AN ABSTRACT OF THE THESIS OF

<u>Doreen L. Weller</u> for the degree of <u>Doctor of Philosophy</u> in

<u>Chemistry</u> presented on <u>October 4, 1983</u>

Title: <u>An approach to the Morphine Alkaloids: Synthesis of 9-</u>

 <u>Methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]-</u>

 <u>isoquinoline-7(7aH)-ones</u>

Abstract approved:

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         Dwight D. Weller

A short, convergent route to the ACNO ring fragment of the morphine alkaloids has been demonstrated by the synthesis of 9-methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinoline-7-(7aH)-ones V, VI from the 4-arylpyridinium salt precursor II in 47% overall yield. The ester enolate of the A ring side chain in II added nucleophilically to the pyridinium ring to give the spirocyclic dihydropyridine III. Subsequent Dieckmann condensation effected closure of the C ring to yield tetracyclic IV. Catalytic hydrogenation and decarboethoxylation of IV gave predominantly the trans CN ring junction stereoisomer V (V:VI, 88:12). Alternately, catalytic hydrogenation of III, followed by Dieckmann condensation of the resulting spirocyclic piperidine, and decarboethoxylation, gave largely the cis isomer VI (VI:V, 71:29).

Various routes to β-substituted 4-arylpyridine I, precursor to II, were investigated. In one case, acylfurans were used as the

I

II

III

IV

V: R = α-H

VI: R = β-H

VII

VIII

IX
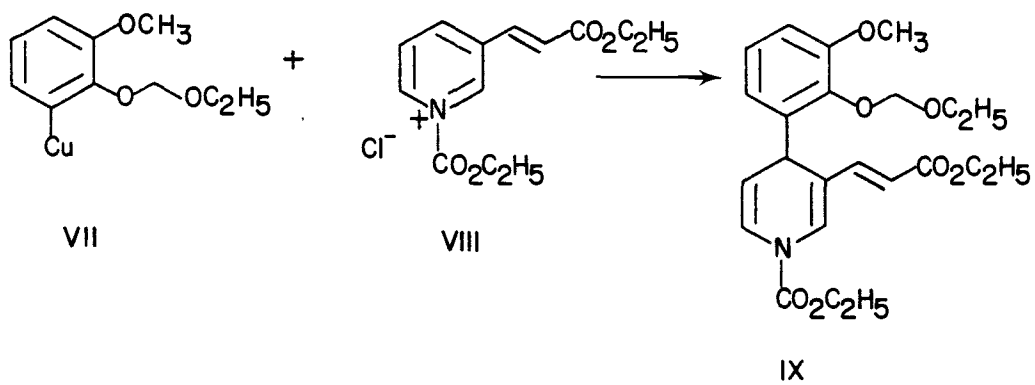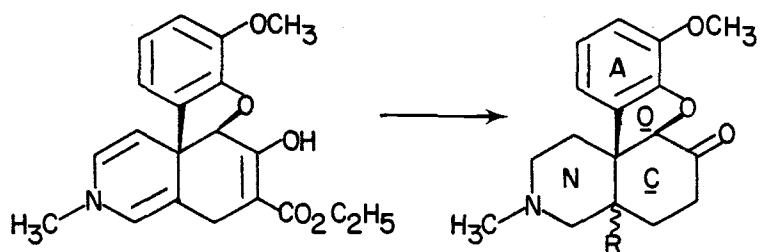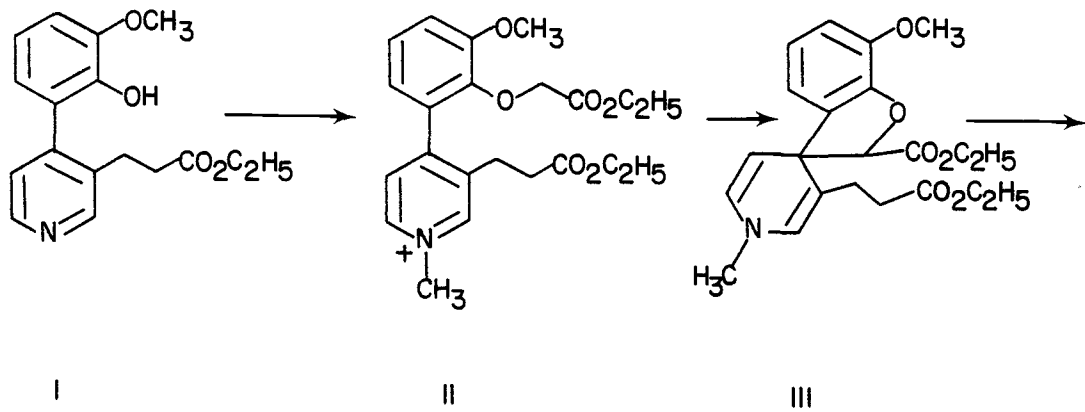
methylenic components in the Michael reaction with chalcones leading to 2,6-difuryl-4-arylpyridines by an improvement of the Weiss method. The α-furyl moieties were selectively oxidized and decarboxylated to give the corresponding 4-arylpyridines. This method, however, was not suitable for incorporation of a side chain larger than methyl at the pyridine C-3. By an alternate route, 4-arylpyridine-3-carboxaldehydes were prepared from α-methylstyrene derivatives by Vilsmeier formylation and subsequent cyclization with ammonia. The aldehyde group then permitted introduction of the propionate side chain via Knoevenagel condensation and reduction. While this method gave good yields of the nor-methoxy analog of I, the presence of the methoxy group gave consistently poor results in the pyridine formation step. An efficient and convergent synthesis of I was achieved by the ready addition of aryl copper derivative VII to pyridinium salt VIII to give dihydropyridine IX. Upon oxidation, hydrogenation and phenolic deprotection, I was obtained in overall 69% yield. Successive N- and O-alkylations then gave II quantitatively.

AN APPROACH TO THE MORPHINE ALKALOIDS:   SYNTHESIS OF
9-METHOXY-3-METHYL-2,3,4,4a,5,6-HEXAHYDRO-1H-
BENZOFURO[3,2-e]ISOQUINOLINE-7(7aH)-ONES

by

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Dean of Graduate School

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Typed by Jackie Poppleton for _____ Doreen L. Weller _____

## ACKNOWLEDGEMENT

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## INTRODUCTION

The importance of the morphine alkaloids as analgesic agents and
the lack of a natural domestic supply has made this class of compounds
a prime synthetic target.[1]  Several syntheses have recently proven
successful in preparing morphine (1a) and codeine (1b).[2]  However,
few of the current approaches possess all the elements of an efficient
synthesis.  Any practical synthesis of morphine must meet the require-
ments of 1) readily available precursors, 2) overall brevity, and 3)
efficient control of absolute stereochemistry.  The key criterion,
control of absolute stereochemistry, is the element most consistently
lacking in morphine syntheses.

The most stereoefficient synthesis to date is that of Rice[2a] and
Brossi,[3] utilizing the Grewe morphinan cyclization (Equation I).  The
key chiral precursors, the 1-benzyltetrahydroisoquinolines are readily
prepared via the Bischler-Napieralski synthesis.[4]  After resolution,
the incorrect enantiomer should be recyclable via oxidation and
reduction to give the racemic mixture (Equation II) as has been demon-
strated for several 1-benzyltetrahydroisoquinolines.[3]  Other
approaches, such as the oxidative coupling (biomimetic) approach
(Equation III),[2c,5] which utilize 1-benzyltetrahydroisoquinolines as
intermediates would also benefit from this resolution/racemization
sequence.  Unfortunately, it does not appear general for all

Ia: R = H

Ib: R = CH₃
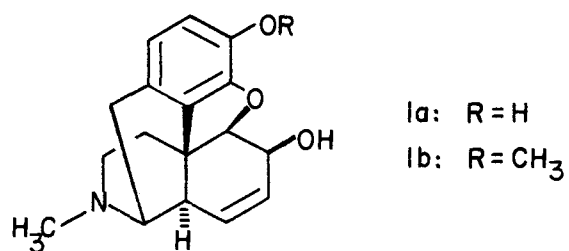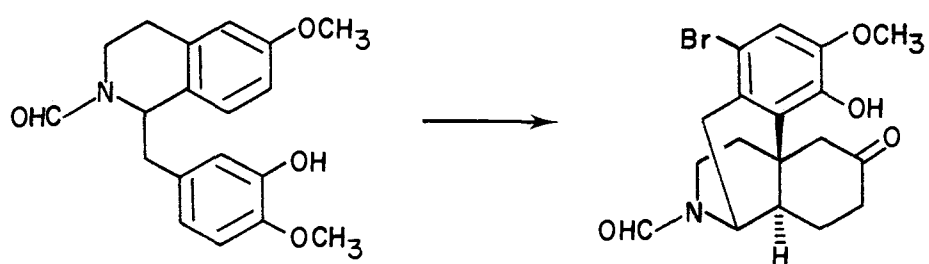
**Equation I**



**Equation II**
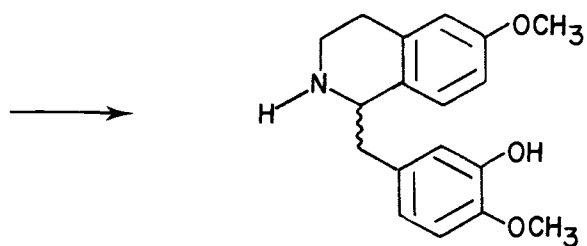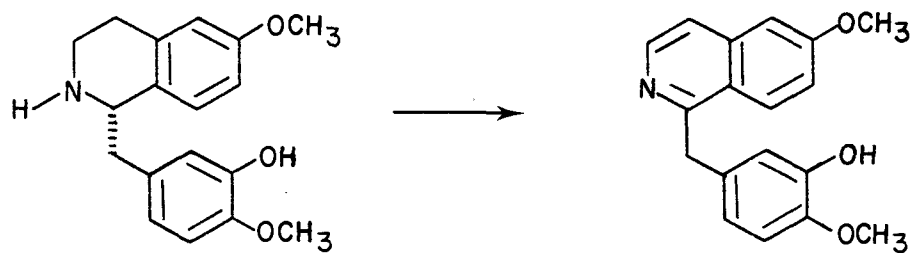
Equation III



Equation IV



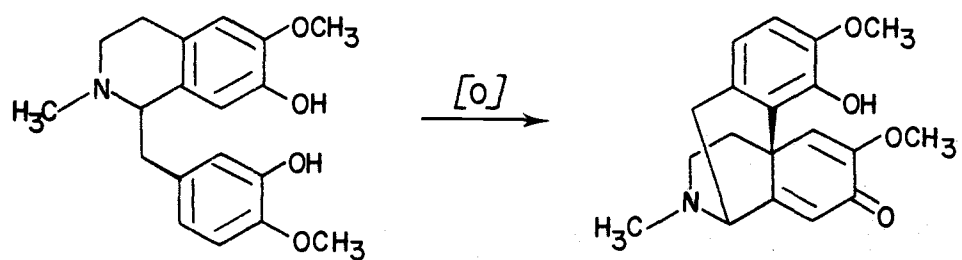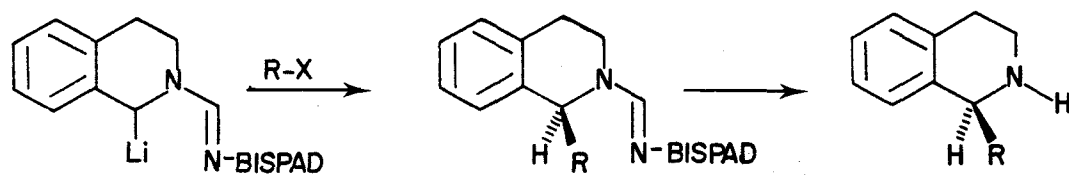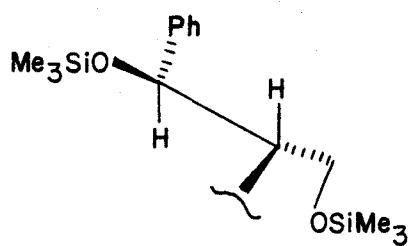(S,S(+)-BISPAD) =

reticuline analogs.[3,6] Methodology developed by Meyers[8] should
allow access to these intermediates in enantiomerically pure form.
As demonstrated for the preparation of (S)-1-alkyltetrahydroisoquino-
lines (Equation IV), utilization of α-amino carbanions derived from
tetrahydroisoquinoline formamidines, bearing an appropriate chiral
auxiliary to effect diastereofacial selectivity, results in a highly
successful asymmetric alkylation (>90% enantiomeric excess) with pre-
dictable absolute configuration.

Recently, a new fragment of the morphine skeleton which
possesses the A, C, N, and O ring system has been investigated. This
class of compounds, the benzofuroisoquinolines, are of general struc-
ture 2. Of particular interest are those which possess the trans CN
ring junction characteristic of morphine, since some have recently
been found to be potent analgesic agents in their own right.[9] Being
viewed as advanced intermediates in the synthesis of morphine (lack-
ing only C-10), several synthetic approaches to this ring system have
been reported in the literature.

The earliest preparation of the ACNO ring fragment was reported
by Schultz in 1976 while investigating a heteroatom-directed photo-
arylation sequence as a potential route to the morphine alkaloids.[10]
The key step involved photocyclization/rearrangement of aryloxyenone
6, to give the tetracyclic intermediate 7 having cis CN ring junction
stereochemistry (Scheme I). Significantly, this benzofuroisoquino-
line possesses the substituents necessary to form the remaining car-
bon-carbon bond of the B ring in the morphine skeleton. However, in
this approach, chirality is introduced in the Michael addition of
piperidone 4 to 3 and, while this reaction is in principle reversible,

2

Scheme I



3 + 4 → 5



6 → 7
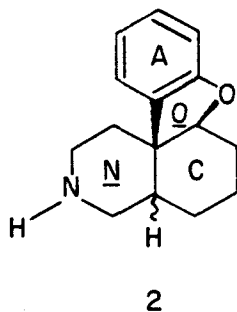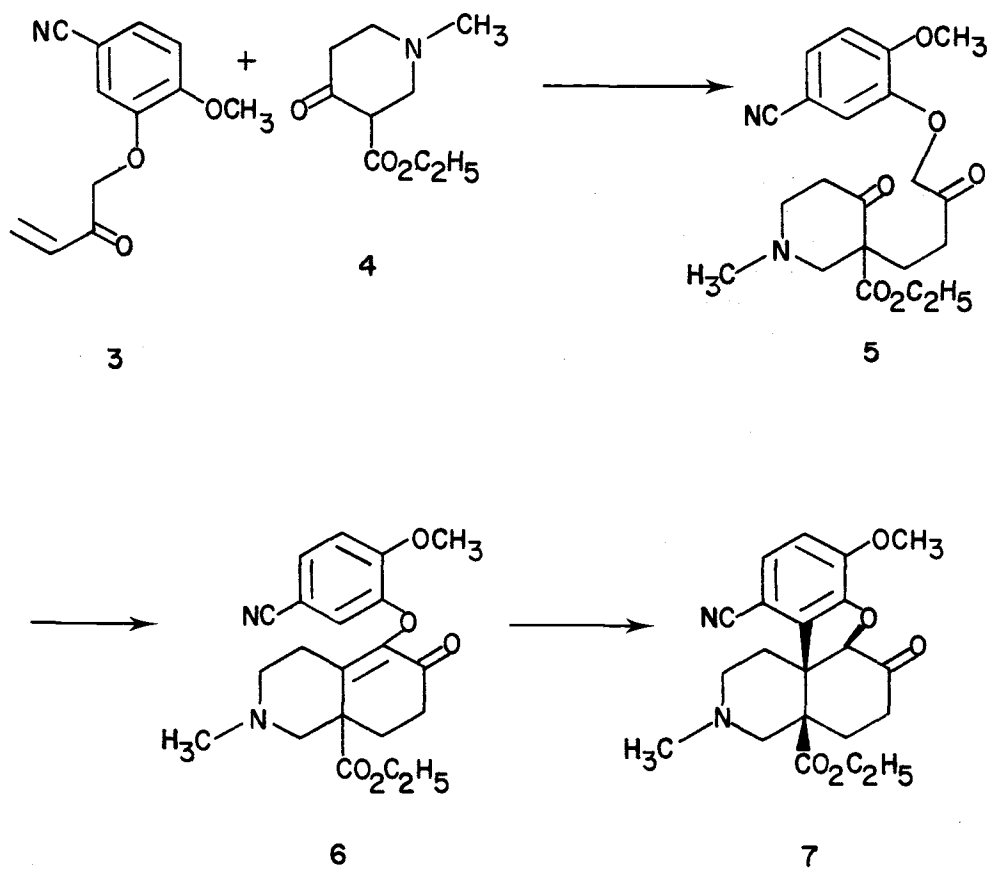
the enone component is reported to be very unstable and might not be recoverable.

During the course of studying routes to a number of morphine fragments, Rapoport also prepared the benzofuroisoquinolines 16 (Scheme II).[11] Thus, from piperidone 8, the sequence is characterized by an α-chloro ortho ester Claisen rearrangement (9 to 10) to establish functionality for O ring closure. The Claisen rearrangement also forms the key quaternary carbon and introduces the chirality of the system, but in an irreversible fashion. Thus, the unwanted enantiomer would not be easily recycled following resolution. Subsequent chromone-benzofuran rearrangement of 11 effects formation of the O ring to give 12. Michael addition of a β-keto ester to an α-methylene lactam then constructs the C ring (14). Finally, the CN ring junction stereochemistry is determined by hydrogenation of enamine 15, and yields an approximately 1:1 mixture of the cis and trans isomers of 16.

Recently, derivatives of octahydro-1H-benzofuro[3,2-e]isoquinolines have been prepared by Ciganek for the purpose of examining the biological properties inherent in this tetracyclic ring fragment of morphine.[9] Some of these were found to be potent analgesic agents. Importantly, compounds possessing the N-cyclopropylmethyl substituent (i.e., 17) exhibit both strong agonistic and antagonistic properties, and are thus likely to have a low potential for addiction. Ciganek's approach to this ring system utilizes an intramolecular Diels-Alder reaction, and leads to either the cis or the trans ring junction stereoisomer by variation of the diene moiety in the Diels-Alder precursor (Scheme III). In one case, the cis-fused isomer 19 is

Scheme II



8

9

10

11

12

13

14

15

16

17

Scheme III



18

19

20



21

22

23
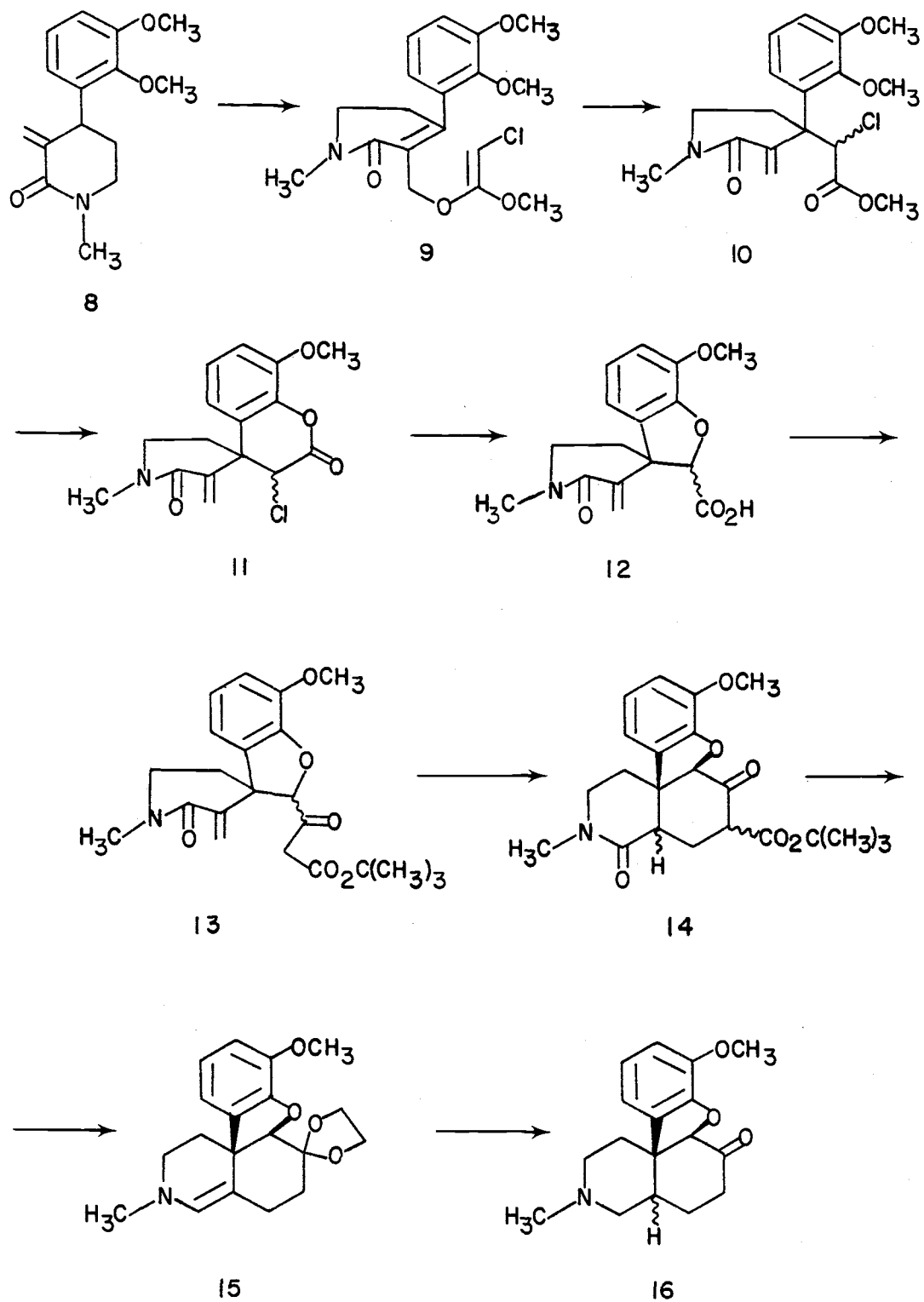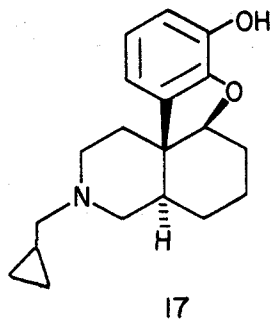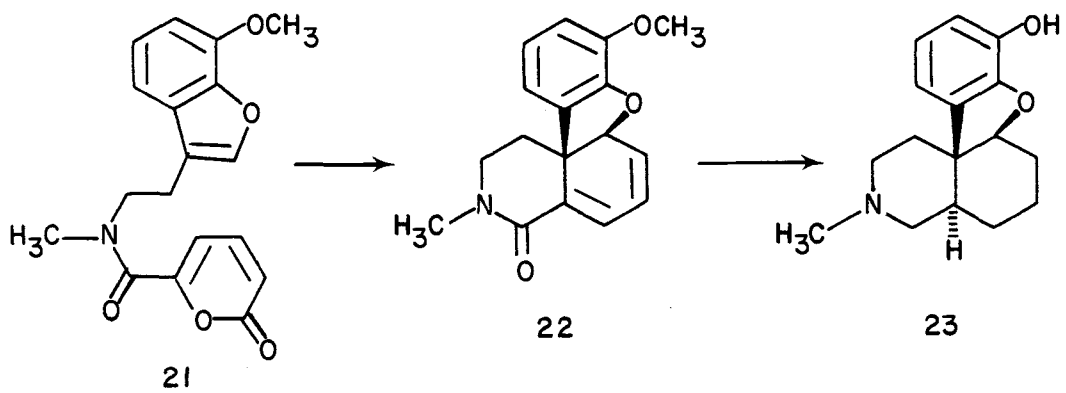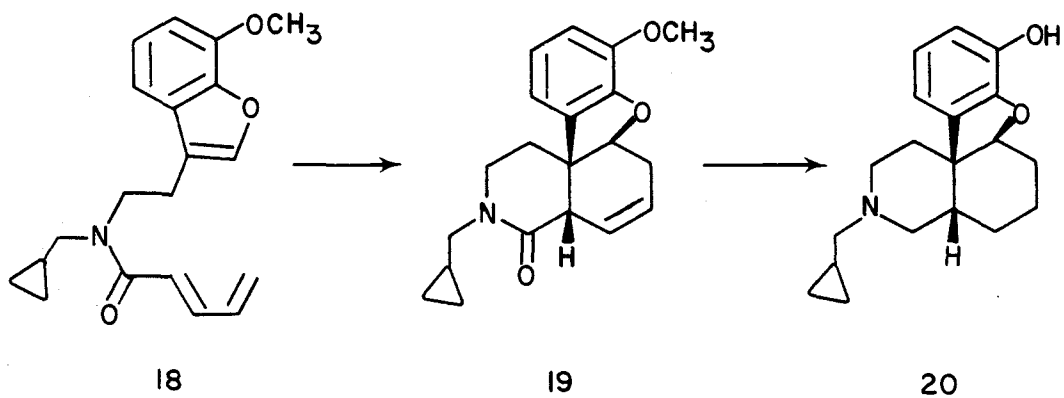
obtained directly from the Diels-Alder reaction of 18, and can be further hydrogenated to 20. In another case, the trans isomer 23 is obtained from 21 upon hydrogenation of the first-formed dihydrobenzo-furoisoquinoline 22. The quaternary carbon in this synthesis is generated irreversibly by the Diels-Alder addition. Although incorporation of a chiral auxiliary might be employed to provide asymmetric induction, this possibility was not addressed.

Elaboration of the benzofuroisoquinolines into morphine (1a) or codeine (1b) requires functionalization of the nitrogen ring by introducing a one-carbon unit to allow construction of the B ring, with formation of the epoxymorphinan skeleton. Several strategies have been demonstrated for nitrogen ring functionalization and subsequent B ring closure. In one approach, Rapoport has constructed the B ring in the conversion of methylene lactam 24 to the 6,7-benzomorphans 29a,b utilizing a procedure for converting an amide oxygen into a functionalized single carbon moiety suitable for substitution into an aromatic nucleus (Scheme IV).[12] In this case, the amide oxygen of 25a,b was replaced by a methyl ketone via a nitrile (26a,b) to give 27a,b. Lewis acid-catalyzed ring closure into the aryl nucleus, oxidation of the resulting methylene to carbonyl, and subsequent reduction/hydrogenolysis gave the target 6,7-benzomorphans 29a,b. In another approach, the morphinan skeleton was constructed from an ACN ring fragment by Evans[13] in a sequence later repeated by Rapoport.[14] The cis-fused iminium perchlorate 31, obtained from enamine 30 as the thermodynamically more stable isomer, was converted to the morphinan system in three steps in 72% yield (Scheme V). Treatment of 31 with diazomethane gave aziridinium salt 32 which, upon oxidative cleavage,

Scheme IV



24

25a: R = α-CH₃
25b: R = β-CH₃

26a: R¹ = α-CH₃, R² = β-CN
26b: R¹ = β-CH₃, R² = α-CN

27a: R¹ = α-CH₃, R² = β-COCH₃
27b: R¹ = β-CH₃, R² = α-COCH₃

28a: R = α-CH₃
28b: R = β-CH₃

29a: R = α-CH₃
29b: R = β-CH₃

Scheme V



30

31

32

33

34a

34b
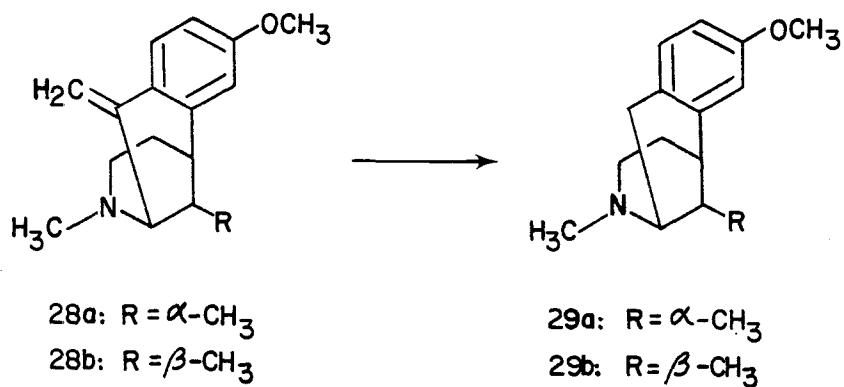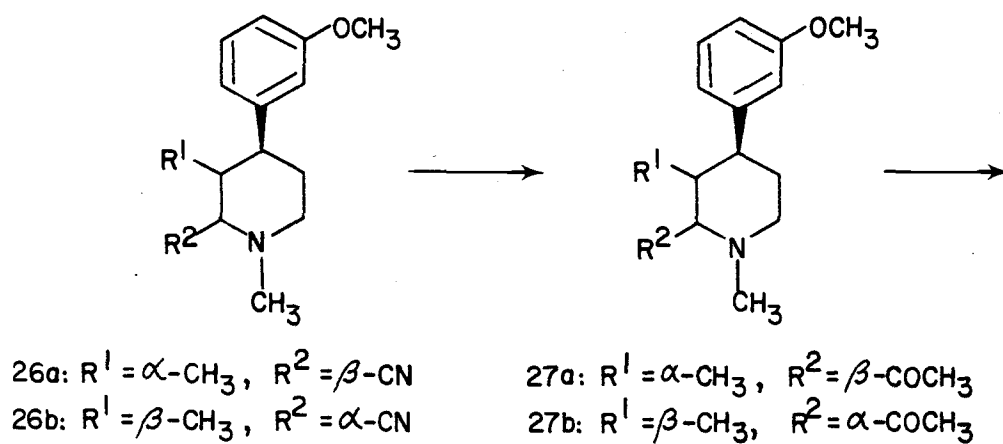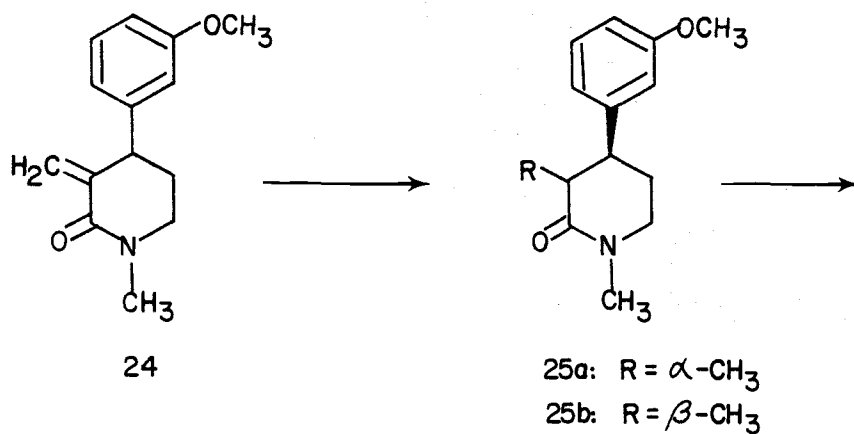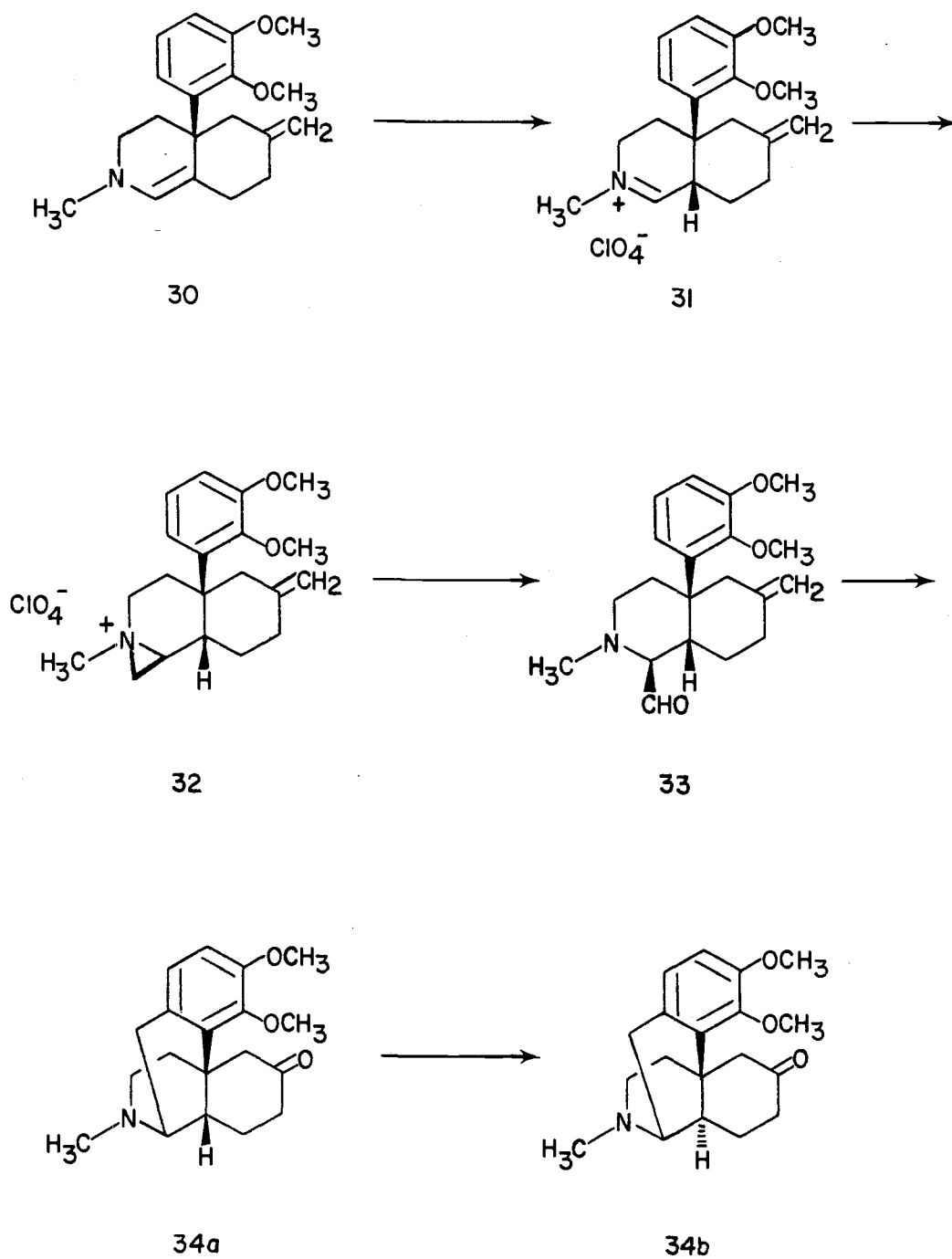
gave the amino aldehyde 33. Lewis acid-catalyzed cyclization to a morphinan carbinol, followed by successive methanesulfonylation/ mesylate reduction and Lemieux-Johnson oxidation of the exocyclic methylene gave morphinan 34a. The CN ring junction stereoisomer could be converted to the natural trans isomer, 34b, by the method of Gates.[15]

While the aforementioned syntheses of benzofuroisoquinolines offer a wide variety of approaches to this morphine ring fragment, none have made provisions for the control of absolute stereochemistry. The focus of this thesis, then, is to present a short, convergent route to the ACNO ring system which will allow for the efficient control of absolute stereochemistry. In this approach, the benzofuro- isoquinoline skeleton is viewed as arising from a 4-arylpyridinium salt precursor such as 35, which contains the functionality needed to construct the remaining O and C rings. As shown in Scheme VI, the ester enolate of the A ring side chain would add nucleophilically to the pyridinium ring and give the spirocyclic dihydropyridine 36. Sub- sequent Dieckmann condensation would effect closure of the C ring to give the tetracyclic structure 37.

Precedent for this approach is based on earlier studies whereby treatment of the 4-arylpyridinium salts 40 with base generates an enolate which adds intramolecularly to the 4-position of the pyri- dinium ring to give the spirocyclic dihydropyridines 41, the tri- cyclic skeleton of which corresponds to the ANO fragment of mor- phine.[16] By this methodology, construction of the important quater- nary center of the morphine alkaloids is easily achieved. Signifi- cantly, the addition may be reversed upon treatment with acid as was

Scheme VI



35

36

37

38

39
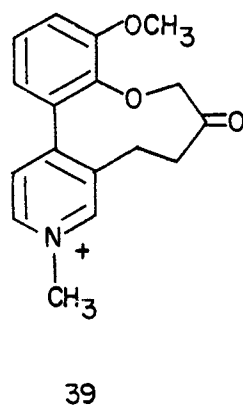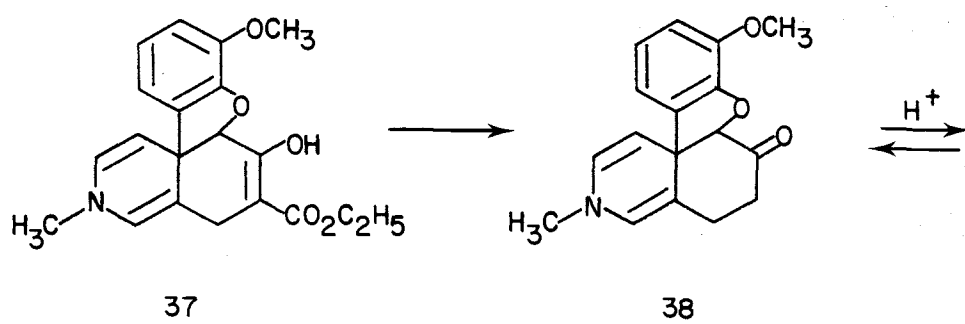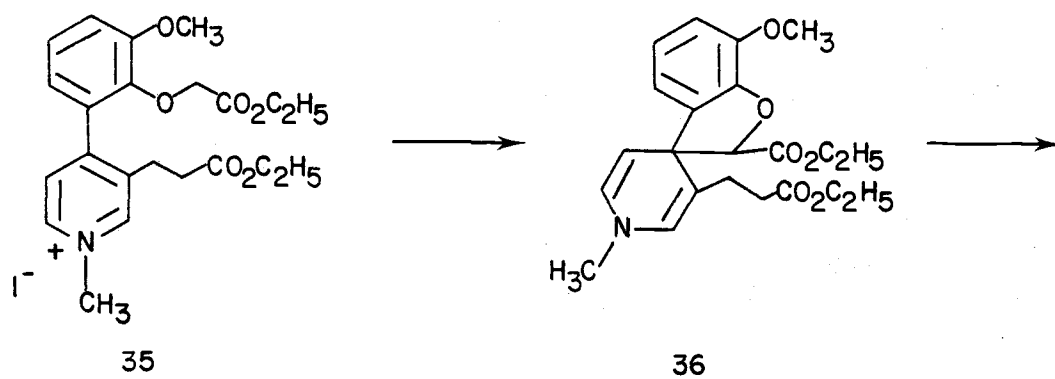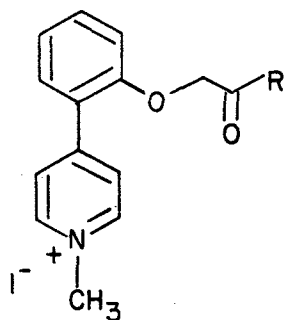
40a: R = OC$_2$H$_5$
40b: R = CH$_3$
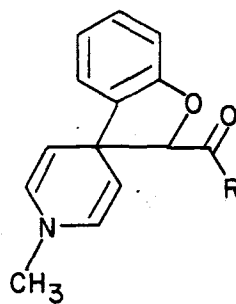
41a: R = OC$_2$H$_5$
41b: R = CH$_3$

Equation V
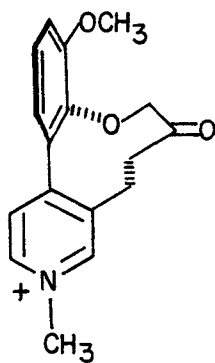


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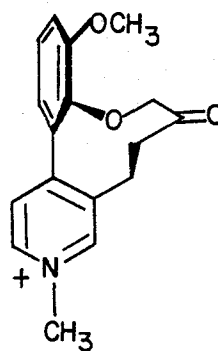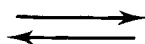
R - 39

demonstrated for the conversion of spirocyclic dihydropyridine 41b to 40b. Application of the reversal to the 5,6-dihydro-3H-benzofuro-[3,2-e]isoquinoline 38 would produce the medium ring ketone 39. Importantly, 39 should racemize by rotation about its biaryl axis (Equation V). Treatment with base would then return 38. Thus, following resolution of 38 or 39, the incorrect enantiomer could be recycled. Because of the simplicity and high yields attending the reactions interconverting 38 and 39, efficiency would be maximized. Completion of the morphine system from 38 would then proceed by construction of the B ring.

DISCUSSION

An investigation into the synthesis of benzofuroisoquinolines
from 4-arylpyridinium salts by means of intramolecular enolate addi-
tion to the pyridinium ion and subsequent Dieckmann cyclization was
undertaken. This required that initial efforts be directed towards
preparation of the necessary 4-arylpyridine precursors. Earlier work
on the study of intramolecular enolate addition reactions from 4-aryl-
pyridinium salts, employed an efficient route for synthesis of 4-aryl-
pyridine 42 from simple aromatic precursors.[16] It was hoped that this
synthesis could be adapted to the preparation of 43 which contains the
propionic ester side chain required for C ring construction.

The earlier studies[16] had shown that 4-(2-hydroxyphenyl)-pyridine
42 could be prepared from 2-methoxybenzaldehyde (44a) and 2-acetyl-
furan (45a) in overall 54% yield (Scheme VII) by an improvement of
the Weiss method for the preparation of 2,4,6-triarylpyridines.[17] The
use of acylfurans as the methylenic components in the condensation
reaction with chalcones, leading to 2,6-difuryl-4-arylpyridines, had
first been described by Carbateas in 1974.[18] In this work, the
oxidatively labile 2,6-difuryl groups allowed the preparation of the
2,6-unsubstituted-4-arylpyridines 52a,b from chalcone 50 (Scheme
VIII). Thus, 50 underwent Michael addition and subsequent cycliza-
tion in the presence of 45a,b and ammonium acetate/acetic acid to
give difurylpyridines 51a,b. The furan moieties could be selectively
oxidized to the corresponding diacids, which underwent ready decar-
boxylation to give 52a,b. The principle drawback inherent in the
Weiss procedure is the low yield of triarylpyridine obtained (less

42

43

Scheme VII



44a  45a

46a

47a

48a

49a  →  42

Scheme VIII



45a: R = H
45b: R = CH₃

50

51a: R = H
51b: R = CH₃

52a: R = H
52b: R = CH₃
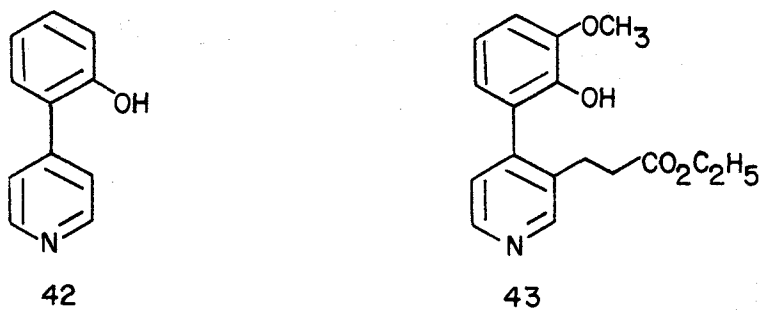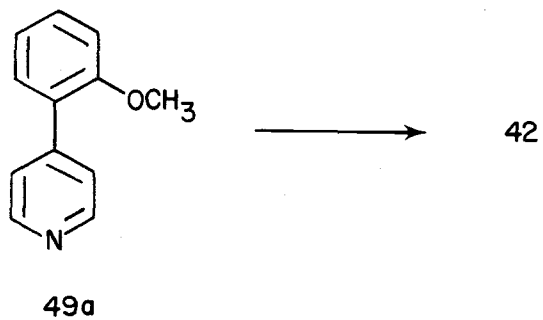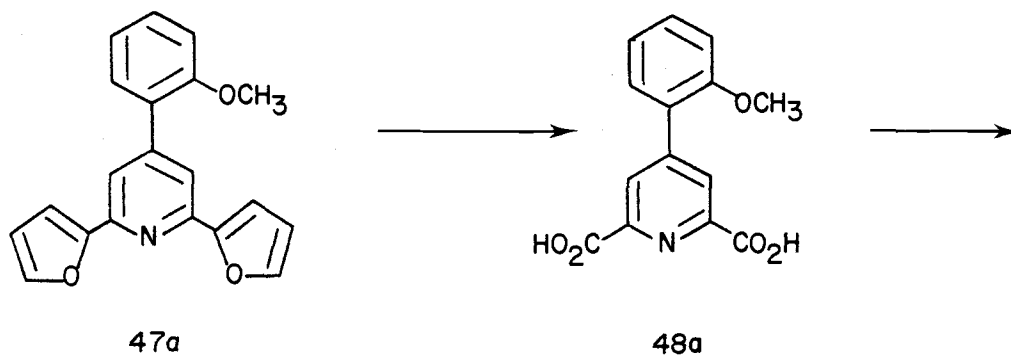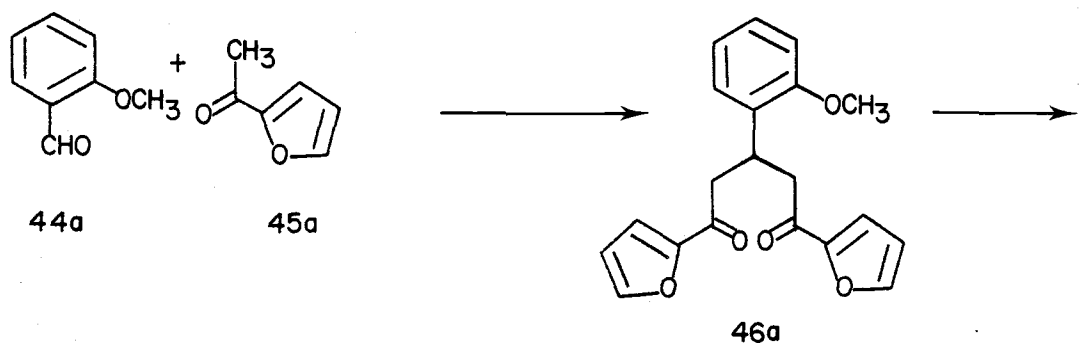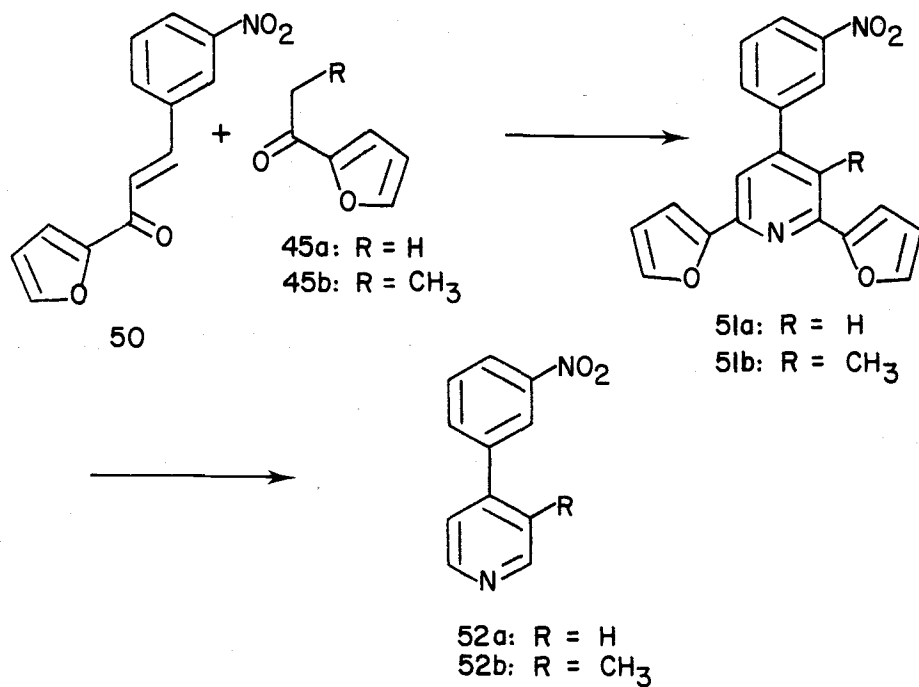
Scheme IX
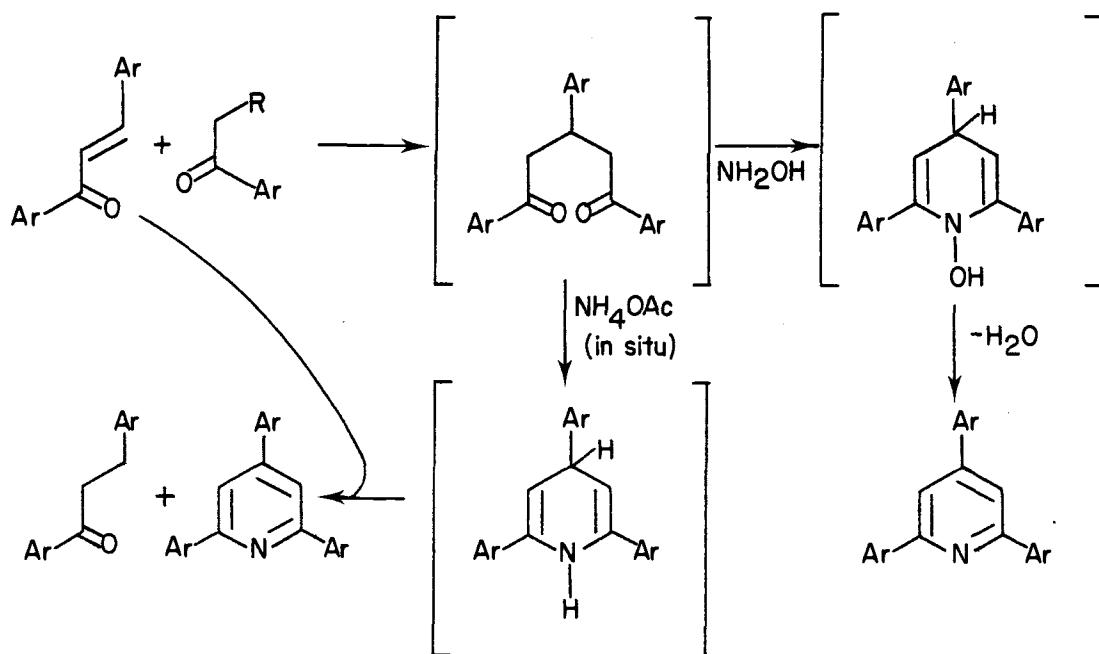
than 30% in this case) since the intermediate dihydropyridine, formed in the initial stages of this reaction, aromatizes by the transfer of hydrogen to another molecule of chalcone, yielding both the desired pyridine and the dihydrochalcone (Scheme IX).[17] This inefficient utilization of the aldehyde-derived precursor prohibits the use of expensive or difficult to obtain aldehydes. In order to provide a satisfactory synthesis of 4-arylpyridines from the corresponding alde-hydes, the simple and classical alternative to the Weiss procedure was utilized, involving the preparation of 3-aryl-1,5-difuryl-1,5-pen-tanediones and their reaction with hydroxylamine to give pyridines.[19] In this case, the intermediate would be an N-hydroxydihydropyridine, and subsequent pyridine formation does not involve simultaneous reduc-tion of chalcone (Scheme IX). Thus, the diketone 46a, available from 2-methoxybenzaldehyde (44a) by combination aldol and Michael reac-tions, gave pyridine 47a in 71% yield when subjected to the modified reaction conditions. Furan oxidation with potassium permanganate to 48a and thermal decarboxylation proceeded in high yield to give 49a. Methyl ether cleavage was subsequently effected with HBr at reflux to give 42.[16]

With an attractive route for the synthesis of 4-arylpyridines at hand, 3-methyl-4-(2-methoxyphenyl)pyridine 49b was chosen as the initial target molecule. Its synthesis would determine the feasi-bility of incorporating a substituent onto the β-position of the pyridine ring by this method. Additionally, after conversion of 49b to the suitably N- and O-alkylated pyridinium salt 54, the conse-quences of a C-3 substituent on the important intramolecular enolate addition reaction could be observed. Chalcone 53a,[20] prepared in 95%

Scheme X



53a   +   45b   →   46b

→   47b   →   48b

→   49b   →   54a: R = CH₃
54b: R = OC₂H₅
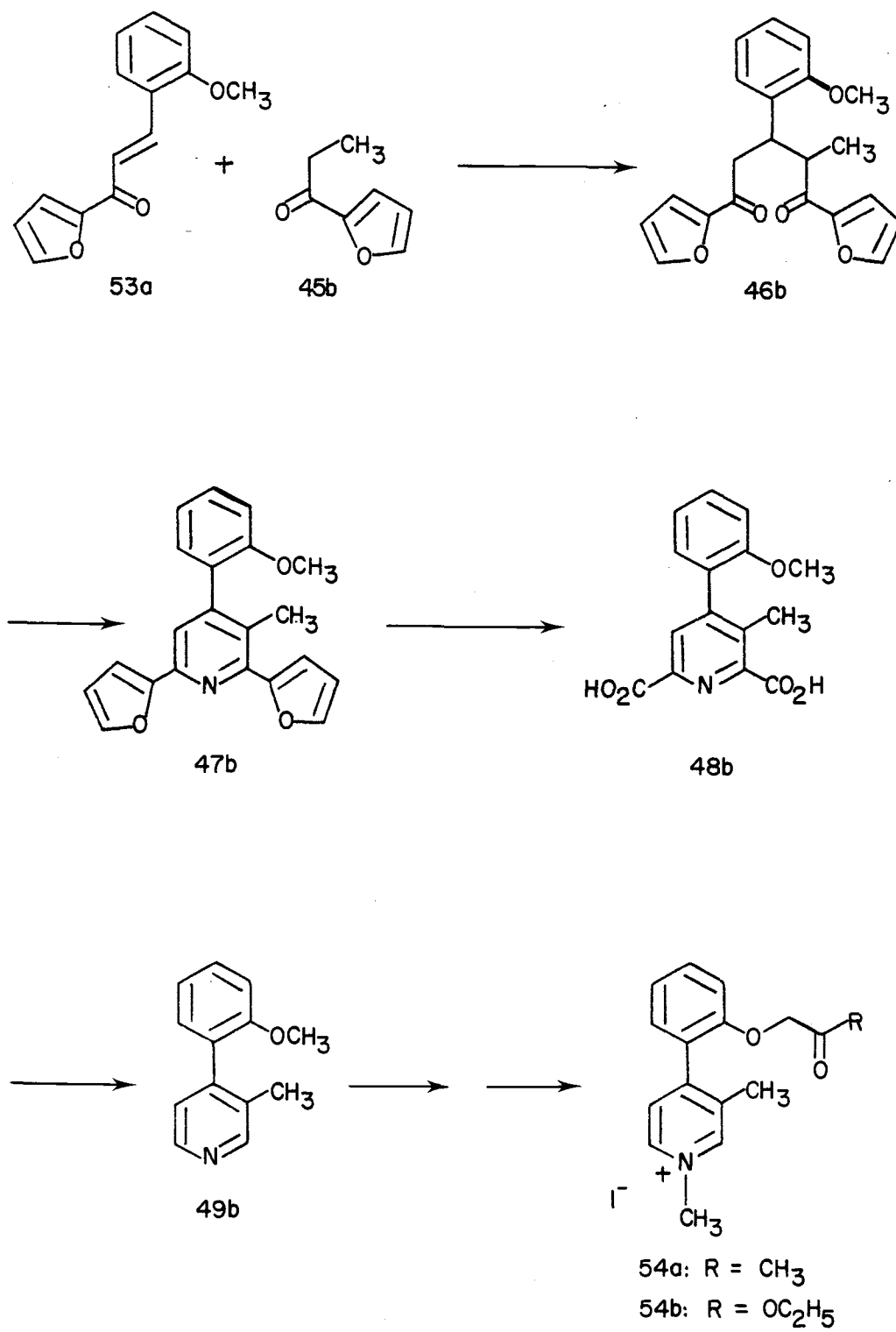
yield by Claisen-Schmidt condensation of 2-methoxybenzaldehyde (44a) and 2-acetylfuran (45a), underwent a Michael reaction with 2-propionylfuran (45b) in the presence of alcoholic base to give a high yield (99%) of the unsymmetrical diketone 46b as the sole product (Scheme X). The reaction was first carried out with an equimolar ratio of reactants but, although 46b was the only product obtained, the reaction was very slow. With a four-fold excess of 2-propionylfuran, a more convenient reaction time was obtained, and the excess 45b was easily recovered.

Since the preparation of a 1,5-diketone from a chalcone and an aromatic ketone in the presence of base is a theoretically reversible reaction, cross products 46a and 46h were expected from an equilibrium between 46b and retro-Michael products, chalcones 53a,h and acylfurans 45a,b (Scheme XI). Investigation of the Michael reaction, however, revealed it to be irreversible under these conditions. A mixture of excess 2-acetylfuran (45a) and 46b under the standard reaction conditions yielded no other products, and a parallel experiment with 46a and 2-propionylfuran (45b) similarly determined that 46b is stable to alcoholic base. Experiments carried out by Andrews and Connor in 1935 had suggested this possibility.[21] They found that reaction of chalcone (55) with acetophenone (56a) or propiophenone (56b) in the presence of sodium ethoxide in ethanol gave the corresponding 1,5-diketones (57a,b) with no evidence of cross-addition products (Equation VI). Yields, however, of 57a and 57b were only moderate (27% and 54%, respectively) in this case, and the diketones were accompanied by significant amounts of higher order addition products 58a,b (56% and 27%, respectively) resulting from further

Scheme XI



53a    45b            46b           45a    53h

46a             46h

Equation VI



55          56a: R = H
            56b: R = CH$_3$

57a: R = H (27%)
57b: R = CH$_3$ (54%)

58a: R = H (56%)
58b: R = CH$_3$ (27%)

Equation VII



53c          45b                                    46d
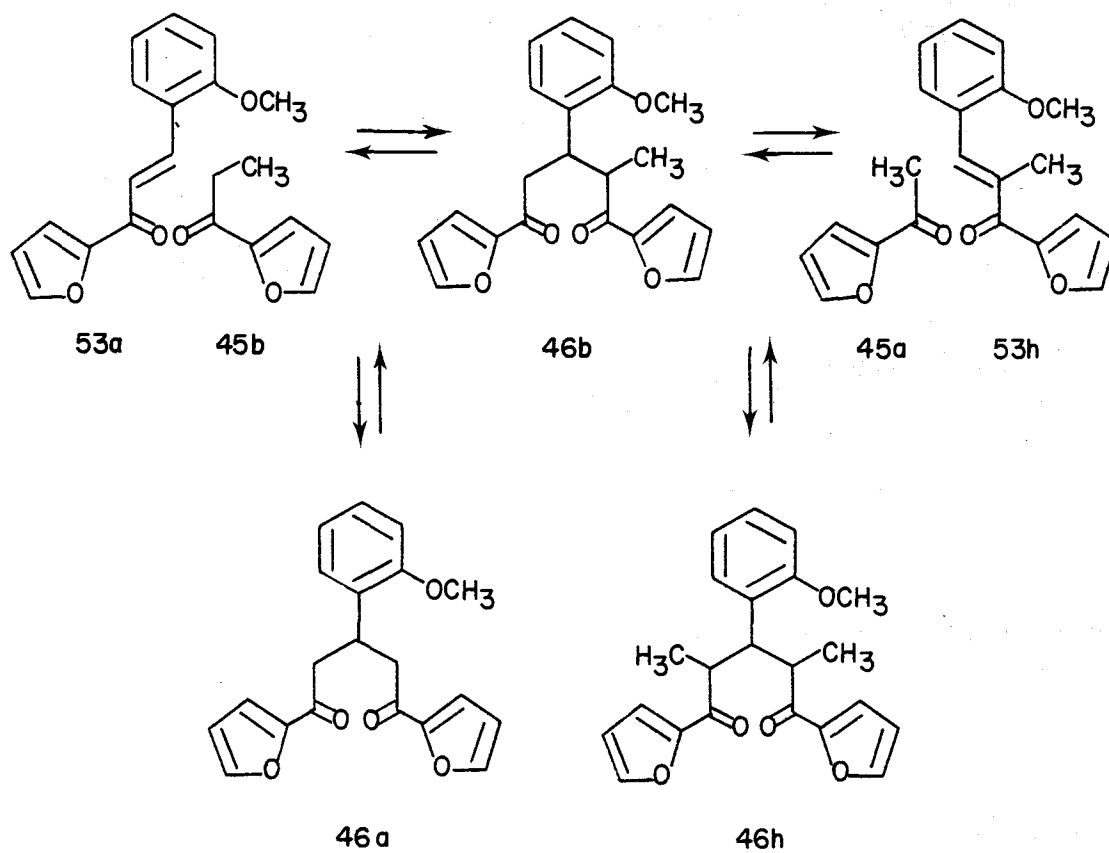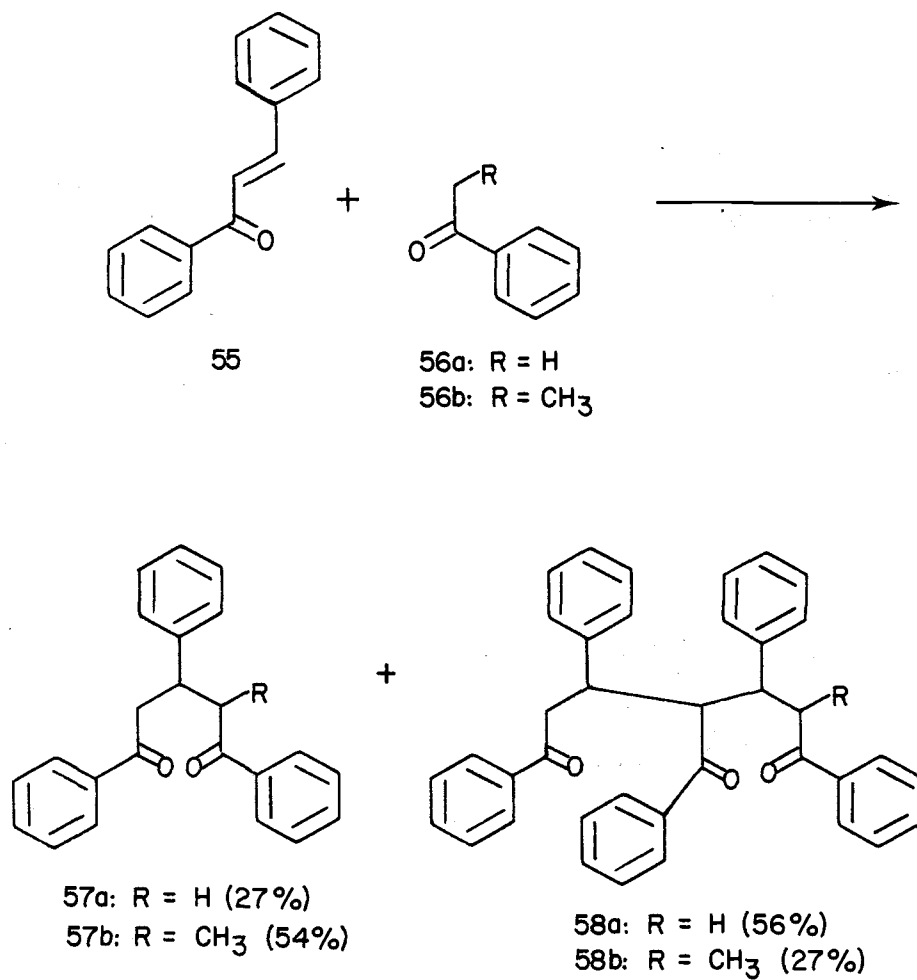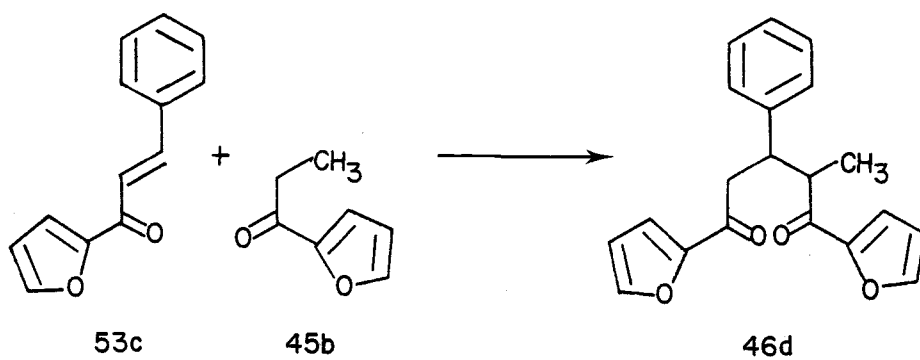
Michael reaction of 57a,b with chalcone. In view of this, it was sur-
prising that no higher order products were observed upon reaction of
chalcone 53a with acylfurans 45a,b. To more closely parallel the
system of the earlier studies, the furylchalcone 53c[22] was reacted
with an equimolar amount of 2-propionylfuran (45b) in the presence of
sodium hydroxide and, indeed, a mixture of products was observed.
Nonetheless, the unsymmetrical diketone 46d could be obtained as the
sole product by use of a four-fold excess of the acylfuran (Equation
VII). From these results, it was concluded that in the condensation
of 53a with equimolar amounts of 45a,b, the ortho methoxy group must
sterically hinder further Michael addition of the first formed dike-
tones 46a,b, thus preventing formation of higher order products.

Reaction of diketone 46b with hydroxylamine hydrochloride in n-
butanol at reflux produced the corresponding pyridine 47b in 71%
yield. The difurylpyridine, however, is contaminated with a con-
siderable amount of tar which hinders purification by vacuum distil-
lation. The most efficient purification was achieved by allowing a
solution of the crude product to stand over silica gel (20% by
weight) prior to distillation. The tar is apparently due to acid-
catalyzed decomposition of the furan rings in the product since
addition of sulfuric acid to the butanol reaction to facilitate ring
closure of the oxime intermediates, or running the reaction in acetic
acid, produced mainly tar. Unfortunately, addition of sodium acetate
to neutralize liberated HCl caused the reaction to be extremely slow,
with no increase in the amount of pyridine formed. An attempt to use
higher temperature (ethylene glycol, 140-150°C) to offset the longer
reaction times with sodium acetate present gave even lower yield

(25%) and more tar.

The sensitivity of the furan rings in this system is in contrast to the ease of pyridine formation observed with 1,5-diphenyl-1,5-pentanediones (Scheme XII). Formation of the unsymmetrical pyridine 59 proceeded cleanly in 96% yield under the usual reaction conditions. The high overall yield of 59 from chalcone 55a (89%) makes this method superior to the recent method of Tewari, using isoquinolinium ylides for the preparation of 59 (55% yield).[23]

Oxidation of the furan rings of 47b was easily accomplished in 90% yield with potassium permanganate in acetone at ambient temperatures. Although efficient, the procedure is inconvenient since the optimal conditions call for portionwise addition of the oxidant (1500 mol%) over several days to a dilute (0.5%) solution of the difurylpyridine in acetone. When the oxidation of 47b was performed under more concentrated conditions (2% solution), with less permanganate (110 mol%), and at a higher temperature (40°C), the reaction was complete in five hours and 48b was isolated in 83% yield (Scheme XIII; Table I). This procedure, however, was not found generally applicable on larger scale due to the rapid temperature rise upon addition of oxidant, and the accompanying difficulty of maintaining the desired temperature. A more practical procedure involved permanganate oxidation in t-butanol/water at 75°C. After twelve to eighteen hours, standard workup gave 48b in 70% yield. Oxidation of the unalkylated analog 47a by this method gave a high yield (95%) of 48a[24] and suggests that the yield for oxidation of 47b is potentially much better than observed. The thermal decarboxylation of 48b to produce pyridine 49b may be performed neat, but use of diphenyl ether was

Scheme XII
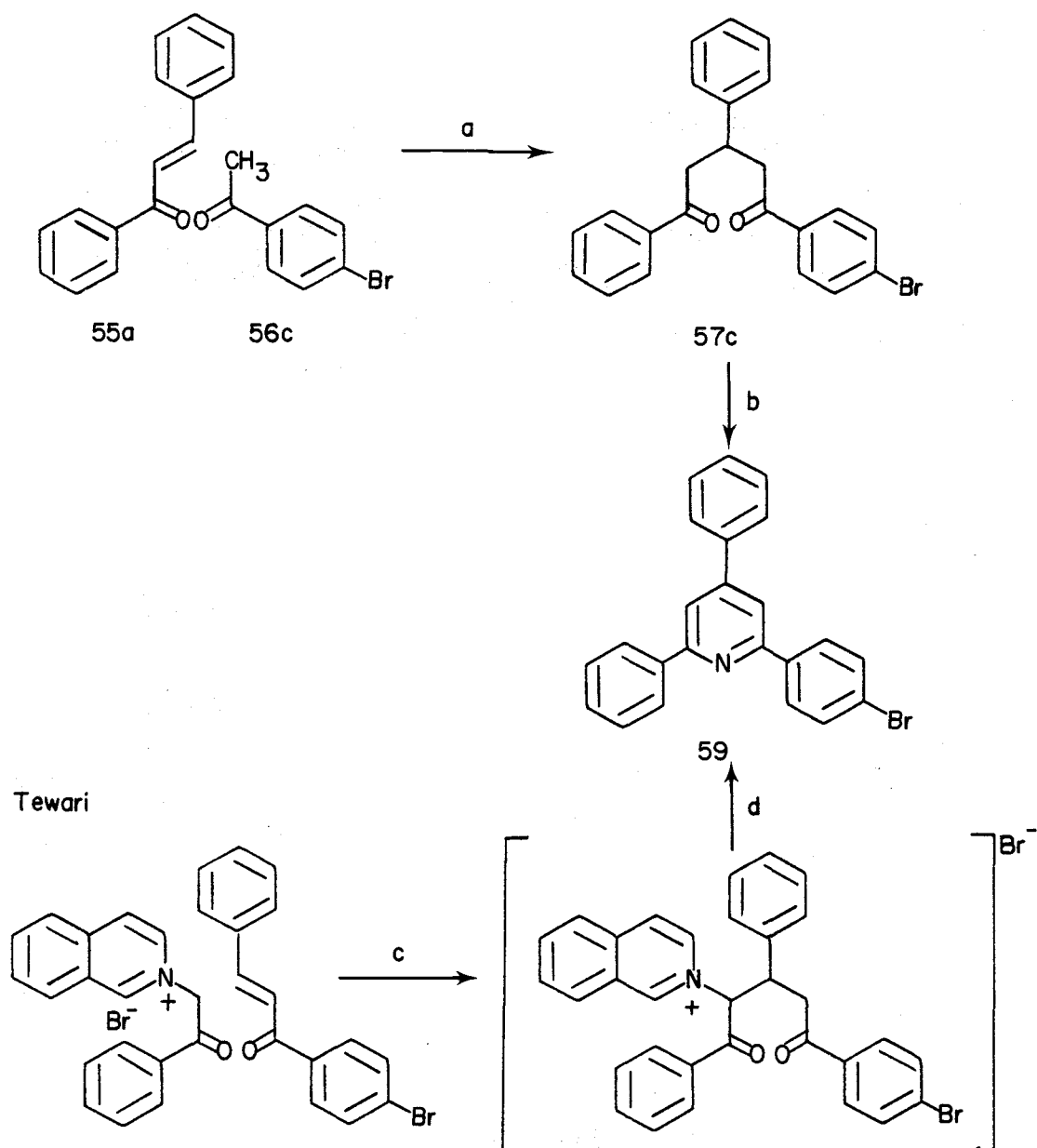


(a) NaOH, MeOH; 92%. (b) NH$_2$OH·HCl, $\underline{\text{n}}$-BuOH, $\triangle_\text{x}$; 96%. (c) AcOH, $\triangle_\text{x}$. (d) NH$_4$OAc (55% overall).

Scheme XIII



53 + 45 → 46

47 48

49
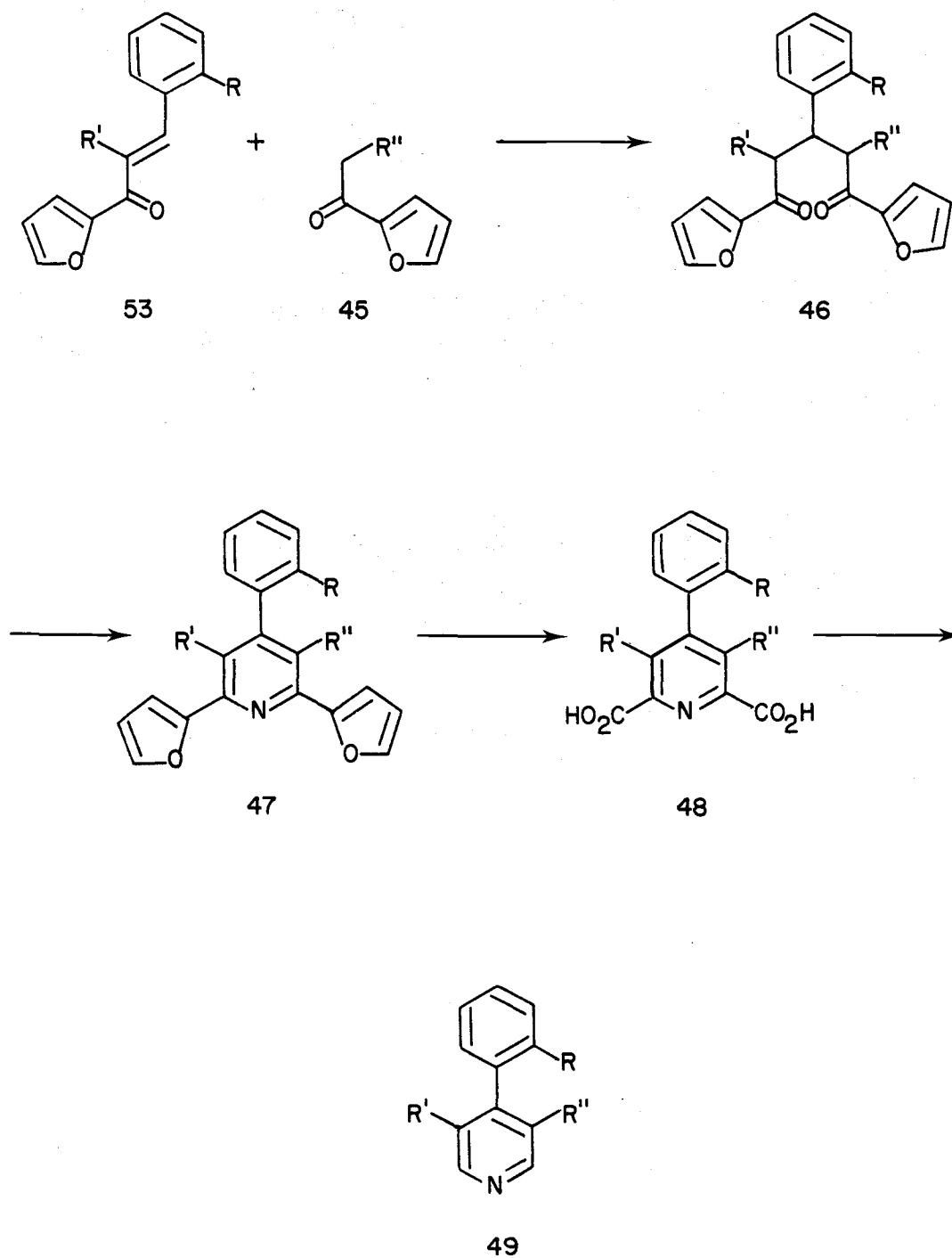
Table I.   Preparation of 4-Arylpyridines

| | R | R' | R" | 46 | 47 | 48[a] | 49 |
|---|---|---|---|---|---|---|---|
| a | $OCH_3$ | H | H | 93(82)[b] | 81 | 87 | 88 |
| b | $OCH_3$ | H | $CH_3$ | 99 | 71 | 90 | 83 |
| c | H | H | H | (85)[c] | 72 | 87 | 71 |
| d | H | H | $CH_3$ | 97 | 68 | 90 | 63 |
| e | H | H | $CH_2CH_3$ | 98 | 39 | 86 | 71 |
| f | H | $CH_3$ | $CH_3$ | d | 57[e] | 91 | 61 |
| g | H | $CH_3$ | $CH_2CH_3$ | d | 20[e] | f | f |
| h | $OCH_3$ | $CH_3$ | $CH_3$ | | | | |

[a] $KMnO_4$/Acetone.   [b] Yield directly from 2-methoxybenzaldehyde.   [c] Yield directly from benzaldehyde.   [d] Not purified; converted into 47.   [e] Yield from chalcone 53.   [f] These products were not obtained; see text.

generally preferred. Thus, 49b was obtained from 48b in 83% yield, and from 2-methoxybenzaldehyde (44a) in 50% overall yield.

Although not required for investigation of our approach to the morphine system, several additional pyridines (49c-g) were prepared to briefly examine the constraints on the reaction sequence (Scheme XIII, Table I). Although the facile preparation of 49b,d suggested the general utility of this method for obtaining 3-alkylated pyridines from aromatic aldehyde precursors, the formation of the 3-ethyl analog 49e was less successful. Here, in the preparation of difuryl-pyridine 47e, from diketone 46e (prepared under the usual conditions from chalcone 53c and 2-butyrylfuran 45e), ring closure of the oxime intermediates was very slow, leading to product decomposition and low yield (39%). However, the subsequent oxidation and decarboxylation to give 49e proceeded without difficulty. For the 3-alkylpyridine series, then, a more acid-stable aryl group is required to ensure product stability and allow more rapid pyridine ring formation via acid catalysis.

Preparation of 4-aryl-3,5-dialkylpyridines 49f-h required the formation of the corresponding dialkyl-1,5-diketones 46f-h from methyl chalcones 53f,h and acylfurans 45b,e. However, reaction of 2-methoxy-benzaldehyde (44a) or benzaldehyde (44b) with 45b in the presence of alcoholic base, as for the preparation of 53a,c, failed to give any of the desired methyl chalcones. Likewise, benzaldehydes 44a,b failed to react in the presence of 250 mole % of 45b and base, in a reaction analogous to the direct preparation of 46a,c, to give symmetrically substituted diketones 46f,h. These difficulties were not without literature precedent, as unsatisfactory results were reported by

Abell for the base-catalyzed condensation of benzaldehyde (44b) and
phenyl ethyl ketone (56b) to prepare 55b (Equation VIII) due to
failure of the initial aldol addition product 60a to eliminate
water.[25]  However, it was reported that 70-80% yields of 55b were
obtained when the condensation was effected with anhydrous HCl, and
the intermediate chloro compound 60b eliminated under thermal or basic
conditions.[25]  Thus, a neat mixture of benzaldehydes 44a,b and 45b was
treated with anhydrous HCl and gave an intermediate which, upon pro-
longed heating at 80°C, yielded chalcones 53f,h in high yield (82 and
86%, respectively).  Dehydrohalogenation of the intermediate could
also be effected by treatment with t-butoxide in t-butanol.  Once
formed, the methyl chalcones were found to be stable in the presence
of hydroxide since a 10% solution of 53f in methanol was stirred for
five days at 25°C in the presence of an equimolar amount of sodium
hydroxide without effect.

Methyl chalcones 53f,h are much less reactive than their unalky-
lated analogs.  Formation of dialkyl diketones 46f,g was extremely
slow using the usual conditions, as only a trace of diketone could be
observed in each case after prolonged reaction times, but proceeded
to completion in a more practical length of time with concentrated
sodium ethoxide in ethanol.  Only 110 mole % of acylfuran was employed
since these diketones are thermally labile and excess ketone could not
be removed by distillation.  Furthermore, product mixtures were not as
clean as those from the unalkylated chalcones, and the dialkyl dike-
tones 46f,g were usually not purified at this stage, but carried on
directly to the pyridine formation step.  The difficulty in the
Michael reaction of the alkyl chalcones is clearly illustrated by the

Equation VIII



44b        56b

55b
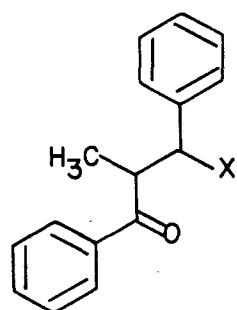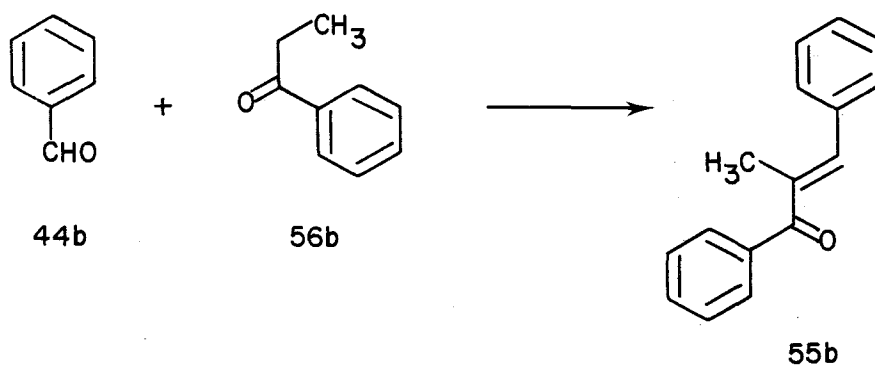


60a: X = OH
60b: X = Cl
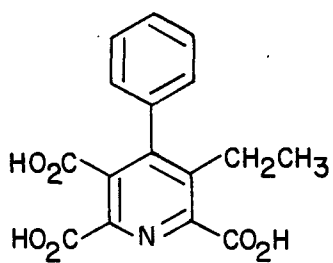


61
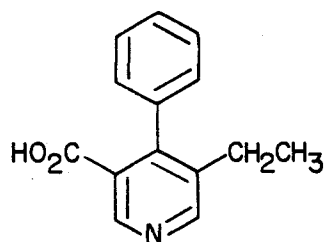


62

observation that acetylfuran (45a) reacted with 53f to yield only 41%
of 46d although this diketone was efficiently produced (97%) beginning
with the unalkylated chalcone 53c.  Interestingly, the dimethyl dike-
tone 46h in the 2-methoxyphenyl series could not be prepared.

While the dimethyl diketone 46f gave moderate yields in the
pyridine synthesis, the reaction of hydroxylamine hydrochloride with
the methyl ethyl diketone 46g was extremely slow.  Even after extended
times, the reaction did not achieve completion and only low yields of
47g could be isolated.  Pyridine 47f was successfully oxidized and
decarboxylated to 49f but permanganate oxidation of 47g led to oxida-
tion of the ring methyl.  The product obtained from 47g was presumably
the triacid 61 although characterization was more convenient after
decarboxylation to the nicotinic acid 62.  This example is in dis-
tinct contrast to the previous examples, and to the attempted oxida-
tion of the side chain in 49b which was resistant to potassium per-
manganate in refluxing aqueous dioxane.  Thus, except for the dimethyl
case, this method does not appear to be generally applicable to the
synthesis of 3,5-dialkyl pyridines.

An additional limitation on the utility of this sequence became
apparent when several samples of the 4-arylpyridines (49d,e) were
found to contain isomeric pyridines by ^{1}H NMR.  In both cases, these
products arose from difurylpyridines 47 which, although distilled,
were not recrystallized prior to the permanganate oxidation.  The
minor isomer contaminating 49d (10% by NMR) was isolated and charac-
terized as 5-methyl-3-phenylpyridine 63a.  That this isomer was formed
during the pyridine ring closure step was supported by the isolation
of 64 during the purification of large batches of 47a.[23]  Oxidation

49a: R$^I$ = OCH$_3$,  R$^2$ = H
49d: R$^I$ = H,  R$^2$ = CH$_3$
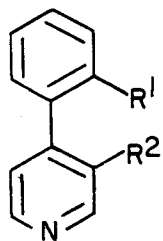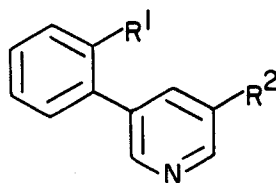
63a:  R$^I$ = H,  R$^2$ = CH$_3$
63b:  R$^I$ = OCH$_3$,  R$^2$ = H
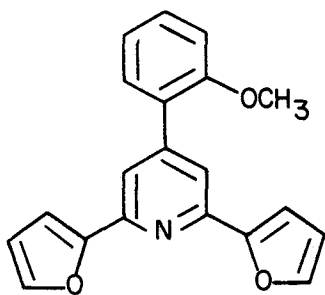
47a
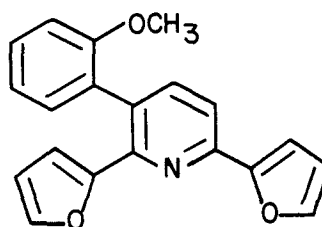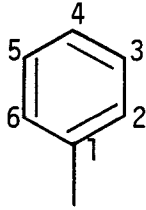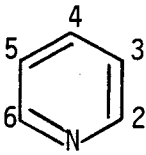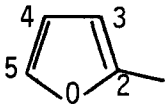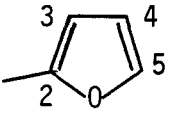
64
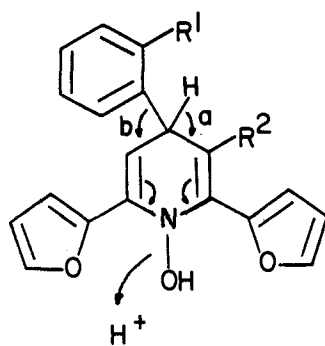
65

Table II.  $^{13}$C NMR Data for 47a,[24] 64,[24] 49a,[24] 63a,[24] 49d, 63b

## Chemical Shift (δ)$^a$



| Carbon | | 47a$^a$ | 64$^b$ | 49a$^c$ | 63a$^c$ | 49d$^b$ | 63b$^b$ |
|---|---|---|---|---|---|---|---|
| | 1 | 128.2 | 129.1* | 130.2* | 129.6 | 139.2 | 137.9 |
| | 2 | 156.8 | 156.3 | 156.3 | 156.3 | 128.4 | 127.1 |
| | 3 | 111.1 | 111.1° | 111.9 | 111.7 | 128.5 | 128.9 |
| | 4 | 130.0* | 130.5‡ | 130.3* | 130.4 | 127.9 | 127.9 |
| | 5 | 121.0 | 120.8 | 121.0 | 120.9 | | |
| | 6 | 130.5* | 129.3‡ | 126.9 | 126.4 | | |
| 2-O$\underline{C}$H$_3$ | | 55.6 | 55.6 | 55.5 | 55.4 | | |
| | 2 | 149.0 | 147.8$^\Delta$ | 149.4 | 149.7 | 151.4 | 148.9 |
| | 3 | 117.6 | 129.5* | 124.0 | 133.8 | 130.5 | 132.9 |
| | 4 | 147.8 | 139.7 | 145.6 | 136.5 | 149.1 | 134.9 |
| | 5 | | 116.3 | | 123.0 | 123.9 | 136.1 |
| | 6 | | 147.5$^\Delta$ | | 147.8 | 147.4 | 145.5 |
| 3-$\underline{C}$H$_3$ | | | | | | 17.1 | 18.4 |
| | 2 | 154.1 | 153.8$^+$ | | | | |
| | 3 | 108.7 | 108.8 | | | | |
| | 4 | 111.9 | 111.9 | | | | |
| | 5 | 143.0 | 143.1 | | | | |
| | 2 | | 155.3$^+$ | | | | |
| | 3 | | 110.6 | | | | |
| | 4 | | 111.0° | | | | |
| | 5 | | 142.6 | | | | |

$^a$Chemical shift assignments marked with the same symbol (Δ, ‡, etc.) may be interchanged.  $^b$CDCl$_3$.  $^c$d$_6$-DMSO.

and decarboxylation of 64 by the usual methods gave pyridine 63b as expected.[24] The identification of these pyridine isomers rests primarily on their $^{13}$C and $^{1}$H NMR spectra. The difuryl pyridine 47a is clearly distinguished from its isomer 64 by $^{13}$C NMR (Table II). The symmetry of the pyridine ring of 47a gives rise to a spectrum which is characterized by two identical α carbons (149.0 ppm) bearing identical furan substituents, a single quaternary γ carbon (147.8 ppm), and two identical protonated β carbons (117.6 ppm). The spectrum of 64, however, shows two pyridine α carbons (147.5 and 147.8 ppm) with distinguishable furan groups, both a protonated (129.5 or 129.1 ppm) and a nonprotonated (116.3 ppm) β carbon, and a protonated γ carbon (139.7 ppm). The $^{1}$H NMR of 47a reveals two identical furan rings, and two pyridine β protons as a singlet at δ = 7.73. The $^{1}$H NMR of 64 shows two distinct furan groups, and coincidentally, the β and γ protons as a singlet at δ = 7.37.

The $^{13}$C NMR spectra of the 3-arylpyridines 63a and 63b (Table II) reveal protonated pyridine γ carbons at 136.5 and 134.9 ppm, respectively, as compared to the quaternary γ carbons of 49a (145.6 ppm) and 49d (149.1 ppm). Accordingly, 63b possesses a single protonated β carbon (C-3, 133.8 ppm) and a quaternary β carbon (C-5, 123.0 ppm), while 63a exhibits resonances for two quaternary β carbons at 132.9 ppm (C-3) and 136.1 (C-5). The $^{1}$H NMR of 4-arylpyridine 49a reveals an AA'XX' pattern for the α and β pyridine protons (δ = 7.45 and 8.60, $J_{AX} \sim 5$ Hz) while the isomeric 63b shows the α protons as a two-proton multiplet (δ = 8.63-8.73), with the β and γ protons under the aromatic envelope (δ = 6.90-7.60). The $^{1}$H NMR of the 3-methylpyridine 49d reveals two distinct α protons (δ = 8.50,

singlet, and δ = 8.47, doublet, J = 6 Hz) and one β proton (δ = 7.12, doublet). The spectrum of isomeric 63a is characterized by two α protons, each as a broad singlet (δ = 8.41 and 8.64), with the γ proton under the aromatic envelope (δ = 7.30-7.71). The aryl migration to produce 64 can be accounted for by considering an intermediate dihydropyridine 65 formed from 46a and hydroxylamine. This molecule can proceed to a pyridine by two pathways. The expected route, producing 47a (path a), involves simple elimination of $H_2O$. In the minor pathway (path b), the loss of the hydroxyl function is accompanied by migration of the 4-aryl substituent, with subsequent loss of a proton from C-5 giving 64.

In concluding these investigations into the applicability of this sequence for 3-alkylated-4-arylpyridine synthesis, it was apparent that the route would not be suitable for the preparation of key precursor 43 with the propionic ester side chain. As already described, the attempt to incorporate an ethyl group at the pyridine C-3 position suffered from a pyridine ring formation step that was extremely slow and proceeded with significant aryl migration. Nonetheless, the model 4-arylpyridine 49b, prepared in high yield, offered a means of studying the effect of a pyridine C-3 substituent on the construction of the morphine ANO fragment. As outlined in Scheme XIV, 49b underwent ether cleavage upon treatment with concentrated HBr at reflux to give phenol 66 in 96% yield. Subsequently, 66 gave the corresponding N-methyl salt 67 in 99% yield when reacted with methyl iodide in dimethylformamide. The dihydropyridine 68a was formed directly in 82% yield, as a mixture of epimers, by O-alkylation of 67 with potassium carbonate and chloroacetone in dimethyl

Scheme XIV



49b

66

67

54a: R = CH₃
54b: R = OC₂H₅

68a: R = CH₃
68b: R = OC₂H₅
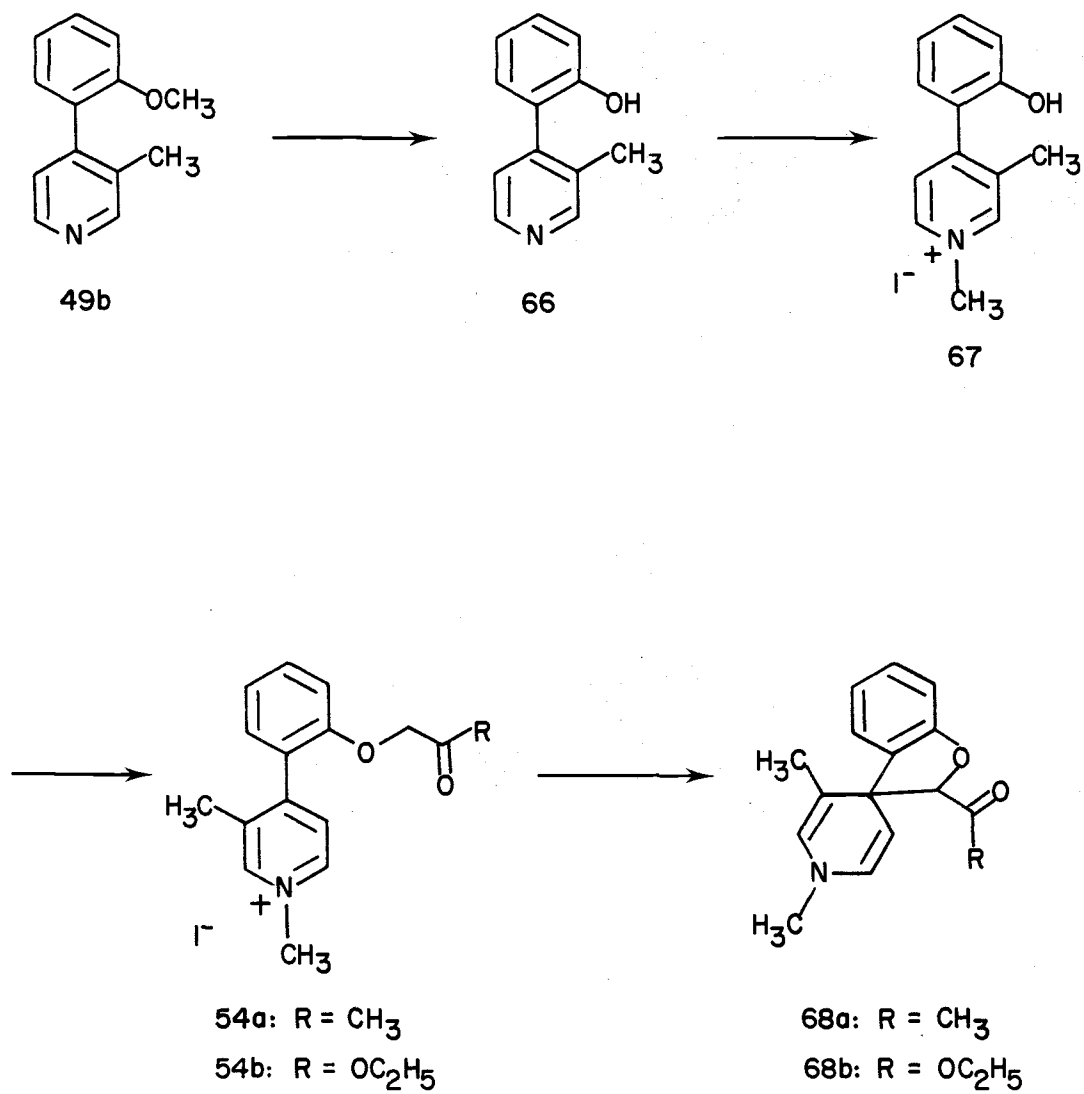
sulfoxide, then workup with 4$\underline{N}$ sodium hydroxide to generate the ketone enolate and effect ring closure. Although the anti isomer was expected to predominate by a large margin, the ratio of anti to syn epimers was 60/40. The assignment of structure and the determination of isomer ratio were done by ^{1}H NMR. In the minor (syn) isomer the C-3 methyl appears significantly upfield at $\delta$ = 1.20 ppm, an effect ascribed to the adjacent side chain carbonyl. The observed isomer ratio is reflective of the equilibrium composition (Equation IX). Treatment of the isomer mixture with sodium ethoxide in ethanol caused no change in the ratio of products.

O-Alkylation of N-methylpyridinium salt 67 with ethyl bromoacetate in the presence of potassium carbonate gave the corresponding salt 54b. Ethoxide in ethanol was then employed to effect ring closure, and dihydropyridine 68b was obtained in overall 78% yield from 66 as an approximately 1:1 mixture of isomers. Formation of the spirocyclic dihydropyridines possessing a substituent at the pyridine C-3 was thus shown to be facile. It would be expected, then, that pyridinium salt 35, having a propionate side chain at C-3, would suffer ready intramolecular addition under the same conditions to give dihydropyridine 36 as an isomeric mixture (Scheme VI). From models, it is apparent that only the syn stereoisomer of 36 has the proper configuration to undergo Dieckmann cyclization. The basic conditions required for reaction, though, would allow for the interconversion of syn and anti epimers through the enolate, and cyclization would proceed via the syn isomer to give 37 (Equation X). The problem of preparing the appropriately substituted pyridinium salt precursor 35, however, remained to be addressed.

Equation IX



syn (40)   68a   anti (60)

Equation X



36

37
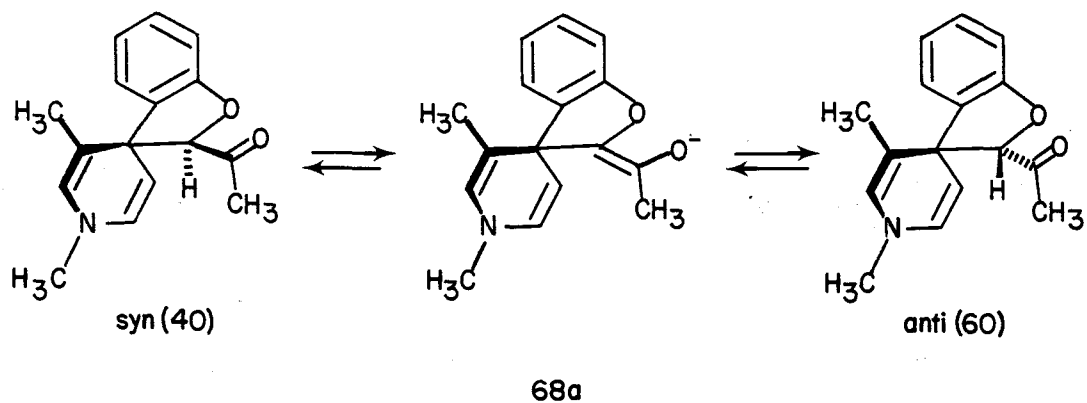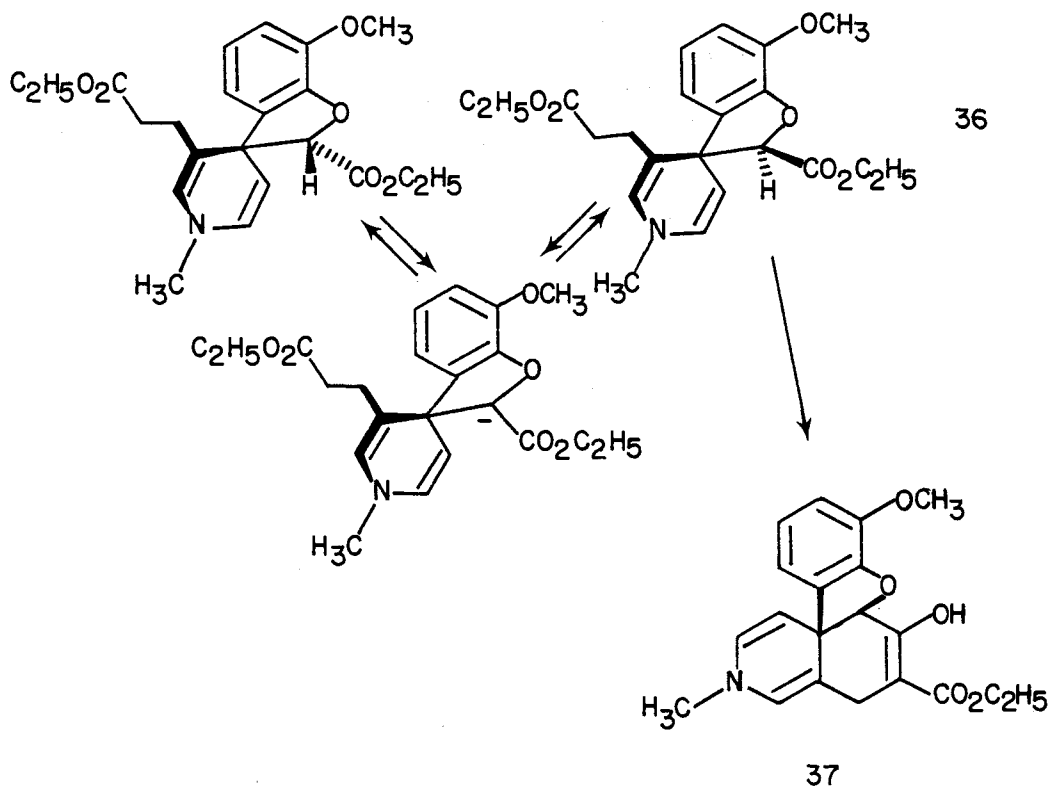
The next attempt at preparation of the required β-substituted pyridines focused on the preparation and reactions of 4-arylpyridine-3-carboxaldehydes 73. It was expected that the aldehyde group would provide a convenient handle for the introduction of the propionate side chain via Knoevenagel condensations and reduction (Scheme XV). Further, Jutz had shown that 4-arylpyridine-3-carboxaldehydes are readily available from the corresponding α-methylstyrene derivatives.[26] In examining suitable precursors to 73, the ready availability of 2-hydroxyacetophenone (69) prompted an initial examination of the proposed sequence in the model series, 72a → 76. Thus, 69 was benzylated, reacted with methyl magnesium iodide and the resulting carbinol thermally dehydrated to 72a. An attempt to prepare 72a directly from ether 70a via a Wittig reaction with triphenylphosphonium methylide resulted in only a 44% yield due to competing enolization of the acetophenone derivative. In a modification of the procedure of Jutz,[26] 72a was heated in the presence of excess Vilsmeier reagent and, without isolation, the intermediate iminium salt was heated at reflux with $NH_4OAc/HOAc/H_2O$ to give the pyridinecarboxaldehyde 73a in 78% yield. Condensation of 73a with ethyl hydrogen malonate in the presence of pyridine and piperidine gave an 85% yield of the α,β-unsaturated ester 74a. Catalytic hydrogenation of 74a over palladium on charcoal in the absence of added acid selectively reduced the side chain double bond to give 75 in 91% yield. Upon addition of 110 mole % of ethanolic HCl, hydrogenolysis proceeded smoothly. Typically, 74a was hydrogenated until formation of 75 was complete, acid was then added to the reaction vessel, and further shaking under hydrogen produced the 4-arylpyridine 76 in 95%

Scheme XV



69 → 70a: R = H / 70b: R = OCH₃ → 71a: R = H / 71b: R = OCH₃ →

72a: R = H / 72b: R = OCH₃ → 73a: R = H / 73b: R = OCH₃ → 74a: R = H / 74b: R = OCH₃

76: R = H / 43: R = OCH₃ ← 75
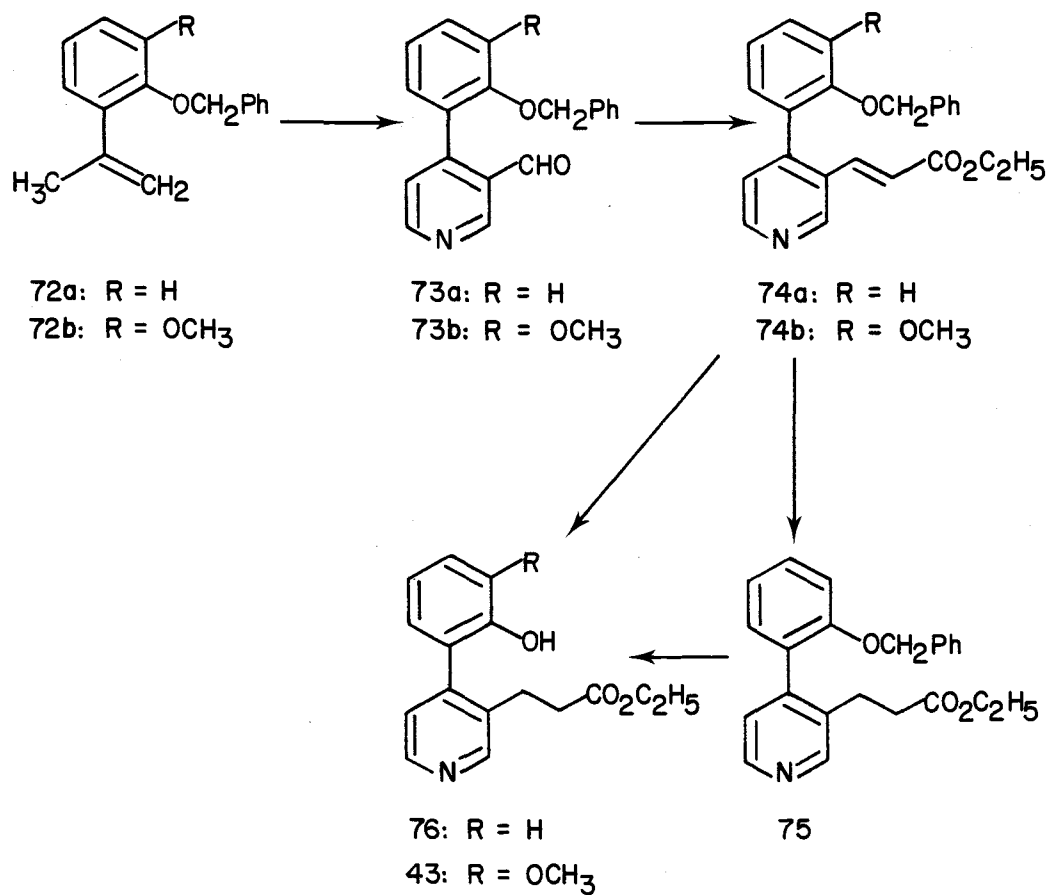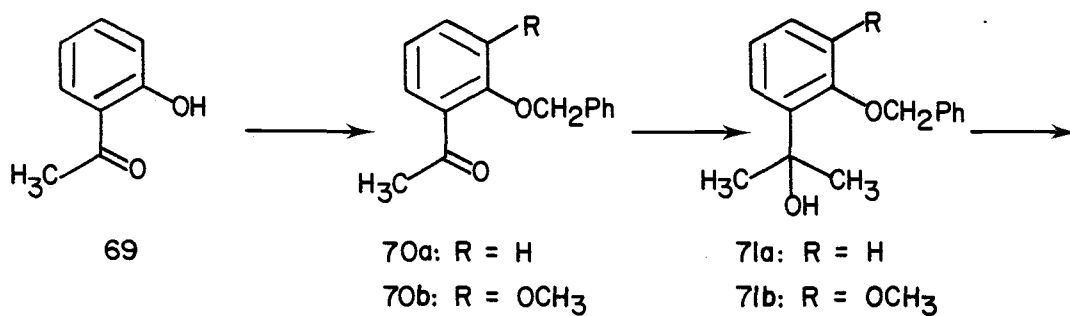
yield.

The sequence described above for the preparation of 76 proved to be much less attractive when applied to the synthesis of the methoxy analog 43. Firstly, since the 3-methoxy analog of 69 is not commercially available, extra steps were necessary to prepare the aceto- phenone 70b. As shown in Scheme XVI, o-vanillin 77 was treated with benzyl iodide and potassium carbonate to give the corresponding benzyl ether 78 in 91% yield. Addition of methyllithium, followed by pyridinium chlorochromate oxidation of the resulting alcohol, gave acetophenone derivative 70b in 88% yield. As in the model series, Grignard reaction of 70b with methylmagnesium iodide gave a carbinol which underwent thermal dehydration to yield 82% of α-methylstyrene 72b. The yield for the Grignard/dehydration sequence was lower in this series than in the earlier case, apparently due to a competing debenzylation reaction, since significant amounts of phenol 80 can be isolated from the dehydration reaction. Secondly, although 72b is converted to 73b by the Vilsmeier formylation/cyclization procedure used to prepare 73a from 72a, the yield is only 41%, presumably due to the added activation of the aromatic ring itself towards attack by the Vilsmeier reagent. Additionally, whereas 73a can easily be purified by distillation, 73b is thermally labile and must be iso- lated from the complex reaction mixture by chromatography. An attempted distillation of 73b resulted in the isolation of a 1:1 mix- ture of 73b and lactone 81. Although the remaining steps in the con- version of 73b into 43 proceeded without incident, the overall yield from o-vanillin was only 15%.

An attractive and convergent alternative for the synthesis of

Scheme XVI



77 → 78 → 79 → 70b
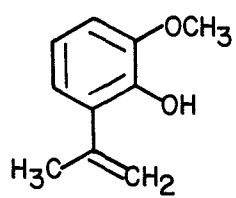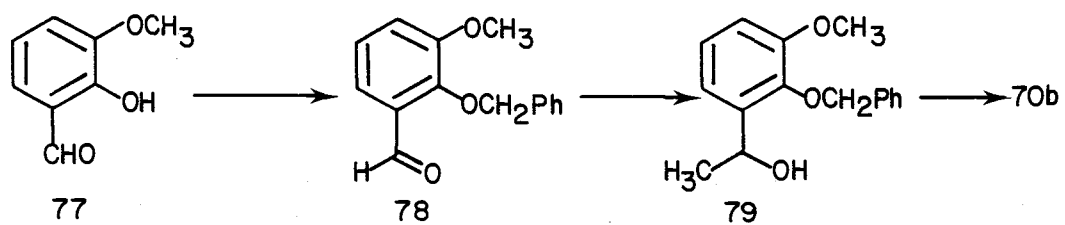
80
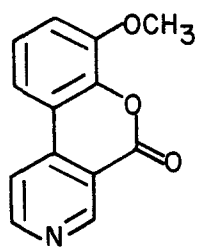
81

43 would achieve a direct combination of the carbocyclic and hetero-
cyclic aromatic rings. One method of accomplishing this procedure is
the addition of organometallic reagents to pyridines, an often low
yield process due to the number of reactive sites on the pyridine,
and the instability of the dihydropyridine product.[27] A general
method for the introduction of alkyl and aryl groups at C-4 of pyri-
dine was recently put forth by Akiba,[28] who found that alkyl and aryl-
copper boron trifluoride complexes add readily to the salt of pyridine
and ethyl chloroformate. Comins has also described a similar proce-
dure which was applicable to β-picoline.[29] To investigate the
applicability of this method, we briefly studied the reaction of 83d
with N-ethoxycarbonylpyridinium chloride 84a (Scheme XVII). Ether
83a was prepared from guiacol (82) by alkylation with chloromethyl
ethyl ether in the presence of sodium hydride in 99% yield. The
corresponding arylcopper/boron trifluoride species 83d was then
formed by the following sequence: selective lithiation of 83a with
n-BuLi, transfer of the lithio salt 83b, as a suspension in tetrahy-
drofuran, to a mixture of copper iodide in tetrahydrofuran at -20°C,
and finally, addition of boron trifluoride etherate to the solution
of arylcopper derivative 83c at -78°C. The resulting solution
(representing a 20% excess of the organometallic reagent 83d) was
transferred to a suspension of the pyridinium salt 84a, formed from
pyridine and ethyl chloroformate, in tetrahydrofuran at -78°C. After
allowing the reaction mixture to warm to 18°C over a two-hour period,
then stirring two hours longer, dihydropyridine 85a was obtained as
an air-sensitive oil. Although Akiba's procedure called for air
oxidation,[28] we found this to be inefficient, and instead, immediate

Scheme  XVII



82

83a:  Y = H

83b:  Y = Li

83c:  Y = Cu

83d:  Y = Cu·BF$_3$

84a:  R = H

84b:  R = CH$_2$CH$_2$CO$_2$C$_2$H$_5$

84c:  R = CH=CHCO$_2$C$_2$H$_5$



85a: R$^1$ = H,
          R$^2$ = CO$_2$C$_2$H$_5$

85b: R$^1$ = CH$_2$CH$_2$CO$_2$C$_2$H$_5$,
          R$^2$ = CO$_2$C$_2$H$_5$

85c: R$^1$ = CH=CHCO$_2$C$_2$H$_5$,
          R$^2$ = CO$_2$C$_2$H$_5$

85d: R$^1$ = CH=CHCO$_2$C$_2$H$_5$,  R$^2$ = H

86a:  R = H

86b:  R = CH$_2$CH$_2$CO$_2$C$_2$H$_5$

86c:  R = CH=CHCO$_2$C$_2$H$_5$

43

Scheme   XVIII



87

88

89
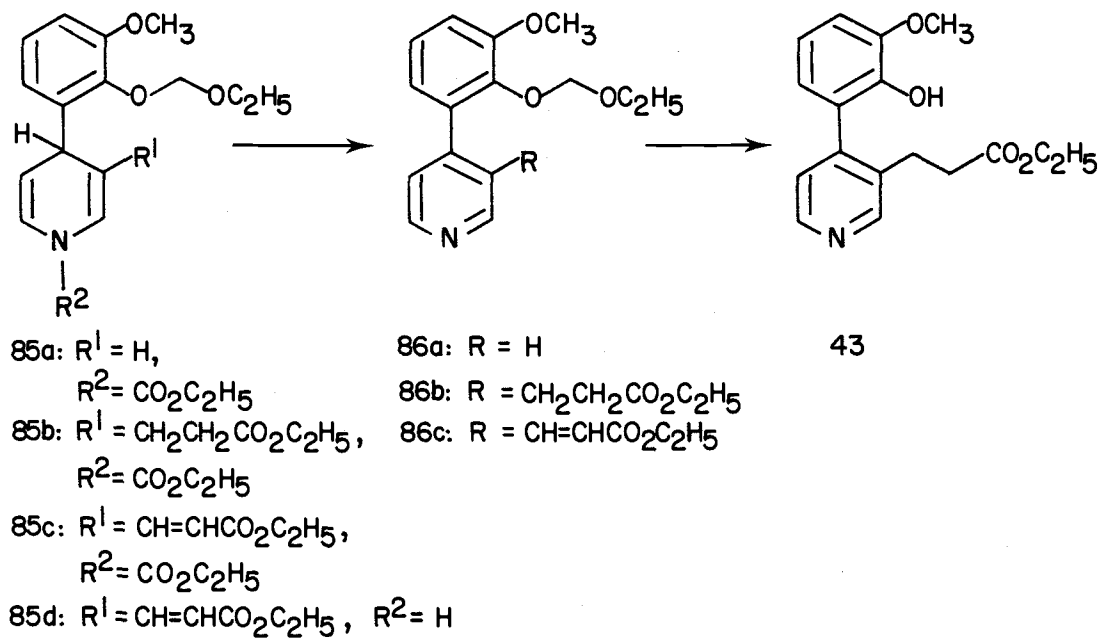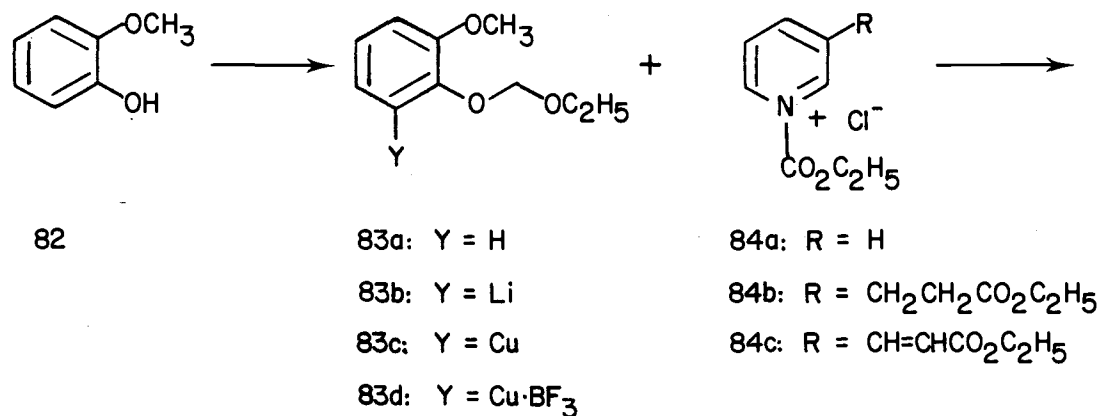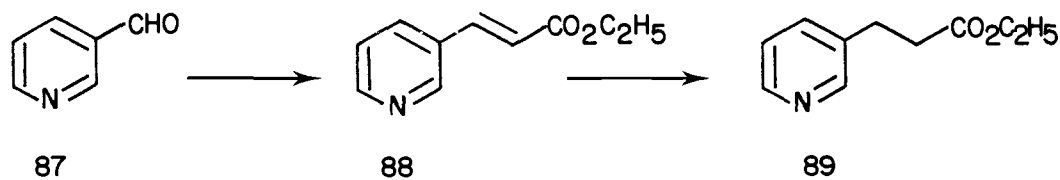
oxidation with o-chloranil gave the corresponding pyridine 86a in 75% overall yield from pyridine.

Extension of this methodology to the preparation of 43 required the synthesis of the 3-substituted pyridine 89. This was readily available from pyridine-3-carboxaldehyde (87) in 89% yield (Scheme XVIII).[30] When the corresponding pyridinium salt 84b was reacted with 83d, as above, dihydropyridine 85b was obtained as part of a multi-component mixture which gave, upon oxidation with p-chloranil, 86b, but in only 18% overall yield from 89. To enhance the reactivity of the substituted pyridine moiety, the reaction was carried out using pyridinium salt 84c derived from pyridine 88, which posesses an α,β-unsaturated ester side chain (Scheme XVII). In this event, stable dihydropyridine 85c was produced as a crystalline solid, but the yield was not much improved. By ^{1}H NMR, the reaction mixture contained significant amounts of byproducts which were apparently derived from the arylcopper reagent. To determine the origin of these byproducts, an investigation of the stability of the two inter-mediate arylcopper species, 83c and 83d, was undertaken. The first-formed derivative, 83c, was found to be stable as a tetrahydrofuran solution at -20°C. The boron trifluoride derivative 83d, however, while stable at -78°C, rapidly decomposed at -20°C, and both 83c and 83d were converted to the unidentified reaction byproducts above this temperature. Addition of the more stable 83c to pyridinium salt 84b, showed no marked improvement over results employing the derivative 83d. However, addition of 83c to 84c, proceeded at -20°C over two hours to give dihydropyridine 85c as a nicely crystalline solid in 89% isolated yield, with only minimal byproduct formation. Best

yields were obtained using either freshly opened commercial copper iodide, or the repurified salt.[31] The use of the copper bromide/dimethyl sulfide complex[32] in place of copper iodide, or the use of catalytic copper iodide (5%),[29] gave predominant formation of the aryl ether byproducts.

While resistant to air oxidation, dihydropyridine 85c was converted to the corresponding pyridine 86c, cleanly and efficiently, with o-chloranil in benzene/toluene at 0°C. Quinone reduction products were easily removed by treatment of the crude product with sodium ethoxide in ethanol, and subsequent base wash, to give 86c in 81% yield. Oxidation of 85c with p-chloranil in benzene gave no reaction at 19°C, and only 19% isolated yield of 86c after heating at 80°C. As an alternative, oxidation may be performed on the N-H derivative 85d, which is prepared in quantitative yield from 85c upon treatment with sodium ethoxide in ethanol. Since N-H dihydropyridines are generally more easily oxidized than their N-substituted analogs, the oxidation of 85d was expected to be facile. However, air oxidation proceeded only very slowly, and bubbling oxygen through a benzene solution of 85d for one hour gave a 40% yield of 86c, along with unidentified polar material. Interestingly, inclusion of triethyl amine in the reaction mixture resulted in no oxidation of 85d. Treatment of an ethanolic solution of 85d with iodine gave no recognizable products, as was the case when a benzene solution of 85d was reacted with o-chloranil at ambient temperature for twenty-four hours. Substitution of p-chloranil in the latter case did provide a 34% yield of 86c. Finally, catalytic hydrogenation of the pyridine side chain in 86c over palladium on charcoal gave 86b in 96% yield, and removal

of the ethoxymethyl ether protecting group with ethanolic acid pro-
duced the desired phenol 43 in 98% yield.  By this route, 43 was
obtained in overall 69% yield from the 3-substituted pyridine 88, a
marked improvement over construction of the 4-arylpyridine system by
the α-methylstyrene sequence.

The formation of the remaining rings of the benzofuroisoquino-
line system was initiated by N-alkylation of 76 with methyl iodide to
give 90a and O-alkylation with ethyl bromoacetate to give the pyridi-
nium salt 91 in 98% yield (Scheme XIX).  The conversion of 91 into 92
occurred instantaneously upon addition of 110 mole % of sodium
ethoxide (as a 1.69M ethanol solution) to a 10% w/v solution of 91 in
dimethyl sulfoxide.  The reaction was monitored by observing the dis-
appearance of the α-pyridinium protons of 91 [δ = 8.89 (1H, d, J = 6
Hz) and 9.07 (1H,s)] in the $^1$H NMR.  The reaction was found to pro-
ceed more cleanly with dimethylformamide as the solvent, and 92 was
obtained in 92% yield as a mixture of syn and anti epimers (40/60).
The further conversion of 92 to 93 was effected in 34% yield upon
heating a benzene/dimethylformamide solution of 92 at reflux with 132
mole % of sodium ethoxide (as a 1M solution in ethanol) for 30 min
with azeotropic removal of ethanol.  When the amount of base was
increased to 200 mole %, and the temperature lowered to 80°C, the
reaction was complete after 45 min, but the yield (42%) of 93 was
still low.  Investigation of the Dieckmann reaction showed it to be
fairly sensitive to the concentration of diester, and the optimum
yields were obtained at 5% concentrations of diester in dimethylfor-
mamide.  Improved results were also obtained when the ethanol concen-
tration of the reaction mixture was kept to a minimum.  Although

Scheme XIX



76: R = H
43: R = OCH₃

90a: R = H
90b: R = OCH₃

91: R = H
35: R = OCH₃

92: R = H
36: R = OCH₃

93: R = H
37: R = OCH₃
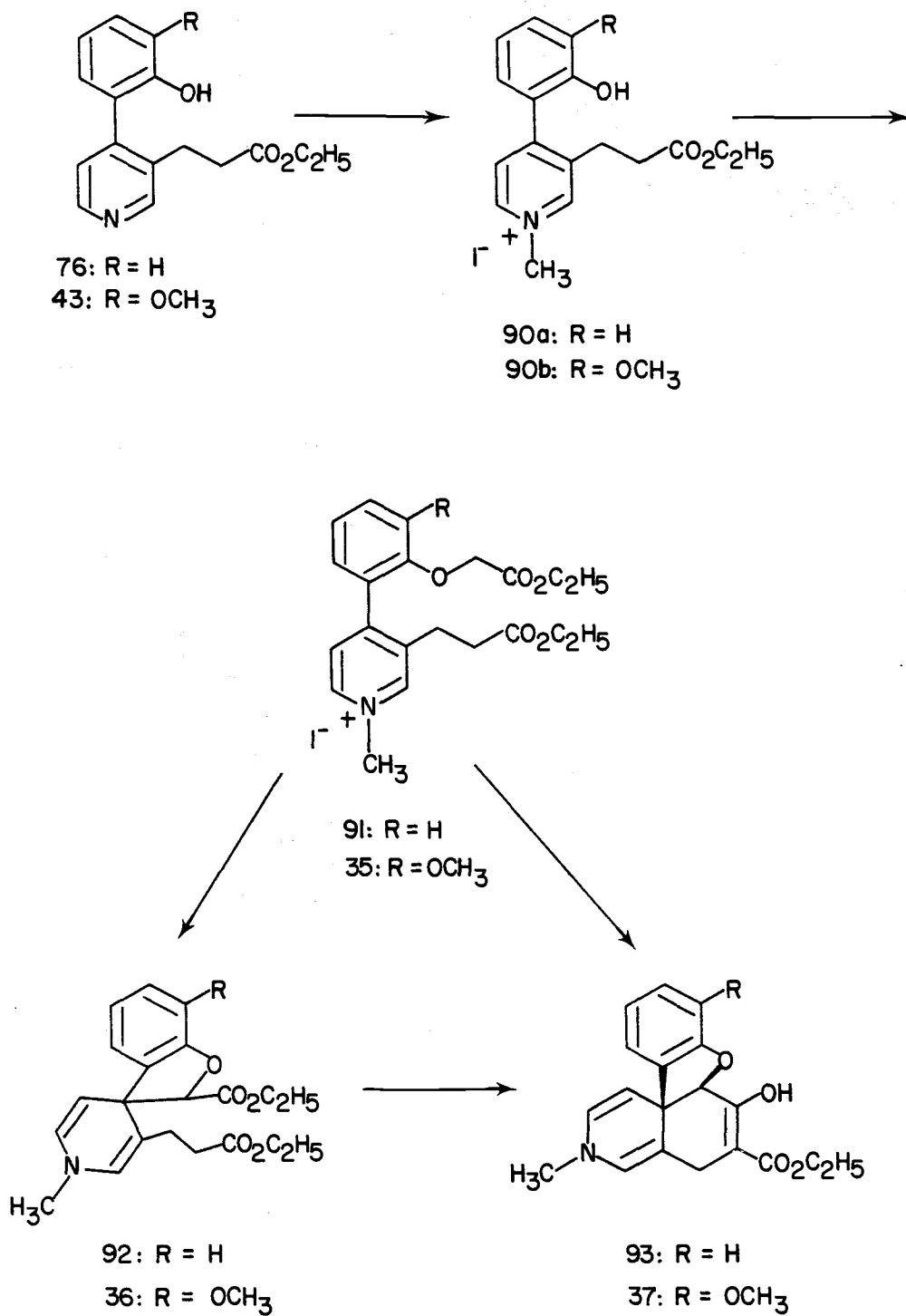
closure of the O-ring was instantaneous and was not affected by the ethanol concentration, the Dieckmann reaction was very slow in the presence of added ethanol. However, treatment of 91 as a 5% w/v solution in dimethylformamide, with 620 mole % of ethanol-free sodium ethoxide at 25°C for fourteen hours, gave sequential ring closures to yield 72% of the benzofuroisoquinoline derivative 93.

The conversion of 93 into simpler members of the benzofuroiso-quinoline series proceeded via catalytic hydrogenation over platinum to give a 98% yield of 95a (Scheme XX). A mixture of stereo-isomers was produced, but these were not separated, and the reduction product was instead subjected to vigorous acidic hydrolysis to afford 96a and 96b in 76% yield in a ratio of 88:12. The trans isomer 96a was readily obtained pure by recrystallization. Although the cata-lytic hydrogenation of 93 is highly selective for the trans ring junction stereoisomer, the trans/cis ratio can be reversed by cata-lytic hydrogenation of the spirocyclic dihydropyridine 92 prior to closure of the C ring. Thus, hydrogenation of 92 over platinum gave a 96% yield of the spiro[benzofuran-3(2H),4'-piperidine] derivative 94 as an isomeric mixture. Subsequent Dieckmann condensation of 94 with sodium ethoxide in dimethylformamide yielded 64% of 95a. Again, by $^1$H NMR, one isomer appeared to predominate, but the major isomer in this case was the minor isomer obtained upon hydrogenation of 93. Decarboethoxylation of 95a, as before, gave 96a and 96b, but in a ratio of 29:71, respectively.

Synthesis of the benzofuroisoquinolines in the methoxy series was initiated by successive N- and O-alkylations of 43 to yield 35 in quantitative yield (Scheme XIX). Treatment of salt 35 with

Scheme XX



92: R = H
36: R = OCH₃

94

91: R = H
35: R = OCH₃

93: R = H
37: R = OCH₃

95a: R = H
95b: R = OCH₃

96a: R = H
16a: R = OCH₃

96b: R = H
16b: R = OCH₃
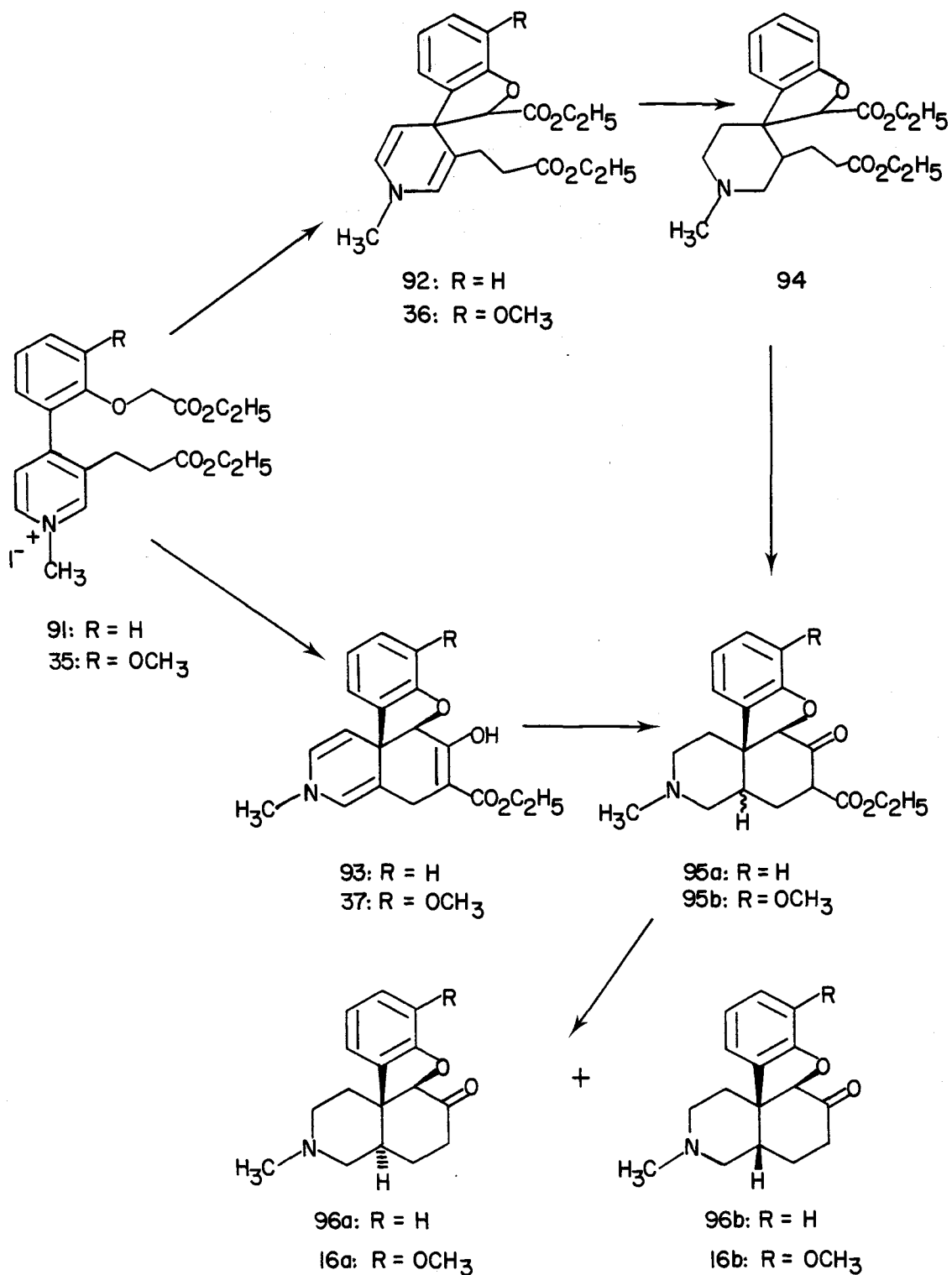
sodium ethoxide in ethanol/dimethylformamide, as before, gave 63%

yield of the spiro[benzofuran-3(2H)-4'(1'H)-pyridine] 36 (syn/anti =

40/60). Reaction in ethanol-free dimethylformamide resulted in over-

all conversion of 35 to 37 (69%) after eighteen hours at 25°C. Cata-

lytic hydrogenation of 37 over platinum gave a quantitative yield of

the mixture 95b. Decarboethoxylation (Scheme XX) returned a 68%

yield of 16a and 16b in an 88:12 ratio. Identification of the cis

and trans isomers of 96 and 16 is based on spectral and chromato-

graphic comparison of each isomer with the data reported by Rapoport,

et al.,[11] for 16a and 16b. For these compounds, the trans isomer

shows a methine proton in the ^{1}H NMR upfield from that of the cis

isomer, and an N-methyl group downfield from that of the cis isomer.

Also consistent with Rapoport's results, the trans isomers are chroma-

tographically less mobile on silica gel than the cis isomers.

Several alternate O and C ring closure schemes were attempted.

In the first (Scheme XXI), phenolic methiodide 90a was alkylated with

chloroacetonitrile to give salt 97. Treatment of 97 with potassium

t-butoxide/t-butanol in dimethyl sulfoxide gave the spirodihydro-

pyridine 98 in 53% yield. Prolonged reaction of 97 with t-butoxide

in t-butanol-free dimethylformamide produced the enamine 99, but the

yield was only 11%. The second alternative for benzofuroisoquinoline

formation would reverse the order of the Dieckmann and pyridinium/

enolate addition steps. To this end (Scheme XXII), 76 was selectively

O-alkylated with ethyl bromoacetate to 100 in moderate (63%) yield

using potassium carbonate in dimethylformamide. However, all attempts

to achieve Dieckmann cyclization to the nine-membered ring 101 failed.

Scheme XXI



90a        97        98

99

Scheme XXII



76        100        101
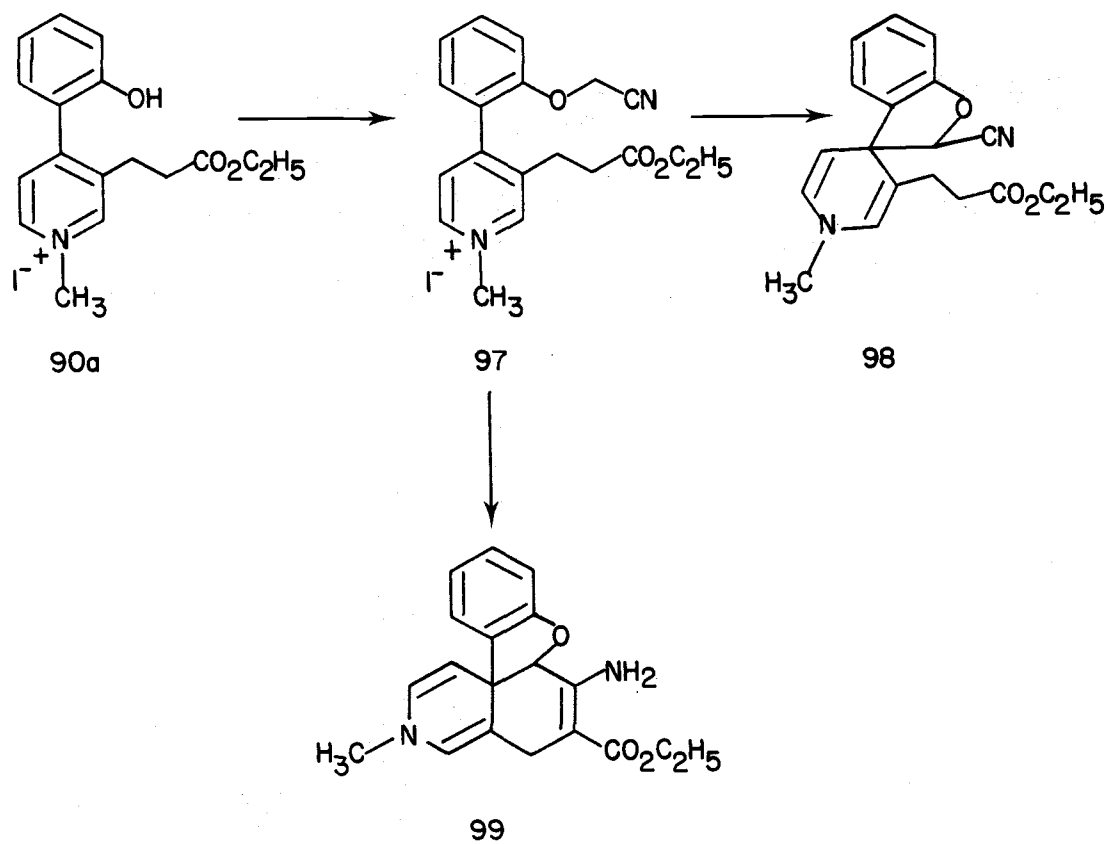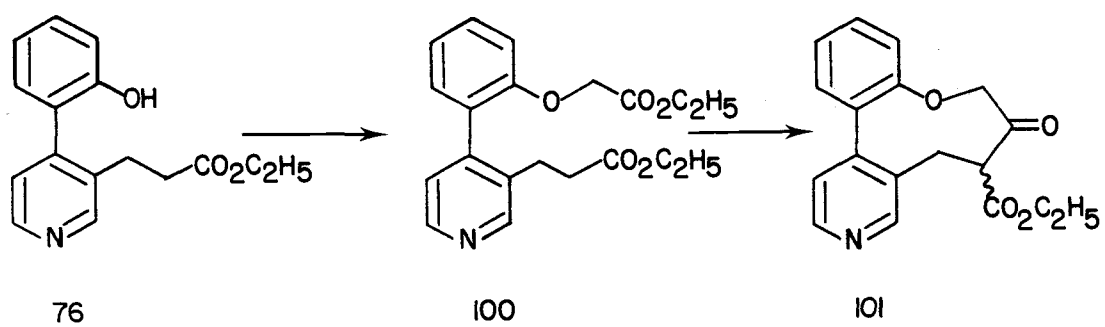
In conclusion, we have developed a convergent, efficient synthesis of the benzofuroisoquinoline nucleus. The overall yield of 37 from pyridine-3-carboxaldehyde (87) was 44%, and it was readily converted into the perhydro series with the trans stereochemistry. Further, acidic hydrolysis of 93 and 37, and subsequent base treatment, provided the 5,6-dihydro-3H-benzofuro[3,2-e]isoquinoline-7(7aH)-ones 102 and 38 in 71% and 60% yield, respectively (Scheme XXIII). Finally, 102 was converted to pyridinium salt 103 upon treatment with hydriodic acid in ethanol. As expected, 103 was reconverted to 102 with sodium hydroxide in dimethyl sulfoxide. The demonstration of the interconvertibility of 102 and 103 now sets the stage for future studies on the resolution of this system.

Scheme XXIII



93: R = H
37: R = OCH$_3$

102: R = H
38: R = OCH$_3$

103: R = H
39: R = OCH$_3$
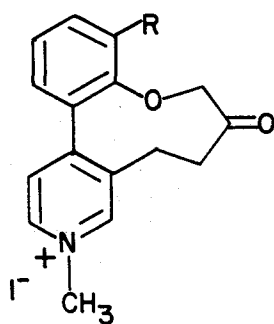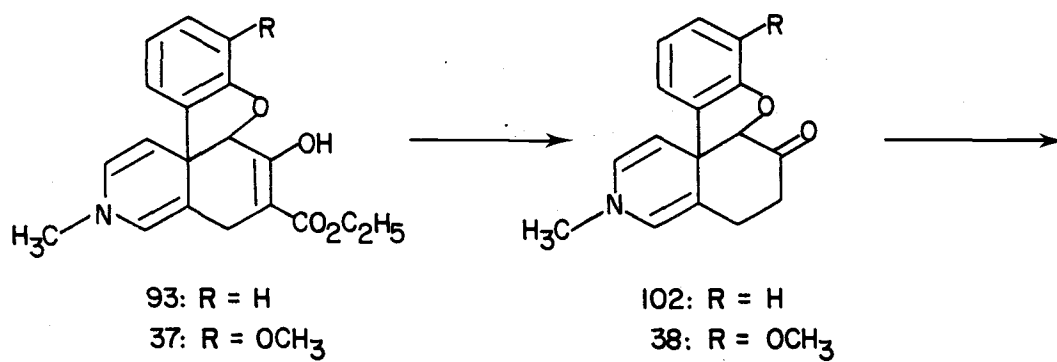
# EXPERIMENTAL

Low resolution mass spectrometry was performed on a Varian MAT CH-7 or a Finnigan 3500. Infrared spectra were recorded on Perkin-Elmer spectrophotometers, Model 727B and Model 137. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. ^{1}H NMR analyses were performed on Varian spectrometers, Model FT-80, Model HA-100, or Model EM-360. Chemical shifts ($\delta$) are reported as parts per million downfield from tetramethylsilane as internal standard. ^{13}C NMR analyses were performed on Varian spectrometer, Model FT-80. High resolution mass spectra were obtained on a CEC-103B mass spectrometer by Richard Wielesek at the University of Oregon Micro-Analytical Laboratory. Combustion analyses were performed by Richard Wielesek at the University of Oregon Micro-Analytical Laboratory and by MicAnal, Tucson, Arizona.

<u>1-(2-Furyl)-3-(2-methoxyphenyl)-2-methyl-2-propen-1-one</u> (53h). A mixture of 2-methoxybenzaldehyde (3.00 g, 0.0221 mol) and 2-propionylfuran[33] (2.74 g, 0.0221 mol) was cooled to 0°C. Anhydrous HCl was bubbled into the flask for 30 sec and the resulting thick, black solution was warmed to room temperature and HCl was again introduced for 1 min (until saturated). The reaction mixture was stirred for 11.5 h at 25°C, and then 48 h at 80°C. Direct Kugelrohr distillation (120-130°C, 0.10 mm Hg) yielded 53h (4.62 g, 86%) as a pale, yellow liquid which crystallized upon standing. Recrystallization from EtOH gave colorless crystals of 53h: mp 80.5-81.5°C; MS $\underline{m/z}$ 242 (M[+]), 241, 227, 211(100), 131, 115, 95; IR (KBr) 1625, 1475, 1455, 1300, 1265, 1240, 1020, 875, 768, 762, 739 cm$^{-1}$; ^{1}H NMR (CDCl$_3$) $\delta$ = 2.14 (3H, d,

J = 1.5 Hz), 3.81 (3H, s), 6.52 (1H, dd, J = 2, 3.5 Hz), 7.20 (1H, d, J = 3.5 Hz), 7.70 (1H, d, J = 1.5 Hz), 7.62-7.64 (1H, m), 6.86-7.70 (4H, m).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.84. Found: C, 74.26; H, 5.52.

1-(2-Furyl)-2-methyl-3-phenyl-2-propen-1-one (53f). By the procedure described above for the preparation of 53h, benzaldehyde (6.27 g, 0.0591 mol) and 2-propionylfuran[33] (7.32 g, 0.0591 mol) gave 53f (10.3 g, 82%) as colorless crystals after 18 h of heating, subsequent Kugelrohr distillation (80-120°C, 0.05 mm Hg), and recrystallization from EtOH: mp 51.5-54°C; MS m/z 212 ($M^+$, 100), 211, 197, 195, 183, 169, 155, 141, 115, 95, 91; IR (KBr) 1625, 1455, 1390, 1035, 1015, 945, 890, 793, 760, 750, 688 $cm^{-1}$; ^{1}H NMR ($CDCl_3$) δ = 2.21 (3H, d, J = 1.5 Hz), 6.53 (1H, dd, J = 2, 3.5 Hz), 7.16 (1H, d, J = 3.5 Hz), 7.49 (1H, d, J = 1.5 Hz), 7.28-7.47 (5H, m) 7.62-7.64 (1H, m).

Anal. Calcd for $C_{14}H_{12}O_2$: Mol wt, 212.084. Found: Mol wt, 212.084.

1,5-Di(2-furyl)-3-(2-methoxyphenyl)-2-methyl-1,5-pentanedione (46b). At 0°C, 2-propionylfuran[33] (96.91 g, 0.782 mol) was added to a mixture of 53a[20] (35.64 g, 0.156 mol) and NaOH (6.25 g, 0.156 mol) in $CH_3OH$ (356 mL). The reactants were stirred for 1 h at 0°C and 40 h at 25°C. The resulting solution was acidified with 1N HCl and extracted with ether. The ether extracts were washed once with water and once with brine, and then dried over $MgSO_4$. Ether was evaporated and excess 2-propionylfuran (62.81 g, 81% of theoretical) was recovered by Kugelrohr distillation (150°C, 1 mm Hg), leaving 46b

54.23 g, 99%) as an amber-colored glass and as a mixture of stereo-isomers: MS $\underline{m/z}$ 352 ($M^+$), 243, 229, 211, 95(100); IR (thin film) 3150, 1660, 1460, 1240, 740 $cm^{-1}$; $^1H$ NMR (CDCl$_3$) $\delta$ = 0.87 and 1.06 (each d, J = 7 Hz, total intensity 3H; relative intensity 1.2:1), 2.91-4.26 (m, total intensity 4H), 3.62 and 3.74 (each s, total intensity 3H), 6.37-6.51 (m, total intensity 2H), 6.63-7.60 (m, total intensity 8H).

$\underline{Anal}$. Calcd for $C_{21}H_{20}O_5$: Mol wt, 352.132. Found: Mol wt, 352.131.

$\underline{1,5-Di(2-furyl)-3-phenyl-1,5-pentanedione}$ (46c). By the pro-cedure outlined for the preparation of 46b, 2-acetylfuran[33] (12.49 g, 0.114 mol) and benzaldehyde (1.55 mL, 0.0153 mol) gave 46c (3.97 g, 85%) after 12 h as a white crystalline solid which separated directly from the reaction mixture: mp 103.5-104°C (lit[22b] 103-104°C). Excess 2-acetylfuran was recovered by Kugelrohr distillation.

$\underline{1,5-Di(2-furyl)-2-methyl-3-phenyl-1,5-pentanedione}$ (46d). By the above procedure, 2-propionylfuran[33] (28.20 g, 0.277 mol) and chalcone 53c[22] (9.00 g, 0.0455 mol) gave 46d (14.23 g, 97%) after 17 h as an amber-colored glass: MS $\underline{m/z}$ 213 ($M^+$), 199(100), 124, 117, 115, 110, 103, 90(100); IR (thin film) 3140, 3040, 2980, 2950, 1665, 1565, 1465, 1395, 1260, 1160, 1085, 1030, 1015, 980, 910, 880, 775, 700 $cm^{-1}$; $^1H$ NMR (CDCl$_3$) isomeric mixture $\delta$ = 1.00 and 1.24 (each, d, J = 6 Hz; total intensity 3H, relative intensity 1.6/1), 3.10-3.90 (m, total intensity 4H), 6.31-6.48 (overlapping dd, J = 2, 4 Hz; total intensity 2H), 6.89-7.25 (m, total intensity 7H), 7.31-7.43 (m) and 7.50 (bs), total intensity 2H.

<u>Anal</u>. Calcd for $C_{20}H_{18}O_4$: Mol wt, 322.121. Found: Mol wt, 322.119.

<u>1,5-Di(2-furyl)-2-ethyl-3-phenyl-1,5-pentanedione</u> (46e). By the above procedure, 2-butyrylfuran[18] (8.36 g, 0.0606 mol) and chalcone 53c[22] (3.00 g, 0.0152 mol) gave 46e (4.98 g, 98%) after 24 h as an amber colored glass following removal of excess 2-butyrylfuran by Kugelrohr distillation (100°C, 0.1 mm Hg): MS <u>m/z</u> 336 ($M^+$), 307, 299, 227, 199, 138, 110, 95(100); IR (thin film) 3200, 3000, 1670, 1570, 1465, 1390, 1275, 1160, 1040, 1030, 1018, 990, 915, 882, 832, 763, 702 cm$^{-1}$; $^1$H NMR (CDCl$_3$) isomeric mixture $\delta$ = 0.73 and 0.83 (each t, J = 8 Hz, total intensity 3H), 1.31-2.11 (m, total intensity 2H), 3.07-3.99 (m, total intensity 4H), 6.03-6.54 (overlapping dd, J = 2, 4 Hz, total intensity 2H), 7.00-7.20 (m, total intensity 7H), 7.48 and 7.51 (each bs, total intensity 2H).

<u>Anal</u>. Calcd for $C_{21}H_{20}O_4$: Mol wt, 336.136. Found: Mol wt, 336.134.

<u>1,5-Di(2-furyl)-2,4-dimethyl-3-phenyl-1,5-pentanedione</u> (46f). A solution of 1<u>N</u> NaOEt/EtOH (18.87 mL, 0.0189 mol) was evaporated to near-dryness. To this was added 2-propionylfuran[33] (2.57 g, 0.0208 mol) and 53f (4.00 g, 0.0189 mol), and the deep red-colored mixture was stirred for 45 h at 25°C. The mixture was acidified with 2<u>N</u> HCl, extracted with CHCl$_3$, and the combined extracts washed with brine, dried (MgSO$_4$), and evaporated to an amber-brown glass (6.87 g crude yield of 46f). This was carried on to 47f without further purification. An analytical sample of 46f was prepared by chromatography on a column of silica gel, eluting with 5% acetone/CHCl$_3$: MS <u>m/z</u> 336

($M^+$), 318, 303, 241, 213, 157, 124, 117, 115, 95(100), 91; IR (thin film) 3170, 3020, 1670, 1560, 1455, 1385, 1250, 1160, 1080, 1030, 1015, 978, 909, 895, 884, 762, 703 cm$^{-1}$; $^1$H NMR (CDCl$_3$) isomeric mixture $\delta$ = 0.73-1.49 (m, total intensity 6H), 3.45-4.03 (m, total intensity 3H), 6.25-6.55 (m, total intensity 2H), 6.85-7.43 (m, total intensity 7H), 7.46 and 7.51 (each bs, total intensity 2H).

<u>Anal</u>. Calcd for C$_{21}$H$_{20}$O$_4$: Mol wt, 336.136. Found: Mol wt, 336.136.

<u>1,5-Di(2-furyl)-2-ethyl-4-methyl-3-phenyl-1,5-pentanedione</u> (46g). Using the procedure outlined above for the preparation of 46f, 2-butyrylfuran[18] (2.15 g, 0.0156 mol) and 53f (3.00 g, 0.0142 mol) gave 8.93 g of very impure 46g after 11.5 h. Without further purification this was carried on to pyridine 47g. An analytical sample was prepared by silica gel chromatography (CHCl$_3$): MS <u>m/z</u> 350 ($M^+$), 332, 321, 303, 279, 255, 253, 227, 213, 138, 124, 95(100); IR (thin film) 3170, 3000, 1670, 1560, 1460, 1385, 1260, 1160, 1080, 1030, 1015, 990, 975, 910, 885, 760, 702 cm$^{-1}$; $^1$H NMR (CDCl$_3$) isomeric mixture $\delta$ = 0.63-1.81 (m, total intensity 8H), 3.39-3.95 (m, total intensity 3H), 6.15-6.51 (m, total intensity 2H), 6.87-7.59 (m, total intensity 9H).

<u>Anal</u>. Calcd for C$_{22}$H$_{22}$O$_4$: Mol wt, 350.152. Found: Mol wt, 350.150.

<u>1-(4-Bromophenyl)-3,5-diphenyl-1,5-pentanedione</u> (57c). By the procedure described above for the preparation of 46b, p-bromoaceto-phenone (0.95 g, 4.80 mmol) and 1,3-diphenyl-2-propen-1-one (0.51 g, 2.45 mmol) gave 57c (0.89 g, 92%) directly as a white powder isolated by filtration after 11.5 h: mp 118.5-120.0°C; MS <u>m/z</u> 406 (408) ($M^+$),

287 (289), 209(100), 183 (185), 155 (157), 131, 105, 77; IR (KBr) 1680, 1670, 1585, 1495, 1450, 1414, 1400, 1350, 1270, 1205, 1070, 985, 815, 725, 685 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 3.11-3.59 (4H, m), 3.86-4.16 (1H, m), 7.14-7.86 (14H, m).

Anal. Calcd for C$_{23}$H$_{19}$BrO$_2$:  C, 67.82; H, 4.71.  Found:  C, 67.42; H, 4.66.

2,6-Di(2-furyl)-4-(2-methoxyphenyl)-3-methylpyridine (47b).  A mixture of diketone 46b (5.00 g, 0.0142 mol) and hydroxylamine hydrochloride (3.95 g, 0.0568 mol) in n-BuOH (50 mL) was heated at reflux for 6 h.  Toluene (50 mL) and water (50 mL) were added and the black reaction mixture was basified with 2N NaOH.  The aqueous layer was extracted twice more with toluene, and the combined extracts washed with water, saturated brine and then dried over MgSO$_4$.  The solvents were evaporated, the residue was dissolved in CHCl$_3$ and 20% by weight of silica gel was added.  After standing, the silica gel was filtered off and CHCl$_3$ evaporated to give a thick, black tar.  Kugelrohr distillation (150-190°C, 0.1-0.05 mm Hg) gave 47b (3.32 g, 71%) as a glass which crystallized from EtOH.  An analytical sample was prepared by sublimation (110°C, 0.1 mm Hg): mp 113-114°C; MS m/z 331 (M$^+$, 100), 316, 302, 300, 242, 165; IR (KBr) 3110, 2960, 2940, 2750, 1600, 1490, 1250, 1020, 1010, 730 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 2.30 (3H, s), 3.76 (3H, s), 6.45-6.56 (2H, m), 6.92-7.60 (8H, m), 7.48 (1H, s).

Anal. Calcd for C$_{21}$H$_{17}$NO$_3$:  Mol wt, 331.121.  Found:  Mol wt, 331.120.

2,6-Di(2-furyl)-4-phenylpyridine (47c).  Following the procedure described for the preparation of 47b, and refluxing for 3.5 h,

diketone 46c (3.80 g, 0.0123 mol) gave 47c (2.54 g, 72%) as off-white crystals upon crystallization from MeOH. An analytical sample was prepared by sublimation (120°C, 1.0 mm Hg): mp 131-132°C; MS $\underline{m/z}$ 287 ($M^+$, 100), 259, 230, 202; IR (KBr) 3100, 2750, 1615, 1585, 1560, 1495, 1385, 1230, 1170, 910, 890, 870, 830, 740 $cm^{-1}$; $^1H$ NMR (CDCl$_3$) δ = 6.60 (2H, dd, J = 2, 4 Hz), 7.23 (2H, d, J = 4 Hz), 7.44-7.66 (5H, m), 7.74 (2H, d, J = 2 Hz), 7.81 (2H, s).

<u>Anal</u>. Calcd for $C_{19}H_{13}NO_2$: C, 79.4; H, 4.57; N, 4.88. Found: C, 79.1; H, 4.57; N, 4.71.

2,6-Di(2-furyl)-3-methyl-4-phenylpyridine (47d). Using the above procedure, and refluxing for 6 h, diketone 46d (13.97 g, 0.0434 mol) gave 47d (8.83 g, 68%) as an amber-colored glass which crystallized from EtOH. An analytical sample was sublimed: mp 84-85°C; MS $\underline{m/z}$ 301 ($M^+$, 100), 300, 272, 242, 213; IR (thin film) 3225, 1780, 1670, 1610, 1570, 1495, 1470, 1455, 1160, 1010, 960, 885, 745, 700 $cm^{-1}$; $^1H$ NMR (CDCl$_3$) δ = 2.41 (3H, s), 6.49 (1H, dd, J = 2, 3.5 Hz), 6.53 (1H, dd, J = 2, 3.5 Hz), 7.03 (1H, dd, J = 1, 3.5 Hz), 7.09 (1H, dd, J = 1, 3.5 Hz), 7.27-7.51 (6H, m), 7.56 (1H, d, J = 2 Hz), 7.57 (1H, d, J = 2 Hz).

<u>Anal</u>. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.03; N, 4.65. Found: C, 79.46; H, 4.64; N, 4.46.

2,6-Di(2-furyl)-3-ethyl-4-phenylpyridine (47e). Following the above procedure, and refluxing for 6.5 h, diketone 46e (11.59 g, 0.0345 mol) gave 47e (7.87 g, 72%, crude) as an amber-colored glass. Purification on SiO$_2$ (400 g; 5% acetone/CHCl$_3$) gave pure 47e (4.28 g, 39%). An analytical sample was prepared by redistillation (150-180°C,

0.05 mm Hg): MS $\underline{m/z}$ 315 ($M^+$, 100), 300, 286, 272, 178, 149; IR (thin film) 3050, 1670, 1605, 1555, 1530, 1480, 1215, 1150, 1000, 906, 881, 820, 770, 750, 738, 702 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ = 0.98 (3H, t, J = 7 Hz), 2.85 (2H, q, J = 7 Hz), 6.41 and 6.45 (each, 1H, dd, J = 2, 4 Hz), 7.00 (2H, d, J = 4 Hz), 7.14-7.35 (6H, m), 7.46 (2H, bs).

$\underline{Anal}$. Calcd for C$_{21}$H$_{17}$NO$_2$: Mol wt, 315.126. Found: Mol wt, 315.127.

2,6-Di(2-furyl)-3,5-dimethyl-4-phenylpyridine (47f). Using the above procedure, and refluxing for 5 h, crude 46f (6.87 g, derived from 0.0189 mol of chalcone 53f) gave 47f (3.39 g, 57% from 53f) as an amber-colored glass which crystallized from EtOH. An analytical sample was sublimed (120-125°C, 0.1 mm Hg): mp 129-130°C; MS $\underline{m/z}$ 315 ($M^+$, 100), 314, 286, 213, 115, 95; IR (KBr) 1530, 1480, 1435, 1370, 1220, 1145, 1030, 1005, 988, 908, 885, 775, 737, 727, 709, 702 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ = 2.19 (6H, s), 6.52 (2H, dd, J = 2, 4 Hz), 6.92 (2H, d, J = 4 Hz) 7.15-7.57 (7H, m).

$\underline{Anal}$. Calcd for C$_{21}$H$_{17}$NO$_2$: C, 79.97; H, 5.44; N, 4.44. Found: C, 79.57; H, 5.31; N, 4.35.

2,6-Di(2-furyl)-3-ethyl-5-methyl-4-phenylpyridine (47g). Following the above procedure, and refluxing for 11 h, crude diketone 46g (8.93 g, derived from 0.0141 mol of chalcone 53f) gave 47g (0.901 g, 20% from 53f) after silica gel chromatography (4% acetone/CH$_2$Cl$_2$) of the glass obtained from Kugelrohr distillation. From the solidified chromatography fractions, an analytical sample of 47g was obtained as a white powder upon sublimation (90-115°C, 0.10 mm Hg): mp 107.5-109°C after recrystallization from EtOH; MS $\underline{m/z}$ 329 ($M^+$, 100), 314,

300, 286; IR (KBr) 1530, 1480, 1375, 1215, 1145, 1070, 1050, 1045, 1005, 908, 885, 815, 797, 770, 740, 730, 705 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 0.93 (3H, t, J = 7 Hz), 2.10 (3H, s), 2.64 (2H, q, J = 7 Hz), 6.45 (2H, dd, J = 2, 4 Hz), 6.80-7.50 (9H, m).

<u>Anal</u>. Calcd for C$_{22}$H$_{19}$NO$_2$: Mol wt, 329.142. Found: Mol wt, 329.141.

<u>2-(4-Bromophenyl)-4,6-diphenylpyridine</u> (59). Following the above procedure, diketone 57c (0.876 g, 0.116 mmol) gave 59 (0.801 g, 96%) as a white solid directly by filtration after 1 h at reflux. Recrystallization from CHCl$_3$/MeOH gave fine needles: mp 153-154°C (lit[23] 152-153°C).

<u>4-(2-Methoxyphenyl)-3-methylpyridine-2,6-dicarboxylic acid</u> (48b).

1) <u>KMnO$_4$/Acetone</u>. To a solution of 47b (4.00 g, 0.012 mol) in acetone (800 mL) was added KMnO$_4$ (5.73 g, 0.0363 mol). While vigorously stirring at 25°C, additional KMnO$_4$ (22.92 g) was added, in four identical portions (5.73 g, 0.0363 mol) as the previous portion was consumed, over a period of 4 days. Water (400 mL) was then added and the contents of the reaction flask stirred for 1 h. Manganese dioxide was removed by suction filtration, washed with water and filtered again. Acetone was then evaporated from the combined filtrates, and subsequent ether extraction of the basic solution removed unreacted starting material. The aqueous solution was acidified with 30% H$_2$SO$_4$ and extracted three times with ether. The combined extracts were washed with brine and dried over MgSO$_4$. Ether was evaporated and the resulting yellow oil solidified under vacuum giving 48b (3.11 g, 90%): mp 173-184°C dec; MS <u>m/z</u> 287 (M$^+$), 243, 199(100); IR (KBr) 1720, 1600,

1250 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) δ = 1.55 (3H, s), 4.08 (3H, s), 7.10-7.92 (4H, m), 8.14 (1H, s).

2) KMnO$_4$/t-butanol/H$_2$O. A mixture of 47b (1.00 g, 3.02 mol), t-BuOH (200 mL) and water (40 mL) was heated to 75-80°C, and KMnO$_4$ (6.19 g, 0.0392 mol) was then added. After 17 h, the solution was filtered while hot to remove MnO$_2$, and a 20% t-BuOH/H$_2$O mixture was used to wash the solid well. Enough aq. NaHSO$_3$ was added to the filtrate to destroy and residual MnO$_2$. Solvents were evaporated until a minimum amount of water remained. When the aqueous solution was acidified with 2N HCl, 48b (0.61 g, 70%) precipitated as a yellow solid.

4-Phenylpyridine-2,6-dicarboxylic acid (48c). Following the first procedure for the preparation of 48b, 47c (1.50 g; 5.23 mmol) gave 48c (0.97 g) as a white solid, isolated directly from the acidified aqueous solution by filtration. An additional 0.13 g (87% total yield) was obtained upon ether extraction of the filtrate: mp 300°C dec; MS m/z 243 (M$^+$), 199, 181, 153(100); IR (KBr) 3450, 3200, 2950, 2750, 1725, 1590, 1370, 1260, 770, 700 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) δ = 4.88 (2H, bs), 7.58 and 7.90 (each, bs, total intensity 5H), 8.48 (2H, bs).

3-Methyl-4-phenylpyridine-2,6-dicarboxylic acid (48d). Following the above procedure, 47d (1.35 g, 4.49 mmol) gave 48d (0.37 g) as a white solid isolated directly from the acidified aqueous solution by filtration. Additional 48d (0.67 g, 90% total yield) was obtained upon ether extraction of the filtrate: mp 180-200°C dec; MS m/z 257 (M$^+$), 256, 210, 169(100), 167, 166, 140, 139, 115; IR (KBr) 3420, 3000, 2750, 1725, 1600, 1255, 760, 690 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) δ = 2.35

(3H, s), 7.15-7.55 (5H, m), 7.81 (1H, s).

3-Ethyl-4-phenylpyridine-2,6-dicarboxylic acid (48e). Using the procedure described above, 47e (1.96 g, 6.22 mmol) gave 48e (1.45 g, 86%) as a beige solid: mp 163-167°C dec; MS m/z 271 (M$^+$), 270, 227, 224, 183(100); IR (KBr) 3300, 3040, 1730, 1360, 1270, 1225, 768, 701 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) δ = 0.96 (3H, t, J = 7 Hz), 2.75 (2H, q, J = 7 Hz), 7.44 (5H, bs), 7.81 (1H, s).

3,5-Dimethyl-4-phenylpyridine-2,6-dicarboxylic acid (48f). Following the above procedure, 47f (1.20 g, 3.81 mmol) gave 48f (0.94 g, 91%) as a beige solid: mp 182-190°C dec; MS m/z 271 (M$^+$), 270, 252, 226, 224, 209, 208, 194, 182, 180(100), 166, 153, 152, 140, 139, 128, 127, 115; IR (KBr) 3050, 2250, 1710, 1540, 1310, 1210, 1125, 985, 965, 762, 692 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) δ = 2.12 (6H, bs), 7.13-7.55 (5H, m).

4-(2-Methoxyphenyl)-3-methylpyridine (49b). In diphenyl ether (36 mL), 48b (7.28 g, 0.0254 mol) was heated at 220°C until $CO_2$ evolution was complete. The dark brown solution was taken up in diethyl ether and extracted four times with 3N HCl. The resulting aqueous solution was backwashed with diethyl ether and brought to pH 9 with concentrated $NH_4OH$. The basic solution was extracted three times with $CH_2Cl_2$. The combined extracts were washed with water and brine, and then dried over $MgSO_4$. Solvent was evaporated and the resulting crude oil was distilled by Kugelrohr (100-130°C, 0.2 mm Hg) to give 49b (4.20 g, 83%) as a clear oil: MS m/z 199 (M$^+$, 100), 184, 168; IR (thin film) 2970, 2840, 1600, 1480, 1270, 1240, 750 cm$^{-1}$; $^1$H

NMR (CDCl$_3$) $\delta$ = 2.12 (3H, s), 3.74 (3H, s), 6.93-7.46 (5H, m), 8.43 (1H, d, J = 5 Hz), 8.46 (1H, s).

Anal. Calcd for C$_{13}$H$_{13}$NO: Mol wt, 199.100. Found: Mol wt, 199.100.

4-Phenylpyridine (49c). As above, 48c (0.75 g, 3.09 mmol) was heated to 300°C, and gave 49c (0.34 g, 71%) as a solid obtained directly from evaporation of solvent. This was recrystallized from hexane: mp 75.0-75.5°C (lit[34] 77-78°C).

3-Methyl-4-phenylpyridine (49d) and 5-methyl-3-phenylpyridine (63a). As above, 48d (62.7 mg, 0.244 mmol) was heated to 220°C, and gave 49d (25.8 mg, 63%) as a clear oil: mp 161-162.5°C (picrate, from benzene; lit[35] 168-169°C from benzene). The ^{1}H NMR spectrum was in accord with the published spectrum.[35] The ^{13}C NMR data are in Table II.

In one preparation of 49d, 5-methyl-3-phenylpyridine 63a was evident as a minor isomer to the extent of 10% by ^{1}H NMR. Recrystallization of the corresponding picrate mixture (from 500 mg pyridine mixture) from EtOH gave 317 mg of pure 49d picrate as a first crop. The second crop of crystals, enriched in the minor isomer, was chromatographed on silica gel (20% acetone/CHCl$_3$) and the free pyridine 63a (10.0 mg) was isolated as an oil: MS m/z 169 (M$^+$, 100), 154, 149, 141, 139, 115; IR (CHCl$_3$) 1580, 1460, 1440, 1400 cm$^{-1}$; ^{1}H NMR (CDCl$_3$) $\delta$ = 2.39 (3H, s), 7.30-7.71 (6H, m), 8.41 (1H, bs), 8.64 (1H, bs). ^{13}C NMR data are listed in Table II.

Anal. Calcd for C$_{12}$H$_{11}$N: Mol wt, 169.089. Found: Mol wt, 169.089.

3-Ethyl-4-phenylpyridine (49e). As above, 48e (0.551 g, 2.03 mmol) was heated in 2.5 mL of diphenyl ether at 210-220°C, and gave 49e (0.264 g, 71%) as a white solid upon Kugelrohr distillation (70-100°C, 0.05 mm Hg). An analytical sample was prepared by recrystallization (EtOH) and sublimation (40°C, 0.02 mm Hg): mp 55-58°C; MS m/z 183 ($M^+$, 100), 182, 168, 167, 154; IR (KBr) 2960, 2930, 2860, 1585, 1470, 1440, 1055, 1045, 835, 750, 700 $cm^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.09 (3H, t, J = 7 Hz), 2.65 (2H, q, J = 7 Hz), 7.12 (1H, d, J = 5 Hz), 7.24-7.51 (5H, m), 8.47 (1H, d, J = 5 Hz), 8.55 (1H, s).

Anal. Calcd for C$_{13}$H$_{13}$N: Mol wt, 183.105. Found: Mol wt, 183.104.

3,5-Dimethyl-4-phenylpyridine (49f). Using the procedure described above, and heating to 210°C, 48f (0.50 g, 1.85 mmol) was converted to 49f (0.21 g, 61%) as a white, crystalline solid upon extraction, evaporation of solvent, and subsequent sublimation (65-70°C, 0.05 mm Hg): mp 83-85°C; MS m/z 183 ($M^+$, 100), 182, 168, 167, 153, 152, 141, 139, 128, 115; IR (KBr) 1575, 1480, 1460, 1430, 1400, 1370, 1270, 1260, 1155, 1145, 1070, 1040, 877, 774, 756, 710 $cm^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.99 (6H, s), 6.95-7.46 (5H, m), 8.23 (2H, s).

Anal. Calcd for C$_{13}$H$_{13}$N: C, 85.19; H, 7.16; N, 7.64. Found: C, 84.90; H, 7.14; N, 7.40.

5-Ethyl-4-phenylpyridine-2,3,6-tricarboxylic acid (61). Following the first procedure for the preparation of 48b, 47g (0.683 g, 2.11 mmol) gave 61 (0.532 g, 80%) as a white solid: mp 178-180°C dec; MS (no $M^+$) m/z 271, 270, 253, 227, 226, 209, 183, 180, 166, 153, 152, 44(100); IR (KBr) 3200, 2950, 1730, 1710, 1420, 1250, 1200, 1105,

908, 758, 696 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) $\delta$ = 0.90 (3H, t, J = 7 Hz), 7.05-7.67 (5H, m), methylene protons obscured by water band which could not be removed by extensive vacuum treatment.

5-Ethyl-4-phenylpyridine-3-carboxylic acid (62). The triacid 61 (26.0 mg, 0.0825 mmol) was heated neat to 200°C and gave 62 directly: MS m/z 227 (M$^+$), 209, 194, 182, 180, 166, 152, 139(100), 127, 115; IR (thin film) 3000, 2520, 1710, 1290, 1150, 915, 803, 755, 700 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ = 1.00 (3H, t, J = 7 Hz), 2.47 (2H, q, J = 7 Hz), 7.00-7.50 (5H, m), 8.53 (1H, bs), 8.90 (1H, bs).

Anal. Calcd for C$_{14}$H$_{13}$NO$_2$: Mol wt, 227.095. Found: Mol wt, 227.095.

3-Methoxy-2-(phenylmethoxy)benzaldehyde (78). Dried and finely ground K$_2$CO$_3$ (18.2 g, 0.132 mol) was added to a mechanically stirred solution of o-vanillin (10.0 g, 65.8 mmol) in acetone (100 mL, distilled from K$_2$CO$_3$). Benzyl chloride (11.4 mL, 98.7 mmol) and NaI (16.3 g, 0.109 mol) were then added. The reaction mixture was refluxed for 12 h. Solids were removed by filtration and washed well with ether. Solvents were evaporated and remaining benzyl iodide was removed by Kugelrohr distillation (0.05 mm Hg, 90°C). Finally, 78 (14.5 g, 91%) was distilled (0.05 mm Hg, 140-150°C) as a pale yellow oil which crystallized upon standing. An analytical sample was recrystallized from MeOH: mp 43-44°C (lit[36] 45°C); MS m/z 242 (M$^+$), 213, 150, 91(100); IR (KBr) 2930, 1680, 1575, 1470, 1355, 1260, 1235, 1215, 1075, 1055, 965, 754, 698 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ = 3.86 (3H, s), 5.15 (2H, s), 7.04-7.48 (8H, m), 10.21 (1H, s).

<u>1-[2-(Phenylmethoxy)-phenyl]-ethanone</u> (70a). Dried and finely ground $K_2CO_3$ (36.43 g, 0.264 mol) was added to a mechanically stirred solution of 2-hydroxyacetophenone (15.9 mL, 0.132 mol) in acetone (180 mL, distilled from $K_2CO_3$). Benzyl chloride (22.8 mL, 0.198 mol) and NaI (32.67 g, 0.218 mol) were then added. The reaction mixture was refluxed for 20 h. Additional $K_2CO_3$ (18.00 g) was added, and refluxing continued for 23 h. The solids were removed by filtration and washed well with ether. Solvents were evaporated and remaining benzyl iodide and 69 were removed by Kugelrohr distillation (2.5 mm Hg, 120°C). Finally, 70a was distilled as an oil (0.1 mm Hg, 130°C), 27.64 g (93%), which solidified upon standing. An analytical sample was recrystallized from MeOH: mp 39-41°C (lit[37] 40°C); MS <u>m/z</u> 226 ($M^+$), 183, 121, 91(100); IR (thin film) 1670, 1590, 1475, 1440, 1345, 1280, 1225, 1155, 1120, 1005, 754, 694 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 2.56 (3H, s), 5.09 (2H, s), 6.86-7.79 (9H, m).

<u>1-[3-Methoxy-2-(phenylmethoxy)-phenyl]-ethanone</u> (70b). To a solution of 78 (11.0 g, 46.2 mmol) in ether (76 mL) at 0°C was added a 1.4<u>M</u> solution of MeLi/LiBr complex in ether (34.1 mL, 47.7 mmol). The resulting mixture was stirred for 1 h at 0°C, then excess 10% aq. $NaHCO_3$ was added to decompose the Li salt. Following extraction with ether, the extracts were washed once with brine, dried ($Na_2SO_4$), and evaporated to give 1-[3-methoxy-2-(phenylmethoxy)-phenyl]-ethanol (79) (11.8 g, 99%) as a pale yellow oil: MS <u>m/z</u> 240 $(M-H_2O)^+$, 150, 121, 107, 91(100); IR (thin film) 3600, 3050, 1580, 1475, 1450, 1260, 1200, 1175, 1050, 1010, 915, 848, 789, 749, 697 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 1.34 (3H, d, J = 6.5 Hz), 2.50 (1H, s), 3.82 (3H, s), 4.95-5.21 (1H,

m), 5.03 (2H, s), 6.75-7.49 (8H, m).

Pyridinium chlorochromate (14.8 g, 68.6 mmol) was added to a solution of 79 (11.8 g, 45.7 mmol) in dry $CH_2Cl_2$ (118 mL) and the mixture was stirred for 5 h at 25°C. Ether (120 mL) was added, and the solid chromium species was removed by filtration. The filtrate was washed twice with 2$\underline{N}$ HCl, once with brine, and dried ($Na_2SO_4$). Solvent was evaporated and Kugelrohr distillation of the resulting oil (0.05 mm Hg, 160°C) gave 70b (10.41 g, 89%) as a pale yellow oil: MS $\underline{m/z}$ 256 ($M^+$), 238, 214, 213, 181, 166, 151, 136, 105, 91(100); IR (thin film) 3000, 1680, 1530, 1465, 1450, 1430, 1350, 1305, 1260, 1215, 1045, 972, 790, 754, 698 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ = 2.52 (3H, s), 3.88 (3H, s), 5.08 (2H, s), 7.00-7.51 (8H, m).

$\underline{Anal}$. Calcd for $C_{16}H_{16}O_3$: Mol wt, 256.110. Found: Mol wt, 256.110.

2-(Phenylmethoxy)-α-methylstyrene (72a). In a 1-liter three-necked flask equipped with mechanical stirrer and reflux condenser were mixed Mg turnings (3.19 g, 0.133 mol), ether (68 mL), and $CH_3I$ (0.43 mL, 6.97 mmol). A few crystals of $I_2$ were added to initiate the reaction. An ice-cold solution of $CH_3I$ (8.25 mL, 0.132 mol) in ether (112 mL) was then added dropwise and the resulting mixture was refluxed for 3 h. To the cooled solution (25°C) was slowly added 70a (15.00 g, 66.4 mmol) in ether (60 mL). The mixture was refluxed for 5 h, the complex decomposed by the slow addition of aq. $NH_4Cl$ and the carbinol 71a extracted with ether. The extracts were washed with brine, dried ($Na_2SO_4$), and evaporated to give 71a (16.56 g, crude) as a pale yellow oil: MS $\underline{m/z}$ 242 ($M^+$), 227, 134, 91(100); IR (thin film)

3570, 3030, 1600, 1575, 1482, 1438, 1370, 1280, 1240, 1010, 862, 751, 697 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.59 (6H, s), 4.19 (1H, s), 5.09 (2H, s), 6.84-7.46 (9H, m).

The carbinol 71a (16.56 g) was heated at 200°C in the presence of a trace amount of hydroquinone for 30 min. The sample was taken up with CHCl$_3$, washed with 2N NaOH and brine, and dried (Na$_2$SO$_4$). Solvent was evaporated, and the resulting oil was purified by Kugelrohr distillation (0.05 mm Hg, 120°C) to give 13.96 g (94%) of α-methylstyrene 72a as a colorless oil: MS m/z 224 (M$^+$), 209, 133, 105, 91(100); IR (thin film) 3120, 2995, 1630, 1595, 1480, 1435, 1370, 1225, 1090, 1020, 898, 750, 692 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 2.15 (3H, s), 5.08 (2H, s), 5.02-5.18 (2H, m), 6.82-7.47 (9H, m).

<u>Anal</u>. Calcd for C$_{16}$H$_{16}$O: Mol wt, 224.120. Found: Mol wt, 224.120.

<u>3-Methoxy-2-(phenylmethoxy)-α-methylstyrene</u> (72b). In a 250-mL, three-necked flask equipped with mechanical stirrer and reflux condenser were mixed Mg turnings (0.94 g, 39.1 mmol), ether (23 mL), and CH$_3$I (0.13 mL, 2.05 mmol). A few crystals of I$_2$ were added to initiate the reaction. An ice-cold solution of CH$_3$I (2.43 mL, 39.0 mmol) in ether (37 mL) was added dropwise and the resulting mixture was refluxed for 2 h. To the cooled solution (25°C) was slowly added 70b (5.00 g, 19.5 mmol) in ether (20 mL). The mixture was refluxed for 5 h, the complex decomposed by the slow addition of aq. NH$_4$Cl, and the carbinol 71b extracted with ether. The extracts were washed with brine, dried (Na$_2$SO$_4$), and evaporated to give 71b (5.10 g, crude) as a pale yellow oil: MS m/z 254 (M-H$_2$O)$^+$, 239, 163, 150, 135,

105, 91(100); IR (thin film) 3540, 3000, 1570, 1460, 1425, 1360, 1250, 1050, 745, 735, 695, cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ =1.58 (6H, s), 3.87 (3H, s), 4.20 (1H, s), 5.17 (2H, s), 6.75-7.57 (8H, m).

The carbinol 71b (5.10 g) was then heated at 180-200°C in the presence of a trace amount of hydroquinone for 30 min. The sample was taken up in CHCl$_3$, washed with 10% aq. NaHCO$_3$ and brine, and dried (Na$_2$SO$_4$). Solvent was evaporated, and the resulting oil was purified by Kugelrohr distillation (0.05 mm Hg, 130°C) to give 72b (4.05 g, 82% from 70b) as a pale yellow oil: MS m/z 254 (M$^+$), 239, 222, 163, 150, 135, 91(100); IR (thin film) 3020, 1580, 1470, 1370, 1310, 1260, 1215, 1080, 1060, 1010, 988, 900, 794, 753, 697 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 2.10 (3H, d, J = 1 Hz), 3.84 (3H, s), 4.90 (2H, s), 4.97-5.18 (2H, m), 6.66-7.52 (8H, m).

Anal. Calcd for C$_{17}$H$_{18}$O$_2$: Mol wt, 254.131. Found: Mol wt, 254.131.

Trace amounts of phenol 80 were obtained with 72b: MS m/z 164 (M$^+$, 100), 149, 131, 121, 103, 91, 77; IR (CHCl$_3$) 3650, 3000, 1720, 1580, 1455, 1270, 1060, 1000, 900, 735 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 2.15 (3H, d, J = 1 Hz), 3.88 (3H, s), 5.20 (2H, d, J = 1 Hz), 5.85 (1H, s), 6.77 (3H, bs).

Anal. Calcd for C$_{10}$H$_{12}$O$_2$: Mol wt, 164.084. Found: Mol wt, 164.084.

<u>4-[2-(Phenylmethoxy)-phenyl]-pyridine-3-carboxaldehyde</u> (73a).
Oxalyl chloride (4.73 mL, 54.4 mmol) was added dropwise to a solution of ClCH$_2$CH$_2$Cl (6.30 mL) and DMF (4.71 mL, 61.0 mmol). Reaction was vigorous, and a thick, white precipitate formed. To this was added,

dropwise, a solution of 72a (3.00 g, 13.4 mmol) in ClCH$_2$CH$_2$Cl (2.70

mL). Additional ClCH$_2$CH$_2$Cl (0.6 mL) was added to facilitate stirring.

The mixture was brought to reflux and the resulting red-brown solu-

tion was heated for 3 h. The ClCH$_2$CH$_2$Cl was removed _in vacuo_, HOAc

(5.0 mL), H$_2$O (1.25 mL) and NH$_4$OAc (4.19 g, 54.4 mmol) were added,

and the resulting mixture was heated for 1 h at 100°C. When cool, it

was neutralized with 4N̲ NaOH and extracted with CHCl$_3$. The extracts

were washed once with brine and dried (Na$_2$SO$_4$). Solvent was evapora-

ted and 73a (3.02 g, 78%) was isolated as an oil by Kugelrohr distil-

lation (0.005 mm Hg, 190°C): MS m/z 289 (M$^+$), 288, 277, 261, 198,

182, 170, 115, 91(100); IR (thin film) 2970, 2890, 1690, 1580, 1435,

1375, 1220, 1115, 750, 693 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 5.06 (2H, s),

7.04-7.55 (10H, m), 8.79 (1H, d, J = 4 Hz), 9.12 (1H, s), 9.92 (1H,

s).

An analytical sample was prepared by preparative thin layer

chromatography on silica gel (5% acetone/CHCl$_3$).

_Anal_. Calcd for C$_{19}$H$_{15}$NO$_2$: Mol wt, 289.110. Found: Mol wt,

289.108.


## 4-[3-Methoxy-2-(phenylmethoxy)-phenyl]-pyridine-3-carboxaldedyde

(73b). Oxalyl chloride (2.05 mL, 23.6 mmol) was added, dropwise, to

a solution of DMF (2.08 mL, 26.9 mmol) and ClCH$_2$CH$_2$Cl (2.5 mL). A

solution of 72b (1.50 g, 5.91 mmol) in ClCH$_2$CH$_2$Cl (1.50 mL) was added

dropwise. The resulting mixture was refluxed for 3 h. The

ClCH$_2$CH$_2$Cl was removed _in vacuo_, HOAc (3.0 mL), H$_2$O (1.0 mL) and

NH$_4$OAc (1.82 g, 23.6 mmol) were added, and the resulting mixture was

heated for 1 h at 100°C. When cool, it was neutralized with 2N̲ NaOH

and extracted with $CHCl_3$. The extracts were washed once with brine, dried ($Na_2SO_4$), and evaporated to a dark liquid. The crude product was flushed through a $SiO_2$ column (35 g) with 10% acetone/$CHCl_3$, and 73b (0.78 g, 41%) was obtained as an oil which crystallized upon standing. An analytical sample was recrystallized from EtOH, then sublimed (0.05 mm Hg, 95°C): mp 97.0-98.0°C; MS m/z 319 ($M^+$), 290, 228, 200, 91(100); IR (KBr) 2990, 2880, 1680, 1570, 1460, 1255, 1190, 1115, 1025, 964, 836, 789, 761, 703 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 3.94 (3H, s), 4.81 (2H, s), 6.70-7.27 (9H, m), 8.63 (1H, d, J = 5 Hz), 8.99 (1H, s), 9.68 (1H, s).

Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.20; H, 5.38; N, 4.39. Found: C, 75.10; H, 5.25; N, 4.41.

In one trial, Kugelrohr distillation (0.05 mm Hg, 200°C) was employed to purify the crude product isolated after extraction. The resulting distillate (0.52 g) appeared as an approximately 1:1 mixture of two components by TLC (10% acetone/$CHCl_3$). Using this solvent system, it was chromatographed through a $SiO_2$ column (25 g). Isolated was 73b (0.12 g, 10%), along with lactone 81 (0.08 g, 9%). An analytical sample of 81 was recrystallized from MeOH: mp 206.0-207.0°C; MS m/z 227 ($M^+$), 213, 212, 197, 184, 170, 156, 149, 142, 91(100); IR (KBr) 1730, 1580, 1550, 1455, 1270, 1165, 1110, 1030, 769 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 3.99 (3H, s), 7.08-7.68 (3H, m), 7.89 (1H, d, J = 5 Hz), 8.93 (1H, d, J = 5 Hz), 9.54 (1H, s).

Anal. Calcd for $C_{13}H_9NO_3$: C, 68.70; H, 4.00; N, 6.17. Found: C, 68.41; H, 4.10; N, 6.15.

<u>Ethyl 3-(3-(4-(2-(phenylmethoxy)-phenyl)-pyridyl))-propenoate</u>

(74a). A mixture of 73a (0.100 g, 0.346 mmol), ethyl hydrogen malonate[38] (0.046 g, 0.346 mmol), pyridine (0.0275 mL, 0.346 mmol) and piperidine (0.5 μL) was stirred for 3 h at 100°C. Pyridine and piperidine were removed <u>in vacuo</u>, and 74a (0.1048 g, 84%) was isolated by Kugelrohr distillation (170°C, 0.025 mm Hg): MS <u>m/z</u> 359 ($M^+$), 358, 330, 302, 286, 272, 258, 182, 180, 91(100); IR (thin film) 1705, 1580, 1495, 1470, 1435, 1300, 1260, 1215, 1180, 1025, 753, 695 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.26 (3H, t, J = 7 Hz), 4.20 (2H, q, J = 7 Hz), 5.04 (2H, s), 6.38 (1H, d, J = 16 Hz), 6.96-7.35 (10H, m), 7.55 (1H, d, J = 16 Hz), 8.59 (1H, d, J = 4 Hz), 8.89 (1H, s).

<u>Anal</u>. Calcd for C$_{23}$H$_{21}$NO$_3$: Mol wt, 359.152. Found: Mol wt, 359.156.

<u>Ethyl 3-(3-(4-(3-methoxy-2-(phenylmethoxy)-phenyl)-pyridyl))-</u>
<u>propenoate</u> (74b). A mixture of 73b (0.72 g, 2.26 mmol), ethyl hydrogen malonate[38] (0.31 g, 2.37 mmol), pyridine (0.18 mL, 2.26 mmol) and piperidine (3.8 μL) was stirred at 100°C for 6 h. Pyridine and piperidine were removed <u>in vacuo</u>, and the resulting glass (0.76 g) was chromatographed through a column of silica gel with 10% acetone/CHCl$_3$ to give 74b (0.53 g, 60%) as an amber-colored oil: MS <u>m/z</u> 389 ($M^+$), 360, 316, 298, 212, 91(100); IR (CHCl$_3$) 3050, 1720, 1640, 1580, 1455, 1305, 1255, 1155, 1105, 975 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.25 (3H, t, J = 7 Hz), 3.92 (3H, s), 4.16 (2H, q, J = 7 Hz), 4.75 (2H, s), 6.27 (1H, d, J = 16 Hz), 6.54-7.30 (9H, m), 7.23 (1H, d, J = 16 Hz), 8.42 (1H, d, J = 6 Hz), 8.77 (1H, s).

Anal. Calcd for $C_{24}H_{23}NO_4$: Mol wt, 389.163. Found: Mol wt, 389.162.

<u>Ethyl 3-(3-(4-(2-(phenylmethoxy)-phenyl)-pyridyl))-propanoate</u>

(**75**). A mixture of **74a** (53.7 mg, 0.150 mmol) and 10% Pd/C (5 mg) in 100% EtOH (0.65 mL) was stirred under 1 atm of $H_2$ for 5 h. Additional catalyst (5 mg) in EtOH (0.4 mL) was added, and the mixture stirred under $H_2$ for 5 h longer. Catalyst was filtered off through Celite and washed with EtOH. Solvent was evaporated to give **75** (49.2 mg, 91%) as a clear oil: MS $\underline{m}/\underline{z}$ 361 ($M^+$), 360, 359, 358, 357, 344, 341, 332, 329, 316, 313, 288, 284, 273, 269, 175, 173, 91(100), 79; IR $(CHCl_3)$ 1715 cm$^{-1}$; $^1$H NMR $(CDCl_3)$ δ = 1.12 (3H, t, J = 7 Hz), 2.25-2.55 (2H, m), 2.76-3.06 (2H, m), 4.01 (2H, q, J = 7 Hz), 5.03 (2H, s), 6.98-7.52 (10H, m), 8.38-8.50 (1H, bd) overlapping 8.50 (1H, bs).

Anal. Calcd for $C_{23}H_{23}NO_3$: Mol wt, 361.168. Found: Mol wt, 361.170.

<u>3-Methyl-4-(2-hydroxyphenyl)-pyridine</u> (**66**). To **49b** (3.89 g, 19.6 mmol) was added conc HBr (40 mL) and the mixture heated at reflux for 11 h. After cooling to 0°C, water (120 mL) was added and the solution brought to pH = 12 with 4$\underline{N}$ NaOH. After the addition of $Na_2HPO_4$ (200 mg) the pH was lowered to 7 with conc HBr. From the clear solution, **66** precipitated as a white solid which was isolated by filtration (3.48 g, 96%): mp 189-190°C; MS $\underline{m}/\underline{z}$ 185 ($M^+$, 100), 184, 170, 158; IR (KBr) 3040-2560 (br), 1600, 1440 cm$^{-1}$; $^1$H NMR ($d_6$-DMSO) δ = 2.12 (3H, s), 6.70-7.32 (5H, m), 8.34 (1H, d, J = 6 Hz), 8.38 (1H, s), 9.55 (1H, s).

<u>Anal</u>. Calcd for $C_{12}H_{11}NO$: C, 77.8; H, 6.00; N, 7.56. Found: C, 77.7; H, 5.98; N, 7.45.

<u>Ethyl 3-(3-(4-(2-hydroxyphenyl)-pyridyl))-propanoate</u> (<u>76</u>). A solution of <u>74a</u> (3.33 g, 9.28 mmol) in 100% EtOH (34 mL) over 10% Pd/C (0.34 g) was shaken on a Parr hydrogenator under 30 lbs of $H_2$. Additional catalyst (0.20 g in 14 mL of EtOH) was added after 19 h. After another 12 h, TLC indicated complete double bond hydrogenation to give ethyl 3-(3-(4-(2-phenylmethoxyphenyl)-pyridyl))-propanoate ($R_f$ = 0.20, 5% acetone/chloroform).

Additional 10% Pd/C (0.34 g) in EtOH (10 mL) and HCl/EtOH (1.02<u>M</u>, 10 mL) were added to the reaction vessel. The resulting mixture was shaken under 30 lbs of $H_2$ for 10 h at which time additional catalyst (0.20 g in 10 mL of EtOH) was added, and reaction mixture was stirred under $H_2$ for 11 h longer. Catalyst was filtered off through Celite and washed well with EtOH. The ethanolic solution was poured into an excess of 10% aq. $NaHCO_3$, and the resulting aqueous solution was extracted with ether. The ether extracts were washed once with brine, dried ($Na_2SO_4$) and evaporated to give <u>76</u> (2.38 g, 95%) as a white, crystalline solid. An analytical sample was prepared by recrystallization from EtOH: mp 155-156°C; MS <u>m/z</u> 271 ($M^+$), 226, 225, 215, 201, 196, 184, 183, 180(100); IR (KBr) 3000, 2720, 2600, 1730, 1610, 1580, 1440, 1370, 1275, 1175, 762 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) $\delta$ = 1.11 (3H, t, J = 7 Hz), 2.24-2.91 (4H, m), 3.95 (2H, q, J = 7 Hz), 6.72-7.34 (5H, m), 8.38 (1H, d, J = 4 Hz), 8.43 (1H, s), 9.60 (1H, bs).

Anal. Calcd for $C_{16}H_{17}NO_3$: Mol wt, 271.121. Found: Mol wt, 271.121.

Ethyl 3-(3-(4-(2-hydroxy-3-methoxyphenyl)-pyridyl))-propanoate

(43). Procedure a. From 74b. A solution of 74b (0.33 g, 0.85 mmol) in 100% EtOH (20 mL) over 10% Pd/C (33 mg) was shaken on a Parr hydro-genator under 30 lbs of $H_2$. After 9 h, additional catalyst (33 mg) was added. After another 10 h, catalyst was filtered off through Celite and washed well with EtOH. EtOH was evaporated to give 43 (0.23 g, 92%) as a white, crystalline solid. An analytical sample was prepared by recrystallization from EtOH: mp 108.0-108.5°C; MS m/z 301 ($M^+$), 256, 227, 212, 210(100), 196, 184, 167, 154, 128, 115; IR (KBr) 3000, 1730, 1580, 1455, 1285, 1250, 1175, 1050, 752 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) $\delta$ = 1.11 (3H, t, J = 7 Hz), 2.23-2.94 (4H, m), 3.85 (3H, s), 3.95 (2H, q, J = 7 Hz), 6.54-7.12 (4H, m), 8.37 (1H, d, J = 5 Hz), 8.45 (1H, s), 8.76 (1H, bs).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.74; H, 6.37; N, 4.65. Found: C, 67.73; H, 6.45; N, 4.72.

Procedure b. From 86b. A solution of p-TsOH·$H_2O$ [0.64 g, 3.38 mmol; twice dissolved in EtOH (2 mL) and evaporated in vacuo] in EtOH (3.0 mL) was added to a solution of 86b (1.1027 g, 3.07 mmol) in EtOH (8.0 mL). The reaction mixture was heated at 55°C for 2 h, then added to a mixture of 10% aq. NaHCO$_3$ (50 mL) and 20% acetone/CHCl$_3$ (30 mL). The aqueous layer was extracted further with 20% acetone/ CHCl$_3$ (2 x 20 mL). The extracts were washed with brine (30 mL), dried (Na$_2$SO$_4$), and evaporated to give 43 (0.9061 g, 98%) as an oil which crystallized upon standing.

<u>1,3-Dimethyl-4-(2-hydroxyphenyl)-pyridinium iodide (67)</u>. The phenol, 66 (2.00 g, 10.8 mmol), was dissolved in DMF (10 mL) and $CH_3I$ (2.69 mL, 43.2 mmol) was introduced. The resulting amber solution was stirred for 1 h, then added, dropwise, to 80 mL of stirring benzene. The product oiled out, the solvent layer was removed, and fresh benzene was added. After stirring for 10 min, solvent was replaced again. The oil solidified upon further stirring, and methiodide 67 (3.49 g, 99%) was isolated by filtration as a pale yellow solid: mp 90°C dec; IR (KBr) 3170 (br) $cm^{-1}$; $^1H$ NMR ($d_6$-DMSO) δ = 2.29 (3H, s), 4.31 (3H, s), 6.79-7.45 (4H, m), 7.89 (1H, d, J = 6 Hz), 8.76 (1H, d, J = 6 Hz), 8.89 (1H, s).

<u>4-(2-Hydroxyphenyl)-1-methyl-3-(3-oxo-3-ethoxypropyl)-pyridinium</u> <u>iodide (90a)</u>. $CH_3I$ (0.27 mL, 4.35 mmol) was added to a solution of 76 (0.295 g, 1.09 mmol) in DMF (3.0 mL), and the mixture was stirred for 1 h at 25°C. DMF and excess $CH_3I$ were removed <u>in vacuo</u> to give 90a (0.449 g, 100%) as a pale yellow oil: IR (thin film) 3550, 3220, 1730, 1660, 1445, 1380, 1250, 1185, 1090, 1055, 1015, 830, 762 $cm^{-1}$; $^1H$ NMR ($d_6$-DMSO) δ = 1.11 (3H, t, J = 7 Hz), 2.41-3.06 (4H, m), 4.00 (2H, q, J = 7 Hz), 4.36 (3H, s), 6.84-7.72 (4H, m), 7.95 (1H, d, J = 6 Hz), 8.85 (1H, d, J = 6 Hz), 9.01 (1H, bs).

<u>4-(2-Hydroxy-3-methoxyphenyl)-1-methyl-3-(3-oxo-3-ethoxypropyl)-</u> <u>pyridinium iodide (90b)</u>. $CH_3I$ (0.600 mL, 0.960 mmol) was added to a solution of 43 (72.2 mg, 0.240 mmol) in DMF (0.70 mL), and the mixture was stirred for 5 h at 25°C. DMF and excess $CH_3I$ were removed <u>in vacuo</u> to give 90b (0.106 g, 100%) as a pale yellow oil: IR (thin film) 3500, 3020, 1720, 1640, 1460, 1265, 1220, 1180, 1100, 1060, 822,

785, 740 cm$^{-1}$; $^{1}$H NMR (d$_6$-DMSO) δ = 1.11 (3H, t, J = 7 Hz), 2.40-3.03 (4H, m), 3.85 (3H, s), 3.97 (2H, q, J = 7 Hz), 4.33 (3H, s), 6.63-7.20 (3H, m), 7.86 (1H, d, J = 6 Hz), 8.80 (1H, d, J = 6 Hz), 8.96 (1H, s), 9.32 (1H, bs).

1,3-Dimethyl-4-(2-(2-ethoxy-2-oxoethoxy)-phenyl)-pyridinium iodide (54b). To a solution of 66 (0.2111 g, 1.14 mmol) in DMF (2.1 mL) was added CH$_3$I (0.28 mL, 4.56 mmol). The mixture was stirred for 11 h at 25°C. DMF and excess CH$_3$I were removed in vacuo, leaving the N-methylpyridinium salt 67 as a glass. Dry, finely-ground K$_2$CO$_3$ (0.24 g, 1.71 mmol) was added to a solution of the salt in DMF (3.7 mL). Finally, ethyl bromoacetate (0.19 mL, 1.71 mmol) was added, and the reaction mixture was stirred for 30 min at 25°C. Benzene (4 mL) was then added, and the mixture stirred 10 min longer. The salts were removed by filtration and washed well with DMF/benzene (1:1). The filtrate was evaporated to remove DMF and excess ethyl bromoacetate, and 54b was thus obtained as an amber oil. This sample was carried directly on to the preparation of 68b. IR (thin film) 3050, 1740, 1635, 1480, 1440, 1290, 1200, 1125, 1070, 1020, 765 cm$^{-1}$; $^{1}$H NMR (d$_6$-DMSO) δ = 1.19 (3H, t, J = 7 Hz), 2.34 (3H, s), 4.12 (2H, q, J = 7 Hz), 4.39 (3H, s), 4.85 (2H, s), 6.91-7.63 (4H, m), 7.94 (1H, d, J = 6 Hz), 8.89 (1H, d, J = 6 Hz), 9.06 (1H, s).

4-(2-(2-Ethoxy-2-oxoethoxy)-phenyl)-1-methyl-3-(3-oxo-3-ethoxy-propyl)-pyridinium iodide (91). To a solution of 90a (0.450 g, 1.09 mmol) in DMF (4.0 mL) was added dry, finely-powdered K$_2$CO$_3$ (0.23 g, 1.63 mmol). Ethyl bromoacetate (0.18 mL, 1.63 mmol) was then intro-duced to the red-orange mixture. After stirring for 1 h at 25°C,

benzene (5 mL) was added to the pale yellow reaction mixture. The solids were removed by filtration and washed with DMF/benzene (1:1). Solvents were removed in vacuo to give 91 (0.534 g, 98%) as an amber-colored oil which crystallized upon standing. An analytical sample was prepared by recrystallization from EtOH: mp 135.0-135.5°C; IR (KBr) 3550, 3010, 1750, 1730, 1640, 1480, 1470, 1460, 1290, 1065, 1045, 1010, 860, 757 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) $\delta$ = 1.13 (3H, t, J = 7 Hz), 1.19 (3H, t, J = 7 Hz), 2.40-3.06 (4H, m), 3.98 (2H, q, J = 7 Hz), 4.12 (2H, q, J = 7 Hz), 4.40 (3H, s), 4.83 (2H, s), 7.00-7.63 (4H, m), 7.93 (1H, d, J = 6 Hz), 8.89 (1H, d, J = 6 Hz), 9.07 (1H, s).

Anal. Calcd for C$_{21}$H$_{26}$NO$_5$I: C, 50.49; H, 5.26; N, 2.81. Found: C, 50.28; H, 4.96; N, 2.80.

4-(2-(2-Ethoxy-2-oxoethoxy)-3-methoxyphenyl)-1-methyl-3-(3-oxo-3-ethoxypropyl)-pyridinium iodide (35). To a solution of 90b (90.7 mg, 0.205 mmol) in DMF (0.90 mL) was added dry, finely-powdered K$_2$CO$_3$ (40.0 mg, 0.308 mmol). Ethyl bromoacetate (0.040 mL, 0.308 mmol) was then introduced to the deep red mixture. After stirring for 30 min at 25°C, benzene (1 mL) was added to the pale yellow reaction mixture. The solids were removed by filtration and washed with DMF/benzene (1:1). Solvents were removed in vacuo to give 35 (0.108 g, 100%) as a pale yellow oil: IR (thin film) 3600, 3070, 1730, 1640, 1580, 1465, 1255, 1205, 1050, 1015, 747 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) $\delta$ = 1.12 (6H, t, J = 7 Hz), 2.40-3.02 (4H, m), 3.84 (3H, s), 3.97 (2H, q, J = 7 Hz), 4.01 (2H, q, J = 7 Hz), 4.35 (3H, s), 4.57 (2H, s), 6.72-7.30 (3H, m), 7.91 (1H, d, J = 6 Hz), 8.84 (1H, d, J = 6 Hz), 9.03 (1H, s).

<u>1-Methyl-3-(3-oxo-3-ethoxypropyl)-4-(2-(cyanomethoxy)-phenyl)-</u>

<u>pyridinium iodide</u> (<u>97</u>). To a solution of <u>90a</u> (0.50 g, 1.20 mmol) in

DMF (5.0 mL) was added dry, finely-powdered $K_2CO_3$ (0.25 g, 1.80 mmol).

Chloroacetonitrile (0.12 mL, 1.80 mmol) was then introduced to the

orange mixture. After stirring for 10 h at 25°C, benzene (5 mL) was

added. The solids were removed by filtration and washed with DMF/

benzene (1:1). Solvents were removed <u>in</u> <u>vacuo</u> to give <u>97</u> (0.51 g,

93%) as a thick, dark oil: IR (thin film) 3050, 2200, 1730, 1645,

1610, 1580, 1485, 1440, 1215, 1050, 1025, 1010, 755 cm$^{-1}$; $^1$H NMR

($d_6$-DMSO) δ = 1.10 (3H, t, J = 7 Hz), 2.39-2.97 (4H, m), 3.96 (2H, q,

J = 7 Hz), 4.35 (3H, s), 5.18 (2H, s), 7.12-7.75 (4H, m), 7.93 (1H, d,

J = 6 Hz), 8.85 (1H, d, J = 6 Hz), 9.02 (1H, s).

<u>3-(3-(4-(2-(2-Ethoxy-2-oxoethoxy)-phenyl)-pyridyl))-propionic</u>

<u>acid, ethyl ester</u> (<u>100</u>). $K_2CO_3$ (0.0770 g, 0.561 mmol), dried and

finely-powdered, was added to a solution of <u>76</u> (0.1013 g, 0.374 mmol)

in DMF (1.0 mL). Ethyl bromoacetate (0.062 mL, 0.561 mmol) was added

and the mixture was stirred at 25°C for 25 min. Benzene (2 mL) and

hexane (1 mL) were added and salts were removed by filtration. Sol-

vents and excess ethyl bromoacetate were evaporated, leaving a yellow

glass which was Kugelrohr distilled (185°C, 0.1 mm Hg) to give <u>100</u>

(0.0840 g, 63%) as a yellow oil. An analytical sample was prepared by

chromatography on $SiO_2$ (20% acetone/CHCl$_3$): MS <u>m/z</u> 357 (M$^+$), 328,

312, 269, 256, 196, 182, 180(100); IR (thin film) 3020, 1730, 1605,

1470, 1440, 1365, 1280, 1195, 1070, 1025, 755 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ =

1.18 (3H, t, J = 7 Hz), 1.23 (3H, t, J = 7 Hz), 2.17-3.20 (4H, m),

4.08 (2H, q, J = 7 Hz), 4.23 (2H, q, J = 7 Hz), 4.60 (2H, s), 6.77-

7.40 (5H, m), 8.50 (1H, d, J = 6 Hz), 8.62 (1H. s).

Anal. Calcd for $C_{20}H_{23}NO_5$: Mol wt, 357.158. Found: Mol wt, 357.157.

Spiro[(2-(1-oxoethyl)-benzofuran)-3(2H),4'(1'H)-(1',3'-dimethyl-pyridine)] (68a). Finely ground, anhydrous $K_2CO_3$ (0.32 g, 2.32 mmol) was added to a solution of 67 (0.50 g, 1.53 mmol) in DMSO (3 mL). Chloroacetone (0.20 mL, 2.29 mmol) was then added and the red mixture stirred for 1 h at 25°C. The resulting amber-colored reaction mixture was poured into a rapidly stirring solution of benzene/hexane/4N NaOH (36 mL, 1:1:1). The aqueous layer was further extracted with benzene/hexane (1:1). The extracts were washed once with 4N NaOH/brine (1:1), dried ($Na_2SO_4$), and evaporated to give 68a (0.3192 g, 82%) as an off-white solid as a mixture of isomers: mp 96-101°C; MS m/z 255 ($M^+$), 240, 212, 182(100); IR (KBr) 1720, 1680, 1595, 1205 cm$^{-1}$; $^1$H NMR (CDCl$_3$) 60/40 mixture of anti/syn isomers; anti: δ = 1.53 (3H, s), 2.18 (3H, s), 2.91 (3H, s), 4.10 (1H, d, J = 8 Hz), 5.03 (1H, s), 5.87 (1H, dd, J = 8, 2 Hz), 5.90 (1H, m); syn: δ = 1.20 (3H, d, J = 1 Hz), 2.29 (3H, s), 2.94 (3H, s), 4.50 (1H, d, J = 8 Hz), 4.62 (1H, s), 5.68 (1H, m), 6.17 (1H, dd, J = 8, 2 Hz), 6.76-7.36 (total intensity 4H, m).

Anal. Calcd for $C_{16}H_{17}NO_2$: Mol wt, 255.126. Found: Mol wt, 255.127.

To a solution of 68a (0.25 g, 0.98 mmol) in THF (1.0 mL) was added 1M NaOEt/EtOH (1.0 mL). After stirring for 1 h at 25°C, the solution was worked up. $^1$H NMR showed no change in isomer ratio. Heating with ethoxide at 60°C also caused no change.

Spiro[(benzofuran-2-carboxylic acid)-3(2H),4'(1'H)-(1',3'-di-
methylpyridine)] ethyl ester (68b). To a solution of crude 54b
(derived from 1.14 mmol of phenol 66) in DMF (4.7 mL) was added 1.69M
NaOEt/EtOH (0.74 mL, 1.25 mmol). After stirring 5 min at 25°C, the
reaction mixture was added to a mixture of benzene/hexane/10% aq.
NaHCO₃ (37 mL, 2:1:2). The aqueous layer was extracted twice more
with benzene/hexane (2:1). The extracts were washed once with 10%
aq. NaHCO₃, once with 10% aq. NaHCO₃/brine (1:1), and dried (Na₂SO₄).
Solvent was evaporated to give 68b as a crude oil, which was flushed
through a column of Al₂O₃ (12 g, 5% acetone/CHCl₃). Pure 68b (0.2549
g, 78% from 66) was thus isolated as an amber-colored oil: MS m/z
285 (M⁺), 270, 212(100), 198, 185, 182; IR (thin film) 2950, 1740,
1675, 1610, 1590, 1465, 1450, 1365, 1270, 1195, 1060, 845, 754 cm⁻¹;
¹H NMR (CDCl₃) isomeric mixture δ = 1.25 and 1.28 (each, t, J = 7 Hz,
total intensity 3H), 1.49 (s, total intensity 3H), 2.91 and 2.92
(each, s, total intensity 3H), [4.08-4.42 (m) and 4.40 (d, J = 8 Hz),
total intensity 3H], 4.52 and 5.00 (each, s, total intensity 1H),
[5.67 (bs) and 5.81-5.96 (m) and 6.11 (dd, J = 8, 2 Hz), total
intensity 2H], 6.76-7.32 (m, total intensity 4H).

Anal. Calcd for C₁₇H₁₉NO₃: Mol wt, 285.136. Found: Mol wt,
285.137.

Spiro[(benzofuran-2-carboxylic acid)-3(2H),4'(1'H)-(1'-methyl-
3'-(3-oxo-3-ethoxypropyl)pyridine)] ethyl ester (92). To a solution
of 91 (0.3011 g, 0.6030 mmol) in DMF (3 mL) was added 1.69M NaOEt/
EtOH (0.39 mL, 0.661 mmol). The resulting solution was stirred at
25°C for 5 min, then poured into a mixture of benzene/10% aq. NaHCO₃/

hexane (25 mL, 2:2:1). The aqueous layer was extracted twice more
with benzene/hexane (2:1). The extracts were washed once with 10%
aq. NaHCO$_3$, once with 10% aq. NaHCO$_3$/brine (1:1), dried (Na$_2$SO$_4$), and
evaporated to give 92 (0.2191 g, crude). Product was purified by
flushing it through a column of neutral Al$_2$O$_3$ (10 g) with 5% acetone/
CHCl$_3$. Pure 92 (0.2073 g, 92%) was obtained as an amber oil: MS m/z
371 (M$^+$), 326, 298(100), 270, 215, 201, 196; IR (thin film) 3000,
1730, 1640, 1440, 1365, 1245, 1190, 1025, 753 cm$^{-1}$; $^1$H NMR (CDCl$_3$)
mixture of 2 isomers (54.5/45.5) $\delta$ = 1.10-1.34 (m, total intensity
6H, 4 overlapping triplets), 1.79-2.42 (m, total intensity 4H), 2.93
and 2.94 (each, s, total intensity 3H, rel. intensity 1:1.2), 3.92-
4.33 (m, 4 2H-quartets and a 1H-doublet), 4.43 (1H, d, J = 8 Hz)
[3.92-4.43, total intensity 5H], 4.53 and 4.99 (each, s, total
intensity 1H, rel. intensity 1:1.2), 5.73 (1H, bs), 5.81-5.96 (2H, m),
6.12 (1H, dd, J = 8, 2 Hz) [5.73-6.12, total intensity 2H], 6.79-7.56
(m, total intensity 4H).

Anal. Calcd for C$_{21}$H$_{25}$NO$_5$: Mol wt, 371.173. Found: Mol wt,
371.174.

Spiro[(benzofuran-7-methoxy-2-carboxylic acid)-3(2H),4'(1'H)-
(1'-methyl-3'-(3-oxo-3-ethoxypropyl)pyridine)] ethyl ester (36). To
a solution of 35 (0.0944 g, 0.178 mmol) in DMSO (0.94 mL) was added
1.69M NaOEt/EtOH (0.12 mL). After stirring 5 min at 25°C, the
reaction mixture was added to benzene/hexane/10% aq. NaHCO$_3$ (9 mL,
1:1:1). The aqueous layer was extracted twice more with benzene/
hexane (1:1). The extracts were washed once with 10% aq. NaHCO$_3$,
once with 10% aq. NaHCO$_3$/brine (1:1), dried (Na$_2$SO$_4$) and evaporated to

give 36 (0.0447 g, 63%) as an amber oil: MS m/z 401 (M$^+$), 328, 300 (100), 226, 210, 196, 182; IR (thin film) 2980, 1745, 1730, 1680, 1610, 1485, 1445, 1365, 1270, 1190, 1110, 1055, 1020, 840, 773, 732 cm$^{-1}$; $^1$H NMR (CDCl$_3$) 2 isomers: δ = 1.11-1.33 (m, total intensity 6H), 1.81-2.36 (m, total intensity 4H), 2.94 (s, total intensity 3H), 3.88 (s, total intensity 3H), 3.91-4.36 (9H, m) and 4.42 (1H, d, J = 8 Hz) [total intensity 3.91-4.42, 5H], 4.54 and 5.01 (each, s, total intensity 1H), 5.74 (1H, bs) and 5.80-5.94 (2H, m) and 6.10 (1H, dd, J = 8, 2 Hz) [total intensity 5.74-6.10, 2H], 6.67-7.02 (m, total intensity 3H).

Anal. Calcd for C$_{22}$H$_{27}$NO$_6$: Mol wt, 401.184. Found: Mol wt, 401.183.


Spiro[(2-cyanobenzofuran)-3(2H),4'(1'H)-(1'methyl-3'-(3-oxo-3-ethoxypropyl)pyridine)] (98). To a solution of 97 (0.1656 g, 0.3664 mmol) in DMSO (2.0 mL) was added 1.57M KOt-Bu/t-BuOH (0.26 mL, 0.40 mmol). The resulting solution was stirred at 25°C for 5 min, then poured into a mixture of benzene/hexane/10% aq. NaHCO$_3$ (15 mL, 1:1:1). The aqueous layer was extracted twice more with benzene/hexane (1:1). The extracts were washed once with 10% aq. NaHCO$_3$/brine (1:1), dried (Na$_2$SO$_4$), and evaporated to give 98 (0.0603 g, 51%) as a red-brown oil: MS m/z 324 (M$^+$), 295, 279, 268, 251, 237, 236, 223(100), 196, 194, 181; IR (thin film) 2250, 1730, 1680, 1600, 1455, 1365, 1210, 1175, 1030, 962, 753 cm$^{-1}$; $^1$H NMR (CDCl$_3$) mixture of 2 isomers, δ = 1.17 and 1.20 (each, t, J = 7 Hz, total intensity 3H), 1.82-2.43 (m, total intensity 4H), 2.99 (s, total intensity 3H), 4.04 and 4.07 (each, q, J = 7 Hz, total intensity 2H), 4.28 and 4.55 (each,

d, J = 8 Hz, total intensity 1H), 4.55 and 5.19 (each, s, total intensity 1H), 5.82 and 5.94 (each, total intensity 1H), 6.16 and 6.18 (each, dd, J = 8, 2 Hz, total intensity 1H), 6.75-7.47 (m, total intensity 4H).

Anal. Calcd for $C_{19}H_{20}N_2O_3$: Mol wt, 324.147.  Found:  Mol wt, 324.146.

3-Methyl-7-hydroxy-5,7a-dihydro-3H-benzofuro[3,2-e]isoquinoline-6-carboxylic acid, ethyl ester (93).  A solution of 1.69M NaOEt/EtOH (1.55 mL, 2.62 mmol) was evaporated in vacuo.  The residue was dissolved in DMF (2.0 mL) and added to a solution of 91 (0.2111 g, 0.423 mmol) in DMF (2.0 mL).  The reaction mixture was stirred at 25°C for 12 h, then poured into a mixture of benzene/hexane/10% aq. $NaHCO_3$ (30 mL, 2:1:2).  The aqueous layer was extracted three times further with benzene/hexane (12 mL, 2:1).  The extracts were washed once with 10% aq. $NaHCO_3$/brine (1:1), dried ($Na_2SO_4$), and evaporated to give 93 (0.0981 g, 72%) as an amber oil:  MS m/z 325 ($M^+$), 308, 296, 279, 252, 238, 224, 210, 197(100), 182, 169, 152; IR ($CHCl_3$) 2930, 2850, 1720, 1690, 1660, 1610, 1590, 1460, 1380, 1350, 1285, 1145, 1120, 950 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ = 1.24 (3H, t, J = 7 Hz), 2.74 (2H, s), 2.91 (3H, s), 4.18 (2H, q, J = 7 Hz), 4.46 (1H, d, J = 8 Hz), 4.74 (1H, s), 5.77 (1H, dd, J = 2, 8 Hz), 6.06 (1H, bs), 6.76-7.35 (4H, m), 11.94 (1H, s); resonance at δ = 11.94 exchanges with $D_2O$.

Anal. Calcd for $C_{19}H_{19}NO_4$: Mol wt, 325.131.  Found:  Mol wt, 325.132.

9-Methoxy-3-methyl-7-hydroxy-5,7a-dihydro-3H-benzofuro[3,2-e]-isoquinoline-6-carboxylic acid, ethyl ester (37).  A 1.69M NaOEt/EtOH

solution (5.16 mL, 8.73 mmol) was evaporated in vacuo. The residue was taken up in DMF (7.0 mL) and added to a solution of 35 (0.7446 g, 1.41 mmol) in DMF (7.0 mL). The resulting solution was stirred for 18 h at 25°C. The reaction mixture was then added to a mixture of benzene/hexane/10% aq. $NaHCO_3$ (100 mL, 2:1:2). The aqueous layer was extracted twice more with benzene/hexane (30 mL, 2:1). The extracts were washed once with 10% aq. $NaHCO_3$/brine (1:1), dried ($Na_2SO_4$), and evaporated to give 37 (0.3438 g, 69%) as an amber oil: MS m/z 355 ($M^+$), 338, 309, 298, 282, 227(100), 198; IR (thin film) 2970, 1720, 1680, 1650, 1620, 1485, 1440, 1270, 1205, 1030, 1015, 949, 937, 830, 732 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ = 1.26 (3H, t, J = 7 Hz), 2.70-3.02 (2H, m), 2.92 (3H, s), 3.85 (3H, s), 4.18 (2H, q, J = 7 Hz), 4.46 (1H, d, J = 8 Hz), 4.77 (1H, s), 5.79 (1H, dd, J = 8, 2 Hz), 6.03 (1H, bs), 6.64-6.99 (3H, m), 11.81 (1H, s, OH).

Anal. Calcd for $C_{20}H_{21}NO_5$: Mol wt, 355.142. Found: Mol wt, 355.144.

3-Methyl-7-amino-5,7a-dihydro-3H-benzofuro[3,2-e]isoquinoline-6-carboxylic acid, ethyl ester (99). A solution of 1.57M KOt-Bu/t-BuOH (0.59 mL, 0.93 mmol) was evaporated in vacuo. The residue was dissolved in DMF (0.7 mL) and added to a solution of 97 (67.7 mg, 0.150 mmol) in DMF (0.7 mL). The reaction mixture was stirred at 25°C for 16 h, then poured into a mixture of benzene/hexane/10% aq. $NaHCO_3$ (15 mL, 2:1:2). The aqueous layer was extracted twice with benzene/hexane (2:1). The extracts were washed once with 10% aq. $NaHCO_3$/brine (1:1), dried ($Na_2SO_4$), and evaporated to give 99 (5.40 mg, 11%) as a red-brown oil: MS m/z 324 ($M^+$, 100), 307, 295, 279, 251, 249,

231, 223, 197, 182; IR (thin film) 3550, 3400, 2980, 1670, 1620, 1480, 1245, 1205, 1090, 1060, 1015, 753 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.21 (3H, t, J = 7 Hz), 2.59-2.81 (2H, m), 2.89 (3H, s), 4.09 (2H, q, J = 7 Hz), 4.38 (1H, d, J = 8 Hz), 4.64 (1H, s), 5.76 (1H, dd, J = 8, 2 Hz), 6.05 (1H, bs), 6.13 (2H, bs), 6.70-7.44 (4H, m).

<u>Anal</u>. Calcd for C$_{19}$H$_{20}$N$_2$O$_3$: Mol wt, 324.147. Found: Mol wt, 324.148.

<u>3-Methyl-7-oxo-2,3,4,4a,5,6,7,7a-octahydro-1H-benzofuro[3,2-e]-isoquinoline-6-carboxylic acid, ethyl ester</u> (95a). <u>Procedure a</u>. A mixture of 93 (0.1216 g, 0.374 mmol) and PtO$_2$ (6.1 mg) in EtOH (20 mL) was shaken under 30 lbs of H$_2$ on a Parr hydrogenator for 21 h. Catalyst was removed by filtration and the filtrate evaporated to give 95a (0.1203 g, 98%) as an oil which solidified upon standing. The sample is a 12/88 mixture of cis/trans ring junction stereoisomers: MS m/z 329 (M$^+$, 100), 283, 282, 256, 255, 236, 200, 71, 70; IR (thin film) 3000, 1720, 1650, 1620, 1465, 1455, 1275, 1215, 1045, 1025, 1005, 974, 834, 807, 755, 748 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.24 (t, J = 7 Hz, total intensity 3H), 1.75-3.04 (m, total intensity 10H), 2.34 and 2.44 (each, s, total intensity 3H), 4.16 (q, J = 7 Hz, total intensity 2H), 4.76 and 4.96 (each, s, total intensity 1H; relative intensity 88/12), 6.77-7.58 (m, total intensity 4H).

<u>Anal</u>. Calcd for C$_{19}$H$_{23}$NO$_4$: Mol wt, 329.163. Found: Mol wt, 329.163.

<u>Procedure b</u>. A 1.69<u>M</u> NaOEt/EtOH solution (2.52 mL, 4.26 mmol) was evaporated <u>in vacuo</u>. The residue was taken up in DMF (2.5 mL) and added to a solution of 94 (0.2576 g, 0.687 mmol) in DMF (2.5 mL).

The resulting mixture was stirred for 5.5 h at 25°C, after which time it was added to a mixture of benzene/10% aq. $NaHCO_3$/hexane (40 mL, 2:2:1). The aqueous layer was extracted twice more with benzene/hexane (2:1). The extracts were washed once with 10% aq. $NaHCO_3$/brine (1:1), dried ($Na_2SO_4$), and evaporated to give 95a (0.1453 g, 64%) as an oil: MS and IR are identical to those of 95a obtained via Procedure a, above. $^1H$ NMR shows a mixture of cis/trans isomers, 71/29, respectively: ($CDCl_3$) $\delta$ = 1.25 (t, J = 7 Hz, total intensity 3H), 1.71-3.01 (m, total intensity 10H), 2.34 and 2.44 (each, s, total intensity 3H), 4.18 (q, J = 7 Hz, total intensity 2H), 4.76 and 4.95 (each, s, total intensity 1H; relative intensity 29/71), and 6.72-7.55 (m, total intensity 4H).

9-Methoxy-3-methyl-7-oxo-2,3,4,4a,5,6,7,7a-octahydro-1H-benzo-furo[3,2-e]isoquinoline-6-carboxylic acid, ethyl ester (95b). A mixture of 37 (0.0180 g, 0.051 mmol) and $PtO_2$ (3.0 mg) in EtOH (20 mL) was shaken under 30 lbs of $H_2$ in a Parr hydrogenator for 12 h. Catalyst was removed by filtration and the filtrate evaporated to give 95b (0.0182 g, 100%) as an oil: MS m/z 359 ($M^+$, 100), 313, 71, 70; IR (thin film) 2970, 1730, 1650, 1620, 1480, 1445, 1270, 1210, 1050, 827, 735 cm$^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ = 1.24 (t, J = 7 Hz, total intensity 3H), [1.85-3.07 (m) and 2.47 (s), total intensity 13H], 3.86 (s, total intensity 3H), 4.16 (q, J = 7 Hz, total intensity 2H), 4.83 and 4.99 (each, s, total intensity 1H, relative intensity 88/12), 6.72-7.17 (m, total intensity 3H).

Anal. Calcd for $C_{20}H_{25}NO_5$: Mol wt, 359.173. Found: Mol wt, 359.171.

3-Methyl-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinoline-

7(7aH)-one (96a,b). Trial 1.  A solution of 95a (0.0678 g, 0.206 mmol)

(prepared via Procedure a) in 6N HCl (2.0 mL) was refluxed for 3 h.

When cool, the reaction mixture was basified with 4N NaOH and

extracted with benzene.  The extracts were washed once with brine,

dried (Na$_2$SO$_4$), and evaporated to give 96 (0.0405 g, 76%) as a white

solid, a mixture of cis and trans ring junction stereoisomers (12/88,

96b:96a, respectively).  The trans isomer (96a) was isolated by re-

crystallization from benzene/hexane and an analytical sample was then

sublimed:  mp 187.5-188.3°C; IR (KBr) 2950, 2800, 1710, 1440, 978,

860, 825, 753, 740 cm$^{-1}$; MS m/z 257 (M$^+$, 100); $^1$H NMR (CDCl$_3$) δ =

1.43-2.99 (11H, m), 2.43 (3H, s), 4.37 (1H, s), 6.69-7.43 (4H, m).

Anal. Calcd for C$_{16}$H$_{19}$NO$_2$:  C, 74.66; H, 7.46; N, 5.45.  Found:

C, 74.39; H, 7.43; N, 5.30.

Trial 2.  As described above, 95a (0.0325 g, 0.099 mmol) (pre-

pared via Procedure b) was dissolved in 6N HCl (2.0 mL) and refluxed

for 4 h.  Upon workup, 96 (0.0170 g, 67%) was isolated as an oil, a

29/71 mixture of trans/cis ring junction stereoisomers.

An analytical sample of the cis isomer (96b) was obtained by

preparative TLC (5% MeOH/1% Et$_3$N/CHCl$_3$):  IR (thin film) 2990, 1725,

1470, 1450, 990, 875, 853, 832, 752 cm$^{-1}$; MS m/z 257 (M$^+$, 100); $^1$H

NMR (CDCl$_3$) δ = 2.35 (3H, s), 4.59 (1H, s).

Anal. Calcd for C$_{16}$H$_{19}$NO$_2$:  Mol wt, 257.142.  Found:  Mol wt,

257.143.

9-Methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]-

isoquinoline-7(7aH)-one (16a,b).  A solution of 95b (0.3234 g, 0.901

mmol) in 6N HCl (10.0 mL) was refluxed for 4 h. When cool, the reaction mixture was basified with 4N NaOH and extracted with benzene. The extracts were washed once with brine, dried (Na$_2$SO$_4$), and evaporated to give 16 (0.1751 g, 68%) as an oil which solidified upon standing. The product is an 88/12 mixture of trans/cis ring junction stereoisomers.

The trans isomer (16a) was isolated by recrystallization from benzene/hexane and an analytical sample was then sublimed: mp 139.5-140.0°C; MS m/z 287 (M$^+$, 100), 244, 164, 70; IR (KBr) 2950, 1720, 1475, 1265, 1045, 978, 860, 820, 775, 738 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.49-2.99 (11H, m), 2.43 (3H, s), 3.89 (3H, s), 4.42 (1H, s), 6.78-7.09 (3H, m).

Anal. Calcd for C$_{17}$H$_{21}$NO$_3$:  C, 71.03; H, 7.39; N, 4.88.  Found: C, 70.97; H, 7.70; N, 4.84.

An analytical sample of the cis isomer (16b) was obtained by preparative TLC (5% MeOH/CHCl$_3$): MS m/z 287 (M$^+$, 100), 244, 216, 174, 164, 115, IR (thin film) 3000, 1720, 1620, 1485, 1450, 1275, 985, 860, 827, 773, 731 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.67-2.94 (11H, m), 2.33 (3H, s), 3.89 (3H, s), 4.60 (1H, s), 6.62-7.00 (3H, m).

Anal. Calcd for C$_{17}$H$_{21}$NO$_3$:  Mol wt, 287.152.  Found:  Mol wt, 287.153.

Spiro[(benzofuran-2-carboxylic acid)-3(2H),4'-(1'-methyl-3'-(3-oxo-3-ethoxypropyl)piperidine)] ethyl ester (94).  A mixture of 92 (0.2643 g, 0.712 mmol) and PtO$_2$ (20 mg) in EtOH (20 mL) was shaken under 30 lbs of H$_2$ on a Parr hydrogenator for 10 h.  Catalyst was removed by filtration and washed with EtOH.  The filtrate was

evaporated to give 94 (0.2576 g, 96%) as an oil: MS m/z 375 (M$^+$, 100), 330, 302, 170; IR (thin film) 3000, 1730, 1600, 1470, 1455, 1370, 1270, 1190, 1035, 919, 859, 845, 755, 734 cm$^{-1}$; $^1$H NMR (CDCl$_3$) mixture of 4 isomers, δ = 4.63, 4.97, 5.04, and 5.09 (each, 1H, s).

_Anal_. Calcd for C$_{21}$H$_{29}$NO$_5$: Mol wt, 375.205. Found: Mol wt, 375.205.


3-Methyl-5,6-dihydro-3H-benzofuro[3,2-e]isoquinoline-7(7aH)-one (102). A solution of 93 (0.0655 g, 0.202 mmol) in 6N HCl (2.0 mL) was refluxed for 4 h. When cool, the reaction mixture was basified with 4N NaOH and extracted with benzene. The extracts were washed once with 4N NaOH/brine (1:1), dried (Na$_2$SO$_4$), and evaporated to give 102 (0.0363, 71%) as an oil: MS m/z 253 (M$^+$), 197(100), 196, 169, 91, 77; IR (thin film) 2970, 1720, 1680, 1610, 1600, 1460, 1215, 990, 834, 752 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 2.22-2.87 (4H, m), 2.97 (3H, s), 4.43 (1H, s), 4.50 (1H, d, J = 8 Hz), 5.87 (1H, dd, J = 8, 2 Hz), 6.02 (1H, bs), 6.82-7.17 (4H, m).

_Anal_. Calcd for C$_{16}$H$_{15}$NO$_2$: Mol wt, 253.110. Found: Mol wt, 253.110.


9-Methoxy-3-methyl-5,6-dihydro-3H-benzofuro[3,2-e]isoquinoline-7(7aH)-one (38). A solution of 37 (0.1112, 0.313 mmol) in 6N HCl (4.0 mL) was heated at reflux for 4 h. When cool, the solution was basified with 4N NaOH and extracted with benzene. The extracts were washed once with 4N NaOH/brine (1:1), dried (Na$_2$SO$_4$), and evaporated to give 38 (0.0534 g, 60%) as a greenish-yellow solid: mp 137-139°C dec; MS m/z 283 (M$^+$), 227, 226(100), 212, 210, 198, 169; IR (KBr) 2950, 1720, 1680, 1610, 1480, 1445, 1265, 1115, 1035, 950, 874, 862,

828, 774 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ = 2.10-2.77 (4H, m), 2.95 (3H, s), 3.89 (3H, s), 4.42 (1H, s), 4.45 (1H, d, J = 8 Hz), 5.86 (1H, dd, J = 8, 2 Hz), 5.92 (1H, s), 6.56-6.97 (3H, m).

<u>Anal</u>. Calcd for C$_{17}$H$_{17}$NO$_3$: Mol wt, 283.121. Found: Mol wt, 283.121.

<u>4,5-Benzo[6,7-c]pyrido-3-oxacyclononadienone, methiodide</u> (103). To a solution of 102 (0.2645 g, 1.05 mmol) in EtOH (2.0 mL) was added 47% HI (0.19 mL, 1.06 mmol). Solvents were removed <u>in vacuo</u> from the resulting yellow precipitate. This gave 103 as a crude residue (0.4227 g). Trituration of 0.3238 g of the residue with EtOH/H$_2$O gave 103 (0.1343 g, 42%) as a pale yellow solid: mp 196°C dec; IR (KBr) 1710, 1275, 1215, 1050, 837, 775 cm$^{-1}$; $^1$H NMR (d$_6$-DMSO) $\delta$ = 2.18-3.68 (4H, m), 4.37 (3H, s), 4.91 (2H, AB quartet), 7.14-7.80 (5H, m), 8.06 (1H, d, J = 7 Hz), 8.88 (1H, dd, J = 7, 2 Hz), 9.07 (1H, bs).

<u>2-(Ethoxymethoxy)anisole</u> (83a). To a mixture of NaH (50% oil dispersion, 5.28 g, 0.110 mol, hexane-washed) in DMF (60 mL) at 0°C was added quiacol (11.00 mL, 0.100 mol), dropwise. After the evolution of H$_2$ had ceased, chloromethyl ethyl ether (9.98 mL, 0.105 mol) was added dropwise at 25°C. The reaction mixture was stirred for 23 h at 25°C. MeOH (6 mL) was added to quench excess NaH, then followed by H$_2$O (120 mL) and benzene (60 mL). The aqueous layer was extracted further with benzene (2 x 40 mL). The extracts were washed with 5% NaOH (2 x 100 mL), H$_2$O (100 mL), brine (100 mL), dried (Na$_2$SO$_4$), and

evaporated to an oil. Kugelrohr distillation of the crude oil (1.0 mm Hg, 100°C) gave 83a (18.17 g, 99%) as a colorless oil: MS m/z 182 (M$^+$), 152, 137, 124, 109, 77, 59(100); IR (thin film) 3020, 1590, 1500, 1455, 1245, 1100, 1080, 1000, 745 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.20 (3H, t, J = 7 Hz), 3.76 (2H, q, J = 7 Hz), 3.83 (3H, s), 5.25 (2H, s), 6.74-7.27 (4H, m).

Anal. Calcd for C$_{10}$H$_{14}$O$_3$: Mol wt, 182.094. Found: Mol wt, 182.094.

Ethyl 3-(3-pyridyl)propanoate (89). A solution of 88 (28.53 g, 0.161 mol)$^{30}$ in EtOH (280 mL) over 9% Pd/C (2.85 g) was shaken on a Parr hydrogenator under 30 lbs of H$_2$ for 12 h. Catalyst was filtered off through Celite and washed with EtOH. The filtrate was evaporated to give 89 (28.23 g, 98%) as a colorless oil. Final purification was effected by spinning band distillation (0.05 mm Hg, 72-74°C): MS m/z 179 (M$^+$), 150, 135(100), 108, 106, 105, 92; IR (thin film) 3020, 1730, 1180, 1035, 1025, 804, 714 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 1.22 (3H, t, J = 7 Hz), 2.40-3.06 (4H, m), 4.09 (2H, q, J = 7 Hz), 7.14 (1H, dd, J = 5, 8 Hz), 7.48 (1H, bd, J = 8 Hz), 8.39 (1H, dd, J = 5, 2 Hz), 8.43 (1H, d, J = 2 Hz).

Anal. Calcd for C$_{10}$H$_{13}$NO$_2$: C, 66.99; H, 7.33; N, 7.82. Found: C, 66.70; H, 7.34; N, 7.87.

4-(2-Ethoxymethoxy-3-methoxyphenyl)pyridine (86a). An n-BuLi/ hexane solution (1.7M, 3.24 mL, 5.50 mmol) was added to a solution of 83a (0.50 g, 2.75 mmol) in ether (2.0 mL) at 0°C. The resulting slurry was stirred for 30 min at 18°C. In situ, the lithio salt was filtered, washed with hexane (5 x 1 mL), and transferred in THF (2.0

mL) to a suspension of CuI[31] (0.52 g, 2.75 mmol) in THF (6.0 mL) at -20°C.[39] The resulting solution was stirred for 30 min at -20°C, then cooled to -78°C and $BF_3$-etherate (0.34 mL, 2.75 mmol) was added. After 10 min at -78°C, the dark brown solution was transferred to the slurry of 84a formed upon addition of $ClCO_2Et$ (0.22 mL, 2.29 mmol) to pyridine (0.18 mL, 2.29 mmol) in THF (8.0 mL) at -78°C. The reaction mixture was allowed to warm to 18°C over a 2 h period, then stirred 2.5 h longer. Aq. $NaHCO_3$ (5%, 20 mL) was added, THF evaporated, and solids were removed by filtration. The filtrate was extracted with ether, and the extracts were washed once with brine, dried ($MgSO_4$), and evaporated to an amber oil. Filtration of the crude oil through $SiO_2$ (40 g) with 5% acetone/$CHCl_3$ gave 85a (0.76 g, 100%) as an air-sensitive, pale yellow oil: MS $m/z$ 333 ($M^+$), 332, 304, 290, 274, 168, 161, 152, 91, 80, 59(100); ^{1}H NMR ($CDCl_3$) $\delta$ = 1.23 (3H, t, J = 7 Hz), 1.30 (3H, t, J = 7 Hz), 3.80 (2H, q, J = 7 Hz), 3.82 (3H, s), 4.26 (2H, q, J = 7 Hz), 4.67-4.79 (1H, m), 4.85-5.07 (2H, m), 5.15 (2H, s), 6.37-7.17 (5H, m).

To a solution of 85a (0.1045 g, 0.301 mmol) in benzene (1.0 mL) was added a solution of o-chloranil (0.0740 g, 0.301 mmol) in benzene (1.0 mL). After stirring for 2 h at 20°C, additional benzene was added and the solution washed with 10% aq. $NaHSO_3$, brine, aq. $NaHSO_3$, twice with 0.1N NaOH and brine. It was dried ($Na_2SO_4$) and evaporated to give 86a (0.0584 g, 75%) as an oil. An analytical sample was obtained by chromatography on $SiO_2$ (5% acetone/chloroform) as an amber oil which solidified upon standing: mp 67-70°C; MS $m/z$ 259 ($M^+$), 201, 200, 186, 185, 59(100); IR (KBr) 3000, 1590, 1465, 1250, 1105, 1070, 1025, 945, 784 $cm^{-1}$; ^{1}H NMR ($CDCl_3$) $\delta$ = 0.88 (3H, t, J = 7 Hz), 3.22

(2H, q, J = 7 Hz), 3.88 (3H, s), 4.93 (2H, s), 6.88-7.19 (3H, m), 7.45 (2H, bd, J = 5 Hz), 8.35-8.85 (2H, br).

Anal. Calcd for $C_{15}H_{17}NO_3$: Mol wt, 259.121. Found: Mol wt, 259.119.

1,4-Dihydro-4-(2-ethoxymethoxy-3-methoxyphenyl)-3-(3-ethoxy-3-oxopropenyl)-pyridine-1-carboxylic acid, ethyl ester (85c). An n-BuLi/hexane solution (1.6M, 3.44 mL, 5.50 mmol) was added to a solution of 83a (0.50 g, 2.75 mmol) in ether (2.5 mL) at 0.°C. The resulting slurry was stirred for 30 min at 18°C. The lithio salt was filtered in situ, washed with hexane (4 x 1 mL), and transferred in THF (3.0 mL) to a suspension of CuI[31] (0.52 g, 2.75 mmol) in THF (5.0 mL) at -20°C.[39] The resulting solution was stirred for 30 min at -20°C, cooled to -78°C, and transferred to the slurry of 84c formed upon addition of $ClCO_2Et$ (0.22 mL, 2.29 mmol) to 88[30] (0.41 g, 2.29 mmol) in THF (8.0 mL) at -78°C. The reaction mixture was warmed to -20°C and stirred for 2 h. The solution was added to a mixture of benzene/hexane/10% aq. $NaHCO_3$/brine (100 mL, 2:1:1:1). Solids were filtered off and the aqueous layer extracted further with benzene/hexane (2:1). The extracts were washed with brine, dried ($Na_2SO_4$), and evaporated to an amber oil which crystallized upon standing. Chromatography on $SiO_2$ (35 g) with 5% acetone/$CHCl_3$ removed soluble Cu salts and gave a pale yellow oil which crystallized upon standing. Recrystallization from benzene/hexane gave white crystals of 85c (0.88 g, 89%): mp 111.5-112.0°C; MS m/z 431 ($M^+$), 430, 371(100), 299, 282, 281; IR (KBr) 3020, 1720, 1670, 1610, 1465, 1390, 1370, 1335, 1320, 1285, 1270, 1200, 1155, 1065, 1015, 955 $cm^{-1}$; ^{1}H NMR

(CDCl$_3$) δ = 1.21 (3H, t, J = 7 Hz), 1.26 (3H, t, J = 7 Hz), 1.35 (3H, t, J = 7 Hz), 3.18-4.25 (4H, m), 3.83 (3H, s), 4.31 (2H, q, J = 7 Hz), 4.89 (1H, bd, J = 5 Hz), 5.11-5.34 [5.16 (1H, d, J = 6 Hz), 5.25 (1H, d, J = 6 Hz), overlapping 1H, m], 5.65 (1H, d, J = 16 Hz), 6.55-7.07 (4H, m), 7.24 (1H, d, J = 16 Hz), 7.43 (1H, bs).

Anal. Calcd for C$_{23}$H$_{29}$NO$_7$: C, 64.00; H, 6.79; N, 3.25. Found: C, 63.82; H, 6.57; N, 3.17.

Ethyl 3-(3-(4-(2-ethoxymethoxy-3-methoxyphenyl)pyridyl))pro-penoate (86c). o-Chloranil (0.58 g, 2.35 mmol) was added to a solution of 85c (0.5066 g, 1.18 mmol) in benzene/toluene (5.0 mL, 1:1) at 0°C. After 2 h at 0°C, the reaction mixture was added to excess aq. NaHSO$_3$ and benzene. The organic layer was washed with 0.5N NaOH (3 x) and brine, dried (Na$_2$SO$_4$), and evaporated to a dark oil. To remove remaining quinone derivatives, the crude oil was taken up in EtOH (4.0 mL) and treated with NaOEt/EtOH (1.69M, 0.70 mL, 1.18 mmol). After 10 min, the solution was added to a mixture of benzene/0.5N NaOH (40 mL, 1:1). The benzene layer was washed further with 0.5N NaOH (2 x 20 mL), and the aqueous layers back extracted with benzene (20 mL). The combined benzene solutions were washed once with brine, dried (Na$_2$SO$_4$), and evaporated to give 86c (0.3810 g) as a dark oil which crystallized upon standing. Traces of polar, highly-colored impurities were removed by filtration through SiO$_2$ (15 g) with 20% acetone/CHCl$_3$ and gave 86c (0.3381 g, 81%). An analytical sample was prepared by recrystallization from EtOH to give white crystals: mp 91.0-91.2°C; MS m/z 357 (M$^+$), 328, 59(100); IR (KBr) 3020, 1710, 1580, 1460, 1255, 1105, 1040, 948, 798 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ = 0.86

(3H, t, J = 7 Hz), 1.27 (3H, t, J = 7 Hz), 3.04 (2H, q, J = 7 Hz), 3.89 (3H, s), 4.18 (2H, q, J = 7 Hz), 4.88 (2H, s), 6.38 (1H, d, J = 16 Hz), 6.60-7.34 (4H, m), 7.53 (1H, d, J = 16 Hz), 8.54 (1H, bd, J = 5 Hz), 8.85 (1H, bs).

<u>Anal</u>. Calcd for $C_{20}H_{23}NO_5$: C, 67.19; H, 6.50; N, 3.92. Found: C, 67.08; H, 6.40; N, 3.91.

<u>Ethyl 3-(3-(4-(2-ethoxymethoxy-3-methoxyphenyl)pyridyl))pro</u>-<u>panoate</u> (86b). <u>Procedure a</u>. An <u>n</u>-BuLi/hexane solution (1.7<u>M</u>, 6.47 mL, 11.0 mmol) was added to a solution of 83a (1.00 g, 5.50 mmol) in ether (4.0 mL) at 0°C. The resulting slurry was stirred for 30 min at 18°C. The lithio salt was filtered <u>in situ</u>, washed with hexane (4 x 5 mL), and transferred in THF (4.0 mL) to a suspension of CuI[31] (1.05 g, 5.50 mmol) in THF (12.0 mL) at -20°C.[39] The resulting solution was stirred for 30 min at -20°C, cooled to -78°C, and $BF_3$·etherate (0.68 mL, 5.50 mmol) was added. After 10 min at -78°C, the black solution was transferred to the slurry of 84b formed upon addition of $ClCO_2Et$ (0.44 mL, 4.58 mmol) to 89 (0.82 g, 4.58 mmol) in THF (16.0 mL) at -78°C. The reaction mixture was allowed to warm to 18°C over 1 h, then stirred 8 h longer. Ether and 5% aq. $NaHCO_3$ (80 mL, 1:1) were added, solids were filtered off, and ether and THF were evaporated. The resulting aqueous solution was extracted with ether. The extracts were washed with brine, dried ($Na_2SO_4$), and evaporated to give crude 85b as an amber oil. Chromatography on $SiO_2$ (75 g) with 5% acetone/ $CHCl_3$ to remove remaining 89 and soluble Cu salts gave 85b (2.08 g) as a pale yellow oil which was carried on directly to the next step without further purification.

p-Chloranil (1.30 g, 5.29 mmol) was added to a solution of 85b in benzene (20.0 mL), and the mixture stirred for 4 h at 18°C. Excess aq. $NaHSO_3$ was added, and the resulting benzene layer was washed with 0.1N NaOH (2 x) and brine, dried ($Na_2SO_4$), and evaporated to a dark oil (2.05 g). Chromatography on $SiO_2$ (75 g), first with 5% acetone/ $CHCl_3$ to remove high $R_f$ impurities, then with 20% acetone/$CHCl_3$ gave 86b (0.29 g, 18%) as a pale yellow oil: MS m/z 359 ($M^+$), 342, 330, 314, 286, 271, 212, 59(100); IR (thin film) 3020, 1730, 1580, 1465, 1255, 1110, 1070, 1030, 955, 791 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ =0.90 (3H, t, J = 7 Hz), 1.18 (3H, t, J = 7 Hz), 2.24-3.22 (4H, m), 3.88 (3H, s), 4.03 (4H, q, J = 7 Hz), 4.87 (2H, s), 6.63-7.32 (4H, m), 8.47 (2H, bs).

Anal. Calcd for $C_{20}H_{25}NO_5$: Mol wt, 359.173. Found: Mol wt, 359.171.

Procedure b. From 86c. A solution of 86c (0.3381 g, 0.947 mmol) in EtOH (20 mL) over 9% Pd/C (34 mg) was shaken on a Parr hydrogenator under 30 lbs of $H_2$ for 12 h. Catalyst was filtered off through Celite and washed with EtOH. The filtrate was evaporated to give 86b (0.3262 g, 96%).

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concentrated, neutralized with 10% aq. $Na_2CO_3$ and extracted with ether. Ester 88 (25.00 g, 94%) was obtained as a colorless oil upon Kugelrohr distillation (0.5 mm Hg, 90°C; lit.[30b]: 14 mm Hg, 156-158°C). (b) L. Panizzon, Helv. Chim. Acta, 24, 24E (1941). (c) H. K. Hall, Jr., J. Am. Chem. Soc., 82, 1209 (1960).

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