{365}$ − 1863° (*c* 1.32, benzene), ω (optical purity) 34.7%; $[\alpha]^{26}_{435}$ −671° (*c* 1.32, benzene), ω 34.9%) and 198.4 mg. of 6-ol as an oil ($[\alpha]^{26}_{365}$ + 26.9° (*c* 2.36, acetone), ω 11.7%; $[\alpha]^{26}_{435}$ +3.6° (*c* 2.36, acetone), ω 12.0%; $[\alpha]^{26}_{546}$ − 2.33° (*c* 2.36, acetone), ω 11.5%). Average ω of 6-ol: 11.7%; calcd.[9] from ω of I (34.8%): 9.7%; calcd. k_R/k_S = log [0.216 (1–0.348)]/log [0.216(1+0.348)] = 1.59. Signs of residual I and produced 6-ol are internally consistent.[8,9]

Values of k_R/k_S for the other reductions are listed in Table I.

In several runs, unreacted alkylmethylcarbinols were recovered; the properties as compared with those of starting carbinol (expressed as rotation of acid phthalates) are listed in Table III.

The asymmetric reduction using (+)-IId was carried out essentially in the same manner; residual I was optically inactive at wave lengths down to 435 mμ. Recovered unreacted IId was isolated as the acid phthalate, m.p. 78–82°.

Anal. Calcd. for $C_{11}H_9D_3O_4$: 25.00 at. % excess D [3.00]. Found: 23.95, 23.77 [2.87].

Partial Equilibration of I and Derived Alcohol.—A solution of (−)-6-ol[8] (150 mg.) and 276 mg. of aluminum *t*-butoxide in 29 ml. of dioxane was heated for 14.75 hr. at 63°. After addition of 163 mg. of (±)-I[8], the mixture was heated at 63° for another hour. The usual workup yielded, after chromatography on neutral alumina III, 157 mg. of I, $[\alpha]^{27}_{435}$ −92° (*c* 6.2, C_6H_6), ω 4.8%, and 134 mg. of 6-ol, $[\alpha]^{27}_{435}$ − 22.4° (*c* 6.1, acetone), ω 75%.

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[36] L. Friedman and J. Turkevich, ref. 25.

[37] A comparison with the spectrum of 2-propanol shows that this fragmentation accounts for *ca.* 3% of the peak at *m/e* 48.

[38] J. H. Beynon, "Mass Spectrometry and Its Applications to Organic Chemistry," Elsevier Publ. Co., Amsterdam, 1960, p. 486 ff. (Appendix I).

[39] W. A. Mosher and J. C. Cox, Jr., *J. Am. Chem. Soc.*, **72**, 3701 (1950), describe precursor ketone.