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

David J. Hart, Paul A. Cain, and David A. Evans

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-quinones 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,4 wood pigments,5 and insect pigments6. In addition, quinone methides have been implicated as intermediates in oxidative phosphorylation2 and in the biosynthesis of chromans,3,5 lignin,6,7 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 quinone precursors.8 In principle, olefination of a quinone carbonyl group offers the most direct route from a quinone to a quinone methide. 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.10-12

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-quinones,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

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

0002-7863/78/1500-1548$01.00/0

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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-trimethylsilylamides16-17 and the ease with which trimethylsilanyl carbamions condense with ketones to produce olefins18 encouraged us to explore the reaction between anions of N,N-dimethyl-α-trimethylsilylacrylamide16 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 reagents12b,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.21b 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 14a24 was N-acetylated (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 CDCl3 and CD2Cl2 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
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). 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. 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. 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 ter-

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. 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. 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 with trimethylsilylketene. Amide 23b was treated sequentially with lithium disopropylamide 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 benzylic protecting group gave crystalline phenolic lactam 20b in a 97% yield. This material was isomeric with phenol 20a obtained from rearrangement of diene 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 system24 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 sequencially attributed with lithium disopropylamide and 9a to afford the requisite p-quinol ketal 28. Hydroxy amide 28 was dehydrated cleanly to 24 upon treatment with sulfoxane 2935 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 Isovanillin37 was treated with methyleneamine 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 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-1H-3-benzazepines.39

Conclusions

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

\[\text{[R]} \overset{\rm OMe} \longleftrightarrow \overset{\rm A} \longleftrightarrow \overset{\rm OMe} \longleftrightarrow \overset{\rm B} \longleftrightarrow \overset{\rm OMe} \longleftrightarrow \overset{\rm C} \]

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 29a–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. 13C 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); chlorotrimethylsilane, 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 were combustion analyses.

Exact mass. Caled for C12H17N03. 223.121. Found: 223.119.

Exact mass. Caled for C12H18NO2. 227.071. Found: 227.069.


Exact mass. Caled for C12H17N02. 223.121. Found: 223.119.

Exact mass. Caled for C12H17N02. 223.121. Found: 223.119.
3.4,4-Trimethoxy cyclohexa-2,5-dien-1-one (9b). To a solution of 25.0 g (56 mmol) of thallium(I) 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 two 300-mL portions of ether-ethyl acetate (4:1). The combined extracts were dried (Na2SO4) and concentrated in vacuo to afford 140 mg (54%) of amide 13.

Exact mass. Calcld for C15H13NO5: 283.0946. Found: 283.0943.

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 (NaOH), 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.

3,4,4,5-Tetramethoxy cyclohexa-2,5-dien-1-one (9c). A solution of 1.07 g (5.6 mmol) of 3,4,4,5-tetramethoxy cyclohexa-2,5-diene (9c)21 in 10 mL of 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 (Na2SO4) and concentrated in vacuo to afford 1.31 g of a 4:1 mixture of ketal 10c, dienone 9c, and starting α-trimethylsilylamine, 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 (CDCl3) δ 3.10 (broad s, 6, −CH2), 3.20 (s, 6, geminal −OCH3), 3.78, 3.82 (s’s, 6, vinyl −OCH3), 5.70 (broad s, 1, =CH−), 5.83 (s, 1, =CH−), 7.28 (broad s, 1, =CH− on one of the carbons γ to −CONMe2).

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 11e which crystallized on standing: mp 90–95 °C; IR (CDCl3) 1684 (s, 6, =CH− on carbon γ to −CONMe2); 1520 (s, 6, −CONMe2); 1499 (s, 6, −COCH3); 1386 (s, 6, −OCH3); 1260 (s, 6, −OCH3), 1240 (s, 6, −OCH3); 1177 (s, 6, −OCH3); 1051 (s, 6, −OCH3), 984 (s, 6, −OCH3); 820 (s, 6, −OCH3); 750 (s, 6, −OCH3); 650 (s, 6, −OCH3), 600 (s, 6, −OCH3), 560 (s, 6, −OCH3), 520 (s, 6, −OCH3), 480 (s, 6, −OCH3), 420 (s, 6, −OCH3), 390 (s, 6, −OCH3), 360 (s, 6, −OCH3), 340 (s, 6, −OCH3), 320 (s, 6, −OCH3), 300 (s, 6, −OCH3). Mass spectrum m/e (rel intensity) 283 (M*, 6), 212 (55), 151 (base), 97 (6), 72 (17).

Anal. (C13H25NO5) C, H.

N-3,4-Dimethoxybenzyl-N-methylacetamide (14b). To a solution of 16.5 g (89.0 mmol) of amine 14a24 and 10.1 mL (89.0 mmol) of triethylsilane in 400 mL of chloroform cooled to −70 °C was added 17.85 g (0.1 mol) of acetyl chloride via syringe. The resulting yellow solid was recrystallized from 100 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 (Na2SO4), and concentrated in vacuo. The residual liquid was distilled to give 17.9 g (95%) of amide 14b (89.0 mmol). IR (CDCl3) δ 203.0 (s, 3, =CO2), 287.3 (s, 3, =NCH3), 380.8 (s, 6, −OCH3), 4.40 (s, 2, −CH2), 6.58–6.88 (m, 3, amines); mass spectrum m/e (rel intensity) 223 (M*, 91), 151 (base), 43 (26).

Anal. (C13H21NO3) C, H.

N-3,4-Dimethoxybenzyl-N-methyltrimethylsilyleacetamide (14c). To a solution of lithium diisopropylamide [from 2.1 mL (1.0 mol) of amine 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 linearize the reaction from taking place prior to complete cyclization 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 (MgSO4), 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-o-bis(trimethylsilyl)acetamide: mp 80–82 °C; IR (KBr) 1667 cm−1; NMR (CDCl3) δ 6.02 (s, 3, =CH−), 1.87 (s, 1, -CH), 2.86 (s, 3, −NCH3), 3.77 (s, 6, −OCH3), 4.45 (broad s, 2, benzyl −CH2−), 6.64–6.95 (m, 3, amines); mass spectrum m/e (rel intensity) 367 (M*, 78), 151 (base), 73 (88).

Anal. (C13H21NO3Si) C, H.

Continued elution gave 1.85 g (85%) of α-trimethylsilylamine 14c: IR (KBr) 1652 cm−1; NMR (CDCl3) δ 3.010 [s, 9, −Si(CH3)3], 1.90 (s, 2, −CH2C(=O)N=CH2), 2.83 (s, 3, −NCH3), 3.80 (s, 6, −OCH3), 4.25 (s, 2, −CH2−), 5.60 (s, 1, =CH−), 6.66–6.98 (m, 3, aromatics); mass spectrum m/e (rel intensity) 283 (M*, 55), 151 (base), 97 (27).
4.40 (s, 2, benzylic -CH2-), 6.58-6.88 (m, 3, aromatics); mass spectrum m/e (rel intensity) 295 (M+*, 49), 180 (20), 151 (base), 73 (31).


N-(3,4-Dimethoxybenzyl)-N-methyl-α-(4,4-dimethylcyclohexa-2,5-dienylidene)acetamide (15). To a solution of lithium disopropylamide [from 0.36 mL (2.6 mmol) of disopropylamine 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 15 min, warmed to -20 °C, and poured into 50 mL of chloroform and 20 mL of 5% aqueous sodium bicarbonate, dried (Na2SO4), and concentrated in vacuo. The residual oil was subjected to medium-pressure chromatography over 25 mL 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).

The spectral properties of 16, generated by neutralization of 18-HCl as white, crystalline substance: mp 229-230 °C (lit. 177-178 °C); 1H NMR (CDCl3) δ 2.92 (s, 3, -NCH3), 3.67, 3.68, 3.77 (s, 9, aryl -OCH3), 4.08, 4.50 (AB q, J = 16 Hz, -CH2N<), 5.50 (s, aromatic), 6.50 (s, 1, aromatic), 6.67, 6.95 (AA'BB', J = 9 Hz aromatics); mass spectrum m/e (rel intensity) 375 (M+*, 91), 85 (base).


6,7-Dimethoxy-4-(4-phenoxymethyl)-1,2,3,4-tetrahydroisoquinoline (18). To a suspension of 93 mg (2.51 mmol) of lithium aluminium 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 2.5 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-dimethylchelerythrine (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 (14c). 

The spectral properties of 18, generated by neutralization of 18-HCl as white, crystalline substance: mp 229-230 °C (lit. 177-178 °C); IR (KBr) 3431, 3278, 3078, 2922, 2854, 1599, 1585, 1503, 1490, 1427, 1372, 1353, 1300, 1236, 1159, 1111, 1049, 987, 912, 870, 767, 748, 707, 696, 684, 665, 644, 629, 612, 590, 570, 547, 501, 466 (cm-1); IR (KBr) 3340, 3279, 3078, 2930, 1595, 1503, 1457, 1371, 1340, 1278, 1222, 1106, 1039, 961, 898, 869, 802, 780, 767, 751 (cm-1); mass spectrum m/e (rel intensity) 339 (M+*, 27), 275 (70), 239 (base).

6-7-Methoxy-4-(4-phenoxymethyl)-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 (0.30 mmol) of boron trifluoride etherate. The mixture was stirred at room temperature for 45 min, poured into 30 mL of dichloromethane, washed with 5% aqueous sodium bicarbonate, dried (Na2SO4), and concentrated in vacuo. The residue 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 (CHCl3) 3540, 1640 cm-1; 1H NMR (CDCl3) δ 3.05 (s, 3, -NCH3), 3.75 (s, 3, aromatic -OCH3), 3.90 (s, 3, aromatic -OCH3), 4.18, 4.62 (AB q, J = 16 Hz, benzylic -CH2N<), 6.67 (broad s, 1, -CH), 6.62 (s, 1, aromatic), 6.70, 7.18 (AA'BB', J = 9 Hz aromatics); mass spectrum m/e (rel intensity) 313 (M+*, 52), 270 (75), 239 (base).

Treatment of a-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.
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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 on 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.

7-4-Methoxy-6-oxo-2-methyl-1,2,3,4-tetrahydroisoquinoline (25). A solution of 403 mg (1.0 mmol) of 25 in 20 mL of ethyl acetate was added to 2.0 g of Celite, the resulting mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude residue was recrystallized from methanol–chloroform to give 52 mg of pure (S)-cherylline (3) whose spectral properties and chromatographic behavior were identical with those of authentic samples of (S)-3 and (−)-3: mp 160–161.5 °C (lit. 176–177 °C; IR (KBr) 1585, 1496, 1363, 1330, 1270, 1252, 1212, 1158, 1117, 1080, 1021, 1005, 909, 823 cm⁻¹; NMR (acetone-d₆) δ 1.88 (s, 3, -OCH₃), 3.39 (s, 3, -OCH₃), 4.38 (m, 2, aromatics); 13C NMR (acetone-d₆) δ 169.7, 158.4, 149.4, 144.1, 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/z (rel intensity) 403 (M⁺, 91) (base).

Anal. (C₁₆H₁₉NO₄) 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 aluminium 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 Na₂SO₄/10H₂O. 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 (Na₂SO₄) 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 139–140 °C. A second crop of 40 mg, which did not exceed -50 °C. The mixture was stirred for 20 min at -60 °C, and recooled to 0 °C. To the mixture was added 0.16 mL of N,N-dimethylformamide cooled in an ice bath was added 0.16 mL of 2.27 M n-butyllithium in 80 mL of tetrahydrofuran] cooled to -55 °C. A solution of the crude 24 in 220 mL of dichloromethane was added such that the reaction temperature did not exceed -50 °C. The mixture was stirred for an additional 10 min and the cooling bath was removed. The yellow solution was warmed to 0 °C and poured into 250 mL of saturated aqueous sodium bicarbonate, dried (Na₂SO₄·10H₂O). The mixture was cooled to room temperature and 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 Na₂SO₄ and concentrated in vacuo. The yellow foam (129 mg) was subjected to preparative thin layer chromatography over two silica gel plates (eluted with ethylene dichloride). A band with Rₜ0.3-0.33 was eluted with methanol (4:1). The material was recrystallized from acetone to give 52 mg of pure (S)-cherylline (3) whose spectral properties and chromatographic behavior were identical with those of authentic samples of (S)-3 and (−)-3: mp 210–212 °C (lit. 209–212 °C; IR (KBr) 1585, 1496, 1363, 1330, 1270, 1252, 1212, 1158, 1117, 1080, 1021, 1005, 909, 823 cm⁻¹; NMR (acetone-d₆) δ 2.32 (s, 3, -NCH₃), 3.48 (m, 2, aromatics); 13C NMR (acetone-d₆) 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/z (rel intensity) 299 (M⁺, 54), 256 (71), 255 (43), 225 (25), base). Anal. (C₁₉H₂₆NO₄) 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 (1.03 mmol) of ethanethiol. The mixture was stirred at -50 °C for an additional 5 min at -60 °C, and recooled to 0 °C. To the mixture was added 0.16 mL of 2.27 M n-butyllithium in 80 mL of tetrahydrofuran] cooled to -55 °C. A solution of the crude 24 in 220 mL of dichloromethane was added such that the reaction temperature did not exceed -50 °C. The mixture was stirred 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 (Na₂SO₄) and concentrated in vacuo to afford 4.6 g of crude p-quinone methide ketal 2. This material was used without purification: IR (CCl₄) ν 1637, 1510 cm⁻¹; NMR (CCl₄) δ 2.78 (s, 3, -NCH₃), 3.18 (s, 6, geminal –OCH₃), 3.78 (s, 3, aryl –OCH₃), 4.40 (broad s, 2, -CH₂N-), 5.00 (s, 2, -CH₂O-), 5.82-6.48 (m, 4, =CH-). 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 sodium bicarbonate, dried (Na₂SO₄), 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 (CCl₄) 1635, 1500 cm⁻¹; 1H NMR (CCl₄) δ 2.24–2.48 (m, 2, aromatics); 13C NMR (CCl₄) δ 169.7, 158.4, 149.4, 144.1, 136.7, 131.4, 128.7, 128.4, 127.1, 127.1, 123.1, 113.8, 111.3, 110.8, 71.2, 56.0, 55.1, 52.1, 51.2, 44.7; mass spectrum m/z (rel intensity) 403 (M⁺, 37), 91 (base).

Anal. (C₁₇H₁₇NO₃) C, H.
dichloromethane was added to a solution of the crude product in 5 mL of dichloromethane to give a yellow oil which was crystallized from ethyl ether-hexane (1:1) to yield 7.1 g (88%) of amine 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 syringes. The mixture was stirred for 24 h and poured into 100 mL of water. The organic phase was dried (Na2SO4) and concentrated in vacuo to afford 2.42 g (44%) of crude amine 24. 

N-(3-Benzoyloxy-4-methoxybenzyl)-N-methylacetaimide (28). To a solution of lithium diisopropylamide [from 0.29 mL (1.87 mmol) of amide (26) and 2.07 mmol] of diisopropylamine and 0.88 mL (2.0 mmol) of 2.27 M n-butyllithium in 10 mL of tetrahydrofuran was added a solution of 308 mg (2.0 mmol) of 9a in 1 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 (Na2SO4) and concentrated in vacuo to give 855 mg of crude 28 which was used in the next reaction without purification: IR (CCl4) 3400, 1625 cm⁻¹; NMR (CDCl3) δ 2.38 (s, 2, -CH3-), 2.65, 2.78 (s's, 3, -NCH3), 3.10, 3.17, 3.20 (s's, 9, geminal -OCH3), 3.77 (s, 3, aryl -OCH3), 4.23, 4.38 (s's, 2, -CH2N<), 5.00 (s, 2, ArCH2-), 5.35 (broad s, 2, benzylic -CH2-), 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 (43), 10 (1). 

Anal. (C12H10N2O2) C, H. 

Preparation of 25 via N-(3-Benzoyloxy-4-methoxybenzyl)-N-methyl-α-(1-Hydroxy-4,4-dimethoxycyclohexa-2,5-dien-1-yl)-acetaimide (28). To a solution of lithium diisopropylamide [from 0.29 mL (1.87 mmol) of amide (26) and 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 2.83 g (7.65 mmol) of amine 23a in 20 mL of tetrahydrofuran at -25 °C. The solution was allowed to warm to room temperature for 15 min and the mixture was warmed to 50 °C. 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 (Na2SO4) and concentrated in vacuo to give a brown oil. The 1H NMR spectrum of this material exhibited the following signals attributed to 25: NMR (CDCl3) δ 2.17 (s, -CH3), 5.57, 6.13 (AAPB', 4, J = 11 Hz, =CH2N<), 5.00 (s, 2, ArCH2-), 5.35 (broad s, 2, -OH), 5.77, 6.13 (AAPB', 4, J = 11 Hz, =CH2N<, =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 sulfonate 29 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 to -25 °C and 3.03 g (30.0 mmol) of 9a in 1.0 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 (Na2SO4), and concentrated in vacuo. The residue was crystallized from methanol to afford 502 mg (67%) of 25, mp 164-165 °C. 

3-Hydroxy-4-methoxybenzaldehyd-N-methylimine (30). To a slurry of 10.0 g (66 mmol) of isovanillin3 in 50 mL of methanol was added 7.43 mL of a 40% aqueous methanolic 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 (Na2SO4) and concentrated in vacuo. The residual solid was sublimed to afford 9.3 g (86%) of analytically pure sample: mp 176-178 °C; IR (CHCl3) 3555, 1650 cm⁻¹; NMR (CDCl3) δ 3.43 (δ, 3, J = 2 Hz, -CH2N<), 2.87, 5.53 (AAPB, 5, J = 2 Hz, -OCH3), 5.2-5.8 (broad s, 1, -OH), 6.6-7.4 (m, 4, aromatics), 8.04 (s, 1, J′ = 1 Hz, =CH-), 7.25-7.63 (m, 5, aromatics). 

Anal. (C12H10N2O2) C, H. 

N-(3-Hydroxy-4-methoxybenzyl)imine (6a).43 To a solution of 2.86 g (17.3 mmol) of imine 30 in 285 mL of dry methanol was added 6.66 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 (Na2SO4) 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 (CDCl3) δ 2.42 (s, 3, -NCH3), 3.60 (s, 2, benzylic -CH2-), 3.82 (s, 3, -OCH3), 4.05 (s, 2, -OH, -NH), 6.6-6.8 (m, 3, aromatics). 

Anal. (C8H9NO3) C, H. 

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

References and Notes

and references cited therein.


Ar-5 participation was originally observed by R. Baird and S. Winston, J. Am. Chem. Soc., 84, 788 (1962), and references cited therein.


For another procedure for selective nucleophile allyl ether cleavage see C. Hanson and B. Wickberg, Syntheses, 191 (1976). (b) For a review on selective O-demethylation of isoxazolines see S. Teitel and A. Bossi, Heterocycles, 1, 73 (1973).

A pure sample of 27 was inadvertently obtained in low yield when 20b was subjected to an excess of lithium aluminum hydride at elevated temperatures for a long time (see Experimental Section).


Purchased from Aldrich Chemical Co.

It has been shown that the phosphorane route to quinone methide ketals is quite general. For example, unsubstituted phosphoranes react smoothly with quinone ketals 9a-c. Benzylidenebenzophenone phosphorane reacts with 9a, but is inert to the less electrophilic ketal 9c.


Purchased from Vantron/Alfa inorganic.

Assignments are based on chemical shifts, incomplete multiplicities data, and the enhanced intensity of signals that arose from the presence of magnetically equivalent carbons. Two signals appear to be coincident in the range 48.2-57.7 ppm range.