suggest an 8% impurity or isomer.

Fractions 21–24 contained 13.1 mg (6%) of ketol **24**: IR ($CHCl_3$) ν_{max} 3300 (br, OH), 2900, 1705 (C=O), 1210 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.09 (d, 3 H, J = 6 Hz, $CHCH_3$), 1.13 (s, 3 H, CH_3), 1.5–1.6 (m, 2 H), 1.9–2.0 (m, 2 H), 2.1–2.4 (m, 3 H), 2.55 (br d, 1 H, J = 9 Hz, C(O)C*H*COH).

Fractins 15–20 were combined (86 mg) and examined by GC (column A, 170 °C) and ^1H NMR. GC analysis indicated that the oil was a 1:1 mixture of ketol(s) **24** and/or **25** and lactone **23**. The ^1H NMR spectrum indicated that the oil was primarily composed of 48% of lactone **23**, 14% of ketol **24**, and 39% of ketol **25**. The ^1H NMR chemical shifts of the methyl protons for ketol **25** were 1.17, 1.23, and 1.33 ppm.

Method B. Sodium Methoxide. Ketone **11** (210 mg, 1 mmol) was allowed to react with sodium methoxide in methanol with conditions identical with those described under Method A for preparation of enone **20b**. The yield, after flash chromatography, was 128 mg (56%) of enone **22b** and 32 mg (15%) of lactone **23**, each having identical TLC, GC, and spectral properties to those samples prepared in Method A.

Single-Crystal X-ray Structure Determination of 18. Crystals suitable for X-ray diffraction analysis were grown from dichloromethane–pentane.[30] The crystal used for data collection was a colorless, transparent prism measuring 0.05 × 0.08 × 0.22 mm. Lattice constants and intensity data were measured at 298 K and λ 1.54178 Å (Cu K_α) on a Syntex $P2_1$ automated four-circle diffractometer equipped with a graphite crystal monochromotor.

Data collection was attempted only to $2\theta < 120.0°$. A total of 2469 reflections were collected (one form, $\pm h,k,l$) yielding 2092 unique intensities and 1250 reflections with $I > 2.58\sigma(I)$. This set of reflections was used in the structure solution and refinement. Data reduction included corrections for background, extinction, Lorentz and polarization effects, and anomalous dispersion effects. No absorption correction was necessary. Systematic absences for $0k0$, $k = 2n + 1$, and $h0l$, $l = 2n + 1$, unambiguously indicated the space group to be $P2_1/c$ (C^5_{2h}). Cell data: monoclinic; a = 14.072 (6) Å, b = 13.395 (7) Å, c = 7.803 (3) Å, V = 1411 (1) Å^3, ρ_c = 1.263 g cm^{-3}, Z = 4.

The structure was solved by direct methods (MULTAN).[31] Calculations were performed on a DEC VAX 11/780 computer system. Correct positions for all of the non-hydrogen atoms were deduced from an E map. Subsequent least-squares difference Fourier calculations revealed positions for all of the hydrogen atoms; however, owing to the paucity of data, the hydrogen positions were not refined. In the final cycle of least squares, all non-hydrogen atoms were refined independently with anisotropic thermal coefficients and the hydrogen atoms were fixed in "idealized" positions while an isotropic thermal parameter was refined for the group. Refinement converged at R = 0.053 (R_w = 0.060). The final difference Fourier map was featureless. An ORTEP drawing[32] of the molecule in the crystal is presented in Figure 1. The non-hydrogen atoms are depicted as 35% probability ellipsoids. The hydrogen atoms are shown as arbitrary spheres and are not labeled.

Acknowledgment. This research was supported in part by grants from the National Science Foundation (81-11843 and 82-04485). High-field NMR spectra were obtained with the aid of the University of Illinois NSF Regional Instrumentation Facility (NSF CHE 79-16100). The acquisition of GC/MS analyses in the School of Chemical Sciences Mass Spectrometry Center was aided by a grant from the National Institute of General Medical Sciences (GM 27029). The X-ray crystal analysis was performed by Dr. Scott Wilson of the School of Chemical Sciences Crystallography Facility.

Registry No. 1, 93350-19-7; **5**, 37457-15-1; **6**, 93350-16-4; **7**, 93350-17-5; **8**, 93350-18-6; **10**, 20990-14-1; **11**, 93350-20-0; *cis*-**12**, 93350-22-2; *trans*-**12**, 93350-23-3; **13**, 93350-21-1; **14a**, 93350-26-6; **14b**, 93350-25-5; **15**, 93350-27-7; (*R**,*R**)-**17**, 93350-24-4; (*R**,*S**)-**17**, 93350-28-8; **18**, 93382-93-5; **19**, 5073-65-4; **20a**, 52086-93-8; **20b**, 93350-29-9; **21**, 6134-90-3; **22b**, 93350-30-2; **23**, 93350-31-3; **24**, 93350-32-4; **25**, 93350-33-5; DBU, 6674-22-2; $BrCH_2CO_2Bu$-*t*, 5292-43-3; CH_2=$CHCOCH_3$, 78-94-4; pyrrolidine, 123-75-1.

Supplementary Material Available: Tables of bond distances, bond angles, atomic positional parameters, and atomic thermal parameters for keto lactone **18** (4 pages). Ordering information is given on any current masthead page.

(30) The crystal was grown by Sharbil Firsan. We are grateful for his assistance with this structure determination.

(31) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.-P.; Woolfson, M. M. "MULTAN 80, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data"; Universities of York, England, and Louvain-1a-Neuve, Belgium, 1980.

(32) Johnson, C. K. "ORTEP-II: A Fortran Thermal Ellipsoid Plot Program", ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1971.

Reduction of Aromatic Carbonyl Compounds Promoted by Titanium Trichloride in Basic Media. Stereochemistry Studies

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Aromatic ketones, which are not affected by Ti(III) chloride in acidic medium, react smoothly in basic media to afford the reductively coupled products according to the increase of the reducing power of Ti(III) ion with increasing pH. Benzil, benzoin, and methoxybenzoin give the corresponding alcohols. The observed stereochemistry is discussed in terms of intermolecular Ti bridging control (*dl* > meso) when intramolecular Ti complexation is prevented and in terms of steric control (meso > *dl*) when two sites of potential Ti complexation are available in the molecule. The reagent, Ti(III) chloride, is selective in that many other functional groups are unaffected by it.

Within the past few years there have been a number of investigations that have used the McMurry reagents ($TiCl_3/LiAlH_4$ or $TiCl_3$/K, Li, Zn, and Cu) to affect the reduction of aldehydes and ketones.[1] These reductions

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Table I. Reduction of p-XPhC(=O)CH$_3$ and PhC(=O)R in Basic Media

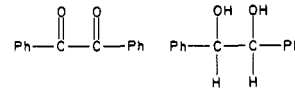
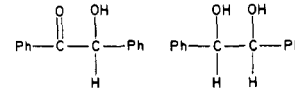
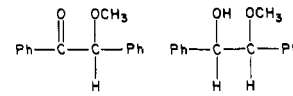
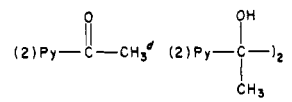
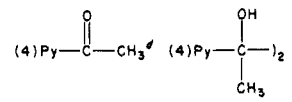
entry	p-X	R	alcohol 12,[a] %	dimer 13,[a] %	dl/meso ratio[b]
a	OCH_3	CH_3		83	3.2
b	CH_3	CH_3		92	3.0
c	H	CH_3		83	2.7
d	Cl	CH_3		90	2.3
e	CF_3	CH_3		95	2.2
f	CN	CH_3		75	2.0[c]
g	OH	CH_3	75		
h	NH_2	CH_3	90		
i	NH_3^{+d}	CH_3	40		
m	H	C_2H_5[d]		95	2.5
n	H	t-C_4H_9[d]	30	30	1.2
p	H	CH_2Ph		62	2.7
q	H	Ph	44	50	

[a] Yield of alcohol and dimer are based on the starting substrate. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by ^{13}C NMR spectroscopy. [d] 50%, 35%, and 24% of the starting ketone has been recovered for entries i, n, and p, respectively.

lead, depending upon the exact reducing agent, to either dimeric pinacols[2] or dimeric olefin products.[1] For some time we have been focusing our attention on the coupling properties of the Ti(III) ion, which, unlike the low valent titanium species, is commercially available as titanium trichloride in aqueous solution. The Ti(III) ion certainly is a milder reducing agent and in the course of our investigations it has been observed that at low pH only carbonyl compounds activated toward reduction by an electron-withdrawing group (CN, COOH, $COOCH_3$, or CHO) are coupled to the corresponding pinacols in high yields.[3] As we have reported and stressed in a preliminary note,[4] the reducing power of Ti(III) ion markedly increases by increasing the pH to such an extent that in strongly basic media it promotes the reduction of simple aromatic carbonyl compounds (benzaldehyde and acetophenone) to the corresponding pinacols, like the Ti(II) species does under anhydrous conditions.[2] The possiblity of increasing the reducing power of the Ti(III) ion simply by changing the medium from acidic to basic considerably extends the scope and generality of this reductive coupling method. Furthermore, the present reaction is applicable to carbonyl compounds bearing other functional groups, such as an ester, acid, alcohol, ether, and nitrile. In contrast, the previous methods are not useful for such functionalized compounds because complicated side reactions also occur.[1,2] This notable characteristic, together with the operationally simple experimental conditions required by the Ti(III) species, prompted us to extend our investigation to several other carbonyl compounds with the aim to define (a) the synthetic utility and limitations of the method and (b) the possible mechanism for the titanium-mediated pinacol coupling by studying the steric and inductive factors that can affect the dl/meso ratio in the pinacolic products.

The data of this investigation are summarized in two tables. Table I summarizes the yields and ratios of dl/meso diastereomers formed in basic media in the dimerization of para-substituted acetophenones with groups of suitable inductive characteristics and of alkyl aromatic

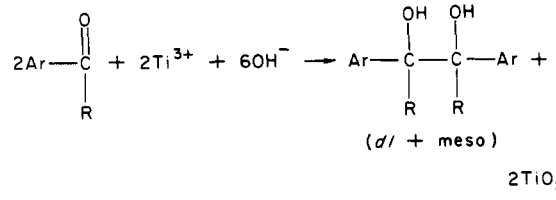
Table II. Reduction of α-Functionalized Carbonyl Compounds in Basic Media

entry	substrate	reactn product 14	yield, %[a]	dl/meso ratio[b]
r			98	0.23
s			98	0.30
t			95	2.70[c]
u			50	0.80
v			20	4.50

[a] Yields are based on the starting substrate. [b] Determined by ^{1}H NMR spectroscopy. [c] Threo/erythro ratio. [d] 30% and 75% of the alcohol has been obtained for entries u and v, respectively.

ketones for which the steric hindrance of the alkyl group is increased from methyl to *tert*-butyl. In Table II are collected the results of experiments involving the reduction in basic media of α-dicarbonyl, α-functionalized carbonyl compounds, and alkyl pyridinyl ketones that are potentially capable of intramolecular complexation with the titanium ion. In all cases investigated both diastereoisomers were obtained. The relative amounts of each diastereomer in each crude reaction mixture were measured by ^{1}H or ^{13}C NMR spectroscopy. Employing pure diastereomers, the configurations of which had been previously established, we were able to correlate the ^{1}H or ^{13}C NMR spectra to an individual stereomer. The reactions, which were completed within few minutes, were performed at ambient temperature under nitrogen. Optimum yields of reduction products were obtained by the rapid addition of a 15% aqueous acidic Ti(III) chloride solution to the ketones in methanol and enough 30% NaOH or 30% NH_4OH solution to keep the pH 11–12 at the end of the addition.

The reducing power of the Ti(IV)/Ti(III) system is strongly pH dependent. The equation[5] $E = 0.100 - 0.1182\ pH + 0.0591 \times lg[TiO^{2+}/Ti^{3+}]$ is valid in acidic solution where Ti(IV) is present as soluble TiO^{2+}, and the equation[5] $E = 0.029 - 0.2364\ pH - 0.0591 \times lg[Ti^{3+}]$ is valid in basic medium where insoluble TiO_2 is formed. According to this the carbonyl compounds of Table I are recovered unchanged when allowed to react with Ti(III) chloride in aqueous acidic solution but undergo rapid one-electron reduction with formation of the corresponding pinacols in aqueous alkaline solution in agreement with the stoichiometry of the following reaction.



(1) (a) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708. (b) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255. (c) McMurry, J. E. *Acc. Chem. Res.* **1983**, 405. (d) Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147. (e) Makuiyama, T.; Sato, T.; Hama, J. *Chem. Lett.* **1973**, 1041.

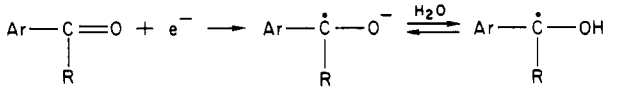
(2) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260.

(3) Clerici, A.; Porta, O. *J. Org. Chem.* **1982**, *47*, 2852.

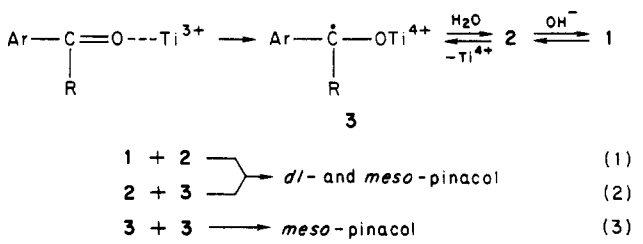
(4) Clerici, A.; Porta, O. *Tetrahedron Lett.* **1982**, *23*, 3517.

(5) Pourbaix, M. "Atlas d'Equilibrês Electrochimiquês"; Gouthier-Villars: Paris, 1963, p 213.

The hydrodimerization of aromatic carbonyl compounds in aqueous alkaline media[6] occurs via coupling of the radical anion 1 and the neutral ketyl radical 2 according to

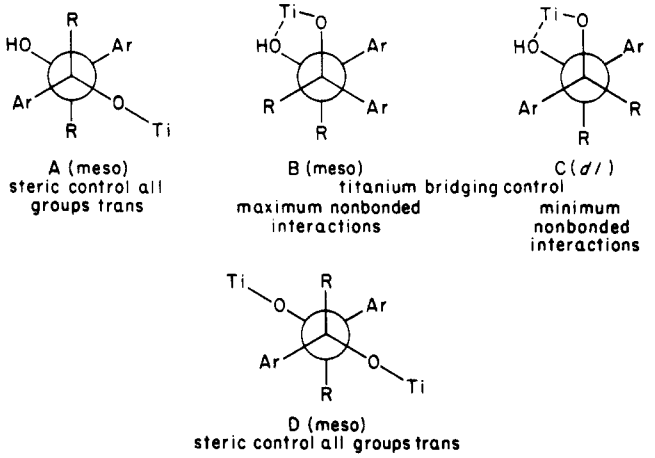


The dimerization of 2 is appreciable in neutral or acidic solution and is negligibly small in basic medium, and the dimerization of 1 would be expected to occur only in nonaqueous solution in the presence of a strong base like alkoxide anion. In our reaction conditions, because of the great affinity of titanium for oxygen, the electron-transfer step may well involve an initial coordination between the carbonyl group and the Ti(III) ion as shown.[2,7] Radical

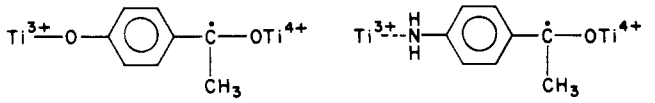


anions bonded to titanium species, such as 3, have been recently detected by ESR spectroscopy and their hyperfine splitting constants reported.[7] There are three modes of combination (eq 1, 2, and 3) that should be considered and the resultant stereochemistry of pinacol products will depend on whether steric or polar interactions are important in the transition state. It is known that radicals sterically crowded predominantly yield meso dimers,[8] while others afford equal amounts of both dimers.[9] Considering the most likely conformation at the time of carbon–carbon formation, only A and D avoid nonbonded interactions between like groups. Consequently, if steric factors predominated, the above reasoning would predict predominance of the meso isomer. The results of this study, in contrast, consistently demonstrate that for a series of aromatic ketones investigated (Table I) the *dl* isomer is favored.

The preference for the *dl* product may be explained by a titanium bridging control in the dimerization step. Because of the great affinity of titanium ion for the oxygen atom, at the time of coupling, radical 2 will be most likely oriented to maximize the electrostatic interaction with the Ti(IV) ion of 3. This stabilizing effect due to the titanium bridging would preferentially lead to the *dl* form as shown with C where interactions have been minimized. Since structural effects are usually excellent criteria for evaluating a mechanism with respect to its generality, we have undertaken a detailed study of the substituent effect of the radical on the stereochemistry of its dimerization. Relative to unsubstituted acetophenone, the observed ratios of *dl* to meso pinacols (Table I, entries a–f) increase



or decrease with the corresponding electron-releasing facility of the para substituent. Substitution on the phenyl ring with an electron releasing group would be expected to enhance the electron availability of the bridging oxygen for the titanium ion. This would make C more actractive relative to A and reflect an increase in the *dl*/meso ratio. On the contrary, electron-withdrawing groups should decrease the electron availability on the bridging oxygen and produce a decrease in the *dl*/meso ratio. The results of entries a–f well correlate with this reasoning and the observed ratios of *dl*- to *meso*-pinacols follow a Hammet correlation with the σ para values[10] of the substituents in the phenyl ring (correlation coefficient, $r = -0.968$, $\rho = -1.47$). The results of entries g and h, which do not follow the observed trend are of interest in that they emphasize the fundamental role played by Ti(III) ion in these reactions. In fact, if the para substituents on the phenyl ring are hydroxy and amino, the reduction leads not to pinacols but to the corresponding alcohol. This behavior has to be ascribed to the great affinity of Ti(III) ion for oxygen and nitrogen. There are structural and thermodynamic indications that the aryloxy group does not only form a σ-bond with titanium but also acts as a strong π-donor and donates at least three electrons to the metal.[12,13] This complexation should make an important contribution to the stability of the intermediate radicals 4 and 5 and will reverse the polar nature of the substituent.



Disproportionation[13] or further reduction of 4 and 5 lead to the corresponding alcohols.[14] In agreement with this the *p*-aminoacetophenone is the only acetophenone investigated that reacts with Ti(III) ion in acidic medium

(6) (a) Stocker, J. H.; Kern, D. H. *J. Org. Chem.* **1968**, *33*, 291. (b) Madjo, L.; Saveant, J. M. *J. Electroanal. Chem.* **1973**, *47*, 146. (c) Rusling, J. F.; Zuman, P. *J. Org. Chem.* **1981**, *46*, 1906.

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(10) Jaffè, H. H. *Chem. Rev.* **1953**, *53*, 191.

(11) Huffman, J. C.; Moloy, K. G.; Marsella, J. A.; Caulton, K. G. *J. Am. Chem. Soc.* **1980**, *102*, 3009.

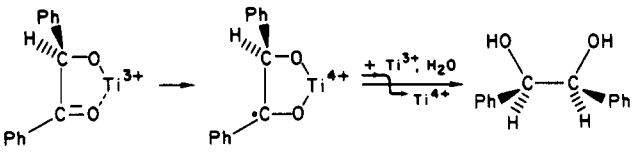
(12) Marsella, J. A.; Moloy, K. G.; Caulton, K. G. *J. Organometal. Chem.* **1980**, *201*, 389.

(13) (a) Evans, A. G.; Evans, J. C.; Emes, P. J.; Haider, S. I. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1121. (b) Cohen, S. G.; Sherman, W. V. *J. Am. Chem. Soc.* **1963**, *85*, 1642. (c) Huyser, E.; Neckers, D. C. *Ibid.* **1963**, *85*, 3641.

(14) It is worth noting that the ^{1}H NMR spectrum of the crude reaction mixture of entry g shows four doublets, four singlets, and four quartets at δ values corresponding to CH_3 (δ 1.2–1.6), OH (δ 4.0–4.3) and CH (δ 4.0–5.2) groups, respectively, suggesting that the crude alcohol exists as a mixture of four possible titanium complexes. While addition of D_2O does not produce any change, the addition of CF_3COOH simplifies the spectrum and the well-resolved doublet and quartet patterns of the pure alcohol appear.

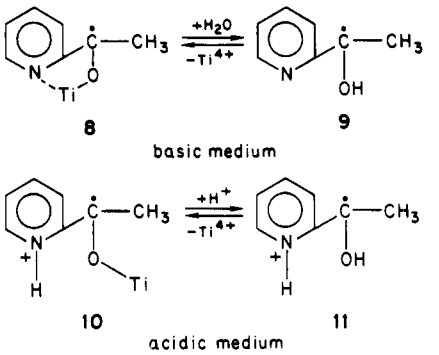
also (entry i). This means that both protonation of the amino group and its coordination with Ti(III) ion produce the same effect on the reduction of the carbonyl group. To prove whether the determining factor in the stereochemistry would be the titanium bridging over the steric control even in the presence of bulky groups, we have increased the size of R from methyl to *tert*-butyl and examined the reduction in basic medium (Table I, entries m, n, and p). In the conformer A an R–R interaction is not present while in the conformer C an R–R interaction is important, thus the bulkier the R group the smaller the *dl*/meso ratio should be. The R–R interaction increases from methyl to ethyl group, but little change was observed in the *dl*/meso ratio (2.7 and 2.5, respectively, for entry c and m). This interaction is certainly greater by replacing the methyl with a *tert*-butyl group (entry n), where the *dl*/meso ratio decreases from 2.7 to 1.2 and the dimeric product is isolated in lower yield. In the case of R = CH_2Ph (entry p), the *dl*/meso ratio (2.7) is mostly determined by the titanium bridging control, being the steric hindrance far away from the radicalic center. Both for pivalophenone and benzophenone the corresponding alcohol is also obtained; disproportionation equilibria[13,15] of their intermediate radicals may be the preferred path.

All the factors so far discussed (e.g., increase of Ti(III) ion reducing power with increasing the pH and titanium bridging control in the *dl*/meso ratio) are strengthened from the data of Table II. Treatment of benzil by Ti(III) ion in acidic solution affords benzoin in 95% yield, while benzoin and methoxybenzoin are recovered unchanged. In basic media, owing to the increased reducing power of Ti(III) ion, the reduction of both benzil and benzoin (entry r and s) leads to hydrobenzoin in almost quantitative yield, and the meso is strongly favored over the *dl* form (81:19 and 77:23, respectively). In contrast the reduction of methoxybenzoin (entry t) is threo selective (threo/erythro ratio is 73:27). The preference for the meso form is in line with an intramolecular titanium chelation where the formation in strong basic medium of the stable complex **6**, which evolves to the reacting chelate radical **7**, determines the stereochemistry in accordance with the Cram's cyclic model.[16]



6 **7**

In the analogous reduction of methoxybenzoin an intramolecular titanium complexation is now prevented and the open chain model of Cram[16] or Ahn[17] rationalizes the preference for the threo isomer. Rather revealing is the stereochemistry observed for the dimers of 2- and 4-acetylpyridine in acidic and basic media. On going from low to high pH the *dl*/meso ratio decreases from 1.7[18] to 0.8 for 2-acetylpyridine (entry u) while it increases from 1.1[18] to 4.5 for the analogous reaction of 4-acetylpyridine (entry v). The following reasoning, modeled after that employed for the acetophenone system, may be considered to account for these results. In basic solution, 2-acetylpyridine is present as a free base and an intramolecular N complexation of titanium does not permit the occurence of the intermolecular titanium bridging between radicals **8** and **9**, which are about to couple. Their combination would be subject to simple steric control, yielding predominantly the meso form. In acidic solution, the protonated nitrogen is not available for the intramolecular titanium complexation and the combination of **10** and **11** with possible interspecies titanium bridging favors the formation of the *dl* isomer. In the case of 4-acetylpyridine,



8 **9**

basic medium

10 **11**

acidic medium

an intramolecular complexation of titanium is prevented in basic media as well and the intermolecular titanium bridging controls the stereochemistry in both acidic and basic solution. The increase of the *dl*/meso ratio from 1.1 in acidic to 4.5 in basic medium is in accord with the stronger electron-withdrawing power of the protonated to the unprotonated nitrogen atom. The stronger is the electron-withdrawing nature of a substituent, the lower is the *dl*/meso ratio (Table I) because of a decrease of the electron availability for the bridging oxygen.[19]

Experimental Section

General Methods. Melting points were obtained on a Kofler apparatus (uncorrected). IR spectra were determined on a Perkin-Elmer Model 177. Mass spectra were determined on a Hitachi Perkin-Elmer Model RMU 6D at 70 eV. ^1H NMR spectra were obtained on a 90-MHz Varian Model EM-390, 100-MHz Varian Model XL-100, and 300-MHz Bruker Model CX P-300 (solvent $CDCl_3$, δ values, Me_4Si internal standard). ^{13}C NMR spectra were obtained on a Varian Model XL-100. Column and thin-layer chromatography were carried out by using Merck silica gel 60 (0.06–0.24 mm) and Merck Kieselgel GF-254 (2 mm) plates, respectively. The starting materials were commercially available research grade chemicals and were used as received.

General Procedure. To a well stirred solution of the ketone (10 mmol) in CH_3OH (40–60 mL) was added 25 mL of a 30% NaOH (or NH_4OH) solution. To the resulting solution an excess of a 15% $TiCl_3$ aqueous solution was added dropwise (1–2 min) by keeping the temperature (ice–water bath) below 20 °C. After 5–10 min, the resulting suspension was diluted with 30 mL of water and then extracted with ethyl acetate (3 × 50 mL). Quantitative recovery of the reaction products was generally achieved by continuous liquid-liquid extraction of the aqueous layer with ethyl acetate. The combined organic extracts were washed with 30 mL of water and dried over anhydrous Na_2SO_4. After removal of the solvent the compounds of Tables I and II were obtained as sole reaction products. To obtain the *dl*/meso ratio, a suitable aliquot of the crude reaction mixture was dissolved in $CDCl_3$ and analyzed by NMR spectroscopy. The *dl*/meso ratio was determined by comparison of peak heights of the methyl groups of the two diastereomers or by comparison of peak heights of the same groups having different shifts depending on their *dl* or meso configurations.

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(19) The 1.7 and 1.1 *dl*/meso ratio for 2- and 4-acetylpyridine, respectively, correlate well with the σ^* values of position 2 and 4 in the pyridine ring (e.g., considering the nitrogen atom as a substituent in position 2 and 4 of the aromtic ring): Jaffè, H. H. *Chem. Rev.* **1953**, *53*, p 246.

Spectroscopic Data. All compounds of Table I and II were isolated and their structural assignments were consistent with the data reported in the literature. The structures of *dl* and meso, threo and erythro stereomers were deduced from the following data:

2,3-Bis(*p*-methoxyphenyl)-2,3-butanediol (13a). Repeated recrystallization of the crude reaction product from MeOH gave the low melting point form which, according to the configurational assignment of Mosher et al.,[20] showed it to be the *dl* isomer: mp 121 °C (lit.[20] mp 122–123 °C); NMR ($CDCl_3$) δ 1.42 (6 H, 2 CH_3, s), 3.0 (2 H, 2 OH, s, D_2O exchange), 3.76 (6 H, 2 OCH_3, s), 6.7 (4 H, Ph H, m), 7.2 (4 H, Ph H, m). Similar treatment of the crude mixture with CH_3COOH (the *dl* isomer is quite soluble in this solvent) followed by repeated recrystallization from EtOH yielded the meso isomer: mp 190 °C (lit.[21a] mp 192–193 °C); NMR ($CDCl_3$) δ 1.50 (6 H, 2 CH_3, s), 2.7 (2 H, 2 OH, s, D_2O exch), 3.8 (6 H, 2 OCH_3, s), 6.8 (4 H, Ph H, m), 7.2 (4 H, Ph H, m).

2,3-Di-*p*-tolyl-2,3-butanediol (13b). Separation of the pure isomers from the crude reaction mixture was achieved as described by Backer et al.[22] *dl*: mp 97 °C (lit.[21b] mp 95 °C); NMR ($CDCl_3$) δ 1.43 (6 H, $2CH_3C(OH)$, s), 2.35 (6 H, 2 CH_3, s), 2.6 (2 H, 2 OH, s, D_2O exch), 7.2 (8 H, Ph H, s). Meso: mp 133–134 °C (lit.[21b] mp 134–135 °C); NMR ($CDCl_3$) δ 1.49 (6 H, 2 $CH_3C(OH)$, s), 2.35 (6 H, 2 CH_3, s), 2.4 (2 H, 2 OH, br, D_2O exchange), 7.2 (8 H, Ph H, s).

2,3-Diphenyl-2,3-butanediol (13c). The *dl* isomer was obtained by repeated crystallization from petroleum ether/ether (9:1) of the crude isomeric mixture: mp 124–125 °C (lit.[6a] mp 125 °C); NMR ($CDCl_3$ δ 1.40 (6 H, 2 CH_3, s), 2.6 (2 H, 2 OH, s, D_2O exchange), 7.2 (10 H, Ph H, s). The meso isomer was isolated by preparative thin-layer chromatography (30% hexane in ethyl acetate as eluant) and recrystallized from petroleum ether/ether (8:2): mp 120 °C (lit.[6a] 121 °C); NMR ($CDCl_3$) δ 1.50 (6 H, 2 CH_3, s), 2.3 (2 H, 2 OH, s, D_2O exch), 7.2 (10 H, Ph H, s).

2,3-Bis(*p*-chlorophenyl)-2,3-butanediol (13d). Separation of the pure isomers from the crude reaction mixture was not achieved. Preparation of the *dl* isomer according to the procedure reported[23] by a method employing Cram's rule of asymmetric induction,[24] permitted the configurational assignment of the crude isomeric mixture. *dl*: mp 184 °C (lit.[23] mp 185.5–186.5 °C); NMR ($CDCl_3$) δ 1.40 (6 H, 2 CH_3, s), 2.8 (2 H, 2 OH, br, D_2O exchange), 7.2 (8 H, Ph H, m). *dl* and meso mixture: NMR ($CDCl_3$) δ 1.40 (6 H, 2 CH_3, *dl*, s), 1.45 (6 H, 2 CH_3, meso, s), 2.5 (2 H, 2 OH, br, D_2O exchange), 7.2 (8 H, Ph H, m).

2,3-Bis[*p*-(trifluoromethyl)phenyl]-2,3-butanediol (13e). Complete separation of the two pure isomers was unsuccessful. Only a small crop of the pure meso isomer was isolated by repeated crystallization from hot heptane of the crude isomeric mixture. Meso: mp 120–121 °C (lit.[25] mp 119–120 °C); NMR ($CDCl_3$) δ 1.53 (6 H, 2 CH_3, s), 2.4 (2 H, 2 OH, br, D_2O exchange), 7.2–7.8 (8 H, Ph H, m). *dl* and meso mixture: NMR ($CDCl_3$) δ 1.50 (6 H, 2 CH_3, *dl*, s), 1.53 (6 H, 2 CH_3, meso, s), 2.3–2.9 (2 H, 2 OH, br, D_2O exchange), 7.2–7.8 (8 H, Ph H, m).

2,3-Bis(*p*-cyanophenyl)-2,3-butanediol (13f). *dl* and meso mixture: NMR ($CDCl_3$) δ 1.47 (6 H, $2CH_3$, s), 2.8 (2 H, 2 OH, br, D_2O exch), 7.2–7.6 (8 H, Ph H, m); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 24.2 (CH_3, *dl*), 24.4 (CH_3, meso).

1-(4-Hydroxyphenyl)-1-ethanol (12g). Removal of the solvent gave a white solid[14] that was recrystallized from ethanol/benzene to afford **12g**: mp 130–131 °C (lit.[26] mp 132–133 °C), NMR ($CDCl_3$) δ 1.4 (3 H, CH_3, J = 6 Hz, d), 4.1 (1 H, 1 OH, s, D_2O exchange), 4.75 (1 H, CH, J = 6 Hz, q), 6.75 (2 H, Ph H, d), 7.2 (2 H, Ph H, d).

1-(4-Aminophenyl)-1-ethanol (12h and 12i): mp 92 °C (lit.[27] mp 92–93 °C); NMR ($CDCl_3$) δ 1.35 (3 H, CH_3, J = 6 Hz, d), 3.3–4.0 (3 H, OH, NH_2, br, D_2O exchange), 4.65 (1 H, CH, J = 6 Hz, q), 6.5 (2 H, Ph H, d), 7.1 (2 H, Ph H, d).

3,4-Diphenyl-3,4-hexanediol (13m). The pure isomers were obtained by fractional crystallization of the crude isomeric mixture. Meso: mp 135 °C (from pentane) (lit.[28] mp 133–134 °C, lit.[29] mp (138 °C); NMR ($CDCl_3$)[22] δ 0.59 (6 H, 2 CH_3, J = 7.5 Hz, t), 1.55 (2 H, CH_2, J = 14.6, 7.5 Hz, dq), 2.0 (2 H, 2 OH, br, D_2O exchange), 2.36 (2 H, CH_2, J = 14.6, 7.5 Hz, dq), 7.2 (10 H, Ph H, s). *dl*: mp 100 °C (from pentane) (lit.[28] mp 98 °C, lit.[29] mp 86 or 114 °C); NMR ($CDCl_3$)[22] δ 0.60 (6 H, 2 CH_3, J = 7.3, t), 1.7 (2 H, CH_2, J = 14.6, 7.3 Hz, dq), 2.08 (2 H, CH_2, J = 14.6, 7.3 Hz, dq), 7.1 (10 H, Ph H, s).

2,2,5,5-Tetramethyl-3,4-diphenyl-3,4-hexanediol (13n). The crude reaction mixture was fractionated on silica gel (benzene as eluant). Early fractions gave the *dl*–meso mixture of **13n**. Further elution afforded 2,2-dimethyl-1-phenyl-1-propanol (**12n**): mp 80 °C (lit.[28] mp 84–87 °C, lit.[30] mp 40–45 °C); NMR (CCl_4) δ 0.9 (9 H, *t*-C_4H_9, s), 1.6 (1 H, OH, s, D_2O exchange), 4.28 (1 H, *H*C(OH), s), 7.17 (5 H, Ph H, s). The isomers **13n** were separated by preparative thin-layer chromatography, the meso form eluting first with pentane. Meso: mp 198–200 °C (from ether) (lit.[28] mp 200 °C); NMR ($CDCl_3$) δ 0.60 (18 H, 2 *t*-C_4H_9, s), 2.5 (2 H, 2 OH, s), 7.2–7.4 and 7.9–8.2 (10 H, Ph H, m). *dl*: mp 135–137 °C (from ether) (lit.[28] mp 136 °C); NMR ($CDCl_3$) δ 0.64 (18 H, 2 *t*-C_4H_9), 3.5 (2 H, 2 OH, s, D_2O exchange), 7.2–7.4 and 7.9–8.2 (10 H, Ph H, m).

1,2,3,4-Tetraphenyl-2,3-butanediol (13p). The crude reaction product was fractionated on silica gel (eluant 30% ethyl acetate in hexane). The initial fractions gave the unreacted deoxybenzoin. Further elution provided a mixture of *dl*- and *meso*-**13p**. Fractional crystallization in heptane afforded the pure meso isomer: mp 210 °C (lit.[31] mp 213–214 °C); NMR ($CDCl_3$)[31] δ 2.0 (2 H, 2 OH, br, D_2O exchange), 2.97 (2 H, CH_2, J = 14 Hz, d), 3.68 (2 H, CH_2, J = 14 Hz, d), 7.2 (10 H, Ph H, m). *dl*: mp 170–172 °C (lit.[31] mp 171–172 °C); NMR ($CDCl_3$)[31] δ 2.5 (2 H, 2 OH, s, D_2O exchange), 3.0 (2 H, CH_2, J = 14 Hz, d), 3.48 (2 H, CH_2, J = 14 Hz, d), 7.2 (10 H, Ph H, m).

Tetraphenylethanediol (13q). Recrystallization of the crude crystalline product from acetone afforded pure **13q**: mp 200 °C (lit.[32a] mp 182, mp 193–195 °C); NMR ($CDCl_3$) δ 3.0 (2 H, 2 OH, s, D_2O exchange), 7.2 (20 H, Ph H, m). Concentration of the mother liquor gave a thick oil, which after recrystallization from ligroin, afforded colorless needles of diphenylmethanol **12q**: mp 68–70 °C (lit.[22b] mp 69 °C); NMR ($CDCl_3$) δ (1 H, OH, J = 6 Hz, d, D_2O exchange), 5.82 (1 H, CH, J = 6 Hz, d), 7.3 (10 H, Ph H, m).

1,2-Diphenyl-1,2-ethanediol (14r and 14s). The crude reaction product was chromatographed on Merck silica gel with 10% ethyl acetate in hexane. The first fractions provided the meso isomer: mp 137 °C (from ether) (lit.[6a] mp 136 °C); NMR ($CDCl_3$) δ 2.6 (2 H, 2 OH, D_2O exchange), 4.84 (2 H, 2 CH, s), 7.0–7.3 (10 H, Ph H, m). Further elution with 30% ethyl acetate in hexane provided a mixture of *dl* and meso isomers that was chromatographed on a Merck silica gel preparative thin-layer plate to afford the pure *dl* isomer: mp 120 °C (lit.[6a] mp 120 °C); NMR ($CDCl_3$) δ 2.0 (2 H, 2 OH, s, D_2O exchange), 4.62 (2 H, 2 CH, s), 7.0–7.3 (10 H, Ph H, m).

2-Methoxy-1,2-diphenylethanol (14t). Separation of the isomers was not achieved. Threo and erythro mixture:[33] NMR ($CDCl_3$) δ 2.0–3.0 (1 H, OH, br, D_2O exchange), 3.2 (3 H, OCH_3, erythro, s), 3.25 (3 H, OCH_3, threo, s) 4.1 (1 H, *H*C(OCH_3), AB system, J = 8.4 Hz, threo), 4.3 (1 H, *H*C(OCH_3), AB system, J = 5.4 Hz, erythro), 4.65 (1 H, *H*C(OH), AB system, J = 8.4 Hz,

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threo), 4.85 (1 H, HC(OH), AB system, J = 5.4 Hz, erythro), 7.0–7.35 (10 H, Ph H, m); mass spectrum (70 eV), m/e 210 ($M^+ - H_2O$), 178, 121, 107.

2,3-Di-2-pyridyl-2,3-butanediol (14u) and 2,3-Di-4-pyridyl-2,3-butanediol (14v). For detailed separation of *dl* and meso isomers and spectroscopic assignments see ref 18.

Registry No. (±)-**12g**, 93453-79-3; (±)-**12h**, 93453-80-6; (±)-**12n**, 57377-60-3; **12g**, 91-01-0; *dl*-**13a**, 93453-74-8; *meso*-**13a**, 62154-11-4; *dl*-**13b**, 22985-88-2; *meso*-**13b**, 22985-87-1; *dl*-**13c**, 22985-90-6; *meso*-**13c**, 4217-65-6; *dl*-**13d**, 93453-75-9; *meso*-**13d**, 93453-77-1; *dl*-**13e**, 93528-45-1; *meso*-**13e**, 93528-46-2; *dl*-**13f**, 93453-76-0; *meso*-**13f**, 93453-78-2; *dl*-**13m**, 16020-87-4; *meso*-**13m**, 16020-86-3; *dl*-**13n**, 63882-18-8; *meso*-**13n**, 63846-48-0; *dl*-**13p**, 93453-81-7; *meso*-**13p**, 93453-82-8; **13g**, 464-72-2; *dl*-**14r**, 655-48-1; *meso*-**14r**, 579-43-1; *threo*-**14t**, 50778-88-6; *erythro*-**14t**, 50778-87-5; *dl*-**14u**, 20445-39-0; *meso*-**14u**, 20445-38-9; *dl*-**14v**, 83179-65-1; *meso*-**14v**, 83179-64-0; $TiCl_3$, 7705-07-9; *p*-$MeOC_6H_4C(O)CH_3$, 100-06-1; *p*-$MeC_6H_4C(O)CH_3$, 122-00-9; $PhC(O)CH_3$, 98-86-2; *p*-$ClC_6H_4C(O)CH_3$, 99-91-2; *p*-$CF_3C_6H_4C(O)CH_3$, 709-63-7; *p*-$CNC_6H_4C(O)CH_3$, 1443-80-7; PhC(O)C(O)Ph, 134-81-6; (±)-PhC(O)CH(OH)Ph, 579-44-2; (±)-PhC(O)CH(OMe)Ph, 5987-95-1; 2-$PyC(O)CH_3$, 1122-62-9; 4-$PyC(O)CH_3$, 1122-54-9; *p*-$HOC_6H_4C(O)CH_3$, 99-93-4; *p*-$NH_2C_6H_4C(O)CH_3$, 99-92-3; *p*-$NH_3^+C_6H_4C(O)CH_3$, 93453-73-7; $PhC(O)CH_2CH_3$, 93-55-0; $PhC(O)CH_2Ph$, 451-40-1; PhC(O)-*t*-Bu, 938-16-9; PhC(O)Ph, 119-61-9.

New Preparation and Controlled Alkaline Hydrolysis of 21-Bromo-20-ketopregnenes. A Facile Synthesis of Deoxycorticoids[1]

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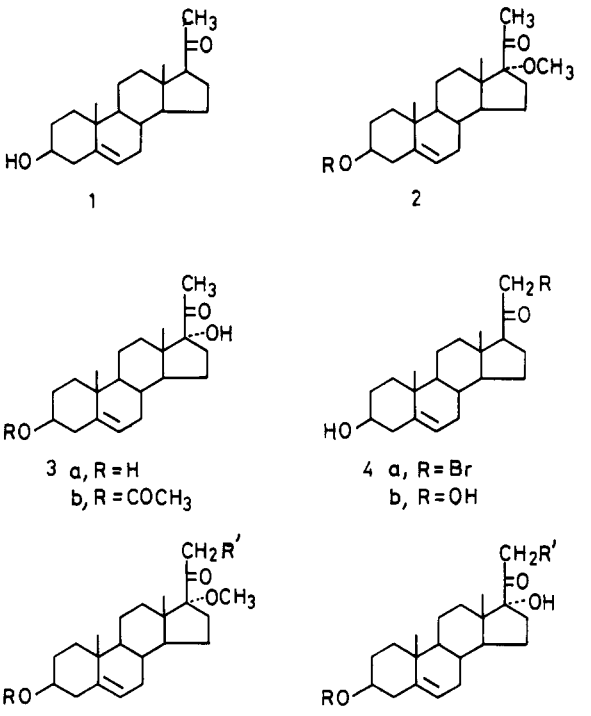
Syntheses of deoxycorticoids **7b**, **8b**, and **9b** are described. Treatment of 20-oxo steroid 1 with 3 mol equiv of $CuBr_2$ in MeOH in the presence or absence of pyridine gave the 21-bromide **4a** or the 17α-methoxide **2** in high yields, respectively. When 6 mol equiv of the brominating reagent was used in the absence of pyridine, the 21-bromo 17α-methoxide **5a** was formed. 17α-Hydroxy 20-ones **3** could be similarly converted to the 21-bromides **6a** and **6b**. Oxidation of **4a**, **5a**, and **6a** with CrO_3 and subsequent isomerization of a double bond at C-5 with acid gave the corresponding 4-en-3-ones **7a**, **8a**, and **9a**, of which **7a** and **9a** were efficiently hydrolyzed to **7b** and **9b** under controlled conditions with a K_2CO_3–H_2O–acetone system. On the other hand, **8a** was converted to **8b** by reaction with $NaOCH_3$ in MeOH.

Introduction of the 21-hydroxyl function into the 17-acetyl side chain of a 20-ketopregnene is of central importance in the partial synthesis of corticoids. One of the attractive chemical methods involves direct C-21 halogenation of a 20-ketopregnane and subsequent displacement of the resulting 21-halo compound by acetate or hydroxide.

Direct halogenation of a 20-oxo steroid lacking a substituent (e.g., OH or CH_3) at C-17 with the common reagent such as Br_2 generally does not give a satisfactory yield of the 21-bromo derivative,[2] although Ringold and Stork[3] reported a versatile method for direct C-21 iodination of 20-ketopregnenes with a 4-en-3-one or 5-en-3β-ol system. While displacement of a 21-bromo 20-one by hydroxyl can be accomplished by careful control of reaction conditions,[4] it is preferable to use acetate instead, because a Favorskii rearrangement[5] is involved in the reaction and the product, 21-hydroxy 20-one, is sensitive to basic reagents.

Glazier[6] reported that the reaction of 3β-hydroxy-5-pregnen-20-one (**1**) with $CuBr_2$ in MeOH resulted in the formation of 17α-methoxy derivative (**2**) in a modest yield without affecting the integrity of the olefinic bond at C-5. We recently discovered a high yield and controlled stereoselective alkaline hydrolysis of steroidal 16α-bromo 17-ones[7,8] and 2α-bromo 3-ones.[9]

Chart I



We now report the previously unreported direct bromination at C-21 of 20-ketopregnenes **1**, **2**, and **3** with

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