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HYDROBORATION OF TERPENES—VIII

CYCLIC HYDROBORATION OF D-(+)-LIMONENE. A STEREOSELECTIVE SYNTHESIS OF D-(−)-(1R, 2R, 4R)-LIMONENE-2,9-DIOL AND D-(−)-(1R, 2R, 4R)-CARVOMENTHOL[1]

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Abstract—D-(+)-Limonene can be converted into the corresponding bicyclic organoborinate intermediate, B-methoxy-4,8-dimethyl-2-borabicyclo[3.3.1]nonane, by cyclic hydroboration with borane in THF, followed by methanolysis, and distillation of the product. Alternatively, cyclic hydroboration of D-(+)-limonene with thexylborane provides the related bicyclic organoborane intermediate, B-thexyl-4,8-dimethyl-2-borabicyclo[3.3.1]nonane. Oxidation of the respective intermediates produces D-(−)-(1R, 2R, 4R)-limonene-2,9-diol. Protonation of the bicyclic thexyl intermediate, followed by oxidation, provides D-(−)-(1R, 2R, 4R)-carvomenthol. These results suggest that the cyclic hydroboration of dienes can provide a valuable means for controlling the exact site of hydroboration, leading to a stereoselective synthesis of alcohols.

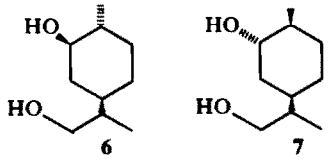
The hydroboration-oxidation of terpenes in favorable cases leads to a stereoselective synthesis of the corresponding alcohols with predictable configurations (Eq. 1).[3] In many other cases, however, a hydroborating agent attacks from both sides of a double bond producing a mixture of alcohols after oxidation. Typically, the simple hydroboration of dihydrolimonene[4] (1) with borane in THF followed by oxidation leads to a 61:39 mixture of carvomenthol (2) and isocarvomenthol (3), exceedingly difficult to separate (Eq. 2).

Our recent studies[1,5] indicated that cyclic hydroboration could provide a valuable means for controlling such hydroborations. Thus, we envisioned the following stereoselective synthesis of carvomenthol (2) from limonene (4) (Eq. 3).

With this objective in mind, we undertook to explore the cyclic hydroboration of D-(+)-limonene with borane in THF as well as with thexylborane in order to establish reaction conditions suitable for the formation of the cyclic intermediate 5. We then investigated the conversion of 5 to D-(−)-(1R, 2R, 4R)-limonene-2,9-diol[1] (6) and D-(−)-(1R, 2R, 4R)-carvomenthol (2).

RESULTS AND DISCUSSION

A stereoselective synthesis of D-(−)-(1R, 2R, 4R)-*Limonene-2,9-diol* via *the cyclic hydroboration of* D-(+)-*limonene.* Hydroboration of D-(+)-limonene was studied in detail using borane in THF and thexylborane as the hydroborating agents. In order to find the optimum conditions for the formation of the maximum quantity of D-(−)-(1R, 2R, 4R)-limonene-2,9-diol (6), the mode of addition and the ratio of the reactants were varied.



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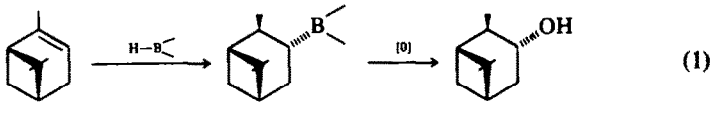

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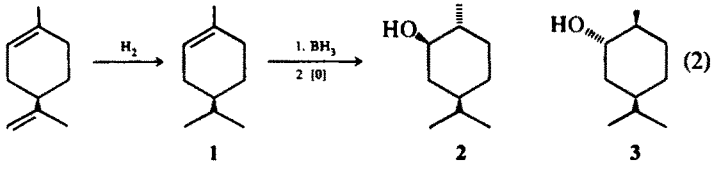

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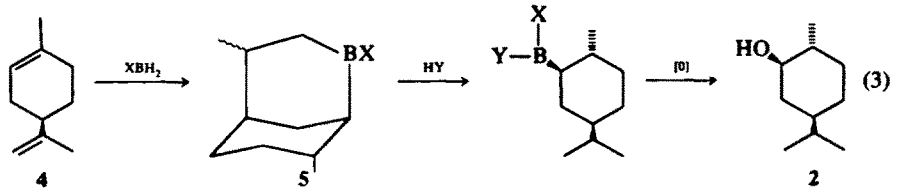

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Table 1. Hydroboration of D-(+)-limonene with borane in THF or thexylborane at 0°

Hydroborating agent	Mode of addition[a]	Hydride/C=C	Oxidation product,[b] % β[c]	γ[d]	Total
Borane in THF	B→L	1	71	26	97
	L→B	1	69	30	99
	B→L	3/2	72	28	100
	L→B	3/2	70	30	100
	B→L	3	67	27	94
	L→B	3	65	28	93
	S	3/2	70	28	98
	S (at -22°)	3/2	71	29	100
Thexylborane	B→L	1	76	14	90
	L→B	1	72	17	89
	S	1	84	12	96

[a] B→L: borane or thexylborane added to limonene; L→B: limonene added to borane or thexylborane; S: simultaneous addition of borane or thexylborane and limonene to THF.

[b] By glpc analysis of the corresponding diacetates on a capillary column of polyphenyl ether.

[c] D-(-)-(1R, 2R, 4R)-limonene-2,9-diol.

[d] D-(1S, 2S, 4R)-limonene-2,9-diol.

Table 2. A stereoselective synthesis of D-(−)-(1R, 2R, 4R)-carvomenthol from D-(+)-limonene via protonolysis-oxidation of B-thexyl-4,8-dimethyl-2-borabicyclo[3.3.1]nonane[a]

Protonolysis temp, °C	Protonolysis time, hr	D-(-)-(1R, 2R, 4R)-Carvomenthol Glpc yield, %	$n^{20}D$[b]
86	8	32	
86 and then 110	5 and 5	67	1.4613
110	12	95[c]	1.4610

[a] Thexylborane used as hydroborating agent. Glacial acetic acid used as protonolysis agent.

[b] Lit.[11] $n^{20}D$ 1.4613.

[c] A minor amount (~ 2%) of trans-p-menthane also formed in the reaction mixture.

After the usual oxidation of the reaction mixture, the product was converted to the corresponding diacetate and analyzed by GLPC.

The experimental results are summarized in Table 1.

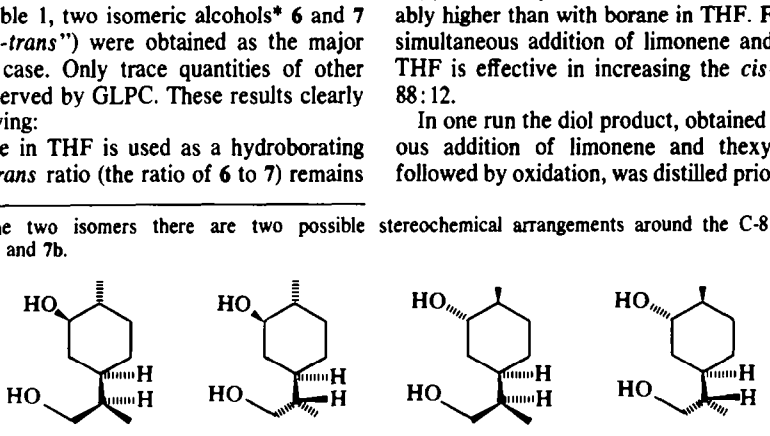
As shown in Table 1, two isomeric alcohols* **6** and **7** ("*m-cis*" and "*m-trans*") were obtained as the major products in each case. Only trace quantities of other products were observed by GLPC. These results clearly indicate the following:

(1) When borane in THF is used as a hydroborating agent, the *cis*-to-*trans* ratio (the ratio of **6** to **7**) remains virtually constant at *ca* 70:30. Neither the mode of addition nor the reactant ratio exerts any noticeable effect on the *cis*-to-*trans* ratio.

(2) With thexylborane the *cis*-to-*trans* ratio is considerably higher than with borane in THF. Furthermore, slow simultaneous addition of limonene and thexylborane to THF is effective in increasing the *cis*-to-*trans* ratio to 88:12.

In one run the diol product, obtained by the simultaneous addition of limonene and thexylborane to THF followed by oxidation, was distilled prior to conversion to

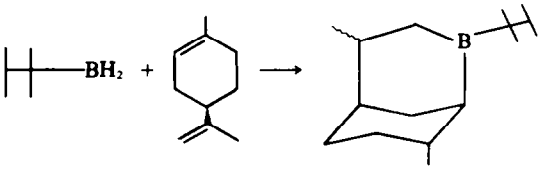
*For each of the two isomers there are two possible stereochemical arrangements around the C-8 carbon atom, as shown by **6a**, **6b**, **7a**, and **7b**.



6a **6b** **7a** **7b**

However, we have not observed such *cis* and *trans* pairs as separate peaks even on capillary GLPC columns.

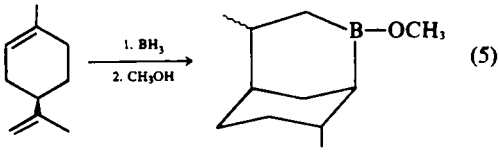
the diacetates. GLPC examination of the diacetates revealed the presence of the "*m-cis*" isomer (**6**) in 92% yield. The high *cis*-to-*trans* ratio observed with thexylborane must be a result of cyclic hydroboration. It then occurred to us that if the reaction were indeed highly cyclic, distillation of the organoborane intermediates might permit the isolation of B - thexyl - 4,8 - dimethyl - 2 - borabicyclo[3.3.1]nonane (**8**) (Eq. 4).



8 (4)

Indeed, distillation of the hydroboration mixture obtained by the addition of thexylborane to limonene produced essentially pure **8** in 72% yield, b.p. 88° (0·4 mm).*† As expected, oxidation of the distillate produced pure "*m*-cis"-diol (**6**) m.p. 92–92·5°; $[\alpha]^{26}D$ −60° (*c* 0·25 in THF and CCl_4 (1:3)).

When borane in THF was used as a hydroborating agent, distillation of the mixture was exceedingly sluggish and led to the isolation of many different fractions. On the other hand, distillation of the methanolyzed mixture was smoother and produced B - methoxy - 4,8 - dimethyl - 2 - borabicyclo[3.3.1]nonane (**9**) in 65 per cent yield, b.p. 92–94° (5 mm) (Eq. 5).



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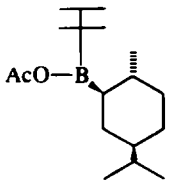
Oxidation of **9** provides an alternative route to pure "*m*-cis"-diol (**6**).

A stereoselective synthesis of D-(−)-(1R, 2R, 4R)-*carvomenthol from* D-(+)-*limonene* via *protonolysis-oxidation of B-thexyl-4,8-dimethyl-2-borabicyclo-*[3.3.1]*nonane.* The primary C–B bond of organoboranes is much more rapidly protonolyzed with carboxylic acids than is the secondary or tertiary C–B bond under identical reaction conditions.[7] Furthermore, each successive step in the protonolysis of a trialkylborane becomes increasingly difficult to achieve.† Consequently, protonolysis of either B - thexyl - 4,8 - dimethyl - 2 - borabicyclo[3.3.1]nonane (**8**) or the corresponding B-methoxy derivative (**9**) with acetic acid under suitable reaction conditions would selectively cleave the primary C-B bond of **8** or **9** to yield **10** or **11**, respectively. In either case, subsequent oxidation should lead to pure carvomenthol (**2**).

We selected a distilled sample of **8** as an intermediate. It was protonolyzed with acetic acid under various reaction conditions and then was oxidized *in situ* with alkaline hydrogen peroxide. The products were analyzed by GLPC on a capillary of Carbowax 20M.



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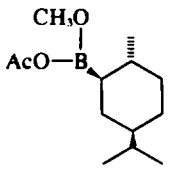

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The experimental results are summarized in Table 2.

In no case was the presence of D-(+)-isocarvomenthol detected. Adopting the most favorable conditions for protonolysis, D-(−)-(1R, 2R, 4R)-carvomenthol (**2**) was obtained in 83 per cent isolated yield, b.p. 85–88° (0·4 mm); $n^{20}D$ 1·4610; $[\alpha]^{33}D$ −23° (*c* 16 in CCl_4).

In conclusion D-(+)-limonene can be converted to the corresponding bicyclic organoborane intermediate by the cyclic hydroboration with borane in THF or thexylborane, followed by distillation. Oxidation of the bicyclic intermediate produces D-(−)-(1R, 2R, 4R)-limonene-2,9-diol, and protonolysis of the bicyclic intermediate followed by oxidation provides D-(−)-(1R, 2R, 4R)-carvomenthol. These results suggest that the cyclic hydroboration of dienes can provide a valuable means of controlling the exact cite of hydroboration, leading to a stereoselective synthesis of alcohols.

EXPERIMENTAL

Materials. D-(+)-limonene, obtained from Minute-Maid, was distilled from LAH, b.p. 55° (5 mm); $n^{20}D$ 1·4724; $[\alpha]^{20}D$ +118°. Diglyme (Ansul), THF (Mallinckrodt) and BF_3-etherate (Matheson) were purified by distillation as described previously.[8] The other materials used in the present study were used as purchased. The preparations of borane[8] and thexylborane[5b] solutions were carried out as described previously. The organoboranes were always handled under N_2 with careful exclusion of O_2 and moisture. PMR and IR spectra were obtained with a Varian A-60 and a Perkin-Elmer 21. Optical rotations were determined in a Carl Zeiss polarimeter. The b.ps and m.ps were uncorrected.

Hydroboration of D-(+)-*limonene*

(a) *Addition of borane in THF to* D-(+)-*limonene.* To a 200-ml 3-necked flask, fitted with a thermometer well, a magnetic stirring bar, a condenser, and a septum inlet, was placed a 33·3-ml THF soln containing 6·8 g (50 mmol) of D-(+)-limonene and 50 mmol of n-tetradecane. Borane (1·80 M, 27·8 ml, 50 mmol) in THF was added to the flask at a rate such that the reaction temp did not rise above 3°. After stirring the mixture for 3 hr at 0°, the residual hydride was destroyed with a 1:10 mixture of water and THF. Hydroboration of D-(+)-limonene by the addition of 1·5 and 3 molar equivs of borane in THF were carried out in the same manner except for the amount of borane in THF.

(b) *Addition of* D-(+)-*limonene to borane in THF.* This experiment was carried out in a manner similar to that described above except that a soln of D-(+)-limonene was added to borane in THF.

(c) *The simultaneous addition of borane in THF and* D-(+)-*limonene to THF.* A 33·3-ml THF soln containing 50 mmol of D-(+)-limonene and 50 mmol of n-tetradecane and 33·3 ml of 1·5 M borane‡ in THF were added simultaneously over 1 hr using a constant-speed syringe pump to 50 ml of THF at 0°. After the hydroboration was complete, the residual hydride was destroyed by the dropwise addition of 15 ml of a 1:10 mixture of water and THF. An experiment at 22° was carried out in a manner similar to that described above except that a dry ice-CCl_4 slush bath was used instead of an ice bath.

(d) *Addition of thexylborane to* D-(+)-*limonene.* This experiment was carried out in a manner similar to that described in (a) except

*The isolation and characterization of **8** was carried out by Dr. E. Negishi.

†An interesting application of **8** is its conversion to the corresponding trialkylborohydride for the stereoselective reduction of a prostaglandin intermediate.[6]

‡It is essential to lubricate the plunger of the syringe containing borane in THF with a lubricant (halogenated hydrocarbons recommended) in order to prevent freezing of the syringe.

that 40·7 ml (50 mmol) of 1·23 M thexylborane in THF was used instead of borane in THF.

(e) *Addition of* D-(+)-*limonene to thexylborane.* This experiment was carried out in a manner similar to that described above except that a solution of D-(+)-limonene was added to thexylborane in THF.

(f) *The simultaneous addition of* D-(+)-*limonene and thexylborane to THF.* This experiment was carried out in a manner similar to that described in (c) except that 40·7 ml of 1·23 M thexylborane in THF and 40·7 ml of a THF soln containing 50 mmol each of D-(+)-limonene and n-tetradecane were added simultaneously.

Oxidation of the hydroboration products. Oxidation of the limonene-borane reaction products (50 mmol scale) was carried out in the usual manner[7] using 18 ml each of 3 N NaOH and 30% H_2O_2. The limonene-thexylborane mixtures were more difficult to oxidize than the limonene-borane mixtures. Consequently, 6 N NaOH was used instead of 3 N NaOH and 18 ml EtOH was added as a co-solvent before the addition of 30% H_2O_2.[5b] After the oxidation, the aqueous phase was saturated with K_2CO_3 and extracted 3 times with THF. All organic fractions were combined and dried over $CaSO_4$.

Acetylation and GLPC *examination of the hydroboration mixture.* Each of the hydroboration mixtures (50 mmol scale) obtained above was evaporated. To this was added 110 mmol (10% excess) of Ac_2O and 1·5 ml pyridine. After fitting a condenser protected with a drying tube, the mixture was heated on a steam cone for 3 hr. The acetylated products were analyzed on a Perkin-Elmer 226 using a 150 ft × 0·01 in capillary column of polyphenyl ether. The results are summarized in Table 1.

Isolation of a mixture of limonene-2,9-diols obtained by the simultaneous addition of D-(+)-*limonene and thexylborane to THF.* Twenty milliliters each of 1·5 M D-(+)-limonene and thexylborane were simultaneously added to 50 ml of THF over 1 hr. After oxidation and the usual workup, distillation yielded a mixture of limonene-2,9-diols, b.p. 152–155° (4·8 mm). The mixture was acetylated and distilled to give a mixture of the corresponding diacetates, b.p. 143–145° (5 mm). Examination of the mixture of diacetates by GLPC revealed the presence of the diacetete of **6** in 92% along with a few other minor products.

Preparation of B-thexyl - 4,8 - dimethyl - 2 - borabicyclo[3.3.1]*nonane* (**8**).[7] A limonene-thexylborane mixture was obtained by the addition of 27·5 ml (50 mmol) of 1·82 M thexylborane to 6·81 g (50 mmol) D-(+)-limonene in 19 ml of THF at 0°. After evaporation of the volatile substances, distillation provided 8·4 g (72% yield) of the title substance, b.p. 88° (0·4 mm); PMR (CCl_4, TMS): a series of unresolved peaks between 0·6 and 2·2 ppm.

Preparation of B-methoxy - 4,8 - dimethyl - 2 - borabicyclo[3.3.1]*nonane* (**9**). A 1:1 limonene-borane mixture was obtained by the addition of 4·80 g (30·7 mmol) of D-(+)-limonene to 18·5 ml (34 mmol) of borane in THF at 0°. After stirring the mixture at 25° for 3 hr, 2·4 ml (60 mmol) of anhyd MeOH was added and the resultant mixture was distilled to produce 3·58 g (65%) of the title substance, b.p. 92–94° (5 mm); ppm (CCl_4, TMS): δ 3·66 (s, 3H), 2·2–0·3 (m, 18H); IR (neat): 7·4, 7·6 μ.(Found: C, 73·34; H, 12·00. Calc. for $C_{11}H_{21}BO$: C, 73·35; H, 11·75.

Preparation of D-(−)-(1R, 2R, 4R)-limonene-2,9-diol (**6**). Oxidation of 3·0 g (16·7 mmol) of B - methoxy - 4,8 - dimethyl - 2 - borabicyclo[3.3.1]nonane with 6 ml each of 3 N NaOH and 30% H_2O_2 lead to the isolation of 2·3 g (80%) of crude **6** which readily crystallized from ether to give 1·76 g of pure **6**, m.p. 92–92·5°; $[\alpha]^{26}D$ −60° (*c* 0·25 in THF and CCl_4 (1:3)); PMR (benzene and DMSO-d_6, TMS): δ 4·35 (m, 2H); 3·44 (m, 2H), 3·0 (m, 1H), 2·5–0·7 (m, 15H) ppm; IR (Nujol): 2·88, 9·6 μ. (Found: C, 69·60; H, 11·65. Calc. for $C_{10}H_{20}O_2$: C, 69·72; H, 11·70.

GLPC analysis after converting the diol product to the corresponding diacetate indicated that the product was essentially pure **6** uncontaminated with **7**. The identical compound was obtained by the oxidation of a distilled sample of **8**.

Treatment of D-(−)-(1R, 2R, 4R)-limonene-2,9-diol in pyridine with an equimolar quantity of *p*-toluenesulfonyl chloride at 0° followed by reduction of the monotosylate with LAH in THF led to an 85:15 mixture of D-(−)-(1R, 2R, 4R)-carvomenthol and *trans-p*-methan-9-ol. Neither isocarvomenthol nor *trans-p*-methane was detected.

Protonolysis of B-thexyl - 4,8 - dimethyl - 2 - borabicyclo[3.3.1]*nonane with acetic acid.* To 7·02 g (30 mmol) of B - thexyl - 4,8 - dimethyl - 2 - borabicyclo[3.3.1]nonane was added 30 ml of glacial AcOH. Protonolysis was effected under various reaction conditions (Table 2). After neutralizing the AcOH with 3 N NaOH, the mixture was oxidized with 30% H_2O_2. The oxidized mixture was extracted with ether and analyzed by GLPC on a capillary column (150 ft × 0·01 in) of Carbowax 20M. The results are summarized in Table 2.

Preparation of D-(−)-(1R, 2R, 4R)-*carvomenthol.* To 46·8 g (200 mmol) of B - thexyl - 4,8 - dimethyl - 2 - borabicyclo[3.3.1]nonane was added 200 ml (3.5 mol) of glacial AcOH. The mixture was heated at 110° for 12 hr, cooled to 0° and neutralized by the slow addition of 1·25 *l* (3·75 mol) of 3 N NaOH. Oxidation was effected by the slow dropwise addition of 75 ml of 30% H_2O_2 while maintaining the temp below 50°. When the initial reaction subsided, the mixture was maintained between 35 and 50° for 1 hr. After cooling, the mixture was repeatedly extracted with ether (total *ca.* 600 ml). The ether layer was washed with water and dried over $MgSO_4$. Distillation of the concentrated material provided 25·9 g (166 mmol, 83%) of D-(−)-(1R, 2R, 4R)-carvomenthol, b.p. 84–85° (0·4 mm); $n^{20}D$ 1·4609; $[\alpha]^{33}D$ −23° (*c* 16 in CCl_4). (lit.[9] b.p. 84–86° (0·3 mm); $n^{20}D$ 1·4613; $[\alpha]^{16}D$ −26°. The 3,5-dinitrobenzoate, m.p. 106–106·5° (lit.[10] m.p. 107°). GLPC examination of a sample of the mixture on a Perkin-Elmer 226 using a capillary column of Carbowax 20M (150 ft × 0·01 in) indicated the presence of 2% *trans-p*-methane. No D-(1S, 2S, 4R)-isocarvomenthol was present.

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REFERENCES

[1]For a preliminary report, see H. C. Brown and C. D. Pfaffenberger, *J. Am. Chem. Soc.* **89**, 5475 (1967). In this report the stereochemical representation for **6** was in error and is here corrected.

[2]Research Assistant on Grants No. 12-14-100-7152 (72) supported by the Southern Utilization Research and Development Division of the U.S. Department of Agriculture and GM 10937-05 supported by the National Institutes of health.

[3]H. C. Brown, *Hydroboration*, Benjamin, New York, N.Y., (1962).

[4a]W. F. Newhall, *J. Org. Chem.* **23**, 1274 (1958); [b]C. A. Brown and H. C. Brown, *J. Am. Chem. Soc.* **84**, 2829 (1962).

[5a]H. C. Brown, E. Negishi and P. L. Burke, *Ibid.* **94**, 3561 (1972); [b]H. C. Brown and E. Negishi, *Ibid.* **94**, 3567 (1972); [c]E. Negishi, P. L. Burke and H. C. Brown, *Ibid.* **94**, 7431 (1972); [d]P. L. Burke, E. Negishi and H. C. Brown, *Ibid.* **95**, 3654 (1973); [e]E. Negishi and H. C. Brown, *Ibid.* **95**, 6757 (1973).

[6]E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf and R. K. Varma, *Ibid.* **93**, 1491 (1971).

[7a]H. C. Brown and K. J. Murray, *Ibid.* **81**, 4108 (1959); [b]H. C. Brown and K. J. Murray, *J. Org. Chem.* **26**, 631 (1961); [c]K. J. Murray, Ph.D. Thesis, Purdue University (1961).

[8]G. Zweifel and H. C. Brown, *Org. React.* **13**, 1 (1963).

[9]J. Simonsen and L. N. Owen, *The Terpenes*, (2nd Edn) Vol. III, p. 515. Cambridge University Press, Cambridge (1951).

[10]E. E. Royals and J. C. Leffingwell, *J. Am. Chem. Soc.* **86**, 2067 (1964).