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Preparation of 3,3′-bis(1-benzyl-1,4-dihydro-3-pyridyl-carbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl, a potential NAD(P)H model compound

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PREPARATION OF 3,3′-BIS(1-BENZYL-1,4-DIHYDRO-3-PYRIDYL-CARBONYLAMINOMETHYL)-2,2′-DIHYDROXY-1,1′-BINAPHTHYL, A POTENTIAL NAD(P)H MODEL COMPOUND

by

PATRICIA M. LUTZ

A dissertation submitted to the Graduate Faculty in Chemistry in partial fullfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1994

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

9/22/94
Date

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Chair of Examining Committee

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Date

Executive Officer

Supervisory Committee

The City University of New York

ABSTRACT

PREPARATION OF 3,3′-BIS(1-BENZYL-1,4-DIHYDRO-3-PYRIDYL-CARBONYLAMINOMETHYL)-2,2′-DIHYDROXY-1,1′-BINAPHTHYL, A POTENTIAL NAD(P)H MODEL COMPOUND

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PATRICIA M. LUTZ

Advisor: Professor Howard Haubenstock

The design, synthesis, and characterization of the title compound, a novel bis-1,4-dihydronicotinamide possessing the 2,2′-dihydroxy-1,1′-binaphthyl as the chiral source with C_2 symmetry rather than a chiral center, is described. The synthesis involved the condensation of nicotinoyl chloride with newly prepared chiral bisnicotinamide, 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl, followed by quaternization with alkyl halide, and then reduction by $Na_2S_2O_4$. The synthesis and characterization of the new binaphthyls (intermediates) 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide, 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl, and 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl is also described.

In another series of experiments, acetophenone was found to be reduced in 4-24% enantiomeric excess by the chiral hydride reagent formed by the complexation of $LiAlH_4$, (R)-(−)-3,3-dimethyl-1,2-butanediol and achiral alcohols.

ACKNOWLEDGEMENTS

First and foremost, I wish to express by depest gratitude for the great patience and continuing support of my husband, Timothy, and my daughter Michele. I am also very grateful to my parents, Marguerite and Edward Gregory, for their support and help throughout the years.

I would also like to express my appreciation to all of my teachers at the City University of New York, and especially thank Dr. Howard Haubenstock, my mentor, for his guidance and advice.

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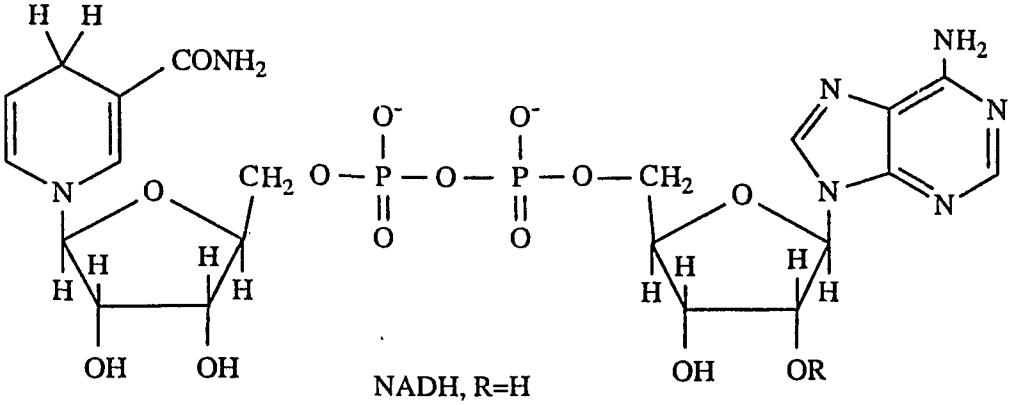
1.0 INTRODUCTION

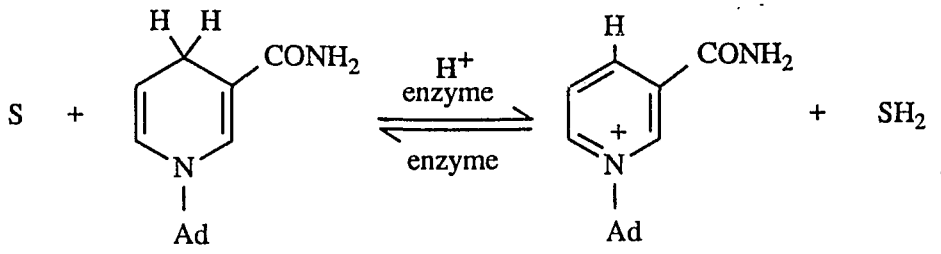
The stereoselectivity of biological reactions is a very important part of natural processes. The high stereospecificity of the enzymic reactions is of interest in the characterization of the nature of asymmetric induction. Recently, the coenzymes NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate) have received widespread attention. The structure of the reduced form of the coenzymes is shown below:



NADH, R=H
NADPH, R=PO_3^{2-}

The coenzymes, nicotinamide derivatives, are important nucleotides responsible for electron transfer in a large number of enzyme-catalyzed biological reduction-oxidation reactions. In living cells, many hydrogenation and dehydrogenation reactions are catalyzed by dehydrogenases which may be specific for one or both

coenzymes. The nicotinamide portion of the nucleotide stereospecifically transfers hydrogen in these reactions. The general reaction is a reversible reduction-oxidation of a substrate (S):



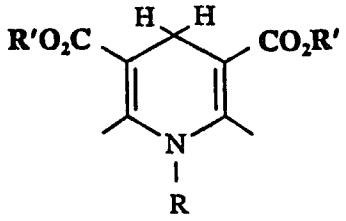
NAD(P)H NAD(P)$^+$

The reactions occur within enzyme-coenzyme-substrate complexes, often requiring metal ions. The reaction is stereospecific with respect to both coenzyme and substrate.

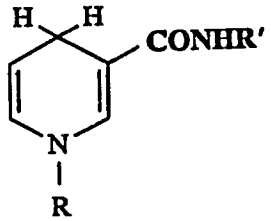
Because of the ability of the reduced coenzymes in natural systems to asymmetrically reduce unsaturated compounds such as carbonyls and conjugated olefins, there is much interest in the synthesis of models for the coenzymes. Much work has been done in the synthesis of 1,4-dihydropyridines as NADH models (1-7), exploring the reactions of these compounds and using the models in a variety of synthetic reactions in the hope of imitating the high stereospecificity of enzymic reactions. Many of these model systems are stable and are readily analyzed due to their simplicity. Chemists studying these nonenzymatic-model systems have generally attempted to obtain an understanding of the nature of the

hydrogen transfer process between the coenzyme and the substrate. However, analogies made between "NADH mimics" and natural systems using the coenzymes must be made with caution. Unlike the natural systems which function in aqueous media, the model systems are generally employed in organic solvents. An obvious advantage in the use of organic solvents in an asymmetric reduction would be the ability to reduce substrates which are non-soluble in aqueous media. Although it has been suggested (8,9) that a ternary complex in the transition state of a model system reduction process may be analagous to a coenzyme-enzyme-substrate complex in natural systems (vide infra), the mechanism for the NAD(P)H system will probably require a clearer understanding of the enzymes involved in the natural process.

However, the reactions of NAD(P)H models are of great interest in themselves to organic chemists as synthetic reagents, particularly in the area of asymmetric synthesis. The NADH models being constructed generally fall into two categories, the Hantzsch esters 1, and the N-substituted 1,4-dihydronicotinamides, 2.

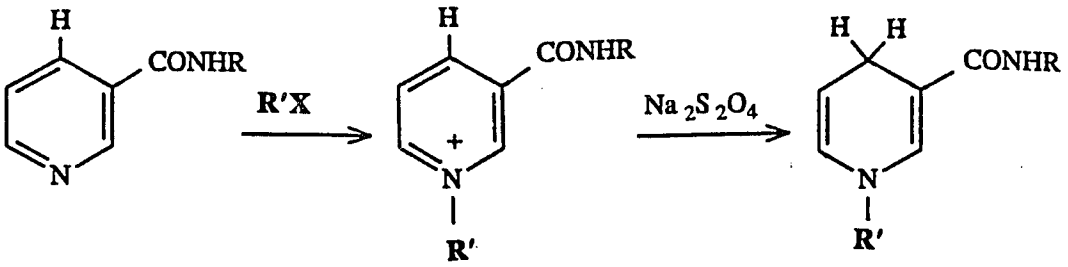


1



2

In general, in the synthesis of model compound 2, a nicotinamide is reacted with an alkyl halide to form the quaternary salt of the nicotinamide. The quaternized salt is then reduced with sodium dithionite to form the model compound, the N-substituted 1,4-dihydronicotinamide:



Simple carbonyl groups are not generally reduced by NAD(P)H or 1,4-dihydronicotinamides (8). However, a variety of activated carbonyl substrates have been shown to be reduced by NADH models, in the presence of a metal ion (vide infra).

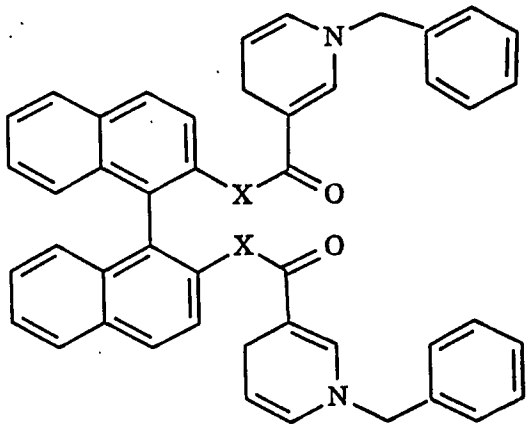
In general, chiral 1,4-dihydronicotinamide model systems have given a wide range of optical yields in reductions of activated carbonyl compounds. A few chiral reagents have been highly successful with certain substrates (vide infra). Salient features found in the design of 1,4-dihydropyridines as successful asymmetric reducing agents and which improved the optical yields obtained previously are:

1) a chirally substituted nicotinamide,

2) the presence of a hydroxy group, and

3) the presence of the **oxidized** pyridinium moiety during the course of the reaction.

The binaphthalene moiety, an axially dissymmetric molecule of high chiral recognition (vide infra) has been used in the construction of bispyridyl compounds 3, (where X = -O-, -NH-, $-CH_2O-$, or $-OCH_2CH_2O-$, to form various ester or amide linkages) by Amano et al (9). The idea was to confer chirality to the 1,4-dihydropyridyl compounds by virtue of axial dissymmetry rather than centro-asymmetry and to study the effect of C_2 symmetry in the disubstituted models versus C_1 symmetry in the monosubstituted models bearing the same chirality. (In an additional variation, a model was synthesized in which the binaphthyl was linked at the pyridyl Nitrogen position, rather than at the ester or amide at C-3 of the pyridine ring.)

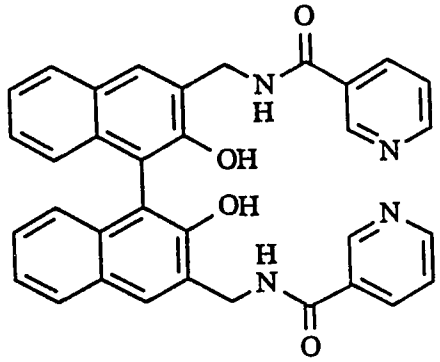


3

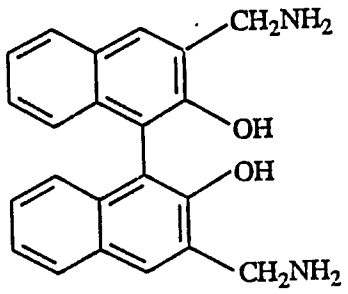
The pyridyl compounds were further reacted to form 1,4-dihydropyridine compounds which were used as reagents in the asymmetric reduction of the activated carbonyl compound, ethylbenzoylformate. Optical yields obtained were modest, ranging from a low 5.7% to a high of 45.6% (but with a low chemical yield of 14.3%). Only one of the compounds synthesized had the nicotinamide moiety linked to the chiral binaphthyl at the 3-position of the dihydropyridine, an apparently important feature in the design of a successful model compound (vide infra). None of the model compounds contained hydroxy groups, another apparently important feature. All of the model compounds were chiral by virtue of the binaphthalene moiety, and apparently the binaphthalene moiety, when in close proximity to the dihydropyridine ring, sterically enhanced access of the substrate to one specific face of the dihydropyridine moiety.

This investigation deals with the design, synthesis, and characterisation of a novel, improved chiral bispyridyl compound 4, 3,3′-bis(3-pyridylcarbonylamino-methyl)-2,2′-dihydroxy-1,1′-binaphthyl.

4



The bisnicotinamide 4 incorporates the new axially dissymmetric binaphthol 5 as the chiral moiety in the molecule:



5

The bisnicotinamide was prepared by the reaction of nicotinoyl chloride and the bisamine 5, 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl. The bisamine was prepared in a series of derivatizations of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl, an axially dissymmetric compound of high chiral recognition, which has been well characterized, resolved, and whose absolute configuration has been established (vide infra).

The bisnicotinamide is a precursor to a potential NADH model compound. The bisnicotinamide contains the binaphthalene moiety of high chiral recognition In addition, it contains hydroxy groups, which have been reported to significantly enhance the reactivity and stereoselectivity in some NADH model compounds (vide infra). The two nicotinamide groups are in close proximity to the hydroxy groups and because of these structural features, may lead to an interesting NADH

model compound in which the following may be found to occur:

1) significant chelative interaction with the metal ion (found to be significant and responsible for the dependence of enantiomeric excess) and

2) upon oxidation of one of the dihydronicotinamide groups, an intramolecular interaction of the oxidized pyridinium moiety with the second dihydronicotinamide group (enhanced optical yields were obtained in the later stages of reduction upon addition of added pyridinium species) (vide infra).

2.0 BACKGROUND

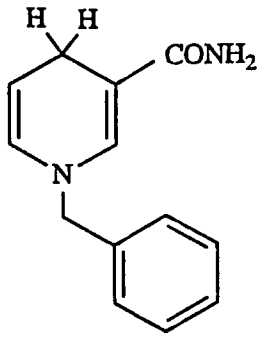
2.1 Survey of NADH Model Compounds

2.1a NADH Model Compounds

The discovery of the structure of the coenzyme NADH as a reduced nicotinamide derivative stimulated work on the construction and study of 1,4-dihydropyridines as NADH models. Model dihydropyridines have been studied extensively in order to elucidate the mechanism of hydrogen transfer by NAD(P)H in natural systems. As described earlier, the model compounds generally fall into two categories, the Hantzsch esters 1, and the N-substituted 1,4-dihydronicotinamides 2 (see p. 3). This investigation deals with the synthesis of a precursor to the latter type of model compound, therefore, the discussion will deal primarily with the N-substituted 1,4-dihydropyridines as model compounds. Many of the chiral, N-substituted 1,4-dihydronicotinamide model compounds are of interest as synthetic reagents, particularly in the area of asymmetric synthesis.

In an early experiment, Mauzerall and Westheimer prepared the achiral

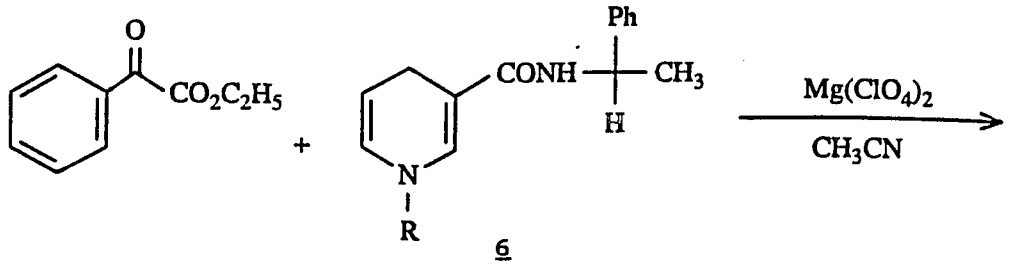
1-benzyl-1,4-dihydronicotinamide (BNAH), a model for reduced NADH, and illustrated that it reduced malachite green to its leuco base (10). Several carbonyl compounds were not reduced by BNAH in this study.

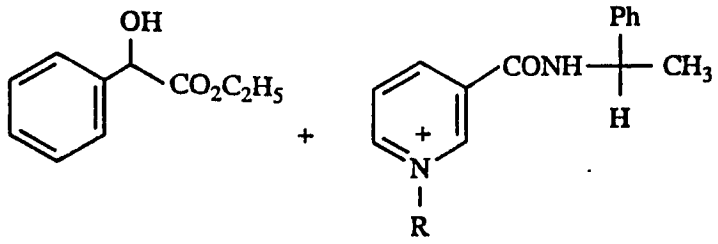


BNAH

BNAH was shown not to reduce the activated carbonyl compound, ethyl benzoylformate at room temperature in the dark in acetonitrile. However, in the presence of an equimolar amount of magnesium perchlorate, racemic ethyl mandelate was quantitatively formed (11). In the same study, ethyl benzoylformate was asymmetrically reduced in the presence of a bivalent metal ion such as magnesium or zinc with (R)-(−)-N-α-methylbenzyl-1,4-dihydronicotinamide derivatives, 6, with optical purities ranging from 20% to 11%. Similarly, the reduction of n-butyl pyruvate afforded (R)-(+)-butyl lactate in 38% optical yield, but only 20% chemical yield. Apparently, the chiral center in the model compound is responsible for the asymmetric reduction (see reaction next page). It was suggested that the role of metal ion in the reduction may resemble its catalytic function in enzymatic systems, i.e., that there may be a

strong coordination of metal ion to either the reducing agent, the substrate, or both.

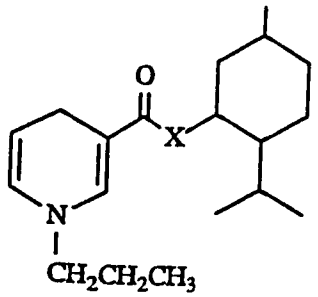




The NADH model system 6 was thoroughly studied, and the importance of the metal ion demonstrated. Reduction of trifluoroacetophenone with the (R)-(−)-enantiomer gave the (S)-carbinol in 16% optical yield (58% chemical yield) in the presence of magnesium perchlorate (12). Reduction in the absence of metal salt gave optically inactive carbinol in lower yield. The magnesium ion was shown to accelerate the reactions as well as to play a critical role in the stereochemical outcome. The same model compound reduced 2-acetylpyridine in the presence of magnesium perchlorate to give the corresponding chiral alcohols in up to 39% optical yield (chemical yield 66%) (13). The optical purity of the

product was found to depend on the molar ratio of the metal ion to the coenzyme model.

The effect of substituents on a 1,4-dihydropyridine model compound at C-3 was studied in the reduction of ethyl benzoylformate (14). It was found that high stereospecificity and percent conversion of the reduction was effected in the presence of magnesium perchlorate with the existence of a chirally substituted amide group in the model compound 7:



7

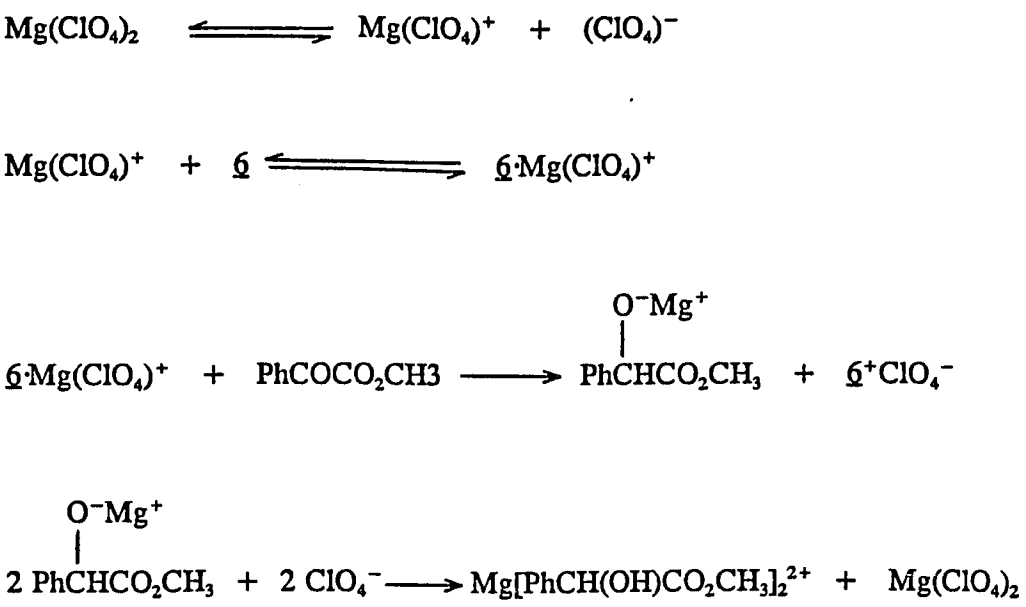
When X was NH, 99% conversion with 26% enantiomeric excess was observed. When X was CH_2 and O, the results obtained, respectively, were 30% conversion with 9% enantiomeric excess and 55% conversion with 2% enantiomeric excess.

NAD(P)H coenzymes transfer a hydride equivalent to a variety of substrates when catalyzed by enzymes in natural systems. Since it was found that many

simple dihydropyridines will transfer a hydride equivalent to an activated substrate, mechanistic studies of the have been carried out with the 1,4-dihydro-nicotinamide model systems as a model for the enzymatic process. The key mechanistic question is whether the hydride equivalent is transferred in a single step or whether intermediates are involved.

In one mechanistic study on the role of metal ion in the reduction process by Ohno and coworkers (15, 16), it was suggested that the transition state consists of a ternary complex, analagous to a coenzyme-enzyme-substrate complex in an enzymic system. The authors postulate that an electron migrates from the model compound 6 (see p. 11) to methylbenzoylformate, the substrate (S), in the transition state ternary complex 6-Mg^{2+}-S, followed by migration of a proton from the cation radical of 6 to the anion radical of the substrate, then followed by a rapid transfer of a second electron. A complex 6·$Mg(ClO_4)^+$ was proposed as the reactive species in the scheme 1. The role of magnesium ion is not only to activate the substrate, but also to activate the model compound. The optical yield was shown to depend on the ratio of salt to 6, with optimal values dependent on the substrate reduced (13). Spectral studies suggest that the metal ion coordinates with the dihydropyridine moiety. The authors also felt that as a minor effect, it may be better to take into account the interaction between the amide-carbonyl group and metal ion because the stereospectificity of the reaction seemed to depend on the basicity of the carbonyl.

Scheme 1

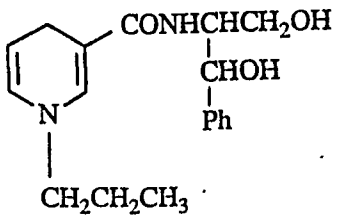


Although early studies of natural redox reactions carried out by Westheimer (17) suggested that hydrogen transfer from dihydropyridines was hydride-like, many reactions have been investigated for signs of electron transfer mechanisms, and in reactions of dihydropyridines with certain substrates evidence for radical pathways and electron-transfer pathways have been found (18). In other mechanistic studies, such as systems relating to dihydropyridine reductions of flavins and reductions of substituted isoquinolinium salts a hydride transfer is favored, and still other studies with probes for radical intermediates provide no evidence for radical intermediates (18). In yet another study on the mechanism of reduction of α-halo ketones by BNAH and related derivatives, it was

concluded that the reduction proceeds by a free radical chain process, which appears to be incompatible with the natural enzymic processes (19). Apparently, the reductions of various substrates by NADH model compounds are of interest in themselves, but a broad spectrum of possible mechanisms exist depending on the substrates used, and the reactions in general, do not give conclusive mechanistic information about the mechanisms involved in enzymatic processes.

However, an important direction in the study of NADH model reactions for organic chemists, particularly in the area of asymmetric synthesis, is the effort to mimic the stereospecificity obtained in the enzymatic process.

In the asymmetric reduction of methyl benzoylformate by 6 (see p. 11), it was found that the optical yield obtained was dependent on conversion, and the effect of added oxidized pyridinium salt on the optical yield was tested (20). Similarly, in another NADH model reduction of ethyl benzoylformate, it was observed that optical yield increased with conversion, to a limit. The best optical yield obtained in the reduction of the substrate with chiral 1,4-dihydronicotinamide 8 (see next page) in the presence of magnesium perchlorate in acetonitrile was reported as 29.1%, with a reaction yield of 46% after 2 hours (21).

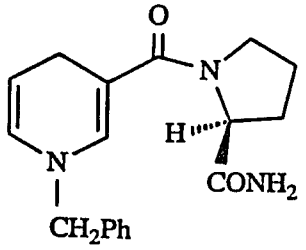


8

It was rationalized by taking into account the effect of the accumulation of the oxidized form of the model compound during the reaction. When the oxidized pyridinium form of 8 was added to the mixture, the optical yield was increased to 52%, with a reaction yield of 54%. It was then proposed that the asymmetric reduction involves two processes. One process involves substrate, metal ion, and dihydronicotinamide 8. The other process involves the oxidized form and becomes more important as the reaction proceeds. The formation of a ternary species of 8, the oxidized form, 8^+, and the metal ion, which creates a new chiral environment, was proposed. The presence of hydroxy groups in the model compound apparently affected the optical yield in the asymmetric reduction. When the reaction was run in absolute alcohol rather than acetonitrile, the reaction after 5 hours gave an optical yield of 13.3% in 33% chemical yield. In the presence of the oxidized form, the stereochemical outcome was unaffected. Apparently, in the hydroxylic solvent, 8^+ did not interact with 8, and the metal was inactivated as a result of greater solvation with the protic solvent. Apparently, the enantioselectivity is substantially dependent on the intermolecular chelation of metal ion with the hydroxyl groups in both forms of the nicotinamide

(reduced and oxidized forms).

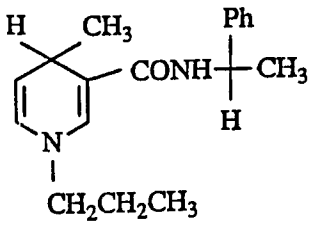
The model system 9, an L-prolinamide modified 1,4-dihydronicotinamide, was observed to asymmetrically reduce ethylbenzoylformate in acetonitrile with $Mg(ClO_4)_2$ in high optical yield, 83%, with enantiomeric excess increasing as the reaction proceeded (22). This was also accounted for in terms of a "feedback effect" of the oxidized nicotinamide, which accumulates during the reaction and interacts with the reactant (the dihydronicotinamide) by chelative mediation of the metal ion and/or charge transfer interaction (23). An expected enhancement in enantioselectivity was observed on increasing the initial substrate concentration.



9

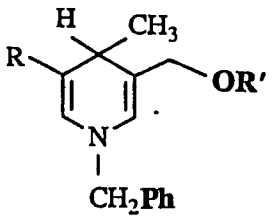
An increase in optical yield for the reduction of ketoesters was achieved by modifying the model compound 6 (see p. 11) by introducing chirality at the C-4 position of the dihydropyridine 10 (24). Reduction of methyl benzoylformate in acetonitrile with $Mg(ClO_4)_2$ gave methyl mandelate in 97% optical yield, 100% conversion. A variety of activated substrates were reduced with optical yield

varying from 50% to 98%. The configuration of the predominent enantiomer of the product was found to be determined by the configuration at the C-4 position and independent of the configuration at the benzylic carbon.



10

Meyers et al (25) synthesized interesting 1,4-dihydropyridine model compounds 11 in which the only stereochemical element is the chiral center at the C-4 position. The reducing agent formed here was found to transfer hydride, in a "self-immolative" (as described by the author) process to methyl benzoylformate to form methyl mandelate in good to excellent optical yields.



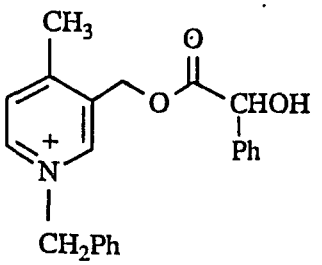
11

R	%e.e. R′=H	%e.e. R′=CH_3
H	95	62
$CO_2C_2H_5$	91	52
$CON(CH_3)_2$	62	52

Modification of the hydroxymethyl group to methoxymethyl kept chemical yields essentially unchanged but lowered the stereospecificity significantly. In all cases, when R was H or CO_2Et, the (S)-(+)-methyl mandelate was formed in excess. When R was replaced by the amide, the (R)-(−)-enantiomer was preferentially formed. These results were explained in terms of the conformation of the model-Mg ion-substrate ternary complex, in which the hydride is transfered only from one face. In the case of the hydroxymethyl model, (compound 11, $R'=CH_3$, see p. 18) when R=H or CO_2Et, the hydroxymethyl interacts with the carbonyl of the ester group either by hydrogen bonding, non-bonding electron pair donation, or both. With the methoxymethyl model, also with R=H or CO_2Et, the interaction was not as great (% e.e. dropped from greater than 91% to less than 63%). When $R=CONMe_2$, the drop in %e.e. was not as drastic as in the other cases, i.e., %e.e. went from 62% to 52%, and the stereochemical outcome was reversed. Apparently, the carboxamide group in position C-5 competes favorably with the hydroxy- or methoxy methyl in position C-3, resulting in a reversal of stereochemistry. The author postulates that a replacement of a non-polar group in the C-3 position, when R is a carboxamide group, may lead to higher enantioselectivity.

Meyers and Brown modified their model in a very interesting way (26). The dihydrocarbinol 11, R=H, was transformed to its magnesium alkoxide by reaction with 1 equivalent of MeMgCl in THF. The THF solution was then

treated with benzoylformyl chloride and an instantaneous reaction to a pyridinium salt 12 was observed.



12

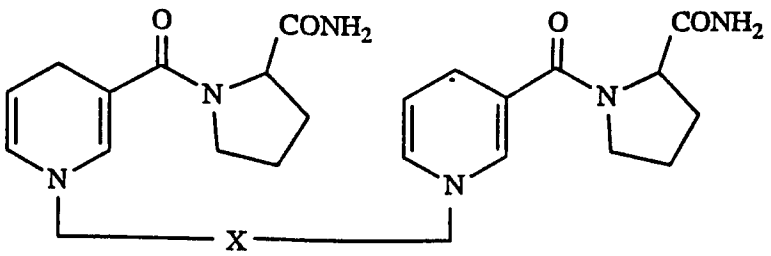
Solvolysis of the ester with methanol-methoxide ion yielded methylmandelate in 90% optical purity (65% chemical yield), corrected to greater than 99% stereoselectivity based upon enantiomeric purity of reagent. In this intramolecular reduction, the placement of the magnesium ion in close proximity by nature of the esterification process, greatly enhances the rate of the asymmetric reduction (the previous reductions required several days to reach completion).

Several other interesting dihydronicotinamide systems have been studied, including the crown ether 1,4-dihydropyridine compounds, with the nicotinamide group bridged at the C-3 and C-5 positions, synthesized by Kellogg and coworkers (27, 28) in which e.e.'s were obtained as high as 90%. Another notable bridged 1,4-dihydronicotinamide model system was synthesized by Verhoeven et al (29). In this study, deuterium isotope exchange experiments

were explored, in which differential reactivity of the diastereotopic H's at the C-4 position was shown to lead to diastereomeric purity greater than 90%.

2.1b Bis(NADH) Model Compounds

Chiral bis(NADH) model compounds 13 were designed with C_2 symmetry (30, 31). Apparently, the equivalent dihydropyridine moieties would block the specific face of each other, in an intramolecular chelation with the metal ion:



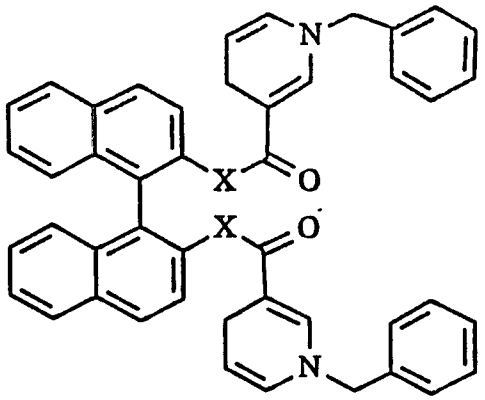
X = o-, m-, p-xylene, $(CH_2)_n$ (n=4 - 8)

13

High optical yields (95.6 - 98.1%) of reduction product were obtained with p-xylylene- and hexamethylene-bridged bis(NADH) models.

In another study, bis 1,4-dihydropyridines were prepared in which axially dissymmetric binaphthyls were used as the chiral moiety of NADH model compounds 3 (vide supra) (9). The importance of the C_2 symmetry for

stereospecificity was demonstrated. Models were synthesized in which the binaphthyl group contained only one pyridyl group, where X=O, and contained a benzyl- or methoxy group in place of the other pyridyl group shown in model 3.

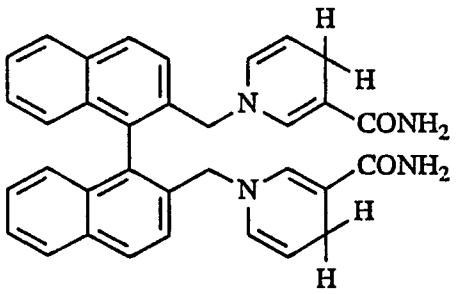


3

Reduction of ethyl benzoylformate produced ethyl mandelate in about 10% e.e., with a chemical yield (c.y.) of 50-55%. Reduction with the corresponding bispyridyl compound produced ethyl mandelate in higher optical yield, 43%, c.y. 24.8%. In this model compound, it was shown by UV spectrometry that the interaction of the dihydropyridyl group with magnesium ion was little. The author suggested that the increase in optical yield was observed because access of the substrate to one specific face of the dihydropyridine moiety was enhanced by steric interaction, as had been suggested earlier (30) (vide supra). In this study, the chelative interaction of the bisnicotinamide model with metal ion, as well as reaction conversion, was shown to be significant for enantiomeric excess.

Enantiomeric excess changed by variation of the catalyst amount, with optical yields varying by as much as 20%. Enantiomeric excess was also shown to increase as the reaction proceeded. Interestingly, in the same study, the product configuration was reversed and the chemical yield was increased when the nicotinamide group was attached to the binaphthyl at the pyridyl-N (compound 14) rather than at the amide-N (compound 3 where X=NH). In the reduction using the (S)-enantiomer of the model compounds in acetonitrile with magnesium perchlorate, the following results were obtained:

model	ethyl mandelate formed
(S)-3, X=NH	R, in 45.6% e.e, 14.3% c. y.
(S)-14	S, in 43.5% e.e, 26.0% c. y.



14

The other models synthesized in this study gave very poor optical yields (less than 12%).

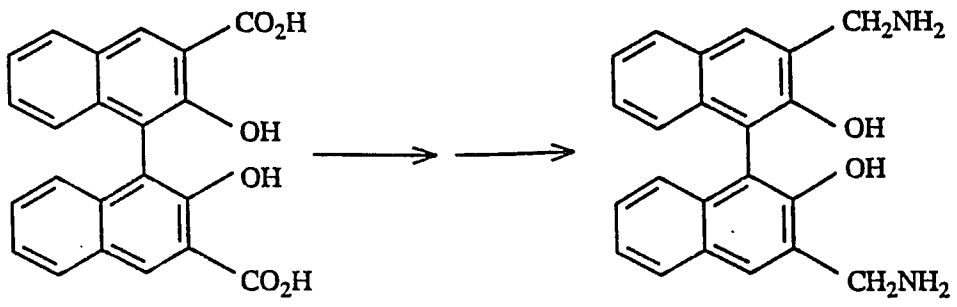
2.2 Synthesis of 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

2.2a Molecular Design of Novel Chiral Bisnicotinamide.

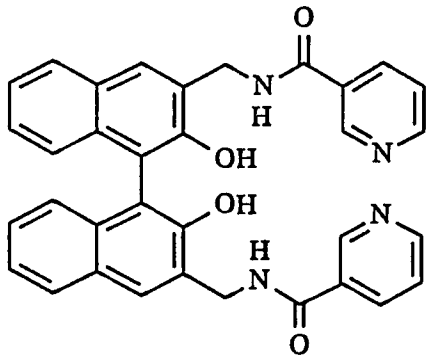
The 1,1′-binaphthyl compounds have been found to have high chiral recognition. An effective asymmetric reduction with (S)-(−)-2,2′-dihydroxy-1,1′binaphthyl as the auxiliary agent of $LiAlH_4$ was observed with high enantioselectivity (32). The synthesis of both C_1- and C_2-symmetric NADH model compounds with chiral binaphthyls has been reported (vide supra)(9). The binaphthyls were chosen to introduce axial dissymmetry into the chiral moiety rather than a chiral carbon atom. It was found that NADH models possessing C_2-symmetry (the "bis" compounds) reduced the substrate in higher enantiomeric excess, although the best optical yields obtained were 45.6% (c.y. only 14.3%) and 43.4% (c.y. 26%) (vide supra). It was determined that the amide group interacts with the metal ion and that the interaction is significant in the asymmetric reduction (vide supra). It was further determined that the enantiomeric excess was dependent on reaction conversion.

It was decided that it would be interesting to incorporate the binaphthalene moiety as the chiral source of a novel bisnicotinamide, which may be considered a precursor to a potential bis(NADH) model compound. The axially

dissymmetric binaphthalene, 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl (diacid), was chosen as the starting material in the synthesis of 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl (bisamine).



This optically active bisamine was used as the chiral moiety in the synthesis of the bisnicotinamide 3,3′-bis-(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl, a precursor to a potential bis(NADH) model compound:



The bisnicotinamide contains the binaphthalene moiety, a compound with a C_2-axis of high chiral recognition, the chirality being an important factor in the design of an NADH model and necessary for asymmetric reduction (vide infra).

Note that most of the models previously studied contained a chiral carbon rather than a C-2 axis of symmetry, with the exception of the work discussed earlier reported by Amano et al (9). The binaphthalene moiety also contains hydroxy groups, a factor which has been shown to be significant in the chelation properties of potential NADH model compounds (vide supra).

The bisnicotinamide contains the nicotinamide groups in the 3,3′ positions of the binaphthalene rather than in the 2,2′ positions as seen in model compound 3 (vide supra). The nicotinamide groups in this compound are located in close proximity to the hydroxy groups, another factor which may improve the chelation properties of the molecule with metal ion. Since both nicotinamide groups are located on the same molecule, the potential exists that when one pyridyl group is oxidized in the NADH model compound, it may interact in an intramolecular fashion with the reduced group, another important consideration.

2.2b Synthesis of 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

The preparation of optically active 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl began with the synthesis and resolution of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl (diacid). The diacid has been resolved and the absolute configuration has been established by X-ray diffraction as (R)-(+) (33).

Upon identification and purification of optically active diacid, the optically active 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide (bisamide) was prepared and characterised. The bisamide was then reduced to the optically active bisamine, 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

The optical purity of the bisamine was determined by preparing the MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) derivative and obtaining the ^1H NMR spectrum. It was necessary to complex the MTPA derivative with a chiral lanthanide shift reagent in order to resolve the diastereomeric signals. The bisamine prepared from optically active bisamide was found to be of high optical purity.

The acid chloride derivative of nicotinic acid was prepared and then reacted with the optically active bisamine to form 3,3′-bis(3-pyridylcarbonylamino-methyl)-2,2′-dihydroxy-1,1′-binaphthyl (the bisnicotinamide). The bisnicotinamide was purified, characterised, and then reacted with benzyl halide to form quaternized bisnicotinamide benzyl halide salts (new NAD^+ model compound). The novel NAD^+ model was reduced to form an NADH model compound.

3.0 EXPERIMENTAL

3.1 General

Melting points were taken on a Thomas Hoover Capillary Melting Point apparatus and are uncorrected. Optical rotations were obtained with a Perkin Elmer model 141 polarimeter in a 1 decimeter thermostated cell. Rotations were taken at the indicated temperature, either after having equilibrated the solution and cell at the measured room temperature, or using a Lauda Circulator (thermostated water bath) attached to the cell.

Silica gel glass plates (commercial brand EM 60 F-254, 5 x 10 cm size) precoated with fluorescent indicator were used for analytical thin layer chromatography (TLC), with solvent systems used as indicated. Visualization of TLC results was effected by use of ultraviolet light at wavelength 254 nm, or by staining in an iodine chamber. Column chromatography was carried out using silica gel, chromatographic grade, with mesh size as indicated. Chromatographic separations were followed by analysis of collected fractions by TLC.

Analytical high performance liquid chromatography (HPLC) was performed

on a Waters Model 6000 Solvent Delivery System equipped with a Model 450 Variable Wavelength Ultraviolet Detector, or Model 510 Automated Gradient Control System, using Waters Reversed Phase C-18 columns, with the indicated solvent systems. Flow rate generally used was 1.5 mL/min. Preparative HPLC was performed on a Waters Prep LC/System 500, using a Reversed Phase C-18 column. HPLC grade organic solvents were degassed either by bubbling helium gas through the solvent, or by vigorously stirring the solvent with a magnetic stirring bar while under suction from a water aspirator. The solvents were further treated by filtering through millipore filters before being used. Glass distilled water was also degassed and filtered. Trifluoroacetic acid (TFA) was reagent grade and used without further purification. Microliter syringes were used to measure the amounts of TFA in the solvent systems used.

Infrared spectra were obtained on a Beckman Infrared Spectrometer, model 4260, generally using a nujol mull of the sample, with a scanning range of 4000-600 cm^{-1}, and a scanning speed of 300 cm^{-1}/min. Absolute band position for IR spectra was calibrated with standard polystyrene film.

Nuclear magnetic resonance (NMR) spectra were generally recorded on an IBM NR 80, or IBM Instruments WP 200 spectrometer, in pulsed fourier transform mode, with variable temperature 5 mm probes. Spectrometers operated at frequencies of 80.06 and 200.13 MHz, for ^{1}H measurements, and at

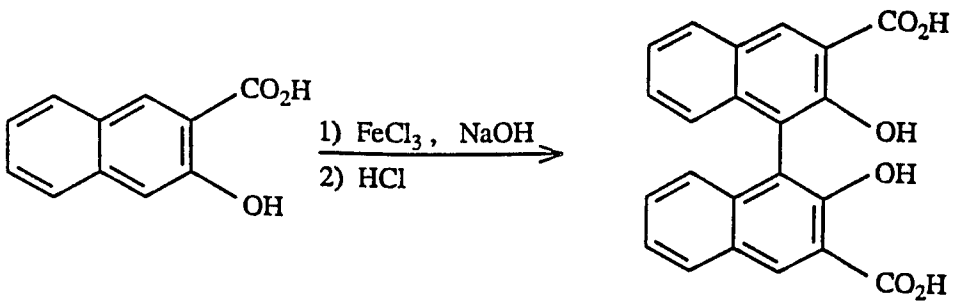
20.13 and 50.33 MHz for ^{13}C measurements; lock, internal deuterium; temperature generally ambient. ^{1}H NMR spectra were also obtained on a Jeol GX 400 NMR spectrometer (400 MHz, pulsed fourier transform mode, ambient temperature, 5 mm probe), in the determination of the optical purity of 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl. Chemical shifts for both ^{1}H and ^{13}C spectra are reported as δ values in ppm with internal tetramethylsilane (TMS) as reference unless otherwise indicated. In general, sample concentrations for ^{1}H NMR ranged from 1-5%, and for ^{13}C NMR from 5-20%, in the indicated solvent. Acquisition parameters used are indicated on individual spectra.

3.2 Preparation of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl.

Tetrahydrofuran was distilled from $LiAlH_4$ prior to use. Triethylamine was purified and dried by distillation from NaOH. Methanol was dried by distillation from magnesium shavings and iodine (catalyst) immediately prior to use. Thionyl chloride was purified by distillation from quinoline (in a ratio of 50 g $SOCl_2$ to 10 mL quinoline) immediately prior to use. All other chemicals used were reagent grade and were used without further purification.

3,2a Synthesis of racemic 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl (34).

The oxidative coupling of 3-hydroxy-2-naphthoic acid is used in the synthesis of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl:



Sodium hydroxide (7.25 g, 0.181 mol) and 3-hydroxy-2-naphthoic acid (36.07 g, 0.191 mol) were stirred into 500 mL of distilled water and heated to reflux. A hot solution of $FeCl_3 \cdot 6H_2O$ (54.3 g, 0.285 mol) in 100 mL H_2O was added dropwise to the vigorously stirred, refluxing mixture. Stirring was continued at reflux for an additional 45 minutes. The reaction mixture was allowed to cool to room temperature. A solution of sodium hydroxide (45 g, 1.1 mol) in 500 mL H_2O was added to dissolve all solids, followed by the addition of 300 mL of concentrated HCl with stirring. The yellow precipitate was filtered, washed with 175 mL of 10% aqueous HCl and 300 mL of H_2O. The yellow precipitate was dried in an oven, under vacuum, at 75-80°C. Triethylamine

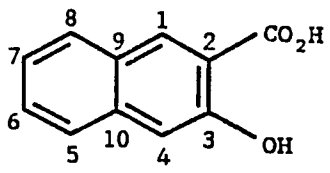
(29.9 g, 0.296 mol) was added to a hot, stirred solution of 35.33 g of the dried solid in 185 mL of tetrahydrofuran. The solution was allowed to cool to room temperature for one day, and cooled at 0°C for one day. Brown plates were collected from the solution and washed twice with cold tetrahydrofuran. The dry salt (21.02 g) was dissolved in 90 mL of 5% aqueous sodium hydroxide. The solution was washed once with diethyl ether, filtered, and acidified to pH 1 with concentrated HCl. The yellow solid was collected, washed with H_2O, and dried. The weight of the crude yellow powder was 13.90 g, (0.037 mol, 38.7% yield), mp 290°C, dec.

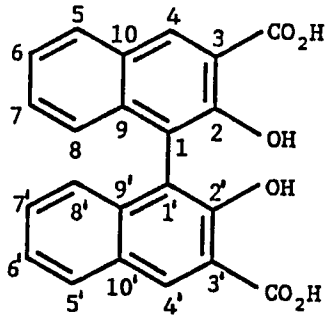
After recrystallization from 80% acetic acid, the yellow crystals melted at 331-334°C, reported mp 331-333°C (35). IR (nujol mull) 3300-2400 cm^{-1} (OH stretch), 1660 cm^{-1} (carbonyl stretch). Analytical thin-layer chromatography (TLC) was used to check the purity of the final product. TLC conditions used: developing solvent 1-butanol, acetic acid, and water (4:1:5, volume:volume, upper phase of the two phase system is used); development time 60 min. TLC showed only one product, with an R_f value of 0.54 obtained for the diacid.

The 200 MHz ^1H NMR spectrum of the diacid in DMSO-d_6 was obtained. Acquisition parameters include: temperature 297K, spectral width 15.3 ppm, pulse width 30°, number of transients 64. The spectrum (see figure 1, p. 35) gave the following chemical shifts in the aromatic region: 8.76 (s, C4-H, 2H),

8.13-8.08 (m, Ar-H, 2H), 7.39-7.33 (m, Ar-H, 4H), 7.04-6.99 (m, Ar-H, 2H). The ^{1}H NMR spectrum also gave a very broad signal centered at about 11.3 and was assigned to the COOH and OH protons combined. This region is the expected downfield position for the carboxylic acid proton. The single peak results from the exchange of the carboxylic acid proton and the hydroxylic proton (36). This peak disappeared upon addition of H_2O (see figure 2, p. 36).

The 20 MHz broad band decoupled ^{13}C NMR spectrum, 10% in DMSO-d_6, taken at 297K, pulse width 20°, (see figure 3, p. 37), gave 11 peaks (reference peak, DMSO-d_6, at 39.5 ppm). The chemical shifts of the spectrum are compared to the ^{13}C NMR chemical shifts reported for 3-hydroxy-2-naphthoic acid in table 1, p. 39. The difference in the numbering of carbons in the two compounds is noted below:





The off resonance ^{1}H-decoupled ^{13}C NMR spectrum was obtained for the diacid in DMSO-d_6, at 297K, pulse width 20°, 2,499 transients (see figure 4, p. 38). The spectrum showed 6 non-protonated, singlet signals, as expected, at

172.1, 154.1, 136.6, 126.7, 116.4, and 114.7. The Ar-CH signals were assigned as shown in table 1, p. 39. The results of these experiments support the assignments reported (37).

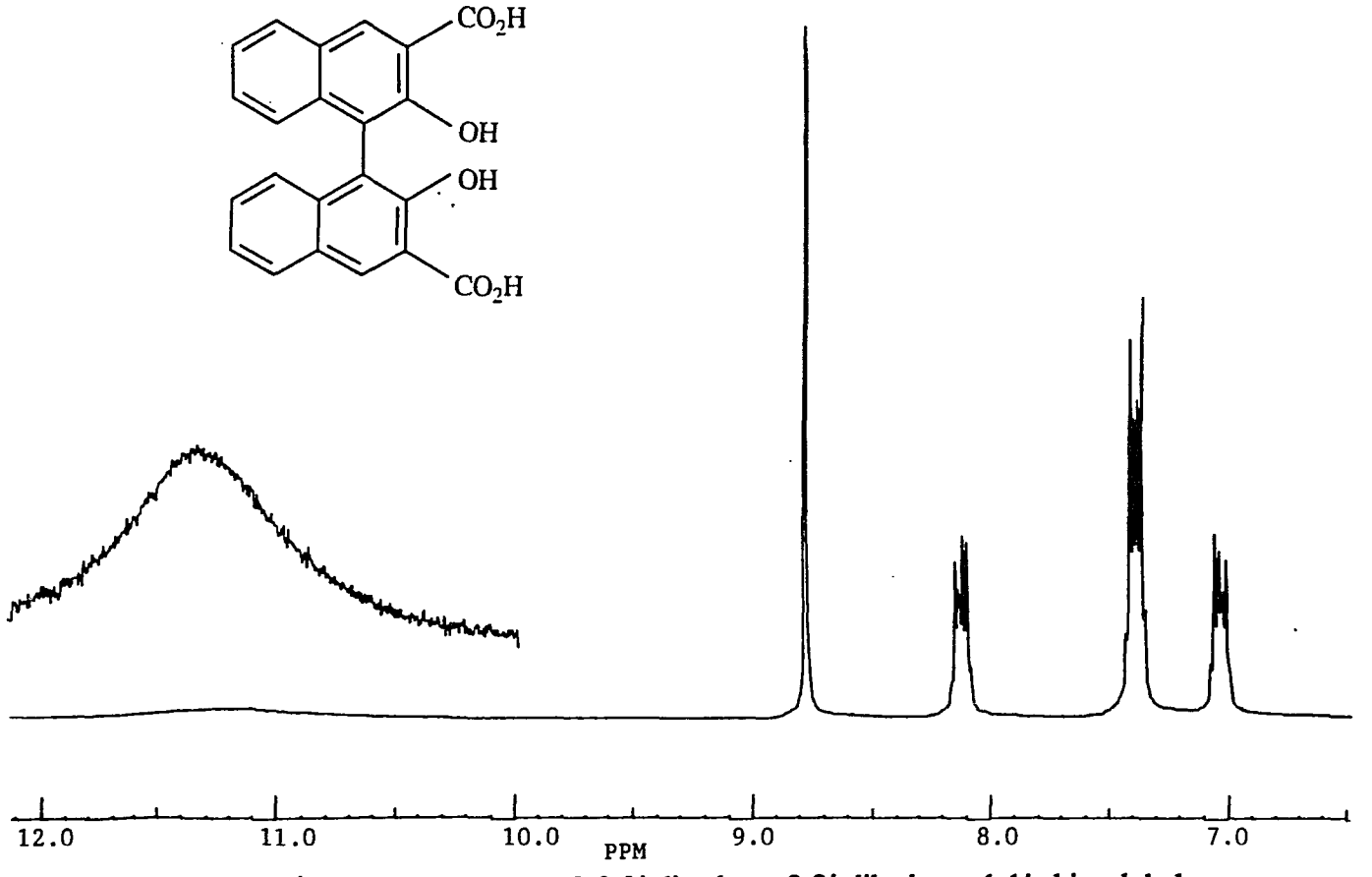


Figure 1 200 MHz ^{1}H-NMR spectrum of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′- binaphthyl.

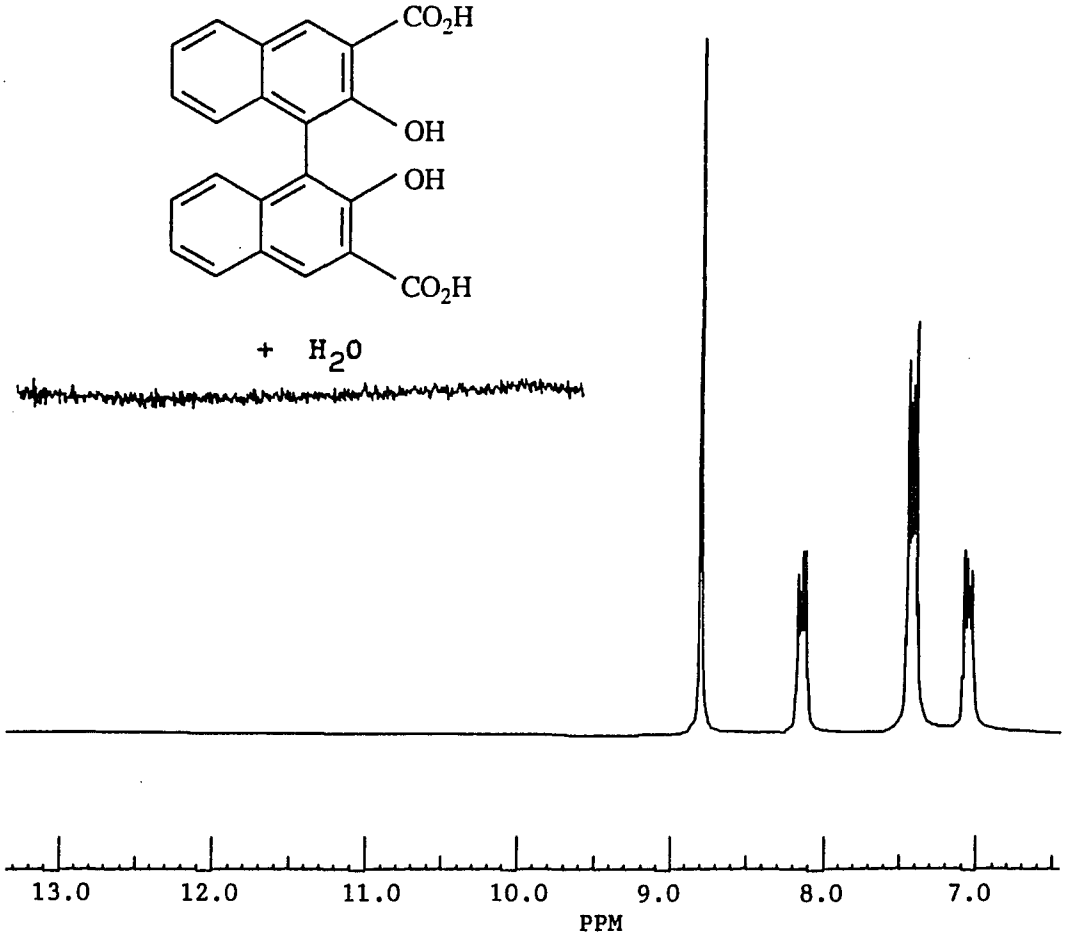


Figure 2 200 MHz ^{1}H-NMR spectrum of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′binaphthyl in DMSO-d_6 with water added.

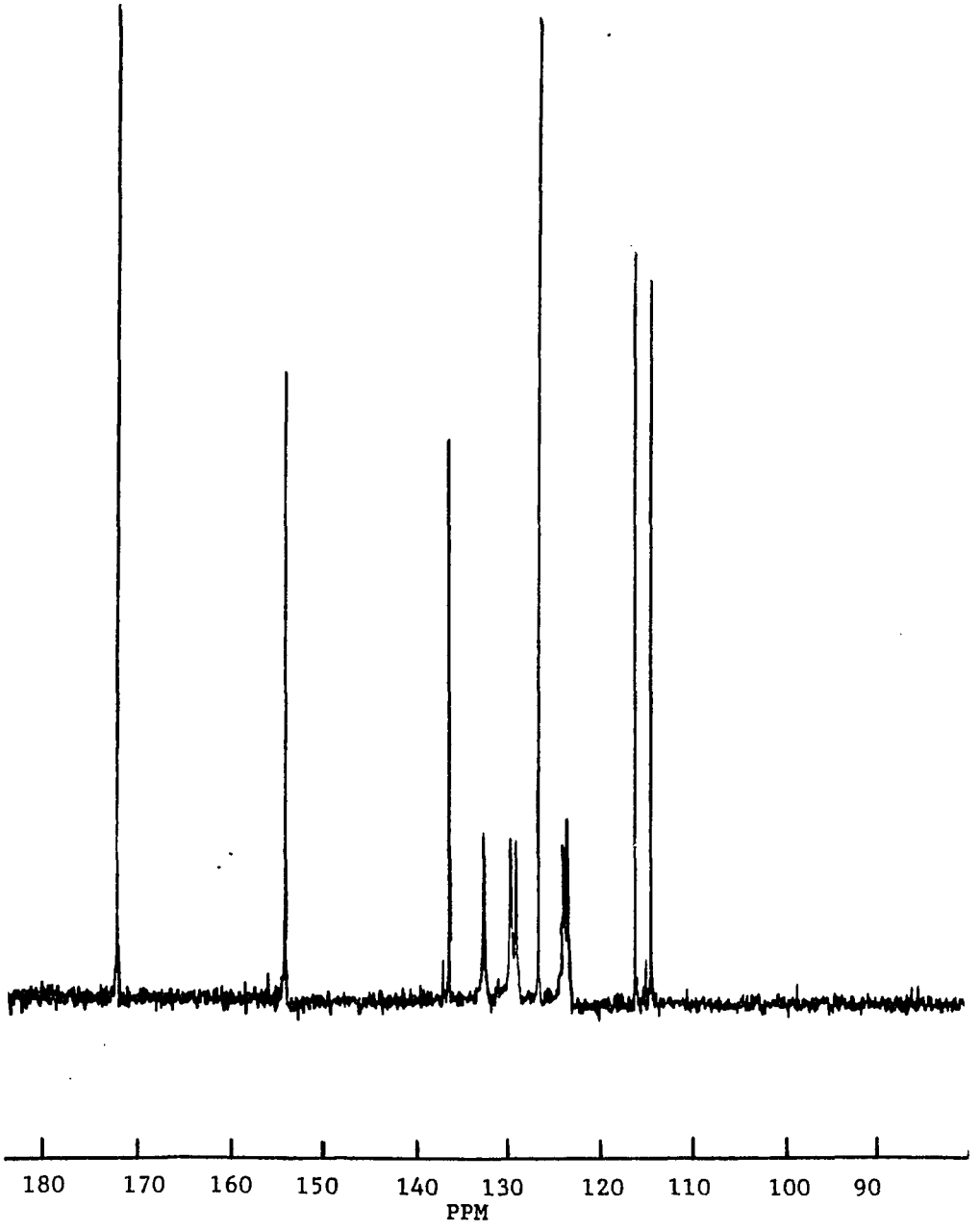


Figure 3 20 MHz ^{13}C-NMR spectrum of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl. Number of transients, 9215.

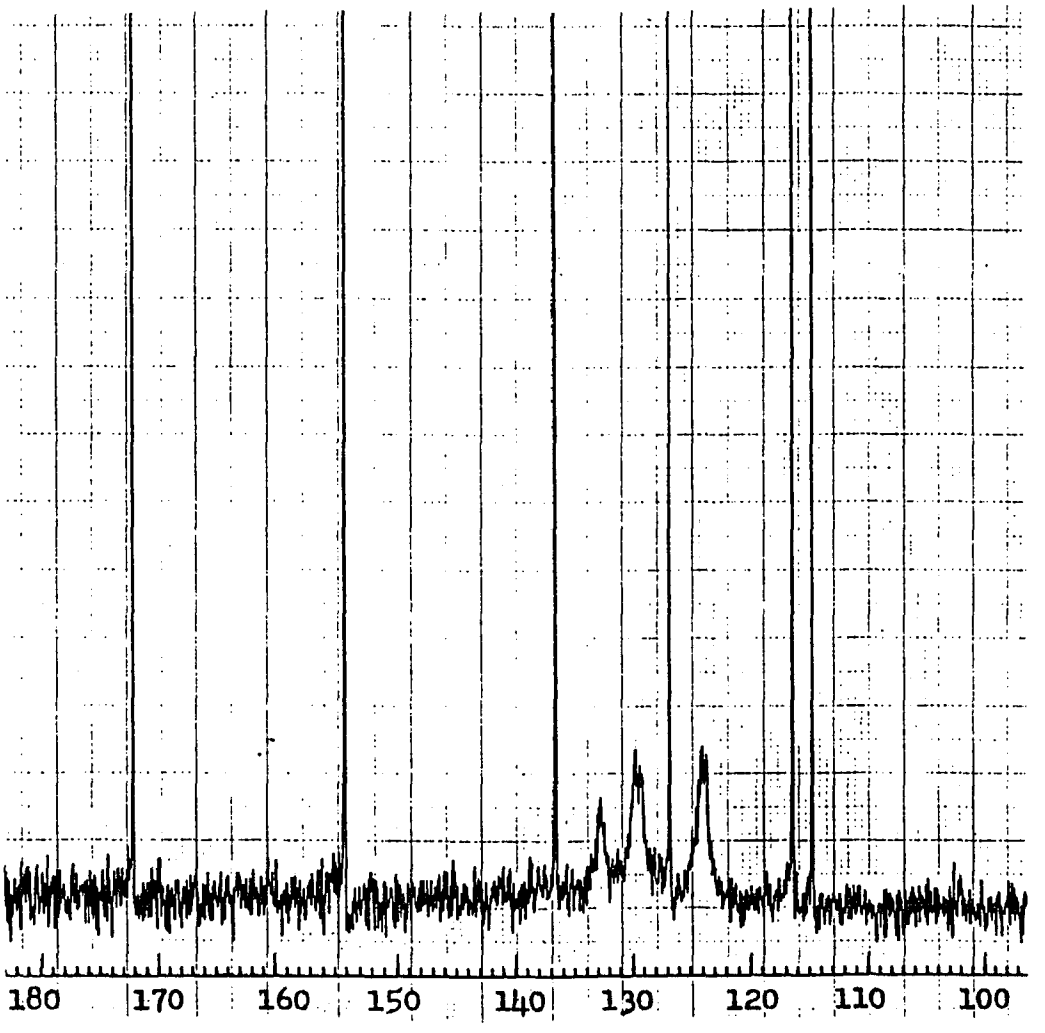


Figure 4 20 MHz ^{13}C-NMR off resonance decoupled spectrum of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl.

TABLE 1
^{13}C NMR Chemical Shifts (ppm) of
3,3'-dicarboxy-2,2'-dihydroxy-1,1'-binaphthyl
& 3-hydroxy-2-naphthoic acid

diacid[a]	assigned to[b]	3-hydroxy-2-naphthoic acid[c]	assigned to[c]
171.30	COOH	172.6	COOH
153.36	quat-C[d]	156.7	C-3
135.73	quat-C	138.1	C-10
131.88	CH	133.4	C-1 (CH)
128.99	CH	129.9	C-6 (CH)
128.38	CH	129.9	C-8 (CH)
125.94	quat-C	127.5	C-9
123.28	CH	126.8	C-5 (CH)
122.82	CH	124.8	C-7 (CH)
115.63	quat-C	115.9	C-2
113.92	quat-C	111.7	C-4 (CH)

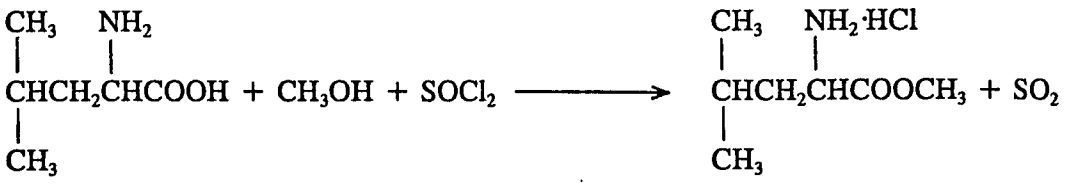
a. 20 MHz broad band decoupled spectrum
b. as determined by off resonance ^{1}H decoupled ^{13}C NMR
c. literature values (37)
d. quaternary Carbon

This synthetic reaction was run several times on approximately the same scale (i.e., between 36 and 50 g of 3-hydroxy-2-naphthoic acid), with yields on the order of 40%, until approximately 120 g of diacid was collected. The combined crude diacid was used directly in the following optical resolution.

3.2b Preparation of optically active 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl (34).

3.2b.1 Preparation of L-leucine methyl ester (38).

L-leucine methyl ester, used in the resolution of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl (34), was prepared from L-leucine.



Thionyl chloride (64 mL, 0.89 mol), was added dropwise into 240 mL of cold (dry ice, acetone bath), stirring methanol in a 3-necked, 2 liter flask fitted with a mechanical stirrer and a drying tube filled with $CaSO_4$ (drierite) to protect from moisture. L-leucine (102.31 g, 0.780 mol) was added in portions to the stirred solution, which was kept below −7°C during the addition. The stirred reaction

mixture was then slowly heated to 40°C, and kept at this temperature for 2 hours. During this period, the leucine slowly dissolved. The solution was then transfered to a round bottom flask and then attached to a rotary evaporator. Methanol and excess $SOCl_2$ was evaporated, using a water aspirator attached to the rotary evaporator. The aspirator was removed, a vacuum pump was attached, and the residue was then dried under vacuum at 100°C in the rotary evaporator for 1 hour. The residue, crude L-leucine methyl ester hydrochloride salt, was stored in a dessicator at 0°C over indicating $CaSO_4$, at atmospheric pressure.

Immediately prior to use in the resolution of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl, the L-leucine hydrochloride salt was dissolved in water. The aqueous solution was layered with ether, followed by addition of phenolphthalein and concentrated ammonia until the solution turned red. The ether layer was separated, washed with water, dried over sodium sulfate, and concentrated. The crude free amine obtained was distilled as needed for the resolution of the diacid.

A portion of the crude free amine, 37.26 g, was distilled, yielding the following fractions:

Fraction	Temperature (°C)	Pressure	Weight
1	72.5-73.0	13 mm Hg	1.54 g
2	73.0-73.5	13 mm Hg	31.25 g
Residue	-	-	4.25 g

Reported b.p. 69-70°C/12 mm Hg (38). Fraction 2 was obtained in 84% yield, with $[\alpha]^{27}_D$ +14.34° (neat), reported $[\alpha]^{25}_D$ +15.3° (neat) (34), optical purity 94%.

3.2b.2 Resolution of 3,3'-dicarboxy-2,2'-dihydroxy-1,1'-binaphthyl (34).

3,3'-Dicarboxy-2,2'-dihydroxy-1,1'-binaphthyl (105 g, 0.280 mol) was added to 1200 mL dry methanol. To the suspension was added L-leucine methyl ester (85.83 g, 0.591 mol), $[\alpha]^{22}_D$ +14.74° (neat), 96.3% optical purity, n^{25}_D=1.4275, reported n^{25}_D=1.4269 (35) in 34 mL methanol. The reddish brown solution was heated over a steam bath for 5 minutes. The solution was allowed to cool to room temperature for 1 day, then kept at 0°C for another day. The salt that separated was filtered, washed with cold, dry methanol, and air dried to give (R)-(+)-3,3'-dicarboxy-2,2'-dihydroxy-1,1'- binaphthyl·L-leucine methyl ester salt, 81.92 g. (87.8%), $[\alpha]^{25}_D$ +92.7° (c 0.3, CH_3OH), reported (34) $[\alpha]^{25}_D$ +99.7° (c 0.3, CH_3OH). The yellow crystals were powdered in a mortar, and digested in 3 successive portions of 325 mL dry CH_3OH at reflux, with stirring, for 1 hour. Specific rotations obtained at 25°C after each successive digestion were:

$[\alpha]^{25}_D$	lit. $[\alpha]^{25}_D$ (34)
+111.3° (c 0.3, CH_3OH)	+117.8° (c 0.3, CH_3OH)
+113.3° (c 0.3, CH_3OH)	+124.9° (c 0.3, CH_3OH)
+117.9° (c 0.29, CH_3OH)	+123.0° (c 0.3, CH_3OH)

The weight of the salt after the third digestion was 66.16 g. This salt was dissolved in 350 mL of water containing 10.6 g of NaOH. The resulting solution was acidified with concentrated HCl. The yellow precipitate was filtered and dried to give 36.41 g (69.4% yield) of (R)-(+)-3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl. An analytical sample was recrystallized once from 80% acetic acid, and was dried in a vacuum oven for 24 hours at 120°C, to give yellow needles, $[\alpha]^{25}_{D}$ +177° (c 1.08, pyridine), m.p. 335-337°C, reported $[\alpha]^{25}_{D}$ +185° (c 1.08, pyridine), m.p. greater than 285°C (34), optical purity, 95.7% (optical purity of resolving agent, L-leucine methyl ester was 96%). The ^{1}H and ^{13}C NMR spectra of resolved 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl (see figures 5 and 6, p. 45 and 46) were identical to those of the racemic diacid.

The mother liquor from the original salt was evaporated to an oil and dissolved in 100 mL CH_3OH. An insoluble yellow powder was filtered from the methanol solution. The yellow powder was washed with additional methanol. The combined methanol solutions were evaporated. The residual salts were dissolved in NaOH solution. The basic solution was acidified with concentrated HCl to precipitate the diacid and was then filtered. The precipitate was suspended in 350 mL dry CH_3OH. Triethylamine (55.5 mL, 40.3 g, 0.4 mol) was added. The dark-red solution was warmed on a hot plate until it was clear, then cooled to room temperature for 2 days.

The solid that separated was filtered, air-dried (weight 40.57 g) and recrystallized from 406 mL CH_3OH containing 3.33 mL of triethylamine, giving 27.52 g of the (S)-(−)-diacid salt. This salt was converted to the diacid by dissolving in NaOH, acidifying the solution with HCl, and then filtering, to yield 15.5 g (30% yield), of the (S)-(−)-diacid, $[\alpha]^{25}_D$ −192° (c 0.750, pyridine), m.p. 342-345°C, reported $[\alpha]^{25}_D$ −190° (c 0.750, pyridine), m.p. greater than 285°C (note that the reported specific rotation for the (+) enantiomer was measured at a different concentration than was the (−) enantiomer) (34).

The optically active diacid was soluble in acetone, as compared to the racemic diacid, which was only slightly soluble in acetone.

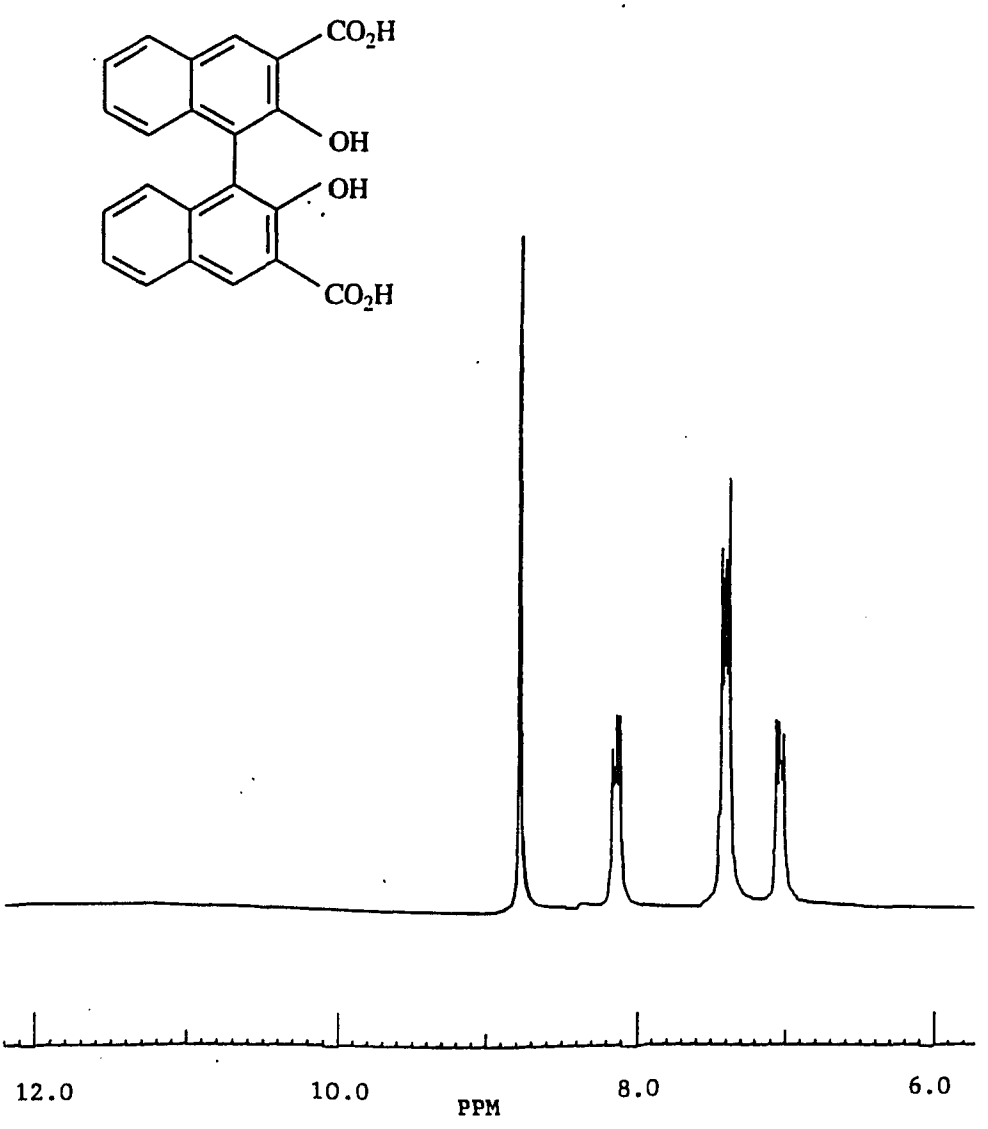


Figure 5 200 MHz ^{1}H-NMR spectrum of (R)-(+)-3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl.

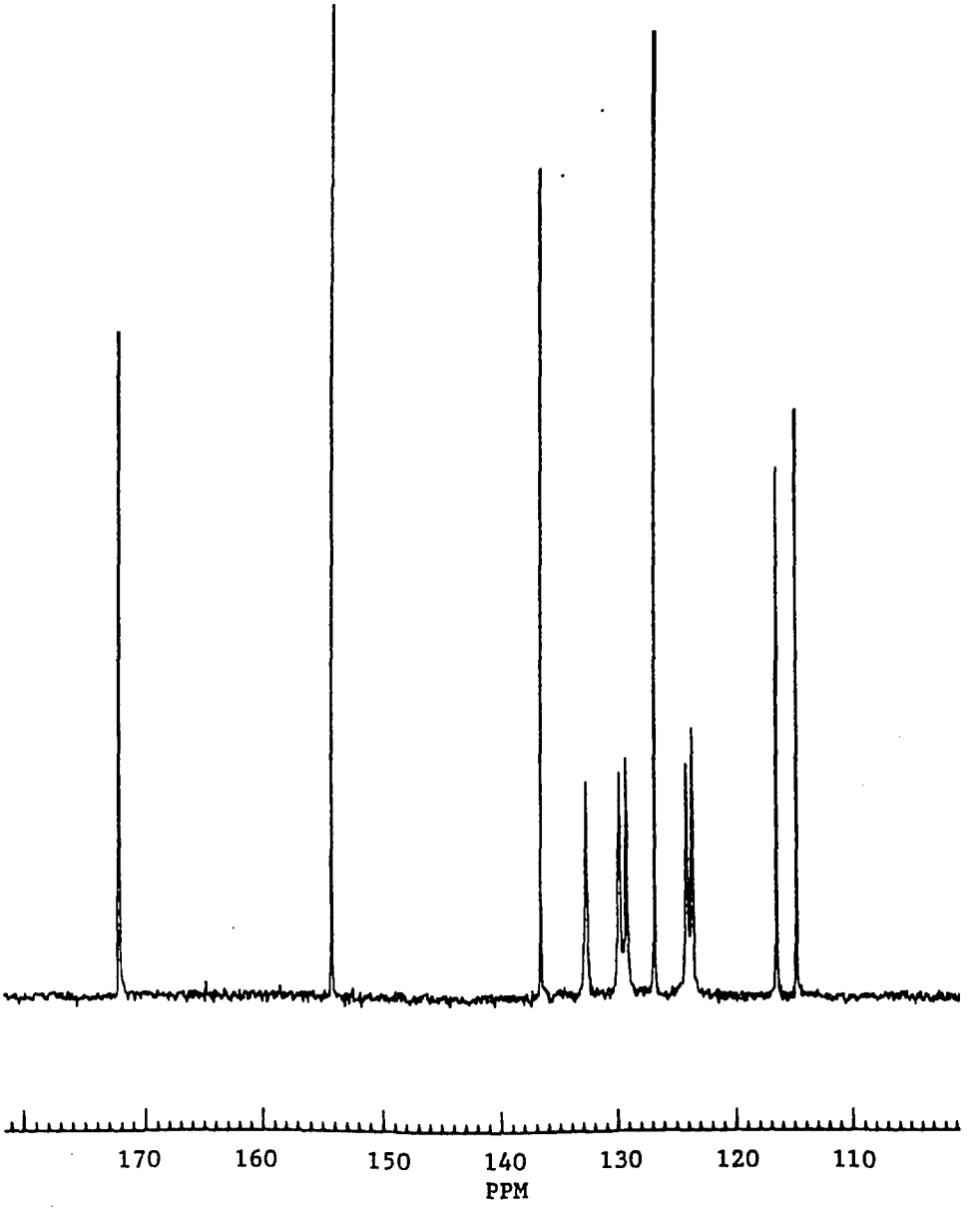


Figure 6 20 MHz ^{13}C-NMR spectrum of (R)-(+)-3,3′-2,2′-dihydroxy-1,1′-binaphthyl. Acquisition parameters include relaxation delay 5 seconds, pulse width 20°, number of transients, 8255.

3.3 Preparation of 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide.

Thionyl Chloride was purified by distillation from quinoline (in a ratio of 50 g $SOCl_2$ to 10 mL quinoline) (39) immediately prior to use. All other chemicals used (except the solvents used for HPLC) were reagent grade and were used without further purification. HPLC grade solvents were treated as described previously (see section 3.1).

The synthetic reaction conditions were initially determined using racemic 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl. The synthesis of 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide (bisamide) was to be attempted using three different methods because of the presence of phenolic -OH groups, which potentially might cause undesired side reactions. One method was to prepare the diethyl ester of the diacid, which could then be converted to the bisamide. Direct amidation of the diacid was also attempted, first, in the reaction of an acid with urea, and second, in the reaction of an acid with thionyl chloride and ammonia. The esterification of the diacid and the reaction of the diacid with urea are discussed briefly in the following sections. More attention is given to the amidation of the diacid with thionyl chloride and ammonia, because the initial results of the latter reaction indicated continued efforts in that direction.

3.3a Preparation of the diethyl ester of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl.

The method used was essentially that reported by Stanley and Adams (35). Hydrogen chloride gas (more than 11 g) was bubbled through a cold solution (−78°C, dry ice, acetone bath used) of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl (4.3 g, 11 mmol) in 500 mL absolute ethanol. The solution was brought to reflux for 6 hours. The solution was then concentrated. Dilute sodium carbonate solution (3N) was added until an alkaline reaction to litmus paper was observed. The solution was filtered, and the diester precipitate was washed with additional sodium carbonate and water. The crude dry product weight was 4.9 g (11 mmol, 100% yield). After recrystallization from ethyl acetate, the product had a m.p. of 239-240°C, reported m.p. 230-232°C, corr. (35). IR (nujol mull) 3300-2800 cm^{-1} (OH stretch), 1670 cm^{-1} (carbonyl stretch). Analytical TLC, with 1-butanol, acetic acid, and water, (4:1:5, volume:volume, upper phase) as the developing solvent showed one major product, with an R_f value of 0.92, different than and clearly resolved from the starting material, the diacid, which has an R_f value of 0.54 in this developing solvent.

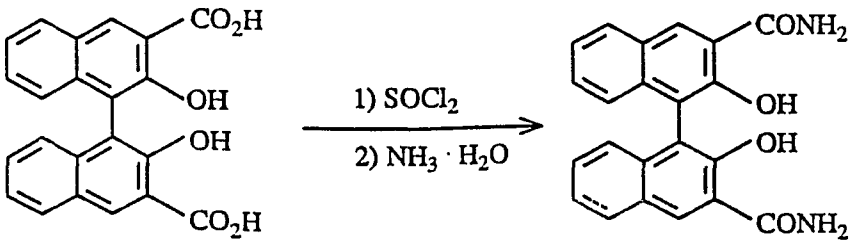
3.3b Preparation of 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide by the reaction of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl with urea (40).

Recrystallized diacid (3.0 g, 8.0 mmol), a large excess of urea (120 g, 2 mol), and several drops of phosphoric acid were mixed together and heated to 170°C. A clear, dark red solution was obtained. The solution was heated, with stirring, for 4.5 hours. Water was then added to the solution to form a slurry while being cooled by an ice bath. On addition of a 25% aqueous NaOH solution, a clear red solution was obtained. An orange precipitate was formed after stirring for 3 hours. The solution was filtered and HCl was added to precipitate the bisamide. The precipitate was washed with sodium bicarbonate solution and water several times. The crude product weighed 1.87 g, 62% yield, m.p. 300°C (dec).

Analytical TLC showed one major product, with an R_f value identical to the product obtained in the reaction of the diacid with thionyl chloride and ammonia (vide infra).

3.3c Preparation of 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide by the reaction of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl with thionyl chloride and ammonia.

The reaction of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl, first with thionyl chloride and then with aqueous ammonia, was used in the preparation of 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide:



3,3′-Dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl (4.0 g, 10.7 mmol) was added to thionyl chloride (64 ml, 0.89 mol). The reaction mixture was refluxed for 8 hours. Excess thionyl chloride was then distilled at reduced pressure, using a water aspirator, at 50°C. The product was protected from moisture by use of a drying tube filled with $CaSO_4$ in between the reaction vessel and the water aspirator. The dry residue was added cautiously to stirring concentrated aqueous ammonia, which was cooled by an ice bath. Concentrated hydrochloric acid was then added slowly, with the temperature kept below 30°C. When the solution became acidic, the yellow precipitate was filtered, washed with copious amounts of water, and dried to

give 3.75 g (10.1 mmol, 94% yield) of crude 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide. The crude product, a yellow powder, was analyzed by thin layer chromatography, using methylene chloride, methanol, acetic acid, 10:1:0.5 (volume:volume), as the developing solvent. TLC showed one major product (R_f value 0.68), 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide, and one minor product (R_f value 0.53), with little or no starting material (R_f value about 0.3)[1].

Several recrystallizations of a portion of the bisamide from 80% acetic acid were required to obtain an analytical sample. Recrystallization gave yellow needles, 2.62 g (7.04 mmol, 66% yield), m.p. 347°C (dec). IR spectroscopy (nujol mull), 1660-1560 cm^{-1} (carbonyl stretch, NH_2 deformation). Elemental analysis: calculated for $C_{22}H_{16}N_4O_2$: C, 70.95; H, 4.34; N, 7.52; found: C, 70.70; H, 4.17; N, 7.24. The racemic bisamide was soluble in dimethylformamide, hot dimethylsulfoxide, and slightly soluble in tetrahydrofuran.

The 200 MHz ^1H NMR spectrum of the bisamide, taken at 303K, with a pulse width of 30°, 4.5% in DMSO-d_6 (see figure 7, p. 53), gave the following chemical shifts: 12.88 (s, OH, 1.9 H), 8.88 (s, $CONH_2$, 2.0 H), 8.73 (s, C4-H, 2.0 H), 8.21 (s, $CONH_2$, 2.0 H), 7.94-7.89 (m, Ar-H, 1.9 H), 7.39-7.29 (m, Ar-H, 4.0 H),

---

[1] The starting material, the diacid, is not clearly resolved using this developing solvent (i.e., the spot tails), however, the R_f value is clearly less than that of the bisamide and the minor product formed in the reaction. The presence of diacid was determined using butanol:acetic acid:water, 4:1:5, upper phase, as the developing solvent, which gave good separation of diacid from the other products.

6.99-6.95 (m, Ar-H, 2.0 H). The hydroxy and nonequivalent amide protons were assigned after adding D_2O to the NMR sample and obtaining a new ^1H NMR spectrum. The new spectrum (see figure 8, p. 54) gave chemical shifts at: 8.65 (s, Ar-H, 2.0 H), 8.05-8.00 (m, Ar-H, 2.0 H), 7.41-7.36 (m, Ar-H, 4.0 H), 6.98-6.94 (m,Ar-H, 1.9 H). The 50 MHz, quantitative ^{13}C NMR spectrum (see figure 9, p. 55), an inverse gated decoupled spectrum in DMSO-d_6, with trisacetylacetonato-chromium (III), $Cr(acac)_3$, as relaxation agent gave 11 peaks with the indicated areas at: 172.55 (1.8 C), 154.85 (1.9 C), 135.69 (2.1 C), 129.26-129.14 (4.0 C), 128.44 (2.0 C), 126.30 (2.0 C), 123.99 (2.1 C), 123.31 (2.0 C), 116.57 (2.0 C), 116.08 (2.1 C).

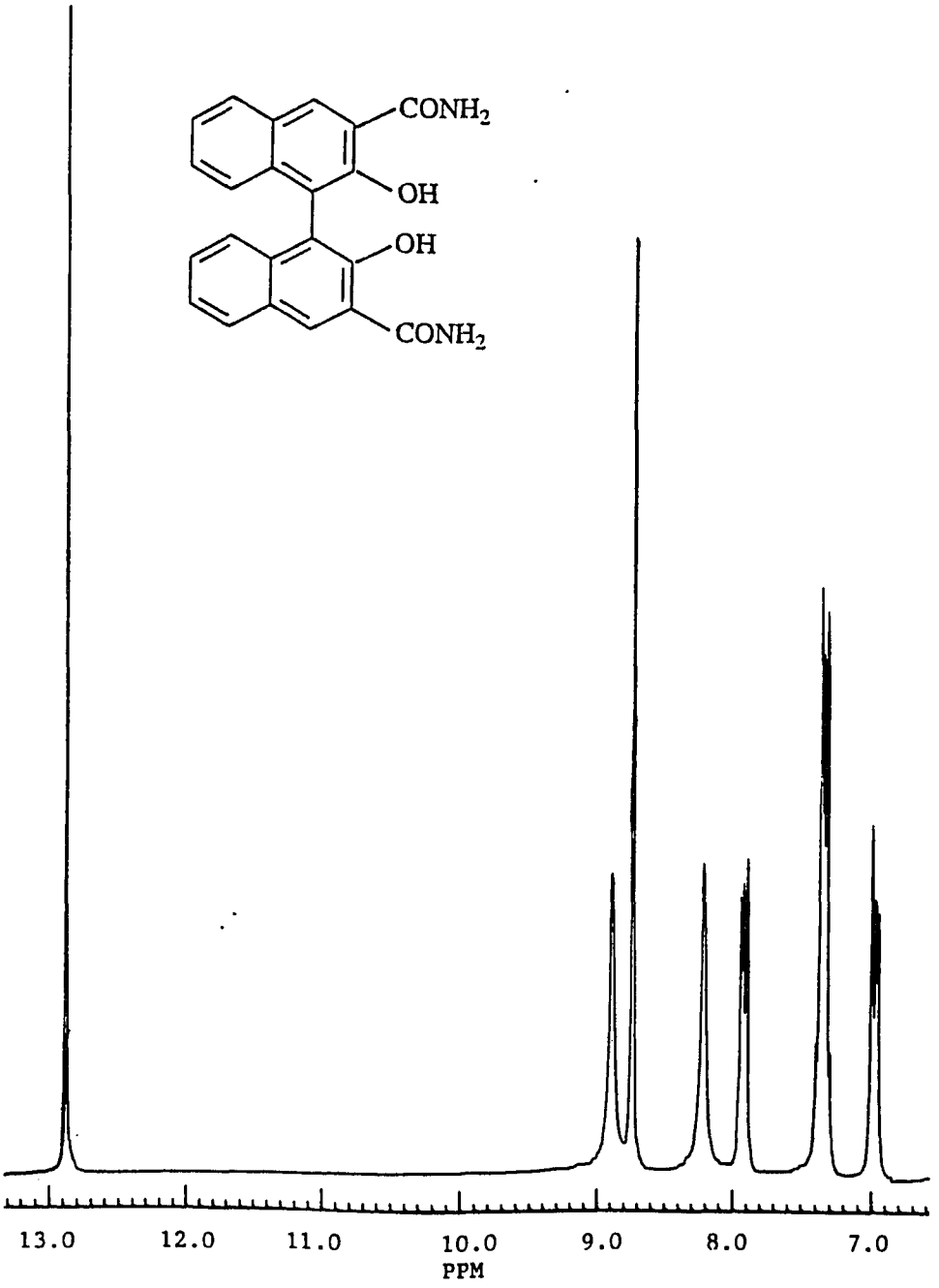


Figure 7 200 MHz ^{1}H-NMR spectrum of 2,2′-dihydroxy-1,1′-3,3′-dicarboxamide. Acquisition parameters include relaxation delay 2 seconds, no. of transients, 64.

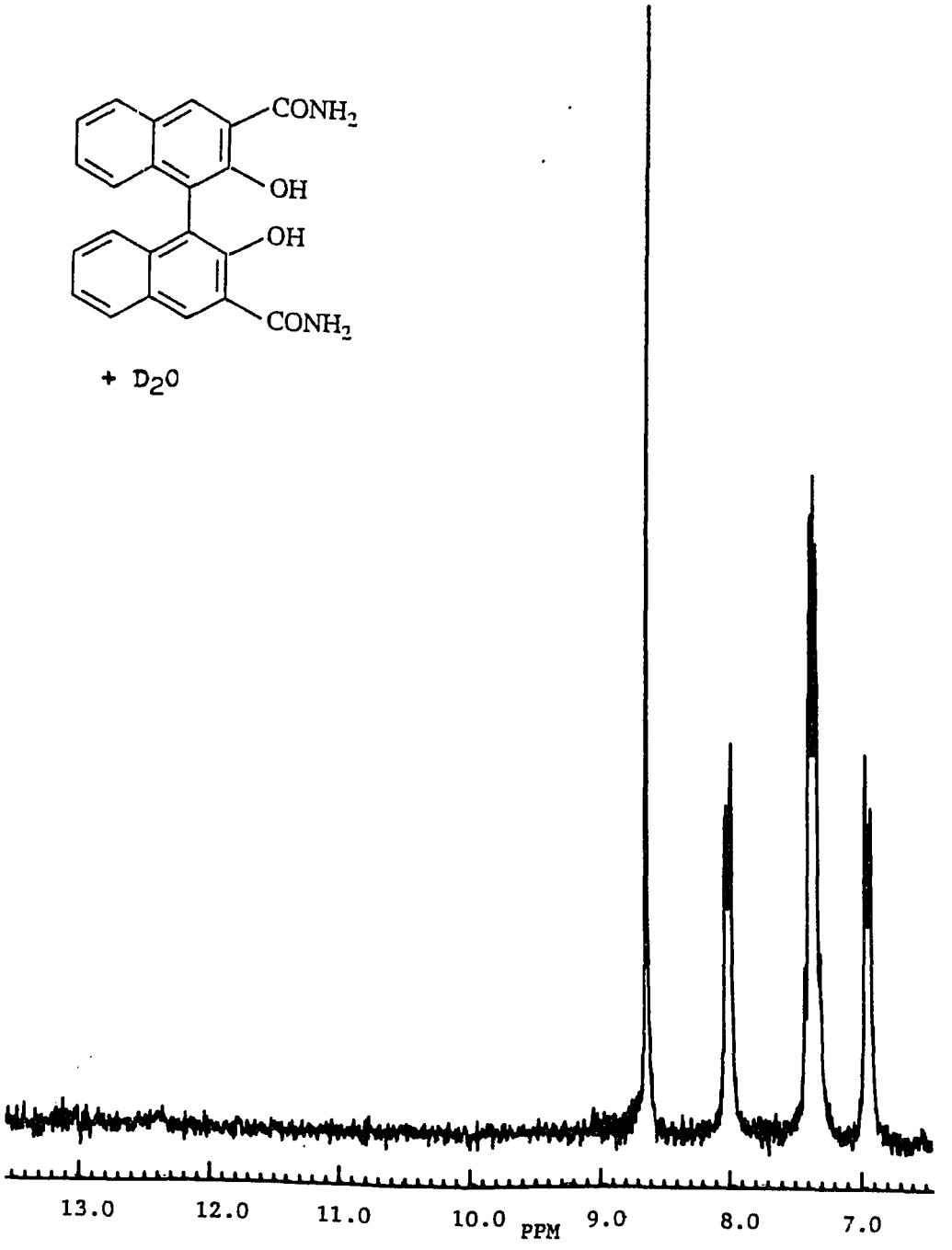


Figure 8 200 MHz ^{1}H-NMR spectrum of 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide in DMSO-d_6 with D_2O added.

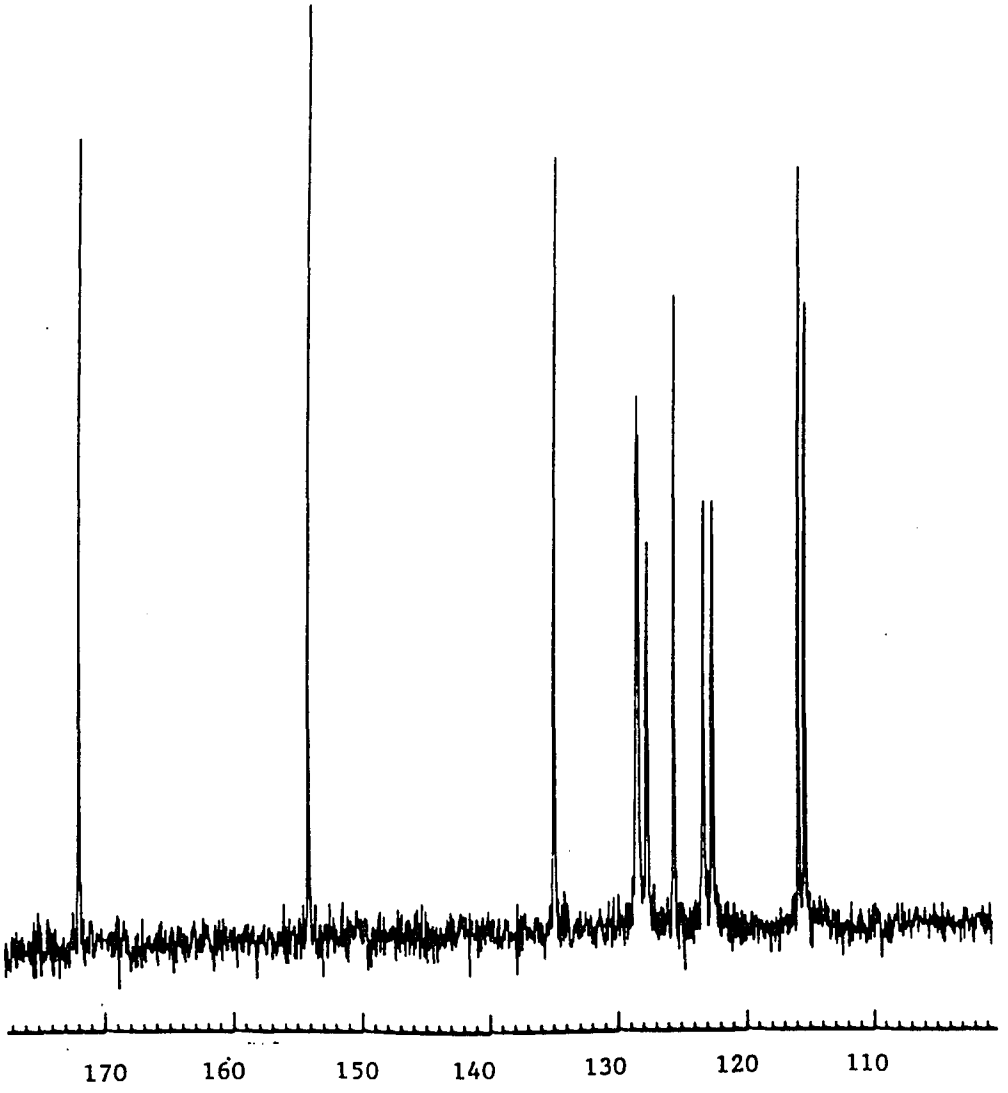


Figure 9 50 MHz ^{13}C-NMR inverse gated decoupled spectrum of 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide, $Cr(acac)_3$ added. Number of transients 22,311.

3.3d Preparation of optically active 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide.

(S)-(−)-2,2′-Dihydroxy-1,1′-binaphthyl has been reported to racemize to the extent of 72% in 1.2N in HCl solution at 100°C for 24 hours (41). For this reason, an attempt was made to synthesize the optically active bisamide using milder conditions than had been used for the racemic bisamide, which required refluxing the diacid in $SOCl_2$ for several hours.

(R)-(+)-3,3′-Dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl (8.21 g, 22.0 mmol), $[\alpha]^{25}_D$ +177 (c 1.08, pyridine), 95.7% optically pure (34), was added to 1 L thionyl chloride, with stirring, at room temperature. After 1 hour, much of the diacid had not dissolved. The reaction temperature was brought up to 40°C slowly, but complete dissolution was still not attained. Finally, the reaction temperature was raised to 70°C for 1 hour before all of the 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl was dissolved. The reaction temperature was then brought down quickly to 20°C. The solvent was distilled under reduced pressure at 40°C. The residue was added to cold aqueous ammonia, and hydrochloric acid was added until an acidic reaction was obtained to litmus paper. The precipitate was filtered and dried. Both TLC and HPLC (see figure 10, p. 59 for HPLC chromatogram) showed that the reaction was incomplete, with the previously minor product (presumably a monoacid-monoamide binaphthol) being a major product, along with 2,2′-dihydroxy-

1,1′-dinaphthyl-3,3′-dicarboxamide, estimated at 50%, but with very little starting diacid. Final weight of reaction product was 7.28 g. Yield of bisamide, 45% based on HPLC determined purity of 50%.

The reaction product (0.5 g) was chromatographed on a silica gel column (35-70 mesh, chromatographic grade) using methylene chloride:acetic acid, 20:1, volume:volume, as the initial eluent. Thin layer chromatography was used to follow the chromatographic separation. The unreacted diacid and much of the second major product was eluted. The solvent system was then changed to methylene chloride:methanol:acetic acid, 20:2:1, volume:volume, to elute the bisamide to approximately 90% purity, as estimated by HPLC (see figure 11, p. 60). It was necessary to use preparative HPLC with a reversed phase C-18 column (solvent system 60% methanol, 40% water, 0.025% trifluoroacetic acid, volume:volume) in order to obtain a purified sample, verified by TLC, HPLC (see figure 12, p. 61), and NMR, of (R)-(+)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide, $[\alpha]^{21}_{D}$ +183° (c 0.975, acetone).

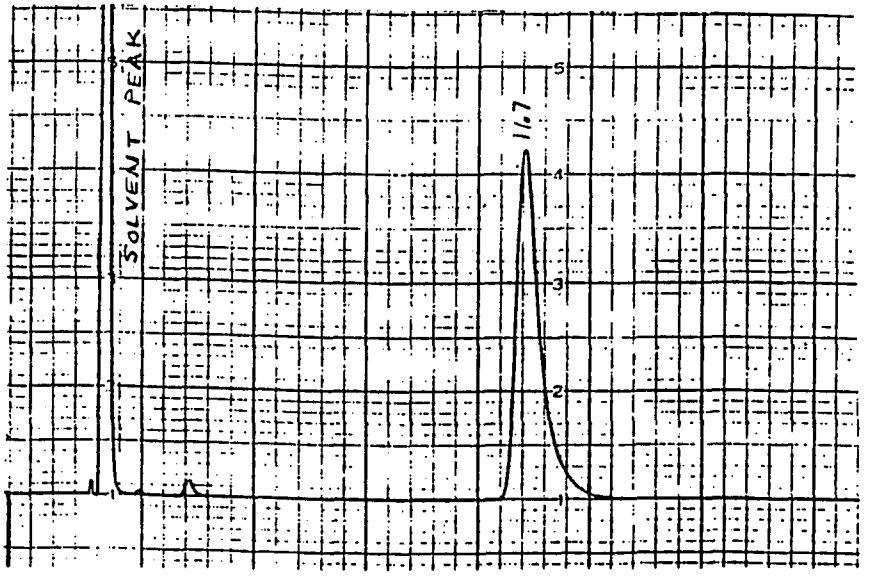
Another portion (1.00 g) of the original crude reaction product was subjected to further reaction under the conditions used for the racemic compound, i.e., overnight at reflux in thionyl chloride. The product, 0.91 g (2.4 mmol), was analyzed by TLC and HPLC and shown to be 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide 98% pure (see figure 13, p. 62), with no starting material and very

little of the second product. A preparative HPLC separation of 0.15 g yielded a purified sample of 0.06 g (40% isolated) of the bisamide (see figure 14, p. 63), $[\alpha]^{21}_{D}$ +177° (c 0.990, acetone).

Under the reaction conditions of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl at reflux for 8 hours in $SOCl_2$, significant racemization apparently does not occur, (compare the rotations reported above) and 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide is formed in 85-90% yield, as determined by HPLC. Depending on the method of purification, the yield of purified isolated bisamide varies, i.e., preparative HPLC - 40% yield (high purity), recrystallizations, 65% yield (purity greater than 98%).

Optically active 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide is soluble in acetone, as compared to the racemic bisamide, which is insoluble. The optically active bisamide is also soluble in dimethylformamide and dimethylsulfoxide. The 200 MHz ^{1}H NMR spectrum (see figure 15, p. 64) obtained of the optically active bisamide is identical to the ^{1}H NMR spectrum obtained of the racemic bisamide (see figure 7, p. 53).

a)



b)

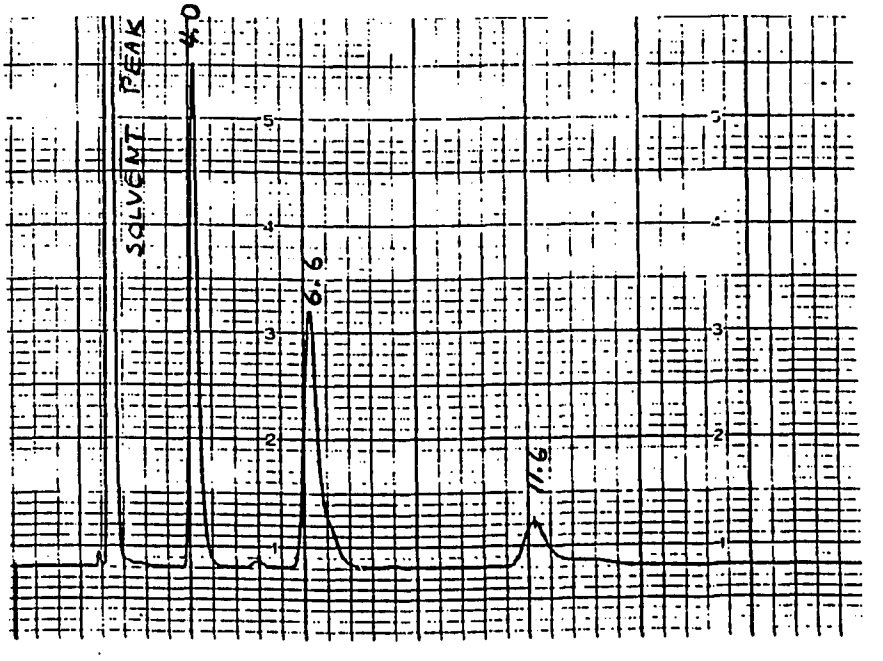


Figure 10 HPLC chromatograms - 254 nm, 70% CH_3OH, 30% H_2O, 0.025% TFA
a) (R)-(+)-diacid (starting material) in acetone.
b) crude product; bisamide, run time 4.0, estimated purity, 50%.

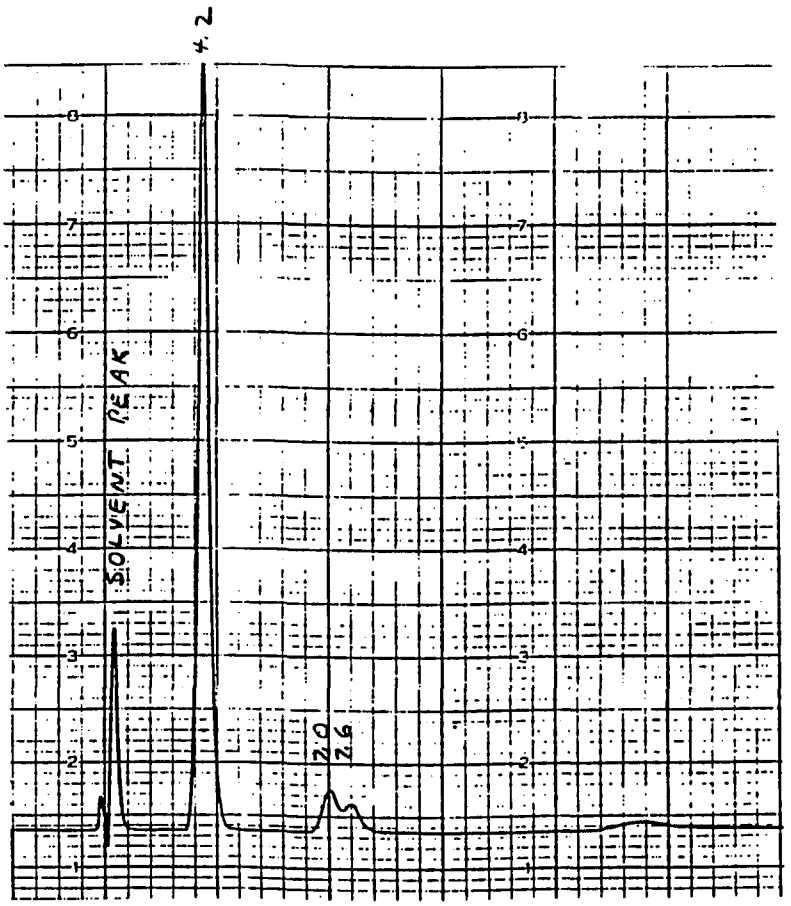


Figure 11 HPLC chromatogram (254 nm) of (R)-(+)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide, estimated purity 90%. Solvent 70% CH_3OH, 30% H_2O, 0.025% TFA.

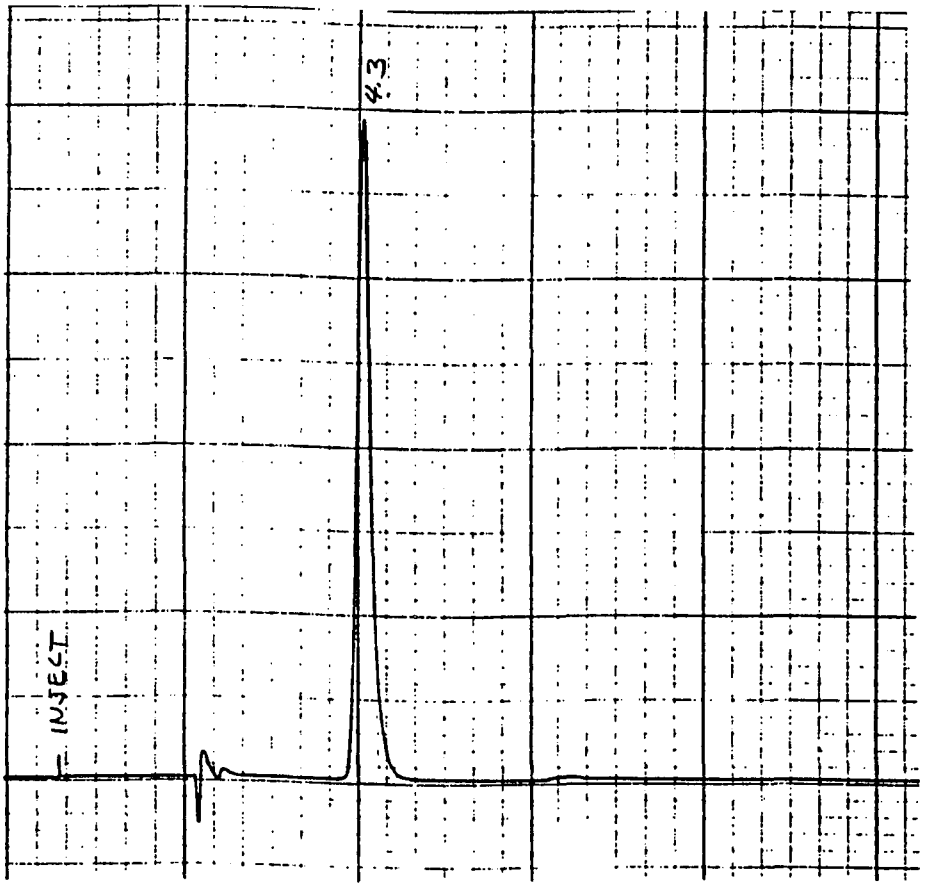


Figure 12 HPLC chromatogram (210 nm) of preparatively separated (R)-(+)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide. Solvent - 70% CH_3OH, 30% H_2O, 0.025% TFA.

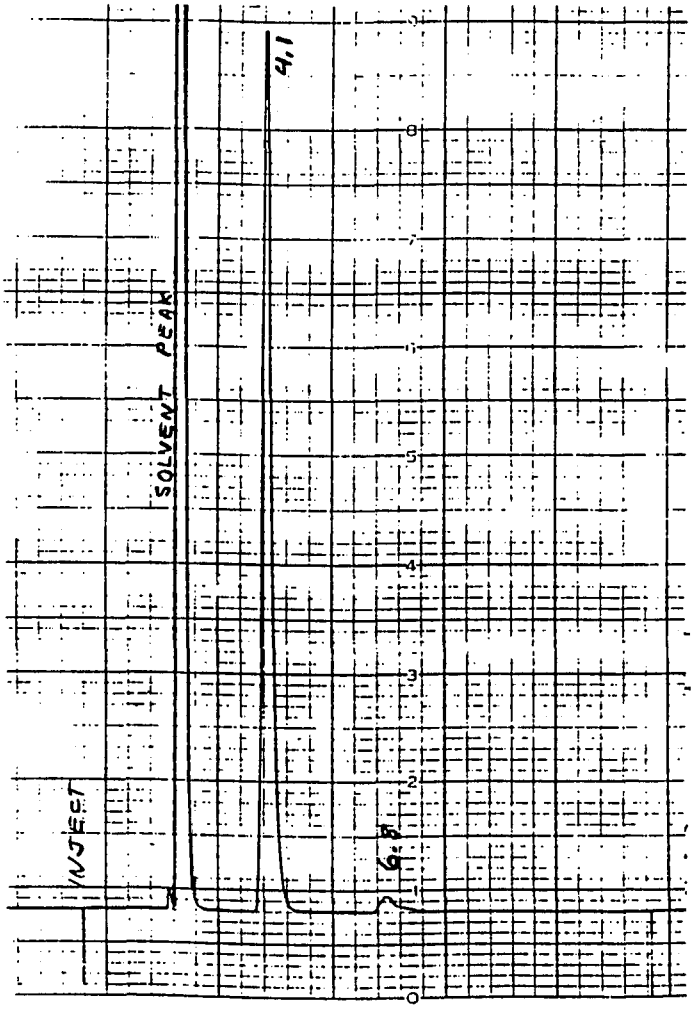


Figure 13 HPLC chromatogram (254 nm) of crude (R)-(+)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide. Solvent system - 70% CH_3OH, 30% H_2O, 0.025% TFA.

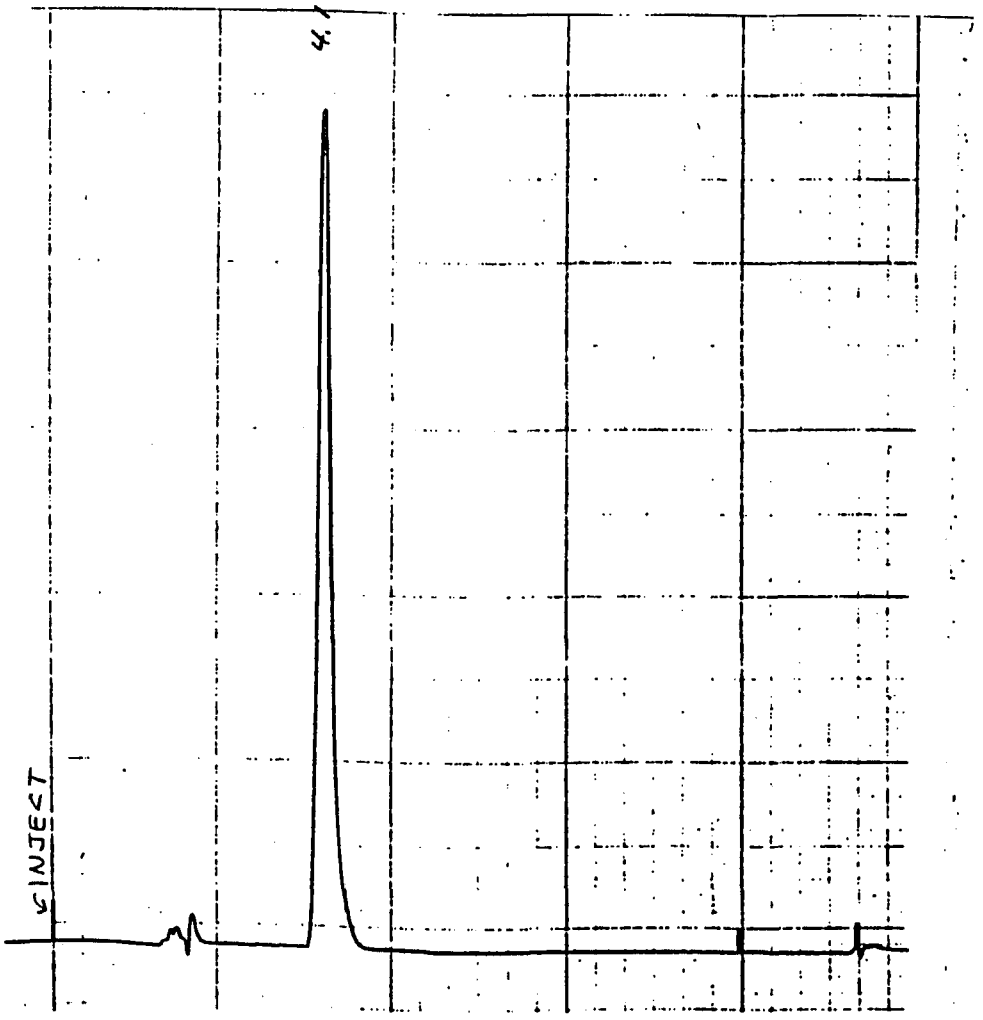


Figure 14 HPLC chromatogram (254 nm) of preparatively separated (R)-(+)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide. Solvent - 70% CH_3OH, 30% H_2O, 0.025% TFA.

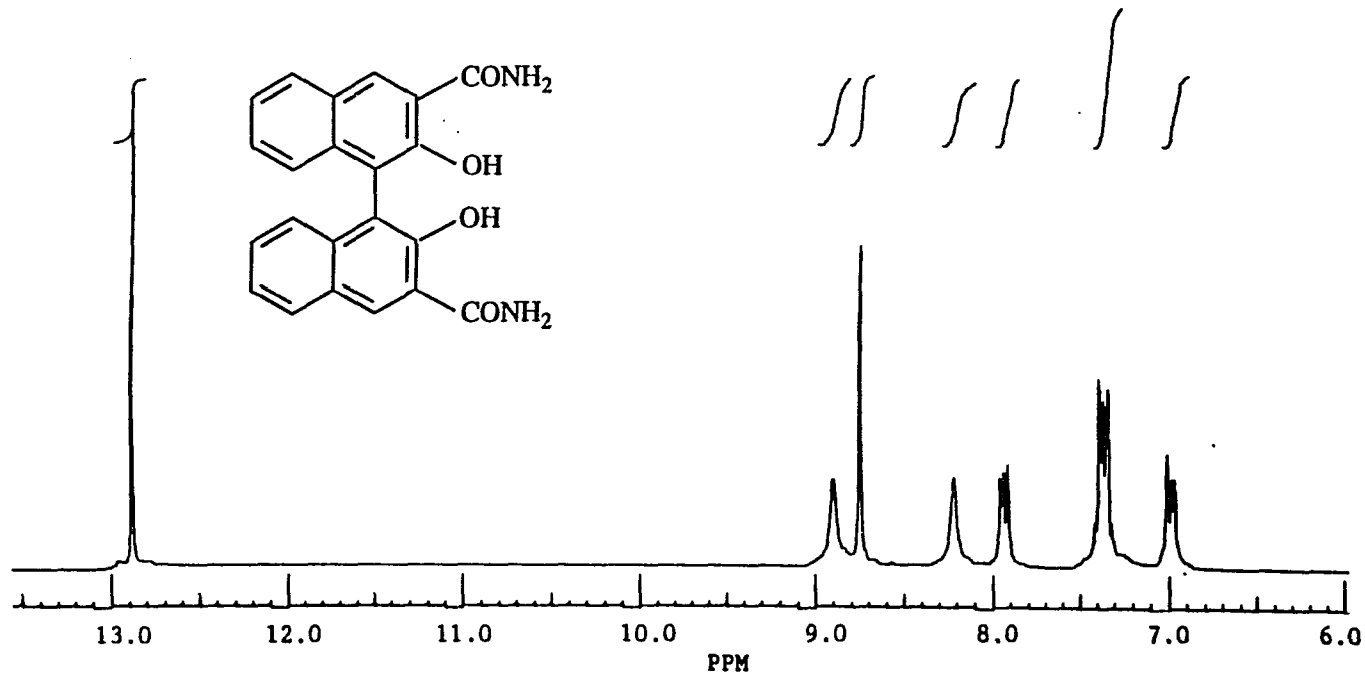


Figure 15 200 MHz ^{1}H-NMR spectrum (R)-(+)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide.

3.4 Preparation of 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

Air sensitive reagents, BH_3·THF, $LiAlH_4$ and $BH3{\cdot}S(CH_3)_2$ were purchased in the desired concentrations, stored and used under dry nitrogen atmosphere. Nitrogen was dried by passing over activated $CaSO_4$ (drierite), indicating silica gel, 3A molecular sieves, and 5A molecular sieves. Drying agents were activated by heating overnight (for at least 12 hours) at 180°, and then cooling to room temperature in a dessicator. Air sensitive reagents were transferred by syringe to reaction vessels (as individually described) which had been flamed under vacuum, then cooled to the indicated temperature under nitrogen.

Reversed phase C-18 columns were used for analytical and preparative HPLC. Before use, HPLC grade solvents and glass distilled water were degassed and filtered through millipore filters as described earlier (see section 3.1).

Attempts were made to reduce 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide to 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl (bisamine) using three different reducing agents, $LiAlH_4$, $BH_3{\cdot}S(CH_3)_2$, and BH_3·THF. The crude product hydrolyzed with difficulty in the reduction of the bisamide with $LiAlH_4$. The reduction of the bisamide with $BH_3{\cdot}S(CH_3)_2$ was incomplete, with 2 major products including the bisamine in an estimated yield of 16% (see figure 16, p. 67).

The reduction of 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide with BH_3·THF yielded one major product (see figure 17, p. 68), 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl in the highest yield, approximately 80%, indicating this to be the preferred method. Furthermore, the crude product of the BH_3·$S(CH_3)_2$ reduction was subjected to further reduction by BH_3·THF, and was converted to the same product (see figure 18, p. 69).

Reaction conditions were initially determined using crude racemic 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide.

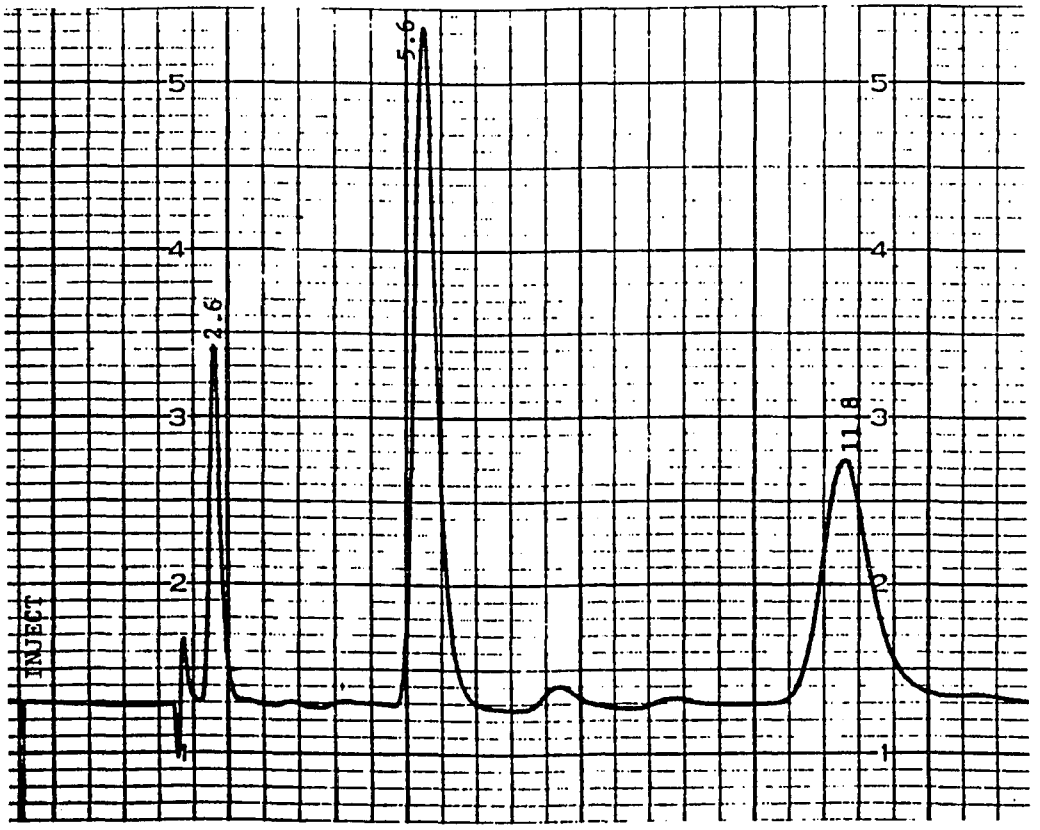


Figure 16 HPLC chromatogram of product of $BH_3 \cdot S(CH_3)_2$ reduction. Solvent - 40% CH_3OH, 60% H_2O, 0.025% TFA.

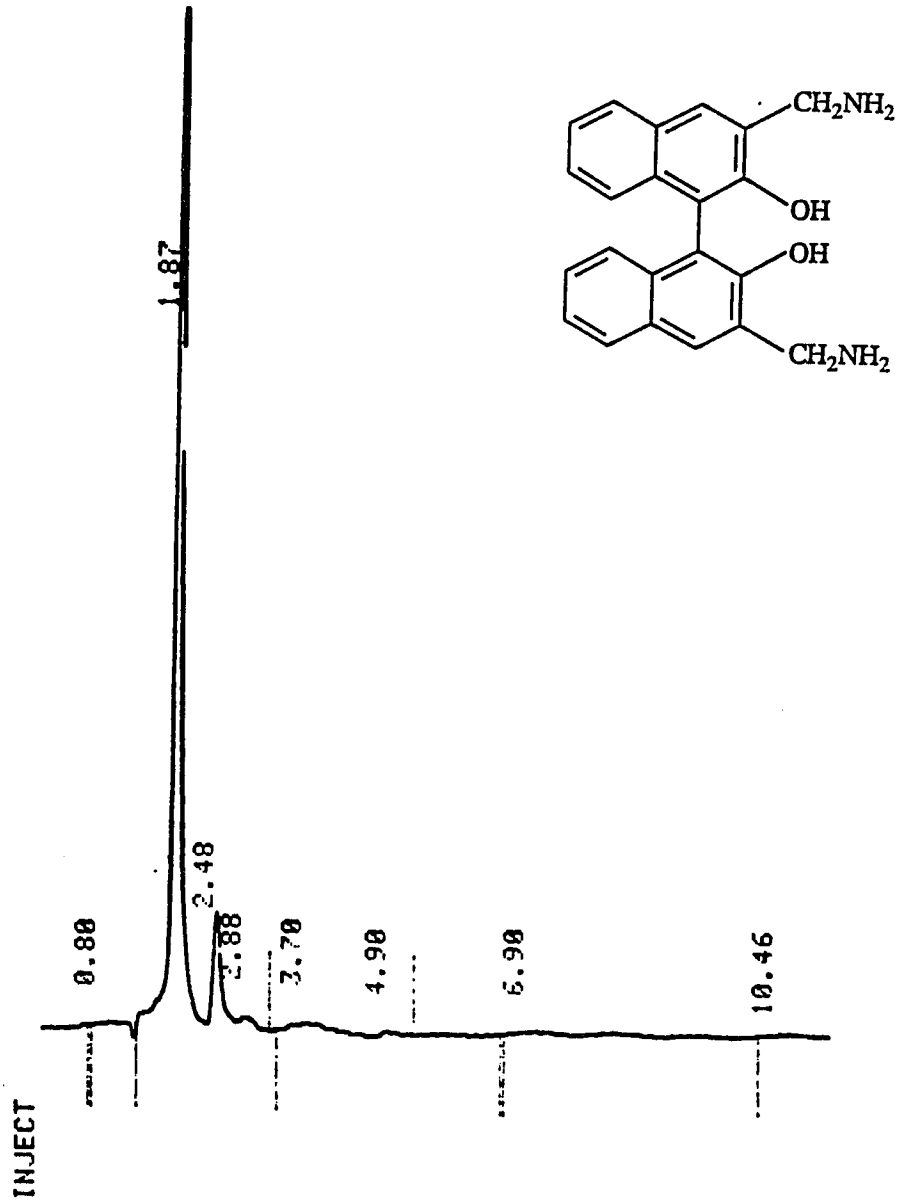


Figure 17 HPLC of BH_3·THF reduction product, 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl hydrochloride. Solvent - 75% CH_3OH, 25% H_2O, 0.025% TFA. (note: bisamide elution time is 3)

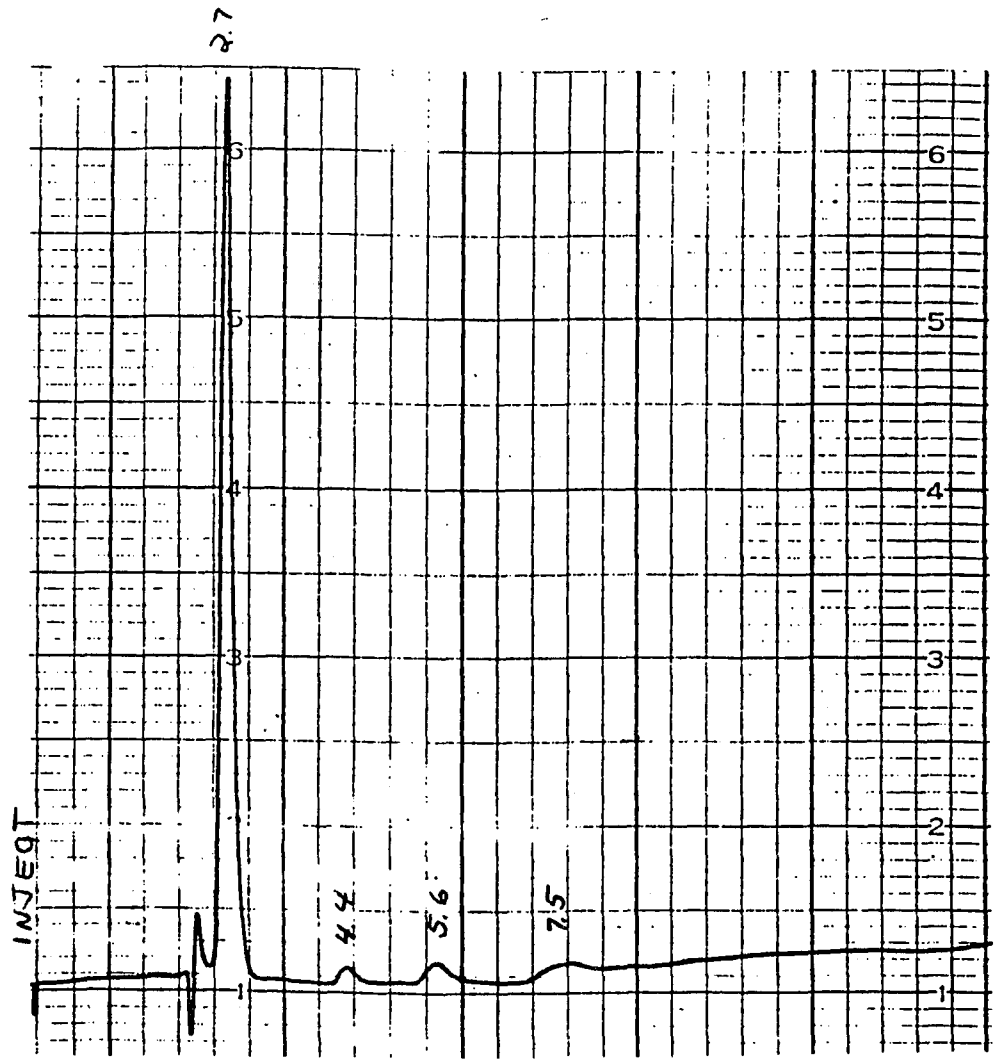
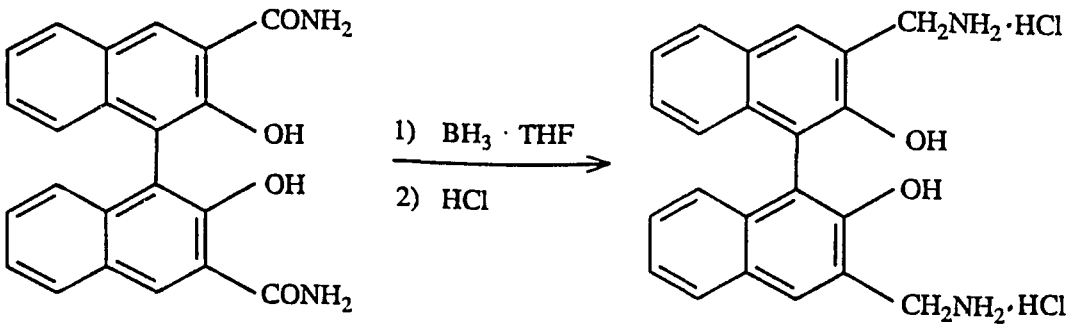


Figure 18 HPLC of BH_3·THF reduction product, 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl hydrochloride. Solvent - 40% CH_3OH, 60% H_2O, 0.025% TFA.

3.4a Reduction of racemic 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide with borane-tetrahydrofuran complex.

3,3′-Bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl (bisamine) was prepared by the reduction of 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide with BH_3·THF, using the general procedure reported by Brown et al for the reduction of primary amides (42):



A 500 mL round bottom flask with a 4 necked adaptor was fitted with a condenser, a mechanical stirrer, and rubber septa. This reaction vessel was flamed under vacuum, then cooled to 0°C under nitrogen. The inert atmosphere was maintained throughout the reduction. A solution of 1M BH_3·THF (330 mL, 330 mmol, or 960 hydride equivalents)[2] was delivered by syringe to the reaction vessel at 0°C. A powder addition funnel with 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-

[2] Each mole of 2,2′-dihydroxy-1,1′-dinaphthyl-3,3′-dicarboxamide requires 16 hydride equivalents (42). This reduction was carried out with a twofold excess of BH_3·THF.

dicarboxamide (12.5 g, 33.6 mmol) was blanketed with nitrogen and attached to the reaction vessel. The bisamide was added cautiously to the stirring borane solution which was cooled to 0°C by an ice bath. Upon addition, the mixture was heated to reflux.

The reaction mixture was stirred, under nitrogen, at reflux for 7 hours. The solution was cooled to room temperature and left overnight under nitrogen. The solution was then cooled to 0°C by an ice bath and opened to the air. Aqueous hydrochloric acid (50 mL of 6N solution, 300 mmol) was added cautiously, dropwise, to the cold, stirred solution. After the addition of the 6N HCl was complete, it was necessary to reflux the solution for one hour in order that hydrolysis be complete.

Tetrahydrofuran was then distilled. Methanol was added to dissolve the residue. The solution was evaporated to dryness (rotary evaporator and water aspirator). The residue was subjected to a flame test, in which a greenish flame indicates the presence of boron (43). The residue was then disolved in methanol and evaporated to dryness several times to remove the residual boric acid as the volatile methyl borate (43, 44) until the complete absence of a greenish flame was observed in a flame test of the product. The crude product was dissolved in hot water, decolorized with Norit Charcoal and crystallized rapidly upon cooling to room temperature. Dry weight, 11.6 g.

3,3′-Bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl hydrochloride salt was soluble in water, methanol, tetrahydrofuran, pyridine, and dimethylsulfoxide. TLC (butanol, acetic acid, water, 4:1:5, upper layer, developing solvent; R_f value of bisamine, 0.26) and HPLC showed that one major product was formed, (80% as determined by HPLC), one minor product, and little or no starting material (see figure 17, p. 68). Chemical yield of bisamine hydrochloride salt, 66% (based on 80% purity). Several precipitations of methanol solutions of the salt, followed by several crystallizations from water or methanol was not effective in purifying the reaction products. It was necessary to do a chromatographic separation in order to obtain a sample of greater than 99% purity. The IR (nujol mull) spectrum of the recrystallized bisamine hydrochloride salt shows the carbonyl peak gone; NH_3^+ bending at 1630 and 1460 cm^{-1}, OH and NH_3^+ stretching at 3600-2800 cm^{-1}.

1.0 g (1.9 mmol) of 80% pure bisamine hydrochloride salt was injected onto a C-18 reverse phase preparative column. Eluting solvent system was 50% CH_3OH, 50% H_2O, 0.025% TFA. Three fractions of bisamine salt in 99% or better purity were obtained. The "free" amine, 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl, was generated by dissolving the crude hydrochloride salt in water, followed by the addition of a slight excess of triethylamine. An immediate precipitate was formed, which was filtered and washed with water. Combined weights of the purified, bisamine isolated, 0.432 g (1.25 mmol), recovery, 66%

racemic 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

The 200 MHz ^{1}H NMR spectrum of the free amine, 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl (see figure 19, p. 74), 8% in DMSO-d_6, was obtained at 323K, with pulse width at 30° and a relaxation delay of 1.0 sec. The spectrum gave the following chemical shifts with the indicated areas: 7.77-7.65 (m, Ar-H, 3.9 H), 7.19-6.93 (m, Ar-H, 6.1 H), 5.74 (broad peak, NH_2 and OH, 6.1 H), 4.16 (s, CH_2, 3.9 H). The 50 MHz ^{13}C NMR spectrum of the free amine (see figure 20a, p. 88) in DMSO-d_6, obtained at 323K, gave 10 signals. In order to demonstrate that the ^{13}C NMR was in agreement with the structure, which has 11 different carbons, the quantitative 50 MHz ^{13}C NMR spectrum was obtained (see figure 20b, p. 88). The spectrum, an inverse gated decoupled experiment of the free amine in DMSO-d_6 with $Cr(acac)_3$ as relaxation agent, gave 10 peaks with the indicated areas: in the aromatic region at 155.0 (1.0 C), 133.0 (1.1 C), 128.2 (1.1 C), 127.1 (2.1 C), 125.7 (0.9 C), 124.6 and 124.1 (2.0 C), 121.6 (1.0 C), and 116.0 (0.9 C), and the methylene carbon at 44.1 (0.9 C).

Mass spectral analysis was obtained on the optically active material (vide infra).

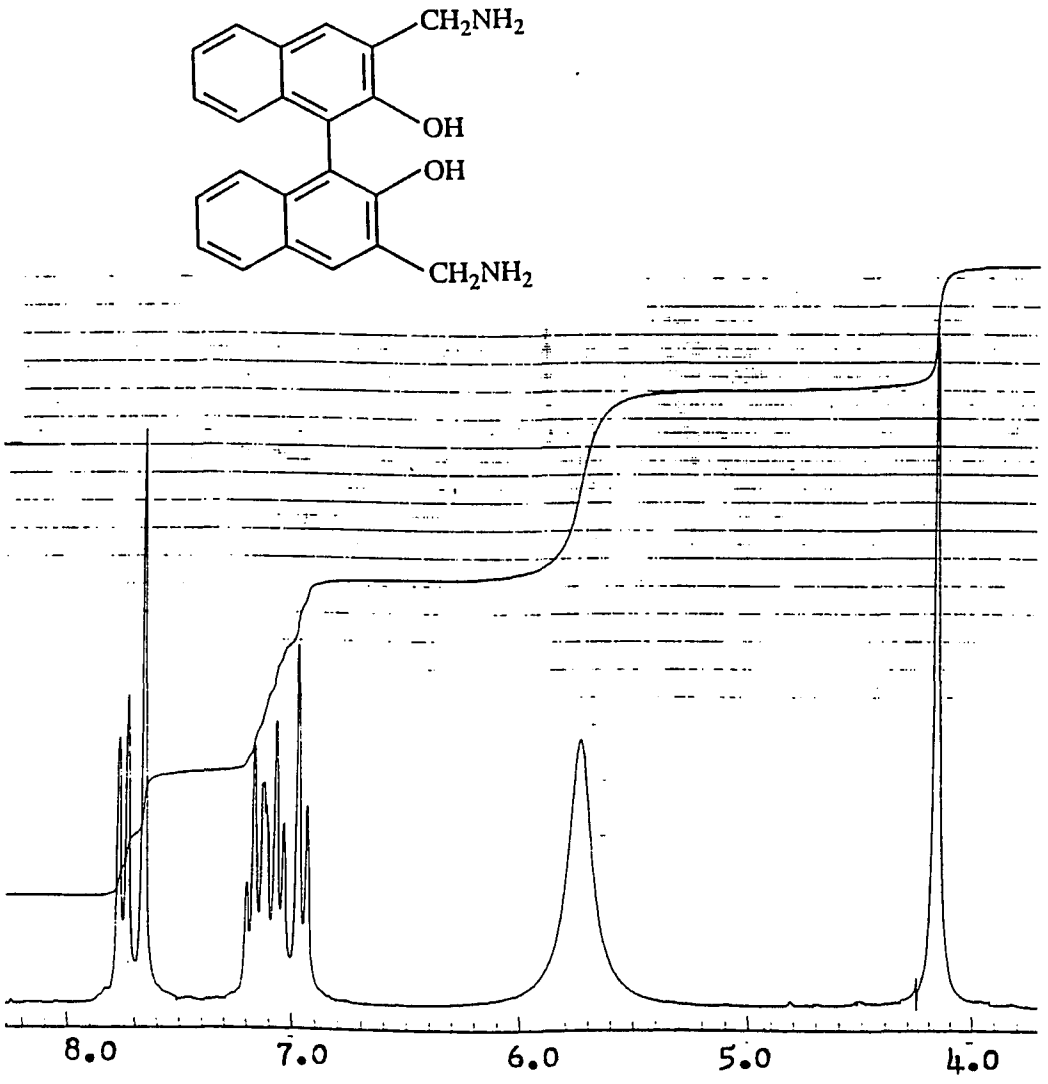


Figure 19 200 MHz ^{1}H NMR spectrum of racemic bisamine in DMSO-d_6. Number of transients, 32.

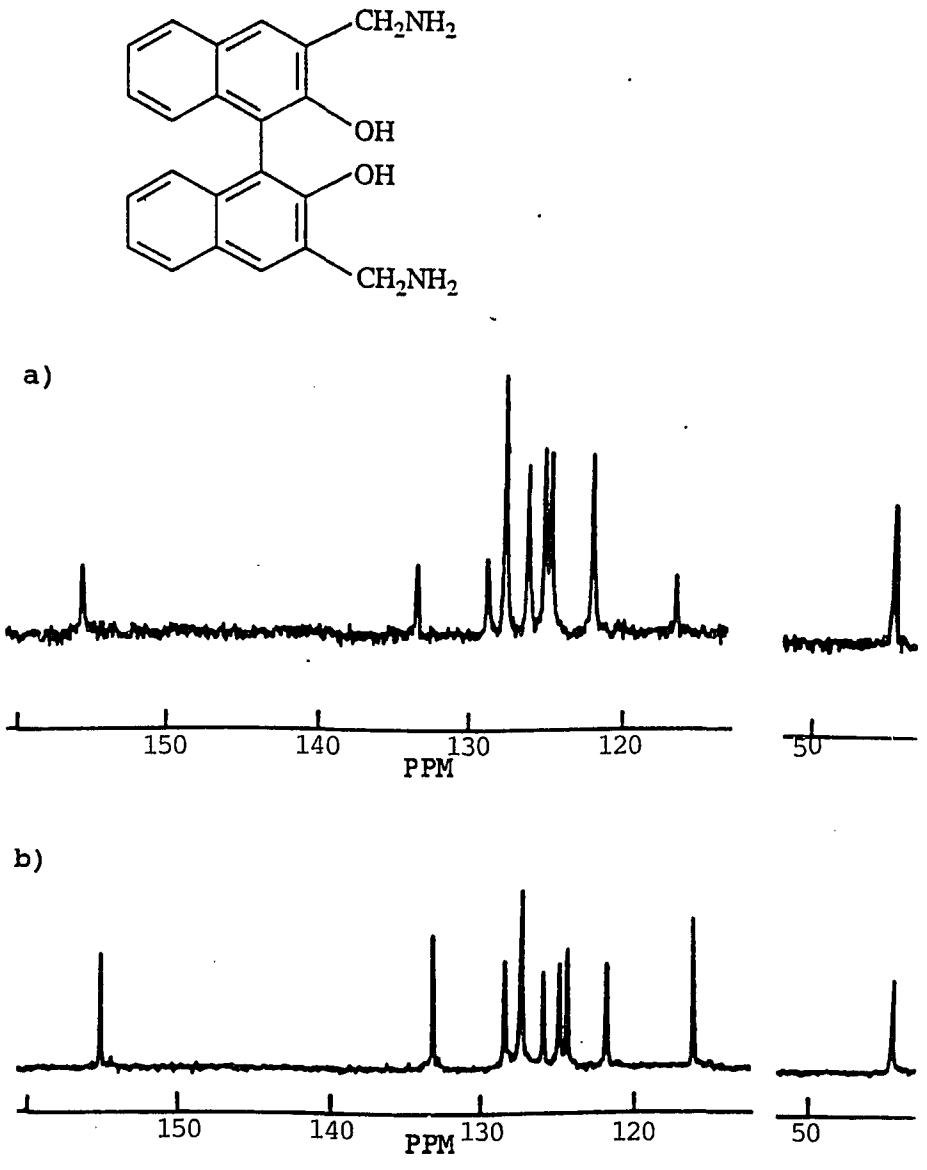


Figure 20 50 MHz ^{13}C NMR spectra of bisamine in DMSO-d_6.
a) Number of transients 11,766.
b) Inverse gated decoupled - $Cr(acac)_3$ added. Number of transients, 8863.

3.4b Preparation of optically active 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

The method used in the reduction of optically active 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide was essentially the same as that used for the racemic bisamide. Initially, exploratory attempts were made to minimize the harsh conditions of hydrolysis, in order to minimize possible racemization of the bisamine. However, it was determined that reflux of the reaction mixture with 1N HCl added for at least one hour was required in order that hydrolysis be complete.

The optically active 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide which was prepared from (R)-(+)-3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl, $[\alpha]^{25}_{D}$ +177° (c 1.08, pyridine), 95.7% optically pure, was used in this experiment. Bisamide (3.75 g, 10.0 mmol) was added to 170 mL BH_3·THF (1M solution, 510 hydride meq) under nitrogen, at 0°C. The reaction mixture was stirred under nitrogen for 7 hours at reflux, and kept overnight at room temperature. The reaction mixture was then cooled down with an ice water bath, opened to the air, and hydrolyzed with 30 mL of 6N HCl. After refluxing the solution for one hour, tetrahydrofuran was distilled. The residue was dissolved in methanol and evaporated to dryness several times, until the complete absence of a greenish flame was observed in a flame test. The crude amine salt weighed 4.5 g, estimated purity 68% (see HPLC chromatogram, figure 21, p. 81), chemical yield 73% of the bisamine

hydrochloride salt based on purity of reaction product. The bisamine hydrochloride salt was dissolved in methanol. Ether was added to the stirred solution and the bisamine hydrochloride salt was precipitated. The precipitate was recrystallized from methanol, the bisamine hydrochloride salt weighed 3.29 g (83% pure as determined by HPLC, recovery in the recrystallization process, 89%).

Several attempts were made in the recrystallization of both the bisamine and the bisamine hydrochloride salt. "Feathery" crystals of the bisamine were grown from benzene in low yield (greater than that 50% recovery) after several days. One gram of the bisamine was dissolved, upon heating and stirring, in benzene. Norit charcoal was added to the heated solution. The mixture was filtered and allowed to cool slowly to room temperature. After 2 days at room temperature, the solution was placed in a refrigerator and left for several days. The recrystallized material (0.34 g, 41% recovery) was shown to be pure by TLC (butanol:acetic acid:water, 4:1:5, upper phase).

The crude bisamine hydrochloride salt crystallized rapidly from methanol (greater than 85% recovery), yielding a white powder, also shown to be pure by TLC, after several recrystallizations. One gram yielded 0.42 g of the purified bisamine hydrochloride salt (51% recovery).

Attempts were also made in the preparation of the picrate salts of the

bisamine, in the hopes that better crystallization would be achieved. Solubility of the bisamine, when combined with the picric acid was not good, however, and the bisamine was not fully converted to the picrate salts. TLC (butanol:acetic acid: water, 4:1:5, upper phase) of the final product formed showed incomplete reaction. Three spots were found, probably the dipicrate salt and the monopicrate salt, along with unreacted bisamine.

Optically active bisamine hydrochloride salt was soluble in water, methanol, tetrahydrofuran, pyridine, and dimethylsulfoxide, as was the racemic material. The specific rotation of the product precipitated from ether and recrystallized from methanol was measured: $[\alpha]^{25}_{D}$ +62.2 (0.990, H_2O). It was attempted to generate the free amine, similar to the racemic, by dissolving in water and adding a small excess of triethyl amine, however, the optically active compound was more soluble than the racemic compound, and did not precipitate readily. The free amine was generated by dissolving the amine salt in a minimal amount of water, and by adding a small excess of dilute ammonium hydroxide solution. An alternate method was to dissolve the amine salt in a minimal amount of pyridine and then to precipitate the free amine by adding the pyridine solution dropwise to stirred diethyl ether in recoveries greater than 98%. The free amine was soluble in acetone, unlike the racemic.

^{1}H and ^{13}C NMR spectra, TLC and HPLC analysis of the optically active 3,3′-

bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl (both the bisamine hydrochloride and the free amine) were essentially identical to that of racemic 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

Optically active 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl was only able to be isolated to greater than 99% purity by preparative HPLC (see figure 21, p. 81 for the chromatogram of the crude product, and figure 22, p. 82 for the chromatogram of the isolated bisamine), using a reversed phase C-18 column with a solvent system of 50% methanol, 50% water, 0.025% trifluoroacetic acid (volume:volume). The pure fractions which were collected were evaporated to dryness. Total combined weights, 0.27 g (79% recovery of the bisamine salts). The residue of the purest fraction (greater than 99.8% purity by HPLC determination) was dissolved in the minimal amount of water, and the pure free amine generated by adding, dropwise, dilute aqueous ammonia. The precipitate was filtered and dried under vacuum, over phosphorus pentoxide at 56°C. The specific rotation of the isolated 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl was obtained: $[\alpha]^{25}_{D}$ +176° (c 0.995, acetone). Mass spectral analysis of the preparatively separated 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl, $C_{22}H_{20}N_2O_2$, gave M^+ 344.20, calculated, 344.15, and M+1 345.10, abundance 29% of M, calculated, 26%.

Purified 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl hydrochloride

salt, crystallized from methanol (purity of the salts generally estimated by HPLC to be about 95%) was used in the continuing derivatization.

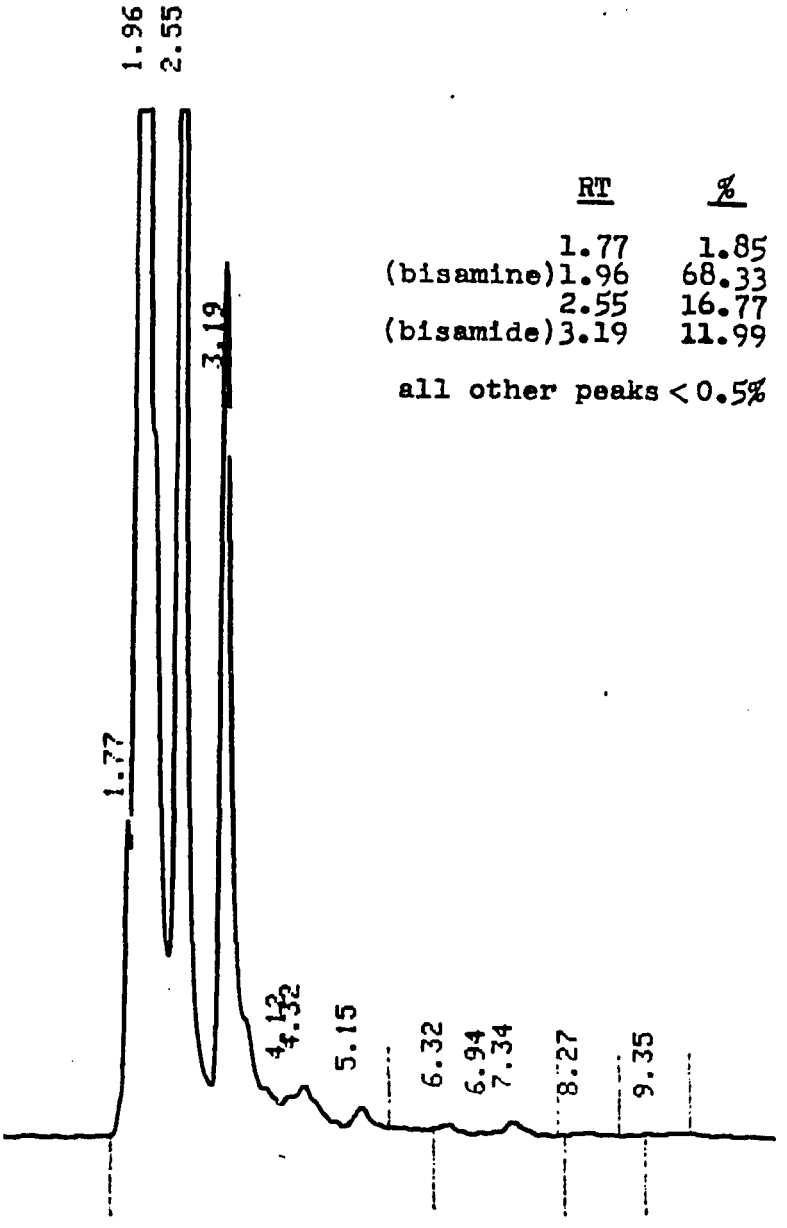


Figure 21 HPLC chromatogram of crude, optically active bisamine hydrochloride prior to preparative separation; solvent 75% CH_3OH, 25% H_2O, 0.025% TFA.

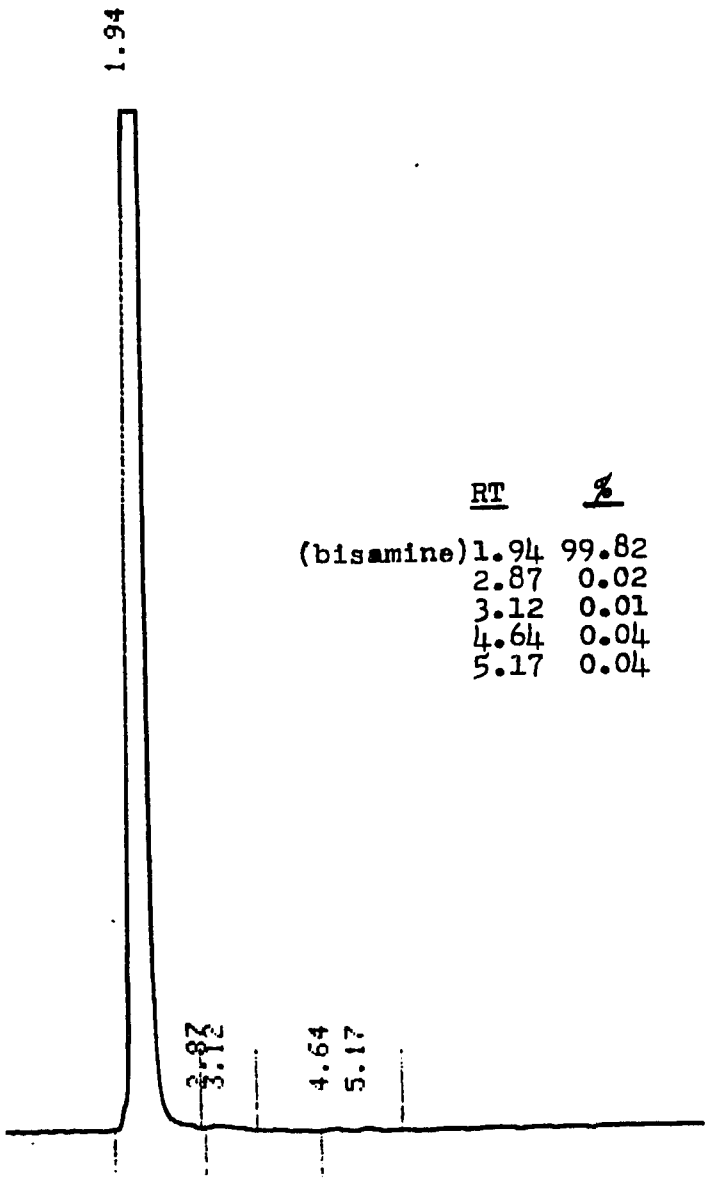


Figure 22 HPLC chromatogram of purified (R)-(+)-3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl. Solvent 75% CH_3OH, 25% H_2O, 0.025% TFA.

3,5 Determination of enantiomeric purity of R-(+)-3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

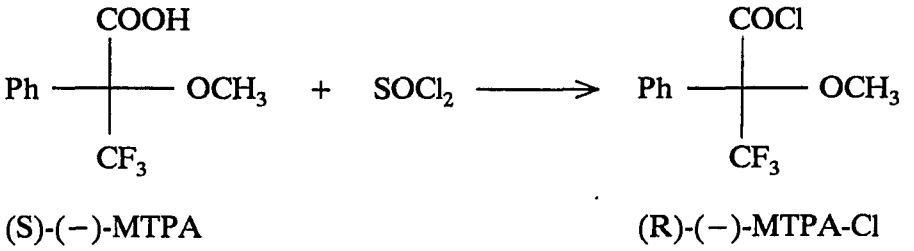
The enantiomeric purity of the bisamine was determined by ^1H NMR of the MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) derivative.

3.5a Preparation of the α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) amide derivative of 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

Reagent grade (S)-(−)α-methoxy-α-trifluoromethylphenylacetic acid and distilled α-methoxy-α-trifluoromethylphenylacetyl chloride were stored in a dessicator over $CaSO_4$ until used. Pyridine was distilled from CaH_2 immediately prior to use. All bisamine samples were dried under vacuum, over P_2O_5 (56°C), for at least 12 hours immediately prior to use. All other chemicals used were reagent grade and were used without further purification.

3.5a.1 Preparation of α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl).

The method used in the preparation of MTPA-Cl was that reported by Dale, Dull and Mosher (45).



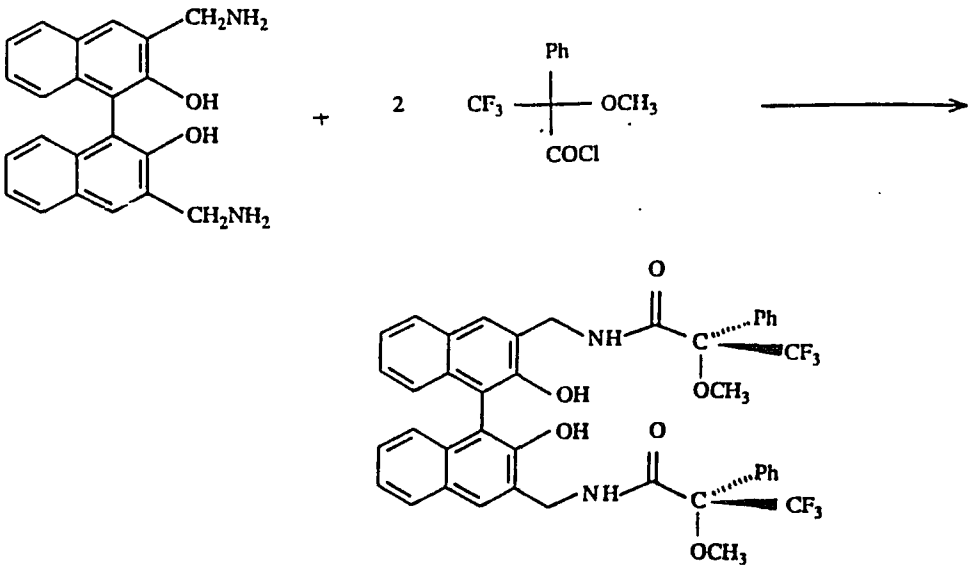
(S)-(−)-MTPA (R)-(−)-MTPA-Cl

(S)-(−)-α-Methoxy-α-trifluoromethylphenylacetic acid (1.1 mL), thionyl chloride (4 mL), and sodium chloride (15.8 mg) were placed in a 10 mL flask fitted with a reflux condenser and protected from moisture with a $CaSO_4$ drying tube. The reaction mixture was stirred at reflux for 70 hours. It was then cooled to room temperature, and the thionyl chloride was distilled under reduced pressure (a water aspirator was used with a drying tube of $CaSO_4$ placed between the source and the reaction vessel). The residue was then vacuum distilled, and the distillate, (R)-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride, (0.9 mL, 1.2 g) collected at 66-68°C/1.1 mm Hg, $[\alpha]^{25}_D$ −128° (c 5.39, CCl_4), reported for (S)-(+)-MTPA-Cl, b.p. 54-56°C/1mm, $[\alpha]^{25}_D$ +129° (c 5.17, CCl_4) (45).

3.5a.2 Preparation of 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl MTPA amide.

The method used in the derivatization of α-methoxy-α-trifluoromethyl-phenylacetic acid with 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl was a modified version of the procedure described by Dale and Mosher for the preparation

of MTPA amides (46).



The conditions were initially determined using crude racemic bisamine. Once reaction conditions were optimized, samples were prepared using purified racemic and (R)-(+)-3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl, $[\alpha]^{25}_{D}$ +176° (c 0.995, acetone), each of which had been isolated by preparative HPLC. A representative preparation of the MTPA-amide follows. The same procedure was used for the derivatization of both racemic and optically active bisamine.

3,3′-Bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl (15.5 mg, 0.045 mmol) was delivered to an oven dried, 9 mL glass vial containing a magnetic stirring bar. The vial was fitted with a rubber septum which had been stored in a dessicator, and was then flushed with nitrogen. Pyridine (2 mL) was added via syringe to the powder and the reaction mixture was stirred until all had dissolved.

(R)-(−)-MTPA-Cl (23.4 microliters, 31.5 mg, 0.12 mmol) was added via syringe to the stirring solution. The solution was stirred for at least 24 hours at room temperature under nitrogen. 3-Dimethylamino-1-propylamine (23 microliters, 19 mg, 0.19 mmol) was then added via syringe to react with excess MTPA-Cl, and the solution was stirred for several minutes.

The solution was diluted in anhydrous ether (20-30 mL), washed (three times with 1N HCl, twice with saturated $NaHCO_3$ solution, twice with saturated NaCl solution, twice with H_2O)[3], and dried over $MgSO_4$. The ether solution was filtered and evaporated to dryness. The residue was dissolved in CCl_4 and evaporated to dryness again, under vacuum (to be sure all traces of ether were removed) (31). The final residue was dissolved in $CDCl_3$ (0.5 mL), and the ^1H NMR spectrum was obtained.

3.5a.3 NMR analysis of 3,3'-bis(aminomethyl)-2,2'-dihydroxy-1,1'-binaphthyl MTPA amide.

Diastereomeric MTPA esters and amides have been used in the analysis of enantiomeric purity, based on the chemical shift nonequivalence in ^1H NMR

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[3] Each aqueous layer, including all washings, was made basic with ammonium hydroxide to be sure that all of the bisamine had reacted with the MTPA-Cl to form the MTPA-amide. If any unreacted bisamine were present, it should have precipitated out of solution. No precipitate was observed.

spectroscopy of the respective diastereomers (45, 46). The 400 MHz ^{1}H NMR spectrum of the diastereomeric mixture of MTPA amides formed from racemic bisamine was obtained in $CDCl_3$ at 293K (see figure 23, p. 93). Acquisition parameters include a pulse width of 70°. The proton spectrum should show aromatic signals with an area of 20, amide NH signal with an area of 2, phenolic OH with an area of 2, methylene signal with an area of 4 and methoxy signals with an area of 6. The spectrum showed signals for OH, NH and Ar-H in the region 7.8-8.0 ppm (4.0 H), 7.2-7.6 (18 H), 6.9-7.1 (2.0 H), the methylene signal at 4.8-4.7 (m, 4.0 H), and the methoxy signal at 3.36-3.37 (s, 6.0 H). The chemical shift of the methoxy signal came in the same region as that reported by Dale, Dull, and Mosher for MTPA amides, which ranged from 3.2-3.4 ppm (45). However, the two signals from the diastereomeric methoxy groups in the MTPA acid moiety were not sufficiently separated (see figure 24, p. 93) for an analysis of enantiomeric purity.

3.5b Use of shift reagent with diastereomeric MTPA amide for determination of enantiomeric purity of bisamine by NMR spectroscopy.

The use of shift reagent with diastereomeric MTPA esters for the determination of enantiomeric purity in ^{1}H NMR spectroscopy has been reported (47). A series of ^{1}H NMR spectra, first of the MTPA amide of the racemic bisamine, and then of the MTPA amide of (R)-(+)-bisamine, were obtained.

Chiral lanthanide shift reagent, $Eu(hfc)_3$, tris [3-(heptafluoropropylhydroxy methylene)-d-camphorato] europium (III), was dried under vacuum over P_2O_5, at 56°C, and was stored over nitrogen. The chiral shift reagent was transferred over nitrogen into several preweighed, oven dried vials, the vials were sealed, and the weight of shift reagent determined for each vial. The vials were not opened to air until the shift reagent was added to the NMR sample solution.

The 400 MHz ^1H NMR spectra of the MTPA amide of the racemic bisamine were obtained in $CDCl_3$. In these experiments, increasing amounts of the chiral lanthanide shift reagent, $Eu(hfc)_3$, were added. The NMR spectra were obtained after each addition, recording the lanthanide induced shift of the methoxy signals after each addition. $Eu(hfc)_3$ was added to the NMR solution until resolution of the diastereomeric signals of the methoxy protons were obtained. The lanthanide induced downfield chemical shift of the methoxy signals upon addition of increasing amounts of the shift reagent is tabulated in table 2, p. 91, and the ^1H NMR spectra follow, figures 23-30, p. 93-96.

Figure 23 shows the ^1H NMR spectrum of the MTPA amide (0.045 mmol) in 0.5 mL $CDCl_3$ (0.09 M solution), immediately prior to addition of $Eu(hfc)_3$. Figures 29 and 30 show the ^1H NMR spectra of the separated, diastereomeric $-OCH_3$ signals, with $Eu(hfc)_3$ added. The methoxy signals were shifted downfield

1.24 and 1.40 ppm with a difference in chemical shift of 0.17 ppm. The integrals of the two peaks were essentially equal (greater than 4% difference).

The MTPA amide (0.027 mmol) of (R)-(+)-3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl, $[\alpha]^{25}_{D}$ +176° (c 0.995, acetone), was then analyzed in the same manner. The 400 MHz ^{1}H NMR spectrum gave a single -OCH_3 peak at 3.7 ppm (see figures 31 and 32, p. 97; compare to figures 23 and 24, p. 93). The lanthanide induced downfield chemical shift of the methoxy peak with added $Eu(hfc)_3$ is tabulated in table 3, p. 92. The methoxy peak was shifted 0.8 ppm to 4.50 ppm (see figure 34, p. 99). Careful inspection of the expanded NMR spectrum, figure 35, p. 99 reveals a small nonintegratable peak, at about 4.7 ppm or about 0.2 ppm downfield of the singlet methoxy peak. The appearance of another small methoxy peak was expected, as the (R)-(+)-bisamine used in the preparation of the MTPA amide was in turn prepared from (R)-(+)-3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl which was 95.7% optically pure, $[\alpha]^{25}_{D}$ +177° (c 1.08, pyridine).

An additional NMR spectrum was obtained in order to assign each methoxy signal to a specific diastereomer, i.e. to the (S)-MTPA amide formed from the (R)-(+)-bisamine or the (S)-MTPA amide formed from the (S)-(−)-bisamine.

A small portion of the NMR solution of MTPA-amide of the racemic bisamine

containing 43 mg $Eu(hfc)_3$ (see table 2, p. 91) was added to the NMR solution of MTPA-amide of (R)-(+)-bisamine containing 28 mg $Eu(hfc)_3$ (see table 3, p. 92). The ^1H NMR spectrum obtained (see figures 36 and 37, p. 100) showed two methoxy peaks, with the larger peak, at 4.52 ppm assigned to the MTPA amide of (R)-(+)-bisamine, and the smaller peak, at 4.66 ppm assigned to the MTPA amide of the (S)-(−)-bisamine. The ^1H NMR signal of the methoxy group of the (S,S) MTPA amide was shifted further downfield with shift reagent than that of the (S,R) diastereomer. The spectra obtained show a high enantiomeric purity of the (R)-(+)-bisamine, probably corresponding to or very close to the optical purity of the starting diacid, 95.7%.

TABLE 2

Lanthanide Induced NMR Chemical Shifts of Methoxy Group in the MTPA Acid Moiety of Diastereomeric (S)-(−)-MTPA Amides of 3,3′-Bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

chemical shift (δ) of -OC<u>H</u>$_3$	$\Delta\delta$ of -OC<u>H</u>$_3$ signals	mg of Eu(hfc)$_3$ added	NMR spectra (figures)
3.36, 3.37	0.01	0	23, 24
3.60, 3.64	0.04	18.8	25
4.00, 4.10	0.10	26.0	26
4.18, 4.30	0.12	32.8	27, 28
4.60, 4.77	0.17	43.0	29, 30

TABLE 3

Lanthanide Induced NMR Chemical Shifts of Methoxy Group in the MTPA Acid Moiety of (S)-(−)-MTPA Amide of (R)-(+)-3,3′-Bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl[a]

chemical shift (δ) of -OC<u>H</u>$_3$	mg of Eu(hfc)$_3$ added	NMR spectra (figures)
3.40	0	31, 32
4.15	23.4	33
4.50	28	34

a. $[\alpha]^{25}_D$ +176° (c, 0.995, acetone). This sample of 3,3′-bis(aminomethyl)-2,2′dihydroxy-1,1′-binaphthyl was prepared from 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-binaphthyl, $[\alpha]25_D$ +177°, optical purity 95.7%.

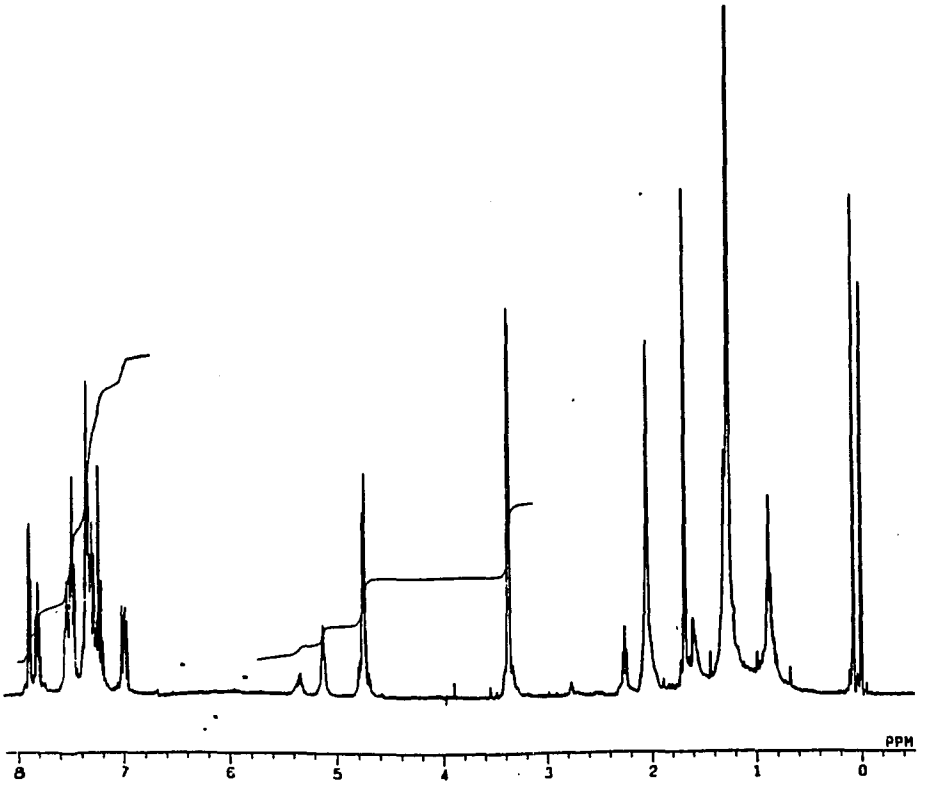


Figure 23 400 MHz ^{1}H-NMR spectrum of diastereomeric MTPA amides formed from racemic bisamine.

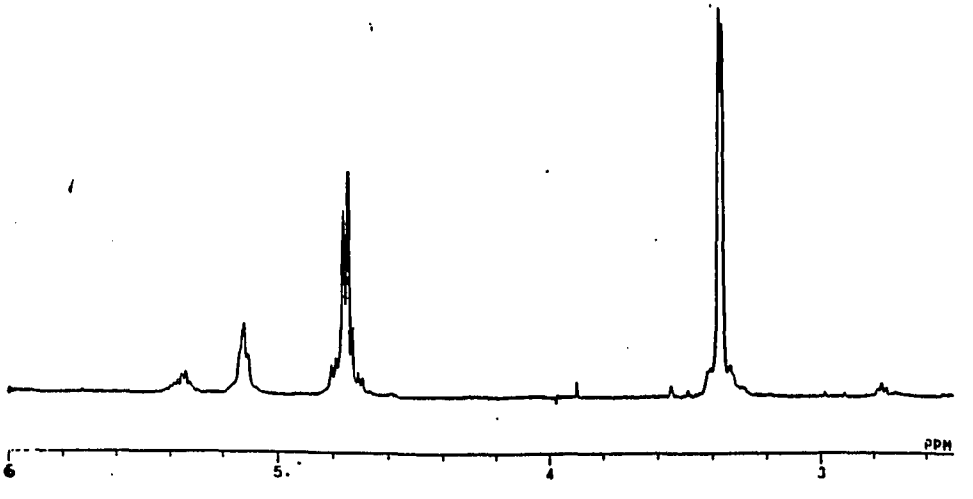


Figure 24 Partial Spectrum of that shown in fig. 23.

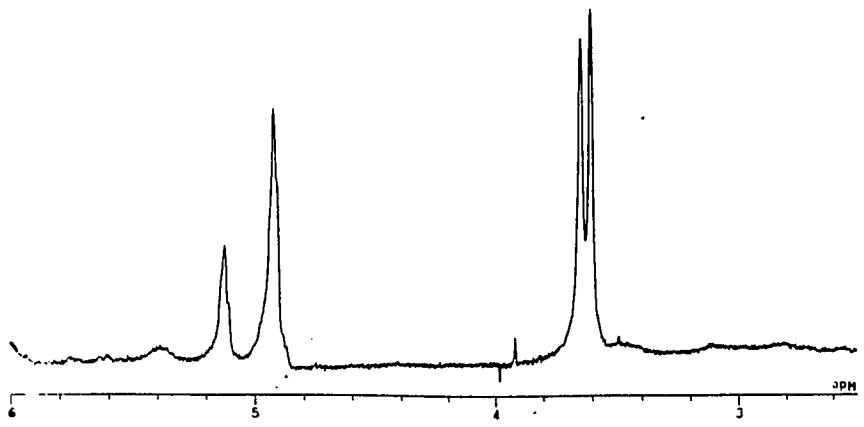


Figure 25 MTPA amide with 18.8 mg $Eu(hfc)_3$ added.

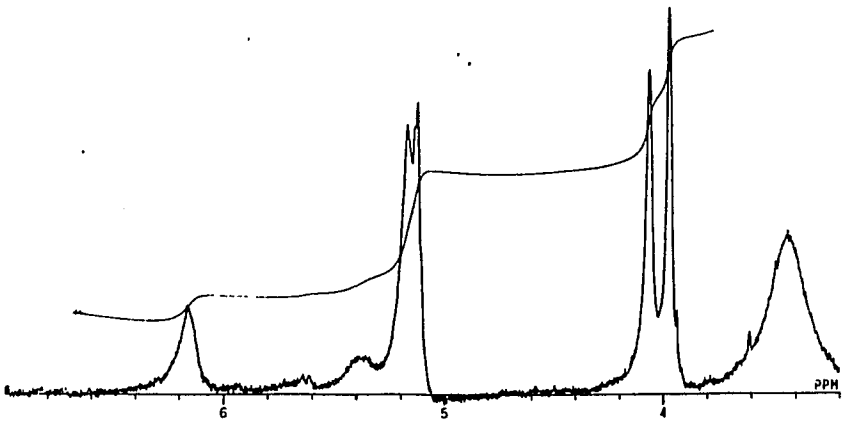


Figure 26 MTPA amide with 26.0 mg $Eu(hfc)_3$ added.

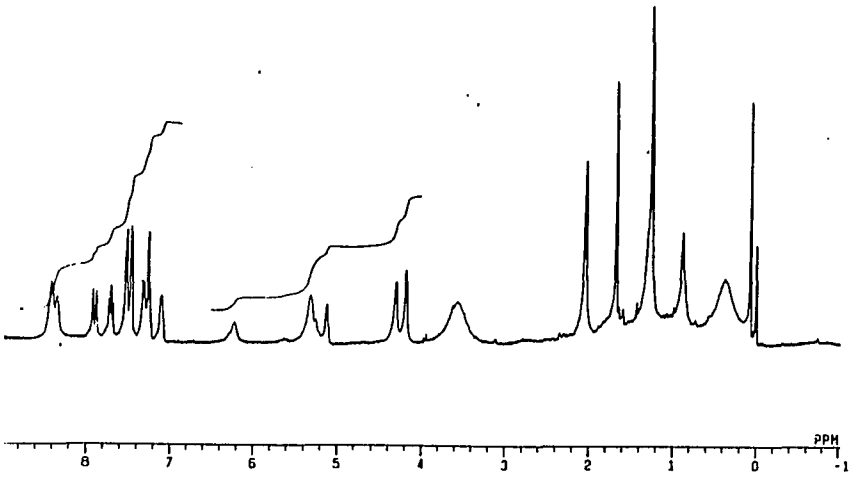


Figure 27 MTPA amide with 32.8 mg $Eu(hfc)_3$ added.

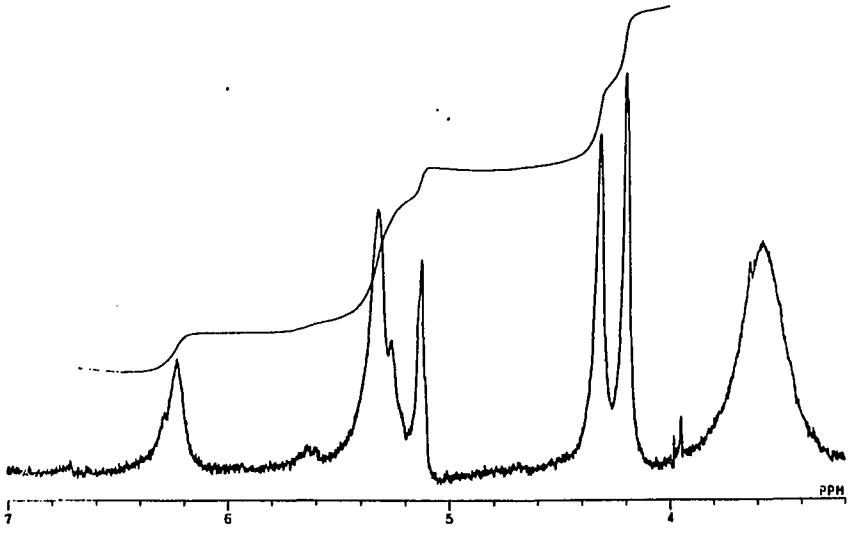


Figure 28 Partial spectrum of that shown in fig. 27.

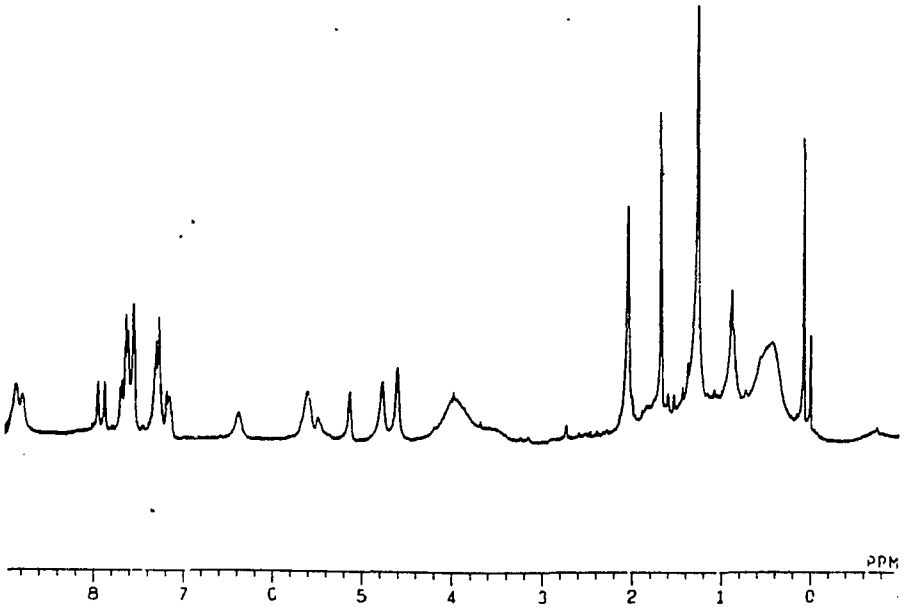


Figure 29 MTPA amide with 43.0 mg Eu(hfc) added.

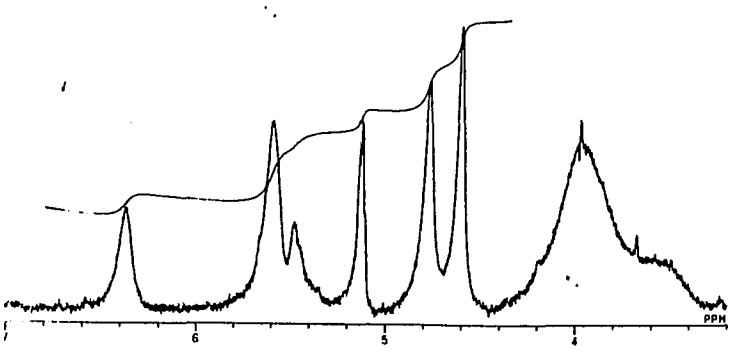


Figure 30 Partial spectrum of that shown in fig. 29.

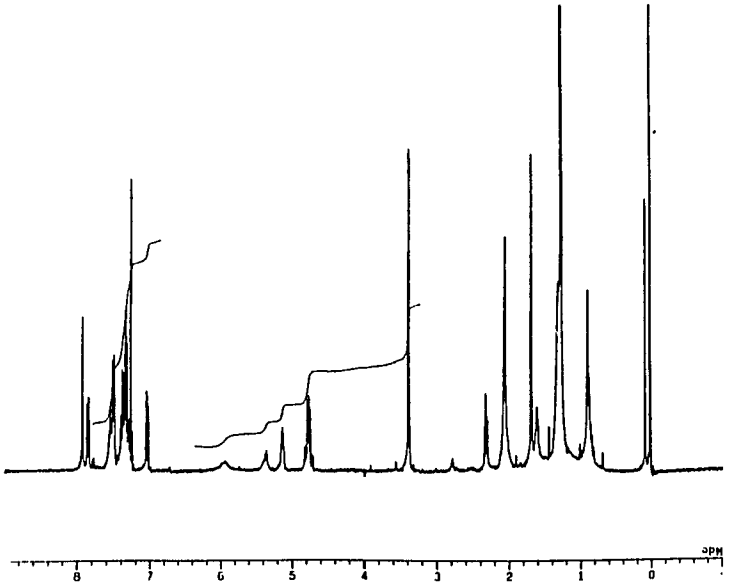


Figure 31 400 MHz ^{1}H-NMR apectrum of MTPA amide formed from (R)-(+)-bisamine (see fig. 32 for expanded -OCH_3 region).

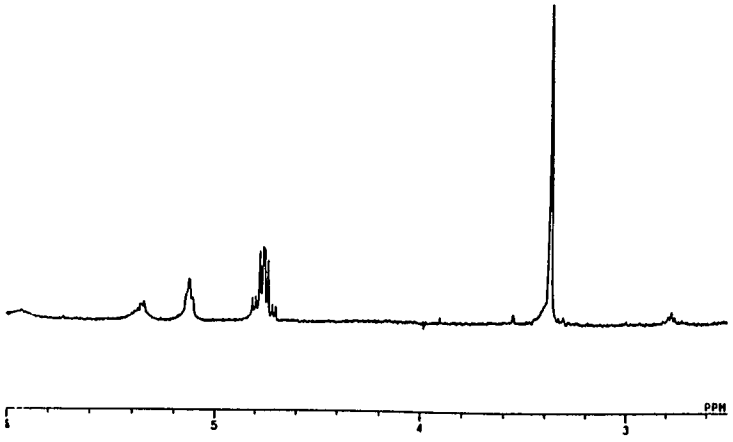


Figure 32 Partial spectrum of that shown in fig. 31.

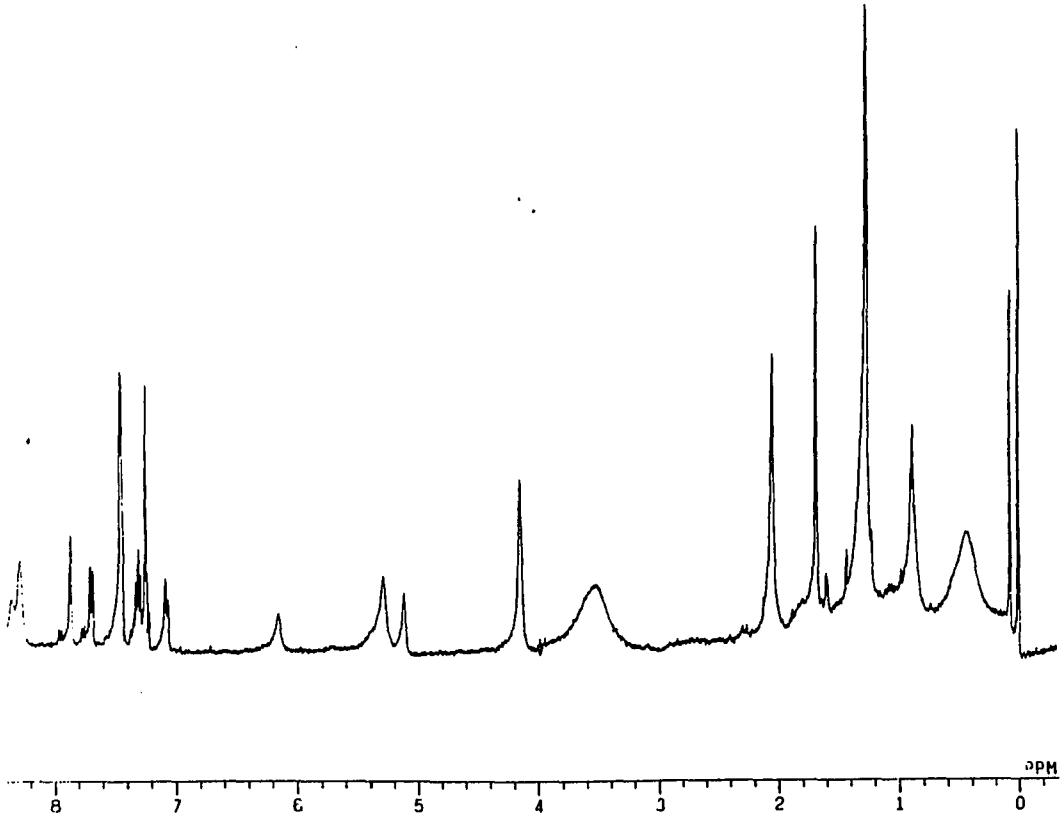


Figure 33 MTPA amide with 23.4 mg $Eu(hfc)_3$ added.

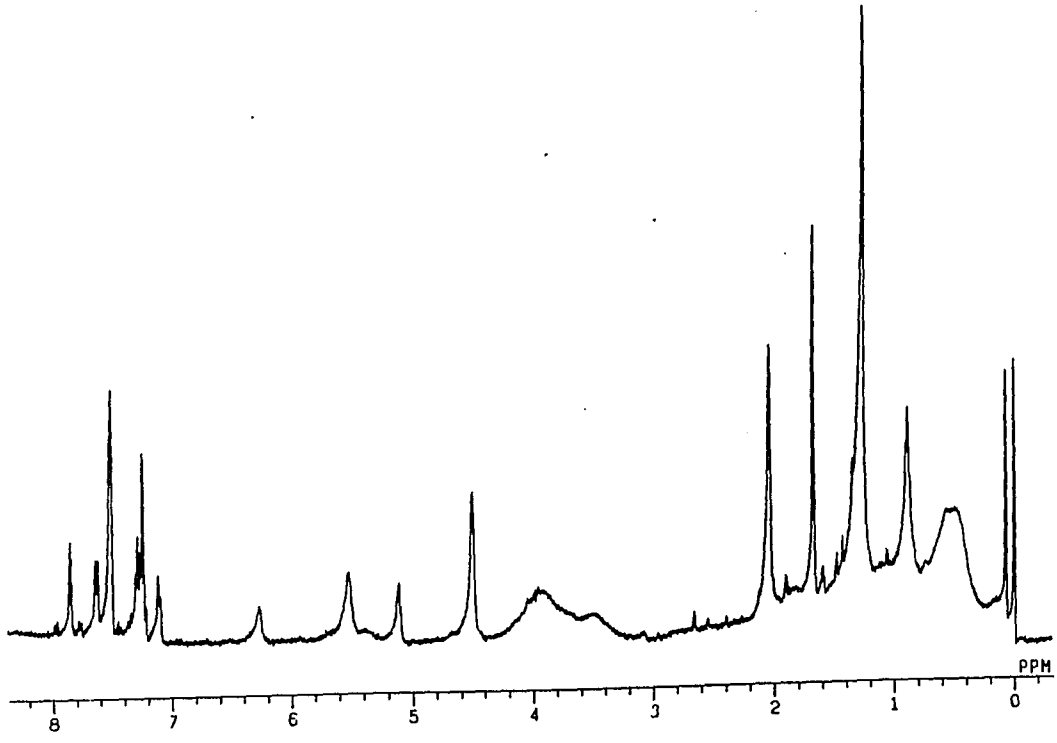


Figure 34 MTPA amide with 28 mg $Eu(hfc)_3$ added.

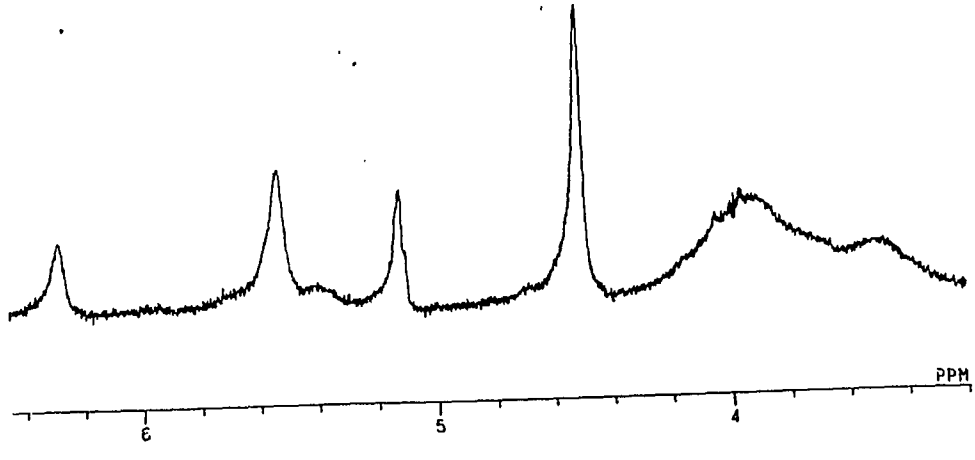


Figure 35 Partial spectrum of that shown in fig. 34.

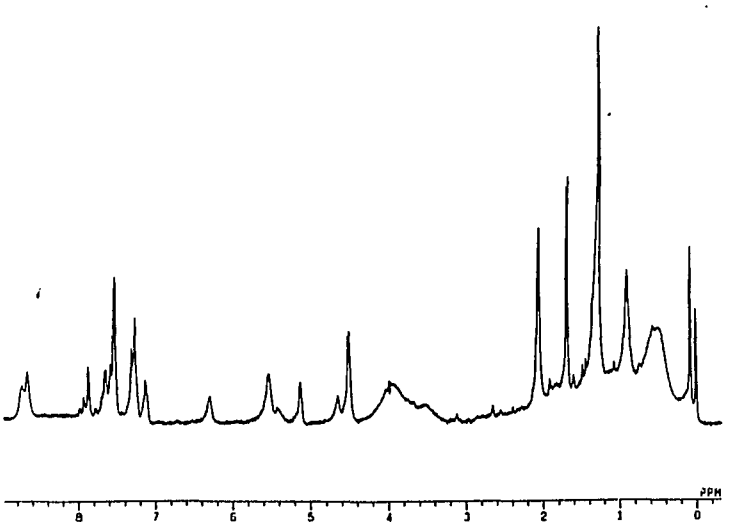


Figure 36 400 MHz ^{1}H-NMR spectrum of (S)-MTPA amide diastereomers, with (R)-(+)-bisamine MTPA amide in excess, with Eu(hfc)$_3$ added (see fig. 37 for expanded -OCH_3 region.

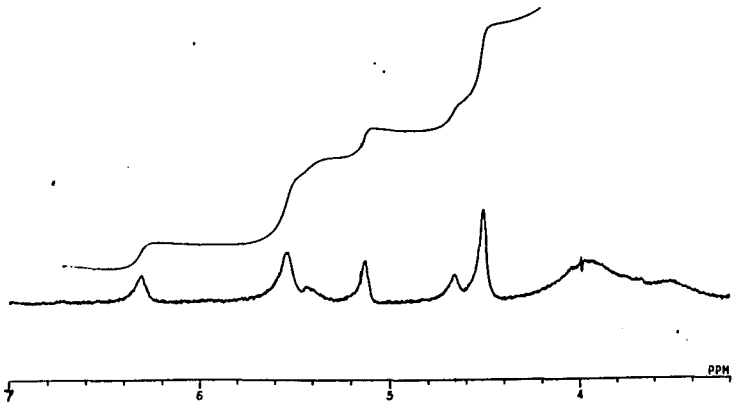


Figure 37 Partial spectrum of that shown in fig. 36.

3.6 Preparation of 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

Pyridine was distilled from CaH_2 immediately prior to use. 3,3′-Bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl hydrochloride was dried, under vacuum, over phosphorus pentoxide, prior to use. Nicotinoyl chloride hydrochloride was prepared, with the crude product stored over $CaSO_4$ until purification immediately prior to reaction, as described below. All other reagents were reagent grade and used without further purification.

Reversed phase C-18 columns were used for analytical and preparative HPLC. HPLC grade solvents and glass distilled water were degassed and filtered through millipore filters, as previously described (see section 3.1).

3.6a Preparation of nicotinoyl chloride from nicotinic acid.

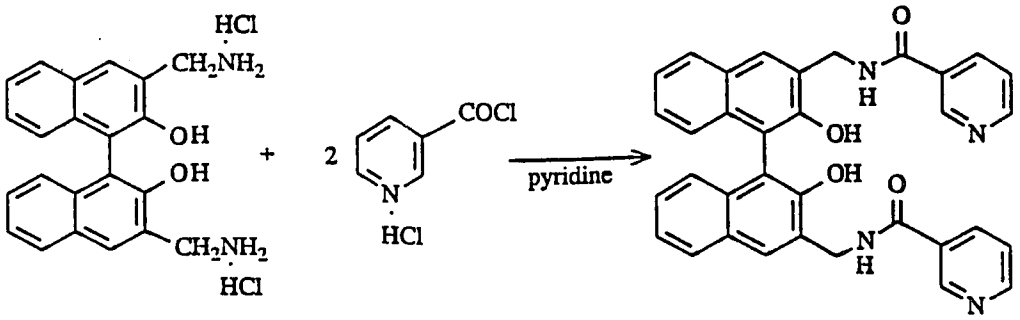
Nicotinic acid (20 g, 0.16 mol) was suspended in thionyl chloride (40 mL, 0.55 mol) in a round bottom flask containing a magnetic stirring bar, fitted with a condenser, and protected from moisture (drying tube filled with $CaSO_4$). Dimethylformamide as catalyst (48), 2 mL, was added to the stirred suspension. The mixture was stirred and kept at reflux overnight.

The solution was cooled to 35-40°C, and excess thionyl chloride was distilled under reduced pressure (using a water aspirator with a drying tube filled with $CaSO_4$ between the reaction vessel and the aspirator). The residue was evaporated to dryness. The crude nicotinoyl chloride hydrochloride was purified by sublimation, mp, 150-152°C, reported mp, 155.5-156.5°C (49).

Crude nicotinoyl chloride hydrochloride was stored in a dessicator over indicating $CaSO_4$ and purified by sublimation immediately prior to the coupling reaction with 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

3.6b The coupling reaction of 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl and nicotinoyl chloride.

3,3′-Bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl (bisnicotinamide) was prepared by the reaction of 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl and nicotinoyl chloride using a modified procedure of that used by Amano et al (9) for the preparation of related compounds:



Reaction conditions were initially determined using racemic 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl hydrochloride.

3,3′-Bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl hydrochloride (2.04 g, 4.89 mmol), crystallized from methanol, was added to 185 mL of dry pyridine in a 3 necked round bottom flask containing a magnetic stirring bar, fitted with a condenser, an addition funnel, and protected from moisture (drying tube filled with $CaSO_4$). The stirred solution was warmed to 50°C. Nicotinoyl chloride hydrochloride (5.22 g, 29.3 mmol), was dissolved in 30 mL pyridine. The nicotinoyl chloride solution was added to the stirred bisamine solution. The reaction was heated to 80°C, and stirred for two days. The reaction was followed by TLC, using 1-butanol, acetic acid, water, 4:1:5, upper phase of the two phase system, as the developing solvent. TLC showed two products and starting material, in a ratio that did not appear to change significantly after the reaction had proceeded for approximately 2 hours.

Saturated aqueous $NaHCO_3$ solution was added at room temperature, until reaction ceased. The solution was extracted several times with methylene chloride. The organic layers were combined, washed with saturated aqueous NaCl solution three times, then evaporated to an oil. The oil was dissolved in hot methanol. The hot methanol solution was filtered, then stirred over activated NORIT charcoal for several minutes. The mixture was filtered, the filtrate cooled to room temperature,

and dried over $MgSO_4$. The solution was then evaporated to dryness. The crude, dry product weighed 1.5 g, 56% yield.

TLC of the final residue showed one major product, in large excess, a minor product, and a small amount of starting material. Developing solvent used: butanol, acetic acid, water, 4:1:5, upper phase, R_f value of the major product, 0.6. Analytical HPLC showed the major product in an estimated 96% yield, (see figure 38, p. 106), solvent system used, 75% methanol, 25% water, 0.025% TFA . 3,3′-Bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl was isolated by preparative HPLC using 60% methanol, 40% water, 0.025% TFA eluting solvent system. The racemic bisnicotinamide was soluble in dimethylformamide, dimethylsulfoxide, and pyridine, and slightly soluble in methanol.

The 200 MHz ^1H NMR spectrum (see figure 39, p. 107), of the racemic bisnicotinamide was obtained at 297K, pulse width 30°, with a relaxation delay of 2.0 seconds. The spectrum was consistent with the structure of 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl, giving the following chemical shifts, with the indicated areas, in DMSO-d_6: 9.41-9.35 (t, CONH, 2.0 H), aromatic, OH, and pyridine protons at 9.16 (s, 2.0 H), 8.80 (s, OH) overlapped with peaks at 8.78-8.75, (4.0 H), 8.36-8.31 (d, 2.0 H), 7.90-7.85 (4.0 H), 7.61-7.54 (m, 2.0 H), 7.28-7.12 (m, 4.0 H), 6.86-6.82 (d, 2.0 H), and 4.74-4.72 (d, CH_2, 4.0 H). The amide and methylene protons were assigned after a homonuclear

decoupling experiment in which the -C<u>H</u>$_2$ region was irradiated. The triplet at 9.4 ppm collapsed to a singlet (see figure 40a, p. 108, compare to figure 39, p. 107). In an additional experiment, the -CON<u>H</u> region was irradiated, causing the -C<u>H</u>$_2$ doublet to collapse to a singlet (see figure 40b, p. 108).

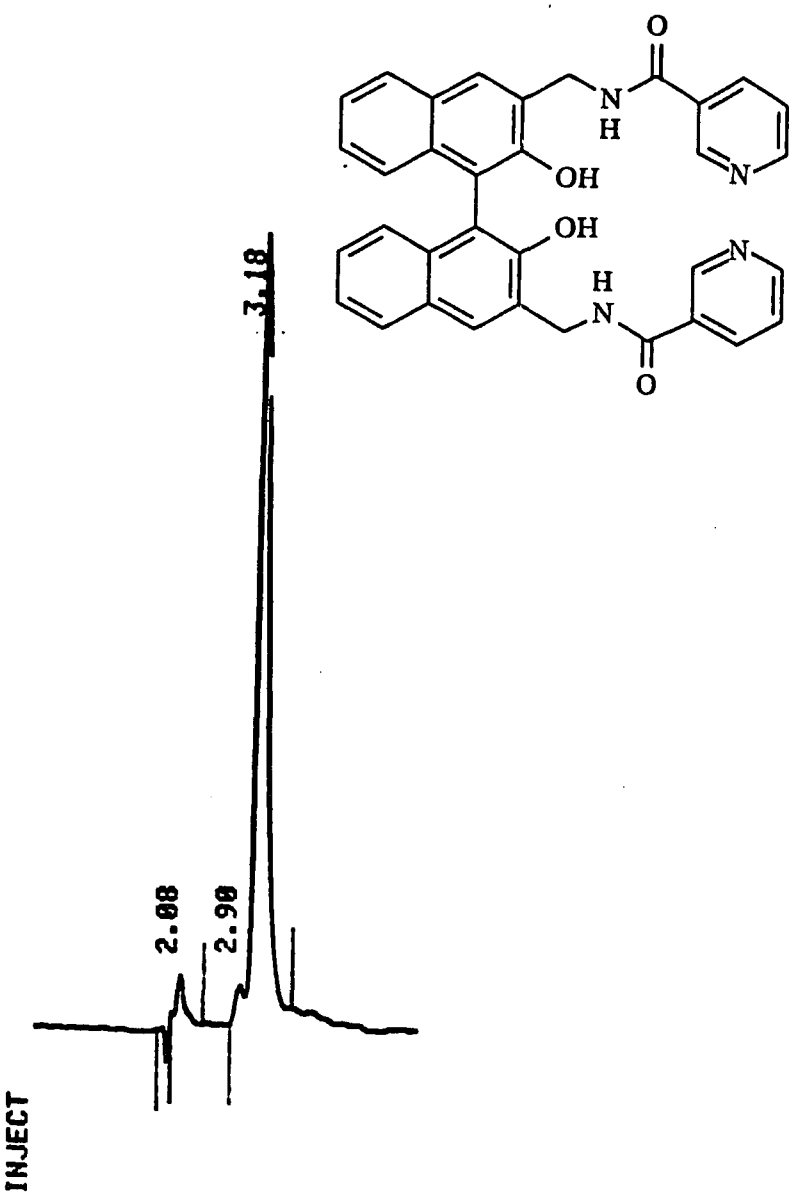


Figure 38 HPLC chromatogram (254 nm) of racemic bisnicotinamide. Solvent, 75% CH_3OH, 25% H_2O, 0.025% TFA.

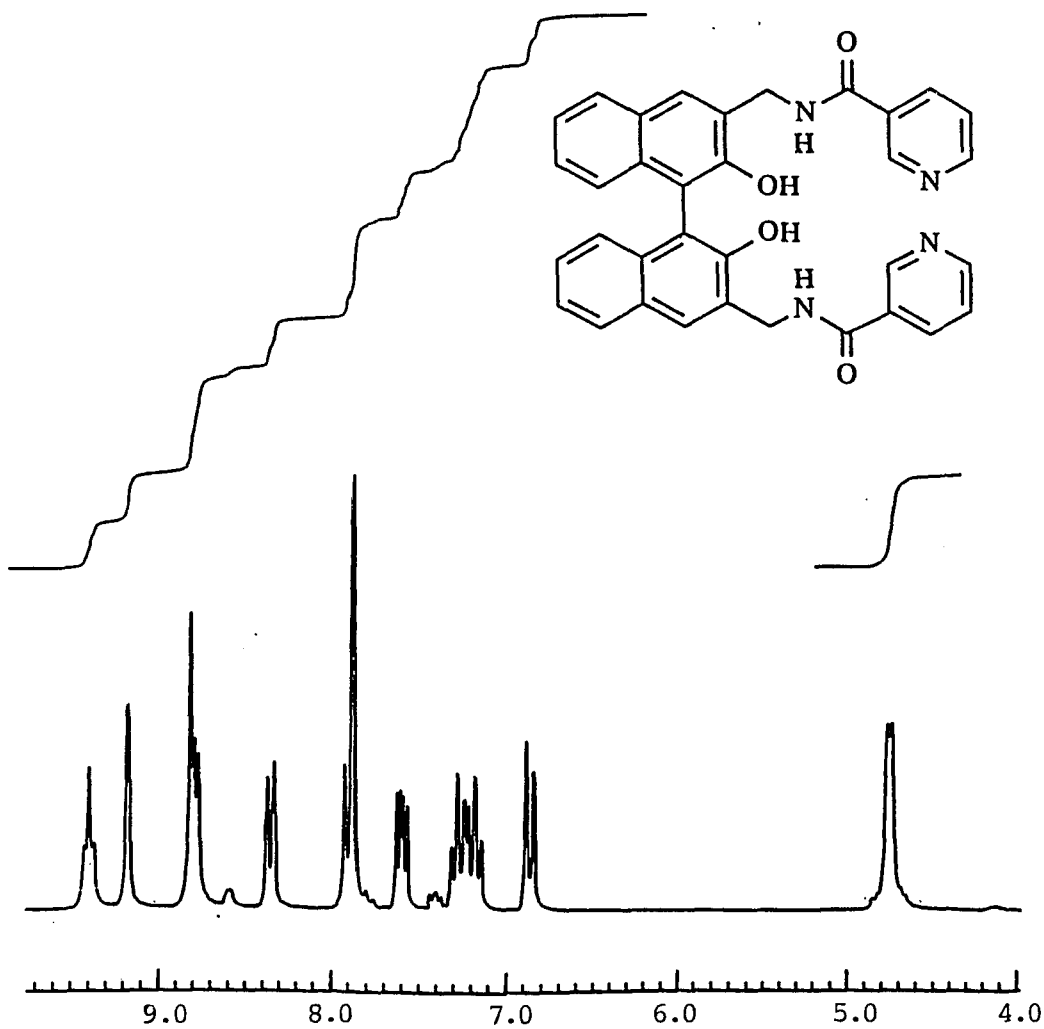


Figure 39 200 MHz ^{1}H-NMR spectrum of racemic bisnicotinamide. Number of transients, 200. Relaxation delay, 2.0 seconds.

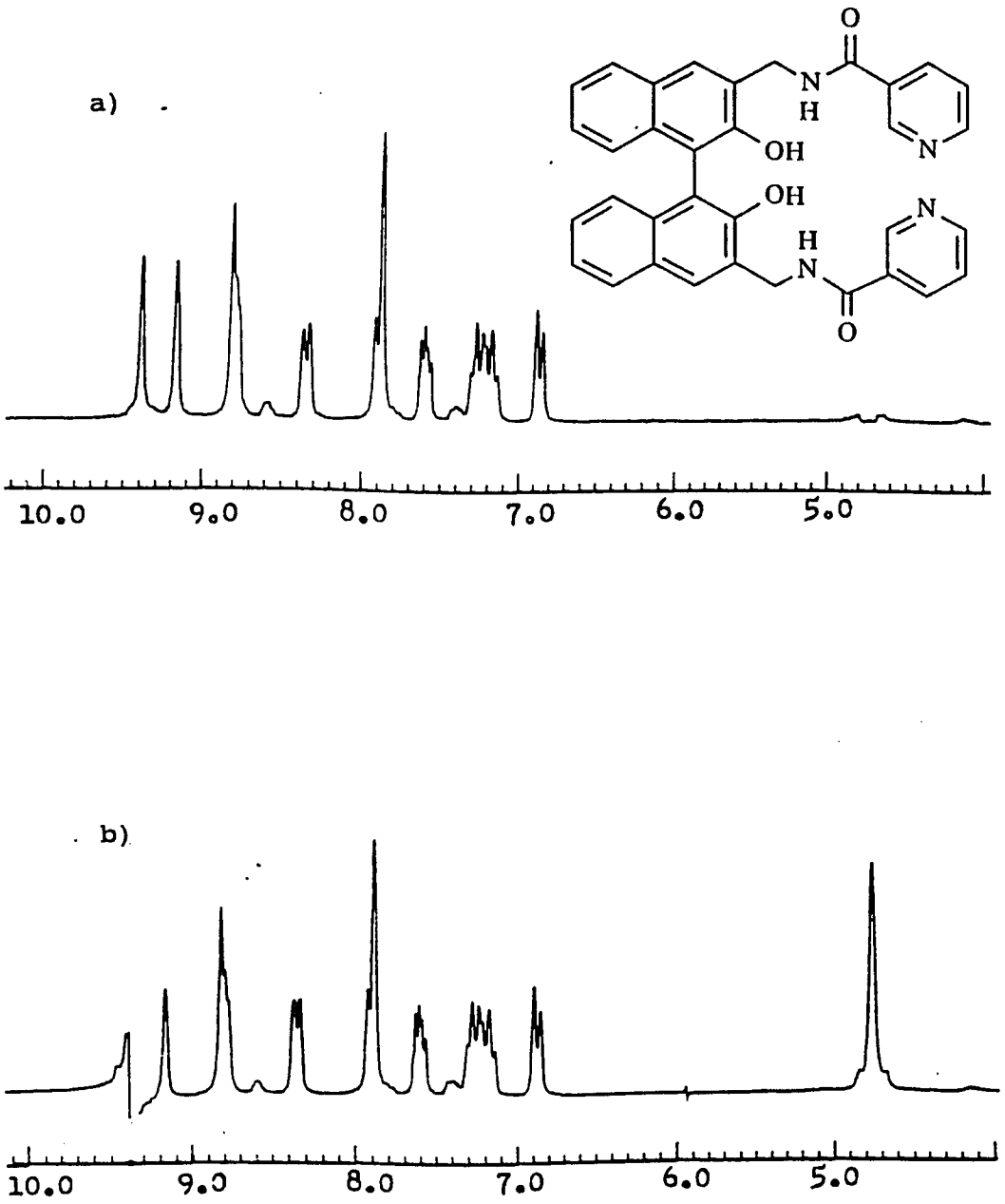


Figure 40 200 MHz ^{1}H-NMR homodecoupled spectra of bisnicotinamide.
a) irradiated at -CH_2 region (4.7 ppm)
b) irradiated at -CONHR region (9.4 ppm)

3.6c Preparation of optically active 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

Optically active 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl was prepared in essentially the same manner as the racemic bisnicotinamide. In general upon addition of nicotinoyl chloride solution to bisamine solution, the reaction was kept stirring at 80°C for 3 hours. Crude yields on the order of 50-60% were obtained. The crude product was isolated by dissolving the final residue in a minimal amount of pyridine and then precipitating from anyhydrous diethyl ether, to yield optically active, 3,3′-bis(3-pyridylcarbonyl-aminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl. Optically active bisnicotinamide was soluble in pyridine, dimethylformamide, and dimethylsulfoxide, and slightly soluble in methanol. It is not soluble in water or common organic solvents, i.e., ethanol, diethyl ether, benzene, ethyl acetate, acetone, dichloromethane, chloroform, carbon tetrachloride, toluene, petroleum ether, and hexane.

TLC (1-butanol, acetic acid, water, 4:1:5, upper phase, developing solvent) showed only one product after precipation from diethyl ether, with no starting material. Analytical HPLC of the (R)-(+)-bisnicotinamide, also showed one product, (see figure 41, p. 112), eluting solvent system 65% methanol, 35% water, 0.025% TFA. This sample of (R)-(+)-bisnicotinamide was prepared using (R)-(+)-bisamine hydrochloride, $[\alpha]^{25}_{D}$ +62.1 (0.990, H_2O), optical purity estimated at

96%, based on $[\alpha]^{25}_D$ +62.2 (0.990, H_2O) for bisamine hydrochloride of 96% optical purity (as determined by NMR analysis of MTPA amide prepared from the free amine of this salt, vide infra).

The specific rotation of this (R)-(+)-bisnicotinamide was measured in several solvents:

$[\alpha]^{25}_D$	concentration (g/100 mL)	solvent
+19.5	0.505	dimethylsulfoxide
+35	0.49	pyridine
+32	0.50	acetic acid
+20	0.51	dimethylformamide

The 200 MHz ^1H NMR spectrum (see figure 42, p. 113) obtained in DMSO-d_6 for the optically active bisnicotinamide was identical to that obtained for the racemic, with the exception of the hydroxyl peak, seen at 8.8 ppm in the racemic spectrum, which appeared as a broad peak centered at 3.5 ppm. The spectrum, obtained at 297K, pulse width of 30°, with a relaxation delay of 2.0 seconds, gave the following chemical shifts with the indicated areas: 9.40 (2.1 H, CONH), aromatic and pyridyl protons at 9.16 (2.0 H), 8.76 (2.1 H), 8.36-8.32 (2.0 H),

7.89-7.85 (4.0 H), 7.57 (2.0 H), 7.24-7.14 (4.0 H), 6.88-6.85 (1.8 H), 4.74 (3.9 H, $-CH_2$), and a broad hydroxy peak at 3.5 (2.2 H). The 50 MHz broad band decoupled ^{13}C NMR spectum (see figures 43 and 44, p. 114-115) was obtained in DMSO-d_6 for the (R)-(+)-bisnicotinamide at 297K, pulse width of 40°, with a relaxation delay of 1.4 seconds. The spectrum showed 16 peaks with the following chemical shifts: 165.5, 152.1, 152.0, 148.5, 135.1, 133.4, 129.6, 128.4, 128.0, 127.7, 127.0, 125.6, 124.1, 123.5, 122.6, 115.3. The $-\underline{C}H_2$ peak was assumed to be vitiated by the DMSO peaks (the $-\underline{C}H_2$ of the bisamine in DMSO was found at 44 ppm, see figure 20, p. 88).

The FT-IR spectrum of the (R)-(+)-bisnicotinamide (see figure 45, p. 116) showed the C=O stretch at 1643 cm^{-1} and the NH bend at 1531 cm^{-1}.

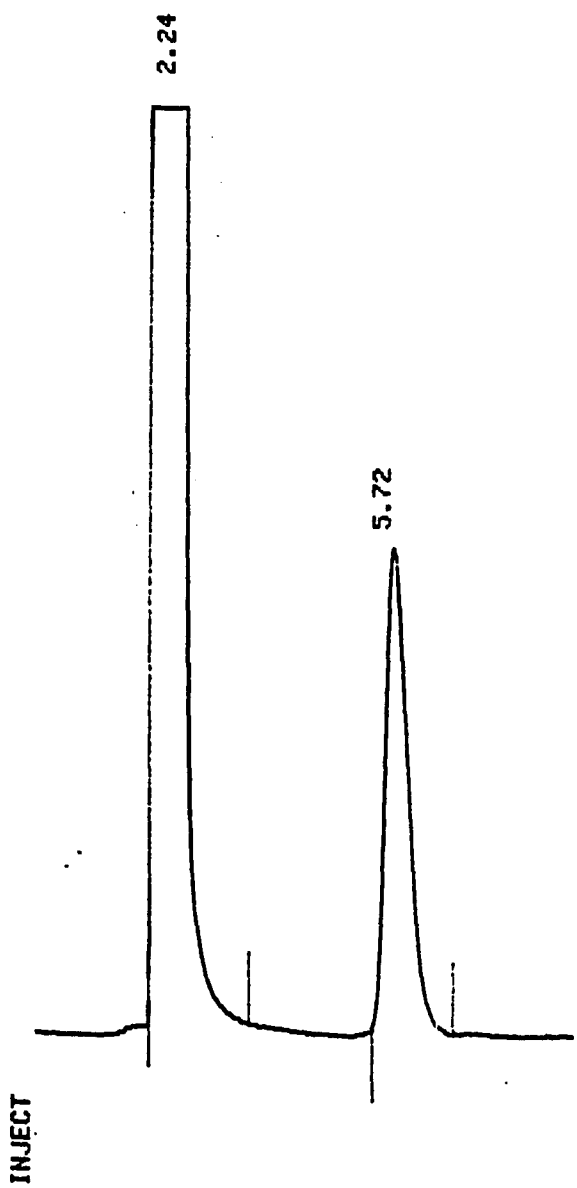


Figure 41 HPLC chromatogram (268 nm) of (R)-(+)-bisnicotinamide in pyridine.

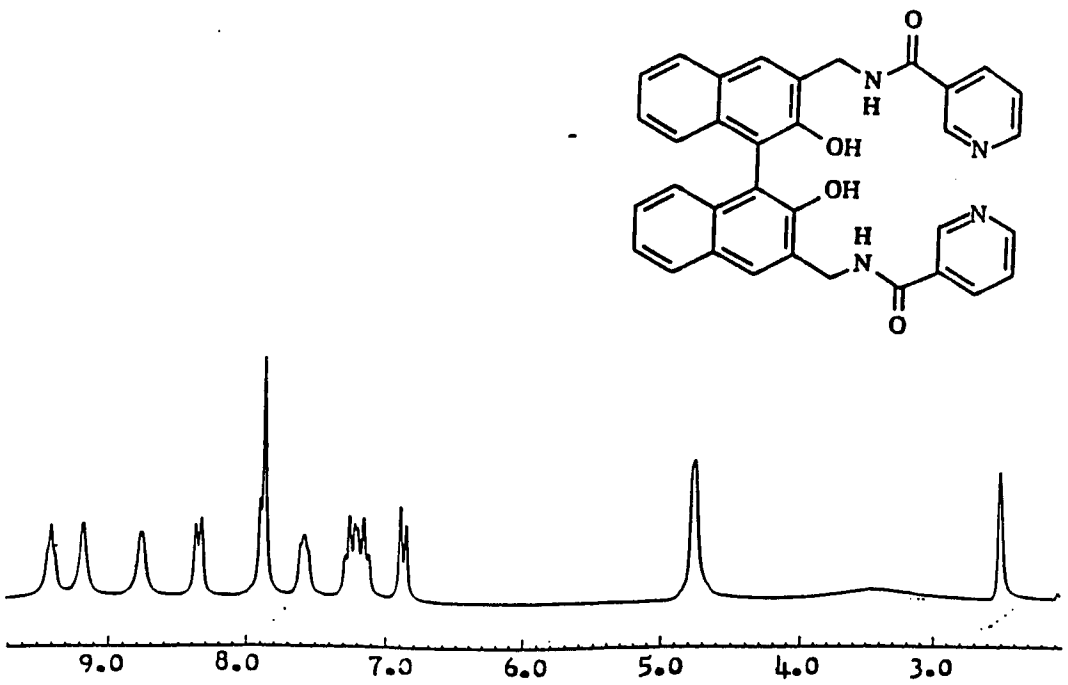


Figure 42 200 MHz ^{1}H NMR spectrum of (R)-(+)-bisnicotinamide.

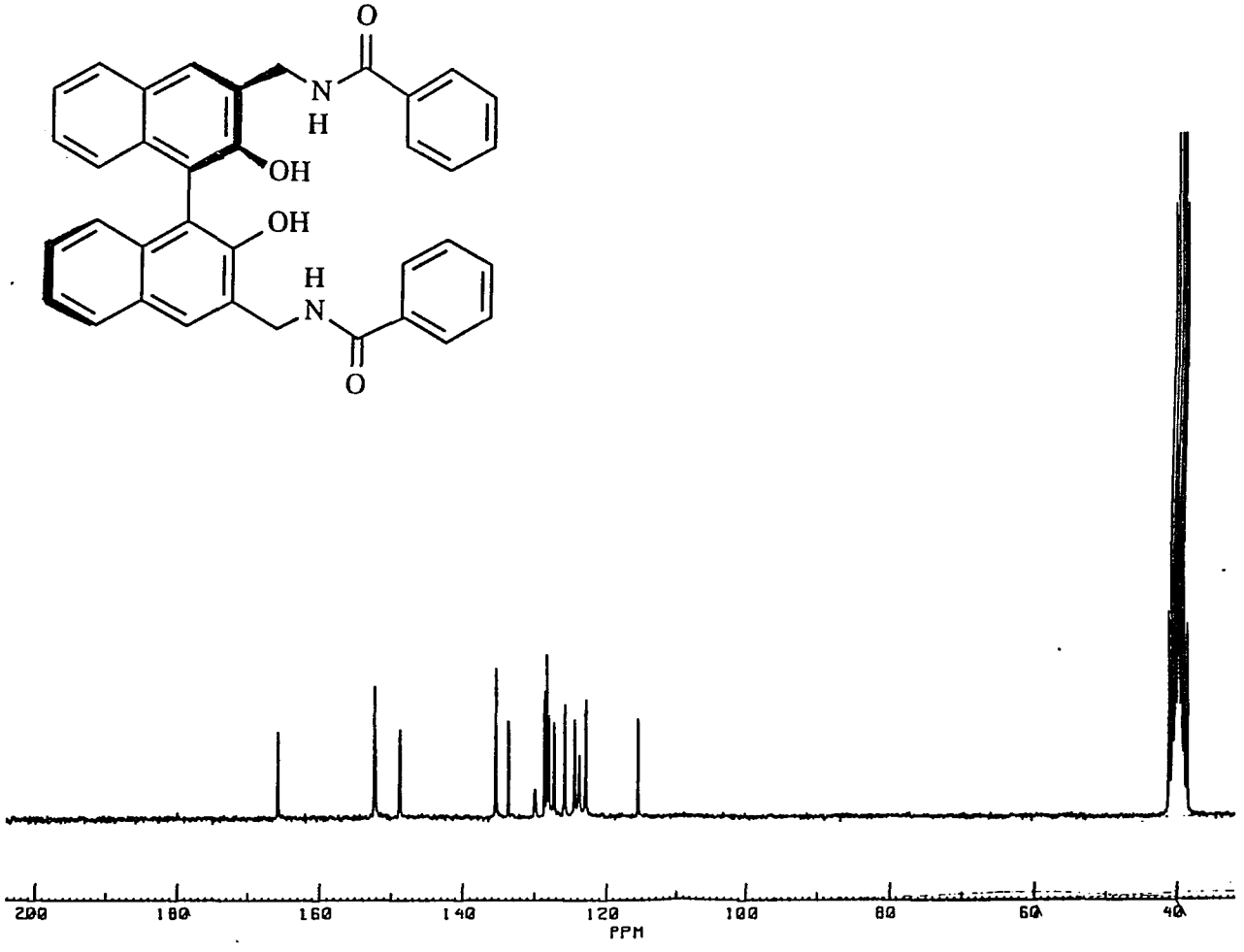


Figure 43 50 MHz ^{13}C NMR spectrum of (R)-(+)-bisnicotinamide.

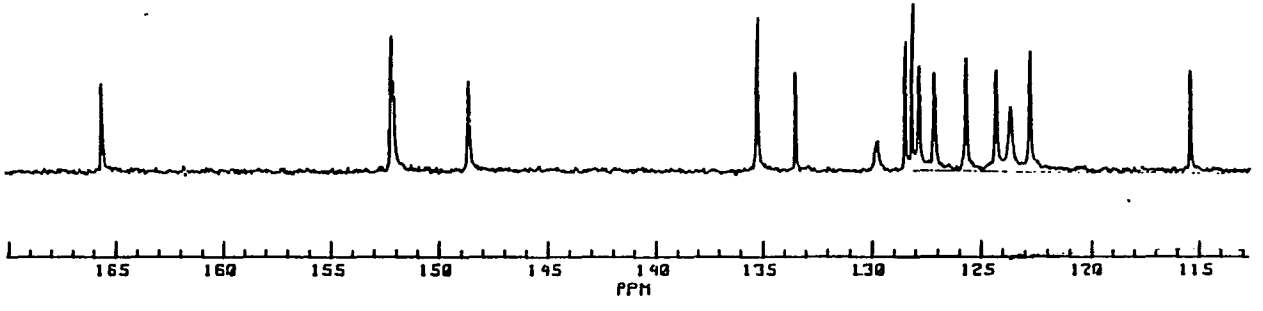


Figure 44 50 MHz ^{13}C NMR spectrum of (R)-(+)-bisnicotinamide (partial spectrum of that shown in figure 43).

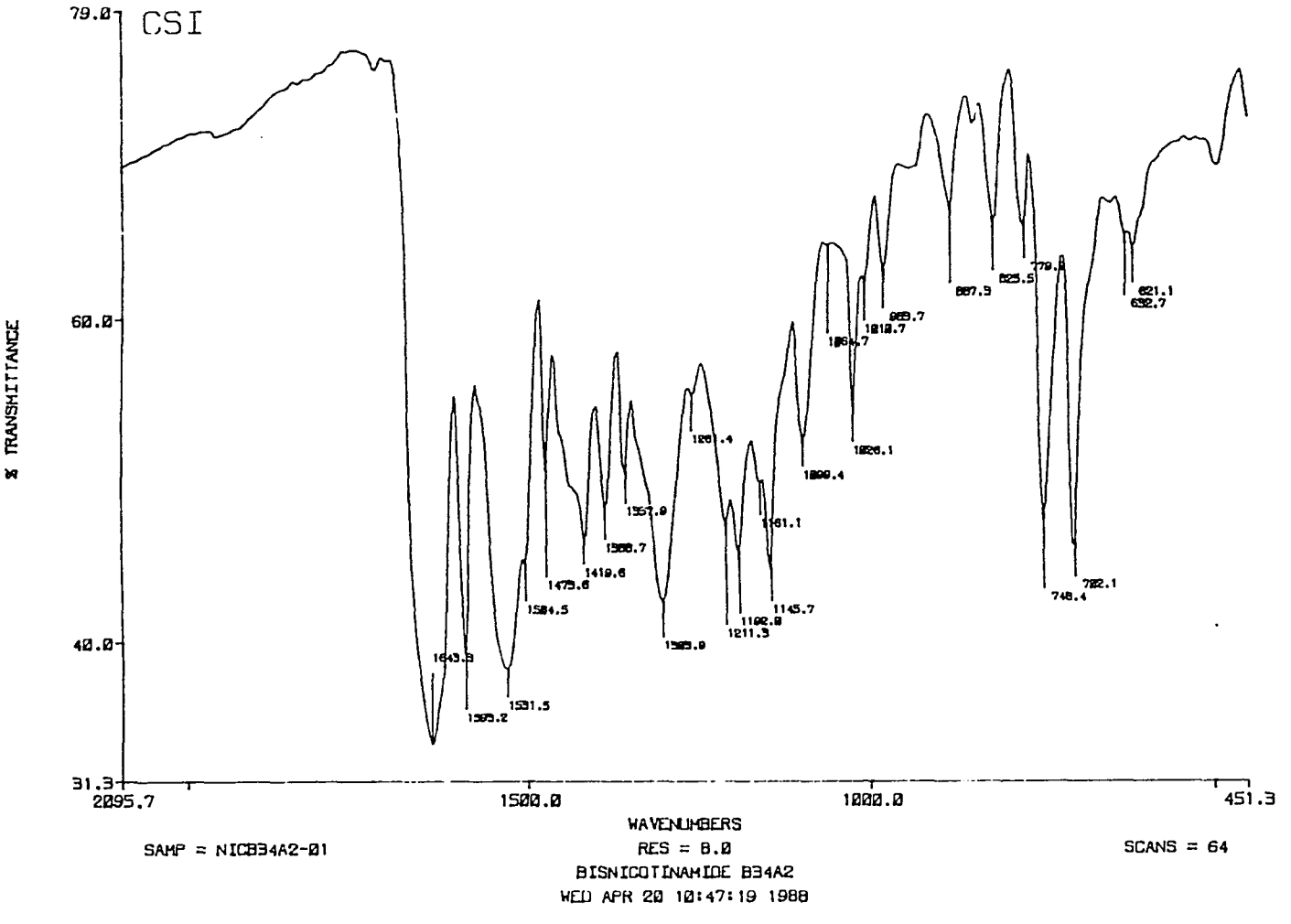


Figure 45 FT IR spectrum of (R)-(+)-bisnicotinamide.

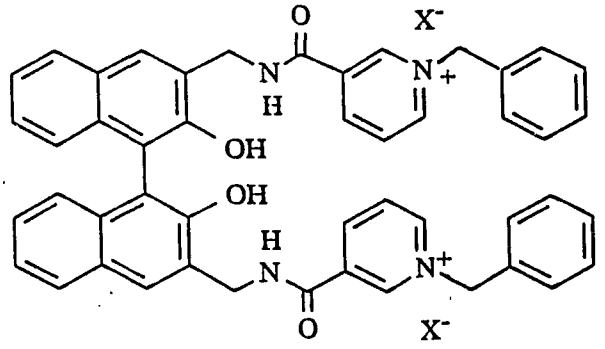
3,3′-Bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl (0.5 g) was purified by silica gel chromatography in order to obtain a sample for elemental analysis. A well mixed slurry of silica gel and the bisnicotinamide in solvent (CH_2Cl_2:CH_3OH:HOAc, 10:1:0.5, volume:volume) was put into an evaporating dish. The solvent was allowed to evaporate and the silica gel mixture was layered on a prepared column of silica gel in dichloromethane. The column was filled with dichloromethane and several fractions (totalling 100 mL) were collected (the band of bisnicotinamide is yellow and readily seen to barely move down the column). The solvent system was then changed to the CH_2Cl_2:CH_3OH:HOAc (10:1:0.5, v:v) mixture, and a purified sample was isolated. 3,3′-Bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl (probably the acetate salt) crystallized out of three of the fractions collected after being stored several days in the refrigerator. Elemental analysis of the bisnicotinamide, $C_{34}H_{26}N_4O_4$, gave 73.91% C, 4.44% H; calculated 73.63% C, 4.72% H.

3.7 Preparation of 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl benzyl halide.

Acetonitrile was distilled over phosphorus pentoxide. Optically active bisnicotinamide was dried under vacuum over phosphorus pentoxide for at least 24 hours prior to reaction. Benzyl bromide and benzyl chloride were reagent grade and used without further purification.

3.7a Quaternization of 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

(R)-(+)-3,3′-Bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl was quaternized, using a procedure described by Amano et al for the quaternization of related compounds (9). Both benzyl bromide and benzyl chloride were used in acetonitrile to form the benzyl halide salt of the bisnicotinamide:



(R)-(+)-bisnicotinamide (0.50 g, 0.90 mmol) was suspended in 15 mL dry acetonitrile in a round bottom flask containing a magnetic stirring bar, fitted with a condenser, and protected from moisture (drying tube containing indicating silica gel). Benzyl bromide (2 mL, approximately 17 mmol) was then added to the mixture at room temperature. The temperature of the reaction mixture was raised to 80°C, when all materials dissolved. The reaction was kept at 80°C for several hours and was followed by TLC (butanol, acetic acid, water, 4:1:5, upper phase, solvent system). After 5 hours, TLC showed no starting material and one major

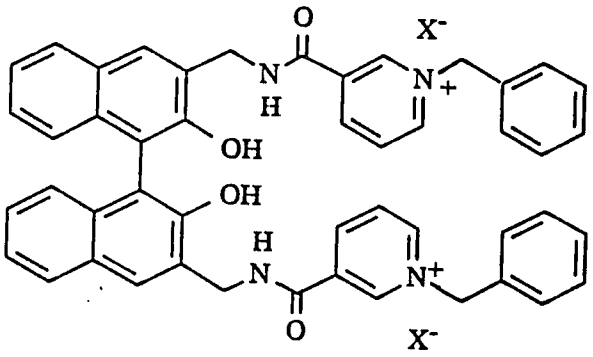
product (R_f value 0.16), with only a slight amount of another product (R_f value 0.32).

An oil had formed on the bottom of the flask. When the reaction was cooled to room temperature, a yellow precipitate had also formed. The oil had hardened upon cooling. The precipitate was filtered, dissolved in methanol, and reprecipitated from anhydrous diethyl ether to give 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl benzyl bromide. The oil was also dissolved in methanol and precipitated from diethyl ether to give the bisnicotinamide benzyl bromide salt. The combined dry weight of the product was 0.79 g, in 98% yield. TLC of the product showed only one spot, the bisnicotinamide salt. The bisnicotinamide benzyl bromide salt was soluble in water, methanol, dimethylsulfoxide, dimethylformamide, and pyridine.

The quaternization of the bisnicotinamide with benzyl chloride was carried out in the same solvent, but the reaction, again followed by TLC, required two days to go to completion. (R)-(+)-bisnicotinamide, (0.50 g, 0.90 mmol) was stirred in 15 mL dry acetonitrile. Benzyl chloride (2 mL) was then added to the mixture at room temperature. The temperature of the reaction mixture was raised to 80°C, when all materials dissolved. The reaction was kept stirring at reflux for two days. After two days, the reaction was cooled to room temperature, forming a precipitate. The precipitate was filtered, rinsed with cold acetonitrile and allowed to air dry. The

crude dry weight was 0.70 g in 96% yield. TLC (butanol, acetic acid, water, 4:1:5, upper phase) showed only one major product, R_f value 0.16, the same as in the benzyl bromide salt of the bisnicotinamide. The bisnicotinamide benzyl bromide salt was soluble in water, methanol, dimethylformamide, dimethylsulfoxide, and pyridine. It was rapidly crystallized from methanol, TLC showing only one spot. Elemental analysis of an analytical sample was obtained, calculated 71.37%C, 4.99%H; obtained 72.25%C, 4.78% H. The ^{1}H NMR spectrum of the benzyl bromide bisnicotinamide salt was consistent with the structure (vide infra).

The 200 MHz ^{1}H NMR spectrum of the benzyl bromide bisnicotinamide salt was obtained in DMSO-d_6 at 297K, pulse width 40°, with a relaxation delay of 2.0 seconds. The spectrum (see figure 46, p. 121) gave the following chemical shifts, with the indicated areas: 9.87-9.82 (m, 4.0 H), 9.41-9.38 (d, 2.0 H), 9.19-9.15 (d, 2.0 H), 8.64 (s, 2.0 H), 8.38-8.34 (t, 2.1 H), 7.91-7.85 (m, 4.0 H), 7.67-7.62 (m, 4.0 H), 7.51-7.46 (m, 6.2 H), 7.31-7.13 (m, 4.2 H), 6.86-6.82 (d, 2.0 H), 6.01 (s, 3.8 H, benzyl -C$\underline{H}_2$), 4.79-4.77 (d, 3.8 H, amide -C$\underline{H}_2$). The amide proton (CON$\underline{H}$) was shown to be included in the multiplet (actually a triplet overlapped with a singlet) at 9.87-9.82 ppm in a homodecoupled experiment where the methylene peak at 4.79-4.77 was irradiated (see figure 47, p. 122).



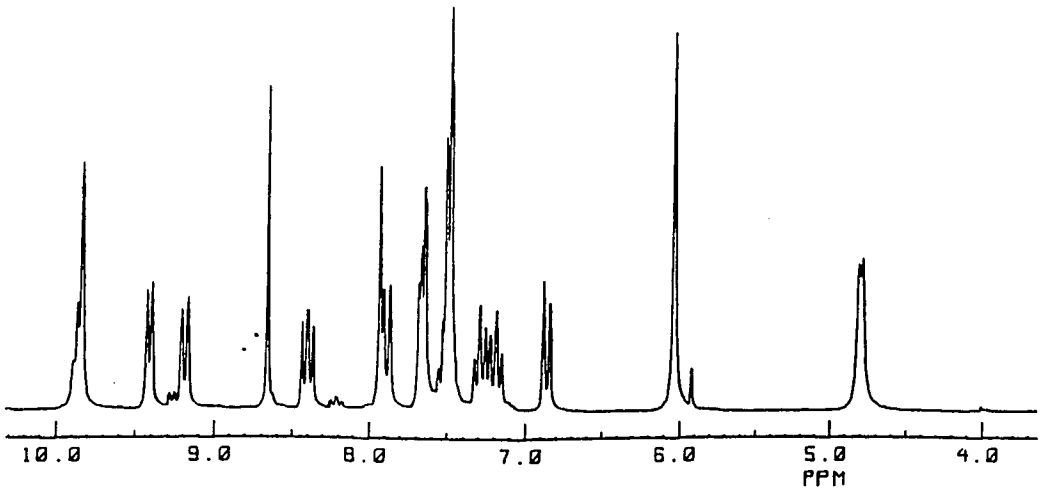


Figure 46 200 MHz ^{1}H NMR spectrum of benzylbromide bisnicotinamide salt.

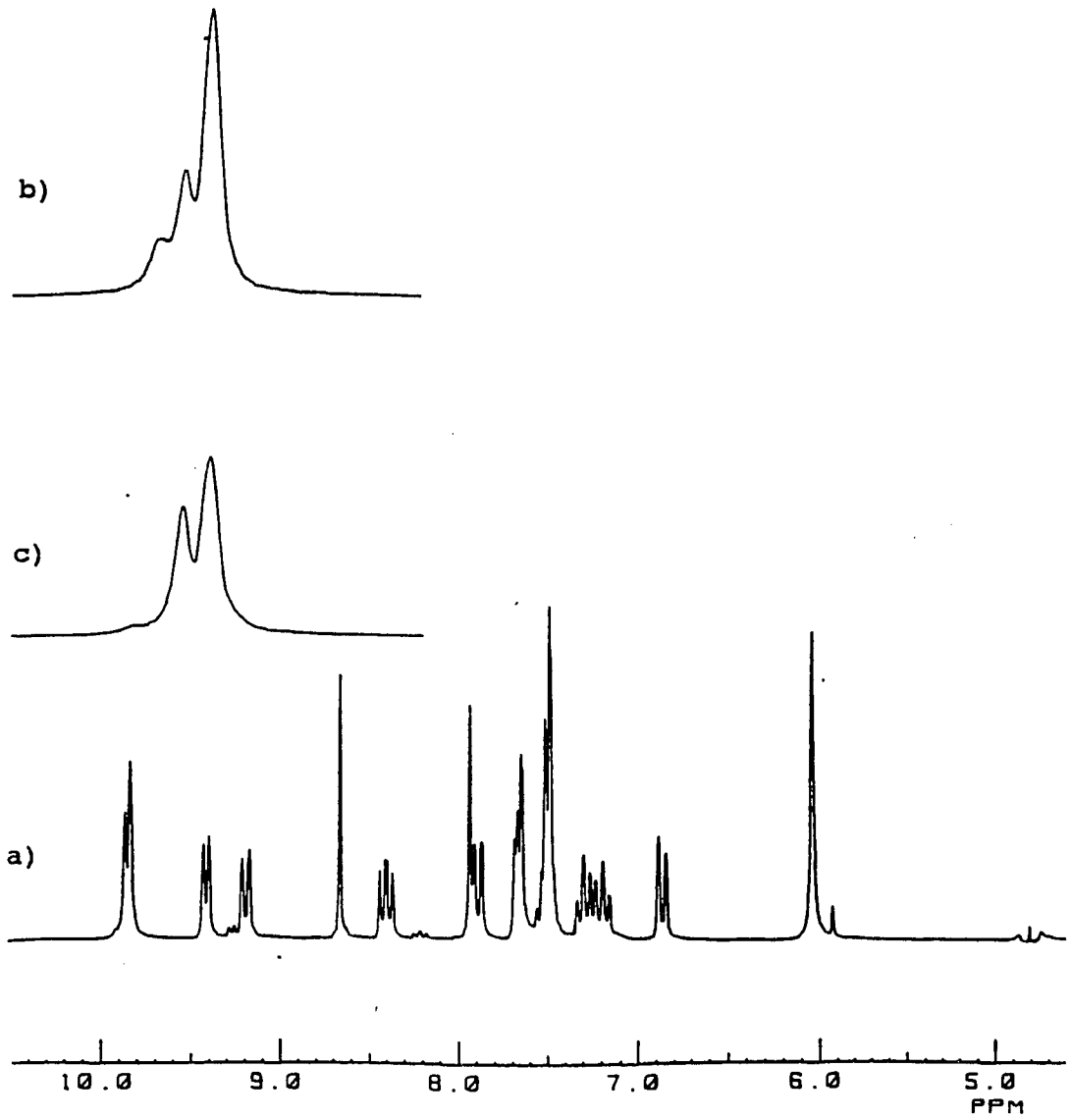


Figure 47 a) 200 ^{1}H NMR homodecoupled spectrum irradiated at -CH_2 region
b) expanded region at 10.0-9.6 ppm of normal spectrum (see fig. 46)
c) expanded region at 10.0-9.6 ppm of homodecoupled spectrum in (a)

3.8 Exploratory Reduction of 3,3′-bis(3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl benzyl halide.

Optically active bisnicotinamide benzyl halide salts were crystallized from methanol before use. All other reagents were reagent grade and used without further purification.

Reactions were carried out in inert atmosphere in the dark. Nitrogen was passed through an oxygen trap, as well as molecular sieves, silica gel, and $CaSO_4$ (drierite). Water was degassed by stirring under reduced pressure (water aspirator). CO_2 saturated solutions were prepared by warming dry ice and bubbling the CO_2 gas through the solution for several minutes. Column chromatography was carried out with chromatographic grade silica gel using the indicated solvent system, and was followed by TLC.

3.8a Discussion

Initial exploratory experiments were carried out using the bisnicotinamide benzyl bromide salt. In general, the procedures used were modified procedures of those reported for the sodium dithionite reduction of nicotinamide salts in basic, aqueous media (9, 21, 41-52).

The experiments were carried out varying the organic solvent and the concentration used in an aqueous solvent mixture, usually using either dimethylformamide or methanol. Complete dissolution of all reactants (bisnicotinamide bromide salt, sodium dithionite, and sodium bicarbonate or sodium carbonate) was not attained because of a salting out effect. In one experiment, pyridine and water were used as cosolvents. In this case all reagents dissolved, however, many different products were formed, as opposed to the formation of only one or two products in the other cases (as determined by TLC). In all cases where temperatures were kept below 50°C, the same major product was obtained in low yields (as estimated by TLC). Reaction temperatures could not exceed 50°C without decomposition.

The bisnicotinamide benzyl chloride salt was more soluble than the bromide salt and salting out did not appear to be a problem in the sodium dithionite reduction. The same major product was formed in apparently higher yield (as estimated by TLC).

An attempt was made to reduce the bisnicotinamide bromide salt using 1-benzyl-1,4-dihydronicotinamide (BNAH) in a procedure similar to that described by F. Rob et al for the reduction of nicotinamide benzyl bromide salts (52). The BNAH was prepared as described by Kim et al (53). Two products, one of which was the same product as formed in the sodium dithionite reduction, were formed in

very low yield (as determined by TLC).

Depending upon the reaction conditions used, crude product was obtained either by filtration of the reaction mixture, or by layering the reaction mixture with chloroform or methylene chloride (both starting material and final product are yellow). Filtration of a reaction mixture containing a yellow precipitate gave a mixture of starting material and product, with the major portion (as estimated by TLC) being the starting material. The organic solution obtained by layering the reaction mixture with methylene chloride contained one major product. The reduced product was isolated by column chromatography using methylene chloride and methanol (50:2) as the eluting solvent. In all cases, the final reduced product, 3,3′-bis(1-benzyl-1,4-dihydro-3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl, decomposes readily once isolated, and was found to be unstable to air, light, or both (as shown by TLC). The ^{1}H-NMR spectra obtained for the reduced product was found to be consistent with the structure (vide infra).

The following procedures describe the sodium dithionite reductions of the bisnicotinamide halide salts.

3,8b Sodium dithionite reduction of 3,3'-bis(3-pyridylcarbonylaminomethyl)-2,2'-dihydroxy-1,1'-binaphthyl benzyl bromide.

Bisnicotinamide benzyl bromide salt (4.00 g, 4.46 mmol) was dissolved in 200 mL dimethylformamide. Sodium dithionite (4.66 g, 26.7 mmol) and sodium bicarbonate (0.36 g, 4.2 mmol) in 50 mL water were added at 35°C to the stirred solution under nitrogen. An immediate precipitate was formed, and additional dimethylformamide (200 mL) was added to the reaction vessel, which was then covered to exclude light. The reaction temperature was raised to 50°C.

A 1 mL aliquot was collected and centrifuged to separate the precipitate from the solution. The white precipitate was water soluble (probably $NaHCO_3$ or $Na_2S_2O_4$) and the solution was yellow. TLC (butanol, acetic acid, and water, 4:1:5, upper phase, developing solvent) showed starting material and one major product in the solution. After one hour, sodium dithionite (4.72 g, 27.1 mmol) and sodium bicarbonate (0.63 g, 7.5 mmol) was added to the stirred reaction mixture at 50°C. The stirred reaction mixture was kept in the dark, under N_2, at room temperature, overnight. The next day, the temperature was raised to 50°C, and additional sodium dithionite (4.70 g, 27.0 mmol) in 20 mL water was added to the stirred reaction mixture. After 2 hours, a final portion of sodium dithionite (4.66 g, 26.7 mmol) was added. After 7 hours, the reaction temperature was lowered and the reaction was left stirring, in the dark, under nitrogen, at room temperature

overnight. Throughout the reaction, 1 mL aliquots were obtained, centrifuged, and found to contain a white precipitate and a yellow solution containing unreacted starting material and one major product (as determined by TLC).

The reaction mixture was filtered. The filtrate was extracted several times with methylene chloride. The aqueous layer remained yellow, indicating the presence of unreacted bisnicotinamide benzyl bromide salt. The combined organic layers (yellow solution, indicating the presence of final product) were dried over magnesium sulfate and then evaporated to dryness. The residue obtained from the evaporation was dissolved in a minimal amount of dimethylformamide and precipitated from diethyl ether. The dry weight of the light yellow precipitate was 0.90 g, crude yield 27%. TLC of this precipitated material showed one major product and little starting material. The 200 MHz ^1H NMR was obtained of the sample and was consistent with the structure of the reduced pyridinium salt (see representative NMR spectrum in section 3.8d below).

In another run, the bisnicotinamide benzyl bromide salt, recrystallized once from ethanol (purity verified by TLC), 1.00 g (1.12 mmol) was dissolved in 50 mL DMF. A solution of 10 mL H_2O containing 1.20 g $Na_2S_2O_4$ and 0.10 g $NaHCO_3$ was added to the DMF solution. An additional 40 mL DMF was added and the solution was warmed up to 50°C for twenty minutes. The reaction mixture was kept in the dark under nitrogen at room temperature for three days after two more

additions of 1.20 g $Na_2S_2O_4$. At the end of the period, the reaction mixture was concentrated. A white, water soluble precipitate was filtered. The yellow solution was evaporated to dryness. The yellow powder was stored in the dark under a vacuum, over P_2O_5, for two days. The product, dry weight 0.34 g (42% yield) was shown by TLC to be mainly the bis(1,4-dihydronicotinamide), with small amounts of starting material.

3.8c Reduction of 3,3'-bis(3-pyridylcarbonylaminomethyl)-2,2'-dihydroxy-1,1'-binaphthyl benzyl chloride.

Saturated sodium bicarbonate solution (36 mL) was diluted with 105 mL water and saturated with CO_2. Sodium dithionite (2.07 g, 11.9 mmol) was added to the stirred solution. Bisnicotinamide benzyl chloride salt (0.50g, 0.60 mmol) was dissolved in 36 mL methanol. The methanol solution was added to the aqueous solution. Upon addition of the methanol solution, the solution turned from an orange-yellow color to a yellow color before a yellow precipitate was formed. The reaction mixture was stirred in the dark under N_2 overnight.

The reaction mixture was filtered. The yellow precipitate was washed with water. TLC (1-butanol, acetic acid water, 4:1:5, upper phase) showed one major product and starting material. The precipitate was quickly stirred in $CDCl_3$ and filtered. TLC showed only the final product in the solution. The 200 MHz

^{1}H NMR spectrum was quickly obtained of the solution, and was essentially identical to that obtained in the reduction of the benzyl bromide salt (see representative NMR spectrum below).

3.8d Representative NMR spectra of the final product obtained in the sodium dithionite reduction of the bisnicotinamide benzyl halide salts.

The ^{1}H NMR chemical shifts obtained by two separate groups for 1-benzyl-1,4-dihydronicotinamide (BNAH) in $CDCl_3$ are listed below, (see table 4, p. 131) with assignments made (54, 55). The 200 MHz ^{1}H NMR spectrum obtained in $CDCl_3$ of a sample of BNAH prepared in this laboratory, corraborated the assignments given (see figure 48, p. 132).

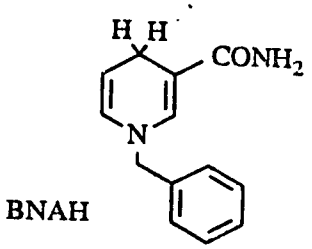
Amano et al reported the chemical shifts listed below (see table 4, p. 131) with the assignments made for the NADH model compound 3 (vide supra) (9). The ^{1}H NMR spectrum of a sample which was separated by column chromatography (vide supra) showed the reduction of the bisnicotinamide benzyl halide salt to the novel bis(dihydronicotinamide) compound (see figure 49, p. 133). The peak found at 4.65 ppm was assigned to the amide -CH_2 (see assignment for bisnicotinamide benzyl halide salt, p. 120). Another peak in the CH_2 region, at 4.15 ppm was assigned to the benzyl -CH_2. The "oxidized" pyridyl peaks found between 8-10 ppm in the NMR spectrum of the benzyl halide salt disappeared, with new peaks found at δ

6.18, 5.6, 3.1, and 1.3 ("reduced" pyridyl CH's), in agreement with the reported spectra. The NMR spectrum obtained was not well resolved enough to get good integral data and showed the sample to be impure. Another spectrum was obtained of the same sample the following day, and it was found that the product had decomposed. All reduced products gave essentially the same ^{1}H NMR spectrum, and showed the same major product being formed in each reduction.

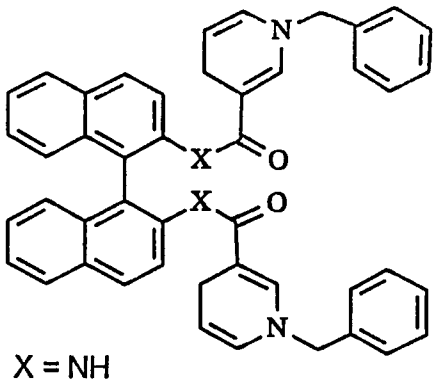
TABLE 4

Reported ^{1}H NMR Chemical Shifts of Model NADH Compounds

BNAH (54, 55)		Compound 3 (9)	
δ	assigned to	δ	assigned to
7.12	pyridyl C-2	6.83	pyridyl C-2
5.72	pyridyl C-6	5.53	pyridyl C-6
4.72	pyridyl C-5	4.40	pyridyl C-5
3.12	pyridyl C-4	2.26	pyridyl C-4
7.2	aromatic-H	6.9-8.1	aromatic-H
4.23	benzyl CH_2	4.13	benzyl CH_2



BNAH



X = NH

3

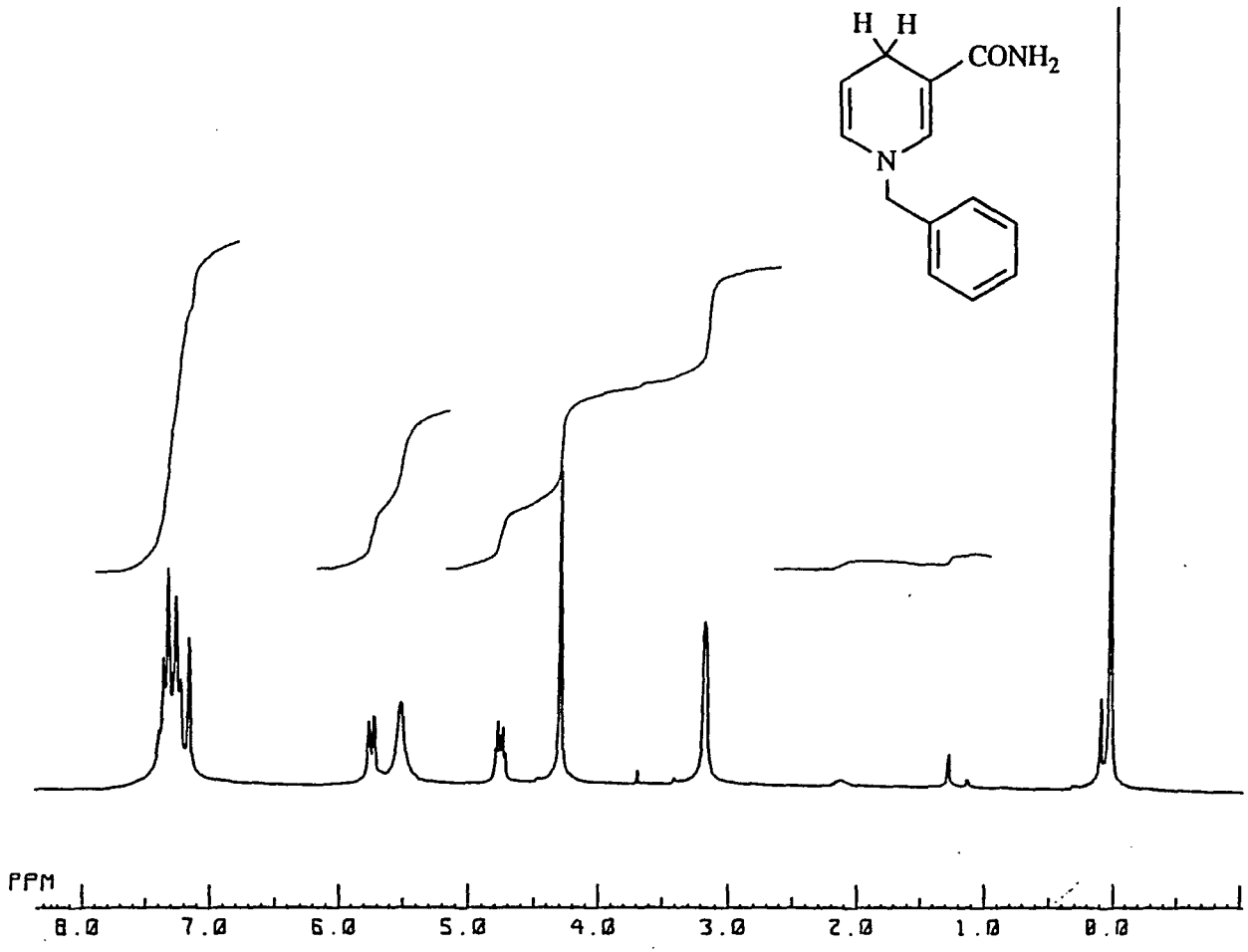


Figure 48 200 MHz ^{1}H-NMR spectrum of BNAH.

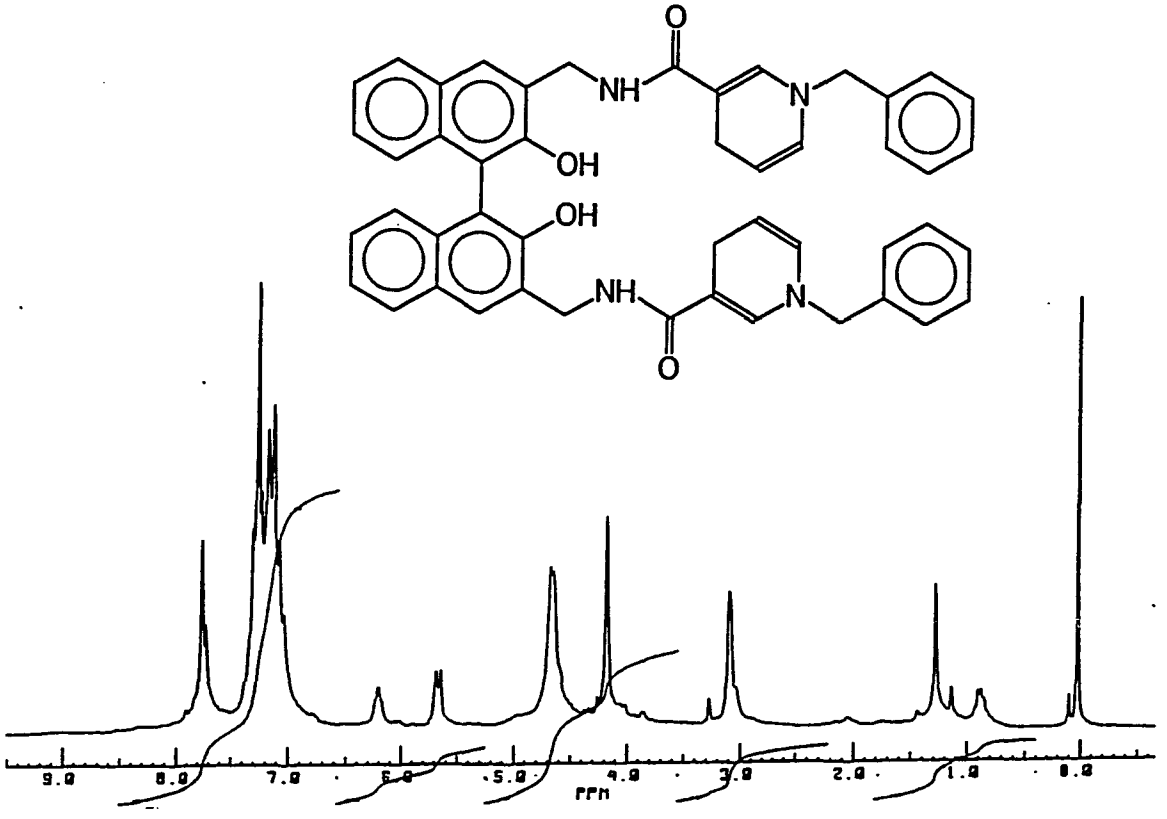


Figure 49 200 MHz ^{1}H-NMR spectrum of bis(1-benzyl-1,4-dihydro-3-pyridylcarbonylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthyl.

3.8e Reduction of Methylbenzoylformate With Bis(1-benzyl-1,4-dihydro-3-pyridylcarbonylaminomethyl)-2,2'-dihydroxy-1,1'-binaphthyl.

An attempt was made to reduce methylbenzoylformate, using the novel NADH model compound, the bis(1,4-dihydronicotinamide)binaphthol. Chloroform was distilled from K_2CO_3, methanol was distilled from magnesium shavings with iodine added as catalyst. Methylbenzoylformate was purified by column chromatography (silica gel - Aldrich, 70-230 mesh, 60 angstrom packing, solvent system, hexane/ethyl acetate). Magnesium perchlorate was dried overnight at 100°C. The model compound was stored under vacuum in the dark over P_2O_5.

The bis(1,4-dihydronicotinamide)binaphthol, 0.3003 g (0.40 mmol) was added to 6 mL $CHCl_3$. $Mg(ClO_4)_2$ (43.3 mg, 0.19 mmol) was added to the stirring mixture. Methylbenzoylformate (89.2 mg, 0.54 mmol) in 1 mL $CHCl_3$ was added to the stirred solution via syringe. The reaction was left stirring under nitrogen, in the dark for 24 hours. The reaction was quenched with water and extracted with dichloromethane. TLC (CH_2Cl_2:CH_3OH, 9:1, developing solvent) of the organic solution showed starting material, with little product formed. Gas chromatographic analysis showed little more than 1% methyl mandelate formed. Neither the oxidized nor the reduced form of the bis(1,4-dihydronicotinamide) was able to be recovered from the reaction mixture.

3.9 Exploratory Complexation of NAD^+ Model Compound With BNAH.

3.9a Discussion

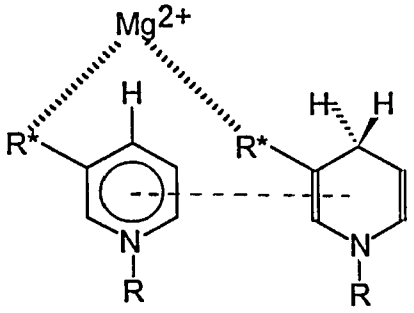
It has been reported that optical yields were increased when a ternary complex was (apparently) formed with the 1,4-dihydronicotinamide (NADH model compound), its oxidized form (NAD^+ model), and $Mg(ClO_4)_2$ (20-23).

The model compound PPNAH (N-α-methylbenzyl-1-propyl-1,4-dihydro-nicotinamide) asymmetrically reduced methylbenzoylformate to optically active methyl mandelate (%e.e. 25), as reported by Ohno et al (20). It was found that the optical purity of the product formed was dependent not only on the molar ratio of metal ion (see discussion p. 15) to NADH model, but also to the percent conversion of reaction. The effect of added $PPNA^+$ (oxidized form) on the optical yield was studied, since the oxidized salt is accumulated as the reduction proceeds. A significant interaction between PPNAH and $PPNA^+$ was observed. However, the authors felt that the effect was too small to account for the large variation which is still observed during the course of reaction.

Makino et al (21) obtained similar results with their model system, N-{(1S)-2-hydroxy-1-[(S)-α-hydroxybenzyl]-ethyl}-1-propyl-1,4-dihydronicotinamide. Again, the added oxidized salt of their NADH model compound effectively increased the

%e.e. obtained. With no added oxidized salt, the %e.e. was 29%, chemical yield, 75%; with added oxidized salt, the %e.e. was increased up to 52.4, chemical yield, 54%. The authors suggested the presence of a ternary species formed from the NADH model, the oxidized NAD^+ model, and the metal ion (M), i.e., a new chiral environment close to the reaction site resulting in a higher optical purity of product formed. When an excess of metal ion was added to a reaction mixture of equimolar amounts of the NADH/NAD^+ model system, the asymmetric yield was lowered implying that the oxidized salt was strongly bound to M only (ternary complex not formed) and did not participate in the reaction.

Baba, Oda, and Inouye (22, 23) similarly reported an increase in %e.e. as reaction of their model system proceeded. The authors also accounted for the increase in terms of a chelative interaction of NADH/NAD^+ models with M:



The quaternized bisnicotinamide benzyl chloride salt (oxidized form) was combined with achiral 1-benzyl-1,4-dihydronicotinamide (BNAH - NADH model compound) and $Mg(ClO_4)_2$, in the hopes of forming a ternary complex. The

derivatized binaphthol would act as the chiral moiety of the resulting ternary complex, which might then be used as a reducing agent.

Several attempts were made to form the complex in acetonitrile. The bisnicotinamide benzyl chloride salt is known to be insoluble in acetonitrile, therefore, it was necessary to first attempt to dissolve the salt, perhaps being brought into solution by interaction with BNAH and/or $Mg(ClO_4)_2$.

3.9b Experimental

BNAH was synthesized and purified as described in the literature, and stored in the dark over dessicant until use. (R)-bisnicotinamide benzyl chloride salt was oven dried (80°C) for several days and stored over dessicant, prior to use. $Mg(ClO_4)_2$ was dried at more than 100°C for several days. Acetonitrile was distilled two times from P_2O_5. Dimethylsulfoxide was distilled two times - the first time in a simple distillation, the second time in a fractional distillation (collected fraction boiling 189-190°C). The reactions were run under Argon atmosphere, in the dark.

The quaternized bisnicotinamide benzyl chloride salt (0.365 g, 0.45 mmol), BNAH (0.048 g, 0.224 mmol) and 9.0 mL acetonitrile were added to the reaction flask. The mixture was stirred for several minutes. The acetonitrile turned yellow,

with the BNAH apparently dissolving. The bisnicotinamide salt did not dissolve. After a while, additional BNAH was added (0.048 g, 0.224 mmol) in an attempt to bring the bisnicotinamide salt into solution. The solid bisnicotinamide benzyl chloride salt did not dissolve. The stirring mixture was warmed slowly, with dissolution still not occurring. The mixture was left stirring overnight. The solid never dissolved.

In another attempt to form the complex, the quaternized bisnicotinamide binaphthol benzyl chloride salt (0.4030 g, 0.0500 mmol), BNAH (0.2150 g, 1.00 mmol), $Mg(ClO_4)_2$ (0.0620 g, 0.500 mmol) and acetonitrile (10.0 mL) were added to a reaction vessel under Argon. The mixture was left stirring several hours, with warming (40-50°C). The quaternized bisnicotinamide salt did not dissolve. An aliquot of the solution was analyzed by TLC to show BNAH dissolved, and still in the reduced form. DMSO was added dropwise, through a syringe, until all of the residue dissolved. Complete dissolution was not obtained until an equal amount of DMSO (10 mL) was added.

Since complexation between the oxidized bisnicotinamide and the reduced nicotinamide, BNAH is apparently mediated through $Mg(ClO_4)_2$, and since DMSO may interfere with the complexation, the reaction mixture was distilled to dryness under reducted pressure, in an attempt to form and isolate the ternary complex formed by the nonvolatile components. Dry acetonitrile was then added to the

residue, in order to dissolve the complex, if formed, in the preferred solvent. The residue did not dissolve, even after stirring overnight.

3.9c Reduction of Methylbenzoylformate.

Attempts were made to reduce methylbenzoylformate using the ternary complex of the bisnicotinamide salt, BNAH, and $Mg(ClO_4)_2$.

In one experiment, 0.4039 (0.50 mmol, 1.0 mmol equivalent) of the bisnicotinamide benzyl chloride salt, 0.1238 g (1.00 mmol) $Mg(ClO_4)_2$, and 0.2140 g BNAH (1.00 mmol) was dissolved in 5 mL DMSO and 5 mL CH_3CN under Argon atmosphere. Methylbenzoylformate, 0.140 mL (0.16g, 1.0 mmol), was added by syringe and the reaction was kept in the dark under Argon for several days. The reaction was quenched with water and extracted several times with dichloromethane. TLC (CH_2Cl_2:CH_3OH, 9:1) of the reaction product showed no product was formed.

In another experiment, 0.4038 (0.50 mmol) of the bisnicotinamide benzyl chloride salt, 0.2140 g BNAH ((1.00 mmol), and 0.1238 g (1.00 mmol) $Mg(ClO_4)_2$ was dissolved in 5 mL CH_3CN and 5 mL DMSO. The solution was evaporated to an oil. Acetonitrile (10 mL) was added. The precipitate formed did not dissolve, even upon warming to 45°C. TLC (CH_2Cl_2:CH_3OH, 9:1) of the yellow solution

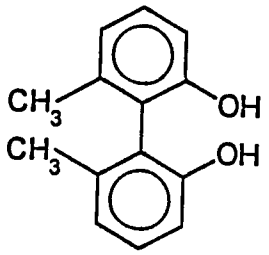
showed that BNAH was in solution. Methylbenzoylformate, 0.140 mL (0.16g, 1.0 mmol) was added by syringe to the stirring reaction mixture and was left under argon, in the dark for several days. The reaction mixture was quenched with water and extracted several times with dichloromethane. TLC of the reaction product obtained showed very little product formed (presumably some methylbenzoylformate was reduced by the BNAH).

4.0 ASYMMETRIC REDUCTION OF ACETOPHENONE WITH NOVEL CHIRAL HYDRIDE REAGENT

As part of the ongoing interest in preparing novel chiral reagents to be used in asymmetric reductions, a novel chiral hydride reagent was prepared. Acetophenone was reduced to give optically active 1-phenyl-ethanol in 4-24% enantiomeric excess.

4.1 Background

Chiral reagents prepared by modifying metal hydrides, such as lithium aluminum hydride and borane, with optically active diols and diamines have been used in the asymmetric reduction of prochiral ketones (56-63). Diols used in the hydride modification include (see structures next page) the optically active 2,2′-dihydroxy-6,6′-dimethylbiphenyl, 1 (56, 57), the polymer supported 2,2′-dihydroxy-6,6′-dimethylbiphenyl, 2 (56), the optically active 2,2′-dihydroxy-1,1′-binaphthyl, 3 (59-62) and (1S,2S)-1,2-diphenylethanediol, 4 (63).



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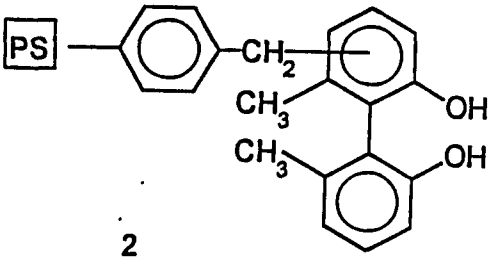

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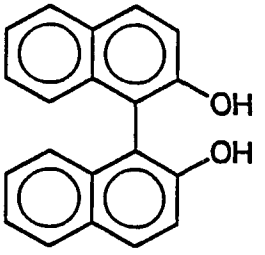

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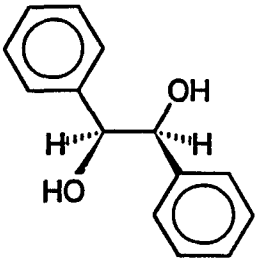

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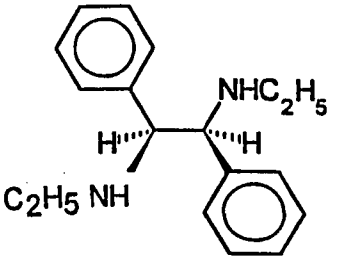
Diamines used in the hydride modification include (1S,2S)-N,N′-diethyl-1,2-diphenylethanediamine, 5 (62) and 2,2′-diamino-6,6′-dimethylbiphenyl, 6 (56).



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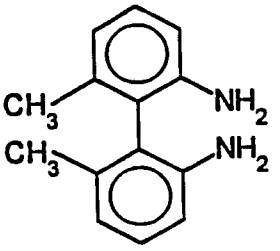

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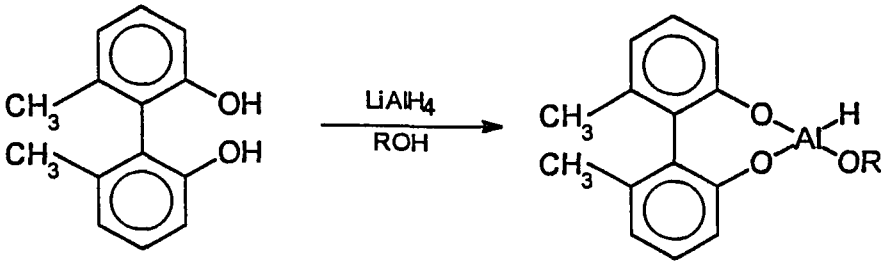
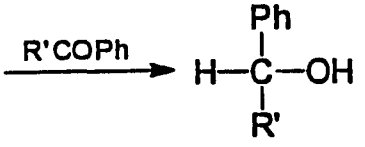
In general, all of the above mentioned compounds were used as the chiral moiety in a complexation with lithium aluminum hydride and an achiral alcohol. Compounds 1 and 3 were also used as the chiral moieties in complexation with borane and an achiral amine or alcohol. Chemical yields for all asymmetric reductions ranged from 12-100% with optical yields ranging from 2-98% depending on the chiral compound, reaction conditions and on the achiral compound used.

It has been suggested that a complex aluminum hydride reagent of the form shown below may be formed, which asymmetrically reduces prochiral alkyl phenyl ketone (56):



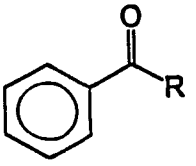


Chemical yields ranged from 39-81% with optical yields ranging from 2-98%

depending on reaction conditions and alcohol (ROH).

Noyori et al reported the asymmetric reduction of prochiral carbonyl compounds by the chiral hydride reagent containing 2,2′-dihydroxy-1,1′-binaphthyl and an achiral alcohol (32). Acetophenone was reduced using the chiral reagent with a variety of achiral alcohols. When methanol was the alcohol used, optical yields obtained were 73% at 30°C and 87% at -78°C. The ethanol complexed chiral hydride gave 64% and 90% optical yields at 30°C and -78°C. The *i*-propyl alcohol complex gave 46% optical yield at 30°C; the *t*-butyl alcohol complex gave 38% optical yield; other alcohols gave 10-44% optical yields. In all cases, at 30°C the chemical yields ranged from 95-100% and at -78°C, approximately 60%. Two equivalents of hydride reagent were used in the reductions.

The chiral hydride reagent complexed with ethanol was used to reduce various prochiral substrates (R= -D, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$):



Three equivalents of reagent were used in the reductions. The reactions were run at

-100°C for three hours and -78°C for 16 hours. Chemical yields ranged from 61-78% with optical yields 71-100%.

The general experimental procedure for the preparation of the chiral hydride complexes discussed was to add the achiral alcohol to the hydride solution under inert atmosphere at O°C, followed by the addition of the chiral diol. The resulting mixture was stirred for one hour at room temperature before the substrate was added at the desired reaction temperature.

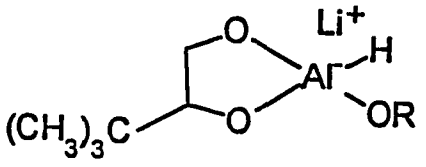
Noyori et al noted (32) that "Complex hydride reagents of type $LiALH_n(OR')_{4-n}$ are known to exist in a complicated equilibrium with a variety of disproportionated and aggregated species." In an additional experiment, the reaction of acetophenone and a reagent formed with equimolar amounts of lithium aluminum hydride and (R)-(+)-binaphthol with no added achiral alcohol afforded a negligible optical yield (2%), compared to the hydride with added ethanol (64%). It was noted that $LiAlH_4$ was probably the major reducing agent in that case.

Additional evidence for the suggestion that the ethanol might prevent the disproportionation reaction was reported by Yamashita et al (63). Aluminum-27 NMR spectroscopy was used to examine alkoxyhydroaluminate species, and indicated that "the addition of ethanol is effective to exclude the unmodified $LiAlH_4$ species" in the diol hydride system. The stereochemical outcome of all of the

previously mentioned chiral hydride systems apparently involves the chelated transition state suggested previously (56-62).

4,2 Experimental

Chiral diol 3,3-dimethyl-1,2-butanediol was reacted with $LiAlH_4$ and achiral alcohol in the formation of a complex aluminum hydride reagent, conceivably of the form shown below, and used in the asymmetric reduction of acetophenone.



4.2a General

Tetrahydrofuran (THF) was distilled under nitrogen from $LiAlH_4$. Ethanol was distilled under nitrogen from magnesium shavings and iodine. Isopropyl alcohol was distilled under nitrogen from aluminum isopropoxide. Tertiary butyl alcohol was first refluxed over CaO for several hours, left stirring overnight at room temperature and distilled, with the middle fraction then distilled from CaH. Optically active (R)-(−)- 3,3-dimethyl-1,2-butanediol was available in our

laboratory, and was purified via sublimation to yield 96.8% optically pure material, $[\alpha]_D^{25}$ -27.2 (c=0.69, $CHCl_3$), reported $[\alpha]_D^{25}$ -28.1 (c=0.69, $CHCl_3$). $LiAlH_4$ solution, 1M in THF, was obtained commercially from Aldrich and was standardized iodimetrically prior to use.

Reductions were run under nitrogen atmosphere, using syringe technique for delivery of all reagents. All additions of alcohol to $LiAlH_4$ were monitored by observing hydrogen gas evolution with a wet test meter. Chemical yields were determined by standard gas chromatographic methods (using DEGS - 6 foot column) with benzyl alcohol used as internal standard. Purification and isolation of the final product was effected using silica gel column chromatography. Enantiomeric excess of the final product was determined by ^{1}H-NMR spectroscopy using chiral shift reagents.

4.2a.1 Standardization of $LiAlH_4$

Reagent grade 1M $LiAlH_4$ in THF solution (1.0 mL) was added rapidly to stirring 0.392N iodine in toluene solution (20.0 mL, 0.784 mmol). Water (10-15mL) and glacial acetic acid (3-4 drops) were added to the solution. The solution was titrated with sodium thiosulfate, 0.0988N, to starch end point.

4.3 Reduction of Acetophenone with Chiral Hydride Complex

The following procedure is representative of the procedure used in all reductions, with changes only in the temperature of the reduction, the length of the reaction, the molar ratio of chiral hydride complex to acetophenone reduced, and the achiral alcohol used in the formation of the complex.

A solution of $LiAlH_4$, 0.99 M in THF (5.25 mL, 5.20 mmol) was added by syringe to a reaction vessel under a nitrogen atmosphere. The solution was cooled to 0°C by an ice bath. Isopropyl alcohol, 1.32 M in THF (4.0 ml, 5.28 mmol) was added by syringe to the stirring solution at 0°C. 3,3-Dimethyl-1,2-butanediol (0.6166 g, 5.22 mmol) was added in 9 mL THF to the stirring mixture at O°C. The solution was left stirring at room temperature for one hour. The solution was then cooled to -100°C (slush bath with liquid nitrogen and methylene chloride). A solution of acetophenone (0.219 g, 1.82 mmol) in two mL THF was added slowly to the stirring hydride solution. The reaction was stirred at 96-100°C for four hours. After the period, the reaction temperature was brought up to -78°C and left overnight.

The reaction was quenched with 2N HCl at -78°C, and the reaction product extracted with ether. The ether extract was washed with saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, then concentrated in vacuo.

The concentrate was brought up to a volume of 25.0 mL with diethyl ether. Internal standard, benzyl alcohol, was added to 1.0 mL of the final ether solution, and a chemical yield of 76.7% was calculated by gas chromatographic analysis.

The final product was purified and isolated by column chromatography (silica gel, methylene chloride eluant) and analyzed by ^{1}H-NMR after addition of Eu(hfc)$_3$. (S)-(–)- *Sec*-phenethyl alcohol was produced with 24% enantiomeric excess.

4.4 Results and Discussion

The molar ratio of chiral hydride:acetophenone was varied from 1:1 to 3:1 in an attempt to optimize both chemical yield and optical yield. The results of the exploratory reductions of acetophenone, using racemic 3,3-dimethyl-1,2-butanediol diol and ROH modified $LiAlH_4$ are tabulated in table 5 (see p. 151). The temperature of the reduction refers to the temperature at which acetophenone was added to the hydride solution and allowed to react.

At ambient temperatures, both with and without ethanol added, reaction was essentially complete within 1-2 hours. With no added ethanol, at -78°C, chemical yield is still high within 3 hours (83%), however, the reducing agent is probably the $LiAlH_4$ species (vide infra). The next several reactions with ethanol added, indicated the necessity of allowing the reaction to proceed for 20 hours in order to

optimize the chemical yield at low temperatures (below -70°C). It was also shown that the optimum hydride concentration at these temperatures was about 0.3-0.4M (see entries where after eight hours, yields of 1-28% were obtained).

TABLE 5

Reduction of Acetophenone
Racemic, Modified $LiAlH_4$

ROH[1]	ratio[2]	hydride conc (M)	Temp (°C)	Reaction time (h)	Chemical Yield[3]
-	1:1	0.38	-78	3	83%
-	1:1	0.55	ambient	1	>99%
EtOH	3:1	0.32	ambient	2	>99%
EtOH	2:1	0.31	-100	20	8%
EtOH	2:1	0.23	-78	20[3]	58%
EtOH	3:1	0.28	-78, -28	3, 15	97%
EtOH	2:1	0.18	-78	8	<1%
EtOH	2:1	0.17	-70	8	11%
EtOH	2.4:1	0.37	-78	8	28%
EtOH	2:1	0.35	-84	20	<1%

1. ratio of ROH:diol:$LiAlH_4$ in all complexes 1:1:1 molar
2. molar ratio of hydride (complex) to acetophenone
3. as determined by gas chromatography

The results of the asymmetric reductions of acetophenone, using (R)-(−)-3,3-dimethyl-1,2-butanediol are tabulated in table 6 (see p. 153). It was found that the chiral complex formed with 3,3-dimethyl-1,2-diol and ROH (ethanol, *i*-propyl alcohol, or *t*-butyl alcohol) reduced acetophenone in chemical yields of 58-84%, with enantiomeric excess ranging from 4-24% as determined by ^{1}H-NMR spectroscopy using chiral shift reagent, Eu(hfc)$_3$.

The first reaction, run at 0°C, did not include an achiral diol in the complex, and as expected, a high yield with no enantiomeric excess was obtained. Probably, the reducing agent was the $LiAlH_4$ species. When the complex with ethanol added was used as the reducing agent, at 0°C, the enantiomeric excess was low - only 4%. The chiral hydride reagent was prepared successively with ethanol, isopropyl alcohol, and *t*-butyl alcohol and reductions were run at about -80°C. The highest optical yield was obtained in the complex formed with isopropyl alcohol, 14% enantiomeric excess, as determined by ^{1}H-NMR spectroscopy.

In the final entry, an experiment proceeded initially at a reaction temperature of -100°C for the first four hours, followed by a temperature of −78°C for fifteen additional hours. An enantiomeric excess of 24%, chemical yield 77%, was obtained in the last experiment. It is reasonable to suggest that a chiral complex formed with (R)-(−)-3,3-dimethyl-1,2-butanediol, conceivably of the form shown below is responsible for the asymmetric reduction of acetophenone.

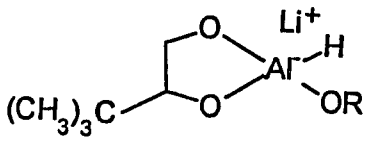


Table 6

Asymmetric Reduction of Acetophenone Using Chiral Diol Modified $LiAlH_4$[1]

ROH	Temp (°C)	Chemical Yield	Enantiomeric Excess
-	0	83%	0%
EtOH	0	84%	4%
EtOH	-80	59%	-
EtOH	-84	80%	10%
*i*PrOH	-80	58%	14%
*t*BuOH	-78	58%	8%
*i*PrOH	-100, -78[2]	77%	24%

1. reaction conditions generally 20 h run time; ratio of hydride complex:acetophenone, 3:1; hydride complex 0.3 M.
2. reaction run at -100°C for 4 h, then at -78°C for 15 h.

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