Favorskii Rearrangement and Grob Fragmentation of Carvone Tribromides

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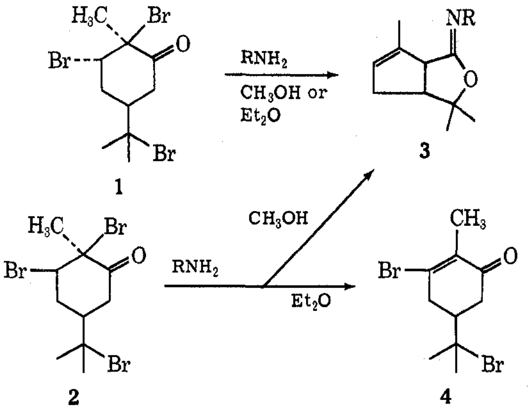
The reaction of *trans*-carvone tribromide (1) and *cis*-carvone tribromide (2) with bases is shown to depend on the base, solvent, and configuration of the β-bromo group. Products derived from Favorskii rearrangement are formed when 1 or 2 are treated with sodium methoxide in methanol or ether. An epoxy ether (11) also results from the reaction of 1 with sodium methoxide in ether. Grob fragmentation occurs when 1 and 2 are treated with sodium hydroxide in water. Vinyl bromides 19, 20, and 21, along with epoxycarone 22, are formed from 2, whereas 1 gives homoterpenyl methyl ketone (27), keto acid derivatives 25 and 26, and 4-methyl-3-pentenoic acid (46).

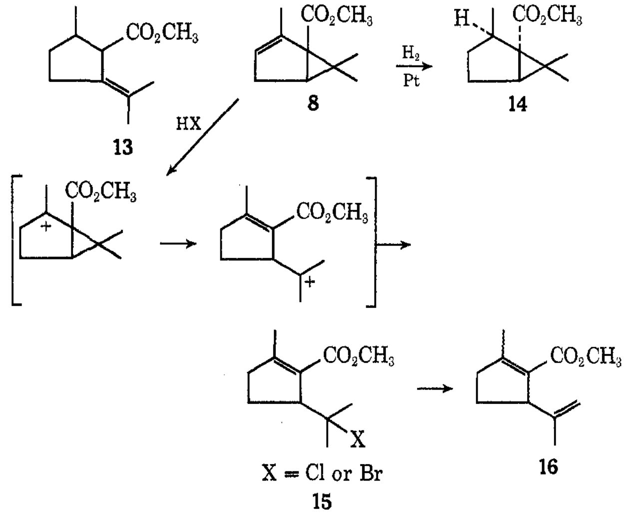
trans-Carvone tribromide (1)[2a,3] undergoes a Favorskii rearrangement to afford iminolactone **3** when treated with primary amines in methanol or ether. *cis*-Carvone tribromide (2)[2a] likewise yields **3** when treated with isopropylamine in methanol, but affords the dehydrobromination product **4** when the reaction is conducted in ether.[2b] In view of the divergent paths followed by **2**, it became of interest to study the reaction of **1** and **2** with methoxide and hydroxide ions in various solvents.



Sodium Methoxide.—In solvent methanol, sodium methoxide converted **1** and **2** into complicated mixtures of products from which the compounds shown in Chart I were isolated and identified. Qualitatively, the two bromides yield the same major products, except for the formation of 17% of bicyclo[3.1.0]hexane derivative **8** in the reaction with **2**.

In ether, the reaction with sodium methoxide takes a new path for each isomer (see Chart II). Both **1** and **2** yield substantial amounts of bicyclic ester **8**. In addition, **1** also affords the dibromo hydroxy ketone **12** if the reaction is worked up with water, or the dibromo epoxy ketone **11** if water is excluded in the isolation step.

The structures assigned **5–12** are based on spectral data (see Experimental Section) and conversion, where possible, into known compounds. Thus, unsaturated ester **5** was transformed by partial catalytic hydrogenation into methyl *cis*-pulegenate (**13**).[4] Bicyclic ester **8** absorbed 1 equiv of hydrogen in the presence of platinum to yield **14**, whose stereochemistry is assigned on the assumption that hydrogenation occurs from the least hindered side of the molecule. Treatment of **8** with hydrogen chloride or hydrogen bromide gave halo esters **15** which were dehydrobrominated to the known **16**.[5]



Carvenolide (**7**) and carvacrol (**10**) were identified by spectral comparison with authentic samples. Complete characterization of **6** and **9** was not achieved because of the instability of **6** and the small amount of **9** isolated.

Epoxy ether **11** lacks carbonyl absorption in the infrared and shows a methoxy signal at 3.46 ppm in its nmr spectrum. An apparent one-proton triplet at 4.53 ppm (J = 2.5 Hz) suggests an equatorial orientation for the C-3 proton and, hence, an axial position for the C-3 bromine. The crystalline epoxy ether **11** is stable in solution in the absence of acid, but on standing at room temperature for a few days is converted into vinyl ether **17**. Vinyl ether **17** displays a strong olefin stretching vibration at 6.10 μ and an nmr doublet at 4.76 ppm attributed to a vinyl proton. Hydrolysis of **17** with hydrobromic acid or sodium hydroxide solution gave hydroxy ketone **18**. The assignment of an equatorial hydroxyl group in **18** was substantiated by an ultraviolet maximum at 283 nm (ϵ 37.4) and by an upfield shift of 16.2 Hz for the C-2 methyl group when the nmr spectrum was determined in benzene rather than $CDCl_3$.[6] Similar spectral properties were shown by acetate **18a**.

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[1] David Ross Research Fellow, Purdue University, 1964–1966.

[2] (a) J. Wolinsky, J. J. Hamsher, and R. O. Hutchins, *J. Org. Chem.*, **35**, 207 (1970); (b) J. Wolinsky, R. O. Hutchins, and T. W. Gibson, *ibid.*, **33**, 407 (1968).

[3] Unless otherwise indicated all the reactions were carried out with racemic products.

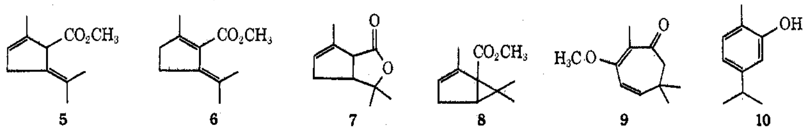
[4] J. Wolinsky, H. Wolf, and T. W. Gibson, *J. Org. Chem.*, **28**, 274 (1963); J. Wolinsky and D. Chan, *ibid.*, **30**, 41 (1965).

[5] J. Wolinsky and D. Nelson, *Tetrahedron*, **25**, 3767 (1969).

[6] J. Ronayne and D. H. Williams, *J. Chem. Soc. B*, 540 (1967).

CHART I

REACTION OF **1** AND **2** WITH SODIUM METHOXIDE IN METHANOL[a]

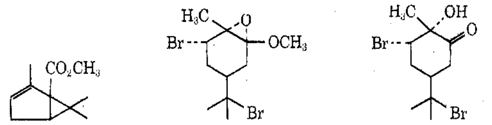


Bromide	5	6	7	8	9	10
1	36%	Trace	12.9%			4.6%
2	49%	14%	4%	22%	7%	

[a] The reaction yields were determined by glpc and are not corrected for detector response differences.

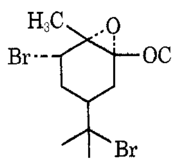
CHART II

REACTION OF **1** AND **2** WITH SODIUM METHOXIDE IN ETHER

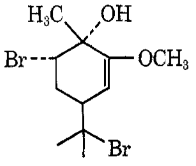


Bromide	8	11	12
1	36-47%	(29-33%)[a]	(21%)[b]
2	59-67%		

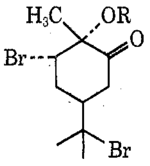
[a] Isolated when care is taken to avoid moisture in the reaction work-up. [b] Isolated when water is added during work-up.



11



17



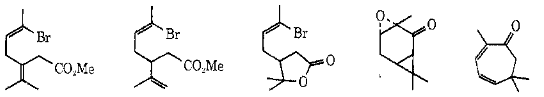
18, R = H
18a, R = Ac

NaOH.—The reactions of carvone tribromides **1** and **2** with sodium hydroxide in water and ether were conducted under a nitrogen atmosphere at room temperature. Since these systems are heterogeneous, one experiment was performed in dioxane–water in order to examine the effect of homogeneity on the reaction course. The acidic products were converted to methyl esters with diazomethane in order to facilitate their separation and isolation.

The action of sodium hydroxide on *cis*-carvone tribromide (**2**) produced the array of products shown in Chart III. The reaction proved to be qualitatively similar in water, dioxane–water, or ether. However, in ether, epoxide **22** was not found and eucarvone **23** was isolated in low yield.

CHART III

ACTION OF SODIUM HYDROXIDE ON *cis*-CARVONE TRIBROMIDE (**2**)[a]



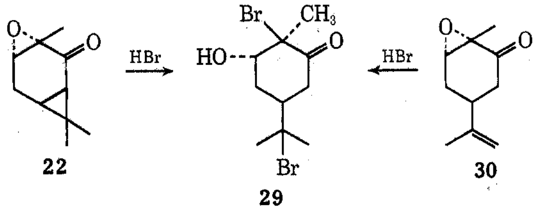
Solvent	19	20	21	22	23
Water	4-9%	3-8%	39-56%	25-27%	
Water-dioxane	8%	2%	12%	41%	
Ether[b]	11%	22%	25%		13%

[a] Reaction yields were determined by glpc and are not corrected for detector response differences. [b] Carvenolide (**7**) (3.5%) and unsaturated ester **16** (5.3%) were also isolated.

Little or no Favorskii rearrangement occurs in the reaction of **2** with sodium hydroxide; instead the carbonyl group of **2** is attacked, leading to compounds **19**, **20**, and **21** by a Grob fragmentation[7] or to epoxide **22** by a multistep process.

The reaction of sodium hydroxide with **1** changes dramatically with solvent (see Chart IV). In ether a Favorskii rearrangement prevails, while in water compounds **24**, **25**, **26**, and **27** are formed by way of a Grob fragmentation.[7]

Methyl homoterpenyl ketone (**27**), eucarvone (**23**), unsaturated ester **24**, and keto ester **25** were identified by comparison with authentic samples. Keto ester **26**, bromo esters **19** and **20**, and bromolactone **21** were identified by elemental analyses and spectral data (see Experimental Section). Treating epoxycarone **22**[8] with hydrobromic acid gave dibromo ketohydrin **29**, which proved to be identical with an authentic sample prepared from epoxycarvone (**30**).[2]



The skeletal rearrangement of α-halo ketones induced by bases which leads to carboxylic acid derivatives is known as the Favorskii rearrangement. The use of this transformation as a synthetic tool, as well as studies of its mechanism, are complicated by the multifunctional nature of the α-halo ketone, which permits a variety of competing reactions, such as dehydrohalogenation, substitution, and epoxy ether formation, sometimes to the exclusion of the Favorskii rearrangement.[9]

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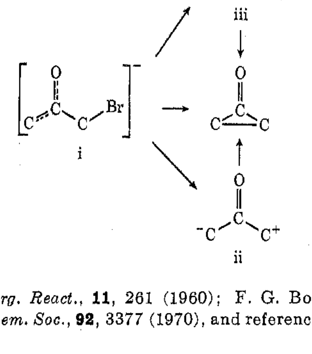
[7] C. A. Grob and P. W. Schiess, *Angew. Chem.*, **6**, 1 (1967), and references cited therein.

[8] W. D. P. Burns, M. S. Carson, W. Cocker, and P. V. R. Shannon, *J. Chem. Soc. C*, 3073 (1968).

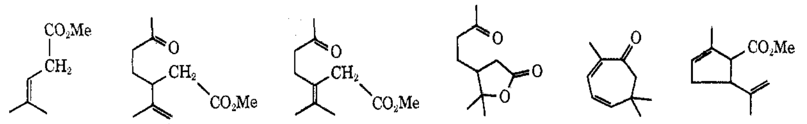
[9] It is now generally acknowledged that the Favorskii rearrangement proceeds by way of a cyclopropanone intermediate. The exact path to the cyclopropanone intermediate may vary with the reaction conditions, and may involve a direct intramolecular displacement of enolate i, collapse of dipolar ion ii, or rearrangement of an allene oxide iii.[10]



[10] A. Kende, *Org. React.*, **11**, 261 (1960); F. G. Bordwell and M. W. Carlson, *J. Amer. Chem. Soc.*, **92**, 3377 (1970), and references cited therein.

CHART IV

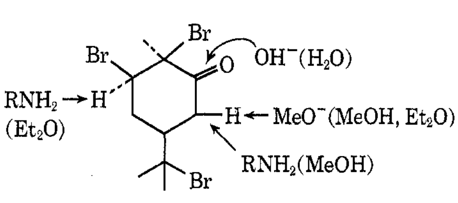
ACTION OF SODIUM HYDROXIDE ON *trans*-CARVONE TRIBROMIDE (1)[a]



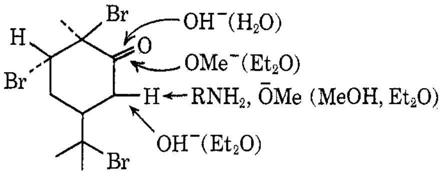
Solvent	**24**	**25**	**26**	**27**	**23**	**28**
H_2O	31%	2.6%	10%	36.5%	7%	0%
Et_2O[b]	1%					10%

[a] Reaction mixture was esterified with diazomethane prior to analysis and isolation of products was by preparative glpc. Yields were determined by glpc and are uncorrected for detector response differences. [b] Products: carvenolide (**7**) (3.5%), unsaturated ester **5** (5.3%), and bicyclic ester **8** (4.6%).

A spectrum of these transformations is observed with the multifunctional carvone tribromides **1** and **2**. The product determining attack of base, summarized in A and B, appears to depend upon the nature of the base, the solvent, and the configuration of the β-bromine atom.



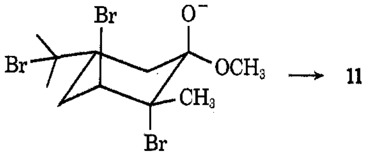
A



B

The reaction of *cis*-carvone tribromide (**2**) with the strong base sodium methoxide in methanol or ether favors the removal of the α′ proton and subsequent Favorskii rearrangement. The initially formed product is most likely **31**, which loses hydrogen bromide to yield **5** and **6** or affords **8** *via* the anion **32**. Carvenolide **7** most likely is formed by lactonization, during reaction work-up, of the acid corresponding to **5**. In ether, the 1,2 elimination of hydrogen bromide is minimized and cyclization of anion **32** to **8** becomes the favored pathway.

The mechanism shown in Scheme I also accounts for the reaction of *trans*-carvone tribromide (**1**) with sodium methoxide when the reaction is conducted in methanol; however, in ether concurrent attack at the carbonyl group, formation of the axial alkoxide **33**, and subsequent intramolecular displacement of the α-bromo group leads to epoxy ether **11**.



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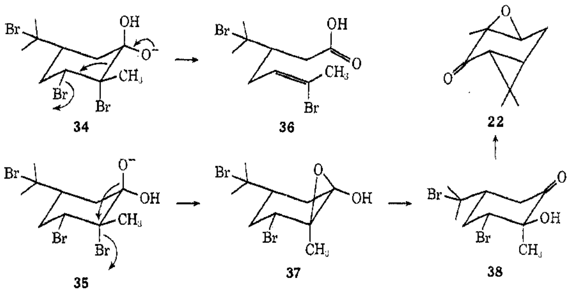
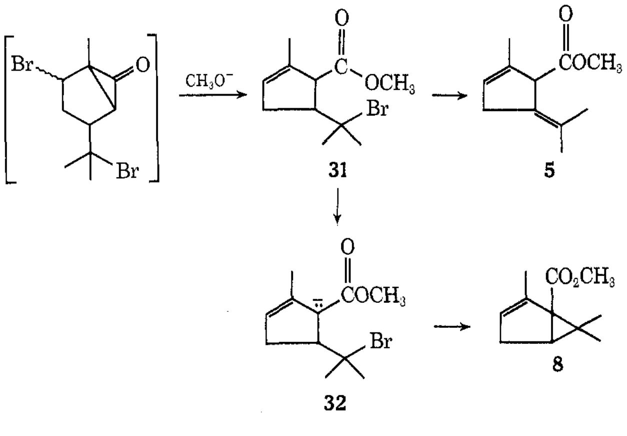
On using the weaker base, hydroxide ion in water, the products appear to arise exclusively from attack at the carbonyl group. The reaction of *cis*-carvone tribromide (**2**) can be rationalized assuming axial and equatorial attack at the carbonyl group generating **34** and **35**. Alkoxides **34** and **35** have the trans antiperiplanar configuration[11] required for a Grob type of fragmentation generating **36**, which is ultimately transformed into the observed products **19**, **20**, and **21**. The failure to observe Grob fragmentation products in ether or methanol may be attributed to the lower polarity of these solvents.[12]



Alkoxide **35** also possesses a configuration permitting intramolecular displacement of the α-bromine atom, resulting in the formation of epoxy alcohol **37**. Hydrolysis of **37** results in **38**, which can cyclize to epoxycarone **22**. It is not clear whether epoxide formation precedes or follows the formation of the cyclopropane ring in these last steps.

SCHEME I



Hydroxide ion addition to the carbonyl group of *trans*-carvone tribromide (**1**) affords alkoxide **39**, which lacks the necessary antiperiplanar configuration for a Grob fragmentation, but which can undergo intramo-

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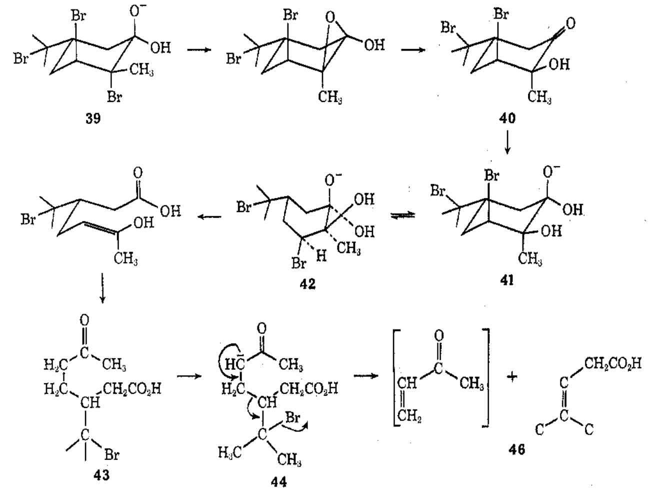
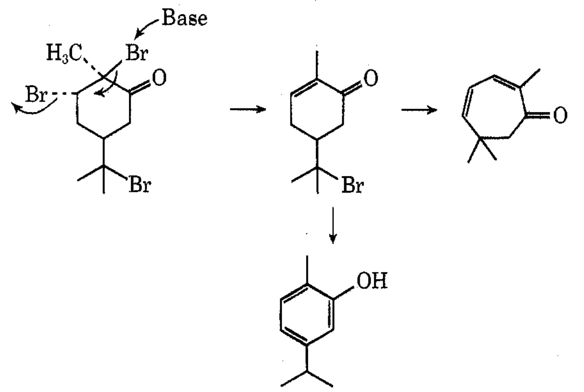
[11] C. A. Grob, H. R. Kiefer, H. J. Lutz, and H. J. Wilkens, *Helv. Chim. Acta*, **50**, 416 (1967).

[12] *Cf.* P. Brenneisen, C. A. Grob, R. A. Jackson, and M. Ohta, *Helv. Chim. Acta*, **48**, 146 (1965).

lecular displacement and subsequent hydrolysis to yield hydroxy ketone **40**.[13] Competing Favorskii rearrangement and epoxide formation is no longer possible for **40**, but alkoxide **41** may undergo a Grob fragmentation by way of a high-energy conformation such as **42** to yield **43**, which subsequently is transformed into **24**, **25**, **26**, and **27**. The conversion of **43** to **46**, which yields **24** during the reaction work-up, is most easily visualized as another Grob fragmentation proceeding by way of anion **44**.



Finally, it is worth noting that eucarvone (**23**) or carvacrol (**10**) are among the products of reaction of **1** with bases under a variety of conditions. These compounds probably result by debromination of **1**, followed by cyclization or decomposition of carvone hydrobromide.



Experimental Section[14]

Reaction of *cis*-Carvone Tribromide (2) with Sodium Methoxide. A. Methanol.—To a stirred solution of 6.90 g (0.1275 mol) of sodium methoxide in 150 ml of absolute methanol was added 5.0 g (0.1275 mol) of *dl-cis*-carvone tribromide (**2**). The mixture was stirred for 20 hr, 500 ml of water was added, and the mixture was then extracted with ether. The ether solution was dried, the ether was removed, and the residue was distilled, affording 1.70 g of liquid, bp 60–110° (1.2 mm). Analysis by glpc using a 3-m DEGS column at 150° indicated the presence of 22.5% of 1-carbomethoxy-2,6,6-trimethylbicyclo[3.1.0]-2-hexene (**8**), 48.6% of 3-carbomethoxy-2-methyl-4-isopropylidene-1-cyclopentene (**5**), 14% of 2-carbomethoxy-1-methyl-3-isopropylidene-1-cyclopentene (**6**), 6.7% of 3-methoxyeucarvone (**9**), 3.5% of carvenolide (**7**), and a total of 4.8% of several unidentified components.

The aqueous layer remaining after ether extraction was acidified with concentrated hydrochloric acid and extracted with ether to yield 134 mg of dark tar.

Pure samples of **5**, **6**, **7**, **8**, and **9** were collected by preparative glpc. Carvenolide (**7**) was identified by comparison with glpc retention time and ir and nmr spectra of an authentic sample.[4]

1-Carbomethoxy-2,6,6-trimethylbicyclo[3.1.0]-2-hexene (**8**) showed $n^{20}\mathrm{D}$ 1.4709; ir 5.78 μ; nmr (CCl_4) δ 0.94 and 1.23 (s, 6, CH_3CCH_3), 1.83 (s, 3, $CH_3CH{=}$), 1.72–2.5 (m, 3), 3.65 (s, 3, OCH_3), and 5.15 ppm (m, 1, $CH{=}C$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.31; H, 8.95. Found: C, 73.40; H, 9.28.

3-Carbomethoxy-2-methyl-4-isopropyl-1-cyclopentene (**5**) displayed $n^{20}\mathrm{D}$ 1.4789; ir 5.75 μ; nmr (CCl_4) δ 1.66 (broad s, 9, $CH_3C{=}C$), 3.00 (m, 2, $C{=}CCH_2C{=}C$), 3.66 (s, 3, OCH_3), 3.89 [m, 1, $(C{=}C)_2CHC{=}O$], and 5.61 ppm (m, 1, $CH{=}C$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.31; H, 8.95. Found: C, 72.98; H, 9.16.

Since only a small quantity of 3-methoxyeucarvone (**9**) and the unstable 2-carbomethoxy-1-methyl-3-isopropylidene-1-cyclopentene (**6**) were isolated, they were not completely characterized. 3-Methoxyeucarvone (**9**) exhibited strong carbonyl absorption at 6.1 μ; nmr (CCl_4) 1.08 (s, 6, CH_3CCH_3), 1.79 (s, 3, $CH_3C{=}C$), 2.54 (s, $O{=}CCH_2C{=}C$), 3.69 (s, 3, $-OCH_3$), and 5.98 ppm (AB q, 2, $-CH{=}CH-$). A glpc pure sample of **6** showed nmr signals at δ 1.54, 1.67 and 1.82 (s, 9, 3 $CH_3C{=}C$) and 2.43 (broad s, 4, $C{=}CCH_2CH_2C{=}C$).

B. Diethyl Ether.—A mixture of 6.90 g (0.1275 mol) of sodium methoxide, 75 ml of anhydrous ether, and 5.00 g (0.01275 mol) of *dl-cis*-carvone tribromide (**2**) was stirred for 24 hr. The resulting pink-brown mixture was diluted with 200 ml of ether and 500 ml of water and the layers were separated. The aqueous phase was extracted with ether, the combined ether fractions were dried, and the ether was removed, affording 2.03 g of orange oil. Distillation *in vacuo* gave 1.31 g (67%) of 1-carbomethoxy-2,6,6-trimethylbicyclo[3.1.0]-2-hexene (**8**), bp 40–42° (0.5 mm). Analysis of the distillate by glpc showed only the presence of bicyclic ester **8**.

Work-up of the basic aqueous layer gave only a small amount (186 mg) of tar.

Hydrogenation of 8.—A solution of 1.5 g of bicyclic ester **8** in 25 ml of ethanol was hydrogenated over 150 mg of PtO_2. The uptake of 1 equiv of hydrogen required 3 hr. The catalyst and solvent were removed and analysis of the residue by glpc indicated the presence of one product contaminated by a small amount of **8**. Distillation *in vacuo* gave 1.4 g of 1-carbomethoxy-2,6,6-trimethylbicyclo[3.1.0]hexane (**14**), bp 63–65° (2 mm). The analytical sample was prepared by distillation: bp 55° (1.3 mm); $n^{20}\mathrm{D}$ 1.4646; ir 5.81 μ; nmr (CCl_4) δ 1.08 and 1.27 (s, 6, CH_3CCH_3), 1.12 and 1.27 (d, 3, $CHCH_3$), 1.4–2.9 (m), and 3.58 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.50; H, 9.93. Found: C, 72.72; H, 10.08.

Reaction of 8 with Hydrohalides. A. HBr.—A solution of 1.027 g of bicyclic ester **8** in 7 ml of chloroform and 12 ml of fuming hydrobromic acid was stirred at ambient temperature for 1 hr. The mixture was diluted with water, the layers were separated, and the aqueous phase was extracted with methylene chloride. The combined organic phases were washed with water and 5% sodium bicarbonate solution, and dried. The solvents were removed under diminished pressure, affording 1.21 g of a light tan oil which darkened rapidly on standing, ir 5.80 and 6.05 μ. Attempts to purify this material led to extensive decomposition.

A solution of 380 mg of the crude product in 10 ml of 2,6-lutidine was refluxed for 48 hr. Ether was added and the mixture was extracted with 5% hydrochloric acid. The ether phase was dried and evaporated to give 253 mg of tan oil. Evaporative

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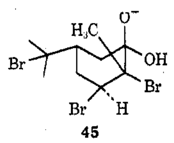
[13] It is not surprising that the conversion **39** → **40** occurs more rapidly than a Grob fragmentation, since the latter transformation requires the ring to assume the high-energy boat conformation **45**.



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[14] All boiling and melting points are uncorrected. Nuclear magnetic resonance spectra were measured at 60 MHz with a Varian Associates A-60 spectrometer. Chemical shifts are given as δ values in parts per million with reference to tetramethylsilane as an internal standard. Microanalyses were performed by Dr. C. S. Yeh and associates. The reactions of **1** and **2** were conducted under an atmosphere of nitrogen at ambient temperature, and drying of organic solutions was accomplished with anhydrous $MgSO_4$.

distillation gave a liquid whose infrared spectrum and glpc retention time were identical with those of authentic methyl 5-isopropenyl-2-methyl-1-cyclopentene carboxylate (**16**).[5]

B. HCl.—A mixture of 1.050 g of bicyclic ester **8** in 7 ml of chloroform and 12 ml of concentrated hydrochloric acid was stirred vigorously at ambient temperature for 1 hr. The mixture was worked up as described above to give 1.18 g of pale yellow liquid. Evaporative distillation gave a colorless liquid which rapidly darkened on standing. An accurate microanalysis could not be obtained due to the instability of the compound.

A solution of 508 mg of the chloro ester in 10 ml of 2,6-lutidine was refluxed for 38 hr. The mixture was cooled, diluted with ether, and extracted with 5% hydrochloric acid. The ether solution was dried and concentrated, affording 388 mg of an orange oil. Distillation *in vacuo* gave a liquid whose infrared and nmr spectra as well as glpc retention time were identical with those of an authentic sample of **16**.

Hydrogenation of 3-Carbomethoxy-2-methyl-4-isopropylidene-1-cyclopentane (5).—A solution of 100 mg of **5** in 15 ml of methanol and 2 ml of acetic acid was hydrogenated over 10 mg of platinum oxide until a slight excess of 1 equiv of hydrogen had been absorbed (1 hr). The mixture was filtered and the solvents were removed. The glpc retention time and infrared spectrum of the residue were identical with those of an authentic sample of *cis*-methyl pulegenate (**13**).[4]

Reaction of *trans*-Carvone Tribromide (1) with Sodium Methoxide. A. Methanol.—A solution of 6.30 g (0.1275 mol) of sodium methoxide and 4.94 g (0.127 mole) of *dl-trans*-carvone tribromide (**1**) in 50 ml of methanol was stirred for 20 hr. After 500 ml of water was added, the mixture was extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated. The residue was distilled *in vacuo* and the material distilling at 60–200° (0.5 mm) was collected. A small amount of solid distilled at the higher temperature, but was not investigated further.

Analysis of the liquid distillate (1.35 g) using a 3-m DEGS column at 170° indicated the presence of a number of compounds. The major products, 3-carbomethoxy-2-methyl-4-isopropylidene-1-cyclopentene (**5**) (62%), carvenolide (**7**) (22.4%), and carvacrol (**10**) (4.6%), were isolated by glpc and identified by comparison of glpc retention times and nmr spectra. Trace amounts of 2-carbomethoxy-1-methyl-3-isopropylidene-1-cyclopentene (**6**) and 3-methoxyeucarvone (**9**) were also detected.

B. Diethyl Ether.—A mixture of 20.7 g (0.383 mol) of sodium methoxide, 15.0 g (0.0383 mol) of *dl-trans*-carvone tribromide (**1**), and 225 ml of anhydrous ether was stirred for 25 hr. Water (1 l.) was added and the aqueous phase was extracted with ether. The ether solution was dried and evaporated to afford 8.21 g of orange oil. When kept at −20° the oil partially solidified. The solid was removed by filtration and washed with cold pentane. This process was repeated again to give a total of 2.08 g of solid. Recrystallization from hexane gave the analytical sample of dibromo hydroxy ketone **12**: mp 100.5–101.5°; ir (melt) 2.85 and 5.80 μ; λ_{max} 283 nm (ϵ 37.4); nmr ($CDCl_3$) δ 1.60 (s, 3, CH_3CO), 1.82 and 1.86 (s, 6, CH_3CBrCH_3), 2.1–3.0 (m), 3.96 (s, 1, −OH), and 3.96 ppm (t, 1, J = 2.5 Hz, HCBr). In benzene, the CH_3CO signal was shifted upfield by 16.2 Hz, indicating the presence of an axial methyl group.

Anal. Calcd for $C_{10}H_{16}Br_2O_2$: C, 36.61; H, 4.92; Br, 48.72. Found: C, 36.40; H, 4.70; Br, 49.02.

The filtrate obtained after removing **12** was distilled *in vacuo* to afford 2.90 g of liquid bp 45–55° (0.6 mm). Glpc analysis of this product indicated the presence of 91% of bicyclic ester **8** and a total of 9% of four unidentified compounds. A sample of **8** was collected and identified by ir and nmr comparison with that of an authentic sample.

Recrystallization of the distillation residue from hexane afforded an additional 0.61 g of hydroxy ketone **12**.

The acetate derivative of 3-bromo-2-hydroxy-2-methyl-5-(2-bromoisopropyl)cyclohexanone (**12**) was prepared by stirring with magnesium and acetyl chloride and after the usual work-up was purified by recrystallization from hexane: mp 91–92°; ir 5.75 μ; λ_{max}^{EtOH} 283 nm (ϵ 43.5); nmr ($CDCl_3$) δ 1.77 and 1.82 [2, s, 6, $(CH_3)_2CBr$], 1.90 (s, 3, CH_3COAc), 2.16 (s, 3, $O{=}CCH_3$), and 5.35 ppm (t, 1, J = 3 Hz, −CHBr). In benzene, the nmr signal assigned to the α-methyl group was shifted 19.8 Hz upfield, indicative of an axial methyl group.

Anal. Calcd for $C_{12}H_{18}Br_2O_3$: C, 38.75; H, 4.89; Br, 43.19. Found: C, 39.06; H, 4.94; Br, 43.18.

C. Diethyl Ether. Work-Up without Water.—A mixture of 20.7 g (0.383 mol) of sodium methoxide, 20.7 g (0.0383 mol) of *dl-trans*-carvone tribromide (**1**), and 210 ml of anhydrous ether was stirred for 38.5 hr and then filtered. The ether was removed under diminished pressure, pentane was added to the residue, and the mixture was kept at −20° to yield 4.33 g (33.8%) of white solid (two crops). Several recrystallizations from hexane gave the analytical sample of epoxy ether **11**: mp 85–87°; ir ($CHCl_3$) no −OH or carbonyl absorption; nmr ($CDCl_3$) δ 1.44 (s, 3, CH_3CO), 1.76 and 1.79 [2 s, 6, $(CH_3)_2CBr$], 3.46 (s, 3, $-OCH_3$), and 4.53 ppm (t, 1, J = 2.5 Hz, −CHBr).

Anal. Calcd for $C_{11}H_{18}Br_2O_2$: C, 38.64; H, 5.29; Br, 46.72. Found: C, 38.71; H, 5.33; Br, 46.60.

Epoxy ether **11** liquified upon standing at room temperature for a few hours, and after several days resolidified. Recrystallization from hexane gave hydroxy enol ether **17**: mp 43–45°; ir 6.1 μ; nmr ($CDCl_3$) δ 1.54 (s, 3, CH_3CO), 1.76 and 1.85 [2 s, 6, $(CH_3)_2CBr$], 3.64 (s, 3, $CH_3OC{=}C$), 4.60 (m, 1, $W_{1/2}$ = 7.5 Hz, −CHBr), and 4.76 ppm (d, 1, J = 2.8 Hz, $-C{=}CH-$).

Anal. Calcd for $C_{11}H_{18}Br_2O_2$: C, 38.64; H, 5.29; Br, 46.72. Found: C, 38.64; H, 5.43; Br, 47.02.

Distillation of the mother liquors obtained from the crystallization of epoxy ether **11** gave 2.60 g of bicyclic ester **8**, bp 63–65° (1.8 mm).

A solution of epoxy ether **11** in chloroform was stirred vigorously at ambient temperature with 3 ml of fuming hydrobromic acid. The chloroform layer was washed with 5% sodium bicarbonate, dried, and evaporated under diminished pressure. The solid residue was crystallized from hexane to afford colorless crystals of hydroxy ketone **18**,[2] mp 101–103°.

Hydroxy ketone **18** was also obtained from epoxy ether **11** by shaking an ether solution of **11** with 1.0 *N* sodium hydroxide solution.

D. Hexane—A mixture of 13.80 g (0.256 mol) of sodium methoxide, 10.0 g (0.0256 mol) of *dl-trans*-carvone tribromide (**1**), and 150 ml of spectroscopic grade hexane was stirred for 24 hr. The mixture was diluted with 500 ml of water and 200 ml of ether. The aqueous layer was extracted with ether and the combined organic layers were dried. The solvents were removed *in vacuo*, leaving 4.81 g of orange oil. Distillation *in vacuo* gave 2.10 g of liquid, bp 44–48° (0.2 mm), n^{20}D 1.4726. Analysis by glpc indicated this material was largely (90%) bicyclic ester **8**.

The distilland was recrystallized from hexane and afforded 440 mg of hydroxy ketone **12**, mp 101–103°.

Reaction of *cis*-Carvone Tribromide (2) with Sodium Hydroxide in Water.—A mixture of 30.0 g (0.0765 mol) of *dl-cis*-carvone tribromide (**2**) and 49.2 g (1.23 mol) of sodium hydroxide in 300 ml of water was stirred for 71 hr. The mixture was extracted with ether, and the ether solution was dried and distilled to give 3.23 g (25.4%) of α-3,4-epoxycaran-2-one (**22**): bp 59–63° (0.5 mm); nmr (CCl_4) δ 0.95, 1.18, and 1.28 (3 s, 9, CH_3C- and CH_3CO), and 3.08 ppm (m, 1, $W_{1/2}$ = 5 Hz, epoxide H).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.25; H, 8.48. Found: C, 71.92; H, 9.01.

The basic aqueous solution remaining after the ether extraction described above was saturated with carbon dioxide to pH 6 and extracted with ether. The ether solution was washed with saturated salt solution and dried, and an ethereal solution of diazomethane was added. The solvent was removed, leaving 1.6 g of oil. Analysis by glpc indicated that this material was composed of 51% of methyl 3-isopropenyl-6-bromo-5-heptenoate (**20**), 40% of methyl 3-isopropylidene-6-bromo-5-heptenoate (**19**), and 9% of 3-(4-bromo-2-butenyl)-4,4-dimethylbutyrolactone (**21**).

The aqueous solution remaining after ether extraction described above was acidified with hydrochloric acid to pH 1 and extracted with ether. The ether solution was dried and concentrated to afford 11.2 g of orange oil. Distillation gave 10.5 g of lactone **21**, bp 126–128° (0.24 mm). An analytical sample of lactone **21** was obtained by glpc: n^{20}D 1.4985; ir (neat) 5.70 μ; nmr (CCl_4) δ 1.27 and 1.43 (2 s, 6, CH_3COCH_3), 2.29 (s, 3, $CH_3BrC{=}C-$), 5.63 ppm (m, 1, $-C{=}CH-$). A sample of lactone **21** prepared from *d-cis*-carvone tribromide in the manner described above showed mp 44–45°.

Anal. Calcd for $C_{10}H_{15}BrO_2$: C, 48.61; H, 6.09; Br, 32.24. Found: C, 48.38; H, 6.26; Br, 32.00.

A pure sample of methyl 3-isopropylidene-6-bromo-5-heptenoate (**19**) was obtained by glpc: ir 5.7 and 6.0 μ; nmr (CCl_4) 1.71 and 1.77 (2 s, 6, $CH_3C{=}C-$), 2.30 (d, 3, J = 1.5 Hz, $CH_3C{=}C-$), 2.97 (s, 2, $-C{=}CCH_2CO$), 2.92 (d, 2, $C{=}CHCH_2C{=}C-$), 3.58 (s, 3, CH_3O-), and 5.46 (t of d, 1, J = 7, 1.5 Hz, $CH_3C{=}CHCH_2-$).

Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.58; H, 6.57; Br, 30.60. Found: C, 50.70; H, 6.47; Br, 30.40.

A pure sample of methyl 3-isopropenyl-6-bromo-5-heptenoate (**20**) was obtained by glpc: ir 5.7 and 6.05 μ; nmr (CCl_4) δ 1.70 (m, 3, J = 0.5 Hz, $CH_3C{=}C$–), 2.24 (m, 3, J = 0.5 Hz, $CH_3BrC{=}C$–), 3.56 (s, 3, CH_3O–), and 5.46 ppm (m, 1, $BrC{=}CH$–).

Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.58; H, 6.57; Br, 30.60. Found: C, 50.17; H, 6.54; Br, 30.32.

Reaction of Sodium Hydroxide with *cis*-Carvone Tribromide (2) in Aqueous Dioxane.—A solution of 10 g (0.0256 mol) of *dl-cis*-carvone tribromide (**2**) and 16.4 g (0.411 mol) of sodium hydroxide in 70 ml of pure dioxane and 40 ml of water was stirred for 45 hr. After the usual work-up, distillation of the neutral fraction gave 1.73 g (40.8%) of epoxy ketone **22**, bp 55–58° (0.25 mm).

Work-up of the acidic fraction and treatment with diazomethane, followed by distillation *in vacuo*, gave 0.80 g of a mixture (glpc analysis) of 16.4% of isopropyl ester **20**, 60% of isopropylidine ester **19**, and 24% of several unidentified products, bp 65–90° (0.4 mm), and 0.32 g of bromolactone **21**, bp 100–110° (0.4 mm). The yields of **20**, **19**, and **21** were 2, 8, and 41%, respectively.

Reaction of Sodium Hydroxide with *cis*-Carvone Tribromide in Ether.—A mixture of 16.4 g (0.410 mol) of powdered and vacuum dried sodium hydroxide, 10.0 g (0.0256 mol) of *dl-cis*-carvone tribromide (**2**), and 150 ml of anhydrous ether was stirred for 64 hr. The usual work-up gave 447 mg of a neutral fraction. Analysis by glpc showed only one major component, which was collected and identified as eucarvone (**23**) on the basis of its ir and nmr spectra.

Work-up of the acid fraction and treatment with diazomethane gave 4.83 g of liquid. Distillation *in vacuo* afforded 2.36 g, bp 74–90° (0.55 mm), and 1.47 g, bp *ca.* 120° (0.45 mm). Analysis of the first fraction by glpc indicated the presence of 55% of the isopropenyl ester **20** and 28% of the isopropylidene ester **19**. The second fraction was comprised of bromo lactone **20**. The yields of **20**, **19**, and **21** were 22, 11, and 23%, respectively.

Reaction of *trans*-Carvone Tribromide with Sodium Hydroxide in Water.—A mixture of 20.0 g (0.0512 mol) of *d-trans*-carvone tribromide (**1**) and 32.8 g (0.82 mol) of sodium hydroxide in 200 ml of water was stirred for 70 hr. The mixture was extracted with ether. The ether solution was dried and evaporated to afford 1.2 g of liquid. Analysis by glpc indicated the presence of eucarvone (**23**) (49%), carvacrol (**10**) (28%), and small amounts of several unidentified substances.

The basic solution remaining after ether extraction was acidified with hydrochloric acid and extracted with ether. The ether solution was dried and treated with diazomethane, and then concentrated under diminished pressure to afford 6.73 g of liquid. Analysis by glpc indicated the presence of methyl 4-methyl-3-pentenoate (**24**) (30%), methyl 3-isopropenyl-6-ketoheptenoate (**25**) (4%), methyl 3-isopropylidene-6-ketoheptanoate (**26**) (15%), and homoterpenyl methyl ketone (**27**) (51%).

Pure samples of eucarvone (**23**), carvacrol (**10**), **24**, **25**, and **26** were obtained by preparative glpc. Carvacrol, eucarvone (n^{20}D 1.5068), and keto ester **25**[15] were identified by spectral comparison with known samples. Pure homoterpenyl methyl ketone was obtained by recrystallization from pentane at −20°, and showed mp 43–44° and ir and nmr spectra identical with those of an authentic sample.

Methyl 4-methyl-3-pentenoate (**24**) showed carbonyl absorption at 5.74 μ; nmr (CCl_4) δ 1.63 and 1.74 [2 s, 6, $(CH_3)_2C{=}C$], 2.92 (d, 2, J = 7 Hz, –$CH_2C{=}C$), 3.59 (s, 3, –OCH_3), and 5.22 ppm (t, 1, J = 7 Hz, $C{=}CH$).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.36; H, 9.43. Found: C, 65.40; H, 9.48.

Reaction of *trans*-Carvone Tribromide with Sodium Hydroxide in Ether.—A mixture of 32.8 g (0.822 mol) of powdered and dried sodium hydroxide, 20.0 g (0.0512 mol) of *dl-trans*-carvone tribromide (**1**), and 300 ml of anhydrous ether was stirred for 79 hr. The resulting brown mixture was diluted with water and the layers were separated. The aqueous phase was extracted with ether and the combined ether fractions were washed with water, dried, and distilled *in vacuo* to yield 1.51 g (19.7%) of liquid, bp 34–36° (0.25 mm), which was identified as eucarvone (**23**) on the basis of its infrared spectrum.

The aqueous phase remaining after ether extraction was acidified with hydrochloric acid and extracted with ether. The ether solution was washed with water, dried, and treated with excess diazomethane. Distillation under reduced pressure gave 110 mg (1.4%) of methyl 4-methyl-3-pentenoate (**24**), bp 45° (10 mm), and 2.5 g of liquid, bp 55–90° (0.25 mm). Preparative gas chromatography (Carbowax at 190°) gave 17% of bicyclic ester **8**, 19% of 3-carbomethoxy-4-isopropenyl-2-methylcyclopentene (**28**), 38% of unsaturated ester **5**, and 12% of carvenolide (**7**).

3-Carbomethoxy-4-isopropenyl-2-methylcyclopentene (**28**) displayed n^{20}D 1.4722; ir 5.75 and 6.05 μ; nmr (CCl_4) δ 1.69 (s, 6, $CH_3C{=}C$), 3.65 (s, 3, CO_2CH_3), 4.68 (m, 2, $C{=}CH_2$), and 5.38 ppm (m, 1, $CH{=}C$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.53; H, 8.99.

Reaction of Epoxycarone 22 with Hydrobromic Acid.—A solution of 240 mg of epoxycarone **22** in 5 ml of chloroform was stirred vigorously for 1 hr with 5 ml of fuming hydrobromic acid. The layers were separated and the aqueous phase was extracted with methylene chloride. The combined organic layers were dried and the solvents were removed under diminished pressure to afford 345 mg of pale yellow oil. Recrystallization from hexane at −20° gave flat needles, mp 95–97°. The analytical sample of hydroxy ketone **29** was obtained by repeated recrystallization from hexane: mp 96–97°; ir ($CHCl_3$) 2.7 and 2.85 μ; λ_{max}^{EtOH} 307 nm (ϵ 95); nmr ($CDCl_3$) δ 1.77, 1.79, and 1.83 (3 s, 9, CH_3CBr), 2.03–3.5 (m), and 4.38 ppm (t, 1, J = 2.5 Hz, –CH—O). In benzene, the nmr signal of the α-methyl group was only shifted to higher field by 5.4 Hz, indicating an equatorial α-methyl group.

Anal. Calcd for $C_{10}H_{16}Br_2O_2$: C, 36.61; H, 4.97; Br, 48.72. Found: C, 36.90; H, 4.97; Br, 48.45.

The acetate of hydroxy ketone **29** was prepared by treatment with magnesium and acetyl chloride. Repeated recrystallization from hexane at −20° gave an analytical sample: mp 47–50°; ir 5.72 and 5.8 μ; λ_{max}^{EtOH} 306 nm (ϵ 153); nmr ($CDCl_3$) δ 1.75 and 1.77 (2 s, 9, CH_3CBr), 2.04 (s, 3, $OCOCH_3$), and 5.51 ppm (t, 1, J = 3 Hz, –CHOAc).

Anal. Calcd for $C_{12}H_{18}Br_2O_3$: C, 38.95; H, 4.89; Br, 43.19. Found: C, 39.04; H, 5.10; Br, 43.52.

Reaction of Epoxycarvone (30) with Hydrobromic Acid.—A solution of 1.0 g of epoxycarvone (**30**)[16] in 5 ml of chloroform was stirred vigorously at ambient temperature, with 10 ml of fuming hydrobromic acid. The layers were separated, the purple chloroform solution was washed with 5% sodium bicarbonate solution and dried, and the solvent was removed under diminished pressure. The deep purple solid was recrystallized from hexane, Norit, to afford 0.56 g of colorless needles, mp 94–96°, whose ir spectrum was identical with that of hydroxy ketone **29** obtained from epoxycarone **22**.

When 1 ml of acetic acid saturated with hydrogen bromide was added to an ice-cooled solution of 200 mg of epoxycarvone (**30**) in 1 ml of acetic acid and the solution was stirred for 2 min and then worked up, there was obtained 96 mg of hydroxy ketone **29**.

When the reaction of epoxycarvone (**30**) with hydrogen bromide in acetic acid was allowed to proceed for 1 hr at 0°, work-up and recrystallization from hexane gave *cis*-carvone tribromide (**2**), mp 112–116°.

Registry No.—**1**, 22249-53-2; **2**, 22249-55-4; **5**, 35324-51-7; **8**, 35427-26-0; **11**, 35324-04-0; **12**, 35324-05-1; **12** acetate, 35324-06-2; **14**, 35324-07-3; **17**, 35324-08-4; **19**, 35324-52-8; **20**, 35324-53-9; **21**, 35324-54-0; **22**, 35324-55-1; **24**, 2258-65-3; **28**, 35324-57-3; **29**, 35324-09-5; **29** acetate, 35324-10-8.

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[15] J. Wolinsky and D. Chan, *J. Org. Chem.*, **31**, 2471 (1966).

[16] W. Treibs, *Ber.*, **65**, 1314 (1932); E. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963).