Total Synthesis of the Tumor-Inhibitory Alkaloid Thalicarpine[1,2]

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Abstract: An efficient total synthesis of thalicarpine **(13b)**, a tumor-inhibitory aporphine benzylisoquinoline alkaloid, is described. The diaryl ether **(8a)**, prepared from **1b** and **4a**, was condensed with the 3,4-dihydroisoquinolinium salt **2a** to give **9a**. Reduction of **9a**, followed by diazotization in phosphoric acid and heating, yielded the aporphine **10a** and the phenol **9h**. Formylation of **10a** gave (±)-hernandaline (**10b**), which was resolved with (+)-α-bromocamphor-π-sulfonic acid. The overall yield of the hernandaline precursor **10a** was improved by a reaction sequence involving the phenolic intermediates **2b, 9f, 9g,** and **10c**. Hernandaline (**10b**, *S* configuration) was condensed with the Reissert compound **5** and the product **(12)** was reduced with zinc in acetic acid to a mixture of nor bases (**13a** and epimer). Methylation with formalin–formic acid gave thalicarpine **(13b)**.

The alkaloid thalicarpine,[3] which has the aporphine benzylisoquinoline structure **13b**,[4] exhibits a significant inhibitory activity against the Walker intramuscular carcinosarcoma in rats over a wide dosage range.[5] The alkaloid has undergone extensive preclinical toxicological studies, and is now in clinical trial, under the auspices of the National Cancer Institute.

In anticipation of potential needs for the alkaloid in a quantity far exceeding that readily available from natural sources, we have undertaken studies directed toward a practical total synthesis of thalicarpine. Our earlier communications[6,7] have outlined synthetic approaches to thalicarpine, by routes which proceed *via* the synthesis of hernandaline (**10b**),[8] a cytotoxic[9] aporphine alkaloid. The present paper describes, in detail, the total synthesis of thalicarpine.

The synthesis of thalicarpine carried out in the course of structural studies[4] was limited by the inaccessibility of the starting materials, derivatives of alkaloids from natural sources, and the low yield sustained in the final step, the formation of the diaryl ether by an Ullmann-type ether synthesis.

An approach was devised which utilizes readily available starting materials and an activated aryl halide as a precursor in a more efficient diaryl ether synthesis. Consideration of the aporphine portion of thalicarpine (**13b**) suggested an opportunity for application of this concept. The intermediate **3** seemed appropriate for the construction of the aporphine segment, since the nitro group could be expected to facilitate aryl ether formation by activation of the para halogen substituent and at a later stage could itself be reduced to an amino group to provide the means for ring closure to the aporphine.

In the event, the nitrobenzylisoquinoline **3** was readily formed by the condensation of the nitrotoluene **1b** with the dihydroisoquinolinium salt **2a**[10] in *N,N*-dimethylformamide, in the presence of sodium hydride. A route to the phenolic component **7**, necessary for this synthesis, was developed starting from 3,4-dimethoxyphenol (**4a**).[11] After conversion of **4a** to the benzyl ether **4b**, formylation was effected by brief heating with phosphorus oxychloride–*N,N*-dimethylformamide, affording the aldehyde **4c** in good yield. The condensation of **4c** with the Reissert compound **5**[12] gave the phenol precursor **6**. However, an attempt to obtain **7** by catalytic reduction of the methiodide of **6** with concomitant hydrogenolysis was thwarted by sluggish absorption of hydrogen, which ceased completely before the reaction was complete. Presumably this difficulty is attributable to the effect of iodide ion as a hydrogenation catalyst poison.[13] This difficulty was circumvented by prior reduction of the isoquinoline ring of the methiodide of **6** with sodium borohydride. Hydrogenation of the crude basic product in the presence of 5% Pd/C catalyst gave the required phenol, **7**.

Subsequent attempts to prepare a diaryl ether by linking **3** and the potassium salt of **7** yielded intractable mixtures. In addition, when the products of the reaction between the activated aryl halide **3** and the potassium salt of the phenol **4a** were examined, large amounts of the nitrotoluene **1b** were recovered, the basic reaction medium having caused disproportionation of **3**.[14]

Consequently, the scheme was modified to provide for the formation of a simple diaryl ether at an early stage in the synthesis, preceding elaboration of the heterocyclic systems. The need for the labile nitroisoquinoline **3** was obviated by direct condensation of the active aryl halide **1b** with the potassium salt of **4a** in refluxing acetonitrile, to afford 64% of the diaryl ether **8a**. A subsequent Robinson–Hope-type con-

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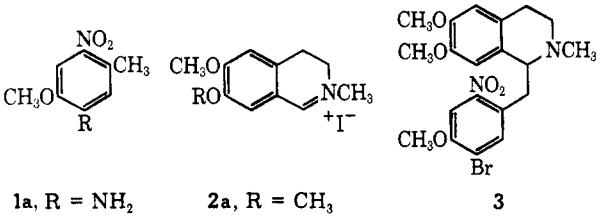
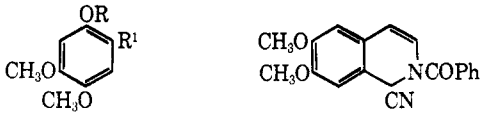
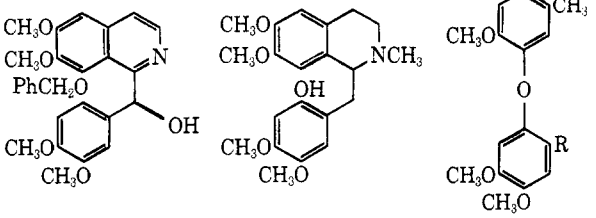
densation[15] between the diaryl ether **8a** and the 3,4-dihydroisoquinolinium salt **2a** yielded the amorphous nitrobenzylisoquinoline **9a**, which gave the crystalline diamine **9b** upon hydrogenation over 5% Pd/C in ethanol. Diazotization of **9b** followed by cyclization in hot 50% aqueous phosphoric acid and chromatography of the products gave the required aporphine **10a** (15%), as well as the phenolic by-product **9h** (13%). A formyl group was introduced into the aporphine (**10a**) hydrobromide by heating with a mixture of phosphorus oxychloride and *N*,*N*-dimethylformamide in nitrobenzene at 85°. The product was characterized as (±)-hernandaline (**10b**) by comparison of its ir, nmr, and mass spectra with those of a sample of hernandaline obtained (33% yield) by oxidation of thalicarpine (**13b**) with sodium metavanadate in 10% aqueous sulfuric acid. In addition to hernandaline a small amount of oxothalicarpine (**11**) was obtained from this oxidation.[16]



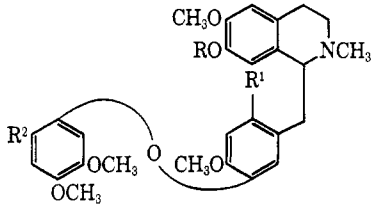
1a, R = NH_2 **2a**, R = CH_3 **3**
b, R = Br **b**, R = H



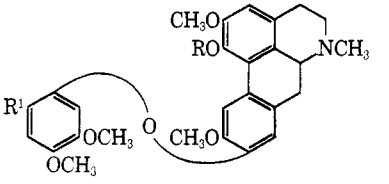
4a, R = R′ = H **5**
b, R = CH_2Ph; R′ = H
c, R = CH_2Ph; R′ = CHO



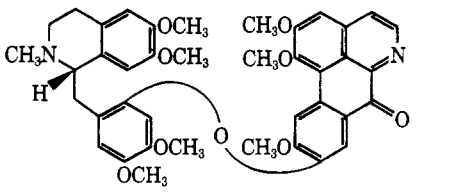
6 **7** **8a**, R = H
b, R = CHO



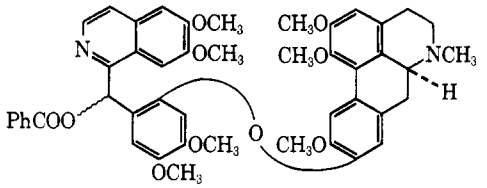
9a, R = CH_3; R′ = NO_2; R^2 = H
b, R = CH_3; R′ = NH_2; R^2 = H
c, R = CH_3; R′ = NO_2; R^2 = CHO
d, R = CH_3; R′ = NO_2; R^2 = CH(-OCH_2CH_2O-)
e, R = CH_3; R′ = NH_2; R^2 = CH(-OCH_2CH_2O-)
f, R = H; R′ = NO_2; R^2 = H
g, R = H; R′ = NH_2; R^2 = H
h, R = CH_3; R′ = OH; R^2 = H



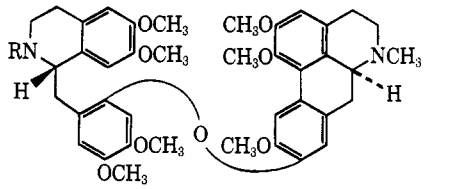
10a, R = CH_3; R′ = H
b, R = CH_3; R′ = CHO
c, R = H; R′ = H



11



12



13a, R = H
b, R = CH_3

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The disappointing yield encountered in the key Pschorr cyclization prompted an exploration of the alternative reaction sequence wherein the formyl group was introduced at an earlier stage. Thus the diaryl ether **8a** was formylated by the Vilsmeier–Haack procedure to **8b**, which afforded the crystalline nitrobenzylisoquinoline **9c** by condensation with **2a** in the presence of sodium hydride and *N*,*N*-dimethylacetamide. Attempts to achieve selective reduction of the nitro group by treating **9c** with alkaline ferrous sulfate[17] were unsuccessful and necessitated preparation of the ethylene acetal **9d** for protection of the aldehyde group during catalytic reduction. However, diazotization of the crude amine **9e** followed by treatment of the solution at 0° with copper powder led to the isolation of only 7% of (±)-hernandaline (**10b**) after extensive chromatography.

The recently developed Pschorr cyclization of 1-(2′-aminobenzyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinolines has been shown to give enhanced yields of aporphines[7] and offered good prospects for improvement of this troublesome ring closure. A modified sequence of intermediates was initiated by condensation of the diaryl ether **8a** with the readily available 6-methoxy-7-hydroxy-3,4-dihydroisoquinolin-

ium methiodide (**2b**)[18] in *N,N*-dimethylacetamide in the presence of KO-*t*-Bu, to give **9f** in 92% yield. Following catalytic reduction of **9f**, the crude amine **9g** was diazotized and cyclized in the presence of copper powder to give **10c**, the *O*-demethyl analog of **10a**, readily isolated in 36% yield. Methylation of **10c** with diazomethane proceeded in 90% yield to complete the improved route to the hernandaline precursor **10a**.

A solution of (±)-hernandaline (+)-α-bromocamphor-π-sulfonate in aqueous ethanol deposited crystals, which, after basification and recrystallization of the liberated alkaloid gave pure hernandaline (**10b**, *S* configuration). The condensation of hernandaline with the Reissert compound **5** in *N,N*-dimethylformamide in the presence of sodium hydride gave an amorphous basic product (ir absorption at 5.87 μ), homogeneous by tlc (silica, alumina) but having a nmr spectrum indicative of a mixture of the expected epimers (**12**). Although catalytic hydrogenation of **12** proceeded only slowly in both neutral and acidic media, treatment of an aqueous acetic acid solution of **12** at 50° with zinc powder overnight gave the nor bases (**13a** and epimer), indistinguishable by chromatography. The synthesis was completed by methylation of the mixture of nor bases with formaldehyde–formic acid, yielding an amorphous product identical with thalicarpine by tlc. A solution of this material in 60% aqueous ethanol gradually deposited crystals of **13b** (25% overall yield from hernandaline), mp 108–110°, identical (melting point, mixture melting point, $[\alpha]_D$, and spectra) with an authentic sample of thalicarpine (**13b**) crystallized from aqueous ethanol. Recrystallization from ether yielded the isomorphic form, mp 155–157°.[19]

The synthesis of the optical antipode of thalicarpine, and of other diastereomers, is in progress, for biological studies directed at elucidation of stereochemical requirements for tumor-inhibitory activity in this alkaloidal series.

Experimental Section

Melting points were determined on a Mettler FP2 melting point apparatus. Values of $[\alpha]_D$ were obtained with a Perkin-Elmer PE-141 polarimeter. Ultraviolet spectra were determined on a Beckman DK-2A recording spectrophotometer. Nmr spectra were recorded on a Varian HA100 spectrometer in deuteriochloroform solution (except as otherwise noted) containing tetramethylsilane as internal standard. Infrared spectra were determined on a Perkin-Elmer 337 recording spectrophotometer. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. Commercially prepared tlc plates (E. M. Reagents) were used exclusively. Preparative tlc was carried out with either aluminum oxide (type T, 1.5 × 200 × 200 mm) or silica gel (F-254, 2 × 200 × 200 mm) plates. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

3-Bromo-4-methoxy-6-nitrotoluene (1b). A slurry of 3-amino-4-methoxy-6-nitrotoluene (18 g) in water (20 ml) containing acetic acid (20 ml) and hydrobromic acid (47%, 35 ml) was stirred until a fine suspension of the hydrobromide had formed, cooled to 0°, and treated with a solution of sodium nitrite (7 g) in water (20 ml), added over 20 min. After a further 10 min, the yellow-brown solution was poured into a stirred mixture of cuprous bromide (30 g) and hydrobromic acid (47%, 30 ml) in water (50 ml); the mixture was warmed on the steam bath until an effervescence commenced and then was kept at 70° for 1 hr. The mixture was cooled and diluted with water (500 ml), and the solid was collected and recrystallized from aqueous ethanol to give **1b** as pale yellow needles (18 g, 72%), mp 91–92°.

Anal. Calcd for $C_8H_8BrNO_3$: C, 39.05; H, 3.28; N, 5.69. Found: C, 39.40; H, 3.11; N, 5.93.

1-(2′-Nitro-4′-methoxy-5′-bromobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3). Sodium hydride (0.35 g, 50% in oil) was added in portions (115 mg each) to a mixture of 2-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide (**2a**, 1.9 g) and 3-bromo-4-methoxy-6-nitrotoluene (**1b**, 1.5 g) in *N,N*-dimethylformamide (15 ml) over 30 min. After an initiation period an effervescence occurred, followed by a moderate rise in temperature. The mixture was stirred overnight, treated with methanol (2 ml) to destroy any residual sodium hydride, poured into water (150 ml), and extracted with ether (three 50-ml portions). The combined ethereal solutions were extracted with 3% hydrochloric acid (two 50-ml portions); the combined acid extracts were basified at 5° by addition of ice and ammonium hydroxide. The yellow precipitate was extracted with 15% chloroform–ether (two 50-ml portions). The organic phase was washed with water, and evaporated, and the residue was crystallized from aqueous methanol to give **3** (1.1 g, 43%) as yellow needles: mp 143–145°; nmr δ 2.40 (3 H, s, NCH_3), 3.86, 3.90, 3.98 (each 3 H, 3 OCH_3), 6.57, 6.62, 7.42, 7.47 (1 H each, s, Ar H).

Anal. Calcd for $C_{20}H_{23}BrN_2O_5$: C, 53.22; H, 5.14; N, 6.21; Br, 17.71. Found: C, 53.16; H, 5.31; N, 6.17; Br, 17.65.

1-Benzyloxy-3,4-dimethoxybenzene (4b). Potassium hydroxide (1.4 g) was added to a solution of 3,4-dimethoxyphenol[11] (3.6 g) in methanol (20 ml) and stirred until homogeneous. After solvent evaporation the potassium salt was dissolved in absolute ethanol (30 ml), benzyl chloride (2.5 g) was added, and the mixture refluxed for 3 hr. Ethanol was removed as completely as possible with a rotary evaporator, water (50 ml) added to the residue, and the mixture stirred until the oily precipitate solidified. The granular material was collected and dissolved in hot hexane (150 ml), a little tan material was filtered, and crude **4b** (5.1 g, 81%), mp 49–51°, was collected from the cooled filtrate. Recrystallization from hexane gave colorless needles (4.7 g, 74%), mp 53–54°.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.77; H, 6.51.

1-Benzyloxy-2-formyl-4,5-dimethoxybenzene (4c). A solution of **4b** (2 g) in a mixture of *N,N*-dimethylformamide and phosphorus oxychloride (2:1, 10 ml) was heated on a steam bath for 20 min, cooled, and poured with stirring into cold water (80 ml); the solution was heated at 60° for 10 min. The cooled solution (containing a flocculent crystalline precipitate) was stirred for 3 hr, and the precipitate was filtered and recrystallized from aqueous ethanol to give pale yellow needles (1.8 g, 61%), mp 139–140° (lit.[20] 141°).

1-(α-Hydroxy-2′-benzyloxy-4′,5′-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (6). Sodium hydride (0.14 g, 50% in oil) was added in one portion to a solution of **4c** (0.6 g) and the Reissert compound **5** (0.52 g) in dry *N,N*-dimethylformamide (6 ml). After the mixture was stirred for 5 hr, it was cooled to 0° and methanol (5 ml) added to destroy excess sodium hydride, and the mixture was poured into water (80 ml). The mixture was extracted with 10% chloroform–ether (three 40-ml portions), and the combined ethereal solution was extracted with 2% hydrochloric acid (two 50-ml portions). The acid extract was chilled, basified with ammonium hydroxide, and extracted with methylene chloride (three 30-ml portions). The methylene chloride extract was evaporated and the residue stirred 20 hr with ether (7 ml). The precipitate was recrystallized from aqueous ethanol to give **6** (0.55 g, 73%): mp 160–162°; nmr δ 3.62, 3.63, 3.80, 3.92 (each 3 H, 4 OCH_3), 5.20 (2 H, s, CH_2Ph), 6.62, 6.81, 6.99 (2 H, 1 H, 1 H, each s, Ar H), 7.4 (7 H, broad, CH_2Ph, isoquinoline H and CH(OH)), 8.37 (H, d, J = 6 Hz, isoquinoline H).

Anal. Calcd for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.04. Found: C, 70.17; H, 5.94; N, 3.02.

The methiodide of **6** (92 mg), mp 202–204°, was obtained as pale yellow prisms by refluxing a solution of **6** (100 mg) in acetone (5 ml) containing methyl iodide (3 ml) for 36 hr.

Anal. Calcd for $C_{28}H_{30}NO_6I$: C, 55.73; H, 5.01; N, 2.32. Found: C, 55.65; H, 5.08; N, 2.34.

1-(2′-Hydroxy-4′,5′-dimethoxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7) Hydrobromide. A suspension of **6** methiodide (1.2 g) in ethanol (20 ml, 95%) was stirred during the portionwise addition of sodium borohydride (1.0 g) during 4 hr.

(18) A. Brossi, J. O'Brien, and S. Teitel, *Org. Prep. Proced.*, **2**, 281 (1970).

(19) S. M. Kupchan, T.-H. Yang, M. L. King, and R. T. Borchardt, *J. Org. Chem.*, **33**, 1052 (1968).

(20) A. H. Jackson and J. A. Martin, *J. Chem. Soc. C*, 2222 (1966).

The mixture was stirred for 16 hr, water (10 ml) added, and the ethanol removed under reduced pressure at room temperature. After the addition of water (100 ml) to the residue, the organic material was extracted with ether (two 50-ml portions). The ethereal phases were combined, washed with water, dried, and evaporated to dryness. The residue was dissolved in ethanol (15 ml), Pd/C catalyst (0.2 g, 5%) added, and the mixture stirred at room temperature under a hydrogen atmosphere until absorption ceased (*ca.* 3 days). The catalyst was filtered and washed on the filter with a little ethanol, and the combined filtrates were evaporated under reduced pressure. The crude product was dissolved in tetrahydrofuran (20 ml), the solution cooled to 0°, and gaseous hydrogen bromide passed through for 3 min. The precipitate was recrystallized from ethanol–ethyl acetate to afford **7** hydrobromide as pale yellow needles (0.57 g, 69%): mp 209–210°; nmr δ 3.70, 3.80, 3.90 (6 H, 3 H, 6 H, each s, 4 OCH_3 and $^+NCH_3$), 6.55, 6.96, 7.03, 7.51 (4 H, each s, Ar H).

Anal. Calcd for $C_{21}H_{28}NO_5Br$: C, 55.51; H, 6.21; N, 3.08. Found: C, 55.77; H, 6.33; N, 3.21.

Attempted Condensation of 4a with 3. The potassium salt of 3,4-dimethoxyphenol (200 mg) was added to a solution of **3** (200 mg) in pyridine (2 ml) containing precipitated copper[21] (200 mg) and dry, powdered potassium carbonate. After 3 hr reflux under nitrogen, tlc of the reaction mixture indicated absence of **3**. The mixture was cooled, poured into water (100 ml), and extracted with ether (two 20-ml portions). The combined ether extracts were washed with aqueous potassium hydroxide (2%) and then water. Evaporation of the ether followed by crystallization of the residue from ethanol gave **1b** (20 mg), mp, mmp 90–91°.

2,3′,4′-Trimethoxy-5-methyl-4-nitrodiphenyl Ether (8a). A mixture of 3,4-dimethoxyphenol (20 g) and potassium hydroxide (8 g) in methanol was heated under reflux until a homogeneous solution was formed, and then evaporated under reduced pressure to a thick syrup. The residue was stirred thoroughly with acetonitrile (200 ml) and the mixture evaporated under reduced pressure. Acetonitrile (150 ml) followed by **1b** (30 g) were added to the product and the mixture was heated under reflux for 42 hr. Water (100 ml) was added to the product and the mixture was concentrated under reduced pressure until the organic solvent had been removed. Aqueous potassium hydroxide (1%, 500 ml) was added and the mixture extracted with chloroform (2 × 200 ml). The combined chloroform extracts were evaporated, the residue was dissolved in a minimum of benzene, and the solution was applied to a chromatographic column prepared from silica gel (Merck 0.2–0.05 mm, 400 g) in benzene. Elution was carried out with benzene followed by chloroform (increased by 10% increments up to 50%) in benzene to give unchanged **1b** (9.3 g), followed by diphenyl ether **8a**. Recrystallization of the crude **8a** from chloroform–hexane gave pale yellow prisms (17.0 g, 64%): mp 127–128°; nmr δ 2.45 (3 H, CH_3), 3.82, 3.88, 3.94 (3 H each, 3 OCH_3). 6.40–7.70 (5 H, Ar H).

Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.31; H, 5.40; N, 4.35.

2-Formyl-2′,4,5-trimethoxy-5′-methyl-4′-nitrodiphenyl Ether (8b). Phosphorus oxychloride (66 g) was added dropwise to a stirred solution of **8a** (12.5 g) in *N*,*N*-dimethylformamide (60 ml) at 15° during 1 hr. The mixture was heated at 85° for 3 hr, cooled, poured into ice–water (600 ml), warmed to 50° for 10 min, and cooled, and **8b** was collected by filtration (11 g, 79%), mp 176–179°. Recrystallization from chloroform–ethanol gave yellow prisms: mp 178.5–180°; λ_{max}^{MeOH} (log ε) 236 nm (4.33), 277 (4.12), 329 (4.05); λ_{max}^{KBr} 5.97, 6.33, 7.52 μ; nmr δ 2.50 (3 H, ArCH_3), 3.88, 3.95, 3.93 (each 3 H, 3 OCH_3), 6.51, 6.70, 7.42, 7.75 (each 1 H, s, Ar H), 10.21 (1 H, CHO).

Anal. Calcd for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.93; N, 4.03. Found: C, 58.69; H, 5.05; N, 4.00.

1-[2′-Amino-4′-methoxy-5′-(3′′,4′′-dimethoxy)phenoxybenzyl]-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9a).[22] A solution of imidazole (1.76 g) in anhydrous *N*,*N*-dimethylacetamide (40 ml) was treated with sodium hydride (1.2 g, 50% in oil) under nitrogen. After 30 min the mixture was cooled with ice and **2a** (8.4 g) added in one portion. After 5 min a further portion of sodium hydride (1.16 g) was added and the mixture stirred at room temperature for 6 hr. Methanol (8 ml) followed by chloroform (40 ml) were added; the mixture was poured into 5% aqueous sodium chloride (600 ml) and extracted with 10% chloroform–ether (two 300-ml portions). The combined organic extracts were washed with 5% aqueous sodium chloride (200 ml) and then 1% hydrochloric acid (three 100-ml portions). The acidic extracts were basified with ammonium hydroxide and extracted with ether (two 200-ml portions). A small portion of the glassy residue obtained after evaporation of the ether was dissolved in acetone containing oxalic acid, and the salt which precipitated upon addition of ether was collected and crystallized from ethanol–ethyl acetate to give **9a** oxalate, mp 127–129°.

Anal. Calcd for $C_{30}H_{34}N_2O_{12}$: C, 58.25; H, 5.53; N, 4.52. Found: C, 58.07; H, 5.67; N, 4.59.

Reduction to 9b. The bulk of the crude **9a** was dissolved in ethanol (250 ml) containing 5% Pd/C (3.2 g) and stirred under a hydrogen atmosphere until absorption ceased. After the addition of chloroform the reaction mixture was filtered to remove the catalyst, and the filtrate was evaporated almost to dryness. The residue was dissolved in warm methanol (30 ml); the mixture was stirred at room temperature for 12 hr and filtered to give **9b** (6.77 g, 64%) as colorless prisms, mp 170–172°. An analytical sample was obtained from aqueous ethanol: mp 172–173°; $\lambda_{max}^{CHCl_3}$ (log ε) 238 nm (4.32), 291 (4.04); nmr δ 2.54 (NCH_3), 3.64, 3.75, 3.83 (3 H, 3 H, 9 H, 5 OCH_3), 6.15–6.71 (7 H, Ar H).

Anal. Calcd for $C_{28}H_{31}N_2O_6$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.08; H, 6.89; N, 5.53.

Pschorr Cyclization of 9b. A solution of **9b** (2.4 g) in aqueous phosphoric acid (45%, 22 ml) at 0° was diazotized by the dropwise addition during 5 min of a solution of sodium nitrite (0.4 g) in water (2 ml). Excess nitrous acid was destroyed by sulfamic acid (0.2 g); the solution was heated at 80° for 1 hr, poured into water (300 ml), made alkaline with aqueous sodium hydroxide, and extracted with ether (three 100-ml portions). The combined extracts were evaporated; the residue was dissolved in chloroform, applied to preparative layer silica plates, and eluted with methanol–chloroform (4%). The two principal high R_f bands were collected and extracted with methanol–chloroform (20%). Each extract was evaporated to dryness; the residues were dissolved in ethyl acetate (25 ml) and treated with hydrobromic acid (47%, 0.6 ml each); and the mixtures were stirred overnight. The more polar fraction was crystallized from ethanol–ethyl acetate to give the aporphine (**10a**) hydrobromide (405 mg, 15%): mp 212–214° dec; λ_{max}^{MeOH} (log ε) 280 nm (4.25), 300 (4.18), 316 sh (4.04); nmr δ 3.03 (broad s, $^+NCH_3$), 3.59, 3.82, 3.86, 3.90 (3 H, 3 H, 3 H, 6 H, 5 OCH_3), 6.51–8.17 (6 H, Ar H).

Anal. Calcd for $C_{28}H_{32}BrNO_6$: C, 60.22; H, 5.78; N, 2.51. Found: C, 60.02; H, 5.83; N, 2.45.

The second fraction yielded the phenol **9h** hydrobromide (370 mg, 13%), mp 164–166°. Treatment of **9h** hydrobromide with aqueous potassium carbonate gave the free base, which crystallized from aqueous ethanol: mp 135.5–137°; nmr δ 2.62 (3 H, NCH_3), 3.71, 3.81, 3.82 (6 H, 6 H, 3 H, 5 OCH_3), 5.90–6.75 (7 H, Ar H).

Anal. Calcd for $C_{28}H_{33}NO_7$: C, 67.86; H, 6.71; N, 2.83. Found: C, 67.81; H, 6.71; N, 2.81.

1-[2′-Nitro-4′-methoxy-5′-(3′′,4′′-dimethoxy)phenoxybenzyl]-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (9f). The diphenyl ether **8a** (6.38 g) was added to *N*,*N*-dimethylacetamide (125 ml) under nitrogen; the mixture was stirred for 5 min and treated with **2b** (7.65 g). Potassium *tert*-butoxide (4.93 g) was then added in small portions over 15 min. The reaction mixture was stirred under nitrogen at room temperature for 7 hr, diluted with cold water (600 ml), stirred for 10–15 min, and refrigerated overnight. The supernatant aqueous layer was decanted from the solid, which was collected and washed with 1:1 methanol–ether (20 ml) followed by ether (100 ml) and sucked dry (9.40 g, 92%), mp 169–171°. An analytical sample was crystallized from chloroform–methanol: mp 173–174°; nmr δ 2.40 (3 H, NCH_3) 3.85, 3.88, 3.92, and 3.98 (each 3 H, 4 OCH_3), 6.37–7.60 (7 H, Ar H).

Anal. Calcd for $C_{27}H_{30}N_2O_8$: C, 63.52; H, 5.92; N, 5.49. Found: C, 63.46; H, 5.89; N, 5.34.

1-[2′-Amino-4′-methoxy-5′-(3′′,4′′-dimethoxy)phenoxybenzyl]-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (9g). A mixture of **9f** (3.0 g) in absolute methanol (200 ml) containing Pd/C catalyst (0.9 g, 5%) was stirred under hydrogen until absorption ceased. The catalyst was filtered and washed with 1:1 methanol–chloroform (50 ml), and the filtrate was evaporated to give a brownish-yellow glass (2.7 g, 95%). The aminophenol **9g** was found to be unstable in solution and hence used as the crude material.

Pschorr Cyclization of 9g to 10c. A solution of crude **9g** (7.65 g) in aqueous sulfuric acid (20%, 128 ml) and glacial acetic acid (128 ml) at 0° was treated dropwise with a solution of sodium nitrite

(21) R. Q. Brewster and T. Groening, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 446.

(22) Procedure developed with Dr. C. Roy Taylor, Jr.

(1.12 g) in water (12 ml) over 10 min. The solution was stirred for 30 min; excess nitrous acid was destroyed with sulfamic acid. Copper powder (8.00 g, Merck) was added and the reaction mixture was stirred at 0° for 1 hr or until the diazonium salt had disappeared (alkaline β-naphthol test). The copper powder was filtered and washed with water (100 ml). The filtrate was diluted to 300 ml with water, made alkaline with concentrated ammonium hydroxide solution (30%), and extracted with chloroform (four 100-ml portions). The extracts were washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated to give a dark brown oil (8 g). This was applied to a silica gel column (Merck 0.2–0.05 mm, 400 g, packed in chloroform) and eluted with chloroform (*ca.* 3 l.) followed by 5% methanol–chloroform, which gave the crude aporphine **10c** as an off-white solid (3.54 g). Crystallization from ethanol–ether gave the pure aporphine **10c** (2.62 g, 36%), mp 150.5°. An analytical sample was obtained by recrystallization from ethanol–ether: mp 150–151°; λ_{max}^{MeOH} (log ε) 278 nm (4.29), 302 (4.25), 268 sh (4.18); nmr δ 2.52 (3 H, NCH_3), 3.84, 3.86, and 3.90 (3 H, 3 H, 6 H, 4 OCH_3), 6.51–6.80 (5 H, Ar H), and 8.16 (1 H, s, C-11 H).

Anal. Calcd for $C_{27}H_{29}NO_6$: C, 69.95; H, 6.31; N, 3.02. Found: C, 69.68; H, 6.55; N, 3.20.

1,2,10-Trimethoxy-9-(3′,4′-dimethoxy)phenoxyaporphine (10a) Hydrobromide. A mixture of **10c** (5.0 g) and methanol (100 ml) was treated with an excess of diazomethane (*ca.* 8 g) in ether solution over a period of 3 days and the reaction was kept in the refrigerator with occasional swirling. The solution was evaporated to an oil, which was dissolved in ethyl acetate (120 ml), treated with HBr (48%, 1 ml), and stirred overnight. The white solid was collected, washed with ethyl acetate, and dried to give **10a** hydrobromide (5.42 g, 90%), mp 211–214° dec.

Oxidation of Thalicarpine (13b) to Hernandaline and Oxothalicarpine (11). Sodium metavanadate (12 g, powdered) was added in portions (1 g) during 1 hr to a stirred solution of thalicarpine (8 g) in aqueous sulfuric acid (10% v/v, 80 ml). The mixture was stirred at room temperature for 24 hr, diluted with water (600 ml), rendered alkaline with ammonium hydroxide, and extracted with methylene chloride–ether (1:3, two 300-ml portions). The solvents were removed from the organic phase and the residue was subjected to preparative tlc on silica plates eluted with 5% methanol–chloroform. The foremost, principal band was collected and extracted with 20% methanol–chloroform, the extract evaporated, and the residue stirred with benzene (15 ml). The next day the solution was freed from a little insoluble material, the benzene evaporated, and the residue crystallized from aqueous methanol to afford hernandaline (1.8 g, 31%), mp 169–171°, identical melting point, $[\alpha]_D$, and spectra with reported values.[8] The yellow band (R_f 0.05) was separated from the silica plates and extracted with 10% methanol–chloroform containing 3% triethylamine. The extract was evaporated, the residue stirred with methanol, and the precipitate recrystallized from chloroform–ethanol to give **11** as yellow needles (60 mg, 0.8%): mp 220–222° dec; $\lambda_{max}^{CHCl_3}$ (log ε) 272 nm (5.58), 292 (5.49), 318 (5.11), and 246 sh (5.67); nmr δ (CF_3COOH) 3.04 (3 H, $^+NCH_3$), 3.57, 3.64, 3.81, 4.07, 4.16, 4.22 (3 H, 3 H, 6 H, 3 H, 3 H, 3 H, 7 OCH_3), 6.15, 6.70, 6.84, 6.86, 7.57, 7.58, 8.60 (7 H, each s, Ar H), 8.22, 8.90 (1 H, 1 H, d, d, J = 6 Hz, isoquinoline H).

Anal. Calcd for $C_{40}H_{40}N_2O_9$: C, 69.35; H, 5.82; N, 4.04. Found: C, 69.11; H, 5.92; N, 4.03.

(±)-Hernandaline (10b). A mixture of **10a** hydrobromide (300 mg), *N*,*N*-dimethylformamide (1 g), and phosphorus oxychloride (1 g) in nitrobenzene (2 ml) was heated on the steam bath for 45 min, poured into aqueous phosphoric acid (2%, 100 ml), and extracted with ether (three 30-ml portions). The aqueous phase was separated, made alkaline with aqueous sodium hydroxide (10%), and extracted with ether (three 30 ml portions). The latter ether extracts were combined and evaporated, and the residue was crystallized from aqueous ethanol to give **10b** (174 mg, 65%): mp 148–149.5°; nmr, ir, and uv spectra identical with those of hernandaline.

Anal. Calcd for $C_{29}H_{31}NO_7$: C, 68.91; H, 6.18; N, 2.77. Found: C, 68.79; H, 6.10; N, 2.78.

1-[2′-Nitro-4′-methoxy-5′-(2″-formyl-4″,5″-dimethoxy)phenoxybenzyl]-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9c). A mixture of **8b** (4 g) and **2a** (4.8 g) in *N*,*N*-dimethylacetamide at 10–15° (50 ml) was stirred under nitrogen. To this mixture was added sodium hydride (0.8 g, 50% in oil) in portions with stirring at 10–15° during 1 hr. The mixture was stirred under nitrogen at 10–15° for 12 hr, during which time the color became green. Stirring was continued at room temperature for an additional 10 hr, and then ethanol (5 ml) was added to the reaction mixture, which was then poured into ice–water (150 ml) and extracted with ether–chloroform (10:1). The organic layer was extracted with 2% aqueous hydrochloric acid; the acid layer was made alkaline with concentrated ammonium hydroxide and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and concentrated to give an oil (5 g). The oil crystallized upon addition of a few drops of ethanol. The crystals were filtered and washed with aqueous ethanol to give **9c** (3.6 g), mp 153–162°. Recrystallization from ethanol gave yellow prisms: mp 168.5–169.5°; λ_{max}^{MeOH} (log ε) 279 nm (4.16), 327 (3.99); λ_{max}^{KBr} 6.03, 6.45, 7.57 μ; nmr δ 2.31 (3 H, s, NCH_3), 3.84, 3.87, 3.97 (each 3 H, 3 OCH_3), 3.97 (6 H, 2 OCH_3), 6.41, 6.45, 6.50, 6.58, 7.40, 7.60 (each 1 H, s, Ar H), 10.35 (1 H, s, CHO).

Anal. Calcd for $C_{29}H_{32}N_2O_9$: C, 63.03; H, 5.84; N, 5.07. Found: C, 63.01; H, 6.01; N, 5.03.

Ethylene Acetal Formation from 9c. A mixture of **9c** (1.66 g), ethylene glycol (0.93 g), and *p*-toluenesulfonic acid (0.26 g) in benzene (30 ml) was refluxed for 20 hr with azeotropic removal of the water formed. After cooling, the reaction mixture was slowly added to 3% aqueous potassium carbonate (60 ml) with stirring and ice cooling. The organic layer was separated and washed with cold water. Removal of the solvent gave **9d** as a powder (1.5 g): λ_{max}^{MeOH} (log ε) 286 nm (4.04); λ_{max}^{KBr} 6.45, 7.64 μ; nmr δ 2.31 (3 H, s, NCH_3), 3.75, 3.79, 3.82, 3.92, 3.96 (each 3 H, 5 OCH_3), 5.85 (1 H, s, acetal H), 6.41, 6.45, 6.49, 6.55, 7.11, 7.62 (each 1 H, s, Ar H).

Reduction of 9d. A mixture of **9d** (1.5 g), Pd/C (450 mg, 10%), and ethanol (20 ml) was vigorously stirred in a hydrogen atmosphere at room temperature for 15 hr. The reaction mixture was clarified by filtration and the ethanol removed *in vacuo* to leave powdery **9e** (1.1 g): λ_{max}^{MeOH} (log ε) 289 nm (4.03); nmr δ 2.63 (3 H, s, NCH_3), 3.65, 3.69, 3.78, 3.84, 3.87 (each 3 H, 5 OCH_3), 6.14 (1 H, s, acetal H), 6.14, 6.23, 6.33, 6.46, 6.55, 7.07 (each 1 H, s, Ar H). Attempts at salt formation using hydrochloric acid, or oxalic acid, were unsuccessful because of the sensitivity of **9e** to acids.

Pschorr Cyclization of 9e to (±)-Hernandaline (10b). The amine **9e** obtained from 2.1 g of the aldehyde **9c** as described was dissolved in a mixture of sulfuric acid (98%, 4 ml) and 30% aqueous acetic acid (30 ml) at 0°. The solution was treated with sodium nitrite (0.36 g) in water (2 ml), added during 2 min. After 5 min the excess of nitrous acid was destroyed by the addition of sulfamic acid (0.3 g), and copper powder (2 g) was added, leading to a brisk effervescence. After 1 hr at 0° the copper powder was filtered; the filtrate was diluted with cold water (200 ml), basified with ammonium hydroxide, and extracted with chloroform (three 50-ml portions). The solvent was removed and the residue chromatographed on alumina preparative tlc plates with chloroform as eluent. The diffuse band with R_f 0.8–0.9 was collected, the organic material extracted and rechromatographed on silica gel (5% methanol–chloroform eluent), and the band with R_f 0.5–0.8 chromatographed again upon alumina (10% chloroform–benzene). The organic material contained in the foremost band (R_f 0.3) was extracted and crystallized from ethyl acetate–hexane and then aqueous methanol, to give (±)-hernandaline, mp 147–148.5° (0.14 g, 7% from **9c**).

Hernandaline (+)-α-Bromocamphor-π-sulfonate. A mixture of hernandaline (**10b,** *S* configuration, 100 mg) and (+)-α-bromocamphor-π-sulfonic acid (ammonium salt, 100 mg) in aqueous ethanol (30%, 2 ml) containing acetic acid (50 mg) was stirred at 50° until crystal formation began and then overnight at room temperature. The precipitate was collected and crystallized from aqueous ethanol to give the salt as pale yellow needles (100 mg): mp 158° dec; $[\alpha]_D^{26°}$ +46.5° (*c* 1.42, methanol).

Anal. Calcd for $C_{39}H_{46}BrNO_{11}S \cdot H_2O$: C, 56.11; H, 5.79; N, 1.68. Found: C, 56.16; H, 5.81; N, 1.59.

Resolution of (±)-Hernandaline (10b). Acetic acid (140 mg) was added to a mixture of (±)-hernandaline (**10b,** 200 mg) and (+)-α-bromo-π-camphorsulfonic acid (ammonium salt, 180 mg) in aqueous ethanol (35%, 2.5 ml). The mixture was warmed to effect solution and seeded with a few crystals of the pure hernandaline salt. The mixture was stirred at 40° for 2 hr (with occasional brief heating to redissolve oil precipitated with the crystalline material) and at 20° for 18 hr. The precipitate was collected, washed with a little 25% aqueous ethanol, dissolved in aqueous ethanol (30%, 5 ml) at 70°, and treated with concentrated ammonium hydroxide (100 mg). The solution was cooled and stirred for 20 hr at room temperature, and the precipitate crystallized from aqueous ethanol to give hernandaline (64 mg, 64%), mp 170–171°.

Condensation of Hernandaline with Reissert Compound 5. A solution of hernandaline (2.9 g) in *N*,*N*-dimethylformamide (50 ml) containing **5** (2.3 g) was cooled in an ice bath and treated under

nitrogen with sodium hydride (50% in oil, 0.4 g) added in portions over 1 hr. The brown solution was stirred for a further 2 hr at 0° and then for 2 hr at 20°. Methanol (3 ml) was added dropwise; the mixture was stirred for 10 min and poured into a mixture of water (500 ml) and ether–chloroform (6:1). The lower layer was discarded and the ether solution washed with water and then extracted with hydrochloric acid (2%, three 100-ml portions). The acid solution was basified by addition of ammonium hydroxide and extracted with methylene chloride (two 100-ml portions). Evaporation of the solvent gave the crude product **12** (4.8 g), λ_{max}^{KBr} 5.87 μ.

Formation of Thalicarpine (13b). A solution of the crude product **12** (0.48 g) in acetic acid (30 ml) containing water (6 ml) was stirred with zinc powder (30 mesh, 15 g) at 45–50° for 24 hr. The mixture was diluted with water (200 ml), warmed to dissolve zinc acetate, and filtered, and the filtrate was cooled and basified with ammonium hydroxide. Extraction of the alkaline mixture with ether (three 50-ml portions) followed by evaporation of the ether gave **13a** as a pale brown glass, which was dissolved in formic acid (97%, 4 ml) containing formalin (40%, 1 ml) and heated for 45 min on the steam bath. The cooled solution was diluted with water (50 ml), made alkaline with ammonium hydroxide, and extracted with ether (three 20-ml portions). The residue remaining after removal of the ether was dissolved in ethanol (3 ml); the solution was diluted slowly with water (2 ml) (warming if necessary to inhibit precipitation) to a faint turbidity and stirred 48 hr. The precipitate crystallized from aqueous ethanol to yield thalicarpine (**13b**, 101 mg, 25%), mp 108–110°, identical melting point, mixture melting point, and spectra with an authentic sample crystallized from aqueous ethanol. A portion crystallized from ether gave the isomorphic form,[19] mp 155–157°.

Total Synthesis of Racemic Cryptosporiopsin[1]

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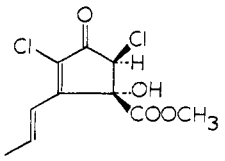
Abstract: A short synthesis of the fungitoxic chlorine-containing metabolite cryptosporiopsin (**1**) in racemic form is described. A key intermediate in the synthesis was 3,5,5-trichloro-1,4-dihydroxy-2-*n*-propyl-2-cyclopentene-1-carboxylic acid (**3d**), prepared from *m*-*n*-propylphenol through the agency of alkaline hypochlorite.

Several biogenetically related chlorine-containing metabolites of polyketide origin have been isolated from fermentations of the coprophilous fungus *Sporormia affinis* Sacc., Bomm and Rouss.[3,4] The most abundant of these was the fungitoxic dichlorocyclopentenone **1**. This compound, designated cryptosporiopsin, was discovered in an independent study[5] in culture filtrates of a *Cryptosporiopsis* species, an imperfect fungus isolated from yellow birch, *Betula alleghaniensis* Britt. Cryptosporiopsin was later detected chromatographically in extracts from *Periconia macrospinosa*,[6] from which, *inter alia*, the related metabolite **2** was also isolated. A plausible biosynthetic route to cryptosporiopsin has been postulated,[4] involving contraction of a six-membered cyclic precursor, similar to that demonstrated for terrein.[7]



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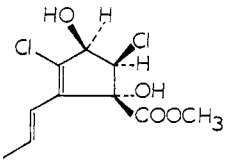

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The distribution of functionality of cryptosporiopsin (**1**) suggested that this interesting, generously functionalized molecule should be accessible by a short synthetic route, involving skeletal rearrangement of a suitably substituted phenol through the agency of alkaline hypochlorite. Base-catalyzed chlorination of phenol, originally investigated by Hantzsch in 1887,[8] gives rise, *inter alia*, to 3,5,5-trichloro-1,4-dihydroxy-2-cyclopentene-1-carboxylic acid (**3a**).[9,10] Favorskii-type ring contraction of an intermediate such as **4** is one of several mechanisms which have been advanced for this transformation.[9,10] Although rigorous evidence for the stereochemistry at the asymmetric centers of **3a** was lacking, a trans relationship of the two hydroxyl groups was favored on the basis of ir data.[10] Reductive removal of one of the geminal chlorine atoms was effected by treatment of **3a** with sodium amalgam,[8] yielding a dichloro product **5a**.[9,10] In the nmr spectrum of **5a**, the coupling constant (6.5 Hz) of the protons on C-4 and C-5 is indicative of cis stereochemistry at these centers.[9,10] If, therefore, the tentative stereochemical assignment[10] for the Hantzsch acid is correct, similar reduction of a related compound, possessing a potential allyl chain precursor at C-2, could be expected to lead to the stereochemistry at C-1 and C-5 appropriate for a synthesis of cryptosporiopsin.

Consideration of the mechanism of formation of **3a** suggested that hypochlorite-induced rearrangement of a *m*-alkylphenol might lead to a C-2 alkylated Hantzsch acid, **3b**, in which the R group could subsequently be elaborated to the allyl side chain. A series of model

(1) All synthetic substances described herein are racemic whether or not this is specified.

(2) From the Ph.D. Thesis of A. S. C., University of New Brunswick, Fredericton, Canada, 1971.

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