Table I. Reactions of Ketone Diperoxides

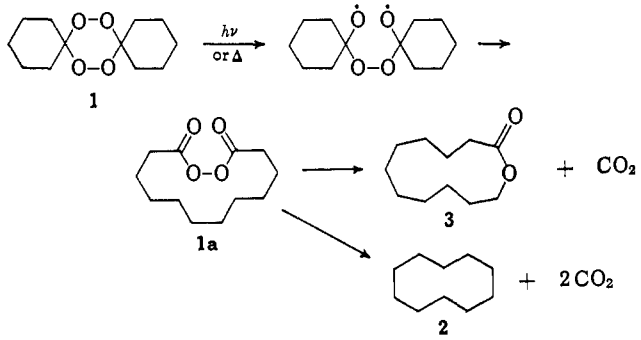
Diperoxide	Method	Products	Yields, %	Regenerated ketone, %
Cyclohexanone[1,7]	*hν*	Cyclodecane	14	20
	Δ		44	21
	hν	11-Undecanolactone	9	
	Δ		23	
Cycloheptanone[7]	*hν*	Cyclododecane	32	24
	Δ		22	33
	hν	13-Tridecanolactone	7	
	Δ		<1	
Cyclododecanone[7]	Δ	Cyclodocosane	20	9
		23-Tricosanolactone	11	

Table II. Reactions of Ketone Triperoxides

Triperoxide	Method	Products	Yields, %	Regenerated ketone, %
Cyclopentanone[a]	Δ	Cyclododecane	20	24
		13-Tridecanolactone	2	
Cyclohexanone[b]	*hν*	Cyclopentadecane	15	20
	Δ		16	15
	hν	16-Hexadecanolactone	25	
	Δ		<1	

[a] W. Dilthey, M. Inckel, and H. Stephan, *J. Prakt. Chem.*, **154**, 219 (1940).

peroxides[8] and ozonides.[9] For example, we have shown that ozonides on photolysis or thermolysis undergo a double β scission following homolysis of the oxygen–oxygen bond. β Scission to produce alkyl radicals is followed by a very efficient cage recombination to form a new carbon–carbon bond. We envision peroxides reacting in similar fashion. Such a reaction path leads to formation of an intermediate acyl peroxide (**1a**). The cyclic hydrocarbon presumably results from homolytic decomposition[10] of **1a** followed by loss of 2

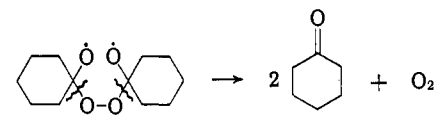


moles of carbon dioxide and cage recombination of the resulting alkyl radicals.

The observation of lactone in the thermal reactions is probably understandable in terms of a carboxy inversion reaction.[11] It may prove possible to reduce or eliminate lactone formation in the photochemical reaction by the use of sensitizers.[10]

(8) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley and Sons, Inc., New York, N. Y., 1966, pp 443–450.
(9) P. R. Story, W. H. Morrison, III, T. K. Hall, J. Farine, and C. E. Bishop, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 11–16, 1967, Abstract S-30; to be published.
(10) C. Walling and M. J. Gibian, *J. Am. Chem. Soc.*, **87**, 3413 (1965), and references cited therein.
(11) F. D. Greene, H. P. Stein, C.-C. Chu, and F. M. Vane, *ibid.*, **86**, 2080 (1964); C. Walling and Z. Cekovic, *ibid.*, **89**, 6681 (1967).

The regeneration of ketone from both the photolysis and thermolysis of peroxides is viewed most simply as a double β scission of carbon–oxygen bonds to generate oxygen (probably singlet) and two molecules of ketone.



Because of the ready availability of the starting materials and the simplicity of the reactions, the procedure described here now constitutes the most generally useful synthesis of macrocyclic systems. In particular, this promises to be the most convenient and inexpensive method for preparation of a wide variety of musk compounds used in perfumes.[12] In fact, some of the lactones described in this communication, particularly dihydroambrettolide (**6**), are important musk compounds. Application of this synthesis to particular substituted macrocyclic compounds such as muscone is in progress. *A priori*, this synthesis also appears applicable to the preparation of oxygen-containing macrocycles (ethers) such as 11-oxa-16-hexadecanolactone[13] *via* γ-pyrone peroxides. In addition to the synthesis of musk compounds, the method appears to hold considerable promise for the preparation of very large ring systems. Ultimately the reaction may find application in the synthesis of antibiotic macrolides.

Acknowledgment. We thank the Public Health Service, National Center for Air Pollution Control, for partial support of this work through Grant AP00580-01.

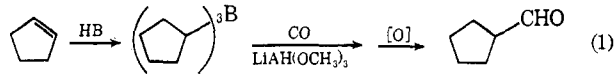
(12) P. Z. Bedoukian, *Am. Perfumer Cosmet.*, **80**, 23 (1965); P. Z. Bedoukian, "Perfumery Synthetics and Isolates," D. Van Nostrand, Co., Inc., New York, N. Y. 1951.
(13) W. Berends, *Am. Perfumer Cosmet.*, **80**, 35 (1965).

Paul R. Story, Donald D. Denson, Clyde E. Bishop, B. C. Clark, Jr., Jean-Claude Farine
Department of Chemistry, The University of Georgia, Athens, Georgia 30601
Received December 20, 1967

Reaction of Organoboranes with Ethyl Bromoacetate under the Influence of Potassium *t*-Butoxide. A Convenient Procedure for the Conversion of Olefins into Esters *via* Hydroboration

Sir:

The reaction of organoboranes with carbon monoxide in the presence of alkali metal borohydrides[1] or of lithium trimethoxyaluminohydride[2] provides a convenient method for a one-carbon-atom homologation, providing a simple route for the synthesis of aldehydes from the corresponding olefins (1). Similarly, the



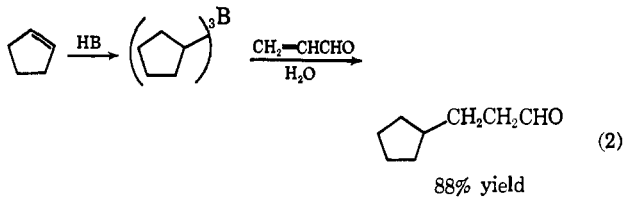
(1)

95% yield

reaction of trialkylboranes with acrolein provides a convenient procedure for the three-carbon-atom

(1) M. W. Rathke and H. C. Brown, *J. Am. Chem. Soc.*, **89**, 2740 (1967).
(2) H. C. Brown, R. A. Coleman, and M. W. Rathke, *ibid.*, **90**, 499 (1968).

homologation of the alkyl group, also providing the aldehydes as products[3] (2).



(2)

88% yield

We now wish to report that organoboranes react with amazing rapidity at 0° with ethyl bromoacetate under the influence of potassium *t*-butoxide to provide in excellent yield the corresponding ester as product, involving a two-carbon-atom homologation[4] (3).

$$R_3B \xrightarrow[t\text{-BuOK},\ t\text{-BuOH}]{BrCH_2CO_2C_2H_5} RCH_2CO_2C_2H_5 \qquad (3)$$

Consequently, it is now possible, by remarkably simple procedures, to achieve the synthesis in excellent yields of functional derivatives, involving one-, two-, or three-carbon-atom homologations, from olefins *via* hydroboration.

The present reaction is exceedingly simple. The olefin is converted into the organoborane in tetrahydrofuran at 0° by the addition of the calculated quantity of diborane in tetrahydrofuran. An equimolar quantity of ethyl bromoacetate is added, followed by the addition of an equimolar quantity of potassium *t*-butoxide in *t*-butyl alcohol. The reaction is exceedingly rapid. As far as we could ascertain, the reaction was over immediately following completion of the addition.

The reaction appears to be of wide generality, as indicated by our examination of the applicability of the synthesis to the usual representative olefin types (4–11). High yields were realized[5] (glpc analysis).

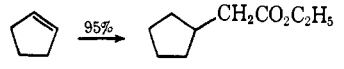
$$CH_2{=}CH_2 \xrightarrow{98\%} CH_3CH_2CH_2CO_2C_2H_5 \qquad (4)$$

$$CH_3CH_2CH{=}CH_2 \xrightarrow{93\%} CH_3(CH_2)_4CO_2C_2H_5 \qquad (5)$$

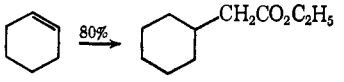
$$CH_3CH{=}CHCH_3 \xrightarrow{80\%} CH_3CH_2CH(CH_3)CH_2CO_2C_2H_5 \qquad (6)$$

$$(CH_3)_2C{=}CH_2 \xrightarrow{98\%} (CH_3)_2CHCH_2CH_2CO_2C_2H_5 \qquad (7)$$

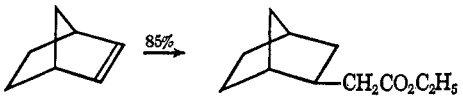
$$CH_3(CH_2)_3CH{=}CH_2 \xrightarrow{93\%} CH_3(CH_2)_6CO_2C_2H_5 \qquad (8)$$



(9)



(10)



(11)

(3) H. C. Brown, M. M. Rogic, M. W. Rathke, and G. W. Kabalka, *J. Am. Chem. Soc.*, **89**, 5709 (1967).

(4) An alternative route to such functionally homologated derivatives is provided by the reaction of organoboranes with suitable ylides, such as ethyl (dimethylsulfuranylidene)acetate, as recently reported by J. J. Tufariello, L. T. C. Lee, and P. Wojkowski, *ibid.*, **89**, 6804 (1967). Attention is also called to the two-carbon atom homologation of olefins *via* hydroboration (cyclohexene → vinylcyclohexane) recently described by G. Zweifel, H. Arzoumanian, and C. C. Whitney, *ibid.*, **89**, 3652 (1967).

(5) It should be pointed out that, as in the related one- and three-carbon atom homologations,[1-3] only one of the three alkyl groups of the organoborane is utilized. Fortunately, we have found a means of circumventing this difficulty for the carbonylation reaction,[2] and we are exploring means of circumventing it in the other cases.

In the case of the organoborane from 1-butene (eq 5), the product contained 95% ethyl hexanoate and 5% ethyl 3-methylpentanoate. Since hydroboration of 1-butene produces 94% 1-butyl and 6% 2-butyl groups, it is evident that this reaction, in contrast to the acrolein reaction,[3] exhibits little selectivity between primary and secondary alkyl groups.

Ethyl chloroacetate can also be used. However, the reaction involving this derivative appears to be somewhat slower and provides slightly lower yields. Consequently, we concentrated our study on the application of the bromoacetate.

The following procedure is representative. A dry 500-ml flask equipped with a septum inlet, thermometer well, pressure-equalizing dropping funnel, and magnetic stirrer was flushed with nitrogen and then maintained under a static pressure of the gas. The flask was charged with 50 ml of tetrahydrofuran and 13.3 ml (150 mmoles) of cyclopentene, and then cooled in an ice bath. Conversion to tricyclopentylborane was achieved by dropwise addition of 25 ml of a 2.00 *M* solution of borane (150 mmoles of hydride) in tetrahydrofuran. The solution was stirred for 1 hr at 25° and again cooled in an ice bath, and 25 ml of dry *t*-butyl alcohol was added, followed by 5.5 ml (50 mmoles) of ethyl bromoacetate. Potassium *t*-butoxide in *t*-butyl alcohol (50 ml of a 1.00 *M* solution) was added over a period of 10 min. There was an immediate precipitate of potassium bromide. Glpc analysis of the reaction mixture, following addition of *n*-octane as internal standard, indicated a 95% yield of ethyl cyclopentylacetate. The reaction mixture was filtered from the potassium bromide and distilled. There was obtained 5.85 g (75% yield) of ethyl cyclopentylacetate, bp 101° (30 mm), n^{20}D 1.4398, ir spectrum identical with literature spectrum.

Although we have not yet undertaken a detailed study of the mechanism, it is probable that the reaction involves the steps in Scheme I: (a) formation of the carbanion from the ester; (b) coordination of the carbanion with the trialkylborane; (c) rapid rearrangement of the intermediate;[6] (d) protonolysis of the organoboron derivative.

Scheme I

(a) $t\text{-BuO}^-\text{K}^+ + \text{H}_2\text{CBrCO}_2\text{Et} \longrightarrow \text{K}^+\ ^-\text{HCBrCO}_2\text{Et} + t\text{-BuOH}$

(b) $\text{R}_3\text{B} + \text{K}^+\ ^-\text{HCBrCO}_2\text{Et} \longrightarrow \text{K}^+\ ^-[\text{R}_3\text{BCHBrCO}_2\text{Et}]$

(c) $\text{K}^+\ ^-[\text{R}_3\text{BCHBrCO}_2\text{Et}] \longrightarrow \text{K}^+\ ^-[\text{R}_2\text{BrBCHRCO}_2\text{Et}] \downarrow \text{KBr} + \text{R}_2\text{BCHRCO}_2\text{Et}$

(d) $\text{R}_2\text{BCHRCO}_2\text{Et} + t\text{-BOH} \longrightarrow \text{RCH}_2\text{CO}_2\text{Et} + t\text{-BuOBR}_2$

The carbonylation[1,2] and acrolein[3] homologation reactions produce the corresponding aldehydes. It would be somewhat more elegant to have a two-carbon-atom homologation reaction which also provides the aldehyde, rather than the ester, as described in the present development. We are actively exploring this possibility. Even more important is the promise, suggested by the mechanism in Scheme I, that it may prove

(6) The facile migration of alkyl substituents from boron to the α carbon in α-halo substituted organoboranes has been previously noted: D. J. Pasto and J. L. Miesel, *J. Am. Chem. Soc.*, **85**, 2118 (1963); D. S. Matteson and R. W. H. Mah, *ibid.*, **85**, 2599 (1963); G. Zweifel and H. Arzoumanian, *ibid.*, **89**, 5086 (1967).

possible to utilize organoboranes for alkylations of a wide variety of α-halo-substituted carbanions. Moreover, the mechanism also suggests that such alkylations should proceed with retention of the stereochemistry at the migrating center, opening up major new synthetic opportunities. This question is under examination.

(7) National Science Foundation Postdoctorate Fellow at Purdue University, 1967–1968.

(8) Graduate research assistant on Grant GM 10937 from the National Institutes of Health.

Herbert C. Brown, Milorad M. Rogić
Michael W. Rathke,[7] George W. Kabalka[8]
Richard B. Wetherill Laboratory
Purdue University, Lafayette, Indiana 47907
Received December 26, 1967

The Role of Substrate Structure in the Initiation of Enzymic Cyclization of Squalene 2,3-Oxide. Studies with 2,3-*cis*-1′-Norsqualene 2,3-Oxide and 2,3-*trans*-1′-Norsqualene 2,3-Oxide

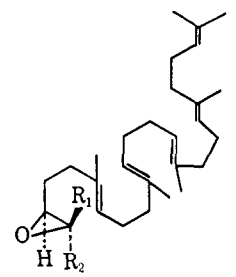
Sir:

Squalene 2,3-oxide (I) is cyclized to lanosterol (II) by a microsomal enzyme system of mammalian liver,[1–4] and squalene 2,3-oxide analogs, modified in the terminal[5,6] and more central[7] portions of the molecule, are also cyclized by this enzyme system. Structural modifications of the squalene 2,3-oxide molecule in the proximity of the oxide ring should exert strong electronic and steric effects upon the initiation of enzymic cyclization. Exploration of these effects may elucidate features of enzyme–substrate interaction that govern this initial phase of cyclization. We have therefore subjected 2,3-*cis*- and 2,3-*trans*-1′-norsqualene 2,3-oxides (IIIa,b) to the action of the cyclase system and have found that only the 2,3-*trans*-oxide IIIb yields a 4-desmethyllanosterol analog (4α,14α-dimethyl-$\Delta^{8,24}$-cholestadien-3β-ol, IV).

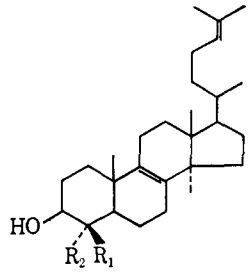
2,3-*cis*- and 2,3-*trans*-1′-norsqualene 2,3-oxides (IIIa and IIIb) were prepared from [4-^{3}H]1,1′,2-trisnorsqualene-3-carboxaldehyde[8] by reaction with diethylsulfonium ethylide.[9] The more mobile *trans* isomer was separated from the *cis* by repeated continuous tlc[10] on silica gel with 3% EtOAc–hexane for 2.5 hr. IIIa and IIIb, with $HClO_4$–H_2O, gave the corresponding glycols Va and Vb which afforded the corresponding pure acetonides VIa and VIb. These, unlike the oxides, were stable on glpc[11] on columns of Carbowax, with R_c 1.71 (VIa) and 2.03 (VIb).

The *cis* and *trans* structures of IIIa and IIIb were established by hydrogenation to the corresponding perhydro oxides and conversion to *cis*- and *trans*-alkenes VIIa and VIIb, respectively.[12] These separated on glpc (SE-30) by a factor, *cis*:*trans* = 1.06. The *trans*-alkene VIIb showed a characteristic strong band at 965 cm^{-1} which was absent in VIIa.

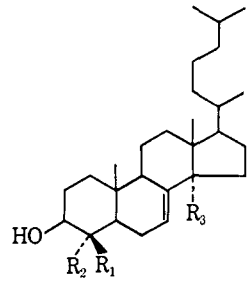
IIIa (3.2×10^4 dpm/μg) and IIIb (2.92×10^4 dpm/μg) were incubated with a clarified 100,000*g* supernatant



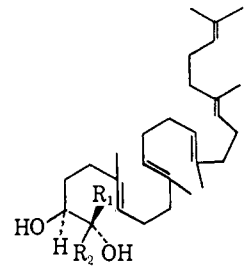
I, $R_1 = R_2 = CH_3$
IIIa, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$



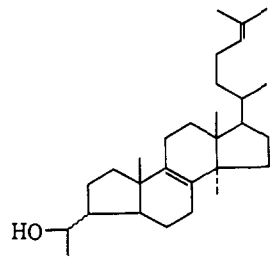
II, $R_1 = R_2 = CH_3$
IV, $R_1 = H$; $R_2 = CH_3$



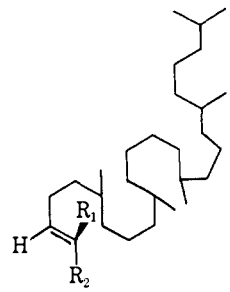
VIII, $R_1 = H$; $R_2 = R_3 = CH_3$
IX, $R_1 = R_2 = H$; $R_3 = CH_3$
X, $R_1 = R_3 = H$; $R_3 = CH_3$



Va, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$



XI



VIIa, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

preparation of deoxycholate-treated microsomes of rat liver[13] in 0.08 *M* phosphate buffer, pH 7.4. The substrate (60 μg) was incubated anaerobically at 37° for 1 hr with enzyme solution (3 ml) from 1 g of liver or with boiled enzyme as a control. Products isolated by standard methods[3] and separated by tlc with EtOAc–hexane (1:3) gave materials moving as: (a) unchanged oxide (R_f 0.60–0.67), (b) "sterols" (R_f 0.37–0.45), and (c) "glycol" (R_f 0.11–0.17). Recoveries of radioactivity were *cis*-oxide, IIIa: 80% unchanged, 1.8% "sterol," 15% "glycol," other regions <0.3%; *trans*-oxide, IIIb: 90% unchanged, 3.5% "sterol," 2.2% "glycol," other regions <0.3%. In each case boiled enzyme con-

(1) E. E. van Tamelen, J. D. Willett, R. B. Clayton, and K. E. Lord, *J. Am. Chem. Soc.*, 88, 4752 (1966).
(2) E. J. Corey and W. E. Russey, *ibid.*, 88, 4750 (1966).
(3) J. D. Willett, K. B. Sharpless, K. E. Lord, E. E. van Tamelen, and R. B. Clayton, *J. Biol. Chem.*, 242, 4182 (1967).
(4) P. D. G. Dean, P. R. Ortiz de Montellano, K. Bloch, and E. J. Corey, *ibid.*, 242, 3014 (1967).
(5) E. E. van Tamelen, K. B. Sharpless, J. D. Willett, R. B. Clayton, and A. L. Burlingame, *J. Am. Chem. Soc.*, 89, 3920 (1967).
(6) E. J. Corey and S. K. Gross, *ibid.*, 89, 4561 (1967).
(7) E. E. van Tamelen, K. B. Sharpless, R. Hanzlik, R. B. Clayton, A. L. Burlingame, and P. C. Wszolek, *ibid.*, 89, 7150 (1967).
(8) R. G. Nadeau and R. P. Hanzlik, *Methods Enzymol.*, in press.
(9) E. J. Corey and W. Oppolzer, *J. Am. Chem. Soc.*, 86, 1899 (1964).
(10) All thin layer chromatography (tlc) was carried out on 0.25–0.5-mm layers of silica gel G.
(11) Gas–liquid partition chromatographic (glpc) conditions were: with SE-30, 3% on Chromosorb W, column temperature 240°, N_2 flow rate 90 cc/min; with DEGS, 5% on Chromosorb G, column temperature 200°, N_2 flow rate 90 cc/min; and with Carbowax, 5% on Chromosorb W, column temperature 220°, nitrogen flow rate 90 cc/min. Retention times are reported in relation to that of cholestane (R_c values).
(12) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).
(13) The preparation was modified from that of Dean, *et al.*[4]