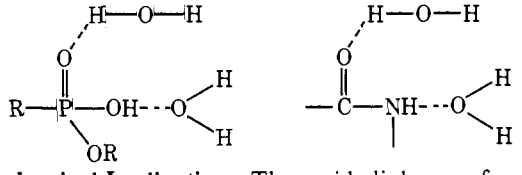
The monoacid and amide can also be solvated in parallel fashion, as shown below. These hypotheses have not been tested further in our case, but they do provide an explanation based on the assumption used in employing acidity functions.



Biochemical Implications. The amide linkages of proteins and peptides are widely distributed in organisms. These often exist in proximity to phosphate bonds of nucleotides. It is usually assumed that covalent interactions between the two types of functional groups do not occur. This assumption is obviously a necessary one and no experimental evidence to the contrary exists. However, our interest in the possibility of covalent interactions is related to the formation of transient "high-energy" intermediates in reactions involving formation or breakage of interphosphate bonds. Since it is unlikely that these can be observed directly, information on the facility of their occurrence and methods for trapping them need to be obtained. We have previously suggested[4] that conformational changes of proteins could be used to generate an interphosphate bond, if the change led to a situation which caused the peptide bond to become a reactive electrophile toward a phosphate, forming a phosphorylated peptide intermediate (analogous to that proposed in DCC-catalyzed dehydration), which would then transfer phosphate to form a new interphosphate bond. This can provide a chemical mechanism for oxidative phosphorylation via conformational coupling. In addition, other phosphate transfers could occur via this type of reactive intermediate.

References and Notes

(1) Supported by a grant from the National Research Council of Canada and, previously, at the University of Chicago, by a grant from the National Institute of Arthritis, Metabolism, and Digestive Diseases (AM15013).
(2) Author to whom inquiries should be addressed.
(3) Fellow of the Alfred P. Sloan Foundation.
(4) R. Kluger and J. L. W. Chan, *J. Am. Chem. Soc.*, **95**, 2362 (1973). See also ref 6 for related work by others.
(5) R. F. Hudson and L. Keay, *J. Chem. Soc.*, 2463 (1956).
(6) G. M. Steinberg, C. N. Lieske, R. Boldt, J. C. Goan, and H. E. Podall, *J. Med. Chem.*, **13**, 435 (1970).
(7) W. Wachter, *Ber.* **26**, 1744 (1893).
(8) J. B. Plumb and C. E. Griffin, *J. Org. Chem.*, **27**, 4711 (1962).
(9) L. P. Hammett and A. J. Deyrup, *J. Am. Chem. Soc.*, **54**, 2721 (1932).
(10) R. Kluger, P. Wasserstein, and K. Nakaoka, *J. Am. Chem. Soc.*, **97**, 4298 (1975).
(11) L. Zucker and L. P. Hammett, *J. Am. Chem. Soc.*, **61**, 2791 (1939).
(12) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).
(13) J. N. Bronsted, *Z. Phys. Chem.*, **102**, 169 (1922).
(14) K. Yates, J. B. Stevens, and A. R. Katritzky, *Can. J. Chem.*, **42**, 1957 (1964); K. Yates and J. C. Riordan, *ibid.*, **43**, 2328 (1965).
(15) J. I. G. Cadogan, D. Eastlick, F. Hampson, and R. K. Mackie, *J. Chem. Soc. B*, 144 (1969).
(16) M. L. Bender, "Homogeneous Catalysis from Protons to Proteins", Wiley, New York, N.Y., 1971, pp 147–193.
(17) A. J. Kirby and G. Meyer, *J. Chem. Soc., Perkin Trans. 2*, 1446 (1972).
(18) R. Kluger and J. L. W. Chan, *J. Am. Chem. Soc.*, **96**, 5637 (1974).
(19) F. H. Westheimer, *Acc. Chem. Res.*, **1**, 70 (1968).
(20) E. A. Dennis and F. H. Westheimer, *J. Am. Chem. Soc.*, **88**, 3432 (1966).
(21) R. A. McClelland, *J. Am. Chem. Soc.*, **97**, 3177 (1975).
(22) L. P. Hammett, "Physical Organic Chemistry", 2d ed, McGraw-Hill, New York, N.Y., 1970, p 275.

Hydroboration. 42. Cyclic Hydroboration of Representative Acyclic α,ω-Dienes with Monochloroborane Etherate

Herbert C. Brown* and Marek Zaidlewicz[1]

Contribution from the Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907.

Received December 22, 1975

Abstract: Hydroboration of representative acyclic α,ω-dienes, such as 1,4-pentadiene, 1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene, 1,6-heptadiene, 1,7-octadiene, and 1,13-tetradecadiene, with monochloroborane etherate has been examined in order to establish the utility of this reagent for cyclic hydroboration and to attain an understanding of the reaction processes involved in such cyclic hydroborations. The initial hydroboration product is partially polymeric in the case of 1,4-pentadiene and 1,5-hexadiene and essentially polymeric in the case of higher dienes. The polymeric products could be depolymerized in many cases by careful distillation and the desired cyclic *B*-chloroboracycloalkanes isolated in excellent yields. No extensive isomerization of the ring moiety was observed for products derived from C_5–C_7 dienes. Pure *B*-chloroborinane, *B*-chloroborepane, and *B*-chloro-3,6-dimethylborepane were readily isolated. A 75:10:15 mixture of *B*-chloroborocane, *B*-chloro-2-methylborepane, and *B*-chloro-2-ethylborinane was obtained from 1,6-heptadiene. Distillation of the *B*-chloroorganoboranes from 1,7-octadiene was accompanied by extensive isomerization leading to a mixture of substituted *B*-chloroborocane, *B*-chloroborepanes, and *B*-chloroborinanes. The *B*-chloroboracycloalkanes were transformed into *B*-methoxyboracycloalkanes which were in turn converted into cyclic ketones via the DCME reaction. Pure cycloheptanone, 3,6-dimethylcycloheptanone, and cyclooctanone were isolated from the reaction products derived from 1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene, and 1,6-heptadiene, respectively. Hydroboration of 1,7-octadiene under high dilution conditions followed by methanolysis and the DCME reaction gave 1,10-cyclooctadecanedione in 6% yield. Under the same conditions, 1,13-tetradecadiene produced cyclopentadecanone in 7% yield.

In recent years cyclic hydroboration of dienes has been actively investigated.[2-7] The conversion of the boron heterocycles thus produced into cyclic carbon structures by the carbonylation reaction opened promising new synthetic possibilities.[8-10] However, relatively few hydroborating agents have been explored for this reaction. Monosubstituted borane derivatives would appear to be best suited for the cyclic hydroboration of dienes. One such reagent, thexylborane, has proved to possess valuable characteristics in this area.[11] The low aptitude of the thexyl group for migration in carbonylation reaction made possible the syntheses of various cyclic and bicyclic ketones.[8]

Table I. GLC Examination of Oxidation Products Derived from Hydroboration Product (Undistilled *B*-Chloroorganoboranes)

Diene	Diol composition[a]	% (GLC)
1,4-Pentadiene	1,4-Pentanediol	43
	1,5-Pentanediol	57
1,5-Hexadiene	2,5-Hexanediol	1
	1,5-Hexanediol	6
	1,6-Hexanediol	93
2,5-Diethyl-1,5-hexadiene	2,5-Dimethyl-1,6-hexanediol	99
1,6-Heptadiene	1,6-Heptanediol	2
	1,7-Heptanediol	98
1,7-Octadiene	1,7-Octanediol	1
	1,8-Octanediol	99

[a] Analyzed as trimethylsilyl ethers on 7-ft column 5% SE-30 on Varaport.

Table II. GLC Examination of *B*-Methoxyorganoboranes Derived from the Methanolysis of the Undistilled Hydroboration Products of Dienes and Monochloroborane[a]

Diene	Yield of volatile products, %	Composition[b]	% (GLC)
1,4-Pentadiene	31.3	*B*-Methoxy-2-methylborolane	44.0
		B-Methoxyborinane	56.0
1,5-Hexadiene	24.4	*B*-Methoxy-2,5-dimethylborolane	2.5
		B-Methoxy-2-methylborinane	12.3
		B-Methoxyborepane	85.2
1,6-Heptadiene	3.0	*B*-Methoxy-2-methylborepane	43–45[c]
		B-Methoxyborocane	55–57[c]
1,7-Octadiene	0		

[a] Diene was hydroborated by addition of the diene to monochloroborane in ether, followed by methanolysis of the reaction product at 0 °C. [b] Analyzed on 2-ft 5% SE-30/Varaport 30 column. [c] Not completely separated.

The procedure suffers, however, from the fact that the carbonylation of such cyclic thexyl derivatives frequently requires both high pressures and elevated temperatures, conditions that are undesirable for the more labile structures.[12] Cyanidation of organoboranes offers one means around this difficulty.[13] Esters of borinic acids offer another highly promising solution. Such esters are transformed under exceptionally mild conditions by α,α'-dichloromethyl methyl ether (DCME) and lithium triethylcarboxide into an intermediate which can readily be oxidized to the corresponding ketones.[14] Clearly, a convenient procedure for the preparation of cyclic borinic acid esters would be helpful. Monochloroborane ethyl etherate appeared to offer promise for this objective: (a) it is readily prepared;[15a,16] (b) it shows high regioselectivity in hydroboration of terminal olefins;[15b,16] and (c) dialkylchloroboranes are readily methanolyzed to the corresponding borinic acid methyl esters.[16]

Preliminary observations on the reaction of monochloroborane etherate with 1,4-pentadiene and 1,5-hexadiene appeared promising.[17] Consequently, we undertook a systematic study of the reaction of monochloroborane–ethyl etherate with representative acyclic α,ω-dienes.

Results and Discussion

In the present study the hydroboration of dienes was generally carried out by the addition of the diene to an equimolar quantity of monochloroborane in ether at 0 °C. The reagents were approximately 1 M except in those cases where precipitation of a polymer made it desirable to utilize more dilute conditions. At appropriate intervals of time the reaction mixture was examined for the completion of the reaction by analysis of aliquots for residual hydride.

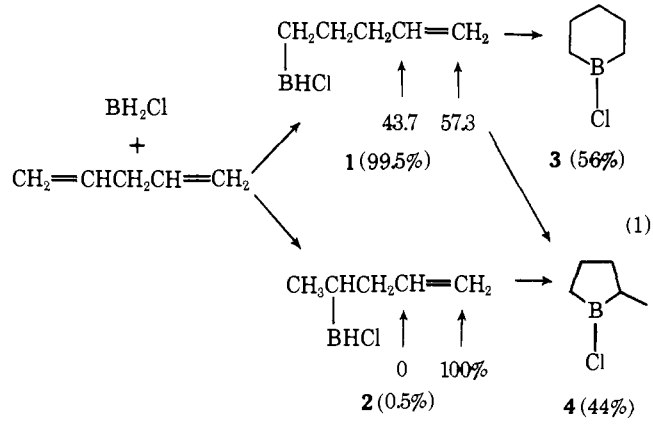
Initially the *B*-chloroboracycloalkanes, presumably formed as the reaction products, were isolated by distillation. However, it was observed that much of the initial reaction product was polymeric, depolymerizing into the desired *B*-chloroboracycloalkanes during distillation. Accordingly, the procedure was revised to permit a detailed examination of the *B*-chloroorganoboranes formed in the reaction both before and after distillation.

The following standard procedure for examination of the reaction products was adopted. (A) An aliquot of the initial hydroboration product was oxidized with alkaline hydrogen peroxide[10] and the oxidation products (diols) examined by GLC (Table I). (B) An aliquot of the reaction mixture was methanolyzed with excess methanol and examined by GLC for the volatile *B*-methoxyboracycloalkanes present, using conditions in the GLC analysis which would not cause depolymerization of the polymeric product (Table II). (C) The *B*-chloroorganoborane product was distilled under conditions favorable for depolymerization, and the *B*-chloroboracycloalkanes were isolated and characterized (Table III). (D) The *B*-chloroboracycloalkanes were converted into the *B*-methoxyboracycloalkanes by methanolysis, and these were isolated and characterized (Table IV). (E) Finally, the *B*-methoxyboracycloalkanes were converted into the corresponding ketones by the DCME reaction (Table V).

These results permit the formulation of a reasonably complete picture as to the precise course of the hydroboration of such α,ω-dienes with chloroborane.

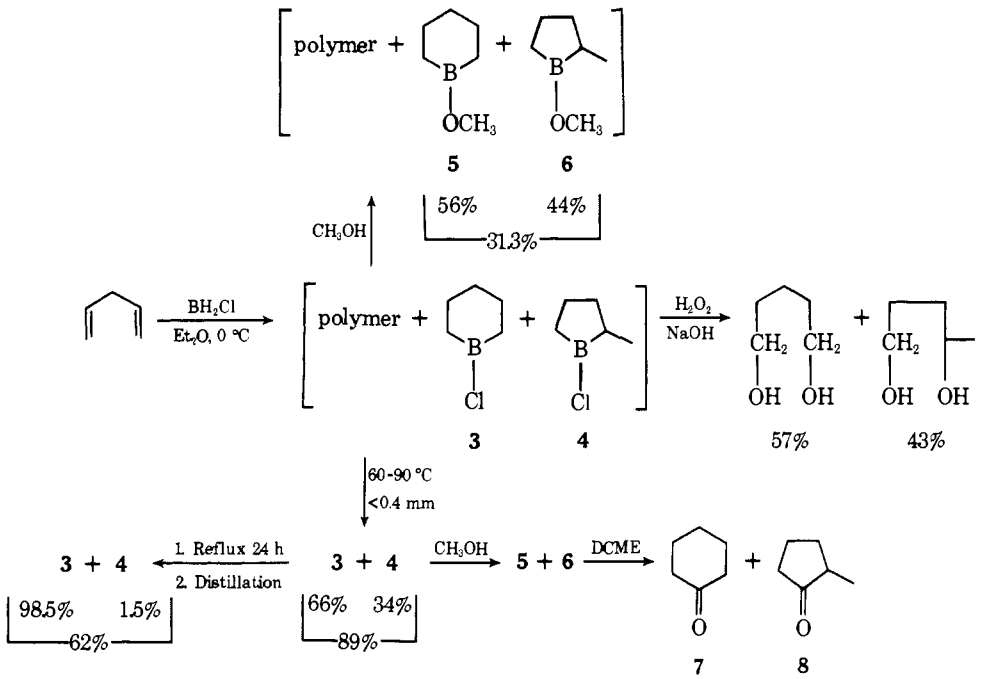
1,4-Pentadiene. Hydroboration of 1,4-pentadiene was carried out by addition of the diene to a 1 M solution of monochloroborane in ether at 0 °C. After 2 h, the reaction was complete and a clear solution of *B*-chloroorganoboranes was obtained. Oxidation of an aliquot of the reaction mixture and GLC analysis revealed a 57:43 mixture of 1,5- and 1,4-pentanediols (Table I). The same ratio of both diols was realized after methanolysis and oxidation of the *B*-methoxyorganoboranes. This indicates that no isomerization occurs in the methanolysis step. GLC analysis of the *B*-methoxyorganoboranes showed 31.3% of volatile material which was identified as a 56:44 mixture of *B*-methoxyborinane (**5**) and *B*-methoxy-2-methylborolane (**6**) (Table II).

In an earlier study, it was established that monochloroborane in ether is a highly regioselective reagent that hydroborates terminal olefins to place 99.5% of the boron at the ter-



(1)

Scheme I



minal position.[15b,16] Assuming that the first step in the hydroboration of 1,4-pentadiene is not significantly influenced by the second double bond and proceeds with the same regioselectivity as for a terminal olefin, a 99.5:0.5 mixture of intermediates **1** and **2** should be formed (eq 1). The effect of **2** on product distribution may be considered as negligible. In order to account for the observed 56:44 distribution of **3** and **4**, 43.7% of **1** must cyclize to form **4**. There must be a strong preference for five-membered ring formation, which offsets the usual directive effect of substituted chloroborane.

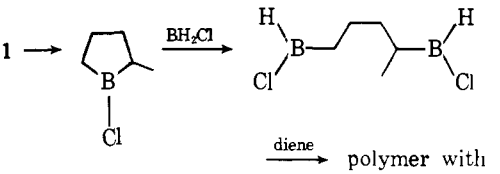
We are now faced with a problem. Had the reaction product been the monomeric **3** and **4**, we could have readily accounted for the results in terms of a competitive cyclization of the intermediate **1** to form **3** and **4**. Alternatively, had the reaction product been polymeric **3** and monomeric **4**, we could have readily accounted for the results in terms of a reaction of **1** with chloroborane to form polymeric **3** competing with a cyclic hydroboration of **2** to produce **4**.

However, the reaction product is 31% monomeric **3** and **4** and 69% polymeric **3** and **4**. Moreover, both monomer and polymer contain the five- and six-membered ring moieties in approximately the same amounts.

Thus the polymeric material was readily transformed into the monomeric *B*-chloroboracycloalkanes in 89% yield by heating under vacuum at 60–90 °C. GLC examination of the oxidation products from this distilled material showed a 66:34 mixture of 1,5- and 1,4-pentanediols. Methanolysis of the *B*-chloroboracycloalkanes followed by the DCME reaction[11] gave a 70:30 mixture of cyclohexanone (**7**) and 2-methylcyclopentanone (**8**) (Scheme I).

We can only conclude that polymerization of initially formed *B*-chlorocycloalkanes must occur in the course of the hydroboration stage. We have previously observed that the borolane ring is exceptionally sensitive to rupture by borane.[2] Possibly, the same type of reaction occurs here. In eq 2 is shown a possible reaction sequence which provides a reasonable explanation for the results. The results are summarized in Tables III, IV, and V.

The mixture of monomeric **3** and **4** was heated under reflux at atmospheric pressure in an attempt to convert **4** into **3** by thermal isomerization. At appropriate intervals of time, an aliquot was withdrawn and oxidized, and the oxidation products were analyzed by GLC. The results are presented in Table



(2)

VI. Prolonged heating caused partial polymerization of the *B*-chloroboracycloalkanes. Distillation after 24 h reflux gave a 62% yield of a 98.5:1.5 mixture of **3** and **4**. After 60 h reflux, only 34% of 99% pure **3** was obtained. It appears that both **3** and **4** undergo polymerization during reflux, **4** at a more rapid rate than **3**.

1,5-Hexadiene. Hydroboration of 1,5-hexadiene was carried out as described for 1,4-pentadiene. GLC examination of the oxidation products indicated the presence of 1,6-, 1,5-, and 2,5-hexanediols in a ratio of 93:6:1 (Table I). Methanolysis and GLC examination of the *B*-methoxyorganoboranes (Table II) revealed 24.4% of volatile material composed of *B*-methoxyborepane (**9**), *B*-methoxy-2-methylborinane (**10**), and *B*-methoxy-2,5-dimethylborolane (**11**) in a ratio of 85.2:12.3:2.5. These results indicate that 1,5-hexadiene gives somewhat less of the monomeric species than 1,4-pentadiene. Hydroboration at the terminal position is greatly increased. Clearly, cyclization to a six-membered ring does not possess the driving force indicated by the cyclization to the five-membered ring in **1**.

Depolymerization was somewhat slower and required somewhat higher temperatures than in the previous case. Therefore, distillation-depolymerization was carried out at 130–150 °C. The monomeric *B*-chloroboracycloalkanes were collected in 92.6% yield. GLC examination of oxidation products showed a 91.3:7.4:1.3 mixture of the 1,6-, 1,5-, and 2,5-hexanediols (Table III). Methanolysis of the distilled *B*-chloroboracycloalkanes (Table IV) followed by the DCME reaction produced a 90.5:9.5 mixture of cycloheptanone (**15**) and 2-methylcyclohexanone (**16**) (Table V). 2,5-Dimethylcyclopentanone was not detected among the reaction products.

In order to isolate pure *B*-chloroborepane (**12**), the distilled mixture of **12, 13,** and **14** was fractionated under vacuum. **13** and **14** were separated in the first fractions. However, after 3

Table III. Distillation of the Hydroboration Products Derived from Dienes and Monochloroborane[a]

Diene	Distillation–depolymerization temperature,[b] °C	*B*-Chloroorganoboranes Yield,[c] %	*B*-Chloroorganoboranes Bp, °C (mm)	Diol distribution[d]	% (GLC)
1,4-Pentadiene	60–90	89	45–58 (80)	1,4-Pentanediol	34
				1,5-Pentanediol	66
1,5-Hexadiene	130–150	92.6	56–58 (30)	2,5-Hexanediol	1.3
				1,5-Hexanediol	7.4
				1,6-Hexanediol	91.3
2,5-Dimethyl-1,5-hexadiene	60	87	70–72 (15)	2,5-Dimethyl-1,6-hexanediol	
1,6-Heptadiene	200–250	91	66–68 (18)	1,5-Heptanediol	15
				1,6-Heptanediol	10
				1,7-Heptanediol	75
1,7-Octadiene	300	77	68–70 (10)	2,5-Octanediol	4
				2,6-Octanediol	8
				1,4-Octanediol	6
				1,5-Octanediol	66
				1,6-Octanediol	12
				1,7-Octanediol	3
				1,8-Octanediol	1

[a] The hydroboration was carried out by the addition of diene to an equimolar quantity of monochloroborane in ether at 0 °C. [b] Bath temperature. [c] Isolated by distillation. [d] Diols silylated and trimethylsilyl ethers analyzed on a 7-ft 5% SE-30/Varaport 30 column.

Table IV. Characterization of Distilled *B*-Methoxyboracycloalkanes[a]

Diene	*B*-Methoxyorganoborane Yield,[b] %	*B*-Methoxyorganoborane Bp, °C (mm)	Diol distribution[c]	% (GLC)
1,4-Pentadiene	84	50–52 (40)	1,4-Pentanediol	33.5
			1,5-Pentanediol	66.5
1,5-Hexadiene	86	70–72 (35)	2,5-Hexanediol	1.0
			1,5-Hexanediol	7.0
			1,6-Hexanediol	92.0
2,5-Dimethyl-1,5-hexadiene	97	78 (18)[d]	2,5-Dimethyl-1,6-hexanediol[e]	98.0
1,6-Heptadiene	90	62–66 (15)	1,5-Heptanediol	16.0
			1,6-Heptanediol	10.0
			1,7-Heptanediol	74.0
1,7-Octadiene	97	74–76 (10)	2,5-Octanediol	4.0
			2,6-Octanediol	8.0
			1,4-Octanediol	5.0
			1,5-Octanediol	67.0
			1,6-Octanediol	13.0
			1,7-Octanediol	2.0
			1,8-Octanediol	1.0

[a] Distilled *B*-chloroboracyclanes derived from dienes and monochloroborane were methanolyzed in ether at 0 °C. [b] Isolated by distillation. [c] Analyzed as trimethylsilyl ether on a 7-ft 5% SE-30/Varaport 30 column. [d] Mass spectrum *m/e* 154, 153 (M^+); ^1H NMR (CCl_4, Me_4Si) τ 6.42 (s, 3 H), 7.8–8.9 (m, 6 H), 8.9–9.4 (m, 10 H). [e] Bp 102–103 °C (0.5 mm), $n^{20}D$ 1.4569.

Table V. Cycloalkanones Derived from Distilled *B*-Methoxyboracycloalkanes by DCME Reaction

Diene	Cycloalkanones Yield, %	Cycloalkanones Composition	% (GLC)
1,4-Pentadiene	82[a]	2-Methylcyclopentanone	30.0
		Cyclohexanone	70.0
1,5-Hexadiene	74[b]	2-Methylcyclohexanone	9.5
		Cycloheptanone	90.5
2,5-Dimethyl-1,5-hexadiene	86[b]	3,6-Dimethylcycloheptanone[c]	
1,6-Heptadiene	70[b]	2-Ethylcyclohexanone	17.0
		2-Methylcycloheptanone	13.0
		Cyclooctanone	70.0
1,7-Octadiene	63[b]	2-Propylcyclohexanone[d]	64–65

[a] GLC, 12-ft 5% NGA/Varaport 30 column. [b] Isolated by distillation. [c] Bp 92–94 °C (15 mm). Purified by preparative GLC 20% SE-30/Chromosorb W, $n^{20}D$ 1.4569, ir 1695 cm^{-1}, ^1H NMR (CCl_4, Me_4Si) τ 7.2–8.6 (m, 10 H), 1.05 (d, 6 H, J = 6 Hz). [d] Seven ketones only partially separated.

h of distillation, the material in the distillation flask became viscous, and no more volatile product could be collected. Apparently **12** partially polymerizes when heated at 80 °C (bath temperature). Depolymerization at 130–150 °C was fast and gave 99% pure **12** in 44% yield. The high purity of this product indicates that no isomerization takes place in the depolymer-

Table VI. Thermal Isomerization of a Mixture of *B*-Chloroborinane and *B*-Chloro-2-methylborolane. GLC Examination of the Oxidation Products

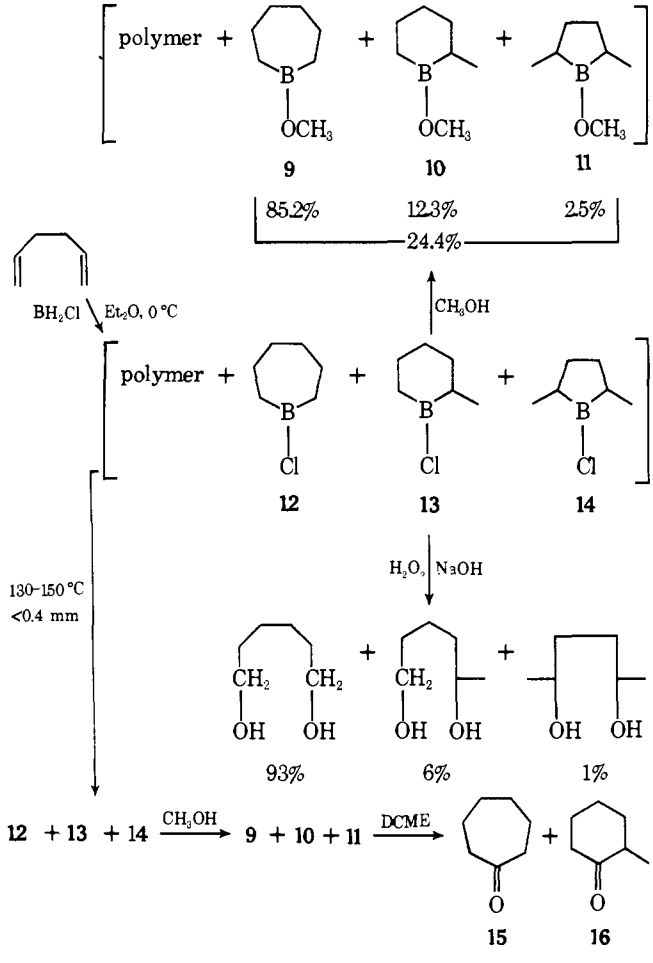
Reflux in h[a]	% of pentanediols[b]	
	1,4-	1,5-
0	31.0	69.0
12	12.0	78.0
24	7.5 (1.3)[c]	92.5 (98.7)[c]
36	6.7	93.3
48	6.3	93.7
60	5.8 (1)[c]	94.2 (99)[c]

[a] Under normal pressure. [b] Analyzed as the trimethylsilyl ether on a 7 ft × ⅛ in. column packed with 5% SE-30/Varaport 30. [c] *B*-Chloroboracycloalkanes distilled.

ization step. Methanolysis of **12** followed by the DCME reaction gave cycloheptanone in 78% yield.

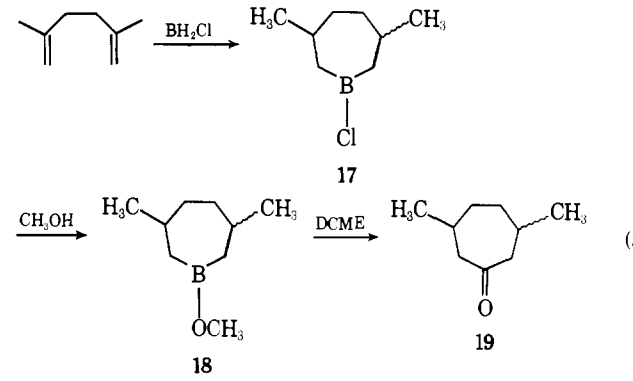
The various transformations are summarized in Scheme II.

Scheme II



2,5-Dimethyl-1,5-hexadiene. The hydroboration mixture derived from 2,5-dimethyl-1,5-hexadiene was distilled under 0.4 mm pressure while the bath temperature was maintained at 60 °C. No polymeric material was observed, and *B*-chloro-3,6-dimethylborepane (**17**) was isolated in 87% yield (Table III). GLC examination of the oxidation product showed 98% of 2,5-dimethyl-1,6-hexanediol. Methanolysis (Table IV) of **17** gave *B*-methoxy-3,6-dimethylborepane (**18**) which was transformed into 3,6-dimethylcycloheptanone (**19**) by the DCME reaction (Table V). The structure of **19** was confirmed by ir and ^{1}H NMR. No attempt was made to separate the cis and trans isomers, presumably present.

These transformations are summarized by the following equation:



(3)

Evidently there is little tendency to form polymeric products in this system, either during the hydroboration reaction or during a subsequent reaction of the reagent with the *B*-chloroboracycloalkane structure, as postulated in (3). It would be of considerable interest to understand the precise basis for the differences in the behavior of 1,5-hexadiene and 2,5-dimethyl-1,5-hexadiene.

1,6-Heptadiene. Hydroboration of 1,6-heptadiene was carried out using a more dilute (0.5 M) solution of BH_2Cl in order to avoid precipitation of polymeric *B*-chloroorganoboranes. GLC examination of the methanolyzed reaction mixture revealed only 3% of volatile material (Table II). This suggests that the hydroboration of 1,6-heptadiene under the conditions employed is essentially polymeric. The GLC examination of the oxidation products revealed a 2:98 mixture of 1,6- and 1,7-heptanediols (Table I).

Depolymerization of the *B*-chloroorganoborane product was achieved by heating under 0.4 mm at 200–250 °C. At this temperature, the breakdown of polymeric material was fast, and monomeric product was obtained in 91% yield (Table III).

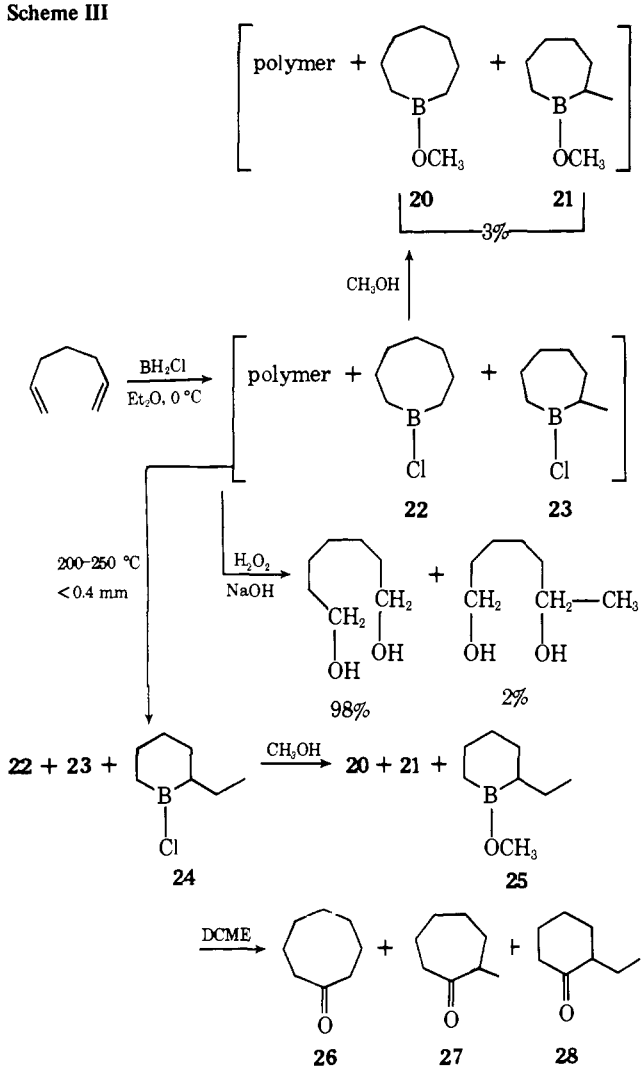
GLC examination of the oxidation products from the depolymerized material showed a 75:10:15 mixture of 1,7-, 1,6-, and 1,5-heptanediols. This mixture of *B*-chloroboracycloalkanes was methanolyzed (Table IV) and converted into ketones by the DCME reaction (Table V). A mixture of cyclooctanone (**26**), 2-methylcycloheptanone (**27**), and 2-ethylcyclohexanone (**28**) (70:13:17) was obtained. Cyclooctanone was separated and identified (GLC, ir, ^{1}H NMR) by comparison with an authentic sample. These results demonstrate that the polymeric *B*-chloroorganoboranes formed in the hydroboration of 1,6-heptadiene largely contain the 1,7-diboraheptane moiety. Depolymerization yields preferentially the eight-membered boron heterocycle, *B*-chloroborocane (**22**), with smaller amounts of ring contracted products, *B*-chloro-2-methylborepane (**23**), and *B*-chloro-2-ethylborinane (**24**).

The transformations are summarized in Scheme III.

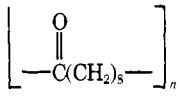
Formation of the eight-membered boron heterocycle **22** is highly interesting. In many earlier studies[2,18,19] only five-, six-, and seven-membered boron heterocycles were reported. This study is the first demonstration that a medium ring containing boron can survive distillation without extensive isomerization. Its further conversion into cyclooctanone by the DCME reaction provides a direct entry via hydroboration into the cyclooctane ring system from an acyclic precursor.

1,7-Octadiene. Hydroboration of 1,7-octadiene under the conditions described above results in the precipitation of a gelatinous material. This precipitation could be avoided by using even less concentrated (0.2–0.3 M) solutions of monochloroborane. GLC examination of the oxidation products showed the presence of 1,8- and 1,7-octanediol in a ratio of 99:1. GLC examination of the methanolyzed hydroboration mixture revealed the absence of any volatile material (Table

Scheme III



II). Application of the DCME reaction to the reaction product produced an amorphous material with a broad melting point range, 110–120 °C, mol wt 2272, ir 1700 cm^{-1}. These data, the ^1H NMR spectrum, and the elementary analysis suggest a polymeric ketone



The hydroboration product was heated under vacuum in an attempt to depolymerize the *B*-chloroorganoboranes. The reaction was very slow at 200–250 °C and required several hours. At 300 °C the breakdown of polymer was fast and monomeric *B*-chloroorganoboranes were obtained in 77% yield. GLC analysis of oxidation products revealed a mixture composed of several octanediols (Table III). Methanolysis (Table IV) and the DCME reaction (Table V) gave a mixture of ketones. 2-Propylcyclohexanone (**29**) was identified by GLC as a major component (64–65%).

These transformations are summarized in Scheme IV.

These results indicate that hydroboration of 1,7-octadiene under the standard conditions employed gives essentially polymeric *B*-chloroorganoboranes. These undergo an extensive isomerization in the depolymerization step.

It appeared to us that formation of monomeric (not isomerized) products might be facilitated by carrying the hydroboration reaction under high dilution conditions. Thus equimolar amounts of diene and monochloroborane were introduced simultaneously to ether at 0 °C over 4 h. The reaction product was methanolyzed, and the *B*-methoxyorganoboranes were transformed into ketones by the DCME reaction. GLC examination of the reaction product did not show cyclononanone. However, a compound with much longer retention time was observed. The compound was isolated by distillation in the Kügelrohr apparatus, purified by crystallization, and identified (ir, ^1H NMR, mol wt, elementary analysis) as 1,10-cyclooctadecanedione (**31**), mp 96–97 °C, yield 6% based on 1,7-octadiene (eq 4).

1,13-Tetradecadiene. Hydroboration of 1,13-tetradecadiene was carried out under high dilution conditions. Methanolysis of the reaction product, followed by the DCME reaction and GLC analysis of the products, revealed cyclopentadecanone (**33**) as the only volatile material. It was obtained in a yield of 7% (eq 5). The ketone was isolated by distillation and purified by preparative GLC, mp 60–62 °C, not depressed when mixed with an authentic sample. It showed identical ir and ^1H NMR spectra with the authentic sample.

Conclusion

The hydroboration of acyclic α,ω-dienes (C_5–C_7) gives cyclic *B*-chloroorganoboranes in addition to polymeric products. These polymers can be easily converted to monomers by distillation. Consequently, *B*-chloroboracycloalkanes with six- to eight-membered rings can be obtained in good yield. The mixtures of isomers which are formed can be separated either by fractionation or by conversion into more thermodynamically stable isomer by thermal isomerization. Thus, *B*-chloroborinane, *B*-chloroborepane, and *B*-chloro-3,6-dimethylborepane were obtained in high purity and satisfactory yield. The synthesis of *B*-chloroborocane is of special interest since this medium ring boron heterocycle has not been characterized previously, either using other hydroborating agents or by various thermal transformations of organoboranes.[18]

On the other hand, hydroboration of 1,7-octadiene under standard conditions gave exclusively polymeric products. Depolymerization of this material, although producing *B*-chloroboracycloalkanes, is accompanied with extensive isomerization leading to a mixture of substituted *B*-chloroborolanes, *B*-chloroborinanes, and *B*-chloroborepanes; the desired *B*-chloroboronane was not detected.

However, under high dilution conditions, 1,7-octadiene produced an 18-membered boron heterocycle **30**. 1,13-Tetradecadiene under the same conditions gave a 15-membered ring derivative **32**. These large ring boron heterocycles were not isolated. Instead they were directly converted into ketones under mild conditions using DCME reaction. The yields of these large ring ketones were low; however, no effort has been made in the present study to optimize the reaction conditions. Hopefully with a more detailed study of the hydroboration reaction leading to such large rings, it will prove possible to increase the yields and to develop this reaction into a valuable route to large rings.

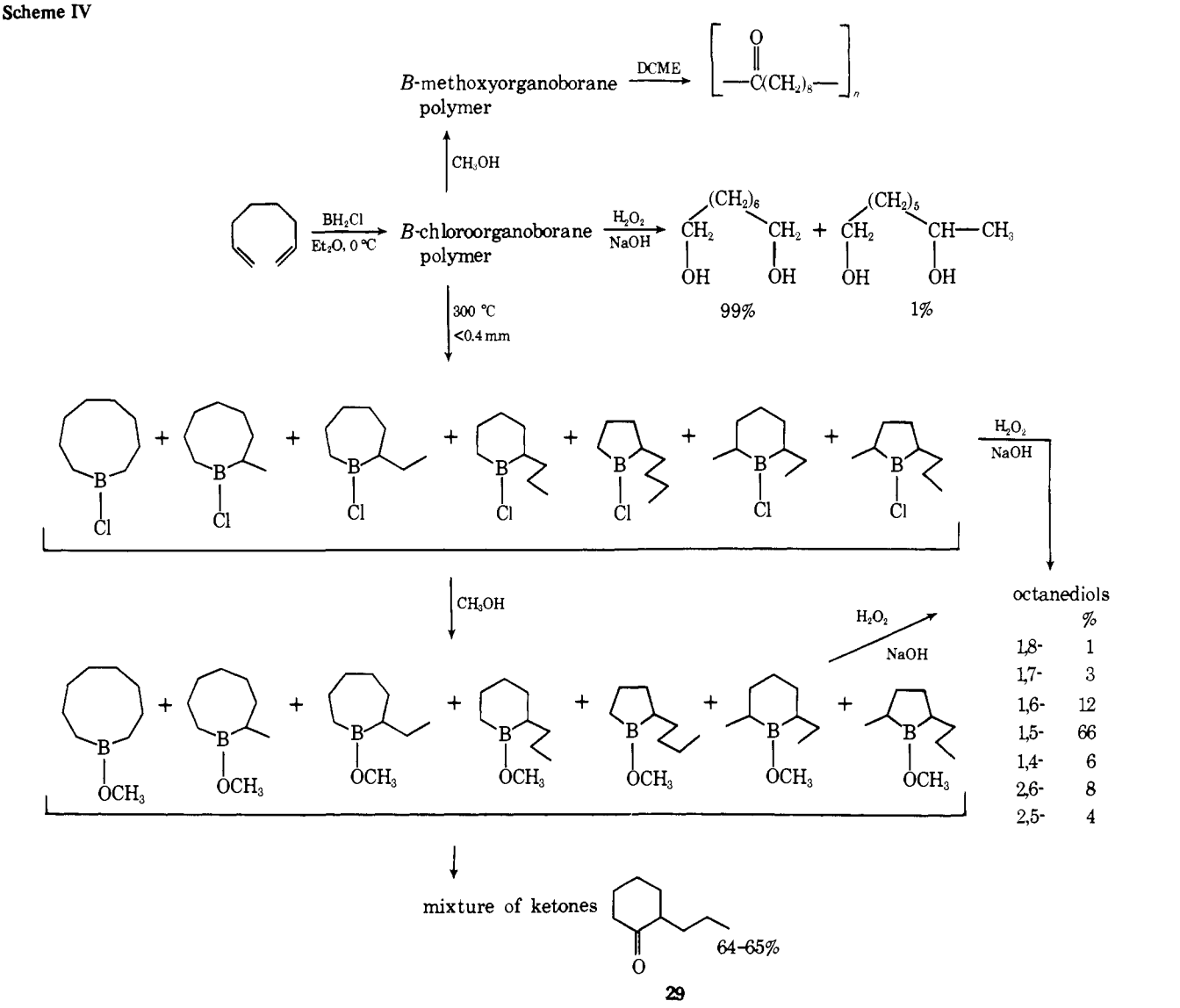
Finally, monochloroborane has proved to be a valuable hydroborating agent for the cyclic hydroboration of dienes to produce *B*-chloroboracycloalkanes in the six- to eight-membered ring range.

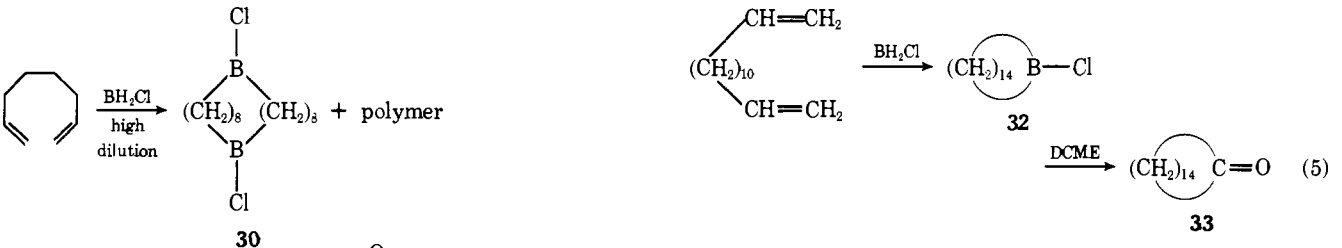
Experimental Section

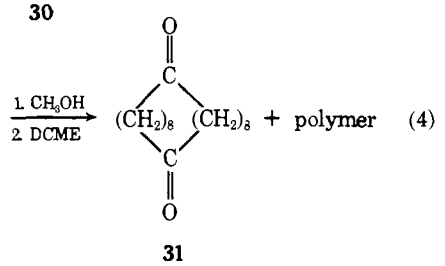
Materials. The preparation of monochloroborane solution in ether was carried out as described previously.[10,15a,16] Dienes were obtained from commercial sources and distilled from a small quantity of lithium aluminum hydride before use. *n*-Alkanes and cycloalkanones were employed as internal standards and were used as supplied. Comparison samples of diols and organoboranes were either available in this laboratory or prepared by standard methods. The organoboranes were always handled under nitrogen.

Ir spectra were determined using the Perkin-Elmer Model 137B

Scheme IV







spectrophotometer. ^{1}H NMR spectra were measured using the Varian T-60 instrument.

Oxidation of Organoboranes. Oxidation of organoboranes was carried out with alkaline hydrogen peroxide, as described previously.[10,20]

GLC Analysis. (a) Oxidation Products (Diols). Penta-, hexa-, hepta-, and octanediols were converted into the trimethylsilyl ethers prior to analysis. Thus a sample of diol was treated with BSA (Pierce Chemical Co.). The mixture was left for 0.5 h at room temperature and then heated at 50 °C for 15 min. Trimethylsilyl ethers were analyzed on a 7 ft × ⅛ in. column containing 5% SE-30 on Varaport 30, using *n*-alkanes as internal standards.

(b) Organoboranes. GLC examination of *B*-methoxyorganoboranes was carried out on a Varian 1400 chromatograph provided with a 2 ft × ⅛ in. column containing 5% SE-30 on Varaport 30. The column was pretreated with 100 μl of Silyl-8 (Pierce Chemical Co.) and 10 μl of distilled *B*-methoxyborinane at 120 °C. The injection port and column temperature was kept at 50 or 70 °C, depending on the material analyzed, to avoid depolymerization. *n*-Alkanes were used as internal standards. The GLC response ratios of *B*-methoxyorganoboranes were determined using distilled products. The same response ratios were assumed for isomeric products.

A. Examination of Primary Hydroboration Products (*B*-Chloroorganoboranes Not Distilled). General Procedures. (a) Hydroboration of Dienes. A solution of diene (10 mmol) in 10 ml of ether was introduced to ca. 1 M solution of BH_2Cl (10 mmol) in ether at 0 °C. After 2 h of stirring the reaction was essentially complete, as indicated by active hydride analysis.

(b) **Oxidation.** An aliquot of the reaction mixture was oxidized using 3 M NaOH/30% H_2O_2. Oxidation products were converted into trimethylsilyl ethers and analyzed by GLC. The results are presented in Table I.

(c) **Methanolysis.** Methanol (20% excess, except for 1,4-pentadiene where the stoichiometric amount was used) was added to a solution of *B*-chloroorganoboranes prepared as described in (a). The mixture was stirred at 0 °C for 2 h. Solvent and excess of methanol were removed under reduced pressure at room temperature. Ether was added to make the solution ca. 1 M, followed by an internal standard (*n*-alkane). The monomeric *B*-methoxyorganoboranes were analyzed by GLC (note precaution described under GLC analysis of organoboranes). The results are presented in Table II.

Hydroboration–DCME Reaction of Dienes. (a) 1,7-Octadiene. The diene (4.84 g, 44 mmol) was introduced to a stirred solution of 1.1 M BH_2Cl (40 ml, 44 mmol) in 150 ml of ether at 0 °C. After stirring the solution for 1 h, 2 ml (44 mmol + 10% excess) of methanol was added and the stirring was continued for 2 h at 0 °C. THF (80 ml) was added and about 150 ml of solvent was removed. α,α'-Dichloromethyl methyl ether (4.4 ml) was introduced followed with 62.8 ml of 1.41 *M* lithium triethylcarboxide. After stirring the solution for 2 h at room temperature 20 ml of EtOH (95%) was added, and the organoborane was oxidized with 4 g of NaOH and 15 ml of 30% H_2O_2 at 50 °C for 1 h. Salt was added, and the solution was decanted from solid salts which were washed with THF. Solutions were combined, solvents and triethylcarbinol were removed, and the residue was refluxed with ether. A pale yellow solid material which was obtained (5.95 g) was dissolved in chloroform. The solution was filtered and added to a fivefold excess (by volume) of ether. A white precipitate which was collected was dissolved in hot ethanol. An amorphous material precipitated after cooling to room temperature. It was filtered off and kept under vacuum for several days. The substance had a broad melting point range, 110–120 °C.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.97; H, 11.60; mol wt (cryoscopic), 2272. Ir ($CHCl_3$) 1700 cm^{-1}, ^1H NMR ($CDCl_3$, Me_4Si) τ 7.6 (t, J = 6 Hz), 8.2–8.9 (m). Integration t/m 1:4.

(b) **1,10-Cyclooctadecanedione (31).** A solution of 1,7-octadiene (1.1 g, 10 mmol) in 50 ml of ether and a solution of BH_2Cl (10 mmol) in 50 ml of ether were introduced into 300 ml of ether at 0 °C over 4 h. The solution was stirred for 1 h after the addition had been completed. Methanol (0.5 ml, 20% excess) was added and stirring was continued for 1 h at 0 °C. Ether was removed at room temperature. When about 20 ml of solution was left, the flask was immersed in an ice bath and 1 ml of α,α'-dichloromethyl methyl ether was added followed with 20 ml of THF and 10.4 ml (20 mmol) of a 1.92 M solution of lithium triethylcarboxide. The mixture was stirred at room temperature for 1 h. Ethanol (5 ml) was added, followed by 0.8 g of solid sodium hydroxide and 3 ml of 30% H_2O_2. Oxidation was carried out at 50–60 °C for 1 h. The organic solution was decanted and the solid salts washed with THF. Solvents and triethylcarbinol were removed. For isolation, the product from 25 mmol of 1,7-octadiene was used. Distillation under 0.05 mm in Kügelrohr apparatus gave 0.5 g of a volatile material and a polymeric residue. Redistillation and crystallization from methanol gave 0.21 g, 6% yield, of 1,10-cyclooctadecanedione, mp 96–97 °C [lit.[21] 96–97 °C].

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 77.07; H, 11.51. Ir (CS_2) 1720 cm^{-1}, ^1H NMR ($CDCl_3$, Me_4Si) τ 7.6 (t, 8 H, J = 6 Hz), 8.0–9.0 (m, 24 H), mol wt (cryoscopic) 279.1, mass spectrum *m/e* 280 (M^+).

(c) **Cyclopentadecanone (33).** 1,13-Tetradecadiene was hydroborated with monochloroborane following the procedure described above. Cyclopentadecanone was obtained in 7% yield (GLC 7 ft × ⅛ in. 5% Carbowax 20M/Varaport 30 column, cyclododecanone was used as an internal standard). The ketone was separated from polymeric materials by distillation and purified by preparative GLC (20% SE-30 on Chromosorb W), mp 60–62 °C [lit.[22] 63 °C].

Anal. Calcd for $C_{15}H_{28}O$:C, 80.29; H, 12.58. Found: C, 80.51; H, 12.38. Ir and ^1H NMR spectra were identical with an original sample.

B. Examination of Distilled *B*-Chloroorganoboranes. (a) *B*-Chloroorganoboranes. General Procedures. Dienes were hydroborated with monochloroborane in 1:1 ratio as described above. Solvent was removed under reduced pressure at room temperature. Material which was left was distilled-depolymerized by heating under 0.4 mm. Volatile material was collected in a flask immersed in dry ice–methanol bath. *B*-Chloroorganoboranes were redistilled and analyzed by oxidation with NaOH–H_2O_2. The results are presented in Table III.

Table VII. Fractional Distillation of the Product from Hydroboration of 1,5-Hexadiene. GLC examination of the Oxidation Products

	% of pentanediols		
	2,5-	1,5-	1,6-
Fraction 1	11.6	19.2	69.2
Fraction 2	1.0	11.0	80
Fraction 3	1.0	10.0	89.0
Fraction 4		1.0	99.0

(b) ***B*-Chloroborinane (3).** A 31:69 mixture (10.5 g) of **3** and **4** obtained by distillation of hydroboration product of 1,4-pentadiene was refluxed under normal pressure for 24 h. Distillation gave 6.5 g (62%) of 98.5% pure *B*-chloroborinane, bp 64 °C (95 mm). GLC analysis of oxidation product showed a 1.5:98.5 mixture of 1,4- and 1,5-pentanediols.

(c) **B-Chloroborepane (12).** A 91.3:7.4:1.3 mixture (29.5 g) of **12, 13,** and **14** obtained by hydroboration of 1,5-hexadiene and distillation of the reaction product was fractionated under 25 mm. After 3 h distillation, three fractions, (1) 3.5 g, bp 45–52 °C, (2) 8.8 g, bp 52 °C, (3) 1.7 g, bp 52–53 °C, were collected. Material in the distillation flask became viscous, and further distillation required raising the bath temperature to 130–150 °C. At that temperature, distillation was fast, and 99% pure *B*-chloroborepane (13.1 g, 44%), bp 52–53 °C, was collected. GLC examination of oxidation products is presented in Table VII.

(d) ***B*-Methoxyorganoboranes.** Ca. 1 M solution of *B*-chloroorganoborane in ether was treated with 100% excess of methanol at 0 °C. After 2 h, solvent and excess methanol were removed, and the products were isolated by distillation. The results are presented in Table IV.

(e) **DCME Reaction.** α,α'-Dichloromethyl methyl ether (1 ml, 5% excess) was added to a stirred solution of *B*-methoxyorganoboranes (10 mmol) in 10 ml of THF at 0 °C, followed by ca. 2 M solution of lithium triethylcarboxide (20 mmol) in hexane. The mixture was allowed to warm up to room temperature and stirring was continued for 1 h. A heavy white precipitate was formed. Ethanol (5 ml) was added, followed with 0.8 g of solid sodium hydroxide and 3 ml of 30% H_2O_2. Oxidation was carried out at 50–60 °C for 1 h. Internal standard was added, and the mixture was analyzed by GLC. The results are presented in Table V.

(f) **Cyclooctanone.** A mixture (2.7 g, 19 mmol) of *B*-chloroorganoboranes obtained by hydroboration of 1,6-heptadiene and distillation of the reaction products was methanolyzed (1 ml of CH_3OH). *B*-Methoxyorganoboranes were transformed without isolation into ketones by the DCME reaction following the procedure described above. GLC analysis showed a 17:13:70 mixture (70% yield) of 2-ethylcyclohexanone, 2-methylcycloheptanone, and cyclooctanone. Cyclooctanone was isolated by preparative GLC using 20% SE-30 on Chromosorb W column, mp 39–42 °C not depressed when mixed with an authentic sample. Ir and ^1H NMR spectra wre identical with authentic material.

Cycloheptanone (15). Cycloheptanone was obtained in 78% (GLC yield) starting from 1.3 g (10 mmol) of *B*-chloroborepane [fraction 4, (c)] following procedures (d) and (e) described above. The ketone was isolated and identified (GLC, ir, ^1H NMR) by comparison with an authentic sample.

References and Notes

(1) Postdoctorate Research Associate on Grant GM 10937 provided by the National Institutes of Health.
(2) H. C. Brown, E. Negishi, and P. L. Burke, *J. Am. Chem. Soc.*, **94**, 3561 (1972).
(3) H. C. Brown and E. Negishi, *J. Am. Chem. Soc.*, **94**, 3567 (1972).
(4) E. Negishi, P. L. Burke, and H. C. Brown, *J. Am. Chem. Soc.*, **94**, 7431 (1972).
(5) P. L. Burke, E. Negishi, and H. C. Brown, *J. Am. Chem. Soc.*, **95**, 3654 (1973).
(6) E. Negishi and H. C. Brown, *J. Am. Chem. Soc.*, **95**, 6757 (1973).
(7) H. C. Brown, E. F. Knights, and C. G. Scouten, *J. Am. Chem. Soc.*, **96**, 7765 (1974).

(8) H. C. Brown, *Acc. Chem. Res.*, **2**, 65 (1969).
(9) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972.
(10) H. C. Brown, G. W. Kramer, A. B. Levy, and M. M. Midland, "Organic Syntheses via Boranes", Wiley-Interscience, New York, N.Y., 1975.
(11) E. Negishi and H. C. Brown, *Synthesis*, 77 (1974).
(12) H. C. Brown and E. Negishi, *J. Am. Chem. Soc.*, **89**, 5285 (1967).
(13) A. Pelter, K. Smith, M. G. Hutchings, and K. Rowe, *J. Chem. Soc., Perkin Trans. 1*, 129 (1975).
(14) B. A. Carlson and H. C. Brown, *J. Am. Chem. Soc.*, **95**, 6876 (1973).
(15) (a) H. C. Brown and N. Ravindran, *J. Am. Chem. Soc.*, **94**, 2112 (1972); (b) H. C. Brown and N. Ravindran, *J. Org. Chem.*, **38**, 182 (1973).
(16) H. C. Brown and N. Ravindran, *J. Am. Chem. Soc.*, **98**, 1785 (1976).
(17) T. A. Shehegoleva, G. M. Shashkova, V. G. Kisielev, and B. M. Mikhailov, *Izv. Akad. Nauk SSSR*, 365 (1964).
(18) R. Köster, G. Griasnow, W. Larbig, and P. Binger, *Justus Liebigs Ann. Chem.*, **672**, 1 (1964).
(19) R. Köster, *Prog. Boron Chem.*, **1**, 289 (1964).
(20) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).
(21) L. Ruzicka, W. Brugger, C. F. Seidl, and H. Schinz, *Helv. Chim. Acta*, **11**, 496 (1928).
(22) L. Ruzicka, M. Stoll, and H. Schinz, *Helv. Chim. Acta*, **9**, 249 (1926).

Selective γ Alkylation of Dienolate Anions Derived from α,β-Unsaturated Acids. Applications to the Synthesis of Isoprenoid Olefins[1]

John A. Katzenellenbogen* and Ann L. Crumrine

Contribution from the Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801. *Received November 20, 1975*

Abstract: Lithium dienolates derived from α,β-unsaturated carbonyl compounds generally undergo alkylation reactions nearly exclusively at the α (rather than the γ) carbon. Changing the counterion from lithium to copper(I), however, has a remarkable effect on the alkylation regioselectivity of these dienolates. A systematic investigation has been made of the reaction of dienolates derived from (*Z*)- and (*E*)-3-methyl-2-hexenoic (**2a** and **3a**) and crotonic (**4a**), senecioic (**5a**), tiglic (**6a**), and angelic (**7a**) acids with a variety of allylic electrophiles. The lithium dianions all undergo exclusive α alkylation, but the dicopper dianions undergo γ-selective alkyation (62–99%). (Lower γ selectivities were found in a previous study of the corresponding esters.[16]) The γ-substituted products of the acids **4a, 6a,** and **7a** were exclusively of the *E* geometry, while 50% and 81% *Z* isomers were found with the acids **5a** and **2a,** respectively. Allylic electrophiles that are unsubstituted at the γ carbon react with the copper dienolates mainly in an SN2′ fashion, giving products in which the allylic portion has been transposed. Those electrophiles that are γ disubstituted react exclusively by direct (SN2) displacement, but those with only one substituent undergo a mixture of SN2 and SN2′ attack. The γ-selective alkylation of copper dienolates can be used as a convenient prenologation process in natural product synthesis. Farnesoic acid has been synthesized from geranyl bromide, and *dl*-lanceol, from an allylic bromide derived from limonene.

Conceptually, one of the simplest approaches to the synthesis of isoprenoid 1,5-polyolefins[2] is the conjoining of two allylic units containing the appropriate olefinic stereochemistry. The biosynthetic condensation of isopentenyl pyrophosphate with an allylic pyrophosate is, in fact, just such a transformation. In terms of laboratory synthesis, however, this approach is fraught with difficulties. If the reaction involves the attack upon an allylic electrophile by an allylic nucleophile, there is positional ambiguity at both reaction centers, as allylic nucleophiles have ambident character,[3] and allylic electrophiles can undergo SN2 or SN2′ attack.[4] Furthermore, the olefinic stereochemistry of the nucleophile is subject to ready isomer equilibration,[5] and the geometric integrity of the electrophile is not certain. When the coupling is radical in nature (Wurtz type[6]) or does not proceed via clearly identifiable electrophiles and nucleophiles (promoted by nickel,[7] titanium,[8] or other metals[9]), additional complications arise in terms of the possibilities for symmetrical vs. unsymmetrical coupling. Solutions to these problems have taken various forms.

We have found that the crossed nature of a Wurtz-type coupling can, in some cases, be improved by the selective generation of an allylic organolithium reagent by reacting allylic mesitoates with lithium metal in tetrahydrofuran, with subsequent coupling to an allylic bromide present in situ.[10] Although the yields of cross-coupled products from this procedure are reasonably high, positional and double-bond isomers of the mesitoate-derived allylic portion (nucleophile) are still produced.

Approaches using a charge-stabilized allylic organometallic reagent,[11,12] generated, for example, from an allylic sufide or phosphonium salt, have been more successful; these reagents can be made to alkylate predominantly at the charge-stabilized site, the final 1,5-diene being generated by reductive cleavage of the sulfide or phosphonium substituent. Although they have not been investigated in depth, the stereochemistry of the anion-derived unit seems to be preserved in the coupling, and double-bond transposition is not a serious problem during the reductive cleavage.

A very different approach to allylic–allylic coupling utilizes [3,3] sigmatropic rearrangements. The Claisen rearrangement,[13] particularly the vinyl acetal modification of Johnson,[13b] has been applied widely to the construction of trisubstituted olefinic systems in a stereoselective fashion; this reaction, however, as well as the related Carroll rearrangement of allylic esters,[14] requires a subsequent series of steps to convert the ketonic or ester products into 1,5-polyenes. The ingenious Claisen–Cope rearrangement of Thomas[15] provides an efficient synthesis of isoprenoid 1,5-dienes.

Although some of the above methods are attractive in terms of their stereoselectivity, many of them suffer from two basic disadvantages. First, the rearrangement reactions are only highly stereoselective when the isoprenoid chain is being constructed in a head-to-tail direction. Second, these and some of the other methods do not produce a product diene that is functionalized in an optimal manner; often several subsequent steps are required in order to transform it into a "natural" type of functionalization.[13a-c]