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Title: ALKYLATION STUDIES ON HAGEMANN'S ESTER. AN APPROACH TO THE SYNTHESIS OF THE TRISPORIC ACIDS.

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James D. White

Sequential alkylation of Hagemann's ester with methyl and methallyl halides has been studied. Treatment of Hagemann's ester with methyl iodide and sodium ethoxide gave a mixture of 21 and 25 in a ratio of 4:1. Alkylation of 21 with methallyl chloride and potassium t-butoxide afforded a mixture of 37 and 38 in a ratio of 2:1. Keto ester 37 reacted with methyl iodide to furnish 47, which underwent Cope rearrangement to give 33. Oxidative cleavage of the terminal C=C of 33 with osmium tetroxide and sodium periodate afforded diketo ester 48.

ALKYLATION STUDIES ON HAGEMANN'S ESTER. AN APPROACH TO THE SYNTHESIS OF THE TRISPORIC ACIDS

by

Wing Lam Sung

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Chairman of Department of Chemistry

Redacted for Privacy

Dean of Graduate School

Date thesis is presented 6 Dec., 1973

Typed by Cheryl E. Curb for Wing Lam Sung

To my parents

"In the beginning was the Word, and the Word was with God, and the Word was God.

The same was in the beginning with God.

All things were made by him, and without Him was not anything made that was made."

---John 1:1-3.

ACKNOWLEDGEMENTS

I feel very fortunate to have had the opportunity to collaborate with Professor James D. White whose guidance and encouragement during my years of graduate research have been invaluable. It is with the greatest appreciation that I express my thanks to Dr. White.

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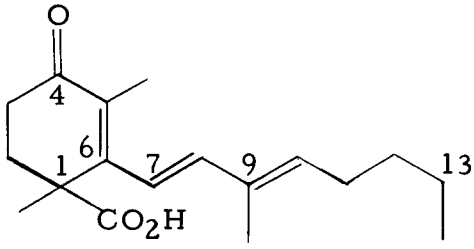
AKLYLATION STUDIES ON HAGEMANN'S ESTER. AN APPROACH TO THE SYNTHESIS OF THE TRISPORIC ACIDS

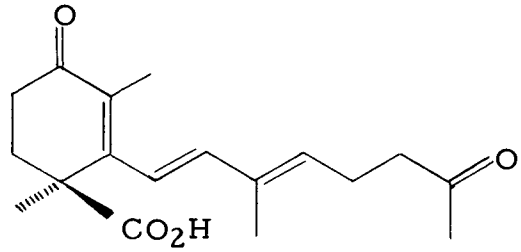
I. INTRODUCTION

The trisporic acids are a mixture of naturally occurring fungal hormones which have been isolated from the fungi Mucor mucedo and Blakeslea trispora[1]. They have been shown to initiate the formation of sexual hyphae in Mucorales[2] and to promote carotene and steroid synthesis in Blakeslea trispora[3]. Together with antheridiol and sirenin, they belong to a small group of substances having an established hormonal function in microorganisms[4].

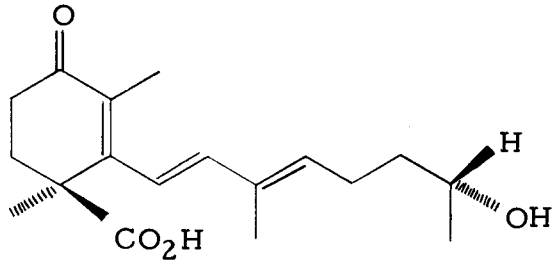
"Trisporic acid" consists of several closely related C_{18}-monocyclic trienoic acids[1] identified as trisporic acids A (1), B (2) and (principally) C(3)[5]. Natural trisporic acids C and B exist as both 9-cis and 9-trans isomers (with trans configuration at C-7)[6]. The absolute configuration is 1S in trisporic acid B and 1S, 13R in C[7,8]. The stereochemistry of trisporic acid A, a very minor metabolite, has not yet been established[9].



Trisporic Acid A (1)



Trisporic Acid B (2)
(also 9-cis)



Trisporic Acid C (3)
(also 9-cis)

Synthesis of (±)-7-trans-9-trans-trisporic acid B as its methyl ester was first reported by the Syntex group of Edwards, et al.[10]. The synthetic route adopted by these workers is outlined in Figure 1. This route involves construction of an acyclic precursor 9 which, in a key step, undergoes an intramolecular aldol condensation to 10 in poor yield.

A second synthesis has been reported by Isoe, Hayase and Sakan[11], and is outlined in Figure 2. This scheme, like that of the Syntex group, relies upon a relatively inefficient intramolecular aldol condensation for assembly of the cyclohexenone ring. The Isoe

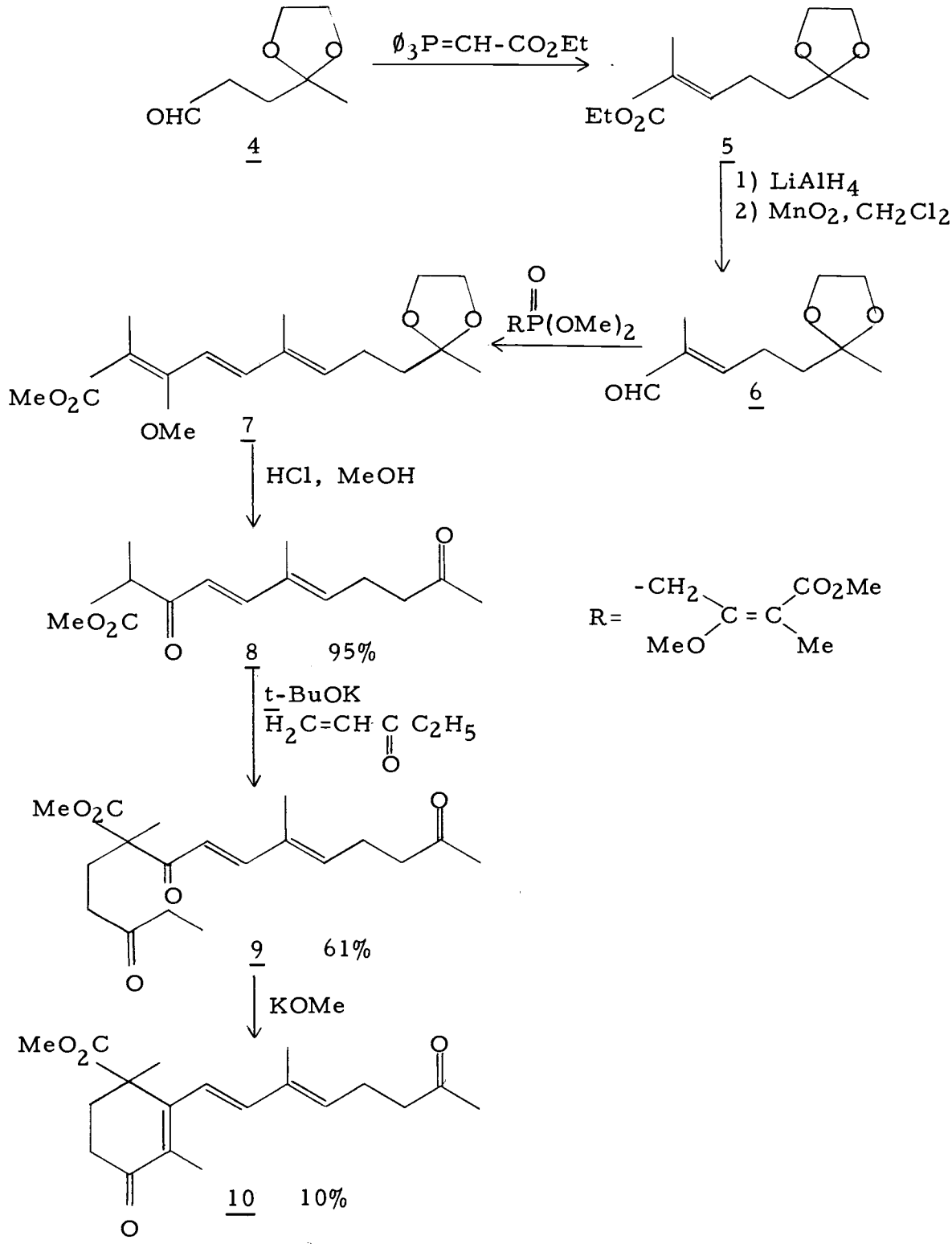

$\phi_3P=CH-CO_2Et$
OHC
4
EtO_2C
5
1) $LiAlH_4$
2) MnO_2, CH_2Cl_2
$RP(OMe)_2$
OHC
6
MeO_2C
OMe
7
HCl, MeOH
MeO_2C
8
95%
R=
$-CH_2$
CO_2Me
C = C
MeO
Me
t-BuOK
$H_2C=CH-C(=O)-C_2H_5$
MeO_2C
9
61%
KOMe
MeO_2C
10
10%

Figure 1.

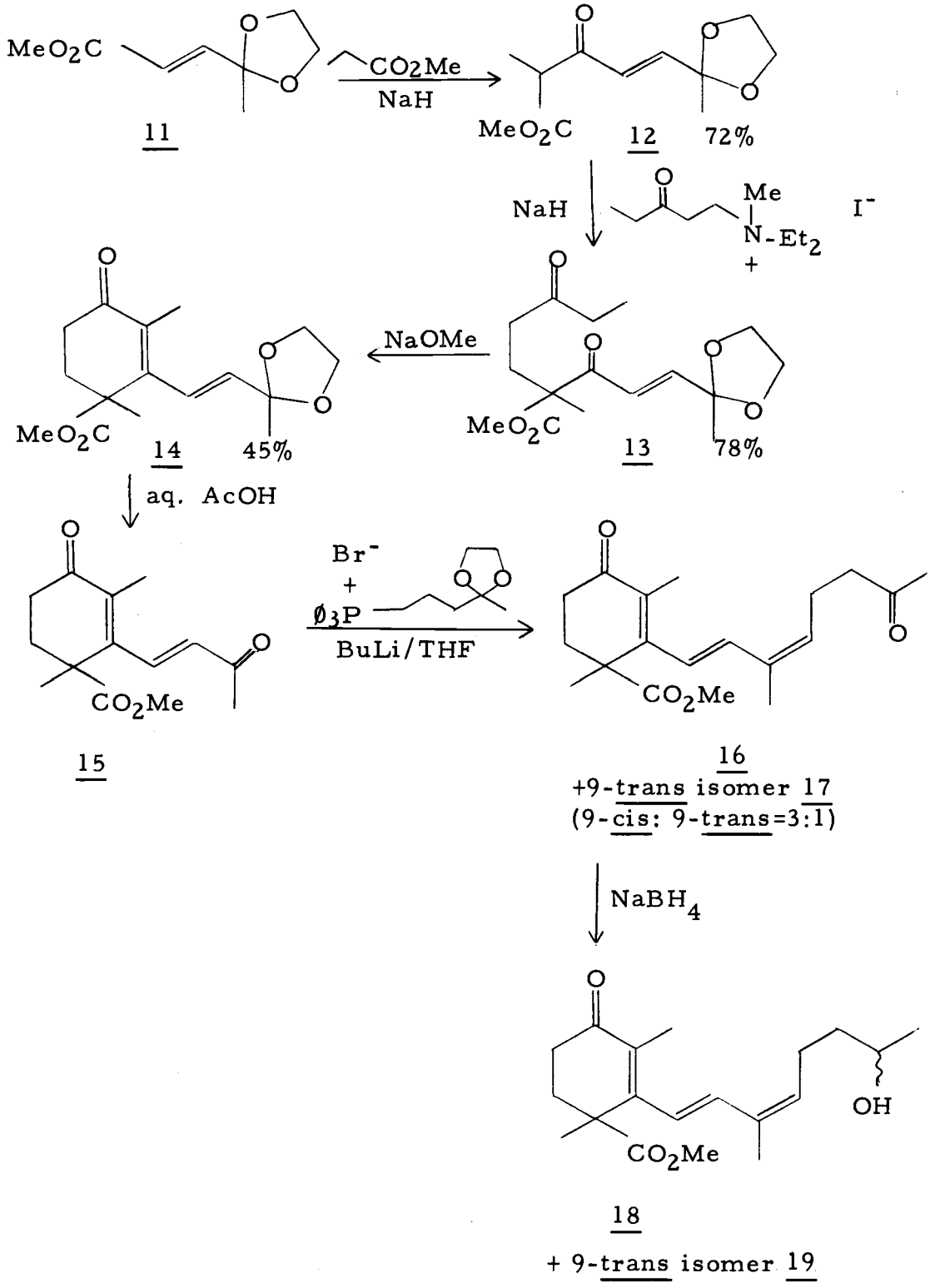
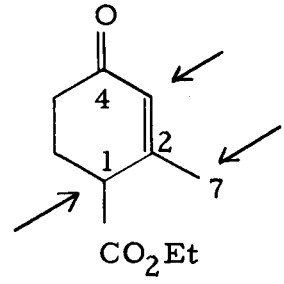

MeO2C
CO2Me
NaH
11
MeO2C
12
72%
NaH
Me
N-Et2
I-
+
NaOMe
MeO2C
14
45%
MeO2C
13
78%
aq. AcOH
Br-
+
Ø3P
BuLi/THF
CO2Me
15
CO2Me
16
+9-trans isomer 17
(9-cis: 9-trans=3:1)
NaBH4
OH
CO2Me
18
+ 9-trans isomer 19

Figure 2.

synthesis, however, does provide a useful method for chain elongation from the key intermediate 15 to give 9-cis and 9-trans isomers of methyl trisporate B.

We were attracted to an approach to the trisporic acid skeleton via an intermediate such as 15 for several reasons. Among these were the possibility of introducing structural variation at C-7, 8 (for example, as the dihydro derivative) in the trisporic acids, and also the prospect of achieving a short, efficient synthesis of this intermediate from Hagemann's ester (20).

Hagemann's ester (ethyl 2-methyl-4-oxocyclohex-2-enyl-1-carboxylate) (20) has proven to be a ubiquitous starting material in organic synthesis,[12, 13] primarily because of its reactivity toward alkylation. In fact, it appeared feasible that the structure of 15, or its 7, 8-dihydro derivative, could be built up quite simply by a sequential alkylation process starting from 20. Since the three sites (indicated by arrows) of 20 at which alkylation is to be effected all contain potentially enolizable hydrogen atoms, a logical approach would entail generation and alkylation of successive enolate anions. Introduction of the correct substitution pattern, however, requires a knowledge of the preference for alkylation site by various alkylating agents.



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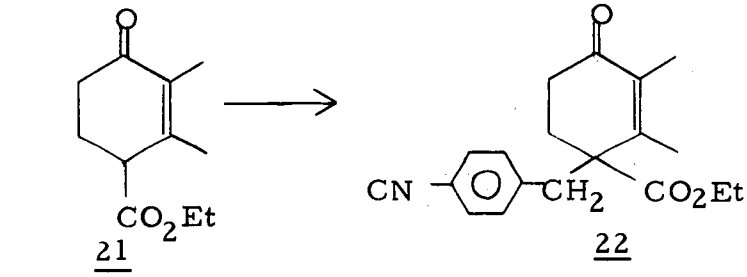
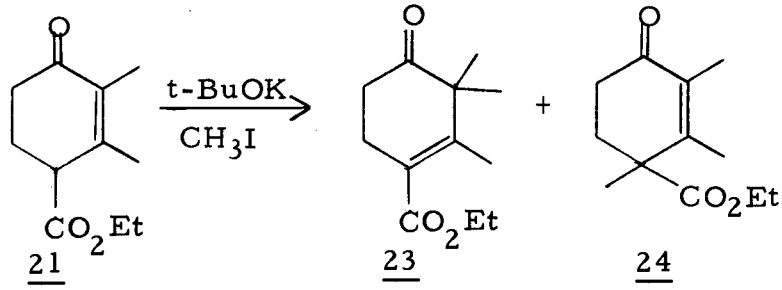
II. ALKYLATION OF HAGEMANN'S ESTER

The Methyl-Methyl-Methallyl Sequence

Although Hagemann's ester (20) has four possible sites (C-1, 3, 5, and 7) at which alkylation could, in principle, take place, alkylation has been reported by two groups to occur exclusively at C-3[14, 15]. However, Nasipuri and coworkers claimed that, with isopropyl bromide and butyl bromide, attack at C-1 accompanies C-3 substitution[16, 17].

Alkylation of a C-3 substituted derivative of Hagemann's ester was first attempted by Dyer, Kidd and Walker[18]. They obtained ethyl 1-(p-cyanobenzyl)-2, 3-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (22) from treatment of 21 with p-cyanobenzyl bromide. In a more extensive study, Mukharji carried out the methylation of 21,





and obtained a mixture of 23 and 24, with 23 as major product[19].

However, contrary to Mukharji's findings, Narzarov and Zavyalov reported that the 2,3,3-trimethyl derivative 23 was the sole product from the alkylation of 21[20].

One of the objectives at the outset of this study was therefore to establish the correct site preference for alkylation in this system. Apparently, no further alkylation of a disubstituted Hagemann's ester derivative (such as 23 or 24) has been attempted previously.

Our initial approach to synthesis of the trisporic acids was to introduce methyl groups at C-1 and C-3, and then to extend the side chain at C-2. Following the procedure of Mukharji[17], Hagemann's ester (20) was allowed to react with methyl iodide in the presence of sodium ethoxide to give a mixture of C-1 and C-3 alkylated isomers, 21 and 25, in 83% yield (Figure 3). Nmr evidence revealed the ratio of 21 (C-3 CH_3, δ 1·81) to 25 (C-1 CH_3, δ 1·42) as 4:1. The mixture of methylated ketoesters, 21 and 25, underwent a second methylation with methyl iodide, in the presence of potassium t-butoxide, leading to a mixture of 1,3- and 3,3-dimethyl derivatives (23 and 24), accompanied by some unreacted keto ester 25. Nmr evidence showed the distribution of 23 (C-2 CH_3, δ 2·00), 24 (C-3 CH_3, δ 1·82) and 25 (C-2 CH_3, δ 1·96) in the mixture as 2:2:1. These results are thus in reasonable accord with those of Mukharji[19] but are in disagreement with the findings of Narzarov and Zavyalov[20]. Furthermore, the assumption of Dyer et al. that the preferred site for

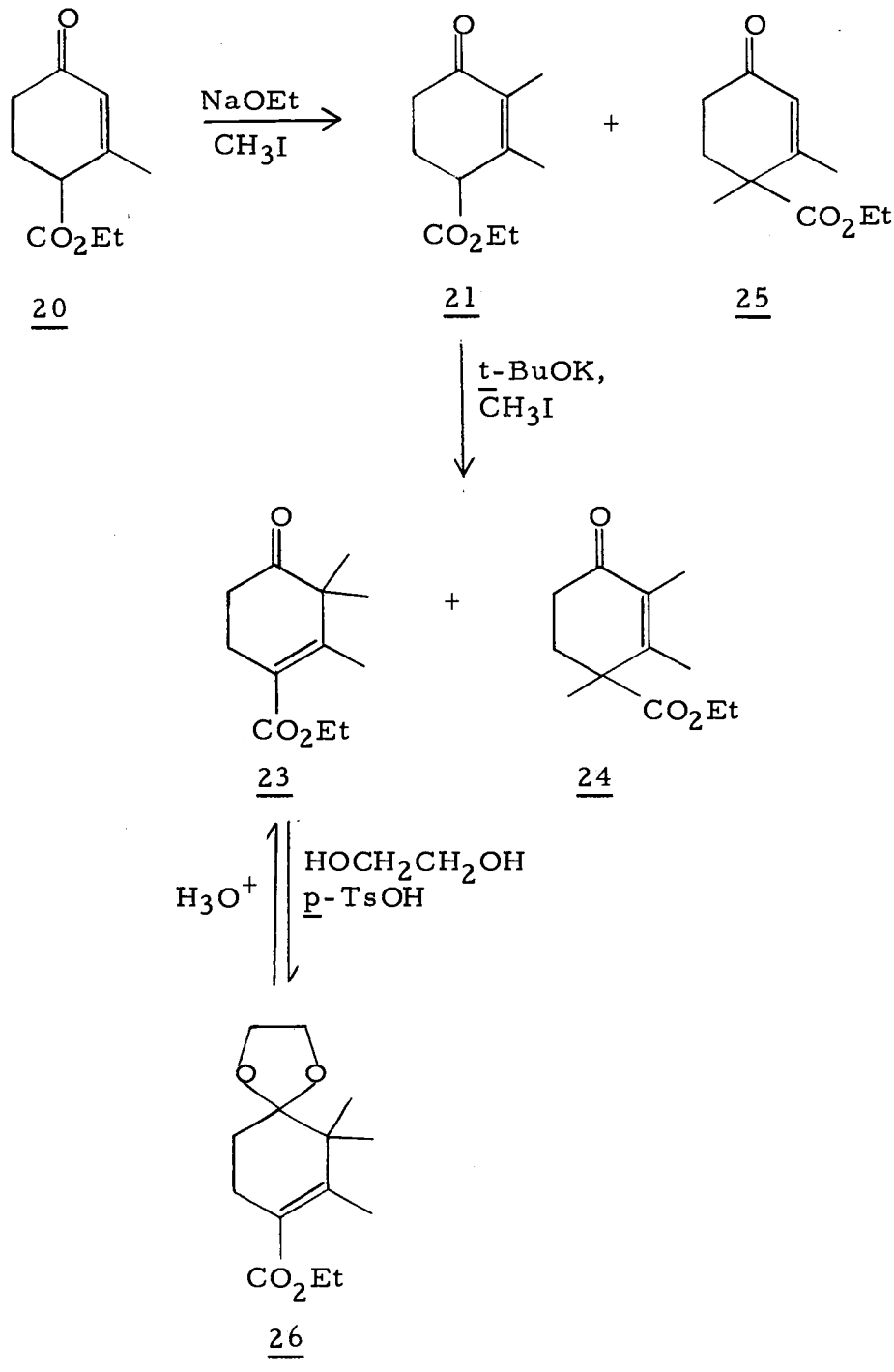

NaOEt
CH3I
CO2Et
20
21
25
t-BuOK,
CH3I
23
24
H3O+
HOCH2CH2OH
p-TsOH
26

Figure 3.

alkylation of 21 would be C-1 is seen to be groundless.

Careful gas chromatographic analysis of the methylation products of the 21/25 mixture reveals that 25 is alkylated only very slowly, if at all, and that 23 and 24 are derived almost exclusively from 21. This accords well with the anticipated ease of formation of endocyclic enolate from 21, as contrasted with the exocyclic enolate from 25. Separation of the isomers 23 and 24 by distillation proved difficult, and so a chemical method, based upon the differential reactivity of keto groups in these compounds[21], was devised, in which 23 was removed from the mixture in the form of its ketal. Upon refluxing the mixture of 23 and 24 in benzene containing ethylene glycol and a catalytic amount of p-toluenesulfonic acid, the ketal 26 (C-2 CH_3, δ 1·93; C-3 $2CH_3$, δ 1·11) was formed, whereas the α, β - unsaturated keto ester 24 (C-1 CH_3, δ 1·44; C-2 CH_3, δ 1·90; C-3 CH_3, δ 1·82) remained unreacted. These could then be separated readily by distillation through a spinning-band column. The yield of 24 from 21 was 25%. Keto ester 23 (C-2 CH_3, δ 2·00; C-3 $2CH_3$, δ 1·22) was recovered in 91% yield by subsequent hydrolysis of its ketal 26 with concentrated hydrochloric acid in ethanol-water (3:1) for 15 hr.

The 2, 3, 4-trimethyl keto ester 24 was also synthesized by an alternate route intended to avoid formation of its isomer 23 (Figure 4). Ketalization of the keto ester 21 with ethylene glycol (catalytic amount

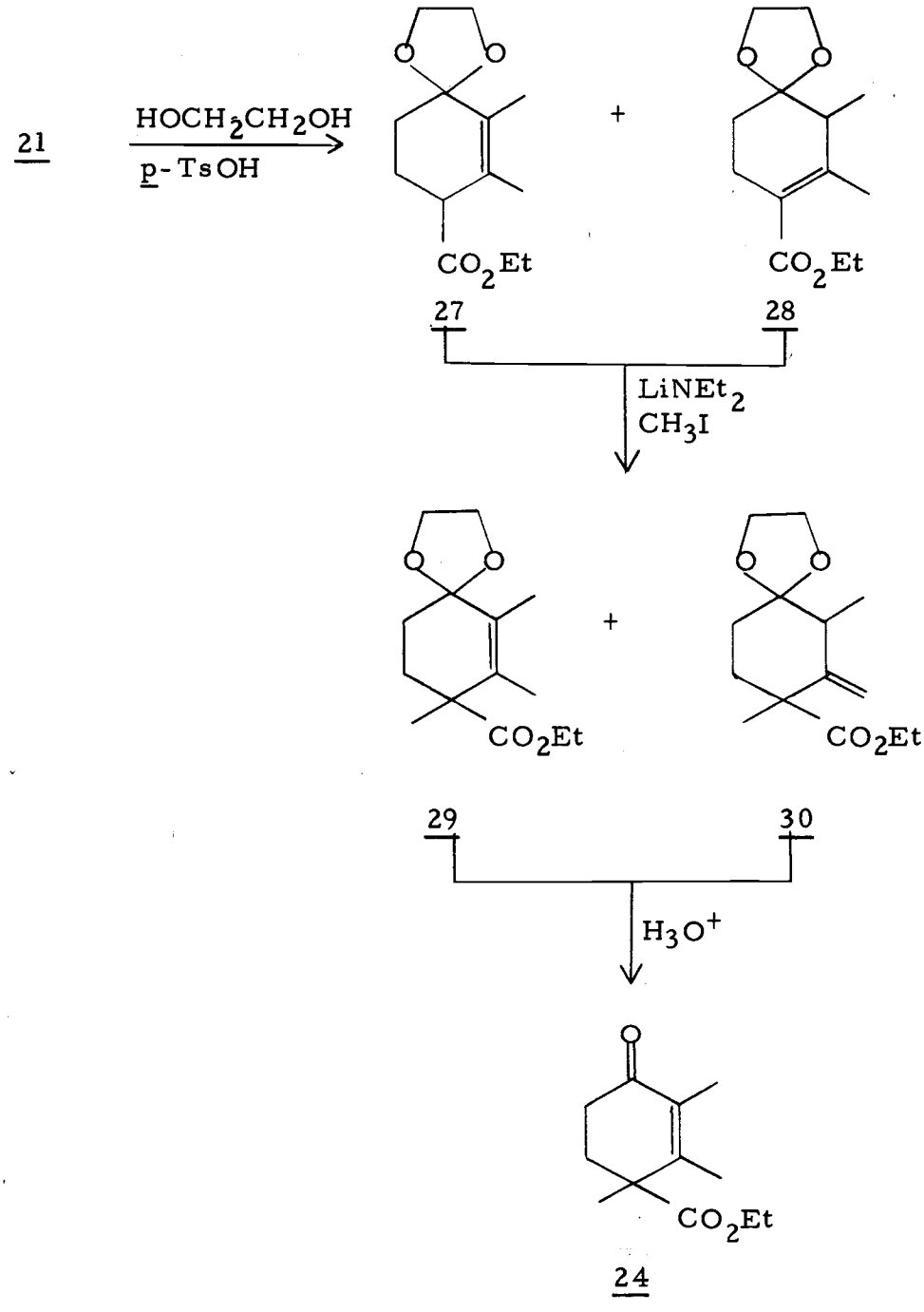

21
HOCH2CH2OH
p-TsOH
CO2Et
CO2Et
27
28
LiNEt2
CH3I
CO2Et
CO2Et
29
30
H3O+
CO2Et
24

Figure 4.

of p-toluenesulfonic acid) furnished a pair of ketals 27 (two CH_3 singlets at δ 1·68 and 1·71) and 28 (C-2 CH_3, δ 2·03) in the ratio 1:1 [22, 23] (yield 86%). Alkylation of this mixture of double bond isomers with methyl iodide in the presence of lithium diethylamide[24,25] produced a mixture of 29 (two CH_3, δ 1·62) and 30 (vinyl H, δ 4·97, doublet) in a ratio of 1:1 (yield 75%). Acidic hydrolysis gave a single keto ester 24 in 86% yield.

The effect of ketalization in directing alkylation towards C-1 was also used to synthesize ester 25 (Figure 5). Ketalization of Hagemann's ester (20) with ethylene glycol and a catalytic amount of p-toluenesulfonic acid gave 31 [26] (in which a double bond shifted to the 1,2-position had occurred) in 78% yield. Ketal 31 underwent alkylation with lithium diethylamide and methyl iodide to give 32 (1 vinyl H, δ 5·47; C-1 CH_3, δ 1·30) in 71% yield, and the latter was hydrolysed to give keto ester 25. An attempt to further alkylate keto ester 25 with sodium ethoxide and methyl iodide in ethanol at 75° failed, confirming that 25 is significantly less reactive toward substitution than its isomer 21.

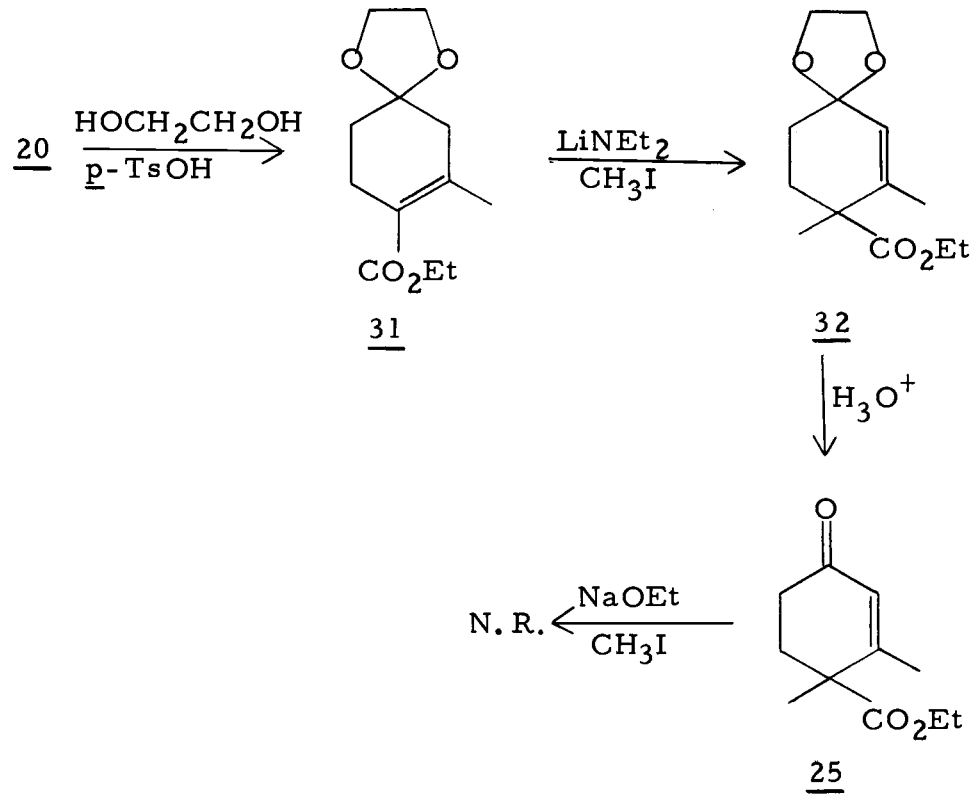


Figure 5.

It was intended at this point to introduce a third substituent into the nucleus of Hagemann's ester by alkylation of 24, the objective being keto ester 33. Toward this end, alkylation of keto ester 24 with methallyl bromide [27] and potassium t-butoxide in tetrahydrofuran was attempted (Figure 6). Gas chromatographic analysis of the product mixture (SE-30 column, 5' x 1/4", column temperature 170°, flow rate 100 ml/min) showed that 60% was the unreacted keto ester 24, 35% was the transesterified compound 34 (2 vinyl H at

δ 4·92; 4 CH_3 singlets at δ1·89, 1·79, 1·72 and 1·44) and only 5% was the desired alkylated product 33 (2 vinyl H at δ 4·76; 3 CH_3 singlets at δ 1·82, 1·75 and 1·45). Other bases such as lithium diethylamide, lithium hexamethyldisilylamide[28], and sodium hydride/benzene failed to initiate any alkylation of the keto ester 24. The low conversion of 24 to 33 therefore prompted a search for a more efficient alkylation sequence.

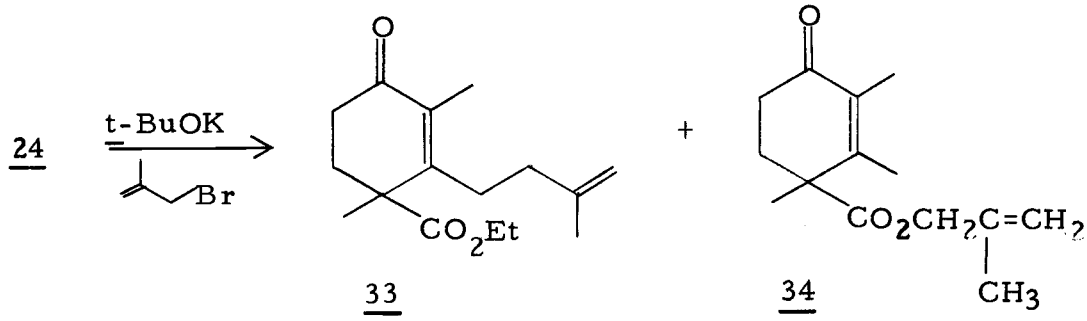


Figure 6.

The Methallyl-Methyl Sequence

It is apparent from the foregoing results that the introduction of a substituent into the structure of Hagemann's ester makes succeeding alkylations more difficult. The effect is most pronounced when the substituent is first incorporated at C-1 (for example, 25 cannot be further alkylated), but is attenuated when C-3 is alkylated in the primary step (21 → 23 + 24). The failure of 24, with C-1 and

C-3 substituents, to undergo satisfactory alkylation suggested that a substitution sequence in which the C-1 methyl group was introduced last would be the most productive. This reasoning therefore allows that the initial alkylation be accomplished with either methyl or methallyl halide.

The reaction of Hagemann's ester (20) with methallyl chloride and sodium ethoxide gave the 3-methallyl derivative 35 (2 vinyl H at δ 4·65, 1 allylic H at δ 3·34, 2 allylic H at δ 3·06) in 82% yield (Figure 7). However, methylation of 35 with methyl iodide and potassium t-butoxide proceeded in only 56% yield and gave a mixture containing 36 (C-1 CH_3, δ 1·44) and 37 (vinyl CH_3 of C-3 methallyl δ 1·63) in a ratio of 1:1. The low yield of the desired isomer 37 therefore prompted consideration of the alternate methyl-methallyl-methyl sequence for introduction of substituents.

The Methyl-Methallyl-Methyl Sequence

Alkylation of 21 with methallyl chloride and sodium ethoxide gave 33% of keto ester 37 (C=O absorption at 1715 cm^{-1}; C-3 CH_3, δ 1·22) together with 17% of its isomer 38 (C=O absorption at 1738 and 1675 cm^{-1}; C-3 CH_3, δ 1·81) and ca. 50% of unreacted 21 (Figure 8). Since neither 37 nor 38 were alkylated further under the reaction conditions, the mixture was recycled until all of the starting material 21 was consumed. This gave a total yield of 55% of alkylated product.

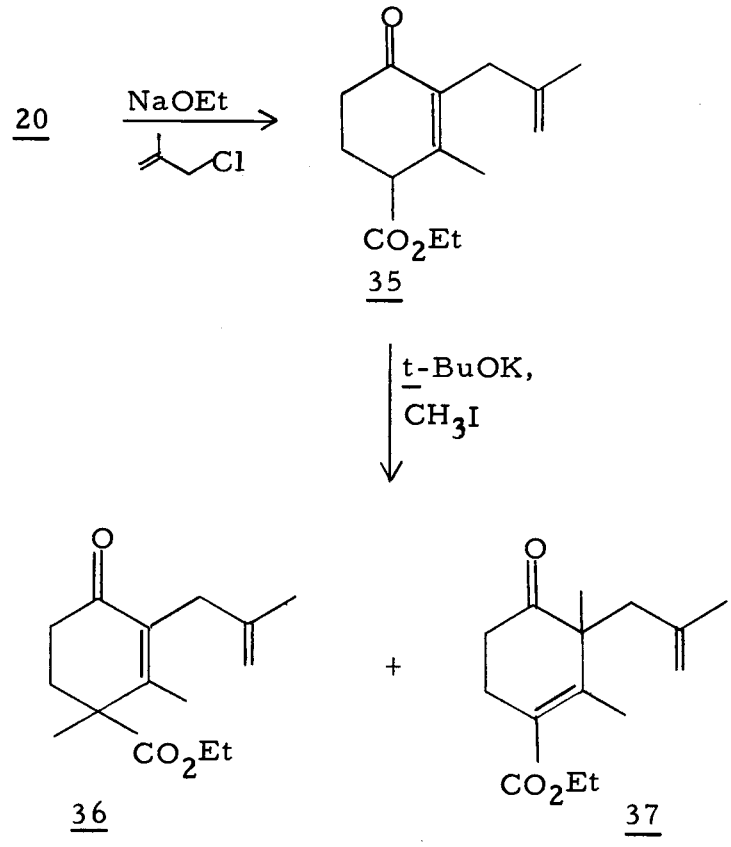


Figure 7.

It was subsequently found that pyrolysis of 37 at 220° for 25 min resulted in its conversion to 38 in 90% yield. Evidently, the favored direction of the Cope rearrangement in this system is strongly toward the α , β -unsaturated ketone 38.

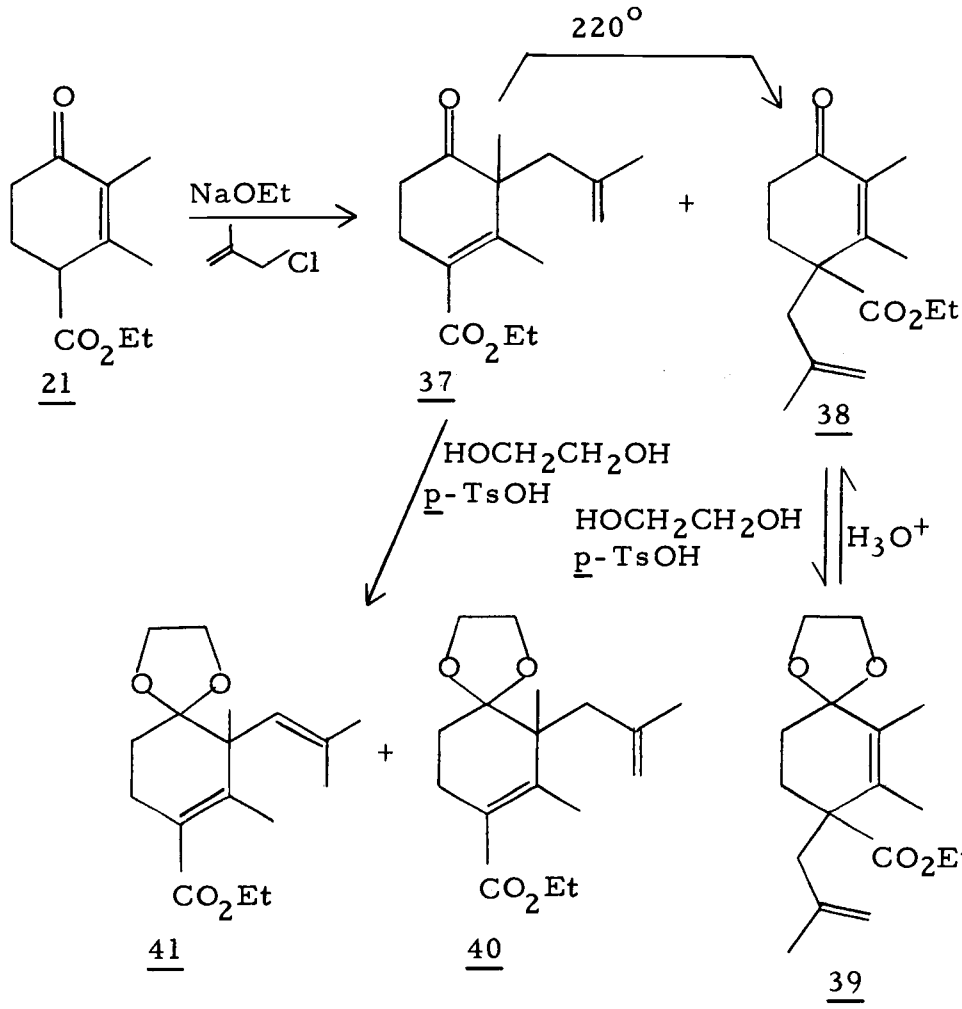


Figure 8.

Numerous attempts were made to improve the methallylation of 21. As can be seen from Table 1, variation of base, alkylating agent, and solvent brought little reward in terms of an increase in the proportion of 37. In general, more vigorous reaction conditions promoted the formation of 38.

Table 1. Methallylation of keto ester 21.

Base	T(°C)	Methallyl Halide	Yield of Alkylated Product	Ratio[a] 37:38
LDA[b]	-70	Chloride	40%	3:5
LICA[c]	-5	Chloride	10%	1:1
NaH/Dioxane	101	Chloride	40%	38 only
t-BuOK/t-BuOH	83	Chloride	57%	38 only
t-BuOK/t-BuOH	83	Bromide	ca. 60%	38 only

[a]Ratio calculated from area comparison on gc chromatogram. Data were collected using 0.25" x 5' SE-30 (20% on Chrom G) column at 170°.

[b]Lithium diethylamide.

[c]Lithium N-isopropylcyclohexylamide.

In an alternate version of this approach, 21 was converted to the mixture of ketals 27 and 28. Alkylation of this mixture with methallyl chloride and lithium diethylamide as base gave, not unexpectedly, exclusive C-1 substitution (78%) with formation of C=C isomers 39 (2 vinyl H at δ 4·80; 3 CH_3 singlets at δ 1·72, 1·65 and 1·61) and 42 (presumably) in approximate ratio of 1:1 (Figure 9). Pyrolysis of the alkylated mixture at 220° resulted in the formation of 43 (2 vinyl H at δ 4·74; one CH_3 singlet at δ 1·74) from 42, but attempts to

introduce the third (methyl) substituent into the C-1 position of 43 were without success.

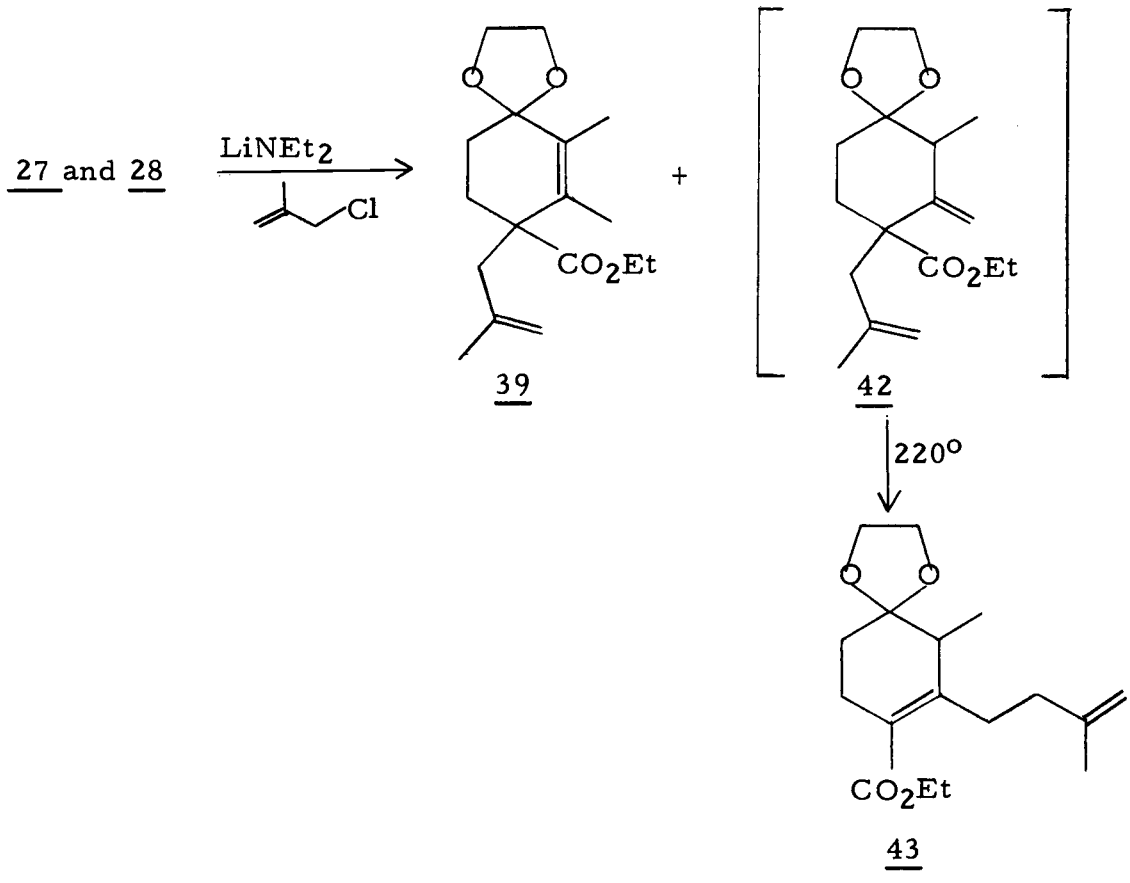
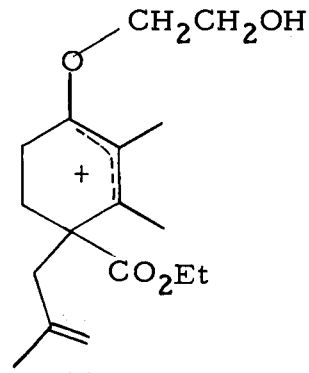


Figure 9.

Keto ester 37 thus became the focal intermediate for effecting this final methylation and, in order to separate 37 from 38, the mixture was subjected to ketalization with the expectation that the differential reactivity of ketone carbonyls in these isomers would assure selective ketal formation by 37 (as in the case of 23 and 24). In the present case, however, a mixture of ketals 39, 40 (2 vinyl H at

δ 4·82; 3 CH_3 singlets at δ 1·94, 1·74 and 1·09) and 41 (1 vinyl H at δ 5·01; 4 CH_3 singlets at δ 1·91, 1·71, 1·61 and 1·22) were obtained in the ratio of 2:3:1, indicating that partial isomerization of the terminal olefin of either 37 or 40 had occurred during ketalization. When the mixture was shaken with water-p-toluenesulfonic acid-benzene for three min, the ketal 39 was completely hydrolysed. The facile hydrolysis of ketals derived from α,β-unsaturated ketones, as compared to their saturated counterparts, is in accord with the findings of others[22], and can be explained by invoking the stabilized oxoallyl cation intermediate 44.



44

After separation of ketal 40 from 38 and 41 by distillation in a spinning-band column (yield from 37 was 48%), efforts were directed toward introduction of the methyl substituent at C-1. A possible advantage in retaining the ketal function at this stage lay in the removal of activation at C-5. In order to establish conditions for the

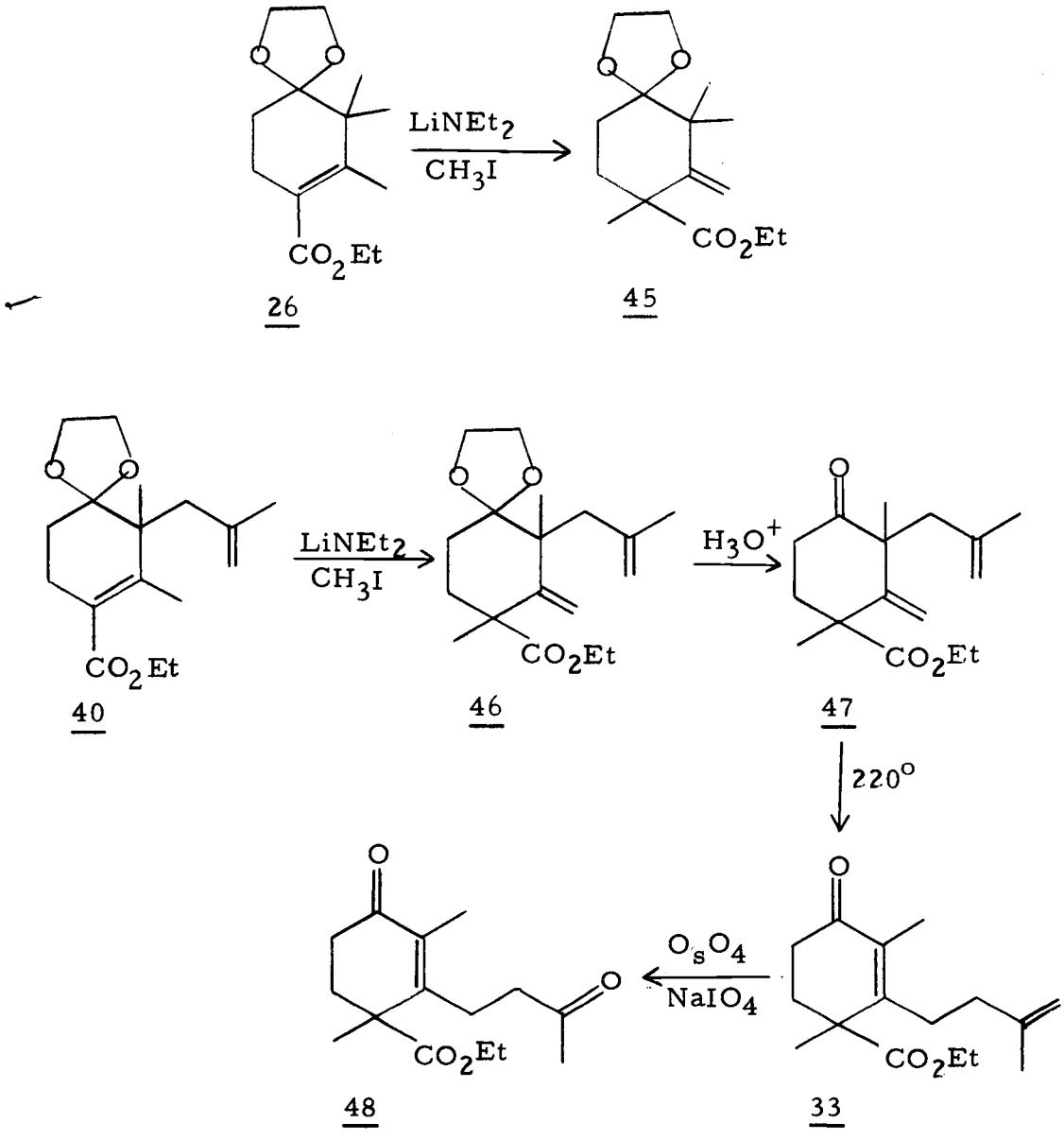


Figure 10.

C-1 alkylation of 40, methylation of the model system 26, byproduct in the previous alkylation sequence, was explored (Figure 10). Treatment of 26 with lithium diethylamide followed by methyl iodide gave 45 in 83% yield. The presence of a new methyl group and an exocyclic methylene function could be discerned from the nmr spectrum (2 vinyl H at δ 5·21, C-1 CH_3 at δ 1·35). The analogous methylation of 40 gave 46 (2 pairs of vinyl H at δ5·30 and 4·77, C-1 CH_3 at δ 1·37). Hydrolysis of ketal 46 in 5N hydrochloric acid-ethanol (1:3) for 20 hr furnished the trialkylated keto ester 47 in 72% overall yield from 40.

The direct alkylation of keto ester 37 gave 47 in 46% yield (Figure 11). However, a complicating feature in this reaction is the formation of a significant amount (15%) of amide 49 (amide absorption at 1625 cm^{-1}, $C=CH_2$ at 890 cm^{-1}). The amide was apparently resistant to alkylation.

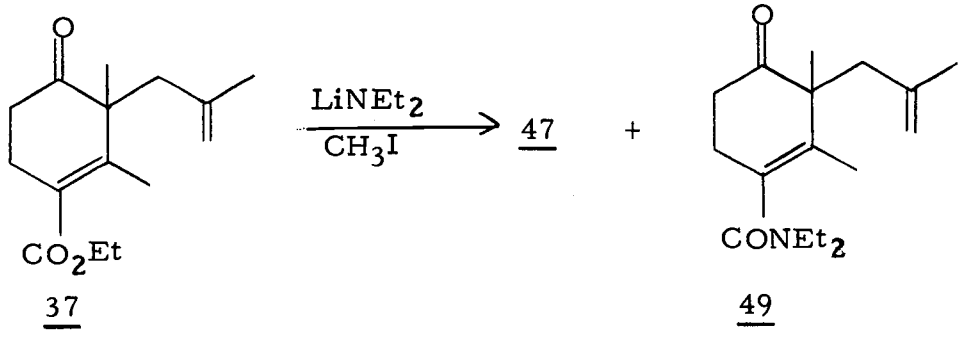
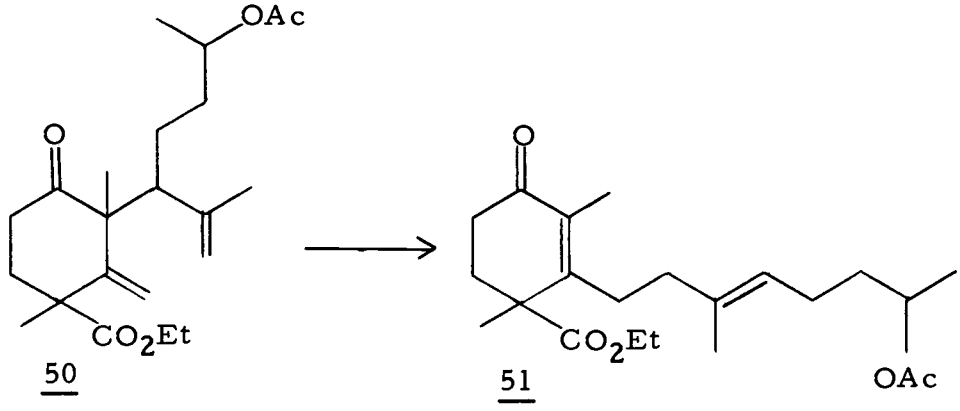


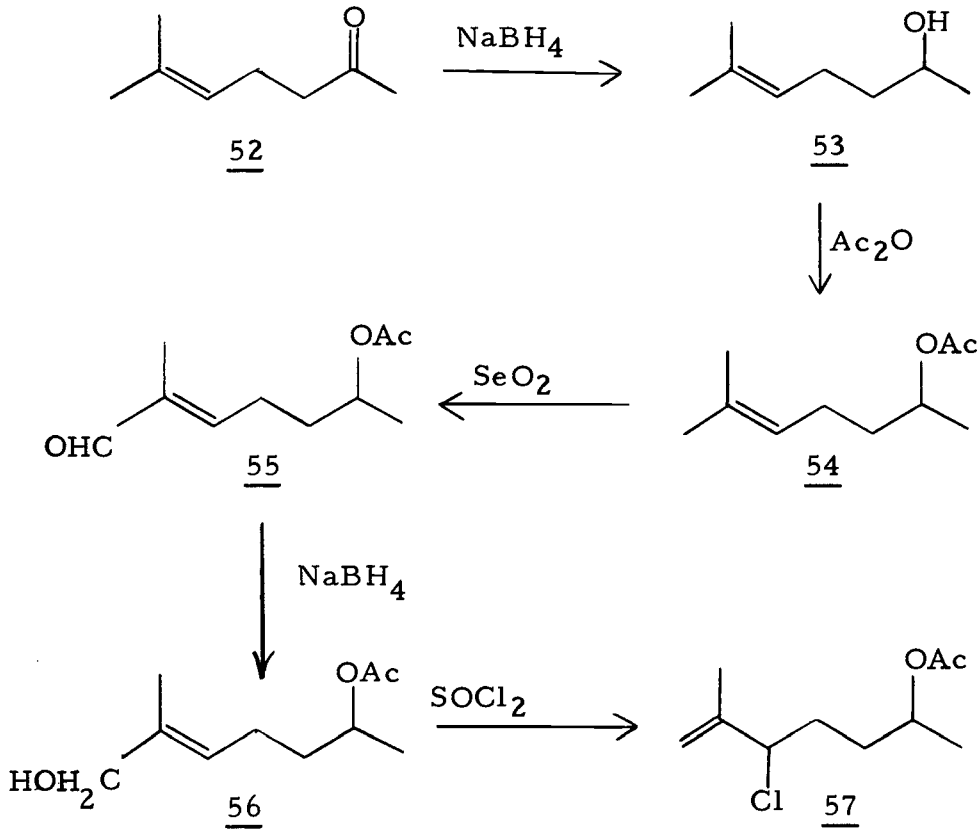
Figure 11.

The functionality present in 47, specifically the exo methylene group and the 1,5-diene relationship, sets the stage for the transposition of the methallyl group from C-3 to C-7 via Cope rearrangement. Thermodynamic advantage in the desired direction derives from the generation of an α, β-unsaturated ketone as well as a tetrasubstituted C=C bond. Pyrolysis of keto ester 47 at 220° for 13 min resulted in a smooth Cope rearrangement with formation of the anticipated isomeric keto ester 33 in 97% yield. This step completes the placement of alkyl groups at the requisite sites in Hagemann's ester and lays the groundwork for an entry to the trisporic acid system.

The efficient Cope rearrangement of 47 to 33 encouraged the belief that if the methallyl group of 47 were replaced by a 2-methylheptenyl substituent, as in 50, rearrangement would lead directly to a substance 51 having the 7,8-dihydrotrisporic acid skeleton. A synthesis of chloroacetate 57 was therefore devised along the lines shown in Figure 12, with the intention of alkylating either 21 or 24.



50 51


O
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OH
52
53
Ac2O
OAc
OAc
SeO2
OHC
55
54
NaBH4
OAc
SOCl2
OAc
HOH2C
Cl
56
57

Figure 12.

2-Methyl-2-hepten-6-one (52) was reduced with sodium borohydride to alcohol 53 in 93% yield and the latter was acetylated with acetic anhydride to give 54 (92% yield). Selenium dioxide oxidation of 54 furnished the α,β-unsaturated aldehyde 55 as the trans-isomer exclusively*. This was reduced with sodium borohydride in quantitative yield to allylic alcohol 56 [29] (OH absorption at 3850 cm^{-1}), which was treated with thionyl chloride to give the rearranged allylic chloride 57 (2 vinyl H at δ 4·97) in 76% yield[30]. Unfortunately, all attempts to effect alkylation of either 21 or 24 with 57 met with failure, and this approach was therefore abandoned in favor of one departing from keto ester 33.

It was expected that the terminal C=C of 33, for both steric and electronic reasons, would be more rapidly cleaved under oxidative conditions than the conjugated double bond. Consequently, 33 was allowed to react with a catalytic quantity of osmium tetroxide, followed by one equivalent of sodium periodate in aqueous dioxane, to give a 78% yield of diketo ester 48 [31, 32] (disappearance of vinyl H in nmr; 3 CH_3 singlets at δ 2·15, 1·80 and 1·44). This substance is the dihydro analog of the trisporic acid intermediate 15 (Figure 2) prepared by Isoe and coworkers. The further elaboration of 48 into 7,8-dihydrotrisporic acid is envisaged by means of a Wittig reaction with the ylide from triphenyl-4,4-ethylenedioxypentylphosphonium bromide along lines similar to those presented in Figure 2.

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* This sequence (52 ⟶ 55) had been carried out previously by D. W. Perkins (Harvard University).

III. EXPERIMENTAL

General

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 standard. Analyses were performed by Micro-Tech Laboratories, Inc., Illinois, or by Dr. Susan Rottschaefer at the Department of Chemistry, University of Oregon, Eugene, Oregon. Mass spectra and exact mass determinations were provided by Dr. Rottschaefer. Analytical vpc was performed on a Varian aerograph model 700 gas chromatograph using a 5' x 0.25" SE-30 (20% on Chrom G) column.

Methylation of Hagemann's Ester (20)

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 one 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 keto esters 21 (C-3 CH_3, δ 1.81) and 25 (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 (21)

The mixture of keto ester (2.01 g, 10.2 mmol) prepared above was added to a solution prepared from 1.60 g (14.5 mmol) of potassium t-butoxide in 30 ml of dry t-butanol. The solution was stirred at 50° under nitrogen for 30 min. The solution was cooled to room temperature, and 2 ml of methyl iodide was added. The solution was stirred for ten min 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 mixture of keto esters 23 (C-2 CH_3, δ 2.00), 24 (C-3 CH_3, δ 1.82) and 25 (C-2 CH_3, δ 1.96) in a ratio of 2:2:1. Preparative vpc afforded a sample of 24:ir (film) 1725, 1667, 1620, 1242, 1180, 1095, 1020 cm^{-1}; nmr ($CDCl_3$) δ 4.18 (2H, q, J=7.2 Hz), 2.60-1.80 (4H, m), 1.90 (3H, s), 1.82 (3H, s), 1.44 (3H, s), 1.26 (3H, t, J=7.2 Hz); mass spectrum m/e 210 (M^+).

Anal Calcd for 24 $C_{12}H_{18}O_3$: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 (26)

A 20.0 g sample of keto esters (23, 24 and 25) was stirred at reflux for 12 hr with a catalytic amount of p-toluenesulfonic acid and 6 ml of ethylene glycol in 150 ml of benzene, with 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 was 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 21) of keto ester 24, 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 21) of ketal ester 26:ir (film) 1715, 1630, 1235, 1205, 1086, 1056 cm^{-1}; nmr ($CDCl_3$) 4.19 (2H, q, J=7.0 Hz), 3.99 (4H, s), 2.45 (2H, t, J=6.6 Hz), 1.93 (3H, s), 1.77 (2H, t, J=6.6 Hz), 1.27 (3H, t, J=7.0 Hz), 1.11 (6H, s); mass spectrum m/e 254 (M^+).

Anal Calcd for 26 $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.66; H, 8.79.

Hydrolysis of Ketal Ester 26

Ketal ester 26 (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 keto ester 23: ir (film) 1725, 1630, 1222, 1048 cm^{-1}; nmr ($CDCl_3$) δ 4.25 (2H, q, J=7.0 Hz), 2.80-2.40 (4H, m), 2.00 (3H, s), 1.30 (3H, t, J=7.0 Hz), 1.22 (6H, s); mass spectrum m/e 210 (M^+).

Anal Calcd for 23 $C_{12}H_{18}O_3$: C, 68.55; H, 8.65. Found: C, 68.20; H, 8.54.

Ketalization of Keto Ester 21

Keto ester 21 (8.50 g, 0.043 mol) was added to a solution containing 0.5 g of p-toluenesulfonic acid and 20 ml of ethylene glycol in 200 ml of benzene, and was stirred at reflux for 20 hr, with water removal via a Dean-Stark trap. The benzene layer was washed with potassium bicarbonate solution and saturated brine, and was 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 ketal esters 27 (2 CH_3, s, δ 1.68 and 2.03) and 28 (CH_3, s, δ 2.03).

Methylation of Ketal Esters 27 and 28

A mixture of ketal esters 27 and 28 (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 two 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 29 and 30. The nmr spectrum of this mixture showed the following: a doublet (equivalent to 1H) at δ 4.97, two singlets at 4.02 and 3.95, a strong singlet at 1.62, two singlets at 1.35 and 1.28.

Ethyl 1,2,3-Trimethyl-4-oxocyclohex-2-enyl--1-carboxylate (24)

A 70 mg (0.27 mmol) sample of the mixture of methylated ketal esters (29 and 30) was stirred with 20 ml of 6N hydrochloric acid in 60 ml of ethanol for seven 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 *24*, identical to the material prepared by methylation of *21*.

Ethyl 4,4-Ethylenedioxy-2-methylcyclohex-1-enyl-1-carboxylate (*31*)

A 2.0 g (0.011 mol) sample of Hagemann's ester was stirred at reflux for 21 hr with a catalytic amount of *p*-toluenesulfonic acid and 3 ml of ethylene glycol in 50 ml of benzene with water removal *via* a Dean-Stark trap. The benzene layer was washed with potassium bicarbonate solution and saturated brine, and was 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 *31*: ir (film) 1720, 1650, 1238, 1088, 1066 cm^{-1}; nmr ($CDCl_3$) δ4.21 (2H, q, J=7.0 Hz), 3.99 (4H, s), 2.55 (2H, t, J=6.5 Hz), 2.39 (2H, s), 2.03 (3H, s), 1.75 (2H, t, J=6.5 Hz), 1.28 (3H, t, J=7.0 Hz).

Ethyl 4,4-Ethylenedioxy-1,2-dimethylcyclohex-2-enyl-1-carboxylate (*32*)

Ketal ester *31* (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 one 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 ketal ester 32: ir (film) 1738, 1648, 1250, 1106, 1080, 1022 cm^{-1}; nmr ($CDCl_3$) δ 5.47 (1H, s), 4.18 (2H, q, J=7.0 Hz), 3.98 (4H, s), 2.50-1.70 (4H, m), 1.73 (3H, s), 1.30 (3H, s), 1.23 (3H, t, J=7.0 Hz); mass spectrum m/e 240 (M^+).

Ethyl 1,2-Dimethyl-4-oxocyclohex-2-enyl -1-carboxylate (25)

Ketal ester 32 (250 mg, 1.04 mmol) was shaken with 50 ml of 3N hydrochloric acid in 50 ml of ether for three 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 keto ester 25: ir (film) 1738, 1685, 1635, 1245, 1175, 1090, 1020 cm^{-1}; nmr ($CDCl_3$) δ 5.94 (1H, s), 4.21 (2H, q, J=6.4 Hz), 2.70-1.60 (4H, m), 1.96 (3H, s), 1.42 (3H, s), 1.26 (3H, t, J=6.4 Hz); mass spectrum m/e 196 (M^+).

Anal Calcd for 25 $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.60; H, 8.27.

Methallylation of Keto Ester 24

Keto ester 24 (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 t-butanol and 6 ml of tetrahydrofuran. The mixture was stirred at room temperature for one 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 24, 35% was the transesterified compound 34 and 5% was the methallylated product 33.

Methallyl 1,2,3-trimethyl-4-oxocyclohex-2-enyl-1-carboxylate (34): ir (film) 1735, 1671, 1624, 1230, 1170, 1085, 895 cm^{-1}; nmr ($CDCl_3$) δ 4.92 (2H, s), 4.52 (2H, s), 2.70-1.50 (4H, s), 1.89 (3H, s), 1.79 (3H, s), 1.72 (3H, s), 1.44 (3H, s).

Ethyl 2-(2-methylbut-2-enyl)-1,3-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (33): ir (film) 1728, 1668, 1620, 1240, 1180, 1092, 1022, 890 cm^{-1}; nmr ($CDCl_3$) δ 4.76 (2H, s), 4.17 (2H, q, J=7.0 Hz), 2.70-1.55 (8H, m), 1.82 (3H, s), 1.75 (3H, s), 1.45

(3H, s), 1.24 (3H, t, J=7.0 Hz); mass spectrum m/e 264 (M^+).

Anal Calcd for 33 $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.37; H, 9.35.

Ethyl 3-Methallyl-2-methyl-4-oxocyclohex-2-enyl-1-carboxylate (35)

Hagemann's ester (10.0 g, 0.055 mol) was added to a solution of sodium ethoxide, prepared from 1.5 g (0.065 mol) of sodium in 40 ml of absolute ethanol, and the mixture was stirred at 80° for five 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 keto ester 35: ir (film) 1730, 1672, 1635, 890 cm^{-1}; nmr ($CDCl_3$) δ 4.65 (2H, d, J=14 Hz), 4.22 (2H, q, J=7.0 Hz), 3.34 (1H, t, J=4.2 Hz), 3.06 (2H, d, J=5.0 Hz), 2.80-1.80 (4H, m), 1.94 (3H, s), 1.72 (3H, s), 1.26 (3H, t, J=7.0 Hz).

Methylation of Keto Ester 35

Keto ester 35 (2.0 g, 8.5 mmol) was stirred with 1.05 g (9.4 mmol) of potassium t-butoxide in 60 ml of glyme at room temperature for ten hr. A dark solution was obtained. Methyl iodide (2.0 g, 14 mmol) was added and the mixture was stirred for two hr, 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 36 (3 CH_3 singlets at δ 1.85, 1.73 and 1.44) and 37 (3 CH_3 singlets at δ 2.04, 1.63 and 1.22) in a ratio of 1:1.

Ethyl 3-Methallyl-2,3-dimethyl-4-oxocyclohex-1-enyl-1-carboxylate (37)

Keto ester 21 (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, then for a further four 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 21, 37 and 38. Gas chromatographic analysis (SE-30 column, column temperature 170°) showed that ca. 50% was the unreacted keto ester 21, 33% was 37 and 17% was 38. Nmr analysis confirmed the ratio of 37 to 38 as 2:1. Distillation of the product through a 36 in. spinning-band column afforded 37 (bp 88°/0.15 mm, ca. 85% pure): ir (film) 1715, 1645, 1242, 1202, 1044, 898 cm^{-1}; nmr ($CDCl_3$) δ 4.70 (2H, d, J=16 Hz), 4.25 (2H, q, J=7.0 Hz), 2.80-2.10 (6H, m), 2.04 (3H, s), 1.63 (3H, s), 1.35 (3H, t, J=7.0 Hz), 1.22 (3H, s); mass spectrum m/e 250.157 (parent, calcd for $C_{15}H_{22}O_3$ 250.157).

Pyrolysis of Keto Ester 37

Keto ester 37 (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 keto ester 38: ir (film) 1738, 1675, 1623, 1204, 1168, 1072, 1018, 895 cm^{-1}; nmr ($CDCl_3$) δ 4.86 (2H, d, J=11 Hz), 4.20 (2H, q, J=7.0 Hz), 3.00-2.00 (6H, m), 1.97 (3H, s), 1.81 (3H, s), 1.69 (3H, s), 1.25 (3H, t, J=7.0 Hz); mass spectrum m/e 250.156 (parent, calcd for $C_{15}H_{22}O_3$ 250.157).

Methallylation of the Mixture of 27 and 28

A mixture of ketal esters 27 and 28 (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 39 and 42 (vinyl H at δ 5.36, exocyclic methylene).

Ethyl 4,4-Ethylenedioxy-2-(2-methylbut-2-enyl)-3-methylcyclohex-1-enyl-1-carboxylate (43)

A mixture of 39 and 42 (0.50 g) was heated in an air bath at 220° for 15 min. Evaporative distillation afforded 0.43 g of mixture of 39 and 43. Preparative vpc afforded a sample of 39: ir (film) 1728, 1655, 1064, 892 cm^{-1}; nmr ($CDCl_3$) δ 4.80 (2H, d, J=5.8 Hz), 4.14 (2H, q, J=7.0 Hz), 4.00 (4H, s), 3.00-1.50 (6H, m), 1.72 (3H, s), 1.65 (3H, s), 1.61 (3H, s), 1.23 (3H, t, J=7.0 Hz).

A mixture of 39 and 43 (0.35 g) was added to a solution containing 50 ml of ether and 50 ml of 6N hydrochloric acid, and was shaken for two min. The ether layer was dried with anhydrous magnesium sulfate Ether was removed in vacuo, leaving 0.25 g of residua oil. Gas chromatographic analysis of the residual solution showed that ca. 50% was 38 and the other 50% was 43. Preparative vpc afforded a sample of 43: ir (film) 1719, 1652, 1635, 1240, 1138, 1083, 886 cm^{-1}; nmr ($CDCl_3$) δ 4.74 (2H, s), 4.19 (2H, q, J=7.0 Hz), 3.97 (4H, s), 3.00-1.50 (9H, m), 1.74 (3H, s), 1.27 (3H, t, J=7.0 Hz), 1.16 (3H, d, J=7.4 Hz); mass spectrum m/e 294 (M^+).

Ethyl 4,4-Ethylenedioxy-3-methallyl-2,3-dimethylcyclohex-1-enyl-1-carboxylate (40)

A mixture of keto esters 37 and 38 (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 at reflux for 12 hr, with water removal via a Dean-Stark trap. The benzene layer was washed with potassium bicarbonate solution and saturated brine, and was dried with anhydrous magnesium sulfate. Benzene was removed in vacuo, leaving 16.5 g of a mixture of ketals 39, 40 and 41 in the ratio of 2:3:1.

The ketal mixture (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 five 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° (head)/0.06 mm afforded 3 gm of a mixture of keto esters 37, 38 and ketal ester 41. Preparative vpc afforded a sample of 41: nmr ($CDCl_3$) δ 5.01 (1H, s), 4.18 (2H, q, J=7.0 Hz), 3.51 (2H, t, J=6.4 Hz), 2.0-1.5 (2H, m), 1.91 (3H, s), 1.71 (3H, s), 1.61 (3H, s), 1.27 (3H, t, J=7.0 Hz), 1.22 (3H, s); mass spectrum m/e 294 (M^+).

Evaporative distillation of the high-boiling residue at 130-145°/0.6 mm gave 2.5 g (ca. 48% from 37) of 40: ir (film) 1740, 1678, 1240, 1078, 1054, 890 cm^{-1}; nmr ($CDCl_3$) δ 4.82 (2H, d, J=6.0 Hz), 4.20 (2H, q, J=7.0 Hz), 4.00 (4H, s), 2.60-1.50 (6H, m), 1.94 (3H, s), 1.74 (3H, s), 1.28 (3H, t, J=7.0 Hz), 1.09 (3H, s); mass spectrum m/e 294.181 (parent, calcd for $C_{17}H_{26}O_4$ 294.183).

Ethyl 4,4-Ethylenedioxy-1,3,3-trimethyl-2-methylenecyclohexyl-1-carboxylate (45)

Ketal ester 26 (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 five min. Methyl iodide (2 ml) was added,

and the mixture was stirred for a further five 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 45: ir (film) 1730, 1635, 1254, 1090, 906, 806 cm^{-1}; nmr ($CDCl_3$) δ 5.21 (2H, d, J=4.8 Hz), 4.12 (2H, q-q, J=7.2 Hz), 3.95 (4H, s), 2.40-1.30 (4H, m), 1.35 (3H, s), 1.22 (3H, s, J-7.2 Hz), 1.11 (3H, s), 1.03 (3H, s); mass spectrum m/e 268.169 (parent, calcd for $C_{15}H_{24}O_4$ 268.167).

Ethyl 4,4-Ethylenedioxy-3-methallyl-1,3-dimethyl-2-methylenecyclohexyl-1-carboxylate (46)

Ketal ester 40 (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 in a dry ice-acetone bath. The mixture was stirred for one 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 46: ir (film) 1730, 1630, 1250, 1080, 895 cm^{-1}; nmr ($CDCl_3$) δ 5.30 (2H, d, J=7.2 Hz), 4.77 (2H, s), 4.21 (2H, q, J=7.2 Hz), 3.93 (4H, s), 2.50-1.50 (6H, m), 1.67 (3H, s), 1.37 (3H, s), 1.22 (3H, t, J=7.2 Hz), 1.05 (3H, s); mass spectrum m/e 308.199 (parent, calcd for $C_{18}H_{28}O_4$ 308.199)

Anal Calcd for 46 $C_{18}H_{28}O_4$: 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 (47)

From Ester 46

Ketal ester 46 (0.25 g, 0.81 mmol) was stirred with 10 ml of 5N 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 47: ir (film) 1730, 1675, 1633, 1242, 1168, 1020, 898 cm^{-1}; nmr ($CDCl_3$) δ 5.22 (2H, d, J=3.0 Hz), 4.73 (2H, d, J=17 Hz), 4.19 (2H, q, J=7.0 Hz), 2.80-1.40 (6H, m), 1.63 (3H, s), 1.40 (3H, s), 1.25 (3H, t, J=7.0 Hz), 1.25 (3H, s).

From Keto Ester 37

Keto ester 37 (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, pre-cooled 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 five 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 47 and 0.13 g of a high-boiling residue which was identified as amide 49: ir (film) 1712, 1625 (strong), 895 cm^{-1}; nmr ($CDCl_3$) 4.73 (2H, d, J=16 Hz), 3.00-3.80 (4H, broad), 1.73 (3H, s), 1.70 (3H, s), 1.21 (3H, s).

Pyrolysis of Keto Ester 47

Keto ester 47 (0.44 g) was pyrolysed at 220° for 13 min. Evaporative distillation afforded 0.43 g (97%) of keto ester 33, identified by comparison with the methallylation product from 24.

Trans-6-acetoxy-2-methyl-2-hepten-1-ol (56)

A solution of 1.50 g (8.1 mmol) of acetoxy aldehyde 55 in 10 ml of isopropyl alcohol was added slowly to an ice-cold suspension of 0.45 g (13 mmol) of sodium borohydride in 10 ml of absolute alcohol-isopropyl alcohol (1:1). Stirring was maintained through the addition. The solution was allowed to stir at room temperature for one hr. Saturated brine was added and the mixture was extracted with ether. The ethereal solution was dried with anhydrous sodium sulfate, and ether was removed in vacuo. Evaporative distillation of the crude product at 81°/0.2 mm afforded 1.5 g (99%) of 56: ir (film) 3500, 1742, 1238, 1130, 850 cm^{-1}; nmr ($CDCl_3$) δ 5.41 (1H, t), 4.92 (1H, sextet), 3.99 (2H, s), 2.65 (1H, s), 2.09 (2H, q), 2.00 (3H, s), 1.63 (3H, s), 1.58 (2H, m), 1.20 (3H, d).

6-Acetoxy-3-chloro-2-methylhept-1-ene (57)

Allylic alcohol 56 (1.07 g, 5.75 mmol) in 20 ml of dry ether was added dropwise to 0.82 g (6.9 mmol) of thionyl chloride in 20 ml of ether at room temperature. The solution was heated under reflux for one hr. Ether was removed in vacuo, and evaporative distillation of the residual oil at 75°/0.05 mm afforded 0.90 g (76%) of 57: ir (film) 1745, 1652, 1242, 1130, 1022, 908 cm^{-1}; nmr ($CDCl_3$) δ 4.97 (2H, d), 4.90 (1H, m), 4.36 (1H, t), 2.00 (3H, s), 2.00-1.40

(4H, m), 1.79 (3H, s), 1.19 (3H, d).

Ethyl 2-(2-Oxobutyl)-1,3-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (48)

Keto ester 33 (0.50 g, 1.9 mol) was added to a solution of a catalytic amount 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 two hr, and the mixture was stirred for a further four hr. Saturated brine (100 ml) was added, and the solution was extracted with ether twice. 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 132°/0.6 mm afforded 0.39 g (78%) of 48: ir (film) 1725, 1670, 1620, 1244, 1184, 1164, 1095, 1022 cm^{-1}; nmr ($CDCl_3$) δ 4.20 (2H, q, J=7.2 Hz), 2.70-1.75 (8H, m), 2.15 (3H, s), 1.80 (3H, s), 1.44 (3H, s), 1.26 (3H, t, J=7.2 Hz); mass spectrum m/e 266 (M^+).

Anal Calcd for 48 $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.47; H, 8.26.

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