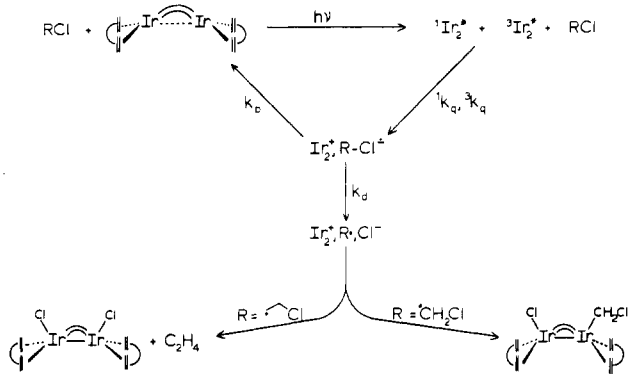
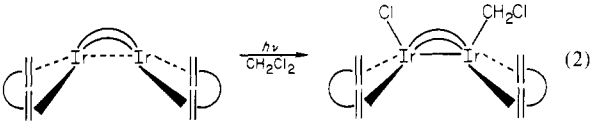


Figure 2. Proposed mechanism for the photochemical reaction of $[Ir(\mu\text{-pz})(COD)]_2$ with RCl.

Isolation of the product of the photoreaction of **1** with methylene chloride gave adduct **3** as identified by NMR.[6,7] Toepler pumping



(2)

showed the formation of no gaseous products. As in the case of DCE, net two-electron reduction of the substrate has occurred, leading in this case to the two-center oxidative addition product analogous to that observed in the thermal reaction of **1** with methyl iodide.[2]

The maximum quantum yield (0.047 ± 0.004) for the photoreaction with DCE was observed for 577-nm irradiation, corresponding to direct excitation of the $^1A_1 \rightarrow {}^3B_2$ electronic transition. However, both the $^1B_2$ and $^3B_2$ states appear to be reactive as shown by the fact that for hexane solutions of **1** with added methylene chloride or DCE both the $^1B_2$ emission intensity and the $^3B_2$ emission lifetime are quenched in accord with Stern-Volmer kinetics. The measured quenching rate constants (^3k_q) for the $^3B_2$ state by methylene chloride and DCE are 5.8×10^5 and 7.3×10^5 M^{-1} s^{-1}, respectively. The Stern-Volmer quenching constants for the $^1B_2$ state are 0.13 and 0.30 M^{-1}, which place lower limits of 1.3×10^9 and 3.0×10^9 M^{-1} s^{-1} on the singlet quenching rates (^1k_q), based on an upper limit of 100 ps for the singlet lifetime.[8]

Electrochemical reductions of halocarbons (RX) have been demonstrated to proceed via initial one-electron transfer to form the anion radical $RX^{-}\cdot$, which undergoes rapid unimolecular decomposition to form R· and X^- ($k_d = 3 \times 10^8$ s^{-1} for methyl chloride).[9] Because the reduction potentials for methylene chloride and DCE are -2.14 and ca. -2.1 V vs. SSCE,[10] respectively, outer-sphere reduction of either of these substrates by the $^3B_2$ excited state ($E° \sim -1.81$ V) is energetically feasible. The $^1B_2$ excited state also should be capable of reducing these materials, as it is predicted to be an even more powerful reductant ($E° \sim -2.1$ V vs. SSCE) than $^3B_2$. Using as a basis the results obtained for the rates of reversible electron-transfer quenching (k_q) of $^3B_2$ by simple organic electron acceptors,[2] we were able to obtain rough estimates for ^3k_q and ^1k_q for the halocarbon substrates. Neglecting effects due to changes in the reorganizational barrier to electron transfer, the experimentally determined dependence of ln (k_q) on quencher reduction potential predicts a value of $^3k_q = 1 \times 10^5$ M^{-1} s^{-1} for a halocarbon with a reduction potential of -2.1 V, in remarkably good agreement with the observed quenching rate constant. Analogous quenching data are not available for the singlet state; however, using an excited-state potential of -2.1 V and making the reasonable assumption that the overall shape of the quenching curve is the same as for the triplet state, we predict $^1k_q = 2 \times 10^6$ M^{-1} s^{-1}.

The results described above suggest that the mechanism of the observed photoreactions of **1** is that shown in Figure 2. The absence of radical recombination or disproportionation products indicates that the organic radical intermediates are effectively trapped within the solvent cage. Note that in the mechanistic scheme we have assumed that the only singlet and triplet reactivity difference is in the rate of the initial quenching step. However, the possibility of rate differences in reactions of the singlet- and triplet-generated radical pairs cannot be ruled out.

Acknowledgment. We thank Janet Marshall and Stephen Stobart for helpful discussions. This research was supported by National Science Foundation Grant CHE81-20419.

Registry No. 1, 89710-83-8; **2**, 89710-84-9; **3**, 89710-85-0; DCE, 107-06-2; methylene chloride, 75-09-2.

(6) Photolysis of 300 mg of **1** in 25 mL of methylene chloride for 1 h followed by the addition of 50 mL hexane and cooling to -10 °C for 48 h gave **3** as a red-brown powder in low yield (ca. 10%): NMR (CD_2Cl_2) (90 MHz) δ 7.70 (d, 2 H), 7.45 (d, 2 H), 6.14 (t, 2 H), 4.90 (s, 2 H). The COD protons appear as complicated multiplets in the range 2.0-4.7 (24 H). Irradiation of **1** in CD_2Cl_2 gave an identical NMR with the exception of the absence of the signal at δ 4.90. Calcd for $[Ir(\mu\text{-pz})(COD)]_2 \cdot CH_2Cl_2$: C, 33.69; H, 3.93; N, 6.86. Found: C, 33.61; H, 3.97; N, 6.91.

(7) The iodo analogue of **3** has been structurally characterized (Stobart, S. R., private communication).

(8) Milder, S., private communication.

(9) Kochi, J. K. "Organometallic Mechanisms and Catalysis"; Academic Press: New York, 1978; Chapter 7.

(10) Meikes, L.; Zuman, P. "Electrochemical Data"; Wiley: New York, 1974; Part I, Vol. A.

Total Synthesis of *d,l*-Fulvine and *d,l*-Crispatine

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Considering their interesting and diverse biological activity,[1] 11-membered pyrrolizidine dilactones such as fulvine (**1**), crispatine (**2**), or monocrotaline (**3**) have attracted little synthetic attention. These compounds are challenging targets for total synthesis due to their potential for stereochemical equilibration, β-elimination, and intramolecular carbonyl interaction. A successful synthesis of the less substituted dicrotaline (**4**) by Robins et al. using a variant of Corey lactonization and related work by Meinwald et al. on crobarbatine acetate[3] suggested to us that a general solution to these problems might be at hand. We were therefore somewhat surprised to find that none of the published techniques involving carboxyl activation were successful when applied to the more complex but structurally similar substrates **5a-c**, Potential preursors of crispatine (**2**).[4] Recognizable byproducts could be isolated from the 2-pyridyl thioester **5b**, which decomposed to protected crispatic anhydride **7**, and from the mixed phosphoric anhydride **5c**, which suffered a more peculiar but mechanistically related intramolecular cyclization.[5] We have

(1) Bull, L. B.; Culvenor, C. C. J.; Dick, A. I. In "Frontiers of Biology"; Neuberger, A., Tatum, E. L., Eds.; Wiley: New York, (1968; Vol. 9, *The Pyrrolizidine Alkaloids*; *Alkaloids (London)* **1971-1982**, *1-12* and references cited therein. Culvenor, C. C. J. In "Toxicology in the Tropics"; Smith, R. L., Bababunmi, E. A., Eds.; Taylor & Francis: London, 1980. Mattocks, A. R. *Chem.-Biol.* Interact. **1981**, *35*, 301.

(2) Brown, K.; Devlin, J. A.; Robins, D. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1819.

(3) Huang, J.; Meinwald, J. *J. Am. Chem. Soc.* **1981**, *103*, 861.

(4) X-ray structure of crispatine: Mackay, M. F.; Sadek, M.; Culvenor, C. C. J. *Acta Crystallogr.* **1984** *C40*, 470. Isolation: Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1963**, *16*, 239. Jones, A. J.; Culvenor, C. C. J.; Smith L. W. *Ibid.* **1982**, *35*, 1173.

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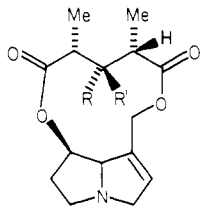
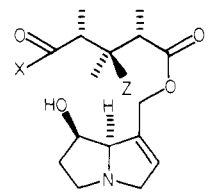
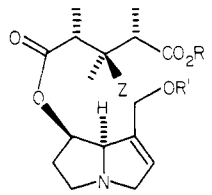


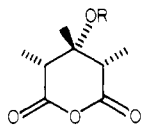
1, R = OH; R′ = CH_3
2, R = CH_3; R′ = OH
3, R = OH; R′ = CH_3; H = OH
4, R = OH; R′ = CH_3; Me = H
15, R = CH_3; R′ = OCH_2OCH_3



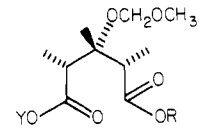
5a, X = StBu; Z = OCH_2OCH_3
b, X = SPy; Z = OCH_2OCH_3
c, X = $(PhO)_2PO_2$; Z = OCH_2OCH_3



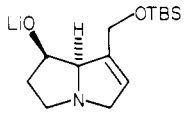
12, R = $CH_2CH_2SiMe_3$; R′ = TBS; Z = OCH_2OCH_3
13, R = $CH_2CH_2SiMe_3$; R′ = H; Z = OCH_2OCH_3
14, R = $CH_2CH_2SiMe_3$; R′ = Ms; Z = OCH_2OCH_3



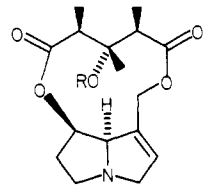
7, R = CH_2OCH_3
8, R = H



9, Y = H; R = $CH_2CH_2SiMe_3$
10, Y = $PO(OEt)_2$; R = $CH_2CH_2SiMe_3$



11

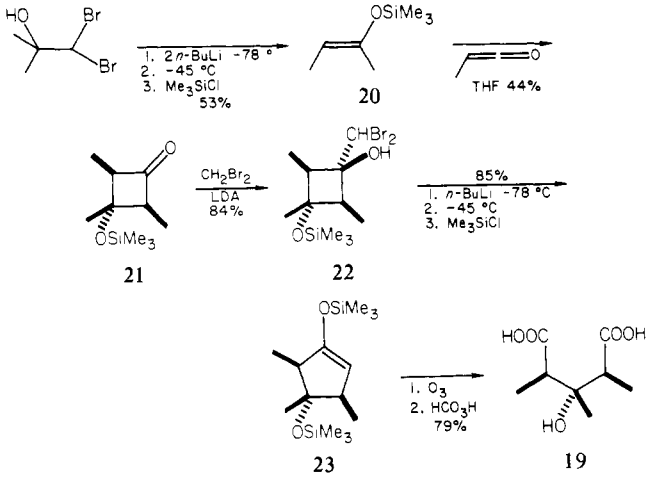


16, R = CH_2OCH_3
17, R = H

found a simple alternative cyclization method that avoids the intramolecular cyclization hazards inherent in carboxyl activation procedures and allows high-yield cyclizations and total synthesis of pyrrolizidine dilactones.

Our synthesis of crispatine begins with crispatic anhydride **8**, available from crispatic acid[6] by DCC cyclization (>95%). Hydroxyl protection ($P_2O_5/(CH_3O)_2CH_2$, −23 °C, >95%) affords **7** and anhydride cleavage with $(CH_3)_2AlOCH_2CH_2Si(CH_3)_3$ (C_6H_6, 28 h, reflux, 90%) results in the glutarate monoester **9**. Coupling of **9** via the mixed phosphoric anhydride **10** + DMAP with the lithium alkoxide **11** of synthetic monosilylated *d,l*-retronecine[7] gives the key intermediate **12**. Structure **12** is accompanied by equal amounts of a diastereomer (not shown) from nonselective coupling of *d,l*-**10** with *d,l*-**11**, 50–60% combined yield.

Scheme I



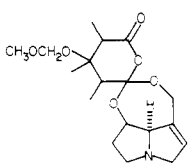
20 21 22 23 19

These isomers can be separated after cyclization as follows.

First, the primary hydroxyl group is liberated (H_2O–HF, THF, 95%) followed by mesylation with CH_3SO_2Cl/Et_3N–CH_2Cl_2. The mesylate **14** is not isolated but is diluted with acetonitrile and added over approximately 3 h to excess $(C_4H_9)_4N^+F^-$ hydrate in acetonitrile at 30 °C. This procedure results in spontaneous macrolactonization to give separable diastereomers **15** and **16** in 73–80% yield. Quantitative deprotection ($BF_3{\cdot}Et_2O$–C_2H_5SH) of **15** affords *d,l*-crispatine, mp 96–98 °C. Similarly, **16** can be deprotected to give *d,l*-isocrispatine (**17**), mp 112–114 °C. An exactly analogous sequence has been used to prepare *d,l*-fulvine (**1**),[8] mp 189–190 °C (dec), and *d,l*-isofulvine (**18**) (not shown), mp 124–126 °C, from fulvinic acid **19**, 85% yield for macrolactonization and 95–99% for deprotection. Both *d,l*-crispatine and *d,l*-fulvine are identical with samples of the natural products by all chromatographic and spectroscopic comparisons.[9] Due to the close parallels, the sequence from fulvinic acid to **1** and **18** will not be detailed. However, the published synthesis[6] of fulvinic acid is impractical and an alternative route has been devised (Scheme I). Features of general interest include the bromocarbenoid method for synthesis of the thermodynamically unstable *E* enol silane **20** (11:1 *E*:*Z*). The stereochemistry of this process was anticipated from the analogous outcome of highly efficient bromocarbenoid ring expansions[10] such as **22** to **23**. Also of interest is the selective 2 + 2 cycloaddition of methyl ketene[11] with **20** to give *meso*-cyclobutanone **21** having stereochemistry that corresponds to fulvinic acid after ring expansion and conventional oxidative cleavage. The cycloaddition stereochemistry corresponds to that predicted by the usual 2s + 2a model, although at least some of the historical reasons for accepting this strained transition-state geometry now seem suspect.[12]

The cyclization method described here works with similar efficiency on four different diastereomers of the fulvine–crispatine series. Comparable results are obtained with the simpler dicrotaline case (**4**) where the cyclization affords a 60% yield of dilactone, even without protecting the tertiary hydroxyl. We are hopeful that this approach will prove generally applicable to the

(5) The product of this cyclization is tentatively assigned the orthoester structure below, on the basis of consistent NMR signals and the presence of



a δ-lactone carbonyl absorption.

(6) Matsumoto, T.; Fukui, K.; Edwards, J. D., Jr. *Chem. Lett.* **1973**, 283.

(7) Prepared by reaction of *t*-$Bu(CH_3)_2SiCl$ + DMAP with synthetic *d,l*-retronecine: Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993.

(8) X-ray structure of fulvine: Sussman, L.; Wodak, S. J. *Acta Crystallogr., Sect. B* **1973**, *29*, 2918. Isolation: Schoental, R. *Aust. J. Chem.* **1963**, *16*, 233.

(9) We are grateful to Prof. C. J. Culvenor for samples of natural crispatine and fulvine.

(10) Taguchi, H.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1588. We have also observed a 4:1 preference for *E* enolate formation from $(C_3H_7)_2C(OH)CHBr_2$ + BuLi.

(11) McCarney, C. C.; Ward, R. S. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1600.

(12) The 2s + 2a transition state gained acceptance in part because monosubstituted ketenes gave "endo" substituted products with cyclopentadiene. It was assumed that these products are thermodynamically less stable than the "exo" diastereomers, and therefore the heroic 2s + 2a geometry seemed reasonable. Recently, it has been shown that the endo products are often *more* stable in these systems: Rey, M.; Roberts, S. M.; Dreiding, A. S. Roussel, A.; Vanlierde, H.; Toppet, S.; Ghosez, L. *Helv. Chim. Acta* **1982**, *65*, 703.

important monocrotaline system and analogous structures of other ring sizes. Only one example (integerrimine; Narasaka et al. ~30% in the activation-cyclization-isolation sequence)[13] of a 12-membered pyrrolizidine dilactone synthesis is reported to date. We will describe additional studies in these areas shortly.

Acknowledgment. This work was supported by the National Institutes of Health (CA 17918).

Registry No. (±)-**1**, 89772-18-9; (±)-**1** (methoxymethyl ether), 89772-21-4; (±)-**2**, 89772-17-8; **8**, 89710-44-1; (±)-**9**, 89710-45-2; **7**, 89710-46-3; (±)-**11**, 89710-47-4; (±)-**12** (isomer 1), 89710-48-5; (±)-**14**, 89725-98-4; (±)-**15**, 89710-49-6; (±)-**16**, 89772-16-7; (±)-**17**, 89772-19-0; (±)-**18**, 89772-20-3; (±)-**18** (methoxymethyl ether), 89772-22-5; **19**, 41478-07-3; (*E*)-**20**, 19980-31-5; (*Z*)-**20**, 19980-29-1; **21**, 89710-53-2; **22**, 89710-54-3; (±)-**23**, 89710-55-4; $(CH_3)_2C(OH)CN(Br)_2$, 24482-83-5; $(CH_3)_2AlOCH_2CH_2Si(CH_3)_3$, 89710-50-9; fulvinic acid, 89710-51-0; fulvinic anhydride methoxymethyl ether, 89710-52-1; crispatic acid, 41478-08-4; methyl ketene, 6004-44-0; (±)-**12** (isomer 2), 89772-23-6.

Supplementary Material Available: NMR data for synthetic crispatine and fulvine isomers and key precursors (2 pages). Ordering information is given on any current masthead page.

(13) Narasaka, K.; Sakakura, T.; Uchimura, T. Morimoto, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 455.

Stereoselectivity of Enzymatic Transfer of Hydrogen from Nicotinamide Coenzymes: A Stereochemical Imperative?

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Pyridine coenzyme-dependent dehydrogenases can be placed into two discrete groups based on stereoselectivity of reduction, namely those that transfer the *pro-R* hydrogen and those that transfer the *pro-S* hydrogen of the reduced nicotinamide ring. Many attempts have been made to provide a rational explanation for the stereochemical preferences of dehydrogenases.[1] Unfortunately, all the approaches thus far have suffered either from significant exceptions or, in the case of the empirical correlations, from having no demonstrable underlying mechanistic principle to explain the pattern.

Recently Benner and co-workers have proposed a correlation between the stereospecificity of dehydrogenases that reduce unconjugated carbonyls and the value of the equilibrium constant for the catalyzed reactions.[2-4] This proposal has two attractive features. First, they report an apparently strong correlation; that is, reactions with a value of $-\log E_{eq} > 11.2$ are *pro-R* specific and those with a value of $-\log E_{eq} < 11.2$ are *pro-S* specific. Second, a mechanistic rational is provided to explain their correlation. They argue that in order for a dehydrogenase to proceed with optimum efficiency, the redox potentials of the substrate and coenzyme must be matched. This is to be achieved by having the *pro-R*-specific dehydrogenases bind the coenzyme with the dihydronicotinamide ring anti and the *pro-S*-specific enzymes binding the ring syn. The proposed differences in microscopic redox potential engendered by these conformations, especially in regard to puckering of the ring, would then result in the desired matching of potentials.

The criteria for selecting enzymes to consider for their correlation are as follows:[3] "the enzyme must catalyze the interconversion of "simple" unconjugated carbonyls[5] with their corresponding alcohols, its natural substrate must be well-defined, and the equilibrium constant for the overall reaction of that substrate must lie at least 1 log unit away from the position of the "break" between *pro-R*- and *pro-S*-specific enzymes. *Any enzyme conforming to these criteria and not fitting the correlation we consider a violation of the correlation, necessarily prompting the reevaluation of the correlation and the theories supporting it.*" (Italics added.)

This communication reviews the published data for three dehydrogenases that meet the required criteria outlined by Benner and co-workers but do not fit their correlation. A reevaluation of the underlying theories is therefore justified and is also presented.

20α-Hydroxysteroid Dehydrogenase (1.1.1.149). In 1960, Wiest and Wilcox[6] isolated from rat ovaries an NADP-requiring 20α-hydroxysteriod dehydrogenase that transferred the *pro-R* hydrogen.[7] This enzyme conducts the crucial conversion of progesterone to 20α-hydroxy-4-pregnen-3-one based upon the hormone dependence of the enzyme levels.[8] The enzyme has a narrow range of substrate specificity and the value of $-\log E_{eq}$ for this reaction is 6.8.[6] A 20α-hydroxysteroid dehydrogenase has also been isolated form porcine testes[9] and it too conducts transfer of the *pro-R* hydrogen.[10]

3α-Hydroxysteroid Dehydrogenase (1.1.1.50). In 1967, an NADP-requiring 3α-hydroxysteroid dehydrogenase was isolated from rat liver and shown to have *pro-R* specificity.[11-13] The enzyme is specific for reduction of the 3-keto group of steroids. No equilibrium constant was measured for the reaction catalyzed by this particular enzyme; however, the reaction is the same (except for the sterochemistry of the hydrogen transfer) as that of 3α-hydroxysteroid dehydrogenase from *P. testosteroni* (1.1.1.50) where $-\log E_{eq} = 8.0$.[3] In summary, both the 3α- and 20α-hydroxysteroid dehydrogenases, which are *pro-R* specific, have equilibrium constants that are well within the "*pro-S* range" as defined by Benner and co-workers.

21-Hydroxysteroid Dehydrogenase (1.1.1.150). In 1963, Monder and White[14] purified a bovine adrenal 21-hydroxysteroid dehydrogenase that utilizes NAD and conducts a stereospecific transfer of the *pro-S* hydrogen.[15] The restricted specificity suggests that the 21-hydroxysteroid dehydrogenase plays a role in corticosteroid metabolism.[16] The value of $-\log E_{eq}$ for the reaction catalyzed by this *pro-S* enzyme is between 13.5 and 14,[14] placing it solidly within the "*pro-R* range" as defined by Benner and co-workers.

The lack of conformity of these enzymes to the correlation presented by Benner and co-workers calls for an objective look at the enzymes that *do* fit the pattern. First it should be noted

(1) (a) Bentley, G; Ludoweig, J; Mather, J. H.; Normore, W. M.; Tosi, L.; Udaka, S.; Vennesland, B. *Biochemistry* **1963**, *2*, 1009-1014. (b) Bentley, R. In "Molecular Asymmetry in Biology"; Academic Press: New York, 1970; Vol. 2, pp 1-89. (c) Alizade, M. A.; Brendel, K. *Naturwissenschaften* **1975**, *62*, 346-348. (d) You, K.; Arnold, L. J., Jr.; Kaplan, N. O. *Arch. Biochem. Biophys.* **1977**, *180*, 550-554. (e) You, K.-S.; Arnold, L. J., Jr.; Allison, W. S.; Kaplan, N. O. *Trends Biochem. Sci. (Pers. Ed.)* **1978**, *3*, 265-268.

(2) Benner, S. A. *Experientia* **1982**, *38*, 633-637.

(3) Nambiar, K. P.; Stauffer, D. M.; Kolodziej, P. A.; Benner, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 5886-5890.

(4) The initial impression made by Benner and co-workers in ref 3 was one of offering a solution to the puzzle of the stereochemical choices made by dehydrogenases. In reality the correlation is for only one, albeit important, category of dehydrogenases, the alcohol dehydrogenases. The category has been further narrowed by exclusion of polyol dehydrogenases and enzymes that reduce aldehydes or ketones conjugated to olefins.

(5) One assumes that only conjugation to olefins is to be excluded since a number of the indicated substrates contain carbonyl-carbonyl conjugation, e.g., all the α-keto carboxylic acids.

(6) Wiest, W. G.; Wilcox, R. B. *J. Biol. Chem.* **1961**, *236*, 2425-2428.

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(8) Rodway, R. G.; Rothchild, I. *J. Endocrinol.* **1980**, *84*, 391-395.

(9) Sato, F., Takagi, Y. and Shikita, M. *J. Biol.* Chem. **1972**, *247*, 815-823.

(10) Hatano-Sato, F., Takagi, Y.; Shikita, M. *J. Biochem. (Tokyo)* **1973**, *74*, 1065-1067.

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(12) Bjorkhem, I.; Danielsson, H. *Eur. J. Biochem.* **1970**, *12*, 80-84.

(13) Berseus, O. *Eur. J. Biochem.* **1967**, *2*, 493-502.

(14) Monder, C; White, A. *J. Biol. Chem.* **1963**, *238*, 767-774.

(15) Furfine, C. S.; White, A. *J. Biol. Chem.* **1968**, *243*, 1190-1197.

(16) Bradlow, H. L.; Monder, C. In "Steroid Biochemistry"; Hobkirk, R., Ed.; CRC Press: Boca Raton, Florida, 1979; Vol. 1, pp 47-79.

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