PRELIMINARY STUDIES IN THE TOTAL SYNTHESIS OF VERRUCAROL

by

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ABSTRACT

A preliminary investigation was undertaken to find a route to the cis A-B ring fusion of the sesquiterpene alcohol verrucarol (1). To synthesize the desired cis-γ-lactone (47), methylacetoacetate (60) was alkylated with methyl-2-bromopropionate (62) to give compound (64). Michael addition of (64) with methylvinylketone yielded (66). Acid catalyzed cyclization of (66) gave the d,β-unsaturated ketodiester (67). Although a second isomer, structure (68), could also be obtained; sodium borohydride reduction of (67) gave a 1,4-reduction leading to the saturated γ-lactone (69) and not to the δ-lactone (70). This reduction was confirmed by catalytic hydrogenation of (67) to the saturated ketodiester (75) and subsequent sodium borohydride reduction of (75) leading also to compound (69). Furthermore, the saturated ketodiester (75) was hydrolyzed and decarboxylated to the mono acid (76) which was converted to its corresponding methylester (77), hence also excluding the formation of compound (68) in the acid catalyzed cyclization. Meerwein-Ponndorf-Verley reduction on compound (67) failed to give the unsaturated γ-lactone (46), which could have been equilibrated to the desired cis isomer (47).
\[
\text{(60)} \quad \text{CH}_2\text{CO}_2\text{CH}_3 + \text{Br}\text{CH}_3\text{CO}_2\text{CH}_3 \rightarrow \text{(64)}
\]

\[
\text{(66)}
\]

\[
\text{(67)} \quad \text{(68)}
\]

\[
\text{(69)} \quad \text{(70)} \quad \text{(75)}
\]

\[
\text{(76)} \quad R = \text{H} \\
\text{(77)} \quad R = \text{CH}_3
\]

\[
\text{(46)} \quad \text{(47)}
\]
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INTRODUCTION

In 1962 Tamm and coworkers \(^1\) isolated from cultures of *Myrothecium verrucaria* and *Myrothecium roridum* a new structural class of mold metabolites, called verrucarines and roridines. The main constituents, verrucarine A and B and roridine A show \textit{in vitro} antifungal and high cytostatic activity. For example, a cell culture containing 0.0006\(^\text{g}\) of verrucarine A per ml causes a 50\% suppression of mice tumor cells. Toxicity determination with mice showed that 1.5 mg of verrucarine A per kg was the critical amount.\(^2\) Therefore, these new antibiotics show not only a highly effective cytostatic activity \textit{in vitro}, but are also very toxic. Furthermore, cultures, crude extracts and pure substances cause skin irritations.

Verrucarine A (2), \(\text{C}_{27}\text{H}_{34}\text{O}_{9}\), is a macrocyclic triester, whose eighteen-membered cyclic triester constitutes a novel structural type in the field of mold metabolites. Verrucarine A yields on base-catalyzed hydrolysis three products:\(^3,4\)

1) the sesquiterpene alcohol verrucarol (1), \(\text{C}_{15}\text{H}_{22}\text{O}_{4}\),

2) \textit{cis-trans} muconic acid (4), \(\text{C}_{6}\text{H}_{6}\text{O}_{4}\),

and 3) verrucarino lactone (3), \(\text{C}_{6}\text{H}_{10}\text{O}_{3}\), the \(\delta\)-lactone of the hitherto unknown \textit{trans-\(\alpha\),\(\delta\)-dihydroxy-\(\beta\)-methyl valeric acid, verrucarinic acid.}
The verrucarines B, J and H as well as the roridines A, D and E yield verrucarol on base hydrolysis, but differ in the acidic hydrolysis products. 5

The first structure for verrucarol (1) was proposed by Tamm and Gutzwiller 6 in 1963 as that of (5). However, a conversion of
verrucarol to trichothecon (16), an antifungal metabolite of known structure, led to a revision of the original structure proposal for the sesquiterpene alcohol. Verrucarol contains a primary and secondary hydroxyl group. On treatment with Jones reagent, it is converted to a ketoaldehyde (6). This compound exhibits a single aldehyde proton in the NMR and shows, besides the aldehyde absorption, a further carbonyl band at 5.70 μ in the infrared, characteristic for a five-ring ketone. Verrucarol has therefore a tertiary hydroxymethyl group and a secondary OH group, which is attached to a five-membered ring. Further physical and chemical evidence show the presence of a trisubstituted olefinic double bond, carrying a methyl group and also a tertiary methyl group.
that appears as a singlet at $\sim 81.0$ in the nmr. The third oxygen atom is present in an ether linkage of the following type, $\text{-CH}_2\text{-O-C-}$, which is evident from the AB-system appearing in the nmr at $\sim 83$ ($J = 4 \text{ cps}$). Since geminal H atoms with a normal valence angle of $109.5^\circ$ have $J$ values of 12-15 cps, such a small value would indicate a terminal oxirane. This was further proven with a LiAlH$_4$ reduction of (1) to yield (7), which on dehydration yielded compound (8) with a terminal methylene group. Verrucarol does not contain a carbonyl group. The fourth oxygen atom is inert and part of a saturated six-membered ring system. An exact analysis of the nmr spectra of (1) and (6) lead to the following partial structure for (1):

![Structure](image-url)
At this point 14 structures can be written for verrucarol. The choice for structure (1) was made possible by linking verrucarol together with trichodermin (12) and trichothecolon (16) and also on the basis of further degradation to known fragments. Verrucarol was converted into the di-O-methyl derivative (9), which on selective nucleophilic substitution with NaI in acetone gave the mono-iodide (10). Reductive dehalogenation of (10) with zinc yielded (11). Since the mesyl derivative (11) did not hydrolyze even under extreme alkaline conditions, trichodermol (13) was mesylated to give (14). Compound (14) was identical in all respects with substance (11). Since no asymmetric center was involved in the above reaction sequence, the structure and relative configuration of verrucarol was proven, except for the position of the hydroxymethyl group.

It was further possible to convert verrucarol (1) to tricothecolon (16). The mesyl derivative (11) was allowed to react with SeO₂ in dioxane to yield the α,β-unsaturated ketone (15). Compound (15) was
Godtfredsen and Vangedal were also able to link trichodermol to trichothecolon. Furthermore, Abrahamsson and Nilson made an X-ray analysis of the p-bromobenzoyl derivative of trichodermol and confirmed the proposed structure.

The only remaining question was now the localization of the primary hydroxyl group of verrucarol. On treatment with HCl, verrucarol rearranged to the chlorohydrin (17). Compound (17) is reacted with Jones reagent and yields a dicarboxylic acid, which is converted to the keto-dimethylester (18). The α,β-unsaturated five-ring ketone group was
formed by a simultaneous elimination of HCl. Compound (18) was now reacted with SeO₂ in acetic acid to give the diketoester (19). On catalytic hydrogenation, (19) yielded the tetrahydrodiketoester (20).

Treatment of (20) with base lead to a complete retro-Michael fragmentation to give the known 2-methyl-3-oxo-Δ⁴-cyclopentene-1-carboxylic acid (21). A second fragment, the cyclohexene carboxylic acid (22), could not be isolated, but was oxidized immediately to an aromatic system, which was isolated after treatment with CH₂N₂ as a methyl-2,5-dihydroxy-4-methylbenzoate. Furthermore, a 2-methylcyclohexan-1,4-dione (23) was obtained, which was formed by isomerization and decarboxylation of the acid (22).
Since verrucarol (1) has been linked with trichodermin (12) and trichothecolon (16), coupled with an X-ray structure determination of trichodermol and degradation to known fragments, a vigorous structure proof of verrucarol has been established.

The chemistry of verrucarol is quite unique and warrants some further discussion.\textsuperscript{7,11} The above mentioned reaction with HCl is a general acid catalyzed rearrangement that can be written in the following manner:
The sterical conditions are ideal for such a rearrangement, since the 0-1-C-2 and C-12-oxide oxygen bonds are antiparallel and coplanar and also the attacking nucleophile can come in antiparallel to the 0-1-C-2 bond. A similar, but base catalyzed rearrangement is observed with the ketoaldehyde (6):

Here we have a not very often found example of a base and acid catalyzed rearrangement leading to the same basic carbon skeleton.

Verrucarol yields a dimeric cyclic sulfite with thionylchloride in pyridine, whereas compound (25) gives instead substitution with rearrangement to form the di-O-acetylchloride (26).
If the di-O-acetate of verrucarol (27) is heated with water, a hydrate of structure (28) is obtained. This ring closure is possible if the tetrahydropyran ring is in its chair form.

The reaction of verrucarol with perbenzoic acid yields, besides 40% \( \alpha \)-epoxyverrucarol (29), a dihydroxyether (31). Compound (31) is an O-analogue of a bicyclo[2.2.2]octane skeleton. Its formation
can be explained, if one assumes that verrucarol first forms the \( \beta \)-epoxide (30). After protonation of the epoxide, a nucleophilic attack of the 15-hydroxy group from below leads to the new ring closure and compound (31). This is further substantiated by the fact that (27) yielded as a major product the \( \beta \)-epoxide (30).
DISCUSSION

Verrucarol (1), a sesquiterpene alcohol with six asymmetric centers, poses an interesting synthetic challenge to an organic chemist trying to design a stereospecific synthesis. Obviously, many possible synthetic schemes can be devised for such a synthesis. However, only one particular approach will be considered in this discussion.

A total synthesis of (1) can be divided into three major stages:

1) Synthesis of (32), with particular emphasis on a cis A-B ring fusion.

2) Formation of a two carbon bridge joining C-2 and C-5.

3) Replacing the C-12 carbonyl group of (32) with a terminal oxirane.

\(\text{(32)}\)

Compound (32), having a carbonyl group at C-12, offers the advantage for delaying the introduction of the chemically rather labile terminal epoxide until the last stage of the synthesis. Furthermore, several methods are available for converting a carbonyl function to an oxirane. An excellent one is Corey's method of treating a ketone with dimethyloxosulfonium methyliade (33).
A simple Wittig reaction of (34) with methylenetriphenylphosphine would lead to a compound (35) with a terminal methylene group, which

on further treatment with peracid or with the alkaline hydrogen peroxide-benzonitrile system\textsuperscript{14,15} would yield a terminal oxirane. However, in all these reactions, the stereochemical outcome is uncertain. To obtain the desired oxirane configuration with Corey's method, the attack of the ylide (33) on the carbonyl group would have to come from behind, a sterically rather hindered approach (A). Frontal attack (B), being the least hindered one, would lead to (36) with the undesired configuration.

In connection with epoxidation of (35), Carlson and Belm\textsuperscript{15} have studied the stereochemistry of epoxidation of rigid methylene cyclohexane systems with both reagents. They have shown that peracid epoxidation of trans-10-methyl-2-methylenedecahydronaphthalene gives predominantly axial attack, whereas epoxidation with the alkaline \( \text{H}_2\text{O}_2 \)-benzonitrile system gives predominantly equatorial attack. Without
consideration for the influence of steric hindrance, one could expect from these results a preferential formation of a particular terminal epoxide with either reagent.

Several routes are available for the formation of a two carbon bridge at C-2 and C-5. Work by Turner and coworkers\textsuperscript{16,17} opens the possibility for a base catalyzed internal aldol condensation, as is demonstrated in the conversion of (37) to (38) during the investigation of synthetic routes to diterpene alkaloids of the atisine-garryine
type. However, difficulties might arise, since a similar case in this laboratory, conversion of (39) to (41), did not lead to an internal aldol product, but instead a hydride transfer (40) occurred to yield (41).

An alternative route would be the reaction of compound (32) with \( \text{XCH}_2\text{OAc} \) (\( \text{X} = \text{halide} \)) to yield (42) as is indicated below. Compound (42) is then

\[
\begin{align*}
\text{(32)} & \quad \xrightarrow{\text{XCH}_2\text{OAc}} \quad \text{(42)} \\
\text{(44)} & \quad \xrightarrow{\text{R} = -\text{Ac}} \quad \text{(43)} \\
\text{(45)} & \quad \text{(42)} \quad \text{R} = -\text{Tos}
\end{align*}
\]
converted to the tosylate (43), which on subsequent treatment with base should lead to (44). The bridge carbonyl at C-4 of (44) should reduce more readily than the strongly hindered keto group at C-12. Although a mixture of C-4 OH-epimers would mostly be obtained (45), separation should be possible.

The remaining problem is now to formulate a synthetic plan for the construction of compound (32). To achieve the desired cis-stereochemistry at the A-B ring fusion, the \(\gamma\)-lactone (46) is desirable. Since a cis-\(\gamma\)-lactone is thermodynamically more stable than the trans-isomer, equilibration of a cis- and trans-\(\gamma\)-lactone mixture should lead to the desired cis-product (47). This equilibration process is further enhanced by the presence of the allylic system, as is outlined below:

With the established cis-configuration at C-11 and C-6, LiAlH\(_4\)-reduction of (47) would lead to (48), which should easily convert to the triacetate (49). To form the tetrahydropyran ring B, one carbon has to be added. This could be achieved with the scheme outlined in Chart I.
CHART I

(49) → (50)

(52) → (51)

(53) → (54)

(54) → (32)
Selective hydrolysis of (49) to (50) should be possible, since one acetate group is secondary and two are primary, one of which (C-15) is a strongly hindered one. Although one might expect some partial hydrolysis of the other two acetates, recycling should lead to a pure diacetate (50). Chromium trioxide in pyridine oxidation of (50) should give the aldehyde (51). Conversion of (51) to the nitro derivative (52) and a subsequent Nef-reaction of (52) should yield (53). Hydrolysis of (53) to acetal (54) followed by dehydration should give the desired compound (32), as is mechanistically indicated in Chart I.

An interesting alternative for the formation of (32) and also (34), using the γ-lactone (47) as an intermediate, is outlined in Chart II. If (47) is treated with alkoxide ion, an equilibrium between (47), (55) and (56) should exist. Structure (56) should therefore have the possibility for O-alkylation to yield (57). A Dieckmann cyclization of (57) would give (58), which could either be decarboxylated to (32) or subjected to the Arndt-Eistert reaction to obtain the next higher acid to yield finally, after reduction and reoxidation, the aldehyde (59). An internal aldol condensation of (59) would lead to (34), which could then be further converted to (1) as described above.

To synthesize the desired cis-γ-lactone (47), methylacetoacetate (60) was alkylated with methyl-2-bromopropionate (62) to give in 70% yield compound (64). Its infrared spectrum possessed the expected ester peak at 5.77 μ and its nmr spectrum showed the following major signals: a methyl doublet at δ 1.18 (J = 7.5 cps) of which each peak is further split (J = 1' cps), a doublet for the methylketone at δ 2.30 (J = 2 cps), a methylketone at δ 2.30 (J = 2 cps), a methylester singlet at δ 3.74
CHART II

(47) \rightarrow (55)

(57) \rightarrow (56)

(58) \rightarrow (32)

(59) \rightarrow (34)
and a second methylester doublet at $\delta$ 3.82 ($J = 3$ cps). It is perhaps somewhat surprising to observe long-range splitting of the methyl group, methylketone and one of the methylesters. This alkylation reaction has also been done with the corresponding ethylesters (61) and (63) leading to (65). However, it seems to be advantageous to use the methylester, since interpretation of the nmr spectra of (64) and latter substances is much more simplified than with the corresponding ethylesters. A Michael addition of (64) with methylvinylketone yielded (66) and already some cyclized material (67), as can be observed from a new infrared band at 5.95 $\mu$ and a vinyl proton appearing in the nmr at $\delta$ 5.80. The crude Michael addition product is without any further purification subjected to an acid catalyzed cyclization to yield (67). Fractional distillation
of crude Michael addition product failed to separate (66) from (67). Attempts were also made to complete cyclization to (67) with base. Although different bases were tried, none of them would yield (67) without any competing decomposition reaction. However, refluxing the crude Michael adduct in benzene with a catalytic amount of p-toluene-sulfonic acid led smoothly to the cyclized product (67). Its infrared spectrum showed an ester peak at 5.78 μ, a characteristic conjugated ketone group band at 5.95 μ and also a weak double bond absorption at 6.09 μ. The nmr exhibited a methyl doublet at δ 1.20 (J = 7.5 cps), a very slightly split singlet for a methyl group on a double bond at δ 2.02, two split methylester peaks (J = 1 cps) at δ 3.75 and δ 3.80 and a broad singlet for a vinyl proton at δ 6.08. Furthermore, the U.V. spectrum showed a characteristic trisubstituted α,β-unsaturated six-membered ring carbonyl chromophore at λ<sub>max</sub><sup>EtOH</sup> 235 mμ, ε = 11,700. Aldol condensation of (66) cannot only lead to (67), but also to the isomer (68). The above given physical data for (67) did not allow a
differentiation for the two isomers. However, reduction of (67) with sodium borohydride yields mainly (69). Only compound (67) can give a \( \gamma \)-lactone, whereas a \( \delta \)-lactone (70) would be obtained from isomer (68). However, no \( \delta \)-lactone has been isolated, as was evident from the infra-red band at 5.60 \( \mu \), characteristic for a \( \gamma \)-lactone. It might be argued, however, that compound (70), a strained bicyclo \( \delta \)-lactone, might perhaps absorb at a lower frequency than would be expected for a saturated \( \delta \)-lactone absorbing in the normal region of 5.71-5.76 \( \mu \). Although the "strained" \( \delta \)-lactone of 4-methyl-4-hydroxycyclohexanecarboxylic acid (71) has an infrared absorption in the expected region at 5.75 \( \mu \), some further experiments were undertaken to gather additional evidence for structure (67). Treatment of compound (67) with base at room temperature yielded the mono acid (72), which was then subjected to conditions used by Woodward, et al., (acetic anhydride and a catalytic amount of sodium acetate) for enol-lactone formation. No single reaction product was obtained. Separation of the reaction mixture with preparative thin-layer chromatography indicated the presence of a mixed anhydride (73), infrared bands at 5.50, 5.65, 5.75 and 5.95 \( \mu \), and probably an enol-lactone (74), having an infrared absorption at 5.69 \( \mu \) and showing several vinyl proton signals in the nmr between \( \delta \) 5.0 and \( \delta \) 6.2. Both of these substances still contained some impurities.
Rather than to investigate this reaction further, a new approach was pursued. Compound (67) was converted on catalytic hydrogenation with palladium-on-charcoal to the dihydro compound (75), which was treated under nitrogen for 15 hrs with base at 70° to obtain the keto acid (76).

Compound (76) has three asymmetric centers and hence theoretically a total of six isomers are possible. Woodward and Eastman have obtained two of these isomers by reacting the autooxidation product of menthofurane (78) with sodium amalgam. Rather than trying to equilibrate
compound (76) to one of Woodward's isomers, the keto acid was esterified with diazomethane to yield the keto ester (77). If one assumes structure (68) to be correct and if one would carry out the above reaction sequence on it, then after esterification one should have starting material, compound (68) back. However, the keto ester (77) showed only one methylester signal in the nmr at $\delta 3.86$, indicating that dicarboxylation has occurred and hence the presence of a $\beta$-keto ester as in structure (67). Although compound (75) and (77) have an infrared absorption at 5.78 $\mu$ (ester) and 5.84 $\mu$ (six ring carbonyl), they differ distinctly in the fingerprint region. A different route for preparing compound (76) was also tried by reducing (75) to the trialcohol (79) and then reoxidizing (79) with chromium trioxide in pyridine and decarboxylation to (76). However, reoxidation of (79) did not lead to the desired product, since some lactonized material was obtained, probably because of different rates of oxidation for the three OH groups. Time was not available to convert compound (76) into
a substance of known structure, such as a menthone derivative that could be obtained by converting the carboxyl group into methyl by standard procedures.

It has already been mentioned that reduction of (67) with sodium borohydride led mainly to (69); see p 21. The desired \( \gamma \)-lactone (47) was not obtained. This result was not expected and is somewhat surprising, although other 1,4-reductions with sodium borohydride have been observed. Besides the \( \gamma \)-lactone (69), two minor components were also obtained and whose structures have been tentatively assigned as that of (80) and (81). To confirm the 1,4-reduction of (67) with sodium borohydride, compound (75), p 23, was prepared by catalytic hydrogenation of (67). The infrared spectrum of the dihydro compound

\[
\begin{align*}
(47) & & (80) & & (81) \\
(67) & \rightarrow & (75) & \rightarrow & (69) + (80) + (81)
\end{align*}
\]
(75), showed the expected peaks at 5.75 µ and 5.82 µ for the ester and saturated six-membered ring ketone groups respectively. In addition, the nmr spectrum showed the absence of the vinyl proton and olefinic methyl group. Instead, a complex mixture of methyl doublets was observed centered around δ 1.00, indicating epimerization at C-9. Sodium borohydride reduction of (75) gave (69), identical in all respect with the compound obtained by direct sodium borohydride reduction of (67). Also the same side products (80) and (81) were obtained.

Since the γ-lactone (47) is essential to the synthesis outlined here, a Meerwein-Ponndorf-Verley reduction was tried on (67) with aluminum isopropoxide in isopropanol and also in toluene. Various conditions were employed, but starting material was always recovered unchanged. The carbonyl group is probably too hindered to allow a direct reduction. To circumvent this, the mono acid (72) should be subjected to a MPVO-reduction. The aluminum isopropoxide should now have a chance to coordinate with the acid group, hence a hydride transfer to the carbonyl group should be easier. Different conditions for the sodium borohydride reduction of (67) were also tried, but a 1,4-reduction occurred in all of them.

Although the desired γ-lactone (47) was not obtained, this investigation has led to the useful intermediate (67). However, further work needs to be carried out before the general approach to a total synthesis of verrucarol (1) as outlined in this discussion should be abandoned. Time, however, was not available to pursue this goal.
EXPERIMENTAL*

Alkylation of Methylacetoacetate to (64). To a stirred and ice-cooled suspension of 10.88 g of sodium hydride (0.453 mole) in 150 ml of dry and freshly distilled N,N-dimethylformamide (dried by azeotropic distillation with 10% benzene, bp 150-152°) was added dropwise and under nitrogen (bubbled through Fieser solution) a solution of 50.01 g of methylacetoacetate (0.431 mole) over a period of 2 hrs and 20 min. The reaction mixture was kept between 3° and 10° during the entire addition. At the end, a clear yellow solution was obtained and no more gas evolved. A solution of 72.03 g of distilled (bp 70-75° at 50-60 mm) methyl-DL-2-bromopropionate (0.431 mole) in 50 ml of dry N,N-dimethylformamide was now added dropwise over a period of 2 hrs. During the first hour of addition, the reaction mixture was slowly allowed to warm up to 20° and was increased to 45-50° during the last hour of addition. The mixture was then continued to be stirred, still under nitrogen, at 65-70° for 14 hrs. During this period a white precipitation (NaBr) appeared, which dissolved on workup by addition of 200 ml of water. This brownish-yellow colored solution was extracted with 600 ml of ether. The extract was washed with water, a saturated solution of sodium chloride and was dried over anhydrous magnesium sulfate. After evaporation of the solvent, the oily residue was subjected to fractional vacuum distillation at 2 mm Hg. The first

* NMR spectra were determined on a Varian A-60 spectrometer. Vapor phase chromatography was carried out on an Aerograph "Hy-Fi" Model A-600-B with a hydrogen flame ionization detector and a 5' x 1/8" column with 5% SE-30 on 60/80 Chromosorb W was employed.
fraction, bp 26-70° (5.70 g), contained mostly a mixture of unreacted starting materials, methylacetoacetate and methyl-2-bromopropionate. The second fraction, bp 99-103° (61.2 g), was chromatographically (vpc) pure compound (64), corresponding to a yield of 70%. About 2.6 g of a rather viscous yellow oil was obtained as a third fraction, bp 113-117°, but was not further investigated. A second distillation afforded a colorless and analytically pure compound (64), bp 71° (0.1 mm), \( \lambda_{\text{max}}^{\text{CS}_2} 5.77 \mu \).

**Anal. Calcd. for C_9H_{14}O_5:** C, 53.46; H, 6.98.

**Found:** C, 53.52; H, 6.89.

**Nmr:** S (ppm from TMS) neat; 1.18 (3H, doublet, J = 7.5 cps), 2.30 (3H, doublet, J = 2 cps), 3.29 (1H, multiplet), 3.74 (3H singlet), 3.82 (3H, doublet, J = 3 cps).

**Alkylation of Ethylacetoacetate to (65).** This alkylation was carried out analogous to the above described procedure, except that ethylacetoacetate and ethyl-2-bromopropionate were used in place of the methylesters. Compound (65) was obtained as a colorless liquid in a yield of about 60%, bp 130-135° (8 mm), \( \lambda_{\text{max}}^{\text{CHCl}_3} 5.82 \mu \).

**Michael Addition of (64) to (66).** To an ice-cooled solution of 10.34 g of compound (64) (0.0512 mole), bp 99-103° (2 mm) in 10 ml of anhydrous methanol was added at once 2.0 ml (0.00265 mole) of a freshly prepared sodium methoxide solution (61 mg of sodium dissolved in 2 ml of anhydrous methanol). To this solution was added dropwise and under stirring 8.0 ml (6.91 g) of undistilled methylvinylketone (0.0985 mole). The reaction mixture was allowed to warm up to room temperature and was
continued to be stirred for 23 hrs. After the addition of 5 ml of 3N HCl and 100 ml of water, the solution was extracted with 300 ml of ether. The organic layer was washed neutral with water and once with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent in vacuo, 11.6 g of a yellow-colored oil was obtained, \( \lambda_{\text{CS}_2}^{\text{max}} 5.75 \mu \) (strong), 5.95 \( \mu \) (weak). This latter band indicates the presence of some compound (67), which was also evident from vpc analysis.

Cyclization of (66) to the \( \alpha, \beta \)-unsaturated Ketodiester (67). A solution of 11.6 g of the above compound (66) and 544 mg of a \( \rho \)-toluenesulfonic acid in 700 ml of benzene was refluxed for 24 hrs. During this period, 0.90 ml of water was collected in an attached Dean-Stark adapter. After standing at room temperature for 2 days, the benzene was removed almost to complete dryness in vacuo to yield a dark, oily residue, which was dissolved in 300 ml of ether. The ether solution was washed with 50 ml of 1N NaOH, twice with 50 ml portions of water and once with a solution of saturated sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent in vacuo, 7.43 g of a dark, brownish-yellow oil was obtained, \( \lambda_{\text{CS}_2}^{\text{max}} 5.75, 5.95 \mu \), with both peaks being almost equal in intensity. This oil was subjected to a fractional distillation with a short-neck distillation apparatus:
The gas chromatographic analysis indicates the presence of 5.41 g of pure compound (67), corresponding to a 42% yield. It should also be noted that the structures of compounds other than (67) in the above VPC analysis have not been determined. After distilling fraction 3 two more times, a colorless and very viscous oil was obtained.

\[ \lambda_{\text{CS}}^{\max} = 5.75, 5.95, 6.09 \text{ } \mu \text{ (weak)} \]
\[ \lambda_{\text{EtOH}}^{\max} = 235 \text{ m} \mu \text{ } (\varepsilon \text{ 11,700}) \]

**Anal.** Calcd. for C_{13}H_{18}O_{5}: C, 61.40; H, 7.14.
**Found:** C, 61.03; H, 7.23.

**Nmr:** \$ (ppm from TMS) in CDCl3; 1.20 (3H, doublet, J = 7.5 cps), 2.02 (3H, doublet, J = 1 cps), 2.48 (4H, broad singlet), 3.43 (1H, multiplet), 3.75 (3H, doublet, J = 1 cps), 3.80 (3H, doublet, J = 1 cps), 6.08 (1H, broad singlet).

**Sodium Borohydride Reduction of (67) in Methanol at Room Temperature.** To a stirred and ice-cooled solution of 2.133 g of compound (67), purity 98% by VPC (8.25 mmol), in 30 ml of methanol was added in short intervals a total of 1.114 g of sodium borohydride (29.5 mmol).

<table>
<thead>
<tr>
<th>Fractions</th>
<th>bp (0.08 mm)</th>
<th>Weight (g)</th>
<th>VPC Analysis; Temp = 145°</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Flow rate of carrier gas was not determined</td>
<td>Retention Times</td>
</tr>
<tr>
<td>1</td>
<td>100-110°</td>
<td>0.504</td>
<td>~1.6-2.0 min, ~5 min, ~10 min, ~12 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~16%</td>
<td>~48%, ---, ~36%</td>
</tr>
<tr>
<td>2</td>
<td>115-118°</td>
<td>3.50</td>
<td>~1%, ~16%, ~2%, ~81%</td>
</tr>
<tr>
<td>3</td>
<td>118-126°</td>
<td>2.42</td>
<td>-----, -----, ~2%, ~98%</td>
</tr>
</tbody>
</table>
The reaction mixture was allowed to warm up to room temperature and was continued to be stirred for 14 hrs. After 40 ml of water and 10 ml of 3N HCl was added, the reaction mixture was extracted with 300 ml of ether. The organic layer was washed twice with 50 ml portions of water and once with 20 ml of saturated sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent, 1.709 g of a slightly yellow oil with a characteristic sweet odor was obtained, $\lambda_{\text{max}}^{\text{CS}_2} = 2.88$ (weak), 5.60, 5.75 $\mu$. The above material was combined with 687 mg from an earlier experiment and was subjected to a high-vacuum distillation in a short-neck distillation apparatus:

Fraction 1: bp 102-110° (0.2 mm), 268 mg
Fraction 2: bp 112-115° (0.2 mm), 528 mg
Fraction 3: bp 116-120° (0.2 mm), 787 mg
Fraction 4: bp 125-127° (0.2 mm), 187 mg

The infrared spectra of these four fractions were basically all identical in exhibiting a weak OH band at 2.88 $\mu$, a $\delta$-lactone peak at 5.60 $\mu$ and an ester band at 5.75 $\mu$. Vapor phase chromatography at 165° showed that all fractions contained three major peaks within 7.0 to 11.0 min. In addition, fraction 1 and to a much lesser degree fractions 2 and 3 had several minor peaks between 2 and 6 min. None of these fractions showed a nmr signal in the vinyl proton region. Fraction 4 was subjected to preparative thin layer chromatography. A 20 x 20 cm Merck plate with a 2 mm dry layer of silica gel GF-254 in an 80% benzene and 20% ethylacetate solvent system was used for separation. After two runs in the same solvent system, three separate bands were obtained (detected under UV light). These bands were scraped off the plate and extracted with
ether. After evaporation of the solvent, fraction I (numbered in increasing order of $R_f$ values) yielded 38 mg of an odorless and colorless oil, which partially crystallized on standing at room temperature. Thin layer chromatography still indicated the presence of two compounds. The infrared spectrum of fraction I showed the following major bands: 2.90 $\mu$ (medium), 5.68 $\mu$ (strong) and 5.75 $\mu$ (strong), indicating the possibility of a mixture of compounds (80) and (81). Fraction II, 44 mg of a yellow oil with a characteristic sweet odor, had no infrared absorption around 2.90 $\mu$, but showed two strong bands at 5.60 and 5.77 $\mu$, indicating the presence of compound (69). Thin layer chromatography indicated the presence of mainly one compound. The nmr spectrum in CDCl$_3$ showed no signal for a vinyl proton and also no methyl signal around $\delta$ 2.0, hence indicating the loss of the double bond in a 1,4 reduction. The rest of the nmr is not very conclusive, except for the integration which is fitting for (69), a C$_{12}$H$_{18}$O$_4$ compound. Fraction III, 19 mg of a yellow oil with the characteristic odor, had an infrared spectrum identical with fraction II, although on thin layer chromatography two additional minor spots were observed. The rest of the distillation fractions were also subjected to preparative thin layer chromatography. However, time was not available to obtain analytically pure compounds.

**Sodium Borohydride Reduction of (67) in Methanol at Zero Degrees.**

To an ice-cooled solution of 109 mg of compound (67) (0.430 mmole) in 10 ml of methanol was added at once and under stirring a freshly prepared solution of 53 mg of sodium borohydride (1.40 mmole) in 5 ml of methanol. The reaction mixture was continued to be stirred for 1 hr.
at 0°. After a solution of 15 ml of water and 5 ml of 3N HCl was added, the mixture was extracted with 100 ml of ether. The organic layer was washed neutral with water, once with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent in vacuo, 95 mg of a yellow oil was obtained,\[ \lambda_{\text{max}}^\text{CS_2} = 2.89 \, \mu (\text{weak}), \ 5.60 \, \mu (\text{medium}), \ 5.76 \, \mu (\text{strong}), \ 5.95 \, \mu (\text{medium}). \] This indicated that only partial lactonization had occurred, which was also evident from the vinyl proton (\$6.20) still partially present in the nmr. No new vinyl proton signal was observed.

**Sodium Borohydride Reduction of (67) in N,N-Dimethylformamide.**

To a stirred solution of 105 mg of compound (67) (0.414 mmoles) in 20 ml of dry N,N-dimethylformamide was added at once 54 mg of sodium borohydride (1.43 mmoles). The reaction mixture was continued to be stirred at room temperature for 20 hrs. After the addition of 20 ml of water and 5 ml of 3N HCl, the reaction mixture was extracted with 100 ml of ether. The organic layer was washed neutral with water, once with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent in vacuo, 62 mg of a yellow oil was obtained, \[ \lambda_{\text{max}}^\text{CS_2} = 5.60, 5.77 \text{ and } 5.95 \, \mu (\text{weak}). \] The nmr showed only a very minor signal in the vinyl proton region (\$6.20) which is probably due to some unreacted starting material.

**Catalytic Hydrogenation of (67) to the Saturated Ketodiester (75).**

To a solution of 206 mg of compound (67) (0.812 mmoles) in 20 ml of methanol was added 49 mg of the catalyst (10% palladium on charcoal).
After 12-1/2 hrs of hydrogenation, during which time the calculated amount of hydrogen was taken up, the solution was filtered through Celite. After the filtrate was evaporated to dryness under reduced pressure, 206 mg of a yellow-colored oil was obtained, \( \lambda_{\text{CS}_2}^{\text{max}} \) 5.75, 5.82 \( \mu \). The nmr showed no vinyl proton and no methyl peak at \& 2.02, instead a complex mixture of methyl doublets is observed centered around \& 1.00. Vapor phase chromatography indicated a purity of \( \approx \) 97%. This material was subjected without any further purifications to a sodium borohydride reduction in the experiment described below.

**Sodium Borohydride Reduction of Saturated Ketodiester (75).** To a stirred solution of 205 mg of the above compound (75) in 20 ml of methanol was added at once 101 mg of sodium borohydride. This solution was continued to be stirred for 21 hrs at room temperature. After 18 ml of water and 2 ml of 3N HCl was added, the reaction mixture was extracted with 100 ml of ether. The organic layer was washed twice with 30 ml portions of water, once with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent, 155 mg of a slightly yellow oil with a characteristic sweet odor was obtained, \( \lambda_{\text{CS}_2}^{\text{max}} \) 2.90 (weak), 5.60, 5.76 \( \mu \). Vapor phase chromatography at 165\(^\circ\) showed the three major peaks within 7.0 to 11.0 min that were also obtained by direct sodium borohydride reduction of (67).
Reduction of (75):

<table>
<thead>
<tr>
<th>Retention Times</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.4 min</td>
<td>8%</td>
</tr>
<tr>
<td>8.8 min</td>
<td>69%, compound (69)</td>
</tr>
<tr>
<td>9.9 min</td>
<td>23%</td>
</tr>
</tbody>
</table>

Direct Reduction of (67):

<table>
<thead>
<tr>
<th>Retention Times</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.7 min</td>
<td>18%</td>
</tr>
<tr>
<td>8.8 min</td>
<td>56%, compound (69)</td>
</tr>
<tr>
<td>10.3 min</td>
<td>26%</td>
</tr>
</tbody>
</table>

It should be noted, however, that in both calculations the several minor peaks appearing in either reduction between 2 and 6 min were not included.

Hydrolysis of α,β-unsaturated Ketodiester (67) to Mono Acid (72).

To a stirred solution of 692 mg of compound (67) in 1 ml of methanol was added at room temperature 5 ml of a 1N sodium hydroxide solution. Small oil drops were formed and the solution turned dark yellow. After 45 min of stirring, the solution became homogenous and was continued to be stirred for an additional 1 hr and 15 min at room temperature. Ten ml of water was added and the solution was cooled with an ice bath. After 5 ml of 3N HCl had been added, the solution was extracted with 200 ml of ether. The organic layer was washed twice with water, once with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent, 574 mg of a brown viscous oil was obtained. This material was subjected to sublimation
at 100-110° (0.2 mm Hg) which yielded 489 mg of a slightly yellow-
colored oil that started slowly to crystallize after standing at room
temperature for several days. Its infrared spectrum had major bands
at 5.77, 5.86 and 5.96 μ. The nmr spectra in CHCl₃ showed a singlet
for the acid proton at δ 9.16 and a methyl ester doublet at δ 3.80
(J = 1 cps) integrating for 3 protons. Sublimation of 27 mg of the
above material at 90-120° (0.1 mm) yielded 20 mg of white crystalline
compound (72), mp 80-109°.

Attempt to Convert Mono Acid (72) to Enol Lactone (74). A solu-
tion of 102 mg of the above prepared compound (72) in 5 ml of acetic
anhydride was heated in an oil bath, kept between 148° to 154°, and
under nitrogen (bubbled through Fieser solution) for 2-1/2 hrs. After
16 mg of anhydrous sodium acetate had been added, the solution was
continued to be heated for another 2 hrs at the same temperature.
After evaporation of the acetic anhydride under reduced pressure, the
obtained residue was dissolved in 100 ml of ether. The ether extract
was washed three times with water, once with a saturated solution of
sodium chloride and dried over anhydrous magnesium sulfate. After
evaporation of the solvent in vacuo, 82 mg of a brown oil was obtained,
λmaxCS2 5.50 μ (strong), 5.69 μ (strong), 5.74 μ (strong), 5.99 μ (medium).
The nmr spectra in CHCl₃ showed several signals in the vinyl proton
region between δ 5.00 and δ 6.20, two methyl ester signals at δ 3.83
and δ 3.88 and a methyl signal slightly upfield from starting material
at δ 1.87. Thin layer chromatography indicated the presence of at
least three compounds and no starting material (72) left. Preparative
thin layer chromatography (20 x 20 cm Merck plate coated with a 2 mm
dry layer of silica gel GF-254 in an 80% benzene and 20% ethylacetate
solvent system) led to two fractions, a and b. Fraction a (larger
$R_f$ value), 16 mg, $\lambda_{max}^{CS_2}$ 5.50, 5.65, 5.75 and 5.97 $\mu$ (all strong bands),
$\lambda_{max}^{EtOH}$ (qualitative) 235 m$\mu$ and 272 m$\mu$ (smaller than 235 peak), is
probably mostly the mixed anhydride (73), whereas fraction b (smaller
$R_f$ value), 8 mg, $\lambda_{max}^{CS_2}$ 5.50 (weak), 5.69 (strong) and 5.97 $\mu$ (weak),
$\lambda_{max}^{EtOH}$ (qualitative) 217 m$\mu$ and 274 m$\mu$ (smaller than 217 peak),
probably contains mostly enol lactone (74). This reaction was not
further investigated.

Hydrolysis and Decarboxylation of Saturated Ketodiester (75) to
Keto Acid (76). To a stirred solution of 147 mg of compound (75) in
0.5 ml of methanol was added 4 ml of a 1N solution of sodium hydroxide.
This solution was continued to be stirred for 15 hrs under nitrogen
(bubbled through Fieser solution) and was heated in an oil bath kept
between 65° to 70°. After 5 ml of a 3N HCl solution was added, the
solution was extracted with 100 ml of ether. The organic layer was
washed neutral with water, once with a saturated solution of sodium
chloride and dried over anhydrous magnesium sulfate. After evaporation
of the solvent in vacuo, 100 mg of a yellow oil was obtained,
$\lambda_{max}^{CS_2}$ 5.86 $\mu$. The nmr spectra in CHCl$_3$ showed a one proton acid
singlet at $\delta$ 7.93. No methylester signals were observed. The rest of

* Charles J. Barnett, private communication, has developed this method
for a base hydrolysis of 2-acetyl-2-ethyl glutaric acid diethylester to
$\gamma$-acetyl hexanoic acid in this laboratory.
the spectra integrated for a total of 15 protons, hence being in agreement for structure (76), a C_{10}H_{16}O_{3} compound. This keto acid (76) was esterified in the following experiment.

**Esterification of Keto Acid (76) to (77).** The above 100 mg of compound (76) were esterified in ether solution with diazomethane, using Diazald as the diazomethane precursor. After evaporation of the solvent in vacuo, 92 mg of a yellow oil was obtained, \( \lambda_{\text{max}}^{\text{CS}_{2}} 5.77, 5.84 \). The nmr spectrum in CHCl_{3} showed a methylester singlet at \( \delta 3.86 \). The ratio of integration for the methylester singlet to the rest of the spectrum was found to be 3:15, hence being in agreement with a monoester (77) of the keto acid (76).

**Comparison of infrareds of monoester (77) with the saturated ketodiester (75):**

*Monoester (77)*

\[ \lambda_{\text{max}}^{\text{CS}_{2}} 3.45, 5.77, 5.84, 7.48, 8.00, 8.25, 8.35, 8.55, 8.84, 9.28, 9.41, 9.98, 11.75. \]

*Saturated ketodiester (75)*

\[ \lambda_{\text{max}}^{\text{CS}_{2}} 3.44, 5.78, 5.84, 7.48, 7.58, 7.68, 8.10, 8.33, 8.56, 8.77, 9.12, 9.29, 9.96, 10.33, 11.27, 11.89, 12.37, 13.17. \]

**Reduction of Saturated Ketodiester (75) to the Trialcohol (78).**

To a stirred suspension of 144 mg of lithium aluminum hydride (3.80 mmoles) in 20 ml of dry ether was added during about 5 min a solution of 201 mg of compound (75) (0.786 mmoles) in 10 ml of dry ether. The reaction mixture was continued to be stirred and refluxed for 6 hrs.
After addition of ether saturated with water, the lithium aluminate was allowed to settle. The ether was decanted from the precipitate. After repeating this process several times, the ether decantates were combined and once washed with a solution of saturated sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent in vacuo, 153 mg of a slightly yellow-colored oil was obtained, $\lambda_{\text{max}}^\text{CS} = 3.02, 3.46, 9.52 \mu\text{m}$ (all strong bands, the latter one indicating the C-O stretching vibration of a primary alcohol). Thin layer chromatography indicated the presence of only one compound, namely (78).

**Chromium Trioxide Oxidation of the Trialcohol (78).** To a stirred solution of 153 mg of the above compound (78) in 6 ml of acetic acid was added a solution of 198 mg of chromium trioxide in 4 ml of acetic acid (the CrO$_3$ was first dissolved in a few drops of water and then the acetic acid was added). After stirring at room temperature for 24 hrs, 15 ml of water was added and the solution was extracted with 100 ml of ether. The organic layer was washed once with a 5% sodium bicarbonate solution, several times with water and once with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent in vacuo, 81 mg of a yellow oil was obtained, $\lambda_{\text{max}}^\text{CS} = 5.61, 5.65, 5.79, 5.85 \mu\text{m}$. Thin layer chromatography indicated the presence of at least four compounds. This reaction was not further investigated.

**Meerwein-Ponndorf-Verley Reductions of (67).** To a solution of 131 mg of compound (67) (0.516 mmoles) in 40 ml of dry isopropanol (prepared by refluxing isopropanol for 10 hrs over calcium oxide and
distilled at 83°) was added 391 mg of freshly distilled aluminum isopropoxide (1.915 mmoles). After the solution was refluxed for 2-1/2 hrs, 25 ml of isopropanol was distilled off during a period of 2 hrs. An additional 25 ml of dry isopropanol was added and was again distilled off during a 2 hr period. A test for acetone in the distillate with 2,4-dinitrophenylhydrazin was negative. The distillation residue was evaporated to almost dryness and was cooled in an ice bath. After the addition of 15 ml of 3N HCl, the solution was extracted with 100 ml of ether. The organic layer was washed twice with water, once with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent in vacuo, 125 mg of an oil was obtained, identical with starting material (67) on the basis of infrared and nmr spectra and also thin layer chromatography. A higher boiling solvent, toluene, was used as a substitute for isopropanol and the above described conditions were employed. However, starting material was also obtained mostly unchanged, although a new methyl doublet appeared centered at 8 1.27 and some minor signals appeared between 8 5.00 and 8 6.70. Compound (67) was also refluxed for 53 hrs in isopropanol with aluminum isopropoxide. After the above described workup procedure, starting material was obtained unchanged. Time did not permit a further investigation of this reaction.
REFERENCES


