AN ABSTRACT OF THE THESIS OF

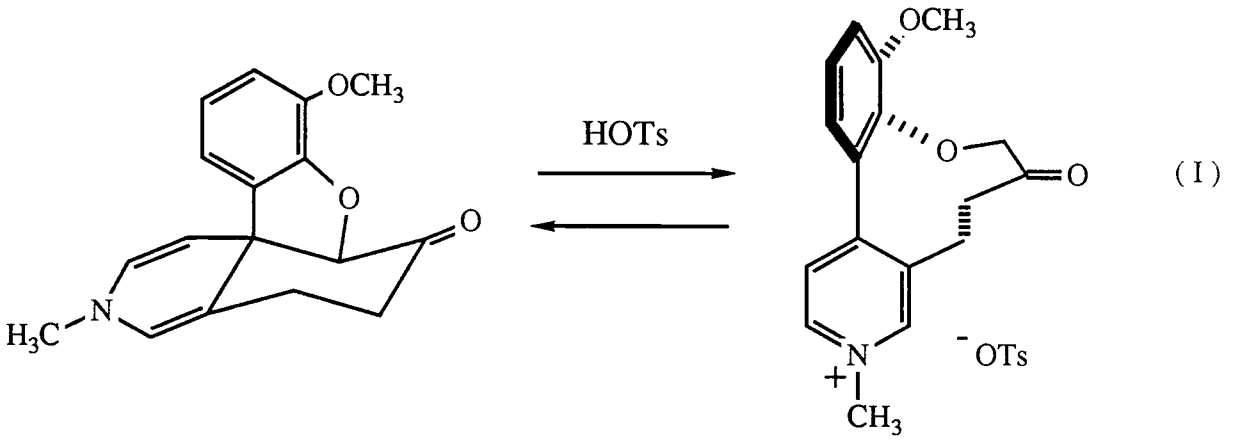
Mark T. Runyan for the degree of Master of Science in Chemistry presented on September 4, 1986

Title: A Stereochemically Controlled Approach to the Morphine Alkaloids: Racemization of 8,9-Benzo-4,5-dihydro-6,7-pyrido[4,3-d]oxanin-3(2H)-ones

Abstract approved: Redacted for Privacy

Dwight D. Weller

A method for the control of absolute stereochemistry in morphine syntheses has been demonstrated by the resolution and efficient racemization of the advanced morphine precursor, 9-methoxy-3-methyl-5,6-dihydro-3H-benzofuro[3,2-e]isoquinoline-7(7aH)-one, I. This was accomplished by the facile coversion of optically resolved I to its ring opened form, 5,6,7,8-tetrahydro-10-methoxy-3-methyl-7-oxo[1]benzoxonino[6,7-c]pyridinium tosylate, II, (Equation I). Racemization via biaryl rotation in the oxaninone II was found to be very rapid. A detailed analysis of the biaryl rotation in II was completed by a dynamic NMR experiment. From this experiment, $\Delta G^{\ddagger}$ for the biaryl rotation was calculated to be 15.8 Kcal/mol.



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A Stereochemically Controlled Approach to the Morphine Alkaloids: Racemization of 8,9-Benzo-4,5-dihydro-6,7-pyrido[4,3-d]oxanin-3(2H)-ones

by

Mark Talbott Runyan

A THESIS

submitted to

Oregon State University

in partial fulfillment of
the requirements for the
degree of

Master of Science

Completed September 4, 1986

Commencement June 1987

APPROVED:

Redacted for Privacy

Professor of Chemistry in charge of major

Redacted for Privacy

Chairman of the Department of Chemistry

Redacted for Privacy

Dean of Graduate School

Date thesis is presented September 4, 1986

Typed by Christine P. Nathman for Mark T. Runyan

ACKNOWLEDGEMENTS

I would like to thank Dr. Dwight D. Weller for his helpful guidance and enthusiasm. Rodger Kohnert is acknowledged for his assistance, patience, and excellent instruction in operating the Brüker AM-400 NMR. I would also like to thank professors James H. Krueger, Peter K. Freeman, Rod A. Badger, and Parinya Theramongkol for their sound advice and encouragement. And a special thanks to all my friends whom I shared time with both in and out of lab, especially the spirited members of our group: Fred, Jeff, Ben, Jong Hwan, Dan, Doreen, and Lisa. Most importantly, I wish to thank my family for their never failing love and support.

The financial support provided by the National Institute on Drug Abuse is also acknowledged.

To Joan :

who through her love and friendship,
contributed enormously to my well-being
and happiness during these last four years.

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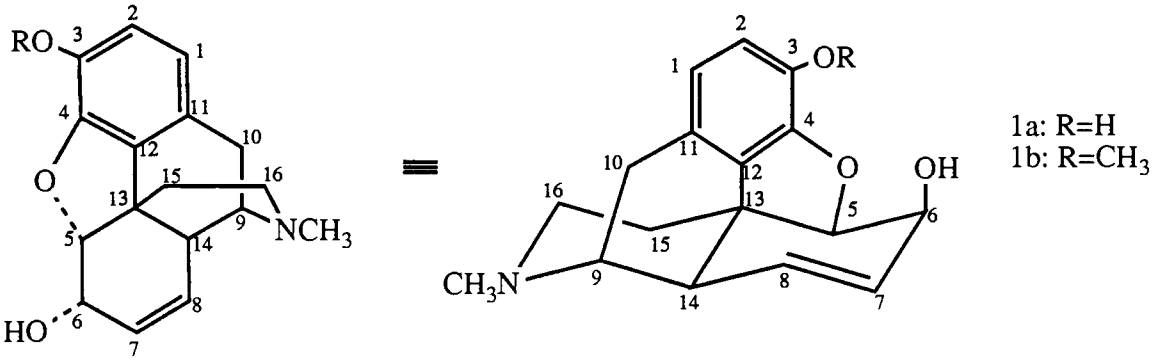
A Stereochemically Controlled Approach to the Morphine Alkaloids: Racemization of 8,9-Benzo-4,5-dihydro-6,7-pyrido[4,3-d]oxanin-3(2H)-ones

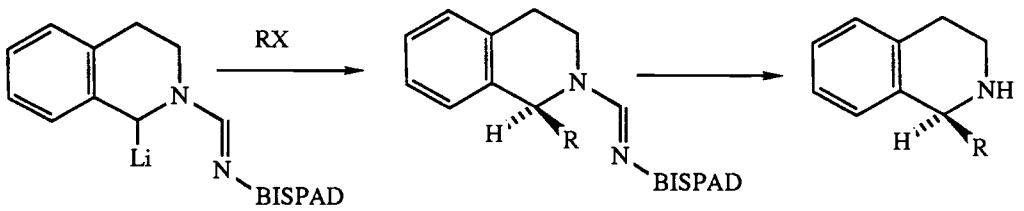
INTRODUCTION

The synthesis of morphine alkaloids continues to be of prime importance due to the valuable analgesic properties of these materials coupled with the lack of a natural domestic supply.[1] Perhaps more importantly, synthetic efforts may lead to analogs or partial structures that possess more desirable properties such as lower addiction potential and fewer side effects. Several syntheses have recently proven successful in preparing morphine (1a) and codeine (1b).[2]



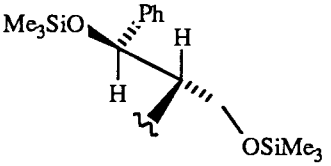
Central to the development of an efficient synthesis of morphine-related analgesics is the control of absolute stereochemistry. The various methods developed for an enantioselective synthesis include 1) asymmetric induction 2) structural elaboration of an available optically pure precursor, and 3) resolution. The latter provides efficiency only if the unwanted enantiomer can be recycled. The literature provides examples of each of these approaches.

Meyers has recently developed a method to introduce a C-C bond adjacent to nitrogen with high stereoselectivity. The procedure involves the formation and alkylation of carbanions derived from chiral formamidines. Diastereoselectivity has been found to be 96-99%. This transformation would provide access to many alkaloids in enantiomeric form as demonstrated by the preparation of (S)-1-alkyltetrahydroisoquinolines (Equation 1).[3] Recently Meyers developed a route to the (+)-morphinans utilizing this methodology (Scheme 1).[4] In this scheme, the N,N-dimethylformamidine of valinol tert-butyl ether, 2 is condensed with 1,2,3,4,5,6,7,8-octahydroisoquinoline to give the valineformamidine derivative 3. Alkylation was acheived by metalation with n-butyllithium followed by treatment with p-methoxybenzyl chloride to give 4. Hydrazinolysis then removed the chiral auxiliary

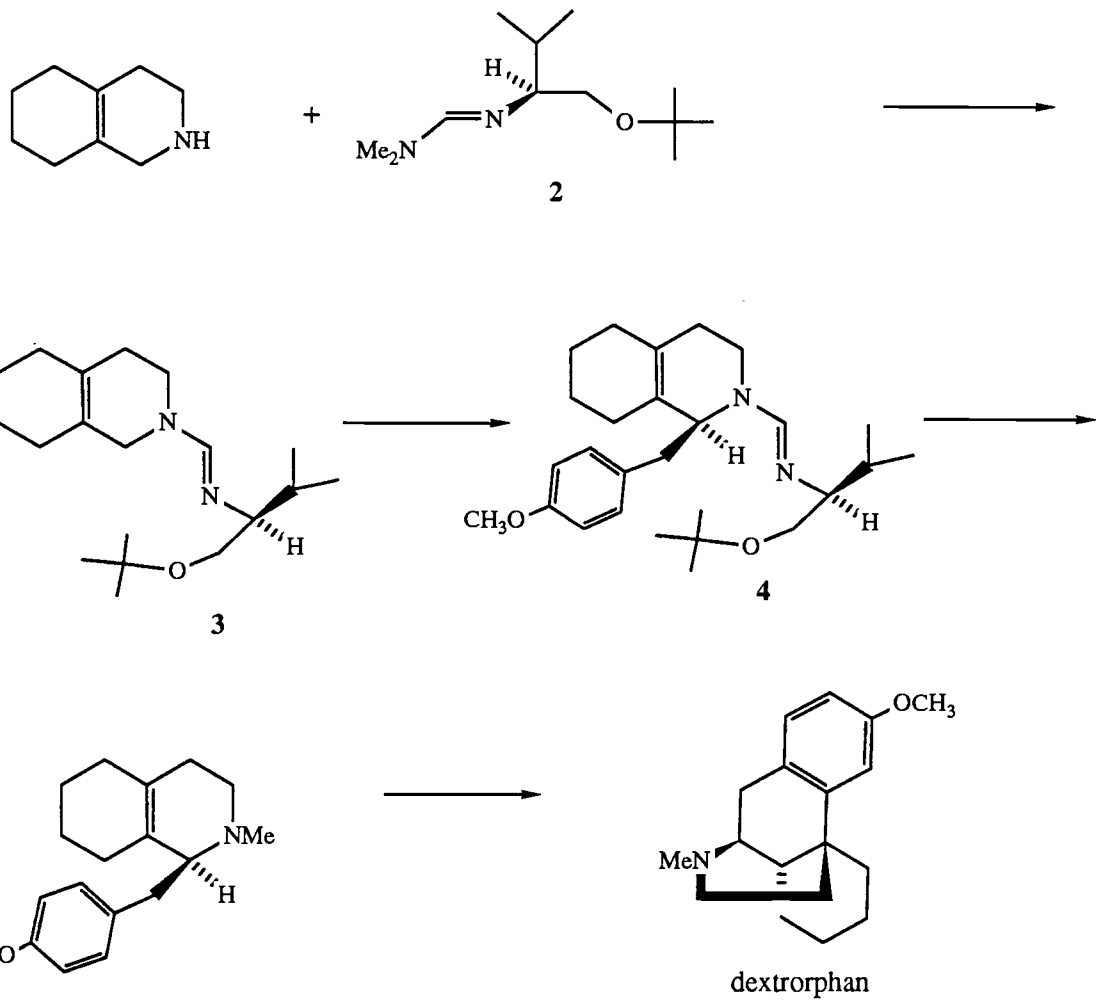


(1)

(S,S(+)-BISPAD)=



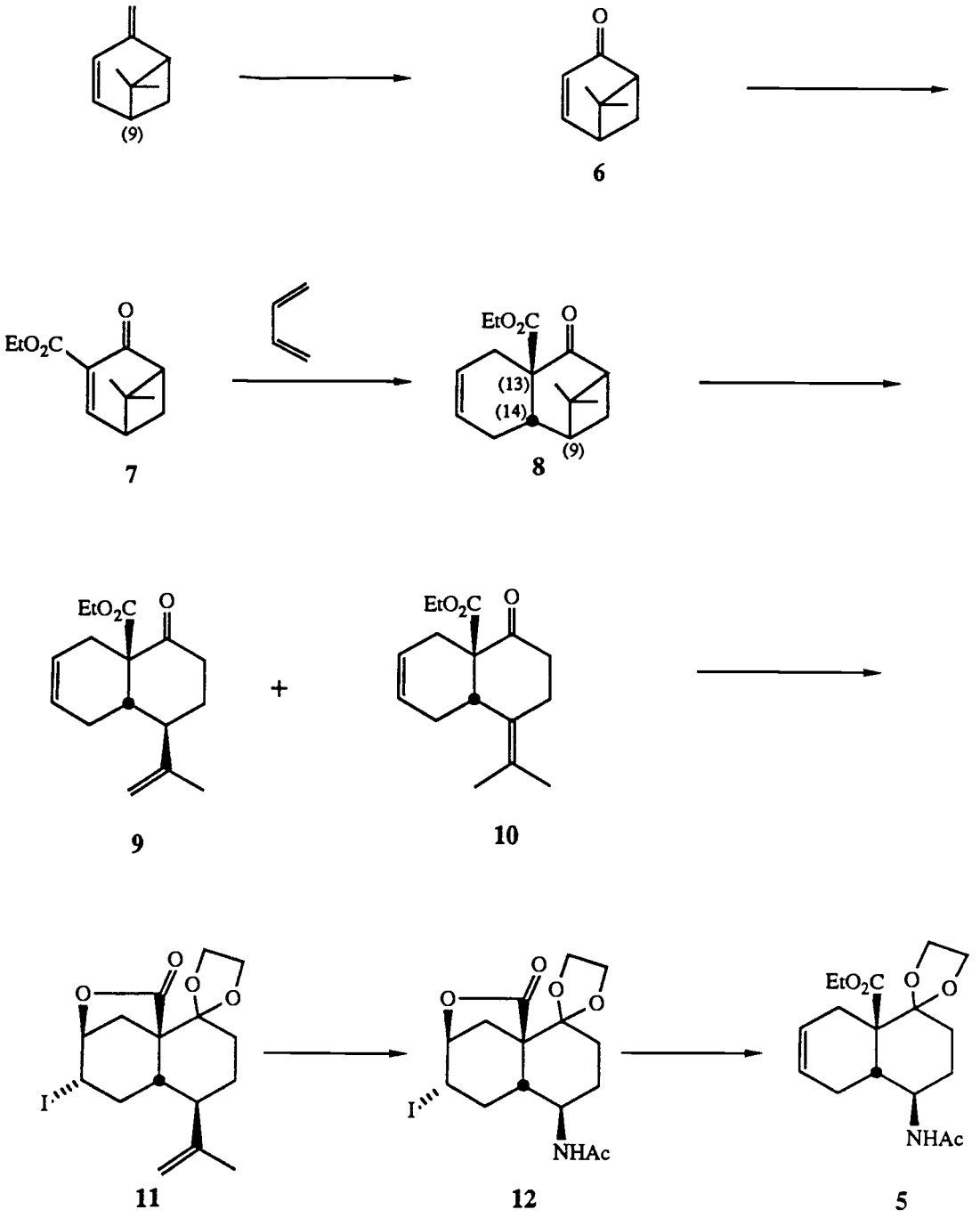
Scheme 1



to give a 2-benzyloctahydroisoquinoline which was N-methylated and transformed to the morphinan, dextrorphan, by the Grewe morphinan cyclization.[5]

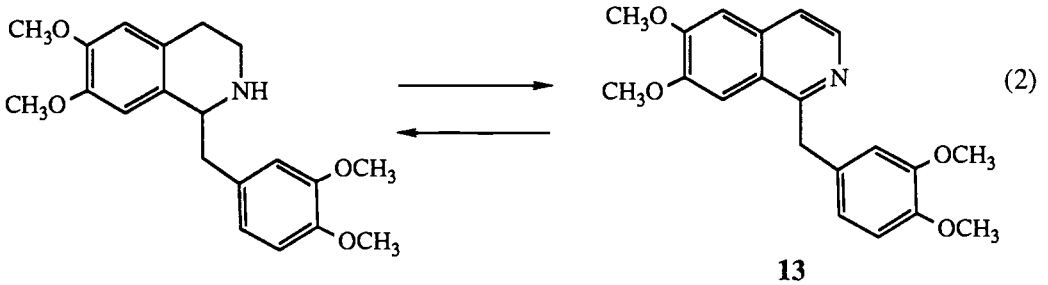
Boger has recently proposed to synthesize morphine starting with readily available natural materials.[6] His plan involved the production of cis-Δ^6-1-octalones, 5, starting from (1S,5S)-(-)-β-pinene, which provided the correct absolute stereochemistry corresponding to C-9 of morphine. The gem-dimethyl-2,4-methano bridge in pinene served to direct a Diels-Alder addition that stereospecifically introduced two more asymmetric centers corresponding to C-13 and C-14 of morphine. The sequence was carried out as depicted in Scheme 2. (-)-β-Pinene was first transformed to (1R,5S)-(+)-nopinone 6 by ozonolysis. Nopinone was then converted to the enone 7 by sequential treatment with sodium hydride and diethyl carbonate, phenylselenenyl bromide, and hydrogen peroxide. Diels-Alder reaction of enone 7 with 1,3-butadiene afforded (2R,4S,9R,10S)-(+)-3,3-dimethyl-9-(ethoxycarbonyl)-2,4-methano-cis-Δ^6-1-octalone 8. The gem-dimethyl-2,4-methano bridge was then cleaved with some difficulty by cyclobutane ring opening followed by elimination to form a mixture of the isopropenyl derivative 9 (60%) and the unwanted isopropylidene derivative 10 (30%). The two double bonds in 9 were differentiated by the conversion to the iodo

Scheme 2


(9)
O
6
EtO2C
O
7
EtO2C
O
(13)
(14)
(9)
8
EtO2C
O
9
+
EtO2C
O
10
O
O
O
O
I
11
O
O
O
O
I
NHAc
12
EtO2C
O
O
NHAc
5

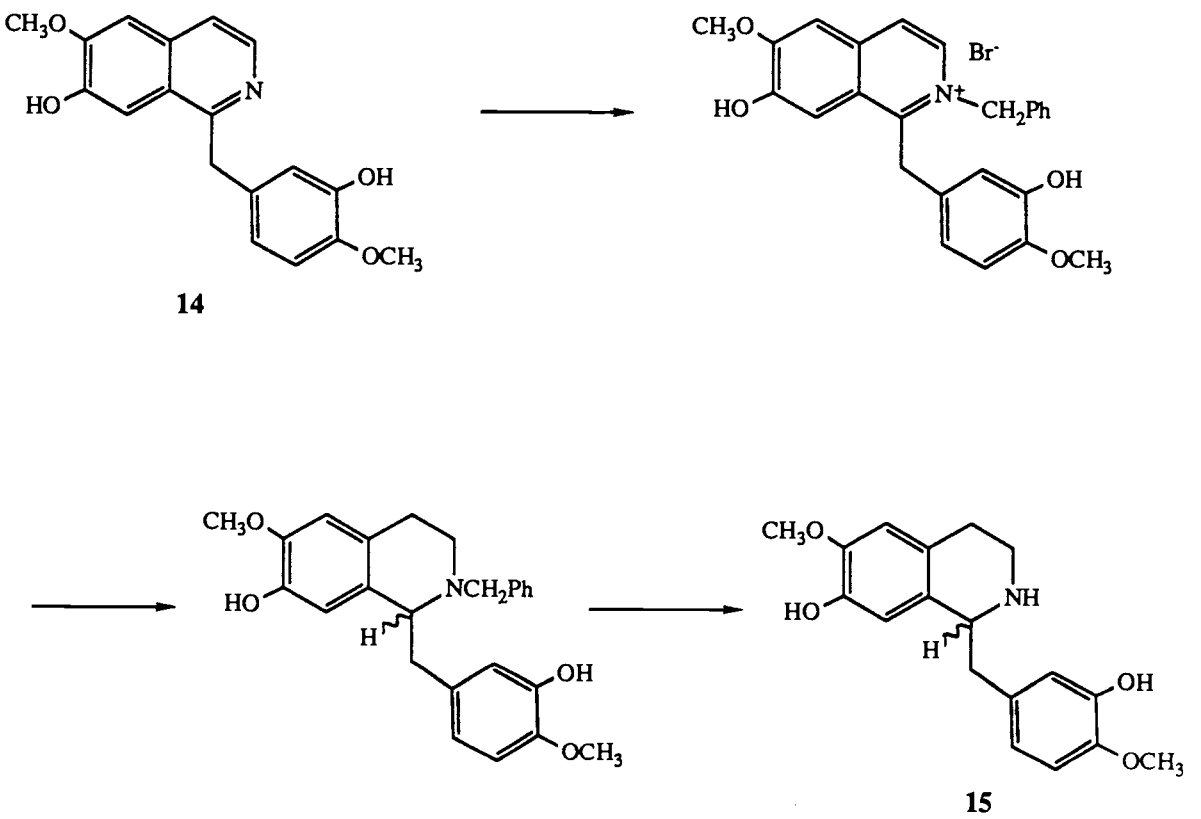
lactone 11. Completion of the preparation of 5 requried conversion of the isopropenyl group to an amine functionality and olefin/ester regeneration from the iodo lactone. Nitrogen functionality was incorporatated by ozonolysis, treatment with hydroxylamine hydrochloride to form the oxime, and Beckman rearrangement to give amide 12. Finally, treatment with zinc dust in hot ethanol and esterification with diazomethane gave 5. Although 5 possesses three of the required stereocenters, it only has two of the five rings required of morphine.

Buchs and Brossi have developed an efficient resolution of 1,2,3,4-tetrahydroisoquinolines, key intermediates in the total synthesis of natural opium alkaloids.[7] Their scheme involves recycling of the unwanted enantiomer to the racemate to increase efficiency. Recycling is effected by racemization of the unwanted enantiomer by aromatization and subsequent reduction (Equation 2). Although the aromatization reaction worked well for most reticuline analogs it failed in the case of the 3-deoxymorphine



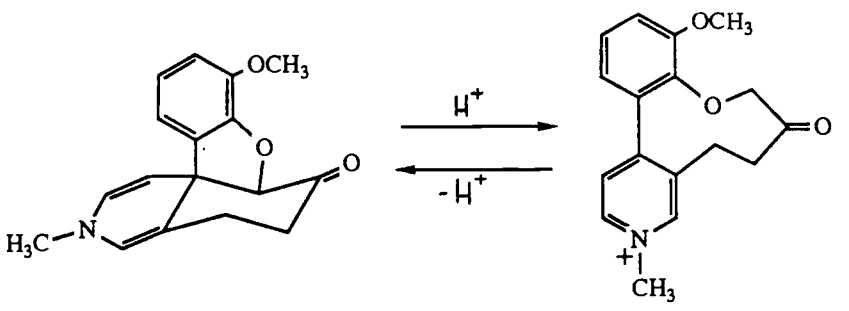
13 (2)

Scheme 3

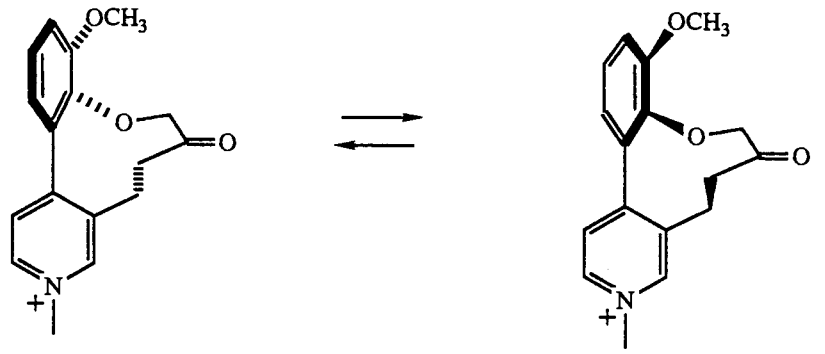


series. Of more concern was the reduction. The method of choice, catalytic hydrogenation, worked well for papaverine, 13, but failed for several other important analogs. Such was the case for the diphenol, 14, in which reduction was indirectly accomplished by formation of the N-benzylisoquinolinium bromide which was reduced with sodium borohydride and then N-debenzylated to afford racemic 15 in 55% overall yeild (Scheme 3).

During our synthetic studies in the morphine field we have developed the use of the intramolecular addition of enolates to pyridinium ions as a way of constructing advanced morphine precursors, such as the key intermediate 5,6-dihydro-3H-benzofuro[3,2-e]isoquinoline-7(7aH)-one, 16, which contains the important quaternary carbon of the morphine system.[8] Significantly the addition can be reversed upon treatment with acid. Thus 16 is expected to ring open to the oxaninone 17 (Equation 3). Importantly 17 can racemize by rotation about the biaryl axis (Equation 4). Treatment of 17 with base would readily yield 16.



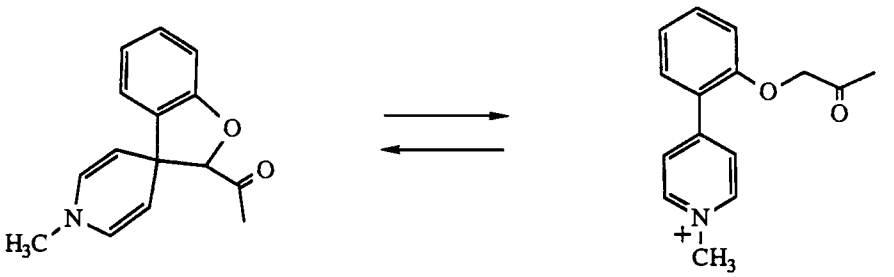
16 17 (3)



(4)

Thus following resolution of 16 or 17, the correct isomer can be converted to morphine and the incorrect enantiomer can be effectively recycled to the racemic mixture.

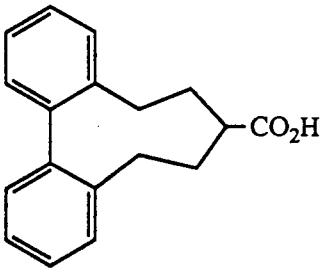
In part, precedent for this approach is based on earlier studies[8b] whereby treatment of the spirocyclic dihydropyridine 18 (initially formed by intramolecular enolate addition to the 4-position of the corresponding pyridinium salt) with one equivalent of acetic acid in methanol resulted in the reversal of the initial addition to give the pyridinium salt, 19. Treatment of the salt with 4N NaOH and benzene then returned the spirocyclic dihydropyridine in quantitative yield (Equation 5).



(5)

18 19

In considering the feasibility of the racemization of 17, as depicted in Equation 4, barriers to rotation of structurally related biphenyls were compared. The closest nine-membered bridging analog found in the literature was the dibenzocyclononane carboxylic acid 20.[9] This biphenyl has a barrier to rotation of 24 Kcal/mol from which its (-)antipode racemizes with a half-life of 24 hours at room temperature. Heating under reflux in benzene (80°C) for one hour resulted in complete racemization.

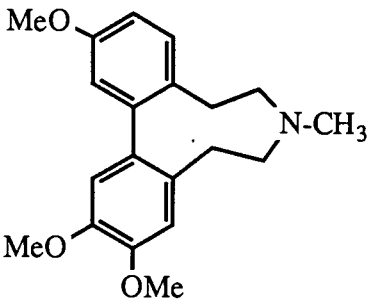
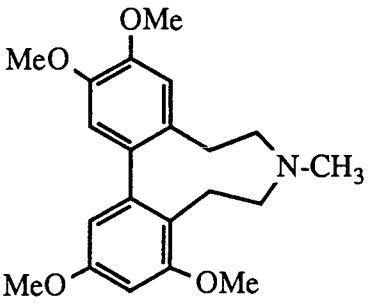
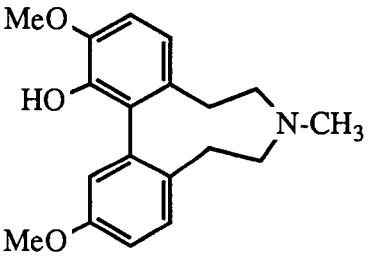
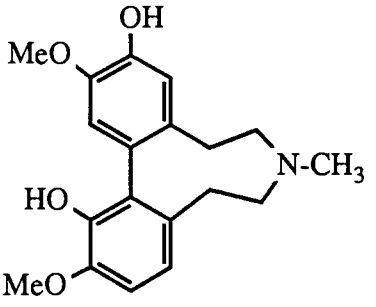


20

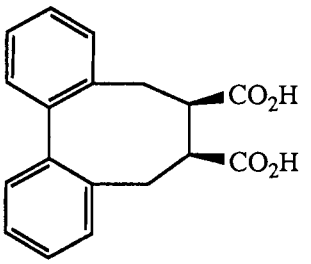
Other nine-member bridging biphenyls include the Dibenzazonine Alkaloids. Only the dibenzazonines which have additional ortho substituents have yet been isolated optically active (see Table 1). This is most likely attributable to a facile rate of rotation and hence racemization.

Since most of the steric barrier to rotation in dibenzocyclononane 20 lies in the interaction of opposing hydrogens on methylene carbons ortho to their respective benzene rings,[9] we expect a further decrease in the

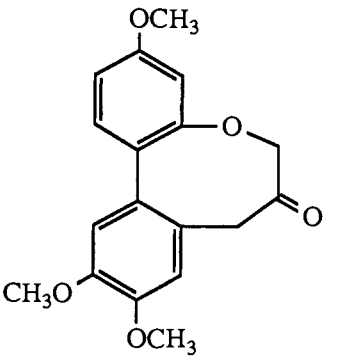
Table I. Dibenzazonines

Structure	Optical activity $[\alpha]_D^{20}$	Reference
	0	10
	0	11
	+63.7°	12
	-50°	13

activation energy due to the substitution of an oxygen for a methylene group. This is further supported by comparing the corresponding eight membered bridged biphenyls 21 and 22. It is reported that optically active 21 racemizes with a free energy of activation of 23.3 Kcal/mol, corresponding to a half-life of 85 minutes at 31.5°C.[14] Whereas the dibenzoxocin derivative, 22, was isolated as the racemate and furthermore exhibits broadened signals in the NMR spectra at room temperature indicating rapid biaryl rotation.[15]



21



22

It is evident that the rate of racemization of 17 should be facile, and because of the simplicity and high yields attending the reactions interconverting 18 and 19, efficiency should be maximized in a resolution/racemization scheme involving the benzofuroisoquinoline 16. Since several schemes could be envisioned to take advantage of this relationship between 16 and 17, we decided to confirm this sequence and investigate the rate of rotation about the biaryl bond in 17.

RESULTS AND DISCUSSION

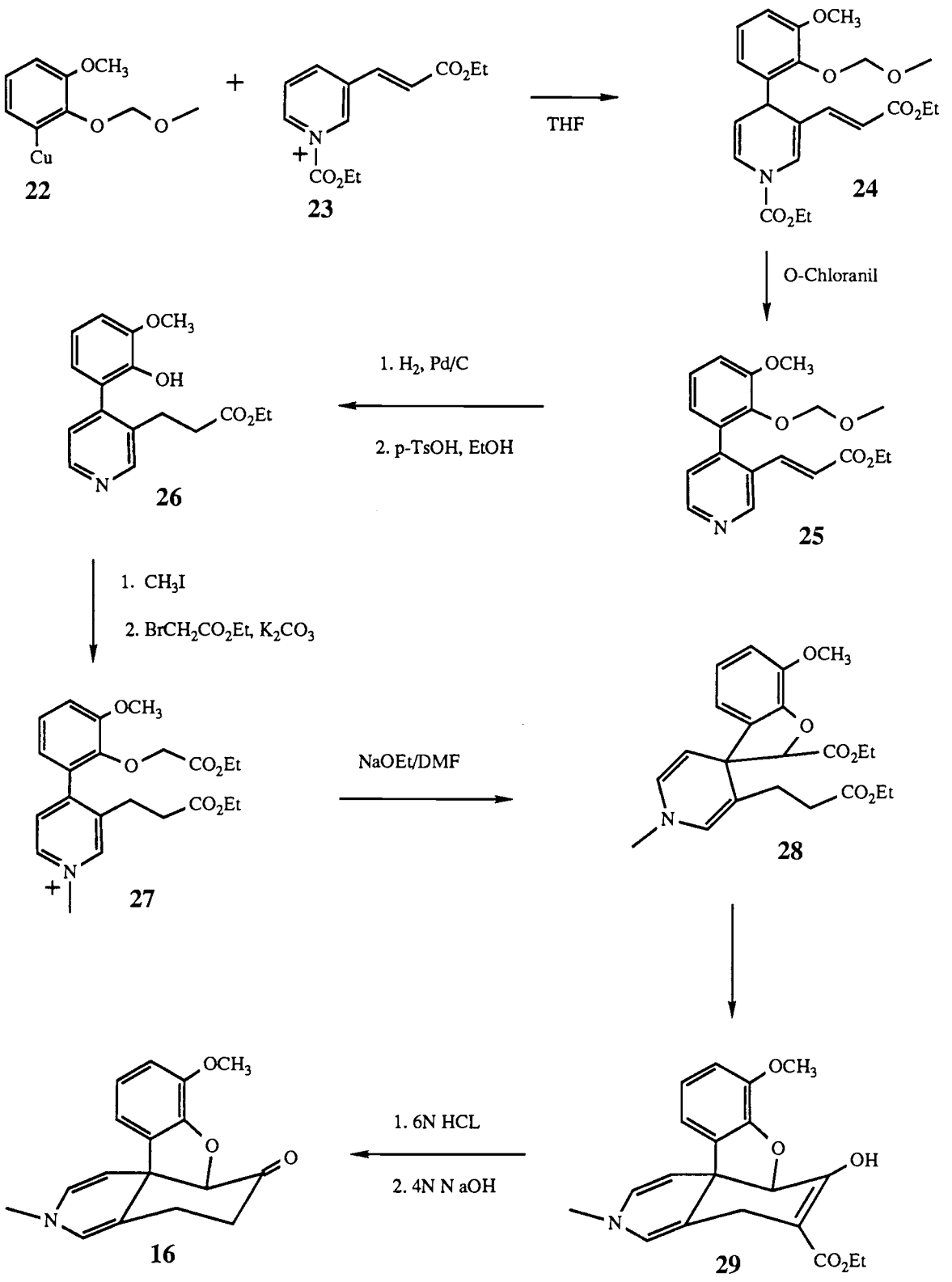
A short convergent route to the ACNO ring fragment of the morphine alkoloids has been previously demonstrated by the synthesis of various benzofuroisoquinolines.[8] As mentioned eariler, of particular importance is the key intermediate 16 of which its synthesis will now be briefly described (Scheme 4).

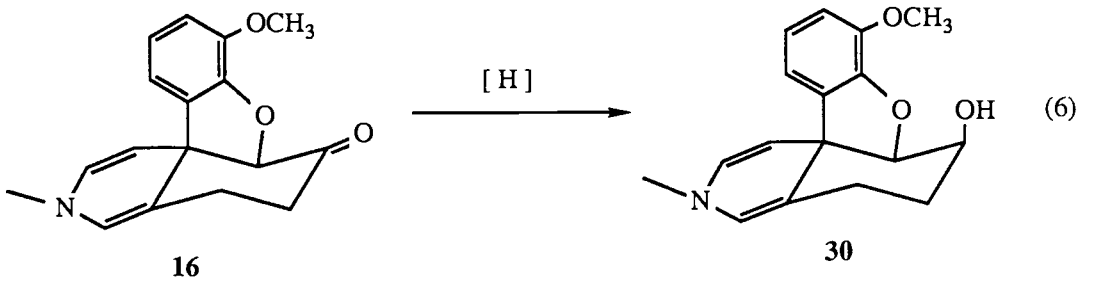
The benzene ring was first coupled to the pyridine ring by an intramolecular coupling reaction between the aryl copper derivative 22, and the pyridinium salt 23. The aryl copper derivative was made starting with the methoxymethyl (MOM-) ether of guiacol. The following sequence was then carried out: selective lithiation ortho to the MOM-ether group with n-BuLi, followed by transfer of the lithio salt to a mixture of copper iodide in tetrahydrofuran to produce 22. The pyridinium salt was made from pyridine-3-carboxaldehyde by Knoevenagel condensation with malonic acid, esterification, and then N-acylation with ethyl chloroformate. Coupling of 22 and 23 gave the dihydropyridine 24 in 90% yield. Oxidation with ortho-chloranil was then immediately carried out to provide the pyridine 25 in 80% yield. Catalytic hydrogenation followed by phenolic deprotection then provided the phenolic substituted

pyridine 26 in 90% yield. N-methylation with methyl iodide followed by O-alkylation with potassium carbonate and ethyl bromoacetate afforded the intermediate 27 in quantitative yield. This system is now ready for the intramolecular enolate addition to the pyridinium salt. Thus, treatment of 27 with sodium ethoxide in dimethylformamide produced initially the spirocyclic dihydropyridine 28. Upon prolonged exposure to base, 28 suffered a Dieckmann condensation and produced tetracyclic intermediate 29 in 70% overall yield from 26. Decarboethoxylation was then effected by refluxing in 6N HCl and upon basic workup the desired benzofuroisoquinoline 16 was isolated in 70% yield. Thus, 16, which possesses all the structural characteristics of the morphine skeleton except the B-ring, was efficiently synthesized in 30% overall yield starting from commerically available pyridine-3-carboxaldehyde.

In order to investigate the biaryl rotation and thus the rate of racemization in 17, we first sought to obtain optically active 16. With this urgent goal in mind we devised a classical scheme for the resolution of 16. This entailed stereoselective reduction of 16 to the alcohol 30 (equation 6). The alcohol would then be esterified with an optically active acid and resolved via the diastereomeric ester derivatives. Hydrolysis followed by oxidation would then provide the optically active antipodes of 16.

Scheme 4

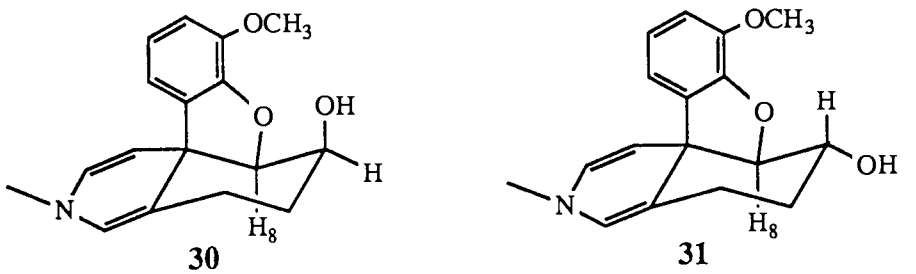

OCH3
Cu
22
CO2Et
N
CO2Et
23
THF
OCH3
O
O
CO2Et
N
CO2Et
24
O-Chloranil
OCH3
O
O
CO2Et
N
25
1. H2, Pd/C
2. p-TsOH, EtOH
OCH3
OH
CO2Et
N
26
1. CH3I
2. BrCH2CO2Et, K2CO3
OCH3
O
CO2Et
CO2Et
N
27
NaOEt/DMF
OCH3
O
CO2Et
CO2Et
N
28
OCH3
O
OH
N
CO2Et
29
1. 6N HCL
2. 4N N aOH
OCH3
O
O
N
16



16 30 (6)

One obvious concern for the feasibility of this resolution was the final oxidation step (30 to 16) which appeared to require mild and basic conditions to avoid decomposition of the acid sensitive dihydropyridine moiety and to prevent ring opening and thus possible racemization at an unwanted stage.

The alcohol, 30 was first obtained from 16 by reduction with lithium aluminium hydride. Analysis of the adduct mixture by 400 MHz ^{1}H NMR revealed it to be a mixture of the axial and equatorial alcohols 30 and 31. The stereochemistry was assigned by ^{1}H NMR analysis of the coupling constants of the C-8 protons for each isomer. The C-8 proton (4.58 ppm) of the minor equatorial isomer 31 was



30 31

a doublet with a coupling constant (J = 7.5 Hz) consistent with its anti relationship with the neighboring carbinol proton. By contrast, the C-8 proton (4.60 ppm) of the major isomer 30 revealed a smaller coupling (J = 2.8 Hz) as expected for its gauche relationship to the carbinol proton. In an effort to increase the selectivity of reduction, we tried the bulkier reagent lithium tri-t-butoxyaluminum hydride. This indeed resulted in increased selectivety, but a significant amount of the equatorial isomer still was present and chemical yields were lower (see table II). Finally, reduction with lithium tri-sec-butylborohydride (L-Selectride) gave a completely stereoselective reduction in quantitative yield.

Table II. Reduction of 16

Reagent	Temp.	equatorial	axial	yield
$LiAlH_4$	0°C	18%	82%	95%
$LiAl[(CH_3)_3CO]_3H$	0°C	10%	90%	81%
$LiB[CH(CH_3)C_2H_5]_3H$	-78°C	--	100%	100%

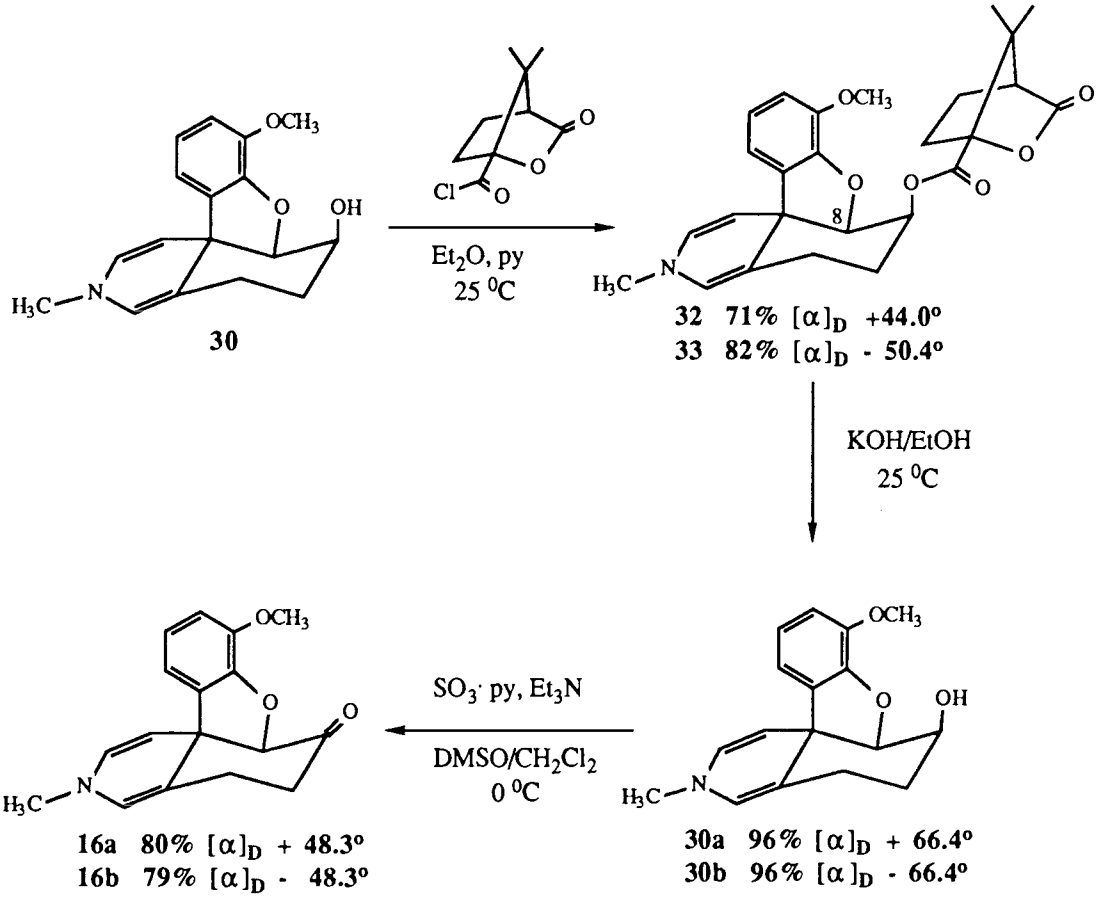
With the reduction optimized we then turned to the problem of the oxidation of 30 to 16 (see Table III). Since we anticipated difficulties if acidic reagents were employed, we first explored the strongly basic conditions of the Oppenauer oxidation[16] and the Mukaiyama oxidation[17]. Both of these methods gave no detectable product by either IR or ^{1}H NMR. The modified Oppenauer oxidation[18] using either fluorenone or benzophenone as hydride acceptor gave on occasion yields of 50%. However, the yields were not readily reproducible and were often lower. Oxidation with pyridinium dichromate in dichloromethane gave a 7.5% yield of ketone, 16. When the reaction was carried out in dimethylformamide enhanced rates were observed but even lower yields resulted. When pyridinium chlorochromate was used with either 4Å sieves or basic alumina as acid scavengers in dichloromethane, the ketone, 16, was recovered in 12.1% and 10.1% yields respectively. Finally, we investigated the conditions of the modified Moffat oxidation[19] using the combination of sulfur trioxide/pyridine complex and dimethyl sulfoxide as the oxidizing agent, in dichloromethane in the presence of triethylamine. This gave us a satisfactory yield of 80% of the ketone, 16.

The resolution of alcohol 30 was carried out by esterification with (1R)-(-)-camphanic acid chloride

Table III. Investigated Oxidation Methods for Alcohol 30

	Reagents	Conditions	Yield(%)
1.	cyclohexanone $Al[OCH(CH_3)_2]_3$	110°C toluene	0
2.	a)n-PrMgBr b)1,1'-(Azodicarbonyl)-dipiperidine	25°C THF	0
3.	Fluorenone 5 eq. t-BuOK 2.5 & 5 eq.	25°C benezene	0-40
4.	Benzophenone 5 eq. t-BuOK 2.5 & 5 eq.	80°C benzene	0-50
5.	Pyridinium dichromate 2 eq.	25°C CH_2Cl_2	10
6.	Pyridinium dichromate 2 eq.	25°C DMF	5
7.	Pyridinium chloro-chromate, 4Å sieves	25°C CH_2Cl_2	12.1
8.	Pyridinium chloro-chromate, Al_2O_3	25°C CH_2Cl_2	10.1
9.	SO_3-pyridine DMSO, Et_3N	0°C CH_2Cl_2/DMSO	80

Scheme 5


OCH3
OH
H3C
N
O
30
Cl
O
Et2O, py
25 °C
8
32 71% [α]D +44.0°
33 82% [α]D - 50.4°
KOH/EtOH
25 °C
30a 96% [α]D + 66.4°
30b 96% [α]D - 66.4°
SO3· py, Et3N
DMSO/CH2Cl2
0 °C
16a 80% [α]D + 48.3°
16b 79% [α]D - 48.3°

(Scheme 5). This gave two products, which were separable by chromatography on alumina, and proved to be the diastereomeric esters 32 and 33 by 400 MHz ^{1}H NMR. Particularly distinquishable were the C-8 protons of each diastereomer occuring at 4.66 and 4.71 ppm respectively. The isolated diastereomers contained between 10 to 30% of the other isomer as judged by ^{1}H NMR. Final purification to homogeneity was effected by preparative TLC on alumina. The diastereomers were then hydrolyzed in ethanolic potassium hydroxide to afford a pair of optically active alcohols which in turn provided a pair of optically pure ketones upon oxidation. The purity of the resolved ketones was confirmed by the effect of the chiral shift reagent, tris[(3-trifluoromethylhydroxymethylene)-d-camphorato], europium(III) derivative, upon the 400 MHz ^{1}H NMR of 16. In racemic 16, the methoxy peak originally at 3.57 ppm (Figure 1 lower spectrum) is shifted downfield and split into widely separated peaks representing the different diastereomeric ketone-Eu(tfc)$_3$ complexes (Figure 1 upper spectrum). Figure 2 shows only a single methoxy resonance is observed when resolved ketone is subjected to this analysis.

Prior to obtaining racemization data for 16, we first needed to explore the ring opening to 17 (Equation 7). Earlier studies had shown that conversion of related

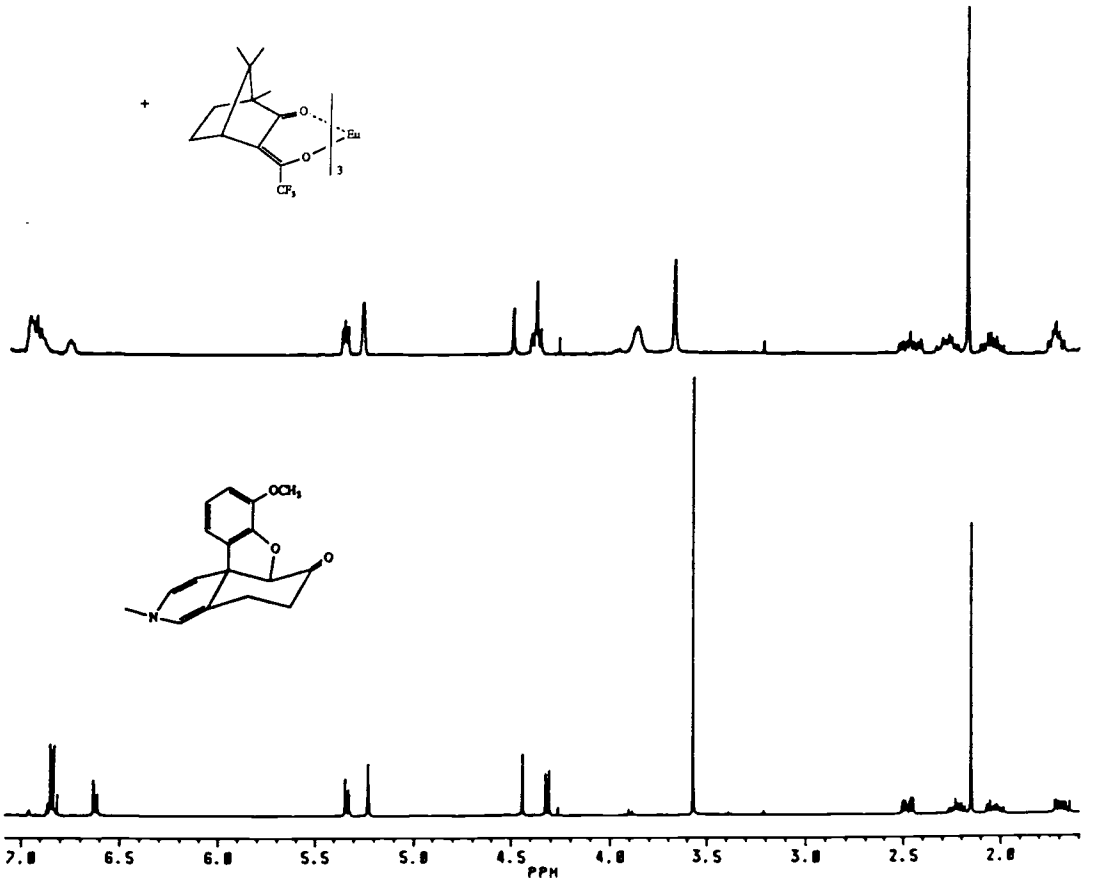


Figure 1. The effect of chiral shift reagent on the proton NMR spectrum of racemic 16.

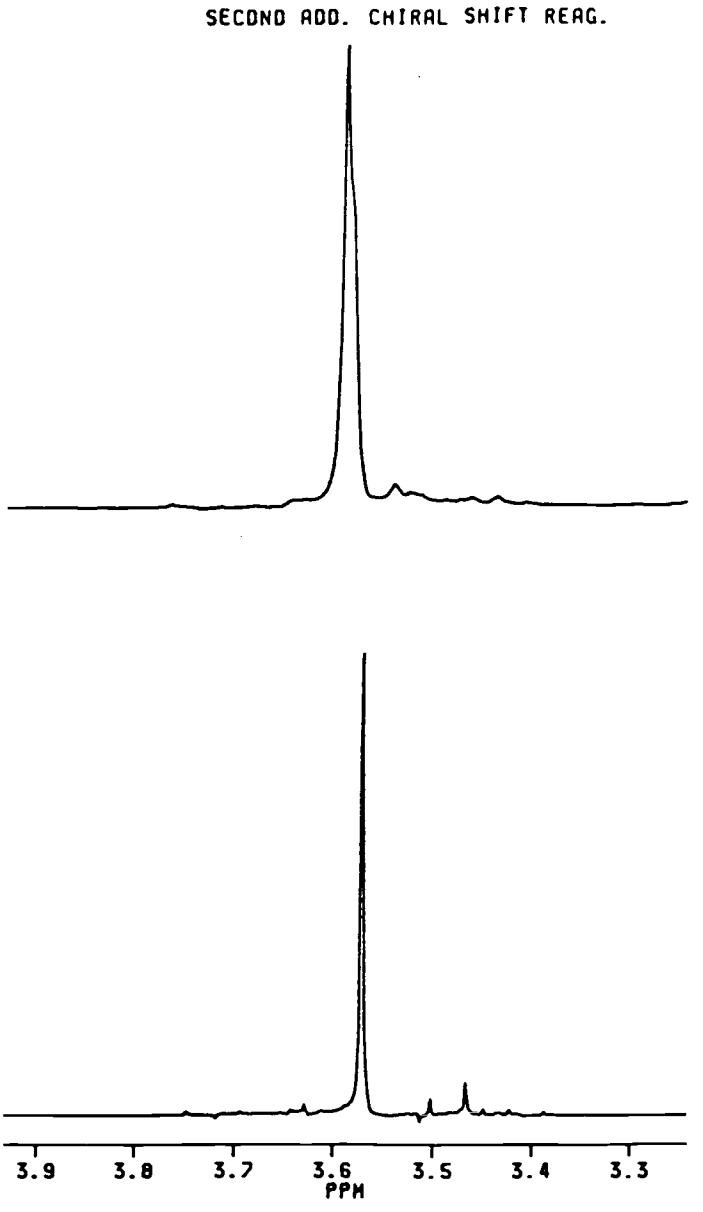
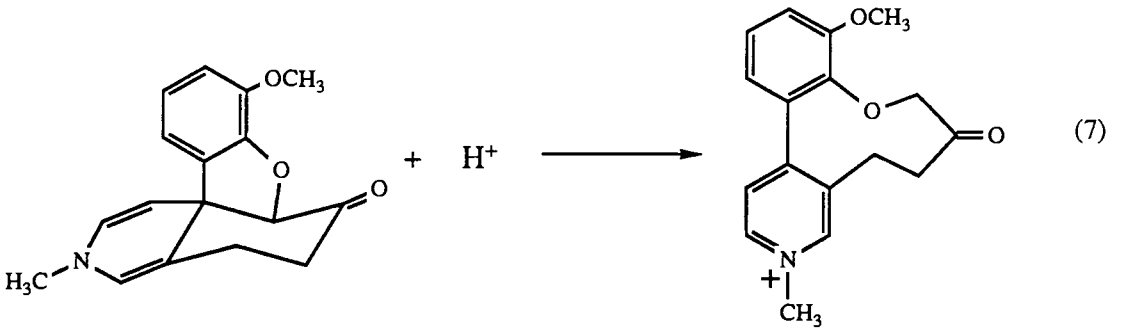
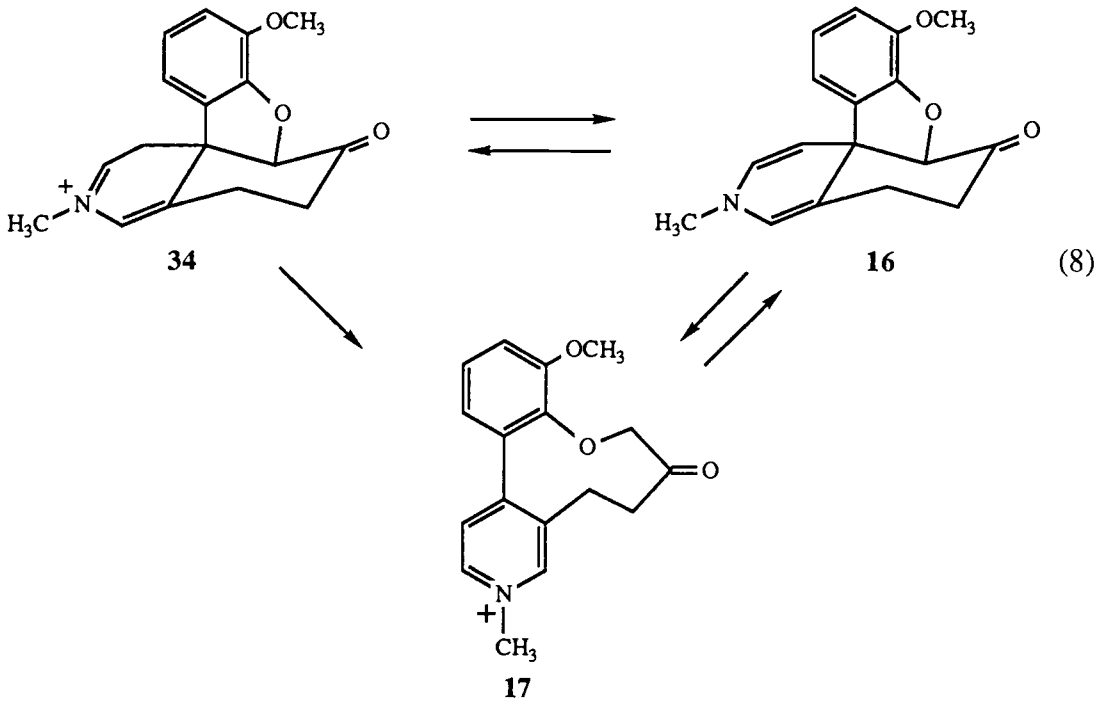


Figure 2. The effect of chiral shift reagent on the methoxy resonance of resolved 16.



16 17 (7)

N-alkyldihydropyridines to pyridinium salts was easily accomplished.[8b] As mentioned earlier the reversal could be carried out by addition of a stoichiometric quantity of acetic acid to a solution of the ketone 11 in ethanol. These reactions were conveniently monitored by ^{1}H NMR, wherein disappearance of the dihydropyridine protons (4.3-5.5 ppm) and the appearance of the pyridinium protons (8-9 ppm) is easily monitored. Ketone 16, however existed exclusively in the ring closed form when treated with acetic acid in deuterated methanol. When 16 was treated with an equimolar amount of trifluoroacetic acid in deuteromethanol an equilibrium was established containing 66% of the ring opened form as judged by ^{1}H NMR. Additional trifluoroacetic acid shifted the equilibrium but did not result in complete conversion to 17. In this case significant decomposition occured, possibly via condensation reactions of the iminium salt, 34, produced by competitive protonation on carbon (equation 8). Evidence for the species 34 was derived from the disappearance (or



(8)

deuterium exchange) of the β-pyridinium proton of 17 with time (see figure 3). Exchange of the β-pyridinium proton in 17 can only occur via deuteration of the less substituted enamine in 16 (Equation 8). Subsequent elimination of a proton will result in deuterium exchange. We then set out to force this ring opening to completion by using yet a stronger acid. One equivalent of p-toluenesulfonic acid in deuterated methanol resulted in complete conversion to the oxaninone 17, as judged by ^{1}H NMR. After 20 minutes, basification followed by extraction provided a 70% yield of 16.

At this point we were able to check the rate of racemization of optically active 16. To this end,

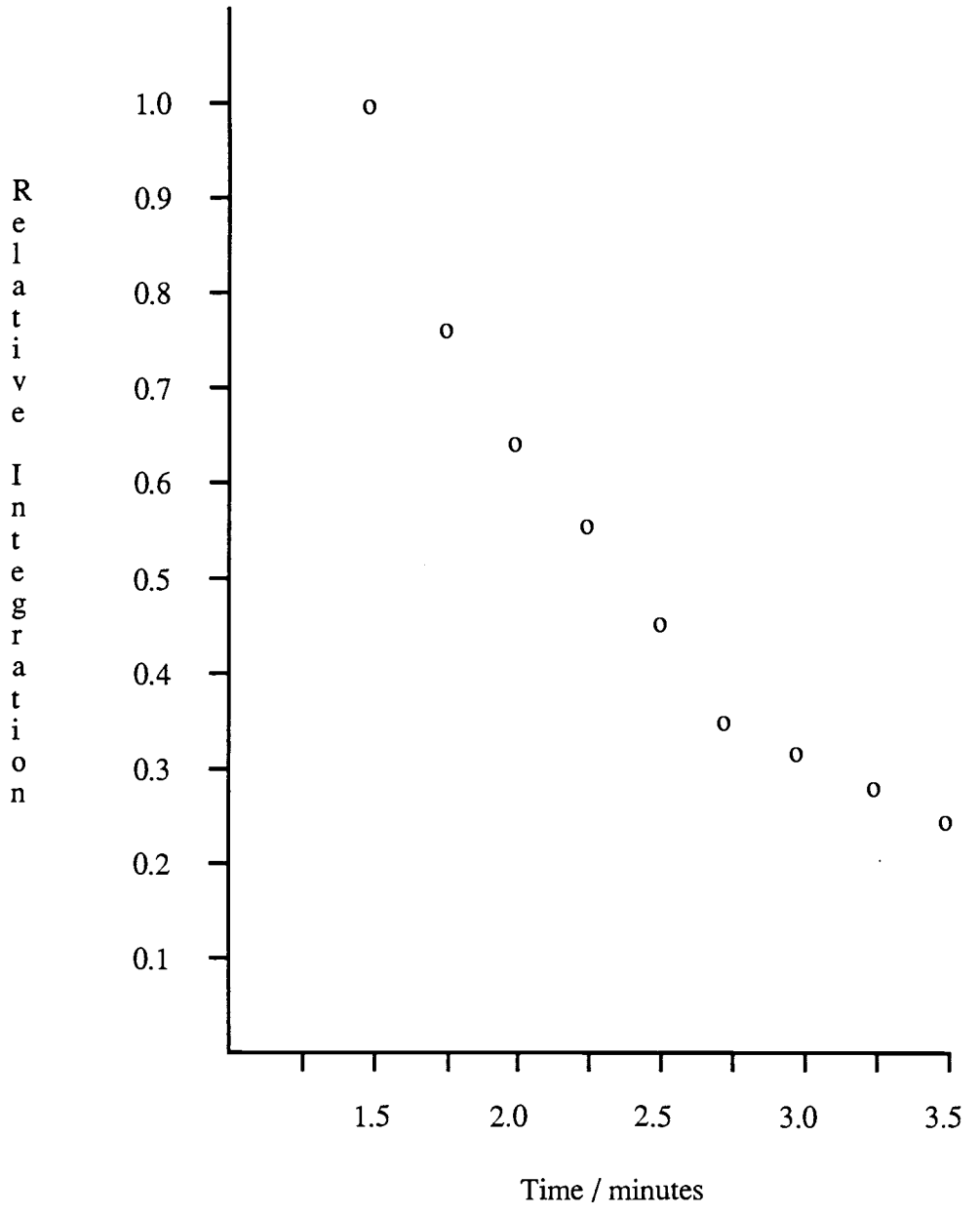
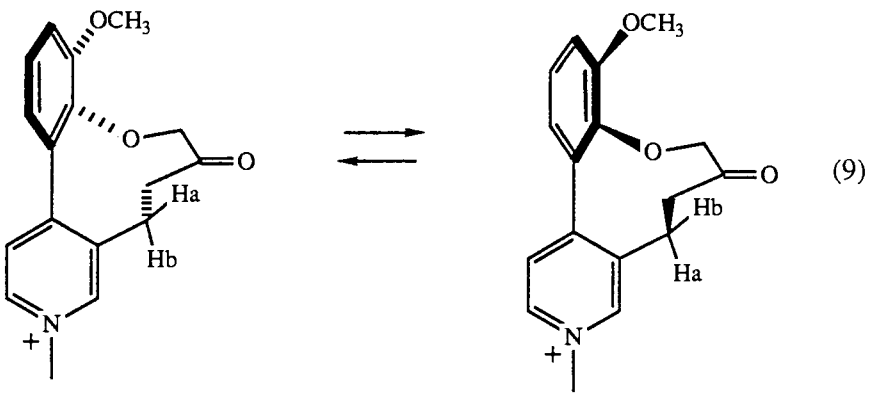


Figure 3. Disappearance of the β-pyridinium proton of 17: relative integration in the ^{1}H NMR.

optically pure 16 was treated with one equivalent of p-toluenesulfonic acid in methanol. After stirring for 60 seconds at room temperature, the reaction was quenched by the addition of 4N NaOH and benzene. Dihydropyridine 16, was isolated in 90% yield and was determined to be racemic by the chiral shift technique in the ^{1}H NMR. For comparison, the dibenzocyclononane carboxylic acid 20 racemizes with a half life of 24 hours at 25°C.

The extremely rapid rotation in 17 provided the possibility of a more detailed analysis of the racemization by dynamic proton NMR. Provided there is initially magnetic nonequivalence of two interchangeable diastereotopic protons in the bridging ring, it would be expected that the resonances of two such interchanging protons would collapse to a singlet as exchange became rapid compared to the NMR time scale. For example, two diastereotopic protons such as H_a and H_b exchange magnetic environments as biaryl rotation occurs to interconvert the antipodes (equation 9). As a consequence,



(9)

when a sample is heated in a NMR tube it is expected that the resonances of H_a and H_b will broaden and eventually collapse to a singlet as the temperature is increased. Data obtained from such an experiment would provide valuble kinetic and thermodynamic information.

A more detailed analysis of the proton NMR of oxaninone 17 was then attemped. However 17 was found to be unstable for prolonged periods (45 min) under the conditions described for the racemization experiment (TsOH/MeOH). There still appeared to be some of the competing equilibria denoted in equation 10, again evidenced by significant deuterium exchange. Dimerization through the iminium salt appeared to be a major side reaction as evidenced by the appearance of multiple NMR lines. At this point it was clear that strongly acidic conditions were needed to force the ring opening equilibrium to completion, and avoid significant concentrations of dihydropyridine. Since 16 is obtained from 29 in 70% yield, we explored conditons similar to the hydrolysis and decarboethoxylation reaction (6N HCl). Aqueous deuterium chloride and anhydrous d_4-acetic acid were investigated as solvents. Both solvents formed the oxaninone upon dissolution. Although some decomposition seemingly occured at the interface during dissolution (along with 70% deuterium exchange at the β-pyridinium position), satisfactory spectra of 17 could be recorded

which did not change with time. d_4-Acetic acid was chosen as the better solvent because of its slightly cleaner looking spectra and stronger lock signal.

Of interest in the d_4-acetic acid spectrum of 17 were two sets of multiplets representing the two methylene groups α and β to the pyridine ring. The multiplets were centered at 2.85 and 3.15 ppm, respectively, and each integrated for two protons. It was uncertain whether each multiplet represented protons on the same carbon or protons on adjacent carbons. Upon heating to 50°C, these peaks partially coalesced (figure 5), suggesting an assignment where $\delta H_a \simeq \delta H_c$ and $\delta H_b \simeq \delta H_d$ (see figure 4).

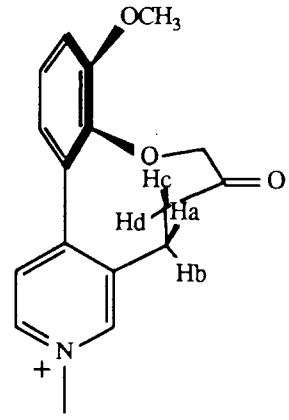


Figure 4. Coalescing protons of Oxaninone 17

To confirm this assignment, and to simplify an NMR analysis, the tetradeuterated oxaninone, 36, was prepared (Equation 10). The positions α to the carbonyl in 16 were exchanged with deuterium by heating (40°C) ketone 16 in a

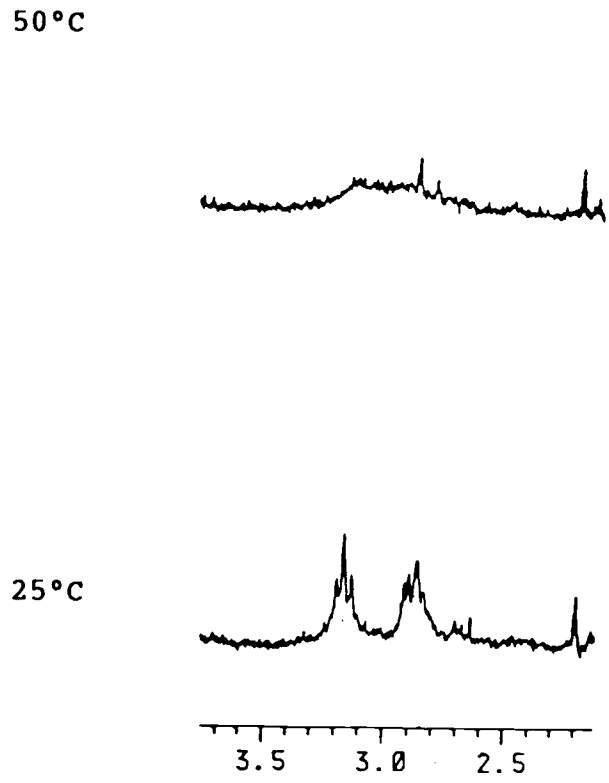
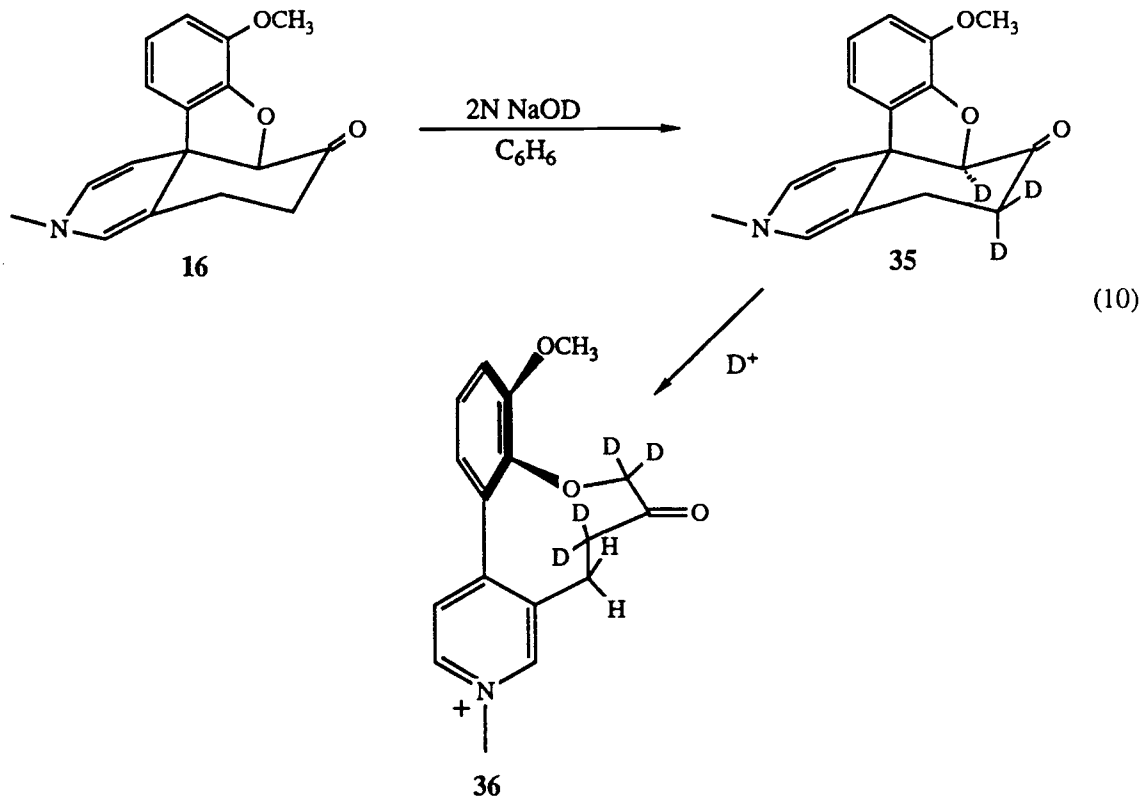


Figure 5. Variable temperature NMR of oxaninone 17.

mixture of 2N NaOD and benzene to give 35. In the final conversion of 35 into 36 the deuterated solvent provided the final deuterium.



(10)

As anticipated the NMR spectrum of 36 revealed an AB quartet thus confirming our original assignment. The NMR spectrum was then obtained at various temperatures (figure 6). At 10°C the protons are a sharp doublet of doublets (δ=2.81, 3.14, J=15.2 Hz). They eventually collapsed to a singlet at 90°C and the coalescence temperature was deduced to be approximatly 60°C.

Provided the difference in chemical shift, $\delta\upsilon$, is much

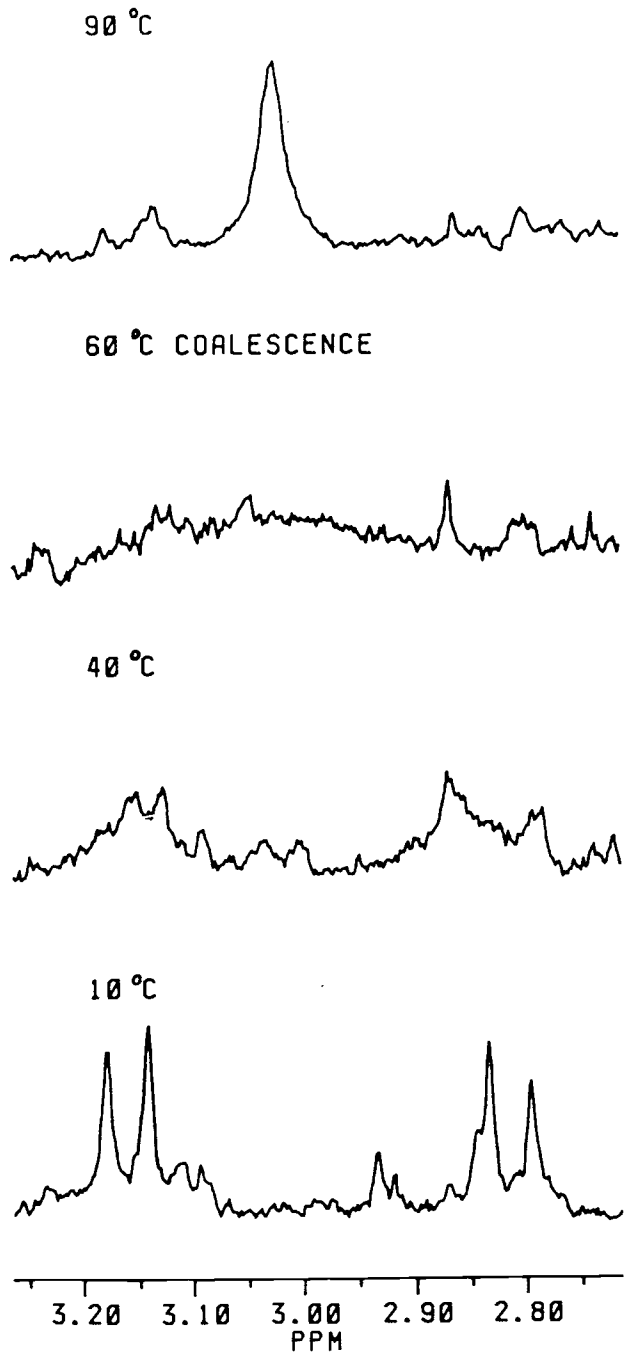


Figure 6. Variable temperature NMR of tetradeuterated oxaninone 36

larger than the bandwidth in the absence of exchange, the rate constant at the coalescence temperature for an AB spectrum with exchange between A and B is given by equation 10.[20] The Eyring equation

$$k = \pi[\tfrac{1}{2}((\delta\upsilon)^2 + 6J_{AB}{}^2)]^{\frac{1}{2}} \qquad (10)$$

$$k = \kappa k_B T/h \; e^{-\Delta G^{\ddagger}/RT} \qquad (11)$$

(equation 11) then relates the rate constant to the property of interest, $\Delta G^{\ddagger}$. Combination of equations 10 and 11 gives equation 12 for a coalescing AB system.[21]

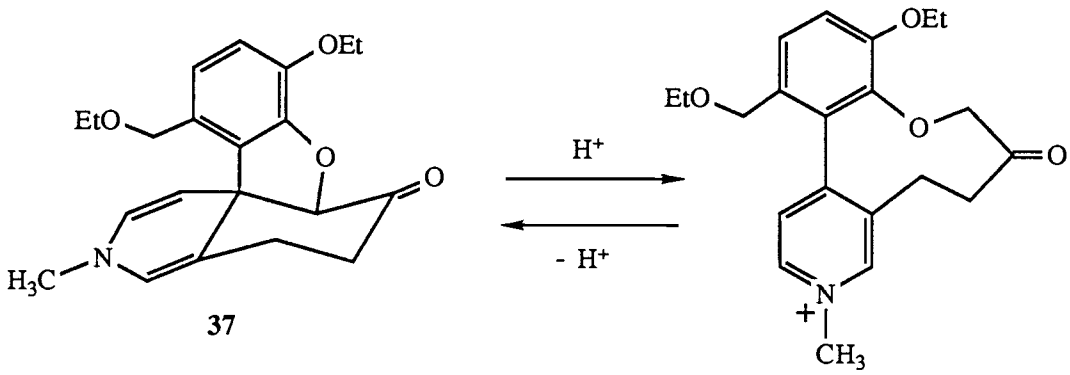
$$\Delta G^{\ddagger} = aT[9.972 + \log(T/(\delta\upsilon^2 + 6J_{AB}{}^2)^{\frac{1}{2}})] \qquad (12)$$

$$a = 4.575 \times 10^{-3} \text{ kcal mol}^{-1}$$

Application of equation 12 gives the free energy of activation, $\Delta G^{\ddagger}$, for the biaryl rotation in 36 to be 15.8 ± 0.3 Kcal/mol.

In comparison to the carbocyclic analog, 20, in which $\Delta G^{\ddagger}$ is 24.5 kcal/mol, we find that substitution of an oxygen for a methylene group results in a decrease in the free energy of activation of approximately 9 kcal/mol. This result not only confirms the feasibility of the

resolution/racemization sequence of 16 but also provides promising possibilities for the application of this scheme to other benzofuroisoquinolines such as 37 which bear additional ortho substituents in their ring opened forms.



37

EXPERIMENTAL

Proton (^1H) nuclear magnetic resonance spectra (NMR) were recorded on a Brüker AM-400 spectrometer. Chemical shifts (δ) are reported as parts per million downfield from tetramethylsilane as internal standard. Infrared spectra (IR) were recorded on Perkin-Elmer Model 727B or Nicolet 5DXB FT-IR spectrometers. Low resolution mass spectrometry was performed on a Varian MAT CH-7. High resolution mass spectra (HRMS) were obtained on a Kratos MS 50 TC or on a CEC-103B at the University of Oregon. Optical rotations were measured with a Perkin-Elmer 243 polarimeter. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Dimethylformamide (DMF), dimethylsulfoxide (DMSO), methylene chloride (CH_2Cl_2), and pyridine were distilled from powdered calcium hydride and stored over 3Å molecular sieves. Tetrahydrofuran (THF) and ether (Et_2O) were distilled immediately prior to use from sodium/benzophenone. Chromatographic solvents (CH_2Cl_2, EtOAc, hexane) were distilled before use. All reactions were run under a positive pressure of nitrogen or argon. Reactions worked up by extractive procedures were dried over Na_2SO_4 and filtered prior to evaporation under reduced pressure.

9-methoxy-3-methyl-5,6,7,8-tetrahydro-3H-benzofuro-[3,2-e]isoquinoline-7-ol (30). To a solution of 16[8c] (0.550 g, 1.94 mmol) in 12 ml THF at -78°C was added 3.90 ml (3.88 mmol) of lithium tri-sec-butylborohydride (1 M in THF). After stirring for 2 hours, the reaction mixture was maintained at -78°C while 4.0 ml of 10% NaOH/30% H_2O_2 (1:1) solution was added dropwise. The quenched solution was then extracted twice with benzene. The combined extracts were washed with water, brine, dried, and evaporated to give 30 a pale yellow solid (0.533 g, 100%) which was used without further purification.

An analytical sample was prepared by chromatography on alumina (60/40 EtOAc/hexane): mp 123-124; MS m/e 285 (M^+, 100), 284, 268, 256, 240, 228, 227, 226, 212, 210; IR (KBr) 3497, 2940, 2912, 1689, 1616, 1489, 1458, 1273, 1193, 1123, 1033, 977, 948, 880, 772, 734 cm^{-1}; ^1H NMR (C_6D_6) δ = 1.65-1.80 (3H, m), 2.13-2.20 (1H, m) overlapping 2.21 (3H, s), 3.47 (3H, s), 4.13 (1H, bs), 4.21 (1H, d, J=7.6 Hz), 4.60 (1H, d, J=2.8 Hz), 5.21 (1H, d, J=1.6 Hz), 5.43 (1H, dd, J=7.6, 1.6 Hz), 6.58 (1H, dd, J=7.8, 1.3 Hz), 6.85 (1H, t, J=7.7 Hz), 7.00 (1H, dd, J=7.8, 1.3 Hz); HRMS calcd for $C_{17}H_{19}NO_3$: 285.1364. Found: 285.1339.

The minor isomer 31 obtained by reduction with $LiAlH_4$ or $LiAl[(CH_3)_3CO]_3H$ had the following NMR signals distinctly different from 30: (C_6D_6) δ = 2.20 (s), 3.46

(s), 4.33 (d, J=7.3 Hz), 4.58 (d, J=7.7 Hz). Product percentages (Table II) were based on the intergration of the peaks at 4.21 ppm and 4.33 ppm of compounds 30 and 31 respectively.

9-methoxy-3-methyl-5,6,7,8-tetrahydro-3H-benzofuro-[3,2-e]isoquinoline-7-ol, esters with (1R)-(-)-camphanic acid (32,33). To a mixture of 30 (0.075 g, 0.263 mmol) and (-)-camphanic acid chloride (0.114 g, 0.526 mmol) partially dissolved in 3.0 ml ether was added pyridine (0.045 ml, 0.522 mmol), and stirred for 2.5 hr. The reaction mixture was diluted with ether, washed with 10% $NaHCO_3$ solution, dried, and evaporated to an oil which was immediately chromatographed on a column of alumina. Elution with CH_2Cl_2 gave two isolated products, each containing 10-30% of the other diastereomer (0.094 g total, 76.8%). The diastereomers were then completely separated by preparative TLC (aluminum oxide, CH_2Cl_2). First eluted 32: dec 62°C; $[\alpha]_D^{23}$ -50.4° (C_6H_6); MS m/e 465 (M^+), 269, 268(100), 256, 240, 226,212; IR (thin film) 2960, 2925, 2850, 1790, 1750, 1690, 1615, 1495, 1455, 1275, 1200, 1170, 1100, 1060, 950, 770, 720 cm^{-1} ; ^1H NMR (C_6D_6) δ = 0.85 (3H, s), 0.87 (3H, s), 0.90 (3H, s), 1.19-1.32 (2H, m), 1.69-1.76 (2H, m), 1.78-1.87 (1H, m), 1.95-2.04 (1H, m), 2.05-2.12 (1H, m), 2.15-2.20 (1H, m), 2.23 (3H, s),

3.47 (3H, s), 4.19 (1H, d, J=7.6 Hz), 4.71 (1H, s), 5.19 (1H, s), 5.50 (1H, d, J=7.6 Hz), 5.62 (1H, ddd, J=11.0, 6.4, 2.5 Hz), 6.59 (1H, d, J=7.8 Hz), 6.85 (1H, t, J=7.8 Hz), 6.97 (1H, d, J=7.8 Hz); HRMS calcd for $C_{27}H_{31}NO_6$: 465.2151. Found: 465.2141.

Second eluted 33: dec 67°C; $[\alpha]_D^{23}$ +44.0° (C_6H_6); MS m/e 4.65 (M^+), 269, 268(100), 256, 240, 226, 212; IR (thin film) 2970, 2950, 1793, 1755, 1690, 1618, 1495, 1455, 1278, 1200, 1170, 1108, 1060, 952, 730, 688 cm^{-1}; ^1H NMR(C_6D_6) δ = 0.71 (3H, s), 0.86 (3H, s), 0.95 (3H, s), 1.19-1.29 (2H, m), 1.65-1.76 (2H, m), 1.81-1.90 (1H, m), 1.92-2.01 (1H, m), 2.10-2.19 (2H, m), 2.21 (3H, s), 3.47 (3H, s), 4.20 (1H, d, J=7.6 Hz), 4.66 (1H, d, J=2.2 Hz), 5.18 (1H, s), 5.49 (1H, d, J=7.6 Hz) 5.60 (1H, ddd, J=10.7, 6.5, 2.7 Hz), 6.60 (1H, d, J=7.6, 8.4 (1H, t, J=7.6 Hz), 6.97 (1H, d, J=7.6 Hz; HRMS calcd for $C_{27}H_{31}NO_6$: 465.2151. Found: 465.2141.

(-)-9-methoxy-3-methyl-5,6,7,8-tetrahydro-3H-benzofuro-[3,2-e]isoquinoline-7-ol (30a). Camphonate ester 32 (42.1 mg, 0.091 mmol) partially dissolved in 1.0 ml ethanol was treated with 0.5 ml 2N KOH for 20 min. The solution was extracted with methylene chloride, washed with 2N KOH, dried, and evaporated to cleanly afforded 30a (24.8 mg, 95.8%): mp 114-115; $[\alpha]_D^{23}$ - 66.4°.

(+)-9-methoxy-3-methyl-5,6,7,8-tetrahydro-3H-benzofuro-[3,2-e]-isoquinoline-7-ol (30b). As described above, 33 (33.1 mg, 0.071 mmol) afforded 30b (19.4 mg, 95.7%): mp 114-115; $[\alpha]_D^{23}$ + 66.4°.

(-)-9-methoxy-3-methyl-5,6-dihydro-3H-benzofuro[3,2-e]-isoquinoline-7-(7aH)-one (16a). To a 0.1 M solution of 30a (9.6 mg, 0.034 mmol) in CH_2Cl_2/DMSO(1:1) at 0°C was added triethylamine (14.0 μl, 0.10 mmol) followed by sulfur trioxide/pyridine complex (16.1 mg, 0.10 mmol). The solution was stirred for 1 hr at 0°C. The mixture was diluted with CH_2Cl_2, washed with 1% aq $NaHCO_3$, dried and evaporated to an oil. The residue was taken up in ether and filtered through a short column of alumina to yield 16a (7.6 mg, 79.3%) as white a solid: mp 128-129; $[\alpha]_D^{23}$ - 48.3° (C_6H_6); MS m/e 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}; ^1H NMR (C_6D_6) δ = 1.71 (1H, ddd, J=13.4, 7.0, 2.0 Hz), 1.99-2.07 (1H, m), 2.18 (3H, s), 2.19-2.26 (1H, m), 2.47 (1H, ddd, J=14.8, 6.3, 2.0 Hz), 3.57 (3H, s), 4.32 (1H, d, J=7.7 Hz), 4.44 (1H, s), 5.26 (1H, d, J=1.5 Hz), 5.36 (1H, dd, J=7.1, 1.5 Hz), 6.62 (1H, dd, J=7.1, 2.2 Hz), 6.83 (1H, t, J=7.1 Hz) overlapping 6.85 (1H, d, J=7.1 Hz); HRMS calcd for $C_{17}H_{17}NO_3$: 283.121. Found 283.121.

(+)-9-methoxy-3-methyl-5,6-dihydro-3H-benzofuro[3,2-e]-isoquinoline-7-(7aH)-one (16b). By the above procedure 30b (10.5 mg, 0.037 mmol) afforded 16b (8.4 mg, 80.0%): mp 128-129 $[\alpha]_D^{23}$ + 48.3° (C_6H_6).

Racemization. Methanol solutions (0.01 M) of 16a or 16b were treated with 1 eq of p-toluenenesulfonic acid and stirred at 25°C for 60 seconds. The mixtures were quenched by the addition of 1.0 ml 4N NaOH/benzene (1:1), extracted with benzene, dried, and evaporated to give racemic 16 in 90% yields.

Ring opening reaction (16 → 17). Approximately 1-2 mg of 16 was triturated with 0.5ml d_4-acetic acid and stirred while under a stream of argon. After approximately one minute, the sample completely dissolved, was transferred to an NMR tube. ^1H NMR (CD_3CO_2D) δ = 2.91-2.84 (2H, m), 3.19-3.13 (2H, m), 3.96 (3H, s), 4.45 (3H, s), 4.83 (0.67H, s), 7.05 (1H, dd, J=7.1, 1.7 Hz), 7.87 (0.33H, d, J=6.3 Hz), 8.76 (1H, s), 8.97 (1H, s). Spectra were then acquried at 50°C and again at 25°C. Partial coalesence of the signals centered at δ = 2.85 and 3.15 was observed at 50°C and these peaks returned to their original pattern upon cooling.

9-methoxy-3-methyl-5,6-dihydro-3H-[6,6,8-$^2H_3$]benzofuro[isoquinoline-7-(7aH)-one (35). The positions α to the ketone in 16 (5.0 mg, 0.018 mmol) were deuterated by treatment with (0.5 ml) 4N NaOD/D_2O at 40°C for 12 hours in the presence of 7 drops of benzene. Extraction with benzene and evaporation affored trideuterated 16 (4.4 mg, 87%). Partial ^1H NMR (C_6D_6) δ = 1.68 (1H, d, J=13.4 Hz), 2.21 (1H, d, J=13.4 Hz), 4.44 (s, 95% exchanged).

Ring opening reaction (35 → 36). Approximately 1 mg of trideuterated 35 was triturated with 0.5ml d_4-acetic acid and stirred while under a stream of argon. After approximately one minute, the sample completely dissolved and was transferred to an NMR tube. ^1H NMR (CD_3CO_2D) δ = 2.82 (1H, d, J=15.2 Hz), 3.16 (1H, d, J=15.2 Hz), 3.95 (3H, s), 4.45 (3H, s), 7.04 (1H, dd, J=7.3, 1.9 Hz), 7.27-7.34 (2H, m), 7.86 (0.33H, d, J=6.2 Hz), 8.76 (1H, s), 8.97 (1H, s).

Variable temperature NMR: Spectra were then acquired at the following temperatures 10°, 5°, 20°, 30°, 40°, 50°, 60°, 80°, 90°, 100°, 55°, and 25°C. Coalesence of the signals at 2.82 ppm and 3.16 ppm was observed at 60°C and these peaks return to their original AB quartet upon cooling to 25°C.

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