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MARUOKA, KEIJI

NEW APPLICATIONS OF ORGANOMETALLIC REAGENTS IN THE  
SYNTHESIS OF NATURAL PRODUCTS

*University of Hawaii*

PH.D.

1980

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NEW APPLICATIONS OF ORGANOMETALLIC REAGENTS  
IN THE SYNTHESIS OF NATURAL PRODUCTS

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE  
UNIVERSITY OF HAWAII IN PARTIAL FULFILLMENT  
OF THE REQUIREMENTS FOR THE DEGREE OF  
DOCTOR OF PHILOSOPHY

IN CHEMISTRY

AUGUST 1980

By

Keiji Maruoka

Dissertation Committee:

Hisashi Yamamoto, Chairman  
Richard G. Inskeep  
Robert S. H. Liu  
Paul J. Scheuer  
Harry Y. Yamamoto

## ACKNOWLEDGEMENTS

The author wishes to express his sincere thanks and special gratitude to Professor Hisashi Yamamoto without whose constant guidance, encouragement, enthusiasm, optimistic outlook, and occasional admonition this work would not have been completed.

He is indebted to a number of persons for their generous assistance: Miss Meng Yu Cheng and Mr. John Ikeda helped with a part of this work. Mr. James Loo determined 100 MHz  $^1\text{H}$  NMR spectra and 25.2 MHz  $^{13}\text{C}$  NMR spectra. Mr. Norman Liu determined electron impact mass spectra. Dr. Alfred E. Asato gave fruitful suggestions of several areas concerning this work.

Grateful acknowledgement is also made to Drs. Hitosi Nozaki, Kiitiro Utimoto, and Tamejiro Hiyama for their helpful discussions. Furthermore, it is a pleasure to express his appreciation for the pleasant talk and inspiring discussion with his colleagues in the University of Hawaii and Kyoto. This good companionship has made his graduate life in both Hawaii and Japan enjoyable.

He is grateful to have performed a portion of this work as a Chemistry Department Research Fellow during the 1979-1980 academic year.

He would finally like to express his special thanks to Professors Harry Y. Yamamoto, Richard G. Inskeep, Robert S. H. Liu, and Paul J. Scheuer for serving on his dissertation committee.

## ABSTRACT

Five new synthetic reactions are described. These methods are characterized by exquisite selectivity and stereochemical control, using organometallic reagents to realize the key step in the total synthesis of various natural products. The organometallics used in this study include zinc, aluminum, iron, copper, lithium, magnesium, and boron compounds.

A new approach has been demonstrated for the regio-specific aldol synthesis by simultaneous addition of  $\alpha$ -halo carbonyl derivatives and aldehydes or ketones to a suspension of diethylaluminum chloride and zinc in tetrahydrofuran at low temperature. This technique is also employable under mild conditions for the Reformatsky reaction to give  $\beta$ -hydroxy esters in excellent yield. One of the unique synthetic applications of this process is illustrated by the intramolecular cyclization of  $\alpha$ -bromo esters of  $\omega$ -hydroxyaldehyde, which produces macrolides, an important class of compounds in the antibiotic field.

A biogenetically patterned synthesis of camphor-type terpenoid compounds is described. 1,3-Dibromo-3,7-dimethyl-6-octen-2-one can be obtained from geraniol through five steps in 68% overall yield. Reaction of the dibromoketone and  $\text{Fe}_2(\text{CO})_9$  in benzene at 100 - 110°C leads directly to ( $\pm$ )-camphor in 38% yield. In addition, several six-membered monocyclic terpenoids, ( $\pm$ )-dihydrocarvone and ( $\pm$ )-carvenone have also been isolated. In a similar manner, reaction of

1,3-dibromo-3,7,11-trimethyl-6,10-dodecadien-2-one and  $\text{Fe}(\text{CO})_5$  produces a 2:1 mixture of ( $\pm$ )-campherenone and ( $\pm$ )-epicampherenone in 58% yield.

A new, selective, and mild approach to N-alkylation of polyamines has been demonstrated, which involves the novel reductive cleavage of the carbon-nitrogen bond in cyclic amidines by diisobutylaluminum hydride. This method provides a new entry to a wide variety of N-alkylated polyamines and many interesting macrocyclic polyamines hitherto accessible only by length or complicated synthesis. Moreover, the synthesis of the plant alkaloid, spermine, was successfully accomplished by the reductive cleavage of carbon-nitrogen bonds in 1,2-bis(2'-tetrahydropyrimidyl)-ethane, which was readily available from succinonitrile and 1,3-diaminopropane mono-p-toluenesulfonate.

An efficient method for the N-alkylation of amines is described based on the oxidative coupling of lithium alkyl-copper amide, which is derived from lithium dialkylcuprates and primary or secondary amines. The high chemospecificity of the method was demonstrated by the selective tert-butylation of m-aminoacetophenone without any protection of the carbonyl group. The present N-alkylation process should be extremely useful for complex or polyfunctional molecules, the reaction conditions being so mild as to minimize the possibility of involvement of most functional or protecting groups.

A total synthesis of spermidine alkaloids, celacinnine, celabenzine, and celafurine, is described in which a key step is the boron-templated cyclization of ethyl 3-phenyl-4,9,13-triazatridecanoate to 12-phenyl-2,6,11-triazacyclo-tridecanone. Further transformation of the amide involving selective acylation with the corresponding acid chlorides led to the natural products, celacinnine, celabenzine, and celafurine. A noteworthy feature of the present cyclization apart from its simplicity and high overall yield is that carbon-nitrogen bond formation takes place only intramolecularly. Thus, high dilution or slow addition techniques are no longer necessary for the new process.

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## LIST OF ABBREVIATIONS

Short forms of abbreviations of journal titles are according to the "Chemical Abstracts Service Guide for Abbreviating Periodical Titles."

## Abbreviations for words

Anal	Elemental Analysis
<u>aq</u>	aqueous
bp	boiling point
br	broad
calcd	calculated
cmr	<sup>13</sup> C NMR; C-13 magnetic resonance (spectrum)
d	doublet
DIBAH	diisobutylaluminum hydride
DMSO	dimethyl sulfoxide
equiv	equivalent
glpc	gas liquid partition chromatography
h	hour
HMPA	hexamethyl phosphotriamide
ir	infrared (spectrum)
m	multiplet
mass	mass (spectrum)
mp	melting point
p	page
pmr	<sup>1</sup> H NMR; proton magnetic resonance (spectrum)
q	quartet

$R_f$	relative mobility
s	singlet
t	triplet
temp	temperature
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	tetramethylsilane
%	percent

## Chapter I

### Introduction and General Summary

The application of organometallic reagents to organic synthesis dates back to 1863, when Frankland and Butlerow reported the use of the newly discovered organozinc compounds in the preparation of various types of organic compounds.<sup>1</sup> However, it was the advent of the Grignard reagents around 1900 which established the importance of organometallic reagents as valuable aids to the organic chemist.<sup>2</sup> Later, the organolithium<sup>3</sup> and organoaluminum reagents<sup>4</sup> were developed and applied to preparative organic chemistry and in the sixties the applications of organoboron compounds by H. C. Brown in organic chemistry began to receive considerable attention.<sup>5</sup> The discovery of ferrocene in 1951 was followed by the rapid development of the organometallic reagents and reactions.<sup>6</sup> The commercial availability of new solvents such as tetrahydrofuran (THF), the glycol ethers, dimethyl sulfoxide (DMSO), and hexamethyl phosphortriamide (HMPA) has extended the scope of application of the older organometallic reagents.

Organic chemists now have organic derivatives of virtually all main group and transition metals at their command. The tailor-making of new ones for specific

applications has become the main thrust of research efforts throughout the world. Today, it is not only unwise but rather difficult to accomplish an efficient and selective multistep synthesis without using organometallics.

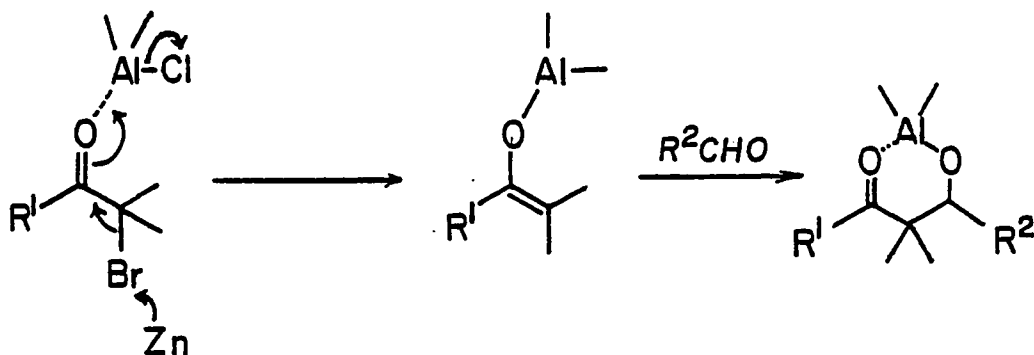
Despite widespread use of organometallics, there still exists a strong tendency to view organic chemistry as a branch of science dealing primarily with carbon, hydrogen, nitrogen, oxygen, sulfur, and halogens. Except for a few classes of organometallics, such as organolithiums and the Grignard reagents, the organometallics are often viewed as toxic. Persuaded by the literature that promises an attractive route to the desired compound, chemists occasionally use some organometallics with much hesitation. The results are often disappointing and frustrating. Poor results appear to stem, at least in part, from lack of sufficient knowledge of the scope and limitations of the procedure and of the proper handling of organometallics in such a procedure. Another frequent problem is one of selecting the most suitable procedure for the desired transformation. Therefore, the proper choice of organometallic reagents and reaction conditions must be necessary to accomplish the synthetic work.

At the outset of the present work, this author was interested in the development of the new synthetic methods and reactions, characterized by exquisite selectivity and stereochemical control, using organometallic reagents to realize the key step in the total synthesis of various

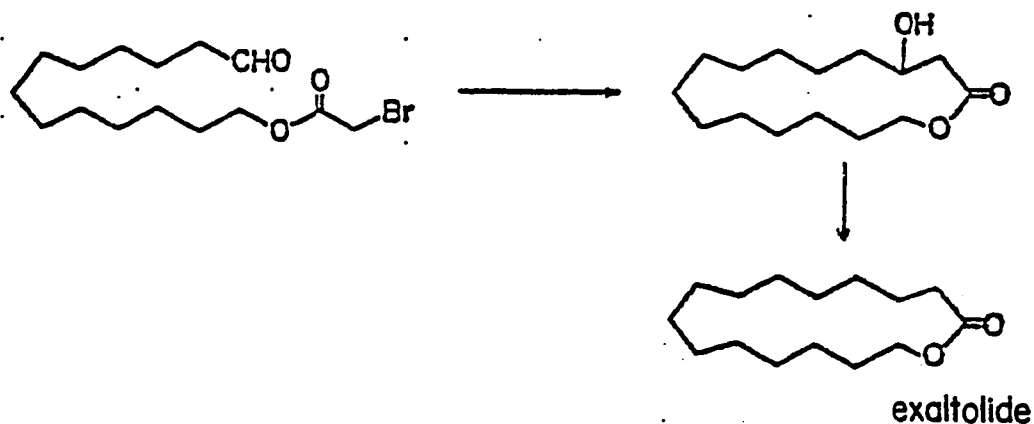
natural products. The organometallics used in this study include zinc, aluminum, iron, copper, lithium, magnesium, and boron compounds.

The aldol condensation has long been recognized to be one of the most versatile synthetic methods in organic chemistry.<sup>7</sup> However, this reaction is often complicated by the fact that the aldol product is less stable than the starting materials and contains di-, poly-, or self-condensation products owing to more than one mode of condensation. As a consequence of this nonselectivity, the separation of the desired product from the complex reaction mixture is particularly troublesome. Therefore, the use of this otherwise efficient reaction has frequently been limited. In order to overcome this difficulty, a useful synthetic procedure has been developed with the zinc-diethylaluminum chloride system, which permitted the successful preparation of hitherto unavailable aluminum enolate<sup>8</sup> from  $\alpha$ -bromo ketones, as shown in Chapter II. The aluminum enolate could be among the best, since it highly activates the carbonyl compound in a nucleophilic fashion and also intercepts the resulting aldol as a plausibly stable aluminum chelate.

Although two molecules of an  $\alpha$ -bromo ketone may condense with each other, simultaneous addition of  $\alpha$ -bromo ketones and carbonyl compounds permits clean generation of the desired aldol product. This enables the intramolecular cyclization of  $\alpha$ -bromoacetate of  $\omega$ -hydroxyaldehyde



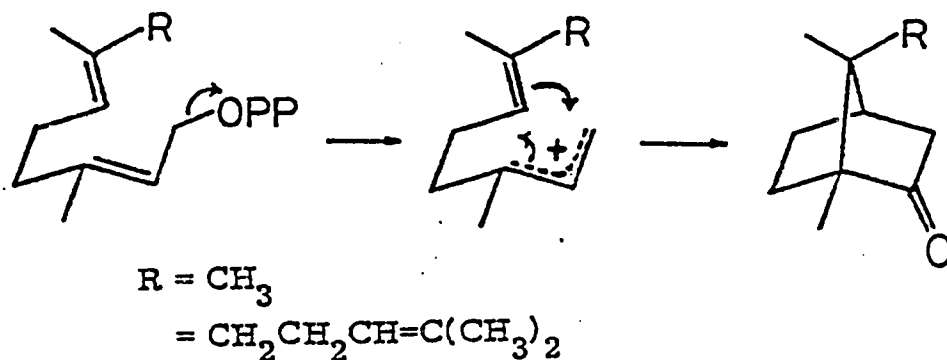
efficiently. Thus, gradual addition of the bromoacetate of 13-hydroxytridecanal to zinc-silver couple and diethylaluminum chloride in THF led to the formation of 3-hydroxypentadecanolide, a key intermediate for preparation of naturally occurring exaltolide in two steps. The wide applicability of this methodology in the field of natural



products was illustrated by the recent synthesis of diploidalides and muscone by Tsuji and his coworkers.<sup>9</sup>

Recently there has been much interest in devising synthetic routes to sesquiterpenoids along plausible biogenetic pathways. In Chapter III, the biomimetically patterned synthesis of (±)-camphor and (±)-campherenone are described. In a biogenetic hypothesis, the known

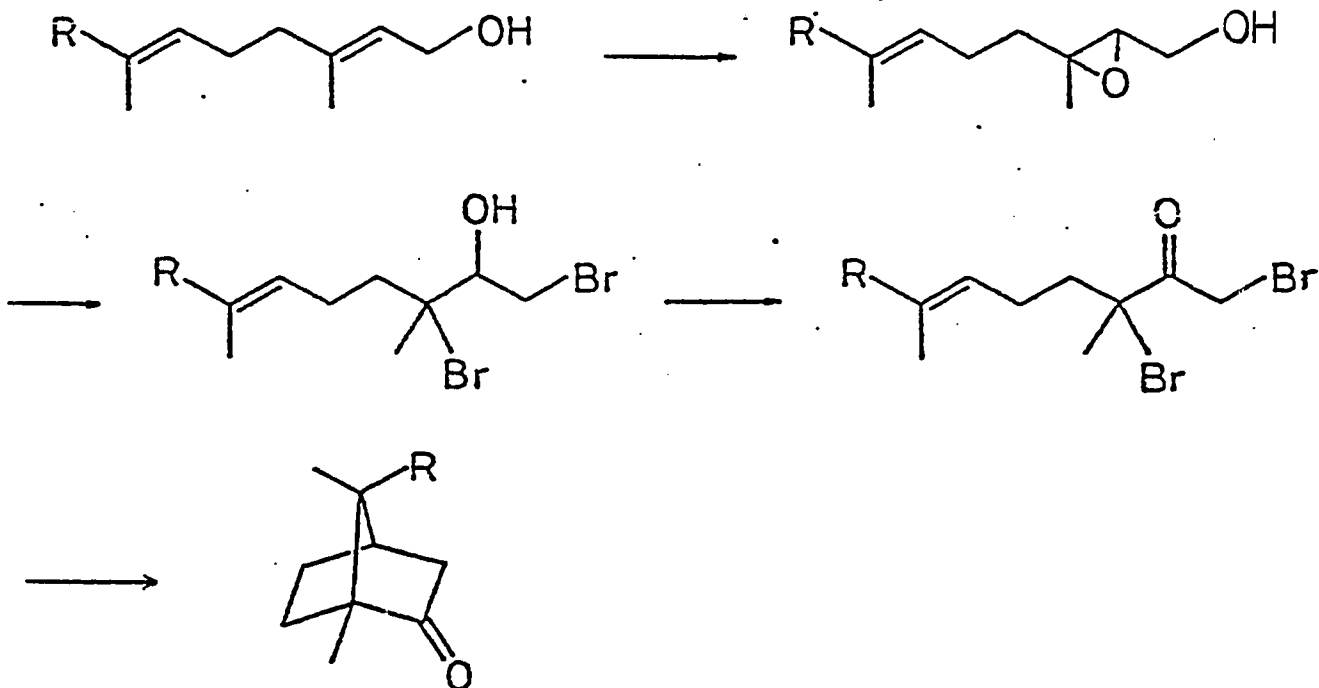
terpenes having the bicyclo[2.2.1]heptane system, camphor and campherenone, are supposed to be derived from acyclic terpenes, geraniol and farnesol, by cation-olefin cyclization. Although Money's route to bicyclo[2.2.1]heptane systems using monocyclic enol acetate intermediate<sup>10</sup> is of great value by the efficient conversion of dihydrocarvone to



(±)-campherenone, the synthetic strategy according to the biogenesis would open an elegant route to the synthesis of bicyclic mono- and sesquiterpenes.

In 1972, Noyori reported that reaction of  $\alpha, \alpha'$ -dibromoketones and  $\text{Fe}_2(\text{CO})_9$  generates the reactive 2-oxyallyl-Fe(II) species, which can be trapped by certain olefins in a 3 + 2  $\rightarrow$  5 manner, producing cyclopentanone derivatives highly efficiently.<sup>11</sup> However, the intramolecular counterpart of this novel transformation is impeded by the difficult preparation of  $\alpha, \alpha'$ -dibromoketones possessing the olefin moieties in the same molecules, since the common method for preparation of  $\alpha, \alpha'$ -dibromoketones consists of the direct bromination of ketones with bromine, which also attacks the olefin. In order to clear away this obstacle, the author

devised a new methodology of preparing  $\alpha,\alpha'$ -dibromoketones in the presence of olefin moieties as indicated by the following scheme.



Selective epoxydation of geraniol or (E,E)-farnesol produced the epoxy alcohol, which was transformed to the tosylate, and then to the bromo epoxide. Regioselective ring opening of the bromo epoxide led to the dibromohydrin, which was oxidized into the key intermediate,  $\alpha,\alpha'$ -dibromoketone. The iron carbonyl promoted intramolecular cyclization of the  $\alpha,\alpha'$ -dibromoketones, derived from geraniol or (E,E)-farnesol, furnished ( $\pm$ )-camphor or ( $\pm$ )-campherone, respectively.

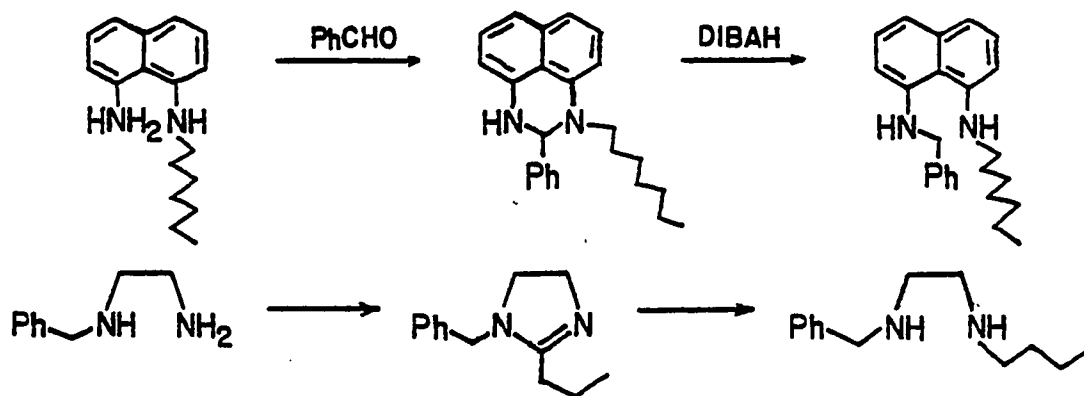
The following chapters are concerned with the development of several new reactions and their applications to the synthesis of natural products based on the formation

of carbon-nitrogen bonds. Over the years, a large reservoir of carbon-carbon bond forming reactions has been developed; these provide a wide variety of tools to synthetic chemists, who can now have their own way in adequate functional group transformations and rational stepwise organizations in total synthesis of natural products. However, little is known in the organic chemistry dealing with the nitrogen atom.

Classical methods such as N-alkylation of amines, the formation of amides, and imines etc. are in our hands, but most of them are less selective and obsolete ones. Although some improved methods are recently reported for N-alkylations,<sup>12</sup> and novel carbonyl aminations with sodium or lithium cyanoborohydride<sup>13</sup> are also noteworthy, the scope and limitations of these tools are constantly under scrutiny. The concept of the nitrogen chemistry is somewhat different from that of the chemistry for carbon-carbon bond formation. Considering the importance of the nitrogen atom in the plant kingdom as alkaloids and in the animal kingdom as constituent elements of proteins, exploitation of organic nitrogen chemistry could be of great significance.

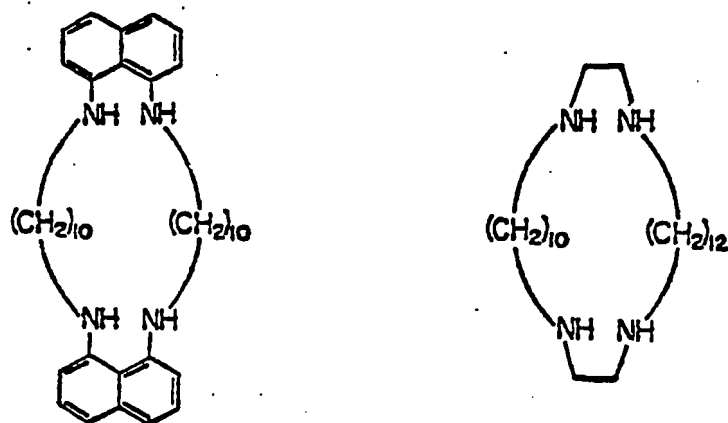
Regioselective carbon-nitrogen bond cleavage of amidine systems by diisobutylaluminum hydride (DIBALH) is mentioned in Chapter IV. N-Alkylation of amines is one of the most convenient synthetic tools to form carbon-nitrogen bonds.<sup>14</sup> A number of N-alkylation methods are already known, but most of them suffer from severe disadvantage on practical

application to polyamines. This is due to the troublesome separation of the desired monoalkylated polyamine from the di- or polyalkylation products. The present author has found that N-heptyl-1,8-diaminonaphthalene was converted in a regioselective manner to N-benzyl-N'-heptyl-1,8-diaminonaphthalene by the reaction with benzaldehyde, followed by reduction with DIBAH. Similarly, selective N-butylation of N-benzylethylenediamine on the primary amino group was accomplished via the formation of 1-benzyl-2-propyldihydroimidazole.

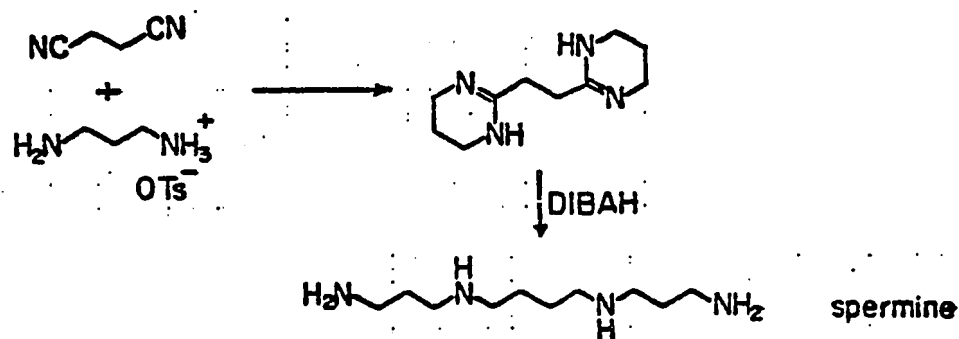


This reaction provides a facile route with success to the synthesis of various new and interesting macrocyclic polyamines, as shown on the following page.

The utility of the present method in the synthesis of natural products was exemplified by the simple route to spermine, which forms a basic skeleton of spermine plant alkaloids.<sup>15</sup> Thus, reaction of succinonitrile with 1,3-diaminopropane mono-p-tosylate produced 1,2-bis(2-tetrahydroimidyl)ethane, which was subjected to ring opening



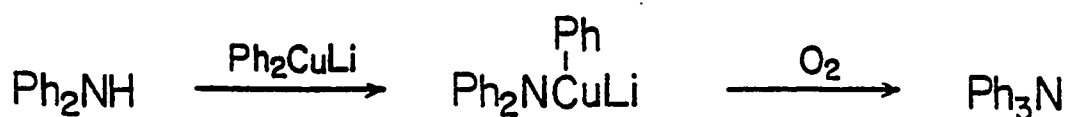
with DIBAH to give spermine. The novel carbon-nitrogen bond cleavage described above may provide a powerful



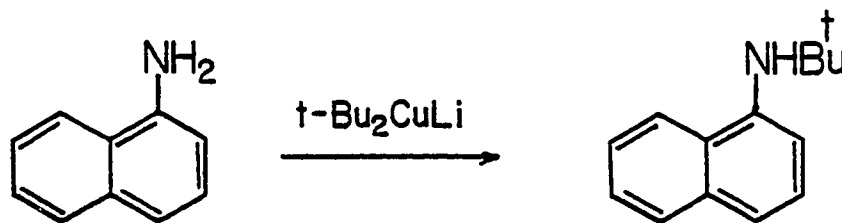
synthetic tool in the synthesis of plant alkaloids, *i.e.* spermidine and spermine alkaloids, since those alkaloids always have a 1,3-diaminopropane moiety.

Chapter V is concerned with a mild and selective *N*-alkylation of amines with organocopper reagents.<sup>16</sup> Although the methodologies for construction of carbon-nitrogen bond are plentiful, the introduction of amino groups at donor sites is ascribed to the limited utility of a few existing methods. Haloamines or hydroxyamide derivatives<sup>17</sup> are hitherto available reagents which function as the equivalent of amino groups having inverted, *i.e.* electrophilic, reactivity. However, drastic reaction

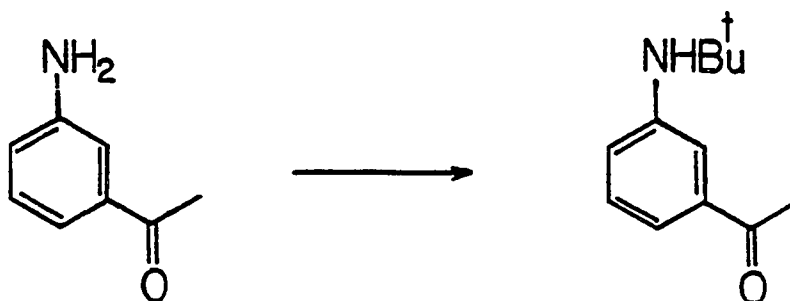
conditions and poor selectivity in these methodologies lack the applicability in organic synthesis. The author has now discovered an entirely different approach based on the oxidative coupling of lithium alkylcopper amide, which is prepared in situ from lithium dialkylcuprates and primary or secondary amines. Thus, addition of diphenylamine to lithium diphenylcuprate, followed by oxidative



work-up gave the desired triphenylamine in 94% yield. Even tert-butylation at donor sites, which was totally ineffective in the classical methods, was realized with excess lithium di-tert-butylcuprate under mild conditions. A unique advantage of this method is illustrated by the



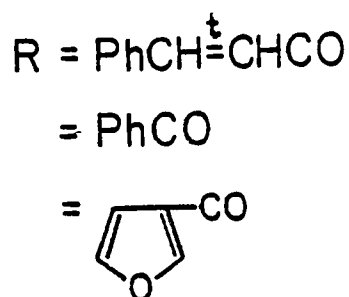
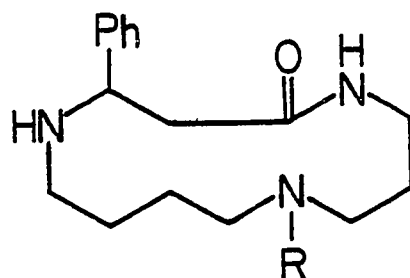
selective N-alkylation of m-aminoacetophenone without any protection of the carbonyl group. The present method will prove to be potentially useful for the selective



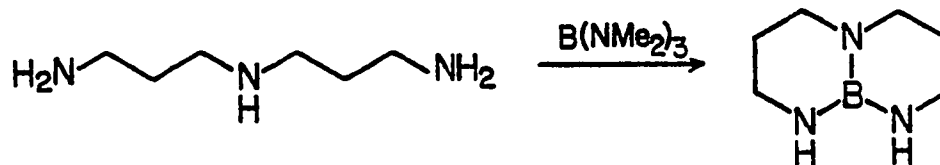
N-alkylation in the synthesis of alkaloids, since the reaction conditions are so mild as to minimize the possibility of involvement of most functional or protecting groups.

To the synthetic chemists nature continues to be exceedingly generous in providing ample opportunity for discovery and creative endeavor of highest magnitude and in surrounding them with an incredible variety of fascinating and complicated molecular structures. In total synthesis, the desire to construct intricate and complex natural products has led to the demonstration of the synthetic chemists' utmost ingenuity in the design of route using established reactions or in the production of new methods in order to achieve a specific transformation. The suitable selection of reactions without any use of protecting groups is the key in effecting elegant total synthesis. Organometallic reagents often provide novel and unique methods for accomplishing this task.

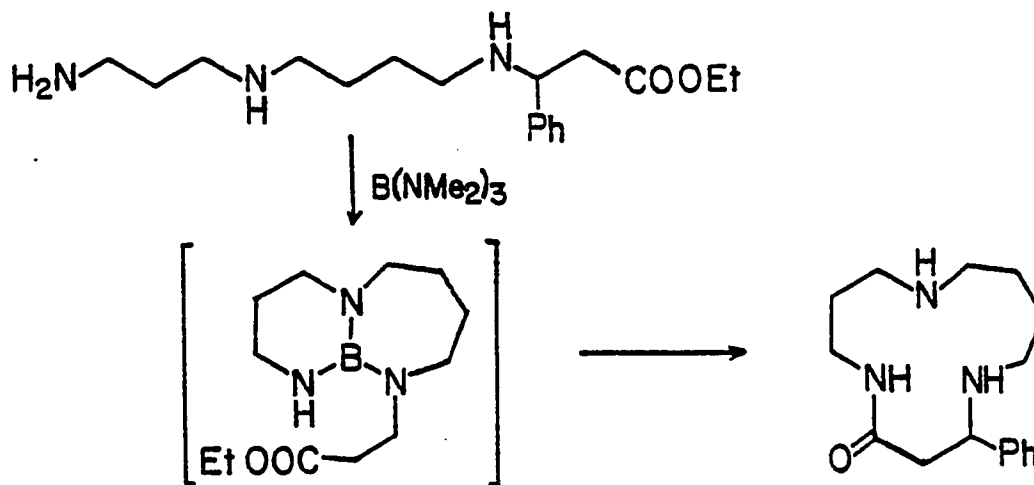
The last Chapter draws the total synthesis of plant alkaloids, celacinnine (R = trans-cinnamoyl), celabenzine (R = benzoyl), and celafurine (R = 3-furoyl), with brief commentary on the strategy involved with particular emphasis on the cyclization step.



Boron-nitrogen compounds are well known and the coordination phenomena of the nitrogen to boron were extensively studied in inorganic chemistry.<sup>18</sup> In particular, some new boron-nitrogen heterocycles are of great interest to the author, since such compounds are readily produced through a transamination reaction between tris(dimethylamino)borane and aliphatic triamines,<sup>19</sup> and might be quite useful in effecting the boron-templated cyclization step to realize the total synthesis of spermidine alkaloids. The boron-nitrogen heterocycles are



extremely sensitive toward moisture. This property would be a great advantage in the present synthesis, because usual aqueous work-up gave the desired diaminolactam free from boron. Selective acylation using trans-cinnamoyl chloride, benzoyl chloride, and 3-furoyl chloride afforded



the three spermidine alkaloids, celacinnine, celbenzine, and celafurine, respectively.

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## Chapter II

A New and Highly Effective Aldol Synthesis<sup>1</sup>

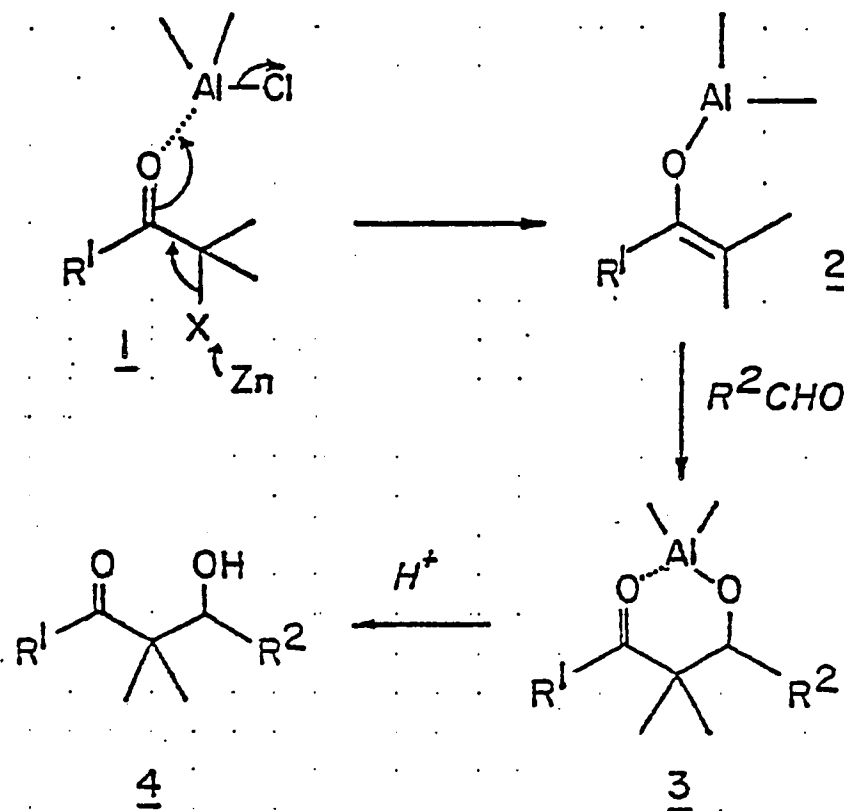
Abstract-----A new approach has been demonstrated for the regiospecific aldol synthesis by the simultaneous addition of  $\alpha$ -halo carbonyl derivatives and aldehydes or ketones to a suspension of diethylaluminum chloride and zinc in tetrahydrofuran at low temperature. This technique is also employable under mild conditions for the Reformatsky reaction to give  $\beta$ -hydroxy esters in excellent yield. One of the unique synthetic applications of this process is illustrated by the intramolecular cyclization of  $\alpha$ -bromoesters of  $\omega$ -hydroxyaldehyde, which produces macrolides, an important class of compounds in the antibiotic field.

Carbon-carbon  $\sigma$ -bond formation, one of the most fundamental operations in organic chemistry, is often accomplished by the aldol synthesis.<sup>2</sup> During the past decade numerous directed intermolecular aldol condensations have been explored with generation of the regiospecific metal enolates and interception of the initially formed aldol products as stable metal chelates.<sup>3</sup> Certain regio-specifically generated, kinetic lithium enolates can retain their integrity in the aldol reaction at low temperature. The use of magnesium and zinc enolates prevents the unfavorable dissociation of the metal chelate, and boron enolates have recently been employed in stereoselective aldol syntheses.<sup>4</sup>

Compared to the metals described above, aluminum shows an exceptionally high affinity for oxygen atom (138 Kcal/mol for Al-O bond),<sup>5</sup> and, therefore, its enolate would be one of the most attractive candidates to enhance the stability of the metal chelates in the aldol condensation. In principle, organoaluminum compounds have a vast potential as agents for the aldol reaction. However, this concept has not been generally accepted for synthesis owing to the lack of an effective procedure for converting a carbonyl compound into a reactive aluminum enolate.<sup>6</sup>

Herein, we describe a new process for regioselective generation of an aluminum enolate by the coupled attack of dialkylaluminum chloride and zinc on the  $\alpha$ -halo ketone.<sup>7</sup> The enolate 2, thus obtained, is sufficiently reactive to

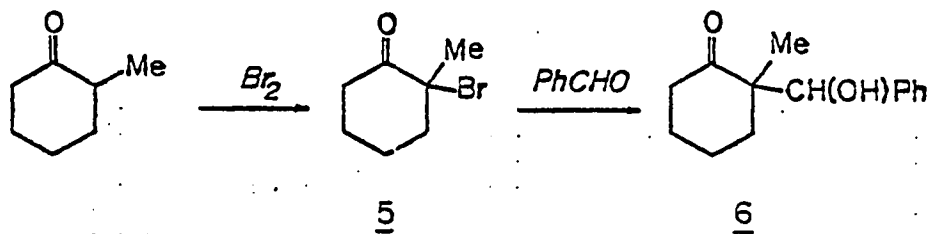
carbonyl compound activated by trivalent aluminum producing the stable tetradentate chelate of the ketolate 3. Aqueous work-up yields the aldol 4 in excellent yield.



Although a comparable path can be followed by two molecules of an  $\alpha$ -halo ketone condensing with each other, this would be subject to experimental control using the simultaneous addition of  $\alpha$ -halo ketones and carbonyl compounds at low temperature provided that the reduction is sufficiently faster under acceptable conditions.<sup>8</sup> This new approach has now been realized. Gradual addition (40 min) of a mixture of carbonyl compound and  $\alpha$ -halo ketone in dry tetrahydrofuran (THF) to a suspension of zinc dust and diethylaluminum

chloride ( $\text{Et}_2\text{AlCl}$ ) in THF-hexane in the presence of a catalytic amount of cuprous bromide with stirring at  $-20^\circ\text{C}$  under argon resulted in clean generation of the ketolate. Addition of pyridine, removal of cooling bath, and aqueous work-up afforded the desired  $\beta$ -hydroxy ketone in high yield (Table I).

The regioselectivity of this reaction was demonstrated by the treatment of 2-bromo-2-methylcyclohexanone (5) and benzaldehyde with  $\text{Et}_2\text{AlCl-Zn}$  in THF at  $-20^\circ\text{C}$  to furnish the expected  $\beta$ -hydroxy ketone 6 in quantitative yield, without any contamination of the regioisomer (Table I). Since the starting bromide 5 may be prepared with high regioselectivity,<sup>9</sup> the present method must be the simplest route to the  $\beta$ -hydroxy ketone 6.



Additional examples are also summarized in Table I. It should be noted that the use of diethylaluminum chloride and the choice of solvents and temperatures are crucial to the success of these reactions. In the absence of diethylaluminum chloride, only unchanged carbonyl compounds were recovered under these mild conditions. The relative effect of solvents and temperatures was indicated by the reaction of 2-bromocyclohexanone with isobutyraldehyde. In diethyl

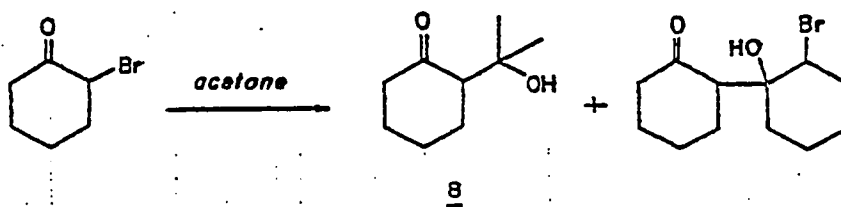
Table I. Synthesis of  $\beta$ -Hydroxy Carbonyl Compounds<sup>a</sup>

Entry	Bromo ketone or Bromo ester	Aldehyde or Ketone	Temp. (°C)	Additive <sup>b</sup>	Product	Isolated Yield(%) (erythro/threo)
1	$\alpha$ -Bromoacetophenone	Isobutyraldehyde	-20	CuBr	PhCOCH <sub>2</sub> CH(OH)CH(CH <sub>3</sub> ) <sub>2</sub>	92
		Cinnamaldehyde	-20	CuBr	PhCOCH <sub>2</sub> CH(OH)CH=CHPh	92
		Cyclohexanone	-20	CuBr	PhCOCH <sub>2</sub> C(OH)(CH <sub>2</sub> ) <sub>5</sub>	83
2	2-Bromocyclohexanone	Benzaldehyde	-20	CuBr	2-(1-Hydroxy-phenylmethyl)-cyclohexanone	97 (1/1) <sup>f</sup>
		Isobutyraldehyde	-20	CuBr	2-(1-Hydroxy-2-methyl-propyl)cyclohexanone	93 <sup>g</sup>
		Acetone <sup>c</sup>	-20	d	2-(1-Hydroxy-1-methyl-ethyl)cyclohexanone	75
3	2-Bromo-2-methyl-cyclohexanone	Benzaldehyde	-20	CuBr	2-(1-Hydroxyphenylmethyl)-2-methylcyclohexanone	100 (4/3) <sup>f</sup>
4	2-Bromocamphor	Acetone	r. t.	d	3-(1-Hydroxy-1-methyl-ethyl)camphor	79
5	Ethyl bromoacetate	Benzaldehyde	0	CuBr	PhCH(OH)CH <sub>2</sub> COOEt	94
		Cyclohexanone	r. t.	CuBr	(CH <sub>2</sub> ) <sub>5</sub> C(OH)CH <sub>2</sub> COOEt	93
6	Methyl $\gamma$ -bromo-crotonate	Benzaldehyde	-20	CuBr	PhCHCHCOOMe <sup>e</sup>   OHCH=CH <sub>2</sub>	100 (50/44) <sup>h</sup>

- a) Unless specified, the reactions were carried out according to the general procedure in the experimental section.  
b) A catalytic amount of cuprous bromide (0.05 equiv) was added.  
c) Excess acetone (5 equiv) was used for this reaction.  
d) Zn-Ag couple was employed without any additive.  
e) None of the  $\gamma$ -alkylation product ("normal Reformatsky ester") was detected in the reaction mixture. See ref. 7.  
f) The ratio of the stereoisomers (threo and erythro) was determined by an absorption due to the benzylic proton (CDCl<sub>3</sub>) as shown in the experimental section. See also refs. 3-a and 3-b.  
g) Erythro/threo ratio could not be determined by nmr and tlc analyses.  
h) Determined by the isolated yield: See the experimental section for this compound.

ether at  $-40^{\circ}\text{C}$ , only a trace amount of the desired 2-(1-hydroxy-2-methylpropyl)cyclohexanone (7) was produced, whereas at high temperature ( $25^{\circ}\text{C}$ ) many side products were detected by tlc. The use of THF as solvent with reaction temperature of  $-78$  and  $-40^{\circ}\text{C}$  afforded 7 in yields of 0 and 85%, respectively. At  $0^{\circ}\text{C}$ , the reaction proceeds as expected (86%), but with some contamination of undesired dehydrated and retro-aldol products of 7.

Treatment of 2-bromocyclohexanone (1 equiv) and acetone (1.1 equiv) with  $\text{Et}_2\text{AlCl-Zn}$  gave the cross-aldol product 8 (42%) along with the self-condensation product. Thus, with less reactive carbonyl compounds, the relative amount of self-condensation product increases. Such difficulty might be circumvented by using excess carbonyl compounds with more reactive zinc. Accordingly, the zinc-silver couple<sup>10</sup> was chosen with excess acetone (5 equiv) to furnish 8 in 79% yield (Table I).



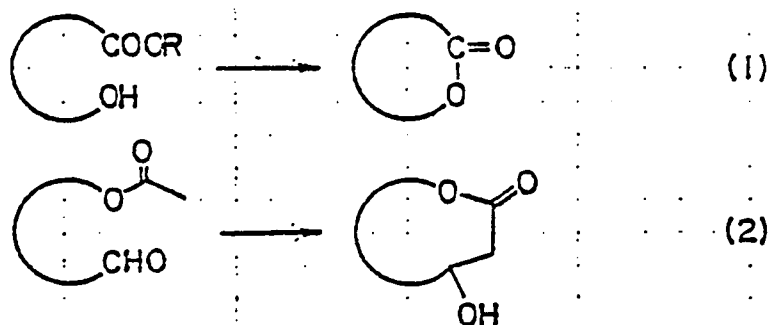
This technique can be employed equally well under mild conditions for the Reformatsky reaction.<sup>11</sup> In a similar manner as described above, Reformatsky products were produced from the corresponding  $\alpha$ -halo esters and carbonyl compounds

in excellent yield as were indicated in Table I (5, 6). In contrast with the normal Reformatsky reaction,<sup>12</sup> the reaction of methyl  $\gamma$ -bromocrotonate with benzaldehyde in the presence of  $\text{Et}_2\text{AlCl-Zn}$  afforded only the  $\alpha$ -adduct in quantitative yield. This result suggests that the addition of aluminum enolate to the carbonyl component (initially activated by trivalent aluminum) proceeds via a six-membered transition state to furnish the stable aluminum chelate 3.

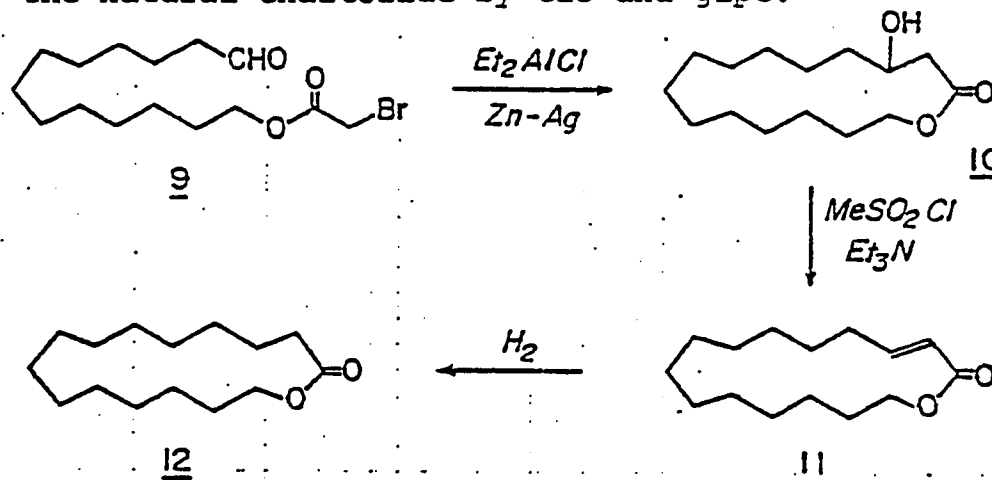
Although simplicity and convenience of this aldol synthesis are appealing, the fact that the reaction proceeds in high yield with simultaneous addition of a halo ketone and an aldehyde is even more important. The highly successful application of the new method is the synthesis of macrocyclic lactones which forms the next subject of this chapter.

Although macrolides have been the attractive synthetic targets in a number of laboratories, most synthetic methodologies for macrolides are based on the internal esterification in the cyclization step (eq. 1) and there exist few basically different approaches.<sup>13</sup>

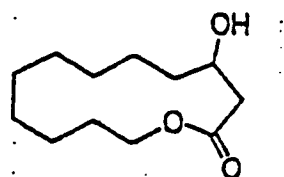
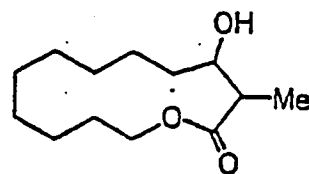
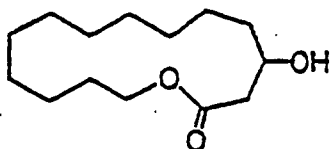
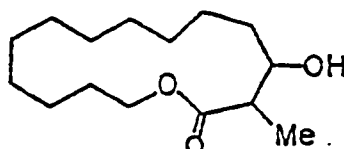
Indeed at the outset of this work there were no known synthetic methods capable of generating efficiently 3-hydroxylactones from acyclic structures (eq. 2). Gradual



addition of the bromoacetate of 13-hydroxytridecanal 9<sup>14</sup> in THF from a mechanically driven syringe over 4 h to a stirred suspension of zinc-silver couple and diethylaluminum chloride in THF at 35°C under argon effected cyclization to 3-hydroxypentadecanolide (10) as the major product. Termination of the reaction with pyridine, followed by acidic work-up gave the crude product, which was purified by column chromatography on silica gel (ether-hexane, 1:1) to afford pure lactone 10 in 48% yield. Dehydration of 10 in CH<sub>2</sub>Cl<sub>2</sub> with methanesulfonyl chloride and excess triethylamine at room temperature for 11 h gave 2-pentadecenolide (11). Hydrogenation of 11 in ethanol-ethyl acetate over palladium on charcoal produced exaltolide (12), which was identical with the natural exaltolide by tlc and glpc.



Similarly, several 3-hydroxymacrolides 13 - 16 were prepared starting from  $\alpha$ -bromo esters of  $\omega$ -hydroxyaldehydes,  $\text{BrCHRCOO}(\text{CH}_2)_n\text{CHO}$  with  $n = 9$  or  $11$ , and  $\text{R} = \text{H}$  or  $\text{CH}_3$ . The following list of macrolides shows the effectiveness of the new method with good yields as indicated in parentheses. Of crucial importance to this macrolide synthesis was the

13 (35%)14 (48%)<sup>15</sup>15 (48%)16 (68%)<sup>15</sup>

observation that the more substituted aluminum enolates derived from  $\text{BrCHR}(\text{COO}(\text{CH}_2)_n\text{CHO})$  with  $\text{R} = \text{CH}_3$  are substantially more reactive toward the carbonyl component to give 14 or 16 in higher yield relative to that of the unsubstituted homologs. Since the  $\alpha$ -methyl- $\beta$ -hydroxy unit in macrolides 14 or 16 is a common functionality in a variety of macrolide antibiotics including erythromycin and methymycin,<sup>16</sup> this method may provide a useful entry to the antibiotic field, starting with simple  $\alpha,\omega$ -diols.<sup>17</sup>

### Experimental

Instrumentation. Following instrumentation and abbreviations are pertinent to the experimental part in Chapter III. The infrared spectra were taken with a Shimadzu IR-27-G spectrometer; the mass spectra with a Hitachi RMU-6L mass spectrometer; the glpc analyses with a Yanagimoto GCG-550F; and  $^1\text{H}$  NMR spectra (pmr) with a JNM-PMX 60 or

Varian EM-360 spectrometer. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane ( $\delta = 0$ ). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The microanalyses were performed at the Elemental Analyses Center of Kyoto University. All experiments were carried out under an atmosphere of dry argon. The products were purified by preparative thin layer chromatography on silica gel PF-254 plates (Merck), or by preparative column chromatography on silica gel E. Merck Art. 7734.

Purification or Preparation of Solvents, Metals, and Reagents. The following solvents were used: tetrahydrofuran -- freshly distilled from sodium benzophenone ketyl; methylene chloride -- dried over  $4\text{\AA}$  molecular sieves. Zinc dust was washed with 5% hydrochloric acid.<sup>17</sup> Zinc-silver couple was obtained from zinc dust and silver acetate by a literature procedure.<sup>10</sup> A 1 M solution of diethylaluminum chloride was prepared by the dilution of neat diethylaluminum chloride (Ethyl Co.) with n-hexane under argon. Commercially available  $\alpha$ -bromoacetophenone, 3-bromocamphor, ethyl bromoacetate, and methyl  $\gamma$ -bromocrotonate were used without purification. 2-Bromocyclohexanone was prepared according to the procedure in the literature.<sup>18</sup> 2-Bromo-2-methylcyclohexanone was obtained by the bromination of 2-methylcyclohexanone with bromine in ether at  $-40 \sim -50^\circ\text{C}$ .<sup>9</sup> 1,10-Decanediol and 1,12-dodecanediol were the commercial

products of the highest purity. 1,13-Tridecanediol was prepared as follows: Reaction of cyclododecanone with diethyl carbonate and metallic sodium under reflux gave diethyl tridecanedioate, which was reduced with lithium aluminum hydride in THF to afford 1,13-tridecanediol.<sup>19</sup>

Preparation of  $\beta$ -Hydroxy Ketones. The  $\beta$ -hydroxy ketones were prepared by reaction of  $\alpha$ -bromo ketones with either ketones or aldehydes according to the following general procedure: A solution of diethylaluminum chloride (1.1 mmol) in hexane was added to a slurry of zinc dust (1.5 mmol) and a catalytic amount of cuprous bromide (0.05 mmol) in anhydrous THF (3 ml) with stirring under argon at 20°C. The resulting mixture was cooled to -20°C, and a solution of an  $\alpha$ -bromo ketone (1 mmol) and an aldehyde (or a ketone) (1.1 mmol) in anhydrous THF (5 ml) was added slowly over 40 min at -20°C. After 15 min at -20°C, the cooling bath was removed. The reaction mixture was quenched by the addition of pyridine (0.3 ml)<sup>20</sup> and then poured into 2 N hydrochloric acid (10 ml). The ether extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to afford a  $\beta$ -hydroxy ketone after purification by preparative tlc (ether-benzene, 1:5).

3-Hydroxy-4-methyl-1-phenylpentan-1-one. Reaction of  $\alpha$ -bromoacetophenone with isobutyraldehyde gave the title compound as a colorless oil:<sup>21</sup> ir (neat) 3450  $\text{cm}^{-1}$  (OH), 1673  $\text{cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  7.10 - 8.13 (5H, m, aryl CH), 3.79 - 4.20 (1H, m, CH-O), 3.69 (1H, s, OH), 3.00 (2H, m,

$\text{CH}_2\text{C}=\text{O}$ ), 1.78 (1H, m, CH), 0.99 (6H, d,  $\underline{J}$  = 6.6 Hz,  $\text{CH}_3$ ); mass  $\underline{m/z}$ (%) 174 (4,  $\text{M}^+$  - 18), 105 (100); mp 50.5 - 52.0°C (recrystallized from pentane as white crystals).

1,5-Diphenyl-3-hydroxy-4-penten-1-one. The title compound was prepared by the reaction of  $\alpha$ -bromoacetophenone with cinnamaldehyde as a yellow oil: ir (neat) 3470  $\text{cm}^{-1}$  (OH), 1675  $\text{cm}^{-1}$  (C=O); pmr ( $\text{CHCl}_3$ )  $\delta$  6.94 - 8.31 (10H, m, aryl CH), 6.70 (1H, d,  $\underline{J}$  = 16 Hz, PhCH=C), 6.24 (1H, dd,  $\underline{J}$  = 16, 5.6 Hz, PhC=CH), 4.91 (1H, q,  $\underline{J}$  = 5.6 Hz, CH-O), 3.22 (2H, d,  $\underline{J}$  = 6 Hz,  $\text{CH}_2\text{C}=\text{O}$ ), 2.84 - 3.61 (1H, s, OH); exact mass spectrum  $\underline{m/z}$  252.301 (calcd for  $\text{C}_{17}\text{H}_{16}\text{O}_2$ , 252.313); mp 51 - 53°C (recrystallized from pentane-ether as white crystals).

$\alpha$ -(1-Hydroxycyclohexyl)acetophenone. Reaction of  $\alpha$ -bromoacetophenone with cyclohexanone afforded the title compound as a colorless oil:<sup>22</sup> ir (neat) 5313  $\text{cm}^{-1}$  (OH), 1672  $\text{cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  7.05 - 8.18 (10H, m, aryl CH), 3.88 - 4.01 (1H, s, OH), 3.10 (2H, s,  $\text{CH}_2\text{C}=\text{O}$ ), 1.05 - 2.17 (10H, broad s, aliphatic CH); mass  $\underline{m/z}$ (%) 200 (3,  $\text{M}^+$  - 18), 105 (100); mp 79-80°C (recrystallized from pentane as white crystals).

2-(1-Hydroxyphenylmethyl)-2-methylcyclohexanone (6). Reaction of 2-bromo-2-methylcyclohexanone (191 mg, 1 mmol) with benzaldehyde (117 mg, 1.1 mmol) afforded erythro and threo mixtures of 6 (218 mg) as a pale yellow oil<sup>21</sup> in quantitative yield after purification by preparative tlc (ether-hexane, 1:1): pmr ( $\text{CDCl}_3$ )  $\delta$  7.23 (5H, s, aryl CH),

4.92, 5.00 (1H, s, CH-O), 3.53 (1H, s, OH), 2.26 - 2.66 (2H, m, CH<sub>2</sub>C=O), 1.35 - 2.09 (6H, br s, aliphatic CH), 1.00, 1.09 (3H, s, CH<sub>3</sub>). The ratio of the erythro and threo isomers was determined by the relative intensities of the benzylic proton absorptions [nmr (CDCl<sub>3</sub>) δ 4.92 (erythro) and 5.00 (threo)] to be nearly 4:3. Column chromatography of pure 6 on silica gel (ether-hexane, 3:1) gave the fraction of pure threo isomer and a mixture of erythro and threo isomers (34 mg). The pure threo isomer has the following physical properties: ir (neat) 3503 cm<sup>-1</sup>, (OH), 1690 cm<sup>-1</sup> (C=O); pmr (CDCl<sub>3</sub>) δ 7.15 (5H, s, aryl CH), 4.97 (1H, s, CH-O), 2.87 (1H, s, OH), 2.27 - 2.59 (2H, m, CH<sub>2</sub>C=O), 1.35 - 2.05 (6H, broad s, aliphatic CH), 1.01 (3H, s, CH<sub>3</sub>); mass m/z(%) 200 (0.1, M<sup>+</sup> - 18), 77 (100).

2-(1-Hydroxyphenylmethyl)cyclohexanone (15). Condensation of 2-bromocyclohexanone with benzaldehyde yielded 15 (198 mg, 97% yield) as white solid after purification by preparative tlc (ether-hexane, 1:1). The nmr spectrum (CDCl<sub>3</sub>) of 15 showed the ratio of the threo and erythro isomers to be 1:1. This analysis was determined by an absorption due to the benzylic proton peak at δ 4.73 and 5.30. Column chromatography of 15 on silica gel (benzene-ether, 10:1) separated the two isomers. The first fraction was the erythro isomer 15a: ir (neat) 3496 cm<sup>-1</sup> (OH), 1697 cm<sup>-1</sup> (C=O); pmr (CDCl<sub>3</sub>) δ 7.27 (5H, s, aryl CH), 5.35 (1H, d, J = 2.3 Hz, CH-O), 2.90 (1H, s, OH), 1.08 - 2.73 (9H, broad s, aliphatic CH and CHC=O); mass m/z(%) 77 (100), 186

(2.5,  $M^+$  - 18); mp 103 - 105°C (recrystallized from hexane-ethyl acetate. lit.<sup>21</sup> 103.5 - 104.5°C). From the second fraction the threo isomer 15b was obtained: ir (neat) 3483  $\text{cm}^{-1}$  (OH), 1698  $\text{cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  7.30 (5H, s, aryl CH), 4.77 (1H, d,  $J$  = 9 Hz, CH-O), 3.72 (1H, s, OH), 1.03 - 2.86 (9H, broad s, aliphatic CH and CHC=O); mass  $m/z$ (%) 186 (3.5,  $M^+$  - 18), 77 (100); mp 75.5 - 77.5°C (recrystallized from hexane. lit.<sup>21</sup> 75°C).

2-(1-Hydroxy-2-methylpropyl)cyclohexanone (7). Reaction of 2-bromocyclohexanone with isobutyraldehyde produced 7 as a pale yellow oil<sup>21</sup>: bp 74 - 78°C (bath temp., 1 mmHg); ir (neat) 3510  $\text{cm}^{-1}$  (OH), 1688  $\text{cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  3.47 (1H, m, CH-O), 3.03 (1H, s, OH), 1.32 - 2.74 (9H, broad s, aliphatic CH and CHC=O), 0.89 (6H, m,  $\text{CH}_3$ ); mass  $m/z$ (%) 152 (15,  $M^+$  - 18), 55 (100). The erythro/threo ratio of 7 could not be determined by tlc and nmr analyses.

2-(1-Hydroxy-1-methylethyl)cyclohexanone. The title compound was obtained from 2-bromocyclohexanone (1 equiv) and excess acetone (5 equiv) in the presence of diethylaluminum chloride and zinc-silver couple at -20°C: bp 68 - 71°C (bath temp., 1 mmHg (lit.<sup>23</sup> 78 - 80°C/4 mmHg)); ir (neat) 3488  $\text{cm}^{-1}$  (OH), 1690  $\text{cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  3.95 (1H, s, CH-O), 1.42 - 2.62 (10H, aliphatic CH, CHC=O, and OH), 1.22 (6H, m,  $\text{CH}_3$ ): mass  $m/z$ (%) 141 (5,  $M^+$  - 15), 43 (100).

3-(1-Hydroxy-1-methylethyl)camphor. Reaction of 3-bromocamphor with acetone was performed at 20°C using zinc-silver couple. Stirring was further continued for 1 h

at 20°C. The mixture was then quenched in a usual manner and purified by preparative tlc (ether-hexane, 1:1) to give the title compound as white crystals: mp 88 - 90.5°C (re-crystallized from hexane); ir (nujol) 3473  $\text{cm}^{-1}$  (OH), 1728  $\text{cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  1.27, 1.46 (6H, two s,  $\text{CH}_3\text{C-O}$ ); exact mass spectrum  $\underline{m/z}$  210.330 (calcd for  $\text{C}_{13}\text{H}_{22}\text{O}_2$ , 210.317).

Preparation of  $\beta$ -Hydroxy Esters. The  $\beta$ -hydroxy esters were prepared in the same way as the  $\beta$ -hydroxy ketones.

Ethyl 3-Hydroxy-3-phenylpropionate. The title compound was produced from ethyl bromoacetate and benzaldehyde as a colorless oil: bp 120 - 123°C (bath temp., 1 mmHg (lit.<sup>24</sup> 154°C/12 mmHg)); ir (neat) 3435  $\text{cm}^{-1}$  (OH), 1728  $\text{cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  7.28 (5H, s, aryl CH), 5.06 (1H, t,  $\underline{J}$  = 7 Hz, CH-O), 4.08 (2H, q,  $\underline{J}$  = 7 Hz,  $\text{CH}_2\text{-O}$ ), 3.40 (1H, s, OH), 2.65 (2H, d,  $\underline{J}$  = 7 Hz,  $\text{CH}_2\text{C=O}$ ), 1.18 (3H, t,  $\underline{J}$  = 7 Hz,  $\text{CH}_3$ ); mass  $\underline{m/z}$ (%) 194 (22,  $\text{M}^+$ ), 176 (4,  $\text{M}^+ - 18$ ), 165 (5,  $\text{M}^+ - 29$ ), 107 (100).

Ethyl 1-Hydroxycyclohexylacetate. Reaction of ethyl bromoacetate with cyclohexanone at 20°C yielded the title compound as a colorless oil: bp 85 - 88°C/2 mmHg (lit.<sup>25</sup> 89 - 93°C/4 mmHg); ir (neat) 3499  $\text{cm}^{-1}$  (OH), 1710  $\text{cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  4.32 (2H, q,  $\underline{J}$  = 7 Hz,  $\text{CH}_2\text{-O}$ ), 3.37 (1H, s, OH), 2.43 (2H, s,  $\text{CH}_2\text{C=O}$ ), 1.52 (10H, broad s, aliphatic CH), 1.26 (3H, t,  $\underline{J}$  = 7 Hz,  $\text{CH}_3$ ); mass  $\underline{m/z}$ (%) 186 (6.5,  $\text{M}^+$ ), 168 (6.8,  $\text{M}^+ - 18$ ), 55 (100).

Methyl 2-(1-Hydroxyphenylmethyl)-3-butenate (16).

Reaction of methyl  $\gamma$ -bromocrotonate (179 mg, 1 mmol) with

benzaldehyde (117 mg, 1.1 mmol) at  $-20^{\circ}\text{C}$  gave the erythro and threo isomers of 16 in quantitative yield as a colorless oil<sup>12</sup> after purification by preparative tlc (ether-hexane, 1:1). None of the  $\gamma$ -alkylation product was detected in the crude product. Column chromatography of pure 16 on silica gel (ether-hexane, 1:3) separated the pure erythro isomer 16a (92 mg), a mixture of two isomers (16 mg), and the pure threo isomer 16b (80 mg). These isomers, 16a and 16b, have the following physical properties:

16a: ir (neat)  $3549\text{ cm}^{-1}$  (OH),  $1726\text{ cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  7.24 (5H, s, aryl CH), 5.96 (1H, ddd,  $J = 8.0, 11.4, 18.8$  Hz, =CH-C), 5.36 - 4.98 (3H, m,  $\text{CH}_2=\text{C}$  and CH-O), 3.63 (3H, s,  $\text{CH}_3$ ), 3.39 (1H, dd,  $J = 6.4, 8.0$  Hz, C=C-CH), 2.92 (1H, s, OH); mass  $m/z$  (%) 188 (18.8,  $\text{M}^+ - 18$ ), 77 (100):

16b: ir (neat)  $3437\text{ cm}^{-1}$  (OH),  $1707\text{ cm}^{-1}$  (C=O); nmr ( $\text{CDCl}_3$ )  $\delta$  7.31 (5H, s, aryl CH), 5.72 (1H, ddd,  $J = 7.8, 10.8, 17.2$  Hz, =CH-C), 4.79 - 5.40 (3H, m,  $\text{CH}_2=\text{C}$  and CH-O), 3.77 (3H, s,  $\text{CH}_3$ ), 3.50 (1H, dd,  $J = 8.8, 17.2$  Hz, C=C-CH), 2.84 (1H, s, OH).

Preparation of macrolides. Five hydroxy macrolides were prepared by the intramolecular aldol condensation of  $\alpha$ -bromo esters of  $\omega$ -hydroxy aldehydes. The synthesis of 3-hydroxypentadecanolide (10), starting from 1,13-tridecanediol is representative.

13-Hydroxytridecyl bromoacetate (17). A solution of bromoacetyl bromide (5.18 g, 24 mmol) in anhydrous THF (20 ml) was added dropwise to a solution of 1,13-tridecanediol

(4.32 g, 20 mmol) in THF (100 ml) containing N,N-dimethylaniline (2.79 ml, 22 mmol) under argon at 20°C. Stirring was continued for 15 min at 20°C. Then the solution was diluted with ether and washed with 2 N hydrochloric acid. The ether extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to afford 17 (3.57 g, 53%) as white crystals after purification by column chromatography on silica gel (ethyl acetate-hexane, 2:5): ir (nujol)  $3375\text{ cm}^{-1}$  (OH),  $1731\text{ cm}^{-1}$  (C=O); pmr (CDCl<sub>3</sub>)  $\delta$  4.10 (2H, t,  $J = 6\text{ Hz}$ , CH<sub>2</sub>OC=C), 3.76 (2H, s, CH<sub>2</sub>Br), 3.57 (2H, t,  $J = 6\text{ Hz}$ , CH<sub>2</sub>-O), 1.00 - 1.98 (23H, broad s, aliphatic CH and OH).

Found: C, 53.32; H, 8.98. Calcd for C<sub>15</sub>H<sub>28</sub>BrO<sub>3</sub>:  
C, 53.41; H, 8.67.

Bromoacetate of 13-hydroxytridecanal (9). Collins oxidation of 17 was slightly modified as follows: Chromium trioxide (5 g, 50 mmol) was added portionwise to a solution of pyridine (8.09 ml, 100 mmol) in dry methylene chloride (125 ml) at 0°C, and the resulting brown suspension was stirred for 5 min at 0°C followed by 1 h at 20°C. Celite-545 (dried in vacuo for 1 h at 150°C before use) and then 17 (1.685 g, 5 mmol) dissolved in dry methylene chloride (25 ml) were added at 0°C. After further stirring for 10 min, the suspension was treated with powdered NaHSO<sub>4</sub>·H<sub>2</sub>O (6.25 g). The complete removal of pyridine was checked by tlc. The suspension was diluted with hexane (200 ml), filtered through celite-545, and washed with hexane. The

filtrate was concentrated in vacuo to afford 9 (1.495 g, 89% yield) as a colorless oil after purification by column chromatography on silica gel (ether-hexane, 1:2): ir (neat)  $2723\text{ cm}^{-1}$  (CHO),  $1721$ ,  $1731\text{ cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  9.65 (1H, m, CHO), 4.06 (2H, t,  $\underline{J} = 6\text{ Hz}$ ,  $\text{CH}_2\text{O}$ ), 3.67 (2H, s,  $\text{CH}_2\text{Br}$ ), 2.33 (2H, t,  $\underline{J} = 6\text{ Hz}$ ,  $\text{CCH}_2\text{C=O}$ ), 1.28 (20H, broad s, aliphatic CH).

Found: C, 53.51; H, 8.33. Calcd for  $\text{C}_{15}\text{H}_{27}\text{BrO}_3$ :  
C, 53.74; H, 8.12.

3-Hydroxypentadecanolide (10). A solution of diethylaluminum chloride (1.5 mmol, 1.5 ml of a 1 M solution) in hexane was added to a slurry of zinc-silver couple (3.27 g, 50 mmol) in anhydrous THF (50 ml) under argon at  $20^\circ\text{C}$ . After 10 min, the suspension was warmed to  $35^\circ\text{C}$  and a solution of 9 (335 mg, 1 mmol) in THF (10 ml) was added slowly over a period of 4 h. Stirring was continued for an additional 20 min, and the reaction was terminated by the addition of pyridine (0.9 ml). Then the suspension was diluted with ether, washed with iced 2 N hydrochloric acid, and brine. The organic layer and ether extracts of the aqueous washings were dried and concentrated to afford 10 (175 mg, 48% yield) as a colorless oil after purification by column chromatography on silica gel (ether-hexane, 1:1): ir (neat)  $3427\text{ cm}^{-1}$  (OH),  $1729\text{ cm}^{-1}$  (C=O); pmr ( $\text{CDCl}_3$ )  $\delta$  3.58 - 4.25 (1H, m, CH-O), 4.13 (2H, t,  $\underline{J} = 5\text{ Hz}$ ,  $\text{CH}_2\text{O}$ ), 2.82 (1H, s, OH), 2.53 (2H, d,  $\underline{J} = 5.5\text{ Hz}$ ,  $\text{CH}_2\text{C=O}$ ), 1.35 (22H, broad s, aliphatic CH); mass  $\underline{m}/\underline{z}(\%)$  238 ( $\text{M}^+ - \text{H}_2\text{O}$ ).

Found: C, 70.30; H, 10.88. Calcd for  $C_{15}H_{28}O_3$ : C, 70.27, H, 11.01.

2-Pentadecenolide (11). A solution of 10 (85 mg, 0.33 mmol) in methylene chloride (15 ml) was treated with methanesulfonyl chloride (51  $\mu$ l, 0.66 mmol) in the presence of triethylamine (0.37 ml, 2.66 mmol) at  $-20^\circ\text{C}$ . The resulting white suspension was allowed to warm to room temperature. Further stirring was continued for one day at room temperature. The mixture was poured onto iced water and extracted with ether. Purification of the crude product by column chromatography on silica gel (ether-hexane, 1:15) gave 11 in 79% yield as a colorless oil: ir (neat)  $1716\text{ cm}^{-1}$  (C=O),  $983, 1460\text{ cm}^{-1}$  (C=C); pmr ( $\text{CCl}_4$ )  $\delta$  6.75 (1H, dt,  $J = 7.2, 15.4\text{ Hz}$ , CH=C-C=O), 5.63 (1H, d,  $J = 15.4\text{ Hz}$ , CH-C=O), 4.10 (2H, t,  $J = 5.2\text{ Hz}$ ,  $\text{CH}_2\text{O}$ ), 2.19 (2H, m,  $\text{CH}_2\text{C}=\text{C}$ ), 1.31 (20H, broad s, aliphatic CH); mass  $m/z$  (%) 238 ( $\text{M}^+$ ).

Found: C, 75.31; H, 10.92. Calcd for  $C_{15}H_{26}O_2$ : C, 75.58; H, 10.99.

Synthesis of Exaltolide (12). 2-Pentadecenolide (11) (65 mg) was hydrogenated in ethanol-ethyl acetate over 10% palladium on charcoal at room temperature for two days to give 12 (48 mg) as colorless semi-solids: ir (neat)  $1730\text{ cm}^{-1}$  (C=O); pmr ( $\text{CCl}_4$ )  $\delta$  4.02 (2H, t,  $J = 5.2\text{ Hz}$ ,  $\text{CH}_2\text{O}$ ), 2.22 (2H, t,  $J = 6.2\text{ Hz}$ ,  $\text{CH}_2\text{C}=\text{O}$ ), 1.32 (24H, broad s, aliphatic CH): mass  $m/z$  (%) 240 ( $\text{M}^+$ ).

The syntheses of other hydroxy macrolides such as 3-hydroxydodecanolide (13), 3-hydroxy-2-methyldodecanolide

Table II. Physical Properties and Analytical Data of Macrolides and their Precursors

Product	Boiling Point (°C) <sup>a</sup> (Melting Point)	Ir (cm <sup>-1</sup> ) <sup>b</sup>	Nmr (δ)	Anal. Found, (%) (calcd)
BrCH <sub>2</sub> COO(CH <sub>2</sub> ) <sub>10</sub> OH		3345 (OH) 1735 (C=O)	4.08 (2H, t, $\underline{J}$ = 6, CH <sub>2</sub> OC=O), 3.75 (2H, s, CH <sub>2</sub> Br), 3.54 (2H, t, $\underline{J}$ = 6, CH <sub>2</sub> O), 1.90 (1H, s, OH), 1.30 (16H, br s, aliphatic CH)	C, 48.57 (48.82) H, 7.90 (7.85)
BrCH <sub>2</sub> COO(CH <sub>2</sub> ) <sub>9</sub> CHO		2733 (CHO) 1720, 1735 (C=O)	9.57 (1H, t, $\underline{J}$ = 1.8, CHO), 4.08 (2H, t, $\underline{J}$ = 6, CH <sub>2</sub> O), 3.75 (2H, s, CH <sub>2</sub> Br), 2.38 (2H, td, $\underline{J}$ = 1.8, 6.4, CH <sub>2</sub> C=O), 1.30 (14H, br s, aliphatic CH)	C, 48.90 (49.16) H, 7.03 (7.22)
<u>13</u>	165/2 mm Hg	3430 (OH) 1724 (C=O)	4.02 (3H, m, CH <sub>2</sub> O, CH-O), 2.60 (1H, s, OH), 2.07-2.57 (2H, m, CH <sub>2</sub> C=O), 1.32 (14H, br s, aliphatic CH)	C, 67.05 (67.25) H, 10.11 (10.35)
CH <sub>3</sub> CHBrCOO(CH <sub>2</sub> ) <sub>10</sub> OH	170/1 mm Hg	3360 (OH) 1731 (C=O)	4.31 (1H, q, $\underline{J}$ = 6.6, CHBr), 4.10 (2H, t, $\underline{J}$ = 6.2, CH <sub>2</sub> OC=O), 3.57 (2H, t, $\underline{J}$ = 5.6, CH <sub>2</sub> O), 1.79 (3H, d, $\underline{J}$ = 6.6, CH <sub>3</sub> ), 1.66 (1H, s, OH), 1.30 (16H, br s, aliphatic CH)	C, 50.23 (50.49) H, 8.32 (8.15)
CH <sub>3</sub> CHBrCOO(CH <sub>2</sub> ) <sub>9</sub> CHO	(72-75)	2710 (CHO) 1731 (C=O)	9.54 (1H, t, $\underline{J}$ = 1.6, CHO), 4.31 (1H, q, $\underline{J}$ = 6.6, CHBr), 4.02 (2H, t, $\underline{J}$ = 6.6, CH <sub>2</sub> O), 2.33 (2H, td, $\underline{J}$ = 1.6, 6, CH <sub>2</sub> C=O), 1.76 (3H, d, $\underline{J}$ = 6.6, CH <sub>3</sub> ), 1.32 (14H, br s, aliphatic CH)	C, 46.59 (46.82) H, 5.35 (5.59)
<u>14</u>		3432 (OH) 1710, 1726 (C=O)	3.37-4.25 (3H, m, CH <sub>2</sub> O, CH-O), 2.10-2.97 (2H, m, CHC=O, OH), 1.32 (16H, br s, aliphatic CH)	C, 68.43 (68.38) H, 10.47 (10.60)

BrCH <sub>2</sub> COO(CH <sub>2</sub> ) <sub>12</sub> OH	170-173/1 mm Hg	3279 (OH)	4.15 (2H, t, $\underline{J}$ = 6.2, CH <sub>2</sub> OC=O), 3.80	C, 52.05 (52.01)
		1737 (C=O)	(2H, s, CH <sub>2</sub> Br), 3.60 (2H, t, $\underline{J}$ = 6, CH <sub>2</sub> O), 2.22 (1H, s, OH), 1.29 (20H, br s, aliphatic CH)	H, 8.57 (8.42)
BrCH <sub>2</sub> COO(CH <sub>2</sub> ) <sub>11</sub> CHO		2730 (CHO)	9.68 (1H, t, $\underline{J}$ = 2, CHO), 4.13 (2H, t, $\underline{J}$ = 6.2, CH <sub>2</sub> O), 3.79 (2H, s, CH <sub>2</sub> Br), 2.40 (2H, td, $\underline{J}$ = 6.2, CH <sub>2</sub> C=O), 1.29 (18H, br s, aliphatic CH)	C, 52.30 (52.34) H, 7.55 (7.84)
		1723, 1736 (COO)		
15	168/2 mm Hg	3398 (OH)	3.57-4.13 (3H, m, CH <sub>2</sub> O, CH-O), 2.47 (2H, d, $\underline{J}$ = 4.8, CH <sub>2</sub> C=O), 1.30 (21H, br s, aliphatic CH, OH)	C, 69.41 (69.38) H, 10.89 (10.81)
CH <sub>3</sub> CHBrCOO(CH <sub>2</sub> ) <sub>12</sub> OH	174-177/1 mm Hg	3352, 3405 (OH) <sup>c</sup>	4.28 (1H, q, $\underline{J}$ = 6.6, CHBr), 4.08 (2H, t, $\underline{J}$ = 6, CH <sub>2</sub> OCO), 3.55 (2H, t, $\underline{J}$ = 6, CH <sub>2</sub> O), 1.89 (1H, s, OH), 1.76 (3H, d, $\underline{J}$ = 6.6, CH <sub>3</sub> ), 1.27 (20H, s, aliphatic CH)	C, 53.67 (53.41) H, 8.87 (8.67)
		1723 (C=O)		
CH <sub>3</sub> CHBrCOO(CH <sub>2</sub> ) <sub>11</sub> CHO	(51-53)	2737 (CHO)	9.57 (1H, t, $\underline{J}$ = 1.6, CHO), 4.29 (1H, q, $\underline{J}$ = 7, CHBr), 4.09 (2H, t, $\underline{J}$ = 6.4, CH <sub>2</sub> O), 2.39 (2H, td, $\underline{J}$ = 1.6, 6.8, CH <sub>2</sub> C=O), 1.78 (3H, d, $\underline{J}$ = 7, CH <sub>3</sub> ), 1.28 (18H, s, aliphatic CH <sub>2</sub> )	C, 48.58 (48.93) H, 6.40 (6.06)
		1733 (C=O)		
16	180/2 mm Hg	3425 (OH)	3.40-4.53 (3H, m, CH <sub>2</sub> O, CH-O), 2.80 (1H, s, OH), 2.52 (1H, q, $\underline{J}$ = 6.8, CHC=O), 1.33 (23H, br s, aliphatic CH, CH <sub>3</sub> )	C, 70.31 (70.27) H, 11.21 (11.01)
		1725 (C=O)		

- a) Bath temperature.  
b) Liquid film.  
c) Nujol mull.

(14), 3-hydroxytetradecanolide (15), and 3-hydroxy-2-methyl-tetradecanolide (16), starting from the corresponding 1, $\omega$ -diols, HO(CH<sub>2</sub>)<sub>n</sub>OH with n = 10, 12 were carried out exactly as described above. The physical properties and analytical data of these four macrolides and their precursors are shown in Table II.

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the classical Reformatsky reaction.

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14) Compound 9 was conveniently prepared from 1,13-tridecanediol by (1) monoesterification of 1,13-tridecanediol with bromoacetyl bromide in the presence of N,N-diethylamine, followed by (2) Collins oxidation.

15) Compounds 14 and 16 were found to be mixtures of erythro and threo isomers:  $\sim$ 1:1 by tlc assay (ether-hexane, 1:2, two developments) and trimethylsilylations; attempted separation of these isomers by glc or column chromatography was unsuccessful.

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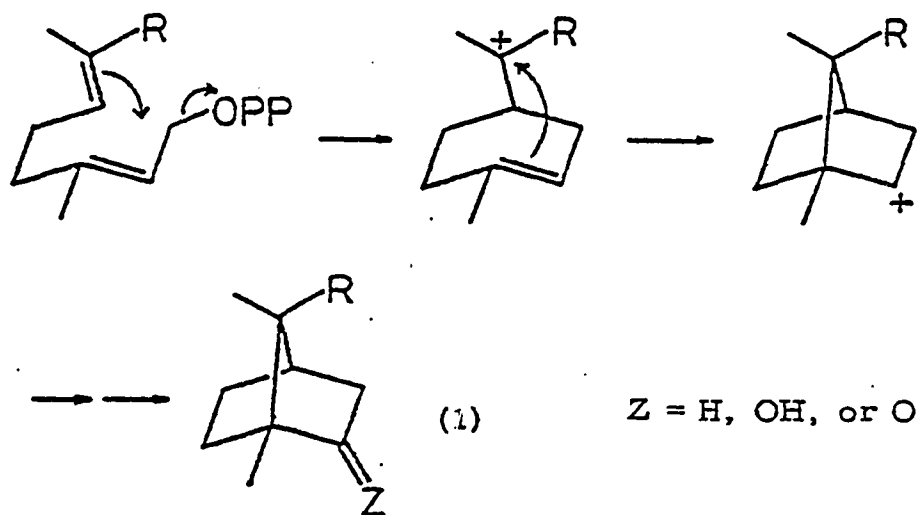
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## Chapter III

Biomimetic Entry to Camphor and Campherenone  
Iron Carbonyl Promoted  
Cyclocoupling Reaction in Terpene Synthesis

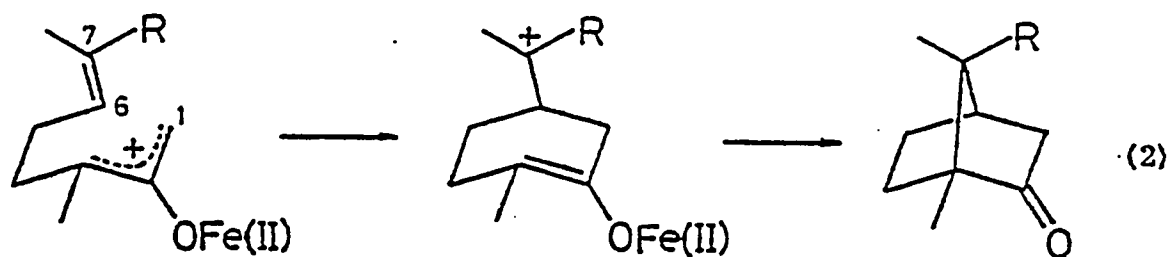
Abstract-----A biogenetically patterned synthesis of camphor-type terpenoid compounds is described. The dibromo-ketone 1a can be obtained from geraniol through five steps in 68% overall yield. Reaction of 1a and  $\text{Fe}_2(\text{CO})_9$  (1:1.2 molar ratio) in benzene at 100 - 110°C leads directly to ( $\pm$ )-camphor (2) in 38% yield. In addition, several six-membered monocyclic terpenoids, ( $\pm$ )-dihydrocarvone (3) and ( $\pm$ )-carvenone (5) have also been isolated. In a similar manner, reaction of the dibromide 1b (derived from farnesol in 64% yield) and  $\text{Fe}(\text{CO})_5$  produces a 2:1 mixture of ( $\pm$ )-campherenone (7) and ( $\pm$ )-epicampherenone (8) in 58% yield.

The carbon skeleton of the known mono- and sesqui-terpenes having a bicyclo[2.2.1]heptane system can be derived from acyclic terpenes formally by carbocation--olefin cyclization (eq 1) and this formulation of the biogenesis presents a distinct challenge to the synthetic chemist.<sup>1</sup> Outlined here is a direct terpene construction via such biogenetically patterned route.

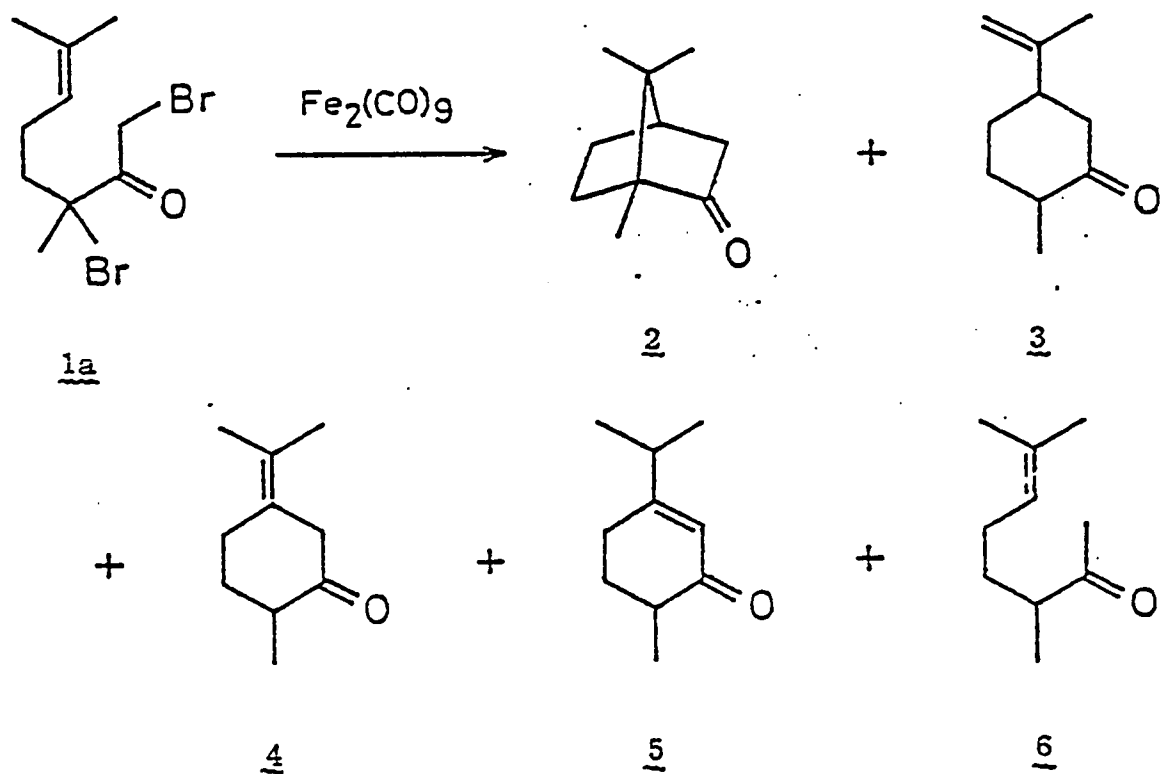


The point of origin for the synthetic plan to be described below was the previous observation that reaction of  $\alpha, \alpha'$ -dibromo ketones and iron carbonyls generates the reactive 2-oxallyl--Fe(II) species, which can be trapped by certain olefins in a 3 + 2 + 5 manner, producing cyclopentanone derivatives highly efficiently.<sup>2,3</sup> The intramolecular version of this transformation, if successful, would constitute a sequence (eq 2) which could be applied to the synthesis of camphor and campherenone<sup>4,5</sup> from geraniol and farnesol, respectively.

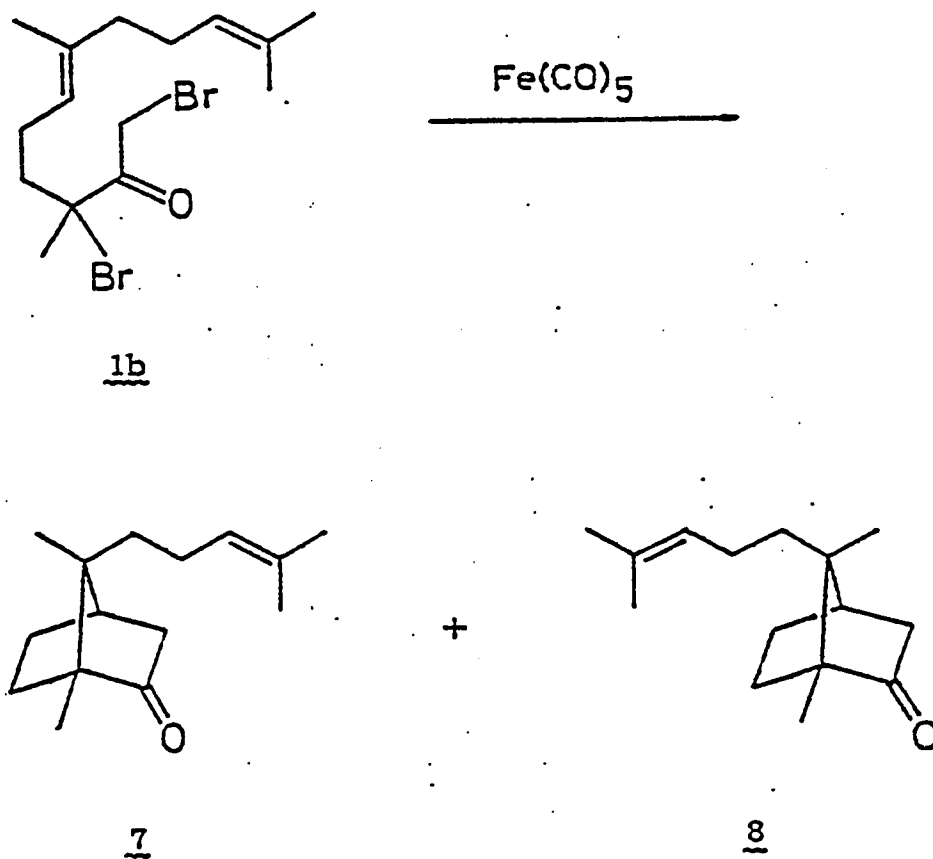
This plan has worked indeed well. When a mixture of the dibromo ketone 1a and  $\text{Fe}(\text{CO})_5$  (1:1.2 mol ratio) in



benzene under argon was heated in a pressure bottle at 100 - 110°C for 1.5 h, a C<sub>10</sub> fraction was obtained in up to 70% yield. The major component (54% of this fraction) was ( $\pm$ )-camphor (2). In addition, ( $\pm$ )-dihydrocarvone (3) (20%, cis/trans = 1:2:5), 4 ( $\sim$ 4%), ( $\pm$ )-carvenone (5) (10%), and 6 (4--7%) were formed. These products were identified by comparison of the spectral (ir, pmr, and mass spectra) and chromatographic properties with those of authentic samples.<sup>5e,6</sup> Several minor components (total  $\sim$ 6%) remained still unidentified.



In a similar fashion, reaction of the dibromo ketone 1b and  $\text{Fe}(\text{CO})_5$  (1:1 mol ratio) in benzene at  $100^\circ\text{C}$  afforded a 2:1 mixture of ( $\pm$ )-campherenone (7) and ( $\pm$ )-epicampherenone (8) in 58% yield.

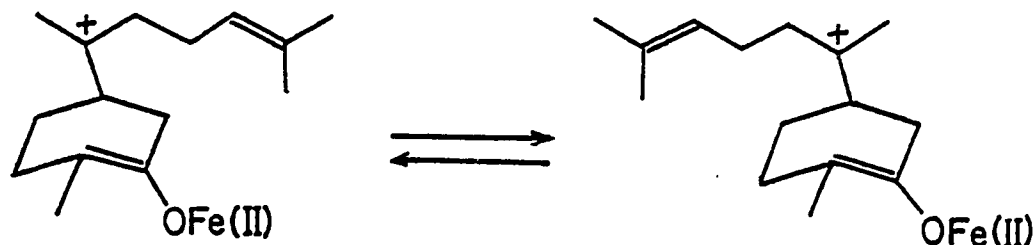


Apparently the feasibility of the acyclic to bicyclic conversion of eq 2 is based on the high stability of the zwitterionic intermediate that plays a crucial role in the stepwise cycloaddition; the regioselective C(1)-C(6) bonding leaves a positive charge on the tertiary carbon atom, C(7), and concurrently produces a fully substituted enolate moiety.<sup>7,8</sup>

Electrophilic cyclization in the oxallyl species derived from 1b is occurring selectively across the internal, C(6)--C(7) double bond rather than than the C(10)--C(11) bond.

The lack of stereospecificity of the present reaction is to be noted in view of the stereospecific nature of the previously observed intermolecular 3 + 2 cyclocoupling reaction. The final stage of cyclization (eq 2) involves a zwitterionic intermediate whose stereochemical integrity is kept by the strong electrostatic interaction between the cationic and enolate moieties. In this particular case, however, owing to steric constraints the boat-like intermediate would tend to leak into the more favorable half-chair conformers in which attractive interactions between the charged moieties are negligible. The presence of such conformational equilibrium can no longer lead to any stereospecific transformations. Acid catalyzed reaction of 2-acetoxy-4-(4-chloro-1-methylbut-1-enyl)-1-methylcyclohexene is known to afford the camphenone type products in a nonstereospecific manner.<sup>5c</sup> The starting material 1b does not isomerize to any considerable extent under the reaction conditions.

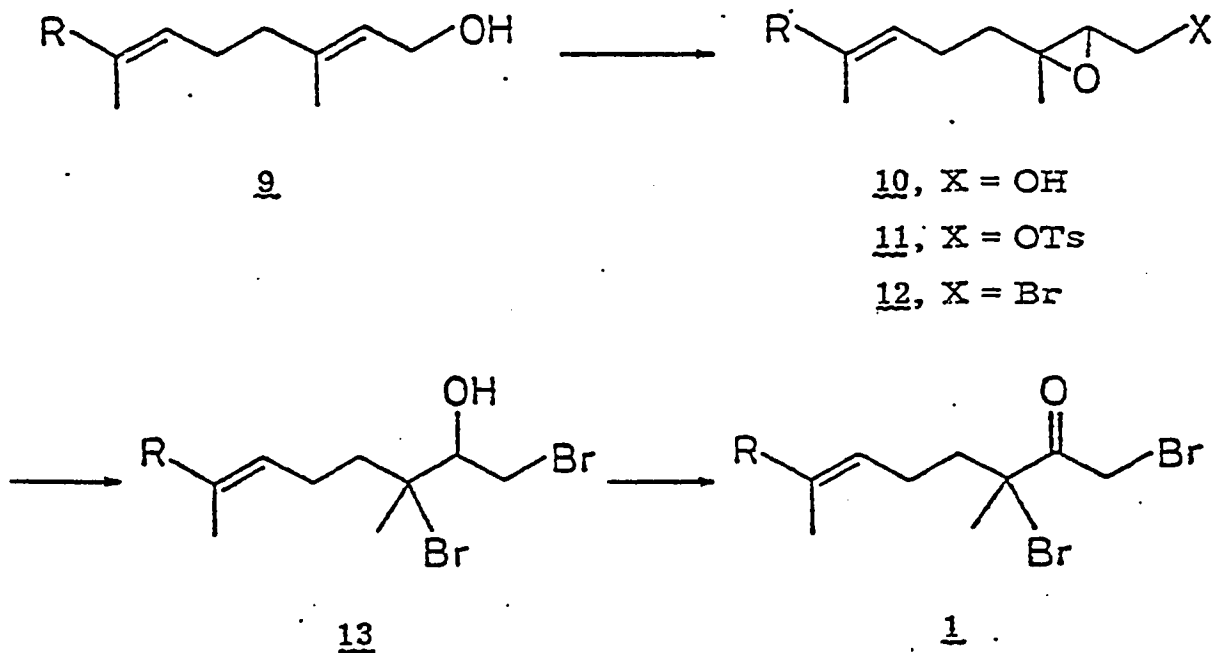
Realization of such a chemical analog of biosynthesis owes particularly to development of a new method of preparing dibromo ketones that contain olefinic linkage(s) in the same molecules. The conversion of farnesol (9b) to the dibromide 1b would be illustrative. Reaction of



(E,E)-farnesol [9b, containing ca. 9% of the (Z,E)-isomer, the stereochemical purity of 6-E is >99%]<sup>9</sup> with vanadium acetylacetonate--tert-butyl hydroperoxide in benzene at 25°C for 3 h produced the epoxy alcohol 10b in 95% yield,<sup>10</sup> which was transformed in 85% yield to the corresponding tosylate 11b by exposure to tosyl chloride in pyridine at 5°C for 12 h. Treatment of the tosylate 11b with excess lithium bromide in ether at 25°C for 19 h produced cleanly the bromo epoxide 12b (95% yield). The bromo epoxide 12b was subjected to the regioselective ring opening using 47% hydrobromic acid (1.6 equiv) in ether at 25°C for 2 h to give the dibromohydrin 13b in 93% yield.<sup>11</sup> Oxidation of 13b with 1.6 equiv of (CH<sub>3</sub>)<sub>2</sub>S--NCS complex in toluene (Corey-Kim reagent)<sup>12</sup> at -25°C for 2 h followed by the exposure to triethylamine (1.6 equiv) at 0°C for 15 min led to the desired α,α'-dibromo ketone 1b in 90% yield (64% overall yield from farnesol). Analogously, starting with geraniol (9a) and using a series of reactions generally paralleling those described above,

the  $\alpha, \alpha'$ -dibromo ketone 1a was obtained efficiently via the intermediates (in sequence) 10a to 13a in 68% overall yield.

It seems clear that the methodology described herein can encompass a variety of bicyclo[n.2.1]alkanone syntheses.



series a, R = CH<sub>3</sub>

series b, R = CH<sub>2</sub>CH<sub>2</sub>CH=C(CH<sub>3</sub>)<sub>2</sub>

### Experimental

Epoxy Farnesol 10b. To a solution of vanadyl acetylacetonate (2.6 mg, 0.8 mmol) in dry benzene (150 ml) was added one drop of 90% t-butyl hydroperoxide at 25°C. The initially bright green solution of VO(acac)<sub>2</sub> in benzene turned red upon addition of t-butyl hydroperoxide. After 5 min a solution of (E,E)-farnesol (18.1 g, 81.5 mmol) in benzene (30 ml), followed by 90% t-butyl hydroperoxide

(12.2 g, 122 mmol) in benzene (50 ml) were added dropwise at 25°C. The reaction was monitored by tlc and judged complete after 3 h. During that time, the color turned yellow and then faded gradually. The reaction was quenched by the addition of saturated aqueous sodium sulfite solution. Further stirring was continued for 20 min to decompose excess t-butyl hydroperoxide. The aqueous layer was extracted with ether twice, and the combined organic layers were washed with brine once. The concentrated crude product was subjected to column chromatography on silica gel (ether-hexane, 1:1) to afford the pure epoxy farnesol 10b (18.43 g, 95% yield) as a colorless oil: ir (liquid film) 3410, 1450, 1376, 1129  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  5.07 (2H, br t, olefinic H), 3.54 - 3.89 (2H, m,  $\text{CH}_2\text{-O}$ ), 2.95 (1H, t,  $J = 5.4$  Hz,  $\text{CH-O}$ ), 2.50 (1H, m, OH), 1.82 - 2.24 (6H, m,  $\text{C=C-CH}_2$ ), 1.41 - 1.76 (2H, m,  $\text{CH}_2\text{C-O}$ ) 1.59, 1.67 (2:1 ratio, 9H, two s,  $\text{C=C-CH}_3$ ), 1.28 (3H, s,  $\text{CH}_3\text{C-O}$ ).

Epoxy Tosylate 11b. To a solution of the epoxy farnesol 10b (17.4 g, 73.1 mmol) in pyridine (100 ml) was added in small portions at -20°C ( $\text{CCl}_4$ -dry ice bath) p-toluene-sulfonyl chloride (18.1 g, 95.0 mmol). The resulting solution was allowed to stand in the refrigerator ( $\sim 4^\circ\text{C}$ ) overnight. The reaction mixture was then diluted with ether and poured onto ice-cold water. The aqueous layer was separated and extracted with ether twice. The combined extracts were washed with dilute hydrochloric acid and water. The concentrated crude product was purified by

column chromatography on silica gel (ether-hexane, 1:2) to furnish the pure tosylate 11b (24.207 g, 85% yield) as a colorless oil: tlc,  $R_f$  0.38 (ether-hexane, 1:2); ir (liquid film) 1598, 1452, 1359, 1187, 1176, 1096, 968, 836, 820, 776, 672  $\text{cm}^{-1}$ ; pmr ( $\text{CCl}_4$ )  $\delta$  7.06 - 7.83 (4H, m, Aryl CH), 4.97 (2H, br t, olefinic H), 3.97 (2H, d,  $J = 5.6$  Hz,  $\text{CH}_2\text{-O}$ ), 2.81 (1H, t,  $J = 5.6$  Hz,  $\text{CHC-O}$ ), 2.42 (3H, s, Aryl- $\text{CH}_3$ ), 1.48 - 2.23 (8H, m,  $\text{C=C-CH}_2$ ,  $\text{CH}_2\text{C-O}$ ), 1.57, 1.64 (2:1 ratio, 9H, two s,  $\text{C=C-CH}_3$ ), 1.22 (3H, s,  $\text{CH}_3\text{C-O}$ ).

Epoxy Bromide 12b. An ethereal solution (50 ml) of the tosylate 11b (20 g, 51 mmol) was treated with anhydrous lithium bromide (20 g) at 25°C for 15 h. The white suspension was then diluted with *n*-hexane and poured into ice-cold water. The organic layer and *n*-hexane extracts of the aqueous washing were dried over  $\text{Na}_2\text{SO}_4$ , and freed of solvent. The residue was applied to column chromatography on silica gel (ether-hexane, 1:15) to give the epoxy bromide 12b (17.214 g, 95% yield) as a colorless oil: tlc,  $R_f$  0.5 (ether-hexane, 1:5); ir (liquid film) 1451, 1377, 1215, 890, 658  $\text{cm}^{-1}$ ; pmr ( $\text{CCl}_4$ )  $\delta$  5.04 (2H, br t, olefinic H), 2.75 - 3.64 (3H, m,  $\text{CHCH}_2\text{Br}$ ), 1.78 - 2.31 (6H, m,  $\text{C=C-CH}_2$ ), 1.57, 1.65 (2:1 ratio, 9H, two s,  $\text{C=C-CH}_3$ ), 1.27 (3H, s,  $\text{CH}_3\text{C-O}$ ); mass  $m/z$  300, 302 ( $M^+$ ), 257, 259 ( $M^+ - 43$ ); exact mass  $m/z$  300.104 (Calcd for  $\text{C}_{15}\text{H}_{25}\text{OBr}$ , 300.108).

Dibromohydrin 13b. An ethereal solution (50 ml) of the epoxy bromide 12b (13 g, 43 mmol) was added to a stirred suspension of 47% hydrobromic acid (50 ml) in ether (200 ml) at

25°C and the resulting mixture was stirred vigorously at 25°C for 2 h. The mixture was then poured onto ice-cold water and the product was extracted with ether three times. The combined extracts were washed with water until the aqueous layer turned to neutral, dried and freed of solvent. Purification of the concentrated crude product by column chromatography on silica gel (ether-hexane, 1:15) gave the dibromohydrin 13b (15.35 g, 93% yield) as a colorless oil: tlc,  $R_f$  0.41 (ether-hexane, 1:5); ir (liquid film) 3515, 1448, 1371, 1059  $\text{cm}^{-1}$ ; pmr ( $\text{CCl}_4$ )  $\delta$  4.75 - 5.27 (2H, m, olefinic H), 3.62 - 4.10 (2H, m,  $\text{CH}_2\text{Br}$ ), 3.36 (1H, t,  $J = 10.8$  Hz, CH-O), 1.77 - 2.53 (9H, m, C=C- $\text{CH}_2$ ,  $\text{CH}_2\text{C-Br}$ , OH), 1.69 (3H, s,  $\text{CH}_3\text{C-Br}$ ), 1.47 - 1.77 (9H, m, C=C- $\text{CH}_3$ ).

$\alpha,\alpha'$ -Dibromoketone 1b. To a stirred solution of N-chlorosuccinimide (1.77 g, 13.2 mmol) in toluene (90 ml) was added dimethylsulfide (1.49 ml, 20.3 mmol) under argon at 0°C. A white precipitate appeared immediately. The mixture was cooled to -25°C ( $\text{CCl}_4$ -dry ice bath) and a solution of the dibromohydrin 13b (3.37 g, 8.8 mmol) on toluene (18 ml) was added. Vigorous stirring was carried out at -25°C for 2 h. Then triethylamine (1.84 ml, 13.2 mmol) in pentane (3.5 ml) was added slowly. The cooling bath was removed, and further stirring was continued at 0°C for 20 min. The reaction mixture was diluted with ether (200 ml), and washed with 1% hydrochloric acid followed by water twice. Evaporation of the solvent left the crude oil, which was purified by column chromatography on silica gel (ether-hexane,

1:30) to afford the dibromoketone 1b (3.03 g, 90% yield) as a colorless oil: tlc,  $R_f$  0.39 (ether-hexane, 1:30); ir (liquid film) 1721, 1446, 1372, 1061, 1044  $\text{cm}^{-1}$ ; pmr ( $\text{CCl}_4$ )  $\delta$  5.00 (2H, m, olefinic H), 4.30 (2H, s,  $\text{COCH}_2\text{Br}$ ), 1.85 - 2.20 (8H, m,  $\text{C}=\text{C}-\text{CH}_2$ ,  $\text{CH}_2\text{C}-\text{Br}$ ), 1.88 (3H, s,  $\text{CH}_3\text{C}-\text{Br}$ ), 1.58, 1.59, 1.65 (9H, three s,  $\text{C}=\text{C}-\text{CH}_3$ ); mass  $m/z$  335, 337, 339, (1:2:1 ratio,  $M^+ - 41$ ), 229, 301 ( $M^+ - 78$ ), 229, 231 ( $M^+ - 148$ ); exact mass  $m/z$  378.008 (Calcd for  $\text{C}_{15}\text{H}_{24}\text{OBr}$ , 378.019).

Similarly, starting with geraniol and using a series of reactions generally paralleling those described for preparation of 1b, the  $\alpha,\alpha'$ -dibromoketone 1a was synthesized. The spectral data for each derivative are shown below.

Epoxy Tosylate 11a: ir (liquid film) 1598, 1451, 1354, 1177, 1096, 963, 816, 771, 669  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.96 - 7.65 (4H, m, Aryl CH), 4.86 (1H, br t, olefinic H), 3.97 (2H, d,  $J = 5.4$  Hz,  $\text{CH}_2-\text{O}$ ), 2.85 (1H, t,  $J = 5.4$  Hz,  $\text{CH}-\text{O}$ ), 2.36 (3H, s, Aryl  $\text{CH}_3$ ), 1.31 - 2.31 (4H, m,  $\text{C}=\text{C}-\text{CH}_2\text{CH}_2$ ), 1.54, 1.61 (6H, two s,  $\text{C}=\text{C}-\text{CH}_3$ ), 1.17 (3H, s,  $\text{CH}_3\text{C}-\text{O}$ ).

Epoxy Bromide 12a: ir (liquid film) 1451, 1378, 1211, 1067, 891, 657  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  4.83 (1H, br t, olefinic H), 2.75 - 3.59 (3H, m,  $\text{CHCH}_2\text{Br}$ ), 1.37 - 2.20 (4H, m,  $\text{C}=\text{C}-\text{CH}_2\text{CH}_2$ ), 1.53, 1.60 (6H, two s,  $\text{C}=\text{C}-\text{CH}_3$ ), 1.24 (3H, s,  $\text{CH}_3\text{C}-\text{O}$ ); mass  $m/z$  231, 233 ( $M^+$ ), 189, 191 ( $M^+ - 42$ ), 176, 178 ( $M^+ - 55$ ), 163, 165 ( $M^+ - 68$ ); exact mass  $m/z$  232.044 (Calcd for  $\text{C}_{10}\text{H}_{17}\text{OBr}$ , 232.046).

Dibromohydrin 13a: ir (liquid film) 3388, 1452, 1374, 1067  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  4.91 (1H, br t, olefinic H), 3.53 - 3.92 (2H, m,  $\text{CH}_2\text{Br}$ ), 3.30 (1H, t,  $J = 10$  Hz, CH-O), 2.47, (1H, br s, OH), 1.40 - 2.22 (4H, m,  $\text{C}=\text{C}-\text{CH}_2\text{CH}_2$ ), 1.67 (3H, s,  $\text{CH}_3\text{C}-\text{Br}$ ), 1.59, 1.63 (6H, two s,  $\text{C}=\text{C}-\text{CH}_3$ ); mass  $m/z$  216, 218 ( $M^+ - 95$ ), 164, 166 ( $M^+ - 147$ ).

Dibromoketone 1a: ir (liquid film) 1721, 1448, 1374, 1065, 1044  $\text{cm}^{-1}$ ; pmr ( $\text{CCl}_4$ )  $\delta$  5.01 (1H, m, olefinic H), 4.31 (2H, s,  $\text{COCH}_2\text{Br}$ ), 1.95 - 2.25 (4H, m,  $\text{C}=\text{C}-\text{CH}_2\text{CH}_2$ ), 1.86 (3H, s,  $\text{CH}_3\text{C}-\text{Br}$ ), 1.60, 1.66 (6H, two s,  $\text{C}=\text{C}-\text{CH}_3$ ); mass  $m/z$  310, 312, 314 (1:2:1 ratio,  $M^+$ ), 231, 233 ( $M^+ - 80$ ); exact mass  $m/z$  309.959 (Calcd for  $\text{C}_{10}\text{H}_{16}\text{OBr}_2$ , 309.957).

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- 6) Spectral characteristics of 6 were: ir (CCl<sub>4</sub>) 1706 cm<sup>-1</sup> (C=O); pmr (CCl<sub>4</sub>)  $\delta$  1.04 (d, J = 6.5 Hz, 3H, CHCH<sub>3</sub>), 1.59 (d, J = 1 Hz, 3H, vinyl methyl cis to vinyl proton), 1.67 (d, J = 1 Hz, 3H, vinyl methyl trans to vinyl proton), 2.04 (s, 3H, COCH<sub>3</sub>), 1.5 - 2.2 (m, 4H, two CH<sub>2</sub>), 2.42 (m, 1H, CHCH<sub>3</sub>), 5.00 (m, 1H, =CH); mass spectrum m/z 154 (M<sup>+</sup>).
- 7) R. Noyori, F. Shimizu, K. Fukuta, H. Takaya, and Y. Hayakawa, J. Am. Chem. Soc., 99, 5196 (1977).
- 8) Y. Hayakawa, K. Yokoyama, and R. Noyori, Tetrahedron Lett., 4347 (1976), and ref. 3.
- 9) Prepared from geraniol (>99%) by the following sequence of reactions: (1) PBr<sub>3</sub> in ether, (2) methyl acetate--NaH--C<sub>4</sub>H<sub>9</sub>Li, (3) hydrolysis followed by decarboxylation, (4) Wittig reaction of (C<sub>2</sub>H<sub>5</sub>O)<sub>2</sub>P(O)CH<sub>2</sub>-COOC<sub>2</sub>H<sub>5</sub>--NaH, and (5) AlH<sub>3</sub> reduction.
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present case, benzene was not suitable solvent (ca. 20% yield).

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## Chapter IV

Regioselective Carbonyl Amination  
using Diisobutylaluminum Hydride

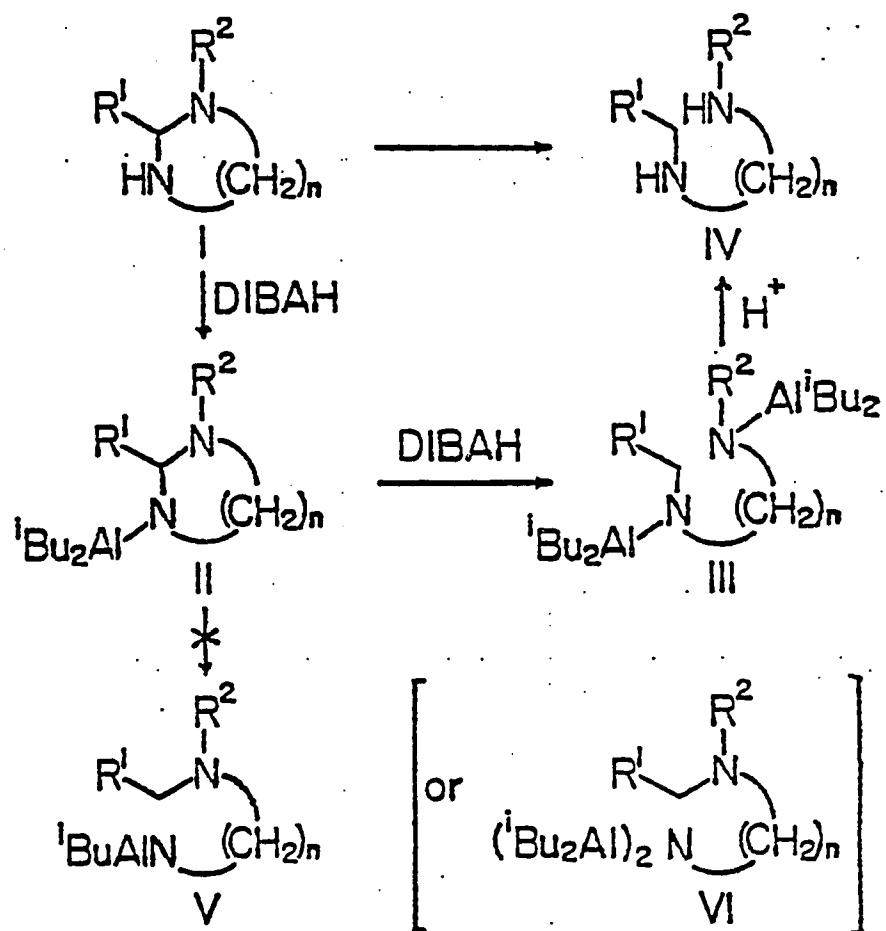
Abstract-----A new, selective, and mild approach to N-alkylation of polyamines has been demonstrated, which involves the novel reductive cleavage of the carbon-nitrogen bond in cyclic amidines by diisobutylaluminum hydride. This method provides a new entry to a wide variety of N-alkylated polyamines and many interesting macrocyclic polyamines hitherto accessible only by lengthy or complicated synthesis. Moreover, the synthesis of the plant alkaloid, spermine, was successively accomplished by the reductive cleavage of carbon-nitrogen bonds in 1,2-bis(2-tetrahydropyrimidyl)ethane, which was readily available from succinonitrile and 1,3-diaminopropane mono-p-toluenesulfonate.

The N-alkylation reaction of amines has long been recognized to be one of the most fundamental reactions for the formation of carbon-nitrogen bonds.<sup>1</sup> However, the alkylation of polyamines is often accompanied by di- or polyalkylations such that the separation of the desired monoalkylated polyamine from the reaction mixture is at best complicated. The hitherto available methodologies for monoalkylation are partially useful only when a large excess of polyamines are used. Therefore, a selective monoalkylation of polyamines has still been awaited with interest.

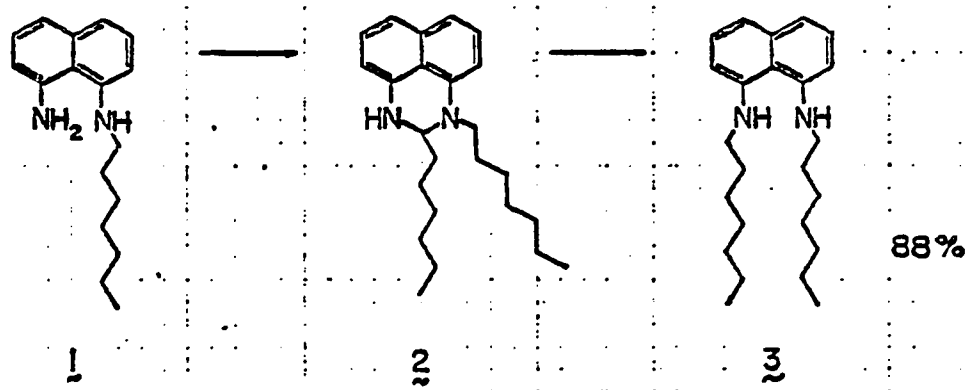
During the course of an investigation into the chemistry of cyclic polyamines and their metal cation inclusion complexes,<sup>2</sup> we devised a new, selective and mild approach to monoalkylation of polyamines, which involves the novel reductive cleavage of some heterocyclic derivatives by diisobutylaluminum hydride (DIBAH).<sup>3</sup>

The general type of transformation which is described herein is summarized in Scheme I. DIBAH is an effective and selective reducing agent which cleanly converts the aluminum amide II to the bis(aluminum amide) III leading to the monoalkylated 1,(n + 2)-diamine IV after hydrolysis.<sup>4</sup> The reaction should proceed regioselectively, since the formation of the aluminum imide V (or dialuminum amide VI) would be energetically much less favorable.<sup>3</sup>

## Scheme I

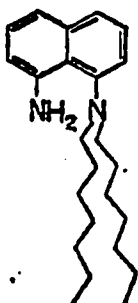


Our process is typified by the conversion of N-heptyl-1,8-diaminonaphthalene (1) to N,N'-diheptyl-1,8-diaminonaphthalene (3).

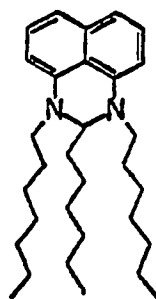


Treatment of 1 in benzene with heptaldehyde (1 equiv) gave the 1-heptyl-2-hexyl-2,3-dihydroperimidine (2) in quantitative yield.<sup>5</sup> Reduction of 2 with DIBAH (6 equiv) in *n*-hexane afforded the diamine 3 as the major product, which was diluted with benzene, treated successfully with sodium fluoride (4 molar equiv to DIBAH)<sup>6</sup> and water (3 molar equiv to DIBAH), and stirred vigorously for 20 min. Filtration, washing of the white precipitates with benzene, and removal of the solvent gave the diamine 3 in 88% yield after purification. Without isolation of the intermediate 2, the diamine 3 was obtained in 88% yield by direct treatment of the crude 2 with DIBAH under similar reduction conditions described above.

Difficulty to distinguish between the structure of 3 and its regioisomer 4 was encountered with the spectral data (pmr, ir, and mass) of 3, which might be identical with those of 4. Therefore, the structure of 3 was established by treatment of 3 with heptaldehyde according to the procedure described above, followed by careful examination of the methine peak (N-CH-N,  $\delta$  4.00 - 4.33) in the <sup>1</sup>H NMR spectrum (pmr) of 5. It was further confirmed by regioselective

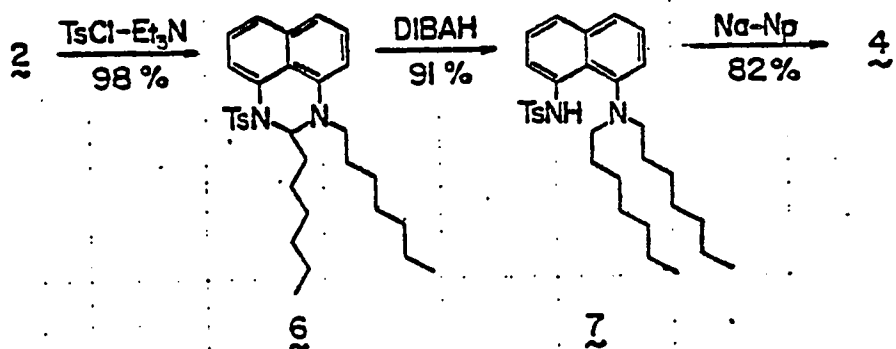


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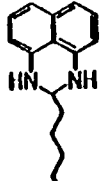
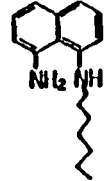
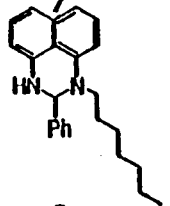
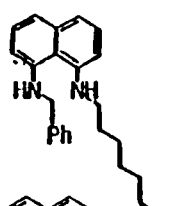
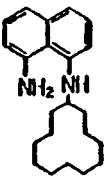
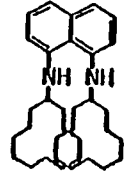
synthesis of 4 according to the following reaction sequence: Tosylation of 2 with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane gave *p*-toluenesulfonamide 6 in 98% yield. Followed by DIBAH reduction in *n*-hexane afforded *N,N*-diheptyl-*N'*-*p*-toluenesulfonyl-1,8-diaminonaphthalene (7) (91% yield), regioselectively. Lastly removal of the *p*-toluenesulfonyl group in 7 with sodium-naphthalene in tetrahydrofuran (THF)<sup>7</sup> generated *N,N*-diheptyl-1,8-diaminonaphthalene (4) in 82% yield.



Further examples are listed in Table I, which exemplifies the effectiveness of this method. Even bulky cyclododecyl groups can be cleanly introduced with complete regioselectivity (Table I, 3, 4.)

Some applications of this novel reductive cleavage were demonstrated by the selective synthesis of macropoly-cyclic polyamines. Although interesting "guest" compounds are plentiful,<sup>8</sup> the synthesis of the corresponding "host" structures<sup>9</sup> (e.g., macrocyclic polyethers, and polyamines) is limited by the utility of most of the existing methods. The invention of new synthetic methodology for

Table I. N-Alkylation of 1,8-Diaminonaphthalene Derivatives by Reductive Cleavage

Entry	Diamine	Carbonyl Compound	Reaction Condition <sup>a</sup>	Dihydroperimidine	Reduction with DIBALH	Product	Overall Yield (%) <sup>d</sup>
1	1,8-Diamino-naphthalene	$\text{CH}_3(\text{CH}_2)_5\text{CHO}$	25°C, 20 min		0°C, 2 h		94
2	<u>N</u> -Heptyl-1,8-diamino-naphthalene	$\text{PhCHO}$	25°C, 10 h <sup>b</sup>		80°C, 30 min		85
3	1,8-Diamino-naphthalene	$(\text{CH}_2)_{11}\text{C=O}$	cat. <i>p</i> -TsOH 80°C, 3 h	c	25°C, 45 min		98
4	<u>N</u> -Cyclododecyl-1,8-diamino naphthalene	$(\text{CH}_2)_{11}\text{C=O}$	cat. <i>p</i> -TsOH 110°C, 10 h	c	25°C, 12 h		84

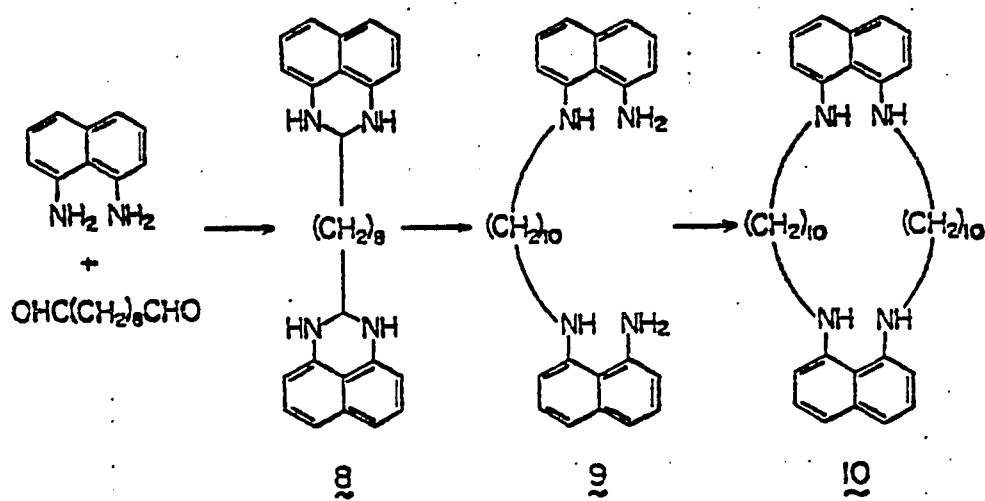
a) The resulting water was removed azeotropically.

b) Water was evaporated with benzene.

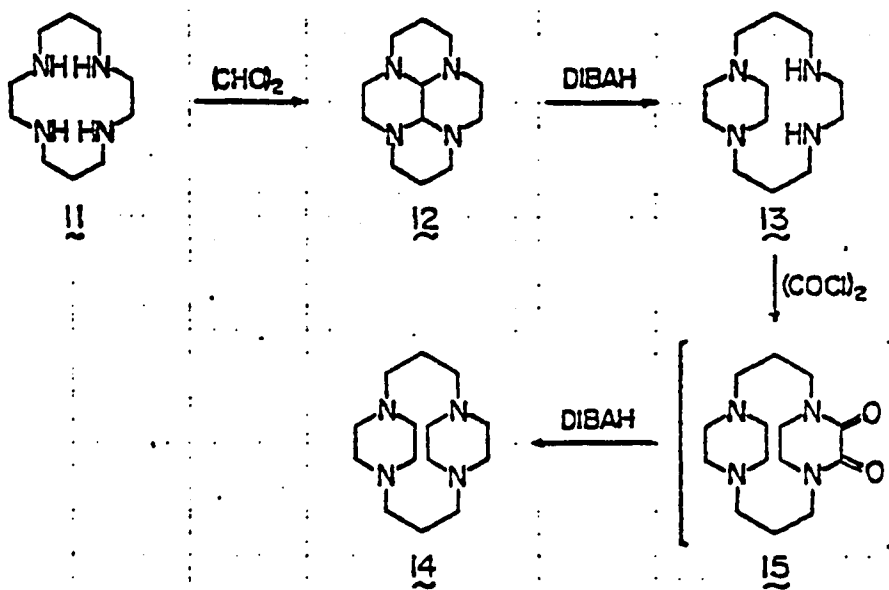
c) Without isolation of the dihydroperimidines, the reaction mixture was directly treated with excess DIBALH at 0° or 25°C.

d) Yield from 1,8-diaminonaphthalene derivatives.

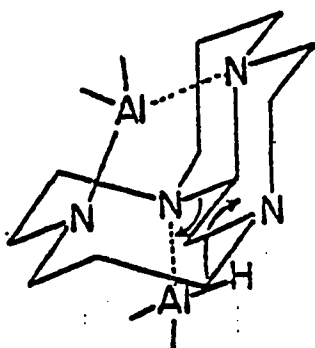
host molecules is, therefore, one of the more crucial elements for the development of bioorganic as well as bioinorganic chemistry. Thus, reaction of 1,8-diaminonaphthalene with 1,10-decanedial<sup>10</sup> (0.5 equiv) in benzene at 25°C for 2 h afforded 1,8-bis(2-dihydroperimidyl)octane (8), which was directly treated with DIBAH in *n*-hexane (4 equiv) at 25°C for 3 h to furnish *N,N'*-decamethylenebis(1,8-diaminonaphthalene) (9) in 85% yield after purification. Similar reaction sequence was applied to introduce the other decamethylene bridge for preparation of macrocyclic tetramine 10: Simultaneous and separate addition of 9 and 1,10-decanedial to refluxing benzene over 75 min led to the formation of the bis(2-dihydroperimidyl) derivative, which was reduced with DIBAH in *n*-hexane (10 equiv) at 25°C for 15 h to give 10 in 40% yield.



Another attractive approach to the synthesis of macro-polycyclic polyamines was illustrated in the following sequence: Reaction of 1,4,8,11-tetraazacyclotetradecane (11) in methanol with aq. glyoxal<sup>11</sup> at 0°C for 30 min gave the tetracyclic adduct 12 quantitatively, which was converted by DIBAH in xylene under reflux for 4 days into 1,5,8,12-tetraazabicyclo[10.2.2]hexadecane (13) in 96% yield. The structure of 13 followed from (a) spectral data (see experimental), (b) transformation to the dimethyl derivative (aq. CH<sub>2</sub>O-NaBH<sub>3</sub>CN-AcOH, 25°C for 5 h)<sup>12</sup> and di-p-toluene-sulfonamide (p-TsCl-NEt<sub>3</sub>, 25°C for 2 h) of 13. The introduction of ethylene bridge was performed by the reaction of 13 with oxalyl chloride at 0°C for 1.5 h, and then the reduction of the resulting diamide 14 using DIBAH at 25°C for one day to furnish 1,5,8,12-tetraazatricyclo[10.2.2.2<sup>5,8</sup>]-octadecane (15). The selective cleavage of 12 by DIBAH can

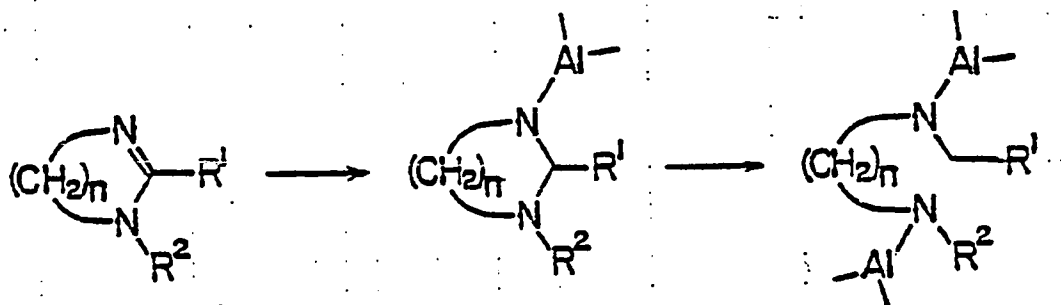


be explained by initial chelate formation of diisobutylaluminum amide, followed by the coordination of another nitrogen atom to DIBAH, and finally the C-N bond cleavage by DIBAH as shown below.

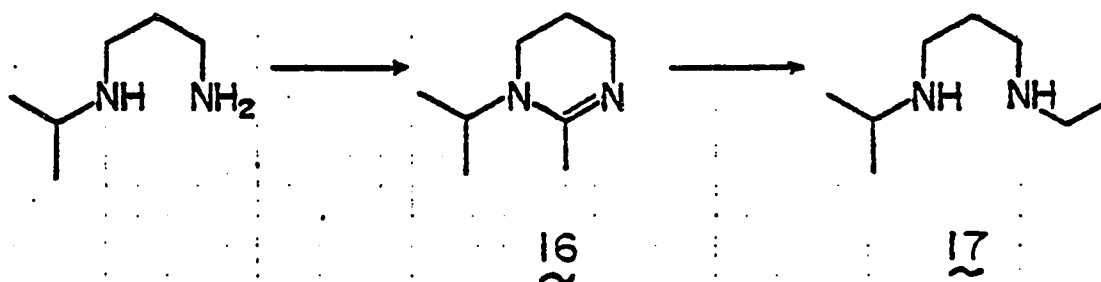


Since DIBAH is an effective reducing agent to convert imines to amino derivatives,<sup>13</sup> our new process can be extended to the reductive cleavage of amidine system by DIBAH (Scheme II) to furnish the regiospecifically alkylated polyamines. Thus, reaction of *N*-*i*-propyl-1,3-diaminopropane with ethyl acetoacetate in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate<sup>14</sup> produced 1-isopropyl-2-methyltetrahydropyrimidine (16), which was

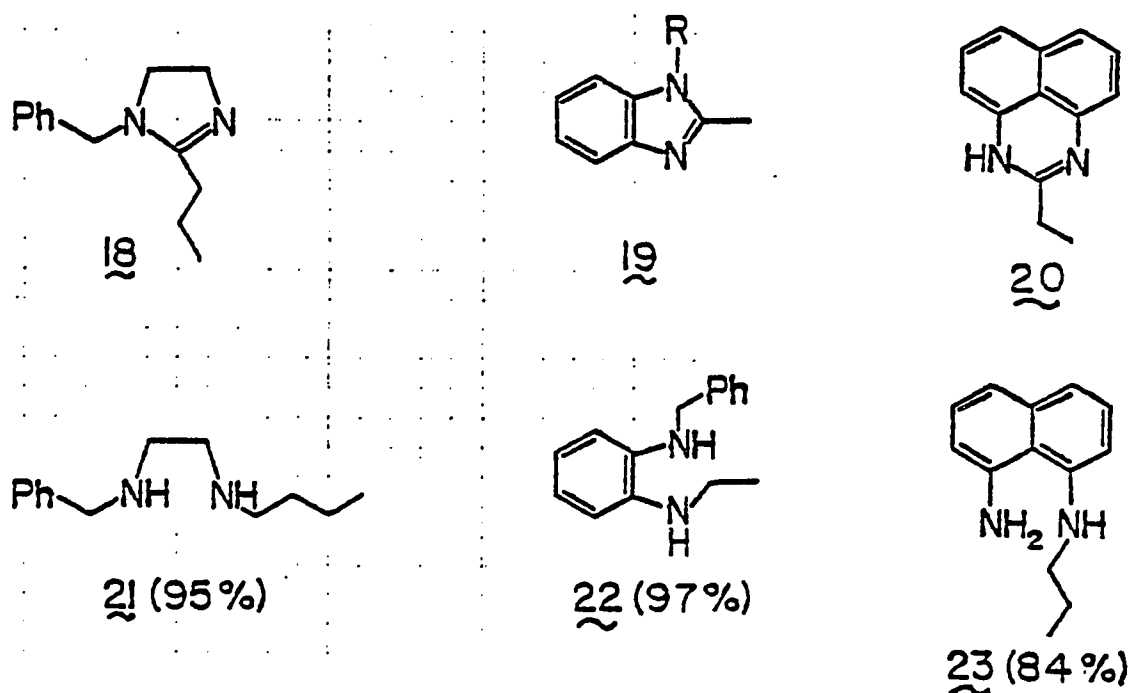
Scheme II



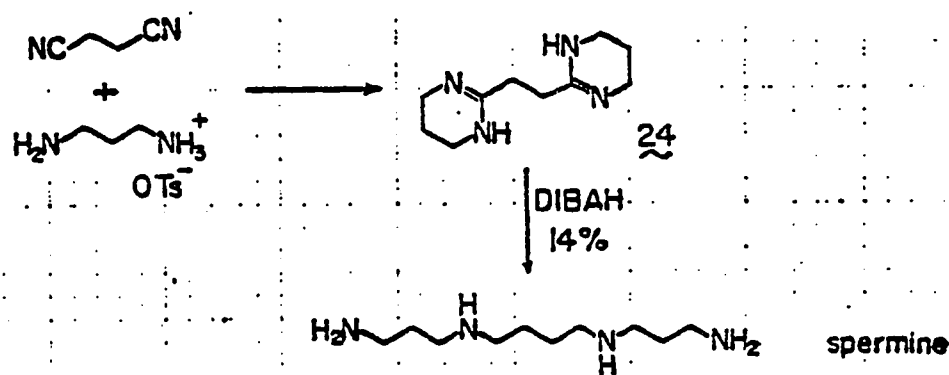
converted to DIBAH in *n*-hexane to *N*-isopropyl-*N'*-ethyl-1,3-diaminopropane (17) in 97% yield. Similarly, several cyclic



amidines (18), (19) ( $R = \text{PhCH}_2$ ), and (20) were cleanly reduced by DIBAH in a regioselective manner to give the corresponding diamines (21), (22) ( $R = \text{PhCH}_2$ ), and (23) respectively in high yield as indicated in the parenthesis. On the other hand, reduction of 2-methylbenzimidazole (19) ( $R = \text{H}$ ) with DIBAH recovered the starting material even under vigorous reaction conditions.<sup>15</sup>



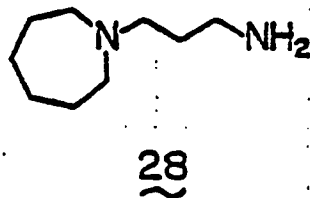
The present method was employed in the facile synthesis of spermine which is widely distributed in the animal kingdom and in microorganisms, and forms a basic skeleton of spermine plant alkaloids.<sup>16</sup> Thus, succinonitrile was treated with 1,3-diaminopropane mono-p-toluenesulfonate at 140°C for 30 min to furnish 1,2-bis(2-tetrahydropyrimidyl)ethane (24) in 95% yield. Although the direct transformation of 24 into spermine (14% yield) did not proceed smoothly



under vigorous reaction conditions, the difficulty was easily overcome by protection of the amino group with hexamethyldisilazane.<sup>18</sup> The trimethylsilyl group was favorable for our purpose for ease of both introduction and removal. Thus, the bis(tetrahydropyrimidine) 24 was converted in situ to the bis(trimethylsilylamide) 25 by treatment with hexamethyldisilazane in the presence of a catalytic amount of fuming sulfuric acid under reflux for 12 h. The bis(silylamide) 25, after evaporation of excess hexamethyldisilazane, was directly subjected to the reductive cleavage by excess DIBAH



27 was further established (a) by comparison with the isomeric diamine 28 made from the reduction of N-(3-aminopropyl)-



$\epsilon$ -caprolactam with DIBAH (b) and by transformation to the corresponding N,N'-dimethyl derivative (aq.  $\text{CH}_2\text{O-NaBH}_3\text{CN-AcOH}$ ) or di-p-toluenesulfonamide (p-TsCl- $\text{NEt}_3$ ) of 27.

The additional examples presented in Table II illustrate the wide generality and flexibility of the new approach. Macrocyclic amines of up to the 30-membered ring (9) can be readily prepared. It can also be seen that even highly strained 9-membered ring structure (1), which cannot be prepared by other methods, can be prepared efficiently. In addition, a simple route to an optically-active cyclic diamine (10) is now possible based on the present procedure.

For the synthesis of cyclic polyamines, the author found it necessary to develop efficient synthetic routes to the cyclic amidine system<sup>20</sup> in addition to those already in the literature.<sup>21,22</sup> Below he outlines the three general procedures he followed in preparing the amidines used in this study (Scheme III): (A) Conversion of the lactam to the imino ether ( $\text{Et}_3\text{O}^+\text{BF}_4^-$ )<sup>23</sup> followed by treatment with aziridine, and subsequent rearrangement to the dihydroimidazole with iodine<sup>21</sup> or trimethylsilyl iodide; (B) Conversion of the lactam to

Table II. Synthesis of Cyclic Polyamines


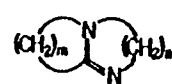

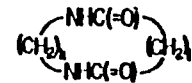
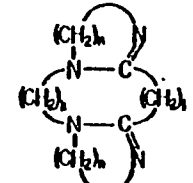
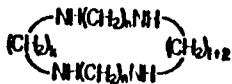
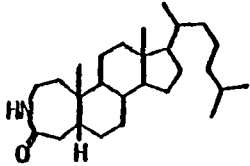
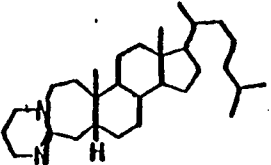
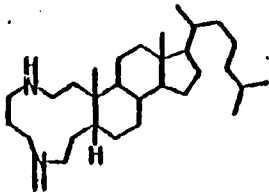
Entry	Lactam	Method <sup>a</sup>	Yield (%)	Amidine	Reaction Conditions <sup>b</sup> (°C, h)	Yield <sup>c</sup> (%)	Amine <sup>d</sup>
							
1	m = 4	A	60	n = 2	110, 3	79	
2	m = 5	---	---	n = 3 (DBU)	110, 7	96	
3	m = 7	A	62	n = 2	110, 1.5	90	
4	m = 7	B	55	n = 3	110, 4	74	
5	m = 11	A	78	n = 2	110, 1.5	92	
6	m = 11	B	56	n = 3	110, 1.5	83	
7	m = 11	C	77	n = 3			
							
8	k = 6, l = 8 <sup>e</sup>	A	39 <sup>g</sup>	n = 2	110, 1.5	68	
9	k = 12, l = 8 <sup>e</sup>	A	37 <sup>g, h</sup>	n = 2	110, 1.5	83	

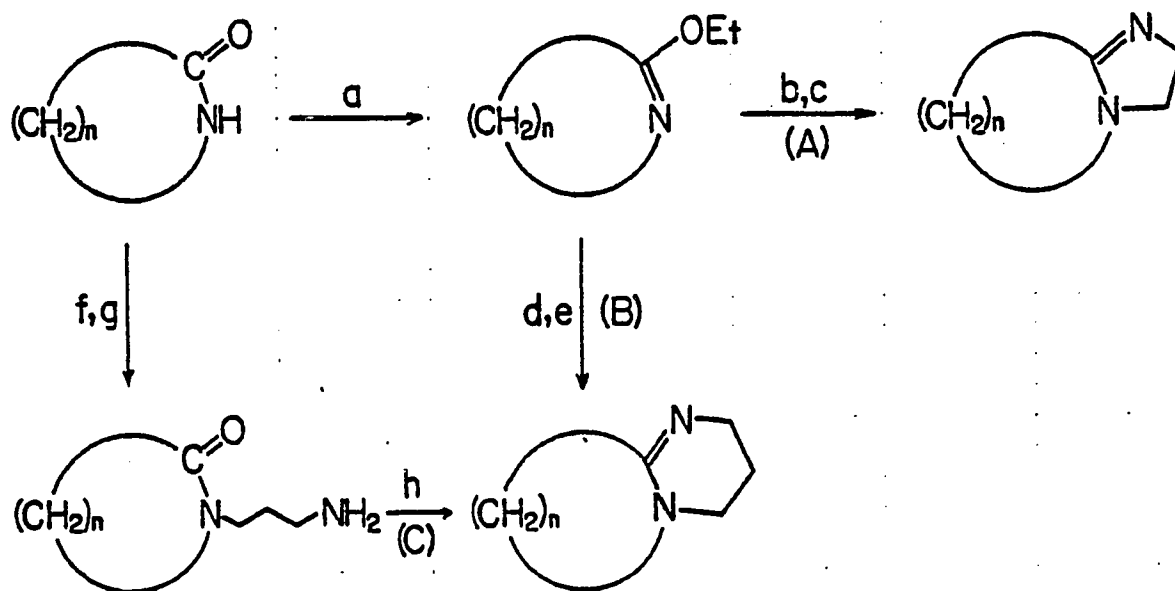
Table II. (Continued)

Entry	Lactam	Method <sup>a</sup>	Yield (%)	Amidine	Reaction Conditions <sup>b</sup> (°C, h)	Yield <sup>c</sup> (%)	Amine <sup>d</sup>
10		C	97		110, 12	86	

- a) Method A, B, C refer to the three general methods in the experiment.  
 b) All reductions were carried out as described for DBU (experimental) using 6 - 12 equiv of DIBAL.  
 c) Yields were determined by isolation involving chromatography on silica gel.  
 d) All compounds have been adequately characterized by spectral data (pmr, cmr, ir, and mass), see Table III.  
 e) H. Stetter and J. Marx, *Ann.*, **607**, 59 (1957).  
 f) K. Oka and S. Hara, *J. Org. Chem.*, **43**, 3790 (1978).  
 g) In addition to the desired bis(amidine), the monoamide-monoamidine was also obtained in ca. 20% yield.  
 h) The aziridine derivative was treated with 0.3 equiv of trimethylsilyl iodide in  $\text{CH}_2\text{Cl}_2$  (0.3 M) at 25°C for 2 h, then under reflux for 9 h.

the imino ether ( $\text{Et}_3\text{O}^+\text{BF}_4^-$ ), followed by stirring with 3-bromopropylamine hydrobromide, and subsequent neutralization with potassium carbonate to give the tetrahydropyrimidine; (C) Cyanoethylation of the lactam with acrylonitrile,<sup>22</sup> followed by hydrogenation over  $\text{PtO}_2$ , and finally cyclization with titanium tetrachloride to produce the tetrahydropyrimidine.

### Scheme III



a,  $\text{Et}_3\text{O}^+\text{BF}_4^-$ ; b,  $(\text{CH}_2)_2\text{NH}\cdot\text{NH}_4\text{Br}$ ; c,  $\text{I}_2$ -benzene or  $(\text{CH}_3)_3\text{SiI}$ ;  
 d,  $\text{Br}(\text{CH}_2)_3\text{NH}_3^+\text{Br}^-$ ; e,  $\text{K}_2\text{CO}_3$ ; f,  $\text{CH}_2=\text{CHCN}\cdot\text{EtONa}$ ; g,  $\text{H}_2$ ,  
 $\text{PtO}_2$ ; h,  $\text{TiCl}_4$ .

The synthetic method described herein provides a new entry to a wide variety of N-alkylated polyamines and many unusual macrocyclic ligands hitherto accessible only by

lengthy or complicated synthesis.

### Experimental

General. The infrared spectra were recorded on a Perkin-Elmer 710A spectrometer; the mass spectra on a Varian MAT high resolution mass spectrometer;  $^1\text{H}$  NMR spectra (pmr) on a Varian EM-360 or HA-100 spectrometer; and Fourier transfer  $^{13}\text{C}$  NMR spectra (cmr) on a Varian XL-100 spectrometer. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane ( $\delta = 0$ ). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Melting points were measured using a Büchi-510 capillary melting point apparatus in open capillaries and are uncorrected. All experiments were carried out under an atmosphere of dry argon. For tlc analysis throughout this work, Merck pre-coated tlc plates (silica gel 60 F<sub>254</sub>, 0.2 mm) were used. The products were purified by preparative tlc on silica gel plates (Merck) or by preparative column chromatography on silica gel E. Merck Art. 9385, or silanized silica gel E. Merck Art. 7719.

In experiments requiring dry solvents, tetrahydrofuran was freshly distilled from sodium metal under an argon atmosphere using benzophenone ketyl as indicator. Dichloromethane was distilled from phosphorus pentoxide and stored over  $4\text{\AA}$  molecular sieves. Benzene and toluene were dried

over sodium metal. Triethylamine was stored over potassium hydroxide pellets. Diisobutylaluminum hydride in *n*-hexane (1.0 M) was a commercial product. Other simple chemicals were purchased and used as such.

1-Heptyl-2-hexyl-2,3-dihydroperimidine (2). Heptaldehyde (1.14 g, 10 mmol) was added dropwise to a solution of *N*-heptyl-1,8-diaminonaphthalene (2.56 g, 10 mmol) in benzene (50 ml) at 0°C. Stirring was continued at 0°C for 30 min. Then the solvent was evaporated and the crude product was directly subjected to column chromatography on silica gel (ether-hexane, 1:10 to 1:5) to afford 2 as a light orange oil: tlc,  $R_f$  0.49 (ether-hexane, 1:9, 2 developments); ir (liquid film) 3440, 1610, 1482, 1447, 1175, 813, 758  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.23 - 7.39 (6H, m, Aryl CH), 4.08 - 4.60 (2H, m, NH, NCHN), 2.68 - 3.73 (2H, m, NCH<sub>2</sub>); mass  $m/z$  352.291 (Calcd for  $\text{C}_{24}\text{H}_{36}\text{N}_2$ , 352.288).

*N,N'*-Diheptyl-1,8-diaminonaphthalene (3). A solution of DIBAH in *n*-hexane (6 ml, 6 mmol) was added to 2 (352 mg, 1 mmol) at 0°C. The resulting solution was stirred at 25°C for 8 h, then under reflux for 1 h. The mixture was cooled to 0°C, diluted with benzene (18 ml), treated successively with sodium fluoride (1 g, 24 mmol) and water (0.3 ml, 18 mmol) at 0°C, and stirred vigorously for 20 min at 25°C. Filtration, washing of the white precipitate with chloroform, and removal of the solvents left the crude oil, which was purified by column chromatography on silica gel (ether-hexane, 1:30) to give 3 (319 mg, 88% yield) as white crystals:

tlc,  $R_f$  0.37 (ether-hexane, 1:30); ir ( $\text{CHCl}_3$ ) 3373, 1589, 1464, 1300, 1135, 1100  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.37 - 7.26 (6H, m, Aryl CH), 5.40 (2H, br s, NH), 3.00 (4H, t,  $J = 6.0$  Hz,  $\text{NCH}_2$ ); mass  $m/z$  354.304 (Calcd for  $\text{C}_{24}\text{H}_{38}\text{N}_2$ , 354.304.) The diamine 3 could be obtained in 88% yield by the direct treatment of the crude 2 with DIBAH in *n*-hexane under the similar conditions described above.

1,3-Diheptyl-2-hexyl-2,3-dihydroperimidine (5). A mixture of the diamine 3 (178 mg, 0.5 mmol) and heptaldehyde (68 mg, 0.6 mmol) in benzene (4 ml) was refluxed for 3 h. Evaporation of the solvent left the crude oil, which was directly subjected to column chromatography on silica gel (ether-hexane, 1:40) to give 5 (205 mg, 91% yield) as a colorless oil: tlc,  $R_f$  0.48 (ether-hexane, 1:40); ir (liquid film) 1580, 1451, 1419, 1331, 1145, 727  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.27 - 7.49 (6H, m, Aryl CH), 4.00 - 4.33 (1H, br t, NCHN), 2.65 - 3.85 (4H, m,  $\text{NCH}_2$ ); mass  $m/z$  450.397 (Calcd for  $\text{C}_{31}\text{H}_{50}\text{N}_2$ , 450.397).

1-Heptyl-2-hexyl-3-p-toluenesulfonyl-2,3-dihydroperimidine (6). *p*-Toluenesulfonyl chloride (1.144 g, 6 mmol) was added portionwise to a stirred solution of 2 (1.036 g, 3 mmol) and triethylamine (2.51 ml, 18 mmol) in dichloromethane (6 ml) at 0°C. The resulting mixture was allowed to warm to 25°C and further stirring was continued at 25°C for 2 days. Then the mixture was poured onto water and extracted with chloroform. The combined extracts were washed with water once, dried, and concentrated. Purification of the

crude product by column chromatography on silica gel (benzene-hexane, 1:2, then only benzene) gave 6 (1.488 g, 98% yield) as a light brown oil: tlc,  $R_f$  0.58 (ether-hexane, 1:9, 2 developments); ir (liquid film) 1596, 1419, 1355, 1166, 1090, 805, 759  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.08 - 8.00 (10H, m, Aryl CH), 5.39 (1H, br s, NCHN), 2.80 - 3.17 (2H, m,  $\text{NCH}_2$ ), 2.14 (3H, s, Aryl- $\text{CH}_3$ ); mass  $m/z$  506.300 (Calcd for  $\text{C}_{31}\text{H}_{42}\text{N}_2\text{O}_2\text{S}$ , 506.297).

N,N-Diheptyl-N'-p-toluenesulfonyl-1,8-diaminonaphthalene (7). A solution of DIBAH in *n*-hexane (8.8 ml, 8.8 mmol) was added dropwise to 6 at 0°C. The resulting solution was stirred at 25°C for 30 min. The solution was then diluted with benzene (18 ml) and treated successively with sodium fluoride (1.478 g, 35.2 mmol) and water (0.48 ml, 26.4 mmol) at 0°C. After vigorous stirring at 25°C for 20 min, the suspension was filtered and washed with chloroform. Evaporation of the solvents, followed by column chromatography on silica gel (ether-hexane, 1:8, then 1:5) gave 7 (407 mg, 91% yield) as a pink oil: tlc,  $R_f$  0.35 (ether-hexane, 1:5); ir (liquid film) 1592, 1473, 1419, 1352, 1307, 1164, 1093, 762  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.97 - 7.96 (10H, m, Aryl CH), 2.76 - 3.24 (4H, m,  $\text{NCH}_2$ ), 2.26 (3H, s, Aryl- $\text{CH}_3$ ); mass  $m/z$  508.313 (calcd for  $\text{C}_{31}\text{H}_{44}\text{N}_2\text{O}_2\text{S}$ , 508.312).

N,N-Diheptyl-1,8-diaminonaphthalene (4). Sodium naphthalene in dry THF (0.5 M) was prepared by treatment of naphthalene (1.018 g, 7.9 mmol) in THF (14.4 ml) with metallic sodium (166 mg, 7.2 mmol) at 25°C for 1 h.<sup>7</sup> This

solution (3.5 ml, 1.75 mmol) was added to a solution of 7 (180 mg, 0.35 mmol) in THF (1 ml) at 25°C. The reaction was over immediately. Then a little water was added. The mixture was poured onto water, and extracted with ether several times. The combined extracts were dried, concentrated, and purified by column chromatography on silica gel (ether-hexane, 1:50, then 1:10) to afford 4 (102 mg, 82%); tlc,  $R_f$  0.53 (ether-hexane, 1:9); ir (liquid film) 3490, 3299, 1595, 1472, 1305, 758  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.31 - 7.63 (6H, m, Aryl CH), 6.06 (1H, s, NH), 2.75 - 3.14 (4H, m,  $\text{NCH}_2$ ); mass  $m/z$  354.304 (calcd for  $\text{C}_{24}\text{H}_{38}\text{N}_2$ , 354.304).

2-Hexyl-2,3-dihydroperimidine. Heptaldehyde (1.14 g, 10 mmol) was added dropwise to a stirred solution of 1,8-diaminonaphthalene (1.58 g, 10 mmol) in benzene (50 ml) at 25°C. The reaction proceeded exothermically. The water was removed azeotropically. During this operation about 40 ml of benzene was distilled off. The residue was directly applied to column chromatography on silica gel (benzene) to furnish the title compound (2.507 g, 98% yield) as red crystals: tlc,  $R_f$  0.4 (benzene, 2 developments); ir ( $\text{CDCl}_3$ ) 3443, 1613, 1419, 1135, 1105  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.30 - 7.20 (6H, m, Aryl CH), 4.24 (1H, t,  $J = 5.2$  Hz,  $\text{NCHN}$ ), 4.05 (2H, s, NH); mass  $m/z$  254.185 (Calcd for  $\text{C}_{17}\text{H}_{22}\text{N}_2$ , 254.178).

N-Heptyl-1,8-diaminonaphthalene (1). The crude 2-hexyl-2,3-dihydroperimidine, obtained above, was treated with DIBAH in n-hexane (70 ml, 70 mmol) at 0°C for 2 h. The reaction mixture was diluted with benzene (140 ml), treated with

water (3.78 ml, 210 mmol) at 0°C, and stirred vigorously at 25°C for 15 min. Then anhydrous magnesium sulfate (30 g) was added at 0°C, and further stirring was continued at 25°C for 5 min. Filtration, followed by washing of the residue with chloroform gave the crude diamine, which was purified by column chromatography on silica gel (benzene) to give 1 (2.417 g, 94% yield) as a red oil: tlc,  $R_f$  0.5 (Benzene); ir (liquid film) 3390, 1593, 1531, 1300, 800, 741  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.26 - 7.14 (6H, m, Aryl CH), 4.52 (3H, s, NH), 2.92 (2H, t,  $J = 6.0$  Hz,  $\text{NCH}_2$ ); mass  $m/z$  256.192 (Calcd for  $\text{C}_{17}\text{H}_{24}\text{N}_2$ , 256.194).

N-Cyclododecyl-1,8-diaminonaphthalene. A mixture of 1,8-diaminonaphthalene (1.58 g, 10 mmol) and cyclododecanone (2 g, 11 mmol) in benzene (30 ml) was refluxed for 3 h in the presence of a catalytic amount of *p*-toluenesulfonic acid. During this time 10 ml of benzene was distilled off azeotropically. The solution was cooled to 0°C, and treated with DIBAH in *n*-hexane (70 ml, 70 mmol) at 0°C. Upon warming to 25°C, the white-brown suspension turned to a solution. Stirring was continued at 25°C for 45 min. Then the reaction mixture was worked up in a similar manner as described for preparation of 1, and purified by column chromatography on silica gel (benzene-hexane, 1:1, then only benzene) to furnish the title compound (3.225 g, 98% yield) as pink crystals: tlc,  $R_f$  0.50 (benzene); ir ( $\text{CHCl}_3$ ) 3397, 1595, 1534, 1306, 1135, 1106  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.34 - 7.32 (6H, m, Aryl CH), 4.74 (3H, br s, NH), 3.34 - 3.67 (1H, m, NCH),

1.39 (22H, br s, CCH<sub>2</sub>C); mass  $m/z$  324.262 (Calcd for C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>, 324.257).

N,N'-Dicyclododecyl-1,8-diaminonaphthalene. A mixture of N-cyclododecyl-1,8-diaminonaphthalene (648 mg, 2 mmol), cyclododecanone (400 mg, 2.2 mmol), and a catalytic amount of *p*-toluenesulfonic acid in toluene (30 ml) was refluxed for 10 h. Water was removed azeotropically with 10 ml of toluene. The mixture was then cooled to 0°C and treated with DIBAH in *n*-hexane (12 ml, 12 mmol) at 0°C for 30 min, then at 25°C for 12 h. The reaction was terminated in a usual manner with benzene (30 ml), water (0.65 ml), and anhydrous magnesium sulfate (6 g). Filtration, and washing of the residue with hot benzene gave the green filtrates, which was concentrated and purified by column chromatography on silica gel (benzene-hexane, 1:2) to afford the title compound (820 mg, 84% yield) as light brown crystals: tlc,  $R_f$  0.47 (benzene, 1:2); ir (CHCl<sub>3</sub>) 3376, 1591, 1473, 1446, 1112 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  6.44 - 7.28 (6H, m, Aryl CH), 5.18 (2H, br s, NH), 3.46 (2H, m, NCH); mass  $m/z$  490.435 (Calcd for C<sub>34</sub>H<sub>54</sub>N<sub>2</sub>, 490.429).

1-Heptyl-2-phenyl-2,3-dihydroperimidine. A solution of benzaldehyde (2.2 mg, 2 mmol) in benzene (2 ml) was added dropwise to a solution of N-heptyl-1,8-diaminonaphthalene (512 mg, 2 mmol) in benzene (8 ml) at 0°C. Stirring was continued at 25°C for 10 h. Then the solvent was evaporated, and the residue was subjected to column chromatography on silica gel (ether-hexane, 1:9) to furnish the title compound

(653 mg, 95% yield) as a colorless oil: tlc,  $R_f$  0.38 (ether-hexane, 1:9, 2 developments); ir (liquid film) 3440, 1583, 1466, 1420, 1373, 1275, 1163, 1080, 805, 760  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.17 - 7.47 (6H, m, Aryl CH), 5.22 (1H, s, NCHN), 4.40 (1H, br s, NH), 2.58 - 3.35 (2H, m,  $\text{NCH}_2$ ); mass  $m/z$  344.224 (Calcd for  $\text{C}_{24}\text{H}_{28}\text{N}_2$ , 344.225).

N-Benzyl-N'-heptyl-1,8-diaminonaphthalene. The crude 1-heptyl-2-phenyl-2,3-dihydroperimidine, obtained above, was dissolved in benzene (5 ml) and treated with DIBAH in n-hexane (12 ml, 12 mmol) at 25°C. The resulting mixture was refluxed for 30 min, and worked up in a usual manner. Purification of the crude diamine by column chromatography on silica gel (benzene-hexane, 1:1) gave the title compound (587 mg, 85% yield) as light red crystals: tlc,  $R_f$  0.39 (ether-hexane, 1:10); ir ( $\text{CHCl}_3$ ) 3388, 1597, 1144, 1118  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.37 - 7.38 (6H, m, Aryl CH), 5.50 (2H, br s, NH), 4.14 (2H, s,  $\text{PhCH}_2\text{N}$ ), 2.88 (2H, t,  $J = 6.2$  Hz,  $\text{CCH}_2\text{N}$ ); mass  $m/z$  346.248 (Calcd for  $\text{C}_{24}\text{H}_{30}\text{N}_2$ , 346.241).

N,N'-Decamethylenebis(1,8-diaminonaphthalene) (9).

1,10-Decanedial (1.70 g, 10 mmol) in benzene (20 ml) was added dropwise to a solution of 1,8-diaminonaphthalene (3.16 g, 20 mmol) in benzene (80 ml) at 25°C, and the resulting mixture was stirred at 25°C for 2 h. The water was then removed azeotropically with 20 ml of benzene. The residual solution was treated with DIBAH in n-hexane (80 ml, 80 mmol) at 0°C. Further stirring was continued at 25°C for 3 h, and the mixture was worked up by the  $\text{NaF-H}_2\text{O}$  method. Filtration,

washing of the residue with chloroform, and purification of the concentrated filtrates by column chromatography on silica gel ( $\text{CH}_2\text{Cl}_2$ -hexane, 2:1, then 3:1) to give 9 (3.860 g, 85% yield) as pink crystals: tlc,  $R_f$  0.28 ( $\text{CH}_2\text{Cl}_2$ -benzene, 2:1) mp 104.5 - 105.5°C (recrystallized from benzene-hexane); ir ( $\text{CHCl}_3$ ) 3400, 1590, 1295, 1130, 1100  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  6.37 - 7.41 (12H, m, Aryl CH), 4.72 (6H, br s, NH), 3.06 (4H, t,  $\text{NCH}_2$ ), 1.13 - 1.93 (16H, br s,  $\text{CCH}_2\text{C}$ ); mass  $m/z$  454.304 (Calcd for  $\text{C}_{30}\text{H}_{38}\text{N}_4$ , 454.310).

The Macrocyclic Tetramine 10. The tetramine 9 (454 mg, 1 mmol) in chloroform-benzene (40 ml, ratio = 1/3), and 1,10-decanedial in benzene (40 ml) were added separately and simultaneously to refluxing benzene (40 ml) over 75 min. The resulting water was distilled off azeotropically with 10 ml of benzene. The residual solution was then cooled to 0°C, and DIBAH in *n*-hexane was added at this temperature. Further stirring was carried out at 25°C for 15 h. The reaction mixture was worked up by the NaF- $\text{H}_2\text{O}$  method. Filtration, washing of the residue with hot benzene, and purification of the concentrated filtrates by column chromatography on silica gel (hot benzene) gave 10 (237 mg, 40% yield) as white crystals: tlc,  $R_f$  0.41 ( $\text{CH}_2\text{Cl}_2$ -hexane, 1:1); mp 198 - 199°C (Recrystallized from benzene); ir (nujol) 3333, 1580, 1292, 1150, 1086, 790, 742  $\text{cm}^{-1}$ ; pmr (benzene- $d_6$ , at 50°C)  $\delta$  6.48 - 7.46 (12H, m, Aryl CH), 2.90 (8H, t,  $\text{NCH}_2$ ), 1.18 - 1.66 (32H, br s,  $\text{CCH}_2\text{C}$ ), 0.42 (4H, nr s, NH); mass  $m/z$  592.917 (Calcd for  $\text{C}_{40}\text{H}_{56}\text{N}_4$ , 592.919).

Tetracyclic tetramine 12. Aqueous 40% glyoxal (290 mg, 2 mmol) in methanol (2 ml) was added dropwise to 1,4,8,11-tetraazacyclotetradecane (400 mg, 2 mmol) in methanol (15 ml) at 0°C. The reaction was over immediately. Further stirring was continued at 0°C for 30 min. Then the solvent was evaporated, and the residue was directly applied to column chromatography on silica gel (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:30) to give 12 (426 mg, 97% yield) as light yellow crystals<sup>11</sup>: tlc, R<sub>f</sub> 0.35 (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:19); ir (liquid film) 1460, 1440, 1356, 1340, 1295, 1143, 1100, 890, 820, 742 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>) δ 3.00 (2H, s, NCHN), 1.73 - 3.87 (18H, m), 0.91 - 1.50 (2H, m); cmr (CHCl<sub>3</sub>, ppm from TMS) 77.15 (NCN), 44.91, 52.58, 54.51, 56.10 (NC), 19.73 (C-C-C), mass m/z 222.183 (Calcd for C<sub>12</sub>H<sub>22</sub>N<sub>4</sub>, 222.184).

1,5,8,12-Tetraazabicyclo[10.2.2]hexdecane (13). DIBAH in n-hexane (150 ml, 150 mmol) was added dropwise to the tetramine 12 (1.11 g, 5 mmol) at 0°C and the resulting solution was allowed to warm to 25°C. Then n-hexane was replaced by toluene (70.7 ml). This solution was refluxed for 4 days. The reaction mixture was cooled to 0°C, and worked up in a usual manner with benzene (300 ml), sodium fluoride (25.2 g) and water (8.1 ml). Filtration, washing of the residue with ethanol, and purification of the concentrated filtrates by column chromatography on silanized silica gel (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:9) gave 13 (1.085 g, 96% yield) as a colorless oil: silanized tlc, R<sub>f</sub> 0.29 (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:9); ir (liquid film) 3280 cm<sup>-1</sup> (NH); pmr (CDCl<sub>3</sub>) δ 2.12 -

3.87 (22H, m, NCH<sub>2</sub>, NH), 1.44 - 1.93 (4H, m, CCH<sub>2</sub>C); cmr (CDCl<sub>3</sub>, ppm from TMS) 50.02, 51.69, 57.42 (NC), 25.98 (C-C-C); mass  $m/z$  226.212 (Calcd for C<sub>12</sub>H<sub>26</sub>N<sub>4</sub>, 226.216).

1,5,8,12-Tetraazatricyclo[10.2.2.2<sup>5,8</sup>]octadecane (15).

A solution of oxalyl chloride (140 mg, 1.1 mmol) in dichloromethane (2 ml) was added dropwise over 30 min at 0°C to a stirred solution of the tetramine 13 (226 mg, 1 mmol). During this operation, a white precipitate has appeared. Stirring was continued at 0°C for 1 h. Then the solvent was evaporated and the residue was directly applied to column chromatography on silica gel (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:20) to furnish the diamide 14 (117 mg, 42% yield); tlc,  $R_f$  0.56 (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:9).

A solution of DIBAH in n-hexane (2 ml, 2 mmol) was added dropwise to the diamide 14 at 0°C, and the resulting solution was stirred at 25°C for one day. Then the reaction was quenched at 0°C in a usual manner with benzene (6 ml), sodium fluoride (336 mg), and water (0.1 ml). Filtration, washing of the white precipitate with ethanol, and purification by column chromatography on silanized silica gel (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:4) afforded 15 (35 mg, 80% yield): silanized tlc  $R_f$  0.4 (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:2); pmr (CDCl<sub>3</sub>)  $\delta$  2.04 - 3.91 (24H, m, NCH<sub>2</sub>), 1.37 - 2.04 (4H, m, CCH<sub>2</sub>C); cmr (CDCl<sub>3</sub>, ppm from TMS) 49.58, 56.01 (NC), 23.87 (C-C-C); mass  $m/z$  252.227 (Calcd for C<sub>14</sub>H<sub>28</sub>N<sub>4</sub>, 252.231).

N,N'-Dimethyl derivative of 13. Aqueous 37% formaldehyde (0.2 ml, 2.5 mmol) and sodium cyanoborohydride (50 mg,

0.8 mmol) were added successively to a stirred solution of the tetramine 13 (56 mg, 0.25 mmol) in acetonitrile (1.5 ml) at 25°C. Stirring was continued for 5 h at 25°C. During this period, the reaction mixture was kept neutral by the addition of acetic acid (8 drops). Evaporation of the solvent left the viscous oil, which was directly subjected to column chromatography on silica gel (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:7) to furnish the title compound (62 mg, 98% yield) as a colorless oil: ir (liquid film) 1682, 1469, 1360, 1136, 1070, 752 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>) δ 2.21, 2.44, (6H, s, NCH<sub>3</sub>); cmr (CDCl<sub>3</sub>, ppm from TMS) 23.95, 42.01, 46.41, 51.61, 56.45, 56.89; mass m/z 254.243 (Calcd for C<sub>14</sub>H<sub>30</sub>N<sub>4</sub>, 254.247).

Di-p-toluenesulfonamide of 13. p-Toluenesulfonyl chloride (210 mg, 1.1 mmol) was added portionwise to a solution of the tetramine 13 (113 mg, 0.5 mmol) and triethylamine (0.28 ml, 2 mmol) in dichloromethane (3 ml) at 0°C. The ice bath was removed, and further stirring was continued at 25°C for 2 h. Evaporation of the solvent, and purification of the residue by column chromatography on silica gel (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:30) furnished the title compound (191 mg, 72% yield) as white crystals: tlc, R<sub>f</sub> 0.39 (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:19); ir (Nujol) 1505, 1607 cm<sup>-1</sup> (C=C), 1166, 1348 cm<sup>-1</sup> (SO<sub>2</sub>); pmr (CDCl<sub>3</sub>) δ 7.07 - 7.85 (8H, m, Aryl CH), 2.21 - 3.52 (20H, m, NCH<sub>2</sub>), 2.44 (6H, s, CH<sub>3</sub>), 1.44 - 2.00 (4H, m, CCH<sub>2</sub>C); cmr (CDCl<sub>3</sub>, ppm from TMA) 21.75, 28.09, 47.82, 48.17, 48.79, 53.28, 127.43, 129.81, 136.59, 143.37; mass m/z 378 (M<sup>+</sup> - Ts-H).

1-Isopropyl-2-methyltetrahydropyrimidine (16). A mixture of N-isopropyl-1,3-diaminopropane (11.6 g, 0.1 mmol) and ethyl acetoacetate (12.76 ml, 0.1 mmol)<sup>14</sup> in the presence of a catalytic amount of p-toluenesulfonic acid monohydrate (10 mg) were heated at 210°C for 5 h. The resulting dark orange viscous oil was directly distilled under reduced pressure to give 16 (7.81 g, 56% yield) as a colorless oil: bp 104.5°C/22 mmHg; ir (liquid film) 1635, 1443, 1320, 1220, 1145, 1025, 948  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  3.97 (1H, h,  $J = 6.8$  Hz, NCH), 2.93 - 3.47 (4H, m,  $\text{NCH}_2$ ), 1.99 (3H, s,  $\text{N}=\text{CCH}_3$ ), 1.53 - 2.13 (2H, m,  $\text{CCH}_2\text{C}$ ), 1.18 (6H, d,  $J = 6.8$  Hz,  $\text{C}(\text{CH}_3)_2$ ); mass  $m/z$  140.142 (Calcd for  $\text{C}_8\text{H}_{16}\text{N}_2$ , 140.131).

N-Ethyl-N'-isopropyl-1,3-diaminopropane (17). A solution of DIBAH in n-hexane (12 ml, 12 mmol) was added dropwise to 16 at 0°C, and the resulting solution was stirred at 25°C for one day, then under reflux for 30 min. The mixture was worked up in a usual way with benzene (12 ml), sodium fluoride (2 g), and water (0.65 ml). Purification of the crude diamine by column chromatography on silica gel (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:7) gave 17 (278 mg, 97% yield) as a colorless oil: tlc,  $R_f$  0.33 (i-PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:5); bp 111 - 114°C (29 mmHg, Bath temp.); ir (liquid film) 3448, 1465, 1306, 1177, 1135  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  3.10 - 3.73 (1H, m, NCH), 2.43 - 3.00 (6H, m,  $\text{NCH}_2$ ), 2.30 (2H, s, NH), 1.48 - 1.97 (2H, m,  $\text{CCH}_2\text{C}$ ), 1.09 (3H, t,  $J = 7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.07 (6H, d,  $J = 7.0$  Hz,  $\text{C}(\text{CH}_3)_2$ ); mass  $m/z$  144.165 (Calcd for  $\text{C}_8\text{H}_{20}\text{N}_2$ , 144.163).

1-Benzyl-2-propyl-4,5-dihydroimidazole (18). A mixture of N-benzylethylenediamine (7.5 g, 50 mmol) and ethyl butyrate (7.9 g, 50 mmol)<sup>24</sup> in the presence of p-toluenesulfonic acid monohydrate (5 mg) was heated at 210°C for 5 h. The mixture was allowed to cool to 25°C and then distilled under reduced pressure to give 18 (6.89 g, 68% yield) as a light yellow oil: tlc  $R_f$  0.33 (i-PrNH<sub>2</sub>-ether, 1:20); bp 124 - 126°C/0.3 mmHg; ir (liquid film) 1668, 1620, 1452, 1425, 1213, 989, 728, 690 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  7.30 (5H, s, Aryl CH), 4.26 (2H, s, PhCH<sub>2</sub>N), 2.92 - 3.92 (4H, m, NCH<sub>2</sub>CH<sub>2</sub>N), 2.05 - 2.47 (2H, m, N=CCH<sub>2</sub>), 1.38 - 1.95 (2H, m, N=C-C-CH<sub>2</sub>), 0.98 (3H, t,  $J$  = 7.0 Hz, CH<sub>3</sub>); mass  $m/z$  202.152 (Calcd for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>, 202.147).

N-Benzyl-N'-butylethylenediamine (21). The reduction of 18 (202 mg, 1 mmol) with DIBAH in n-hexane (6 ml, 6 mmol) was carried out at 25°C for 1 h, then under reflux for 1 h. The reaction mixture was worked up in a usual manner with sodium fluoride and water. Purification of the crude diamine by column chromatography on silica gel (i-PrNH<sub>2</sub>-ether, 1:30) gave 21 (196 mg, 95% yield) as a colorless oil: tlc,  $R_f$  0.44 (i-PrNH<sub>2</sub>-ether, 1:20); bp 148 - 151°C (0.45 mmHg, Bath temp.); ir (liquid film) 3350, 1478, 1126, 738, 200 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  7.34 (5H, s, Aryl CH), 3.79 (2H, s, PhCH<sub>2</sub>), 2.75 (4H, s, NCH<sub>2</sub>CH<sub>2</sub>N), 2.57 (2H, t,  $J$  = 6.2 Hz, NCH<sub>2</sub>), 1.77 (2H, s, NH), 1.12 - 1.66 (4H, m, CCH<sub>2</sub>C), 0.72 - 1.12 (3H, m, CH<sub>3</sub>); mass  $m/z$  206.174 (Calcd for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>, 206.178).

1-Benzyl-2-methylbenzimidazole (19). Benzyl chloride (0.92 ml, 8 mmol) was added dropwise to a methanolic solution (5 ml) of 2-methylbenzimidazole (396 mg, 3 mmol) at 25°C, and the resulting mixture was refluxed for 40 h. Then the solvent was evaporated. The residue was washed with saturated sodium bicarbonate, and extracted with chloroform. Purification of the concentrated extracts by column chromatography on silica gel (ethyl acetate) gave 19 (176 mg, 26% yield) as a brown oil: tlc,  $R_f$  0.37 (ethyl acetate); pmr ( $CDCl_3$ )  $\delta$  6.84 - 7.80 (9H, m, Aryl CH), 5.16 (2H, s,  $NCH_2$ ), 2.46 (3H, s,  $CH_3$ ); mass  $m/z$  222.290 (Calcd for  $C_{15}H_{14}N_2$ , 222.292).

N-Benzyl-N'-ethyl-o-phenylenediamine (22). A solution of DIBAH in *n*-hexane (4.46 ml, 4.46 mmol) was added dropwise to 19 (164 mg, 0.74 mmol) at 0°C. Stirring was continued at 25°C for 16 h. Then the mixture was worked up by the sodium fluoride-water method. Column chromatography of the crude diamine on silica gel (ethyl acetate-hexane, 1:6, then 1:4) furnished 22 (162 mg, 97% yield) as a yellow oil: tlc,  $R_f$  0.70 (ethyl acetate); pmr ( $CDCl_3$ )  $\delta$  6.45 - 7.46 (9H, m, Aryl CH), 4.18 (2H, s,  $PhCH_2N$ ), 3.23 (2H, br s, NH), 3.04 (2H, q,  $J = 7.2$  Hz,  $NCH_2CH_3$ ), 1.19 (3H, t,  $J = 7.2$  Hz,  $CH_3$ ); mass  $m/z$  226.317 (Calcd for  $C_{15}H_{18}N_2$ , 226.324).

N-Propyl-1,8-diamoninaphthalene (23). A solution of DIBAH in *n*-hexane (7 ml, 7 mmol) was added dropwise to a solution of 2-ethylperimidine<sup>25</sup> (196 mg, 1 mmol) in benzene (3.5 ml) at 0°C, and the resulting mixture was refluxed for

15 h. Work-up with NaF-H<sub>2</sub>O, followed by the purification of the crude diamine by column chromatography on silica gel (benzene) gave 23 (167 mg, 84% yield) as a purple oil: tlc, R<sub>f</sub> 0.45 (benzene); ir (liquid film) 3340, 3300, 2925, 1588, 1510, 1408, 1132, 782, 727 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>) δ 6.29 - 7.23 (6H, m, Aryl CH), 4.64 (3H, br s, NH), 2.93 (2H, t, J = 7.2 Hz, NCH<sub>2</sub>), 1.60 (2H, hexset, J = 7.2 Hz, N-C-CH<sub>2</sub>), 0.92 (3H, t, J = 7.2 Hz, CH<sub>3</sub>); mass m/z 200.289 (Calcd for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>, 200.286).

Reduction of 2-methylbenzimidazole with DIBAH. A solution of DIBAH in *n*-hexane (7 ml, 7 mmol) was added dropwise to 2-methylbenzimidazole (132 mg, 1 mmol) at 0°C. The resulting mixture was heated to reflux for 5 h. After removal of the solvent under reduced pressure, the mixture was further heated at 50°C for 1 h, then at 140°C for 4 h to give only the recovery of the starting material.

1,2-Bis-(2-tetrahydropyrimidyl)ethane (24). The di-*p*-toluenesulfonate of 24 was prepared from succinonitrile, 1,3-diaminopropane, and its di-*p*-toluenesulfonate. Recrystallization from 95% ethanol gave the white needle crystals: mp 270 - 272°C (lit.<sup>17</sup> 285°C). The di-*p*-toluenesulfonate (5.38 g, 10 mmol) of 24, thus obtained, was treated with sodium methoxide (1.188 g, 22 mmol) in methanol (20 ml) at 0°C for 20 min. Evaporation of methanol, and addition, followed by evaporation of chloroform to remove a trace methanol left the white solid, which was washed with hot benzene several times to afford 24 (1.876 g, 97% yield) as

white crystals: mp 194 - 197°C (Recrystallized from benzene, lit.,<sup>17</sup> 200°C (decomp.)); pmr (CDCl<sub>3</sub>) δ 7.31 (2H, s, NH), 3.27 (8H, t,  $J = 5.8$  Hz, NCH<sub>2</sub>), 2.42 (4H, s, CH<sub>2</sub>CH<sub>2</sub>), 1.43 - 2.00 (4H, m, CCH<sub>2</sub>C); mass  $m/z$  194.154 (Calcd for C<sub>10</sub>H<sub>18</sub>N<sub>4</sub>, 194.153).

Spermine from 24. A solution of DIBAH in *n*-hexane (16 ml, 16 mmol) was added to bis-amidine 24 (194 mg, 1 mmol) at 0°C. The solvent was evaporated, and the residue was heated at 150°C for 11 h. The reaction mixture was then cooled to 25°C, diluted with benzene, and worked up by the NaF-H<sub>2</sub>O method. Purification of the crude product by column chromatography on silica gel (aq. EtNH<sub>2</sub>-MeOH, 1:3) gave spermine (29 mg, 14% yield) as a colorless oil: bp 172 - 176°C (40 mmHg, Bath temp. (Authentic sample, 150°C/5 mmHg)); ir (liquid film) 3997, 3307, 1620, 1487, 1382, 1140 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>) δ 2.46 - 2.93 (12H, m, NCH<sub>2</sub>), 1.53 (6H, s, NH), 1.33 - 1.88 (8H, m, CCH<sub>2</sub>C); mass  $m/z$  202.218 (Calcd for C<sub>10</sub>H<sub>20</sub>N<sub>4</sub>, 202.216). This product was dissolved in ethanol and treated with concentrated hydrochloric acid to give the ammonium salt as white solids, which was recrystallized from 12% HCl-EtOH: mp 309 - 311°C (lit.<sup>26</sup> 310 - 311°C (dec.)).

Spermine from bis-trimethylsilylamide of 24. A mixture of bis-amide 24 (388 mg, 2 mmol) and hexamethyldisilazane (6.5 ml, 30 mmol) was refluxed gently in the presence of fuming sulfuric acid (1 drop) for 12 h.<sup>18</sup> Then excess hexamethyldisilazane was evaporated under reduced pressure, and a solution of DIBAH in *n*-hexane (24 ml, 24 mmol) was added at

0°C. The solvent was replaced by xylene (11 ml), and the resulting solution was refluxed for 3 days. Usual work-up, followed by purification of the crude product as described above afforded spermine (254 mg, 63% yield).

General Method for Preparation of Cyclic Polyamines.

Cyclic polyamines were prepared by the reduction of cyclic amidines with DIBAH in toluene (1.0 M) under reflux. Synthesis of 1,5-diazacycloundecane (27) from DBU (26) is representative.

1,5-Diazacycloundecane (27). A solution of DIBAH in toluene (12 ml, 12 mmol) was added to DBU (304 mg, 2 mmol) at 0°C. The resulting colorless solution was heated to reflux for 7 h. At this stage, analysis of the reaction mixture by tlc indicated complete or nearly complete consumption of the starting material. The solution was diluted with benzene (36 ml), treated successively with sodium fluoride (2.016 g, 48 mmol) and water (0.65 ml, 36 mmol) at 0°C, and stirred vigorously at 25°C for 20 min. Filtration, washing of the residue with hot chloroform, and removal of the solvent left the essentially pure 27, which was further purified by preparative tlc (aq. EtNH<sub>2</sub>-MeOH, 1:4) to furnish the pure diamine 27 (300 mg, 96% yield) as a colorless oil: tlc, R<sub>F</sub> 0.31 (aq. EtNH<sub>2</sub>-MeOH, 1:4); ir (liquid film) 3339, 760 cm<sup>-1</sup> (NH), 1157 cm<sup>-1</sup> (CN); pmr (CDCl<sub>3</sub>) δ 2.90 (2H, s, NH), 2.80 (4H, t, J = 4.8 Hz, NCH<sub>2</sub>); 2.44 - 2.87 (4H, m, NCH<sub>2</sub>), 1.26 - 1.75 (10H, br s, CCH<sub>2</sub>C); cmr (CDCl<sub>3</sub>, ppm from TMS) 25.72, 25.89, 26.95, 28.71, 29.06, 48.61, 50.46, 53.37,

53.63; mass  $m/z$  156.166 (Calcd for  $C_9H_{20}N_2$ , 156.163).

The syntheses of other cyclic polyamines starting from the corresponding cyclic amidines were carried out in a similar manner as described above. The physical properties and analytical data of these cyclic polyamines are listed in Table III.

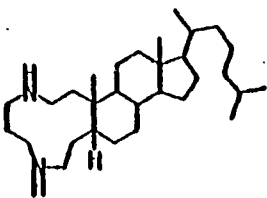
N-(3-Aminopropyl)hexamethyleneimine (28). A solution of DIBAH in *n*-hexane (16 ml, 16 mmol) was added dropwise to  $\epsilon$ -(N-cyanoethyl)caprolactam (332 mg, 2 mmol) at 0°C. Stirring was continued at 25°C for 10 h, then under reflux for 1 h. The solution was diluted and worked up with sodium fluoride (2.688 g, 64 mmol) and water (0.86 ml, 48 mmol). Filtration, washing of the residue with hot chloroform, and purification of the concentrated filtrate by column chromatography on silica gel (aq.  $NH_3$ -MeOH, 1:8) gave 28 (170 mg, 55% yield): tlc,  $R_f$  0.35 (aq.  $NH_3$ -MeOH, 1:5); bp 144 - 148°C (3.8 mmHg, Bath temp.); pmr ( $CDCl_3$ )  $\delta$  2.39 - 2.85 (8H, m,  $NCH_2$ ), 1.41 - 1.79 (12H, br s,  $CCH_2C$  and  $NH_2$ ); cmr ( $CDCl_3$ , ppm from TMS) 27.12, 28.27, 31.62, 41.04, 55.75, 56.26; mass  $m/z$  156.164 (Calcd for  $C_9H_{20}N_2$ , 156.163).

N,N'-Dimethyl-1,5-diazacycloundecane. The diamine 27 (780 mg, 5 mmol) in acetonitrile (30 ml) was treated successively with aq. 37% formaldehyde (4.05 ml, 50 mmol) and sodium cyanoborohydride (754 gm, 12.5 mmol) at 25°C. The mixture was stirred at 25°C for 1 h. Then glacial acetic acid (25 drops) was added dropwise at 25°C to neutralize the reaction mixture. Further stirring was continued at 25°C

Table III. Physical Properties and Analytical Data of Cyclic Polyamines

Cyclic Polyamine (m,n) or (k,l,n)	Physical Properties	Ir (cm <sup>-1</sup> ) <sup>a</sup>	Pmr (δ)	Cmr (ppm from TMS)	Mass (m/z)
(4,2)	128-133°C/24 mmHg <sup>b</sup>	3355 (NH) 1138 (CN)	2.59-3.00 (4H, m, NCH <sub>2</sub> ), 2.74 (4H, s, NCH <sub>2</sub> CH <sub>2</sub> N), 2.31 (2H, s, NH), 1.41-1.83 (6H, m, CCH <sub>2</sub> C)		128.135 (Calcd for C <sub>7</sub> H <sub>16</sub> N <sub>2</sub> 128.131)
(7,2)	132-135°C/0.5 mmHg <sup>b</sup>	3424 (NH) 1133 (CN)	2.50-2.78 (4H, m, NCH <sub>2</sub> ), 2.68 (4H, s, NCH <sub>2</sub> CH <sub>2</sub> N), 1.77 (2H, s, NH), 1.19-1.62 (12H, br s, CCH <sub>2</sub> C)	21.12, 24.57, 26.68 45.27, 46.32	170.179 (Calcd for C <sub>10</sub> H <sub>22</sub> N <sub>2</sub> , 170.178)
(7,3)	159-162°C/3.6 mmHg <sup>b</sup>	3303 (NH) 1136 (CN)	2.25-2.80 (10H, m, NCH <sub>2</sub> & NH), 1.13-1.79 (14H, br s, CCH <sub>2</sub> C)	24.40, 26.24, 27.65 45.27, 46.32	184.200 (Calcd for C <sub>11</sub> H <sub>24</sub> N <sub>2</sub> , 184.194)
(11,2)	159-161°C/0.6 mmHg <sup>b</sup>	3335 (NH) <sup>c</sup> 1164 (CN)	2.48-2.72 (4H, m, NCH <sub>2</sub> ), 2.68 (4H, s, NCH <sub>2</sub> ), 1.65 (2H, s, NH) 1.17-1.68 (20H, br s, CCH <sub>2</sub> C)	25.54, 26.24, 26.95 27.12, 29.06, 48.44 48.88	226.247 (Calcd for C <sub>14</sub> H <sub>30</sub> N <sub>2</sub> , 226.241)
(11,3)	165-168°C/0.9 mmHg <sup>b</sup>	3315 (NH) 1133 (CN)	2.45-2.88 (8H, m, NCH <sub>2</sub> ), 1.85 (2H, s, NH), 1.15-1.58 (22H, br s, CCH <sub>2</sub> C)	24.92, 25.54, 26.24 26.60, 28.53, 48.52 48.79	240.260 (Calcd for C <sub>15</sub> H <sub>32</sub> N <sub>2</sub> , 240.257)
(6,8,2)	mp 47-49°C (ether)	3318 (NH) 1136 (CN)	2.76 (8H, s, NCH <sub>2</sub> CH <sub>2</sub> N), 2.57 (8H, br t, J=5.0 Hz, NCH <sub>2</sub> ) 1.56 (4H, br s, NH), 1.08-1.73 (24H, br s, CCH <sub>2</sub> C)	27.04, 27.39, 29.50 29.94, 30.29, 48.88, 49.49	339.955 (Calcd for C <sub>20</sub> H <sub>44</sub> N <sub>4</sub> , 340.357)

Table III. (Continued)

Cyclic Polyamine (m,n) or (k,l,n)	Physical Properties	Ir (cm <sup>-1</sup> ) <sup>a</sup>	Pmr (δ)	Cmr (ppm from TMS)	Mass (m/z)
(12,8,2)	mp 71-72°C (ether)	3342 (NH) 1145 (CN)	2.68 (8H, s, NCH <sub>2</sub> CH <sub>2</sub> N), 2.59 (8H, t, J=6.0 Hz, NCH <sub>2</sub> ), 1.94 & 1.72 (4H, br s, NH), 1.04- 1.65 (36H, br s, CCH <sub>2</sub> C)	27.12, 29.41, 30.03 48.96, 49.41	424.445 (Calcd for C <sub>26</sub> H <sub>56</sub> N <sub>4</sub> , 424.451)
	mp 138.5-140°C (i-PrNH <sub>2</sub> )	3297 (NH) <sup>d</sup> 1132 (CN)	2.30-3.10 (10H, NCH <sub>2</sub> & NH), 0.65, 0.73, 0.83, 0.92, (15H, four s, CH <sub>3</sub> )	12.15, 16.64, 18.93, 21.58, 22.81, 23.07, 24.04, 24.57, 28.62, 31.26, 32.14, 35.67, 36.02, 36.37, 39.72, 39.98, 40.33, 42.45, 42.71, 46.15, 47.38, 49.85, 56.45, 56.80	444.444 (Calcd for C <sub>30</sub> H <sub>56</sub> N <sub>2</sub> , 444.444)

- a) Unless otherwise specified, the ir spectra were taken as a liquid film.  
 b) Bath temperature.  
 c) Nujol mull.  
 d) Chloroform solution.

for 2 h. Evaporation of the solvents, followed by purification of the residue by column chromatography on silica gel ( $i$ -PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:20) gave  $N,N'$ -dimethyl-1,5-diazacycloundecane (825 mg, 90% yield) as a colorless oil: tlc,  $R_f$  0.40 ( $i$ -PrNH<sub>2</sub>-CHCl<sub>3</sub>, 1:9); ir (liquid film) 1471, 1460 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  2.21 - 2.57 (8H, m, NCH<sub>2</sub>), 2.12 (6H, s, NCH<sub>3</sub>), 1.30 - 1.69 (10H, br s, CCH<sub>2</sub>C); cmr (CDCl<sub>3</sub>, ppm from TMS) 24.39, 25.80, 25.98, 42.01, 53.19, 57.24; mass  $m/z$  184.200 (Calcd for C<sub>11</sub>H<sub>24</sub>N<sub>2</sub>, 184.194).

Di- $p$ -toluenesulfonamide of 27. Treatment of the diamine 27 with  $p$ -toluenesulfonyl chloride (2.5 equiv) and triethylamine (5 equiv) in dichloromethane at 0°C for 1 h, then at 25°C for 2 h, followed by purification of the resulting crude product by column chromatography on silica gel (ether-hexane, 1:1) gave the di- $p$ -toluenesulfonamide as white crystals: tlc,  $R_f$  0.29 (ether-hexane, 1:1); ir (nujol) 1340, 1159 cm<sup>-1</sup> (SO<sub>2</sub>); pmr (CDCl<sub>3</sub>)  $\delta$  7.10 - 7.77 (8H, m, Aryl CH), 2.76 - 3.26 (8H, br t, NCH<sub>2</sub>), 2.42 (6H, s, CH<sub>3</sub>), 1.41 - 2.01 (10H, br s, CCH<sub>2</sub>C); mass  $m/z$  309 (M<sup>+</sup> - Ts-H).

General Methods for Preparation of Cyclic Amidines.

Method A. Lactam (10 mmol) was added to a solution of triethyloxonium tetrafluoroborate<sup>27</sup> (11 mmol) in dichloromethane (25 ml) at 25°C, and the resulting mixture was stirred at 25°C for 17 h. Then the mixture was poured onto 5% potassium hydroxide solution (50 ml). The organic layer was separated and washed with cold water three times (3 X 50 ml). Each aqueous layer was washed with dichloromethane.

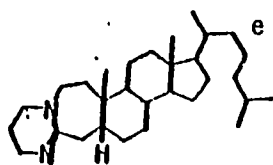
The combined extracts were concentrated to give the imino ether in quantitative yield. Without purification this was dissolved in aziridine<sup>28</sup> (15 mmol)-dichloromethane (3.3 ml), and treated with ammonium bromide (0.2 mmol) at 25°C. Further stirring was continued at 25°C for 30 h to ensue the formation of amidine, which was rearranged by exposure to iodine (0.5 ml) in benzene (15 ml) at 25°C for 4 h, then under reflux for 1 h to furnish the dihydroimidazole after purification by column chromatography on silica gel.

Method B. Lactam (10 mmol) was converted as described above into the imino ether in quantitative yield, which was treated with 3-bromopropylamine hydrobromide (11 mmol) in absolute ethanol (15 ml) at 25°C. Stirring was continued at 25°C for 40 h. Then powdered potassium carbonate (22 mmol) was added at 0°C and the whole mixture was stirred at 0°C for 150 min. Dilution with chloroform (300 ml), filtration, and washing of the residue with chloroform gave the tetrahydropyrimidine after purification by preparative tlc.

Method C. Sodium ethoxide was prepared by dissolving metallic sodium (10 mmol) in absolute ethanol (5 ml), followed by evaporation of excess ethanol. Toluene (30 ml) and lactam (10 mmol) were added at 25°C, and the resulting suspension was heated gently until the clear yellow solution was produced. Then acrylonitrile (100 mmol) was added slowly over 4 h at 25°C with vigorous stirring. Further stirring was carried out at 25°C for 3 h. The mixture was diluted with ethyl acetate to separate the polymer as yellow

Table IV. Physical Properties and Analytical Data of Cyclic Amidines

Amidine <sup>a</sup> (m,n) <sup>b</sup>	Boiling Point (°C/mmHg)	ir (cm <sup>-1</sup> )	pmr (δ)	mass (m/z)
(4,2)	90-93/1.55	1641, 1291, 1010	2.77-3.99 (6H, m, NCH <sub>2</sub> ), 2.16-2.62 (2H, m, N=C-CH <sub>2</sub> ), 1.47-2.08 (4H, m, CCH <sub>2</sub> C)	124.103 (Calcd for C <sub>7</sub> H <sub>12</sub> N <sub>2</sub> , 124.100)
(7,2)	159-161/6.0	1607, 1452, 1004	3.05-3.94 (6H, m, NCH <sub>2</sub> ), 2.08-2.58 (2H, m, N=C-CH <sub>2</sub> ), 1.11-2.08 (10H, m, CCH <sub>2</sub> C)	166.143 (Calcd for C <sub>10</sub> H <sub>18</sub> N <sub>2</sub> , 166.147)
(7,3)	154-159/0.7	1615, 1454, 1374, 1320	2.91-3.53 (6H, m, NCH <sub>2</sub> ), 2.08-2.60 (2H, m, N=C-CH <sub>2</sub> ), 1.10-2.08 (12H, m, CCH <sub>2</sub> C)	180.165 (Calcd for C <sub>11</sub> H <sub>20</sub> N <sub>2</sub> , 180.163)
(11,2)	188-192/5.0	1608, 14391, 1239	2.88-3.91 (6H, m, NCH <sub>2</sub> ), 2.15-2.51 (2H, m, N=C-CH <sub>2</sub> ), 1.21-1.84 (18H, m, CCH <sub>2</sub> C)	222.213 (Calcd for C <sub>14</sub> H <sub>26</sub> N <sub>2</sub> , 222.210)
(11,3)	180-183/0.6	1627, 1451 <sup>d</sup>	2.90-3.43 (6H, m, NCH <sub>2</sub> ), 1.97-2.43 (2H, m, N=C-CH <sub>2</sub> ), 1.07-1.97 (20H, m, CCH <sub>2</sub> C) 3.06-3.43 (6H, m, NCH <sub>2</sub> ), 0.66, 0.82, 0.89, 0.92 (15H, four s, CH <sub>3</sub> )	236.229 (Calcd for C <sub>15</sub> H <sub>28</sub> N <sub>2</sub> , 236.225) 440.415 (Calcd for C <sub>30</sub> H <sub>52</sub> N <sub>2</sub> , 440.413)



- a) The bis-amidines (Entry 8 & 9 in Table II) were characterized by mass spectra: The bis-amidine in Entry 8:  $m/z$  332.290 (Calcd for C<sub>20</sub>H<sub>36</sub>N<sub>4</sub>, 332.294); The bis-amidine in Entry 9:  $m/z$  416.695 (Calcd for C<sub>26</sub>H<sub>48</sub>N<sub>4</sub>, 416.699).  
b) For this abbreviation, see Table II.  
c) Bath temperature.  
d) Nujol.  
e) Cmr (ppm from TMS) 12.24, 18.85, 21.66, 22.02, 22.99, 24.04, 24.39, 28.18, 31.00, 32.23, 34.96, 35.93, 36.37, 38.31, 39.01, 39.72, 40.16, 41.04, 42.45, 42.80, 45.88, 48.35, 48.61, 54.34, 56.45, 162.48.

precipitates. The filtrate was concentrated and directly subjected to column chromatography on silica gel to give N-cyanoethylactam. The N-cyanoethylactam (6.6 mmol) was dissolved in absolute ethanol (165 ml)-chloroform (3.3 ml), and hydrogenated over platinum oxide (50 mg) at 25°C for 9 h. Filtration, washing of the residue with chloroform, and purification of the concentrated filtrate by column chromatography on silica gel gave N-3-aminopropylactam. Titanium tetrachloride (1.5 mmol) was added dropwise to a solution of N-3-aminopropylactam (1 mmol) in xylene (5 ml) at 25°C, and the resulting mixture was refluxed for 9.5 h. The mixture was then cooled to 25°C, and treated with a methanolic solution (5 ml) of sodium hydroxide (6 mmol). Filtration, washing of the residue with chloroform, and purification by column chromatography on silica gel gave the tetrahydropyrimidine.

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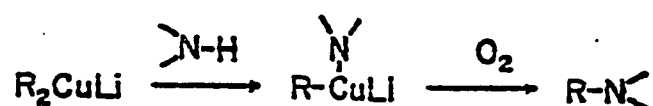
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## Chapter V

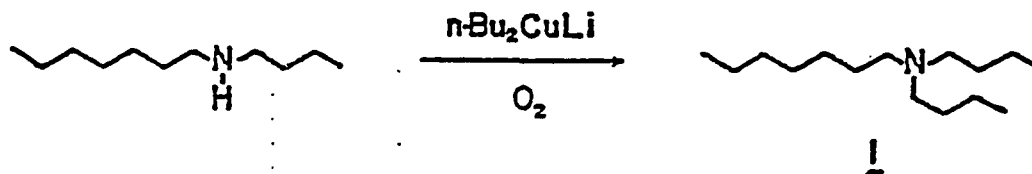
## A Novel N-Alkylation of Amines with Organocopper Reagents

Abstract-----An efficient method for the N-alkylation of amines is described based on the oxidative coupling of lithium alkylcopper amide, which is derived from lithium dialkylcuprates and primary or secondary amines. The high chemospecificity of the method was demonstrated by the selective tert-butylation of m-aminoacetophenone without any protection of the carbonyl group. The present N-alkylation process should be extremely useful for complex or polyfunctional molecules, the reaction conditions being so mild as to minimize the possibility of involvement of most functional or protecting groups.

There is a lack of methodologies which cleanly introduce nitrogen at donor sites.<sup>1</sup> The use of halamine or hydroxyamine derivatives is a classical solution to this problem.<sup>2</sup> Herein we describe an entirely different approach based on the oxidative coupling of lithium alkylcopper amide,<sup>3</sup> which is derived in situ from lithium dialkylcuprates and primary or secondary amines.<sup>4</sup>



In a typical example, butylheptylamine (1 equiv in ether) was added to lithium dibutylcuprate (5 equiv in ether-hexane) at  $-20^\circ\text{C}$ . Stirring was continued at  $-20^\circ\text{C}$  for 2 h.<sup>5</sup> Excess molecular oxygen was bubbled into the suspension via syringe at  $20^\circ\text{C}$  over 5 min. The mixture was then quenched in concentrated ammonium hydroxide and extracted with ethyl acetate. Purification by column chromatography on silica gel (i-PrNH<sub>2</sub>-MeOH = 1:200) gave dibutylheptylamine (1) in 73% yield.<sup>6</sup>



The conditions cited above were crucial for efficient N-alkylation of amines. Under similar conditions without oxygen, only a trace amount of 1 was obtained with the recovery of butylheptylamine. Etheral solvents (diethyl ether or tetrahydrofuran (THF)) were preferable, and less

polar solvents (toluene, or hexane) decreased the yield.<sup>7</sup> The use of ether as solvent with 3 and 1 equiv of lithium dibutylcuprate afforded 1 in yields of 62 and 54%, respectively.<sup>8</sup>

Representative results obtained on oxidation of other alkylcopper amides are listed in Table I. The method seems to be highly effective for the oxidative coupling of amines with primary alkyl and aryl groups.<sup>9</sup> Furthermore, the bulky t-butyl group can also be introduced by this method. Although introduction of tertiary alkyl groups gave poor yields (23-46%), the conversion yields are usually very high (94% yield<sup>10</sup> for m-(t-butylamino)acetophenone (2)). In fact, the classical methods are totally ineffective for such transformations. For t-butylation, the polar solvent system, e.g., THF, is preferable and only the starting amine was recovered in the ether solvent. In some cases (Entry 1 and 5), Grignard reagents were found to give somewhat higher yield of coupling products than the corresponding organolithium compounds.

Application of the method to m-aminoacetophenone led to the desired N-alkylation product 2 without any undesirable complication. Similarly, N-alkylation of m-(1-hydroxyethyl) aniline, and 2-anilinoethanol was achieved successfully without any protection of the hydroxy function.<sup>11</sup> A darkened bond in the formula indicates the bond created by carbon-nitrogen bond forming reactions.

Table I. N-Alkylation Reaction with Organocopper Reagents

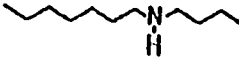
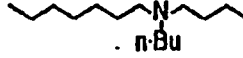

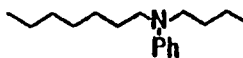
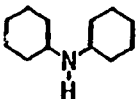
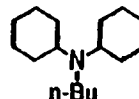


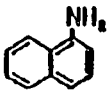
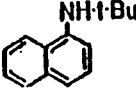
Entry	Amine	RLi for R <sub>2</sub> CuLi (RMgX for RCu)	Reaction Condition <sup>a</sup>	Product	Yield
1		<u>n</u> -BuLi	A		
		MeLi	B		39
		MeMgCl	F		52
		PhLi	C		64
2		<u>n</u> -BuLi	A		38
		<u>n</u> -BuLi	A	(PhCH <sub>2</sub> ) <sub>2</sub> N- <u>n</u> -Bu	62
		<u>t</u> -BuLi	D	(PhCH <sub>2</sub> ) <sub>2</sub> N- <u>t</u> -Bu	26
3	(PhCH <sub>2</sub> ) <sub>2</sub> NH	MeLi	B	(PhCH <sub>2</sub> ) <sub>2</sub> NMe	76
		<u>t</u> -BuLi	D		
4		<u>t</u> -BuLi	D		23

Table I. (Continued)

Entry	Amine	RLi for R <sub>2</sub> CuLi (RMgX for RCu)	Reaction Condition <sup>a</sup>	Product	Yield
5	PhNHMe	<u>n</u> -BuLi	A	PhNMe   <u>n</u> -Bu	57
		MeLi	E	PhNMe   Me	33
		MeMgCl	F <sup>b</sup>		46
		PhLi	C <sup>c</sup>	PhNMe   Ph	72
6	Ph <sub>2</sub> NH	PhLi	C	Ph <sub>2</sub> NPh	94
7	PhNH <sub>2</sub>	<u>t</u> -BuLi	D	PhNH- <u>t</u> -Bu	46 (42 <sup>d</sup> ) 15 (17 <sup>d</sup> , 19 <sup>e</sup> )
8		<u>t</u> -BuLi	D		35

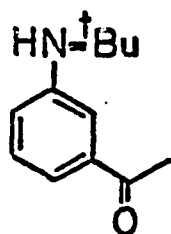
a) A: Ether (-20°C, 2 h), O<sub>2</sub> at -20°C; B: Ether (25°C, 2 h), O<sub>2</sub> at 25°C; C: Ether (reflux, 6 h), O<sub>2</sub> at -78°C;  
 D: THF (-20°C, 2 h), O<sub>2</sub> at -20°C; E: Toluene (0°C, 2 h), O<sub>2</sub> at -78°C; F: THF (25°C, 2 h), O<sub>2</sub> at 25°C;  
 G: THF-HMPA (20:1) (-20°C, 2 h), O<sub>2</sub> at -20°C.

b) Addition of HMPA (10 vol. %).

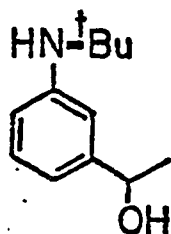
c) Use of THF instead of ether.

d) Use of 1,2-dimethoxyethane (DME).

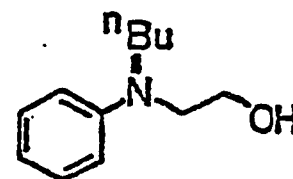
e) Use of DME-HMPA (20:1).



2 (32% (94%)<sup>10</sup>)

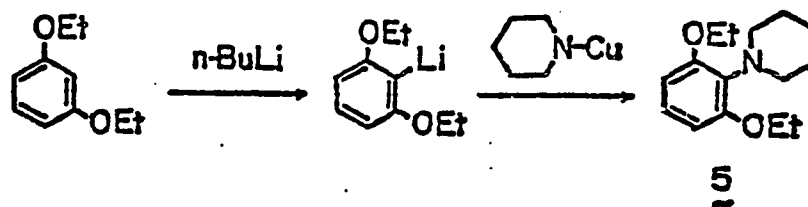


3 (39%)



4 (37%)

The introduction of amino groups to organic substrates (*i.e.*, the reverse methodology described above) was also realized with excess copper amide. Thus, treatment of o,o'-diethoxyphenyl lithium, derived from m-diethoxybenzene and n-butyllithium by metalation,<sup>12</sup> with 5 equiv of copper piperidide (from lithium piperidide and cuprous iodide<sup>13</sup> in THF-hexane under reflux for 2 h, followed by quenching with molecular oxygen gave N-(o,o'-diethoxyphenyl)piperidine (5) in 51% yield. This shows that a wide variety of organolithium compounds and lithium alkylamides can be efficiently coupled in the presence of cuprous iodide with the formation of a new carbon-nitrogen bond under mild conditions.<sup>2</sup>



## Experimental

N-Alkylation of Amines with Organocopper Reagents.

Method A. n-Butyllithium in n-hexane (2.2 M, 4.5 ml, 10 mmol) was added dropwise to a stirred suspension of cuprous iodide (952 mg, 5 mmol) in ether (30 ml) at -20°C (CCl<sub>4</sub>- dry ice bath), and the resulting black suspension was stirred at -20°C for 30 min. Then the starting amine (1 mmol) dissolved in ether (2 ml) was added at -20°C. The whole mixture was further stirred at -20°C for 2 h. The reaction was quenched by the gradual addition of molecular oxygen (150 ml) via syringe at -20°C. The mixture was treated with concentrated ammonium hydroxide (25 ml) for 20 min and extracted with ethyl acetate. Purification of the concentrated crude products by column chromatography on silica gel gave the desired N-butylation product.

Method B. Lithium dimethylcuprate was prepared by the reaction of methyllithium in ether (1.8 M, 5.6 ml, 10 mmol) with cuprous iodide (952 mg, 5 mmol) in ether (30 ml) at 0°C for 30 min. To this suspension was added the starting amine (1 mmol) in ether (2 ml) at 0°C. Further stirring was continued at 25°C for 2 h. Then molecular oxygen (150 ml) was bubbled into the suspension at 25°C. The reaction mixture was worked up in a similar manner as described in the method A to give the desired N-methylamino derivative after purification by column chromatography on silica gel.

Method C. Lithium diphenylcuprate was prepared by treatment of cuprous iodide (952 mg, 5 mmol) in ether (30 ml)

with phenyllithium in ether-benzene (1.6 M, 6.2 ml, 10 mmol ; solvent ratio, 3:7) at 25°C for 30 min. After the starting amine (1 mmol) in ether (2 ml) was added at 25°C, the whole mixture was heated to reflux for 6 h. Then the mixture was cooled to -78°C and treated with molecular oxygen (150 ml) at -78°C. Usual work-up, followed by purification gave the aniline derivative.

Method D. The reaction was carried out according to the method A except the use of t-butyllithium in pentane (1.42 M, 7 ml, 10 mmol) and THF as the solvent.

Method E. The N-methylamino derivative was prepared by treatment of the starting amine in toluene (2 ml) with lithium dimethylcuprate (5 mmol) in ether-toluene, followed by oxidative work-up at -78°C.

Method F. Methylcopper was prepared by the reaction of methylmagnesium chloride in THF (2.8 M, 2.1 ml, 6 mmol) with cuprous iodide (952 mg, 5 mmol) in THF (30 ml) at 0°C for 30 min. The starting amine (1 mmol) in THF (2 ml) was added at 0°C and the resulting mixture was further stirred at 25°C for 2 h. Usual work-up and purification gave the desired N-methylamine derivative.

Dibutylheptylamine: ir (liquid film) 1473, 1382, 1095  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  2.41 (6H, br t,  $\text{NCH}_2$ ), 1.02 - 1.75 (18H, m,  $\text{CCH}_2\text{C}$ ), 0.72 - 1.15 (9H, br t,  $\text{CH}_3$ ); mass m/z (%) 227 (11), 184 (100), 142 (72); exact mass m/z 227.265 (Calcd for  $\text{C}_{15}\text{H}_{33}\text{N}$ , 227.261).

Butylheptylmethylamine: pmr (CDCl<sub>3</sub>)  $\delta$  2.06 - 2.56 (4H, m, NCH<sub>2</sub>) 2.20 (3H, s, NCH<sub>3</sub>); mass  $\underline{m/z}$  (%) 185 (13) 142 (59), 100 (100); exact mass  $\underline{m/z}$  185,211 (Calcd for C<sub>12</sub>H<sub>27</sub>N, 185.214).

N-Butyl-N-heptylaniline: pmr (CDCl<sub>3</sub>)  $\delta$  6.43 - 7.42 (5H, m, Aryl CH), 3.23 (4H, br t, NCH<sub>2</sub>); mass  $\underline{m/z}$  (%) 247 (48), 204 (79), 162 (100), 120 (92), 106 (64); exact mass  $\underline{m/z}$  247.233 (Calcd for C<sub>17</sub>H<sub>29</sub>N, 247.230).

Butyldicyclohexylamine: pmr (CDCl<sub>3</sub>)  $\delta$  2.60 - 3.56 (4H, m, NCHNCH<sub>2</sub>), 0.95 - 2.25 (24H, m, CCH<sub>2</sub>C), 0.92 (3H, br t, CH<sub>3</sub>); mass  $\underline{m/z}$  (%) 237 (24), 195 (26), 194 (100); exact mass  $\underline{m/z}$  237.245 (Calcd for C<sub>16</sub>H<sub>31</sub>N, 237.246).

Butyldibenzylamine: ir (liquid film) 3080, 3048, 1712, 1499, 1458, 750, 698 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  7.33 (10H, m, Aryl CH), 3.55 (4H, s, PhCH<sub>2</sub>N), 2.40 (2H, br t, NCH<sub>2</sub>), 1.03 - 1.67 (4H, m, CCH<sub>2</sub>C) 0.65 - 1.03 (3H, m, CH<sub>3</sub>); mass  $\underline{m/z}$  (%) 253 (13), 211 (24), 210 (99), 92 (17), 91 (100); exact mass  $\underline{m/z}$  253.181 (Calcd for C<sub>18</sub>H<sub>23</sub>N, 253.183).

tert-Butyldibenzylamine: pmr (CDCl<sub>3</sub>)  $\delta$  7.00 - 7.42 (10H, m, Aryl CH), 3.68 (4H, s, NCH<sub>2</sub>), 1.12 (9H, s, CH<sub>3</sub>).

Dibenzylmethylamine: pmr (CDCl<sub>3</sub>)  $\delta$  7.30 (10H, br s, Aryl CH) 3.50 (4H, s, NCH<sub>2</sub>), 2.17 (3H, s, NCH<sub>3</sub>).

tert-Butyldecylamine: pmr (CDCl<sub>3</sub>)  $\delta$  2.54 (2H, br t, NCH<sub>2</sub>), 1.30 (16H, br s, CCH<sub>2</sub>C), 1.10 (9H, s, t-Bu), 0.88 (3H, br t, CH<sub>3</sub>).

N-Butyl-N-methylaniline: ir (liquid film) 1610, 1510, 1370, 1214, 746, 690 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  6.48 - 7.40 (5H,

m, Aryl CH), 3.28 (2H, br t, NCH<sub>2</sub>), 2.91 (3H, s, NCH<sub>3</sub>); mass  $\underline{m/z}$  163 (26), 120 (100), 106 (37); exact mass  $\underline{m/z}$  163.138 (Calcd for C<sub>11</sub>H<sub>17</sub>N, 163.136).

N,N-Dimethylaniline: pmr (CDCl<sub>3</sub>)  $\delta$  6.53 - 7.43 (5H, m, Aryl CH), 2.94 (6H, s, NCH<sub>3</sub>); mass  $\underline{m/z}$  121 (66), 120 (71), 106 (80), 77 (100); exact mass  $\underline{m/z}$  121.086 (Calcd for C<sub>8</sub>H<sub>11</sub>N, 121.089).

Diphenylmethanamine: pmr (CDCl<sub>3</sub>)  $\delta$  6.74 - 7.47 (10H, m, Aryl CH), 3.30 (3H, s, CH<sub>3</sub>); mass  $\underline{m/z}$  (%) 183 (100), 182 (46), 167 (25), 77 (39); exact mass  $\underline{m/z}$  183.108 (Calcd for C<sub>13</sub>H<sub>13</sub>N, 183.105).

Triphenylamine: pmr (CDCl<sub>3</sub>)  $\delta$  6.90 - 7.33 (15H, m, Aryl CH); exact mass  $\underline{m/z}$  245.122 (Calcd for C<sub>18</sub>H<sub>15</sub>N, 245.120).

N-tert-Butylaniline: pmr (CDCl<sub>3</sub>)  $\delta$  6.52 - 7.33 (5H, m, Aryl CH) 3.15 (1H, s, NH), 1.44 (9H, s, CH<sub>3</sub>).

N-tert-Butyl-naphthylamine: pmr (CDCl<sub>3</sub>)  $\delta$  6.80 - 7.90 (7H, m, Aryl CH), 3.97 (1H, s, NH), 1.44 (9H, s, CH<sub>3</sub>).

m-tert-Butylaminoacetophenone: The title compound was prepared according to the method D: pmr (CDCl<sub>3</sub>)  $\delta$  6.76 - 7.42 (4H, m, Aryl CH), 3.41 (1H, s, NH), 2.51 (3H, s, CH<sub>3</sub>C=O), 1.37 (9H, s, CH<sub>3</sub>-C); mass  $\underline{m/z}$  (%) 191 (23), 176 (57), 44 (100); exact mass  $\underline{m/z}$  191.130 (Calcd for C<sub>12</sub>H<sub>17</sub>NO, 191.131).

N-tert-Butyl-m-(1-hydroxyethyl)aniline: pmr (CDCl<sub>3</sub>)  $\delta$  6.47 - 7.31 (4H, m, Aryl CH), 4.71 (1H, q,  $\underline{J}$  = 6.2 Hz, CH-O), 3.01 (1H, s, NH), 1.41 (3H, d,  $\underline{J}$  = 6.2 Hz, CH<sub>3</sub>C-O), 1.30 (9H, s, t-Bu); mass  $\underline{m/z}$  (%) 193 (74), 178 (100); exact

mass  $m/z$  193.145 (Calcd for  $C_{12}H_{19}NO$ , 193.147).

N-Butyl-2-anilinoethanol. The title compound was synthesized using the method A: pmr ( $CDCl_3$ )  $\delta$  6.55 - 7.44 (5H, m, Aryl CH), 3.59 - 3.98 (2H, m,  $CH_2-O$ ), 3.06 - 3.59 (4H, m,  $NCH_2$ ), 2.08 (1H, s, OH), 1.00 - 1.81 (4H, br s,  $CCH_2C$ ), 0.94 (3H, m,  $CH_3$ ); mass  $m/z$  (%) 193 (100).

N-(o,o'-Diethoxyphenyl)piperidine. n-Butyllithium in n-hexane (1.6 M, 1.3 ml, 2 mmol) was added dropwise to an ethereal solution (5 ml) of resorcinol diethyl ether (166 mg, 1 mmol) at 25°C, and the resulting solution was heated to reflux overnight to give o,o'-diethoxyphenyllithium. On the other hand, copper piperidide was prepared as follows: n-Butyllithium in n-hexane (1.6 M, 3.1 ml, 5 mmol) was added dropwise to a solution of piperidine (426 mg, 5 mmol) in THF (25 ml) at 0°C and the mixture was stirred at 0°C for 30 min. Then cuprous iodide (952 mg, 5 mmol) was added at 0°C. Further stirring at 0°C for 30 min resulted in the formation of copper piperidide. To this mixture was added o,o'-diethoxyphenyllithium, prepared above. The whole mixture was heated to reflux for 2 h, and then treated with molecular oxygen (150 ml) at 25°C. Usual work-up, followed by purification by column chromatography on silica gel (EtOAc-hexane, 1:25, then 1:10) gave the title compound (126 mg, 51% yield) as a light yellow oil: pmr ( $CDCl_3$ )  $\delta$  6.34 - 7.30 (3H, m, Aryl CH), 4.01 (4H, q,  $J = 7.0$  Hz,  $CH_2-O$ ), 3.07 (4H, br s,  $NCH_2$ ), 1.58 (6H, br s,  $CCH_2C$ ), 1.40 (6H, t,

$\underline{J}$  = 7.0 Hz,  $\text{CH}_3$ ); mass  $\underline{m/z}$  (%) 249 (100), 220 (74), 150 (68); exact mass  $\underline{m/z}$  249.170 (Calcd for  $\text{C}_{15}\text{H}_{23}\text{NO}_2$ , 249.173).

#### References

- 1) D. Seebach, Angew. Chem. Int. Ed. Engl., 18, 239 (1979).
- 2) Recent example, see D. I. C. Scopes, A. F. Kluge, and J. A. Edwards, J. Org. Chem., 42, 376 (1977).
- 3) For the oxidative coupling of lithium dialkylcuprates, see (a) G. M. Whitesides, J. SanFilippo, Jr., C. P. Casey, and E. J. Panek, J. Am. Chem. Soc., 89, 5302 (1967); (b) G. H. Posner, Org. Reactions, 22, 253 (1975).
- 4) Although we have no evidence on the formation of lithium alkylcopper amide, the following reaction infers its existence: The reaction of butylcopper with lithium butylheptylamide in the presence of excess lithium dibutylcuprate at  $-20^\circ\text{C}$  for 2 h gave 1 in 78% yield after oxidative work-up.
- 5) A total of 36.5 ml of solvent was used per mmol of organocopper reagent. All operations were performed under argon atmosphere.
- 6) This compound was characterized by ir, mass, and nmr spectra.
- 7) Decomposition products were formed at the origin of tlc.
- 8) The use of 10 equiv of n- $\text{Bu}_2\text{CuLi}$  gave the yield comparable to that with 5 equiv of n- $\text{Bu}_2\text{CuLi}$ .
- 9) Despite numerous information on organocopper reactions, the available data, in our hands, are not sufficient to allow formulation of a detailed course of this reaction. However,

the reactivity of the alkylcopper amide, and the yield of the reaction seem to be closely dependent on the type of solvents used and on coordination phenomena of the nitrogen atom.

10) The yield based on consumed m-aminoacetophenone.

11) The same reaction conditions as described for the preparation of 1 were used.

12) H. Gilman, H. B. Willis, T. H. Cook, F. J. Webb, and R. N. Meals, J. Am. Chem. Soc., 62, 667 (1940).

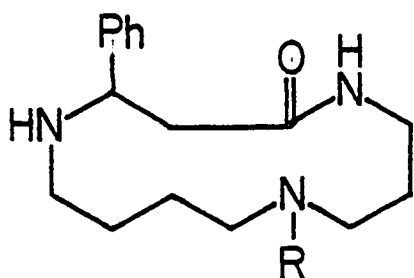
13) The copper piperidide was prepared in situ by treatment of lithium piperidide with cuprous iodide in THF-hexane at 0°C for 30 min. See also, T. Tsuda, M. Miwa, and T. Saegusa, J. Org. Chem., 44, 3734 (1979).

## Chapter VI

## Total Synthesis of Celacinnine, Celabenzine, and Celafurine

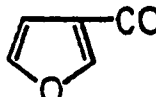
Abstract-----A total synthesis of spermidine alkaloids, celacinnine (1), celabenzine (2), and celafurine (3), is described in which a key step is the boron-templated cyclization of ethyl 3-phenyl-4,9,13-triazatridecanoate (5) to 12-phenyl-2,6,11-triazacyclotridecanone (4). Further transformation of 4 involving selective acylation with the corresponding acid chlorides led to the natural products 1, 2, and 3. A noteworthy feature of the present cyclization apart from its simplicity and high overall yield (65% overall yield from 6) is that carbon-nitrogen bond formation takes place only intramolecularly. Thus, high dilution or slow addition techniques are no longer necessary for the new process.

Celacinnine (1), isolated from Maytenus arbutifolia (Hochst., ex a. Rich) R. Wilczek<sup>1</sup> is the prototype of a novel series of alkaloids present in members of the Celastraceae family. Celacinnine (1) has also been isolated from the roots of Tripterygium wilfordii Hook,<sup>2</sup> together with the related alkaloids celabenzine (2) and celafurine (3).<sup>3</sup> These alkaloids are characterized by the presence of



1, R = trans-PhCH=CHCO

2, R = PhCO

3, R = 

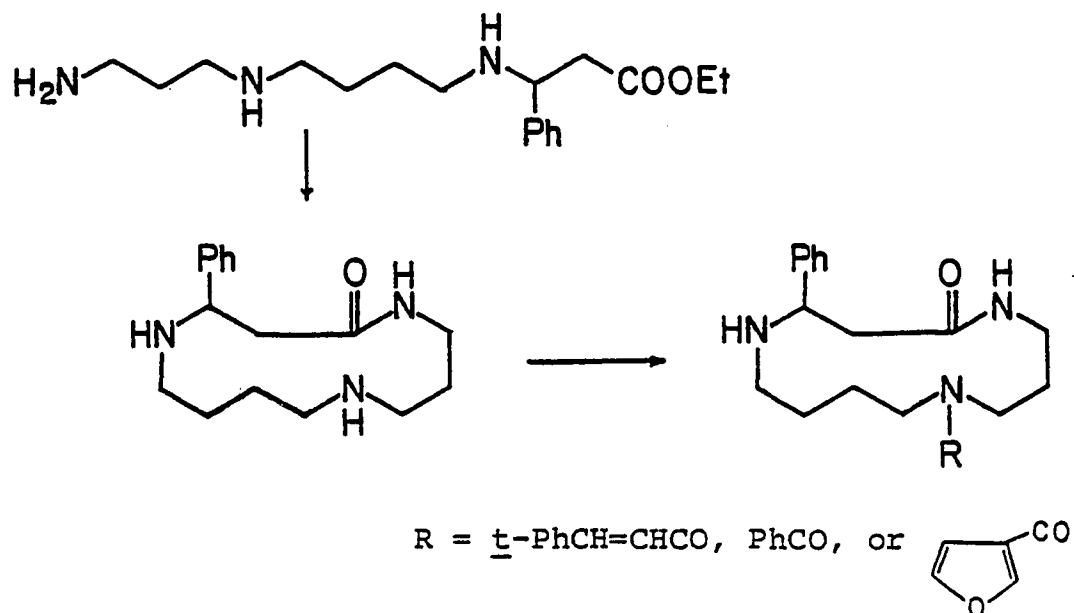
a 13-membered ring reflecting spermidine and cinnamoyl precursorial units,<sup>4</sup> and represent novel variants of the few known macrocyclic lactam alkaloids derived from spermidine.<sup>5</sup>

The biological and physiological importance of the macrolactams,<sup>6</sup> along with the novel structure of celacinnine (1), celabenzine (2) and celafurine (3) have stimulated great interest in their synthesis. However, only a handful of synthetically useful methodologies for macrolactam formation<sup>7</sup> and the high polarity of the spermidine alkaloids have conspired to prevent solution of the problem.

The goal of this synthesis could be the macrolactam 4, since this should be easily convertible to three spermidine alkaloids 1, 2, and 3 by selective acylation using trans-cinnamoyl, benzoyl, and 3-furoyl chloride, respectively.

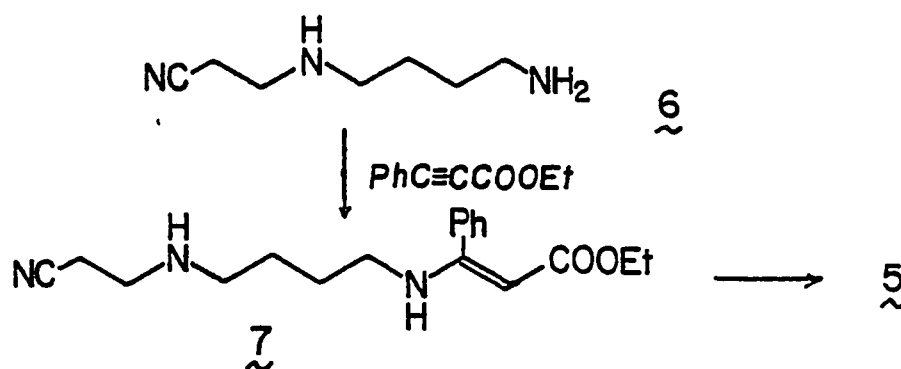
Therefore, the rational pathway to these natural products may be divided into three stages: (1) Synthesis of the triamino ester 5; (2) Formation of the macrolactam 4; and (3) Selective acylation leading to 1, 2, and 3 (Scheme I).

Scheme I



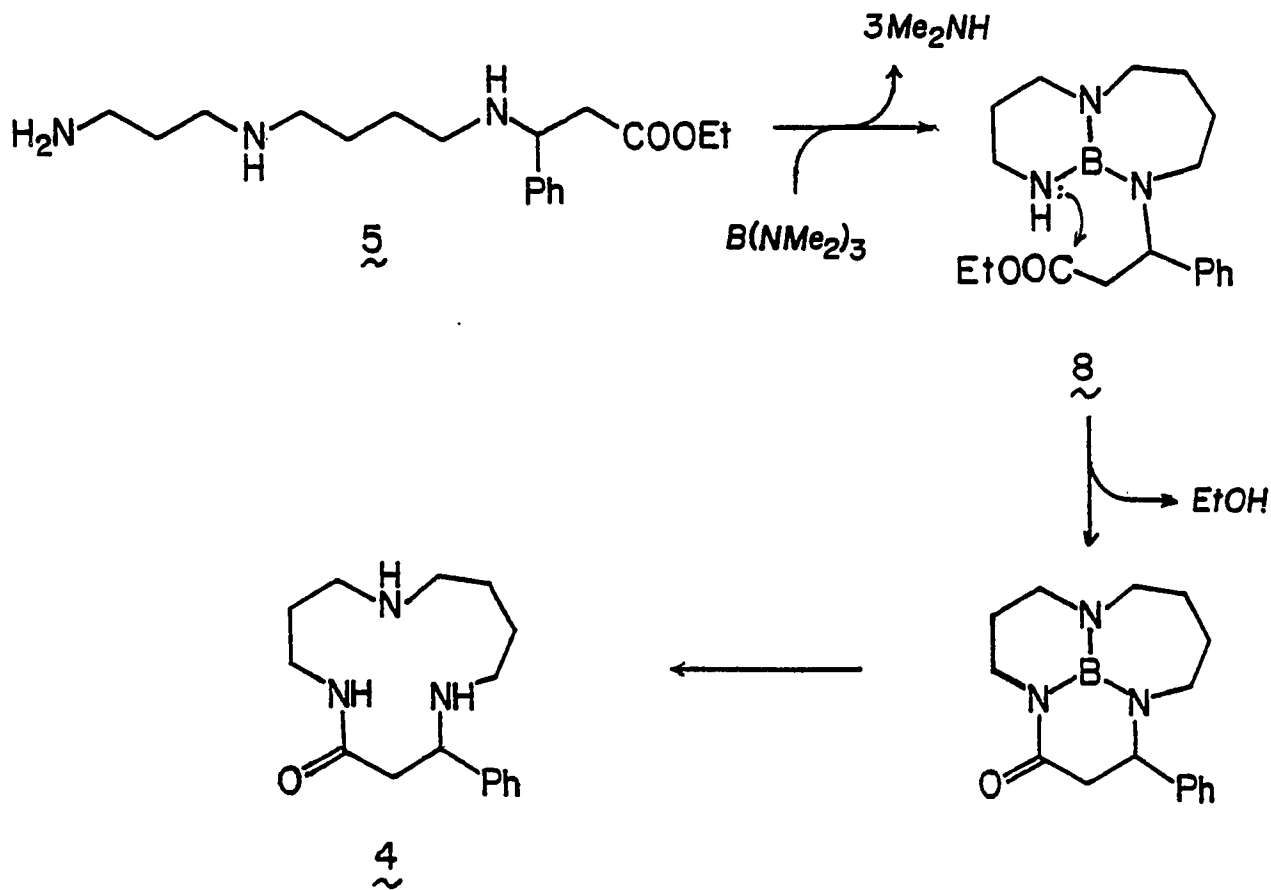
The first objective in the present synthesis is an efficient route to the precursor 5 for macrolactam formation. Michael addition of N-cyanoethyl-1,4-diaminobutane (6)<sup>8</sup> to ethyl phenylpropiolate (2 equiv) in ethanol at 68°C for 2 h gave ethyl 11-cyano-4,9-diaza-3-phenyl-2-undecenoate (7) in 92% yield after purification. Catalytic hydrogenation of both cyano and olefin functions in 7 over platinum oxide in chloroform-ethanol (1:50) at 25°C and 1 atm for 8 h led to the formation of ethyl 3-phenyl-4,9,13-triazatridecanoate (5) in 81% yield.<sup>9</sup> A further refinement for preparation of 5 (74% yield starting from 6) was performed by direct hydrogenation

of the intermediate 7 without isolation under the similar reaction conditions as described above.



The key step in the synthetic pathway to spermidine alkaloids (Scheme I) is the effective cyclization of the triamino ester 5. While great strides have been made in developing methods for macrolactonization,<sup>10</sup> only a few methods are available for closure to large ring lactams from the corresponding  $\omega$ -amino acids or esters.<sup>6</sup> However, they are used with much hesitation due to the lack of the regioselectivity for the ring closure of 5 without any protection of secondary amino groups. The disadvantage described above led the author to identify such a cyclization as his target. Herein, the first boron-templated synthesis of the macrolactam 4 is described, which is a conceptually new, and hitherto unexplored mode of cyclization.

The novel cyclization of the triamino ester 5 was accomplished by the use of tris(dimethylamino)borane as a key reagent.<sup>11</sup> Thus, treatment of 5 in freshly distilled xylene with tris(dimethylamino)borane (1.1 equiv) in xylene under reflux for 3 h led to the formation of the macrolactam 4 in 90% yield.



Apparently the efficiency of this cyclization reaction is ascribed to the boron mediated template effect as shown in  $\text{\textcircled{8}}$ . Although the boron amide  $\text{\textcircled{8}}$  is a highly reactive species to the ester group in the present cyclization, tris(dimethylamino)borane itself does not react at all with esters intermolecularly. Attempted reaction of tris(dimethylamino)borane with ethyl 3-phenylpropanoate in the presence or absence of spermidine under comparable conditions resulted in recovery of the starting materials.

It is well known that certain cations facilitating the formation of large rings have been ascribed to a template effect,<sup>12</sup> which presumably operates by complexing the

open-chain precursor(s) prior to ring formation and organizing the latter in a conformation close enough to the ring being formed. In the present cyclization, the covalent attachment of the substrate  $\underline{5}$  to boron atom produced structure  $\underline{8}$  for cyclization.<sup>13</sup>

Finally selective acylation at  $\underline{N(6)}$  position of  $\underline{4}$  was accomplished at low temperature using  $\underline{N,N}$ -dimethylaminopyridine. Thus, celacinnine ( $\underline{1}$ ), celabenzine ( $\underline{2}$ ), and celafurine ( $\underline{3}$ ) were obtained from  $\underline{4}$  and the corresponding acid chlorides in 97, 98, and 96% yield, respectively. The physical properties and spectral data of the synthetic  $\underline{1}$ ,  $\underline{2}$ , and  $\underline{3}$  are completely identical with those of the natural products. Furthermore, the synthetic celacinnine is in good agreement with the authentic celacinnine by tlc using several different developing solvent systems.

A noteworthy feature of this cyclization apart from its simplicity and unusual high overall yield (65% yield starting from  $\underline{6}$  for  $\underline{1}$ ,  $\underline{2}$ , and  $\underline{3}$ ) is that the carbon-nitrogen bond formation takes place only intramolecularly but not intermolecularly under certain reaction conditions. Thus, high dilution or slow addition techniques are no longer necessary for the new process.

### Experimental

N-Cyanoethyl-1,4-diaminobutane ( $\underline{6}$ ). Acrylonitrile (9.94 ml, 0.15 mol) was added dropwise to a solution of

1,4-diaminobutane (13.22 g, 0.15 mol) in methanol (3.5 ml) at 25°C over 1 h. The reaction is exothermic. The resulting mixture was allowed to stand at 25°C overnight. Purification of the mixture by column chromatography on silica gel (i-PrNH<sub>2</sub>-MeOH-CHCl<sub>3</sub>, 1:5:15) gave the pure 6 (13.38 g, 68% yield) as a colorless oil: tlc, R<sub>f</sub> 0.37 (i-PrNH<sub>2</sub>-MeOH-CHCl<sub>3</sub>, 1:4:4); pmr (CDCl<sub>3</sub>) δ 2.35 - 3.10 (8H, m, NCH<sub>2</sub>), 1.37 (3H, s, NH), 1.27 - 1.70 (4H, m, CCH<sub>2</sub>C).

Ethyl 11-Cyano-4,9-diaza-3-phenyl-2-undecenoate (7).

A mixture of 6 (7.05 g, 50 mmol) and ethyl phenylpropiolate (17.4 g, 100 mmol) in dry ethanol (50 ml) was heated at 68°C for 2 h. The solvent was then evaporated and the residue was directly applied to column chromatography on silica gel (MeOH-CHCl<sub>3</sub>, 1:40) to give 7 (14.5 g, 92% yield) as a colorless oil: tlc, R<sub>f</sub> 0.37 (MeOH-CHCl<sub>3</sub>, 1:15); ir (liquid film) 3330, 2260, 1659, 1614, 1488, 1300, 1175, 1147, 1040, 750 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>) δ 8.63 (1H, br s, C=C-NH), 7.44 (5H, s, Aryl CH), 4.59 (1H, s, C=CH), 4.13 (2H, q, J = 7.2 Hz, OCH<sub>2</sub>), 2.29 - 3.27 (8H, m, NCH<sub>2</sub>, CH<sub>2</sub>CN), 1.23 - 1.66 (5H, m, CCH<sub>2</sub>C, NH), 1.27 (3H, t, J = 7.2 Hz, CH<sub>3</sub>); mass m/z 315, 270, 232, 206, 192; exact mass m/z 315.199 (Calcd for C<sub>18</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>, 315.195).

Ethyl 3-Phenyl-4,9,13-triazatridecenoate (5). The cyanodiamino ester 7 (12.8 g, 40.6 mmol) in chloroform-ethanol (1:50 ratio, 408 ml) was hydrogenated over platinum oxide (1.2 g) under hydrogen at 25°C and 1 atm for 8 h. Filtration of the mixture, washing of the residue with

methanol, and concentration of the combined filtrates left the white ammonium salt, which was purified by column chromatography on silica gel (*i*-PrNH<sub>2</sub>-MeOH-CHCl<sub>3</sub>, 1:5:15) to furnish the triamino ester 5 (10.51 g, 81% yield) as a light yellow oil: tlc,  $R_f$  0.33 (*i*-PrNH<sub>2</sub>-MeOH-CHCl<sub>3</sub>, 1:5:15); ir (CHCl<sub>3</sub>) 3340, 1733, 1462, 1375, 1178, 1110 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  7.36 (5H, s, Aryl CH), 4.49 (5H, br s, NH), 4.09 (2H, q,  $J = 7.2$  Hz, OCH<sub>2</sub>), 4.03 (1H, t,  $J = 7.2$  Hz, PhCH), 2.29 - 3.10 (10H, m, NCH<sub>2</sub>, CH<sub>2</sub>C=O), 1.39 - 2.09 (6H, m, CCH<sub>2</sub>C), 1.17 (3H, t,  $J = 7.2$  Hz, CH<sub>3</sub>); mass  $m/z$  321, 277, 235, 193, 161, 136, 128; exact mass  $m/z$  321.249 (Calcd for C<sub>18</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>, 321.242).

The title compound 5 was converted to its triacetamide derivative using acetic anhydride-pyridine (1:1 ratio) at 25°C for one day: tlc,  $R_f$  0.28 (MeOH-CHCl<sub>3</sub>, 1:10); ir (CHCl<sub>3</sub>) 3410, 1748, 1652, 1543, 1435, 1385, 1040 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  7.37 (5H, s, Aryl CH), 5.53 (1H, t,  $J = 7.2$  Hz, PhCH), 4.18 (2H, q,  $J = 7.2$  Hz, OCH<sub>2</sub>), 2.83 - 3.52 (10H, m, NCH<sub>2</sub>CH<sub>2</sub>C=O), 1.98, 2.03, 2.37 (9H, three s, CH<sub>3</sub>C=O), 1.01 - 1.53 (9H, m, CCH<sub>2</sub>C, O-CCH<sub>3</sub>); mass  $m/z$  447, 404, 358, 270, 169; exact mass  $m/z$  447.270 (Calcd for C<sub>24</sub>H<sub>37</sub>N<sub>3</sub>O<sub>5</sub>, 447.273).

The title compound 5 was also obtained by the direct hydrogenation of the crude 7 with platinum oxide. Thus, the intermediate 7 prepared from 6 (282 mg, 2 mmol) and ethyl phenylpropiolate (696 mg, 4 mmol) in ethanol (2 ml) in a similar manner was, without isolation, diluted with

chloroform-ethanol (1:50 ratio, 18.4 ml) and hydrogenated over  $\text{PtO}_2$  (60 mg) according to the procedure described above to give 5 (477 mg) in 74% yield from 6 after purification.

12-Phenyl-2,6,11-triazacyclotridecanone (4). A solution of tris(dimethylamino)borane (393 mg, 2.76 mmol) in xylene (4 ml, freshly distilled) was added to a stirred solution of the triamino ester 5 (804 mg, 2.5 mmol) in xylene (21 ml) at 25°C to give the colorless solution, which turned to the white suspension in about 30 sec. Stirring was continued at 25°C for 30 min, then under reflux for 3 h. Removal of the solvent, and purification by column chromatography on silica gel (i-PrNH<sub>2</sub>-MeOH-CHCl<sub>3</sub>, 1:5:5) gave a mixture of 4 and 5. Repurification with i-PrNH<sub>2</sub>-MeOH-CHCl<sub>3</sub> (1:5:10, then 2:5:5) afforded the pure 4 (619 mg, 90% yield) as white crystals: tlc,  $R_f$  0.37 (i-PrNH<sub>2</sub>-MeOH-CHCl<sub>3</sub>, 1:5:5); mp 132 - 133°C (Recrystallized from EtOAc); ir (CHCl<sub>3</sub>) 3224, 1640, 1525, 1103  $\text{cm}^{-1}$ ; pmr (CDCl<sub>3</sub>)  $\delta$  8.70 (1H, br s, HNC=O), 7.37 (5H, s, Aryl CH), 4.01 (1H, t,  $J = 7.0$  Hz, PhCHN), 2.40 (2H, d,  $J = 7.0$  Hz, CH<sub>2</sub>C=O), 2.30 - 4.19 (10H, br m, CH<sub>2</sub>N, NH), 1.15 - 2.07 (7H, br m, CCH<sub>2</sub>C, NH), mass  $m/z$  (%) 275 (12), 259 (18), 258 (100), 208 (15); exact mass  $m/z$  275.207 (Calcd for C<sub>16</sub>H<sub>25</sub>N<sub>3</sub>O, 275.200).

The title compound 4 was converted to its diacetamide derivative using acetic anhydride-pyridine (1:1 ratio) at 25°C for 1 day: tlc,  $R_f$  0.34 (MeOH-CHCl<sub>3</sub>, 1:9); ir (CHCl<sub>3</sub>)

3367, 1640, 1430, 1370, 1318, 1220  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  7.30 (5H, s, Aryl CH), 5.53 - 5.93 (1H, m, PhCH), 2.54 - 4.23 (8H, br m,  $\text{NCH}_2$ ), 2.12, 2.48 (2:1 ratio, 9H, two s,  $\text{CH}_3\text{C}=\text{O}$ ), 1.43 - 1.93 (6H, m,  $\text{CCH}_2\text{C}$ ); mass  $\underline{m/z}$  359, 316, 269; exact mass  $\underline{m/z}$  359.218 (Calcd for  $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_3$ , 359.221).

Celacinnine (1). A solution of trans-cinnamoyl chloride (109 mg, 0.65 mmol) in dichloromethane (2 ml) was added dropwise at  $-78^\circ\text{C}$  to a stirred solution of the lactam 4 (120 mg, 0.44 mmol) and N,N-dimethylaminopyridine (150 mg, 1.23 mmol) in dichloromethane (20 ml). Stirring was continued at  $-78^\circ\text{C}$  for 2.5 h, then at  $-20^\circ\text{C}$  for 3 h. The reaction mixture was poured onto 14% ammonium hydroxide (10 ml) and extracted with dichloromethane three times. Purification of the concentrated crude product by column chromatography on silica gel ( $\text{MeOH}-\text{CHCl}_3$ , 1:15) gave celacinnine (1) (172 mg, 97% yield) as a colorless oil: tlc,  $\underline{R}_f$  0.33 ( $\text{MeOH}-\text{CHCl}_3$ , 1:9); mp  $178 - 181^\circ\text{C}$  (Recrystallized from EtOAc-Hexane) [Lit.<sup>3</sup> mp  $203 - 204^\circ\text{C}$  ( $\text{CHCl}_3$ -Hexane)]; ir ( $\text{CHCl}_3$ ) 3357, 1659, 1603, 1415, 1113  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ )  $\delta$  7.76 (1H, d,  $\underline{J} = 15.2$  Hz, PhCH=C), 7.14 - 7.58 (10H, m, Aryl CH), 6.58 (1H, d,  $\underline{J} = 15.2$  Hz, PhC=CH), 4.02 (1H, t,  $\underline{J} = 7.0$  Hz, PhCHN), 2.94 - 3.91 (6H, m,  $\text{CH}_2\text{NC}=\text{O}$ ), 2.52 (2H, d,  $\underline{J} = 7.0$  Hz,  $\text{CH}_2\text{C}=\text{O}$ ), 2.34 - 2.71 (2H, m,  $\text{NCH}_2$ ), 1.21 - 2.18 (7H, m,  $\text{CCH}_2\text{C}$ , NH); mass  $\underline{m/z}$  (%) 405 (23), 274 (100), 260 (25), 160 (19), 146 (23), 131 (62); exact mass  $\underline{m/z}$  405.239 (Calcd for  $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_2$ , 405.242). Tlc behaviors

of the synthetic celacinnine with several solvent systems (MeOH-CHCl<sub>3</sub>, 1:20; MeOH-EtOAc, 1:15; *i*-PrNH<sub>2</sub>-Ether, 1:20) are completely identical with those of the authentic celacinnine.

Mild acetylation of 1 using acetic anhydride-pyridine (1:4 ratio) at 25°C for one day furnished N-acetylcela-cinnine (9): tlc,  $R_f$  0.32 (MeOH-EtOAc, 1:9); ir (CHCl<sub>3</sub>) 3406, 1640, 1596, 1445, 1423, 1360, 1320, 1110, 967 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  7.76 (1H, d,  $J$  = 15 Hz, PhCH=C), 7.07 - 7.58 (10H, m, Aryl CH), 6.87 (1H, d,  $J$  = 15 Hz, PhC=CH), 5.71 (1H, br d,  $J$  = 12 Hz, PhCHN), 2.64 - 4.55 (10H, m, NCH<sub>2</sub>, CH<sub>2</sub>C=O), 2.46 (3H, s, CH<sub>3</sub>C=O), 1.43 - 1.91 (6H, m, CCH<sub>2</sub>C); mass  $m/z$  (%) 447 (39), 404 (68), 316 (%), 149 (100); exact mass  $m/z$  447.256 (Calcd for C<sub>27</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>, 447.252).

Celabenzine (2). A solution of benzoyl chloride (42 mg, 0.3 mmol) in dichloromethane (2 ml) was added dropwise to a stirred solution of the lactam 4 (55 mg, 0.2 mmol) in dichloromethane (8 ml) in the presence of N,N-dimethylaminopyridine (73 mg, 0.6 mmol) at -20°C. Stirring was continued at -20°C for 7 h, then at 0°C for one day. The reaction mixture was worked up and purified as described for preparation of celacinnine to give celabenzine (2) (74 mg, 98% yield) as a colorless oil: tlc,  $R_f$  0.40 (MeOH-CHCl<sub>3</sub>, 1:9); mp 172 - 173°C (Recrystallized from EtOAc) [Lit.<sup>3</sup> mp 156 - 158°C (EtOAc)]; ir (CHCl<sub>3</sub>) 3370, 1665, 1630, 1438, 1110 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  7.19 - 7.53

(10H, m, Aryl CH), 3.94 (1H, t,  $J = 7.0$  Hz, PhCHN), 2.83 - 3.80 (6H, m, CH<sub>2</sub>NC=O), 2.46 (2H, d,  $J = 7$  Hz, CH<sub>2</sub>C=O), 2.30 - 2.67 (2H, m, NCH<sub>2</sub>), 1.10 - 2.17 (7H, m, CCH<sub>2</sub>C, NH); mass  $m/z$  (%) 379 (24), 274 (23), 146 (24), 106 (100); exact mass  $m/z$  379,234 (Calcd for C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>, 379.226).

3-Furoyl Chloride. A mixture of 3-furoic acid (920 mg, 8.2 mmol) and thionyl chloride (3 ml) was heated to reflux for 1.5 h. Then excess thionyl chloride was removed, and the residue was distilled under reduced pressure to furnish 3-furoyl chloride (910 mg, 85% yield) as a colorless oil: bp 119 - 123°C (62 mmHg, Bath temp.); pmr (CDCl<sub>3</sub>)  $\delta$  6.84 (1H, m, C(4)-H), 7.55 (1H, t,  $J = 1.8$  Hz, C(5)-H), 8.27 (1H, d,  $J = 1.8$  Hz, C(2)-H).

Celafuline (3). The lactam 4 (110 mg, 0.4 mmol) in dichloromethane (16 ml) was treated with 3-furoyl chloride (78 mg, 0.6 mmol) in dichloromethane (4 ml) in the presence of N,N-dimethylaminopyridine (146 mg, 1.2 mmol) at -20°C for 3 h, at 0°C for 5 h, then at 25°C for 7 h. The reaction was quenched in a similar manner. Purification by column chromatography on silica gel (MeOH-CHCl<sub>3</sub>, 1:5) gave celafuline (3) (142 mg, 96% yield) as a colorless oil: tlc,  $R_f$  0.42 (MeOH-CHCl<sub>3</sub>, 1:9; mp 151 - 152°C (Recrystallized from EtOAc) [Lit.<sup>3</sup> mp 154 - 155°C (EtOAc)]; ir (CHCl<sub>3</sub>) 3355, 1665, 1625, 1440, 1320, 1170, 1113, 865 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>)  $\delta$  7.73 (1H, d,  $J = 1.5$  Hz, Furyl CH), 7.45 (1H, t,  $J = 1.5$  Hz, Furyl CH), 7.33 (5H, m, Aryl CH), 6.58 (1H, d,  $J = 1.5$  Hz, Furyl CH), 3.98 (1H, t,  $J = 7.2$  Hz, PhCHN),

2.95 - 3.81 (6H, m, CH<sub>2</sub>NC=O), 2.28 - 2.72 (2H, m, NCH<sub>2</sub>), 2.49 (2H, d,  $J = 7.2$  Hz, CH<sub>2</sub>C=O), 1.15 - 2.18 (7H, m, NH, CCH<sub>2</sub>C); mass  $m/z$  (%) 369 (65), 274 (31), 224 (32), 160 (24), 146 (50), 95 (100); exact mass  $m/z$  369.201 (Calcd for C<sub>21</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>, 369.205).

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