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THE UNIVERSITY OF ALBERTA

I. α CARBALKOXYMETHYLATION OF CONJUGATED ENONES VIA CYCLOBUTANE INTERMEDIATES.

II. SOME SYNTHETIC STUDIES OF ISOLONGIFOLENE.

by

PATRICK CHI LIN YAO

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1975

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

I α CARBALKOXYMETHYLATION OF CONJUGATED ENONES VIA CYCLOBUTANE INTERMEDIATES

II SOME SYNTHETIC STUDIES OF ISOLONGIFOLENE

submitted by PATRICK CHI LIN YAO in partial fulfilment of the requirements for the degree of Master of Science.

.....
Supervisor

.....

.....

Date .....

TO MY PARENTS AND OPHELIA

ABSTRACT

A novel and apparently general photochemical approach to introduce a single carbalkoxymethyl chain specifically to the α carbon of an α,β unsaturated enone has been developed. Of special significance is that the method is equally applicable to enones which do not possess any enolizable β hydrogen atom and thus to which normal alkylation reactions cannot be applied. Three basic steps were involved in the transformation. Photocycloaddition of the starting enone to 1,1 dimethoxyethylene gave rise to the head to tail adduct. The subsequent oxidative cleavage of a specific peripheral bond of resulting cyclobutane ring was effected by selective Baeyer Villiger oxidation of the cyclobutanone generated in situ followed by concomitant β-elimination and esterification.

Starting from ethyl isobutyrylacetate, the synthesis of 6-isopropyl-10,10-dimethylspiro[4.5]dec-6-ene-1,2-diol, a potential precursor of isolongifolene was accomplished, in the following sequence. Robinson annelation of ethyl isobutyrylacetate with mesityl oxide gave rise to 4-carbethoxy-3-isopropyl-5,5-dimethyl-2-cyclohexen-1-one. Thioketal formation followed by desulfurization effected the removal of its ketone group to give 3-carbethoxy-2-isopropyl-4,4-dimethylcyclohexene, which was subjected to lithium aluminum hydride reduction and Collin's oxidation to give 3-formyl-2-isopropyl-4,4-dimethylcyclohexene. Its α-alkylation with allyl bromide furnished 3-allyl-3-carbethoxyl-2-isopropyl-4,4-dimethylcyclohexene which was converted to 3-formyl-2-isopropyl-4,4-dimethyl-3-(3'-oxopropyl)cyclohexene in four steps, acetal formation, hydroboration-oxidation, Collin's oxidation, and hydrolysis. Treatment of 3-formyl-2-isopropyl-4,4-dimethyl-3-(3'-oxopropyl)cyclohexene with magnesium amalgam followed by hydrolysis effected the formation of the spiro system.

ACKNOWLEDGEMENTS

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INTRODUCTION

Initial studies on carvone by Clamician and Silber [1], and Sernaggiotto [2] at the turn of century illustrated the feasibility of adding a conjugated enone to an olefin photochemically for the construction of a cyclobutane ring. The rapid development in this area, however, was not begun until about forty years later when Büchi and Goldman [3] re-investigated the intramolecular photocycloaddition of carvone. This was followed by extension of the reaction to intermolecular scope by de Mayo and his co-workers [4] and by Eaton [5]. During a relatively short period, progress has now reached the point where the synthetic potential and versatility of the reaction have become evident. By the use of the method many syntheses of otherwise difficultly accessible organic compounds, most noticably strained molecules of theoretical interest and natural products of structural or biological significance, have been achieved in remarkably simplified fashion with either retention or modification of the resulting cyclobutane ring [6].

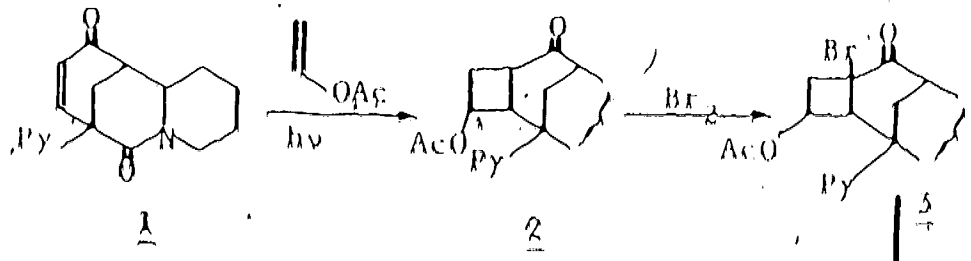
The utilization of the photocycloaddition reaction as a potential method for the introduction of a single alkyl chain specifically to the α-carbon of an α,β-unsaturated ketone was first demonstrated in the total synthesis of the Ormosia skeleton [7]. The crucial step of alkylation of the non-enolizable enone 1 in the synthesis was achieved via a suitably substituted cyclobutane intermediate 2 using a three-step sequence (Scheme I). This procedure was, however, later shown to be limited to α,β-unsaturated ketones in which the enolization of the ketone group towards the α'-carbon was not possible due to either substitution or strain;

the preferential incorporation of a leaving group into the desirable α-position which was required for a Grob fragmentation (i.e. 3→4)[8] was found difficult in cases in which the α'-carbon was also reactive[9]. Using a photocycloaddition reaction as a general entry, two additional methods were developed subsequently. Valenta and his co-workers[9] showed that the photoadducts of 2-cyclohexen-1-ones and vinyl acetates after hydrolysis underwent oxidative cleavage of the cyclobutane ring upon treatment with a variety of oxidants, in particular, ceric ammonium nitrate, to give products of type 5 (Scheme II). More recently, photoadducts of conjugated enones and vinylene carbonate were found to undergo fragmentation with alkali to yield compounds of type 6 (Scheme III)[10]. These α-monoalkylation procedures are synthetically attractive. In addition to providing useful 1,4-dicarbonyl compounds of broad synthetic interest[9], by virtue of the mode of the initial photocycloaddition reaction, they have the following outstanding features in comparison with the conventional alkylation methods[11]. (i) An enolizable γ-hydrogen atom is not required to effect the alkylation. (ii) The position of the double bond in the starting enone fully determines the site of the addition. (iii) The introduction of a single activated alkyl chain can be readily controlled.

Although the above procedures differ from each other in principle, they all furnish 1,4-dicarbonyl compounds of the type 5, in which, of the three possible sites for nucleophilic attack, the side chain carbonyl has been shown to be usually more reactive[7,12]. Consequently, in cases in which the transformation of the enone system, e.g., addition of Grignard reagent,

is subsequently desired, it is necessary to modify the side chain in advance [12]. In order to circumvent this deficiency, complementary methods allowing the direct incorporation of a less reactive functionality into the side chain is needed. The first part of this thesis describes a new photochemical route which facilitates the α-monocarbalkoxymethylation of both enolizable and non-enolizable (towards the γ-position) α,β-unsaturated ketones.

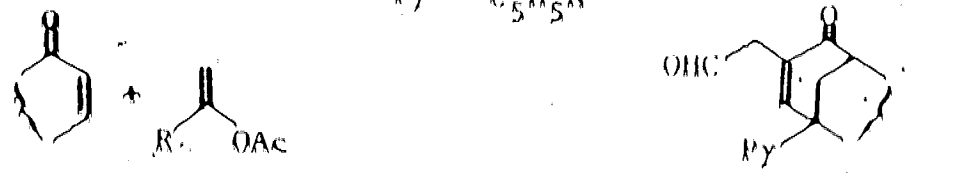
Scheme I



1 2

Py = C_5H_5N

Scheme II



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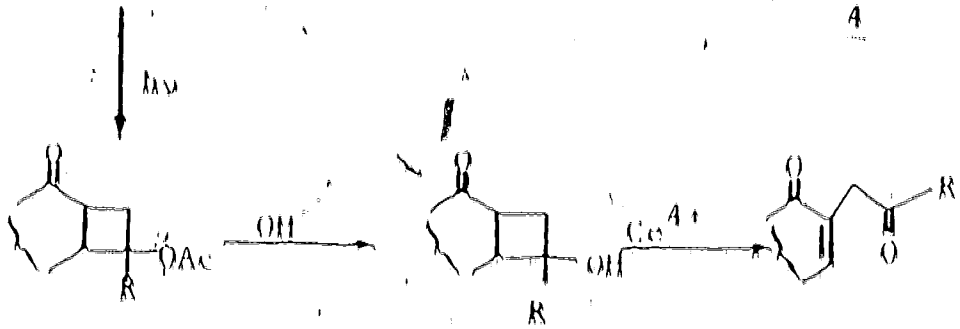
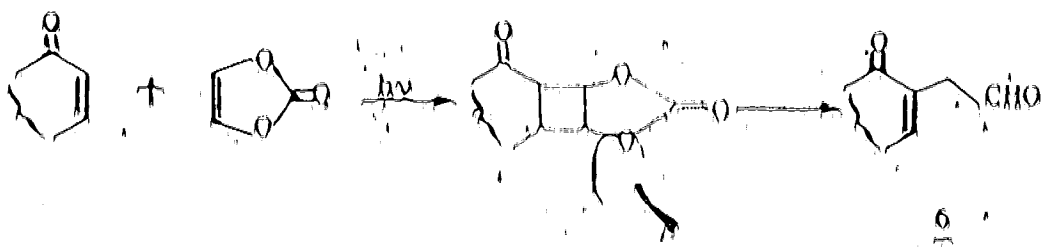


5

R = H or CH_3

Scheme III



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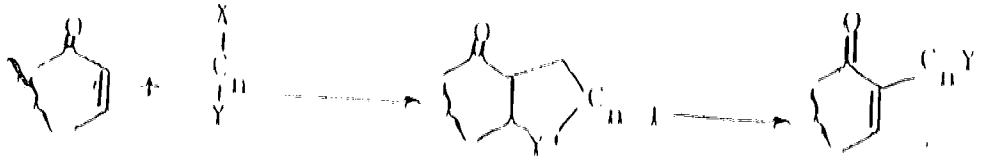
RESULTS AND DISCUSSION

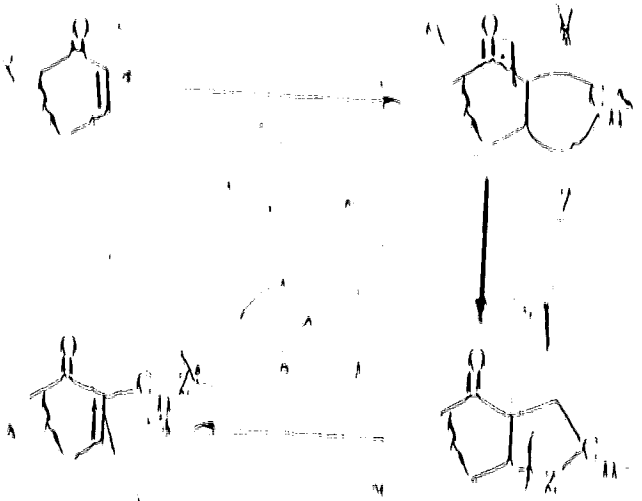
Conceptually, The α-alkylation of both enolizable and non-enolizable α,β-unsaturated ketones can be achieved by concomitant Michael-type addition and cyclisation, using a reagent which possesses both a nucleophilic center and a leaving group, followed by β-elimination as illustrated schematically in Scheme IV. In practice, such a scheme poses obvious problems; the reagent chosen may easily undergo polymerization or internal cyclisation. It is conceivable, however, to achieve a similar transformation by the use of a cycloaddition reaction, e.g., Diels-Alder reaction or photocycloaddition, to form two carbon-carbon bonds to give compounds of type 7 (as shown in Scheme V) followed by selective introduction of a leaving group at the β-position as shown in 8. The present studies followed this principle and the photochemical route has been used as the initial cycloaddition. In order to facilitate the incorporation of the desired leaving group, it is necessary to activate the cyclobutane ring resulting from the photochemical process. 1,1-dimethoxyethylene was selected for this purpose since it has been well established that its addition to conjugated enones proceeds in a head-to-tail fashion to give adducts of type 9[13]. The hydrolysis product of 9, 10, was expected to undergo selective Baeyer-Villiger oxidation under controlled reaction conditions to give desirable intermediates such as 11 for the regeneration of the initial double bond in the starting enone and thus completed an overall α-alkylation of a conjugated enone. In order to test the feasibility and generality of this alkylation procedure, four

Scheme IV



X = Leaving group
Y = Nucleophile

Scheme V



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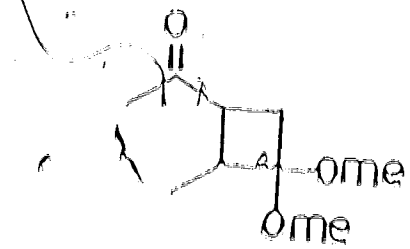

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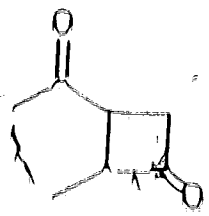

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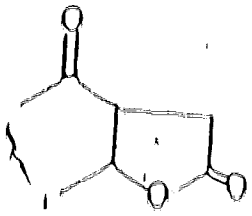

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representative enones 12-15 were examined. The results of their photocycloaddition to 1,1-dimethoxyethylene are compiled in Table I.

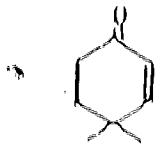
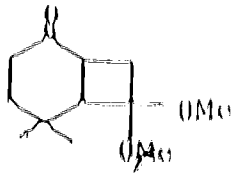
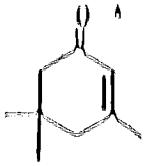
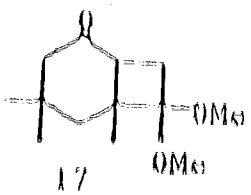
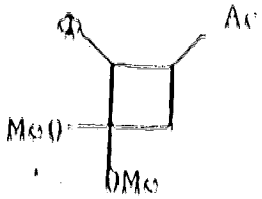
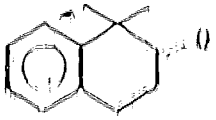
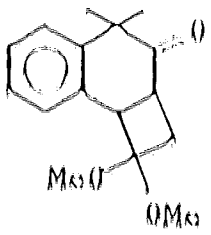
The photocycloadditions proceeded with a high degree of regioselectivity. The relative orientation of the functionality of the photoadduct in each case follows unambiguously from further transformations. Photoadducts 16 and 17 were obtained as mixture of cis and trans isomers. The mixture nature of these products was revealed by their nmr spectra. Four singlets at τ 8.93, 8.89, 8.86, and 8.74 were observed for the gem-dimethyl group of 16 in its nmr spectrum whereas compound 17 showed in the nmr spectrum a total of six singlets at τ 9.04, 8.98, 8.95, 8.88, 8.78, and 8.69 for the three methyl substituents. Since the two asymmetric centers presented in these molecules would be destroyed subsequently, no attempts were made to separate the two isomers.

Photoadduct 18 was thought to be a single stereoisomer since glc (gas-liquid chromatography) analysis showed a single peak for the distilled compound and its nmr spectrum displayed a singlet for the acetyl group at τ 8.10 and two singlets at τ 7.05 and τ 6.92 for the methoxy groups. The data available however do not permit unambiguous definition of its stereochemistry.

Photocycloaddition of enone 15 to 1,1-dimethoxyethylene gave a mixture of two isomers, one of which crystallized readily from Skelly B. The mother liquor enriched in the other isomer was subsequently boiled with aqueous sodium hydroxide in methanol to epimerize it and to provide an additional crop of the first isomer. The ring junction of the crystalline compound thus obtained could readily be assigned as cis, since it has been established that in the bicyclo[4.2.0]octan-2-one systems, the trans ring junction is readily epimerized

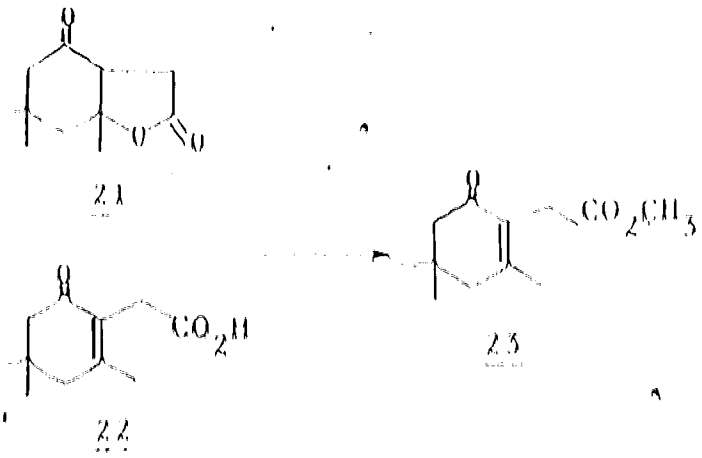
TABLE I

Photocycloaddition of Conjugated Enones to 1,1 Dimethoxy ethylene

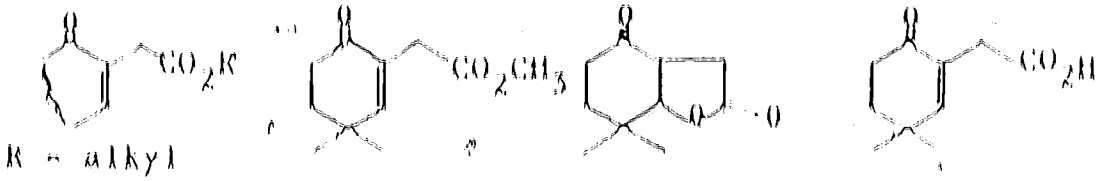
Enones Used	Photoadducts Obtained	Isolated Yields
 12	 16	78%
 13	 17	71%
 14	 18	57%
 15	 19	81%

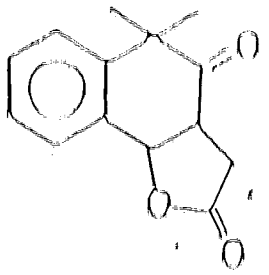
upon treatment with base to give the thermodynamically more stable cis form[13]. The nmr spectrum of the isolated crystalline photoadduct was in full agreement with its assigned stereochemistry. The two singlets for the methoxy groups appeared at τ 6.73 and 7.07. The appearance of one methoxy group at abnormally high field could be attributed to the shielding effect of the benzene ring and suggested that the ring junction of the compound was cis, since inspection of Dreiding models revealed that the methoxy group could be shielded by the benzene ring only when the rings were so fused.

The subsequent transformations of the photoadducts 16--19 into compounds of type 20 thus completed the overall α-carbalkyoxyalkylation of a conjugated enone involving two synthetic steps. This is illustrated in Eq. 1 for the conversion of photoadduct 17 to 2-carbomethoxymethyl-3,5,5-trimethyl-2-cyclohexen-1-one (23). Treatment of 17 with a solution of 30% hydrogen peroxide in glacial acetic acid (1:1) furnished a mixture of keto lactone 21 and acid 22 as a result of concomitant deketalization, selective Baeyer-Villiger oxidation and partial lactone ring cleavage. For the purpose of identification, the crystalline lactone 21 could be isolated by extensive chromatography of the crude mixture, and was found to be identical in all respects (ir, nmr, tlc, and mass spectrum) with an authentic sample prepared by a different route[14]. Attempts to purify the acid 22 were futile, due to its rapid conversion to the lactone 21. For further conversion, the mixture of 21 and 22 was boiled with four-fold excess of anhydrous potassium carbonate and large excess of methyl iodide in acetone. After 40 hr, keto ester 23 was isolated in 40% yield based



Eq. 1





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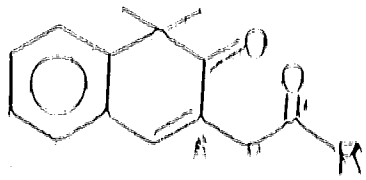


28 R = OH

29 R = OMe

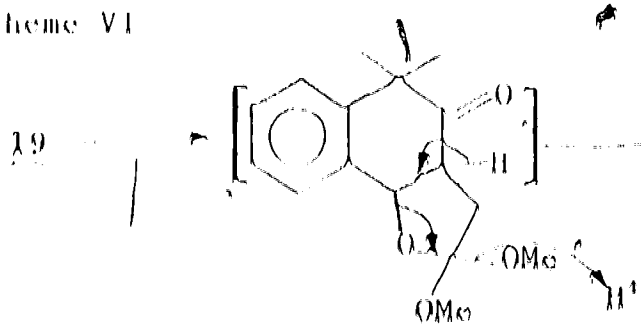
on 17. The structure of 23 was readily assigned on the basis of its spectral data. The ir spectrum showed the α,β-unsaturated ketone and the ester carbonyls at 1665 and 1740 cm^{-1} respectively. In the nmr spectrum six singlets were observed at τ 8.95 (gem-dimethyl), 8.10 (methyl), 7.82 (CH_2), 7.72 (CH_2), 6.73 (CH_2), and 6.38 (OCH_3). The mass spectrum exhibited a molecular ion peak at 210.1263 (Calcd for $C_{12}H_{20}O_3$: 210.1256).

Similarly photoadduct 16 was transformed into 2-carbomethoxy-4,4-dimethyl-2-cyclohexen-1-one (24) via intermediates lactone 25 and acid 26 in 41% overall yield.

In case of photoadduct 19, the hydorlysis-oxidation proceeded abnormally. In addition to the expected products, lactone 27 and acid 28, (a total yield of 51%) a 23.8% yield of ester 29 was also obtained showing, in the nmr spectrum, three diagnostic singlets at τ 6.33 (OCH_3), 6.07 (CH_2), and 8.57 (gem-dimethyl) and a multiplet at τ 2.60-2.88 region for a total of five aromatic and vinylic hydrogen atoms and, in the ir spectrum the enone and the ester carbonyls at 1660 and 1735 cm^{-1} respectively. The mass spectrum was also in full agreement with the assigned structure displaying a molecular ion peak at 244.1099 (Calcd for $C_{15}H_{16}O_3$: 244.1086). Although the formation of this compound was rather unexpected it could be rationalized by invoking the direct oxidation of the photoadduct 19 followed by β-elimination of the resulting intermediate 30 as shown in Scheme VI.

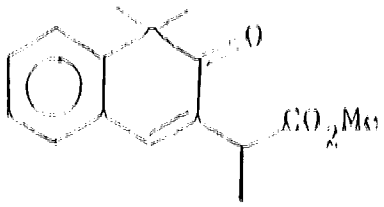
When the mixture of 27, 28, and 29 was subjected to alkylation under the condition described previously, another mixture was obtained. Though it was found to be homogeneous on tlc (thin-layer chromatography), glc analysis showed two peaks of very similar retention times. Besides the expected peak at 244, the mass

Scheme VI



19 → 29

30



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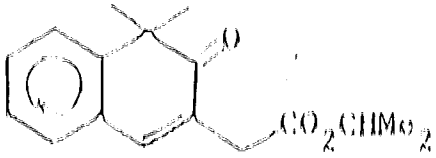

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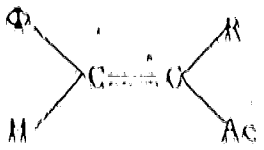

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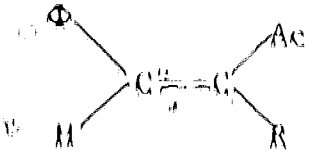

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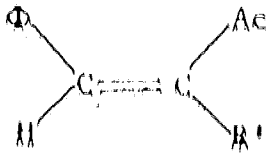


35

R = $CH_2CO_2CH_3$

R' = $CH(CH_3)CO_2CH_3$

spectrum showed an additional peak of similar intensity at 258. Exact mass measurements of these two peaks indicated a difference of a methylene unit. Although no sufficient data would permit conclusive assignments of the identities of the two components, it was logical to deduce from the mode of the reaction that the mixture consisted of the desired ester 29 and the dialkylated compound 31.

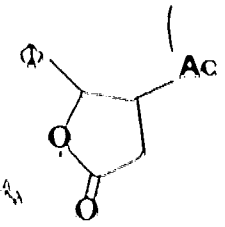
As a consequence of this finding, methyl iodide was replaced by a less reactive alkylating agent, namely, isopropyl iodide, in the alkylation step. As anticipated, this modification circumvented the dialkylation problem and a mixture of ester 29 and 32 was obtained. Separation of these two compounds was achieved by extensive column chromatography on silica gel. The yields of the pure substances were low, due to the loss of material incurred during the purification. It was found more convenient to separate ester 29 from lactone 27 and acid 28 prior to the alkylation reaction. Subsequent treatment of 27 and 28 with isopropyl iodide and potassium carbonate in acetone resulted in the formation of ester 32 in 71% yield. Accordingly, from the photoadduct 19, methyl ester 29 and isopropyl ester 32 were obtained in a ratio of 1:1.5 and in a total yield of 60%.

In the case of photoadduct 18, the complication was the stereochemistry of the final products since the resulting ester chain could be either cis or trans with respect to the phenyl group. Upon hydrolysis, oxidation and subsequent alkylation under the same conditions which effected the transformation of 17→23, photoadduct 18 gave rise to a 58% yield of a mixture of 33, 34, and 35 in the ratio of 4:4:1. The major

product could be separated from the others by column chromatography and its structure readily assigned as 33 on the basis of the spectral data. In the ir spectrum the ketone carbonyl and the ester carbonyl appeared at 1660 and 1740 cm^{-1} respectively. The nmr spectrum displayed four singlets at τ 2.48 (vinylic), 6.35 (OCH_3), 6.65 (CH_2), and 7.60 ($COCH_3$), and a multiplet at 2.58-2.85 (aromatics). The molecular ion peak appearing in the mass spectrum at 218.0947 was consistent with the molecular formula of $C_{13}H_{14}O_3$ (Calcd: 218.0943).

The minor components were obtained as a mixture consisting possibly of 34 and 35 as suggested by the mass spectrum showing two molecular ion peaks at 232 and 218. The two singlets at τ 8.10 and 8.07 of the nmr spectrum confirmed the presence of two acetyl groups while the high field doublet at τ 8.47 was explained as the extra methyl group introduced during alkylation. The stereochemistry of 34 and 35 was assigned as shown because of the shielding on the acetyl groups with respect to trans-benzalacetone as observed in the nmr spectrum. The shielding effect suggested that the acetyl group in each case, was located in the proximity of the phenyl group. Hence the acetyl and phenyl groups in 34 and 35 were assumed to be in cis relationship. Accordingly, the major ester was depicted as the trans isomer as shown in 33.

The results tabulated in Table II showed a new photochemical route whereby a single carbalkoxymethyl chain could be introduced specifically to the α-position of a conjugated enone.



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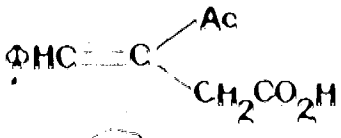

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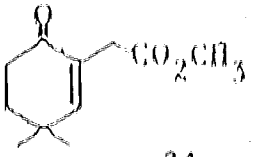
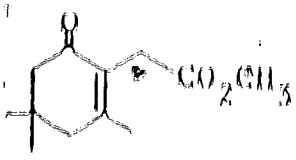
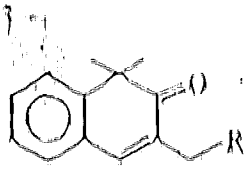
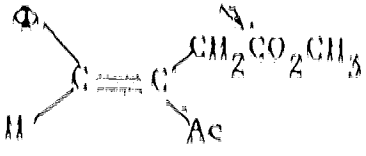
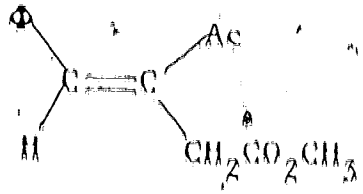
TABLE II

Transformation of Photoadducts into α-Carbalkoxymethyl Enones

Photoadducts used	Product(s) Isolated	% yield based on Photoadduct used
16	 24	41%
17	 23	40%
19	 29 R = CO_2CH_3 32 R = $CO_2CH(CH_3)_2$	60%
18	 33	 34 (9%) 49%

EXPERIMENTAL

General

Melting points were determined on Kofler hot stage apparatus and are uncorrected. Mass spectra were recorded on AEI MS-9 and MS-2. Infrared (ir) spectra were obtained by using Perkin Elmer model 457, 7 and 337 spectrophotometers. Nuclear magnetic resonance (nmr) spectra were recorded on Varian A-60 and HR-100 spectrometers. Unless otherwise stated, carbon tetrachloride was employed as the solvent and tetramethylsilane as internal standard. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Elemental analyses were performed by the microanalytical laboratory of this department.

Gas chromatographic (glc) analyses were performed using an Aerograph A-90 - P 3 with a column of 15% SE 30 on Chromosorb W.

Material

The commercially available isophorone (13) and trans-benzalacetone (14) were freshly distilled under reduced pressure before use. 4,4-Dimethyl-2-cyclohexen-1-one (12)[16] and 1,1-dimethyl-2-oxo-1,2-dihydronaphthalene (15)[16] were synthesized according to the described procedures. 1,1-Dimethoxyethylene was obtained from dehydrobromination[18] of bromoacetaldehyde dimethylacetal which was prepared according to the reported procedure[17] with the modification of using methanol instead of ethanol as a solvent.

General Procedure for Photocycloaddition Reactions[1]

The apparatus used for the photocycloaddition reaction is shown in Figure 1. The enone used was dissolved in 15 molar excess of 1,1-dimethoxyethylene. The solution was then diluted with benzene to four or five times of its original volume. A constant and moderate flow of dry and oxygen-free nitrogen[18] was maintained to agitate the solution throughout the reaction period. Shortly after filling up the Dewar flask with crushed ice and water, the solution was irradiated with a 450 W Hanovia high-pressure quartz mercury-vapor lamp for 9-20 hr. The progress of reaction was monitored by checking the ir of an aliquot of the reaction mixture.

7,7-Dimethoxy-5,5-dimethylbicyclo[4.2.0]octan-2-one (16).

Enone 12 (3.589 g, 28.94 mmol) and 1,1-dimethoxyethylene (40 g, 0.45 mol) were dissolved in benzene (~120 ml). The solution was irradiated for 15 hr. The solvent and the unreacted olefin were distilled off at atmospheric pressure and the residue was subjected to bulb-to-bulb distillation at 108-112° / 3 mm to give 16 (4.767 g, 78%): nmr τ 8.93, 8.89, 8.86, and 8.74 (all s, total 6H, gem-dimethyl group), 6.82 (s, 6H, 2 OCH_3); ir (film) 1735 cm^{-1} (ketone); mass spectrum M^+ 212.1419 (Calcd for $C_{12}H_{20}O_3$: 212.1413).

7,7-Dimethoxy-4,4,6-trimethylbicyclo[4.2.0]octan-2-one (17).

Photoaddition of isophorone (4.272 g, 30.96 mmol) with 1,1-dimethoxyethylene furnished (4.969 g, 71%), after distilling the crude product from bulb-to-bulb at 107-112° /1.7 mm, photoadduct 17: nmr τ 9.04, 8.98, 8.93, 8.88, 8.78, and 8.69 (all s, total 9H, 3 CH_3),

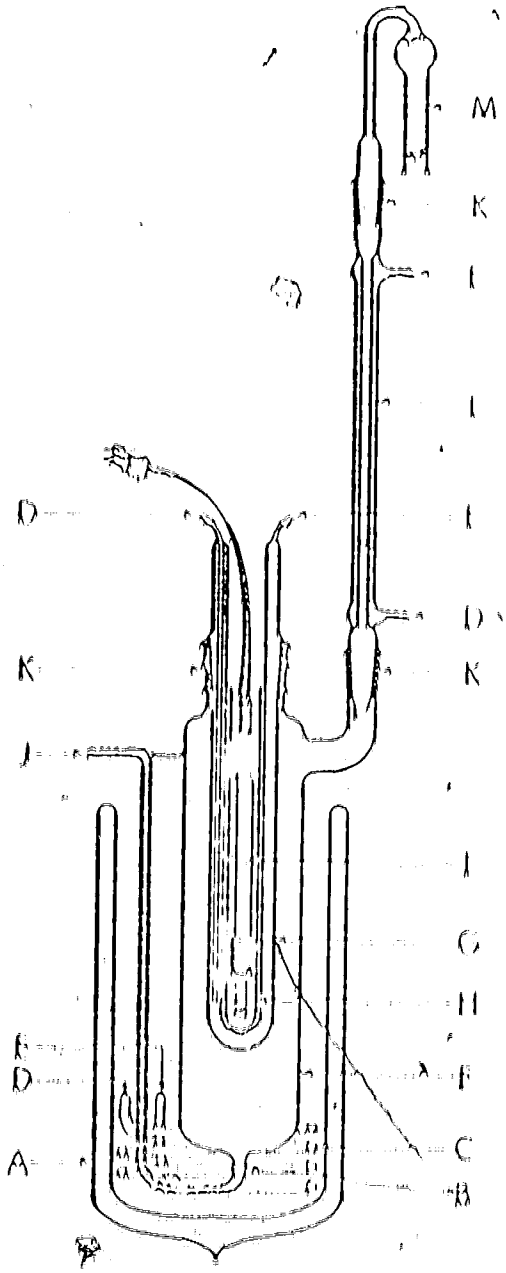


Fig. 1. A, Dewar flask; B, sintered glass filter; C, metal cooling coil; D, water inlet; E, water outlet; F, reaction vessel; G, quartz immersion well; H, pyrex filter; I, lamp; J, nitrogen gas inlet; K, ground glass joint; L, condenser; M, calcium chloride drying tube.

0.88 and 0.84 (both s, total 6H, 2 OCH_3); ir (film) 1720 cm^{-1} (ketone); mass spectrum M^+ 220.1214 (Calcd for $C_{13}H_{22}O_3$: 220.1205).

3-Acetyl-1,1-dimethoxy-2-phenylcyclobutane (18).

Photoaddition of trans-benzalacetone (14) (15.08 g, 0.103 mol) with 1,1-dimethoxyethylene gave rise to, after bulb-to-bulb distillation of the crude product at 82-125°/0.8-3.1 mm, 18 (8.850 g, 37%): nmr τ 8.10 (s, 3H, $COCH_3$), 7.05 (s, 3H, OCH_3), and 6.92 (s, 3H, OCH_3); ir (film) 1710 cm^{-1} (ketone); mass spectrum M^+ 234.1259 (Calcd for $C_{14}H_{18}O_3$: 234.1250).

Cis-6,6-dimethoxy-2,2-dimethyltricyclo[6.4.0.0^{1,7}]dodecan-1,9,11-trione-5-one (19).

The crude product obtained from the photocycloaddition of 1,1-dimethyl-2-oxo-1,2-dihydronaphthalene (15) (8.250 g, 48 mmol) to 1,1-dimethoxyethylene was dissolved in a minimum amount of Skelly B. Upon standing at 0° crystalline material 19, m.p. 104.5-106°, was obtained. The mother liquor was concentrated and dissolved in 10 ml of methanol. One drop of 2.5 N aqueous sodium hydroxide was added and the resulting solution was refluxed under nitrogen for 4 hr. The reaction mixture was diluted with water and extracted with ether. The product obtained after the usual work-up of the organic solution was dissolved in Skelly B. After standing at 0°, it afforded an additional crop of 19. The total amount of 19 thus obtained was 11.76 g (80.5%). 19 exhibited the following spectral data: nmr ($CDCl_3$) τ 8.65 (s, 3H, CH_3), 8.45 (s, 3H, CH_3), 7.07 (s, 3H, OCH_3), 6.73 (s, 3H, OCH_3), and 2.60-2.82 (m, 4H, aromatic); ir ($CHCl_3$) 1710 cm^{-1} (ketone); mass spectrum M^+ 260.1408 (Calcd for $C_{16}H_{20}O_3$:

260.1415).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.71. Found: C, 65.65; H, 6.92.

General Procedure for the Hydrolytic Oxidation of the Photoadducts 16-19.

The reaction was carried out in such a manner that 1 g of the photoadduct was dissolved in 10 ml of acetic acid 30% hydrogen peroxide (1:1) solution and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by tlc. At the end of the reaction (6-7 hr. for photoadducts 16-18 and 5 hr. for 19), the solution was diluted with water and extracted with chloroform, the chloroform solution was washed with aqueous sodium bisulfite and saturated sodium chloride solutions. Drying ($MgSO_4$), filtration and concentration gave the crude product.

Cis 4,4,6-trimethyl-7-oxabicyclo[4.3.0]nonane-2,8-dione (21) and 2-carboxymethyl-3,5,5-trimethyl-2-cyclohexen-1-one (22).

From photoadduct 17 (1.352 g, 6.00 mmol) a mixture of lactone 21 and acid 22 (700 mg, 60%) was obtained. The crude mixture was used without purification for further transformation (see below). An analytical sample of 21 was obtained by column chromatography of the crude reaction product on silica gel with 30% benzene in Skelly B elution, followed by crystallization and was found to be identical in the following respects with an authentic sample: m.p. 116-117° (pet ether-ether); nmr τ 6.45-7.40 (m, 3H, CH_2 and CH), 7.68 (s, 2H, CH_2), 8.49 (s, 3H, CH_3), 8.90 (s, 3H, CH_3), and 9.10 (s, 3H, CH_3); ir ($CHCl_3$) 1770 (lactone) and 1712 cm^{-1} (ketone);

mass spectrum M^+ 196.1104 (Calcd for $C_{11}H_{16}O_3$: 196.1101).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.56; H, 8.20.

The acid 22 was found to undergo rapid lactonization to give 21 and was not obtained in pure form.

5,5-Dimethyl-7-oxabicyclo[4.3.0]nonane-2,8-dione (25) and 2-carboxymethyl-4,4-dimethyl-2-cyclohexen-1-one (26).

Photoadduct 10 (962 mg, 4.54 mmol) was treated with acetic acid-30% hydrogen peroxide according to the general procedure to give a mixture of lactone 25 and acid 26 (908 mg, 81%) which was used directly for the subsequent alkylation reaction.

2,2-Dimethyl-7-oxatricyclo[7.4.0.$0^{5,9}$]trideca-1,10,12-triene-3,6-dione (27), 3-carboxymethyl-2,2-dimethyl-2-oxo-1,2-dihydronaphthalene (28), and 3-carbomethoxymethyl-2,2-dimethyl-2-oxo-1,2-dihydronaphthalene (29).

Hydrolysis-Oxidation of photoadduct 19 (2.04 g) under the described conditions gave 1.623 g of the crude product. A portion of this material (1.258 g) was purified by column chromatography on silica gel. Elution with a solution of 30% (by volume) benzene in Skelly B gave 90 mg (6.8%) of lactone 27. Further elution with the same solvent, gave 301 mg (23.8%) of ester 29. Final elution with a solution of 10% methanol-ether afforded acid 28 (620 mg, 44.5%). Compound 27 was crystallized from chloroform to give a constant m.p. of 109-110° and showed the following spectral data: nmr (CD_3OD) τ 2.55-2.82 (m, 4H, aromatic), 5.05 (t of d, J = 10 Hz, J' = 1.5 Hz, 1H, CO_2CH), 6.18-6.77 (m, 3H,

CHCO, and CH_2CO_2), 8.45 (s, 3H, CH_3), and 8.55 (s, 3H, CH_3); ir ($CHCl_3$) 1765 (lactone), 1715 cm^{-1} (ketone); mass spectrum M$^+$ 230. An analytical sample of 29 was obtained by bulb to bulb distillation at 127-131° (oven temperature)/0.2 mm and showed the following spectral data: nmr τ 2.66-2.88 (m, 5H, aromatic and vinylic), 6.33 (s, 3H, CO_2CH_3), 6.67 (s, 2H, $CH_2CO_2CH_3$), and 8.57 (s, 6H, gem-dimethyl); ir (film) 1755 (ester) and 1660 cm^{-1} (ketone); mass spectrum M$^+$ 244.1099 (Calcd for $C_{15}H_{16}O_3$: 244.1080).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.69; H, 6.59.

Acid 28 was crystallized from chloroform to a constant m.p. of 144-145° and displayed the following spectral data: nmr ($CDCl_3$) τ 2.50-2.82 (m, 5H, aromatic and vinylic), 6.55 (s, 2H, CH_2CO_2H), and 8.55 (s, 6H, gem-dimethyl); ir ($CHCl_3$) 2700-3500 (acid), 1720 (acid) and 1660 cm^{-1} (ketone); mass spectrum M$^+$ 230.0945 (Calcd for $C_{14}H_{14}O_3$: 230.0935).

3-Acetyl-5-oxo-2-phenyl-cyclopentane (36) and 3-benzylidene-4-oxo-pentanoic acid (37).

Photoadduct 18, (3.128 g, 13.4 mmol) was subjected to acetic acid-30% hydrogen peroxide treatment to give 2.599 g (95%) of crude mixture of 36 and 37 which was used without purification for the subsequent transformation.

General Procedure for Methylation of Hydrolysis-Oxidation Products of Photoadducts 16-19.

The crude mixture obtained from the hydrolysis-

oxidation of the photoadduct was dissolved in acetone (0.1 g/1 ml) and five molar equivalent of anhydrous potassium carbonate and large excess of methyl iodide (c. 2 ml/0.1 g reactant) were added. The resulting mixture was refluxed under nitrogen atmosphere for 1-4 days. After cooling to room temperature, the solution was diluted with water and extraction with chloroform. The organic solution was washed with water, dried with $MgSO_4$, filtered, and concentrated. The crude product thus obtained was purified by column chromatography on silica gel using a solution of 10% ether in benzene as eluent.

2-Carbomethoxymethyl-3,5,5-trimethyl-2-cyclohexen-1-one (23).

The crude mixture of 21 and 22 (0.458 g) obtained directly from 17 was subjected to methylation conditions for two days according to the general procedure resulting in the formation of 23 (326 mg, 40% based on 17): nmr τ 8.95 (s, 9H, gem-dimethyl group), 8.10 (s, 3H, CH_3), 7.82 (s, 2H, CH_2), 7.72 (s, 2H, CH_2), 6.73 (s, 2H, $CH_2CO_2CH_3$), and 6.38 (s, 3H, CO_2CH_3); ir (film) 1665 (ketone), and 1740 cm^{-1} (ester); mass spectrum M^+ 210.1203 (Calcd for $C_{12}H_{20}O_3$: 210.1256).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 68.28; H, 8.89. Found: C, 68.54; H, 8.63.

2-Carbomethoxymethyl-4,4-dimethyl-2-cyclohexen-1-one (24).

The crude mixture of 25 and 26 (688 mg) directly obtained from photoadduct 10, was treated under the described reaction conditions for two days to give 24

(362 mg, 41% based on 10): nmr τ 3.54 (s, 1H, vinylic), 6.34 (s, 3H, CO_2CH_3), and 6.96 (s, 2H, $CH_2CO_2CH_3$); ir (film) 1740 (ester), and 1665 cm^{-1} (ketone); mass spectrum M^+ 196.1101 (calcd for $C_{11}H_{16}O_3$: 196.1099).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.52; H, 8.16.

3-(1'-Carbomethoxyethyl)-1,1-dimethyl-2-oxo-1,2-dihydronaphthalene (31) and 3-carbomethoxymethyl-1,1-dimethyl-2-oxo-1,2-dihydronaphthalene (29).

Attempted monomethylation of a mixture of 27, 28, and 29 (800 mg) in crude form with methyl iodide and potassium carbonate under the usual conditions for three days gave 640 mg of a mixture consisting of 31 and 29: ir (film) 1740 (esters) and 1660 cm^{-1} (ketones); mass spectrum M^+ 258.1240 (Calcd for $C_{16}H_{18}O_3$: 258.1256) and 244.1094 (Calcd for $C_{15}H_{16}O_3$: 244.1099).

(R)-methyl-3-benzylidene-4-oxo-pentanoate (33), (Z)-methyl-3-benzylidene-4-oxo-pentanoate (34), and (Z)-methyl-3-benzylidene-2-methyl-4-oxo-pentanoate (35).

A crude mixture (279 mg) obtained from the hydrolysis-oxidation reaction of photoadduct 18 was methylated according to the general procedure. After purification, the major product 33 (127 mg, 40% based on 18; slower moving) was obtained in pure form and 34 and 35 as a 1:1 (nmr) mixture (58 mg, 18% based on 18). The major product showed the following spectral data: nmr τ 2.42 (s, 1H, vinylic), 2.58-2.85 (m, 5H, aromatic), 6.65 (s, 2H, $CH_2CO_2CH_3$), 6.35 (s, 3H, CO_2CH_3), and 7.60 (s, 3H, $COCH_3$); ir (film) 1740 (ester) and

1660 cm^{-1} (ketone); mass spectrum $M^{\uparrow}$ 218.0947 (Calcd for $C_{13}H_{14}O_3$: 218.0943).

The mixture showed the two parent molecular ion peaks in the mass spectrum at 218 and 232. The nmr spectrum showed signals at τ 8.07 (s, $COCH_3$), 8.10 (s, $COCH_3$), and 8.58 (d, J = 7 Hz), in 1:1:1 ratio.

Isopropylation of 27 and 28.

To a solution of lactone 27 (96 mg) and acid 28, (483 mg) in acetone (20 ml), anhydrous potassium carbonate (1.7 g) and isopropyl iodide (1g) were added. The resulting mixture was refluxed under nitrogen for 20 hr. After the usual work-up, the oily product was purified by column chromatography on silica gel. Elution with a solution of 10% ether in benzene afforded 3-carbisopropoxymethyl 1,1-dimethyl-2-oxo-1,2-dihydronaphthalene 32 (320 mg, 71% based on consumed starting material (see below)): nmr τ 2.55-2.80 (m, 5H, aromatic and vinylic), 8.53 (s, 6H, gem-dimethyl), 8.78 (d, 6H, J = 6 Hz, $CO_2CH(CH_3)_2$); ir (film) 1740 (ester) and 1660 cm^{-1} (ketone); mass spectrum $M^{\uparrow}$ 272.1412. (Calcd for $C_{17}H_{20}O_3$: 272.1413). Further elution with a solution of 10% methanol in ether afforded 210 mg of the starting acid 28.

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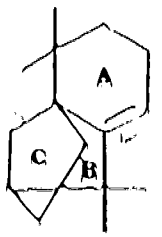
INTRODUCTION

Isolongifolene (1), also known as β-longifolene, was obtained as an artifact from longifolene (2) under various acidic conditions[1]. In 1964 Dev and co-workers[2] assigned its structure as shown on the basis of degradation and spectral evidence.

More recently, an X-ray determination[3] of racemic isolongifolene epoxide prepared by epoxidation of isolongifolene revealed its structure as shown in 3 and thus verified the previous structure assignment of isolongifolene (1).

An elegant seven-step synthesis of racemic isolongifolene (1) has been accomplished by Sobti and Dev[4] starting with the known camphene-1-carboxylic acid (4), prepared from d,l-camphor[5]. In view of the structural significance of isolongifolene, in particular, the unusual tricyclic system and the two gem-dimethyl substitutions, it became of interest to study the synthesis by a different route. The second part of the thesis describes an eleven-step synthesis of the diol 5, a potential precursor of 1, from ethyl isobutyrylacetate.



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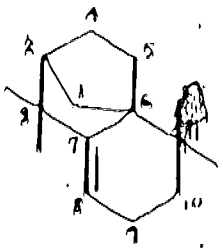

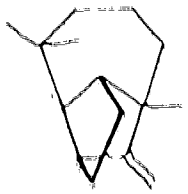

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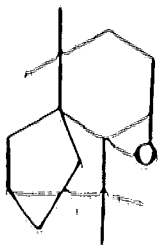

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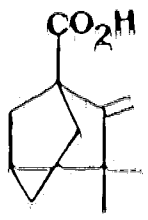

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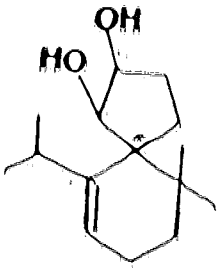
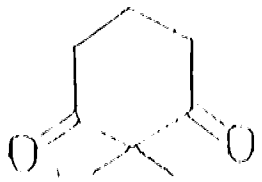


5

In examining the target molecule of isolongifolene (1), the direct incorporation of the two gem-dimethyl groups seemed to be a challenging task. Among the many schemes assessed with such an intention in mind, the particularly attractive one was to condense 2,2-dimethylcyclohexane-1,3-dione (6) and mesityl oxide by a Robinson annelation reaction[6], thereby providing the complete decalin skeleton present in isolongifolene (1). It was also anticipated that the two ketonic carbonyls in the condensation product 7 could be easily differentiated because one was conjugated with a double bond. The non-conjugated carbonyl was expected to be the more reactive one and therefore could be used directly for the incorporation of an activated carbon unit to give a compound of type 8. Its cyclisation by an intramolecular γ-alkylation (i.e., formation of C^{α}-C^{α} bond) would then provide the complete skeleton of isolongifolene (1).

Towards this end, the immediate goal was to prepare the desired starting material 6. Although 2-methycyclohexane-1,3-dione could be prepared readily either from 2-methylresorcinol by catalytic hydrogenation[7] or from cyclohexane-1,3-dione by monomethylation[8], its further methylation has been shown to give only a trace amount of 6[8]. Consequently, the preparation of 6 was attempted by condensing ethyl isobutyrylacetate (9), with ethyl acrylate to give the intermediate 10. However, the reaction was unsuccessful under various conditions. Subsequently, 3-ethoxy-2-methyl-2-cyclohexen-1-one (11), was prepared from 2-methylcyclohexane-1,3-dione[9] in an attempt to synthesize enone 12.

It is quite conceivable that this type of compound could be transformed to 8 by selective methylation followed by a Robinson annelation reaction with mesityl oxide. In order to prepare the potential intermediate



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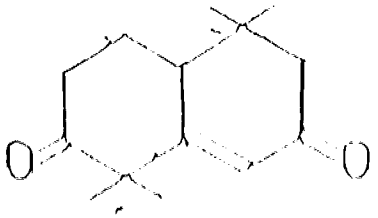

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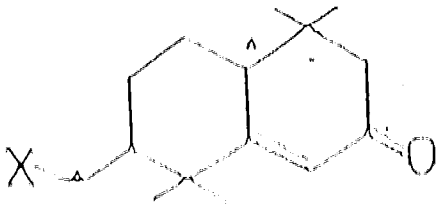
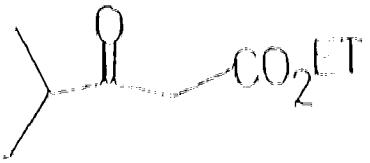


X = Leaving group



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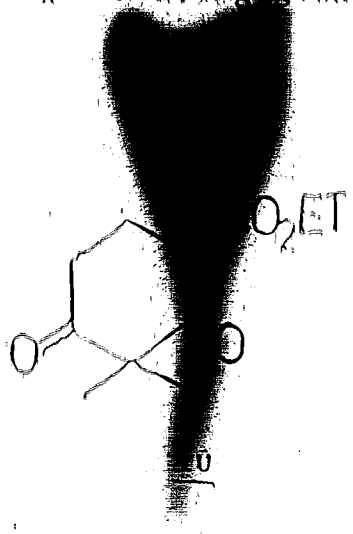

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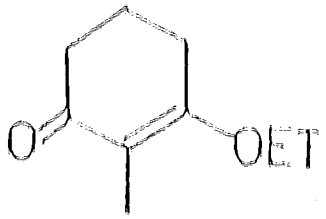

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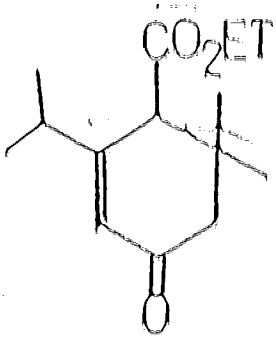

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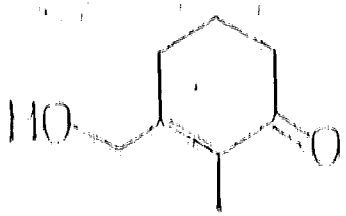
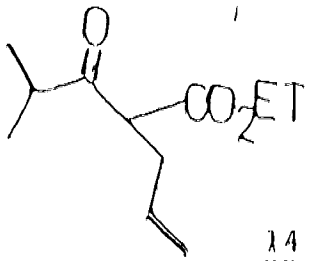


12

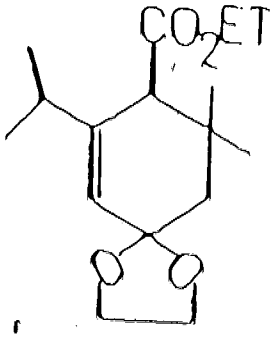
12, 11 was treated with dimethylsulfonium methylide[10]. This resulted in complete recovery of starting material. Alternatively, the addition of methoxy methyl lithium or methoxy methyl magnesium chloride to 11 was considered. However neither of these reagents could be prepared according to the described procedures[11-13].

It was found at this stage that ethyl isobutyryl-acetate (9) condensed readily with mesityl oxide to give, in 61% yield, the keto ester 13 whose nmr spectrum showed a singlet at τ 4.13 diagnostic of the vinylic proton. In the ir spectrum the ester and ketone carbonyls appeared at 1735 and 1660 cm^{-1} respectively. Although 13 had not been seriously considered as a starting material, it offered a new possibility for carrying out the task in question. The molecule had the advantage that the required two gem-dimethyl groups of the synthetic target were introduced directly and it possessed the desirable functionalities for the further construction of the B and C rings of isolongifolene. In order to form the B and C rings it was necessary to introduce an activated three-carbon unit α to the ester group. This could be achieved, in principle, by incorporating a desirable chain into 9 prior to its condensation with mesityl oxide. Alkylation of 9 with allyl bromide in the presence of sodium ethoxide gave rise to 14 in 54% yield. The attempted condensation of 14 with mesityl oxide was unsuccessful, presumably due to the steric hindrance. These findings led to the use of 13 directly. In order to alkylate the molecule at the desired position (α to the ester) it was necessary to block the ketone carbonyl to prevent the alkylation to take place at the α position of the conjugated enone. When 13 was refluxed with ethylene glycol containing a

trace of p toluenesulfonic acid in benzene, a mixture of ketals 15 and 16 was obtained. In the nmr spectrum the vinylic proton of 16 appeared at τ 4.68 as a singlet and the characteristic singlet of the isopropylidene group present in 15 was observed at τ 8.28. The ratio of 15:16 was determined to be ~ 2:1 on the basis of the relative intensities of the nmr signals (see experimental). Although the mixture gave two spots on tlc, attempted column chromatography resulted in the isolation of the starting material 14. The presence of the exocyclic double bond in 15 was suitable for the formation of the B ring of isolongifolene (1) but the ease of the hydrolysis of the ketal group made this scheme less attractive. Consequently, the ketone carbonyl of 15 was converted into the thioketal form using standard conditions. No isomerization occurred during the reaction and the thioketal 17 was obtained as the sole product. Attempts made to shift the double bond to the exocyclic position by the use of p-toluenesulfonic acid in refluxing benzene or toluene resulted in recovery of the starting material. In order to prevent any complication that might be caused by the presence of the thioketal group (which is vinylogously α to the ester), 17 was subjected to Raney nickel (W2) treatment in boiling ethanol to effect the desulfurisation. The product 18 thus obtained showed a vinyl proton at τ 4.47 as a triplet in the nmr spectrum and in the ir spectrum an ester peak at 1735 cm^{-1}. Direct alkylation of 18[13] in 1,2-dimethoxyethane (DME), with or without hexamethylphosphoramide, with epibromohydrin, 1,3-diiodopropane, and allyl bromide using lithium diisopropyl amide as a base in attempts to introduce the desirable three carbon chain to the α-carbon of



14



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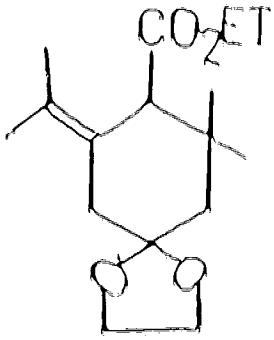

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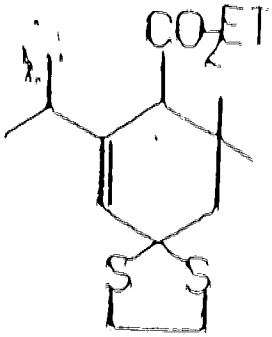

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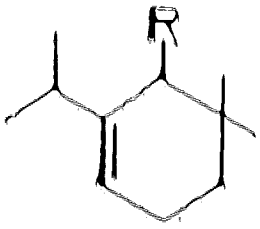
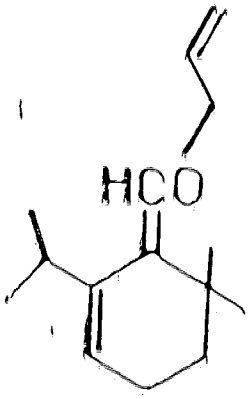


18 R = CO_2ET

19 R = CH_2OH

20 R = CHO



22

the ester was fruitless; in all cases, starting material was recovered. As a consequence, 18 was converted, via alcohol 19, into aldehyde 20 in 80% yield in two steps, lithium aluminum hydride reduction and oxidation with Collins reagent[15]. Alkylation of aldehyde 20 with allyl bromide in the presence of sodium hydride in DME at reflux resulted in the formation of two products, 21 and 22 in a combined yield of 91%. The ratio of these two compounds ranged from 2:3 to 3:2 in different runs. Enol ether 22 was readily separated from aldehyde 21 by column chromatography and showed no carbonyl absorption in the ir spectrum. Its nmr spectrum displayed multiplets at τ 3.92-5.05 region for a total of five vinylic protons and a multiplet at τ 5.98-6.69 for the two protons of the methylene group attached to the oxygen atom. The cis or trans nature of this compound, however could not be assigned unambiguously on the basis of the available spectral data. Aldehyde 21 showed a completely different set of spectra. In the nmr spectrum, the characteristic aldehydic proton appeared at τ 0.43 as a singlet whereas the four vinylic protons appeared at τ 4.08-5.25 as multiplets. Its ir spectrum showed the characteristic aldehyde absorption bands at 2700 and 1715 cm^{-1}. Exact mass measurement of the parent peak gave the same molecular formula as that of 22, although the fragmentation pattern was different.

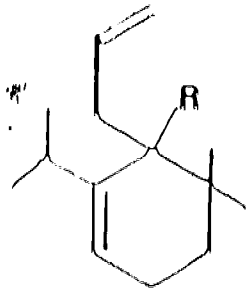
Although the alkylation reaction was found to proceed smoothly with sodium hydride in small scales (ca. 200 mg), the results were not reproducible on a preparative scale. Under the same reaction conditions (vide supra) a substantially lower yield of compounds 22 and 21 was obtained. An attempt to circumvent this difficulty by lowering the reaction

temperature to room temperature resulted in the recovery of starting material. However when sodium hydride was substituted by a considerably stronger base, potassium hydride[15], the reaction proceeded smoothly at room temperature to give comparable yields of 21 and 22. The simultaneous formation of 22, though undesirable, did not present a serious problem to the synthesis as a whole; its conversion to 21 could be easily achieved by Claisen rearrangement[16]. Thus, boiling a solution of 22 in xylene overnight gave rise to 21 in virtually quantitative yield. For a more effective preparation, the crude mixture of 21 and 22 was used without separation. This procedure not only simplified the preparation of 21 but also increased its overall yield from 20 substantially.

In order to complete the skeleton of isolongifolene from 21, the formation of two carbon-carbon bonds (C_1-C_8 or C_9-C_{10} and C_2-C_3 with respect to isolongifolene) were required. Conceptually, this could be achieved in a single step by the use of a suitable acid. It is quite conceivable that, under the influence of acid, aldehyde 21 would undergo isomerization and two consecutive cyclisations to furnish the required skeleton as illustrated schematically by 21→23→24→25. Experimentally, the scheme was not productive; only starting material was recovered when 21 was treated at room temperature with various acids such as aqueous hydrochloric acid in tetrahydrofuran (THF), stannic chloride and boron trifluoride etherate in benzene or chloroform. When the reaction was carried out with boron trifluoride etherate in refluxing benzene, a complex mixture was obtained. No detectable amount of the desirable product was present. The ir spectrum of the crude mixture showed

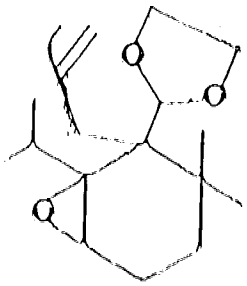
the absence of hydroxy absorption band and in its nmr spectrum, the signals expected for the vinylic protons were not present. It has been shown by Johnson and co workers[17] that a similar kind of cyclisation could be facilitated by the use of the corresponding acetal of the carbonyl group. Aldehyde 21 was thus converted to acetal 20 using standard conditions and the cyclisation was attempted. Treatment of 20 with stannic chloride in nitromethane according to the described procedure resulted again in complex mixture whose ir and nmr spectra indicated the absence of the desirable product.

As a consequence of these negative results, it became necessary to construct the two remaining rings in a stepwise manner. In examining aldehyde 21 and its precursors it was decided to form the C ring first because of the difficulty that might be encountered in activating the isopropyl group at this point. The failure of the acid catalysed cyclisation discussed above suggested that the double bond of the side chain in 21 could not be used directly. In order to form the spiro system it was thus necessary to convert the side chain double bond selectively into another functional group or to introduce a suitably functionalized three-carbon chain directly into aldehyde 20. The latter possibility was explored first. Aldehyde 20 was subjected to alkylation, using potassium hydride as a base, with a number of alkylating reagents containing potential functional groups at specific centers; namely, 1,3-diiodopropane, methyl acrylate, epibromohydrin, 1-bromo-3-chloropropane, and propylene oxide. Except in the case of epibromohydrin, in which only the O-alkylation product was obtained, no reaction occurred in any of the other instances. Our attention was then



21 R = CHO

26 R = $CH(OCH_2)_2$



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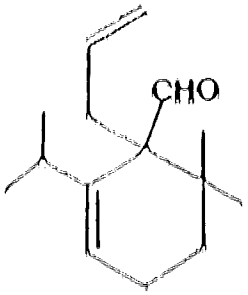

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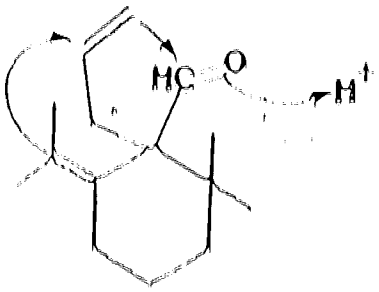

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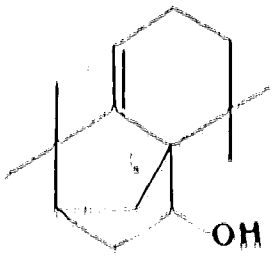

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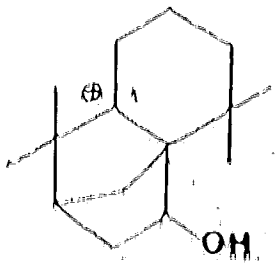


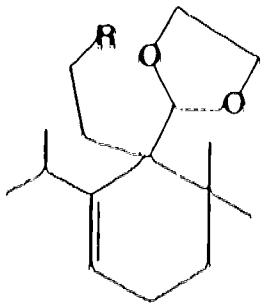
24

drawn to the modification of 26. In order to differentiate between the two double bonds in the molecule, the respective relative reactivities of each towards the sterically unhindered electrophiles had to be first ascertained. Epoxidation was used as the means of acquiring this necessary information. Treatment of 26 with one equivalent of m-chloroperbenzoic acid resulted in crystalline product whose structure could be readily assigned as 27 on the basis of the nmr spectrum which showed the signals of the three vinyl protons of the allyl side chain at τ 4.86-5.30 and lacked the triplet at τ 4.32 characteristic of the ring vinyl proton of 26. This result suggested that the more substituted double bond was the more reactive. Hence this double bond had to be blocked prior to the modification of the side chain double bond with sterically unhindered reagents.

On the other hand, it has been shown that substituted boranes such as disiamylborane react preferentially with sterically less hindered double bonds. This provided an opportunity to functionalize the side chain double bond directly. When actual 26 was allowed to react with dicyclohexylborane, alcohol 28 was isolated in 95% yield after oxidative work-up. The nmr spectrum was consistent with the assigned structure showing a triplet at τ 4.53 characteristic of the vinylic proton. It is noteworthy that the yield of 28 was very dependent on the procedure involved in the oxidative work-up. Reproducible results could only be obtained when an excess of 30% hydrogen peroxide and 2.5 N aqueous sodium hydroxide solution (1:1) was added in one portion to the chilled hydroboration reaction mixture. When the addition was carried out sequentially with sodium hydroxide and hydrogen peroxide, very little or none of the desirable alcohol 28 was obtained; instead, compound 29 was

found to be the major product.

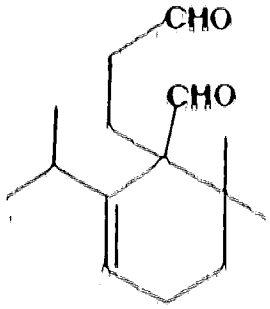
The subsequent formation of the spiro system corresponding to the A and C rings of isolongifolene was achieved in three steps from 28. Oxidation of 28 with Collin's reagent followed by hydrolysis of the resulting acetal aldehyde 30 with aqueous hydrochloric acid in THF gave rise to dialdehyde 31 in 87% yield. The characteristic aldehyde peaks appeared in the ir spectrum at 2720 and 1720 cm^{-1}. The nmr spectrum displayed two partially superimposed signals at τ 0.28-0.38 for the two aldehyde protons and a triplet at τ 4.10 for the vinylic hydrogen atom. The ring closure of 31 was effected upon treatment with magnesium amalgam in THF in the presence of dimethyldichlorosilane at room temperature. After three hours, the reaction mixture was treated with aqueous sodium hydroxide in methanol to give three isomers of diol 5 in a total of 68% yield based on 31. Two of the isomers were obtained in pure form after column chromatography and crystallization. Both isomers showed strong hydroxy absorption bands and no carbonyl peaks in the ir spectra. One isomer, m.p. 97-97.5°, showed in the nmr spectrum, a triplet at τ 4.17 for the vinylic proton and multiplets at τ 6.15-6.10 for the two hydrogen atoms adjacent to the hydroxy groups. The corresponding hydrogen atoms of the other crystalline isomer, m.p. 127-128°, appeared at τ 4.36 and τ 5.77-6.75. Their isomeric nature was further defined by their mass spectra which showed in both cases a molecular peak at 238.1933 consistent with the molecular formula of $C_{15}H_{20}O_2$. The third isomer of 5 was isolated as a liquid which was shown to contain a small amount of impurities, since the ir spectrum showed, in addition to the expected hydroxy absorption, a weak peak at 1720 cm^{-1}. The nmr and mass spectra of this mixture were



28 R = CH_2OH

29 R = CH_3

30 R = CHO



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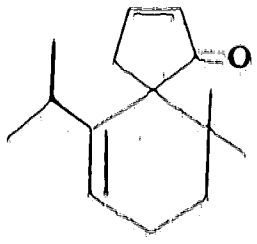

32

similar with those obtained for the crystalline isomers. Although the spectral data characterised clearly the structures of these isomers, their stereochemistry could not be defined without further exploration. Since the two chiral centers bearing the hydroxy groups in 5 would be destroyed in proceeding towards the synthesis of isolongifolene (1), the stereochemistry of 5 was nevertheless of secondary importance.

The acquisition of the isomeric diols 5 represents the current position in the synthetic studies of isolongifolene. The further transformation of 5 into 1 could be conceivably achieved *via* intermediate 32 which, in turn, might be prepared from 5 by selective monotolsylation of the considerably less hindered C_8 hydroxy group followed by oxidation and β-elimination. A preliminary investigation along this line was found to be promising.

EXPERIMENTAL

General

Spectra, melting points, elemental analyses, and glc (gas-liquid chromatography) analyses were obtained and reported as indicated in the Experimental section of Part I. Other than samples 5 and 27, which were run in chloroform solutions, all ir (infrared) samples were run as thin films. Silica gel was used as an adsorbant in all cases where column chromatography was used for purification.

Material

Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were freshly distilled over lithium aluminum hydride prior to use. Allyl bromide was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solutions and distilled. Mesityl oxide was freshly distilled before use.

Synthesis of 4-carbethoxy-2-methyl-6-hepten-3-one (14).

Sodium (1.45 g, 63.0 mmol) was dissolved in absolute ethanol (120 ml). To this solution, ethyl isobutyrylacetate (9) (9.99 g, 63.2 mmol) was added. After the resulting solution was heated under a nitrogen atmosphere to reflux, allyl bromide (7.69 g, 78.5 mmol) was added dropwise over a period of 15 min. The reflux was continued for an additional 15 min. After cooling to room temperature the reaction mixture was

acidified with aqueous hydrochloric acid and extracted with ether. The organic solution was washed with water, dried ($MgSO_4$), and concentrated. The crude product after distillation under reduced pressure gave 14 (0.76 g, 54%); b.p. 48.8-50° /0.2 mm; nmr τ 4.05-5.22 (m, 3H, $H_2C{=}CH$), 5.92 (q, 2H, J ~ 7 Hz, $CO_2CH_2CH_3$), 6.45 (t, 1H, J' ~ 7 Hz, $COCHCO_2Et$), 8.64-9.00 (superimposed t and d, 9H, J ~ J' ~ 7 Hz); ir 1735 cm^{-1} (ester); mass spectrum M^+ 198.1252 (Calcd for $C_{12}H_{20}O_3$: 198.1260).

4-Carbethoxy-5-isopropyl-5,5-dimethyl-2-cyclohexen-1-one (13).

To an ethanolic solution of sodium ethoxide (prepared by the addition of 7.5 g of sodium to 250 ml of ethanol), ethyl isobutyrylacetate (9) (40 g, 0.25 mol) and mesityl oxide (30 g, 0.37 mol) were added. The solution was refluxed under a nitrogen atmosphere overnight. After cooling to room temperature, the reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The organic solution was successively washed with saturated sodium bicarbonate and sodium chloride solutions, dried ($MgSO_4$), and concentrated. The crude product was fractionally distilled to give 13 (37 g, 61%); b.p. 98° /0.5 mm; ir 1670 (ketone), and 1735 cm^{-1} (ester); nmr τ 4.13 (s, 1H, $C{=}CH$), and 5.83 (q, 2H, OCH_2CH_3); mass spectrum M^+ 238.1517 (Calcd for $C_{14}H_{22}O_3$: 238.1569).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.43; H, 9.19.

8-Carbethoxy-7-isopropyl-9,9-dimethyl-1,4-dioxaspiro [4.5]dec-6-one (16) and 8-carbethoxy-7-isopropylidene-9,9-dimethyl[4.5]decane (15).

A solution of [redacted] (4.29 g, 18 mmol) in benzene (1 l.), containing a [redacted] p toluenesulfonic acid and ethylene glycol [redacted] ml), was refluxed with a Dean-Stark water separator for [redacted]. After cooling to room temperature, the solution was successively washed with saturated sodium bicarbonate and sodium chloride solutions. Drying ($MgSO_4$), filtration and concentration gave the crude product which was distilled from bulb-to-bulb at 105-110° (oven temperature)/0.2 mm to give a mixture of 15 and 16 (3.32 g, 66%); nmr τ 8.28 (s, C-C$(CH_3)_2$), 6.15 (s, OCH_2CH_2O), and 6.17 (s, OCH_2CH_2O); mass spectrum M^+ [redacted]; ir 1740 cm^{-1} (ester).

The relative intensities of the signals at τ 8.28 and 5.73-6.25 were 42 and 60 respectively. The signal at τ 5.73-6.25 represented six protons consisting of the methylene in the carbethoxy and the ketal groups of both 15 and [redacted] while the signal at τ 8.28 accounted for six protons in 15 only. Hence the ratio of 15 : 16 was 7:3 or approximately 2:1.

8-Carbethoxy-7-isopropyl-9,9-dimethyl-1,4-dithiospiro [4.5]dec-6-one (17).

A solution of 13 (3.64 g, 15.3 mmol) in methylene chloride (20 ml), containing 1,2-ethanedithiol (3 g, 32 mmol) and boron trifluoride etherate (5ml), was stirred at room temperature overnight. The solution was diluted with ether and washed with 4 N-potassium hydroxide solution and water. After drying ($MgSO_4$) and evaporation of the solvent, the crude material was distilled to give 17 (4.62 g, 96%); b.p.: 135-137°/0.2 mm.; nmr τ 4.38 (s, 1H, C=CH), 5.82 (q, 2H, J = 8 Hz, OCH_2CH_3), and 6.70 (s, 4H, $(SCH_2)_2$); ir

1755 cm^{-1} (ester); mass spectrum M^+ 314.1384 (Calcd for $C_{16}H_{26}O_2S_2$: 314.1374).

Anal. Calcd for $C_{16}H_{26}O_2S_2$: C, 61.10; H, 8.33, S, 20.39. Found: C, 61.12; H, 8.25; S, 20.18.

3 Carbethoxy-2 isopropyl 4,4 dimethylcyclohexene (18).

To a solution of 17 (958 mg, 5.05 mmol) in absolute ethanol (50 ml), was added Raney nickel (W2; ~15 g). The resulting mixture was refluxed for 8 hr. After filtration and washing of the Raney nickel, the filtrate was concentrated. Bulb-to-bulb distillation of the crude product at 90° (oven temperature)/0.2 mm gave 760 mg (98%) of 18: nmr τ 4.47 (t, 1H, J = 3 Hz, C=CH), 5.93 (q, 2H, J = 8 Hz, OCH_2CH_3), and 7.57 (s, 1H, C=CCHCO$_2$Et); ir 1755 cm^{-1} (ester); mass spectrum M^+ 224.1785 (Calcd for $C_{14}H_{24}O_2$: 224.1776).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.98. Found: C, 74.97; H, 10.92.

3-Hydroxymethyl-2-isopropyl-4,4-dimethylcyclohexene (19).

To a suspension of lithium aluminum hydride (0.3 g, 7.89 mmol) in ether (50 ml), 18 (1.68 g, 7.50 mmol) was added slowly. The resulting mixture was stirred at room temperature for an hr. Ethyl acetate was added to destroy the excess of lithium aluminum hydride and the solution was then acidified with dilute sulfuric acid and extracted with ether. The ether extract was washed with saturated aqueous sodium bicarbonate and aqueous sodium chloride solutions, dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by column chromatography using a solution

of 30% ether in benzene as eluent, followed by bulb-to-bulb distillation at 77° (oven temperature)/0.2 mm giving 1.24 g (91%) of 19; nmr τ 4.50 (t, 1H, J = 3 Hz, C=CH), and 6.48 (d, 2H, J = 3.5 Hz, CH_2OH); ir 3350 cm^{-1} (hydroxy); mass spectrum M^+ 182.1671 (Calcd for $C_{12}H_{22}O$: 182.1671).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06, H, 12.16. Found: C, 79.35; H, 12.20.

3-Formyl-2-isopropyl-4,4-dimethylcyclohexene (20).

To a solution of pyridine (3.61 g, 45.7 mmol), in methylene chloride (57 ml), dry chromium trioxide (2.28 g, 22.8 mmol) was added. The solution was stirred for 15 min. and a solution of 19 (692 mg, 3.80 mmol; in 1 ml of CH_2Cl_2) was added in one portion. Stirring was continued for another 15 min. After decanting the liquid, the gummy residue was washed with ether. The combined organic solution was washed with 5% aqueous sodium hydroxide solution for four times (~50 ml each time). After drying, filtering and evaporating the solvent, the crude product was distilled from bulb-to-bulb at 45° (oven temperature)/0.1 mm to give 20 (645 mg, 94%); nmr τ 0.58 (d, 1H, J = 5 Hz, CHO), and 4.30 (t, 1H, J = 3 Hz, C=CH); ir 2700, and 1720 cm^{-1} (aldehyde); mass spectrum M^+ 180.1511 (Calcd for $C_{12}H_{20}O$: 180.1514).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.00, H, 11.26.

3-Allyl-3-formyl-2-isopropyl-4,4-dimethylcyclohexene (21), and 2-isopropyl-4,4-dimethyl-3-(2'-propenyl-oxymethylene) cyclohexene (22).

(i) Small Scale

To a solution of 20 (165 mg; 0.917 mmol) and allyl bromide (200 mg) in DME (10 ml), was added sodium hydride (50% dispersion in oil, 64 mg, 1.33 mmol). The resulting mixture was refluxed under a nitrogen atmosphere for 4 hr. After cooling to room temperature, the reaction mixture was poured into aqueous ammonium chloride solution and extracted with ether. Drying ($MgSO_4$), filtration, and concentration gave the oily crude product which was subjected to column chromatography. Elution with Skelly B gave 22 (91.0 mg, 45%); nmr τ 3.92-5.05 (m, 5H, C=CH), and 5.69-5.98 (m, 2H, OCH_2); ir 1640 and 1610 cm^{-1} (C=C); mass spectrum M^+ 220.1828 (Calcd for $C_{15}H_{24}O$: 220.1827).

Further elution with 10% of benzene in Skelly B solution furnished 21 (95.7 mg 40.5%); nmr τ 4.13 (t, 1H, J = 3 Hz, $H_2C=CH$), 4.22-5.25 (m, 3H, $H_2C=CH$), and 0.45 (s, 1H, CHO); ir 2720, and 1715 cm^{-1} (aldehyde); mass spectrum M^+ 220.1828 (Calcd for $C_{15}H_{24}O$: 220.1827).

(ii) Preparative Scale

To a suspension of an excess of potassium hydride (mineral oil was removed in advance by washing with dry Skelly B) in DME (75 ml), a mixture of 20 (3.24 g, 18 mmol) and allyl bromide (4 g) was added. The reaction mixute was stirred under an atmosphere of nitrogen overnight. Isopropanol was added to destroy the unreacted potassium hydride. The mixture was poured into aqueous ammonium chloride solution and extracted with ether.

After the usual work up, the crude product was distilled (bulb to bulb at 110 115° (oven temperature)/0.1 mm) to give 5.92 g of a mixture of 21 and 22 which was used without separation for the conversion of 22 to 21 (see immediately below).

Rearrangement of 22 to 21.

(i) From 22

A solution of 22 (1.57 g, 6.25 mmol) in N,N-dimethyl aniline (5 ml) was heated at 120-150° under a nitrogen atmosphere overnight. The reaction mixture after cooling to room temperature, was poured into chloroform and washed with aqueous hydrochloric acid. The organic solution was dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography gave 21 (850 mg, 62%).

(ii) From the mixture of 21 and 22.

The mixture of 21 and 22 (3.92 g) obtained from the alkylation of 20 [see part (ii) above] was dissolved in dry xylene (10 ml) and the resulting solution was refluxed under an atmosphere of nitrogen overnight. After concentration, the crude product was purified by column chromatography to give 3.53 g (89% yield based on 20) of 21.

6-Allyl-2-isopropyl-4,4-dimethyl-3-(2',5'-dioxacyclopentanyl)-cyclohexene (26).

Ethylene glycol (5 ml) and 21 (2.14 g, 9.75 mmol)

were dissolved in benzene (100 ml) containing a trace of p toluenesulfonic acid. The mixture was refluxed with a Dean Stork water separator under nitrogen atmosphere overnight. The reaction mixture was worked up in the usual manner. The crude product was purified by column chromatography. Elution with a solution of 10% benzene in Skelly B gave 26 (2.09 g, 81%); nmr τ 4.33 (t, 1H, J = 3 Hz, C-CH), 4.80-5.30 (m, 3H, CH=CH_2), and 6.00-6.35 (m, 4H, $(OCH_2)_2$); ir 1640 cm^{-1} (olefin); mass spectrum M^+ 264.2089 (Calcd for $C_{17}H_{28}O_2$: 264.2098).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.47, H, 10.77.

3-Allyl-2-isopropyl-4,4-dimethyl-5-(2',5'-dioxacyclopentanyl)-7-oxabicyclo[4.1.0]heptane (27).

To a solution of m-chloroperbenzoic acid (102 mg, 0.594 mmol) in methylene chloride (4 ml) at 0°, 26 (115 mg, 0.430 mmol) was added. After stirring for 6 hr., the solution was diluted with methylene chloride and washed with sodium bicarbonate and saturated sodium chloride solutions. After drying, filtering, and concentration, the crude product was purified by column chromatography with 10% ether in benzene solution as eluent and crystallization (chloroform) to give 27 (45 mg, 37%); m.p. 98-99° ; nmr τ 4.80-5.30 (m, 3H, CH=CH_2), and 6.00-6.35 (m, 4H, $(OCH_2)_2$); ir 1630 cm^{-1} (olefin); mass spectrum M^+ 280.

3-(3'-Hydroxypropyl)-2-isopropyl-4,4-dimethyl-3-(2',5'-dioxacyclopentanyl)hexene (28), and 2-isopropyl-4,4-dimethyl-3-(2',5'-dioxacyclopentanyl)-3-propylcyclohex-1-ene (29).

A solution of cyclohexene (10 mmol, 1 ml in 2 ml of THF) was added to a cooled solution of diborane (4.5 ml, 4.5 mmol, 1 N in THF) under a nitrogen atmosphere. The nitrogen flow was stopped and the mixture was stirred for 10 min. at room temperature. The dicyclohexyl borane slurry was cooled to 0° again and a solution of 20 (1.08 g, 4.12 mmol) in THF (1 ml) was introduced slowly so the temperature was kept below 20° during addition. The resulting solution was stirred at room temperature for 1 hr during which time, the slurry turned into a clear solution. The solution was cooled to about -10° and a mixture of 2.5 N sodium hydroxide and 30% hydrogen peroxide (3 ml each) was added. After the addition, the resulting mixture was stirred at room temperature for another hr and extracted with ether. The extract was washed with saturated sodium chloride solution, dried with $MgSO_4$ and filtered. Concentration of the filtrate followed by the removal of cyclohexanol under reduced pressure (0.5 mm) gave an oil which was purified by column chromatography. Elution with 50% ether in benzene gave 28 (1.10 g, 95%); nmr τ 4.53 (t, 1H, J = 4 Hz, C=CH), and 5.50 (s, 1H, $CH(OCH_2)_2$), and 6.38 (s, 4H, $(OCH_2)_2$); ir 3430 cm^{-1} (hydroxy); mass spectrum M^+ 282.2199 (Calcd for $C_{17}H_{30}O_3$: 282.2195).

If sodium hydroxide solution was introduced before hydrogen peroxide during the oxidation stage, a different set of products were obtained as could be shown by the tlc. The major product was worked up as in 28 and the spectra suggested it to be 29: nmr τ 4.30 (t, 1H, J = 4 Hz, C=CH), 5.20 (s, 1H, $CH(OCH_2)_2$), 6.13-6.50 (m, 4H, $(OCH_2)_2$); ir 1460, 1380, and 1360 cm^{-1} (gem-dimethyl groups); mass spectrum M^+ 268.

2-Isopropyl-4,4-dimethyl-3-(2',5'-dioxacyclopentanyl)-3-(3'-oxopropyl)hexene (30).

The reaction was carried under the same conditions for the preparation of 20. From 574 mg of 28 (2.04 mmol), 470 mg (83%) of 30 was obtained after the crude product was purified by column chromatography. 30 showed the following spectral data: nmr τ 0.33 (t, 1H, J = 1.5 Hz, O=CH), 4.30 (t, 1H, J = 3.5 Hz, C=CH), 5.22 (s, 1H, $CH(OCH_2)_2$), and 5.95-6.30 (m, 4H, $(OCH_2)_2$); ir 2750 and 1722 cm^{-1} (aldehyde); mass spectrum M^+ 280.2032 (Calcd for $C_{17}H_{28}O_5$: 280.2039).

3-Formyl-2-isopropyl-4,4-dimethyl-3-(3'-oxopropyl)hexene (31).

30 (470 mg, 1.08 mmol) was dissolved in a mixture of 2 N hydrochloric acid (5 ml) and THF (5 ml) and the mixture was stirred at room temperature for 20 hr. After the usual work-up, the crude product was purified by column chromatography using 10% ether in benzene as eluent to give 31 (320 mg, 81%); nmr τ 0.25-0.37 (2H, 2 CHO), and 4.10 (t, 1H, J = 3.5 Hz, C=CH); ir 2720 and 1720 cm^{-1} (aldehyde); mass spectrum M^+ 236.1781 (Calcd for $C_{15}H_{24}O_2$: 236.1776).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.51; H, 10.28.

6-Isopropyl-10,10-dimethylspiro[4,5]dec-6-ene-1,2-diol (5).

Mercuric chloride (300 mg) and dimethyldichlorosilane (0.22 ml, 1.8 mmol) were added to a suspension of magnesium (285 mg, 11.9 mmol) in THF (20 ml).

The mixture was stirred under nitrogen for 15 min. A solution of 31 (212 mg, 0.897 mmol) in THF (0.5 ml) was added slowly by means of a syringe. After the addition, the mixture was stirred for 3 hr at room temperature. The liquid was decanted and the residue was thoroughly washed with THF. The combined organic solution was concentrated. The residue was dissolved in a mixture of methanol and 2.5 N sodium hydroxide solution (1:1, 5 ml of each). After stirring at room temperature overnight, the mixture was poured into water and extracted with ether. The usual work-up of the extract gave 184 mg of the crude product which was mixed with the crude product (369 mg, from 420 mg of 31) from another run and subjected to column chromatography purification. Elution with chloroform gave, in order of increasing polarity, three fractions which were designated as fraction A, B, and C. Fraction A (185 mg) showed the following spectral data: nmr ($CDCl_3$) τ 4.22 (t, 1H, J = 3.5 Hz, C=CH), and 5.84-6.35 (m, 4H, CHOH); ir 3470 (hydroxy), and 1720 cm^{-1} (weak, impurities ?). Fraction B (137 mg) had a m.p. of 97-97.5° and showed the following spectra: nmr ($CDCl_3$) τ 4.17 (t, 1H, J = 3.5 Hz, C=CH), and 6.15-6.40 (m, 2H, CH-OH); ir ($CHCl_3$) 3700 and 3440 cm^{-1} (hydroxy). Fraction C (107 mg) had a m.p. of 127-128° and displayed the following spectral data: nmr ($CDCl_3$) τ 4.36 (t, 1H, J = 3.5 Hz, C=CH), and 5.77-6.75 (m, 4H, CHOH); ir ($CHCl_3$) 3700 and 3400 cm^{-1} (hydroxy). The total amount of the three fractions was 430 mg (68% based upon 31).

All three fractions gave similar mass spectra with M^+ at 238.1941 (Calcd for $C_{15}H_{26}O_2$: 238.1933).

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