The infrared spectrum revealed a strong carbonyl absorption at 5.71 μ.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethanol–ethyl acetate mixtures, mp 159.0–160.0°.

Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.09; N, 17.71. Found: C, 57.08; H, 5.33; N, 17.52.

The same ketone was obtained *via* manganese dioxide oxidation in methylene chloride and by Sarett oxidation.[27] The yields in the latter case (43%) were superior to those in the other procedures.

endo-7-Hydroxy-*endo*-tricyclo[4.2.1.$0^{2,5}$]nonane (40).—The ketone **39** was reduced with lithium aluminum hydride in ether. From 3.29 g (24 mmol) of **39** there was obtained 2.48 g of alcohol. Gas chromatography (C, 170°) revealed the presence of *ca.* 6% of alcohol **36**. A pure sample of **40** was collected for analysis.

Anal. Calcd for $C_9H_{14}O$: C, 78.22; H, 10.21. Found: C, 77.95; H, 10.29.

The infrared spectrum displayed distinctive absorptions at 10.53, 11.12, and 11.39 μ. The nmr spectrum showed a broad multiplet (1 H) at 4.45 attributed to the H–C–O proton and complex absorptions extending from 3.20 to 0.83 ppm.

The bromobenzene sulfonate **41** was recrystallized from petroleum ether (30–60°) and had mp 82.8–83.8°.

Anal. Calcd for $C_{15}H_{17}BrO_3S$: C, 50.43; H, 4.80; Br, 22.37. Found: C, 50.44; H, 4.56; Br, 22.56.

Acetolysis of brosylate **41** by the above procedure led to a 58% yield of alcohols which contained 95.5% **35**, 3% **26**, and 1.5% **40**, as shown by gas chromatography (U, 115°). The major component was isolated by preparative gas chromatography (C, 170°) and shown by nmr spectroscopy to be identical with **35**. The small amount of **40** found may have resulted from reduction of unreacted **41** (sulfide odor).

(27) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953); see also S. J. Cristol, W. K. Seifert, and S. B. Soloway, *ibid.*, **82**, 2351 (1960).

Registry No.—**1**, 16526-27-5; **2**, 16526-28-6; *exo-syn* **7**, 16545-17-8; *exo-anti* **7**, 16529-68-3; **8**, 16529-69-4; **9**, 16529-70-7; **10**, 16529-71-8; **10** 3,5-dinitrobenzoate, 10414-10-5; **12**, 16545-19-0; **16**, 16529-72-9; **16** 2,4-dinitrophenylhydrazone, 16529-73-0; **16** tosylhydrazone, 16529-74-1; **17**, 16529-75-2; **18**, 16529-76-3; **19**, 16529-77-4; *exo*-tricyclo[4.2.1.$0^{2,5}$]nonan-3-ol, 16545-20-3; **20**, 16529-78-5; **20** tosylhydrazone, 16529-79-6; **21**, 16529-80-9; **22**, 16529-81-0; **23**, 16529-82-1; **24**, 16529-83-2; **35**, 16529-84-3; **36**, 16529-91-2; **37**, 16529-85-4; **38**, 16529-86-5; **39**, 16529-87-6; **39** 2,4-dinitrophenylhydrazone, 16529-90-1; **40**, 16529-88-7; **41**, 16529-89-8.

Acknowledgments.—We are grateful to the National Institutes of Health (RG 08701) and to the donors of the Petroleum Research Fund (1676-A1), administered by the American Chemical Society, for generous financial support. Helpful discussions with P. von R. Schleyer and K. Wiberg are also gratefully acknowledged.

Synthesis of (−)-(3*S*)- and (+)-(3*R*)-4-Methyl-3D$_1$-pentan-1-ols and (−)-(3*S*)- and (+)-(3*R*)-3D$_1$-Isocaproic Acids[1a,b]

E. CASPI AND K. R. VARMA[1c]

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

Received December 8, 1967

The (+)-(3*R*)- and (−)-(3*S*)-hydroxytetrahydropyranyl ethers (IVb) were prepared by asymmetric reduction of the keto ether (V) using (+)- and (−)-diisopinocampheylborane,[3] respectively. The absolute configurations at C-3 of the two hydroxy ethers were determined by the method of Horeau and the results were rationalized on the basis of Brown's model for the (+)- and (−)-diisopinocampheylboranes. The enantiomeric hydroxy ethers were converted into the mesylates and hydrogenolyzed with lithium aluminum deuteride. It is assumed that introduction of deuterium proceeded with inversion at the asymmetric center. However, in addition to hydrogenolysis, other significant side reactions were noted. Removal of the tetrahydropyranyl moiety from the resulting (−)-(3*S*)-3D$_1$ and (+)-(3*R*)-3D$_1$ ethers (VIb) gave the alcohols (VIa) which were oxidized to the corresponding (−)-(3*S*)-3D$_1$ and (+)-(3*R*)-3D$_1$ acids (VII).

For studies of the biosynthesis of polyisoprenoids the enantiomeric (3*R*)- and (3*S*)-3D$_1$-4-methylpentan-1-ols and (3*R*)- and (3*S*)-3D$_1$-4-methylpentanoic acids were required. The synthesis of the four specimens and their configurational assignments are described.

Two synthetic approaches were projected both of which were based on the use of optically active dialkylboranes.[2] In one instance it was planned to hydroborate asymmetrically the olefin $(CH_3)_2C{=}CHCH_2R$ (II or III) (Figure 1) and displace stereospecifically the derived hydroxyl with deuterium. The alternative route, which proved successful, consisted of the asymmetric reduction of the carbonyl in $(CH_3)_2CHCOCH_2CH_2R$ (V) and subsequent displacement of the hydroxyl with deuterium.

Diisopinocampheylborane has been used as a highly selective reagent for the preparation of optically active alcohols from olefins and ketones.[2,3] Recently Streitwieser, *et al.*,[4] employed optically active diisopinocampheylborane to synthesize optically active 1-butanol-1-D from *cis*-1-butene-1-D. Preparation of optically active benzyl alcohol-1-D by reduction of benzaldehyde with diisopinocampheyldeuterioborane has also been reported.[5] The reduction of carbonyl groups with fermenting yeast is not practical for α-branched ketones.[6]

The starting material for the syntheses, methyl 4-methyl-3-pentenoate (IIb), was prepared from I,

(1) (a) This work was supported by Grant B6-1877R from the National Science Foundation and CA-K3-16614 from the U. S. Public Health Service. (b) For the configurational notations, see R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964); R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Intern. Ed. Engl.*, **5**, 385 (1966). (c) Postdoctoral Fellow, 1966–present.

(2) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, p 205.

(3) (a) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1964); (b) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 486 (1961); (c) G. Zweifel, N. R. Ayyangar, T. Munekata, and H. C. Brown, *ibid.*, **86**, 1076 (1964); (d) H. C. Brown and D. B. Bigley, *ibid.*, **83**, 3166 (1961).

(4) A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).

(5) S. Wolfe and A. Rauk, *Can. J. Chem.*, **44**, 259 (1966).

(6) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 3595 (1966), and earlier papers.

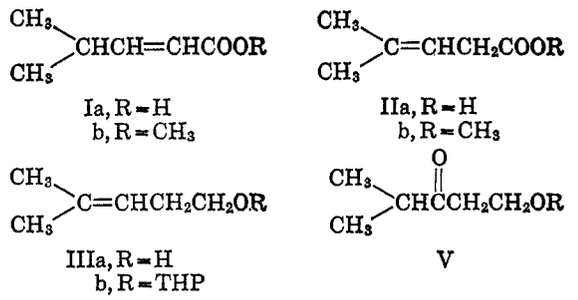


Figure 1.

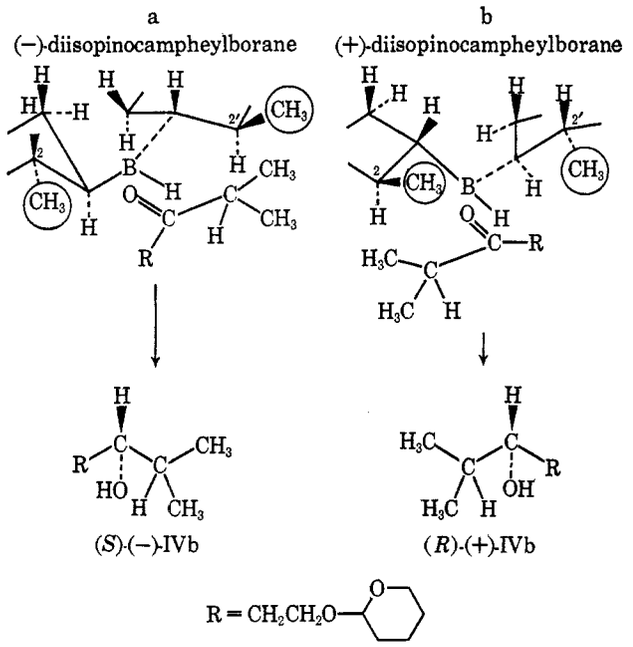


Figure 2.

essentially as previously described.[7,8] Attempted selective hydroboration of the double bond in the ester (IIb) with diisopinocampheylborane in diglyme or tetrahydrofuran failed. Under the conditions employed, the hydroboration was incomplete and the ester group was reduced first.

In an attempt to circumvent this difficulty, the ester was reduced with lithium aluminum hydride to IIIa and the resulting alcohol was converted into the ether (IIIb). Unfortunately the reaction of the ether (IIIb) with (+)-diisopinocampheylborane still did not proceed to completion and in the best case only about 50% hydroboration was achieved. These results were not totally unexpected in view of the reported resistance of trialkylated double bonds to the attack of diisopinocampheylborane.[9] However, a matter of much greater concern was the fact that the derived alcohol (IVb) was devoid of optical activity. The lack of asymmetric selectivity was disappointing and it could be the result of certain side reactions. It is known that diisopinocampheylborane exists in equilibrium with small amounts of the monoalkylborane. The considerably less stereoselective monoalkylborane could have reacted preferentially with the olefin. Alternatively, the displacement of α-pinene from diisopinocampheylborane by the olefin could have occurred.

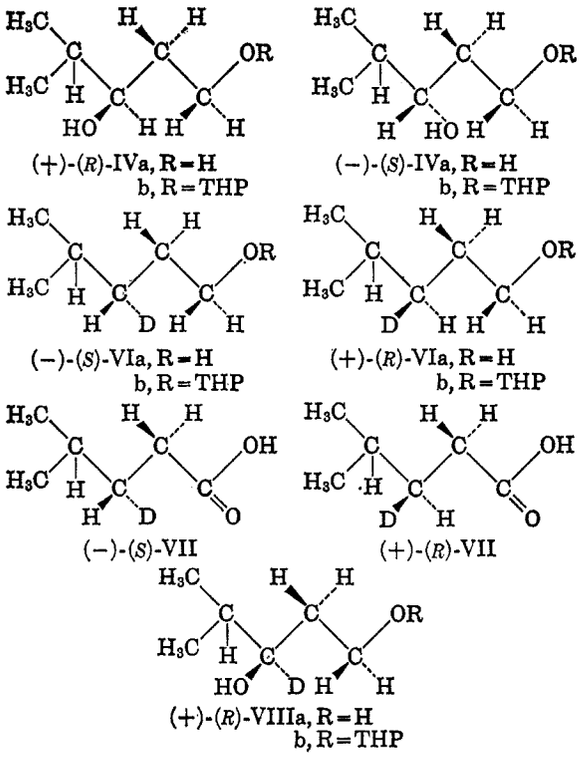


Figure 3.

In view of these results the approach was abandoned and the asymmetric reduction of the ketone (V) was explored. For the preparation of the ketone the olefinic ether (IIIb) was hydroborated and oxidized in the conventional manner to yield the racemic hydroxy ether (IVb) along with a small amount of the isomeric tertiary alcohol. Oxidation of the (±)-IVb with the aqueous chromium trioxide–pyridine reagent described by Cornforth, *et al.*,[10] yielded the keto ether (V). Attempts to oxidize (±)-IVb with chromium trioxide in acetic acid, Jones reagent, Brown's[11] method (at 0°), and Sarrett's procedure failed.

A tetrahydrofuran suspension of (+)-diisopinocampheylborane was prepared from (−)-α-pinene ($\alpha^{23}D$ −39.15°) as described by Brown, *et al.*[3] Reduction of ketone V with the (+) reagent gave the dextrorotatory hydroxy ether (IVb), $[\alpha]^{25}D$ + 2.4° (Figure 2). A product of similar optical purity was obtained when the reaction was carried out in diglyme. With (−)-diisopinocampheylborane prepared from (+)-α-pinene ($\alpha^{25}D$ +39.65°), the reduction of V yielded the levorotatory alcohol (IVb), $[\alpha]^{25}D$ −2.33°. Exposure of the (+)- and (−)-hydroxy ethers (IVb) to methanolic hydrochloric acid gave the $[\alpha]^{23}D$ +7.84° and $[\alpha]^{25}D$ −8.02° diols (IVa), respectively (Figure 3). The infrared, nuclear magnetic resonance, and mass spectra were in full agreement with the assigned structures. The (−)-diol (IVa), $[\alpha]^{27}D$ −6.9 ± 0.2°, has been previously prepared by a different route by Büchi, *et al.*[12] Evi-

(7) K. Babor and I. Jezo, *Chem. Zvesti*, **8**, 18 (1954); *Chem. Abstr.*, **49**, 7495*g* (1955).

(8) For pertinent references, see J. B. Rogan, *J. Org. Chem.*, **27**, 3910 (1962).

(9) (a) G. Zweifel, N. R. Ayyangar, and H. C. Brown, *J. Amer. Chem. Soc.*, **85**, 2055 (1963); (b) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *ibid.*, **86**, 397 (1964); (c) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *ibid.*, **86**, 1071 (1964).

(10) R. H. Cornforth, J. W. Cornforth, and G. Popjak, *Tetrahedron*, **18**, 1357 (1962).

(11) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

(12) G. Büchi, L. Crombie, P. J. Godin, J. S. Katlenbronn, K. S. Siddalingaiah, and D. A. Whiting, *J. Chem. Soc.*, 2843 (1961).

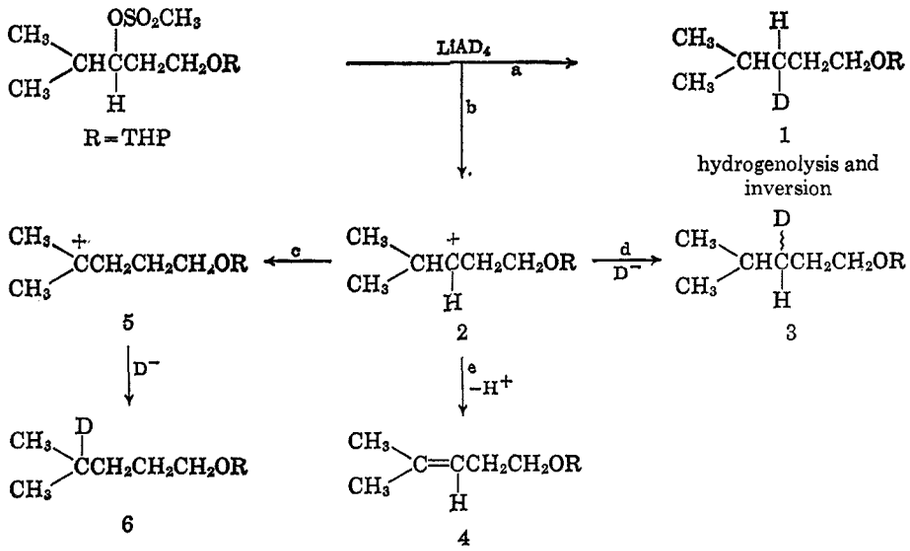


Figure 4.

dently the present sample is of a higher optical purity.

We now turned our attention to the question of the absolute configurations at C-3 of the enantiomeric alcohols IV. The configurations were determined for the (+) and (−) ethers (IVb) by the method of Horeau, *et al.*[13] Esterification of (−)-hydroxy ether (IVb) with racemic α-phenylbutyric anhydride led to the recovery of (−)-α-phenylbutyric acid. Consequently, the (−)-hydroxy ether (IVb) has the (3*S*) configuration.[13] From the analogous experiment with (+)-hydroxy ether (IVb), (+)-α-phenylbutyric acid was recovered indicating the (3*R*) configuration. Obviously the diols (IVa) will have the same configurations as the respective parent ethers (IVb). As indicated above the (−)-(3*S*) ether (IVb) gave the (−)-(3*S*)-diol (IVa) and the (+)-(3*R*) ether (IVb) gave the (+)-(3*R*)-diol (IVa). Our assignment of the (3*S*) configuration to the (−)-diol (IVa) agrees with that of Büchi, *et al.*, who have correlated the glycol with L-glyceraldehyde.[12] Therefore the (+)-diol must have the (3*R*) configuration.

A model of (−)-diisopinocampheylborane obtained from (+)-α-pinene (Figure 2) has been proposed by Brown and coworkers[9b,c] and has been successfully used to predict the configurations of alcohols resulting from hydroboration of acyclic *cis* olefins. Accordingly, all acyclic *cis* olefins on hydroboration with the (−) reagent should give the (*R*) alcohol. Similarly, alcohols resulting from hydroboration with (+)-diisopinocampheylborane prepared from (−)-α-pinene will have the (*S*) configuration. The same model was applied also to the reduction of carbonyl compounds. In actuality the dimeric tetraisopinocampheyldiborane is the reactive species and the group of McKenna has advanced a model based on this dimer.[14] The latter proposal is more encompassing since it is applicable to acyclic *cis* and *trans* olefins.

The reduction of ketone V to the enantiomeric alcohols (IVb) can be correctly interpreted on the basis of both the Brown and McKenna hypotheses. An interpretation of the reduction based on Brown's model is presented. The most stable conformations of the (−)- and (+)-diisopinocampheylboranes can be represented as is shown in Figure 2. The carbonyl may approach the B—H bond from the top or the bottom side of the reagent. However, inspection of models (Prentice-Hall F. M. U. models) reveals that the carbonyl can reach within reacting distance of the B—H bond only when the isopropyl group is directed away from the 2 (Figure 2, pathway a) or 2′ methyl (pathway b). The configurations predicted for the hydroxy ethers (IV) on this basis agree fully with those derived by Horeau's[13] and Büchi's[12] methods. In any event we have obtained from (−)-diisopinocampheylborane derived from (+)-α-pinene the (−)-(3*S*)-hydroxy ether (IVb) and from (+)-diisopinocampheylborane derived from (−)-α-pinene the (+)-(3*R*)-hydroxy ether (IVb) as anticipated.

With the two enantiomeric hydroxy ethers (IVb) in hand, it was possible to plan the stereoselective introduction of deuterium at C-3. The method adopted was to convert the alcohols into the corresponding tosylates or mesylates and then to hydrogenolyze these esters with lithium aluminum deuteride. It has been established that the hydrogenolysis proceeds with inversion and is accompanied by partial racemization.[15,16]

When the mesylate or tosylate of (+)-(3*R*)-hydroxy ether (IVb) was treated with lithium aluminum deuteride in ether the sulfonate group was cleaved, but the reduction was accompanied by formation of *ca.* 30% of the olefinic ether (IIIb) and of a small amount of hydroxy ether (IVb). To facilitate separation of the products it was advantageous to hydroborate the crude mixture, whereby the olefin was converted into the higher boiling alcohol. Deuterio ether VIb (Figure 3) was isolated by fractional distillation and glpc, $[\alpha]^{25}D$ −0.80°. When subjected to the same procedures, the (−)-hydroxy ether (IVb) gave (+)-deuterio ether VIb $[\alpha]^{24}D$ +0.82°. The deuterium content of the two

(13) A. Horeau and B. Kagan, *Tetrahedron*, **20**, 2431 (1964), and references therein.

(14) D. R. Brown, S. F. A. Kettle, J. McKenna, and J. M. McKenna, *Chem. Commun.*, 667 (1967).

(15) G. K. Helkamp and B. F. Rickborn, *J. Org. Chem.*, **22**, 479 (1957).

(16) E. J. Corey, M. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 5036 (1956).

ethers was determined by combustion analysis and mass spectroscopy and was *ca.* 100%.

The nmr spectra of the enantiomeric ethers (VIb) were revealing and interesting. In each case, in addition to the doublet for the isopropyl methyls, a less intense singlet was centered between the peaks of the doublet. The relative intensities of the doublet and the singlet were of the order of 9:1. This led us to suspect that a certain amount (11%) of the deuterium was located at the methine carbon of the isopropyl moiety. That this was the case was proved by an alternative synthetic route.

The (3*R*)-deuteriohydroxy ether (VIII), $[\alpha]^{24}D$ +4.0° (Figure 3), was prepared by reduction of keto ether V with (+)-diisopinocampheyldeuterioborane. The deuterated reagent was prepared in the conventional way from (−)-α-pinene and deuteriodiborane. The derived D-mesylate was reduced with lithium aluminum hydride to furnish (+)-(3*R*)-3D_1 ether (VIb), $[\alpha]^{24}D$ +0.55°. Hydrolysis of the 3D_1 ether (VIb) provided the (3*R*)-3D_1 alcohol (VIa) which showed a somewhat lower deuterium content (84.5%). In this instance the nmr spectrum of the D ether (VIb) exhibited only a sharp doublet for the isopropyl methyls. The (3*R*) configuration of VIII follows from the positive rotations of derived 3D_1 ether (VIb) and 3D_1 alcohol (VIa).

The formation of the observed products can be rationalized by assuming that the $LiAlD_4$ (or $LiAlH_4$) reaction with mesyl esters proceeds by two competing routes. Apparently the hydrogenolysis (pathway a, Figure 4) is accompanied by some C—O bond breakage and formation of the cation 2 (pathway b). Addition of a deuteride to 2 will give the racemic ether 3 (pathway d). Alternatively elimination of a proton will result in the olefin 4 (pathway e). Rearrangement of the secondary cation 2 to the more stable tertiary cation 5 (pathway c) and subsequent addition of a deuteride will yield 6. That pathway b is a major competing route is evident from the amounts of the olefin 4 (30%), the product 6 (*ca.* 10%), and the racemic ether 3 formed. The magnitude of racemization was not determined but was estimated by others[16] to be of the order of 20%. Obviously the methyl "singlet" was absent in the nmr of the product of reduction of the mesylate of VIII with $LiAlH_4$ because in this instance a hydride ion rather than a deuteride ion was added to the methine carbon.

The lithium aluminum deuteride reduction is known to proceed with inversion.[15] Therefore, the (−)-deuterio ether (VIb) and (−)-4-methyl-3-deuteriopentanol (VIa) derived from the (+)-(3*R*)-hydroxy ether (IVb) must have the (3*S*)-3D_1 configuration. Alternatively, the (+)-deuterio ether (VIb) and (+)-4-methyl-3-deuteriopentanol (VIa) derived from (−)-(3*S*)-hydroxy ether (IVb) have the (3*R*)-3D_1 configuration.

Certain observations, not of immediate consequence to this study, deserve mention. Of interest were the nmr and mass spectra of the tetrahydropyranyl ethers. The magnetic nonequivalence of protons of the X group in systems of type X_2 AB where A and B are different groups or atoms have been studied in some detail.[17-19] Protons of a methylene group or isopropyl group removed by one or more bonds from a center of asymmetry may be magnetically nonequivalent and display AB-type quartets. In the present case no such splitting was observed and only doublets for the isopropyl methyls were recorded.

Without exception the mass spectra of the tetrahydropyranyl ethers were devoid of peaks for molecular ions and showed low intensity peaks corresponding to $(M - 1)^+$ ions. This led to some initial confusion because the D ethers VIb (M = 187) obtained by $LiAlH_4$ reduction of mesyl esters had only the $(M - 1)^+$ peak (*m/e* 186) which could correspond to the nondeuterated molecular ion. The point was cleared up when it was observed that methoxytetrahydropyranyl ether (M = 116) and the nondeuterated tetrahydropyranyl ether VIc (M = 186) both gave only the $(M - 1)^+$ peaks. This observation is analogous to results obtained by Friedel and Sharkey[20] for the mass spectra of acetals.

There remained the problem of oxidizing the alcohols (VIa) to the required 3D_1-isocaproic acids. The acids were prepared by treating the hydroxy products with Jones reagent, whereby the (−)-(3*S*) alcohol (VIa) gave (−)-(3*S*)-3D_1-isocaproic acid ($[\alpha]^{23}D$ −0.453°) and the (+)-(3*R*) alcohol (VIa) gave (+)-(3*R*)-3D_1-isocaproic acid ($[\alpha]^{23}D$ +0.486°).

Experimental Section

Tetrahydrofuran, diglyme, and boron trifluoride etherate were purified according to procedures previously described.[3a] The sodium borohydride (minimum 98% pure) was used as supplied by Fisher Scientific Co. The lithium aluminum deuteride and sodium borodeuteride (purchased from Metal Hydride Inc.) were of high isotopic purity (at least 95% D content). The samples of α-pinene used in this investigation showed specific rotations of $\alpha^{23}D$ −39.15° and +39.65° (neat, *l* = 1).

Preparative and analytical gas–liquid partition chromatography were carried out on an F & M Model 720 dual-column, programmed instrument and helium was used as carrier gas. Two columns were employed: column A, 5% XE 60 on Chromosorb (8 ft × 0.25 in. o.d.); column B, 5% SE-30 on Chromosorb (8 ft × 0.25 in. o.d.). In all cases the identity of samples was confirmed by mixed injection with authentic samples. Solutions were dried with anhydrous sodium sulfate prior to distillation. The melting points were determined on a hot plate and are corrected. The ir spectra were recorded on a Perkin-Elmer spectrophotometer, Model 237. The mass spectra were run on a Varian Associates M-66 instrument. The nmr spectra were recorded at 60 Mc on a Varian A-60 instrument either neat or in the indicated solvents using tetramethylsilane as an internal standard. The peak positions (in cycles per second), number of protons, nature of signal (s, singlet; d, doublet; bs, broad singlet; q, quartet; m, multiplet), splitting constant (*J*, Hz), and their assignments are indicated in that order. Analyses were by I. Beetz, Kronach, Germany. Deuterium analyses by combustion method were carried out by J. Nemeth, Urbana, Ill. The Hilger MK-III polarimeter was used.

4-Methylpent-2-enoic Acid (Ia).—A mixture of isobutyraldehyde (62 g, 1 mol) and malonic acid (156 g, 1.5 mol) in pyridine (150 ml) was heated on a steam bath. Vigorous evolution of carbon dioxide was noticed in the early stages and, after 3.5 hr, the evolution of gas had nearly stopped. The mixture was cooled and poured over excess hydrochloric acid and ice. The oily layer was separated and the aqueous phase was extracted twice with ether. The oil and the extracts were combined, washed with dilute hydrochloric acid and a saturated sodium chloride solution, and dried. The solvent was removed and the remaining liquid was distilled through a 6-in. packed column under reduced pressure to yield 4-methylpent-2-enoic acid: bp 83–85° (1.85 mm); 86% yield; ν_{max}^{film} 1700, 1650 cm^{-1}.

(17) E. I. Snyder, *J. Amer. Chem. Soc.*, **85**, 2624 (1963).
(18) G. M. Whitesides, D. Holtz, and J. D. Roberts, *ibid.*, **86**, 2628 (1964).
(19) R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965.
(20) R. Friedel and A. G. Sharkey, *Anal. Chem.*, **28**, 940 (1956).

4-Methylpent-3-enoic Acid (IIa).—The isomerization of Ia was carried out essentially according to the published procedure[11] except that a lower concentration of alkali was used.

The acid (250 g) was mixed with potassium hydroxide (1.5 kg) and water (2 l.) and refluxed for 20 hr, in an atmosphere of nitrogen. The mixture was cooled in ice and acidified with concentrated hydrochloric acid. The obtained oil was separated and the aqueous layer extracted with ether. The oil and the extracts were combined and the solution was washed with brine and dried. The solvent was removed and the residue was distilled through a 1-ft.-long Vigreux column under reduced pressure. The fraction with bp 77–85° (2.4–2.7 mm) contained IIa (yield, 89.5%): ν_{max}^{film} *ca.* 1725 (broad C=O) and 1665 (double bond) cm^{-1}.

Methyl 4-Methylpent-3-enoate (IIb).—The published procedure was followed.[11] Esterification of the crude isomerized acid (IIa) gave, after distillation through a short column, 4-methylpent-3-enoate (98 g): bp 153–154° (1 atm); ν_{max}^{film} 1745 cm^{-1} (broad, ester); nmr (neat), 96.0 and 101.5 [6, d, *ca.* 1, $(\mathbf{CH_3})_2$–C=C], 177.0 (2, d, 7, =CH–$\mathbf{CH_2}$–$COOCH_3$), 213.5 (3, $COO\mathbf{CH_3}$), and 316 [1, quartet of a triplet, J = 7 and 1.5, $(CH_3)_2$–C=$\mathbf{CH}$]. Judging from the spectrum the sample contained *ca.* 1–2% of the isomeric methyl 4-methylpent-2-enoate. No other impurity was detected by glpc.

The recovered acids were again deconjugated to yield upon esterification more of IIb.

4-Methylpent-3-en-1-ol (IIIa).—To a stirred and cooled suspension of $LiAlH_4$ (8.0 g) in ether (500 ml) methyl 4-methylpent-3-enoate (IIb, 26.05 g) was added during 20 min and the mixture was refluxed for 1 hr. The reaction was terminated by the addition of moist ether which was followed by a saturated solution of ammonium chloride. The ether phase was separated and the aqueous layer was extracted with ether. The ether extracts were combined, then washed with a saturated ammonium chloride solution and dried. The solvent was removed through a 100-cm Vigreux column and the residual liquid (21.2 g) proved to be IIIa. Upon distillation an analytical sample was obtained: bp 105–106° (110 mm); ν_{max}^{film} 3350 (strong, –OH), 1660 (weak, C=C) cm^{-1}; nmr (CCl_4), 97.0 (s) and 101 (d) [6, ≃1.0, $(\mathbf{CH_3})_2$–C=C–], 130 (2, sym q, $J_{ax} \simeq J_{bx} \simeq 6.5$, =CH–$\mathbf{CH_2}$–$CH_2OH$), 204.25 (3, unsym q, 7–8, –$\mathbf{CH_2}$–OH + CH_2–$\mathbf{OH}$), 304 [1, q of t, 7 and 1.5, $(CH_3)_2$–C=$\mathbf{CH}$–]. The sample was contaminated with *ca.* 1% of 4-methylpent-2-en-1-ol.

4-Methylpent-3-en-1-ol Tetrahydropyranyl Ether (IIIb).—A mixture of the crude alcohol (IIIa, 21.2 g), benzene (300 ml), dihydropyran (19.5 g), and several crystals of *p*-toluenesulfonic acid was left at ambient temperature. Periodically samples were removed for ir analysis and after 3 hr the hydroxyl band disappeared. The reaction mixture was washed with a dilute sodium carbonate solution and water and dried. Removal of the solvent in a rotary evaporator furnished a liquid (38.5 g) with a characteristic sweet odor. Upon distillation through a short Vigreux column (it was advantageous to add Triton X-100 as an antifoaming agent) IIIb was isolated, bp 96.5–98.5° (9–10 mm), in an 89.3% yield. In contrast to the ir spectrum of IIIa, the spectrum of IIIb showed in addition to the expected ether bands, a complex pattern of peaks. The nmr spectrum (CCl_4) showed peaks at 100 [6, d, 1.0, $(\mathbf{CH_3})_2$–C=CH–], 131.5 (2, sym q, 7, =CH–$\mathbf{CH_2}$–), ∼206 (4, m, –O–$\mathbf{CH_2}$–C), 269 (1, s, –O–$\mathbf{CH}$–O), 304.5 [1, complex t, ∼7.5, $(CH_3)_2$–C=$\mathbf{CH}$–]. Glpc on columns A and B (140–150°) showed that the ether IIIb is contaminated with *ca.* 2% of an impurity with a higher retention time.

Hydroboration of IIIb with (+)-Diisopinocampheylborane.—The apparatus consisted of a 100-ml flask carrying a side arm and a socket for a thermometer. The flask was equipped with a dry nitrogen inlet, a thermometer, and a magnetic stirring bar. The system was flamed and cooled in a flow of nitrogen and the side arm was closed with a rubber stopple. A positive pressure of nitrogen was maintained thereafter.

A. Experiment in Diglyme.—A mixture of sodium borohydride (0.7125 g, 18.5 mmol), (−)-α-pinene (7.48 g, 55 mol), and dry diglyme (45 ml) was cooled to 0° in an ice bath.[21] To the stirred slurry, purified boron trifluoride etherate (3.15 ml, 25 mmol) was added from a hypodermic syringe during 15 min and the stirring was continued at 0–3° for 5 hr. To the stirred white suspension of the reagent the olefinic ether (IIIb, 4.60 g, 25 mmol) was added during 5 min at 0–3°. The stirring was continued at 0–3° for 3 hr and then at 8–9° for 18 hr. The solution at this point was clear. Careful addition of water from a syringe liberated 10 mmol of hydrogen indicating the consumption of 15 mmol of hydride.

The organoborane was oxidized by adding first 3 *N* sodium hydroxide (20 ml) and then 30% hydrogen peroxide (11 ml) and stirring the mixture for 2 hr at *ca.* 40°. The product was recovered with ether; the extract was washed with ice-cold water and dried. The solvent was removed *in vacuo* and the residual liquid was fractionated through a short, packed column. Fraction 1, bp 45–48° (14–15 mm), consisted of α-pinene and diglyme as indicated by glpc analysis on column B. Fraction 2, bp 86–96° (1.6 mm), was a mixture of unreacted IIIb and isopinocampheol (glpc). Fraction 3, bp 77–84° (0.1 mm), was mainly the hydroxy ether (IVb) contaminated with some isopinocampheol. Fraction 3 was purified by preparative glpc on column B at 180° to furnish (after redistillation) a colorless viscous oil: bp 100° (0.35 mm) (bath temp); ν_{max}^{film} 3450 cm^{-1} (–OH). The ir, nmr, tlc, and glpc data of this material were identical with those of (+)- or (−)-IVb described below. A 10% chloroform solution of the product in a 1-dm tube did not show detectable optical rotation.

B. Experiment in Tetrahydrofuran.—The previous experiment was repeated on a 10-mmol scale using sodium borohydride (0.313 g, 8.14 mmol), tetrahydrofuran (25 ml), (−)-α-pinene (3.1 g, 11 mmol), boron trifluoride etherate (1.26 ml, 10 mmol), and the olefinic ether (1.84 g, 10 mmol). The reagent was stirred at 0–3° for 4 hr. Subsequently, the olefinic ether was added slowly and stirred at 8–9° for 24 hr. The reaction mixture was not clear and hydrolysis gave *ca.* 5 mmol of hydrogen suggesting the consumption of *ca.* 50% of the hydride.

The product was oxidized in the usual manner (H_2O_2 + NaOH) and the resulting alcohol was recovered with ether. Analytical glpc showed the presence of α-pinene, isopinocampheol, unreacted olefinic ether, and hydroxy ether (IVb). The hydroxy ether was purified by preparative glpc and distilled to furnish pure IVb (750 mg) whose physical characteristics were identical with those of the compound prepared by procedure A. A 10% chloroform solution in a 1-dm tube was optically inactive.

(±)-4-Methyl-1,3-dihydroxypentan-1-tetrahydropyranyl Ether (IVb).—A 2-l., three-necked flask was equipped with a magnetic stirring bar, a dropping funnel, a thermometer, and an inlet through which a positive pressure of dry nitrogen could be maintained. The system was flamed in a flow of dry nitrogen and cooled to room temperature. The flask was charged with sodium borohydride (14.3 g, 360 mmol) and dry tetrahydrofuran (1 l.); then the mixture was stirred and cooled in an ice–salt bath. Subsequently, boron trifluoride etherate (480 mmol, 68.2 g) was slowly added from the dropping funnel (0–5°). After about 30 min the olefinic ether (IIIb, 176.6 g, 960 mmol) was added dropwise and the mixture was stirred for 4 hr (0–3°). The excess hydride was decomposed with water.

Oxidation was carried out with 3 *N* sodium hydroxide (220 ml) and 30% hydrogen peroxide (110 ml) first by stirring the reaction mixture for 1 hr at the temperature of an ice bath and then for 2 hr at 40°. The tetrahydrofuran phase was separated and the aqueous portion was extracted with small amounts of ether. The combined tetrahydrofuran and ether solution was washed with brine and dried and the solvent was removed *in vacuo*. The residual liquid was distilled through a 6-in. Vigreux column.

The bulk of IVb distilled at 77–80° (0.25 mm). An additional amount of the product, bp 77–80° (0.25 mm), was obtained upon redistillation of the forerun (15 g). A total of 153 g (79% yield) of (±)-IVb was obtained. Analysis (glpc) on columns A and B revealed that the material is slightly contaminated (*ca.* 4%) with an alcohol (ir) having a lower retention time. Judging from the stability of the hydroxyl group toward chromic acid the impurity seemed to be the isomeric 4-hydroxy ether (glpc, see below).

The crude (±)-IVb showed ν_{max}^{film} 3475 cm^{-1} (–OH); nmr (CCl_4), 53.5 [6, d, 7, $(\mathbf{CH_3})_2$CH–], 219 (5, m, –$\mathbf{CH_2}$–O and –$\mathbf{CH}$–OH), 176 (1, broad s, –$\mathbf{OH}$, exchanged with D_2O), 277 (1, s, –O–$\mathbf{CH}$–O); mass spectrum, *m/e* 85 (100%), 57 (52%), 55 (52%), 101 (46%), 56 (30%), 73 (27%).

4-Methyl-3-keto-1-pentanoltetrahydropyranyl Ether (V).—A solution of chromic oxide (50 g) in water (30 ml) was added to pyridine (500 ml) in an ice bath under stirring.[10] To this reagent, the hydroxy ether (IVb, 33.7 g) in pyridine (100 ml) was added slowly with stirring. Glpc of aliquots removed periodically showed that the oxidation was completed after 48 hr. The reac-

(21) A small excess of sodium borohydride was employed to ensure complete consumption of boron trifluoride etherate. To minimize dissociation of the dialkylborane a 10% excess of α-pinene was used.

tion mixture was diluted with a large volume of ethyl acetate, the precipitate was filtered off and washed with small amounts of ethyl acetate. The filtrate was stirred with solid sodium bicarbonate (150 g) and filtered over Celite. The treatment was repeated once more. The slightly colored filtrate was concentrated on a rotary evaporator and the combined material from three oxidations was fractionated through a 1-ft packed column. After an initial forerun [bp 68° (2 mm)] product V distilled at 70–71° (0.3 mm) (82% yield): ν_{max}^{film} 1716 cm^{-1} (strong, C=O); nmr (CCl_4), 64.5 [6, d, 7.0, $(CH_3)_2CH$–], 93.5 (6, broad, ring methylene protons), 153.5 (3, m, –CH–CO–CH_2–), 222.5 (4, m, –CH_2–O), 270.5 (1, s, –O–CH–O–); mass spectrum, *m/e* 85 (100%), 101 (66%), 71 (51%), 117 (14%), 111 (9%), 142 (4%), 182 (4%), 157 (2%). The purity of the material was established by tlc [silica gel; benzene–ethyl acetate (1:1)] and by glpc on columns A and B at 160–180°.

(+)-4-Methyl-1-(3*R*)-dihydroxypentan-1-tetrahydropyranyl Ether (IVb).—(−)-α-Pinene (136.8 g, 1008 mmol) was added to a cooled (0–3°) and stirred solution of diborane in tetrahydrofuran[3a] (558.4 ml, 0.752 *M* in borane). A white precipitate appeared soon after the addition and the reagent was stirred overnight in an ice bath at 6–7°. The keto ether (V, 70.0 g, 350 mmol) was added at 0–3° during 30 min and the mixture was stirred overnight in an ice bath (6–7°). The solution was clear and the excess hydride was decomposed with water. Then 3 *N* sodium hydroxide (280 ml) was added and this was followed by a slow addition of 30% hydrogenperoxide (113 ml) (*cooling*). The mixture was stirred at *ca.* 40° for 1.5 hr. The tetrahydrofuran layer was separated and the aqueous layer was extracted with ether. The tetrahydrofuran solution was combined with the ether extracts, washed with brine, and dried and the solvent was removed *in vacuo*. The residual liquid was distilled through a 1-ft packed column. The excess α-pinene and isopinocampheol were removed below 70° (0.6 mm) and the product (+)-IVb, bp 85–86° (0.55 mm) (yield, 57.5 g), was collected. More of IVb (6.5 g) was isolated by redistillation of the forerun thus increasing the yield to 64.0 g (91.4%). The ir spectrum of the sample was identical with that of (±)-IVb. The optically active specimen had a specific rotation of $[\alpha]^{23}D$ +2.43° (*c* 30%, chloroform); nmr (CCl_4), 56.5 [6, d, 6.5, $(CH_3)_2$–CH], 175 (1, s, –OH, exchanged with D_2O), 277.5 (1, s, –O–CH–O), 228.5 (5, m, O–CH_2–C + –CH–OH). The sample contained traces of isopinocampheol (glpc) and was purified by preparative glpc on column B and then distilled to furnish material with a specific rotation of $[\alpha]^{25}D$ +2.40° (*c* 30%, chloroform). The homogeneity of the sample was confirmed by tlc (silica gel).

(+)-4-Methyl-1-(3*R*)-dihydroxypentane (IVa).—To a solution of (+)-IVb (1.5 g) in methanol (10 ml) concentrated hydrochloric acid (2 drops) was added and the mixture was warmed (40–50°) for 30 min. The reaction was terminated by the addition of solid sodium hydrogen carbonate (1 g) and then diluted with ether (50 ml). The inorganic solid was separated by filtration and the solvent was removed through a Vigreux column. The diol (IVa) was isolated by fractional distillation of the residue. A sample, purified twice by glpc first on column A and then on column B and distilled, gave (+)-IVa as a viscous oil: ν_{max}^{film} 3350 cm^{-1} (broad, –OH); $[\alpha]^{23}D$ +7.84° (*c* 30.7%, chloroform). The solid 1,3-bis-3,5-dinitrobenzoyl ester was prepared and showed mp 117–120° (ethanol–methylene chloride).

Anal. Calcd for $C_{20}H_{18}N_4O_{12}$: N, 11.07%. Found: N, 10.9%.

(−)-4-Methyl-1-(3*S*)-dihydroxypentane-1-tetrahydropyranyl Ether (IVb).—The experiment was carried out exactly as described for the (+)-hydroxy ether (IVb). The keto ether (V, 50 g) was reduced with (−)-diisopinocampheylborane [from (+)-α-pinene] to give (−)-hydroxy ether IVb (84% yield): bp 73–76° (0.15 mm); $[\alpha]^{25}D$ −2.33° (*c* 30%, chloroform). The ir spectrum and the chromatographic behavior of this material were identical with those of the previously described enantiomeric product.

(−)-4-Methylpentane-1-(3*S*)-diol (IVa).—Cleavage of (−)-hydroxy ether (IVb) with methanolic hydrochloric acid was carried out as described above for (+)-4-methylpentane-1-(3*R*)-diol (IVa). A sample twice purified by glpc on column B at 140° and distilled showed $[\alpha]^{25}D$ −8.02°. The purity and identity of the product was confirmed by glpc and tlc.

Configurational Assignment to the (+)- and (−)-Hydroxy Ethers (IVb) by Horeau's Method.[20]—α-Phenylbutyric anhydride was prepared by the general procedure for anhydrides.[22] The anhydride was freed of excess acid and acid chloride by washing with a dilute sodium bicarbonate solution and water and dried. The product was distilled under high vacuum to furnish a slightly colored material which was shown to be homogeneous by tlc; ir showed ν_{max}^{film} 1815 (strong) and 1748 (m) cm^{-1}.

The (+)- and (−)-hydroxy ethers IVb were treated in an identical manner. The ether IVb (202 mg) was dissolved in 7 ml of a 0.4 *M* solution of α-phenylbutyric anhydride in dry pyridine and stored for 24 hr in a well-stoppered flask at ambient temperature. To decompose the excess anhydride, water (1 ml) was added and the mixture was kept for 1 hr at room temperature. Benzene (1 ml) was added and the excess acid was titrated with 1 *N* sodium hydroxide (phenolphthalein). In each case 4.62 mmol of free acid was found. The neutral material was recovered with several 10-ml portions of chloroform. The combined chloroform extracts was washed with dilute hydrochloric acid and water and dried. Removal of the solvent under reduced pressure provided the ester (340 mg). The ir spectrum of each ester was devoid of hydroxylic absorption and showed a strong band for a carbonyl indicating complete esterification.

The aqueous layer was acidified with concentrated hydrochloric acid and extracted with several 10-ml portions of chloroform. The chloroform extracts were combined, washed with water, and dried and the solvent was removed *in vacuo* to furnish the acids.

The acid (763.0 mg) recovered from the esterification of (+)-hydroxy ether (IVb) had a specific rotation of $[\alpha]^{25}D$ +0.982° (*c* 32.6%, benzene), optical yield 4.68%. This indicates the (3*R*) configuration for the (+)-hydroxy ether (IVb).

The acid (763.5 mg) recovered from the esterification of (−)-hydroxy ether (IVb) had a specific rotation of $[\alpha]^{25}D$ −1.04° (*c* 25.0%, benzene), optical yield 4.96%. This indicates the (3*S*) configuration for the (−)-hydroxy ether (IVb).

Preparation of Mesyl and Tosyl Esters of (+)- and (−)-Hydroxy Ethers (IVb). A. Mesylate.—To a cooled solution of the hydroxy ether (IVb, 31.0 g, 155 mmol) in pyridine (100 ml), methanesulfonyl chloride (22.0 g, 186 mmol) was added and the mixture was left for 2.5 hr at room temperature. After dilution with ice and water the mixture was extracted several times with ether. The ether extracts were combined, washed successively with cold dilute hydrochloric acid, a sodium bicarbonate solution, and water, and dried. The solvent was removed *in vacuo* (bath temperature was below 40°) to furnish the mesylate as an oil (41.0 g) which had no hydroxyl absorption in the ir spectrum.

B. Tosylate.—The tosylates were prepared in an identical manner except that *p*-toluenesulfonyl chloride was used instead of the methanesulfonyl chloride. The product was devoid of hydroxyl absorption in the ir spectrum.

(−)-(3*S*)-3D$_1$-4-Methyl-1-hydroxypentane-1-tetrahydropyranyl Ether. A. Reduction with Lithium Aluminum Deuteride of the Tosyl Ester of (+)-IVb.—A solution of the crude tosylate (5.8 g) in dry ether (30 ml) was added slowly to a cooled and stirred suspension of lithium aluminum deuteride (1 g) in dry ether (50 ml). After completion of the addition, stirring was continued for 30 min at room temperature and then the mixture was refluxed for 5 hr. The reaction was terminated with water and the solids were removed by filtration. The filtrate was washed with a sodium carbonate solution and water, dried, and concentrated to a residue (2.92 g); the ir spectrum, ν_{max}^{film}, contained a trace hydroxyl band.

Glpc analysis on column A at 150° revealed the presence of three components of retention times 7.9, 10.0, and 12.0 min in a ratio of 75:32:2. The 7.9- and 10.0-min components were (−)-(3*S*)-3D$_1$-4-methyl-1-hydroxypentane tetrahydropyranyl ether (IVb) and the olefinic ether (IIIb). The unidentified component (retention time 12 min) was presumably an olefin isomeric with IIIb.

The crude product was distilled under reduced pressure and the fraction distilling below 100° (2 mm) was collected. This fraction was twice purified by preparative glpc to furnish, after distillation, 1.6 g of (−)-VIb: ν_{max}^{film} 2160 (w, –D); $[\alpha]^{24}D$ −0.80° (*c* 30%, chloroform); nmr (CCl_4), 53.75 [d, 6.5 $(CH_3)_2CH$–], 53 [s, $(CH_3)_2$–CD–]; the total number of protons in the methyl signals was six. The mass spectrum had peaks at *m/e* 85 (100%), 86 (68%), 57 (41%), 56 (40%), 84 (28%), 186 (15%), 101 (13%), 87 (11%), 115 (8%), 185 (1%). The amount of D$_1$ product estimated from the mass spectrum was 99–100%.

(22) C. F. H. Allen, C. J. Kilblev, D. M. McLachlin, and C. V. Wilson, *Org. Syn.*, **26**, 1 (1946).

Reduction of the tosylate of (±)-IVb with lithium aluminum hydride gave a mixture of VIc (79.7%) and the olefin IIIb (20.3%). The mixture was purified as above to yield pure (±)-D_0 VIc. The mass spectrum of the product was devoid of a peak for M^+ but showed a peak at m/e 185 $(M-1)^+$ and 85 (100%).

B. Reduction of the Mesyl Ester.—To a cooled and stirred suspension of lithium aluminum deuteride (5.5 g) in dry ether (200 ml) a solution of the crude mesyl ester (35.5 g) of (+)-IVb in dry ether (50 ml) was slowly added and the mixture was stirred for 16 hr at room temperature. Subsequently the mixture was refluxed for 1 hr; then after cooling the reaction was terminated with water. Solid sodium carbonate (10 g) was added, the stirring was continued for 1 hr, and finally the solids were separated by filtration over celite. The filtrate was freed of solvent by evaporation through a Vigreux column and the remaining liquid (23.1 g) was devoid of hydroxyl bands in the ir spectrum. Glpc (column B; 150°) indicated the presence of VIb (72.5%) and IIIb (27.5%).

To the crude product (23 g) in tetrahydrofuran (50 ml) at 0–3° a diborane solution in the same solvent (27 ml, 0.75 *M* in borane) was added. After 3 hr the mixture was oxidized in the usual manner [3 *N* sodium hydroxide (25 ml), 30% hydrogen peroxide (10 ml); stirring at *ca.* 40°, 1.5 hr] to yield upon the conventional work-up an oily residue. The residue was distilled and the fraction with bp 44–47° (0.25 mm) consisted of nearly homogeneous (−)-VIb (13.4 g), $\alpha^{24}D$ −0.80° (*c* 30%, chloroform). Glpc (column B; 150°) revealed the presence of a trace amount of IIIb. The mass spectrum (D content *ca.* 100%) was identical with that of the sample prepared by reduction of the tosylate. Combustion analysis indicated *ca.* 95% incorporation of deuterium; the nmr spectrum (CCl_4) showed peaks at 54 [d, 6, $(CH_3)_2CH$–], 58.5 [s, $(CH_3)_2CD$–], 205 (4, m, O–CH_2–C–), 268 (1, s, O–CH–O). The total number of protons in the methyl signals was six.

(−)-(3S)-3D1-4-Methylpentan-1-ol (VIa).—A mixture of (−)-VIb (12.0 g), methanol (25 ml), and concentrated hydrochloric acid (5 drops) was warmed at 45–50° for 3 hr. The acid was neutralized with solid sodium hydrogen carbonate (2.0 g), then ether was added (100 ml), and the solids were separated by filtration.

Most of the solvent was removed by distillation through a 30-cm packed column and the residual liquid was fractionated through a 15-cm packed column at atmospheric pressure. The fraction boiling below 135° (750 mm) contained ether, methanol, tetrahydropyranyl ether of methanol, and a small amount of the deuterio alcohol VIa. The next fraction [bp 149–51° (750 mm), 5.6 g] was nearly 99% pure (glpc) deuterio alcohol VIa. A sample purified by preparative glpc and distilled furnished VIa: $[\alpha]^{25}D$ −0.168° (*c* 31.6%, chloroform), $\alpha^{25}D$ −0.17° (neat, l = 1); nmr (CCl_4), 54 [*ca.* 6, d, 6, $(CH_3)_2CH$–], 53 [d, *ca.* 1, $(CH_3)_2$-CD–], 85.5 (4, t, 6.0 and 8.5, other protons), 209 (2, t, 6.5, $-CH_2$–OH), 252 (1, s, **–OH**, exchanged with D_2O); mass spectrum, m/e 57 (100%), 28 (92%), 43 (84%), 70 (65%), 85 (18%), 84 (2%), 83 (2%). The mass spectrum indicated that the product contains *ca.* 100% monodeuterated species. The behavior of the sample on glpc and tlc was identical with that of authentic 4-methyl-1-pentanol (Aldrich Chemical Co.) whose mass spectrum showed peaks at m/e 56 (100%), 69 (90%), 43 (81%), 28 (75%), 84 (27%), 83 (7%).

(+)-(3R)-3D1-4-Methylpentan-1-ol Tetrahydropyranyl Ether (VIb). **A.**—The (−)-(3*S*)-hydroxy ether (IVb) was converted into the mesylate (41.0 g) and treated with $LiAlD_4$ (6.0 g) exactly as previously described. The resulting products contained VIb (72.5%) and IIIb (27.5%). The crude mixture was hydroborated and oxidized in the conventional manner to yield, after fractional distillation 12.8 g of (+)-VIb: bp 67–68° (1.5 mm); $[\alpha]^{24}D$ +0.82° (*c* 30%, chloroform). The sample was more than 99% pure when analyzed by glpc and the main contaminant was the olefinic ether (IIIa). Its tlc and nmr and mass spectra were identical with those of the (−) enantiomer.

B.—(+)-(3*R*)-3D1-3-Hydroxy ether (VIII, 3.2 g) was converted into the mesylate (4.25 g) by the general procedure described previously and the mesylate was reduced with lithium aluminum hydride (0.75 g) in ether (80 ml). The product was worked up as in the previous cases and was shown by glpc to be a mixture of the ether VIb (79%) and the olefinic ether IIIb (21%). The crude material was purified by preparative glpc on column A and distilled to furnish pure (+)-(3*R*)-3D1 ether (VIb, 1.3 g): ν_{max}^{film} 2125 (w, –D); $[\alpha]^{24}D$ +0.55° (*c* 20%, chloroform); nmr (CCl_4), 54.25 [6, d, 6.5, $(CH_3)_2CH$–], 204 (4, m, 7 and 3.5, –O–CH_2–C–), 269 (1, s, –O–CH–O–); mass spectrum, m/e 57 (100%), 43 (76%), 70 (46%), 28 (43%), 85 (15%). The sample was more than 99% pure when analyzed at 150° on columns A and B and the main impurity was the olefinic ether (IIIb).

(+)-(3R)-3D1-4-Methylpentan-1-ol (VIa). **A.**—The (+)-deuterio ether VIb (11.8 g) was cleaved as described above for the (−)-deuterio ether VIb. The product was fractionated through a 15-cm packed column to furnish (+)-(3*R*)-3D1-4-methylpentan-1-ol (VIa, 5.5 g): bp 150–51° (753 mm); ir spectrum identical with that of VIa; $\alpha^{25}D$ +0.19° (neat, l = 1); nmr (CCl_4), 54 [*ca.* 6, d, 6, $(CH_3)_2$–CH–], 53.5 [d, *ca.* 1, $(CH_3)_2$–CD–], 86 (4, t, 6.5 and 7.5, other protons), 209 (2, t, 6.5, $-CH_2$–OH), 251 (1, s, **–OH** exchanged with D_2O); mass spectrum, m/e 57 (100%), 43 (76%), 70 (46%), 28 (43%), 85 (15%). Analysis of the mass spectrum indicated the presence of *ca.* 100% monodeuterated species. A sample subjected to preparative glpc on column B at 100° and distilled showed the same optical rotation.

B.—The (+)-(3*R*)-3D1 ether obtained *via* VIII was hydrolyzed and purified as described in procedure A to yield (+)-(3*R*)-3D1 alcohol VIa. Microanalysis indicated 80.5% deuterium incorporation and the mass spectrum indicated 84.5% of monodeuterated species.

(+)-(3R)-3D1-4-Methyl-1,3-dihydroxypentan-1-tetrahydropyranyl Ether (VIII).—A solution of deuteriodiborane in tetrahydrofuran was prepared from sodium borodeuteride and boron trifluoride etherate.[3a]

To a cooled and stirred solution of deuterioborane in tetrahydrofuran (67.6 ml, 0.22 *M* in deuteriodiborane) at 0–3° (−)-α-pinene (9.3 g, 72 mmol) was added through a hypodermic syringe and then the mixture was stirred at 0–5° overnight. The keto ether (V, 5.0 g, 25 mmol) was added to the stirred reagent at 0–3° during 10 min and the mixture was stirred for 24 hr at 0–5°. The excess deuteride in the clear solution was decomposed by the addition of water. The organoborane was oxidized with alkaline hydrogen peroxide as described above. The product was isolated in the usual manner and the solvent was removed *in vacuo*. The residual liquid was fractionally distilled through a 15-cm packed column to furnish 5.22 g of (+)-VIb, bp 72–73° (0.15 mm), which was contaminated with a small amount of isopinocampheol. A sample twice purified by preparative glpc on column B at 180° and distilled *in vacuo* furnished pure VIII: $[\alpha]^{24}D$ +4.0° (*c* 30%, chloroform); ν_{max}^{film} 3450 (s, –OH), 2100 (w, –D) cm^{-1}; nmr (CCl_4), 54 [6, d, 6, $(CH_3)_2CH$–], 179 (1, s, **–OH**), 221 (4, m, –O–CH_2–C–), 272.5 (1, s, –O–CH–O); mass spectrum, m/e 85 (100%), 101 (74%), 84 (56%), 83 (47%), 86 (42%), 102 (33%), 160 (11%), 100 (8%), 118 (5%). The homogeneity of the material was established by glpc and tlc.

(+)-(3R)-3D1-4-Methylpentan-1-oic Acid (VII).—To a solution of (+)-4-methyl-(3*R*)-3D1-pentan-1-ol (VIa, 500 mg) in acetone (10 ml) at 0°, Jones reagent was added until the color persisted. The mixture was stirred at 0° for 10 min, diluted with water, (100 ml) and extracted several times with small amounts of ether. The ether extracts were combined and washed once with water and the acidic material was extracted with 5% sodium hydroxide solution (30 ml). The aqueous alkaline solution was acidified with concentrated hydrochloric acid and the acidic material was isolated with ether. The solvent was removed and the residual oil was distilled through a short-path column to furnish (+)-(3*R*)-3D1-4-methylpentanoic acid (VII, 450 mg), $[\alpha]^{23}D$ +0.486° (*c* 28%, chloroform). The acid proved to be homogeneous by tlc (silica). The purity of the material was further established by glpc analysis of the methyl ester (diazomethane). Glpc analysis of the ester on columns A and B at 120° showed it to be more than 99% pure and its retention time was identical with that of authentic methyl 4-methylpentanoate.

(−)-(3S)-3D1-4-Methylpentan-1-oic Acid (VII).—The (−) acid (VII) was prepared from the (−) alcohol (VIa) as described above. The (−) acid (VII) had a specific rotation of $[\alpha]^{23}D$ −0.453° (*c* 30%, chloroform). The acid was homogeneous when tested on tlc (benzene (67%), methanol (21%) and glacial acetic acid (12%)). The methyl ester (diazomethane) was homogeneous when analyzed on column B.

Registry No.—Ia, 10321-71-8; IIa, 504-85-8; IIb, 2258-65-3; IIIa, 763-89-3; IIIb, 16451-46-0; (±)-IVb, 16451-47-1; (+)-(3*R*)-IVa, 16451-48-2; 1,3-bis-3,5-dinitrobenzoyl derivative of (+)-(3*R*)-IVa, 16451-49-3;

(−)-(3S)-IVa, 16451-50-6; (+)-(3R)-IVb, 16451-51-7; (−)-(3S)-IVb, 16451-52-8; V, 16451-53-9; (+)-(3R)-VIa, 16451-54-0; (−)-(3S)-VIa, 16451-55-1; (+)-(3R)-VIb, 16451-56-2; (−)-(3S)-VIb, 16451-57-3; (+)-(3R)-VII, 16503-30-3; (−)-(3S)-VII, 16462-50-3; (+)-(3R)-VIIIb, 16503-31-4.

The Stereochemistry of Methylene Transfer from Sulfonium Ylides to Unsaturated Bicyclic Ketones[1]

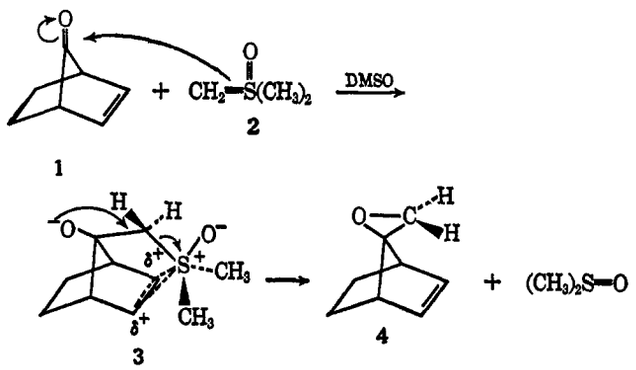
ROBERT S. BLY, COIT M. DUBOSE, JR., AND GEORGE B. KONIZER

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Received September 12, 1967

In contrast to other nucleophilic reagents, dimethyloxosulfonium methylide attacks dehydronorcamphor predominantly from the *endo* direction to yield a 71:29 ratio of spiro[norborn-2-en-*exo*- and -*endo*-5,2′-oxacyclopropanes]. Dimethylsulfonium methylide, however, produces the same two oxides in a 6:94 ratio. Both the oxosulfonium and the sulfonium ylide attack norcamphor preponderantly from the *exo* side to yield spiro[norbornan-*exo*- and -*endo*-2,2′-oxacyclopropanes] in a 10:88 or 5:95 ratio, respectively. Competitive rate studies have been used to demonstrate that dehydronorcamphor exhibits an enhanced *endo* and decreased *exo* reactivity toward the oxosulfonium ylide. Participation by the π electrons of the double bond has been suggested as the cause of this unusual kinetic and stereochemical effect.

During the course of some synthetic investigations undertaken in connection with another problem, it was observed that the reaction of norbornen-7-one (**1**) with dimethyloxosulfonium methylide (**2**) occurs in a stereospecific manner to yield spiro[norbornen-*anti*-7,2′-oxacyclopropane] (**4**)[2] and suggested that π-electron participation *via* the intermediate **3**[3-5] might be responsible for the preferential *syn* addition, *viz.*



However, since the *syn* side of a 7-substituted norbornene is apparently less sterically hindered than the *anti*—the irreversible reaction of norbornen-7-one (**1**) with a mixed-metal hydride or an organometallic produces an *anti* alcohol predominantly,[2] while equilibration of the mixed 7-carbomethoxynorbornenes with methanolic sodium methoxide yields more *syn* than *anti* ester[6]—a steric factor could not be ruled out as the cause of the observed stereospecificity. To test these ideas and to learn more of the path by which sulfur ylides react with ketones to yield epoxides, we have extended our investigations to include the ketones norcamphor (**13**), dehydronorcamphor (**5**), and norbornan-7-one (**18**) and the ylide dimethylsulfonium methylide (**12**).[7]

Results

The reaction of dehydronorcamphor (**5**) at 25° with a 10% excess of dimethyloxosulfonium methylide (**2**)[7] in dimethyl sulfoxide (DMSO) yields a mixture containing 65% spiro[norbornen-*exo*-5,2′-oxacyclopropane] (**7**), 27% spiro[norbornen-*endo*-5,2′-oxacyclopropane] (**9**), and 8% the unreacted ketone, **5**. The composition of the product mixture was determined by gas–liquid partition chromatography (glpc) on a basic Quadrol/SAIB column[8] at 115°, conditions which permit analysis of the reactive unsaturated *anti* oxide, **4**,[2] without rearrangement. The major products, **7** and **9**, respectively, were identified from their analyses and infrared and nmr spectra (see Experimental Section) and by their reduction with lithium aluminum hydride to the known[9] unsaturated alcohols 5-methylnorbornen-*exo*- and -*endo*-5-ols (**10** and **11**), respectively (Chart I).

At a lower temperature **5** reacts with an ~20% excess of dimethylsulfonium methylide (**12**) in DMSO to yield a mixture containing 6% the unsaturated *exo* oxide **7** and 94% the unsaturated *endo* oxide **9**.

$$\underset{}{5} + \underset{12}{CH_2{=}S(CH_3)_2} \longrightarrow 7\ (6\%) + 9\ (94\%)$$

In contrast to dehydronorcamphor (**5**), norcamphor (**13**) reacts with **2** to produce a mixture containing about 10% spiro[norbornan-*exo*-2,2′-oxacyclopropane] (**15**), at least 88% spiro[norbornan-*endo*-2,2′-oxacyclopropane] (**17**), and less than 2% unreacted norcamphor (**13**). Since the two saturated oxides, **15** and **17**, which constitute at least 98% (by glpc) of the distilled reaction product could not be separated by glpc, they were collected together, and their relative proportion

(1) Portions of this work have been presented before the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstracts, p 8K.

(2) R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963).

(3) We represent this intermediate as charge delocalized purely as a matter of convenience and analogy,[4] but do not intend to imply that our experimental results permit us to distinguish it from a tricyclic charge-localized structure(s).

(4) Analogous structures have been suggested to accommodate the observed stability of positively charged carbon,[5a-c] and sulfur[5d] exocyclic, *syn* and β to the 5 or 7 position of 2-norbornene.

(5) (a) E. L. Allred and T. J. Maricich, *Tetrahedron Lett.*, 949 (1963); (b) R. M. Hawthorne, Jr., Ph.D. Dissertation, Rutgers, 1963, part II; (c) R. S. Bly, R. K. Bly, A. O. Bedenbaugh, and O. R. Vail, *J. Amer. Chem. Soc.*, **89**, 880 (1967); (d) P. Wilder, Jr., and L. A. Feliu-Otero, *J. Org. Chem.* **31**, 4264 (1966).

(6) R. R. Sauers and R. M. Hawthorne, Jr., *ibid.*, **29**, 1685 (1964).

(7) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(8) The preparation and properties of this liquid phase have been described earlier; *cf.* J. A. Broderick, "Aerograph Research Notes," Wilkins Instrument and Research, Walnut Creek, Calif., Fall Issue, 1960.

(9) (a) N. J. Toivonen and P. J. Mälkönen, *Suomen Kemistilehti*, *B*, **32**, 277 (1959); (b) *ibid.*, **33**, 53 (1960).