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Alkylation of Hagemann's Ester. Preparation of an Intermediate for Trisporic Acid Synthesis

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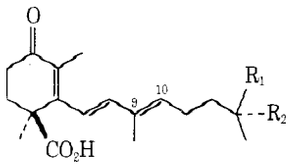
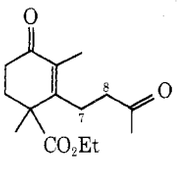
Alkylation of Hagemann's ester (3) with methyl and methallyl halides gave predominantly C-3 substitution. Further alkylation afforded a mixture of 1,3- and 3,3-disubstituted products. A method for the separation of these isomers based upon selective ketalization is described. Methylation at C-1 of a 3,3-dialkylated derivative of 3 was found to proceed well when lithium diethylamide was used as the base. By a sequence in which first a methyl and then a methallyl group were introduced into Hagemann's ester, 18 was prepared and separated from 19 by formation of a ketal (23). Methylation of the latter gave 26, which upon hydrolysis furnished keto-diene 27. This substance underwent Cope rearrangement with transposition of the methallyl group from C-3 to C-7. Selective, oxidative cleavage of the terminal olefin led to 2, a key intermediate for synthetic entry to the trisporic acid system.

The family of naturally occurring, fungal hormones known as trisporic acids (1a-c)[1] possesses a structure based upon an alkylated cyclohexenone carboxylic acid.[2] Two previous syntheses of this system have each relied upon a relatively inefficient, intramolecular aldol condensation of an acyclic precursor for construction of the cyclohexenone moiety.[3,4]

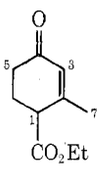


1a, $R_1 = R_2 = H$
b, $R_1 = R_2 = O$ (and cis-9,10)
c, $R_1 = H$, $R_2 = OH$ (and cis-9,10)

The diketo ester 2 potentially represents a highly versatile intermediate for elaboration of the trisporic skeleton and its analogs. In fact, Isoe, *et al.*,[4] have shown that the 7,8-dehydro version of 2 can be converted into cis and trans isomers of methyl trisporates B and C by a straightforward Wittig reaction. A particularly attractive means of access to 2 appeared to lie through sequential alkylation of Hagemann's ester (3), and we describe herein the outcome of alkylation studies on 3 with methyl and methallyl halides which has led to a convenient synthesis of the key trisporic acid intermediate 2.



2



3

Since Hagemann's ester has four possible sites (C-1, -3, -5, and -7) at which alkylation could, in principle, occur, and since the synthesis of 2 depends upon selective introduction of substituents at three of these, it became of primary importance to determine the relative site preference for alkylation in this ambident system. Aside from the generally accepted dictum that alkylation of Hagemann's ester occurs at C-3,[5] little is known of the behavior of 3 in multiple alkylation, and such scanty information as exists is largely contradictory.[6-8]

Results

Hagemann's ester (3) was allowed to react with methyl iodide in the presence of sodium ethoxide to give monomethylated product in 83% yield. Nmr evidence revealed that 4 (C-3 CH_3, δ 1.81) and 5 (C-1 CH_3, δ 1.42) were formed in an approximate ratio of 4:1, a result in general agreement with the findings of Nasipuri, *et al.*[9] Alkylation of 3 under similar conditions with methallyl chloride gave 6 in 82% yield. No C-1 methallyl derivative could be found in this case, although possibly as much as 5% could have escaped detection.

The mixture of 4 and 5 was treated with methyl iodide and potassium *tert*-butoxide as base to give a mixture of 7 and 8 accompanied by unreacted 5 (Scheme I). The three keto esters were easily distinguished by means of their characteristic methyl group shifts, which indicated the ratio of 7 (C-2 CH_3, δ 2.00):8 (C-3 CH_3, δ 1.82):5 (C-2 CH_3, δ 1.96) as 2:2:1. By monitoring this reaction using gas chromatography, it was ascertained that both 7 and 8 arose from 4 and that 5 was methylated only very slowly if at all. This accords with the anticipated ease of formation of the endocyclic and more extensively conjugated enolate from 4, as contrasted with the exocyclic enolate from 5. The formation of both 7 and 8 from 4 is at variance with the results of Nazarov and Zavyalov,[7] who reported exclusive formation of 7, but it does support the earlier work of Mukharji.[6] The mixture of 7 and 8 could not be cleanly separated by distillation, and hence a method based upon their differing reactivity toward ketalization was employed.[10] Upon treatment of the mixture with ethylene

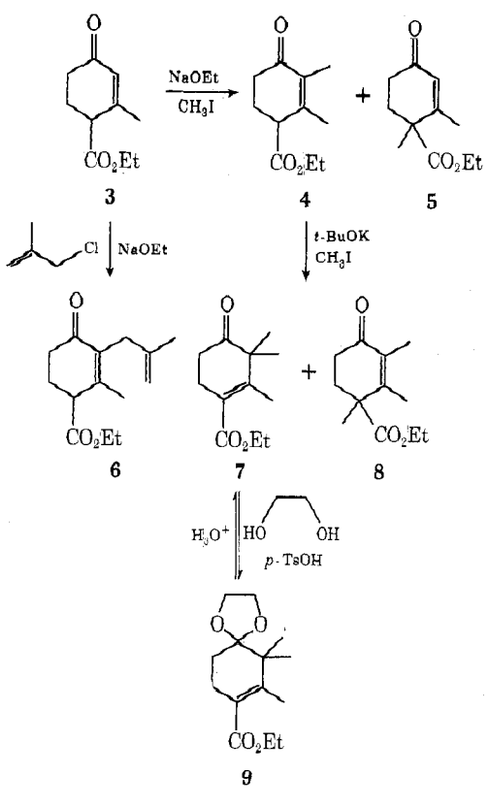
Table I
Methallylation of Keto Ester 4

Base	Temps °C	Methallyl halide	Ratio[a] of 18:19
NaOEt–EtOH	−25	Chloride	2:1
LICA[b]	−5	Chloride	1:1
LDA[c]	−70	Chloride	3:5
NaH–dioxane	101	Chloride	**19** only
t-BuOK–*t*-BuOH	83	Chloride	**19** only
t-BuOK–*t*-BuOH	83	Bromide	**19** only

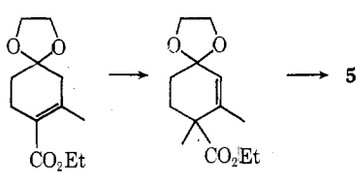
[a] Ratio calculated from area comparison on gas chromatogram. [b] Lithium *N*-isopropylcyclohexylamide. [c] Lithium diethylamide.

glycol in benzene containing *p*-toluenesulfonic acid, only 7 formed a ketal (9). This was readily separated from 8 by distillation, and 7 was recovered in high yield by hydrolysis. The overall yield of the desired isomer 8 from Hagemann's ester was *ca.* 20%.

Scheme I

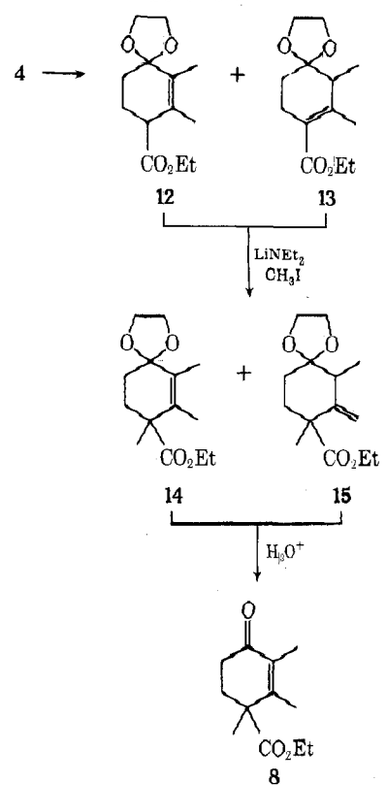


An alternate route to 8 which avoids formation of the unwanted 2,3,3-trisubstituted isomer 7 is shown in Scheme II. As a model for this approach, the ethylene ketal (**10**),[11] derived from Hagemann's ester, was treated with methyl iodide in the presence of lithium diethylamide to give **11** in 71% yield. The latter, upon hydrolysis of

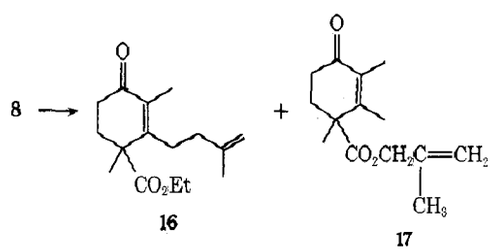


the ketal function, afforded **5**. The strong preference by **10** for α- rather than γ-alkylation of the unsaturated ester function has ample precedent,[12] and methylation at C-1 of this enolate is probably further enhanced by hindrance from the spiro center adjacent to the γ site. An analogous alkylation of the mixture of isomeric ketals **12** and **13** (1:1) derived from **4** (86%)[13] gave endocyclic (**14**) and exocyclic (**15**), C-1 methylated, β,γ-unsaturated esters (*ca.* 1:1) in 75% yield (Scheme II). Acidic hydrolysis of this mixture gave keto ester **8** in 56% overall yield from **4**.

Scheme II



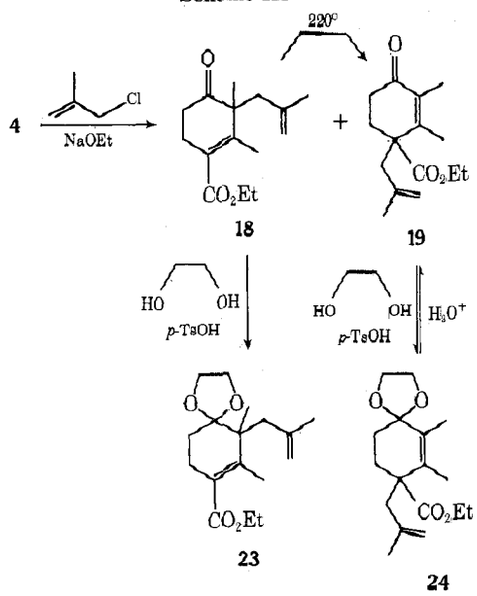
Unfortunately, attempts to alkylate **8** were less successful. For example, treatment of **8** with methallyl bromide and potassium *tert*-butoxide gave only 5% of **16**; vigorous conditions gave up to 35% of transesterification product **17**. The use of other bases such as lithium diethylamide,



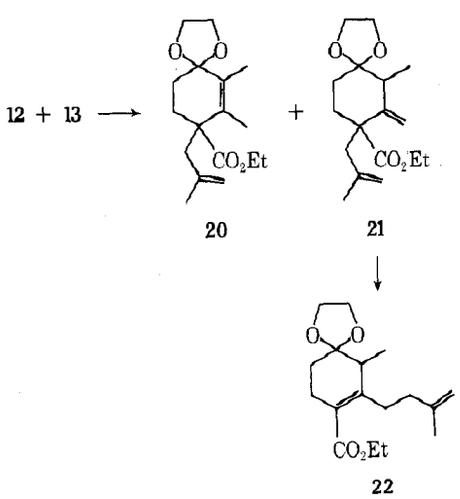
lithium hexamethyldisilylamide, and sodium hydride in benzene were equally unrewarding. It became apparent from these studies that the conjugated enolate from α,β-unsaturated ketone **8** is formed with considerable difficulty and only under conditions where side reactions, particularly decarboxylation, become competitive.

The introduction of alkyl substituents into the nucleus of Hagemann's ester clearly makes succeeding alkylations more difficult, with the effect most pronounced when the alkyl group is first incorporated at C-1 (for example, **5** is resistant to further alkylation). On the other hand, the introduction of the initial alkyl substituent at C-3 does not interfere with a subsequent C-1 alkylation, since **12** and **13** undergo smooth methylation to **14** and **15**, respectively. Consequently, **4** was subjected to methallyl chloride and sodium ethoxide (Scheme III), leading to a mixture of **18** (1715 cm^{-1}; C-3 CH_3, δ 1.22) and **19** (1738, 1675 cm^{-1}; C-3 CH_3, δ 1.81). As can be seen from the results in Table I, the proportion of methallylated products is markedly

Scheme III



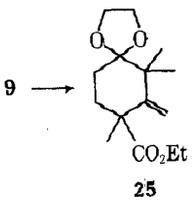
dependent upon temperature and the base employed. That 19 is the thermodynamically favored isomer of this pair is apparent from the Cope rearrangement of 18 to 19 in >90% yield at 220°. Presumably, a similar driving force is operative in the alkylation reaction, since more vigorous conditions generally led to a higher proportion of 19. In contrast to the methallylation of 4, the analogous alkylation of the mixture of ketals 12 and 13 gave exclusively C-1 methallyl derivatives as a mixture of endocyclic (20) and exocyclic (21) olefins. The latter underwent a Cope



rearrangement to 22 upon pyrolysis, the migration of the exo double bond to an endo position in concert with its conjugation to the ester providing obvious thermodynamic advantage. No Cope rearrangement of 20 is observed under these conditions. Attempts to complete the alkylation sequence by methylation of 22 at C-1 in analogy with the methylation of 13 gave extensive polymerization, with little prospect of a viable synthesis of 2 by this route.

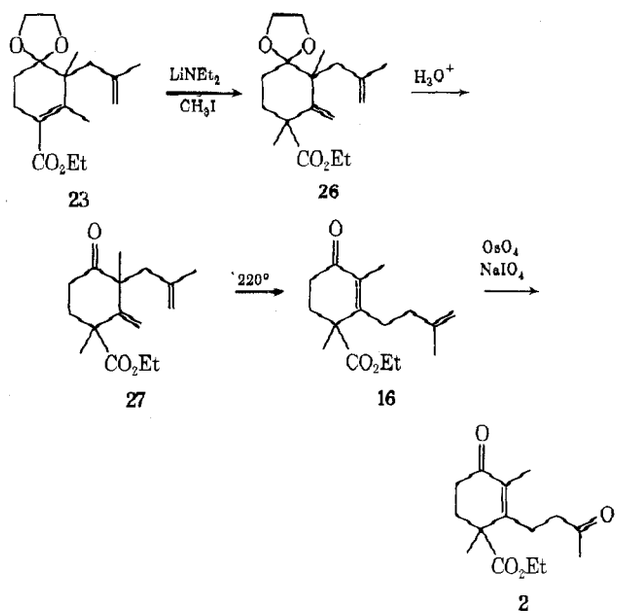
The remaining avenue to a derivative of Hagemann's ester having appropriate substitution for conversion to 2 lay through keto ester 18. In order to separate 18 from its isomer 19 produced in the methallylation of 4, the mixture was treated with ethylene glycol in the presence of *p*-toluenesulfonic acid to effect a selective ketalization of 18. In contrast to the situation with 7 and 8, where only the β,γ-unsaturated ketone formed an ethylene ketal, both ketals 23 and 24 were isolable. However, 24 was hydrolyzed very rapidly in water, thus permitting a facile removal of 23 by distillation.

As a model for the projected C-1 methylation of 23, ketal 9 was treated with methyl iodide and lithium diethylamide to give 25 in 83% yield. The presence of a new

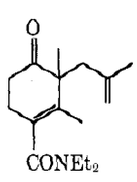


methyl group and an exocyclic methylene function was confirmed by both ir (906 cm^{-1}) and nmr data [δ 5.21 (2 H), 1.35 (3 H, s)]. The analogous methylation of 23 gave 26 [δ 5.30 (2 H), 4.77 (2 H), 1.37 (3 H, s)], which upon hydrolysis with ethanolic hydrochloric acid for 20 hr produced keto ester 27 in 72% overall yield based upon 23 (Scheme IV). Direct methylation of 18 was less satisfacto-

Scheme IV



ry and led to 27 in only 46% yield, accompanied by a substance having the properties of amide 28.



Transposition of the methallyl group from C-3 to C-7 in 27 was effected by pyrolysis at 220° for 13 min, resulting in a 97% yield of 16 (1728, 1668, 1620 cm^{-1}). As in the conversion 21 → 22, the genesis of a conjugated carbonyl as well as an endocyclic, tetrasubstituted olefin makes this reorganization highly favorable. The terminal C=C of 16 underwent rapid, oxidative cleavage with a catalytic quantity of osmium tetroxide, followed by 1 equiv of sodium periodate in aqueous dioxane, to give a 78% yield of diketo ester 2. The synthesis of 2 from Hagemann's ester *via* 4, 18, 23, 26, 27, and 16 allows its preparation in an overall yield of *ca.* 15%, and requires only one distillative separation (of 23) en route. This approach therefore offers a convenient pathway from a readily available starting

material to a system having appropriate substitution for elaboration of the trisporic acids.

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 137 infrared spectrophotometer as liquid films. Nmr spectra were obtained with a Varian HA-100 spectrometer in $CDCl_3$ solution, with TMS as internal reference. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., or by Dr. Susan Rottschaefer at the Department of Chemistry, University of Oregon, Eugene, Oreg. Low- and high-resolution mass spectra were measured by Dr. Rottschaefer. Analytical and preparative gas chromatography was carried out on a Varian Aerograph Model 700 gas chromatograph, using a 5 ft × 0.25 in. SE-30 (20% on Chromosorb G) column.

Methylation of Hagemann's Ester (3). Hagemann's ester (27.0 g, 0.148 mol) was added to a solution of sodium ethoxide, prepared from 3.85 g (0.167 mol) of sodium in 250 ml of absolute ethanol. After stirring at 65° for 2.5 hr, 25 ml of methyl iodide was added. The solution was stirred at room temperature for 20 min, and then at 65° for 1 hr. Ethanol was removed under reduced pressure and the residue was taken up into ether and water. The aqueous layer was extracted with ether twice. The combined ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo* and the residue was distilled at 95–105° (0.2 mm), affording 24.3 g (83%) of **4** (C-3 CH_3, δ 1.81) and **5** (C-1 CH_3, δ 1.42) in a ratio of 4:1.

Methylation of Ethyl 2,3-Dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (4). The mixture of keto esters **4** and **5** (2.01 g, 10.2 mmol) was added to a solution prepared from 1.60 g (14.5 mmol) of potassium *tert*-butoxide in 30 ml of dry *tert*-butyl alcohol. The solution was stirred at 50° under nitrogen for 30 min. The solution was then cooled to room temperature, and 2 ml of methyl iodide was added. The resulting mixture was stirred for 10 min at 26° and then at 45° for another 20 min. The solvent was removed under reduced pressure, ether was added to dissolve the residue, and the solution was filtered. The filtrate was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 96–110° (0.2 mm) afforded 1.51 g (66%) of a mixture of keto esters **7** (C-2 CH_3, δ 2.00), **8** (C-3 CH_3, δ 1.82), and **5** (C-2 CH_3, δ 1.96) in a ratio of 2:2:1. Preparative gas chromatography afforded a sample of **8**: ir (film) 1725, 1667, 1620, 1242, 1180, 1095, 1020 cm^{-1}; nmr ($CDCl_3$) δ 4.18 (2 H, q, J = 7.2 Hz), 2.60–1.80 (4 H, m), 1.90 (3 H, s), 1.82 (3 H, s), 1.44 (3 H, s), 1.26 (3 H, t, J = 7.2 Hz); mass spectrum m/e 210 (M^+).

Anal. Calcd for **8** $C_{12}H_{18}O_3$: C, 68.55; H, 8.65. Found: C, 68.36; H, 8.73.

Ethyl 4,4-Ethylenedioxy-2,3,3-trimethylcyclohex-1-enyl-1-carboxylate (9). A 20.0-g sample of keto esters **7**, **8**, and **5** was heated under reflux in 150 ml of benzene with a catalytic amount of *p*-toluenesulfonic acid and 6 ml of ethylene glycol for 12 hr, with provision for water removal *via* a Dean-Stark trap. Benzene was removed from the mixture under reduced pressure, and the solution was extracted with ether. The ethereal extract was washed with aqueous potassium carbonate solution and brine, and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. The crude product weighed 20.5 g. Distillation of the product through a 36-in. spinning-band column afforded 5.9 g (25% overall yield from **4**) of keto ester **8**, 90% pure, bp 63° (0.15 mm). Evaporative distillation of the high-boiling, residual oil at 110° (0.3 mm) yielded 6.4 g (*ca.* 22% overall yield from **4**) of **9**: ir (film) 1715, 1630, 1235, 1205, 1086, 1056 cm^{-1}; nmr ($CDCl_3$) 4.19 (2 H, q, J = 7.0 Hz), 3.99 (4 H, s), 2.45 (2 H, t, J = 6.6 Hz), 1.93 (3 H, s), 1.77 (2 H, t, J = 6.6 Hz), 1.27 (3 H, t, J = 7.0 Hz), 1.11 (6 H, s); mass spectrum m/e 254 (M^+).

Anal. Calcd for $C_{14}H_{22}O_4$(9): C, 66.12; H, 8.72. Found: C, 66.66; H, 8.79.

Ethyl 2,3,3-Trimethyl-4-oxocyclohex-2-enyl-1-carboxylate (7). Ketal ester **9** (140 mg, 0.55 mmol) was added to a solution of 10 ml of 6 *N* hydrochloric acid in 30 ml of ethanol, and the mixture was stirred at room temperature for 15 hr. Brine (100 ml) was added and the solution was extracted twice with dichloromethane. The dichloromethane extract was washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*. Evaporative distillation of the residue at 90° (0.2 mm) afforded 105 mg (91%) of **7**: ir (film) 1725, 1630, 1222, 1048 cm^{-1}; nmr ($CDCl_3$) δ 4.25 (2 H, q, J = 7.0 Hz), 2.80–2.40 (4 H, m), 2.00 (3 H, s), 1.30 (3 H, t, J = 7.0 Hz), 1.22 (6 H, s); mass spectrum m/e 210 (M^+).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.65. Found: C, 68.20; H, 8.54.

Ketalization of Keto Ester 4. Keto ester **4** (8.50 g, 0.43 mol) was added to a solution containing 1.5 g of *p*-toluenesulfonic acid and 20 ml of ethylene glycol in 200 ml of benzene, and the mixture was heated under reflux for 20 hr, with provision for water removal *via* a Dean-Stark trap. The benzene layer was washed with potassium bicarbonate solution and saturated brine, and dried with anhydrous magnesium sulfate. Benzene was removed *in vacuo*, and evaporative distillation of the residue at 111° (1.5 mm) gave 8.9 g (86%) of **12** (2 CH_3, s, δ 1.68 and 2.03) and **13** (CH_3, s, δ 2.03).

Methylation of Ketal Esters 12 and 13. A mixture of ketal esters **12** and **13** (120 mg, 0.50 mmol) was added to a solution of lithium diethylamide, prepared from 2.8 mmol (1.5 ml of a 1.9 *M* hexane solution) of *n*-butyllithium and 300 mg (4.1 mmol) of diethylamine in 10 ml of tetrahydrofuran, precooled in an ice–water bath. A red solution was formed after stirring for 30 min. Methyl iodide (1 ml) was added and the mixture was stirred for a further 2 min. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*, leaving 95 mg (75%) of ketal esters **14** and **15**. The nmr spectrum of this mixture showed the following: a doublet (equivalent to 1 H) at δ 4.97, two singlets at δ 4.02 and 3.95, a singlet at δ 1.62, and two singlets at δ 1.35 and 1.28.

Ethyl 1,2,3-Trimethyl-4-oxocyclohex-2-enyl-1-carboxylate (8). A 70-mg (0.27 mmol) sample of the mixture of methylated ketal esters **14** and **15** was stirred with 20 ml of 6 *N* hydrochloric acid in 60 ml of ethanol for 7 hr. Brine (100 ml) was added and the solution was extracted twice with dichloromethane. The dichloromethane extract was washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*, leaving 50 mg (86%) of **8** identical with the material prepared by methylation of **4**.

Ethyl 4,4-Ethylenedioxy-2-methylcyclohex-1-enyl-1-carboxylate (10). A 2.0-g (0.011 mol) sample of Hagemann's ester (**3**) was heated under reflux in 50 ml of benzene with a catalytic amount of *p*-toluenesulfonic acid and 3 ml of ethylene glycol for 21 hr, with provision for water removal *via* a Dean-Stark trap. The benzene layer was washed with potassium bicarbonate solution and saturated brine, and dried with anhydrous magnesium sulfate. Benzene was removed *in vacuo*. Evaporative distillation of the residual oil at 105° (0.25 mm) gave 1.9 g (78%) of **10**: ir (film) 1720, 1650, 1238, 1088, 1066 cm^{-1}; nmr ($CDCl_3$) δ 4.21 (2 H, q, J = 7.0 Hz), 3.99 (4 H, s), 2.55 (2 H, t, J = 6.5 Hz), 2.39 (2 H, s), 2.03 (3 H, s), 1.75 (2 H, t, J = 6.5 Hz), 1.28 (3 H, t, J = 7.0 Hz).

Ethyl 4,4-Ethylenedioxy-1,2-dimethylcyclohex-2-enyl-1-carboxylate (11). Ketal ester **10** (0.10 g, 0.44 mmol) was added to a solution of lithium diethylamide, prepared from 1.9 mmol (1.0 ml of a 1.9 *M* hexane solution) of *n*-butyllithium and 0.20 g (2.7 mmol) of diethylamine in 10 ml of tetrahydrofuran, precooled in an ice–water bath. A dark solution was obtained after stirring for 30 min. Methyl iodide (0.5 ml) was added and the mixture was stirred for a further 1 min. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 115° (0.2 mm) afforded 75 mg (71%) of **11**: ir (film) 1738, 1648, 1250, 1106, 1080, 1022 cm^{-1}; nmr ($CDCl_3$) δ 5.47 (1 H, s), 4.18 (2 H, q, J = 7.0 Hz), 3.98 (4 H, s), 2.50–1.70 (4 H, m), 1.73 (3 H, s), 1.30 (3 H, s), 1.23 (3 H, t, J = 7.0 Hz); mass spectrum m/e 240 (M^+).

Ethyl 1,2-Dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (5). Ketal ester **11** (250 mg, 1.04 mmol) was shaken with 50 ml of 3 *N* hydrochloric acid in 50 ml of ether for 3 min. The aqueous layer was extracted with ether once. The combined, ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 95° (0.2 mm) afforded 140 mg (65%) of **5**: ir (film) 1738, 1685, 1635, 1245, 1175, 1090, 1020 cm^{-1}; nmr ($CDCl_3$) δ 5.94 (1 H, s), 4.21 (2 H, q, J = 6.4 Hz), 2.70–1.60 (4 H, m), 1.96 (3 H, s), 1.42 (3 H, s), 1.26 (3 H, t, J = 6.4 Hz); mass spectrum m/e 196 (M^+).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.60; H, 8.27.

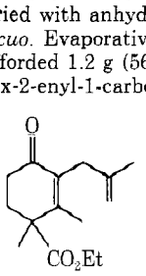
Methallylation of Keto Ester 8. Keto ester 8 (0.50 g, 2.4 mmol) was added to a solution prepared from 98 mg (2.5 mmol) of potassium in 0.5 ml of *tert*-butyl alcohol and 6 ml of tetrahydrofuran. The mixture was stirred at room temperature for 1 hr, during which a deep red color was formed. Methallyl bromide (0.34 g, 2.5 mmol) in 2.5 ml of tetrahydrofuran was added, and the mixture was stirred for 15 min and then at 73° for 14 hr. Solvent was removed under reduced pressure. The residue was taken up into water and ether. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*, leaving 0.40 g of crude product. Gas chromatographic analysis of the product showed that 60% was the unreacted keto ester **8**, 35% was the transesterified compound **17**, and 5% was the methallylated product **16**. The latter two compounds were obtained in pure form by preparative gas chromatography. Methallyl 1,2,3-trimethyl-4-oxocyclohex-2-enyl-1-carboxylate (**17**) had ir (film) 1735, 1671, 1624, 1230, 1170, 1085, 895 cm^{-1}; nmr ($CDCl_3$) δ 4.92 (2 H, s), 4.52 (2 H, s), 2.70–1.50 (4 H, s), 1.89 (3 H, s), 1.79 (3 H, s), 1.72 (3 H, s), 1.44 (3 H, s).

Ethyl 2-(3-methylbut-3-enyl)-1,3-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (**16**) had ir (film) 1728, 1668, 1620, 1240, 1180, 1092, 1022, 890 cm^{-1}; nmr ($CDCl_3$) δ 4.76 (2 H, s), 4.17 (2 H, q, J = 7.0 Hz), 2.70–1.55 (8 H, m), 1.82 (3 H, s), 1.75 (3 H, s), 1.45 (3 H, s), 1.24 (3 H, t, J = 7.0 Hz); mass spectrum m/e 264 (M^+).

Anal. Calcd for $C_{16}H_{24}O_3$ (**16**): C, 72.69; H, 9.15. Found: C, 72.37; H, 9.35.

Ethyl 3-Methallyl-2-methyl-4-oxocyclohex-2-enyl-1-carboxylate (6). Hagemann's ester (**3**, 10.0 g, 0.055 mol) was added to a solution of sodium ethoxide, prepared from 1.5 g (0.065 of sodium in 40 ml of absolute ethanol, and the mixture was stirred at 80° for 5 hr. Methallyl chloride (8.0 g, 0.087 mol) was added, and the mixture was stirred for 13 hr. Ethanol was removed under reduced pressure, and the residue was taken up into ether and water. The aqueous layer was extracted with ether twice. The combined ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 106–130° (0.7 mm) afforded 10.5 g (82%) of **6**: ir (film) 1730, 1672, 1635, 890 cm^{-1}; nmr ($CDCl_3$) δ 4.65 (2 H, d, J = 14 Hz), 4.22 (2 H, q, J = 7.0 Hz), 3.34 (1 H, t, J = 4.2 Hz), 3.06 (2 H, d, J = 5.0 Hz), 2.80–1.80 (4 H, m), 1.94 (3 H, s), 1.72 (3 H, s), 1.26 (3 H, t, J = 7.0 Hz).

Methylation of Keto Ester 6. Keto ester 6 (2.0 g, 8.5 mmol) was stirred with 1.05 g (9.4 mmol) of potassium *tert*-butoxide in 60 ml of glyme at room temperature for 10 hr. A dark solution was obtained. Methyl iodide (2.0 g, 14 mmol) was added, and the mixture was stirred for 2 hr at 26° and for a further 0.5 hr at 55°. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The aqueous layer was extracted with ether twice. The combined ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 110° (0.05 mm) afforded 1.2 g (56%) of ethyl 3-methallyl-1,2-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (**29**) (3 CH_3 singlets at δ 1.85, 1.73, and 1.44) and 18 (3 CH_3 singlets at δ 2.04, 1.63, and 1.22) in a ratio of 1:1.



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Ethyl 3-Methallyl-2,3-dimethyl-4-oxocyclohex-1-enyl-1-carboxylate (18). Keto ester 4 (34.0 g, 0.173 mol) in a solution of sodium ethoxide, prepared from 4.9 g (0.21 mol) of sodium in 250 ml of absolute ethanol, was stirred at room temperature for 33 hr. Methallyl chloride (40 ml) was added, and the mixture was stirred for 40 min, and then for a further 4 hr at 60°. Ethanol was removed under reduced pressure and the residue was taken up into ether and water. The aqueous layer was extracted with ether twice. The combined ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residual oil at 105–130° (0.7 mm) afforded 35.1 g of a mixture of **4**, **18** and **19**, which gas chromatographic analysis (column temperature 170°) showed to be in the ratio 50:33:17. Nmr analysis confirmed the ratio of **18** to **19** as 2:1. Distillation of the product through a 36-in. spinning-band column afforded **18**: bp 88° (0.15 mm); *ca.* 85% pure; ir (film) 1715, 1645, 1242, 1203, 1044, 898 cm^{-1}; nmr ($CDCl_3$) δ 4.70 (2 H, d, J = 16 Hz), 4.25 (2 H, q, J = 7.0 Hz), 2.80–2.10 (6 H, m), 2.04 (3 H, s), 1.63 (3 H, s), 1.35 (3 H, t, J = 7.0 Hz), 1.22 (3 H, s); mass spectrum m/e 250.157 (parent, calcd for $C_{15}H_{22}O_3$, 250.157).

Pyrolysis of Keto Ester 18. Keto ester **18** (0.10 g, 0.40 mmol) was heated in an air bath at 220° for 25 min. Evaporative distillation at 110–120° (0.2 mm) gave 0.09 g (90%) of **19**: ir (film) 1738, 1675, 1623, 1204, 1168, 1072, 1018, 895 cm^{-1}; nmr ($CDCl_3$) δ 4.86 (2 H, d, J = 11 Hz), 4.20 (2 H, q, J = 7.0 Hz), 3.00–2.00 (6 H, m), 1.97 (3 H, s), 1.81 (3 H, s), 1.69 (3 H, s), 1.25 (3 H, t, J = 7.0 Hz); mass spectrum m/e 250.156 (M^+, calcd for $C_{15}H_{22}O_3$, 250.157).

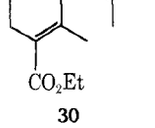
Methallylation of the Mixture of 12 and 13. A mixture of ketal esters **12** and **13** (8.65 g, 0.036 mol) was added to a solution of lithium diethylamide, prepared from 0.112 mol (48 ml of a 2.34 *M* hexane solution) of *n*-butyllithium and 8.6 g (0.18 mol) of diethylamine in 180 ml of tetrahydrofuran, precooled in an ice–water bath. The solution was stirred for 25 min, methallyl chloride (20 g, 0.215 mol) was added, and the mixture was stirred for a further 40 min. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the residue at 120–160° (0.4 mm) afforded 8.1 g (76%) of a mixture of **20** and **21** (vinyl H at δ 5.36, exocyclic methylene).

Ethyl 4,4-Ethylenedioxy-2-(3-methylbut-3-enyl)-3-methylcyclohex-1-enyl-1-carboxylate (22). A mixture of **20** and **21** (0.50 g) was heated in an air bath at 220° for 15 min. Evaporative distillation afforded 0.43 g of a mixture of **20** and **22**. Preparative gas chromatography afforded a sample of **20**: ir (film) 1728, 1655, 1064, 892 cm^{-1}; nmr ($CDCl_3$) δ 4.80 (2 H, d, J = 5.8 Hz), 4.14 (2 H, q, J = 7.0 Hz), 4.00 (4 H, s), 3.00–1.50 (6 H, m), 1.72 (3 H, s), 1.65 (3 H, s), 1.61 (3 H, s), 1.23 (3 H, t, J = 7.0 Hz).

The mixture of **20** and **22** (0.35 g) was shaken with a solution containing 50 ml of ether and 50 ml of 6 *N* hydrochloric acid for 2 min. The ether layer was separated and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*, leaving 0.25 g of residual oil which by chromatographic analysis was found to be a mixture of **19** and **22** (1:1). Preparative gas chromatography afforded a sample of **22**: ir (film) 1719, 1652, 1635, 1240, 1138, 1083, 886 cm^{-1}; nmr ($CDCl_3$) δ 4.74 (2 H, s), 4.19 (2 H, q, J = 7.0 Hz), 3.97 (4 H, s), 3.00–1.50 (9 H, m), 1.74 (3 H, s), 1.27 (3 H, t, J = 7.0 Hz), 1.16 (3 H, d, J = 7.4 Hz); mass spectrum m/e 294 (M^+).

Ethyl 4,4-Ethylenedioxy-3-methallyl-2,3-dimethylcyclohex-1-enyl-1-carboxylate (23). A mixture of keto esters **18** and **19** (18.0 g, 0.072 mol) was added to a solution containing 200 mg of *p*-toluenesulfonic acid and 20 ml of ethylene glycol in 150 ml of benzene. The solution was heated under reflux for 12 hr, with provision for water removal *via* a Dean-Stark trap. The benzene layer was washed with potassium bicarbonate solution and saturated brine, and dried with anhydrous magnesium sulfate. Benzene was removed *in vacuo*, leaving 16.5 g of a mixture of ketals **20**, **23**, and **30** in the ratio of 2:3:1.

The mixture of ketals (6.6 g, 0.024 mol) was shaken with a mixture of 0.20 g of *p*-toluenesulfonic acid, 20 ml of water, and 20 ml of benzene for 5 min. The benzene layer was washed with brine and dried with anhydrous magnesium sulfate. Benzene was removed *in vacuo*. The crude product was distilled with a 12-in. spinning-band column at 83° (0.06 mm), affording 3.0 g of a mixture of keto esters **18** and **19** and ketal ester **30**. Preparative gas chromatography gave **30**: nmr ($CDCl_3$) δ 5.01 (1 H, s), 4.18 (2 H, q, J = 7.0 Hz), 3.51 (2 H, t, J = 6.4 Hz), 2.0–1.5 (2 H, m), 1.91 (3 H, s), 1.71 (3 H, s), 1.61 (3 H, s), 1.27 (3 H, t, J = 7.0 Hz), 1.22 (3 H, s); mass spectrum m/e 294 (M^+).



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Further distillation of the residue at 130–145° (0.6 mm) gave 2.5 g (*ca.* 48% from **18**) of **23**: ir (film) 1740, 1678, 1240, 1078, 1054, 890 cm^{-1}; nmr ($CDCl_3$) δ 4.82 (2 H, d, J = 6.0 Hz), 4.20 (2 H, q, J = 7.0 Hz), 4.00 (4 H, s), 2.60–1.50 (6 H, m), 1.94 (3 H, s), 1.74 (3 H, s), 1.28 (3 H, t, J = 7.0 Hz), 1.09 (3 H, s); mass spectrum m/e 294.181 (M^+, calcd for $C_{17}H_{26}O_4$, 294.183).

Ethyl 4,4-Ethylenedioxy-1,3,3-trimethyl-2-methylenecyclohexyl-1-carboxylate (25). Ketal ester 9 (0.30 g, 1.18 mmol) was added to a solution of lithium diethylamide, prepared from 5.7 mmol (3.0 ml of 1.9 *M* hexane solution) of *n*-butyllithium and 0.43 g (5.7 mmol) of diethylamine in 40 ml of tetrahydrofuran, precooled in an ice–water bath. The mixture was stirred for 5 min. Methyl iodide (2 ml) was added, and the mixture was stirred for a further 5 min. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the crude product at 112° (0.1 mm) afforded 0.26 g (83%) of **25**: ir (film) 1730, 1635, 1254, 1090, 906, 806 cm^{-1}; nmr ($CDCl_3$) δ 5.21 (2 H, d, J = 4.8 Hz), 4.12 (2 H, q, J = 7.2 Hz), 3.95 (4 H, s), 2.40–1.30 (4 H, m), 1.35 (3 H, s), 1.22 (3 H, s, J = 7.2 Hz), 1.11 (3 H, s), 1.03 (3 H, s); mass spectrum *m/e* 268.169 (M^+, calcd for $C_{15}H_{24}O_4$, 268.167).

Ethyl 4,4-Ethylenedioxy-3-methallyl-1,3-dimethyl-2-methylenecyclohexyl-1-carboxylate (26). Ketal ester 23 (1.9 g, 6.5 mmol) was added to a solution of lithium diethylamide, prepared from 28.1 mmol (12 ml of 2.34 *M* hexane solution) of *n*-butyllithium and 2.2 g (30.1 mmol) of diethylamine in 50 ml of tetrahydrofuran, precooled to −78°. The mixture was stirred for 1 hr. Methyl iodide (5 g, 35.1 mmol) was added, and the mixture was stirred for a further 0.5 hr. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the crude product at 140° (0.4 mm) afforded 1.6 g (81%) of **26**: ir (film) 1730, 1630, 1250, 1080, 895 cm^{-1}; nmr ($CDCl_3$) δ 5.30 (2 H, d, J = 7.2 Hz), 4.77 (2 H, s), 4.21 (2 H, q, J = 7.2 Hz), 3.93 (4 H, s), 2.50–1.50 (6 H, m), 1.67 (3 H, s), 1.37 (3 H, s), 1.22 (3 H, t, J = 7.2 Hz), 1.05 (3 H, s); mass spectrum *m/e* 308.199 (M^+, calcd for $C_{18}H_{28}O_4$, 308.199).

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.04; H, 9.19.

Ethyl 3-Methallyl-1,3-dimethyl-2-methylene-4-oxocyclohexyl-1-carboxylate (27). A. From 26. Ketal ester 26 (0.25 g, 0.81 mmol) was stirred with 10 ml of 5 *N* hydrochloric acid and 30 ml of ethanol for 20 hr. Brine (100 ml) was added and the solution was extracted twice with dichloromethane. The dichloromethane extract was washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*. Evaporative distillation of the crude product at 99–105° (0.4 mm) afforded 0.19 g (89%) of keto ester **27**: ir (film) 1730, 1675, 1633, 1242, 1168, 1020, 898 cm^{-1}; nmr ($CDCl_3$) δ 5.22 (2 H, d, J = 3.0 Hz), 4.73 (2 H, d, J = 17 Hz), 4.19 (2 H, q, J = 7.0 Hz), 2.80–1.40 (6 H, m), 1.63 (3 H, s), 1.40 (3 H, s), 1.25 (3 H, t, J = 7.0 Hz), 1.25 (3 H, s).

B. From Keto Ester 18. Keto ester 18 (0.90 g, 3.6 mmol) was added to a solution of lithium diethylamide, prepared from 18.0 mmol (7.7 ml of 2.34 *M* hexane solution) of *n*-butyllithium in 40 ml of tetrahydrofuran, precooled in an ice–water bath. The mixture was stirred for 25 min. Methyl iodide (3.0 g, 21 mmol) was added, and the mixture was stirred for a further 5 min. Solvent was removed under reduced pressure, and the residue was taken up into ether and water. The ethereal extract was washed with brine and dried with anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the crude product at 117° (0.15 mm) afforded 0.44 g (46% yield) of **27** and 0.13 g of a high-boiling residue which was identified as amide **28**: ir (film) 1712, 1625 (strong), 895 cm^{-1}; nmr ($CDCl_3$) δ 4.73 (2 H, d, J = 16 Hz), 3.00–3.80 (4 H, broad), 1.73 (3 H, s), 1.70 (3 H, s), 1.21 (3 H, s).

Pyrolysis of Keto Ester 27. Keto ester 27 (0.44 g) was heated at 220° for 13 min in an air bath. Evaporative distillation afforded 0.43 g (97%) of keto ester **16**, identified by comparison with the methallylation product from **8**.

Ethyl 2-(3-Oxobutyl)-1,3-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (2). Keto ester 16 (0.50 g, 1.9 mol) was added to a solution containing *ca.* 10 mg of osmium tetroxide in 100 ml of water–dioxane (1:3) and the mixture was stirred for 0.5 hr. Sodium periodate (0.45 g, 2.1 mmol) in 3 ml of water was added dropwise during 2 hr, and the mixture was stirred for a further 4 hr. Saturated brine (100 ml) was added, and the solution was extracted with ether twice. The ethereal extract was washed with brine and dried over anhydrous magnesium sulfate. Ether was removed *in vacuo*. Evaporative distillation of the crude product at 132° (0.6 mm) afforded 0.39 g (78%) of **2**: ir (film) 1725, 1670, 1620, 1244, 1184, 1164, 1095, 1022 cm^{-1}; nmr ($CDCl_3$) δ 4.20 (2 H, q, J = 7.2 Hz), 2.70–1.75 (8 H, m), 2.15 (3 H, s), 1.80 (3 H, s), 1.44 (3 H, s), 1.26 (3 H, t, J = 7.2 Hz); mass spectrum *m/e* 266 (M^+).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.47; H, 8.26.

Registry No.—**2**, 51716-30-4; **3**, 487-51-4; **4**, 39880-26-7; **5**, 28790-87-6; **6**, 25533-27-1; **7**, 51716-31-5; **8**, 51716-32-6; **9**, 51716-33-7; **10**, 32917-26-3; **11**, 51716-34-8; **12**, 51716-35-9; **13**, 51716-36-0; **14**, 51716-37-1; **15**, 51716-38-2; **16**, 51716-39-3; **17**, 51716-40-6; **18**, 51716-41-7; **19**, 51752-02-4; **20**, 51716-42-8; **21**, 51716-43-9; **22**, 51716-44-0; **23**, 51716-45-1; **25**, 51716-46-2; **26**, 51716-47-3; **27**, 51716-48-4; **29**, 51716-49-5; **30**, 51716-50-8; methallyl bromide, 1458-98-6; methallyl chloride, 563-47-3.

References and Notes

(1) L. Caglioti, G. Cainelli, B. Camerino, R. Mondelli, A. Prieto, A. Quilico, T. Salvatori, and A. Selva, *Chim. Ind. (Milan)*, **46**, 961 (1964); D. J. Austin, J. D. Bu'Lock, and G. W. Gooday, *Nature (London)*, **233**, 1178 (1969). For accounts of the hormonal function of the trisporic acids, see D. M. Thomas and T. W. Goodwin, *Phytochemistry*, **6**, 355 (1967), and G. W. Gooday, *Biochem. J.*, **127**, 2P (1972).

(2) L. Caglioti, G. Cainelli, B. Camerino, R. Mondelli, A. Prieto, A. Quilico, T. Salvatori, and A. Selva, *Tetrahedron. Suppl.*, **7**, 175 (1966). Absolute configurations have been recently established: T. Reschke, *Tetrahedron Lett.*, 3455 (1969); J. D. Bu'Lock, D. J. Austin, G. Snatzke, and L. Hruban, *Chem. Commun.*, 255 (1970).

(3) J. A. Edwards, V. Schwarz, J. Fajkos, M. L. Maddox, and J. H. Fried, *Chem. Commun.*, 292 (1971).

(4) S. Isoe, Y. Hayase, and T. Sakan, *Tetrahedron Lett.*, 3691 (1971).

(5) L. I. Smith and G. F. Rouault, *J. Amer. Chem. Soc.*, **65**, 631 (1943); E. C. Horning, M. G. Horning, and E. J. Platt, *ibid.*, **71**, 1771 (1949).

(6) P. C. Mukharji, *J. Indian Chem. Soc.*, **33**, 99 (1956).

(7) I. N. Nazarov and S. I. Zavyalov, *Bull Acad. Sci. USSR. Div. Chem. Sci.*, 339 (1957).

(8) F. J. Dyer, D. A. A. Kidd, and J. Walker, *J. Chem. Soc.*, 4778 (1952).

(9) D. Nasipuri, G. Sarkan, M. Guha, and R. Roy, *Tetrahedron Lett.*, 927 (1966); D. Nasipuri, M. Mitra, and S. Venkataraman, *J. Chem. Soc., Perkin Trans. 1*, 1836 (1972).

(10) R. E. Ireland, "Organic Synthesis," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 40.

(11) E. Babbiolini, H. P. Hamlow, and K. Schaffner, *J. Amer. Chem. Soc.*, **92**, 4906 (1970).

(12) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).

(13) J. J. Brown, R. H. Lenhard, and S. Bernstein, *J. Amer. Chem. Soc.*, **86**, 2183 (1964); C. Djerassi and M. Gorman, *ibid.*, **75**, 3704 (1953).