

## Stereochemistry of the Primary Carbon. XVI. Optically Active 1-Butanol-1-*d* by Hydroboration<sup>1</sup>

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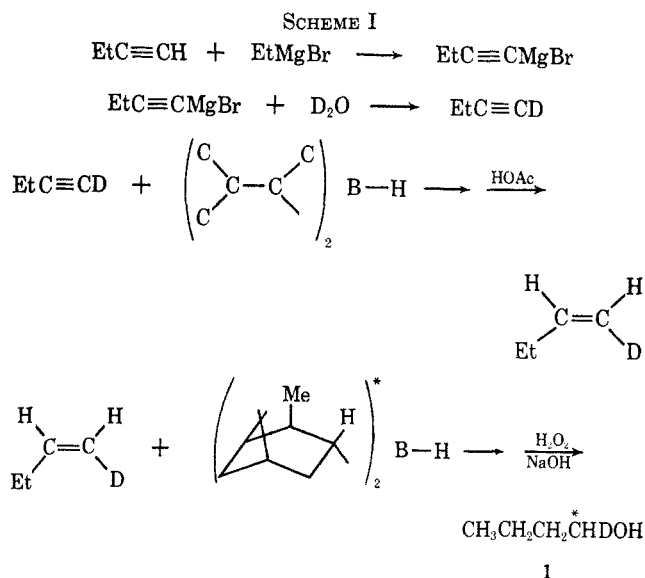
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Optically active 1-butanol-1-*d* was prepared by partially asymmetric hydroboration from diisopinocampheylborane and *cis*-1-butene-1-*d*. The latter compound was prepared by hydroboration of 1-butyne-1-*d*. To account for the stereochemistry of the 1-butanol-1-*d* produced, a small modification of Brown's mechanism for hydroboration is proposed.

Optically active primary alcohols with H-D asymmetry of the type RCHDOH have been prepared in synthetically useful quantities by enzymatic reduction and by chemical asymmetric reductions. The former method was pioneered by Loewus, Westheimer, and Vennesland<sup>3</sup> using yeast alcohol dehydrogenase; subsequent use of a large amount of the enzyme gave an isolable amount of ethanol-1-*d*.<sup>4</sup> This general method was made practical by Mosher, *et al.*,<sup>5</sup> who developed convenient procedures for reduction of deuterioaldehydes by actively fermenting yeast. The enzymatic reduction has the advantage of yielding optically pure product.<sup>3</sup> The chemical reductions, on the other hand, are only partially asymmetric but have the advantage of generality. Previous work was based on the use of Grignard modification of the Meerwein-Ponndorf reduction in the preparations of butanol-1-*d*<sup>6</sup> and benzyl- $\alpha$ -*d* alcohol.<sup>7</sup> In this paper we report the use of Brown's asymmetric hydroboration reaction<sup>8</sup> as an alternative synthesis of optically active butanol-1-*d*. This procedure can also be generalized for the preparation of other such alcohols.<sup>9</sup> The synthetic scheme shown in Scheme I commenced from 1-butyne which was converted to the acetylenic Grignard reagent by treatment with ethylmagnesium bromide in diglyme solution. Decomposition of 1-butyne-1-*d* which, by infrared analysis, contained one deuterium atom per molecule in the acetylenic position.

Hydroboration of 1-butyne-1-*d* with the sterically hindered di(3-methyl-2-butyl)borane<sup>10</sup> followed by protonolysis afforded *cis*-1-butene-1-*d*. The *cis* relationship of the deuterium and ethyl group at the double bond was indicated by the nmr spectrum which



showed the vinyl protons to have a coupling constant of 10.4 cps, characteristic of *cis*-vinyl protons in this system.<sup>11</sup>

Hydroboration of *cis*-1-butene-1-*d* with the optically active organoborane derived from treatment of (+)- $\alpha$ -pinene with diborane followed by oxidation with alkaline hydrogen peroxide yielded (-)-butanol-1-*d* (1) in 70% yield. Purification *via* the crystalline acid phthalate ester, followed by regeneration of the alcohol by lithium aluminum hydride reduction, afforded gas chromatographically pure alcohol. The nmr spectrum indicated the presence of one deuterium atom per molecule; the infrared spectrum was identical with the published spectrum of 1.<sup>6</sup> This alcohol had  $[\alpha]^{21\text{D}} -0.210 \pm 0.006^\circ$ . Since the  $\alpha$ -pinene utilized in the asymmetric synthesis had an optical purity of 80% (see the Experimental Section), correction of the specific rotation for optically pure  $\alpha$ -pinene gives  $[\alpha]^{21\text{D}} -0.262 \pm 0.007^\circ$ . This rotation corresponds to an optical purity of 56%.<sup>12</sup> Note that the highest rotation previously obtained for 1 as prepared by Grignard reduction was  $[\alpha]_{\text{D}} 0.185^\circ$ .<sup>13</sup>

### Discussion

For the asymmetric hydroboration of *cis* olefins with diisopinocampheylborane (or its dimer), Brown has

(11) A. A. Bothner-By and C. A. Naar-Colin, *J. Am. Chem. Soc.*, **83**, 231 (1961).

(12) Mosher, *et al.*,<sup>5b</sup> have obtained butanol-1-*d* by the reduction of butyraldehyde-1-*d* with actively fermenting yeast and find  $[\alpha]^{27.5\text{D}} +0.468^\circ$ . This rotation is assumed to correspond to optical purity.

(13) A. Streitwieser, Jr., J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 338 (1959).

(1) Paper XV: A. Streitwieser, Jr., and M. R. Granger, *J. Org. Chem.*, **32**, 1528 (1967). Presented in part at the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, Abstracts, p 50N. Supported in part by a grant from the Petroleum Research Fund of the American Chemical Society.

(2) (a) U. S. Public Health Service Postdoctoral Research Fellow, 1963-1964; (b) U. S. Public Health Service Predoctoral Research Fellow, 1963-1965.

(3) F. A. Loewus, F. H. Westheimer, and B. Vennesland, *J. Am. Chem. Soc.*, **75**, 5018 (1953).

(4) H. R. Levy, F. A. Loewus, and B. Vennesland, *ibid.*, **79**, 2949 (1957).

(5) (a) W. A. Sanderson and H. S. Mosher, *ibid.*, **83**, 5033 (1961); (b) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *ibid.*, **88**, 3595 (1966).

(6) A. Streitwieser, Jr., *ibid.*, **75**, 5014 (1953).

(7) A. Streitwieser, Jr., and J. R. Wolfe, Jr., *ibid.*, **79**, 903 (1957).

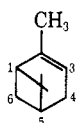
(8) G. Zweifel, N. R. Ayyangar, T. Munekata, and H. C. Brown, *ibid.*, **86**, 1076 (1964).

(9) After this work was complete it came to our attention that D. Arigoni and his research group have used a similar sequence to prepare optically active hexanol-1-*d*; cf. H. Weber, P. Loew, and D. Arigoni, *Chimia*, **19**, 595 (1965).

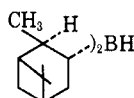
(10) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, Chapters 11 and 12.

had considerable success in rationalizing the observed absolute configurations of the products in terms of an optimal steric fit of the olefin to the reagent in a transition state whose geometry is presumed to be known.<sup>14</sup> Ample evidence exists that the hydroboration reaction involves a stereospecific *cis* addition of boron and hydrogen to an unsaturated carbon center with the boron adding to the least hindered carbon.<sup>14</sup> Replacement of the boron atom by hydroxyl or hydrogen (oxidation with alkaline hydrogen peroxide or protonolysis with a carboxylic acid, respectively) also appears to be stereospecific.<sup>15</sup>

From the assigned absolute configuration of  $\alpha$ -pinene<sup>16</sup> (2) and an assumed lowest energy conformation of diisopinocampheylborane (3) derived from an exami-

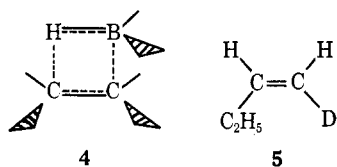


2, (1*R*:5*R*)-(+)- $\alpha$ -pinene



3, (1*R*:2*S*:3*R*:5*R*)-(-)-diisopinocampheylborane

nation of molecular models,<sup>17</sup> Brown concludes that the addition of the boron-hydrogen bond to a double bond involves a four-center transition state, 4.<sup>18</sup>



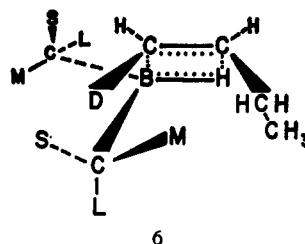
Steric interactions of the asymmetric groups on the boron with the hydrogen and alkyl group on the attached carbon in the *cis* olefin allows successful prediction of the configuration of the resulting alcohol enantiomer produced in excess. Applied to some *unsym* olefins such as 2-methyl-1-butene, this model also predicts correctly the relative magnitudes of the longer ranged steric interactions with the now more distant groups.

Applying Brown's model and symbolism to *cis*-1-butene-1-*d* (5) involves consideration of the two possible transition states (6 and 7).

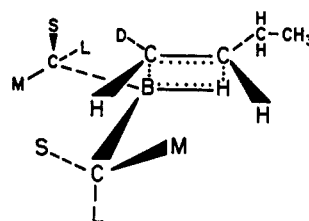
In a very sensitive Meerwein-Ponndorf-Verley asymmetric reduction the differences in nonbonded interactions between deuterium and hydrogen have been shown to be negligibly small<sup>19</sup> and we shall consider only the groups attached to C-2 of 5.

The groups of C-3 and C-3' of the organoborane must discriminate between a hydrogen and an ethyl group of 5, in order for asymmetric induction to occur. On the basis of the above model, transition state 6 is preferred by the same reasoning used with 2-methyl-1-butene.<sup>8</sup> This transition state leads to the prediction

of the *S* configuration<sup>20</sup> for (-) 1. In fact, this prediction is incorrect; (-) 1 is known to possess the *R* configuration.<sup>13,21</sup>



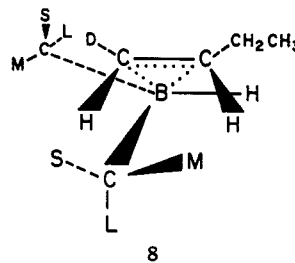
6



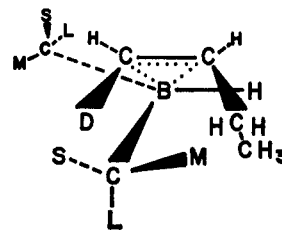
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It has been shown previously that, in the case of hindered or *trans* olefins, the proposed model for the transition state predicts the opposite absolute configuration.<sup>14</sup> However, such cases are marked by the displacement of  $\alpha$ -pinene from the reagent during the course of reaction.<sup>14</sup> In the present case only the equilibrium concentration of  $\alpha$ -pinene was found.<sup>22</sup>

We propose a small but significant change in Brown's model that maintains the same predictions for *cis* olefins and will apply successfully as well to the present case. In this model, we suggest that the olefin-borane complex is a triangular  $\pi$  complex and that the transition state involves a relatively small perturbation from this triangular structure. This structure is clearly analogous to many other olefin complexes. The present case then involves consideration of the two transition states (8 and 9). Now the more favorable interaction of the S group with ethyl and of the M group with hydrogen allows the clear prediction that 8 is favored over 9 and assigns the *R* configuration to



8



9

(14) The configurational results are summarized in H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Am. Chem. Soc.*, **86**, 1071 (1964).

(15) Reference 10, Chapters 1 and 3.

(16) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5493 (1959).

(17) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *ibid.*, **86**, 397 (1964).

(18) H. C. Brown and G. Zweifel, *ibid.*, **83**, 2544 (1961).

(19) K. Mislow, R. E. O'Brien, and H. Schaefer, *ibid.*, **82**, 5512 (1960).

(20) Notation of R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); see also R. S. Cahn, *J. Chem. Educ.*, **41**, 116, 508 (1964).

(21) A. Streitwieser, Jr., I. Schwager, L. Verbit, and H. Rabitz, *J. Org. Chem.*, **32**, 1532 (1967).

(22) Because of an equilibrium dissociation of diisopinocampheylborane, approximately 6% of  $\alpha$ -pinene normally is present in diglyme solution.<sup>8</sup>

(-) 1, in agreement with experiment. In this model the steric interactions with substituents on the C-1 of the olefin are similar to those in Brown's rectangular model and the old predictions for internal *cis* alkenes are preserved. Morrison<sup>23</sup> has pointed out that the present model is also more successful than Brown's original model in accounting for the asymmetric reduction of ketones by hydroboration.

### Experimental Section

**1-Butyne-1-*d*.**—A solution of 61 g (1.1 moles) of 1-butyne (Matheson Co., 95% pure) in 50 ml of diglyme at Dry Ice temperature was added to the cold Grignard reagent prepared from 48.6 g (2.0 g-atoms) of magnesium and 218 g (2.0 moles) of ethyl bromide in 800 ml of diglyme. After stirring overnight the mixture was cooled to 0° and quenched with 40 g of deuterium oxide. The butyne-1-*d* (41 g, 0.75 mole, 68% yield) was distilled directly from the reaction vessel into a Dry Ice trap. The product had an acetylenic C-D band at 2600 cm<sup>-1</sup> in the infrared and showed the absence of the corresponding C-H. A concentrated solution in CCl<sub>4</sub> showed a weak band at 1970 cm<sup>-1</sup> assigned to triple-bond stretching.

***cis*-1-Butene-1-*d*.**—A solution of 156 g (1.1 moles) of boron fluoride etherate in 25 ml of diglyme was added to a well-stirred mixture of 28.4 g (0.75 mole) of sodium borohydride and 140 g (2.0 moles) of 2-methyl-2-butene (Matheson Coleman and Bell Co.) in 500 ml of freshly distilled (from sodium) diglyme maintained at 0°. After 4 hr at 0° the temperature was lowered

(23) J. D. Morrison, *Surv. Prog. Chem.*, **3**, 170 (1966), and personal communication.

to -15° and a solution of 41 g (0.75 mole) of 1-butyne-1-*d* in 40 ml of diglyme at Dry Ice temperature was added in several portions. The mixture was stirred overnight and excess hydride was decomposed with ethylene glycol. The organoborane was decomposed with 240 ml of glacial acetic acid and the resulting 1-butene-1-*d* (28 g, 0.49 mole, 65% yield) was distilled directly into a Dry Ice trap. The infrared spectrum showed double-bond absorption at 1615 and vinyl C-D at 2250 cm<sup>-1</sup>. The nmr spectrum gave *J* = 10.4 cps for the vinyl protons characteristic of *cis*-vinylic hydrogens.

**1-Butanol-1-*d*.**—To a solution of 28.4 g (0.75 mole) of sodium borohydride in 1 l. of diglyme was added 272 g (2.0 moles) of  $\alpha$ -pinene (99.8% pure by gc,  $[\alpha]^{25}_D +41.1^\circ$ , 80% optically pure)<sup>24</sup> followed, at 0°, by 155.8 g (1.1 moles) of boron fluoride etherate. After 4 hr at 0° the reaction mixture was cooled to -15° and 28 g (0.49 mole) of *cis*-1-butene-1-*d* was added. After standing overnight excess hydride was decomposed with ethylene glycol and the organoborane was oxidized at 30-50° with 330 ml of 3 *N* NaOH and 330 ml of 30% hydrogen peroxide. The mixture was extracted with ether. Distillation of the extract gave 27 g (0.34 mole, 70% yield) of 1, most of which was converted to the hydrogen phthalate<sup>25</sup> and recrystallized five times from cyclohexane-benzene: mp 74.0-75.0°,  $[\alpha]^{25}_D 0.437 \pm 0.009^\circ$  (*c* 24.0, acetone), pure by gc on a silicone oil column.

Cleavage of the ester with lithium aluminum hydride gave pure (gc) 1-butanol-1-*d*, having 1.0 deuterium by nmr and  $[\alpha]^{25}_D -0.210 \pm 0.006^\circ$  (neat).

**Registry No.**—1, 10060-19-2; 1-butyne-1-*d*, 10036-58-5; *cis*-1-butene-1-*d*, 10036-59-6.

(24) F. H. Thurber and R. C. Thielke [*J. Am. Chem. Soc.*, **53**, 1030 (1931)] report  $[\alpha]_D +51.1^\circ$  for  $\alpha$ -pinene purified via the nitrosochloride.

(25) A. Streitwieser, Jr., *ibid.*, **77**, 1117 (1955).

## Stereochemistry of the Primary Carbon. XVII. Absolute Configuration of 1-Butanol-1-*d*<sup>1</sup>

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(*S*)-(+)-1-Butanol-1-*d* was converted by reactions of known stereochemistry to (*R*)-(-)-1-bromopentane-2-*d* which was also related to (*S*)-(-)-pentane-2-*d* via asymmetric hydroboration reactions on 1-pentene-2-*d*. The configurations previously assigned to the deuterio alcohols on the basis of mechanisms are confirmed by these interconversions.

1-Butanol-1-*d* is significant among primary alcohols whose optical activity results from hydrogen-deuterium asymmetry. It was the first such alcohol shown to have measurable optical activity<sup>3</sup> and its configuration has been related to those of benzyl- $\alpha$ -*d* alcohol and a number of derivatives.<sup>4</sup> The absolute configurations of these compounds, however, rests entirely on an assumed mechanism for the asymmetric reduction by which the alcohols are synthesized<sup>4</sup> and on Brewster's empirical rules for relating structure and stereochemistry.<sup>5</sup> In the present paper 1-butanol-1-*d* is configurationally related to pentane-2-*d*. The existing assignments are confirmed.

The reaction sequence used is summarized in Chart I in which all rotations are given as specific rotations

relative to the value,  $[\alpha]_D 0.47^\circ$ , obtained for 1-butanol-1-*d* prepared by enzymatic reduction by Mosher, *et al.*<sup>6</sup> Assuming that this value represents optical purity, all of the numbers in Scheme I correspond to optically pure compounds of the indicated configuration.

The 1-butanol-1-*d* was converted to the *p*-nitrobenzenesulfonate ester and allowed to react with sodiomalonic ester. The formation of the butylmalonic ester undoubtedly occurs with complete inversion of configuration as shown. This ester had no observable rotation but hydrolysis gave caproic- $\beta$ -*d* acid that was optically active. The Cristol-Firth modification<sup>7</sup> of the Hunsdiecker reaction gave the corresponding 1-bromopentane-2-*d*. Reduction of this halide to the hydrocarbon with lithium aluminum hydride did not give consistent results; so the amyl bromide was synthesized by an alternant route. Methyl valerate was treated with sodium methoxide in methanol-*d* to ex-

(1) (a) This research was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society. (b) Paper XVI: A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).

(2) U. S. Public Health Service Postdoctoral Research Fellow, 1963-1964.

(3) A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **75**, 5014 (1953).

(4) A. Streitwieser, Jr., J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 338 (1959).

(5) J. H. Brewster, *Tetrahedron Letters*, No. 20, 23 (1959).

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

(7) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).