Preparation of 6-cyclopentyl derivatives of 2-naphthalenone

Bonnie Ann Bukwa
The University of Montana

Follow this and additional works at: https://scholarworks.umt.edu/etd
Let us know how access to this document benefits you.

Recommended Citation
https://scholarworks.umt.edu/etd/3289

This Thesis is brought to you for free and open access by the Graduate School at ScholarWorks at University of Montana. It has been accepted for inclusion in Graduate Student Theses, Dissertations, & Professional Papers by an authorized administrator of ScholarWorks at University of Montana. For more information, please contact scholarworks@mso.umt.edu.
THE PREPARATION OF 6-CYCLOPENTYL DERIVATIVES OF 2-NAPHTHALENONE

by

BONNIE A. BUKWA

B.S. Michigan Technological University, 1964

Presented in partial fulfillment of the requirements for the degree of

Master of Science

UNIVERSITY OF MONTANA

1966

Approved by:

[Signatures]

[Position]

[Date] 1967
ACKNOWLEDGMENTS

I wish to express my gratitude to my advisor, Dr. R. E. Juday, for his guidance and suggestions throughout this project, which was sponsored by a research grant from the National Cancer Institute, National Institute of Health, U. S. Public Health Service.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>ACKNOWLEDGMENTS</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>II. ANDROGEN ANALOGS LACKING RING C.</td>
<td>4</td>
</tr>
<tr>
<td>III. SYNTHESIS OF ANDROGEN ANALOGS WITH</td>
<td></td>
</tr>
<tr>
<td>FIVE MEMBERED RING D</td>
<td>9</td>
</tr>
<tr>
<td>IV. EXPERIMENTAL</td>
<td>27</td>
</tr>
<tr>
<td>V. SUMMARY</td>
<td>41</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>48</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

The purpose of this research was to synthesize compounds 1, 2, 3, and 4, as possible cancer chemotherapeutic agents. These compounds will be tested for steroid hormone activity and hormone antagonist activity. Such compounds would also be of interest in obtaining more information concerning the relationship between structure and biological activity of steroid analogs lacking ring C.

1 (α,β-unsaturated C=O) 3 (α,β-unsaturated C=O)
2 (β,γ-unsaturated C=O) 4 (β,γ-unsaturated C=O)
The discovery of the hormone dependence of certain cancers led to the synthesis of many natural and synthetic steroids with biological activity. Naturally occurring androgens and estrogens have caused remissions in patients with cancer of the breast and prostate, and this prompted the study of related steroids for their effects on the growth of tumors and human cancer. It was found that certain hormones can be of great significance in the maintenance of four neoplasms—those of the breast, the prostate, the thyroid gland, and the lymphomas.

Potential synthetic estrogens have been made containing phenyl, hydronaphthalene, and hydrophenanthrene nuclei. The effect of estrogens in the control of mammary cancer may be due, in part, to inhibition of the pituitary. Androgens, in addition to pituitary inhibition, also exhibit an antagonistic effect toward estrogens in controlling the growth of mammary cancer. It was this antiestrogenic effect that first prompted the investigation of the androgens as possible cancer chemotherapeutic agents.

Associated with the antitumor effect of the androgen or estrogen were certain toxic effects, e.g., virilization or feminization, depending on the hormone used, and fluid retention. It was hoped that related compounds could be found possessing the desired antitumor effects, which would not stimulate the development of the undesirable sex characteristics.

The compound Δ4-testololactone, which represents a variation on the steroid nucleus, was found to be hormonally inactive but effective in modifying the course of breast cancer. Other examples
of compounds producing temporary remission are: dihydrotestosterone, 17α-vinyltestosterone, 19-nortestosterone, and 9α-fluoro-11β-hydroxy-17α-methyltestosterone.7

It was found that the introduction of a 2α-methyl group into dihydrotestosterone and similar compounds lead to the formation of very potent androgenic, anabolic, and anti-breast-tumor agents. However, when fluorine was substituted in the 2α-position there was a reduction in primary hormone activity, even though fluorine is much closer in size to the original hydrogen atom than is the methyl group. The compound 2α-fluorodihydrotestosterone acetate was inactive as an androgen, yet was quite active in inhibiting mammary cancer as well as being a potent anabolic agent. This illustrates the variation of biological activity with structure. This compound has practically the same shape and size as active androgens, yet it shows low primary hormonal activity while retaining secondary characteristics.8

Since less work has been done on androgen analogs than estrogen analogs, preparation of several synthetic analogs of androgen was undertaken. It is hoped that structural modification with retention of molecular shape and size will result in increased anticancer activity and a decrease in undesirable side effects. Accordingly, the 6-cyclopentyl derivatives 1, 2, 3 and 4 of androgen analogs lacking ring C were synthesized. Since it was not possible to separate compound 1 from compound 2 or compound 3 from compound 4, the two samples submitted for bioassay were mixtures of 1 and 2 and of 3 and 4.
II. ANDROGEN ANALOGS LACKING RING C

Androgenic hormones have the basic structure 5, consisting of rings A, B, C and D, with angular methyls at C_{10} and C_{13}. R' is usually a carbonyl or hydroxyl group, and there is an \( \alpha \), \( \beta \)-unsaturated ketone at C_3. 10

\[
\text{CH}_3 \quad R' \\
5
\]

A number of steroid analogs lacking ring C have been prepared with a six membered D ring. Wilds and Shunk synthesized compound 6 which closely resembles testosterone. 11 It was found to be weakly androgenic. They also synthesized analogs of progesterone and deoxycorticosterone (7a,b) lacking the angular methyl groups. 12 The A ring was closed on the B,D bicyclohexyl system using an improved Robinson-Mannich base procedure for the synthesis of \( \alpha \), \( \beta \)-unsaturated cyclic ketones. Wilds and coworkers later synthesized two more analogs of testosterone (8a,b) using the same procedure. 13 The compounds were
feebly androgenic, but were not tested for hormone antagonist activity.

Other analogs lacking ring C have been prepared by adding the D ring to the A, B ring system using derivatives of 4,4-tetralone as starting materials. Derivatives of 1-ethyl-2-benzylnapthalene (9a,b) showed some estrogenic activity at the 1 mg. level.

In order to study the effect of varying the C₂ alkyl substituent and the C₆ ring on biological activity, a number of 6-cyclohexyl and 6-phenyl derivatives of 2-naphthalenone were prepared. The two compounds that showed some biological activity (10 and 11) had C₅ ethyl substituents. Corresponding compounds lacking the ethyl
group were inactive. Compound 10 was found to be antiestrogenic while compound 11 was weakly estrogenic. It was suggested that such a group is in itself essential for activity, or that its function is to change the shape of the molecule by twisting the adjacent ring so it no longer lies in the general plane of the rest of the molecule.

Although most research has been directed toward the preparation of six membered D ring systems, several analogs with a five membered D ring have been prepared. Koebner and Robinson prepared the substituted cyclopentanones (12) with R = phenyl, β-naphthyl, 6-methoxy-2-naphthyl, or halogenated derivatives. They prepared the substituted cyclopentenone ring by condensing ethyl phenacyl bromide with the sodio derivative of ethyl propanoylacacetate, followed by hydrolysis with alcoholic sodium hydroxide. By selective hydrogenation this can be reduced to the substituted cyclopentanone. These compounds were not bioassayed; the authors intended them for modifications of 18-norequilenin in the methyl ether series.
Wilds cyclized 1,4 diketones of type 13 to cyclopentanone derivatives 14. Wilds and Johnson also synthesized 3-(hydroxyphenyl)-cyclopentanone-l (15a) and the related compound 15b.

Two recently prepared compounds (16 and 17) proved antiandrogenic when bioassayed, however, the related compound 18 was inactive. Compounds 1,2,3 and 4, whose preparation is described herein, are the cyclopentanol analogs of compounds 16 and 17. Thus it was hoped that they might show biological activity equal to or greater than that of the related ketones.
The compound 6-methoxy \( \alpha \)-tetralone (19) was chosen as the basic starting material in the preparation of compounds 1, 2, 3, 4, and 16 (see outline on page 41). The \( \beta \)-keto aldehyde (20) and the \( \beta \)-keto ester (21) were prepared as intermediates to facilitate the addition of a cyclopentenyl group. This was necessary to activate carbon 2 of the ketone. With no activation, attempted alkylation of 19 merely resulted in the decomposition of the cyclopentenyl bromide.

\[
\begin{align*}
\text{HCO}_2\text{Et} & \xrightarrow{\text{NaH} \text{, } \text{H}} \text{20} \\
\text{19} & \xrightarrow{\text{Et}_2\text{CO}_2 \text{H} \text{, } \text{NaH}} \text{21}
\end{align*}
\]

The hydroxymethylene group was obtained at position two by condensation of 19 with ethyl formate using sodium hydride in benzene.\(^{21}\) The \( \beta \)-keto ester (21) was prepared by condensation of 19 with ethyl
carbonate using sodium hydride in ether and a small amount of dimethylformamide. The hydroxymethylene group was removed later by refluxing in alcoholic sodium hydroxide. This treatment was also sufficient to hydrolyze the ester (21) to an acid. Decarboxylation was accomplished by acidification with dilute hydrochloric acid. Alkylation of the \( \beta \)-keto aldehyde (20) was found preferable to alkylation with the ester (21) because the aldehyde was easily purified by recrystallization. The ester, an oil, was difficult to separate from starting material (19) and alkylation performed with this compound gave an impure product.

Compound 22 had previously been prepared using the malonic ester synthesis:

\[
\begin{array}{c}
\text{39} \\
\text{CH}_3 \\
\text{EtO}_2 \\
\text{CO}_2 \text{Et} \\
\end{array} + \begin{array}{c}
\text{Cl} \\
\text{C}_5 \text{H}_5 \\
\end{array} \xrightarrow{-\text{HCl}} \begin{array}{c}
\text{44} \\
\text{CH}_3 \\
\text{EtO}_2 \\
\text{CO}_2 \text{Et} \\
\end{array}
\]

\[
\begin{array}{c}
\text{45} \\
\text{OH}^- \\
\text{CH}_3 \\
\text{HO}_2 \\
\text{CO}_2 \text{H} \\
\end{array} \xrightarrow{-\text{CO}_2} \begin{array}{c}
\text{46} \\
\text{CH}_3 \\
\text{HO}_2 \\
\text{CH} \\
\end{array}
\]

\[
\begin{array}{c}
\text{22} \\
\text{H} \\
\text{O} \\
\text{C} \\
\text{H}_5 \\
\end{array} \xrightarrow{\text{1) SOCl}_2} \xrightarrow{\text{2) AlCl}_3} \xrightarrow{-\text{HCl}} \begin{array}{c}
\text{22} \\
\text{CH}_3 \\
\text{O} \\
\text{H} \\
\end{array}
\]
Compound 39 was condensed with freshly distilled $\Delta^2$-cyclopentenyl chloride using potassium in dry toluene. The ester (44) was then hydrolysed to 45 by refluxing with alcoholic potassium hydroxide for 24 hours, and decarboxylated with the loss of 1 mole of carbon dioxide to obtain 46. Treatment of 46 with thionyl chloride, followed by ring closure, gave compound 22 in 21 per cent yield for this step. Buchta and coworkers had also attempted the preparation of 22 from 6-methoxytetralone (19) by formation of the methyl glyoxalate of 19, decarbonylation to the methyl ester, and alkylation with $\Delta^2$-cyclopentenyl chloride. When alkylation of the potassium derivative of the methyl ester of 19 in toluene was attempted, decomposition occurred.
Yields of 80-90 per cent of 22 were obtained by preparing the sodio derivative of 20 or 21 with sodium hydride in DMF. With the addition of freshly distilled $\Delta^2$-cyclopentenyl bromide at $-10^\circ$, alkylation occurred rapidly, accompanied by a $25^\circ$ temperature increase. Other solvents, such as ether, resulted in decomposition of the $\Delta^2$-cyclopentenyl bromide. The mixture of $\Delta^2$-cyclopentenyl bromide and the sodio derivative of 20 or 21 was stirred for a few minutes until the mixture thickened. After isolation of the product, it was refluxed in alcoholic sodium hydroxide under an argon atmosphere to decarbonylate the aldehyde. Longer reflux time was necessary to hydrolyze the ester group to the acid. The acid was decarboxylated with dilute hydrochloric acid. The product (22) provided the basis for synthesis of androgen analogs containing rings A, B, and D.

Hydroboration of the cyclopentenyl and keto groups of 22, followed by alkaline oxidation, gave two isomeric alcohols (23a and 23b). In addition, 2 pairs of epimers were formed for each of the two position
The hydroboration method of Brown and Rao was used. However, reduction of the keto group leads to side products, some of which are water soluble. The yield for this step is only 65 per cent which may be compared to a 99 per cent yield obtained in the hydroboration of the very similar compound 40 to give 41 and 42.
Hydrogenation of compounds 23a and 23b with a palladium catalyst gives an almost quantitative yield of 24a and 24b which is a mixture of 4 isomers, 2 position isomers and their cis and trans epimers.
Reduction of the acetate esters (24a,b) with sodium borohydride in ethanol gave a quantitative yield of the isomeric alcohols (25 and 26). Thin layer chromatography of the mixture showed 3 spots. Later work showed that this was probably due to poor resolution of the epimers of 25 rather than the absence of an epimer.

The first step in the separation of isomers 25 and 26 was the chromic acid oxidation of the alcohols to the ketones. Then the ketone (27) was separated by its formation of a bisulfite derivative. The keto group in 28 was too hindered for bisulfite formation; and the thin layer chromatogram of 27 after hydrolysis of the bisulfite showed only one spot, indicating complete separation of isomers. Compound 28 was separated from non-ketonic material through formation of its semicarbazone.
The 3-oxocyclopentyl isomer (27) was treated in two ways. First, the carbonyl group was protected by formation of the ethylene ketal, and this compound (29) was reduced to the unsaturated ketone (16). Second, the ketone (27) was reduced with sodium borohydride to the alcohol (25) and this was reduced to the unsaturated ketones (1 and 2).
The ethylene ketal (29) was prepared in 90 per cent yield by refluxing 27 with \( \alpha \)-toluenesulfonic acid. The phenol ether was reduced by the Birch method using redistilled ammonia with isopropyl alcohol as the proton source to form 30.\(^{26}\) The alkali metal used was lithium, and the alcohol was added after lithium addition.

\[
\begin{align*}
1) \text{Li, NH}_3 \\
2) i\text{-pro alcohol}
\end{align*}
\]

\[
29 \xrightarrow{\text{HCOOH, H}_2\text{O}} 30 \xrightarrow{\text{OH spot}} 16
\]

Compound 16 had been previously prepared and bioassayed.\(^{19}\) However, hydrolysis of the enol ether had been accomplished with hydrochloric acid and dioxane, giving a high percentage of \( \alpha,\beta \) - unsaturation.\(^{27}\) It was hoped that the milder formic acid hydrolysis would result in the predominance of \( \beta,\gamma \) -unsaturation. The desired result was not achieved, and ultraviolet spectral analysis indicated 66 per cent conjugation was obtained. Therefore, no bioassay sample was submitted.

Reduction of ketone 27 to the alcohol was accomplished with sodium borohydride and by hydrogenation with Raney nickel catalyst. The products obtained by both methods were identical in infrared spectra, and both gave only one spot with thin layer chromatography. This is additional evidence that both epimers were present though unresolved.
The Birch reduction of 25 to its enol ether was accomplished using two different modifications of Dryden's procedure. In one reduction, redistilled ammonia, sodium, and isopropyl alcohol were used. The isopropyl alcohol was added before the sodium to reduce the basicity of the reaction medium and suppress rearrangement. Redistillation of the ammonia is necessary when sodium is used because commercial ammonia often contains colloidal iron particles which catalyse the reaction between sodium and alcohol which decreases the reducing power of the sodium. The corresponding reaction between lithium and alcohol is less strongly catalysed, being unaffected up to 25 ppm of iron. This explains the reported advantage of lithium when ammonia is used without distillation.

A second reduction was carried out using lithium, undistilled ammonia, and isopropyl alcohol. The isopropyl alcohol was added last in this reduction. The enol ethers (31) obtained by these two methods were hydrolysed separately using acetic acid. However, infrared spectral analysis indicated percentage conjugation of the resulting unsat-
urated ketones (1 and 2) was nearly identical for both methods.

The ultraviolet extinction coefficient of the unsaturated ketones (1 and 2) obtained by acetic acid hydrolysis was 5,900. Assuming an extinction coefficient of 14,000 for the conjugated isomer (1), based on a value of 14,000 for the conjugated unsaturated octalone (43), the isomeric mixture of 1 and 2 contains 41 per cent of 1.\(^{13}\)

In order to increase the percentage of the conjugated isomer (1), the isomeric mixture was refluxed in dioxane and 6M hydrochloric acid
for 1½ hours. The ultraviolet spectra of the product then gave a value for the extinction coefficient of 12,600, indicating 90 per cent conjugation.

The fraction of the isomeric mixture (1 and 2) distilling at 156-160° (.01 mm.) was submitted for bioassay.

The ketone (28) was reduced to the alcohol (26) by two methods. The first method was the simple sodium borohydride reduction previously used for reducing ketone 27. Thin layer chromatography of the alcohol showed two equal sized spots for the two epimers. The reagent was not stereospecific. In an attempt to exert a directive effect on epimer formation, reduction with disiamylborane was performed as the second method. It was felt that the large steric requirements of the two highly branched organic groups would favor formation of one epimer over the other. However, there was no indication of any directive effect. Thin layer chromatography again showed 2 equal sized spots.
The alcohol (26) was reduced to its enol ether by the Birch reduction using undistilled ammonia, lithium, and isopropyl alcohol. The enol ether (32) was hydrolysed with acetic acid to the ketones (3 and 4). Ultraviolet spectral analysis gave an extinction coefficient value of 4,200 which indicated 30 per cent conjugation was present. To increase the amount of conjugated isomer (4), the isomeric mixture was refluxed 1½ hours with 6M hydrochloric acid and dioxane. After this treatment the extinction coefficient had increased to 9,900 and the double bond was shifted to 70 per cent conjugation.

The fraction of the isomeric mixture (3 and 4) distilling at 152-155° (.01 mm.) was submitted for bioassay.

Repeated thin layer chromatography of compound 25 with various solvents was unable to resolve the expected cis-trans epimers. With isomer 26, resolution was easily achieved, indicating a 50-50 mixture of epimers. The ketone group of 27 was clearly less hindered than that of 28, as exhibited by the formation of its bisulfite derivative. Therefore, stereo-
specific reduction of 27 to 25 by both sodium borohydride and catalytic hydrogenation did not seem likely.

In order to gain evidence that 25 was indeed an unresolved epimer mixture, a reaction sequence was followed in which a single inversion at carbon 3' was achieved. Then thin layer chromatography of the inverted sample of 25 versus the original alcohol would reveal two spots if the epimers were resolvable.

The inversion sequence involved 3 steps. First, the p-toluene-sulfonate ester of the alcohol was formed. Then the sulfonate ester was displaced in a $S_{n2}$ type reaction by the formate ion, thus inverting the configuration at carbon 3. Lastly, hydrolysis of the formate ester restored the original alcohol.

The resolvable epimer pair of alcohol 26 was first run as a model compound. The tosyl ester (33) of 26 was prepared following a method described by Sarett.$^{31}$ Bright red crystals of the ester were formed when the alcohol was allowed to stand overnight in a solution of p-toluene-
sulfonyl chloride and pyridine.

Thin layer chromatography of the product showed that the epimers were even better resolved with the bulky ester group present.

Inversion to form the formate ester was achieved by stirring a mixture of compound 33 and sodium formate in DMF at 100° for 3 days. Samples were removed periodically for thin layer chromatography. Chromatograms showed the appearance of a large non-polar spot as well as the expected formate ester spot. Apparently inversion was accompanied by considerable elimination to form the alkene (34) which absorbed iodine strongly and traveled with the solvent front.
The mixture of ester (35) and alkene (34) was treated with sodium borohydride in ethanol to regenerate the alcohol (26). Thin layer chromatography of the product showed two equal sized alcohol spots which were identical to that of the uninverted sample. However, the epimer spots were much weaker than the dark alkene spot. The infrared hydroxyl peak (2.9μ) of the inverted alcohol was less than 1/3 of its original size, indicating that about 2/3 of the formate ester had undergone elimination.
The preparation of the p-toluenesulfonate ester of alcohol 25 was carried out just as with alcohol 26 except that an argon atmosphere and light shields were supplied. It was hoped that these precautions would prevent the dark red color from developing. Nevertheless, dark red crystals appeared after the mixture of alcohol 25, p-toluenesulfonyl chloride and pyridine had stood 16 hours. Although the sulfonate ester of alcohol 26 had shown improved epimer resolution with thin layer chromatography, compound 36 was not resolved.

\[
\begin{align*}
\text{OH} & \quad \mathbf{25} \\
\text{CH}_3\text{O} & \\
\text{C}_6\text{H}_5\text{SO}_2\text{Cl} & \text{pyridine} \\
\rightarrow & \\
\text{CH}_3\text{O} & \quad \mathbf{36} \\
\text{C}_6\text{H}_5 & \\
\text{TOSYL} & \\
\end{align*}
\]

The inversion of ester 36 was accomplished by stirring a mixture of 36 and sodium formate in DMF at 100°C for 3 days. Thin layer chromatography was used to follow the progress of the reaction. The non-polar alkene spot appeared after 12 hours, but never became as large or dark as it had when inverting ester 33. The formate ester spot showed no resolution of the epimers.
Regeneration of the alcohol (25) from the formate ester (37) was accomplished by refluxing with sodium borohydride in ethanol.

Thin layer chromatography of the inverted alcohol (25) when compared to the original alcohol, revealed only one alcohol spot, identical for both samples. Since no stereospecificity was expected in reduction of ketone 27, one may thus conclude that both epimers are probably present and are unresolved by ordinary thin layer chromatography techniques.
IV. EXPERIMENTAL

2-Hydroxymethylene-6-methoxytetralone (20). - Sodium hydride (15.0 g., 0.335 mole) was added to a solution of 6-methoxytetralone (19) (35.0 g., 0.199 mole), ethyl formate (30.0 ml., 0.593 mole), and 300 ml. of dry benzene while keeping the reaction temperature below 30°. The mixture was then stirred at room temperature under an argon atmosphere for 4 hours. The reaction mixture was cooled in an ice bath and ice water was added. The water layer was separated and acidified with 30 ml. of concentrated hydrochloric acid and ice. The pale yellow precipitate was collected and washed with sodium bicarbonate solution and water until the wash was neutral. The crude product was recrystallized from methanol to give a yield of 36.0 g. (88%); m.p. 88-90°, lit. 24 m.p. 93°.

Ethyl ester of 6-methoxy-1-keto-1,2,3,4-tetrahydro-2-naphthoic acid (21). - A mixture of sodium hydride (11.2 g., 0.247 mole), 6-methoxytetralone (19) (35.2 g., 0.200 mole), ethyl carbonate (28.0 ml., 0.230 mole), and 200 ml. of dry ether was heated to reflux and 24 ml. of dry dimethylformamide added. After refluxing for 3 hours, the mixture was cooled, and ice water and benzene added. The water layer was acidified

---

\(^{a)}\) Melting points are uncorrected. Microanalysis by Galbraith Microanalytical Laboratories. Ultraviolet spectra were taken in 95% ethanol (Beckmann DU) and infrared spectra in carbon tetrachloride, unless otherwise indicated (Beckmann IR5).

\(^{b)}\) The sodium hydride used throughout was a 53% suspension in mineral oil. Prior to use it was washed with dry benzene.
with hydrochloric acid and extracted with benzene. After washing the combined benzene layers with water until neutral, the solvent was evaporated in vacuo and the product distilled. A yield of 40.0 g. (81%) of product distilling at 159-166° (.01 mm.) was obtained. Anal. Calc. for C_{14}H_{16}O_4: C, 67.74; H, 6.45. Found: C, 67.40; H, 6.76.

Cyclopentene. - Polyphosphoric acid (52 g. of phosphorous pentoxide and 26 g. of 85% phosphoric acid) was added to cyclopentanol (156 ml., 1.72 mole) and the mixture distilled, keeping the temperature below 60°. The cyclopentene was dried over calcium chloride and redistilled giving a yield of 111 g. (95%) of product boiling at 43-44° (670 mm.), lit. 44°.

Δ²-Cyclopentenyl bromide. - A mixture of Δ²-Bromosuccinimide (22.0 g., 0.125 mole), cyclopentene (18.0 ml., 0.204 mole), carbon tetrachloride (25 ml.), and benzoyl peroxide (1.0 g.) was refluxed with stirring using a 150 watt flood lamp as the heat source. As the reaction proceeded the reflux temperature rose steadily until about 75°, at which point the reflux level in the condenser dropped, indicating the reaction had reached completion. The flask was immediately cooled to room temperature and the mixture filtered. The succinimide residue was washed with petroleum ether and the filtrate was evaporated and distilled under vacuum (w 20 mm., 25-40°) using a cold water condenser with the receiving flask imbedded in ice.

The reaction time is dependent upon the amount of carbon tetrachloride used as solvent, an additional 5 ml. of carbon tetrachloride increases the reaction time to 40 minutes. Cyclopentenyl bromide is very unstable to moisture and must be used immediately. Thus, yields were not determined.
2-(\Delta^2\text{-cyclopentenyl})-1,2,3,4-tetrahydro-6-methoxynaphthalenone (22).

- Freshly distilled \Delta^2\text{-cyclopentenyl bromide (approximately 16 g., 0.11 mole)} was added all at once to a mixture of 2-hydroxymethylene-6-methoxytetralone (20) (12.0 g., 0.0589 mole), or the ethyl ester of 6-methoxy-1-keto-1,2,3,4-tetrahydro-2-naphthoic acid (21) (15.0 g., 0.0604 mole), 70 ml. of DMF, and sodium hydride (3.8 g., 0.084 mole) at -10\degree. Alkylation, accompanied by a 20-30\degree temperature rise, occurred immediately and a characteristic color change was noted. The mixture became green if excess \Delta^2\text{-cyclopentenyl bromide was present or purple if the reaction was incomplete. After stirring until the mixture thickened (\approx 10 minutes), water and benzene were added. The product was extracted with benzene and the solvent evaporated. If 20 was used, the oil obtained was refluxed 30 minutes with 25 ml. of 95\% ethanol and 25 ml. of 20\% sodium hydroxide. For the ester (21), 30 ml. of ethanol and 30 ml. of sodium hydroxide were used, the reflux time was increased to 45 minutes, and after refluxing, 35 ml. of 6N hydrochloric acid was added to decarboxylate the acid. The product was then extracted with benzene and the solvent evaporated. The product distilled at 156-163\degree (0.01 mm.) to give a yield of 12.0 g. (82\%).

The combined products of two alkylations were later fractionated to remove the low boiling forerun which consisted primarily of tetralone.

Lit.\textsuperscript{33} b.p. 174-178\degree (1.3-1.5 mm.). n\textsubscript{D}^2 1.5873.

Anal. Calc. for C\textsubscript{16}H\textsubscript{18}O\textsubscript{2}: C, 79.33; H, 7.43. Found: C, 79.40; H, 7.29.

3-(1-Hydroxy-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol
and 2-(1-hydroxy-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol (23).\textsuperscript{c} Using the method of Brown and Rao\textsuperscript{23} diborane was generated with

\textsuperscript{c}This product is a mixture of eight isomers. It contains the cis and trans epimers of both position isomers.
29.0 g. (0.212 mole) of boron trifluoride etherate and 5.0 g. (0.13 mole) of sodium borohydride in an argon atmosphere. The diborane was passed with stirring into a flask containing 2-(Δ²-cyclopentenyl)-1,2,3,4-tetrahydro-6-methoxynaphthalenone (22) (20.6 g., 0.0852 mole), dioxane (40 ml.) and tetrahydrofuran (50 ml.) at 5°. After stirring at room temperature for 3 hours, the mixture was cooled to -10° and 60 ml. of 10% sodium hydroxide was slowly added followed by dropwise addition of 30 ml. of 30% hydrogen peroxide. The solution was stirred for 10 minutes, water and benzene were added and the product was extracted with benzene. The benzene solution was evaporated in vacuo and the residue distilled to give a yield of 14.5 g. (65%) of product distilling at 152-175° (0.1 mm.). The infrared spectrum showed an hydroxyl band at 2.9 μ. nD 1.5558.

3-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol ethanoate (23). - Hydrogenation of 23 (14.5 g., 0.0553 mole) in 40 ml. of acetic acid with 2.0 g. of 5% palladium-charcoal catalyst and 4 drops of methanesulfonic acid resulted in the absorption of about 1500 ml. of hydrogen. The mixture was filtered and the solvent evaporated. A yield of 15.0 g. (94%) of product distilling at 160-175° (0.01 mm.) was obtained. nD 1.5337. Anal. Calc. for C20H22O3: C, 75.00; H, 8.83. Found: C, 75.20; H, 8.48.

3-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol (25) and 2-(1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol (26). - A mixture of sodium borohydride (4.6 g., 0.12 mole) and 24 (15.6 g., 0.0542 mole) is a mixture of four isomers. It contains the cis and trans epimers of both position isomers.

This product is a mixture of four isomers. It contains the cis and trans epimers of both position isomers.
mole) was refluxed 2 hours in 125 ml. of 95% ethanol. The solution was acidified with 3N hydrochloric acid, water was added, and the product was extracted with benzene. The solvent was evaporated and the product distilled. A yield of 13.0 g. (98%) of product distilling at 150-160° (.01 mm.) was obtained. The infrared spectra showed an hydroxyl band at 2.9 μ. The thin layer chromatogram showed three spots instead of the expected four, indicating that one of the epimer pairs had not been resolved.

1,2,3,4-Tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene (27) and 1,2,3,4-tetrahydro-6-methoxy-2-(2-oxocyclopentyl)-naphthalene (28). - A pyridine solution of 26 and 27 (14.0 g., 0.569 mole) was added to a solution of chromic oxide (14.0 g., 0.140 mole) in pyridine (300 ml.). The mixture was stirred 6 hours at room temperature, water and benzene were added and the mixture filtered. The filtrate was extracted with benzene and the benzene extracts washed with dilute hydrochloric acid until no pyridine odor remained. The solvent was evaporated in vacuo. A yield of 13.0 g. (94%) of product distilling at 160-170° (.01 mm.) was obtained. The infrared spectra showed a carbonyl band at 5.7 μ. The thin layer chromatogram showed two ketone spots of equal size. \( n_D^{22} 1.5544 \).

Separation of the isomers 1,2,3,4-tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene (27) and 1,2,3,4-tetrahydro-6-methoxy-2-(2-oxocyclopentyl)-naphthalene (28). - Compounds 27 and 28 (18.7 g., 0.767 mole) were shaken at room temperature for 24 hours with sodium metabisulfite (90.0 g., 0.474 mole) dissolved in water (130 ml.), methanol (41 ml.), and 95% ethanol (47 ml.).

The precipitate (the bisulfite derivative of 27) was collected and washed with petroleum ether. The bisulfite was hydrolyzed with 30 ml. of
concentrated hydrochloric acid by heating to $60^\circ$ for 45 minutes. The free ketone (27) was extracted with benzene and the solvent was evaporated in vacuo. A yield of 6.5 g. (35%) of product distilling at 168-172$^\circ$ (.01 mm.) was obtained.

Anal. Calc. for (27) $C_{16}H_{20}O_2$: C, 78.68; H, 8.20. Found: C, 78.70; H, 8.17.

The filtrate was extracted with benzene and the solvent evaporated. The ketone (28) was purified through formation of the semicarbazone derivative with semicarbazide hydrochloride (0.125 mole), sodium acetate (0.146 mole), methanol (30 ml.), and water (20 ml.). The mixture was refluxed two hours and the semicarbazone precipitate collected. The semicarbazone was hydrolysed at reflux with pyruvic acid (10 ml.), acetic acid (100 ml.), water (60 ml.). The free ketone (28) was extracted with benzene and the solvent evaporated. A yield of 7.0 g. (37%) of product distilling at 150-160$^\circ$ (.01 mm.) was obtained.

Anal. Calc. for (28) $C_{16}H_{20}O_2$: C, 78.68; H, 8.20. Found: C, 78.52; H, 7.91.

The thin layer chromatograms of 27 and 28 each showed only one spot, indicating complete separation.

3-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol (25).

1. Sodium borohydride reduction:

A mixture of 27 (4.9 g., 0.020 mole) and sodium borohydride (1.7 g., 0.045 mole) was refluxed one hour in 95% ethanol (100 ml.). The solution was acidified with 3N hydrochloric acid, water was added, and the product was extracted with benzene and the solvent evaporated. A yield of 4.7 g. (96%) of product distilling at 155-160$^\circ$ (.01 mm.) was obtained, m.p. 65-66$^\circ$. The infrared spectra showed an hydroxyl band at 2.9$\mu$. The thin
layer chromatogram showed only one spot, indicating the epimers were not resolved.

2. Hydrogenation:

Compound 27 (1.3 g., 0.0053 mole) was hydrogenated in acetic acid (30 ml.) with Raney nickel catalyst (1.0 g.) and one drop of perchloric acid. The mixture was filtered and the filtrate evaporated. A yield of 1.3 g. (99%) of product distilling at 150-160° (.01 mm.) was obtained. The thin layer chromatogram showed only one spot, identical to that obtained through borohydride reduction.

2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol (26).

1. Sodium borohydride reduction:

A mixture of sodium borohydride (2.6 g., 0.068 mole) and 23 (77 g., 0.032 mole) was refluxed one hour with 95% ethanol (150 ml.). 3N Hydrochloric acid was added until the solution was acidic, water was added, and the product was extracted with benzene. The benzene was evaporated in vacuo. A yield of 7.4 g. (95%) of product distilling at 152-160° (.01 mm.) was obtained. An hydroxyl peak at 2.9μ appeared on the infrared spectra. The thin layer chromatogram showed two equal sized spots indicating that the cis and trans epimers were both present and had been resolved.

2. Disiamylborane method:

Diborane was generated in situ by the addition of boron trifluoride etherate (9.4 g., 0.067 mole) to a solution of trimethylethylene (9.2 g., 0.132 mole) and sodium borohydride (1.9 g., 0.050 mole) in diglyme (40 ml.) at -5°. The solution was stirred at 0° for ½ hour and at room temperature for 1 hour. The solution was cooled to 5° and compound 28 (7.0 g., 0.029
mole) dissolved in 10 ml. of dry ether was added. After stirring 4 hours at room temperature, the mixture was cooled to 10° and 10% sodium hydrox-ide (30 ml.) was added followed by 30% hydrogen peroxide (30 ml.). Water and benzene were added, the product was extracted with benzene and the solvent evaporated. A yield of 6.3 g. (90%) of product distilling at 150-160° (.01 mm.) was obtained. The infrared spectra showed an hydroxyl band at 2.9μ. The thin layer chromatograph showed two equal sized spots identical to those obtained through sodium borohydride reduction. Thus, disiamylborane showed no stereospecificity in this reaction.

1,2,3,4-Tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene ethylene ketal (29). - A mixture of ethylene glycol (5.9 ml. 0.11 mole), 27 (7.0 g., 0.029 mole), and p-toluenesulfonic acid (0.25 g.) was refluxed 4 hours in dry benzene (175 ml.) using a water separator. The benzene was evaporated, the residue poured into a solution of sodium bicarbonate, and the product extracted with benzene. The solvent was evaporated in vacuo. A yield of 7.5 g. (90%) of product distilling at 125-135° (.01 mm.) was obtained.

Anal. Calc. for C_{12}H_{22}O_3: C, 75.00; H, 8.33. Found: C, 75.06; H, 8.14.

4, 4a,5,6,7,8-Hexahydro-6-(3-hydroxycyclopentyl)-2 (3H)-naphthalenone (1) and 3,4,5,6,7,8-hexahydro-6-(3-hydroxycyclopentyl)-2-(1H)-naphthalenone (2). -

1. Sodium reduction:

Following the procedure of Dryden, 25 (5.4 g., 0.022 mole) was dissolved in dry ether (50 ml.) and added to redistilled ammonia (150 ml.) at -35°, followed by the addition of isopropyl alcohol (50 ml., 0.65 mole).
Sodium (2.1 g, 0.088 mole) was added and the mixture stirred until the color changed from blue to white which indicated complete reaction. The ammonia was evaporated, the solution warmed to room temperature, water was added, and the product extracted with benzene. The benzene layer was washed once with 50 ml. of 5% acetic acid, twice with water, and the benzene was evaporated. A yield of 4.0 g. (73%) of product distilling at 140-155° (.01 mm.) was obtained. The infrared spectra showed some hydrolysis of the enol ether had occurred during the acetic acid washing. A ketone peak was visible at 5.8μ as well as the enol ether doublet at 5.9μ and 6.0μ.

The enol ether was hydrolyzed to the unsaturated ketone by dissolving the enol ether in 53% (40 ml.) acetic acid and allowing the solution to stand for 2 hours. An infrared spectra of the product, when compared to the same unsaturated ketone obtained by lithium reduction (below), indicated that the ratio of isomers 1 and 2 obtained was the same for both methods. Therefore, the products were combined and distilled. A yield of 3.0 g. (70%) of product distilling at 158-165° (.01 mm.) was obtained.

λ max. 238μ (ε 5,900).

Approximately 41% of the conjugated isomer (1) was present. To shift the double bond to the conjugated position, the mixture of isomers was refluxed 1½ hours with dioxane (30 ml.) and 20% (5 ml.) hydrochloric acid. The product was extracted with benzene and the benzene evaporated. A yield of 2.7 g. (90%) of product distilling at 155-160° (.01 mm.) was obtained. The ultraviolet spectra indicated that the mixture now contained 90% of the conjugated isomer. The thin layer chromatogram of the product showed two ketone spots. The larger, slower moving spot was evidently the conjugated isomer (1). A sample of this product was submitted for bioassay. λ max. 238μ
(ε 12,600); λ max. 5.8 μ (ketone C = 0), 5.95 μ (α, β-unsaturated C = 0), 2.9 μ (OH).

2. Lithium reduction:

Compound 25 (4.0 g., 0.016 mole), dissolved in a solution of dry ether (25 ml.) and morpholine (25 ml.) was added to lithium (2.0 g., 0.29 mole) in liquid ammonia (100 ml.) at -45°. The mixture was stirred 5 minutes and isopropyl alcohol (40 ml., 0.52 mole) was added. The ammonia was evaporated and the product distilled. A yield of 1.3 g. (33%) of product distilling at 168-175° (.01 mm.) was obtained. The enol ether was hydrolyzed with acetic acid and then combined with the product of the sodium reduction described above.

4,4a,5,6,7,8-Hexahydro-6-(2-hydroxycyclopentyl)-2(3H)-naphthalenone (3) and 3,4,5,6,7,8-hexahydro-6-(2-hydroxycyclopentyl)-2-(1H)-naphthalenone (4) - A solution of compound 26 (6.8 g., 0.028 mole) in tetrahydrofuran (70 ml.) was added dropwise to redistilled ammonia (200 ml.) at -40°. Isopropyl alcohol (35 ml., 0.45 mole) was added and the solution was warmed to -35°. At this point lithium (3.5 g., 0.50 mole) was added in small pieces and the mixture was stirred for 10 minutes. Then more isopropyl alcohol (30 ml.) and ethanol (10 ml.) were added. Upon warming to -30° the blue color disappeared, indicating complete reaction. The ammonia was evaporated the product extracted with benzene, the benzene extract was washed with acetic acid, and the solvent evaporated. A yield of 3.5 g. (43%) of product distilling at 160-175° (.01 mm.) was obtained. The infrared spectra showed the enol ether doublet at 5.9 μ and 6.9 μ. A thin layer chromato-
graph of the product showed two slow running spots corresponding to the cis and trans epimers of the enol ether.

The enol ether was hydrolysed with 53% acetic acid (40 ml.). The solution of enol ether in acetic acid was allowed to stand 3 hours at room temperature before addition of water and extraction with benzene. A yield of 1.9 g. (57%) of product distilling at 145-155° (.01 mm.) was obtained. The thin layer chromatogram of the unsaturated ketone showed two spots approximately equal in size corresponding to the two isomers (3 and 4).

\[ \lambda_{\text{max.}} 238\mu \text{ (} \epsilon 4,200 \). \]

Approximately 30% of the conjugated isomer (3) was present. To shift the double bond to the conjugated position, the mixture of isomers 3 and 4 was refluxed 1½ hours with dioxane (30 ml.) and 20% hydrochloric acid (5 ml.). The product was extracted with benzene and the solvent was evaporated in vacuo. A yield of 1.7 g. (90%) of product distilling at 150-155° (.01 mm.) was obtained. Ultraviolet spectral analysis indicated that 70% of the conjugated isomer was present. A thin layer chromatogram showed two ketone spots approximately equal in size corresponding to the two isomers. A sample of this product was submitted for bioassay.

\[ \lambda_{\text{max.}} 235\mu \text{ (} \epsilon 9900 \); \lambda_{\text{max.}} 5.8\mu \text{ (ketone } C = 0), 5.95\mu \text{ (} \alpha, \beta \text{ - unsaturated } C = 0), 2.9\mu \text{ (OH).} \]


4,4a,5,6,7,8 Hexahydro-6-(3-oxocyclopentyl)-2(3H)-naphthalenone and 3,4,5,6,7,8 hexahydro-6-(3-oxocyclopentyl)-2(1H)-naphthalenone (16). - A solution of compound 29 (7.5 g., 0.026 mole) in morpholine (80 ml.) was added to a solution of lithium (4.0 g., 0.57 mole) in redistilled ammonia
(200 ml.) at -40°. The mixture was then cooled to -45° and isopropyl alcohol (60 ml., 0.78 mole) was added. The mixture was stirred 15 minutes at -35°. The blue color disappeared and the ammonia was evaporated. The enol ether was extracted with benzene and distilled in vacuo. A yield of 6.2 g. (82%) of product distilling at 170-180° (.01 mm.) was obtained.


To hydrolyse both the enol ether and ketal groups, the product was dissolved in 88% formic acid (25 ml.) and water (2 ml.). After 2 hours the unsaturated ketone was extracted with benzene and distilled. A yield of 3.8 g. (77%) of product distilling at 135-142° (.01 mm.) was obtained. The ultraviolet spectral analysis indicated that the product contained approximately 66% of the conjugated isomer.

λ max. 237μ (ε 9310); λ max. 5.8μ (ketone C = O), 5.95μ (ο, β-unsaturated C = O).


2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-cyclopentanly p-toluenesulfonate (33). - A solution of 26 (4.2 g., 0.017 mole) and p-toluenesulfonyl chloride (6.5 g., 0.034 mole) in pyridine (10 ml.) was allowed to stand overnight during which time it developed a dark red color. Water and benzene were added and the product was extracted with benzene. The solvent was evaporated in vacuo (.020 mm.) and the coarse red crystals of the ester collected. The yield was not determined. The thin layer chromatogram showed two well resolved spots;
(35) - A mixture of 33 (6.5 g., 0.017 mole) and sodium formate (2.3 g., 0.034 mole) in dimethylformamide (100 ml.) was stirred at 100° for 3 days. Periodic sample removal for thin layer chromatography showed 2 ester spots, but also revealed the appearance of a large, fast-moving spot which strongly absorbed iodine. This spot was apparently due to formation of the alkene (34) instead of the expected inversion. The products were extracted with benzene and the solvent was evaporated. A yield of 3.5 g. (75%) of product distilling at 140-145° (0.01 mm.) was obtained.

2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol (26). - A solution of 35 (3.2 g., 0.012 mole) and sodium borohydride (1.1 g., 0.029 mole) dissolved in 95% ethanol (50 ml.) was refluxed 2 hours. Hydrochloric acid (3N) was added until the mixture was acidic to Litmus paper and the product was extracted with benzene. A yield of 3.0 g. (100%) of product distilling at 140-145° (0.01 mm.) was obtained. The thin layer chromatogram showed the two slow moving alcohol isomer spots identical with those obtained for the original 26 as well as the large alkene spot. The infrared spectra showed an hydroxyl peak at 2.9 μμ which was about one-third the size of the peak of the original alcohol (26).

3-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-cyclopentanyl p-toluene-sulfonate (36). - Compound 25 (3.2 g., 0.013 mole) was mixed with p-toluene-sulfonyl chloride (4.6 g., 0.024 mole) in pyridine (8 ml.). The solution was allowed to stand overnight under an argon atmosphere. Light was excluded by an inverted box, but the solution became dark red in spite of these precautions. Water and benzene were added and the product was extracted with benzene. The solvent was evaporated in vacuo (0° 20 mm.) and
the red crystals of the ester were collected. The yield was not determined. The thin layer chromatogram showed only one spot indicating either the two epimers were not resolved or that only one epimer was present.

3-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-cyclopentanyl formate (37). - A mixture of 36 (3.7 g., 0.013 mole) and sodium formate (1.8 g., 0.026 mole) in dimethylformamide (50 ml.) was stirred at 100° for 3 days. Periodic sample removal for thin layer chromatography revealed the appearance of a small, fast-moving spot in addition to a single ester spot. The small size and light color of the spot compared with compound 34 indicated less dehydration was occurring than had occurred with the 2-position isomer (33). The products were extracted with benzene and the solvent was evaporated in vacuo. A yield of 2.7 g. (76%) of product distilling at 140-150° (.01 mm.) was obtained.

3-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol (25). - A solution of 37 (2.7 g., 0.0098 mole) and sodium borohydride (1.0 g., 0.026 mole) in 95% ethanol (50 ml.) was refluxed 2 hours. Hydrochloric acid (3N) was added until the mixture was acidic to Litmus paper and the product was extracted with benzene. The solvent was evaporated in vacuo. A yield of 2.2 g. (91%) of product distilling at 140-153° (.01 mm.) was obtained. The thin layer chromatogram showed a single spot identical to that obtained with the original, uninverted alcohol. Therefore, it was assumed that both epimers were present but were unresolved by chromatography. The infrared spectra of the product showed an hydroxyl peak at 2.9μ which was approximately one-half the size obtained for a purified sample of compound 25. Yield: white solid, 2.2 g. (91%). b.p. 140-153° (.01 mm.).
V. SUMMARY

\[ \text{19} \xrightarrow{\text{HCOOEt, NaH}} \text{20} \]

\[ \text{19} \xrightarrow{\text{Et_2CO_3, NaH}} \text{21} \]

\[ \text{20, 21} \xrightarrow{\text{D, NaH, } \text{H_2}} \text{22} \xrightarrow{\text{2. NaOH}} \xrightarrow{\text{3. (21, HCl)}} \]
22 \[ \text{B}_2\text{H}_6 \rightarrow \text{NaOH, EtOH} \]

23

23 \[ \text{H}_2, \text{Pd, HAc} \rightarrow \]

24

24 \[ \text{NaBH}_4 \rightarrow \text{EtOH} \]

25 (3'-OH)

26 (2'-OH)
25 \text{ CrO}_3 \rightarrow \text{ Pyridine} \rightarrow 27, 28

27 \overset{\text{Separation of isomers through bisulfite formation}}{\rightarrow} 27, 28

27 \text{ NaBH}_4 \text{ or } \text{ H}_2 \text{ Ni} \rightarrow \text{ EtOH} \rightarrow 25
28 $\xrightarrow{\text{NaBH}_4, \text{EtOH}}$ \( \text{26} \)

27 $\xrightarrow{\text{Ethylene glycol, Catalyst}}$ \( \text{29} \)

25 $\xrightarrow{\text{H}^+, \text{H}_2\text{O}}$

1 \( \alpha, \beta\text{-unsaturated } \text{C=O} \)

2 \( \beta, \gamma\text{-unsaturated } \text{C=O} \)
26 \[
\text{d) } \text{NH}_3 \\
\text{iso propyl alcohol} \\
\text{2) Li} \\
\text{H}^+ \\
\text{H}_2\text{O}
\] \rightarrow \text{3 (}\alpha,\beta\text{-unsaturated }\text{C}=\text{O}\text{)}

4 \text{ (}\beta,\gamma\text{-unsaturated }\text{C}=\text{O}\text{)}
26 \( \xrightarrow{\text{p-toluenesulfonyl chloride, pyridine}} \)

33

33 \( \xrightarrow{\text{HCONa, DMF}} \)

34

35

35 \( \xrightarrow{\text{NaBH}_4, \text{EtOH}} \)

26
25 \rightarrow \text{[Reaction with toluene sulfonic chloride in pyridine]} \rightarrow 36

36 \xrightarrow{\text{HCONa in DMF}} 37

37 \xrightarrow{\text{NaBH}_4 \text{ in EtOH}} 25
BIBLIOGRAPHY


15. R. E. Juday, D. P. Page, and G. A. DuVall, Medicinal Chem. 7, 519 (1964)
27. L. Cubbage, unpublished work, University of Montana.