Synthesis of *anti*- and *syn*-Diol Epoxides of *trans*-4,5-Dihydro-4,5-dihydroxybenzo[*j*]fluoranthene and *trans*-9,10-Dihydro-9,10-dihydroxybenzo[*j*]fluoranthene

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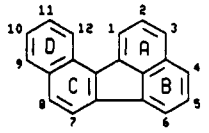
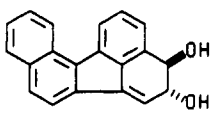
The preparation of diastereomeric *anti*- and *syn*-epoxides of benzo[*j*]fluoranthene (BjF) 4,5- and 9,10-dihydrodiols is described. The *anti*-diol epoxides were prepared from the corresponding dihydrodiols by epoxidation with *m*-chloroperoxybenzoic acid. The isomeric *syn*-diol epoxides were synthesized by base-catalyzed (Amberlyte IRA-400) cyclization of the bromo triol derivatives which in turn were prepared from the respective dihydrodiols by treatment with *N*-bromoacetamide in aqueous THF. New methods were employed for the preparation of 4- and 10-hydroxyBjF which are precursors for BjF-4,5-dihydrodiol and BjF-9,10-dihydrodiol. Cyclodehydration of 2-[2-(9-methoxy-11-hydroxybenzo[*a*]fluoren-11-yl)ethyl]-1,3-dioxane in polyphosphoric acid afforded 4-methoxyBjF (from which the phenol is readily prepared) in 87% yield. Reaction of 1-(4-methoxyphenyl)-acenaphthylene with ethyl diazoacetate is catalyzed by copper–bronze and gave a mixture of diastereomeric cyclopropane carboxylates. These were converted to the corresponding aldehydes by diisobutylaluminum hydride reduction and Swern oxidation followed by cyclodehydration with polyphosphoric acid to give 10-methoxyBjF in 91% yield. It had previously been reported that reduction of BjF-4,5-quinone to BjF-4,5-dihydrodiol occurs in low yield due to overreduction to a mixture of tetrahydro diols and triols. We now report that complexation of the quinone with silver nitrate followed by reduction with potassium borohydride in the presence of oxygen affords BjF-4,5-dihydrodiol in 91% yield.

Introduction

Benzo[*j*]fluoranthene (BjF) is a nonalternant polycyclic aromatic hydrocarbon (PAH) which is tumorigenic to mice and is prevalent in the human respiratory environment.[1] Despite the extensive studies which have been performed to determine the mechanisms of action of alternant PAH such as benzo[*a*]pyrene and chrysene, relatively little work has been done on nonalternant PAH such as BjF.[2,3] Studies performed in our laboratories indicate that two dihydrodiol metabolites, *trans*-4,5-dihydro-4,5-dihydroxyBjF (**1**) and *trans*-9,10-dihydro-9,10-dihydroxyBjF (**2**) may be associated with the tumorigenic activity of the parent hydrocarbon.[1d,4] Dihydrodiols frequently undergo



BjF



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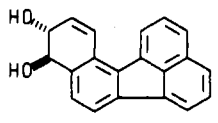

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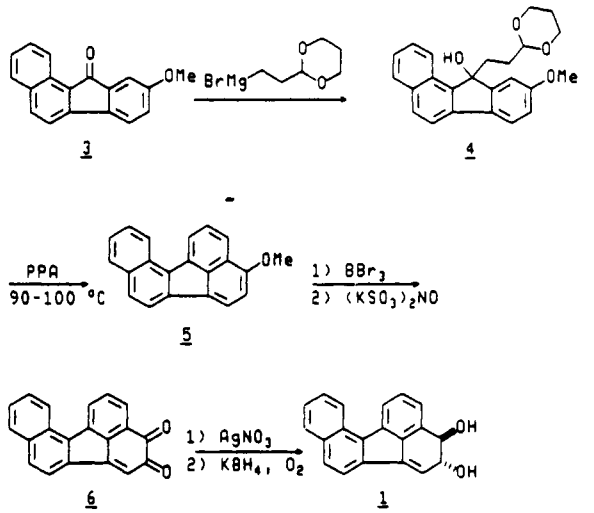
Scheme I



further metabolic activation to electrophilic diol epoxides which can alkylate DNA and initiate a tumorigenic response.[5] To evaluate the possibility that diol epoxides derived from **1** and **2** may serve as ultimate carcinogenic metabolites of BjF, we have synthesized the diastereomeric *anti*- and *syn*-diol epoxides of **1** and **2**. The *anti*- and *syn*-diol epoxides of **1** are structurally unique among electrophilic PAH metabolites in that one of the carbons of the epoxide ring is quaternary and doubly benzylic. Distinctive structural features such as these may impart unusual biological activity to these diol epoxides. We also report new and more expedient syntheses for both **1** and **2**. As a pivotal step in these syntheses we report a modification of a widely-used procedure for the preparation of *trans*-dihydrodiols by reduction of *o*-quinones.[6] This procedure may find utility in cases where overreduction

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(3) (a) Nordqvist, M.; Thakker, D. R.; Vyas, K. P.; Yagi, H.; Levin, W.; Ryan, D. E.; Thomas, P. E.; Conney, A. H.; Jerina, D. M. *Mol. Pharmacol.* **1981**, *19*, 168. (b) Hodgson, R. M.; Weston, A.; Grover, P. L. *Carcinogenesis* **1983**, *4*, 1639. (c) Weston, A.; Hodgson, R. M.; Hewer, A. J.; Kuroda, R.; Grover, P. L. *Chem.-Biol. Interact.* **1985**, *54*, 223.

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of *o*-quinones to tetrahydro diols is problematic.[6b,7,8]

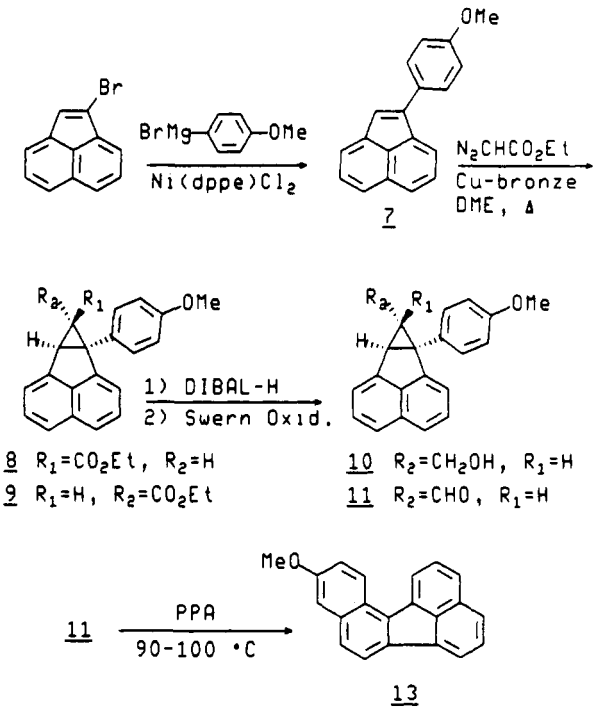
Results and Discussion

Preparation of 1. Dihydrodiols are common precursors to both *anti*- and *syn*-diol epoxides. Previously we reported syntheses for the 4,5- and 9,10-dihydrodiols of BjF.[7] The synthesis of 1 relied upon stereospecific reduction of BjF-4,5-dione which occurred in low yield due to overreduction to the tetrahydro diol. The immediate precursor to BjF-4,5-dione is 4-hydroxyBjF which was prepared by a rather lengthy synthesis. We recently reported new procedures for the preparation of BjF derivatives substituted in the B or D ring.[9] Modifications of these procedures have been employed here for the preparation of 4- and 10-hydroxyBjF.

Reaction of 9-methoxy-11*H*-benzo[*a*]fluoren-11-one (**3**)[7] with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane afforded hydroxy acetal **4** in 93% yield. Cyclodehydration in polyphosphoric acid at 90 °C gave 4-methoxyBjF **5** in 87% yield (Scheme I). Conversion of **5** to BjF-4,5-dione **6** was accomplished in good yield as described previously.[7]

The reduction of *o*-quinones of polycyclic aromatic compounds with sodium or potassium borohydride in the presence of oxygen has been widely used for the synthesis of dihydrodiols.[6,10] The mechanism for this transformation is believed to involve reduction of the quinone by borohydride to give a small amount of dihydrodiol accompanied by the catechol. In the absence of oxygen, the reaction may stop at the catechol intermediate, providing only a low yield of dihydrodiol. Oxygen converts the catechol back to its quinone form so that the cycle can continue until all of the starting material has been transformed to dihydrodiol. Evidence for this process is provided by the reduction of catechols and catechol diacetates to dihydrodiols under the same conditions.[6] In most instances this reaction gives good to excellent yields of dihydrodiols. Several examples of quinones which resist reduction or undergo overreduction have been reported. Most of the compounds falling into this category are quinones in which one of the carbonyl groups forms part of a bay region. Among these compounds are benz[*a*]anthracene-1,2-dione, triphenylene-1,2-dione, and benzo[*e*]pyrene-9,10-dione.[6b,8b] We had previously observed that BjF-4,5-dione was totally consumed by treatment with KBH_4 in the presence of air. The major product was 4,5,6,6a-tetrahydroBjF-4,5-diol accompanied by a pair of diastereomeric 4,5,6,6a-tetrahydroBjF-4,5,6a-triols and the 4,5-dihydrodiol.[7] It was thought at the time that overreduction was occurring as a result of conjugate addition of the hydride reagent to the double bond of the quinone, followed by further reduction of the dione. Lanthanide salts, particularly cerium(III) chloride, have been used in selective 1,2-reductions of enones.[11] However, the use of cerium(III) chloride to alter the product ratios in favor of the dihydrodiol met with no success. In a control experiment it was shown that reduction of the 6,6a-double bond in BjF-4,5-dihydrodiol is remarkably facile in the presence of excess potassium borohydride. Reductions of 1,1-diarylethenes by hydride reagents have been reported previously.[12] Attempts to use stoichiometric amounts of potassium borohydride for the reduction of BjF-4,5-dione were to no avail. It is well-known that silver can complex with the π-electrons of olefinic double bonds. A search of the literature revealed at least one instance where such a complex has been used to protect an olefin from reduction under catalytic hydrogenation conditions.[13] In an enone system such as found in BjF-4,5-dione, coordination of Ag^+ (a soft Lewis acid) with the C=C bond (a soft Lewis base) is more likely than with the harder carbonyl oxygen. BjF-4,5-dione was stirred with silver nitrate in 95% EtOH for 30 min, and then air was bubbled through the solution as potassium borohydride was added portionwise, 1 equiv every 30 min, until the red-violet fluorescence of the catechol was no longer detected by TLC. In general 5–6 equiv were required for the reaction. After filtration of the black precipitate of silver(0) and normal workup, the mixture was purified by flash chromatography to afford dihydrodiol **1** in 91% yield (Scheme I). For unknown reasons the yield of this reduction is sensitive to the scale on which the reaction is performed with reactions on less than 50 mg of substrate giving the highest yields. It should also be noted that **1** has a propensity for oxidation back to the quinone and should be stored under argon and protected from light.

Scheme II



Preparation of 2. The synthesis of **2** began with the Ni(II)-catalyzed coupling[14] of 1-bromoacenaphthylene with (4-methoxyphenyl)magnesium bromide which gave **7** in 72% yield (Scheme II). Reaction of **7** with ethyl diazoacetate in the presence of copper–bronze afforded a 1:2.5 ratio of the diastereomeric *syn*- and *anti*-cyclopropanecarboxylates **8** and **9** in 68% yield accompanied by diethyl maleate and/or diethyl fumarate. Syn diastereomer **8**, in which the naphthyl and ester moieties are on the same side of the cyclopropane ring, is identified by the upfield

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(10) Harvey, R. G. *Synthesis* **1986**, 605.
(11) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
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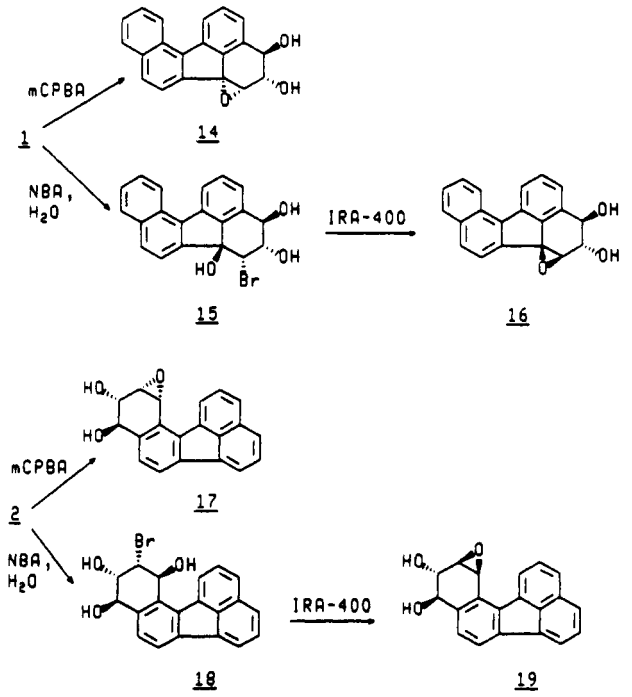
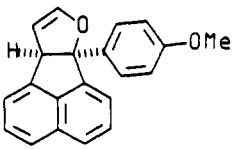
(13) Subbarao, R.; Venkateswara, G.; Achaya, K. T. *Tetrahedron Lett.* **1966**, 379.
(14) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

Scheme III



chemical shifts for the CH_2 and CH_3 of the ester (3.63 and 0.65 ppm) relative to anti diastereomer **9** (4.00–3.96 and 1.06 ppm). This upfield shift is due to shielding of the ester by the large aromatic naphthalene ring. Reduction of **8** and **9** with excess DIBALH afforded predominantly a single carbinol, identified as anti alcohol **10** in 96% yield. Apparently during the reduction some isomerization of syn ester **8** to anti ester **9** occurs. In a previous study pyridinium chlorochromate (PCC) had been used for oxidization of the alcohol to the aldehyde.[9] However, the use of PCC in the present case afforded a complex mixture of products. Swern oxidation (oxalyl chloride, DMSO, Et_3N, −78 °C),[15] however, cleanly gave aldehyde **11** in 84% yield. A sample of the aldehyde in $CDCl_3$ gave the expected ^{1}H-NMR spectrum when recorded immediately after preparation of the solution. When the spectrum of the same solution was recorded after standing at room temperature for 15 min, no aldehyde protons were observed. The ^{1}H- and ^{13}C-NMR spectra were consistent with fused furan derivative **12** which may be formed upon rearrangement of aldehyde **11** in the presence of traces of acid found in $CDCl_3$. No similar products were observed previously from the *p*-fluoro derivative,[9] suggesting that the electron-donating *p*-methoxy group may make such a process particularly facile in the case of aldehyde **11**. Treatment of either **11** or **12** with polyphosphoric acid at 90–100 °C gave 10-methoxyBjF **13** in 91% yield. Conversion of **13** to **2** was carried out as previously described.[7]



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Synthesis of Diol Epoxides of 1 and 2 (Scheme III). Conversion of BjF-4,5-dihydrodiol to *trans*-4,5-dihydroxy-*anti*-6,6a-epoxy-4,5,6,6a-tetrahydroBjF (**14**) was accomplished in 95% yield by treatment with freshly purified *m*-chloroperoxybenzoic acid[16] in anhydrous THF. The syn diastereomer was not detected by ^{1}H-NMR spectroscopy. Partial NMR data for the diol epoxides and their immediate presursors are given in Table I. The vicinal hydroxyl groups exist in the trans diequatorial conformation in acetone solution as evidenced by the coupling constant of the methine protons $J_{4,5}$ = 8.3 Hz. This conformation is similar to that which has been reported for other *anti*-diol epoxides of PAH in which the hydroxy groups do not reside in a bay region.[17] The orientation of H_6 is observed to be cis with respect to H_5 ($J_{5,6}$ = 1.0 Hz), confirming the identity of **14** as the *anti*-diol epoxide.

syn-Diol epoxide **16** was prepared in near quantitative yield from tetrahydro bromo triol **15** by treatment with Amberlite IRA-400 basic anion exchange resin (freshly activated) in anhydrous THF under Ar for 2.5 h. Best results were obtained when **15** was used soon after its purification. The bromo triol was in turn prepared from **1** in 78% yield by treatment with *N*-bromoacetamide in aqueous THF in the presence of a catalytic amount of 6 N HCl. The reaction was stereoselective and regiospecific with the product being that which had a 6-bromo substituent oriented cis with respect to the 5-hydroxy group ($J_{5,6}$ = 2.9 Hz). The vicinal OH groups of **15** exist in the diequatorial conformation in acetone ($J_{4,5}$ = 7.2 Hz). The ^{1}H-NMR spectrum of **16** indicates that it exists in a different conformation as compared to **14**. This is most readily seen from the coupling constants $J_{4,5}$ = 2.8 Hz and $J_{5,6}$ = 2.5 Hz which indicate a trans diaxial conformation for the vicinal hydroxyl groups. Hydrogen bonding between OH_4 and the oxirane ring may stabilize such a conformation. Such stabilization is not possible when the hydroxyl groups are equatorial. Additional evidence for this conformation comes from the strong upfield chemical shift observed for OH_4 from 5.76 ppm in **14** to 4.7–4.5 ppm in **16**. Such an effect has been observed previously for *trans*-7,8-dihydroxy-*syn*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene.[18]

Table I. Partial NMR Data for Dihydrodiols, Bromo Triols, and Diol Epoxides of Benzo[*j*]fluoranthene[a]

compd	H_4	H_5	H_6
1	5.08	4.95	6.91
	$J_{4,5}$ = 8.0; $J_{5,6}$ = 3.2		
14	4.93	3.92	4.50
	$J_{4,5}$ = 8.3; $J_{5,6}$ = 1.0		
15	4.67	4.99	5.09
	$J_{4,5}$ = 7.2; $J_{5,6}$ = 2.9		
16[b]	4.66	4.54	4.60
	$J_{4,5}$ = 2.8; $J_{5,6}$ = 2.5		

compd	H_9	H_{10}	H_{11}	H_{12}
2	4.80	4.46	6.27	7.40
	$J_{9,10}$ = 10.8; $J_{10,11}$ = 2.0; $J_{10,12}$ = 2.4; $J_{11,12}$ = 10.0			
17	4.65	3.92	3.81	5.02
	$J_{9,10}$ = 9.6; $J_{10,11}$ = 1.1; $J_{11,12}$ = 4.5			
18	4.83	4.28	4.75	5.75
	$J_{9,10}$ = 8.1; $J_{10,11}$ = 2.6; $J_{11,12}$ = 2.9			
19	4.66	4.22	3.90	4.90
	$J_{9,10}$ = 4.8; $J_{10,11}$ = 2.1; $J_{11,12}$ = 4.1			

[a] Recorded in acetone-d_6. [b] Recorded in DMSO-d_6.

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(17) Glusker, J. P. *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; American Chemical Society: Washington, D.C., 1985, p 125.

The *anti*-diol epoxide 17 of BjF-9,10-dihydrodiol was prepared stereospecifically and in quantitative yield by treatment of diol 2 with *m*-chloroperoxybenzoic acid in dry THF as described above. No evidence of *syn*-diol epoxide was observed in the proton spectrum. The preferred conformation of the OH groups in acetone solution (diequatorial) is deduced from the diaxial coupling constant of the methine protons ($J_{9,10}$ = 10.8 Hz). Confirmation of 17 as the *anti*-diol epoxide is provided by the small coupling constant $J_{10,11}$ = 1.1 Hz.

Treatment of BjF-9,10-diol with *N*-bromoacetamide in aqueous THF in the presence of a catalytic amount of 6 N HCl afforded bromo triol 18 in 98% yield. The ^{1}H-NMR spectrum of BjF-9,10-dihydrodiol recorded in acetone-d_6 indicates that the hydroxyl groups are trans diequatorial ($J_{9,10}$ = 8.1 Hz). The cis relationship of the 11-bromo substituent and OH_{10} was determined from $J_{10,11}$ = 2.6 Hz. The high degree of stereoselectivity observed for this reaction is a consequence of the equatorial allylic alcohol directing the brominating agent to the same face of the double bond.[18] Treatment of bromo triol 18 with IRA-400 resin in dry THF afforded *syn*-diol epoxide 19 in 83% yield. As with the *syn*-diol epoxide of BjF-4,5-diol, 19 exists preferentially with the vicinal OH groups in a trans diaxial conformation so as to allow for H bonding between OH_9 and the epoxide oxygen. Comparison of ^{1}H-NMR spectra taken in DMSO-d_6 show an upfield shift for OH_9 in 19 (5.13 ppm) as compared to 5.71 ppm for 17. A small increase in J_{C9-OH} (7.0 Hz) is also seen in 19 as compared to that in 17 (6.5 Hz). Both of these effects are consistent with intramolecular H bonding between benzylic OH_9 and the oxiranyl oxygen.[18]

We have previously reported that BjF-4,5-diol is at least as potent as BjF as a tumor initiator on mouse skin, while BjF-9,10-diol is significantly less active.[1d] The availability of the *anti*- and *syn*-diol epoxides of these diols will now allow for a thorough evaluation of these electrophiles as ultimate carcinogenic metabolites of BjF. These results will be reported at a later date.

Experimental Section

Ether, THF, and benzene were distilled from sodium benzophenone and stored under argon. Methylene chloride was distilled from CaH_2. [Bis(diphenylphosphino)ethane]nickel(II) chloride was purchased from Alfa Products, Ward Hill, MA, and was dried under vacuum at 67 °C overnight prior to use. All other reagents were purchased from Aldrich Chemical Co., Milwaukee, WI. Radial chromatography was performed under nitrogen using a Harrison Research Model 8924 Chromatotron with a 1-mm silica gel rotor. ^{1}H-NMR spectra were determined at 200 MHz and ^{13}C-NMR spectra at 50 MHz in $CDCl_3$ solution unless otherwise noted. Chemical shifts were measured as ppm downfield from internal tetramethylsilane. Coupling constants are reported in hertz. Infrared spectra were recorded as solutions in CCl_4 unless otherwise specified. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. High- and low-resolution mass spectra were obtained at the Center for Advanced Food Technology, Cook College, Rutgers–The State University of New Jersey. Mass spectral data was obtained in the electron-impact mode (70 eV) unless otherwise noted.

2-[2-(9-Methoxy-11-hydroxybenzo[*a*]fluoren-11-yl)-ethyl]-1,3-dioxane (4). A Grignard reagent was prepared from 2-(2-bromoethyl)-1,3-dioxane (3.05 g, 15.6 mmol) and magnesium turnings (420 mg, 17.3 mmol) in THF (15 mL). Complete formation of the Grignard reagent required 2 h while warming at 40 °C. A portion (1.2 equiv) of this solution was added via cannula over 20 min to a solution of 3[7] (2.03 g, 7.8 mmol) in THF (20 mL) at 50 °C. TLC analysis of the reaction indicated that substantial starting material remained unreacted. Additional Grignard reagent was added in 0.3-equiv aliquots with no substantial improvement in product formation until 2 equiv had been added. At that time the color of the solution changed from red to dark brown and TLC indicated that the starting material had been largely consumed. The solution was stirred at 50 °C for an additional 1 h and was then cooled to room temperature and treated with saturated NH_4Cl. The mixture was extracted with EtOAc, and the organic layer was washed with H_2O and then brine and dried over Na_2SO_4. Solvent was removed in vacuo, and the product was separated by flash chromatography eluting with 1:2 EtOAc/hexanes to afford 4 as a yellow oil: 2.73 g (93%); ^{1}H-NMR δ 8.43 (d, H_1, $J_{1,2}$ = 8.4), 7.89–7.82 (m, 2), 7.68 (d, 1, J = 8.4), 7.58–7.50 (m, 2), 7.42 (m, 1), 7.16 (d, H_{10}, $J_{8,10}$ = 2.4), 6.89 (dd, H_8, $J_{7,8}$ = 8.1), 4.11 (t, 1, J = 5.2), 3.95–3.87 (m, 2), 3.87 (s, 3), 3.48 (m, 2), 2.53 (m, 2), 1.90 (m, 1), 1.29–0.83 (m, 3); ^{13}C-NMR δ 160.68, 152.24, 141.90, 137.81, 133.89, 133.15, 130.57, 130.35, 129.62, 127.08, 125.43, 124.54, 121.01, 118.44, 114.75, 109.80, 102.31, 84.60, 66.97, 55.93, 34.37, 30.04, 25.85; IR ($CHCl_3$) ν_{OH} 3589 cm^{-1}; mass spectrum, m/e (relative abundance) 376 (M^+, 64), 271 (13), 261 (100); exact mass calcd for $C_{24}H_{24}O_4$ 376.16752, observed 376.16840.

4-Methoxybenzo[*j*]fluoranthene (5). Polyphosphoric acid (20 mL) was stirred at 90 °C as a solution of 4 (855 mg, 2.3 mmol) in CH_2Cl_2 was added dropwise. The CH_2Cl_2 evaporated, leaving a suspension of the acetal in PPA. The dark-colored solution was stirred at 90 °C for 3 h, cooled to room temperature, and partitioned between H_2O and EtOAc. The organic layer was washed with H_2O, saturated $NaHCO_3$, and then brine and dried over Na_2SO_4. Following removal of solvent under reduced pressure the residue was purified by flash chromatography, eluting with 2% EtOAc/hexanes to give 5 as a yellow solid, 562 mg (87%). Recrystallization from EtOH/benzene afforded the product as yellow needles: mp 189 °C (lit.[7] mp 192–193.5 °C); ^{1}H-NMR δ 8.70 (d, H_{12}, $J_{11,12}$ = 8.4), 8.48 (d, H_1, $J_{1,2}$ = 7.0), 8.16 (d, H_3, $J_{2,3}$ = 8.1), 7.99 (d, H_8, $J_{7,8}$ = 8.4), 7.94–7.82 (m, $H_{6,7,9}$), 7.69 (dd, H_2), 7.61 (m, H_{11}), 7.46 (m, H_{10}), 6.87 (d, H_5, $J_{5,6}$ = 7.7), 4.07 (s, OMe); ^{13}C-NMR δ 158.46, 138.22, 137.75, 134.01, 133.86, 133.81, 131.27, 130.15, 129.82, 128.78, 127.73, 127.39, 125.26, 124.85, 124.54, 123.16, 122.62, 122.34, 120.00, 106.02, 56.18.

***trans*-4,5-Dihydro-4,5-dihydroxybenzo[*j*]fluoranthene (1).** A solution of 6 (27 mg, 0.1 mmol) in 15 mL of 95% EtOH was stirred with $AgNO_3$ (17 mg, 0.1 mmol) for 15 min. KBH_4 (5 mg, 0.1 mmol) was then added, and air was bubbled through the solution. The solution immediately turned black and fluoresced with a red-violet color (the hydroquinone) when irradiated at 365 nm with a portable UV lamp. Additional portions of KBH_4 (5 mg) were added at 30-min intervals until a total of 6 equiv had been added. Toward the end of the reaction the yellow fluorescence of the dihydrodiol became prominent. The reaction mixture was diluted with ether, and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvents under reduced pressure the residue was purified by flash chromatography eluting with $CHCl_3$ and gradually adding MeOH up to 5% MeOH/$CHCl_3$ giving 1 as a yellow solid, 25 mg (91%): mp >170 °C dec (lit.[7] mp >170 °C dec); ^{1}H-NMR (acetone-d_6) δ 8.72 (d, H_{12}, $J_{11,12}$ = 8.7), 8.19 (d, H_1, $J_{1,2}$ = 5.1), 8.03 (d, 1, J = 8.9), 8.01 (d, 1, J = 8.4), 7.91 (d, 1, J = 8.4), 7.74–7.47 (m, 4), 6.91 (d, H_6, $J_{5,6}$ = 3.2), 5.08 (d, H_4, $J_{4,5}$ = 8.0), 4.95 (dd, H_5); ^{13}C-NMR (DMSO-d_6) δ 146.54, 137.01, 136.16, 135.03, 134.69, 134.28, 134.06, 133.37, 129.44, 129.34, 128.94, 128.13, 127.56, 126.36, 125.56, 124.58, 121.56, 120.54, 74.89, 73.47.

1-(4-Methoxyphenyl)acenaphthylene (7). (4-Methoxyphenyl)magnesium bromide was prepared from 4-bromoanisole (4.6 mL, 36 mmol) and magnesium turnings (888 mg, 36 mmol) in 20 mL of diethyl ether at reflux for 20 h. The solution was cooled to room temperature, diluted with 50 mL of ether, and added dropwise to a cold (0 °C) magnetically stirred solution of 1-bromoacenaphthylene[9] (4.2 g, 18 mmol) and [bis(diphenylphosphino)ethane]nickel(II) chloride (96 mg, 0.18 mmol) in 300 mL of dry ether. The color of the solution gradually changed from yellow to red-brown. The reaction mixture was allowed to warm to room temperature and was stirred for 5 h. The solution was treated with 1 N HCl (100 mL) at 0 °C for 5 min, and the organic

(18) Yagi, H.; Hernandez, O.; Jerina, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 6881.

layer was then separated. The aqueous layer was extracted once with ether, and the combined organic layers were washed sequentially with saturated $NaHCO_3$, water, and brine and then dried over Na_2SO_4. After removing the solvents the oil was purified by flash chromatography, eluting with hexanes and then 4:1 hexanes/EtOAc. The product fractions were repurified on a second flash column eluting with 1:4 benzene/hexanes to give a red solid, 3.39 g (72%). Crystallization from benzene–EtOH afforded red needles: mp 76.5–77.5 °C; ^{1}H-NMR δ 8.01–7.76 (m, 5), 7.73–7.57 (m, 3), 7.15 (s, 1), 7.09 (d, 2, J = 8.8), 3.91 (s, 3); ^{13}C-NMR δ 160.06, 143.72, 140.00, 139.53, 129.97, 129.67, 129.43, 128.08, 128.58, 128.13, 128.06, 127.25, 124.92, 124.82, 124.03, 114.84, 55.72. Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found: C, 88.16; H, 5.50.

Reaction of Ethyl Diazoacetate with 7. A mixture of 7 (661 mg, 2.56 mmol) and copper–bronze (164 mg, 2.56 mmol) in 1,2-dimethoxyethane (1 mL) was heated to 80–85 °C and treated with 0.27 mL of ethyl diazoacetate every hour for a total of four treatments (1.08 mL, 10.24 mmol total). After 6 h the reaction was complete by TLC. Upon cooling, the reaction mixture was filtered, the filtrate was concentrated, and the oily product was distilled in a Kugelrohr apparatus to remove diethyl fumarate and diethyl maleate which are byproducts of the reaction. The material remaining in the pot was purified by flash chromatography (hexanes; 20:1 hexanes/EtOAc; and then 9:1 hexanes/EtOAc) to give 600 mg of a brown oil (68% yield) which is a 1:2.5 mixture of the syn and anti diastereomers 8 and 9. Compound 8: ^{1}H NMR δ 7.68–7.62 (m, 2), 7.50–7.36 (m, 5), 7.15 (d, 1, J = 7.0), 6.94 (d, 2, J = 8.8), 3.84 (s, 3), 3.63 (q, 2, J = 7.2), 3.53 (d, 1, J = 8.6), 3.02 (d, 1, J = 8.4), 0.65 (t, 3, J = 7.2); ^{13}C-NMR δ 168.99, 159.64, 144.53, 143.25, 136.01, 132.13, 131.60, 131.00 (2 C), 128.11, 128.07, 124.45, 124.11, 122.31, 121.80, 114.53 (2 C), 60.38, 55.66, 39.85, 38.22, 35.92, 13.77; mass spectrum (CI, isobutane), m/e (relative abundance) 345 (MH^+, 100), 344 (M^+, 7), 315 (5), 299 (11), 273 (17), 271 (24), 239 (62), 237 (93). Compound 9: ^{1}H NMR δ 7.66–7.60 (m, 2), 7.51–7.34 (m, 5), 7.20 (d, 1, J = 6.6), 6.92 (d, 2, J = 8.8), 4.00–3.96 (m, 3), 3.83 (s, 3), 2.15 (d, 1, J = 3.6), 1.06 (t, 3, J = 7.2); ^{13}C NMR δ 169.74, 159.57, 147.35, 143.21, 135.96, 132.07, 131.56 (2 C), 128.31, 128.09 (2 C), 124.43, 124.17, 120.79, 120.75, 114.45 (2 C), 60.93, 55.55, 47.23, 45.21, 35.95, 14.29; mass spectrum (CI, isobutane), m/e (relative abundance) 345 (MH^+, 100), 344 (M^+, 9), 315 (8), 299 (13), 273 (20), 271 (26), 239 (100), 237 (97).

Preparation of Carbinol 10. A solution of the diastereomeric esters 8 and 9 (600 mg, 1.74 mmol) in 30 mL of dry toluene was cooled to −23 °C under argon and treated with DIBALH (3.9 mL of a 1 M solution in toluene). The solution was stirred at −23 °C for 2 h and was treated with an additional 1.5 mL of DIBALH and then stirred for 0.5 h at room temperature. MeOH (4 mL) was added slowly, and then the solution was diluted with 100 mL of ether, washed with H_2O and brine, and then dried over Na_2SO_4. Solvents were removed in vacuo, and the residue purified by flash chromatography eluting with 1:4 EtOAc/hexanes and then 1:2 EtOAc/hexanes to give 503 mg (96%) 10 as a yellow oil: ^{1}H-NMR δ 7.61–7.57 (m, 2), 7.49–7.36 (m, 5), 7.19 (d, 1, J = 6.8), 6.94 (d, 2, J = 8.4), 3.80 (s, 3), 3.50 (m, 2), 3.19 (d, 1, J = 3.3), 1.64 (td, 1, J = 7.2, J = 3.3); ^{13}C-NMR δ 159.49, 149.16, 145.31, 136.54, 132.42, 131.97, 129.39, 127.98(2), 123.66, 123.39, 119.79, 119.53, 114.71, 63.02, 55.55, 47.01, 44.67, 34.21; IR ν_{OH} 3631 cm^{-1}.

Preparation of Aldehyde 11. A solution of oxalyl chloride (0.5 mL, 5.7 mmol) in CH_2Cl_2 (15 mL) was stirred under argon at −78 °C as DMSO (0.85 mL, 12 mmol) was added. The solution was stirred for 10 min, and 10 (1.2 g, 3.97 mmol) in CH_2Cl_2 (10 mL) was added. The solution was stirred at −78 °C for 1 h and was treated with Et_3N (4 mL, 28.7 mmol) and stirred for an additional 15 min. The solution was allowed to warm to room temperature, treated with 50 mL of H_2O, and then extracted three times with CH_2Cl_2. The organic layers were combined, washed with 0.1 N HCl, H_2O, and then brine, and dried over Na_2SO_4. Solvents were removed under reduced pressure, and the residue was purified by flash chromatography, eluting with hexanes and then 1:5 EtOAc/hexanes to give 1.0 g (84%) of 11: ^{1}H-NMR δ 8.97 (d, 1, J = 6.1), 7.74–7.68 (m, 2), 7.61–7.39 (m, 5), 7.22 (d, 1, J = 7.0), 7.00 (d, 2, J = 8.8), 4.27 (d, 1, J = 3.2), 3.82 (s, 3), 2.11 (dd, 1, J = 3.2, J = 6.1); ^{13}C-NMR δ 197.60, 160.82, 147.87, 143.55, 136.42, 133.03, 132.74 (2 C), 129.11, 128.97, 128.42, 125.46, 125.11, 121.83, 121.45, 115.57 (2 C), 55.82, 54.49, 48.52, 36.14; IR $\nu_{C=O}$ 1708 cm^{-1}; mass spectrum, m/e (relative abundance) 300 (M^+, 4), 272 (48), 256 (31), 240 (59), 228 (100), 227 (87). Upon standing at room temperature in $CDCl_3$ for 15 min aldehyde 11 was converted to an isomeric product 12: ^{1}H-NMR δ 7.84 (d, 1, J = 8.1), 7.76 (d, 1, J = 8.1), 7.65–7.53 (m, 2), 7.41–7.33 (m, 2), 7.26 (d, 2, J = 8.8), 6.89 (d, 2, J = 8.8), 6.54 (m, 1), 5.23 (m, 1), 4.78 (m, 1), 3.81 (s, 3); ^{13}C-NMR δ 159.60, 146.54, 145.63, 137.76, 136.78, 132.37, 129.11, 128.97, 128.22, 127.09, 125.83, 123.81, 122.00, 119.70, 114.21, 102.99, 98.73, 62.97, 55.62; IR 3067, 3046, 3005, 2954, 2933, 2913, 2844, 1615, 1535, 1251, 1174, 1154, 1056, 1041, 1026 cm^{-1}.

10-Methoxybenzo[*j*]fluoranthene (13). This reaction was performed as described above for 5 using 1.00 g of 11 (5 h, 90 °C) to give 13 as a yellow solid, 853 mg (91% yield): mp 129–130 °C (lit.[7] mp 126–127 °C); ^{1}H-NMR δ 8.62 (d, H_{12}, $J_{11,12}$ = 9.1), 8.40 (d, H_1, $J_{1,2}$ = 6.9), 7.99 (d, 1, J = 8.3), 7.97 (d, 1, J = 6.6), 7.89–7.59 (m, 5), 7.32 (d, H_9, $J_{9,11}$ = 2.6), 7.26 (dd, H_{11}); ^{13}C-NMR δ 157.75, 138.38, 137.95, 136.28, 135.94, 135.11, 130.16, 128.60, 128.41, 127.54, 127.45, 127.38, 126.58, 126.26, 124.43, 120.90, 120.81, 120.23, 107.73, 55.50.

***trans*-4,5-Dihydroxy-*anti*-6,6a-epoxy-4,5,6,6a-tetrahydrobenzo[*j*]fluoranthene (14).** A solution of 1 (30 mg, 0.1 mmol) in THF (20 mL) under argon was treated with mCPBA (272 mg, 1.6 mmol, freshly purified[15]) at room temperature. After 2 h the solution was diluted with ether, washed with ice-cold 1 N NaOH and brine, and then dried over K_2CO_3. The solvents were removed in vacuo, and the residue was purified by chromatotron, eluting with THF containing 1% Et_3N to give diol epoxide 14 as a pale yellow solid, 30 mg (95%). Recrystallization from THF–hexanes afforded 14 as a white powder: mp 142 °C dec; ^{1}H-NMR (acetone-d_6) δ 8.77 (d, H_{12}, $J_{11,12}$ = 8.3), 8.27 (d, H_1, $J_{1,2}$ = 6.5), 8.07 (d, 1, J = 8.7), 7.97 (d, 1, J = 8.7), 7.83–7.49 (m, 5), 4.93 (d, H_4, $J_{4,5}$ = 8.3), 4.50 (d, H_6, $J_{5,6}$ = 1.0), 3.92 (dd, H_5); ^{13}C-NMR (DMSO-d_6) δ 138.72, 138.01, 137.90, 137.68, 134.79, 130.31, 129.59, 129.32, 128.87, 127.84, 126.76, 124.25, 123.38, 122.05, 120.79, 74.46, 69.82, 63.51, 60.30; mass spectrum, m/e (relative abundance) 302 (M^+, 15), 300 (100), 284 (77), 268 (90), 244 (49), 226 (60), 215 (97); exact mass calcd for $C_{20}H_{14}O_3$ 302.09432, observed 302.09419.

***r*-6-Bromo-*t*-4,*c*-5,*t*-6a-trihydroxy-4,5,6,6a-tetrahydrobenzo[*j*]fluoranthene (15).** A solution of 1 (41 mg, 0.14 mmol) in 24 mL of 2:1 THF/H_2O was treated with *N*-bromoacetamide (29 mg, 0.17 mmol) and a drop of 6 N HCl at 0 °C for 6 h. An additional 29 mg of *N*-bromoacetamide and 1 drop of 6 N HCl was added, and the solution was stirred for an additional hour at 0 °C. EtOAc was added, and the organic layer was separated. The aqueous layer was extracted with an additional portion of EtOAc, and the organic layers were combined, washed with brine, and dried over Na_2SO_4. Removal of solvents under reduced pressure followed by purification by flash chromatography eluting with 1:1 EtOAc/hexanes and then 3:1 EtOAc/hexanes afforded the product as a white powder, 43 mg (78%): mp 115 °C dec; ^{1}H-NMR (acetone-d_6) δ 8.67 (d, H_{12}, $J_{11,12}$ = 8.4), 8.12 (d, H_1, $J_{1,2}$ = 6.2), 8.01 (d, 1, J = 8.1), 7.92 (d, 1, J = 8.4), 7.76–7.41 (m, 5), 5.09 (d, H_6, $J_{5,6}$ = 2.9), 4.99 (dd, H_5, $J_{4,5}$ = 7.2), 4.67 (d, H_4); ^{13}C-NMR (DMSO-d_6) δ 147.55, 143.33, 139.43, 137.08, 135.65, 131.96, 130.58, 130.16, 128.53, 128.15, 127.89, 126.76, 126.32, 125.16, 122.22, 122.08, 79.41, 72.50, 72.13, 58.85.

***trans*-4,5-Dihydroxy-*syn*-6,6a-epoxy-4,5,6,6a-tetrahydrobenzo[*j*]fluoranthene (16).** A solution of 15 (43 mg, 0.11 mmol) in 6 mL of dry THF containing 2 g of Amberlite IRA-400 resin was stirred under argon at room temperature for 2.5 h. The solution was filtered and evaporated to give 33.8 mg (99.7%) of the diol epoxide as a pale yellow solid: mp 160–170 °C dec; ^{1}H-NMR (DMSO-d_6) δ 8.77 (d, 1, J = 8.6), 8.38 (d, 1, J = 7.8), 8.11 (d, 1, J = 8.0), 8.00 (d, 1, J = 8.3), 7.79–7.55 (m, 4), 7.37 (d, 1, J = 7.6), 5.39 (d, OH_5, J = 5.4), 4.66 (dd, H_4, $J_{4,5}$ = 2.8 Hz), 4.60 (d, H_6, $J_{5,6}$ = 2.5 Hz), 4.54 (m, H_5); ^{13}C-NMR (acetone-d_6) δ 139.27, 138.95, 138.89, 136.31, 136.13, 131.65, 130.58, 130.01, 129.44, 129.25, 128.63, 127.62, 125.19, 124.46, 121.33, 73.93, 70.60, 67.91, 64.25; mass spectrum, m/e (relative abundance) 302 (M^+, 28), 300 (26), 284 (46), 271 (90), 226 (61), 215 (100); exact mass calcd for $C_{20}H_{14}O_3$ 302.09432, observed 302.09419.

***trans*-9,10-Dihydroxy-*anti*-11,12-epoxy-9,10,11,12-tetrahydrobenzo[*j*]fluoranthene (17).** Prepared as described above from 17 mg of 2 (26 h, room temperature) to give 18 mg (100%) of 17; recrystallization from THF–hexanes afforded a pale-yellow

solid: mp 204–206 °C dec; ^{1}H-NMR (acetone-d_6) δ 8.41 (d, H_1, $J_{1,2}$ = 7.1), 8.15–7.95 (m, 4), 7.80–7.70 (m, 3), 5.02 (d, H_{12}, $J_{11,12}$ = 4.5), 4.65 (dd, H_9, $J_{9,10}$ = 9.6, $J_{9,11}$ = 1.1), 3.92 (dd, H_{10}), 3.81 (m, H_{11}, $J_{10,11}$ = 1.1); ^{13}C-NMR (DMSO-d_6) δ 141.15, 138.45, 138.01, 135.83, 130.04, 128.76, 128.61, 128.50, 127.50, 127.29, 125.26, 124.16, 121.56, 120.75, 71.39, 69.95, 56.28, 50.50; mass spectrum, *m/e* (relative abundance) 302 (M^+, 57), 284 (74), 256 (99), 255 (98), 244 (70), 226 (64), 215 (100), 202 (50); exact mass calcd for $C_{20}H_{14}O_3$ 302.09432, observed 302.09419.

***r*-11-Bromo-*t*-9,*c*-10,*t*-12-trihydroxy-9,10,11,12-tetrahydrobenzo[*j*]fluoranthene (18).** Prepared as described above from 32 mg of **2** (0.5 h, 0 °C) to give **18**, 42 mg (98% yield). Recrystallization from THF–hexanes gave colorless needles: mp 136 °C dec; ^{1}H-NMR (acetone-d_6) δ 8.32 (d, 1, J = 7.2), 8.11–8.03 (m, 2), 7.94 (d, 2, J = 8.3), 7.76–7.65 (m, 3), 5.83 (dd, 1, J = 5.9, J = 2.9), 5.33 (d, 1, J = 6.2), 4.91–4.79 (m, 3), 4.72 (dd, 1, J = 4.6, J = 1.6), 4.32 (m, 1); ^{13}C-NMR (acetone-d_6) δ 140.57, 139.82, 139.69, 137.60, 137.45, 131.59, 131.29, 129.64, 129.19, 128.63, 128.20, 128.16, 127.62, 126.24, 122.78, 121.40, 73.43, 72.68, 70.78, 60.58. Anal. Calcd for $C_{20}H_{15}BrO_3$: C, 62.66; H, 3.92. Found: C, 62.26; H, 4.44.

***trans*-9,10-Dihydroxy-*syn*-11,12-epoxy-9,10,11,12-tetrahydrobenzo[*j*]fluoranthene (19).** Prepared as described above from **18** (59 mg, 1 h, room temperature) to give **19** (38.4 mg, 83% yield); recrystallization from THF–hexanes afforded colorless needles: mp 209–212 °C dec; ^{1}H-NMR (acetone-d_6) δ 8.37 (d, H_1, $J_{1,2}$ = 7.0), 8.14 (d, 1, J = 6.9), 8.07 (d, 1, J = 7.7), 8.01 (d, 1, J = 8.3), 7.99 (d, 1, J = 8.1), 7.80–7.70 (m, 2), 7.53 (d, 1, J = 7.7), 4.90 (d, H_{12}, $J_{11,12}$ = 4.1), 4.66 (d, H_9, $J_{9,10}$ = 4.8), 4.22 (dd, H_{10}, $J_{10,11}$ = 2.1), 3.90 (m, H_{11}); ^{13}C-NMR (DMSO-d_6) δ 139.35, 138.63, 138.46, 135.78, 135.64, 132.04, 129.89, 128.72, 128.58, 128.43, 127.84, 127.53, 127.31, 123.88, 122.29, 121.05, 71.73, 70.18, 58.27, 47.94; mass spectrum, *m/e* (relative abundance) 284 ($M - H_2O$, 100), 255 (12), 238 (17), 237 (25). A molecular ion peak for **19** was not detected although an ion at *m/e* 284 corresponding to $M - H_2O$ was observed: exact mass calcd for $C_{20}H_{12}O_2$ ($M - H_2O$) 284.08373, observed 284.08448.

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Supplementary Material Available: ^{1}H-NMR spectra for compounds **4**, **8–12**, **14–17**, and **19** and ^{13}C-NMR spectra for compounds **8–10**, **12**, **14**, **17**, and **19** (12 pages). Ordering information is given on any current masthead page.

Reductions with NADH Models. 3. The High Reactivity of Hantzsch Amides

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Aromatic ketones and aldehydes are rapidly reduced to alcohols by various 1,4-dihydropyridines, several of which can be considered to be a model of the coenzyme NADH. The reducing agents bear amide groups and are closely related to Hantzsch esters. They exhibit the highest reactivity among NADH models so far described. In some cases, the rate and completeness of reduction by Hantzsch amides compare favorably with those of reduction by the usually employed metal hydrides.

Introduction

Performing organic reactions in a manner similar to that in which they occur in living cells is a fascinating challenge to organic chemists. The results may assist in the development of new synthetic methods of increased efficiency in terms of enhanced rate of reaction and chemo-, regio-, and stereoselectivity.

Because redox reactions are important biological processes, models of the relevant coenzymes have sometime been studied with the aim of developing new useful oxidation or reduction reagents (or catalysts) for synthetic purposes.

Simple models of NAD^+/NADH coenzymes have been synthesized and applied as reagents in biomimetic reductions.[1] All the models that have so far been described possess, as a common feature, a 1,4-dihydropyridine ring which mimics the nicotinamide fragment of the coenzyme. Most of the relevant studies have involved *N*-benzyl-1,4-dihydronicotinamide (BNAH) **1**, and its derivatives. Some bi- and tricyclic models that are structurally related to quinoline,[2] thenopyridine,[3] acridine,[4] and deazaflavin[5] have also been described.

Reduction proceeds by way of the transfer to the substrate of the equivalent of a hydride ion. The source of hydride ion is one of the two chemically equivalent hydrogens at C-4 of the dihydropyridine ring. Mechanistic assessments posit the complexation of the metal cation by the carbonyl(s) group(s) of the NADH models[1a] (Figure 1).

The reduction is catalyzed by Lewis[6] or Broensted[4] acids. In most cases, catalysis by magnesium perchlorate and

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