for 1.5 h and then stirred at 20 °C for 16 h. The mixture was diluted with EtOAc, washed with water, and evaporated to dryness. The product was purified by preparative TLC (20% acetone–hexane, eluted 4 times) and crystallization from acetone–hexane, giving 57 mg (47%) of **48**, mp 250–251 °C dec; UV 235 nm (ε 19345); IR (KBr) 1750 (ester), 1700 (20-C=O), 1675 (3-C=O) $cm^{-1}$; $^1H$ NMR (90 MHz, $Me_2SO$) δ 0.95 (s, 3 H, 18-$CH_3$), 1.34 (d, 3 H, $J$ = 7 Hz, 16-$CH_3$), 1.71 (s, 3 H, 19-$CH_3$), 2.05 (s, 3 H, $COCH_3$), 2.20 (s, 3 H, $SCH_3$), 5.09 (br d, 1 H, $J$ = 4 Hz, 11-H); MS, $m/e$ 503–507 ($MH^+$). Anal. Calcd for $C_{24}H_{29}O_4Cl_2FS$: C, 57.26; H, 5.81. Found: C, 57.19; H, 5.85.

**9α,11β-Dichloro-6α-fluoro-17β-[(methylthio)carbonyl]-17α-(propionyloxy)-16β-methylandrosta-1,4-dien-3-one (49).** Freshly distilled propionic anhydride (0.3 mL, 2.34 mmol) was added to a solution of **47** (140 mg, 0.30 mmol) and DMAP (50 mg, 0.41 mmol) in TEA (3 mL), and the mixture was heated at 70 °C for 16 h. Purification of the product by centrifugal TLC (0.5% acetone–$CH_2Cl_2$) followed by crystallizations from MeOH and EtOAc–hexane gave 55 mg (35%) of **49**, mp 244–246 °C dec; UV 237 nm (ε 18995); IR (KBr) 1745 (ester), 1705 (20-C=O), 1670 (3-C=O) $cm^{-1}$; $^1H$ NMR (300 MHz, $Me_2SO$) δ 0.95 (s, 3 H, 18-$CH_3$), 1.05 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 1.33 (d, 3 H, $J$ = 7 Hz, 16-$CH_3$), 1.71 (s, 3 H, 19-$CH_3$), 2.19 (s, 3 H, $SCH_3$), 2.33 (q, 2 H, $J$ = 7 Hz, $COCH_2$); MS, $m/e$ 468–472 ($M^+ - HSCH_3$). Anal. Calcd for $C_{25}H_{31}O_4Cl_2FS$: C, 58.03; H, 6.04; Cl, 13.70. Found: C, 57.98; H, 6.04; Cl, 13.68.

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**Registry No.** **1**, 67-73-2; **2**, 2135-17-3; **3**, 378-44-9; **4**, 101916-22-7; **4** diacetate, 50630-16-5; **5**, 101916-23-8; **5** diacetate, 101916-49-8; **6**, 28416-82-2; **7**, 37926-75-3; **8**, 101916-24-9; **9**, 101916-25-0; **10**, 65751-34-0; **11**, 101916-26-1; **12**, 65429-42-7; **13**, 37927-21-2; **14**, 37927-23-4; **15**, 101916-27-2; **16**, 37927-22-3; **17**, 74131-78-5; **18**, 101916-28-3; **19**, 101916-29-4; **20**, 74131-73-0; **21**, 73205-13-7; **22**, 101916-30-7; **23**, 101916-31-8; **24**, 79578-14-6; **25**, 74156-42-6; **26**, 79578-08-8; **27**, 101932-58-5; **28**, 101916-32-9; **29**, 101916-33-0; **30** (isomer 1), 101916-34-1; **30** (isomer 2), 101916-35-2; **31** (isomer 1), 101916-36-3; **31** (isomer 2), 101916-37-4; **32**, 101932-54-1; **33**, 101916-38-5; **34**, 101916-39-6; **35**, 101916-40-9; **36**, 101916-41-0; **37**, 74131-77-4; **38**, 101916-42-1; **39**, 101916-43-2; **40**, 101916-44-3; **41**, 101932-61-0; **42**, 101932-59-6; **43**, 101916-45-4; **44**, 101916-46-5; **45**, 74131-76-3; **46**, 87116-72-1; **47**, 101916-47-6; **48**, 101932-60-9; **49**, 101916-48-7; $NaSCH_3$, 5188-07-8; $NaSC_2H_5$, 811-51-8; $NaSC_6H_{13}$, 22487-02-1; $CH_3SH$, 74-93-1; acetyl chloride, 75-36-5; ethyl mercaptan, 75-08-1; propionyl chloride, 79-03-8.

(51) Deceased.

# Organometallic Derivatives of Hormonal Steroids: 500-MHz One- and Two-Dimensional NMR Spectra of 17α-Propynylestra-1,3,5(10)-triene-3,17β-diol and Its $Co_2(CO)_6$ and $(C_5H_5)_2Mo_2(CO)_4$ Complexes

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Treatment of estrone with a propynyl Grignard reagent gives exclusively 17α-propynylestra-1,3,5(10)-triene-3,17β-diol. This 17α-alkynyl steroid reacts with $Co_2(CO)_8$ or $(C_5H_5)_2Mo_2(CO)_4$ to yield the cluster complexes $(RC{\equiv}CR')M_2$, where R = methyl, R′ is the steroidal moiety, and M = $Co(CO)_3$ or $(C_5H_5)Mo(CO)_2$. The cobalt complex of mestranol has likewise been prepared. The 500-MHz $^1H$ NMR spectra of these molecules are reported and are assigned by the two-dimensional COSY technique. The shifts of the 12α- and 14α-protons of the steroid are discussed in terms of the anisotropy in diamagnetic susceptibility of the alkyne linkage. $^{13}C$ spectra are also reported.

## Introduction

The incorporation of organometallic moieties into biologically important molecules is a field of burgeoning importance. Typically, in steroid chemistry, $Fe(CO)_3$ fragments may be used as temporary protecting agents,[1] and allylpalladium[2] or $Cr(CO)_3$ units[3] have been exploited for synthetic purposes. Recently, advances in bioorganometallic chemistry have been directed toward immunology,[4] and we have described the use of steroidal hormones labeled with metal carbonyls to assay receptor sites.[5] This latter concept takes advantage of the strong infrared absorptions of metal carbonyls in the range 2100–1850 $cm^{-1}$—a window in which proteins do not absorb. Our goal is to monitor the hormone dependence of breast cancer while avoiding the use of radioactivity and its associated inconveniences.

In the particular case of estrogenic hormones, it has been reported that the 7α-, 11β-, and 17α-positions of estradiol (**I**) can tolerate substitution by bulky groups and still ex-

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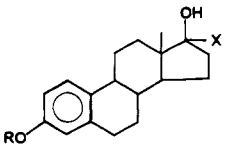
hibit an acceptable relative binding affinity (RBA).[6] Now the ready availability of 17α-alkynyl derivatives of estradiol coupled with the abundance of organometallic chemistry possible on coordinated acetylenes and the stability of these complexes prompted us to select 17α-propynylestra-1,3,5(10)-triene-3,17β-diol (**2**) as the substrate on which to try to achieve some of our goals.

We here describe the synthesis of **2** and of its $(C_5H_5)_2Mo_2(CO)_4$ and $Co_2(CO)_6$ derivatives **3** and **4**; furthermore, the one- and two-dimensional $^1H$ NMR spectra of **1** through **4**, obtained at 500 MHz, are reported, and the assignments are discussed in terms of anisotropic effects of the free and complexed alkyne moieties.

## Results and Discussion

In our earlier studies on organometallic derivatives of steroidal hormones, we were able to incorporate a tricarbonylchromium group into estradiol and a series of related molecules.[7] In those cases, the metal carbonyl fragment achieved an 18-electron configuration via π-complexation to the aromatic ring. Indeed, the $Cr(CO)_3$ moiety can complex to either the α- or the β-face of the hormone; these two diastereomers can be distinguished readily with high-field (500 MHz) NMR spectroscopy. We have also demonstrated that estradiol complexes bearing an α-$Cr(CO)_3$ group compete with the natural hormone for the receptor site more successfully than do their β-analogues.[3a] We therefore decided to coordinate metal carbonyl fragments to a functionality positioned on the α-face of the hormone. To this end, we examined 17α-propynylestra-1,3,5(10)-triene-3,17β-diol (**2**) and its $(C_5H_5)_2Mo_2(CO)_4$ and $Co_2(CO)_6$ complexes **3** and **4**. It is also




**1** R = H ; X = H

**2** R = H ; X = $-C\equiv C-CH_3$

**3** R = H ; X = $-C(CpMo(CO)_2)-C(CpMo(CO)_2)-CH_3$

**4** R = H ; X = $-C(Co_2(CO)_6)-C(Co_2(CO)_6)-CH_3$

**5** R = $CH_3$ ; X = $-C(Co_2(CO)_6)-CH$

noteworthy that several 17α-alkynyl derivatives of estradiol have found use as contraceptives. Thus, the 17α-ethynyl derivative is sold under the name estranol; the corresponding 3-methoxy analogue is mestranol.

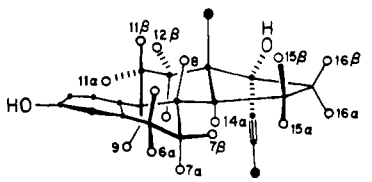
Tetrahedral clusters of the type $(RC\equiv CR')Co_2(CO)_6$ are readily synthesized via the reaction of $Co_2(CO)_8$ with the appropriate alkyne and a wide variety of such complexes is known.[8] Furthermore, the hexacarbonyldicobalt moiety has been utilized as a protecting group for alkynes in the presence of alkenes.[9] Similarly, the reaction of alkynes with metal–metal triple-bonded species, such as $Cp(CO)_2Mo\equiv Mo(CO)_2Cp$, readily yields stable complexes.[10]

**Table I. 500-MHz $^1H$ NMR Chemical Shifts (δ) in $C_6D_6$ Solvent**

| proton | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 6α | 2.63 | 2.68 | 2.78 | 2.75 | 2.78 |
| 6β | 2.68 | 2.75 | 2.78 | 2.82 | 2.80 |
| 7α | 1.08 | 1.23 | 1.37 | 1.27 | 1.28 |
| 7β | 1.65 | 1.75 | 1.84 | 1.80 | 1.78 |
| 8 | 1.25 | 1.39 | 1.63 | 1.42 | 1.38 |
| 9 | 1.99 | 2.24 | 2.21 | 2.27 | 2.25 |
| 11α | 2.10 | 2.32 | 2.21 | 2.32 | 2.28 |
| 11β | 1.38 | 1.52 | 1.55 | 1.54 | 1.48 |
| 12α | 1.02 | 2.09 | 1.56 | 1.55 | 1.46 |
| 12β | 1.82 | 1.82 | 1.56 | 1.70 | 1.58 |
| 14 | 0.81 | 1.86 | 1.57 | 1.49 | 1.68 |
| 15α | 1.32 | 1.70 | 1.80 | 1.72 | 1.60 |
| 15β | 1.12 | 1.27 | 1.38 | 1.27 | 1.21 |
| 16α | 1.88 | 2.42 | 2.30 | 2.14 | 2.18 |
| 16β | 1.40 | 2.11 | 2.12 | 2.14 | 2.05 |
| 17 | 3.40 | | | | |
| 18-$CH_3$ | 0.65 | 0.96 | 0.98 | 0.96 | 0.83 |
| $CH_3C\equiv C$ | | 1.63 | 2.82 | 2.50 | |
| $C_5H_5$ | | | 5.03/5.05 | | |

Our preliminary studies[11] have shown that the alkynyl estradiol **2** and its molybdenum and cobalt complexes **3** and **4** do indeed possess a satisfactory power of recognition for the receptor of estradiol (RBA value of 44% for **2**, 13% for **3**, and 12% for **4**). This result opens up a new area of application for multimetallic complexes.

These molecules are also particularly interesting to the NMR spectroscopist, not merely to confirm the identity of the products but rather because they provide a rigid skeleton with a plethora of protons and carbons enticingly positioned so as to probe the diamagnetic anisotropy of the newly introduced groups. We have already examined the effect of a $Cr(CO)_3$ fragment on the nuclei proximate to the A ring in estradiol[7,12] and one can now study the influence of the free and complexed alkyne moiety on the protons in the C and D rings, assuming that complete assignment of the spectra is possible.




**2**

The high-field $^1H$ NMR spectra of steroids provide a challenge to the spectroscopist since even at 11.74 T (500 MHz for protons) there is considerable peak overlap and conventional homonuclear decoupling techniques lead to ambiguous results. We therefore chose to take advantage of one of the multipulse sequences recently developed for two-dimensional NMR spectroscopy.[13] The COSY experiment allows molecular structure elucidation through scalar coupling between protons.[14] Figure 1 shows the result of a COSY experiment presented as a contour plot in which the one-dimensional spectrum lies along the diagonal and coupling between two spins is manifested as

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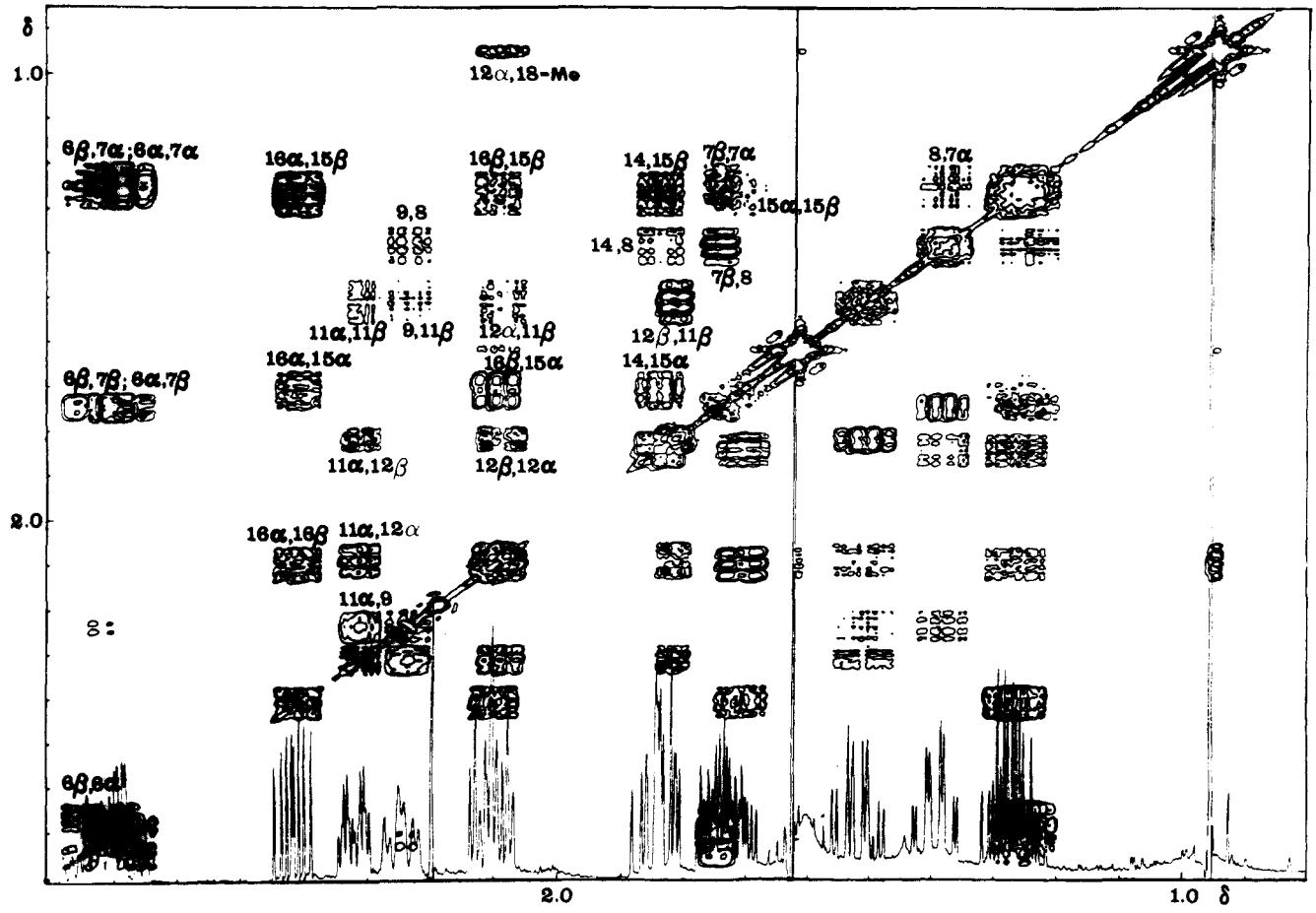


**Figure 1.** Two-dimensional 500-MHz NMR spectrum of 17α-propynylestra-1,3,5(10)-triene-3,17β-diol (2). Expanded contour plot of a portion of the matrix for a COSY experiment. The matrix has been symmetrized.

a symmetrically positioned pair of off-diagonal peaks. As can be seen in Figure 1, the superb resolution achievable at 500 MHz yields a spectrum that demonstrates the power of multipulse NMR techniques. Careful examination of the two-dimensional matrix clearly shows all scalar couplings and allows unequivocal assignment of the framework of the steroid despite the complexity of the normal one-dimensional spectrum. The $^1H$–$^1H$ COSY experiment clearly indicates the sites of attachment of all the protons but does not, of course, distinguish between α- and β-hydrogens in a given methylene group. This distinction was readily achieved by using NOE difference spectroscopy measurements. Typically, irradiation of the protons of the methyl group at C-13 enhances the signals of its neighbors in space, viz., the 11β-, 12β-, 15β-, and 16β-protons as well as H-8.

Table I lists the complete assignments for the protons in 1 through 4, and, in general, there is excellent agreement between the data for these molecules with the shifts reported by Hall and Sanders for the analogous protons in 1-dehydrotestosterone and in 11β-hydroxyprogesterone.[15] The only serious discrepancies occur for the 12α- and 14α-protons in 2, and these provide an excellent opportunity to evaluate the diamagnetic anisotropy of the alkyne linkage.[16]

It was long ago realized that the anomalously shielded resonance of a terminal alkyne proton can be attributed to the anisotropic electron density distribution associated with the triple bond. It was originally proposed[17] that one could use the McConnell relationship,[18] viz.,

$$\sigma = \chi(1 - 3\cos^2\theta)/3R^3$$

where σ is the chemical shift increment, $R$ is the distance from the electrical center of gravity of the bond to the proton, and θ is the angle made by $R$ with the multiple bond axis, to quantify this effect. This formula, together with a value for the diamagnetic anisotropy, χ, of −16.5 $m^3$/mol allows one to evaluate the neighbor anisotropy effect of the alkyne moiety. It was later demonstrated[19] that this dipolar approximation is not reliable for protons close to the triple bond and that a better model invokes local anisotropic contributions. Inspection of models reveals that the 12α- and 14α-protons of 2 lie near the equatorial plane of the alkyne moiety and so should be deshielded relative to their resonance positions in estradiol itself. As shown in Table I, the aforementioned protons are indeed dramatically deshielded. The quantitative aspects of this phenomenon are deferred to another paper.

The incorporation of a $Co_2(CO)_6$ moiety has a negligible effect on the protons distant from the organometallic functionality. It is noteworthy that the deshielding of the protons at 12α and 14α is much decreased relative to that in the free alkyne (See Figure 2). Similar effects are seen for mestranol and its cobalt complex, 5. Examination of

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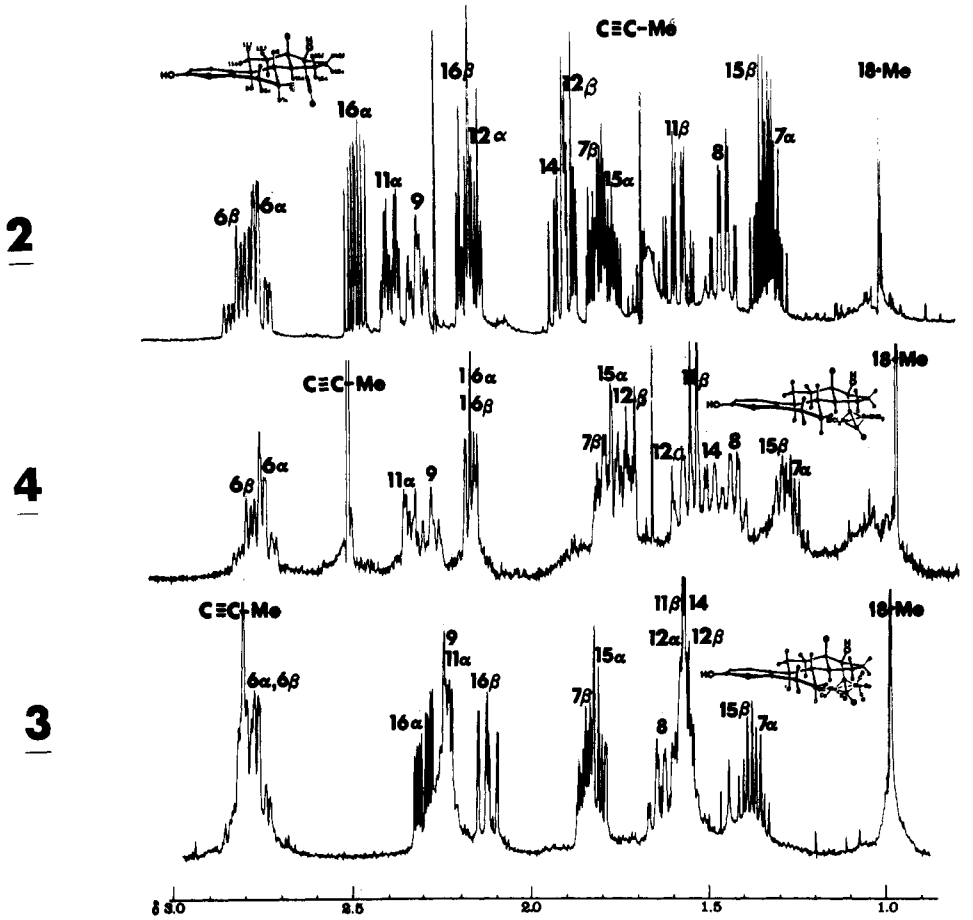


**Figure 2.** Section of the 500-MHz $^1H$ NMR spectra of molecules 2–4.

molecular models indicates that the 12$\alpha$-proton is positioned almost along the axis of a terminal carbonyl ligand. We have shown already[12] that the diamagnetic anisotropy of a Cr–C–O linkage is slightly larger than that of an alkyne group; by analogy, therefore, one can envisage a similar shielding cone for the Co–C–O fragment in a molecule. Nevertheless, one would need crystallographic data on 4 before attempting to evaluate $\chi$ for a carbonyl ligand attached to cobalt. When a $(C_5H_5)_2Mo_2(CO)_4$ unit is bonded to the propynyl substituent, its effect is again localized to the protons in the C and D rings. As with 4, the deshielding of the 12$\alpha$- and 14$\alpha$-positions, attributable to the diamagnetic anisotropy of the free acetylenic group, is not observed. However, this time another factor—the ring currents of the cyclopentadienyl moieties—can come into play and this is probably the cause of the shift changes at 12$\alpha$, 12$\beta$, and 16$\alpha$ (See Figure 2).

The $^{13}C$ NMR data for the molecules 1 through 5 are presented in Table II. The effects of complexation are minimal in the A, B, and C rings but are clearly visible in ring D. The assignments are based on heteronuclear $^1H$–$^{13}C$ shift correlated (COSY) experiments in conjunction with DEPT experiments which correlate the phase of the $^{13}C$ peak with the number of attached protons.

Of especial interest is the observation of two cyclopentadienyl resonances in both the $^1H$ and $^{13}C$ spectra of 3 (Tables I and II). This situation arises because of the asymmetric nature of the steroidal hormone which renders the $C_5H_5$ rings diastereotopic.[20] The same situation arises for the $Co_2(CO)_6$ derivative, 4, and in this case the two $Co(CO)_3$ moieties should be different. However, only a single carbonyl resonance is observed; this is rationalizable on the basis of carbonyl exchange between cobalts. In principle, the diastereotopic nature of the groups would be detectable via $^{59}Co$ NMR spectroscopy.

**Table II. 125-MHz $^{13}C$ NMR Chemical Shifts ($\delta$) in $C_6D_6$ Solvent**

| carbon | 1[a] | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| C-1 | 126.9 | 126.5 | 126.9 | 127.2 | 126.4 |
| C-2 | 113.5 | 112.7 | 113.6 | 113.7 | 111.6 |
| C-3 | 155.6 | 153.0 | 154.9 | 155.0 | 157.5 |
| C-4 | 115.9 | 115.3 | 116.3 | 116.2 | 113.6 |
| C-5 | 138.4 | 138.3 | 138.8 | 138.6 | 137.8 |
| C-6 | 30.2 | 29.6 | 30.4 | 30.3 | 29.0 |
| C-7 | 28.0 | 27.2 | 28.6 | 28.4 | 26.9 |
| C-8 | 39.8 | 39.5 | 38.8 | 40.6 | 39.2 |
| C-9 | 44.8 | 43.6 | 44.5 | 44.4 | 42.8 |
| C-10 | 132.3 | 132.7 | 133.4 | 132.7 | 131.5 |
| C-11 | 27.1 | 26.4 | 27.8 | 27.2 | 25.8 |
| C-12 | 37.6 | 32.9 | 32.4 | 34.0 | 31.9 |
| C-13 | 43.9 | 47.2 | 51.3 | 50.0 | 48.3 |
| C-14 | 50.8 | 49.4 | 50.1 | 50.5 | 49.3 |
| C-15 | 23.7 | 22.8 | 27.2 | 23.9 | 22.1 |
| C-16 | 31.0 | 39.0 | 37.1 | 44.1 | 43.6 |
| C-17 | 81.9 | 80.2 | 91.1 | 87.0 | 84.8 |
| C-18 | 11.5 | 12.8 | 15.7 | 16.2 | 14.7 |
| $C{\equiv}CCH_3$ | | 81.9[c] | 106.1 | 106.9 | |
| $C{\equiv}CCH_3$ | | 82.8[c] | 95.2 | 94.5 | |
| $C{\equiv}CCH_3$ | | 3.7 | 18.3 | 23.2 | |
| $C{\equiv}CH$ | | | | | 73.2 |
| $C{\equiv}CH$ | | | | | 106.5 |
| CO | | | *b* | 201.0 | 199.9 |
| $C_5H_5$ | | | 93.5/93.0 | | |
| MeO | | | | | 53.82 |

[a] These data (recorded in dioxane) are from: Blunt J. W.; Stothers J. R. *Org. Magn. Reson.* **1977**, *9*, 439. [b] Peaks too weak to observe. [c] Assignments could be reversed.

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To conclude, we report the syntheses and complete $^1H$ and $^{13}C$ NMR assignments of 17$\alpha$-propynyl estradiol and its $Co_2(CO)_6$ and $(C_5H_5)_2Mo_2(CO)_4$ derivatives. The proton shifts in the C and D rings of the hormone are discussed in terms of the anisotropy in diamagnetic susceptibility associated with the free and complexed acetylenic fragments.

## Experimental Section

NMR spectra were acquired at 11.74 T with a Bruker AM500 spectrometer. Proton spectra (500 MHz) and carbon spectra (125.7 MHz) were observed by using proton and proton/carbon dual probeheads, respectively. All spectra were recorded at 300 K and all chemical shifts measured relative to the chemical shift of tetramethylsilane. Homonuclear chemical shift correlation (COSY) experiments were carried out by using the following pulse sequence: delay-($\pi$/2,$^1$H)-$t_1$-($\pi$/2,$^1$H)-acquisition. Pulses were phase cycled according to reference 21. A 2-s recycle delay was used: the $\pi$/2,$^1$H pulse was 8 $\mu$s. A total of 32 transients were collected per unit time; 256 time increments of 1 ms were applied to characterize the $t_1$ domain and 1024 points were used to characterize $t_2$. A pseudo echo window function was applied in both $t_1$ and $t_2$ following zero filling once in the $t_2$ domain. Heteronuclear shift correlated experiments were carried out as described previously.[7]

All syntheses were carried out under an atmosphere of argon. Dry tetrahydrofuran and diglyme were distilled from sodium benzophenone ketyl. Infrared data were obtained on Perkin-Elmer 325 and 457 spectrometers.

**Synthesis of 17$\alpha$-Propynylestra-1,3,5(10)-triene-3,17$\beta$-diol.** Magnesium turnings (2.4 g, 0.1 mol) covered with THF were placed in a three-necked flask fitted with a thermometer and a dropping funnel. Pure ethyl bromide was added dropwise until the magnesium began to react; at this point the remaining ethyl bromide (7 mL, 0.1 mol) was dissolved in 50 mL of THF, and this solution was added dropwise to the reaction mixture. When the addition was complete, a gas inlet tube was fitted to the flask and propyne (13 mL, 0.1 mol) was gradually led from a -78 °C cold trap into the reaction mixture, which was stirred a further 2 h. Estrone (5.44 g, 0.02 mmol) in THF was added to the excess propynyl magnesium complex and the reaction mixture stirred for 4 h. After hydrolysis with aqueous ammonium chloride solution, extraction with ether and recrystallization from $H_2O$-MeOH, the sole product was the 17$\alpha$-propynylestradiol (**2**) (5.0 g, 16.1 mmol; 80%), mp 134 °C, exhibiting in the mass spectrum a parent peak at $m/z$ 310.[22] $^1H$ and $^{13}C$ data are collected in Tables I and II.

**Reaction of 2 with $Cp_2Mo_2(CO)_4$.** As described by Curtis,[23] $[CpMo(CO)_3]_2$ (1.1 g, 2.25 mmol) in diglyme was heated under reflux for 2 h to form $[CpMo(CO)_2]_2$. The solution was filtered and cooled, and **2** (0.6 g, 2.25 mmol) was added, and the solution was then heated at 80 °C for 3 h. After removal of solvent, the crude product was purified by TLC on silica gel plates using $CH_2Cl_2$ as eluent to give **3** (0.74 g, 0.99 mmol; 45%), mp 115 °C dec. The IR in $CH_2Cl_2$ exhibited $\nu_{CO}$ at 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.

**Reaction of 2 with Dicobalt Octacarbonyl.** $Co_2(CO)_8$ (0.4 g, 1.1 mmol) in THF (25 mL) was placed in a Schlenk tube, and **2** (0.31 g, 1.0 mmol) in THF (5 mL) was added dropwise and stirred at room temperature for 2 h. After filtration of the solution and evaporation of the solvent, the product was purified by TLC on silica gel plates using $CH_2Cl_2$/ethyl acetate (2:1) as eluent to give dark red crystals of **4** (0.24 g, 0.4 mmol; 40%), mp 125 °C. The IR in hexane exhibited $\nu_{CO}$ at 2088, 2049, 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.

**Reaction of $Co_2(CO)_8$ with Mestranol.** As with **4**, treatment of mestranol and dicobalt octacarbonyl gave dark red crystals of **5** (62%), mp 140 °C.[24] The IR in cyclohexane exhibited $\nu_{CO}$ at 2090, 2050, 2023, 2019, and 2010 cm$^{-1}$. An analytically pure sample was obtained by recrystallization from ether/petroleum ether. Anal. Calcd for $C_{27}H_{26}O_8Co_2$: C, 54.35; H, 4.36. Found: C, 54.51; H, 4.48.

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# Synthesis of Optically Active Isoquinuclidines Utilizing a Diastereoselectivity Control Element

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The development of a palladium-mediated cyclization via isomerization using a vinyl epoxide as an initiator and an amine as a terminator led to a facile cyclization to produce isoquinuclidines. The synthesis of the requisite cyclization precursor from (-)-quinic acid led to obtention of the isoquinuclidines in optically pure form. The substitution pattern of the resultant isoquinuclidine would allow further cyclization to either enantiomeric series of the iboga alkaloids. This "pseudo-meso" intermediate then can become a common intermediate to either ibogamine or catharanthine, the latter of particular importance in the synthesis of vinblastine analogues. During this study it has been observed that the olefination of an epoxy ketone proceeds with high geometrical control.

The azabicyclo[2.2.2]octane skeleton is found in many biologically active natural products, including the iboga alkaloids catharanthine (**1**) and ibogamine (**2**) as well as nonindole-containing alkaloids such as the cannivonines

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