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THE UNIVERSITY OF ALBERTA

TOTAL SYNTHESIS OF (-)-QUADRONE AND (±)-CORONAFACIC ACID

by

MONTSE LLINAS-BRUNET

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

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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 TOTAL SYNTHESIS OF (-)-QUADRONE AND (±)-CORONAFACIC ACID

submitted by MONTSE LLINAS-BRUNET

in partial fulfilment of the requirements for the degree of DOCTOR OF PHILOSOPHY

Supervisor

External Examiner

DATE June 16th 1986

ABSTRACT

The first chapter of this thesis describes the total synthesis of (-)-guadrone (I) starting from the commercially available (-)-10-camphorsulfonic acid ammonium salt (II).

Fusion of the salt II with potassium hydroxide pellets afforded (-)-campholenic acid (III). Lithium aluminum hydride reduction of III followed by treatment of the resulting (-)-campholenic alcohol (IV) with sodium hydride and dimethyl sulfate in 1,2-dimethoxyethane gave (-)-ether V. Photooxygenation of V in methylene chloride in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine using 5,10,15,20-tetraphenyl-21H,23H-porphine (TPP) as a photosensitizer gave (-)-enone VI. Epoxidation of VI with lithium hydroxide and hydrogen peroxide in methanol furnished an epimeric mixture of (-)-epoxides VII which, upon treatment with a solution of sodium hydroxide in aqueous methanol, underwent epoxide ring opening and deformylation to give (-)-ketone VIII. Selective alkylation of VIII with lithium diisopropylamide and diethyl 3-bromo-2-ethoxypropenylphosphonate followed by hydrolysis of the ethyl enol ether afforded (-)-diketone IX which underwent cyclization upon treatment with potassium carbonate and 18-crown-6 ether in benzene to furnish (-)-bicyclic enone X. Irradiation of a solution

of X and allene in tetrahydrofuran afforded (-)-photoadduct XI with the required all-cis stereochemistry. Ozonolysis of XI in methanol-methylene chloride followed by reductive work up with dimethyl sulfide furnished (-)-ester XII. The conversion of XII into (-)-iodo compound XIII was effected by treatment with chlorotrimethylsilane and sodium iodide in acetonitrile followed by ketalization. Treatment of XIII with lithium hexamethyl disilylazide in tetrahydrofuran followed by deketalization with p-toluenesulfonic acid in acetone afforded (-)-ester XIV.

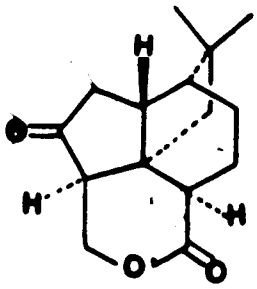
Application of the reported synthetic sequence to the optically active ester XIV resulted in the first total synthesis of the naturally occurring (-)-quadrone (I) as follows. Alkaline hydrolysis gave (-)-acid XV which after selenenylation and oxidation of the resulting C3-phenylseleno derivative furnished enone acid XVI. Treatment of XVI with lithium diisopropylamide followed by addition of formaldehyde gave, after hydrogenation of the carbon-carbon double bond, hydroxy acid XVII. Pyrolysis of XVII at 190-192°C resulted in the formation of (-)-quadrone (I).

In the second chapter of this thesis, the total synthesis of (±)-coronafacic acid (XVIII) is described. Diels-Alder reaction of 4-ethyl-2,4-pentadienoate (XIX) and

4-cyclopenten-1,3-dione (XX) in refluxing toluene afforded adduct XXI. Treatment of the lithium salt of XXI, generated *in situ* using lithium hydride, with phenyl dichlorophosphate and lithium chloride in tetrahydrofuran resulted in the formation of the two isomeric chlorides XXII and XXIII. Chlorides XXII and XXIII were individually transformed to keto ester XXIV as follows.

On hydrogenation in benzene in the presence of 5% palladium on carbon and sodium bicarbonate, chloride XXIII underwent selective reduction to give an epimeric mixture of keto esters XXIV. Chloride XXII was subjected to treatment with silver nitrate in hot methanol and the resulting esters XXV and XXVI were reduced with lithium aluminum hydride. Acidic work up using hydrochloric acid gave alcohol XXVII. Jones oxidation followed by esterification of the resulting acid with potassium carbonate and ethyl iodide in refluxing acetone gave rise to enone ester XXVIII. Subsequent hydrogenation in ethyl acetate using 5% Pd/C as a catalyst furnished the epimeric keto esters XXIV.

To effect the isomerization of the double bond, keto esters XXIV were treated with sodium ethoxide in ethanol. Hydrolysis of the resulting α,β-unsaturated esters XXIX in refluxing aqueous hydrochloric acid gave, after recrystallization, (±)-coronafacic acid (XVII).



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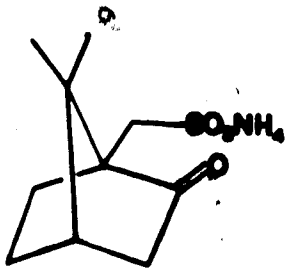

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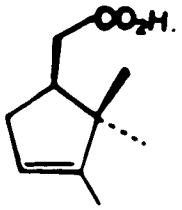

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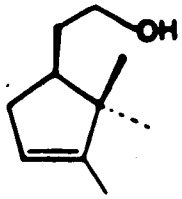

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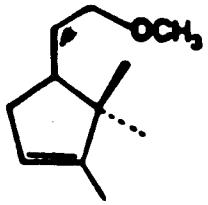

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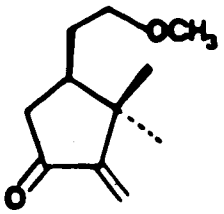

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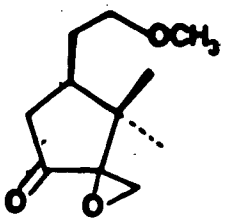

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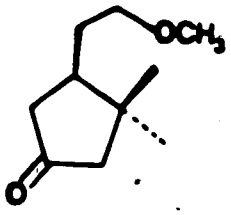

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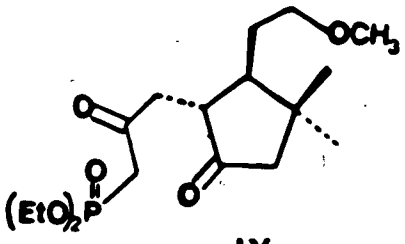

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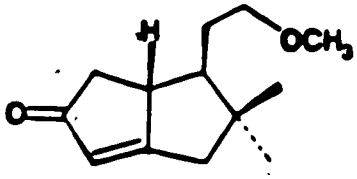

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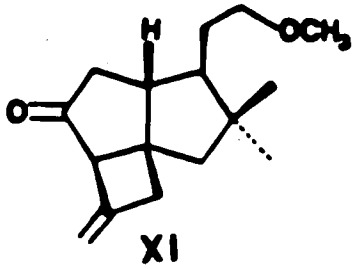

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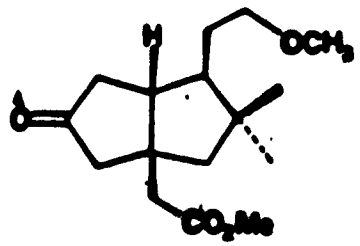

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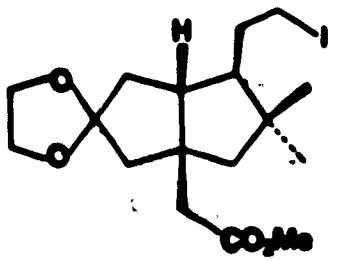

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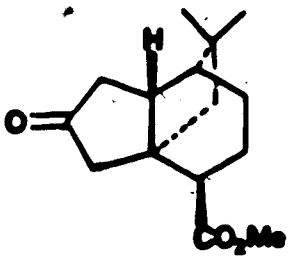

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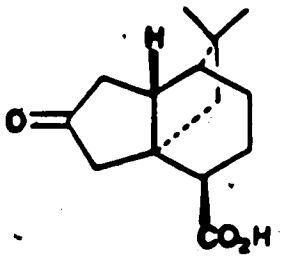

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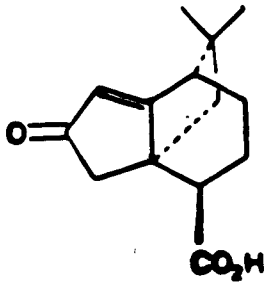

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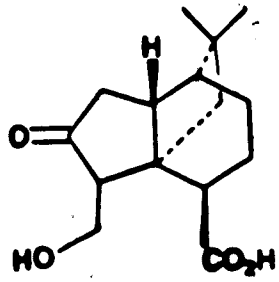

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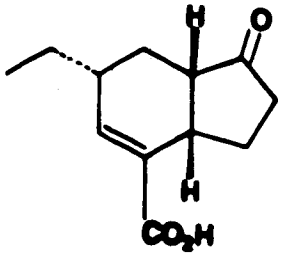

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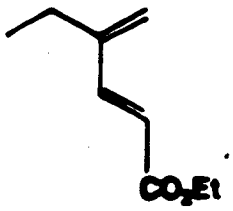

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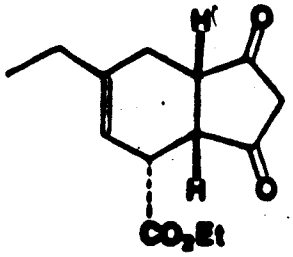

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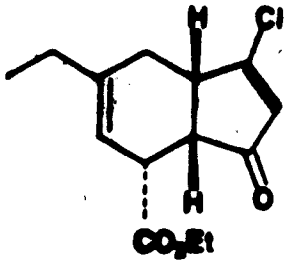

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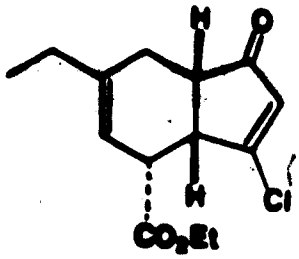

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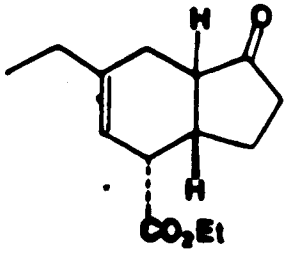

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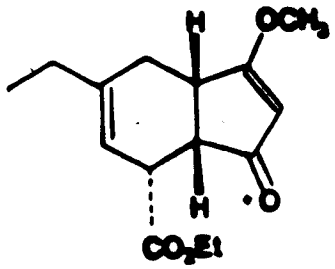

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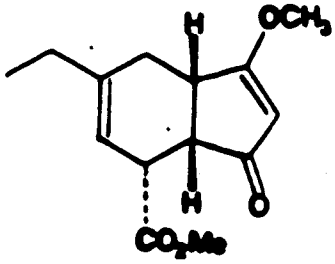

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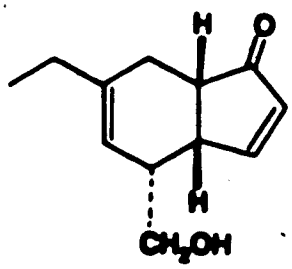

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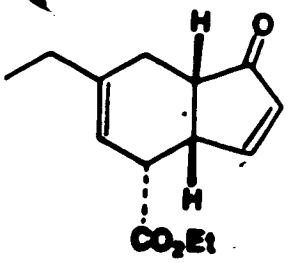

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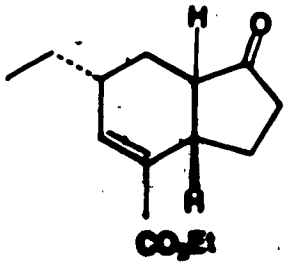

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Special thanks also go to Dr. T. Dieck Abularach, Mr. M. Ralitsch and Mr. B. Ramani for their help in recording high-field nmr spectra, to Dr. M. Torres and Ms. V. Wiszniewski for proof reading the thesis, and also to Miss A. Wiseman for typing the entire manuscript.

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Finally, I would like to extend a sincere, collective thanks to everyone in Edmonton whom I have come to know

these past few years. These friendships have always helped me through the bad times and made the good times even better. They will always be a cherished part of my unforgettable stay in Canada.

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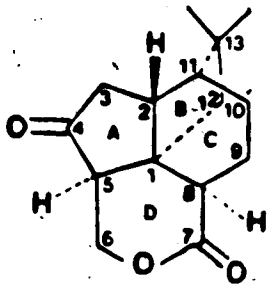
CHAPTER I.

THE TOTAL SYNTHESIS OF (-)-QUADRONE

INTRODUCTION

Quadrone (1) is a sesquiterpene metabolite isolated by Ranieri and co-workers in 1978 from Aspergillus terreus.[1] The novel structure of this sesquiterpene was deduced by the same group[2] from spectroscopic analysis and ultimately confirmed by a single crystal X-ray analysis. However, the absolute configuration was not assigned at that time.



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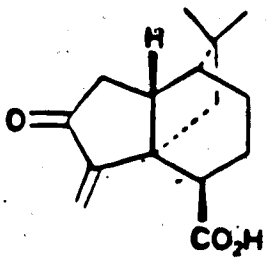

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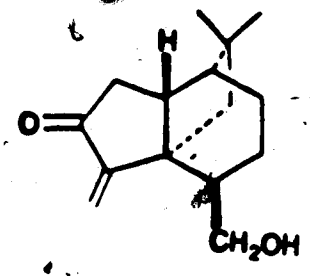
In 1982, Sakai and co-workers[3] isolated also from Aspergillus terreus a tricyclic sesquiterpene, terrecyclic acid A (2). The structure of this new sesquiterpene was elucidated by spectroscopic methods and by its chemical

correlation with quadrone (1).[4] Thus, when neat terrecyclic acid A (2) was heated at 190°C, quadrone (1) was obtained. Terrecyclic acid A (2) has been proposed as the biological precursor of quadrone (1).[4]

To date, four additional sesquiterpenes with a similar skeleton have been isolated from Aspergillus terreus including terrecyclol (3),[5] 8-hydroxyquadrone (4),[6] isoquadrone (5),[6] and 6-hydroxyisoquadrone (6).[6]



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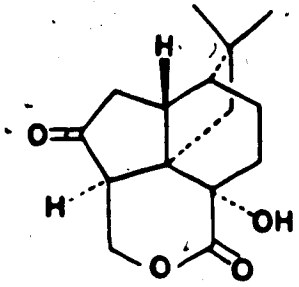

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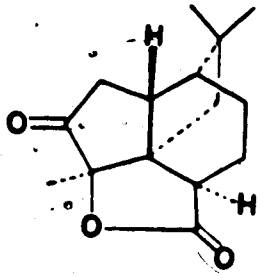

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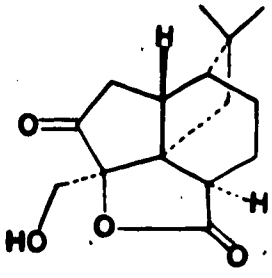

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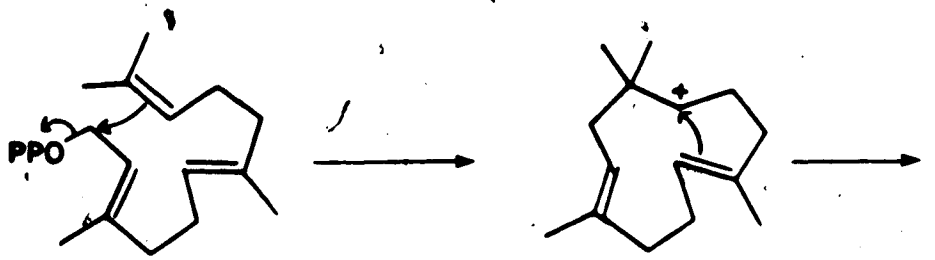
Among the common structural features of this small sesquiterpene family, two bicyclooctane subunits are in

evidence; rings A and B constitute a cis-fused bicyclo-[3.3.0]octane system, while rings B and C describe a bicyclo[3.2.1]octane system. Although each of these bicyclic subunits is widely represented among natural products (e.g. the cedrane, gymnomitrane, hirsutane, isocomane, kaurane, and gibberellane skeletons), the C8-C10 propano bridge across the exo-face in the former and the C3-C5 fusion to the one-carbon bridge in the latter are distinctive enough to make these sesquiterpenes the only known natural products with such a carbon frame.

There have been two independent studies in the biosynthesis of quadrone (1). Both proposals suggested that the carbon framework is derived from the humulyl cation 7 which cyclizes to the bicyclic cation 8, but there is a discrepancy from here onwards. In the first proposal, Cane et al.[7] (Scheme I) suggested that a hydride shift followed by a transannular cyclization at C2 (quadrone numbering) on bicyclic cation 8 would generate the fused tricyclic cation 9. A second hydride shift, a Wagner-Meerwein rearrangement, and deprotonation are expected to yield the parent hydrocarbon 10. This intermediate 10 is epimeric to quadrone (1) at C5. Reduction of the C2-C3 double bond and oxidation at carbons 4-7 would lead to terrecyclic acid A (2). Subsequent cyclization of 2 would result in net inversion of the

SCHEME 'I



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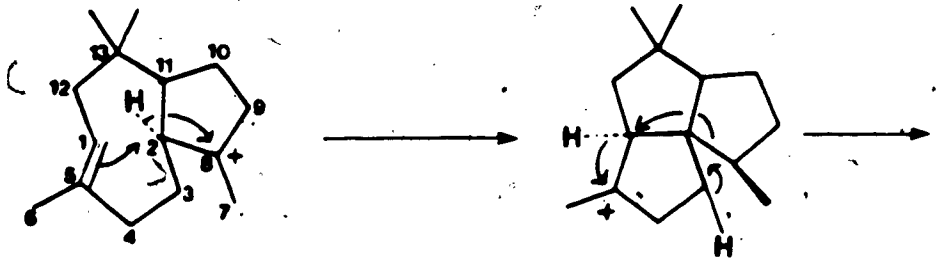

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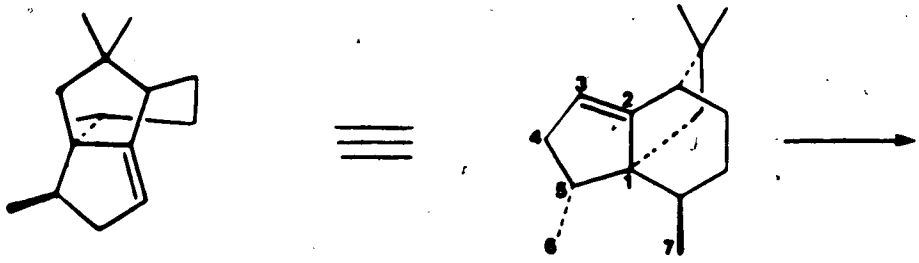

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2 → 1

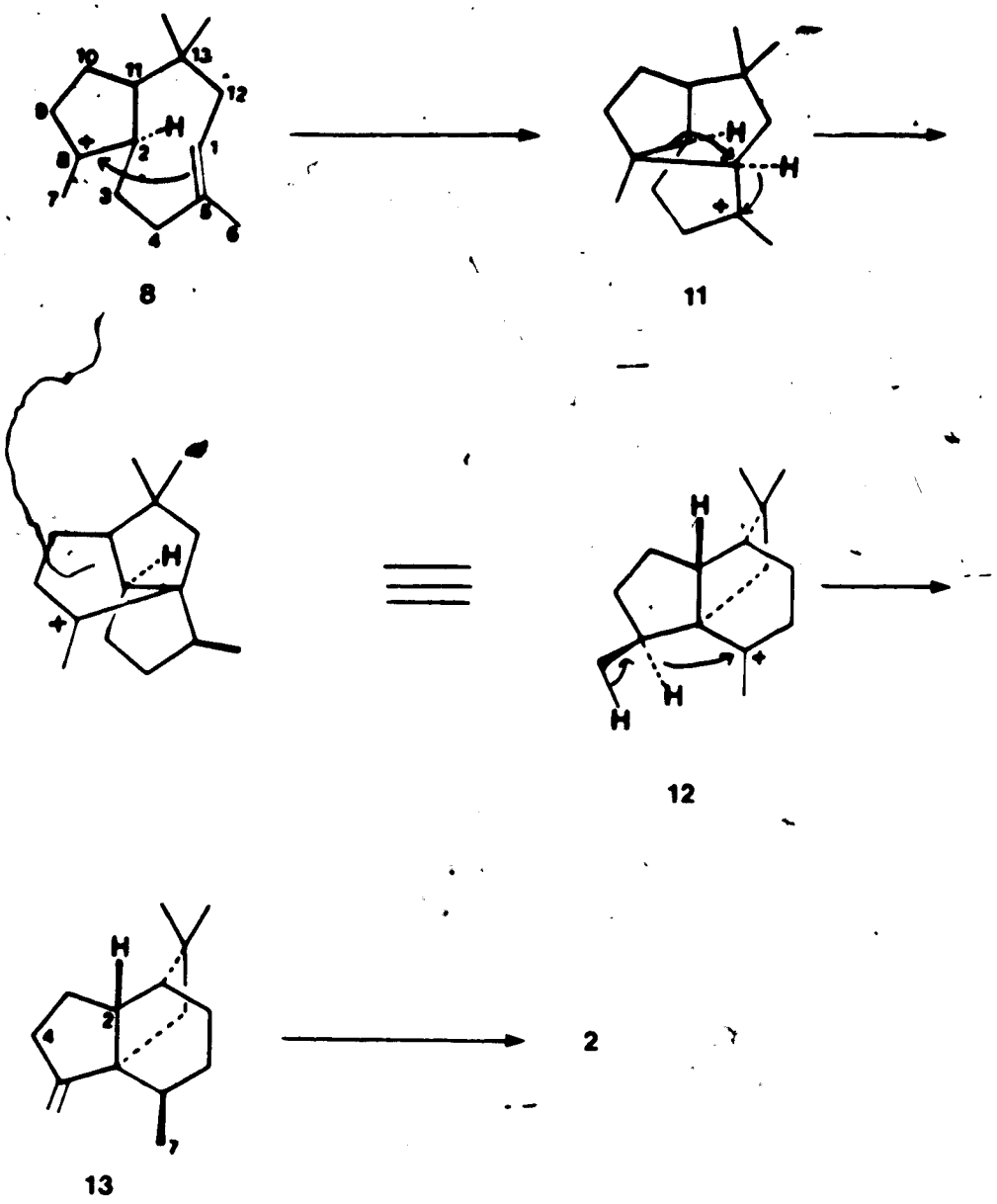
stereochemistry at C5 and yield quadrone (1).

The second proposal was made by Isogai and co-workers[8] (Scheme II). They proposed an intramolecular attack of the carbonium ion on the C1-C5 double bond in the intermediate 8 to give tricyclic cation 11. Subsequent hydride shift and Wagner-Meerwein rearrangement would give cation 12. A second hydride shift, deprotonation (12→13) and oxidation at C4 and C7 would then yield terrecyclic acid A (2).

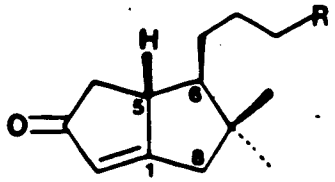
These two pathways could be distinguished by determining whether the proton at C2 has been retained from the acetate unit (Scheme II) or has been incorporated in the reduction of the double bond of the proposed intermediate 10 (Scheme I). Feeding experiments were performed[9] with [2-$^{2}H_3$]acetate and [2-$^{13}C^{2}H_3$]acetate on Aspergillus terreus. The results indicated that deuterium was incorporated into terrecyclic acid A (2) at the C2 position, thus favoring Isogai's proposal (Scheme II).

The interest in quadrone (1) and terrecyclic acid A (2) arises also from their biological activity. Terrecyclic acid A (2) exhibits antitumor activity against lymphocytic leukemia P-388 in mice[3] and quadrone (1) is active against KB cells in vitro.[1] The antitumor activity of the closely related compounds 4, 5, and 6, on the other hand, is very low in comparison with that of 1 and 2.[6]

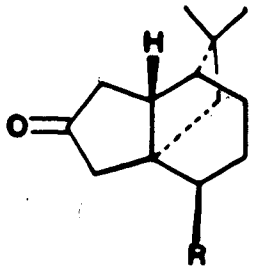
SCHEME II



The interesting cytotoxic properties and the challenging structural features of these novel sesquiterpenes have elicited considerable synthetic activity, which has resulted in the development of a number of elegant approaches leading to the total synthesis of these natural products. In the first approach, a C6 substituted bicyclo[3.3.0]octen-3-one of the type 14, with R being a carbanion stabilizing group, was used as a key intermediate. An intramolecular Michael reaction on 14 would give a tricyclic system of the type 15. This approach was independently studied by Danishefsky,[10] Pattenden,[11] and Vandewalle.[12] In all of



14



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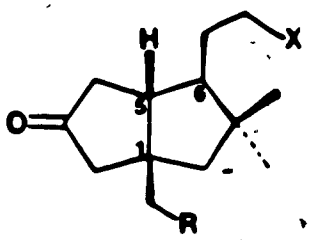
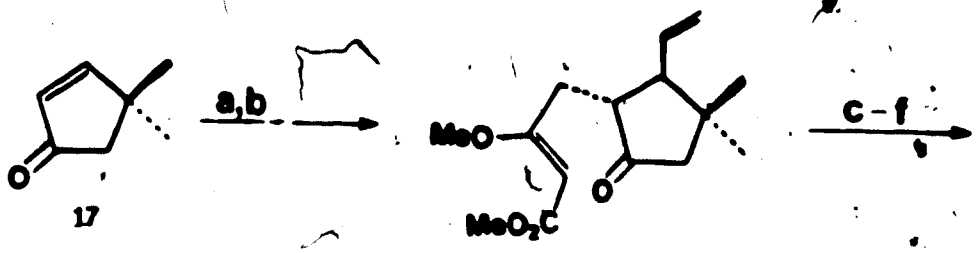


16

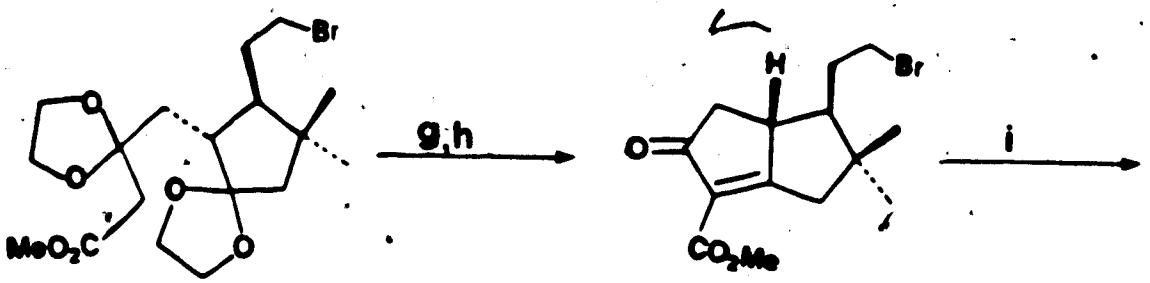
the cases, attempts to induce the Michael reaction of compounds 14, using a wide range of reagents under a variety of reaction conditions, met with total failure. The resistence of 14 to undergo Michael reaction was explained by the unfavorable torsional strain imposed to the C1-C8 bond in the transition state.[11,12]

In the second approach, a C1 and C6 disubstituted bicyclo[3.3.0]octan-3-one of the type 16 was constructed, with R being a carbanion stabilizing group and X a leaving group. With the all cis stereochemistry of C1, C5, and C6 as depicted, compound 16 is expected to cyclize via an internal alkylation reaction to give a tricyclic compound of the type 15. Danishefsky and co-workers reported in 1981 the first successful total synthesis of (±)-quadrone (1) (Scheme III)[13,14] using such an approach. Conjugate addition of vinylmagnesium bromide to enone 17 followed by trapping the resultant metalloenolate with methyl 4-iodo-3-methoxycrotonate afforded compound 18. After a series of functional group manipulations, ketone 18 was converted into bromide 19. Deketalization followed by aldol condensation furnished bicyclic enone 20. A Mukaiyama reaction on 20 with 1-tert-butoxy-1-(tert-butyldimethylsilyloxy)ethane afforded diester 21. Treatment of diester 21 with hydrochloric acid gave, after esterification, keto ester 22. Ketalization followed by a Finkelstein reaction

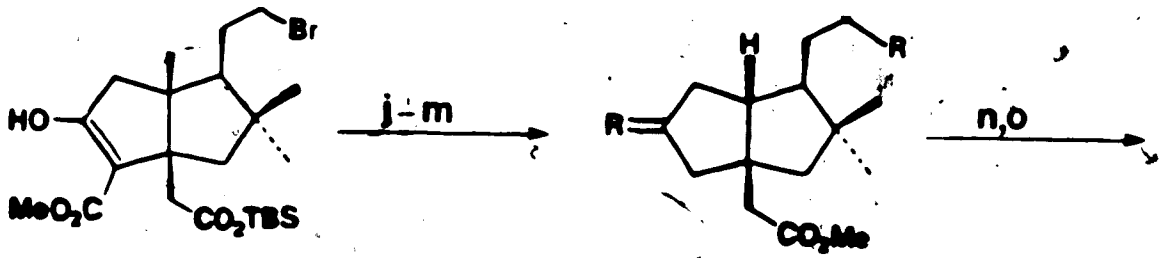
SCHEME III



17 18

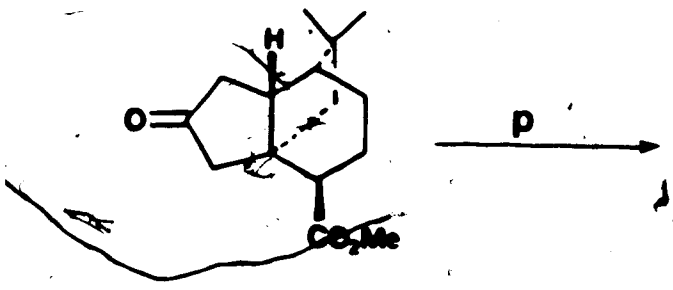


19 20



21

22 R = O; R' = Br
23 R = OCH_2CH_2O; R' = I



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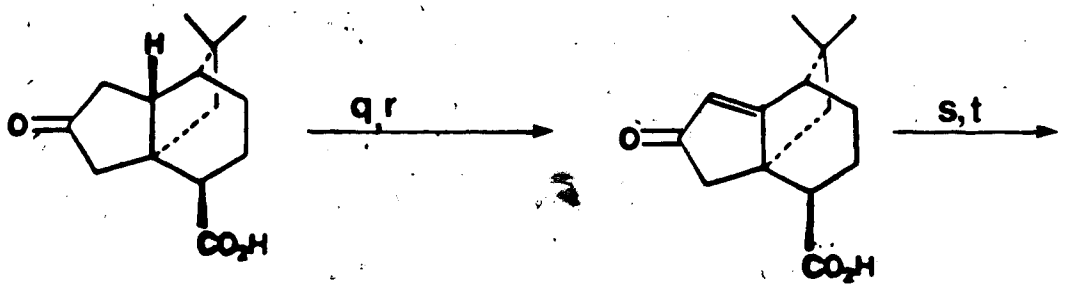
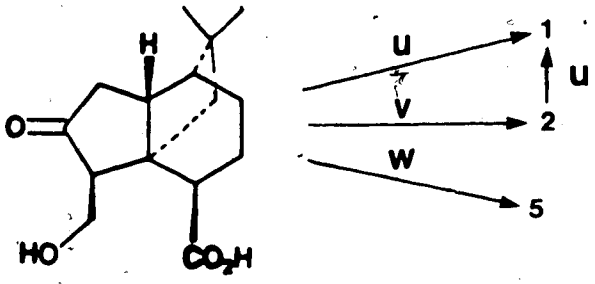
SCHEME III (Cont'd.)



25 26



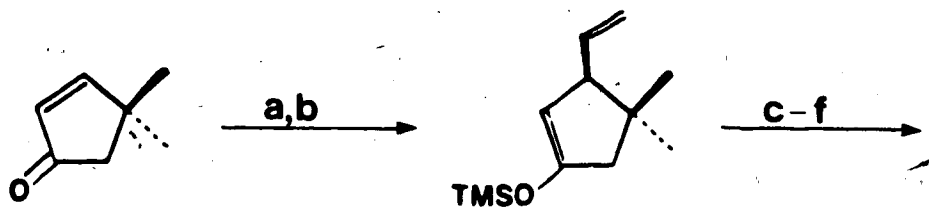
27

a. $(\underline{n}\text{-}Bu_3P{\cdot}CuI)_4$, $CH_2{=}CHCH_2MgBr$, THF, -45° to -20°C. b. HMPA, $MeO_2CCH{=}\overset{OMe}{C}\text{-}CH_2I$, r.t. c. $HOCH_2CH_2OH$, $\underline{p}$-$TsOH{\cdot}H_2O$, reflux. d. $BH_3{\cdot}THF$, H_2O_2, NaOH(aq). e. MsCl, NEt_3, Et_2O. f. LiBr, acetone, reflux. g. H_3O^+. h. NaOMe, MeOH, reflux. i. $CH_2{=}\overset{O\underline{t}\text{-}Bu}{C}OSi\underline{t}\text{-}BuMe_2$, CH_2Cl_2, $TiCl_4$, -78°C to r.t. j. 1 M HCl, dioxane, reflux. k. CH_2N_2, CH_2Cl_2. l. $HOCH_2CH_2OH$, $\underline{p}$-$TsOH{\cdot}H_2O$, $PhCH_3$, reflux. m. NaI, pyr, acetone, reflux. n. LDA, HMPA, THF -78 to r.t. o. $\underline{p}$-$TsOH{\cdot}H_2O$, acetone, r.t. p. KOH(aq)., MeOH, reflux. q. PhSeCl, EtOAc. r. 30% H_2O_2, pyr, CH_2Cl_2. s. LDA, CH_2O (gas), THF, -23°C to r.t. t. H_2, 5% Pd-C, MeOH. u. neat, 190-195°C. v. $\underline{p}$-$TsOH{\cdot}H_2O$, PhH, 40-50°C. w. $\underline{p}$-$TsOH{\cdot}H_2O$, PhH, reflux.

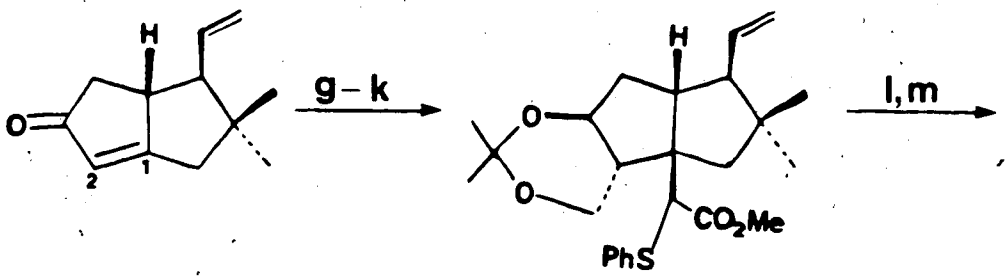
afforded iodide **23**. Reaction of **23** with lithium diisopropylamide in tetrahydrofuran in the presence of hexamethylphosphoramide followed by deprotection of the ketone afforded tricyclic ketone **24** with the carbomethoxy group in the axial position. Alkaline hydrolysis of the ester produced acid **25**. Selenenylation of **25**, followed by oxidation of the resulting C3-phenylseleno derivative, provided the enone acid **26**. The C2-C3 double bond was used to ensure enolization of the ketone carbonyl towards C5. Indeed, treatment of **26** with three equivalents of lithium diisopropylamide followed by addition of formaldehyde gave, after catalytic hydrogenation of the C2-C3 double bond, the keto acid **27**. Treatment of keto acid **27** with p-toluenesulfonic acid in benzene at 40-50°C gave terrecyclic acid A (**2**), while isoquadrone (**5**) was formed at refluxing temperature. Direct pyrolysis of either terrecyclic acid A (**2**) or keto acid **27** afforded quadrone (**1**).

Shortly after, Helquist *et al.* achieved a synthesis of terrecyclic acid A (**2**) using a very similar approach.[15] Starting also from cyclopentenone **17**, enone **28** was prepared (Scheme IV). A salient feature of this synthesis is the regioselective introduction of the hydroxymethyl group to the C2 carbon of enone **28**. This was achieved by trapping the anion produced by the 1,4-

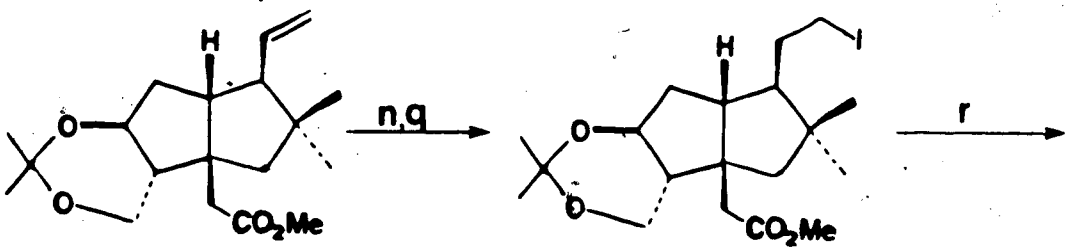
SCHEME IV



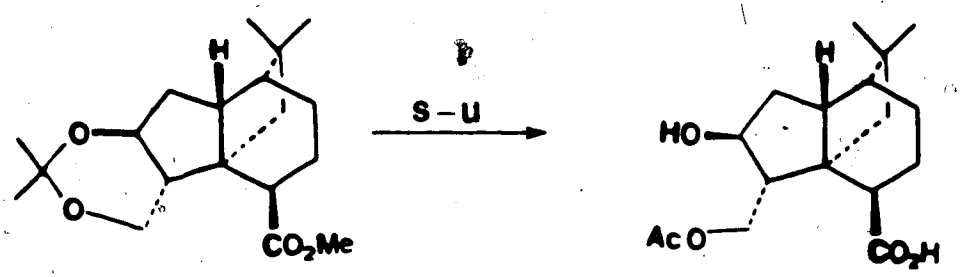
17



28 29



SCHEME IV (Cont'd.)



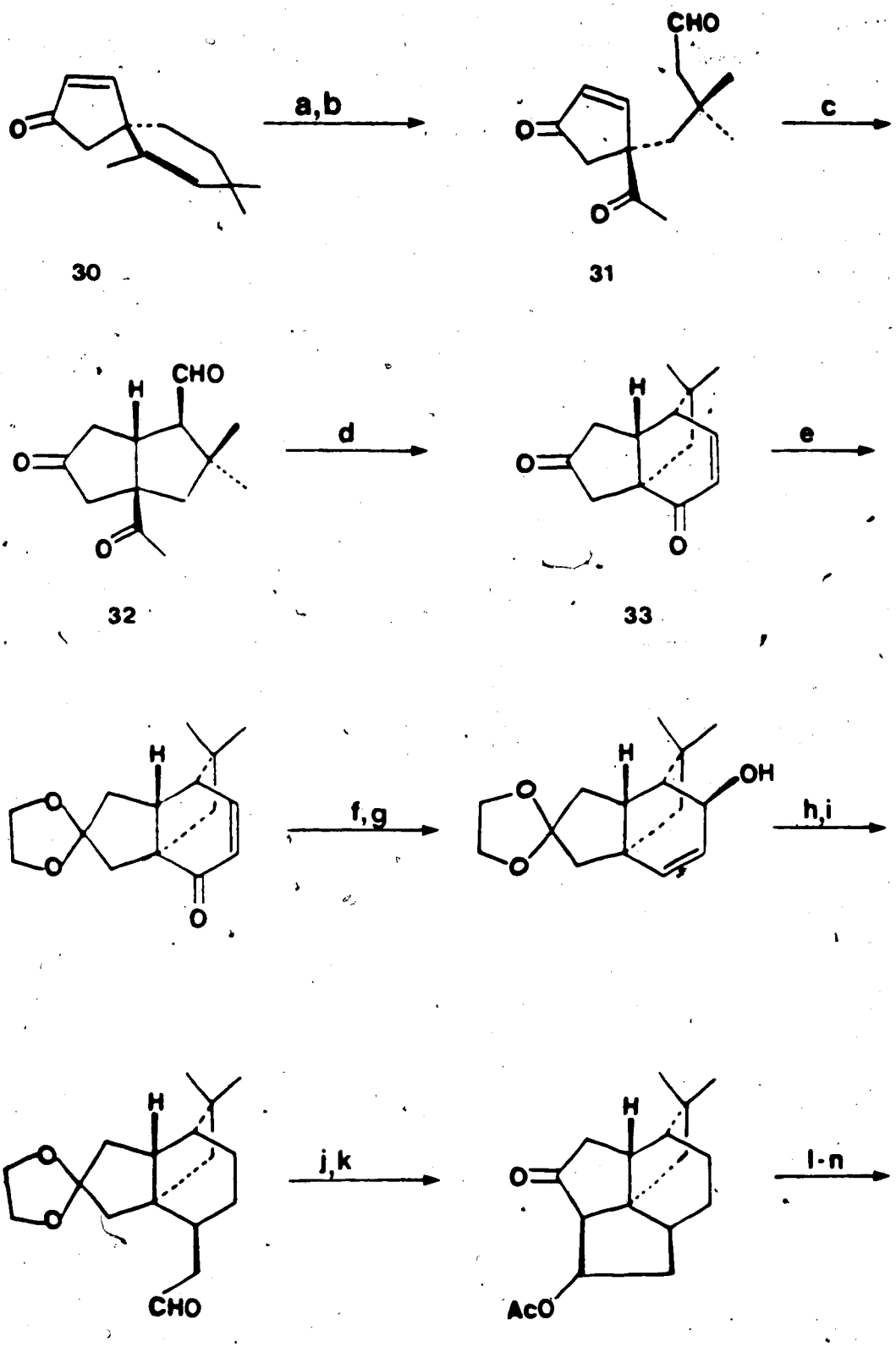
a. CH_2=CHMgBr, CuBr•Me_2S, THF, -78°C. b. Me_3SiCl, Et_3N, HMPA, -78° to 25°C. c. CH_3Li, THF, Et_2O, 0°C. d. $BrCH_2C(OEt)$=CHPO$(OCH_3)_2$, THF, HMPA, -78°C to 25°C. e. 1N HCl, H_2O, acetone, 25°C. f. NaH, DME, 0° to 25°C. g. $PhSCHLiCO_2CH_3$, THF, -60° to 35°C. h. CH_2O, -60°C. i. NH_4Cl, H_2O. j. $NaBH_4$, EtOH, 25°C. k. p-TsOH (cat.), $(Me)_2C(OMe)_2$, 25°C. l. Li, $NH_3(l)$, THF, -78°C. m. NH_4Cl, H_2O. n. 9-BBN, THF, 25°C. o. H_2O_2, NaOH, H_2O, 25°C. p. TsCl, pyr, 0°C. q. NaI, acetone, reflux. r. $(Me_3Si)_2NLi$, THF, HMPA, -78° to 25°C. s. 1N HCl, 25°C, H_2O, THF. t. KOH, reflux, dioxane, H_2O. u. Ac_2O, pyr, 25°C. v. PCC, CH_2Cl_2, 25°C. w. neat, 200°C.

addition of the lithium salt of methyl phenylmercapto-acetate to enone 28 with formaldehyde. The hydroxymethyl ketone thus formed was shown to be unstable and had to be reduced to the corresponding diol which was then protected as the acetonide to give compound 29. The conversion of 29 to terrecyclic acid A (2) was carried out by a sequence similar to that reported by Danishefsky (vide supra).[14]

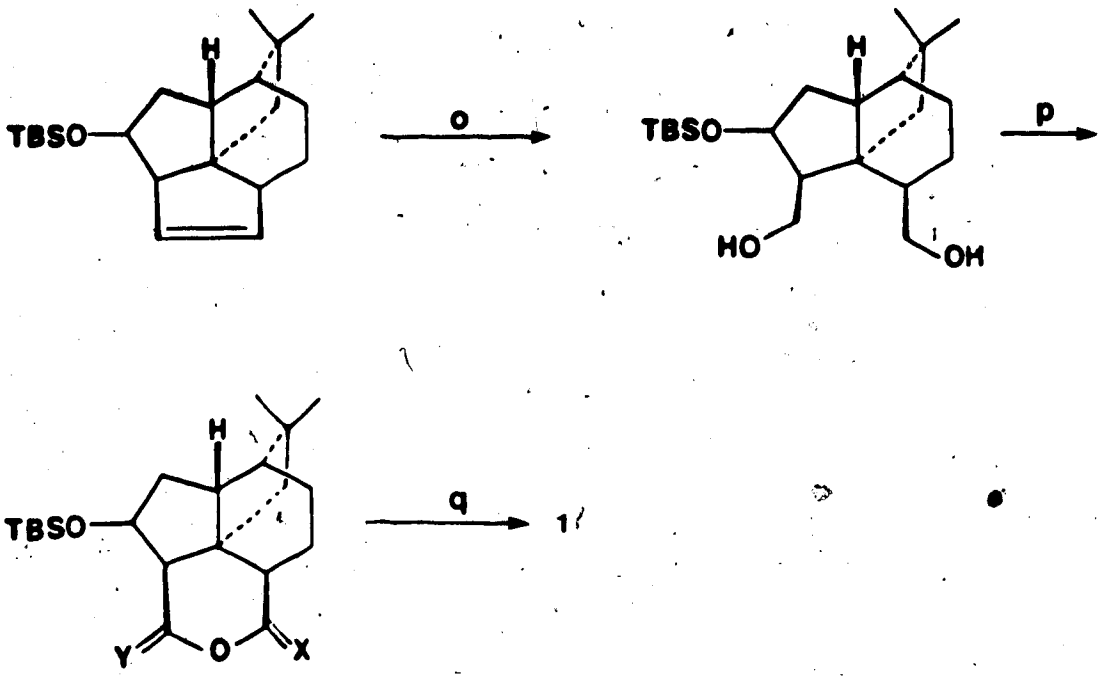
Another synthesis was accomplished by Burke and co-workers.[16,17,18] Starting from spiro[4.5]decadienone 30, the synthesis made extensive use of intramolecular reactions for the formation of the parent carbon skeleton. Oxidative cleavage of compound 30 gave diketo aldehyde 31 which was subjected to a Michael reaction. Aldol condensation of the resulting bicyclic compound 32 afforded the tricyclic enone 33. This compound was converted to quadrone (1) by the synthetic sequence outlined in Scheme V.

The third approach to quadrone (1) is based on the modification of a bicyclo[3.2.1]octane derivative of the type 34. In the formal synthesis of quadrone (1) reported by Kende et al.,[19] an intramolecular cycloalkenylation of enol 35 was used for the construction of such a compound 36. By a series of transformations (Scheme VI), this compound was converted to the Danishefsky's intermediate 26.

SCHEME V



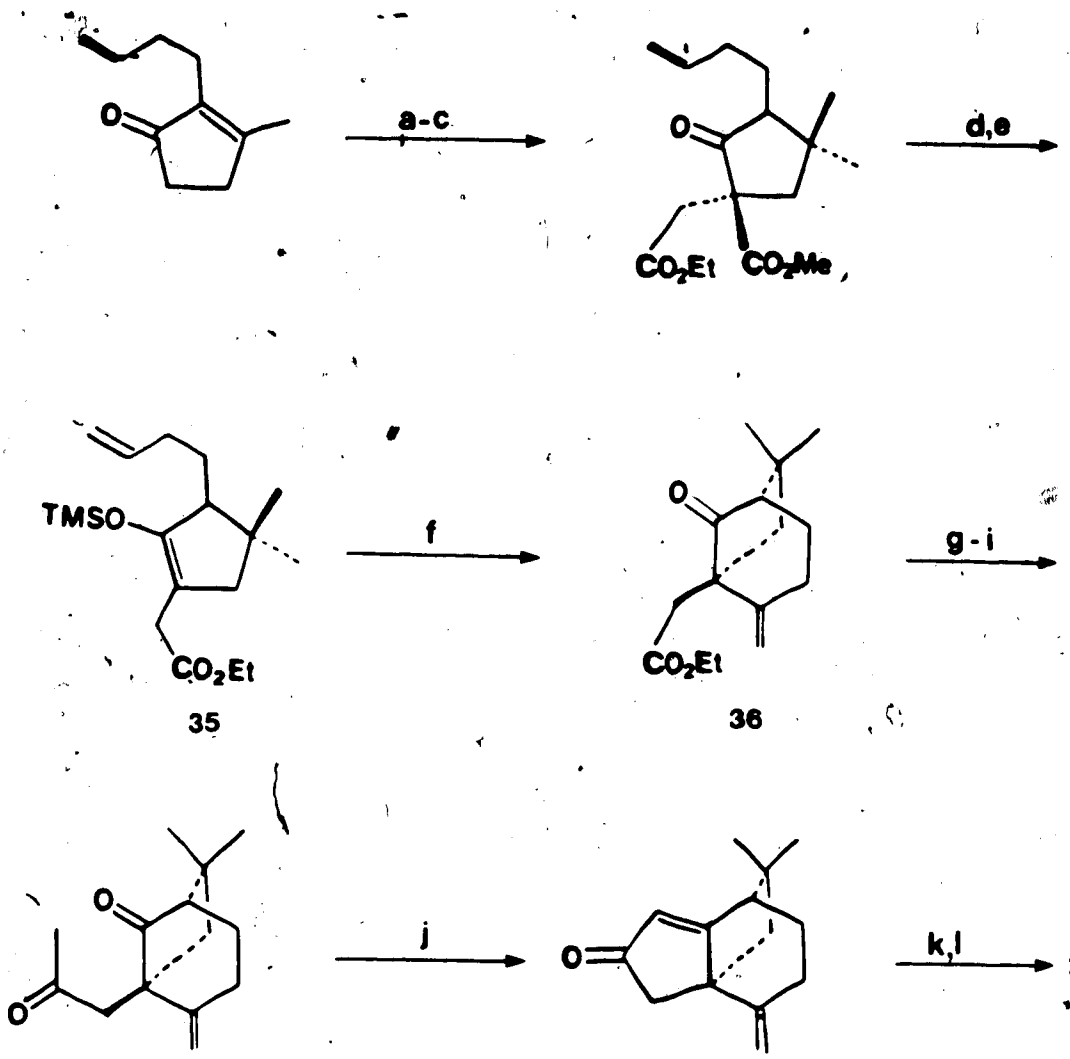
SCHEME V (Cont'd.)



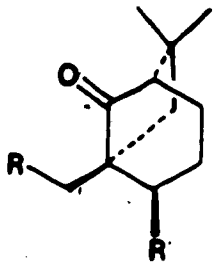
X=O; Y=H_2
X=H_2; Y=O

a. OsO_4, N-methylmorpholine N-oxide, 1:1 acetone-H_2O. b. $NaIO_4$ (8 equiv), 1:1 THF-H_2O. c. morpholine, p-TsOH, PhH, reflux. d. KOH, dibenzo-18-crown-6, PhH, reflux. e. $HOCH_2CH_2OH$, p-TsOH, PhH, reflux. f. t-BuOOH, NaOH, MeOH, H_2O, 25°C. g. $H_2NNH_2 \cdot xH_2O$, MeOH, HOAc. h. $CH_3CH_2OCH=CH_2$, $Hg(OAc)_2$, o-xylene, $[(CH_3)_2CH]_2NCH_2CH_3$, sealed tube, 240°C. i. H_2, 5% Pd-C, EtOH, 25°C. j. 2 M HCl, acetone, 25°C. k. HOAc, H_2SO_4, 25°C. l. neat, sealed tube, 400°C. m. $LiAlH_4$, Et_2O, -25° to 25°C. n. t-$BuMe_2SiCl$, imidazole, DMF, 25°C. o. O_3, 1:1 CH_2Cl_2-MeOH, -78°C; Me_2S, -78°C to 25°C; $NaBH_4$, EtOH, 0° to 25°C. p. Ag_2CO_3-Celite, PhH, reflux. q. Jones reagent, acetone, 0° to 25°C.

SCHEME VI



a. $MeCu \cdot BF_3$, Et_2O, -78° to [illegible] $(MeO)_2CO$, NaH, THF, reflux. c. $BrCH_2CO_2C_2H_5$, NaH, DMF, [illegible] $\cdot 2H_2O$, 2,6-lutidine, reflux. e. LDA, THF, -78° t[illegible]Cl. f. $Pd(OAc)_2$, CH_3CN, 25°C. g. 1N KOH, aq. MeOH, refl[illegible]n. $(ClCO)_2$, Et_2O, 25°C. i. Me_4Sn, $PhCH_2Pd(Ph_3P)_2Cl$, HMPA, 65°C. j. NaH, $PhCH_3$, reflux. k. thexylborane, THF, 0° to 25°C. l. CrO_3, 25°C.

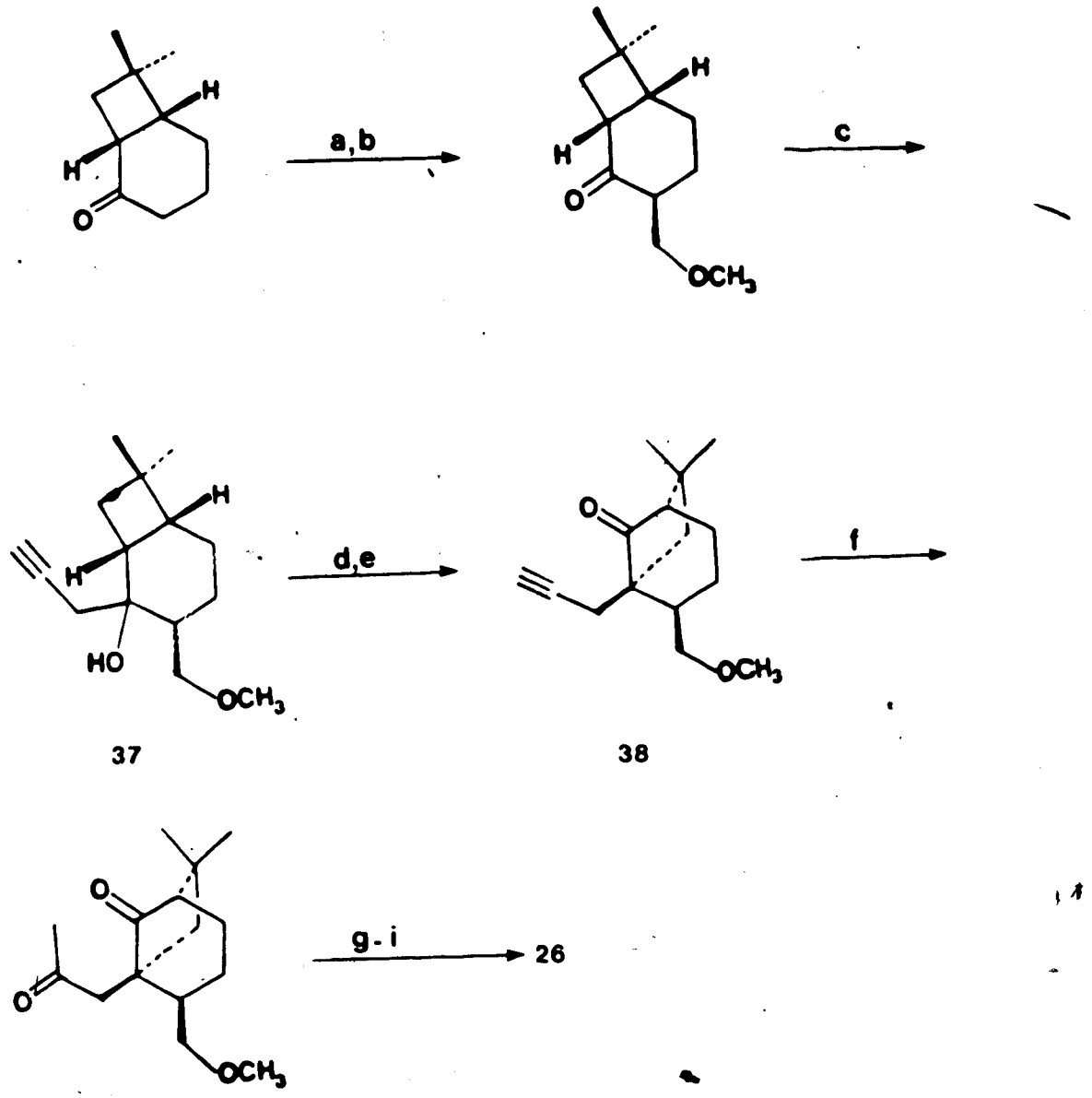


34

A similar approach was also applied by Yoshii et al.[20] to the synthesis of the Danishefsky's intermediate **26**. In this case the bicyclo[3.2.1]octane derivative **38** was obtained by solvolytic rearrangement of bicyclo-[4.2.0]octane **37** as shown in Scheme VII.

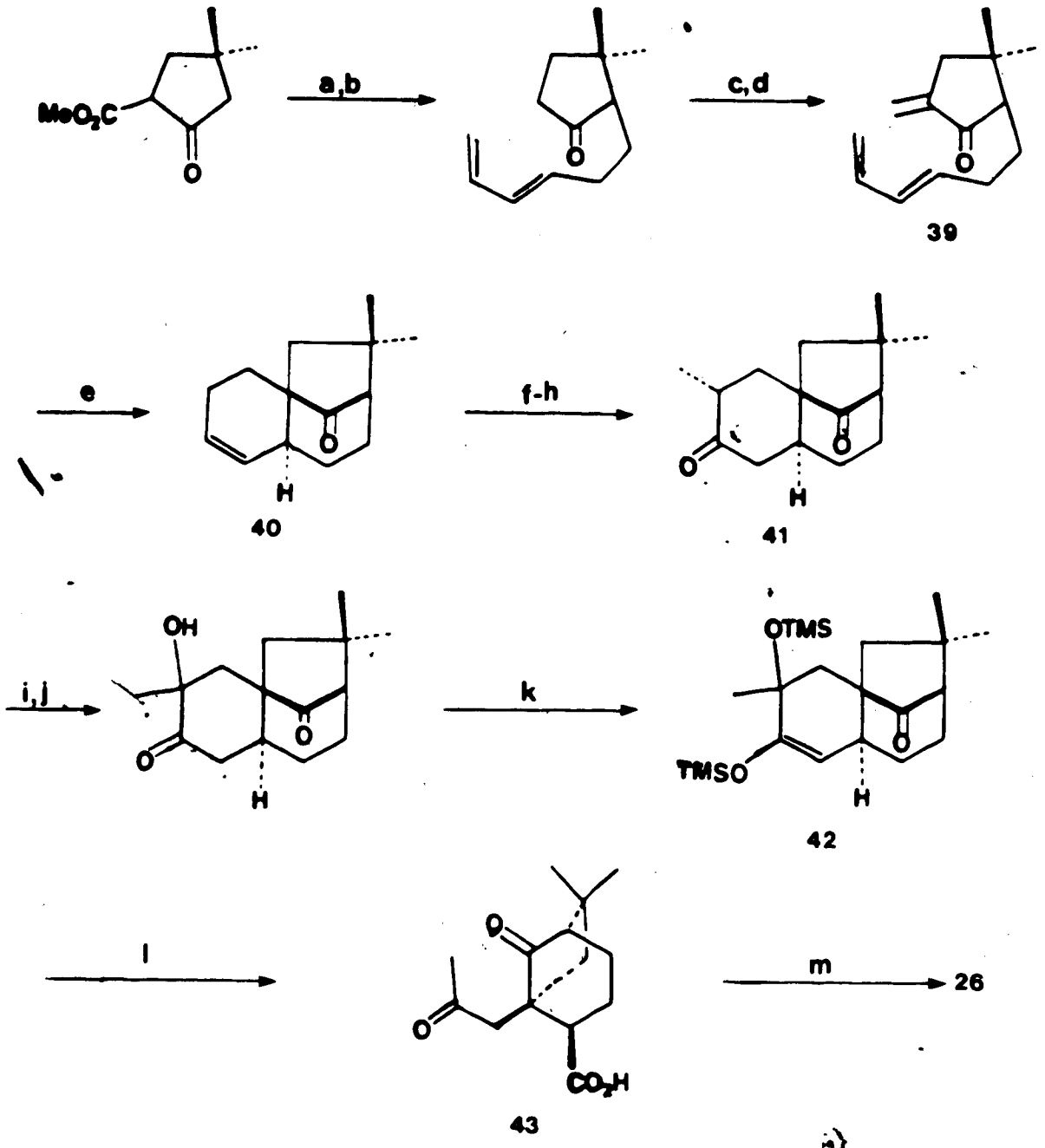
The fourth approach to the synthesis of quadrone (**1**) and related compounds makes use of an intramolecular Diels-Alder cycloaddition for the construction of the required framework. This synthetic strategy was first demonstrated by Schlessinger and co-workers who carried out the thermal cycloaddition of triene **39** to obtain the tricyclic ketone **40** (Scheme VIII).[21] This compound was transformed, in three steps, to diketone **41** which was further modified to give tricyclic ketone **42**. Subsequent ring cleavage afforded bicyclic diketo acid **43** which in turn furnished **26** by an aldol condensation.

SCHEME VII



a. LDA, Me_3SiCl. b. CH_3OCH_2Cl, CH_2I_2, Zn-Cu. c. Al, $HC{\equiv}C\text{-}CH_2Br$. d. HCO_2H, aq. NaOH, 25°C. e. PCC, CH_2Cl_2. f. HgO, H_2SO_4, MeOH-H_2O. g. tert-$C_5H_{11}OH$, NaH, PhH, reflux. h. BBr_3, CH_2Cl_2. i. Jones reagent.

SCHEME VIII.



a. 2 eq B^-, CH_2=CHCH=CHCH$_2$CH$_2$I. b. LiCl, Me_2SO-H_2O.

c. $[(CH_3)_2N]_2CHO$-t-Bu. d. DIBAL. e. $PhCH_3$-CH_3CN, 120°C. f. CrO_3, 3,5-dimethylpyrazole. g. LDA, MeI. h. 5% Pd-C, EtOH-HCl.

i. $(Me)_3SiI$, $(Me_3Si)_2NH$. j. 4-methylmorpholine 4-oxide, OsO_4.

k. LDA, Me_3SiCl. l. O_3, $NaIO_4$, CrO_3. m. NaH, xylene, reflux.

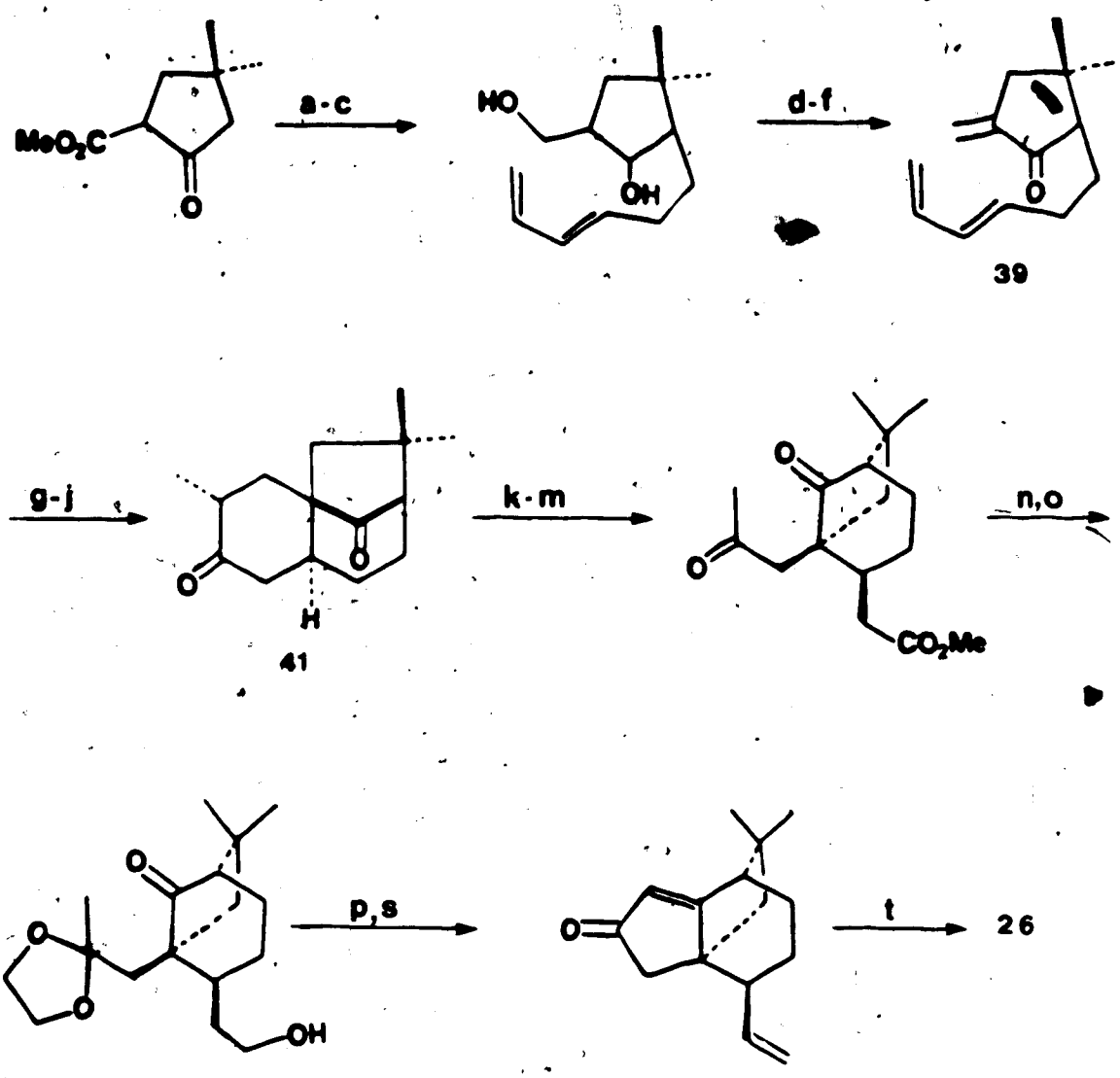
Vandewalle and co-workers[12] carried out the Diels-Alder reaction of the same triene 39, prepared by a somewhat different route as shown in Scheme IX. The conversion of 39 to compound 26 was carried out by a sequence similar to that reported by Schlessinger (vide supra).[21]

Wender and Wolanin[22] obtained the tricyclic compound 45 by a cycloaddition on triene 44. The carbomethoxy group in 45 was degradated. Rearrangement of the resulting chloride 46 gave tricyclic enone 47 which was subsequently converted to terrecyclic acid A (2) by a series of functional group transformations as summarized in Scheme X.

The most recent synthesis of (±)-quadrone in a formal sense has been accomplished by Piers and Moss.[23] The key step for the construction of the basic carbon framework involves a thermal Cope rearrangement of the highly functionalized divinylcyclopropane derivative 50, a method developed earlier in their laboratory.[24] Keto ketal 49 was obtained from compound 48 following the synthetic sequence outlined in Scheme XI. After the introduction of the necessary appendages and appropriate functional group modifications, compound 51 was converted to keto aldehyde 52 a known intermediate in Burke's synthesis.[18]

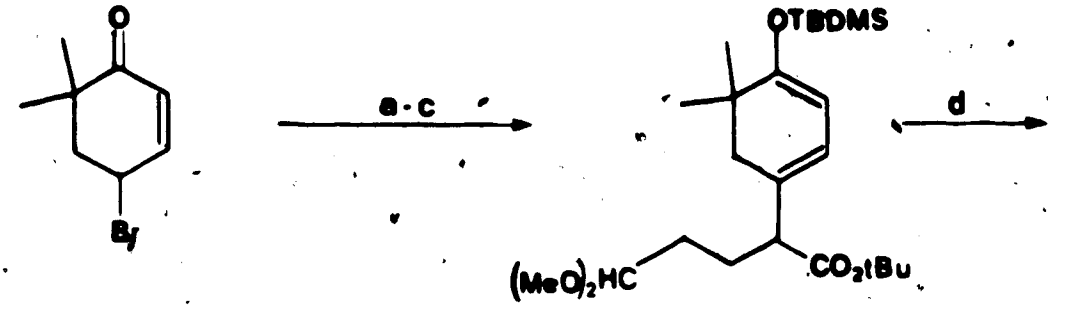
The absolute configuration of the natural

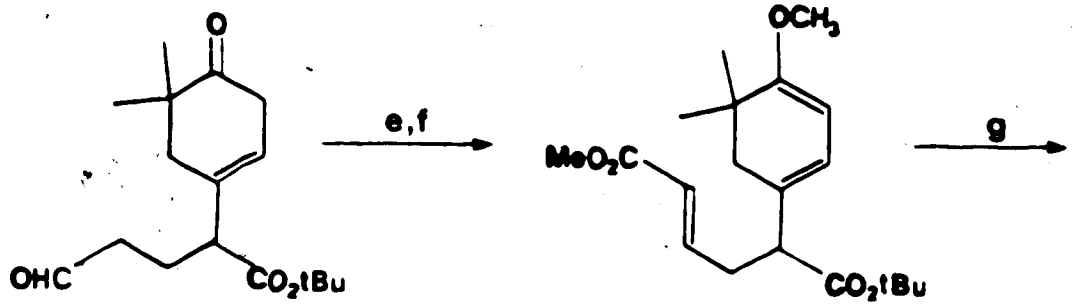
SCHEME IX



a. LDA, THF, C_6H_9I. b. $NaBH_4$, MeOH. c. $LiAlH_4$, Et_2O. d. TsCl, Et_3N, CH_2Cl_2. e. Jones reagent. f. DBU, PhH. g. $PhCH_3$, reflux. h. CrO_3, 3,5-dimethylpyrazole. i. LDA, MeI. j. 5% Pd-C, H_2, EtOAc. k. Me_3SiI, $(Me_3Si)_2NLi$. l. O_3, CH_2Cl_2, -60°C, Zn, HOAc. m. CH_2N_2. n. $HOCH_2CH_2OH$, p-TsOH. o. $LiBEt_3H$, THF. p. o-$NO_2C_6H_4SeCN$, Bu_3P, THF, pyr. q. 30% H_2O_2, THF. r. H_3O^+, THF. s. NaH, t-AmOH, PhH. t. RuO_4, CCl_4-CH_3CN-H_2O.

SCHEME





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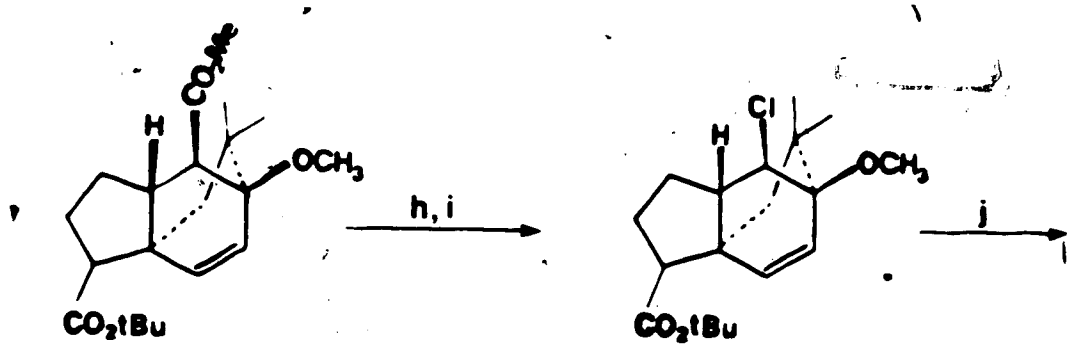
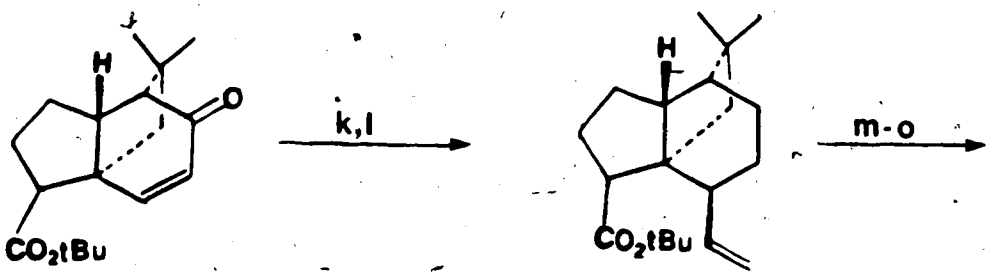


45 46

SCHEME X (Cont'd.)



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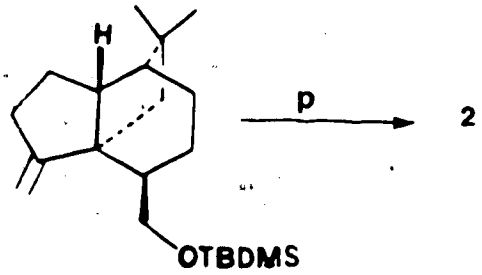
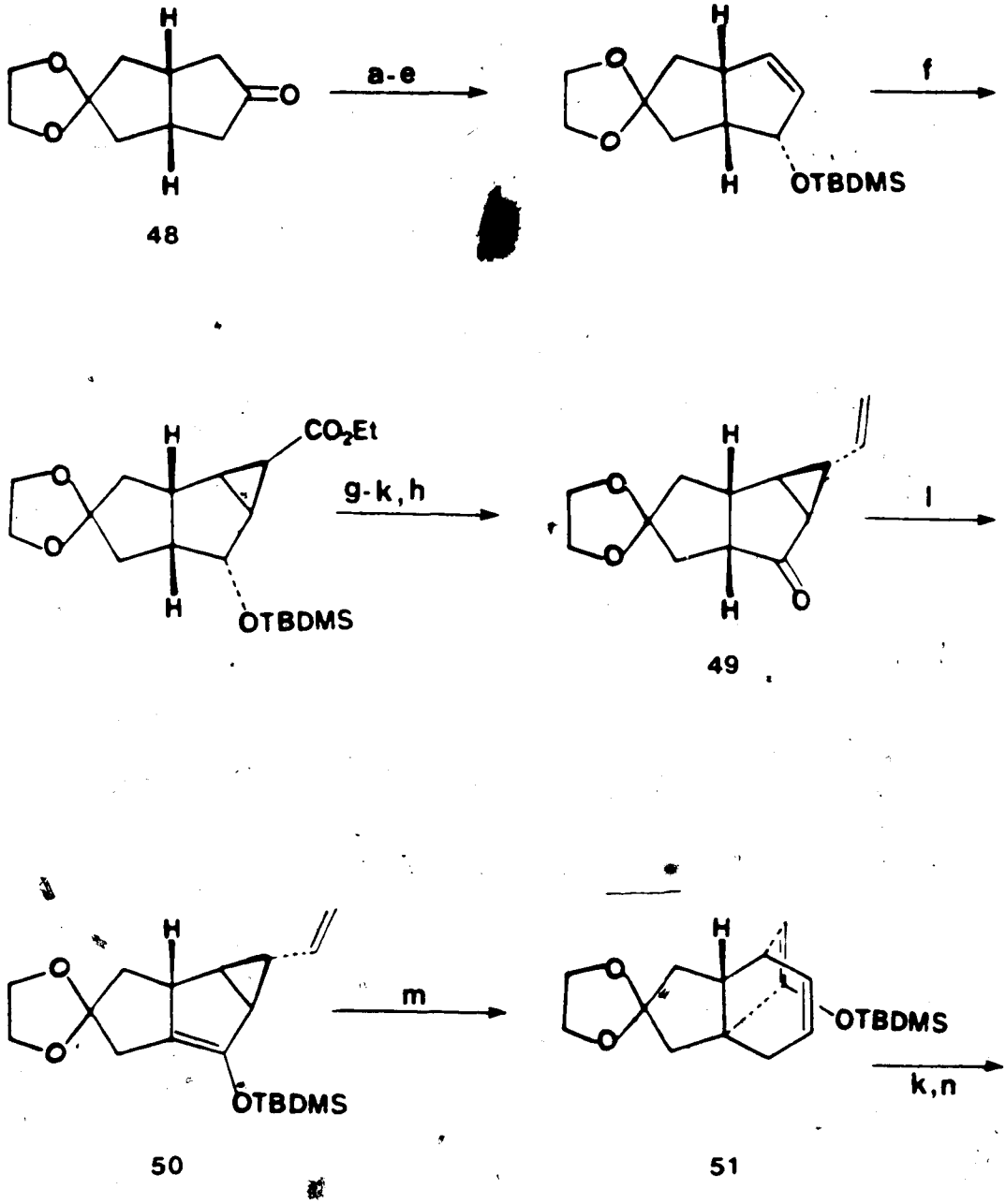


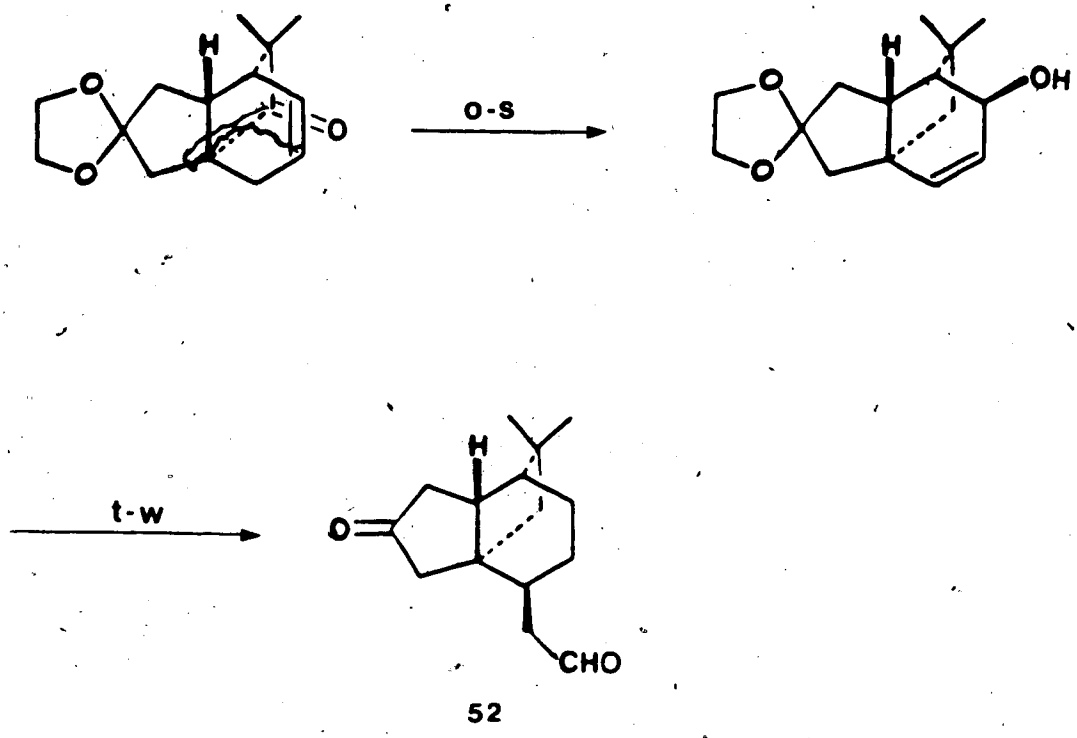
2

a. $(Me_3Si)_2NLi$, DME, -20°C; TBDMSCl. b. $NiBr_2$, n-BuLi, THF, -78°C. c. t-$BuO_2CCHLiCH_2CH_2CH(OCH_3)_2$, THF, -78° to 25°C. d. SiO_2, CH_2Cl_2, $(CO_2H)_2$, 25°C. e. $Ph_3P{=}CHCO_2Me$, $PhCH_3$, reflux. f. $HC(OMe)_3$, MeOH, p-TsOH, 25°C. g. $EtAlCl_2$, $PhCH_3$, 25°C. h. NaOH, MeOH. i. NCS, $Pb(OAc)_4$, DMF-AcOH. j. $AgNO_3$, DMF, 75°C. k. $(CH_2{=}CH)_2CuLi$, -78°C. l. $NaBH_4$; N,N'-thiocarbonyldiimidazole; n-Bu_3SnH, $PhCH_3$. m. O_3, MeOH-CH_2Cl_2, -78°C, $NaBH_4$, TBDMSCl. n. DIBAL, hexane. o. o-$NO_2C_4H_6SeCN$, P(n-Bu)$_3$, THF; H_2O_2. p. SeO_2, t-BuO_2H; Jones reagent.

SCHEME XI



SCHEME XI (Cont'd.)

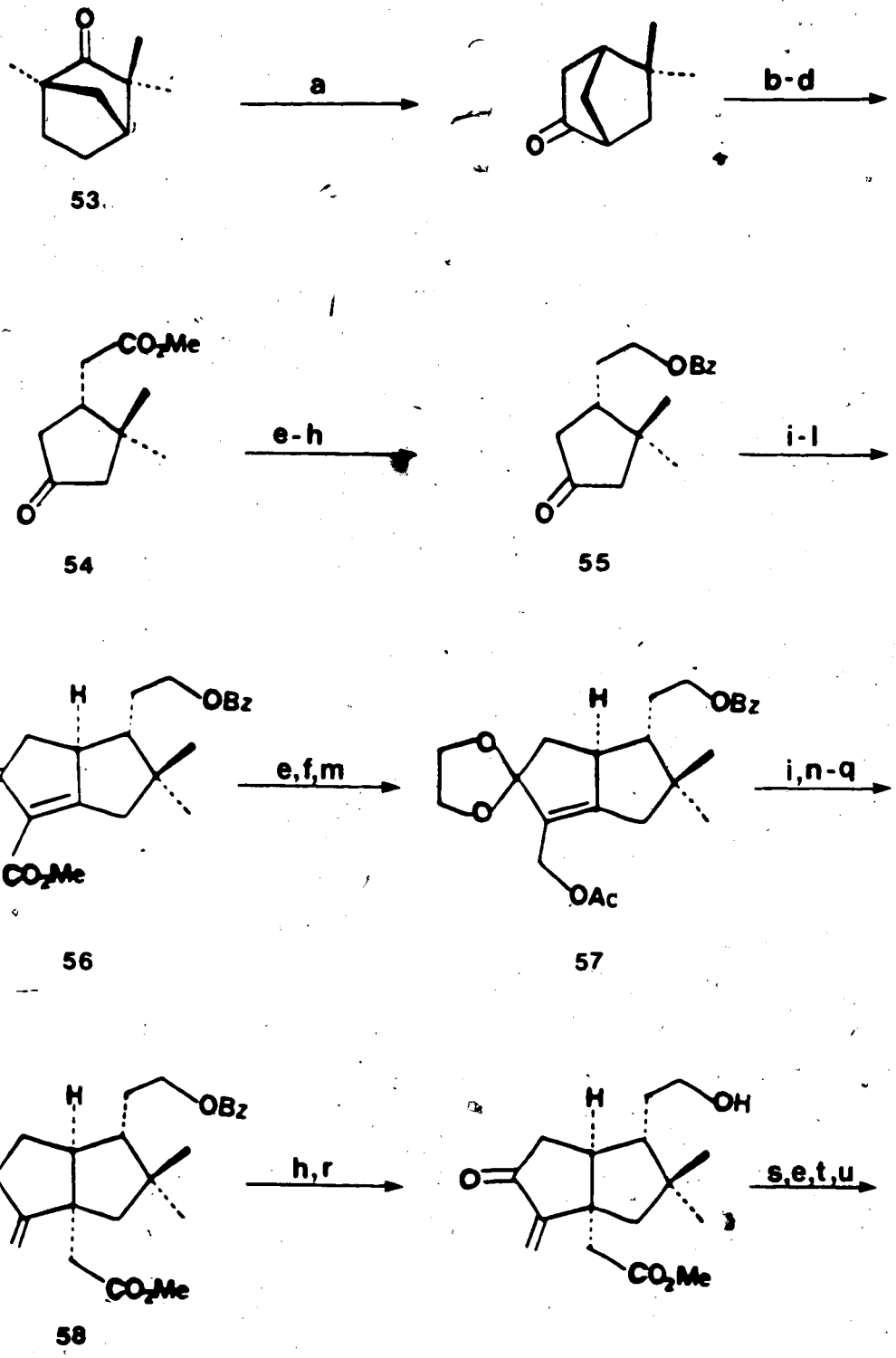


52

a. p-$TsNHNH_2$, EtOH. b. n-BuLi, Et_2O-HMPA. c. NBS, DMSO-H_2O; K_2CO_3, MeOH. d. PhSeNa, EtOH-THF; H_2O_2-H_2O, heat. e. t-$BuMe_2SiCl$, imidazole, DMF. f. N_2CHCO_2Et, $Rh_2(OAc)_4$. g. $LiAlH_4$, Et_2O. h. $C_5H_5N \cdot CrO_3 \cdot HCl$, NaOAc, CH_2Cl_2. i. t-BuOK, t-BuOH-THF. j. $PH_3P{=}CH_2$, THF. k. n-Bu_4NF, THF. l. LDA, THF, -78°C; t-$BuMe_2SiOTf$, THF-HMPA. m. 170-175°C, 5 h, C_6H_6, sealed tube. n. LDA, THF; MeI. o. Li(n-Bu)(i-$Bu)_2AlH$, Et_2O. p. n-BuLi, THF; $ClPO(NMe_2)_2$, THF-HMPA. q. Li, $MeNH_2$, -20°C, 10 min. r. m-chloroperoxybenzoic acid, CH_2Cl_2. s. $LiNEt_2$, C_6H_6, reflux. t. $EtOCH{=}CH_2$, $Hg(OAc)_2$. u. 240°C, 4.5 h, C_6H_6, sealed tube. v. H_2, 10% Pd-C, hexane. w. HCl, H_2O, acetone.

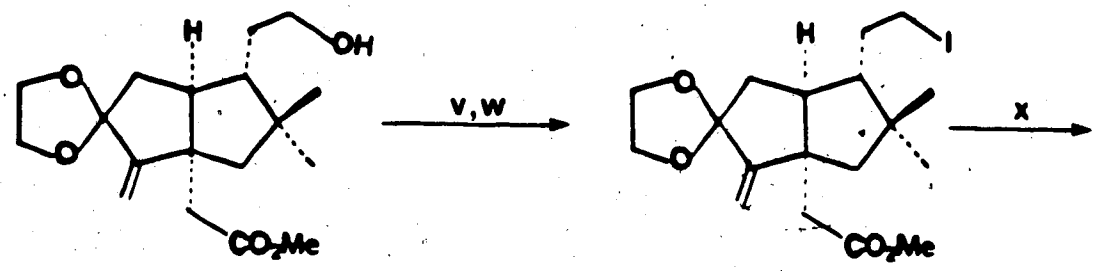
(-)-quadrone (**1**) was not elucidated until the first chiral synthesis was achieved. Isoe[25] and Smith[26] completed independently and concurrently the total synthesis of optically active terrecyclic acid A (**2**) and quadrone (**1**) respectively. In each case, however, the antipode of the naturally occurring compound was synthesized. In the synthesis of (-)-terrecyclic acid A (**61**) by Isoe and his collaborators[25] (Scheme XII), (+)-fenchone (**53**) was used as the starting material from which cyclopentanone **54** was obtained in the optically active form. Regioselective alkylation of the corresponding benzyl ether **55** with methyl 4-bromo-3-methoxycrotonate, followed by hydrolysis and aldol condensation, afforded bicyclic keto ester **56**. Ketalization and reduction with lithium aluminum hydride followed by acetylation of the resulting alcohol gave acetate **57**. Introduction of the carbomethoxymethyl group to the angular position was effected by an Ireland-Claisen rearrangement on acetate **57** to yield ester **58**. By a series of functional group transformations, ester **58** was converted into iodo ester **59**. Upon treatment of iodo ester **59** with lithium hexamethyl disilylazide, tricyclic keto ester **60** was formed. Deketalization and hydrolysis of the ester group gave (-)-terrecyclic acid A (**61**), the enantiomer of the naturally occurring compound. On the basis of this synthesis, the absolute configuration of the

SCHEME XII

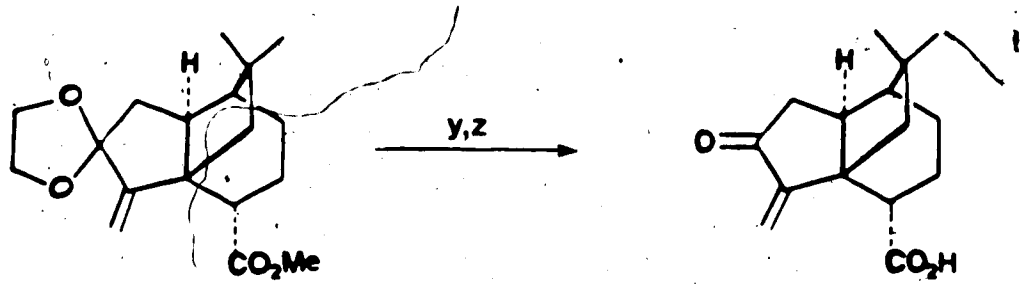


53 54 55 56 57 58

SCHEME XII (Cont'd.)



59



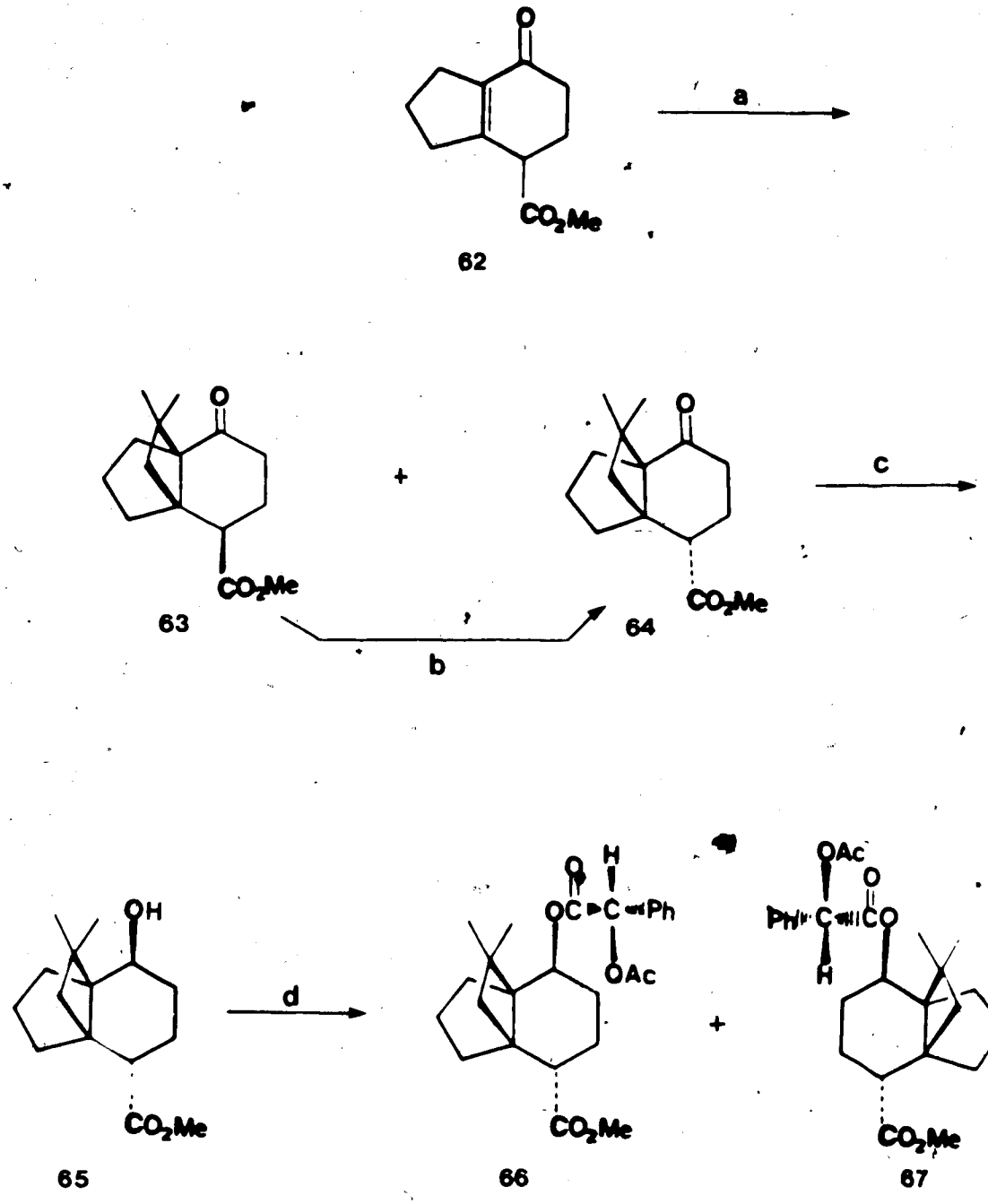
60 61

a. NH_2NH_2; HgO (yellow); $KHSO_4$; OsO_4-$NaIO_4$. b. m-CPBA. c. NaOMe. d. CrO_3, pyr. e. $HOCH_2CH_2OH$, p-TsOH. f. $LiAlH_4$. g. NaH, $PhCH_2Br$. h. p-TsOH, THF-H_2O. i. LDA. j. $BrCH_2\overset{OCH_3}{\overset{|}{C}}=CHCOOMe$. k. HCl, MeOH-$H_2O$. l. t-BuOK. m. Ac_2O, pyr. n. TBDMSCl. o. reflux, 70-80°C. p. KF. q. MeI. r. $TiCl_4$. s. $(PhSe)_2$, $NaBH_4$. t. H_2O_2. u. heat, 70°C. v. TsCl, pyr. w. NaI. x. $(Me_3Si)_2NLi$. y. n-PrSLi. z. H_3PO_4, THF-H_2O.

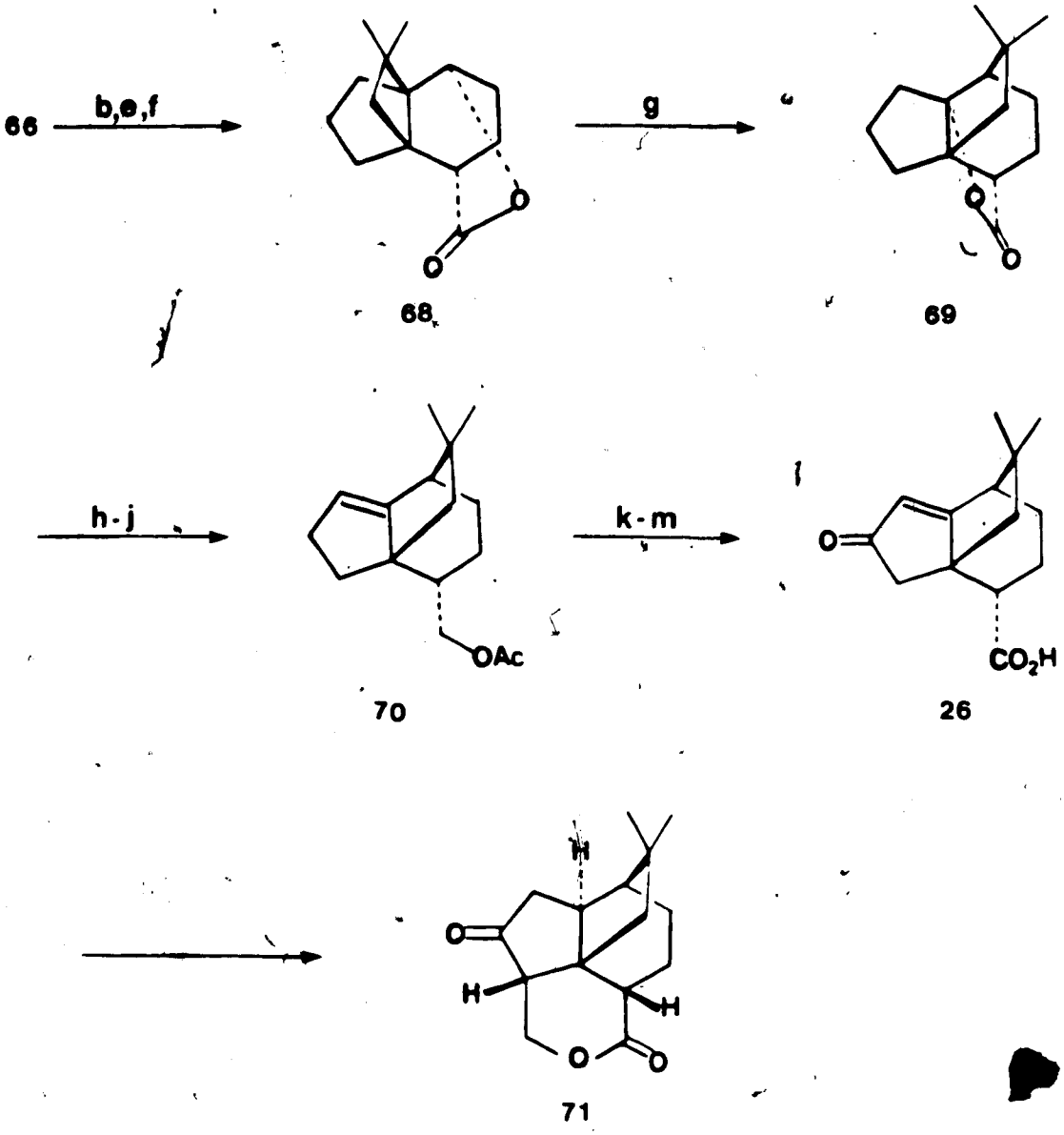
natural (+)-terrecyclic acid A was concluded as shown in structure 2.

The synthesis of (+)-quadrone (71) by Smith and Konopelski[26] began with the [2+2]-photochemical cycloaddition of isobutylene to racemic enone 62 to afford a mixture of epimeric propellanes 63 and 64 with the former predominating (Scheme XIII). Treatment of this mixture with sodium methoxide in methanol resulted in the partial epimerization of 63 to give mainly the desired propellanone 64. Reduction of 64 with sodium borohydride afforded alcohol 65 which was resolved by treatment with (S)-(+)-O-acetylmandelic acid to give a diastereomeric mixture of esters 66 and 67 separable by high-pressure liquid chromatography. The major isomer 66, which was shown by X-ray analysis to possess the depicted absolute configuration, was hydrolyzed to give the dextrorotatory enantiomer of alcohol 65. This alcohol was transformed into lactone 68 via the corresponding mesylate. Acid catalyzed rearrangement of lactone 68 yielded a new lactone 69 which was subjected to reduction with lithium aluminum hydride. Selective acetylation of the resulting diol followed by dehydration gave rise to olefin 70. The transformation of 70 to Danishefsky's intermediate 26 in optically active form was carried by a three-step reaction sequence: allylic oxidation, hydrolysis of the acetate

SCHEME XIII


O
a
CO2Me
62
O
+
O
c
CO2Me
63
CO2Me
64
b
OH
d
CO2Me
65
O
H
OC
C
Ph
OAc
CO2Me
66
+
OAc
O
Ph
C
CO
H
CO2Me
67

SCHEME XIII (Cont'd.)

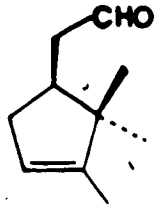


a. $CH_2=C(CH_3)_2$, hν. b. $NaOCH_3$. c. $NaBH_4$. d. (S)-(+)-o-acetyl-mandelic acid, DCC, DMAP, CH_2Cl_2. e. MsCl, pyr. f. MeSLi, HMPA. g. 40% H_2SO_4, THF. h. $LiAlH_4$. i. Ac_2O, pyr. j. $SOCl_2$, pyr. k. CrO_3, 3,5-DMP. l. K_2CO_3, MeOH. m. Jones reagent.

functionality, and Jones oxidation. Chiral **26** was further transformed into (+)-quadrone (**71**) according to the procedure described by Danishefsky[14] for the racemate series. The direction of the optical rotation of the synthetic material was found to be opposite to that of the natural product. Consequently, the naturally occurring levorotatory quadrone must possess the absolute configuration depicted in **1**.

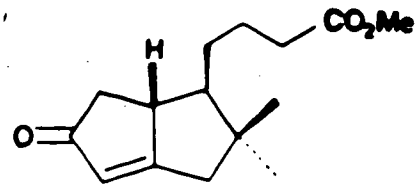
We have also been intrigued by the unique structural features of quadrone (**1**) and its biological activity. When our synthetic studies on quadrone (**1**) were initiated several years ago, only a limited amount of work had been carried out in this area. At the outset, our synthetic strategy was to construct, from α-campholenic aldehyde (**72**) obtained in optically active form from the commercially available (-)-α-pinene oxide (**73**), the bicyclo[3.3.0]octen-3-one derivative **74**, and to use an intramolecular Michael reaction for the formation of rings A, B, and C of the target molecule. This approach, which resembles the first general approach discussed earlier, was abandoned due to the difficulties encountered in the preparation of compound **74**. During the course of these studies, an alternative approach to the synthesis of quadrone (**1**) emerged. In this approach, bicyclo[3.3.0]-octan-3-one **75** was envisioned as a key intermediate. This

compound was prepared in both the racemic and levorotatory form starting from (±)- and (-)-10-camphorsulfonic acid (76) respectively. Further transformations of 75 led to the preparation of the racemic ester 24 and the levorotatory enantiomer. Since compound 24 has already been converted to quadrone (1) by Danishefsky,[14] the preparation of (±)-24 constitutes a formal synthesis of (±)-1. Application of Danishefsky's synthetic sequence to (-)-24 resulted in the first total synthesis of the naturally occurring (-)-quadrone (1). The details of this synthetic work will be described in the next chapter.

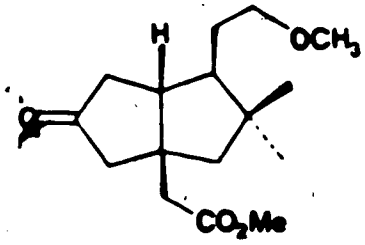


72

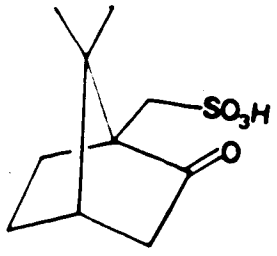
73



74



75



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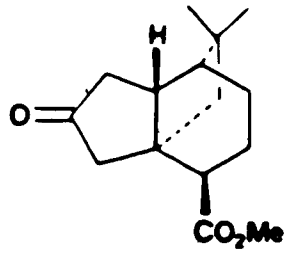


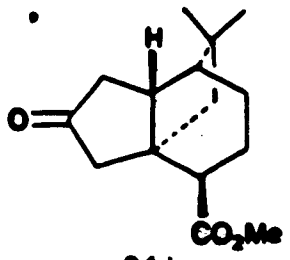
24

RESULTS AND DISCUSSION

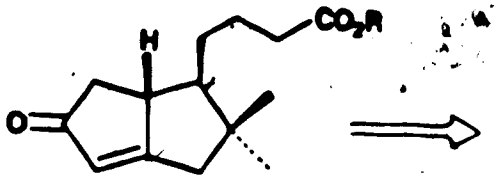
In our first approach towards the synthesis of quadrone (1), tricyclic keto ester 24 was visualized as the key intermediate. From a retrosynthetic analysis (Scheme XIV), it was recognized that tricyclic keto ester 24 could arise from bicyclic keto ester 77 by an intramolecular Michael reaction. Keto ester 77 could, in principle, be prepared from enone 79. The methylidene group in enone 79 would serve as a protecting group for the selective alkylation at the C5 position. After alkylation with an acetone equivalent, the methylidene group could be removed by a retroaldol reaction (79→78). Enone 79, in turn, could be prepared from commercially available α-pinene oxide (73) by a Lewis acid catalyzed ring opening (73→72) followed by a two-carbon chain extension (72→80) and functional group modifications. The details of this approach are described below.

Treatment of (-)-α-pinene oxide (73) with zinc chloride in benzene furnished campholenic aldehyde (72)[27,28] in 73% yield. Nuclear Overhauser Effect (NOE) and decoupling experiments allowed the assignment of individual gem-dimethyl absorptions in the nuclear magnetic resonance (nmr) spectrum of aldehyde 72.

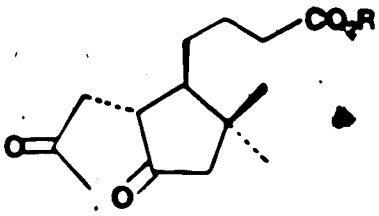
SCHEME XIV



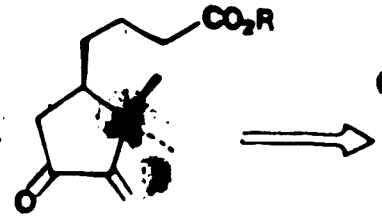
24



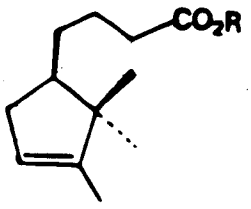
77



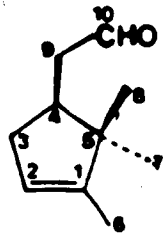
78



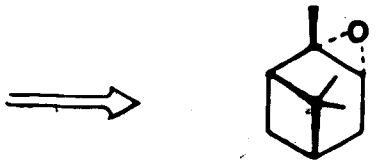
79



80

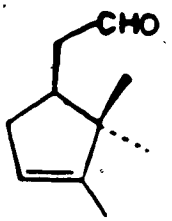


72

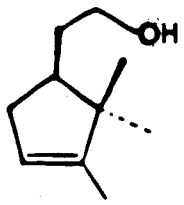


73

Irradiation of the methyl signal at δ1.00 produced enhancements of 11% on the C4 proton (δ2.28) and 5% on the α-faced C3 proton (δ1.88), while irradiation of the methyl signal at δ0.79 produced an enhancement of 9% on the C9 protons (δ2.53 and 2.37). These data established that the higher field singlet at δ0.79 corresponded to the methyl cis with the aldehyde side chain.



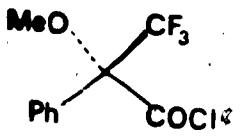
72



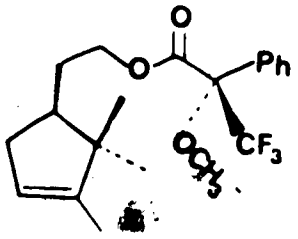
81

To study the optical purity, aldehyde 72 was reduced to the corresponding alcohol 81 in 90% yield using sodium borohydride in methanol. Alcohol 81 was then esterified with (S)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (82),[29] prepared from the corresponding carboxylic acid ((-)-Mosher's acid)[30] by treatment with oxalyl chloride in benzene in the presence of a catalytic amount of dimethylformamide. The resulting ester 83 displayed only one set of signals in the ^{1}H and ^{13}C nmr

spectra. However, in the ^{19}F nmr spectrum two signals were observed at δ-71.7141 and -71.7351 (relative to $CFCl_3$) in a ratio of 5:1 respectively. From this result, it can be concluded that the enantiomeric excess of **81** is only 60%. The following synthetic studies were carried out with this material. Specific rotations of the compounds derived from it were not measured due to the low optical purity of the starting material.



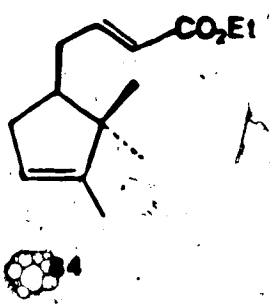
82



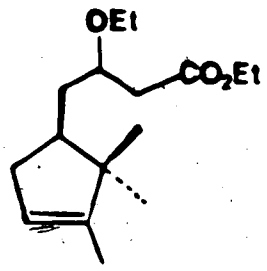
83

The two-carbon chain extension was achieved by a Wadsworth-Emmons[31] reaction. Treatment of aldehyde **72** with triethyl phosphonoacetate in tetrahydrofuran using sodium hydride as a base gave the α,β-unsaturated ester **84** in 96% yield. Only one isomer was obtained which showed a band at 1722 cm^{-1} in the infrared (ir) spectrum, indicating the presence of an α,β-unsaturated ester. The nmr spectrum displayed signals at δ6.98 (dd, 1H, J = 15,

J' = 7 Hz) and 5.89 (d, 1H, J = 15 Hz) for the vinylic protons of the α,β-unsaturated ester. The magnitude of the coupling constant (15 Hz) indicated a trans configuration of the double bond. The other vinylic proton appeared at δ5.22 as a broad singlet. The ethyl ester appeared at δ4.19 for the methylene protons and at δ1.30 for the methyl protons. Singlets at δ1.00 and 0.80 were observed for the gem-dimethyl group. The mass spectrum showed a molecular ion at m/e 222.1622 corresponding to the molecular formula $C_{14}H_{22}O_2$. When the Wadsworth-Emmons reaction was carried out in ethanol using sodium ethoxide as a base, a significant amount of β-ethoxy esters **85** was also obtained. Two sets of [illegible] signals were observed in the nmr spectrum, one [illegible] δ4.16 (q, 2H, J = 7 Hz) and 1.28 (t, 3H, J = 7 [illegible] the ethyl ester, and the ~~other~~ at δ3.54 (q, 2H, J = 7 Hz) and 1.19 (t, 3H, J = 7 Hz) for the ethyl ether. The mass spectrum showed a molecular ion at m/e 268.2033 ($C_{16}H_{28}O_3$).



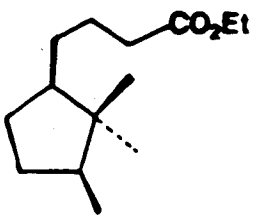
84



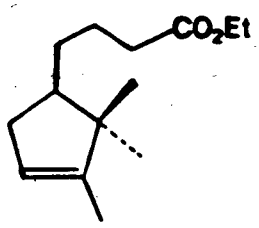
85

The selective reduction of the conjugated double bond of diene ester **84** was first attempted by catalytic hydrogenation using 5% palladium on carbon. When ethanol and ethyl acetate were used as solvents, both double bonds were reduced completely within 1 h to give, in 96% yield, ester **86** which showed the absorption band of a saturated ester (1740 cm^{-1}) in the ir spectrum. The nmr spectrum showed the absence of any vinylic proton and the presence of a gem-dimethyl group with singlets at δ0.87 and 0.51 and a methyl group attached to a methine carbon with a doublet (J = 6.5 Hz) at δ0.8[redacted] The mass spectrum displayed a molecular ion at m/e 226.1930 indicating the chemical formula $C_{14}H_{26}O_2$ in agreement with the fully saturated compound. The stereochemistry was tentatively assigned as shown in structure **86** resulting from the hydrogenation from the less hindered face. When the hydrogenation was performed in benzene in the presence of sodium bicarbonate,[32] the desired ester **87** was formed as the major compound (nine parts) along with a small amount of the fully reduced compound **86** (one part). Unfortunately, these compounds could not be separated and the results were not highly reproducible. The problem was solved by using triethylsilane and Wilkinson's catalyst (tris-triphenylphosphine rhodium(I) chloride).[33] In the

presence of Wilkinson's catalyst hydrosilanes have been shown[34] to react with α,β-unsaturated ketones exclusively by 1,4-addition to give silyl enol ethers which readily undergo hydrolysis[35] to give saturated ketones. Research carried out in our group[36] has successfully extended the method to α,β-unsaturated esters. Thus, when ester **84** was subjected to these conditions, ester **87** was obtained in 89% yield after purification. The ir spectrum showed a shift of the carbonyl absorption band to 1730 cm^{-1} characteristic of a saturated ester. In the nmr spectrum signals at δ6.98 and 5.89 disappeared and only the one at δ5.23 remained in the vinylic region. The molecular ion peak at m/e 224.1778 in the mass spectrum, as well as elemental analysis, verified the $C_{14}H_{24}O_2$ molecular formula.



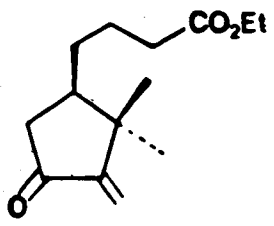
86



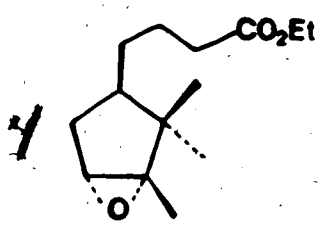
87

For the transformation of ester **87** to enone **88**,

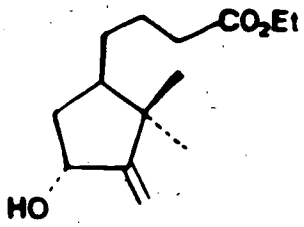
several methods were explored. Firstly, a three-step reaction sequence was studied involving epoxidation of the carbon-carbon double bond followed by ring opening of the resulting epoxide **89**. It was anticipated that the base induced ring opening of the epoxide would occur to afford the desired allylic alcohol **90** as a result of the preferential deprotonation of the methyl substituent.[37] Subsequent oxidation of the resulting allylic alcohol **90**, would give the desired enone **88**.



88



89



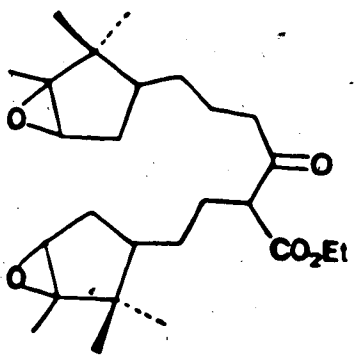
90

Towards this end, ester **87** was treated with m-chloroperbenzoic acid in methylene chloride furnishing epoxide

89 as a single isomer in 83% yield. The ir spectrum displayed absorption bands at 1736 cm^{-1} due to the ester and at 1248 and 844 cm^{-1} due to the epoxide. The nmr spectrum showed a singlet at δ3.21 for the proton on the epoxide ring. The stereochemistry of this epoxide was not elucidated but was tentatively assigned as shown in structure 89 resulting from the peracid attack from the less hindered face. The mass spectrum gave a molecular ion at m/e 240.1728 confirming the molecular formula of $C_{14}H_{24}O_3$.

To open the epoxide ring, 89 was subjected to treatment with lithium diisopropylamide generated in situ from n-butyllithium and diisopropylamine. One product was isolated along with starting epoxide 89. The ir spectrum of the new compound showed carbonyl absorption bands at 1741 (ester) and 1715 cm^{-1} (aliphatic ketone). Absorption bands at 1189, 1152, and 844 cm^{-1} suggested the presence of epoxide rings. The nmr spectrum displayed signals for an ethyl ester at δ4.17 (q, 2H, J = 7 Hz) and 1.26 (t, 3H, J = 7 Hz). Three pairs of methyl groups were observed as singlets at δ1.32, 0.98, and 0.73 integrating to six protons each. A signal at δ3.38 was assigned to the α-proton of a β-keto ester moiety. It appeared as a triplet with a coupling constant of 7 Hz. A two-proton singlet at δ3.22 was attributed to the protons attached to two

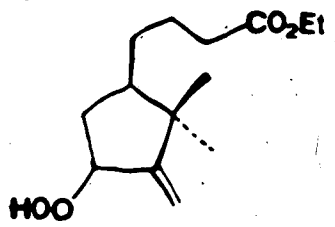
epoxide rings. The mass spectrum showed a molecular ion at m/e 434.3039 indicating the chemical formula $C_{26}H_{42}O_5$. The preceding spectral data led us to propose structure **91** for the new compound. Obviously the methylene protons α to the ester group are more acidic than the protons of the methyl group resulting in a Claisen condensation instead of a ring opening of the epoxide.



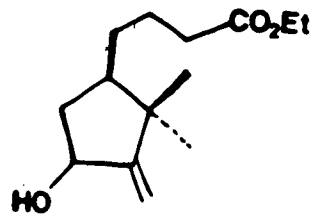
91

The second attempt was also a three-step reaction sequence involving a photooxygenation of ester **87** followed by reduction of the resulting hydroperoxides **92** to the allylic alcohols **93**, which in turn could be oxidized to enone **88**. For this purpose, ester **87** was subjected to photooxygenation in ethanol using methylene blue as the photosensitizer.[38] Reduction of the resulting hydroperoxides **92** with sodium borohydride afforded a

mixture of epimeric allylic alcohols **93** in a 7:3 ratio (by nmr analysis) and in a 65% overall yield. The ir spectrum of these compounds revealed a characteristic stretching band of an alcohol (3410 cm^{-1}). The nmr spectrum contained a pair of doublets at δ 5.00 and 5.16 (1H each, J = 2.5 Hz each) for the vinyl protons of the major isomer and another pair at δ 4.90 and 5.10 (1H each, J = 3 Hz each) for those of the minor isomer. The methine proton adjacent to the hydroxyl group appeared at δ 4.55 as a doublet (J = 7 Hz) for both isomers. The molecular ion at m/e 240.1719 in the mass spectrum confirmed the chemical formula of $C_{14}H_{24}O_3$.



92

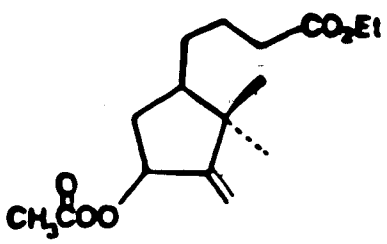


93

Swern oxidation[39] on the mixture of the epimeric alcohols **93** with oxalyl chloride, dimethyl sulfoxide, and triethylamine gave enone **88** in 73% yield. The ir spectrum showed a strong absorption at 1729 cm^{-1} for the ester

group and the α,β-unsaturated five-membered ring ketone, and also a band at 1630 cm^{-1} due to the conjugated carbon-carbon double bond. The nmr spectrum displayed two singlets at δ5.96 and 5.21 for the enone protons. Two doublets of doublets appeared at δ2.54 (1H, J = 18, J' = 7 Hz) and 2.06 (1H, J = 18, J' = 11 Hz) due to the protons α to the ketone. The gem-dimethyl group appeared as a pair of singlets at δ1.24 and 0.99. The molecular formula $C_{14}H_{22}O_3$ was verified by the presence of a molecular ion at m/e 238.1596 in the mass spectrum and by elemental analysis.

Later, it was found that ester **87** could be converted into enone **88** in a single pot reaction.[40] The method is based on the conversion in situ, with acetic anhydride, of the hydroperoxides **92** formed by the photooxygenation to the allylic peracetic ester **94** which readily undergoes β-elimination under mild basic conditions to give the corresponding α,β-unsaturated ketone **88** and acetic acid. When ester **87** was subjeced to photooxygenation in methylene chloride in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine using 5,10,15,20-tetraphenyl-21H,23H-porphine (TPP) as a photosensitizer, enone **88** was obtained directly in 65% yield.



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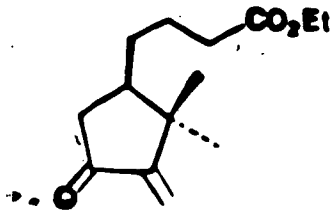
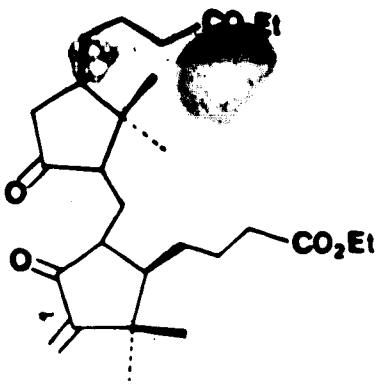


88

With enone 88 in Hand, we set out to investigate its alkylation with an acetone equivalent. This proved to be a very difficult task. A variety of alkylating agents including 2-bromoacetone,[41] 2,3-dichloropropene,[42] allyl bromide, and 2-chloro-3-iodopropene were explored. The reactions were carried out in tetrahydrofuran or 1,2-dimethoxyethane using a number of bases such as sodium hydride, potassium hydride, and lithium diisopropyl-amide. A typical procedure is described below.

To a solution of lithium diisopropylamide, enone 88 was added at -78°C. After stirring for one hour at this temperature, the alkylating agent was added and the temperature was allowed to raise slowly. When the temperature was maintained below -30°C only starting enone 88 was recovered. In the case that the temperature was allowed to rise above -10°C, invariably a dimeric product was isolated along with starting enone 88. This product was identified as compound 95 which showed, in the ir

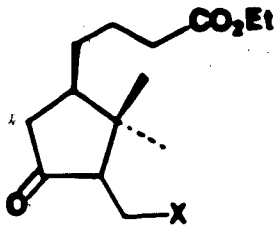


95

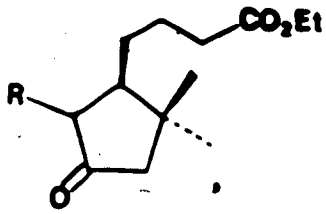
spectrum, a broad carbonyl band centered at 1735 cm^{-1} and an absorption at 1640 cm^{-1} indicative of an olefin. The nmr spectrum displayed two one-proton singlets at δ5.93 and 5.18 characteristic of the geminal protons of a methylidene group. Two ethyl groups appeared at δ4.15 (q, 2 × 2H, J = 7 Hz) and 1.28 (t, 2 × 3H, J = 7 Hz). Four methyl singlets were obtained at δ1.26, 1.18, 1.03, and 0.60. The mass spectrum showed a molecular ion at m/e 476.3138 indicating the molecular formula of $C_{28}H_{44}O_6$.

The above results indicated that enone **88** is a very good Michael acceptor and that the Michael reaction is faster than the alkylation. To address this problem, we decided to protect the methylidene group by 1,4-addition of a nucleophile (X) to give compounds of the type **96**. Clearly, the X group must also be able to serve as a leaving group after a kinetic alkylation at the less

substituted α-carbon. Elimination of the protecting group followed by the removal of the resulting methylidene moiety possibly via a retroaldol process could, in principle, furnish a compound of the type 97.



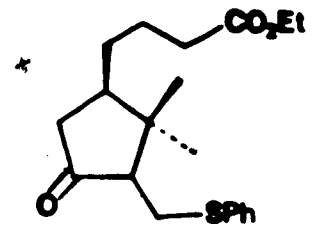
96



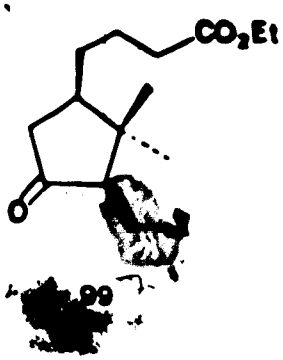
97

Sodium thiophenoxide was chosen initially as the nucleophile. Treatment of enone 88 with sodium thiophenoxide, generated *in situ* from thiophenol and sodium hydride, in tetrahydrofuran afforded a single product 98 in 94% yield. The ir spectrum showed an absorption band at 1735 cm^{-1} compatible with an ester and a five-membered ring ketone. The nmr spectrum showed five aromatic protons at δ7.30 as a multiplet, and an ethyl ester group with a quartet at δ4.14 and a triplet at δ1.27. Two doublets of doublets at δ3.33 (J = 14, J' = 5 Hz), and [illegible] (J = 14, J' = 7 Hz) were assigned to the methylene protons α to the thiophenoxide group. The mass

spectrum showed a molecular ion at m/e 348.1759 indicating the chemical formula $C_{20}H_{28}O_3S$. These spectral data are consistent with the assignment of structure 98 for the addition product with stereochemistry undefined.



98



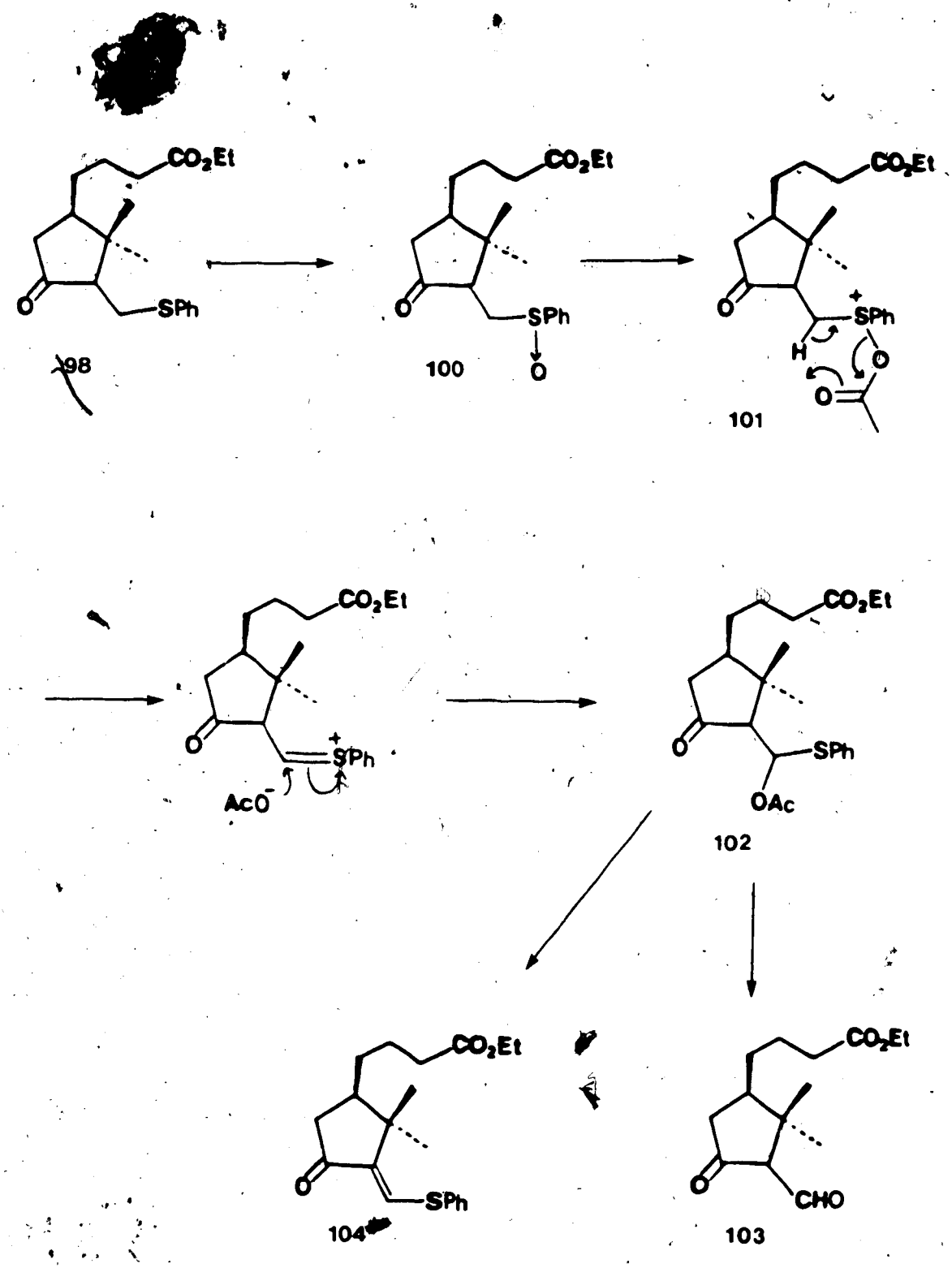
99

Alkylation of compound 98 was attempted using lithium diisopropylamide and 2-chloro-3-iodopropene. At -78°C, no reaction occurred. When the temperature was raised to -15°C the only product isolated was enone 88 resulting from the elimination of the thiophenoxy group. In order to circumvent this problem, it was attempted to prepare substrate 99 which cannot undergo the elimination due to the presence of the carbon-carbon double bond. Furthermore, the presence of a substituent (X) on the β-carbon of the conjugated enone moiety should provide enough steric hinderance as to prevent a Michael reaction encountered previously with 88. We envisioned that the

best method to obtain compounds of the type **99**, was via a variation of the Pummerer reaction.[43,44] As shown in Scheme XV, the method requires the generation of sulfoxide **100** from sulfide **98**. Acetylation of sulfoxide **100** with concomitant rearrangement of the product **101** would give compound **102** which is expected to yield keto aldehyde **103** upon hydrolysis and enone **104** upon pyrolysis.

Towards this end, sulfide **98** was treated with m-chloroperbenzoic acid in methylene chloride and the corresponding sulfoxide **100** was obtained. Upon treatment of sulfoxide **100** with acetic anhydride and sodium acetate two products were formed. One product was identified as enone **88**. The second product showed, in the ir spectrum, carbonyl absorption bands at 1770 cm^{-1} due to a vinyl ester and at 1735 cm^{-1} due to a saturated ester. The nmr spectrum displayed three vinylic protons at δ5.90, 4.84, and 4.63 as singlets. The ethyl ester group appeared at δ4.10 as a quartet and at δ1.22 as a triplet. Three methyl singlets were observed at δ2.19, 1.13, and 0.99. The presence of the band at 1770 cm^{-1} in the ir spectrum together with the methyl group at δ2.19 and the vinyl proton at δ5.90 in the nmr spectrum strongly suggested structure **105** for the second product. This was confirmed by a molecular ion at m/e 280.1675 ($C_{16}H_{24}O_4$) in the mass spectrum. A plausible mechanism for the formation of

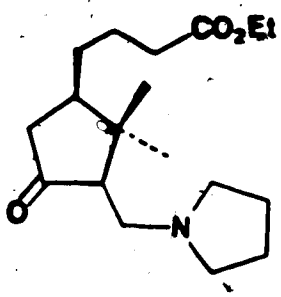
SCHEME XV



enone 88 and the corresponding enol acetate 105 is shown in Scheme XVI.

The second nucleophile chosen for the protection of enone 88 was pyrrolidine. Treatment of enone 88 with pyrrolidine in benzene afforded compound 106 as a single isomer in quantitative yield. The structure of 106 was confirmed by the presence of a multiplet at δ2.45 (4H) in the nmr spectrum for the methylene protons adjacent to the nitrogen atom and by a molecular ion at m/e 309.2306 ($C_{18}H_{31}NO_3$) in the mass spectrum. Attempts of alkylation on 106 were, however, also unsuccessful. The products isolated were starting material 106, enone 88, and sometime quaternary ammonium salt arising from the alkylation at the nitrogen.

An epoxide ring was the third choice as a protecting group. Treatment of enone 88 with hydrogen peroxide and a



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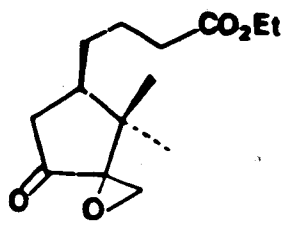
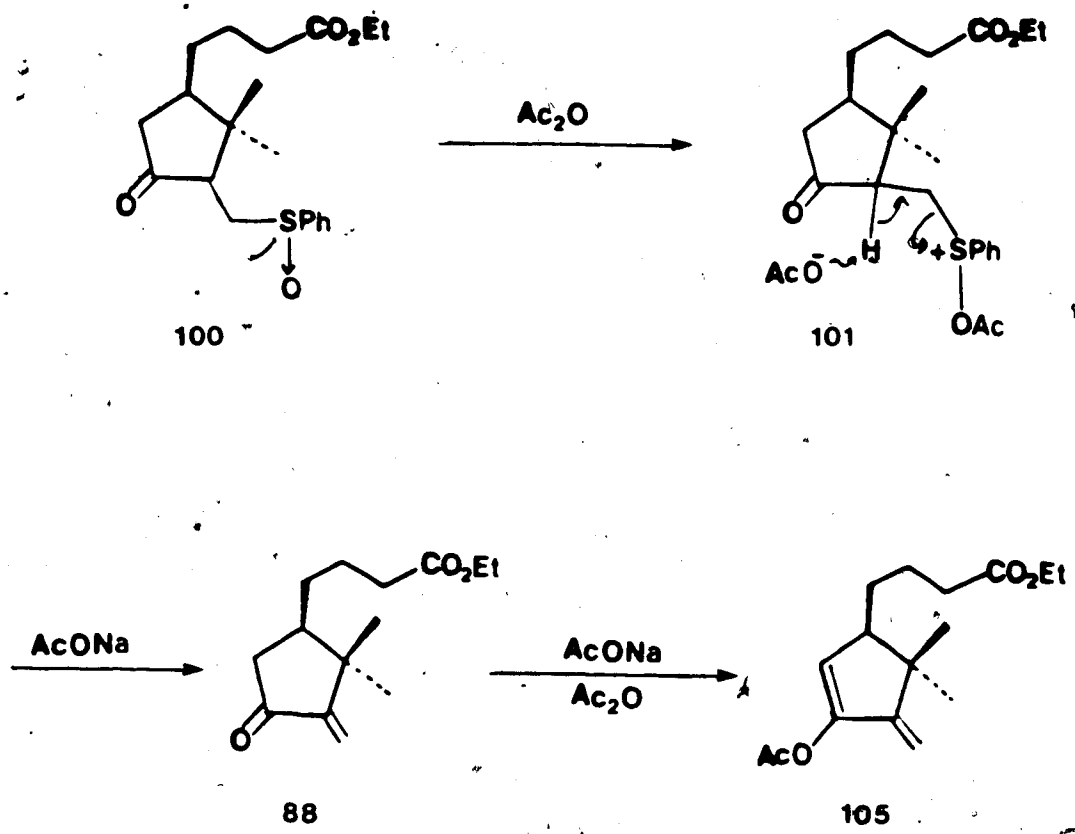


107

SCHEME XVI



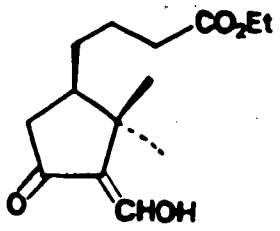
100 101

88 105

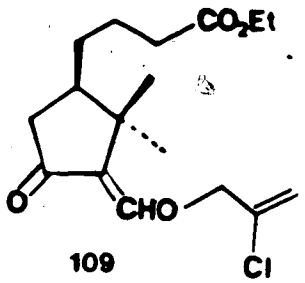
catalytic amount of lithium hydroxide[45] afforded two epimeric epoxides **107** in a ratio of about 3:2. The first epoxide obtained in 52% yield displayed, in the ir spectrum, an absorption band at 1187 cm^{-1} due to the epoxide. Carbonyl bands were observed at 1752 cm^{-1} (saturated five-membered ring ketone) and 1736 cm^{-1} (ester). The nmr spectrum showed doublets at δ 3.11 (1H) and 2.79 (1H) each with a coupling constant of 6 Hz. These signals were assigned to the protons on the epoxide ring. The mass spectrum displayed a molecular ion at m/e 254.1154 confirming the molecular formula of $C_{14}H_{22}O_4$. The minor epoxide, obtained in 34% yield, showed an epoxide absorption band at 1185 cm^{-1} in the ir spectrum. The nmr spectrum displayed the two protons on the epoxide ring at δ 2.97 and 2.87 also as doublets (J = 6.5 Hz each).

Having obtained epoxides **107** in good yield, studies were undertaken for the alkylation at the C5 position. Treatment of the mixture of epoxides **107** with sodium hydride and 2-chloro-3-iodopropene in refluxing benzene afforded β-hydroxy enone **108** in 37% yield and the O-alkylated product **109** in 18% yield. The ir spectrum of **108** showed an absorption band at 1739 cm^{-1} due to the ester and bands at 1670 and 1600 cm^{-1} due to the β-hydroxy enone. The nmr spectrum displayed a singlet at δ 7.09 (1H) for the β-proton of the β-hydroxy enone. The ethyl ester

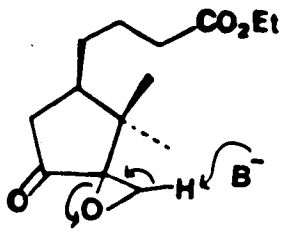
group appeared at δ4.15 as a quartet and at δ1.26 as a triplet. Two sets of doublets of doublets at δ2.60 (1H, J = 17.5, J' = 7.5 Hz) and 2.12 (1H, J = 17.5, J' = 11 Hz) were observed for the methylene protons α to the ketone. The methylene protons α to the ester appeared at δ2.34 as a triplet with a coupling constant of 7 Hz. The gem-dimethyl group displayed two sharp singlets at δ1.18 and 0.98. The mass spectrum showed a molecular ion at m/e 254.1522 indicating the molecular formula $C_{14}H_{22}O_4$.



108



109



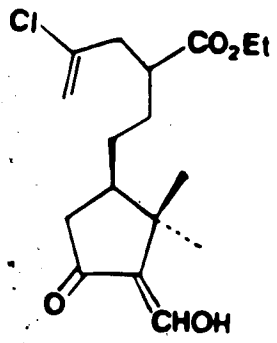
110

Compound **109** showed a carbonyl absorption band at 1735 cm^{-1} for the ester and the unsaturated five-membered ring ketone. A strong band at 1630 cm^{-1} was observed for

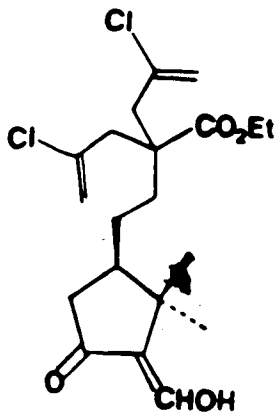
the carbon-carbon double bonds. The nmr spectrum displayed a singlet at δ7.13 for the β-proton of the enone. The remaining vinylic protons were observed at δ5.47 and 5.45 as broad singlets. That **109** was the O-alkylated product was clearly indicated by the presence of a singlet at δ4.49 for the allylic protons. The mass spectrum displayed molecular ions at m/e 328.1445 and 330.1425 confirming the molecular formula of $C_{17}H_{25}ClO_4$. Evidently, under the basic conditions the epoxide ring was cleaved as shown in **110** to give enone **108** which underwent O-alkylation to yield **109**.

We reasoned that β-hydroxy enone **108** would be a good substrate for the selective alkylation at the C5 position via a dianion intermediate.[46] Treatment of epoxides **107** individually or as a mixture with sodium hydride, in refluxing benzene gave **108** in 81% yield. When **108** was treated with two equivalents of lithium diisopropylamide followed by the addition of 2-chloro-3-iodopropene, three compounds were obtained. Partial separation by flash chromatography gave rise to two mixtures. One mixture consisted of two compounds in 1:1 ratio as determined by nmr analysis. The mass spectrum showed molecular ions at m/e 330.1418 and 328.1440 ($C_{17}H_{25}ClO_4$) indicating that monoalkylation had occurred. In the nmr spectrum, four methyl singlets appeared at 1.17, 0.98, and 0.97

for a pair of gem-dimethyl groups. Singlets were also obtained at δ7.09 for the β-proton of a β-hydroxy enone moiety and at δ5.23 and 5.20 for two additional vinylic protons indicating that alkylation had occurred. Signals at δ2.50 and 2.10 were complex due to the mixture nature, but the disappearance of the triplet at δ2.34, due to the α-protons of the ester, strongly suggested that the alkylation had occurred at the carbon α to the ester giving rise to an isomeric mixture of keto esters 111.



111



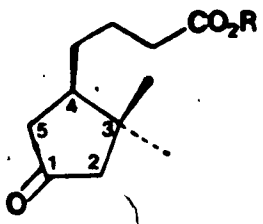
112

The second mixture consisted of three compounds in equal amounts, two of them were found to be identical with the monoalkylated products 111. The structure 112 was tentatively assigned to the third component on the basis of the mass spectrum of the mixture which showed molecular

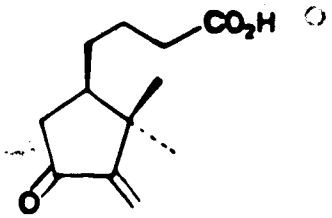
ion peaks at m/e 406.1355, 404.1335, and 402.1361 in agreement with the molecular formula of $C_{20}H_{28}Cl_2O_4$.

Due to our inability to effect the selective alkylation at the C5 position in enone **88** by using different protecting groups for the C2 methylidene group, we decided to remove the exocyclic carbon-carbon double bond to obtain ketone **113** which could, in principle, be selectively alkylated at the C5 position over the C2 position due to steric factors. In order to remove the exocyclic double bond, enone **88** was treated with aqueous sodium hydroxide and aqueous potassium carbonate. When the reactions were performed at room temperature, the ester group was hydrolyzed to give acid **114**, while at reflux temperature only decomposition products were obtained. Under acidic conditions such as aqueous hydrochloric acid, a new acid was obtained. Esterification with potassium carbonate and ethyl iodide in acetone[47] give ester **115** in 72% yield. The ir spectrum displayed an ester absorption band at 1735 cm^{-1}. Bands at 1706 and 1615 cm^{-1} were readily assigned to the α,β-unsaturated five membered ring ketone system. The nmr spectrum displayed a broad singlet at δ5.88 for the α-proton of the enone. The ethyl ester group displayed a quartet at δ4.16 and a triplet at δ1.27. A pair of singlets at δ1.08 and 1.00 was observed for the gem-

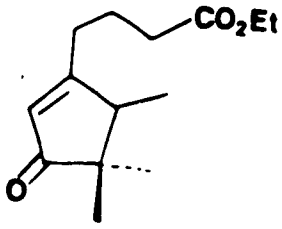
dimethyl group and a doublet (J = 7 Hz) at δ1.08 for the methyl group attached to the methine carbon. The mass spectrum showed a molecular ion at m/e 238.1569 ($C_{14}H_{22}O_3$).



113



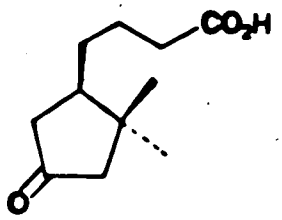
114



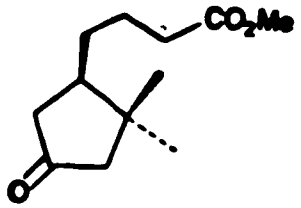
115

The problems encountered in the removal of the exocyclic double bond in enone **88** led us to examine the deformylation[46] in β-hydroxy enone **108**. When **108** was treated with sodium hydroxide in refluxing aqueous ethanol, it underwent the desired reaction with concomitant hydrolysis of the ester group giving keto acid **116**. Esterification of keto acid **116** using potassium carbonate and methyl iodide in acetone gave keto ester **117**

in 65% yield over the two steps. The ir spectrum showed an absorption band at 1741 cm^{-1} due to an ester and a saturated five-membered ring ketone. The nmr spectrum displayed two doublets of doublets integrating to one proton each at δ2.38 (J = 17, J' = 11 Hz) and 2.00 (J = 17, J' = 5.5 Hz) and a two proton singlet at δ2.12 for the four protons α to the ketone. The protons next to the ester group appeared at δ2.34 as a triplet with a coupling constant of 7 Hz. Three methyl singlets were observed at δ3.67, 1.12, and 0.86. The mass spectrum showed a molecular ion at m/e 212.1408, corroborating the chemical formula of $C_{12}H_{20}O_3$.



116



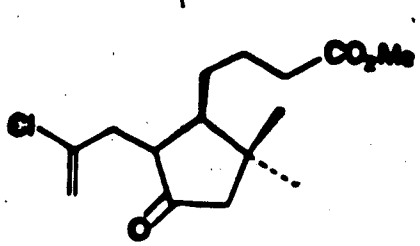
117

Later, it was found that keto acid **116** could be obtained directly from epoxides **107** by treatment with sodium hydroxide in refluxing aqueous ethanol. Esterification using the same conditions as before afforded keto ester **117** in 46% overall yield.

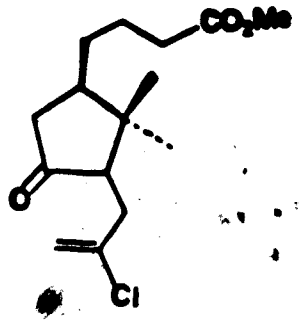
Next, studies on the regioselective alkylation of

ketone 117 were undertaken. When lithium diisopropylamide was used as a base with a variety of alkylating agents, only decomposition products were obtained. However, alkylation of ketone 117 with 2-chloro-3-iodopropene, using sodium hydride in tetrahydrofuran, afforded a mixture of two inseparable compounds in a 3:1 ratio (by nmr analysis) and in a total yield of 16%. The mass spectrum showed molecular ions at m/e 286.1332 and 288.1306 ($C_{15}H_{23}ClO_3$), indicating that monoalkylation had taken place. The nmr spectrum displayed singlets at δ5.22 and 5.29 for the vinylic protons of the major and minor isomers repectively. The observation that the triplet at δ2.34 (J = 7 Hz), assigned to the methylene protons α to the ester, was intact indicated that the alkylation had occurred involving the ketone carbonyl. Furthermore, the major isomer showed a two-proton singlet at δ2.18 readily assigned to the methylene protons adjacent to the gem-dimethyl group suggesting structure 118 for this compound. Structure 119 was tentatively asigned to the minor isomer.

The poor yield of the alkylation coupled with low regioselectivity prompted us to examine the Michael reaction.[50] A Michael reaction of keto ester 117 with methyl vinyl ketone followed by an aldol condensation would give bicyclo[4.3.0]nonen-3-one 120.[51] A ring



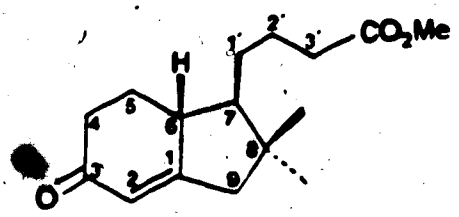
118



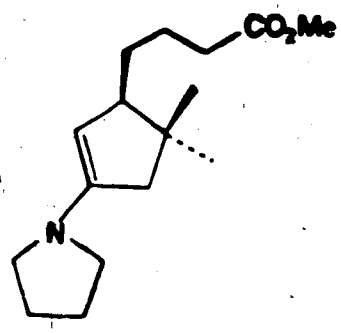
119

contraction on the six-membered ring should give the desired bicyclo[3.3.0]octane system. Since enamines are known to undergo Michael reaction efficiently,[52] ketone 117 was converted to the corresponding enamine 121 by treatment with pyrrolidine in refluxing benzene in the presence of a catalytic amount of p-toluenesulfonic acid. Enamine 121 was then treated with methyl vinyl ketone in refluxing dioxane. After four hours water was added and the mixture was heated to reflux for an additional period of twelve hours. Along with recovered ketone 117, four new compounds (by nmr analysis) were isolated. The mixture was subjected to Kugelrohr distillation at 80°C/0.5 torr. The residue thus obtained was shown to be mainly compound(s) resulting from the incorporation of two molecules of methyl vinyl ketone. The mass spectrum displayed a molecular ion peak at m/e 316.2056 for the chemical formula $C_{20}H_{28}O_3$. The

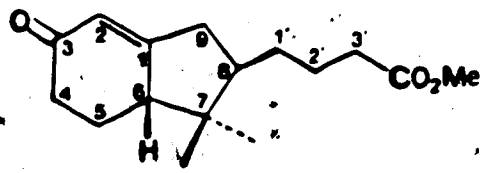
distillate was found to consist of two compounds in a ratio of 3:2 (nmr analysis). The mass spectrum of this mixture showed a molecular ion at m/e 264.1734 indicating the chemical formula $C_{16}H_{24}O_3$. The ir spectrum displayed an ester absorption at 1738 cm^{-1} and bands at 1667 and 1640 cm^{-1} indicating the presence of six-membered ring α,β-unsaturated ketone. The nmr spectrum showed two singlets at δ5.92 and 5.85 for the vinylic proton of the major and minor isomers respectively. The gem-dimethyl group of the major isomer appeared at δ1.09 and 0.91 while the corresponding methyls of the minor isomer were found at δ1.06 and 0.57. At this point, structures **120** and **122** were tentatively assigned to the major and minor isomers respectively. These assignments were based on the findings[48,49] that in compounds such as **123**, with the gem-dimethyl group neighboring the ring junction, one of the methyl groups shifted consistently to an abnormally higher field in the nmr spectrum. Compound **123** displayed the gem-dimethyl group at δ1.06 and 0.61. The structural assignments were conclusively proven by a subsequent experiment (vide infra). Since the annulation was carried out under thermodynamically controlled conditions, the stereochemistry of the products **120** and **122** was tentatively assigned as depicted.



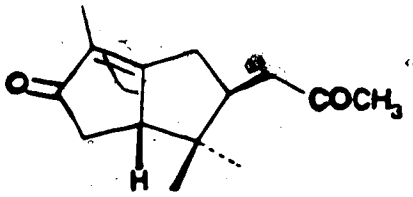
120



121



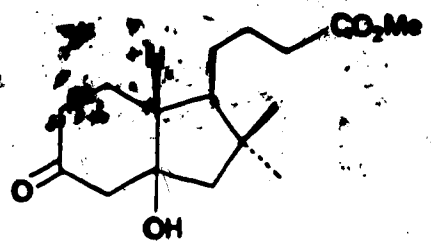
122



123

In order to improve the regioselectivity, the annulation reaction was carried out at room temperature. In this case a very complex mixture was obtained, from which only one product could be isolated in 19% yield. The ir spectrum showed a hydroxyl absorption at 3500-3400 cm^{-1} and carbonyl bands at 1737 (ester) and 1718 cm^{-1} (saturated six-membered ring ketone). The nmr spectrum displayed a two-proton singlet at δ2.52 in addition to the methyl singlets at δ3.68, 1.06, and 1.02. The mass

spectrum exhibited a molecular ion at m/e 282.1830 ($C_{16}H_{26}O_4$). Based on these spectral data, structure **124** was assigned to the alcohol. This assignment was confirmed by conversion of alcohol **124** into enone **120** by treatment with 10-d,l-camphorsulfonic acid in benzene.



124

Having pure bicyclic enone **120** in our hands, some nmr studies were performed to verify the structure. The nmr spectrum showed a multiplet at δ 2.25-2.55 integrating to seven protons. These protons are those at C4, C6, C9, and C3' in either isomer **120** or **122**. If the compound has structure **120**, each of the C9 protons would appear as a doublet with a large geminal coupling constant (J ~ 14-20 Hz). In the case that **122** is the structure, the protons at C9 would each also have a vicinal coupling proton and thus appear as a pair of doublets of doublets. Since all of the aforementioned seven protons are affected by the ketone or the ester, they could be resolved by using a lanthanide chemical shift reagent.[53] When the nmr

spectrum was run in the presence of $Eu(fod)_3$ (tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octadionato)europium), the complex multiplet at δ2.25-2.55 was deconvoluted into multiplets at δ3.38 (1H), 3.15 (1H), and 2.76 (1H), a triplet at 2.45 (2H, J = 7 Hz), and doublets at 2.62 (1H) and 2.54 (1H) each with a coupling constant of 19 Hz. The appearance of two mutually coupled doublets with a large coupling constant is consistent only with structure **120**.

In further attempts to improve the regioselectivity and the yield of the annulation reaction, dioxane was substituted by other solvents[54] such as acetonitrile, benzene, and methanol. In none of the cases, however, could any improvement be achieved.

An intramolecular Michael reaction was attempted on the mixture of compounds **120** and **122**. When the reaction was carried out using sodium methoxide in methanol, only decomposition products were obtained. The use of sodium hydride in 1,2-dimethoxyethane in the presence of a small amount of t-amyl alcohol resulted in complete recovery of the starting material.

At this point, some adjustments had to be made in our strategy. We thought that the problem of the regioselectivity in the Michael reaction could be solved by using a shorter side chain such as that in keto ester **128** in

which the C5 position is less hindered. A new strategy for the formation of tricyclic compound **24** was devised (Scheme XVII). Compound **125** could be obtained by a controlled Dieckmann condensation[55] on diester **126** followed by a ring contraction. Diester **126** could, in turn, be obtained from enone **127** by introducing a two carbon chain to the C1 position. Bicyclic enone **127** could be derived from ketone **128** which, in turn, could be obtained from 10-camphorsulfonic acid (**76**).

10-Camphorsulfonic acid (**76**) was chosen as the starting material for the following reasons. First of all, it can be easily converted to campholenic acid **129*** which already contains the desired side chain. Secondly, both antipodes are readily available in >99% enantiomeric excess[56] and a suitable choice of the starting enantiomer should lead to a chiral synthesis of the natural (-)-quadrone (**1**).

At the initial stage of our investigations, the racemic material was used. Fusion of the sodium salt of (±)-10-camphorsulfonic acid with potassium hydroxide furnished campholenic acid **129**[57] which was esterified

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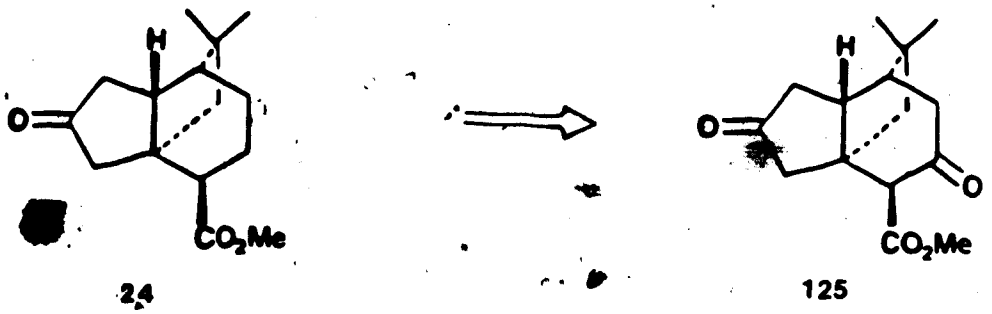
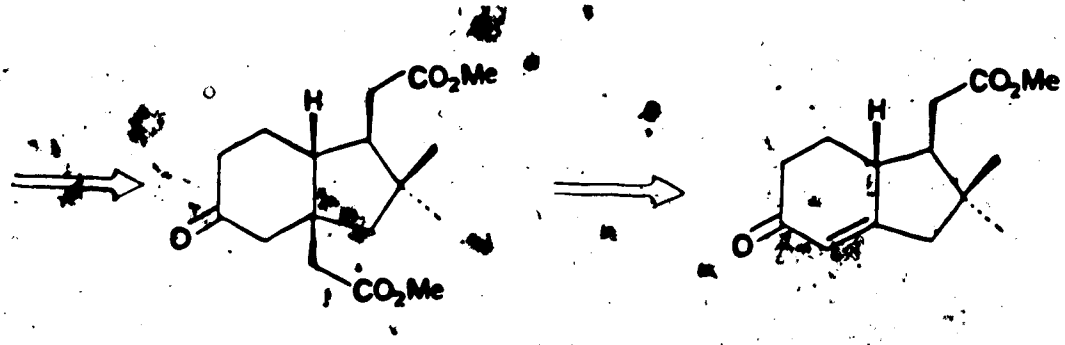
*Although racemic compounds were used and obtained in this approach, this and all other structures are depicted with the required absolute stereochemistry.

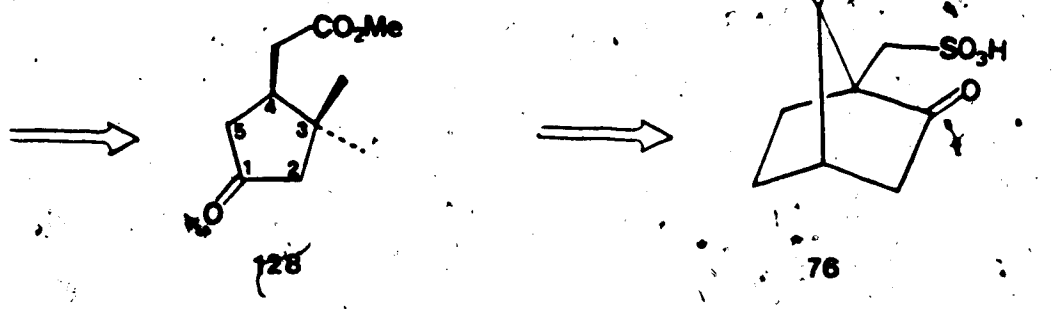
SCHEME XVII



24 125

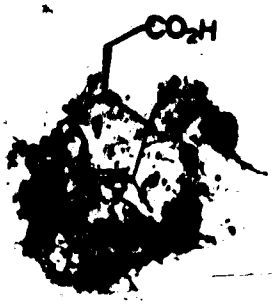


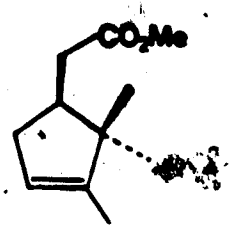
126 127



128 76

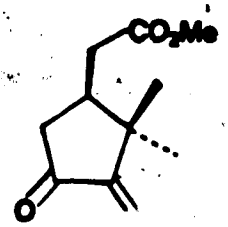
using potassium carbonate and methyl iodide in acetone to give the corresponding methyl ester 130 in 76% overall yield.



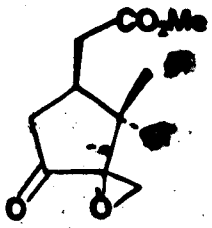


130

The conversion of ester 130 into enone 131 was effected as follows. Photooxygenation of methyl ester 130 in methylene chloride in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine using TPP as a photosensitizer gave enone 131. The ir spectrum showed an absorption band at 1728 cm^{-1} due to an ester and an unsaturated ketone in a five-membered ring. In the nmr spectrum two singlets appeared at δ6.00 and 5.24 for the vinylic protons whereas methyl singlets were observed at δ3.71 (methyl ester), 1.26, and 1.04 (gem-dimethyl group). A molecular ion at m/e 196.1100 in the mass spectrum, as well as elemental analysis, further verified the chemical formula $C_{11}H_{16}O_3$.

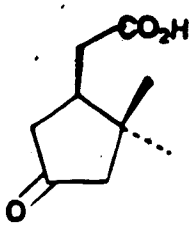


131

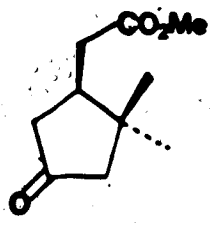


The removal of the methylidene group in enone 131 was effected by the same reaction sequence used for the conversion of enone 88 into ketone 116. Epoxidation of 131 with hydrogen peroxide and a catalytic amount of lithium hydroxide gave a 1:1 mixture of epoxides 132 in 89% yield. The nmr spectrum displayed the protons on the epoxide ring at δ3.13 and 2.86 as doublets with a coupling constant of 6 Hz each for one isomer, and at δ3.00 and 2.96 also as doublets (J = 6 Hz) for the other isomer. Treatment of the mixture of epoxides 132 with a large excess of sodium hydroxide in refluxing aqueous methanol resulted in the epoxide ring opening followed by fragmentation. Under these conditions the ester was also hydrolyzed to give acid 133. When acid 133 was esterified using potassium carbonate and methyl iodide in acetone, methyl ester 128 was obtained in very low yield together with several unidentified products. Improved yield of 128 was obtained when the reaction was carried out under

Fisher esterification conditions.[58] Thus, treatment of a methanolic solution of acid 133 with anhydrous hydrogen chloride resulted in the formation of ester 128 in 51% overall yield from epoxides 132. The ir spectrum showed an absorption band at 1736 cm^{-1} due to a five-membered ring ketone and an ester. The nmr spectrum displayed four singlets, one at δ2.16 for the C2 methylene protons and the others at δ3.70, 1.18, and 0.92 for a total of three methyl groups. The mass spectrum showed a molecular ion at m/e 184.1104 ($C_{10}H_{16}O_3$).



133

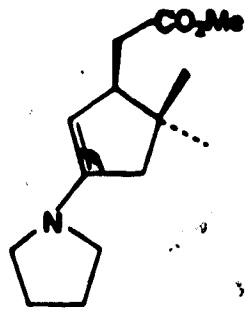


128

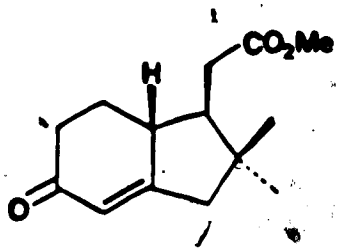
Treatment of keto ester 128 with pyrrolidine and a catalytic amount of p-toluenesulfonic acid in refluxing benzene afforded enamine 134 which, without purification, was allowed to react with methyl vinyl ketone in dioxane at 80-90°C for 5 hours. Water was added and the solution was maintained at the same temperature for an additional period of twelve hours. A mixture of products was isolated in addition to the unreacted keto ester 128. Gc and

nmr analyses of the mixture revealed the presence of four compounds approximately in the ratio of 5:15:6:3.5 in increasing order of retention time. A gc-ms analysis gave a molecular ion at m/e 236.1419 for the major and fastest-moving component, indicating the molecular formula $C_{14}H_{20}O_3$. The minor and slowest-moving component gave a molecular ion at m/e 288.1730 ($C_{18}H_{24}O_3$) indicating that two molecules of methyl vinyl ketone had been introduced. The ir spectrum of the mixture showed an ester absorption band at 1737 cm^{-1} and bands at 1667 and 1635 cm^{-1} indicative of the presence of a 2-cyclohexenone moiety. In the nmr spectrum, the major component displayed a vinylic proton with a singlet at δ5.87 and methyl groups with singlets at δ3.72 (methyl ester), 1.21, and 0.94 (gem-dimethyl group). The second major compound showed a vinylic proton at δ5.92 (s) and methyl groups at δ3.71 (methyl ester), 1.20, and 0.62 (gem-dimethyl group). On the basis of these spectral data, particularly the chemical shifts of the gem-dimethyl groups (vide supra), structure 127 was assigned to the major component and 135 to the second major one. The stereochemistry of these compounds was tentatively assigned as depicted under the consideration of their greater thermodynamic stability in each case than the respective epimer. The structures of the two minor compounds could not be fully elucidated

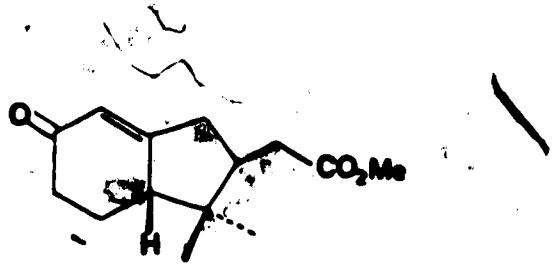
due to insufficient information.



134



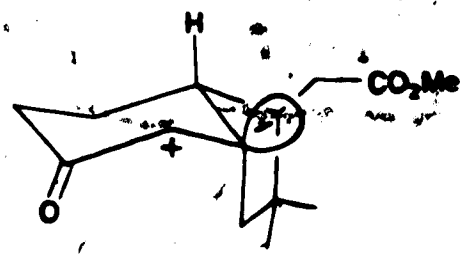
127



135

Since the desired compound 127, although very difficult to separate, was the major component, we decided to carry on the synthesis with the mixture. In order to prepare bicyclic diester 126, a carbomethoxymethyl group had to be introduced to enone 127. The method chosen was a 2+2 photoaddition of allene to enone 127. It has been well established that the addition of allene to conjugated enones occurs in a head-to-head manner.[59,60] With respect to the stereochemical outcome of enone photocycloadditions

in general, it has been postulated[61] that the controlling factor is the preferred configuration of the excited state which is assumed to have a carbonium ion character at the α-carbon of the carbonyl group and a carbanion character at the β-carbon. In the present case, the most stable configuration of such an excited state would be the one shown in formula 136 in which the rings are cis-fused! Consequently, the addition should proceed from the β-face, which is also the sterically less hindered side, giving the photoadduct with the required stereochemistry.

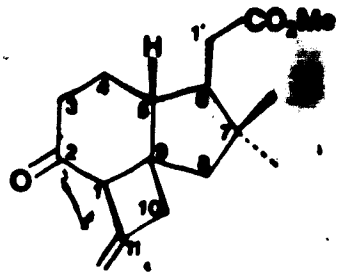


136

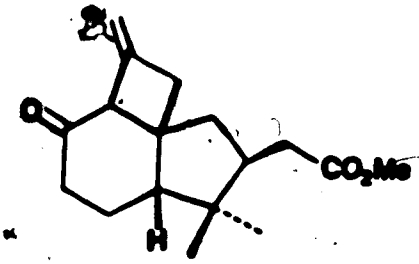
When a solution of the mixture of enones 127 and 135, and the two unidentified minor components and an excess of allene in tetrahydrofuran at -20°C was irradiated with a 450 W Hanovia high-pressure quartz mercury vapor lamp for 9 h, two inseparable photoadducts 137 and 138 were obtained in a 5:1 ratio (determined by gc and nmr analyses) and in 70% yield. The ir spectrum of the mixture displayed six-membered ring ketone (1707 cm^{-1}),

ester (1737 cm^{-1}), and olefin (1670 cm^{-1}) absorptions. Gc-ms showed a molecular ion at m/e 276.1724 for the mixture suggesting the presence of two isomeric compounds with the same molecular formula $C_{17}H_{24}O_3$. The major adduct 137 displayed, in the nmr spectrum, two doublets of doublets of doublets (J = J' = J" = 2.5 Hz each) at δ4.90 and 4.85 for the vinylic protons. The sharp methyl singlets were observed at δ3.73 (methyl ester), 1.03, and 0.90 (gem-dimethyl group). The regiochemistry of this adduct was indicated by the presence of the C1 methine proton at δ3.34 as a doublet of doublets resulting from the allylic coupling (J = 2.5 Hz) with a vinylic proton and the W coupling (J = 6 Hz) with a C10 proton. A cis relationship of the four-membered ring and the carbomethoxymethyl side chain was established by the following NOE experiments. Irradiation of the methyl singlet at δ0.90 produced an enhancement of the signals due to the C8, C1', and C10 protons, while irradiation of the methyl singlet at δ1.03 produced an enhancement of the signals due to the C6 and C1 protons. These results clearly demonstrated that the higher field methyl singlet is cis to the carbomethoxymethyl [illegible] ring. The minor isomer 138 showed, in the nmr spectrum, the vinylic protons at δ4.93 and 4.89 also as doublets of doublets of doublets (J = J' = J" = 2.5 Hz each). Methyl

singlets were observed at δ3[illegible].08, and 0.73.

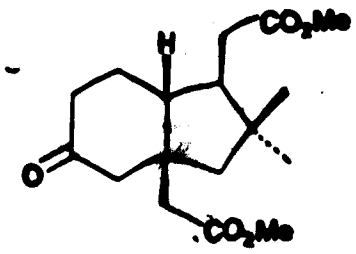


137

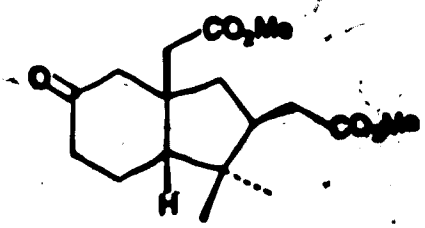


138

The mixture of 137 and 138 was subjected to ozonolysis in methylene chloride-methanol. Reductive workup of the resulting ozonide with dimethyl sulfide[62] afforded directly diesters 126 and 139 in a 5:1 ratio and in 68% yield. The ir spectrum of the mixture revealed the presence of esters (1735 cm^{-1}) and six-membered ring ketone (1716 cm^{-1}). The mass spectrum showed a molecular ion at m/e 310.1782 indicating the molecular formula $C_{17}H_{26}O_5$. The nmr spectrum of the major isomer 126 displayed sharp methyl singlets at δ3.70 and 3.68 for the methyl esters and at δ1.05 and 0.92 for the gem-dimethyl group. The corresponding methyl groups of the minor isomer 139 appeared at δ3.72, 3.70, 1.07, and 0.77.

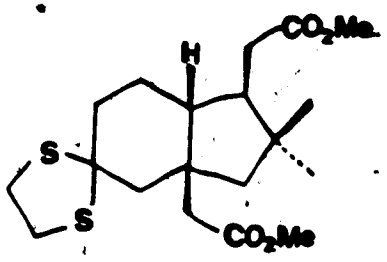


126

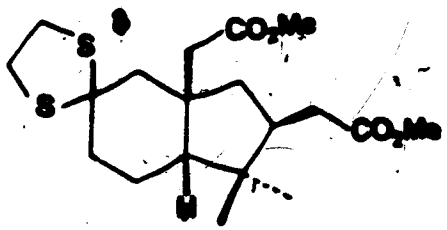


139

Prior to the intended cyclization of keto diester **126** via a Dieckmann reaction, the protection of the ketone carbonyl was required. Treatment of the mixture of keto diesters **126** and **139** with 1,2-ethanedithiol and boron trifluoride in methylene chloride afforded thioketals **140** and **141** in 81% yield. These thioketals showed ester absorption (1737 cm^{-1}) in the ir spectrum. The nmr



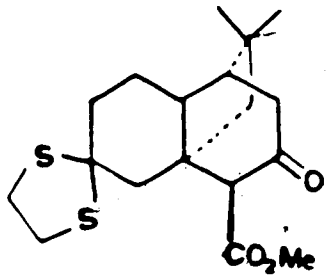
140



141

spectrum of the mixture displayed a multiplet at δ3.28 due to the methylene protons adjacent to the sulfur atoms. The mass spectrum showed a molecular ion at m/e 386.1588 indicating the chemical formula $C_{19}H_{30}O_4S_2$.

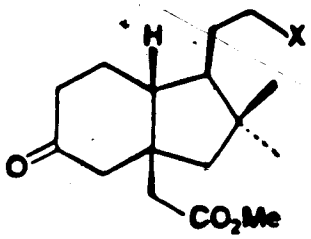
Attempts to induce the Dieckmann condensation on the mixture of diesters **140** and **141** using sodium hydride in refluxing toluene and a small amount of methanol met with total failure. No detectable amount of the desired product **142** was formed.



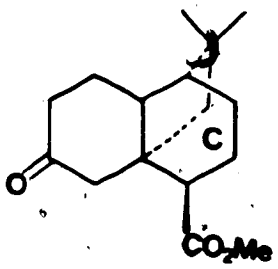
142

Our inability to bring about the Dieckmann condensation required a modification of the synthetic strategy. We reasoned that the C ring of the target molecule could be installed *via* an intramolecular alkylation of compounds of structural type **143** leading to tricyclic compound **144**. Ketone **145** was envisioned as a suitable intermediate. The methyl ether functionality is sufficiently stable to allow extensive modification of the

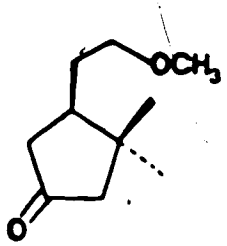
molecule required prior to its eventual conversion into a leaving group.



143



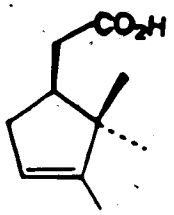
144



145

For the preparation of ketone **145**, campholenic acid (**129**) was reduced with lithium aluminum hydride in ether to give, in 93% yield, campholenic alcohol (**81**) identical with that obtained previously from the reduction of campholenic aldehyde (**72**) (vide supra). Treatment of **81** with sodium hydride and dimethyl sulfate in 1,2-dimethoxyethane afforded methyl ether **146** in 91% yield. The ir spectrum showed absorption bands for an olefin (1640 cm^{-1})

and an ether (1118 cm^{-1}). The nmr spectrum displayed a vinylic proton with a singlet at δ5.25. Methyl singlets were found at δ3.38 (methoxy), 1.62 (vinylic methyl), 1.00, and 0.80 (gem-dimethyl group). A molecular ion at m/e 168.1513 in the mass spectrum, as well as elemental analysis, verified the required chemical formula of $C_{11}H_{20}O$.



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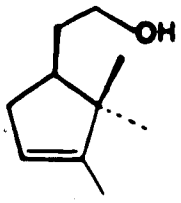

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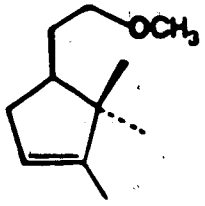
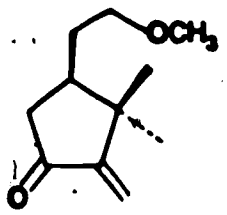


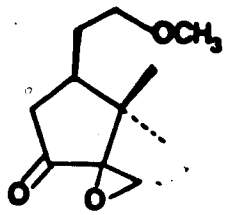
146

Photooxygenation of **146** in methylene chloride in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine using TPP as a photosensitizer afforded enone **147** in 78% yield. The ir spectrum displayed absorption bands at 1727 and 1640 cm^{-1} characteristic of an α,β-unsaturated five-membered ring ketone. The nmr spectrum showed the vinylic protons at δ5.97 and 5.20 as mutually coupled doublets with a coupling constant of 1

Hz. Methyl singlets appeared at δ3.35 (methoxy), 1.23, and 0.99 (gem-dimethyl group). The mass spectrum displayed a molecular ion at m/e 182.1309 indicating the molecular formula $C_{11}H_{18}O_2$.



147



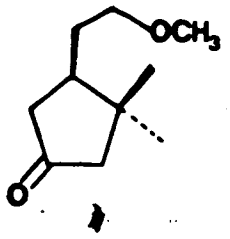
148

For the removal of the methylidene group, enone **147** was epoxidized with hydrogen peroxide in methanol in the presence of a catalytic amount of lithium hydroxide giving a 1:1 mixture of epimeric epoxides **148** in 90% yield. The ir spectrum showed a carbonyl absorption band at 1752 cm^{-1} for the five-membered ring ketone in both isomers. The nmr spectrum of one isomer displayed a pair of doublets at δ3.13 and 2.18 with a coupling constant of 6 Hz each for the protons attached to the epoxide ring. The corresponding protons of the other isomer were found at δ2.96 and 2.87 also as doublets with a coupling constant of 6 Hz each.

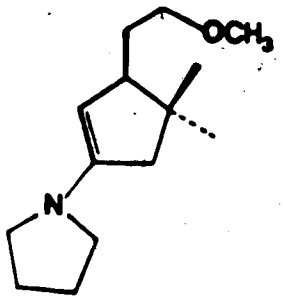
When the mixture of epoxides **148** was treated with sodium hydroxide in refluxing aqueous methanol, ketone **145**

was obtained in 68% yield. The ir spectrum displayed absorption bands at 1742 cm^{-1} due to a saturated five-membered ring ketone and at 1119 cm^{-1} due to an ether. The nmr spectrum displayed signals at δ2.47 (dd, 1H, J = 10.5, J' = 5 Hz), 2.00 (dd, 1H, J = 10.5, J' = 11 Hz), and 2.24 (s, 2H) for the methylene protons α to the ketone. Methyl singlets were observed at δ3.35 (methoxy), 1.18, and 0.92 (gem-dimethyl group). A molecular ion at m/e 170.1304 in the mass spectrum, as well as elemental analysis, verified the chemical formula of $C_{10}H_{18}O_2$.

Having obtained ketone **145**, a Robinson annulation was performed using the same reaction conditions as those used previously for the transformation of keto ester **128** to bicyclic enones **127** and **135**. Enamine **149**, derived from



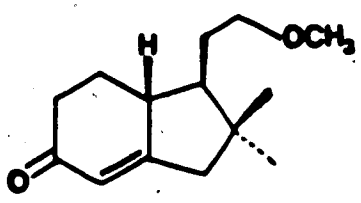
145



149

ketone **145** and pyrrolidine, was allowed to react with methyl vinyl ketone in refluxing dioxane. Subsequent treatment with water resulted in the formation of a mixture of adducts **150** and **151** in 41% yield. The ir

spectrum of the mixture displayed absorption bands characteristic of conjugated cyclohexenone moiety (1668 and 1640 cm^{-1}). The mass spectrum showed a molecular ion at m/e 222.1619 ($C_{14}H_{22}O_2$) indicating that only one molecule of methyl vinyl ketone had been introduced. The nmr spectrum indicated the presence of two compounds in a 2:1 ratio. The major isomer displayed a singlet at δ5.85 for the α-proton of the enone and sharp methyl singlets at δ3.38 (methoxy), 1.11 and 0.95 (gem-dimethyl group). The minor isomer exhibited the enone proton with a singlet at δ5.93 and three methyls with singlets at δ3.39 (methoxy), 1.09, and 0.63 (gem-dimethyl group). On the basis of the chemical shifts observed for the gem-dimethyl groups structure 150 was assigned to the major isomer and 151 to the minor one. The stereochemistry was tentatively assigned on the basis of thermodynamic considerations.



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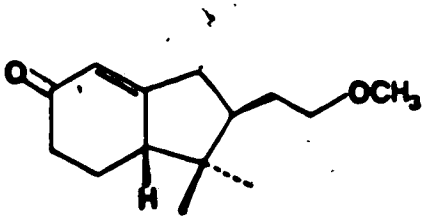
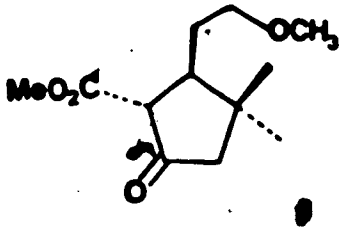


151

Since the regioselectivity of the Michael reaction in ketone 145 was very poor, we decided to modify the

synthetic scheme by introducing a carbomethoxy activating group to C2. Compound 152 thus obtained is expected to undergo alkylation with a masked acetone equivalent and the resulting alkylation product could, in principle, be converted into the desired bicyclo[3.3.0]octenone 153 after an array of rather standard operations, including unmasking the acetone unit, decarbomethoxylation and aldol condensation.



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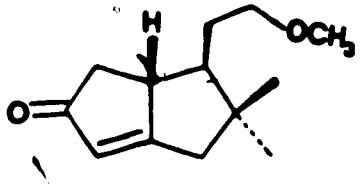

153

Towards this end, ketone 145 was treated with sodium hydride and dimethyl carbonate in refluxing benzene. Keto esters 152 and 154 were obtained in a 15:1 ratio (by nmr analysis) and in 69% yield. The ir spectrum of the mixture showed carbonyl absorption bands at 1736 cm^{-1} (ester) and 1727 cm^{-1} (five-membered ring ketone). The presence of a carbomethoxy group was corroborated by the appearance of a molecular ion at m/e 228.1361 ($C_{12}H_{20}O_4$) in the mass spectrum, as well as by methyl singlets at δ 3.29 (major) and 3.37 (minor) in the nmr spectrum. The regiochemistry of keto esters 152 and 154 was assigned on

the basis of the following observations. The nmr spectrum of the major isomer displayed a set of mutually coupled doublets at δ2.34 (1H) and 2.25 (1H) with a geminal couping constant of 18 Hz due to the C5 methylene p[redacted]. Consequently, the carbomethoxy group must be attac[redacted]o the C2 position next to the methoxyethyl side chain.* The minor isomer also displayed a set of mutually coupled doublets at δ2.12 (1H) and 2.06 (1H) with a coupling constant of 12.5 Hz for the C5 methylene protons. Accordingly, structure **154** was assigned to it. The stereochemistry of each isomer was elucidated on the basis of the following findings. The major isomer displayed the methine proton of the β-keto ester moiety at δ3.11 as a doublet with a coupling constant of 11 Hz. The magnitude of the coupling constant indicated a <u>trans</u> relationship between the carbomethoxy group and the methoxy ethyl group as depicted in **152**. The corresponding hydrogen atom of the minor isomer was found at δ3.07 as a broad singlet indicating the <u>cis</u> stereochemistry shown in formula **154**.

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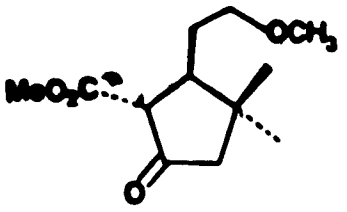
*If the regiochemistry was as shown in **155** then the methylene protons on C5 should appear as doublets of doublets.



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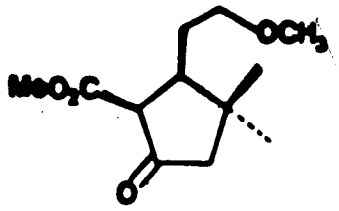

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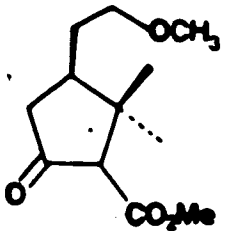

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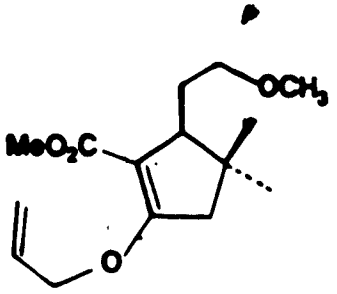
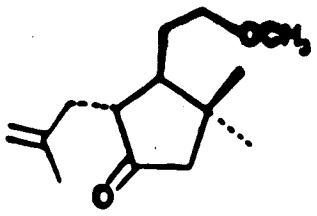


156

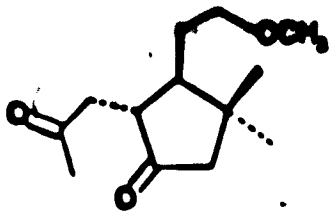
Disappointingly, treatment of keto esters **152** and **154** with allyl bromide using sodium hydride in refluxing 1,2-dimethoxyethane gave only the O-alkylated product **156** in 69% yield. The ir spectrum showed an absorption band at 1710 cm^{-1} due to the ester. Absorption bands at 1689 and 1626 cm^{-1} were observed for the vinyl ether. In the nmr spectrum, complex signals were found at δ5.96 (1H), 5.41 (1H), and 5.27 (1H) for the vinylic protons, and at δ4.54 for the allylic protons. Methyl singlets appeared at δ3.72 (methyl ester), 3.31 (methoxy), 1.10, and 1.07 (gem-dimethyl group). The mass spectrum showed a molecular ion

at m/e 268.1670 confirming the chemical formula $C_{15}H_{24}O_4$. Due to our inability to induce C-alkylation on keto esters 152 and 154, it was decided to examine the direct alkylation on ketone 145. Methallyl iodide was chosen as the alkylating agent. Treatment of 145 with lithium diisopropylamide followed by the addition of methallyl iodide afforded the desired product 157 as a single isomer in 57% yield along with unreacted ketone 145. The ir spectrum of 157 showed a carbonyl absorption band at 1741 cm^{-1} and an olefin band at 1657 cm^{-1}. The nmr spectrum displayed vinylic protons at δ4.85 (1H) and 4.77 (1H) as singlets. The allylic methylenic protons appeared at δ2.37 and 2.31 both as doublets of doublets with coupling constants of 14 and 6 Hz each. Sharp methyl singlets were observed at δ3.36 (methoxy), 1.70 (allylic methyl), 1.16, and 0.94 (gem-dimethyl group). The regiochemistry of the alkylation product was substantiated by the appearance of a two-proton singlet at δ2.16 assigned to the C5 methylene. The C2 methine proton at δ2.12 was shown to couple with the allylic protons with a coupling constant of 6 Hz and with the C3 methine proton with a coupling constant of 10 Hz. The magnitude of this coupling constant suggested a trans-relationship between the two side chains as depicted in 157. The mass spectrum displayed a molecular ion at m/e 224.1776 confirming the

chemical formula $C_{14}H_{24}O_2$.



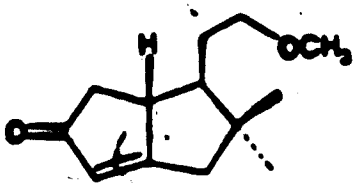
157



158

Ozonolysis of **157** in methylene chloride-methanol followed by reductive workup with trimethylphosphite afforded diketone **158** in 90% yield. The ir spectrum showed carbonyl absorption bands at 1750 cm^{-1} (five-membered ring ketone) and 1715 cm^{-1} (acyclic ketone). The nmr spectrum displayed sharp methyl singlets at δ3.32 (methoxy), 2.15 (methyl ketone), 1.16, and 0.94 (gem-dimethyl group). The methylene protons α to the ketone side chain appeared at δ2.90 and 2.82 both as doublets of doublets with coupling constants of 18 and 5 Hz each. The methine proton at C2 appeared at δ2.32 as a doublet of triplets of doublets with coupling constants of 10, 5, and 1.5 Hz. A molecular ion at m/e 226.1573 in the mass spectrum verified the chemical formula $C_{13}H_{22}O_3$.

Although diketone **158** could be readily prepared, its conversion to the desired bicyclic enone **153** proved to be



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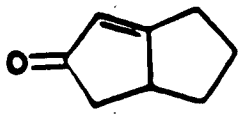

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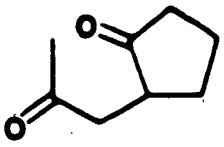
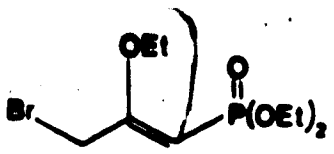


160

difficult. Disappointingly, all attempts to induce the required aldol condensation were fruitless. With sodium hydride and methanol, diketone 158 underwent extensive decomposition while, with benzoic acid and triethylamine in benzene,[63] the starting material was recovered intact. A literature search[64,65,66] revealed that bicyclo[3.3.0]octen-3-one (159) and its derivatives devoid of substituents at C2 and/or C5 can not be prepared by direct aldol condensation of the corresponding diketones (e.g. 160). These results prompted us to seek an alternative method for the ring formation. Diethyl 3-bromo-2-ethoxypropenylphosphonate (161) was chosen as the alkylating agent[67,68] as the cyclization in question could be conceivably effected by an intramolecular Horner-Emmons reaction via the intermediacy of diketo phosphate

162.[67,68]



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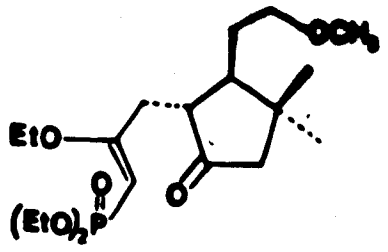

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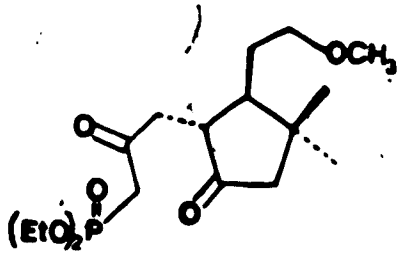

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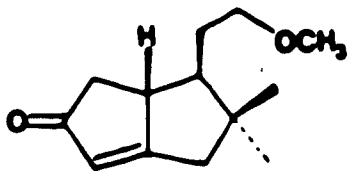


153

The alkylation reaction was carried out according to a reported procedure.[68] Treatment of the lithium enolate of ketone 145, generated with lithium diisopropylamide, with a slight excess of diethyl 3-bromo-2-ethoxypropenyl-phosphonate (161), followed by acid mediated hydrolysis of the resulting enol ether 163 furnished diketo phosphonate 162 in 48% yield. The ir spectrum displayed carbonyl absorption bands at 1741 cm^{-1} for the five-membered ring ketone and at 1716 cm^{-1} for the other. Absorption bands at 1260 (P=O) and 1026 cm^{-1} (P-O-C) indicated the presence of a phosphate. The nmr spectrum displayed a doublet (J_{H-P} = 2 Hz) of quartets at δ4.16 (4H) and a triplet at

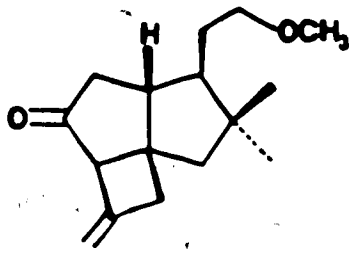
δ1.33 (6H) for the ethyl group of the phosphate. The methylene group flanked by the ketone and the phosphate appeared at δ3.11 as a doublet with a coupling constant (J_{H-P}) of 22.5 Hz. The regiochemistry of the product was proven by the presence of a doublet at δ2.37 (1H, J = 18 Hz) and a doublet of doublets at δ2.18 (1H, J = 18, J' = 1 Hz) attributed to the methylene protons at C5. The stereochemistry of 162 was tentatively assigned as depicted on thermodynamic grounds. A molecular ion at m/e 362.1867 in the mass spectrum confirmed the chemical formula of $C_{17}H_{31}O_6P$.

The intramolecular Horner-Emmons reaction was carried out initially using sodium hydride in 1,2-dimethoxyethane.[68] Under these conditions, extensive decomposition of the starting material was detected. However, to our delight, when the reaction was performed in benzene in the presence of 18-crown-6 ether using potassium carbonate as a base,[69] the desired bicyclo[3.3.0]octen-3-one derivative 153 was produced in 85% yield. The ir spectrum displayed absorption bands at 1708 and 1630 cm^{-1} for the conjugate five-membered enone. The nmr spectrum showed a doublet at δ5.86 with a coupling constant of 2 Hz for the enone proton and methyl singlets at δ3.35 (methoxy), 1.11, and 1.04 (gem-dimethyl group). Two doublets of doublets were observed at δ2.64 (J = 18, J' = 6 Hz) and 2.15 (J = 18, J'

= 3 Hz) for the methylene protons α to the ketone. A molecular ion at m/e 208.1466 in the mass spectrum, as well as elemental analysis, verified the chemical formula $C_{13}H_{20}O_2$. The stereochemistry of enone **153** could not be deduced unambiguously from the nmr spectrum and was assumed on the basis of literature precedents.[14,15] The assignment was shown later to be correct.

For the introduction of the carbomethoxymethyl side chain to the C1 position of enone **153**, a reaction sequence similar to that used for the conversion of esters **127** and **135** into diesters **126** and **139** was applied. Irradiation of enone **153** with an excess of allene in tetrahydrofuran afforded a mixture of photoadducts in 74% yield. The ir spectrum of the mixture showed a shift of the carbonyl absorption band from 1708 cm^{-1} observed for the starting enone to 1735 cm^{-1} suggesting that a saturated five-membered ring ketone was produced. The absorption band of the newly introduced carbon-carbon double bond was found at 1660 cm^{-1}. The nmr spectrum showed the presence of two compounds in a 6:1 ratio and the parallelism between the two sets of signals strongly suggested an isomeric relationship of these compounds. In the major set, two doublets of doublets of doublets (J = J' = J" = 2.5 Hz each) appeared at δ4.98 and 4.85 for the vinylic protons. The methylene protons on the four-membered ring

were found as doublets of doublets of doublets at δ3.02 (J = 16, J' = J" = 2.5 Hz) and 2.73 (J = 16, J' = 5, J" = 2.5 Hz). Methyl singlets were observed at δ3.39, 0.96, and 0.81. The minor component showed vinylic protons at δ4.97 (ddd, J = J' = 2.5, J" = 1 Hz) and 4.79 (m, 1H). Methyl singlets were observed at δ3.39, 0.98, and 0.93. The isomeric nature of the compounds was further supported by the appearance of a single molecular ion at m/e 248.1776 ($C_{16}H_{24}O_2$) in the mass spectrum of the mixture. Based on these observations and on the preferential addition of allene in a head-to-head manner, structure **164** was assigned to the major component and **165** to the minor one. The depicted stereochemistry was assigned to these compounds on the basis of previous findings that keto diester **126** was formed as the only stereoisomer from enone **127** via the same reaction sequence.



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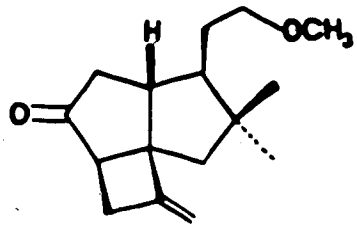
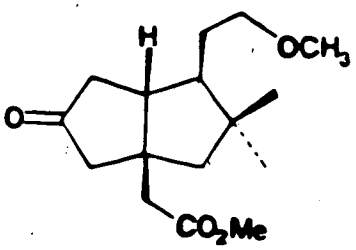


165

Ozonolysis of the mixture of photoadducts 164 and 165 in methanol followed by reduction of the resulting ozonide with dimethyl sulfide afforded three chromatographically separable products. The major product 75, obtained in 76% yield, displayed in the ir spectrum a strong absorption band at 1740 cm^{-1} due to the ester and the five-membered ring ketone. The nmr spectrum displayed sharp methyl singlets at δ3.65 (methyl ester), 3.31 (methoxy), 0.99, and 0.90 (gem-dimethyl group). A molecular ion at m/e 282.1833 in the mass spectrum confirmed the molecular formula of $C_{16}H_{26}O_4$. Evidently, the four-membered ring ketone formed after ozonolysis underwent further ring opening in the methanolic solution.



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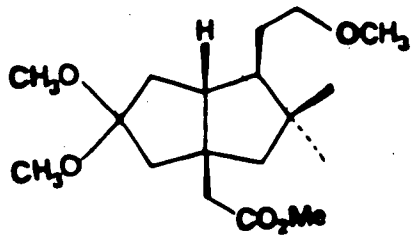

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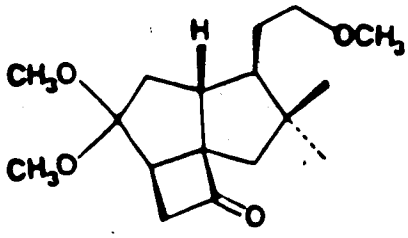


167

The second product, obtained in 8% yield, displayed sharp methyl singlets at δ3.68, 3.35, 3.20, 3.21, 0.96, and 0.85 in the nmr spectrum. The observation of methyl singlets at δ3.20 and 3.21 together with the absence of signals for methylene protons α to a ketone carbonyl suggested the formation of a dimethyl ketal. Structure **166** was confirmed by the mass spectrum showing a molecular ion at m/e 378.2247 ($C_{18}H_{32}O_5$).

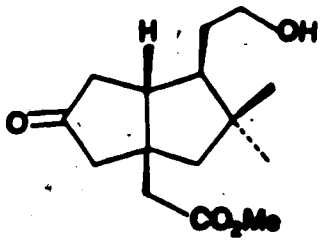
The third product (6% yield) showed an absorption band at 1772 cm^{-1} in the ir spectrum suggesting the presence of a four-membered ring ketone. This was also supported by the nmr spectrum which displayed two doublets of doublets at δ2.91 (J = 18, J' = 9 Hz) and 2.82 (J = 18, J' = 6 Hz) for the methylene protons on the four-membered ring. That these protons appeared as doublets of doublets indicated the presence of a vicinal proton. The presence of a dimethyl ketal was evident from methyl singlets at δ3.28 and 3.22 and supported by the mass spectrum which exhibited a molecular ion at m/e 296.1988 for the chemical formula $C_{17}H_{28}O_4$. These spectral data clearly suggested structure **167** for the compound which apparently arose from the ozonolysis of compound **165** with concomitant ketalization.

Conversion of the methyl ether moiety in **75** into a good leaving group would allow an intramolecular

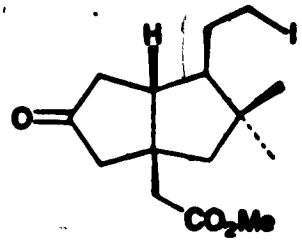
alkylation leading to Danishefsky's intermediate 24. Iodide was chosen as the leaving group.

Olah et al.[70] reported a method for the direct conversion of ethers to the corresponding alcohols or iodo compounds under mild conditions using chlorotrimethylsilane and sodium iodide in acetonitrile. It has also been shown that esters are less prone to cleavage under these conditions. When compound 75 was treated with chlorotrimethylsilane (1 equiv.) and sodium iodide (1 equiv.) in acetonitrile at 50°C the corresponding alcohol 168 was obtained in 76% yield with the methyl ester intact. The ir spectrum displayed an absorption band at 3440 cm^{-1} due to the alcohol. A carbonyl absorption band was observed at 1738 cm^{-1} for the five-membered ring ketone and ester. The nmr spectrum showed a triplet at δ3.71 with a coupling constant of 7 Hz for the protons on the carbon bearing the hydroxyl group. Three sharp methyl singlets were observed at δ3.63 (methyl ester), 1.00, and 0.92 (gem-dimethyl group). The mass spectrum showed a molecular ion at m/e 268.1677 ($C_{15}H_{24}O_4$).

We were very pleased to find out that when compound 75 was subjected to treatment with a large excess of chlorotrimethylsilane and sodium iodide (3-5 equiv.) at 60°C, the desired iodo compound 169 was obtained in 90%



168



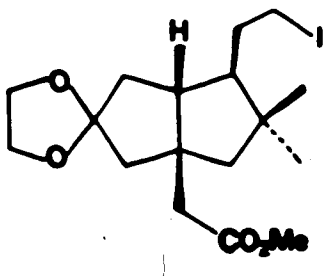
169

yield with the ester group again intact. Thin layer chromatographic (tlc) analysis of the reaction mixture revealed the initial formation of alcohol **168** which was then slowly converted into iodo compound **169**. The ir spectrum of **169** displayed a carbonyl absorption band at 1738 cm^{-1} for the five-membered ring ketone and the ester. A multiplet at δ3.32 in the nmr spectrum was assigned to the protons on the carbon bearing the iodine. Methyl singlets were observed at δ3.65, 1.04, and 0.92. A molecular ion at m/e 378.0689 in the mass spectrum verified the chemical formula $C_{15}H_{23}IO_3$.

Jung et al.[71] reported the cleavage of dimethyl ketals to the corresponding ketones using iodotrimethylsilane in carbon tetrachloride. Thus, it is highly conceivable that ketal **166** could also be directly converted to the desired iodo compound **169** under conditions effecting the transformation of **75**→**169**.

Indeed, when dimethyl ketal 166 was treated with 6-7 equivalents each of chlorotrimethylsilane and sodium iodide in acetonitrile, the cleavage of the dimethyl ketal group was also effected and the iodo compound 169 was formed in 87% yield.

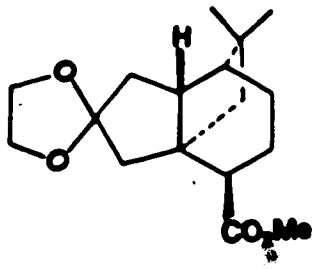
Prior to the intramolecular alkylation of iodo compound 169, the ketone group was protected in the form of an ethylene ketal by transketalization with 2-ethyl-2-methyl-1,3-dioxolane and a catalytic amount of p-toluene-sulfonic acid in refluxing benzene. Ketal 23 thus obtained in 72% yield displayed an ester carbonyl absorption band at 1735 cm^{-1} in the ir spectrum. The nmr spectrum showed a multiplet at δ3.89 for the protons attached to the dioxolane ring. Multiplets were also observed at δ3.28 and 3.16 for the methylene protons neighboring the iodine atom. Sharp methyl singlets appeared at δ3.66, 0.99, and 0.86. The mass spectrum showed a molecular ion at m/e 422.0942 indicating the chemical formula $C_{17}H_{27}IO_4$.



23

The intramolecular alkylation on iodo ketal **23** was performed under the same reaction conditions as those reported by Danishefsky. It was found that when the reaction was carried out using lithium diisopropylamide as base,[14] the corresponding tricyclic ketal **170** could be obtained in 75% yield. This result was, however, not highly reproducible. On the other hand, when lithium hexamethyl disilazide was used as a base,[13] tricyclic ketal **170** was produced consistently in ~70% yield. Tricyclic ketal **170** displayed, in the ir spectrum, an absorption band at 1731 cm^{-1} due to the ester. The nmr spectrum displayed a multiplet at δ3.79 for the protons of the dioxolane ring and a methyl singlet at δ3.58 for the methyl ester. The methine proton α to the ester displayed a doublet at δ2.56 with a coupling constant of 6 Hz indicating that the carbomethoxy group is in the axial position. A pair of singlets at δ1.13 and 1.00 were observed for the gem-dimethyl group. The mass spectrum showed a molecular ion at m/e 294.1838 confirming the chemical formula $C_{17}H_{26}O_4$.

Transketalization of ketal **170** with acetone in the presence of a small amount of p-toluenesulfonic acid furnished an 80% yield of tricyclic ketone **24**, the spectral data of which were found to be in good agreement with those described.[14] Since racemic **24** has previously



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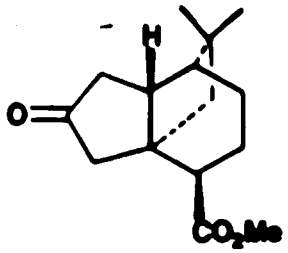
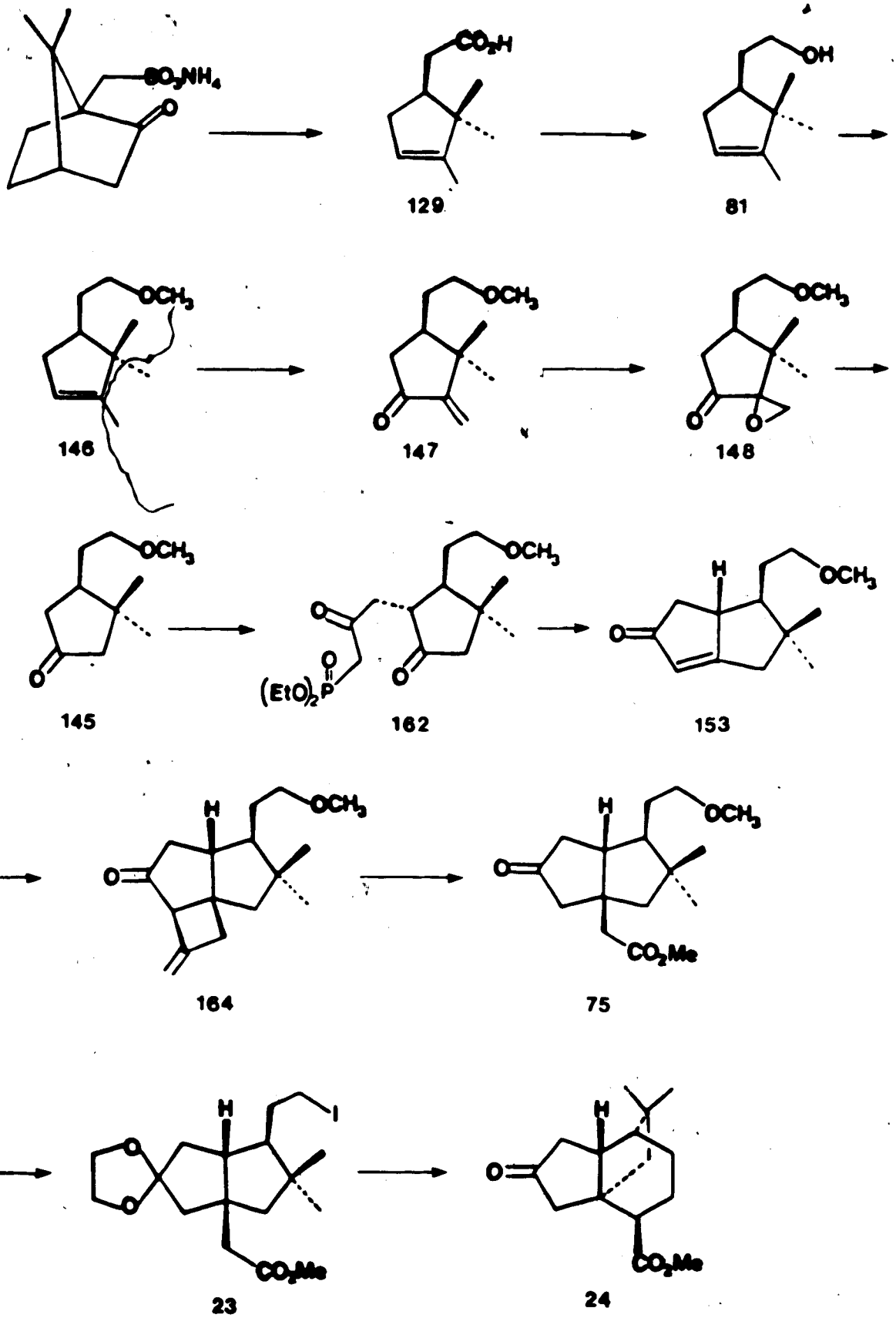


24

been converted by Danishefsky and co-workers to (±)-quadrone (**1**), a new total synthesis of the latter compound is thus formally accomplished from d,l-10-camphorsulfonic acid (**76**) which was converted to (±)-**24** in an overall yield of 3% by a fourteen-step reaction sequence outlined in Scheme XVIII.

At the completion of the synthesis of compound **24** in racemic form, the same reaction sequence was repeated starting with the commercially available (-)-10-camphorsulfonic acid (**76**) ammonium salt. Fusion with potassium hydroxide pellets afforded (-)-campholenic acid (**129**) in 79% yield. Lithium aluminum hydride reduction of (-)-**129**, followed by treatment of the resulting (-)-campholenic alcohol (**81**) with dimethyl sulfate in 1,2-dimethoxyethane afforded (-)-**146**. Photooxygenation of (-)-**146** in methylene chloride in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine using TPP as a

SCHEME XVIII

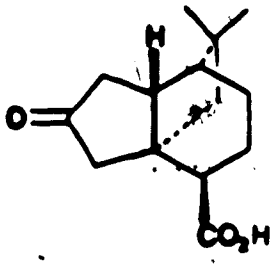


photosensitizer gave (-)-enone 147. Epoxidation of (-)-147 with lithium hydroxide and hydrogen peroxide in methanol furnished an epimeric mixture of (-)-epoxides 148 which, upon treatment with a solution of sodium hydroxide in aqueous methanol underwent epoxide ring opening and deformylation to give (-)-ketone 145. Selective alkylation of (-)-145 with lithium diisopropylamide and diethyl 3-bromo-2-ethoxypropenylphosphonate (161) in tetrahydrofuran followed by hydrolysis of the ethyl enol ether afforded (-)-diketone 162. Horner-Emmons reaction on (-)-162 using potassium carbonate and 18-crown-6 ether in benzene gave (-)-bicyclic enone 153. Irradiation of a solution of (-)-153 and allene in tetrahydrofuran afforded (-)-photoadduct 164 with the required all-cis stereochemistry. Ozonolysis of (-)-164 in methanol-methylene chloride followed by reductive workup with dimethyl sulfide furnished (-)-ester 75. The conversion of (-)-methyl ether 75 into (-)-iodo compound 23 was effected by treatment with chlorotrimethylsilane and sodium iodide in acetonitrile followed by ketalization. Treatment of (-)-23 with lithium hexamethyl disilylazide in tetrahydrofuran followed by deketalization with p-toluenesulfonic acid in acetone afforded (-)-ester 24.

Application of Danishefsky's synthetic sequence to the optically active ester 24 resulted in the first total

synthesis of the naturally occurring (-)-quadrone (1). Alkaline hydrolysis of the ester produced (-)-acid 25.* Selenenylation of (-)-25, followed by oxidation of the resulting C3-phenylseleno derivative afforded enone acid 26 contaminated by a small amount (~15%) of the starting acid (-)-25. Treatment of this mixture with three equivalents of lithium diisopropylamide followed by addition of formaldehyde gave a mixture of acids 171, 26, 25, 172, and 27 in which 171 was predominating. Owing to the highly polar nature of these compounds, separation was found to be difficult. Hydrogenation of the mixture gave a new mixture of acids which showed the absence of any vinylic protons in the nmr spectrum. Without separation, the mixture thus obtained was subjected to pyrolysis at 190-192°C for 6 min. Flash chromatography of the crude

*Some discrepancies were observed in the nmr spectral data of (-)-25 and those reported.[14] The reported values for the methylene protons α to the ketone are δ2.24 and 2.73 (both d, 1H each, J = 19.5 Hz each) for the methylene protons adjacent to the quaternary carbon and δ2.51 (dist. t, 2H, J = 8.25, J' = 10 Hz) for those neighboring the methine carbon. We observed these protons at δ2.27, 2.55 (both d, 1H each, J = 18.5 Hz each), and 2.49 (d, 2H, J = 10 Hz) respectively. To confirm the structure, (-)-acid 25 was esterified using diazomethane in ether, The resulting ester displayed the same spectral data as (-)-24. When this ester was hydrolyzed using the same reaction conditions as before, (-)-acid 25 was again obtained showing the same nmr data. Enone acid 26 obtained from the next reaction, displayed nmr data in agreement with those reported.



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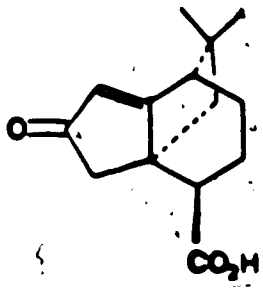

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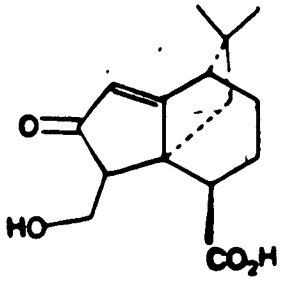

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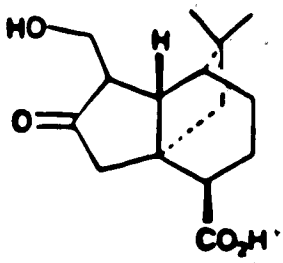

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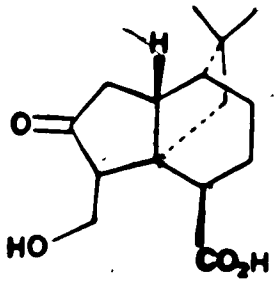

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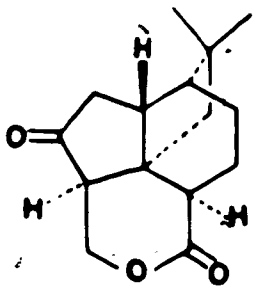


1

product on silica gel afforded (-)-quadrone (1) as a homogeneous solid, m.p. 182-184° (lit.[1] 185-186°C). The ^{1}H nmr, ir, and ms spectral data were found to be identical with those reported.[1,2,4] The specific rotation of the synthetic quadrone ($[\alpha]_D^{22}$ = -42.2° (c 0.05, EtOH)) was also shown to be virtually the same as that of the natural material ($[\alpha]_D^{21}$ = -44.6° (c 1.3, EtOH)). Thus, direct evidence for the absolute configuration of the natural quadrone is provided for the first time.

The specific rotations obtained for the intermediate compounds are summarized in Table I.

Table I. Specific rotations of the intermediate compounds in (-)-quadrone synthesis.[a]

Compound	$[\alpha]_D^{22}$	c (g/100 mL)
129	-11.1	0.11
81	-5.6	1.48
146	-2.6	1.07
147	-132.4	0.29
148[b]	-155.0	0.23
148[b]	-160.8	1.16
145	-94.5	0.78
162	-46.1	0.13
153	-262.7	0.41
164	-92.7	0.18
75	-53.3	0.66
169	-48.1	0.21
23	-5.4	0.17
170	-52.1	0.98
24	-4.9	1.06
25	-0.4	1.08
1[c]	-42.2	0.05

a. The solvent used was $CHCl_3$ unless otherwise indicated.

b. Specific rotation of each individual epoxide.

c. The solvent used was EtOH.

EXPERIMENTAL

General

Melting points were recorded on a Köfler hot stage apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department. Infrared (ir) spectra were recorded on a Perkin-Elmer model 457 or Nicolet 7-199 FT-IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker WP-80, Bruker WH-200 or Bruker WH-400 spectrometer and, except where otherwise stated, were obtained on solutions in deuterochloroform with tetramethylsilane as internal reference. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Bruker WH-200 or WH-400 spectrometer and were obtained on solutions in deuterochloroform. Fluorine nuclear magnetic resonance (^{19}F nmr) were recorded at 376 MHz on a Bruker WH-400 spectrometer. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra (ms) were recorded using A.E.I. model MS9, MS12 or MS50 mass spectrometer. Gas chromatography (gc) analyses were performed on a Hewlett-Packard 5750 instrument using a column of 15% SE-30 on

Chromosorb W with helium as the carrier gas. A Perkin-Elmer 241 polarimeter was used for measuring all optical rotations. Ozone was generated using a Welsbach ozonator (80 V). Anhydrous magnesium sulfate was used for drying organic solutions. Crystalline samples were recrystallized and liquid samples were subjected to Kuhrgebohr distillation before submitting for elemental analysis.

Materials

Flash chromatography developed by Still[72] was used routinely for purification and separation of product mixtures. Nitrogen or argon was passed through a purification train of Fieser's[73] solution, concentrated sulfuric acid, and potassium hydroxide pellets. Solvents were purified as follows: tetrahydrofuran and 1,2-dimethoxyethane by distillation from a blue or purple solution of sodium benzophenone ketyl under an argon atmosphere; dimethylsulfoxide and hexamethylphosphoramide by distillation over calcium hydride at reduced pressure; triethylamine, pyridine, diisopropylamine and acetonitrile by distillation over calcium hydride; benzene and dioxane by distillation over lithium aluminum hydride; methanol and ethanol by distillation over magnesium metal; acetone by distillation over potassium permanganate crystals and methylene chloride over phosphorous pentoxide. All solvents were stored over 3Å molecular sieves after

distillation.

α-Campholenic aldehyde (72)

In a 250 mL three-necked round-bottom flask zinc chloride (0.40 g, 0.003 mol) was melted slowly to prevent burning. α-Pinene oxide (73) (95%, 14.5 g, ~0.095 mol) in benzene (80 mL) was added and the mixture was refluxed under an atmosphere of argon for 3 h. After the solvent was removed, the residue was distilled to give aldehyde 72 (10.6 g, 73% yield): b.p. 97°C/1.5 torr; ir (neat) 2868 and 1726 cm^{-1} (aldehyde); ^1H nmr δ10.80 (dd, 1H, J = 2, J' = 2.5 Hz, -CHO), 5.25 (br s, 1H, =CH-), 2.53 (ddd, 1H, J = 16, J' = 4.5, J" = 2 Hz, -CHHCHO), 2.37 (ddd, 1H, J = 16, J' = 10, J" = 2.5 Hz, -CHHCHO), 2.37, 1.18 (both m, 1H each, $-CH_2CH=$), 1.60 (m, 3H, $=CCH_3$), 1.00 (s, 3H, $-CH_3$), and 0.79 (s, 3H, $-CH_3$); ^{13}C nmr δ202.70, 147.99, 121.62, 47.00, 45.18, 44.35, 35.63, 25.70, 20.06, 12.55; ms M^+ 152.1200 (calcd. for $C_{10}H_{16}O$: 152.1200).

α-Campholenic alcohol (81)

At 0°C, to a solution of aldehyde 72 (403 mg, 2.65 mmol) in methanol (10 mL), sodium borohydride (98 mg, 2.65 mmol) was added. After stirring at 0°C under an atmosphere of argon for 10 min, ice-cold water (10 mL) and dilute hydrochloric acid solution (5 mL) were added. The

mixture was extracted with ether. The organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 25% ether in petroleum ether, gave alcohol 81 (367 mg, 90% yield): b.p. 74°C/0.4 torr; ir ($CHCl_3$ cast) 3322, 3036 (alcohol), and 1645 cm^{-1} (olefin); ^1H nmr δ 5.25 (br s, 1H, =CH-), 3.70 (m, 2H, $-CH_2OH$), 1.16 (br s, 3H, $=CCH_3$), 0.99 (s, 3H, $-CH_3$), and 0.79 (s, 3H, $-CH_3$); ms M^+ 154.1355 (calcd. for $C_{10}H_{18}O$: 154.1358). Anal. calcd. for $C_{10}H_{18}O$: C 77.87, H 11.76; found: C 77.67, H 11.76.

(3'S,2S)- and (3'R,2S)-2',2',3'-trimethylcyclopent-3'-enylethyl 2-methoxy-2-trifluoromethyl-2-phenylethanoate (83)

To a solution of (-)-α-methoxy-α-trifluoromethyl)-phenylacetic acid (92 mg, 0.39 mmol) in benzene (5 mL), a small drop of N,N-dimethylformamide and oxalyl chloride (0.1 mL, 1.16 mmol) were added and the solution was stirred at room temperature for 45 min. The solvent was removed under vacuum. Benzene (7 mL) was added to the residue and the resulting solution concentrated under reduced pressure. The residual acid chloride was then kept in an argon atmosphere. A solution of alcohol 81 (41 mg, 0.26 mmol) in pyridine (1 mL) containing a crystal of 4-dimethylaminopyridine was added to the neat acid

chloride prepared above. After 20 min the suspension was diluted with ether and treated with aqueous hydrochloric acid solution. The organic layer was washed once more with acid, then with aqueous sodium bicarbonate solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ether in petroleum ether, gave two epimeric esters 83 [(3'S,2S):(3'R,2S) = 1:5; 85 mg, 88% yield]: ir ($CHCl_3$ cast) 1748 cm^{-1} (ester); ^1H nmr δ 7.53, 7.42 (both m, 5H total, $-C_6H_5$), 5.23 (br s, 1H, =CH-), 4.42, 4.34 (both m, 1H each, $-CH_2O-$), 3.58 (br s, 3H, $-OCH_3$), 1.62 (br s, 3H, $=CCH_3$), 0.98 (s, 3H, $-CH_3$), and 0.79 (s, 3H, $-CH_3$); ^{13}C nmr δ 166.65, 141.47, 132.45, 129.59, 128.43, 127.38, 123.39 (q, J_{C-F} = 287 Hz), 121.47, 84.67 (q, J_{C-F} = 27 Hz), 66.17, 55.43, 46.86, 46.65, 35.22, 28.94, 25.66, 19.69, and 12.55; ^{19}F nmr δ -71.7141 (br s, major) and -71.7351 (br s, minor); ms M^+ 370.1750 (calcd. for $C_{20}H_{25}F_3O_3$: 370.1744).

4-(3-Carbethoxy-2-propenyl)-1,5,5-trimethylcyclopentene (84)

At 0°C, to a suspension of sodium hydride (80% dispersion in oil, 1.97 g, 50.6 mmol) in tetrahydrofuran (100 mL) under argon atmosphere, a solution of triethyl phosphonoacetate (10 mL, 50.6 mmol) in tetrahydrofuran (10

mL) was added dropwise. After the addition was complete, the solution was stirred at room temperature until no more hydrogen evolved. The solution was cooled again to 0°C and a solution of aldehyde **72** (7 g, 46.1 mmol) in tetrahydrofuran (10 mL) was added dropwise to prevent a raise in temperature. After the addition was completed, the solution was stirred at room temperature for 30 min. Ice-cold water (200 mL) was added and the mixture extracted with petroleum ether. The organic solution was dried, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave ester **78** (9.8 g, 96% yield): ir (neat) 1722 (ester), and 1651 cm^{-1} (olefin); ^1H nmr δ6.98 (dt, 1H, J = 15, J' = 7 Hz, -CH=CHCOO-), 5.89 (d, 1H, J = 15 Hz, -CH=CHCOO-), 5.22 (s, 1H, =CH), 4.19 (q, 2H, J = 7 Hz, $-COOCH_2-$), 1.61 (br s, 3H, $=CCH_3$), 1.30 (t, 3H, J = 7 Hz, $-COOCH_2CH_3$), 1.00 (s, 3H, $-CH_3$); and 0.80 (s, 3H, $-CH_3$). ms M^+ 222.1622 (calcd. for $C_{14}H_{22}O_2$: 222.1620). Anal. [illegible]d. for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 7[illegible]39.

4-[illegible]oxy-2-ethoxypropyl)-1,5,5-trimethylcyclopent[illegible]5) and α,β-unsaturated ester **84**

At 0°C, to a solution of sodium ethoxide (0.20 g, prepared from 0.0087 g-atom of sodium) in ethanol (8 mL),

triethyl phosphonoacetate (1.30 mL, 6.56 mmol) was added slowly. After 15 min, aldehyde **72** (0.98 g, 6.48 mmol) was added slowly and the mixture stirred at room temperature under a nitrogen atmosphere for an additional 4 h. Saturated aqueous sodium chloride solution (75 mL) was added and the mixture extracted with n-hexane. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ether in petroleum ether, gave α,β-unsaturated ester **84** (1.15 g, 78% yield) identical with that obtained previously. Further elution with the same solvent system gave a mixture (~3:1) of two epimeric esters **85** (0.22 g, 12% yield): ir ($CHCl_3$ cast) 1737 (ester) and 1094 cm^{-1} (ether); ms M^+ 268.2033 (calcd. for $C_{16}H_{28}O_3$: 268.2038). The following ^1H nmr data were obtained for the major isomer: δ5.50 (br s, 1H, =CH), 4.16 (q, 2H, J = 7 Hz, $-COOCH_2-$), 3.76 (m, 1H, -CHO-), 3.54 (q, 2H, J = 7 Hz, $-CHOCH_2-$), 1.62 (br s, 3H, $=CCH_3$), 1.28 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), 1.19 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), 0.98 (t, 3H, $-CH_3$), and 0.77 (s, 3H, $-CH_3$). The following ^1H nmr data were obtained for the minor isomer: δ1.17 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), 0.99 (s, 3H, $-CH_3$), and 0.75 (s, 3H, $-CH_3$).

2-(3-Carbethoxypropyl)-1,1-5-trimethylcyclopentane (86)

To a solution of diene ester 84 (92 mg, 0.41 mmol) in ethyl acetate (2 mL), 5% Pd/C (9.2 mg) was added. After stirring under an atmosphere of hydrogen for 1 h, the reaction mixture was filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave ester 86 (90 mg, 96% yield): ir (neat) 1740 cm^{-1} (ester); ^1H nmr δ4.15 (q, 2H, J = 7 Hz, $-COOCH_2-$), 2.31 (br t, 2H, J = 7 Hz, $-CH_2COO-$), 1.32 (t, 3H, J = 7 Hz, $-COOCH_2\underline{CH_3}$), 0.87 (s, 3H, $-CH_3$), 0.84 (d, 3H, J = 6.5 Hz, $-HC\underline{CH_3}$), and 0.51 (s, 3H, $-CH_3$); ms M^+ 226.1930 (calcd. for $C_{14}H_{26}O_2$: 226.1933).

4-(3-Carbethoxypropyl)-1,5,5-trimethylcyclopentene (87)

Wilkinson's catalyst (20 mg, 0.022 mmol) and triethylsilane (371 mg, 3.2 mmol) were added to a solution of ester 84 (113 mg, 0.5 mmol) in benzene (3 mL). After stirring at room temperature under an argon atmosphere for 5 h, the reaction mixture was concentrated. The residue was subjected to column chromatography on silica gel. Elution with 5% ethyl acetate in petroleum ether gave ester 87 (101 mg, 89% yield): ir (neat) 1730 cm^{-1} (ester); ^1H nmr δ5.23 (br s, 1H, $=\underline{CH}$), 4.15 (q, 2H, J = 7 Hz, $-COOCH_2-$), 2.32 (t, 2H, J = 7 Hz, $-CH_2COO-$), 1.61 (br

s, 3H, $=CCH_3$), 1.27 (t, 3H, J = 7 Hz, $-COOCH_2\underline{CH_3}$), 0.98 (s, 3H, $-CH_3$), and 0.76 (s, 3H, $-CH_3$); ms M^+ 224.1778 (calcd. for $C_{14}H_{24}O_2$: 224.1776). Anal. calcd for $C_{14}H_{24}O_2$: C 74.95, H 10.78; found: C 74.88, H 10.88.

Ester 86 and ester 87

To a solution of ester 84 (122 mg, 0.55 mmol) in benzene (3 mL), sodium bicarbonate (46 mg, 0.55 mmol) and 5% Pd/C (6 mg) were added. After stirring under an atmosphere of hydrogen for 1.75 h, the mixture was filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave a 9:1 mixture of ester 87 and ester 86 (115 mg, 84% yield of 87 and 9% yield of 86).

5-(δ-Carbethoxypropyl)-2,3-epoxy-1,1,2-trimethylcyclopentane (89)

A solution of m-chloroperbenzoic acid (80-85% purity, 76.5 mg, ~0.48 mmol) in methylene chloride (5 mL) was added dropwise to a solution of ester 87 (90 mg, 0.40 mmol) in methylene chloride (5 mL) at room temperature. After the addition, the reaction mixture was stirred for 1.5 h under an argon atmosphere. A 10% aqueous sodium sulfite solution (5 mL) was added to the reaction mixture. The organic fraction was separated and washed

with 5% aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution. The organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether, gave epoxide **89** (80 mg, 83% yield): ir (CH_2Cl_2 cast) 1736 (ester), 1248, and 844 cm^{-1} (epoxide); ^1H nmr δ 4.10 (q, 2H, J = 7 Hz, $-COOCH_2-$), 3.21 (s, 1H, $-CHO-$), 2.26 (td, 2H, J = 7 Hz, J' = 2 Hz, $-CH_2COO-$), 1.29 (s, 3H, $-OCCH_3$), 1.23 (t, 3H, J = 7 Hz, $-COOCH_2\underline{CH_3}$), 0.97 (s, 3H, $-CH_3$), and 0.73 (s, 3H, $-CH_3$); ms M^+ 240.1728 (calcd. for $C_{14}H_{24}O_3$: 140.1723).

3-Carbethoxy-1,7-bis(3,4-epoxy-2,2,3-trimethylcyclopentyl)heptan-4-one (**91**)

A 1.43 M solution of methyllithium in ether (0.15 mL, 0.21 mmol) was added to a solution of diisopropylamine (0.04 mL, 0.29 mmol) in tetrahydrofuran (5 mL) at -78°C under an argon atmosphere. The mixture was stirred for 10 min and a solution of epoxide **89** (51 mg, 0.21 mmol) in tetrahydrofuran (2 mL) was added dropwise. After the addition, the mixture was allowed to warm up gradually to room temperature over a period of 10 h. The reaction mixture was poured into ice-cold water (10 mL) and extracted with methylene chloride. The organic extracts were washed with dilute hydrochloric acid solution and

saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave unreacted epoxide 89 (13 mg). Further elution with the same solvent system gave keto ester 91 (15 mg, 44% yield based on consumed starting material): ir (CH_2Cl_2 cast) 1741 (ester), 1715 (ketone), 1189, 1152, and 844 cm^{-1} (epoxides); ^1H nmr δ4.17 (q, 2H, J = 7 Hz, $-COOCH_2-$), 3.38 (t, 1H, J = 7 Hz, $-COCHCOO-$), 3.22 (br s, 2H, 2 × $-CHO-$), 1.32 (s, 6H, 2 × $-OCCH_3$), 1.26 (t, 3H, J = 7 Hz, $-COOCH_2CH_3$), 0.98 (s, 6H, 2 × $-CH_3$), and 0.73 (s, 6H, 2× $-CH_3$); ms M^+ 434.3039 (calcd. for $C_{26}H_{42}O_5$: 434.3032).

4-(3-Carbethoxypropyl)-3,3-dimethyl-2-methylidenecyclopentanol (93)

A solution of ester 87 (420 mg, 1.87 mmol) and methylene blue (20 mg) in ethanol (100 mL) was irradiated with two 200 W tungsten light bulbs for 24 h. During this period, a moderate stream of oxygen was bubbled through the solution. After cooling the solution at 0°C, sodium borohydride (72 mg, 1.90 mmol) was added and the mixture was stirred at 0°C under a nitrogen atmosphere for 20 min. The mixture was poured into ice-cold 1N aqueous hydrochloric acid solution (100 mL) and extracted with

methylene chloride. The organic extracts were dried, filtered, and concentrated to give the crude residue, which was chromatographed on silica gel. Elution with 25% ethyl acetate in petroleum ether afforded a ~7:3 mixture of epimeric alcohols **93** (292 mg, 65% yield): ir ($CHCl_3$ cast) 3410 (alcohol) and 1736 cm^{-1} (ester); ms M^+ 240.1719 (calcd. for $C_{14}H_{24}O_3$: 240.1726). The following ^1H nmr data were obtained for the major alcohol: ^1H NMR δ5.16, 5.00 (both d, 1H each, J = 2.5 Hz each, $=CH_2$), 4.55 (d, 1H, J = 7 Hz, -CHO-), 4.15 (q, 2H, J = 7 Hz, $-COOCH_2-$), 2.33 (br t, 2H, J = 7 Hz, $-CH_2COO-$), 1.28 (t, 3H, J = 7 Hz, $-COOCH_2\underline{CH_3}$), 1.15 (s, 3H, $-CH_3$), and 0.82 (s, 3H, $-CH_3$). The following ^1H nmr data were observed for the minor alcohol: ^1H nmr δ5.10, 4.90 (both d, 1H each, J = 3 Hz, $=CH_2$), 1.08 (s, 3H, $-CH_3$), and 0.90 (s, 3H, $-CH_3$).

4-(3-Carbethoxypropyl)-3,3-dimethyl-2-methylidenecyclopentanone (88)

At -78°C, to a solution of oxalyl chloride (0.98 mL, 11.4 mmol) in methylene chloride (20 mL), a solution of dimethyl sulfoxide (1.48 mL, 20.8 mmol) in methylene chloride (8 mL) was added dropwise under a nitrogen atmosphere. After the addition, the mixture was stirred for 15 min and a solution of epimeric alcohols **93** (2.84 g, 10.4 mmol) in methylene chloride (15 mL) was added

slowly. The mixture was allowed to warm up gradually to -10°C and triethylamine (12 mL) was added. After stirring at room temperature overnight, ice-cold water (30 mL) was added. The organic fraction was washed with water and saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Chromatography of the residue on silica gel, eluting with 8% ethyl acetate in petroleum ether, afforded enone **88** (1.79 g, 73% yield): ir ($CHCl_3$ cast) 1729 (ketone and ester) and 1630 cm^{-1} (olefin); ^1H nmr δ5.96, 5.21 (both s, 1H each, $=CH_2$), 4.16 (q, 2H, J = 7 Hz, $-COOCH_2-$), 2.54 (dd, 1H, J = 18, J' = 7 Hz, $-COCHH-$), 2.36 (br t, 2H, J = 7 Hz, $-CH_2COO-$), 2.06 (dd, 1H, J = 18, J' = 11 Hz, $-COCHH-$), 1.28 (t, 3H, J = 7 Hz, $-COOCH_2CH_3$), 1.24 (s, 3H, $-CH_3$), and 0.99 (s, 3H, $-CH_3$); ms M^+ 288.1569 (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 70.24, H 9.16.

Enone **88** from ester **87**

To a solution of ester **87** (3.01 g, 13.5 mmol) in methylene chloride (200 mL), acetic anhydride (1.34 mL, 14.2 mmol), pyridine (0.55 mL, 6.8 mmol), 4-dimethylaminopyridine (40 mg), and TPP (10 mg) were added and the solution was irradiated with two 200 W tungsten light bulbs for 24 h. During this period a moderate stream of

oxygen was bubbled through the solution. The solution was diluted with methylene chloride (50 mL) and extracted with saturated sodium bicarbonate solution, 1N hydrochloric acid solution, saturated aqueous cupric sulfate solution, and saturated aqueous sodium chloride solution. The organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 8% ethyl acetate in petroleum ether, gave enone **88** (2.06 g, 65% yield) identical with that obtained previously from alcohols **93**.

Preparation of 2-chloro-3-iodopropene

To a suspension of potassium iodide (302 g, 1.82 mol) in acetone (600 mL), 2,3-dichloropropene (41.5 mL, 0.45 mol) was added and the mixture was heated at reflux for 3 h. The reaction mixture was then filtered and the precipitate washed with acetone. The solvent was distilled at atmospheric pressure using a 10 cm Vigreaux column and the residual liquid was then distilled under reduced pressure (water aspirator). In this way 2-chloro-3-iodopropene (45 g, 49% yield) was obtained as a purple liquid: b.p. 25-30°C (ca. 15 torr).

5-[3-(3-Carbethoxypropyl)-2,2-dimethyl-5-oxocyclopentyl-methyl]-4-(3-carbethoxypropyl)-3,3-dimethyl-2-methylidene-cyclopentanone (95)

Potassium hydride (35% dispersion in oil, 11 mg, 0.96 mmol) was freed from the mineral oil by washing with petroleum ether (3 × 5 mL). At 0°C, to a suspension of the oil free potassium hydride in tetrahydrofuran (2 mL), a solution of enone **88** (152 mg, 0.64 mmol) in tetrahydrofuran (2 mL) was added slowly. After stirring for 5 min under a nitrogen atmosphere, a solution of 2-chloro-3-iodopropene (163 mg, 0.81 mmol) in tetrahydrofuran (2 mL) was added and the mixture was stirred at 0°C for 1 h and at room temperature for an additional hour. Ice-cold water and dilute hydrochloric acid solution were added and the mixture was extracted with ether. The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered, and evaporated. Flash chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave unreacted 2-chloro-3-iodopropene (153 mg). Elution with 8% ethyl acetate in petroleum ether gave unreacted enone **88** (20 mg). Further elution with 20% ethyl acetate in petroleum ether gave product **95** (24 mg, 26% yield based on consumed starting material): ir (CH_2Cl_2 cast) 1735 (br; ketones and esters) and 1640 cm^{-1} (olefin); ^1H nmr δ5.93, 5.18

(both s, 1H each, $=CH_2$), 4.15 (q, 4H, J = 7 Hz, 2 x $-COOCH_2-$); 1.28 (t, 6H, J = 7 Hz, 2 x $-COOCH_2\underline{CH_3}$), 1.26 (s, 3H, $-CH_3$), 1.18 (s, 3H, $-CH_3$), 1.03 (s, 3H, $-CH_3$), and 0.60 (s, 3H, $-CH_3$); ms M^+ 476.3130 (calcd. for $C_{28}H_{44}O_6$: 476.3138).

4-(3-Carbethoxypropyl)-3,3-dimethyl-2-(phenylthiomethyl)-cyclopentanone (98)

At 0°C, to a solution of enone **88** (0.22 g, 0.93 mmol) in tetrahydrofuran (8 mL), thiophenol (0.12 mL, 1.87 mmol) and sodium hydride (60% dispersion in oil, 5 mg, 0.12 mmol) were added and the mixture stirred at 0°C under a nitrogen atmosphere for 1 h. Ice-cold water and dilute hydrochloric acid solution were added and the mixture was extracted with ether. The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave product **98** (0.31 g, 94% yield): ir ($CHCl_3$ cast) 1735 cm^{-1} (ester); ^1H nmr δ7.30 (m, 5H, $-C_6H_5$), 4.14 (q, 2H, J = 7 Hz, $-COOCH_2-$), 3.33 (dd, 1H, J = 14, J' = 5 Hz, $-C\underline{H}HS-$), 2.78 (dd, 1H, J = 14, J' = 7 Hz, $-CH\underline{H}S-$), 1.27 (t, 3H, J = 7 Hz, $-COOCH_2\underline{CH_3}$), 1.25 (s, 3H, $-CH_3$), and 0.72 (s, 3H, $-CH_3$); ms M^+ 348.1756 (calcd. for $C_{20}H_{28}O_3S$: 348.1759).

1-Acetoxy-3-(3-carbethoxypropyl)-4,4-dimethyl-5-methylidenecyclopentene (105) and enone (88)

At -78°C, to a solution of ketone **98** (210 mg, 0.62 mmol) in methylene chloride (5 mL), a solution of *m*-chloroperbenzoic acid (161 mg, 0.93 mmol) in methylene chloride (10 mL) was added slowly. After 0.5 h the mixture was warmed to 0°C and 10% aqueous sodium sulfite solution was added. The mixture was extracted with methylene chloride. The organic extracts were washed with 5% aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution, dried, filtered, and concentrated to give crude sulfoxide **100** (213 mg). To a solution of sulfoxide **100** (213 mg, 0.53 mmol) in acetic anhydride (5 mL), sodium acetate (215 mg, 2.56 mmol) was added. After the mixture was refluxed under an atmosphere of argon for 7 h, the volatiles were removed under reduced pressure and the residue chromatographed on silica gel. Elution with 20% ether in benzene gave enol acetate **105** (58 mg, 33% yield): ir ($CHCl_3$ cast) 1770 (vinyl acetate) and 1735 cm^{-1} (ester); ^1H nmr δ 5.90 (br s, 1H, $-OC(=CH-)$), 4.84, 4.63 (both s, 1H each, $=CH_2$), 4.10 (q, 2H, J = 7 Hz, $-COOCH_2-$), 2.34 (m, 1H, $=CHCH-$), 2.29 (t, 2H, J = 7 Hz, $-CH_2COO-$), 2.19 (s, 3H, CH_3COO-), 1.22 (t, 3H, J = 7 Hz, $-COOCH_2CH_3$), 1.13 (s,

3H, $-CH_3$), and 0.99 (s, 3H, $-CH_3$); ms M^+ 280.1675 (calcd. for $C_{16}H_{24}O_4$: 280.1675). Further elution with the same solvent system gave enone **88** (51 mg, 35% yield) identical with that obtained previously from alcohols **93**.

4-(3-Carbethoxypropyl)-3,3-dimethyl-2-(N-pyrrolidinylmethyl)cyclopentanone (**106**)

To a solution of enone **88** (0.18 g, 0.74 mmol) in benzene (3 mL), pyrrolidine (0.25 mL, 2.96 mmol) was added. The mixture was stirred under an argon atmosphere for 19 h. Removal of the volatiles gave product **106** (0.29 g, 100% yield): ir ($CHCl_3$ cast) 1737 (ester) and 1695 cm^{-1} (ketone); ^1H nmr δ 4.14 (q, 2H, J = 7 Hz, $-COOCH_2-$), 2.45 (m, 4H, $-CH_2NCH_2-$), 1.25 (t, 3H, J = 7 Hz, $-COOCH_2\underline{CH_3}$), 1.22 (s, 3H, $-CH_3$), and 0.65 (s, 3H, $-CH_3$); ms M^+ 309.2306 (calcd. for $C_{18}H_{31}NO_3$: 309.2303).

5-(3-Carbethoxypropyl)-4,4-dimethyl-7-oxo-1-oxaspiro[2.4]heptane (**107**)

At 0°C, to a solution of enone **88** (0.70 g, 2.97 mmol) in ethanol (15 mL), hydrogen peroxide (30% aqueous solution; 0.28 mL, 8.93 mmol) and lithium hydroxide monohydrate (10 mg, 0.24 mmol) were added and the reaction mixture was stirred at 0°C for 1 h and at room temperature for 4 h. Ice-cold water and dilute hydrochloric acid

solution were added and the solution was extracted with methylene chloride. The organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether, gave one epoxide **107** (0.39 g, 52% yield): ir ($CHCl_3$ cast) 1752 (ketone), 1736 (ester), and 1187 cm^{-1} (epoxide); ^1H nmr δ 4.15 (q, 2H, J = 7 Hz, $-COOCH_2-$), 3.11, 2.79 (both d, 1H each, J = 6 Hz each, $-OCH_2-$), 2.35 (br t, 2H, J = 7 Hz, $-CH_2COO-$), 1.25 (t, 3H, J = 7 Hz, $-COOCH_2\underline{CH_3}$), 0.93 (s, 3H, $-CH_3$), and 0.94 (s, 3H, $-CH_3$); ms M^+ 254.1511 (calcd. for $C_{14}H_{22}O_4$: 254.1518). Further elution with the same solvent system gave the other epoxide **107** (0.26 g, 34% yield): ir ($CHCl_3$ cast) 1752 (ketone), 1733 (ester), and 1185 cm^{-1} (epoxide); ^1H nmr δ 4.16 (q, 2H, J = 7 Hz, $-COOCH_2-$), 2.97, 2.89 (both d, 1H each, J = 6.5 Hz each, $-OCH_2-$), 2.37 (br t, 2H, J = 7 Hz, $-CH_2COO-$), 1.27 (t, 3H, J = 7 Hz, $-COOCH_2\underline{CH_3}$), 0.96 (s, 3H, $-CH_3$), and 0.91 (s, 3H, $-CH_3$); ms M^+ 254.1515 (calcd. for $C_{14}H_{22}O_4$: 254.1518).

<u>4-(3-Carbethoxypropyl)-2-[(2-chloro-2-propenyloxy)-methylidene)]-3,3-dimethylcyclopentanone (**109**) and 4-(3-Carbethoxypropyl)-2-(hydroxymethylidene)-3,3-dimethyl-cyclopentanone (**108**)</u>

At 0°C, to a suspension of sodium hydride (50%

dispersion in oil; 21 mg, 0.43 mmol), freed from the mineral oil by washing with petroleum ether (3 × 5 mL), in benzene (2 mL), a solution of epoxides **107** (83 mg, 0.33 mmol) in benzene (1 mL) was added. After stirring for 5 min under a nitrogen atmosphere, a solution of 2-chloro-3-iodopropene (47 μL, 0.45 mmol) in benzene (1 mL) was added and the mixture was stirred at room temperature for 3 h and at reflux temperature for an additional 6 h. Ice-cold water and dilute hydrochloric acid solution were added and the mixture extracted with methylene chloride. The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered, and evaporated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether, gave β-hydroxy enone **108** (31 mg, 37% yield): ir ($CHCl_3$ cast) 1735 (ester), 1670 and 1600 cm^{-1} (β-hydroxy enone); ^1H nmr δ7.09 (s, 1H, $-C\underline{H}=$), 4.15 (q, 2H, J = 7 Hz, $-COOC\underline{H}_2-$), 2.50 (dd, 1H, J = 17.5, J' = 7.5 Hz, $-C\underline{H}HCO-$), 2.34 (br t, 2H, J = 7 Hz, $-CH_2COO-$), 2.12 (dd, 1H, J = 17.5, J' = 11 Hz, $-CH\underline{H}CO-$), 1.26 (t, 3H, J = 7 Hz, $-COOCH_2\underline{CH}_3$), 1.18 (s, 3H, $-CH_3$), and 0.98 (s, 3H, $-CH_3$); ms M^+ 254.1522 (calcd. for $C_{14}H_{22}O_4$: 254.1518). Further elution with the same solvent system gave compound **109** (20 mg, 18% yield): ir ($CHCl_3$ cast) 1735 (ester and ketone) and 1630 cm^{-1} (olefin); ^1H nmr δ7.13 (s, 1H, =CHO-), 5.47,

5.45 (both br s, 1H each, $=CH_2$), 4.49 (s, 2H, $-CH_2C=$), 4.14 (q, 2H, J = 7 Hz, $-COOCH_2-$), 1.34 (s, 3H, $-CH_3$), 1.26 (t, 3H, J = 7 Hz, $-COOCH_2\underline{CH_3}$), and 1.04 (s, 3H, $-CH_3$); ms M^+ 328.1445 and 330.1425 (calcd. for $C_{17}H_{25}ClO_4$: 328.1441 and 330.1412).

β-Hydroxy enone **108**

At 0°C, to a suspension of sodium hydride (60% oil dispersion; 41 mg, 1.02 mmol) in benzene (5 mL), a solution of epoxides **107** (~3:2 ratio; 129 mg, 0.51 mmol) in benzene (2 mL) was added. After the mixture was heated to reflux under an argon atmosphere for 6 h, ice-cold water and dilute hydrochloric acid solution were added and the mixture was extracted with methylene chloride. The combined organic extracts were dried, filtered, and concentrated to give product **108** (105 mg, 81% yield) identical with that obtained previously.

4-(3-Carbethoxy-5-chloro-5-hexenyl)-2-(hydroxymethylidene)-3,3-dimethylcyclopentanone (**111**) and 4-[3-Carbethoxy-5-chloro-3-(2-chloro-2-propenyl)-5-hexenyl]-2-(hydroxymethylene)-3,3-dimethylcyclopentanone (**112**)

At -78°C a solution of diisopropylamine (0.53 mL, 3.74 mmol) in tetrahydrofuran (3 mL) was treated with n-butyllithium (1.6 N in hexanes, 1.12 mL, 1.80 mmol). The

solution was stirred under an atmosphere of argon for 5 min at -78°C, 10 min at 0°C, cooled again to -78°C and treated with a solution of β-hydroxy enone **108** (0.19 g, 0.75 mmol) in tetrahydrofuran (1 mL). After 45 min the temperature was raised to -60°C and 3-iodo-2-chloropropene (0.21 mg, 1.02 mmol) was added. The resulting solution was stirred at -30°C for 10 h, diluted with water and acidified with dilute hydrochloric acid solution. The mixture was extracted with methylene chloride. The organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether, gave an epimeric mixture of products **111** in ca. 1:1 ratio (102 mg, 31% yield): ir ($CHCl_3$ cast) 1730 (ester), 1670, and 1600 cm^{-1} (β-hydroxy enone); ^1H nmr δ 7.09 (s, total 1H, -OCH=), 5.23, 5.20 (both s, total 2H, $=CH_2$), 4.17 (q, total 2H, J = 7 Hz, $-COOCH_2-$), 2.70 (m, total 2H, $=C(Cl)CH_2-$), 1.26 (t, total 3H, J = 7 Hz, $-COOCH_2\underline{CH_3}$), 1.25, 1.17 (both s, total 3H, $-CH_3$), 0.98, and 0.97 (both s, total 3H, $-CH_3$); ms M^+ 330.1418 and 328.1440 (calcd. for $C_{17}H_{25}ClO_4$: 330.1412 and 328.1441). Further elution with the same solvent system gave a mixture of products **111** and the dialkylated product **112** (40 mg) in about 1:1:1 ratio. ms M^+ 406.1322, 404.1343 and 402.1370 (calcd. for

$C_{20}H_{28}Cl_2O_4$: 406.1355, 404.1335, and 402.1365); also M^+ 330.1419 and 328.1441 (calcd. for $C_{17}H_{25}ClO_4$: 330.1412 and 328.1441). The following ^1H nmr data were observed for the dialkylated product **112**: δ7.14 (s, 1H, -OCH=), 5.30 (m, 4H, 2 x CH_2=), 4.17 (q, 2H, J = 7 Hz, -$COOCH_2$-), 1.26 (t, 3H, J = 7 Hz, -$COOCH_2CH_3$), 1.22 (s, 3H, -CH_3), and 1.04 (s, 3H, -CH_3).

3-(3-Carbethoxypropyl)-4,5,5-trimethyl-2-cyclopentenone (115)

A solution of enone **88** (42.1 mg, 0.18 mmol) in 4 N aqueous hydrochloric acid solution (4 mL) was refluxed for 6 h. The solution was allowed to cool to room temperature, diluted with water (5 mL), and extracted with methylene chloride. The organic extracts were dried, filtered, and concentrated. The residue was disolved in acetone (3 mL) and anhydrous potassium carbonate (37.3 mg, 0.25 mmol) was added. After stirring at room temperature under an argon atmosphere for 1 h, ethyl iodide (0.28 mL, 3.53 mmol) was added and the mixture was stirred for an additional 12 h. After most of the solvent had been evaporated, the mixture was taken up in methylene chloride (8 mL) and washed with dilute hydrochloric acid solution, water, and saturated aqueous sodium chloride solution. The organic layer was dried, filtered, and concentrated.

Flash chromatography of the residue on silica gel, eluting with 8% ethyl acetate in petroleum ether, gave keto ester **115** (31 mg, 72% yield): ir ($CHCl_3$ cast) 1735 (ester), 1706 (ketone), and 1615 cm^{-1} (olefin); ^1H nmr δ5.88 (br s, 1H, =CH), 4.16 (q, 2H, J = 7 Hz, $-COOCH_2-$), 2.38 (q, 4H, J = 7 Hz, $=CCH_2CH_2CH_2COO-$), 2.18 (q, 1H, J = 7 Hz, $-CHCH_3$), 1.27 (t, 3H, J = 7 Hz, $-COOCH_2CH_3$), 1.19 (s, 3H, $-CH_3$), 1.08 (d, 3H, J = 7 Hz, $-CHCH_3$), and 1.00 (s, 3H, $-CH_3$); ms M^+ 238.1569 (calcd. for $C_{14}H_{22}O_3$: 238.1569).

4-(3-Carboxypropyl)-3,3-dimethylcyclopentanone (**116**)

From β-hydroxy enone **108**

A solution of β-hydroxy enone **108** (45 mg, 0.18 mmol) and sodium hydroxide pellets (0.90 g, 22.5 mmol) in water (4 mL) was refluxed for 36 h. The solution was allowed to cool to room temperature, acidified with 6 N hydrochloric acid solution, and extracted with methylene chloride. The organic extracts were dried, filtered, and concentrated to give acid **116** (29 mg, 83% yield): ir (neat) 3280-2600, 1708 (acid), and 1739 cm^{-1} (ketone); ^1H nmr δ2.41 (m, 2H, $-CH_2COO-$), 2.13 (s, 2H, $-CCH_2CO-$), 1.15 (s, 3H, $-CH_3$), and 0.87 (s, 3H, $-CH_3$); ms M^+ 198.1253 (calcd. for $C_{11}H_{18}O_3$: 198.1256).

From epoxides **107**

A solution of epoxides **107** (ca. 3:2 mixture, 1.13 g,

4.45 mmol) and sodium hydroxide pellets (0.98 g, 24.5 mmol) in ethanol (30 mL) was refluxed for 12 h. Water (15 mL) was added and reflux was continued for an additional 60 h. The solution was allowed to cool to room temperature, acidified with 6 N hydrochloric acid solution, and extracted with methylene chloride. The organic extracts were dried, filtered, and concentrated to give acid 116 (0.61 g, 80% yield).

4-(3-Carbomethoxypropyl)-3,3-dimethylcyclopentanone (117)

To a solution of crude acid 116 (0.61 g, 3.08 mmol) in acetone (50 mL), anhydrous potassium carbonate (0.98 g, 7.13 mmol) was added. After stirring at room temperature under an argon atmosphere for 1 h, methyl iodide (1.5 mL, 24.1 mmol) was added and the mixture stirred for an additional 18 h. After most of the solvent had been evaporated, the mixture was taken up in methylene chloride (50 mL) and washed with ice-cold dilute hydrochloric acid solution, water, and saturated aqueous sodium chloride solution. The organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave keto ester 117 (0.43 g, 46% yield from epoxides 107): ir ($CHCl_3$ cast) 1741 cm^{-1} (ester and ketone); ^1H nmr δ 3.67 (s, 3H, $-COOCH_3$), 2.38 (dd, 1H, J =

17, J' = 11 Hz, -CHCHHCO-), 2.35 (m, 2H, -CH_2COO-), 2.12 (s, 2H, -CCH_2CO-), 2.00 (dd, 1H, J = 17, J' = 5.5 Hz, -CHCHHCO-), 1.12 (s, 3H, -CH_3), and 0.86 (s, 3H, -CH_3); ms M^+ 212.1408 (calcd. for $C_{12}H_{20}O_3$: 212.1412 .

3-(3-Carbomethoxypropyl)-2-(2-chloro-2-propenyl)-4,4-dimethylcyclopentanone (118) and 4-(3-Carbomethoxypropyl)-2-(2-chloro-2-propenyl)-3,3-dimethylcyclopentanone (119)

Sodium hydride (50% oil dispersion, 17.1 mg, 0.36 mmol) was washed with 1,2-dimethoxyethane (3 × 2 mL) at 0°C, to a suspension of the oil free sodium hydride in 1,2-dimethoxyethane (3 mL) under an argon atmosphere, a solution of keto ester 117 (63 mg, 0.30 mmol) in 1,2-dimethoxyethane (1 mL) and 2-chloro-3-iodopropene (72.6 mg, 0.36 mmol) were added. The solution was stirred at 0°C for 1.5 h and at room temperature for 18 h. The mixture was poured into ice-cold water, acidified with dilute aqueous hydrochloric acid solution, and extracted with methylene chloride. The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 8% ethyl acetate in petroleum ether, gave a mixture of alkylated products 118 and 119 in a 3:1 ratio respectively (10 mg, 16% yield based on consumed starting material):

ir ($CHCl_3$ cast) 1740 (ester and ketone) and 1630 cm^{-1} (olefin); ms M^+ 288.1306 and 286.1332 (calcd. for $C_{15}H_{23}ClO_3$: 288.1306 and 286.1336). The following nmr data were assigned to the major product **118**: ^1H nmr δ5.22 (s, 2H, $=CH_2$), 3.65 (s, 3H, $-COOCH_3$), 2.69 (d, 2H, J = 6 Hz, $=\overset{|}{C}CH_2-$), 2.36 (m, 1H, $-\overset{|}{C}HCO-$), 2.34 (t, 2H, J = 7 Hz, $-CH_2COO-$), 2.18 (s, 2H, $-\overset{|}{C}CH_2CO-$), 1.18 (s, 3H, $-CH_3$), and 0.90 (s, 3H, $-CH_3$). The following nmr data were assigned to the minor product **119**: ^1H nmr δ5.29 (s, 2H, $=CH_2$), 1.16 (s, 3H, $-CH_3$), and 0.64 (s, 3H, $-CH_3$). Further elution with 10% ethyl acetate in petroleum ether gave unreacted keto ester **117** (17 mg).

7-(3-Carbomethoxypropyl)-8,8-dimethyl-bicyclo[4.3.0]non-1-en-3-one (**120**) and 8-(3-Carbomethoxypropyl)-7,7-dimethyl-bicyclo[4.3.0]non-1-en-3-one (**122**)

To a solution of keto ester **117** (84.3 mg, 0.40 mmol) in benzene (5 mL), pyrrolidine (0.4 mL, 4.79 mmol) and p-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) were added. After refluxing the mixture under an argon atmosphere with azeotropic removal of water-benzene for 5 h, the solvent and the excess of pyrrolidine were removed by distillation. The residue was further dried in vacuo for 2 h. To a solution of the residue in dioxane (3 mL), methyl vinyl ketone (34 μL, 0.42 mmol) was added and the

solution heated at 80-90°C (oil bath temperature) under an argon atmosphere for 5 h. Water (1 mL) was added and the mixture was kept at the same temperature for an additional 14 h. After cooling to 0°C, ice-cold water was added and the mixture was extracted with ether. The combined organic extracts were washed with 1 N hydrochloric acid solution, saturated aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution. The organic layer was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave unreacted keto ester **117** (13 mg). Further elution with 20% ethyl acetate in petroleum ether gave a mixture of compounds **120**, **122**, and two unidentified compounds (58 mg): ms M^+ 316.2051 (calcd. for $C_{20}H_{28}O_3$: 316.2039) and 264.1735 (calcd. for $C_{16}H_{24}O_3$: 264.1724). Molecular distillation of this material in a Kugelrohr apparatus (80°C, 0.5 torr) gave a mixture of compounds **120** and **122** (3:2 ratio, 34 mg, 38% yield based on consumed starting material): ir ($CHCl_3$ cast) 1738 (ester), 1667 (ketone), and 1640 cm^{-1} (olefin); ms M^+ 264.1725 (calcd. for $C_{16}H_{24}O_3$: 264.1725). The following nmr data were assigned to the major compound **120**: ^1H nmr δ 5.84 (s, 1H, =CH), 3.71 (s, 3H, $-COOCH_3$), 2.35 (t, 2H, J = 7 Hz, $-CH_2COO-$), 1.12 (s, 3H, $-CH_3$), and 0.93 (s, 3H, $-CH_3$). The following nmr data were assigned

to the minor compound 122: ^{1}H nmr δ 5.98 (s, 1H, =CH), 1.06 (s, 3H, $-CH_3$), and 0.57 (s, 3H, $-CH_3$).

7-(3-Carbomethoxypropyl)-1-hydroxy-8,8-dimethyl-bicyclo[4.3.0]nonan-3-one (124)

To a solution ~~of keto~~ keto ester 117 (115 mg, 0.54 mmol) in benzene (5 mL), pyrrolidine (0.5 mL, 5.98 mmol) and p-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) were added. After refluxing the mixture under an atmosphere of argon with azeotropic removal of water-benzene for 5 h, the solvent and excess of pyrrolidine were removed by distillation. The residue was further dried in vacuo for 2 h. To a solution of the residue in dioxane (4 mL), methyl vinyl ketone (45 μL, 0.55 mmol) was added and the solution stirred at room temperature under an argon atmosphere for 12 h. Water (1 mL) was added and the mixture was stirred for an additional 12 h. The mixture was poured into ice-cold water and extracted with ether. The combined organic extracts were washed with 1 N hydrochloric acid solution, saturated aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution. The organic layer was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave unreacted keto ester 117 (13.5 mg). Further

elution with 50% ethyl acetate in petroleum ether gave alcohol **124** (26 mg, 19% yield based on consumed starting material): ir ($CHCl_3$ cast) 3500-3400 (alcohol), 1737 (ester), and 1718 cm^{-1} (ketone); ^1H nmr δ3.68 (s, 3H, $-COOCH_3$), 2.52 (s, 2H, $-COCH_2COH$), 1.16 (s, 3H, $-CH_3$), and 1.02 (s, 3H, $-CH_3$); ms M^+ 282.1830 (calcd. for $C_{16}H_{26}O_4$: 282.1830).

Bicyclic enone **120** from bicyclic alcohol **124**

To a solution of bicyclic alcohol **124** (26 mg, 0.09 mmol) in benzene (2 mL), d,l-10-camphorsulfonic acid monohydrate (5 mg, 0.02 mmol) was added. The mixture was refluxed with azeotropic removal of water-benzene for 6 h. The solution was allowed to cool to room temperature, poured into ice-cold water, and extracted with ether. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether, gave bicyclic enone **120** (23 mg, 96% yield) identical with that obtained previously from keto ester **117**.

α-Campholenic acid (**129**)

To the fused potassium hydroxide (40 g, 0.72 mol) in a porcelain casserole, was added slowly with stirring d,l-

10-camphorsulfonic acid (**76**) sodium salt (50 g, 0.19 mol). After the completion of the addition (ca. 20 min), the molten mass was allowed to cool to room temperature and then dissolved in water (350 mL). The resulting solution was extracted with ether and the aqueous fraction acidified with 6 N hydrochloric acid solution. The acidified solution was extracted with methylene chloride. The combined organic extracts were dried, filtered, and concentrated. The crude residue was distilled to give acid **129** (24.7 g, 77% yield): b.p. 90-91°C/0.4 torr; ir ($CHCl_3$ cast) 3200-2500 and 1709 cm^{-1} (acid); ^1H nmr δ5.24 (br s, 1H, =CH-), 1.60 (br s, 3H, $=CCH_3$), 1.02 (s, 3H, $-CH_3$), and 0.82 (s, 3H, $-CH_3$); ms M^+ 168.1149 (calcd. for $C_{10}H_{16}O_2$: 168.1151). Anal. calcd. for $C_{10}H_{16}O_2$: C 71.39, H 9.59; found: C 71.38, H 9.69.

Methyl α-campholenate (**130**)

To a solution of campholenic acid (**129**) (7.56 g, 45 mmol) in acetone (75 mL), anhydrous potassium carbonate (12.4 g, 89 mmol) was added. After stirring at room temperature under an argon atmosphere for 1 h methyl iodide (5.6 mL, 90 mmol) was added and the mixture stirred for an additional 18 h. After most of the solvent had been removed, the mixture was taken up in methylene chloride (75 mL) and washed with ice-cold 1 N hydrochloric

acid solution, water, and saturated aqueous sodium chloride solution. The organic fraction was dried, filtered, and concentrated. The residue was distilled to afford ester **130** (7.85 g, 96% yield): b.p. 76-78°C/0.6 torr; ir 1745 cm^{-1} (ester); ^1H nmr δ5.25 (br s, 1H, $=CH$), 3.70 (s, 3H, $-COOCH_3$), 1.63 (m, 3H, $=CCH_3$), 1.02 (s, 3H, $-CH_3$), and 0.80 (s, 3H, $-CH_3$); ms M^+ 182.1308 (calcd. for $C_{11}H_{18}O_2$: 182.1307).

4-Carbomethoxymethyl-3,3-dimethyl-2-methylidenecyclopentanone (**131**)

To a solution of ester **130** (2.79 g, 15.4 mmol) in methylene chloride (200 mL), acetic anhydride (1.53 mL, 16.2 mmol), pyridine (0.62 mL, 7.7 mmol), 4-dimethylaminopyridine (30 mg), and TPP (10 mg) were added. The solution was irradiated with two 200 W tungsten light bulbs for 26 h. During this period a moderate stream of oxygen was bubbled through the solution. The solution was diluted with methylene chloride (50 mL) and extracted with saturated aqueous sodium bicarbonate solution, 1 N hydrochloric acid solution, saturated aqueous cupric sulfate solution, and saturated aqueous sodium chloride solution. The organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 7% ethyl acetate in petroleum

ether, gave enone **131** (1.97 g, 65% yield): ir (CH_2Cl_2 cast) 1728 cm^{-1} (ketone and ester); ^1H nmr δ6.00, 5.24 (both s, 1H each, $=CH_2$), 3.71 (s, 3H, $-COOCH_3$), 1.26 (s, 3H, $-CH_3$), and 1.04 (s, 3H, $-CH_3$); ms M^+ 196.1100 (calcd. for $C_{11}H_{16}O_3$: 196.1099). Anal. calcd. for $C_{11}H_{16}O_3$: C 67.32, H 8.28; found: C 67.08, H 8.13.

5-Carbomethoxymethyl-4,4-dimethyl-7-oxo-1-oxaspiro[2.4]-heptane (**132**)

At 0°C, to a solution of enone **131** (2.11 g, 11 mmol) in methanol (30 mL), hydrogen peroxide (30% aqueous solution, 2.81 mL, 28 mmol) and lithium hydroxide monohydrate (50 mg, 1.2 mmol) were added and the reaction mixture was stirred at room temperature under an atmosphere of argon for 3 h. Ice-cold water and diluted hydrochloric acid solution were added and the solution was extracted with methylene chloride. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 25% ethyl acetate in petroleum ether, gave one epoxide **132** (1.05 g, 46% yield): ir ($CHCl_3$ cast) 1752 (ketone) and 1737 cm^{-1} (ester); ^1H nmr δ3.72 (s, 3H, $-COOCH_3$), 3.16, 2.85 (both d, 1H each, J = 6 Hz each, $-OCH_2-$), 1.03 (s, 3H, $-CH_3$), and 0.99 (s, 3H, $-CH_3$); ms M^+ 212.1043 (calcd. for $C_{11}H_{16}O_4$: 212.1049). Anal. calcd. for $C_{11}H_{16}O_4$: C

62.23, H 7.60; found: C 62.19, H 7.66. Further elution with the same solvent system gave the other epoxide **132** (0.99 g, 43% yield): ir ($CHCl_3$ cast) 1748 (ketone) and 1730 cm^{-1} (ester); ^1H nmr δ3.72 (s, 3H, $-COOCH_3$), 3.00, 2.94 (both d, 1H each, J = 6 Hz, $-OCH_2-$), 1.00 (s, 3H, $-CH_3$), and 0.96 (s, 3H, $-CH_3$); ms M^+ 212.1046 (calcd. for $C_{11}H_{16}O_4$: 212.1049).

4-Carboxymethyl-3,3-dimethylcyclopentanone (**133**)

A solution of epoxides **132** (ca. 1:1 mixture, 835 mg, 3.94 mmol) and sodium hydroxide pellets (500 mg, 12.5 mmol) in methanol (15 mL) was refluxed for 12 h. Water (5 mL) was added and reflux was continued for an additional 68 h. The solution was allowed to cool to room temperature, acidified with 6 N hydrochloric acid solution, and extracted with methylene chloride. The organic extracts were dried, filtered, and concentrated giving acid **133** (433.5 mg, 65% yield): ir ($CHCl_3$ cast) 3500-2500 (acid), 1737 (ketone), and 1709 cm^{-1} (acid); ^1H nmr δ9.7-9.2 (br s, 1H, -COOH), 2.18 (s, 2H, $-COCH_2\overset{|}{C}-$), 1.22 (s, 3H, $-CH_3$), and 0.94 (s, 3H, $-CH_3$); ms M^+ 170.0940 (calcd. for $C_9H_{14}O_3$: 170.0943).

4-Carbomethoxymethyl-3,3-dimethylcyclopentanone (128)

Using potassium carbonate and methyl iodide

To a solution of acid 133 (628 mg, 3.69 mmol) in acetone (15 mL), anhydrous potassium carbonate (1.02 g, 7.39 mmol) was added. The mixture was stirred at room temperature under an argon atmosphere for 1 h and methyl iodide (4.6 mL, 73.88 mmol) was added. After a gentle reflux overnight, the reaction mixture was poured into ice-cold water and extracted with methylene chloride. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 12% ethyl acetate in petroleum ether gave keto ester 128 (390 mg, 58% yield): ir (neat) 1736 cm^{-1} (ketone and ester); ^1H nmr δ 3.70 (s, 3H, $-COOCH_3$), 2.16 (s, 2H, $-COCH_2\overset{|}{C}-$), 1.18 (s, 3H, $-CH_3$), and 0.92 (s, 3H, $-CH_3$); ms M^+ 184.1104 (calcd. for $C_{10}H_{16}O_3$: 184.1099). Anal. calcd. for $C_{10}H_{16}O_3$: C 65.19, H 8.75; found: C 65.22, H 8.66.

Using hydrochloric acid in methanol.

Hydrochloric acid gas was bubbled through a solution of acid 133 (368 mg, 2.16 mmol) in methanol (8 mL) for 5 min. After stirring at room temperature under an argon atmosphere for 8 h, the reaction mixture was poured into ice-cold water and extracted with ether. The organic extracts were dried, filtered, and concentrated. Flash

chromatography of the residue on silica gel, eluting with 12% ethyl acetate in petroleum ether gave keto ester **128** (301 mg, 76% yield).

7-Carbomethoxymethyl-8,8-dimethylbicyclo[4.3.0]non-1-en-3-one (**127**) and 8-Carbomethoxymethyl-7,7-dimethylbicyclo-[4.3.0]non-1-en-3-one (**135**)

To a solution of keto ester **128** (101 mg, 0.51 mmol) in benzene (5 mL), pyrrolidine (0.5 mL, 6 mmol) and p-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) were added. After refluxing the mixture using a Dean-Stark apparatus for 5 h under an argon atmosphere, the solvent and the excess of pyrrolidine were removed by distillation. The residue was further dried in vacuo for 2 h. To a solution of the residue in dioxane (3 mL), methyl vinyl ketone (41 μL, 0.51 mmol) was added and the solution heated at 80-90°C (oil bath temperature) under an argon atmosphere for 5 h. Water (1 mL) was added and the mixture was kept at the same temperature for an additional 14 h. After cooling at 0°C, ice-cold water was added and the mixture extracted with ether. The combined organic extracts were washed with 1 N hydrochloric acid solution, saturated aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution. The organic solution was dried, filtered, and concentrated. Flash

chromatography of the residue on silica gel, eluting with 8% ethyl acetate in petroleum ether gave unreacted keto ester **128** (20 mg). Further elution with 20% ethyl acetate in petroleum ether gave a mixture of compounds **127**, **135**, and two unidentified compounds (75:15:6:3.5 respectively by nmr and gc analyses; 43.4 mg, 31% yield of compound **127** based on unrecovered starting material); ir ($CHCl_3$ cast) 1737 (ester), 1667 (ketone), and 1635 cm^{-1} (olefin); ms M^+ 288.1730 (calcd. for $C_{18}H_{24}O_3$: 288.1725) and 236.1419 (calcd. for $C_{14}H_{20}O_3$: 236.1412). The following nmr data were obtained for compound **127**: ^1H nmr δ5.87 (br s, 1H, =CH-), 3.72 (s, 3H, $-COOCH_3$), 1.21 (s, 3H, $-CH_3$), and 0.94 (s, 3H, $-CH_3$). The following nmr data were obtained for compound **135**: ^1H nmr δ5.92 (br s, 1H, =CH-), 3.71 (s, 3H, $-COOCH_3$), 1.20 (s, 3H, $-CH_3$), and 0.62 (s, 3H, $-CH_3$).

6-Carbomethoxymethyl-7,7-dimethyl-11-methylidenetricyclo-[7.2.0.0^{5,9}]undecan-2-one (**137**) and 7-Carbomethoxymethyl-6,6-dimethyl-11-methylidenetricyclo[7.2.0.0^{5,9}]undecan-2-one (**138**)

At -78°C, allene (ca. 2 mL) was condensed into a 25 mL three necked round-bottomed flask. A solution of enones **127** and **135** (ca. 90%; 98 mg, 0.37 mmol) in tetrahydrofuran (4 mL) was added. The resulting mixture was irradiated with a 450 W Hanovia high-pressure quartz

mercury vapor lamp for 9 h at -20°C. After removal of the solvent, the residue was subjected to flash chromatography on silica gel. Elution with 7% ethyl acetate in petroleum ether gave adducts **137** and **138** (ca. 5:1 respectively by nmr analysis; 72 mg, 70% yield): ir ($CHCl_3$ cast) 1737 (ester), 1707 (ketone), and 1670 cm^{-1} (olefin); ms M^+ 276.1728 (calcd. for $C_{17}H_{24}O_3$: 276.1725). The following nmr data were obtained for adduct **137**: ^1H nmr δ4.90, 4.85 (both ddd, 1H each, J = 2.5, J' = 2.5, J" = 2.5 Hz each, $=CH_2$), 3.73 (s, 3H, $-COOCH_3$), 3.34 (dd, 1H, J = 6, J' = 2.5 Hz, $-\underline{C}HC=$), 2.95 (ddd, 1H, J = 16, J' = 2.5, J" = 2.5 Hz, $-C\underline{H}HC=$), 2.70 (ddd, 1H, J = 16, J' = 6, J" = 2.5 Hz, $-CH\underline{H}C=$), 1.82, 1.79 (both d, 1H each, J = 14 Hz each, $-\overset{|}{\underset{|}{C}}CH_2\overset{|}{\underset{|}{C}}-$), 1.03 (s, 3H, $-CH_3$), and 0.90 (s, 3H, $-CH_3$). The following nmr data were assigned to adduct **138**: ^1H nmr δ4.93, 4.89 (both ddd, 1H each, J = 2.5, J' = 2.5, J" = 2.5 Hz each, $=CH_2$), 1.08 (s, 3H, $-CH_3$), and 0.73 (s, 3H, $-CH_3$).

1,7-Bis(carbomethoxymethyl)-8,8-dimethylbicyclo[4.3.0]-nonan-3-one (**126**) and 1,8-Bis(carbomethoxymethyl)-7,7-dimethylbicyclo[4.3.0]nonan-3-one (**139**)

At -78°C, a stream of ozone-oxygen gas was allowed to pass through a methylene chloride-methanol (1:1, 7 mL) solution of photoadducts **137** and **138** (30 mg, 0.11 mmol)

until a light blue color was retained. The reaction mixture was purged with argon to remove the excess ozone and methyl sulfide (0.2 mL) was added at 0°C. After stirring at room temperature for 5 h, the mixture was concentrated under reduced pressure. The residue was partitioned in methylene chloride and water. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 25% ethyl acetate in petroleum ether, gave the diesters **126** and **139** (ca. 5:1 respectively by nmr analysis; 23 mg, 68% yield): ir ($CHCl_3$ cast) 1735 (ester) and 1716 cm^{-1} (ketone); ms M^+ 310.1782 (calcd. for $C_{17}H_{26}O_5$: 310.1780). The following nmr data were obtained for diester **126**: ^1H nmr δ 3.70 (s, 3H, $-COOCH_3$), 3.68 (s, 3H, $-COOCH_3$), 1.83, 1.80 (both d, 1H each, J = 14 Hz each, $-\overset{|}{\underset{|}{C}}CH_2\overset{|}{\underset{|}{C}}-$), 1.03 (s, 3H, $-CH_3$), and 0.92 (s, 3H, $-CH_3$). The following nmr data were obtained for diester **139**: ^1H nmr δ 3.72 (s, 3H, $-COOCH_3$), 3.70 (s, 3H, $-COOCH_3$), 1.07 (s, 3H, $-CH_3$), and 0.77 (s, 3H, $-CH_3$).

1,7-Bis(carbomethoxymethyl)-3,3-ethylenedithio-8,8-dimethylbicyclo[4.3.0]octane (**140**) and 1,8-Bis(carbomethoxymethyl)-3,3-ethylenedithio-7,7-dimethylbicyclo[4.3.0]octane (**141**)

At 0°C, to a solution of diesters **126** and **139** (ca.

5:1 mixture, 22 mg, 0.06 mmol) in methylene chloride (2 mL) were sequentially added 1,2-ethanedithiol (11 μL, 0.13 mmol) and boron trifluoride etherate (9 μL, 0.07 mmol). After stirring under an argon atmosphere for 1 h, ice-cold 10% aqueous sodium carbonate solution was added and the resulting mixture extracted with methylene chloride. The organic extracts were washed with water, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave a ca. 5:1 mixture of thioketals **140** and **141** (22 mg, 31% yield): ir ($CHCl_3$ cast) 1737 cm^{-1} (esters); ms M^+ 386.1588 (calcd. for $C_{19}H_{30}S_2O_4$: 386.1583). The following nmr data were attributed to thioketal **140**: ^1H nmr δ3.67 (s, 3H, $-COOCH_3$), 3.65 (s, 3H, $-COOCH_3$), 3.28 (m, 4H, $-SCH_2CH_2S-$), 1.06 (s, 3H, $-CH_3$), and 0.83 (s, 3H, $-CH_3$). The following nmr data were obtained for thioketal **141**: ^1H nmr δ0.94 (s, 3H, $-CH_3$), and 0.74 (s, 3H, $-CH_3$).

α-Campholenic alcohol (**81**) from α-campholenic acid (**129**)

At 0°C, to a suspension of lithium aluminum hydride (8.38 g, 0.22 mol) in tetrahydrofuran (400 mL), was added dropwise a solution of acid **129** (30.4 g, 0.18 mol) in tetrahydrofuran (100 mL). After the completion of the addition (ca. 1 h), the reaction mixture was allowed to warm up to room temperature and was stirred overnight

under an atmosphere of argon. The mixture was cooled to 0°C and treated successively with water (8.2 mL), 15% aqueous sodium hydroxide solution (8.2 mL), and again with water (24.6 mL). After stirring for 10 min, the inorganic salt was removed by filtration. Concentration of the filtrate and distillation of the crude product gave alcohol **81** (25.9 g, 93% yield) identical with that obtained previously from α-campholenic aldehyde (**72**).

4-(2-Methoxyethyl)-1,5,5-trimethylcyclopentene (**146**)

At 0°C, to a suspension of sodium hydride (60% dispersion in oil, 11.8 g, 0.30 mol) in tetrahydrofuran (800 mL), a solution of alcohol **81** (30.4 g, 0.20 mol) in tetrahydrofuran (50 mL) was added dropwise. After stirring for 0.5 h, a solution of dimethyl sulfate (28.01 mL, 0.30 mol) in tetrahydrofuran (25 mL) was added slowly and the reaction mixture was refluxed for 12 h. The mixture was allowed to cool to room temperature and 1 N sodium hydroxide solution (30 mL) was added. After stirring at room temperature overnight, the reaction mixture was diluted with ice-cold water, acidified with dilute aqueous hydrochloric acid solution, and extracted with ether. The organic extracts were dried, filtered, and concentrated. Distillation of the crude product gave ether **146** (30.2 g, 91% yield): b.p. 39°C/0.5 torr; ir

($CHCl_3$ cast) 1460 (olefin) and 1118 cm^{-1} (ether); ^1H nmr δ5.25 (br s, 1H, $=CH$), 3.45 (m, 2H, $-CH_2O-$), 3.38 (s, 3H, $-OCH_3$), 1.62 (br s, 3H, $=CCH_3$), 1.00 (s, 3H, $-CH_3$), and 0.80 (s, 3H, $-CH_3$); ms M^+ 168.1513 (calcd. for $C_{11}H_{20}O$: 168.1514). Anal. calcd. for $C_{11}H_{20}O$: C 78.51, H 11.98; found: C 78.23, H 11.65.

4-(2-Methoxyethyl)-3,3-dimethyl-2-methylidenecyclopentanone (**147**)

To a solution of ether **146** (7.74 g, 0.078 mol) in methylene chloride (200 mL), acetic anhydride (5.20 mL, 0.055 mol), pyridine (1.86 mL, 0.023 mol), dimethylaminopyridine (0.12 g), and TPP (0.02 g) were added. The resulting solution was irradiated with two 200 W tungsten light bulbs for 16 h. During this period a moderate stream of oxygen was bubbled through the solution. The solution was diluted with methylene chloride (50 mL) and extracted with saturated aqueous sodium bicarbonate solution, 1 N hydrochloric acid solution, saturated aqueous cupric sulfate solution, and saturated aqueous sodium chloride solution. The organic solution was dried, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave enone **147** (6.56 g, 78% yield): ir ($CHCl_3$ cast) 1727 (ketone), 164[illegible] (olefin), and 1119 cm^{-1}

(ether); ^{1}H nmr δ 5.97, 5.20 (both d, 1H each, J = 1 Hz each, $=CH_2$), 2.42 (m, 2H, $-OCH_2-$), 3.35 (s, 3H, $-OCH_3$), 2.52 (dd, 1H, J = 17.5, J' = 6.5 Hz, $-CHCHHCO-$), 2.09 (dd, 1H, J = 17.5, J' = 11 Hz, $-CHCHHCO-$), 1.23 (s, 3H, $-CH_3$), and 0.99 (s, 3H, $-CH_3$); ms M^+ 182.1309 (calcd. for $C_{11}H_{18}O_2$: 182.1307). Anal. calcd. for $C_{11}H_{18}O_2$: C 74.49, H 9.95; found: C 74.50, H 9.98.

5-(2-Methoxyethyl)-4,4-dimethyl-7-oxo-1-oxaspiro[2.4]-heptane (148)

At 0°C, to a solution of enone **147** (12.30 g, 0.07 mol) in methanol (300 mL), hydrogen peroxide (30% aqueous solution, 17.3 mL, 0.17 mol) and lithium hydroxide monohydrate (0.21 g, 0.005 mol) were added and the reaction mixture was stirred at room temperature under an atmosphere of argon for 3 h. Ice-cold water and dilute aqueous hydrochloric acid solution were added and the resulting mixture was extracted with methylene chloride. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 25% ethyl acetate in petroleum ether, gave one epoxide **148** (6.18 g, 46% yield): ir ($CHCl_3$ cast) 1752 (ketone) and 1118 cm^{-1} (ether); ^{1}H nmr δ 3.45 (m, 2H, $-CH_2OCH_3$), 3.35 (s, 3H, $-OCH_3$), 3.13, 2.18 (both d, 1H each, J = 6 Hz each, $-CH_2O-$), and 0.98 (s, 6H,

2 x $-CH_3$); ms M^+ 198.1255 (calcd. for $C_{11}H_{18}O_3$: 198.1256). Anal. calcd. for $C_{11}H_{18}O_3$: C 66.64, H 9.15; found: C 66.93, H 9.10. Further elution with the same solvent system gave the other epoxide **148** (5.98 g, 44% yield): ir ($CHCl_3$ cast) 1752 (ketone) and 1119 cm^{-1} (ether); ^1H nmr δ 3.45 (m, 2H, $-CH_2OCH_3$), 3.33 (s, 3H, $-OCH_3$), 2.96, 2.87 (both d, 1H each, J = 6 Hz each, $-OCH_2-$), 0.96 (s, 3H, $-CH_3$), and 0.92 (s, 3H, $-CH_3$); ms M^+ 198.1256 (calcd. for $C_{11}H_{18}O_3$: 198.1256).

4-(2-Methoxyethyl)-3,3-dimethylcyclopentanone (**145**)

A solution of epoxides **148** (ca. 1:1 mixture, 8.10 g, 0.04 mol) and sodium hydroxide pellets (3.60 g, 0.09 mol) in methanol (200 mL) was refluxed for 12 h. Water (80 mL) was added and reflux was continued for an additional 72 h. The solution was allowed to cool to room temperature, acidified with 6 N hydrochloric acid solution, and extracted with methylene chloride (4 x 300 mL). The organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 8% ethyl acetate in petroleum ether, gave ketone **145** (4.71 g, 68% yield): ir (neat) 1742 (ketone) and 1119 cm^{-1} (ether); ^1H nmr δ 3.42 (m, 2H, $-CH_2O-$), 3.35 (s, 3H, $-OCH_3$), 2.47 (dd, 1H, J = 10.5, J' = 5 Hz, $-CHCHHCO-$), 2.24 (s, 2H, $-CCH_2CO$), 2.00 (dd, 1H, J = 11, J' = 10.5 Hz,

-CHCHHCO-), 1.18 (s, 3H, $-CH_3$), and 0.92 (s, 3H, $-CH_3$); ms M^+ 170.1304 (calcd. for $C_{10}H_{18}O_2$: 170.1306). Anal. calcd. for $C_{10}H_{18}O_2$: C 70.55, H 10.66; found: C 70.76, H 10.66.

7-(2-Methoxyethyl)-8,8-dimethylbicyclo[4.3.0]non-1-en-3-one (150) and 8-(2-Methoxyethyl)-7,7-dimethylbicyclo-[4.3.0]non-1-en-3-one (151)

To a solution of ketone **145** (103 mg, 0.60 mmol) in benzene (5 mL), pyrrolidine (0.5 mL, 6 mmol) and p-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) were added. The mixture was refluxed using a Dean-Stark apparatus with azeotropic removal of water-benzene under an argon atmosphere for 4 h. The solvent and the excess of pyrrolidine were removed by distillation. The residue was further dried in vacuo for 2 h. To a solution of the residue in dioxane (3 mL), methyl vinyl ketone (49 μL, 0.60 mmol) was added and the solution heated at 80-90°C (oil bath temperature) under an argon atmosphere for 5 h. Water (1 mL) was added and the mixture was kept at the same temperature for an additional 14 h. After cooling to 0°C, ice-cold water was added and the mixture extracted with ether. The combined organic extracts were washed with 1 N hydrochloric acid solution, saturated aqueous sodium bicarbonate solution, water, and saturated aqueous

sodium chloride solution. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 7% ethyl acetate in petroleum ether, gave unreacted ketone **129** (28 mg). Further elution with 20% ethyl acetate in petroleum ether gave a mixture of products **150** and **151** (ca. 2:1 ratio by nmr analysis; 39 mg, 41% yield based on unrecovered starting material): ir (CH_2Cl_2 cast) 1668 (ketone), 1640 (olefin), and 1118 cm^{-1} (ether); ms M^+ 222.1619 (calcd. for $C_{14}H_{22}O_2$: 222.1619). The following nmr data were obtained for product **150**: ^1H nmr δ5.85 (br s, 1H, -CH=), 3.46 (m, 2H, $-CH_2O-$), 3.38 (s, 3H, $-OCH_3$), 1.11 (s, 3H, $-CH_3$), and 0.95 (s, 3H, $-CH_3$). The following nmr data were obtained for product **151**: ^1H nmr δ5.93 (br s, 1H, =CH), 3.39 (s, 3H, $-OCH_3$), 1.09 (s, 3H, $-CH_3$), and 0.63 (s, 3H, $-CH_3$).

2-Carbomethoxy-3-(2-methoxyethyl)-4,4-dimethylcyclopentanones (**152** and **154**)

Sodium hydride (60% dispersion in oil, 0.67 mg, 1.68 mmol) and dimethyl carbonate (0.5 mL, 5.73 mmol) were added to benzene (4 mL) and heated to reflux. A solution of ketone **145** (82 mg, 0.48 mmol) in benzene (2 mL) was added slowly. After refluxing for 18 h, the reaction mixture was cooled to 0°C and methanol was added with

vigorous stirring to destroy excess sodium hydride. The mixture was poured into ice-cold dilute aqueous hydrochloric acid solution and extracted with methylene chloride. The organic extracts were washed with water, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 6% ethyl acetate in petroleum ether, gave a 15:1 mixture (by nmr analysis) of epimeric keto esters **152** and **154** respectively (76 mg, 69% yield): ir (CH_2Cl_2 cast) 1736 (ester) and 1727 cm^{-1} (ketone); ms M^+ 228.1361 (calcd. for $C_{12}H_{20}O_4$: 228.1361). The following nmr data were obtained for keto ester **152**: ^1H nmr δ 3.80 (s, 3H, $-COOCH_3$), 3.41 (m, 2H, $-CH_2O-$), 3.29 (s, 3H, $-OCH_3$), 3.11 (d, J = 11 Hz, 1H, $-COCHCOO-$), 2.34, 2.25 (both d, 1H each, J = 18 Hz each, $-COCH_2\overset{|}{C}-$), 1.23 (s, 3H, $-CH_3$), and 0.92 (s, 3H, $-CH_3$). The following nmr data were assigned to keto ester **154**: ^1H nmr δ 3.77 (s, 3H, $-COOCH_3$), 3.37 (s, 3H, $-OCH_3$), 3.07 (br s, 1H, $-CO\overset{|}{C}HCOO-$), 1.29 (s, 3H, $-\overset{|}{C}H_3$), and 0.93 (s, 3H, $-CH_3$).

Allyl 2-carbomethoxy-3-(2-methoxyethyl)-4,4-dimethylcyclopentenyl ether (**156**)

A suspension of sodium hydride (60% dispersion in oil, 47.6 mg, 1.19 mmol) in 1,2-dimethoxyethane (5 mL), allyl bromide (0.10 mL, 1.19 mmol) and a solution of keto

esters **152** and **154** (ca. 15:1 mixture, 136 mg, 0.6 mmol) in 1,2-dimethoxyethane (2 mL) were added. The reaction mixture was refluxed under an argon atmosphere for 22 h. After cooling at 0°C, the reaction mixture was poured into ice-cold dilute aqueous hydrochloric acid solution and extracted with methylene chloride. The organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave ester **156** (110 mg, 69% yield): ir ($CHCl_3$ cast) 1710 (ester), 1689, and 1626 cm^{-1} (vinyl ether); ^1H nmr δ 5.96 (ddt, 1H, J = 17, J' = 11, J" = 5 Hz, -CH=), 5.41 (ddd, 1H, J = 17, J' = 3, J" = 1.5 Hz, =CHH), 5.27 (ddd, 1H, J = 11, J' = 3, J" = 1.5 Hz, =CHH), 4.54 (ddd, 2H, J = 5, J' = 1.5, J" = 1.5 Hz, $-OCH_2CH=$), 3.72 (s, 3H, $-COOCH_3$), 3.36 (m, 2H, $-CH_2O-$), 3.31 (s, 3H, $-OCH_3$), 2.54, 2.24 (both d, 1H each, J = 17 Hz each, $-CH_2\overset{|}{\underset{|}{C}}-$), 1.10 (s, 3H, $-CH_3$), and 1.07 (s, 3H, $-CH_3$); ms M^+ 268.1670 (calcd. for $C_{15}H_{24}O_4$: 268.1674).

2-Methallyl-3-(2-methoxyethyl)-4,4-dimethylcyclopentanone (157)

At -78°C, to a solution of diisopropylamine (0.16 mL, 1.13 mmol) in tetrahydrofuran (3 mL), methyllithium (1.35 M in ether, 0.80 mL, 0.91 mmol) was added under an argon

atmosphere. The solution was stirred for 5 min at -78°C, 10 min at 0°C, cooled again at -78°C and treated with a solution of ketone **145** (0.13 g, 0.75 mmol) in tetrahydrofuran (2 mL). After stirring at -78°C for 1 h, methallyl iodide (0.17 mL, 1.51 mmol) was added. The resulting solution was stirred at -40°C for 2 h and at 0°C for 1 h, diluted with saturated aqueous sodium chloride solution, and extracted with methylene chloride. The organic extracts were washed with water, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave ketone **157** (72 mg, 57% yield based on unrecovered starting material): ir ($CHCl_3$ cast) 1741 (ketone) and 1118 cm^{-1} (ether); ^1H nmr δ4.84, 4.77 (both s, 1H each, $=CH_2$), 3.48 (t, 2H, J = 7 Hz, $-CH_2O-$), 3.36 (s, 3H, $-OCH_3$), 2.37, 2.31 (both dd, 1H each, J = 14, J' = 6 Hz each, $=CCH_2-$), 2.16 (s, 2H, $-COCH_2-$), 1.70 (s, 3H, $=CCH_3$), 1.16 (s, 3H, $-CH_3$), and 0.94 (s, 3H, $-CH_3$); ms M^+ 224.1771 (calcd. for $C_{14}H_{24}O_2$: 224.1776). Further elution with 15% ethyl acetate in petroleum ether gave unreacted ketone **145** (32 mg).

3-(2-Methoxyethyl)-4,4-dimethyl-2-(2-oxopropyl)cyclopentanone (158)

At -78°C, a stream of ozone-oxygen gas was allowed to

pass through a methylene chloride–methanol solution (1:1, 6 mL) of ketone **157** (33.1 mg, 0.15 mmol) until a light blue color was retained. The reaction mixture was purged with argon to remove the excess ozone. Trimethyl phosphite (0.5 mL) was added at 0°C and after stirring at room temperature for 5 h the mixture was concentrated under reduced pressure. The residue was partitioned in methylene chloride and water. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether, gave diketone **158** (30 mg, 90% yield): ir ($CHCl_3$ cast) 1750 (cyclopentanone), 1715 (acyclic ketone), and 1117 cm^{-1} (ether); ^1H nmr δ 3.40 (m, 2H, $-CH_2O-$), 3.22 (s, 3H, $-OCH_3$), 2.90, 2.82 (both dd, 1H each, J = 18, J' = 5 Hz each, CH_3COCH_2-), 2.40, 2.20 (both d, 1H each, J = 18 Hz each, $-CHCOCH_2-$), 2.15 (s, 3H, $-COCH_3$), 1.16 (s, 3H, $-CH_3$), and 0.94 (s, 3H, $-CH_3$); ms M^+ 226.1573 (calcd. for $C_{13}H_{22}O_3$: 226.1569).

Diethyl 2-ethoxy-3-[2-(2-methoxyethyl)-3,3-dimethyl-5-oxocyclopentyl]propenylphosphonate (**163**)

At 0°C, to a solution of diisopropylamine (0.98 mL, 6.98 mmol) in tetrahydrofuran (4 mL), methyllithium (1.42 M in ether, 2.95 mL, 4.19 mmol) was added under an argon atmosphere. The solution was stirred for 5 min at -78°C,

10 min at 0°C, cooled again to -78°C and treated with a solution of ketone **145** (0.47 g, 2.79 mmol) in tetrahydrofuran (2 mL). After stirring at -78°C for 1 h, hexamethylphosphoramide (0.54 mL, 3.07 mmol) and a solution of diethyl 3-bromo-2-ethoxypropenylphosphonate (**161**) (0.83 g, 3.63 mmol) in tetrahydrofuran (2 mL) were added. The resulting solution was stirred at -78°C for 30 min and at 0°C for 2 h, diluted with saturated aqueous sodium chloride solution, and extracted with ethyl acetate. The organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether, gave unreacted ketone **145** (0.10 g). Further elution with 80% ethyl acetate in petroleum ether gave product **162** (0.51 g, 63% yield based on unrecovered starting material): ir ($CHCl_3$ cast) 1741 (ketone), 1613 (enol ether), 1243 (P=O), 1115 (ether), and 1031 cm^{-1} (P-O-C); ^1H nmr δ4.45 (d, 1H, J = 5.5 Hz, OCH=), 4.06 (m, 4H, $-PO(OCH_2-)_2$), 3.81 (m, 2H, $=COCH_2-$), 3.48 (m, 2H, $-CH_2O-$), 3.35 (s, 3H, $-OCH_3$), 3.23 (ddd, 1H, J = 15, J' = 7, J" = 1.5 Hz, $-CHHC=$), 2.85 (ddd, 1H, J = 15, J' = 7, J" = 2 Hz, $-CHHC=$), 2.27 (m, 1H, $-CHCO-$), 2.24 (d, 1H, J = 17 Hz, $-CCHHCO-$), 2.12 (dd, 1H, J = 17, J' = 1.5 Hz, $-CCHHCO-$), 1.30, 1.29 (both t, 3H each, J = 7 Hz each, $-PO(OCH_2CH_3)_2$), 1.15 (s, 3H, $-CH_3$), and 0.91 (s, 3H, $-CH_3$); ms M^+ 390.2177 (calcd. for

$C_{19}H_{35}O_6P$: 390.2171).

Diethyl 2-oxo-3-[2-(2-methoxyethyl)-3,3-dimethyl-5-oxocyclopentyl]propylphosphonate (162)

A solution of enol ether **163** (0.45 g, 1.25 mmol) and 1 N hydrochloric acid solution (0.8 mL) in acetone (10 mL) was stirred for 6 h at room temperature and then treated with anhydrous potassium carbonate (0.20 g). Most of the acetone was removed under reduced pressure. The residue was diluted with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with ethyl acetate, gave phosphonate **162** (0.29 g, 71% yield): ir ($CHCl_3$ cast) 1741 (cyclopentanone), 1716 (acyclic ketone), 1260 (P=O), 1115 (ether), and 1026 cm^{-1} (P-O-C); ^1H nmr δ 4.16 (dq, 4H, J = 7, J'_{P-H} = 2 Hz, $-PO(OCH_2CH_3)_2$), 3.44 (m, 2H, $-CH_2O-$), 3.34 (s, 3H, $-OCH_3$), 3.11 (d, 2H, J_{P-H} = 22.5 Hz, $-POCH_2CO$), 3.30, 3.01 (both dd, 1H each, J = 18, J' = 5 Hz each, $-COCH_2CHCO-$), 2.37 (d, 1H, J = 18 Hz, $-CCHHCO-$), 2.36 (m, 1H, $-CHCO-$), 2.18 (dd, 1H, J = 18, J' = 1 Hz, $-CCHHCO-$), 1.33 (t, 6H, J = 7 Hz, $-PO(OCH_2CH_3)_2$), 1.16 (s, 3H, $-CH_3$), and 0.93 (s, 3H, $-CH_3$); ms M^+ 362.1867 (calcd. for $C_{17}H_{31}O_6P$: 362.1859).

6-(2-Methoxyethyl)-7,7-dimethylbicyclo[3.3.0]oct-1-en-3-one (153)

A suspension of diketo phosphonate 163 (290 mg, 0.69 mmol), anhydrous potassium carbonate (95 mg, 0.69 mmol) and 18-crown-6 ether (547 mg, 2.07 mmol) in benzene (30 mL) was stirred at 60°C for 6.5 h under an argon atmosphere. The mixture was cooled to room temperature, diluted with saturated aqueous sodium chloride solution, and extracted with ether. The combined organic extracts were washed with water, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether gave bicyclic ketone 153 (122 mg, 85% yield): ir ($CHCl_3$ cast) 1708 (ketone), 1630 (olefin), and 1118 cm^{-1} (ether); ^1H nmr δ 5.86 (d, 1H, J = 2 Hz, =CH), 3.44 (m, 2H, $-CH_2O-$), 3.35 (s, 3H, $-OCH_3$), 2.64 (dd, 1H, J = 18, J' = 6 Hz, $-OCCHHCH-$), 2.56, 2.50 (both d, 1H each, J = 18 Hz each, $-CCH_2C=$), 2.15 (dd, J = 18, J' = 3 Hz, $-OCCHHCH-$), 1.11 (s, 3H, $-CH_3$), and 1.04 (s, 3H, $-CH_3$); ms M^+ 208.1466 (calcd. for $C_{13}H_{20}O_2$: 208.1463). Anal. calcd for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 74.83, H 9.51.

5-(2-Methoxyethyl)-6,6-dimethyl-10-methylidenetricyclo-[6.2.0.0^{4,8}]decan-2-one (164) and 5-(2-Methoxyethyl)-6,6-dimethyl-9-methylidenetricyclo[6.2.0.0^{4,8}]decan-2-one (165)

At -78°C, allene (ca. 4 mL) was condensed into a 25 mL three necked round-bottomed flask. A solution of enone **153** (590 mg, 2.83 mmol) in tetrahydrofuran (6 mL) was added. The resulting mixture was irradiated with a 450 W Hanovia high-pressure quartz mercury vapor lamp for 15 h. After removal of the solvent, the residue was subjected to flash chromatography on silica gel. Elution with 5% ethyl acetate in petroleum ether gave adducts **164** and **165** (ca. 6:1 ratio by nmr analysis; 412 mg, 74% yield): ir ($CHCl_3$ cast) 1733 (ketone) and 1119 cm^{-1} (ether); ms M^+ 248.1776 (calcd. for $C_{16}H_{24}O_2$: 248.1776). Anal. calcd. for $C_{16}H_{24}O_2$: C 77.38, H 9.74; found: C 77.24, H 9.64. The following nmr data were obtained for adduct **164**: ^1H nmr δ 4.98, 4.87 (both ddd, 1H each, J = J' = J" = 2.5 Hz each, $=CH_2$), 3.37 (m, 2H, $-CH_2O-$), 3.29 (s, 3H, $-OCH_3$), 3.23 (br dd, 1H, J = 5, J' = 2.5 Hz, $-COCHC=$), 3.02 (ddd, 1H, J = 16, J' = 2.5, J" = 2.5 Hz, $=CCHHC-$), 2.93 (ddd, 1H, J = 18, J' = 9, J" = 1 Hz, $-CHCHHCO-$), 2.73 (ddd, 1H, J = 16, J' = 5, J" = 2.5 Hz, $=CCHHC-$), 2.32 (dd, 1H, J = 9, J' = 4.5 Hz, $-COCH_2CHCH-$), 2.24 (ddd, 1H, J = 18, J' = 4.5, J" = 1.5

Hz, -COCHHCH-), 0.96 (s, 3H, $-CH_3$), and 0.81 (s, 3H, $-CH_3$). The following nmr data were observed for adduct **165**: ^1H nmr δ 4.94 (td, 1H, J = 2.5, J' = 1 Hz, =CHH), 4.79 (m, 1H, =CHH), 0.98 (s, 3H, $-CH_3$), and 0.93 (s, 3H, $-CH_3$).

1-Carbomethoxymethyl-6-(2-methoxyethyl)-7,7-dimethyl-bicyclo[3.3.0]octan-3-one (**75**), 1-Carbomethoxymethyl-3,3-dimethoxy-6-(2-methoxyethyl)-7,7-dimethylbicyclo[3.3.0]-octane (**166**), and 2,2-Dimethoxy-5-(2-methoxyethyl)-6,6-dimethyltricyclo[6.2.0.$0^{4,8}$]decan-9-one (**167**)

At -78°C, a stream of ozone-oxygen gas was allowed to pass through a methanolic solution (30 mL) of photoadducts **164** and **165** (ca. 5:1 mixture; 510 mg, 2.05 mmol) until a light blue color was retained. The reaction mixture was purged with argon to remove excess ozone. Dimethyl sulfide (3 mL) was added at 0°C and after stirring at room temperature for 5 h, the mixture was concentrated under reduced pressure. The residue was partitioned between methylene chloride and water. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel; eluting with 15% ethyl acetate in petroleum ether, gave dimethyl ketal **166** (53.4 mg, 8% yield): ir ($CHCl_3$ cast) 1738 cm^{-1} (ester); ^1H nmr δ 3.68 (s, 3H, $-COOCH_3$), 3.42 (m, 2H, $-CH_2O-$), 3.35 (s, 3H,

$-OCH_3$), 3.20, 3.21 (both s, 3H each, $CH_3OC(=O)OCH_3$), 2.62, 2.49 (both d, 1H each, J = 15 Hz each, $-CH_2COO-$), 0.96 (s, 3H, $-CH_3$), and 0.85 (s, 3H, $-CH_3$); ms M^+ 328.2247 (calcd. for $C_{18}H_{32}O_5$: 328.2249). Continued elution with the same solvent system afforded **167** (35.6 mg, 6% yield): ir ($CHCl_3$ cast) 1772 cm^{-1} (ketone); ^1H nmr δ 3.43, 3.45 (both d, 1H each, J = 6 Hz each, $-CH_2O-$), 3.35 (s, 3H, $-OCH_3$), 3.28, 3.22 (both s, 3H each, $CH_3OC(=O)OCH_3$), 2.91 (dd, 1H, J = 18, J' = 9 Hz, $-CHHCO-$), 2.82 (dd, 1H, J = 18, J' = 6 Hz, $-CHHCO-$), 0.97 (s, 3H, $-CH_3$), and 0.83 (s, 3H, $-CH_3$); ms M^+ 296.1988 (calcd. for $C_{17}H_{28}O_4$: 296.1988). Further elution gave keto ester **75** (439 mg, 76% yield): ir ($CHCl_3$ cast) 1740 cm^{-1} (ketone and ester); ^1H nmr δ 3.65 (s, 3H, $-COOCH_3$), 3.39 (t, 2H, J = 6 Hz, $-CH_2O-$), 3.31 (s, 3H, $-OCH_3$), 1.88, 1.71 (both d, 1H each, J = 18.5 each, $-CCH_2C-$), 0.99 (s, 3H, $-CH_3$), and 0.90 (s, 3H, $-CH_3$); ms M^+ 282.1833 (calcd. for $C_{16}H_{26}O_4$: 282.1833).

1-Carbomethoxymethyl-6-(2-hydroxyethyl)-7,7-dimethyl-bicyclo[3.3.0]octan-3-one (168)

To a solution of keto ester **75** (9 mg, 0.03 mmol) in acetonitrile (2 mL), sodium iodide (5 mg, 0.03 mmol) and chlorotrimethylsilane (4 μL, 0.03 mmol) were added. After heating at 50-60°C (oil bath temperature) under an argon atmosphere for 30 h, the reaction mixture was poured into

ice-cold water (3 mL) and extracted with ether. The organic extracts were washed with 10% aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave unreacted keto ester **146** (2 mg). Further elution with 50% ethyl acetate in petroleum ether, gave alcohol **168** (5 mg, 76% yield): ir ($CHCl_3$ cast) 3440 (alcohol) and 1738 cm^{-1} (ketone and ester); ^1H nmr δ 3.72 (t, 2H, J = 7 Hz, $-CH_2O-$), 3.36 (s, 3H, $-COOCH_3$), 1.92, 1.73 (both d, 1H each, J = 14 Hz each, $-\overset{|}{C}CH_2\overset{|}{C}-$), 1.00 (s, 3H, $-CH_3$), and 0.92 (s, 3H, $-CH_3$); ms M^+ 268.1677 (calcd. for $C_{15}H_{24}O_4$: 268.1675).

1-Carbomethoxymethyl-6-(2-iodoethyl)-7,7-dimethylbicyclo-[3.3.0]octan-3-one (**169**)

To a solution of keto ester **75** (439 mg, 1.56 mmol) in acetonitrile (15 mL), sodium iodide (700 mg, 4.67 mmol) and chlorotrimethylsilane (0.8 mL, 6.24 mmol) were added. After heating at 60-70°C (oil bath temperature) under an argon atmosphere for 30 h, the reaction mixture was poured into ice-cold water (50 mL) and extracted with ether. The organic extracts were washed with 10% aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution, dried, filtered, and concentrated.

Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave ester **169** (529 mg, 90% yield): ir ($CHCl_3$ cast) 1738 cm^{-1} (ketone and ester); ^1H nmr δ 3.65 (s, 3H, $-COOCH_3$), 3.20 (m, 2H, $-CH_2I$), 1.19, 1.74 (both d, 1H each, J = 14.5 Hz each, $-\overset{|}{\underset{|}{C}}CH_2\overset{|}{\underset{|}{C}}-$), 1.04 (s, 3H, $-CH_3$), and 0.92 (s, 3H, $-CH_3$); ms $M^{+\cdot}$ 378.0689 (calcd. for $C_{15}H_{23}IO_3$: 378.069

Iodo ester **169** from dimethyl ketal **166**

To a solution of ketal **166** (50 mg, 0.15 mmol) in acetonitrile, sodium iodide (114 mg, 0.76 mmol) and chlorotrimethylsilane (0.1 mL, 0.76 mmol) were added. After heating at 60-70°C (oil bath temperature) under an argon atmosphre for 30 h, the reaction mixture was poured into ice-cold water (5 mL) and extracted with ether. The organic extracts were washed with 10% aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave ester **169** (51 mg, 87% yield) identical with that obtained previously from keto ester **75**.

1-Carbomethoxymethy-3,3-ethylenedioxy-6-(2-iodoethyl)-7,7-dimethylbicyclo[3.3.0]octane (23)

p-Toluenesulfonic acid monohydrate (30 mg, 0.16 mmol) was dried by refluxing in benzene with azeotropic removal of water-benzene (3 * 5 mL). To a solution of the dry p-toluenesulfonic acid in benzene (4 mL), 2-methyl-2-ethyl-1,3-dioxolane (8 mL) and a solution of keto ester **169** (529 mg, 1.4 mmol) in benzene (4 mL) were added. The mixture was heated at 80-90°C (oil bath temperature) for 3.5 h. After cooling to 0°C, 10% aqueous sodium bicarbonate solution was added and the mixture extracted with ether. The organic extracts were washed with water and saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 7% ethyl acetate in petroleum ether, gave ketal **23** (481 mg, 72% yield): ir ($CHCl_3$ cast) 1735 (ester), 1120, 1160, 1170, and 1190 cm^{-1} (ketal); ^1H nmr δ3.89 (m, 4H, $-OCH_2CH_2O-$), 3.66 (s, 3H, $-COOCH_3$), 3.28, 3.16 (both m, 1H each, $-CH_2I$), 2.64, 2.48 (both d, 1H each, J = 15 Hz each, $-CH_2COO-$), 0.99 (s, 3H, $-CH_3$), and 0.86 (s, 3H, $-CH_3$); ms M^+ 422.0942 (calcd. for $C_{17}H_{27}IO_4$: 422.0956).

2-Carbomethoxy-8,8-ethylenedioxy-1,5-(2',2'-dimethylethano)bicyclo[4.3.0]nonane (170)

Using lithium diisopropylamide

To a solution of diisopropylamine (0.06 mL, 0.42 mmol) in tetrahydrofuran (1.5 mL) at -78°C under an argon atmosphere, was added methyllithium (1.42 M in ether, 0.23 mL, 0.28 mmol). The solution was stirred at -78°C for 5 min and at 0°C for 10 min. After cooling to -78°C, a solution of iodo ketal 23 (117 mg, 0.28 mmol) in tetrahydrofuran (1.5 mL) was added dropwise. The reaction mixture was stirred for 20 min at -78°C, 15 min at -45°C, then brought to -23°C. Hexamethylphosphoramide (0.1 mL) was immediately added. The solution was stirred at -23°C for an additional 15 min and then brought to room temperature for 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution, diluted with petroleum ether and washed with water and saturated aqueous sodium chloride solution. The organic layer was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 6% ethyl acetate in petroleum ether gave tricyclic ketal 170 (58 mg, 75% yield): ir ($CHCl_3$ cast) 1731 (ester), 1194, 1163, and 1119 cm^{-1} (ketal); ^1H nmr δ 3.79 (m, 4H, $-OCH_2CH_2O-$), 3.58 (s, 3H, $-COOCH_3$), 2.56 (d, 1H, J = 6 Hz, $-CHCOO-$), 2.51 (dd, 1H, J = 11.5, J' = 9 Hz, $-CHCH_2CO-$), 1.95 (dd,

1H, J = 14, J' = 1 Hz, -CHCHHCO-), 1.86 (ddd, 1H, J = 14, J' = 9, J" = 1 Hz, -CHCHHCO-), 1.90, 1.81 (both d, 1H each, J = 14 Hz each, $-CCH_2CO-$), 1.13 (s, 3H, $-CH_3$), and 1.00 (s, 3H, $-CH_3$); ms, M^+ 294.1838 (calcd for $C_{17}H_{26}O_4$: 294.1831).

Using lithium hexamethyl disilazide

At -78°C, to a solution of hexamethyl disilazane (0.38 mL, 1.80 mmol) in tetrahydrofuran (5 mL), n-butyllithium (2.5 M in n-hexane, 0.37 mL, 0.94 mmol) was added under an argon atmosphere. The solution was stirred at -78°C for 5 min and at 0°C for 15 min. After cooling again to -78°C, a solution of iodo ketal 23 (272 mg, 0.72 mmol) in tetrahydrofuran (3 mL) was added dropwise. The reaction mixture was stirred for 20 min at -78°C, 15 min at -45°C, then brought to [illegible]. Hexamethylphosphoramide (0.1 mL) was immediately added. The solution was stirred at -23°C for an additional 15 min and then brought to room temperature for 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution, diluted with petroleum ether and washed with water and saturated aqueous sodium chloride solution. The organic layer was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 6% ethyl acetate in petroleum ether, gave tricyclic ketal 170 (132 mg, 70% yield).

2-Carbomethoxy-1,5-(2,2-dimethylethano)bicyclo[4.3.0]-nonan-7-one (24)

A solution of ketal 170 (58 mg, 0.20 mmol) in acetone containing a crystal of p-toluenesulfonic acid monohydrate was stirred for 2 h at room temperature under an atmosphere of argon. Solid sodium bicarbonate (10 mg) was added and the mixture was stirred for an additional 30 min. The mixture was filtered and the solvent evaporated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave tricyclic keto ester 24 (39 mg, 80% yield). The spectral data was identical with those reported by Danishefsky.[14]

(-)-α-Campholenic acid (129)

To fused potassium hydroxide (80 g, 1.43 mol) in a porcelain casserole was added slowly with stirring (-)-10-camphorsulfonic acid (76) ammonium salt (73 g, 0.29 mmol). After the completion of the addition (ca. 30 min), the molten mass was allowed to cool to room temperature and then dissolved in water (700 mL). The resulting solution was extracted with ether and the aqueous fraction acidified with 6 N hydrochloric acid solution. The acidified solution was extracted with methylene

chloride. The combined organic extracts were dried, filtered, and concentrated. The crude residue was distilled to give (-)-acid **129** (38.7 g, 79% yield): b.p. 90-91°C/0.3 torr; $[\alpha]_D^{22}$ = -11.1° (c = 0.11, $CHCl_3$). The spectral data were identical with those obtained previously from d,l-10-camphorsulfonic acid sodium salt. The conversion of (-)-α-campholenic acid (**129**) into (-)-**24** was effected by the reaction sequence outlined in Scheme XVIII. The reaction conditions were identical to those described above. (-)-Quadrone (**1**) was obtained from (-)-**24** following the reaction sequence reported for the racemic **24**.[14] (-)-Quadrone (**1**), obtained in crystalline form (m.p. 182-184°C), showed a specific rotation of $[\alpha]_D^{22}$ = -42.2 (c = 0.05, EtOH) and displayed the following spectral data: ir (KBr) 1738 cm^{-1} (ketone and lactone); ^1H nmr 4.64 (dd, 1H, J = 12, J' = 1 Hz, -CHHO-), 4.20 (dd, 1H, J = 12, J' = 2.5 Hz, -CHHO-), 2.74 (br d, 1H, J = 6.5 Hz, -CHCOO-), 2.66 (dd, 1H, J = 17, J' = 14 Hz, -CHHCO-), 2.44 (dd, 1H, J = 17, J' = 7 Hz, -CHHCO-), 2.42 (br d, 1H, J = 5.5 Hz, -CHCO-), 2.36 (dd, 1H, J = 14, J' = 7 Hz, -CHCH$_2$CO-), 2.07, 1.89 (both d, 1H each, J = 14 Hz each, -CCH$_2$C-), 2.00 (t, 1H, J = 2 Hz, -CHC-), 1.67, 1.72-1.98 (both m, total 4H, -CHCH$_2$CH$_2$CH-), 1.28 (s, 3H, $-CH_3$), and 1.22 (s, 3H, $-CH_3$); ms M^+ 248.1418 (calcd. for $C_{15}H_{20}O_3$: 248.1412).

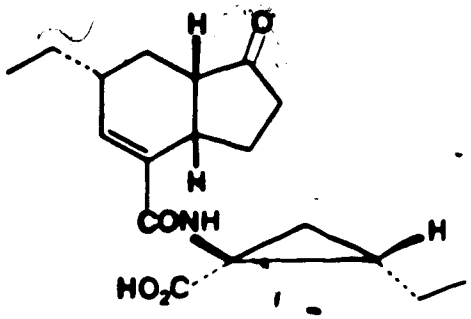
CHAPTER II.

THE TOTAL SYNTHESIS OF (±)-CORONAFACIC ACID

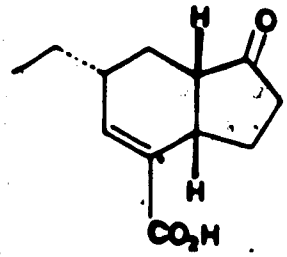
INTRODUCTION

In 1977, Ichihara and co-workers[74] reported the isolation, from the culture broth of Pseudomonas coronafacience var. atropurpurea, of a phytotoxic compound[75,76] named coronatine. It induces chlorosis on the leaves of Italian ryegrass and also hypertrophic growth of potato tuber tissue. These investigators also established the structure[74] and the absolute stereochemistry[74,77,78] of the dextrorotatory phytotoxin as 1 on the basis of the following observations.

Hydrolysis of coronatine (1) gave (+)-coronafacic acid (2) and (+)-coronamic acid (3). Conversely, condensation of coronafacic acid (2), via the corresponding acid chloride, and coronamic acid (3) gave rise to the parent molecule 1.[77] Coronafacic acid (2), which was found to be also present in the culture broth of the phytopathogenic bacterium, was found to be rapidly interconvertible with its C6 epimer 4 and, depending upon the conditions of recrystallization, each of these compounds could be isolated in pure form.[74] The isomer 4 is easily converted through enolization to 2. Esterification of 2 or 4 by methanolic hydrochloric acid afforded the same methyl ester 5.[74] The structure and relative configuration of coronafacic acid (2) were



1



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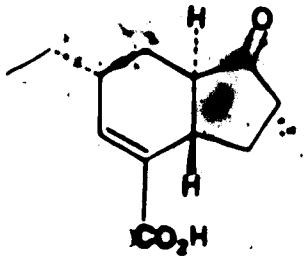

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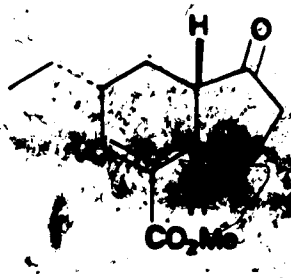

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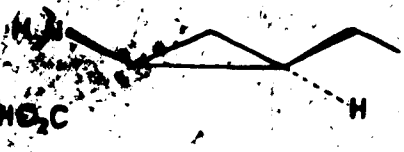

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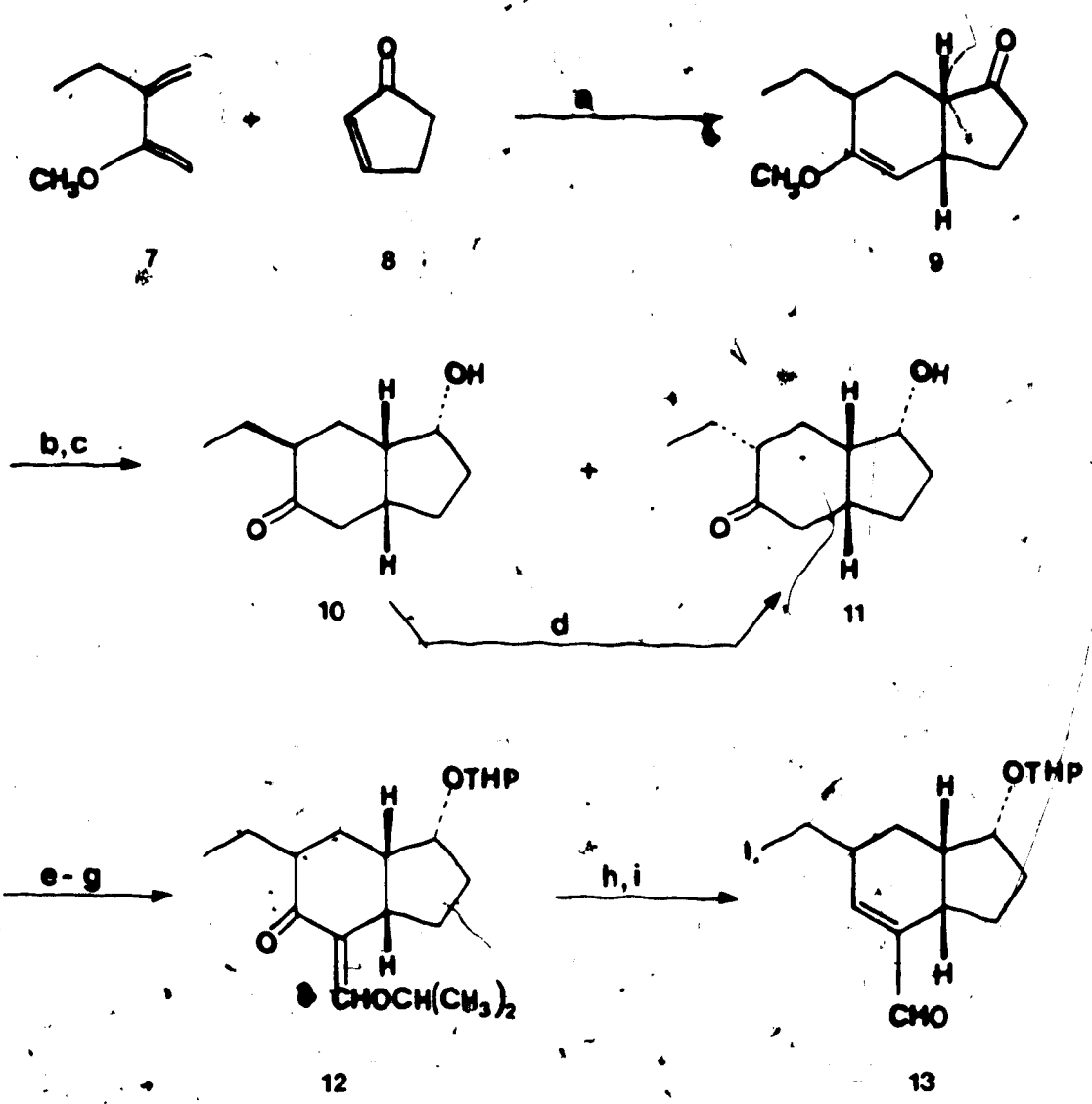
elucidated by spectroscopic analyses on both isomers 2 and 4 and ultimately by X-ray analysis on the latter isomer.[74] The structure of (+)-coronamic acid (3) was determined by spectroscopic methods.[75] The absolute configuration was first assigned as in structure 6 on the basis of ORD measurements.[77] However, further investigation by the enzymatic method and X-ray analysis[78] revealed the absolute configuration shown in formula 3 for (+)-coronamic acid.

Coronofacic acid (2) has been the subject of considerable synthetic activity and several total syntheses have been accomplished during the past few years. The first total synthesis of (±)-coronafacic acid (2), reported shortly after its isolation by Ichihara and co-workers,[79] made use of a Diels-Alder reaction (Scheme I) as the key step. Addition of 2-ethyl-3-methoxy-1,3-butadiene (7) to 2-cyclopentenone (8) in refluxing xylene, with concomitant isomerization of the double bond of the expected adduct, afforded a stereoisomeric mixture of products 9. Reduction with sodium borohydride followed by hydrolysis of the methyl enol ether gave ketols 10 and 11. After protecting the alcohol group as a tetrahydropyranyl ether, the compound was sequentially treated with ethyl formate and sodium hydride in diglyme and then with isopropyl iodide to give the corresponding isopropyl ether 12. Reduction of 12 with lithium aluminum hydride in

SCHEME I

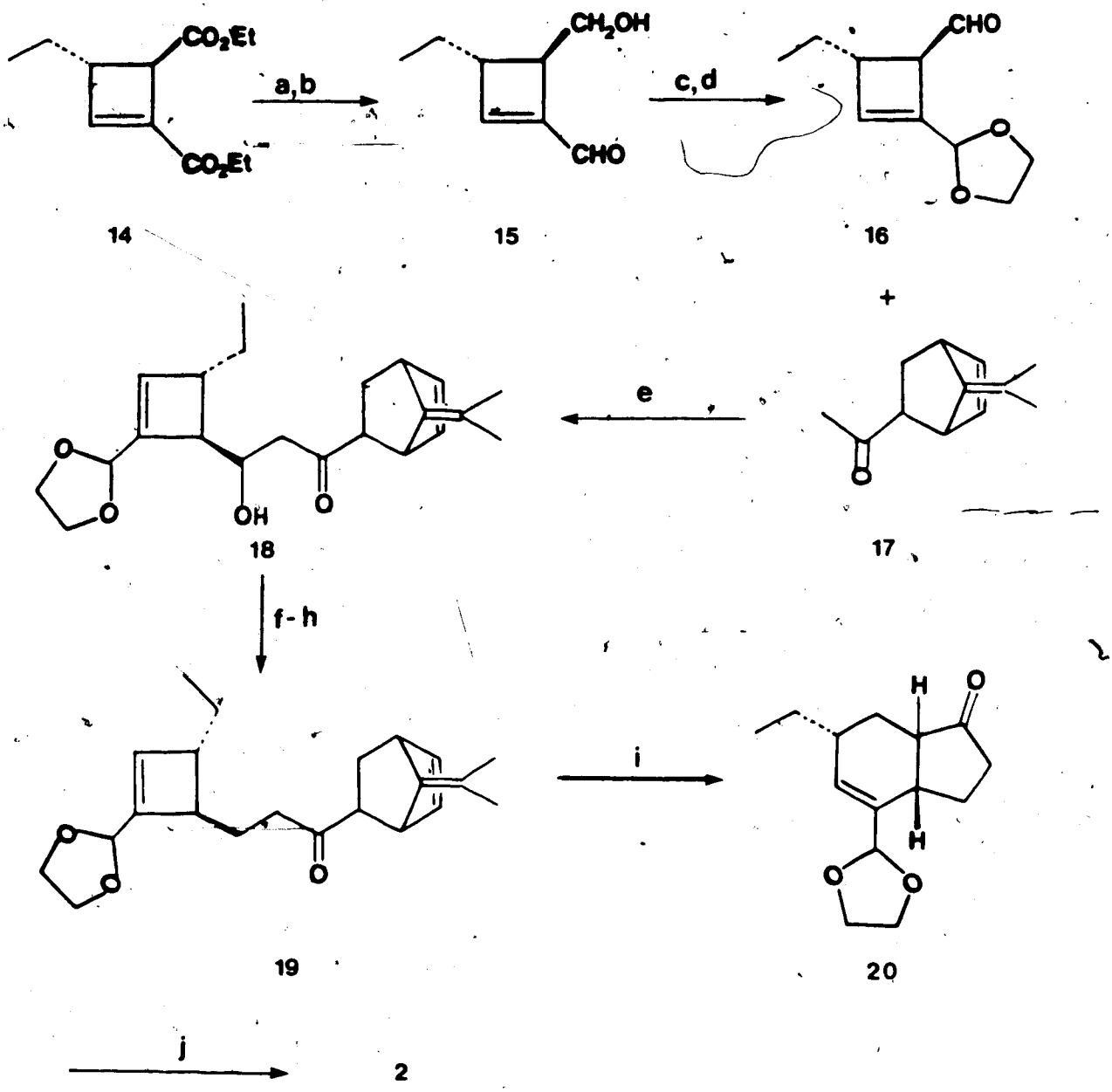


a. xylene, 200°C, 27 h. b. $NaBH_4$, THF. c. 1.2N HCl. d. NaOMe. e. DHP. f. HCOOEt, NaH, diglyme. g. $ICH(CH_3)_2$. h. $LiAlH_4$, THF. i. AcOH. j. H_3O^+. k. Jones reagent.

tetrahydrofuran and subsequent treatment of the resulting alcohol with acetic acid afforded a stereoisomeric mixture of α,β-unsaturated aldehydes **13**. Hydrolysis of the tetrahydropyranyl ether followed by Jones oxidation gave (±)-coronafacic acid (**2**).

In 1980, the same group[80] reported an improved synthesis using an intramolecular Diels-Alder reaction (Scheme II). Reduction of diester **14** with lithium aluminum hydride afforded the corresponding diol which was converted to aldehyde **15** by oxidation with manganese dioxide. Ketalization of aldehyde **15** followed by Collins oxidation yielded acetal aldehyde **16**. Aldol condensation of ketone **17** with **16** by means of lithium diisopropylamide afforded ketol **18**. Mesylation of the hydroxyl group followed by elimination induced by 1,5-diazabicyclo-[5.4.0]undec-5-ene yielded the corresponding α,β-unsaturated ketone which was reduced to the saturated ketone **19** by treatment with sodium bis(2-methoxyethoxy)-aluminum hydride. As expected, when ketone **19** was heated at 170-180°C in toluene in a sealed tube, compound **20** was formed *via* three successive reactions: conrotatory opening of the cyclobutene ring, retro-Diels-Alder reaction eliminating fulvene, and intramolecular Diels-Alder reaction. Treatment of **20** with Jones reagent resulted in simultaneous deacetalization, isomerization,

SCHEME II



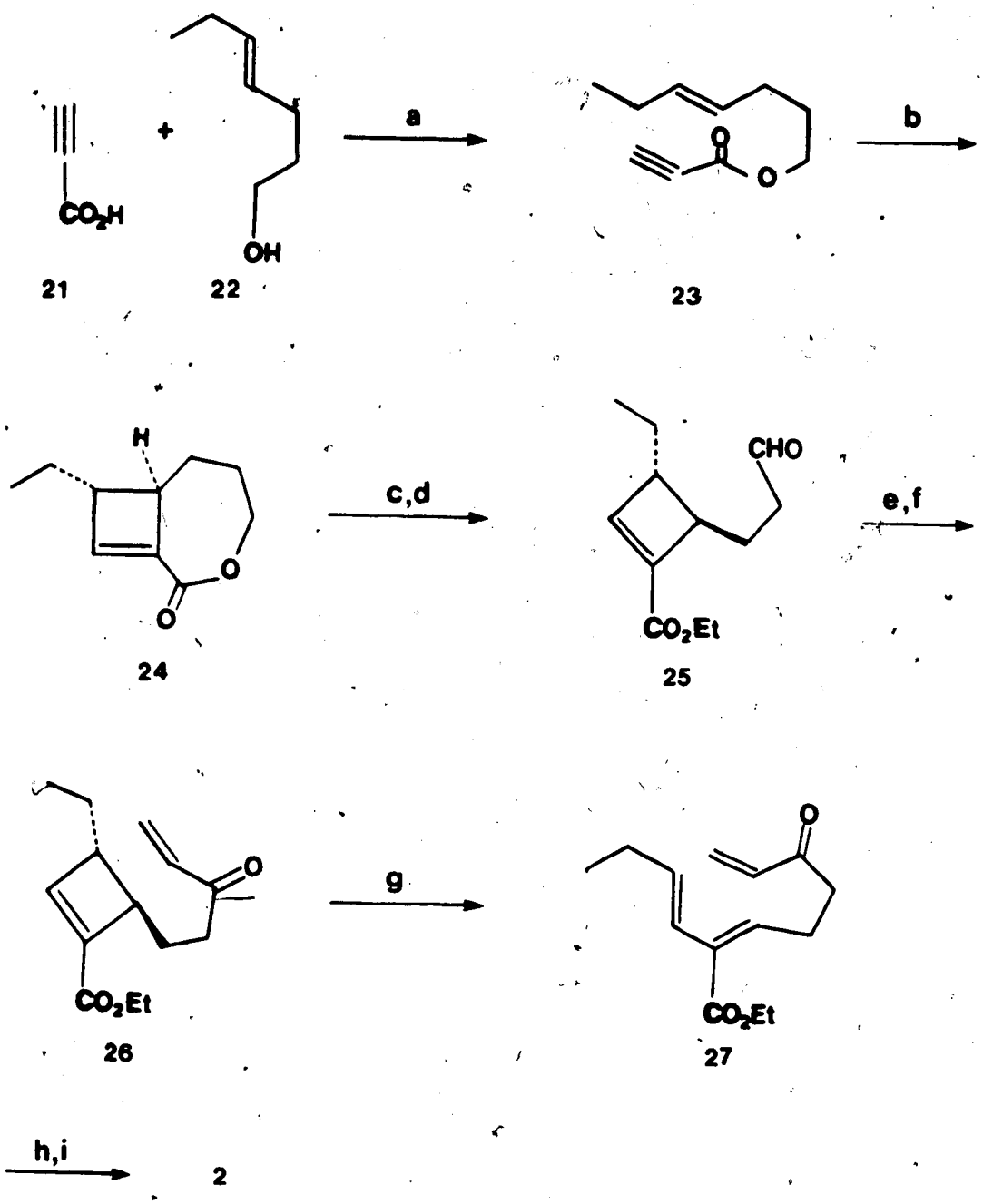
a. $LiAlH_4$, Et_2O, EtOH. b. MnO_2, pet. ether, PhH, reflux. c. $HOCH_2CH_2OH$, p-TsOH, PhH. d. Collins, CH_2Cl_2. e. LDA, THF, -45°C. f. MsCl, pyr. g. DBU, toluene. h. $NaAlH_2(OCH_2CH_2OCH_3)_2$, CuI, THF, -45° to -10°C. i. toluene, 180°C, 3 h. j. Jones reagent.

and oxidation yielding (±)-coronafacic acid (**2**).

Shortly after, Jung *et al.*[81] reported a similar approach to the synthesis of **2** *via* the trienone **27** prepared by a completely different route in which the key cyclobutene formation step was effected by an intramolecular (2+2) cycloaddition as shown in Scheme III. Esterification of propiolic acid (**21**) with alcohol **22** afforded ester **23** which, on treatment with aluminum chloride, gave cyclobutene **24**. Opening of the lactone in acidic ethanol followed by oxidation produced aldehyde **25**. Addition of vinylmagnesium bromide followed by oxidation of the resulting allylic alcohol gave enone **26**. Upon heating to 100°C, the cyclobutene ring was cleanly opened to furnish the desired trienone **27** which was shown to be stable at this temperature. However, heating a solution of **27** in toluene in a sealed tube at 180°C effected the desired cyclization to afford isomeric esters which were subjected to hydrolysis to give (±)-coronafacic acid (**2**).

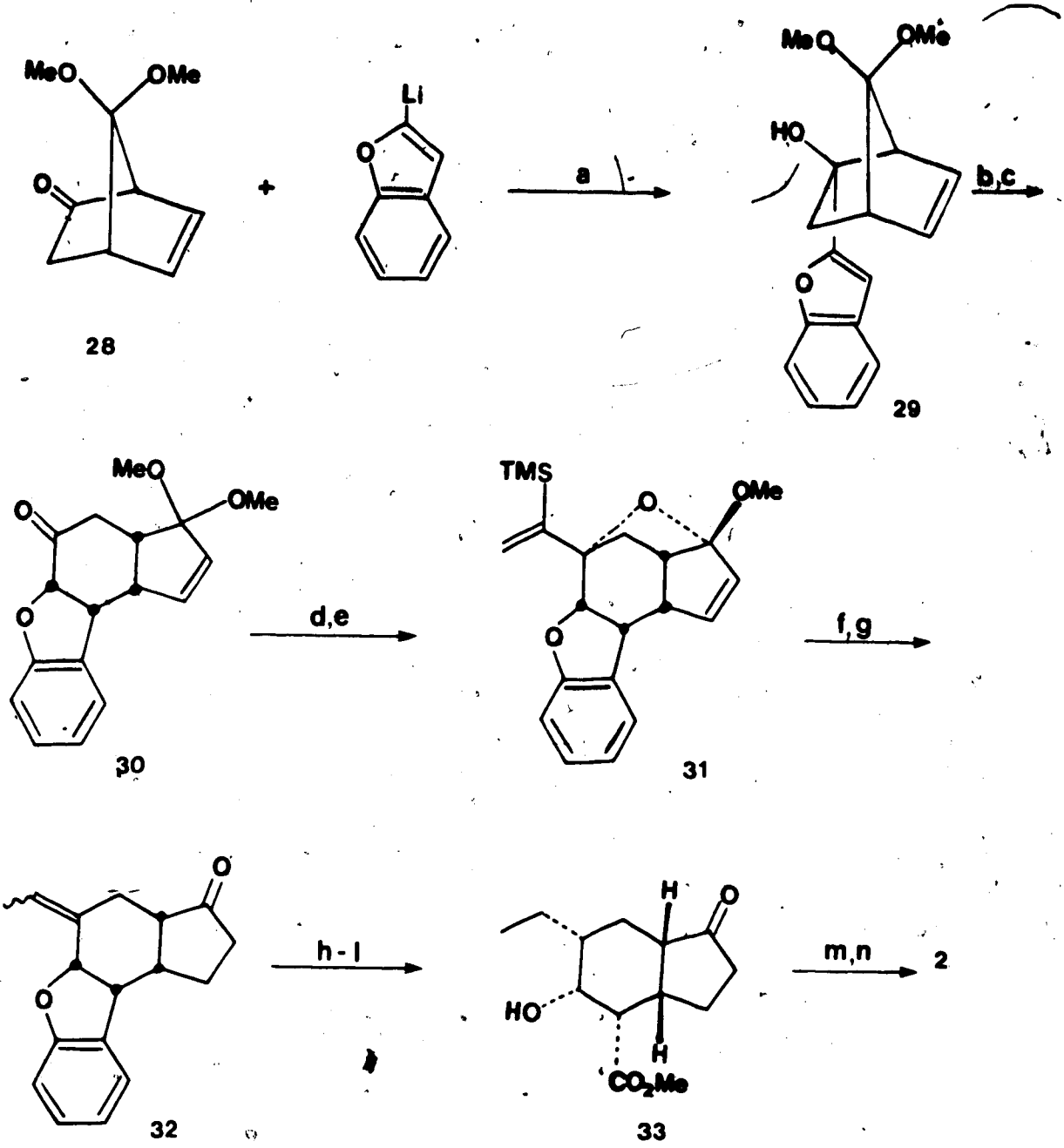
A completely different approach to the synthesis of (±)-coronafacic acid (**2**) was also reported by Jung and Hudspeth.[82] The synthesis employed as a key step an anionic oxy-Cope rearrangement reaction as shown in Scheme IV. Enone **28** was treated with 2-lithiobenzofuran to furnish the exo alcohol **29**. Refluxing a solution of **29**

SCHEME III



a. H_2SO_4. b. $AlCl_3$. c. EtOH, HCl. d. PCC. e. CH_2=CHMgBr. f. PDC. g. 100°C. h. toluene, 180°C. i. HCl.

SCHEME IV

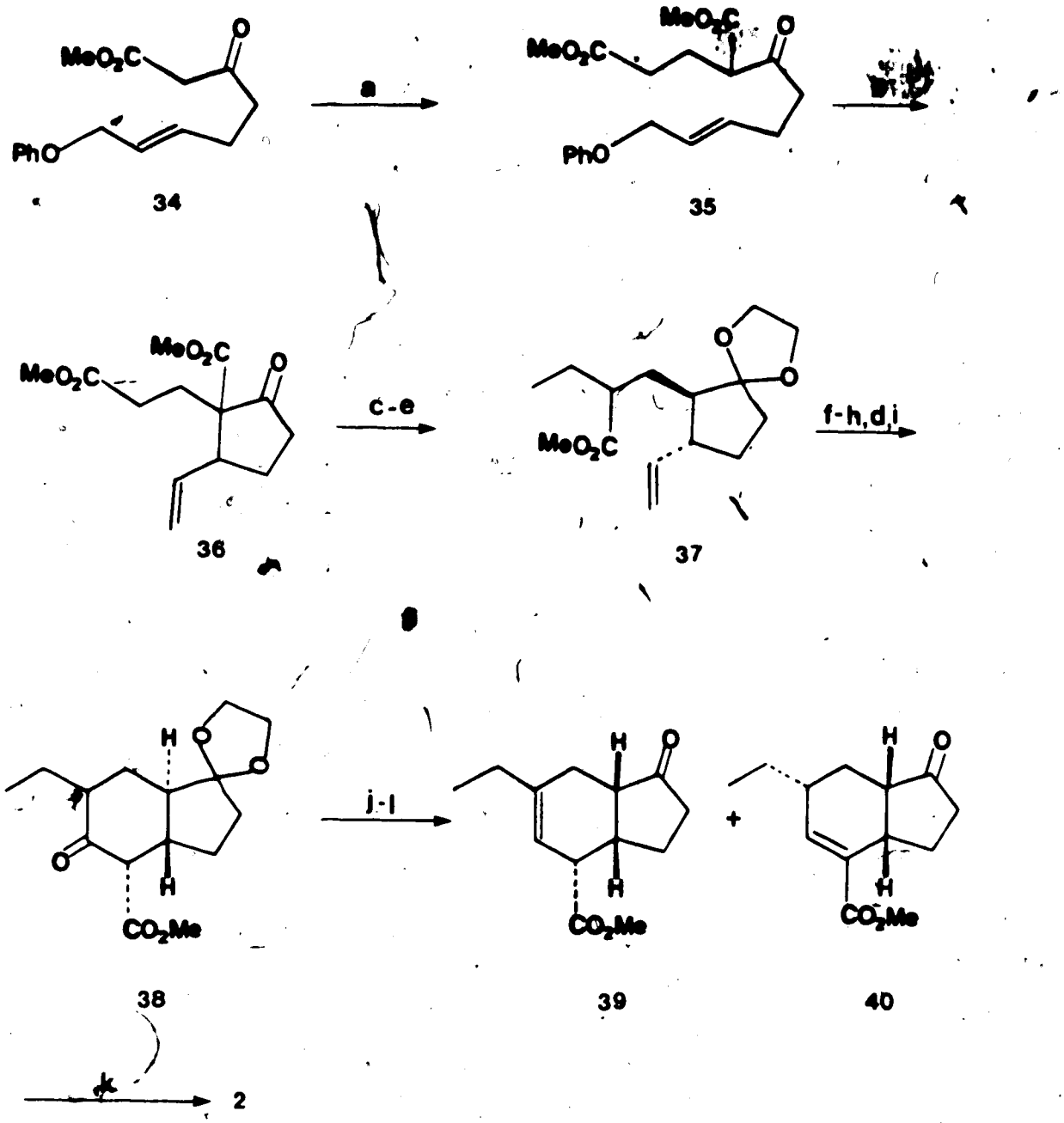


a. Et_2O. b. NaH, THF, Δ, 1 h. c. H_2O. d. $CH_2{=}C(SiMe_3)Li$, THF. e. SiO_2, PhH. f. H_2, $Rh\text{-}Al_2O_3$. g. $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 2 h. h. H_2, $Rh\text{-}Al_2O_3$. i. O_3, HOAc, 0°C, 1 h. j. aq. H_2O_2. k. aq. OH^-. l. CH_2N_2. m. $POCl_3$, pyr, Δ, 30 min. n. aq. HCl, Δ, 3 h.

and sodium hydride in tetrahydrofuran afforded the rearranged product 30. Addition of α-trimethylsilylvinyllithium to 30 followed by treatment with silica gel in benzene afforded the ketal 31. Catalytic hydrogenation produced the tetrahydro compound which underwent desilylative olefin formation upon treatment with boron trifluoride to give an isomeric mixture of keto olefins 32. Catalytic hydrogenation of 32 followed by ozonolysis in acetic acid, oxidation, hydrolysis, and esterification gave ester 33. The final conversion to (±)-coronafacic acid (2) was effected by dehydration with phosphorous oxychloride-pyridine and acid hydrolysis of the ester.

Tsuji[83] made use of a palladium-catalyzed cyclization on compound 35 in his synthesis of (±)-coronafacic acid (2) (Scheme V). Michael addition of keto ester 34 to methyl acrylate afforded diester 35. The cyclized product 36 was obtained by treatment of 35 with palladium acetate and triphenylphosphine. After demethoxycarbonylation and ketalization, the ethyl group was introduced by treatment with lithium diisopropylamide and ethyl iodide to give 37. Hydroboration, oxidation with Jones reagent, and esterification gave the diester which, after reprotection of the ketone carbonyl, was subjected to Dieckmann condensation using potassium t-butoxide in tetrahydrofuran to give the keto ester 38. Reduction of the ketone and

SCHEME V

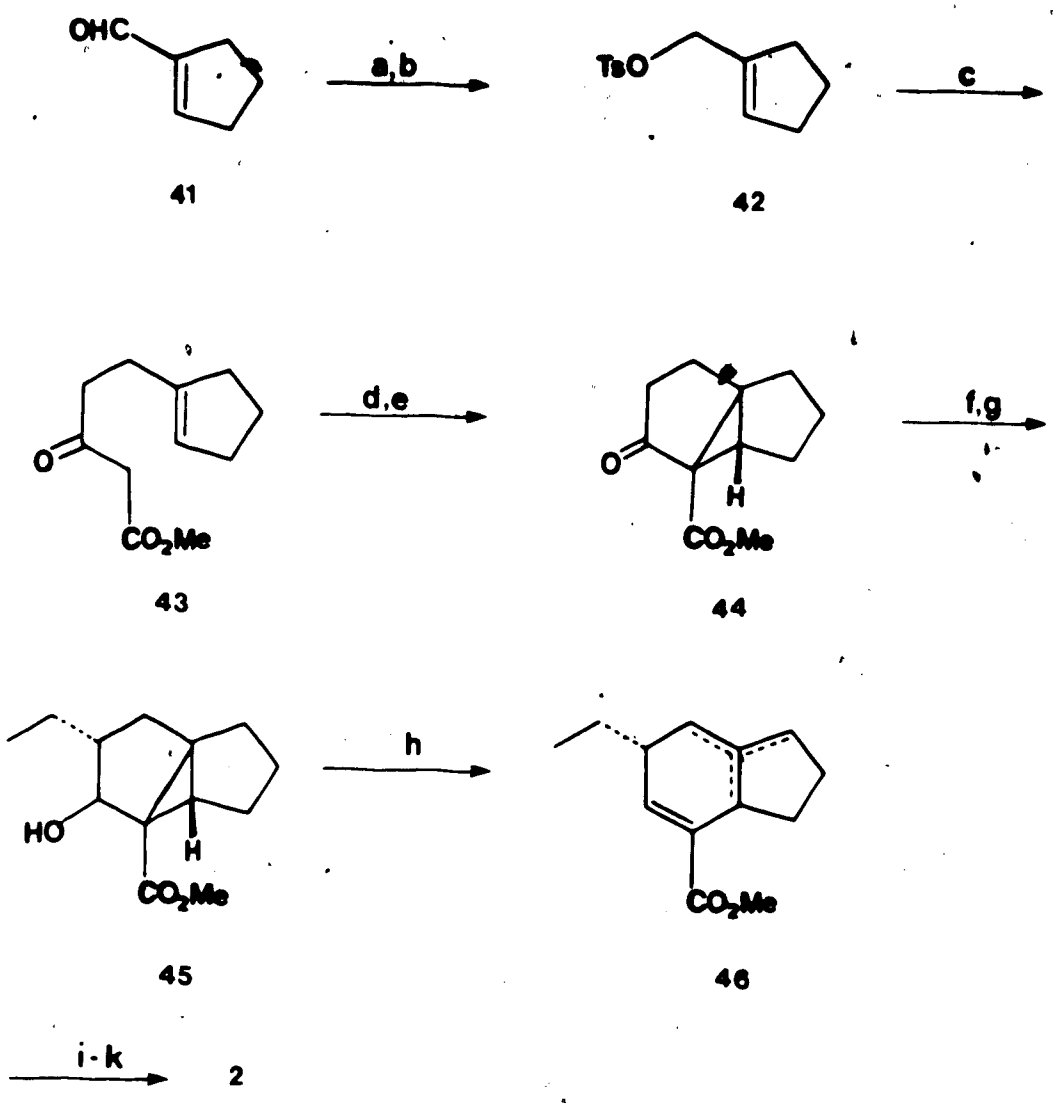


a. CH_2=CHCOOCH$_3$. b. Pd(OAc)$_2$, PPh$_3$. c. demethoxycarbonylation. d. HOCH$_2$CH$_2$OH. e. LDA, EtI. f. BH_3. g. Jones reagent. h. esterification. i. K t-BuO, THF. j. NaBH$_4$. k. H_3O^+. l. $POCl_3$.

hydrolysis of the ketal produced the keto alcohol which was dehydrated to give a mixture of double bond isomers 39 and 40. Treatment of these esters with aqueous acid gave (±)-coronafacic acid (2).

The first and only synthesis of optically active (+)-coron[redacted] (2) was accomplished by Nakayama and Ohira[85], [redacted]sed on their previous synthesis of racemic 2[84,86] from aldehyde 41 (Scheme VI). Lithium aluminum hydride reduction of 41 followed by treatment of the resulting alcohol with p-toluenesulfonyl chloride under the phase-transfer catalysis conditions yielded the corresponding sulfonate 42 which was subjected to reaction with the dianion of methyl acetoacetate. Treatment of the resulting β-keto ester 43 with p-toluenesulfonyl azide in the presence of triethylamine afforded a diazo compound, which upon heating in refluxing toluene with a catalytic amount of trimethylphosphite-copper(I) iodide complex gave cycloadduct 44. Alkylation of 44 with lithium diisopropylamide and ethyl bromide in tetrahydrofuran followed by reduction with sodium borohydride gave an epimeric mixture of alcohols 45. Treatment of 45 with p-toluenesulfonyl chloride in pyridine afforded an inseparable mixture of α,β-unsaturated esters 46 which was subjected to hydroboration. Subsequent oxidation with pyridinium chlorochromate gave a complex mixture from which the

SCHEME VI

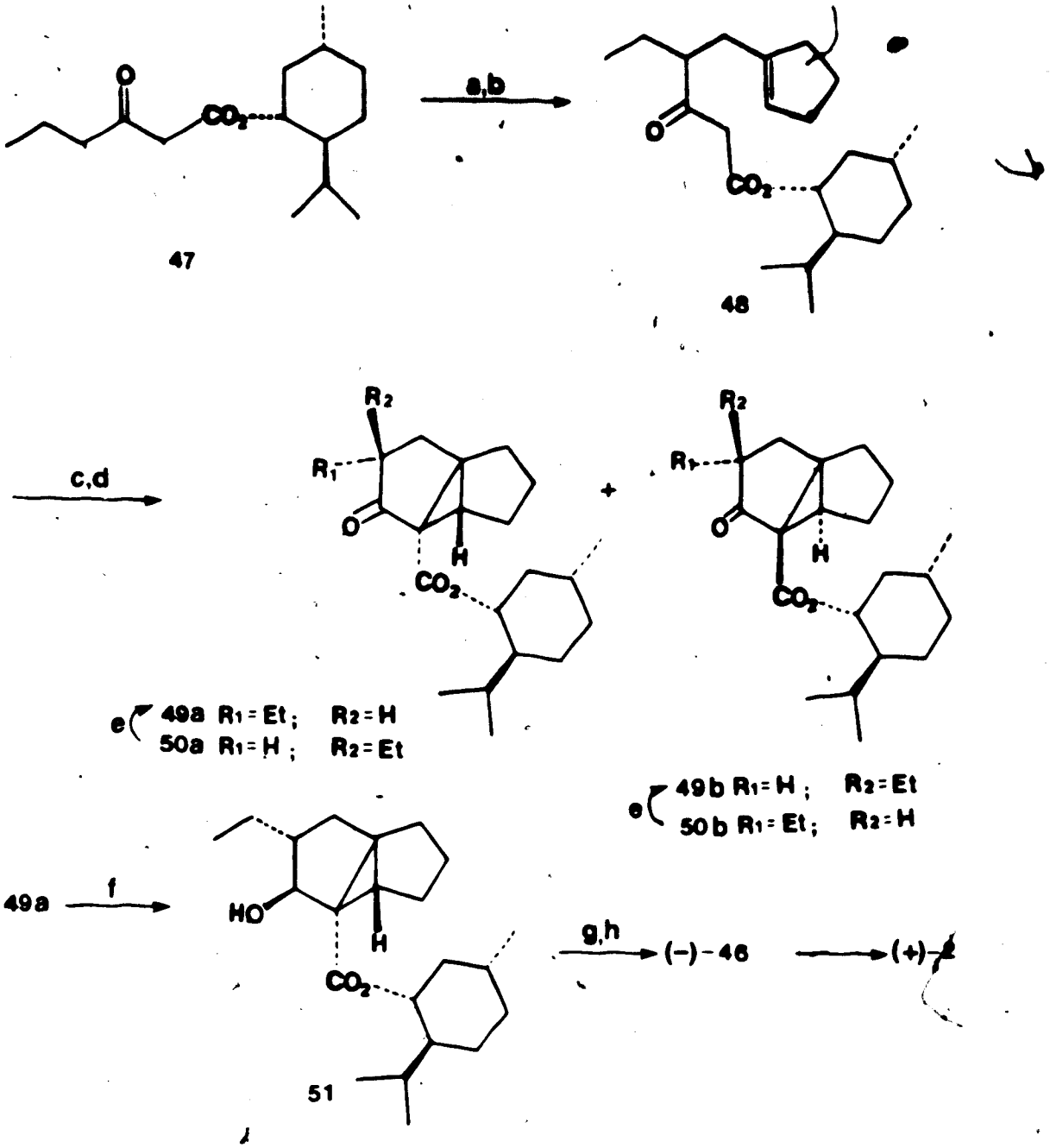


a. $LiAlH_4$, ether. b. TsCl, PhH–aq. NaOH. c. $\bar{C}H_2C\bar{O}CHCOOMe$, THF, -10°C to r.t., 8 h. d. TsN_3, Et_3N, CH_3CN. e. toluene, CuI-$(MeO)_3P$, Δ. f. LDA, HMPA, THF, EtI, 0°C, 10 h. g. $NaBH_4$, MeOH, r.t., 1 h. h. p-TsCl, pyr, r.t. overnight. i. BH_3, THF, 0°C. j. PCC, CH_2Cl_2. k. 2.4 M HCl.

methyl ester of (±)-coronafacic acid was isolated. Acid hydrolysis afforded (±)-coronafacic acid (2).

In the chiral synthesis, l-menthyl acetoacetate was used as a chiral auxiliary (Scheme VII). The dianion of l-menthyl acetoacetate was first alkylated with ethyl bromide to give the optically active 3-oxohexanoate 47. Alkylation of the dianion derived from 47 with tosylate 42 afforded keto ester 48 which was subjected to diazotization. Subsequent cyclization via a carbenoid intermediate gave a mixture of the desired keto esters 49a and 49b along with their respective epimers 50a and 50b. Treatment of the mixture with sodium methoxide in refluxing methanol caused the epimerization of the latter isomers giving rise to the more stable 49a and 49b (1:1) as the only products which were separated by column chromatography on silica gel and recrystallization from methanol. Reduction of 49a with zinc borohydride gave alcohol 51. Hydrolysis of 51 with aqueous sodium hydroxide-dimethyl sulfoxide followed by esterification with etheral diazomethane gave (-)-46. By a similar transformation as described for the synthesis of (±)-2 from (±)-46, (-)-46 was converted to (+)-2 identical in all respects with the natural product including optical rotation. Similarly, the levorotatory enantiomer (-)-2 was prepared from 49b.

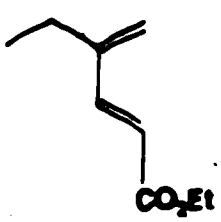
SCHEME VII



a. NaH, THF, n-BuLi. b. 42, THF. c. TsN_3, Et_3N, CH_3CN. d. CuI-$(MeO)_3P$, toluene, Δ. e. NaOMe, MeOH. f. $ZnBH_4$, ether. g. aq. NaOH-DMSO, Δ. h. CH_2N_2, ether.

Our approach[87] to the synthesis of (±)-coronafacic acid is based on an intramolecular Diels-Alder reaction. Ethyl 4-ethyl-2,4-pentadienoate (52) was chosen as the diene and 4-cyclopentene-1,3-dione (53) as the dienophile for its high dienophilicity and symmetry. The use of unsymmetrical 2-cyclopentenones is expected to produce adducts such as 54 possessing the undesirable regiochemistry according to the ortho and para rules[88] governing the Diels-Alder reaction. The cycloaddition of enedione 53 and diene 52, on the other hand, would lead to adduct 55, the conversion of which to the target molecule requires only minor adjustments of the functionalities.

Based on the synthetic strategy outlined above, an efficient total synthesis of (±)-coronafacic acid (2) has been achieved. The details are reported in the next chapter.



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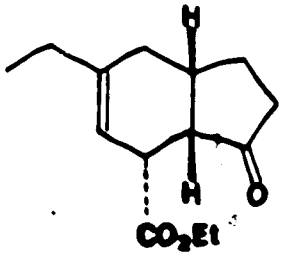

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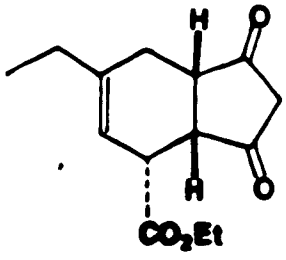
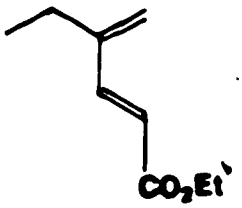


55

RESULTS AND DISCUSSION

Ethyl 4-ethyl-2,4-pentadienoate (52) was prepared according to the procedure of Holcombe et al.[89] Treatment of α-ethylacrolein (56), obtained from n-butanal via a Mannich reaction with formaldehyde and dimethylamine hydrochloride,[90] with the sodium salt of triethylphosphonoacetate in ethanol afforded diene 52 in 58% yield. The nmr spectrum displayed two mutually coupled doublets at δ7.30 and 5.86 (J = 16 Hz) integrating to one proton each for the β and α protons of the unsaturated ester moiety respectively. A broad singlet at δ5.32 was observed for the δ protons. A quartet and a triplet appeared at δ4.18 and 1.28 for the ethyl ester. The vinylic ethyl group also appeared as a pair of quartet (δ2.25) and triplet (δ1.10).



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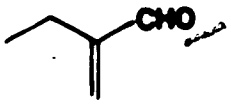
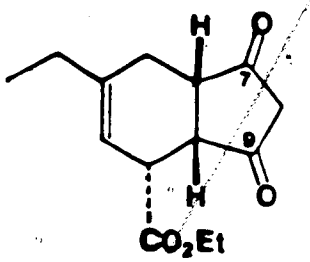


56

The Diels-Alder reaction between diene **52** and the commercially available 4-cyclopentene-1,3-dione (**53**) was attempted under a variety of conditions. In refluxing toluene the cycloaddition occurred smoothly to give a 67% yield of the crystalline adduct **55**, m.p. 86-88°C. In refluxing xylene the reaction proceeded more rapidly but the yield of the product was lower (48%). The reaction was also attempted under Lewis acid catalysis which is known to facilitate the Diels-Alder addition.[91,92] Disappointingly, when the reaction was performed in the presence of ferric chloride or stannic chloride in methylene chloride at 0°C or room temperature, no reaction was observed. The nmr spectrum of adduct **55** indicated that the compound was completely enolized in chloroform solution and that the two enol forms were present in a ratio of ca. 5:1. In both cases, the proton of the hydroxyl group of the enol appeared at δ6.04 as a broad singlet. The major isomer displayed a singlet at δ5.26 for the enone proton and a doublet of doublets at δ5.58 with coupling constants of 6 and 1 Hz for the vinylic proton of the isolated double bond. The ethyl ester displayed a quartet at δ4.26 and a triplet at δ1.34. The minor isomer showed the enone proton at δ5.29 as a singlet and the other vinylic proton at δ5.62 as a doublet (J = 6 Hz). The presence of enols was further confirmed by

absorption bands at 3400, 1642 and 1549 cm^{-1} in the ir spectrum. A molecular ion at m/e 250.1202 in the mass spectrum, as well as elemental analysis, verified the chemical formula of $C_{14}H_{18}O_4$.



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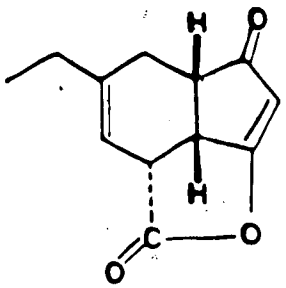

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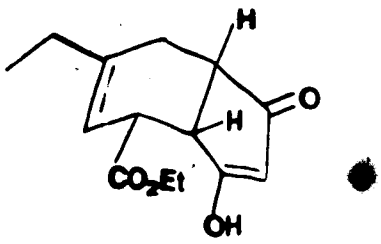
After obtaining adduct 55, a method had to be devised that would enable us to differentiate between the two carbonyl groups. Since the ketone group at the C9 position is in the proximity to the ester group, it could, in principle, undergo lactonization with the latter to form the vinyl lactone 57. Unfortunately, when adduct 55 was treated with 10-camphorsulfonic acid in benzene or with p-toluenesulfonic acid in refluxing toluene, the starting material was recovered intact. In fact, a close examination of Drieding models reveals that the C9 hydroxyl group of the enolized diketone 58 is not sufficiently close to the ester group to warrant the

lactonization. Furthermore, the resulting lactone 57 would be highly strained.

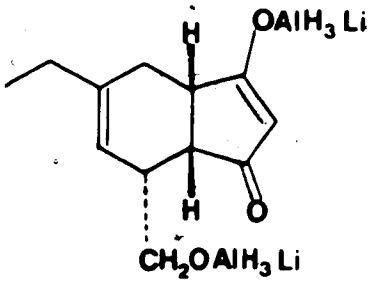


58

Due to our inability to effect the lactonization, an alternative method was sought to distinguish the two ketone carbonyls in diketone 55. The C9 ketone carbonyl being γ to the carbethoxy group is conceivably more hindered than the C7 ketone. Consequently, the two carbonyl groups should show different reactivities towards a bulky reagent. Along this line, several reactions were attempted. First, diketone 55 was treated with lithium aluminum hydride* in refluxing ether. It was expected that the ester group would be reduced to the primary alcohol and that the salt 59 would be formed with the aluminum ~~moiety~~ attached to the less hindered oxygen

*The reduction with sodium borohydride was not attempted because after the initial acid-base reaction, the reagent is not strong enough to reduce the incipient vinylogous carboxylate ion.

atom. Further reduction would then result in the formation of enone **60** which might be further reduced to the unsaturated alcohol **61**. In practice, however, the reaction gave a complex mixture from which the desired product **61** could not be recognized.



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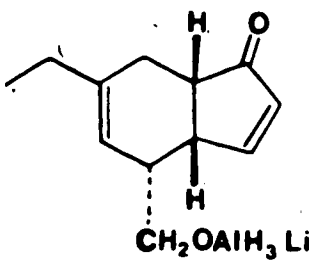

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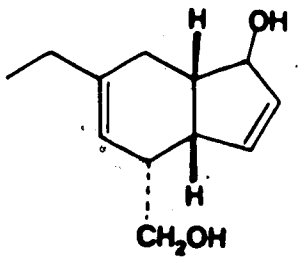
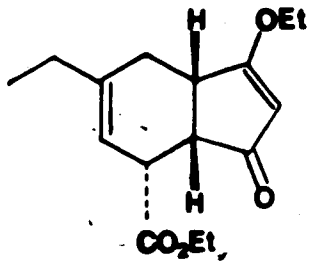


61

The second reaction attempted was the treatment of diketone **55** with ethylenedithiol and boron trifluoride etherate in methylene chloride to induce selective thioketalization of the less hindered C7 ketone carbonyl. However, no reaction occurred probably because compound **55** behaves more like an acid than a β-diketone due to complete enolization.

The third attempt to differentiate the two carbonyl groups of diketone **55** was focused on the preparation of the vinylogous ester **62**. Towards this end, diketone **55** was treated with triethyl orthoformate in ethanol in the



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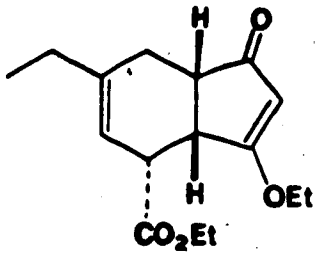
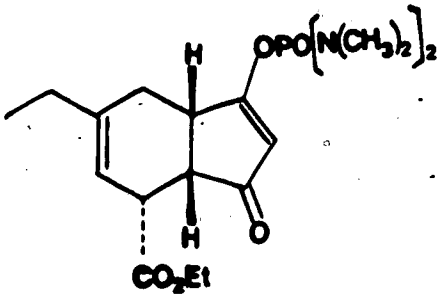


63

presence of a catalytic amount of concentrated sulfuric acid.[93] Two inseparable compounds **62** and **63** were obtained in a 1:1 ratio as determined by nmr analysis and in a combined yield of 60%. The ir spectrum showed an absorption band at 1735 cm^{-1} for the ester. Enone absorption bands were observed at 1700 and 1595 cm^{-1}. In the nmr spectrum, one isomer displayed a broad singlet at δ5.59 for the enone proton, while the corresponding proton of the other isomer appeared at δ5.49. The nmr spectrum also showed the presence of ethyl esters and ethoxy groups with a multiplet at δ4.12 for the methylene protons and triplets at δ1.41, 1.43, 1.29, and 1.27 for the methyl protons. The mass spectrum displayed a molecular ion at m/e 278.1516 ($C_{16}H_{22}O_4$). We reasoned that maybe triethyl orthoformate was not bulky enough and thus gave poor selectivity. We thought that the problem could be solved

by using a much bulkier reagent such as bis(dimethylamino)phosphorochloridate. However, when the lithium salt of diketone 55, generated *in situ* using lithium hydride, was treated with bis(dimethylamino)phosphorochloridate in 1,2-dimethoxyethane in the presence of a small amount of hexamethylphosphoramide,[93] poor selectivity was again observed. Two isomeric tetramethyl phosphorodiamidate derivatives **64** and **65** were obtained in *ca.* 1:1 ratio (by nmr analysis) and in a combined yield of 58%. The ir spectrum showed carbonyl absorption bands at 1730 cm^{-1} for the ester and at 1700 cm^{-1} for the unsaturated five-membered ring ketone. A strong absorption band at 1298 cm^{-1} was also observed due to the phosphate group. The nmr spectrum showed the proton on the enone moiety at δ5.87 for one isomer and at δ5.78 for the other, each as a broad singlet. Methyl signals for the tetramethyl phosphorodiamidate group were observed at δ2.74, 2.71, 2.69, and 2.61 as doublets with a coupling constant (J_{P-H}) of 10 Hz each. The mass spectrum showed a molecular ion at m/e 384.1827 indicating the molecular formula $C_{18}H_{29}N_2O_5P$. Although the reaction did not show any selectivity and compounds **64** and **65** could not be easily separated by column chromatography, several reduction reactions were attempted. Sodium borohydride reduction of the mixture of **64** and **65** in ethanol gave a complex mixture



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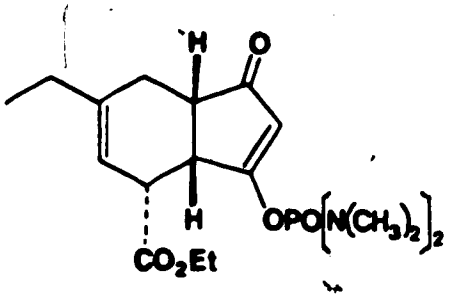
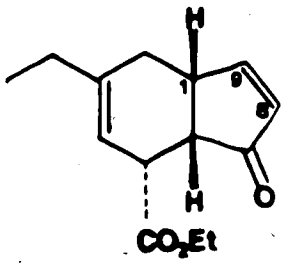


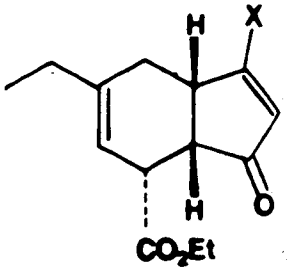
65

from which enone **66** could be isolated in 22% yield. Enone **66** displayed, in the ir spectrum, an ester band at 1730 cm^{-1} and enone absorptions at 1720 and 1595 cm^{-1}. The nmr spectrum displayed two doublets of doublets at δ7.49 (J = 6, J' = 3 Hz) and 6.16 (J = 6, J' = 2 Hz) for the β and α protons of the enone system respectively. The vinylic proton of the isolated double bond appeared at δ5.50 also as a doublet of doublets (J = 6, J' = 1 Hz). The ethyl ester displayed a quartet at δ4.12 and a triplet at δ1.27. The regiochemistry of the enone **66** was proven by spin-spin decoupling experiments which showed that the C1 methine proton (δ3.48, m) was coupled with the α (J = 2 Hz) and β (J = 3 Hz) protons of the enone. The mass spectrum showed a molecular ion at m/e 234.1256 in accordance with the chemical formula $C_{14}H_{18}O_3$.



66

The Birch reduction was also attempted on the mixture of **64** and **65** using lithium in liquid ammonia.[95] The reaction gave rise to a complex mixture of saturated keto esters and keto alcohols, the nmr spectrum of which showed the absence of any conjugated double bond.



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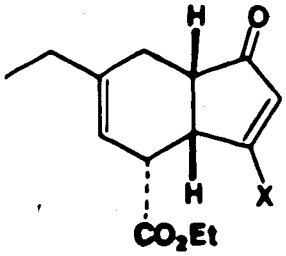

68

From the above results, we concluded that the ketone carbonyls in **55** could not be cleanly differentiated even

with rather bulky reagents. To circumvent this problem, we focused our attention to the preparation of derivatives of the types **67** and **68** that could be separated and then individually converted to coronafacic acid (**2**). Towards this end, the isomeric chlorides **69** and **70** were synthesized. Most of the reported methods[96] for the conversion of 1,3-diketones into the corresponding β-chloro-α,β-unsaturated ketones employ a tertiary amine for the initial deprotonation of the 1,3-diketone. Application of these methods to diketone **55** resulted invariably in severe loss of material. In order to overcome this problem, lithium hydride was selected as a base. When the lithium salt of diketone **55** was treated with phosphorous oxychloride in tetrahydrofuran in the presence of hexamethylphosphoramide, chlorides **69** and **70** were obtained in a 3:2 ratio and in a total yield of 45%. When the reaction was carried out using phenyl dichlorophosphate and lithium chloride,* the yield of the products was improved considerably to 64% although the ratio remained the same. The two isomeric chlorides were separable by high pressure liquid chromatography. The ir spectrum of

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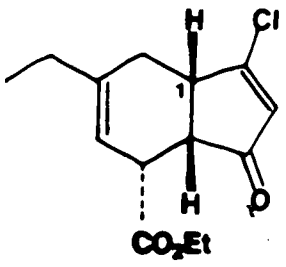
*A combination of lithium hydride, lithium chloride, and phenyl dichlorophosphate proved to be highly effective for the conversion of cyclic 1,3-diones to the corresponding β-chloro-α,β-unsaturated ketones.[97]

the major isomer **69** showed absorption bands at 1716 (ester and unsaturated five-membered ring ketone) and 1591 cm^{-1} (olefin). The nmr spectrum displayed a doublet (J = 2 Hz) at δ6.21 for the enone proton and a triplet of doublets of doublets (J = 7, J' = 2, J" = 1 Hz) at δ5.53 for the proton attached to the isolated double bond. The methylene protons of the ethyl ester group appeared as quartets at δ4.16 and 4.15 while the methyl protons displayed a triplet at δ1.26. Molecular ions at m/e 270.0842 and 268.0865 in the mass spectrum, as well as elemental analysis, verified the chemical formula of $C_{14}H_{17}ClO_3$. The nmr spectrum of the minor isomer **70** showed a doublet at δ6.23 (J = 2 Hz) for the proton on the enone and a doublet of doublets at δ5.43 (J = 7, J' = 2 Hz) for the proton on the isolated double bond. The ethyl ester displayed a quartet at δ4.17 and a triplet at δ1.28. The mass spectrum showed molecular ions at m/e 270.0850 and 268.0875 ($C_{14}H_{17}ClO_3$).



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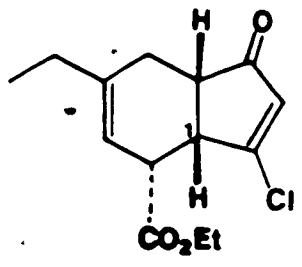

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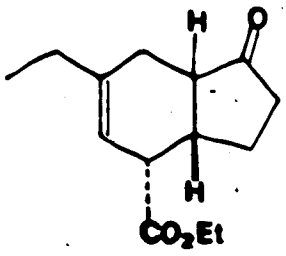
The regiochemistry of chlorides **69** and **70** was deduced on the basis of the following observations. In the nmr spectrum the Cl proton of the major isomer appeared at δ3.51 as a doublet of doublets of doublets of doublets with coupling constants of 7, 7, 2.5, and 2 Hz. This proton was shown by spin-spin decoupling experiments to be coupled to the enone proton which appeared at δ6.21 as a doublet with a small coupling constant of 2 Hz. On the other hand, the enone proton (doublet at δ6.23) of the minor isomer was found to be coupled, with a coupling constant of 2 Hz, to the Cl proton at δ3.78 (ddd, J = 7, J' = J" = 2 Hz).

At this point, studies were undertaken for the individual transformation of chlorides **69** and **70** to keto ester **71**. For the conversion of **70** into **71**, the chlorine atom had to be removed and the double bond of the enone selectively hydrogenated. Chloride **70** was converted to enone **72** using a zinc-silver couple, prepared from 30 mg of silver acetate per gram of zinc.[98] Thus, treatment of **70** with the zinc-silver couple in methanol afforded enone **72** in 64% yield along with the unreacted starting material. The ir spectrum showed absorption bands for an ester (1730 cm^{-1}), an unsaturated five-membered ring ketone (1712 cm^{-1}), and an olefin (1590 cm^{-1}). The nmr spectrum displayed two doublets of doublets at δ7.62 (J =

6, J' = 3 Hz) and 6.26 (J = 6, J' = 2 Hz) for the β and α protons of the enone respectively. The proton of the isolated double bond appeared at δ5.51 as a doublet of doublets with coupling constants of 7 and 2 Hz. The ethyl ester group displayed a quartet at δ4.22 for the methylene protons and a triplet at δ1.31 for the methyl protons. A molecular ion at m/e 234.1256 in the mass spectrum indicated the molecular formula $C_{14}H_{18}O_3$.



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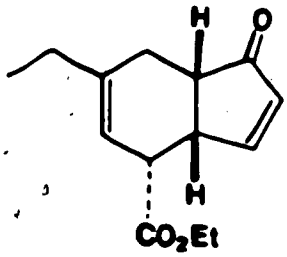

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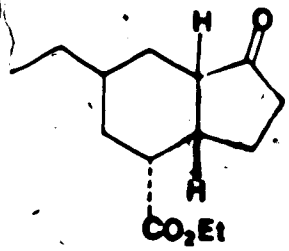


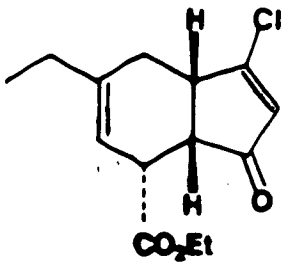
73

Hydrogenation of enone 72 in ethanol using 5% palladium on carbon as a catalyst gave a mixture of fully saturated keto esters 73 in 91% yield. The ir spectrum showed a carbonyl absorption band at 1732 cm^{-1} due to the ester and the saturated five-membered ring ketone. The nmr spectrum showed the absence of any vinylic protons. The presence of four stereoisomers was suggested by triplets at δ0.91, 0.90, 0.87, and 0.86 for the methyl

group of the ethyl side chain. The mass spectrum showed a molecular ion at m/e 238.1566 indicating the molecular formula $C_{14}H_{22}O_3$. When the hydrogenation was carried out in ethyl acetate, the less substituted carbon-carbon double bond was reduced exclusively to give a 92% yield of keto ester 71 as a mixture of two stereoisomers in ca. 9:1 ratio (by nmr analysis). The ir spectrum showed a carbonyl absorption band at 1732 cm^{-1} for the saturated five-membered ring ketone and the ester. The major isomer displayed, in the nmr spectrum, a vinylic proton at δ5.37 as a broad singlet and an ethyl ester with a quartet at δ4.18 and a triplet at δ1.33. The minor isomer showed a vinylic proton at δ5.44 and an ethyl ester at δ4.18 and 1.34. A molecular ion at m/e 236.1410 in the mass spectrum, as well as elemental analysis, verified the chemical formula of $C_{14}H_{20}O_3$.

Later, we were very pleased to find that chloride 70 could be directly converted to keto ester 71 by a single reaction. It is known that vinyl halides undergo hydrogenolysis of the carbon-halogen bond when treated with hydrogen in the presence of a variety of catalysts.[99] Several studies[100,101] have also indicated that in the presence of a base the rate of the carbon-halogen bond cleavage is enhanced. Thus, chloroenone 70 was subjected to hydrogenolysis using 5% palladium on

carbon and a variety of solvents and bases. The combination of ethyl acetate and potassium acetate resulted in the formation of the desired keto esters 71 and the fully hydrogenated keto esters 73 in a ratio of ca. 5:1 (by nmr analysis). When 1,4-diazabicyclo[2.2.2]-octane (DABCO) was used as a base, similar results were obtained. The use of a less polar solvent such as benzene was found to enhance the selectivity. The best results were obtained when benzene was used as a solvent and sodium bicarbonate as a base. Under these conditions, chloride 70 was converted in consistently high yield of ca. 83% to the epimeric keto esters 71.



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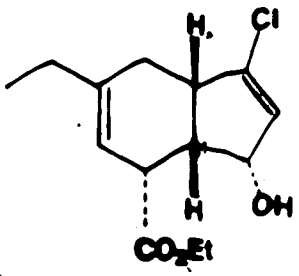
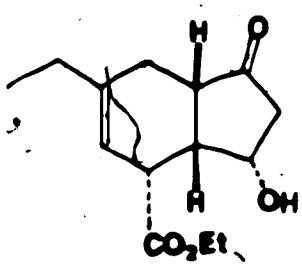


74



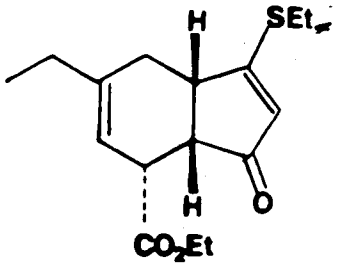
75

The conversion of chloride, 69 into 71 was less straightforward. Our initial plan was to reduce chloroenone 69 to alcohol 74 which could be hydrolyzed to the corresponding keto alcohol 75. Subsequent dehydration

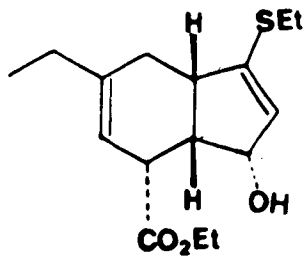
of **75** would lead to the desired intermediate **72**. Accordingly, chloroenone **69** was reduced with sodium borohydride in ethanol to give alcohol **74** in 76% yield. The ir spectrum showed a broad absorption band at 3400 cm^{-1} indicative of an alcohol. A carbonyl band was observed at 1730 cm^{-1} due to the ester. The nmr spectrum displayed a broad singlet at δ 5.85 for the proton on the six-membered ring olefin and a doublet of doublets at δ 5.76 with coupling constants of 2 and 4 Hz for the proton on the five-membered ring olefin. A complex signal at δ 4.76 was assigned to the methine proton adjacent to the hydroxyl group. A molecular ion at m/e 270.0985 in the mass spectrum verified the chemical formula of $C_{14}H_{19}Cl^{35}O_3$. The stereochemistry of alcohol **74** was tentatively assigned as shown, resulting from the hydride attack from the less hindered face of the starting substrate. Alcohol **74** was treated with a variety of acids as well as with titanium tetrachloride. Unfortunately, in all cases it underwent extensive decomposition without apparent formation of the desired hydrolysis product **75**.

To overcome this difficulty, we studied the possibility of replacing the chlorine atom in **69** with a different functionality which, after the selective reduction of the ketone carbonyl, could be easily hydrolyzed to a ketone. Our first choice was a vinyl

sulfide. It was expected that the vinylogous thioester group of compound **76** would undergo selective reduction over the ethyl ester group and the resulting alcohol **77** could be easily hydrolyzed to **75**. On treatment of **69** with ethanethiol and triethylamine in benzene, enone **76** was obtained in 84% yield. The ir spectrum showed an absorption band at 1725 cm^{-1} due to the ester. Absorption bands at 1696 and 1548 cm^{-1} were observed for the enone moiety. The nmr spectrum displayed two doublets, one at δ [illegible] (J = 1 Hz) for the enone proton, and the other at [illegible] J = 7 Hz) for the proton on the isolated double bo[illegible]. The ethylthio group appeared as a quartet at δ2.93 and a triplet at δ1.41. Two quartets at δ4.14 and 4.16 and a triplet at δ1.30 were observed for the methylene and methyl protons of the ethyl ester. The mass spectrum displayed a molecular ion at m/e 294.1287 indicating the chemical formula $C_{16}H_{22}O_3S$.



76

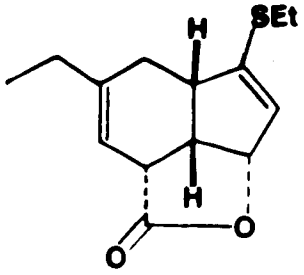


77

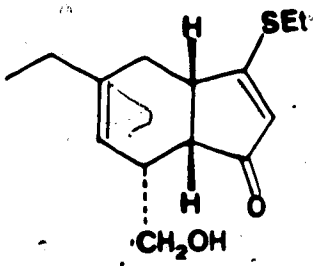
For the selective reduction of the carbonyl group of the vinylogous thioester, several methods were attempted. Treatment of **76** with sodium borohydride[102] in ethanol at 0°C resulted in the recovery of the starting material. When the reaction was carried out at room temperature two products were obtained along with unreacted **76**. The first product, obtained in 26% yield, showed in the ir spectrum a carbonyl absorption band at 1756 cm^{-1}. The nmr spectrum displayed a broad doublet at δ5.53 with a coupling constant of 7 Hz for the proton on the isolated olefin. An up-field shift observed for the proton originally attached to the enone double bond from δ5.93 to 5.59 together with the presence of a broad singlet at δ5.39, attributable to an allylic methine proton on a carbon bearing an oxygen atom, suggested that the desired reduction had occurred. The ethylthio group displayed a quartet at δ2.79 and a triplet at δ1.39. The absence of signals for the ethyl ester group in the nmr spectrum and absorption band for alcohol in the ir spectrum suggested the presence of a lactone. The mass spectrum showed a molecular ion at m/e 250.1039 indicating the molecular formula $C_{14}H_{18}O_2S$. On the basis of all these spectral data, structure **78** was assigned to the compound.

The second product, obtained in 10% yield, showed, in

the ir spectrum, an absorption band at 3400 cm^{-1}



78



79

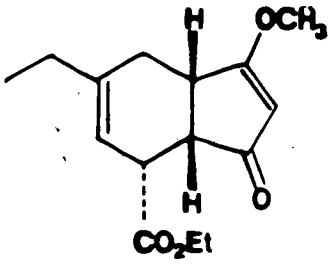
indicating the presence of an alcohol. Absorption bands at 1685 and 1554 cm^{-1} indicated the presence of an enone. The nmr spectrum displayed a doublet at δ5.93 (J = 1 Hz) for the proton on the enone and a broad singlet at δ5.32 for the proton on the isolated double bond. The ethylthio group displayed a quartet at δ2.97 and a triplet at δ1.44. The absence of signals for the ethyl ester coupled with the presence of complex signals at δ4.20 and 3.89 integrating to one proton each strongly suggested that the ester group had been reduced to the alcohol level. The mass spectrum showed a molecular ion at m/e 252.1189 for the chemical formula $C_{14}H_{20}O_2S$. On the basis of these spectral data structure **79** was assigned to the alcohol.

A second attempt on the selective reduction of

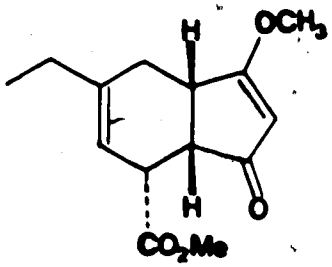
compound **76** was made using lithium tri-t-butoxyaluminum hydride. In this case, alcohol **79** was obtained as the sole product in 48% yield.

The unexpected difficulties associated with the selective reduction of the vinylogous thiol ester group in **76** led us to explore an alternative route. Treatment of chloride **69** with silver nitrate in hot methanol furnished esters **80** and **81** in ca. 9:1 ratio and in 82% yield. The ir spectrum of ester **80** displayed an ester absorption band at 1724 cm^{-1}. Absorption bands at 1698 and 1600 cm^{-1} were observed for the unsaturated five-membered ring ketone. The nmr spectrum displayed a triplet of doublets of doublets at δ5.53 (J = 7, J' = 2, J" = 1 Hz) for the proton on the isolated olefin and a doublet at δ5.32 (J = 1 Hz) for the proton on the enone. The ethyl ester group displayed quartets at δ4.16 (1H) and 4.14 (1H) for the methylene protons and a triplet at δ1.27 for the methyl protons. A sharp singlet at δ3.83 was obtained for the methoxy group. The mass spectrum showed a molecular ion at m/e 264.1365 ($C_{15}H_{20}O_4$). The nmr spectrum of ester **81** showed sharp singlets at δ3.83 and 3.71 for the methoxy and methyl ester groups respectively. A molecular ion at m/e 250.1210 in the mass spectrum verified the chemical formula $C_{14}H_{18}O_4$. Obviously, in hot methanol partial transesterification occurred leading to the formation of

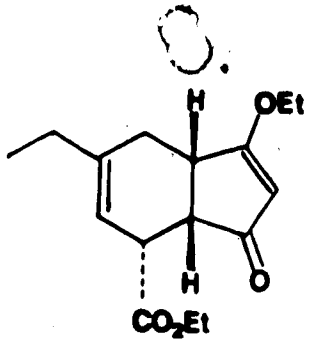
methyl ester **81**. To avoid this problem, ethanol was used instead of methanol. The reaction, however, was found to be very slow and the yield of the desired ester **62** was rather poor.



80



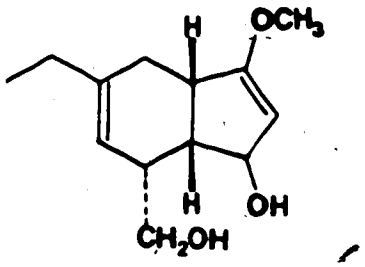
81



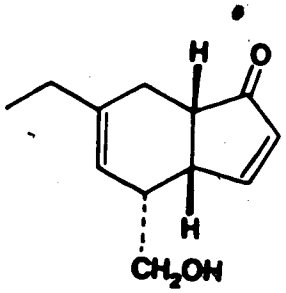
62

In view of these results, it was decided to carry on the synthesis with the mixture of **80** and **81**. Selective reduction of the enone carbonyl was attempted with sodium borohydride and with lithium tri-t-butoxyaluminum hydride but without much success. Reduction with lithium aluminum hydride in ether, followed by hydrolysis of the resulting diol **82** with dilute hydrochloric acid afforded hydroxy enone **83** in 70% yield. The ir spectrum showed absorption bands at 3425 (alcohol), 1704 (ketone), and 1585 cm^{-1} (enone double bond). The nmr spectrum displayed a pair of doublets of doublets at δ7.64 (J = 6, J' = 3 Hz) and 6.17 (J = 6, J' = 2 Hz) for the β and α protons of the enone.

A doublet at δ5.35 (J = 5 Hz) was obtained for the proton on the isolated double bond. Signals at δ3.75 (1H) and 3.69 (1H), each as a doublet of doublets with coupling constants of 18 and 6 Hz, were assigned to the methylene protons neighboring the hydroxyl group. A molecular ion at m/e 192.1143 in the mass spectrum, as well as elemental analysis, verified the molecular formula $C_{12}H_{16}O_2$.



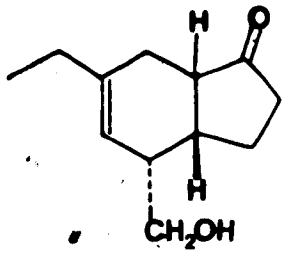
82



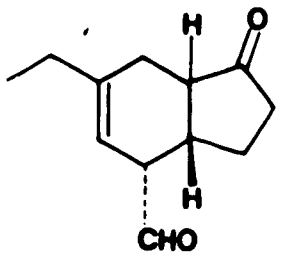
83

Catalytic hydrogenation of enone 83 using 5% palladium on carbon in ethyl acetate afforded a mixture of the epimeric keto alcohols 84 in ca. 9:1 ratio (by nmr analysis) and in 86% yield. The ir spectrum showed an absorption band at 3440 cm^{-1} due to the alcohol. The appearance of a carbonyl absorption at 1739 cm^{-1} indicated the presence of a saturated five-membered ring ketone. The nmr spectrum displayed broad singlets at δ5.25 and 5.23 for the vinylic protons of the major and minor

isomers respectively. A molecular ion at m/e 194.1305 in the mass spectrum confirmed the chemical formula of $C_{12}H_{18}O_2$.



84

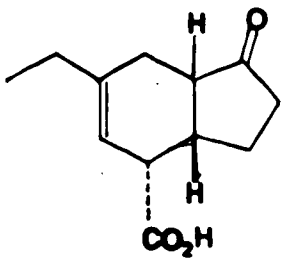


85

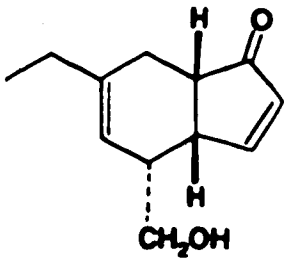
The final conversion of **84** into (±)-coronafacic acid (**2**) requires the isomerization of the carbon-carbon double bond and the oxidation of the alcohol to an acid. In order to facilitate the isomerization of the double bond the alcohol was first converted to an aldehyde. Treatment of the epimeric mixture of keto alcohols **84** with chromium trioxide and pyridine in methylene chloride,[103] afforded a mixture of [illegible]ic aldehydes **85** in ca. 9:1 ratio (by nmr analysis [illegible] rather low yield of 53%. The ir spectrum [illegible] rption bands at 2840 and 1689 cm^{-1} due to the al[illegible] at 1710 cm^{-1} due to the saturated five-membered [illegible]ng ketone. The nmr spectrum showed the presence of two isomers in ca. 9:1 ratio. The major

isomer displayed the vinylic proton at δ5.41 as a broad singlet while the corresponding proton of the minor isomer appeared at δ5.36 also as a broad singlet. The aldehydic proton was observed at δ9.73 as a broad singlet for both isomers. The mass spectrum showed a molecular ion at m/e 192.1145 ($C_{12}H_{16}O_2$). Attempts to isomerize the double bond using potassium carbonate in water-methanol resulted in extensive decomposition of the material. The use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene also gave a complex mixture.

The above results led us to examine the direct oxidation of alcohol **84** to the carboxylic acid **86**. Surprisingly, treatment of keto alcohol **84** with Jones reagent in acetone[104] caused substantial loss of material without apparent formation of the desired product.



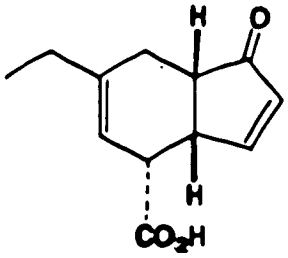
86



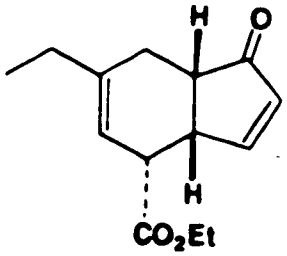
83

At this point, it was decided to investigate the

oxidation of enone alcohol **83** as an alternative means to the target molecule. We were very pleased to find that **83** could be easily oxidized to the corresponding acid using 8 N Jones reagent in acetone. The crude acid **87**, which showed absorption bands at 3060 (acid), 1700 (acid and ketone) and 1590 cm^{-1} (olefin) in the ir spectrum, without purification, was esterified with potassium carbonate and ethyl iodide in acetone to give ester **72** in 65% yield from alcohol **83**. Ester **72** thus obtained was shown to be identical with that obtained previously from chloride **70** by zinc-silver couple reduction (vide supra). Further hydrogenation of enone ester **72** under the previously described conditions gave epimeric keto esters **71**. Thus, both chlorides **69** and **70** were successfully



87



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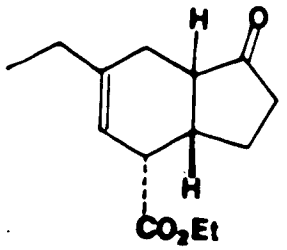
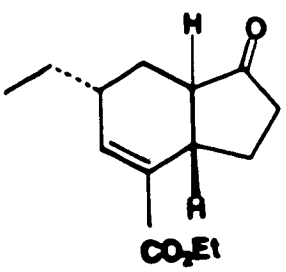


71

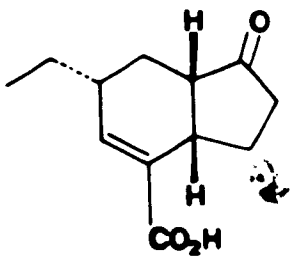
converted to keto esters **71**; **69** directly by hydrogenation and **70** via a five-step reaction sequence. By a total of

seven operations, diketone 55 was transformed to 71 in an overall yield of 35%.

To effect the isomerization of the carbon-carbon double bond, the mixture of the epimeric keto esters 71 was subjected to treatment with sodium ethoxide in ethanol at room temperature. A mixture of epimeric α,β-unsaturated esters 88 was obtained in 71% yield. The ir spectrum of the mixture showed, in addition to the ketone absorption at 1742 cm^{-1}, bands at 1711 and 1642 cm^{-1} due to the α,β-unsaturated ester. The nmr spectrum showed the presence of two stereoisomers in ~5:2 ratio. The vinylic proton of the major isomer appeared at δ6.92 as a broad singlet. In case of the minor isomer, the corresponding proton was found at δ6.98 also as a broad singlet. A molecular ion at m/e 236.1408 in the mass spectrum, as well as elemental analysis, verified the chemical formula of $C_{14}H_{20}O_3$.



88



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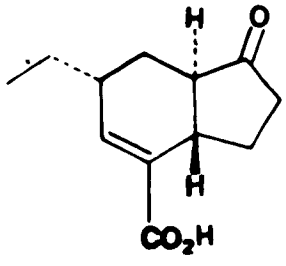

4

Hydrolysis of the mixture of esters 88 in refluxing aqueous hydrochloric acid gave, in 73% yield, a solid material consisting of coronafacic acid (2) and its C6 epimer 4* in ca. 4:1 ratio as determined by nmr analysis. Recrystallization from ether-hexane gave pure (±)-coronafacic acid (2) (m.p. 121-125°C) identical in all respects with an authentic sample.

The effective yield of (±)-coronafacic acid was 11% over nine steps from diene 52 and dienone 53 as outlined in Scheme VIII.

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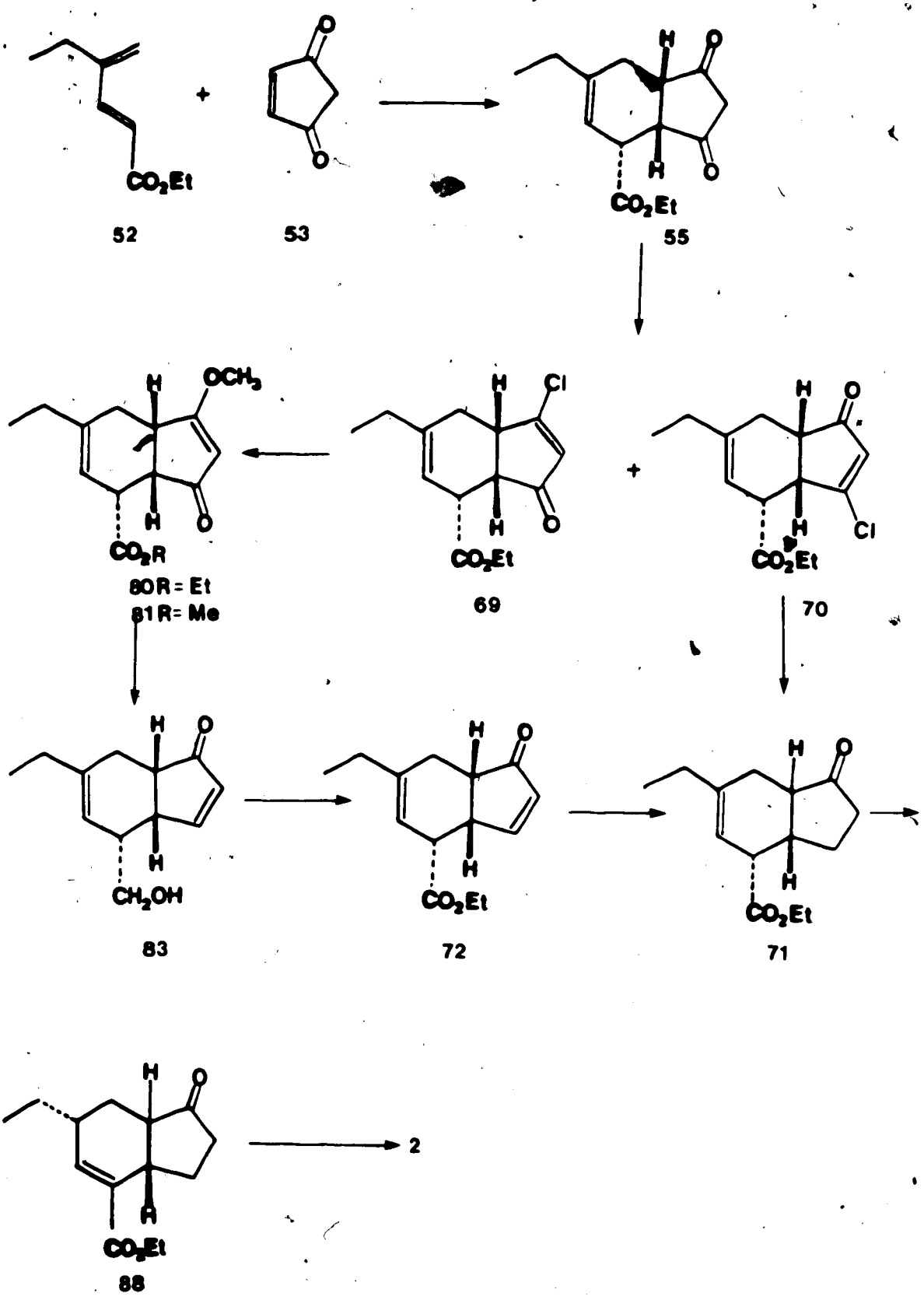
*Compound 4 was also isolated directly from the culture broth of Pseudomonas coronafacience var. atropurpurea. Its epimerization to 2 during recystallization and vice versa have been observed previously.

SCHEME VIII



EXPERIMENTAL

General

High pressure liquid chromatography was performed on a Waters Associates Prep LC/system 500 using silica gel cartridge. For other general remarks, see Chapter 1 of this thesis.

Materials

Toluene, xylene, benzene, and ether were freshly distilled over lithium aluminum hydride. 1,2-Dimethoxyethane and tetrahydrofuran were freshly distilled from a blue or purple solution of sodium benzophenone ketyl under an argon atmosphere. Ethanol and methanol were distilled over magnesium metal and stored over 3A molecular sieves. Ethyl acetate was freshly distilled over calcium hydride. Hexamethylphosphoramide was distilled over calcium hydride at reduced pressure and stored over 3A molecular sieves. Acetone was distilled over potassium permanganate crystals. Nitrogen or argon was passed over a purification train of Fieser's solution, concentrated sulfuric acid and potassium hydroxide pellets. Ethyl

4-ethyl-2,4-pentadienoate (52) was prepared according to the procedure of Holcombe et al.[89] 4-Cyclopenten-1,3-dione (53) was purchased from Aldrich Chemical Co.

2-Carbethoxy-4-ethylbicyclo[4.3.0]non-3-ene-7,9-dione (55)

a. Using toluene as the solvent.

A solution of 4-cyclopentene-1,3-dione (53) (290 mg, 3 mmol) and ethyl 4-ethyl-2,4-pentadienoate (52) (1.175 g, 7.6 mmol) in toluene (20 mL) was refluxed for 30 h under an atmosphere of nitrogen. The resulting solution was concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with a solution of 10% petroleum ether in ethyl acetate gave diketone 55 (500 mg, 67% yield): m.p. 86-88°C (ether-petroleum ether); ms M^+ 250.1202 (calcd. for $C_{14}H_{18}O_4$: 250.1205). The compound existed completely in two enol forms (~5:1) in chloroform solution as indicated by the following spectral data: ir ($CHCl_3$, cast) 3440 (OH), 1730 (ester), 1642, and 1549 cm^{-1} (β-hydroxy-α,β-unsaturated ketone); ^1H nmr: two sets of signals with the major at δ6.04 (br s, 1H, -OH), 5.58 (dd, 1H, J = 6, J' = 1 Hz, =CH-), 5.26 (s, 1H, =CHCO-), 4.24 (q, 2H, J = 7 Hz, $-OCH_2-$), 2.06 (q, 2H, J = 7 Hz, $-CH_2CH_3$), 1.34 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), and 0.99 (t, 3H, J = 7 Hz, $-CH_3$) and the minor at δ6.04 (br s, 1H, -OH), 5.62 (d, 1H, J = 8 Hz, =CH-), 5.29 (s, 1H, =CHCO-),

4.29 (q, 2H, J = 7 Hz, $-OCH_2-$), 2.09 (q, 2H, J = 7 Hz, $-CH_2CH_3$), 1.36 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), and 0.96 (t, 3H, J = 7 Hz, $-CH_3$). Anal. calcd. for $C_{14}H_{18}O_4$: C 67.17, H 7.25; found: C 67.01, H 7.07.

b. Using xylene as the solvent

A solution of 4-cyclopentene-1,3-dione (**53**) (3.19 g, 0.033 mol) and ethyl 4-ethyl-2,4-pentadienoate (**52**) (10.23 g, 0.066 mol) in xylene (120 mL) was refluxed for 16 h under an atmosphere of nitrogen. The resulting solution was concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with a solution of 10% petroleum ether in ethyl acetate gave diketone **55** (3.96 g, 48% yield).

5-Carbethoxy-9-ethoxy-3-ethylbicyclo[4.3.0]nona-3,8-dien-7-one (**62**) and 2-Carbethoxy-9-ethoxy-4-ethylbicyclo-[4.3.0]nona-3,8-dien-7-one (**63**)

To a solution of diketone **55** (113 mg, 0.45 mmol) in ethanol (3 mL), triethyl orthoformate (0.35 mL, 2.10 mmol) and a small drop of concentrated sulfuric acid were added. The reaction mixture was refluxed under a nitrogen atmosphere for 36 h. After cooling at 0°C, ice-cold water was added and the mixture extracted with chloroform. The organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered, and concentrated.

Column chromatography of the residue on silica gel, eluting with 40% ethyl acetate in petroleum ether, gave a 1:1 mixture (by nmr analysis) of products **62** and **63** (75 mg, 60% yield): ir ($CHCl_3$, cast) 1735 (ester), 1700 (ketone), and 1595 cm^{-1} (olefin); ^1H nmr δ5.55, 5.45 (both br d, ~1:1, total 1H, J = 7 Hz each, -CH=), 5.31 (br s, 1H, =CHCO-), 4.12 (m, 4H, 2 × $-OCH_2-$), 2.01 (m, 2H, $-CH_2CH_3$), 1.41, 1.43, 1.29, 1.27 (all t, ~1:1:1:1, total 6H, J = 7 Hz each, 2 × $-OCH_2CH_3$), 0.96 and 0.92 (both t, ~1:1, total 3H, J = 7 Hz each, $-CH_3$); ms M^+ 278.1516 (calcd. for $C_{16}H_{24}O_4$: 278.1518).

5-Carbethoxy-3-ethyl-9-(N,N,N',N'-tetramethylphosphoro-diamidyloxy)bicyclo[4.3.0]nona-3,8-dien-7-one (**64**) and 2-Carbethoxy-4-ethyl-9-(N,N,N',N'-tetramethylphosphoro-diamidyloxy)bicyclo[4.3.0]nona-3,8-dien-7-one (**65**)

At 0°C, to a solution of diketone **55** (0.60 g, 2.4 mmol) in 1,2-dimethoxyethane (15 mL) under a nitrogen atmosphere, were added lithium hydride (23.1 mg, 2.91 mmol) and hexamethylphosphoramide (0.43 mL, 3.85 mmol) with stirring. After 10 min, bis(dimethylamino)phosphoro-chloridate (0.99 mL, 6.69 mmol) was added. The reaction mixture was stirred at room temperature for 10 h. Ice-cold water and dilute aqueous hydrochloric acid solution were added and the resulting mixture was extracted with

chloroform. The organic solution was washed with water, dried, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 4% methanol in ethyl acetate gave a ca. 1:1 mixture (by nmr analysis) of products **64** and **65** (0.53 g, 58% yield): ir ($CHCl_3$, cast) 1730 (ester), 1700 (ketone), 1600 (olefin), and 1298 cm^{-1} (P=O); ^1H nmr δ5.87, 5.78 (both br s, ~1:1, total 1H, =CHCO-), 5.54 (dd, 1/2H, J = 7, J' = 2 Hz, -CH=), 5.41 (dd, 1/2H, J = 7, J' = 1 Hz, -CH=), 4.17, 4.13 (both q, ~1:1, total 2H, J = 7 Hz each, $-OCH_2-$), 2.72, 2.71, 2.69, 2.61 (all d, ~1:1:1:1, total 12H, J_{P-H} = 10 Hz each, 2 x $-N(CH_3)_2$), 1.26, 1.24 (both t, ~1:1, total 3H, J = 7 Hz each, $-OCH_2\underline{CH_3}$), 0.95 and 0.94 (both t, ~1:1, total 3H, J = 7 Hz each, $-CH_3$); ms M^+ 384.1824 (calcd. for $C_{18}H_{29}N_2O_5P$: 384.1814).

5-Carbethoxy-3-ethylbicyclo[4.3.0]nona-3,8-dien-7-one (**66**)

At 0°C, to a solution of enones **64** and **65** (523 mg, 1.36 mmol) in ethanol (20 mL) under an argon atmosphere, was added sodium borohydride (102 mg, 2.64 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 6 h. Water (4 mL), saturated aqueous ammonium chloride solution (10 mL), and dilute aqueous hydrochloric acid solution (5 mL) were added and the mixture extracted with chloroform. The organic extracts

were washed with water, saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether, gave enone **66** (70 mg, 22% yield): ir ($CHCl_3$, cast) 1730 (ester), 1720 (ketone), and 1595 cm^{-1} (olefin); ^1H nmr δ7.49 (dd, 1H, J = 6, J' = 3 Hz, -OCCH=C<u>H</u>-), 6.16 (dd, 1H, J = 6, J' = 2 Hz, -OC<u>C</u>H=CH-), 5.50 (dd, 1H, J = 6, J' = 1 Hz, -$\underset{|}{C}$=CH-), 4.12 (q, 2H, J = 7 Hz, -COOC<u>H</u>$_2$-), 3.55 (dd, 1H, J = 8, J' = 1 Hz, -$\underset{|}{C}$HCOO-), 3.48 (m, 1H, -$\underset{|}{C}$HCH=CHCO-), 2.98 (dd, 1H, J = 7, J' = 2 Hz, -$\underset{|}{C}$HCO-), 1.95 (m, 2H, $CH_3CH_2\underset{|}{C}$=), 1.27 (t, 3H, J = 7 Hz, -COOCH$_2$CH$_3$), and 0.92 (t, 3H, J = 7 Hz, $CH_3CH_2\underset{|}{C}$=); ms M^+ 234.1256 (calcd. for $C_{14}H_{18}O_3$: 234.1256).

<u>5-Carbethoxy-9-chloro-3-ethylbicyclo[4.3.0]nona-3,8-dien-7-one (**69**) and 2-Carbethoxy-9-chloro-4-ethylbicyclo-[4.3.0]nona-3,8-dien-7-one (**70**)</u>

a. <u>Using phenyl dichlorophosphate</u>

At 0°C, to a solution of diketone **55** (1.03 g, 4.1 mmol) in tetrahydrofuran (15 mL) under a nitrogen atmosphere, were added lithium hydride (43 mg, 5.4 mmol) and hexamethylphosphoramide (0.94 mL, 5.2 mmol) with stirring. After 10 min, phenyl dichlorophosphate (1.36 mL, 9.1 mmol) and lithium chloride (380 mg, 9 mmol) were

added. The reaction mixture was stirred at room temperature for 16 h. Ice-cold water and dilute hydrochloric acid were added and the resulting mixture was extracted with chloroform. The extracts were washed with water, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 8% ethyl acetate in n-hexane, gave a 3:2 mixture (nmr analysis) of chlorides **69** and **70** (707 mg, 64% yield). The mixture was separated by preparative high pressure liquid chromatography on a Waters Associates Prep LC/System 500 using one silica gel cartridge and eluting with 7% ethyl acetate in n-hexane. Fractions were collected by shaving the leading and trailing edges of the single peak and recycling the central portion. The combined "leading edge" fractions were concentrated to give pure chloride **69** (178 mg): ir (neat) 1716 (ester and ketone) and 1591 cm^{-1} (olefin); ^1H nmr δ 6.21 (d, 1H, J = 2 Hz, =CHCO-), 5.53 (tdd, 1H, J = 7, J' = 2, J" = 1 Hz, -CH=), 4.15, 4.13 (both q, 1H each, J = 7 Hz each, $-OCH_2-$), 3.61 (dd, 1H, J = 7, J' = 2 Hz, -CHCOO-), 3.51 (dddd, 1H, J = J' = 7, J" = 2.5, J'" = 2 Hz, -CHCCl=), 3.23 (dd, 1H, J = 7, J' = 2 Hz, -CHCO-), 2.47 (ddd, 1H, J = 16, J' = 7, J" = 2 Hz, -CHH-), 2.29 (dd, 1H, J = 16, J' = 2.5 Hz, -CHH-), 1.98, 1.96 (both dq, 1H each, J = 7, J' = 1 Hz each, $-CH_2CH_3$), 1.26 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), and 0.94 (t, 3H, J = 7 Hz,

$-CH_3$); ms M^+ 270.0842 and 268.0865 (calcd. for $C_{14}H_{17}ClO_3$: 270.0837 and 268.0865). Anal. calcd. for $C_{14}H_{17}ClO_3$: C 62.55, H 6.38, Cl 13.20; found: C 62.50, H 6.58, Cl 12.89. The "trailing edge" fractions were combined and concentrated to give chloride **70** (196 mg): ir (neat) 1716 (ester and ketone) and 1593 cm^{-1} (olefin); ^1H nmr δ6.23 (d, 1H, J = 2 Hz, =CHCO-), 5.43 (dd, 1H, J = 7, J' = 2 Hz, -CH=), 4.17 (q, 2H, J = 7 Hz, $-OCH_2-$), 3.78 (ddd, 1H, J = 7, J' = J" = 2 Hz, -CHCCl=), 3.53 (dd, 1H, J = 7, J' = 2 Hz, -CHCOO-), 2.96 (ddd, 1H, J = J' = 7, J" = 4 Hz, -CHCO-), 2.32 (m, 2H, $-CH_2-$), 1.99 (q, 2H, J = 7 Hz, $-CH_2CH_3$), 1.28 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), and 0.94 (t, 3H, J = 7 Hz, $-CH_3$); ms M^+ 270.0850 and 268.0876 (calcd. for $C_{14}H_{17}ClO_3$: 270.0837 and 268.0865). The remaining material was recovered as a mixture of **69** and **70**.

b. Using phosphorous oxychloride

At 0°C, to a solution of diketone **55** (183 mg, 0.73 mmol) in tetrahydrofuran (5 mL) under a nitrogen atmosphere, were added lithium hydride (9 mg, 1.12 mmol) and hexamethylphosphoramide (0.19 mL, 1.10 mmol) with stirring. After 10 min, phosphorous oxychloride (0.14 mL, 1.46 mmol) was added. The reaction mixture was stirred at room temperature for 7 h. Ice-cold water and dilute hydrochloric acid were added and the mixture was extracted with chloroform. The extracts were washed with water,

dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 8% ethyl acetate in petroleum ether, gave a 3:2 mixture (by nmr analysis) of chlorides **69** and **70** (89 mg, 45% yield).

2-Carbethoxy-4-ethylbicyclo[4.3.0]nona-3,8-dien-7-one (**72**)

Aqueous 10% hydrochloric acid solution (1 mL) was added to zinc dust (207 mg, 3.15 mmol) and the resulting suspension was shaken periodically. After several minutes the supernatant liquid was decanted and the zinc was washed with acetone (2 × 1 mL) and ether (1 mL). A suspension of silver acetate (70 mg, 0.42 mmol) in boiling acetic acid (1 mL) was added. After the mixture was stirred for 1 min, the supernatant was decanted and the black zinc-silver couple was washed with acetic acid (5 mL), ether (4 × 1 mL), and methanol (1 mL). To one-third of the moist coupe was added chloroenone **70** (48 mg, 0.18 mmol) in methanol (1 mL). The mixture was stirred at room temperature under an argon atmosphere for 5 days. The zinc was filtered off and washed with methanol. The solvent was evaporated and the residue was partitioned between ether and 10% aqueous hydrochloric acid solution. The organic layer was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum

ether gave starting chloroenone **70** (23 mg). Further elution with 10% ethyl acetate in petroleum ether gave enone **72** (14 mg, 64% yield based on unrecovered chloroenone **70**): ir (CH_2Cl_2, cast) 1730 (ester), 1712 (ketone), 1590 cm^{-1} (olefin); ^1H nmr δ7.62 (dd, 1H, J = 6, J' = 3 Hz, -C<u>H</u>=CHCO-), 6.26 (dd, 1H, J = 6, J' = 2 Hz, =CHCO-), 5.51 (dd, J = 7, J' = 2 Hz, -CH=), 4.22 (q, 2H, J = 7 Hz, $-OCH_2-$), 2.05 (q, 2H, J = 7 Hz, $-C\underline{H_2}CH_3$), 1.31 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H_3}$), and 0.99 (t, 3H, J = 7 Hz, $-CH_3$); ms M^+ 234.1256 (calcd. for $C_{14}H_{18}O_3$: 234.1256).

<u>2-Carbethoxy-4-ethylbicyclo[4.3.0]nonan-7-one (**73**)</u>

To a solution of enone **72** (59 mg, 0.25 mmol) in ethanol (3 mL), 5% Pd/C (6 mg) was added. After stirring under an atmosphere of hydrogen for 1 h, the reaction mixture was filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% ethyl acetate in <u>n</u>-hexane, gave keto ester **73** as a mixture of four stereoisomers (54 mg, 91% yield): ir ($CHCl_3$, cast) 1732 cm^{-1} (ketone and ester); ^1H nmr δ4.17 (m, 2H, $-OCH_2-$), 1.28, 1.27, 1.29 (all t, total 3H, J = 7 Hz each, $-OCH_2C\underline{H_3}$), 0.91, 0.90, 0.87, and 0.86 (all t, total 3H, J = 7 Hz each, $-CH_3$); ms M^+ 238.1566 (calcd. for $C_{14}H_{22}O_3$: 238.1596).

2-Carbethoxy-4-ethylbicyclo[4.3.0]non-3-en-7-one (71)

a. From enone ester 72

Enone ester 72 (85 mg, 0.36 mmol) was dissolved in ethyl acetate (3 mL) and 5% Pd/C (9 mg) was added. The mixture was stirred under an atmosphere of hydrogen at room temperature for 1 h. Filtration and concentration gave the crude product which was purified by flash chromatography on silica gel. Elution with 5% ethyl acetate in n-hexane gave a mixture of keto esters 71 (78 mg, 92% yield): ir (neat) 1732 cm^{-1} (ketone and ester); ^1H nmr δ 5.44 , 5.37 (both br s, ~1:9, total 1H, -CH=), 4.18 (q, 2H, J = 7 Hz, $-OCH_2-$), 1.33, 1.34 (both t, ~9:1, total 3H, J = 7 Hz each, $-OCH_2\underline{CH_3}$), and 1.03 (t, 3H, J = 7 Hz, $-CH_3$); ms M^+ 236.1410 (calcd. for $C_{14}H_{20}O_3$: 236.1413). Anal. calcd. for $C_{14}H_{20}O_3$: C 71.14, H 8.54; found: C 70.85, H 8.54.

b. From chloride 70

To a solution of chloride 70 (48 mg, 0.18 mmol) in benzene (1.2 mL), were added sodium bicarbonate (15 mg, 0.18 mmol) and 5% Pd/C (4.8 g). After stirring under an atmosphere of hydrogen for 4 h, the reaction mixture was filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% ethyl acetate in n-hexane gave a mixture of epimeric keto esters 71 (35 mg, 83% yield).

5-Carbethoxy-9-chloro-3-ethylbicyclo[4.3.0]-nona-3,8-dien-7-ol (74)

At 0°C, to a solution of chloroenone **69** (200 mg, 0.74 mmol) in ethanol (7 mL) under a nitrogen atmosphere, was added sodium borohydride (101 mg, 2.64 mmol). After stirring for 1.5 h, ice-cold water and dilute aqueous hydrochloric acid solution were added and the mixture extracted with chloroform. The organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether, gave alcohol **74** (153 mg, 76% yield): ir (CCl_4, cast) 3400 (alcohol) and 1730 cm^{-1} (ester); ^1H nmr δ5.85 (br s, 1H, =CH-), 5.76 (dd, 1H, J = 2, J' = 4 Hz, =CHCHOH-), 4.76 (m, 1H, -CHOH), 4.26 (q, 2H, J = 7 Hz, $-OCH_2-$), 1.29 (t, 3H, $-OCH_2CH_3$), and 1.02 (t, 3H, $-CH_3$); ms M^+ 270.0985 (calcd. for $C_{14}H_{19}O_3Cl^{35}$).

5-Carbethoxy-3-ethyl-9-ethylthiobicyclo[4.3.0]nona-3,8-dien-7-one (76)

To a solution of chloride **69** (238 mg, 0.89 mmol) in benzene (6 mL), ethanethiol (4 mL, 76.7 mmol) and triethylamine (2 mL, 27.2 mmol) were added and the mixture was stirred at room temperature under a nitrogen atmosphere for 5 days. Ice-cold water and dilute aqueous

hydrochloric acid solution were added and the mixture extracted with methylene chloride. The organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in n-hexane, gave ester **76** (220 mg, 84% yield): ir ($CHCl_3$, cast) 1725 (ester), 1696 (ketone), and 1548 cm^{-1} (olefin); ^1H nmr δ 5.93 (d, 1H, J = 1 Hz, =CHCO-), 5.54 (br d, 1H, J = 7 Hz, =CH-), 4.17, 4.16 (both q, 1H each, J = 7 Hz each, $-OCH_2-$), 3.61 (dd, 1H, J = 7, J' = 2 Hz, -CHCOO-), 3.47 (dddd, 1H, J = J' = 7, J" = 3, J'" = 1 Hz, $-CHCH_2-$), 3.17 (dd, 1H, J = 7, J' = 2 Hz, -CHCO-), 2.93 (q, 2H, J = 7 Hz, $-SCH_2-$), 2.51 (ddd, 1H, J = 16, J' = 7, J" = 2 Hz, -CHHCH-), 2.17 (dd, 1H, J = 16, J' = 3 Hz, -CHHCH-), 2.00 (br q, 2H, J = 7 Hz, $-CH_2CH_3$), 1.41 (t, 3H, J = 7 Hz, $-SCH_2CH_3$), 1.30 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), and 0.95 (t, 3H, J = 7 Hz, $-CH_3$); ms M^+ 294.1287 (calcd. for $C_{16}H_{22}O_3S$: 294.1290).

3-Ethyl-5-hydroxymethyl-9-ethylthiobicyclo[4.3.0]nona-3,8-dien-7-one (**79**)

At 0°C, to a solution of ester **76** (62 mg, 0.21 mmol) in tetrahydrofuran (2 mL) under a nitrogen atmosphere, was added lithium tri-t-butoxyaluminum hydride (53 mg, 0.21 mmol). After stirring for 24 h at room temperature, ice-

cold water and dilute aqueous hydrochloric acid solution were added. The mixture was extracted with methylene chloride. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in n-hexane, gave unreacted ester **76** (10 mg). Further elution with 45% ethyl acetate in n-hexane gave alcohol **79** (21 mg, 48% yield based on unrecovered ester **76**): ir ($CHCl_3$, cast) 3400 (alcohol), 1685 (ketone), and 1545 cm^{-1} (olefin); ^1H nmr δ5.93 (d, 1H, J = 1 Hz, -COCH=), 5.32 (br s, 1H, -CH=), 4.20, 3.89 (both m, 1H each, $-CH_2O-$), 2.97 (q, 2H, J = 7 Hz, $-SCH_2-$), 2.09 (q, 2H, J = 7 Hz, $-CH_2CH_3$), 1.44 (t, 3H, J = 7 Hz, $-SCH_2CH_3$), and 1.03 (t, 3H, J = 7 Hz, $-CH_3$); ms M^+ 252.1189 (calcd. for $C_{14}H_{20}O_2S$: 252.1184).

9-Ethylthio-6-ethyl-2-oxatricyclo[6.2.1.$0^{4,11}$]undeca-5,9-dien-3-one (**78**) and Alcohol **79**

At 0°C, to a solution of ester **76** (54 mg, 0.18 mmol) in ethanol (2 mL) under a nitrogen atmosphere, was added sodium borohydride (29 mg, 37.83 mmol). After stirring for 5 h at room temperature, ice-cold water, saturated aqueous ammonium chloride solution, and dilute aqueous hydrochloric acid solution were added. The mixture was extracted with methylene chloride. The organic solution was dried, filtered, and concentrated. Flash

chromatography of the residue on silica gel, eluting with 10% ethyl acetate in n-hexane, gave lactone **78** (10 mg, 26% yield based on unrecovered ester **76**): ir ($CHCl_3$, cast) 1756 cm^{-1} (lactone); ^1H nmr δ 5.59 (br s, 1H, =C<u>H</u>CHO-), 5.53 (br d, 1H, J = 7 Hz, =CH-), 5.39 (br s, 1H, -CHO-), 2.79 (q, 2H, J = 7 Hz, $-SCH_2-$), 2.09 (br q, 2H, J = 7 Hz, $-C\underline{H}_2CH_3$), 1.32 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H}_3$), 1.04 (t, 3H, J = 7 Hz, $-CH_2C\underline{H}_3$); ms M^+ 250.1039 (calcd. for $C_{14}H_{18}O_2S$: 250.1027). Further elution with the same solvent system gave unreacted ester **76** (9 mg). Elution with 40% ethyl acetate in n-hexane gave alcohol **79** (4 mg, 1%).

<u>5-Carbethoxy-3-ethyl-9-methoxybicyclo[4.3.0]nona-3,8-dien-7-one (**80**) and 5-Carbomethoxy-3-ethyl-9-methoxybicyclo-[4.3.0]nona-3,8-dien-7-one (**81**)</u>

Chloride **69** (381 mg, 1.42 mmol) was dissolved in methanol (10 mL) under a nitrogen atmosphere in a flask wrapped in aluminum foil to exclude light. Silver nitrate (482 mg, 2.84 mol) was introduced and the reaction mixture heated at 70°C for 19 h. Filtration and concentration gave the crude product which was subjected to flash chromatography on silica gel. Elution with 35% ethyl acetate in n-hexane gave ethyl ester **80** (276 mg, 74% yield): ir (neat) 1724 (ester), 1698 (ketone), and 1600 cm^{-1} (olefin); ^1H nmr δ 5.53 (tdd, 1H, J = 7, J' = 2, J" =

1 Hz, -CH=), 5.32 (d, 1H, J = 1 Hz, =CHCO-), 4.16, 4.14 (both q, 1H each, J = 7 Hz each, $-OCH_2-$), 3.86 (s, 3H, $-OCH_3$), 3.62 (dd, 1H, J = 7, J' = 2 Hz, $-\underline{C}HCOO-$), 3.33 (dddd, J = J' = 7, J" = 3, J'" = 1 Hz, $-\underline{C}H\underline{C}H_2-$), 3.15 (dd, 1H, J = 7, J' = 2 Hz, $-\underline{C}HCO-$), 2.39 (ddd, 1H, J = 16, J' = 7, J" = 2 Hz, $-C\underline{H}H-$), 2.24 (dd, 1H, J = 16, J' = 3 Hz, $-C\underline{H}H-$), 1.98, 1.96 (both dq, 1H each, J = 7, J' = 1 Hz each, $-\underline{C}H_2CH_3$), 1.27 (t, 3H, J = 7 Hz, $-OCH_2\underline{C}H_3$), and 0.94 (t, 3H, J = 7 Hz, $-CH_3$); ms M^+ 264.1365 (calcd. for $C_{15}H_{20}O_4$: 264.1362). Further elution with the same solvent system gave methyl ester **81** (24 mg, 8% yield): ir (neat) 1735 (ester) 1695 (ketone), and 1598 cm^{-1} (olefin); ^1H nmr δ 5.56 (br d, 1H, J = 7 Hz, -CH=), 5.30 (s, 1H, =CHCO-), 3.83 (s, 3H, $-OCH_3$), 3.71 (s, 3H, $-COOCH_3$), and 0.93 (t, 3H, J = 7 Hz, $-CH_2\underline{C}H_3$); ms M^+ 250.1210 (calcd. for $C_{14}H_{18}O_4$: 250.1205).

4-Ethyl-2-hydroxymethylbicyclo[4.3.0]nona-3,8-dien-7-one (**83**)

At -20°C, to a solution of esters **80** and **81** (11:1; 389 mg, 1.48 mmol) in ether (8 mL) under a nitrogen atmosphere, was added lithium aluminum hydride (112 mg, 2.95 mmol). After stirring for 20 min, the reaction mixture was allowed to warm up to -5°C. Water (2 mL) was slowly added. The resulting mixture was acidified with 1

N hydrochloric acid solution, stirred at 0°C for 45 min, and extracted with methylene chloride. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 45% ethyl acetate in n-hexane, gave alcohol **83** (198 mg, 70% yield): ir (neat) 3425 (alcohol), 1704 (ketone), and 1585 cm^{-1} (olefin); ^1H nmr δ 7.64 (dd, 1H, J = 6, J' = 3 Hz, -CH=CHCO-), 6.17 (dd, 1H, J = 6, J' = 2 Hz, =CHCO-), 5.35 (d, 1H, J = 5 Hz, -CH=), 3.75, 3.69 (both dd, 1H each, J = 18, J' = 6 Hz each, $-CH_2O-$), 2.03 (q, 2H, J = 7 Hz, $-CH_2CH_3$), and 0.98 (t, 3H, J = 7 Hz, $-CH_3$); ms M^+ 192.1143 (calcd. for $C_{12}H_{16}O_2$: 192.1150). Anal. calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.78, H 8.57.

4-Ethyl-2-hydroxymethylbicyclo[4.3.0]non-3-en-7-one (**84**)

Enone alcohol **83** (129 mg, 0.67 mmol) was dissolved in ethyl acetate (5 mL) and 5% Pd/C (13 mg) was added. After stirring under an atmosphere of hydrogen for 45 min, the reaction mixture was filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 30% ethyl acetate in n-hexane, gave alcohols **84** (112 mg, 86% yield): ir ($CHCl_3$, cast) 3440 (alcohol) and 1739 cm^{-1} (ketone); ^1H nmr δ 5.25, 5.20 (both br s, ~9:1, total 1H, -CH=), 3.62 (m, 2H, $-CH_2O-$), 1.00, and 0.98 (both t, ~9:1, total 3H, J = 7 Hz each, $-CH_3$); ms M^+ 194.1305 (calcd. for

$C_{12}H_{18}O_2$: 194.1307).

4-Ethyl-2-formylbicyclo[4.3.0]non-3-ene (**85**)

To a solution of chromium trioxide (180 mg, 1.8 mmol) in methylene chloride (3 mL), pyridine (0.3 mL, 3.7 mmol) was added and the mixture was stirred under a nitrogen atmosphere for 15 min. To the deep red solution, a solution of alcohol **84** (51 mg, 0.26 mmol) in methylene chloride (2 mL) was added. After stirring for 45 min, the solution was diluted with methylene chloride (5 mL) and filtered. The organic solution was washed with 5% aqueous sodium hydroxide solution, 5% aqueous hydrochloric acid solution, 5% aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution. The organic layer was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in n-hexane, gave aldehydes **85** (26 mg, 53% yield): ir ($CHCl_3$, cast) 2840, 1689 (aldehyde), and 1710 (ketone); ^1H nmr δ 9.73 (br s, 1H, -CHO), 5.41, 5.36 (both br s, ~9:1, total 1H, -CH=), and 1.00 (t, 3H, $-CH_3$); ms M^+ 192.1144 (calcd. for $C_{12}H_{16}O_2$: 192.1150).

2-Carboxy-4-ethylbicyclo[4.3.0]nona-3,8-dien-7-one (**87**) and Enone ester **72**

At 0°C, to a solution of alcohol **83** (131 mg, 0.68

mmol) in acetone (4 mL), was added dropwise 1 mL of 8 N Jones reagent with stirring. After 1 h, the reaction mixture was diluted with water and extracted with ethyl acetate. Drying, filtration, and concentration gave 120 mg of acid **87** [ir ($CHCl_3$, cast) 3060 (acid), 1700 (acid and ketone), and 1590 cm^{-1} (olefin)]. This compound without purification was dissolved in acetone (4 mL) and potassium carbonate (161 mg, 1.17 mmol) was added. The mixture was stirred at room temperature under a nitrogen atmosphere for 1 h and iodoethane (0.7 mL, 8.75 mmol) was then introduced. After heating at reflux for 16 h, the reaction mixture was poured into ice-cold water and extracted with methylene chloride. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 8% ethyl acetate in n-hexane, gave enone ester **72** (103 mg, 65% yield from alcohol **83**) identical with that obtained previously from chloride **70**.

2-Carbethoxy-4-ethylbicyclo[4.3.0]non-2-en-7-one (**88**)

At 0°C, to a solution of keto esters **71** (35 mg, 0.15 mmol) in ethanol (1.5 mL), was added sodium hydride (80% oil dispersion; 10 mg, 0.33 mmol). After stirring at room temperature under a nitrogen atmosphere for 16 h, the reaction mixture was diluted with ice-cold water,

acidified with dilute aqueous hydrochloric acid, and extracted with methylene chloride. The organic solution was dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% ethyl acetate in n-hexane, gave a mixture of epimeric esters **88** (25 mg, 71% yield): ir ($CHCl_3$, cast) 1742 (ketone), 1711 (ester), and 1642 cm^{-1} (olefin); ^1H nmr δ6.98, 6.92 (both br s, 2:5, total 1H, -CH=), 4.21 (m, 2H, $-OCH_2-$), 1.32, 1.27 (both t, 5:2, total 3H, J = 7 Hz each, $-OCH_2\underline{CH_3}$), 1.01, and 0.99 (both t, 5:2, total 3H, J = 7 Hz each, $-CH_3$); ms M^+ 236.1408 (calcd. for $C_{14}H_{20}O_3$: 236.1412). Anal. calcd. for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 71.14, H 8.53.

d,l-Coronafacic Acid (**2**)

A solution of esters **88** (20 mg, 0.085 mmol) in 2.4 N aqueous hydrochloric acid (1.5 mL) was heated at reflux under a nitrogen atmosphere for 5.5 h. After cooling to room temperature, the resulting solution was diluted with water (2 mL) and extracted with ethyl acetate. The extracts were dried, filtered, and concentrated. Flash chromatography of the residue on silica gel, eluting with 40% ethyl acetate in n-hexane, gave 13 mg (73% yield) of a 4:1 (nmr integration) mixture of coronafacic acid (**2**) and its C6 epimer **4**. In the nmr spectrum, the vinyl proton of

the latter compound appeared as a doublet of doublets (J = 4, J' = 2 Hz) at δ7.12 in agreement with the reported value.[74] Recrystallization of the mixture from ether-hexane resulted in partial epimerization of the minor isomer to coronafacic acid (**2**) and gave 11 mg of the latter compound in crystalline form, m.p. 121-125°C. Concentration of the mother liquid gave 2 mg of a 1:1 mixture of **2** and its C6 epimer. The ir, nmr, and mass spectra of the synthetic coronafacic acid were found to be identical with those of an authentic sample and displayed the following characteristic features: ir ($CHCl_3$, cast) 3040, 2634, 2532, 1685 (acid), 1741 (ketone), and 1634 cm^{-1} (olefin); ^1H nmr δ7.06 (br s, 1H, -CH=), and 1.01 (t, 3H, J = 7 Hz, $-CH_3$); ms M^+ 208.1104 (100%; calcd. for $C_{12}H_{16}O_3$).

REFERENCES

1. G.J. Calton, R.L. Ranieri, and M.A. Espenshade, J. Antibiot., **31**, 38 (1978).
2. R.L. Ranieri and G.J. Calton, Tetrahedron Lett., 499 (1978).
3. N. Nakagawa, A. Hirota, H. Sakai, and A. Isogai, J. Antibiot., **35**, 778 (1982).
4. A. Hirota, M. Nakagawa, H. Sakai, and A. Isogai, J. Antibiot., **35**, 783 (1982).
5. M. Nakagawa, H. Sakai, A. Isogai, and A. Hirota, Agric. Biol. Chem., **48**, 117 (1984).
6. M. Nakagawa, H. Sakai, A. Isogai, and A. Hirota, Agric. Biol. Chem., **48**, 2279 (1984).
7. D.E. Cane, Y.G. Whittle, and T.C. Liang, Tetrahedron Lett., **25**, 1119 (1984).
8. A. Hirota, M. Nakagawa, H. Sakai, and A. Isogai, Agric. Biol. Chem., **48**, 835 (1984).
9. A. Hirota, M. Nakagawa, H. Sakai, A. Isogai, K. Furihata, and H. Seto, Tetrahedron Lett., **26**, 3845 (1985).
10. S. Danishefsky, K. Vaughan, R.C. Gadwood, and K. Tsuzuki, Tetrahedron Lett., **21**, 2625 (1980).
11. K. Cooper and G. Pattenden, J. Chem. Soc. Perkin Trans. I, 799 (1984).

12. J.M. Dewanckele, F. Zuttermand, and M. Vandewalle, Tetrahedron, **39**, 3235 (1983).

13. S. Danishefsky, K. Vaughan, R.C. Gadwood, and K. Tsuzuki, J. Am. Chem. Soc., **102**, 4262 (1980).

14. S. Danishefsky, K. Vaughan, R.C. Gadwood, and K. Tsuzuki, J. Am. Chem. Soc., **103**, 4136 (1981).

15. W.K. Bornock, S.S. Bagwat, J. Ponton, and P. Helquist, J. Am. Chem. Soc., **103**, 4647 (1981).

16. S.D. Burke, C.W. Murtiashaw, J.O. Saunders, and M.S. Dike, J. Am. Chem. Soc., **104**, 872 (1982).

17. S.D. Burke, C.W. Murtiashaw, and J.A. Oplinger, Tetrahedron Lett., **24**, 2949 (1983).

18. S.D. Burke, C.W. Murtiashaw, J.O. Saunders, J.A. Oplinger, and M.S. Dike, J. Am. Chem. Soc., **106**, 4558 (1984).

19. A.S. Kende, B. Roth, P.J. Sanfilippo, and T.J. Blacklock, J. Am. Chem. Soc., **104**, 5808 (1982).

20. K. Takeda, Y. Shimono, and Y. Yoshii, J. Am. Chem. Soc., **105**, 563 (1983).

21. R.H. Schlessinger, J.L. Wood, A.J. Poss, R.A. Nugent, and W.H. Parsons, J. Org. Chem., **48**, 1146 (1983).

22. P.A. Wender and D.J. Wolanin, J. Org. Chem., **50**, 4418 (1985).

23. E. Piers and N. Moss, Tetrahedron Lett., **26**, 2735 (1985).

24. E. Piers, G.L. Jung, and N. Moss, Tetrahedron Lett., **25**, 3959 (1984).

25. K. Kon, K. Ito, and S. Isoe, Tetrahedron Lett., **25**, 3739 (1984).

26. A.B. Smith and J.P. Konopelski, J. Org. Chem., **49**, 4094 (1984).

27. B. Arbusow and I. Mitteil, Ber., **68**, 1430 (1935).

28. J. Meinwald and R. Chapman, J. Am. Chem. Soc., **90**, 3218 (1968).

29. G. Hoefle, W. Steglich, and H. Vorbruenggen, Angew. Chem. Int. Ed. Engl., **17**, 569 (1978).

30. J.A. Dale, D.L. Dull, and H.S. Mosher, J. Org. Chem., **34**, 2543 (1969).

31. W.S. Wadsworth and W.D. Emmons, J. Am. Chem. Soc., **83**, 1733 (1961).

32. R.L. Augustine, D.C. Migliorini, R.E. Foscante, C.S. Sodano, and M.J. Sisbarro, J. Org. Chem., **34**, 1075 (1969).

33. J.A. Osborn, F.H. Jardine, Y.F. Young, and G. Wilkinson, J. Chem. Soc., A, 1711 (1966).

34. I. Ojima, M. Nihonyanagi, T. Kogure, M. Kumagai, S. Horiuchi, K. Nakatsugawa, and Y. Nagai, J. Organomet. Chem., **94**, 449 (1975).

35. I. Ojima, T. Kogure, M. Nihonyanagi, and Y. Nagai, Bull. Chem. Soc. Japan, **45**, 3506 (1972).

36. H.J. Liu and B. Ramani, Synth. Commun., **11**, 965 (1985).

37. A.C. Cope, H.H. Lee, and H.E. Petree, J. Am. Chem. Soc., **80**, 2849 (1958).

38. W. Fenical, D.R. Kearns, and P. Radlick, J. Am. Chem. Soc., **91**, 3396, 7771 (1969).

39. A.J. Mancuso, D.S. Brownfain, and D. Swern, J. Org. Chem., **44**, 4148 (1979).

40. E.D. Mihelich and D.J. Eickhoff, J. Org. Chem., **48**, 4135 (1983).

41. A.W. Dox and B. Houston, J. Am. Chem. Soc., **46**, 252 (1924).

42. E.J. Nienhouse, R.M. Irwin, and G.R. Finni, J. Am. Chem. Soc., **89**, 4557 (1967).

43. G. Tsuchihashi, S. Iruchijima, and K. Maniwa, J. Am. Chem. Soc., **96**, 4280 (1974).

44. T. Katsuki, A.W.M. Lee, P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, D. Tuddenham, and F.J. Walker, J. Org. Chem., **47**, 1373 (1982).

45. B. Zwanenburg and J. ter Wiel, Tetrahedron Lett., 935 (1970).

46. S. Boatman, T.M. Harris, and C.R. Hauser, Org. Syn., **48**, 40 (1968).

47. H.J. Liu and P.C.L. Yao, Can. J. Chem., **55**, 822 (1977).

48. W.H. Chan, Ph.D. Dissertation, the University of Alberta, 1979.

49. I.V. Oppong, Ph.D. Dissertation, the University of Alberta, 1984.

50. E.D. Bergmann, D. Ginsburg, and R. Pappo, Org. Reactions, **101**, 179 (1959).

51. R.L. Augustine and J.A. Caputo, Org. Syn., **45**, 80 (1965).

52. S. Hünig, E. Lücke, and W. Brenninger, Org. Syn., **41**, 65 (1961).

53. R.E. Sievers, NMR Shift Reagents. New York: Academic Press, 1973.

54. N.F. Firrell and P.W. Hickmott, Chem. Commun., 544 (1969).

55. J.P. Schaefer and J.J. Bloomfield, Org. Reactions, **15**, 1 (1967).

56. T. Dieck-Abularach, Ph.D. Dissertation, the University of Alberta, 1984.

57. R.S. Sauers, J. Am. Chem. Soc., **81**, 925 (1959).

58. E. Fisher, Ber., **34**, 433 (1901).

59. E.J. Corey, J.P. Bass, R. Lemahieu, and R.B. Mitra, J. Am. Chem. Soc., **86**, 5570 (1964).

60. R.W. Guthrie, A. Philipp, Z. Valenta, and K. Wiesner, Tetrahedron Lett., 2945 (1965).

61. K. Wiesner, Tetrahedron, **31**, 1655 (1975).

62. J.J. Pappas and W.P. Keaveney, Tetrahedron Lett., 4273 (1966).

63. P. Wieland, H. Ueberwasser, G. Amuer, and K. Miescher, Helv. Chim. Acta, **36**, 376 (1953).

64. M.J. Begley, K. Cooper, and G. Pattenden, Tetrahedron Lett., 257 (1981).

65. M. Miyashita, T. Yanami, and A. Yoshikoshi, J. Am. Chem. Soc., 4679 (1976).

66. R.M. Jacobson, R.A. Raths, and J.H. McDonald III, J. Org. Chem., **42**, 2545 (1977).

67. E. Piers, B. Abeysekera, and J.R. Scheffer, Tetrahedron Lett., 3279 (1979).

68. E. Piers and B. Abeysekera, Can. J. Chem., **60**, 1114 (1982).

69. P.A. Aristoff, Synth. Commun., **13**, 145 (1983).

70. G.A. Olah, S.C. Norang, B.G.B. Gupta, and R. Malhorta, J. Org. Chem., **44**, 1247 (1979).

71. M.E. Jung, W.A. Andrus, and P.L. Ornstein, Tetrahedron Lett., 4175 (1977).

72. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., **43**, 2923 (1978).

73. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley and Sons, Inc., New York, 1967.

74. A. Ichihara, K. Shiraishi, H. Sato, S. Sakamura, K. Nishiyama, R. Sakai, A. Furusaka, and T. Matsumoto, J. Am. Chem. Soc., **99**, 636 (1977).

75. K. Nishiyama, R. Sakai, A. Ezuka, A. Ichihara, K. Shiraishi, M. Ogasawara, H. Sato, and S. Sakamura, Ann. Phytopath. Soc. Jpn., **42**, 613 (1976).

76. K. Nishiyama, R. Sakai, A. Ezuca, A. Ichihara, K. Shiraishi, and S. Sakamura, Ann. Phytopath. Soc. Jpn., **43**, 219 (1977).

77. A. Ichihara, K. Shiraishi, S. Sakamura, K. Nishiyama, and R. Sakai, Tetrahedron Lett., 269 (1977).

78. A. Ichihara, K. Shiraishi, S. Sakamura, A. Furusaki, N. Hashiba, and T. Matsumoto, Tetrahedron Lett., 365 (1979).

79. A. Ichihara, R. Kimura, K. Moriyasu, and S. Sakamura, Tetrahedron Lett., 4331 (1977).

80. A. Ichiara, R. Kimura, S. Yamada, and S. Sakamura, J. Am. Chem. Soc., **102**, 6335 (1980).

81. M.E. Jung and K.M. Halweg, Tetrahedron Lett., **22**, 2735 (1981).

82. M.E. Jung and J.P. Hudspeth, J. Am. Chem. Soc., 102, 2463 (1980).

83. J. Tsuji, Pure & Appl. Chem., 53, 2371 (1981).

84. M. Nakayama, S. Ohira, Y. Okamura, and S. Soga, Chem. Lett., 731 (1981).

85. M. Nakayama and S. Ohira, Agric. Biol. Chem., 47, 1689 (1983).

86. S. Ohira, Bull. Chem. Soc. Jpn., 57, 1902 (1984).

87. H.J. Liu and M. Llinas-Brunet, Can. J. Chem., 62, 1744 (1984).

88. A.S. Onishenko, [illegible] Synthesis. Israel Program for Scientific Translation, Jerusalem, 1964.

89. R.J. Sundberg, P.A. Burowich, and F.O. Holcombe, J. Org. Chem., 32, 2938 (1967).

90. C.S. Marvel, R.L. Myers, and J.H. Saunders, J. Am. Chem. Soc., 70, 1694 (1948).

91. P. Yates and P. Eaton, J. Am. Chem. Soc., 82, 4436 (1960).

92. T. Inukai and M. Kasai, J. Org. Chem., 30, 3567 (1965).

93. H.J. Liu, W.H. Chan, and S.P. Lee, Tetrahedron Lett., 4461 (1978).

94. H. Cohen and J.D. Mier, Chem. Ind. (London), 349 (1965).

95. R.E. Ireland and G. Pfister, Tetrahedron Lett., 2145 (1969).

96. E. Piers, J.R. Grierson, C.K. Lau, and I. Nagakura, Can. J. Chem., **60**, 210 (1981) and references therein.

97. H.J. Liu, G.V. Lamoureux, and M. Llinas-Brunet, Can. J. Chem., **64**, 520 (1986).

98. R.D. Clark and C.H. Heathcock, J. Org. Chem., **41**, 636 (1976).

99. C.K. Alden and D.I. Davies, J. Chem. Soc., C, 700 (1978).

100. M.G. Reinecke, J. Org. Chem., **29**, 299 (1964).

101. D.A. Denton, F.J. McQuillin, and P.L. Simpson, J. Chem. Soc., 5535 (1964).

102. H. Wynn, Ph.D. Dissertation, The University of Alberta, 1984.

103. R. Ratcliffe and R. Rodehorst, J. Org. Chem., **35**, 4000 (1970).

104. D. Djerassi, R.R. Engle, and A. Bowers, J. Org. Chem., **21**, 1547 (1956).