^{1}H NMR analyses, contained 85% of 4-ethyl-1-naphthol (0.59 mmol, 59% yield) and 15% of unidentified components.[15] Purified 4-ethyl-1-naphthol[16] was obtained following extraction with 5% aqueous sodium hydroxide: NMR (CCl_4) δ 8.3–7.8 (2 H, m), 7.6–7.3 (2 H, m), 7.04 (1 H, AB d, J = 7.5 Hz), 6.61 (1 H, AB d, J = 7.5 Hz), 6.1–5.6 (1 H, br, phenolic OH), 3.02 (2 H, q), and 1.32 (3 H, t); IR (CCl_4) 3600 (free O–H), 3600–3100 (associated O–H), 3070, 2970, 2940, 2880, 1590, 1508, 1452, 1380, 1270, 1258, 1140, 1048, and 880 cm^{-1}.

4-Phenylcycloheptanone (3). 4-(1-Phenylcyclopropyl)butanoyl chloride (0.223 g, 1.00 mmol) in 2 mL of dry methylene chloride was added to a continuously stirred, ice-bath cooled mixture of aluminum chloride (0.35 g, 2.6 mmol) in 10 mL of anhydrous methylene chloride. The rate of addition was sufficiently slow so that the reaction temperature did not rise above 10 °C. During the addition the reaction solution turned orange and a black solid formed at the bottom of the reaction flask. After addition was complete, the reaction mixture was allowed to warm to room temperature and became progressively darker. The dark brown reaction mixture was again cooled in an ice bath after a reaction time of 12 h. Following the workup procedure described for the synthesis of **2**, 0.18 g of a dark brown solid was obtained that, by GC and ^{1}H NMR analyses, contained 0.32 mmol (32% yield) of **3**. Purified **3** was obtained by GC collection using a 20% SE-30 column, and its physical and spectral properties were identical with those reported for **3**.[17]

4,4-Diphenylcycloheptanone. 4-(1-Phenylcyclopropyl)butanoyl chloride (0.223 g, 1.00 mmol) in 2 mL of dry benzene was added to a continuously stirred, ice-bath cooled mixture of aluminum chloride (0.45 g, 3.4 mmol) in 10 mL of anhydrous benzene. The rate of addition was sufficiently slow so that the reaction temperature did not rise above 10 °C. During the addition the reaction solution turned yellow and a dark colored solid formed at the bottom of the reaction flask. After 1 h the reaction mixture was allowed to warm to room temperature, and after a reaction time of 12 h the resulting dark brown reaction mixture was again cooled in an ice bath. Following the workup procedure described for the synthesis of **2**, 0.32 g of a dark oil was obtained that, by GC and ^{1}H NMR analyses, contained 0.26 mmol (26% yield) of **3** and 0.48 mmol (48% yield) of an additional product identified as 4,4-diphenylcycloheptanone: mp 100.5–101.5 °C; NMR ($CDCl_3$) δ 7.27 (10 H, s), 2.8–2.3 (2 H, m), 2.56 (4 H, s), and 2.3–1.5 (4 H, m); IR (CCl_4)[18] 3084, 3062, 3028, 2940, 2872, 1702 (C=O), 1597, 1492, 1444, 1333, 1060, and 908 cm^{-1};[19] mass spectrum, *m/e* (relative intensity)[20] 264 (47, parent ion), 236 (37, M − C_2H_4), 200 (40), 199 (28), 194 (43), 182 (37), 167 (25), and 91 (23).

Acknowledgment. We wish to thank Peter W. Raynolds for the preparation of the acid chlorides employed in this study, Thomas R. Bade for his preliminary investigations of the Lewis acid promoted reactions, and Carl C. Druskovich for his assistance in product analyses.

Registry No.—1 (n = 3), 67688-25-9; 1 (n = 4), 67688-26-0; **2**, 67688-27-1; **3**, 67688-28-2; 4-ethyl-4-phenyl-1-tetralone, 67688-29-3; 4-ethyl-1-naphthol, 10240-09-2; 4,4-diphenylcycloheptanone, 67688-30-6.

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(11) The corresponding reaction of **1** (n = 4) with aluminum chloride in benzene that contained 1.2 molar equiv of triphenylmethane produced **3** (34% yield), 4,4-diphenylcycloheptanone (31% yield), and triphenylmethanol (14% yield based on **1**). Thus, hydride transfer from triphenylmethane, even in the nucleophilic benzene solvent, occurs at the expense of electrophilic substitution. These results and the difference in product-forming steps from aluminum chloride promoted reactions of 4-cyclopropylbutanoyl chloride[2] and **1** (n = 4) may reflect the nature of the reaction intermediates involved in these processes. The results from intramolecular acylation reactions of 4-cyclopropylbutanoyl chloride have been interpreted by invoking a protonated cyclopropane intermediate from which the observed chloro ketones could be formed directly. In contrast, the additional stabilization from the phenyl substituent may promote either direct formation of the stabilized benzyl cation or collapse of the protonated cyclopropane intermediate to the benzyl cation on a time scale in which migration of the tetrachloroaluminate ion to the developing cationic center is slower than hydride transfer.

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(15) The characteristic NMR and IR absorptions of 4-phenylcyclohexanone[17] were absent within the limits of detection (5%) in the spectra of these reaction mixtures.

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(18) Spectral bands from 4000 to 800 cm^{-1} with intensities ≥ 20% that of the carbonyl stretching frequency are given.

(19) Observed spectral band positions closely match those reported for **3**.[17]

(20) Relative intensities of molecular fragments above *m/e* 91, relative to base peak at *m/e* 40.

Influence of Some Metal Salts on the Electroreduction of Aryl Ketones[1]

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The electrolytic reduction of 2,3:6,7-dibenzotropone was studied in aprotic solvent in the presence of various anhydrous metal salts. While the cyclic voltammogram shows this reaction to be a reversible one-electron reduction in CH_3CN and DMF, the presence of salts such as $CoCl_2$ and Ni(acac)$_2$ is found to affect the reversibility of the electrochemical reaction without influencing the reduction potential.

Few reports appear which describe the influence of metal cation salts on the electrolytic reductions of ketones in aprotic solvents. The reduction in these solvents does provide some technical disadvantages over the reactions carried out in protic media. Some of the differences are the higher overpotentials required and the greater amounts of dimeric product formed in aprotic solvents. Since metal cations can be quite efficient in promoting the ionization reactions of alkyl halides in aprotic solvents by acting as Lewis acids (eq 1),[2] it seemed appropriate to study their influence in the electroreduction reactions of

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Table I. Electroreduction of 2,3:6,7-Dibenzotropone and Benzophenone in Aprotic Solvents [a]

added salt	E_{pc}, V	i_a/i_c [b]	$E_{pa} - E_{pc}$, mV	$i_p/CV^{1/2}$ [b,c]
	2,3:6,7-dibenzotropone			
[e]	−1.73	1.0	60	271
1 × 10^{-3} M $CoCl_2$ [e]	−1.74	0		380
4 × 10^{-3} M Ni(acac)$_2$ [e]	−1.75	0.5	80	396
2 × 10^{-3} M Fe(acac)$_2$ [e]	−1.75	~0.6	~150	330
12 × 10^{-3} M Al(acac)$_3$ [e]	−1.75	~1	65	297
[f]	−1.72	1.0	65	231
1 × 10^{-3} M $CoCl_2$ [f]	−1.70	0		250
[g]	−1.65	1.0	60	176
2 × 10^{-3} M $CoCl_2$ [g]	−1.60	0		260
	benzophenone			
[e]	−1.82	0.9	65	208
1 × 10^{-3} M $CoCl_2$ [e]	−1.78	0		161
[g]	−1.72 [d]	1.0	60	180
2 × 10^{-3} M $CoCl_2$ [g]	−1.74	0		133

[a] Solutions contain 10^{-3} M ketone plus 0.1 M Et_4NBF_4. [b] 100 mV/s sweep rate. [c] A/(mol/mL)(V/s)$^{1/2}$. [d] Literature value for $E_{1/2}$ is 1.72 V/[4] [e] In CH_3CN. [f] In 1:1 CH_3CN–dioxane. [g] In DMF.

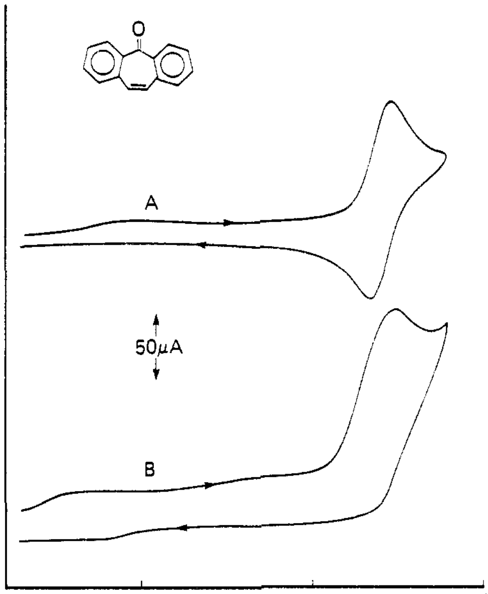


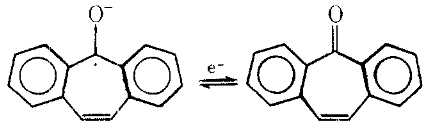
Figure 1. Cyclic voltammograms measured in CH_3CN using Pt vs. NaCE and a 100 mV/s sweep rate: curve A, 10^{-3} M ketone; curve B, 10^{-3} M ketone plus 10^{-3} M $CoCl_2$.

ketones.

$$RCl + MCl_2 \rightarrow R^+ MCl_3^- \quad (1)$$

The electrochemical reduction of ketones is a complicated reaction since it involves a series of electron-transfer and protonation steps which can occur in separate stages. This is particularly true in aprotic conditions. This behavior, however, is helpful for the present study since the main interest is in the first electron-transfer step of the reduction reaction rather than the follow-up reaction steps.

The electrochemical reduction of 2,3:6,7-dibenzotropone (I-ketone) in aprotic solvent seemed like the appropriate system for this study since the cyclic voltammogram for this system reveals that the first electron-transfer step is electrochemically reversible. This behavior permits us to probe the influence of the salt on the reaction of the initial ketone and of the produced radical anion.



I-ketone I-radical anion

Results

All electrochemical measurements were carried out in anhydrous solvent containing 0.1 M tetraethylammonium tetrafluoroborate using a platinum working electrode and a sodium calomel reference electrode. The measurements were carried out using 85–90% iR compensation. The i–V plot for a solution containing 10^{-3} M I-ketone in acetonitrile shows a peak with E_{pc} at −1.73 V and i_a/i_c equal to unity using a 100 mV/s sweep rate. The value of $i_p/CV^{1/2}$ provides a value for $n^{3/2}D^{1/2}$ equal to 5.2×10^{-3} cm/s$^{1/2}$ using a value for the constant in the Randles and Sevcik equation equal to 2.6×10^5 (s-electron)$^{-1/2}$.[3] From this result the value for D is estimated to be equal to 2.7×10^{-5} cm^2/s with n equal to 1. These values are listed in Table I.

The addition of small amounts of $CoCl_2$ to the reaction solution causes a gradual broadening of the peaks with an accompanying reduction in the i_a/i_c value but no noticeable change in E_{pc}. When the solution contains 1 mole of $CoCl_2$/mol of ketone, the anodic peak disappears and the $i/CV^{1/2}$ value for the cathodic peak is increased. This effect can be seen in Figure 1. Higher concentrations of $CoCl_2$ produced no further changes.

The influence of several acetylacetonate salts on the reduction reaction was also tested. With the presence of 4×10^{-3} M Ni(acac)$_2$ or of 2×10^{-3} M Fe(acac)$_2$ the reduction reaction shows electrochemical irreversibility as in the case with $CoCl_2$. Very little change was noted with Al(acac)$_3$ even at 0.012 M concentrations. The influence of these salts on the reaction is consistently less than that of $CoCl_2$.

The reaction was also probed briefly with $ZnCl_2$ although these results are not included in the table. $ZnCl_2$ shows the same general effect, but is not as effective as $CoCl_2$. With 2×10^{-3} M $ZnCl_2$ the i_a/i_c value reduces to 0.82 in CH_3CN, and it reduces to 0.25 in DMF. With the majority of the salts considered, higher concentrations were not used because the solutions became turbid.

The influence of $CoCl_2$ on the reaction with benzophenone compares qualitatively with that observed with dibenzotropone. This is seen in Table I.

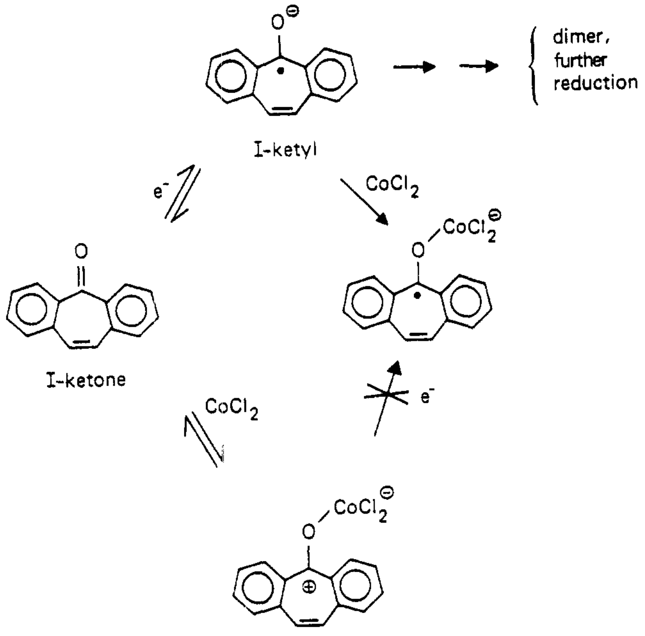
In the absence of ketone, broad irreversible peaks for the reduction of $CoCl_2$ are observed at −1.47 V in CH_3CN and −1.45 V in DMF. However, these peaks are barely detectable in the presence of ketone. For comparison purposes, the half-wave reduction potentials for $CoCl_2$ and $ZnCl_2$ in acetic acid are −1.35 V (SCE) and −1.25 V (SCE), respectively, while for nickel(II) acetylacetonate and iron(II) acetylacetonate in dimethylformamide they are −1.5 V (SCE) and ca. −2.3 V (SCE), respectively.[5]

Since this ketone is not the best candidate for a quantitative study of the reaction products, only a brief qualitative study was performed. Constant potential electrolysis of dibenzotropone in CH_3CN or DMF at 0.1 V past E_{pc} produces one major product, presumed to be dimeric material, plus a trace amount of carbinol. These results are from TLC analysis. The same results were obtained when the reaction was carried out in the presence of 2 mol of $CoCl_2$/mol of ketone, and the only observable difference is a possible lower conversion, presumably due to the concurrent reduction of $CoCl_2$.

Discussion

The results indicate that the electrochemical reduction of the ketone can be drastically influenced by the presence of

Scheme I



transition metal salts. However, the effectiveness of the salt will depend on the nature of the solvent since certain salts like $\mathrm{CoCl_2}$ can be specifically solvated,[6] and each solvated form will affiliate the ketone structure differently (eq 2 and 3).

$$\mathrm{CoCl_2(solvent)_2} \overset{K}{\rightleftharpoons} \mathrm{CoCl_2} + \text{solvent} \qquad (2)$$

$$3\mathrm{CoCl_2(solvent)_2} + \text{solvent} \rightleftharpoons \mathrm{Co(solvent)_6}^{2+} + 2\mathrm{CoCl_3(solvent)}^{-} \qquad (3)$$

When the reduction of I-ketone is carried out in acetonitrile containing $\mathrm{CoCl_2}$, the value for E_p is not changed. Thus, in the vicinity of the electrode surface the $\mathrm{CoCl_2}$ complex is either formed in negligible amounts or it is involved in a rapid dissociation equilibrium. On the other hand, $\mathrm{CoCl_2(solvent)_2}$ intervenes efficiently after the first electron-transfer step, affiliates the radical anion, and minimizes its reoxidation reaction. The $\mathrm{CoCl_2}$–ketyl complex must be quite stable since there is no evidence that it is reoxided or further reduced under these conditions. It cannot be decided from these results whether the ketyl is affiliated near the electrode by dissolved $\mathrm{CoCl_2}$ or at the electrode surface by possibly adsorbed $\mathrm{CoCl_2}$. This behavior is shown schematically in Scheme I.

The behavior observed for $\mathrm{CoCl_2}$ is not changed in going to the less polar $\mathrm{CH_3CN}$–dioxane solvent mixture. However, in DMF, where $\mathrm{CoCl_2}$ is more strongly solvated, a higher concentration of $\mathrm{CoCl_2}$ is required to make the i_a/i_c value reduce to 0.

The results obtained in the electroreduction of benzophenone in the presence of $\mathrm{CoCl_2}$ compare qualitatively with those for dibenzotropone. In the reaction with benzophenone, however, the reduction peaks in the presence of $\mathrm{CoCl_2}$ appear wider and with lower $i_p/CV^{1/2}$ values than in the dibenzotropone reaction.

Several acetylacetonate salts were also tested for their influence in this reaction. These salts were selected because the dissociation equilibrium constants are small. For example, in 75% dioxane the dissociation constant[6] for $\mathrm{Ni(acac)_2} \rightleftharpoons \mathrm{Ni(acac)^+} + \mathrm{acac^-}$ is $10^{-8.1}$. Similar values are found for $\mathrm{Fe(acac)_2}$ and $\mathrm{Al(acac)_3}$.[6] Thus, any interaction between the acetylacetonate salt and the carbonyl derivative is expected to be in the form of ion aggregates where the ketone cannot enter the intercoordination sphere of the metal cation. Of equal interest is the fact that these salts are reported to have catalytic activity in the electroreduction reactions of alkyl bromides in DMF.[7] For example, electrolysis of a 1-octyl bromide in the presence of $\mathrm{Fe(acac)_3}$ gives 94% conversion in 50 h, where the products formed are 49% octane, 18% octene, and 31% hexadecane. In contrast, a similar electrolysis in the absence of $\mathrm{Fe(acac)_3}$ produced ca. 3% conversion. Similar results are obtained with $\mathrm{Ni(acac)_2}$. The authors propose the reduction of the metal to a lower valence metal complex which then interacts with the alkyl halide.

In our reaction conditions, no peaks are observed for the reduction of the acetylacetonate salts in $\mathrm{CH_3CN}$. The ketone reaction is influenced by the presence of $\mathrm{Ni(acac)_2}$. With 4×10^{-4} M $\mathrm{Ni(acac)_2}$ not only is the reaction rendered irreversible without any noticeable change in the reduction potential for the first electron-transfer step, but the reaction is now a two-electron process. In contrast, no change is observed in the reactions with $\mathrm{Al(acac)_2}$. Some changes are observed with $\mathrm{Fe(acac)_2}$, where the reaction appears to become a two-electron process, but the ketyl intermediate can still be oxidized.

The results presented here indicate that certain transition metal salts can influence the electrochemical reduction of ketones in aprotic solvents. These salts intervene late in the reaction, that is, after the first electron transfer to the ketone, affiliating the radical anion and consequently minimizing the reoxidation reaction to regenerate ketone. In certain cases, as with $\mathrm{CoCl_2}$, there may be a specific interaction between the metal cation and the radical anion. However, with $\mathrm{Ni(acac)_2}$ interaction may be purely Coulombic with the formation of ion pairs or triplets. The presence of these salts, however, does not appear to influence the subsequent steps in the overall reaction.

It should be mentioned at this point that in the reduction of benzil in aprotic solvent, the addition of $\mathrm{Li^+}$, $\mathrm{Na^+}$, and $\mathrm{K^+}$ in large excess produces a marked effect on the second reduction step and only a small effect on the first reduction step.[8]

In a report by K. Sasaki, magnesium ions are reported to effect the electrolytic reduction of cinnamaldehyde.[9] The reduction of cinnamaldehyde in acetonitrile shows two one-electron waves. The reduction products in acetonitrile and in aqueous acetonitrile are tar and tar plus dimers, respectively. When the reaction is carried out in the presence of 1 equiv of $\mathrm{Mg(ClO_4)_2{\cdot}4H_2O}$, the first wave shifts anodically ca. 0.4 V and the products are cinnamyl alcohol and dehydrocinnamyl alcohol plus dimer. The authors interpret the results in terms of ion pair formation between the organic radical anion and the metal cation. It should be mentioned, however, that these results are also consistent with an acid-catalyzed reaction[10] resulting from the equilibrium amounts of $\mathrm{HClO_4}$ present in solution. It is suspected that the influence of $\mathrm{Mg(ClO_4)_2}$ on this reaction under completely anhydrous conditions will be similar to what is observed in the present study.

In another study by J. M. Saveant,[11] the electrochemical reduction of diethyl 1,7-diene-2,7-diphenylsebacate is reported to be influenced by the presence of $\mathrm{LiClO_4}$. The reduction products are cyclized products when the reaction is performed in "dry" $\mathrm{CH_3CN}$. However, in moist $\mathrm{CH_3CN}$ or in the presence of $\mathrm{LiClO_4}$, hydrogenation products are formed. Again in this case because of the hydroscopic nature of $\mathrm{LiClO_4}$, it is not clear to what extent the salt introduces moisture into the reaction. This point was not clarified in the report; thus, it is difficult to determine the influence of the $\mathrm{LiClO_4}$ on the reaction.

Experimental Section

The solvents were flushed with nitrogen to remove oxygen before distillation. Acetonitrile was distilled from $\mathrm{P_2O_5}$ and dimethylformamide from $\mathrm{CaH_2}$ before use.[12] Dry $\mathrm{CoCl_2}$ and $\mathrm{ZnCl_2}$ were obtained by heating the hydrates at 110 and 150 °C, respectively, in an Abderhalder drying apparatus under 0.1 mm pressure.[13] All of the other salts used were dried at 65 °C, except $\mathrm{SnBr_4}$, which was used without any pretreatment. Commercially available 2,3:6,7-dibenzotropone and benzophenone were recrystallized from hexane–ether mixtures.

All electrochemical measurements were carried out in anhydrous solvent containing 0.1 M tetraethylammonium tetrafluoroborate and 10^{-3} M ketone. A divided cell equipped with a platinum button (0.2 cm^2) working electrode and a NaCl calomel (0.01 M) reference electrode was used. The *iR* compensation used was 85–90% of oscillation. The instrumentation used was designed and constructed in these laboratories.[14]

The solutions used for product analyses were as above, except ca. 0.01 M ketone was used. The reactions were performed in a divided cell using a platinum gauze for the working electrode. The solutions were electrolyzed at 0.1 V past the E_{pc} value until 0.6 faraday/mol of ketone was consumed, ca. 35 min. During the electrolysis the solution became intensely colored. After the prescribed electrolysis time, the reaction vessel was left standing until the color faded, and then the solution was worked up. The reaction products were isolated by extraction between ethyl ether and water in the usual manner. The recovered yellow oil, 80–90% yield, was analyzed by TLC on Eastman no. 13252 alumina using either 3:1 ethyl ether–hexane or 1:1 ethyl ether–methanol. The analysis revealed the presence of the ketone as expected and a trace amount of carbinol plus a large unidentified peak, presumedly a dimeric product.

The IR and NMR spectra of this mixture were not informative because of their similarity to the spectra of the starting material.

When the reaction was repeated with the presence of 2 mol of $CoCl_2$, no difference was detected in the product mixture except for a possible lower reaction conversion.

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Registry No.—2,3:6,7-Dibenzotropone, 2222-33-5; benzophenone, 119-61-9; $CoCl_2$, 7646-79-9; $Ni(acac)_2$, 3264-82-2; $Fe(acac)_2$, 14024-17-0; $Al(acac)_3$, 13963-57-0.

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New Biogenetic-Type Approach to *Cephalotaxus* Alkaloids and the Mechanism of *Schelhammera*-Type Homoerythrinadienone Formation in Vitro

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Three monophenolic dibenz[*d,f*]azecines, **3b**, **3c**, and **3d**, were synthesized by taking advantage of VOF_3–TFA/TFAA induced oxidative coupling of nonphenolic and monophenolic phenethyltetrahydroisoquinolines to homoneospirinedienones and homoproerythrinadienones. The oxidation of 2-hydroxydibenz[*d,f*]azecine **3b** with potassium ferricyanide yielded the cephalotaxine precursor **5b** (10%), which represents the first reported synthesis of such a compound along the biogenetic-type route. Similar oxidation of 3-hydroxydibenz[*d,f*]azecine **3c** gave naturally unknown homoerysodienone **6b** in 15% yield. However, when 12-hydroxydibenz[*d,f*]azecine **3d** was oxidized, no *Schelhammera*-type homoerythrinadienone **7b** was detectable. This implies that the diphenoquinone 4 may be an intermediate in the formation of the *Schelhammera*-type homoerythrinadienone.

Cephalotaxus is a genus of yew-like coniferous trees native to Japan and China and is the sole known source of the cephalotaxine family of alkaloids.[1] The tumor inhibitory activity of several esters of cephalotaxine (**1**) has generated considerable interest in both the synthesis of these alkaloids[2] and the elucidation of their biogenesis.[3]

In *Cephalotaxus harringtonia*, cephalotaxine (**1**; Scheme I) and its esters are accompanied by several *Schelhammera*-type alkaloids[4,5] such as 3-*epi*-schelhammericine (**2**). The presence of *Schelhammera*-type alkaloids in *Cephalotaxus* species has led some researchers[5a,6] to propose that both the *Schelhammera*-type and *Cephalotaxus* alkaloids are biogenetically related and may be classified as homoerythrina alkaloids. Marino and Samanen[6] have examined a unified approach to homoerythrina skeletons via the pivotal diphenolic dibenz[*d,f*]azecine **3a**. The compound **3a** seemed to be a common precursor of *Cephalotaxine*-type skeleton **5a**, homoerysodienone **6a**, and *Schelhammera*-type skeleton **7a**, and, indeed, **3a** was cleanly transformed into two cyclized homoerythrina skeletons using potassium ferricyanide in methylene chloride–sodium bicarbonate solution. The *Schelhammera*-type skeleton **7a** was isolated in 45% yield along with the homoerysodienone **6a** (15%) and the unreacted starting material (35%). That no cephalotaxine precursor **5a** was observed in the above oxidation is suggestive of the absence of either diphenoquinone intermediate **4** or a suitably disposed *p*-hydroxy group. The *Cephalotaxine*-type skeleton such as **5b** should also be obtainable via oxidation of monophenolic dibenz[*d,f*]azecine **3b**, and valuable information regarding the mechanism of homoerythrinadienone formation

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