Aromatic Hydroxylation of Some Isoquinoline-Type Alkaloids

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Isoquinoline-type alkaloids which undergo selective halogenation can be converted to analogues containing an additional oxygen in the form of a phenolic hydroxyl by the sequence of bromination, metal–halogen interchange, and reaction of the organometallic intermediate with nitrobenzene. Examples are reported using a simple benzyltetrahydroisoquinoline (*dl*-laudanosine, **1**), an aporphine (nuciferine, **8**), and a bisbenzylisoquinoline (tetrandrine, **15**). The method makes possible overall oxidative transformations of a type hitherto not possible, i.e., the synthesis of homomoschatoline (**14**) from nuciferine (**8**), and the synthesis of hernandezine (**19**) from tetrandrine (**15**).

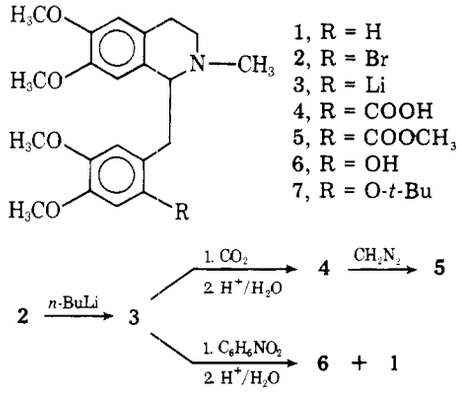
Naturally occurring isoquinoline alkaloids cover a range of structural subtypes, within which there is considerable latitude in the degree of oxygenation of the aromatic rings. A procedure for the introduction of an additional phenolic hydroxyl into a specific position of a known isoquinoline alkaloid would be valuable for several reasons. It would allow not only the preparation of unnatural alkaloid derivatives for pharmacological evaluation, but also the partial synthesis of certain rare natural bases from more readily available ones.

We now report the successful development of such a procedure, based upon the observation of Buck and Köbrich[1,2] that phenol is produced when nitrobenzene is attacked by phenyllithium at low temperatures. To our knowledge, the only synthetic application of this reaction subsequently reported has been the conversion of 5-lithio[3,3]paracyclophane to the corresponding 5-hydroxy derivative.[3] In our work, we have explored the application of the Buck–Köbrich reaction to examples of three different types of isoquinoline alkaloids: the simple benzyltetrahydroisoquinoline laudanosine (**1**), the aporphine nuciferine (**8**), and the bisbenzylisoquinoline tetrandrine (**15**).

Results

In all of the three cases discussed below, hydroxylation was carried out on lithiated alkaloids prepared from the corresponding bromo derivatives, all of which were homogeneous crystalline intermediates. Preliminary attempts to lithiate the parent alkaloids directly were unpromising, since lithium–hydrogen interchange was slow, and O-demethylation to phenolic products was a serious side reaction.

Hydroxylation of Laudanosine (1). Direct bromination of *dl*-laudanosine (**1**) takes place selectively to give the 6′-bromo derivative **2** in good yield,[4] making **2** the most readily

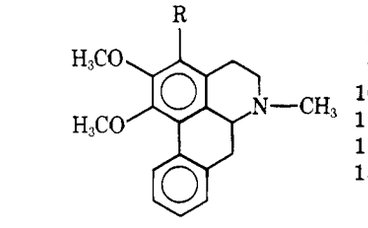


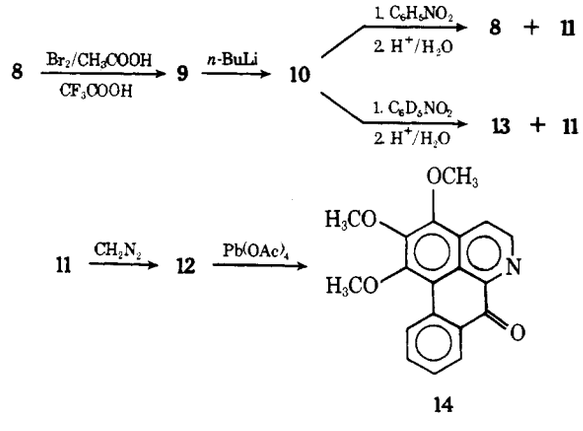
available halo derivative of a simple benzyltetrahydroiso quinoline alkaloid. We have found that bromide **2** undergoes a very clean halogen–lithium interchange when treated with *n*-butyllithium; carbonation of the resulting 6′-lithiolaudanosine (**3**) results in the almost quantitative formation of the crystalline 6′-carboxylaudanosine (**4**), further characterized as its methyl ester **5**.

Reaction of the lithio derivative **3** with excess nitrobenzene at −60 °C afforded, as the major product (65%), 6′-hydroxylaudanosine (**6**), previously known only as a thalicarpine degradation product.[5] The only significant by-product of the reaction (30%) was laudanosine (**1**).

Since simple phenols have been prepared by the reaction of aryllithiums with *tert*-butyl perbenzoate,[6] followed by acid hydrolysis, we also investigated this route to 6′-hydroxylaudanosine. Reaction of lithio derivative **3** with *tert*-butyl perbenzoate, followed by direct acid cleavage of the *tert*-butyl ether **7**, did indeed afford phenol **6**, but only in low yield (13%).

Hydroxylation of Nuciferine (8). Whereas laudanosine is brominated smoothly in an acetic acid–sodium acetate medium,[4] attempts to brominate (*R*)-nuciferine (**8**) under the same conditions afforded a mixture of products as evidenced by TLC. It was suspected that this result was due to a very facile attack of the bromine on the basic nitrogen, leading to a dehydroaporphine, a reaction known to be brought about by iodine.[7] In accord with this supposition, bromination of nuciferine took place cleanly in the presence of the strongly acidic trifluoroacetic acid, giving 3-bromonuciferine (**9**) in high



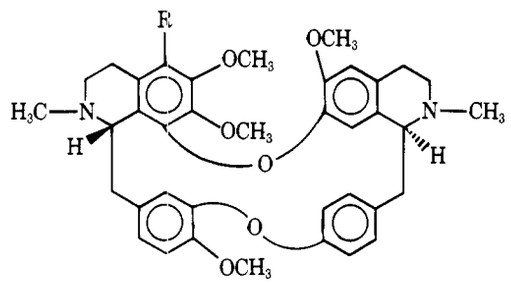


yield (90%). Conversion of bromide **9** to the corresponding lithio derivative **10**, followed by reaction with excess nitrobenzene, afforded 3-hydroxynuciferine (**11**) in about 50% yield, the major by-product being nuciferine.

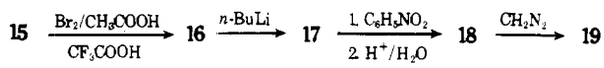
Confirmation of the structure of phenol **11** was obtained not

only from its NMR spectrum (loss of the C-3 nuciferine singlet), but also by further chemical transformations. Thus, diazomethane treatment of **11** afforded 3-methoxynuciferine (**12**),[8] which on oxidation with lead tetraacetate[9] gave homomoschatoline (**14**),[10,11] the structure of which has been secured by a total synthesis.[11]

Hydroxylation of Tetrandrine (15). Although the bisbenzylisoquinoline alkaloid tetrandrine (**15**) contains eight different aromatic sites which are activated by an ether substituent, only one of these sites (C-5) is *doubly* activated by both an ortho and a para ether substituent. In fact, monobromination of tetrandrine in the presence of trifluoroacetic acid afforded, in high yield, the crystalline 5-bromotetrandrine (**16**). The position of the bromine in **16** was not only consistent with its spectroscopic properties, but was proven chemically by the following reactions. Conversion of **16** to the corresponding lithio derivative **17**, followed by treatment with excess nitrobenzene, afforded 5-hydroxytetrandrine (**18**) in



15, R = H
16, R = Br
17, R = Li
18, R = OH
19, R = OCH_3

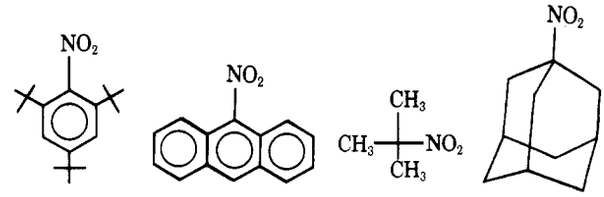


good yield (57%), the major by-product consisting of tetrandrine; diazomethane methylation of **18** gave 5-methoxytetrandrine (**19**). Comparison with authentic samples showed **18** and **19** to be identical in all respects with the natural alkaloids thalidezine[12] and hernandezine,[13] respectively. The conversion of the antitumor alkaloid tetrandrine to the closely related rare base thalidezine (**18**) is especially interesting, since it has permitted the preparation of the latter for the first time in quantities sufficient for biological testing.

Discussion

As mentioned in the previous section, the major nonphenolic products of the reaction of excess nitrobenzene with the lithiated alkaloids **3**, **10**, and **17** are the original alkaloids (**1**, **8**, and **15**). It seemed at first that this unwanted side reaction was due simply to protonation of the lithio compounds by traces of moisture, although the protonation reaction could not be suppressed even under the most rigorously anhydrous conditions. It then became evident that the observed products would also be obtained if the lithiated alkaloid were to abstract an ortho (or para) hydrogen from the nitrobenzene at a rate comparable to its attack on the nitro group of the reagent. *o*-Nitrophenyllithium is indeed a known species and is fairly stable at low temperatures.[1,2] Confirmation of this idea was obtained by treatment of 3-lithionuciferine (**10**) with pentadeuterionitrobenzene. The nuciferine recovered from this reaction was shown by NMR to contain about 75% of 3-deuterionuciferine (**13**).

Several unsuccessful attempts were made to find a nitro compound which would be superior to nitrobenzene as a hydroxylating agent, 3-lithionuciferine (**10**) being employed as the test reagent. 2,4,6-Tri-*tert*-butylnitrobenzene (**20**),[14]



20 **21** **22** **23**

which should not be metalated, proved to be very unreactive as an oxidant, only about 5% of phenol **11** being formed after 12 h at room temperature. 9-Nitroanthracene (**21**), which has only a free para position, gave a fair yield (40%) of phenol **11**, but was still not as effective as nitrobenzene. The aliphatic reagents 2-methyl-2-nitropropane (**22**) and 1-nitroadamantane (**23**)[15] were totally ineffective, and produced only a trace of phenolic product.

Experimental Section

Melting points are uncorrected. NMR spectra were determined using a Varian A-60 instrument, with tetramethylsilane as internal standard. Infrared spectra (KBr), ultraviolet spectra (EtOH), mass spectra, and optical rotations were determined using Perkin-Elmer instrument Models 137, 202, 270, and 140, respectively.

3-Bromonuciferine (9). To a solution of (−)-nuciferine (2.95 g, 10 mmol) in trifluoroacetic acid (15 mL) and water (10 mL), a solution of bromine in acetic acid (11 mL of 1.1 M solution, 12 mmol) was added dropwise over a period of 5 min, while stirring and warming on a steam bath. A precipitate formed, which quickly redissolved. After the addition of bromine was complete, the solution was further stirred for 45 min, then poured into a mixture of ice and water (150 mL) and slowly basified with concentrated aqueous ammonium hydroxide. Extraction with chloroform (300 mL) and evaporation of the extract gave a brown oil which was passed through a dry silica column (30 g) with chloroform elution. Evaporation of the eluent afforded 3-bromonuciferine as an oil which crystallized upon cooling. The crystals (3.4 g, 90%) were recrystallized from methanol to give fine, pale yellow needles: mp 117–118 °C; $[\alpha]^{28}_D$ −79.7° (*c* 1.0, chloroform); UV λ_{max} (EtOH) 211 nm (ϵ 31 100), 288 (sh, 16 100), 276 (18 800); NMR ($CDCl_3$) δ 2.15–3.43 (m, 7 H, aliphatic H), 2.48 (s, 3 H, NCH_3), 3.71 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 7.17–7.51 (m, 3 H, $H_{8,9,10}$), 8.20–8.47 (m, 1 H, H_{11}); mass spectrum *m/e* 375 (M^+).

Anal. Calcd for $C_{19}BrH_{20}NO_2$: C, 60.97; H, 5.39; N, 3.74; O, 8.55. Found: C, 60.98; H, 5.35; N, 3.75; O, 8.58.

Bromotetrandrine (16). To a solution of tetrandrine (207 mg, 0.33 mmol) in trifluoroacetic acid (1 mL) and water(0.5 mL), a solution of bromine in acetic acid (0.35 mL of 1.1 M solution, 0.385 mmol) was added dropwise over a period of 5 min while stirring and warming over a steam bath. The solution was stirred for a further 45 min, then poured into a mixture of ice and water (20 mL) and slowly basified with concentrated ammonium hydroxide. Extraction with chloroform (2 × 50 mL) and evaporation of the extract gave a pale yellow oil which crystallized upon addition of anhydrous ether. The crystals (220 mg, 94%) were recrystallized from methanol–ether mixture (1:1) to give colorless needles of **16**: mp 142–144 °C; $[\alpha]^{28}_D$ +218.6° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} 209 nm (ϵ 79 200), 238 (28 700), 285 (7700); NMR ($CDCl_3$) δ 2.26 (s, 3 H, NCH_3), 2.46–4.47 (m, 14 H, aliphatic H), 2.60 (s, 3 H, NCH_3), 3.20 (s, 3 H, OCH_3), 3.32 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.02 (s, 1 H, ArH), 6.12–7.47 (m, 9 H, ArH); mass spectrum (high resolution) M^+ *m/e* 700.20734, 702.20702 (calcd for $C_{38}H_{41}N_2O_6Br$, 700.21583).

General Procedure for Bromine–Lithium Exchange. Reactions were carried out in a dry three-necked flask containing a magnetic stirring bar. Two of the necks were fitted with rubber septums and the third with an argon inlet. The flask was flushed with argon for 5 min while being heated with a Bunsen burner, and then kept under argon until the reaction was completed. Tetrahydrofuran (freshly distilled over lithium aluminum hydride) was introduced, then the flask containing the solvent was cooled in an acetone–dry ice bath. A solution of *n*-butyllithium (2.5 M in hexane) was introduced by a syringe through one of the rubber septums, followed by dropwise addition of the brominated starting material in tetrahydrofuran (freshly distilled over lithium aluminum hydride), again by a syringe through a rubber septum. The mixture was stirred in the acetone–dry ice bath for 45 min before carrying out the subsequent reaction of the lithiated alkaloid.

6′-Carboxylaudanosine (4). Bromolaudanosine (1.03 g, 2.35

mmol) in THF (12 mL) was added to a mixture of *n*-butyllithium (2.9 mL, 7.05 mmol) in hexane and THF (10 mL), and the mixture was allowed to stir for 45 min. The solution was then quickly poured into a dry ice–ether mixture. After evaporation of the solvent, the residue was distributed between 2 N hydrochloric acid and ether. The aqueous layer was washed once with ether, neutralized with sodium bicarbonate, then extracted five times with 100-mL portions of chloroform. After drying (Na_2SO_4), the chloroform extract was concentrated to 50 mL and diluted with anhydrous ether. Heavy white crystals formed on cooling at 0 °C over a period of 48 h. The crystals (905 mg, 95.8%) were recrystallized from benzene–ether to give the pure acid: mp 141–143 °C; UV (EtOH) λ_{max} 206 nm (ϵ 51 700), 250 (sh, 10 000), 283 (8000); ir (KBr) ν 1700 cm^{-1} (m, –COOH); NMR ($CDCl_3$) δ 2.58 (s, 3 H, NCH_3), 2.58–4.45 (m, 7 H, aliphatic H), 3.66 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.18 (s, 1 H, ArH), 6.41 (s, 1 H, ArH), 6.67 (s, 1 H, ArH), 7.65 (s, 1 H, ArH). Several attempts at elemental analysis gave erratic results. This compound was then characterized as its methyl ester (**5**).

6′-Carbomethoxylaudanosine (5). A solution of 6′-carboxylaudanosine (100 mg, 0.25 mmol) in methanol (50 mL) was treated twice with excess diazomethane (generated from 1.5 g of *N*-nitrosomethylurea) at room temperature at 24-h intervals. After evaporation of the solvent, the residue was shaken with a mixture of chloroform (50 mL) and water (50 mL). The chloroform layer was separated, dried (Na_2SO_4), and evaporated to a yellow oil, which crystallized upon addition of anhydrous ether. The white crystals (101 mg, 97%) had mp 130–131 °C; UV (EtOH) λ_{max} 207 nm (ϵ 35 500), 221 (sh, 3100), 256 (12 800), 286 (8900); IR (KBr) ν 1730 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 2.5 (s, 3 H, NCH_3), 2.45–3.7 (m, 7 H, aliphatic H), 3.62 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.19 (s, 1 H, ArH), 6.52 (s, 1 H, ArH), 6.63 (s, 1 H, ArH), 7.52 (s, 1 H, ArH); mass spectrum *m/e* 415 (M^+).

Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.43; H, 7.11; N, 3.52.

6′-Hydroxylaudanosine (6). A. Using *tert*-Butoxyperbenzoate. 6′-Bromolaudanosine (437 mg, 1 mmol) in THF (7 mL) was added to a solution of *n*-butyllithium (0.5 ml, 1.5 mmol) in hexane and THF (2 mL), then allowed to stir as described in the general procedure. To this mixture kept at the same temperature, a solution of *tert*-butoxyperbenzoate (316 mg, 1.63 mmol) in freshly distilled THF (10 mL) was added dropwise over a period of 15 min. After the addition was complete, the mixture was stirred for a further 3 h before being brought to room temperature, then poured into 3 N hydrochloric acid (50 mL). The mixture was heated on a steam bath until all THF had evaporated, cooled to room temperature, and washed with ether (2 × 50 mL). The aqueous layer was basified with sodium bicarbonate and then extracted with chloroform (3 × 50 mL). Evaporation of the extract gave a brown oil which was subjected to thin layer chromatography, eluting with chloroform–methanol (9:1). The band of R_f 0.7 gave a yellow oil which crystallized upon cooling. Recrystallization of the product (49 mg 13%) gave white needles of **6**: mp 133–134 °C; UV (EtOH) λ_{max} 210 nm (ϵ 29 300), 230 (sh, 13 700), 289 (7800); NMR ($CDCL_3$) δ 2.51 (s, 3 H, NCH_3) 2.51–3.76 (m, 7 H, aliphatic H), 3.64 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 6.34 (s, 1 H, ArH), 6.39 (s, 1 H, ArH), 6.45 (s, 1 H, ArH), 6.59 (s, 1 H, ArH); mass spectrum *m/e* 373 (M^+).

Anal. Calcd for $C_{21}H_{27}O_5N$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.56; H, 7.29; N, 3.71.

A small sample was converted to its HI salt, mp 183–185 °C (lit.[5] monohydrate, 184–186 °C) and HBr salt, mp 208–210 °C (lit.[16] 209–210 °C).

B. Using Nitrobenzene. A solution of 6′-bromolaudanosine (437 mg, 1 mmol) in THF (12 mL) was added to a solution of *n*-butyllithium (1.2 mL, 3 mmol) in hexane and THF (4 mL) and the mixture was allowed to stir as described in the general procedure. The solution was then immersed in a liquid nitrogen bath and nitrobenzene (1 g, 8.1 mmol) was added quickly. The mixture turned brown when brought up to −60 °C. After stirring at this temperature for 3.5 h the solution was brought to room temperature. A 10% solution of sulfuric acid (20 mL) was added and the mixture was washed with ether (2 × 50 mL). The aqueous layer was basified with concentrated ammonium hydroxide, then extracted with chloroform. Evaporation of the chloroform extract gave a brown oil which was separated by thin layer chromatography eluting with chloroform–methanol (9:1). The band of R_f 0.7 gave a yellow solid (251 mg, 65%) which was recrystallized from ether to give white needles of 6′-hydroxylaudanosine, identical in all respects with the sample obtained previously.

The band of R_f 0.5 afforded a slightly brown solid (107 mg, 30%) which, after recrystallization from petroleum ether, gave white needles, identical in all respects with authentic laudanosine.

3-Hydroxynuciferine (11). A. Using Nitrobenzene. A solution of 3-bromonuciferine (330 mg, 0.88 mmol) in THF (10 mL) was added to a solution of *n*-butyllithium (1.2 mL, 3 mmol) in hexane and THF (3 mL), then the mixture was allowed to stir as described in the general procedure. Addition of nitrobenzene (1 g, 8.1 mmol) followed by workup as described for 6′-hydroxylaudanosine gave the basic fraction which was separated by silica TLC eluting with chloroform–methanol (96:4).

The band of R_f 0.5 gave a yellow oil which crystallized upon addition of anhydrous ether. Recrystallization of the product (135 mg, 50%) from anhydrous ether afforded white needles of 3-hydroxynuciferine: mp 150–152 °C; $[\alpha]^{28}_D$ −83.7 (*c* 1.0, chloroform); UV (EtOH) λ_{max} 215 nm (ϵ 49 700), 240 (sh, 19 200), 283 (31 100), 292 (sh, 27 000); IR (KBr) ν 3200–3400 cm^{-1} (weak, OH); NMR ($CDCl_3$) δ 2.35–3.53 (m, 3 H, aliphatic H), 2.59 (s, 3 H, NCH_3), 3.77 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.87 (broad s, 1 H, disappeared on addition of D_2O, OH), 7.22–7.55 (3 H, $H_{8,9,10}$), 8.19–8.40 (m, 1 H, H_{11}); mass spectrum *m/e* 311 (M^+).

Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.49. Found: C, 73.40; H, 6.82; N, 4.48.

The band of R_f 0.6 gave a yellow oil (123 mg, 47%) which, after crystallization from petroleum ether, afforded needles identical in all respects with nuciferine.

The yield of 3-hydroxynuciferine was improved to 53%, along with 26% of nuciferine, in a larger scale reaction (6 mmol of bromonuciferine).

B. Using Pentadeuterionitrobenzene. A similar reaction was carried out using pentadeuterionitrobenzene in place of nitrobenzene. The yields of 3-hydroxynuciferine and nuciferine were comparable to those obtained from the previous reaction. The NMR of the nuciferine, however, showed 75% deuterium incorporation at the 3 position. Its mass spectrum showed M^+ at *m/e* 296 and characteristic peaks corresponding to the combination of nuciferine and 3-deuterionuciferine.

C. Using Other Reagents. Reactions were repeated using reagents **20, 21, 22,** and **23** under these conditions: (1) at −60 °C for 3 h, (2) at −60 °C for 1 h, then at room temperature overnight. Compounds **20, 21,** and **22** gave a trace of **11** and nuciferine (**8**) as the major product, while **23** gave approximately 40% of **11** and more than 50% of nuciferine.

3-Methoxynuciferine (12). A solution of 3-hydroxynuciferine (160 mg) in methanol (30 mL) was treated four times in succession with diazomethane generated from *N*-nitrosomethylurea (1 g) at 24-h intervals. The solvent was evaporated on a steam bath and the residue redissolved in chloroform (50 mL), then washed with 5% sodium hydroxide (50 mL). After drying with sodium sulfate, the solution was evaporated to give a pale yellow oil (120 mg, 72%). Crystallization from hexane afforded pale yellow needles of 3-methoxynuciferine: mp 105–106 °C (lit.[8] *dl* 105–106 °C); $[\alpha]^{28}_D$ −112.149° (*c* 0.214, chloroform); UV (EtOH) λ_{max} 212 nm (ϵ 43 000), 228 (sh, 25 100), 275 (21 400); NMR ($CDCl_3$) δ 2.42–3.48 (m, 7 H, aliphatic H), 2.66 (s, 3 H, NCH_3), 3.87 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 7.31–7.81 (m, 3 H, $H_{8,9,10}$), 8.35–8.60 (m, 1 H, H_{11}).

Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.13; N, 4.31. Found: C, 73.82; H, 7.21; N, 4.27.

A small sample was converted to its methiodide, which crystallized from methanol–ether, mp 212–216 °C dec (lit.[8] 214–216 °C).

Homomoschatoline (*O*-Methylmoschatoline, 14). A solution of 3-methoxynuciferine (108 mg, 0.33 mmol) in acetic acid (5 mL) was stirred with lead tetraacetate (492 mg of 90% reagent, 1.0 mmol) at room temperature for 12 h, then poured into a dilute sulfuric acid solution (20 mL) and the mixture was extracted with chloroform until the extract was almost colorless. Evaporation of the extract gave a dark brown oil which was separated by alumina thin layer chromatography eluting with chloroform. The band of R_f 0.7 gave an orange oil (32 mg, 30%) which had an NMR spectrum identical with that of homomoschatoline. Crystallization from methanol gave orange needles, mp 184–187 °C, alone or on admixture with an authentic sample.[11]

Thalidezine (Hydroxytetrandrine, 18). A solution of bromotetrandrine (525 mg, 0.75 mmol) in THF (10 mL) was added to a solution of butyllithium (0.9 ml, 2.25 mmol) in hexane and THF (3 mL), and the mixture was then stirred as described in the general procedure. Treatment with nitrobenzene (720 mg, 6 mmol) and workup as described for 6′-hydroxylaudanosine gave a brown oil which was separated by silica TLC, eluting with chloroform–methanol (95:5, saturated with concentrated ammonium hydroxide). The band of R_f 0.6 gave an oil which crystallized on addition of ether. The crystals (190 mg, 41%) were identical in all respects with tetrandrine. The band of R_f 0.5 gave an oil (270 mg, 57%) which was crystallized from acetone

to give pale yellow needles of thalidezine, mp 155–159 °C and undepressed on admixture with an authentic sample (lit.[12] mp 158–159 °C). These crystals have identical NMR and UV spectra and similar TLC behavior to the authentic sample.

Hernandezine (19). Treatment of thalidezine (110 mg) with diazomethane was carried out as described for 3-methoxynuciferine. Hernandezine (90 mg, 80%) was obtained which was identical in all respects with an authentic sample.[13]

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Cannabinoids. 3.[1] Synthetic Approaches to 9-Ketocannabinoids. Total Synthesis of Nabilone

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The 9-ketocannabinoid, nabilone (**6**), is of clinical interest as one of a new group of totally synthetic cannabinoids that possesses interesting central nervous system properties. Synthetic approaches to **6** from the resorcinol **1** were explored. Three unique approaches to 9-ketocannabinoids are reported (Schemes III, IV, and V) as well as two other approaches (Schemes I and II) that have precedent in the literature. The most efficient synthesis of **6** proceeds through the cis isomer **7** which is isomerized to **6** with $AlCl_3$ in CH_2Cl_2. The optical antipodes, **6a** and **6b**, of nabilone (**6**) can be prepared by two different synthetic routes (Schemes II and III). The most efficient method for the preparation of the optical isomers **6a** and **6b** is from nopinone (**14b**) by the method outlined in Scheme III.

The natural products of marijuana, *Cannabis sativa* L., have been the subject of intensified synthetic endeavors during the past decade.[2a,b] Undoubtedly, some of these efforts were undertaken with the recognition of the therapeutic potentials[3] manifested by this group of interesting compounds. Certainly, our synthetic efforts were motivated by the search for a therapeutically effective drug in the cannabinoid area.

During the course of these studies, our interest focused on a group of compounds containing a keto group at the 9 position of the dibenzo[*b,d*]pyran nucleus.[4] One of these 9-ketocannabinoids, nabilone (**6**), has been selected for clinical evaluation[5a,b] on the basis of its preclinical pharmacology.[5c]

Because the original synthesis (Scheme I) of **6** that we employed was low yielding and cumbersome, we looked for new approaches to the synthesis of 9-ketocannabinoids. This paper describes the results of this search for an efficient synthesis of **6**. Additionally, we report herein the application of a new and shorter synthetic route to the synthesis of the 3-*n*-pentyl analogue (**26**). Previously, **26** has been converted by others[6] into racemic Δ^8- and Δ^9-tetrahydrocannabinol (THC). We also report the preparation of the optical antipodes, **6a** and **6b**, of the parent compound **6** by two different approaches.

Results and Discussion

Scheme I outlines our initial approach to the synthesis of **6**. This reaction sequence follows the stepwise approach used by Fahrenholtz et al.[6] for the synthesis of the 3-*n*-pentyl analogues **25** and **26**. The resorcinol **1** was converted into the coumarin **2** by reaction with diethyl 2-acetylglutarate. Cyclization of **2** with NaH in Me_2SO[7] gave the tricyclic ketone **3** in 57% yield. Ketalization to **4** followed by Grignard reaction and strong acid hydrolysis afforded the α,β-unsaturated ketone **5**. Reduction of **5** with Li[8] in liquid NH_3 gave, after separation of the cis isomer **7**, the desired trans isomer **6**. The overall yield from **1** was 24% by this route. The cyclization of **2** to **3** was difficult to perform on a scale larger than 1 mol and never gave greater than 70% yield. Additionally, the chromatographic (and/or crystallization) separation of the trans isomer **6** from the approximately 20% impurity of the cis isomer **7** was difficult. Thus, we sought a better synthetic approach to 9-ketocannabinoids of the type represented by nabilone **6**.

The approach described in Scheme II was chosen primarily because it permitted the use of either (−)- or (+)-α-pinene as