SYNTHETIC AND HIGH FIELD NMR STUDIES OF ORGANOMETALLIC DERIVATIVES OF STEROIDS

by

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ORGANOMETALLIC DERIVATIVES OF STEROIDS

To my Mother and Father

for their loving encouragement

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ABSTRACT

An area of organometallic chemistry which has gained recent prominence involves the incorporation of transition metal fragments into biologically active molecules. One such series, whose complexes have been exploited from both a chemical (synthetic) and biochemical perspective is the steroidal system. With the advent of higher field NMR spectrometers and two dimensional NMR techniques, it is possible to characterize such complexes without relying on X-ray crystallographic means.

A program was, therefore, developed aimed at synthesizing and examining the high field NMR spectroscopic properties of the organometallic complexes of aromatic A-ring and B-ring dienyl steroids. The purpose of this investigation was to analyze the resulting 2D spectra not merely to deduce the complexation site of the organometallic moiety but also to probe the influence this group has on the chemical shifts of nearby protons and carbons.

The first molecules investigated involved coordination onto either the α or β face of the aromatic A-ring using a $Cr(CO)_3$ or a $CpRu^+$ fragment. The anisotropic behaviour of these groups was examined by studying their ^1H NMR spectra. Subsequent to this, the anisotropic behaviour of a $Co_2(CO)_6$

and a $Cp_2Mo_2(CO)_4$ fragment coordinated onto an alkynyl unit located at the 17α position was determined.

The next phase of this program involved studying the spectroscopic changes attributable to complexation of a B-ring dienyl steroid with a $Fe(CO)_3$ or Rh(acac) group. One particular complex, 7-dehydrocholesteryl acetate $Fe(CO)_3$, yielded suitable crystals for its x-ray structure determination.

The final aspect of this work involved protonation of both simple, e.g., $CpRh(C_2H_4)_2$, and complex organometallic systems, e.g., steroidal derivatives, in order to investigate their synthetic potential.

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During the course of this work, numerous people have influenced my life and I would like to take this opportunity to acknowledge them.

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CHAPTER 1

INTRODUCTION

1.1 PREAMBLE

The use of organometallic compounds as intermediates in organic synthesis has been well documented,[1] and in recent years organometallic groups have been incorporated into biologically significant molecules. In particular, one biomolecular system which has received considerable attention is the steroid nucleus. This type of system intrigued organometallic chemists since the group encompasses compounds with diverse structures containing a wide variety of functional groups that can be utilized as complexation sites for transition metals.

Before dealing with the chemical and biochemical implications of such complexes, it is imperative that one familiarize themselves with the steroid system and examine how these molecules are well suited as possible ligands; thus, the following section will centre on structural aspects of the steroidal group.

1.2 BACKGROUND ON STEROIDAL STRUCTURES

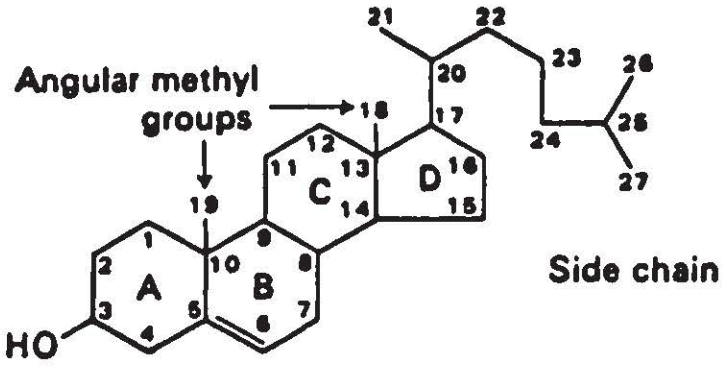
Steroids are comprised of a wide range of compounds, many of which are of vital importance to our everyday lives.

Well known examples include cholesterol, testosterone, vitamin D, and cortisone. As well, recent world events, such as the "Ben Johnson scandal" and the French controversy over the so-called "morning after pill", RU 486, have only of heightened the public's awareness the importance of steroids and their role in society today. As a result of their pharmacological as well as academic importance, steroids have become one of the more extensively studied systems in chemistry today with numerous books[2,3] and journals[4,5] documenting their chemistry and biochemistry. In addition, much of the research performed on steroids has played a vital part in the development of new reactions, concepts and instrumentational techniques with no other field gaining the recognition from as many Nobel Prize Awards. In part, this popularity arises from the rigid skeletal framework they possess, from their highly crystalline nature and from the enormous number of derivatives available.

The term "steroid" arose from the "sterol" part of cholesterol whose word origin is derived from the Greek words "chole" meaning bile and "stereos" meaning solid. The steroid expression was, therefore, intended to represent something that was cholesterol-like, implying a structural similarity. As a result, cholesterol became the focal point of early steroidal research. This is not astonishing as cholesterol was the first steroid to be isolated, in 1812 by Chevreul[6], and therefore became the most readily available as

it is a main constituent in brain and nerve tissues, gall stones, and egg yolks. The main thrust of this initial work centred on the determination of cholesterol's structural formula and culminated in 1945 when Carlisle and Crowfoot[7] verified its correct ring configuration by X-ray crystal structure analysis.

This initial research involving cholesterol led to a rapid development in steroid chemistry and was quickly followed by the work of Butenandt and Ruzicka[8] on the isolation and structural elucidation of the sex hormones in 1935, and that of Kendall, Reichstein, and Wintersteiner,[9] in 1938, on the discovery of the corticosteroids. By the mid 1950's, a more formal definition for the term "steroid" was required and Fieser and Fieser[2] proposed that: "the term steroid be employed to indicate all those substances that are structurally related to the sterols and bile acids to the extent of possessing the characteristic perhydro-1,2-cyclopentenophenanthrene system." Steroids are, therefore, characterized by a tetracyclic ring system consisting of three fused cyclohexyl rings and a terminal D ring which is cyclopentyl in nature. The structure of the prototypical steroid, cholesterol, 1, is illustrated below along with the conventional numbering sequence for the carbon framework.

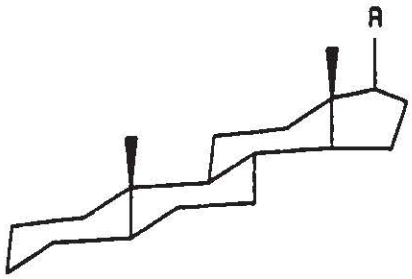


Cholesterol

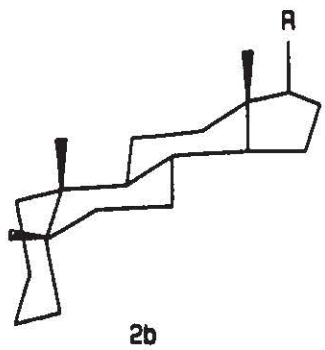
1

This figure, in particular, portrays the two dimensionality of the steroid structure, but with three of the rings cyclohexyl in nature, the presence of axial and equatorial protons gives rise to a more complex three dimensional network. Cholestanol, 2a, depicts this framework while also indicating the relative positions of these protons. From this representation, a second aspect to the steroidal structure can be circumstantiated, namely, the α and β faces or the top and bottom of the molecule. These faces are readily distinguished by attachment of angular β-methyls at the ring junctions, C-10 and C-13; these methyls serve as reference points for stereochemical designations. Therefore, groups which lie on the same side as the methyls are said to be β substituents, while those positioned on the bottom, or *trans* to the methyls are referred to as α substituents. As will be shown in the succeeding sections, the positioning of

functionalities on a particular face plays a predominant role in the stereochemistry of subsequent chemical and biochemical reactions.



2a



2b

It is also worth noting that in 2a, all the ring junctions of the steroidal skeleton are *trans*, meaning the groups are opposite to one another, but the AB ring junction may adopt a *cis* conformation, where these groups lie on the same side, as in 2b, thus giving rise to a second general group of steroids. To be more precise, when the hydrogen at C-5 is in an α position, thereby being opposite to the C-19 methyl, a *trans* ring junction occurs giving rise to the 5α steroidal series, while when this proton is in a β position, the 5β series results with its characteristic *cis* AB ring junction. With the general steroidal structure firmly authenticated, one can now focus on how other steroids can be related to the cholesterol structure by means of simple modifications within the steroidal skeleton or by bond cleavage within the side chain. Figure 1 serves to illustrate such relationships between the cholestane series, 3,

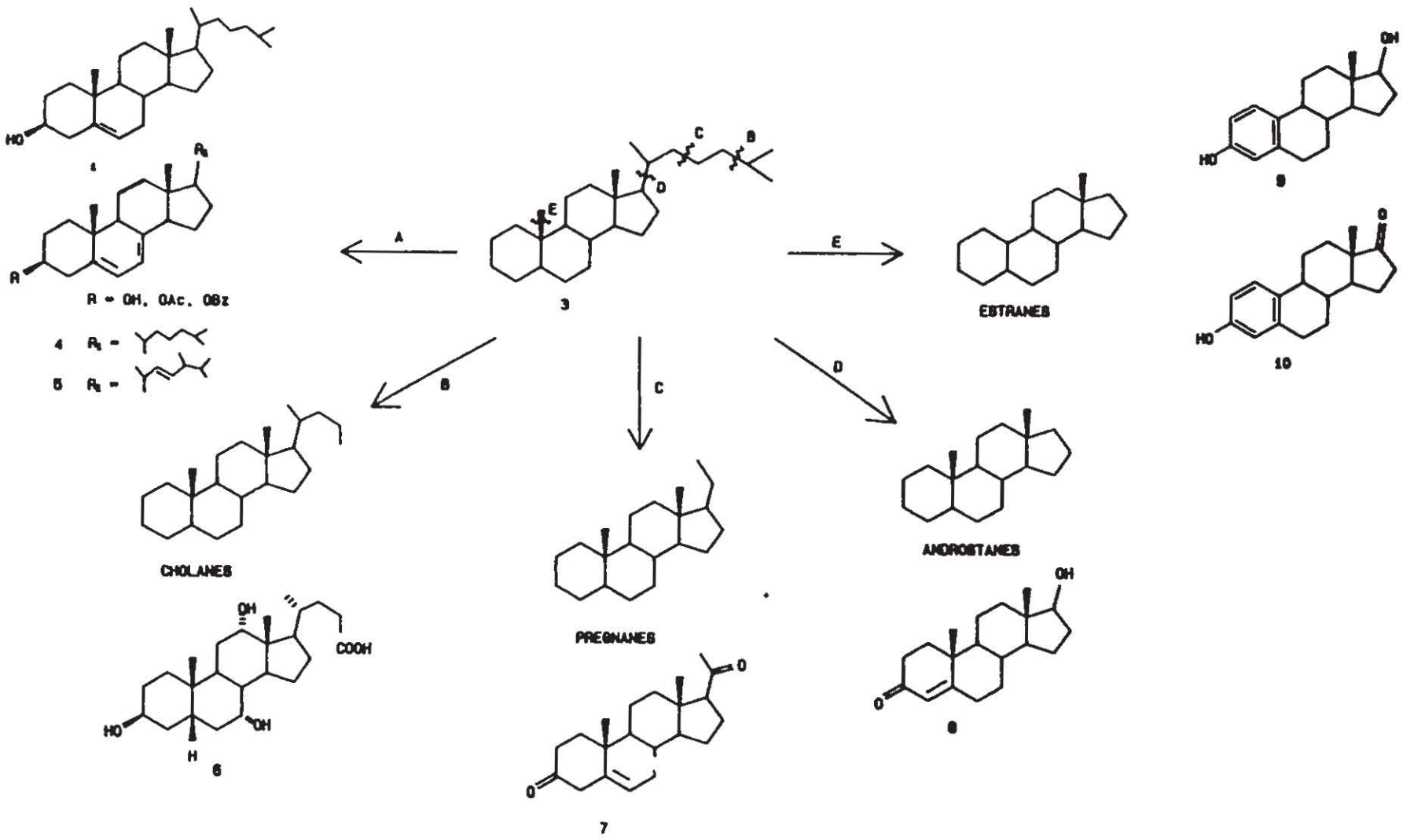
and the other important steroidal parents and is not intended to indicate their chemical transformations.

The initial route, path A, centres on the conversion of cholestane into well-known cholesterol, 1, by way of simple changes within the steroidal skeleton, for example, the introduction of a 3β hydroxyl functionality and a double bond between C-5 and C-6. Further incorporation of double bonds either within the skeleton or in the side chain gives rise to other related steroids, namely 7-dehydrocholesterol, 4, and ergosterol, 5, with the latter being one of the more important steroids since its photochemical reaction results in the opening of the B ring dienoid system thereby yielding a conjugated triene system from which Vitamin D arises.

The subsequent routes involve bond fission of the side chain with the first path involving fragmentation of the C-C bond at the isopropyl group at C-24, thereby yielding the cholane series. (Route B) An example of a steroid belonging to this series is cholic acid, 6, a typical bile acid, whose main role is the emulsification and adsorption of lipids in the intestines. The pregnane series (Route C) arises by further bond cleavage in the side chain between C-20 and C-24. The most important progestin is progesterone, 7, which is often referred to as the pregnancy hormone since it prepares the lining of the uterus for implantation of the fertilized egg. The fourth pathway, Route D, centres on the total removal of the side chain yielding the androstanes, while

FIGURE 1.1

General Structural Relationships between the Cholestane Series, 3 and the other Steroidal Series.


HO
4
R
R = OH, OAc, OBz
4 R₁ =
5 R₁ =
A
3
C
B
D
E
E
ESTRANES
OH
HO
9
O
HO
10
B
CHOLANES
OH
COOH
HO
OH
H
6
C
PREGNANES
O
O
7
D
ANDROSTANES
OH
O
8

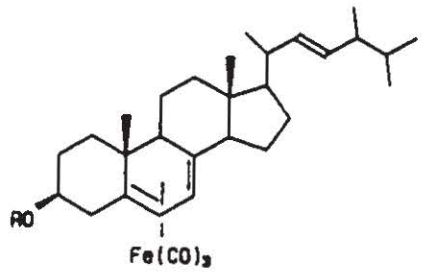
further removal of the C-19 methyl provides the estrane series (Route E). The principal members of these steroidal series are the sex hormones, testosterone, 8, and estradiol, 9, respectively. These steroids promote an individual's "male" and "female" characteristics.

From this figure, one can get an impression of the wide variety of steroids available as each series consists of an enormous number of derivatives, both naturally occurring and synthetically prepared. In addition, each series contains members with an assortment of functional groups present in their skeleton or side chain which can be utilized as coordination sites for transition metals. For example, the arene A-ring in estrone, 10, and the conjugated diene in the B ring of ergosterol, 5, are prime locations for complexation of an organometallic moiety. As a result, numerous research groups have utilized steroids as potential ligands and the forthcoming sections will illustrate the chemistry and biochemistry performed on such complexes.

1.3 CHEMICAL SIGNIFICANCE OF ORGANOMETALLIC COMPLEXES OF STEROIDS

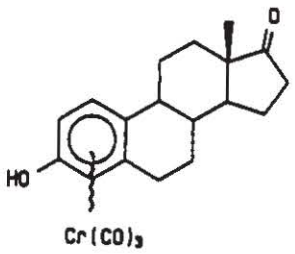
Twenty five years have passed since the first reported isolation of stable π complexes between steroids and transition metals. In this initial study, Nakamura and Tsutsui[10,11] treated two entirely different steroidal systems, ergosteryl acetate [where the OH in 5 is replaced by an

OAc group] and estrone, 10, with $Fe_3(CO)_{12}$ and $Cr(CO)_6$, respectively. In both instances, stable π complexes were isolated, purified, and characterized on the basis of their infra-red, ultraviolet and elemental analysis data. In the former example, 11, the conjugated diene located in the B-ring is coordinated by a $Fe(CO)_3$ moiety. This group is postulated to be coordinated onto the α face of the molecule in order to avoid the angular methyl group located at C-10. In the estrone case, 12, the arene A-ring is complexed by a $Cr(CO)_3$ group, but, these workers were unable to distinguish whether the metal fragment was bound onto either the α or β face of the molecule due to the planarity of this ring and concluded that the resulting complex was a mixture of both isomers.



R = H, Ac, or Bz

11



12

As a result of Nakamura and Tsutsui's work, other groups, such as those of Barton, Trost and Jaouen, began to synthesize and utilize organometallic complexes of steroids as intermediates in the preparation of new steroidal derivatives, which would have been difficult to isolate using conventional organic methods. Rather than dealing with the

research performed in this area in a chronological order, the succeeding subsections will focus on how such steroidal organometallic complexes have been utilized. The subsections are as follows:

A) Protecting Agents

B) Bond Rearrangements

C) Nucleophilic and Electrophilic Additions

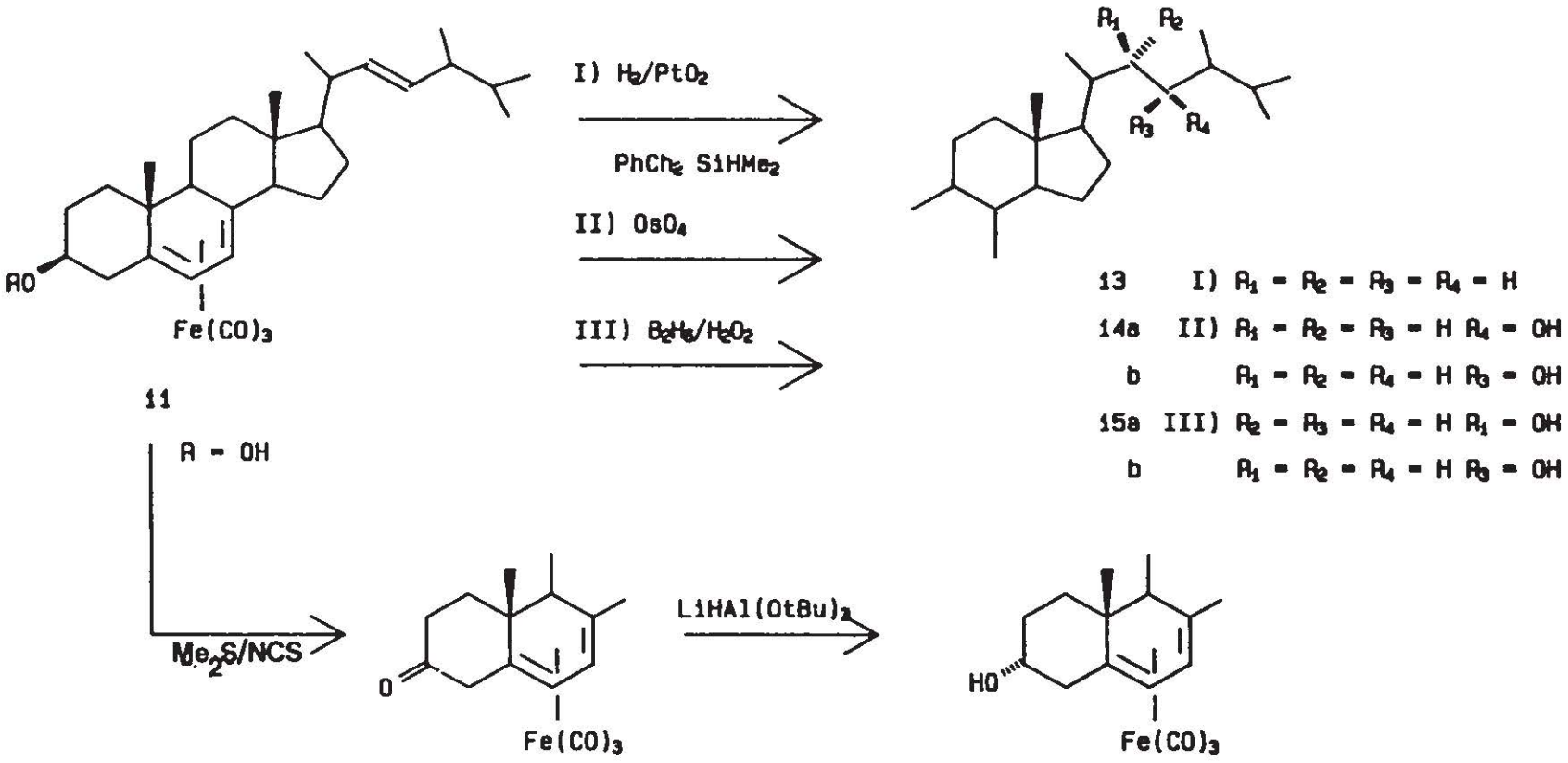
D) Total Syntheses of Steroids

A) Protecting Agents

As alluded to earlier, Nakamura and Tsutsui were the first to isolate the $Fe(CO)_3$ complex of ergosteryl acetate, 11, but it was the work of Barton's[12] and Johnson's[13] groups that illustrated the effectiveness of the $Fe(CO)_3$ group as a temporary protecting agent. In their independent studies, the $Fe(CO)_3$ moiety was utilized to protect the C-5/C-7 diene unit while the exocyclic double bond at C-22/C-23 was being manipulated by a variety of electrophilic reactions, such as hydration, osmylation, selective hydrogenation, and hydroboration. Once the transformation was complete, the C-5/C-7 diene could be regenerated by removal of the $Fe(CO)_3$ group with ferric chloride, thus, this intermediate provided a means of synthesizing C-22 and C-23 substituted ergosterols, 13,14,15 (see Scheme 1.1).[14]

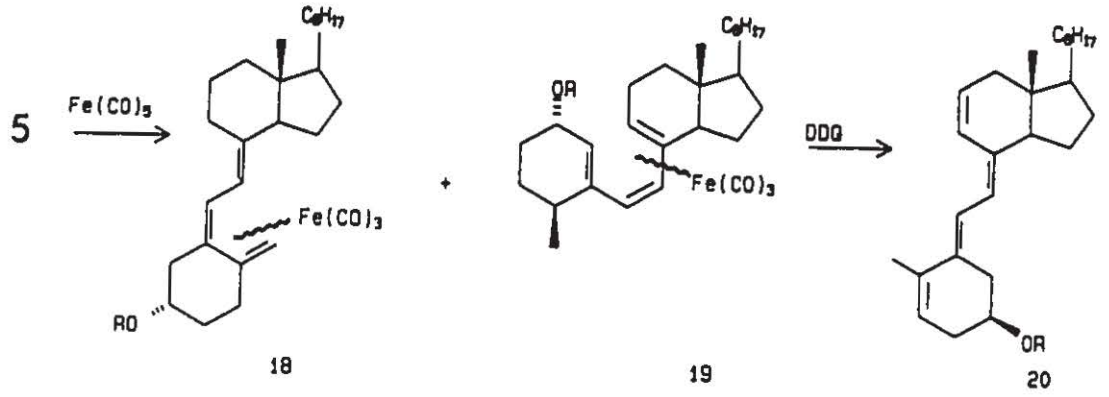
Subsequent to this work, Barton and his co-workers[15] demonstrated that the 3β-OH function in ergosterol, 5, could

SCHEME 1.1


RO
Fe(CO)3
11
R = OH
I) H2/PtO2
PhCH2 SiHMe2
II) OsO4
III) B2H6/H2O2
R1 R2
R3 R4
13 I) R1 = R2 = R3 = R4 = H
14a II) R1 = R2 = R3 = H R4 = OH
b R1 = R2 = R4 = H R3 = OH
15a III) R2 = R3 = R4 = H R1 = OH
b R1 = R2 = R4 = H R3 = OH
Me2S/NCS
O
Fe(CO)3
16
LiHAl(OtBu)3
HO
Fe(CO)3
17

be epimerized into its 3α isomer, 17, via the same $Fe(CO)_3$ complex (see Scheme 1.1). Specifically, oxidation using the dimethylsulphonium method generated a ketone at C-3, 16, which was reduced with $LiAlH_4$ to yield a 1:1 mixture of ergosterol and its epimer. This ratio indicated the ability of the bulky $Fe(CO)_3$ group to block the α face of the steroid from hydride attack. Upon use of a bulkier hydride, such as lithium hydrido-t-butoxyaluminate, epi-ergosterol, 17, was obtained with greater selectivity (92% yield).

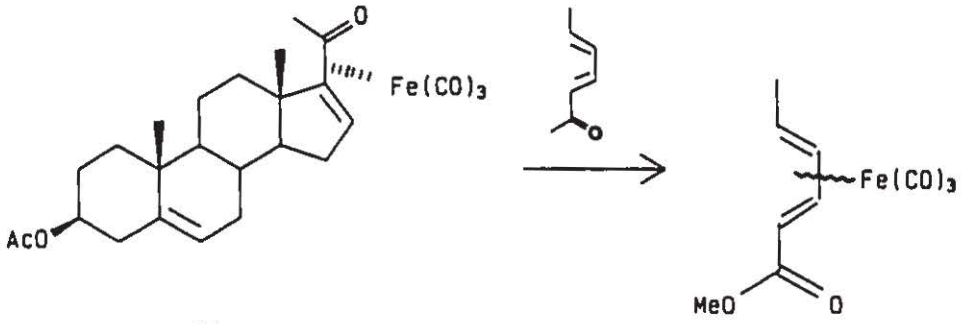
Barton's group[16] further extended the use of a $Fe(CO)_3$ complex into previtamin D steroids and showed that introduction of $Fe(CO)_5$ during the photolysis of ergosterol, 5, results in the formation of the α and β $Fe(CO)_3$ complexes of tachysterol$_2$, 18, as the major components and the α and β precalciferol$_2$ $Fe(CO)_3$ complexes, 19, as the minor ones. Removal of the metal by conventional means afforded tachysterol$_2$ and precalciferol$_2$ in better yields than previously reported. In addition, when a mixture of the benzoate $Fe(CO)_3$ complexes of either component was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), a single product which did not contain iron, but had a pentaene unit within the skeleton was obtained and identified as the previously unknown 9,10-secoergosta-1(10),5,7,9(11),22-pentaen-3β-ol, 20.



18 19 20

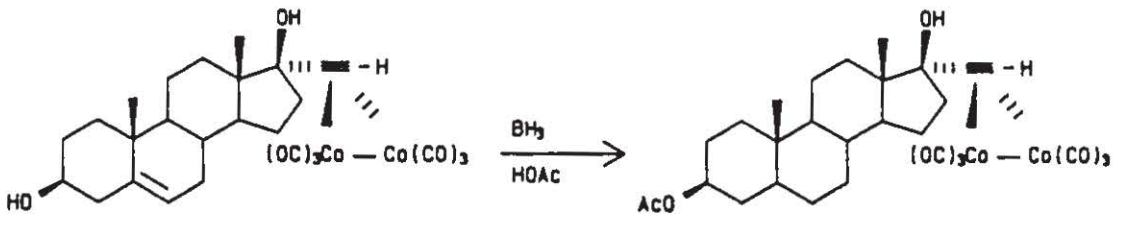
As a result of the efforts of these groups, the $Fe(CO)_3$ complexes of ergosterol and its esters have become valuable intermediates in the preparation of new ergosterol derivatives. Their value is exemplified by the ease of complex formation using a variety of iron reagents, such as $Fe(CO)_5$, $Fe_2(CO)_9$ and the arylmethyleneacetone $Fe(CO)_3$ precursors (benzylideneacetone [bda] and p-methoxybenzylideneacetone [mba]). Johnson and co-workers[17] have recently shown that one of the CO ligands in $(bda)Fe(CO)_3$ can be replaced with a PPh_3 or $P(OPh_3)_3$ group. Subsequent treatment of the triphenylphosphite $Fe(CO)_3$ precursor with ergosteryl acetate afforded the corresponding $Fe(CO)_2(P(OPh_3)_3$ complex which was characterized by its spectroscopic properties and microanalysis. However, its isolation was difficult and the overall yield was too poor to enable extensive use of this complex in steroidal synthesis. In a related aspect, Birch's group[18] has reported the use of a steroid $Fe(CO)_3$, similar to that of $(bda)Fe(CO)_3$, as a chiral tranfer agent for the asym-

metric synthesis of optically active $Fe(CO)_3$ complexes of 1,3 dienes. In particular, the $Fe(CO)_3$ complex of 3β-acetyloxy-pregna-5,16 diene-20-one, 21, was synthesized and utilized for the direct synthesis of optically active complexes of methyl sorbate, 22.



21 22

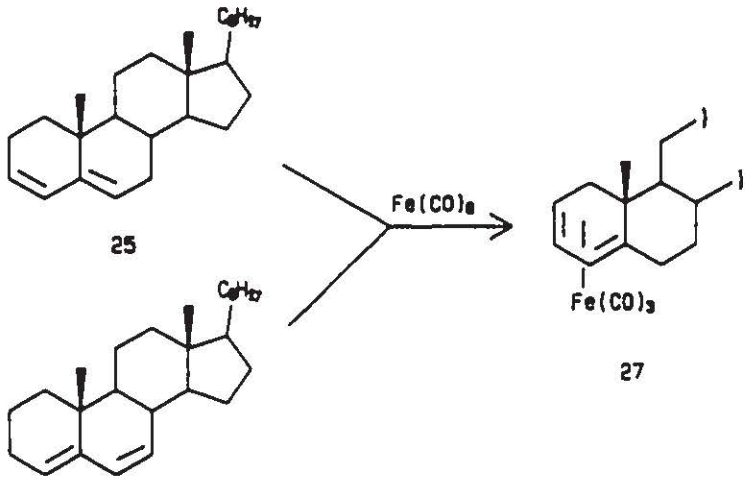
Besides the effective use of the $Fe(CO)_3$ moiety to protect dienes, Nicholas and co-workers[19] have illustrated that a triple bond can be protected with the $Co_2(CO)_6$ moiety, thus enabling the chemical manipulation of a double bond located within the skeleton. They demonstrated that the double bond between C-5 and C-6 in the cobalt complex of 17-ethynyl-$\delta^{5,6}$-dehydroisoandrosterone, 23, can be easily reduced using BH_3/HOAc to yield 17-ethynylisoandrosterone-$Co_2(CO)_6$, 24, in 60% yield.



23 24

B) Bond Rearrangements

While organometallics have been shown to smoothly and effectively bring about selective bond migrations in molecules,[1] Alper and Edwards[20] were the first to exploit this property in steroidal chemistry, by the conversion of steroidal transoid dienes into their cisoid isomers using an $Fe(CO)_3$ complex. In particular, they treated cholesta-3,5-diene, 25, or cholesta-4,6-diene, 26, with $Fe(CO)_5$ and isolated a 2,4-dienyl $Fe(CO)_3$ complex, 27, which afforded the desired cisoid isomer after decomplexation. Thus, the formation of such an $Fe(CO)_3$ complex offered a means of converting heteroannular steroidal dienes into their thermodynamically less stable homoannular forms.



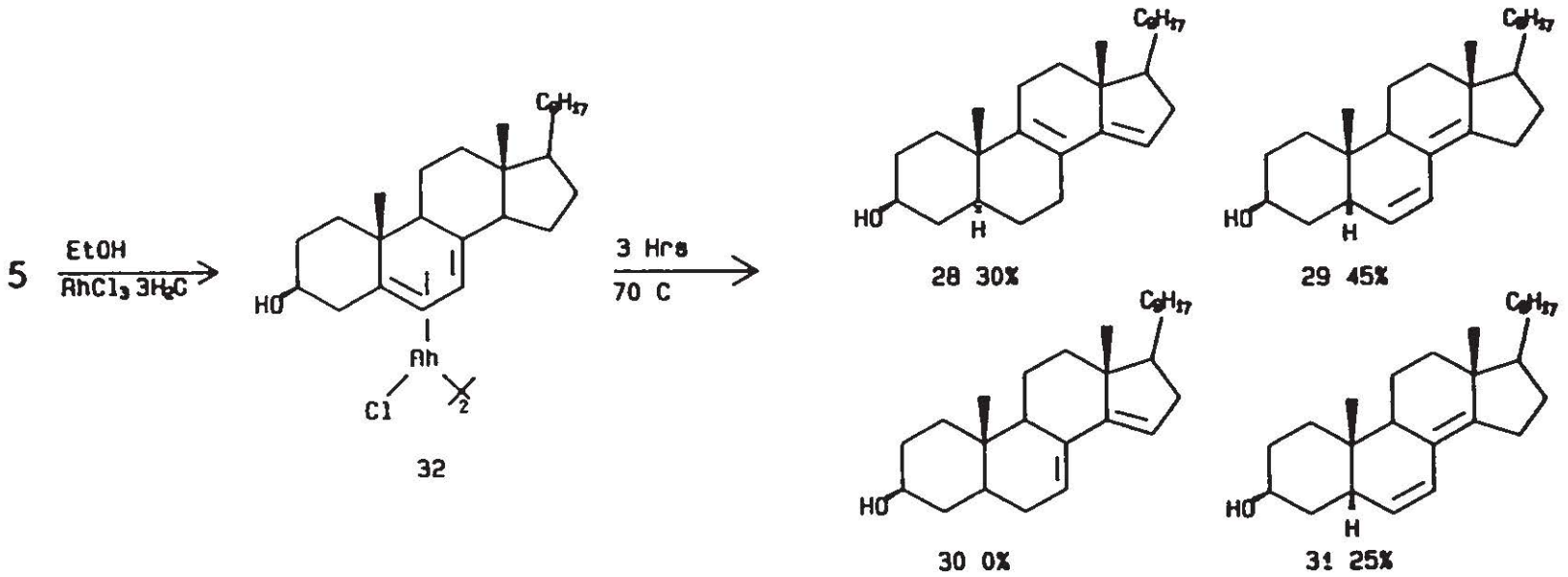
25 26 27

The reverse isomerization, cisoid to transoid, has been shown to be plausible by Barton and co-workers. It was well documented[21] that ergosterol rearranges by HCl addition

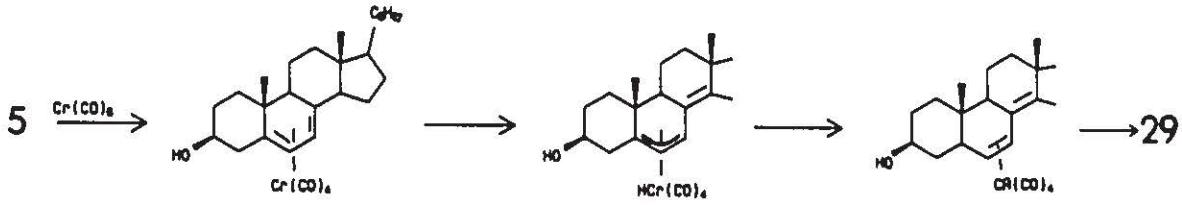
into a mixture of its B_1, 28, B_2, 29, and B_3, 30, isomers. Barton and co-workers[22] illustrated that organometallic reagents can also bring about this isomerization in a smoother and more selective fashion. Consequently, treatment of ergosteryl acetate, a cisoid diene, with a catalytic amount of $RhCl_3.3H_2O$ provided the transoid isomers, ergosterols B_1, 28, and B_2, 29, and the previously unknown, coprostatrienol, 30, which has a *cis* AB ring junction in respectable yields. Convenient reaction conditions were also established for the isolation of the dimeric Rh(I) intermediate, 32, (see Scheme 1.2). The mechanism for this organometallic induced isomerization was postulated to initially involve protonation of this dimeric intermediate at the C-5 position on both faces of the steroid skeleton in a ratio of 5:1(α:β). β-protonation would give rise to 31 while α-protonation leads to ergosterol B_2, 29, which readily rearranges to its B_1 isomer, 28. They further postulated this rearrangement proceeds due to the presence of a small quantity of HCl or an unknown rhodium hydride species.

Within a short period of time, Barton's group[23] revealed that $Cr(CO)_6$ was a much more efficient reagent for this *cis* to *trans* isomerization by readily and irreversibly converting ergosteryl acetate, 5, into its B_2 isomer, 29, in 81% yield. The mechanism was demonstrated to involve initial coordination of the C-5/C-7 diene by a $Cr(CO)_4$ group and subsequent hydrogen migration to the metal fragment thereby

SCHEME 1.2

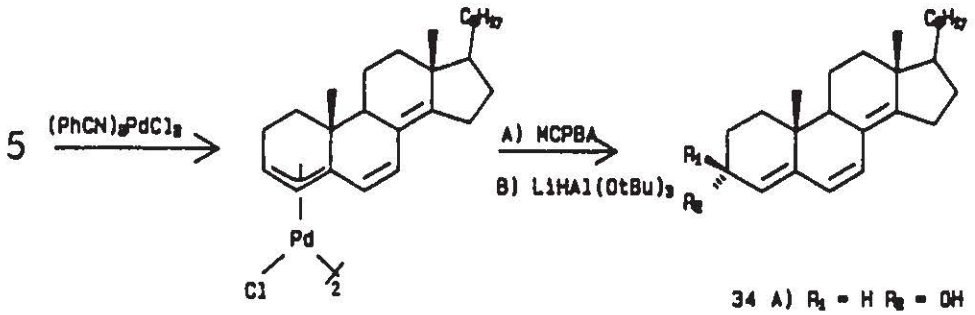

5
EtOH
RhCl3 3H2O
HO
C8H17
Rh
Cl
2
32
3 Hrs
70 C
HO
H
C8H17
28 30%
29 45%
30 0%
31 25%

yielding the transoid product, which now can not function as a four electron donor to the metal: this explains the irreversibility of the reaction. To verify further this mechanism, ergosteryl B_3 acetate, 30, was treated with $Cr(CO)_6$ and converted into the B_1 isomer, 28.



The Barton group[24,25] continued to exploit the use of organometallics to bring about isomerization of the double bonds in ergosterol and recently isolated a brown dimeric PdCl complex, 33, in 62% yield upon treatment of ergosterol, 5, with bis(benzonitrile) palladium dichloride, $(PhCN)_2PdCl_2$. The interesting feature of this complex was the apparent loss of the 3β-OH functionality, on the basis of its spectroscopic results. Both ^1H and ^{13}C nmr data suggested an endocyclic π allyl PdCl complex with the palladium positioned in the A-ring on the α face. Subsequent reactions of this complex involving reduction with $LiHAl(OBu^t)_3$ or oxidation with MCPBA led to products 34 and 35, respectively, which verified the original structure of the PdCl complex. When the unreacted steroid fraction from this reaction was analyzed, Barton noted that it contained mostly coprosta-6,8(14)22-trien-3β-ol, 31, which was first observed in the $RhCl_3$ isomerization,

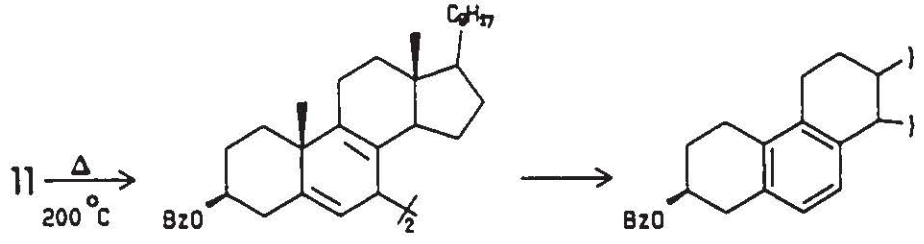
along with small quantities of ergosterols B_1 and B_2. These products indicated that small amounts of HCl were being formed in the palladation process which helped to promote the initial isomerization.



33

34 A) R_1 = H R_2 = OH
35 B) R_1 = R_2 = H

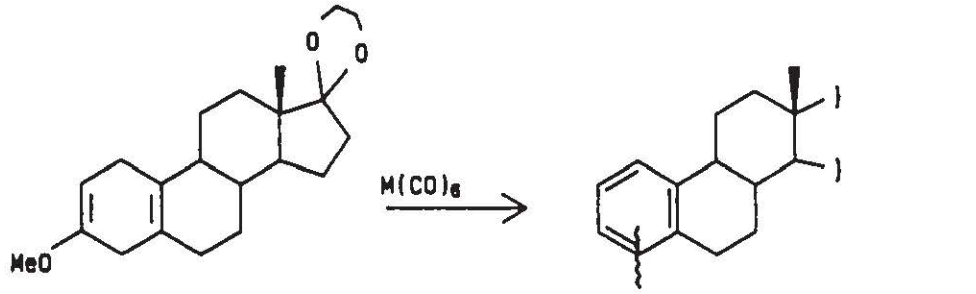
In a slightly different vein, Mateos' group[26] has focussed on the thermal rearrangement of ergosteryl benzoate $Fe(CO)_3$, 11, and isolated neoergosteryl benzoate, 36, whereby the B-ring has now become aromatic after pyrolysis and decomplexation. This particular rearrangement was presumed to involve a radical decomposition process yielding bisergostatrienyl benzoate, 37, which was known to decompose thermally to give neoergosteryl benzoate.[2]



37

36

Birch and co-workers[27] have also examined the use of organometallics in the aromatization of the A-ring in steroids. Specifically, treatment of 1,4-dihydroestrone 3-methyl ether 17-ethylene ketal, 38, with $Cr(CO)_6$ resulted in the formation of a chromium tricarbonyl complex, 39, in 70-80% yield where the A-ring becomes aromatic due to loss of MeOH. They further showed that $Mo(CO)_6$ and $W(CO)_6$ can bring about this A-ring aromatization, but the resulting adducts were of lower stablity and formed in lower yields.



38 39

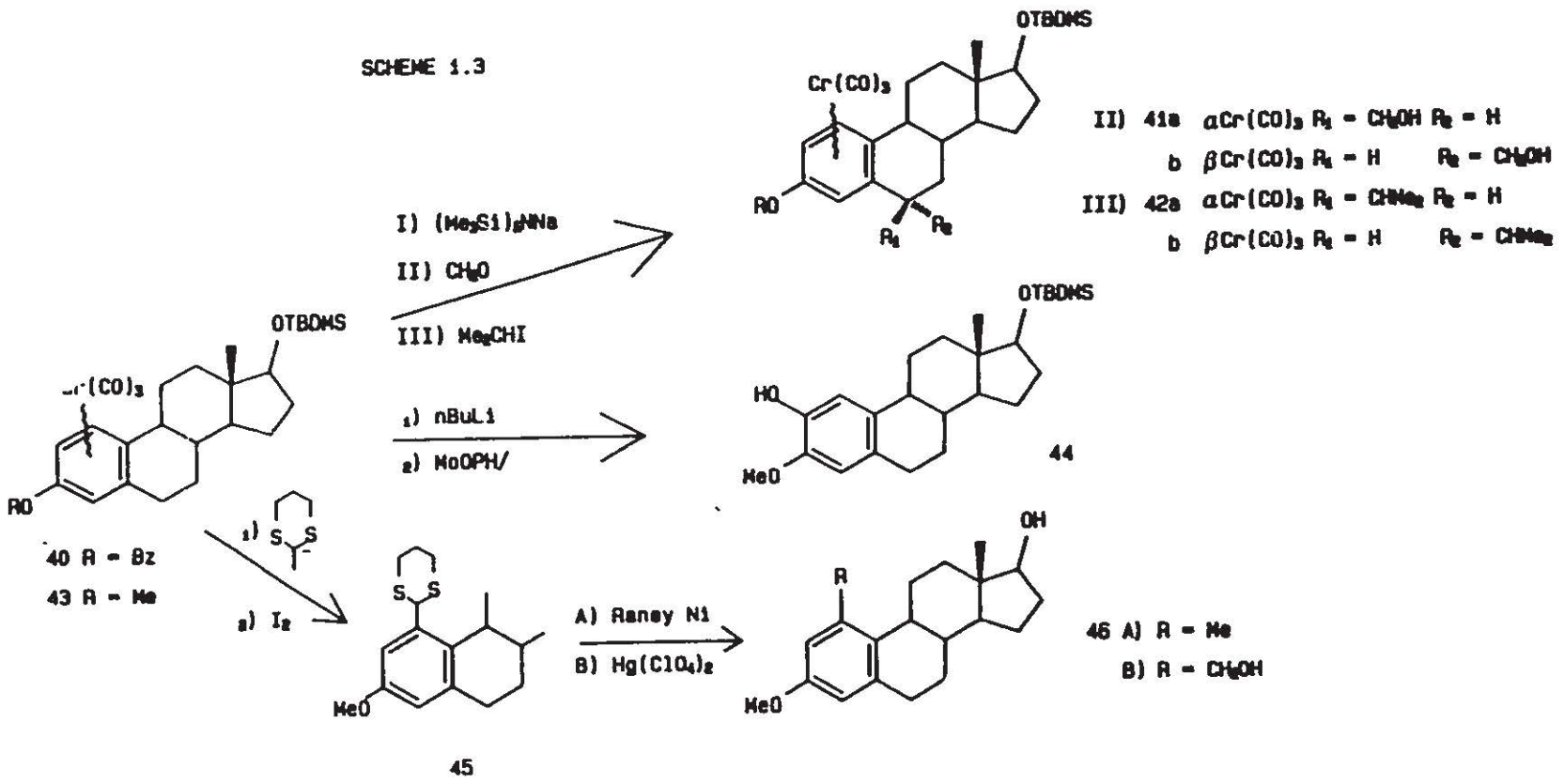
C) Nucleophilic and Electrophilic Additions

By far the principal reason for incorporating organometallics into steroidal frameworks is to utilize the ability of organometallic groups to offer sites for the formation of new carbon-carbon bonds. In particular, coordination of a functional group by a transition metal often activates this functionality towards nucleophilic or electrophilic attack.[1] An example of such an activation is the increase in reactivity of an arene ring upon complexation to a $Cr(CO)_3$ moiety.

Jaouen's group[28], by utilizing the knowledge that the arene and benzylic protons in a $Cr(CO)_3$ complex become more acidic and therefore easily lithiated, have illustrated that the 6 position in estradiols can be alkylated in a stereospecific manner with a high degree of regioselectivity. They demonstrated that treatment of either α or β [3-O-benzyl-17β-O-(tbutyl-dimethyl) silyl estradiol] $Cr(CO)_3$, 40, with $(Me_3Si)_2NNa$, generates an anion at the 6 position which subsequently can be treated with paraformaldehyde to yield products with a CH_2OH substituent at the 6 position, 41, (see Scheme 1.3). The stereospecificity of this reaction is exemplified by the fact that the complexes obtained, a 6β CH_2OH product from the α complex and, a 6α product for the β isomer, have the alcohol function anti to the $Cr(CO)_3$ group. It was also noted by these researchers that even though there are two benzylic sites available for proton abstraction (6 and 9), it was only the product corresponding to a meta attack of the 3β benzyl group which was observed.

Shortly thereafter Jaouen[29] extended this methodology by reporting that the benzylic anion above reacts readily with Me_2CHI to yield complexes whereby an alkyl substituent is incorporated exclusively at the 6 position and trans to the metal fragment, 42. The main thrust of this investigation, as will be presented in section 1.4, was to utilize these newly alkylated steroidal organometallic derivatives in receptor binding assays.

SCHEME 1.3


OTBDMS
Cr(CO)3
RO
I) (Me3Si)2NNa
II) CH2O
III) Me2CHI
1) nBuLi
2) MoOPH/
HO
MeO
44
1) S S
2) I2
S S
MeO
45
A) Raney Ni
B) Hg(ClO4)2
OH
R
MeO
40 R = Bz
43 R = Me
II) 41a αCr(CO)3 R1 = CH2OH R2 = H
b βCr(CO)3 R1 = H R2 = CH2OH
III) 42a αCr(CO)3 R1 = CHMe2 R2 = H
b βCr(CO)3 R1 = H R2 = CHMe2
46 A) R = Me
B) R = CH2OH

Deprotonation of the arene protons in the α and β $Cr(CO)_3$ complexes of 17β-(t-butyl dimethyl)silyl-3-methoxy-estra-1,3,5(10)-triene, 43, has recently been shown feasible by Marples'[30] and Kunzer's[31] groups (see Scheme 1.3). In the former case, a mixture of these complexes was treated with n-BuLi, thus removing the proton at C-2 and subsequent reaction of the newly formed anion with MoOPh afforded 2-hydroxy derivatives, 44, upon workup. Kunzer's methodology involved removal of the proton at C-1 with the Li anion of 1,3 dithiane and subsequent workup to yield a heterocyclic intermediate, 45, which can readily be converted into various C-1 derivatives, 46, either by desulfurization with Raney nickel to give a C-1 methylated compound or by hydrolysis of the thioacetal group with mercury(II) perchlorate yielding an aldehyde at C-1, which can then be reduced to its alcohol and acetylated.

Recently, Bond and co-workers[32] have examined the electrochemical and chemical oxidation of these steroidal arene $M(CO)_3$ [M = Cr, Mo, and W] in the hopes of determining if the steroid is modified during the oxidation process and whether an eliminative oxidation of a CO ligand and the steroid occurs. Their cyclovoltammogram results indicated two one-electron oxidation processes involving $[M(CO)_3$ steroid$]^+$ and $[M(CO)_3$steroid$]^{2+}$, thus they concluded the overall oxidation process based on the fact the uncomplexed steroid was quantitatively recovered to be as follows:

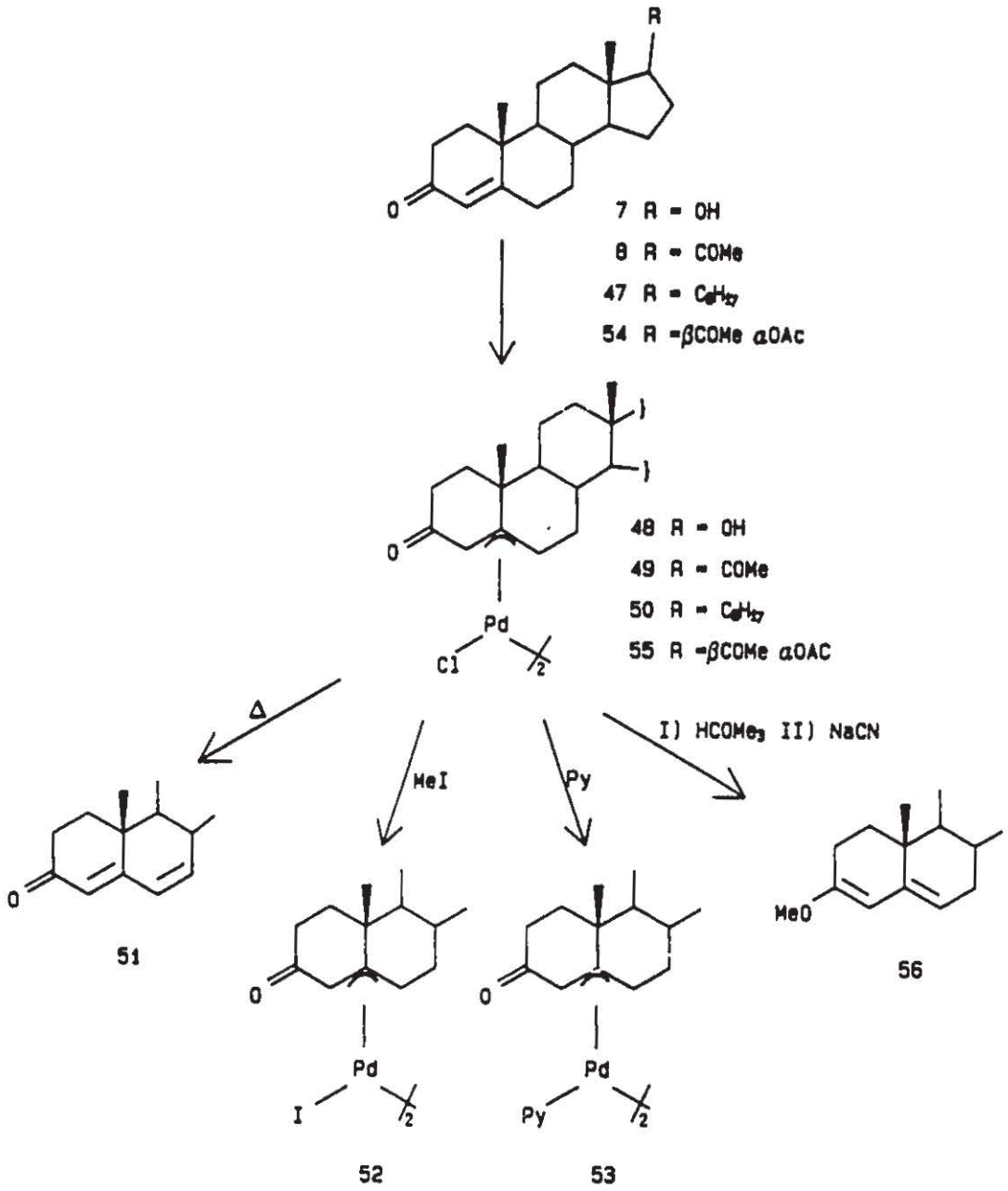
$$M(CO)_3\text{steroid} \longrightarrow M(II) + 3CO + \text{steroid} + 2e^-$$

Results obtained from chemical oxidation with $NO^+PF_6^-$, which also generated the free steroid, were consistent with an oxidative-elimination type reaction.

The above series of reactions illustrate the versatility of steroidal arene $Cr(CO)_3$ complexes, but the most extensively studied organometallic steroidal complex involves the (η^3 π-allyl) PdCl fragment which has been known to react readily with nucleophiles in a regiospecific manner.[33] The use of the PdCl steroidal complexes dates back to the late 1960's when Howsam and McQuillin[34] investigated the reaction of various Pd(II) derivatives with a group of steroidal 4-en-3-ones. Specifically, progesterone, 7, testosterone, 8, and cholestenone, 47, were treated with Na_2PdCl_4, $(PhCN)_2PdCl_2$), and $[(C_2H_4)_2PdCl]_2$ and the corresponding stable (π-allyl) PdCl complexes, 48,49,50, were isolated (see Scheme 1.4). The PdCl complexes were then subjected to various chemical transformations involving thermolysis, which afforded a dienone, 51, halogen exchange using MeI, which yielded the iodo derivative, 52, and a monomeric complex, 53, from their reaction with pyridine.

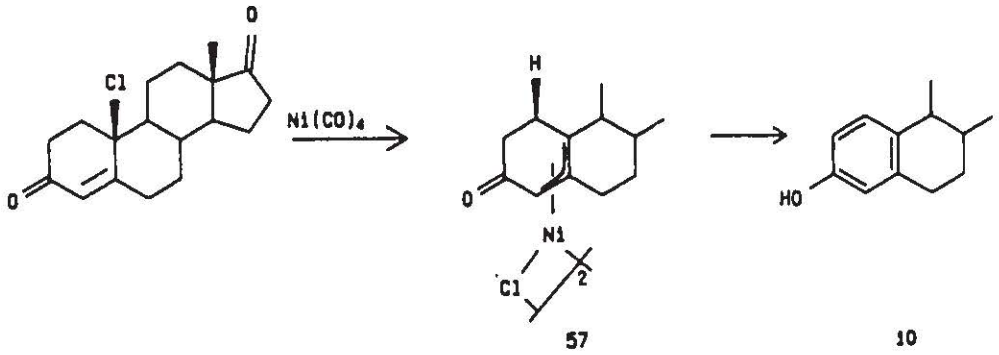
Within a short period of time, Harrison and his colleagues[35] prepared a similar Pd complex, 55, from the reaction of 17α-acetoxyprogesterone, 54, with $PdCl_2$ in DMF.

SCHEME 1.4



51 52 53 56

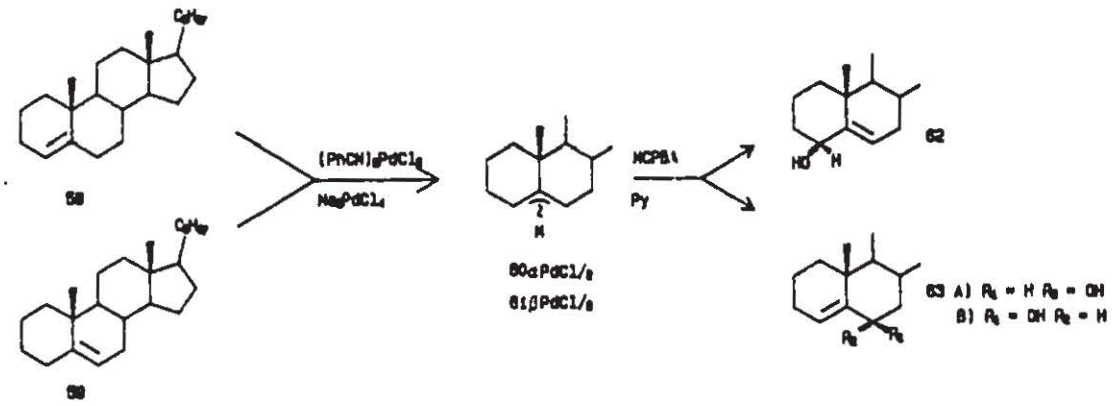
Attempts to functionalize this complex using strong nucleophiles, such as CN^- or malonate ion, resulted in the formation of an elimination product similar to that reported by McQuillin during the thermolysis reaction. However, they were able to synthesize an enol ether, 56, by treatment of 55 with methyl orthoformate and subsequent reduction with NaCN. Also reported in this communication was the synthesis of a $NiCl_2$ (π-allyl complex), 57, by reaction of a chloro-derivatized steroid with $Ni(CO)_4$. Attempts to alkylate this complex resulted in the elimination of a β-hydrogen at C-1, trans to the $NiCl_2$ moiety, thus yielding estrone, 10, in reasonable yield.



57 10

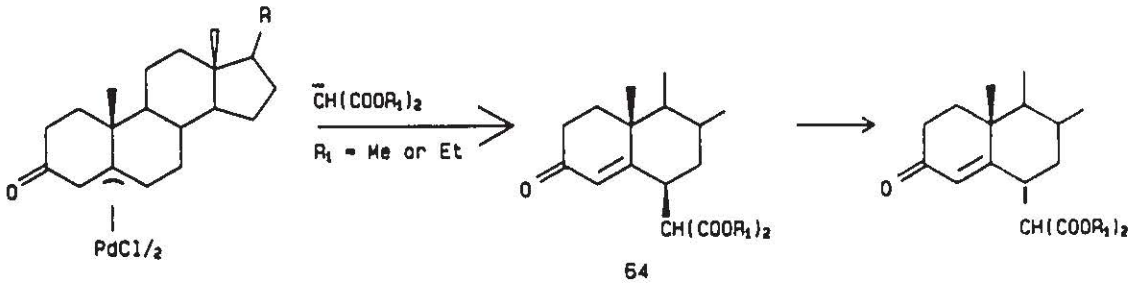
These early reports prompted others, such as Jones and Knox[36], to explore the stereochemical aspects in the formation of (π-allyl) PdCl complexes from steroidal olefins. They examined the different reaction conditions utilized for this palladation process [$(PhCN)_2PdCl_2$ versus Na_2PdCl_4] with cholest-4-ene, 58, and cholest-5-ene, 59, and concluded that the latter steroid gave exclusively an α 4-6η complex when

treated with bis(benzonitrile)$PdCl_2$, while reaction with the former yielded a mixture of α and β complexes, 60,61, with the α complex predominating since it was sterically favoured. A similar mixture of complexes was observed when these steroidal olefins were treated with Na_2PdCl_4. This greater regioselectivity and stereoselectivity of $(PhCN)_2PdCl_2$ was attributed to its greater steric demands and the fact that the β face in 59 was much more sterically hindered by the presence of the methyl at C-10.



In the succeeding communication,[37] they reported the oxidation of these complexes by treatment in sequence with pyridine and MCPBA and obtained the corresponding allylic alcohols, 62,63. They demonstrated that the presence of pyridine greatly enhanced the hydroxylation process since poor results were obtained in its absence. It was presumed that the pyridine cleaves the halogen bridge to form a transient monomeric species with pyridine acting as a ligand, but they were unable to isolate this intermediate.

Concurrent to this work, Collins and his co-workers[38] reinvestigated the work of Harrison and established reaction conditions whereby the 6-position in the (π-allyl) Pd complexes of testosterone, 48, progesterone, 49, and cholestenone, 50, could be stereospecifically functionalized. They demonstrated that when the anions of dimethyl and diethyl malonate are generated in DMSO and not EtOH or MeOH, as in Harrison's case, the corresponding 6β malonate esters, 64, are isolated in virtually quantitative yield with no evidence of an elimination product, such as, cholesta-4,6-diene-3-one. To verify the stereochemistry of their final product, the resulting malonate ester was heated with p-toluenesulphonic acid and converted to its thermodynamically more stable 6α isomer.

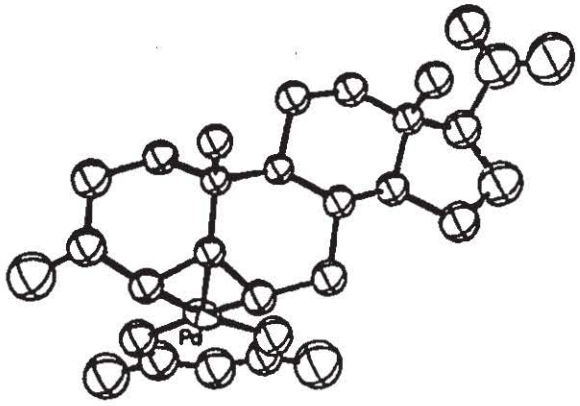


64

48 R = OH
49 R = COMe
50 R = C_8H_{17}

More recently, Collins and his colleagues[40] have firmly established the stereochemistry of the formation of α-(4-6η)-PdCl complexes from steroidal α,β-unsaturated ketones by reporting the X-ray crystal structure of the monomeric α-

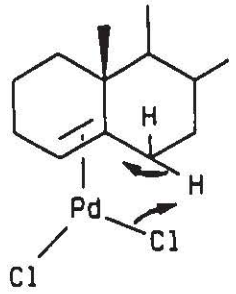
Pd(acac) complex of progesterone, 65.



65

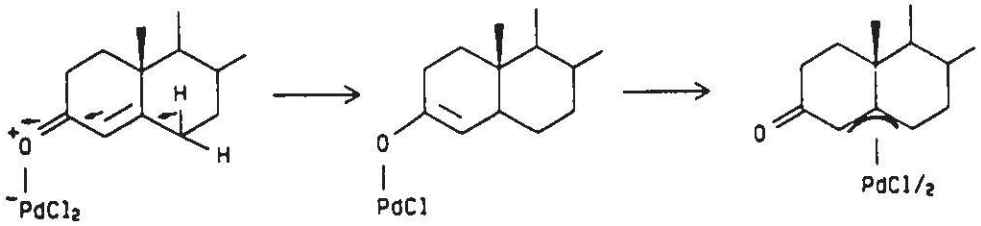
With the stereochemistry well established, McQuillin's group[41] subsequently set out to explore the mechanistic aspects of the Pd complex formation of steroidal olefins. In a communication, they reported the reaction of $(PhCN)_2PdCl_4$ with 6β[^{2}H] 2,2 dimethylcholest-4-en 3-one with the aim of determining the degree of stereoselectivity between elimination of the 6α and 6β proton. The method utilized for deuterium analysis involved decomposition of the newly formed complex with aqueous KCN followed by mass-spectral analysis of the newly formed products. The results obtained for these complexes were somewhat ambiguous, as indicated by a lack of stereospecificity in the products. They, therefore, concluded that a dual mechanism involving syn transfer of the 6α proton to the palladium or trans elimination to the PdCl residue by the 6β proton, which was known to be labilized by the 3-oxo functionality was occuring. Subsequently, they treated 6β[^{2}H] cholest-4-ene, an unconjugated steroidal

olefin, under the same palladation conditions and obtained results indicating a stereospecific syn elimination of the 6α-H during complex formation.[42] They postulated an intermediate, 66, in which the 6α proton is transferred as a H^+ to a leaving chloride ligand, which acts as a proton acceptor.

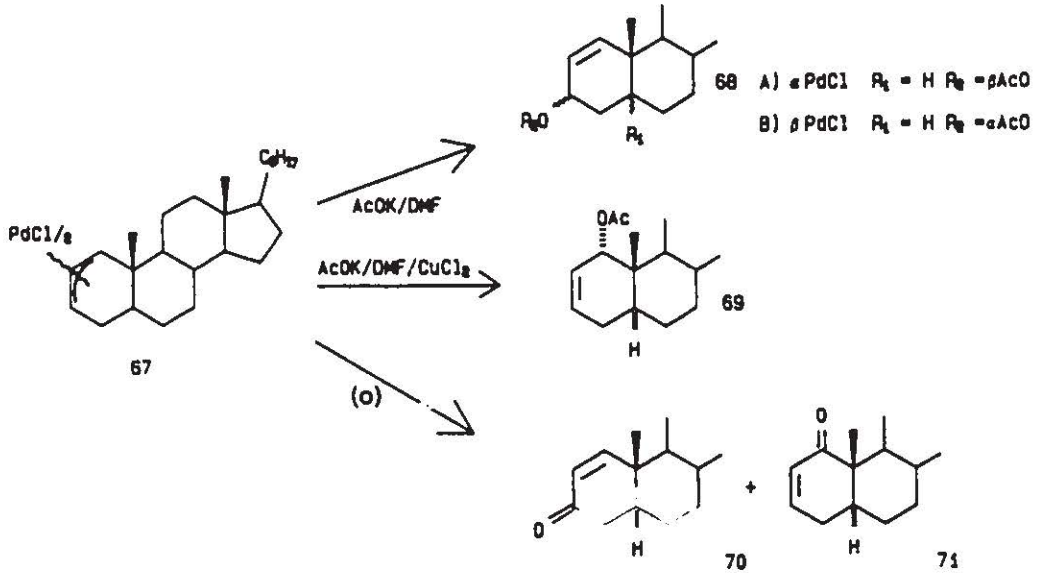


66

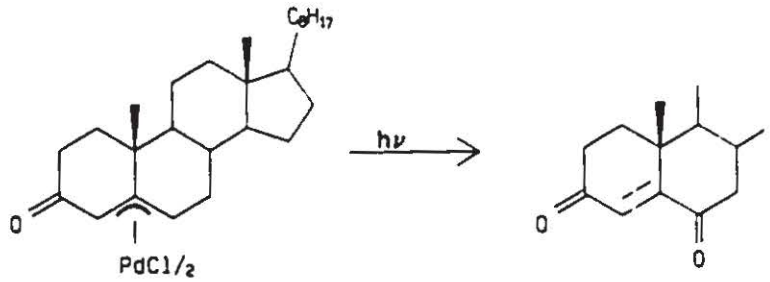
Returning to the steroidal 4-en-3-ones, they concluded the preference for 6β axial proton loss in their PdCl complex formation and postulated a mechanism involving coordination of the $PdCl_2$ fragment to the oxo function, followed by loss of the 6β-H, trans to the metal, to produce an enol which undergoes a 1,3 shift to afford the allyl complex. Shortly thereafter, Collins' group[43] showed that this postulated mechanism involving preferential 6β proton elimination was correct on the basis of the proportion of deuterium present when measured by the ^1H NMR intergrations of the 6 proton.



While the (π-allyl) Pd complexes discussed so far have involved complexation at the AB ring junction, Horiuchi's group[44] has synthesized a number of (cholestenyl) type Pd complexes, 67, where the double bond is situated in the A ring. Their palladation process involved the use of $PdCl_2$ and AcOK in acetic acid and exhibited a greater regioselectivity than that observed with bis(benzonitrile)$PdCl_2$,[45] i.e., 5α steroidal olefins gave α-(π-allyl) Pd complexes while β-(π-allyl) complexes were obtained from 5β steroidal systems. Recent work from this group has focussed on the nucleophilic substitution of these complexes and has demonstrated that reaction of either α or β PdCl complex with AcOK in DMF results in products, 68, due to trans attack on the face of the steroid opposite to the coordinated palladium and in the direction of C-3 due to greater ring flexibility and less steric hindrance of the C-19 methyl group.

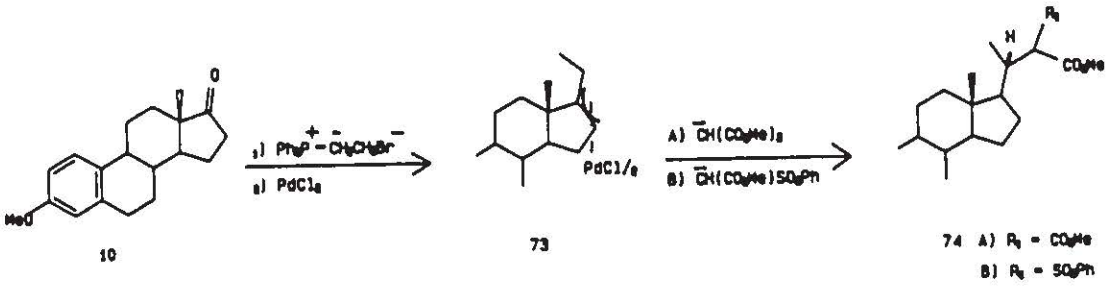


Addition of $CuCl_2$ to this palladating reagent results in products, 69, due to cis attack towards the direction of the C-1 axial position. They believed during this reaction that the initial PdCl complex formed from either steroidal systems occurs on the same face, i.e, 5α gave α-(π-allyl) complexes, and that these complexes underwent displacement at C-1 rather than at C-4 due to cis nucleophilic attack of a coordinated acetoxy ion. They, however, did not speculate on the role of $CuCl_2$ during this process. In addition,[46] they investigated the oxidation of these complexes using Cr(VI) oxide in N,N dimethylformamide and isolated the corresponding α,β unsaturated ketones, 70, and 71. For the α(1-3η) Pd complex, the oxo function was introduced at both C-1 and C-3, while in the β complex, the oxidation occurred at the less hindered C-3 site. More recently, a French group headed by Muzart[47] has examined the photochemical oxidation of the (π-allyl) PdCl complex of cholest-4-en-3-one at λ = 366nm and obtained products whereby a ketone is generated at the 6 position, 72.



50 72

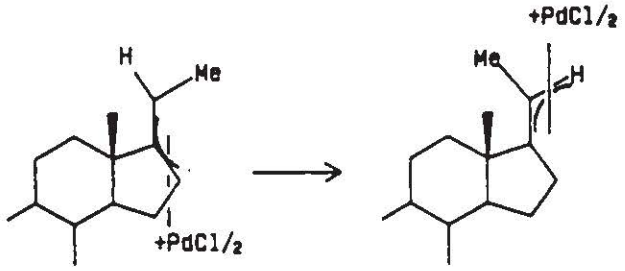
Such (π-allyl) PdCl complexes are not limited to coordination of double bonds present within the steroidal framework. Trost and his colleagues[48,49] have developed a stereo-controlled approach to incorporation of a side chain onto a steroidal skeleton via an allyl palladium intermediate. In this study, they converted estrone methyl ether, 10, into its 17-ethylidene derivative via a Wittig reaction and synthesized the α(π-allyl) PdCl complex, 73.



10 73 74 A) R_1 = CO_2Me B) R_1 = SO_2Ph

Alkylation of this complex with malonate anion or methyl phenylsulfonyl acetate occurs exclusively at the side chain carbon and trans to the metal. These derivatives, 74, were subsequently converted into their corresponding acetates, which were hydrolyzed into the carboxylic acid analogues via decarbomethylation with tetramethylammonium acetate or reductive desulfurization, respectively. Trost's group[50] have also illustrated that 4,5-dihydroxytestosterone can be converted into 5α-cholestanone using this methodology. They, also, have examined this alkylation process under catalytic conditions involving $(Ph_3P)_4Pd$.[48] Under these conditions, the 17-ethylidene derivative was oxidized with SeO_2, epoxidized, and acetylated to afford an allylic acetate at C-

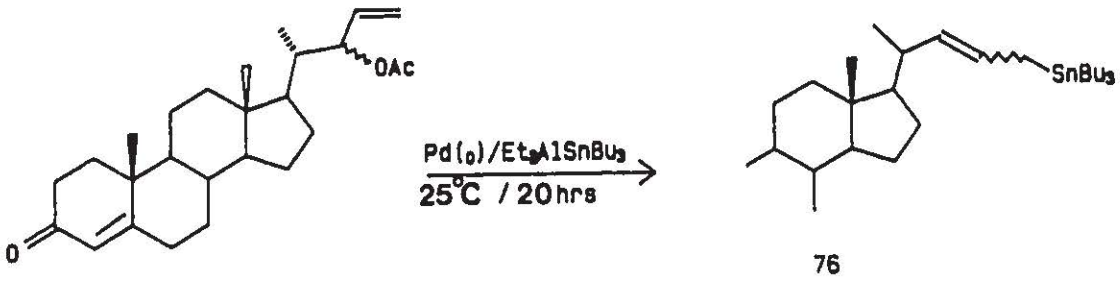
20 with the inverse stereochemical configuration to that observed in 74. Subsequent treatment of this acetate with $(Ph_3P)_4Pd$ in the presence of dimethyl sodiomalonate and Ph_3P was believed to yield a product with the same configuration as 74 via trans attack to the metal of malonate ion. However, the replacement of this acetate moiety by malonate ion proceeded with retention of configuration. They reasoned that the initial step in this catalytic process involved oxidative addition of the Pd^0 fragment and the allylic acetate with inversion of configuration since it was well established that incoming nucleophiles add to the opposite face of the metal. They suspected that cationic PdCl complexes, such as 75a and b, were involved and that the alkylation step occurred faster than the equilibration of these complexes which would result in a double inversion of configuration and an overall retention of configuration.



75a b

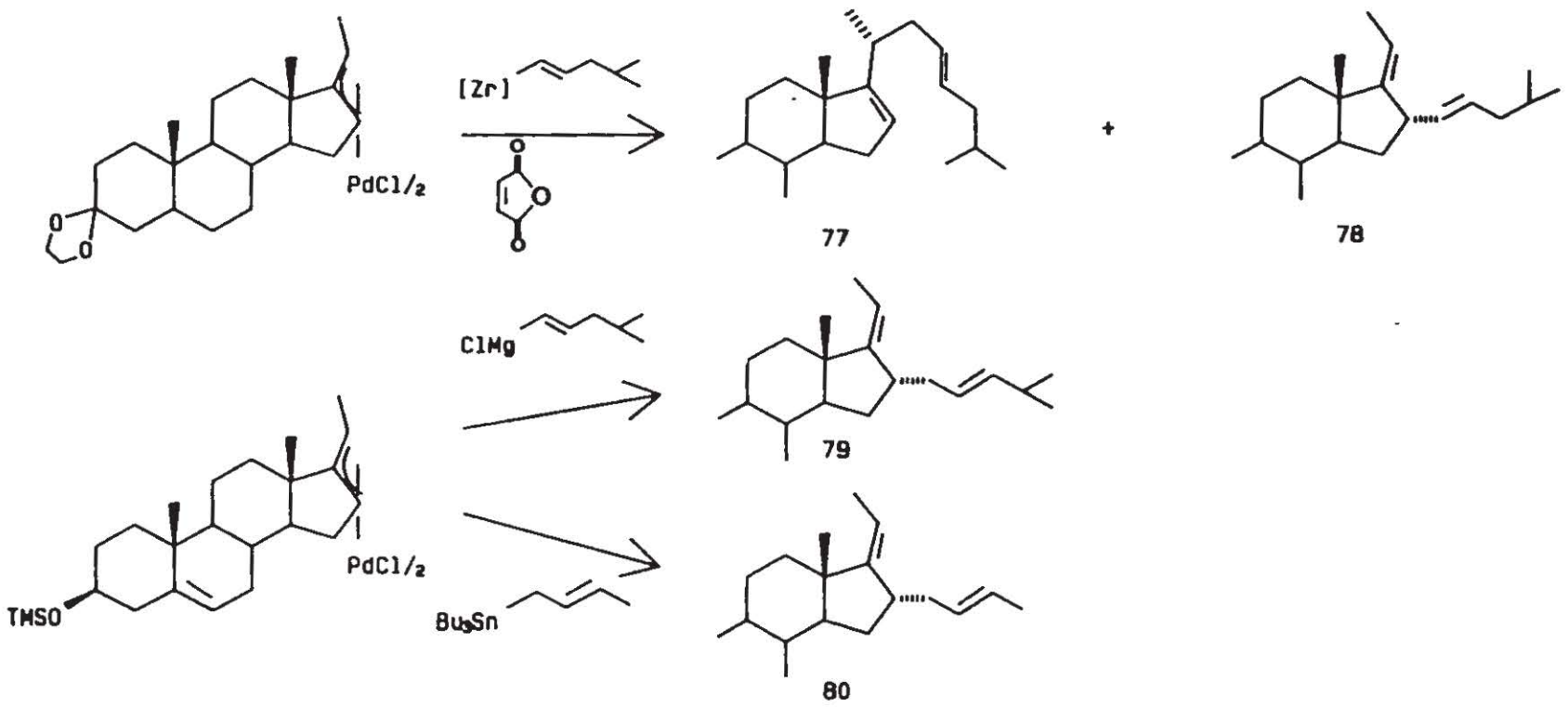
Recently, Trost and his co-workers[51] have examined the reactivity of these allylic acetates using an aluminum tin reagent ($Et_2AlSnBu_3$) in the presence of the Pd^0 catalyst and observed that this reaction proceeded with inversion of

configuration of the allylic acetate carbon, 76.



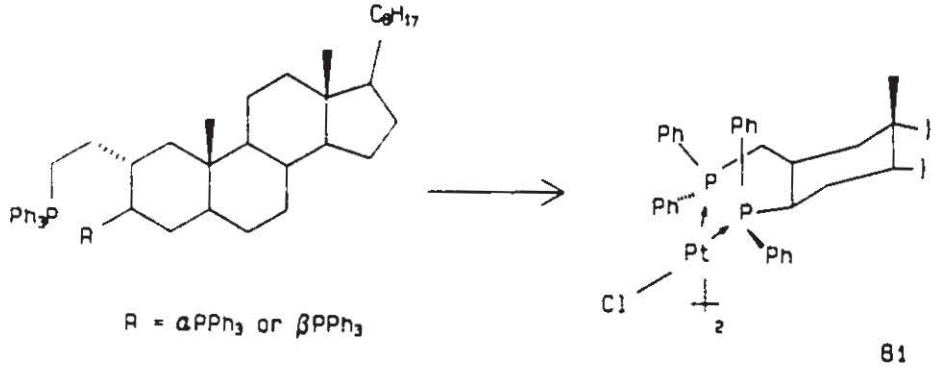
76

Schwartz's group[52] has also exploited the stereospecific addition of nucleophiles to steroidal (π-allyl) PdCl complexes and prepared [20(R)]-cholesten-3-one, 77, via a similar coupling reaction. They demonstrated that an alkenylzirconium complex, derived from hydrozirconation of the corresponding terminal acetylene, can transfer an alkyl group to the PdCl complex of 3-oxopregn-17(20)(2)ene-ethylene ketal via a transmetallation process from the more electropositive zirconium to the less electropositive palladium. The regiochemistry of this coupled product is controlled by the presence of good π-acceptor ligands, such as maleic anhydride, which preferentially promoted coupling at C-20. Donor ligands, such as μ-Cl, favoured coupling at C-16, 78. In both cases, the organozirconium species delivers the alkenyl functionality on the same face of the steroid as the bound palladium, which is opposite to that observed for the nucleophilic addition of stabilized anions to (π-allyl) PdCl complexes. Recently, they[53,54] have shown this selective cross-coupling technique can include allylic Grignards, 79,


PdCl/2
[Zr]
77
+
78
ClMg
79
PdCl/2
TMSO
Bu3Sn
80

and allylic tin species, 80. With these groups, the coupling occurs primarily at C-16 and on the α face of the steroidal molecule.

Finally, Thomson's group[55] has synthesized various steroidal 1,3-, 1,4-, and 1,6-diphosphines and diphosphine oxides where one of the phosphorus atoms is attached at the C-3 position of the steroidal skeleton and examined their ability as chelating ligands for metal-catalyzed asymmetric syntheses. They attempted to prepare the divalent metal complexes by reaction of the isomeric 1,4-diphosphine (3α and 3β), 81, with bis(benzonitrile)MCl_2 [M=Pd,Pt], but based on ^{31}P NMR spectroscopy and far-infrared, the reaction involving the 3β isomer and the Pd(II) salt was the only one to yield a single product, which had a cis square-planar stereochemistry; the others afforded inseparable mixtures. In addition, they attempted a ligand exchange reaction with bis(dibenzylideneacetone)Pd^0, but ^{31}P NMR results suggested that neither the 3α or 3β isomers coordinates readily that only the side chain phosphorus atom appears to be complexed.



R = αPPh3 or βPPh3

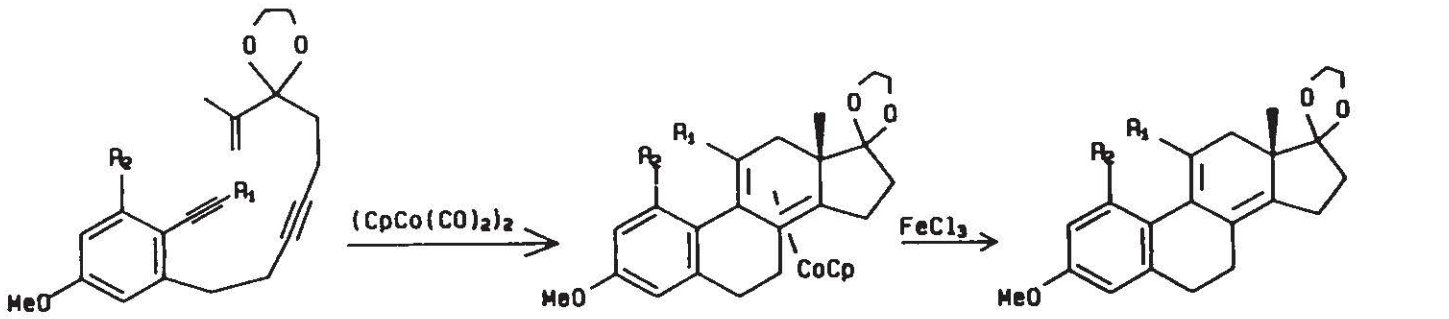
81

D) Total Syntheses of Steroids

Numerous approaches have evolved, over the years, for the total synthesis of steroids. Recently, two groups have adopted the utilization of organometallic complexes as the key intermediates for their approach to the total synthesis of steroids. The first developed by Vollhardt's group[56] involves a cobalt-mediated approach to preparing aromatic A-ring steroids via an intramolecular [2+2+2] cycloaddition of the B,C,D portions of the steroid skeleton onto the A-ring. The key step in this synthesis consists of the cyclization of an enediyne steroidal precursor, 82, using $CpCo(CO)_2$ to yield a stable cobalt complex, 83. The role of the cobalt moiety is to bring about complete stereoselectivity to this cyclization and to function as a temporary protecting group. Demetalation of this complex affords the hitherto unknown pentaene system, 84, which is isomeric to the well-known 8,14-diene, a key intermediate in the Torgov synthesis of estrone (see Scheme 1.5).

During their investigations of this cyclization process, Vollhardt and his colleagues[57,58] noted an unusual phenomenon in one of the resulting cobalt complexes which involved the hindered rotation of a TMS group when positioned at C-11, 85, based on the observation of a broad ^1H NMR signal at room temperature which subsequently splits into three signals at -35°C. To examine this effect, they prepared cobalt complexes where a TMS group was positioned at

SCHEME 1.5



82

83

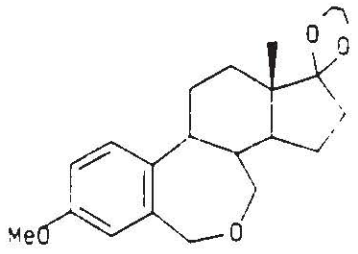
84 R_1 = H R_2 = H

85 R_1 = TMS R_2 = H

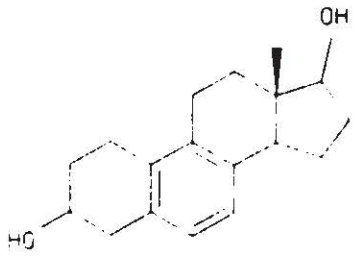
86 R_1 = H R_2 = TMS

87 R_1 = TMS R_2 = TMS

C-1, 86, and at both C-1 and C-11, 87, and observed that the former complex's ^1H NMR spectrum revealed no hindered rotation as its signals were sharp even at -80°C. In contrast, one of the TMS ^1H NMR signals splits into three at -60°C in the bis TMS complex, thus indicating a hindered rotation which they postulated to be the result of an electronic effect involving the silicon orbitals. More importantly, these resulting complexes illustrated the efficiency of the cyclization process as these systems are highly substituted. Vollhardt's group[59] has, recently, extended this methodology to the preparation of B ring homoxasteroids, 88, and has since reported the synthesis of an aromatic B ring steroid, 89, where all four rings are assembled in one step from its correspnding enetriyne precursor.



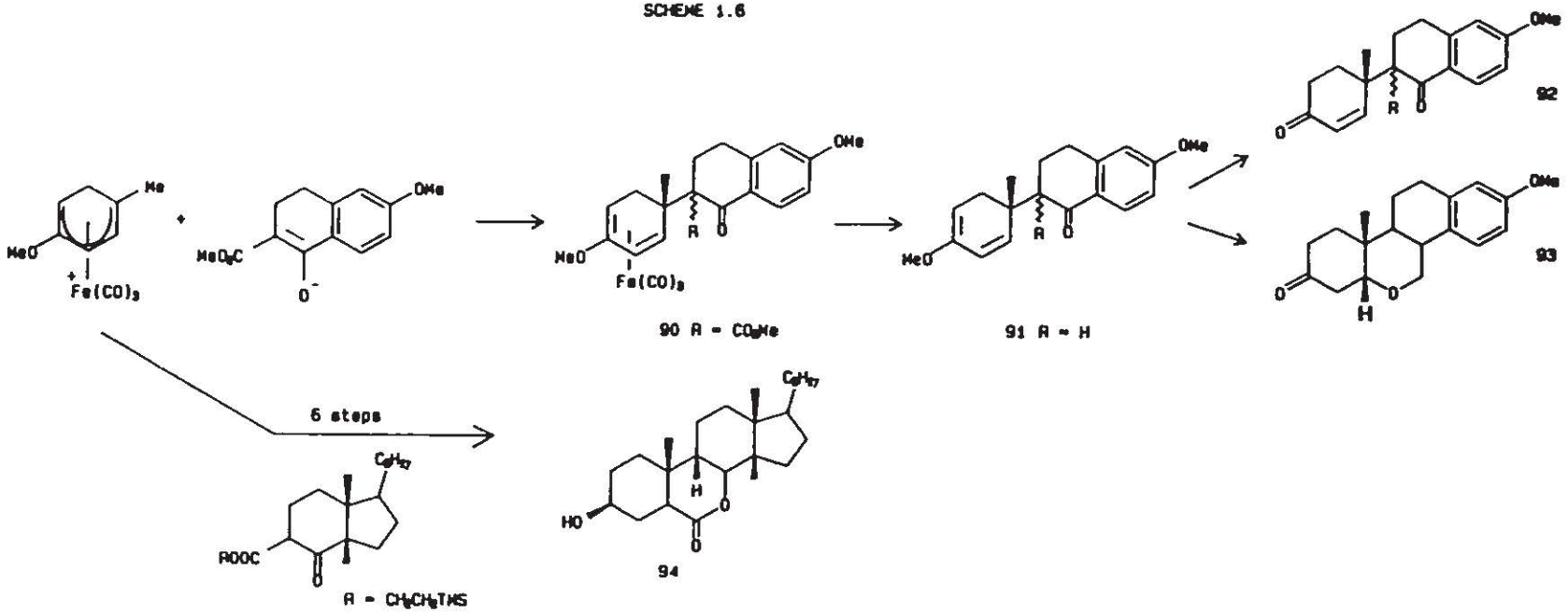
88



89

The other synthetic approach utilizes the well-established (4-methoxy-1-methylcyclo-2,4-dienylium)$Fe(CO)_3$ cation as its key intermediate. Pearson and co-workers[60-63] have described the elegant conversion of this cation into an equimolar mixture of diastereomeric $Fe(CO)_3$ complexes, 90a and b, which were subsequently converted into their 4,4-

SCHEME 1.6

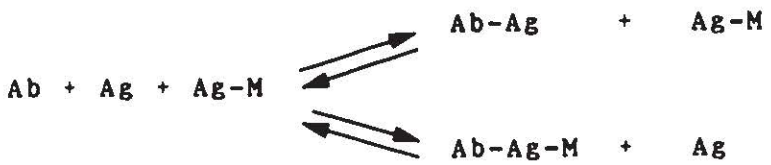

Me
MeO
+
Fe(CO)3
MeO2C
OMe
O-
OMe
MeO
R
O
Fe(CO)3
90 R = CO2Me
91 R = H
92
93
6 steps
C8H17
ROOC
O
R = CH2CH2TMS
C8H17
H
HO
O
O
94

disubstituted cyclohexenone steroidal precursor, 92, after demethoxycarbonylation and demetalation. The important step in their approach involves the reaction of this dienyl $Fe(CO)_3$ cation with the tetralone carboxylic ester malonate anion and results in a regiospecific attack at the methylated terminus of the cation. Subsequent work by this group has centred on the chemical tranformations of 91 into various steroids, 92, via known organic methods (see Scheme 1.6). Recent work by Mincione's group[64] has also dealt with reactions of this steroidal precursor and afforded the 6-oxa D-homo steroid, 93. In addition, they[65] have prepared an ergosta-type steroid, 94, using a similar dienyl $Fe(CO)_3$ cation intermediate (see Scheme 1.6).

1.4 BIOLOGICAL IMPORTANCE

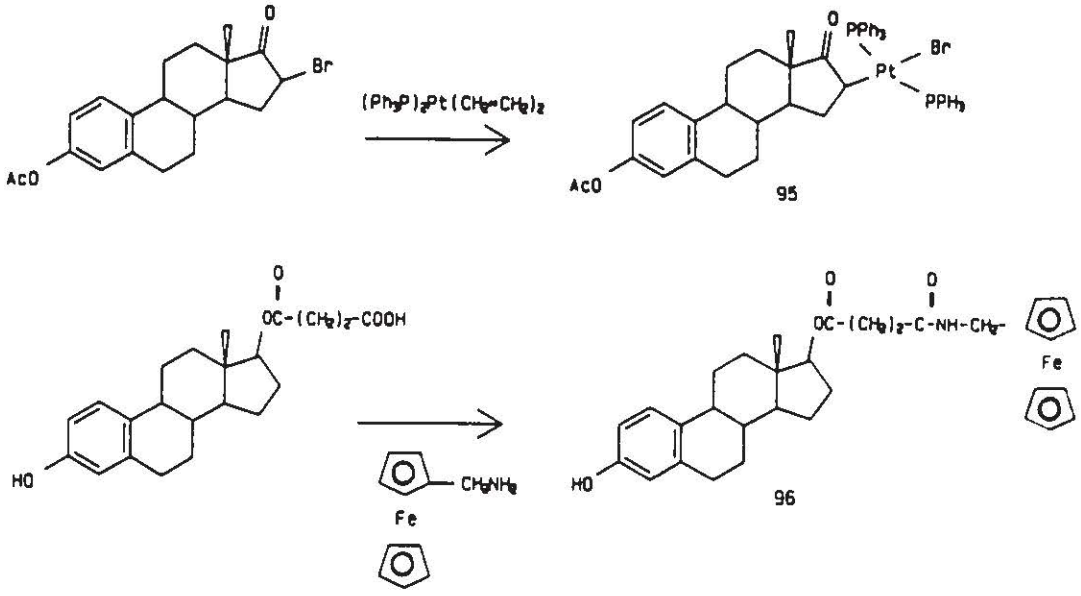
The previous section has illustrated the exploitation of organometallic complexes of steroids from a chemical point of view, but within the past ten years, it is important to note that their biochemical significance has gained recognition. An approach, known as metalloimmunoassay, developed by Cais and co-workers[66-69], has utilized a variety of metal atoms in the form of their organometallic or coordination complexes as nonradioactive agents in the study of antigen-antibody interactions. The general principle of this method is based on the ability of the antibodies (Ab) to specifically recognize and bind to antigens (Ag) thereby forming a

bound antibody-antigen complex (Ab-Ag). If the antigen is replaced by metal-labelled antigen (metalloantigen, Ag-M) and the binding process is not disturbed by the presence of the metal, a competitive reaction can now be established when both types of antigens react with a limited quantity of specific antibody.



Once the competition reaction has been carried out, these antibody-antigen complexes (Ab-Ag, Ab-Ag-M) are separated from unbound antigen (Ag-M, Ag) and the amount of metal present is determined by selected analytical techniques, such as atomic absorption spectrometry, emission and fluoresence spectrometry, electrochemical methods, and neutron activation. The quantity of metal isolated is then plotted on calibration curves for standard amounts of metalloantigens and unlabelled antigens, thus the result is a means of counting the antibodies present in an unknown sample. The main development in this concept lies in the synthesis of the metalloantigens. Generally, they are prepared either by direct reaction of a metal with an derivatized antigen to form a carbon-metal bonded organometallic complex or by the reaction of the antigen with a functionalized metal con-

taining reagent with coordination usually through a hetero-atom. An example of the former is the preparation of a Pt labelled estrogen, 95, by the reaction of 3-acetoxy 16-bromoestrone with bis(triphenylphosphine)diethylene platinum.[70] The latter route is represented by the reaction of an amine attached to a metal centre, as in aminomethyl-ferrocene, 96, with an carboxylic acid incorporated in the steroid to form an amide linkage.[71]



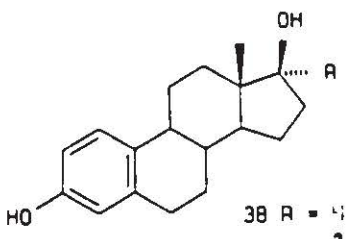
Shortly after this approach had been developed, Jaouen and co-workers[72] initiated a concept utilizing steroidal hormones labelled with metal carbonyls for the purpose of studying the interaction of such hormones with high affinity proteins, called receptors. As these interactions are of a highly stereospecific nature, slight alterations in the structure of the hormone will often affect the

Receptor's Binding Affinity (RBA), thereby lowering its biological potency. Their concept was based on the metal labelled hormone's ability to recognize its specific receptor and the fact that metal carbonyls have strong absorptions in the infra-red region between 2100-1850 cm^{-1}, a region devoid of other protein absorptions. In addition, this organo-metallic labelling/infra-red spectroscopic approach appeared to avoid the inconveniences associated with the other methods which utilize radiolabelled hormones.

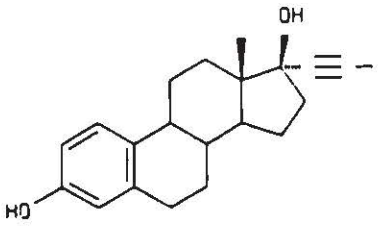
Their initial studies utilized the α and β $Cr(CO)_3$ complexes of derivatized estradiol, 38, (see Section 1.3c). RBA studies were performed on both the α and β $Cr(CO)_3$ complexes and their results indicated the α complex had a similar RBA value (28%) to that of the uncomplexed silylated derivative (35%) while the β site appeared to be more sensitive to steric hindrance due to the $Cr(CO)_3$ group as observed by its low RBA value (1.8%). The α complex was then incubated with the lamb uterine cytosol, and the resulting FT-IR spectra illustrated the specific binding of the organometallic steroid by the observation of two CO peaks. Recently, they[73] have prepared a radioactive transition metal carbonyl steroid hormone, 97, with the 17α position labelled with a tritium and are currently performing its RBA studies .

The steroidal $Cr(CO)_3$ complexes had one downfall, that being, their photosensitivity, which prevented their use in routine clinical studies. Consequently, 17β estradiol was

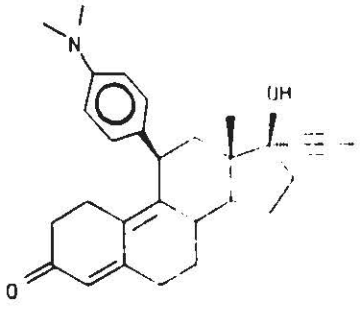
modified with a 17α alkynyl group, 98, since it was well established that this position could be modified without affecting the binding affinity of the hormone. This alkyne readily reacts with $Co_2(CO)_8$ and $Cp_2Mo(CO)_6$, as will be illustrated in the succeeding chapters, to form the appropriate cobalt and molybdenum complexes, which were then utilized for their in-vitro experiments.[74] The FT-IR spectrum of the Mo complex after incubation clearly indicated showed 3 of the 4 ν_{CO} absorptions, thereby becoming the first direct measure of the specific binding of an organometallic steroid to the estradiol receptor site.



38 R = H
97 R = ^{3}H



98



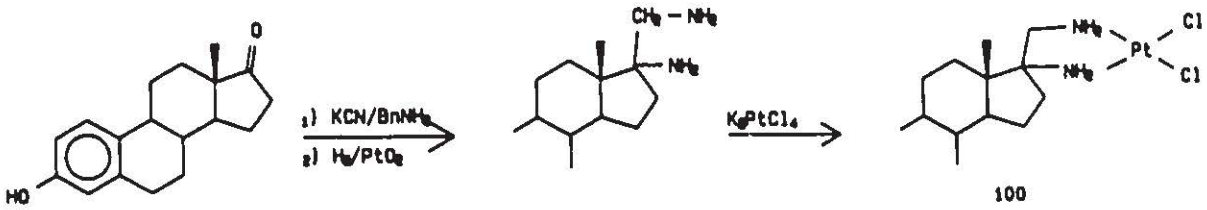
99

Recently, their studies[75] have centred on the controversial steroid, mifepristone (RU 486), 99, which is known to have high affinity for both the progesterone and glucocorticoid receptor sites. The RU486 molecule is ideally set up for complexation with an organometallic group since it contains both an alkynyl group at the 17α position and an arene ring at the 11β site, thus the corresponding complexes were synthesized and their RBA values which gave an indic-

ation of the recognition of the receptor site were obtained. The $Cr(CO)_3$ complex had somewhat lower values than those for the 17α-alkynyl complexes due to a possible steric hindrance of the metal fragment with the receptor site. Subsequent incubation studies found that the Co complex was the best suited for analysis of the progesterone receptor site and its FT-IR spectrum, after incubation, showed 2 ν_{CO} bands, thus indicating its binding to the receptor site. From these studies, Jaouen and co-workers were able to show the feasibility of their concept in order to obtain a direct measure of the amount of hormone specifically bound to its receptor.

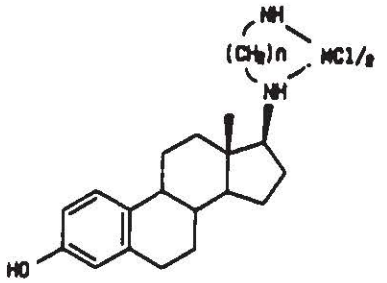
Besides these immunoassay approaches, other groups have investigated the potential of steroidal organometallic complexes as antitumor agents. Chondros and co-workers[76] have, recently, reported the conversion on the ketonic oxygen in estrone, 10, and three other steroids into a diamino function via a modified Strecker reaction and subsequent hydrogenation of the α-benyzlaminonitrile. This diamino ligand was then treated with K_2PtCl_4 to generate an estrogenic Pt complex, 100, and the resulting spectral data indicated a cis metal-chlorine structure. Subsequent experiments for the evaluation of antitumor activity indicated that the Pt complex of 3-methoxy-pregnan-20-one had comparable activity to that of the well known cis-platin compound. Fernandez's group[77] has synthesized similar diamino derivatized estrogens and converted them into their corresponding

Pt and Pd complexes, 101. Pharmacological studies on these complexes are currently on-going to determine their antitumor activity.

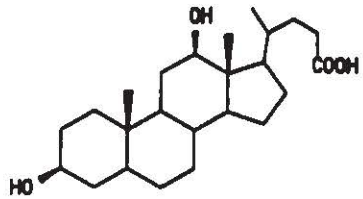


100

Organotin steroidal adducts have also been investigated for their antitumor potential. Saxena and his colleagues[78] have prepared a variety of adducts [R_3M(CHOL), $R_2Sn(CHOL)_2$ and $(R_3M)_2$(DESCHOL)] from the reaction of the appropriate organoelement chlorides with cholesterol, 1, and desoxycholic acid, 102. In all adducts, the metal was coordinated via the oxygen atom as evidence by the disappearance of the $\nu_{(OH)}$ in the infra-red as well as ^{119}Sn NMR and Mössbauer data. Subsequent to this report, they[79] synthesized ten other diorganotin dichloride adducts, R_2SnCl_2 2L (R = Me, tBu, Ph, and Et) where coordination occurs via the ketonic oxygen giving rise to an octahedral geometry around the Sn with trans R groups and two steroidal fragments as evidenced by ^{119}Sn Mössbauer and ^{13}C NMR data. As in the above example with the Pt complexes, the antitumor studies involving these tin analogues are currently being investigated.



101 n = 2 or 3
M = Pt or Pd



102

1.5 OBJECTIVES OF THE THESIS

It is readily apparent by the diversity in their usage that organometallic complexes of steroidal systems have been aptly exploited from a chemical and biochemical perspective. However, it is somewhat surprising with the plethora of protons and carbons available in the steroidal skeleton of these molecules that very little high field NMR data have been reported. Consequently, a program was begun aimed at preparing organometallic complexes of steroids and investigating their high field NMR properties in order to examine what influence the organometallic moiety has on the chemical shifts of these protons and carbons. The succeeding chapter will centre on a discussion of the specific 2D NMR techniques utilized during the course of this investigation and the general methodology employed in analyzing the resulting 2D NMR spectra. In addition, it will illustrate how these techniques have been applied and how information regarding a steroid's structure in solution can be attained. Chapter 3 will subsequently delve into the effects induced by complexation of organometallic groups onto aromatic A-ring steroids

and their C-17 alkynyl substituted analogues. Chapter 4 will focus on what influence on steroidal protons is invoked by the incorporation of transition metal fragments into the B-ring of steroids. It will, also, examine the conversion of a particular steroidal organometallic complex into (cyclohexadienyl)$Fe(CO)_3$ cationic type complexes and their synthetic viability. This will be followed in Chapter 5 by a discussion of similar protonation studies involving the Rh(acac) fragment. Finally, the relevant experimental details will be presented in Chapter 6.

CHAPTER 2

HIGH FIELD NMR SPECTROSCOPY OF STEROIDS

2.1 PREAMBLE

Nuclear Magnetic Resonance (NMR) Spectroscopy has become the premier analytical tool for the characterization and structure elucidation in solution of newly formed compounds. With the advent of high field NMR spectrometers and two dimensional NMR methods, it is now possible to completely and unambiguously assign all the protons and carbons in very complex molecules. This chapter is devoted to a discussion on how NMR spectroscopy has been utilized to characterize various steroidal systems. Since there are numerous books available[80,81] which deal with the basic principles of the NMR experiment, the scope of this discussion will centre on the particular 2D NMR methods utilized to assign the protons and carbons in steroidal systems and how information pertaining to their structure can be obtained from 2D NMR data. This chapter will begin with a brief account of the early NMR investigations and will end with a review of the reports cited in the literature on steroid structural analysis by 2D NMR spectroscopy and the general strategy employed for obtaining the complete proton and carbon assignments for steroids.

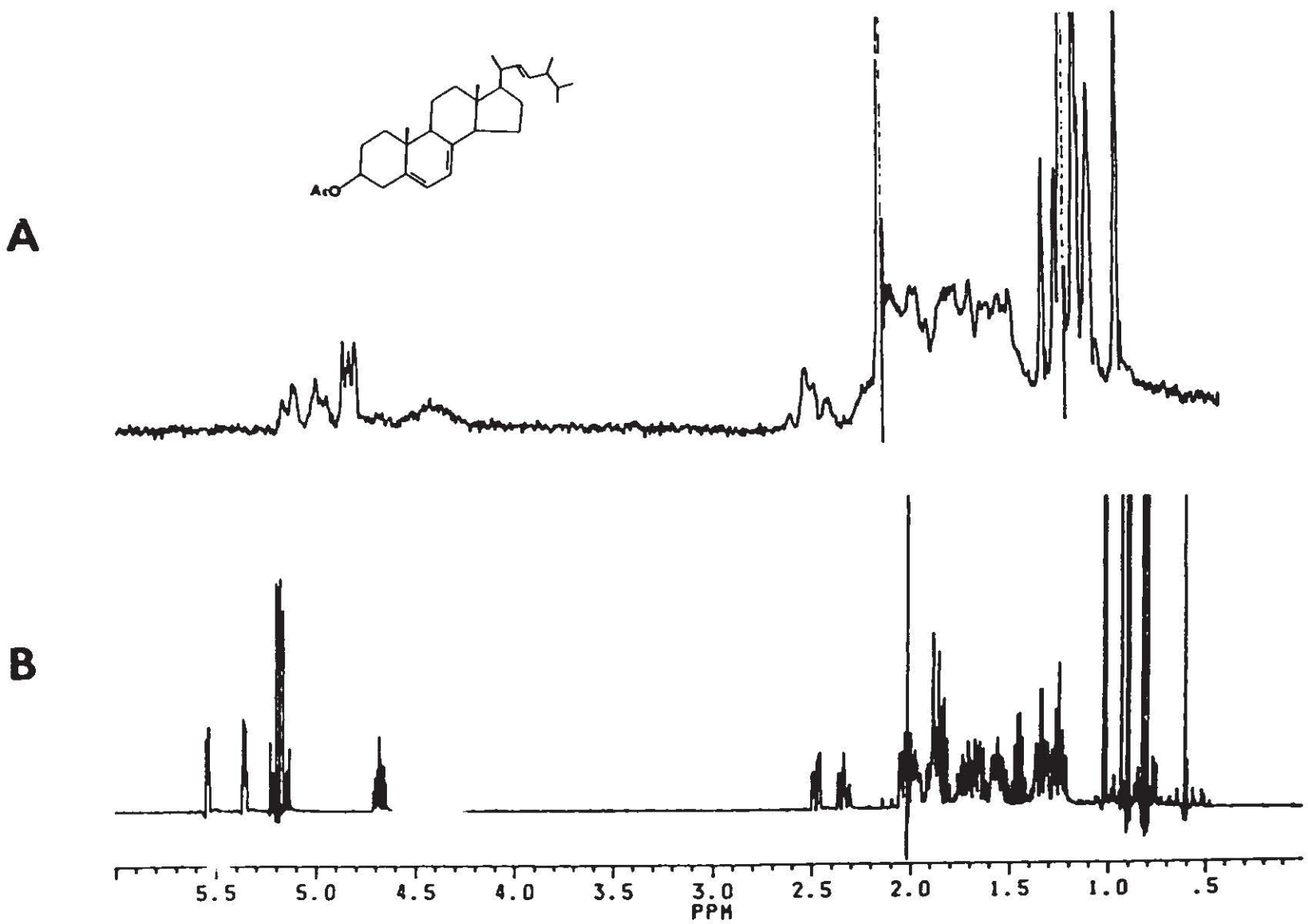
2.2 PREVIOUS NMR SPECTROSCOPIC INVESTIGATIONS

Prior to the technological advances in high field NMR spectrometers and 2D NMR pulse sequences, the knowledge secured from the ^{1}H spectra of steroids was limited to the assignments for methyls, olefinics, or other protons whose signals due to substitution were significantly deshielded. Figure 2.1a illustrates a typical low field steroidal ^{1}H NMR spectrum, in this case for ergosteryl acetate, 5, at 60MHz and it is readily apparent that this particular spectrum is dominated by a large lump in the upfield region caused by severe peak overlap of numerous proton signals over a narrow spectral range (0.5 to 2.5 ppm).

As a result of the limited information one could obtain from ^{1}H NMR spectroscopy, researchers in this area turned their attention to the use of ^{13}C NMR spectroscopy which has the advantage of greater chemical shift dispersion of ≈250 ppm as compared to 10 ppm for ^{1}H NMR spectroscopy. In addition, the use of proton decoupling techniques greatly simplifies the resulting spectrum as all the ^{13}C resonances become single lines. Consequently, throughout the 1960's and 70's, ^{13}C NMR spectroscopy became the method of choice and provided valuable information concerning the stereochemical and structural aspects of the steroid's carbon skeleton. During this timeframe, the ^{13}C NMR spectra of a wide range of steroidal systems were recorded and two excellent

FIGURE 2.1

^1H NMR Spectrum of Ergosteryl Acetate, 5, at low (60MHz) and high (500 MHz) magnetic field, recorded in $CDCl_3$.

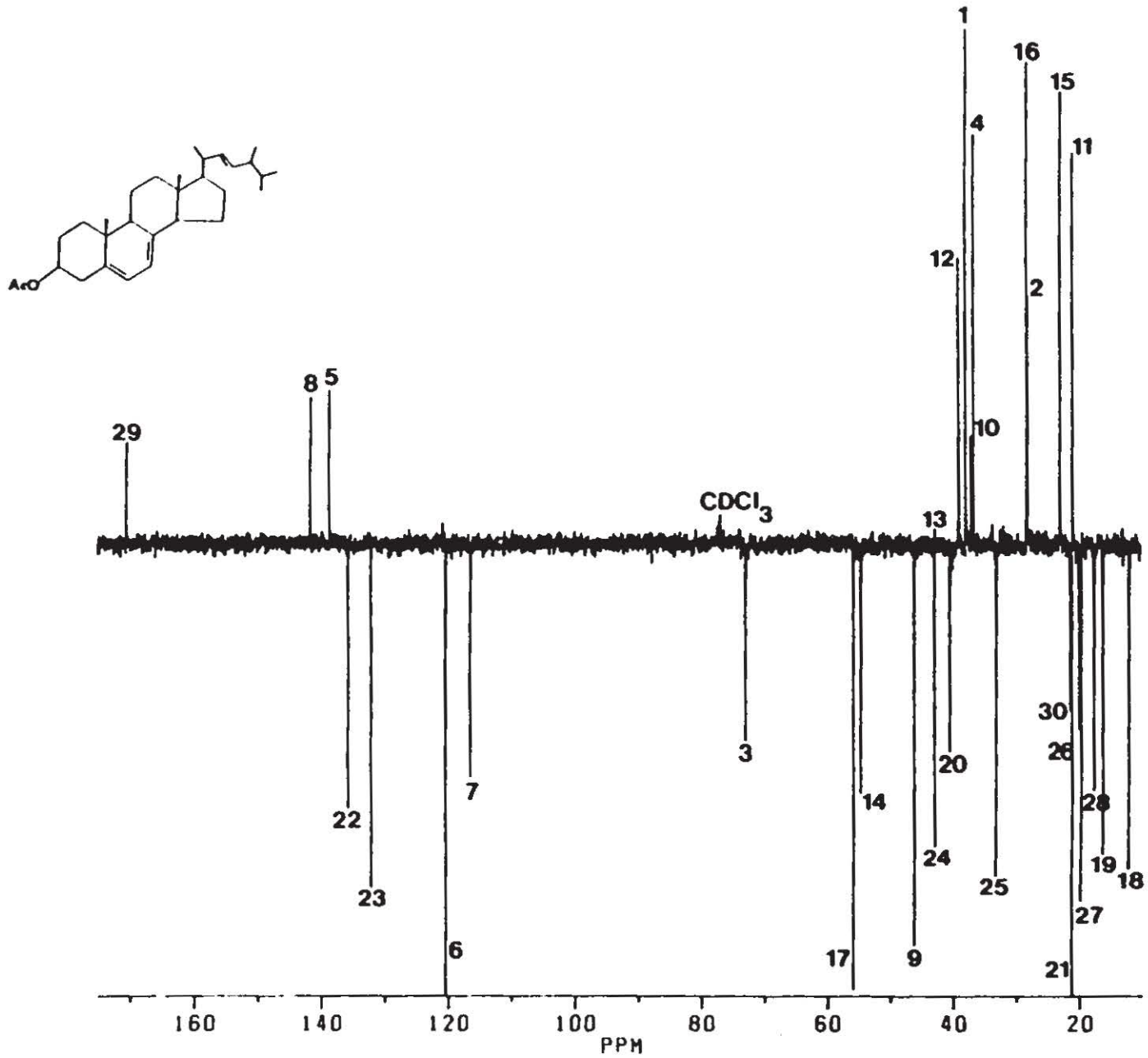

A
AcO
B
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM

compilations are now available in the literature.[82,83] Figure 2.2 shows a typical ^{13}C NMR spectrum of a steroid at 125 MHz, once again, using ergosteryl acetate as the working example. In addition, this particular spectrum demonstrates the utilization of a new ^{13}C NMR technique, the Attached Proton Test (APT),[84] which phases the ^{13}C resonance with the number of attached protons, i.e, C and CH_2 signals appear as positive peaks while CH and CH_3 environments give rise to negative ones. The APT sequence has enabled the assigning of the resulting ^{13}C NMR spectra in a straightforward manner.

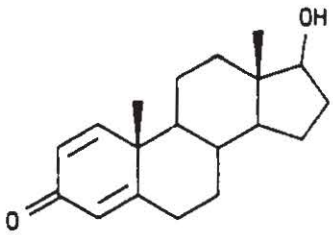
In the early 1980's, the focus of steroidal NMR investigations switched back to the exploitation of ^{1}H NMR spectroscopy due to the rapid development in superconducting magnets for higher field spectrometers. Figure 2.1b illustrates the dramatic improvement in line resolution in the ^{1}H NMR spectrum of ergosteryl acetate recorded at 500MHz over its 60MHz counterpart. At this higher field, the proton signals of the so-called broad hump become better dispersed as well as achieving a definite fine structure. However, peak overlap still precludes the complete proton assignment. This was not overcome until the publication of a series of papers by Hall and Sanders[85-88] who revolutionalized the use of ^{1}H NMR data in steroid structure analysis by being the first to apply 2D NMR methodology in obtaining the complete proton assignments for 1-dehydrotesterone, 103, and 11β-hydroxyprogeterone, 104. Their pioneering efforts prompted

FIGURE 2.2

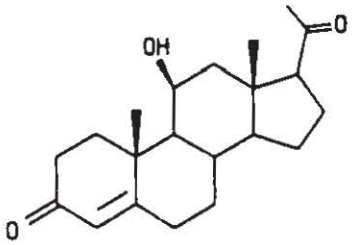
125MHz ^{13}C NMR Spectrum of Ergosteryl Acetate, 5, illustrating the Attached Proton Test (APT) Technique, recorded in C_6D_6.


AcO
1
16
15
4
11
12
2
8
5
10
29
CDCl3
13
3
20
30
26
14
7
22
28
24
19
18
25
23
27
6
17
9
21
160
140
120
100
80
60
40
20
PPM

numerous other research groups to quickly report the ^{1}H NMR data for a wide range of steroidal systems and recently, a chapter written by Croasman and Carlson[89] has been devoted to the steroidal structural analysis by 2D NMR spectroscopy. This particular review article discusses the general strategies currently employed for steroid structural NMR studies. Before dealing with the 2D NMR techniques adopted for this investigation, the following section will focus on a discussion of the initial methodology developed by Hall and Sanders.



103



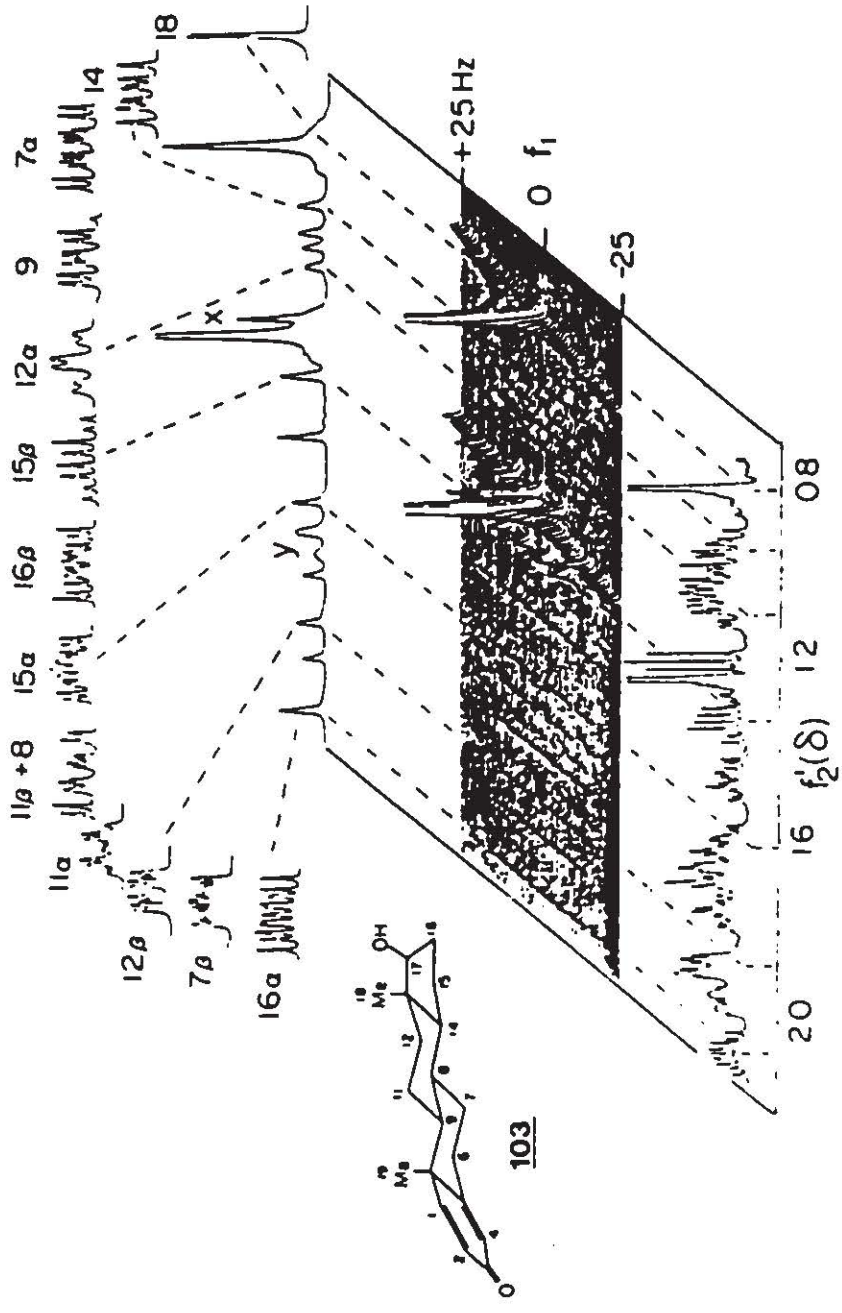
104

2.3 GENERAL STRATEGY TO ASSIGN NMR SPECTRA OF STEROIDS

The approach developed by Hall and Sanders to assign steroidal protons utilized a combination of one- and two-dimensional NMR techniques. Their initial step involved recording of the one-dimensional high field ^{1}H NMR spectrum and assigning as many well resolved proton signals as possible based on their substitution pattern. Subsequently, 2D J-resolved spectroscopy was applied to unravel and analyze the protons distributed in the spectral hump region of the 1D spectrum. The result of this experiment, when performed on

FIGURE 2.3

Two-Dimensional (2D) J-Resolved Spectrum of 1-Dehydrotestosterone, 103, recorded by Hall and Sanders (Ref. 85).


11β +8
11α
15α
16β
15β
12α
9
7α
14
18
12β
7β
16α
X
Y
+25 Hz
0 f1
-25
20
16
12
08
f2(δ)
OH
O
103

103 is illustrated in Figure 2.3. Its partial 400MHz ^{1}H NMR spectrum is positioned at the bottom of this figure while its associated 2D J-spectrum and proton decoupled projections are in the middle and situated at the top is the corresponding proton multiplicity patterns obtained from cross sections of the 2D J-spectrum. Hall and Sanders were able to obtain a list of chemical shift values for 103 from these projections. In addition, they were able to obtain information regarding a given proton's coupling pattern and its associated geminal and vicinal scalar couplings from analysis of the corresponding cross-sections. As a result, they could deduce the configurational and conformational aspects of the steroidal skeleton, i.e., whether the proton is in an axial or equatorial position. Furthermore, their analysis of these multiciplity patterns established values for the steroidal geminal coupling constants, ^{2}J, generally ranging from 12 to 14Hz, and those for vicinal proton-proton couplings, ^{3}J, with axial-axials ranging from 10.9 to 13.5Hz, axial-equatorials from 3.6 to 4.5Hz, and equatorial-equatorials from 2.5 to 2.8Hz. In addition, the observation of long range couplings, such as the 1,3 diaxial interaction between the 12α proton and the C-18 methyl served as important reference points for the identification of these proton resonances.

Although the 2D J-resolved NMR experiment determined the chemical shifts and multiplicity patterns for each proton, Hall and Sanders had to rely heavily on the use of a

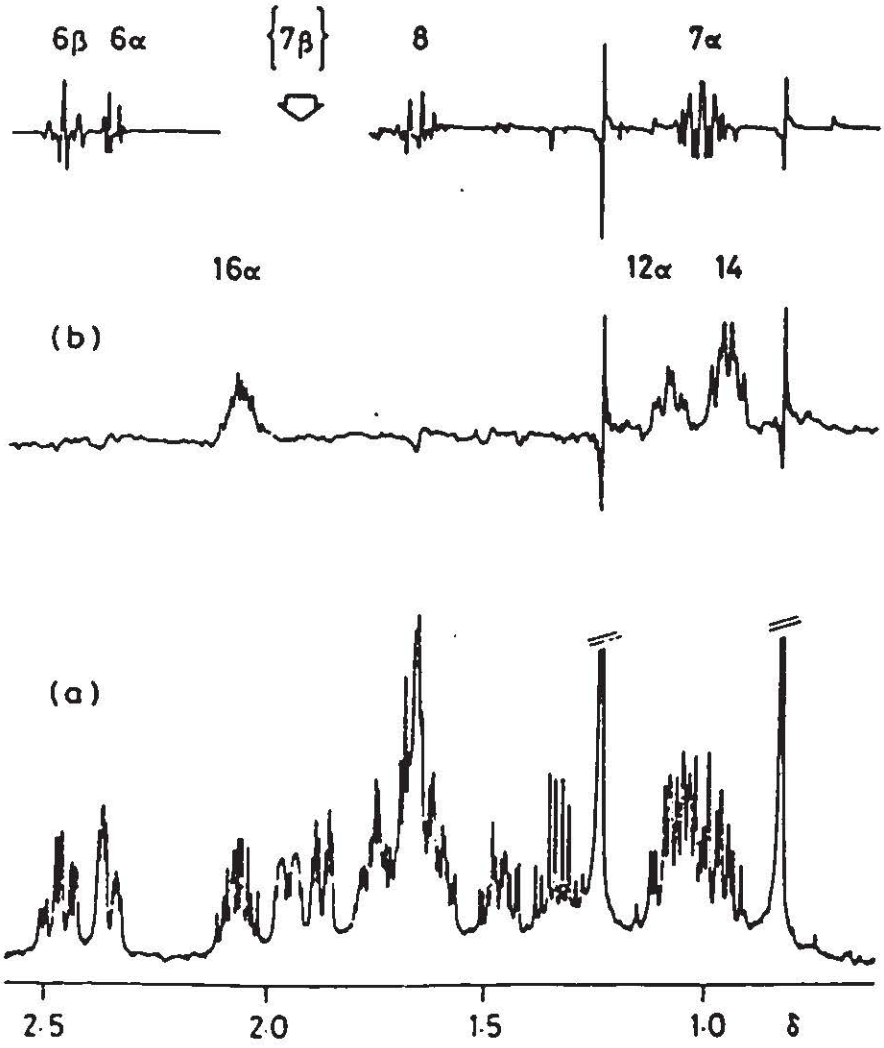
one-dimensional NMR technique, nuclear Overhauser enhancement (nOe) difference spectroscopy, to unambiguously assign the steroidal protons. This technique involves irradiation of a specific proton resonance and observation of any enhancement in the signals of protons which are in close spatial proximity to the irradiated one. Figure 2.4 illustrates the resulting nOe difference spectrum when the 7β proton in 1-dehydrotestosterone is irradiated and the subsequent enhancement of the 6α, 6β, 7α, and 8 proton signals. This experiment in combination with the earlier 2D J-resolved findings allowed Hall and Sanders to completely and unambiguously assign a steroid's proton spectrum.

With the development in homonuclear and heteronuclear correlated spectroscopy, the general strategy employed for assigning steroidal protons and carbons has changed from that developed by Hall and Sanders. Newer 2D NMR techniques have provided the desired assignments more rapidly and somewhat less ambiguously, thereby putting less demand on spectrometer time. As a consequence, these experiment were extensively utilized during the course of this work. The next section will illustrate how one interprets the resulting 2D NMR spectra using data obtained during the course of this work.

Depending on the amount of material available, the initial stage in investigations of the ^{1}H spectra of steroidal systems involves the use of the heteronuclear ^{1}H-^{13}C shift-correlated 2D NMR experiment,[90] thereafter known as

FIGURE 2.4

One-Dimensional Nuclear Overhauser Enhancement (nOe) Spectrum of 1-Dehydrotestosterone, 103, recorded by Hall and Sanders (Ref. 85).



HETCOR. This particular 2D technique is attractive as it provides entry to the proton chemical shift values using the structural correlations between directly bonded carbon and proton nuclei. As alluded to earlier, there is a large library of ^{13}C NMR data on steroids available in the literature, thus the appropriate carbon-proton connectivity patterns can be established as a result of this experiment. Figure 2.5 illustrates the outcome of such an experiment when performed on the $Co_2(CO)_6$ complex of 17-ethynylestradiol 3-methyl ether, 105. This particular HETCOR spectrum is presented as a contour plot with the correlations between carbons and protons exhibited by crosspeaks. For example, the methine C-9 carbon gives rise to a single contour corresponding to the carbon chemical shift at 39.2 ppm and the proton chemical shift at 1.38 ppm, while C-16, being methylene in nature, displays two contours in the proton domain due to its attached α and β protons. In addition, if the HETCOR experiment is performed in conjunction with the APT technique, one further verifies the number of attached protons on a given carbon.

The ^{1}H assignments afforded by this experiment are usually approximate since their signal intensity is often spread out across the proton domain, thus the proton chemical shifts are further determined by the use of the two dimensional ^{1}H-^{1}H homonuclear COSY experiment,[91,92] which establishes proton-proton connectivities through their scalar

FIGURE 2.5

^{1}H-^{13}C Heteronuclear Shift Correlated (HETCOR) 2D Spectrum of the $Co_2(CO)_6$ Complex of 17α-Ethynylestradiol 3-methyl ether, 105, recorded in C_6D_6.

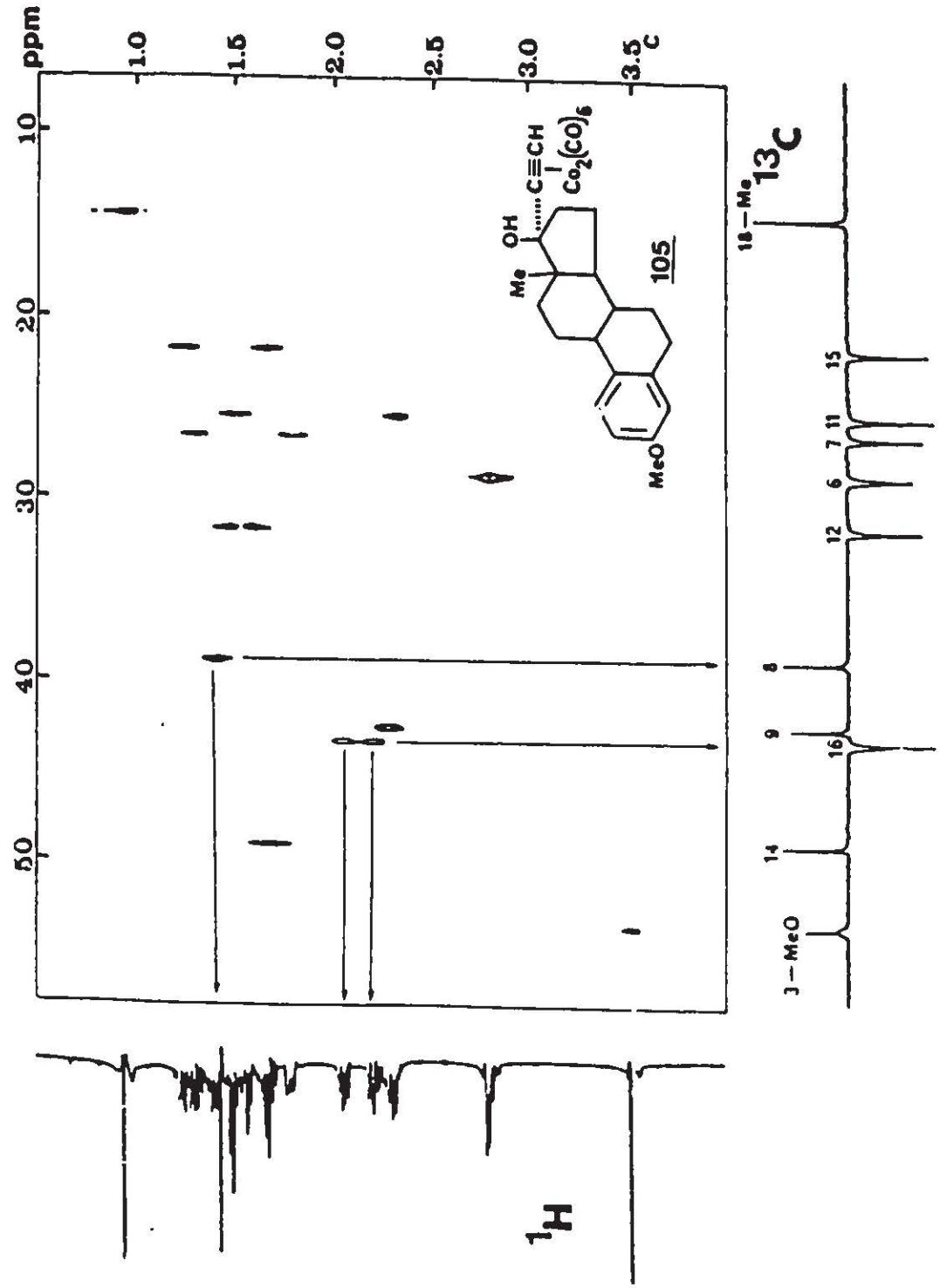
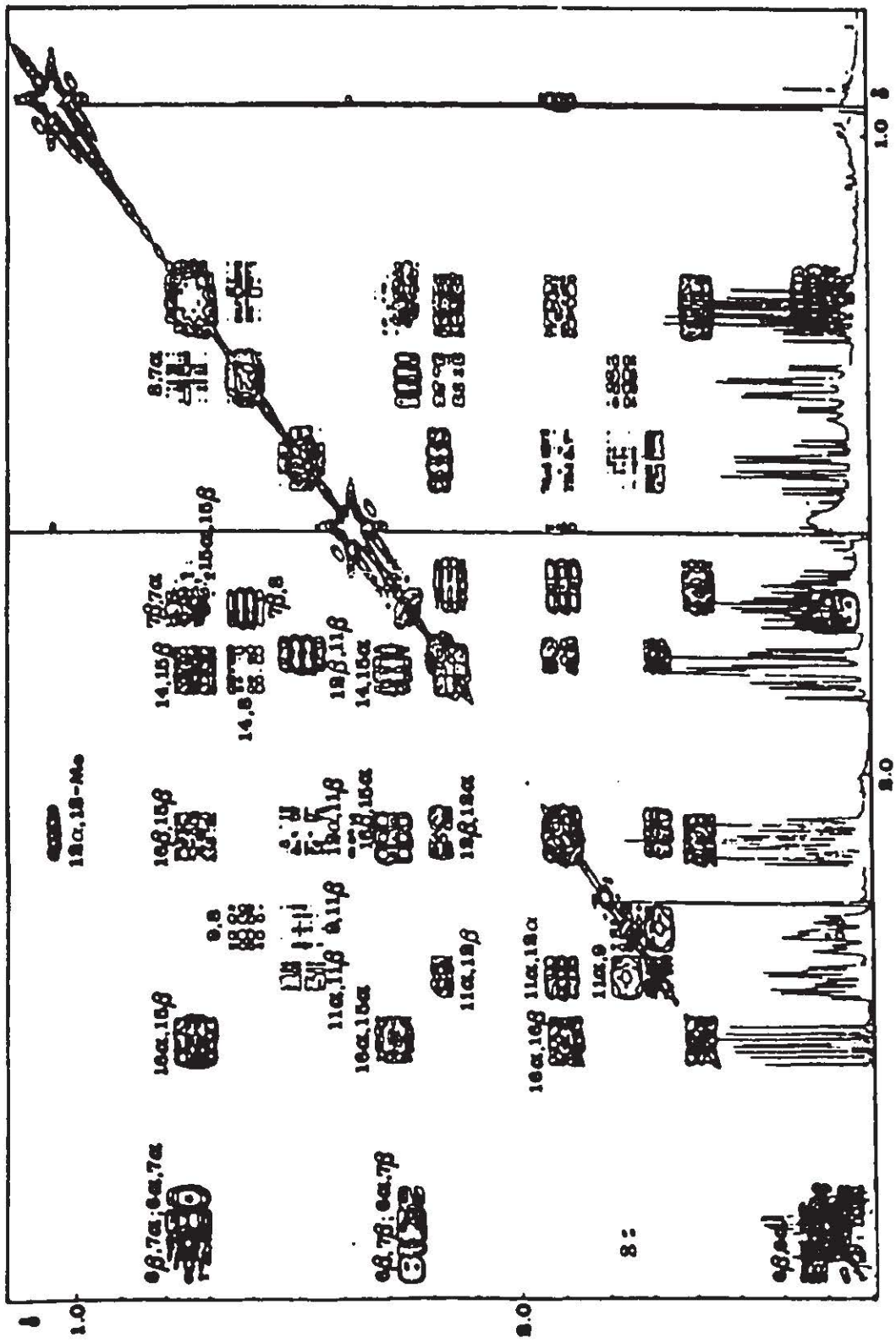

ppm
1.0
1.5
2.0
2.5
3.0
3.5
δ
10
20
30
40
50
OH
C≡CH
Co2(CO)6
Me
MeO
105
18-Me
13C
15
11
7
6
12
8
9
16
14
3-MeO
1H

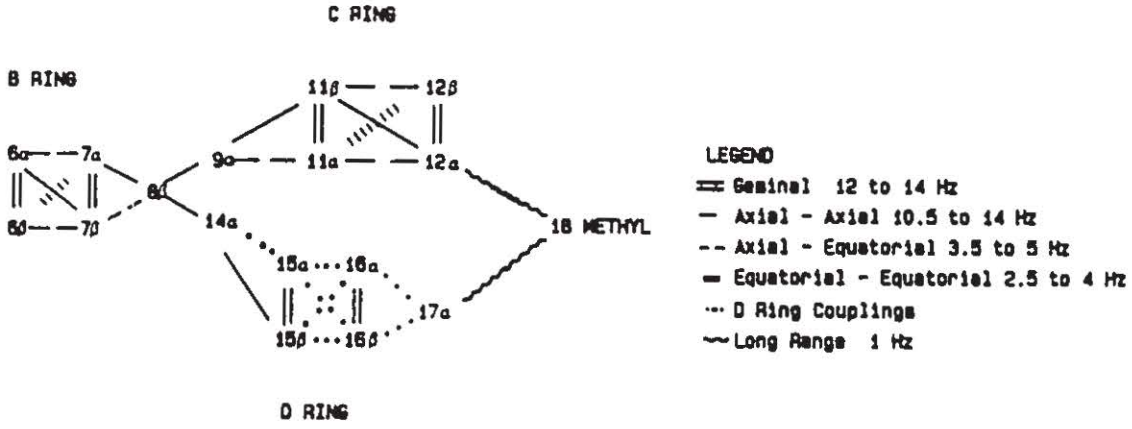
FIGURE 2.6

500MHz ^{1}H-^{1}H 2D COSY Spectrum of 17α-Propynylestradiol, 98, recorded in C_6D_6. The matrix has been symmetrized.



couplings. Figure 2.6 shows the result of the COSY experiment for 17α-propynylestradiol, 98, and is presented as a contour plot in which the one-dimensional ^{1}H spectrum lies along the diagonal and coupling between two spins is manifested as a symmetrically positioned pair of off-diagonal peaks.

In analyzing such a spectrum, Haasnoot's group[93] has shown that construction of a spin coupling diagram aids in determining the number of contours required for a given proton as well as deciding whether these couplings are geminal, vicinal, or long-range in nature. Listed below is the proton-proton connectivity diagram for 17α-propynyl-estradiol.



With the connectivity pattern established, one can begin to interpret the COSY spectrum with an initial step being the assignment of at least one proton which provides an entry point into the various proton spin systems. In practice, several starting positions are necessary to confirm the

original ^{1}H assignments as well as those which may be obscured by crosspeak overlap. Typical starting points are protons whose assignment is obvious since they are adjacent to functionalized centres or those which give rise to a contour in the COSY spectrum due to a stereospecific four-bond coupling interaction with the angular methyl protons. For example, in Figure 2.6, a cross peak results from a coupling interaction between the C-18 methyl and the 12α proton; thereby establishing the position of this proton and entry into the C-ring spin systems. From the ^{1}H-^{1}H connectivity diagram, it was observed that this particular proton would have three additional crosspeaks due to interactions with its 12β counterpart and the two C-11 protons. These particular contours can be distinguished by the appearance of further contours for the C-11 protons due to coupling with the benzylic 9α proton. As a result, the relative positions of the protons in the C-ring can be established, although one can not distinguish between α and β protons at this time. Similarly, by using the same methodology and the other benzylic protons, 6α and 6β, as the starting points, one can locate the protons of the B ring spin systems, i.e., 7α, 7β and 8β. The position of this latter proton enable one to enter the D-ring proton spin systems and is confirmed by the observation of a crosspeak due to its coupling with the previously identified 9α proton. The end result of analysis of this spectrum is the

determination of the sites of attachment of all protons of the steroidal skeleton. In addition, if the digital resolution of the spectrum is excellent, the size of the crosspeaks can provide information regarding the magnitude of the coupling constants, though, in practice, one utilizes the COSY experiment to establish the proton-proton connectivity pattern.

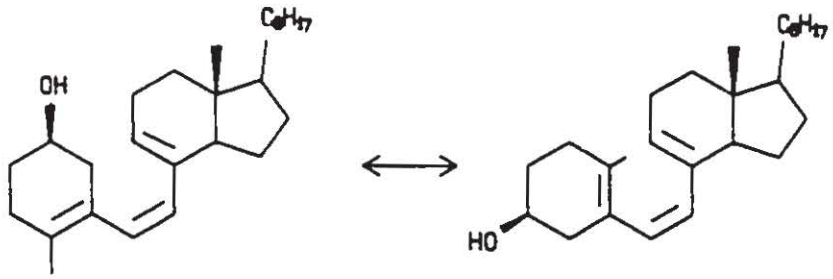
As mentioned above, the COSY experiment does have one limitation as it does not distinguish between the α and β protons of a given methylene group. This distinction can be achieved by analysis of the proton's coupling pattern together with examination of additional long range coupling contours, such as the so called "W" coupling between the 2α and 4α protons in the ergosterol series. If there is still ambiguity in the assignment of a particular set of protons, one can utilize nOe difference spectroscopy measurements, as Hall and Sanders did, to resolve this discrepancy. In addition, further verification may result from the use of the COSY-45 experiment[80,81] which often simplifies the display of the COSY spectrum around the diagonal by reducing the lines of a given contour, thereby revealing additional correlations which may otherwise by hidden in peaks close to the diagonal.

For the purposes of this study, the basic HETCOR and COSY 2D NMR experiments were sufficient in characterizing the newly formed organometallic steroidal complexes. Recently, variations in the COSY and HETCOR experiments as well as

other new 2D pulse sequences have been applied to steroidal systems. For example, Wong's group[94] has shown that incorporation of a BIlinear Rotation Decoupling (BIRD) pulse in the middle of the HETCOR sequence enables the measurement of the proton-proton geminal coupling constants from the corresponding cross-sections along the ^{1}H dimension. This method was applied to a series of substituted progesterone molecules in order to study their ring conformations in solution. Subsequently, Asakawa and co-workers[95] reported the application of the long-range HETCOR sequence in combination with the 2D INADEQUATE technique to completely assign some dammarane-type triterpenes, while Platzer's group[96] has utilized the COSY equivalent, COSY LR, to optimize the detection of weak coupling interactions, such as the 1,3 diaxial coupling between the C-18 methyl and the 12α proton observed in the contour plots of hydrocortisone and three steroids in the cholestane series. In addition to this C-18/12α contour, they observed new long range coupling interactions between the C-18 methyl and the 12β proton as well as contours due to 5 bond coupling between 1β/6α and 12β/15α.

In the area of other new 2D pulse sequences utilized, Haasnoot and his colleagues[97] have illustrated that the 2D spin echo J-correlated (SECSY) experiment is effective in assigning the proton spectra of norethisterone and 17β-hydroxy-19nor-5α,17α-pregn-20-yn-3-one. This technique is

similar to the COSY experiment in that it establishes the J-connectivities between individual proton signals. Another sequence shown to be useful in assigning the ^1H spectra of steroids is the RELAYed coherence transfer (RELAY) 2D NMR experiment. Hughes[98] has employed this technique, which observes proton connectivities over three adjacent carbons, thereby resulting in cross-peaks between protons which are not coupled but are part of the same spin system, to 17β-estradiol. In the resulting RELAY spectrum, Hughes indicated the appearance of contours due to the interaction of the 17α proton with the 15α and 15β protons, thereby confirming the D ring proton assignments. This particular procedure maybe useful when the COSY cross-peaks are very obscured. Finally, Dauben's group[99] has utilized the 2D NOESY sequence to establish the existance in solution of two conformations for previtamin D_3, i.e, tZc, 107, and cZc, 108. Like its one-dimensional analogue, this experiment yields crosspeaks due to nOe interactions between protons.



106 107

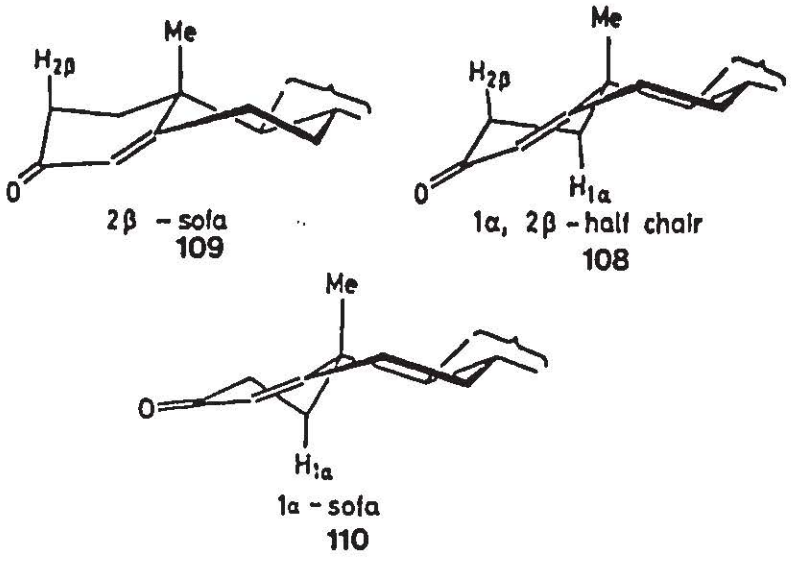
In closing, there is a wide variety of 2D NMR experiments available to chose from, depending on one's

purpose, for analyzing steroidal ^{1}H and ^{13}C spectra. The succeeding section will examine on how 2D NMR techniques have been utilized to obtain information regarding the steroid's ring conformation.

2.4 2D NMR TECHNIQUES USED IN STEROID STRUCTURE ANALYSIS

As alluded to earlier, the principal reason for applying 2D NMR methods is to characterize newly synthesized steroids. As a result, numerous articles documenting their complete proton and carbon assignments have recently appeared in the literature.[100-107] Rather than providing a long list of these assignments, this discussion is limited to a review on how 2D NMR methods were utilized to compare the ring conformations of steroids in solution with their solid state structure.

One steroidal system which is known to exhibit a great deal of conformational flexibility is the 4-en-3-one steroids. In fact, X-ray crystallographic results[108] have shown that there exist three different A-ring conformations; the first being the normal 1α,2β half-chair conformer, 108, where C-3, C-4, C-5, and C-10 are coplanar and C-2 and C-1 respectively lie above and below this plane, the second being its inverted 1β,2α analogue, 109, and the third being the 1α sofa conformation, 110, which has C-2 through C-5 and C-10 coplanar and C-1 below this plane.



Kirk's group[109,110] were the first to apply 2D NMR techniques to examine these conformational differences in solution and compare them with their known solid state conformations. They were able to establish using 2D J-resolved spectroscopy and nOe difference measurements that 17α-acetoxy-6α-methylprogesterone exists in the normal conformation in solution rather than its solid state inverted half-chair conformer. This conclusion was based on their 2D J-resolved results which revealed the typical 4 bond coupling between the C-19 methyl and the 1α proton, thus positioning this proton in an axial environment. In addition, the observation of a W coupling between 2α and H-4 as well as nOe difference measurements which exposed strong positive nOe's to the 1β and 2β protons upon irradiation of the C-19 methyl supported this decision that this compound exists in its

normal half-chair conformation in solution. For the situation to be reversed, i.e., in the inverted conformation, the 1β proton would now be in an axial position and the appropriate long range couplings would not be observed in the 2D J-resolved spectrum. Shortly after this report, Wong and colleagues[111] examined the ^{1}H NMR spectra for 9α-fluorocortisol and found noted this steroid, in solution, adopts the inverted A-ring conformation as in its crystal state. This was deduced on the basis that the C-19 methyl/1α coupling was not observed and that the chemical shifts and geminal coupling constants for the 2α and 2β protons were slightly different to those obtained by Kirk's group.

These initial results prompted others to investigate the different A-ring conformations in other 4-en-3-one steroids as well as examining whether substituents on the steroidal rings influence the adopted conformations. In a comprehensive study, Marat's group[112] examined the ^{1}H NMR spectra of ten 4-en-3-one steroids substituted at the C-2 or C-6 positions. They determined with the exception of a 2β-acetoxy compound that these molecules exist in solution with the A-ring predominantly in the normal 1α,2β half-chair conformation and reasoned the 2β-acetoxy compound resides in its inverted state due to crowding of this group with the C-19 methyl. Barbier and co-workers[113] have recently shown that desoxycorticosterone adopts the same half-chair A-ring conformation. These above findings, however, were not

without controversy as Schneider's group[114,115] concluded that 6α-fluoro-11β-hdyroxy-16α-methylprogesterone assumes a 1α sofa conformation in solution based on analysis of its vicinal coupling constants. In addition, Duddeck's group[116] has presumed that 11β-hydroxy-16α-hydroxyprogesterone adopts the same conformation due to a similarity in the chemical shift values obtained with those of Schneider. Marat[112] has resolved this discrepancy by explaining that the $^{3}J(1\beta,2\alpha)$ coupling constant expected for the sofa conformation would be ≈2.5 Hz rather than the reported value of 4.7 Hz, thus their interpretation of the normal conformation was a better representation. Subsequent studies by Wong's group[117] involving 19-nor-4-en-3-one steroids support this claim as examination of their ^{1}H-^{1}H geminal coupling constants reveal the predominance in solution of the normal half-chair conformation. Finally, while not commenting on the A-ring conformation, Kirk's group[118] has deduced using 2D NMR methods that aldosterone, another 4-en-3-one steroid, exists in solution predominantly as an equilibrating mixture of the 20-oxo-11,18 hemiacetal and the 11,18-epoxy-18,20-hemiacetal.

More recent work in this area has focussed on the A-ring conformations C-2 mono-methyl and dimethyl substituted 5α androstan 3-ones which lack the C-4 double bonds. Marat's group[119] has concluded from analysis of the 2D NMR ^{1}H spectra that the 2α methyl derivative exists in solution with a normal A-ring chair conformation while its 2β analogue

resides in an inverted boat conformer with C-2 and C-5 at the bow/stern positions. The data for the dimethyl substituted steroid suggests a mixture consisting of ≈60:40 normal chair to inverted boat conformers in rapid equilibrium. Subsequent to this, Haasnoot and co-workers[77] have observed that the A-ring in 17β-hydroxy-19-nor-5α-pregn-3-one, another steroid which lacks the C-4 double bond, resides in solution in a normal chair conformation.

In conclusion, this chapter has centred on the utilization of a variety of 2D NMR techniques in assigning the proton and carbon spectrum of steroidal systems. In addition, analysis of the resulting 2D NMR spectra provides valuable information regarding the steroid's conformation in solution. The succeeding chapter will deal with the use of 2D NMR methods to investigate the influence an organometallic moiety has on the chemical shifts of the protons and carbons of the steroidal skeleton. It will focus on this study's work involving aromatic steroids and their $CpRu^{+}$, $Co_2(CO)_6$, and $Cp_2Mo_2(CO)_4$ complexes.

CHAPTER 3

ORGANOMETALLIC COMPLEXES OF AROMATIC A-RING STEROIDS

3.1 PREAMBLE

The preceeding two chapters have illustrated the chemical and biochemical significance of incorporating organometallic groups into the framework of steroids and how a steroid structural conformation in solution be determined utilizing high-field NMR spectrometers and the latest two-dimensional NMR techniques. This chapter will attempt to unify these two aspects under a common theme. It will centre on the use of high field NMR spectroscopy and 2D NMR methods to establish the site of complexation of the organometallic moiety onto a steroidal skeleton. In some instances, diastereomeric complexes may result, thus it is hoped that these experiments can distinguish them without relying on X-ray crystallographic methods. One should, also, bear in mind that the main emphasis of this NMR study is to utilize the 2D NMR results to investigate what influence the organometallic group has on the chemical shifts of steroidal protons and carbons.

The use of NMR spectroscopy to deduce the site of complexation of an organometallic group on a steroidal molecule is not novel as Butler's group[120] has elegantly

shown that ^{13}C NMR spectroscopy can establish the coordination site of a group VIb metal tricarbonyl onto the arene A-ring of estradiol and estrone. Their pioneering efforts showed that coordination of this tripodal fragment onto the arene ring induces a dramatic upfield shift in the ^{13}C resonances of these carbons.

As mentioned in Chapter 1.4, Jauoen and co-workers developed a concept utilizing organometallic labelled hormones. These particular molecules are well suited for this work, thus a collaboration between the two laboratory groups was established. The next section will deal with the research performed prior to my involvement and will be followed by a discussion of the attempts made during the course of this investigation to extend this approach.

3.2 PREVIOUS WORK

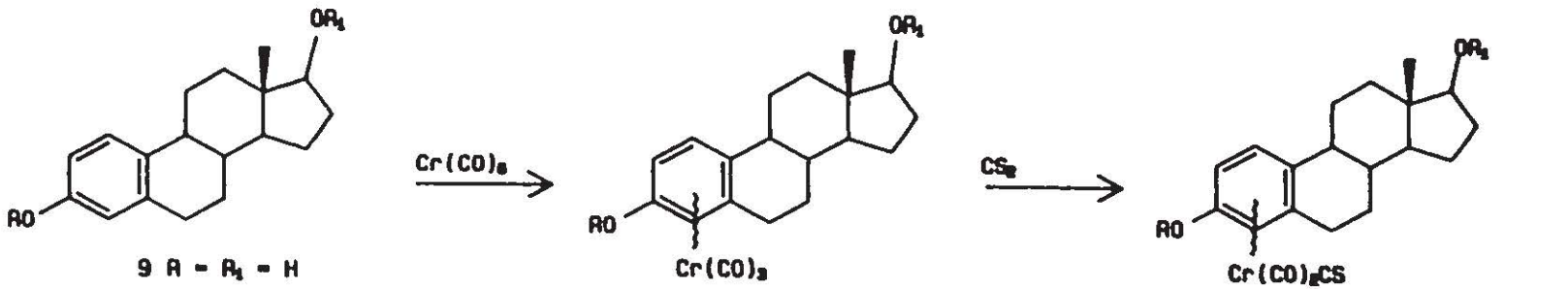
The development of the metal labelled hormone/FT-IR approach relied on the synthesis of the appropriate organometalllic steroidal hormone. As this group had previous extensive knowledge on the preparation of arene chromium tricarbonyl complexes and their use in organic synthesis,[121], it was only natural to utilize the arene A-ring in estradiol, 9. In addition, these complexes had previously been assigned by Butler's group. Subsequently, estradiol and its derivatized versions were treated with $Cr(CO)_6$ and their corresponding $Cr(CO)_3$ complexes isolated

(see Scheme 3.1). As pointed out in chapter 1.3, the planarity of the aromatic A-ring allows the $Cr(CO)_3$ group to bind onto either the α or β face of the molecule thus a pair of diastereomeric complexes were obtained. Since it is not viable to utilize X-ray crystallographic methods to resolve all diastereomer problems, the task at hand was to develop other methods which could establish the site of complexation and possibly distinguish these isomers.[122]

It was initially believed that simple analysis of the product ratios could be a way of differentiating the resulting two $Cr(CO)_3$ complexes. One would naively expect that the β complex would be sterically disfavoured due to an interaction of the organometallic group with the C-13 methyl, and thereby formed in lesser quantities. However, this discrimination was not observed as evidenced by the product ratios for the estradiol complexes (56:44 α:β) and those for its 3-silylated derivative (41:59 α:β). Analysis of their optical rotation values showed a similar anomaly as the β complex exhibited larger values than its α isomer, except for the thiocarbonyl complexes. Finally, it was thought that infra-red spectroscopy might be used to deduce the complexation site, but this method had the downfall that all the bands assignable to CO ligands are identical in each complex.

It was only natural to turn to high field NMR spectroscopy as a potential route since 2D NMR techniques were rapidly being developed in the early 1980's and their

SCHEME 3.1



9 R = R1 = H

R = Bz R1 = TBDMS

40 R = Bz R1 = TBDMS

111 R = Bz R1 = TBDMS

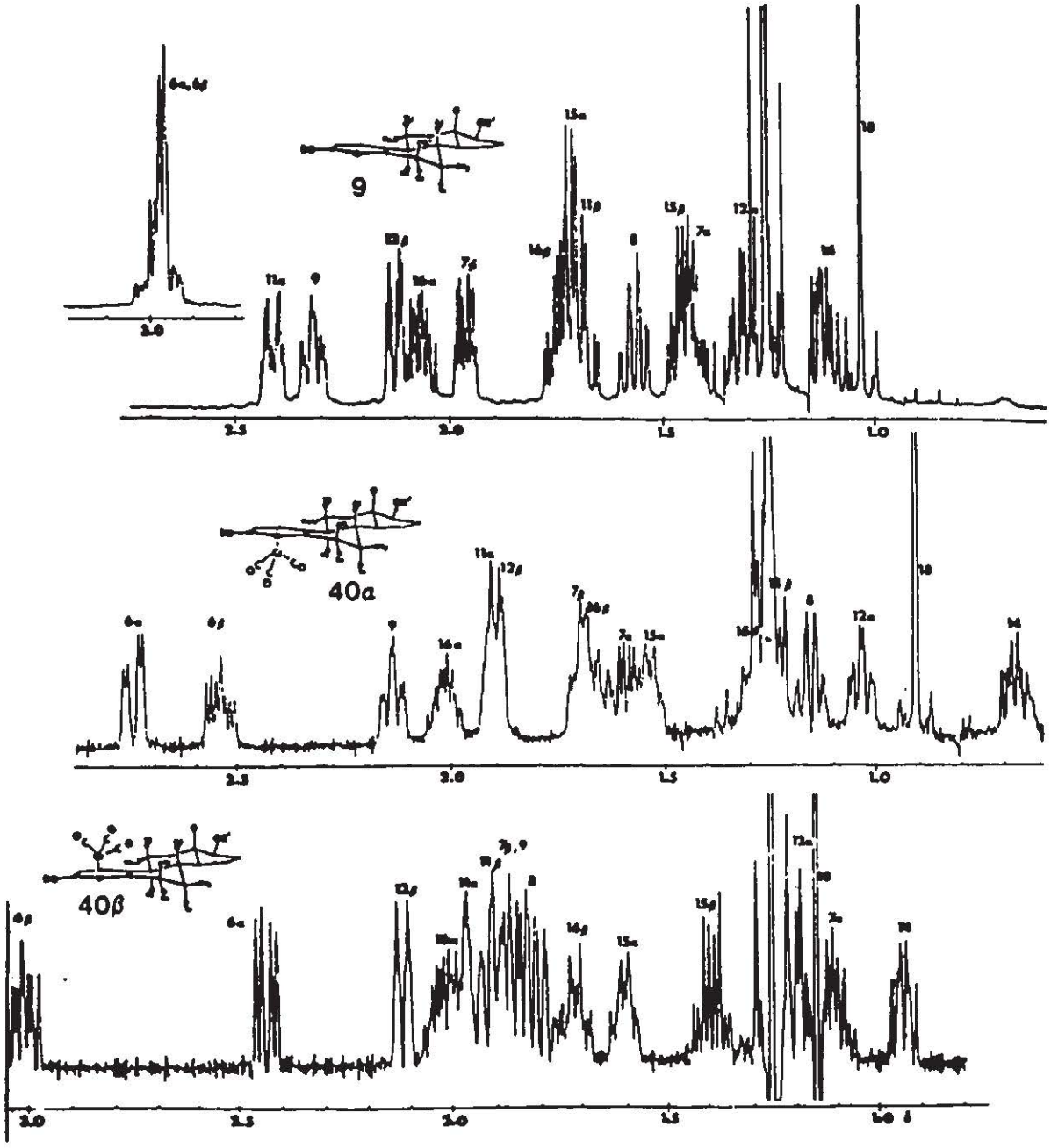
application to steroidal conformations had been well documented (see Chapter 2.4). Thus, this 2D NMR approach became the method of choice for determining the site of complexation of an organometallic moiety onto a steroidal framework.

Figure 3.1 illustrates a portion of the 500 MHz ^1H NMR spectrum obtained for the steroid, 3-(benzyloxy)-17β dimethyl-tbutyl-siloxy) estra-1,3,5(10)-triene and those for the appropriate α and β complexes, 40. The protons and carbons in these molecules were unambiguously assigned utilizing the two dimensional NMR techniques described in the previous chapter, namely, the COSY and HETCOR experiments. In addition, to confirm the identity of one of the complexes, an X-ray structure of the β complex of the thiocarbonyl derivative, 111, was obtained.

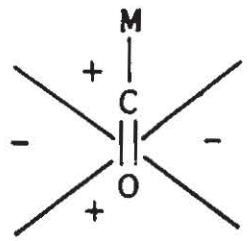
When examining the resulting one-dimensional ^1H spectra, it is readily apparent that the $Cr(CO)_3$ group is complexed onto the aromatic ring A as evidenced by an upfield shift of nearly 2 ppm for the arene proton's resonances. These observations are in accord with other (arene)$Cr(CO)_3$ complexes.[123] Further scrutiny of the ^1H spectra revealed a second aspect, i.e, that the presence of the $Cr(CO)_3$ tripod onto either the α or β face of estradiol greatly influences the chemical shifts of nearby protons, particularly those of 6α and 6β. For example, in the α isomer, the 6β proton signal is shifted to lower frequency than that for 6α by

FIGURE 3.1

Sections of the 500 MHz ^{1}H NMR Spectra of 3-(benzyloxy)-17β-dimethyl-t-butyl-siloxy)estra-1,3,5(10)-triene and its α and β $Cr(CO)_3$ Complexes, 40.


9
40a
40β

nearly 0.2 ppm, while the reverse is observed with an even greater separation of 0.5 ppm in the β complex. Thus, the overall trend appears to be that protons proximate to the $Cr(CO)_3$ moiety had their signals deshielded (shifted to higher frequencies) relative to their resonances when the $Cr(CO)_3$ tripod is on the opposite face; the signals for the 6α, 7α and 9α protons shift upfield while those for the 6β,7β, and 8β protons move downfield when the metal fragment is changed from the α to the β facce. This observation seems to imply that the metal carbonyl group induces zones of anisotropy (see below) similar to those found around in benzene rings and alkyne linkages which shield and deshield, respectively. By the term "anisotropy",[124] it is meant that the external magnetic field induces electron movements which produce a secondary magnetic field that opposes or reinforces the primary field thereby lowering the field or increasing the frequency needed to attain resonance. It is also noteworthy that this effect is reduced dramatically with increasing distance as the signals for protons located in the C- and D-rings remain virtually unchanged in the two complexes relative to the free steroid.



To explain this phenomenon, M^cGlinchey and co-workers[125] proposed a method based on a mathematical model advanced by

M^{c}Connell[126] which relates the chemical shift change to X, the diamagnetic anisotropy term.

$$\sigma = X \cdot G$$

where $G = (1-3\cos^2\theta)/3R^3$

σ = incremental shift in ppm

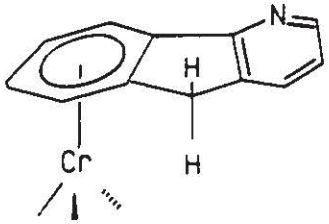
X = diamagnetic anisotropy in cm^3/mole

R = distance of proton in question from centre of anisotropy (cm)

θ = angle made by this line to C_∞ axis

Subsequently, M^{c}Glinchey attempted to estimate the diamagnetic anisotropy of a $Cr(CO)_3$ group by plotting $(\sigma_\alpha - \sigma_\beta)$ vs $(G_\alpha - G_\beta)$ for a series of protons which would generate a line with slope X. The protons in question were positioned at C-6, C-7, C-8, and C-9 since their aromatic ring current contributions should be unchanged, but their anisotropic shifts should depend on their orientation relative to the organometallic moiety. In their first approach, the position of the centre of anisotropy was at the Cr metal atom. A straight line was obtained, but the correlation coefficient of 0.92 indicated a poor choice. They then hypothesized that the centre arose from the C≡O ligand since its electronic distribution was similar to that for an alkyne linkage. Utilizing the midpoint of the C≡O bond as the centre, the

plot obtained gave a straight line with a slope of -490 X 10^{-36} m^3/molecule and an excellent correlation coefficient of 0.98. They also noted that a line exists between the shielding and deshielding zones when the angle is 54.7° where no shift changes occur thereby reducing the geometric term to zero and establishing the boundaries for the anisotropic zones, i.e., when $\theta > 54.7°$, the protons are deshielded while when $\theta < 54.7°$, they become shielded. To establish the reliability of this model,[125] they predicted that the exo methylene proton in the heterocyclic $Cr(CO)_3$ complex, 112, should be 0.315ppm more shielded than its endo partner using the McConnell relationship and the X term; there was good agreement with the observed spectrum. Recently, M^{c}Glinchey's group[127] has been able to distinguish the α and β $Cr(CO)_3$ complexes of the diterpenoid methyl o-methylpodocarpate utilizing this approach and once again, their NMR spectroscopic data were in accord with the X-ray crystallographic structure.



112

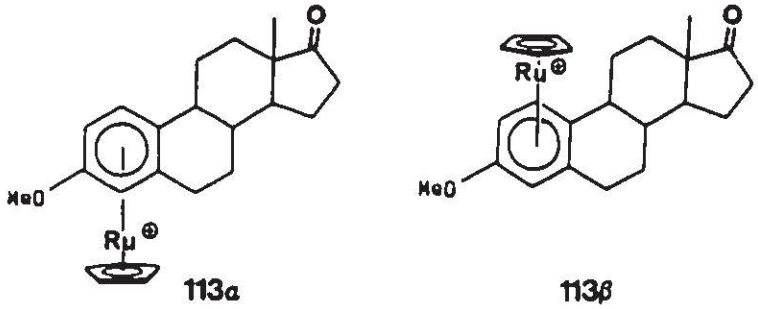
As alluded to earlier, the purpose of the present study was to extend this approach into other steroidal systems and other organometallic groups. One initial goal was

was to investigate what influence a $Co_2(CO)_6$ or a $Cp_2Mo_2(CO)_4$ fragment has on the chemical shifts of D ring protons when coordinated onto an alkyne linkage located at the C-17 position. A discussion of these results is deferred to Section 3.4. The next section will focus on subsequent work which investigated the influence a $CpRu^+$ moiety exerts on the protons in aromatic steroids; thus, one can see the similarity to the previously discussed $Cr(CO)_3$ steroidal systems.

3.3 CpRU COMPLEXES OF ESTRONE

In the opening chapter, it was mentioned that complexation of an arene ring by a $Cr(CO)_3$ group enhances its reactivity. In a similar fashion, Moriarty's group[128] has shown that an aromatic ring bearing a halogen or other potential leaving group readily undergoes nucleophilic substitution when coordinated by a cationic $CpRu^+$ fragment. They further demonstrated that this metal residue can act as a temporary protecting agent in the synthesis of a series of functionalized indoles, including some of biological importance. Since the $Cr(CO)_3$ complexes of aromatic A-ring steroids had been successfully exploited, Moriarty's group[129] decided to explore whether a $CpRu^+$ fragment could be incorporated into such systems and utilizing a ligand exchange reaction, they treated estrone 3-methyl ether with (cyclopentadienyl)tris-(acetonitrile) ruthenium hexafluoro-

phosphate, [$CpRu(MeCN)_3^+$ PF_6^-]. They were able to isolate a 7:3 mixture of α:β $CpRu^+$ complexes, 113, and obtained the individual diastereomers by fractional crystallization. Our involvement during this investigation was to characterize these complexes by 2D NMR methods with the aim of determining the site of complexation and possibly, distinguishing between the diastereomers without relying on X-ray crystallographic techniques. It was hoped that analysis of the ^1H NMR data could provide information regarding the anisotropic behaviour of this organometallic fragment.

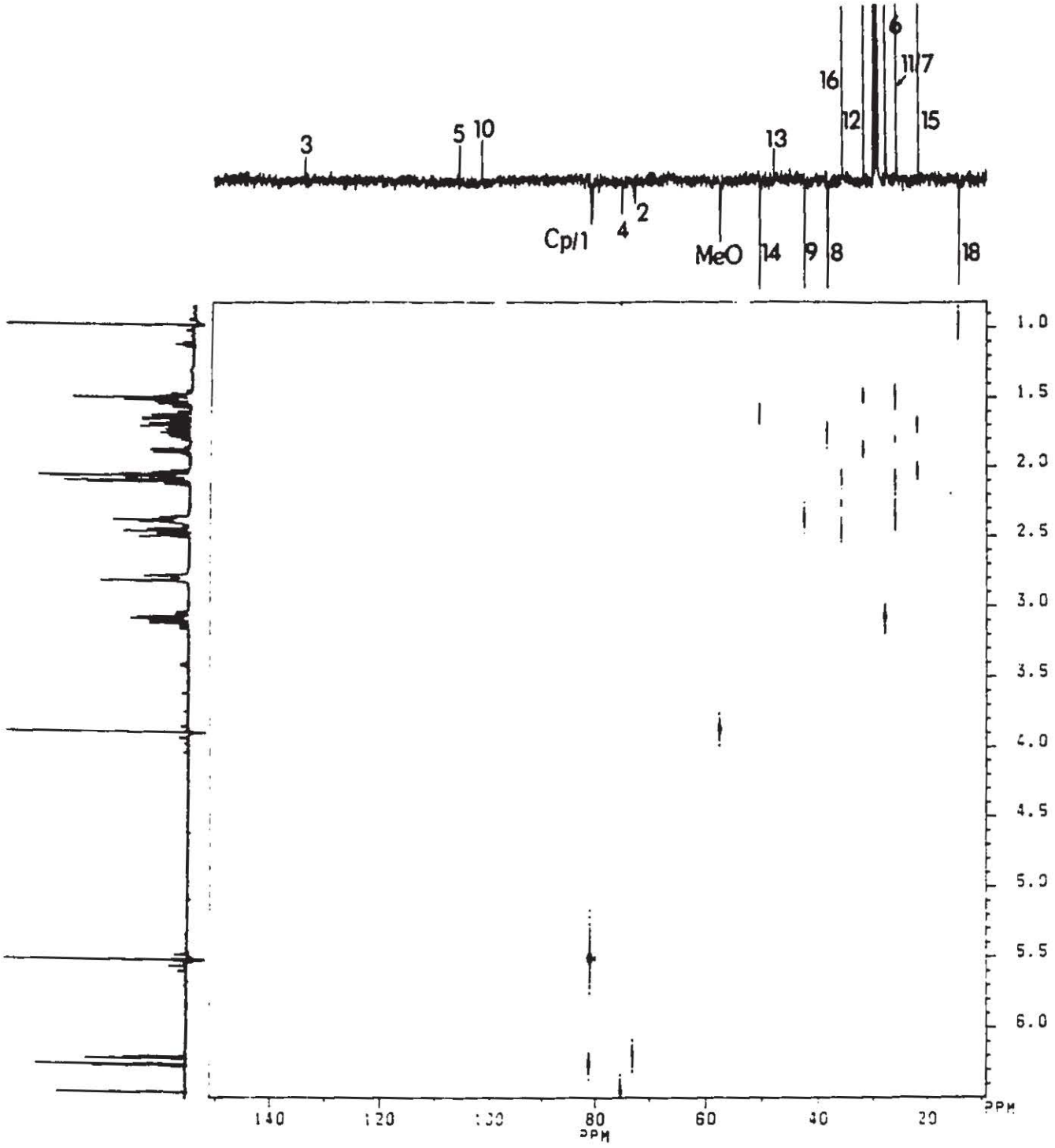


113α 113β

Using the general strategy outlined in the previous chapter, the one-dimensional ^1H and ^{13}C NMR spectra of the free steroid and its complexes were recorded at 500 and 125MHz, respectively. Subsequently, the 2D HETCOR experiment was performed on these systems in conjunction with the APT technique; the result for the β complex is illustrated in Figure 3.2 as a contour plot. Since the ^{13}C NMR spectrum of estrone 3-methyl ether had been previously reported,[82,83] one could readily assign the 2D HETCOR spectra and establish the connectivity pattern between a given carbon and its attached proton(s). For example, C-12 gave rise to two

FIGURE 3.2

2D HETCOR Spectrum of the β-$CpRu^+$ Complex of Estrone 3-methyl ether, 113β, recorded in acetone-d_6.


3
5 10
Cp/1
4
2
MeO
13
14
16
12
6
11
7
9
8
15
18
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
140
120
100
80
60
40
20
PPM
PPM

contours appropriate for a methylene carbon while the methine C-9 carbon yielded a single crosspeak.

The next phase in this investigation was to carry out the 2D COSY-45 NMR experiment in order to further establish the proton chemical shift values. Figure 3.3 illustrates the outcome of this experiment for the α $CpRu^+$ complex. Using the 12α/18Me and 6α/6β contours as the starting points, the resulting COSY spectrum was completely assigned. In addition, any ambiguities in distinguishing α and β protons of a given methylene unit were resolved by examination of their coupling patterns or using nOe difference measurements.

As a result of these two NMR experiments, the complete ^1H and ^{13}C NMR chemical shift values for these molecules were obtained and are collected in Tables 3.1 and 3.2, respectively. The ^1H assignments were in accord with those reported by Bischofberger's group[130] who analyzed the 500MHz ^1H spectra of estrone and its 14α methyl derivative in order to determine whether substitution at this position disturbs the skeletal ring conformations.

Upon analysis of the one-dimensional ^1H spectra for the free steroid and its complexes, it was apparent that incorporation of a $CpRu^+$ moiety onto the arene A-ring brought about similar changes as observed for $Cr(CO)_3$ complexes of estradiol. Figure 3.4 depicts the changes in the ^1H NMR spectra. The initial difference in these spectra is an upfield shift to lower frequency of the aromatic ring A

FIGURE 3.3

A Section of the 2D COSY-45 Spectrum of the α-$CpRu^+$ Complex of Estrone 3-methyl ether, 113α, recorded in acetone-d_6.

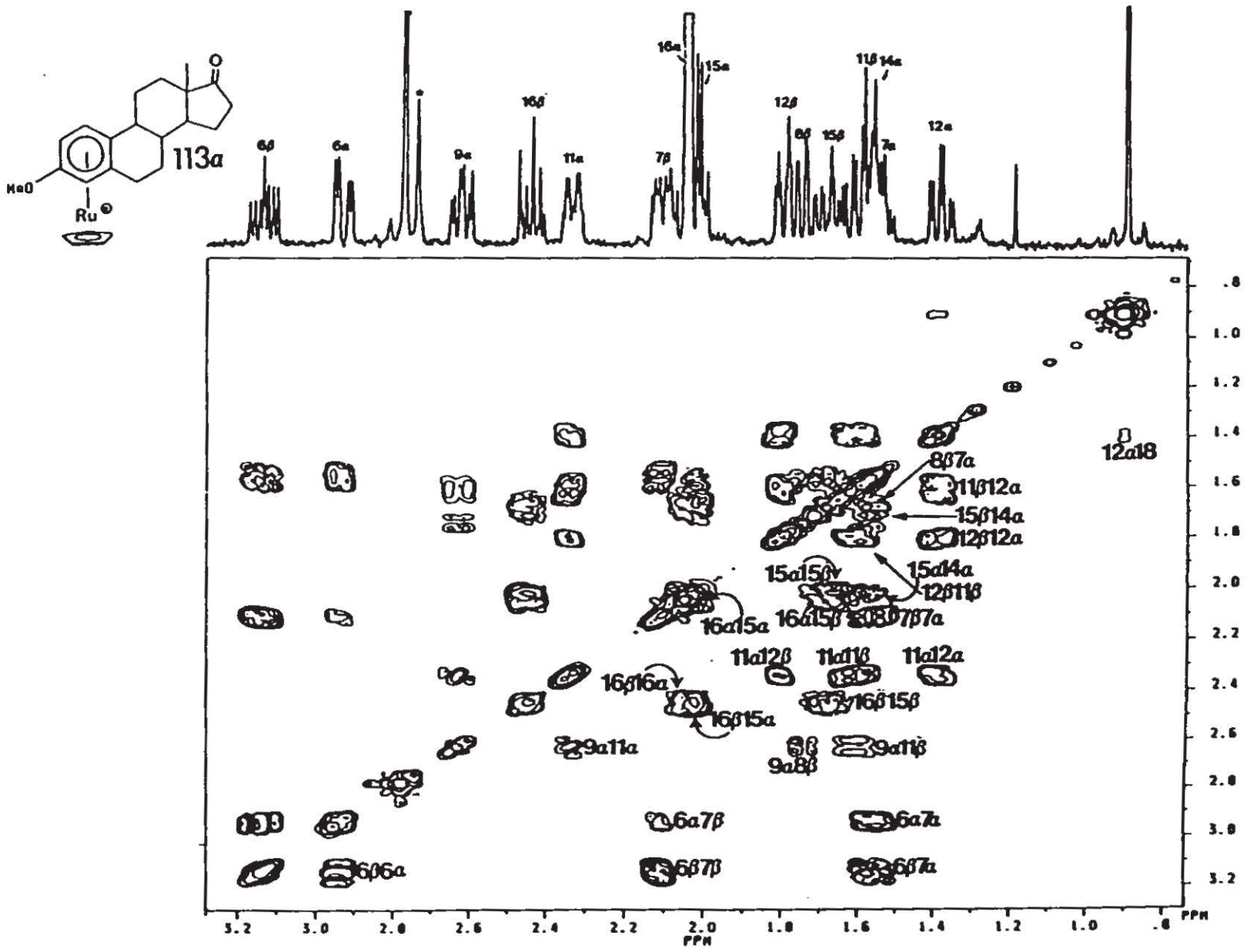

113a
MeO
Ru
6β
6α
9α
16β
11α
16α
15α
7β
12β
8β
15β
11β
14α
7α
12α
12α18
8β7α
11β12α
15β14α
12β12α
15α15β
15α14α
12β11β
16α15α
16α15β
8β8β
7β7α
11α12β
11α11β
11α12α
16β16α
16β15α
16β15β
9α11α
8β
9α11β
9α8β
6α7β
6α7α
6β6α
6β7β
6β7α
PPM
PPM

Table 3.1. ^1H NMR Chemical Shifts for Estrone 3-methyl ether 10 and its α- and β-$[(C_5H_5)Ru]^+$ Complexes 113β and 113β.

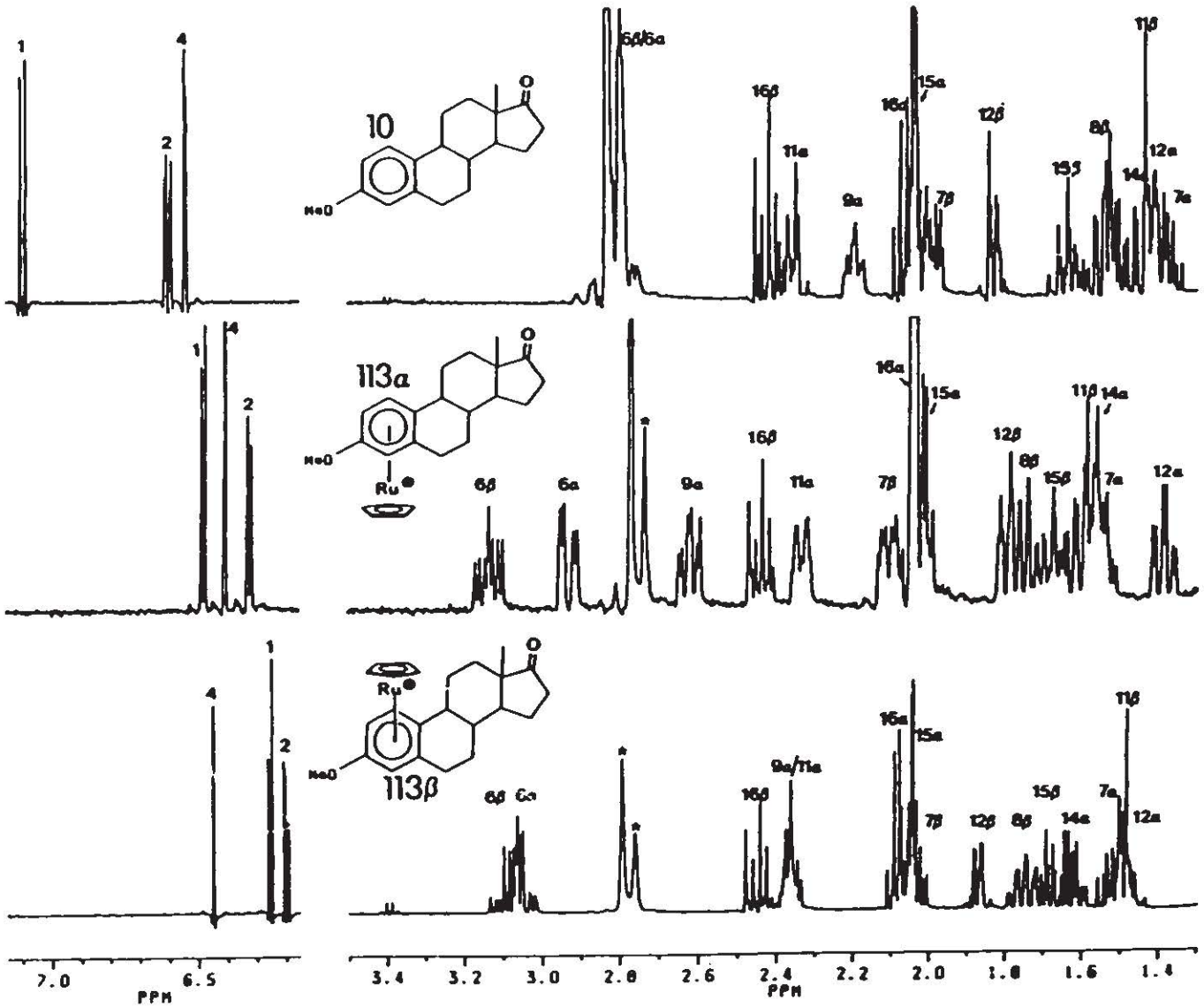
Proton	10	113α	113β
1	7.09	6.47	6.25
2	6.60	6.33	6.20
4	6.54	6.40	6.44
6α	2.79	2.92	3.07
6β	2.84	3.15	3.10
7α	1.40	1.55	1.50
7β	2.00	2.30	2.08
8β	1.60	1.72	1.75
9α	2.20	2.62	2.35
11α	2.38	2.33	2.33
11β	1.45	1.59	1.50
12α	1.48	1.38	1.48
12β	1.85	1.78	1.88
14α	1.55	1.54	1.63
15α	2.05	2.01	2.05
15β	1.67	1.65	1.68
16α	2.09	2.05	2.08
16β	2.45	2.43	2.42
18Me	0.90	0.89	0.97
O-Me	3.80	3.82	3.78
C_5H_5	--	5.46	5.50

Table 3.2. ^{13}C NMR Chemical Shifts for Estrone 3-Methyl ether 10 and its α- and β-$[(C_5H_5)Ru]^+$ Complexes 113α and 113β.

Carbon	10	113α	113β
1	127.30	82.53	81.09
2	112.50	73.41	75.27
3	158.90	134.76	134.19
4	114.70	74.64	78.18
5	138.40	105.50	105.96
6	30.03	27.05	27.96
7	27.30	25.09	26.00
8	39.40	38.95	38.41
9	45.00	44.38	42.50
10	133.20	102.48	101.76
11	26.60	26.09	26.00
12	32.24	32.21	31.85
13	48.30	48.09	47.90
14	51.10	49.97	50.46
15	22.00	21.77	21.05
16	35.90	35.78	35.84
17	219.10	218.58	---
18Me	13.80	13.92	14.85
O-Me	53.82	57.52	57.54
C_5H_5	--	81.64	80.94

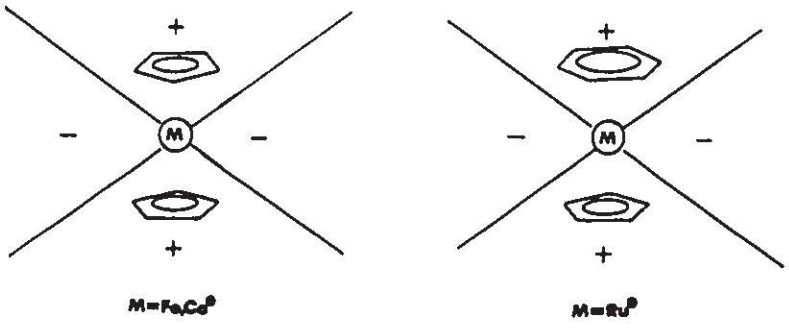
FIGURE 2.4

Sections of the 500 MHz ^{1}H NMR Spectra of Estrone 3-methyl ether, 10, and its α- and β- $CpRu^{+}$ Complexes, 113α, and 113β, recorded in acetone-d_6.


10
113α
113β
MeO
Ru
PPM
PPM

protons when complexed, although it is not as dramatic as observed in the $Cr(CO)_3$ case. This shift indicates that the $CpRu^+$ residue is indeed coordinated onto this ring. Further scrutiny of these spectra reveals a general displacement of the B-ring protons' signals to higher frequency (downfield), which can be attributed to the proximity of these protons to the cationic metal centre.

In examining the anisotropic behaviour of the $CpRu^+$ fragment, the protons chosen for comparison in the α and β complexes must be in the same general environment except for their disposition with respect to the metal centre. The only discrepancy which arises for this situation is for the 9α proton which resonates at 2.62 ppm in the α complex, but at 2.35 ppm in the β case. This implies that the proton lies in a deshielding region of anisotropy in the α situation while being in a shielding zone in the β complex. Recent work by Turbitt and his colleagues[131] on bridged ferrocene systems supports this claim as they proposed that the shielding zone lies above the plane of the cyclopentadienyl ring opposite from the iron atom, while the deshielding region is positioned between the plane of the rings (see below).

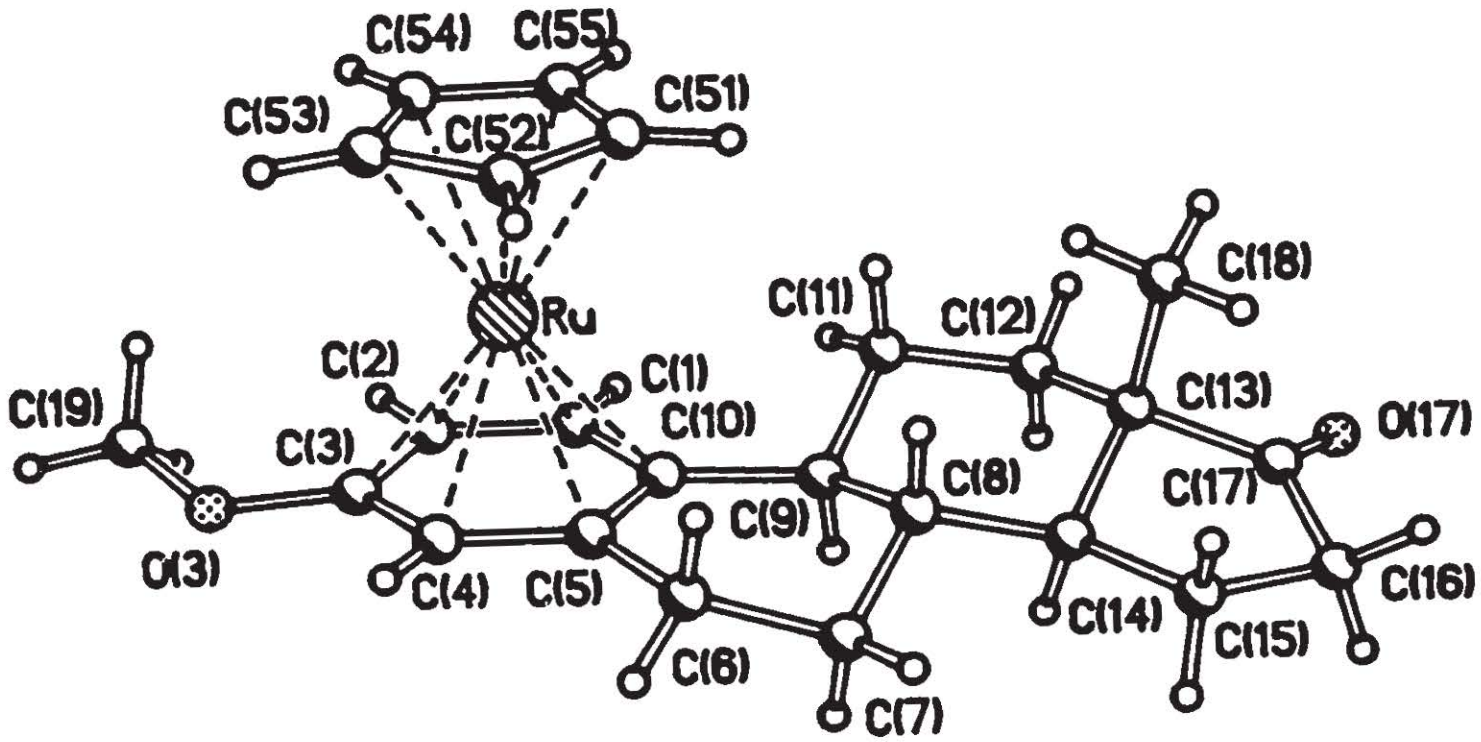


To verify the anisotropic behaviour in these $CpRu(arene)^+$ systems, an X-ray structure of the β complex was obtained. This structure, shown in Figure 3.5, also confirmed the assignment of these two diastereomeric complexes using the 2D NMR approach, thus the chemical shift of the 9α proton provides a probe for the site of attachment of the $CpRu^+$ fragment.

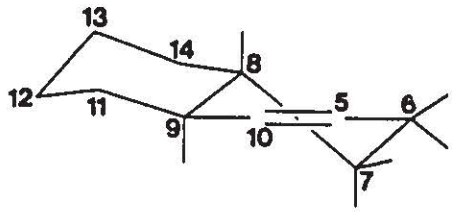
Besides the chemical shift difference for the 9α proton in these two complexes, a similar discrepancy was encountered for the 6α and 6β protons; the 6β signal is downfield of the 6α resonance in the α complex, whereas in the β isomer, it shifts slightly upfield while the 6α signal moves to higher frequency. This situation appears to be similar to that in the $Cr(CO)_3$ complexes of estradiol and could be utilized as possible probes for the differentiation of these diastereomeric complexes. A recent review, however, on X-ray structures of numerous steroidal systems by Duax's group[132] has revealed that the principle point of conformational flexibility in the estratriene series occurs in the B ring and varies over two idealized extremes, the 7α,8β half-chair conformation and the 8β sofa situation. The first structure would place carbons C-9, C-10, C-5, and C-6 in a coplanar environment with C-7 and C-8 are symmetrically positioned above and below this plane, 114. In contrast, the 8β sofa conformation requires the five carbons of the B-ring to be coplanar with C-8 lying on the β face of this plane, 115.

FIGURE 3.5

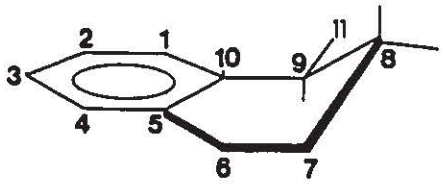
X-ray Structure of the β-$CpRu^+$ Complex of Estrone 3-methyl ether, 113β.


C(54)
C(55)
C(53)
C(52)
C(51)
Ru
C(2)
C(1)
C(19)
C(3)
C(10)
C(11)
C(12)
C(18)
C(13)
O(17)
C(8)
C(17)
C(9)
O(3)
C(4)
C(5)
C(16)
C(14)
C(15)
C(6)
C(7)

These conformations are similar to the ones discussed previously involving the 4-en-3-one steroids.



114



115

Subsequently, Duax[132] developed asymmetry parameters, ΔC_S and ΔC_2, in order to measure the degree of deviation from these idealized systems. The two equations utilized to calculate these deviations are defined as follows with ΔC_S used for the 8β sofa conformer and ΔC_2 for the half-chair situation:

$$\Delta C_S = \{[(\phi_{5-6} + \phi_{5-10})^2 + (\phi_{6-7} + \phi_{10-9})^2 + (\phi_{7-8} + \phi_{9-8})^2]/3\}^{\frac{1}{2}}$$

$$\Delta C_2 = \{[(\phi_{5-6} - \phi_{10-9})^2 + (\phi_{6-7} - \phi_{9-8})^2]/2\}^{\frac{1}{2}}$$

where ϕ is the dihedral angle within the B ring, i.e., ϕ_{5-6} is the angle between C(10)-C(5)-C(6)-C(7).

Upon comparison of the dihedral angles obtained from the crystallographic data for the β $CpRu^+$complex to those for estrone, 10,[133] it was noted there are structural differences in the B-ring. To further examine this point, the CHEMX program[134] was utilized and a $(C_5H_5)Ru$ fragment was grafted

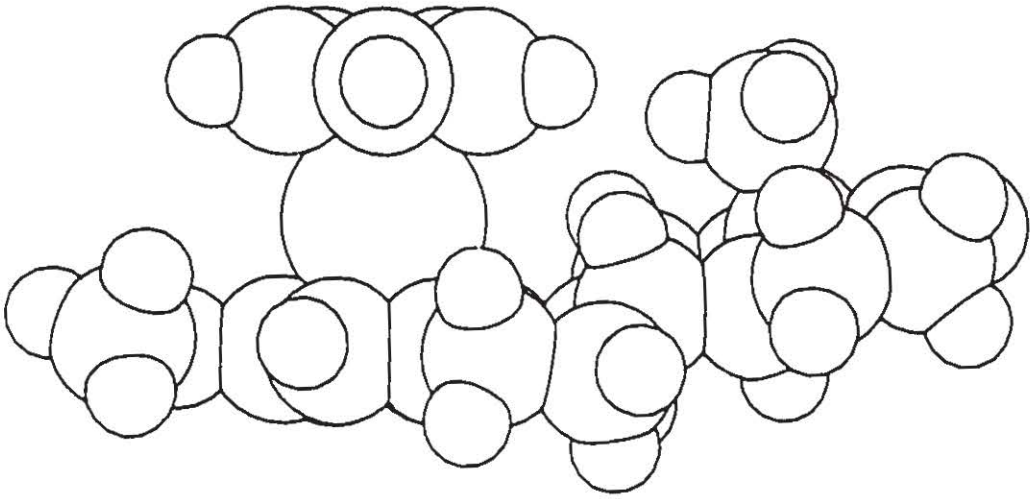
onto the β face of the known structure of free estrone, 113. These representations readily indicated that the cyclopentadienyl ring interacts unfavourably with the C-18 methyl (see Figure 3.6). Specifically in 113, a Cp proton is only 1.98Å from a methyl hydrogen and only 2.35Å from H-8β, thus to provide relief from this predicament, the molecule undergoes a structural modification as evidenced in the β complex's X-ray structure where the nearest proton is now 2.85Å away from a Cp hydrogen. Using Duax's asymmetry parameters, there appears to be little deviation from the half-chair character as ΔC_2(free estrone) is 9.4° compared to 9.9° in the ΔC_2(β-Ru). The 8β sofa contributions, on the other hand, are vastly different with ΔC_s being 17.8° for free estrone and 27.9° for the β complex. These values therefore verify that incorporation of a CpRu fragment modifies the steroidal skeleton, especially within the B-ring.

It was then decided to examine whether this trend is evident in the NMR results. The Karplus equation[135,136], although it has limitations, relates vicinal coupling constants, $^3J_{HH}$, and dihedral angles and can be used to assign molecular conformations. Table 3.3 lists the experimental $^3J_{HH}$ values obtained for the molecules in question and those for free estrone[130] along with the appropriate dihedral angles. It is immediately apparent that there is a large difference in the $J_{6\alpha-7\alpha}$ coupling constants

FIGURE 3.6

CHEMX Representations comparing A) a $CpRu^{+}$ fragment grafted onto the β face of the known structure of estrone and B) the actual X-ray structure.

A



B

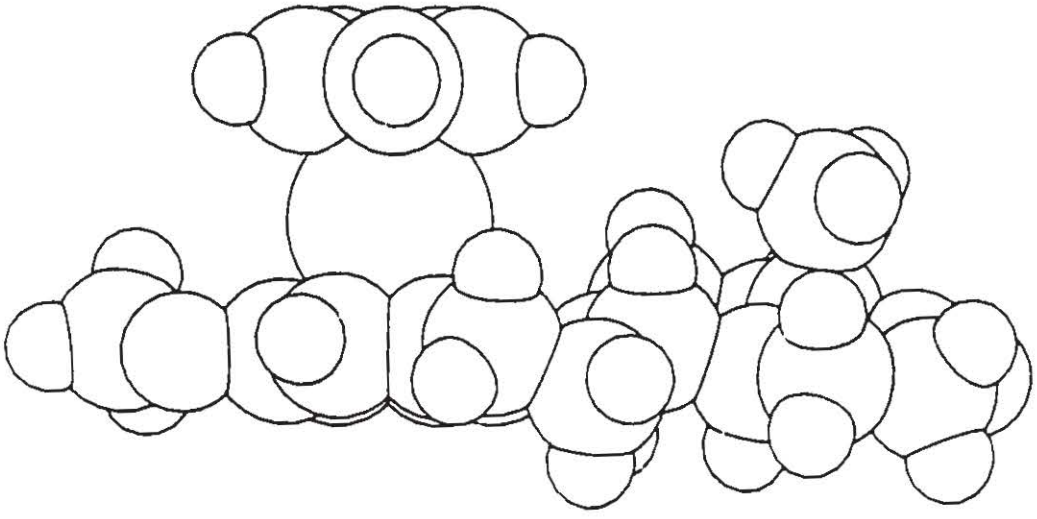


Table 3.3 Dihedral Angles (°) and Vicinal Coupling Constants (Hz) for the Protons at C-6 and C-7.

		10	113α	113β
Dihedral Angle	θ[a]	$^3J_{H-H}$	$^3J_{H-H}$	$^3J_{H-H}$
6α - 7α	42	6.2	4.7	7.4
6α - 7β	68	2.1	≈ 0.5	2.3
6β - 7α	161	12.3	11.8	11.5
6β - 7β	50	6.5	5.8	6.7

a. Dihedral angles are taken from the X-ray crystal structure of estrone, (Reference 133).

with a value in the β complex of 7.4 Hz compared to 4.7 Hz for the α isomer. This implies an opening of the 6α-7α dihedral angle, in the latter case, i.e., the CpRu fragment modifies the free estrone skeleton. To verify this conclusion, a crystal structure of the α complex would be advantageous. The other coupling constants, $J_{6\alpha-7\beta}$ and $J_{6\beta-7\beta}$, in comparison differ very little from the free estrone case. Consequently, one would anticipate these angles to be similar in both systems.

To summarize, it was observed that a $CpRu^+$ group exhibits similar anisotropic behaviour to that of a $Cr(CO)_3$ moiety when incorporated onto an arene ring of an estratriene steroidal system. High field NMR spectroscopy has been utilized to characterize and distinguish the α and β $CpRu^+$ complexes of estrone 3-methyl ether. In addition, changes in their resulting ^1H NMR spectra have been examined in order to establish the boundaries for the anisotropic regions of a $CpRu^+$ fragment. Finally, it should be noted that incorporation of this metal fragment brings about subtle structural changes to the steroidal skeleton, especially in the B-ring.

3.4 COBALT AND MOLYBDENUM COMPLEXES OF 17α-ALKYNYL ESTRADIOLS

The previous two sections have illustrated how organometallic groups, when coordinated onto a steroidal arene ring system, influence the chemical shifts of protons located in the nearby B ring. Since the investigations with

these two systems were successful, it was decided that one should examine what effect metal fragments have on protons at the opposite end of the steroidal skeleton, i.e., in the C- and D-rings. To study these effects, 17α-alkynyl estradiols were chosen since their structure very much resembled estrone except for the alkyne linkage at the 17α position. In addition, the complexes synthesized during this investigation were the focal point in the organometallic labelled hormone/ FT-IR concept developed by Prof. Jaouen's group to assay receptor sites. Thus, much of this work was performed in collaboration. The task at hand was to characterize these newly formed alkynyl complexes using high-field NMR spectroscopy in order to deduce their possible solution structures. As with the $Cr(CO)_3$ complexes of estradiol, the deductions made were based on the possible influence of a metal fragment, when coordinated onto the 17α moiety, on the chemical shifts of protons in the nearby C- and D-rings.

It is well established[137] that alkynes readily react with $Co_2(CO)_8$ to afford tetrahedral clusters of the type $[RC{\equiv}CR'][Co_2(CO)_6]$. In steroidal chemistry, this group has been exploited by Nicholas and co-workers[19] as a temporary protecting agent for alkynes in order that alkenes present in the steroidal skeleton may be manipulated (see Section 1.3a). Bearing this in mind, 17α-propynyl estradiol, 98, and 3-methoxy-17α-ethynylestradiol, 116, often referred to as mestranol, a well known contraceptive, were treated with

$Co_2(CO)_8$ and after purification, the desired deep red alkynyl cobalt complexes, 105 and 117, respectively were obtained. Similarly, a $[CpMo(CO)_2]_2$ complex of 17α-propynyl estradiol, 118, was synthesized via reaction of the steroidal alkyne with $Cp(CO)_2Mo{\equiv}Mo(CO)_2Cp$ using the method developed by Curtis' group[138] (see Scheme 3.2).

The resulting complexes were subsequently characterized using the COSY and HETCOR 2D NMR experiments. Sample spectra for these molecules were previously illustrated in Chapter 2 during the discussion on assigning steroidal COSY and HETCOR contour plots. Tables 3.4 and 3.5, respectively, list the completed ^1H and ^{13}C NMR assignments. It should be noted the ^1H assignments are in accord with those determined by Sedee's group[139] who analyzed mestranol and its photodecomposition products using 2D NMR methods.

From these assignments, one could draw conclusions concerning the presence of a free and complexed alkyne linkage on the chemical shifts of protons located in the C and D rings. Generally speaking, there is little deviation when comparing the ^1H NMR assignments of 17α-propynyl-estradiol and estradiol itself except that the proton signals for 12α and 14α move dramatically downfield by nearly a full ppm compared to those in estradiol. Such large shifts can be attributed to the anisotropic behaviour of the 17α alkynyl moiety and indicates that these particular protons lie in the deshielding region of its cones of anisotropy. Examination

SCHEME 3.2

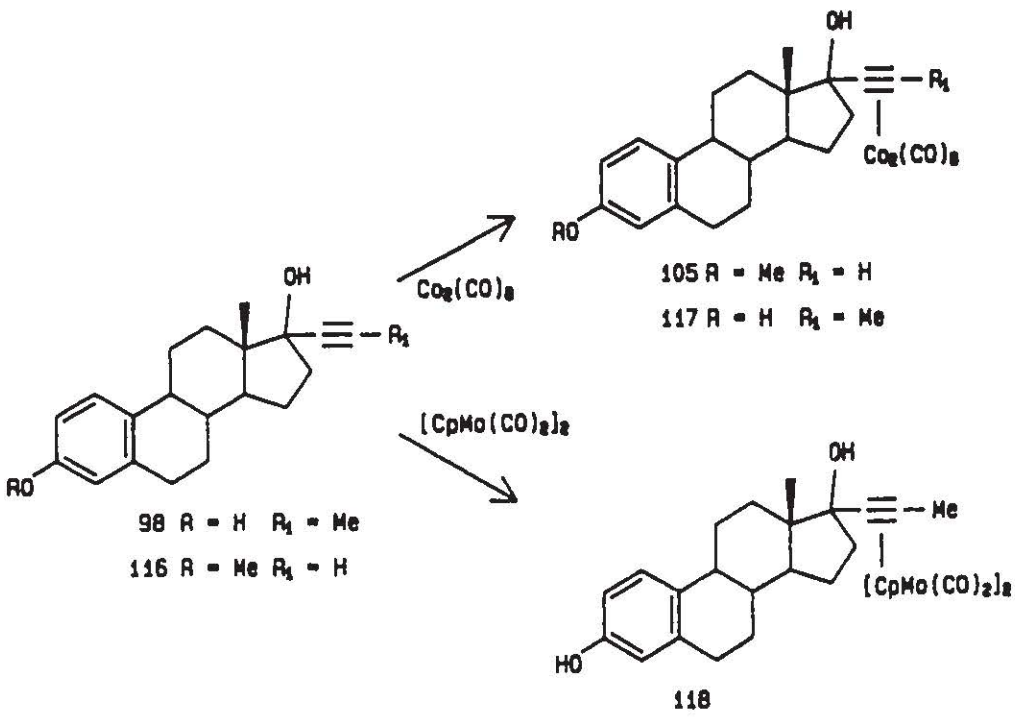

OH
R_1
$Co_2(CO)_6$
RO
105 R = Me R_1 = H
117 R = H R_1 = Me
$Co_2(CO)_8$
OH
R_1
RO
98 R = H R_1 = Me
116 R = Me R_1 = H
$[CpMo(CO)_2]_2$
OH
Me
$[CpMo(CO)_2]_2$
HO
118

Table 3.4. ^1H NMR Chemical Shifts for 17α-Propynyl Estradiol 98, Mestranol 116, and their $Co_2(CO)_6$ 105, 117, and $[CpMo(CO)_2]_2$ 118 Complexes in C_6D_6 Solvent.

Proton	98	116	105	117	118
6α	2.68	2.70	2.75	2.78	2.78
6β	2.75	2.62	2.82	2.80	2.78
7α	1.23	1.18	1.27	1.28	1.37
7β	1.75	1.63	1.80	1.78	1.84
8β	1.39	1.30	1.42	1.38	1.63
9α	2.24	2.32	2.27	2.25	2.21
11α	2.32	2.20	2.32	2.28	2.21
11β	1.52	1.40	1.54	1.48	1.55
12α	2.09	1.95	1.55	1.46	1.56
12β	1.82	1.70	1.70	1.58	1.56
14α	1.86	1.75	1.49	1.68	1.57
15α	1.70	1.55	1.72	1.60	1.80
15β	1.27	1.15	1.27	1.21	1.38
16α	2.42	2.28	2.14	2.18	2.30
16β	2.11	1.88	2.14	2.05	2.12
18Me	0.96	0.91	0.96	0.83	0.98
CH_3-C≡C	1.63	--	2.50	--	2.82
CH-C≡C	--	2.18	--	1.85	--
C_5H_5	--	--	--	--	5.03/5.05

Table 3.5. ^{13}C NMR Chemical Shifts for 17α-Propynyl Estradiol 98, Mestranol 116, and their $Co_2(CO)_6$ 105, 117, and $[CpMo(CO)_2]_2$ 118 Complexes in C_6D_6 Solvent.

Carbon	98	116	105	117	118
1	126.5	126.2	127.2	126.4	126.9
2	112.7	111.5	113.7	111.6	113.6
3	153.0	157.8	155.0	157.5	154.9
4	115.3	113.8	116.2	113.6	116.3
5	138.3	137.4	138.6	137.8	138.8
6	29.6	29.6	30.3	29.0	30.4
7	27.2	27.1	28.4	26.9	28.6
8	39.5	39.4	40.6	39.2	38.8
9	43.6	43.6	44.4	42.8	44.5
10	132.7	132.1	132.7	131.5	133.4
11	26.4	26.4	27.2	25.8	27.8
12	32.9	32.7	34.0	31.9	32.4
13	47.2	46.9	50.0	48.3	51.3
14	49.4	49.4	50.5	49.3	50.1
15	22.8	22.6	23.9	22.1	27.2
16	39.0	38.5	44.1	43.6	37.1
17	80.2	79.3	87.0	84.8	91.1
18	12.8	12.3	16.2	14.7	15.7
$\underline{C}\equiv CCH_3$	81.9[a]	--	106.9	--	106.1
$C\equiv\underline{C}CH_3$	82.8[a]	--	94.5	--	95.2
$\underline{C}\equiv CH$	--	80.2[a]	--	73.2	--
$C\equiv\underline{C}H$	--	81.4[a]	--	106.5	--
CO	--	--	201.0	199.9	(b)
C_5H_5	--	--	--	--	93.5/93.0
MeO	--	54.3	--	53.8	--

a = Assignments could be reversed
b = Peaks too weak to observe

of molecular models of this compound illustrate that this is indeed the case. Upon complexation with a metal fragment, this effect diminishes, however there still is a 0.5 ppm downfield shift in the resonances of these protons relative to their positions in estradiol. This is ascribed to a combination of the loss of triple bond character when coordinated as well as the proximity of the metal fragment and its associated anisotropic effects. Figure 3.7 exhibits these effects by illustrating sections of the 500MHz ^{1}H spectra obtained for the free alkyne and its cobalt and molybdenum complexes. Similar results were obtained for the complexes of mestranol.

In the cobalt complexes, the downfield shift of the 12α and 14α proton signals could be attributed to the proximity of a Co-C-O ligand. One method of emphasizing this situation is to construct a structure using a modelling program, such as CHEMX.[134] Subsequently, a $(HC{\equiv}CH)Co_2(CO)_6$ fragment was grafted onto a known crystal structure of 17β-estradiol and free rotation about the C-17-metal cluster bond was allowed in order to minimize any steric interactions, as well as placing a CoCO group near the 12α proton. The resulting orientation viewed from the α face of the steroidal skeleton is illustrated in Figure 3.8. Clearly, to verify this conformation, one would like to obtain a crystal structure of the cobalt complex and this is currently in progress.

In the $Cp_2Mo_2(CO)_4$ complex, a slightly different

FIGURE 3.7

Sections of the 500MHz ^1H NMR Spectra of 17α-Propynylestradiol, 98, and its $Co_2(CO)_6$ 117, and $Cp_2Mo_2(CO)_4$ Complexes, 118, recorded in C_6D_6.

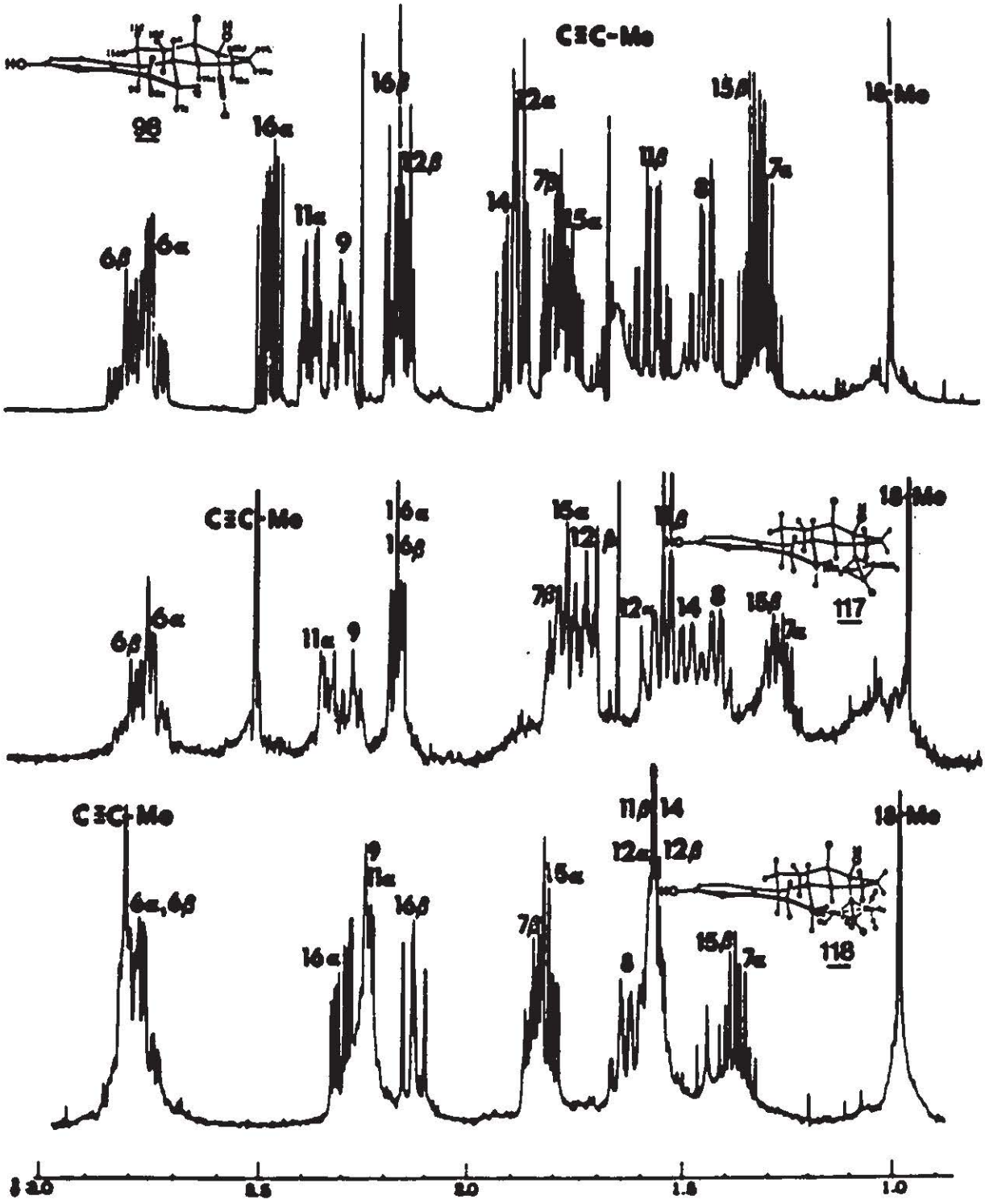
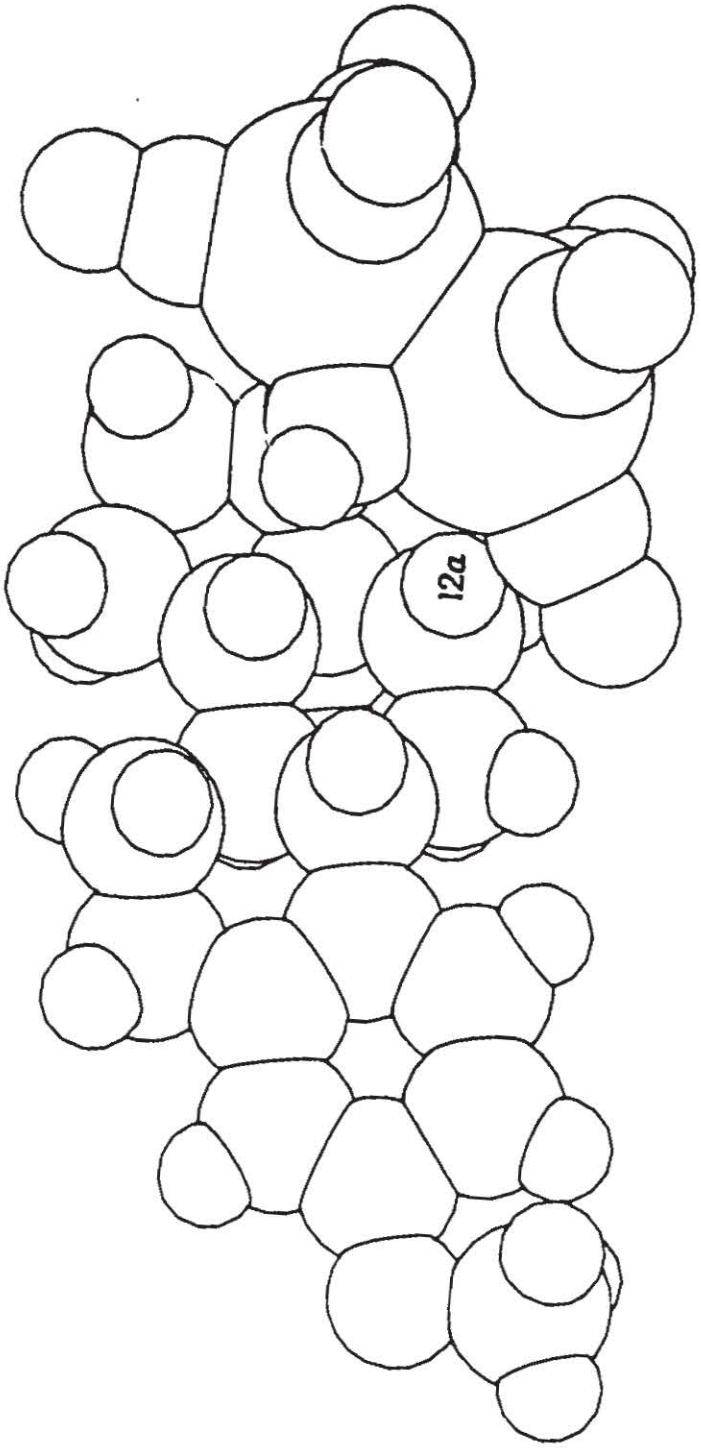

C≡C-Me
18-Me
98
16α
16β
12α
12β
15β
11β
7α
14
7β
15α
11α
9
6β
6α
8
C≡C-Me
16α
16β
15α
12β
11β
18-Me
117
7β
12α
14
8
15β
7α
6β
6α
11α
9
C≡C-Me
11β 14
18-Me
12α
12β
118
6α,6β
9
11α
16β
16α
7β
15α
8
15β
7α
δ 2.0
1.5
1.0

FIGURE 3.8

CHEMX Representation of the energy minimized $Co_2(CO)_6$ Complex of Mestranol, 115.

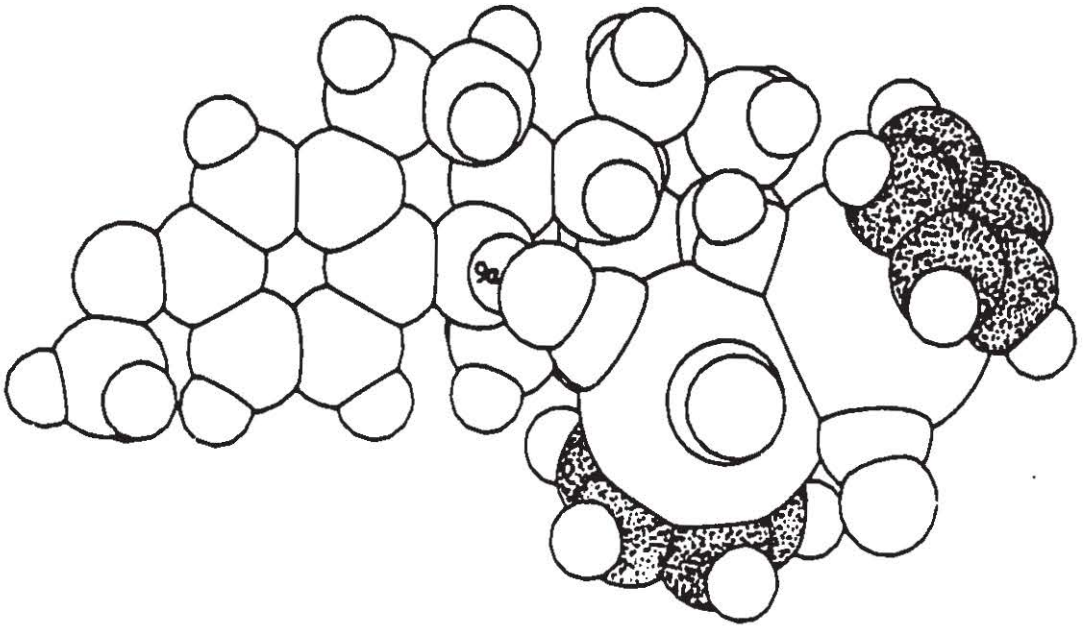

12a

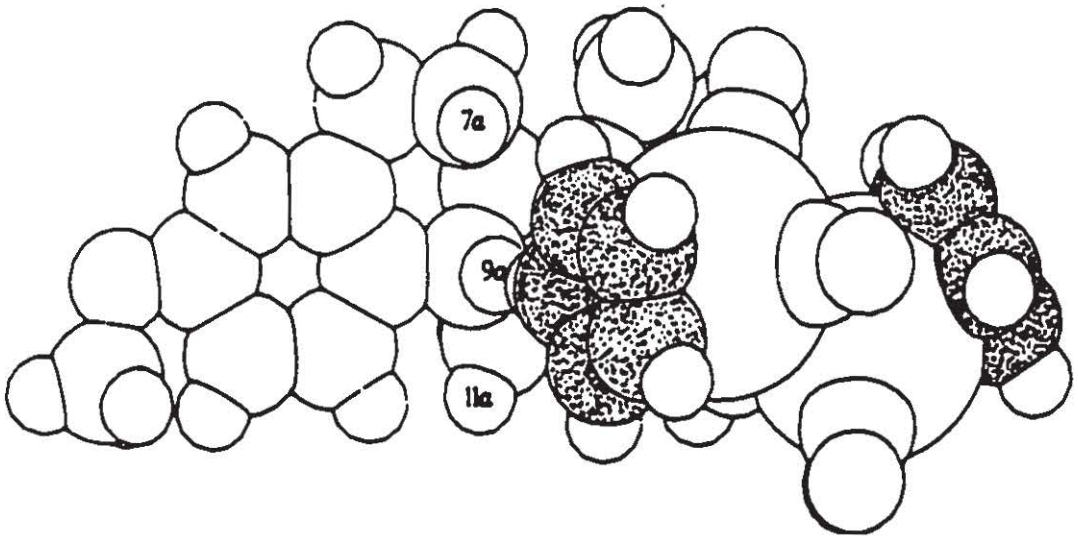
situation arises because of the presence of the cyclopentadienyl rings and the CO ligands. This time, the ring current effects from the Cp moiety predominate as observed by the upfield shifts of the 12α, 12β, and 16α resonances. Once again, one would desire a crystal structure of these complexes to verify these orientations. With the aid of CHEMX, though, one can visualize the possible representations, as shown in Figure 3.9. The first depicts a reasonable conformation and illustrates the observed interaction of a cyclopentadienyl ring and the 16α proton while the latter representation shows another possibility that could exist, however, which would be unlikely since the Cp ring lies in a sterically unfavourable position with respect to the 9α proton. To verify this hypothesis, a NOESY 2D NMR experiment was attempted with the hope that one of the contours present in this spectrum would be due to a nuclear Overhauser enhancement (nOe) between the Cp ring hydrogens and 16α. However, due to decomposition of the complex in the spectrometer, the experiment was unsuccessful and other aspects of these complexes were consequently examined.

Concurrent with these investigations, Nicholas' group[140] has exploited the synthetic potential of the (mestranol)-$Co_2(CO)_6$ complex. In a communication, they demonstrated that the cobalt moiety stabilizes a propargylic cation formed at the C-17 position after treatment of the complex with trifluoroacetic acid. Subsequent reduction of this planar

FIGURE 3.9

CHEMX Representations of the $Cp_2Mo_2(CO)_4$ Complex of 17α-Propynylestradiol, 118.


9a

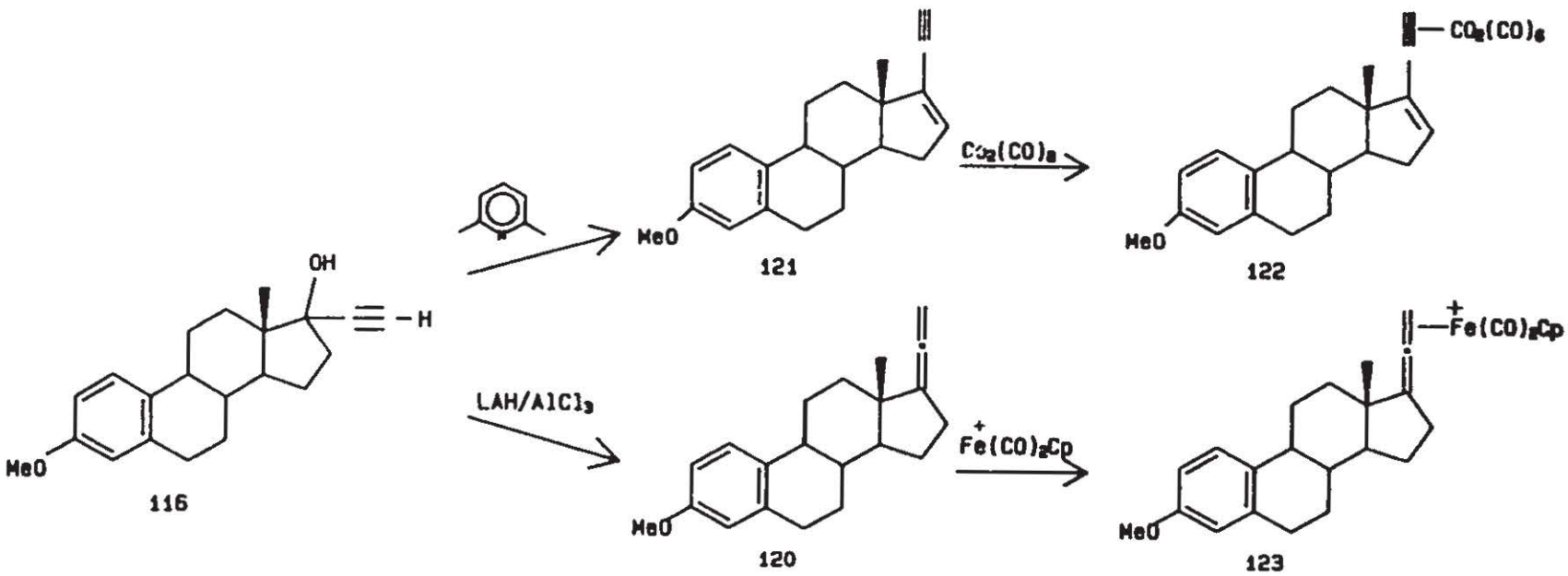

7a
9a
11a

cationic intermediate with $NaBH_4$ yields the β-ethynyl derivative after decomplexation of the cobalt moiety. They also demonstrated that epi-mestranol, which has the alkyne linkage in the 17β position, yields the same product, thus the same cationic centre is involved. An attempt was made to isolate this cationic intermediate and record its 62.5MHz ^{13}C NMR spectrum, but it was unsuccessful due to hydrolysis problems. Subsequently, this study turned to an investigation of the conversion of mestranol into its allene and enyne derivatives and these are the subject of the next section. Before leaving, it should be noted that Nicholas' group have recently reported the introduction of the propargyl dicobalt hexacarbonyl moiety onto the estradiol A-ring.[141]

3.5 CHEMICAL TRANSFORMATIONS OF MESTRANOL

Vermeer's group[142-144] have published a series of papers on the synthetic transformations of mestranol, 116, into epimestranol, 119, substituted allenes, 120, and an enyne system, 121. Like mestranol, it was postulated that these derivatives could function as sites of attachment for organometallic groups and subsequently, the allene and enyne systems were synthesized using Vermeer's method (see Scheme 3.3). The allene, 120, was prepared by means of $LiAlH_4/AlCl_3$ reduction of the 17β-OH functionality in mestranol while dehydration of this hydroxyl group with $POCl_3$ in 2,6-lutidine

SCHEME 3.3


OH
MeO
116
LAH/AlCl3
MeO
120
Fe(CO)2Cp
MeO
123
MeO
121
Co2(CO)8
MeO
122
Co2(CO)6
Fe(CO)2Cp

afforded the enyne system, 121. These compounds were characterized using 2D NMR methods and their ^{1}H and ^{13}C NMR assignments are collected in Tables 3.6 and 3.7, respectively, while Figure 3.10 illustrates the resulting ^{1}H spectra for mestranol and the corresponding enyne and allene systems.

Analysis of the ^{1}H NMR assignments for the enyne and mestranol revealed that the alkyne linkage has changed its position relative to the steroidal skeleton as evidenced by the upfield shift of the 12α proton signal by nearly 0.4 ppm and the corresponding downfield movement of the 12β resonance by 0.38 ppm. This indicates that the alkyne lies more towards the β face of the steroid as expected since the C-17 carbon is now sp^2 in nature rather than sp^3. In addition, there is the associated upfield shift of the 14α signal. Subsequently the enyne's $Co_2(CO)_6$ complex, 122, was synthesized and a dramatic shielding of the 12β signal relative to its resonance in the free enyne was observed. This can be ascribed to the same effects as in the mestranol and 17α-propynylestradiol cobalt complexes, viz., a loss of triple bond character and positioning of a Co-C-O ligand and its zones of anisotropy near the 12β proton.

In the allene system, a similar situation arises with the 12α and 12β proton signals reversing their positions relative to their resonances in mestranol. This may indicate that an allene fragment has similar anisotropic qualities to an alkyne and in order to further explore these properties,

FIGURE 3.10

500 MHz ^{1}H NMR Spectra of Mestranol, 116, and its Enyne, 120, and Allene Derivatives, 121, recorded in C_6D_6.

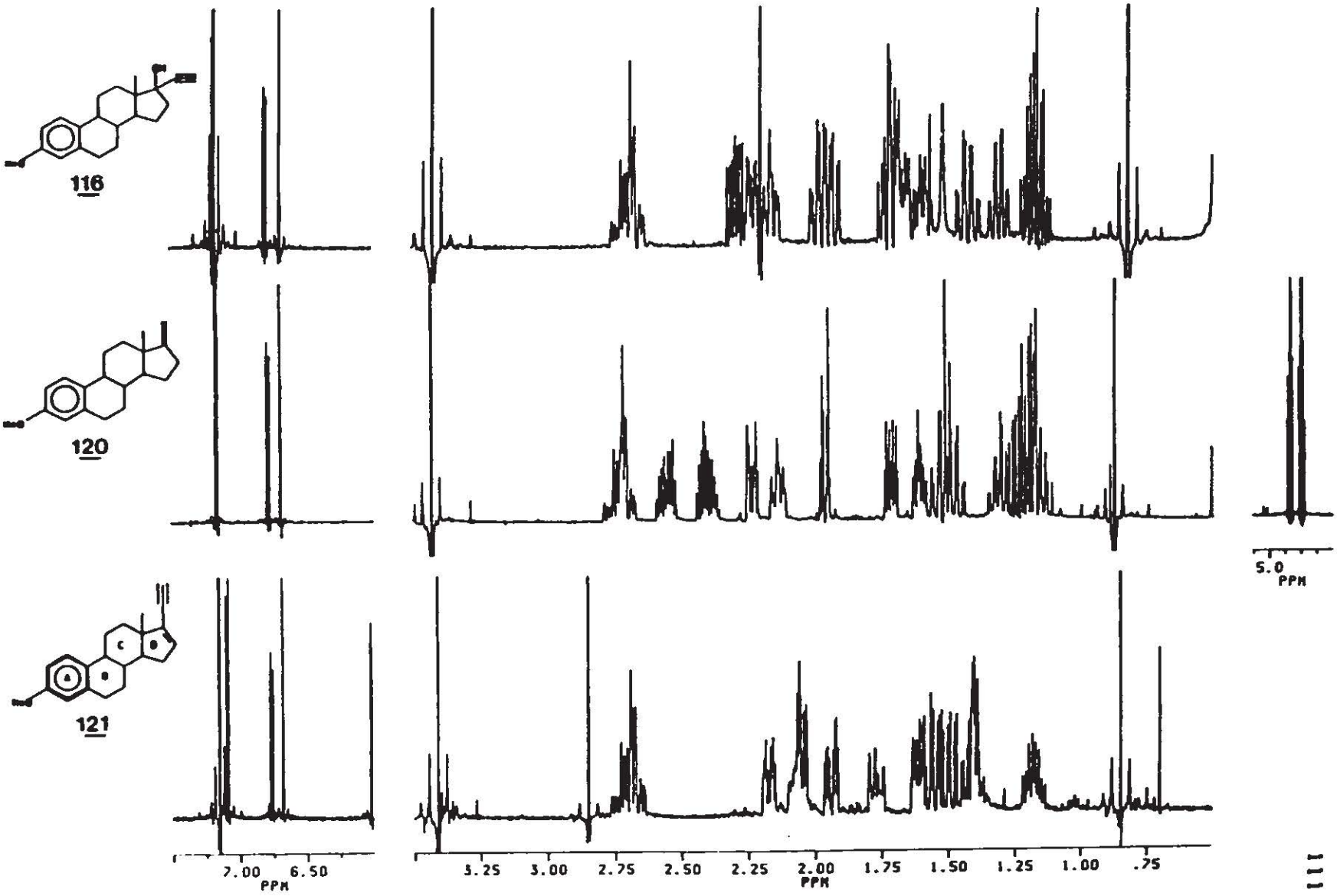

116
120
121
7.00
6.50
PPM
5.25
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
.75
PPM
5.0
PPM

Table 3.6. ^{1}H NMR Chemical Shifts for the Mestranol Derivatives: Allene 120, Enyne 121 and its $Co_2(CO)_6$ Complex 122 in C_6D_6 Solvent.

Proton	120	121	122
1	7.15	7.18	7.20
2	6.77	6.72	6.80
3(OCH_3)	3.50	3.48	3.40
4	6.63	6.60	6.65
6α	2.80	2.73	2.73
6β	2.72	2.68	2.70
7α	1.28	1.20	1.24
7β	1.75	1.63	1.70
8β	1.35	1.38	1.30
9α	2.18	2.10	2.18
11α	2.30	2.20	2.25
11β	1.54	1.48	1.45
12α	1.60	1.55	1.42
12β	2.00	2.08	1.56
14α	1.39	1.42	1.58
15α	1.65	1.95	1.58
15β	1.20	1.78	1.18
16α	2.60	6.03	5.45
16β	2.45	6.03	5.45
18Me	0.91	0.83	0.85
OMe	3.47	3.55	3.50
C≡C<u>H</u>	--	2.88	1.35
C=C=<u>H</u>$_2$	4.90/4.85	--	--

Table 3.7. ^{13}C NMR Chemical Shifts for Mestranol Derivatives: Allene 120, Enyne 121 and its $Co_2(CO)_6$ Complex 122 in C_6D_6 Solvent.

Carbon	120	121	122
1	126.66	126.41	126.60
2	111.90	111.87	112.06
3	158.26	158.30	158.40
4	114.18	114.24	114.35
5	137.82	137.74	137.87
6	28.07	31.82	30.62
7	27.54	28.02	27.82
8	39.07	37.76	40.15
9	44.29	44.58	43.80
10	132.77	132.80	132.34
11	27.01	26.79	26.73
12	30.08	34.88	32.93
13	44.72	48.38	48.94
14	54.63	54.74	50.26
15	24.71	29.90	23.10
16	36.52	137.31	136.40
17	112.70	136.25	136.54
18Me	18.57	16.29	15.70
OMe	54.74	55.54	54.77
$\underline{C}\equiv CH$	--	79.72	85.23
$C\equiv\underline{C}H$	--	81.07	104.52
$C=\underline{C}=CH_2$	201.00	--	--
$C=C=\underline{C}H_2$	77.15	--	--
CO	--	--	200.20

the allene was treated with $Fe_2(CO)_9$ since it was well established[145,146] that an $Fe(CO)_4$ moiety coordinates onto an allene ligand using this reaction. The resulting complex, 123, would be interesting from a spectroscopic point of view since (allene)$Fe(CO)_4$ complexes are known to be fluxional. Unfortunately, this complex could not be isolated after repeated attempts and only the starting allene was recovered. It was apparent that this work would require more extensive investigation, thus it became the subject of another research project. In this work, it was hoped that one could coordinate a $CpFe(CO)_2^+$ fragment onto the steroidal allene, 120, using Rosenblum's method[147] and subsequently utilize this cationic complex as a precursor for stereospecific incorporation by nucleophilic addition of a steroidal side chain.

In summary, this chapter has focussed on the organometallic complexes of aromatic steroids. It has shown how $Cr(CO)_3$ and $CpRu^+$ fragments influence the chemical shifts of protons located in the B ring when they are coodinated onto the aromatic A ring. Subsequently, a similar effect was illustrated for protons at the opposite end of the steroidal skeleton when $Co_2(CO)_6$ and $Cp_2Mo_2(CO)_4$ groups are coordinated to the 17α-alkynyl linkage. The next chapter will focus on a second steroidal system, namely, the ergosterol series and will deal with the attachment of organometallic moieties onto the dienyl system present in the B-ring and how they effect chemical shifts of the nearby protons.

CHAPTER 4

ORGANOMETALLIC COMPLEXES OF B-RING DIENYL STEROIDS

4.1 PREAMBLE

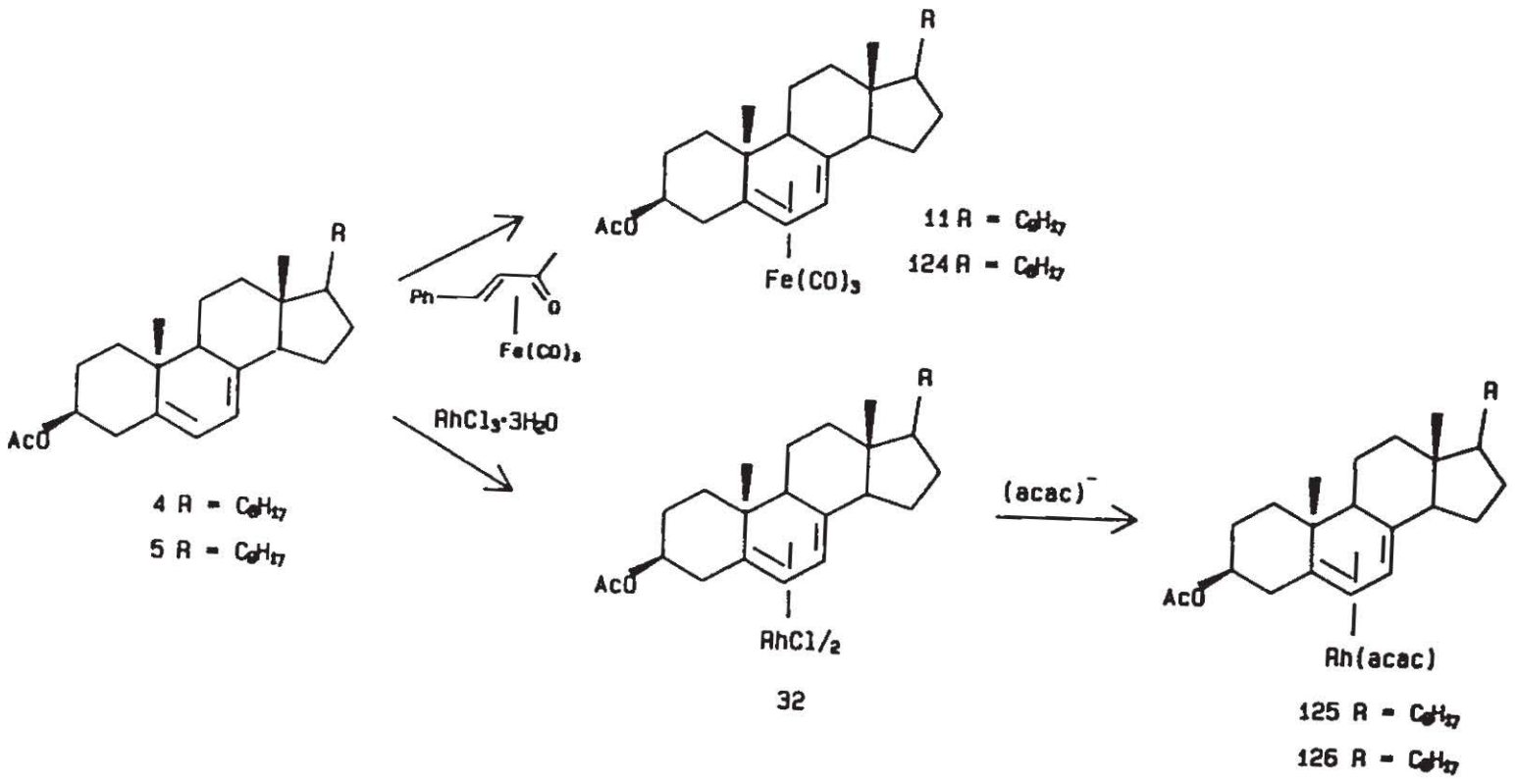
In the introductory chapter, the iron tricarbonyl complexes of ergosterol and its esters were illustrated as valuable synthetic precursors. It is perhaps surprising, though, that their high field NMR spectroscopic properties had not been investigated. It was, therefore, decided to prepare the $Fe(CO)_3$ complex of ergosteryl acetate, 11, and also that for a closely related steroid, 7-dehydrocholesteryl acetate, 124, to explore the diamagnetic anisotropic behaviour associated with the $Fe(CO)_3$ fragment. In these particular complexes, the iron tricarbonyl tripodal unit is coordinated onto the dienyl functionality present in the B-ring thereby influencing the chemical shifts of nearby protons in the A and C rings. In addition, the ^1H NMR spectra for these steroidal systems are anticipated to be much more complex with severe peak overlap as a result of the presence of an eight or nine carbon side chain. Deducing the correct ^1H and ^{13}C assignments should therefore be a good test for two dimensional NMR techniques.

4.2 NMR SPECTROSCOPY OF STEROIDAL DIENE COMPLEXES

The $Fe(CO)_3$ complexes were prepared according to the procedure developed by Johnson and co-workers.[13] The steroidal acetates were treated with the $Fe(CO)_3$ precursor, benzylideneacetone $Fe(CO)_3$, under reflux conditions in a toluene solution. The corresponding complexes, 11 and 124, were obtained as yellow crystals after purification using column chromatography and careful recrystallization. For the 7-dehydrocholesteryl acetate, the crystalline complex afforded was ideal for collection of X-ray diffraction data and its crystal structure determination is discussed later in this chapter. In addition to these complexes, the analogous Rh(acac) complexes, 125 and 126, were synthesized by treatment of the dimeric RhCl steroidal complexes,[22] with acetylacetone anion which is known to cleave the chlorine bridge (see Scheme 4.1). It was hoped that these complexes would be helpful in resolving any ambiguities in the ^1H and ^{13}C NMR assignments obtained by detection of coupling to the Rh centre. ^{103}Rh is 100% naturally abundant and has a nuclear spin of $\frac{1}{2}$.

As alluded to above, the one-dimensional ^1H NMR spectra of these systems will suffer from considerable peak overlap with over 40 protons in a narrow spectral width. The initial phase of these NMR investigations, as shown previously, involved the utilization of the HETCOR 2D NMR experiment, since the ^{13}C NMR assignments for both ergo-

SCHEME 4.1


R
AcO
4 R = C8H17
5 R = C8H17
Ph
O
Fe(CO)3
RhCl3·3H2O
R
AcO
Fe(CO)3
11 R = C8H17
124 R = C8H17
R
AcO
RhCl/2
32
(acac)⁻
R
AcO
Rh(acac)
125 R = C8H17
126 R = C8H17

steryl and 7-dehydrocholesteryl acetates were firmly established.[82,148] Subsequently the 2D COSY NMR experiment was carried out to further establish the proton-proton connectivities and the COSY spectrum for the Rh(acac) complex of 7-dehydrocholesteryl acetate is illustrated in Figure 4.1. In addition, the 2D NMR data were recorded in a strongly anisotropic and in a relatively isotropic solvent, C_6D_6 and $CDCl_3$, respectively, in order to take advantage of the aromatic solvent induced shift (ASIS) effect.[149] This approach can sometimes help to simplify intricate spectra because of a shifting of all resonances due to the formation of weak complexes known as collision complexes. The numerical value of this effect is the difference in chemical shifts of the same proton in two different solvents, i.e. $\delta_{ASIS} = \delta_{CDCl3} - \delta_{C6D6}$ and depends on the structural environment of the proton in question. Figure 4.2 illustrates such subtle changes in the 500MHz ^1H NMR spectrum of ergosteryl acetate when recorded in $CDCl_3$ and C_6D_6. In benzene-d_6, it was observed that the signals for the methylene protons of C-1, C-2, and C-11 and the 9α proton were shielded relative to their resonances in chloroform-d_3, while the side chain protons were generally more shielded when dissolved in $CDCl_3$. This implies that flat disk-like benzene molecule can interact quite favourably with protons in the A, B, and C rings but not so readily with the long aliphatic side chain.

FIGURE 4.1

A Section of the 2D COSY-45 Spectrum of the Rh(acac) complex of 7-Dehydrocholesteryl Acetate, 126.

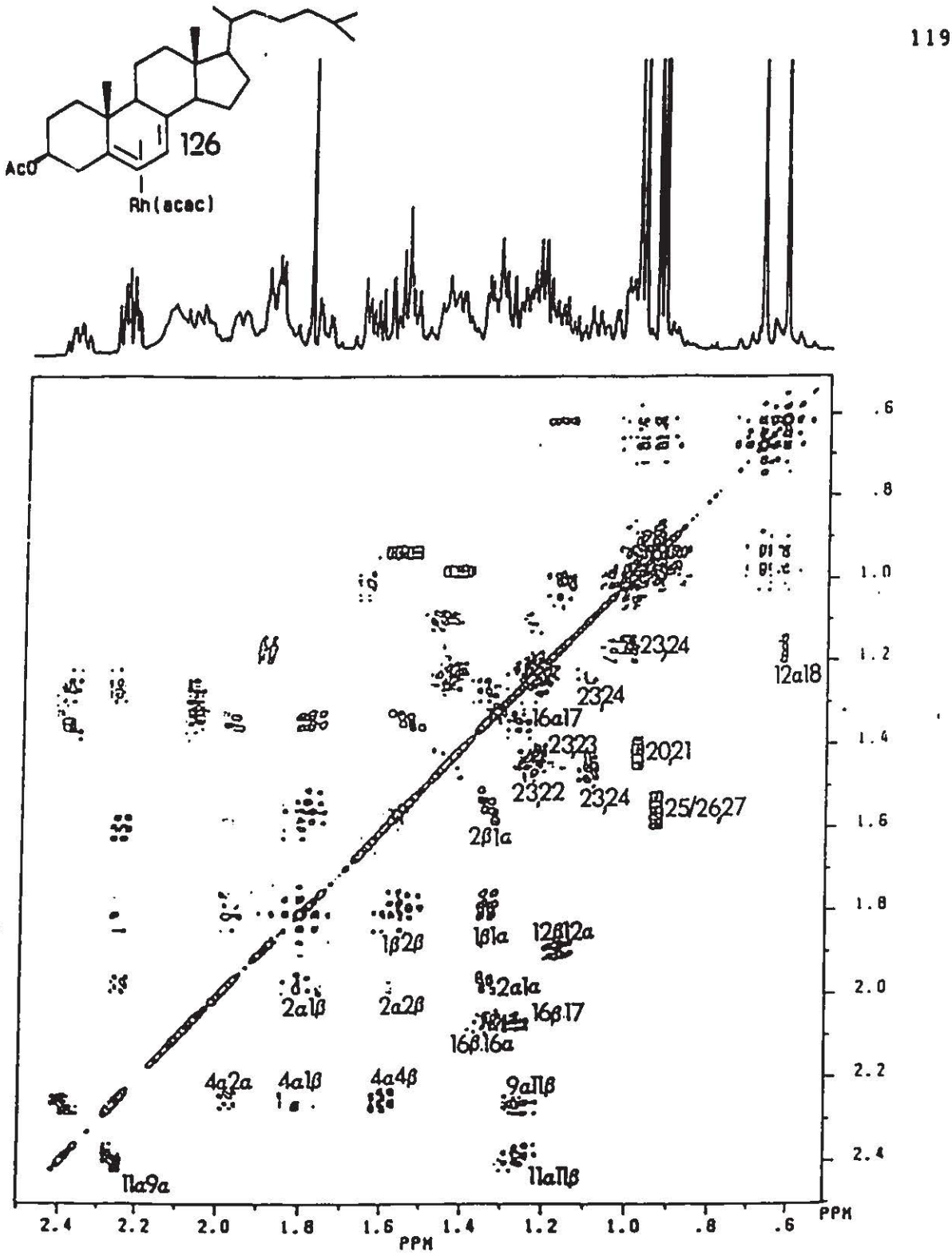
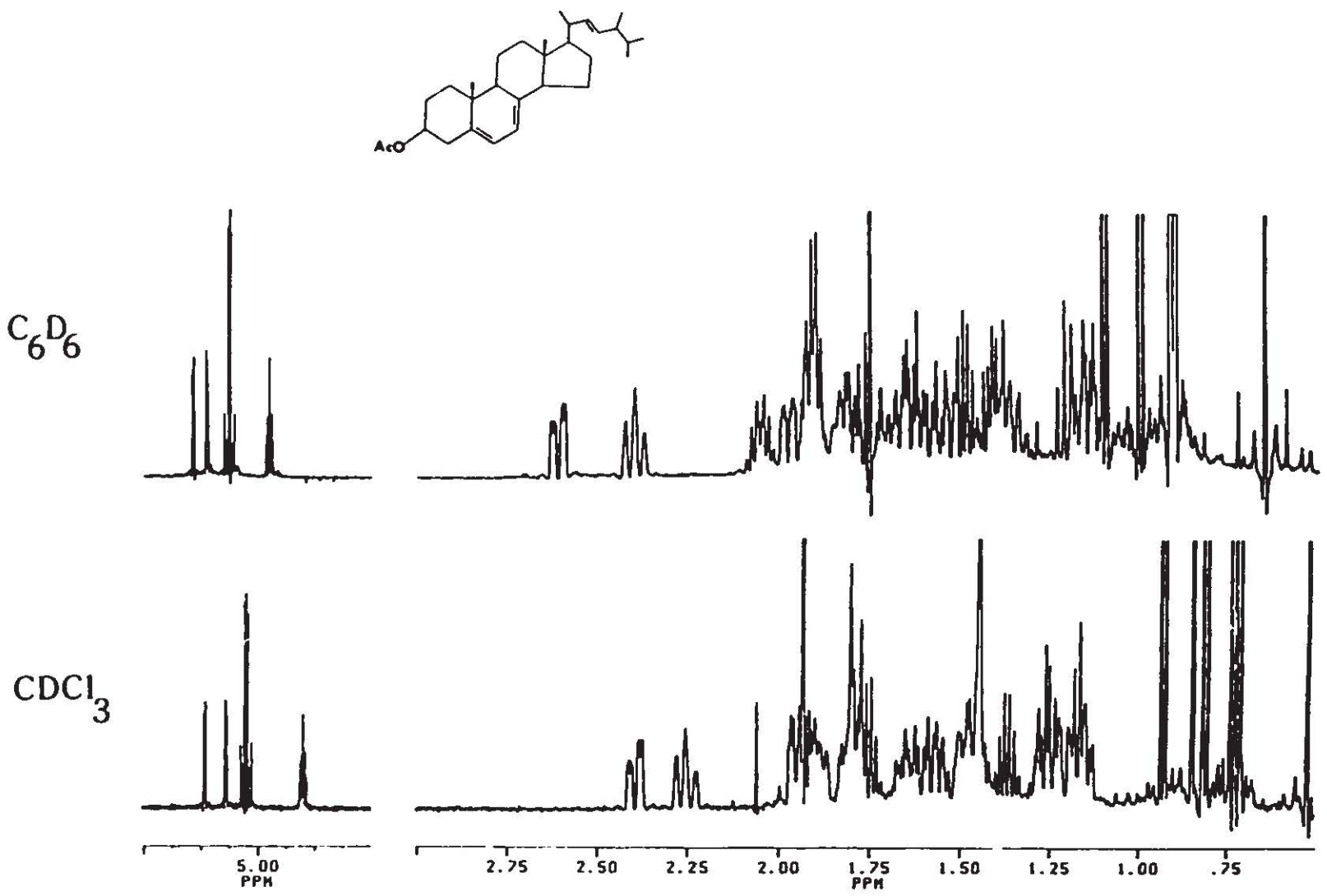

126
AcO
Rh(acac)
23,24
12a18
23,24
16a17
23,23
20,21
23,22
23,24
25/26,27
2β1a
1β2β
1β1a
12β12a
2a1β
2a2β
2a1α
16β17
16β16a
4a2a
4a1β
4a4β
9a11β
11a9a
11a11β
PPM
PPM

FIGURE 4.2

500MHz ^{1}H NMR Spectra of Ergosteryl Acetate, 5, recorded in C_6D_6 and $CDCl_3$.


AcO
C_6D_6
$CDCl_3$
5.00
PPM
2.75
2.50
2.25
2.00
1.75
PPM
1.50
1.25
1.00
.75

Generally, the ^{1}H and ^{13}C NMR assignments obtained are in good agreement with those previously reported for related systems.[103] Tables 4.1 and 4.2 list the respective ^{1}H and ^{13}C assignments for the ergosteryl series while Tables 4.3 and 4.4 list those for the 7-dehydrocholesteryl complexes. Recently, Wilson and Schroepfer[150] have examined the acid isomerization of 7-dehydrocholesteryl benzoate and reported its ^{1}H and ^{13}C NMR assignments. There are some minor discrepancies compared to these results, but they can presumably be attributed to the fact that the previously published data were obtained at 300MHz whereas the above results were measured on a 500MHz instrument.

It was readily apparent from the ^{1}H assignments that the $Fe(CO)_3$ and Rh(acac) moieties were complexed to the dienyl unit as demonstrated by the large upfield shifts, nearly 1 ppm, experienced by the ^{1}H signals of H-6 and H-7. Figure 4.3 illustrates this effect by showing the 500MHz ^{1}H spectra of ergosteryl acetate and its complexes. One can further surmise that the complexes will give rise to diastereomers since the β face is blocked by the methyl substituent at C-13. This supposition is verified by the crystal structure of 7-dehydrocholesteryl acetate $Fe(CO)_3$.

Further scrutiny of the ^{1}H spectra reveals that the $Fe(CO)_3$ moiety has its greatest influence on the 4α and 4β proton signals. A recent study by Ustynyuk's group[151] advanced a possible method of differentiating protons in a

Table 4.1 ^{1}H NMR Chemical Shifts for Ergosteryl acetate 5 and its $Fe(CO)_3$ 11 and Rh(acac) 125 Complexes.

Proton	5		11		125	
	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
1α	1.35	1.15	1.22	1.31	1.59	1.35
1β	1.87	1.62	1.38	1.45	1.82	1.78
2α	1.90	1.92	1.75	1.90	1.95	1.92
2β	1.58	1.55	1.40	1.50	1.50	1.57
3α	4.68	4.84	4.72	5.05	5.32	5.80
4α	2.50	2.62	1.70	2.00	1.95	2.20
4β	2.35	2.40	2.15	2.27	1.52	1.60
6	5.54	5.59	5.20	4.75	4.66	4.53
7	5.35	5.46	4.88	4.45	4.42	4.21
9α	2.02	1.93	1.95	1.95	2.03	2.25
11α	1.68	1.60	1.43	1.55	1.95	2.35
11β	1.58	1.40	1.13	1.08	1.15	1.25
12α	1.23	1.15	1.06	0.95	1.28	1.18
12β	2.08	1.98	1.77	1.70	1.89	1.82
14α	1.88	1.85	1.48	1.60	1.67	1.67
15α	1.60	1.63	1.52	1.55	1.70	2.06
15β	1.37	1.42	1.10	1.15	1.17	1.86
16α	1.24	1.37	1.18	1.08	1.30	1.46
16β	1.74	1.79	0.98	0.90	1.90	1.97
17α	1.31	1.21	1.09	1.05	1.35	1.33
18Me	0.62	0.68	0.70	0.50	0.65	0.61
19Me	0.95	0.92	0.90	1.03	0.78	0.69
20	2.03	2.05	1.80	1.93	2.02	2.03
21Me	1.02	1.11	0.99	0.70	1.00	1.08
22	5.18	5.22	5.17	5.17	5.15	5.23
23	5.21	5.26	5.17	5.25	5.18	5.28
24	1.84	1.90	1.68	1.90	1.83	1.84
25	1.48	1.50	1.30	1.52	1.51	1.51
26Me	0.81	0.91	0.82	0.91	0.85	0.92
27Me	0.81	0.91	0.80	0.92	0.85	0.92
28Me	0.92	1.00	0.89	1.00	0.92	1.03
30Me	2.05	1.78	1.85	1.71	2.02	1.80
acac-CH	--	--	--	--	5.29	5.23
acac-Me	--	--	--	--	1.97	1.80

Table 4.2 ^{13}C NMR Chemical Shifts of Ergosteryl Acetate 5, and its $Fe(CO)_3$ 11 and Rh(acac) 125 complexes.

Carbon	5		11		125	
	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
1	38.13	37.94	39.78	38.42	38.39	38.42
2	28.36	28.37	27.58	28.11	28.19	27.88
3	73.00	72.60	73.46	73.33	72.10	72.45
4	36.87	36.97	37.89	38.69	35.05	34.76
5	138.76	138.50	81.22	81.66	74.85	75.39
6	120.40	120.65	83.31	83.41	73.95	74.13
7	116.51	116.91	78.43	78.75	73.35	73.55
8	141.68	140.96	88.05	87.95	79.24	80.58
9	46.29	46.12	57.93	58.06	54.46	56.69
10	37.33	37.10	a	38.09	36.84	36.92
11	21.23	21.09	24.16	24.40	21.57	21.41
12	39.26	39.19	38.40	39.82	40.36	40.22
13	43.15	42.83	46.40	46.41	45.23	45.47
14	54.74	54.63	56.13	56.54	56.17	54.18
15	23.19	23.20	27.32	27.62	26.00	26.08
16	28.45	28.54	28.38	28.57	28.59	28.26
17	55.96	55.78	56.25	56.11	56.91	56.12
18	12.29	12.01	11.81	11.81	12.38	12.43
19	16.41	16.03	17.56	17.94	21.44	23.00
20	40.61	40.68	40.34	40.63	40.99	40.70
21	21.31	20.78	24.95	24.92	21.68	21.49
22	135.75	135.94	135.17	135.79	136.25	135.88
23	132.20	132.13	132.33	132.42	132.29	132.55
24	43.05	43.14	42.80	43.40	43.32	43.13
25	33.32	33.26	33.06	33.42	35.50	33.37
26	20.13	20.01	19.63	20.23	19.92	20.23
27	19.87	19.70	19.95	19.92	20.23	19.82
28	17.81	17.76	21.07	21.34	17.95	17.98
29	170.60	170.06	170.18	170.58	169.98	170.46
30	21.60	21.20	21.33	20.89	22.76	21.74
$Fe(CO)_3$	--	--	213.97	213.01	--	--
CH(acac)	--	--	--	--	100.16	100.18
Me(acac)	--	--	--	--	27.33	27.50

a = Quaternary carbons not observed due to peak overlap at C-4.

Table 4.3 ^{1}H NMR Chemical Shifts for 7-Dehydrocholesteryl acetate 4 and its $Fe(CO)_3$ 124 and Rh(acac) 126 complexes.

	4		124		126	
Proton	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
1α	1.30	1.18	1.34	1.28	1.57	1.33
1β	1.79	1.66	1.50	1.52	1.80	1.75
2α	1.89	1.83	1.92	1.88	1.87	2.00
2β	1.53	1.50	1.47	1.47	1.25	1.55
3α	4.62	4.86	4.65	5.05	5.35	5.83
4α	2.43	2.60	1.80	1.99	1.90	2.23
4β	2.28	2.40	2.28	2.27	1.55	1.63
6	5.48	5.57	5.16	4.75	4.70	4.54
7	5.31	5.45	4.82	4.45	4.45	4.20
9α	1.93	1.87	2.06	1.96	2.05	2.28
11α	1.60	1.61	1.56	1.57	2.00	2.38
11β	1.49	1.39	1.24	0.97	1.21	1.24
12α	1.13	1.11	1.14	0.93	1.28	1.16
12β	2.00	2.01	1.95	1.76	1.94	1.93
14α	1.83	1.83	1.61	1.62	1.67	1.68
15α	1.63	1.70	1.26	1.04	1.68	2.04
15β	1.33	1.47	1.09	0.92	1.21	1.90
16α	1.29	1.50	1.21	1.10	1.46	1.35
16β	1.91	1.86	1.83	1.64	1.86	2.04
17α	1.09	1.13	1.16	1.00	1.35	1.32
18Me	0.54	0.64	0.65	0.50	0.61	0.61
19Me	0.86	0.90	0.83	0.89	0.90	0.67
20	1.31	1.42	1.31	1.32	1.20	1.22
21Me	0.87	1.00	0.85	0.67	1.10	0.98
22	1.04	1.33	1.18	1.32	1.20	1.22
	0.95	1.06	0.95	1.06	1.00	1.06
23	1.28	1.45	1.29	1.36	1.32	1.45
	1.03	1.22	1.05	1.21	1.15	1.18
24	1.00	1.20	1.02	1.29	1.10	1.12
25	1.45	1.56	1.44	1.56	1.50	1.53
26Me	0.79	0.91	0.80	0.93	0.83	0.93
27Me	0.80	0.92	0.81	0.94	0.83	0.93
30Me	1.96	1.74	1.95	1.71	2.00	1.80
acac-CH	--	--	--	--	5.35	5.24
acac-Me	--	--	--	--	1.98	1.80

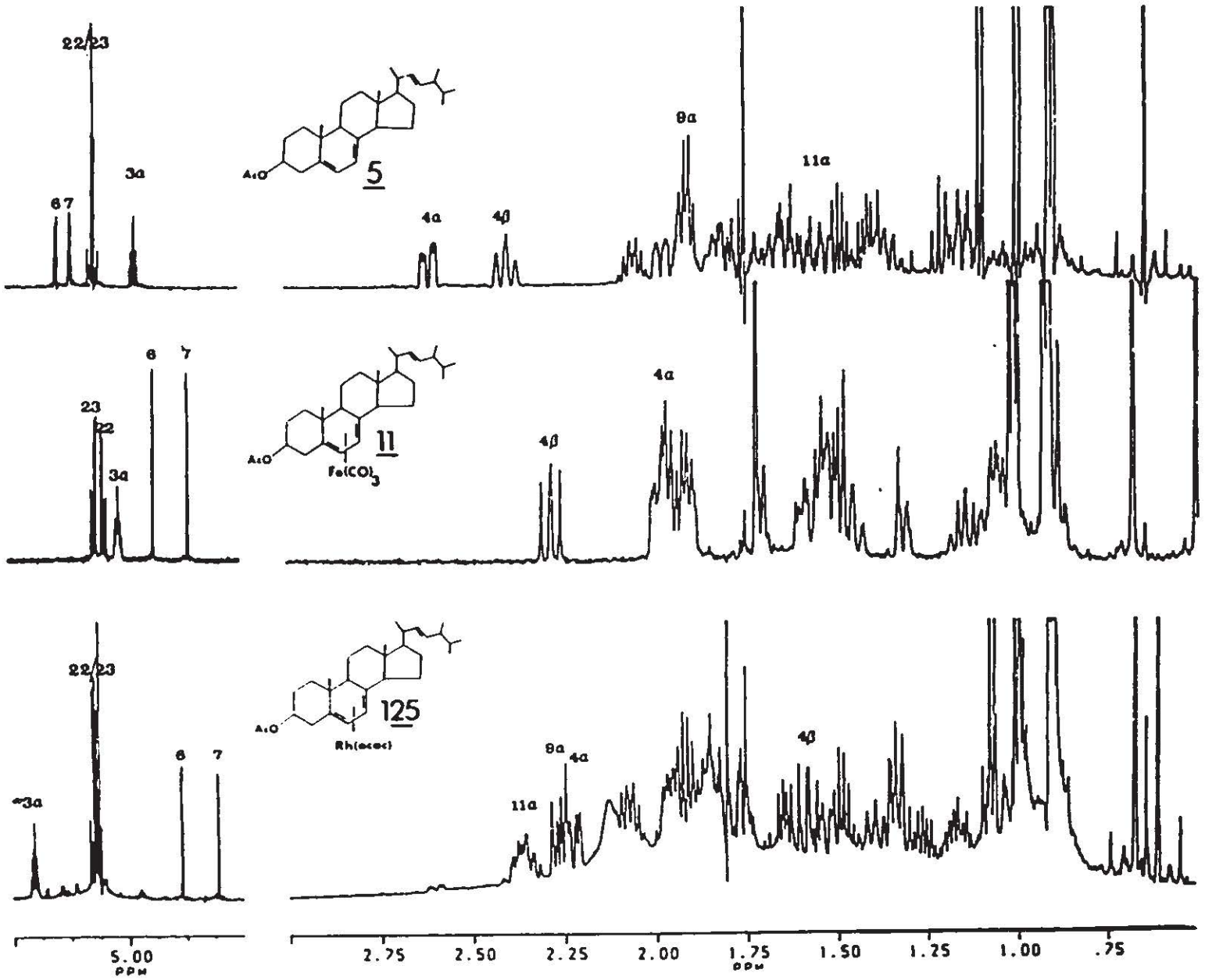
Table 4.4 ^{13}C NMR Chemical Shifts of 7-Dehydrocholesteryl acetate 4 and its $Fe(CO)_3$ 124 and Rh(acac) 126 complexes.

Carbon	4		124		126	
	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
1	37.89	38.12	38.37	38.67	37.88	38.38
2	27.95	28.45	27.55	28.10	27.32	28.38
3	72.80	72.87	73.47	73.55	71.91	72.10
4	37.03	37.15	37.86	38.47	34.21	35.04
5	138.44	138.65	81.22	81.69	74.89	74.81
6	120.19	120.86	83.31	83.39	73.60	73.95
7	116.25	117.06	78.37	78.69	73.02	73.26
8	141.49	141.27	88.27	88.17	80.13	79.32
9	46.02	46.94	57.82	58.00	53.67	56.82
10	a	37.30	a	36.87	36.35	36.84
11	22.50	21.31	24.15	24.42	20.86	21.68
12	39.11	39.55	39.89	39.87	39.80	40.50
13	42.85	43.15	46.51	46.59	45.05	45.40
14	54.42	54.75	56.24	56.51	55.01	54.48
15	22.98	23.41	23.67	24.20	25.60	27.33
16	28.05	28.56	27.09	27.34	27.72	28.38
17	55.87	56.27	56.15	56.28	56.10	56.51
18	11.76	12.00	11.51	11.55	11.61	12.11
19	16.10	16.24	18.75	19.00	22.29	22.73
20	36.09	36.50	35.88	36.19	35.88	36.58
21	18.81	19.09	24.90	24.97	18.64	19.17
22	36.60	36.59	35.88	36.27	35.84	36.58
23	23.84	24.39	28.43	28.62	23.67	24.45
24	39.46	39.92	39.43	39.96	39.28	39.90
25	27.95	28.38	27.98	28.42	27.66	28.21
26	22.98	22.99	22.75	23.00	22.55	23.02
27	22.76	22.74	22.50	22.77	22.46	22.73
29(CO)	170.50	169.15	170.12	169.17	169.50	169.41
30	21.33	20.97	21.30	20.88	21.21	21.14
$Fe(CO)_3$	--	--	212.40	213.49	--	--
CH(acac)	--	--	--	--	100.16	100.16
Me(acac)	--	--	--	--	26.93	24.45

a = Quaternary carbons not observed due to peak overlap at C-4

FIGURE 4.3

Sections of the 500MHz ^{1}H NMR Spectra of Ergosteryl Acetate, 5, and its $Fe(CO)_3$, 11, and Rh(acac) Complexes, 125, recorded in C_6D_6.


22/23
3α
6 7
5
AcO
9α
11α
4α
4β
6
7
23
22
3α
11
AcO
Fe(CO)3
4β
4α
22/23
3α
6
7
125
AcO
Rh(acac)
11α
9α
4α
4β
5.00
ppm
2.75
2.50
2.25
2.00
1.75
ppm
1.50
1.25
1.00
.75

methylene pair situated near an organometallic fragment by utilizing the ASIS effect. They showed that the bulkiness of the fragment can hinder the approach of the aromatic solvent; thus one may be able to determine the site of complexation since protons proximal to the organometallic group will not experience the ASIS effect. In these systems, this postulate seemed not to be significant as evidenced by the fact that in $CDCl_3$ solvent both the 4α and 4β resonances in both of the $Fe(CO)_3$ complexes were upfield relative to their positions in the noncomplexed steroidal precursors. Upon changing to the anisotropic solvent, these resonances are actually deshielded suggesting that the $Fe(CO)_3$ group hinders these protons from experiencing the ASIS effect. One might have expected that the 4β proton should experience a slight ASIS effect since it is located on the β face of the molecule. However, from the crystallographic data, it was observed that both protons are positioned in the shielding region of anisotropy of a terminal metal carbonyl ligand since the relevant angles are less than 54.7°. Once again, it appears that the NMR and crystallographic data are in complete accord.

In the Rh(acac) complex, the effects are localized on the immediate protons as demonstrated by the upfield shift by more than 0.5 ppm for the 4α and 4β ^1H signals and a somewhat smaller deshielding in the 1α and 11α resonances. These changes can be attributed to a possible pseudo aromatic ring current induced by the planar Rh-acac ring. If this were the

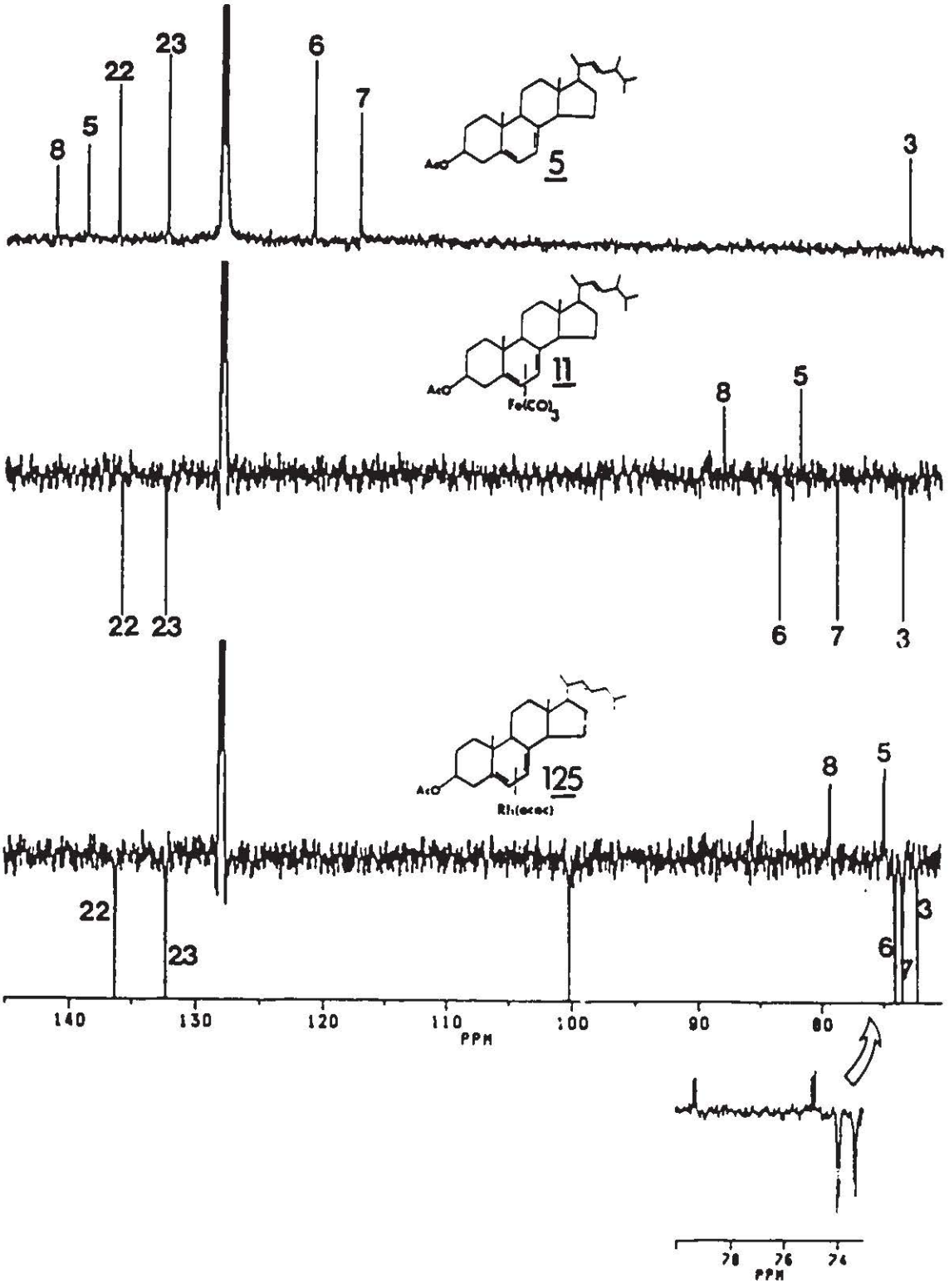
situation, the plane of the Rh(acac) ring would approximately bisect a C-6/C-7 double bond thereby forming a π bond and σ bonds to C-5 and C-8 rather than the usual square planar arrangement around rhodium with the π donating C-5/C-6 and C-7/C-8 double bonds. A suitable crystal for X-ray structural analysis which might help to resolve this situation was unfortunately not obtained as the complex precipitates out of an ethereal solution at -78° as a yellow powder.

Analysis of the ^{13}C NMR data indicates the principal effects of complexation of an organometallic group are again localized in the unsaturated system, as was observed in the aromatic steroidal complexes. This is evidenced by the large upfield shifts of nearly 40 - 60 ppm in their ^{13}C resonances upon coordination. A noteworthy point in these results was the observation of a ^{103}Rh-^{13}C coupling (≈15Hz) which is illustrated in Figure 4.4.

In summary, the complete proton and carbon assignments for the complex ergosteryl steroidal systems were obtained. Subsequent, examination of the changes in the ^{1}H NMR spectra revealed information regarding the diamagnetic anisotropic behaviour of a $Fe(CO)_3$ or Rh(acac) moiety when complexed coordinated onto the dienyl B-ring unit in ergosteryl and 7-dehydrocholesteryl acetates. The following section will centre on a discussion of the crystal structure determination of the $Fe(CO)_3$ complex of 7-dehydrocholesteryl acetate.

FIGURE 4.4

Sections of the 125MHz ^{13}C NMR Spectra of 5, 11, and 125, recorded in C_6D_6.


8
5
22
23
6
7
3
5
11
Fe(CO)3
22
23
8
5
6
7
3
125
Rh(acac)
22
23
8
5
6
7
3
140
130
120
110
100
90
80
PPM
78
76
74
PPM

4.3 CRYSTAL STRUCTURE DETERMINATION

In the preceding section, it was mentioned that yellow plate-like crystals of the $Fe(CO)_3$ complex of 7-dehydrocholesteryl acetate, 124, were isolated from a hexane solution. Consequently, using single crystal X-ray diffraction techniques, its crystal and molecular structure was determined. It should be noted that the determination of this structure was not straightforward as the asymmetric unit contained two independent molecules. Discussion regarding this aspect is deferred to the experimental section. For this chapter's purposes, it can, however, be concluded that the two molecules are virtually identical except for a minor variation in the relative positions of the acetate group and the $Fe(CO)_3$ tripodal unit.

The pertinent crystal data for 124 are assembled in Table 4.5, while Tables 4.6 - 4.9, respectively, list the atomic coordinates, bond distances, valency angles, and endocyclic torsional angles for both molecules. Figure 4.5 illustrates the structure of one of the molecules along with the numbering scheme while a view of the crystal packing arrangement in the unit cell is shown in Figure 4.6.

In analyzing this structure, the first apparent comparison is to other similar steroidal crystal structures in order to examine whether coordination of the B-ring dienyl system by the $Fe(CO)_3$ moiety brings about any structural changes to the steroidal skeleton. Ideally, the logical

FIGURE 4.5

X-ray Structure of 7-Dehydrocholesteryl Acetate $Fe(CO)_3$, 124.

Xray Crystal Structure of
7 Dehydrocholesterol Acetate
$Fe(CO)_3$.

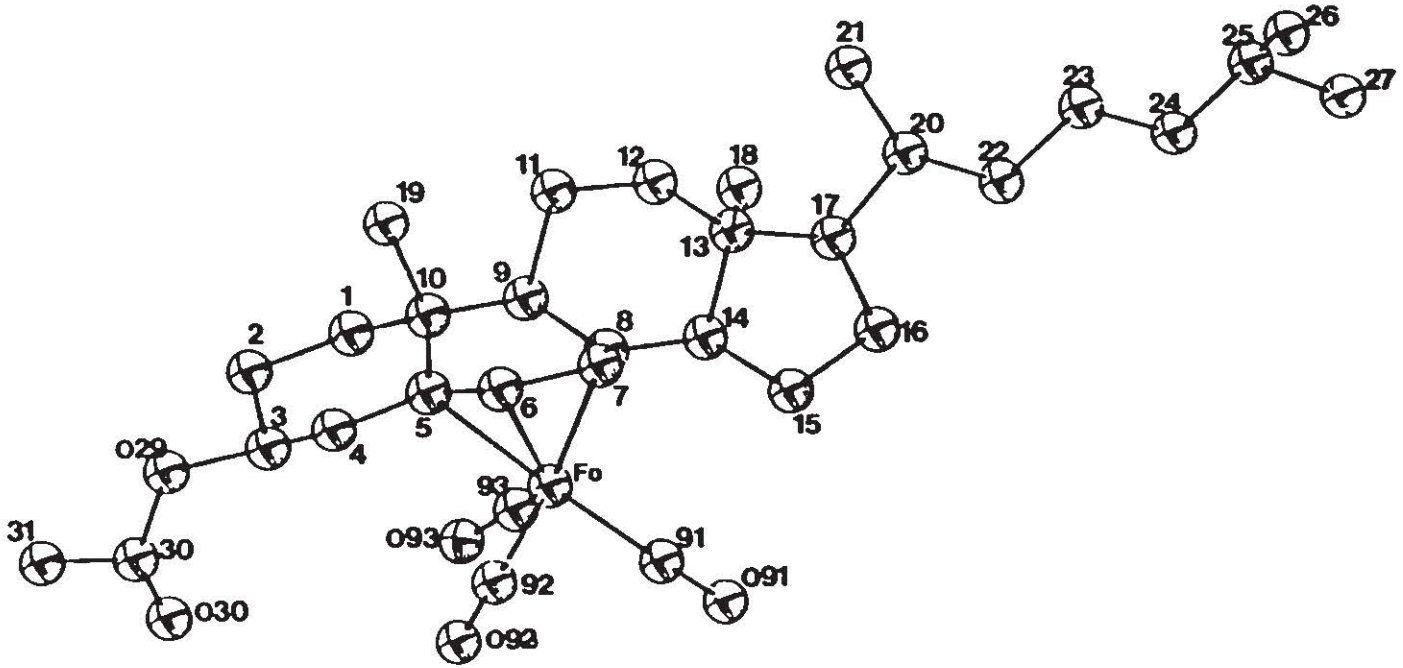


FIGURE 4.6

Crystal Packing Arrangement of the Unit Cell for 124.

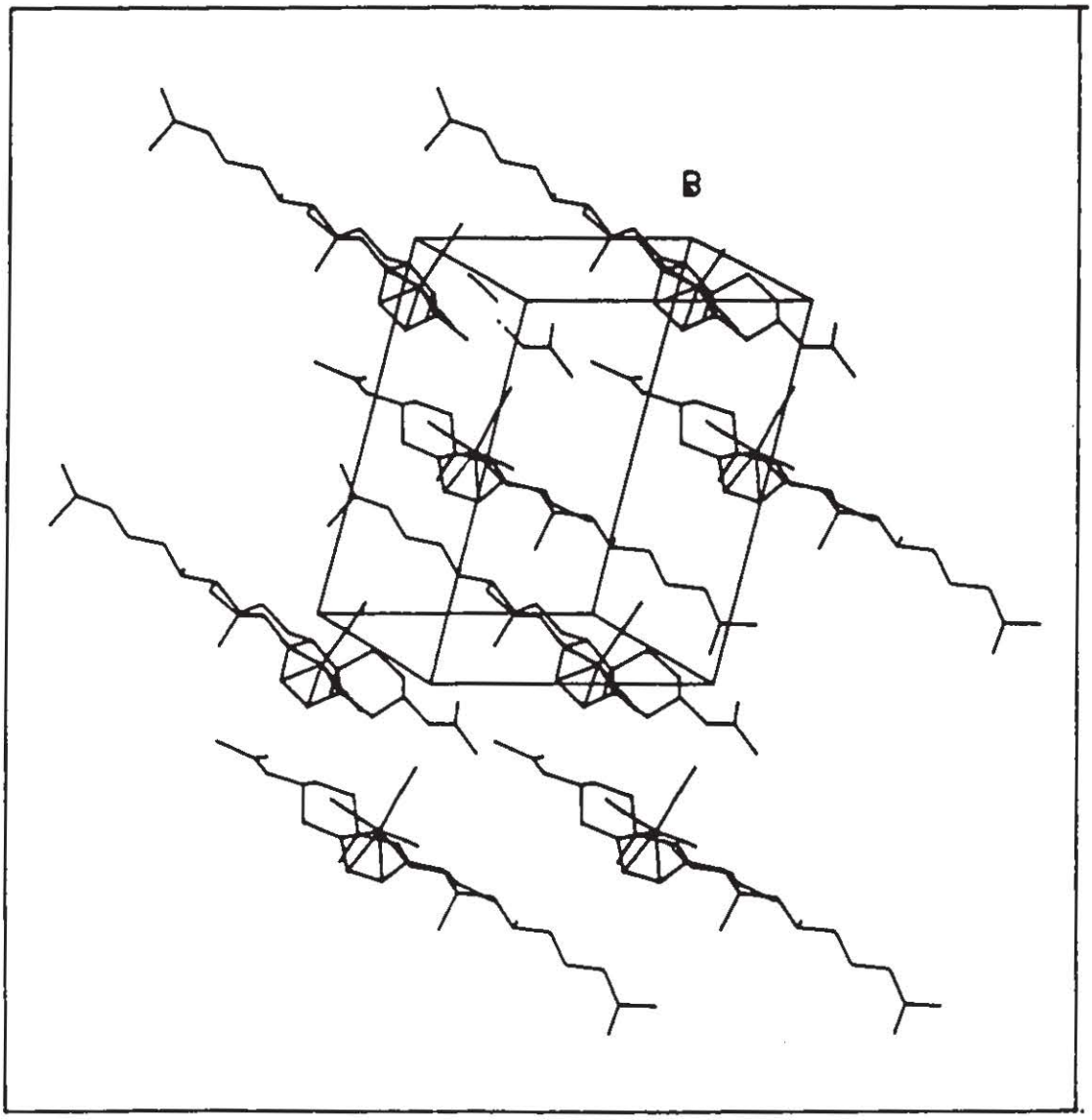

B

Table 4.5 Crystal Data for $[(C_{29}H_{45}O_2Fe(CO)_3]$, 124.

Formula	$C_{32}H_{45}O_5Fe$
f.w.	565.55
System	Triclinic
Space group	P1 No-1
a, Å	11.238(3)
b, Å	14.718(3)
c, Å	10.899(2)
α, °	104.83(2)
β, °	113.77(2)
γ, °	96.75(2)
V, $Å^3$	1544.2(6)
Z	2
Dc,(Dm) g cm^{-3}	1.22, (1.204)
F(000)	606.81 (606)
μ(MoKα), cm^{-1}	5.42 (4.79)
Maximum 2σ reflections collected	45°
No. of reflections collected	4483
No. with $I>3\theta(I)$	3135
No. with $3\theta(I)>I>0$	1348
Final R_1, R_2[a]	0.0572, 0.0668
Weighting scheme	$\omega=(\sigma^2F+0.008126F^2)^{-1}$
Error in observation of unit weight[b]	0.8961
Highest peak, $eÅ^{-3}$; location	0.54; 0.80, 0.12, -0.1
Lowest peak, $eÅ^{-3}$	-0.41

[a] $R_1=\Sigma[|F_o|-|F_c|]/\Sigma|F_o|$; $R_2=(\Sigma\omega(|F_o|-|F_c|)^2/\Sigma\omega F_o^2)^{\frac{1}{2}}$.

[b] $S=(\Sigma\omega(|F_o|-|F_c|)^2/(m-n))^{\frac{1}{2}}$.

m=No. of reflecti,ns, n=No. of variables

Table 4.6 Positional Parameters (x 10^4) and U_{eq} ($Å^2$, x 10^4) for [($C_{29}H_{45}O_2Fe(CO)_3$], 124, with estimated standard deviations in parentheses.

Atom	x	y	z	U_{eq}
Molecule 1.				
Fe(1)	3564(2)	-700(1)	1031(2)	496
C(91)	5037(0)	-77(0)	2769(0)	908
O(91)	5958(0)	3?6(0)	3822(0)	1396
C(92)	4619(0)	-1227(0)	452(0)	702
O(92)	5425(0)	-1555(0)	127(0)	938
C(93)	3402(0)	245(0)	376(0)	703
O(93)	3360(0)	923(0)	-34(0)	895
C(1)	234(12)	-926(8)	-2219(9)	581
C(2)	270(13)	-1638(10)	-3532(12)	776
C(3)	1556(13)	-1931(8)	-3111(11)	693
C(4)	1822(12)	-2392(8)	-2035(10)	585
C(5)	1820(11)	-1752(6)	-677(11)	507
C(6)	2332(11)	-2031(8)	581(10)	492
C(7)	2432(10)	-1331(6)	1848(9)	384
C(8)	1991(9)	-520(6)	1656(10)	351
C(9)	778(10)	-560(6)	336(9)	419
C(10)	555(10)	-1379(8)	-958(10)	461
C(11)	-480(9)	-602(8)	649(9)	435
C(12)	-216(11)	220(9)	2010(10)	560
C(13)	991(9)	218(6)	3269(10)	367
C(14)	2183(9)	362(8)	2970(10)	469
C(15)	3441(13)	574(10)	4387(11)	749
C(16)	2963(10)	1147(9)	5501(12)	590
C(17)	1493(9)	1111(6)	4672(10)	411
C(18)	787(11)	-723(6)	3648(10)	450
C(19)	-633(11)	-2242(8)	-1472(12)	545
C(20)	804(10)	1157(8)	5642(11)	455
C(21)	-778(12)	1056(10)	4884(13)	755
C(22)	1465(11)	2105(8)	6900(10)	552
C(23)	943(11)	2210(6)	8033(10)	462
C(24)	1646(12)	3109(8)	9277(10)	557
C(25)	1095(12)	3324(8)	10326(11)	595
C(26)	1885(13)	4306(9)	11487(11)	730
C(27)	1227(13)	2558(10)	11041(13)	711
O(29)	1533(10)	-2646(6)	-4350(8)	792
C(30)	2340(10)	-2512(9)	-4897(9)	489
O(30)	3167(9)	-1725(6)	-4412(11)	829
C(31)	2117(13)	-3330(10)	-6082(11)	804

Molecule 2.

Fe(2)	4532(0)	5086(0)	7921(0)	388
C(91)	5041(0)	6263(0)	7736(0)	648
O(91)	5340(0)	6943(0)	7551(0)	809
C(92)	3389(0)	5396(0)	8694(0)	508
O(92)	2648(0)	5581(0)	9077(0)	708
C(93)	3091(0)	4562(0)	6223(0)	710
O(93)	2116(0)	4219(0)	5208(0)	884
C(1)	7997(11)	6691(8)	10782(11)	587
C(2)	7967(12)	7030(9)	12221(11)	698
C(3)	6559(11)	6705(8)	11993(10)	519
C(4)	6051(11)	5607(8)	11380(10)	506
C(5)	6142(0)	5226(0)	9971(0)	445
C(6)	5392(10)	4219(6)	9108(10)	444
C(7)	5383(10)	3924(6)	7757(10)	420
C(8)	6064(9)	4583(6)	7370(9)	321
C(9)	7411(9)	5309(6)	8514(9)	351
C(10)	7506(9)	5579(6)	10052(9)	339
C(11)	8625(10)	4967(9)	8385(11)	546
C(12)	8468(10)	4753(9)	6848(11)	600
C(13)	7162(9)	3978(6)	5756(10)	406
C(14)	5968(10)	4352(6)	5956(9)	420
C(15)	4725(9)	3721(8)	4594(10)	492
C(16)	5174(11)	3389(10)	3476(11)	613
C(17)	6710(11)	3768(8)	4142(9)	478
C(18)	7163(11)	3009(6)	6115(11)	487
C(19)	8509(11)	5055(9)	10949(11)	594
C(20)	7433(10)	3124(8)	3504(10)	490
C(21)	8953(10)	3609(10)	4175(12)	691
C(22)	6746(12)	2881(9)	1808(11)	580
C(23)	7129(12)	2082(10)	1134(12)	682
C(24)	6544(13)	1857(9)	-548(12)	696
C(25)	6799(13)	983(11)	-1271(13)	840
C(26)	5914(13)	31(11)	-1595(16)	992
C(27)	7098(15)	1003(13)	-2404(16)	1070
O(29)	6694(8)	7033(6)	13443(6)	609
C(30)	5557(13)	7222(11)	13495(12)	769
O(30)	4469(10)	7050(9)	12547(10)	901
C(31)	5933(13)	7727(12)	15217(12)	912

$U_{eq}=1/3(U_{11}+U_{22}+U_{33}+2\cos\alpha U_{23}+2\cos\beta U_{13}+2\cos\gamma U_{12})$

Table 4.7 Selected Bond Lengths (Å) for 7-Dehydrocholesteryl $Fe(CO)_3$, 124 with estimated standard deviations in parentheses.

Bond	Molecule 1	Molecule 2
Fe Coordination		
Fe-C91	1.843(1)	1.851(1)
Fe-C92	1.725(2)	1.832(2)
Fe-C93	1.714(2)	1.793(2)
Fe-C5	2.139(8)	2.169(8)
Fe-C6	2.077(11)	2.084(11)
Fe-C7	2.081(13)	2.060(11)
Fe-C8	2.155(12)	2.192(11)
C91-091	1.149(0)	1.111(0)
C92-092	1.206(0)	1.103(0)
C93-093	1.192(0)	1.135(0)
Steroidal Skeleton		
C1-C2	1.56(2)	1.54(2)
C1-C10	1.61(2)	1.55(1)
C2-C3	1.48(2)	1.50(2)
C3-C4	1.45(2)	1.52(2)
C3-O29	1.48(2)	1.47(1)
C4-C5	1.54(2)	1.54(1)
C5-C6	1.44(2)	1.47(1)
C5-C10	1.53(2)	1.52(1)
C6-C7	1.45(2)	1.42(2)
C7-C8	1.38(2)	1.41(2)
C8-C9	1.51(1)	1.55(1)
C8-C14	1.59(1)	1.45(2)
C9-C10	1.51(1)	1.58(2)
C9-C11	1.58(2)	1.55(2)
C10-C19	1.53(2)	1.59(2)
C11-C12	1.55(1)	1.55(2)
C12-C13	1.49(1)	1.54(1)
C13-C14	1.51(2)	1.58(2)
C13-C17	1.58(1)	1.55(1)
C13-C18	1.56(2)	1.57(2)
C14-C15	1.54(1)	1.53(1)
C15-C16	1.61(2)	1.49(2)
C16-C17	1.52(1)	1.54(2)
C17-C20	1.54(2)	1.53(2)
C20-C21	1.60(2)	1.55(2)
C20-C22	1.53(1)	1.61(1)
C22-C23	1.55(2)	1.43(2)
C23-C24	1.48(1)	1.60(2)

C24-C25	1.49(2)	1.45(2)
C25-C26	1.53(1)	1.49(2)
C25-C27	1.51(2)	1.41(3)
C30-O29	1.29(2)	1.47(2)
C30-O30	1.19(1)	1.18(1)
C30-C31	1.43(2)	1.68(2)

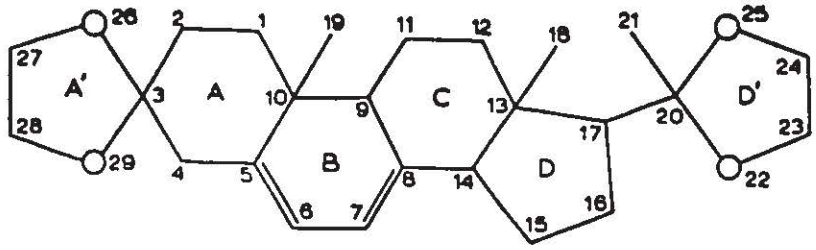
Table 4.8 Selected Bond Angles (°) for 7-Dehydrocholesteryl Acetate $Fe(CO)_3$, 124, with estimated standard deviations in parentheses.

Angle	Molecule 1	Molecule 2
Fe Coordination		
Fe-C91-O91	174.6(1)	176.3(1)
Fe-C92-O92	175.8(1)	175.9(1)
Fe-C93-O93	176.6(1)	173.9(1)
C91-Fe-C92	87.8(1)	99.0(1)
C91-Fe-C93	99.5(1)	97.2(1)
C91-Fe-C5	162.2(4)	101.4(4)
C91-Fe-C6	122.2(3)	138.6(3)
C91-Fe-C7	95.0(2)	127.9(3)
C91-Fe-C8	99.4(2)	89.3(3)
C92-Fe-C93	103.2(1)	88.0(1)
C92-Fe-C5	92.2(4)	92.9(4)
C92-Fe-C6	93.2(4)	98.1(4)
C92-Fe-C7	125.0(3)	131.7(4)
C92-Fe-C8	161.5(3)	168.0(3)
C93-Fe-C5	97.9(4)	161.0(4)
C93-Fe-C6	135.8(3)	120.8(2)
C93-Fe-C7	130.1(3)	95.8(2)
C93-Fe-C8	92.5(3)	99.5(2)
C5-Fe-C6	40.0(4)	40.2(2)
C5-Fe-C7	70.5(4)	69.5(2)
C5-Fe-C8	75.8(4)	76.9(2)
C6-Fe-C7	40.8(4)	40.1(5)
C6-Fe-C8	68.6(4)	70.0(5)
C7-Fe-C8	37.9(4)	38.7(4)
Steroidal Skeleton		
C1-C2-C3	110.9(9)	108.8(8)
C1-C10-C5	110.2(11)	109.3(8)
C1-C10-C9	108.2(9)	109.3(9)
C1-C10-C19	106.9(8)	110.6(7)
C2-C1-C10	110.9(10)	112.9(11)
C2-C3-C4	113.7(13)	111.7(11)
C2-C3-O29	109.8(8)	102.7(7)
C3-C4-C5	112.7(10)	110.0(10)
C3-O29-C30	124.6(9)	113.3(8)
C4-C3-O29	106.0(10)	109.0(10
C4-C5-C6	118.5(10)	114.9(7)
C4-C5-C10	113.5(8)	114.9(5)
C4-C5-Fe	123.0(9)	122.6(4)
C5-C6-C7	114.7(10)	113.4(9)
C5-C6-Fe	72.3(6)	73.0(5)
C5-C10-C9	110.1(7)	110.4(5)

Table 4.9 Endocyclic Torsional Angles (°) for 124

Angle	Molecule 1	Molecule 2
Fe Coordination		
O91-C91-Fe-C5	-168.1	127.5
O91-C91-Fe-C6	-166.1	109.0
O91-C91-Fe-C7	-133.5	54.7
O91-C91-Fe-C8	-95.6	51.0
O92-C92-Fe-C5	-171.6	177.6
O92-C92-Fe-C6	-131.6	-142.2
O92-C92-Fe-C7	-104.0	-117.5
O92-C92-Fe-C8	-123.1	-150.9
O93-C93-Fe-C5	-160.4	68.1
O93-C93-Fe-C6	-175.1	72.9
O93-C93-Fe-C7	-128.5	106.4
O93-C93-Fe-C8	123.6	145.3
Steroidal Skeleton		
C1-C2-C3-C4	58.2	60.8
C2-C3-C4-C5	-56.9	-57.1
C3-C4-C5-C10	52.5	51.7
C4-C5-C-10-C1	-48.4	-49.1
C5-C10-C1-C2	49.3	52.4
C5-C6-C7-C8	1.7	0.3
C6-C7-C8-C9	38.0	36.6
C7-C8-C9-C10	-29.0	-28.5
C8-C9-C10-C5	-16.2	-11.9
C8-C14-C13-C12	-63.4	-55.5
C8-C9-C11-C12	52.5	53.0
C9-C10-C5-C6	53.8	49.5
C9-C8-C14-C13	62.7	53.5
C9-C11-C12-C13	-55.4	-57.8
C10-C1-C2-C3	-53.6	-58.8
C10-C5-C6-C7	-47.4	-45.1
C11-C9-C8-C14	-54.8	-50.7
C11-C12-C13-C14	60.0	55.5
C13-C14-C15-C16	-32.9	-24.9
C13-C17-C16-C15	21.1	21.1
C14-C15-C16-C17	6.0	2.6
C14-C13-C17-C16	-40.5	-35.4
C15-C14-C13-C17	46.1	37.4
C16-C17-C20-C22	60.7	52.9

choice for this comparison would involve the crystal structure of 7-dehydrocholesteryl acetate or possibly, ergosteryl acetate; however, their structures have yet to be determined as they crystallize as very thin platelets. Nevertheless, a comparison was made with the crystal structure of the 3-20-bis(ethylenedioxy) analogue of ergosterol, 127, reported by Romer's group.[152]

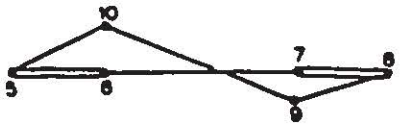


127

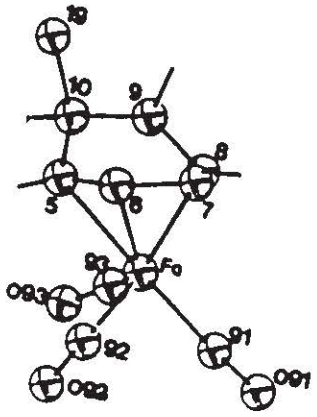
When relating the two structures, one would anticipate that any discrepancies would be localized in the B-ring. This is indeed the result as evidenced by the difference in their B-ring conformations. Specifically, in 127, the B-ring resides in a half-chair conformer where C-5, C-6, C-7, and C-8 are coplanar with C-10 and C-9, respectively, lying above and below this plane. In contrast, this ring, in the $Fe(CO)_3$ complex's structure, sits in an envelope conformation where both C-10 and C-9 lie above the generated plane. Such an arrangement is typical of the X-ray crystal structures of (cyclohexadiene)$Fe(CO)_3$ complexes, vide infra.

In order to quantify this difference in conformations, one can utilize the asymmetry parameters, ΔC_s and

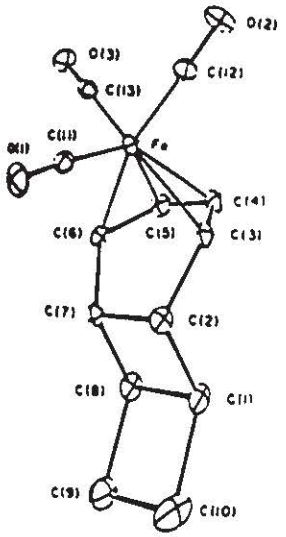
B RING CONFORMATIONS



Romer's Structure, 127



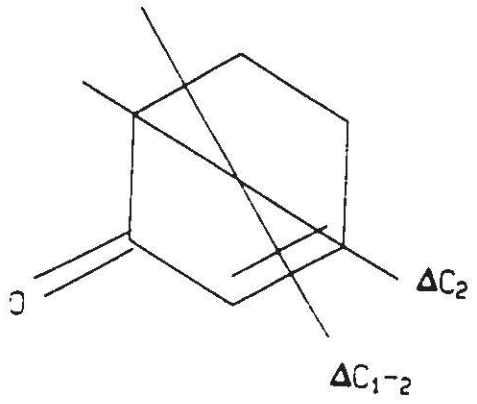
This Work



Typical (cylcohexadienyl)

$Fe(CO)_3$ Complex (Ref. 155)

ΔC_2, calculated from the endocyclic torsional angles.[153] As demonstrated in Chapter 3.4, these parameters provide a measure of the deviation from an ideally symmetrical conformation, i.e., low values of ΔC_s and ΔC_2 indicate a high degree of symmetry in the ring about that mirror plane or two-fold rotation. Table 4.10 furnishes a list of the asymmetry parameters for the B-ring, as well as those for remaining three rings, for Romer's and the two determined structures. It should be noted that each asymmetry parameter includes the lower numbered atom or bond intersected by the symmetry element, thereby identifying its position.



In dealing with the B-ring first, there is a marked difference in the parameters having the lowest value. All remaining parameters have much higher values, thereby

Table 4.10 Asymmetric Parameters for the Crystal structure of 7-Dehydrocholesteryl Acetate $Fe(CO)_3$, 124, and 3,20-bis(ethylene) analogue of Ergosterol, 127.

PARAMETER	124		127
	Molecule 1	Molecule 2	
Ring A			
$\Delta C_s(1)$	6.68	8.30	17.75
$\Delta C_s(2)$	5.64	3.31	9.32
$\Delta C_s(3)$	1.11	5.00	8.54
$\Delta C_2(1-2)$	8.70	8.20	19.00
$\Delta C_2(2-3)$	4.35	1.30	1.58
$\Delta C_2(3-4)$	5.46	9.40	18.56
Ring B			
$\Delta C_s(5)$	10.37	8.55	39.13
$\Delta C_s(6)$	64.32	60.70	24.43
$\Delta C_s(7)$	54.06	52.26	16.78
$\Delta C_s(6-7)$	18.22	16.02	45.06
$\Delta C_2(5-6)$	52.77	48.85	43.53
$\Delta C_2(6-7)$	83.72	79.87	4.00
$\Delta C_2(5-10)$	39.30	51.67	39.53
Ring C			
$\Delta C_s(8)$	8.21	2.54	16.86
$\Delta C_s(9)$	4.83	2.82	4.80
$\Delta C_s(11)$	3.46	4.09	21.49
$\Delta C_2(8-9)$	9.17	1.66	8.63
$\Delta C_2(8-14)$	8.07	3.83	27.01
$\Delta C_2(9-11)$	1.95	5.22	18.67
Ring D			
$\Delta C_s(13)$	9.24	3.04	6.00
$\Delta C_s(14)$	26.11	24.82	84.42
$\Delta C_s(15)$	51.18	44.27	54.56
$\Delta C_s(16)$	19.30	13.33	57.25
$\Delta C_s(17)$	39.31	40.03	39.27

indicating the ring's conformation lacks most of the elements needed for a perfectly symmetrical conformation. In particular, it was noticed that in 124 the lowest value was calculated for the $\Delta C_{s(5)}$ parameter while for Romer's structure, it was the $\Delta C_{2(6-7)}$ parameter. These values confirmed the observation of differing B-ring conformations, that is, half chair versus envelope, as well as revealing the highest element of symmetry in these rings.

Moving on to the asymmetry parameters of the other rings, the relatively low values calculated for all ΔC_s's and ΔC_2's in the A- and C-rings indicated that these rings adopt a slightly distorted chair conformation. One can visualize this by focussing the attention to the A-ring's conformation in Figure 4.5. When relating these values to those obtained for Romer's molecule, it appears that the rings in the determined structure are much more symmetrical in nature. Finally, the D-ring in all structures has a 13β envelope conformation as evidenced by $\Delta C_{s(13)}$ having the lowest value. This is further substantiated when one calculates the pseudo-rotational parameters, Δ and ϕ_m, developed by Altoona and co-workers.[154] The value of these parameters can be utilized to ascertain whether the D-ring resides in a half-chair conformation (Δ = 0°) or the C-13 or C-14 envelope conformations, Δ = +36° or - 36°, respectively. When calculated for the determined structures, it appears that the D-ring sits mainly in a C-13 envelope conformation (Δ = +29° and +18°).

As a result of these calculations, one can rationalize that the determined crystal structure for the $Fe(CO)_3$ complex of 7-dehydrocholesteryl acetate compares quite favourably to the structure reported by Romer's group. The only major discrepancy is the difference in their B-ring's conformation. As alluded to earlier, the envelope conformation observed in the determined structure is universal to crystal structures of (cyclohexadienyl)$Fe(CO)_3$ complexes, thus one might desire to relate them as 124 appears to be essentially a heavy substituted (cyclohexadiene)$Fe(CO)_3$ complex.

Table 4.11 lists the typical structural parameters for (diene)$Fe(CO)_3$[155] as well as those determined in 124. It is readily apparent that 124 does not deviate from the norm as the determined bond lengths and angles lie well within the range of typically observed angles. This table, also, includes the values for the fold angle, a structural feature of cyclic diene $Fe(CO)_3$ complexes, whereby the substituents out of the diene plane are folded through the outer diene carbon atoms, i.e., the envelope conformation. It was observed that the determined fold angle for the determined structures was 38.9°. From these data, one can surmise that the $Fe(CO)_3$ tripodal unit is bound in a typical π fashion to the C-5/C-6 and C-7/C-8 double bonds as evidenced by the fact that the Fe-C(inner) bond distance is shorter than the Fe-C(outer) ones.

As a result of these calculations, one can rationalize that the determined crystal structure for the $Fe(CO)_3$ complex of 7-dehydrocholesteryl acetate compares quite favourably to the structure reported by Romer's group. The only major discrepancy is the difference in their B-ring's conformation. As alluded to earlier, the envelope conformation observed in the determined structure is universal to crystal structures of (cyclohexdienyl)$Fe(CO)_3$ complexes, thus one might desire to relate them as 124 appears to be essentially a heavy substituted (cyclohexadiene)$Fe(CO)_3$ complex.

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Table 4.11
Typical Structural Parameters for (diene)$Fe(CO)_3$ Complexes

Bond Lengths (Å)	Range	Mean	124
Fe-C(inner)	2.03-2.08	2.05	2.08
Fe-C(outer)	2.10-2.16	2.13	2.15
C-C(inner)[2]	1.386-1.426	1.404	1.449
C-C(outer)[2]	1.394-1.434	1.409	1.411
Bond Angles (°)			
a	89-94	92	93.6
b	95-103	103	103.2

In summary, it is apparent that incorporation of a $Fe(CO)_3$ group invokes a conformational change to the B-ring of the steroidal skeleton from the typical half chair conformer to an envelope. As a result, the determined structure for the $Fe(CO)_3$ complex of 7-dehydrocholesteryl acetate very much resembled a typical (cyclohexadiene)$Fe(CO)_3$ complex. The following section will focus on the efforts made to extend the synthetic potential of this complex.

4.4 SYNTHESIS OF A (CYCLOHEXADIENYL)$Fe(CO)_3$ CATIONIC COMPLEX

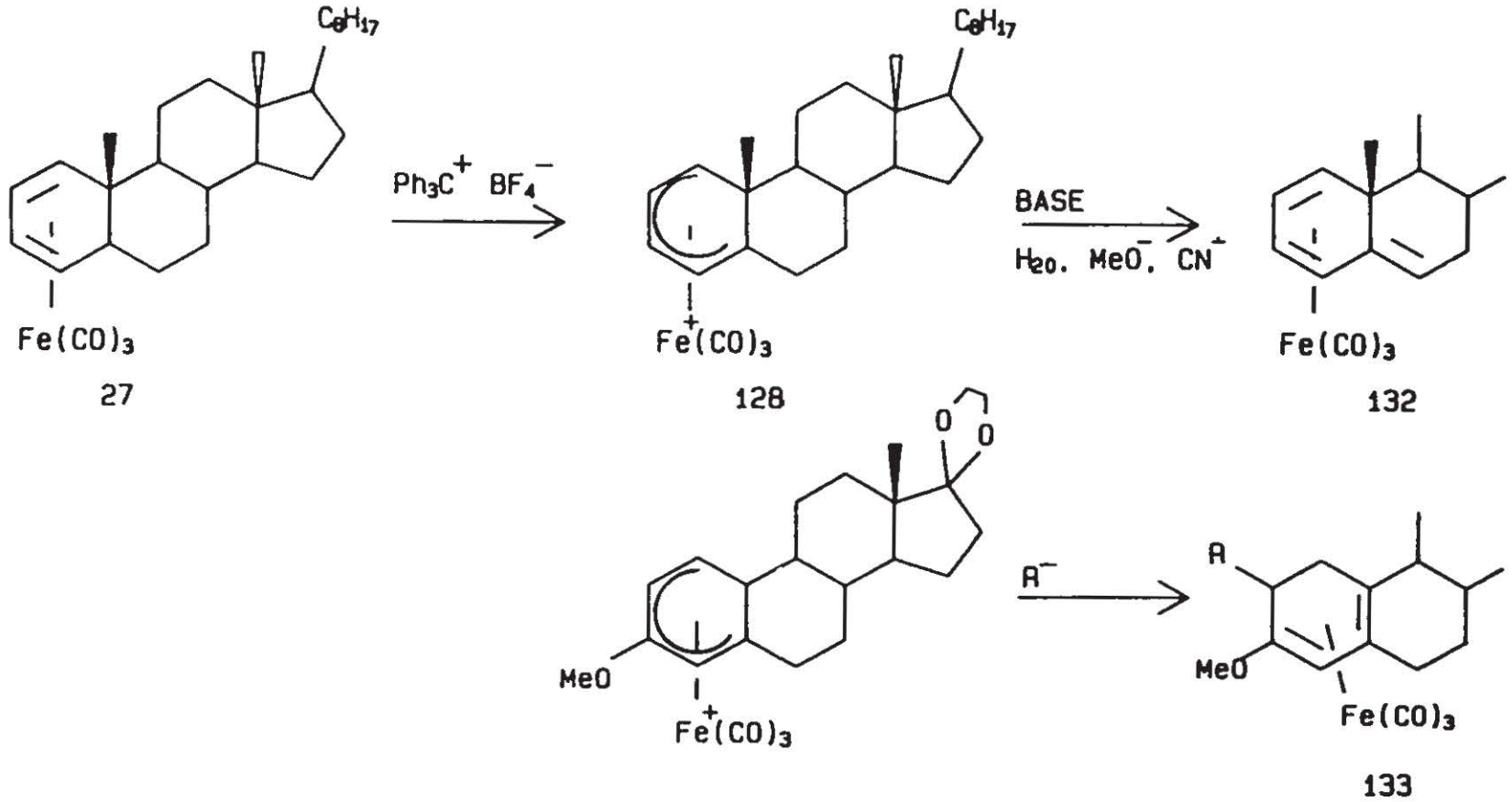
As alluded to earlier in this chapter, these steroidal $Fe(CO)_3$ complexes can be examined from a slightly more organic point of view. Birch's and Pearson's groups[156,157] have amply demonstrated the utilization of (cyclohexadienyl)$Fe(CO)_3$ cationic complexes as synthetic intermediates as illustrated in Section 1.3. Bearing this in mind, it was postulated that one could generate a cation of this type in the B-ring of ergosteryl acetate with the aim of synthesizing new B-ring modified ergosteryl derivatives after the addition of nucleophiles to this steroidal cation. Such a steroidal (cyclohexadienyl) $Fe(CO)_3$ cationic complex would not be the first to be synthesized as Alper's group[158] has prepared an A-ring steroidal cyclohexadienyl $Fe(CO)_3$ cation complex, 128, by the treatment of the iron tricarbonyl complex of cholesta-2,4-diene with triphenylmethyl cation which was known to preferentially abstract a hydride from a

position trans to the organometallic fragment (see Scheme 4.2). Initially, it was hypothesized that treatment of ergosteryl acetate $Fe(CO)_3$, 11, with trityl cation could generate the desired cationic complex. However, the proton to be abstracted, 9α, is rendered completely inaccessible to the attacking reagent by the bulky $Fe(CO)_3$ group, thus this reaction did not work when attempted.

An alternative approach, therefore, had to be developed to generating the desired cation, and a literature search revealed that ergosteryl derivatives can readily be converted into their 9,11-dehydro analogues, 129, via treatment with mercuric acetate.[159] This particular steroidal system, which contains an exocyclic double bond between C-9 and C-11 is ideally set up after complexation with an $Fe(CO)_3$ group for protonation at C-11, thereby generating the desired cationic complex (see Scheme 4.3). Subsequently, this series of experiments was performed beginning with the conversion of ergosteryl acetate into dehydroergosteryl acetate and its complexation by a $Fe(CO)_3$ moiety, 130, using the (benzylideneacetone)$Fe(CO)_3$ precursor. Addition of HPF_6 to an ethereal solution of the purified neutral $Fe(CO)_3$ complex resulted in the formation of 131 as its air-stable PF_6^- salt in 24% overall yield.

Both the neutral and cationic $Fe(CO)_3$ complexes were characterized by 2D NMR spectroscopy with Tables 4.12 and 4.13 listing the complete ^1H and ^{13}C NMR assignments. Once

SCHEME 4.2


C8H17
Fe(CO)3
27
Ph3C+ BF4−
C8H17
Fe+(CO)3
128
BASE
H2O, MeO−, CN−
Fe(CO)3
132
O
O
MeO
Fe+(CO)3
R−
R
MeO
Fe(CO)3
133

SCHEME 4.3

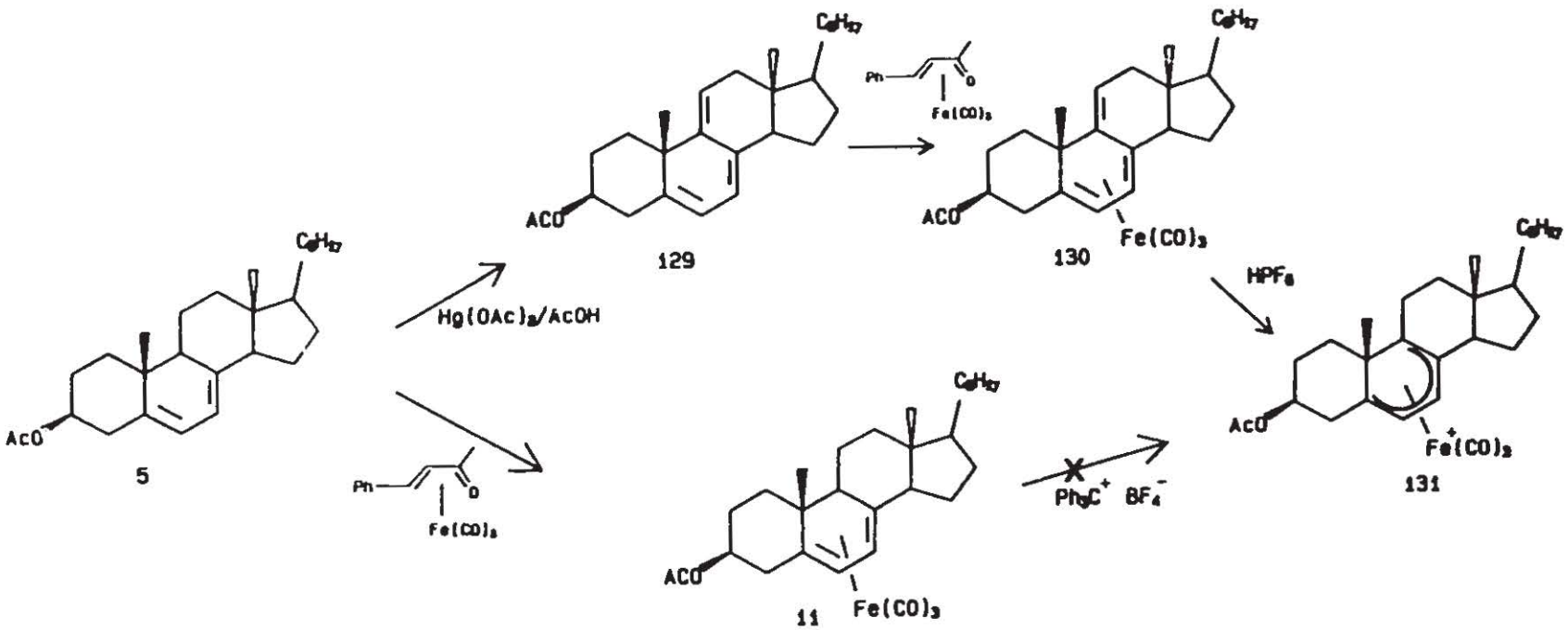

AcO
5
Hg(OAc)₂/AcOH
ACO
129
Ph
O
Fe(CO)₃
ACO
Fe(CO)₃
130
HPF₆
AcO
Fe(CO)₃
131
ACO
Fe(CO)₃
11
Ph₃C⁺ BF₄⁻

Table 4.12. ^{1}H NMR Chemical Shifts for Dehydroergosterol acetate 129 and its $Fe(CO)_3$ 130 and $Fe(CO)_3^+$ 131 Complexes.

Proton	129 C_6D_6	130 C_6D_6	131 CD_3CN
1α	1.55	1.21	2.35
1β	1.78	1.65	2.12
2α	1.90	2.00	2.05
3α	4.90	5.10	4.90
4α	2.50	2.10	2.25
4β	2.50	1.90	1.88
6	5.70	5.12	6.85
7	5.50	4.50	5.53
11α	5.42	5.00	1.98
11β	5.42	5.00	1.68
12α	2.25	1.85	1.85
12β	2.38	2.00	2.38
14α	2.25	2.15	1.95
15α	1.72	1.58	1.82
15β	1.42	1.20	1.35
16α	1.85	1.85	1.75
16β	1.35	1.60	1.45
17	1.25	1.00	1.20
18Me	0.65	0.50	0.58
19Me	1.21	0.95	0.82
20	2.05	1.94	1.95
21Me	1.05	0.99	0.90
22	5.18	5.00	5.10
23	5.30	5.08	5.21
24	1.95	1.90	1.85
25	1.50	1.50	1.30
26Me	0.92	0.80	0.75
27Me	0.92	0.90	0.75
28Me	1.00	1.00	0.85
30Me	1.78	2.00	1.95

Table 4.13 ^{13}C NMR Chemical Shifts for Dehydroergosteryl acetate 129 and its $Fe(CO)_3$ 130 and $Fe(CO)_3^+$ 131 Complexes.

Carbon	129 C_6D_6	130 C_6D_6	131 CD_3CN
1	23.19	22.30	35.40
2	28.73	28.64	27.40
3	74.09	73.23	70.90
4	37.93	37.97	25.70
5	140.39	81.66	87.20
6	119.63	81.99	96.00
7	116.55	79.54	85.10
8	144.75	84.20	109.40
9	145.10	147.30	117.00
10	a	38.86	38.19
11	122.25	115.52	23.40
12	43.27	41.37	35.80
13	42.35	43.35	42.90
14	51.43	53.25	51.60
15	29.37	28.02	35.10
16	38.40	36.12	39.50
17	56.34	55.25	54.80
18Me	11.83	11.46	11.80
19Me	30.24	30.16	32.00
20	40.86	40.69	40.80
21Me	20.92	20 85	21.00
22	136.07	135.81	135.50
23	132.33	132.40	132.30
24	43.27	43.23	43.60
25	33.44	33.44	33.80
26Me	19.88	19.89	19.90
27Me	20.20	20.19	20.20
28Me	17.92	17.88	17.90
29(CO)	169.42	169.10	170.00
30Me	20.92	20.85	21.59
FeCO	--	213.47	204.10

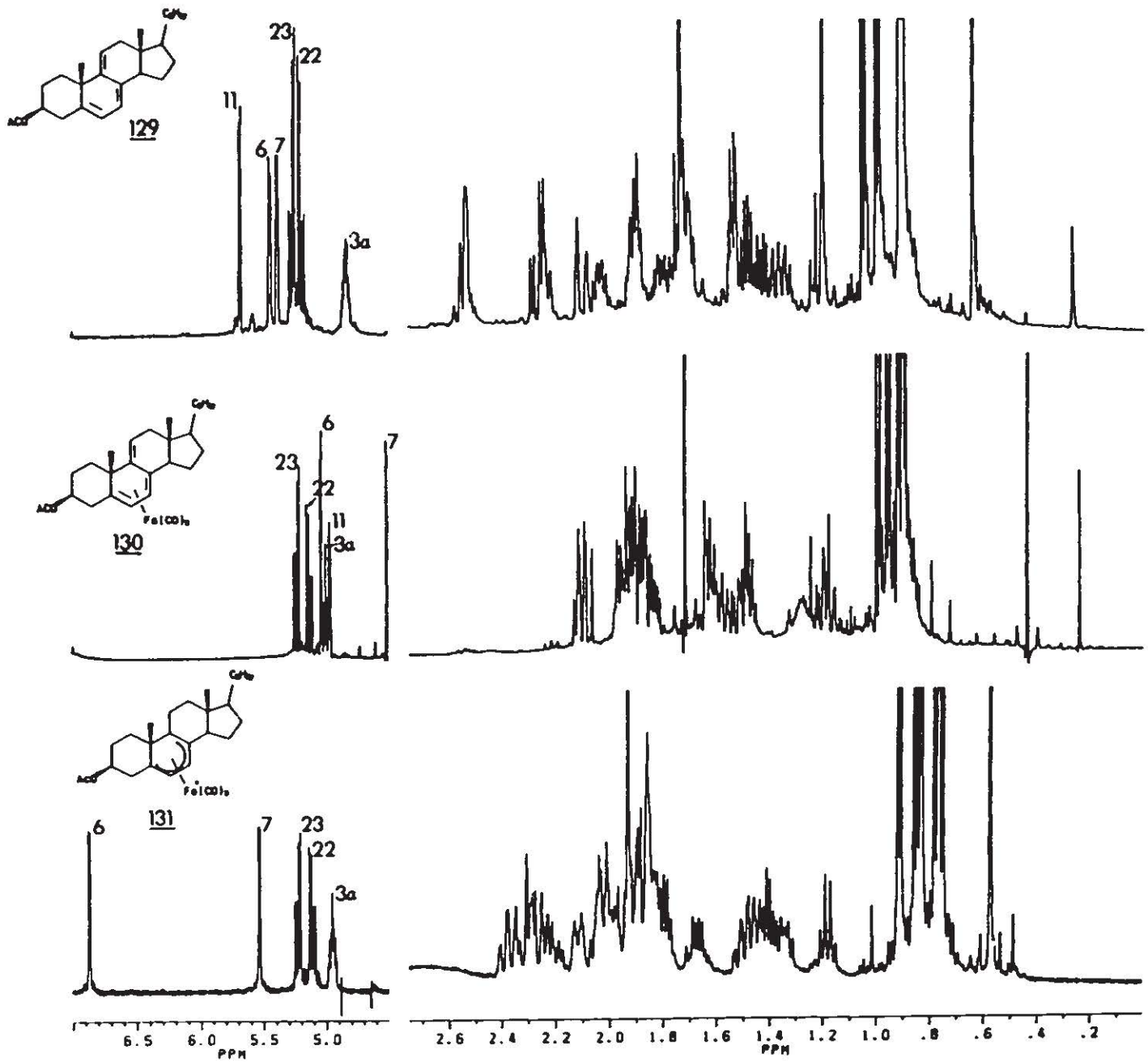
again these results were in complete accord with the previously recorded assignments for ergosteryl acetate $Fe(CO)_3$. It should be noted that the ^1H NMR spectrum of dehydroergosteryl acetate had previously been reported,[160] but this was on a low magnetic field instrument, 100MHz.

Upon scrutinizing the ^1H data, it was apparent one could draw the same conclusions as in the ergosteryl acetate $Fe(CO)_3$ complex. For example, a large upfield shift of nearly 1 ppm for the dienyl proton resonances, H-6 and H-7, was observed upon complexation of the $Fe(CO)_3$ fragment. Upon cation formation, however, these resonances move back to higher frequency with the H-6 signal being deshielded by nearly 1.5 ppm. In addition, the vinylic proton at C-11, which resonates at 5.00 ppm in the neutral complex, changes to a methylene type proton in 131 thus its signal moves upfield thereby confirming the formation of the desired (cyclohexadienyl)$Fe(CO)_3^+$ cation. These features are illustrated in the ^1H NMR spectra for the free steroid and the neutral and cationic complexes presented in Figure 4.7.

Apart from the changes in the chemical shifts of the dienyl protons upon complexation, a further examination of the ^1H NMR spectra confirmed the previous postulate, that the 4α and 4β protons in such complexes lie in the shielding zone of anisotropy of a metal carbonyl fragment. Indeed, it was gratifying to observe an upfield shift in the resonances of these protons in both the neutral and cationic complex; thus

FIGURE 4.7

Sections of the 500MHz ^{1}H NMR Spectra of Dehydroergosteryl Acetate, 129, and its $Fe(CO)_3$, 130, recorded in C_6D_6 and $Fe(CO)_3^+$ Complexes, 131, recorded in CD_3CN.

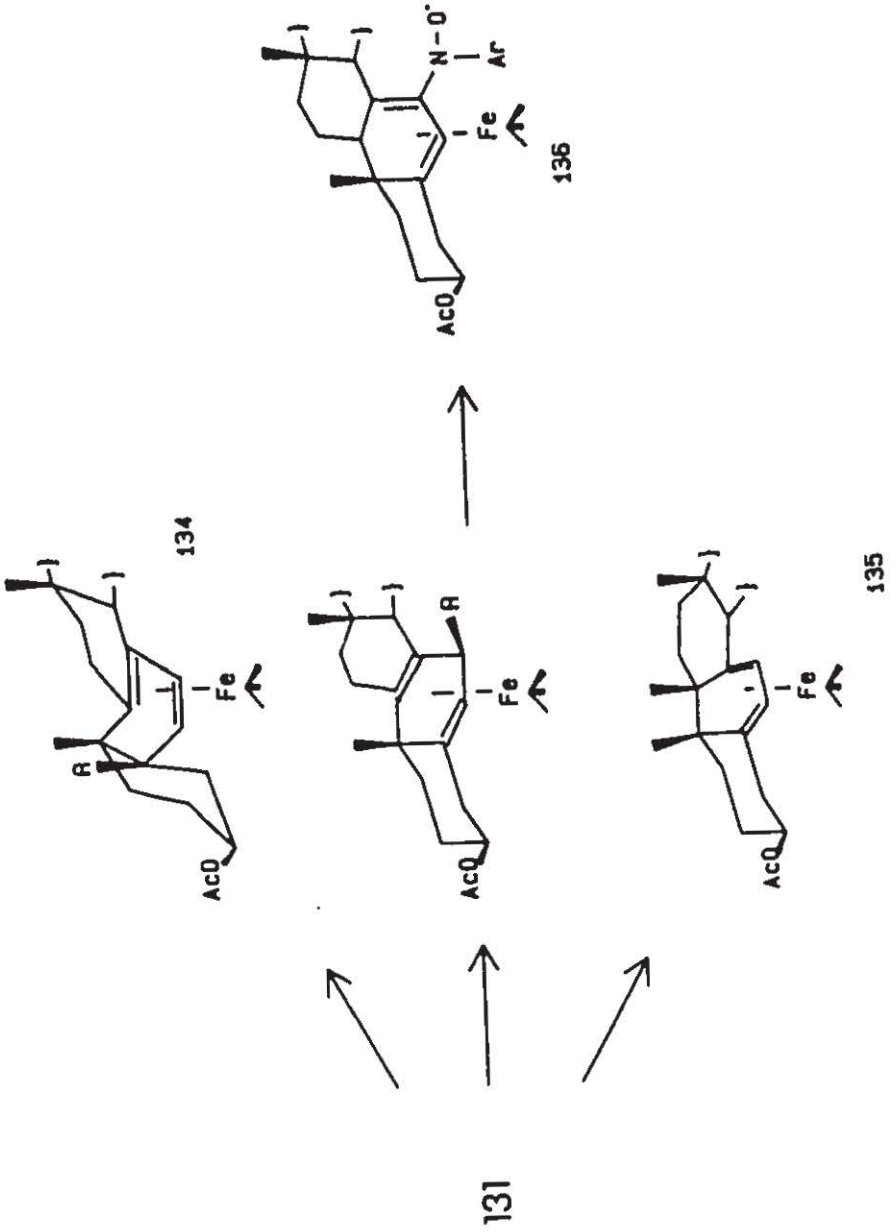

129
11
6
7
23
22
3a
130
6
7
23
22
11
3a
131
6
7
23
22
3a
6.5
6.0
5.5
5.0
PPM
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
.4
.2
PPM

reflecting the proximity of a terminal Fe-C-O ligand.

While the NMR results for these complexes are interesting, the prime reason for synthesizing this cationic complex was to explore its chemistry and conversion into new derivatized B-ring ergosterols. It is well documented by both Pearson's and Alper's groups [157,158] that the addition of nucleophiles to such steroidal (cyclohexadienyl)$Fe(CO)_3$ cations results in the formation of neutral adducts. In particular, the addition of hard nucleophiles, such as methoxide or cyanide ion, yields products having a triene system due to a proton abstraction at C-6, 132. Soft nucleophiles, on the other hand, readily add to a terminal carbon, for example, C-1, 133 (see Scheme 4.2). It was believed that this cation could undergo a similar addition reaction using soft nucleophiles thereby yielding ergosteryl derivatives substituted at either the C-5 or C-9 position, 134,135 (see Scheme 4.4).

When the cation was treated with the soft thiocyanate ion, the only product isolated was the original neutral $Fe(CO)_3$ complex, thus indicating a hydrogen elimination process had occurred. Upon examination of molecular models generated from the MacroModel program,[161] it was apparent that incorporation of nucleophiles at the C-5 or C-9 positions would be difficult due to the presence of the C-19 methyl group. In addition, if attack at the C-5 position was possible, this would invoke a change in the AB

SCHEME 4.4



ring junction from a *trans* fusion to *cis*. It, therefore, appeared that any further reactions involving the steroidal $Fe(CO)_3$ cation with nucleophiles would be fruitless since the elimination product was the only one generated.

Concurrent to these investigations, another member of the laboratory group, Lijuan Li, was examining the reaction of nitroso compounds with diamagnetic organometallic cationic complexes. The basis for this study was a report by Cais' group[162,163] on the reaction of nitrosobenzene with cationic iron complexes having substituted cyclopentadienyl, cycloheptadienyl and other dienyl ligands. The resulting product of this reaction, the nitroxide radical, was characterized by ESR spectroscopy. It therefore occurred that the steroidal iron cation may follow the analogous reactivity pattern established for the unsubstituted (cyclohexadienyl)$Fe(CO)_3^+$ cations. As with the addition of nucleophiles, the nitroso moiety could add to either of the terminal carbons, C-5 or C-9 (see Scheme 4.4). The resulting ESR spectra could be readily distinguished since addition at C-5 would generate a radical whose ESR spectrum would show the characteristic triplet pattern due to coupling through the nitrogen atom as well as an additional weak coupling to the olefinic hydrogen at C-6. In contrast, addition at the C-9 position would result in an ESR spectrum of the simple triplet as there is no alkene hydrogen at C-8. When this experiment was performed with the help of L. Li, the resulting ESR spectrum

resulting ESR spectrum showed the typical 1:1:1 triplet with a_N = 11G for the existance of a nitroxide radical, but also exhibited a further doublet splitting of 2.95G indicating the presence of a single hydrogen only two bonds away from the radical generated (see Figure 4.8).

It was apparent from this spectrum that the aryl nitroso group had not attacked either of the terminal carbons, presumably, due to steric interactions caused by the C-19 methyl, but had attached itself to the more attractive C-7 site. Such an steroidal radical is not unprecedented as Mateos and co-workers have reported the formation of the dimeric bisergostatrienyl benzoate by coupling of a radical generated is coupled at the C-7 position during the photolysis of ergosteryl acetate iron tricarbonyl.[26]

With the radical forming at the C-7 position, the $Fe(CO)_3$ fragment is coordinated to a 1,4 cyclohexadiene system. However, over a short period of time, the ESR spectrum changes with the loss of the doublet splitting. An explanation for this situation is that the radical undergoes a 1,3 hydrogen transfer to produce the more favoured isomer, 136, where the double bond conjugation can be restored. Attempts are currently underway to upgrade this reaction to a larger scale with the aim of reducing the nitroxide radical with $LiAlH_4$ to the more synthetically versatile amino function. The characterization of the resulting neutral compound by 2D NMR methods would verify the postulated

FIGURE 4.8

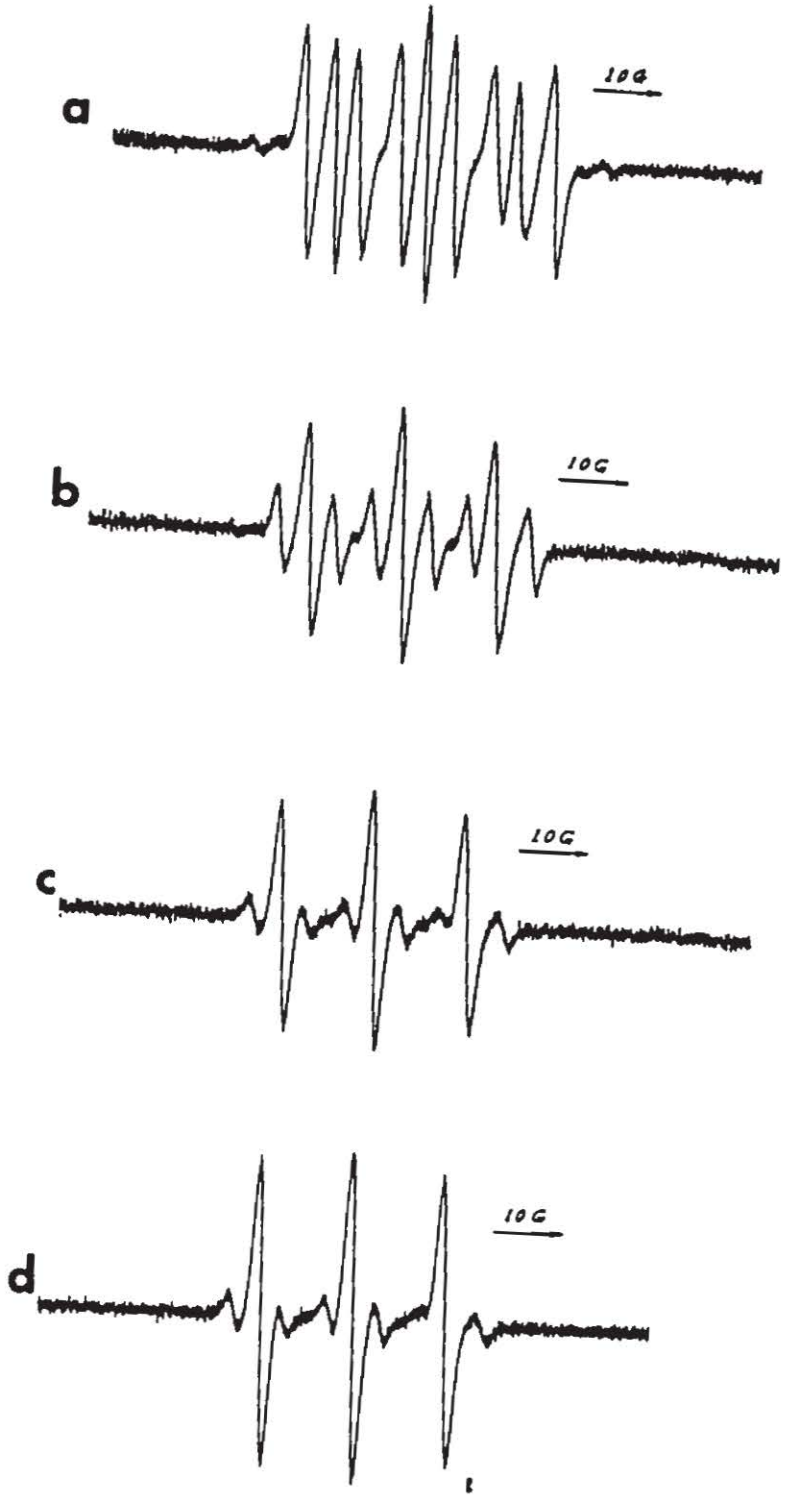
ESR Spectra from the reaction of 131 with C_6Me_5NO in CH_3CN.

a) after 3 hours

b) after 6 hours

c) after 9 hours

d) after 21 hours


a
10G
b
10G
c
10G
d
10G

structure for the original steroidal nitroxide radical.

In closing, this chapter began with a continuation of the approach developed in the previous chapter on the utilization of high field NMR spectrsoscopy to deduce the site of complexation of a $Fe(CO)_3$ and Rh(acac) fragment in the B-ring of the ergosteryl and 7-dehydrocholesteryl acetate series and investigated what influences these groups have on the chemical shifts of nearby protons in the A and C rings. Subsequently, a discussion on the crystal structure determination for the $Fe(CO)_3$ complex of 7-dehydrocholesteryl acetate was provided and its structural features were compared to similar steroidal crystal structures and those of (cyclohexadiene)$Fe(CO)_3$ complexes. In addition, the conversion of the iron tricarbonyl complexes of steroidal dienes into synthetically useful (cyclohexadienyl)$Fe(CO)_3^+$ cations was examined. Although the addition of nucleophiles resulted in the formation of an elimination product, it was illustrated that an nitroso function can be incorporated at the C-7 position.

Concurrent with the protonation of organometallic derivatives of steroids, this study also examined the protonation of much simpler systems, such as the bis(ethylene)Rh(acac) complex. The final chapter is devoted to a discussion of the results obtained for these simpler complexes.

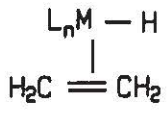
CHAPTER 5

PROTONATION STUDIES OF SIMPLER ORGANOMETALLIC COMPLEXES

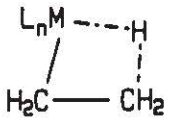
5.1 PREAMBLE

As stated in the previous chapter, the final aspect of this project involved an investigation of the protonation of simpler organometallic complexes, such as $(C_5H_5)Rh(C_2H_4)_2$ and $(acac)Rh(C_2H_4)_2$. The aim of this study was to further elucidate the factors involved in the interconversion of hydrido-olefin complexes into their corresponding alkyl-metal systems. An understanding of such factors is of pivotal importance in catalytic hydrogenation and isomerization processes.[164]

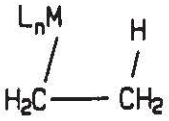
It was originally postulated that the ground state geometry of this interconversion was one of the extremes in which the hydrogen was clearly bonded to the metal, 137, or to a carbon atom, 139,. However, Brookhart and Green[165] have, recently, shown that the minimum energy species is sometimes best viewed as shown in 138 whereby the hydrogen bridges the metal and a carbon atom. This so-called "agostic" interaction has been shown to occur in a wide variety of molecular systems[165] and such behavior has been rationalized using the EHMO approach.[166]



137

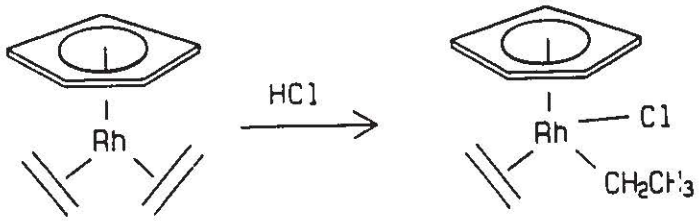


138



139

The chemistry of rhodium-olefin complexes has been elegantly described in series of papers by Cramer. His pioneering efforts showed that the rhodium-catalyzed dimerization of ethylene to give primarily 1-butene proceeds via an $L_nRh(C_2H_4)C_2H_5$ complex which apparently undergoes ethyl--ethylene coupling.[167] Thus, protonation of $(C_5H_5)Rh(C_2H_4)_2$, 140, with HCl at -80° yields $[(C_5H_5)Rh(C_2H_4)(C_2H_5)Cl]$, 141, which decomposes at -10°C to give a product of indeterminate structure (see Figure 5.1).

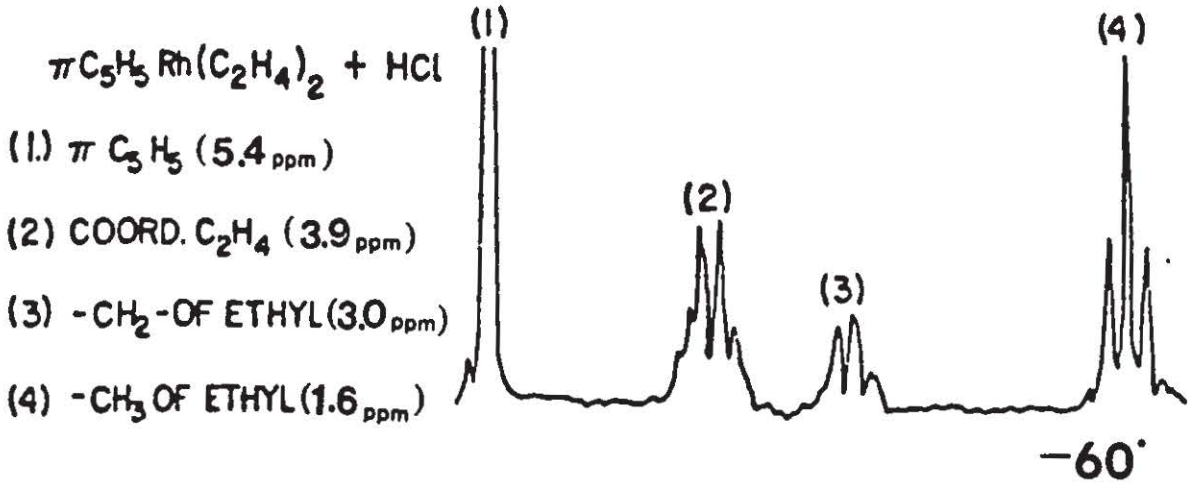


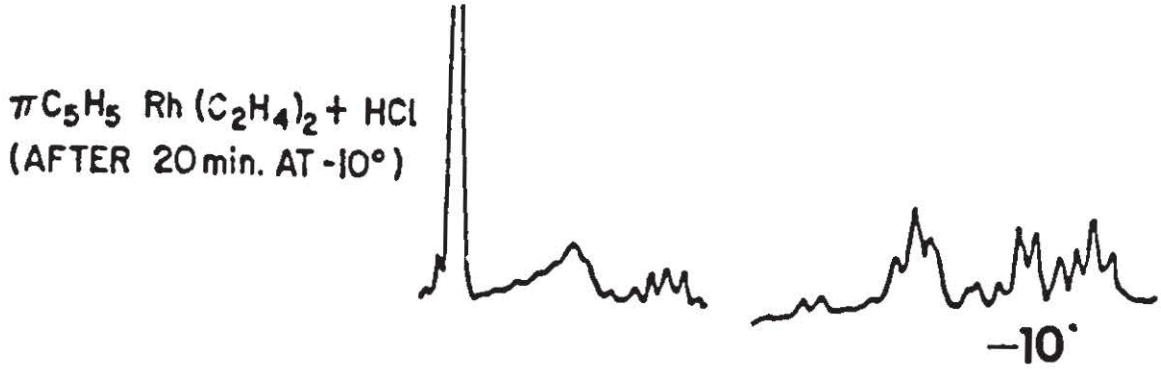
140 141

Recently, Seiwell has extended this work by illustrating that treatment of complexes $(C_5H_5)Rh(C_2H_4)(C_2H_3R)$, 142, where R = F, CN, or CO_2Me, with dry HCl yields mixtures in which both the ethylene and the C_2H_3R ligands are protonated.[168] In addition, analogous interconversions of

FIGURE 5.1

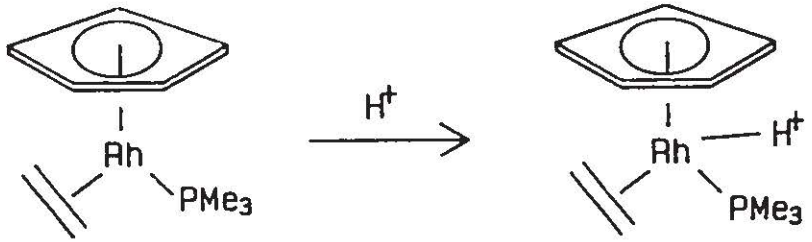
60MHz ^{1}H NMR Spectrum of $CpRh(C_2H_4)_2$ upon Protonation with HCl, recorded by Cramer (Ref. 167).


$\pi C_5H_5Rh(C_2H_4)_2$ + HCl
(1.) π C_5H_5 (5.4 ppm)
(2) COORD. C_2H_4 (3.9 ppm)
(3) $-CH_2-$ OF ETHYL (3.0 ppm)
(4) $-CH_3$ OF ETHYL (1.6 ppm)
(1)
(2)
(3)
(4)
−60°

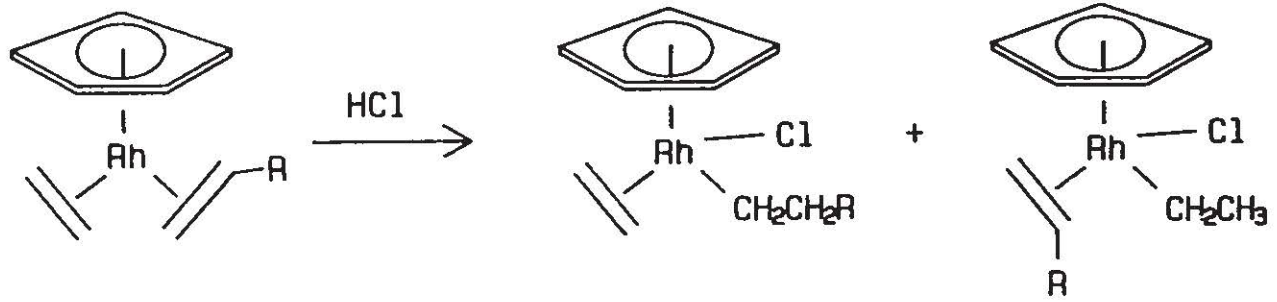

πC_5H_5 Rh $(C_2H_4)_2$ + HCl
(AFTER 20 min. AT -10°)
−10°

bis(ethylene) hydride complexes of molybdenum or cobalt have been reported.[169-171] Of particular relevance is the report by Werner and Feser[172] that protonation of the relatively basic metal atom in $(C_5H_5)Rh(C_2H_4)PMe_3$, 143, occurs to give $[(C_5H_5)Rh(H)(C_2H_4)PMe_3]^+$, 144; in this system, variable-temperature NMR studies, supported by mass spectrometric data on the corresponding deuteronated molecule, clearly revealed the existence of an exchange process which equilibrated the hydrogen (or deuterium) bonded to the metal with the protons in the ethylene. Subsequent to this, Salzer and von Philipsborn[173] have detected an agostic interaction upon low temperature protonation of a series of CpRh(diene) complexes. Furthermore, the literature data on metal-mediated alkyl-alkene couplings, particularly those mechanisms advanced by Cossee[174] and by Green[175], have been thoroughly reviewed by Lehmkuhl.[176]

In continuation of previous work performed by this laboratory group on the protonation and fluxional behavior of (indenyl)Rh(diene) and related systems,[177,178] it was decided that the early work on the protonation $(C_5H_5)Rh(C_2H_4)_2$, 140 and $(acac)Rh(C_2H_4)_2$, 145, be re-examined in order to see whether these reactions could be better understood by following their course by high field NMR spectroscopy at 11.7 Tesla (500 MHz for ^1H; 125 MHz for ^{13}C). In particular, it is hoped that the steps involved in the coupling of the ethyl and ethylene ligands on rhodium could be elucidated.



143 144



R = F, CN, CO_2Me 142

5.2 PROTONATION OF $(C_5H_5)Rh(C_2H_4)_2$

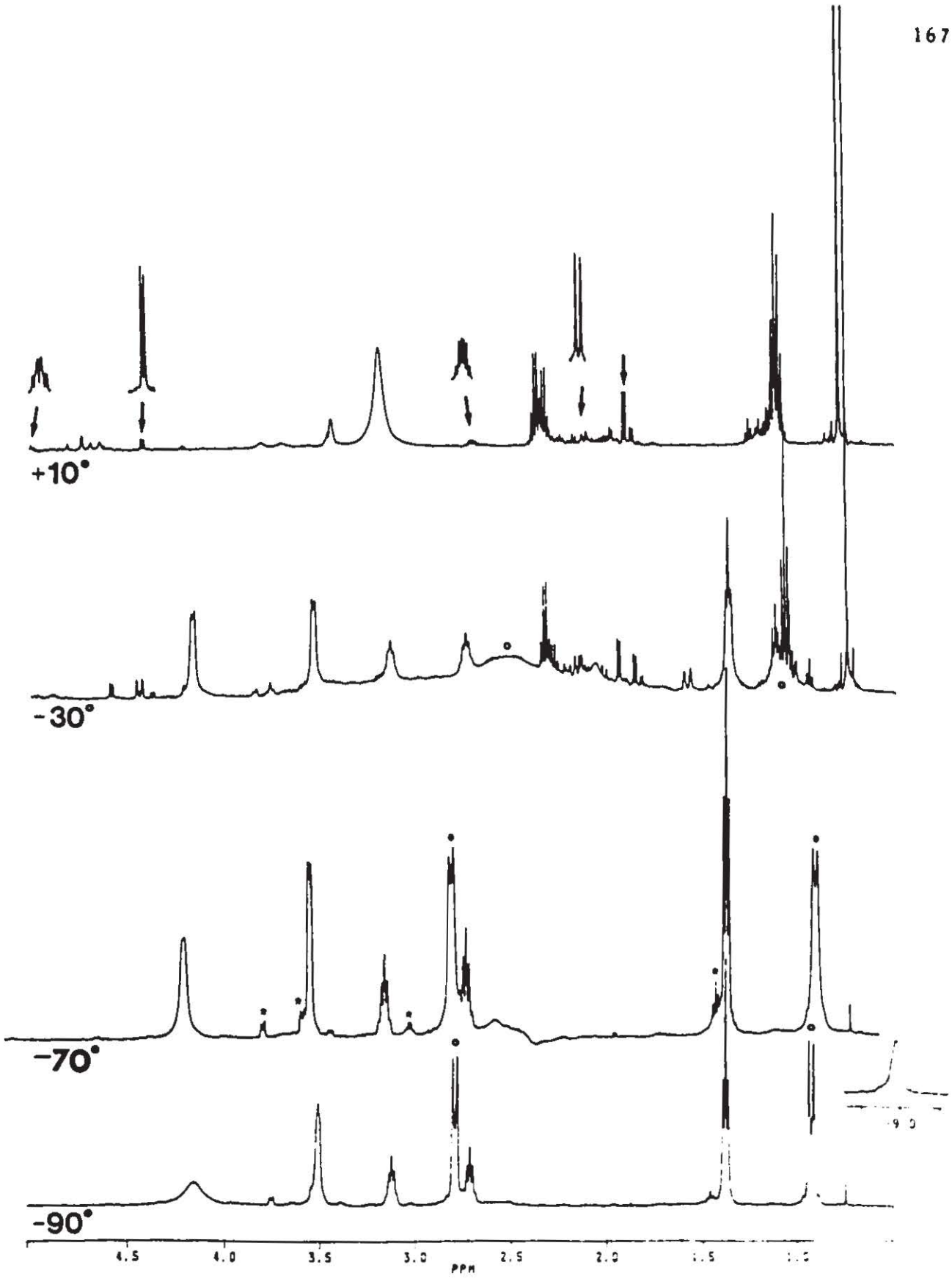
$(C_5H_5)Rh(C_2H_4)_2$, 140, was prepared via literature procedures,[167] Both its 500MHz ^1H and ^{13}C NMR spectra were in complete accord with published results on lower field spectrometers. The 500MHz ^1H NMR spectrum at room temperature exhibited a cyclopentadienyl doublet (5H) with J_{Rh-H} = 0.52 Hz at δ 5.2 and two broad resonances (each 4H) attributable to "outside" and "inside" ethylene protons[179] at δ 2.87 and δ 1.00, respectively. The 125 MHz ^{13}C NMR spectrum at room temperature exhibited a cyclopentadienyl resonance at δ 87.56 and a rhodium-coupled doublet (J_{Rh-C} = 11.6 Hz) at δ 36.1 for the coordinated alkene.

Upon protonation of $(C_5H_5)Rh(C_2H_4)_2$ in CD_2Cl_2 at -90°C using CF_3CO_2H, significant changes occurred, the most visible being a color change from yellow to deep red. In addition, both the ^1H and ^{13}C NMR spectra of the reaction product at -90° had subtle features not visible in the original spectra.

Dealing first with the ^1H NMR spectrum at -90°C which appears in Figure 5.2, one observes a singlet attributable to a cyclopentadienyl ring at δ 5.19, and an ethyl group with a methyl triplet at δ 1.39 and its corresponding methylene signals (both apparent quintets each 1H) at δ 3.15 and δ 2.73. As well, there is a broad peak (2H) at δ 4.17 and another peak (2H) at δ 3.53; these peaks are assignable to a coordinated ethylene ligand. Finally, one sees a relatively

FIGURE 5.2

500MHz ^{1}H NMR Spectrum of $CpRh(C_2H_4)_2$, 140, upon Protonation with CF_3COOH, recorded in CD_2Cl_2.


+10°
-30°
-70°
-90°
4.5
4.0
3.5
3.0
2.5
2.0
PPM

narrow resonance (1H) at δ -8.92 which sharpens upon cooling but, even at -100°, does not become a clearly defined rhodium-coupled doublet. Upon raising the temperature to -70°C, the peak at δ 4.17 sharpened while that at δ 3.53 became a well-resolved multiplet. There also appeared another set of such resonances at δ 3.81 and δ 3.60, as well as another set of methyl and methylene peaks which developed at δ 1.49 and δ 3.06, respectively.

For the most part, the spectrum does not change dramatically on warming the sample to -30°C. The peaks at δ 4.17 and δ 3.53 begin to lose their fine structure and gradually broaden as the temperature is raised. This behavior is entirely characteristic of the commencement of olefin rotation about the Rh-C_2H_4 axis on the NMR time scale.[177,178] The high field resonance at δ -8.9 gradually broadens and ultimately disappears at ≈ -50°C. Interestingly, as the temperature increases, a very sharp singlet at δ 0.80 develops. This peak was suspected to be assignable to ethane and was confirmed by observation of the parallel development of a ^{13}C peak at δ 7.5.

Turning to the ^{13}C spectrum of the protonated species at -90°C, it was entirely in accord with the conclusions drawn from the ^{1}H data. Signals attributable to a cyclopentadienyl group (at δ 90.05), an ethyl ligand (CH_3 at δ 21.69, CH_2 at δ 23.03 with J_{Rh-C} = 14.6 Hz), and a coordinated ethylene (at δ 66.2 with J_{Rh-C} = 13.5 Hz) were

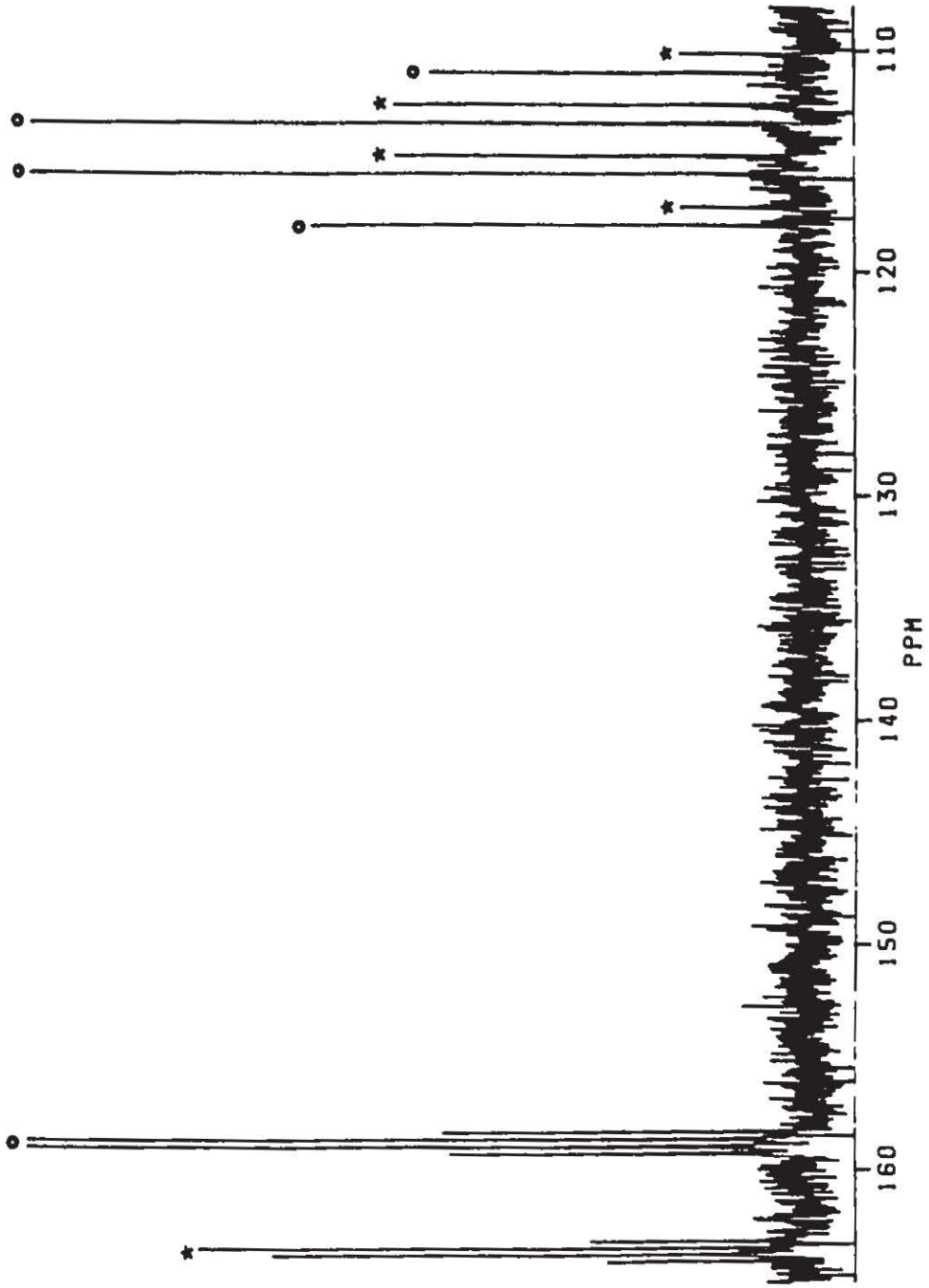
readily apparent. In addition, two fluorine-coupled quartets were present at δ 158.5 (J_{C-F} = 40.6 Hz) and at δ 114.2 (J_{C-F} = 286 Hz) assignable to the carbonyl and trifluoromethyl carbons, respectively, of the trifluoroacetic acid. A more interesting observation, however, was the appearance of another pair of quartets at δ 163.3 (J_{C-F} = 37.5 Hz) and at δ 113.3 (J_{C-F} = 289 Hz) clearly indicating the presence of a different trifluoroacetate environment (see Figure 5.3).

As had been shown by the pioneering work of Cramer,[167] there is an obvious reaction which proceeds moderately rapidly at ≈ -10°C but which can be seen to have started at ≈ -50°C as indicated by small peaks in the low temperature spectra. At -10°C, in both the ^{1}H and ^{13}C spectra, the signals for the coordinated ethylene ligands are lost while new peaks appear. After 12 hours at 10°C, the reaction is essentially complete and one can clearly see in the ^{1}H spectrum the appearance of several overlapping methyl triplets at ≈ δ 1.2 and corresponding methylene quartets at ≈ δ 2.4 indicating the presence of a number of of separate ethyl environments. At the same time, the ^{13}C spectrum exhibits new methyl resonances at δ 11 - 14, methylenes at δ 20 - 22, alkene carbons at δ 61 - 66, and a set of cyclopentadienyl peaks at δ 80 - 85. At this temperature, the only observable trifluoroacetate ^{13}C quartets are clearly those of CF_3CO_2H itself.

In addition, a ^{1}H-^{1}H COSY experiment was

FIGURE 5.3

Sections of the 125MHz ^{13}C NMR Spectrum of the Protonated $CpRh(C_2H_4)_2$ Species recorded in CD_2Cl_2 at -90°C illusrating different trifluoroacetate environments. (* coordinated o uncoordinated)

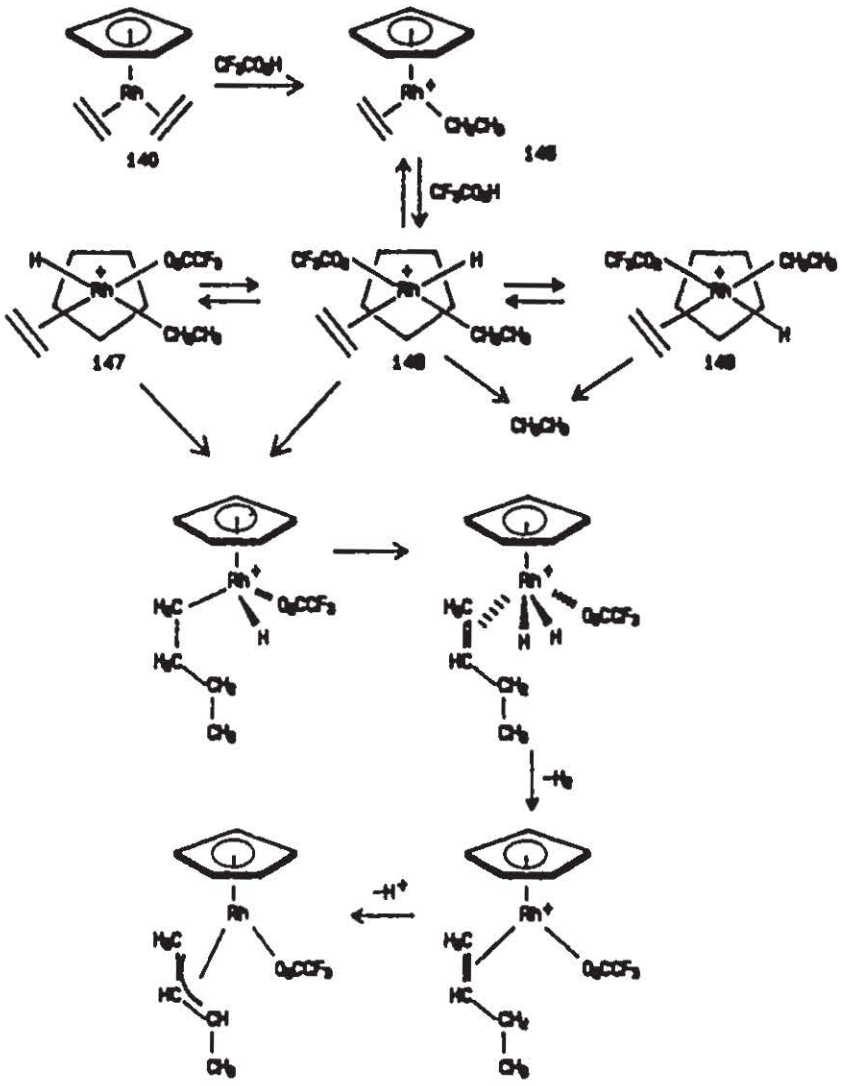

110
120
130
140
150
160
PPM

performed and revealed a network of coupled resonances showing the presence of a rhodium-containing molecule possessing a 1-methylallyl ligand. These particular peaks have been amplified in the uppermost trace of Figure 5.2.

From these NMR results, one can hypothesize as to what is occurring during the interconversion, i.e., the coupling of the ethyl and ethylene ligands. The initial product of the protonation of $CpRh(C_2H_4)_2$ at -90°C is presumably $[CpRh(C_2H_4)C_2H_5]^+$, 146, which possesses a 16-electron configuration. One can readily visualize addition of CF_3CO_2H to this initial product to give (in principle) three isomers 147, 148, and 149, together with their enantiomers. The presence of the metal hydride is shown by the resonance at δ -9 in the ^1H NMR spectrum while the coordinated trifluoroacetate exhibits fluorine-coupled quartets in the ^{13}C spectrum clearly distinct from those assignable to the free acid itself. The chiral nature of the molecules is evident from the diastereotopic character of the methylene protons. Of course, in a chiral molecule where ethylene rotation is slow on the NMR time scale, all four ethylene protons are non-equivalent. Indeed, as the sample is cooled below -90°, one of the peaks attributable to a coordinated ethylene broadens and is apparently on the verge of splitting again. (In the $(acac)Rh(C_2H_4)_2$ system discussed below, this lowered symmetry is even more obvious). If one assumes a square-based pyramidal geometry capped by the

FIGURE 5.4

Suggested Scheme Accounting for the Observed Spectroscopic Changes for the Protonation of 145.



cyclopentadienyl ring, it is clear that only species possessing *cis*-disposed ethylene and ethyl groups, i.e., 147, and 148, could permit coupling to produce a C_4 chain, while 148 and 149 should lead to facile reductive elimination of ethane. The ^1H spectrum at -60°C indicates the presence of two of the isomers 147,148, and 149, at least one of which is capable of liberating ethane. As originally reported by Cramer,[167] the resonances attributable to the ethyl and ethylene moieties are lost and are replaced by those of a mixture of Rh-butene complexes, the exact nature of which remains unclear. There is, however, unequivocal evidence of the formation of a small quantity of a 1-methallyl-rhodium system. Such molecules were first described by Powell and Shaw[180] as a result of the treatment of CpRh(1,3-butadiene) with HCl. Presumably, in this case, the anionic ligand is trifluoroacetate, as in 150. A suggested overall scheme which accounts for the observed spectroscopic changes is shown in Figure 5.4.

5.3 PROTONATION OF (acac)Rh(C_2H_4)$_2$.

As with the CpRh(C_2H_4)$_2$ system, the (acac)Rh(C_2H_4)$_2$ complex was prepared via literature procedures.[181] Once again, both its 500MHz ^1H and 125MHz ^{13}C NMR spectra were in complete accord. The ^1H NMR spectrum exhibited a singlet (6H) at δ 1.99 and another singlet (1H) at δ 5.37; these are readily assignable to the methyl and methyne protons of the

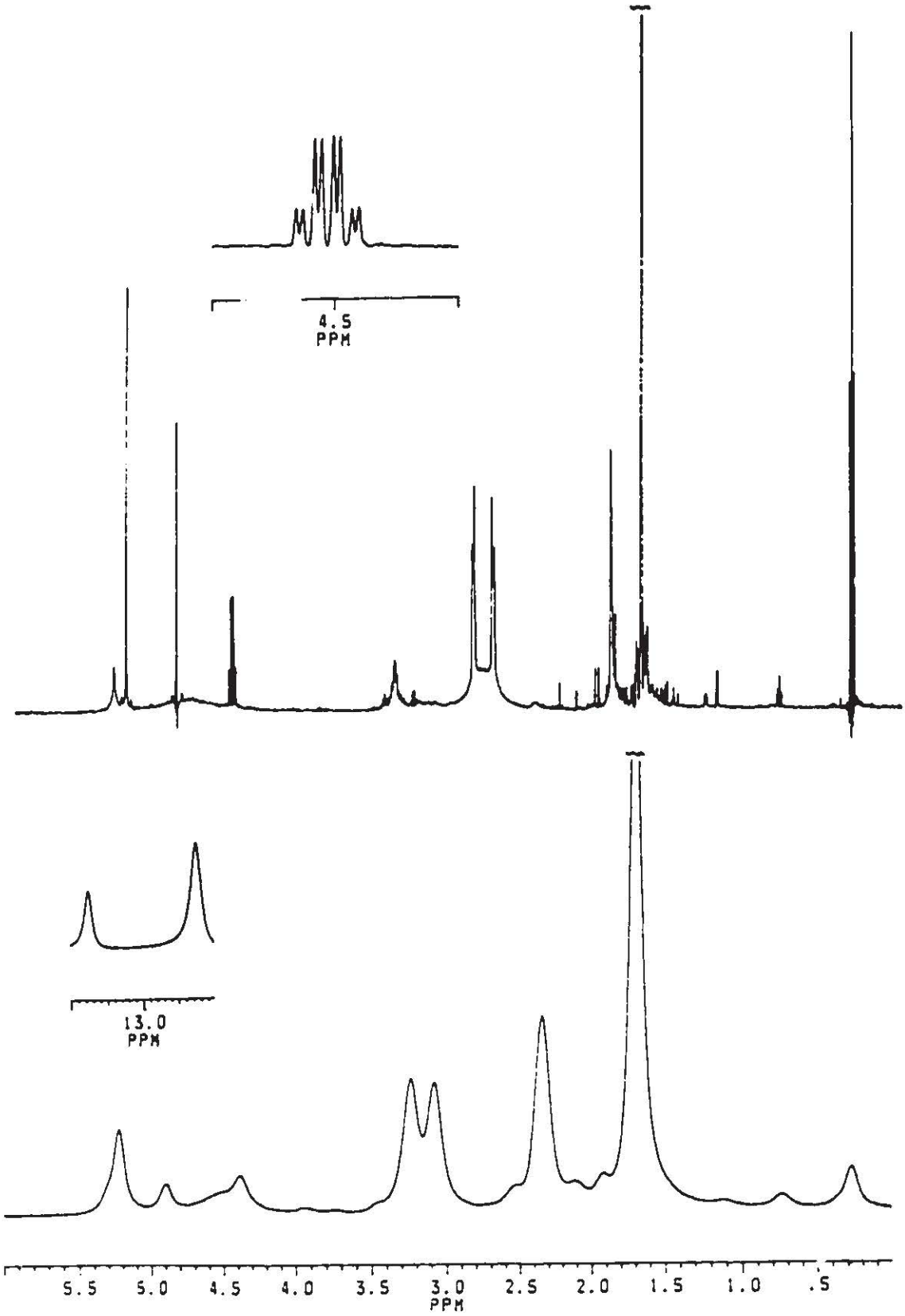
acac ligand. A broad peak (4H) is centred at δ 2.90 and this demonstrates that the coordinated ethylenes are rotating at an intermediate rate about the Rh-C_2H_4 axis at this temperature.[178]

Upon protonation of this complex with CF_3CO_2H at room temperature, an immediate colour change occurs from yellow to deep red, as was observed with the $CpRh(C_2H_4)_2$ system. In addition, the ^1H NMR spectrum of the protonated species as shown in Figure 5.5 deviates from that of the starting material. Specifically, one observes that the acac absorptions are now at δ 2.39 and δ 5.70 for the CH_3 and CH positions, respectively. In addition, there are now new resonances attributable to an ethyl group; the methyl triplet is found at δ 0.76 and the methylene quartet (each component of which is doublet split, J_{Rh-H} = 2.7 Hz) resonates at δ 4.50. The coordinated ethylene resonance is now clearly split into two well resolved doublets at δ 3.35 and 3.15. There is no high field signal which could have been assigned to a rhodium hydride.

In contrast, when the protonation is carried at low temperature, and the ^1H spectrum recorded at -80°C, the results are very different (as shown in Figure 5.5). The ethyl resonances which are so evident at room temperature are very minor peaks at -80°C, the coordinated ethylene protons now appear as three broadened peaks at δ 3.62 (2H), δ 3.51 (2H), and at δ 2.55 (4H). Furthermore, there is a broad

FIGURE 5.5

500MHz ^{1}H NMR Spectrum of (acac)Rh(C_2H_4)$_2$, 145, upon Protonation with CF_3COOH, recorded in CD_2Cl_2.

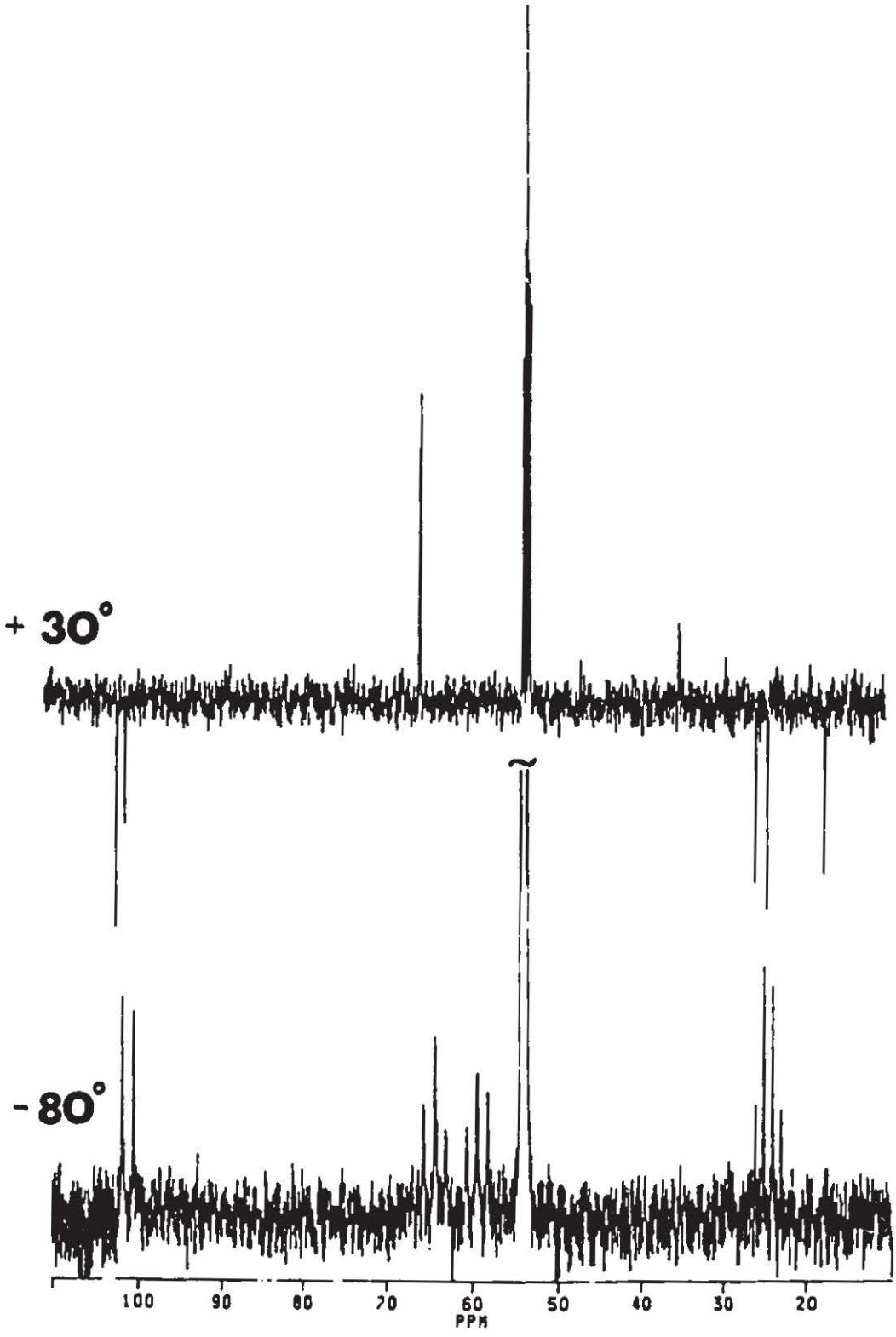

4.5
PPM
13.0
PPM
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM

resonance at δ 14.2 which is well downfield of the trifluoroacetic acid proton (at δ 12.7). Over the range -90° to -40°C, the high frequency peak at δ 14.2 gradually broadens and disappears. As well, the 2:2:4 pattern for the coordinated C_2H_4 ligand collapses and develops into a pair of broad resonances (each 4H) centered around δ 3.5 and δ 2.4. As one continues to raise the temperature to -35°C, the ethyl resonances are growing and are well developed at -10°C by which time the spectrum is essentially identical to that previously seen at room temperature.

This behavior is also clearly mirrored in the proton-coupled ^{13}C spectrum (shown in Figure 5.6) which, at -80°C, exhibits a methyl quartet (J_{C-H} = 129 Hz) at δ 24.4, a methyne doublet (J_{C-H} = 167 Hz) at δ 101.1 and a singlet at δ 194.1 typical of a carbonyl environment; these peaks are obviously assignable to the acetylacetonate ligand. Furthermore, there are two equally intense methylene triplets (J_{C-H} = 156 Hz) at δ 64.2 and δ 59.3 attributable to ethylene ligands in which the termini were in different environments. As with the protonation of $CpRh(C_2H_4)_2$ at low temperature, two sets of trifluoroacetate resonances were observable . As the temperature of the sample was raised, the ethylene carbon resonances at δ 64 and δ 59 broadened and coalesced as would be expected with the onset of alkene rotation. However, further changes are observable. The methyl, methyne and carbonyl resonances of the acac ligand at δ 24.4, 101.1 and

FIGURE 5.6

^{1}H Coupled ^{13}C NMR Spectrum of (acac)Rh(C_2H_4)$_2$, 145, upon Protonation with CF_3COOH, recorded in CD_2Cl_2.

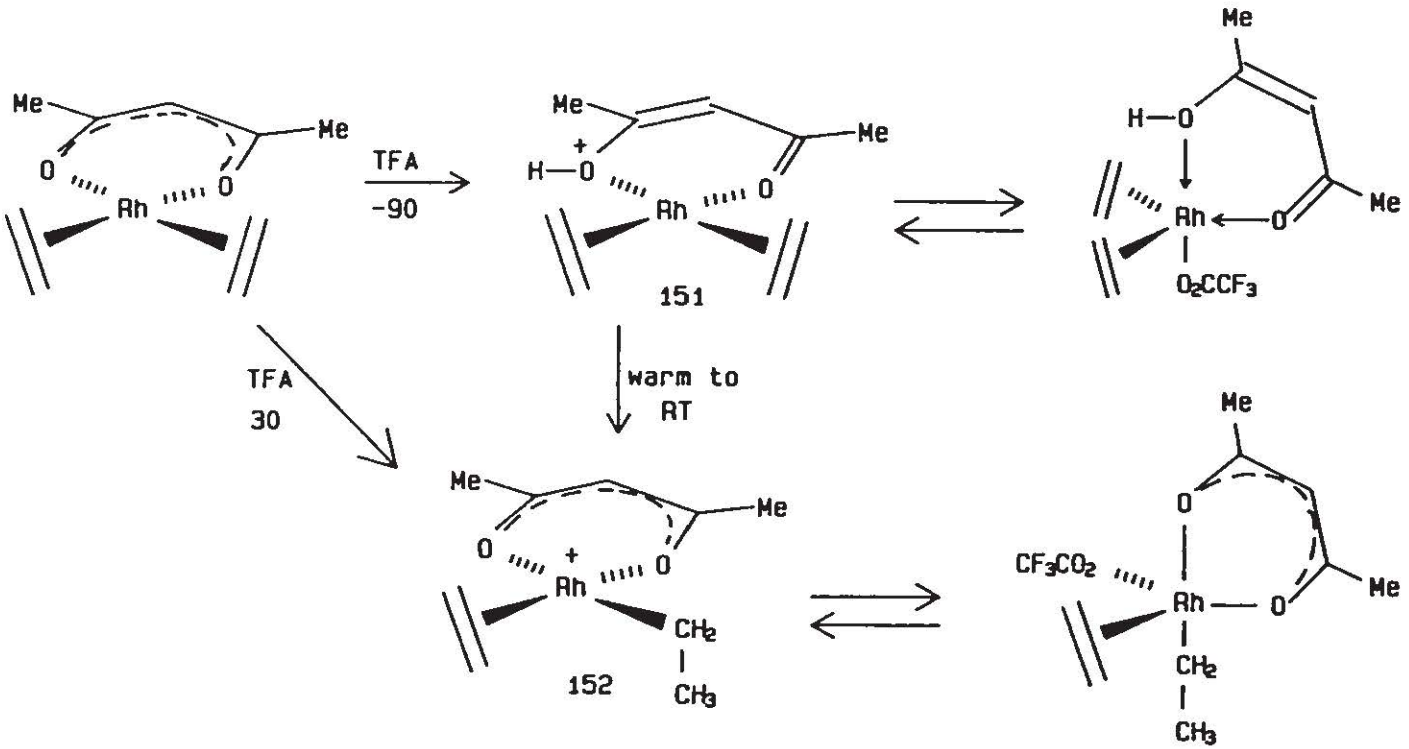

+ 30°
- 80°
100
90
80
70
60
50
40
30
20
PPM

194.1, respectively, are gradually replaced by peaks at δ 24.6. 102.3 and 187.2; moreover, new resonances assignable to an ethyl group become apparent and are clear at -35°C. The methyl peak appears at δ 17.4 while the corresponding methylene absorption occurs at δ 35.5; this latter resonance is doublet split with J_{C-Rh} = 22 Hz.

In describing these spectroscopic results, the course of the protonation of (acac)Rh(C_2H_4)$_2$ apparently proceeds quite differently at room temperature and at -90°C. At low temperature, there is no evidence of ethyl formation, indeed the observation of a proton resonance at δ 14.2 suggests that the kinetic product involves attack at oxygen, perhaps to yield an enol. One must propose a rationale which also accounts for the ^{13}C NMR spectrum at -80°C; this demonstrates the apparent equivalence of the methyl groups of the acac ligand but also reveals that the ethylene carbons are no longer in identical environments. Furthermore, as was seen with the CpRh(C_2H_4)$_2$ system, two sets of trifluoroacetate resonances are visible in the ^{13}C NMR spectrum. The implication is that the original C_{2v} symmetry of the (acac)Rh(C_2H_4)$_2$ molecule has been reduced to C_s. Such a situation could arise via formation of an acacH ligand with subsequent addition of a trifluoroacetate moiety as in the scheme shown in Figure 5.7. Indeed, the broadness of the ^1H NMR resonances at low temperature is also indicative of the involvement of a chemical exchange process.

FIGURE 5.7

Suggested Scheme Accounting for the Observed Spectroscopic Changes for the Protonation of 145.


Me
Me
O
Rh
O
TFA
-90
Me
+
H—O
Me
Rh
O
151
H—O
Me
Rh
O
Me
O2CCF3
TFA
30
warm to
RT
Me
O
+
Rh
O
Me
CH2
CH3
152
Me
O
CF3CO2
Rh
O
Me
CH2
CH3

As shown in Figures 5.5 and 5.6, protonation at room temperature leads directly to an ethyl-rhodium complex which must be the thermodynamically favoured product.; the same spectrum was also observed when a sample initially protonated at -90°C is allowed to warm slowly to room temperature. The product 151 in Figure 5.7 is formally a 14-electron species and is presumably stabilized as the trifluoroacetate complex 152. This latter species would be chiral and thus should render diastereotopic the methylene protons of the rhodium-bound ethyl group. However, at room temperature, these protons show merely a rhodium-coupled doublet of quartets while the ^{13}C spectrum exhibits only a single set of trifluoroacetate peaks. A single structure for 152 is thus depicted in Figure 5.7 with the proviso that it must be only one of several interconverting isomers.

To conclude, the low temperature protonation of $CpRh(C_2H_4)_2$ apparently yields a species $[CpRh(C_2H_4)(C_2H_5)(CF_3CO_2)H]^+$ which formally would be a Rh(V) system. Upon raising the temperature, the various isomers of this molecule can either reductively eliminate ethane or undergo ethyl-ethylene coupling to produce C_4 species. In contrast, the kinetic product of the protonation of $(acac)Rh(C_2H_4)_2$ appears to involve initial attack at oxygen; the thermodynamic product is a $Rh(C_2H_4)(C_2H_5)$ system which shows no evidence of coupling to yield alkenes. In the latter case, one does not observe any NMR resonances attributable to a rhodium-hydride

intermediate as was clearly visible in the protonation of $CpRh(C_2H_4)_2$.

5.4 CLOSING REMARKS

Regarding future research in this area, the results from the present work have raised numerous questions which are currently being investigated by other members of the laboratory group. These future endeavours have been mentioned throughout the course of this thesis.

In closing, this research project has obtained results regarding the assignments of ^1H and ^{13}C spectra of steroidal systems utilizing 2D NMR techniques. In addition, the use of these techniques has enabled one to probe the diamagnetic anisotropic contributions of certain organometallic fragments and their influence on the chemical shifts of steroidal protons and carbons. As well, the synthetic potential of some of the newly prepared complexes has been investigated. Finally, one can rest assured that this area involving organometallic complexes of steroids will be profitably exploited in the future.

CHAPTER 6

EXPERIMENTAL

6.1 GENERAL SPECTROSCOPIC TECHNIQUES

NMR spectra were recorded on a Bruker AM 500 spectrometer. The 500 MHz ^{1}H and 125.7 MHz ^{13}C spectra were acquired using a 5 mm dual frequency $^{1}H/^{13}C$ probe. All steroidal spectra were recorded at 300 K and all chemical shifts are reported relative to tetramethylsilane using the residual C_6H_6 (7.15 ppm) and $CHCl_3$ (7.24 ppm) signals as internal references. Proton spectra were acquired in 16 scans over a 3000 Hz spectral width in 32K data points, processed using Gaussian multiplication for line enhancement and zero filled to 64K before transformation.

Homonuclear chemical shift correlation (COSY) experiments[80,81] were carried out by using the pulse sequence: delay - ($\pi/2$,^{1}H) - t_1 - ($\pi/4$,^{1}H) - acquisition. Pulses were phase cycled according to Ref 42. A 2-s relaxation delay was used: the $\pi/2$ pulse was 18 μs. The spectra were acquired in 8 scans for each of 256 FID's which contained 1024 data points in f_2. The data were zero filled once in the t_2 domain and yielded a 512 x 512 matrix after transformation. The transformed matrix was symmetrized.

Heteronuclear chemical shift correlated spectra[80,81] were obtained by using the pulse sequence: delay - ($\pi/2,^{1}H$) - ($t_1/2$) - ($\pi,^{13}C$) - ($t_1/2$) - Δ_1 - ($\pi/2,^{1}H;\pi/2,^{13}C$) - Δ_2 - acquisition with decoupling. A 2-s relaxation delay was used and the delay times $\Delta_1 = 1/2J$ and $\Delta_2 = 1/4J$ were calculated from a compromise value of $^{1}J(C,H) = 125$ Hz. The $\pi/2,^{1}H$ pulse was 18 μs and $\pi/2,^{13}C$ pulse was 7.3 μs. The spectral width in the t_2(carbon) domain was 17857 Hz (140 ppm) and in the t_1(proton) domain was 3000 Hz. The spectra were acquired containing 4K data points in f_2 for each of 256 FID's. Zero filling twice in f_2, followed by 2-D transformation created a 2K x 512 data matrix. Gaussian enhancement of the data was applied.

Infrared spectra were recorded on a Perkin-Elmer 283 instrument using KBR solution cells. Microanalytical data for all new compounds were obtained from the Guelph Chemical Laboratories, Guelph, Ontario.

6.2 GENERAL PROCEDURES

All syntheses were carried out under a dry nitrogen atmosphere utilizing conventional benchtop and glovebag techniques. Before using, solvents were dried and distilled according to standard methods.[182] Silicagel (60-200 mesh, Baker Analyzed) were employed for column chromatography. The starting steroidal precursors were purchased from Aldrich Chemical Ltd. while the organometallic reagents were

purchased from Pressure Chemical Ltd.

6.3 PROCEDURES FOR CHAPTER 3

Synthesis of (η^6-Estrone-3-methyl ether)(η^5-cyclo pentadienyl) Ruthenium(II) hexafluorophosphate, 113

A solution of estrone 3-methyl ether (569 mg., 2.0 mmol.) in 35 ml of 1,2 dichloroethane was degassed for 10 minutes, with nitrogen, and $[CpRu(CH_3CN)_3]PF_6$[183] (668 mg., 1.54 mmol.) was added. After the mixture was heated for 15 hr at 40°C, the solvent was removed by rotary evaporation and the residue was washed with Et_2O (4 X 15 ml) to remove the unreacted estrone 3-methyl ether. The solid residue was redissolved in acetone and decolourized with charcoal. After concentration of the acetone solution to about 3 ml, Et_2O was added to precipitate 488 mg (0.82 mmol, 53% yield) of a mixture of the α- and β-stereoisomers in a 7:3 ratio, mp 153-157°C.

Anal. Calcd. for $C_{24}H_{29}O_2RuPF_6$: C, 48.40; H, 4.91
Found: C, 48.40; H, 5.03

The β-isomer was found to be much less soluble in acetone than the α-isomer. The separation of the two isomers was achieved by dissolving the mixture in a minimum of acetone, adding a few drops of ether and allowing the clear solution to stand overnight at room temperature. The

crystals were washed with acetone/ether (8:3) to remove the α-isomer. The pure β-isomer, 95 mg, was obtained [mp 288-290°C, IR(KBr) ν_{CO} 1752 cm^{-1}]. The pure α-isomer, 101 mg, was obtained [mp 155-157°C, IR(KBr) ν_{CO} 1750 cm^{-1}] by repeating the above process several times.

Synthesis of the $Co_2(CO)_6$ Complexes of 17α-Alkynyl-Estradiols; 105, 117, and 122

$Co_2(CO)_8$ (0.4 g, 1.1 mmol.) in THF (25 ml) was placed in a 100 ml two-necked round bottom flask and stirred under N_2 for 15 minutes. The appropriate 17α-alkynyl estradiol (1 mmol) in THF (5 ml) was added dropwise to the resulting $Co_2(CO)_6$ solution and the mixture was stirred at room temperature for 2 hours. After filtration of the solution and evaporation of the solvent, the residue was purified via a silicagel column using CH_2Cl_2 as eluent. An analytically pure sample in the form of dark red crystals was obtained by recrystallization from ether/ petroleum ether.

105 (0.24g, 0.4 mmol., 40%) mp 125°C,
IR(hexane) ν_{CO} 2088, 2050, 2027, 2024, and 2016 cm^{-1}
Anal. Calcd. for $C_{27}H_{26}O_8Co_2$: C, 54.35; H, 4.36
Found: C, 54.41; H, 4.45

117 (0.37g, 0.62 mmol., 62%) mp 140°C[184]
IR(cyclohexane) ν_{CO} 2090, 2050, 2023,

2019, and 2010 cm^{-1}

Anal. Calcd. for $C_{27}H_{26}O_8Co_2$: C, 54.35; H, 4.36

Found: C, 54.51; H, 4.48

122 (0.24g, 0.4 mmol., 40%) mp 130°C

IR(cyclohexane) ν_{CO} 2050, 2010, and 1995 cm^{-1}

Synthesis of the $Cp_2Mo_2(CO)_4$ Complex of 17α-Propynyl-Estradiol, 118

As described by Curtis,[138] $[CpMo(CO)_3]_2$ (1.1g, 2.25 mmol.) in diglyme was heated under reflux for 2 hr to form $[CpMo(CO)_2]_2$. The solution was filtered and cooled, and 17α-propynyl-estradiol (0.6g, 2.25 mmol.) was added and the solution was then heated at 80°C for 3 hours. After removal of the solvent, the crude product was purified via a silica-gel column using CH_2Cl_2 as eluent to give 118 (0.74g, 0.9 mmol., 45%) mp 115°C dec IR(CH_2Cl_2) ν_{CO} 1980, 1915, and 1825 cm^{-1}.

Anal. Calcd. for $C_{35}H_{36}O_6Mo_2$: C, 56.45; H, 4.87

Found: C, 56.82; H, 4.88

6.4 PROCEDURES FOR CHAPTER 4

Ergosterol and 7-dehydrocholesterol were converted into their corresponding acetates using the procedures outlined by Stansbury.[185] Their $Fe(CO)_3$ complexes were the

method described by Johnson.[13] Dehydroergosteryl acetate was synthesized from ergosterol using Djerassi's route.[159]

Synthesis of the Rh(acac) Complexes of Ergosteryl and 7-Dehydrocholesteryl Acetate, 125 and 126

Bis[(chloro)(ergosteryl acetate)rhodium(I)] and bis[(chloro)(7-dehydrocholesteryl acetate)rhodium(I)] were prepared according to the procedure of Barton.[22] To the appropriate RhCl dimer (0.5g) in Et_2O (25 mls) was added acetylacetone (0.1 ml). The solution was cooled to -20°C in an ice salt water bath and 6M KOH (1 ml) was added. After stirring for 1 hour, the solution was warmed to room temperature and extracted with Et_2O (2 x 25 mls). The orange Et_2O layer was concentrated and dried over $MgSO_4$. After filtration, the solution was cooled to -78°C (dry ice-acetone) and a light yellow precipitate was deposited. This was filtered off and dried under vacuum to yield:

125 0.17g (62%) mp 200°C decomp.

Anal. Calcd. for $C_{35}H_{53}O_4Rh$: %C 65.5 %H 8.42

Found: %C 64.17 %H 8.18

126 0.15g (53%) mp 180°C decomp.

Anal. Calcd. for $C_{34}H_{53}O_4Rh$: %C 64.9 %H 8.44

Found: %C 64.28 %H 8.24

X-ray Crystal Structure Determination of 7-Dehydrocholesteryl acetate $Fe(CO)_3$, 124

Yellow plate-like crystals of$[(C_{29}H_{45}O_2)Fe(CO)_3]$ were grown from hexane/CH_2Cl_2 and examined under a polarizing microscope for homogeneity. A well formed crystal, 0.52 X 0.39 X 0.26 mm, was selected and sealed in a Lindemann capillary. The density was determined by floatation in an aqueous solution of $ZnBr_2$. Unit cell parameters were obtained from a least squares fit of ω, ϕ, and 2θ for 15 reflections in the range ($19.7° < 2\theta < 27.2°$) recorded on a Nicolet P3 diffractometer with use of graphite monochromated MoKα radiation (λ= 0.71069Å at 22°C). Intensity data were also recorded on a Nicolet P3 diffractometer with a coupled $\theta_{crsytal} - 2\theta_{counter}$ scan, for 4483 reflections (h=k=1) with $2\theta \leq 45°$. The methods of selection of scan rates and initial data treatment have benn described.[186,187] The data were corrected for Lorentz-polarization effects but not for absorption. Two standard reflections (0,-7,3;1.34% and 5,0,-2;.51%) monitored every 48 reflections and showed no sign of crystal decomposition of instrument instability. A summary of crystal data is given in Table 4.5

Solution of the Structure

The coordinates of the iron atoms were found from a three dimensional Patterson synthesis with use of the program SHELXS-86.[188] Full-matrix least-squares refinement of the

coordinates of Fe(1), (the coordinates of Fe(2) were held fixed to define the origin), followed by a three-dimensional electron density synthesis revealed most of the non-hydrogen atoms. The refinement of the carbon and oxygen atoms was hindered by the fact that both independent molecules were strongly correlated and it was necessary in the early stages of refinement to constrain certain bond distances to their theoretical values. A damping factor during refinement was applied and the bond length constraints slowly removed. After refinement, the temperature factors of the non-hydrogen atoms were made anisotropic and further refinement using block-matrix least-squares minimizing $\Sigma\omega(|F_o| - |F_c|)^2$ was terminated when the maximum shift/error reached 0.141 (molecule 1), 0.233 (molecule 2). The damping factor was considerably reduced in the final stages of refinement, however, it proved necessary to fix the parameters of the carbonyl fragments. Correction for secondary extinction was made by the method in SHELX-76[189]. Final R_1 = 0.0572, R_2 = 0.0668 for 3135 reflections with I>3θ(I). Alternate refinement where coordinates x,y,z were replaced by -x,-y,-z gave R_1 = 0.0594, R_2 = 0.0694 and S = 1.0422 for 3135 reflections, confirming the assignment for the correct hand for the structure, (although a full data set of ±h,±k,±l was not taken, the correct hand is implicit from that of the starting material, the chirality of which is known). Throughout the refinement, scattering curves were taken from

Ref 190 and anomalous dispersion corrections form Ref 191 were applied to the curve for iron. All calculations were performed on a VAX 8650 computer. Programs used: XTAL,[192] data reduction; SHELX-86,[188] structure solution; SHELX-76,[189] structure refinement; MOLGEOM,[193] molecular geometry and SNOOPI,[194] diagrams. Final atomic positional parameters are given in Table 4.6, selected bond lengths and bond angles are given in Table 4.7 - 4.9.

Synthesis of the $Fe(CO)_3$ Complex of Dehydrocholesteryl Acetate, 130

Using the method outlined by Johnson,[13] dehydroergosteryl acetate (0.35g, 0.8 mmol.) was placed in toluene (25 ml) in a 100 two-necked round bottom flask. Benzylideneacetone $Fe(CO)_3$ (0.27g, 0.93 mmol.) was added and the resulting mixture was heated under reflux for 6 hours. After filtering the solution through Celite and evaporation of the solvent, the resulting residue was purified via silicagel column chromatography using hexane:toluene (1:1) as eluent. The purified fraction was, then triturated with cold MeOH to remove unreacted dehydroergosteryl acetate. The $Fe(CO)_3$ complex was isolated as an orange oil. IR(cyclohexane) ν_{CO} 1975 and 1965 cm^{-1}.

Synthesis of Ergosta-5-7-dienyl-22-ene 3β-Acetoxy Tricarbonyl Iron(1+) hexafluorophosphate, 131

Dehydroergosteryl Acetate $Fe(CO)_3$ (0.7g, 1.2 mmol.) in Ether (25 ml) was placed in a 100 ml two-necked round bottom flask. HPF_6 (.3ml, 70%) was slowly added and the resulting solution cooled to -78°C in a dry ice/acetone bath. After 20 minutes, a yellow precipitate was obtained (.21g, .29 mmol., 24%) mp 140°C IR(acetonitrile) 2120, 2078, and 2040 cm^{-1}.

Anal. Calcd. for $C_{33}H_{45}O_5FePF_6$: C, 55.00; H, 6.25

Found: C, 54.84; H, 6.10

6.5 PROCEDURES FOR CHAPTER 5

$CpRh(C_2H_4)$ and CpRh(acac) were prepared via literature procedures.[167,179] The complexes were subsequently dissolved in CD_2Cl_2, and the solutions were filtered and degassed. Several drops of trifluoroacetic acid was added either to a room temperature or -80°C sample. The initially yellow solutions became dark amber or red upon protonation.

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