213 (M^+, 19), 184 (63), 156 (100). This forms a striking contrast to the selective 1,6 addition of organocopper reagents to the conjugated dienoates.[18]

Although sodium dimethyl malonate was either unreactive (with **1**, $R_2^1 = -(CH_2)_4-$) or gave many products (with **2**, at least 7 spots except for the starting spot on a silica gel plate, 8:1 PhH–EtOAc), a variety of organolithium and -magnesium compounds,[19] possessing harder carbanion character, reacted with α,β-unsaturated thioamides with similar ease and selectivity. The present reaction with phenylmagnesium bromide, vinylmagnesium bromide, lithiodithiane, and dimsyllithium, coupled with the quenching with a variety of electrophiles, provides an extremely desirable feature since these functionalities may be employed in further structural transformations. Work is in progress to investigate the full scope of the present reaction and to apply our method to the synthesis of naturally occuring compounds.

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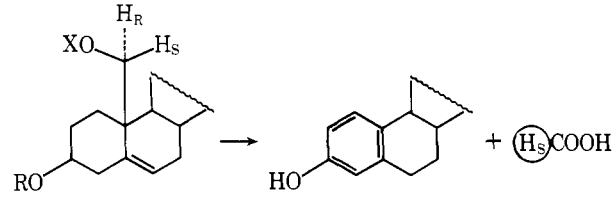
Biosynthesis of Estrogens. Assignment of the Chemical Shift of the 19-*pro*-Chiral Hydrogen Atoms of a 19-Hydroxy Precursor

Sir:

Akhtar and Skinner[1] have shown that the conversion of **1a** to an estrogen (**2**) by placental enzymes is a stereospecific process involving the removal of a specific 19-*pro*-chiral hydrogen atom, as water. The second 19-*pro*-chiral hydrogen atom is retained by the formic acid released in the aromatization reaction. It was then accepted that, in the biosynthetic transformation of androgens to estrogens, a 19-*pro*-chiral hydrogen atom is eliminated during the NADPH-oxygen-dependent oxidation of **1a** to **3** and **4**.[1]

To determine which of the 19-hydrogen atoms is lost as water and which is retained by the formic acid, it was necessary to differentiate the *pro* chiralities of the C-19 hydrogen atoms of **1**. These *pro* chiralities were inferred from an NMR investigation of the chiral 19-$^2H_1$ alcohol(s) and from the product(s) of the rearrangements of the corresponding 19-tosyl ester(s) (**1b**) to a 5(10)-cyclopropyl-6β-hydroxy derivative(s)[2] (**5**). Based on these considerations, the 19-hydrogen atoms of the 19-acetates **1c** and **1d** were assigned the following chemical shifts:[2] δ 4.44 (H_R) and 3.95 (H_S).

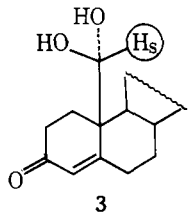
The chemical shifts of the 19-hydrogen atoms of (19*R*)- and (19*S*)-19-methylandrost-5-ene-3β,17β,19-triols, whose configurations were established by x-ray crystallography were in accord with these assignments.[3] The x-ray studies revealed that



1a, R = H; X = H
b, R = CH_3; X = Ts
c, R = CH_3; X = Ac
d, R = H; X = Ac

2

The H_S designation of the encircled hydrogen atoms refers to their prochirality in the parent compound **1**



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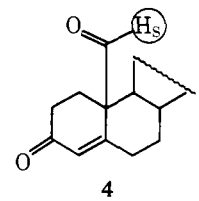

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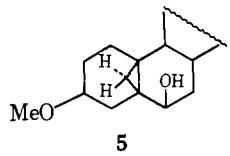

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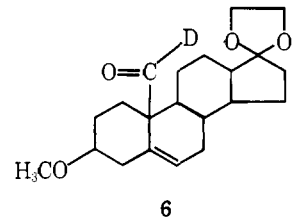

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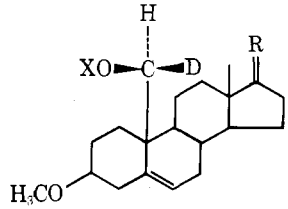

7a, R = $(CH_2O)_2$; X = H
b, R = O; X = Ac

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the initially inferred C-19 chiralities of these compounds had to be reversed.[4]

From these indirect assignments, it was postulated that the "second hydroxylation" of **1a** proceeds with the elimination of the 19-*pro-R* hydrogen and that the formic acid retains the 19-*pro-S* hydrogen atom.[2,3]

Because of the biological importance of the estrogen formation process, we reinvestigated the problem and present direct proof for the assignment of the chemical shifts of the C-19 hydrogen atoms of the 19-acetate **1c.**

It has been conclusively established that the reduction of aldehydes by horse liver alcohol dehydrogenase (HLAD) and NADH involves the stereospecific transfer of a 4-*pro-R* hydrogen atom of NADH to the *re* face of the aldehyde.[5,6] It follows that the hydrogen atom originating from the NADH *is the 1-pro-R* hydrogen atom of the derived alcohol. Therefore, reduction of the 19-deuterioaldehyde (**6**) with HLADH and NADH should yield the 19*S*,19-^{2}H alcohol (**7a**). Previous attempts at reducing 19-aldehydes with HLAD-NADH failed. We have now succeeded, for the first time, in reducing **6** enzymatically and have obtained, presumably, optically pure **7b** in low yield (~0.3–0.8%). It is likely that the low yield of the enzymatic alcohol formation is due, at least in part, to the *very limited* solubility of the aldehyde in the aqueous medium.

The required **6** was obtained by $LiAl^2H_4$ reduction of methyl 17-ethylenedioxy-3β-methoxyandrost-5-ene-10β-carboxylate and oxidation of the resulting 19-d_2 alcohol (CrO_3–pyridine). The expanded NMR spectrum of the aldehyde **6** did not show a signal for an aldehydic hydrogen (~99% deuteration).

The deuterated aldehyde **6** (100 mg) was then diluted with a trace amount of 19-tritiated aldehyde **6** (~40 μg, 4.48×10^6 dpm of ^{3}H) and dissolved in ethylene glycol monoethyl ether acetate (5 mL). An aliquot of the aldehyde solution (~55 μL) was placed in a 25-mL Erlenmeyer flask containing water (5 mL) and Tween 80 (1 drop). The mixture was warmed to 50 °C and hand shaken. The obtained emulsion was cooled to 37 °C and then cyclohexanol (80 μL), phosphate carbonate buffer (0.02 M, pH 8.7, 3 mL), NAD (4 mg), and alcohol free HLAD (1.5 mg) were added sequentially. The mixture was incubated in the air for 20 h at 37 °C. A total of 90 incubations was carried out, using all of the aldehyde solution. The contents of the flasks were combined and continuously extracted with ethyl acetate for 24 h. The extract was washed, dried, and concentrated. The resulting residue was fractionated on TLC (silica gel, hexane–ethyl acetate (7:3)) and most of the aldehyde **6** was recovered (4.03×10^6 dpm of ^{3}H, 90% recovery). The product from the zone corresponding to the 19-alcohol 17-ketal **7a** (3.6×10^4 dpm of ^{3}H, 0.8% yield) was isolated and treated with 0.4 N aqueous methanolic HCl (5 mL, 50 °C, 15 min), and, following acetylation, the crude [19-^{2}H]-(19*S*)-19-acetoxy-3β-methoxyandrost-5-ene-17-one (**7b**) was obtained. The acetate was extensively purified by TLC and high pressure liquid chromatography (Partisil 10/20 column, eluted with isooctane–2-propanol (95:5), pressure 270 lb, flow rate 1 mL per minute). The resulting homogeneous **7b** (1.3×10^4 dpm of ^{3}H, 0.3% yield) was dissolved in $CDCl_3$ (100 μL) and its 90-MHz ^{1}H NMR spectrum was recorded (Bruker SXP instrument).

The spectrum of the **7b** showed a signal for the 19-*pro-R* hydrogen at δ 4.45 and was *devoid* of a signal at δ 3.95. It is evident that, *within the limits of the sensitivity of the NMR procedure,* the HLAD-NADH reduction was *completely* stereospecific. In view of the demonstrated stereospecificity of the reaction and in the absence of *any evidence* to the contrary, it may be assumed with considerable certainty that the reaction proceeded in the proven, conventional manner. Hence, it may be concluded that a hydrogen derived from 4-*pro-R* of NADH was added to the *re* face of the aldehyde **6** to yield 19*S* alcohol. Therefore, our results provide proof for the assignment of the chemical shifts of the 19-*pro-R* and of the 19-*pro-S* (δ 3.95) hydrogen atoms of **7b.** It follows that the biosynthesis of estrogens by placental enzymes indeed involves the removal of the 19-*pro-R* hydrogen of **1** as water, and that the formic acid retains the 19-*pro-S* hydrogen, as previously proposed.[7]

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Synthesis of Transition Metal Complexes of Cycloheptatrienylidene

Sir:

For some years we have been interested in the chemistry of cycloheptatrienylidene, a reactive intermediate in which the vacant p orbital of the carbene is an integral component of an aromatic π system.[1]

The relatively recent widespread interest in the chemistry of transition metal complexes of carbenes and especially those not stabilized by heteroatoms[2] piqued our curiosity as to the physical and chemical properties of transition metal complexes of cycloheptatrienylidene and related carbenes. In this communication we report a synthetic method that may be general for preparing this type of complex.

Although the synthetic approach to carbene complexes of transition metals that has found the widest use (addition of RLi to a CO ligand)[3] had no potential for the synthesis of cycloheptatrienylidene complexes, there have been reported isolated methods[4-7] that appeared to have some chance of being useful for our purposes. Unfortunately, all attempts to apply known methods to the formation of cycloheptatrienylidene complexes failed. Reaction of either dichloro-, dibromo-, or 7,7-dimethoxycycloheptatriene with $Na_2Cr(CO)_5$ or $Na_2Fe(CO)_4$ gave only reduction of the tropyl ring,[8] as did reaction of tropylium salts with $NaFe(CO)_4H$. Reaction of heptafulvene with diphenylcarbene(pentacarbonyl)tungsten(0) gave no trace of 1,1-diphenylethylene and decomposition of the sodium salt of tropone tosylhydrazone in the presence of methylcyclopentadienyldicarbonyl(THF)manganese gave no sign of a carbene complex.

In view of the facile reduction of the tropyl cation, a synthetic approach was sought in which the carbon–metal bond is formed before the final unsaturation is introduced into the ring. Drawing on the well-known displacement of halides from transition metals by alkyl and aryl Grignard and lithium reagents[9] and a reported carbene synthesis by hydride abstraction,[10] the reaction sequence outlined in Scheme I was attempted.

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