I. SYNTHESIS OF CYCLOBUTA-BC-STEROID HOMOLOGS

II. STEREOCHEMICAL ASSIGNMENT OF (*E*)- AND (*Z*)-2-(1-NAPHTHYL)-1-PHENYLPROPENE AND THEIR PHOTOCYCLIZATION TO 5-METHYLCHRYSENE

By

CLINTON EUGENE BROWNE III

Bachelor of Science

Metropolitan State College

Denver, Colorado

1974

Submitted to the Faculty of the Graduate College
of the Oklahoma State University
in partial fulfillment of the requirements
for the Degree of
DOCTOR OF PHILOSOPHY
May, 1978

I. SYNTHESIS OF CYCLOBUTA-BC-STEROID HOMOLOGS

II. STEREOCHEMICAL ASSIGNMENT OF (*E*)- AND (Z)-2-(1-NAPHTHYL)-1-PHENYLPROPENE AND THEIR PHOTOCYCLIZATION TO 5-METHYLCHRYSENE

Thesis Approved:

Thesis Adviser

Dean of the Graduate College

ACKNOWLEDGMENTS

I wish to extend special thanks to my research adviser Dr. E. J. Eisenbraun for his patience, guidance and friendship throughout this study.

I gratefully acknowledge the financial support of the American Petroleum Institute, Continental Oil Company, Environmental Protection Agency, National Institutes of Health, and Texas Eastman Company (Eastman Kodak).

I thank Dr. Dick van der Helm and Mr. Ray Loghry, University of Oklahoma, for obtaining and interpreting X-ray crystallographic data.

I also wish to thank members of the research group for their friendship and help, particularly Dr. Leon Pahler and Mr. Sonny Vickery for their friendship and work on the synthesis of steroid homologs and also Mr. Tom Dobbs for his work in the 5-methylchrysene area. I am especially grateful to Dr. Paul Ruehle for his friendship and contribuitions to the synthesis of steroid homologs.

My wife Jo Ann, and children, Laura and Matthew, deserve a very special thank-you for their encouragement and sacrifices. I am deeply grateful to Jo Ann for typing this dissertation. My Father and Mother, Dr. and Mrs. C. E. Browne, and my inlaws, Mr. and Mrs. E. F. Michels, also rate a very special thanks for their encouragement and support.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

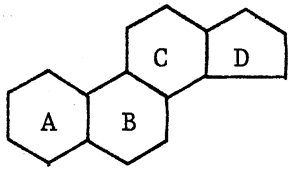
PART I

SYNTHESIS OF CYCLOBUTA-BC-STEROID HOMOLOGS

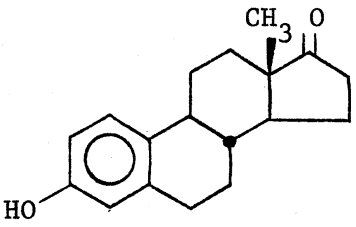
CHAPTER I

INTRODUCTION AND HISTORICAL

Steroids[1] are a class of natural products containing the cyclopentanoperhydrophenanthrene ring system 1. Since the isolation of



1

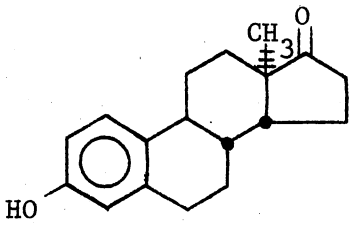


2

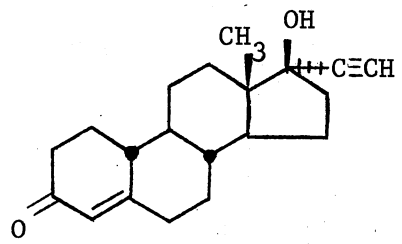
steroid hormones beginning with estrone (2)[2] in 1929, and the structural elucidation of cholesterol[3] in 1932, extensive research has been conducted on the chemistry and biology of steroids. The search for hormonal drugs has resulted in the synthesis of many steroidal and nonsteroidal analogs, some of which are valuable therapeutic agents because of their reduced rate of metabolism, greater selectivity in biological effects, or increased oral potency as compared to natural hormones.

Steroid analogs capable of inducing biological effects similar to natural hormones are chemically diverse. In addition to functionally modified natural steroids, a number of analogs with altered ring systems have been found to possess biological activity. Steroid

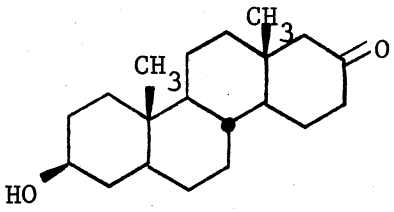
analogs exhibiting modified ring systems are exemplified by the iso-steroid 13-iso-14-iso-estrone (3),[4] the nor-steroid 17α-ethynyl-19-nortestosterone (4),[5] and those having expanded or contracted rings such as D-homo-epiandroster-17-one (5)[6] and D-norprogesterone (6).[7]



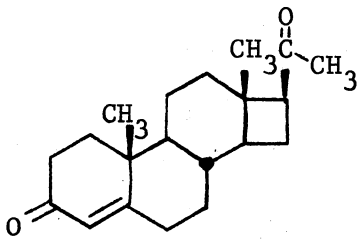
3



4



5



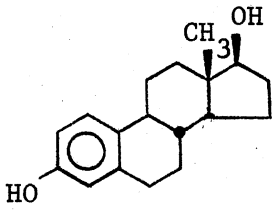
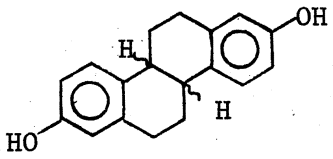
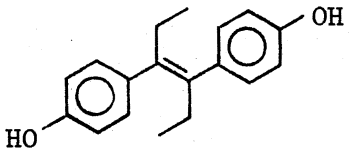
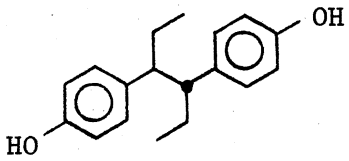
6

Certain phenolic compounds[8] lacking the steroid nucleus possess estrogenic activity. Closer inspection reveals that most of these phenols are similar to estrone (2) and estradiol (7) in shape, width, thickness and length. One parameter in particular, the intramolecular oxygen-oxygen distance,[9] has been considered to be a significant indicator of estrogenic function. In Table I, a comparison of the structure and oxygen-oxygen distance for estradiol (7) and several estrogenic phenols is shown.

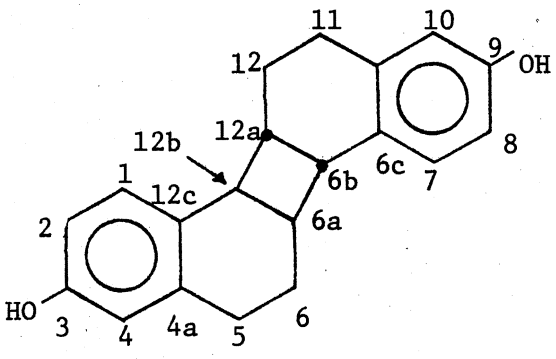
The structural similarities between the steroids, nonsteroidal analogs, and the cyclobutane homologs, 3,9-dihydroxy-5,6,6aα,6bβ,11,

TABLE I

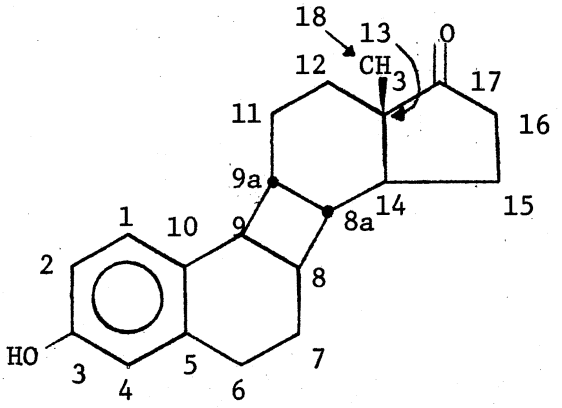
AROMATIC PHENOLS EXHIBITING
ESTROGENIC ACTIVITY

Structure	Oxygen-Oxygen Distance[a]	Reference
 7	10.9[b]	10
 *cis* 8	12.2[c]	11
trans 9	12.0[c]	11
 10	12.1[b]	12
 11	12.8[c,d]	13

[a] In Å. [b] X-ray crystallography data. [c] Obtained from Dreiding models.
[d] Extended conformation.



12



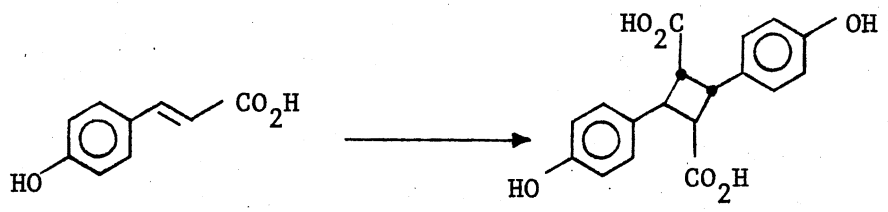
13

12,12aβ,12bα-octahydrodibenzo[a,g]biphenylene (12) and 8α,8aβ,9α,9aβ-cyclobuta-BC-estrone (13), suggested that these novel cyclobuta-BC-steroid homologs might possess antifertility activity. The cyclobutane homologs 12 and 13 have overall lengths similar to the structures 9 and 2 because of a split-level planarity *ie*, the plane of the A and B rings is parallel and below the plane of the C and D rings. These planes are connected by the nearly vertical, flat, cyclobutane ring. X-ray crystallography data,[14] discussed subsequently, indicate the oxygen-oxygen distance in 12 is 12.9 Å, comparable to that of other estrogens (Table I).

The objective of this study was the synthesis of 12 and cyclobuta-BC-steroid homologs for biological evaluation as antifertility agents. It should be noted that throughout this study for the sake of consistency, tetrasubstituted cyclobutane structures are arbitrarily shown in the 6aα,6bβ,12aβ,12bα, or 8α,8aβ,9α,9bβ, configuration (numbering shown in 12 and 13). This is not intended to represent

absolute configuration since those compounds which are not meso were obtained as dl mixtures.

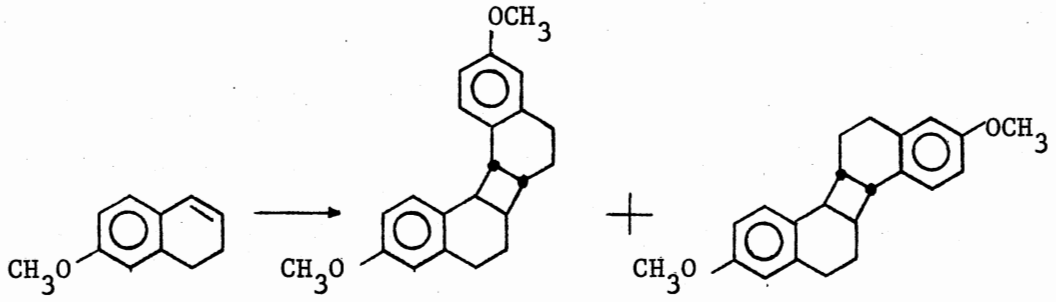
Synthesis of 12 and 13 requires the formation of a tetrasubstituted cyclobutane ring with cis-anti-cis stereochemistry. Stereoselective formation of the cyclobutane ring by photodimerization of an alkene immediately forms the four asymmetric centers present in 12 and four of the six centers present in 13. The starting material selected for synthesis of 12 was 4,4'-dihydroxy-α-truxillic acid (15a), prepared by photodimerization of 4-hydroxycinnamic acid (14).[15] The synthesis of 12 from 15a was envisioned as



14 15a

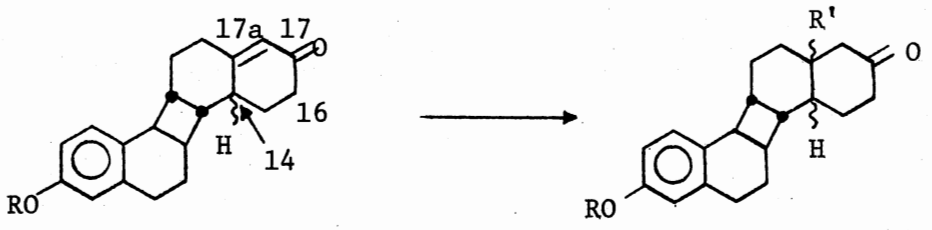
methylation of the phenolic hydroxyl groups and construction of the B and C rings by homologation of the diacid, cyclization, and hydrogenolysis to the diether 16. Demethylation of 16 would then afford 12.

A conceptually simpler route to 16, photodimerization of 7-methoxy-1,2-dihydronaphthalene(17) gave only traces of 16, the major product being the head-to-head isomer 18.[16]



17 18 16

The second phase of this study, synthesis of cyclobuta-BC-steroid analogs including 13, would then utilize the intermediate diether 16, with its defined stereochemistry at the four asymmetric centers. Differentiation of the A and D rings of 16 by mono-demethylation followed by Birch reduction of one aromatic ring, hydrolysis of the enol ether and conjugation should afford the α,β-unsaturated ketone 19. It was assumed that a trans relationship between the C-8a and



19

20 R'= H

21 R'= CH_3

epimerizable C-14 proton would be more stable thermodynamically than a cis relationship. Thus the proton at the newly formed asymmetric center (C-14) would be α. Similar α,β-unsaturated ketones are key intermediates for the introduction of an angular methyl group and

contraction of the D ring in several steroid syntheses.[17]

Reduction of the C-13(17a) double bond in 19 both with or without concomitant introduction of an angular (C-13) methyl group can give four diastereomeric ketones (20 or 21) depending on the configuration of the C-14 proton and the C-13 substituent (H or CH_3). An examination of the stereochemistry generated by various methods of reduction was planned. Oxidative cleavage of the C-17(17a) bond in 20 or 21 should afford diacids from which the desired five-membered D ring could be formed by esterification and Dieckmann cyclization.[18]

This type of AD → BC approach using a symmetrical intermediate has seen comparatively little use in steroid synthesis because of the difficulty in differentiation of the A and D rings from a symmetrical intermediate. A similar AD → BC approach was used in the synthesis of *dl*-18,19-bisnorprogesterone[17a] from the symmetrical dimethyl ether of 9.

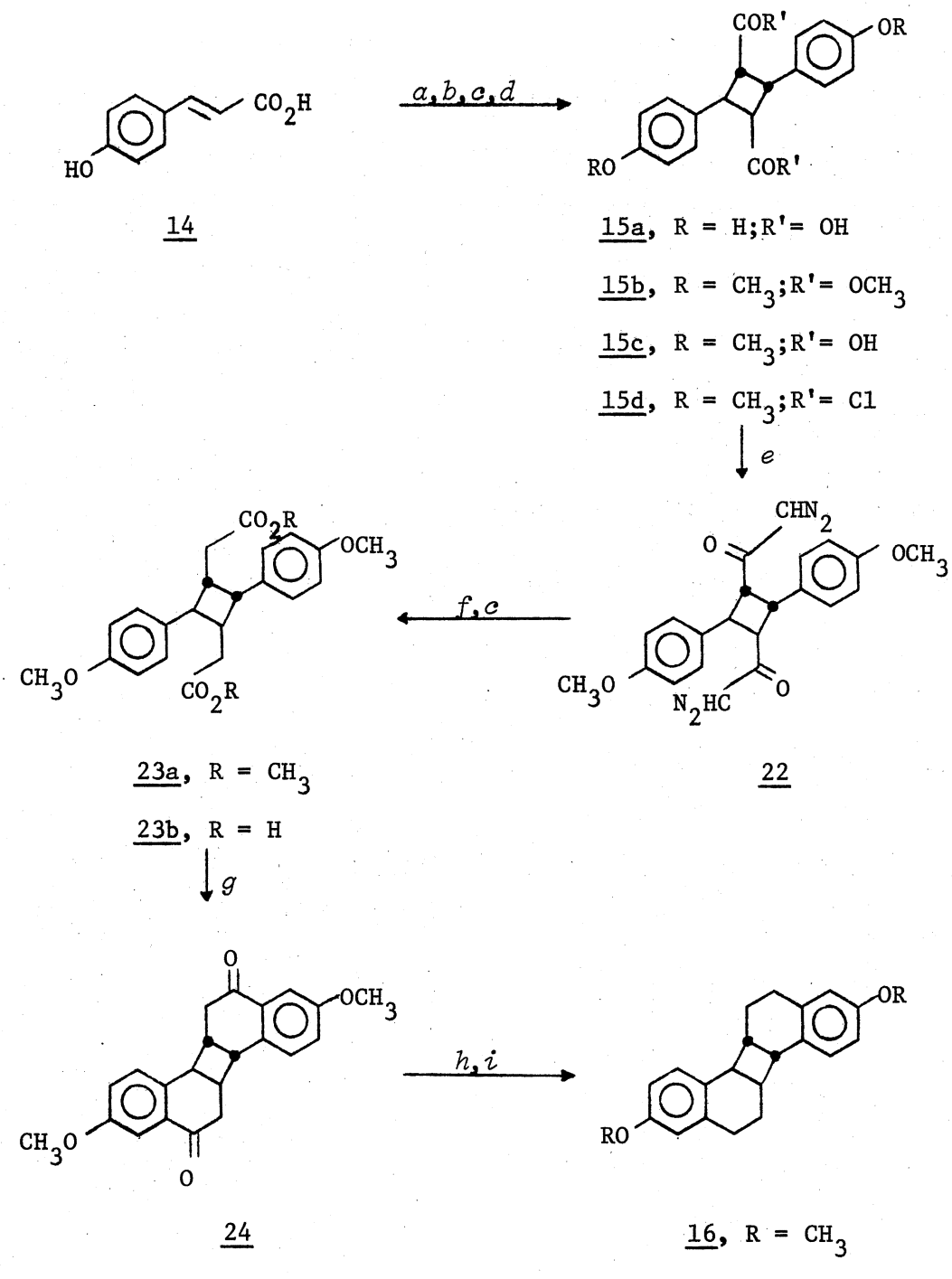
CHAPTER II

RESULTS AND DISCUSSION

The synthesis of the dimethyl ether 16 and the diphenol 12, is shown in Figure 1.

Ultraviolet irradiation of 14 in the solid state gave the diacid 15a stereoselectively, as previously reported,[15] in 90% yield. The problem of efficiently exposing large quantities of solid to ultraviolet radiation was surmounted by irradiating a well-stirred, finely divided slurry of 14 in water. The phenolic hydroxyl groups of 15a were then protected by methylation and the resulting dimethyl ester 15b was hydrolyzed to the diacid 15c in 95% yield.

Bishomologation of the diacid 15c was accomplished via the Arndt-Eistert method.[19] This involved conversion of the diacid 15c to the diacid chloride 15d using thionyl chloride and a catalytic amount of pyridine. Addition of a benzene solution of 15d to an excess of diazomethane in ether gave the bis-diazoketone 22. Wolff rearrangement of 22 to the diester 23a was found to proceed efficiently even on a large scale at room temperature by treating a slurry of 22 in anhydrous methanol with catalytic amounts of silver benzoate dissolved in triethylamine.[20] The product, diester 23a, was easily purified by chromatography over activated acidic alumina and then hydrolyzed to the diacid 23b in an overall yield of 54% based on 15c. Attempted rearrangement of 22 directly to the diacid 23b using silver nitrate,



14

15a, R = H;R'= OH

15b, R = CH_3;R'= OCH_3

15c, R = CH_3;R'= OH

15d, R = CH_3;R'= Cl

22

23a, R = CH_3

23b, R = H

24

16, R = CH_3

12, R = H

[a] hν. [b] $(CH_3)_2SO_4$, NaOH, H_2O. [c] NaOH, H_2O; then HCl. [d] $SOCl_2$, pyridine, C_6H_6. [e] CH_2N_2, Et_2O. [f] CH_3OH, AgOBz, Et_3N. [g] PPA, Δ. [h] H_2, Pd/C, CH_3CO_2H. [i] BBr_3, CH_2Cl_2.

Figure 1. Synthesis of Diphenol 12

sodium thiosulfate, and water[19] was unsuccessful.

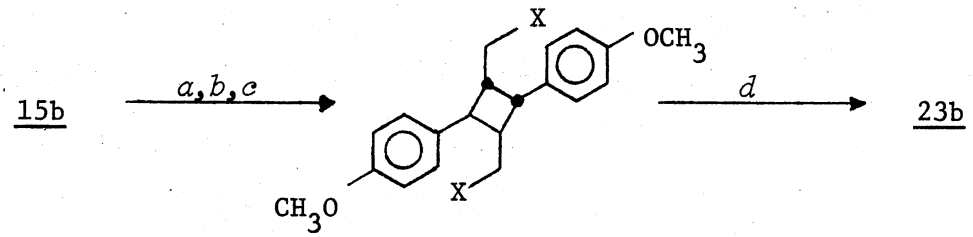
Addition of the diacid 23b to polyphosphoric acid (115% P_2O_5) at 65°C followed by stirring for 40 minutes at 65-70°C gave the diketone 24 in 82% yield. Variations in reaction time (20 minutes to 1 hour) or temperature (40-75°C) gave lower yields. Friedel-Crafts cyclization of 23b by conversion to the diacid chloride followed by addition to aluminum chloride in benzene also gave a lower yield (55%) of 24.

Initial attempts to hydrogenate 24 to the diether 16 using a palladium on carbon catalyst in acetic acid were unsuccessful apparently due to catalyst poisoning. After pretreatment of 24 with Raney-nickel catalyst[21] in refluxing ethyl acetate, hydrogenation proceeded readily to give the diether 16 in 83% yield.

The diphenol 12, an initial target compound for biological testing, was prepared by a cleavage of the diether 16 using an excess of boron tribromide in methylene chloride. Biological test results for anti-fertility activity of 12 and other compounds will be discussed in Chapter III.

An alternative synthesis[22] of 23b from 15b which avoids the use of diazomethane is shown in Figure 2. Reduction of the dimethyl ester 15b with diisobutylaluminum hydride gave the diol 25a which was converted to the ditosylate 25b with *p*-toluenesulfonyl chloride in pyridine. Treatment of 25b with sodium cyanide using dimethyl sulfoxide as solvent gave the dinitrile 25c in 76% overall yield based on 15b. Hydrolysis of 25c by refluxing with concentrated hydrochloric acid for 12 hours gave a low yield (33%) of impure diacid 23b. The base-insoluble product from this reaction appeared to be mainly the amide. Prolonged refluxing with hydrochloric acid gave acidic

material which appeared to have undergone partial demethylation. Attempts to hydrolyze 25c with acetic acid, water, and hydrochloric acid[18] gave mixtures of unidentified products believed to be amides and demethylated products. Until a practical hydrolysis of the dinitrile 25c to the diacid 23b is found, the scheme shown in Figure 1 remains the better synthesis of 23b.



25a, X = OH

25b, X = OTs

25c, X = CN

[a] $(i\text{-Bu})_2AlH$. [b] TsCl, pyridine. [c] NaCN, DMSO. [d] Conc. HCl.

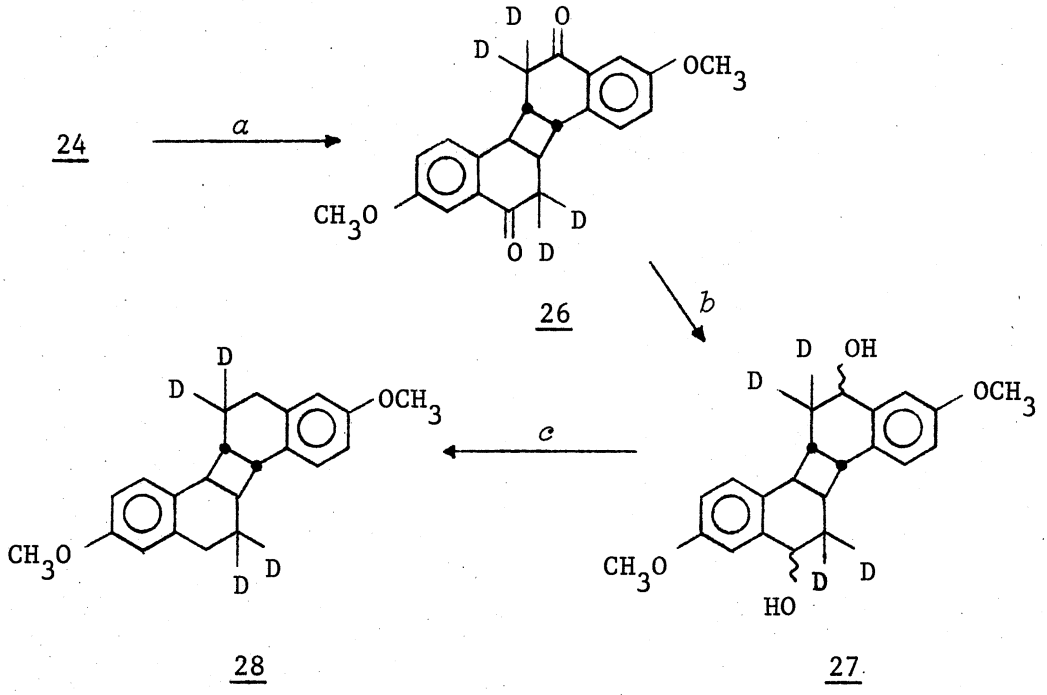
Figure 2. Alternate Scheme for Bishomologation of 15b

The structure and stereochemistry shown for 12, 15a-15d, and 22-25c are consistent with the spectral data for these compounds. The mass spectra as well as ^1H NMR and ^{13}C NMR spectra show specific features confirming the presence and stereochemistry of the cyclobutane ring.

The most striking feature of the 70 eV mass spectra[23] for compounds 12, 15b-15c, and 22-25c is the consistent appearance of parent ions with mass M/2, attributed to hemicleavage of the cyclobutane ring. The molecular ion peaks are extremely weak or absent in 70 eV spectra although they are present as weak ones in low voltage (8-10 eV) spectra. The occurrence of only one M/2 ion is evidence for the head-to-tail structure since similar 1,2-diarylcyclobutanes show two parent ions[24] with mass M/2 arising from different modes of hemicleavage. The presence of strong M/2 ions was valuable for confirming the integrity of the cyclobutane ring in subsequent structures.

The ^{1}H NMR[25] of 12, 15b-15d, and 22-25c exhibit, in addition to other resonances, two multiplets due to the benzylic and nonbenzylic cyclobutane protons. The four cyclobutane protons are coupled to form an AA'BB' system[26] although except for 15b, 15d, and 22, this is complicated by additional coupling and overlapping with other proton resonances. The complete analysis of the cyclobutane proton spectra composing an AA'BB' system allows assignment of stereochemistry to the cyclobutane protons based on the Karplus equation[27] relating vicinal coupling constants (^{3}J) with proton dihedral angles and the relationship between long range coupling constants (^{4}J) and proton stereochemistry in cyclobutane rings.[28]

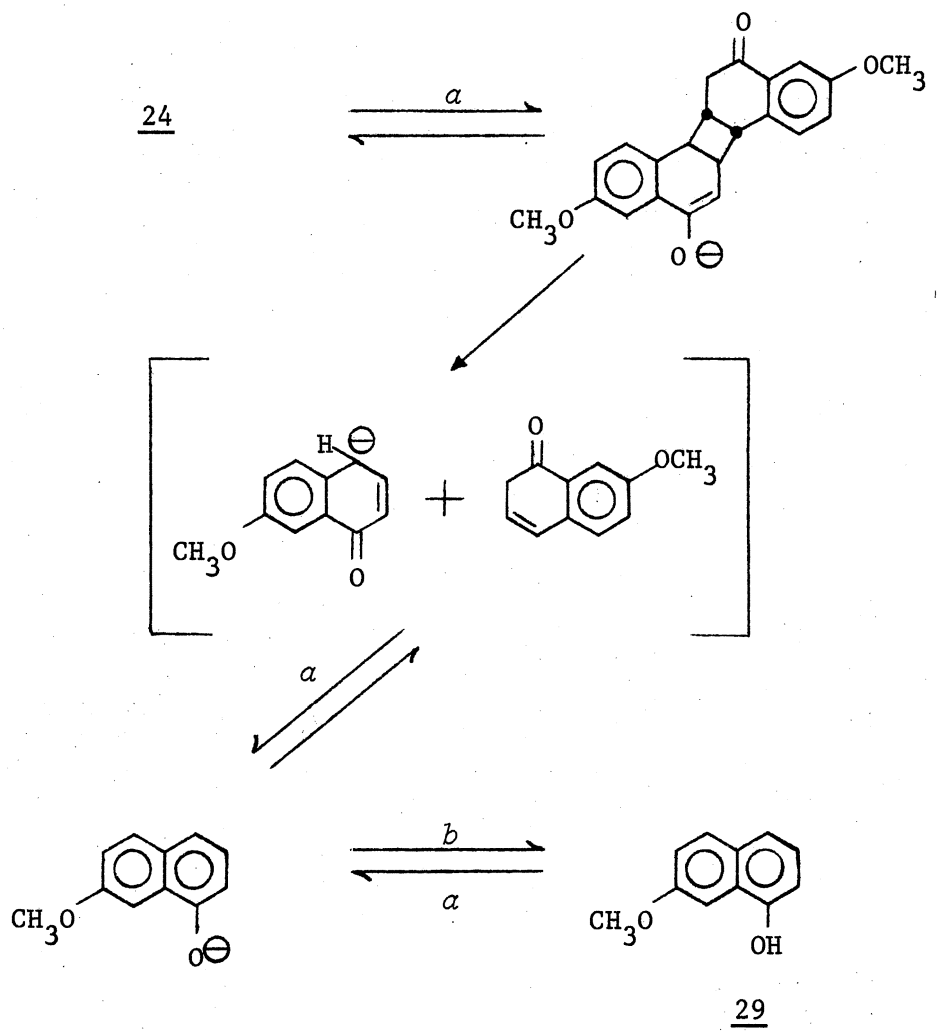
Analysis of the cyclobutane proton spectrum in 16 required prior simplification by decoupling the C-6 and C-12 protons from the C-6a and C-12a cyclobutane protons. Attempted decoupling by double irradiation was unsuccessful but the specturm of the tetradeuterated-diether 28 (synthesis shown in Figure 3) allowed direct observation of the cyclobutane proton subspectra.



[a] D_2O, AcOD, DCl, Δ. [b] $(i\text{-Bu})_2AlH$, C_6H_6. [c] H_2, Pd/C, AcOH, Δ.

Figure 3. Synthesis of 6,6,12,12-D_4-Diether 28

Deuteration of 24 with deuterium oxide, acetic acid-O-*d* and deuterium chloride gave 26 in 90% yield. To avoid possible loss of deuterium by enolization during hydrogenation, 26 was first reduced to the diol 27 (obtained as a mixture). Initial attempts to deuterate 24 by warming (60-70°C) with sodium deuteroxide and deuterium oxide in dioxane for four hours gave a 20% yield of 26. Acidification of the basic solution gave after purification, a 40% yield of 7-methoxy-1-naphthol (29). A possible rationalization of this facile carbon-carbon bond cleavage is shown in Figure 4.

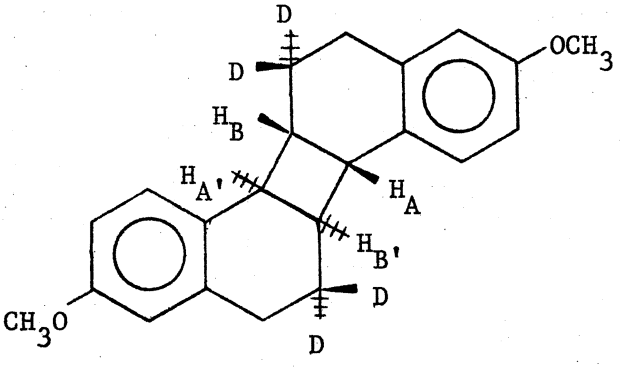


[a] D_2O, NaOD, dioxane. [b] H_3O^+.

Figure 4. Base Cleavage of Diketone 24

The 100 MHz ^1H NMR spectrum of 28 exhibited in addition to aromatic and methoxyl proton resonances, a doublet of doublets (AB system, J_{AB} = 16 Hz, δ_A = 2.98, δ_B = 2.72) due to the C-5 geminal benzylic protons and symmetrical multiplets centered at δ 3.2 (benzylic cyclobutane protons) and δ 2.5 (nonbenzylic cyclobutane protons). The

aromatic proton pattern and the benzylic cyclobutane proton pattern were indentical in 28 and 16 thus confirming that changes in stereochemistry had not occurred. Analysis of the cyclobutane proton subspectra using the iterative computer program ITRACAL[29] gave the spectral parameters shown in Figure 5 (root mean square deviation, 0.18). Trial values for the coupling constants were obtained from previous literature reports[28,30] for other cyclobutane compounds. Presumably, a small uncertainty is introduced in the values obtained because of broadening from long-range coupling of H_A and aromatic protons and between H_B and the C-6 deuterons.



$\delta_A = 2.49$, $\delta_B = 3.18$, ($\Delta\nu_{AB} = 69.0$ Hz)

$^3J_{AB} = 9.06$	$K = J(AA') + J(BB') = -1.32$
$^3J_{AB'} = 5.78$	$L = J(AB) - J(AB') = 3.28$
$^4J_{AA'} = -0.69$	$M = J(AA') - J(BB') = -0.06$
$^4J_{BB'} = -0.63$	$N = J(AB) + J(AB') = 14.84$

Figure 5. 100 MHz ^{1}H NMR Parameters (Hz) for D_4-Diether 28

Although it is possible to assign stereochemistry to substituted cyclobutane systems by assuming $^3J_{cis}$ is larger than $^3J_{trans}$, caution must be exercised when using this assumption because of the sensitivity of ^3J to substituent electronegativities, ring puckering angles, psuedorototation and inversion, etc.[28,31] Using the previously defined parameters[32] K, L, M, and N, a clearer differentiation of isomers is possible and assignments can be made with greater certainty.

From previously reported J values for various isomeric coumarin cyclobutane dimers[30a] and their sodium salts,[30c] carbostyril cyclobutane dimers,[30a] truxinic acids,[24b,28b] truxillic acids,[28b] truxones[30b] and derivatives,[24b,28b] the parameters K, L, M, and N, were obtained. For head-to-head isomers, the value of K is large (+6.5 to +19.4 Hz) because $J_{AA'}$ and $J_{BB'}$ are positive vicinal coupling constants (^3J). Conversely $J_{AA'}$ and $J_{BB'}$ are long-range coupling constants (^4J) for head-to-tail dimers and hence small or negative (-2.3 to +2.4 Hz). The small negative K value for 28, -1.32 Hz, clearly confirms the 1,3 placement (head-to-tail) of substituents in 28.

The differentiation of head-to-tail cis-syn-cis and cis-anti-cis isomers is straightfoward since the cis-syn-cis isomers exhibit an A_2B_2 pattern because of symmetry and hence K, L, and M are equal to 0. Additional confirmation for the cis-anti-cis structure of 28 is evident by considering the magnitude of K and L. In the head-to-tail isomers, K is the sum of two long-range coupling constants. When these protons (A and A', B and B') are trans, $^4J_{trans}$ is expected to be small and negative[28] although in some cases it is positive[28] (-2.3 to +2.4 Hz) while the value of $^4J_{cis}$ appears always to be positive.[28,30] The spectral parameter L, is the difference of two vicinal coupling

constants. Since $^3J_{cis}$ is usually larger than $^3J_{trans}$,[24,28,30] L is usually small but positive (+3.1 to +5.9 Hz) for cis-anti-cis isomers. In 28 the value of L, +3.28 Hz, corresponds closely to those observed for other head-to-tail cis-anti-cis isomers and the negative value of K, -1.32 Hz, appears to confirm the cis-anti-cis configuration of 28.

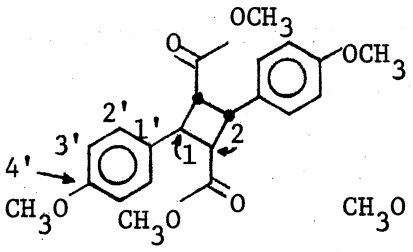
^{13}C NMR spectroscopy, because of the sensitivity of carbon shifts to conformation and structure and the ability to observe each individual carbon resonance in proton decoupled spectra, offers an additional approach to studying the structure and stereochemistry of 16 and precursors.

The ^{13}C NMR chemical shifts[33] and assignments of selected intermediates in Figure 1 and Figure 2 are shown in Table II. Assignments are based on the splitting patterns present in off-resonance proton-decoupled (ORPD) spectra and the use of substituent shift parameters.[34] In all cases the symmetry of these structures leads to the appearance of only half as many lines as there are carbons present. The cyclobutane carbons are easily assigned by their occurrence between 30-50 ppm and their appearance as doublets in ORPD or non-decoupled spectra.

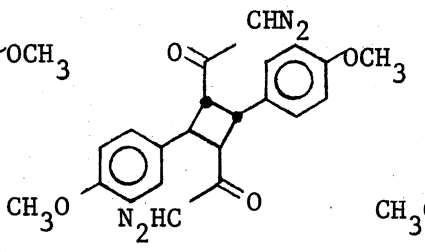
In Table III, the chemical shifts and assignments for the cyclobutane hydrocarbons 30,[30b] 31,[35] 32,[36] 33,[26] 34,[37] and 35,[37] and diethers, 16 and 18,[16] are listed. The number of carbon resonances confirms the symmetry of these molecules. Assignments of carbon resonances were based on model compounds, substituent shift parameters,[34] and the splitting patterns in ORPD spectra. The aromatic resonances were assigned by comparison with the parent monomeric compound (*eg.* 6-methoxytetralin for 16 and 18) and substituent shift parameters.[34] The cyclobutane carbons were identified by their

TABLE II

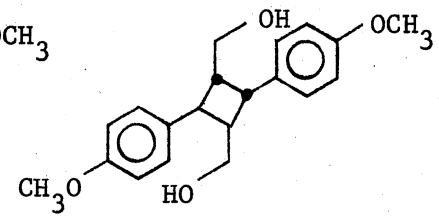
^{13}C NMR CHEMICAL SHIFT[a] ASSIGNMENTS
OF SUBSTITUTED CYCLOBUTANES



15b



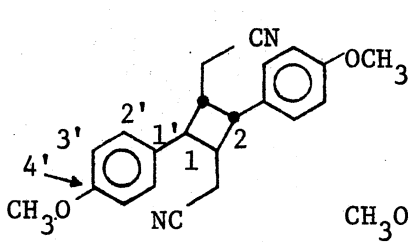
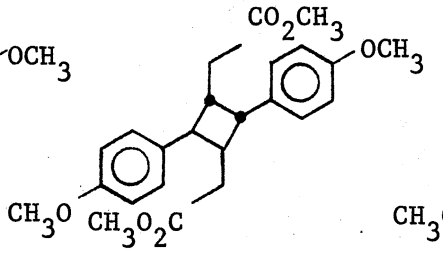
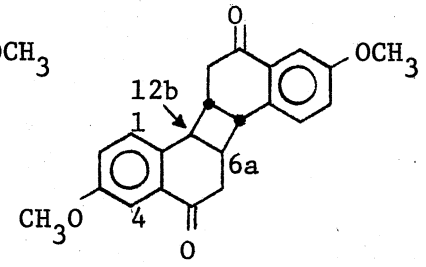
22



25a

	15b		22		25a
C-1	40.8[b]		41.2[b]		40.5[b]
C-2	47.1[b]		52.2[b]		42.8[b]
C-1'	130.6		130.5		131.6
C-2'	128.3		128.6		128.5
C-3'	113.6		113.7		113.8
C-4'	158.4		158.4		157.9
CO	172.1	CO	192.5	CH_2	63.2
$ArO\underline{C}H_3$	55.0	CHN_2	55.2	OCH_3	55.1
OCH_3	51.2	OCH_3	55.0		

TABLE II (continued)

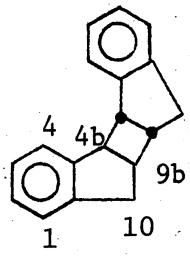
						
	25c		23a		24	
C-1	44.3[b]		44.6[b]	C-1	129.7	
C-2	37.3[b]		37.3[b]	C-2	122.2	
C-1'	128.6		131.2	C-3	158.2	
C-2'	128.8		128.9	C-4	108.6	
C-3'	114.3		113.5	C-4a	136.0	
C-4'	158.8		158.0	C-5	197.0	
CH_2	18.8	CH_2	35.7	C-6	40.0	
CN	118.0	CO	172.4	C-6a	37.8[b]	
OCH_3	55.2	$ArO\underline{CH}_3$	55.0	C-12b	38.8[b]	
		OCH_3	51.1	C-12c	132.8	
				OCH_3	55.3	

[a]Carbon chemical shifts were determined at 25.2 MHz on 0.6-0.9 M solutions in $CDCl_3$ and are expressed in ppm downfield from TMS.

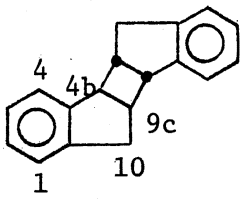
[b]The signals in a vertical column may be reversed.

TABLE III

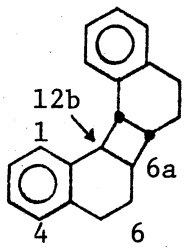
^{13}C NMR CHEMICAL SHIFT [a] ASSIGNMENTS OF CYCLOBUTANE HYDROCARBONS AND DIETHERS



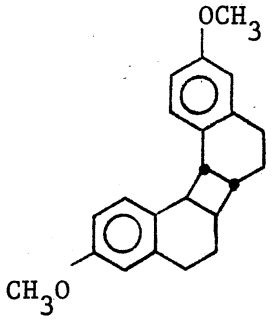
30



31



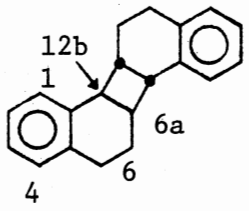
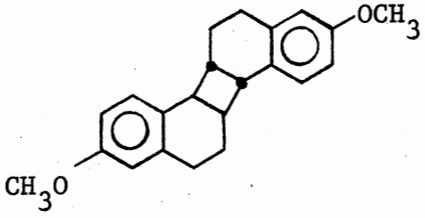
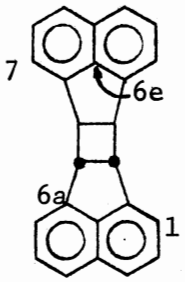
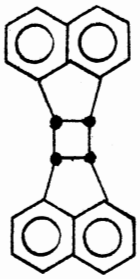
32



18

C-1	125.1[b]		124.8[b]	C-1	127.5[b]		128.6
C-2	126.5		126.3[b]	C-2	126.0[b]		111.9
C-3	126.5		126.4[b]	C-3	125.3[b]		157.6
C-4	124.8[b]		123.9[b]	C-4	128.2[b]		113.9
C-4a	146.2		146.9	C-4a	137.7		138.5
C-4b	53.8		51.8	C-5	27.7		28.2
C-9b	43.1	C-9c	45.6	C-6	26.7		26.8
C-10	39.3		39.8	C-6a	35.1		35.3
C-10a	143.5		143.6	C-12b	44.1		43.9
				C-12c	140.1		132.9
						CH_3O	55.1

TABLE III (continued)

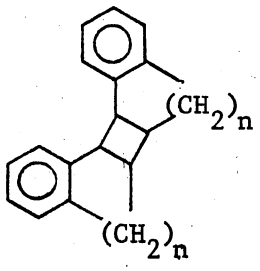
	 33	 16	 34	 35
C-1	127.8[b]	128.7	C-1 119.0	120.0
C-2	126.1[b]	111.9	C-2 128.1	126.6
C-3	125.2[b]	157.1	C-3 122.9	121.9
C-4	128.4[b]	113.4	C-3a 131.9	130.7
C-4a	137.4	138.6	C-6a 147.4	144.3
C-5	27.1	27.5	C-6b 52.4	47.2
C-6	26.3	26.2	C-6e 139.3	141.4
C-6a	37.9	37.1		
C-12b	40.8	41.0		
C-12c	140.5	132.7		
		CH_3O 55.0		

[a]Carbon chemical shifts were determined at 25.2 MHz on 0.6-0.9 M solutions in $CDCl_3$ and are expressed in ppm downfield from TMS.

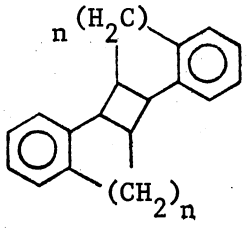
[b]The signals in a vertical column may be reversed.

appearance as doublets in ORPD spectra and the lower-field resonance assigned to the benzylic cyclobutane carbon because of the strongly deshielding effect of an adjacent aromatic ring. The two methylene carbons present in 16, 18, 32, and 33 were difficult to differentiate because of their similar shifts; however, the ORPD spectrum of the deuterated analog 28 lacked the resonance at 26.2 ppm and thus confirmed the assignments of the C-5 and C-6 resonances in 16 . Assignments for the C-5 and C-6 resonances in 18, 32, and 33 are based on their expected and observed similarity to 16.

Comparison of the chemical shifts for compounds shown in Table III reveals several definite trends which further confirm structural and stereochemical assignments of these compounds. In all of the head-to-head dimers (18, 30, and 32), the benzylic cyclobutane carbon resonance appears at lower field than the benzylic cyclobutane carbon resonance of the corresponding head-to-tail isomer (16, 33, and 31, respectively). Conversely, the nonbenzylic cyclobutane carbon resonance occurs at higher field in the head-to-head dimers than in the corresponding head-to-tail isomers. These relative shifts are qualitatively predictable by considering the relative placement and additive effects of a benzo substituent. In the head-to-head isomers each benzylic cyclobutane



Head-to-Head Isomer



Head-to-Tail Isomer

carbon is α to an aromatic ring (strongly deshielding[34]) and β to an aromatic ring (less deshielding[34]) while the in the head-to-tail isomers it is α to an aromatic ring and γ (weakly shielding[34]). In the head-to-head isomers the nonbenzylic cyclobutane carbon is β to an aromatic ring and α while in the head-to-tail isomers it is β to two aromatic rings. An additional expected trend is the upfield shift of carbon resonances in 35 relative to 34. This is probably due to a combination of the known γ effect[38] and to anisotropic shielding[38] and should occur in any of the cis-syn-cis isomers thus facilitating structural assignments.[39] The lack of significant upfield shifts between the C-6 (C-7) carbons of 32 and 18 and the C-6 (C-12) carbons of 33 and 16 confirms the cis-anti-cis configuration assigned to these molecules. Similarly the C-12a (C-12d) carbons of 32 and the C-6a (C-12a) carbon of 33 show nearly identical shifts as do the diethers 18 and 16. The shift differences for the aromatic carbons between the hydrocarbons (32 and 33) and the diethers (18 and 16) is the result of the para substituent effect of a methoxyl group relative to a proton (Lit.,[40] -7.7 ppm; observed for 15 and 23, -7.2 ppm and -7.8 ppm).

The structure and conformation of the diether 16, obtained by single crystal X-ray analysis,[14] are shown in Figure 6. The oxygen-oxygen distance, 12.9 Å, is expected to be identical for the diphenol 12 and hence comparable to that of other estrogenic compounds shown in Table I. Several other features are indicated in the side view, Figure 7. The plane of the A and B rings is 0.95 Å from the plane of the C and D rings. The cyclobutane ring is planar and the C-6a,6b (C-12a,12b) bond is 1.570 Å, somewhat longer than the average carbon-carbon single

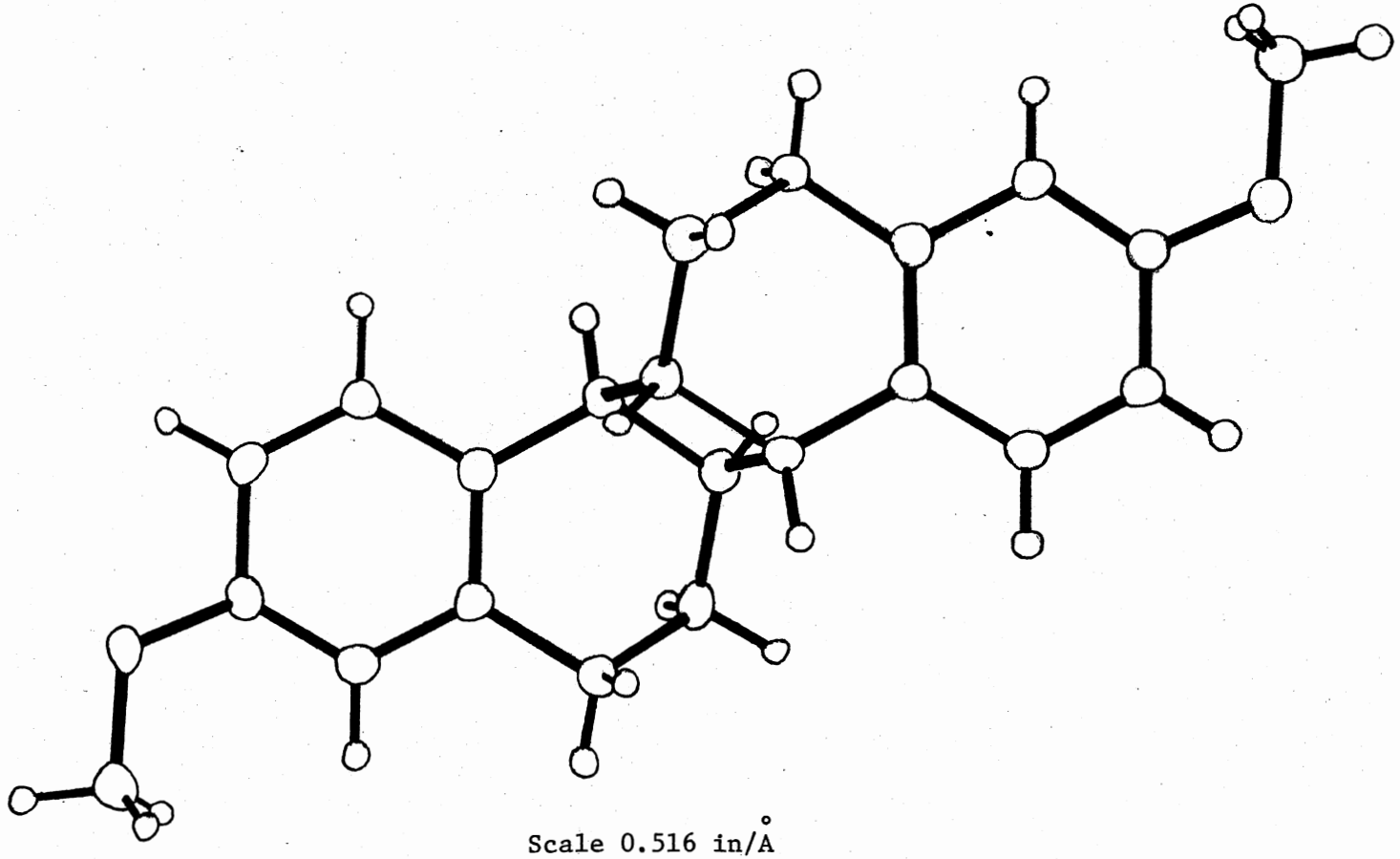
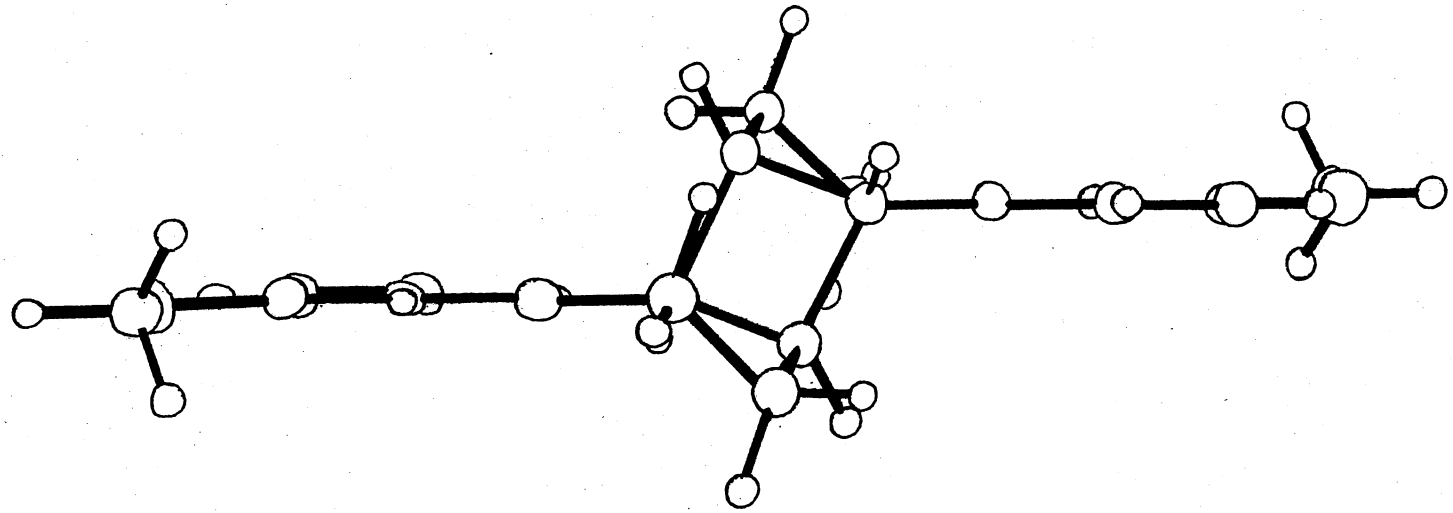


Figure 6. Computer-Generated Drawing of 16 From X-ray Crystallographic Data (Top View)



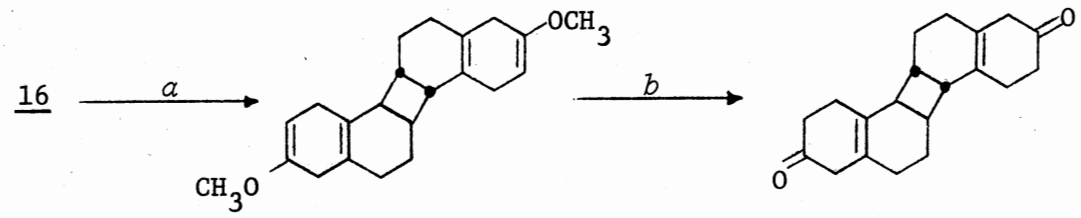
Scale 0.571 in/Å

Figure 7. Computer-Generated Drawing of 16 From X-ray Crystallographic Data (Side View)

bond. An additional feature of interest is the C-5α, C-6bβ proton-proton interaction, these protons being 2.37 Å apart in this conformation. The numbering used in Figure 6 and 7 may be found with structure 12 on page 5.

The synthesis of cyclobuta-BC-steroid homologs from the symmetrical intermediate 16, required differentiation and Birch reduction of the D ring. Attempts to simultaneously effect differentiation and reduction in 16 by Birch reduction of only one aromatic ring using a limited amount of lithium gave a mixture of 16 and the bis-enol ether 36. Reduction of 16 using excess lithium in ammonia, *tert*-butyl alcohol, and tetrahydrofuran (Dryden procedure[41]) gave 36 in 75% yield (Figure 8). Hydrolysis of 36 using oxalic acid as a catalyst gave the bis-β,γ-unsaturated ketone 37 (94%). The structure of the product was confirmed by the lack of vinyl protons in the ^{1}H NMR spectrum and the occurrence of ten lines in the fully decoupled ^{13}C NMR spectrum including a carbonyl carbon resonance at 210.1 ppm and two sp^2 carbon resonances at 125.9 and 131.0 ppm (Table IV). Treatment of 37 with dilute hydrochloric acid gave a mixture of β,γ and α,β-unsaturated ketones which was not further investigated. A sample of 37 was submitted for biological testing.

For selective Birch reduction of one aromatic ring in 16 it was necessary to differentiate the aromatic rings. Because of the known failure of phenols to reduce under normal Birch conditions (1M in lithium)[42] the monophenol 38 was selected.

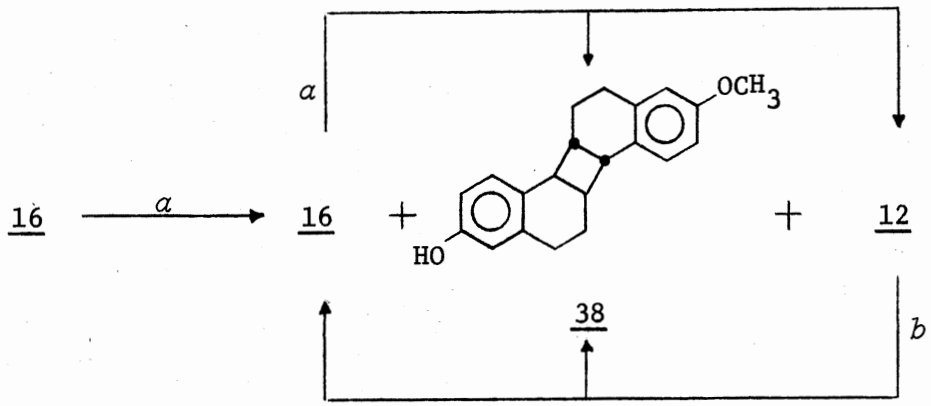


36 37

[a] Li, NH_3, *t*-BuOH, THF. [b] H_2O, oxalic acid, THF, *i*-PrOH, Δ.

Figure 8. Synthesis of Bis-β,γ-Ketone 37

Treatment of 16 with slightly more than one equivalent of boron tribromide in dichloromethane gave a mixture of products (Figure 8) shown by high pressure liquid chromatography (HPLC)[43] to be a statistical mixture of 12, 38, and 16 (1:2:1). The products were efficiently separated by extraction of the diphenol 12 from a mixture of 12, 16, and 38 with 5% potassium hydroxide followed by precipitation of the sodium salt of monophenol 38 using 10% sodium hydroxide solution saturated with sodium chloride.[44] The remaining diether was recovered and again subjected to boron tribromide treatment. The diphenol 12 was methylated using dimethyl sulfate and sodium hydroxide to give a mixture consisting of 65% monophenol 38, 20% diphenol 12, and 10% diether 16 which was separated as above. By recycling 12 and 16 (Figure 8) an essentially quantitative overall yield of 38 was obtained.



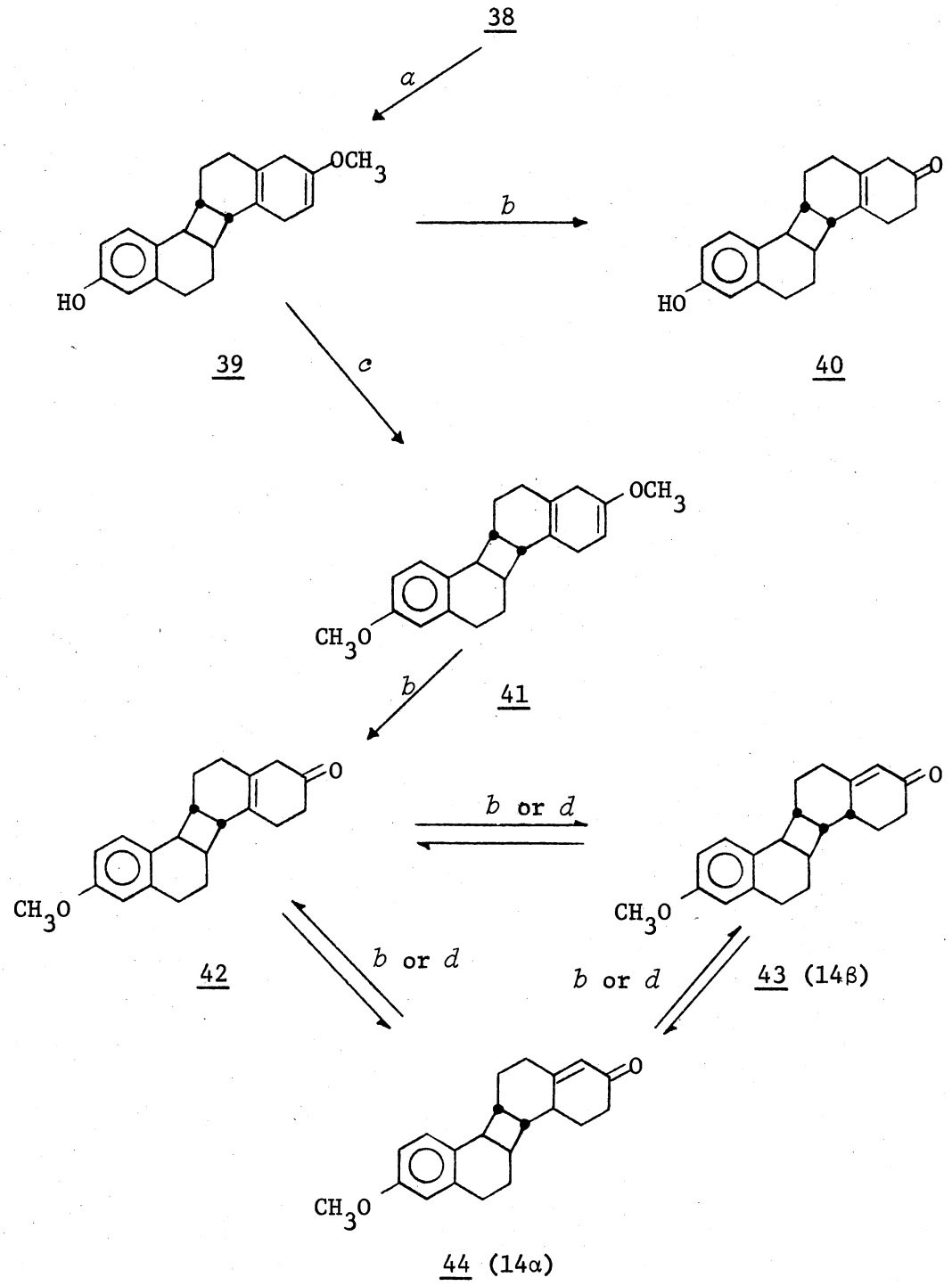
[a] BBr_3, CH_2Cl_2. [b] $(CH_3)_2SO_4$, NaOH, H_2O, CH_3OH.

Figure 9. Synthesis of Monophenol 38

Birch reduction of 38 using lithium, ammonia, *tert*-butyl alcohol and tetrahydrofuran[41] followed by evaporation of ammonia and extraction gave the phenolic enol ether 39 (Figure 10). Hydrolysis of 39 with oxalic acid and water gave the phenolic β,γ-unsaturated ketone 40 in 90% yield. A sample of 40 was submitted for biological testing.

For further elaboration of the D ring it was desirable to protect the phenolic group. The sensitivity of the β,γ-unsaturated ketone function to acid or base prevented methylation of 40 but the enol ether 39 was methylated with methyl iodide and base while keeping the reaction mixture basic to prevent hydrolysis of the enol ether. Hydrolysis of the methylated enol ether 41 with oxalic acid and water gave the protected β,γ-unsaturated ketone 42 in 78% yield based on 38.

Isomerization of the β,γ-unsaturated ketone 42 using acidic catalysts gave a mixture of 42 and two α,β-unsaturated ketones, 43 and



[a]Li, NH_3, *t*-BuOH, THF. [b]H_2O, $(CO_2H)_2$, *i*-PrOH, Δ. [c]CH_3I, NaOH, CH_3OH. [d]*i*-PrOH, PTSA.

Figure 10. Synthesis of α,β-Unsaturated Ketones 43 and 44

44, varying in configuration at C-14 (α or β) as shown in Figure 10. Quantitative analysis of the mixture by integration of the ^{1}H NMR spectrum was possible since 42 exhibits a broad singlet at δ 2.60 (C-17a methylene protons) while the α,β-unsaturated ketones 43 and 44 show the C-17a vinyl proton resonance at δ 6.03 and δ 5.88 respectively.

Brief equilibration of 42 in isopropyl alcohol with oxalic acid (80-100°C) or *p*-toluenesulfonic acid (room temperature) gave a mixture composed of 68% 42, 27% of the α,β-unsaturated ketone 43 showing a vinyl proton resonance at δ 6.03, and only a trace (10%) of the isomer 44 showing a vinyl proton resonance at δ 5.88. After prolonged treatment with acid (24 hours), the concentration of 42 was similar but 44 predominated over 43 (42:43:44; 70:13:17). Treatment of 42 with base led to degradation and numerous by-products. Attempts to drive the isomerization using stronger acid (trifluoroacetic acid or hydrochloric acid) or longer reaction times gave slightly higher ratios of 44:43 but lower overall yields. It appeared that 42 and 43 were selectively degraded. Equilibration of a 1:1 mixture of 43 and 44 with oxalic acid (17 hours) gave a mixture of 42, 43, and 44 (42:43:44; 44:25:36). The above data indicate that while 43 is formed faster (kinetic product), 44 is more stable (thermodynamic product) and that at equilibrium 42 is favored over 43 and 44.

The conjugated isomers 43 and 44 were separated from 42 by preparative HPLC[43] but suitable conditions for the seperation of 43 from 44 were not found. By repeated isomerizations of recovered 42, a high overall conversion to 43 and 44 was obtained. The isomer exhibiting a vinyl proton resonance at δ 6.03 was isolated by recrystallization of an enriched mixture obtained under conditions favoring kinetic

control (warming briefly with oxalic acid) and is tentatively assigned as the C-14β isomer 43. A sample of 43 was submitted for biological testing. The isomer exhibiting a vinyl proton resonance at δ 5.88, believed to be the C-14α isomer 44, was isolated by recrystallization of a mixture obtained under conditions favoring thermodynamic control (oxalic acid, refluxing isopropyl alcohol, 24 hours).

As previously noted, it was anticipated that the product from isomerization of 42 would be the C-14α isomer 44. This assumption was based on the precedent set by Birch reductions of steroids[17,41,42] and by examination of Dreiding models of 43 and 44. Birch reduction of A-ring aromatic steroids[17,41,42,45] affords, after hydrolysis and conjugation, the more stable α,β-unsaturated ketone containing a trans ring junction. Dreiding models indicate that both α,β-unsaturated ketones exhibit severe nonbonded proton-proton interactions arising from the cyclobutane protons (C-8α and C-9α) and certain α oriented axial protons of the C and D rings. It appears however, that 44 has acceptable conformations which reduce the severity of these interactions. Dreiding models of the β,γ-unsaturated ketone 42 suggest that these interactions are diminished because of the planarity of C-13 and C-14 and this may account for its greater stability. Different conformations of a model of 42 also suggest that β attack at C-14 is facilitated because the C-8α and C-9α protons shield the α face. This would lead to the kinetic product 43 (C-14β).

Stereochemical assignments of 43 and 44 are based on their ^{13}C NMR carbon chemical shifts. Consideration of various conformations of 43 suggests that the C and D rings are directed downwards (towards the α face) because of constraints imposed by the rigid C-14 center. This

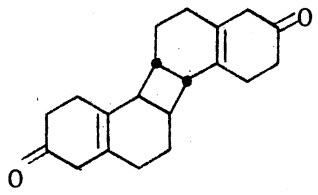
creates γ-gauche interactions between C-8 and C-15, C-9 and C-12, and C-11 and C-14. In structure 44, the C-14 center tends to direct the C and D rings upwards creating a more planar system which appears to lack these interactions. Comparison of various conformations of 43 and 44 suggests that the carbon resonances for C-8, C-15, C-9, C-12, C-11, and C-14 should appear upfield in 43 relative to those in 44 because of strain and a γ-effect due to the proximity of these carbons in 43.[34,38] The ^{13}C NMR chemical shifts and assignments of 43 and 44 are shown in Table V. As expected, methylene and methine carbon resonances of the isomer 43 (vinyl proton resonance at δ 6.03) show a consistent and strong upfield shift relative to those of 44 (vinyl proton at δ 5.88).

Assignments for the ^{13}C NMR carbon resonances of 37, 41, 42, and the saturated ketone 45 to be discussed subsequently, are tabulated in Table IV. In Table V similar data for 43 and 44 are presented. Carbon assignments for these compounds are based on standard methods (ORPD spectra, substituent effects, model compounds, etc).[34,46]

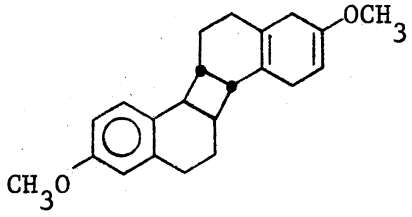
The 100 MHz ^{1}H NMR spectra of 43 and 44 show distinctive differences in the aromatic, vinyl, and cyclobutane proton resonances. The aromatic proton pattern of 44 is very similar to that of 16, 40, and 41 in that the protons ortho to the methoxyl group appear as a multiplet showing numerous peaks. In contrast, 43 exhibits an apparent broad singlet due to overlapping resonances. The benzylic cyclobutane multiplet of 44 is centered at δ 3.32 and is considerably deshielded compared to that of 43, 16, 41, and 42 (δ 3.16, 3.14, 3.16, and 3.15 respectively). The differences in 43 and 44 may be due to a decrease in the angle of the benzylic cyclobutane proton and aromatic ring in

TABLE IV

^{13}C NMR ASSIGNMENTS FOR 37, 41, 42, AND 45



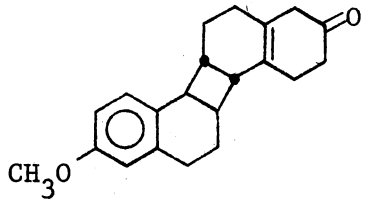
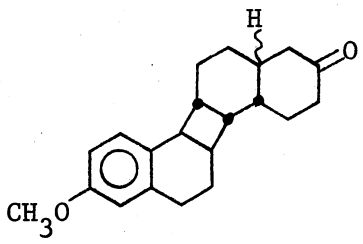
37



41[b]

C-1(C-15)	27.4[c]	C-1	128.3	C-9a	38.4[c]
C-2(C-16)	39.0	C-2	111.7	C-10	133.1
C-3(C-17)	210.1	C-3	157.1	C-11	23.5[c]
C-4(C-17a)	44.7	C-4	113.5	C-12	28.6[c]
C-5(C-13)	125.9	C-5	138.9	C-13	124.5
C-6(C-12)	28.4[c]	C-6	27.8	C-14	128.1
C-7(C-11)	25.6	C-7	26.2	C-15	29.3
C-8(C-9a)	38.1[c]	C-8	36.1[c]	C-16	90.6
C-9(C-8a)	39.0[c]	C-8a	40.0[c]	C-17	152.7
C-10(C-14)	131.0	C-9	40.7[c]	C-17a	34.2

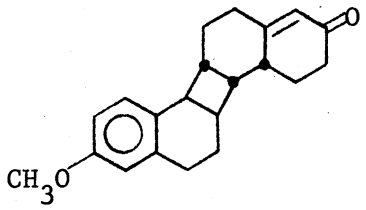
TABLE IV (continued)

 42[b]				 45[b]			
C-1	128.3	C-9a	39.1[c]	C-1	129.1	C-9a	32.5[c]
C-2	111.8	C-10	132.5	C-2	112.4	C-10	132.3
C-3	157.1	C-11	23.2[c]	C-3	157.0	C-11	25.9[c]
C-4	113.5	C-12	28.5[c]	C-4	113.2	C-12	26.6[c]
C-5	138.7	C-13	125.5	C-5	137.8	C-13	33.8[c]
C-6	27.7	C-14	131.0	C-6	27.2[c]	C-14	36.9[c]
C-7	26.4	C-15	28.5[c]	C-7	26.1[c]	C-15	25.5[c]
C-8	35.9[c]	C-16	39.0	C-8	34.7[c]	C-16	39.5
C-8a	40.0[c]	C-17	210.3	C-8a	39.0[c]	C-17	212.9
C-9	40.4[c]	C-17a	44.8	C-9	40.5[c]	C-17a	45.9

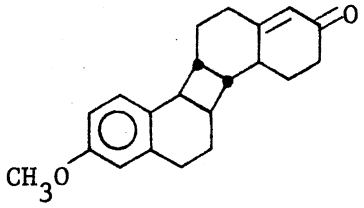
[a]Values in ppm downfield from TMS. [b]δ_{CH_3O} 55.0 or 55.1. [c]Assignments uncertain.

TABLE V

^{13}C NMR ASSIGNMENTS[a] OF 43 AND 44



43[b]



44[c]

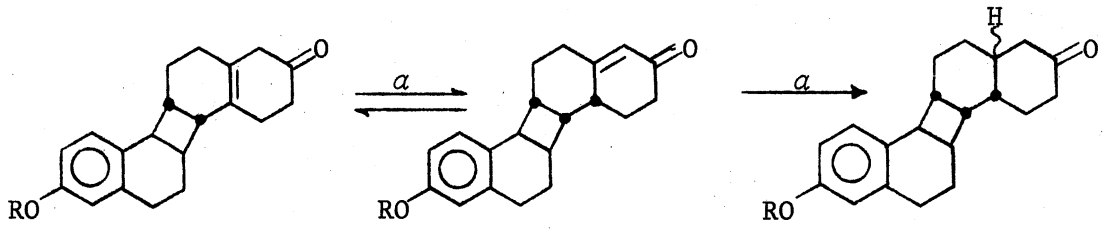
C-1	129.1	C-9a	33.4[d]	C-1	127.8	C-9a	37.4[d]
C-2	112.4	C-10	132.2	C-2	111.5	C-10	131.7
C-3	157.2	C-11	26.0[d]	C-3	157.0	C-11	25.6[d]
C-4	113.3	C-12	26.7[d]	C-4	113.2	C-12	30.2[d]
C-5	138.0	C-13	167.3	C-5	138.5	C-13	167.2
C-6	28.4[d]	C-14	36.3[d]	C-6	28.2[d]	C-14	38.4[d]
C-7	26.8[d]	C-15	24.5[d]	C-7	27.2[d]	C-15	27.2[d]
C-8	36.3[d]	C-16	37.6	C-8	39.4[d]	C-16	36.8
C-8a	37.6[d]	C-17	198.6	C-8a	40.2[d]	C-17	198.4
C-9	40.2[d]	C-17a	127.0	C-9	40.6[d]	C-17a	124.7

[a]Values in ppm downfield from TMS. [b]δ_{CH_3O} 55.1. [c]δ_{CH_3O} 54.7.

[d]Assignments uncertain.

44. The vinyl proton resonance of 43 is deshielded (δ 6.03) relative to 44 (δ 5.88) and Δ^4-3-keto steroids (average; δ 5.75).[47] The origin of this effect is unknown but is probably conformational rather than electronic since the ^{13}C NMR shift of the carbonyl carbon is similar in both 43 and 44.

Because of the unfavorable ratio of 44 to 42 obtained by equilibration of 42, a method for reducing 42 directly to a saturated ketone was desirable. Hydrogenation of the double bond in 42 appeared plausible because of the equilibration of 42 to 43 and 44 under acidic or basic conditions (Figure 11). Hydrogenation of 42 in ethanol with palladium on carbon and trifluoracetic acid or potassium hydroxide gave almost identical ratios of products as indicated by HPLC. The products were separated by preparative HPLC and consisted of monophenol 38 (10%), unknown products (5%) and two saturated ketones (70%) in a ratio of 85:15. The minor isomer was not obtained in a pure state but the ^{13}C NMR of a mixture indicates it is a saturated ketone (δ_{CO} 212.0 ppm) isomeric with 45. The 100 MHz ^1H NMR spectrum of major isomer 45 exhibited a benzylic cyclobutane proton resonance centered at δ 3.00 and an aromatic proton pattern almost identical to that of 43. Because of similarities between 43 and 45 for the benzylic cyclobutane proton shifts and the carbon shifts for C-1, the saturated ketone 45 is tentatively assigned the 14β configuration. This is consistent with the faster formation of 43 from 42 followed by hydrogenation to 45. The configuration of the C-13 proton is unknown. The lack of other isomers or model compounds prevented complete analysis of the ^{13}C NMR data for 45 (Table IV).



42, R = CH_3 45, R = CH_3

40, R = H 46, R = H

[a] TFA or KOH, H_2, Pd/C, EtOH.

Figure 11. Synthesis of Saturated Ketones 45 and 46

Hydrogenation of 40 under conditions identical to those used for 42 gave the phenolic ketone 46 isolated by preparative HPLC and traces of an isomer (85:15). The phenolic ketone 46 was also obtained from demethylation of 45 by brief treatment with boron tribromide. A sample of 46 was submitted for biological testing.

CHAPTER III

BIOLOGICAL TEST RESULTS

The phenols, 12, 40, and 46 and the nonphenolic ketones 37 and 43 were submitted to the National Institute of Health for antifertility testing.[48] Compounds 40, 43, and 46 were submitted as *dl* mixtures and it is unknown which enantiomer, if either, is the more active. The desired biological action was a high degree of antifertility activity without estrogenic effects. More specifically, a desirable compound would completely prevent pregnancy at a low dose (low ED_{100} for postcoital antifertility activity) and yet would not cause an increase in uterine weight (low percent relative activity to known estrogens in the uterotrophic test). The results obtained from tests conducted on rats are shown in Table VI.

The diphenol 12 exhibited considerable activity as a postcoital antifertility agent (ED_{100}=100γ) but is also estrogenic.[49] The phenolic saturated ketone 46, believed to have the 14β configuration although not extermely potent, shows a large separation of effects. The antifertility activity of 40 and 46 suggest that the more steroid-like cyclobuta-BC-steroids may show greater potency.

TABLE VI

TEST RESULTS FROM BIOLOGICAL ASSAYS

Test	Compound 12	37	40	43	46
Postcoital Antifertility[a]	0.1[b]	Inact(2)[c,d]	10[c]	Inact(400)[c,d]	3[c]
Uterotropic[e]	15.6[b,f]	0.37[c,g]	3.4[b,g] 1.6[c,g]	5.5[c,g]	0.07[c,h]

[a] ED_{100} in mg/Kg/day, (4 days). [b] Oral administration. [c] Subcutaneous administration. [d] Numbers in parentheses are highest dose tested. [e] Percent relative activity. [f] Relative to DES. [g] Relative to estrone. [h] Relative to estradiol.

CHAPTER IV

EXPERIMENTAL

2α,4β-Bis(4-hydroxyphenyl)cyclobutane-1α,3β-dicarboxylic acid (15a). (*E*)-4-Hydroxycinnamic acid (14) (300 g, 1.83 mol) and 5.5 L of H_2O were mixed portionwise in a Waring Blendor. The resulting finely divided suspension was added to a cylinder containing a quartz water-jacketed immersion well with a 450-W Hanovia lamp and Pyrex filter. The stirred slurry was irradiated for 7 days (the side of the well was cleaned intermittently and H_2O added to maintain the level of the slurry as needed). The solid was collected by filtration, dried, and extracted with ether in a Soxhlet apparatus, leaving a residue of 270 g (90%) of 15a; mp 335°C(dec.). A small sample recrystallized from 95% ethanol had mp 350°C(dec.) (lit.[15] mp 340°C).

2α,4β-Bis(4-methoxyphenyl)cyclobutane-1α,3β-dicarboxylic acid (15c) and dimethyl ester (15b). To a stirred solution of 1000 g (3.1 mol) of 15a in 6.25 L of 2 M NaOH under a N_2 atmosphere was added 1530 g (12 mol) of dimethyl sulfate over a period of 1 hour, during which time the temperature rose to 50°C. After 30 minutes of stirring, the pH had dropped to 6. A solution of 200 mL of 7.5 M NaOH was then added, followed by dropwise addition of 190 g (1.5 mol) of dimethyl sulfate. After 30 minutes of stirring, the mixture again became acidic. The addition of base and dimethyl sulfate was repeated 3 times. The reaction mixture was then made strongly basic by addition

of 1.5 L of 12 M NaOH and then slowly heated to 80°C. This temperature was maintained for 4 hours, then the homogeneous solution was filtered through Dicalite and acidified. The product was collected by filtration and dried to give 1003 g (95%) of 15c; mp 255-260°C. Recrystallization of small sample from acetic acid gave 15c, mp 260-261°C (lit.[15] 260.5-262.5°C).

The dimethyl ester 15b was prepared by esterification of 19c with methanol and H_2SO_4 in 82% yield; mp 128-129°C (lit.[15] mp 129-130°C); ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 4, ArH *O*- to CH), 6.84 (m, 4, ArH *O*- to OCH_3), 4.38 (m, 2, ArCH-), 3.90 (m, 2, $-CHCO_2CH_3$), 3.76 (s, 6, $ArOCH_3$), 3.32, (s, 6, $-CO_2CH_3$).

1α,3β-Bis(diazoacetyl)-2α,4β-bis(4-methoxyphenyl)cyclobutane (22). To a stirred slurry of 190 g (0.53 mol) of 15c in 1.5 L of benzene containing 3 mL of pyridine was added 175 mL (2.4 mol) of $SOCl_2$. The mixture was cautiously warmed until gas evolution started, then refluxed for 1 hour. The warm solution was filtered through Dicalite and the solvent and excess $SOCl_2$ were then removed under reduced pressure. The residue was dissolved in warm benzene, passed through a small column of acidic alumina and concentrated under reduced pressure leaving 192 g (92%) of the acid chloride 15d; mp 145-147°C.

A solution of 60 g (0.15 mol) of 15d in 600 mL of benzene was added dropwise with stirring to a chilled (0°C) solution of 32 g (0.76 mol) of CH_2N_2 in 2 L of ether.[50] The mixture was stirred overnight, then evaporated to a small volume. The solid was collected by filtration and washed with ether to give 54 g (87%) of 22. An analytical sample was prepared by recrystallization from $CHCl_3$-isohexane[51]; mp 143°C (dec): IR ($CHCl_3$) 2090, 1620 ($COCHN_2$) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20

(m, 4, ArH), 6.82 (m, 4, ArH), 4.88 (s, 2, CHN_2), 4.50 (m, 2, ArCH), 3.80 (m, 2, $C\underline{H}COCHN_2$), 3.76 (s, 6, $ArOCH_3$); MS (70 eV) *m/e*(rel intensity) $M^+/2$ (hemicleavage) 202(13), 174(100), 161(75), 131(49), 103(38).

Due to the instability of 22, a correct elemental analysis could not be obtained.

1α,3β-Bis(carbomethoxymethyl)-2α,4β-bis(4-methoxyphenyl)cyclobutane (23a) and diacid (23b). To a magnetically stirred slurry of 145 g (0.36 mol) of 22 in 1.5 L of anhydrous methanol was added dropwise a solution of 6.0 g of silver benzoate in 48 mL of $(C_2H_5)_3N$[20] at a rate sufficient to maintain a slow steady evolution of N_2. After 24 hours, N_2 evolution ceased and the mixture was heated to reflux for 30 minutes and then filtered while hot through Dicalite. The filtrate was evaporated and dried under reduced pressure. The residue was dissolved in benzene and chromatographed over acidic alumina. The eluate was concentrated, the residue triturated with ether, and the solid collected by filtration to give,after drying 102 g (69%) of 23a; mp 110-115°C. An analytical sample was prepared by recrystallization from methanol; mp 120-121°C; IR (KBr) 1720 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (m, 4, ArH), 6.86 (m, 4, ArH), 3.78 (s, 6, $ArOCH_3$), 3.48-3.30 (m, 4, $ArC\underline{H}C\underline{H}$). 3.40 (s, 6, CO_2CH_3), 2.40-2.10 (m, 4, $C\underline{H}_2CO_2CH_3$), MS (70 eV) *m/e*(rel intensity) $M^+/2$(hemicleavage) 206(100), 148(8), 147(73), 115(5), 91(8).

Anal. Calcd. for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.68; H, 6.61.

Hydrolysis of 23a (101 g, 2.45 mol) with methanolic NaOH gave after workup 90.1 g (96%); mp 240-243°C. Recrystallization from 2-propanol gave 23b, mp 248-250°C; IR (KBr) 3000 (Br, OH), 1700 (CO) cm^{-1} MS (70 eV) *m/e*(rel intensity) $M^+/2$(hemicleavage) 192(77), 147(100),

115(27), 97(29), 91(50).

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.60; H, 6.17.

3,9-Dimethoxy-6aα,6bβ,12aβ,12bα-tetrahydrodibenzo[*a*,*g*]biphenylene-5;11-(6*H*,12*H*)dione (24). To 250 mL of polyphosphoric acid (115% P_2O_5) prewarmed to 65°C was added over 5 minutes, 30 g (0.078 mol) of finely powered 23b. The mixture was stirred for 35 minutes and warmed to 70°C. The contents of the flask were then poured into a slurry of ice and H_2O in a Waring Blendor and stirred until hydrolysis was complete. The solid was collected by filtration, rinsed with H_2O, then slurried in a Waring Blendor for 5 minutes with 10% $NaHCO_3$. The solid was collected by filtration and dried. Recrystallization from ethanol gave 16.5 g of 24. The mother liquor was concentrated to furnish an additional 6.0 g (82% total yield), mp 160-162°C. An analytical sample was prepared by recrystallization and sublimation (170°C, 0.15 mm), mp 170-171°C; IR (KBr) 1675 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (m, 2, ArH), 7.14 (m, 4, ArH), 3.84 (s, 6, $ArOCH_3$), 3.46-3.38 (m, 2, ArCH), 3.06-2.92 (m, 6, $ArCHC\underline{H}C\underline{H}_2$-); MS (70 eV) *m/e*(rel intensity) $M^+/2$(hemicleavage) 174(100), 159(13), 131(20), 103(12), 76(7); (10 eV) 348(1), 174(100).

Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.64; H, 5.82.

3,9-Dimethoxy-5,6,6aα,6bβ,11,12,12aβ,12bα-Octahydrodibenzo[*a*,*g*]-biphenylene (16). A solution of 43 g (0.124 mol) of 24 in 1 L of ethyl acetate and 15 g of Raney Ni were refluxed for 15 minutes, then filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in 800 mL of acetic acid, 8 g of 5% Pd/C were

added and the mixture hydrogenated at 70°C and 50 psig. After H_2 uptake ceased (4 hours), the cooled mixture was filtered through Dicalite and then concentrated under reduced pressure. The residue and the Dicalite containing the used catalyst were placed above a column of basic alumina in a modified Soxhlet apparatus[52] and extracted with an isohexane-benzene mixture (9:1). The eluate was cooled, allowed to crystallize, and the solid collected by filtration to give 33.0 g (83%) of 16, mp 146-147°C; IR (KBr) 1250, 1030 ($ArOCH_3$), 850, 815, 795 (1,2,4 subst aromatic) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00-6.64 (m, 6, ArH), 3.75 (s, 6, OCH_3), 3.24-3.08 (m, 2, ArCH), 3.04-2.68 (m, 4, $ArCH_2$), 2.66-2.34 (m, 2, ArCHCH), 2.04-1.52 (m, 4, $ArCH_2CH_2$); MS (70 eV) *m/e*(rel intensity) M^+/2(hemicleavage) 160(100), 159(12), 145(9), 129(7), 117(5), 115(6); (8 eV), 320(4), 160(100); UV, 95% EtOH λ_{max} (log ε) 232.2 (4.31), 280.0 (3.54) nm.

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.21; H, 7.40.

3,9-Dihydroxy-5,6,6aα,6bβ,11,12,12aβ,12bα-Octahydrodibenzo[*a*,*g*]-biphenylene (12). To a stirred solution of 1.0 g (3.1 mmol) of 16 in 50 mL of CH_2Cl_2 was added dropwise a solution of 1.0 g (4.0 mmol) of BBr_3 in 5 mL of CH_2Cl_2. The mixture was stirred for 12 hours, then the solvent was removed under reduced pressure. The residue was treated with 50 mL of ether and 10 mL of H_2O, and stirred until the blue color disappeared. The organic phase was washed with H_2O, then extracted with 5% KOH. The aqueous phase was separated, acidified and the precipitate collected by filtration. Recrystallization from ether gave 0.60 g (66%) of 12; mp 235-237°C. An analytical sample was prepared by sublimation at 225°C, (0.2 mm); IR (KBr) 3300 (ArOH) cm^{-1}; ^1H NMR

(acetone-d_6) δ 7.84 (s, 2, ArOH), 6.94-6.56 (m, 6, ArH), 3.26-3.06 (m, 2, ArCH), 3.04-2.66 (m, 4, $ArCH_2$), 2.60-2.30 (m, 2, ArCHCH), 2.04-1.56 (m, 4, $ArCH_2CH_2$); MS (70 eV) *m/e*(rel intensity) $M^+/2$(hemicleavage) 146(100), 145(14), 131(8), 127(6), 117(4), 115(5); UV, 95% EtOH λ_{max} (log ε) 2.80 (3.64), with added base, 300 (3.78) nm.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89. Found: C, 82.30; H, 6.90.

1α,3β-Bis(hydroxymethyl)-2α,4β-bis(4-methoxyphenyl)cyclobutane (25a). To a mechanically stirred solution of 150 g (1.06 mol) of diisobutylaluminum hydride in 500 mL of benzene under N_2 was added 74.0 g (0.193 mol) of 15b in 500 mL of benzene at a rate sufficient to maintain a temperature of 40-50°C. After addition, the solution was held at 40-50°C for 2 hours, then chilled, and 35 mL of methanol were added to destroy excess hydride. The solution was poured into a mixture of ice and hydrochloric acid, stirred until gas evolution ceased, then extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 5% $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure to give 61.7 g (97.5%) of 25a; mp 114-115°C. A sample recrystallized from benzene-isohexane has mp 114.5-115°C; IR (KBr) 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32-6.82 (m, 8, ArH), 3.80 (s, 6, OCH_3), 3.60-3.42 (m, 6, ArCH and CH_2OH), 3.30-3.00 (m, 2, ArCHCH), 120 (s, 2, CH_2OC); MS (70 eV) *m/e* (rel intensity) $M^+/2$(hemicleavage) 164(100), 121(88), 180(38), 91(12).

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.12; H, 7.26.

1α,3β-Bis(*p*-toluenesulfonyloxymethyl)-2α,4β-bis(4-methoxyphenyl)-cyclobutane (25b). To a solution of 55.7 g (0.170 mol) of 25a in 475 mL of dry pyridine at 0°C was added in portions with stirring 77.6 g

(0.376 mol) of *p*-toluenesulfonyl chloride, the temperature being held at 0°C. The solution was allowed to stand at -10°C for 24 hours, then poured into a mixture of ice-hydrochloric acid. The precipitate was isolated by filtration, washed with cold 5% HCl and dried under vacuum. Recrystallization from $CHCl_3$-isohexane gave 97.0 g (90%) of 25b; mp 124-125°C; IR (KBr), 1370, 1190, ($-OSO_2-$) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50-6.72 (m, 16, ArH), 3.84-3.70 (m, 4, $-CH_2OTs$), 3.76 (s, 6, $ArOCH_3$), 3.60-3.10 (m, 4, ArCHCH), 2.38 (s, 6, $ArCH_3$); MS (70 eV) *m/e*(rel intensity) $M^+/2$(hemicleavage) 270(12), 172(66), 155(23), 108(78), 91(100).

Anal. Calcd. for $C_{34}H_{36}S_2O_8$: C, 64.14; H, 5.70. Found: C, 64.36; H, 5.81.

1α,3β-Bis(cyanomethyl)-2α,4β-bis(4-methoxyphenyl)cyclobutane (25c). To a stirred solution of 95.5 g (0.150 mol) of 25b in 1 L of dimethylsulfoxide was added 19.5 g (0.398 mol) of NaCN, and the slurry warmed to 50°C. After 1 hour, the solution became homogeneous and the temperature was held at 40-50°C for 4 hours. The solution was chilled, poured into H_2O, extracted with CH_2Cl_2, the extract dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was recrystallized from ethanol to give 45.2 g (87%) of 25c, mp 153-154°C; IR (KBr) 2250 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28-6.88 (m, 8, ArH), 3.82 (s, 6, OCH_3), 3.76-3.58 (m, 2, ArCH), 3.48-3.18 (m, 2, ArCHCH), 2.25-2.10 (m, 4, CH_2CN); MS (70 eV) *m/e*(rel intensity) $M^+/2$(hemicleavage) 173 (100), 158(5), 130(10), 103(7).

Anal. Calcd. for $C_{22}H_{22}O_2N_2$: C, 76.27; H, 6.40; N, 8.09. Found: C, 75.98; H, 6.54; N, 8.02.

2α,4β-Bis(4-methoxyphenyl)cyclobutane-1α,3β-diethanoic acid (23b)

from dinitrile (25c). A slurry of 10 g (0.03 mol) of 25c in 400 mL of concentrated HCl was stirred and warmed (80-90°C) for 12 hours. After cooling, the solid was collected by filtration, then slurried and warmed with 10% Na_2CO_3 for 30 minutes. The undissolved solid was collected by filtration (mp 200-240°C) and appeared to be a mixture of amide and nitrile (IR 2250, 1660 cm^{-1}).

The filtrate was acidified, and the resulting solid was collected by filtration and dried to give 3.7 g (33%) of 23b; mp 230-240°C. Prolonged heating of 25c in concentrated HCl led to a mixture of unidentified products.

Deuteration of 24. A. DCl Catalyzed Exchange. To a solution of 1.5 g (4.3 mol) of 24 in 10 mL of acetic acid-O-*d* was added 5 mL of acetyl chloride and 5 mL of D_2O. The solution was refluxed for 4 hours, then diluted with D_2O and chilled. The solid was collected by filtration, rinsed with acetic acid-O-*d* and dried to give 1.4 g (93%) of 26, mp 160-162°C. ^1H NMR ($CDCl_3$) δ 7.50-7.20 (m, 6, ArH), 3.88 (m, 6, OCH_3), 3.45-3.30 (m, 2, ArCH), 3.08-2.94 (m, 2, ArCHCH); MS (10 eV) *m/e*(rel intensity), 353(2), 352(3.2), 351(1.6), 177(100), 175(42).

B. NaOD Catalyzed Exchange. To a solution of 800 mg (2.3 mmol) of 24 in 20 mL of dioxane and 5 mL of D_2O under a N_2 atmosphere was added a solution of 180 mg (4.3 mmol) of NaOD in 3 mL of D_2O. The resulting solution was warmed (60-70°C) for 4 hours, then diluted with D_2O and chilled. The solid was collected by filtration, rinsed with D_2O, and dried to give 200 mg (25%) of 26; mp 158-160°C. The filtrate was acidified with 10% HCl and extracted with ether (2X). The ether extract was extracted with 10% NaOH and the basic extract acidified with 10% HCl. The acidified solution was extracted with

ether (2X) and the ether solution dried (Na_2SO_4), evaporated, and sublimed (80-95°C, 0.2 mm) to give 400 mg (50%) of 7-methoxy-1-naphthol (29); mp 103-105°C (Lit.[53] 103-105°C). ^1H NMR ($CDCl_3$) δ 7.72-7.04 (m, 6, ArH), 6.10 (s, 1, ArOH), 3.83 (s, 3, $ArOCH_3$).

6,6,12,12-tetradeuterio-diether (28). To a solution of 260 mg (1.8 mmol) of diisobutylaluminum hydride in 10 mL of benzene under N_2 was added a solution of 200 mg (0.57 mmol) of 26 in 10 mL of benzene. The solution was stirred for 3 hours (25°C) then chilled and 5% HCl was cautiously added. The precipitated solid was collected by filtration and extracted with hot benzene. The benzene filtrates were combined, washed with 5% $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residual diol 27 (mp 150-160°C) was dissolved in 30 mL of acetic acid, 100 mg of 5% Pd/c were added and the mixture hydrogenated (15 psig) at 60°C until H_2 uptake ceased. The product, 28, was isolated as previously discribed for 16, in 27% yield. ^1H NMR ($CDCl_3$) δ 7.04-6.66 (m, 6, ArH), 3.78 (s, 6, OCH_3), 3.18, 2.49 (2 sym. m, AA'BB' system, 4, $^3J_{AB}$=9.1 Hz, $^3J_{AB'}$=5.8 Hz, $^4J_{AA'}$=-0.7 Hz, $^4J_{BB'}$=-0.6 Hz, ArCH and ArCHCH), 2.98, 3.72 (d of d, AB system, 4, $^2J_{AB}$=16 Hz, ArCHH'); MS (8 eV) *m/e*(rel intensity) 325(1.2), 324(2), 323(1.8), 163(14), 162(100), 161(22).

3,9-Dimethoxy-1,4,5,6,6aα,6bβ,7,10,11,12,12aβ,12bα-dodecahydrodibenzo[*a*,*g*]biphenylene (36). To a stirred solution of 4.0 g (0.013 mol) of 16 in 125 mL of *tert*-butyl alcohol, 125 mL of tetrahydrofuran and 300 mL of liquid NH_3 (prepared by distillation from cylinder) was added 4.0 g (0.57 mol) of Li over 30 minutes. The NH_3 was refluxed until the blue color faded (3 hours) then allowed to evaporate through a Hg bubbler. The residue was dissolved in H_2O and extracted

with ether (3X). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Crystallization of the residue from isohexane gave 3.1 g (75%) of 36, mp 128-130°C; IR (KBr) 1650 (methoxy enol ether) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.65 (broad s, 2, vinyl H), 3.54 (s, 6, $-OCH_3$), 3.74-3.62 (m, 8, diallylic-CH_2-), 2.35-2.15 (m, 4, cyclobutyl H), 2.05-1.05 (m, 4, allylic-CH_2-), 1.80-1.60 (m, 4, $-CH_2-$); MS *m/e*(rel intensity) (70 eV) 324(15), 162(100), 147 (98), 134(87), 105(30), 95(78).

1,2,5,6,6aα,6bβ,7,8,11,12,12aβ,12bα-Dodecahydrodibenzo[*a*,*g*]-biphenylen-3,9(4*H*,10*H*)-dione (37). To a solution of 3.0 g (0.09 mol) of 36 in 30 mL of isopropyl alcohol and 30 mL of tetrahydrofuran was added 0.1 g of oxalic acid in 6 mL of H_2O. The solution was warmed on a steam bath for 15 minutes, H_2O was added until a turbidity devoloped and the solution allowed to cool. After chilling, the solid was collected by filtration and dried to give 2.3 g of 37, mp 138-140.5°C. A second crop of 0.3 g (94% total) was obtained by diluting the filtrate with H_2O. An analytical sample was prepared by recrystallization from isohexane-benzene, mp 141-142.5°C; IR (CS_2) 1730 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.80 (s, 4, allylic-CH_2-α to CO), 2.60-2.10 (m, 12, allylic and α to CO), 2.10-1.90 (m, 4, cyclobutyl), 1.90-1.60 (m, 4, $-CH_2-$); MS (70 eV) *m/e*(rel intensity) $M^+/2$(hemicleavage) 148 (100), 106(60), 91(30), 32(30), 28(100); UV, 95% EtOH λ_{max} (log ε) 2.30 (2.78) nm.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: H, 8.22.

3-Hydroxy-9-methoxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo-[*a*,*g*]biphenylene (38). (A) From diether 16. To a stirred solution of 32.5 g (0.10 mol) of 16 in 1.2 L of CH_2Cl_2 was added dropwise a

solution of 13.0 g (0.05 mol) of BBr_3 in 20 mL of CH_2Cl_2. After stirring for 12 hours, the solvent was removed under reduced pressure. The residue was treated with ether and H_2O and the mixture stirred until the blue-green color disappeared. Additional ether was added to dissolve the solid, and the aqueous layer was separated and discarded. The ether solution was extracted 2X with 5% KOH. The combined basic extracts were acidified with 10% HCl and the solid collected by filtration and dried to give 5.8 g (20%) of 12. The remaining ether solution was stirred for 30 minutes with 10% NaOH saturated with NaCl. The precipitated sodium salt of 38 was collected by filtration and washed with ether and then saturated NaCl solution. The filtrate was separated from H_2O and the ether solution dried (Na_2SO_4) and then evaporated leaving 9.1 g (28%) of 16. The H_2O layer was acidified to give 0.5 g of impure 38. The solid sodium salt of 38 was dissolved in a mixture of ether and 10% HCl and the ether layer separated. The ether solution was dried (Na_2SO_4) and evaporated to give 15.0 g (51% total) of 38, mp 168-170°C. An analytical sample was prepared by recrystallization from acetone, mp 170-172°C; IR ($CHCl_3$) 3300 (ArOH), 1240, 1030, ($ArOCH_3$) cm^{-1}; ^1H NMR (acetone-d_6) δ 8.84 (s, 1, ArOH), 7.00-6.60 (m, 6, ArH), 3.72 (s, 3, $ArOCH_3$), 3.25-3.10 (m, 2, ArCH), 3.00-2.64 (m, 4, $ArCH_2$), 2.60-2.30 (m, 2, ArCHCH), 2.00-1.50 (m, 4, $ArCH_2CH_2$); MS (70 eV) *m/e*(rel intensity) 161(15), 160(100), 159(13), 146(24), 145(17).

Anal. Calcd. for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.24 H, 7.30.

(B) From diphenol 12. To a stirred solution of 3.0 g (0.07 mol) of NaOH in 75 mL of H_2O and 100 mL of methanol under N_2 was added 14.0 g (0.04 mol) of 12. The mixture was stirred for 10 minutes then

8.0 g (0.06 mol) of dimethyl sulfate were added dropwise. After 2 hours, the mixture was acidified with 10% HCl and extracted with ether (2X). The ether extract was washed with 5% KOH (2X) and the combined basic extracts acidified to give 1.4 g (10%) of 12. The ether layer was stirred for 0.5 hours with 10% NaOH saturated with NaCl and the precipitated sodium salt of 38 was collected by filtration and washed with ether. The ether layer of the filtrate was separated from H_2O, dried (Na_2SO_4), and evaporated to give 3.0 g (20%) of 16. The sodium salt of 38 was dissolved in a mixture of ether and 10% HCl and extracted with ether (2X). The combined ether extracts were dried (Na_2SO_4), and evaporated under vacuum to give 8.8 g (60%) of 38, mp 169-172°C.

3-Hydroxy-18-nor-D-homocyclobuta-BC-estra-1,3,5(10),13(14)-tetraene-17-one (40). To a stirred solution of 9.8 g (0.032 mol) of 38 in 250 mL of tetrahydrofuran and 250 mL of *tert*-butyl alcohol was added 500 mL of liquid NH_3 by distillation from a cylinder. To the resulting solution was added 6 g (0.87 mol) of Li over 45 minutes. The solution was stirred at the reflux temperature of NH_3 until the blue color faded (4 hours) then allowed to warm and NH_3 distilled off through a Hg bubbler trap. The residue was treated with saturated NaCl solution and extracted (3X) with an ether-benzene mixture (8:2). The organic extracts were combined, dried (Na_2SO_4), and the solution concentrated under vacuum, leaving a residue of the phenolic enol ether 39.

The crude enol ether 39 was dissolved in 100 mL of isopropyl alcohol and to this solution was added 0.3 g of oxalic acid in 20 mL of H_2O. The solution was heated on a steam bath for 15 minutes, then H_2O

was added until the solution became faintly cloudy. The solution was chilled, allowed to crystalize overnight, and the solid collected by filtration. Recrystallization from acetone-isopropyl alcohol gave 9.3 g (96%) of 40, mp 204-207°C. An analytical sample was prepared by sublimation (203°C/0.03 mm); IR (KBr) 3300 (OH), 1710 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.90 (s, 1, ArOH), 6.88-6.45 (m, 3, ArH), 3.08-2.94 (m, 1, ArH), 2.80 (broad s, 2, allylic CH_2 α to CO), 2.80-2.10 (m, 9, benzylic CH_2, allylic CH_2, CH_2CO, and allylic cyclobutyl H), 2.00-1.50 (m, 6, CH_2 α to cyclobutyl and cyclobutyl H); MS (70 eV) *m/e*(rel intensity) 296(1), 146(100), 145(14), 131(7), 117(6); (6 eV) 296(6), 146(100); UV, $CHCl_3$ λ_{max} (log ε) 281 (3.50), 287 sh (3.10), 238 (3.30) nm.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.42; H, 7.43.

3,9-Dimethoxy-5,6,6aα,6bβ,7,10,11,12,12aβ,12bα-decahydrodibenzo[*a*,*g*]biphenylene (41). The crude phenolic enol ether prepared as above from 14.0 g (0.046 mol) of 38, and 7.0 g (1.0 mol) of lithium, was dissolved in 150 mL of methanol containing 4.5 g (0.08 mol) of KOH. To this solution was added 5.0 g of methyl iodide (0.035 mol) and the solution was gently warmed (35-40°C). Another 5.0 g of methyl iodide were added after 30 minutes. After 6 hours additional KOH (2.0 g, 0.04 mol) and methyl iodide (5.0 g) were added. The mixture was allowed to stand overnight, then the solid was collected by filtration and dried to give 9.3 g of 41, mp 112-116°C. By treatment of the filtrate with more KOH and methyl iodide and additional 1.1 g of 41 were obtained (total yield, 73%). An analytical sample was prepared by recrystallization from methanol-benzene; mp 112-114°C, IR (KBr) 1650 (enol ether) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98-6.60 (m, 3,

ArH), 4.66 (broad s, 1, vinyl H), 3.74 (s, 3, $ArOCH_3$), 3.54 (s, 3, enol OCH_3), 3.24-3.08 (m, 1, ArCH), 2.94-1.50 (broad hump, 15 protons); MS (70 eV) *m/e*(rel intensity) $M^+/2$(hemicleavage) 162(38), 160(100), 156 (56); (8 eV) 322(4.6), 160(100).

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 82.97; H, 8.23. Found: C, 83.14; H, 8.11.

3-Methoxy-18-nor-D-homocyclobuta-BC-estra-1,3,5(10),13(14)-tetraene-17-one (42). To a solution of 10.2 g (0.032 mol) of 41 in 150 mL of isopropyl alcohol and 30 mL of tetrahydrofuran was added 10 mL of H_2O and 0.3 g of oxalic acid. The mixture was warmed for 30 minutes and H_2O was added until a faint cloudiness devoloped. After cooling, the solid was isolated by filtration and dried affording 9.0 g (91%) of 42, mp 118-122°C. An analytical sample was prepared by recrystallization from methanol, mp 122-124°C; IR (CS_2) 1730 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00-6.65 (m, 3, ArH), 3.76 (s, 3, $ArOCH_3$), 3.24-3.08 (m, 1, ArCH), 2.60 (broad s, 2, C-17a protons), 2.62-1.50 (broad hump, 14 protons); MS (70 eV) *m/e*(rel intensity) $M^+/2$(hemicleavage) 160(100), 145(7), 115(7), 91(8); UV, 95% EtOH λ_{max} (log ε) 280 (3.21) nm.

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.60; H, 7.64.

Isomerization of 42 to 3-methoxy-18-nor-D-homo-14β-cyclobuta-BC-estra-1,3,5(10),13(17a)-tetraene-17-one (43) and the 14α isomer 44. To a solution of 1.0 g of oxalic acid in 100 mL of isopropyl alcohol was added 5.0 g (0.016 mol) of 42. The mixture was gently refluxed for 15 hours. The isopropyl alcohol was removed under reduced pressure and the residue partitioned between H_2O and ether. The ether

layer was separated, dried (Na_2SO_4), and evaporated to leave a residue of 42, 43, and 44 (7:1.8:1.2 by ^1H NMR). The mixture was separated by HPLC[43] on a silica gel column by elution with a 95% CH_2Cl_2-5% ethyl acetate mixture to give 3.2 g (64%) of 42 and 1.4 g (28%) of a mixture of 43 and 44 (3:2). Several recrystallizations from acetone gave pure 44, mp 153-154°C; IR (KBr) 1650 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98-6.90 (m, 1, C-1 ArH), 6.76-6.62 (m, 2, C-2 and C-4 ArH), 5.88 (broad singlet, 1, vinyl H), 3.78 (s, 3, $ArOCH_3$), 3.40-3.24 (app. t, 1, ArCH), 2.80-1.50 (broad hump, 16 protons); MS (70 eV) *m/e*(rel intensity) 308 (1.6), 160(100), 159(15.9), 145(15), 129(10).

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.95; H, 7.94.

Brief equilibration of 42 (20 minutes) with oxalic acid afforded after removal of 42, a mixture rich in 43. Several recrystallizations from methanol gave pure 43, mp 143-144°C; IR (KBr) 1658 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00-6.70 (m, 1, C-1 ArH), 6.80-6.70 (m, 2, C-2 and C-4 ArH), 6.03 (broad s, 1, vinyl H), 3.80 (s, 3, $ArOCH_3$), 3.24-3.04 (m, 1, ArCH), 3.02-1.55 (broad hump, 16 protons); UV, 95% EtOH λ_{max} (log ε) 234 (4.21) nm.

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.90; H, 7.73.

3-Methoxy-18-nor-D-homo-14β-cyclobuta-BC-estra-1,3,5(10)-triene-17-one (45). To a mixture of 5.0 g (0.016 mol) of 42 in 450 mL of 95% ethanol-5% trifluoroacetic acid was added 0.9 g of 5% Pd/C. The mixture was hydrogenated (15 psig, 45°C) until hydrogen uptake ceased (5 hours). The solution was filtered through Dicalite and the catalyst containing Dicalite rinsed with hot ethanol. The filtrate was neutralized with

solid $NaHCO_3$ and concentrated under reduced pressure. The residue was treated with water, extracted with ether, and the ether extract dried (Na_2SO_4) and evaporated leaving a mixture of products. The products were seperated by HPLC[43] on a silica gel column using CH_2Cl_2 as eluant, affording 3.5 g (70%) of a mixture of 45 and an isomer. The ^{13}C NMR spectrum of the mixture indicated it to be composed of 85% 45 and 15% of an isomeric ketone. Several recrystallizations of the mixture from methanol gave pure 45, mp 117-119°C; IR (CS_2) 1740 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98-6.90 (m, 1, C-1 ArH), 6.74-6.62 (m, 2, C-2 and C-4 ArH), 3.74 (s, 3, $ArOCH_3$), 3.02-1.50 (broad hump, 20 protons); MS (70 eV) *m/e*(rel intensity) 160(100), 159(9), 115(7).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.37; H, 8.56.

3-Hydroxy-18-nor-D-homo-14β-cyclobuta-BC-estra-1,3,5(10)-triene-17-one (46). (A) From phenol 40. A mixture of 3.5 g (0.012 mol) of 40 and 1.3 g of 5% Pd/C in 300 mL of ethanol containing 1.5 g of potassium hydroxide was hydrogenated (15 psig, 45°C) until hydrogen uptake ceased (6 hours). The solution was filtered through Dicalite, neutralized (CH_3CO_2H), and concentrated under reduced pressure. The residue was treated with hot water and the solid collected by filtration. The crude phenols were separated by HPLC[43] on a silica gel column using CH_2Cl_2 containing 3% ethyl acetate as an eluant, into a fraction containing 46 and a minor isomer followed by a fraction containing only 46, (2.0 g, 58% yield) mp 200-202°C; IR (CS_2) 1740 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.92 (s, 1, ArOH), 6.84-6.72 (m, 1, C-1 ArH), 6.50-6.36 (m, 2, C-2 and C-4 ArH), 2.90-1.50 (broad hump, 20 protons); MS (70 eV) *m/e*(rel intensity) 296(1), 146(100), 131(7), 117(6); (8 eV)

296(6), 146(100).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.12; H, 8.03.

(B) From ether 45. To a magnetically stirred solution of 40 mg (0.13 mmol) of 45 in 5 mL of CH_2Cl_2 under argon at -70°C was added 32 mg (0.13 mmol) of BBr_3 dropwise. The mixture was stirred at -70°C for 15 minutes then allowed to warm to room temperature for 20 minutes. The mixture was chilled in ice and cautiously treated with H_2O. Ether was added and the organic layer was separated, dried (Na_2SO_4) and evaporated to leave 46, identified by ^1H NMR and HPLC[43] (one product corresponding in retention time to the major product from hydrogenation of 40).

PART II

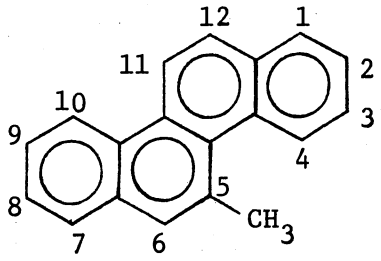
STEREOCHEMICAL ASSIGNMENT OF (*E*)- AND (*Z*)-2-(1-NAPHTHYL)-1-PHENYLPROPENE AND THEIR PHOTOCYCLIZATION TO 5-METHYLCHRYSENE

CHAPTER V

INTRODUCTION AND HISTORICAL

The widespread occurence of polynuclear aromatic hydrocarbons in the environment is well documented. They occur in soils,[54] coal,[55] and petroleum,[56] and are formed during combustion of fuels,[57] and tobacco.[58] Their carcinogenicity and mutagenicity continue to stimulate considerable research and study.[59]

The biologically active neutral subfractions of tobacco smoke condensate contain a large number of polynuclear aromatic hydrocarbons which undoubtably contribute to the carcinogenicity of cigarette smoke.[60] Among these polynuclear aromatic hydrocarbons are chrysene[60,61] and the 1-, 2-, 3-, 5-, and 6-methylchrysenes.[61] 5-Methylchrysene (47) is reported to be more carcinogenic on mouse skin than



47

chrysene or the other mono-methylchrysenes[61] and is one of the most carcinogenic polynuclear aromatic hydrocarbons known.[62]

Previous syntheses [61a,63] of 47 involved multistep routes and gave low yields, none exceeding 5%. To facilitate carcinogenicity

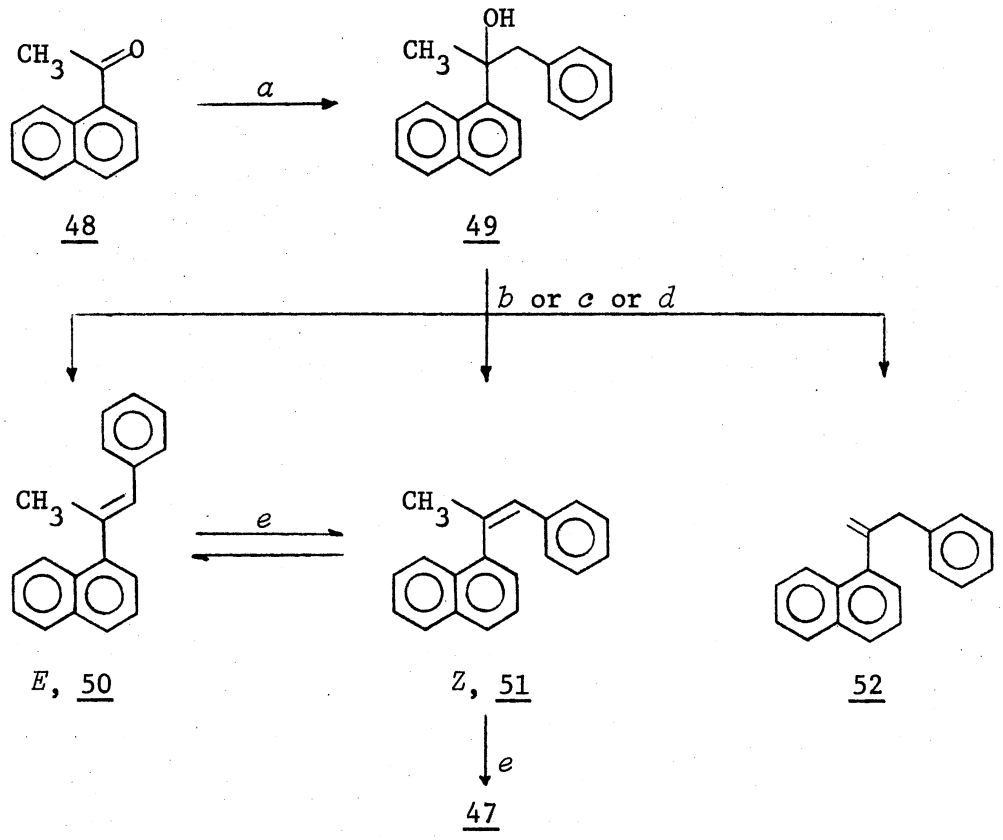
studies of 47, a more efficient synthesis was needed.

Photocyclization of 1,2-diarylethenes appears to be a general method for synthesis of polynuclear aromatic hydrocarbons.[64] The prerequisite 1,2-diarylethenes are readily available from ketones or aldehydes by reaction with Grignard reagents followed by dehydration of the alcohol or directly from ketones by reaction with Wittig reagents. Since chrysene and several derivatives have been prepared by photocyclization of alkenes,[65] it appeared that synthesis and photocyclization of an appropriately substituted alkene would be a shorter, more efficient route to 47.

CHAPTER VI

DISCUSSION AND RESULTS

The synthesis of 5-methylchrysene (47) and the intermediate alkenes 4, 5, and 6, is shown in Figure 12.



[a] $C_6H_5CH_2MgCl$, Et_2O. [b] A-15, C_6H_6, Δ. [c] CF_3CO_2H. [d] $POCl_3$, pyridine. [e] hν, I_2, O_2, C_6H_6.

Figure 12. Synthesis of 5-Methylchrysene (47)

Treatment of 1-acetonaphthone (48)[66] with benzylmagnesium chloride gave 49 in 75% yield. Dehydration of 49 was performed under a variety of conditions in an attempt to control the ratio of the resulting alkenes.[67] In all cases, GC analyses[68] indicated three products were formed in varying ratios as shown in Table VII.

TABLE VII

DEHYDRATION OF ALCOHOL 49

Reagent and Temperature		Ratio of alkenes	
	50	51	52
Amberlyst-15, C_6H_6 (70°C)	48[a]	9	43
	57[b]	30	13
	54[c]	45	1
Trifluoroacetic acid (27°C)	83[d]	16	1
$POCl_3$, pyridine (0°C)	33[e]	5	62

[a]During dehydration of 49. [b]2.5 Hours after the disappearance of 49. [c]36 Hours after disappearance of 49. [d]0.5 Hours. [e]No change over 3 hours.

During dehydration of 49 in refluxing benzene with Amberlyst-15 (A-15) resin,[69] the ratio of alkenes 50:51:52 (48:9:43) remained fairly constant while alcohol 49 was still present. After 49 was consumed, the concentration of exo alkene 52 decreased rapidly with a simultaneous increase of 50 to a maximum of 57%. Alkene 50 then slowly diminished as the concentration of 51 increased. After 36 hours, the ratio 50:51:52 (54:45:1)[70] stabilized and the concentration of 50 was only slightly favored. The kinetic formation of 50 and 52, particularly with trifluoroacetic acid can be rationalized by examination of the presumably most stable conformation of the alcohol 49 and the resulting cation shown in Figure 13.

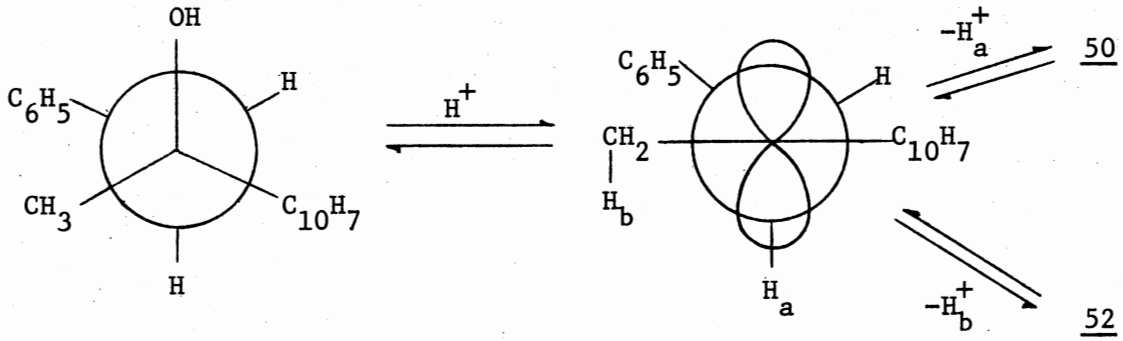


Figure 13. Formation of Alkenes 50 and 52

In the preferred conformation of alcohol 49, the phenyl and naphthyl groups are anti. Protonation of the hydroxyl group followed by loss of water generates the cation which has two protons H_a and H_b

correctly oriented for periplanar elimination[71] to 50 or 52.

The failure of the *E* alkene 50 to predominate to any great extent over the *Z* alkene 51 after prolonged exposure to equilibrating conditions should be noted. Although both 50 and 51 exhibit a steric interaction between the methyl group and the naphthyl *peri*-hydrogen,[72] the net result is to reduce the usual difference in stability between *E* and *Z* isomers.

Under nonequilibrating conditions, the dehydration of 49 using phosphorous oxychloride and excess pyridine at 0°C favored formation of 52 (50:51:52: 6:1:12). This ratio did not change over 3 hours at 0°C. The preponderance of the thermodynamically less stable alkene 52 may be related to the ease of approach of base preceding elimination.[71]

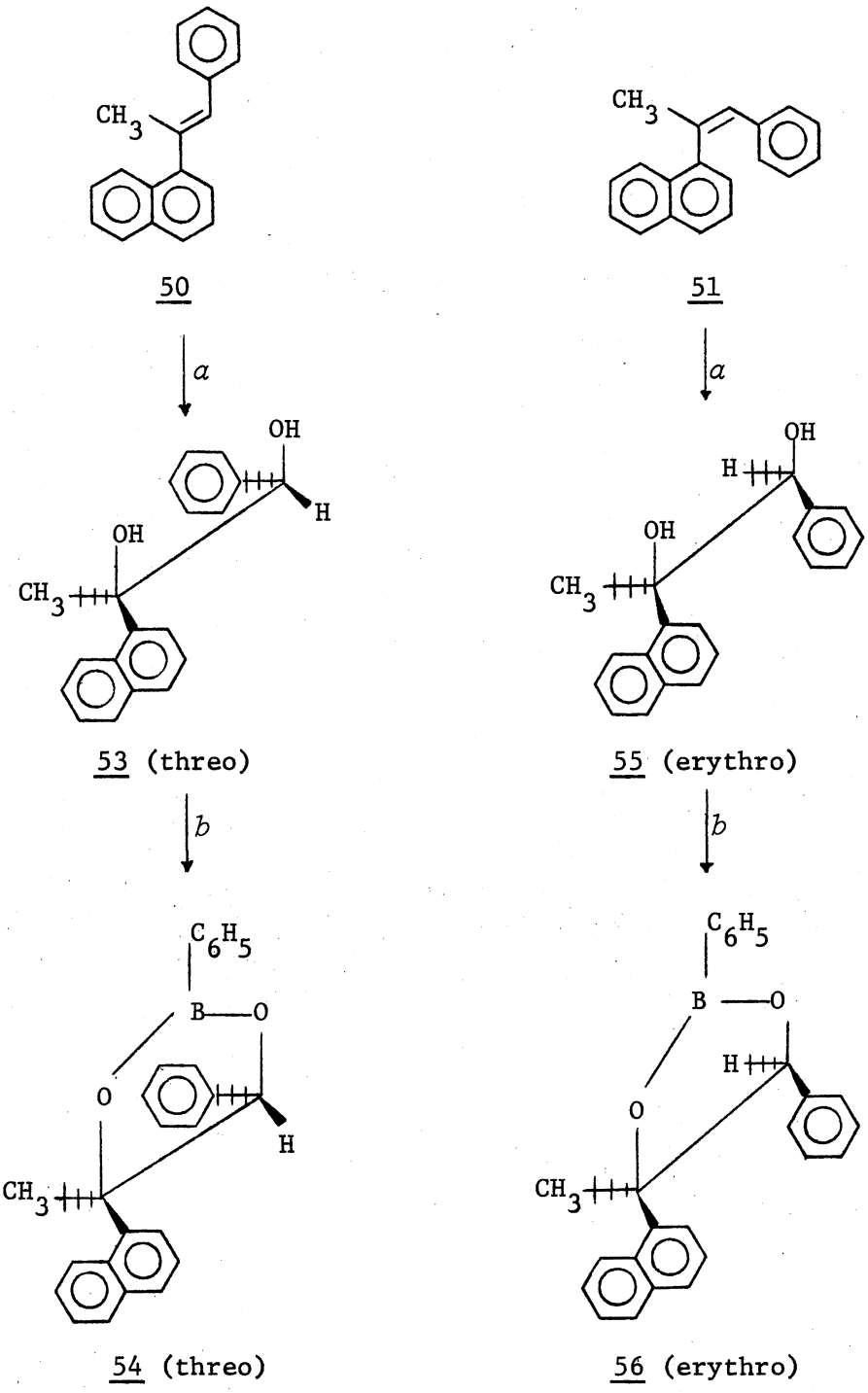
The alkenes 50, 51, and 52 were separated via picric acid with the picrate of 50, mp 94-95°C, being the least soluble and most stable. Successive concentrations of the mother liquor gave the picrate of 52, which is less stable and dissociated on attempted recrystallization from ethanol. The *Z* alkene 51 did not form a picrate under these conditions and was isolated from the mother liquor. Dreiding models and ^{1}H NMR data,[25] subsequently to be discussed, show that the naphthyl ring of the *Z* isomer, 51, is crowded (aryl-aryl interaction) compared to that of 50. This may explain the decreased stability of the picrate of 51.

Attempts to assign configuration to the *E* and *Z* alkenes 50 and 51 using ^{1}H NMR and UV spectroscopy led to uncertain results.[23] However, the assignment of configuration to 50 and 51 was achieved through ^{1}H NMR studies of the diol and the phenylboronate derivatives of these alkenes.[73] The *threo*-2-(1-naphthyl)-1-phenylpropane-1,2-diol (53) was

prepared by treatment of the *E* alkene 50 with osmium tetroxide and hydrolysis of the osmate with sodium sulfite. Analogously, the *Z* alkene 51 gave the erythro diol 55. Treatment of each of these diols (53 and 55) with phenylboronic acid gave the corresponding cyclic phenylboronates 54 and 56 respectively, as shown in Figure 14. The configurations used in Figure 14 are an arbitrary selection for 53, 54, 55, and 56 and should not be considered as an absolute assignment.[74]

Assignments have previously been made for meso and racemic aryl-containing diols[75] and their corresponding phenylboronates[73] based on chemical shifts in the ^{1}H NMR spectra produced by anisotropic effects of the aromatic ring cis to a methyl group. The ^{1}H NMR spectra of the phenylboronates have the advantage of showing enhanced methyl proton shifts relative to what is observed for the diols. Thus, this technique allows stereochemical assignment to *E* and *Z* alkenes 50 and 51, whereas other methods (^{1}H NMR and UV) applied to these isomers failed to give unambiguous assignments. The ^{1}H NMR data of the diols and phenylboronates is presented in Table VIII. Infrared spectroscopy has also been used to establish the relative configuration of vicinal diols.[76]

In making the configurational assignments for the threo isomers relative to the erythro isomers (diols as well as the corresponding phenylboronates), the methyl proton resonances would be expected to appear at higher field because they lie within the shielding region of the phenyl ring.[73,75] The hydroxyl protons (in threo diol 53) should absorb at lower field because of increased intramolecular hydrogen bonding, which decreases electron density on oxygen and thus deshields the hydroxyl protons.[75] The benzylic protons are deshielded in the



[a] OsO_4, pyridine, Et_2O; Na_2SO_3. [b] $C_6H_5B(OH)_2$.

Figure 14. Synthesis of Diols 53 and 55 and Phenylboronates 54 and 56

TABLE VIII

100 MHz ^{1}H NMR DATA[a] FOR DIOLS[b] 53 AND 55 AND PHENYLBORONATES[b] 54 AND 56

	Aromatic H	CH_3	H(C-1)	OH(C-1)	OH(C-2)
Threo diol (53)	6.72-8.86	1.40	3.22	3.20	5.46
Erythro diol (55)	7.00-8.80	1.66	2.38	2.28	5.34
Threo boronate (54)	7.34-8.28	1.62	6.02		
Erythro boronate (56)	6.70-8.20	2.10	5.88		

[a]Values in δ. [b]Concentration; 80 mg/0.5 mL $CDCl_3$.

threo isomers 53 and 54 relative to those of the erythro isomers 55 and 56 and opposite to that which is generally observed.[77] This effect may result from interaction of the methyl group with the *peri*-hydrogen of the naphthyl ring which causes rotation of the naphthyl ring and in turn deshielding of the benzylic proton in the threo isomers. In summary, these directional shifts are consistently observed in the spectra of the diol and phenylboronate derived from the alkene, mp 36-37°C. This allows assignment of stereochemistry to the diols 53 and 55, mp 102-104°C and 109-110.5°C respectively, which in turn allows structural assignment of *E* and *Z* alkenes 50 and 51.

Attention is directed to this use of phenylboronic acid. Addition of an equimolar quantity of phenylboronic acid to a deuterochloroform solution of 53 or 55 followed by 10 minutes shaking and filtration through glass wool to remove water gave quantitative conversion to the cyclic phenylboronates 54 and 56. The locked orientation of substituents on these cyclic esters leads to enhanced chemical shifts in the ^{1}H NMR spectra that are valuable for making diol configuration assignments.[73]

Considering the above stereochemical assignments, it is of interest to examine the ^{1}H NMR and UV data obtained for 50, 51, and 52. The structure of the latter is conclusively established by the 100 MHz ^{1}H NMR specturm, which shows vinyl protons at δ 5.21 (broad d, ^2J = 2 Hz) and δ 5.08 (broad d, ^2J = 2 Hz), and 2 benzylic protons at δ 3.68 (s) as shown in Table IX.

The similarity of the UV data from 50, 51, and 52 precluded[78] satisfactory use as stated previously in making structural assignments. The similarities in the UV spectra of 50 and 51 result from steric

TABLE IX

UV AND ^{1}H NMR ASSIGNMENTS OF ALKENES 50, 51, AND 52

	50	51	52
UV (log ε)[a]	222.5 (4.79)	225 (4.87)	225 (4.77)
	245[b] (4.15)	245[b] (4.28)	[c]
	282.5 (4.04)	285 (3.98)	282.5 (3.85)
^{1}H NMR[d] $\underline{CH}_3$	2.30 (d, ^4J = 1 Hz, 3)	2.24 (d, ^4J = 1 Hz, 3)	$\underline{CH}_2$ 3.68 (s, 2)
vinyl $\underline{H}$	6.52 (s, 1)[e]	[f]	5.08 (d, ^2J = 2 Hz, 1) 5.22 (d, ^2J = 2 Hz, 1)
aryl $\underline{H}$	7.00-8.02 (m, 12)	6.64-7.88 (m, 13)[f]	6.94-8.02 (m, 12)

[a] Wavelength in nm, solvent: EtOH. [b] Shoulder. [c] No shoulder at 245. [d] Values in δ. [e] Broad, but no discernible splitting. [f] The vinyl proton signal was buried within the aromatic proton resonances.

interaction between the *peri*-hydrogen of the naphthyl ring and the methyl group,[72] thus preventing coplanarity in the *E* as well as the *Z* isomer.

The ^{1}H NMR data of 50 and 51 are unusual in that the vinyl proton resonance of the *E* isomer 50 appears at higher field than that of the *Z* isomer 51. Generally in 1,2-diarylethenes, these resonance positions are reversed, although exceptions are known.[79] The usual occurrence of vinyl protons at lower field in *E* isomers is attributed to the coplanarity of the aromatic ring and double bond.[79] This places the vinyl proton in the deshielding region of the aromatic ring. The nonplanarity of the naphthyl ring and alkene double bond in 50 causes the vinyl proton to lie above the naphthyl ring, i.e. in the shielding region, and hence its shift to higher field.[78] Some indication of the angle between the naphthyl ring and the alkene double bond may be seen in the shift of the naphthyl peri proton signal proximal to the methyl group, since an increased angle should lead to an upfield shift due to shielding by the double bond.[72] In 50, 51, 52, and 47, this this appears as a discernible multiplet at δ 7.96, 7.90, 8.02, and 8.90 respectively. The assignments of 50 and 51 are further confirmed by the strong upfield shift of aromatic protons in the *Z* alkene 51, which is caused by the proximity of aromatic rings.[78]

Photocyclization of 50, 51, and 52 with periodic sampling and GC analysis[68] was conducted by irradiation of an air-saturated 0.01 M benzene solution of alkene containing iodine (0.001 M) at 3600 Å. After 7 hours, the exo alkene 52 had not isomerized or cyclized and was recovered unchanged. No other products were detected by GC. The *E* and *Z* alkenes 50 and 51 both rapidly equilibrated to a fairly

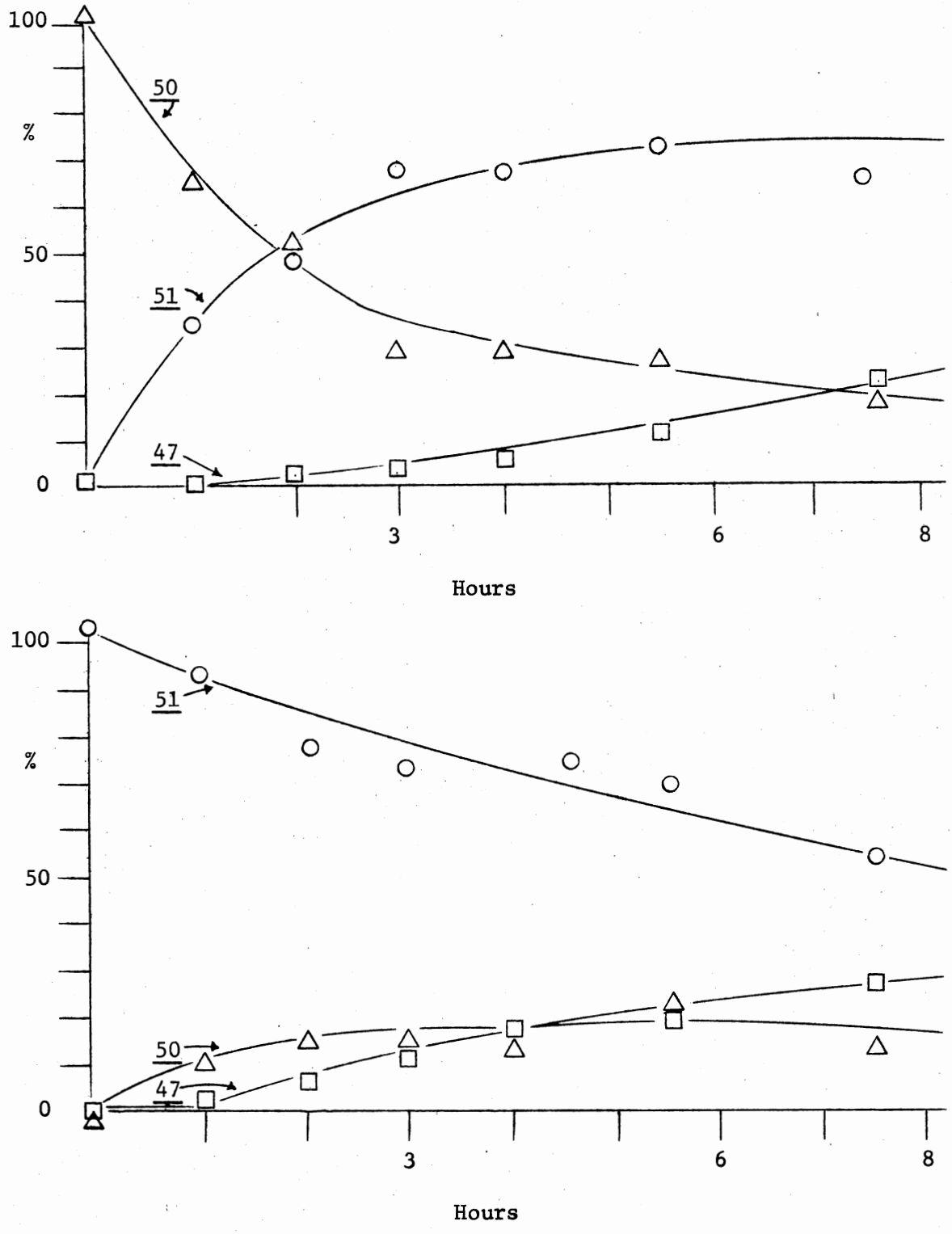


Figure 15. Photolysis of *E* and *Z* Alkenes 50 and 51 (0.01 M) in Benzene with I_2 (0.001 M) and Saturated with O_2 (Irradiation at 3600 Å).

constant *E*:*Z* (50:51, 1:2-3) ratio but the formation of 5-methylchrysene (47) was initially faster as shown in Figure 15 when the *Z* alkene was used as starting material. The photocyclization of 50 and 51 is assumed to proceed by a mechanism similar to that for the photocyclization of stilbene.[64]

Preparative-scale photocyclization of 50 and 51 was most conveniently carried out using the mixture of alkenes obtained from acid-catalyzed dehydration. Attempts to increase the yield (29%) by using cupric cholride[80] or using a higher concentration of oxygen were unsuccessful and actually led to decreased yields. Dilution of the benzene solution of alkenes from 0.01 M to 0.0025 M also failed to give a significant increase in yield.

The structure of the product from photocyclization was identified as 5-methylchrysene (47) by mp 117-117.5°C (lit.[63] mp 117°C), mass spectrum, and ^{1}H NMR.[61a]

CHAPTER VII

EXPERIMENTAL

2-(1-Naphthyl)-1-phenyl-2-propanol (49). To the Grignard reagent prepared from 48.6 g (2.0 mol) of magnesium and 252 g (2.0 mol) of benzyl chloride in 500 mL of ether was added a solution of 314.0 g (1.85 mol) of purified 1-acetonaphthone (48) in 500 mL ether at a rate sufficient to maintain reflux. The mixture was then heated at reflux an additional half hour, cooled, treated with dilute hydrochloric acid and then ether extracted. The ether extracts were washed with $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and concentrated. Recrystallization from a mixture of isohexane[51] and benzene gave 365 g (75%) of 49; mp 74-85°C (dec); IR (KBr) 3150 (s), 800 (s), 740 (s), 700 (s), 695 (s), 680 (s) cm^{-1}; ^1H NMR (CCl_4) δ 8.80-6.76 (m, 12, ArH), 3.49, 3.31 (AB quartet, $^2J_{AB}$=13 Hz, 2, $ArCH_2$), 2.80 (s, 1, OH), 2.72 (s, 3, CH_3); MS (70 eV) *m/e*(rel intensity) M^+ 262(1), 172(12), 171(100), 127(12), 91(16), 43(78).

Anal. Calcd. for $C_{19}H_{18}O$: C, 86.98; H, 6.91. Found: C, 87.00; H, 7.06.

Dehydration of 49 to (*E*)-2-(1-naphthyl)-1-phenylpropene (50), (*Z*)-2-(1-naphthyl)-1-phenylpropene (51), and 2-(1-naphthyl)-3-phenylpropene (52). A. To a magnetically stirred flask containing 500 mL of benzene fitted with a Dean-Stark trap were added 50.0 g (0.191 mol) of 49 and 1.0 g of A-15 resin.[69] The mixture was refluxed until 49 was no longer

detectable by GC.[68] Filtration to remove resin, followed by distillation (140-170°C, 0.3 mm) gave 39.3 g (84%) of alkenes 50/51/52 (2.5:1:2). Equilibration of the alkenes was carried out under similar conditions.

B. To 120 mL of trifluoroacetic acid was added 12.0 g (0.046 mol) of 49. After stirring at 25°C for 30 minutes, the mixture was diluted with water, extracted with isohexane, the organic extract washed with $NaHCO_3$ solution, and dried ($MgSO_4$). Filtration, concentration, drying and distillation gave 8.8 g (78%) of 50/51/52 (83:16:1).

C. To 50 mL of pyridine and 4.6 g (0.30 mol) of phosphorous oxychloride was added 6.6 g (0.025 mol) of 49 at 0°C. The solution was stirred 3 hours and then poured on ice. Extraction with isohexane, drying, and distillation gave 5.4 g(89%) of 50/51/52 (6.6:1:12.4).

Separation of alkenes 50, 51, and 52. To a warm solution of 68.0 g of picric acid in 500 mL of 95% ethanol was added 48.8 g of a mixture of alkenes 50, 51, and 52. After standing overnight, the picrate was collected by filtration. Two successive concentrations of the filtrate gave a second and third crop of picrates and mother liquor. The first crop of picrate (45 g) was recrystallized from ethanol to give 35.0 g of bright red picrate; mp 96-97°C. Cleavage of this picrate by continuous extraction[52] with isohexane over Merck neutral alumina followed by recrystallization of the alkene from isohexane gave 13.5 g of (*E*)-2-(1-naphthyl)-1-phenylpropene (50): mp 36-37°C; IR (NaCl) 915 (m), 800 (s), 775 (s), 750 (s), 705 (s), 695 (s) cm^{-1}; ^1H NMR (CCl_4) δ 8.02-7.00 (m, 12, ArH), 6.52 (broad s, 1, vinyl H), 2.30 (d, ^4J=1 Hz, 3, CH_3); MS *m/e*(rel intensity) M^+ 244(93), 229(100), 166(26), 165(35), 152(20); UV, 95% EtOH λ_{max} (log ε) 222.5

(4.79), 245 (4.15), 282.5 (4.04) nm.

Anal. Calcd. for $C_{19}H_{16}$: C, 93.06; H, 6.94. Found: C, 93.31; H, 6.58.

The second crop of picrate (25 g) was recrystallized from ethanol to give 10.2 g of a mixture consisting of picrates from 50 and 52. The mother liquor was evaporated to give 15.4 g of the yellow picrate of 52; mp 80-95°C. Attempted recrystallization resulted in dissociation. The picrate was cleaved as above and the recovered hydrocarbon was recrystallized from isohexane to give 6.0 g of 2-(1-naphthyl)-3-phenylpropene (52); mp 26-27°C; IR (NaCl) 900 (m), 795 (s), 775 (s), 745 (m), 695 (s), cm^{-1}; ^1H NMR (CCl_4) δ 8.02-6.94 (m, 12, ArH), 5.22 (d, ^2J=2 Hz, 1, vinyl H), 5.08 (d, ^2J=2 Hz, 1, vinyl H), 3.68 (s, 2, CH_2); MS *m/e*(rel intensity) M^+ 244(37), 165(11), 154(32), 153(8), 152(100), 91(26); UV, 95% EtOH λ_{max} (log ε) 225 (4.77), 282.5 (3.85) nm.

Anal. Calcd. for $C_{19}H_{16}$: C, 93.06; H, 6.94. Found: C, 93.06; H, 6.66.

The third crop of picrate (30.6 g) consisted of picrates of 50 and 52. The mother liquor consisted of 51 and picric acid but no picrate could be isolated. The mixture was separated on alumina as above and recrystallized from isohexane to give 5.5 g of (Z)-2-(1-naphthyl)-1-phenylpropene (52); mp 27-28°C; IR (NaCl) 915 (m), 860 (m), 800 (s), 775 (s), 690 (s), cm^{-1}; ^1H NMR (CCl_4) δ 7.88-6.64 (m, 13, vinyl H, ArH), 2.24 (d, ^4J=1 Hz, 3, CH_3); MS *m/e*(rel intensity) M^+ 244(100), 230(19), 299(100), 228(26), 166(17), 165(27), UV, 95% EtOH λ_{max} (log ε) 225 (4.87), 245 (4.28), 285 (3.98) nm.

Anal. Calcd. for $C_{19}H_{16}$: C, 93.06; H, 6.94. Found: C, 93.30; H, 6.94.

threo-2-(1-Naphthyl)-1-phenyl-1,2-propanediol (53). To a magnetically stirred solution of 1.0 g (3.93 mmol) of OsO_4 in 25 mL of ether and 2 mL of pyridine was added 960 mg (3.93 mmol) of 50 in 5 mL of ether. After 60 hours, 70 mL of ethanol and 10 g of Na_2SO_3 in 12 mL of H_2O were added and the mixture was heated at reflux for 3 hours. The solution was cooled and filtered through Dicalite, the Dicalite was rinsed with ethanol, and the filtrate was concentrated to a small volume under reduced pressure. The residue was extracted with ether, the extract was dried ($MgSO_4$), filtered, concentrated, and then recrystallized from isohexane to give 470 mg (43%) of 53: mp 102-104°C; IR (CCl_4) 3570 (OH) (m) cm^{-1}; ^1H NMR (80 mg/0.5 mL $CDCl_3$) δ 8.86-6.72 (m, 12, ArH), 5.46 (s, 1, OH), 3.22 (s, 1, ArCH), 3.20 (s, 1, OH), 140 (s, 3, CH_3); MS *m/e*(rel intensity) M^+ 278(4), 171(20), 170(100), 154(12), 126(12).

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 81.66; H, 6.44.

Cyclic boronate 54. The cyclic boronate 54 was prepared by adding 32 mg (0.328 mmol) of phenylboronic acid and 0.5 mL of $CDCl_3$ to 80 mg (0.328 mmol) of 53 in 0.5 mL of $CDCl_3$, shaking for 5 minutes, and filtering through glass wool. ^1H NMR ($CDCl_3$) δ 8.20-6.70 (m, 17, ArH), 5.88 (s, 1, ArCH), 2.10 (s, 3, CH_3).

erythro-2-(1-Naphthyl)-1-phenyl-1,2-propanediol (55). The diol 55 was prepared as above using 865 mg (3.40 mmol) of OsO_4 and 830 mg (3.40 mmol) of 51, giving 300 mg (32%) of 55: mp 109-110.5°C; IR (CCl_4) 3500 (m), 3450(OH) (m) cm^{-1}; ^1H NMR (80 mg/0.5 mL $CDCl_3$) δ 8.80-7.00 (m, 12, ArH), 5.34 (d, 1, OH), 2.38 (s, 1, ArCH), 2.28 (d, 1, OH), 1.66 (s, 3, CH_3); MS *m/e*(rel intensity) M^+ 278(2),

171(29), 170(100), 154(9), 126(12).

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 82.11; H, 6.60.

Cyclic boronate 56. The cyclic boronate 56 was prepared from 55 as above; ^{1}H NMR ($CDCl_3$) δ 8.28-7.34 (m, 17, ArH), 6.02 (s, 1, ArCH), 1.62 (s, 3, CH_3).

5-Methylchrysene (47). To 15 L of benzene were added 12.2 g (50 mmol) of alkene mixture (50:51:52: 5.3:4.0:1.1) obtained by acid-catalyzed equilibration of 50, 51, and 52 and 0.64 g (5 mmol) of I_2. The solution was throughly mixed and a 3 L aliquot was transferred to a 5 L beaker. Air was bubbled through the aliquot for 30 minutes, the air bubbler was removed, and irradiation was begun (Hanovia, 450-watt, medium-pressure Hg lamp equipped with Corex filter). After 4 hours the irradiation was stopped, the solution removed, and the process repeated until all 15 L were irradiated. After photolysis, the solvent was removed and the resulting oil was placed on a Soxhlet column[52] of Merck basic alumina and eluted for 24 hours with isohexane. Subsequent concentration and crystallization gave 3.6 g (29%) of 5-methylchrysene, mp 115-117°C. A sample recrystallized from isohexane and benzene had mp 117-117.5°C (lit.[63] mp 117°C); ^{1}H NMR ($CDCl_3$) δ 8.82 (m, 1, C-4 H), 8.64-8.52 (m, 2, C-10 and C-11 H), 7.80-7.40 (m, 8, ArH), 3.15 (s, 3, CH_3); MS *m/e*(rel intensity) M^+ 242(100), 241 (39), 240(14), 239(28), 120(18), 119.5(22); UV, 95% EtOH λ_{max} (log ε) 271 (5.00), 286.5 (4.00), 300.5 (3.96), 312.5 (4.10), 326.5 (4.08) nm.

The individual alkenes 50, 51, and 52 were irradiated at 3600 Å in quartz tubes in a Rayonet Reactor. Each alkene solution in benzene was 0.001 M in alkene, 0.001 M in I_2 and saturated with O_2.

BIBLIOGRAPHY AND NOTES

1. (a) L. F. Fieser and M. Fieser, "Steroids", Reinhold Publishing Corp., New York, 1959; (b) C. W. Shoppee, "Chemistry of the Steroids", second edition, Butterworth Inc., Washington D. C., 1964.

2. (a) E. A. Doisy, C. D. Veler, and S. A. Thayer, Amer. J. Physiol., 90, 329 (1929); (b) A. Butenandt, Naturwisserschaften, 17, 879 (1929).

3. (a) O. Rosenheim and H. King, Nature, Lond., 130, 315 (1932); (b) H. Wieland and E. Dane, Hoppe-Seyl. Z., 210, 268 (1932).

4. G. Anner and K. Miescher, Helv. Chim. Acta, 31, 2173 (1948).

5. C. Djerassi, L. Miramontes, L. Rosenkrantz, and F. sondheimer, J. Am. Chem. Soc., 76, 4092 (1954).

6. M. W. Goldberg and E. Wydler, Helv. Chim. Acta, 26, 1142 (1943).

7. A. Hassner, A. W. Coulter, and W. S. Seese, Tet. Letters, 759 (1962).

8. For reviews of nonsteroidal antifertility agents see; (a) D. Lednicer, "The Chemistry of Nonsteroidal Antifertility Agents", in "Contraception: The Chemical Control of Fertiltiy", D. Lednicer (Ed.), Marcel Dekker, Inc., New York, 1969; (b) J. Grundy, Chem. Rev., 57, 281 (1957); (c) U. V. Solmssen, Chem. Rev., 37, 481 (1945).

9. For a review of X-ray crystallography studies of steroids see; W. L. Daux, C. M. Weeks, and D. C. Rohrer, "Crystal Sturctures of Steroids", in "Topics in Stereochemistry", Vol. 9, N. L. Allinger and E. L. Elliel, (Eds.), John Wiley and Sons Inc., New York, 1976, p. 271.

10. (a) B. Busetta, and M. Hospital, Acta Crystallogr., B 28, 560 (1972); (b) B. Busetta, C. Coverseille, S. Geoffre, and M. Hospital, Acta Crystallogr., B 28, 1349 (1972); (c) W. L. Daux, Acta Crystallogr., B 28, 1864 (1972).

11. (a) A. L. Wilds and R. E. Sutton, J. Org. Chem., 16, 371 (1951); (b) E. C. Dodds, L. Goldberg, W. Lawson, and R. Robinson, Proc. Roy. Soc., B 127, 140 (1939).

12. M. Hospital, B. Busetta, R. Bucort, H. Weintraub, and E. Baulien, Mol.Pharmacol., 8, 438 (1972).

13. N. R. Campbell, E. C. Dodds, and W. Lawson, Nature, 142, 1121 (1938).

14. Dr. Dick van der Helm and Mr. Ray Loghry, Department of Chemistry, University of Oklahoma, are thanked for the X-ray crystalographic data and drawings used in Figures 6 and 7.

15. M. D. Cohen, G. M. J. Schimidt, and F. I. Sonntag, J. Chem. Soc., 2000 (1964).

16. Unpublished results, P. H. Ruehle, T. K. Dobbs and E. J. Eisenbraun.

17. (a) G. Stork, H. N. Khastgir, and A. J. Solo, J. Am. Chem. Soc., 80, 6457 (1958): (b) W. F. Johns, J. Org. Chem., 28, 1856 (1963): (c) For other examples see; A. Akhrem and Y. Titov, "Total Steroid Synthesis", (trans. B. Hazzaed), Plenum Press, New York, 1970.

18. J. P. Schaefer and J. J. Bloomfield, "The Dieckmann Condensation", in "Organic Reactions", Vol. 15, A. C. Cope (Ed.), John Wiley and Sons Inc., New York, 1967, p. 1.

19. W. E. Bachmann and W. S. Struve, "The Arndt-Eistert Synthesis", in Organic Reactions", Vol. 1, R. Adams (Ed.), John Wiley and Sons Inc., New York, 1967, p. 38.

20. M. S. Newman and P. F. Beal, J. Am. Chem. Soc., 72, 5163 (1950).

21. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, John Wiley and Sons Inc., New York, 1967, p. 729.

22. This scheme was explored after a recent report described the synthesis of 5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[*a*,*g*]-biphenylene by a similar route; T. G. Dekker, and J. Dekker, J. S. Afr. Chem. Inst., 28, 122 (1975).

23. Mass spectra were obtained on a CEC 21-110B insturment. IR spectra were obtained on a Beckman IRSA and UV spectra on a Cary 14 spectrometer.

24. (a) H. Ulrich, D. V. Rao, F. A. Stober, and A. A. R. Sayigh, J. Org. Chem., 35, 1121 (1970); (b) G. Montaudo and S. Caccamese, J. Org. Chem., 38, 710 (1973).

25. ^{1}H NMR spectra were obtained on a Varian XL-100A spectrometer and are reported in δ relative to internal TMS.

26. The benzylic cyclobutane protons of the parent hydrocarbon corresponding to 12 also occur as an AA'BB' system (AA' portion) and are not a simple doublet of doublets as described in reference 22;

unpublished results, P. H. Ruehle, C. E. Browne, and E. J. Eisenbraun.

27. M. Karplus, J. Chem. Phys., 30, 11 (1959).

28. (a) A. Gamba and R. Mondelli, Tet. Letters, 2133 (1971); (b) G. Montaudo, S. Caccamese, and V. Librando, Org. Mag. Res., 6, 534 (1974).

29. (a) ITRACAL is a version of the LOACOON 3 algorithm,[29b] which which iterates calculated NMR spectra to fit an experimental spectrum. ITRACAL was devoloped for use on a 12K Nicolet 1080 computer system and NIC-294 Disk Memory; (b) S. Castellano and A. A. Bothner-By, J. Chem. Phys., 41, 3863 (1964).

30. (a) L. Paolillo, H. Ziffer and O. Buchardt, J. Org. Chem., 35, 38 (1970); (b) W. Metzner and D. Wendisch, Liebigs Ann. Chem., 730, 111 (1969); (c) A. Heinrich, S. Farid, and G. O. Schenck, Chem. Ber., 99, 625 (1966).

31. E. B. Whipple and G. R. Evanega, Org. Mag. Res., 2, 1 (1970); (b) W. A. Thomas, "NMR Spectroscopy in Conformational Analysis", in "Annual Review of NMR Spectroscopy", Vol. I, F. Mooney (Ed.), Academic Press, New York, 1968, pp. 74.

32. H. M. McConnell, A. D. McLean, and C. A. Reilly, J. Chem. Phys., 23, 1152 (1955).

33. ^{13}C NMR spectra were recorded at 25.2 MHz in the FT mode on a Varian XL-100A interfaced with a 12K Nicolet 1080 computer system. All spectra were run in $CDCl_3$ using a deuterium lock and are reported in ppm downfield from TMS (δ $CDCl_3$=76.9 ppm).

34. (a) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley Interscience, New York, 1972; (b) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972.

35. J. Bowyer and Q. N. Porter, Aust. J. Chem., 19, 1455 (1966).

36. (a) J. E. Burks, D. van der Helm, T. K. Dobbs, L. L. Ansell, P. H. Ruehle, and E. J. Eisenbraun, Acta Crystallogr., B 13, 34 (1978); (b) J. Dekker and T. G. Dekker, J. S. Afr. Chem. Inst., 26, 25 (1973).

37. D. O. Cowan and R. L. Drisko, J. Am. Chem. Soc., 92, 6286 (1970).

38. Ref. 34b, p. 404.

39. R. G. Salomen, K. Folting, W. E. Streib, and J. K. Kochi, J. Am. Chem. Soc., 96, 1120 (1974).

40. (a) B. L. Nelson, G. C. Levy, and J. D. Cargioli, J. Am. Chem.

Soc., 94, (1972); (b) G. C. Levy, G. L. Nelson and J. D. Cargioli, Chem. Commun. 506 (1971).

41. H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, J. Org. Chem., 26, 3237 (1961).

42. H. L. Dryden, "Reductions of Steroids by Metal-Ammonia Solutions", in "Organic Reactions in Steroid Chemistry", Vol. 1, J. Fried and J. A. Edwards (Eds.), Van Nostrand Reinhold Co., New York, 1972, p. 1.

43. Analytical and preparative HPLC seperations were performed on a Waters Associates system and Prep 500 LC system respectively using Microporasil (silica gel) columns manufactured by Waters Associates.

44. A. L. Wilds and W. B. McCormack, J. Am. Chem. Soc., 70, 4127 (1948).

45. A. L. Wilds and N. A. Nelson, J. Am. Chem. Soc., 75, 5366 (1953).

46. For discussions of carbon resonance assignments in steroids see; (a) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, J. Am. Chem. Soc., 91, 26 (1969); (b) T. A. Wittstruck and K. I. H. Williams, J. Org. Chem., 38, (1973).

47. J. N. Schoolery and M. T. Rogers, J. Am. Chem. Soc., 80, 5121 (1958).

48. This information was obtained from the National Institutes of Child Health and Development, Center for Population Research, Contraceptive Development Branch.

49. The diphenol 12 is approximately 1/10 as potent as DES against prostrate carcinoma but shows a similiar dosage response curve; unpublished results, A. Segaloff, Alton Ochsner Medical Foundation.

50. Prepared from Diazald, available from Aldrich Chemical Company.

51. Phillips Isohexanes, bp. 61°C.

52. C. E. Browne, W. L. Buchanan, and E. J. Eisenbraun, Chem. Ind., 35 (1977).

53. A. J. Shand and R. H. Thomson, Tet., 19, 1919 (1963).

54. M. Blumer, Sci. Am., 234, 34 (1976).

55. E. Clar, "Polycyclic Hydrocarbons", Vol. 1, Academic Press, London, 1964, p. 192.

56. R. H. Hunt and M. J. O'Neal, "Encyclopedia of Chemical Technology",

2nd Ed., Vol. 14, R. E. Kerk and D. J. Othmer (Eds.), The Interscience Encyclopedia, Inc., New York, 1967, p. 849.

57. E. E. Tompkins and R. Long, "12th Symposium (International) on Combustion", The Combustion Institute, Pittsburgh, 1969, p. 625.

58. (a) I. Schmeltz and D. Hoffmann, "Carcinogenesis", Vol. 1, R. I. Freudenthal and P. Jones (Eds.), Raven Press, New York, 1976, p. 225; (b) R. Stedman, Chem. Rev., 68, 153 (1968).

59. (a) G. M. Badger, "The Chemical Basis of Carcinogenic Activity", C. C. Thomas Publ., Springfield, 1962; (b) R. Schoental, "Carcinogenesis by Polycyclic Aromatic Hydrocarbons and by Certain Other Carcinogens", in Ref. 55, p. 133; (c) L. Fishbein, W. G. Flamm, and H. L. Falk, "Chemical Mutagenesis", Academic Press, New York, 1970, p. 275; (d) E. C. Miller and J. A. Miller, "Chemical Mutagens", Vol. 1, A. Hollaender (Ed.), Plenum Press, New York, 1971, p. 105.

60. R. F. Severson, M. E. Snook, H. C. Higman, O. T. Chortyk, and F. J. Akin, in Ref. 58c, p. 253.

61. (a) S. S. Hecht, W. E. Bondinell, and D. Hoffmann, J. Natl. Cancer Inst., 53, 1121 (1974); (b) D. Hoffmann, W. E. Bondinell, and E. L. Wynder, Science, 183, 215 (1974).

62. S. S. Hecht, M. Loy, R. R. Maronpot, and D. Hoffmann, Cancer Let., 1, 147 (1976).

63. (a) M. Newman, J. Am. Chem. Soc., 62, 870 (1940); (b) L. Fieser and L. Joshel, J. Am. Chem. Soc., 62, 1211 (1940); (c) W. Bachmann and R. O. Edgerton, J. Am. Chem. Soc., 62, 2550 (1940); (d) Subsequent to the completion of this work, the photocyclization of a mixture of 50 and 51 to 47 was reported in 65% yield by K. L. Nagel, R. Kupper, K. Antonson, and L. Wallcave, J. Org. Chem., 42, 3626 (1977).

64. For reviews see (a) F. R. Stermitz, "Organic Photochemistry", Vol. I, E. D. Chapman (Ed.), Marcel Dekker, Inc., New York, 1967; (b) D. O. Cowan and R. L. Drisko, "Elements of Organic Photochemistry", Plenum Press, New York, 1976, Chapter 9; (c) E. V. Blackburn and C. J.Timmons, Q. Rev. Chem. Soc., 23, 482 (1969).

65. (a) C. S. Wood, and F. B. Mallory, J. Org. Chem., 29, 3373 (1964); (b) E. V. Blackburn, C. E. Loader, and C. J. Timmons, J. Chem. Soc., (c) 163 (1970); (c) C. C. Leznoff, and R. J. Hayward, Can. J. Chem., 50, 528 (1972).

66. Commercial material was purified by means of its picrate.

67. (a) J. W. Cook and R. A. F. Galley, J. Chem. Soc., 2012 (1931). These authors reported mp 139°C for 51 and/or 52, but their later work (cf. ref. 67b) Indicated that impure materials had been used.

It is suggested that their product was actually 2-(2-naphthyl)-1-phenylpropene, mp 139°C (cf. ref. 67c below); (b) J. W. Cook and C. L. Hewett, J. Chem. Soc., 365 (1934); (c) W. Carruthers, J. Chem. Soc., 1525 (1967).

68. GC analyses were done on a Hewlett-Packard 5750 insturment with dual flame ionization detectors using an 8-ft x 0.25-in. copper column packed with 5% UCW-98 coated on 80-100 mesh AW DMCS-treated Chromosorb G at 230°C. The retention times for 48, 49, 50, 51, and 52 were: 47, 21, 17, 10.5 and 11.5 minutes, respectively.

69. Amberlyst-15 is a sulfonic acid resin available from Rohm and Haas Company, Philadelphia, Pa.

70. Beyond this reaction time, GC showed the appearance of three new products with slightly longer retention times. These new products are possibly cyclized materials. Use of *p*-toluenesulfonic acid in the place of A-15 decreased the reaction times but gave similar results.

71. J. March, "Advanced Organic Chemistry", McGraw-Hill, New York, 1977, Chapter 17.

72. For a review of peri-interactions in naphthalene compounds, see V. Balasubramaniyan, Chem. Rev., 66, 567 (1966).

73. W. P. Duncan, E. J. Eisenbraun, and P. W. Flanagan, Chem. Ind., 78 (1972).

74. The assignment of erythro and threo was obtained through application of rules developed by Cahn, Ingold and Prelog, R. S. Cah, C. K. Ingold and V. Prelog, Angew. Chem. Int. Ed. Engl., 5, 385, 511 (1966).

75. (a) H. Lund and A. D. Thomas, Acta. Chem. Scand., 23, 2567, 3582 (1961); (b) J. Wiemann, G. Dana, Sa-Le-Thi-Thuan, and M. Brami, Compt. Rend., 258, 3724 (1964); (c) J. H. Stocker, D. W. Kern, and R. M. Jenevein, J. Org. Chem., 33, 412 (1968); (d) J. H. Stocker, J. Am. Chem. Soc., 88, 2878 (1966); (e) H. Agahigian, J. F. Moraveck, and H. Gauthier, Can. J. Chem., 41, 194 (1963); (f) J. Grimshaw, J. T. Grimshaw, and E. J. F. Rea, J. Chem. Soc., 683 (1971).

76. The IR spectra of the diols (dilute carbon tetrachloride solution) appeared to confirm 55 as the erythro isomer since the intramolecular hydrogen-bonded hydroxyl absorption appeared at lower frequency in 55 (3500 cm^{-1}) than for 53 (3570 cm^{-1}). The tendency for intramolecular hydroxyl absorptions to appear at lower frequency in meso diols has previously been observed; see W. A. Mosher and N. Heidel, J. Org. Chem., 28, 2154 (1963).

77. L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy", 2nd Ed., Pergamon Press, London, 1969.

78. (a) Attempts to use (*E*)- and (*Z*)-1,2-diphenylpropene as model compounds for 50 and 51 were unsatisfactory. The UV spectra of the 1,2-diphenylpropenes show significant differences[78b] (*E*)-isomer, λ_{max}=2700, log ε=4.3; (*Z*)-isomer, λ_{max}=2600, log ε=4.1. The ^1H NMR spectra of 1,2-diphenylpropenes show an upfield shift of aromatic protons in the *Z* isomer[78c] (δ 7.12 vs. 7.25 for the *E* isomer) but the vinyl proton occurs at lower field in the *E* isomer[78c] (δ 6.75 vs. 6.39 for the *Z* isomer). These compounds lack the interaction between the peri-hydrogen of the naphthyl ring and the methyl group present in 50 and 51. (b) D. J. Cram and F. A. Abdelhafez, J. Am. Chem. Soc., 74, 5828 (1952); (c) M. Michman and H. H. Zeiss, J. Organomet. Chem., 15, 139 (1968).

79. (a) H. Gusten and M. Salzwedel, Tetrahedron, 23, 173, 187 (1967); (b) A. F. Casey, A. Parulkar, and P. Pocha, Tetrahedron, 24, 3031 (1968); (c) C. Pascual, J. Meier, and W. Simon, Helv. Chem. Acta, 49, 164 (1966).

80. D. J. Collins and H. J. Hobbs, Chem, Ind., 1725 (1965).

VITA [2]

Clinton Eugene Browne III

Canidate for the Degree of

Doctor of Philosophy

Thesis: I. SYNTHESIS OF CYCLOBUTA-BC-STEROID HOMOLOGS
II. STEREOCHEMICAL ASSIGNMENT OF (*E*)- AND (*Z*)-2-(1-NAPHTHYL)-1-PHENYLPROPENE AND THEIR PHOTOCYCLIZATION TO 5-METHYL-CHRYSENE

Major Field: Chemistry

Biographical:

Personal Data: Born in Pasadena, California, August 15, 1951, the son of Dr. Clinton E. and Eleanor G. Browne II.

Education: Received high school equivalency diploma in 1970; received the Bachelor of Science degree from Metropolitan State College in June 1974, with a major in chemistry and a minor in biology; completed requirements for the Doctor of Philosophy degree at Oklahoma State University in May, 1978.

Professional Experience: Senior Chemist (Head of Chemical Analysis and Chemical Inventory) Thomas Plating Company, Englewood, Colorado, 1973-74; Graduate Research Assistant, American Petroleum Instuite, Oklahoma State University, 1974; Graduate Teaching Assistant, Oklahoma State University, 1975; Graduate Research Assistant, Environmental Protection Agency, Oklahoma State University, 1975-76; Graduate Research Assistant, National Institutes of Health, Oklahoma State University, 1976-77; Continental Oil Company Graduate Research Fellow, Oklahoma State University, 1977; Texas Eastman Kodak Graduate Research Fellow, Oklahoma State University, 1977-78. Member of Phi Lambda Upsilon.