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Approaches to the Synthesis of Masked *p*-Quinone Methides. Applications to the Total Synthesis of (±)-Cherylline

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Abstract: The synthesis and chemistry of *p*-quinone methide ketals, prepared from *p*-quinone monoketals **9a–c** and α-trimethylsilylamides or phosphoranes, is discussed within the context of the total synthesis of Amaryllidaceae alkaloid cherylline (**3**).

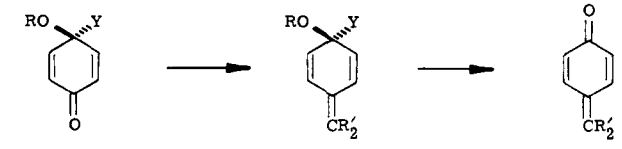
Introduction

o- and *p*-quinone methides constitute a class of highly electrophilic molecules that are frequently encountered in natural products chemistry.[1-3] A large number of quinone methides have been isolated as fungal metabolites,[2] wood pigments,[2] and insect pigments.[4] In addition, quinone methides have been implicated as intermediates in oxidative phosphorylation[2] and in the biosynthesis of chromans,[2,5] lignin,[2,6] and alkaloids.[7] It has also been suggested that some quinoid substances that exhibit antitumor properties may be activated in vivo by conversion to quinone methides.[8]

A recent survey indicates that there are no general methods for preparing *p*-quinone methides such as **2** from quinoid precursors.[9] In principle, olefination of a quinone carbonyl group offers the most direct route from a quinone to a quinone methide.[10] Although several Wittig reactions on quinone substrates have been reported, this method has yet to be established as a generally effective approach to the synthesis of quinone methides.[10d-f]

Recently, research in this laboratory has been directed toward exploiting "blocked" quinones such as **1a**, **1b**, and **1c** as intermediates in the synthesis of naturally occurring quinones,[11] *p*-quinols,[12] and alkaloids. A strategy for generating *p*-quinone methides which is conceptually similar to direct olefination of quinones, but operationally more attractive, is outlined in Scheme I. This report describes the investigation of this reaction sequence within the context of the total synthesis of the unique Amaryllidaceae alkaloid, cherylline (**3**).[13-15]

Scheme I



1, a; Y = CN, R = $SiMe_3$
b; Y = CN, R = $SiEt_3$
c; Y = OR, R = alkyl

2

Synthesis and Reactions of *p*-Quinone Methide Ketals

The general approach which was conceived for the synthesis of cherylline is outlined in Scheme II. The critical feature in

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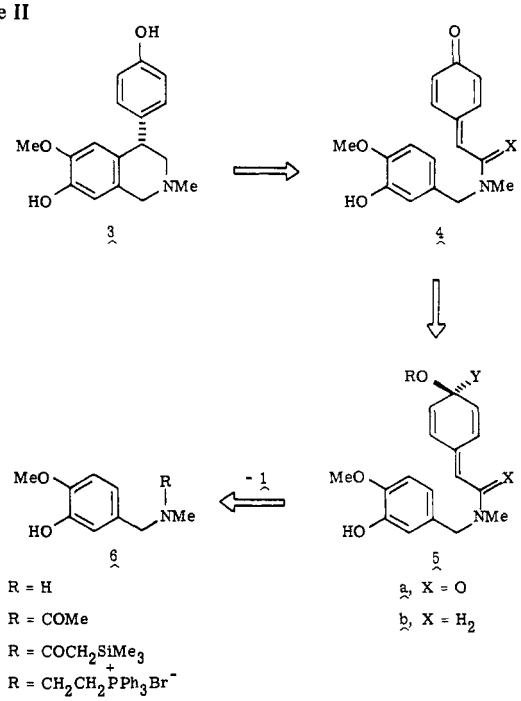
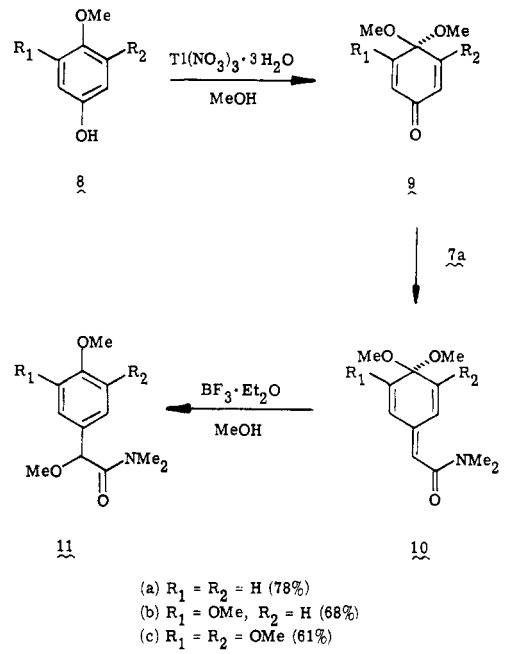
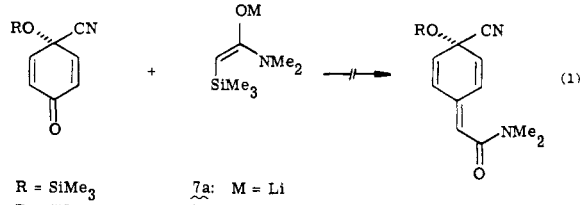
Scheme II



Scheme III



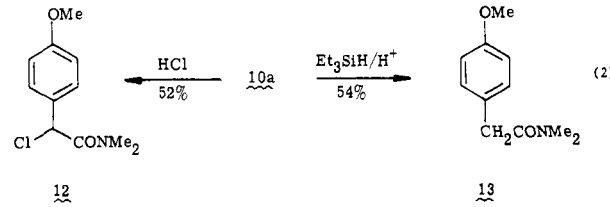
this plan focused upon the potential success in constructing previously unknown latent quinone methides such as **5a** or **5b** from amide or amine precursors **6a** or **6b**, respectively, and a suitable masked quinone derivative **1**. The availability of α-trimethylsilylamides[16,17] and the ease with which trimethylsilyl carbanions condense with ketones to produce olefins[18] encouraged us to explore the reaction between anions of *N,N*-dimethyl-α-trimethylsilylacetamide[16] and "masked" quinones **1a** and **1b** (eq 1).[12a,19] In light of the fact that these quinone



derivatives undergo efficient 1,2-addition reactions upon treatment with enolates and organometallic reagents[12b,19] it was disappointing to find that anions **7a** and **7b** gave only intractable tars upon treatment with **1a** and **1b** under conditions where the starting materials were consumed.[20] It was suspected that the failure of these reactions was due to the susceptibility of these quinone adducts to decompose via nucleophilic attack on silicon or the cyano group. To circumvent these problems, attention was turned to the reaction between enolate **7a** and *p*-quinone monoketals (Scheme III).

p-Quinone ketals have been prepared by a variety of methods.[21,22] In the present study, the *p*-quinone ketals **9a–c** were prepared from the readily available phenols **8a–c** by the excellent method of McKillop and Taylor.[21a] It was gratifying to find that when **7a** was allowed to react with quinone ketal **9a** for a few minutes at −70 °C in tetrahydrofuran followed by warming to room temperature, *p*-quinone methide ketal **10a** was obtained contaminated by small amounts of starting materials and other unidentified substances as indicated by weak signals in the ^1H NMR spectrum of the mixture. Attempts to purify **10a** by chromatography over silica gel or alumina led to decomposition as did bulb-to-bulb distillation. Crude **10a** was stable for several months upon storage in a refrigerator under an argon blanket and was recovered unchanged from neutral methanol after several hours at room temperature. *To the extent of our knowledge this method represents the first entry to this class of molecules.* When a methanolic solution of **10a** was treated with a catalytic amount of boron trifluoride etherate, α-methoxy amide **11a** was obtained in a 77% overall yield from quinone ketal **9a.** Similar treatment of ketals **9b** and **9c** with **7a** followed by treatment of the resulting crude *p*-quinone methide ketals **10b** and **10c** with boron trifluoride etherate in methanol gave α-methoxy amides **11b** and **11c** in 68 and 61% yields, respectively.

The ability of *p*-quinone methide dimethyl ketals to serve as a source of O-methylated *p*-quinone methides was further demonstrated by the conversion of **10a** to α-chloro amide **12** upon treatment with hydrogen chloride in tetrahydrofuran (52%; eq 2). Furthermore, **10a** was reduced to α-acrylamide

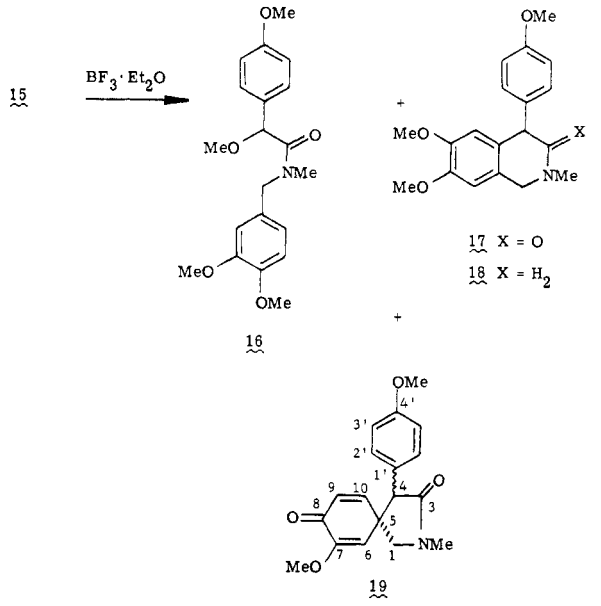


13 upon treatment with either lithium in liquid ammonia (47%) or triethylsilane in trifluoroacetic acid (54%).[23] *This reaction sequence establishes a new protocol for introducing an aryl group α to an amide carbonyl group.*

Having accomplished the goal set forth in Scheme I, we examined the cyclization reaction depicted in Scheme II. Within the context of the projected synthesis of cherylline, *p*-quinone methide ketal **15** was selected as a suitable model for study and was prepared without difficulty (eq 3). Benzylic amine **14a**[24] was N-acylated (95%), and the resulting amide (**14b**) was sequentially treated with lithium diisopropylamide (LDA) and chlorotrimethylsilane (THF, −70 °C) to give the α-silylamide **14c** in 85% yield. As in previous cases, the enolate derived from **14c** underwent condensation with quinone ketal **9a** to give quinone methide ketal **15.** The ^1H NMR spectra of **15** in $CDCl_3$ and C_6D_6 revealed that **15** existed as approximately a 2:3 mixture of amide *E* and *Z* isomers.[25]

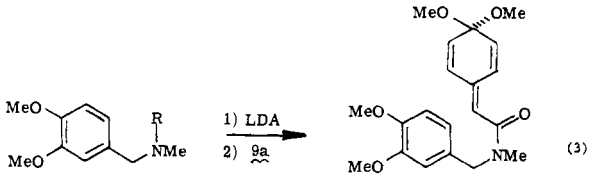
When quinone methide ketal **15** was treated with boron trifluoride etherate in dichloromethane for 24 h at room

Scheme IV



Solvent	Conditions	% Yield (16:17:19)
MeOH	15 min, 25°C	40:23:0
MeOH—H_2O (20:1)	15 min, 25°C	37:16:15
CH_2Cl_2	15 min, 25°C	40:20:0
CH_2Cl_2	24 h, 25°C	0:50:0

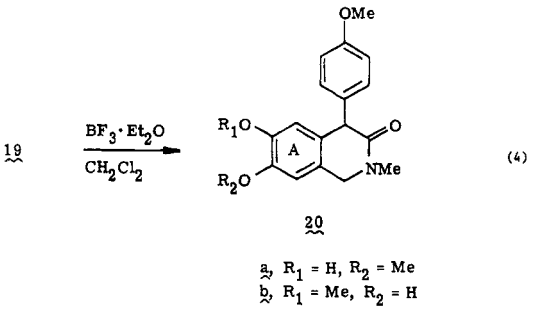
temperature, crystalline lactam **17** was obtained in a 50% overall yield from **14** and **9a.** The identity of **17** was established



by reduction with lithium hydride to the known (±)-*O,O*-dimethylcherylline (**18**).[13] Although this cyclization was superficially straightforward, careful examination of this electrophilic substitution process revealed that a complex series of events intervened during the conversion of **15** to **17.**

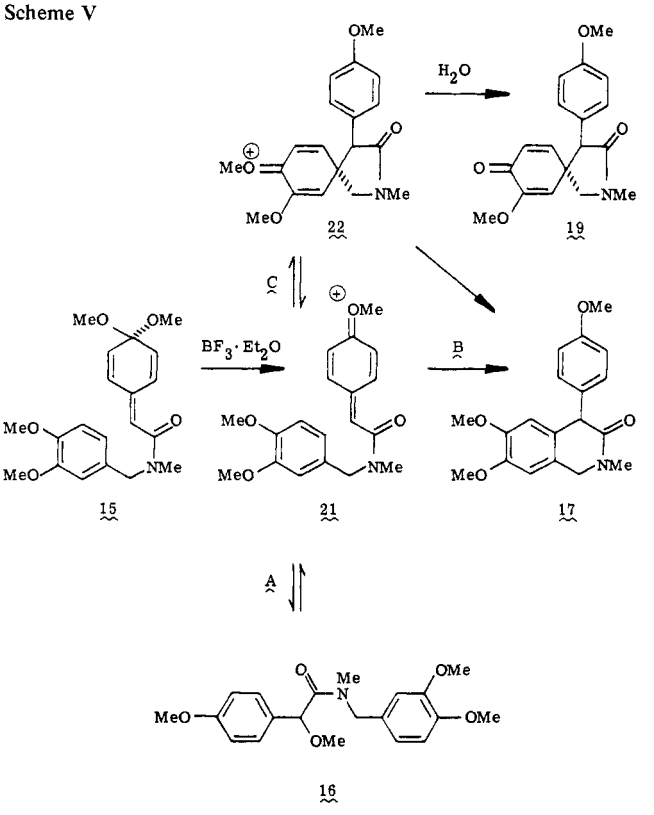
The products obtained upon treatment of **15** with 1.05–1.1 equiv of boron trifluoride etherate under a variety of conditions are shown in Scheme IV. α-Methoxy amide **16,** which was always produced at short reaction times, was stable to the methanolic reaction conditions but was converted to **17** in 75% yield upon exposure to 1.7 equiv of boron trifluoride etherate in dichloromethane for 5 h.

The structure of spirodienone **19,** which was only obtained when **15** was cyclized in aqueous methanol, was deduced from its spectral data.[26] The appearance of only 15 signals in the ^{13}C NMR spectrum of **19** suggested the presence of a single diastereomer. Dienone **19,** which was stable to the aqueous methanolic reaction conditions, underwent a dienone–phenol rearrangement upon treatment with 1 equiv of boron trifluoride etherate in dichloromethane at room temperature for 15 min (eq 4) to give phenolic lactam **20a** in 70% yield. In principle, four products could have been formed via dienone–phenol rearrangement.[26,27] The appearance of the two tetrahydroisoquinoline A-ring protons as singlets as δ 6.67 and 6.70 in the ^1H NMR spectrum of **20a** indicated that the migrating terminus had moved to C-10. The position of the hydroxyl and methoxyl groups on the A ring was evident from the nonidentity of **20a** with an authentic sample of **20b** that was prepared during the course of this study (vide infra).[28]



The data presented above are accommodated by the mechanistic pathways outlined in Scheme V. In either methanol or dichloromethane, **15** ionizes to produce **21,** which (a) gives **16** upon being trapped by methanol; (b) produces **17** via a direct cyclization; and (c) undergoes ipso cyclization to give **22.**[29] In aqueous methanol **22** is trapped to afford dienone **19.** Although the intermediacy of **22** has not been established in the absence of water, it is reasonable to assume that it is formed but eventually affords **17** via a dienone–phenol rearrangement or by reversion to **21.** Indeed, these results suggest that several other 4-aryltetrahydroisoquinoline syntheses that have been reported may proceed in part through spiranyl intermediates.[14,30] In this study there was some initial concern that restricted rotation about the C–N amide bond in ketal **15** could cause difficulties in the acid-catalyzed ring closure to the desired bicyclic lactam **17.** In this regard, the product ratio of **16:17** formed after short reaction times (Scheme IV) could have been dependent upon the ratio of *E* and *Z* amide isomers in **15.** This concern became academic after it was observed that α-methoxy amide **16** could be transformed to lactam **17** on extended acid treatment.

Scheme V



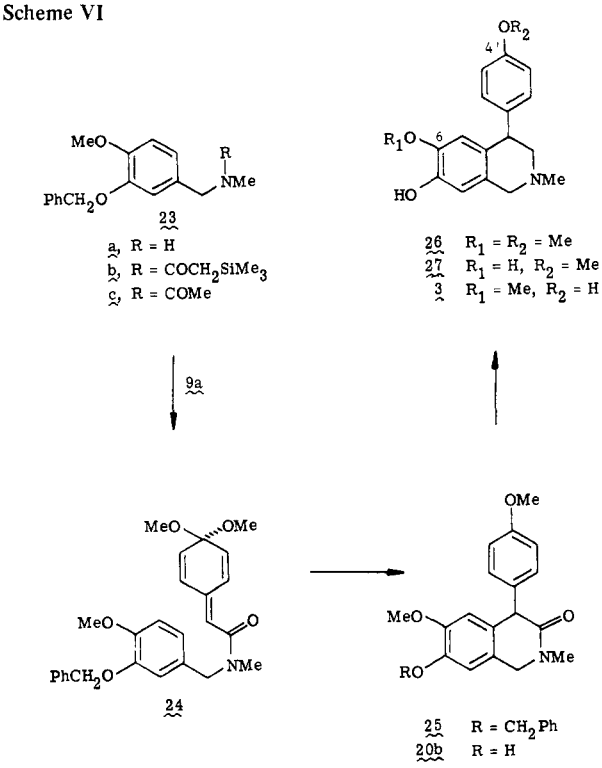
Synthesis of (±)-Cherylline

The synthesis of (±)-cherylline based upon the preceding concepts is summarized in Scheme VI. The requisite α-silyl acetamide **23b** was readily obtained in 80% yield upon treatment of the known benzylic amine **23a**[14] with trimethylsilylketene.[17] Amide **23b** was treated sequentially with lithium diisopropylamide and ketal **9a.** The resulting crude *p*-quinone methide ketal **24** was stirred with 2.0 equiv of boron trifluoride etherate for several hours at room temperature and lactam **25** was crystallized directly from the crude product mixture in a 55% overall yield. Hydrogenolysis of the benzyl protecting group gave crystalline phenolic lactam **20b** in a 97% yield. This material was isomeric with phenol **20a** obtained from rearrangement of dienone **19** (eq 4). Reduction of lactam **20b** with lithium aluminum hydride afforded tetrahydroisoquinoline **26** in a 75% yield. It was anticipated that delocalization of charge onto the ortho positions in the phenolate derived from **26** would retard nucleophilic cleavage of the aryl ether linkage at C-6 relative to that at C-4′. This expectation was supported by qualitative data on thiolate-mediated cleavages of aryl methyl ethers reported by Mirrington.[31,32] Thus, treatment of **26** with sodium ethyl mercaptide in *N,N*-dimethylformamide gave (±)-cherylline (**3**) contaminated with 5–10% of the isomeric diphenol **27** in a 53% yield.[33] One recrystallization gave pure (±)-cherylline that was shown to be identical (TLC, NMR, IR, melting point) with an authentic sample of (±)-cherylline provided to us by Professor M. A. Schwartz.

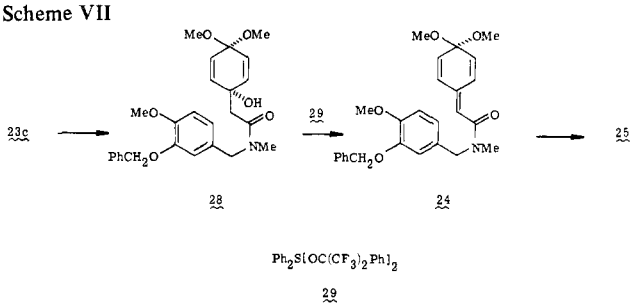
Owing to the increasing availability of *p*-quinols,[12b,19] dehydration of these molecules or derivatives thereof conceptually offers an attractive route to *p*-quinone methides. In practice, however, this transformation has been accomplished efficiently in only one system[34] and has not yet been established as a general reaction in the chemistry of *p*-quinols. Under the acidic and basic conditions employed to date, dienone–phenol rearrangements appear to proceed more rapidly than dehydration. Therefore, in addition to the present method used to construct *p*-quinone methide ketal **24,** we briefly investigated a scheme for generating **24** via dehydration of *p*-quinol ketal **28** (Scheme VII). Amine **23a** was N-acylated (88%) and the resulting amide **23c** was sequentially treated with lithium diisopropylamide and **9a** to afford the requisite *p*-quinol ketal **28.** Hydroxy amide **28** was dehydrated cleanly to **24** upon treatment with sulfurane **29**[35] in dichloromethane. Treatment of the crude mixture of products obtained from the dehydration reaction with boron trifluoride etherate afforded **25** in 67% yield from amine **23c.** The generality of this potentially useful procedure for generating *p*-quinone methide ketals was not pursued.

Although the synthesis of (±)-cherylline (**3**) via amide intermediates was instructive from the standpoint of acquainting ourselves with the construction and properties of *p*-quinone methide ketals, it suffered from the presence of several protection, deblocking, and refunctionalization reactions. In an effort to improve the efficiency of the cherylline synthesis. The preparation and cyclization of phenolic *p*-quinone methide ketal **32** was pursued using a modification of an allylic amine synthesis introduced by Schweizer (Scheme VIII).[36] Isovanillin[37] was treated with methylamine and the resulting imine **30** was reduced with sodium borohydride to give phenolic amine **6a** in 73% overall yield. Equimolar amounts of amine **6a** and vinyltriphenylphosphonium bromide (**31**) reacted exothermically in dichloromethane to afford the phosphonium salt **6d** in 91% yield. Sequential treatment of **6d** with *n*-butyllithium (2.0 equiv) and **9a** followed by treatment of the resulting crude allylic amine **32** with 5.0 equiv of boron trifluoride etherate gave phenolic amine **26** in a 47% yield. The conversion of **26** to (±)-cherylline (**3**) has been previously described (vide supra). In addition to the example described above, it has been shown that the phosphorane route to *p*-quinone methide ketals has considerable generality.[38]

Scheme VI



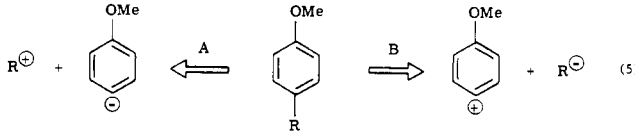
Scheme VII



The efficient and convergent nature of this tetrahydroisoquinoline synthesis should allow the construction of a wide variety of interesting molecules. In addition, it is expected that the utilization of a β-phenethylamine as the amine component in this sequence will provide an entry to the pharmacologically interesting 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepines.[39]

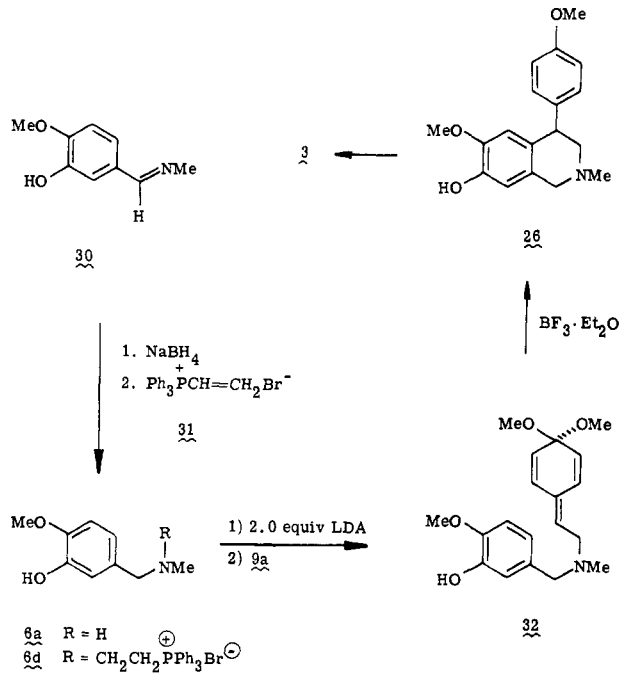
Conclusions

When confronted with the construction of a carbon–aryl bond, two polar bond connections are conceivable (eq 5).



Electrophilic aromatic substitution is most frequently used to accomplish this transformation (path A). It is important to recognize that the syntheses and reactions of *p*-quinone methide ketals described herein define a new protocol for performing a synthetic operation formally equivalent to nucleophilic aromatic substitution.[40] Thus, quinone ketals **9a–c** can be regarded as *p*-methoxyaryl cation equivalents which permit the construction of carbon–aryl bonds as delineated by path B (eq 5).

Scheme VIII



Experimental Section

All melting points were taken with a Buchi SMP-20 melting point apparatus and are uncorrected as are boiling points. ^1H magnetic resonance spectra (60 MHz) were recorded on a Varian Associates A-60 spectrometer and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants (Hz), and interpretation. ^{13}C magnetic resonance spectra were recorded on Varian Associates XL-100 (25.2 MHz) and T-60 (15.1 MHz) spectrometers and are reported in parts per million from internal tetramethylsilane on the δ scale. Infrared spectra were taken with a Beckman 4210 instrument. Mass spectra were recorded on a Du Pont 21-492B spectrometer at 70 eV. Mass spectral analyses were performed by the California Institute of Technology Microanalytical Laboratory as were combustion analyses.

Solvents and reagents were dried prior to use when deemed necessary: tetrahydrofuran, 1,2-dimethoxyethane, ammonia (distilled from Na metal); chlorotrimethylisilane, triethylamine, diisopropylamine, *N,N*-dimethylformamide, benzene, xylene (distilled from calcium hydride); methanol (distilled from magnesium methoxide); dichloromethane, chloroform (passed through a column of activity I alumina). Reactions requiring an inert atmosphere were run under a blanket of nitrogen unless stated otherwise. All reaction temperatures refer to those of the reaction mixture itself unless stated otherwise. Reactions were routinely followed by ^1H NMR analysis of aliquots or by thin layer chromatographic analysis. Analytical and preparative thin layer chromatography was performed using EM Laboratories precoated silica gel 60 F-254 plates that were 0.25 and 2.0 mm thick, respectively. Column chromatography was performed over EM Laboratories silica gel (70–230 mesh) and Woelm neutral alumina. Medium-pressure chromatography was performed over EM Laboratories silica gel H using a Chromatronix MPLC apparatus equipped with a Milton-Roy Mini-Pump. Bulb to bulb distillations were accomplished in a Buchi GKR-50 Kugelrohrapperat.

Lithium diisopropylamide was always prepared in the following manner. A solution of diisopropylamine (1.05 equiv) in tetrahydrofuran was cooled to −50 °C followed by the addition of a hexane solution of *n*-butyllithium[41] (1.00 equiv) via syringe. The cooling bath was removed and the temperature of the reaction mixture was allowed to rise to −20 °C where it was maintained for 3–5 min. The resulting solution of lithium diisopropylamide was then cooled to the temperature desired for subsequent operations.

***N,N*-Dimethyl-α-(4,4-dimethoxycyclohexa-2,5-dienylidene)acetamide (10a).** To a solution of lithium diisopropylamide [from 1.54 mL (11.0 mmol) of diisopropylamine and 4.62 mL (10.5 mmol) of 2.27 M *n*-butyllithium in 80 mL of tetrahydrofuran] cooled to −60 °C was added a solution of 1.59 g (10.0 mmol) of *N,N*-dimethyl-α-trimethylsilylamide[16] in 20 mL of tetrahydrofuran via syringe. The reaction temperature was maintained below −50 °C throughout the addition. The mixture was stirred at −60 °C for 30 min followed by the addition of a solution of 1.54 g (10.0 mmol) of 4,4-dimethoxycyclohexadienone (**9a**)[21a] in 3.0 mL of tetrahydrofuran via syringe. The cooling bath was removed and the mixture was allowed to warm to 0 °C. The resulting solution was cast into 300 mL of dichloromethane and 75 mL of saturated aqueous sodium bicarbonate. The organic phase was washed with 75 mL of saturated aqueous brine–water (1:1), dried (Na_2SO_4), and concentrated in vacuo to give 2.23 g (100%) of crude **10a** as a gray liquid. This material was used in subsequent reactions without purification: IR (CCl_4) 1635 cm^{-1}; NMR (CCl_4) δ 3.00 (broad s, 6, $-NCH_3$), 3.22 (s, 6, $-OCH_3$), 5.83–6.52 (complex m, 4, =CH–), 7.27 (d with fine splitting, 1, J = 10 Hz, =CH– on one of carbons γ to $-CONMe_2$); mass spectrum *m/e* (rel intensity) 223 (M^+, 5), 192 (3), 151 (base).

Exact mass. Calcd for $C_{12}H_{17}NO_3$: 223.121. Found: 223.119.

On one occasion, crude **10a** was subjected to bulb-to-bulb distillation at 150 °C and 0.002 mm to afford a 7:1 mixture of **10a** and **11a**, respectively, as a colorless liquid. The ratio of the two components was determined by integrating appropriate peaks in the ^1H NMR spectrum of the mixture. No **11a** was detected in the crude **10a** prior to distillation. The following spectral data were determined for **10a** by substracting contributions due to **11a:** UV_{max} (MeOH) 232 nm (ϵ 31 500), 271 (24 000); ^{13}C NMR ($CDCl_3$) δ 166.3 (C=O), 135.0, 130.8, 130.2, 129.6, 126.1, 123.8 (=C<), 94.7 (–OCO–), 49.8 (OCH_3), 37.8 34.9 (NCH_3).

***N,N*-Dimethyl-α-methoxy-α-*p*-methoxyphenylacetamide (11a).** To a solution of 340 mg (1.52 mmol) of crude *p*-quinone methide ketal **10a** in 5.0 mL of methanol was added 1 drop of boron trifluoride etherate. The mixture was allowed to stand at room temperature for 30 min and was poured into 30 mL of dichloromethane and 15 mL of saturated aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give 350 mg of a light green liquid which was bulb-to-bulb distilled at 145 °C and 0.01 mm to afford 262 mg (77%) of amide **11a** as a light yellow liquid: IR (CCl_4) 1645, 1507, 1247 cm^{-1}; NMR (CCl_4) δ 2.85 (s, 6, $-NCH_3$), 3.42 (s, 3, benzylic $-OCH_3$), 3.77 (s, 3, aryl $-OCH_3$), 4.87 (s, 1, benzylic –CH), 6.77, 7.25 (AA′BB′, 4, J = 9 Hz, aromatics); mass spectrum *m/e* (rel intensity) 223 (M^+, 3), 178 (32), 153 (23), 151 (base); UV_{max} (MeOH) 232 nm (ϵ 12 800), 275 (1600), 282 (1500); ^{13}C NMR ($CDCl_3$) δ 169.7 (C=O), 159.1 (*C*OMe), 128.2 (C meta to OMe), 128.0 (C para to OMe), 113.6 (C ortho to OMe), 81.8 (*C*–C=O), 56.7, 54.9 (OCH_3), 36.2, 35.7 (NCH_3).

Exact mass. Calcd for $C_{12}H_{17}NO_3$: 223.121. Found: 223.121.

***N,N*-Dimethyl-α-chloro-α-*p*-methoxyphenylacetamide (12).** To 5.0 mL of tetrahydrofuran through which hydrogen chloride gas had been passed for 3 min was added a solution of 364 mg (1.63 mmol) of crude **10a** in 8 mL of tetrahydrofuran via syringe. Hydrogen chloride was passed through the solution during the addition. After the addition of **11a** was complete, passage of hydrogen chloride was stopped and the mixture was stirred for 15 min. The resulting orange solution was poured into 30 mL of dichloromethane and was washed with two 15-mL portions of saturated aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give 350 mg of a yellow liquid which was bulb-to-bulb distilled at 150 °C and 0.01 mm to yield 193 mg (52%) of α-chloro amide **12** as a pale yellow liquid: IR (CCl_4) 1664, 1504, 1247 cm^{-1}; NMR (CCl_4) δ 2.95 (s, 6, $-NCH_3$), 3.77 (s, 3, $-OCH_3$), 5.55 (s, 1, benzylic –CH), 6.80, 7.33 (AA′BB′, 4, J = 9 Hz, aromatics); mass spectrum *m/e* (rel intensity) 229 (M^+, 9), 227 (M^+, 25), 157 (24), 72 (base).

Exact mass. Calcd for $C_{11}H_{14}{}^{35}ClNO_2$: 227.071. Found: 227.070.

***N,N*-Dimethyl-α-*p*-methoxyphenylacetamide (13). A. From Lithium–Ammonia Reduction.** To 35 mL of ammonia cooled in a dry ice–2-propanol bath was added 21 mg (3.0 mmol) of lithium metal. To the resulting blue solution was added 310 mg (1.39 mmol) of crude **10a** in 8 mL of tetrahydrofuran via syringe over a 5-min period. The solution was stirred for 5 min followed by the addition of 168 mg (3.0 mmol) of ammonium chloride in 1.0 mL of water. The ammonia was allowed to evaporate and the residue was portioned between dichloromethane and water. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residual liquid (233 mg) was chromatographed over 25 g of alumina (activity III; eluted with ethyl ace-

tate–hexane, 1:4; 10-mL fractions) and fractions 36–47 were concentrated to afford 125 mg (47%) of amide **13**: IR (CCl_4) 1641, 1502, 1240 cm^{-1}; NMR (CCl_4) δ 2.80, 2.84 (overlapping s's, 6, $-NCH_3$), 3.48 (s, 2, benzylic $-CH_2-$), 3.68 (s, 3, $-OCH_3$), 6.71, 7.07 (AA'BB', 4, J = 9 Hz, aromatics); mass spectrum *m/e* (rel intensity) 193 (M^+, 31), 121 (base), 72 (60).

Exact mass. Calcd for $C_{11}H_{15}NO_2$: 193.110. Found: 193.112.

B. From Triethylsilane–Trifluoroacetic Acid Reduction. To a solution of 297 mg (1.33 mmol) of crude **10a** and 232 mg (2.0 mmol) of triethylsilane in 1.0 mL of dichloromethane was added 0.5 mL (6.7 mmol) of trifluoroacetic acid via syringe. The resulting solution was stirred at room temperature for 18 h followed by the addition of 25 mL of dichloromethane. The mixture was washed with 10 mL of saturated aqueous sodium bicarbonate and 10 mL of 5% aqueous sodium hydroxide, dried (Na_2SO_4), and concentrated in vacuo. The residual pink oil was chromatographed over 15 g of silica gel (eluted with ethyl acetate; 10-mL fractions). Fractions 8–15 were concentrated to afford 140 mg (54%) of amide **13.**

3,4,4-Trimethoxycyclohexa-2,5-dien-1-one (9b). To a solution of 25.0 g (56 mmol) of thallium(III) nitrate trihydrate in 150 mL of dry methanol cooled to −25 °C was added a solution of 8.67 g (56 mmol) of 3,4-dimethoxyphenol in 150 mL of methanol. The resulting mixture was stirred for 5 min at −25 °C and allowed to warm to room temperature. The mixture was poured slowly into 500 mL of saturated sodium bicarbonate and the resulting solution was extracted with five 300-mL portions of ether–ethyl acetate (4:1). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to afford 9.12 g of a yellow-brown solid. A solution of this material in dichloromethane was filtered through 50 g of activity I neutral alumina with the aid of an aspirator. The resulting yellow crystals were recrystallized from cyclohexane–ether and sublimed (50 °C, 0.005 mm) to give 7.21 g (70%) of white, crystalline **9b**: mp 63.5–64.5 °C; IR ($CHCl_3$) 3010, 2960, 1663, 1637, 1605 cm^{-1}; NMR ($CDCl_3$) δ 3.33 (s, 6, geminal $-OCH_3$), 3.83 (s, 3, vinylic $-OCH_3$), 5.65 (d, 1, J = 2 Hz, C-2 vinyl), 6.30 (dd, 1, J = 10, 2 Hz, C-6 vinyl), 6.77 (d, 1, J = 10 Hz, C-5 vinyl).

Anal. ($C_9H_{12}O_4$) C, H.

***N,N*-Dimethyl-α-(3,4,4-trimethoxycyclohexa-2,5-dienylidene) acetamide (10b).** To a solution of lithium diisopropylamide [from 0.31 mL (2.2 mmol) of diisopropylamine and 0.93 mL (2.1 mmol) of 2.27 M *n*-butyllithium in 15 mL of tetrahydrofuran] cooled to −60 °C was added a solution of 0.32 g (2.0 mmol) of *N,N*-dimethyl-α-trimethylsilylamide in 5 mL of tetrahydrofuran via syringe at a rate such that the temperature never exceeded −50 °C. The solution was stirred for 30 min at −60 °C followed by addition of a solution of 0.37 g (2.0 mmol) of 3,4,4-trimethoxycyclohexa-2,5-dienone (**9b**) in 2 mL of tetrahydrofuran in a single portion via syringe. The cooling bath was removed and the mixture was allowed to warm to room temperature followed by stirring for an additional 20–30 min. The resulting yellow solution was cast into 100 mL of dichloromethane and 40 mL of saturated aqueous brine–water (1:1). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 485 mg (96%) of 3:2 mixture of isomeric *p*-quinone methide ketals **10b** as a light yellow liquid. This material was used in subsequent reactions without purification: IR (CCl_4) 1665, 1630, 1605, 1578 cm^{-1}; NMR ($CDCl_3$) δ 3.07 (m, 6, $-NCH_3$), 3.23 (s, 6, geminal $-OCH_3$), 3.78, 3.82 (two s's, 6, vinylic $-OCH_3$), 5.63–6.63 (complex m, 3, =CH–), 7.05 (d, 0.6, J = 1 Hz), 7.52 (dd, 0.4, J = 10, 2 Hz, =CH– on carbon γ to $-CONMe_2$ group); mass spectrum *m/e* (rel intensity) 153 (M^+, 11), 222 (12), 181 (base).

Exact mass. Calcd for $C_{13}H_{19}NO_4$: 253.131. Found: 253.128.

***N,N*-Dimethyl-α-methoxy-α-(3,4-dimethoxyphenyl)acetamide (11b).** To a solution of 217 mg (0.86 mmol) of **10b** in 5 mL of methanol was added 2 drops of boron trifluoride etherate. The mixture was stirred for 45 min at ambient temperature followed by the addition of 30 mL of dichloromethane and 10 mL of saturated aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give 210 mg of a yellow liquid which was bulb-to-bulb distilled to afford 155 mg (71%) of analytically pure amide **11b**: bp 150 °C (0.002 mm); IR (CCl_4) 1642, 1510, 1260 cm^{-1}; NMR (CCl_4) δ 2.87 (s, 6, $-NCH_3$), 3.40 (s, 3, benzylic $-OCH_3$), 3.77, 3.80 (s's, 6, aryl $-OCH_3$), 4.85 (s, 1, benzylic –CH), 6.67–6.88 (m, 3, aromatics); mass spectrum *m/e* (rel intensity) 253 (M^+, 5), 181 (base).

Anal. ($C_{13}H_{19}NO_4$) C, H.

***N,N*-Dimethyl-α-(3,4,4,5-tetramethoxycyclohexa-2,5-dienylidene)acetamide (10c) and *N,N*-Dimethyl-α-methoxy-α-(3,4,5-trimethoxyphenyl)acetamide (11c).** To a solution of lithium diisopropylamide [from 0.77 mL (5.5 mmol) of diisopropylamine and 2.31 mL (5.25 mmol) of 2.27 M *n*-butyllithium in 40 mL of tetrahydrofuran] cooled to −70 °C was added 0.80 g (5.0 mmol) of *N,N*-dimethyl-α-trimethylsilylacetamide in 10 mL of tetrahydrofuran via syringe. The mixture was stirred for 30 min followed by the addition of a solution of 1.07 g (5.0 mmol) of 3,4,4,5-tetramethoxycyclohexa-2,5-dienone (**9c**)[21a] in 10 mL tetrahydrofuran via syringe. The cooling bath was removed and the mixture was allowed to warm to room temperature over a 30-min period. After an additional 90 min at room temperature, the mixture was poured into 200 mL of dichloromethane and 100 mL of saturated aqueous brine–water (1:1). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to afford 1.31 g of a 4:1:1 mixture of ketal **10c,** dienone **9c,** and starting α-trimethylsilylamide, respectively. This material was used in the following reaction without purification. The following peaks in the ^1H NMR spectrum of the mixture were assigned to **10c:** NMR (CCl_4) δ 3.10 (broad s, 6, $-NCH_3$), 3.20 (s, 6, geminal $-OCH_3$), 3.78, 3.82 (s's, 6, vinylic $-OCH_3$), 5.70 (broad s, 1, =CH–), 5.83 (s, 1, =CH–), 7.28 (broad s, 1, =CH– on one of the carbons γ to $-CONMe_2$).

To a solution of crude **10c** prepared above in 30 mL of methanol was added 2 drops of boron trifluoride etherate. The mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residual oil was chromatographed over 45 g of silica gel (eluted with 500 mL of ethyl acetate–hexane (1:1) followed by pure ethyl acetate; 10-mL fractions). Fractions 60–85 were concentrated to give 150 mg of a 4:1 mixture of **9c** and **11c,** respectively. Fractions 86–126 were concentrated to yield 0.75 g (55%, 61% based on converted **9c**) of amide **11c** which crystallized on standing: mp 90–95 °C; IR (CCl_4) 1640 cm^{-1}; NMR ($CDCl_3$) δ 2.97 (s, 6, $-NCH_3$), 3.47 (s, 3, benzylic $-OCH_3$), 3.85 (s, 3, aryl $-OCH_3$), 3.87 (s, 6, aryl $-OCH_3$), 4.97 (s, 1, benzylic –CH), 6.70 (s, 2, aromatics); mass spectrum *m/e* (rel intensity) 283 (M^+, 6), 212 (15), 211 (base), 196 (7), 195 (2), 181 (5), 72 (7).

Anal. ($C_{14}H_{21}NO_5$) C, H.

***N*-(3,4-Dimethoxybenzyl)-*N*-methylacetamide (14b).** To a solution of 16.5 g (89.0 mmol) of amine **14a**[24] and 10.1 g (0.1 mol) of triethylamine in 400 mL of chloroform cooled in an ice bath was added 7.85 g (0.1 mol) of acetyl chloride via syringe. The mixture was stirred at ambient temperature for 15 h followed by the addition of 2 mL of ethanol. The solution was poured into 100 mL of water and the organic phase was washed with 100 mL of 10% aqueous hydrochloric acid and 100 mL of saturated aqueous brine, dried (Na_2SO_4), and concentrated in vacuo. The residual liquid was distilled to give 17.9 g (95%) of amide **14b** as a colorless liquid: bp 150 °C (0.1 mm); IR (CCl_4) 1644 cm^{-1}; NMR (CCl_4) δ 2.03 (s, 3, $-COCH_3$), 2.87 (s, 3, $-NCH_3$), 3.80 (s, 6, aryl $-OCH_3$), 4.40 (s, 2, $-CH_2-$), 6.58–6.88 (m, 3, aromatics); mass spectrum *m/e* (rel intensity) 223 (M^+, 91), 151 (base), 43 (26).

Anal. ($C_{12}H_{17}NO_3$) C, H.

***N*-(3,4-Dimethoxybenzyl)-*N*-methyl-α-trimethylsilylacetamide (14c).** To a solution of lithium diisopropylamide [from 2.1 mL (15.0 mmol) of diisopropylamine and 6.67 mL (14.5 mmol) of 2.17 M *n*-butyllithium in 75 mL of tetrahydrofuran] cooled to −70 °C was added a solution of 3.02 g (13.5 mmol) of amide **14b** in 30 mL of tetrahydrofuran via syringe. The resulting pale yellow solution was stirred at −70 °C for 30–40 min followed by *rapid* addition of 3.43 mL (27.0 mmol) of trimethylsilyl chloride which had been washed free of hydrogen chloride with triethylamine. *Rapid addition of the trimethylsilyl chloride accompanied by vigorous stirring was necessary to limit proton transfer reactions from taking place prior to complete silylation of the intermediate amide anion.* The mixture was allowed to warm to room temperature and was cast into 400 mL of dichloromethane and 100 mL of saturated aqueous sodium bicarbonate. The organic phase was washed with 100 mL of saturated aqueous brine, dried ($MgSO_4$), and concentrated in vacuo. The residual light yellow oil was chromatographed over 150 g of alumina (activity III; eluted with hexane–ethyl acetate, 4:1) to afford 0.2 g of *N*-(3,4-dimethoxybenzyl)-*N*-methyl-α,α-bis(trimethylsilyl)acetamide: mp 80–82 °C; IR (CCl_4) 1607 cm^{-1}; NMR (CCl_4) δ 0.12 [s, 18, $-Si(CH_3)_3$], 1.87 (s, 1, –CH), 2.86 (s, 3, $-NCH_3$), 3.77 (s, 6, aryl $-OCH_3$), 4.45 (broad s, 2, benzylic $-CH_2-$), 6.64–6.95 (m, 3, aromatics); mass spectrum *m/e* (rel intensity) 367 (M^+, 78), 151 (base), 73 (88).

Anal. ($C_{18}H_{33}NO_3Si_2$) C, H.

Continued elution gave 3.40 g (85%) of α-trimethylsilylamide **14c:** IR (CCl_4) 1625 cm^{-1}; NMR (CCl_4) δ 0.10 [s, 9, $-Si(CH_3)_3$], 1.90 (s, 2, $-CH_2C(=O)N<$), 2.83 (s, 3, $-NCH_3$), 3.80 (s, 6, aryl –OMe),

4.40 (s, 2, benzylic $-CH_2-$), 6.58-6.88 (m, 3, aromatics); mass spectrum *m/e* (rel intensity) 295 (M^+, 49), 180 (20), 151 (base), 73 (31).

Exact mass. Calcd for $C_{15}H_{25}NO_3Si$: 295.160. Found: 295.158.

***N*-(3,4-Dimethoxybenzyl)-*N*-methyl-α-(4,4-dimethoxycyclohexa-2,5-dienylidene)acetamide (15).** To a solution of lithium diisopropylamide [from 0.36 mL (2.6 mmol) of diisopropylamine and 1.10 mL (2.5 mmol) of 2.27 M *n*-butyllithium in 20 mL of tetrahydrofuran] cooled to −70 °C was added a solution of 678 mg (2.3 mmol) of amide **14c** in 5 mL of tetrahydrofuran at a rate such that the reaction temperature did not exceed −60 °C. The solution was stirred at −70 °C for 20 min, warmed to −30 °C over a 5-min period, and cooled to −70 °C. A solution of 354 mg (2.3 mmol) of **9a** in 1.0 mL of tetrahydrofuran was added via syringe at a rate such that the reaction temperature did not exceed −60 °C. The resulting mixture was stirred at −70 °C for 10 min, warmed to 0 °C, and poured into 120 mL of dichloromethane and 40 mL of saturated brine-water (1:1). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to constant weight to afford 870 mg of crude **15** as a clear, gray oil which was used in subsequent reactions without purification. NMR analysis of this material indicated the presence of small amounts of **14c** and **9a** in addition to **15:** IR (CCl_4) 1630 cm^{-1}; NMR (CCl_4) δ 2.88 (s, 3, $-NCH_3$), 3.20 (s, 6, geminal $-OCH_3$), 3.76 (s, 6, aryl $-OCH_3$), 4.46 (broad s, 2 benzylic $-CH_2$), 5.82-6.92 (complex m, 7, aromatics and $=CH-$), 7.34 (d, 1, J = 12 Hz, $=CH-$ on one of carbons γ to $-CONMe_2$). Crude **15** was recovered unchanged upon standing in methanol and dichloromethane for 2 and 24 h, respectively.

Treatment of *p*-Quinone Methide Ketal 15 with Boron Trifluoride Etherate in Methanol. *N*-(3,4-Dimethoxybenzyl)-*N*-methyl-α-methoxy-α-*p*-methoxyphenylacetamide (16) and 6,7-Dimethoxy-4-(*p*-methoxyphenyl)-2-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (17). To a solution of 430 mg of crude ketal **15** from above in 15 mL of methanol was added 0.15 mL (1.2 mmol) of boron trifluoride etherate via syringe. The mixture was stirred for 15 min at room temperature and poured into 50 mL of chloroform and 20 mL of 5% aqueous sodium bicarbonate. The aqueous phase was extracted with 25 mL of chloroform and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residual yellow oil (430 mg) was subjected to medium-pressure chromatography over 125 g of silica gel (eluted with benzene-methanol (49:1); 10-mL fractions). Fractions 46-73 were concentrated to afford 250 mg of a 63:37 mixture of amide **16** and lactam **17,** respectively (40% of **16** and 23% of **17** based on starting **14c**). A pure sample of **17,** obtained as a pale yellow oil from early fractions, exhibited the following properties: IR (CCl_4) 1654, 1503, 1248 cm^{-1}; NMR (CCl_4) δ 2.92 (s, 3, $-NCH_3$), 3.67, 3.68, 3.77 (s's, 9, aryl $-OCH_3$), 4.08, 4.50 (AB q, 2, J = 16 Hz, $-CH_2-$), 4.50 (s, 1, $-CH-$), 6.50 (s, 1, aromatic), 6.65 (s, 1, aromatic), 6.67, 6.95 (AA′BB′, 4, J = 9 Hz, aromatics); mass spectrum *m/e* (rel intensity) 327 (M^+, 9), 85 (base).

Exact mass. Calcd for $C_{19}H_{21}NO_4$: 327.147. Found: 327.147.

A pure sample of amide **16,** obtained as a colorless oil from late fractions, exhibited the following properties: IR (CCl_4) 1655 (sh), 1637, 1502, 1245 cm^{-1}; NMR (CCl_4) δ 2.73 (s, 3, $-NCH_3$), 3.43 (s, 3, benzylic $-OCH_3$), 3.67 (broad s, 3, aromatic $-OCH_3$), 4.40 (broad s, 2, $-CH_2-$), 4.95 (broad s, 1, $-CH-$), 6.63 (m, 3, aromatics), 6.78, 7.30 (AA′BB′, 4, J = 9 Hz, aromatics); mass spectrum *m/e* (rel intensity) 359 (M^+, 1), 327 (5), 151 (base).

Exact mass. Calcd for $C_{20}H_{25}NO_5$: 359.173. Found: 359.174.

Treatment of 15 with Boron Trifluoride Etherate in Dichloromethane. A. For Short Time. A solution of 430 mg of the crude **15** prepared above in 15 mL of dichloromethane was stirred with 0.15 mL (1.2 mmol) of boron trifluoride etherate for 15 min at room temperature. The mixture was washed with 10 mL of 5% aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residual oil (388 mg) was chromatographed over 125 g of silica gel at medium pressure as described above. Fractions 61-80 were concentrated to give 239 mg of a 67:33 mixture of **16** and **17,** respectively (40% of **16** and 20% of **17** based on starting **14c**).

B. For Long Time. To a solution of crude **15** [prepared as previously described from 870 mg (2.95 mmol) of **14c**] in 35 mL of dichloromethane was added 0.4 mL (3.2 mmol) of boron trifluoride etherate. The solution was stirred under nitrogen for 23 h and was worked up as above. The crude product was chromatographed over 125 g of silica gel as described above. Fractions 59-78 were concentrated to afford 484 mg (50%) of pure **17.**

Treatment of 15 with Boron Trifluoride Etherate in Aqueous Methanol. To a solution of crude **15** (prepared as previously described from 1.69 mmol of **14c**) in 26 mL of methanol-water (25:1) was added 0.22 mL (1.80 mmol) of boron trifluoride etherate. The mixture was stirred at ambient temperature for 15 min and was worked up as described above. The crude mixture of products was chromatographed over 50 g of silica gel (eluted with benzene-methanol (49:1); 10-mL fractions). The contents of fractions 47-67 (455 mg) were rechromatographed at medium pressure over 125 g of silica gel as previously described to give 310 mg of a 71:29 mixture of **16** and **17,** respectively (37% of **16** and 16% of **17** based on **14c**). Fractions 93-97 from the initial column were concentrated to give 79 mg (15%) of spirodienone **19** as a yellow oil: IR ($CHCl_3$) 1685, 1664, 1636, 1608, 1505, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.04 (s, 3, $-NCH_3$), 3.33, 3.60 (AB q, 2, J, 12-13 Hz, $-CH_2N<$), 3.75 (s, 6, aryl and vinylic $-OCH_3$), 3.87 (broad s, 1, $>CHCO-$), 5.89 (d, 1, J = 3.5 Hz, C-6 vinyl), 6.03 (d, 1, J = 10.5 Hz, C-9 vinyl), 6.65-7.05 (m, AA′BB′ with underlying m, 5, C-10 vinyl and aromatics); ^1H NMR (benzene-d_6) δ 2.54, 2.78 (AB q, 2, J = 12 Hz), 2.66 (s, 3), 3.30, 3.32 (s's, 6) 3.51 (broad s, 1), 5.38 (d, 1, J = 3.5 Hz, C-6 vinyl), 5.87 (d, 1, J = 11 Hz, C-9 vinyl), 6.28 (dd, 1, J = 3.5, 11 Hz, C-10 vinyl), 6.70, 7.04 (AA′BB′, 4, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 180.1 (s, C-8), 172.3 (s, C-3), 159.9 (s, C-4′), 152.3 (s, C-7), 148.4 (C-10), 219.8 (d, C-2′), 128.9 (C-9), 124.9 (s, C-1′), 116.6 (C-6), 113.8 (d, C-3′), 57.7, 55.7, 55.1 (OCH_3; C-1, 4), 48.2 (s, C-5), 30.2 (NCH_3);[42] mass spectrum *m/e* (rel intensity) 313 (M^+, 21), 78 (base).

Exact mass. Calcd for $C_{18}H_{19}NO_4$: 313.131. Found: 313.131.

6,7-Dimethoxy-4-(*p*-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (18). To a suspension of 93 mg (2.51 mmol) of lithium aluminum hydride in 25 mL of tetrahydrofuran was added a solution of 485 mg (1.48 mmol) of **17** in 10 mL of tetrahydrofuran over a 10-min period. The mixture was stirred at room temperature for 2 h followed by the addition of 0.1 mL of water, 0.1 mL of 15% aqueous sodium hydroxide, 0.3 mL of water, 20 mL of diethyl ether, and anhydrous magnesium sulfate. The mixture was filtered and the filter cake was washed with 25 mL of tetrahydrofuran. The filtrate was concentrated in vacuo to give 435 mg of crude *O,O*-dimethylcherylline (**18**).

The crude **18** was dissolved in 10 mL of ethanol and 30 mL of diethyl ether and the solution was saturated with anhydrous hydrogen chloride. The resulting cloudy solution was concentrated in vacuo and the residual damp solid was recrystallized from methanol-ether to give 296 mg (57%) of **18**·HCl as a white, crystalline substance: mp 229-230 °C (lit.[13] 228-229 °C); IR (KBr) 1600, 1500, 1250 cm^{-1}; NMR (Me_2SO-d_6) δ 2.90 (s, 3, $-NCH_3$), 3.28-3.85 [m with s at 3.52 (3 H) and s at 3.78 (6 H), 12, aryl $-OCH_3$, benzylic $-CH$, and $-CH_2N\lessgtr^+$], 4.30-4.58 (m, 2, benzylic $-CH_2-$), 6.30 (s, 1, C-5 vinyl), 6.90 (s, 1, C-8 vinyl), 6.97 7.23 (AA′BB′, 4, aromatics).

Anal. ($C_{19}H_{22}ClNO_3$) C, H.

The spectral properties of **18,** generated by neutralization of **18**·HCl, were in accord with those reported elsewhere:[13] mp 97-99 °C; IR ($CHCl_3$) 2815, 2790, 1602, 1575, 1500, 1455, 1255, 1245 cm^{-1}; NMR ($CDCl_3$) δ 2.42 (s, 3, $-NCH_3$), 2.48 (dd, 1, J = 11.5, 8.5 Hz, $-CHN-$), 2.98 (dd, 1, J = 8.5, 5.5 Hz, benzylic $-CH$), 6.40 (s, 1, C-5 vinyl), 6.60 (s, 1, C-8 vinyl), 6.85, 7.18 (AA′BB′, 4, J = 9 Hz, aromatics); mass spectrum *m/e* rel intensity) 313 (M^+, 52), 270 (75), 239 (base).

6-Hydroxy-7-methoxy-4-(*p*-methoxyphenyl)-2-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (20a). To a solution of 40 mg (0.13 mmol) of spirodienone **19** in 1.3 mL of dichloromethane was added 0.016 mL (0.13 mmol) of boron trifluoride etherate via syringe. The mixture was stirred at room temperature for 45 min, poured into 30 mL of dichloromethane, washed with 5 mL of 5% aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residual oil was subjected to medium-pressure chromatography over 25 g of silica gel (eluted with benzene-methanol (49:1); 10-mL fractions). Fractions 34-42 were concentrated to afford 28 mg (70%) of tetrahydroisoquinoline **20a** as a pale yellow oil: IR ($CHCl_3$) 3540, 1640 cm^{-1}; NMR ($CDCl_3$) δ 3.05 (s, 3, $-NCH_3$), 3.75 (s, 3, aryl $-OCH_3$), 3.90 (s, 3, aryl $-OCH_3$), 4.18, 4.62 (AB q, 2, J = 16 Hz, benzylic $-CH_2-$) 4.67 (broad s, 1, benzylic $-CH$), 6.00 (broad s, 1, $-OH$), 6.67 (s, 1, aromatic), 6.70 (s, 1, aromatic), 6.78, 7.08 (AA′BB′, 4, J = 9 Hz, aromatics); mass spectrum *m/e* 313 (M^+, base).

Exact mass. Calcd for $C_{18}H_{19}NO_4$: 313.131. Found: 313.130.

Treatment of α-Methoxy Amide 16 with Boron Trifluoride Etherate in Dichloromethane. To a solution of 51 mg (0.14 mmol) of **16** in 3 mL of dichloromethane was added 0.03 mL (0.24 mmol) of boron trifluoride etherate. The mixture was stirred at ambient temperature

for 5 h, poured into 30 mL of chloroform, washed with 15 mL of saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residual oil (55 mg) was subjected to thin layer chromatography over silica gel (eluted with methanol–benzene, 1:9) to give 35 mg (75%) of **17.** When a solution of **16** in methanol was treated similarly, starting material was recovered quantitatively.

***N*-(3-Benzyloxy-4-methoxybenzyl)-*N*-methyl-α-trimethylsilylacetamide (23b).** To a solution of 1.32 g (5.13 mmol) of amine **23a**[14] in 10 mL of carbon tetrachloride was added 0.58 g (5.13 mmol) of trimethylsilylketene[17] via syringe. The mixture was stirred for 30 min and concentrated in vacuo, and the residual oil was chromatographed over 100 g of alumina (activity III; eluted with hexane–ethyl acetate (4:1); 20-mL fractions). Fractions 6–11 were concentrated to give 1.44 g (76%) of amide **23b** as a colorless oil: IR (CCl_4) 1620, 1504, 1245 cm^{-1}; NMR (CCl_4) δ 0.08 [s, 9, $-Si(CH_3)_3$], 1.87 (broad s, 2, $-CH_2CO-$), 2.77 (s, 3, $-NCH_3$), 3.82 (s, 3, $-OCH_3$), 4.37 (broad s, 2, $-CH_2N<$), 5.02 (s, 2, $-CH_2O-$), 6.58–6.92 (m, 3, aromatic), 7.13–7.55 (m, 5, aromatic); mass spectrum *m/e* (rel intensity) 371 (M^+, 5).

Exact mass. Calcd for $C_{21}H_{29}NO_3Si$: 371.191. Found: 371.192.

***N*-(3-Benzyloxy-4-methoxybenzyl)-*N*-methyl-α-(4,4-dimethoxycyclohexa-2,5-dienylidene)acetamide (24) and 7-Benzyloxy-6-methoxy-4-(*p*-methoxyphenyl)-2-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (25).** To a solution of lithium diisopropylamide [from 1.54 mL (11.0 mmol) of diisopropylamine and 4.62 mL (10.5 mmol) of 2.27 M *n*-butyllithium in 80 mL of tetrahydrofuran] cooled to −55 °C was added a solution of 3.7 g (10.0 mmol) of **23b** in 25 mL of tetrahydrofuran via syringe at a rate such that the reaction temperature did not exceed −50 °C. The mixture was stirred for 20 min at −60 °C, warmed to −40 °C, and recooled to −60 °C. To the resulting pale yellow solution was added a solution of 1.54 g (10.0 mmol) of dienone **9a** in 5 mL of tetrahydrofuran over a 5-min period. The mixture was stirred at −50 °C for an additional 10 min and the cooling bath was removed. The yellow solution was warmed to 0 °C and poured into 500 mL of dichloromethane and 100 mL of saturated aqueous brine–water (1:1). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to afford 4.6 g of crude *p*-quinone methide ketal **24** as a light brown oil. This material was used in the next reaction without purification: IR (CCl_4) 1637, 1510 cm^{-1}; NMR (CCl_4) δ 2.78 (s, 3, $-NCH_3$), 3.18 (s, 6, geminal $-OCH_3$), 3.78 (s, 3, aryl $-OCH_3$), 4.40 (broad s, 2, $-CH_2N<$), 5.00 (s, 2, $-CH_2O-$), 5.825.83–6.48 (m, 4, $=CH-$), 6.50–7.00 (m, 3, aromatics), 7.08–7.57 (m, 6, aromatics and $=CH-$), (m, 6, aromatics and $=CH-$).

To a solution of the crude **24** in 220 mL of dichloromethane was added 2.46 mL (20.0 mmol) of boron trifluoride etherate via syringe. The solution was stirred at room temperature for 3 h and was stored in a refrigerator for 9 h. The resulting orange solution was washed with 100 mL of saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo to give 3.91 g of a tan solid. The crude product was recrystallized from methanol to give 2.26 g (55%) of lactam **25,** mp 162–163 °C. An analytically pure sample exhibited the following properties: mp 164–165 °C; IR ($CHCl_3$) 1635, 1500, 1248 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (s, 3, $-NCH_3$), 3.77 (s, 3, aryl $-OCH_3$), 3.82 (s, 3, aryl $-OCH_3$), 4.13, 4.58 (AB q, 2, J = 16 Hz, $-CH_2N<$), 4.72 (broad s, 1, C-4 methine), 5.17 (s, 2, $-CH_2O-$), 6.62 (s, 1, aromatic), 6.77 (s, 1, aromatic), 6.80, 7.10 (AA′BB′, 4, J = 9 Hz aromatics), 7.30–7.58 (m, 5, aromatics); ^{13}C NMR ($CDCl_3$) δ 169.7, 158.4, 149.4, 147.1, 136.7, 131.4, 128.7, 128.4, 127.7, 127.1, 123.1, 113.8, 111.3, 110.8, 71.2, 56.0, 55.1, 52.1, 51.2, 34.7; mass spectrum *m/e* (rel intensity) 403 (M^+, 37), 91 (base).

Anal. ($C_{25}H_{25}NO_4$) C, H.

7-Hydroxy-6-methoxy-4-(*p*-hydroxyphenyl)-2-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (20b). A solution of 403 mg (1.0 mmol) of **25** in 20 mL of ethyl acetate–ethanol (1:1) was hydrogenated at 1 atm over 30 mg of 10% palladium on charcoal for 23 h. To the resulting mixture, from which the hydrogenation product had crystallized, was added 50 mL of dichloromethane. The solution was filtered through Celite and the filtrate was concentrated in vacuo. The residual solid was recrystallized from methanol–chloroform to give 304 mg (97%) of phenol **20b,** mp 212–215 °C. An analytically pure sample exhibited the following properties: mp 214–215 °C; IR ($CHCl_3$) 3540, 1634, 1497 cm^{-1}; NMR ($CDCl_3$) δ 3.07 (s, 3, $-NCH_3$), 3.77 (s, 3, aryl $-OCH_3$), 3.83 (s, 3, aryl $-OCH_3$), 4.17, 4.62 (AB q, 2, J = 16 Hz, $-CH_2N<$), 4.72 (s, 1, benzylic $-CH$ at C-4), 5.90 (broad s, 1, $-OH$), 6.58 (s, 1, aromatic), 6.80 (s, 1, aromatic), 6.80, 7.12 (AA′BB′, 4, J = 9 Hz, aromatics); mass spectrum *m/e* (rel intensity) 313 (M^+, 82), 256 (37), 255 (42), 226 (28), 225 (base), 57 (40).

Anal. ($C_{18}H_{19}NO_4$) C, H.

7-Hydroxy-6-methoxy-4-(*p*-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (26). To a solution of 487 mg (1.55 mmol) of phenol **20a** in 115 mL of 1,2-dimethoxyethane at 75 °C was added 230 mg (6.2 mmol) of lithium aluminum hydride. The temperature was maintained at 75 °C for 1 h, the heating bath was removed, and the excess hydride was decomposed by the careful addition of 1.0 g of $Na_2SO_4 \cdot 10H_2O$. The resulting mixture was poured into 250 mL of dichloromethane and 100 mL of water. The aqueous layer was extracted with 250 mL of dichloromethane and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residual yellow solid (470 mg) was recrystallized from 10 mL of acetone to give 297 mg of phenolic amine **26,** mp 129–130 °C. A second crop of 40 mg (73% overall) was obtained, mp 128–130 °C. An analytically pure sample exhibited the following properties: mp 129–130 °C; IR ($CHCl_3$) 3530, 1505, 1276 cm^{-1}, ^1H NMR ($CDCl_3$) δ 2.38 (s, 3, $-NCH_3$), 2.43 (dd, 1, J = 11, 8.5 Hz, $-CHN-$), 3.00 (dd, 1, J = 11, 5.5 Hz, $-CHN-$), 3.55 (broad S, 2, benzylic $-CH_2N<$), 3.62 (s, 3, aryl $-OCH_3$), 3.80 (s, 3, aryl $-OCH_3$), 4.17 (dd, 1, J = 8.5, 5.5 Hz, C-4 methine), 5.37 (very broad s, 1, $-OH$), 6.33 (s, 1, aromatic), 6.57 (s, 1, aromatic), 6.83, 7.13 (AA′BB′, 4, J = 8.5 Hz, aromatics); ^{13}C NMR ($CDCl_3$) δ 157.9 (s), 145.4 (s), 144.0 (s), 136.8 (s), 129.7 (d), 128.4 (s), 127.7 (s), 113.6 (d), 111.7 (d), 111.2 (d), 62.1, 57.8, 55.8 (q), 55 1 (q), 45.8, 44.7; mass spectrum *m/e* (rel intensity) 299 (M^+, 54), 256 (71), 255 (43), 225 (base).

Anal. ($C_{18}H_{21}NO_3$) C, H.

(±)-Cherylline (3). To 3.0 mL of freshly distilled and degassed *N,N*-dimethylformamide cooled in an ice bath was added 0.16 mL (133 mg, 2.15 mmol) of ethanethiol followed by 45 mg (1.86 mmol) of sodium hydride. The mixture was stirred at room temperature under argon for 10 min followed by the addition of 158 mg (0.53 mmol) of solid **26** in one portion. The resulting yellow solution was warmed in an oil bath at 150 °C for 4 h during which an oil was deposited on the walls of the reaction vessel. The mixture was dissolved in 20 mL of water and the aqueous solution was extracted with four 50-mL portions of ethyl acetate. The combined extracts were washed with two 100-mL portions of water, dried (Na_2SO_4), and concentrated in vacuo. The resulting foam (129 mg) was subjected to preparative thin layer chromatography over two silica gel plates (eluted with benzene–methanol (4:1)). A band with R_f 0.3–0.33 was eluted with methanol to give 10 mg of **26.** The material with R_f 0.18–0.28 was eluted in a similar fashion to give 79 mg (53%) of **3** that was contaminated with small amounts (5–10%) of diphenol **27,** mp 198–208 °C. This material was recrystallized from acetone to give 52 mg of pure (±)-cherylline (**3**) whose spectral properties and chromatographic behavior were identical with those of authentic samples of (±)-**3** and (−)-**3:** mp 209–212 °C (lit.[7c] 209–212 °C); IR (KBr) 1585, 1496, 1356, 1330, 1270, 1252, 1212, 1158, 1117, 1080, 1021, 1005, 909, 823 cm^{-1}; NMR (acetone-d_6) δ 2.32 (s, 3, $-NCH_3$), 2.43 (dd, 1, J = 11, 8 Hz, $-CHN-$), 2.87 (dd, 1, J = 11, 5 Hz, $-CHN-$), 3.48 (broad s, 2, benzylic $-CH_2N-$), 3.62 (s, 3, aryl $-OCH_3$), 4.07 (m, 1, benzylic methine), 6.40 (s, 1, C-5 vinylic), 6.58 (s, 1, C-8 vinylic), 6.78, 7.07 (AA′BB′, 4, J = 8.5 Hz, aromatics); UV (EtOH) 227 nm (shoulder, ε 14 900), 285 (4200), 295 (shoulder, 2800); mass spectrum *m/e* (rel intensity) 285 (M^+, 64), 242 (base), 225 (69), 211 (42), 210 (20).

The mother liquor was shown to be a 3:1 mixture of **3** and **27,** respectively, by ^1H NMR spectroscopy.

6,7-Dihydroxy-4-(*p*-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (27). To a solution of 1.58 g (5.0 mmol) of **20b** in 150 mL of 1,2-dimethoxyethane at 70 °C was added 0.9 g (23.0 mmol) of lithium aluminum hydride. The resulting gray slurry was warmed under gentle reflux for 16 h followed by the addition of 2.0 g of $Na_2SO_4 \cdot 10H_2O$. The mixture was cooled to room temperature and filtered through Celite. The filter cake was added to 40 mL of 10% aqueous hydrochloric acid and the mixture was basified with saturated aqueous sodium bicarbonate. The resulting murky suspension was extracted with three 300-mL portions of chloroform. The combined organic phases and original filtrate were dried (Na_2SO_4) and concentrated in vacuo to give 0.5 g of a yellow solid. This material was recrystallized from chloroform–methanol–hexane to give 185 mg (15%) of diphenolic amine **27:** mp 195–198 °C; IR (Nujol) 3200 (broad), 1505 cm^{-1}; NMR (acetone-d_6) δ 2.32 (s, 3, $-NCH_3$), 2.43 (dd, 1, J = 11.5, 8 Hz, $-CHN-$), 2.87 (dd, 1, J = 11.5, 5 Hz, $-CHN-$), 3.48 (broad s, 2, benzylic $-CH_2N-$), 3.80 (s, 3, $-OCH_3$), 4.00 (m, 1, benzylic methine), 6.32 (s, 1, aromatic), 6.60 (s, 1, aro-

matic), 6.85, 7.18 (AA'BB', 4, J = 9 Hz, aromatics); mass spectrum m/e (rel intensity) 285 (M^+, 52), 242 (92), 241 (53), 225 (48), 211 (base).

Exact mass. Calcd for $C_{17}H_{19}NO_3$: 285.136. Found: 285.136.

N-(3-Benzyloxy-4-methoxybenzyl)-N-methylacetamide (23c). To a cooled solution of 7.1 g (27.6 mmol) of amine **23a** and 3.03 g (30.0 mmol) of triethylamine in 100 mL of chloroform was added 2.36 g (30.0 mmol) of acetyl chloride via syringe. The mixture was stirred for 24 h and poured into 100 mL of water. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil which was crystallized from ether–hexane (1:1) to yield 7.1 g (88%) of amide **23c:** mp 62–53.5 °C; IR ($CHCl_3$) 1630, 1500, 1250 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, 3, $-COCH_3$), 2.80, 2.88 (two s's in 3:2 ratio, respectively, 3, $-NCH_3$), 3.92 (s, 3, $-OCH_3$), 4.42, 4.50 (two s's in 2:3 ratio, respectively, 2, benzylic $-CH_2N<$), 5.18 (s, 2, benzylic $-CH_2O-$), 6.67–6.92 (m, 3, aromatics), 7.25–7.63 (m, 5, aromatics); mass spectrum m/e (rel intensity) 299 (M^+, 20), 208 (15), 166 (34), 91 (base), 43 (10).

Anal. ($C_{17}H_{21}NO_3$), C, H.

Preparation of 25 via N-(3-Benzyloxy-4-methoxybenzyl)-N-methyl-α-(1-hydroxy-4,4-dimethoxycyclohexa-2,5-dien-1-yl)acetamide (28). To a solution of lithium diisopropylamide [from 0.29 mL (2.07 mmol) of diisopropylamine and 0.88 mL (2.0 mmol) of 2.27 M n-butyllithium in 10 mL of tetrahydrofuran] cooled to −70 °C was added a solution of 0.56 g (1.87 mmol) of amide **23c** in 5 mL of tetrahydrofuran in one portion via syringe. The solution was stirred for 40 min followed by the addition of 288 mg (1.87 mmol) of **9a** in 1.0 mL of tetrahydrofuran. The cooling bath was removed and the mixture was allowed to warm to room temperature. The resulting solution was poured into 50 mL of dichloromethane and 25 mL of saturated brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give 855 mg of crude **28** which was used in the next reaction without purification: IR (CCl_4) 3400, 1625 cm^{-1}; NMR (CCl_4) δ 2.38 (s, 2, $-CH_2CO-$), 2.65, 2.78 (s's, 3, $-NCH_3$), 3.10, 3.17, 3.20 (s's, 9, geminal $-OCH_3$), 3.77 (s, 3, aryl $-OCH_3$), 4.23, 4.38 (s's, 2, $-CH_2N<$), 5.00 (s, 2, $ArCH_2-$), 5.35 (broad s, 1, -OH), 5.77, 6.13 (AA'BB', 4, J = 11 Hz, $=CH_2N<$), 5.00 (s, 2, $ArCH_2-$), 5.35 (broad s, 1, -OH], 5.77, 6.13 (AA'BB', 4, J = 11 Hz, $=CH-$), 6.42–6.83 (m, 3, aromatics), 7.12–7.53 (m, 5, aromatics).

To a solution of 1.55 g (2.29 mmol) of sulfurane **29**[35] in 10 mL of dichloromethane was added a solution of the crude **28** in 10 mL of dichloromethane at 0 °C over a 5-min period. The cooling bath was removed and the mixture was stirred for an additional 30 min. ^1H NMR analysis of an aliquot indicated that all **28** had been consumed and that the solution now contained p-quinone methide ketal **24** in addition to the normal by-products from sulfurane dehydrations. The mixture was cooled in an ice water bath and 1.0 mL of boron trifluoride etherate in 10 mL of dichloromethane was added. The solution was stirred at room temperature for 24 h, washed with 25 mL of saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residue was crystallized from methanol to afford 502 mg (67%) of **25,** mp 164–165 °C.

3-Hydroxy-4-methoxybenzaldehyde-N-methylimine (30). To a slurry of 10.0 g (66 mmol) of isovanillin[37] in 50 mL of methanol was added 7.43 mL of a 40% aqueous methylamine solution. The resulting homogeneous solution was stirred at room temperature for 60 min, poured into 100 mL of saturated brine–water (1:1), and extracted with five 50-mL portions of chloroform. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residual solid was sublimed to afford 9.3 g (86%) of analytically pure **30:** mp 108.5–110 °C: IR ($CHCl_3$) 3555, 1650 cm^{-1}; NMR ($CDCl_3$) δ 3.43 (d, 3, J = 2 Hz, $-NCH_3$), 3.87 (s, 3, $-OCH_3$), 5.2–5.8 (broad s, 1, -OH), 6.6–7.4 (m, 3, aromatics), 8.04 (q, 1, J = 2 Hz, $-CH=N-$).

Anal. ($C_9H_{11}NO_2$) C, H.

N-(3-Hydroxy-4-methoxybenzyl)methylamine (6a).[43] To a solution of 2.86 g (17.3 mmol) of imine **30** in 285 mL of *dry* methanol was added 0.66 g (17.4 mmol) of sodium borohydride. The solution was stirred for 10.5 h and the solvent was removed in vacuo. The clear, oily residue was added to 300 mL of ethyl acetate and 30 mL of saturated aqueous potassium carbonate. The aqueous phase was extracted with four 100-mL portions of ethyl acetate and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford 2.42 g (84%) of phenolic amine **6a** as a white solid. A small sample was sublimed at 94 °C and 0.03 mm to afford an analytically pure sample: mp 142–143 °C; NMR ($CDCl_3$) δ 2.42 (s, 3, $-NCH_3$), 3.60 (s, 2, benzylic $-CH_2-$), 3.82 (s, 3, $-OCH_3$), 4.05 (s, 2, -OH, -NH), 6.6–6.8 (m, 3, aromatics).

Anal. ($C_9H_{13}NO_2$), C, H.

Amine **6a** prepared in this manner was identical with a sample prepared by hydrogenolysis of the benzyl group from amine **23a.**

β-[N-(3-Hydroxy-4-methoxybenzyl)-N-methyl]aminoethyltriphenylphosphonium Bromide (6d). To a solution of 1.28 g (7.65 mmol) of **6a** in 25 mL of hot chloroform was added 2.83 g (7.65 mmol) of solid vinyltriphenylphosphonium bromide (**31**).[37] The resulting solution was carefully concentrated in vacuo. The resulting foam was slowly warmed to 120 °C under vacuum (0.05 mm). The foam collapsed at 70 °C and slowly solidified at 120 °C. The temperature of the heating bath was maintained at 120 °C for 2 h and the resulting solid was ground into a powder to give 3.73 g (91%) of **6d** as a cream-colored solid, mp 170–177 °C dec. This material was used directly in the following reaction without purification and exhibited the spectral properties shown below. A small sample was recrystallized with difficulty from ethyl acetate–chloroform to afford material with a narrower melting range which analyzed low in carbon: mp 176–178 °C; IR ($CHCl_3$) 3540, 3160 (broad), 1585, 1434 cm^{-1}; NMR ($CDCl_3$) δ 2.18 (s, 3, $-NCH_3$), 2.47–3.18 (m, 2, $-CH_2N<$), 3.33 (broad s, 2, benzylic $-CH_2-$), 3.57–4.17 (m with s at 3.85, 5, PCH_2 and $-OCH_3$), 6.33–7.17 (m, 4, aromatics and -OH), 7.50–8.13 (m, 15, $-{}^+PPh_3$).

Anal. ($C_{29}H_{31}BrNO_2P$) H. C: calcd, 64.93; found, 64.13.

7-Hydroxy-6-methoxy-4-(p-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (26) via Allylic Amine 32. To a suspension of 1.07 g (2.0 mmol) of **6d** in 20 mL of tetrahydrofuran at −25 °C was added 1.76 ml (4.0 mmol) of 2.27 M n-butyllithium. The temperature was maintained at −25 °C for 15 min and the mixture was warmed to room temperature over a period of 15 min. To the resulting red solution was added a solution of 308 mg (2.0 mmol) of **9a** in 1.0 mL of tetrahydrofuran. The mixture was stirred for 2 h and poured into 50 mL of dichloromethane and 25 mL of saturated brine–water (1:1). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give a brown oil. The ^1H NMR spectrum of this material exhibited the following signals attributed to **32:** NMR ($CDCl_3$) δ 2.17 (s, $-NCH_3$), 3.22 (s, geminal $-OCH_3$), 3.79 (s, aryl $-OCH_3$), 5.62–7.00 (complex m, $=CH-$ and aromatics).

To a solution of the crude **32** in 25 mL of dichloromethane was added 1.08 mL (10.0 mmol) of boron trifluoride etherate. The solution was stirred for 15 h, washed with 15 mL of saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residual black oil was chromatographed over 40 g of silica gel (eluted with ethyl acetate–methanol (50:1); 10-mL fractions) and fractions 33–70 were concentrated to afford 306 mg (52%) of phenolic amine **26,** mp 121–128 °C. This material was recrystallized once from acetone to give 280 mg (47%) of pure **26,** mp 129–131 °C.

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