AN ABSTRACT OF THE THESIS OF

Wesley Kwan Mung Chong for the degree of Doctor of Philosophy in Chemistry presented on January 6, 1983.

Title: Phenolic Oxidative Coupling: An Approach to the Synthesis of Pretazettine.

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Dr. James D. White

Various hypervalent iodine compounds were evaluated as reagents for intramolecular phenolic oxidative coupling. It was found that phenyliodine(III) bis(trifluoroacetate) was effective for the coupling of the monophenolic substrate 13a to 14a under neutral conditions. Vanadium oxytrifluoride and hypervalent iodine compounds were compared as oxidants for the conversion of 32 to 33.

In an approach directed at a synthesis of pretazettine (17), phenacylamine 57 was elaborated in two steps to oxazole 50. However, this did not undergo catalytic hydrogenation to the desired oxazolidine 47. Oxazoline 60 proved to be too labile to be isolated upon dehydration of 65, which was prepared from dl-octopamine (64) and the acid chloride of piperonylic acid (58). Finally, 64 and piperonal (69) were condensed and treated with ethyl chloroformate to provide trans-2,5-diaryloxazolidine 73. However, the latter was hydrolyzed under coupling conditions. Alternatively, when octopamine and piperonal were condensed and hydrogenated, amine 74 was obtained, which was in turn reacted with 1,1'-carbonyldiimidazole (75) to furnish the 2-oxazolidinone 76. Exposure of 76 to vanadium oxytrifluoride led

to 78, which apparently arose from an undesired, spontaneous rearrangement of the coupling product 77. Attempts to synthesize ether 79 starting with synephrine (81), 2-nitrostyrenes 86, and 4-hydroxymandelates 90 are described.

The oxazolidine 97 was prepared from the condensation of synephrine 81 and treated with methyl chloroformate in the presence of methanol to afford acetal 100 in 71% yield. Phenyliodine(III) bis-(trifluoroacetate) was employed to couple 100 to 101 in 5 to 7% yield. Hydrolysis of the urethane moiety of 101 with potassium hydroxide in ethylene glycol gave the amine 105, which underwent a spontaneous cyclization to 107. Formation of the unnatural, cis B-D ring fusion stereochemistry in this ring closure was ascertained by nuclear magnetic resonance spectroscopy.

Phenolic Oxidative Coupling:

An Approach to the Synthesis of Pretazettine.

by

Wesley Kwan Mung Chong

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Typed by Jackie Carter, Karen M. Johnson and Judy Davies for Wesley Kwan Mung Chong

To the memory of my grandfather, Kun Ung Chun.

And also to Ranann Taylor's outlook on life.

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PHENOLIC OXIDATIVE COUPLING:

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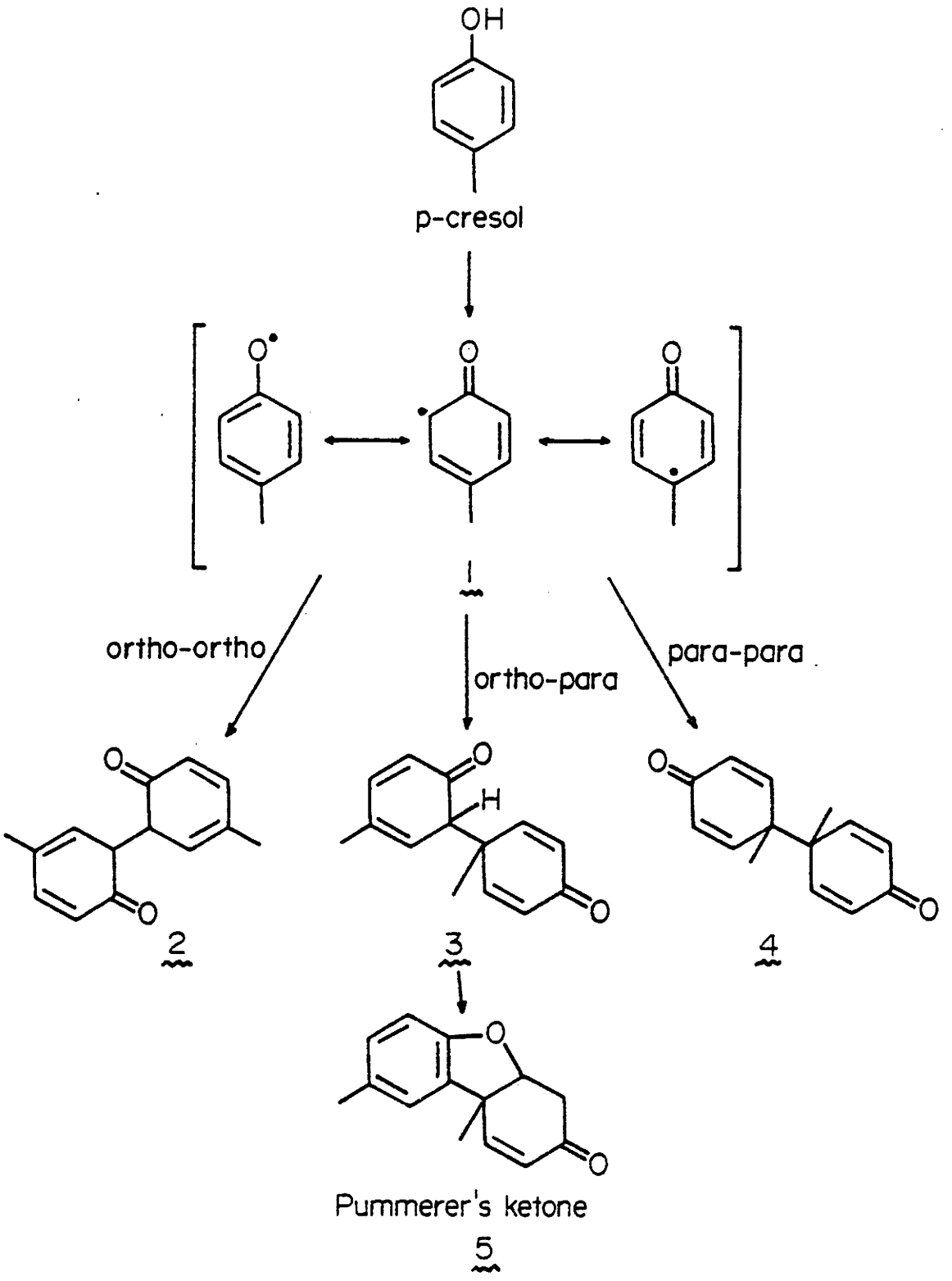
I. INTRODUCTION

The central role of phenolic oxidative coupling in biosynthesis was first proposed by Barton and Cohen in 1957.[1] Extensive feeding experiments employing precursors labelled with radioactive isotopes have been used to verify plant secondary metabolic pathways which use this process for the linkage of aromatic rings. The examples studied encompass a diverse array of compounds, such as lignins, lignans, tannins, plant and insect pigments, the hormone thyroxine, several antibiotics, and an estimated 10% of all known alkaloids. Yet, this direct and elegant approach to complex, multi-ringed natural products remains to be simulated effectively in the laboratory.

As early as 1925, Pummerer had already examined the dimeric products obtained from phenols with certain oxidants.[2] A corrected structure presented for the ketone 5, which is now referred to by his name, was based on a postulated phenoxy radical 1 from p-cresol using simple resonance considerations. Oxidative coupling never reflected oxygen-oxygen or oxygen-carbon bond formation and, as expected, the position meta to the phenol was not substituted. Coupling proceeded ortho-ortho to give intermediate 1, ortho-para to 3, and para-para to 4. The predominance of intermediate 3 was shown after a spontaneous internal Michael addition led to Pummerer's ketone 5 as the major isolable product. Later, Scott[3] used this reaction for a comparison between various oxidative coupling reagents, as seen in Table I.


OH
p-cresol
O
O
O
1
ortho-ortho
ortho-para
para-para
O
O
2
O
H
O
3
O
O
4
O
O
Pummerer's ketone
5

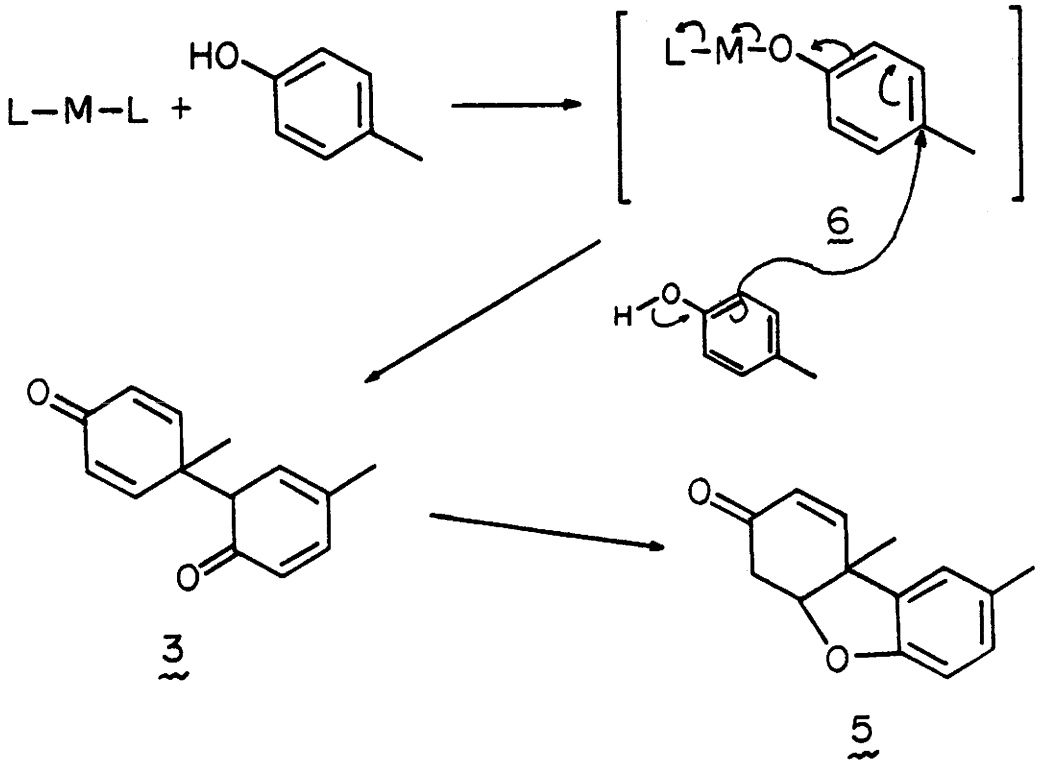
SCHEME 1

Table I. Oxidative Coupling of p-Cresol with Various Oxidants to Pummerer's Ketone (5).

Oxidant	Yield of 5, %
$K_3Fe(CN)_6$	20
$MnO_2/CHCl_3$	22
PbO_2/benzene	18
electrooxidation (Pt anode)	10
$FeCl_3$	1.4
Fenton's reagent	18
Horseradish peroxidase/H_2O_2	13.4
Polyporus versicolor (cell-free extract)	50

Examination of Table I shows that earlier phenolic coupling procedures in the laboratory utilized reagents known to generate radical species, and the one-electron mechanism shown in Scheme 1 was an adequate depiction. More recently, oxidants[4] such as vanadium oxytrichloride, vanadium oxytrifluoride, tris(acetylacetonato)manganese(III), thallium tris(trifluoroacetate) and ferric chloride-dimethylformamide complex have been shown to be effective for intramolecular phenolic oxidative coupling. This newer generation of reagents suggests that coupling can be accomplished via an overall two-electron, heterolytic process, as depicted in Scheme 2. Typically, a metal complex is envisioned as exchanging one of its ligands for a phenol, creating electron-deficient species 6. Electrophilic addition of a phenol in the customary ortho or para manner would then occur, with simultaneous

reductive elimination on the metal center. A more specialized role for the reagent must be recognized for this mechanism, which can explain added regioselectivity due to steric or templating effects.



SCHEME 2

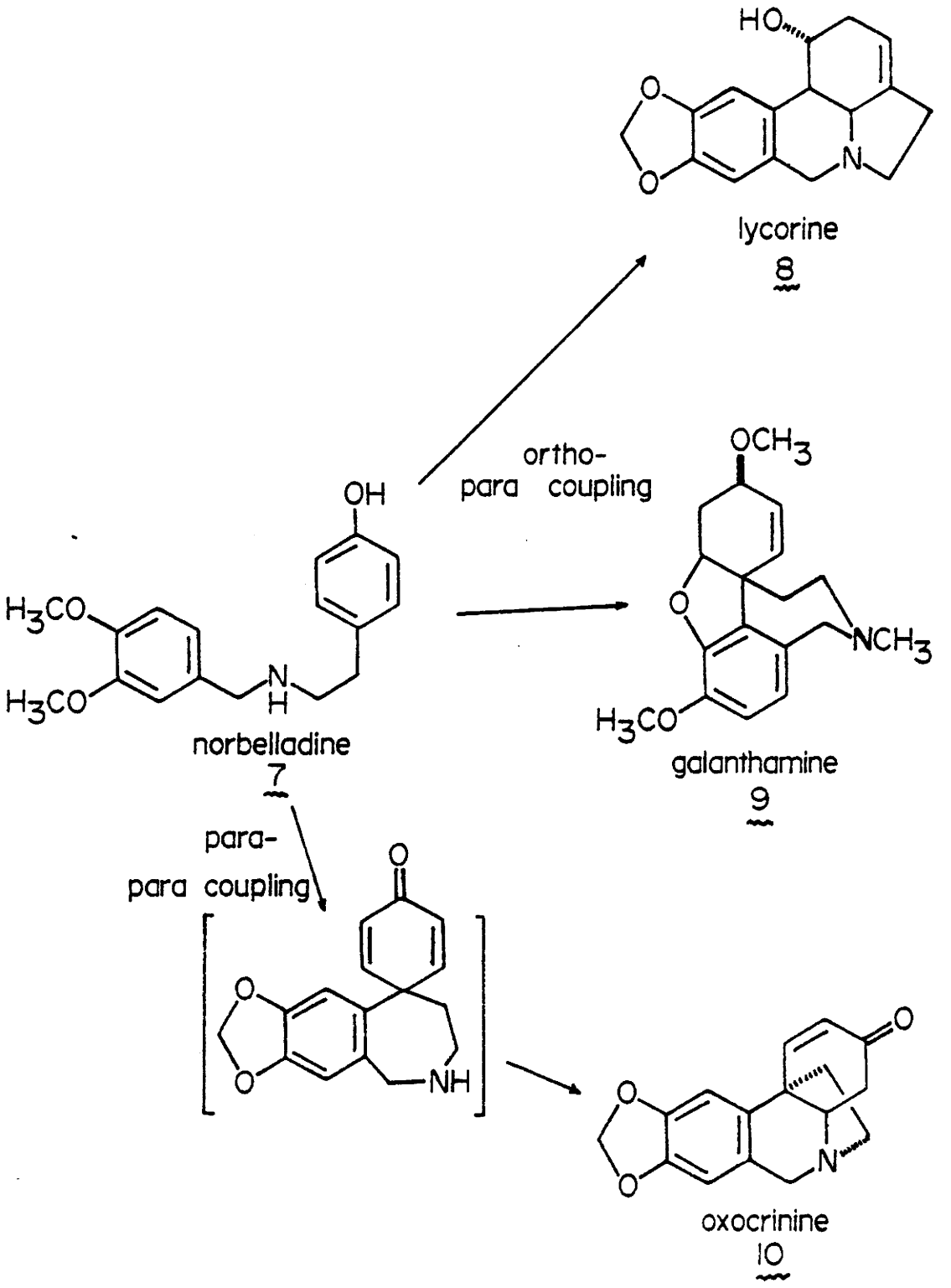
Although these two general mechanisms might only serve as conceptual tools for depicting the coupling process, the exact mechanism probably depends on the particular case.[3,5] Related to the issue of mechanism are several important questions. For example, is the oxidizing species known to exist in discrete oxidation states differing by one or two electrons? Is the substrate in the case of intramolecular coupling a monophenolic, diphenolic, or nonphenolic compound? This field remains open for investigation, and one should be aware of the alternative intermediates recently presented. Ronlán and Parker[6] suggest that radical cations are generated in anodic couplings, while

Miller[7] claims to have observed dications. Taylor and McKillop,[8] in view of the aromatic acetoxylation products isolated in their examples, also proposed that dications are produced by thallium tris(trifluoroacetate).

Regardless of its mechanism, phenolic oxidative coupling in the laboratory has been plagued with low yields of products and its practicality in synthesis has therefore been severely limited. In particular, the presence of polymeric by-products, difficult workup, and separation problems all reduce the efficiency of the reaction. A somewhat more promising view of phenolic oxidative coupling as a general synthetic method has been offered by the heterolytic, or "two electron" oxidants, which should be amenable to more extensive reagent design.

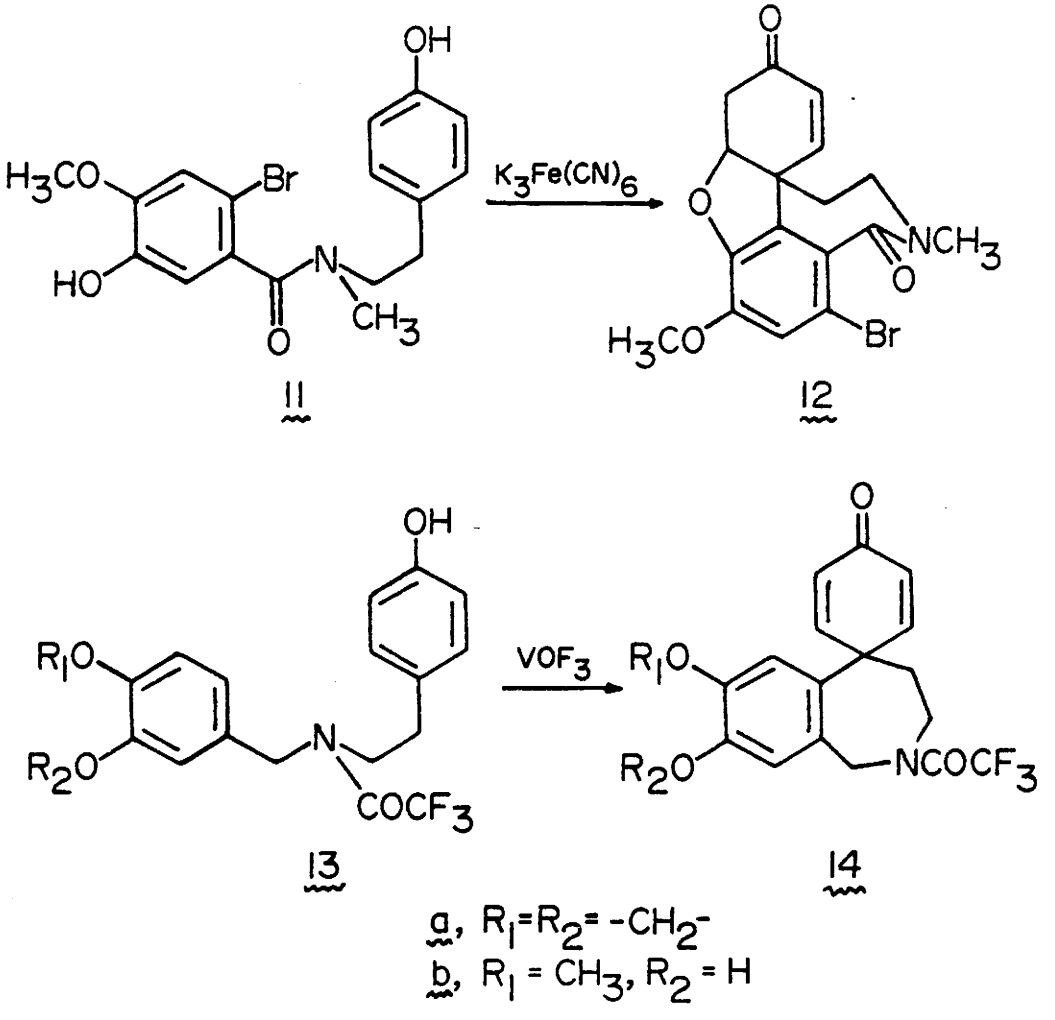
A survey of biomimetic syntheses among alkaloids of the Amaryllidaceae or narcissus family, provides a good overview of the extent to which intramolecular phenolic oxidative coupling has found application. The extensive research carried out on the biosynthetic pathway[9] to this family of metabolites has conclusively proven Barton's original suggestion that O-methylnorbelladine (7) is the single precursor to three distinct structural classes, as shown in Scheme 3. In attempting to simulate the characteristic coupling pattern found in these alkaloid families, Kametani showed that the benzamide 11 was oxidized with potassium hexacyanoferrate(III) to give a precursor 12 of the analgesic galanthamine (9) in 40% yield.[10] Further success has recently been obtained in the para-para coupling of mono[11] and diphenolic[4] N-benzylphenethylamines 13, exemplified by Kupchan's use of vanadium oxytrifluoride to provide synthetically useful yields of dienones 14.

Biosynthesis of Amaryllidaceae Alkaloids



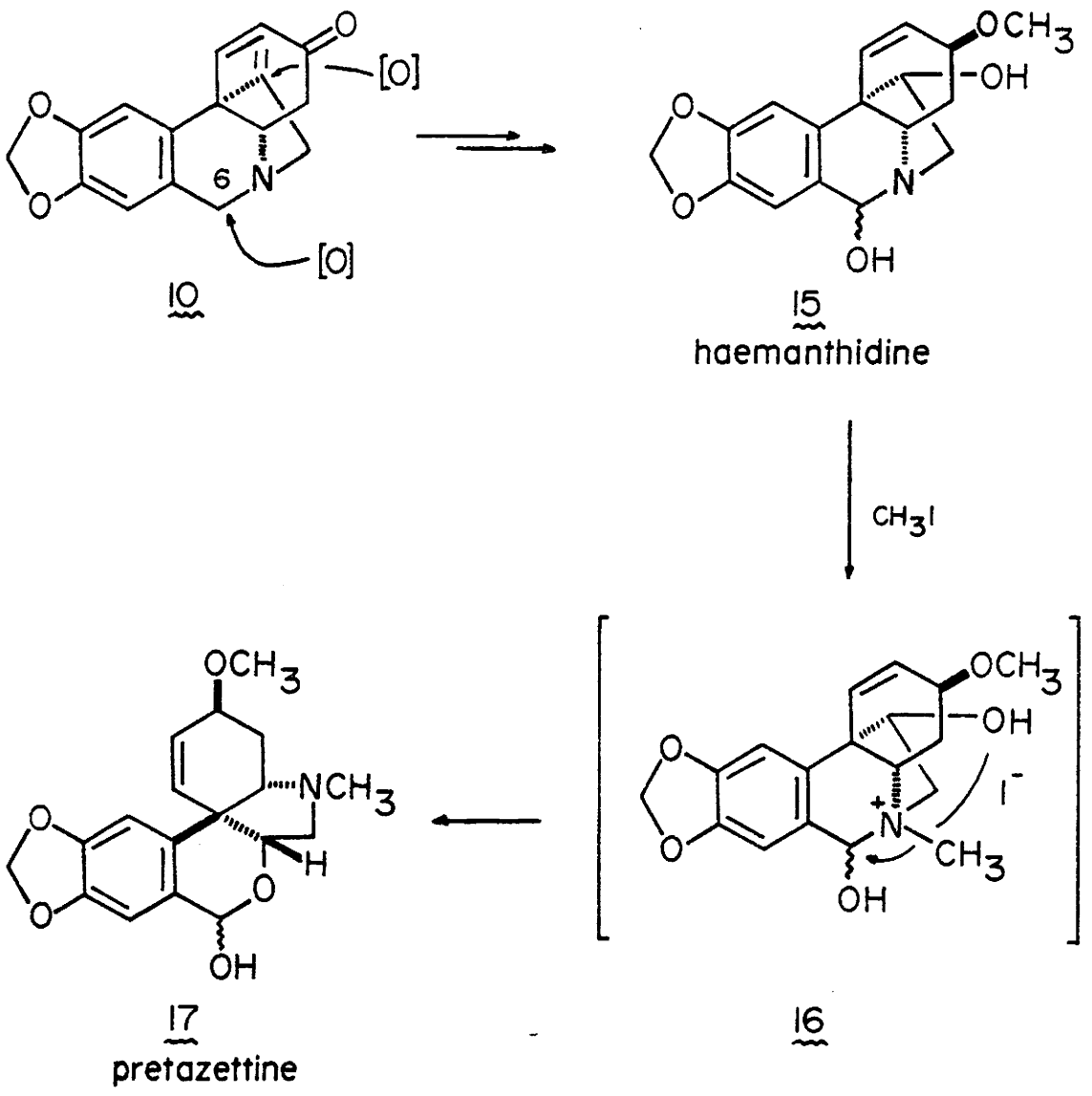
SCHEME 3

Deprotection of the nitrogen in 14b was followed by a spontaneous Michael reaction to yield (±)oxocrinine (10), a representative of the crinine class of alkaloids. It is presumed that subsequent



SCHEME 4

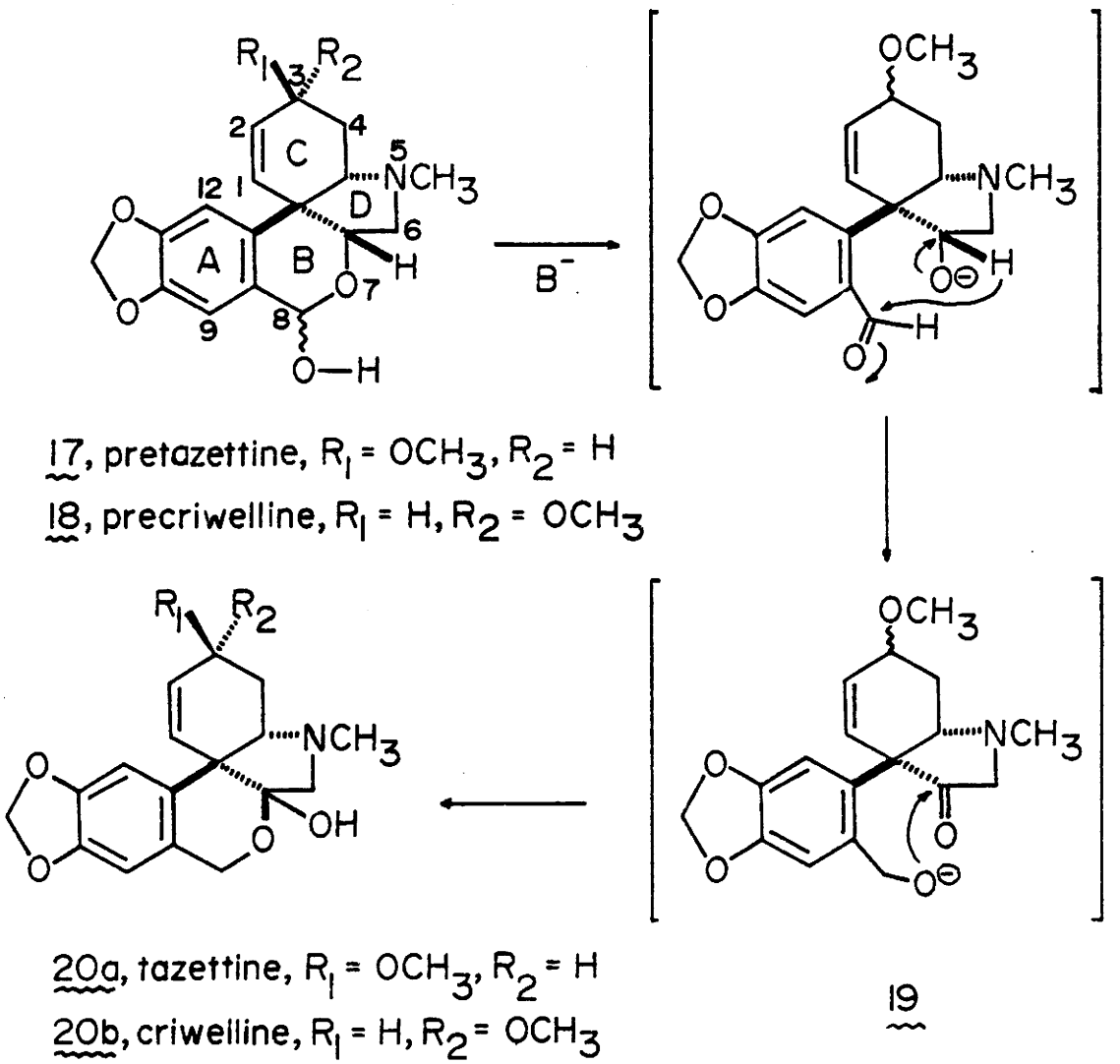
biological oxygenation of the oxocrinine skeleton, 10, at C-6 and C-11 leads to haemanthidine (15). These 6-hydroxy[5,10b]ethanophenanthridine compounds are biological as well as chemical precursors of the [2]benzopyrano[3,4c]indoles, exemplified by pretazettine (17). The latter arises via rearrangement of the quaternary ammonium species 16, as depicted in Scheme 5.[12]



SCHEME 5

A different rearrangement shrouded the discovery of pretazettine until 1968, when Wildman and Bailey re-examined the constituent alkaloids of Ismene calithina (Nichols) and Sprekelia Formosissima L (Herb).[13] They found that tazettine (20) was an artifact of earlier isolation conditions and that pretazettine was, in fact, the major alkaloid of these species. A parallel example was encountered in the less commonly occuring C-3 epimeric series, where precriwelline (18) was found to be the major constituent of Crinum powelli (Herb).

Apparently, in both series, the strain of a trans B-D ring fusion[13,14] in pretazettine and precriwelline powers a quantitative, base-catalyzed, intramolecular Cannizzaro reaction[15] to give 19, as outlined in Scheme 6. The latter subsequently forms the internal hemiketal of tazettine (20a) and precriwelline (20b).

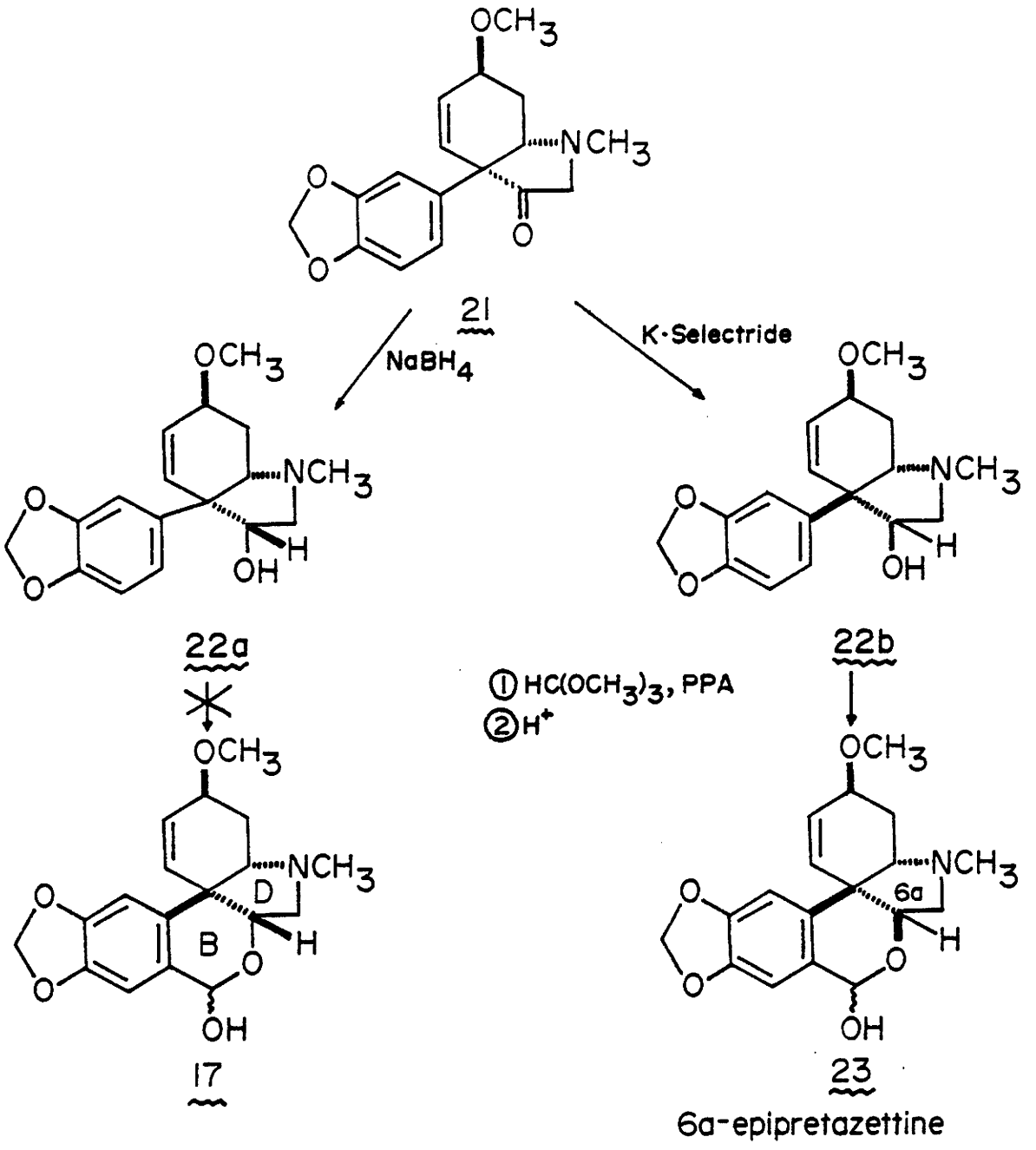


SCHEME 6

Increasing attention has been focussed on pretazettine since Furusawa undertook a massive screening of medicinal plants indigenous to the Pacific area for antiviral agents. "Residual alkaloid A-2", a crude fraction from the dormant bulbs of Narcissus tazetta L., was shown to markedly increase the survival rate of mice with advanced Rauscher leukemia, a transplantable viral murine malignancy.[16] Chirigos of the NIH, a collaborator of Furusawa, found inhibition of avian myoblastosis viral reverse transcriptase at high concentrations.[17] Finally, in 1975 with the aid of Tani and Kitamura, the major component of A-2 was identified as pretazettine and matched with an authentic sample from Wildman.[18] Vázquez, who has carried out extensive studies of the action of the cytotoxic antibiotic narciclasine on the 60s ribosomal subunit of the peptidyl transferase center,[19] suggested that other Amaryllidaceae alkaloids, particularly dihydrolycorine, haemanthamine, lycorine, pseudolycorine, and pretazettine probably act similarly in their specific inhibition of protein synthesis.[20] Investigations into the structure-function relationships[21] of pretazettine revealed that precriwelline (18), its C3 epimer, is equally pharmacologically active. The relative inertness of other alkaloids and derivatives indicated the requirement for the particular arrangement of functionality found in pretazettine: a trans B-D ring fusion, free hemiacetal, and A-ring unsaturation. The precise origin of the antiviral and antitumor activity is not presently understood, since the concentration for inhibition of viral-directed protein synthesis in vivo is 100 times lower than than for reverse transcriptase in vitro.[22] This implies

that inhibitory effects are exerted at a late stage of viral protein synthesis; however, no effects have ever been observed with chronically infected cells. In addition to taking advantage of the low cytotoxicity of pretazettine compared to other standard anticancer drugs,[18a,21,22,23] Furusawa has developed chemotherapies that utilize the beneficial synergistic activity obtained in various combinations as, for example, with DNA alkylators and binders against Ehrlich ascites carcinoma, MCDV-12 BALB/c F1 tumors, and Rauscher leukemia,[18a] with cytotoxan on spontaneous AKR leukemia (which closely resembles human leukemia),[24] and with the adriamycin/bis-(N-chloroethyl)-N-nitrosourea/cyclophosphamide (ABC) regimen on Ehrlich ascites carcinoma.[25]

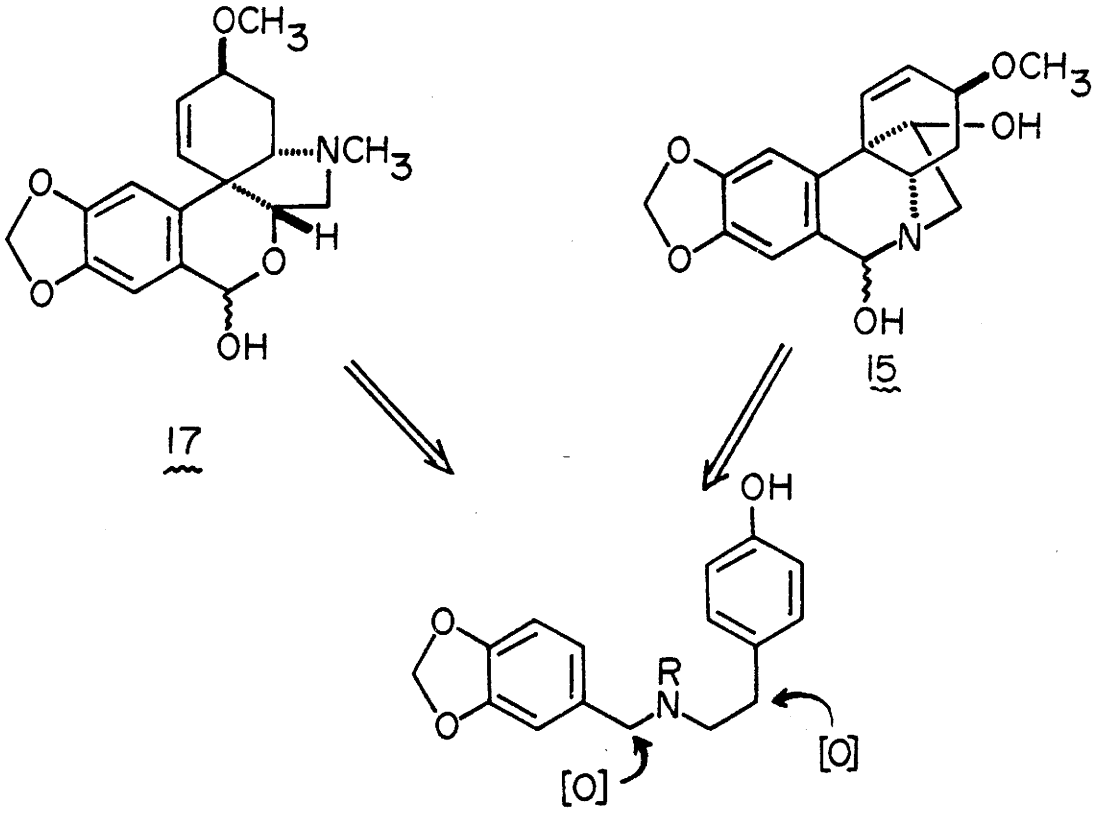
Despite the obvious incentive for a synthesis of pretazettine, this compound has only been accessible preparatively through the known rearrangement of haemanthidine (Scheme 6).[13b] Hendrickson[26] and Tsuda[27] used successive annelations to obtain haemanthidine for their approaches to 6-hydroxy[5,10b]ethanophenanthridines. Danishefsky[28] was the first to obtain the [2]benzopyrano[3,4c]indole skeleton de novo. Although stereoselective reductions of the perhydro-3-indolinone 21 provided both epimeric alcohols 22a,b, only 6a-epipretazettine O-methyl ether 23, with the cis B:D ring fusion, could be obtained from an intramolecular formylation (Scheme 7). The reluctance for the trans B-D ring fusion to form also prohibits many traditional synthetic approaches used for other related alkaloids, where the benzylic carbon is incorporated in the penultimate step using Bischler-Napieralski or Pictet-Spengler methodology.



SCHEME 7

A truly biomimetic synthesis of haemanthidine, and thus pretazettine, would have to overcome the problem of introducing oxygen functionality on a product of phenolic coupling, perhaps the oxocrinine skeleton 10 (Scheme 5), but these difficult oxidations on unactivated sites in the presence of sensitive moieties have prohibited

this approach. However, a retrosynthetic analysis in the context of phenolic oxidative coupling reveals that elements of oxidation placed at the benzylic positions of a biaryl precursor (Scheme 8) could directly produce the functionalized alkaloid skeleton.

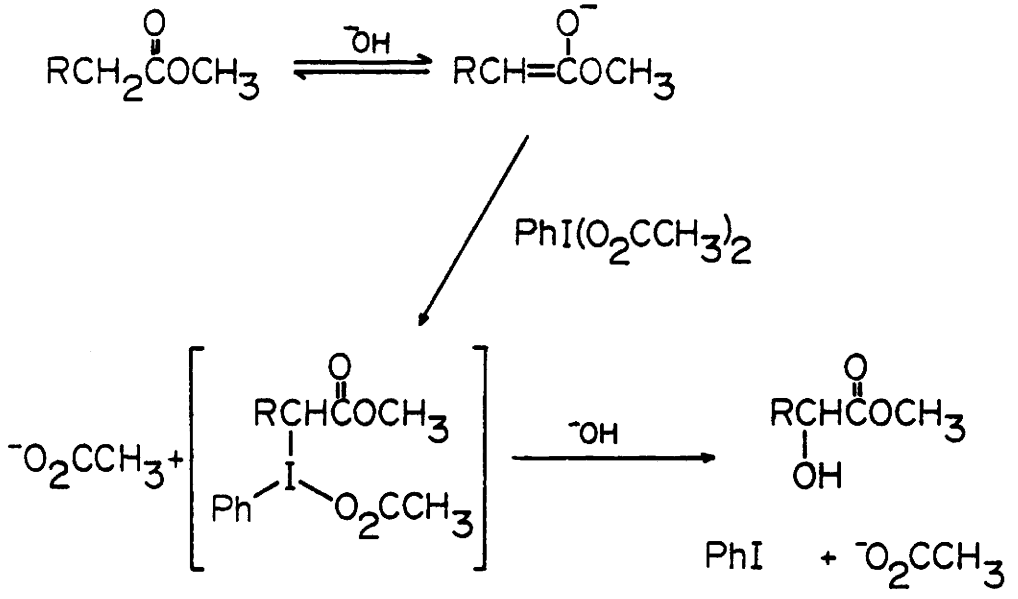


SCHEME 8

Our objective, therefore, was a short synthesis of pretazettine (17) employing known or newly-designed heterolytic, two-electron oxidants for the para-para coupling of a biaryl compound bearing the needed oxygen functionality at the outset.

II. INTRAMOLECULAR PHENOLIC OXIDATIVE COUPLING WITH HYPERVALENT IODINE

Oxidative coupling reagents which function via a two-electron or heterolytic mechanism (Scheme 2) offer advantages which Schwartz did not explore in his studies[5b] of oxidative coupling. In that case, the complexes, 6, which were produced with phenols and vanadium oxytrichloride formed radical cations. We felt it would be possible to avoid radicals by selecting oxidizing species which prefer to undergo reductive elimination during coupling. In this vein, the reactions of hypervalent iodine compounds with phenolic substrates were examined as a possible entry to certain alkaloid structures. Although aryliodine(III) dicarboxylates[29] had previously been reported to react with phenols to produce resinous products,[31] the recent use of phenyliodine(III) diacetate for the α-hydroxylation of carbonyl compounds[32] (Scheme 9) demonstrates the ability for ligand exchange typical of hypervalent iodine.[30]



SCHEME 9

Our initial studies focussed on the reactions of hypervalent iodine compounds with reticuline derivatives 24a,b (Table II), with the aim of finding a solution to the longstanding problem of a synthesis of morphine via oxidative coupling of a benzylisoquinoline system.[33] These substrates, 24a,b, contain a non-basic nitrogen group together with a bromine atom to block unwanted coupling modes.

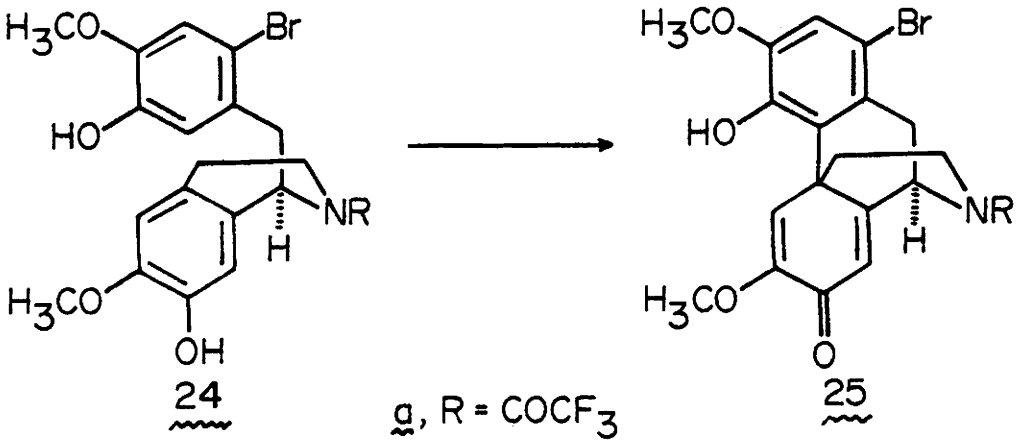


Table II. Phenolic Oxidative Coupling of N-Acyl-4-bromonorreticulines (24), with Hypervalent Iodine

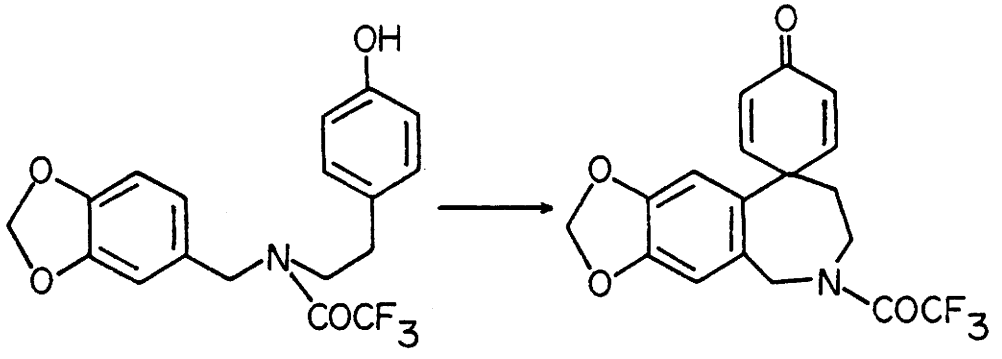
Substrate	Reagent	Yield 25	Reference
24a	$PhI(O_2CCF_3)_2$	21%	33
24b	$PhI(O_2CCF_3)_2$	28%	33
24b	$Et_4N[I(O_2CCX_3)_2]$, 26, X = H,Cl,F	25-58%	34

The most effective reagent for coupling of these systems was phenyliodine(III) bis(trifluoroacetate), which provided salutaridine

derivatives 25a and 25b, in 21 and 23% yields, respectively. The presence of substituents in the aryl ring of the iodine reagent was found to have little effect on the reaction. During the course of this work, a communication by Szántay, et al[34] divulged related results, which claimed that, in addition to phenyliodine(III) dicarboxylates studied, tetraethylammonium diacetoxyiodate(I) salts (26) were also efficient reagents for oxidative phenolic coupling.

In order to further evaluate the efficacy of hypervalent iodine reagents for phenolic oxidative coupling, the phenethylamine derivative 13a was tested as a substrate under a variety of reaction conditions. These reactions assumed characteristic colors depending on the iodine reagent. Varying shades of green were gradually produced by phenyliodine(III) bis(trifluoroacetate), a dark green by phenyliodine(III) diacetate, and a deep red by iodoxybenzene. Crude products contained large amounts of dark-colored byproducts,[35] which was the sole result of oxidation with phenyliodine(III) diacetate. Subsequent purification by column chromatography provided para-para coupled product 14a in low yield from reactions using phenyliodine(III) bis(trifluoroacetate) and iodoxybenzene ($PhIO_2$), as shown in Table III. In each case, more than two equivalents of oxidant were required. The absence of coupled product from phenyliodine(III) diacetate is attributed to a reluctance for an acetate ligand to exchange under these conditions, especially in comparison to trifluoroacetate. Table III shows that vanadium oxytrifluoride has been found to be exceptionally efficient among the numerous reported coupling reagents for 13a, but otherwise the low yield of 14a obtained with phenyliodine(III) bis(trifluoroacetate) is quite

comparable, for example, to thallium tris(trifluoroacetate). In addition, phenyliodine(III) bis(trifluoroacetate) has the unique advantage of causing coupling of 13a to 14a under neutral reaction conditions, in contrast to the required presence of trifluoroacetic acid for vanadium oxytrifluoride, thallium tris(trifluoroacetate) and iodoxybenzene.

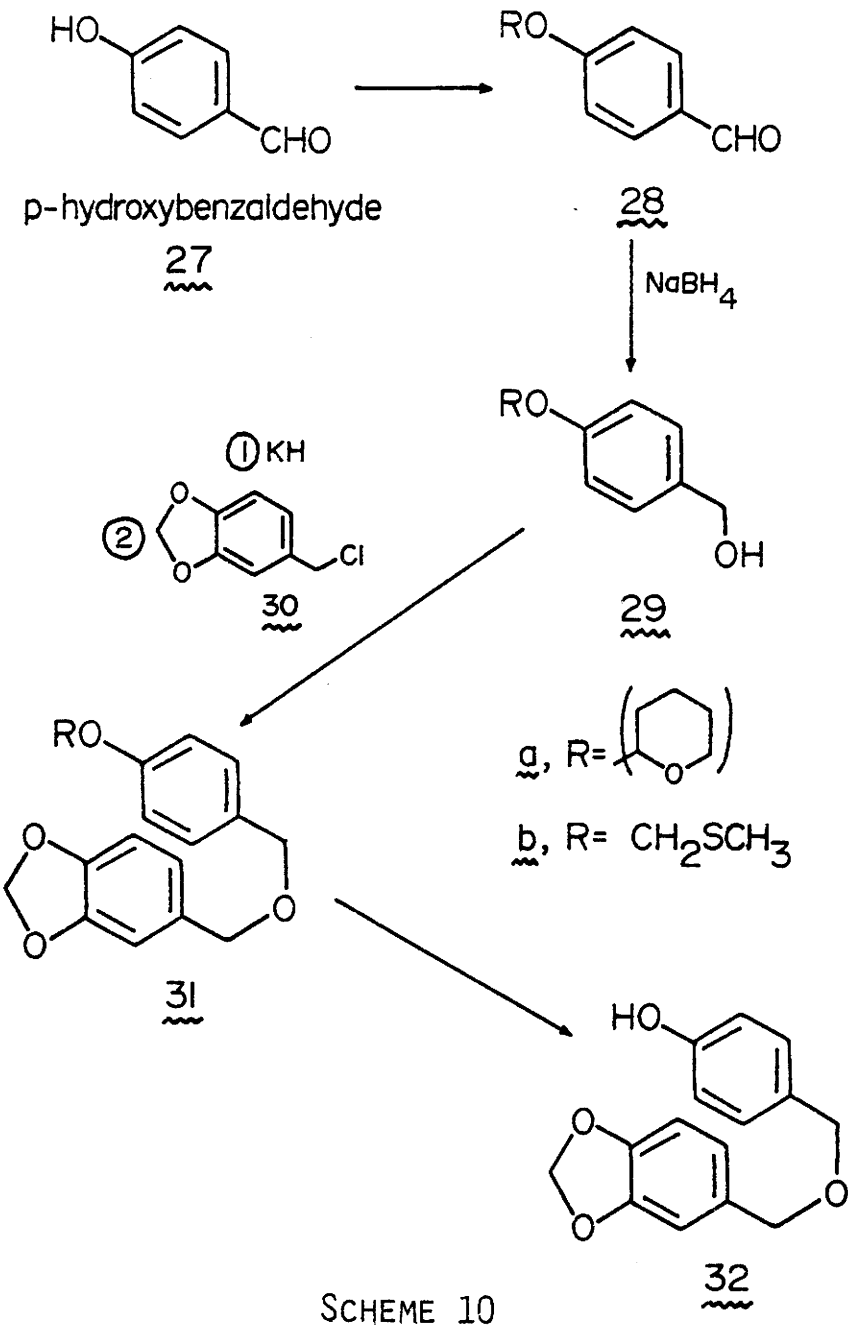


13a 14a

Table III. Phenolic Oxidative Coupling of 13a with Iodine(III) and other Oxidants

Reagent	Yield of 14a	Reference
VOF_3	88%	11
$Tl(O_2CCF_3)_3$	19	37
$PhI(O_2CCH_3)_2$	0	this work
$PhI(O_2CCF_3)_2$	11.8	this work
$PhIO_2$	4.5	this work

Extension of the coupling reaction to systems in which the aryl rings are connected through an oxygen linkage was the next goal. The dibenzyl ether 32 was chosen as a substrate for this purpose, since it was envisioned that an ether of this type would ultimately be employed for the synthesis of pretazettine. The ether 32 was obtained



SCHEME 10

in high yield from p-hydroxybenzaldehyde (27) via the Williamson synthesis outlined in Scheme 10. First, the phenolic group was protected as the tetrahydropyranyl ether 28a. The benzyl alcohol, 29a, resulting from sodium borohydride reduction of 28a, was benzylated by treating the potassium alkoxide with 3,4-methylenedioxybenzyl

chloride (30) to give 31a. The tetrahydropyranyl group of 31a was smoothly hydrolyzed with pyridinium p-toluenesulfonate[38] to the free phenol 32, which was obtained in 90% overall yield. An analogous sequence was also attempted with a methylthiomethyl protecting group[39] for the phenol (Scheme 10). Thus 28b was prepared from p-hydroxybenzaldehyde (27) upon successive treatment with sodium hydride and chloromethyl methyl sulfide and subsequently elaborated to ether 31b. However, the hydrolysis of the methylthioacetal of 31b to afford 32 could not be secured in greater than 55% yield, using Chloramine T in aqueous methanol.[40]

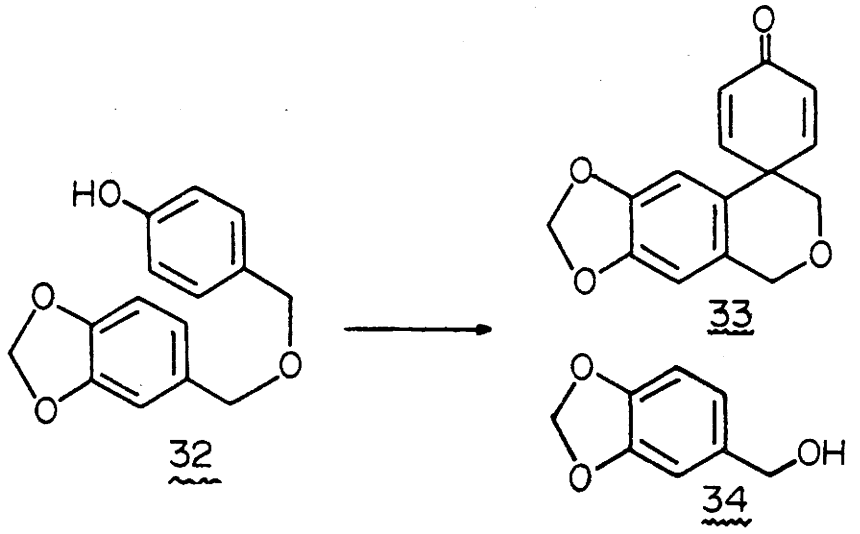
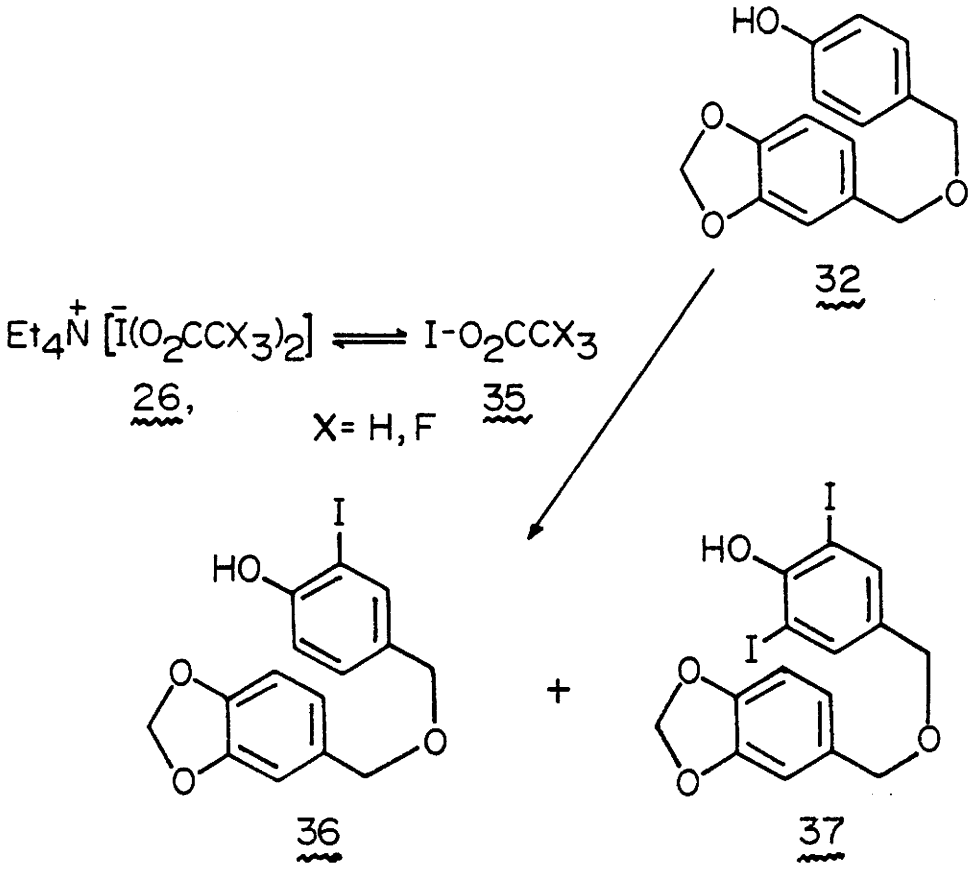


Table IV. Phenolic Oxidative Coupling of 32 with Iodine(III) and other Oxidants

Reagent	Yield of 33 (34)
VOF_3	24%
$PhIO_2$	1-4
$PhI(O_2CCF_3)_2$	9 (29)

The coupling studies on 32 are summarized in Table IV. For vanadium oxytrifluoride and iodoxybenzene, para-para coupled product

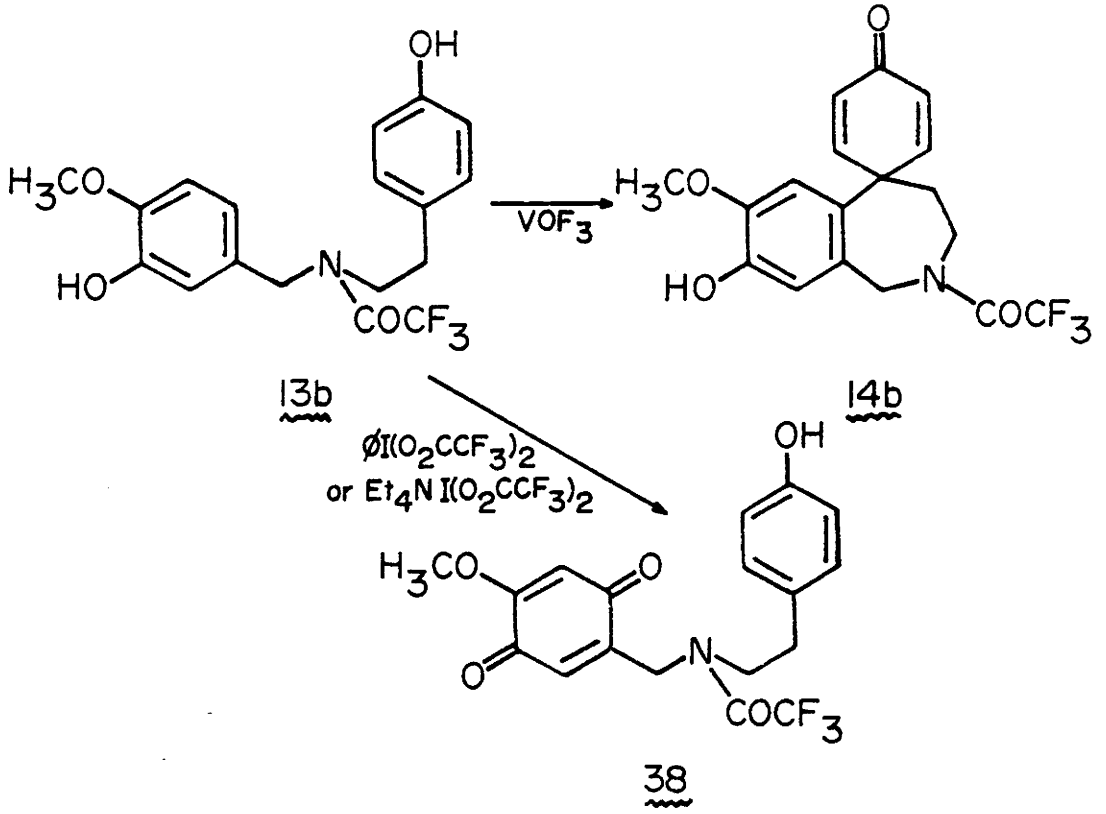
33 was isolated despite previous reports that benzyl ethers were cleaved by trifluoroacetic acid,[41] which was used as a solvent for these oxidants. Phenyliodine(III) bis(trifluoroacetate) was advocated by Spyroudis and Varvoglis[42] as a reagent for oxidative scission of dibenzyl ether, and, in fact, piperonyl alcohol (34) was produced from 32 in 29% yield. Nonetheless, dienone 33 was still formed in 9% yield. Attempts to obtain coupling via oxidation of the phenoxides of 32 by phenyliodine(III) bis(trifluoroacetate) led to intractable, dark-colored reaction products, from which low amounts of phenol 32 were recovered.



Encouraged by the studies of Szántay, et al,[34] tetraethylammonium diacetoxyiodate(I) salts 26 were reacted with phenol 32, but instead of coupling to 33, the mono-and diiodinated phenols 36 and

37 were each isolated in 15% yield (20% based on recovered 32). Therefore, the salts 26 acted as sources of acetyl hypoiodite (35), which iodinated 32, in direct contrast to the results of Doleschall and Toth,[43] who showed via kinetic studies that reactive diacetatoiodate(I) anionic species were obtained from 26.

Curiously, the diphenolic N-benzylphenethylamine 13b would not undergo coupling in the presence of hypervalent iodine compounds. In contrast to previous work, which showed that vanadium oxytrifluoride gave a 71% yield of para-para coupled product 14b,[44] the p-benzoquinone 38 was produced with the salts 26 and phenyliodine(III) bis (trifluoroacetate) in 5 and 29% yield, respectively.



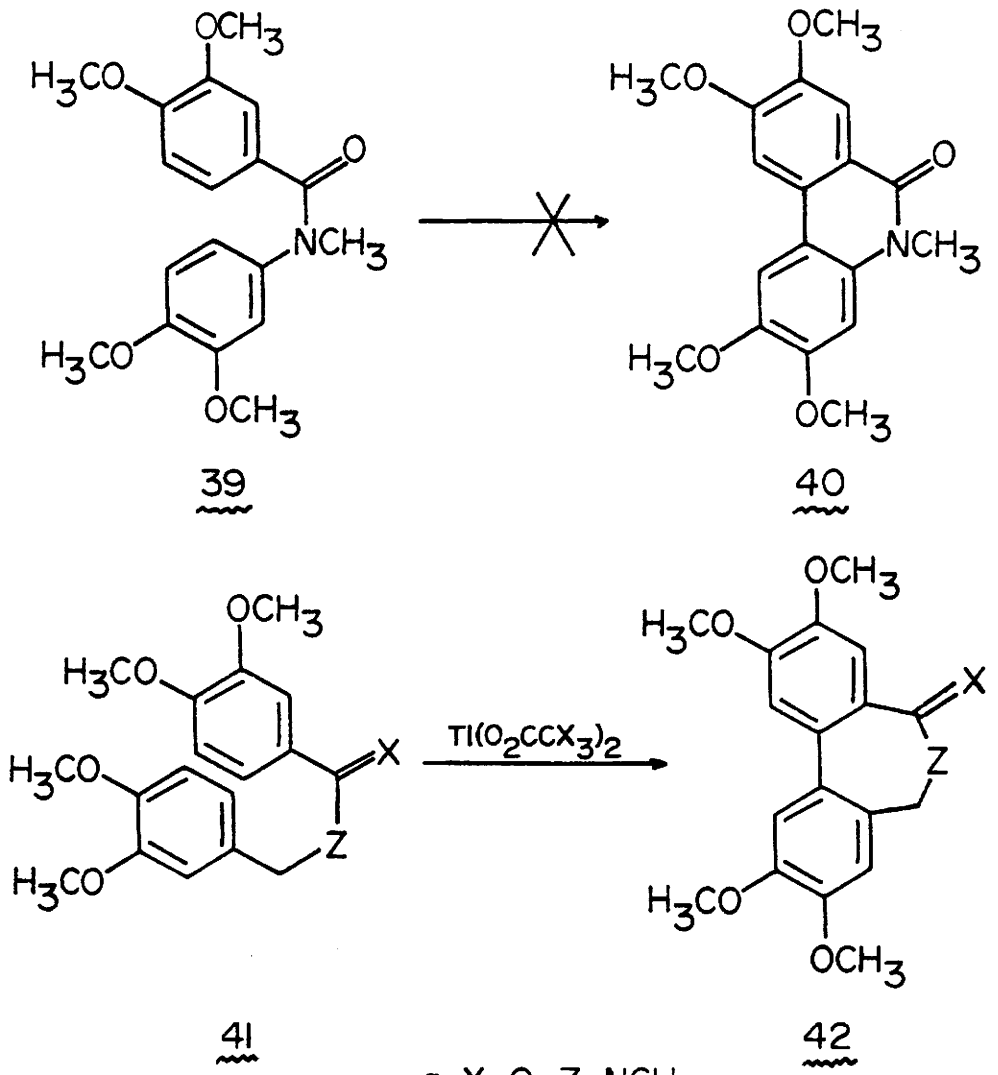
In spite of this disappointing result, the studies described above clearly suggested that phenyliodine(III) bis(trifluoroacetate) could be an effective oxidant for monophenolic coupling. The follow-

ing section reports an application of this concept in an approach to the synthesis of pretazettine (17).

III. SYNTHETIC APPROACHES TO PRETAZETTINE

The field of intramolecular phenolic oxidative coupling abounds with substrates which have aromatic rings connected by relatively featureless chains. For a synthesis of pretazettine employing coupling strategies, possible substrates would have to contain benzylic oxidation that is effectively masked against the harsh conditions under which available reagents operate. The few examples of benzylic functionality in previously successful couplings lend little insight into the design of acceptable substrates, especially since none of these involved two-electron, or heterolytic processes. As mentioned before, Kametani coupled the diphenolic benzamide 11 with potassium hexacyanoferrate (III) in a synthesis of galanthamine (9).[10] Sainsbury and Wyatt,[45] using electrochemical techniques, attempted to couple various nonphenolic biaryl compounds, such as 39 and 41, which contained amides along interconnecting chains of predetermined lengths, and could only obtain the biphenylamide 42a in two percent yield (Scheme 11). Taylor and McKillop[8] have since demonstrated that thallium tris(trifluoroacetate) is an efficient coupling reagent for the benzamide 41a, as well as the dibenzyl ether 41b and the amine 41c (Scheme 11). In order to test this phenolic coupling with a heterolytic reagent, the model benzamide 45 was synthesized from piperonylic acid (43) and tyramine (44). However, 45 failed to give para-para coupled product 46 when vanadium oxytrifluoride was used.

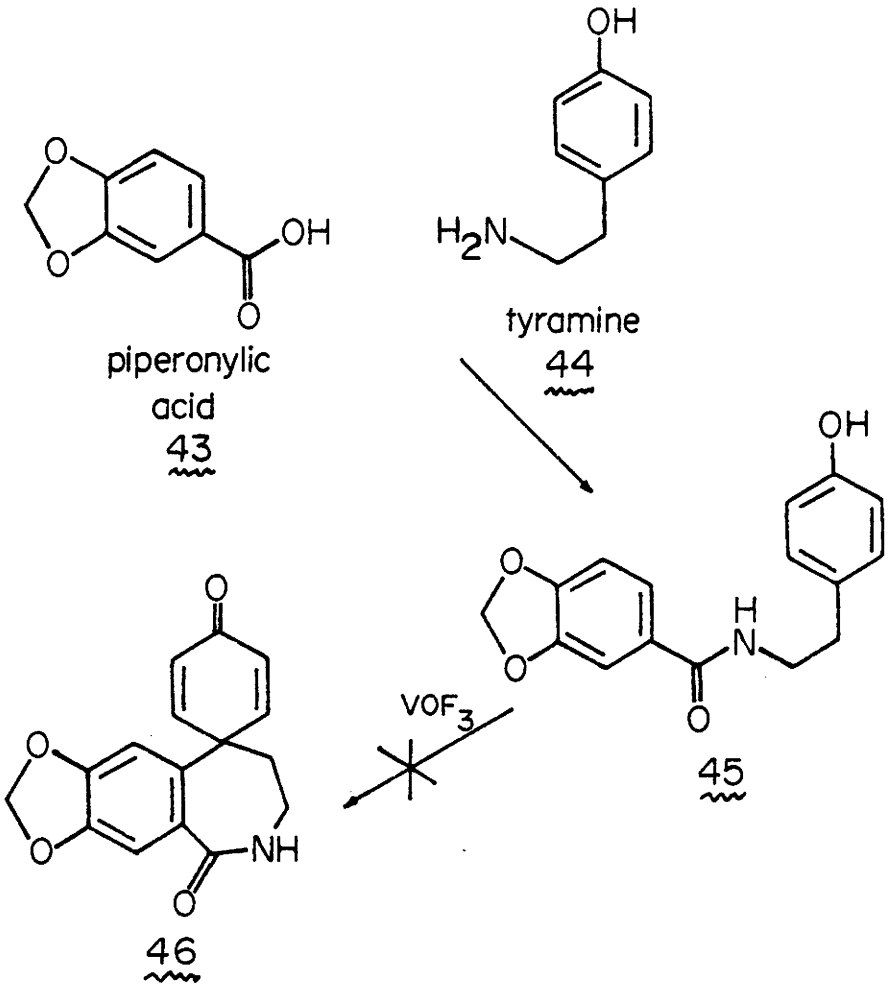
This experiment therefore ruled out a benzoyl derivative as a potential substrate. On the other hand, the ether 41b and amine 41c compared favorably with amide 41a as coupling substrates,[8] and



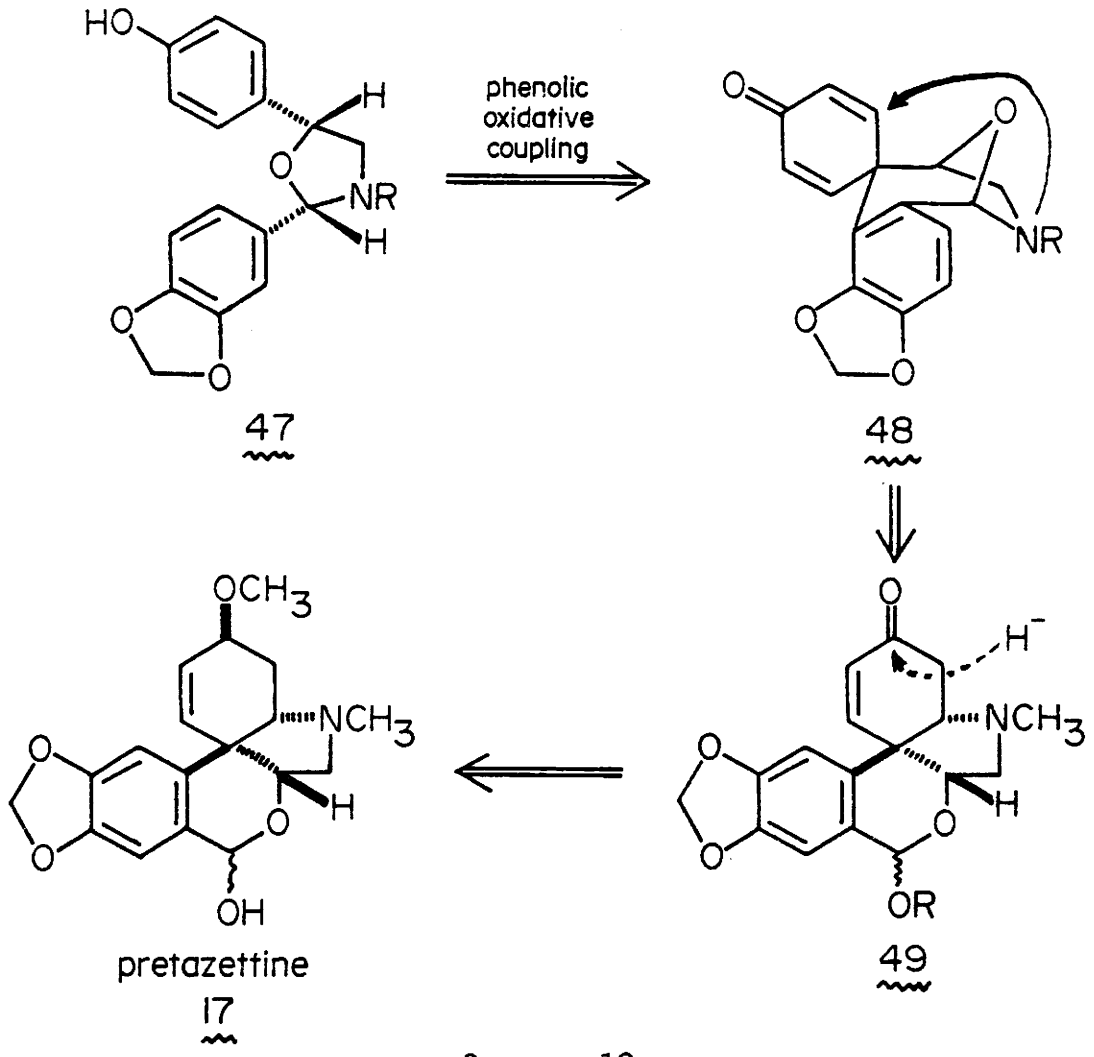
a, X = O, Z = NCH_3
b, X = H_2, Z = O
c, X = H_2, Z = NCH_3

SCHEME 11

consequently, our efforts were focussed on compounds with ether, amine, carbinolamine or acetal groups at the benzylic positions.

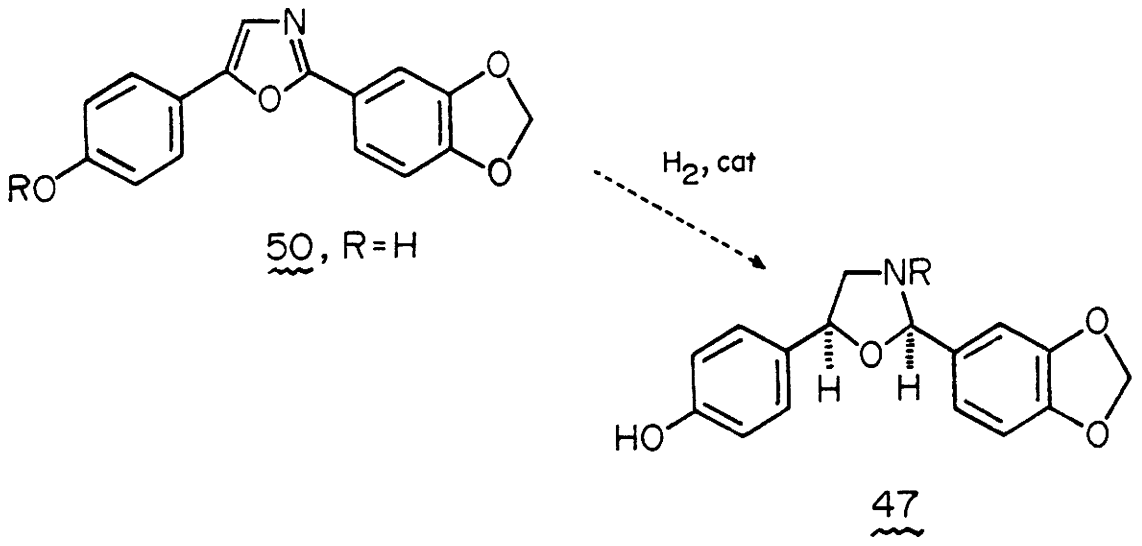


A cis-2,5-diaryloxazolidine, 47, was envisioned as one of several potential coupling substrates for a synthesis of pretazettine (Scheme 12). Besides avoiding the use of protecting groups, this heterocycle contains functionality at the correct oxidation level for the B and D rings of pretazettine. Using classical transformations, the spirobenzobicyclodienone 48 from para-para coupling

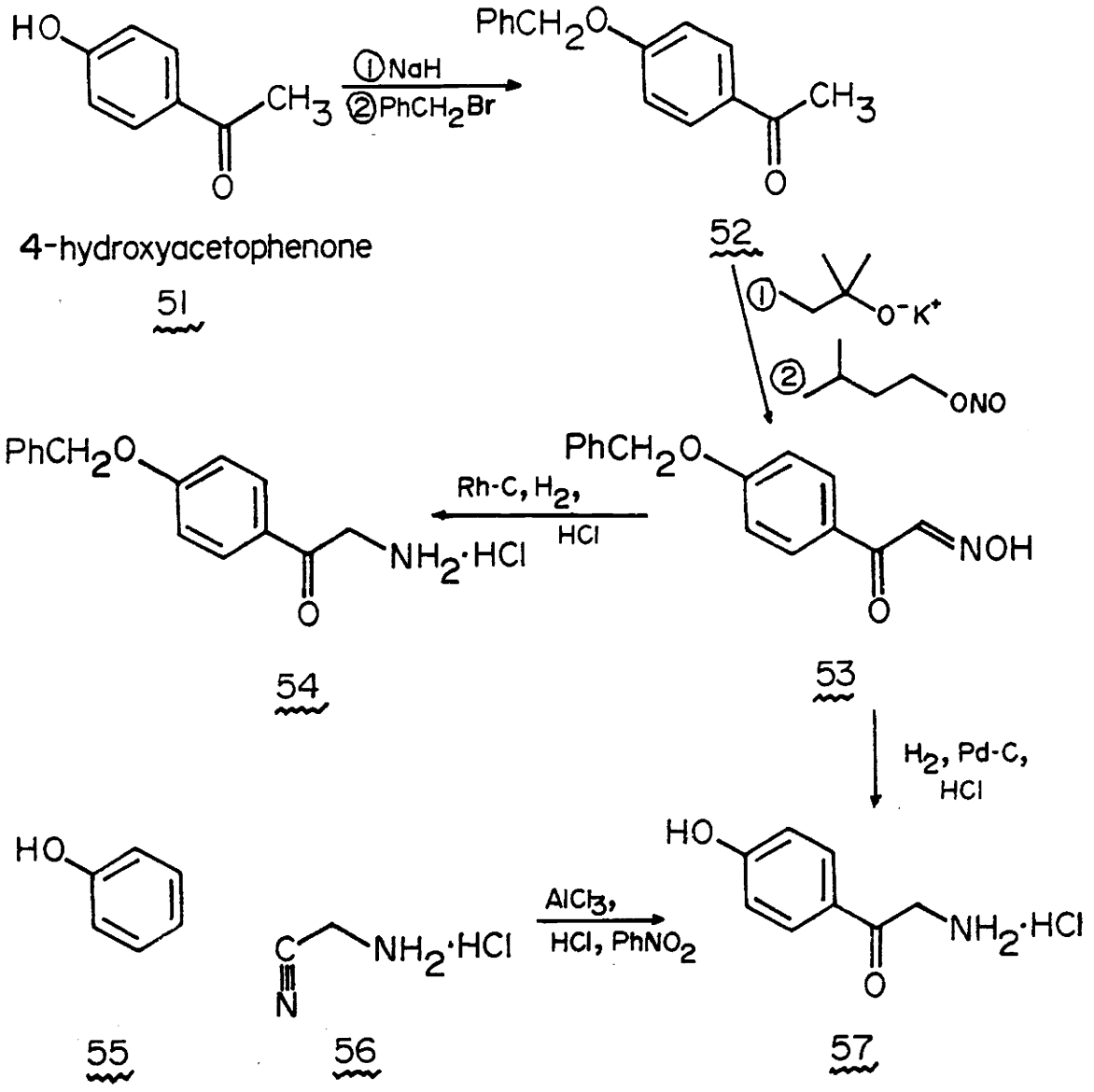


SCHEME 12

of 47 should be converted into pretazettine quite readily. Thus, hydrolysis of the carbinolamine 48 unmasks a hemiacetal with concomitant liberation of the amine for a Michael reaction that would produce the tetracyclic system of the natural product. At this point, the nitrogen methylation to obtain enone 49 would probably precede the introduction of hydride. Stereoselective reduction of enone 49 and subsequent methylation of the resultant allylic alcohol would complete the synthesis of pretazettine (17).

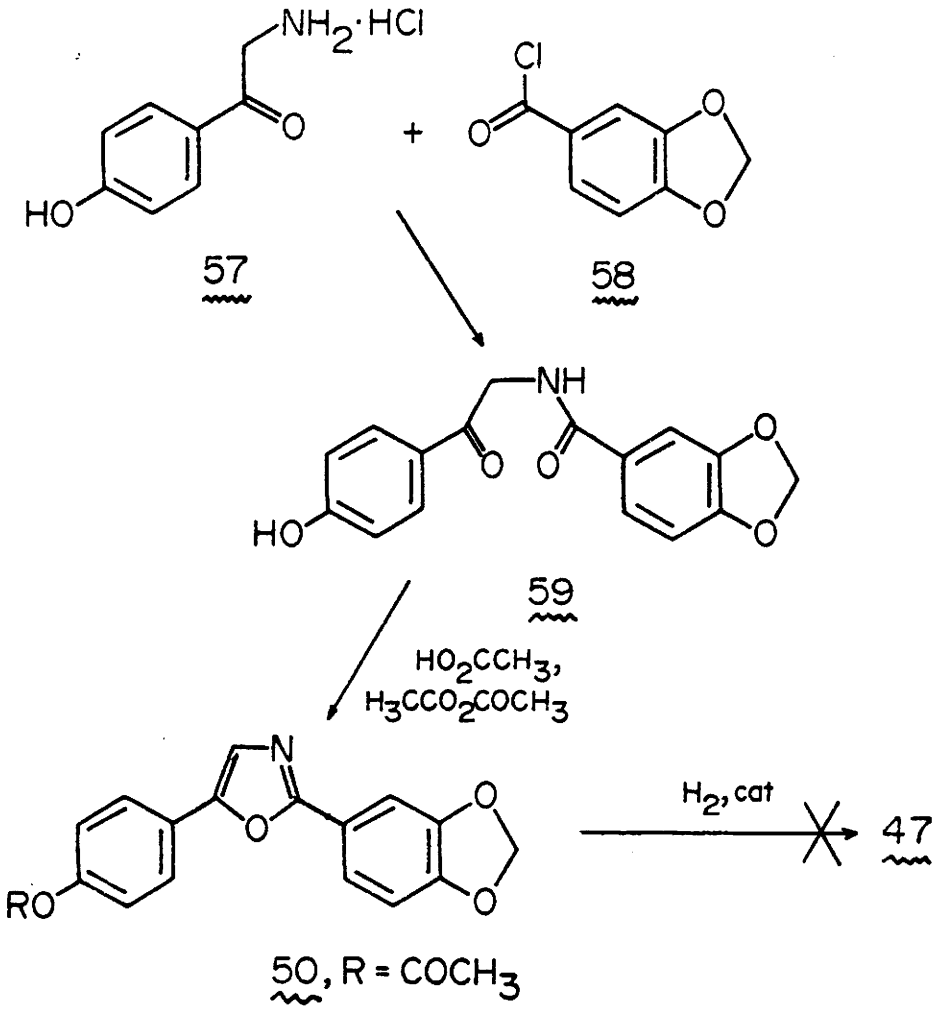


Fixing the cis relationship of the aromatic rings on the oxazolidine 47 is prerequisite to its candidacy as an oxidative coupling substrate. It was expected that this stereochemistry would be obtained upon catalytic hydrogenation of the corresponding oxazole 50 which, in turn, could be derived via a Robinson-Gabriel oxazole synthesis. The desired β-ketoamide 59 was prepared by two routes (Scheme 13). One sequence, which led to phenacylamine 57, paralleled a literature preparation.[46] Thus, 4-hydroxyacetophenone (51) was benzylated in dimethylformamide to give the ether 52. The enolate of 52 was generated with potassium tert-amyloxide and condensed with isoamyl nitrite, resulting in α-oximinoketone 53. Unlike the previous study, over-reduction occurred, and carbonyl-free, debenzylated products were isolated from palladium-catalyzed hydrogenations. By contrast, it was found that rhodium was an efficient and selective catalyst for oxime reduction, and provided benzyl ether 54 in good yield. Alternatively, the Houben-Hoesch reaction of phenol (55) and α-aminoacetonitrile hydrochloride (56) in the presence of aluminum



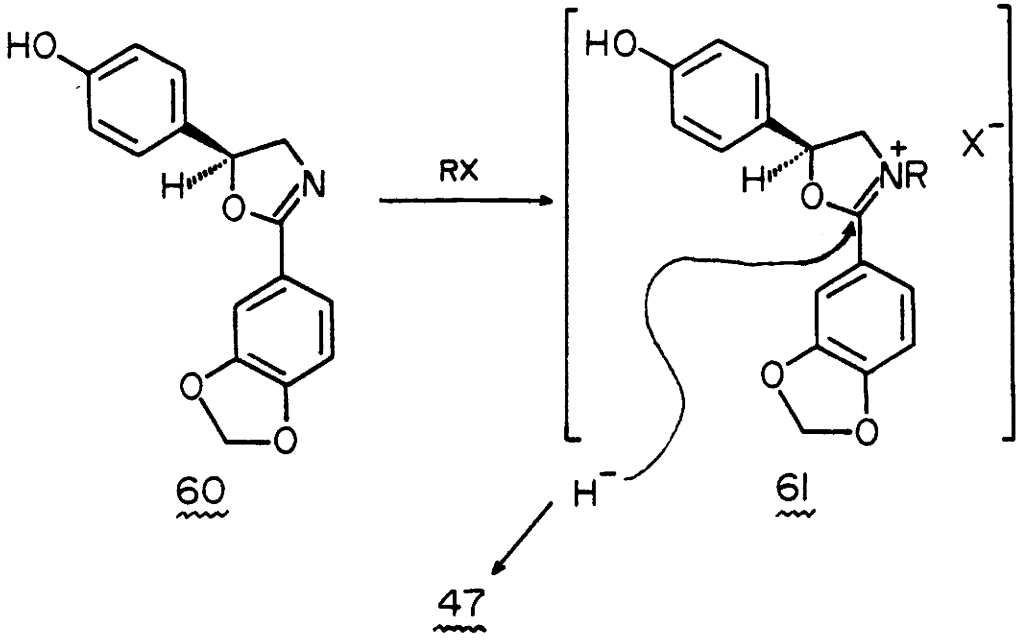
SCHEME 13

chloride, as described by Asscher,[47] was a low yielding, but quite reliable, preparation of phenacylamine 57. The synthesis of amide 59 in 97% yield from amine 57 and the acid chloride of piperonylic acid 58 was carried out under Schotten-Baumann conditions. Dehyd-



rative cyclization of the β-ketoamide 59 in acetic anydride and acetic acid solution furnished oxazole acetate 50 in 52% yield after recystallization. The insolubility of the free phenol of oxazole 50 warranted the preservation of the acetate for hydrogenation studies.

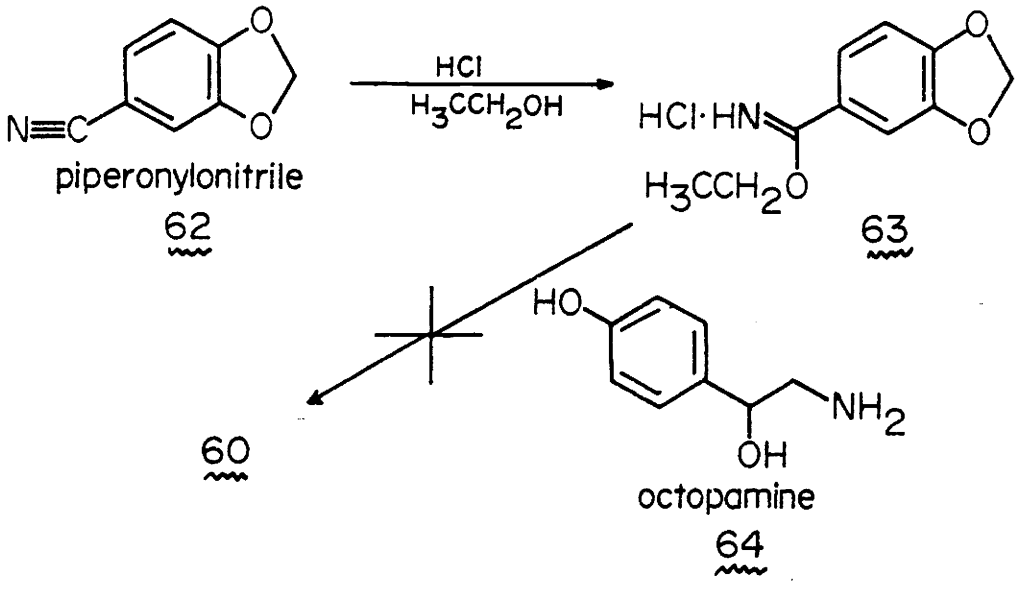
Unfortunately all attempts at this unprecedented catalytic hydrogenation of an oxazole were unsuccessful and starting material was recovered in virtually every case. Despite having more aromatic character,[48] 2,5-diaryl substituted furans undergo the analogous reduction to give a tetrahydrofuran.[49] Therefore, the resiliency of oxazole 50 must be attributed to the catalyst-poisoning nature of



SCHEME 14

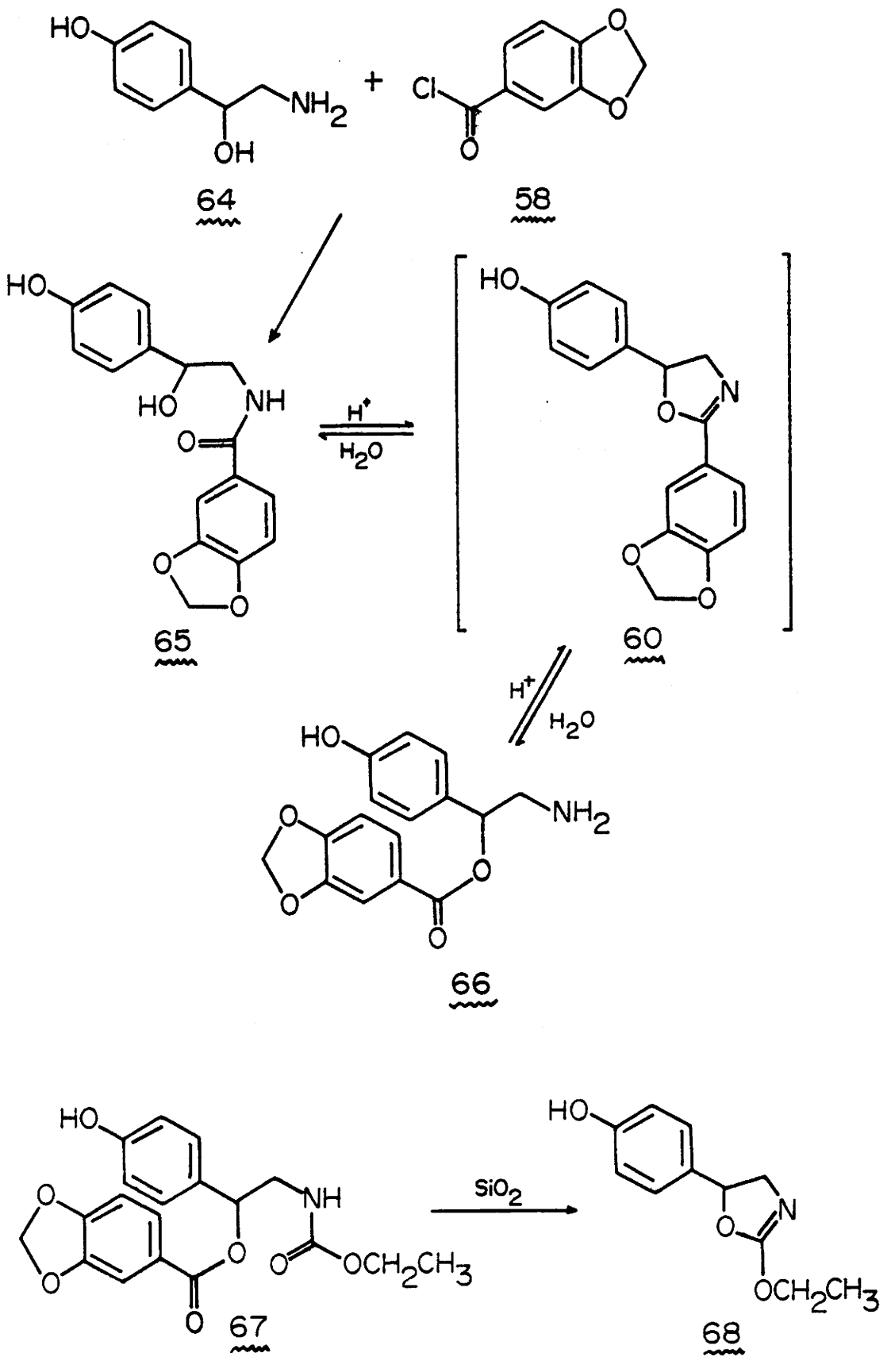
nitrogen, possibly combined with the additional resonance stabilization associated with these particular aryl substituents.

The oxazoline 60 was sought as an alternative precursor for oxazolidine 47. In the reduction of oxazolinium species 61,[50] it was expected that hydride delivery from the side opposite the phenol should result in the desired cis stereochemistry, as illustrated in Scheme 14. Projecting a Fisher synthesis[51] of oxazoline 60, attempts were made to condense octopamine (64) and imino ether 63, which was in turn prepared from piperonyl cyanide (62) via a Pinner reaction.[52] However, no reaction was observed between 63 and 64 in N,N-dimethylformamide, which was one of the few aprotic solvents in which octopamine could be dissolved. Hence, a Robinson-Gabriel strategy[51] was considered once again. The β-hydroxyamide 65 was readily available from acylation of octopamine (64) by the acid chloride of pip-



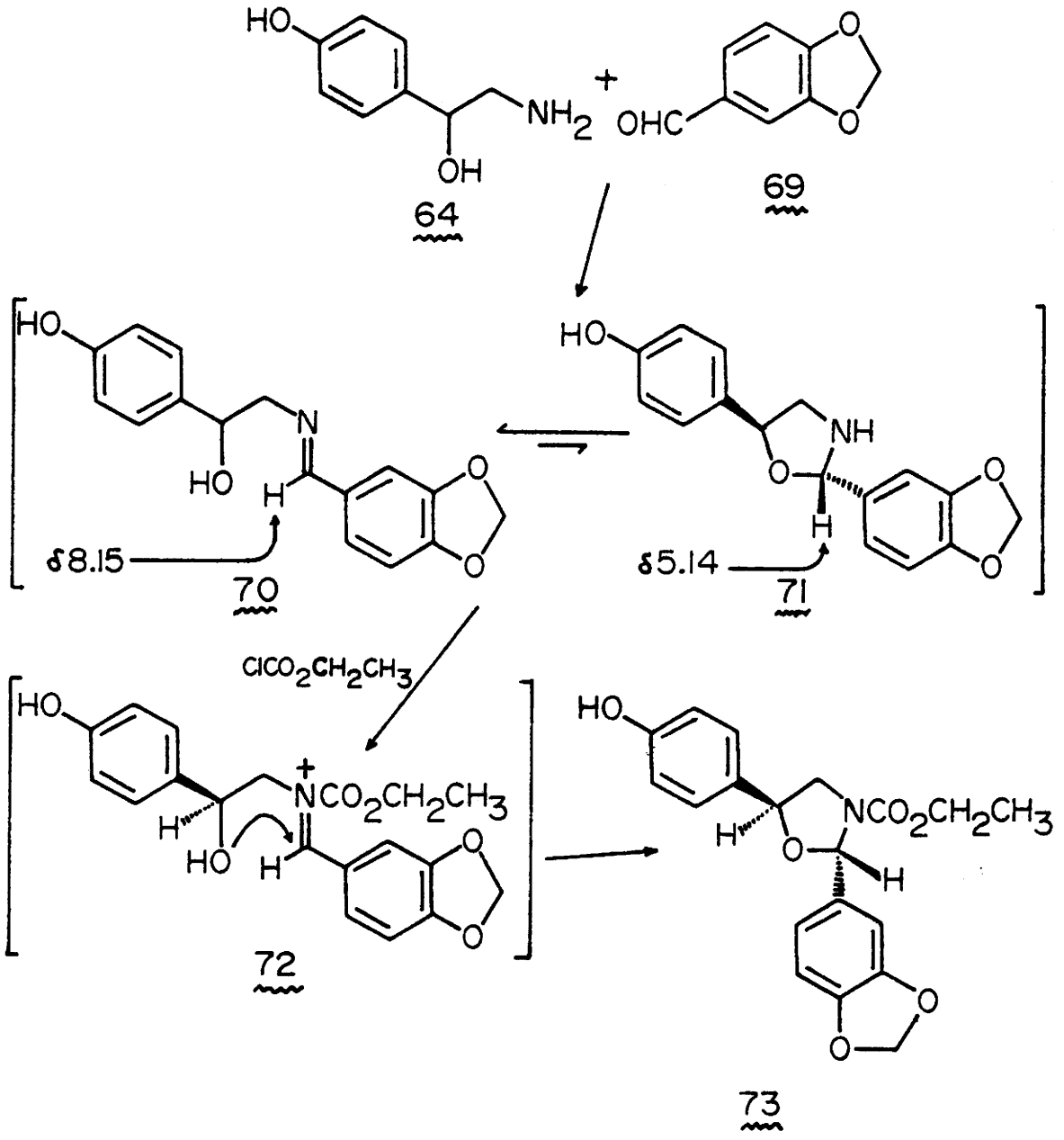
eronylic acid 58. However, instead of isolating oxazoline 60, exposure of 65 to various acidic conditions was accompanied by decomposition, and subsequent aqueous workup furnished a crude solid which exhibited absorptions at 1720 and 1630 cm^{-1} in the infrared spectrum. An inseparable mixture of 65 and benzoate 66 was isolated as a result of the formation of oxazoline 60 *in situ* with subsequent hydrolysis. Unfortunately, the formation of oxazoline 60 in solution could not be detected by nuclear magnetic resonance spectroscopy, since the amide 65 was insoluble in most deuterated solvents, and extensive decomposition took place when trifluoroacetic acid was employed. On the presumption that oxazoline 60 was formed in a solution of amide 65, the latter was treated with alkylating agents, such as methyl chloroformate, in the hope of generating cation 61a *in situ* for a subsequent addition of hydride (Scheme 14). However, no reaction was observed in these attempts to produce oxazolidine 47 directly from 65.

The evident lability of oxazoline 60 was blamed on the presence


HO
NH2
OH
+
Cl
O
O
O
64
58
HO
HO
NH
O
O
O
65
H+
H2O
HO
N
O
O
O
60
H+
H2O
HO
NH2
O
O
O
O
66
HO
NH
O
O
O
O
OCH2CH3
67
SiO2
HO
N
O
OCH2CH3
68

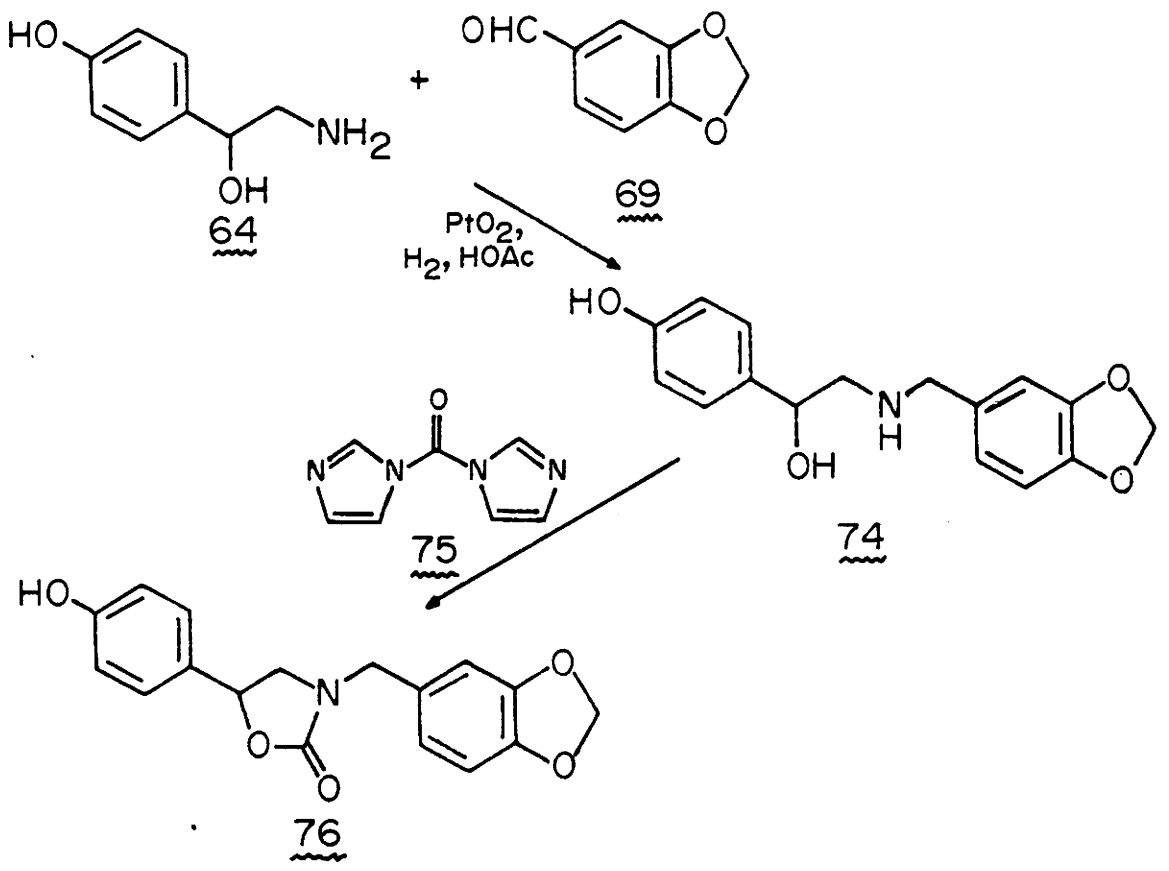
of the piperonyl moiety, since it was found that the crude benzoate 67 was converted quantitatively into oxazoline 68 through an inadvertent hydrolysis which occurred when purification was carried out on silica gel.

Since the reduction of oxazole 50 or oxazoline 60 had failed to produce the desired 2,5-diaryloxazolidine 47, an alternative ap-

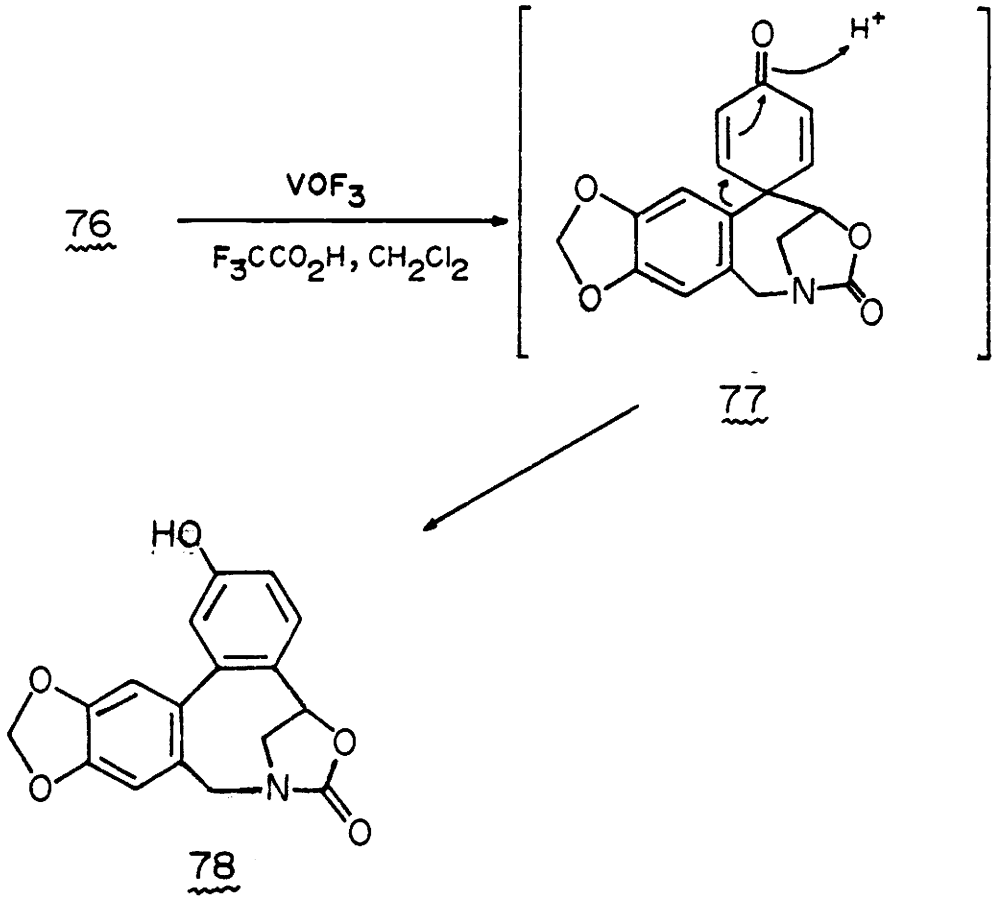


proach to this heterocycle was devised which, however, was not stereoselective. Condensation of (±)octopamine (64) with piperonal (69) gave the Schiff base 70, which was shown by spectral examination to be in equilibrium with oxazolidine 71. A peak in the infrared spectrum at 1640 cm^{-1} was assigned to a C=N stretch, and the 100 MHz nuclear magnetic resonance spectrum displayed absorptions at δ 8.15 for the HC=N proton and a broad doublet at δ 5.14 for the ArCH(OR)NR_2 proton of the minor oxazolidine component. Upon treatment of the mixture of 68 and 69 with ethyl chloroformate, the resultant quaternary imine 72 was trapped internally by the benzylic alcohol to accomplish a complete conversion to the oxazolidine 73 in 98% yield from octopamine (64). It is assumed that the ring closure proceeded under steric control, which therefore should result in a trans configuration of the aryl substituents. This, however, opposed the results of Eliel,[53] who showed that cis stereochemistry is favored in the reversible formation of 2,5-dialkyl-1,3-dioxolanes. A definite stereochemical assignment to 73 by analogy with 1,3-dioxolanes[54] was not possible but urethane 73 was produced as a single isomer: the yellow oil was homogeneous by thin layer chromatography and the proton magnetic resonance spectrum displayed a singlet at δ 6.32 for the C-2 proton. Regardless of its stereochemistry, the conditions for oxidative coupling of 73 with vanadium oxytrifluoride in trifluoroacetic acid and with phenyliodine(III) bis(trifluoroacetate) led in each case to hydrolysis of the oxazolidine and to the isolation of piperonal.

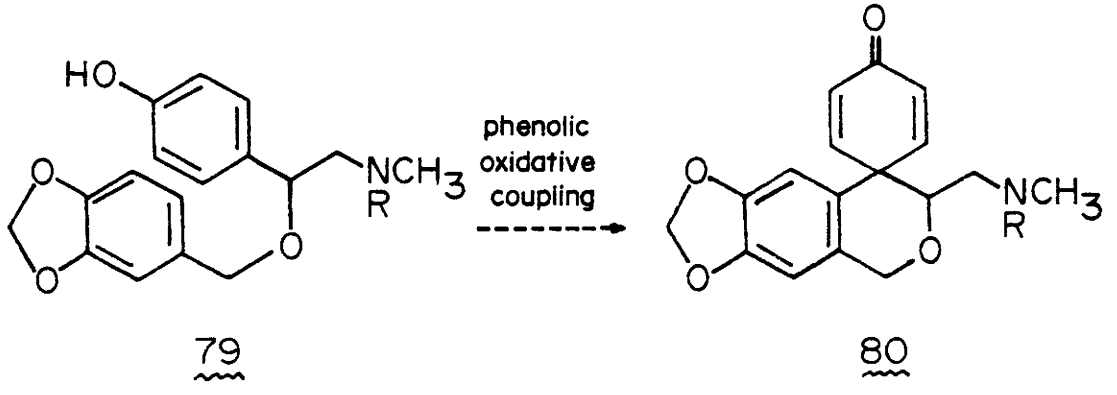
This failure led us to consider an alternative coupling substrate in the form of the 2-oxazolidinone 76, where the nitrogen is protected as an internal urethane. The N-benzylphenylethylamine



derivative 74 was obtained in 87% yield from hydrogenation of piperonal (69) and octopamine (64) in acetic acid over platinum(IV) oxide. Carbonyl diimidazole (75) was employed to form the 2-oxazolidinone 76 in 32% yield. An attempted coupling of 76 with vanadium oxytrifluoride led to the isolation of the biphenyl derivative 78 in 17% yield, along with a 46% recovery of starting material. Apparently, the desired para-para coupled product 77 was formed in this coupling reaction, but strain in the seven-membered ring caused this system to undergo a spontaneous dienone-phenol rearrangement to give the eight-membered ring of 78.

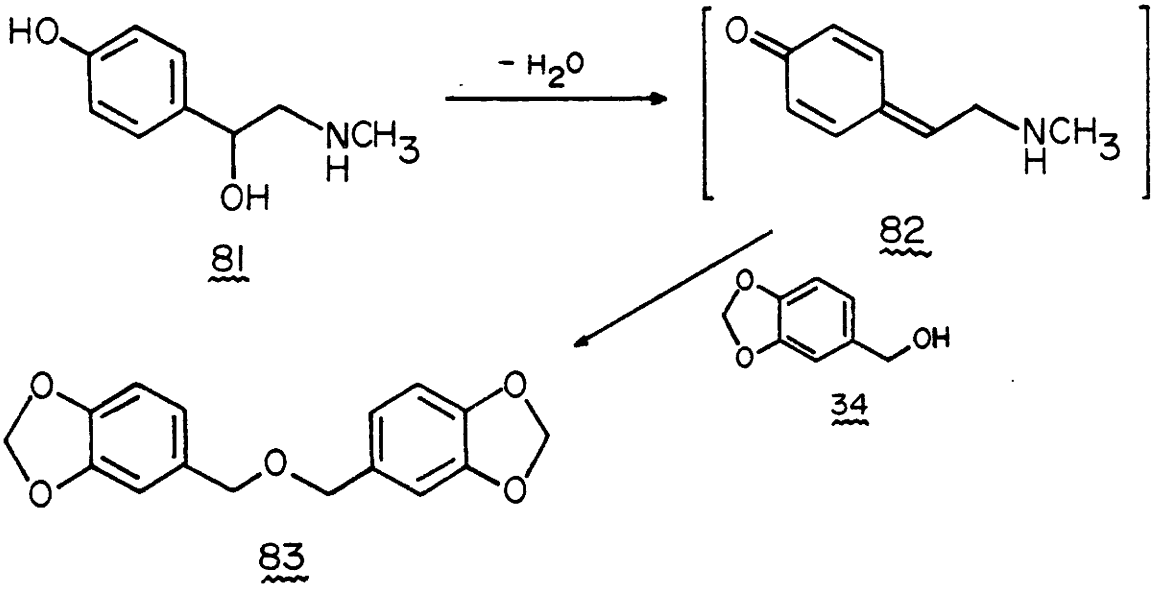


Rather than continue a search for potential coupling substrates containing a nitrogen function in the linkage between the aryl rings, we returned to a strategy based on the earlier, successful coupling of the monophenolic dibenzyl ether 32. Specifically, it was hoped that the combination of vanadium oxytrifluoride and trifluoroacetic

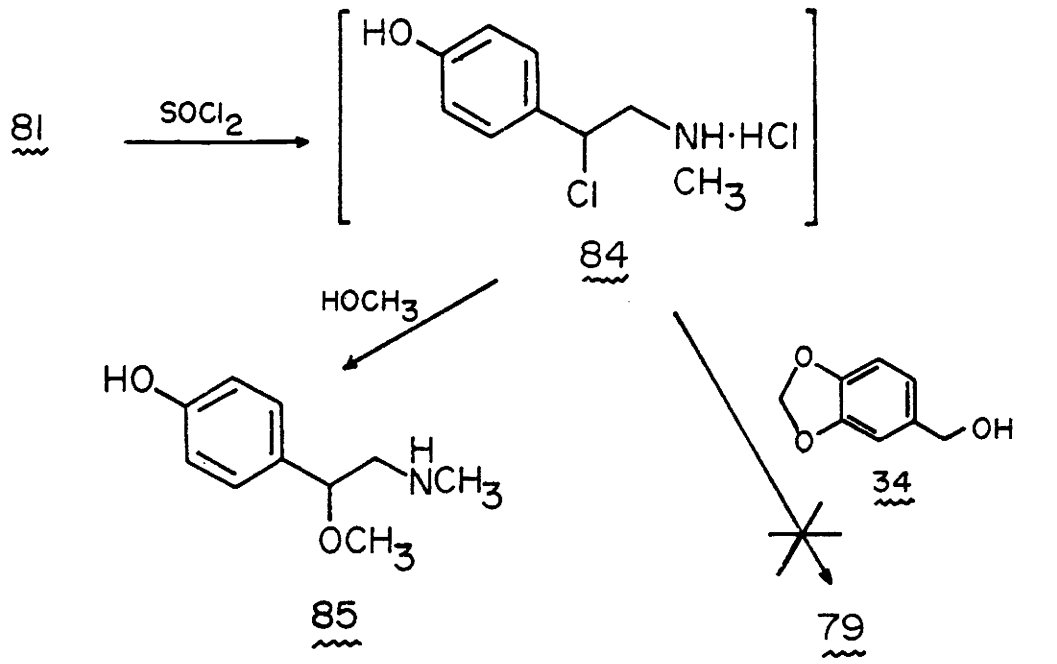


acid would not easily hydrolyze the dibenzyl ether 79, which might therefore cyclize to the pretazettine precursor 80.

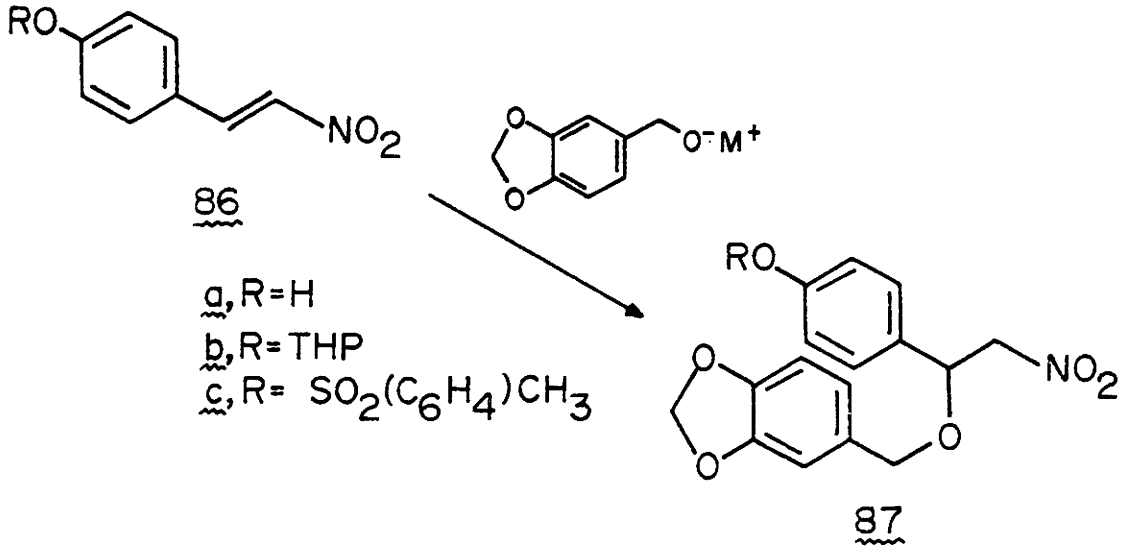
A straightforward synthesis of dibenzyl ether 79 was expected from the reaction of piperonyl alcohol (34) with the quinone methide, 82, which is formed upon dehydration of synephrine (81). In accord with a literature procedure,[55] synephrine (81) was heated in a melt of piperonyl alcohol (34), but the only product which could be isolated was the dipiperonyl ether 83.



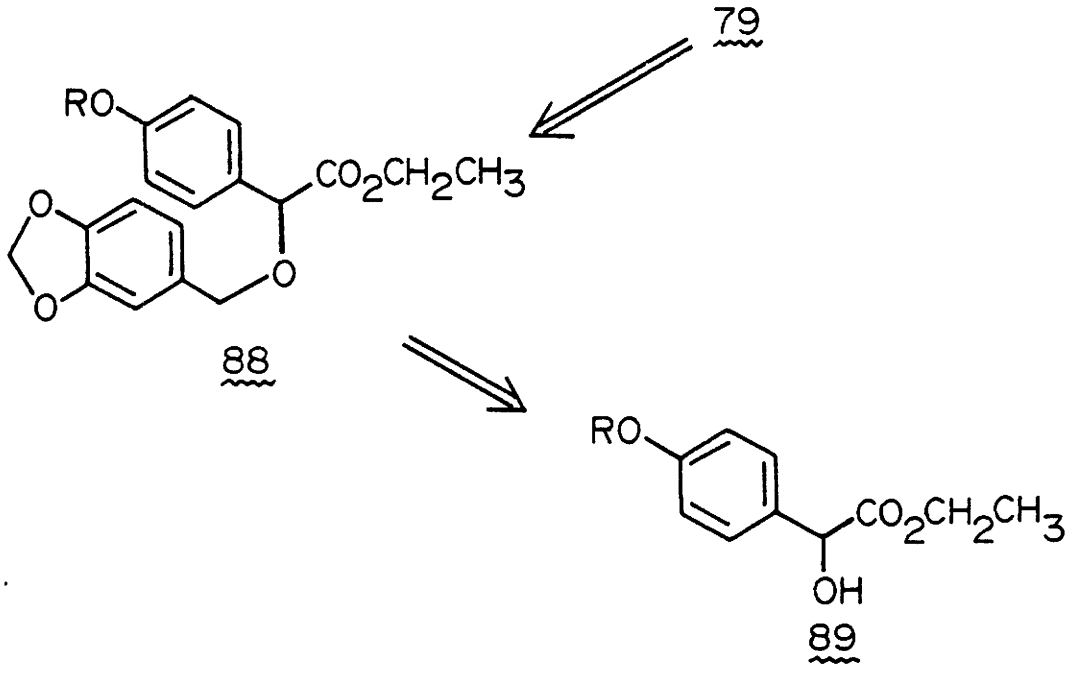
Other selective manipulations of the functionality of synephrine (81) also proved to be difficult. For instance, the evidence for the preparation of unstable chloride 84, which defied spectral characterization, was a reaction with methanol to give methyl ether 85 in 60% yield from synephrine (81). However, the analogous reaction of chloride 80 with piperonyl alcohol (34) to give ether 79 did not take place in chloroform, N,N-dimethylformamide, or tetrahydrofuran containing hexamethylphosphoramide.



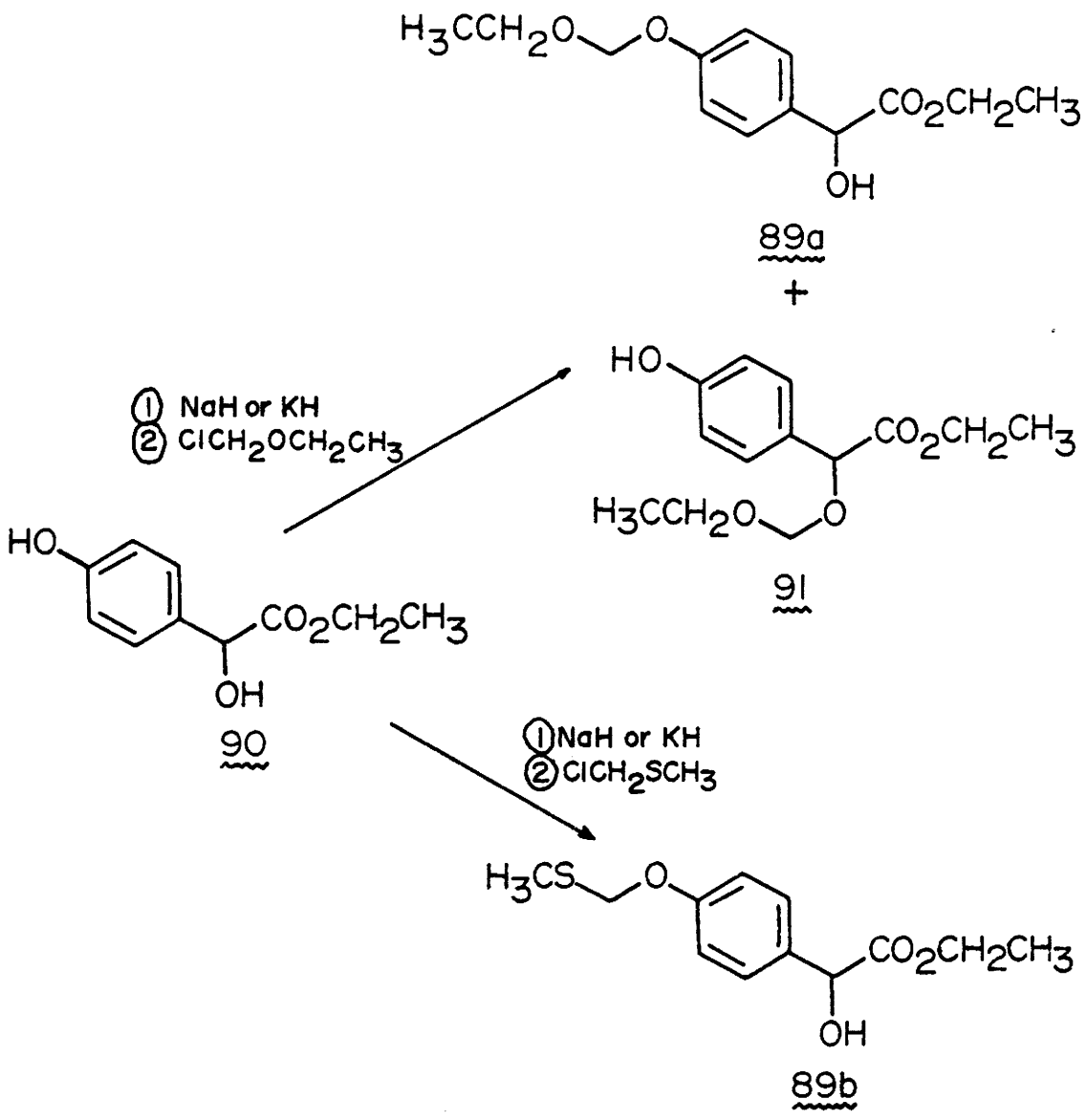
To circumvent the problems encountered with synephrine (81), our attention turned to a synthesis of the nitro compound 87, which conceivably could be converted to an amine at a later stage, either before or after coupling. Based on a patent procedure,[56] the alkoxide of piperonyl alcohol (34) was stirred with 4'-alkoxy-2-nitrostyrenes, 86, in the hope of bringing about addition to the double bond. No formation of the adduct 87 was observed. This could be



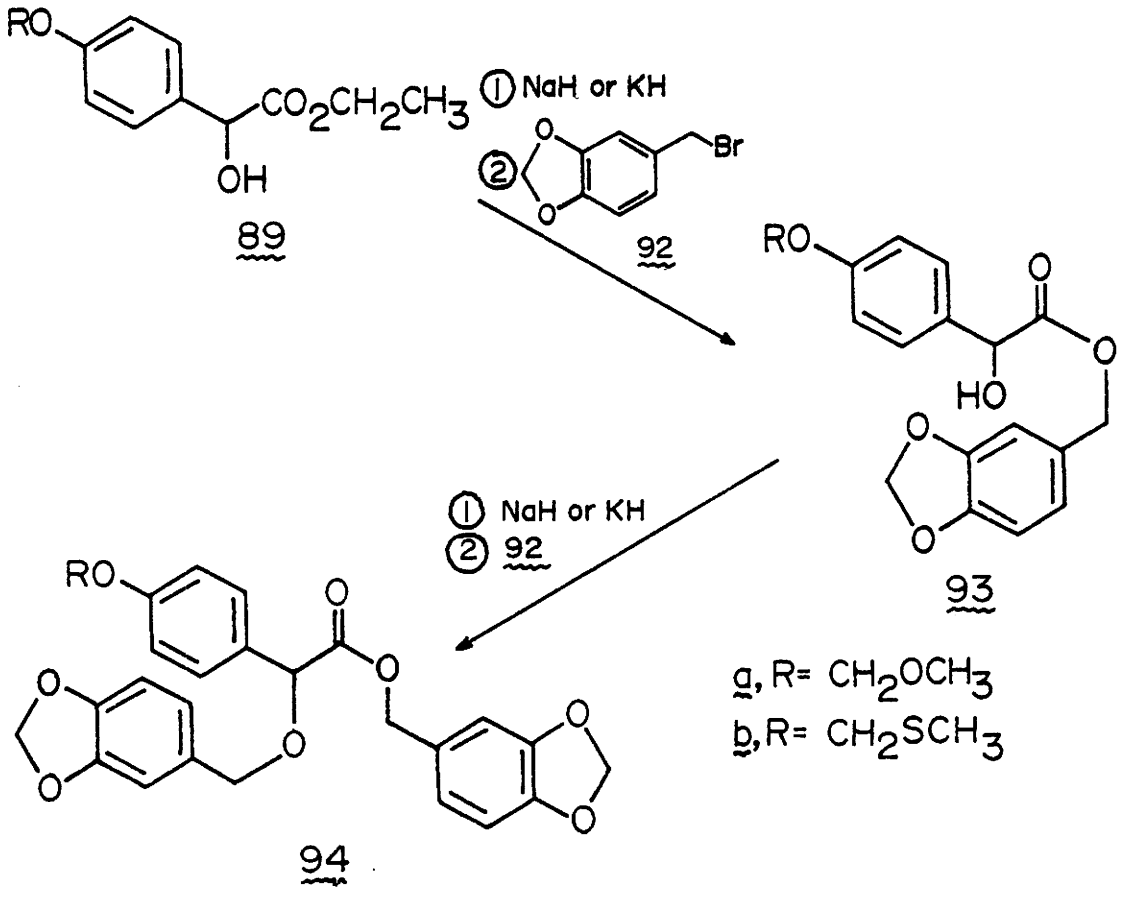
due to the diminished electrophilic character of the nitrostyrene containing a para alkoxy group or to a very ready reversibility of the reaction. In the case of 86c, piperonyl tosylate was produced via a transsulfonation reaction. Furthermore, extensive polymerization hampered the recovery of nitrostyrene in every case.



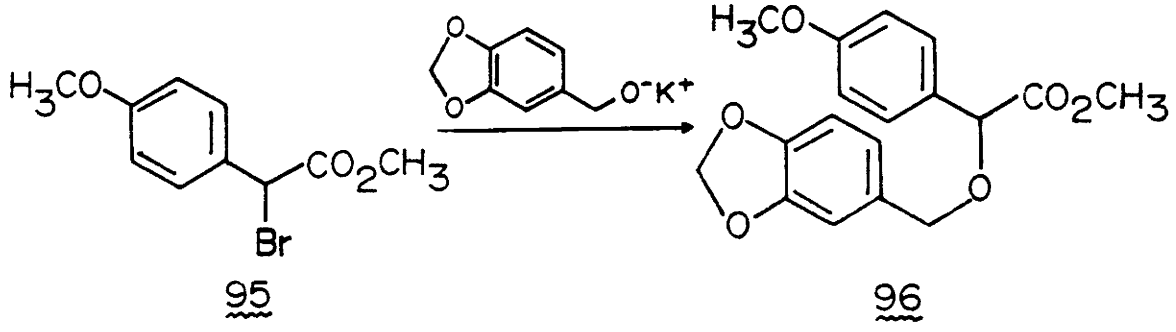
In view of these difficulties, another approach was considered in which amine 79 would be prepared after construction of the ether link. It was hoped that reduction of the amide prepared from ester 88 would give amine 79. Construction of the ether function of 88 was envisaged via a Williamson synthesis for which the preparation of the protected mandelate 89 was a prerequisite. However, when ethyl 4'-hydroxymandelate (90)[57] was treated sequentially with either sodium hydride or potassium hydride and chloromethyl ethyl ether, an inseparable mixture of phenyl acetal 89a and benzyl acetal 91 was obtained in 22-34% yield. The selective protection of the phenolic



hydroxyl group was realized using a procedure that employed chloromethyl methyl sulfide, but this reaction took place in a disappointing 23% yield. On the other hand, it was found that, instead of ether 88, benzyl esters 93a and 93b were obtained from alkylation of the potassium or sodium alkoxides from mandelates 89a and 89b with piperonyl bromide (92). The mechanism for the formation of 93a and 93b remains uncertain. A preparation of the dialkylation product 94 was also attempted, but the reaction of 89a with excess base and bromide (92) resulted only in the isolation of ester 93a. The ether 94a

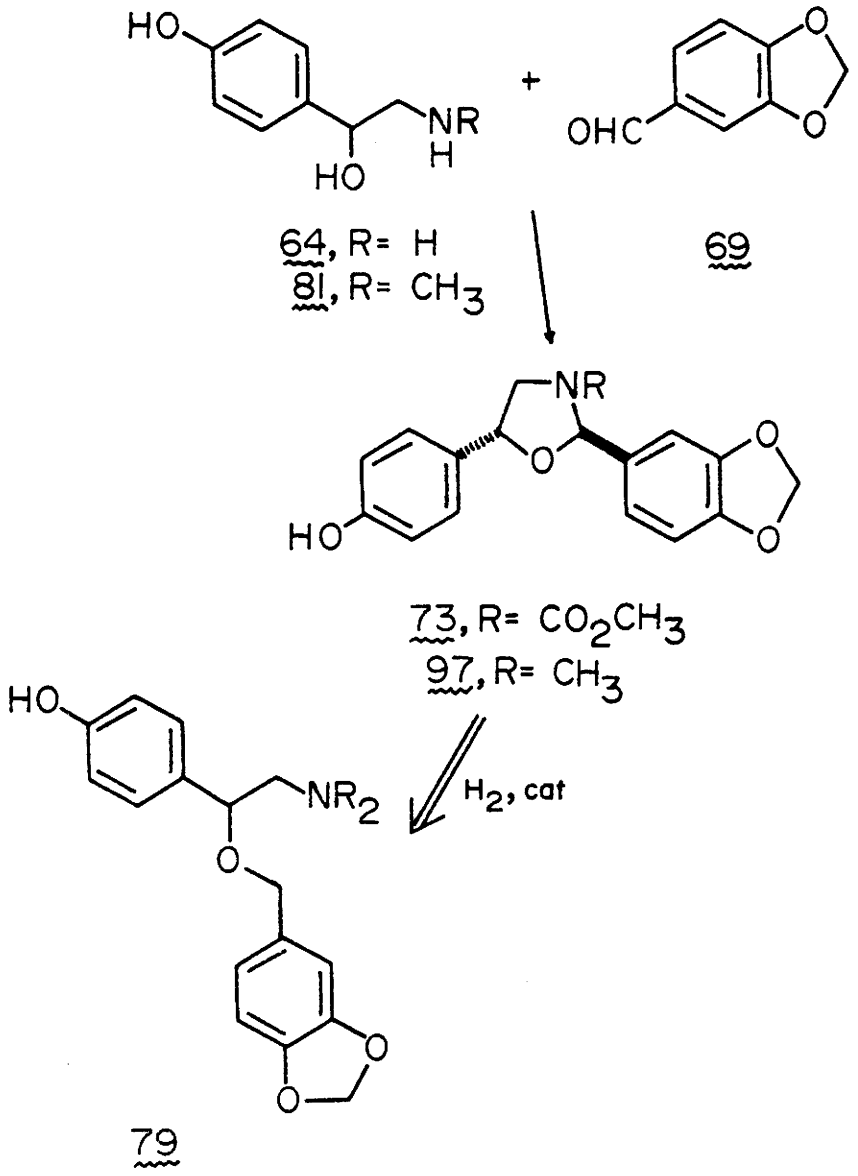


was finally obtained upon alkylation of 93a, in 1.5% yield for the two separate steps from mandelate 89a. However, all of these efforts were shown to be futile, when exposure of 94a to trifluoroacetic acid led to a quantitative cleavage of the ether to give 93a, rather than deprotection of the phenol.



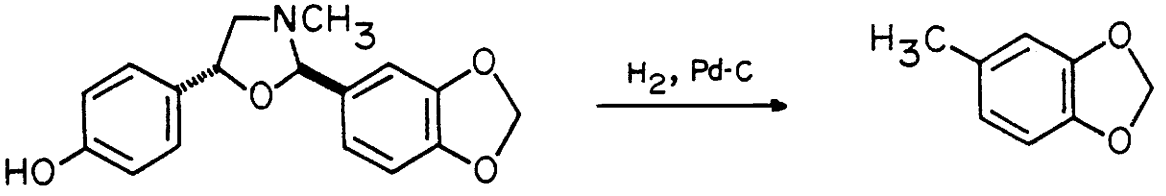
An alternative version of the Williamson synthesis approach to 79, in which the alkoxide prepared from piperonyl alcohol (34) and potassium hydride was treated with methyl 2-bromo-4'-methoxyphenyl-acetate (95)[58] was examined. This afforded the ether 96 in 16% yield. The low yield of this step was discouraging and, since the coupling substrate 79 still remained several steps away, this approach was not pursued further.

Once again attention was given to oxazolidines 73 and 97, this



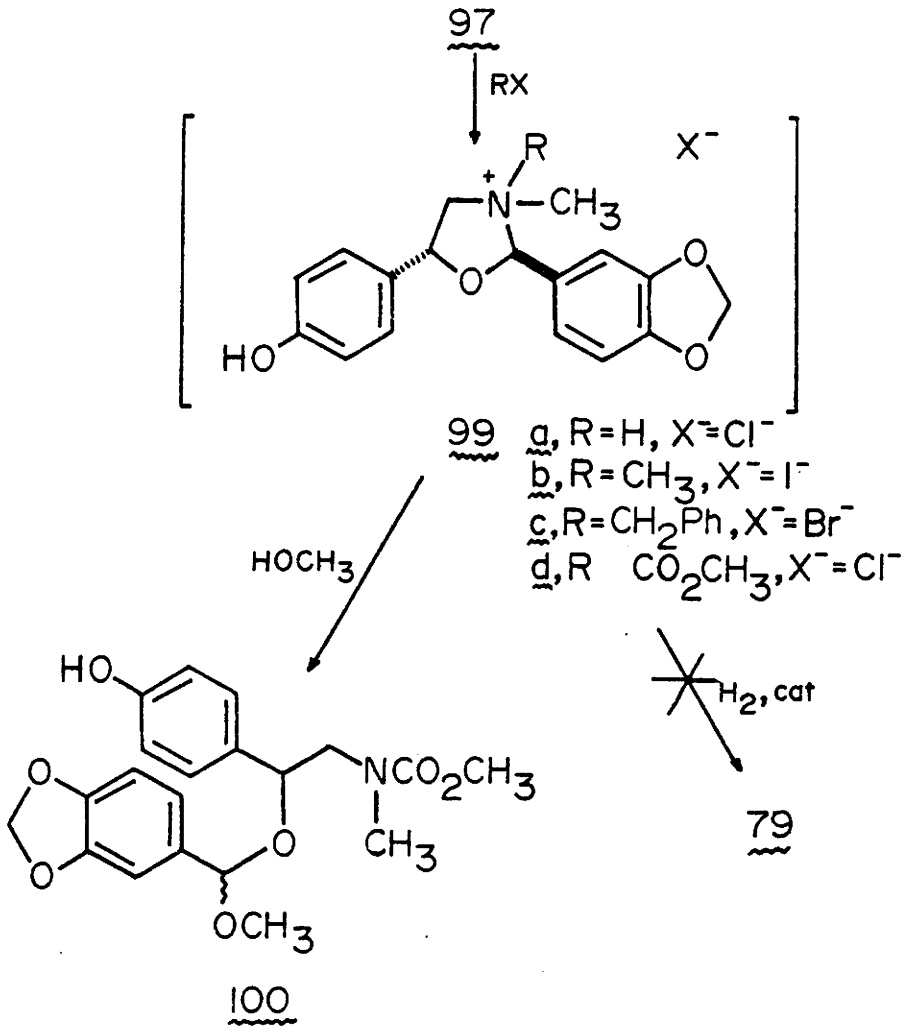
79

time as entries to acyclic coupling substrates, such as 79. The oxazolidine 97 was obtained directly and in high yield from the condensation of synephrine (81) with piperonal (69). This contrasts with the condensation of 69 with octopamine (64) studied earlier, which gave Schiff base 72. In analogy to 73, the oxazolidine 97 was presumed to have a trans configuration, since this compound displayed a singlet absorption at δ 4.72 in the proton magnetic resonance spectrum.



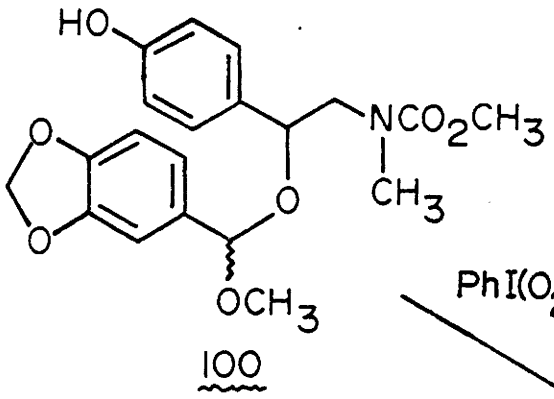
97 98

Initially, it was hoped to obtain a selective hydrogenolysis of the benzylic nitrogen bond. The only previous study of the hydrogenolysis of compounds which contained both benzylic nitrogen and oxygen linkages[59] was carried out with Raney nickel, which brought about the selective cleavage of the benzylic oxygen bond. When hydrogenolysis of oxazolidine 97 was attempted with palladium on carbon, it was found that both benzylic heterobonds were cleaved to give 5-methyl-1,3-benzodioxole (98) in 15% yield, along with recovered piperonal (69) in 17% yield. Attempted hydrogenolysis of the urethane 73 under similar condition to those employed for amine 97 gave no reaction even at three atmospheres of pressure.[60] In an attempt to make the benzylic nitrogen bond more susceptible to reductive cleavage by hydride, the oxazolidinium salts 99a,b,c,d were generated



in situ, but only rapid decomposition of the resultant dark-colored heterogeneous mixtures was observed.

In contrast to these discouraging omens, it was found that when 97 was treated with ethyl chloroformate, the labile salt 99d underwent a rapid reaction in the presence of methanol to give the acetal 100 in 71% yield after column chromatography. A well-resolved doublet at δ 3.24 for the methoxy group in the nuclear magnetic resonance spectrum of 100 indicated a mixture of diastereomers which was not separated. This result appeared distinctly promising, for, if the acetal function of 100 could withstand the conditions required for



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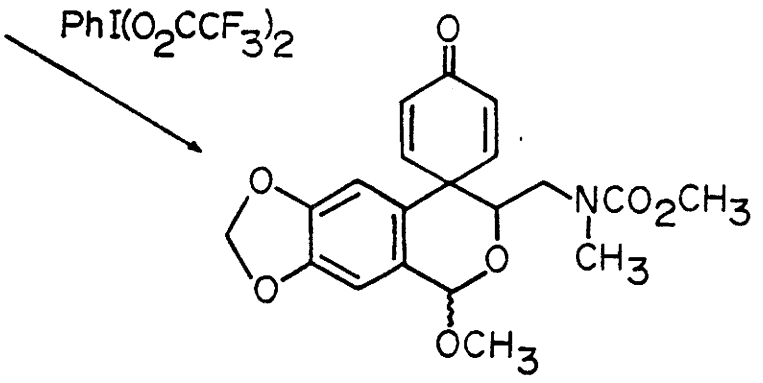

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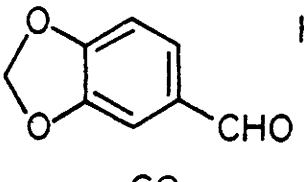
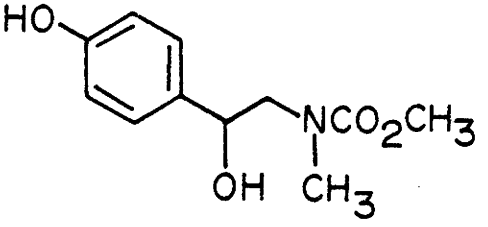


69



102

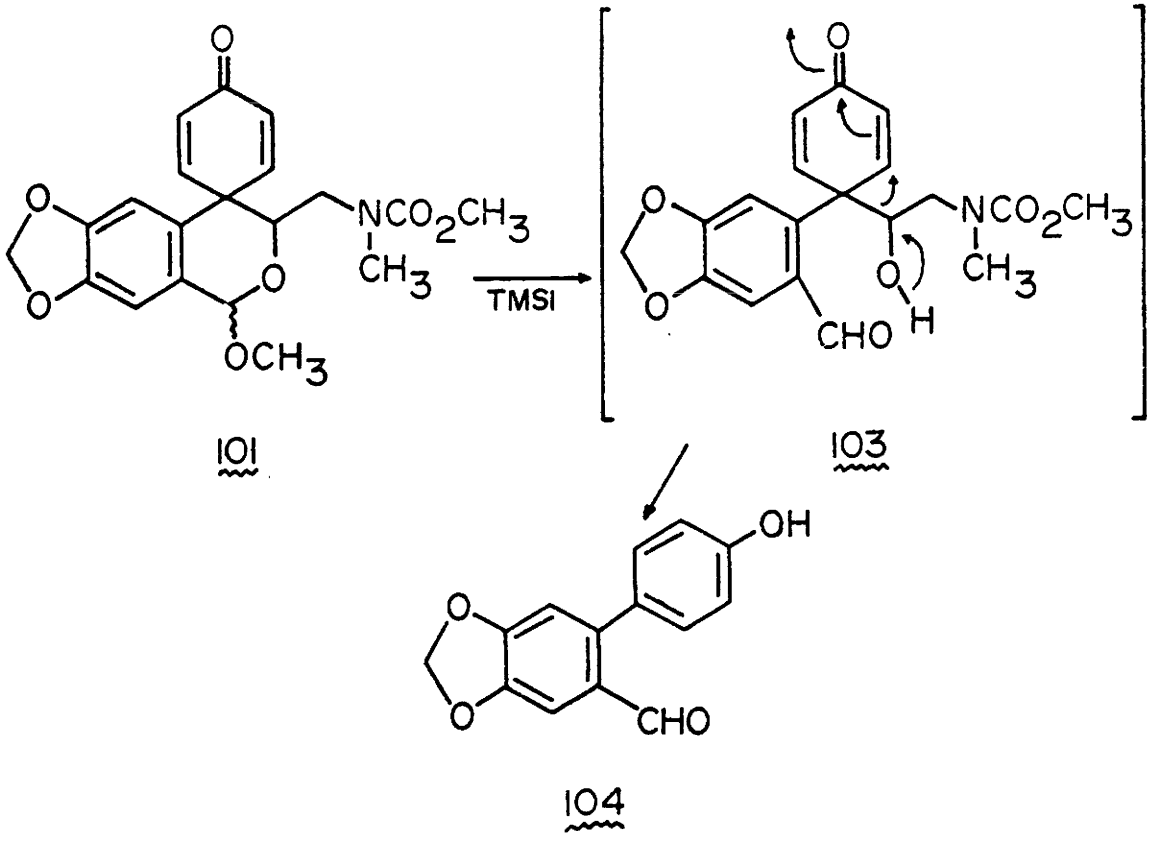
oxidative coupling, the benzylic carbons in the coupled product would already be at the oxidation level required for pretazettine.

Not suprisingly, hydrolysis of acetal 100 occurred even when low temperatures were maintained while in the presence of trifluoroacetic acid, which is the solvent required for oxidative coupling using vanadium oxytrifluoride. However, the desired dienone 101 was successfully isolated in 3-7% yield from the reaction of 100 with two equivalents of phenyliodine(III) bis(trifluoroacetate) in dichloromethane. The isolation of piperonal (69) and N-carbometh-

oxysynephrine (102) in 41 and 16% yields, respectively, was apparently due to competing hydrolysis of acetal 100. Large amounts of dark-colored polymeric material were removed by column chromatography. Unfortunately, this oxidative coupling gives even lower yields on a scale larger than 100 mg, and a batch process, which involved parallel oxidations of 100 mg portions of 100, was adopted in order to furnish sufficient material to continue this route to pretazettine.

Several methods were examined for deprotection of the nitrogen atom of 101. The urethane moiety of 101 was stable to prolonged exposure to excess lithium thiopropoxide in hexamethylphosphoramide,[61] to aqueous potassium hydroxide in tetrahydrofuran in the presence of 18-crown-6, and to lithium hydroxide in a 1:1 solution of dioxane and water.[62] Decomposition of 101 occurred with aqueous potassium hydroxide in diethylene glycol at elevated temperature.[63] Exposure of 101 to trimethylsilyl iodide, generated *in situ* according to a procedure by Olah,[64] gave the aldehyde 104 in almost quantitative yield. This product presumably arises by an initial demethylation at the acetal function to give aldehyde 103. This is followed by opening of the pyran ring and a vinylogous retroaldol fragmentation, in which the aminoethanol appendage is lost. Urethane 101 was also stable to a stoichiometric amount of the dialkoxide prepared from treatment of ethylene glycol with potassium hydride in anhydrous tetrahydrofuran, but a large excess of this base again gave the biphenyl derivative 104. The structure of 104 was readily apparent from the nuclear magnetic resonance spectrum, which prominently displayed a pattern characteristic of a para-disubstituted phenol. Although the formation of 104 intrudes inconveniently on our route to the

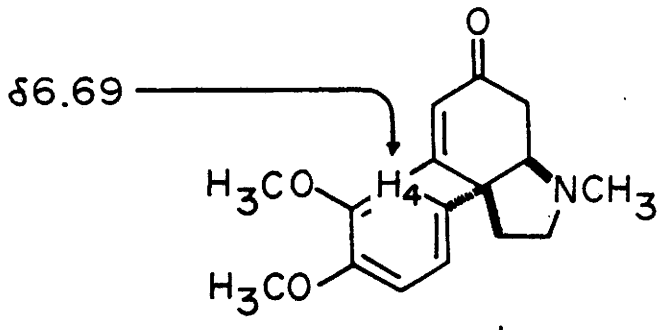
alkaloid, it does provide confirmatory evidence for the structure of the oxidative coupling product 101.



101 103

104

Hydrolysis of the urethane moiety of 101 was finally achieved with an aqueous solution of potassium hydroxide and ethylene glycol at 90°C. Under these conditions, the liberated amine 106 underwent a spontaneous intramolecular Michael reaction to give a product which was readily identified as an α,β-unsaturated ketone from an absorption at 1680 cm^{-1} in the infrared spectrum and a maximum at 226 nm in the ultraviolet spectrum. A doublet of doublets at δ 6.42 with a 10.2 Hz coupling in the nuclear magnetic resonance spectrum of this product was assigned to the β proton of the enone. This chemical shift is consistent with that reported by Jeffs, et al[65] for H_4 of mesembrenone

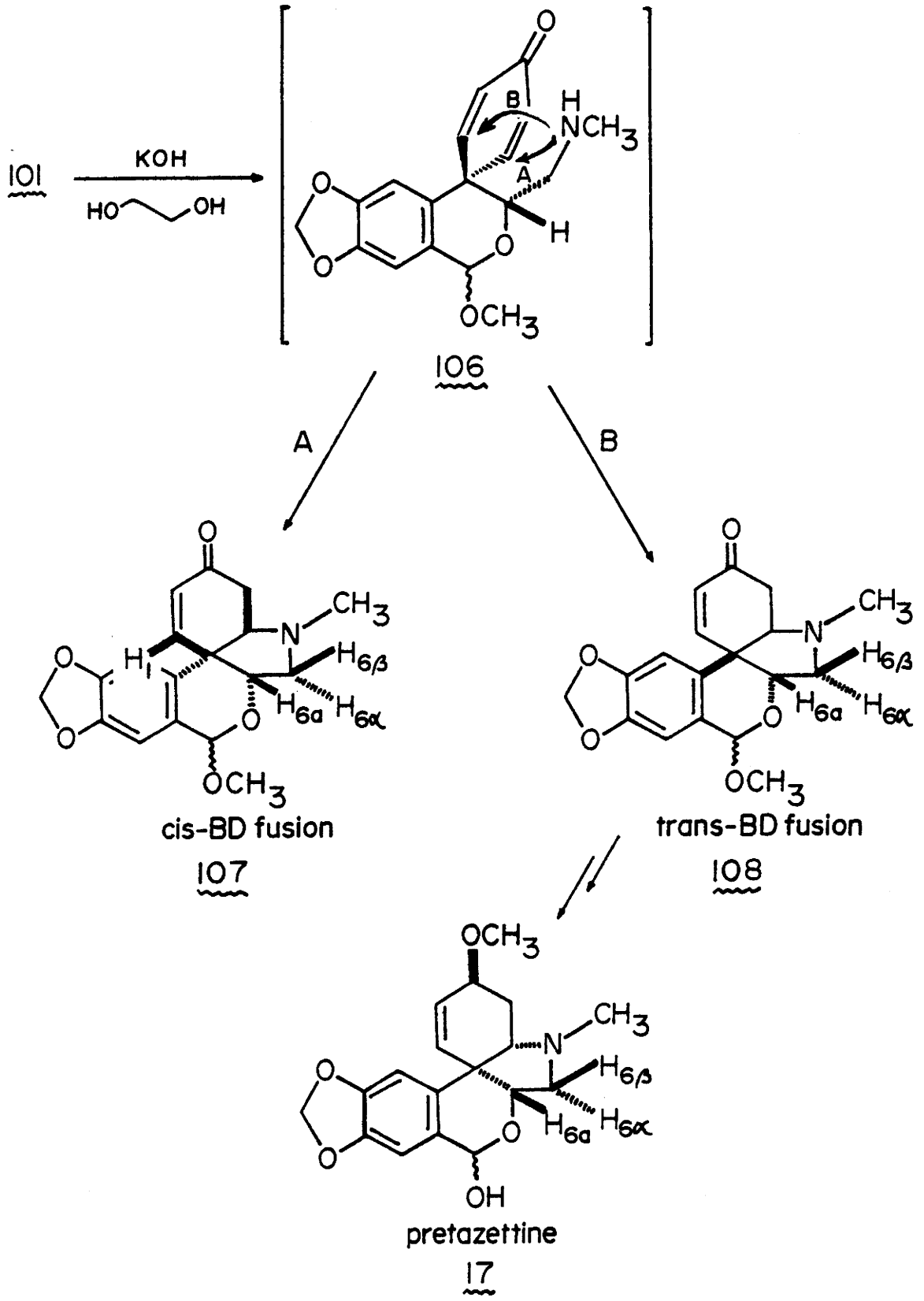


mesembrenone

105

(105), but is still upfield to an unusual extent for a β proton of an αβ- unsaturated carbonyl system. An examination of molecular models reveals that closure of the amine of 106 to give the desired tetracyclic skeleton can only occur on one face of the cyclohexadienone; however, either a cis (107) or trans (108) B-D ring fusion can result, depending upon which double bond serves as electrophile in this cyclization. The two possible fates for 106 are depicted as pathways A and B of Scheme 15. A closer scrutiny of these pathways with molecular models makes it painfully clear that the favored mode of closure should follow route A, which leads to the cis B-D fused structure, 107, rather than the more strained trans fusion of 108, which is representative of pretazettine. That this configuration was indeed the outcome of closure of the pyrrolidine ring of 106 was supported by the upfield shift of H_1, which arises from shielding of this proton by the benzenoid ring. No such shielding effect would be anticipated in a tetracyclic structure having the natural, trans B-D fusion.

Suggestive evidence that 107 possessed the cis B-D orientation was also obtained from a comparison of its nuclear magnetic resonance spectrum at 360 MHz with that of pretazettine. In particular, the


101
KOH
HO
OH
B
A
H
NCH3
O
O
O
O
H
OCH3
106
A
B
O
CH3
N
H1
H6β
H6a
H6α
O
O
O
O
OCH3
cis-BD fusion
107
O
CH3
N
H6β
H6a
H6α
O
O
O
OCH3
trans-BD fusion
108
OCH3
CH3
N
H6β
H6a
H6α
O
O
O
OH
pretazettine
17

SCHEME 15

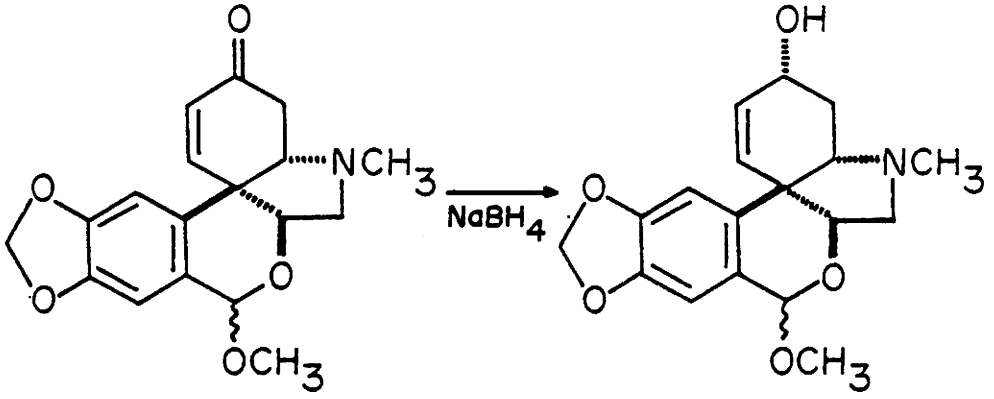
geometric relationship between the C6a and C6 protons were examined. According to spectral data for pretazettine, reported by Furusawa, et al,[18b] the signal for H_{6a} appeared as a doublet of doublets at δ 4.31 with coupling constants of 7.7 and 11.0 Hz. The smaller value corresponded to coupling between the adjacent, cis oriented H_{6a} and $H_{6\beta}$ and hence led to assignment of the resonances at δ 2.97 and 2.63 to $H_{6\alpha}$ and $H_{6\beta}$, respectively, with the determination of the $H_{6\alpha}$-$H_{6\beta}$ geminal coupling as 9.9 Hz. In the spectrum of 107, a doublet with a 4.5 Hz coupling at δ 4.39 was assigned to H_{6a} on the basis of its chemical shift (cf. δ 4.31 for H_{6a} in pretazettine). The adjacent C6 proton signals were then located via decoupling experiments. Irradiation of the signal at δ 4.39(H_{6a}) caused the collapse of a doublet of doublets at δ 3.58 to a doublet with 12.0 Hz coupling. This resonance at δ 3.58 was, in turn, shown to be coupled to a complex multiplet at δ 2.67. Since H_{6a} and $H_{6\beta}$ are cis, the coupling of 4.5 Hz was attributed to the H_{6a}-$H_{6\beta}$ coupling, and $H_{6\beta}$ corresponded to the absorption at δ 3.58. Consequently from the splitting of the H_{β} resonance, the $H_{6\alpha}$-$H_{6\beta}$ geminal coupling was 12.0 Hz, and $H_{6\alpha}$ was assigned to the resonance at δ 2.67. When the latter signal was irradiated, no effect on the H_{6a} signal was observed. This result implies that the H_{6a}-$H_{6\alpha}$ coupling is zero.

Thus, from these couplings, it is shown that H_{6a} and $H_{6\alpha}$ in 107 occupy an orthogonal relationship. Molecular models reveal that the dihedral angle between H_{6a} and $H_{6\beta}$ is approximately 19.5 degrees for the cis B-D fused structure. A different conformation of the C6a-C6 bond is exhibited by a molecular model of pretazettine, which shows a virtually eclipsed relationship between the adjacent substituents.

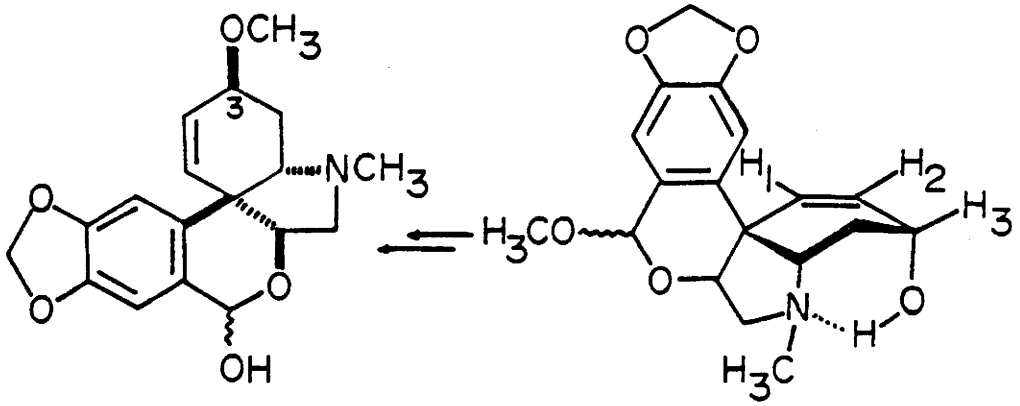
This stereochemistry is supported by the values for H_{6a}-$H_{6\alpha}$ and H_{6a}-$H_{6\beta}$ couplings in 17, which are 11.0 and 7.7 Hz, respectively.

Since formation of the cis B-D ring fusion in the cyclization of 101 denied us access to pretazettine, the synthesis was redefined to provide 6a-epipretazettine (23),[13b,28] in which the configuration at C6a is inverted from the natural compound. Danishefsky[28] has described the synthesis of 23 and its conversion to the alkaloid tazettine, which possesses the cis B-D ring fusion. Further, tazettine (20a) has been converted to pretazettine by Kobayashi, et al,[14] although this was accomplished with an extremely low yield.

The enone 107 was reduced with sodium borohydride in methanol to a single allylic alcohol in 47% yield. A strongly hydrogen-bonded hydroxyl was observed in the infrared spectrum of this substance as a broad absorption at 3300 cm^{-1}, which was unaffected by changes in concentration in chloroform. Jeffs, et al[65] observed this spectral characteristic for 6-epimesembrenol (111), which contains an α alcohol function. This led to verification of the structure which is epimeric at C3 with 23 from interpretation of the nuclear magnetic resonance spectrum. H_3 corresponded to a broad multiplet at δ 4.15, H_1 to a complex multiplet at 5.55 to 5.25, and H_2 to a doublet of doublets at 6.25, with H_1-H_2 and H_2-H_3 couplings of 10.0 and 5.0 Hz, respectively. These couplings are fully consistent with the small dihedral angle between H_2 and H_3 which is observed with the C-ring in a "twist boat" conformation, as illustrated in 110, and documented for these Amaryllidaceae alkaloids.[65,66] An alternate conformation of the C-ring places H_2 and H_3 in an orthogonal relationship, for which a smaller H_2-H_3 coupling would have been expected.

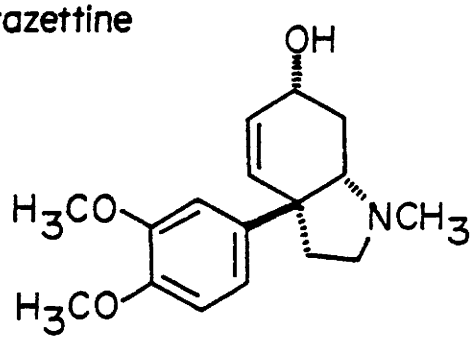


107 109



C6a-epipretazettine
23

110



6-epimesembrenol
111

Numerous methods are available for inversion of the configuration of alcohols.[67] These could be applied to the C3 oxygen in 109, or alternative reduction of enone 107 could be carried out in order to obtain a substance with the stereochemistry of C6a-epipretazettine (23). This will be the aim of future investigations. This partially completed sequence nevertheless demonstrates an expedient synthesis of [2]benzopyrano[3,4c]indoles, such as 107. De novo synthesis of this class via phenolic oxidative coupling using hypervalent iodine species with substrates that contain significant functionality represents a promising new development in alkaloid chemistry.

IV. EXPERIMENTAL

General

Melting points were obtained on a Büchi melting-point apparatus and are uncorrected. Infrared spectra (IR) were obtained with a Perkin-Elmer 727B infrared spectrometer. Ultraviolet spectra (UV) were obtained on a Varian-Cary 210 Ultraviolet/Visible Spectrophotometer. Nuclear magnetic resonance spectra (NMR) were obtained with either a Nicolet 360, Varian EM-360A, HA-100, or FT-80A and are reported in δ units with tetramethylsilane (TMS) as the internal standard; the abbreviations s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, bs=broad singlet, etc. are used throughout. Mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. Exact mass determinations were performed on a CEC-110C spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by MicAnal, Tuscon, Arizona. Column chromatography was performed using neutral silica gel 60 230-400 mesh ASTM or alumina of various activities, 80-200 mesh. Medium pressure liquid chromatography (MPLC) was performed using an FMI solvent pump. Analytical thin layer chromatography (TLC) plates were obtained from Analtech. High pressure liquid chromatography (HPLC) was performed using a Waters M45 solvent pump with a Waters UA5 injector and Waters semipreparative silica or C_{18} reversed phase columns. An Isco UV detector was used for both high pressure and medium pressure liquid chromatography at a wavelength of 300 nm. Dry tetrahydrofuran, ether, and benzene were obtained by distillation over sodium and benzophenone.

All organic solutions were dried and filtered through a sintered glass funnel prior to rotary evaporation at water aspirator pressure. Residual solvent was removed under vacuum, usually at less than 0.2 Torr. All reactions were routinely carried out under an inert atmosphere of argon or nitrogen. All glassware was dried in an oven at 150°C.

Phenyliodine(III) Diacetate.

This was prepared from iodobenzene according to a procedure by Sharefkin and Saltzman[68] and checked for purity by titration with 1N sodium thiosulfate.[69]

Phenyliodine(III) Bis(trifluoroacetate).

This was prepared from phenyliodine(III) diacetate according to a procedure by Loudon, et al[70] and checked for purity by titration with 1N sodium thiosulfate.[69]

Iodoxybenzene.

This was prepared from iodobenzene according to a procedure by Barton, et al[71] and checked for purity by titration with 1N sodium thiosulfate.[69]

Tetraethylammonium Diacetoxyiodate(I) (26a).

This was prepared from tetraethylammonium iodide according to a procedure by Doleschall and Toth[43] and checked for purity by titration with 1N sodium thiosulfate.[69]

Tetraethylammonium Bis(trifluoroacetoxy)iodate(I) (26b).

This was prepared from tetraethylammonium iodide according to a procedure by Szantay, et al[34] and checked for purity by titration with 1N sodium thiosulfate.[69]

2-Trifluoroacetyl-5',6',7',8'-tetrahydrospiro[2,5-cyclohexadien-4-one-1,9'-[9H,1,3]dioxolo[4,5-h][2]benzazepine], (14a).

a. Oxidative Coupling of 13a with Phenyliodine(III) Bis(trifluoroacetate): To a solution of 13a (100 mg, 0.273 mmol) in dry dichloromethane (15 mL) at -30°C was added a solution of phenyliodine(III) bis(trifluoroacetate) (2.2 equiv, 250 mg, 0.581 mmol) in dichloromethane (10 mL). After 12 h the resultant green solution was shaken with freshly prepared 1N sodium thiosulfate (2 x 25 mL) to give a colorless solution. The separated organic layer was washed with saturated aqueous sodium bicarbonate (25 mL) and brine (2 x 25 mL), dried over sodium sulfate, and evaporated to give a dark green oil, which was chromatographed on alumina (Activity I). Elution with ethyl acetate provided 11.8 mg (11.8%) of dienone 14a[11] as a pale yellow oil.

b. Oxidative Coupling of 13a with Iodoxybenzene: To a solution of 13a (100 mg, 0.273 mmol) in dry dichloromethane (15 mL) at -50°C was added a solution of iodoxybenzene (64 mg, 0.273 mmol) in dichloromethane (10 mL) followed by a 20:1 (v:v) mixture of trifluoroacetic acid : trifluoroacetic anhydride (200 µL). A red color was immediately produced, which changed to purple after 10 min. At this time the reaction mixture was shaken with saturated aqueous sodium bicarbonate (20 mL) and the separated aqueous layer was further extracted with dichloromethane (15 mL). The combined dichloromethane layers were

washed with fresh 1N sodium thiosulfate (2 x 25 mL) and brine (3 x 25 mL), dried over sodium sulfate, and evaporated to afford a brown oil, which was chromatographed on alumina (Activity I). Elution with ethyl acetate in hexane provided 4.5 mg (4.5%) of 14a[11] as a pale yellow oil.

2-(4-Hydroxymethylphenoxy)tetrahydropyran (29a).

To a solution of 4-hydroxybenzaldehyde (5.00 g, 41.0 mmol, recrystallized from water containing sodium bisulfite and dried under vacuum over phosphorus pentoxide) in dry tetrahydrofuran (25 mL) at 0°C was added sequentially dihydropyran (7.48 mL, 82.0 mmol) and pyridinium p-toluenesulfonate[38] (200 mg, 0.8 mmol). After 36 h the resultant yellow solution was diluted with ether (100 mL), washed with brine (35 mL), saturated aqueous sodium bicarbonate (3 x 35 mL), again with brine (2 x 25 mL), and dried under vacuum to provide 8.45 g (100%) of 28a as a yellow oil. To a solution of this oil in methanol (50 mL) at 0°C was added sodium borohydride (0.78 g, 82.0 mmol) in portions. After 20 min, the solution was diluted with water (50 mL), saturated with solid sodium chloride, and extracted with ether (3 x 35 mL). The combined ethereal layers were washed with saturated aqueous sodium bicarbonate (2 x 30 mL) and brine (2 x 30 mL), and dried over sodium sulfate. Removal of the solvent under reduced pressure provided 7.91 g (92.7%) of 29a as a yellow oil: IR (neat) 3390 (-OH), 2950, 2875, 1610, 1520, 1240, 1200, 1180, 1170, 1120, 1105, 1070, 1030, 1018, 960, 918 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (d, 2H, J=9.5 Hz, Ar-H ortho to alkoxy), 7.05 (d, 2H, J=9.5 Hz, Ar-H meta to alkoxy), 5.35 (bs, 1H, -OCH(OR)R'), 4.75 (s, 2H, $ArCH_2O$-), 3.90-3.22 (m, 2H, $-OCH_2CH_2$-), 1.86-1.63 (m, 6H,

$-CH_2(CH_2)_3CH(OR)R'$); MS m/z (rel int) 208(1.7), 124(55.0), 85(100).

2-[4-(3,4-Methylenedioxyphenylmethoxymethyl-phenoxy][2H]tetrahydropyran (31a).

A solution of 29a (170 mg, 0.817 mmol) in tetrahydrofuran (3 mL) was added to a suspension of hexane-rinsed potassium hydride (33 mg, 0.817 mmol) in tetrahydrofuran (10 mL). After 45 min the resultant yellow alkoxide solution was treated with a solution of 3,4-methylenedioxybenzyl chloride (139 mg, 0.817 mmol) in tetrahydrofuran (5 mL). After stirring overnight at room temperature the resultant mixture was diluted with water (20 mL) and extracted with ether (1 x 35 mL, 2 x 10 mL). The combined ethereal layers were washed with brine (3 x 15 mL), dried over sodium sulfate and concentrated under reduced pressure to afford 279 mg (100%) of 31a as a yellow oil, which was used without further purification: IR (neat) 2940, 2870, 1510, 1220, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25-6.72 (m, 7H, Ar-H), 5.90 (s, 2H, $-OCH_2O-$), 5.37 (bt, 1H, $-OCH(OR)CH_2-$), 4.93 (s, 2H, $(C_6H_3)CH_2O-$), 4.87 (s, 2H, $(C_6H_4-CH_2O-$), 4.03-3.97 (m, 2H, $-OCH_2CH_2-$), 1.75-1.62 (m, 6H, $-OCH_2(CH_2)_3CH-$); MS m/z (rel int) 342(0.3), 258(35.1), 149(18.9), 136(97.6), 135(98.4), 121(13.7), 108(24.0), 107(34.1).

4-Methylthiomethoxybenzaldehyde (28b)

Following a procedure by Holton and Davis,[39] a solution of 4-hydroxybenzaldehyde (10.0 g, 81.9 mmol, recrystallized from water containing sodium bisulfite and dried under vacuum over phosphorus pentoxide) in freshly dried hexamethylphosphoramide (35 mL) was added to a suspension of hexane-rinsed sodium hydride (4.32 g, 90.1

mmol) in hexamethylphosphoramide (15 mL). After 90 min, the resultant red phenoxide solution was treated with chloromethyl methyl sulfide (7.55 mL, 90.1 mmol). After 18 h at room temperature, the resultant yellow-green suspension was acidified with 10% hydrochloric acid (approximately 2 mL), partitioned between water (100 mL) and benzene (4 x 50 mL). The benzene layers were combined, washed with saturated aqueous sodium bicarbonate (2 x 50 mL) and brine (3 x 25 mL), dried over sodium sulfate, and evaporated to provide 14.2 g (95.3%) of 28b as a yellow oil which was used without further purification: IR (neat) 1690 (-CHO), 1600, 1580, 1510, 1210, 1160, 985, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.88 (s, 1H, -CHO), 7.86 (d, 2H, J=8.1 Hz, Ar-H ortho to thiomethoxy group), 7.10 (d, 2H, J=8.1 Hz, Ar-H meta to thiomethoxy group), 5.28 (s, 2H, $-SCH_2O-$), 1.36 (s, 3H, $-SCH_3$).

4-Methylthiomethoxybenzyl Alcohol (29b).

To a solution of crude 28b (14.2 g, 78.1 mmol) in methanol (150 mL) at 0°C was added sodium borohydride (1.71 g, 45.1 mmol) in portions. After 1 h at 0°C, the methanol was evaporated in vacuo, the resultant red oil was placed in water (50 mL), acidified with 10% hydrochloric acid, and extracted with ether (5 x 25 mL). The combined ethereal layers were washed with saturated aqueous sodium bicarbonate (2 x 50 mL) and brine (4 x 50 mL), dried over sodium sulfate, and evaporated to afford 13.2 g (94.9%) of 29b as a yellow-orange oil, which was used without further purification: IR (neat) 3350 (-OH), 1605, 1510, 1203, 1174, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (d, 2H, J=8.2 Hz, Ar-H ortho to thiomethoxy group), 6.96 (d, 2H, J=8.2 Hz, Ar-H meta to thiomethoxy group), 5.18 (s, 2H, $-SCH_2O-$), 4.63 (s, 2H, $ArCH_2OH$) 2.32 (s, 3H,

-SCH_3).

3,4-Methylenedioxy-4'-methylthiomethoxydibenzyl Ether (31b).

A solution of 29b (300 mg, 1.63 mmol) in dry tetrahydrofuran (20 mL) was added dropwise to a suspension of hexane-rinsed potassium hydride (292 mg, 1.79 mmol) in tetrahydrofuran (5 mL). After 1 h at room temperature, the cloudy yellow alkoxide mixture was treated with 3,4-methylenedioxybenzyl chloride (306 mg, 1.79 mmol). After 10 h at room temperature, the reaction was diluted with water (10 mL), acidified with 10% hydrochloric acid, and extracted with ether (1 x 35 mL, 2 x 15 mL). The combined ethereal layers were washed with brine (2 x 25 mL), saturated aqueous sodium bicarbonate (35 mL) and again with brine (3 x 25 mL), dried over sodium sulfate, and evaporated to furnish a yellow oil, which was chromatographed on silica gel. Elution with ethyl acetate in hexane provided 326 mg (62.9%) of 31b as a yellow oil: IR (neat) 2900, 2850, 1500, 1490, 1440, 1263, 1205, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37-6.82 (m, 7H, Ar-H), 5.98 (s, 2H, -OCH_2O-), 5.19 (s, 2H, -SCH_2O-), 4.52 (d, 4H, ArCH_2O-), 2.32 (s, 3H, -SCH_3); MS m/z (rel int) 318(12.5), 136(28.5), 135(40.6); exact mass m/z 318.091 (calcd for $C_{17}H_{18}O_4S$: 318.093).

4-Hydroxy-3',4'-methylenedioxydibenzyl Ether (32).

a. Deprotection of 31b: Chloramine T (44.0 mg, 0.151 mmol) was added to a solution of 31b (50.0 mg, 0.157 mmol) in 85% aqueous methanol. After stirring for one min, water (5 mL) was added, and the resultant suspension was extracted with ether (2 x 20 mL). The separated, combined ethereal layers were extracted with 2N sodium

hydroxide (5 mL). The separated alkaline solution was acidified with 6N hydrochloric acid and extracted into ether (2 x 15 mL). These ethereal layers were washed with brine (2 x 10 mL), dried over sodium sulfate, and evaporated to provide 22 mg (54.3%) of phenol 32 as yellow crystals, mp 117.8-118.5°C, which was recrystallized from dichloromethane/hexane: IR (KBr) 3420 (-OH), 2900, 1605, 1598, 1490, 1443, 1372, 1235, 1035, 1003 cm^{-1}; ^1H NMR ($CDCl_3$: D_3CSOCD_3) δ 7.17-6.67 (m, 7H, Ar-H), 5.85 (s, 2H, $-OCH_2O-$), 4.35 (d, 4H, $Ar-CH_2O-$); MS m/z (rel int) 258(16.9), 152(10.4), 136(100.0), 135(83.1), 108(18.6), 107(51.6), 106(19.3); exact mass m/z 258.090 (calcd for $C_{15}H_{14}O_4$ 258.090).

b. Deprotection of 31a: Pyridinium p-toluenesulfonate[38] (22 mg, 0.082 mmol) was added to a solution of 31a in methanol (15 mL). After 90 min the reaction mixture was partitioned between brine (20 mL) and ether (3 x 15 mL). The combined ethereal layers were washed with saturated aqueous sodium bicarbonate (2 x 10 mL) and brine (2 x 20 mL), dried over sodium sulfate and evaporated to give 204 mg (96.6%) of 32 as a semi-crystalline yellow solid. Recrystallization from dichloromethane/hexane provided 132 mg (64.7%) of 31a in successive crops as colorless microneedles, mp 117.5-118.5°C.

7',8'-Dihydrospiro[2,5-cyclohexadien-4-one-1,8'-[5H-1,3]dioxolo[4,5-h][2]benzopyran] (33).

a. Oxidative Coupling of 32 with Vanadium Oxytrifluoride: To a solution of 32 (50 mg, 0.20 mmol) in dichloromethane (3.2 mL) and ethyl acetate (0.5 mL) at -40°C was added a solution of 20:1 (v:v) trifluoroacetic acid : trifluoroacetic anhydride (0.40 mL). Subsequently

a solution of vanadium oxytrifluoride (61 mg, 0.49 mmol) in ethyl acetate (0.7 mL) was added and immediately produced a blue solution. After stirring for 30 min at -30°C, the reaction was quenched with 10% aqueous citric acid (10 mL) and made slightly alkaline (pH 7.5 by pH paper) with 58% ammonium hydroxide. The resultant blue layer was extracted with ethyl acetate (35 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over sodium sulfate, and concentrated in vacuo to furnish a brown oil, which was applied to an alumina (Activity I) preparative TLC plate. Development of the plate with 5% ethyl acetate in benzene and subsequent extraction of the adsorbent with 20% methanolic dichloromethane led to recovery of 8 mg (16 %) of 32 and 12 mg (23 %) of 33 as a yellow solid, mp 130-132°C: IR (KBr) 1660 (C=C-C=O), 1623, 1485, 1243, 1040, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03-6.25 (m, 7H, Ar-H and -HC=CH-C=O), 5.88 (s, 2H, $-OCH_2O-$), 4.73 (2H, s, $ArCH_2O$), 3.88 (2H, s, $-OCH_2-$); MS m/z (rel int) 256(26.6), 226(100), 198(27.2), 197(23.2), 196(24.2), 169(15.3), 168(67.9), 167(12.9), 149(13.9), 141(21.1), 140(66.7), 139(63.5), 115 (18.4); exact mass m/z 256.073 (calcd for $C_{15}H_{12}O_4$: 256.074).

b. Oxidative Coupling of 32 with Phenyliodine(III) Bis(trifluoroacetate): A solution of phenyliodine(III) bis(trifluoroacetate) (135 mg, 0.315 mmol) in dichloromethane (5 mL) was added to a solution of 32 (41 mg, 0.16 mmol) in dichloromethane (2 mL) and ethyl acetate (5 mL) at -25°C. The reaction was warmed to 10°C and allowed to stir for 3.5 h before shaking with saturated aqueous sodium bicarbonate (15 mL). The separated organic layer was washed with saturated aqueous sodium bicarbonate (2 x 15 mL) and brine (3 x 20 mL), dried over sodium sulfate and concentrated under reduced pressure to a brown oil,

which was chromatographed on silica gel. Elution with ethyl acetate in benzene provided 6.9 mg (28.7%) of piperonyl alcohol (34) and 3.8 mg (9.3%) of 33 as a colorless solid, mp 130-132°C.

c. Oxidative Coupling of 32 with Iodoxybenzene: A solution of iodoxybenzene (45.7 mg, 0.194 mmol) in trifluoroacetic anhydride (27 μL, 0.194 mmol), trifluoroacetic acid (100 μL), and dichloromethane (5 mL) was added to a solution of 32 (100 mg, 0.388 mmol) in dichloromethane (10 mL) and ethyl acetate (5 mL) at -45°C. An orange color immediately resulted, and after 2.5 h at -45°C another equivalent of iodoxybenzene (45.7 mg, 0.194 mmol) was added. After 30 min, the reaction mixture was shaken with saturated aqueous sodium bicarbonate (20 mL) and extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with fresh 1N sodium thiosulfate (25 mL) and brine (3 x 15 mL), dried over sodium sulfate, and evaporated in vacuo to furnish a brown oil, which was passed through silica gel with 50% ethyl acetate in hexane. The resultant orange oil was chromatographed on alumina (Activity I) and elution with 35% ethyl acetate in hexane led to recovery of 7.0 mg (7.0%) of 32 and the isolation of 3.5 mg (3.5%) of 33 as a colorless solid, mp 130-132°C, which matched previously obtained material on TLC and spectrally.

4-Hydroxy-3-iodo-3',4'-methylenedioxydibenzyl Ether (36) and 3,5-Diiodo-4-hydroxy-3',4'-methylenedioxydibenzyl Ether (37).

a. Reaction of 32 with Tetraethylammonium Bis(trifluoroacetoxy)iodate(I): To a solution of 32 (100 mg, 0.388 mmol) in dichloromethane (10 mL) and ethyl acetate (5 mL) at -35°C was added a solution of tetraethylammonium bis(trifluoroacetoxy)iodate(I) (187 mg, 0.388 mmol) in

dichloromethane (5 mL). After 5 h at -35→-25°C, the reaction was shaken with fresh 0.1N sodium thiosulfate (15 mL). The separated organic layer was washed with saturated aqueous sodium bicarbonate (2 X 15 mL) and brine (25 mL), dried over sodium sulfate, and concentrated *in vacuo* to provide a cloudy oil, which was chromatographed on silica gel. Elution with ethyl acetate in hexane led to the recovery of 21 mg (21%) of **32** and the isolation of 24 mg (15%) of **36** as a colorless oil and 29 mg (15%) of **37** as white platelets, mp 126.5-128°C.

36: IR (neat) 3300 (OH), 2970, 1485, 1440, 1410, 1350, 1240, 1200, 1117, 1090, 1023, 913, 797 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69-7.83 (m, 6H, Ar-H), 6.02 (s, 2H, $-OCH_2O-$), 5.54 (bs, 1H, ArOH), 4.52 (s, 2H, $ArCH_2O-$), 4.50 (s, 2H, $ArCH_2O-$); MS m/z (rel int) 384(36.2), 233(23.6), 136(100), 135(77.5), 106(24.7); exact mass m/z 383.987 (calcd for $C_{15}H_{13}O_4I$: 383.986).

37: IR (KBr) 3500 (OH), 1595, 1560, 1542, 1235 (Ar-I), 1053, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69-6.83 (m, 6H, Ar-H), 6.02 (s, 2H, $-OCH_2O-$), 5.54 (bs, 1H, ArOH), 4.52 (s, 2H, $ArCH_2O-$), 4.50 (s, 2H, $ArCH_2O-$); MS m/z (rel int) 510(33.6), 233(27.6), 149(12.8), 135(100); exact mass m/z 509.885 (calcd for $C_{15}H_{12}O_4I_2$: 509.883).

b. Reaction of **32** with Tetraethylammonium Diacetoxyiodate(I): To a solution of **32** (100 mg, 0.388 mmol) in dichloromethane (5 mL) at -78°C was added a solution of tetraethylammonium diacetoxyiodate(I) (145 mg, 0.388 mmol) in dichloromethane (10 mL). After 5 h at -78°C, the yellow-orange solution was allowed to warm to 0°C and shaken with saturated aqueous sodium bicarbonate (10 mL). The separated organic layer was washed with fresh 1N sodium thiosulfate and brine (3 x 25

mL), dried over sodium sulfate and evaporated to give a yellow, semi-crystalline solid, which was chromatographed on silica gel. Elution with ethyl acetate in hexane provided 23 mg (23%) of recovered 32, 22 mg (14%) of 36 as a colorless oil and 31 mg (16%) of 37 as white platelets, mp 126.5-128°C.

2-Methoxy-5-(N-trifluoroacetyl-4-hydroxyphenethyl-aminomethyl)-2,5-cyclohexadien-1,4-dione (38).

a. Oxidation of 13b with Phenyliodine(III) Bis(trifluoroacetate): To a solution of 13b[11] (116 mg, 0.314 mmol) in dichloromethane (10 mL) at -30°C was added a solution of phenyliodine(III) bis(trifluoroacetate) (135 mg, 0.314 mmol) in dichloromethane (10 mL). After 30 min, another equivalent of phenyliodine(III) bis(trifluoroacetate) (135 mg, 0.314 mmol) in dichloromethane (10 mL) and pyridinium trifluoroacetate (61 mg, 0.314 mmol) in dichloromethane (7 mL) were added in succession. After a total of 8.3 h at -30°C, the reaction was shaken with fresh 1N sodium thiosulfate (15 mL). The separated organic layer was washed with saturated aqueous sodium bicarbonate (4 x 10 mL) and brine (3 x 10 mL), dried over sodium sulfate and evaporated to afford a brown oil, which was chromatographed on silica gel. Elution with 3% methanolic dichloromethane provided 35 mg (29%) of quinone 36 as a yellow oil, which rapidly darkened upon further handling: IR ($CHCl_3$) 3375 (ArOH), 1680 ($NCOCF_3$), 1655 (C=O of quinone), 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (d, 2H, J=8.0 Hz, Ar-H ortho to phenol hydroxyl), 6.73 (d, 2H, J=8.0 Hz, Ar-H meta to phenol hydroxyl), 6.37 (m, 1H, H_2 of quinone), 5.92 (s, 1H, H_6 of quinone), 4.47 (AB system, 2H, $-CCH_2N-$), 3.83 (s, 3H, $-OCH_3$), 3.00 (t, 2H, $-CH_2CH_2N-$), 2.32 (t, 2H, $ArCH_2CH_2-$); UV

(CH_3OH) λ_{max} 225 (ε 13800), 259 nm (ε 11300); MS m/z (rel int) 383 (4.3), 276(7.8), 152(17.9), 120(100).

b. Oxidation of 13b with Tetraethylammonium Bis(trifluoroacetoxy)-iodate(I): To a solution of 13b (100 mg, 0.271 mmol) in dichloromethane (10 mL) at -35°C was added a solution of 24b (131 mg, 0.271 mmol) in dichloromethane (10 mL). After 90 min, another equivalent of 24b (131 mg, 0.271 mg) in dichloromethane (10 mL) renewed the red-violet color. After a total of 3 h had elapsed, the reaction was shaken with 0.1N sodium thiosulfate (35 mL). The separated organic layer was washed with saturated aqueous sodium bicarbonate (2 x 15 mL) and brine (4 x 15 mL), dried over sodium sulfate, and concentrated under reduced pressure to furnish a brown oil, which was applied to a silica gel preparative thin-layer chromatographic plate. After development in 7% methanolic chloroform and extraction of the adsorbent with 25% methanolic dichloromethane, 5.6 mg (5.4%) of quinone 36 was isolated as a yellow oil, which matched previously obtained material.

N-(4-Hydroxyphenethyl)-3,4-methylenedioxybenzamide (45).

Thionyl chloride (1.5 mL) was added to a slurry of piperonylic acid (1.00 g, 6.00 mmol) in dry benzene (1 mL). After refluxing for 1 h, thionyl chloride was removed under reduced pressure, which afforded crude 3,4-methylenedioxybenzoyl chloride (58) as a slightly yellow, acrid solid. A solution of 58 in ether (10 mL) was added dropwise to a rapidly stirring solution of tyramine (0.824 g, 6.00 mmol) in a minimal amount of 1N potassium hydroxide. After evaporation of the ethereal layer under reduced pressure, filtration of the aqueous slurry

provided 1.66 g (97%) of 45 as an amorphous solid, which was recrystallized from methanol/ether as yellow needles, mp 141-142°C: IR (Nujol) 3350 (NH,OH), 1630 (CONH), 1590, 1550, 1510, 1480, 1290, 1240, 1026 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 8.27 (bs, 1H, -OH), 7.42-6.70 (m, 7H, Ar-H), 6.06 (s, 2H, $-OCH_2O-$), 2.65 (t, 2H, $-CH_2CH_2N-$); MS m/z (rel int) 285(9.5), 149(100); exact mass m/z 285.098 (calcd for $C_{16}H_{15}NO_4$: 285.100).

p-Benzyloxyacetophenone (52).

A solution of 51 (6.00 g, 44.1 mmol, recrystallized from water and dried under vacuum over phosphorous pentoxide) in dry N,N-dimethylformamide (4 mL) was added dropwise to a rapidly stirred suspension of sodium hydride (2.10 g, 44.1 mmol) in N,N-dimethylformamide (40 mL) at 0°C. After cessation of hydrogen evolution, benzyl bromide (5.5 mL) was added dropwise via syringe. After 5 min the resultant tan suspension was partitioned between benzene (80 mL) and water (100 mL). The separated organic layer was washed with water (3 x 100 mL), dried over magnesium sulfate and evaporated to give a yellow solid, which was recrystallized from benzene/hexane. In this manner 8.18 g (82.1%) of 52 was isolated as yellow crystals, mp 91.5-92.7°C (lit.[72] 93°C): IR ($CHCl_3$) 1660 (CO), 1604, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60-7.70 (m, 10H, Ar-H), 5.05 (s, 2H, $ArCH_2O-$), 2.38 (s, 3H, $-COCH_3$); MS m/z (rel int) 226(10.2), 91(100).

4-Benzyloxy-ω-isonitrosoacetophenone (53).

To a solution of potassium t-amyloxide, which was prepared from potassium metal (4.5 g, 115 mmol),[73] in tetrahydrofuran (300 mL) was

added 52 (10.0 g, 44.3 mmol) with mechanical stirring. After 4 h, the viscous orange-yellow solution was treated with isoamyl nitrite (12.0 mL, 89.2 mmol). After 12 h, the resultant purple-brown suspension was concentrated under reduced pressure. The residue was shaken with a minimal amount of water (approximately 150 mL) and the potassium salt of 53 was obtained as finely divided red crystals upon filtration. An aqueous paste of this salt was made in a mortar, and 53 was liberated after rubbing with 10% hydrochloric acid and isolated by filtration. The filtrate from the salt of 53 was washed with benzene (50 mL) to remove starting material and acidified to pH 4 (by pH paper) with glacial acetic acid. After cooling, aldoxime 53 precipitated out as a yellow solid. Combined samples of 53 were recrystallized from 95% ethanol to provide 6.42 g (57.0%) of 53 in successive crops as yellow needles, mp 150-151°C (lit.[74] 149°C): IR (Nujol) 3160 (OH), 1665 (C=O), 1645 (C=N), 1602, 1590, 1557, 1307, 1250, 1177, 993 cm^{-1}; ^{1}H NMR reflects syn and anti geometrical isomers present, since shoulders are observed on all peaks (D_3CSOCD_3) δ 5.19 (s, 2H, $ArCH_2O$-), 8.08 (d, 2H, J=9.0 Hz, Ar-H ortho to benzyloxy group), 8.03 (s, 1H, -CHNOH), 7.43 (bm, 5H, ArH), 7.14 (d, 2H, J=9.0 Hz, Ar-H meta to benzyloxy group), 5.19 (s, 2H, $ArCH_2O$-); ^{13}C NMR (D_3CSOCD_3) δ 116.3(s), 161.3(s), 147.3(d), 131.8(s), 131.1(s), 131.0(s), 128.1(s), 127.6(s), 127.4(s), 127.2(s), 114.1(d), 69.4(t); MS m/z (rel int) 255(2.6), 91 (100); exact mass m/z 255.088 (calcd for $C_{15}H_{13}NO_3$:255.090).

p-Benzyloxy-ω-aminoacetophenone Hydrochloride (54)

A suspension of 53 (1.00 g, 3.92 mmol) in absolute ethanol (50 mL) was added to a stirring suspension of 5% rhodium on carbon (300

mass m/z 299.080 (calcd for $C_{16}H_{13}NO_5$: 299.079).

5-(4-Acetoxyphenyl)-2-(3,4-methylenedioxyphenyl)-oxazole (50).

A suspension of 59 (1.50 g, 5.02 mmol) in glacial acetic acid (20 mL) and acetic anhydride (30 mL) was brought to reflux. After 20 h, the resultant yellow solution was chilled in ice, made slightly alkaline by gradual addition of 58% ammonium hydroxide, and extracted with ethyl acetate (1 x 200 mL, 2 x 75 mL). The combined organic layers were washed with water (2 x 75 mL), dried over potassium carbonate, and evaporated in vacuo to furnish a yellow solid. Recrystallization in successive crops from benzene after treatment with activated carbon yielded 0.841 g (51.9%) of 50 as colorless crystals, mp 180-181.5°C: IR (KBr) 1745 (RCO_2Ar), 1500, 1485, 1207, 1203 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 7.08-7.92 (m, 8H, Ar-H), 6.12 (s, 2H, $-OCH_2O-$), 2.30 (s, 3H, RO_2CCH_3); UV ($CHCl_3$) λ_{max} 330 (ε 26100), 261 nm (ε 10500); MS m/z (rel int) 323(40.2), 281(100); exact mass m/z 323.080 (calcd for $C_{18}H_{13}NO_5$: 323.079).

Ethyl Imino(3,4-methylenedioxybenzoate) (63).

In accord with a procedure described by Dox,[52] hydrogen chloride was passed at a rate of approximately 0.5 mL/min through a solution of piperonylonitrile (500 mg, 3.40 mmol) in absolute ethanol (25 mL) until a red color was produced. Upon removal of the ethanol under reduced pressure, red solid was obtained. Treatment of an ethereal solution of the solid with activated charcoal and crystallization afforded 436 mg (66.4%) of 63 as yellow needles, mp 121.0-121.5°C

IR (KBr) 3350-2000 (OH, $\overset{+}{N}H_3$), 1678, 1598, 1493, 1422, 1273, 1255, 1220, 1163, 840 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 8.41 (bs, 1H, $\overset{+}{N}\underline{H}_3$), 7.78 (d, 2H, J=8.0 Hz, Ar-H ortho to phenol hydroxyl), 6.97 (d, 2H, J=8.0 Hz, Ar-H meta to phenol hydroxyl), 4.45 (s, 2H); MS m/z (rel int) 152 (14.2), 138(29.7), 121(100).

b. Houben-Hoesch Reaction: Hydrochloride 57 was prepared from phenol (55) and α-aminoacetonitrile hydrochloride (56) according to a procedure by Asscher.[47]

N-(4-Hydroxyphenacyl)piperonylamide (59).

A suspension of piperonylic acid (3.71 g, 22.3 mmol) in thionyl chloride (25 mL) was brought to reflux for 1 h. The resultant solution was concentrated under reduced pressure. Acid chloride 58 was isolated as a yellow solid, which was taken up into ether (35 mL) and introduced to a solution of 57[47] (2.78 g, 14.9 mmol) in 1N sodium hydroxide (50 mL). After stirring overnight, ether was removed from the resultant two-phase suspension under reduced pressure. The suspended pink solid was collected by filtration. Treatment of a solution of the solid in 95% ethanol with activated charcoal, followed by crystallization, provided 2.97 g (66.8%) of 59 as colorless microcrystals, mp 238-239°C(decomp): IR (KBr) 3380 (ArOH), 3025, 1665 (CO), 1635 (CONH), 1599, 1578, 1540, 1499, 1482, 1358, 1257, 1161, 1037 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 8.60 (bt, 1H, -CONHCH$_2$-), 6.87-7.97 (m, 8H, Ar-OH and Ar-H), 6.10 (s, 2H, -OCH$_2$O-), 4.70 (m, 2H, -COCH$_2$N-); ^{13}C NMR (D_3CSOCD_3) δ 193.5(s), 165.9(s), 162.4(s), 149.9(d), 147.5(s), 130.5 (d), 128.2(s), 126.8(s), 122.4(d), 115.5(d), 108.0(d), 107.5(d), 101.8 (t), 46.0(t); MS m/z (rel int) 299(8.3), 149(42.6), 121(64.1); exact

mg) in absolute ethanol (2 mL) under a hydrogen atmosphere. The catalyst was previously saturated by stirring under hydrogen for 1 h. The mixture consumed 3 equivalents (288 mL) of hydrogen after 215 min, whereupon the catalyst was filtered onto Celite in a sintered glass funnel. The filtrate was acidified with 10% hydrogen chloride in ethanol (1.5 mL) and was concentrated under reduced pressure to provide 0.884 g (81.0%) of 54 as a yellow solid, which was recrystallized from absolute ethanol. In this manner, 0.481 g of 54 as colorless plates, mp 223-225°C (decomposition starting at 200°C; lit.[72] 226°C) was obtained: IR (Nujol) 3300-2500 ($\overset{+}{N}H_3$), 1680 (CO), 1601, 1508, 1250, 1179, 833 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 8.63 (bs, -$\overset{+}{N}H_3$), 8.00 (d, 2H, J=8.5 Hz, Ar-H ortho to benzyloxy group), 7.44 (bm, 5H, Ar-H), 7.18 (d, 2H, Ar-H meta to benzyloxy group), 5.24 (s, 2H, $ArCH_2O$-), 4.52 (s, 2H, -$CH_2\overset{+}{N}H_3$); ^{13}C NMR (D_3CSOCD_3) δ 190.9(s), 163.1(s), 136(s), 128.5(s), 128.2(s), 127.8(s), 126.8(s), 115.0(d), 69.6(t), 44.3(t); MS m/z (rel int) 241(2.1), 211(40.4), 91(95.8).

α-Amino-4-hydroxyacetophenone Hydrochloride (57).

a. Hydrogenation of 53: A solution of 53 (200 mg, 0.784 mmol) in absolute methanol (20 mL) was added to a rapidly stirring suspension of 5% palladium on charcoal (130 mg) in methanol (5 mL) containing hydrogen chloride (0.10 g) under a hydrogen atmosphere. After 2 h, 2 equivalents of hydrogen (19.2 mL) were consumed, and 1 h later the catalyst was filtered onto Celite in a sintered glass funnel. The filtrate was concentrated in vacuo to give 145 mg (100%) of 57 as a yellow foam. Crystallization with methanol/chloroform yielded 7.2 mg of tan crystals, which decomposed above 202°C (lit.[46] mp 241-245°C):

(lit.[74] 122-123°C): IR (KBr) 3680-2450 ($\overset{+}{N}H_2$), 1680, 1602, 1505, 1472, 1450, 1391, 1355, 1258, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18-6.98 (m, 3H, Ar-H), 6.12 (s, 2H, $-OCH_2O$), 4.94 (q, 2H, $-OCH_2CH_3$), 0.62 (t, 3H, $-CH_2CH_3$); MS m/z (rel int) 193(27.3), 149(100).

dl-Octopamine (64).

An aqueous solution of dl-octopamine hydrochloride (1.00 g, 5.27 mmol) containing 1% sodium bisulfite was made alkaline by the addition of 1N ammonium hydroxide (5.3 mL). Upon cooling, 0.687 g (88.0%) of 64 slowly deposited as colorless crystals, mp 156-158°C (lit.[75] 156-158°C) which were collected and dried under vacuum over phosphorous pentoxide.

N-(2,4'-Dihydroxyphenethyl)piperonylamide (65).

Powdered 58 (1.47 g, 7.96 mmol) was added to a solution of 64 (1.22 g, 7.96 mmol) in pyridine (40 mL). After stirring for 52 h, the reaction solution was poured into saturated aqueous sodium bicarbonate (50 mL) and sodium chloride was added until two discrete phases were obtained. The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to give a yellow solid. Recrystallization from 95% ethanol furnished 0.915 g (38.2%) of 65 as colorless crystals, mp 184.0-184.5°C: IR (KBr) 3350 (OH, NH), 1630, (CONH), 1578, 1540, 1605, 1305, 1240 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 9.26 (s, 1H, ArOH), 8.31 (bt, 1H, $-CONHCH_2-$), 7.52-6.70 (m, 7H, Ar-H), 6.11 (s, 2H, $-OCH_2O-$), 5.36 (d, 1H, $ArCH(OH)CH_2-$), 4.70 (bs, 2H, $-CH_2-NHCO-$): MS m/z (rel int) 283(28.1), 149(100). Anal calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.59; H, 4.92; N, 4.59.

2-Ethoxy-5-(4-hydroxyphenyl)oxazoline (68).

Ethyl chloroformate (0.19 mL, 2.0 mmol) was introduced dropwise via syringe to a solution of 64 (306 mg, 2.00 mmol) in N,N-dimethylformamide (15 mL) containing triethylamine (0.28 mL, 2.00 mmol). The resultant suspension of triethylamine hydrochloride was partitioned between ethyl acetate (20 mL) and 10% hydrochloric acid (20 mL). The separated organic layer was washed with water (2 x 30 mL), dried over sodium sulfate, and evaporated to provide 90.7 mg (20.2%) of N-carbethoxy-2-hydroxy-2-(4-hydroxyphenyl)ethylamine as a pink oil, which was used without further purification: IR (neat) 3350 (OH, NH), 1700 (CO), 1610, 1600, 1515, 1450, 1375, 1250, 1170, 1075 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 7.07 (d, 2H, J=8.0 Hz, Ar-H ortho to phenol hydroxyl), 6.68 (d, 2H, J=8.0 Hz, Ar-H meta to phenol hydroxyl), 5.30 (bs, 1H, ArOH), 4.49 (t, 1H, $ArCH(OH)CH_2$-), 3.95 (q, 2H, $-CO_2CH_2CH_3$), 3.10 (m, 2H, $-CH(OH)CH_2N$-), 1.17 (t, 3H, $-CH_2CH_3$); ^{13}C NMR (D_3CSOCD_3) δ 191.30, 156.34, 133.79, 127.07, 114.73, 71.18, 59.52, 48.48, 14.53; MS m/z (rel int) 225(2.6), 207(6.3), 136(21.2), 124(7.7), 123(100), 121(8.8), 103(19.9).

To a solution of N-carbethoxy-2-hydroxy-2-(4-hydroxyphenyl)ethylamine (100 mg, 0.444 mmol) in N,N-dimethylformamide (5 mL) containing triethylamine (33 µL, 0.444 mmol) was added 3,4-methylenedioxybenzoyl chloride (82 mg, 0.44 mmol). After stirring overnight, the reaction was warmed to 90°C for 25 min, poured into 10% hydrochloric acid, (15 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (2 x 25 mL), saturated aqueous sodium bicarbonate (15 mL) and brine (2 x 25 mL), dried over sodium

sulfate, and concentrated under reduced pressure to give 139 mg of crude 67 as a yellow amorphous solid: IR (KBr) 3500 (OH), 1705 ($ArCO_2R$), 1670 (NCO_2R), 1602, 1503, 1452, 1195, 1258, 1030 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 8.53 (s, 1H, ArOH), 7.25-6.20 (m, 7H, Ar-H), 5.82 (s, 2H, $-OCH_2O-$), 5.73-5.52 (m, 1H, $ArCH(OR)CH_2-$), 3.95 (q, 2H, $-OCH_2-CH_3$), 3.35 (bm, 2H, $-CH(OR)CH_2N-$), 1.42 (t, 3H, $-CH_2CH_3$).

Crude 67 was applied to a silica gel preparative thin layer chromatographic plate, which was developed in 5% methanolic chloroform. The adsorbent was extracted with 15% methanol in chloroform to afford 48 mg (53% based on octopamine) of 68 as a yellow waxy solid, which was recrystallized from dichloromethane/hexane. In this fashion 68 was collected as colorless microprisms, mp 162-163°C: IR (KBr) 3485 (ArOH), 1673 ($(RO)_2C=N$), 1645 ($(RO)_2C=N$), 1540, 1505, 1318, 1288, 1255, 1200, 1050 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 9.37 (bs, 1H, ArOH), 7.07 (d, 2H, J=8.5 Hz, Ar-H ortho to phenol hydroxyl), 6.67 (d, 2H, J=8.5 Hz, Ar-H meta to phenol hydroxyl), 6.10-5.85 (m, 1H, $ArCH(OR)CH_2-$), 4.12 (q, 2H, $-OCH_2CH_3$), 3.42 (bm, 2H, $-CH(OR)CH_2N-$), 1.25 (t, 3H, $-CH_2CH_3$); MS m/z (rel int) 207(100), 179(27.8), 166(23.6), 165(23.4), 161(63.2), 135(50.4), 134(79.8), 133(39.8), 123(43.1), 122(29.9), 121(55.4), 116 (22.8), 107(57.9), 106(35.3), 105(25.8), 103(21.4); exact mass m/z 207.090 (calcd for $C_{11}H_{13}NO_3$: 207.090).

trans-N-Carbethoxy-5-(4-hydroxyphenyl)-2-(3,4-methylenedioxyphenyl)oxazolidine (73).

A solution of dl-octopamine (64) (100 mg, 0.654 mmol) and piperonal (98 mg, 0.0654 mmol) in absolute methanol (10 mL) was stirred for 3 h. Removal of the solvent under reduced pressure afforded a

yellow amorphous solid, which was shown to be a (55:45) mixture of 70 and 71 by integration of the NMR spectrum: IR (KBr) 1640 cm^{-1} (C=N); ^1H NMR (D_3CSOCD_3) δ 8.15 (s, ArCHNH-), 5.14 (bd, J=4.5 Hz, ArCH(OR)NH-).

The mixture of 70 and 71 was placed in pyridine (5 mL) and treated with ethyl chloroformate (0.124 mL, 1.30 mmol). After stirring overnight at room temperature, the resultant yellow solution was diluted with chloroform (50 mL), washed with saturated aqueous cupric sulfate (3 x 15 mL) and brine (2 x 15 mL), dried over sodium sulfate and evaporated to give a yellow oil, which was taken up into methanol (5 mL), cooled to 0°C, and treated with 0.25N sodium hydroxide (1 mL). After 5 min the solution was carefully acidified with 10% hydrochloric acid, made alkaline with saturated aqueous sodium bicarbonate, and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (2 x 20 mL), dried over sodium sulfate and concentrated under reduced pressure to provide 229 mg (98.2%) of 73 as a yellow oil: IR ($CHCl_3$) 3325 (OH), 1690 (NCO_2R), 1617, 1505, 1490, 1440, 1383, 1357, 1170, 1128, 1092, 1040, 937 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24-6.75 (m, 7H, Ar-H), 6.32 (s, 1H, ArCH(OR)N-), 5.96 (s, 2H, $-OCH_2O$), 5.14 (t, 1H, $ArCH(OR)CH_2$-), 4.19 (q, 2H, $-CO_2CH_2CH_3$), 4.00-3.60 (m, 2H, $-CH(OR)CH_2N$-), 1.22 (t, 3H, $-CH_2CH_3$); MS m/z (rel int) 357(41.4), 238(37.5), 235(67.0),234(100), 206(24.6), 162(73.2), 150(34.1), 149(85.8), 135(46.8), 121(30.0), 120(39.7); exact mass m/z 357.122 (calcd for $C_{19}H_{19}NO_6$: 357.121).

N-(2,4'-Dihydroxyphenethyl)-3,4-methylenedioxybenzylamine (74).

A solution of piperonal (751 mg, 5.00 mmol) and dl-octopamine (64) (766 mg, 5.00 mmol) in glacial acid (10 mL) was allowed to stir

for 2 h prior to the addition of platinum(IV) oxide (55 mg) and the establishment of a hydrogen atmosphere. After 4 h, one equivalent of hydrogen (125 mL) was consumed and the catalyst was filtered off. The filtrate was concentrated under vacuum to give a brown oil, which was treated with activated carbon. The resultant yellow solution was made basic with 58% ammonium hydroxide. Cooling led to precipitation of a colorless solid, which was collected by filtration and dried under vacuum over phosphorous pentoxide. In this manner 1.24 g (86.5%) of 74 was isolated as a light grey solid, mp 167-168°C, which was used without further purification. An analytical sample was obtained after repeated precipitation from a 10% hydrochloric acid solution, which was neutralized with 58% ammonium hydroxide: IR (KBr) 3600-2300 (OH, NH), 1600, 1500, 1488, 1440, 1235, 1097, 1028 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 6.68-7.17 (m, 7H, Ar-H), 5.98 (s, 2H, $-OCH_2O$), 4.60 (bt, 1H, $ArCH(OH)CH_2-$), 3.69 (s, 2H, $ArCH_2N-$); MS m/z (rel int) 135 (100), 134(61.8), 123(36.6), 121(11.9), 107(24.0), 105(20.1). Anal calcd, for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.53 H, 5.95; N, 4.86.

5-(4-Hydroxyphenyl)-3-(3,4-methylenedioxybenzyl)-2-oxazolidinone (76).

To a solution of 74 (321 mg, 1.12 mmol) in N,N-dimethylformamide (15 mL) was added 1,1'-carbonyldiimidazole (75) (200 mg, 1.23 mmol). The resultant yellow solution was heated to 80°C. After 22 h, the reaction was poured into 10% hydrochloric acid (15 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over sodium sulfate and concen-

trated under reduced pressure to provide a yellow oil, which was chromatographed on silica gel. Elution with 5% methanol in dichloromethane yielded 80 mg (32.2%) of 76 as a yellow oil. Crystallization from dichloromethane gave 76 as yellow microprisms, mp 45-46°C: IR (KBr) 3200 (ArOH), 1725 (NCO_2R), 1618, 1600, 1493, 1445, 1398, 1309, 1238, 1095, 1025, 1000, 917 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12-6.73 (m, 8H, Ar-H and ArOH), 5.93 (s, 2H, $-OCH_2O$), 4.38 (dd, 2H, $ArCH_2NR$), 3.52 (dt, 2H, J=4.9,19 Hz, $-CH(OH)CH_2N-$); MS m/z (rel int) 313(8.9), 194(22.2), 150(49.6), 135(55.8), 120(100.0); exact mass m/z 313.095 (calcd for $C_{17}H_{15}NO_5$: 313.095).

3'-Hydroxy-3,4-methylenedioxydibenz[1,6-c,1,6-e]-bicyclo[5.2.1]-2-oxo-3a-azecin-1-one (78).

A 20:1 (v:v) solution of trifluoroacetic acid : trifluoroacetic anhydride (400 μL) was added to a solution of 76 (77 mg, 0.25 mmol) in dichloromethane (3 mL) and ethyl acetate (1 mL) at 0°C. Subsequent addition of vanadium oxytrifluoride (61 mg, 0.49 mmol) in ethyl acetate (1 mL) produced a blue color. After 20 min at 0°C, the reaction was quenched with 10% aqueous citric acid (15 mL). The resultant mixture was made alkaline with 58% ammonium hydroxide and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over sodium sulfate, and evaporated in vacuo to provide an orange oil, which was applied to a silica gel preparative thin layer chromatographic plate. Development three times with 2% methanol in dichloromethane and extraction of the adsorbent with 15% methanol in chloroform led to recovery of 35 mg (45%) of 76 and isolation of 13 mg (17%) of 78 as a cloudy oil: IR

($CHCl_3$) 3200 (OH), 1740 (NCO_2R), 1499, 1487, 1440, 1368, 1340, 1320, 1095, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07-6.62 (m, 5H, Ar-H), 5.98 (s, 2H, $-OCH_2O-$), 4.56 (s, 2H, $ArCH_2O-$); MS m/z (rel int) 283(15.3), 135 (100); exact mass m/z 283.085 (M^+-CO, calcd for $C_{16}H_{13}NO_4$: 283.085).

Bis(3,4-methylenedioxybenzyl) Ether (83).

To a solution of dl-synephrine (600 mg, 3.59 mmol) in a minimal amount of water was added one equivalent of 38% hydrochloric acid (0.29 mL). Lyophilization provided a quantitative yield of synephrine hydrochloride as colorless prisms which darkened at room temperature. A mixture of dl-synephrine hydrochloride (100 mg, 0.494 mmol) and piperonyl alcohol (83 mg, 0.543 mmol) was heated to 70°C. After 30 min, the red oil was allowed to cool and chromatographed on alumina (Activity I). Elution with 10% methanol/1% acetic acid in chloroform yielded 12.1 mg (7.8%) of 83 as a colorless oil: IR (neat) 1505, 1495, 1450, 1250, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.92-6.82 (m, 3H, Ar-H), 5.98 (s, 2H, $-OCH_2O-$), 4.56 (s, 2H, $ArCH_2O-$); MS m/z (rel int) 286 (15.3), 149(7.5), 137(8.5), 136(96.3), 135(100), 106(19.9), 105(10.1); exact mass m/z 286.084 (calcd for $C_{16}H_{14}O_5$: 286.084).

α-Methylaminomethyl-4-hydroxybenzyl Methyl Ether (85).

A suspension of dl-synephrine hydrochloride (730 mg, 3.59 mmol) in freshly distilled thionyl chloride (12 mL) was allowed to stir for 2 days and was concentrated under reduced pressure to furnish chloride 80 as an amorphous yellow solid. A portion of 80 (55.5 mg, 0.251 mmol) was dissolved in methanol (2 mL). Removal of the methanol in vacuo

provided 32.4 mg (59.6%) of the hydrochloride of 85 as a yellow semi-crystalline solid, mp 172-176°C, which displayed spectral and chromatographic properties identical to those reported by McLaughlin, et al.[75]

4'-Tetrahydropyranoxy-2-nitrostyrene (86b).

To a solution of 4'-hydroxy-2-nitrostyrene[76] (300 mg, 1.82 mmol) in tetrahydrofuran at 0°C was added sequentially dihydropyran (0.166 mL, 1.82 mmol) and p-toluenesulfonic acid (10 mg). The solution was allowed to warm to room temperature, stirred for 5 h, diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (35 mL). The separated organic layer was washed with water (3 x 20 mL), dried over sodium sulfate and evaporated under vacuum to yield a pale yellow amorphous solid. Recrystallization from ethyl acetate/hexane afforded 143 mg (31.5%) of 86b as pale yellow needles, mp 117-118°C: IR (KBr) 1601 (C=C), 1510, 1490 and 1130 (NO_2), 1175, 951, 912 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07 (s, 1H, J=14.0 Hz, ArCH=CH-), 7.58 Id, 1H, J=14.0 Hz, -CH=CHNO$_2$), 7.53 (d, 2H, J=9.0 Hz, Ar-H ortho to alkoxy group), 6.40 (d, 2H, J=9.0 Hz, Ar-H, meta to alkoxy group), 5.51 (s, 1H, -OCH(OR)CH_2-), 3.67 (m, 2H, ROCH$_2$CH$_2$-), 1.91-1.63 (m, 6H, -CH_2(CH_2)$_3$CH-); MS m/z (rel int) 165(2.1), 118(6.8), 85(100). Anal. calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.76; H, 6.17; N, 5.69.

4-(2-Nitroethenyl)phenyl p-Toluenesulfonate (86c).

To a mixture of 4'-hydroxy-2-nitrostyrene[76] (170 mg, 1.03 mmol), chloroform (20 mL) and triethylamine (144 μL, 1.01 mmol) was added p-toluenesulfonyl chloride (196 mg, 103 mmol). After 4 h, the

mixture was shaken with water (20 mL) and extracted with chloroform (2 x 20 mL). The combined organic layers were washed with 1N hydrochloric acid (20 mL), water (15 mL), saturated aqueous sodium bicarbonate (3 x 15 mL) and brine (2 x 15 mL), dried over sodium sulfate, and concentrated under reduced pressure to provide a yellow semicrystalline solid. Recrystallization from ethyl acetate/hexane afforded 117 mg (53.8%) of 86c as colorless needles, mp 164-165°C, in successive crops: IR (KBr) 1502 and 1340 (NO_2), 1370, 1202, 1181, 1150, 860, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06-6.99 (m, 10H, Ar-H and ArCH=CHNO$_2$), 2.42 (s, 3H, ArCH$_3$); MS m/z (rel int) 319(10.9), 115 (59.8), 91(100); exact mass m/z 319.051 (calcd for $C_{15}H_{13}NO_5S$: 319.051).

Ethyl 4-Ethoxymethoxymandelate (89a) and Ethyl 4-Hydroxy-O-ethoxymethylmandelate (91).

A solution of ethyl dl-4-hydroxymandelate (90)[57] (500 mg, 2.55 mmol) in tetrahydrofuran (5 mL) was added via syringe to a suspension of hexane-rinsed sodium hydride (61 mg, 2.55 mmol) in tetrahydrofuran (10 mL). To the orange suspension was added N,N-dimethylformamide (10 mL). After a brief reflux for 2 min and cooling to room temperature, the addition of chloromethyl methyl ether (256 μL, 265 mg, 2.81 mmol) caused the mixture to assume a yellow color. After 30 min, the reaction was poured into dichloromethane (100 mL). The separated organic layer was washed with water (4 x 20 mL, 3 x 100 mL), dried over sodium sulfate and evaporated in vacuo to yield a yellow oil, which was chromatographed on silica gel. Elution with 35% ethyl acetate in hexane led to the recovery of 102 mg (20.4%) of 90 as

colorless platelets, and afforded 137 mg (21.1%) of a yellow oil, which was shown to be a (13:2) mixture of 89a and 91, respectively, by integration of the NMR spectrum.

89a: IR (neat) 3300 (OH), 2975 (CH), 1735 (CO_2R), 1612, 1600, 1515, 1449, 1370, 1270, 1225, 1180, 1105, 1025, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (d, 2H, J=8 Hz, Ar-H ortho to alkoxy group), 6.07 (d, 2H, J=8 Hz, Ar-H meta to alkoxy group), 5.28 (s, 2H, $-OCH_2O-$), 5.19 (m, 1H, $ArCH(OH)CO_2R$), 4.29 (m, 2H, $-CO_2CH_2CH_3$), 3.82 (q, 2H, $-OCH_2CH_3$), 1.34 (t, 6H, $-CH_2CH_3$); MS m/z (rel int) 254(1.1), 151(100), 123 (97.5), 121(27.9).

91: IR (neat) 3575 (OH), 2980, 2930, 2895, 1737 (CO_2R), 1611, 1575, 1395, 1233, 1175, 1075, 990, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.78 (s, 1H, ArOH), 7.35 (d, 2H, Ar-H ortho to phenolic group), 6.90 (d, 2H, Ar-H meta to phenolic group), 5.22 (s, 1H, $ArCH(OR)CO_2-$), 4.84 (dd, 2H, J=6,7 Hz, $-OCH_2O-$), 4.30 (dq, 2H, J=2,7 Hz, $-CO_2CH_2CH_3$), 3.74 (m, 2H, $-OCH_2CH_3$), 1.33 (t, 3H, $-CH_2CH_3$), 1.29 (t, 3H, $-CH_2CH_3$); MS m/z (rel int) 254(15.0), 181(83.9), 151(34.4), 123(33.4), 95(14.2).

3,4-Methylenedioxybenzyl 4-Ethoxymethoxymandelate (93a).

A solution of 89a (100 mg, 0.433 mmol) in tetrahydrofuran (8 mL) was added dropwise via syringe to a stirring suspension of hexane-rinsed sodium hydride (10.4 mg, 0.433 mmol) in tetrahydrofuran (2 mL). The addition of N,N-dimethylformamide (5 mL) provided a red solution, which was brought to reflux and treated with a solution of 3,4-methylenedioxybenzyl bromide (102 mg, 0.476 mmol) in tetrahydrofuran (5 mL). The resultant yellow solution was refluxed for 30 min, allowed to cool, diluted with dichloromethane (50 mL), washed with

water (3 x 10 mL, 4 x 50 mL), dried over sodium sulfate, and evaporated to furnish a yellow oil, which was applied to a silica gel preparative thin-layer chromatographic plate. Development with 10% ethyl acetate in benzene and extraction of the adsorbent with ethyl acetate led to the isolation of 45 mg (28.6%) of 93 as a yellow oil, which was the major component. The only other identifiable product was 17 mg (5.5%) of ethyl 2-O-ethoxymethyl-4-(3,4-methylenedioxybenzyl)mandelate as a yellow oil.

93a: IR (neat) 3575 (OH), 2925, 1735 (CO_2R), 1615, 1505, 1485, 1445, 1235, 1168, 1080, 1032, 992, 833, 800 cm^{-1}; ^1H NMR δ 7.34 (d, 2H, J=8.0 Hz, Ar-H ortho to alkoxy group), 7.06 (d, 2H, J=8.0 Hz, Ar-H meta to alkoxy group), 6.90-6.75 (m, 3H, C_6H_3), 5.98 (s, 2H, $ArOCH_2O$-), 5.26 (s, 2H, $ROCH_2O$-), 5.20-5.11 (m, 1H, $ArCH(OR)CO_2R'$), 4.64 (s, 1H, conc. dependent -OH), 3.81 (q, 2H, $-OCH_2CH_3$), 1.32 (t, 3H, $-CH_2CH_3$); MS m/z (rel int) 360(12.8), 181(54.0), 151(21.4), 135(100); exact mass m/z 360.121 (calcd for $C_{19}H_{20}O_7$: 360.121).

Ethyl 2-O-ethoxymethyl-4-(3,4-methylenedioxybenzyloxy)mandelate: IR (neat) 2970, 2915, 2875, 1737 (CO_2R), 1605, 1502, 1487, 1437, 1240, 1166, 1097, 1035, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46-6.86 (m, 7H, Ar-H), 6.01 (s, 2H, $ArOCH_2O$-), 5.20-5.12 (m, 1H, $ArCH(OR)CO_2R'$), 5.02 (s, 2H, $ArCH_2O$-), 4.84 (dd, 2H, J=6.0,7.0 Hz, $-CH(OCH_2OR)CO_2R$), 4.27 (dq, J=2.0,7.0 Hz, $-CO_2CH_2CH_3$), 3.72 (m, 2H, $ROCH_2CH_3$), 1.33 (t, 3H, $-CO_2-CH_2CH_3$), 1.29 (t, 3H, $ROCH_2CH_3$); MS m/z (rel int) 388(0.2), 315(1.4), 136(8.8), 135(100.0).

3,4-Methylenedioxyphenylmethyl 4-Ethoxymethoxy-2-O-(3,4-methylenedioxyphenylmethyl)mandelate (94a).

A solution of 93a (45 mg, 0.124 mmol) in tetrahydrofuran (2 mL) was introduced via syringe to a stirring suspension of 50% sodium hydride in oil dispersion (6.5 mg, 0.136 mmol) placed in tetrahydrofuran (5 mL). After 90 min at room temperature, the resultant orange solution was treated with a solution of 3,4-methylenedioxybenzyl bromide (29 mg, 0.136 mmol) in tetrahydrofuran (5 mL). The resultant yellow solution was stirred for 3 h, diluted with ether (35 mL), washed with water (3 x 10 mL, 4 x 25 mL), dried over sodium sulfate, and evaporated in vacuo. The residual yellow oil was applied to a silica gel preparative thin layer chromatographic plate. Development with 15% ethyl acetate in benzene and extraction of the adsorbent with ethyl acetate afforded 15 mg (24.0%) of 94a as a yellow oil, which was the major product: IR ($CHCl_3$) 1740 (CO_2R), 1602, 1490, 1450, 1175, 1090, 1040, 990, 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (d, 2H, J=8.1 Hz, Ar-H ortho to alkoxy group, 7.06 (d, 2H, J=8.1 Hz, Ar-H meta to alkoxy group), 7.13-6.76 (m, 6H, Ar-H), 5.98 (s, 4H, $ArOCH_2O$-), 5.33-4.96 (m, 3H, $ArCH(OR)CO_2R'$ and $ROCH_2O$-), 5.28 (s, 2H, $-CO_2CH_2Ar$), 4.54-4.51 (m, 2H, $ArCH_2O$-), 3.83 (q, 2H, $-OCH_2CH_3$), 1.34 (t, 3H, $-CH_2CH_3$); MS m/z (rel int) 494(0.7), 449(8.6), 209(8.6), 179(40.8), 149(25.8), 136(100), 135(99.1), 121(21.6), 105(38.9); exact mass m/z 449.160 ($M^+-OCH_2CH_3$, calcd for $C_{25}H_{21}O_8$: 449.160).

Ethyl 4-Methylthiomethoxymandelate (89b).

A solution of ethyl dl-4-hydroxymandelate[57] (1.00 g, 5.10 mmol) in tetrahydrofuran (10 mL) was added to a suspension of hexane-rinsed

sodium hydride (122 mg, 5.10 mmol) in tetrahydrofuran (5 mL). After 90 min at room temperature, removal of the solvent under reduced pressure provided a yellow solid, which was placed in hexamethylphosphoramide (25 mL) and treated with chloromethyl methyl sulfide (363 μL, 543 mg, 5.62 mmol). After stirring overnight at room temperature, the suspended solid was dissolved in a minimal amount of water, and the solution was extracted with ether (5 x 20 mL). The combined organic layers were washed with brine (4 x 100 mL), dried over sodium sulfate and concentrated under reduced pressure to give a yellow oil with a garlic-like stench. This oil was chromatographed on silica gel. Elution with 25% ethyl acetate in hexane furnished 296 mg (22.7%) of 89b as a yellow oil with a characteristic stench: IR (neat) 3330 (OH), 1735 (CO_2R), 1610, 1507, 1203, 1172, 1090, 998, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (d, 2H, J=8.1 Hz, Ar-H ortho to alkoxy group), 6.96 (d, 2H, J=8.1 Hz, Ar-H meta to alkoxy group), 5.17 (m, 3H, $ArCH(OH)CO_2R'$ and $-SCH_2O-$), 4.26 (dq, 2H, J=7.0,3.0 Hz, $-CO_2CH_2-CH_3$), 3.91 (bs, 1H, -OH), 2.31 (s, 3H, $-SCH_3$), 1.30 (t, 3H, $-CH_2CH_3$); MS m/z (rel int) 256(8.0), 183(33.5), 137(13.1), 61(100); exact mass m/z 256.077 (calcd for $C_{12}H_{16}O_4S$: 256.077).

3,4-Methylenedioxybenzyl 4-Methylthiomethoxymandelate (93b) and 3,4-Methylenedioxybenzyl 2-O-(3,4-Methylenedioxybenzyl)-4-methylthiomethoxymandelate (94b).

A solution of ethyl dl-4-methylthiomethoxymandelate (89b) (100 mg, 0.391 mmol) in tetrahydrofuran (10 mL) was added dropwise to a stirring suspension of hexane-rinsed sodium hydride (19 mg, 0.391 mmol) in tetrahydrofuran (1 mL). After 1 h, the resultant orange solution

was treated with a solution of 3,4-methylenedioxybenzyl bromide (84 mg, 0.391 mmol) in tetrahydrofuran (3 mL). After stirring for 15 h, the suspended solid was dissolved with a minimal amount of water and the aqueous solution was extracted with ether (3 x 25 mL). The combined ethereal layers were washed with brine (5 x 25 mL), dried over sodium sulfate and evaporated to provide a yellow oil, which was applied to a silica gel preparative thin layer chromatographic plate. Development two times with 10% ethyl acetate in benzene followed by extraction of the adsorbent with ethyl acetate yielded 30 mg (21.5%) of 93b as a colorless oil and 22 mg (11.6%) of 94b as a cloudy oil.

93b: IR (CH_2Cl_2) 3520 (OH), 1730 (CO_2R), 1610, 1510, 1500, 1452, 1080, 1050, 995, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (d, 2H, J=8.0 Hz, Ar-H ortho to alkoxy group), 6.98 (d, 2H, J=8.0 Hz, Ar-H meta to alkoxy group), 7.38-6.75 (m, 3H, C_6H_3), 5.98 (s, 2H, $-OCH_2O-$), 5.18 (s, 2H, $-SCH_2O-$), 5.14 (m, 3H, $ArCH(OR)CO_2R'$ and $ArCH_2O-$), 3.52 (bs, 1H, -OH), 2.34 (s, 3H, $-SCH_3$); MS m/z (rel int) 362(12.4), 183(46.0), 182(25.2), 135(100); exact mass m/z 362.083 (calcd for $C_{18}H_{18}O_6S$: 362.082).

94b: IR (CH_2Cl_2) 1740 (CO_2R), 1605, 1510, 1495, 1463, 1100, 1039, 998, 932 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45-6.76 (m, 10H, Ar-H), 5.99 (s, 4H, $-OCH_2O-$), 5.21 (s, 2H, $-SCH_2O-$), 5.11 (dd, 2H, J=5.5,7.0 Hz, $-CH_2CH_2Ar$), 4.96 (m, 1H, $ArCH(OR)CO_2R'$), 4.54 (s, 2H, $ArCH_2O-$), 2.35 (s, 3H, $-SCH_3$); MS m/z (rel int) 486(3.1), 346(10.2), 345(14.1), 317 (41.4), 285(22.3), 269(24.9), 243(12.4), 240(17.3), 239(12.8), 212 (10.1), 211(81.2), 195(15.6), 183(10.0), 181(17.7), 151(16.5), 150 (18.5), 149(23.3), 137(24.0), 135(91.4), 134(25.1), 121(16.5), 106 (18.5), 105(80.4); exact mass m/z 496.119 (calcd for $C_{26}H_{24}O_8S$:

496.119).

Methyl 2-Bromo-(4-methoxyphenyl)acetate (95).

In accord with a preparation described by Wasserman, et al[58] for the ethyl ester corresponding to 95, a mixture of methyl 4-methoxyphenylacetate (500 mg, 2.77 mmol), N-bromosuccinimide (543 mg, 3.04 mmol), benzoyl peroxide (5 mg) and carbon tetrachloride (1 mL) was refluxed for 3.5 h and allowed to stir at room temperature overnight. The suspended solid was filtered off, and the filtrate was concentrated under reduced pressure to provide 715 mg (100%) of 95 as a yellow-orange oil, which was used without further purification: IR (neat) 1745 (CO_2R), 1605, 1515, 1300, 1257, 1220, 1180, 1145, 1030, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (d, 2H, J=8.2 Hz, Ar-H ortho to alkoxy group), 6.92 (d, 2H, J=8.2 Hz, Ar-H meta to alkoxy group), 5.39 (s, 1H, Ar-CH(Br)CO_2R), 3.88 (s, 3H, $-CO_2CH_3$); MS m/z (rel int) 260(3.8), 258 (3.9), 179(100), 151(44.5), 148(12.9), 135(11.5), 120(10.4).

Methyl 4-Methoxy-O-(3,4-methylenedioxybenzyl)mandelate (96).

A solution of piperonyl alcohol (100 mg, 0.658 mmol) in tetrahydrofuran (3 mL) was added to a stirring suspension of hexane-rinsed sodium hydride (16 mg, 0.658 mmol) in tetrahydrofuran (2 mL). After 30 min of reflux, the resultant yellow suspension was allowed to cool, dissolved with N,N-dimethylformamide (10 mL) and treated with a solution of 95 (170 mg, 0.658 mmol) in tetrahydrofuran (3 mL). After 20 min, the red suspension was dissolved with water (20 mL), saturated with sodium chloride, and extracted with ether (3 x 25 mL). The combined ethereal layers were washed with water (5 x 15 mL), dried over

sodium sulfate and evaporated in vacuo to furnish a yellow oil, which was chromatographed on silica gel. Elution with 5% ethyl acetate in benzene afforded 35 mg (16.1%) of 96 as a yellow oil, 9 mg (3.1%) of 3,4-methylenedioxybenzyl 4-methoxy-O-(3,4-methylenedioxybenzyl)mandelate as a colorless oil, and 18 mg (1.5%) of dimethyl 2,3-bis-(4-methoxyphenyl)maleate as a yellow oil.

Ether 96: IR (neat) 1730 (CO_2R), 1604, 1512, 1495, 1250, 1170, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44-6.40 (m, 7H, Ar-H), 5.99 (s, 2H, $-OCH_2O-$), 4.94 (s, 1H, $ArCH(OR)CO_2R'$), 4.53 (s, 2H, $ArCH_2O-$), 3.88 (s, 3H, $-CO_2-CH_3$), 3.78 (s, 3H, $ArOCH_3$); MS m/z (rel int) 330 (3.5), 271(3.4), 180 (6.9), 179(6.0), 151(3.8), 135(100); exact mass m/z 330.108 (calcd for $C_{18}H_{18}O_6$: 330.110).

3,4-Methylenedioxybenzyl 4-methoxy-O-(3,4-methylenedioxybenzyl)mandelate: IR (CH_2Cl_2) 1735 (CO_2R), 1604, 1502, 1487, 1442, 1090, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (d, 2H, J=8.1 Hz, Ar-H ortho to alkoxy group), 6.91 (d, 2H, J=8.1 Hz, Ar-H meta to alkoxy group), 7.00-6.81 (m, 6H, C_6H_3), 5.99 (s, 4H, $-OCH_2O-$), 5.10 (m, 2H, $-CO_2CH_2Ar$), 4.94 (s, 1H, $ArCH(OR)CO_2R'$), 4.53 (s, 2H, $ArCH_2O-$), 3.89 (s, 3H, $ArOCH_3$); MS m/z (rel int) 450(0.4), 356(9.1), 213(4.6), 209(4.2), 180(5.6), 179(33.0), 165(8.6), 151(10.5), 149(5.0), 136(10.5), 135(100), 121 (9.4).

Dimethyl Bis-2,3-(4-methoxyphenyl)maleate: IR (CH_2Cl_2) 1720 (CO_2R), 1605, 1510, 1462, 1437, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (d, 4H, J=8.2 Hz, Ar-H ortho to alkoxy group), 6.96 (d, 4H, J=8.2 Hz, Ar-H meta to alkoxy group), 3.90 (s, 6H, $-CO_2CH_3$), 3.84 (s, 6H, $ArOCH_3$); MS m/z (rel int) 357(21.5), 356(100), 254 (24.8), 239(25.0), 266(46.0), 223 (45.0), 209(39.6), 195(26.9), 181(24.2), 180 (15.8), 152(34.3),

151(34.7), 135(51.4).

trans-5-(4-Hydroxyphenyl)-3-methyl-2-(3,4-methylenedioxyphenyl)oxazolidine (97).

A mixture of dl-synephrine (100 mg, 0.600 mmol) and piperonal (90 mg, 0.60 mmol) in absolute methanol (35 mL) was stirred overnight and concentrated under reduced pressure to provide 180 mg (100%) of 97 as a pale yellow semicrystalline solid, mp 149.5-150.5°C, which darkened at 140°C and which was used without further purification. An analytical sample was obtained by recrystallization in methanol/dichloromethane: IR (KBr) 3700-2200 (ArOH), 1605, 1595, 1442, 1205, 1318, 1250, 1199, 1172, 1132, 1095, 1025, 980, 925, 895, 815 cm^{-1}; ^1H NMR (D_3CSOCD_3) δ 9.20 (bs, 1H, ArO<u>H</u>), 7.72-6.66 (m, 7H, Ar-<u>H</u>), 6.01 (s, 2H, -OC<u>H</u>$_2$O-), 5.07 (dd, 1H, J=6.0,10.0 Hz, ArC<u>H</u>(OR)CH$_2$-), 4.72 (s, 1H, ArC<u>H</u>(OR)N-), 3.55 (m, 1H, -CH$_2$C<u>H</u>$_2$N-), 2.93 (m, 1H, -CHC<u>H</u>$_2$N-), 2.66 (s, 3H, -NC<u>H</u>$_3$). Anal. calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.30; H, 5.82; N, 4.72.

5-Methyl-1,3-benzodioxole (98).

A mixture of 97 (50.0 mg, 0.167 mmol), 10% palladium on carbon (10 mg) and tetrahydrofuran (2 mL) was stirred under a hydrogen atmosphere for 90 min, whereupon 1.5 equivalents of hydrogen (6.0 mL) had been consumed. The catalyst was filtered onto a Celite pad in a sintered glass funnel, and the filtrate was concentrated under reduced pressure. The resultant yellow solid was dissolved in a minimal amount of 10% hydrochloric acid. This solution was made slightly alkaline with 58% ammonium hydroxide and extracted with ether

(2 x 15 mL). The combined ethereal layers were washed with brine (2 x 10 mL), dried over sodium sulfate, and evaporated under reduced pressure to give a colorless oil, which was applied to an alumina (Activity I) preparative thin layer chromatographic plate. Development with 3% methanol in chloroform and subsequent extraction of the adsorbent with 15% methanol in chloroform led to the recovery of 4.5 mg (18%) of piperonal and to the isolation of 3.3 mg (15%) of 98 as a colorless oil, which exhibited a nuclear magnetic spectrum identical to that reported by Sasaki, et al[77] and an ultraviolet spectrum identical to that described by Archer and Claret[78]: IR ($CHCl_3$) 1520, 1420, 1030, 915 cm^{-1}; MS m/z (rel int) 136(68.2).

1-[N-Carbomethoxy(methylaminomethyl)]-
1-(4-hydroxyphenyl)-3-methoxy-
3-(3,4-methylenedioxyphenyl)-2-oxopropane (100).

A mixture of dl-synephrine (877 mg, 5.25 mmol), piperonal (788 mg, 5.25 mmol), and absolute methanol (200 mL) was allowed to stir overnight. Concentration of the resultant solution under reduced pressure afforded 97 as a colorless amorphous solid, which was checked to insure the absence of a carbonyl absorption in the infrared spectrum. A mixture of 97, potassium carbonate (3.63 g, 26.2 mmol), chloroform (75 mL) and absolute methanol (75 mL) was treated with ethyl chloroformate (1.2 mL, 15.8 mmol) and allowed to stir overnight. The remaining suspended potassium carbonate was dissolved with water (5 mL). The resultant two-phased mixture was stirred for 15 min, acidified with saturated aqueous ammonium chloride (25 mL), and separated into two layers. The aqueous layer was extracted with

chloroform (2 x 25 mL). The combined organic layers were washed with brine (5 x 25 mL), dried over sodium sulfate, and evaporated in vacuo to provide a yellow foam, which was chromatographed on alumina (Activity I). Gradient elution with methanol (0→5%) in dichloromethane containing 1% triethylamine furnished the triethylammonium salt of 100, which was placed in dichloromethane (75 mL). This solution was washed with saturated ammonium chloride (2 x 25 mL) and brine (2 x 25 mL), dried over sodium sulfate, and concentrated under vacuum to afford 1.46 g (71.5%) of 100 as a colorless hard foam: IR (KBr) 3300 (OH), 2925, 1665 (NCO_2R), 1605, 1485, 1425, 1385, 1237, 1145, 1097, 1019, 920, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26-6.76 (m, 7H, Ar-H), 6.01 (s, 2H, $-OCH_2O-$), 5.37 (m, 2H, ArOH and ArCH(OR)OR'), 5.10-4.65 (bm, 1H, Ar-CH(OR)CH_2-), 3.80 (d, 3H, $-NCO_2CH_3$), 3.68-3.50 (m, 2H, $-CH(OR)CH_2-N-$), 3.22 (d, 3H, $-OCH_3$), 3.02 (dd, 3H, $-NCH_3$); MS (CI) m/z (rel int) 388(28.81), 207(39.49), 208(100), 127(39.55), 121(39.96), 120(84.06). Anal calcd for $C_{20}H_{23}NO_7$: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.18; H, 5.87; N, 3.57.

7'-[N-Carbomethoxy(methylaminomethyl)]-7',8'-dihydro 5'-methoxyspiro[2,5-cyclohexadien-4-one-1,8'-[5H-1,3]dioxolo[4,5-h][2]benzopyran] (101).

a. Small Scale Oxidative Coupling of 100: To a solution of 100 (74 mg, 0.19 mmol) in dry dichloromethane (20 mL) at -30°C was added a solution of phenyliodine(III) bis(trifluoroacetate) (83 mg, 0.19 mmol) in dichloromethane (10 mL). After 2.5 at -30→-25°C, another equivalent of phenyliodine(III) bis(trifluoroacetate) was added to provide a light green solution. After 90 min the reaction solution was shaken

with saturated aqueous sodium bicarbonate (1 x 25 mL) and extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over sodium sulfate, and evaporated under reduced pressure to furnish a brown oil, which was chromatographed on silica gel. Elution with 35% ethyl acetate in hexane led to the recovery of 16 mg (55%) of piperonal, 7 mg (16%) of N-carbomethoxysynephrine (102) as a colorless oil, and 5 mg (7%) of 101 as a yellow oil.

102: IR ($CHCl_3$) 3600 (ArOH), 3350 (OH), 2930, 1675 (NCO_2R), 1605, 1597, 1492, 1393, 1102, 1073, 1011, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (d, 2H, J=8.1 Hz, Ar-H ortho to phenol group), 6.96 (d, 2H, J=8.1 Hz, Ar-H meta to phenol group), 4.83 (bt, 1H, ArCH(OH)CH_2-), 3.66 (s, 3H, -CO_2CH_3), 3.40 (m, 2H, -CH(OH)CH_2N-), 2.84 (s, 3H, -NCH_3); MS m/z (rel int) 225(2.4), 208(6.0), 149(16.6), 123(100), 121(20.5), 104 (63.0), 103(62.0), 102(61.6); exact mass m/z 207.089 (M^+-H_2O, calcd for $C_{11}H_{13}NO_3$: 207.090).

101: IR ($CHCl_3$) 1685 (C=C-C=O), 1665 (NCO_2R), 1470, 1420, 1385, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) 7.24-6.34 (m, 6H, Ar-H and -CH=CH-CO), 5.99 (s, 2H, -OCH_2O-), 5.57 (s, 1H, ArCH(OR)OR'), 4.62 (bs, 1H, RCH(OR)CH_2-), 3.78 (s, 3H, -CO_2CH_3), 3.74 (m, 2H, -CH(OR)CH_2N-), 3.62 (s, 3H, -OCH_3), 3.13 (s, 3H, -NCH_3); UV (CH_3OH) λ_{max} 247 (ε 27600), 285 nm (ε 3740); MS m/z (rel int) 387(0.9), 356(9.3), 285(30.8), 257(18.6), 256(100), 241(40.3), 225(31.5), 213(29.7), 207(23.3), 197(14.8), 127(12.7), 102 (81.2), exact mass m/z 387.128 (calcd for $C_{20}H_{21}NO_7$: 387.132).

b. Batch Scale Oxidative Coupling of 100: To each of four separate flasks, which each contained a solution of 100 (100 mg, 0.257 mmol)

in dichloromethane (15 mL), was added a solution of phenyliodine(III) bis(trifluoroacetate) (225 mg, 0.523 mmol) in dichloromethane (10 mL). After 90 min, the contents of the four flasks were poured into freshly prepared 1N sodium thiosulfate (75 mL). The separated organic layer was washed with more 1N sodium thiosulfate (25 mL), saturated aqueous sodium bicarbonate (2 x 25 mL), water (50 mL) and brine (2 x 25 mL), dried over sodium sulfate and concentrated in vacuo to provide a brown oil, which was chromatographed on alumina (Activity I). Elution with 35% ethyl acetate in hexane yielded 14 mg (3.5%) of 101 as a yellow oil.

6-(4-Hydroxyphenyl)-3,4-methylenedioxybenzaldehyde (104).

Using a procedure outlined by Olah, et al,[64] trimethylsilyl chloride (3.7 μL, 0.029 mmol) was introduced via syringe to a stirring mixture of 101 (5.7 mg, 0.015 mmol) and sodium iodide (6.6 mg, 0.044 mmol) in freshly dried acetonitrile (5 mL). An immediate yellow color resulted, and after 2 days the reaction mixture was shaken with saturated aqueous sodium bicarbonate (10 mL) and extracted with ether (3 x 15 mL). The combined ethereal layers were washed with brine (3 x 15 mL), dried over sodium sulfate, and concentrated under reduced pressure to provide a yellow oil, which was applied to a silica gel preparative thin layer chromatographic plate. Development in 3% methanol in chloroform and extraction of the absorbent with 15% methanol in dichloromethane yielded 3.4 mg (95.6%) of 104 as colorless microneedles, mp 165-167°C: IR (KBr) 3300 (OH), 1670 (CHO), 1604, 1478, 1430, 1345, 1250, 1208, 1092, 1009, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.22 (s, 1H, -CHO), 8.99 (s, 1H, ArOH), 7.10 (d, 2H, J=8.1 Hz, Ar-H ortho to phenol hy-

droxyl), 6.85 (d, 2H, J=8.1 Hz, Ar-H meta to phenolic hydroxyl), 6.80 (m, 3H, $C_6\underline{H}_3$), 6.06 (s, 2H, -$OC\underline{H}_2O$-); UV (CH_3OH) λ_{max} 245 (ε 13200), 267 (ε 9110), 329 nm (ε 3820); MS m/z (rel int) 242(100), 241(48.3), 183(20.1); exact mass m/z 242.057 (calcd for $C_{14}H_{10}O_4$: 242.058).

4,4a,5,6-Tetrahydro-8-methoxy-5-methyl--8H-[1,3]dioxolo[6,7][2]benzopyrano[3,4-c]indol-3-one (107).

A solution of 101 (12.0 mg, 0.031 mmol) in 6N potassium hydroxide (200 μL) and ethylene glycol (1 mL) was maintained at 90°C for two days. The resultant pink solution was allowed to cool to room temperature, stirred for an additional day, poured into brine (20 mL) and extracted with ether (3 x 20 mL). The combined ethereal layers were washed with brine (4 x 20 mL), dried over sodium sulfate and evaporated under reduced pressure to afford a yellow oil, which was applied to a silica gel thin layer chromatographic plate. Development with 5% methanol in chloroform and extraction of the adsorbent with 20% methanol in dichloromethane furnished 4.5 mg (44.1%) of 107 as a colorless oil: IR ($CHCl_3$) 1680 (C=C-C=O), 1480, 1380, 1338, 1102, 945, 915 cm^{-1}; 360 MHz ^1H NMR ($CDCl_3$) δ 6.78 (s, 1H, Ar-H_{12}), 6.68 (s, 1H, Ar-H_9), 6.42 (dd, J=1.6,10.2 Hz, collapses to d, J=10.2 Hz upon irradiation at 3.12 and d, J=1.6 Hz upon irradiation at 6.23, -$\underline{H}$C=CHCO-), 5.95 (dd, 2H, J=1.0,7.9 Hz, -$OC\underline{H}_2O$-), 5.40 (s, 1H, Ar$\underline{C}$H(OR)OR'), 4.39 (d, 1H, J=4.5 Hz, collapses to s upon irradiation of 3.52, -$\underline{C}$H(OR)-CH_2N-), 3.56 (s, 3H, -$OC\underline{H}_3$), 3.52 (dd, 1H, J=4.5,12.0 Hz, collapses to a d, J=4.5 Hz upon irradiation at 2.67 and d, J=12.0 Hz upon irradiation at 4.39, -CH-CH $_{\alpha}(\underline{H}_{\beta})$N-), 3.12 (dd, 1H, J=1.6,1.8 Hz, col-

lapses to d, J=1.8 Hz upon irradiation at 6.42, -CC<u>H</u>(NR)CH_2-), 2.67 (m, 3H, -CH(NR)$\underline{CH_2}$CO- and -CH-$\underline{CH}_{\alpha}(H_{\beta})$N-), 2.46 (s, 3H, -N$\underline{CH_3}$); UV ($CH_3OH$) λ_{max} 226 nm (ε 8800); MS m/z (rel int) 329(18.7), 298(54.5), 286(66.2), 255(59.5), 254(57.8), 239(34.9), 203(37.9), 199(55.4), 188(26.9), 172(26.1), 171(27.3), 155(27.8), 149(32.8), 148(30.0), 139 (50.0), 129(40.0), 128(69.2), 127(59.4), 123(30.6), 115(100), 114 (33.2), 113(26.7), 110(46.7), 106(49.9), 103(30.1), 102(50.2), 101 (42.8); exact mass m/z 329.125 (calcd for $C_{18}H_{19}NO_5$: 329.126).

4,4a,5,6-Tetrahydro-8-methoxy-5-methyl--8H-[1,3]dioxolo[6,7][2]benzopyrano-[3,4c]indolin-3α-ol (109).

To a solution of 107 (4.5 mg, 0.0137 mmol) in methanol (1 mL) at 0°C was added sodium borohydride (5 mg). This solution was allowed to warm to room temperature over a period of 1 h and concentrated under reduced pressure to give a colorless oil, which was dissolved in brine (3 mL). This aqueous solution was extracted with ether (3 x 5 mL). The separated organic layers were washed with brine (4 x 10 mL), dried over sodium sulfate, and evaporated in vacuo to provide a yellow oil, which was applied to a silica gel thin layer chromatographic plate. After development with 7% methanol in chloroform and extraction of the adsorbent with 20% methanol in dichloromethane, 2.1 mg (46%) of 109 was isolated as a colorless oil: IR ($CHCl_3$) 3350 (OH, which did not change in appearance over the concentration range of 0.21 M to 0.053 M), 1600, 1580, 1540, 1380, 1350, 1100, 1030, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62 (s, 1H, Ar-$\underline{H}_{12}$), 6.51 (s, 1H, Ar-$\underline{H}_9$), 6.95 (dd, 1H, J=5.0,10.0 Hz, collapses to d, J=10.0 Hz upon irradia-

tion at 4.10, -CH=CH-CH(OH)-), 5.81 (s, 2H, $-OCH_2O-$), 5.50-5.21 (m, 1H, -HC=CH-CH(OH)-), 5.30 (s, 1H, ArCH(OR)OR'), 4.23 (d, 1H, J=4.0 Hz, $-CH(OR)CH_2-$), 4.10 (bm, 1H, $-CH-CH(OH)CH_2-$), 3.58-3.45 (m, 1H, $H_{6\beta}$), 3.50 (s, 3H, $-OCH_3$), 3.30 (bs, 1H, exchanged with D_2O, -OH), 3.00 (bm, $-CH_2CHN-$), 2.67-2.50 (m, 1H, $H_{6\alpha}$), 2.52 (s, 3H, $-NCH_3$), 1.98 (bt, $-CH(OH)CH_2CH-$); MS m/z (rel int) 331(40.1), 316(22.1), 300(27.5), 270(22.7), 261(3.5), 70(100); exact mass m/z 331.142 (calcd for $C_{18}H_{21}NO_5$: 331.142).

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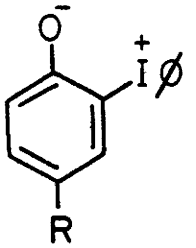

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