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Total synthesis of axane sesquiterpenoids

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The Ohio State University, 1991
Total Synthesis of Axane Sesquiterpenoids

Dissertation

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

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******

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To My Parents
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Chapter I
The Axane Sequiterpenoids — A Review

A. Statement of the Problem

The axanes are a small family of sesquiterpenoids that have been isolated from the marine sponge Axinella cannabina.\textsuperscript{1-5} Several of these compounds (1-6) (1) have a carbon skeleton that is not common among the sesquiterpenes (Figure I), (2) incorporate a series of nitrogen-containing functional groups rarely found in natural products and (3) appear to play an interesting role in a marine predator-prey relationship.\textsuperscript{6} In addition compounds 1-6 are available in only small quantities from the natural source. In fact, our attempts to obtain 1-6 from researchers responsible for their initial isolation and characterization met with failure. Thus, the objective of this research was to develop an efficient laboratory synthesis of compounds of type 1-6. This thesis
will specifically describe total syntheses of (d/-)-axisonitrile-4 (4), (d/-)-axisothiocyanate-4 (5), and (d/-)-axamide-4 (6). To provide the reader with background information, the isolation and structure determination, biological activity, and past synthetic studies related to the axanes will first be reviewed.

B. Isolation and Structure Determination of Axane Sesquiterpenes

As mentioned above, the axanes are a series of sesquiterpenoid natural products isolated from the marine sponge Axinella cannabina. The structures of these compounds are shown in Figures 1 and 2.1-5,7 Although perhydroazulene (7-10) and perhydroindan (1-6) ring systems are commonly found in nature, the nitrogen-containing functional groups that appear in 1-10 are uncommon although not unknown to natural products. Furthermore, the perhydroindan substitution pattern found in axanes 1-6 is only found in a few other sesquiterpenes, such as oppositol (11).8

![Figure 2. Structures of Perhydroazulenoid Axanes and Oppositol](image)

The structures of axanes 1-6 were determined during the 1970's on the basis of chemical and X-ray crystallographic data. In 1973, Sica and coworkers
isolated axisonitrile-1 (1) and axisothiocyanate-1 (2) from ethereal extracts of the acetone extract of the marine sponge *Axinella cannabina*.¹ Elemental and mass spectral analysis indicated that compound 1 had a molecular formula of C_{16}H_{25}N. The infrared spectrum of 1 showed a strong absorption at 2130 cm⁻¹. Along with an intense peak an *m/e* 204 (M⁺-HCN) in the mass spectrum, this information suggested the presence of an isonitrile group in 1. The infrared spectrum of 1 also showed peaks at 3050, 2640 and 895 cm⁻¹ and the ¹H-NMR spectrum displayed a two-proton singlet at δ 4.75, indicative of a terminal methylene group (=CH₂). The ¹H-NMR spectrum provided additional information. A three-proton singlet at δ 0.99 and two three-proton doublets at δ 0.85 (*J* = 6 Hz) and δ 1.03 (*J* = 6 Hz) indicated the presence of a tertiary methyl group and two secondary methyl groups. Infrared bands at 1385 and 1375 cm⁻¹ suggested that the secondary methyl groups were part of an isopropyl group.

\[
\begin{align*}
\text{LiAlH}_4 & \quad 1 \\
\text{H} & \quad \text{H} \\
\text{NC} & \rightarrow \text{NH}_2 \\
1 & \rightarrow 12 \\
1 & \rightarrow 12 \\
1 & \rightarrow 13 \\
1 & \rightarrow 13
\end{align*}
\]

The degrees of unsaturation, calculated from the molecular formula, and the aforementioned information suggested that 1 had a bicyclic skeleton. Reduction of 1 with lithium aluminium hydride gave an amine (*m/e* 233) that eventually was assigned structure 12.⁹ Methylation of 12, followed by treatment of the resulting quaternary salt with silver oxide followed by thermolysis, gave diene 13 (Equation 1).¹⁰ The ¹H-NMR spectrum of 13 showed two vinylic
methyls as singlets at $\delta$ 1.64 and $\delta$ 1.52 and one vinylic proton as a doublet ($J = 9$ Hz) at $\delta$ 4.86. Both of the vinylic methyls as well as the doublet at $\delta$ 4.86 were broadened by long-range coupling, suggesting that compound 13 contained a $-\text{CHCH}=\text{C(CH}_3)_2$ unit. Reduction of 1 using sodium in liquid ammonia gave alkene 14 ($m/e$ 206) which was in turn transformed into ketone 15 ($m/e$ 208) upon ozonolysis (Scheme 1).$^{11,12}$ The infrared spectrum of 15 showed a carbonyl absorption at 1707 cm$^{-1}$, indicating the presence of a cyclohexanone. Deuterium exchange experiments with ketone 15 also showed the presence of three exchangeable protons and established the presence of a CH—C(=CH$_2$)—CH$_2$ substructure within 1. Baeyer-Villiger oxidation of 15 afforded a lactone (16) which was saponified to give hydroxy acid 17.$^{13}$ Acid 17 was further oxidized by Jones reagent to give keto acid 18.$^{14}$ The infrared spectrum of 18 showed a carbonyl absorption at 1738 cm$^{-1}$, indicating the presence of a cyclopentanone and confirming the presence of a perhydroindan ring system with 1. Further examination of the $^1$H-NMR spectrum of 18 showed that only one hydrogen atom was present on the carbons adjacent to the carbonyl group. Based on this information, it was proposed that the three alkyl groups adjacent to the carbonyl group were a methyl group, an acidic sidechain resulting from degradation of the six-membered ring, and an isobutyl group. This was consisant with the fact that the isobutyl group had already been shown to be connected to a methine carbon. Based on this interpretation of the degradation experiments, axisonitrile-1 was assigned structure 1. Confirmation of this assignment, as well as assignment of the stereochemistry at asymmetric centers, was later shown by correlation with a related structure assigned by X-ray crystallography.$^7$
Ongoing with the isolation and structure determination of axisonitrile-1 (1), a second oily compound (2) was isolated from *Axinella cannibina*.\(^1\)\(^2\) The structure of 2 was initially based on the following experiments. The mass spectrum and elemental analysis of 2 established its molecular formula as C\(_{16}\)H\(_{25}\)NS. Evidence from the infrared and \(^1\)H-NMR spectra suggested the presence of a terminal methylene group, a tertiary methyl group, and two secondary methyl groups. Based on the infrared spectrum (2120 cm\(^{-1}\)), ultraviolet spectrum (\(\lambda_{\text{max}} = 243\) nm with \(\varepsilon = 2500\)) and mass spectrum (M\(^+\)-HNCS), it was concluded that the sulfur was contained in an isothiocyanate group. Furthermore, irradiating a multiplet that appeared at \(\delta 2.40\) in the \(^1\)H-NMR spectrum of 2 caused collapse of two methyl doublets at \(\delta 0.89\) and \(\delta 1.00\) into singlets, and a one-proton triplet at \(\delta 3.27\) into a doublet. This experiment
suggested the presence of a —CH—CH(NCS)—CH(CH₃)₂ substructure. These data demonstrated a structural similarity between compounds 1 and 2. In fact, heating compound 1 with sulfur at 120°C gave compound 2, establishing the structural relationship between these compounds (Scheme 2).

Furthermore, compounds 1 and 2 were correlated by reduction experiments. Thus, reduction of 1 using lithium in ethylamine afforded alkane 19 (m/e 208). Reductions of both 1 and 2 by sodium in liquid ammonia, however gave alkene 14 (m/e 206). Reduction of 2 with lithium aluminium hydride gave the same amine (12) obtained from similar treatment of 1. Thus structure 2 was assigned to axisothiocyanate-1 and, although the stereochemistry was not yet established, it was clear that 1 and 2 belonged to the same stereochemical series.

The structure of 2 was firmly established by X-ray crystallographic analysis of an appropriate derivative. Thus, treatment of 2 with p-bromoaniline gave 20 (m.p. 154-156°C), whose structure was established by X-ray crystallography (Scheme 2). This established the relative stereochemistry at the four asymmetric centers of both 1 and 2. The absolute stereochemistry of 1 and 2 has yet to be rigorously proven, although the stereochemistry shown in Figure 1 has been suggested based on CD studies performed on ketone 15.7
Scheme 2. Correlation of Axisonitrile-1 and Axisothiocyanate-1

In 1977, another study of extracts from Axinella cannabina gave three other closely related axane sequiterpenoids named axisonitrile-4 (4), axisothiocyanate-4 (5) and axamide-4 (6). The mass spectrum and elemental analysis suggested that compound 4 had a molecular formula of C\textsubscript{15}H\textsubscript{23}N. In addition, the infrared spectrum (2055 cm\textsuperscript{-1}) and mass spectrum (M\textsuperscript{+}-HCN) indicated the presence of an isonitrile group. From infrared and \textsuperscript{1}H-NMR data, it was also suggested that compound 4 contained a tertiary methyl group, a terminal methylene group and an isopropylidene group that was probably part of an \(\alpha,\beta\)-unsaturated isonitrile group. Finally, treatment of 4 with lithium in ammonia gave the same hydrocarbon (14) as that obtained from identical treatment of 1, establishing the structural relationship between these compounds.
The relationship between of axisothiocyanate-4 (5) and 4 was established as follows (Equation 2). Treatment of 5 with methylamine in chloroform at room temperature gave a thiourea (21) as an amorphous solid with the molecular formula C_{17}H_{28}N_{2}S. Treatment of 4 with sulfur followed by methylamine gave the same thiourea, establishing the relationship between these compounds.\textsuperscript{15}

\[
\begin{align*}
5 & \xrightarrow{\text{NCS, CH}_3\text{NH}_2} 21 \\
 & \xrightarrow{1. S_8, \Delta} 4 \\
 & \xrightarrow{2. \text{CH}_3\text{NH}_2} (2)
\end{align*}
\]

Finally, the structures of axamide-1 (3) and axamide-4 (6), minor components of extracts from \textit{Axinella cannabina}, were established by comparison with authentic samples prepared by hydrolysis of isonitriles 1 and 4, respectively (Equations 3 and 4).\textsuperscript{4}

In summary, the structures of 1-6 are reasonably secure. The structure of 2 has been clearly established by X-ray crystallographic analysis of the derived thiourea 20 and the remaining structures have all been correlated with 2 by a series of chemical reactions. The absolute stereochemistry of the axanes, however, has not been rigorously proven. Finally, we note that it has been suggested that axamides 3 and 6 may not be natural products, but rather may be artifacts derived from the hydrolysis of isonitriles 1 and 4, respectively, during the isolation process.\textsuperscript{3}
C. Biological Activity of Axisonitrile-1 (1)

Axisonitrile-1 (1), axisothiocyanate-1 (2) and axamide-1 (3) were isolated in 1973, but their biological properties were not reported. Although they have a carbon skeleton similar to the antibiotic oppositol (11), no pharmacological effect in humans has been reported for these or other axane sesquiterpenoids. It was suggested that the axanes might play some sort of role in the defense system of the sponge.

In 1982 it was reported that axisonitrile-1 could also be isolated from extracts of the nudibranch *Phyllidia Pulitzer*, a shellless mollusk that grazes on *Axinella cannabina*. Axisonitrile-1 (1) was isolated from ethereal extracts of five specimens of *Phyllidia Pulitzer* grazing on *Axinella cannabina* and thus, the predator-prey relationship between this nudibranch and the sponge was clearly established. The distribution of axisonitrile in extracts of *Phyllidia Pulitzer* indicated the presence of 1 (Scheme 1) in the digestive gland, the mantle slimy
secretion, and the skin. From earlier studies it was believed that these unprotected mollusks must be equipped with a defense mechanism that helps them survive from predators. Such defense mechanisms previously established for nudibranches included secretion of strong acids and poisonous materials, and secretion of antifeedants derived from the food chains of the nudibranches. Although it was shown that axisonitrile-1 was ineffective as a fish antifeedant, it was very active as an ichthiotoxin. For example, it was shown that axisonitrile-1 (1) was lethal to the marine fish Chromis chromis and the fresh water fish Carassius carassius at a minimum concentration of only 8 ppm.

In summary, it appears that Axinella cannabina plays a critical role in the defense system of the nudibranch. It is not clear what benefit the sponge derives from this relationship and the biological properties of axanes 2-6 have yet to be established.

D. Synthetic Studies Directed Toward Axanes 1-6

Two approaches to the axane sesquiterpenes have previously been described. A successful approach was reported by the Piers group and an unsuccessful approach has been described by Chuang. To place the studies described in this thesis in perspective, the Piers and Chuang approaches will now be reviewed.

In 1986 the Piers group reported total syntheses of (dl)-axisonitrile-1 (1), (dl)-axisothiocyanate-1 (2), and (dl)-axamide-1 (3) as well as their C(10) isomers. The initial stages of the synthesis relied upon methylene cyclohexane annulation methodology previously developed in the Piers group. Thus, 2-methyl-2-cyclopenten-1-one (22) and 2-(5-chloro-1-pentenyl)magnesium
bromide (23) were used to construct key intermediate perhydroindan 24 as outlined in Scheme 3. The Grignard reagent (23) was prepared from the corresponding trimethylstannyl alkene 25 and the stannane was prepared by the addition of trimethylstannyl copper-dimethyl sulfide complex to 5-chloro-1-hexyne (26). Sequential treatment of the Grignard reagent (23) with 0.3 equivalents of CuBr-Me₂S complex and enone 22 in tetrahydrofuran at -78°C gave conjugate adduct 24 in a poor yield. When an equivalent of boron trifluoride etherate was added to the enone prior to addition of the organometallic reagent, however, a 67% yield of chloroketone 27 was obtained. Treatment of 27 with 2.5 equivalents of potassium hydride in tetrahydrofuran completed the synthesis of 24 (85%).

Scheme 3. Preparation of Enone 24

(a) Me₃SnCu·Me₂S (1 eq), THF, -78°C, 6 h (b) MeOH (60 eq) (c) MeLi (1 eq) (d) MgBr₂ (1 eq) (e) CuBr·Me₂S (0.3 eq); then 2-methylcyclopent-2-en-1-one (22) (f) KH, THF
The next task was to introduce C(1)-C(2) unsaturation to be eventually used for introduction of the C(7) sidechain. This was accomplished as shown in Scheme 4. Exposure of cyclopentanone 24 to selenenylation-oxidation-elimination or Pd(OAc)$_2$ oxidation procedures failed to afford enone 29 in good yields.$^{22,23}$ In the end, 27 was first converted into the corresponding trimethylsilyl enol ether and then brominated using N-bromosuccinimide to afford bromoketone 28 (89%) as a mixture of epimers.$^{24}$ Dehydrobromination using lithium bromide and lithium carbonate in hot N,N-dimethylformamide gave enone 29 in 78% yield.$^{25}$

**Scheme 4. Preparation of Unsaturated Ketone 29**

\[ 
\begin{array}{c}
\text{24} \\
\text{a, b, c} \\
\text{89%} \\
\text{28} \\
\text{d} \\
\text{78%} \\
\text{29} \\
\end{array} \\
(a) \text{LDA} \quad (b) \text{Me}_3\text{SiCl} \quad (c) \text{NBS, CCl}_4 \quad (d) \text{LiBr, Li}_2\text{CO}_3, \text{DMF, } \Delta 
\]

The C(7) sidechain was then introduced as outlined in Scheme 5. Treatment of enone 29 with (E)-1-ethoxy-3-methyl-1-trimethylsiloxy-1-butene (30) using the Mukaiyama conditions gave diastereomeric conjugate adducts 31 and 32 in 88% combined yield.$^{26}$ From spectroscopic data, it was clear that both 31 and 32 had the same stereochemistry at C(7) wherein conjugate addition had occurred from the convex face of the fused ring structure. Basic hydrolysis of this 1:1 mixture gave diastereomeric acids 33 (23%) and 34 (57%). Thus, it appeared that some epimerization at C(10) occurred during the
hydrolysis. Since the major acid produced using this sequence (34) had the undesired stereochemistry at C(10), the plan was modified. Treatment of enone 29 with 3-methyl-1,1-bis(trimethylsiloxy)-1-butene (35) in the presence of titanium tetrachloride directly gave a 3:2 mixture of acids 33 and 34 in 92% yield. One unique feature mentioned in this report was that the exocyclic methylene unit did not tend to migrate into conjugation with the enone during these chemical transformations.

Scheme 5. Preparation of Keto Acid 33

With the carbon skeleton of the axanes intact, the syntheses of 1-3 were completed as outlined in Scheme 6. The aforementioned mixture of keto acids was separated and the structure of 33 was established by X-ray crystallography.
Acid 33 was subjected to a Wolff-Kishner reduction to give 36 (90%). No epimerization occurred during this basic procedure. Acid 36 was converted into acyl chloride 37 using oxalyl chloride. After removal of excess oxalyl chloride and solvent, the crude 37 was dissolved in dry acetone and treated with an excess of aqueous sodium azide to give acyl azide 38. The crude acyl azide was then heated in toluene at 80°C for 2h to generate intermediate isocyanate 39 which was trapped with an excess of 2-trimethylsilylethanol to yield carbamate 40. The overall yield from acid 36 to carbamate 40 was 89%. Carbamate 40 was then treated with tetra-n-butylammonium fluoride in dry tetrahydrofuran to give amine 41 (72%) as a colorless oil. Finally, treatment of amine 41 with acetic formic anhydride at room temperature gave (dl)-axamide-1 (3) in 90% yield as a colorless oil. The 1H-NMR spectrum of 3 showed that it exists as a 3:2 mixture of cis and trans geometrical isomers about the amide linkage.
Scheme 6. Synthesis of Axanes 1-3

The syntheses of (d/)-axisonitrile-1 (1) and (d/)-axisothiocyanate-1 (2) were accomplished from (dl)-axamide-1 (3). Treatment of 3 with p-toluenesulfonyl chloride in the presence of pyridine gave (d/)-axisonitrile (1) in 86\% yield. Since 1 had previously been converted to 2 (vide supra) this also completed a formal synthesis of (d/)-axisothiocyanate (2). The Piers group also subjected acid 34 to the aforementioned reaction sequence, leading to the synthesis of the C(10) epimers of 2 and 3.

In addition to the Piers total synthesis, an alternate approach to the axananes has been described by Chuang and Chenera. This approach
revolved around a free radical cyclization and the retrosynthetic analysis is shown in Scheme 7. In this approach, ketoester 42 was chosen as a key intermediate. Although several routes to 42 can be imagined, in the Chuang-Chenera approach it was hoped that ketoester 42 would be available from lactone 43 which was to be prepared by a free radical cyclization of iodolactone 44. It was also hoped that axanes 1-6 could be derived from ketoester 42 by appendage of appropriate three-carbon units to the acetic acid sidechain.

Scheme 7. Chuang-Chenera Approach to Axane Sesquiterpenoids

The synthesis started as shown in Scheme 8. Reductive alkylation of m-anisic acid (45) with 4-bromo-1-butene gave dihydrobenzoic acid 46. The crude acid thus obtained was directly treated with iodine in a mixture of
aqueous sodium bicarbonate and ether to give iodolactone 47 in 66% overall yield from m-anisic acid.\textsuperscript{35}

**Scheme 8. Preparation of Iodolactone 47**

\[ \text{OMe} \quad \text{a, b} \quad \text{OMe} \quad \text{c} \quad \text{MeO} \]

45 \quad 46 \quad 47 (66\%)

(a) Li, NH\textsubscript{3} (b) H\textsubscript{2}C=CHCH\textsubscript{2}CH\textsubscript{2}Br (3) NaHCO\textsubscript{3}, I\textsubscript{2}, H\textsubscript{2}O-Et\textsubscript{2}O

As shown in Scheme 9, lactone 47 was subjected to a Johnson-Lemieux oxidation to give aldehyde 48.\textsuperscript{36} Since 48 was not extremely stable, it was treated with (carbethoxymethylidene)triphenylphosphorane immediately after purification to give unsaturated ester 44 in 57% overall yield from iodolactone 47.\textsuperscript{37} Once again problems with stability were encountered as 44 became dark on standing and had to be used immediately in the next reaction.

**Scheme 9. Preparation of Cyclization Substrate 44**

\[ \text{MeO} \quad \text{a} \quad \text{MeO} \quad \text{b} \quad \text{MeO} \]

47 \quad 48 \quad 44 (57\%)

(a) OsO\textsubscript{4}, NaIO\textsubscript{4}, t-BuOH, H\textsubscript{2}O (b) Ph\textsubscript{3}P=CHCO\textsubscript{2}Et
As shown in Scheme 10, reductive cyclization of iodolactone 44 (n-Bu$_3$SnH, AIBN, PhH, Δ) gave an inseparable 5:1 mixture of diastereomeric perhydroindans 43 and 49 in 81% yield.$^{33}$ Hydrogenation of the mixture of 43 and 49 over palladium on charcoal gave an inseparable mixture of esters 50 and 51 in 83% yield.

Scheme 10. Free Radical Cyclization of 44 to Perhydroindans 43 and 49

The cis perhydroindan skeleton required for the preparation of the axanes was derived from ester 50 as shown in Scheme 11. The mixture of esters 50 and 51 was treated with ethylene glycol, trimethylorthoformate and p-toluenesulfonic acid to give ketal acid 52 (74%) and unchanged ester 51 (13%). The cis relationship of the angular carboxyl group and the acetic ester sidechain in compound 52 was proven, as shown in equation 5, by treating acid 52 with diazomethane to give ester 53 (87%) which ras treated with
hexamethyldisilazide in ether to give β-ketoester 54 as a mixture of diastereomers in 83% yield. Ester 51 failed to give the Dieckman product under conditions identical to those shown in equation 5, suggesting that the acetic acid sidechain in 51 was trans to the angular carbonyl group.

**Scheme 11. Conversion of 50 to Cis-Perhydroindan 52**

The cis ring fusion of ketal acid 52 was assigned using arguments based on the conformational analysis of keto acids 55 and 56 shown in Figure
3. It was imagined that trans keto acid 55 would clearly undergo intramolecular acetal formation upon treatment with an alcohol and acid (55 → 57). On the other hand, it was expected that cis keto acid 56 would resist such intramolecular ketal formation because to do so would generate a strained trans-oxabicyclo[3.3.0]octane unit. In fact, hydrolysis of ketal acid 52 did afford a keto acid, assigned structure 56, which resisted intramolecular ketal formation upon treatment with methanol and acid (56 → 58). Instead, keto acid 56 did return to ketal acid 52 upon treatment with ethylene glycol, trimethylorthoformate and p-toluenesulfonic acid (equation 6). The resistance of 56 to intramolecular ketal formation suggested that it and ketal acid 52 were cis-fused perhydroindans. In summary, treatment of lactone 50 with ethylene glycol, trimethylorthoformate and acid resulted in intramolecular ketal hydrolysis, isomerization to the more stable cis perhydroindan and intermolecular ketal formation (56 → 52). On the other hand, the chemical behavior of ketal ester 51 was consistent with that expected from a trans-fused perhydroindan. For example upon treatment with alcohol-orthoester-acid mixtures, it merely underwent ketal exchange (51 → 55 → 59) without ring juncture isomerization as shown in equation 7.
Figure 3. Expectations for Isomeric Perhydroindans 55 and 56

52 \[\overset{\text{HCO}_2\text{H}, \text{H}_2\text{O}}{\rightleftharpoons} \overset{(\text{CH}_2\text{OH})_2, \text{HC(OMe)}_3}{\overset{\text{TsOH (cat)}}{\rightarrow}} 56 \]

58 \[\overset{\text{MeOH, HC(OMe)}_3}{\rightarrow} \overset{\text{TsOH (cat)}}{\rightarrow} 58 \]
With a cis perhydroindan with the required stereochemistry at C-7, C-8 and C-9 in hand, the preparation of key intermediate 42 was accomplished as described in Scheme 12. Ketal acid 52 was treated with oxalyl chloride and the resulting crude acyl chloride was directly reduced with sodium borohydride to give primary alcohol 60 in 83% overall yield. Alcohol 60 was treated with triphenylphosphine and carbon tetrabromide to give a mixture of bromides 61 and 62 which were not separated, but treated with 80% aqueous formic acid to convert 61 to 62. In this manner 62 was obtained in 80% yield from 60. Finally, reduction of bromide 62 using tri-n-butyltin hydride gave ketone ketoester 42 in 90% yield.
Scheme 12. Preparation of Ketoester 42

The next stages of the synthesis involved conversion of the ketone into an exocyclic methylene group and introduction of a three-carbon unit onto the acetic acid sidechain (Scheme 13). Treatment of 42 with 10 equivalents of (methylidene)triphenylphosphorane in toluene gave olefin 63 in 84% yield.\textsuperscript{41} Introduction of the three-carbon appendage on the C-7 sidechain of 63, however, proved not to be an easy task. Attempts to alkylate the enolate derived from 63 using isopropyl iodide met with failure, as did attempts to effect aldol condensations between the same enolate and acetone. A three-carbon sidechain was eventually introduced by way of carboxylic acid 64. Thus 63 was hydrolyzed with 5% aqueous sodium hydroxide to give acid 64 in 84% yield as shown in Scheme 13. Treatment of acid 64 with three equivalents of lithium diisopropylamide at 50°C, followed by treatment of the resulting dianion with...
three equivalents of acetone, gave β-hydroxyacids 65 in 85% yield as an inseparable mixture of diastereomers. Isomeric acids 65 were treated with diazomethane to afford metf esters 66 (27%) and 67 (54%) which were separated by column chromatography. The structure of 67 was established by X-ray crystallography, confirming the stereochemical arguments set forth above. Finally, treatment of 67 with methanesulfonyl chloride in pyridine gave ester 68 in 24% yield.

Scheme 13. Introduction of the C-10 Isopropyl Group

The Chuang-Chenera synthesis, however, was eventually abandoned at this stage for several reasons. Although it was possible to improve the yield of the dehydration (67 → 68) using Martin's sulfurane, it was not possible to
convert the β,γ-unsaturated ester into the α,β-unsaturated ester that would be needed to prepare axanes 4 - 6.\textsuperscript{42} The level of diastereoselectivity in the aldol condensation was also considered to be a bit low for the preparation of axanes 1 - 3. Although a number alternative methods for introducing the C-7 sidechain were explored, the route was eventually abandoned due to its length and low overall yield. For example, the preparation of ester 67 from \textit{m}-anisic acid required 18 steps and proceeded in only about 1% overall yield. It was still thought that the axanes would eventually be preparable from an intermediate ketoester 42 or olefinic ester 63 if a shorter synthesis capable of delivering gram quantities of material could be developed. The next portion of this thesis will present a solution to this problem.
Chapter II

An Alternative Synthesis of Ketoester 42 and Ancillary Studies

A. Retrosynthetic Analysis

An alternative approach to ketoester 42 and alkene 63 is outlined antithetically in Scheme 14. As discussed in chapter I, olefin 63 could be prepared from ketone 42 using a Wittig reaction.\(^{41}\) It was imagined that 42 might be obtained from an intramolecular conjugate addition reaction (69 → 42). Unsaturated ester 69 was to be prepared from aldehyde 70 and the appropriate phosphorane and olefin 71 was to serve as the precursor of the aldehyde. It was projected that olefin 71 would be available from cyclohexan-1,3-dione (74) using well-precedented reactions (74 → 73 → 72 → 71).

The critical issue in this synthesis was regiochemical and stereochemical control in the intramolecular conjugate addition.\(^{43}\) During the course of synthetic studies directed toward dendrobine, Heathcock accomplished the related intramolecular conjugate addition shown in equation 8 (75 → 76).\(^{44}\) Based on this example it was hoped that the required regiochemistry and stereochemistry would be obtained.
Scheme 14. Intramolecular Conjugate Addition Retrosynthetic Analysis

B. Preparation of Unsaturated Ester 69.

Investigation of the proposed conjugate addition route to ketoester 42 began with the preparation of unsaturated ester 69 (Scheme 15). Using a literature procedure, commercially available cyclohexan-1,3-dione (74) was treated with ethanol and p-toluenesulfonic acid to give vinylogous ester 73 in 95% yield. Treatment of 73 with 3-butenylmagnesium bromide at 0°C, followed by an acidic hydrolysis of the addition product, gave α,β-unsaturated ketone 72 in 73% yield. With enone 72 in hand, the angular methyl group was
introduced using a conjugate addition. Treatment of 73 with lithium dimethylcuprate gave ketone 71 in 90% yield.\textsuperscript{46} Ketone 71 was also prepared in 78% yield using a copper-catalyzed conjugate addition of 3-butenylmagnesium bromide to commercially available 3-methylcyclohex-2-en-1-one (77) as shown in equation 9. Due to the expense of 77, however, the route shown in Scheme 15 was preferred for large-scale preparation of 71. Conversion of enone 71 to unsaturated ester 69 was completed using a two-step reaction sequence. Ozonolysis of 71 followed by reduction of the ozonide with dimethyl sulfide gave aldehyde 70 in 88% yield.\textsuperscript{12} Aldehyde 70 was unstable and underwent some reaction of the aldehyde carbonyl group upon standing at room temperature for a few hours (the formyl proton at $\delta$ 9.6 disappeared upon standing). Therefore 70 was directly treated with (carbethoxymethylidene)triphenylphorane in benzene at room temperature to afford unsaturated ester 69 in 81% yield as a separable 5:1 mixture of $E$ and $Z$ isomers, respectively.\textsuperscript{37} Although $Z$-69 could be isomerized to $E$-69 under mild acidic conditions, the mixture of isomers was used in the following studies.
Scheme 15. Preparation of Cyclization Substrate 69

![Scheme 15](image)

C. Cyclization Studies: Conversion of Unsaturated Ester 69 to Ketoester 42.

The cyclization paths available to ester 69 are described in Scheme 16. Treatment of 69 with either base or acid could lead to enolates (enols) 78 and 79. Cyclization of 78 would give bicyclo[4.3.0]nonanes of type 80 while cyclization of 79 would afford bicyclo[3.3.2]nonanes of type 81. Encouraged by the example shown in equation 8, ester 69 was treated with 0.2 equivalents of
potassium t-butoxide in t-butyl alcohol in the hope of obtaining conjugate adduct 42 (equation 10). Instead of obtaining a single product, a total of four inseparable isomers were detected by capillary VPC analysis of the crude reaction mixture. GC-MS analysis showed that the four isomers had the same molecular weight (parent ion at m/e 238). Coinjection of authentic 42, however, indicated that the desired product was only present in minor amounts (7% of isomeric mixture assuming equal response factors). The use of other bases did not improve the yield of 69. For example, the use of 0.3 equivalents of sodium ethoxide in ethanol or 0.3 equivalents of sodium hydride in tetrahydrofuran also gave a mixture of isomeric products. VPC analysis again indicated that ketoester 42 comprised only about 5% of the mixture of isomers. The enolate route to 42 was abandoned at this point and other cyclization conditions were sought.

It is well known that enamines add to α,β-unsaturated esters to afford 1,4-addition products.47 Thus, in separate reactions ester 69 was treated with pyrrolidine, piperidine and diethylamine in the presence of a catalytic amount of acetic acid. Under these conditions, ester 69 cyclized to give a mixture of products that were once again analyzed by VPC. In each case the major product was 42, the best results being obtained when one equivalent of pyrrolidine was used in tetrahydrofuran at 60°C (equation 11). Under these
conditions, ketoester 42 was obtained in 65% isolated yield with 93% purity by VPC.

Scheme 16. Possible Pathways for Cyclization of 69

In summary, ketoester 42 was prepared in six steps and 29% overall yield from 1,3-cyclohexanediione (74). This route was superior to the route developed by Chuang and Chenera and was capable of producing gram quantities of 42. The next section describes attempts to use 42 in the synthesis of axane sesquiterpenes.
D. Attempted Introduction of the Three-Carbon Side Chain.

With key intermediate 42 in hand, the next step was to introduce the required three-carbon unit on the acetic acid side chain. Hoping that the three-carbon unit could be introduced by direct alkylation of an acid dianion, 42 was converted to ketal acid 83 as shown in equation 12.\(^{48}\) Ketal formation (42 \(\rightarrow\) 82) was accomplished in 94% yield and ester hydrolysis (82 \(\rightarrow\) 83) was accomplished in 82% yield using sodium hydroxide in aqueous ethanol. Unfortunately, attempts to alkylate the enolate of ester 82 or the dianion of 83 with 2-iodopropane failed under a variety of conditions. Mixtures of unidentified products were usually obtained.

![Chemical structure](image)

(a) \((\text{CH}_2\text{OH})_2, \text{HC(OMe)}_3, \text{TsOH}\)  (b) \(\text{NaOH, EtOH, H}_2\text{O}\)

Since the alkylations did not give usable results, condensation reactions of 82 and 83 with acetone were next investigated. As with ester 63 (Scheme 13), the lithium enolate of 82 failed to react with acetone. Only starting material was recovered. The dianion of 83, however, did react with acetone to afford isomeric \(\beta\)-hydroxyesters 84 in 28% yield after esterification using diazomethane (equation 13). The low yield in the carbonyl addition (83 \(\rightarrow\) 84) was disappointing as Chuang had obtained good yields using the related dianion of
64 (Scheme 13). It is possible that steric hindrance in 83 is responsible for the low yield.

With all these failures, alternate routes for introducing the required three-carbon unit were sought. Experiments were next conducted to see if the enolate of ester 82 could be acylated. It was found that sequential treatment of 82 with lithium diisopropylamide and ethyl cyanoformate gave malonate 85 in 75% yield (equation 14). Therefore routes starting with acylations of 82 were explored.
The transformations outlined in Scheme 17 (82 → 86 → 87) were next examined. This was based on the known transformation of cyclohexanone (88) to enone 90 shown in Scheme 18.\textsuperscript{49} Prior to working with ester 82, model studies were conducted with ethyl isovalerate (91) as shown in Scheme 19. The \(\alpha\)-dithiomethylenation of esters, for example the conversion of 92 to 93 as shown in equation 15, has been reported.\textsuperscript{50} When these conditions were applied to 91, however, none of the desired product (94) was obtained. It was reasoned that a stronger base might be required. Fortunately, when 91 lithium diisopropyl-amide was used in place of lithium hexamethyldisilazide, ketene dithioacetal 94 was obtained in 90\% yield. When 94 was treated with lithium dimethylcuprate in diethyl ether at low temperature, no reaction occurred and the starting ester was recovered.\textsuperscript{51} When the reaction was conducted at room temperature for ten hours, a complex mixture of products was obtained. The products could not be separated by MPLC, but could be resolved into four components by VPC. The structures of these components were tentatively assigned as 95-98 based GC-MS, \(^{13}\)C-NMR, and \(^1\)H-NMR data collected on the product mixture.

**Scheme 17. Projected Introduction of Isopropylidene Group**
Scheme 18. Isopropylidenation Using Ketene Dithioacetals

\[
\begin{align*}
\text{O} & \quad \text{NaH, CS}_2, \text{Mel} \\
88 & \quad \rightarrow \\
\text{O} & \quad \text{Me}_2\text{CuLi} \\
89 & \quad \rightarrow \\
90 & \quad (96\%) \\
\end{align*}
\]

Scheme 19. Model Studies With Ketene Dithioacetals

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{a, b, c, d} \quad 97\% \\
91 & \quad \rightarrow \\
\text{EtO}_2\text{C} & \quad \text{e} \\
94 & \quad \rightarrow \\
95 & \quad (\text{tentative}) \\
\text{SMe} & \quad + \\
\text{SMe} & \quad + \\
\text{SMe} & \quad + \\
98 & \quad (\text{tentative}) \\
97 & \quad (\text{tentative}) \\
96 & \quad (\text{tentative}) \\
\end{align*}
\]

(a) LDA (1 eq), HMPA, THF (b) CS\textsubscript{2} (1 eq) (c) LDA (1 eq), THF (d) Mel (2 eq) (e) Me\textsubscript{2}CuLi, Et\textsubscript{2}O, 25\textdegree C, 10 h

In spite of the lack of success of the model reaction, the same reaction sequence was attempted with ester 82 with the hope that a suitable cuprate for conducting the coupling would be found. Conversion of 82 to ketene dithioacetal 86 was accomplished in 50% yield as shown in Scheme 20. Treatment of 86 with lithium dimethylcuprate at room temperature in tetrahydrofuran gave a mixture of products, the major components of which were tentatively assigned structure 99. The structure assignment for 99 was based on (1) the appearance of a parent ion at \textit{m}/\textit{z} 354 in MS, (2) the appearance of thiomethyl (SCH\textsubscript{3}) and vinylic methyl (C=CH\textsubscript{3}) resonances at \delta
2.2 and δ 2.1, respectively, in the 1H-NMR spectrum and (3) the appearance of four vinyl carbons of singlet multiplicity at δ 131.6, δ 134.6, δ 136.9, and δ 141.8 (two geometrical isomers) in the 13C-NMR spectrum of the product mixture. A trace amount of material tentatively assigned structure 100, was also present in the product mixture. This structure assigned based on a parent ion (GC-MS) at m/e 340 and the appearance of a vinyl proton (singlet) at δ 7.23 in the product mixture.

Based on the feeling that steric hindrance was part of the problem, it was decided to perform the same reaction sequence starting with ester 63. Remember, the carbonyl addition studies described in Scheme 13 and equation 13 suggest that the ketal (82) might be more hindered than the olefin (63). In the event, ketene dithioacetal 101 was prepared from 63 in 80% yield as described in equation 16 and 101 was treated with several different cuprates under a variety of conditions. The results are listed in Table 1. Since the reaction products were not easily separable, the structures of compounds 102-105 were assigned based principally on mass spectral data. Through a great deal of effort, however, samples enriched in 103 and 104 were obtained. In each case, the one compound was contaminated with the other. GC-MS analysis of these samples gave parent ions at m/e 276 and m/e 294 for 103 and 104, respectively. The 1H-NMR spectrum of the sample enriched in 103 showed two vinylic methyl groups as singlets at δ 1.67 and δ 1.77 and the 13C-NMR spectrum of this material displayed four olefinic resonances with of appropriate multiplicity. The 1H-NMR spectrum of the sample enriched in 104 displayed two singlets at δ 7.09 and δ 7.14 and the 13C-NMR of this material showed two olefinic carbons (=CH) at δ 144.4 and δ 146.0, indicating that 104 was a mixture of geometrical isomers. The structure of 105 was based only on GC-MS analysis which gave a parent ion at m/e 308. The structure of methyl
ketone 102 was based on a parent ion at m/e 246 and a major fragment at m/e 231 (M⁺–Me) in the GC-MS and the appearance of a methyl singlet at δ 2.28 in the 1H-NMR spectrum of the crude product mixture. The reader should note that the isolated yields of products from these reactions were quite low. For example, purification of the product mixture from entry 2 of Table 1 gave samples that were predominantly 103 and 104 in 9% and 12% yields, respectively.

Scheme 20. Preparation and Methylation of Ketene Dithioacetal 86

(82) \[\text{CO}_2\text{Et}\] → (86) \[\text{CO}_2\text{Et}\] 69%

(100) \[\text{CO}_2\text{Et}\] → (99) \[\text{CO}_2\text{Et}\] 69%

(a) LDA (1 eq), HMPA, THF (b) CS₂ (1 eq) (c) LDA (1 eq), THF (d) Mel (2 eq) (e) Me₂CuLi, Et₂O, 25°C, 10 h
Table 1. Reactions Between Ketene Dithioacetal 101 and Cuprates

![Chemical structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Conditions</th>
<th>m/e 246</th>
<th>m/e 276</th>
<th>m/e 294</th>
<th>m/e 308</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me$_2$CuLi (2 eq)</td>
<td>20°C, 1h</td>
<td>—</td>
<td>43</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Me$_2$CuLi (2 eq)</td>
<td>25°C → 50°C, 12 h</td>
<td>—</td>
<td>30$^c$</td>
<td>54$^c$</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Me$_2$CuLi (5 eq)</td>
<td>25°C, 10h</td>
<td>28</td>
<td>63</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Me$_2$Cu(CN)Li$_2$ (5 eq)</td>
<td>0°C, 2h</td>
<td>24</td>
<td>36</td>
<td>25</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>Me$_2$Cu(SCN)Li$_2$ (3 eq)</td>
<td>-10°C, 4h</td>
<td>4</td>
<td>4</td>
<td>61</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>Me$_2$Cu(SCN)Li$_2$ (4 eq)</td>
<td>25°C, 10 h</td>
<td>18</td>
<td>4</td>
<td>28</td>
<td>2</td>
</tr>
</tbody>
</table>

(a) All reactions were run in ether and 25°C means room temperature on the day of the reaction.
(b) Yields represent the percent of a given product in the mixture of products as determined by VPC, assuming that response factors for all compounds are identical. Actual yields were considerably lower than those listed in the Table as mass balance was always far less that 100%.
(c) In this experiment, pure 103 and 104 were isolated in 9% and 12% yields, respectively.
In summary, it was not possible to introduce the required three-carbon unit in satisfactory yield via intermediate ketene dithioacetals such as 86 and 101. Thus, the intramolecular conjugate addition approach to the axanes was modified such that the three-carbon unit would be introduced at an earlier stage of the synthesis. This plan is discussed in the following chapter.
A. Retrosynthetic Analysis

As discussed in Chapter II, difficulties associated with placing an appropriate three-carbon unit on the acetic acid side chain of keto ester 42 forced us to explore the possibility of introducing this unit at an earlier stage of the synthesis. It was hoped that this could be accomplished using the strategy outlined in Scheme 21. Thus, it was expected that keto ester 107 would undergo an intramolecular conjugate addition to afford 106 or its C(10) diastereomer. Unsaturated ester 107 would be derived from addition of Wittig reagent 108 to aldehyde 70.
B. Attempted Preparation of Cyclization Precursor 107

The preparation of 107 was initially attempted using a Wittig reaction between aldehyde 70 (Scheme 15) and the known phosphorane 108. It was disappointing to find that when 70 and 108 were heated at 80°C in dry benzene for a day, only intractable materials were obtained. It was suspected that aldehyde 70 might be unstable to the above conditions, so ketal aldehyde 110 was prepared as outlined in Scheme 22. Thus, ketone 71 was converted to ketal 109 in 83% yield. Ozonolysis of 109 followed by a reductive workup gave aldehyde 110 in 90% yield. Unfortunately, treatment of 110 with Wittig reagent 108 in benzene at reflux for 20 h also led to the formation of intractable material.

Scheme 22. Preparation of Aldehyde 110

\[
\begin{align*}
71 & \xrightarrow{a} 109 \xrightarrow{b, c} 110 \\
& \text{(a) HOCH}_2\text{CH}_2\text{OH, HC(OMe)}_3, \text{TsOH} \quad \text{(b) O}_3, \text{MeOH} \quad \text{(c) Me}_2\text{S}
\end{align*}
\]

Horner-Wittig reagents are better nucleophiles toward ketones and aldehydes. Therefore it was thought that 107 might be prepared from aldehyde 110 and phosphonate 112. Phosphonate 112 was prepared from ethyl α-bromoisovalerate (111) and triethyl phosphite in about 20% yield as shown in equation 17. The yield of this reaction was disappointing as it had been reported that ethyl α-bromopropionate and triethyl phosphite give the corresponding phosphonate in 85% yield. More disappointing was the
observation that the anion of 112 also gave intractable materials upon reaction with aldehyde 110.

\[
\begin{align*}
\text{Br} & \quad \text{CO}_2\text{Et} & \quad \xrightarrow{(\text{EtO})_3\text{P}, \Delta, 20\%} & \quad \text{Br} & \quad \text{CO}_2\text{Et} \\
\text{111} & & & \text{112} \\
\end{align*}
\]

With no success in preparing unsaturated ester 107 using Wittig or Horner-Wittig type reactions, attention was turned to the preparation of 107 using a Peterson olefination. This required the preparation of \(\alpha\)-silyl ester 113. In 1967 it was reported that \(\alpha\)-bromoester 111 reacted with trimethylsilyl chloride in the presence of zinc and a catalytic amount of iodine to afford 113 (equation 18).\(^{53}\) Unfortunately we were unable to repeat this procedure as in each trial, only ethyl isovalerate was obtained. \(\alpha\)-Silyl ester 113 was prepared in 25% yield by alkylation of the lithium enolate of ethyl \(\alpha\)-trimethylsilylacetate (114) as shown in equation 18. Attempts to couple the enolate of 113 with aldehyde 110, however, once again led to the formation of intractable material.

It was next decided to attempt the coupling of a more stable \(\alpha\)-silylated enolate with aldehyde 110. The enolate that was selected was to be prepared from the known \(\alpha\)-silyl ester 115, prepared in 67% yield from 114 as shown in
The use of 115 called for a slight revision of the synthetic strategy as discussed in the following section.

\[
\begin{align*}
\text{SiMe}_3 & \quad \text{CO}_2\text{Et} \\
\xrightarrow{\text{a, b, c}} & \quad 67\% \\
\text{114} & \quad \text{Me}_3\text{Si} \quad \text{CO}_2\text{Et} \\
& \quad \text{115}
\end{align*}
\]

(a) LDA, THF, HMPA (b) n-BuLi / NiBr$_2$ (c) H$_2$C=C(Br)CH$_3$

C. Retrosynthetic Analysis Revisited and Preparation of Keto Ester 117

The use of 115 would not only provide access to axanes 1-3, but would also provide the extra oxidation needed to pursue axanes 4-6. Key intermediates in this approach were projected to be 106 and/or 116. These were to be prepared from 110 and 115 via 118 and 117 as antithetically in Scheme 23.

After such a long struggle, it was a pleasure to find that treatment of 115 with one equivalent of lithium diisopropylamide followed by aldehyde 110 gave the desired ester 118 in 70% yield as a separable mixture of E and Z isomers in a 2:1 ratio, respectively (equation 20). The structure assignments for E and Z isomers of 118 were based on their $^1$H-NMR spectra. The "$\beta$" vinyl proton of E isomer appears as a singlet at $\delta 6.8$ while the "$\beta$" vinyl proton of the Z isomer appears as a singlet at $\delta 5.8$. The lower chemical shift of this proton in the E isomer indicates that the carbonyl group is conjugated with the 1,3-diene. Due to steric hindrance, the Z isomer apparently adopts a conformation in which the diene and ester carbonyl $\pi$-frameworks do not overlap, leading to an upfield shift of the "$\beta$" vinyl proton.
Scheme 23. Projected Synthesis of Keto Esters 106 and 116

\[ \text{Keto Ester 106} \quad \text{and/or} \quad \text{Keto Ester 116} \]

\[ \text{Me}_2\text{Si and} \]

\[ \text{Keto Ester 115} \quad \text{and} \quad \text{Keto Ester 110} \]

\[ \text{Keto Ester 118} \]

\[ \text{Z-118} \quad \text{and} \quad \text{E-118} \]

\[ \text{LDA} \quad (70\%) \]

\[ \text{(20)} \]
The preparation of cyclization substrate 117 from ketal 118 was accomplished as shown in Scheme 24. Thus, independent hydrolysis of the E and Z isomers of 118 using 3N aqueous HCl at room temperature for a three hours gave the E and Z isomers of 117 in 96% and 86% yields, respectively. When the reaction was conducted for longer time period, isomerization of the E and Z isomers of 117 was observed. In fact, when the Z isomer of 117 was treated with 3N aqueous HCl at room temperature for 20 h, nearly complete isomerization occurred and the E isomer of 117 was isolated in 69% yield. In this way, sufficient quantities of 117 were obtained to proceed with the synthesis.

Scheme 24. Preparation of Cyclization Substrate 117

![Scheme 24. Preparation of Cyclization Substrate 117](image-url)
D. Cyclization Studies: Preparation of Axane Precursor 116

Cyclizations of keto ester 117 were attempted under a variety of conditions to give the products shown in Table 2. Thus, cyclization of the E isomer of 117 using the conditions developed for the conversion of 69 to 42 (equation 11) gave β,γ-unsaturated ester 119 in 72% yield along with 10% of α,β-unsaturated ester 116 (Entry 1 of Table 2). The structure of 119 was supported by its 1H-NMR spectrum which showed two vinyl protons at δ 4.86 and δ 4.91 along with a one proton doublet for the C(10) proton at δ 2.90. The 13C-NMR, IR and mass spectra were also consistent with the assigned structure. Confirmation of the structure assignment, including stereochemistry, was sought by converting 119 to an intermediate in Piers's synthesis of 10-epi-axamide-1 (121) as shown in equation 21. Although hydrogenation of 119 followed by Wittig olefination gave esters 119a and 119b accordingly, hydrolysis of ester 119b (aqueous NaOH, aqueous LiOH, aqueous LiOH in DME) did not give acid 121. In each case, only starting ester 119b was recovered. The structure of 119 was eventually based on correlation experiments performed with tert-butyl ester 129 (vide infra). The structure of 116 was assigned on the basis of spectral data. For example, the two vinylic methyl groups appears as singlets at δ 1.63 and 1.73, the C(8) angular hydrogen appeared as a doublet at δ 2.50, and the C(1) proton appeared as a ddd at δ 3.42. Furthermore, treatment of 116 with 4 equivalents of methylidenetriphenylphosphorane gave ester 103 (80%), which was identical to material prepared from 101 as described in Table 1 (equation 22).
Treatment of the Z isomer of 117 with pyrrolidine and acetic acid (Entry 2), using the same conditions that accomplished cyclization of the E isomer, led to no reaction. One possible reason for difference in behavior of the E and Z isomers of 117 is the aforementioned lack of overlap between the ester carbonyl group and diene moiety in the Z isomer. This would be expected to reduce the rate at which an intramolecular conjugate addition might occur.

It was also possible to cyclize 117 using potassium t-butoxide as the base (Entries 3 and 4). This led to the formation of three cyclization products as indicated in Table 2.
Table 2. Cyclizations of Keto Ester 117 to Perhydroindans 116, 120, and 119

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>Conditionsa</th>
<th>116</th>
<th>119</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>117 (E-isomer)</td>
<td>A</td>
<td>10</td>
<td>72</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>117 (Z-isomer)</td>
<td>A</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>117 (E-isomer)</td>
<td>B</td>
<td>44</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>117 (E: Z = 1:1)</td>
<td>B</td>
<td>20</td>
<td>36</td>
<td>21</td>
</tr>
</tbody>
</table>

(a) Conditions A: pyrrolidine (0.2 equivalent), acetic acid (catalytic), THF, 60°C; Conditions B: potassium t-butoxide (0.2 equivalents), t-butyl alcohol, 60°C.
(b) All yields represent isolated material.

E. Attempted Hydrolysis of Ester 103 and Redesign of Synthesis

Examination of ester 119 reveals that it has the wrong C(10) stereochemistry for conversion to axanes 1-3. Ester 116 and the derived dienoate 103, however, are well-suited for conversion to axanes 4-6. To accomplish the conversion of 103 (equation 22) to 4-6 it was first necessary to hydrolyze the
ester. This transformation was attempted using a variety of reaction conditions (aqueous NaOH, aqueous LiOH, NaOH in THF, NH\textsubscript{2}NH\textsubscript{2}•H\textsubscript{2}O in THF). These attempts unfortunately met with failure, perhaps due to steric hindrance in the required tetrahedral intermediate. This general route, however, seemed promising as 103 had been prepared in 5\% overall yield using only a 9-step reaction sequence. It was decided to simply retrace the steps back to the Peterson olefination and replace the ethyl ester with a t-butyl ester which potentially could be removed under acidic conditions via a mechanism that would not require a tetrahedral intermediate.

F. Synthesis of Cyclization Substrates 126 and 127

To begin this investigation, it was necessary to prepare tert-butyl α-trimethylsilylacetate (123). This was accomplished in 49\% yield by treating tert-butyl ester 122\textsuperscript{55} with LDA followed by 2-bromopropene in the presence of a catalyst derived from n-butyllithium and nickel (II) bromide (equation 23).\textsuperscript{54}

\[
\begin{align*}
\text{SiMe}_3 \text{CO}_2\text{-t-Bu} & \quad \xrightarrow{\text{a, b, c}} \quad \text{Me}_3\text{Si} \text{CO}_2\text{-t-Bu} \\
122 & \quad \text{49\%} & \quad 123
\end{align*}
\]

(a) LDA, THF, HMPA (b) n-BuLi / NiBr\textsubscript{2} (c) H\textsubscript{2}C=C(Br)CH\textsubscript{3}

The synthesis of cyclization substrates 126 and 127 was accomplished as outlined in Scheme 25. Treatment of 123 with one equivalent of LDA in tetrahydrofuran followed by addition of aldehyde 110 gave a 63\% yield of esters 124 and 125 as a 1:2 mixture, respectively. The isomeric esters
were separated and independently hydrolyzed to give 126 (95%) and 127 (92%), respectively. Alternatively, the mixture of 124 and 125 could be hydrolyzed to give a mixture of 126 and 127 (96%) and the separation could be conducted at this point. Once again, the \( \beta \)-vinyl protons of the E and Z isomers were very distinct and served as a basis for structure assignment. For example, the vinyl proton of 125 appeared as a triplet at \( \delta \) 6.64 while the \( \beta \)-vinyl proton of 124 was a triplet at \( \delta \) 5.65. Applying the argument used before, it was concluded that the carbonyl group of 125 is conjugated with the diene while the carbonyl group of 124 is not conjugated with the diene. An NOE experiment also supported this structure assignment. For instance, irradiation of the vinylic methyl group (\( \delta \) 1.85) in 125 showed no enhancement of the vinyl proton at \( \delta \) 6.64. On the other hand, irradiation of the vinylic methyl group (\( \delta \) 1.88) in 124 showed an 11% enhancement of the vinyl proton at \( \delta \) 5.65.

**Scheme 25. Preparation of Unsaturated Esters 126 and 127**

\[
\begin{align*}
\text{CHO} & \quad \rightarrow \quad \text{CO}_{2}\cdot\text{t-Bu} \\
110 & \quad \rightarrow \quad 124 \quad (124:125 = 1:2) \\
\rightarrow b & \quad 95\% \\
126 & \\
\rightarrow b & \quad 92\% \\
127
\end{align*}
\]

(a) Li enolate of 123, THF -78°C (b) 5% HCl, room temperature, 3 h
G. Cyclization of Unsaturated Esters 126 and 127

With the cyclization substrates 126 and 127 in hand, cyclizations were attempted using several conditions as documented in Table 3. Not unexpectedly, the results were similar to those observed with ester 117 (Table 2). Thus, conversion of E-olefin 127 to 128 (15%) and 129 (60%) was accomplished using pyrrolidine in the presence of acetic acid (Entry 1) while Z-olefin 126 did not react under identical conditions (Entry 2). On the other hand, both 126 and 127 cyclized to give a mixture of perhydroindans 128, 129 and 130 upon treatment with potassium tert-butoxide in tert-butyl alcohol (Entries 3-5).

To determine whether 128-130 were products of kinetic or thermodynamic control, each ester was treated with 0.2 equivalents of potassium tert-butoxide in dry tert-butyl alcohol at room temperature for 20 h. In each case starting material was recovered unchanged. On the other hand, treatment of 128 with 4.0 equivalents of potassium tert-butoxide under the same conditions gave recovered 128 (60%) along with 129 (13%) and 130 (16%). Thus, the ratios of 128-130 represent kinetic partitioning in the cyclization.

The structure of 128 was assigned on the basis of spectral data. For example, the $^1$H-NMR spectrum shows two vinylic methyl groups as singlets at $\delta$ 1.73 and $\delta$ 1.60, the C(8) angular proton as a doublet at $\delta$ 2.55, and the C(1) proton as a ddd at $\delta$ 3.41. Other data, such as the $^{13}$C-NMR IR and mass spectra, also supported the structure assignment. Finally, the use of 128 in the synthesis of axanes 4-6 confirmed this structure assignment (vide infra).
Table 3. Cyclizations of 126 and 127 to Perhydroindans 128, 129, and 130

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization</th>
<th>Substrate</th>
<th>Conditions&lt;sup&gt;a&lt;/sup&gt;</th>
<th>128</th>
<th>129</th>
<th>130</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>127</td>
<td>A</td>
<td></td>
<td>15</td>
<td>60</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>126</td>
<td>A</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>127</td>
<td>B</td>
<td></td>
<td>52</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>126</td>
<td>B</td>
<td></td>
<td>54</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>127:126 (2:1)</td>
<td>B</td>
<td></td>
<td>45</td>
<td>30</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions A: pyrrolidine (1 equivalent), acetic acid (catalytic), THF, 60°C; Conditions B: potassium t-butoxide (0.2 equivalents), t-butyl alcohol, 60°C.

<sup>b</sup> All yields represent isolated material.

The structure of 129 was initially based on spectral data. For example, the $^1$H-NMR spectrum showed two vinyl protons at δ 4.80 and δ 4.86 and one doublet for the C(10) proton at δ 2.78. The $^{13}$C-NMR, IR and mass spectra also supported the structure assignment. The stereochemical assignment at C(10) was confirmed by converting 129 to 121 (equation 24), an intermediate in the Piers synthesis of 10-epi-axamide-1. Thus, hydrogenation of 129 was followed
by Wittig olefination of the resulting ester 121a to afford 121b. Reduction of 121b gave alcohol 121c which was oxidized using Jones reagent to give acid 121 whose $^1$H-NMR spectrum was identical to a spectrum kindly provided by Professor Piers.

![Chemical structure of compounds](image)

(a) H$_2$, Pd on C  (b) Ph$_3$P=CH$_2$  (c) LiAlH$_4$  (d) Jones oxidation

H. Synthesis of Axanes 4-6 From Keto Ester 128

The aforementioned chemistry gave rapid access to gram quantities of $\alpha,\beta$-unsaturated ester 128. This material was suitable for conversion into axanes 4-6 as outlined in Schemes 26 and 28. Wittig methylenation of 128 gave dienoate 131 in 78% yield. Treatment of 131 with trifluoroacetic acid, however, failed to give the expected acid 134. Instead a $\gamma$-lactone, assigned structure 132 on the basis of spectral data, was obtained. It was suspected that protonation of the exocyclic methylene generated a tertiary carbocation. Migration of a proton followed by capture of the resulting tertiary carbocation by the ester (or acid) produced the observed lactone. To avoid this problem, the tert-butyl group was removed before performing the Wittig methylenation. Thus,
treatment of 128 with trifluoroacetic acid gave keto acid 133 (95%) and olefination of 133 gave 134 in 78% yield.

Scheme 26. Preparation of Carboxylic Acid 134

At this point of the synthesis, an efficient route to carboxylic acid 134 had been developed (10 steps and 9.3% overall yield from 74). What remained to be accomplished was conversion of the carboxyl group into the nitrogen-containing functional groups present in axanes 4-6. It was projected that this could be accomplished if the carboxyl group could be degraded to an isocyanate using a Curtius rearrangement or some related process. First the model studies described in Scheme 27 were performed. Treatment of 3,3-dimethylacrylic acid (135) with thionyl chloride gave acid chloride 136 ($v_{C=O} = 1780 \text{ cm}^{-1}$) in 80% yield. This known compound was treated with sodium azide in acetone to give acyl azide 137 ($v_{C=O} = 1690 \text{ cm}^{-1}$ and $v_{N=N=N} = 2130 \text{ cm}^{-1}$)
in 72% yield. The structure assignment of 137 was supported by the appearance of the vinyl proton as a singlet at $\delta$ 5.55 and the two vinylic methyl groups as singlets at $\delta$ 2.10 and $\delta$ 1.55. Upon heating neat at 80°C, acyl azide 137 rearranged to isocyanate 138 ($v_{CN}=2270$ cm$^{-1}$). Reduction of 138 with one equivalent of lithium triethylborohydride in tetrahydrofuran at -78°C gave enamide 139 in 65% overall yield from 137. The $^1$H-NMR spectrum showed that 139 existed as a pair of rotamers in a 70:30 ratio. For example, the vinyl protons of the two rotamers appeared as doublets at $\delta$ 6.55 and $\delta$ 6.09 in the major and minor isomers, respectively. Although this reaction sequence is straightforward, it appears that this is the first time that it has been used to prepare vinyl formamides.

Scheme 27. Model Studies for Preparation of Axamide-6

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

135 \xrightarrow{(a) SOCl_2, pyridine} 136 \xrightarrow{(b) NaN_3, acetone, rt} 137 \xrightarrow{(c) PhCH_3, \Delta} 139 \xrightarrow{(d) LiBHEt_3, THF, -78^\circ C} 138

(a) SOCl$_2$, pyridine (b) NaN$_3$, acetone, rt (c) PhCH$_3$, $\Delta$ (d) LiBHEt$_3$, THF, -78°C
Encouraged by the successful conversion of acid 135 into enamide 139 (4 steps and 37% overall yield), the final steps in the synthesis of axanes 4-6 were attempted as described in Scheme 28. Treatment of acid 134 with thionyl chloride and pyridine in dichloromethane did not give the expected acyl chloride. It was suspected that migration of the exocyclic double bond was a problem as $^1$H-NMR analysis indicated disappearance of the vinyl protons. After many trials, isocyanate 140 was prepared in 77% yield by treating 134 with one equivalent of sodium hydride followed by stirring the resulting sodium carboxylate with diphenylphosphoryl azide at room temperature. Treatment of 140 with an equivalent of lithium triethylborohydride in tetrahydrofuran at -78°C gave racemic axamide-4 (6) in 90% yield. It is notable that in solution axamide-4 (6) exists as a 3:1 mixture of geometrical isomers. This is apparent from the $^1$H-NMR spectrum which shows signals due to the N—H as broad singlets at δ 6.77 (major isomer) and δ 6.32 (minor isomer). The angular methyl and vinylic protons from both geometrical isomers can also be observed. In addition to the $^1$H-NMR spectrum, the $^{13}$C-NMR, IR, and mass spectra were all in accord with the assigned structure and published data. Treatment of 6 with p-toluenesulfonyl chloride and pyridine gave racemic axisonitrile-4 (4) as a white solid (mp 61-63°C) in 90% yield. Finally, heating 4 with sulfur at 120°C for 20 h gave axisothiocyanate-4 (5) in 70% yield. The spectral data for 4 and 5 were consistent with the assigned structures and, when possible, agreed with data published for the natural products. Although it is typical to make a physical comparison between synthetic and natural materials when conducting a study of the type presented in this thesis, it was not possible to do so in this case. Attempts to obtain authentic material met with no response individuals who were contacted. Indirectly, however, a comparison was made. Recall that our materials were correlated with substances prepared by Professor Piers. He
was in fact able to obtain a natural sample of axisonitrile-1 (1) and thus, our material was indirectly correlated with a member of the axane family of sesquiterpenoids.

Scheme 28. Preparation of Axane Sesquiterpenoids 4-6

\[
\begin{align*}
134 & \xrightarrow{a, b} 77\% \\
    & \hspace{1cm} \downarrow \\
140 & \xrightarrow{c} 90\% \\
    & \hspace{1cm} \downarrow \\
6 & \xrightarrow{d} 90\% \\
    & \hspace{1cm} \downarrow \\
5 & \xrightarrow{e} 70\% \\
\end{align*}
\]

(a) NaH (b) \((\text{PhO})_2\text{P}(\text{O})\text{N}_3\) (c) \(\text{LiEt}_3\text{BH}, \text{THF}, -78^\circ\text{C}\) (d) TsCl pyridine (e) \(\text{S}_8, 120^\circ\text{C}, 20\text{ h}\)

In conclusion, this thesis describes the first synthesis of axanes 4-6. A summary of these syntheses is presented in Scheme 29.
Scheme 29. Summary of Axane Total Syntheses

\[ \text{CHO} \rightarrow 90\% \]

\[ \text{CO}_2\text{H} \rightarrow 78\% \]

\[ \text{N=C=S} \rightarrow 70\% \]

\[ \text{N=CHCHO} \rightarrow 90\% \]

\[ \text{N=C} \rightarrow 77\% \]

\[ \text{NHCHO} \rightarrow 90\% \]
General Experimental. All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are all boiling points. Proton nuclear magnetic resonance spectra ($^{1}$H NMR) were recorded on Varian Associates EM-390, Bruker AC-200, Bruker AM-250, Bruker AM-300, Bruker AC-300, or Bruker AM-500 spectrometers and are recorded in parts per million from internal tetramethylsilane on the $\delta$ scale. The $^{1}$H NMR spectra are reported as follow: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz, integration, interpretation]. Carbon-13 nuclear magnetic resonance spectra ($^{13}$C NMR) were obtained with Bruker AM-250, Bruker AM-300, or Bruker AC-300 spectrometers and are recorded in parts per million from internal tetramethylsilane. The $^{13}$C NMR spectra are reported as follows: chemical shift (multiplicity). Multiplicities were determined by off-resonance decoupling or DEPT experiments. Infrared spectra were taken with Perkin-Elmer 457 or Perkin-Elmer 1600 (FT-IR) instruments. Mass spectra were obtained using Kratos MS-30 or Kratos VG70-250S instruments at an ionization energy of 70 ev. Compounds for which an exact mass is reported exhibited no significant peaks at $m/e$ ratios greater than that of the parent. Combustion analyses were performed by Micro-Analysis, Inc., Winmington, Delaware.

Solvents and reagents were dried and purified prior to use when deemed necessary. Tetrahydrofuran, diethyl ether, and benzene were distilled from
sodium metal. Dichloromethane was distilled from calcium hydride. Diazomethane was prepared from N-methyl-N-nitrosourea\textsuperscript{57} and used immediately. Reactions requiring an inert atmosphere were run under argon. Analytical thin-layer chromatography was conducted using EM Laboratories 0.25 mm thick precoated silica gel 60F-254 plates. Column chromatography was performed over EM Laboratories silica gel (70-230 mesh). Medium pressure liquid chromatography (MPLC) was performed using EM Laboratories Lobar prepacked silica gel columns. All Grignard reagents and organolithiums were titrated prior to use with 2-butanol using 1,10-phenanthroline as the indicator.\textsuperscript{58}

![Chemical Structure](image)

3-Ethoxy-2-cyclohexen-1-one (73).\textsuperscript{45} To a solution of 56 g (0.5 mmol) of 1,3-cyclohexanedione in 1 L of dry benzene and 500 mL of absolute ethanol was added 0.98 mL of concentrated sulfuric acid. The mixture was brought to reflux and the azeotropic mixture of benzene, ethanol, and water was removed using a Dean-Stark apparatus at a rate of about 1.5 mL min\textsuperscript{-1}. When the temperature of the distillate reached 78°C, the reaction was cooled to room temperature, quenched by addition of 5 mL of 10% aqueous sodium carbonate, stirred for 20 min, and concentrated in vacuo. The resulting liquid was diluted with 500 mL of ether, washed with two 100-mL portions of saturated aqueous sodium bicarbonate and two 100-mL portions of brine, dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated in vacuo to yield a brown liquid which was distilled through a Vigreaux column to give 66.5 g (95%) of enol ether 73 as a
3-(3-Butenyl)-2-cyclohexen-1-one (72). To a stirred mixture of 13.8 g (0.58 mmol) of magnesium turnings in 50 mL of dry tetrahydrofuran was added a few crystals of iodine followed by 5.0 g (37.0 mmol) of 4-bromo-1-butene in one portion. After the onset of Grignard formation, a solution of 73.4 g (0.54 mmol) of 4-bromo-1-butene in 150 mL of dry tetrahydrofuran was added at a rate such that the mixture maintained a gentle reflux. After the addition was complete, the reaction mixture was brought to reflux for 1 h. The resulting solution was cooled to 0°C and was added dropwise a solution of 67.2 g (0.48 mmol) of enol ether of 73 in 50 mL of dry tetrahydrofuran over a 1 h period. The resulting mixture was stirred at room temperature for another 1 h and then warmed to 50°C for 30 min. To the solution was added 150 mL of 6 N HCl dropwise at 0°C over 30 min period. The resulting mixture was stirred vigorously at 0°C for 3 h and at room temperature for 1 h. The organic phase was separated and the aqueous layer was extracted with three 100-mL portions of ether. The organic layers were combined and washed with one 50-mL portion of water, two 50-mL portions of saturated aqueous sodium bicarbonate, three 50-mL portions of brine, dried (Na₂SO₄) and concentrated in vacuo. The residual light brown liquid was distilled to give 53.0 g (73%) of enone 72 as a clear liquid: bp 105-106°C at 4.6 mm Hg; IR (neat) 1665, 1625
1^H NMR (CDCl₃, 250 MHz) δ 1.87 (m, 2H, CH₂), 2.2 (m, 8H, CH₂ manifold), 4.9-5.0 (m, 2H, =CH₂), 5.65-5.8 (m, with br s at δ 5.8, 2H, =CH and =CHC=O); 13C NMR (CDCl₃, 62.5 MHz) δ 22.3 (t), 29.3 (t), 30.6 (t), 36.7 (t), 36.9 (t), 115.1 (t), 125.5 (d), 136.6 (d), 164.9 (s), 199.0 (s); exact mass calcd for C₁₀H₁₄O m/e 150.1047, found m/e 150.1044; Anal. calcd. for C₁₀H₁₄O: C, 80.00; H, 9.33. Found: C, 79.88; H, 9.41.

3-(3-Butenyl)-3-methylcyclohexanone (71). To a suspension of 35.7 g (0.17 mmol) of CuBr in 50 mL dry tetrahydrofuran at -20°C was slowly added in 266 mL (0.35 mmol) of 1.3 M etheral methyllithium. The resulting clear solution was allowed to stir at 0°C for 15 min and then cooled to -30°C. To the clear reaction mixture was added dropwise 20.0 g (0.13 mmol) of enone 72 in 50 mL of dry tetrahydrofuran over a 40 min period. The resulting bright yellow mixture was allowed to stir at -30°C for 4 h and at 0°C for 0.5 h. To this mixture at 0°C was slowly added 30 mL of saturated aqueous ammonium chloride. The mixture was diluted with 400 mL of ether and washed with two 300-mL portions of saturated aqueous ammonium chloride. The combined blue aqueous phases were extracted with three 200-mL portions of ether. The organic layers were combined and washed with 200 mL of water, 100 mL of 2% aqueous hydrochloric acid, three 200-mL portions of brine, dried (Na₂SO₄) and concentrated in vacuo. The residual liquid was distilled to yield 19.8 g (89%) of ketone 71 as a clear liquid: bp 68-70°C at 1 mm Hg; IR (neat) 1710,
1640 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 250 MHz), \(\delta\) 0.92 (s, 3H, CH\(_3\)), 1.30-2.28 (m, 12H), 4.89-5.02 (m, 2H, =CH\(_2\)), 5.69-5.85 (m, 1H, =CH); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 22.0 (t), 24.8 (q), 27.8 (t), 35.8 (t), 38.5 (s), 40.8 (t), 40.9 (t), 53.6 (t), 114.3 (t), 138.7 (d), 211.9 (s); exact mass calcd for C\(_{11}\)H\(_8\)O \(m/e\) 166.1370, found \(m/e\) 166.1369.

1-Methyl-2-oxocyclohexanepropionaldehyde (70). Through a stirred solution of 9.00 g (54.2 mmol) of ketone 31 in 50 mL of methanol was passed a stream of ozone (Welsbach ozone generator) at the flow rate of 1 mmol min\(^{-1}\) at \(-78^\circ\)C. When the reaction mixture maintained a blue color for 1 min, the stream of ozone was replaced by nitrogen and the solution was purged for 1 h. To the resulting reaction mixture was added 50 mL of dimethylsulfide. The mixture was stirred at \(-78^\circ\)C for 3 h, allowed to warm slowly to room temperature, and stirred at room temperature for 4 h. Solvents and low boiling materials were removed in vacuo using a mechanical pump and the crude aldehyde 70 thus obtained was quickly used in the next reaction without further purification.

On a smaller scale, 330 mg (1.99 mmol) of ketone 71 was oxidized as above to yield a crude liquid which was chromatographed over 15 g of silica gel (eluted with ethyl acetate-hexane, 1.9) to give 296 mg (88\%) of aldehyde 70 as a clear liquid: IR (neat) 1712 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 0.75 (s, 3H, CH\(_3\)), 1.41-1.49 (m, 4H, CH\(_2\)), 1.65-1.76 (m, 2H, CH\(_2\)), 1.91-2.00 (m, 2H,
64

CH₂), 2.07 (m, 2H, CH₂), 2.23-2.30 (m, 2H, CH₂), 9.60 (s, 1H, CHO); ¹³C NMR (CDCl₃, 62.5 MHz) δ 21.6 (t), 24.1 (q), 32.8 (t), 35.3 (t), 37.6 (s), 38.0 (t), 40.4 (t), 52.8 (t), 201.4 (d), 210.7 (s); exact mass calcd for C₁₀H₁₆O₂ m/e 168.1192, found m/e 168.1188.

Ethyl (E)-5-(1-Methyl-3-oxocyclohexyl)-2-pentenoate (69). To a solution of crude aldehyde 70 (obtained from ozonolysis of 54.2 mmol of 71) in 70 mL dry benzene under dry argon was added 23.4 g (67 mmol) of carbethoxymethylidenetriphenylphosphorane in one portion. The resulting solution was stirred at room temperature for 8 h and at 50°C for 2 h and the mixture was concentrated in vacuo. The resulting slurry was diluted with 200 mL of ether and the solid residue was removed by filtration. The filter cake was rinsed with 150 mL ether and the combined ether solutions were concentrated in vacuo to give a brown liquid which was distilled through a Vigreaux column to yield 10.44 g (81%) of unsaturated ester 69 as an 83:17 mixture of E and Z geometrical isomers, respectively: bp 136-140°C/0.8-1.0 mm Hg. A portion of the mixture was subjected to MPLC to afford pure samples of each isomer. (E)-69: GC-tr = 8.02 min; IR (neat) 1715, 1655 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.83 (s, 3H, CH₃), 1.15 (t, J = 7 Hz, 3H, CH₃), 1.24-2.97 (m, 12H, CH₂), 4.05 (q, J = 7 Hz, 2H, OCH₂) 5.70 (d, J = 15.8 Hz, 1H, =CHC=O), 6.82 (dt, J = 15.8, 6.8 Hz, 1H, =CH); ¹³C NMR (CDCl₃, 62.5 MHz) δ 14.1 (q), 21.9 (t), 24.6 (q), 26.2 (t), 35.7 (t), 38.4 (s), 39.7 (t), 40.8 (t), 53.3 (t), 60.0 (t), 121.4 (d), 148.6 (d), 166.4 (s), 211.3 (s); mass spectrum, m/e (relative intensity) 223 (7), 192 (14),
177 (6), 164 (8), 149 (10), 127 (15), 111 (100); exact mass calcld for C_{14}H_{22}O_{3}
m/e 238.1580, found m/e 238.1579. (Z)-28: GC-tr = 7.20 min; ^1H NMR
(CDCl_3, 250 MHz) δ 0.94 (s, 3H, CH_3), 1.27 (t, J = 7 Hz, 3H, CH_3), 1.34-2.70
(m, 12H, CH_2), 4.17 (q, J = 7 Hz, 2H, OCH_2), 5.75 (d, J = 11.5 Hz, 1H,
=CHC=O), 6.18 (dt, J = 11.5, 7.0 Hz, 1H, =CH); ^13C NMR (CDCl_3, 62.5 MHz) δ
14.3 (q), 22.0 (t), 23.4 (t), 24.8 (q), 35.5 (t), 38.6 (s), 40.6 (t), 41.0 (t), 53.7 (t),
59.8 (t), 119.8 (d), 149.9 (d), 166.1 (s), 211.9 (s).

Ethyl (1R',3aS',7aR')-Hexahydro-3a-methyl-7-oxo-1-indanacetate
(42) To a solution of 1.99 g (8.36 mmol) of unsaturated ester 69 in 7 mL of dry
tetrahydrofuran was added 0.54 g (7.55 mmol) pyrrolidine and 1.4 mg (0.02
mmol) of glacial acetic acid in one portion. The resulting solution was heated
under gentle reflux at 100-110°C (bath temperature) under argon for 4 h. The
mixture was diluted with 60 mL of ether and occasionally shaken with 20 mL of
2% aqueous hydrochloric acid over a 15-20 min period. The aqueous layer
was extracted with three 15-mL portions of ether. The combined extracts were
washed with 10 mL of water, 20 mL of saturated aqueous sodium bicarbonate,
two 20-mL portions of brine, dried (Na_2SO_4) and concentrated in vacuo. The
residue was distilled using a Kugelrohr apparatus (oven temperature of 100-
105°C) at 0.11 mmHg to give 1.30 g (65%) of bicyclic ester 42 as a light yellow
liquid: IR(CH_2Cl_2) 1730, 1695 cm\(^{-1}\); ^1H NMR (CDCl_3) δ 1.00 (s, 3H, CH_3),
1.16 (t, J = 7 Hz, 3H, CH_3), 1.14-1.89 (m, 8H), 2.05-2.50 (m, 5H, CH_2COEt,
CHC=O and CH_2C=O), 2.61-2.71 (m, 1H, CH), 4.02 (q, J = 7 Hz, 2H, OCH_2);
$^{13}$C NMR (CDCl$_3$, 62.5 MHz) $\delta$ 14.09 (q), 22.35 (t), 26.36 (q), 30.32 (t), 33.83 (t), 37.63 (t), 39.63 (t), 39.81 (d), 39.95 (t), 47.23 (s), 60.24 (t), 66.90 (d), 172.36 (s), 214.16 (s); mass spectrum, m/e (relative intensity) 238 (M$^+$), 223 (40), 193 (20), 177 (100), 151 (25), 135 (60), 111 (25), 93 (20), 81 (20); exact mass calcd for C$_{14}$H$_{22}$O$_3$ m/e 238.1569, found m/e 238.1569.

![Chemical Structure](image)

**Ethyl (3'R*,3'aS*,7'aR*)-Tetrahydro-7'a-methylspiro[1,3-dioxalane-2,4'(3'aH)-Indan]-3'-acetate (82).** To a solution of 2.38 g (10 mmol) of bicyclic ester of 42 in 6.2 g (100 mmol) of ethylene glycol was added 10.6 g (100 mmol) of trimethylorthoformate and 30 mg (0.2 mmol) of p-toluenesulfonic acid monohydrate. The resulting solution was stirred at room temperature for 5 h followed by addition of 0.5 g (6 mmol) of solid sodium bicarbonate. The mixture was stirred at room temperature for 30 min, diluted with 50 mL of ether, filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed over 70 g of silica gel (eluted with ethyl acetate-hexane, 1:20) to give 2.58 g (91%) of ketal 82 as a clear liquid: IR (neat) 1733 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.08 (s, 3H, CH$_3$), 1.23 (t, $J$ = 7 Hz, 3H, CH$_3$), 1.10-1.70 (m, 10H, CH$_2$ manifold), 2.02 (ddd, $J$ = 10, 7, 7 Hz, 1H, CHHCOO), 2.16 (dd, $J$ = 15, 10 Hz, 1H, CHHCO$_2$Et), 2.38-2.51 (m, 1H, CHCH$_2$CO$_2$Et), 2.82 (dd, $J$ = 15, 4 Hz, 1H, CHHCO$_2$Et), 3.80-3.94 (m, 4H, OCH$_2$CH$_2$O), 4.09 (q, $J$ = 7 Hz, 2H, OCH$_2$); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.17 (q), 20.03 (t), 25.90 (q), 28.63 (t), 30.46 (t), 32.23 (t), 37.28 (d), 40.55 (t), 41.77 (t), 43.80 (s), 56.87 (d), 59.75 (t), 63.81 (t), 66.90 (d), 87.21 (d), 147.37 (s), 172.36 (s), 214.16 (s).
63.91 (t), 111.34 (s), 173.33 (s); mass spectrum, \( m/e \) (relative intensity) 282 (M⁺), 239 (19), 185 (9), 151 (25), 113 (17), 99 (100); exact mass calcd. for C₁₆H₂₆O₄ \( m/e \) 282.1870, found \( m/e \) 282.1866.

\[
\begin{align*}
\text{(3'}R'^*,3a'R'^*,7'aS'^*)-\text{Tetrahydro-7'a-methylspiro[1,3-dioxolane-2,4'- (3'aH)-indan]-3-acetic acid (83). To a stirred solution of 2.6 g (9.2 mmol) of ester 82 in 15 mL of ethanol and 5 mL of water was added 1.8 g (45 mmol) of sodium hydroxide. The mixture was stirred at room temperature for 8 h. Excess solvent was removed under reduced pressure. The resulting mixture was diluted with 150 mL of water and extracted with two 20-mL portions of ether. The aqueous layer was cooled in an ice bath and the pH of the solution was adjusted to 3 using 25 mL of 2N aqueous hydrochloric acid. The mixture was extracted with three 30-mL portions of ether. The combined ethereal extracts were washed with two 10-mL portions of brine, dried (Na₂SO₄) and concentrated in vacuo. The crude acid was recrystallized (hexane-ethyl acetate, 50:1) to yield 2.14 g (92%) acid 83 as a white solid: mp 88-90°C; IR (CHCl₃) 3028, 1705 cm⁻¹; \(^1\)H NMR (CDCl₃) \( \delta \) 1.08 (s, 3H, CH₃), 1.06-1.72 (m, 10H, CH₂ manifold), 2.06 (ddd, \( J = 10, 9, 8 \) Hz, 1H, CHCHCOO), 2.21 (dd, \( J = 16, 10 \) Hz, 1H, CHHCO₂H), 2.42-2.62 (m, 1H, CHCH₂CO₂H), 2.90 (dd, \( J = 16, 4 \) Hz, 1H, CHHCO₂H), 3.81-3.97 (m, 4H, OCH₂CH₂O), 9.24 (br s, 1H, CO₂H); \(^1\)C NMR (CDCl₃) \( \delta \) 20.10 (t), 25.98 (q), 28.86 (t), 30.52 (t), 32.31 (t), 37.17 (d), 40.61 (t), 41.66 (t), 43.89 (s), 57.03 (d), 63.91 (t), 64.11 (t), 111.48 (s), 179.62
\end{align*}
\]
(s); mass spectrum, m/e (relative intensity) 254 (M+), 211 (65), 195 (15), 177 (35), 157 (15), 135 (15), 113 (15), 99 (100); exact mass calcd. for C\textsubscript{14}H\textsubscript{22}O\textsubscript{4} m/e 254.1518, found m/e 254.1514.

\[ \text{Methyl (}\alpha\text{RS}^*\text{,3'S}^*,\text{3'as}^*,\text{7'aS}^*)\text{-Tetrahydro-}\alpha\text{-}(1\text{-hydroxy-1-methyl-ethyl})\text{-7'a-methylspiro[1,3-dioxolane-2,4'(3'aH)-indan]-3'-acetate (84).} \]

To a solution of 2.2 g (22 mmol) of diisopropylamine in 8 mL of dry tetrahydrofuran at -78°C under argon was added 7.2 mL (19 mmol) of 2.6 M n-butyllithium in hexane. The mixture was stirred at -78°C for 30 min followed by addition of 1.6 g (6.3 mmol) of acid 63 in 2 mL of tetrahydrofuran. The mixture was stirred at -78°C for 5 min, -20°C for 20 min, and then at 50°C for 2 h. The mixture was cooled to -20°C followed by addition of 3.2 g (54 mmol) of acetone over a period of 5 min. The resulting mixture was stirred at -20°C for 6 h followed by addition of 5% aqueous hydrochloric acid at 0°C until the solution reached pH 3. The solution was diluted with 40 mL of ether, washed with two 10-mL portions of brine, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The residue (2.3 g) was dissolved in 30 mL of dichloromethane followed by addition of ethereal diazomethane at room temperature until the reaction mixture became yellow.\textsuperscript{57} To the mixture was added 5 drops of glacial acetic acid and 10 g of powdered magnesium sulfate. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with ethyl acetate-hexane, 1:10) to give 0.6 g (28%) of ester 84 as a pale
yellow oil. This material was a mixture of diastereomers and appeared to be contaminated by other material (NMR) and thus, the structure assignment and yield have to be regarded as tentative: IR (neat) 1720 cm\(^{-1}\); \(^1\)H NMR (250 MHz, CDCl\(_3\)) diagnostic signals include: singlets at \(\delta\) 1.02 (CH\(_3\)), 1.26 (CH\(_3\)), 1.28 (CH\(_3\)), and 3.71 (OCH\(_3\)); a doublet \((J = 8\, Hz)\) at \(\delta\) 2.56 (CHCO\(_2\)Me); a multiplet at \(\delta\) 2.65 (CHCHCO\(_2\)Me); a multiplet at \(\delta\) 3.88-4.04 (OCH\(_2\)CH\(_2\)O).

![Diagram of compound 85]

**Diethyl (3'R*,3'aS*,7'aR*)-Tetrahydro-7'a-methylspiro[1,3-dioxolane-2,4'(3'aH)-inden]-3'-malonate (85).** To a stirred solution of 60 mg (0.6 mmol) of diisopropylamine in 0.2 mL of dry tetrahydrofuran under argon at -78\(^\circ\)C was added 0.25 mL (0.6 mmol) of 2.4 M n-butyllithium in hexane. The mixture was stirred for 20 min at -78\(^\circ\)C, 5 min at 0\(^\circ\)C and cooled to -78\(^\circ\)C. To the mixture was added in a solution of 140 mg (0.5 mmol) of ester 82 in 1 mL of tetrahydrofuran via cannula over a period of 5 min. The resulting mixture was then stirred at -30\(^\circ\)C for 1 h and 0.25 g (2.5 mmol) of ethyl cyanoformate was added in one portion. The mixture was stirred at -30\(^\circ\)C for 4 h and 1 mL of brine was added. The mixture was allowed to warm to room temperature, was diluted with 40 mL of ether and washed with three 10-mL portions of brine. The combined aqueous washes were extracted with two 10-mL portions of ether. The combined ethereal layers were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with ethyl acetate-hexane, 1:20) to give 0.133 g (75%) of ester 85 as a clear liquid: IR (neat) 1729 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 1.07 (s, 3H, CH\(_3\)), 1.25 (t, \(J =\)
7 Hz, 3H, CH₃), 1.28 (t, J = 7 Hz, 3H, CH₃), 1.18-2.25 (m, 11H, CHCOO and CH₂ manifold), 2.7 (septet, 1H, CH₂CHCO₂R), 3.8-3.92 (m, 4H, OCH₂CH₂O), 3.94 (d, J = 5 Hz, 1H, CH(CO₂R)₂), 4.17 (q, J = 7 Hz, 4H, OCH₂CH₃); ¹³C NMR (63 MHz, CDCl₃) δ 14.07 (q), 14.20 (q), 20.12 (t), 25.26 (t), 25.92 (q), 30.73 (t), 32.10 (t), 40.35 (d), 40.93 (t), 43.63 (s), 53.79 (d), 55.33 (d), 60.72 (t), 60.95 (t), 64.09 (t), 64.17 (t), 111.37 (s), 169.75 (s), 169.83 (s); mass spectrum, m/e (relative intensity) 354 (M⁺), 311 (30), 295 (20), 281 (20), 249 (20), 195 (20), 151 (60), 135 (30), 113 (25), 99 (100); exact mass calcd. for C₁₉H₃₀O₆ m/e 354.2042; found m/e 354.2064.

EtO₂C SMe

Ethyl 2-[Bis(methylthio)methylene]-3-methylbutanoate (94). To a stirred solution of 5.6 g (55 mmol) of diisopropylamine in 50 mL tetrahydrofuran at -78°C under argon was added 23 mL (55 mmol) of 2.41 M n-butyllithium in hexane. The mixture was stirred for 20 min at -78°C, 5 min at 0°C, cooled to -78°C and 9.9 g (55 mmol) of hexamethylphosphoramide was added in one portion. The resulting solution was stirred at -78°C for 10 min, followed by addition of 6.5 g (50 mmol) of ethyl isovalerate in 40 mL of tetrahydrofuran over a period of 30 min via a cannula. The reaction mixture was stirred at -78°C for 40 min, followed by addition of 4.2 g (55 mmol) of carbon disulfide in one portion. The resulting red-colored solution was stirred at -78°C for 1 h, at -20°C for 1 h, at 0°C for 1 h and cooled to -78°C. To the mixture was added a second equivalent (55 mmol) of lithium diisopropylamide in 50 mL of tetrahydrofuran (prepared as described above). The reaction mixture was
stirred at -78°C for 1 h and then warmed to -40°C. To the resulting dark red-colored solution at -40°C was added 23.4 g (165 mmol) of methyl iodide in one portion. The mixture was allowed to warm slowly to room temperature over a period of 2 h, stirred for 4 h at room temperature, and 10 mL of saturated aqueous ammonium chloride was added. The solution was diluted with 200 mL of ether and washed sequentially with 100 mL of water and 50 mL of 1 % aqueous hydrochloric acid. The combined aqueous washes were extracted with three 50-mL portions of ether. The combined ethereal layers were washed with 30 mL of saturated aqueous sodium bicarbonate, two 50-mL portions of brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed over 500 g of silica gel (eluted with ethyl acetate-hexane, 1:50) to give 11.4 g (97%) of ketene dithioacetal 94 as a yellow liquid: IR 1722, 1263, 1176, 1142, 1035 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.04 (d, J = 7 Hz, 6H, CH₃), 1.30 (t, J = 7 Hz, 3H, CH₃), 2.21 (s, 3H, SCH₃), 2.28 (s, 3H, SCH₃), 3.19-3.31 (m, 1H, CH₂CH₃), 4.21 (q, 2H, OCH₂); ¹³C NMR (63 MHz, CDCl₃) δ 14.16 (q), 16.02 (q), 17.42 (q), 20.90 (q, two carbons), 31.82 (d), 60.61 (t), 132.15 (s), 148.54 (s), 167.65 (s); mass spectrum, m/e (relative intensity) 234 (M+ 100), 219 (80), 189 (60), 187 (70), 173 (80), 161 (40), 141 (80); exact mass calcd. for C₁₀H₁₈O₂S₂ m/e 234.0748, found m/e 234.0754.
Ethyl (3'R,3'aS',7'aR')-α-Carbonyltetrahydro-7'a-methylspiro[1,3-dioxolane-2,4'(3'aH)-indan]-3'-acetate, dimethyl dithioacetal (86). To a solution of 53 mg (0.52 mmol) of diisopropylamine in 0.5 mL of dry tetrahydrofuran under argon at -78°C was added 0.22 mL (0.52 mmol) of 2.33 M n-butyllithium in hexane. The mixture was stirred for 20 min at -78°C, 5 min at 0°C, and cooled to -78°C. To the mixture was added 93 mg (0.52 mmol) of hexamethylphosphoramide in one portion. The resulting solution was stirred at -78°C for 30 min, followed by slow addition of 139 mg (0.49 mmol) of ester 82 in 0.5 mL of dry tetrahydrofuran via a cannula. The reaction mixture was stirred at -30°C for 3 h followed by addition of 39.5 mg (0.52 mmol) of carbon disulfide in one portion. The mixture was allowed to warm to 0°C, stirred for 3 h, and cooled to -78°C. To the mixture was added a second equivalent (0.52 mmol) of lithium diisopropylamide solution in 0.5 mL of dry tetrahydrofuran (prepared as described above). The mixture was warmed to -20°C, stirred for 2 h, and 150 mg (1.04 mmol) of methyl iodide was added. The mixture was allowed to warm slowly to room temperature, stirred for 4 h, and 1 mL of saturated aqueous ammonium chloride was added. The solution was diluted with 20 mL of ether and washed sequentially with 5 mL of 1% aqueous hydrochloric acid and 10 mL of water. The combined aqueous washes were extracted with three 5-mL portions of ether. The combined ethereal layers were washed with 5 mL of saturated aqueous sodium bicarbonate, two 10-mL portions of brine, dried (Na₂SO₄), concentrated in vacuo. This residue was chromatographed over 8
g of silica gel (eluted with ethyl acetate-hexane, 1:30) to give 91 mg (48%) of ketene dithioacetal 86 as a light yellow liquid: IR (neat) 1710, 1440, 1370, 1270, 1200, 1090, 1020 cm\(^{-1}\); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 1.01 (s, 3H, CH\(_3\)), 1.27 (t, \(J = 7\) Hz, 3H, CH\(_3\)), 1.29-2.00 (m, 10H, CH\(_2\) manifold) 1.82 (d, \(J = 11\) Hz, 1H, CHCOO), 2.18 (s, 3H, SCH\(_3\)), 2.22 (s, 3H, SCH\(_3\)), 3.79 (ddd, \(J = 11, 10, 6\) Hz, 1H, =CCH), 3.80-3.88 (m, 4H, OCH\(_2\)CH\(_2\)O), 4.19 (q, \(J = 7\) Hz, 2H, OCH\(_2\)); \(^{13}\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 14.25 (q), 16.31 (q), 17.45 (q), 20.25 (t), 25.76 (q), 27.57 (t), 31.28 (t), 32.11 (t), 41.49 (t), 43.68 (s), 44.27 (d), 54.21 (d), 60.65 (t), 63.89 (t), 64.16 (t), 110.65 (s), 133.04 (s), 147.35 (s), 168.34 (s); mass spectrum, \(m/e\) (relative intensity) 386 (M\(^+\)), 371 (15), 339 (25), 325 (20), 291 (100), 277 (20), 249 (30), 233 (15), 221 (10), 151 (15), 99 (60); exact mass calcd. for C\(_{19}\)H\(_{30}\)O\(_4\)S\(_2\) m/e 386.1585, found m/e 386.1567.

![Chemical structure](image.png)

**Ethyl α-(E/Z)-(3'R*,3'aS*,7'aR*)-α-[1-(methylthio)ethylidene]tetrahydro-7'a-methyl-spiro[1,3-dioxolane-2,4'(3'aH)-inden]-3'-acetate (99).**

To a suspension of 320 mg (1.68 mmol) of copper(I) iodide in 2 mL of dry tetrahydrofuran under argon at -30°C was added 2.50 mL (3.30 mmol) of 1.32 M ethereal methyllithium. The resulting clear solution was stirred at -30°C for 30 min and then cooled to -78°C. To the resulting cuprate was added a solution of 206 mg (0.53 mmol) of ketene dithioacetal 86 in 4 mL of dry tetrahydrofuran slowly via a cannula. The mixture was warmed to room temperature slowly and stirred for 8 h. To the mixture at 0°C was added
dropwise 1 mL of saturated aqueous ammonium chloride, followed by 20 mL of ether. The solution was filtered and the filtrate was washed with two 10-mL portions of saturated aqueous ammonium chloride. The aqueous washes were combined and extracted with two 10-mL portions of ether. All ethereal layers were combined, washed with two 10-mL portions of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was chromatographed over 6 g of silica gel (eluted with ethyl acetate-hexane, 1:15) to give 130 mg (69%) of and inseparable mixture of unsaturated esters as a light yellow liquid: IR (neat) 1706, 1463 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 1.03 (s, 3H, CH$_3$), 1.25 (t, J = 7 Hz, 3H, CH$_3$), 1.05-2.05 (m, 10H, CH$_2$ manifold), 1.83 (d, J = 11 Hz, 1H, CH(COO), 2.06 (s, 3H, =CCH$_3$), 2.21 (s, 3H, SCH$_3$), 3.58 (ddd, J = 11, 10, 6 Hz, 1H, CHC=), 3.69-3.83 (m, 4H, OCH$_2$CH$_2$O), 4.14 (q, J = 7 Hz, 2H, OCH$_2$); $^{13}$C NMR of major isomer (63 MHz, CDCl$_3$), δ 14.33 (q), 14.53 (q), 19.66 (q), 20.35 (t), 25.93 (q), 27.84 (t), 31.01 (t), 32.43 (t), 41.32 (t), 42.95 (d), 43.64 (s), 54.07 (d), 59.92 (t) 63.97 (t), 64.08 (t), 110.90 (s), 134.56 (s), 136.98 (s), 168.47 (s); mass spectrum, $m/e$ (relative intensity) 355 (M$^+$ +1), 349 (2), 325 (5), 294 (5), 263 (20), 249 (20), 235 (15), 217 (25), 203 (20), 149 (15), 139 (15), 127 (20), 110 (20), 99 (40), 81 (25), 69 (30), 55 (100); exact mass calcd. for C$_{19}$H$_{30}$O$_4$S $m/e$ 354.1865, found $m/e$ 354.1858.

Ethyl (1$^R$,3$_{a}$S$^*$,7$_{a}$R$^*$)-Hexahydro-3$_a$-methyl-7$_a$-methylene-1$_a$-Indan-acetate (63). A mixture of 23 g (64 mmol) of methyltriphenylphosphonium bromide and 6.72 g (10.7 mmol) of potassium tert-butoxide in 200 mL of tert-
butyl alcohol was stirred at room temperature for 8 h followed by the addition of a solution of 4.5 g (18.9 mmol) of 42 in 100 mL of tert-butyl alcohol dropwise over a 20 min period. The reaction mixture was stirred at room temperature for 1 h, acidified with 5% aqueous hydrochloric acid, and concentrated in vacuo. The residue was dissolved in 200 mL of ether and washed with 50 mL of water. The aqueous wash was extracted with two 20-mL portions of ether. The combined ether layers were washed with 30 mL of saturated aqueous sodium bicarbonate, two 50-mL portions of brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with hexane-ethyl acetate, 25:1) to give 4.06 g (91%) of olefin 63 as a clear liquid: IR (CH₂Cl₂) 1735, 1645 cm⁻¹; NMR (250 MHz, CDCl₃) δ 0.94 (s, 3H, CH₃), 1.21 (t, J = 7 Hz, 3H, CH₃), 1.16-1.70 (m, 8H), 1.96-2.58 (m, 6H), 4.05 (q, J = 7 Hz, 2H, OCH₂), 4.57 (broad s, 1H, =CH₂), 4.65 (broad s, 1H, =CH₂); ¹³C NMR (63 MHz, CDCl₃) δ 14.15 (q), 23.88 (t), 25.07 (q), 28.99 (t), 30.49 (t), 33.60 (t), 38.04 (d), 39.83 (t), 39.89 (t), 43.41 (s), 59.91 (t), 61.56 (d), 110.36 (t), 147.63 (s), 173.34 (s); mass spectrum, m/e (relative intensity) 236 (15), 221 (81), 191 (20), 175 (21), 148 (100), 107 (33), 93 (54); exact mass calcd for C₁₅H₂₄O₂ m/e 236.1777, found m/e 236.1772.

Ethyl (1R*,3aS*,7aR*)-α-[Bis(methylthio)methylene]hexahydro-3a-methyl-7-methylene-1-indanacetate (101). To a stirred solution of 200 mg (1.98 mmol) of diisopropylamine in 4 mL of dry tetrahydrofuran under argon at -
78°C was added 0.83 mL (1.98 mmol) of 2.4 M of n-butyllithium in hexane. The solution was stirred for 20 min at -78°C, at 0°C for 5 min, and cooled to -78°C. To the mixture was added 0.354 g (1.98 mmol) of hexamethylphosphoramide in one portion. The resulting solution was stirred at -78°C for 40 min and then 424 mg (1.80 mmol) of ester of 63 in 2 mL of dry tetrahydrofuran was added. The mixture was stirred at -78°C for 3 h and -30°C for 2 h. To the resulting solution was added 151 mg (1.98 mmol) of carbon disulfide in one portion at -30°C. The mixture was allowed to warm slowly to 0°C over a 3.5 h period, and then cooled to -78°C. To the mixture was added a second equivalent (1.98 mmol) of LDA in 4 mL of dry tetrahydrofuran (prepared as described above) using a cannula at -78°C. The reaction mixture was allowed to warm -40°C followed by stirring for 2 h. To the resulting mixture was added 1.70 g (12 mmol) of methyl iodide in one portion at -40°C. The mixture was allowed to warm to room temperature slowly, stirred at room temperature for 5 h, and 1 mL of saturated aqueous ammonium chloride was added at 0°C. The mixture was diluted with 30 mL of ether and then washed with 10 mL of 2% aqueous hydrochloric acid and 20 mL of water. The combined aqueous washes were extracted with two 15-mL portions of ether. The combined etheral layers were washed with 10 mL of saturated aqueous sodium bicarbonate, two 15-mL portions of brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate-hexane, 1:50) to yield 0.464 g (76%) of ketene dithioacetal 101 as a light yellow liquid: IR (neat), 1720, 1645 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.95 (s, 3H, CH₃), 1.19-1.76 (m with t (J = 7 Hz) at δ 1.33, 9H, CH₂ and CH₃), 1.9-2.4 (m with two s at δ 2.21 and 2.22, 11H), 3.84 (ddd, J = 11.0, 10.3, 7.5 Hz, 1H, CH₂=CH(SMe)₂), 4.25 (q, J = 7 Hz, 2H, OCH₂), 4.63 (br t, 1H, =CH), 4.72 (br t, 1H, =CH); ¹³C NMR (CDCl₃, 63 MHz) δ 14.2 (q), 17.0 (q), 17.8 (q), 23.6 (t),
25.0 (q), 27.2 (t), 30.7 (t), 33.2 (t), 40.5 (t), 43.3 (s), 45.6 (d), 59.3 (d), 60.6 (t), 111.4 (t), 135.3 (s), 146.0 (s), 146.5 (s), 168.0 (s); mass spectrum, m/e (relative intensity) 325 (100, M–CH$_3$), 311 (5), 297 (5), 279 (20), 251 (25), 231 (20), 219 (30), 203 (45), 185 (20), 171 (15), 157 (20), 109 (25), 91 (20).

![Structural formula of 103](image)

**Ethyl (1R*,3aR*,7aS*)-Hexahydro-α-isopropylidene-3a-methyl-7-methylene-1-indanacetate (103).**

**A. From Ester 101:** To a suspension of 161 mg (0.85 mmol) of copper (1) bromide dimethyl sulfide complex in 1 mL of dry tetrahydrofuran under argon at -20°C was added 1.2 mL (1.60 mmol) of 1.3 M ethereal methyllithium. The resulting clear solution was stirred at -20°C for 30 min, followed by cooling to -78°C. To the cuprate was added a solution of 52.7 mg (0.16 mmol) of ketene dithioacetal 101 in 2 mL of dry ether slowly via a cannula. The reaction mixture was allowed to stir at -30°C for 2 h, and was then warmed slowly to room temperature, and stirred for an additional 8 h. To the mixture at 0°C was added dropwise 1 mL of saturated aqueous ammonium chloride, followed by 50 mL of ether. The solution was filtered and the filtrate was washed with 5 mL of saturated aqueous ammonium chloride, two 5-mL portions of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was chromatographed over 3.0 g of silica gel (eluted with ethyl acetate–hexane, 1:40) to give 16 mg (36%) of ester 103.

**B. From Ketone 116:** A flask was charged 0.98 g (2.75 mmol) of methyltriphenylphosphonium bromide, 0.27 g (2.41 mmol) of potassium tert-
butoxide, and 5 mL of dry toluene. The mixture was stirred under argon at room temperature for 4h. To the resulting yellow suspension was transferred a solution of 188 mg (0.68 mmol) of ketone 116 in 2 mL of dry tetrahydrofuran slowly via a cannula. The reaction mixture was stirred at room temperature for 4h, followed by the addition of 2 mL of 5% aqueous hydrochloric acid. The reaction was stirred at room temperature for 1h and the resulting mixture was diluted with 30 mL of ether, washed with 5 mL of saturated aqueous sodium bicarbonate, two 5-mL portions of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was chromatographed over 8 g of silica gel (eluted with ethyl acetate-hexane, 1:40) to give 149 mg (80%) of ester 103: IR (neat) 1716, 1644, 1195, 1078 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 0.95 (s, 3H, CH$_3$), 1.32 (t, $J$ = 7 Hz, 3H, CH$_3$), 1.20-2.13 (m, 10H, CH$_2$ manifold), 1.67 (s, 3H, =CCH$_3$), 1.77 (s, 3H, =CCH$_3$), 2.28 (d, $J$ = 11 Hz, 1H, CHC=), 3.27 (ddd, $J$ = 11, 11, 7 Hz, 1H, CHC(=)CO$_2$R), 4.21 (q, $J$ = 7 Hz, 2H, OCH$_2$), 4.62 (br s, 1H, =CH$_2$), 4.69 (br s, 1H, =CH$_2$); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 14.34 (q), 20.44 (q), 22.99 (q), 23.85 (t), 25.06 (q), 27.76 (t), 30.74 (t), 33.23 (t), 40.59 (t), 42.55 (d), 43.41 (s), 58.92 (d), 59.77 (t), 110.87 (t), 131.70 (s), 135.73 (s), 147.16 (s), 170.44 (s); mass spectrum, $m/e$ (relative intensity) 276 (M$^+$), 236 (10), 221 (50), 199 (30), 175 (25), 148 (80), 133 (100), 107 (20), 93 (30); exact mass calcd. for C$_{18}$H$_{28}$O$_2$ $m/e$ 276.2089, found $m/e$ 276.2133.
Ethyl α-(E/Z)-(1R*,3aR*,7aS*)-Hexahydro-3a-methyl-7-methylene-α-[(methylthio)methylene]-1-indanacetate (104). To a suspension of 166 mg (0.87 mmol) of copper(I) bromide dimethyl sulfide complex in 1 mL of dry tetrahydrofuran under argon at -20°C was added 1.34 mL (1.74 mmol) of 1.3 M ethereal methyllithium. The resulting clear solution was stirred at -20°C for 30 min, followed by cooling to -78°C. To the cuprate was added a solution of 141 mg (0.41 mmol) of ketene dithioacetal 101 in 4 mL of dry ether slowly via a cannula. The reaction mixture was allowed to slowly warm to room temperature where it was stirred for 10 h and then brought to gentle reflux (oil bath at 50°C) for 10 h. Mixture was cooled to room temperature and 1 mL of saturated aqueous ammonium chloride was added followed by 100 mL of ether. The solution was filtered and the filtrate was washed with 10 mL of saturated aqueous ammonium chloride, two 10-mL portions of brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed over silica gel using MPLC (Lobar, size C; eluted with ethyl acetate-hexane, 1:20) to give 10 mg (9%) of ester 103 and 15 mg (12%) of material that was tentatively assigne structure 104. NMR spectra of this material were complex due to the presence of two isomers as well as minor impurities and the assignment was based principally on mass spectral data: IR (neat mixture) 1733, 1644, 1457, 1118, 1026, 733, 724, 699 cm⁻¹; ¹H NMR (signals assigned to major stereoisomer, 250 MHz, CDCl₃) δ 1.01 (s, 3H, CH₃), 2.65 and 2.67 (two s, 3H, SCH₃), 4.25 (m, 2H, OCH₂), 4.48 and 4.50 (two br s, 1H, =CH₂),
4.70 and 4.80 (two br s, 1H, =CH₂), 7.14 and 7.19 (two s, 1H, CH=); mass spectrum, m/e (relative intensity) 294 (M⁺), 265 (20), 247 (85), 233 (25), 219 (50), 201 (60), 173 (100), 171 (45), 157 (35), 145 (35), 131(45), 107(50), 91 (65); exact mass calcd. for C₁₇H₂₆O₂S m/e 294.1653, found m/e 294.1666.

![Chemical Structure](image)

**Ethyl 3-methyl-2-(trimethylsilyl)-butanoate (113)**. To a stirred solution of 1.21 g (12 mmol) of diisopropylamine in 2 mL of ether at -78°C under argon was added in 4.43 mL (11 mmol) of 2.48 M n-butyllithium in hexane. The mixture was stirred for 30 min at -78°C and 2.1 g (12 mmol) of hexamethylphosphoramid was added in one portion. The solution was stirred for 10 min and 5.1 g (30 mmol) of 2-iodopropane was added in one portion. The mixture was then stirred at 0°C for 4 h, cooled to -20°C and 8 mL of 5% aqueous hydrochloric acid was added. The resulting mixture was diluted with 50 mL of petroleum ether (bp 35-50°C) and washed with two 10-mL portions of saturated aqueous ammonium chloride. Aqueous washes were extracted with two 15-mL portions of petroleum ether (bp 35-60°C). The combined organic layers were washed with 5 mL of saturated aqueous sodium bicarbonate, two 10-mL portions of brine, dried (Na₂SO₄), concentrated in vacuo. The residue was distilled under reduced pressure to give 0.55 g (28%) of silyl ester 113 as a clear liquid: bp 100°C/30 mm Hg; ¹H NMR (300 MHz, CDCl₃) δ 0.10 (s, 9H, SiMe₃), 0.97 (d, J = 6 Hz, 3H, CH₃), 1.00 (d, J = 6 Hz, 3H, CH₃), 1.30 (t, J = 7 Hz, 3H, CH₃), 1.75 (d, J = 10 Hz, 1H, CHCO₂R), 2.05-2.22 (m, 1H, CH), 4.08 (m, 2H, OCH₂).
7-(3-Butenyl)-7-methyl-1,4-dioxaspiro[4.5]decane (109). A solution of 13.3 g (80 mmol) of ketone (71), 24.8 g (400 mmol) of ethylene glycol, 50 mL of dry benzene, 21.2 g (200 mmol) of trimethylorthoformate and 0.12 g (0.8 mmol) of p-toluenesulfonic acid was stirred at room temperature under argon for 6 h. A solution of 12 mL of saturated aqueous sodium bicarbonate was added slowly. The mixture was concentrated in vacuo and the residue was diluted with 100 mL of ether. The solution was washed with three 20-mL portions of brine, dried (Na₂SO₄) and concentrated in vacuo. The residual liquid (20.6 g) was chromatographed over 350 g of silica gel (eluted with ethyl acetate-hexane, 1:20) to give 13.0 g (78%) of ketal 109 as a clear liquid: IR (neat) 1645 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.93 (s, 3H, CH₃), 1.22-1.64 (m, 10H), 1.95 (m, 2H, =CCH₂), 3.84 (s, 4H, OCH₂), 4.84-5.0 (m, 2H, =CH₂), 5.70-5.86 (m, 1H, =CH); ¹³C NMR (CDCl₃, 62.5 MHz) δ 19.7 (t), 25.3 (q), 28.1 (t), 34.4 (s), 35. (t), 37.1 (t), 42.0 (t), 44.8 (t), 63.8 (t), 64.0 (t), 109.4 (s), 113.7 (t), 139.7 (d), mass spectrum, m/e (relative intensity) 195 (10), 167 (52), 155 (60), 153 (30), 113 (35), 100 (33), 99 (100), 86 (65); exact mass calcd for C₁₃H₂₂O₂ m/e 210.1579, found m/e 210.1574.
7-Methyl-1,4-dioxaspiro[4.5]decane-7-propionaldehyde (110).

Through a stirred solution of 10.5 g (50 mmol) of ketal 109 in 100 mL of methanol at -78°C was passed a stream of ozone (Welsbach ozone generator) at the flow rate of 1.0 mmol min⁻¹. When the reaction mixture maintained a blue color for 1 min, the stream of ozone was replaced by nitrogen and the solution was purged for 1 h. To the resulting clear reaction mixture was added 40 mL of dimethylsulfide. The mixture was stirred at -78°C for 3 h, allowed to warm slowly to room temperature and stirred for 4 h. The solvent was removed in vacuo and the residual crude liquid (17.5 g) was chromatographed over 150 g of silica gel (eluted with ethyl acetate-hexane, 1:10) to give 10.1 g (95%) of ketal aldehyde 110 as a colorless liquid: IR (neat) 1720 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.87 (s, 3H, CH₃), 1.18-1.70 (m, 10H), 2.30 (m, 2H, CH₂C=O), 3.82 (s, 4H, OCH₂), 9.69 (dd, J = 4, 2 Hz, 1H, CHO); ¹³C NMR (CDCl₃, 62.5 MHz) δ 19.4 (t), 25.6 (q), 33.4 (t), 33.9 (s), 34.7 (t), 36.9 (t), 38.8 (t), 44.5 (t), 63.9 (t), 109.0 (s), 202.8 (d); mass spectrum, m/e (relative intensity) 167 (35), 155 (35), 153 (25), 125 (10), 113 (30), 100 (30) 99 (100); exact mass calcd for C₁₂H₂₀O₃ m/e 212.1412, found m/e 212.1763.
Ethyl (E)-2-isopropenyl-5-(7-methyl-1,4-dioxaspiro[4,5]dec-7-yl)-2-pentenoate (E-118) and Ethyl (Z)-2-isopropenyl-5-(7-methyl-1,4-dioxaspiro[4,5]dec-7-yl)-2-pentenoate (Z-118). To a solution of 2.4 g (24 mmol) of diisopropylamine in 10 mL of dry tetrahydrofuran at -78°C under argon was added 15 mL (24 mmol) of 1.6 M of n-butyllithium in hexane. The mixture was stirred at -78°C for 30 min followed by addition of a solution of 4.2 g (24 mmol) of ethyl 3-methyl-2-(trimethylsilyl)-but-3-enoate (115) in 10 mL of tetrahydrofuran. The mixture was stirred at -78°C for 40 min followed by addition of a solution of 4.24 g (20 mmol) of aldehyde 110 in 10 mL of dry tetrahydrofuran via a cannula over a period of 20 min. The resulting solution was stirred at -78°C for 2 h and at 0°C for 1 h. To the reaction mixture was added in 10 mL of saturated aqueous ammonium chloride followed by dilution with 150 mL of ether. The mixture was washed with two 20-mL portions of brine and the combined washes were extracted with two 20-mL portions of ether. The combined ethereal layers were dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was chromatographed over 200 g of silica gel (eluted with ethyl acetate-hexane, 1:10) to give 4.44 g (70%) of light yellow liquid. This material was a 2:1 mixture of E and Z isomers, respectively, by integration of selected peaks in $^1$H NMR spectrum, which was further separated by MPLC (Lobar, size C; eluted with ethyl acetate-hexane, 1:20) to give 2.96 g of E-118 and 1.48 g of Z-118. Ester E-118: IR (neat) 1713, 1458, 1364, 1234, 1102, 1054 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 0.91 (s, 3H, CH$_3$), 1.24 (t, $J = 7$ Hz,
3H, CH₃), 1.16-1.60 (m, 10H, CH₂ manifold), 1.84 (s, 3H, =CH₃), 2.05-2.18 (m, 2H, CH₂CH=), 3.86 (s, 4H, OCH₂CH₂O), 4.15 (q, J = 7 Hz, 2H, OCH₂), 4.71 (s, 1H, =CH₂), 5.10 (s, 1H, =CH₂), 6.72 (t, J = 8 Hz, 1H, HC=); ¹³C NMR (63 MHz, CDCl₃) δ 14.17 (q), 19.61 (t), 23.05 (q), 23.94 (t); 25.76 (q), 34.64 (s), 34.93 (t), 37.09 (t), 41.23 (t), 44.62 (t), 60.35 (t), 63.90 (t), 63.96 (t), 109.23 (s), 115.91 (t), 135.29 (s), 140.18 (s), 143.68 (d), 166.70 (s); mass spectrum, m/e (relative intensity) 322 (M⁺) 279 (25), 195 (10), 155 (80), 113 (30), 99 (100), 86 (30); exact mass calcd. for C₁₉H₃₀O₄ m/e 322.2147, found m/e 322.2151. 

Ester Z-118: IR (neat) 1728, 1456, 1416, 1211, 1102 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.91 (s, 3H, CH₃), 1.28 (t, J = 7 Hz, 3H, CH₃), 1.84 (s, 3H, =CH₃), 1.18-1.60 (m, 10H, CH₂ manifold), 2.09 (m, 2H, CH₂CH=), 3.85 (s, 4H, OCH₂CH₂O), 4.23 (q, J = 7 Hz, 2H, OCH₂), 4.83 (s, 1H, =CH₂), 4.94 (s, 1H, =CH₂), 5.72 (t, J = 8 Hz, 1H, CH=); ¹³C NMR (63 MHz, CDCl₃) δ 14.19 (q), 19.58 (t), 20.10 (q), 24.38 (t), 25.42 (q), 34.48 (s), 34.89 (t), 36.92 (t), 41.60 (t), 44.72 (t), 60.47 (t), 63.85 (t), 63.95 (t), 102.20 (s), 113.96 (t), 133.15 (d), 136.65 (s), 139.46 (s), 168.93 (s); mass spectrum, m/e (relative intensity) 322 (M⁺), 279 (20), 195 (20), 155 (90), 113 (30), 99 (100), 86 (40); exact mass calcd. for C₁₉H₃₀O₄ m/e 322.2144, found m/e 322.2159.

**Ethyl (E)-2-Isopropyl-5-(1-methyl-3-oxocyclohexyl)-2-pentenoate (E-117)**. To a stirred solution of 74 mg (0.23 mmol) of ester E-118 in 1.5 mL of ethanol was added in 0.21 mL (0.62 mmol) of 3N aqueous hydrochloric acid.
The solution was stirred at room temperature for 3 h. The mixture was then diluted with 30 mL of ether, washed with 3 mL of saturated aqueous sodium bicarbonate, two 5-mL portions of brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (eluted with ethyl acetate-hexane, 1:20) to give 60 mg (96%) of ester E-117 as a pale yellow liquid: IR (neat) 1712, 1234, 1057 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.85 (s, 3H, CH₃), 1.20 (t, J = 7 Hz, 3H, CH₃), 1.79 (s, 3H, =CH₃), 2.07 (ddd, J = 8, 8, 7 Hz, 1H, CH=CH₂), 2.17 (ddd, J = 10, 8, 8 Hz, 1H, CH=CH₂), 1.26-2.12 (m, 10H, CH₂ manifold), 4.10 (q, J = 7 Hz, 2H, OCH₂), 4.66 (br s, 1H, =CH₂), 5.06 (s, 1H, =CH₂), 6.64 (t, J = 8 Hz, 1H, =CH); ¹³C NMR (63 MHz, CDCl₃) δ 14.01 (q), 21.83 (t), 22.87 (q), 23.43 (t), 24.55 (q), 35.50 (t), 38.48 (s), 40.64 (t), 40.69 (t), 53.26 (t), 60.31 (t), 115.92 (t), 135.77 (s), 139.93 (s), 142.22 (d), 166.34 (s), 211.42 (s); mass spectrum, m/e (relative intensity) 278 (M⁺), 232 (30), 217 (10), 189 (10), 168 (25), 153 (20), 140 (40), 121 (100), 111 (95), 93 (30); exact mass calcd. for C₁₇H₂₆O₃ m/e 278.1882, found m/e 278.1872.

Z-117

Ethyl (Z)-2-Isopropyl-5-(1-methyl-3-oxocyclohexyl)-2-pentenoate (Z-117). To a stirred solution of 48 mg (0.15 mmol) of ester Z-118 in 1.5 mL of ethanol was added in 0.25 mL (0.75 mmol) of 3N aqueous hydrochloric acid. The solution was stirred at room temperature for 3 h. The mixture was diluted with 30 mL of ether, washed with 3 mL of saturated aqueous sodium bicarbonate, two 5-mL portions of brine, dried (Na₂SO₄) and concentrated in
vacuo. The residue was chromatographed over 2 g of silica gel eluted with ethyl acetate-hexane, 1:20) to give 36 mg (86%) of ester Z-117 as a pale yellow liquid: IR (neat) 1718, 1456, 1224 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.94 (s, 3H, CH₃), 1.34 (t, J = 7 Hz, 3H, CH₃), 1.87 (s, 3H, =CH₃), 2.15 (ddd, J = 10, 9, 8 Hz, 1H, CH₂CH=), 2.25 (ddd, J = 8, 8, 7 Hz, 1H, CHHCH=), 1.38-2.20 (m, 10H, CH₂ manifold), 4.19 (q, J = 7 Hz, 2H, OCH₂), 4.89 (br s, 1H, =CH₂ ), 5.01 (br s, 1H, =CH₂), 5.73 (t, J = 8 Hz, 1H, =CH); ¹³C NMR (63 MHz, CDCl₃) δ 14.27 (q), 20.17 (q), 21.89 (t), 24.16 (t), 24.75 (q), 35.63 (t), 38.54 (s), 40.85 (t), 40.88 (t), 53.53 (t), 60.67 (t), 114.47 (t), 132.21 (d), 137.28 (s), 139.46 (s), 168.83 (s), 211.58 (s); mass spectrum, m/e (relative intensity) 278 (M⁺), 233 (20), 168 (10), 153 (15), 140 (20), 121 (35), 111 (40), 93 (20), 79 (15), 69 (15), 55 (100); exact mass calcd. for C₁₇H₂₆O₃ m/e 278.1882, found m/e 278.1874.

Ethyl (αR*,1S*,3aS*,7aR*)-Hexahydro-α-isopropenyl-3a-methyl-7-oxo-1-indanacetate (119), Ethyl (αR*,1R*,3aR*,7aS*)-Hexahydro-α-isopropenyl-3a-methyl-7-oxo-1-indanacetate (120) and Ethyl (1R*,3aR*,7aS*)-Hexahydro-α-isopropylidene-3a-methyl-7-oxo-1-indanacetate (116). A. From E-117 using pyrrolidine: To a stirred solution of 60 mg (0.22 mmol) of ester E-117 in 0.5 mL of dry tetrahydrofuran at 60°C under argon was added in 1.3 mg (0.02 mmol) of glacial acetic and 3.1 mg (0.04 mmol) of pyrrolidine. The mixture was stirred at 60°C for 8h, cooled to room
temperature, and 0.1 mL of 1 N aqueous hydrochloric acid was added followed by stirring at room temperature for 2h. The mixture was diluted with 30 mL of ether, washed with 5 mL of 5% aqueous hydrochloric acid, 3 mL of saturated aqueous ammonium chloride, two 10-mL portions of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was chromatographed over 3 g of silica gel (eluted with ethyl acetate-hexane, 1:20) to give 43 mg (72%) of ester 119 and 6 mg (10%) of ester 116.

B. From E-117 using potassium tert-butoxide: To a stirred solution of 56 mg (0.2 mmol) of ester E-117 in 1.0 mL of dry tert-butanol at 60°C was added in 0.16 mL (0.04 mmol) of 0.25 M potassium tert-butoxide in tert-butanol. The mixture was stirred at 60°C under argon for 3h. The solution mixture was cooled to room temperature and 20 mg of glacial acetic acid was added. The mixture was diluted with 20 mL of ether, washed with 5 mL of saturated aqueous sodium bicarbonate, two 5-mL portions of brine, dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 8 g of silica gel (eluted with ethyl acetate-hexane, 1:20) to give 25 mg (44%) of ester 116, 12 mg (21%) of ester 119 and 8 mg (14%) of ester 120.

C. From E-117 and Z-117 using potassium tert-butoxide: To a stirred solution of 0.94 g (3.4 mmol) of esters E-117 and Z-117 (1:1) in 6 mL of dry tert-butanol at 60°C was added in 2.7 mL (0.7 mmol) of 0.25 M potassium tert-butoxide in tert-butanol. The mixture was stirred at 60°C for 3 h. The solution mixture was cooled to room temperature and 0.1 g of glacial acetic acid was added. The mixture was then diluted with 50 mL of ether, washed with 10 mL of saturated aqueous sodium bicarbonate, two 10-mL portions of brine, dried (Na$_2$SO$_4$), concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate-hexane, 1:25) to give 188 mg (20%) of ester 116, 340 mg (36%) of ester 119 and 199 mg (21%) of ester 120. Ester
116: IR (neat) 1711, 1458, 1302, 1200 cm\(^{-1}\); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\)
1.00 (s, 3H, CH\(_3\)), 1.24 (t, \(J = 7\) Hz, 3H, CH\(_3\)), 1.61 (s, 3H, =CCH\(_3\)), 1.71 (s, 3H, =CCH\(_3\)), 1.17-2.45 (m, 10H, CH\(_2\) manifold), 2.48 (d, \(J = 11\) Hz, 1H, CHCO), 3.42 (ddd, \(J = 11, 10, 7\) Hz, 1H, CHC(=)CO\(_2\)R), 4.15 (q, \(J = 7\) Hz, 2H, OCH\(_2\)); \(^{13}\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 14.08 (q), 20.46 (q), 22.14 (t), 23.00 (q), 25.90 (q), 29.00 (t), 33.42 (t), 37.54 (t), 40.58 (t), 42.92 (d), 47.26 (s), 59.82 (t), 64.38 (d), 129.93 (s), 137.47 (s), 169.47 (s), 213.62 (s); mass spectrum, \(m/e\) (relative intensity) 278 (M\(^+\)), 232 (40), 217 (100), 204 (20), 189 (60), 161 (20), 133 (20), 91 (10); exact mass calcd. for C\(_{17}\)H\(_{26}\)O\(_3\) \(m/e\) 278.1881, found \(m/e\) 278.1896.

Ester 119: IR (neat) 1731, 1706, 1150, 1030, 898 cm\(^{-1}\); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 1.07 (s, 3H, CH\(_3\)), 1.25 (t, \(J = 7\) Hz, 3H, CH\(_3\)), 1.38-2.57 (m, 10H, CH\(_2\) manifold), 1.69 (s, 3H, =CCH\(_3\)), 2.00 (d, \(J = 8\) Hz, 1H, CHCO), 2.90 (d, \(J = 11\) Hz, 1H, CHCO\(_2\)R), 3.00-3.13 (m, 1H, CJ±CHC\(_{17}\)H\(_26\)O\(_3\)R), 4.14 (q, \(J = 7\) Hz, 2H, OCH\(_2\)), 4.86 (br s, 1H, =CH\(_2\)), 4.91 (br s, 1H, =CH\(_2\)); \(^{13}\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 14.13 (q), 21.16 (q), 23.08 (t), 26.16 (q), 29.00 (t), 33.89 (t), 38.36 (t), 39.33 (t), 41.67 (d), 48.89 (s), 59.72 (d), 60.43 (t), 64.79 (d), 115.02 (t), 141.84 (s), 172.75 (s), 213.52 (s); mass spectrum, \(m/e\) (relative intensity) 278 (M\(^+\)), 263 (10), 232 (10), 217 (25), 204 (15), 189 (35), 151 (100), 107 (30), 91 (45), 81 (50), 73 (90); exact mass calcd. for C\(_{17}\)H\(_{26}\)O\(_3\) \(m/e\) 278.1882, found \(m/e\) 278.1875.

Ester 120: IR (neat) 1728, 1706, 1173, 1119, 899 cm\(^{-1}\); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 1.01 (s, 3H, CH\(_3\)), 1.20 (t, \(J = 7\) Hz, 3H, CH\(_3\)), 1.10-2.73 (m, 11H, CH\(_2\) manifold and CHCO), 1.70 (s, 3H, =CCH\(_3\)), 2.84 (d, \(J = 11\) Hz, 1H, CHCO\(_2\)R), 2.95 (ddd, \(J = 11, 10, 8\) Hz, 1H, CHCHCO\(_2\)R), 4.00 (m, 2H, OCH\(_2\)); 4.86 (br s, 1H, =CH\(_2\)), 4.88 (br s, 1H, =CH\(_2\)); \(^{13}\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 13.93 (q), 19.90 (q), 23.30 (t), 25.65 (q), 27.67 (t), 33.65 (t), 37.61 (t), 39.40 (t), 42.77 (d), 49.03 (s), 59.48 (d), 60.51 (t), 67.43 (d), 115.18 (t), 141.87 (s), 172.36 (s), 214.27 (s); mass spectrum, \(m/e\) (relative intensity) 278 (M\(^+\)), 263
(20), 217 (35), 189 (25), 151 (100), 135 (10), 127 (10); exact mass calcd. for C₁₇H₂₆O₃ m/e 278.1882, found m/e 278.1907.

Ethyl (αR*,1R*,3αR*,7αS*)-Hexahydro-α-isopropyl-3α-methyl-7-oxo-1-indanacetate (119a). A solution of 97 mg (0.35 mmol) of ester 119 and 10 mg of 10% palladium on charcoal in 4 mL of ethyl acetate was hydrogenated at 60 psi at room temperature for 8 h using a Parr apparatus. The mixture was filtered through a short column of Celite (about 0.5 inch in height) and the filtrate was concentrated in vacuo. The residue was chromatographed over 4g of silica gel (eluted with ethyl acetate-hexane, 1:20) to give 90 mg (92%) of ester 119a as a pale yellow liquid: IR (neat) 1727, 1704, 1464, 1378, 1147, 1028 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.73 (d, J = 7 Hz, 3H, CH₃), 0.85 (d, J = 7 Hz, 3H, CH₃), 0.97 (s, 3H, CH₃), 1.20 (t, J = 7 Hz, 3H, CH₃), 1.10-2.50 (m, 13H, CH, CH₂ manifold, CHCO, and CHCO₂R), 2.67 (ddd, J = 10, 8, 7 Hz, 1H, CH(CHCO₂R)), 4.07 (q, J = 7 Hz, 2H, OCH₂); ¹³C NMR (63 MHz CDCl₃) δ 14.34 (q), 18.91 (q), 21.21 (q), 22.72 (t), 25.80 (q), 27.13 (t), 28.05 (d), 33.20 (t), 37.96 (t), 39.91 (t), 41.78 (d), 48.28 (s), 56.80 (d), 59.70 (t), 65.10 (d), 173.93 (s), 214.68 (s); mass spectrum, m/e (relative intensity) 280 (M⁺), 265 (20), 234 (50), 219 (80), 206 (35), 191 (50), 163 (20), 151 (100), 135 (25), 111 (35); exact mass calcd. for C₁₇H₂₈O₃ m/e 280.2038, found m/e 280.2043.
Ethyl ($\alpha R^*, 1 R^*, 3a R^*, 7a S^*$)-Hexahydro-2-isopropyl-3a-methyl-7-
methylene-1-indanacetate (119b). A flask was charged with 0.46 g (1.3
mmol) of methyltriphenylphosphonium bromide, 0.14 g (1.3 mmol) of
potassium tert-butoxide, and 2 mL of dry toluene. The mixture was stirred at
room temperature under argon for 3h. To the resulting yellow suspension in
flask was transferred a solution of 80 mg (0.29 mmol) of ester 119a in 0.5 mL of
dry tetrahydrofuran via a cannula. The reaction mixture was stirred at room
temperature for 1 h, followed by addition of 1 mL of 5% aqueous hydrochloric
acid. The resulting mixture was stirred for 1 h, diluted with 30 mL of ether,
washed with 5 mL of saturated aqueous sodium bicarbonate, dried (Na$_2$SO$_4$),
and concentrated in vacuo. The residue was chromatographed over 5 g of
silica gel (eluted with ethyl acetate-hexane, 1:20) to yield 65 mg (81%) of ester
119b: IR (neat) 1729, 1643, 1463, 1375, 892 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$
$\delta$ 0.85 (d, $J$ = 7 Hz, 3H, CH$_3$), 0.89 (d, $J$ = 7 Hz, 3H, CH$_3$), 0.92 (s, 3H, CH$_3$
1.27 (t, $J$ = 7 Hz, 3H, CH$_3$), 1.15-2.14 (m, 13H, CH, CH$_2$ manifold, CHC=, and
CHCO$_2$R), 2.41 (ddd, $J$ = 11, 8, 7 Hz, 1H, CHCHCO$_2$R), 4.14 (q, $J$ = 7 Hz, 2H,
OCH$_2$), 4.69 (br s, 1H, =CH$_2$), 4.78 (br s, 1H, =CH$_2$); $^{13}$C NMR (63 MHz,
CDCl$_3$ $\delta$ 14.47 (q), 20.62 (q), 20.99 (q), 23.50 (t), 23.98 (t), 24.85 (q), 28.65 (d),
30.54 (t), 32.82 (t), 40.14 (t), 40.63 (d), 43.61 (s), 54.66 (d), 58.93 (d), 59.45 (t),
110.74 (t), 147.91 (s), 175.02 (s); mass spectrum, $m/e$ (relative intensity) 278
(M$^+$), 263 (40), 233 (10), 189 (20), 149 (100), 133 (20), 115 (25), 109 (35), 93
(25); exact mass calcd. for C$_{18}$H$_{30}$O$_2$ $m/e$ 278.2245, found $m/e$ 278.2245.
1,1-Dimethylethyl 3-Methyl-2-trimethylsilyl-3-butenoate (123). To a stirred solution of 10.6 g (115 mmol) of diisopropylamine in 50 mL of dry tetrahydrofuran under argon at -78°C was added 68.8 mL (110 mmol) of 1.6 M n-butyllithium in hexane. The solution was stirred for 30 min at -78°C and the solvent was removed in vacuo at -78°C. To the residual white solid was added 70 mL of dry tetrahydrofuran at -78°C followed by a solution of 18.8 g (100 mmol) of t-butyl α-trimethylsilylacetate in 50 mL of dry tetrahydrofuran followed by stirring at -78°C for 40 min.

A second flask was charged with 10.9 g (50.0 mmol) of nickel(II) bromide, 50 mL of dry tetrahydrofuran and 31 mL (50.0 mmol) of 1.6 M of n-butyllithium in hexane was added. The solution was stirred under argon at -78°C for 12 min. To the resulting black mixture was added in 12.1 g (100 mmol) of 2-bromopropene at -78°C, followed by addition of the ester enolate solution via cannula. The cooling bath was then removed and the mixture was stirred at room temperature for 8 h. The solution was cooled to -78°C and 120 mL of 5% of aqueous hydrochloric acid was slowly added. The mixture was allowed to warm to 0°C, diluted with 200 mL of ether, and filtered through a short column packed with 30 g of alumina topped with a layer of florosil (60-100 mesh). The column was rinsed with two 150-mL portions of ether and the filtrate was concentrated. The residual liquid (21.2 g) was chromatographed over 400 g of silica gel (eluted with diethyl ether-hexane, 1:30) to give 11.0 g (48%) of ester 123 as a light yellow liquid: IR (neat) 1710 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ
0.15 (s, 9H, SiMe3), 1.45 (s, 9H, CMMe3), 1.83 (br s, 3H, =CCH3), 2.8 (s, 1H, CHSi), 4.82 (br s, 1H, =CH), 4.84 (br s, 1H, =CH); \(^{13}\text{C} \text{NMR (CDCl}_3\text{, 62.5 MHz)}\)

δ -2.0 (q), 24.4 (q), 28.2 (q), 47.9 (d), 79.8 (s), 111.5 (t), 140.6 (s), 172.0 (s);
mass spectrum, \(m/e\) (relative intensity) 172 (M\(^+\)-C\(_8\)H\(_8\)), 156 (30), 113 (20), 82 (100), 73 (90), 57 (90).

![Diagram of 124 and 125](image)

1,1-Dimethylethyl (Z)-2-(1-Methylethenyl)-5-(7-methyl-1,4-dioxaspiro[4.5]dec-7-yl)-2-pentenoate (124). 1,1-Dimethylethyl (E)-2-(1-Methylethenyl)-5-(7-methyl-1,4-dioxaspiro-[4.5]dec-7-yl)-2-pentenoate (125). To a stirred solution of 2.13 g (21.1 mmol) of diisopropylamine in 30 mL of dry tetrahydrofuran under argon was added 14.1 mL (21.1 mmol) of 1.5 M \(n\)-butyllithium in hexane at -78°C. The solution was stirred at -78°C for 20 min, 0°C for 5 min, and cooled to -78°C. To the mixture was added a solution of 5.0 g (21.9 mmol) of ester 123 in 40 mL of dry tetrahydrofuran. The solution was stirred at -78°C for 1 h and a solution of 3.58 g (16.9 mmol) of ketal aldehyde 110 in 20 mL of dry tetrahydrofuran was added using a cannula. The resulting solution was stirred at -78°C for 2 h and at room temperature for 8 h. To the mixture was added 20 mL of saturated aqueous ammonium chloride and 300 mL of ether. The organic phase was washed with three 20-mL portions of brine and the combined washes were extracted with two 15-mL portions of ether. The combined ethereal layers were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The residual liquid (8.1 g) was
chromatographed over 100 g of silica gel (eluted with ethyl acetate-hexane, 1:10) to give 3.71 g (63%) of 125 and 124 as a light yellow liquid. This material was a 2:1 mixture of E and Z isomers, respectively, by integration of selected peaks in the $^1$H NMR spectrum of the mixture. Medium pressure liquid chromatography (Lobar size C; eluted with ethyl acetate-hexane, 1:20) gave 1.24 g of Z-isomer 124 and 2.46 g of E-isomer 125. Ester 124: IR (neat) 1722, 1630, cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) δ 0.95 (s, 3H, CH$_3$), 1.24-1.64 (m with s at δ 1.53, 19H, aliphatic and t-Bu), 1.85 (br s, 3H, =CCH$_3$), 2.12 (ddd, $J = 10$, 10, 7 Hz, 2H, CH$_2$C=C), 3.88 (s, 4H, OCH$_2$), 4.91 (br s, 1H, =CH$_2$), 4.96 (br s, 1H, =CH$_2$), 5.59 (t, $J = 7$ Hz, 1H, =CH); $^{13}$C NMR (CDCl$_3$, 62.5 MHz) δ 19.7 (t), 20.1 (q), 24.2 (t), 25.4 (q), 28.2 (q), 34.6 (s), 35.0 (t), 37.1 (t), 41.8 (t), 44.9 (t), 63.9 (t), 64.0 (t), 81.3 (s), 109.3 (s), 113.7 (t), 131.3 (d), 137.7 (s), 139.5 (s), 168.6 (s); mass spectrum, m/e (relative intensity) 350 (M$^+$), 294 (10), 251 (15), 195 (10), 155 (100), 111 (20), 99 (70), 86 (25), 57 (30); exact mass calcd for C$_{21}$H$_{34}$O$_4$ m/e 350.2460, found m/e 350.2466. Ester 125: IR (neat) 1709, 1629, 899, 855 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) δ 0.89 (s, 3H, CH$_3$), 1.14-1.58 (m with s at δ 1.42, 19H, aliphatic and t-Bu), 1.81 (br s, 3H, =CCH$_3$), 2.06 (d,d,d, $J = 10$, 10, 8 Hz, 2H, CH$_2$C=C), 3.84 (s, 4H, OCH$_2$), 4.67 (br s, 1H, =CH$_2$), 5.03 (br s, 1H, =CH$_2$), 6.55 (t, $J = 7$ Hz, 1H, =CH); $^{13}$C NMR (CDCl$_3$, 62.5 MHz) δ 19.6 (t), 23.0 q), 23.8 (t), 25.7 (q), 28.0 (q), 34.6 (s), 34.9 (t), 37.0 (t), 41.3 (t), 44.6 (t), 63.9 (t), 63.9 (t), 80.0 (s), 109.2 (s), 115.4 (t), 136.7 (s), 140.4 (s), 142.3 (d), 166.0 (s); mass spectrum, m/e (relative intensity) 350 (M$^+$), 294 (10), 251 (15), 155 (100), 111 (20), 89 (55), 86 (20), 57 (30); exact mass calcd for C$_{21}$H$_{34}$O$_4$ m/e 350.2405, found m/e 350.2455.
1,1-Dimethylethyl (Z)-2-isopropenyl-5-(1-methyl-3-oxocyclohexyl)-2-pentenoate (126) and 1,1-Dimethylethyl (E)-2-isopropenyl-5-(1-methyl-3-oxocyclohexyl)-2-pentenoate (127). To a stirred solution of 0.82 g (2.34 mmol) of isomeric unsaturated esters 125 and 124 (125:124 = 2:1) in 4 mL of ether and t-butanol (1:1) at room temperature was added 5.9 mL (5.9 mmol) of 1 N aqueous hydrochloric acid and the mixture was stirred at room temperature for 12 h. The mixture was diluted with 30 mL of ether and washed with 5 mL of water and two 5-mL portions of saturated aqueous sodium bicarbonate. The combined etheral layers were washed with two 10-mL portions of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residual liquid (1.1 g) was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexane, 1:10) to give 0.69 g (96%) of a 1.6:1 mixture of unsaturated keto esters 127 and 126, respectively, by integration of selected peaks in the $^1$H NMR spectrum of the mixture. A 0.5 g sample of the mixture was chromatographed using MPLC (Lobar size B; eluted with ethyl acetate-hexane, 1:15) to give 0.32 g of pure E-isomer 127, and 0.18 g of pure Z-isomer 126. Ester 127: IR (neat) 1710, 1630, 900, 854 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 0.89 (s, 3H, CH$_3$), 1.2-2.3 (m with s's at $\delta$ 1.44 (t-Bu) and $\delta$ 1.82 (=CCH$_3$), 24 H), 4.68 (br s, 1H, =CH$_2$) 5.06 (br s, 1H, =CH$_2$), 6.56 (t, $J$ = 7 Hz, 1H, =CH); $^{13}$C NMR (CDCl$_3$, 62.5 MHz) $\delta$ 21.9 (t), 23.0 (q), 23.5 (t), 24.6 (q), 28.0 (q), 35.6 (t), 38.6 (s), 40.8 (t), 53.4 (t), 80.3 (s), 102.7 (s), 115.6 (t), 137.3 (s), 140.3 (s), 141.0 (d), 165.8 (s), 211.8 (s); mass spectrum, m/e (relative intensity) 250 (M$^+$-C$_4$H$_8$), 232 (5), 217 (5), 140 (5), 121
1,1-Dimethylethyl (1R*,3aR*,7aS*)-Hexahydro-α-Isopropylidene-3a-methyl-7-oxo-1-Indanacetate (128), 1,1-Dimethylethyl (αR*,1S*,-3aS*,7aR*)-Hexahydro-α-isopropenyl-3a-methyl-7-oxo-1-Indanacetate (129), and 1,1-Dimethylethyl (αS*,1S*,3aS*,7aR*)-Hexahydro-α-isopropenyl-3a-methyl-7-oxo-1-Indanacetate (130). A. Preparation from 127 + 126: To a stirred solution of 3.0 g (9.8 mmol) of a mixture of unsaturated esters 127 (67%) and 126 (33%) in 20 mL of dry tert-butanol at room temperature under argon was added in 0.5 mL (0.5 mmol) of a 1 M solution of potassium t-butoxide in t-butanol. The reaction mixture was stirred for 30 min at room temperature and 0.1 g (1.67 mmol) of 98% acetic acid was added. The mixture was filtered through 70 g of silica gel (eluted with ethyl acetate-hexane, 1:5) and the filtrate was concentrated in vacuo. The residual liquid (3.42 g)
was chromatographed over 75 g of silica gel (eluted with ethyl acetate-hexane, 1:20) to give 1.38 g (46%) of bicyclic ester 128 and 1.08 g (36%) of mixture of bicyclic esters 129 and 130 which were separated by MPLC (Lobar size B: eluted with ethyl acetate-hexane, 1:50) to give 0.92 g (30%) of ester 129 and 0.16 g (5%) of ester 130.

B. Preparation from 127 using pyrrolidine as base: To a stirred solution of 84 mg (0.27 mmol) of ester 127 in 3 mL of dry tetrahydrofuran at 80°C (oil bath) was added 20 mg (0.28 mmol) of pyrrolidine and 1 mg of glacial acetic acid. The resulting solution was stirred under gentle reflux for 10 h and cooled to room temperature. The mixture was diluted with 30 mL of ether and washed with 5 mL of 5% aqueous hydrochloric acid. The ether layer was washed with 5 mL of water, 5 mL of saturated aqueous sodium bicarbonate and two 5-mL portions of brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with ethyl acetate-hexane, 1:20) to give 50 mg (60%) of ester 50 and 13 mg (15%) of ester 128.

C. Preparation from 127 using t-butoxide as base: To a stirred solution of 88 mg (0.29 mmol) of ester 127 in 1.0 mL of dry t-butanol and 1.5 mL of dry tetrahydrofuran at 60°C was added 0.23 mL (0.06 mmol) of a 0.25 M solution of potassium t-butoxide in t-butanol. The mixture was stirred for 30 min at 60°C, cooled to room temperature, and quenched with 5 mg (0.08 mmol) of glacial acetic acid. The mixture was diluted with 30 mL of ethyl ether, washed with 5 mL of saturated aqueous sodium bicarbonate, two 5-mL portions of brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed using MPLC (Lobar, size A; eluted with ethyl acetate-hexane, 1:40) to give 46 mg (52%) of ester 128, 13 mg (15%) of ester 129 and 7 mg (8%) of ester 130.

Preparation from 126 using t-butoxide as base: To a stirred solution of 74 mg (0.24 mmol) of ester 126 in 1.0 mL of dry t-butanol and 1.0 mL of dry
tetrahydrofuran at 60°C was added 0.2 mL (0.05 mmol) of a 0.25 M solution of potassium t-butoxide in t-butanol. The mixture was stirred for 3 h at 60°C, cooled to room temperature and quenched with 10 mg (0.17 mmol) of glacial acetic acid. The mixture was diluted with 30 mL of ethyl ether, washed 5 mL of saturated aqueous sodium bicarbonate solution, two 5-mL portions of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue (0.2 g) was chromatographed using MPLC (Lobar size A; eluted with ethyl acetate-hexane, 1:40) to give 48 mg (54%) of ester 128, 12 mg (14%) of ester 129 and 3.5 mg (4%) of ester 130. Ester 128: IR (neat) 1719 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 1.04 (s, 3H, CH$_3$), 1.35-2.52 (m with three s's at $\delta$ 1.48 (t-Bu), 1.60 (=CCH$_3$) and 1.73 (=CCH$_3$, 25H), 2.55 (d, $J = 10.5$ Hz, 1H), 3.41 (m, 1H, =CCH); $^{13}$C NMR (CDCl$_3$, 63 MHz) $\delta$ 20.2 (q), 22.3 (t), 22.7 (q), 25.9 (q), 28.1 (q), 28.9 (t), 33.4 (t), 37.6 (t) 40.8 (t), 43.1 (d), 47.8 (s), 64.5 (d), 80.7 (s), 131.2 (s), 135.1 (s), 169.2 (s), 213.6 (s); mass spectrum, m/e (relative intensity) 250 (M$^+$-C$_4$H$_8$), 232 (40), 217 (100), 189 (60), 177 (30), 111 (35), 57 (90). Ester 129: IR (neat) 1726, 1708, 1644, 895, 849 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 0.99 (s, 3H, CH$_3$), 1.32-1.8 (m with two s's at $\delta$ 1.36 (t-Bu) and 1.62 (=CCH$_3$), 19H), 1.90 (d, $J = 8$ Hz, 1H, HCC=O), 2.1 (m, 2H), 2.45 (m, 1H), 2.72 (d, $J = 11$ Hz, 1H, =CCH), 2.95 (m, 1H, HCCCHCO$_2$R), 4.76 (br s, 1H, =CH$_2$), 4.81 (br s, 1H, =CH$_2$); $^{13}$C NMR (CDCl$_3$, 63 MHz) $\delta$ 21.2 (q), 23.0 (t), 26.0 (q), 27.8 (q), 28.9 (t), 33.7 (t), 38.2 (t), 39.3 (t), 41.7 (d), 48.8 (s), 60.6 (d), 64.8 (d), 80.2 (s), 114.4 (t), 142.1 (s), 171.9 (s), 213.4 (s); mass spectrum, m/e (relative intensity) 306 (M$^+$), 250 (30), 233 (25), 204 (20), 191 (20), 164 (10), 151 (100), 137 (15), 111 (55), 93 (15), 81 (20), 67 (15), 57 (100); exact mass calcd for C$_{19}$H$_{30}$O$_3$ m/e 306.2190, found m/e 306.2195. Ester 130: IR (neat) 1722, 1644, 843, 800 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 1.00 (s, 3H, CH$_3$), 1.2-2.2 (m with two s's at $\delta$ 1.35 (t-Bu) and 1.69 (=CCH$_3$), 22H), 2.7 (m, 1H), 2.76 (d, $J = 11$ Hz, 1H,
=CCH), 2.95 (m, 1H, HCCCHCO₂R), 4.85 (br s, 2H, =CH₂); ¹³C NMR (CDCl₃, 63 MHz) δ 19.97 (q), 23.38 (t), 25.75 (q), 27.57 (t), 27.77 (q), 33.94 (t), 37.79 (t), 39.34 (t), 42.41 (d), 48.96 (s), 60.32 (d), 67.61 (d), 80.69 (s), 114.73 (t), 142.29 (s), 171.63 (s), 214.05 (s); mass spectrum, m/e (relative intensity) 306 (M⁺), 250 (10), 233 (15), 217 (10), 206 (15), 191 (20), 163 (10), 151 (30), 135 (15), 111 (25), 93 (10), 81 (10), 57 (100); exact mass calcd for C₁₉H₃₀O₃ m/e 306.2195, found m/e 306.2216.

1,1-Dimethylethyl (αR⁺,1R⁺,3aR⁺,7aS⁻)-Hexahydro-α-isopropyl-3a-methyl-7-oxo-1-indanacetate (121a). A solution of 0.52 g (1.7 mmol) of 129 and 70 mg of 10% palladium on charcoal in 5 mL of ethyl acetate was hydrogenated at 40 psi in a Parr hydrogenation apparatus at room temperature for 10 h. The mixture was filtered through a short column of Celite and the filtrate was concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with hexane-ethyl acetate, 10:1) to give 0.44 g (83%) of ester 52a as a colorless liquid: IR (neat) 1721 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.82 (d, J = 7 Hz, 3H, CH₃), 0.92 (d, J = 7 Hz, 3H, CH₃), 1.04 (s, 3H, CH₃), 1.46 (s, 9H, t-Bu), 1.36-2.30 (m, 12H, CH and CH₂ manifold), 2.5 (m, 1H, CH), 2.7 (m, 1H, CH); ¹³C NMR (CDCl₃, 63 MHz), δ 18.80 (q), 21.24 (q), 22.88 (t), 25.75 (q), 27.08 (t), 28.04 (d), 28.11 (q), 33.06 (t), 37.88 (t), 40.01 (t), 42.07 (d), 48.44 (s), 57.48 (d), 65.21 (d), 80.15 (s), 173.29 (s), 214.67 (s); mass spectrum m/e (relative intensity) 308 (M⁺), 252 (25), 234 (30), 219 (25), 206
(20), 191 (20), 151 (100), 135 (10), 111 (70); exact mass calcd. for C₁₉H₃₂O₃
m/e 308.2364, found m/e 308.2368.

1,1-Dimethylethyl (αR⁺,1R⁺,3aR⁺,7aS⁻)-Hexahydro-α-isopropyl-3a-
methy1-7-methylene-1-indanacetate (121b). A mixture of 0.54 g (1.5 mmol)
of methyltriphenylphosphonium bromide and 0.16 g (1.4 mmol) of potassium
tert-butoxide in 3 mL of toluene was stirred at room temperature under argon
for 3 h. followed by addition of 2 mL of dimethyl sulfoxide. The solution was
stirred for 1 h and a solution of 144 mg (0.47 mmol) of ketone 121a in 1 mL of
dimethyl sulfoxide was added via syringe. The resulting mixture was stirred at
60°C under argon for 4 h, cooled to room temperature, and diluted with 2 mL of
5% aqueous hydrochloric acid. The mixture was stirred at room temperature
for 1 h, diluted with 60 mL of dichlormethane, and washed with three 20-mL
portions of water. The combined aqueous washes were extracted with three
10-mL portions of ether. The combined organic phases were washed with 10
mL of saturated aqueous sodium bicarbonate, two 10-mL portions of brine,
dried (Na₂SO₄), and concentrated in vacuo. The residue was
chromatographed over 10 g of silica gel (eluted with hexane-ethyl acetate,
40:1) to give 140 mg (98%) of ester 121b as a pale yellow liquid: IR (neat)
1742, 1644, 890 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.88 (d, J = 7Hz, 6H,
CH₃), 0.93 (s, 3H, CH₃), 1.47 (s, 9H, t-Bu), 1.15-2.15 (m, 13H, CH and CH₂
manifold), 2.4 (m, 1H, CHCHCO₂R), 4.72 (br s, 1H, =CH₂), 4.76 (br s, 1H,
=CH₂); $^{13}$C NMR (CDCl₃, 63 MHz) δ 20.55 (q), 21.07 (q), 23.14 (t), 23.94 (t), 24.88 (q), 28.25 (q), 28.75 (d), 30.49 (t), 32.60 (t), 40.42 (t), 40.83 (d), 43.61 (s), 55.17 (d), 58.53 (d), 79.80 (s), 110.66 (t), 148.03 (s), 174.48 (s); mass spectrum, m/e (relative intensity) 306 (M+), 250 (20), 235 (40), 149 (100), 133 (20), 109 (38), 93 (35); exact mass calcd. for C₂₀H₃₄O₂ m/e 306.2491, found m/e 306.2531.

![Chemical Structure](image)

(β$^R$,1$^R$,3α$^R$,7α$^S$)-Hexahydro-β-isopropyl-3α-methyl-7-methyl-ene-1-indanethanol (121c). To a stirred solution of 115 mg (0.38 mmol) of ester 121b in 4 mL of ether at room temperature was added 84 mg (2.2 mmol) of lithium aluminum hydride. The mixture was warmed under reflux for 10 h, cooled to 0°C and quenched by dropwise addition of 1 mL of 3N aqueous hydrochloric acid. The mixture was diluted with 50 mL of ether and washed with two 10-mL portions of 5% aqueous hydrochloric acid and two 10-mL portions of water. The combined washes were extracted with three 10-mL portions of ether. The combined ether solutions were washed with 5 mL of saturated aqueous sodium bicarbonate, two 10-mL portions of brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with hexane-ethyl acetate, 20:1) to give 65 mg (74%) of alcohol 121c as a clear liquid: IR (neat) 3330, 1643, 1030, 890 cm⁻¹; $^1$H NMR (CDCl₃, 250 MHz) δ 0.85 (d, J = 7 Hz, 3H, CH₃), 0.89 (d, J = 7Hz, 3H, CH₃), 0.96 (s, 3H, CH₃), 1.15-1.97 (m, 12H), 2.05 (m, 2H), 2.2 (m, 1H) 3.67 (m,
2H, OCH₂), 4.61 (br s, 1H, =CH₂), 4.75 (br s, 1H, =CH₂); ¹³C NMR (CDCl₃, 63 MHz) δ 19.54 (q), 21.02 (q), 24.03 (t), 24.55 (t), 25.00 (q), 28.28 (d), 30.49 (t), 32.91 (t), 39.43 (d), 41.04 (t), 42.76 (s), 48.07 (d), 59.70 (d), 61.98 (t), 110.44 (t), 148.53 (s); exact mass calcd for C₁₆H₂₈O⁻ m/e 236.2162, found m/e 236.2151.

(aR⁺,1R⁺,3aR⁺,7aS⁻)-Hexahydro-α-isopropyl-3α-methyl-7-methyl-ene-1-indanacetic acid (121). To a stirred solution of 41 mg (0.17 mmol) of alcohol 121c in 4 mL of acetone at room temperature was added 0.2 mL (0.48 mmol) of Jones reagent. The solution was stirred at room temperature for 5 h followed by addition of 0.5 mL of saturated aqueous sodium bicarbonate. The mixture was concentrated in vacuo, diluted with 50 mL of ether, washed with two 10-mL portions of aqueous hydrochloric acid-glycine buffer (pH 3) and two 5-mL portions of brine. The combined aqueous washes were extracted with two 10-mL portions of ether. The combined ethereal layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 4 g of silica gel (eluted with hexane-ethyl acetate, 10:1) to give 29 mg (67%) of acid 121 as a yellow oil: IR (neat) 1702, 1644, 894 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.92 (d, J = 7 Hz, 3H, CH₃), 0.94 (d, J = 7 Hz, 3H, CH₃), 0.95 (s, 3H, CH₃), 1.25-2.27 (m, 13H), 2.45 (m, 1H), 4.74 (br s, 1H, =CH₂), 4.79 (br s, 1H, =CH₂) 10.5 (br s, 1H, CO₂H); ¹³C NMR (CDCl₃, 62.5 MHz) δ 20.62 (q), 20.91 (q), 23.81 (t), 24.00 (t), 24.89 (q), 28.44 (d), 30.62 (t), 32.91 (t), 40.18
1,1-Dimethylethyl (1R*,3aS*,7aR*)-Hexahydro-α-isopropylidene-3a-methyl-7-methylene-1-indanacetate (131). A flask was charged with 257 mg (0.72 mmol) of methyltriphenylphosphonium bromide, 77 mg (0.68 mmol) of potassium tert-butoxide, 2 mL of dry toluene and 1 mL of dry dimethyl sulfoxide. The mixture was stirred at room temperature for 8h. A solution of 56 mg (0.10 mmol) of ester 128 in 1 mL of tetrahydrofuran was added via cannula over a period of 30 min at room temperature. The mixture was stirred for 3h, 2 mL of 5% aqueous hydrochloric acid was added, and stirring was continued for 1h. The mixture was diluted with 40 mL of ether-hexane (1:1), washed with two 5-mL portions of saturated aqueous sodium bicarbonate, two 5-mL portions of brine, dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue (0.3 g) was chromatographed over 6 g of silica gel (eluted with ethyl acetate-hexane, 1:40) to give 38 mg (69%) of ester 131 as a pale yellow liquid: IR (neat) 1710 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) δ 0.97 (s, 3H, CH$_3$), 1.2 (m, 1H), 1.4-1.8 (m with three s's at δ 1.54 (t-Bu), 1.63 (=CCH$_3$) and 1.77 (=CCH$_3$), 21H), 2.0 (m, 1H), 2.15 (m, 2H), 2.35 (d, $J=10$ Hz, 1H, =CCH), 3.25 (ddd, $J=10$, 10, 7 Hz, 1H, =CCH), 4.65 (br s, 1H, =CH$_2$), 4.70 (br s, 1H, =CH$_2$); $^{13}$C NMR (CDCl$_3$, 62.5 MHz) δ 20.1 (q), 22.6 (q), 23.8 (t), 25.0 (q), 27.4 (t), 28.11 (q), 30.7 (t), 33.0 (t),

exact mass calcd for C$_{16}$H$_{26}$O$_2$ $m/e$ 250.1929, found $m/e$ 250.1931.
40.7 (t), 42.2 (d), 43.4 (s), 58.8 (d), 80.4 (t), 110.8 (t), 132.8 (s), 133.5 (s), 147.2 (s), 170.0 (s); mass spectrum, \( m/e \) (relative intensity) 248 (M$^+$-C$_4$H$_8$), 233 (100), 215 (30), 193 (45), 148 (40), 133 (40), 109 (60).

(1$R^*$,3$aS^*$,7$S^*$,7$aS^*$)-Hexahydro-7a-hydroxy-$\alpha$-isopropylidene-3a,7-dimethyl-1-indanacetic acid, $\gamma$-lactone (132). To a solution of 121 mg (0.40 mmol) of ester 131 in 1 mL of dichloro-methane was added in 1.5 g (13 mmol) of trifluoroacetic acid in one portion. The resulting mixture was stirred for 10 h at room temperature, diluted with 40 mL of ethyl ether, washed with three 5-mL portions of saturated aqueous sodium bicarbonate, two 5-mL portions of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue (0.12 g) was chromatographed over 5 g of silica gel (eluted with ethylacetate-hexane, 1:20) to give 86 mg (87%) of lactone 132 as a pale yellow solid: mp 90-93$^\circ$C; IR (CHCl$_3$), 1750, 1660 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 0.72 (d, $J = 7$ Hz, 3H, CH$_3$), 1.0 (m, 1H), 1.08 (s, 3H, CH$_3$), 1.3-1.8 (m, 8H), 1.85 (s, 3H, =CCH$_3$), 1.88 (m, 1H), 2.19 (s with underlying m, 4H, =CCH$_3$), 3.18 (br d, $J = 10$ Hz, 1H, =CCH); $^{13}$C NMR (CDCl$_3$, 62.5 MHz) $\delta$ 15.9 (q), 19.4 (q), 19.7 (q), 21.1 (t), 24.0 (q), 30.6 (t), 32.3 (t), 35.0 (d), 35.2 (t), 38.0 (t), 42.2 (d), 45.4 (s), 96.1 (s), 128.9 (s), 147.5 (s), 170.7 (s); mass spectrum, \( m/e \) (relative intensity) 248 (M$^+$), 233 (40), 215 (15), 187 (15), 177 (35), 149 (50), 135 (15), 123 (20), 109 (100), 95
(30), 81 (30), 67 (25), 55 (40); exact mass calcd for C_{16}H_{24}O_{2} m/e 248.1802, found m/e 248.1977.

(1R^*,3aR^*,7aS^*)-Hexahydro-α-isopropylidene-3a-methyl-7-oxo-1-indanacetic acid (133). To a stirred solution of 1.46 g (4.77 mmol) of bicyclic ester 128 in 10 mL of dry methylene chloride was added in 5.47 g (40 mmol) of trifluoroacetic acid in one portion at room temperature. The reaction mixture was stirred at room temperature for 4 h and concentrated in vacuo. The residue was dilute with 30 mL of ether and extracted with three 10-mL portions of saturated aqueous sodium bicarbonate solution. The combined aqueous layers were acidified at 0°C using concentrated aqueous hydrochloric acid. The aqueous layer was extracted with four 30-mL portions of ether. The combined etheral extracts were washed with three 10-mL portions of brine, dried (Na_{2}SO_{4}) and concentrated in vacuo. The residual solid was recrystallized from hexane-ether (5:1) to give 0.94 g (78%) of acid 133: mp 133-135°C; IR (CHCl_{3}) 1690 cm^{-1}; 1H NMR (CDCl_{3}, 250 MHz) δ 1.05 (s, 3H, CH_{3}), 1.38-2.48 (m with two s's at δ 1.68 and 1.84 (=CCH_{3}), 16H), 2.54 (d, J = 10.8 Hz, 1H, CHC=O), 3.43 (m, 1H, =CCH), 11.23 (br s, 1H, CO_{2}H); 13C NMR (CDCl_{3}, 62.5 MHz) δ 20.9 (q), 21.9 (t), 23.4 (q), 26.3 (q), 29.3 (t), 33.9 (t), 37.5 (t), 40.6 (t), 43.6 (d), 46.5 (s), 64.1 (d), 129.1 (s), 140.3 (s), 173.6 (s), 215.3 (s); mass spectrum, m/e (relative intensity) 250 (M^{+}), 232 (28), 217 (100), 204 (38),
189 (76), 161 (38), 111 (50); exact mass calcd for $\text{C}_{15}\text{H}_{22}\text{O}_3$ $m/e$ 250.1569, found $m/e$ 250.1609; Anal calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_3$: C, 72.00; H, 8.80. Found: C, 71.91; H, 8.80.

(1$R^*$,3a$R^*$,7a$S^*$)-Hexahydro-$\alpha$-isopropylidene-3a-methyl-7-methylene-1-indanacetic acid (134). A flask charged 2.71 g (7.6 mmol) of methyltriphenylphosphonium bromide, 0.84 g (7.5 mmol) of potassium t-butoxide and 15 mL of dry toluene was stirred at room temperature under argon for 3 h. To this yellow mixture was added via cannula a solution of 0.93 g (3.74 mmol) of acid 133 and 90 mg (3.74 mmol) of oil-free sodium hydride in 3 mL of dry tetrahydrofuran. The resulting mixture was stirred at room temperature for 1 h and 15 mL of 5% aqueous hydrochloric acid was added. The mixture was diluted with 100 mL of ether. The ethereal layer was washed with two 10-mL portions of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate-hexane 1:5) to give 0.84 g (91%) of acid 134 as an oily liquid: IR (neat) 1680, 900 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 0.98 (s, 3H, CH$_3$), 1.18-2.15 (m with two s's at $\delta$ 1.73 (=CCH$_3$) and 1.92 (=CCH$_3$), 16 H, CH$_2$ manifold), 2.40 (d, $J=10.5$ Hz, 1H, =CCH), 3.32 (ddd, $J=10.5$, 10.0, 7.0 Hz, 1H, =CCH), 4.63 (br s, 1H =CH$_2$), 4.69 (br s, 1H, =CH$_2$), 11.81 (br s, 1H, CO$_2$H); $^{13}$C NMR (CDCl$_3$, 62.5 MHz) $\delta$ 21.2 (q), 23.4 (q), 23.8 (t), 25.0 (q), 27.8 (t), 30.7 (t), 33.3
(t), 40.5 (t), 42.2 (d), 43.4 (s), 58.8 (d), 110.9 (t), 130.6 (s), 139.5 (s), 147.1 (s), 176.0 (s); mass spectrum, \( m/e \) (relative intensity) 248 (M\(^+\)), 233 (100), 215 (40), 187 (35), 107 (80), 93 (80), 79 (70); exact mass calcd for \( \text{C}_{16}\text{H}_{24}\text{O}_2 \) \( m/e \) 248.1775, found \( m/e \) 248.1775.

![3-Methyl-2-butenoyl azide (137)](image)

3-Methyl-2-butenoyl azide (137). To a stirred mixture of 22.8 g (0.35 mol) of sodium azide in 80 mL of dry acetone (freshly distilled from calcium chloride) at 0°C was added a solution of 20.2 g (0.17 mmol) of acyl chloride 136 in 20 mL of dry acetone over a period of 15 min. The resulting mixture was stirred at 0°C for 3 h and then warmed to room temperature. The solids were removed by filtration and the clear filtrate was concentrated in vacuo. The residue (20 g) was diluted with 100 mL of petroleum ether (bp 36-60°C), washed with three 10-mL portions of brine, dried \( \text{Na}_2\text{SO}_4 \) and concentrated in vacuo to give 19.2 g (90%) of azide 137 as a clear liquid: IR (neat) 2130, 1690, 1640 cm\(^{-1}\); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \( \delta \) 1.51 (s, 3H, \( \text{CH}_3 \)), 2.19 (s, 3H, \( \text{CH}_3 \)), 5.54 (s, 1H, HC\(=\)); \(^{13}\)C NMR (63 MHz, CDCl\(_3\)) \( \delta \) 20.61 (q), 27.14 (q), 117.43 (d), 161.27 (s), 170.91 (s).
2-Methylpropenyl Isocyanate (138). Neat acyl azide 137 (3.10 g; 24.8 mmol) was heated under argon at 75°C for 1.5 h until hydrogen evolution stopped to give 2.40 g (99%) of isocyanate 138 as a deep yellow oil which was used in the next reaction immediately: IR (neat) 2260, 1580 cm\(^{-1}\); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta 1.65 (d, J = 0.4 \text{ Hz}, 3\text{H, CH}_3), 1.70 (d, J = 0.4 \text{ Hz}, 3\text{H, CH}_3), 5.67 (\text{br s, 1H, HC=})\); \(^1\)C NMR (63 MHz, CDCl\(_3\)) \(\delta 17.13 (q), 20.81 (q), 111.47 (d), 123.30 (s), 130.47 (s)\).

N-2-Methyl-1-propenylformamide (139). To a stirred solution of 2.40 g (2.47 mmol) of isocyanate 138 in 50 mL of dry tetrahydrofuran at -78°C under argon was added in 24.8 mL (24.8 mmol) of 1.0 M lithium triethylborohydride in tetrahydrofuran over a period of 1.5 h. The mixture was stirred at -78°C for 1 h, followed by the addition of 3.0 g (50 mmol) of glacial acetic acid. The mixture was warmed to room temperature, diluted with 100 mL of ethyl ether, washed with two 10-mL portions of saturated aqueous sodium bicarbonate, two 10-mL portions of brine, dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The residue (2.0 g) was chromatographed over 80 g of silica gel (eluted with ethyl acetate-hexane, 1:3.3) to give 1.51 g (62%) of formamide 139 as a clear liquid. This
material was a 2.3:1 mixture of geometrical isomers by integration of selected peaks in the $^1$H NMR spectrum of the mixture. The $^{13}$C NMR of this mixture also showed one major isomer and one minor isomer: IR (neat) 3283, 1673, 1516 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 1.6-1.8 (m, 6H, CH$_3$), 6.08 (d, $J$ = 11 Hz, 0.3H, HC=), 6.55 (d, $J$ = 11 Hz, 0.7H, HC=), 7.30 (br s, 0.7H, NH), 7.90 (br s, 0.3H, NH), 8.06 (br s, 0.7H, HC=O), 8.19 (d, $J$ = 11 Hz, 0.3H, HC=O). $^{13}$C NMR (63 MHz, CDCl$_3$, major isomer) $\delta$ 16.8 (q), 22.08 (q), 114.94 (d), 117.69 (s), 158.61 (d); mass spectrum, m/e (relative intensity) 99 (M$^+$), 82 (60), 70 (95), 56 (100), 41 (80); exact mass calcd. for C$_5$H$_9$NO m/e 99.0684, found m/e 99.0674.

![140]

1-[(1$R^*$,3a$R^*$,7a$S^*$)-Hexahydro-3a-methyl-7-methylene-1-indanyl]-2-methylpropenyl Isocyanate (140). To a stirred solution of 142 mg (0.57 mmol) of acid 134 in 2.0 mL of dry tetrahydrofuran under argon at room temperature was added 13.7 mg (0.57 mmol) of oil-free sodium hydride. The mixture was stirred for 10 min at room temperature, cooled to 0°C, and a solution of 165 mg (0.60 mmol) of diphenylphosphoryl azide in 10 mL of dry tetrahydrofuran was added in one portion at 0°C. The mixture was stirred at 0°C for 1 h and at room temperature for 10 h. The mixture was diluted with 40 mL of ether, washed with two 5-mL portions of 2% aqueous hydrochloric acid, two 10-mL portions of brine, dried (Na$_2$SO$_4$) and concentrated in vacuo. The
residue (263 mg) was chromatographed over 3 g of silica gel (eluted with ether-hexane, 1:20) to give 108 mg (77%) of isocyanate 140 as a colorless liquid: IR (neat) 2240, 900, 800 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 1.01 (s, 3H, CH₃), 1.28 (m, 1H), 1.45-1.8 (m with two s's at δ 1.62 (=CCH₃) and 1.75 (=CCH₃), 13H, δ), 1.85-2.2 (m, 3H), 3.38 (ddd, J = 10.7, 10.0, 6.5 Hz, 1H, =CCH), 4.58 (br s, 1H, =CH₂), 4.70 (br s, 1H, =CH₂); ¹³C NMR (CDCl₃, 62.5 MHz) δ 19.1 (q), 20.7 (q), 23.6 (t), 24.9 (q), 26.3 (t), 30.7 (t), 33.1 (t), 40.5 (t), 43.5 (s), 43.5 (d), 58.6 (d), 110.8 (t), 121.9 (s), 124.8 (s), 126.0 (s), 146.4 (s); mass spectrum, m/e (relative intensity) 245 (M⁺), 230 (60), 189 (30), 174 (30), 123 (100), 109 (50); exact mass calcd for C₁₆H₂₃NO m/e 245.1780, found m/e 245.1771.

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\text{\chem{\text{NHCHO}}}
\]

6

N-[1-[(1\text{R}^*,3\text{aR}^*,7\text{aS}^*)-\text{Hexahydro-3a-methyl-7-methylene-1-indanyl}]-2-methylpropen-yl]formamide (6). To a stirred solution of 0.54 g (2.21 mmol) of isocyanate 140 in 20 mL of dry tetrahydrofuran at -78°C under argon was added 2.3 mL (2.3 mmol) of 1.0 M of lithium triethylborohydride in tetrahydrofuran. The mixture was stirred at -78°C for 1 h and 3 mL of saturated aqueous sodium bicarbonate was added. The mixture was warmed to room temperature, diluted with 40 mL of ether, washed with three 5-mL portions of brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with ethyl acetate-hexane, 1:5)
to yield 0.50 g (91%) of formamide 6 which slowly solidified. This material was a 3:1 mixture of geometrical isomers by integration of selected peaks in the $^1$H NMR spectrum of the mixture. The $^{13}$C NMR of this mixture also showed one major isomer and one minor one: mp 95-105°C; IR (CHCl$_3$) 3380, 1680, 900 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 0.95 and 0.96 (two s, 3H, CH$_3$ of major and minor isomer, respectively), 0.9-2.12 (m with two s's at $\delta$ 1.70 and 1.72 (=CCH$_3$), 17H), 3.33-3.45 (m, 1H, =CCH), 4.51 (br s, 0.75H, =CH$_2$), 4.57 (br s, 0.25H, =CH$_2$), 4.70 (br s, 1H, =CH$_2$), 6.32 (br s, 0.25H, NH), 6.77 (br d, $J$ = 11 Hz, 0.75H, NH), 7.84 (d, $J$ = 11 Hz, 0.75H, CHO), 8.22 (d, $J$ = 1 Hz, 0.25H, CHO); $^{13}$C NMR (CDCl$_3$, 62.5 MHz, major isomer) $\delta$ 19.69 (q), 20.55 (q), 23.88 (t), 24.91 (q), 25.99 (t), 30.74 (t), 33.64 (t), 40.17 (t), 42.65 (d), 43.19 (s), 57.83 (d), 110.58 (t), 128.30 (s), 129.31 (s), 146.89 (s), 166.15 (d); $^{13}$C NMR (CDCl$_3$, 62.5 MHz, minor isomer) $\delta$ 19.61 (q), 20.95 (q), 23.81 (t), 25.05 (q), 26.17 (t), 30.64 (t), 33.55 (t), 40.53 (t), 43.12 (d), 43.19 (s), 58.21 (d), 110.58 (t), 126.32 (s), 130.12 (s), 147.10 (s), 159.56 (d); mass spectrum, $m/e$ (relative intensity) 247 (M$^+$), 232 (20), 204 (40), 187 (100), 159 (30), 109 (55); exact mass calcd for C$_{16}$H$_{25}$NO $m/e$ 247.1936; found $m/e$ 247.1952. Anal. calcd. for C$_{16}$H$_{25}$NO: C, 77.73; H, 10.12. Found: C, 77.58; H, 10.19.

![Diagram](4)

1-[(1$R^*$,3a$R^*$,7a$S^*$)-Hexahydro-3a-methyl-7-methylene-1-indanyl]-2-methylpropenyl Isonitrile (4). To a solution of 344 mg (1.39 mmol) of
formamide 6 in 5 mL of dry pyridine was added 535 mg (2.8 mmol) of p-toluenesulfonyl chloride at room temperature. The mixture was stirred at room temperature for 15 h. cooled to 0°C and 3 g of crushed ice was added. The mixture was stirred at 0°C for 30 min, diluted with 50 mL of petroleum ether-ethyl ether, (1:1), washed with three 10-mL portions of 3% aqueous hydrochloric acid and two 10-mL portions of brine. Combined aqueous layers were extracted with three 15-mL portions of petroleum ether. Organic layers were combined, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with petroleum ether, bp 35-60°C) to give 0.32 g (100%) of isonitrile 4 as a pale yellow solid: mp 61-63°C; IR (neat) 2100, 1640, 900 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 1.00 (s, 3H, CH₃), 1.25-2.2 (m with two s's at δ 1.67 and 1.89 (=CHCH₃), 17H, CH₂ manifold), 3.20 (br ddd, J = 11.0, 10.0, 6.0 Hz, 1H, =CCH), 4.62 (br s, 1H, =CH), 4.69 (br s, 1H, =CH₂); ¹³C NMR (CDCl₃, 62.5 MHz) δ 19.06 (q), 21.61 (q), 23.64 (t), 24.76 (q), 26.32 (t), 30.69 (t), 33.48 (t), 40.28 (t), 41.69 (d), 43.19 (s), 58.21 (d), 111.05 (t), 124.35 (s), 134.28 (s), 145.99 (s), 161.99 (s); mass spectrum, m/e (relative intensity) 229 (M⁺), 214 (100), 186 (45), 134 (30), 107 (65), 93 (85), 79 (65); exact mass calcd for C₁₆H₂₃N m/e 229.1842, found m/e 229.1841.
1-[(1R*,3aR*,7aS*)-Hexahydro-3a-methyl-7-methylene-1-indanyl]-2-methylpropenyl Isothiocyanate (5). A mixture of 204 mg (0.89 mmol) of isonitrile 4 and 45 mg (1.4 mmol) of sulfur powder was heated at 120°C under argon for 10 h. Mixture was cooled to room temperature diluted with 30 mL of petroleum ether, stirred for 10 min, washed with two 5-mL portions of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue (0.24 g) was chromatographed over 10 g of silica gel (eluted with petroleum ether, bp 35-60°C) to give 166 mg (71%) of thioisocyanate 5 as a yellow oil: IR (neat) 2080, 900 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 1.01 (s, 3H, CH$_3$), 1.24-2.2 (m with two s's at $\delta$ 1.65 and 1.82 (=CCH$_3$), 16H), 3.32 (ddd, $J = 11.0, 10.0, 6.0$ Hz, 1H, =CCH), 4.61 (br s, 1H, =CH$_2$), 4.70 (br s, 1H, =CH$_2$); $^{13}$C NMR (CDCl$_3$, 62.5 MHz) $\delta$ 19.2 (q), 21.2 (q), 23.6 (t), 24.9 (q), 26.4 (t), 30.6 (t), 33.0 (t), 40.3 (t), 43.3 (d), 43.4 (s), 58.5 (d), 111.0 (t), 126.2 (s), 130.8 (s), 131.6 (s), 146.0 (s); mass spectrum, $m/e$ (relative intensity) 261 (M$^+$), 246 (15), 228 (15), 203 (100), 139 (40), 109 (30), 93 (30), 79 (30), 69 (40); exact mass calcd for C$_{16}$H$_{23}$NS $m/e$ 261.1581, found $m/e$ 261.1578.
Bibliography


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LCS-1-210 (250 MHz, CDCl₃)

72

LCS-1-210 (250 MHz, CDCl₃)
LCS-1-259 (250 MHz, CDCl₃)
LCS-1-259 TRANS C13 BB AND DEPT AM-250-2

LCS-1-259 (63 MHz, CDCl₃)

69

CO₂Et

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

PPM
LCS-1-259 (250 MHz, CDCl₃)
LCS-1-259 (63 MHz, CDCl₃)
LCS-1-284 (250 MHz, CDCl₃)
LCS-1-284 C13 BB AND DEPT

LCS-1-284 (63 MHz, CDCl₃)

42
LCS-1-226 (250 MHz, CDCl₃)
LCS-1-226 C13 88 AND DEPT AM-250-2

LCS-1-226 (63 MHz, CDCl₃)

82
LCS-1-211 (250 MHz, CDCl₃)
LCS-1-211 C13 BB AND DEPT AM-250-2

LCS-1-211 (63 MHz, CDCl₃)

* = impurity
85 $E = \text{CO}_2\text{Et}$

LCS-1-225 (200 MHz, CDCl$_3$)
85 \( E = \text{CO}_2\text{Et} \)

LCS-1-225 (63 MHz, CDCl$_3$)
LCS-1-232 (250 MHz, CDCl₃)

* = impurity
EtO₂C

\[
\text{LCS-1-232 (63 MHz, CDCl}_3\text{)}
\]
LCS-1-228 (250 MHz, CDCl₃)

86 (E = CO₂Et)
LCS-1-228 C13 BB AND DEPT

86 (E = CO₂Et)

LCS-1-228 (63 MHz, CDCl₃)
INTEGRAL
LCS-1-238 (E = CO$_2$Et)
LCS-1-238 (250 MHz, CDCl$_3$)
99 (E = CO$_2$Et)

LCS-1-238 (63 MHz, CDCl$_3$)

*= major isomer
o = minor isomer

PPM

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
LCS-3-23 H1 AM-250-2

LCS-3-23 (250 MHz, CDCl₃)
LCS-1-248 (250 MHz, CDCl₃)

101 E = CO₂Et

E

SMe

SMe

PPM
LCS-1-248 C13 BB AND DEPT

101 $E = \text{CO}_2\text{Et}$

LCS-1-248 (63 MHz, CDCl$_3$)
103 $E = \text{CO}_2\text{Et}$

LCS-1-256H (250 MHz, CDCl$_3$)

(impure from cuprate)
103 $E = \text{CO}_2\text{Et}$

LCS-1-256H (63 MHz, CDCl$_3$)

* = impurity
103 \ E = \text{CO}_2\text{Et}

LCS-2-102 (250 MHz, CDCl$_3$)
(from conjugate addition)
103  $E = \text{CO}_2\text{Et}$

LCS-2-102 (63 MHz, CDCl$_3$)
(from conjugate addition)
113
LCS-2-050 (300 MHz, CDCl₃)
LCS-2-55A Hi AM-250

109

LCS-2-55A (250 MHz, CDCl₃)
LCS-2-55A C13 BB AND DEPT AN-250-2

109

LCS-2-55A (63 MHz, CDCl₃)
LCS-2-35B C13 BB AND DEPT AK-250-2

110 LCS-2-55B (63 MHz, CDCl₃)
E-118
LCS-2-056A (250 MHz, CDCl₃)
E-118
LCS-2-056A (63 MHz, CDCl₃)
Z-118
LCS-2-056B (250 MHz, CDCl₃)
Z-118

LCS-2-056B (63 MHz, CDCl₃)
LCS-2-99E H1 AN-250-2

E-117

LCS-2-99E (250 MHz, CDCl₃)
LCS-2-99E C13 BB AND DEPT AM-250-2

$E-117$

LCS-2-99E (63 MHz, CDCl$_3$)
Z-117

LCS-2-66 (250 MHz, CDCl₃)
Z-117
LCS-3-67Z (63 MHz, CDCl₃)

CH₂ only

CH and CH₃
LCS-2-18C C13 BB AND DEPT AN-250-2

116

LCS-2-18C (63 MHz, CDCl₃)
LCS-02-67A (250 MHz, CDCl₃)

119
LCS-02-67A (63 MHz, CDCl₃)

119

LCS-2-67A (63 MHz, CDCl₃)
LCS-2-97B (250 MHz, CDCl₃)
LCS-2-97B C13 BB AND DEPT AM-250-2

LCS-2-97B (63 MHz, CDCl₃)

120
LCS 3-3 (63 MHz, CDCl₃)

119a

LCS 3-3 C13 BB AND DEPT AM-250-2

[Chemical structure diagram]
LCS 3-4 (63 MHz, CDCl₃)

119b

LCS 3-4 H1 AM-250-2
LCS 3-4 (250 MHz, CDCl₃)

119b

LCS 3-4 C13 BB AND DEPT AM-255-2
LCS 2-187 (250 MHz, CDCl₃)
Me₃Si\(\text{CO}_2\)-t-Bu

123

LCS 2-187 (63 MHz, CDCl₃)
INTEGRAL.

LCS-3-014-Z ISOMER H1 AM-250

LCS 3-014-Z (250 MHz, CDCl₃)
LCS 3-014-Z (63 MHz, CDCl₃)

* = impurity
LCS-2-265E C13 BB AND DEPT AM-250-2

PPM

165.378
9.145.419
1.145.419
9.129.238
9.139.238
1.144.261
1.144.261
1.37.614
1.37.614
0.0.77.210
0.0.77.210
0.22.882
0.22.882
1.14.501
1.14.501
1.22.571
1.22.571

LCS 2-265E (63 MHz, CDCl₃)
LCS-2-191Z (250 MHz, CDCl₃)
LCS-2-191Z C13 88 AND DEPT AN-250-2

LCS-2-191Z (63 MHz, CDCl₃)

126
LCS-2-267E (250 MHz, CDCl₃)
LCS-2-267E (63 MHz, CDCl₃)
LCS-3-21C (250 MHz, CDC\(_3\))
128

LCS-3-21C (63 MHz, CDCl₃)
LCS-2-197A (300 MHz, CDCl₃)

129

LCS-2-197A (300 MHz, CDCl₃)
LCS-2-197A (75 MHz, CDCl₃)

129

LCS-2-197A (75 MHz, CDCl₃)
LCS-2-157B (250 MHz, CDCl₃)

130
LCS-2-157B C13 BB AND DEPT AM-250-2

130

LCS-2-157B (63 MHz, CDCl₃)
LCS-3-028 (250 MHz, CDCl₃)
121a
LCS-3-028 (83 MHz, CDCl₃)
LCS-3-30 (250 MHz, CDCl₃)
LCS-3-30 (63 MHz, CDCl₃)

121b

LCS-3-30 BB AND DEPT AM-250.2
LCS-3-63 H1 AH-250-2

121c
LCS-3-63 (250 MHz, CDCl₃)
LCS-3-63 (63 MHz, CDCl₃)

* = impurity
LCS-3-66 (250 MHz, CDCl₃)
LCS-3-66 (63 MHz, CDCl₃)

* = impurity
131
LCS-3-27 (250 MHz, CDCl₃)
LCS-3-27 (63 MHz, CDCl₃)
LCS-2-138 C13 BB AND DEPT AN-250-2

LCS-2-138 (63 MHz, CDCl3)

PPM

99.122

87.966

77.904

65.379

52.160

43.999

32.258

30.673

23.356

13.147

10.388

15.957
LCS-2-198 (250 MHz, CDCl₃)
LCS-2-198 C13 BB AND DEPT AM-250

LCS-2-198 (63 MHz, CDCl₃)

133
LCS-2-199 (250 MHz, CDCl₃)
* = Et₂O
LCS-2-199 (63 MHz, CDCl₃)

*= Et₂O
LCS-2-156 (250 MHz, CDCl₃)

* = impurity
137
LCS-2-156 (63 MHz, CDCl₃)
* = impurity
LCS-2-167 ISOCYANATE H1 AM250

LCS-2-167 (250 MHz, CDCl₃)
LCS-2-167 C13 BB AND DEPT AM-250-2

PPM

LCS-2-167 (63 MHz, CDCl₃)
LCS-2-167 (250 MHz, CDCl$_3$)

* = impurity
LCS-2-167 C13 BB AND DEPT AH-250-2

LCS-2-167 (63 MHz, CDCl₃)

* = impurity
LCS-2-209 (250 MHz, CDCl₃)
LCS-2-209 (63 MHz, CDCl₃)
LCS-2-212 (250 MHz, CDCl₃)
(geometrical isomers)
LCS-2-212 (63 MHz, CDCl₃)

(geometrical isomers)
LCS-2-242 (250 MHz, CDCl₃)
LCS-2-242 C13 BB AND DEPT AN-250-2

LCS-2-242 (63 MHz, CDCl₃)

4

N=C

PPM
LCS-2-246 (250 MHz, CDCl₃)
LCS-2-246 C13 BB AND DEPT AM-250-2

LCS-2-246 (63 MHz, CDCl₃)