SYNTHESIS OF PROAPORPHINE ALKALOIDS

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Abstract - The synthesis of proaporphine alkaloids has been reviewed.

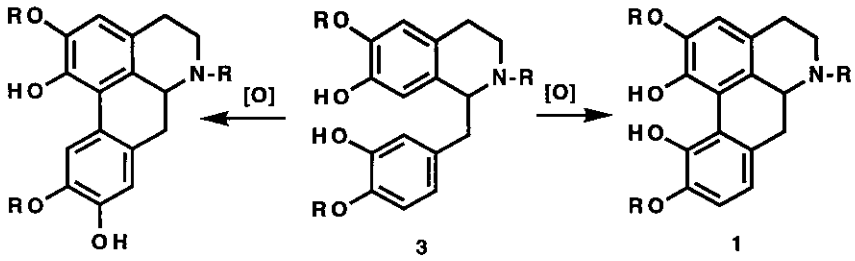
Dedicated to Dr. Arnold Brossi on the occasion of his seventieth birthday

INTRODUCTION

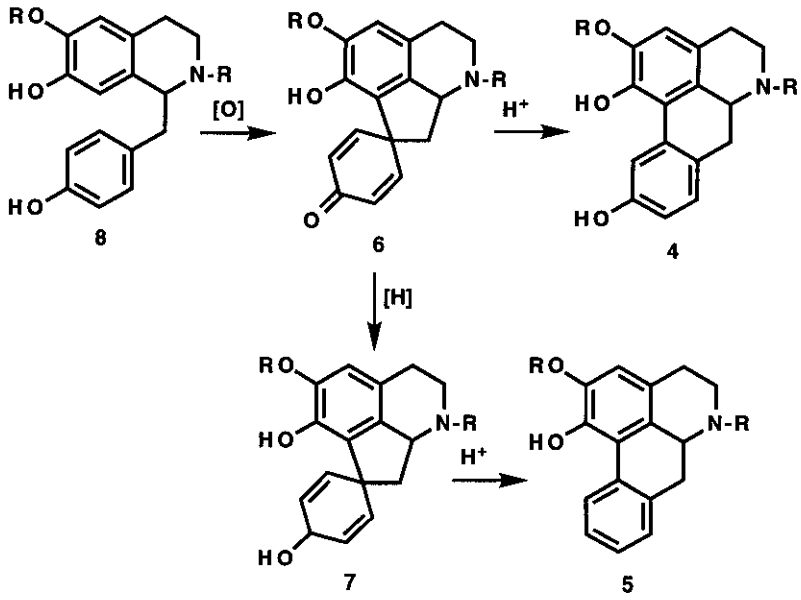
Several syntheses of naturally occurring proaporphine alkaloids have been described. The earlier syntheses utilized classical ring construction methods to develop the 2,5-dienone ring system. The more recent syntheses proceed through a C-8, C-1' coupling reaction of various 1-benzyl-1,2,3,4-tetrahydroisoquinolines. This review will consider the syntheses of proaporphine alkaloids cited in the literature through October 1993.

1. Origin of Proaporphine Alkaloids

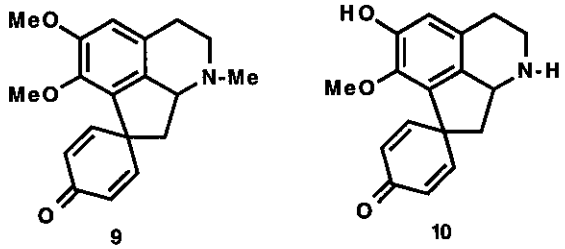
In 1957, Barton and Cohen reported their results of a biogenetic study[1] on a variety of natural products. In considering the mechanistic pathway of aporphine synthesis, they found that aporphines having certain substitution patterns (e.g., **1** or **2**) could be formed by direct phenolic oxidative coupling of the appropriately substituted benzyl-1,2,3,4-tetrahydroisoquinoline (**3**).



In contrast, a direct oxidative coupling mechanism could not explain the formation of aporphine alkaloids having substitution patterns such as **4** or **5**. Barton and Cohen postulated that these aporphines could be produced from a dienone (e.g., **6**) or dienol (e.g., **7**) type intermediate (generated from oxidative coupling of **8**). Since the time of their conception, alkaloids having a skeletal structure like that of **6** have become known as proaporphines.[2,3]



Barton and Cohen's theory received support in 1963 with the isolation and structure elucidation of (±)-pronuciferine[4] (**9**) and (±)-crotonosine[5] (**10**), the first members of the proaporphine class of alkaloids.



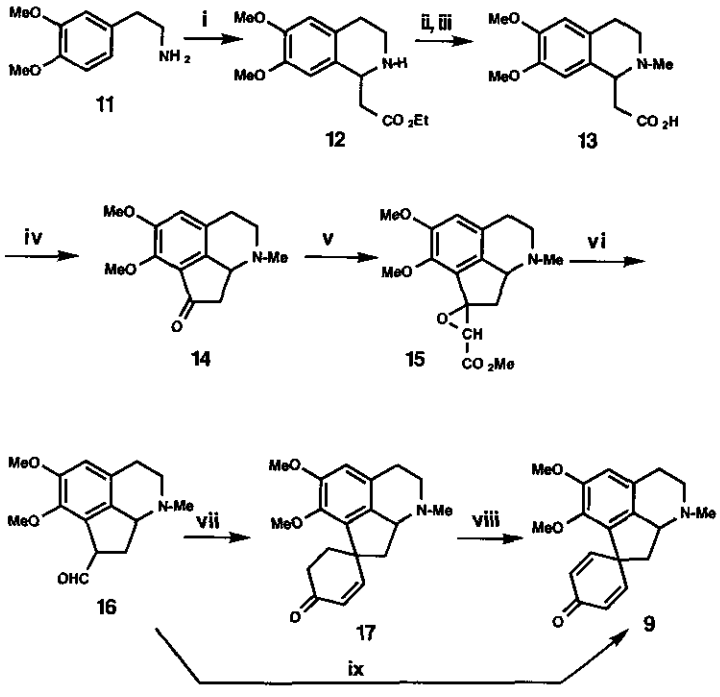
2. Synthetic approaches to the Proaporphine Alkaloids

Since the time of their original isolation, the proaporphine alkaloids have received only moderate synthetic attention. In general, the overall yield of proaporphine formation is quite low. In the following sections we will discuss the different methods of proaporphine synthesis that have been reported. The following section (**2.1**) describes linear multi synthesis not involving benzyltetrahydroisoquinolines as intermediates. The subsequent sections all involve the direct formation of a dienone from a benzyltetrahydroisoquinoline precursor.

2.1 Tricyclic Ketone Cyclization

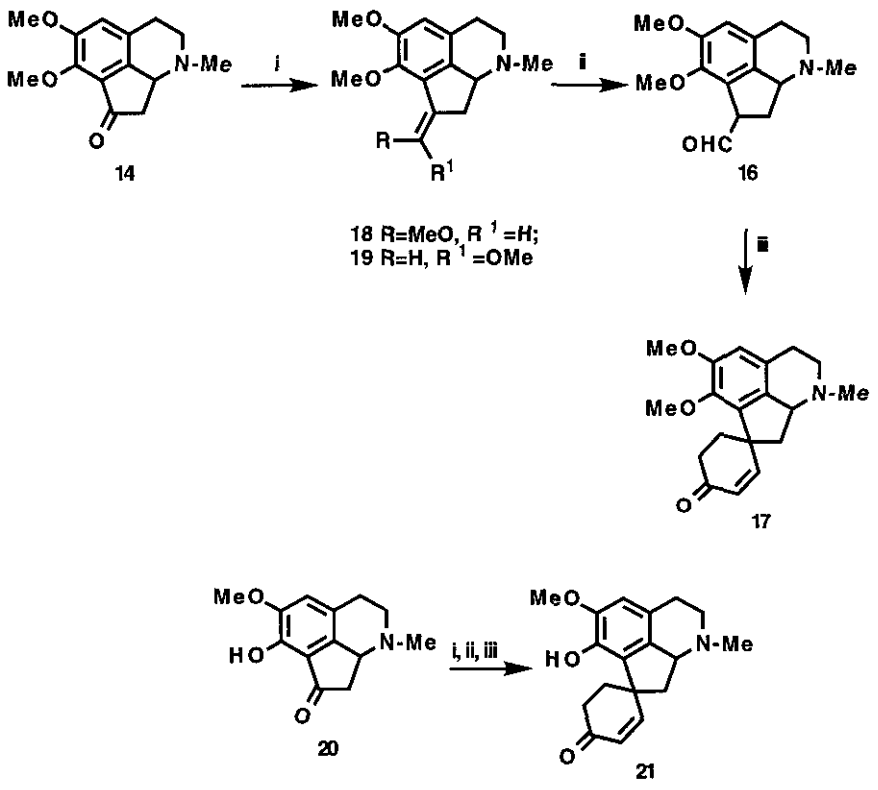
In 1964 Bernauer reported the first total synthesis of a proaporphine alkaloid, pronuciferine[6] (**9**). This approach, which uses a classical Robinson annulation to construct the dienone ring, proceeds as follows. Homoveratrylamine (**11**) was converted to the known amino ester (**12**) *via* a standard Bischler-Napieralski synthesis. *N*-Methylation of **12,** followed by hydrolysis of the ester afforded the amino acid (**13**). Treatment of **13** with polyphosphoric acid gave the cyclic ketone (**14**). Reaction of **14** with methyl chloroacetate and

sodium amide produced the glycidic ester (**15**). Hydrolysis and decarboxylation of **15** afforded the aldehyde (**16**). Under strongly basic conditions, the aldehyde (**16**) was condensed with methyl vinyl ketone to afford (±)-amuronine (**17**) (39%). Oxidation with DDQ provided (±)-pronuciferine (**9**) (14%). Condensation of **16** with methyl ethynyl ketone led directly to (±)-pronuciferine (**9**) (6%).



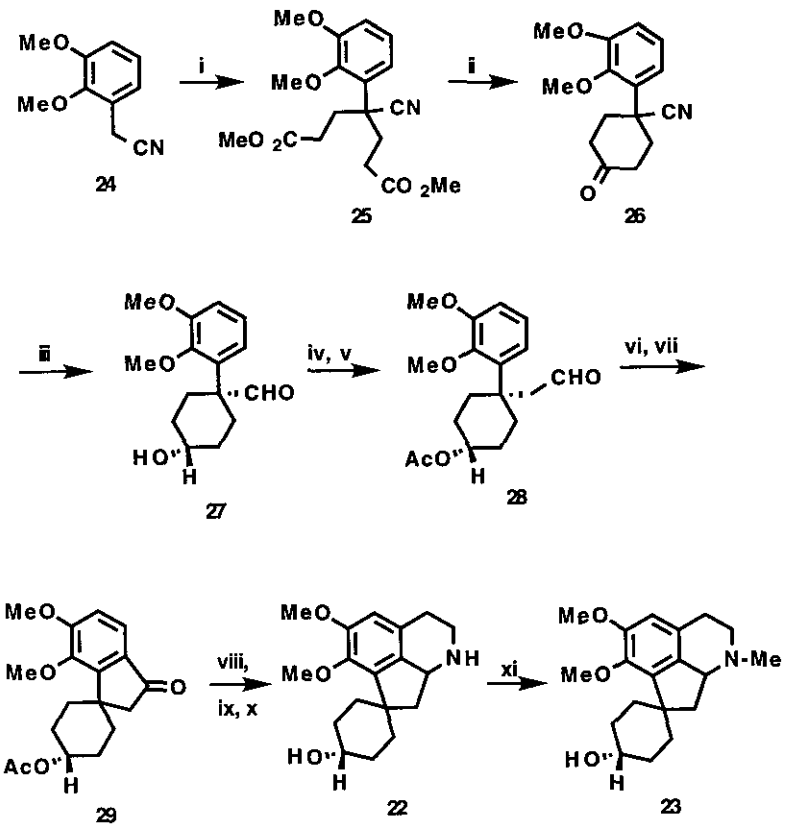
i. $EtO_2CCH_2CO_2Et$; ii. Methylation; iii. ^-OH; iv. PPA; v. $ClCH_2CO_2Me$, $NaNH_2$;vi. ^-OH, heat; vii. $H_2CCHC(O)Me$; viii. DDQ; ix. HCCC(O)Me, base.

In 1975, Casagrande reported an improved variation[7] of Bernauer's approach. Beginning from the tricyclic ketone (**14**), condensation with a methoxymethyl-phosphonium ylide gave a mixture of the enol ethers (**18**) and (**19**). Hydrolysis of this mixture with aqueous methanesulphonic acid produced the aldehyde (**16**) which was then converted to (±)-amuronine (**17**) (12% overall yield) by a Robinson annulation using methyl vinyl ketone. A similar procedure was employed in the conversion of the ketone (**20**) to (±)-11,12-dihydroglaziovine (**21**).



i. $MeOCH_2PPh_3$;ii. aq $MeSO_3H$;iii. $H_2CCHC(O)Me$, base.

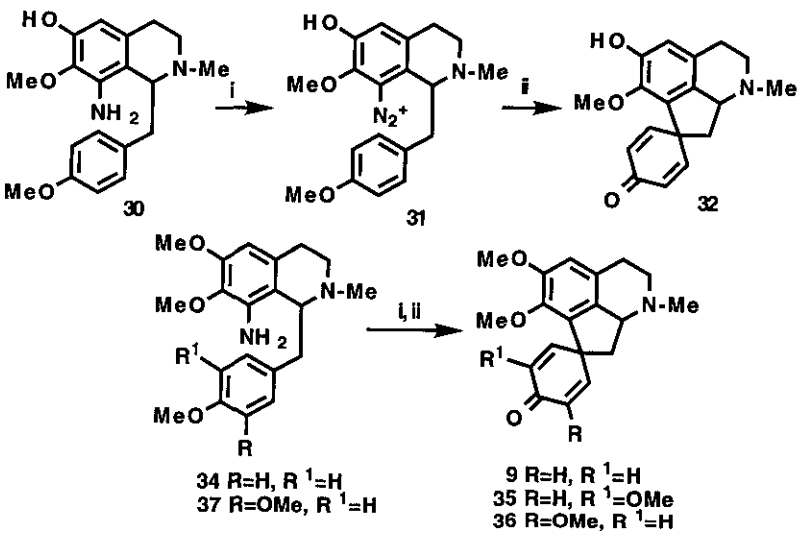
Similar to Bernauer's construction of the proaporphine ring system, Huffman and Opliger's approach[8,9] utilizes classical methods of ring construction. However, in this route the isoquinoline ring system is constructed at the end of the synthesis rather than at the first. A Friedel-Crafts acylation followed by a Bobbitt cyclization led to the two proaporphines (±)-hexahydrostepharine (**22**) and (±)-hexahydropronuciferine (**23**). This type of synthetic approach is illustrated below. Condensation of 2 equivalents of methyl acrylate with 2,3-dimethoxyphenylacetonitrile (**24**) gave the diadduct (**25**), which underwent a classical Dieckmann cyclization to afford the cyclohexanone (**26**). Treatment of **26** with LAH gave the direduced compound(**27**). Protection of the hydroxyl group of **27** as its acetate, followed by treatment with methoxy-methylenetriphenylphosphorane gave, after hydrolysis, the extended aldehyde (**28**). Chromium oxidation and Friedel-Crafts cyclization afforded the cyclic ketone (**29**), which was subjected to standard Bischler-Napieralski conditions to produce (±)-hexahydrostepharine (**22**) (3.3%, overall). Methylation of afforded (±)-hexahydropronuciferine (**23**).



i. 2 equiv CH_2CHCO_2Me; ii. base; iii. LAH; iv. ClCOMe; v. methoxymethylene-triphenylphosphorane; vi. CrO_3; vii. $AlCl_3$; viii. $H_2NCH_2(OMe)_2$; ix. $NaBH_4$; x. 6N HCl, Pd/C; xi. Methylation.

2.2 Pschorr Cyclization

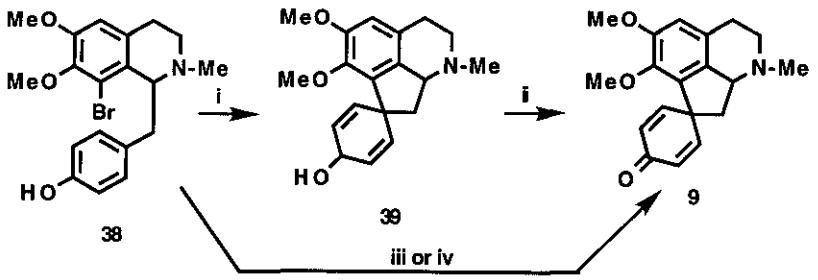
In 1970, Ishiwata reported the first proaporphine synthesis utilizing a Pschorr cyclization.[10,11] Ishiwata found that the 8-aminobenzyltetrahydroisoquinoline (**30**) could be diazotized with sodium nitrite and dilute acid to give the corresponding diazonium salt (**31**). Decomposition of **31** with an excess of sodium acetate resulted in para coupling and *in situ* demethylation affording the proaporphine (±)-homolinearisine (**32**) in a 10% overall yield. Similarly, Ishiwata[12] synthesized (±)-pronuciferine (**9**) from **34**, and obtained a mixture of (±)-*O*-methylorientalinone (**35**) and its diastereomer (**36**) from the 8-aminotetrahydrobenzylisoquinoline (**37**).[13]



i. $NaNO_2$, H^+;ii. $MeCO_2Na$.

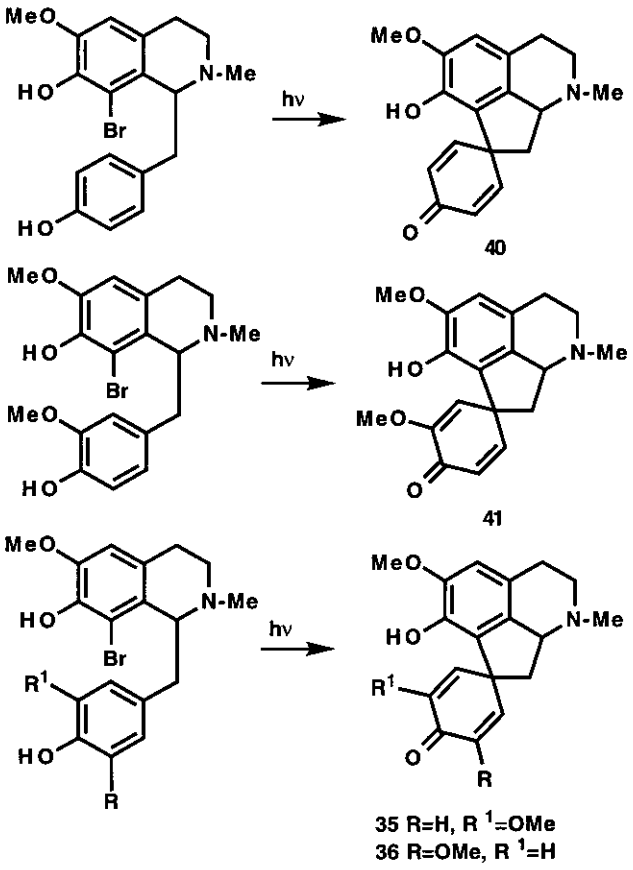
2.3 Photolytic Cyclization

In 1971, Horii reported the first proaporphine synthesis *via* a photolytic cyclization[14] of a 1-benzyltetrahydroisoquinoline. When irradiated in aqueous sodium hydroxide in the presence of sodium borohydride, the 8-bromobenzylisoquinoline (**38**) led to the cyclized dienol (**39**). Oxidation of **39** with manganese dioxide afforded (±)-pronuciferine (**9**) in a 4% overall yield. Kametani[15] found that irradiation of the same starting benzylisoquinoline(**38**) in methanolic sodium hydroxide in the absence of sodium borohydride, led to direct formation of (±)-pronuciferine (**9**) in a slightly improved yield (10%). When the methanol was replaced with ethanol and copper powder was added to the reaction, the yield increased to 17%.

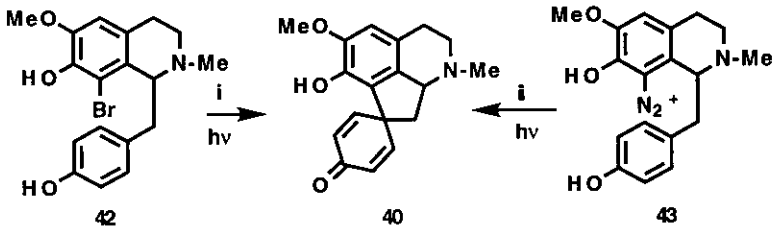


i. aq NaOH, $NaBH_4$, *hv*; ii. MnO_2; iii. MeOH-NaOH, *hv*; iv. EtOH-NaOH, Cu powder.

Similarly, Kametani utilized a photochemical dehydrobromination in the syntheses of the proaporphines (+)-glaziovine[16] (**40**) (7-10%, last step), (±)-orientalinone[17] (**41**) (9%, last step), and a mixture of (±)-*O*-methylorientalinone (**35**) and its diasteromer (**36**) (mixture 10.5%, last step).[15]



In 1975, Casagrande reported an improved synthesis of (±)-glaziovine[18] (**40**) *via* the photolysis of (±)-8-bromo-*N*-methylcoclaurine (**42**) (26% last step, 14.4%overall). Irradiation of the diazo analog (**43**) also gave a better yield of (±)-glaziovine (**40**) (45% last step, 22% overall).



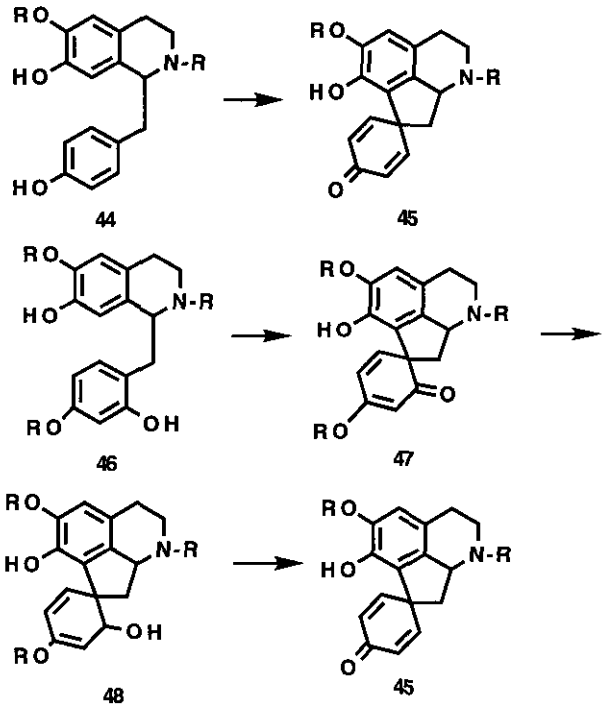
42 40 43

i. trisodium phosphate dodecahydrate, H_2O.

2.4 Phenolic Oxidation

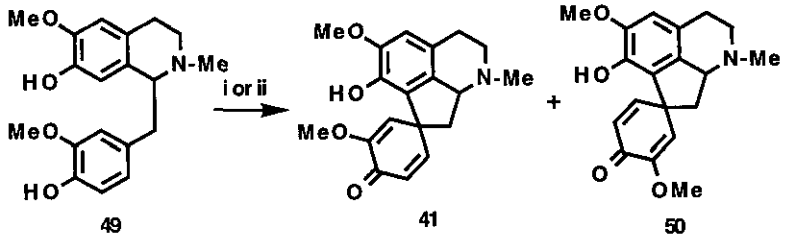
The most frequent method of proaporphine synthesis has been that of chemically produced phenolic oxidative coupling. This route requires as a starting material a 1-benzyltetrahydroisoquinoline with a hydroxyl group at the

C-7 position and one at either the C-2' or C-4' positions. 1-Benzylisoquinolines with a C-4' hydroxy group (e.g., **44**) proceed directly to the expected 2,5-dienone (**45**), while C-2'-hydroxybenzyltetra-hydroisoquinolines (e.g., **46** initially form a 2,4-dienone ring (e.g., **47**) which can be reduced to the dienol (**48**) and rearranged in MeOH-HCl to the corresponding 2,5-dienone (**45**).



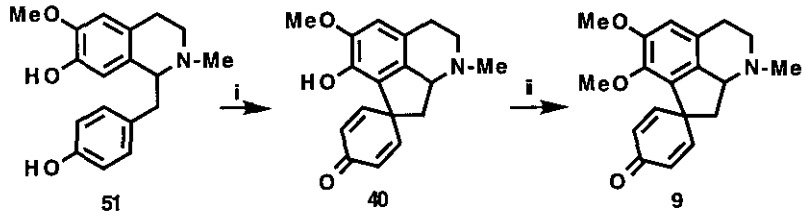
C-4'-Hydroxytetrahydrobenzylisoquinolines

The first synthesis of a proaporphine alkaloid *via* a phenolic oxidative coupling of a C-4'-hydroxytetrahydrobenzylisoquinoline was reported by Battersby in 1964.[19,20] When treated with potassium ferricyanide, (±)- orientaline (**49**) afforded a mixture of (±)-orientalinone (**41**) and its diasteromer (**50**). Similarly, Kametani[21] has reported the oxidation of **49** with cuprous chloride in pyridine, which likewise afforded a mixture of the diastereomers (**41**) and (**50**) (mixture 19.4%, last step).



i. $K_3Fe(CN)_6$;ii. CuCl, C_6H_5N.

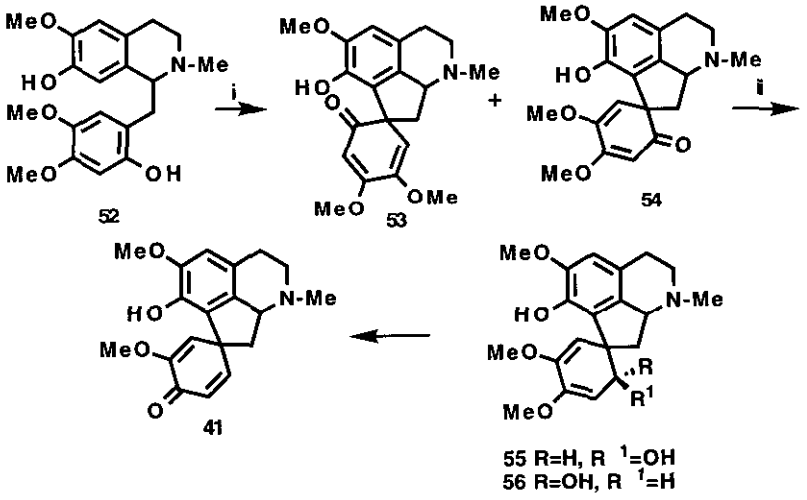
Kametani has also reported the oxidation[22] of (±)-*N*-methylcoclaurine (**51**) with potassium ferricyanide as a new synthesis of (±)-glaziovine (**40**) (1.2%, last step). *O*-Methylation of **40** provided (±)-pronuciferine (**9**).



i. $K_3Fe(CN)_6$, ii. CH_2N_2.

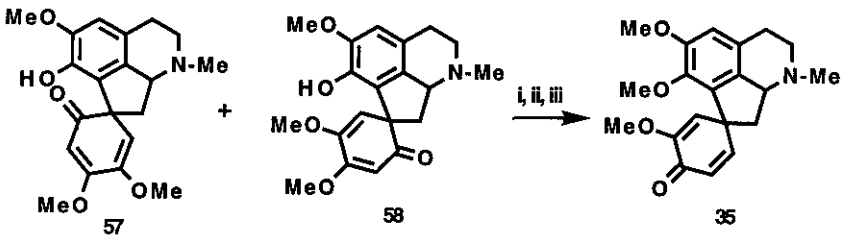
C-2'-Hydroxytetrahydrobenzylisoquinolines

In 1965, Jackson and Martin published their synthesis of (±)-orientalinone (**41**) *via* oxidative coupling of the C-2'-hydroxytetrahydrobenzylisoquinoline (**52**). Treatment of **52** with potassium ferricyanide afforded a separable mixture of the diastereomeric 2,4-dienones (**53**) and (**54**). Sodium borohydride reduction of **54** led to a mixture of dienols (**55**) and (**56**), which was converted to (±)-orientalinone (**41**) (13% overall yield) in aqueous acid.



i. $K_3Fe(CN)_6$, ii. $NaBH_4$, iii. aq. acid.

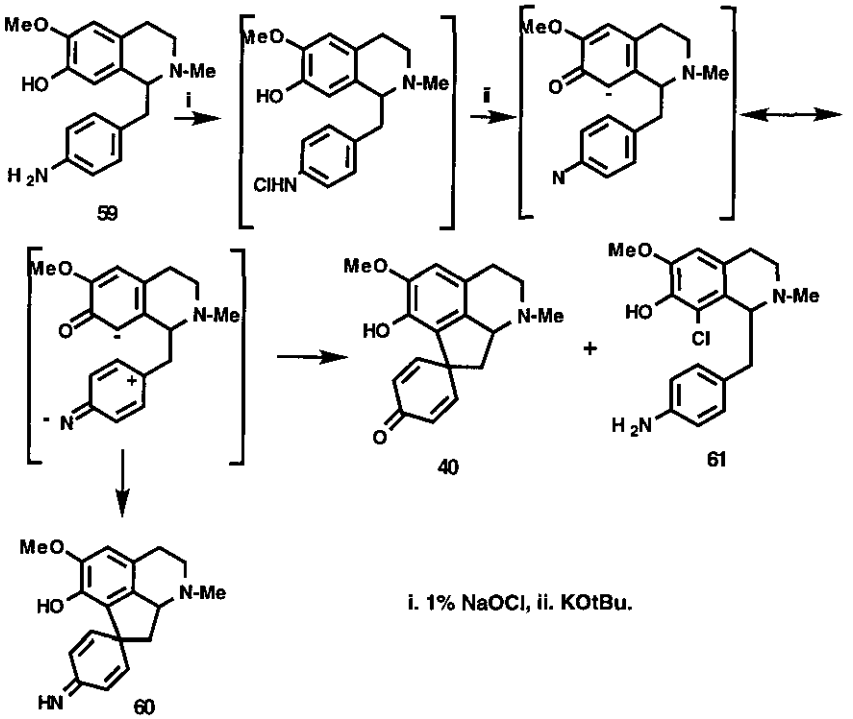
Shamma had previously shown that methylation of the mixture of diastereomeric dienones (**57**) and (**58**), followed by reduction and rearrangement in MeOH-HCl afforded (±)-*O*-methylorientalinone (**35**) (10%, overall).[24]



i. MeI, ii. $NaBH_4$, iii. MeOH-HCl.

2.5 Nitrene-Based Synthesis

In an attempt to improve the usually poor yielding phenolic oxidation and photolytic routes from 1-benzylisoquinolines, Kametani reported an attempt to carry out an 8-1' ring closure *via* a novel nitrene mechanism.[25] Starting from the 4'-aminobenzylisoquinoline (**59**), treatment with 1% sodium hypochloride followed by 2 equivalents of potassium *tert*-butoxide was expected to give the imino compound **60** *via* the pathway shown in Scheme. Upon workup, it was found that its hydrolysis product, (±)-glaziovine (**40**) was produced in only a small amount, with the main product being the simple halogenation product (**61**). No additional reports using this approach since have appeared.



i. 1% NaOCl, ii. KOtBu.

ACKNOWLEDGMENT

This work was supported by a grant from the National Institutes of Health (GM44713).

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Received, 3rd March, 1994