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AN APPROACH TO STRYCHNOS ALKALOIDS VIA INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of the Ohio State University

By

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The Ohio State University

1998

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ABSTRACT

This thesis examines an approach to the Strychnos alkaloids via an intramolecular 1,3-dipolar cycloaddition. The first chapter presents an overview of prior approaches to Strychnos alkaloids to place this work in context.

The next chapter describes the development of a general method for the preparation of \( N \)-trialkylsilylmethyl-2-cyano-1,2,3,6-tetrahydropyridines via reductive cyanation of \( N \)-trialkylsilylmethyl pyridinium salts. \( N \)-Alkylation of substituted pyridines with (tert-butyldiphenylsilyl)methanyl trifluoromethanesulfonate gave \( N \)-[(tert-butyldiphenylsilyl)methyl]pyridinium triflates. Reduction of these salts with NaBH\(_4\) in the presence of NaCN gave the target tetrahydropyridines. Problems associated with the use of trimethylsilylmethyl iodides in this sequence are discussed. It was demonstrated that by carefully selecting non-nucleophilic counterions (triflate instead of iodide) and introducing steric hindrance at silicon (TBDPS instead of TMS), it is possible to retain silicon through the reaction sequence. It was demonstrated that \( N \)-trialkylsilylmethyl-2-cyano-1,2,3,6-tetrahydropyridines gave azomethine ylids upon treatment with AgF, and the azomethine ylid would undergo intermolecular cycloaddition to very reactive dipolarophiles, such as \( N \)-methylmaleimide and \( \text{trans-1,2-bis(phenylsulfonyl)ethylene} \).

Intramolecular versions of this reductive cyanation-cycloaddition sequence were then investigated within the context of the aforementioned approach to Strychnos alkaloids. \( N \)-[(tert-
Butyldiphenylsilyl)methyl]-5-[(Z)-ethylidene]-4-(2-oxo-3-phenyl-3-butenyl)-2-piperidinecarbonitrile was prepared in six steps and 10% overall yield from α-methyl-3-pyridinemethanol. Upon treatment with AgF, this ylid precursor gave no cycloaddition product, but instead gave a perhydroisoquinoline. Formation of this product was attributed to generation of an enamine from the azomethine ylid, followed by an intramolecular Michael addition to the α,β-unsaturated ketone. It was proposed that trapping of the azomethine ylid was inefficient due to an unfavorable conformational equilibrium.

Several studies directed toward the synthesis of N-[(tert-butyldiphenylsilyl)methyl]-5-[(E)-ethylidene]-4-(2-oxo-3-phenyl-3-butenyl)-2-piperidinecarbonitrile were conducted, with the hope that A^1,3-strain would overcome the aforementioned conformational problem. N-[(tert-Butyldiphenylsilyl)methyl]-5-[(E)-ethylidene]-4-(2-hydroxy-3-phenyl-3-butenyl)-2-piperidinecarbonitrile was prepared in 6 steps and 9% yield from 5,6-dihydro-2H-pyran-2-one using a cuprate conjugate addition in the key step. The oxidation of 1-[(tert-butyldiphenylsilyl)methyl]-5-[(E)-ethylidene]-4-(2-hydroxy-3-phenyl-3-butenyl)-2-piperidinecarbonitrile to N-[(tert-butyldiphenylsilyl)methyl]-5-[(E)-ethylidene]-4-(2-oxo-3-phenyl-3-butenyl)-2-piperidinecarbonitrile, however, could not be accomplished. Alternative approaches to N-[trialkylsilylmethyl]-5-[(E)-ethylidene]-4-(2-oxo-3-phenyl-3-butenyl)-2-thiopiperidone are proposed.
To Rachel and Chen
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I am very fortunate to have Dr. Hart as my advisor. It is with him I started to be a chemist, although not a good one. I appreciate the opportunities of being showed how things are supposed to be done by the master, which I probably have to spend my whole life to strive for. I am also fortunate to know him as a human being during my toughest struggles through the program. It is always comforting to know somebody really cares. I hope that I am a better chemist and a more mature person now, and I owe that to Dr. Hart. The only regret is that I wish I actually listened to him more. I certainly hope I will be a better chemist and a better person in the years to come, because I always know I have his reputation at stake.

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The Highpiont Chinese Church is also greatly appreciated for providing me a home away from home and their prayers are well felt.
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Fields of Study

Major Field: Chemistry
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CHAPTER 1

ISOLATION, STRUCTURE ELUCIDATION, BIOLOGICAL ACTIVITY AND SYNTHESIS OF SELECTED STRYCHNOS ALKALOIDS

I. Introduction

This thesis describes an approach to the total synthesis of Strychnos alkaloids via a 1,3-dipolar cycloaddition reaction. For the purpose of this thesis, the term Strychnos alkaloids refers to alkaloids of the strychnan and aspidospermatan (condylocarpine sub-group) types as classified by van Beek and Hesse (Scheme I). This chapter will discuss three areas of research in the field: isolation and structure elucidation, synthetic approaches to pentacyclic Strychnos alkaloids, and total syntheses of strychnine. Since our synthetic approach revolves around 1,3-dipolar cycloaddition chemistry, a short discussion of the generation and cycloaddition chemistry of azomethine ylids will also be included at the beginning of next chapter.

Scheme I. Strychnan and Aspidospermatan Skeletons

![Scheme I. Strychnan and Aspidospermatan Skeletons](image-url)
II. Occurrence and Structure Elucidation of the *Strychnos* Alkaloids

Some representative members of the *Strychnos* alkaloids are depicted in Scheme II. Akuammicine (1), the most widely found α-methyleneindoline *Strychnos* alkaloid, is present, sometimes abundantly, in various genera of Apocynaceae. (+)-Condylocarpine (2) and related alkaloids are unique among *Strychnos* alkaloids, not only because of the position of the ethyl or ethylidene side chain, but also because of their absolute configuration. Wieland-Gumlich aldehyde-type alkaloids, isolated only from plants of the *Strychnos* genus, form a homogeneous group of compounds with a C-2—C-16 single bond. They differ within the group, in oxidation states at C-17 and C-18, in the acylation (or not) of N₆, and in the configuration at C-16. When C-17 is at the oxidation state of an aldehyde and a hydroxyl group is present at the C-18, a hemiketal is formed. For example, the Wieland-Gumlich aldehyde (3) is a natural product and a famous degradation product of strychnine. The Wieland-Gumlich aldehyde plays a special role.

**Scheme II. Representative Members of *Strychnos* Alkaloids**

1. Akuammicine
2. Condylocarpine
3. Wieland-Gumlich aldehyde
4. Strychnine $R_1 = R_2 = H$
5. Brucine $R_1 = R_2 = OMe$
among *Strychnos* alkaloids. It is a demonstrated biosynthetic precursor of strychnine (4) in *nux-vomica*, and is a key target and relay compound in formal total syntheses of strychnine.

The chemistry of strychnine (4) has dominated the field of *Strychnos* alkaloids for a long time. Strychnine and brucine (5) are present only in three Asian and one African species of plant. Strychnine occurs in large amounts in the Indian poison nut (*Strychnos nux-vomica*) and in Saint-Ignatius's bean (*Strychnos ignatii Bergius*). The notorious poison was isolated by Pelletier and Caventou in 1818 and was one of the first alkaloids to be obtained in pure form. The molecular formula of strychnine, C_{21}H_{22}O_{8}N_{2}, was established by Regnault 20 years later. Degradative investigations were documented as early as the 1880s. The seven intertwined rings of this alkaloid, however, represented an enormous challenge to classical chemical structure elucidation. The extensive structure elucidation, led by Leuchs and Robinson, was eventually accomplished after a striking total of 400 communications, consumption of several hundred kilograms of material, and some 40 years of research. The final structure was proposed by Robinson in 1946. At about the same time, Woodward independently suggested the same structure based upon an analysis of the published degradation literature. At that stage, the only way to verify the proposed structure was to synthesize strychnine itself, which was remarkably accomplished only six years later by Woodard and his coworkers. The landmark total synthesis stood as the only total synthesis of strychnine for more than forty years, despite extensive research in the field. The establishment of the structure of strychnine marked the end of the era of structure elucidation by chemical degradation, since the relative and absolute stereochemistry of strychnine was determined by single-crystal X-ray crystallography only three years later.

Owing to their high resolving power, $^1$H and $^{13}$C NMR techniques are the best tools nowadays for collecting information on conformational and configurational assignments of complex molecules such as *Strychnos* alkaloids. Conversely, well behaved and available materials such as brucine and strychnine have been used more than once by NMR specialists and
by chemists to test and illustrate the sensitivity of newly developed experiments to simplify complex spectra. 

To understand the numbering system and ring labels in the Strychnos alkaloids, the

**Scheme III-A. Biosynthesis of Strychnos Alkaloids**

6 Geraniol → Secologanin → Strictosidine

7 Strictosidine → Geissoschizine

8 Geissoschizine → 3 → 4 Strychnine

6 Geraniol

7 Strictosidine

8 Geissoschizine

4 Strychnine

1 Akuammicine

9 Dehydropreakuammicine
biogenetic relationships of indole alkaloids must be addressed. The dogmas of indole alkaloid biosynthesis were laid down more than 35 years ago and have been left virtually untouched ever since (Scheme III-A and Scheme III-B). The alkaloids pertinent to this chapter arise from dehydropreakuammicine (9) and precondylocarpine (10), both of which are generated from geissoschizine (8). The pathway leading from geraniol (6) and tryptophan to geissoschizine (8) has been established with fully characterized intermediates and enzymes isolated for use in bioconversions. Biogenetically, condylocarpine and related alkaloids originated from a pivotal intermediate iminium salt A which rearranges by a 1,3-hydrogen shift and double bond migration to afford B. Cyclization of this conjugated iminium salt leads to precondylocarpine 10, precursor
to the asidospermatan-type *Strychnos* alkaloids. Loss of one of the C-16 hydroxymethyl groups gives condylocarpine (2) (Scheme I). The biosynthesis of most *Strychnos* alkaloids are primarily hypotheses not firmly founded on experiments, with the exception of strychnine (4).\textsuperscript{15}

III. Biological Activities of *Strychnos* Alkaloids.

Strychnine has a long and mysterious history dating back to 16th century Europe, where it was used as a poison. It is a highly toxic compound that is lethal to adults in doses as low as 50 mg.\textsuperscript{16} Although strychnine has been used as the basis for bitters to stimulate appetite, and to increase the tone of skeletal musculature, the alkaloid has no rational therapeutic use.\textsuperscript{17} The high toxicity of strychnine is now known to result from blocking postsynaptic inhibition in the spinal cord and lower brain stem, where glycine is the major inhibitory neurotransmitter.\textsuperscript{18} Binding of strychnine abolishes glycineergic inhibition and results in overexcitation of the motor system and muscular convulsions.\textsuperscript{19} Strychnine poisoning is characterized by exaggerated reflexes manifested by tonic convulsions. These intense contractions interfere with respiration leading to central hypoxia and death. As matter of fact, strychnine was used to help to establish glycine as an inhibitory neurotransmitter in the spinal cord, and binding of strychnine has been used to map glycine receptors autographically. Since strychnine is covalently attached to the α subunit of the glycine receptor upon UV irradiation, it also played an important role in the recent structural characterization of this important ligand-gate ion channel receptor.\textsuperscript{20}

IV. Synthetic Approaches to the Pentacyclic Curare Alkaloids.

Since Woodward's first total synthesis of strychnine in 1953, extensive synthetic efforts have been devoted to this family of indole alkaloids. Consequently, a tremendous amount of publications have accumulated over the years. It is neither our intention nor a possible task to include all the work in the area. The approaches leading to the pentacyclic *Strychnos* alkaloids will be discussed first, followed by a documentation of the total syntheses of strychnine. The first
section will be presented according to strategies leading to the pentacycle, namely, the last ring constructed prior to the targets themselves (Scheme IV). Approaches that eventually led to total syntheses of strychnine will only be mentioned briefly here for the sake of completeness. Details will be presented in the latter part of this section for the purpose of critical comparison.

Scheme IV. Retrosynthetic Overview of Approaches to the Strychnan Pentacyclic Core

1. ABD-CE

Among all the possible approaches to the pentacyclic skeleton of Strychnos alkaloids, the so-called ABD-CE route (C7—C3 bond disconnection) is probably the one closest to the biosynthesis. This route, first explored by Harley-Mason in 1968, was used in the first total synthesis of pentacyclic Strychnos alkaloids (Scheme V). Early observations that the N5—C-11 bond in indole 1 could be cleaved very easily led to a promising start. The use of bis(2-
chlorobutyric) anhydride afforded amido ester 12, which upon successive hydrolysis, oxidation and base-promoted cyclization, was elaborated in a stereoselective manner into keto lactam 13.

Scheme V. Harley-Mason's Biomimic Approach to the Strychnan Skeleton

(a) (EtCHCICO)₂O (b) KOH, H₂O (c) MnO₂ or Pb(OAc)₄ (d) t-AmONa (e) Wolff-Kishner (f) LiAlH₄ (g) Pt, O₂.
having the appropriate relative configuration at C-15 and C-20. Two consecutive reductions of keto lactam 13 afforded tetracyclic indole 14, which is a degradation product obtained earlier from akuammicine and condylocarpine.22 The synthetic tetracyclic indole 14 was converted to the racemic (±)-tubifoline 17 and (±)-condyfoline 18 by air oxidation over platinum, the same conditions used to cyclize its counterpart obtained from biodegradation.22 The process gave a 4:1 mixture of tubifoline and condyfoline, respectively, arising from cyclization of the regioisomeric iminium salts 15 and 16. The synthetic route opened a general entry to pentacyclic Strychnos alkaloids. The ketone carbonyl group in the intermediate 13 allowed the introduction of functionality at C-16. As a result, total syntheses of (±)-geissoschizoline 1923 and (±)-dihydropinfluorocurarine 2024 also were accomplished. It is noteworthy that in these cases, when a substituent is present at the 16-position, the oxidative cyclization step was regioselective and gave only the Strychnan skeleton.

Ban and his coworkers23 renewed interest in this strategy after discovering a photoisomerization of 1-acyl-3-alkylindole 23 (Scheme VI). Application of a Fischer indole synthesis to keto diacid 21 gave 22. This was followed by a Curtius rearrangement, trapping of the intermediate isocyanate and subsequent reduction to furnish 1-acyl-3-alkylindole 23. The photo-Fries rearrangement of 23 afforded tricyclic lactam 26 in 89% yield, presumably by 1,3-acyl migration to give keto amine 24 followed by fragmentation of carbinol amine 25. The D-ring was installed by reduction of lactam 26 to the corresponding amine, followed by N-acylation and oxidation of C-16 to give 27. Base-promoted ring closure gave 13, an intermediate in Harley-Mason's synthesis. Construction of the C-3—C-7 bond was carried out following the protocol described before. This elegant approach suffered from the use for several oxidation, reduction and reoxidation steps in order to construct the D-ring and C-3—C-7 bond.

The Martin group was interested in developing general strategies for synthesis of complex alkaloid natural products involving variants of inter- and intramolecular vinylogous Mannich reactions in tandem with selected biomimetic transformations.26 As one example of a
Scheme VI: Ban's Total Synthesis of Tubifoline and Condyfoline.

\[\text{Scheme VI: Ban's Total Synthesis of Tubifoline and Condyfoline.}\]

\(\text{CO}_2\text{H}\)

\(\text{HCO}_2\)

\(\text{1} \xrightarrow{a} \text{20} \xrightarrow{b-e} \text{23} \xrightarrow{hv, \text{MeOH} \text{89\%}} \text{24} \xrightarrow{t.g.h} \text{25} \xrightarrow{f.g.h} \text{26} \xrightarrow{i} \text{27} \xrightarrow{j,k,l} \text{Tubifoline (17) and Condyfoline (18)}\)

\(\text{Tubifoline (17) and Condyfoline (18)}\)

(a) \(\text{C}_6\text{H}_5\text{NHNNH}_2\), then 10\% \(\text{H}_2\text{SO}_4\) (b) \((\text{COCl})_2\) (c) \(\text{NaN}_3\) (d) \(\text{C}_6\text{H}_5\text{CH}_2\text{OH}\), \(\Delta\) (e) \(\text{H}_2\), \(\text{Pt}\) (f) \(\text{LiAlH}_4\) (g) \(\text{EtCHClCOCl}, \text{NaHCO}_3, \text{CH}_2\text{Cl}_2\) (h) \(\text{I}_2\text{O}_5\) (i) \(\text{t-AmONa}, \text{THF}\) (j) \(\text{NH}_2\text{NH}_2, \text{KOH}\) (k) \(\text{B}_2\text{H}_6, \text{THF}\) (l) \(\text{Pt, O}_2, \text{EtOAc}\).

Vinylogous Mannich reaction (Scheme VII), treatment of 28, (prepared in two steps from tryptamine) with 1-trimethylsilyloxy-2,4-pentadiene (A) in the presence of crotonyl chloride (29a) gave 30a. Then 30a underwent an intramolecular hetero-Diels-Alder cyclization to give the pentacyclic adduct 31a in 70\% yield. Hydration of the enol ether moiety of 31a followed by oxidation of the intermediate lactol gave lactone 32a in 79\% yield. Further elaboration of 32a was carried out by in situ esterification of the acid generated from a \(\beta\)-elimination, followed by a selective reduction of the amide moiety. This provided 33a in 91\% yield. In only eight steps from
Scheme VII. Martin's Biomimetic Approach to the Strychnos Alkaloids: Total Synthesis of (±)-Akuammicine.

\[ \text{CH}_2=\text{CHCH}=\text{CHCH}_2\text{TMS} \quad \text{ZCH}_2=\text{CHCOCI} \]

(a) 29a or 29b, then A  (b) Δ  (c) TsOH, aq. THF  (d) (Ph_3P)_3\text{RuCl}_2, Et_3N, PhCH=CHCOCH_3  (e) NaOMe, MeOH; then (COCl)_2, 0°C  (f) Me_3OBF_4, 2,6-t-Bu-py, NaBH_4  (g) SnCl_4, toluene, tert-BuOCl, -20°C  (h) LiHMDS, -40°C→rt.
tryptamine, a similar sequence of reactions was performed to prepare the oxygenated analog 33b. With the key intermediates 33a and 33b in hand, the biomimetic reorganization of the corynantheoid intermediate into the pentacyclic skeleton of Strychnos alkaloids was investigated. Indole 33a was exposed to tert-butylihypochlorite in the presence of SnCl₄ to give a mixture of epimeric chloroindolenines 34a which were not isolated but rather treated directly with lithium hexamethyldisilazide to give (±)-akuammicine (1) in 30-35% yield. The oxygenated analog underwent a similar conversion to give 37 in approximately 25-30% yield. The mechanism of this novel biomimetic transformation has not been fully established, although the initial oxidation of the indole ring with electropositive halogen to give the chloroindolenines such as 34a and 34b, is well documented.²⁰ It was imagined that 34a (or 34b) gives intermediates 35a (or 35b) or 36a (or 36b), which upon treatment with base undergoes skeletal reorganization to give 1 (or 37). Related rearrangements of substituted tetrahydrocarbolines to the Aspidosperma skeleton are also promoted upon sequential reaction with hypochlorite and base. Furthermore, the base-induced rearrangement of strictamine, which is one of the epimeric forms of 36a, into akuammicine is known. Difficulties were encountered in deprotecting 37 to give 38, although intermediate 38 has been converted to strychnine in 4 steps by Overman.²⁷

Magnus and his coworkers also started their approach following the classical Harley-Mason strategy and eventually finished a total synthesis of strychnine. That work will be discussed in the strychnine total synthesis section (vide infra).

2. ABCD-E Route.

Approaches in this direction revolved around building key tetracyclic skeleton 39 first, and then bringing in the elements for construction of E-ring (Scheme VIII). Depending on the timing of the indole ring construction, different approaches have been investigated.
The approach depicted in Scheme IX represents one of the Barcelona group's early approaches toward *Strychnos* alkaloids.\(^{28}\) Indole 42 was prepared from piperidone 40 by a Wittig-Horner reaction followed by a Fischer indolization. The C-3—C-7 bond was formed with mercury salts at the expense of regioselectivity. An alternative synthesis of 43 was published by Grierson (Scheme X).\(^ {29}\) The indole ring in 42 was installed by reductive cyclization of \(\alpha\)-(o-nitrophenyl) ketone 45. The mercury acetate cyclization was replaced by an \(\alpha\)-aminonitrile strategy, which involved the preparation of a mixture of regioisomeric cyanopiperidines 46a and 46b.

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**Scheme IX. Bosch's Approach to Tetracyclic ABCD System**

![Scheme IX](image)

(a) \((\text{CH}_3\text{O})_2\text{POCH}_2\text{CO}_2\text{C}_2\text{H}_5, \text{NaH, glyme}\)  
(b) \(\text{Pd-C, H}_2\)  
(c) \(\text{CH}_3\text{SOCH}_2\text{Na, DMSO}\)  
(d) \(\text{Zn, AcOH}\)  
(e) \(\text{C}_6\text{H}_5\text{NNH}_2, \text{PPA, } \Delta\)  
(f) \(\text{Hg(OAc)}_2\cdot\text{Na}_2\text{EDTA, CH}_2\text{Cl}_2\)  
(g) \(\text{NaBH}_4, \text{CH}_3\text{OH}\)
Scheme X. Grierson's Approach to Tetracyclic ABCD System

(a) (CH₂O)₂CO, NaH, THF (b) o-FC₆H₄NO₂, NaH, HMPA (c) dil. HCl, Δ (d) H₂, PtO₂ (e) (Boc)₂O, aq. NaOH, toluene, Bu₂NHSO₄, rt (f) m-CPBA, CH₂Cl₂, 0°C (g) TFAA, -15°C (h) aq. KCN, NaOAc (i) AcOH, dioxane, 90°C, 14h.

46b by Polonoski-Potier reaction followed by trapping of the iminium salts with potassium cyanide. Exposure of the mixture to aqueous acetic acid led to tetracycles 43 and 47.

A Fischer reaction allowed Magnus and coworkers to construct a tricyclic ABC intermediate, which was further annulated to an ABCD compound (Scheme XI).
Scheme XI. Magnus' ABC-D Approach for the Preparation of a Tetracyclic Ring System.

(a) C$_6$H$_5$NHNH$_2$, aq. AcOH, reflux, 12h (b) CH$_3$OH-HCl, rt, 2h (c) DDQ, aq. THF, 0°C, 2h (d) p-CH$_3$OC$_6$H$_4$SO$_2$Cl, aq. NaOH, CH$_2$Cl$_2$, Bu$_4$NCl, rt; then LiOH, THF, rt, 1h (e) CICO$_2$C$_6$H$_5$, CH$_2$Cl$_2$, Et$_3$N, 0°C, 1h; then aq. NH$_3$ (f) NaBH$_4$, CH$_3$OH-THF, rt, 2h (g) TFA, CH$_2$Cl$_2$, rt, 12h.

Challenges were encountered in the construction of the E-ring. Studies by the Magnus$^{30}$ and Bosch$^{31}$ groups independently demonstrated the importance of conformational flexibility in the process of E-ring closure (Scheme XII). For example, intermediate sulphonium ions derived from endocyclic and exocyclic amido sulphoxides 53 and 54 were incapable of aligning in a periplanar manner over the π system of the indole 2,3-double bond. The ions derived from amino sulphoxide 56, in contrast, were not as demanding and gave the expected cyclization products. Thus, ring E was closed via thionium ion 57, generated by treating dithioacetal 56 with dimethyl(methylthio)sulphonium tetrafluoroborate.$^{31}$ Desulfurization and simultaneous reduction of the C=N double bond of 58 with Raney nickel afforded tubifolidine 59.
Scheme XII. Magnus' ABC-D Approach for the Pentacyclic Ring System

\[ X = \text{PhSO}^- \]

53 \[ \xrightarrow{a,b} \] 54 \[ \xrightarrow{d,e} \] 55

58 \[ \xrightarrow{a,b} \] 57 \[ \xrightarrow{e,d} \] 59

(a) \((C_2H_5O)_2CHCH_2Br\), dioxane, \(\text{Na}_2\text{CO}_3\)  
(b) \(\text{CH}_3\text{SH}, \text{CH}_2\text{Cl}_2, \text{BF}_3 \text{Et}_2\text{O}, 0^\circ\text{C}\)  
(c) \((\text{CH}_3)_2\text{SSCH}_3\text{BF}_4\), \(\text{CH}_2\text{Cl}_2, 0^\circ\text{C}, 3\text{h}\)  
(d) Raney Ni, \(\text{C}_2\text{H}_5\text{OH}\), reflux  
(e) \(\text{ClCO}_2\text{CH}_3\), \(\text{NaH}, \text{DME}, 60^\circ\text{C}\)  
(f) \(\text{hv}, \text{CH}_3\text{OH}\).

On the other hand, conversion 58 to a carbamate, followed by desulfurization afforded 60. Insertion of the methoxycarbonyl group on C-16 was achieved by photo-Fries rearrangement of 60, which led to 19,20-dihydroakuammicine (61). Despite this success, the E-ring closure process gave the cyclized product in much lower yield in the C-20 ethyldene series.\(^{32}\)
3. ACDE-B Route

Early approaches in this direction focused on different ways to construct the key intermediate ketone 62 (Scheme XIII). Studies with 62 demonstrated that it was impossible to force the Fischer indolization to occur against Bredt's rule, as indole 63a was the only isolated product, not a trace of 63b being detected. With this realization, attention was focused on ketones like 64, which already has an aryl subsituent at C-7 that can be revealed to form the indole ring. This route led to some remarkable syntheses. Utilizing the strategy of tandem cationic aza-Cope rearrangement, followed by Mannich reaction, the Overman group was able to assemble intermediates resembling 64, and from that point on finish a total synthesis of dehydrotubifoline. This was followed by the only enantioselective synthesis of

Scheme XIII. The Attempted ACDE-B Route

![Scheme XIII. The Attempted ACDE-B Route](image)
Scheme XIV. Bosch's Recent Approach to the *Strychnos* Alkaloids

(a) allyl bromide, K₂CO₃, acetone (b) O₃, -78°C; (c) CH₃NH₂-HCl, NaBH₃CN (d) m-CPBA (e) TFAA; (f) NaBH(O₂CR)₃ (g) ClCO₂CHClCH₃ (h) HMDS, TMSI (i) PhSeCl (j) O₂, -78°C; (k) i-Pr₂NH, rt (l) MeOH, reflux (m) MVK (n) (R)-PhCH(CH₃)NH₂ (o) (CH₃SH)₂, BF₃·OEt₂ (p) AIBN, Bu₃SnH (q) Z-BrCH₂C(=CHCH₃), K₂CO₃ (r) Ni(COD)₂, LiCN (s) NaH, ClCO₂CH₃ (t) hv, MeOH.
Bosch and coworkers published a series of papers on an approach to the Strychnos alkaloids starting from diketone 65 (Scheme XIV). The fragment necessary for formation of the E ring was brought in by a Claisen rearrangement. Further elaboration of the allyl group by ozonolysis and reductive amination afforded a 1.5:1 mixture of cis and trans amino ketones 66 in 62% yield from 65. Oxidation of trans-66 with m-CPBA, followed by treatment of the resulting N-oxide with TFAA and reduction of the resulting iminium salt with sodium tri-(2-ethylhexanoyloxy)borohydride, stereoselectively gave the desired cis-66 in 87% yield. After switching to a more easily removable protecting group, ketone 67 was converted to the α-phenylselenyl derivative via the silyl enol ether. Oxidation of the selenide to the corresponding selenoxide followed by warming, gave enone 68 in 50% yield. Deprotection of the nitrogen followed by conjugate addition of the secondary amine 69 to methyl vinyl ketone furnished 70.

The ideal base for promoting the intramolecular Michael addition to close the D ring was found to be α-methylbenzylamine. Hydrolysis of the initially formed imine afforded a 1:3 mixture of tricyclic ketones 71a and 71b. The minor epimer 71a was converted to 71b by treatment with KF in ethanol. With the D-ring in place, diketone 71b was chemoselectively converted to the corresponding dithioacetal, which was transformed directly to tubifolidine 59 in 50% yield upon exposure to tributyltin hydride in the presence of a catalytic amount of AIBN. The one-pot process involves desulfurization and simultaneous indoline ring closure by reductive cyclization of the γ-nitro ketone unit.

The versatility of the aforementioned strategy was demonstrated by syntheses of pentacyclic Strychnos alkaloids bearing the C-20 ethylene unit. The key intermediate 69 was alkylated to give 72. When 72 was treated with Ni(COD)_2 (6.6 equiv) in the presence of LiCN, 19,20-dehydrotubifoline (73) was obtained in 40% yield. This one-pot transformation involves Ni(0)-promoted cyclization of the vinyl iodide to the carbon-carbon double bond and the
controlled reductive cyclization of the γ-nitro ketone to form an imine. N-acylation followed by photoisomerization of N-methoxycarbonyl enamine 74 afforded (±)-akuammicine (2) in 30% yield.

Scheme XV. Kuehne's Total Synthesis of Tubotaliwine (80) and Dihydro-20-epi-akuammicine (82)

(a) NaBH₄, AcOH, 90°C (b) H₂, Pd-C, AcOH (c) (Boc)₂O, Et₂N, CH₂Cl₂ (d) t-BuOCl, Et₂N, CH₂Cl₂, 0°C; then DBU, C₆H₆, reflux, 48h (e) TFA, CH₂Cl₂, rt; 1h, then CH₃(CH₂)₂CHO, K₂CO₃, CH₂Cl₂, rt, 1h (f) TFA, CH₂Cl₂, rt, 1h; then vinyl acetate, CH₂Cl₂, Et₂N, reflux, 48h.
4. ABCE-D Route

Both Rawal and Kuehne chose to prepare the D-ring last in the construction of their pentacyclic Strychnan skeleton. Both groups finished total syntheses of pentacyclic dehydrotubifoline first and then extended their work to total syntheses of strychnine. These results will be presented in the strychnine total synthesis section of this chapter.

5. AB-CDE Route

Kuehne's approach is based on the generation of indoloacrylates and their reactions with enamines (Scheme XV). Tetracycle 75a and its derivative 75b were subjected to reductive ring fragmentation to give 9-membered ring indoles 76a and 76b, respectively. After switching the nitrogen protecting group to a Boc group, followed by a t-BuOCl-mediated oxidation, indoloacrylates 78a and 78b were obtained. The secondary amine was then revealed and subsequent condensation with butyraldehyde or vinyl acetate occurred, with simultaneous generation of C, D and E rings, affording tubotaiwine (80) and 19,20-dihydro-20-epiakuammicine (82), respectively.

V. Total Syntheses of Strychnine.

The first total synthesis of strychnine by Woodward represents a landmark in the field of organic synthesis. The extraordinary synthesis marked the beginning of designed synthesis of complex molecules. Strychnine, with seven intertwining rings and six stereogenic centers spread out over only 24 skeletal atoms, was once called the Mount Everest of organic chemistry and represented a formidable challenge. In the forty year period that has elapsed since the Woodward synthesis, a number of novel approaches to strychnine have appeared in the literature, but the molecules prepared frequently have lacked the functionality required for construction of the seven-membered allylic ether G ring of strychnine. Not until early nineties, did breakthroughs
come along. As of this time, five more groups have accomplished their ultimate goal: Magnus' relay synthesis of (-)-strychnine (1992); total syntheses of (±)-strychnine by Stork (1992), Kuehne (1993), and Rawal (1994); and Overman's first enantioselective synthesis of (-)-strychnine (1993). The six total syntheses fall into two categories. Woodward's total synthesis of strychnine relied on the isostrychnine-strychnine transformation, and Kuehne and Rawal followed suit forty years later. Magnus, Stork, and Overman, on the other hand, chose the Wieland-Gumlich aldehyde as their ultimate precursor to strychnine. The total syntheses via isostrychnine will be documented first, followed by those proceeding via the Wieland-Gumlich aldehyde.

Woodward started his remarkable synthesis with 2-veratrylindole (83), which was readily available from Fischer indolization of acetoveratrone and phenylhydrazine (Scheme XVI-A and Scheme XVI-B). Condensation of indole 83 with formaldehyde in dioxane and acetic acid, followed by exhaustive methylation with methyl iodide and displacement with cyanide afforded the corresponding nitrile, which in turn was reduced to primary amine 84. Condensation of amine 84 with ethyl glyoxylate gave the corresponding Schiff base, which was subsequently treated with p-toluenesulfonyl chloride in the presence of pyridine, reduced with sodium borohydride and protected to give indoline 85, which was isolated as a single isomer. The stereochemistry at C-2 and C-3 depicted in Scheme XVI were assigned principally on the basis of speculation without much experimental proof. Ozonolysis in acetic acid selectively cleaved the electron-rich aromatic ring in the desired manner to give diester 86. This set the stage for elaboration of CDE-ring system. Exposure of the diester 86 to boiling methanolic hydroiodic chloride, revealed N₂ and formed the 6-membered lactam 87. Five-membered lactam formation was prohibited by the trans disposition of the double bond. The initially formed lactam isomerized to the more stable pyridone 88. After attempts to induce Dieckmann condensation of 88 failed, hot hydriodic acid in the presence of red phosphorus was used to cleave the p-toluenesulfonyl group, and the conditions
also hydrolyzed the ester groups. N\textsubscript{p} and the carboxylic acids were protected again to give 89. Treatment of 89 with sodium methoxide in hot methanol epimerized C-3 center, and successfully promoted the Dieckmann condensation to close the D-ring and give pentacycle 90. With the ABCDE rings in place, the next task was to reduce C-14 to its methylene counterpart. This transformation took advantage of the observation that the keto ester existed mainly in its tautomeric form 91. Enol 91 was transformed to its \( p \)-toluenesulfonate derivative, which in turn was transformed to the corresponding thioenol ester with sodium benzylmercaptide via an addition-\( \beta \)-elimination sequence. Treatment of this material with Raney Ni and hydrogenation furnished 92. The stereochemistry at C-20, established in the hydrogenation step, and necessary for assembly of F-ring, was unfortunately inverted in the following hydrolysis step. The identity of the \textit{trans} \( N \)-acetyl acid 93 was established by careful comparison with a degradation product of strychnine. Upon exposure to acetic anhydride, acid 93 was transformed smoothly to methyl ketone 95, presumably via the mixed anhydride intermediate 94. Installation of F-ring was a difficult task because the epimerization at C-20 of 95 was a thermodynamically disfavored process. When amino ketone 96 was treated with selenium dioxide, \textit{trans} glyoxal 97\textsubscript{a} was presumably formed, which was in equilibrium with its \textit{cis} isomer 97\textsubscript{b}. Although not favored, 97\textsubscript{b} could be captured now by nitrogen to form aminal 98, which was further oxidized to amido ketone 99. Addition of sodium acetylide to the ketone followed by hydrogenation in the presence of Lindlar's catalyst afforded tertiary allylic alcohol 100. The pyridone moiety and the amide were reduced simultaneously to give amine 101. The addition of hydride to the pyridone occurred on the concave, more hindered side of the molecule to set the stereochemistry at C-2 in 101. It was demonstrated that the C-20 hydroxyl group had a great impact on the outcome of this reduction. Chelation and intramolecular hydride delivery was evoked in the rationalization of the results. The allylic alcohol was rearranged by hydrogen bromide in acetic acid at 120°C to give a mixture of halides, from which produced isostrychnine 102 upon treatment with boiling aqueous sulfuric
Scheme XVI-A. Woodward's Total Synthesis of Strychnine
acid. According to the protocol reported by Prelog, \(^{42}\) isostrychnine 102 was transformed to strychnine 4. The stereospecific generation of the two new centers, namely, C-16 and C-17 was the result of thermodynamic control, the other isomers at these centers being impossibly strained.
Kuehne and his coworkers started their total synthesis of racemic strychnine by the efficient construction of tetracycle 107 in a single step from tryptamine 103 and butenal 104 in the presence of BF$_3$-etherate (Scheme XVII-A and Scheme XVII-B). The reaction sequence presumably involved an intramolecular Mannich reaction to give intermediate 105, followed by a [3,3]-sigmatropic rearrangement to afford 106, which in turn underwent acid catalyzed cyclization to give 107 as a single diastereomer. After hydrolysis, aldehyde 108 was isolated in 51% yield from 103. This very promising beginning was soon shadowed by the lengthy and difficult sequential construction of the missing F, G, and C rings. The key step in the installation of F ring was intramolecular nucleophilic ring-opening of epoxide 109. This thermodynamically controlled reaction gave ammonium salt 110 as the only product, which after deprotection gave amine 111. Reduction of the amino arylate double bond with NaCNBH$_3$ in acetic acid occurred such that

**Scheme XVII-A. Kuehne’s Total Synthesis of Strychnine**
Scheme XVII-B. Kuehne's Total Synthesis of Strychnine (continued)

\[
\begin{align*}
\text{110} & \xrightarrow{(f,g,h)} \text{111} \\
\text{115} & \xrightarrow{(i,m,n)} \text{114} \\
\text{116} & \xrightarrow{(j,k)} \text{113} \\
\end{align*}
\]

(a) BF$_3$, Et$_2$O (b) 10% HClO$_4$, THF, 30°C (c) Me$_3$Si', n-BuLi, THF (d) DBU, MeOH, 65°C, 10h (e) Pd/C, H$_2$, MeOH (f) NaBH$_4$, HClO$_4$, 23°C (g) Ac$_2$O, pyridine (h) NaOMe, MeOH, 0°C (i) LiN(SiMe$_3$)$_2$ (j) NaBH$_4$, MeOH (k) Ac$_2$O, pyridine (l) DBU, dioxane, H$_2$O, 100°C (m) deprotection (n) Swern (o) (EtO)$_2$P(O)CH$_2$CO$_2$Me (p) DIBAL, BF$_3$ (q) KOH, EtOH.

Hydride added to C-2 from the concave side, while a 3:10 mixture of diastereomers was obtained at C-16 (Scheme XVII-B). The mixture was treated with LiHMDS in refluxing THF to afford intramolecular Claisen product 113. Subsequent ketone reduction and alcohol
protection furnished diacetate 114. Elimination, accompanied by ester hydrolysis, was effected by heating the epimeric acetates at 100°C in aqueous dioxane with an excess of 1,8-diazabicycloundecane, which was followed by Swern oxidation to give ketone 115. Stereoselective installation of the E allylic ether at C-20, critical in the closure of G ring in strychnine, was difficult. Wittig-Horner olefination provided a 1:1 mixture of the (E) and (Z) isomers of 116, which could be enriched by irradiation in favor of the required (E) isomer (8:1). The reduction of 116 to isostrychnine was straightforward, but the problematic conversion of isostrychnine to strychnine was not solved, as strychnine was obtained in only 28% yield. This total synthesis, designed around a new and efficient first step, even though not stereoselective in every key step, is one of the shortest routes to strychnine, requiring only 17 steps and proceeding in 2% an overall yield.

At about the same time, Rawal finished his remarkably short total synthesis of the molecule his mentor once worked on as a graduate student forty years earlier. His strategy combined the advantages of both the intramolecular Diels-Alder and intramolecular Heck reactions. Commercially available 2-nitrophenylacetonitrile 117 was reacted with 1,2-dibromoethane in the presence of base, followed by selective reduction with DIBAL to give aldehyde 118. Condensation of the aldehyde with benzylamine followed by acid promoted cyclopropyl iminium ion rearrangement gave the desired pyrrolidine derivative 119. Treatment of 119 with ethyl chloroformate, followed by reduction of the nitro group, gave aniline derivative 120. Diels-Alder substrate 122 was assembled by condensation of 120 with aldehyde 121, followed by trapping with methyl chloroformate. Heating 122 to 185°C provided tetracycle 123 as the only product in 99% yield. The C-ring was constructed rapidly by indoline deprotection and intramolecular amide formation to give pentacycle 124, which in turn was allylated to furnish the intramolecular Heck substrate 126. A Heck reaction then led to ring closure providing the bridged piperidine system with retention of stereochemistry at the double bond of the vinyl
Scheme XII. Rawal's Total Synthesis of Strychnine

(a) BrCH₂CH₂Br, 50% NaOH, CH₃CN, n-Bu₄NBr, 23°C  (b) DIBAL, toluene, -78°C  (c) BnNH₂, Et₂O
(d) TMSCI, NaI, DMF, 60°C  (e) ClCO₂Me, acetone, 23°C  (f) 10% Pd/C, HCO₂NH₂, MeOH  (g) 23°C
(h) ClCO₂Me, PhNEt₂  (i) MeSi, CHCl₃, 61°C, 5h  (j) MeOH, 65°C, 6h  (k) DMF, acetone, K₂CO₃  (l)
Pd(OAc)₂, Bu₄NCl, DMF, K₂CO₃, 70°C, 3h  (m) 2h, HCl, THF.

Strychnine 102
Isostrychnine 126
Iodide. Deprotection of the alcohol concluded this hitherto shortest synthesis of racemic isostrychnine, in 14 steps and 35% overall yield. This formal synthesis is also confronted with the inefficient conversion from isostrychnine to strychnine. Taking into account of Kuehne's reported yield of 28%, Rawal formally accomplished the total synthesis of strychnine in 15 steps, with an overall yield of almost 10%.

The transformation of isostrychnine to strychnine was first recognized as a problematic step by the Prelog group in 1948. Treatment of isostrychnine with ethanolic potassium hydroxide at 80°C produced strychnine in very low yield. There are three reported yields in the literature: 5-8% by Prelog, 12% by Woodward, and 28% by Keuhne. The majority of the material appeared to be converted into the so-called isostrychnine acids, derived from hydroxide cleavage of the lactam and subsequent β-elimination and epimerization at C-17. The poor conversion was rediscovered almost 40 years later by Keuhne and Magnus. Even with a list of so-called "modern bases", Magnus and his coworkers were not able to improve the outcome of the reaction. As a result, both Magnus and Overman focused their attention on construction of the Wieland-Gumlich aldehyde (3), whose high-yield conversion to strychnine had been demonstrated by Anet and Robinson.

The initial steps in the Magnus synthesis followed Harley-Mason's classical approach to the Strychnos alkaloids (Scheme XIX-A and Scheme XIX-B). The key step in this strategy is the transannular iminium ion cyclization of a nine-membered ring for stereoselective construction of D and E rings of strychnine. Tetracyclic amine 129, which was readily available from tryptamine 127 and keto ester 128, was converted to ring expansion product 130 by β,β,β-trichloroethyl chloroformate induced fragmentation. To construct the F-ring, amide 131 was prepared and treated with sodium hydride in THF to give 132a. The stereoselectivity of this 1,4-addition was attributed to protonation of the intermediate ester enolate from the top face. Oxidation to the corresponding sulfoxide followed by a Pummerer reaction and Hg²⁺-mediated hydrolysis.
furnished keto amide 133 as the only product. Considerable effort was made to build the optically active series. Acylation of 130 with (+)-(R)-p-toluenesulfinyl acetic acid and subsequent cyclization of the resulting sulfoxide afforded 132b with very poor selectivity at C-15. Laborious separation made the process unworkable. Transformation of rac-133 to the corresponding acetal followed by reduction of the amide provided 134, which upon exposure to mercury(II) acetate afforded 136 in 65% yield with remarkable regio- and stereoselectivity. The transannulation occurred presumably via the cyclic iminium intermediate 135. Vinylogous carbamate 136 was reduced with zinc dust whereupon addition of hydride to C-16 occurred from the top face to give 137a. This ester was epimerized to the thermodynamically more favored 137b with sodium methoxide. The subsequent protection at Nα, reduction with lithium borohydride, and acidic hydrolysis of the ketal provided hemiketal 138. Arguing that ketal 138 could be obtained less expensively and in less time from strychnine than that from tryptamine 127, Magnus decided to degrade strychnine to relay hemiketal 138. Gram quantities of 138 was obtained in three steps from the protected Wieland-Gumlich aldehyde 141 in 40% overall yield. Once enough hemiketal 138 was secured, assembly of G-ring was investigated. Treatment of 138 with triisopropylsilyl triflate in the presence of DBU afforded the ring-opened ketone, which was olefinated using a Wittig-Homer reaction to furnish α,β-unsaturated cyanide 139 as a 2:3 mixture of (Z) and (E) isomers. The issue of stereoselective construction of the (E)-double bond at C-20 that once challenged Woodard, presented a difficult task again to Magnus, revisited not too much later by Kuehne. Although irradiation favored the desired E isomer, the process is far from optimal. A number of steps led to unstable aldehyde 140. Upon removal of the silicon protecting group gave 141, which was reductively deprotected with sodium anthracenide to give the Wieland-Gumlich aldehyde (3). According to the protocol reported by Robinson, treatment of 3 with malonic acid gave strychnine (4) in 70% yield. The Magnus total synthesis required 27 steps and proceeded with an overall yield of 0.03%.
The only enantioselective total synthesis of strychnine was accomplished by the Overman group. The key to their approach is the sequential cationic aza-Cope rearrangement/Mannich cyclization (Scheme XX-A and Scheme XX-B). In their synthesis of akuammicine, the authors proved that this strategy offers an efficient route to the Strychnos alkaloids. The strategy revolved around the synthesis of aza-Cope-Mannich substrate 152. The synthesis began with enantiomerically pure 143, which was readily available from enantioselective hydrolysis of cis-3,5-diacetoxycyclopentene in the presence of electric eel.
Scheme XX-A. Overman's Total Synthesis of Strychnine

\[ \text{Scheme XX-A. Overman's Total Synthesis of Strychnine} \]

\[ \begin{align*}
\text{a) } & 142 \quad R = \text{Ac} \\
\text{b, c) } & 143 \quad R = \text{H} \\
\text{d) } & 144 \quad \text{(1:1)} \\
\text{e) } & 145 \\
\text{f) } & 146 \\
\text{g) } & 147 \\
\text{h) } & 148 \\
\text{i) } & 149 \\
\text{j) } & 150 \\
\text{k) } & 151 \\
\text{l) } & 152
\end{align*} \]

\[ \text{X = NHCOCF}_3 \]
Scheme XX-B. Overman’s Total Synthesis of Strychnine (continued)

(a) acetylcholine esterase, (cat), hydrolysis  (b) ClCO₂Me, pyridine, CH₂Cl₂, 23°C  (c) t-BuOCH₂COCH₂CO₂Et, NaH, 1% [Pd₂(db₃)₃], THF, 23°C  (d) NaCNBH₃, TiCl₄, -78°C  (e) DCC, CuCl, C₆H₆, 80°C  (f) DIBAL, CH₂Cl₂, -78°C  (g) TiPS₂Cl, tetramethylguanidine, NMP, -10°C  (h) Jones, -5°C;  (i) L-selectride, PhNTf₂, THF, -78-0°C  (j) Me₃Sn₂, 10% [Pd(PPh₃)₄], LiCl, THF, 60°C  (k) 149, 2.5% [Pd(db₃)₂], 22% Ph₃As, CO, LiCl, NMP, 70°C  (l) t-BuO₂H, Triton-B, THF, -15°C  (m) Ph₃P=CH₂, THF, 0-23°C  (n) TBAF, THF, -15°C  (o) MsCl, i-Pr₂NET, CH₂Cl₂, -23°C  (p) LiCl, DMF, 23°C  (q) NH₂CO₂F, NaH, DMF, -23°C  (r) NaH, C₆H₆, 100°C  (s) KOH, EtOH, H₂O, 60°C  (t) (CH₃)₂CO, Na₂SO₄, CH₃CN, Δ  (u) LDA, NCCO₂Me, THF, -78°C  (v) 5% HCl-MeOH  (w) Zn, 10% H₂SO₄, MeOH, reflux  (x) NaOMe, MeOH  (y) DIBAL, CH₂Cl₂, -78°C  (z) CH(CO₂H)₂, Ac₂O, NaOAc, HOAc, 110°C.

acetylcholine esterase. Palladium-catalyzed allylic substitution furnished the β-keto ester 144, which were reduced with high diastereoselectivity (>20:1) to provide a mixture of anti-β-
hydroxy esters 145. Subsequent syn elimination gave the (E) isomer 146 almost exclusively (97:3). This solved the problem of stereoselective construction of what would eventually become the C-20 allylic ether double bond. Reduction of 146 with DIBAL, followed by selective protection of the diol and Jones oxidation provided cyclopentenone 147. Reduction of this intermediate with lithium tri-sec-butylborohydride and trapping of the resulting enolate with N-phenyltriflimide provided an enol triflate, which underwent palladium-catalyzed stannylation to give alkenylstannane 148. α,β-Unsaturated ketone 150 was prepared by palladium-catalyzed carbonylative cross-coupling of vinyl stannane 148 with protected o-iodoaniline 149. Substrate-controlled stereoselective epoxidation of 150, followed by Wittig methylenation and side chain elaboration provided allylic epoxide 151. Intramolecular aminolysis gave the key intermediate 152. The aza-Cope-Mannich cascade was triggered by heating 152 in the presence of paraformaldehyde and sodium sulfate. Presumably, intermediate 153 was formed and underwent [3,3]-sigmatropic rearrangement to give 154. This intermediate contains all the structural features needed for the ensuing intramolecular Mannich cyclization. At the end of the cascade, 155 was obtained as the single product in almost quantitative yield. Acylation of 155 at C-16 with methyl cyanoformate, followed by cleavage of the triazole and tert-butyl protecting groups simultaneously afforded pentacycle 156. Reduction of the C-2—C-16 double bond, followed by epimerization at C-16, furnished 157. Reduction of the ester with DIBAL gave the target Wieland-Gumlich aldehyde (3) and subsequently strychnine (4). Overman accomplished this first enantoioselective total synthesis of strychnine in 25 steps and an overall yield of approximately 3% and without separation of racemates and without use of relay compounds. The entire synthesis flows beautifully around modern palladium-catalyzed reactions and the elegantly designed aza-Cope-Mannich sequence, a signature of Overman's work.

Whether or not the four new syntheses of strychnine represent a fundamental improvement over Woodward's original plan, and the extent of the improvement, is certainly a
matter of debate. Nevertheless, the significant improvement of overall yield relative to the first total synthesis is noteworthy. Whereas Magnus improved the yield by a factor of 1000, Overman, Kuehne and Rawal raised the overall yield by a factor of 100,000. It is interesting to note how the idea of “designed synthesis” evolved from its infancy to what it is now, with the frequent use of sequential reactions and intramolecular cycloadditions. What is undeniable is that the availability of improved synthetic methods and modern reagents, especially those resulting from the development of organometallic chemistry and its application in organic synthesis, made it possible. Thus, the development of new synthetic methods and reagents are driven to assist in the continuing search for more efficient and selective “designed” syntheses.
I. Introduction: Retrosynthetic Plan

In the last chapter, a number of approaches to the pentacyclic Strychnos alkaloids were discussed. It was seen that successful constructions of the pentacyclic core sometimes served as prelude to total syntheses of strychnine.\textsuperscript{34,36,37,40} This thesis will present a new approach to the pentacyclic skeleton, such as that in (±)-tubifoline (17), an approach that revolves around an intramolecular 1,3-dipolar cycloaddition reaction.

Our retrosynthetic plan is shown in Scheme XXI. The B-ring was to be constructed at the end of the synthesis from a tricyclic compound of type 158. This projected key intermediate resembles compounds seen in the work of Overman and Bosch (see Chapter 1).\textsuperscript{31,34} In terms of completing the synthesis from 158, introduction of functionality at C-16 and closure of the indole ring was well-precedented chemistry.\textsuperscript{31,34} Also it was hoped that hydrogenation of 158 would occur from the convex face of the cage structure to establish stereochemistry at C-20. Continuing with the retrosynthesis, it was hoped that 158 could be prepared by an intramolecular cycloaddition of an azomethine ylid of type 159. This cycloaddition would establish relative
stereochemistry at C-3, C-7 and C-15 in 158. It is also noted that for topological reasons, in the cyclization transition state the C-15 substituent in 159 must be axially disposed for the tethered dipolarophile to be able to approach the azomethine ylid. The importance of this requirement will surface later in the thesis. Continuing with the retrosynthesis, it was imagined that the key azomethine ylid (159) could be prepared from an N-trialkylsilyl-2-cyanopiperidine derivative of type 160 using established methodology for the preparation of azomethine ylids (vide infra). This ylid precursor was to be prepared from an allylic alcohol of type 161 using either a [3,3]-sigmatropic rearrangement or an $S_{n}^{2}$ reaction. Finally, 161 was to be prepared by reductive

**Scheme XXI. Retrosynthetic Plan for Pentacyclic Strychnos Alkaloid via an Intramolecular 1,3-Dipolar Cycloaddition**

```
X = a masked nitrogen or substituent can be converted to nitrogen.
```
cyanation of a pyridinium salt of type 162.

A key aspect of the plan outlined in Scheme XXI is the intramolecular azomethine ylid cycloaddition. Some good reviews have been published on this topic. Thus, only a brief overview of azomethine ylid chemistry relevant to this thesis will be presented here. One versatile method for the generation of azomethine ylids is summarized in Scheme XXII. This general approach involves in situ iminium ion formation from an aminal derivative of type 163 with simultaneous desilylation to generate the azomethine ylid (164). A number of "leaving group" have been used for the iminium ion generation, including phenylthio, cyanide, and methoxy groups. The method used in this thesis involves α-cyanoamines as the iminium ion precursor (163b). The Padwa group was one of the first to examine this route to azomethine ylids. They showed that treatment of 163b (R=Bn) with silver fluoride promoted metal-assisted decyanation and concomitant desilylation to give the 1,3-dipole 164 (R=Bn). When this was done in the presence of electron-deficient dipolarophiles, pyrrolidine derivatives of type 165 were obtained.

Scheme XXII. Generation of Unstable Ylids from Aminal Derivatives

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \begin{array}{c}
\text{N} \\
\text{R}_1
\end{array} \quad \begin{array}{c}
\text{X} \\
\end{array} & \quad \begin{array}{c}
\Theta \\
\text{CH}_2
\end{array} \quad \begin{array}{c}
\text{N} \\
\text{R}_1
\end{array} & \quad \begin{array}{c}
\Theta \\
\end{array} \quad \begin{array}{c}
\text{Y} \\
\end{array} & \quad \begin{array}{c}
\text{Z} \\
\end{array} \\
\text{163a} & \quad X = \text{SPh} & \quad 164 & \quad \text{Y and/or } Z = \text{EWG} & \quad 165 \\
\text{163b} & \quad X = \text{CN} & \quad & \quad & \\
\text{163c} & \quad X = \text{OMe}
\end{align*}
\]

\[
\text{166} \xrightarrow{\text{a,b}} \text{167} \xrightarrow{\text{c}} \text{168} \xrightarrow{\text{d,e,f}} \text{Retronecine (169)}
\]

R = ortho-nitrobenzyl

(a) MeOTf (b) CsF (c) H$_2$C=CHCO$_2$Me (d) DIBAL (e) PhSeCl (f) m-CPBA.
An underlying problem in azomethine ylid chemistry is that the iminium ion and the corresponding enamine can be in equilibrium. Consequently, there can be a competition between the desired 1,3-dipolar cycloaddition and conjugate addition of the enamine to the dipolarophile. Although this is not always a problem, it can be a major pathway to ylid destruction, especially when trapping of the ylid is slow. Nonetheless, there are examples where the chemistry outlined in Scheme XXII has been used to prepare unsymmetrical azomethine ylids, capable of enamine formation, for use in 1,3-dipolar cycloadditions. The example shown in equation 1, used by the Vedejs group in their approach to the total synthesis of (+)-retronecine, is illustrative.48

In summary, whereas 1,3-dipolar cycloaddition chemistry of azomethine ylids promises to be a powerful method for pyrrolidine synthesis, it has not been used too frequently for the synthesis of natural products containing this substructure. Therefore, our approach to the strychnos alkaloids is not without risk and could, in a way, be regarded as treacherous.

II. Model Studies: Synthesis of 1-Trialkysilylmethyl-2-cyano-1,2,3,6-tetrahydropyridines and their Use as Azomethine Ylid Precursors

Rather than beginning with the synthesis of highly substituted azomethine ylid precursors of type 160, this project began with more modest goals. We first set out to answer several key questions: (1) Could azomethine ylid precursors of type 161 be prepared by reductive cyanation of pyridinium salts of type 162? (2) If so, could they (161) be used to generate unsymmetrical azomethine ylids? (3) Would ylids derived from 161 participate in cycloaddition reactions? Therefore, the initial goal was the synthesis of 1-trialkysilylmethyl-2-cyano-1,2,3,6-tetrahydropyridines (Scheme XXIII) and an examination of their behavior upon treatment with silver fluoride in the presence of dipolarophiles (Scheme XXV).

The approach to 1-trialkysilylmethyl-2-cyano-1,2,3,6-tetrahydropyridines that was adopted was based on the reaction shown in equation 2 in Scheme XXIII-A.49 Fry had shown that
reduction of pyridinium salts of type 170 with sodium borohydride in the presence of sodium cyanide gave 1-alkyl-2-cyano-1,2,3,6-tetrahydropiperidines of type 171 in 74% yield (Scheme XXXIIIa, eq 2). Reduction of pyridium salts with trialkylsilylmethyl groups on the nitrogen, however, were unknown. Thus, we started by preparing N-(trialkylsilylmethyl)pyridinium salts from 4-picoline (172), and examining their behavior under reductive cyanation conditions (Scheme XXIII-A).

Treatment of 4-picoline (172) with commercially available trimethylsilylmethyl iodide in acetone at 65-70°C for 54 hours provided a 1:1 mixture of N-trimethylsilylmethyl-4-methylpyridinium iodide (174) and N-methyl-4-methylpyridinium iodide (170). The ratio was determined by integration of the methylene and the methyl signals of each compound in the ¹H NMR spectrum of the mixture, which appeared at δ 4.80 (174) and 4.60 (170). Although these compounds had a reasonable Rₜ difference by TLC, attempts to separate the two salts by chromatography were not successful. Fractions containing the desired 174 were soon

Scheme XXIII-A. Preparation of 2-Cyano-1,2,3,6-Tetrahydropyridines

\[ \text{170} \xrightarrow{\text{a}} \text{171} \]

\[ \text{172} \xrightarrow{\text{b}} \text{173} + \text{170} \]
contaminated with 170 and separation by recrystallization also failed. Independent preparation of 170 from 4-picoline and methyl iodide (94%), however, clearly established its identity and presence as a reaction product.
It was suspected that 170 came from desilylation of 173 by iodide ion, followed by protonation of an intermediate pyridinium ylid. Based on this hypothesis, it was decided to examine triflates as alkylating agents, with the hope that a less nucleophilic counterion might not desilylate the product. Thus, treatment of 4-picoline with commercially available trimethylsilylmethyl triflate in acetone gave the desired pyridinium triflate 174 in 92% yield after recrystallization. This compound was stable for long periods of time and it appeared that changing the counterion had solved the desilylation problem.

We next turned to the reductive cyanation of 174. Exposure of 174 to one equivalent of sodium borohydride and large excess of sodium cyanide in a mixture of water, ether and methanol led only to decomposition without detection of any products. Since the salt (174) was stable to the solvent system used in the reaction, it was presumed that cyanide and/or hydride was behaving as a nucleophile, once again causing desilylation problems. Based on this hypothesis, it was decided that a sterically hindered silicon group might slow desilylation down enough such that nucleophilic addition to the pyridinium ion would become the predominant reaction pathway. Therefore, we decided that tert-butyldiphenylsilylethylmethyl triflate might be the reagent of choice.

Treatment of 4-picoline with tert-butyldiphenylsilylmethyl triflate (186) gave the hygroscopic pyridinium salt 175 in 65% yield. Reductive cyanation of 175 now proceeded smoothly to give 178 in 50% yield. It was necessary to use more than ten equivalents of sodium cyanide, and the reaction was complete in less than 30 min. It was found that decreasing the amount of sodium cyanide or prolonging the reaction time led to the over-reduction product 181. As expected, the cyano group in 178 occupied an axial site, based on the appearance of the C-2 hydrogen as a distinct doublet of doublets at δ 3.58 (J = 6.0, 1.5 Hz). This observation can be rationalized by an anomeric-type effect. The position of the double bond in 178 was secured by comparing its 1H NMR and 13C NMR data with those reported for 183 through 186. For example, the C-2 hydrogen of 2-cyano-1,2,3,6-tetrahydropyridines 183 and 184 appeared as a doublet of doublets at δ 3.67 and 3.69, respectively. In 2-cyano-1,2,5,6-tetrahydropyridines 185
and 186, the C-2 hydrogen appeared at δ 3.83 and 3.75, respectively, slightly deshielded relative to 183 and 184 due to the vicinal double bond. Also an absence of coupling of the C-2 hydrogen with the olefinic proton was obvious in 1,2,5,6-tetrahydropiridines 185 and 186. The formation of 178 (rather than 182) implied that in the reduction of 175, attack of hydride at the 2-position of the pyridine ring initially gives 176. Protonation of the resulting dienamine at C-4 gives iminium ion 177, which is then captured by cyanide ion to give 178. To establish the generality of this process, pyridine was subjected to the same reaction sequence to provide pyridinium salt 179 and tetrahydropyridine 180 in 98% and 30% yields, respectively.

Before proceeding, it should be noted that tert-butyldiphenylsilylmethyl triflate (186) is a new reagent. This reagent was prepared as shown in Scheme XXIV. tert-Butyldiphenylsilyl lithium is not as well known as trimethylsilyl lithium or the more extensively used dimethylphenylsilyl lithium, but it was prepared on a large scale by treating commercially available tert-butyldiphenylchlorosilane (187) with lithium in tetrahydrofuran at 0°C for 4 h according to a reported procedure. Trapping of this carbanion with paraformaldehyde afforded tert-butyldiphenylsilylmethyl alcohol (188) in 78% yield. Although this alcohol had been reported as a side product, the chemistry shown in Scheme XXIV is the first preparative procedure for 188. Alcohol 188 was transformed to triflate 189 in 93% yield following a slightly modified protocol for the preparation trimethylsilylmethyl triflate. Both alcohol 188 and triflate 189 were purified by recrystallization, although sometimes silica gel chromatography was needed to remove impurities. The process allowed the synthesis of over 30-g quantities of both 188 and 189.

**Scheme XXIV. Preparation of tert-Butyldiphenylsilylmethyl Triflate**

![Scheme XXIV](image)

(a) Li, 0°C, THF, 4 h then (HCHO), (b) Tf₂O, pyridine.
With both piperidines 178 and 180 in hand, the possibility of using them as precursors to unstabilized azomethine ylids was investigated (Scheme XXV). When a mixture of 178 and N-methylmaleimide in acetonitrile was stirred overnight in the dark in the presence of 5 equivalents of silver flouride, a 1:1 mixture of diastereomeric cycloadducts 190a and 190b were isolated.

Scheme XXV. Intermolecular 1,3-Dipolar Cycloadditions of 178

(a) AgF, CH3CN, N-methylmaleimide, rt (b) AgF, CH3CN, trans-1,2-bis(phenylsulfonyl)ethylene
in 68% yield. These isomers could be separated with difficulty by column chromatography over silica gel.

Unfortunately, the cycloaddition chemistry of 178 did not extend well to other dipolarophiles. For example, ethyl acrylate, 1,4-benzoquinone and dimethyl acetylene-dicarboxylate all failed to produce cycloaddition products. The only other case when cycloadducts were isolated was in the reaction of 178 with trans-1,2-bis(phenylsulfonyl)ethylene, which gave a 1:1 mixture of 191a and 191b in a combined yield of 20%.

With the help of 'H-13C COSY, 13C-1H COSY, and 13C DEPT spectra, we were able to decide that all of the cycloadducts came from the trapping of an azomethine ylid generated from an iminium of type C. The migration of the double bond presumably involved formation of iminium ion A, followed by isomerization to enamine B and subsequent protonation to provide C. Desilylation of iminium ion C then generated the azomethine ylid which was captured by the electron-deficient double bonds. The position of the double bond was secured by the strong couplings observed between the protons at C-5 and C-6, and also between H₆ and H₇. Difference nOe experiments with 191b showed that H₃, H₄, H₅, and H₆ were on the same side of the molecule, while irradiation of H₁ resulted in a 5.2% enhancement at H₆. Furthermore, H₅ in both 190b and 191b appears to be a broad singlet at δ 3.8. The absence of coupling between H₁ and H₅ was rationalized by a H₁ and H₅ dihedral angle approaching 90° in 190b and 191b. In 190a H₅ shows up as a doublet at δ 3.32 with J = 9.5 Hz, indicating that the dihedral angle between H₁ and H₅ close to 0° in 190a.

To our great disappointment, all attempted cycloadditions using 180 met with failure. In most cases, decomposition of the starting 2-cyanotetrahydropyridine was observed within an hour and complex mixtures of products were produced. Despite laborious separation attempts, not a trace of the desired cycloadducts, nor any other identifiable materials, were isolated. Worst of all, it seemed that the source and quality of the hygroscopic silver fluoride had some influence on the outcome of these rather capricious reactions.
Although we did not have as thorough an understanding of the cycloaddition chemistry as we would have liked, the aforementioned studies had demonstrated that N-(trialkylsilylmethyl)-2-cyano-1,2,3,6-tetrahydropyridines could be prepared by reductive cyanation of the corresponding pyridinium salts, that they could serve as azomethine ylid precursors, and that the azomethine would undergo intermolecular cycloaddition to at least two very reactive dipolarophiles. With the hope that intramolecularity would improve the cycloaddition, we decided to move on to a version of the reaction that would have more direct relevance to our approach to the *Strychnos* family of alkaloids.

**III. Model Studies Directed Toward an Intramolecular 1,3-Dipolar Cycloaddition**

Our initial studies followed a variation of the plan outlined in Scheme XXI. Thus, we began

**Scheme XXVI. Plan for Synthesis of 1,3-Dipolar Cycloaddition Substrate 195**

![Synthesis Scheme](image)

192 \[\rightarrow \] 193

193 \[\rightarrow \] 195

195 \[\rightarrow \] 194

48
Scheme XXVII. Synthesis of 197

![Scheme XXVII](image)

(a) CICONEt₂, Et₂N, PhH (b) sec-BuLi, TMEDA then CH₃I.

with 3-hydroxypyridine derivative 192 with the hope of sequentially introducing the dipolarophile side chain (192→193), transforming the pyridine into the azomethine ylid precursor (193→194→195), and finally examining the key cycloaddition (Scheme XXVI). We began by converting 3-hydroxypyridine (196) to carbamate 192 because of the renowned directing effect of carbamates in metallation reactions (Scheme XXVII). Thus, heating a mixture of 3-hydroxypyridine (196) and N,N-diethylchlorocarbamate in the presence of triethylamine afforded 192 in 94% yield. Treatment of 192 with 1.3 equivalents of sec-butyllithium in the presence of TMEDA effected lithiation at the 4-position due to the powerful directing effect of the carbamate. Alkylation of this carbanion with methyl iodide furnished 197 in 67% yield (Scheme XXVII).

The pyridyl methyl group in 197 was acidic enough to be deprotonated by n-butyllithium. Thus we next studied reactions of this carbanion (198) with a variety of electrophiles. The results are documented in Table 1. To summarize the results, carbanion 198 reacted well with aldehydes such as paraformaldehyde, methacrolein and aldehyde 202 but failed to react with less reactive electrophiles such as N,N-dimethylformamide, Weinreb-amide 199, and ethylene oxide. Most relevant to the projected route to the Strychnos alkaloids was the reaction with methacrolein. When this reaction was maintained and quenched at -78°C, 1,2-adduct 193 and 1,4-adduct 201 were isolated in 52% and 18% yields, respectively. When the reaction mixture
Table 1. Reactions of Carbanion 198

<table>
<thead>
<tr>
<th>Electrophiles</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>No reaction</td>
</tr>
<tr>
<td>PhS</td>
<td>No reaction</td>
</tr>
<tr>
<td>(\text{CH}_3) (\text{NMe}_2)</td>
<td>No reaction</td>
</tr>
<tr>
<td>((\text{HCHO})_n)</td>
<td>(\text{193 (50%) + 201 (18%) + 202 (90%)})</td>
</tr>
<tr>
<td>(\text{CH}_3) (\text{CH}_2) (\text{CHO})</td>
<td>(\text{193 (50%) + 201 (18%) + 202 (90%)})</td>
</tr>
</tbody>
</table>
Scheme XXVIII. Migration of the Carbamate Group

(a) n-BuLi, then methacrolein, THF, -78°C
(b) n-BuLi, then methacrolein, -78°C-50°C
(c) SEMCl, i-Pr₂EtN, benzene, reflux.

was warmed to 45°C for 30 min before quenching, 3-hydroxydipyridine 205 and 1,4-adduct 201 were isolated in 65% and 20% yields (Scheme XXVIII), respectively. Apparently the carbamate group migrates from the pseudo-phenolic oxygen to the hydroxyl group, probably via tetrahedral intermediate 204 (Scheme XXVIII). This acyl transfer is probably facilitated by the ortho disposition of the two groups on the pyridine ring, and the equilibrium clearly lies to the side of the less basic alkoxide.

It was anticipated that protection of the 3-hydroxyl group of 205 with an acid-labile but base-stable protecting group, and subsequent hydrolysis of the carbamate, might be useful in reaching our goal 195. Unfortunately any conditions involving deprotonation of the 3-hydroxyl...
group were non-productive, possibly because intramolecular ring closure to form 204 prohibited attack of the alkoxide on an external electrophile. As a result, starting material 205 was always recovered. Other conditions were examined. For example, treatment of 205 with SEM-CI in the presence of Hunig's base at room temperature led only to recovery of starting material 205. When more forcing conditions were applied, namely heating in benzene at reflux, the 3-hydroxyl group was protected but concommitant elimination occured, leading to the formation of diene 206 in 31% yield. These discouraging results led us to look in other directions.

Scheme XXIX. Preparation of the Thio-substituted Amide and Aldehyde

(a) PhSH, neat  (b) LiOH  (c) (MeO)MeNH-HCl, DCC, Et,N.

Next, we briefly addressed the problem of competitive 1,2-addition and 1,4-addition in the reaction of carbanion 198 with methacrolein. In this regard, we decided to examine the behavior of aldehyde 202 an amide 199 as electrophiles. The former (202) could only undergo 1,2-addition chemistry and sulfur would serve as a handle for later introduction of the double bond of the dipolarophile. The latter (199) would introduce the side chain with the proper oxidation state at C-2'. These electrophiles were prepared as outlined in Scheme XXIX without comment. Whereas Weinreb-amide 199 failed to react with 198 (see Table 1), aldehyde 202 did provide the desired 1,2-addition product (203) in 90% yield (see Table 1). If the temperature was kept low enough, migration of the carbamate was not a problem. We did not proceed with 203, however, due to problems that surfaced in the next few steps of the synthesis (vide infra).
Although the synthesis of 190 was not ideal, it was good enough to proceed with the task of converting it to an azomethine ylid precursor of type 195 (see Scheme XXVI). Therefore, we continued as shown in Scheme XXX. N-Alkylation of 193 with triflate 189 gave pyridinium salt 207 in 90% yield. When the white crystals of 207 were exposed to the reductive cyanation conditions, the corresponding 2-cyanotetrahydropyridine 194 was isolated in 40% yield. Swern oxidation of 194 provided 208 in 72% yield.  

Although enone 208 was remarkably close to the desired intramolecular cycloaddition substrate (195), we were never able to reach that goal because difficulties were encountered.

Scheme XXX. Preparation of Enone 195

(a) TBDPSCH₂OTf, CH₃CN, rt, 98%  (b) NaCN, NaBH₄, H₂O-CH₃OH-Et₂O, 40%  (c) DMSO, (COCl)₂, then Et₃N, 72%.
when we attempted to deprotect the enol carbamate. We first tried basic conditions, such as potassium hydroxide, on both 194 and 208. When those conditions failed, the enolic nature of the carbamate led us to study electrophilic conditions. Different concentrations of mineral acids were tried in an array of solvent systems. Lewis acids such as mercuric acetate were also tested. Most of the time the cyano group was removed, leading to unidentifiable materials. It now will be clear to the reader why the brief search for a more labile protecting group was conducted (vide supra). In the event, this promising start (6 steps from 3-hydroxypyridine to 208) was never brought to completion.

It might appear that 208 could be a possible cycloaddition substrate, but this is not the case because the trigonal planar geometry at C-5 would prevent approach of the dipolarophile to the azomethine ylid. Thus, attention was turned to the preparation of substrate more relevant to the plan described in Scheme XXI.

4. Synthesis and Attempted Cycloaddition of Substrate 223

The initial plan was to use the pyridine alkylation-reductive cyanation sequence described above to convert 3-acetylpyridine (209) to allylic alcohol 210. Claisen rearrangement methodology was then to be used to introduce the dipolarophile-carrying side chain (210→211) (Scheme XXXI). Our first attempt at accomplishing these transformations quickly met with
problems. Although alkylation of commercially available 3-acetylpyridine (209) with triflate 189 gave pyridinium salt 212 in 60% yield, attempted reductive cyanation gave material whose structure was not determined (Scheme XXXII, eq 6). None of the desired product 210 was obtained. Model work with N-methyl-3-acetylpyridinium triflate (213) was promising however, as reductive cyanation of this material provided α-cyanoamine 214 and the over-reduction product 215 (Scheme XXII, eq 7). Although the evidence was not strong, these results suggested that somehow, conducting a “double-reduction” of an N-trialkyisilylpyridinium salt was not advisable and it was decided to sequentially reduce the acetyl group, form the pyridinium salt, and then attempt the reductive cyanation. This approach was successful as shown in Scheme XXXIII. Thus, reduction of 3-acetylpyridine with sodium borohydride in methanol gave alcohol 216 in 84% yield. Treatment of this compound with triflate 189 provided the corresponding pyridinium salt
217 in 87% yield. This crystalline salt was exposed to the reductive cyanation conditions to afford allylic alcohol 210 in 56% yield.

With the α-cyanotetrahydropyridine moiety and allylic alcohol installed, the next task was to introduce the dipolarophile-bearing side chain with transposition of the double bond using [3,3]-sigmatropic rearrangement. The original plan was to prepare α-ketoester 218a and then perform a double-Tebbe\(^*\) or double-Petasis\(^*\) reaction to obtain rearrangement substrate 218b. Whereas esterification of 210 could be accomplished in 48% yield using α-keto benzoic acid, in

**Scheme XXXIII. Synthesis of Allylic Alcohol 210**

(a) TBDPSCH\(_2\)OTf (189), CH\(_3\)CN, rt (b) NaCN, NaBH\(_4\), MeOH-Et\(_2\)O-H\(_2\)O, rt

the presence of DCC and DMAP, the double-methylenation was unsuccessful. This was unfortunate as rearrangement of 218b would have directly provided dipolar cycloaddition substrate 211. Phenylacetate 219 and formate 220 were also prepared as simpler substrates
for investigation of the methylenation-Claisen sequence, in the hope that they would shed some light on the problem, but both substrates failed to render information that allow one to draw firm conclusions.

On the other hand, the Eschenmoser-Claisen rearrangement served nicely to begin introduction of the desired C-4 side chain (Scheme XXXIV). Thus, when allylic alcohol 210 was heated with \( N,N \)-dimethylacetamide dimethyl acetal in xylene, an almost spot-to-spot transformation afforded amide 222 as an 8:1 mixture of trans and cis isomers in 83% yield. The ratio of isomers was determined by integration of signals at \( \delta \) 4.97 and 5.18, corresponding to the vinyllic protons of the trans (222a) and cis (222b) isomers, respectively. Both isomers appeared to have clean double bond geometry, presumably the result of equatorial disposition of the methyl group in the chair-like Claisen rearrangement transition state 221. Although separation of the two isomers by chromatography over silica gel was very difficult, the major trans isomer (222a) could be purified by recrystallization from dichloromethane and hexanes to give an analytically pure sample upon which extensive NMR studies were conducted. It is notable that when pure 222a was allowed to stand overnight in deuteriochloroform, epimerization at C-2 occurred to give

\[
\text{Scheme XXXIV. Preparation of Methylamide 220}
\]

\[
\begin{align*}
\text{210} & \xrightarrow{a} \text{TBDPS} & \text{TBDPS} & \text{TBDPS} \\
\text{H(NCN)} & \text{H(NCN)} & \text{O} & \text{NMe}_2 \\
\text{CH}_2 & \text{CH}_2 & \text{Me}_2N & \text{O} \\
\text{221} & \rightarrow & \text{222a} & R_1 = H, R_2 = \text{CN} \\
& & & 222b & R_1 = \text{CN}, R_2 = H
\end{align*}
\]

(a) \( N, N \)-dimethylacetamide dimethyl acetal, xylene, \( \Delta \).
a 3:1 mixture of trans and cis isomers. This isomerization, however, was much slower in benzene-
\(_d_6\) and therefore most of the NMR studies were conducted in that solvent.

Based on NMR data, it was possible to determine structural and conformational preferences of 222a in great detail. A combination of \(^{13}\)C DEPT, \(^1\)H-\(^1\)H COSY and \(^1\)H-\(^{13}\)C COSY spectroscopy allowed the assignment of most of the peaks in the \(^1\)H and \(^{13}\)C NMR spectra of 222a. For example H-2 appeared as a triplet (\(J = 2.6 \text{ Hz}\)) at \(\delta 3.39\), indicative of its equatorial disposition. Both H-3a and H-3e were also observable as a triplet of doublets (\(J = 12.6\), and 4.4 Hz) and a doublet of triplets (\(J = 15.1\) and 8.5 Hz) at \(\delta 1.27\) and 1.94, respectively. These coupling patterns suggest that H-4 (observed as a multiplet overlapping with other signals at \(\delta 2.84\)) is axially disposed (big coupling with H-3a and small with H-3e). These coupling data alone

\[
\begin{align*}
\text{Proton} & \quad \text{Proton nOe Observed} \\
\text{Irradiated} & \quad \text{(intensity)} \\
\text{CH}_3 & \quad \text{H}_{3a} (8.6 \%) \\
\text{H}_{3a} & \quad \text{H}_2 (6.2 \%) \\
\text{H}_{3a} & \quad \text{H}_{3ae} (2.6 \%) \quad \text{H}_{3a} (6.5 \%) \\
\text{H}_{3ae} & \quad \text{H}_4 (8.5 \%) \quad \text{H}_2 (6.5 \%) \quad \text{H}_{3a} (3.6 \%) \\
\text{H}_2 & \quad \text{H}_{3ae} (4.9 \%) \quad \text{H}_{3ae} (4.5 \%) \quad \text{H}_{7a} (6.2 \%) \\
\text{H}_9 & \quad \text{H}_{6b} (5.4 \%)
\end{align*}
\]

Fig 1. nOe Studies on Amide 222a.
suggest a trans-relationship between substituents at C-2 and C-4, and also suggest that the C-3 side chain is equatorially disposed. Difference NOe studies confirmed the aforementioned conclusions and also provided evidence for the assignment of the double bond geometry (Figure 1). For example, irradiation of H-2 resulted in nearly equal enhancement of the signals due to H-3a and H-3e, consistent with a gauche relationship between these vicinal protons. On the other hand, whereas irradiation of H-3e resulted in large enhancement of H-4, irradiation of H-3a resulted in no enhancement at H-4 indicative of the trans-diaxial relationship between these protons. Finally, irradiation of the vinylic proton (H-9) resulted in a large enhancement of H-8b. This result confirmed the olefin geometry as assigned and indicates that the C-4 side chain is equatorially disposed.

With 222 in hand, attention was turned to the task of dipolarophile introduction. This was accomplished as described in Scheme XXXV and XXXVI, beginning with the conversion of 222 to aldehyde 223. This required the selective reduction of an amide to the aldehyde oxidation state in the presence of a nitrile, a transformation that was nicely accomplished using a procedure reported by Buchwald. Treatment of 222 with 1.1 equivalents of diphenylsilane and 1.0 equivalent of titanium tetraisopropoxide in benzene at room temperature overnight followed by in situ hydrolysis of the initially formed enamine (THF-1N aqueous HCl, 5:1), gave aldehyde 223 in 60% yield. We note that although the mechanism of this reaction has not been established, Buchwald has suggested that a titanium hydride-like complex, formed by a σ-bond methasis reaction between diphenylsilane and titanium tetraisopropoxide, is the active reductant. The initial reduction is presumed to produce a hemiaminal which collapses to an enamine intermediate.

It was decided to next bring in an α-styryl unit by metal-mediated coupling reaction. This system, which lacks the α-amino functionality required for the Strychnos alkaloids, was chosen to simplify matters at this stage of the study. Substrates studied as the organometallic component included α-bromostyrene (225), α-iodostyrene (226) and 1-phenylethenyl triflate (227). These
Scheme XXXV. Synthesis of Allylic Alcohol 224

![Chemical structure](image)

(a) Ph₂SiH₂, Ti(i-OPr)₄, rt, 16h

were prepared as shown in Scheme XXXVI. Treatment of styrene with bromine afforded the corresponding dibromide, which was dehydrobrominated, using potassium hydroxide under phase transfer catalysis conditions, to give a 15:1 mixture of $\alpha$-bromostyrene (225) and $\beta$-bromostyrene, respectively, in 83% yield. $\alpha$-Iodostyrene was prepared in two-steps by treating acetophenone with hydrazine, followed by reaction of the intermediate hydrazone with iodine and triethylamine. This procedure gave 226 in 48% yield. Vinyl triflate 227 was prepared in only 21% yield by treating acetophenone with triflic anhydride in the presence of triethylamine. On the other hand, treatment of phenylacetylene with triflic acid in hexanes gave a mixture of 13:1 mixture of desired triflate 227 and its isomer 228 in 45% yield. Our first attempts of the metal-mediated coupling involved conversion of bromide 225 to the corresponding lithium and Grignard reagents using tert-butyllithium and magnesium, respectively. These reagents, however, reacted with aldehyde 223 to give complex mixtures of products. It was speculated that these organometallic reagents were probably basic enough to deprotonate both the aldehyde and the $\alpha$-cyanoamine groups instead of undergoing nucleophilic addition to the aldehyde. Therefore, based on literature procedure, it was thought that less basic organocerium (Imamoto)⁶³ or organochromium (Kishi-Nakai)⁶⁴ reagents might be superior.
Scheme XXXVI. Syntheses of Vinyl Halides 225, 226 and Vinyl Triflate 227

\[
\begin{align*}
\text{Ph} & \quad \text{H} & \quad \xrightarrow{\text{a,b}} & \quad \text{Ph} & \quad \text{Br} & \quad 83\% & \quad \text{Ph} & \quad \text{Br} & \quad 225 \\
\text{Ph} & \quad \text{CH}_3 & \quad \xrightarrow{\text{c,d}} & \quad \text{Ph} & \quad \text{I} & \quad 48\% & \quad \text{Ph} & \quad \text{I} & \quad 226 \\
\text{Ph} & \quad \text{CH} & \quad \xrightarrow{\text{e}} & \quad \text{Ph} & \quad \text{OTf} & \quad 21\% & \quad \text{Ph} & \quad \text{OTf} & \quad 227 \\
\text{Ph} & \quad \text{H} & \quad \xrightarrow{\text{f}} & \quad \text{Ph} & \quad \text{OTf} & \quad 43\% & \quad \text{Ph} & \quad \text{OTf} & \quad 227 \\
\text{Ph} & \quad \text{OTf} & \quad \text{H} & \quad \xrightarrow{\text{f}} & \quad \text{Ph} & \quad \text{OTf} & + & \quad \text{Ph} & \quad \text{OTf} & \quad 228
\end{align*}
\]

(a) Br\(_2\), CH\(_2\)Cl\(_2\)  (b) KOH, myristyltrimethylammonium bromide, PhH  (c) NH\(_2\)NH\(_2\), EtOH  (d) I\(_2\), Et\(_3\)N  
(e) Tf\(_2\)O, pyridine  (f) TfOH, hexanes

In the model studies (Scheme XXXVII), for example, CrCl\(_2\)-NiCl\(_2\)-mediated coupling\(^{44}\) of vinyl iodide 226 and vinyl triflate 227 with hydrocinnamaldehyde (229) in either DMSO or DMF (15-24 h) gave allylic alcohol 230 in 48-51% yield (Equations 8 and 9). Although 2-6 equivalents of the starting triflate or iodide were used, these reactions were never complete, and in most attempts, starting aldehyde 229 was recovered along with the desired product.

Scheme XXXVII. Model Studies of CrCl\(_2\)-NiCl\(_2\)-Mediated Coupling of Vinyl Iodide and Vinylic Triflate with Aldehydes

\[
\begin{align*}
\text{Ph} & \quad \text{I} & \quad \xrightarrow{\text{a}} & \quad \text{Ph} & \quad \text{CH} & \quad \xrightarrow{\text{b}} & \quad \text{Ph} & \quad \text{CH} & \quad \xrightarrow{\text{a,b}} & \quad \text{Ph} & \quad \text{CH} & \quad \xrightarrow{\text{b}} & \quad \text{Ph} & \quad \text{OH} & \quad 48\% & \quad \text{Ph} & \quad \text{OH} & \quad 230 \\
\text{Ph} & \quad \text{OTf} & \quad \text{H} & \quad \xrightarrow{\text{a,b}} & \quad \text{Ph} & \quad \text{OTf} & \quad \text{H} & \quad \xrightarrow{\text{b}} & \quad \text{Ph} & \quad \text{OTf} & \quad \text{H} & \quad \xrightarrow{\text{b}} & \quad \text{Ph} & \quad \text{OH} & \quad 51\% & \quad \text{Ph} & \quad \text{OH} & \quad 230
\end{align*}
\]

(a) CrCl\(_2\), NiCl\(_2\) (cat), DMSO  (b) CrCl\(_2\), NiCl\(_2\) (cat), DMF

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When aldehyde 223 was treated with four equivalents of triflate 227 in the presence of 
CrCl₂-NiCl₂, however, a mixture of 2:1 mixture of starting aldehyde and diastereomeric allylic 
alcohols 224 was obtained, accounting for 33% mass recovery. The rest of the material obtained 
from this reaction was unidentifiable. Furthermore, 223 and 224 were not readily separable by 
TLC, so monitoring the reaction progress and product separation at the end of the reaction was 
laborious. Iodide 226 was even worse. No sign of the desired addition product was observed in 
the complex reaction mixture.

Organocerium reagents behaved much better in reactions with 223 (Scheme XXXVIII). 
Thus, treatment of α-bromostyrene with tert-butyllithium gave the necessary vinylic lithium 
compound, which was converted to the presumed organocerium reagent upon reaction with a 
slurry of anhydrous cerium chloride in tetrahydrofuran. This reagent reacted with aldehyde 223 
to afford a mixture of four diastereomeric allylic alcohols 224 in 50% yield. Due to the difficulties 
encountered in the separation process, characterization of this mixture was essentially 
impossible. Whereas oxidation of this mixture under Swern conditions failed to go to 
completion, treatment of the mixture of the allylic alcohols with Dess-Martin periodinane at room 
temperature provided the corresponding enone 231 in 90% yield as a 6:1 mixture of 
diastereomers. This material could be nicely purified and fully characterized.

To summarize, we were able to prepare the key cycloaddition precursor 231 from 3- 
acetylpyridine in 6 steps and 12% yield. We were now ready to investigate the intramolecular 1,3- 
dipolar cycloaddition.

Treatment of α,β-unsaturated ketone 231 with silver fluoride in acetonitrile under reflux 
for 16 h in the dark provided a single isolable product in 20% yield. Unfortunately, this material 
was not the desired cycloadduct. The first piece of disturbing structural information was the 
appearance of a parent ion in the mass spectrum at m/z 294, whereas the desired cycloadduct 
233 would have exhibited a parent ion at m/z 267. This difference of 27 mass units between the 
observed and expected products indicated that the product had probably retained the cyano
group. It was eventually shown that the product of this reaction was perhydroisoquinoline 232. Structural arguments were based primarily on $^1$H and $^{13}$C NMR data. For example, the $^{13}$C DEPT spectrum revealed a quartet at $\delta$ 43.3 indicating the presence of an $N$-methyl group. This was confirmed in the $^1$H NMR spectrum by the appearance of a three-proton singlet at $\delta$ 2.0. Three triplets (methylenes) and four doublets (methines) were observed in the aliphatic region of the $^{13}$C DEPT spectrum. Furthermore, a singlet at $\delta$ 113.9 confirmed the presence of a cyano group. The

**Scheme XXXVIII. Attempted Intramolecular Cycloaddition**

(a) $^{225}$, $t$-BuLi; then CeCl$_3$; then 223 (b) Dess-Martin (c) AgF, CH$_3$CN, reflux.

$^1$H-$^{13}$C COSY spectrum disclosed that the protons on the three methylene groups were at $\delta$ 1.52/2.00, 1.86/2.46, and 2.50/3.25. The most downfield of these sets of protons appeared on C-3, which is adjacent to nitrogen and isolated from the other protons. In a difference nOe
experiment (Figure 2), irradiation of the signal at δ 2.50 (H-3e) resulted in a 7.4% enhancement of the vinylic methyl group, providing evidence for the assigned double bond geometry. In another difference nOe experiment, irradiation of the vinylic proton resulted in 7.0% and 6.1% enhancement of the signals at δ 2.46 and 1.86, respectively. This observation not only confirmed the orientation of the double bond, but indicated that this set of protons belonged to the C-5 methylene group. Furthermore, it indicated that the C-10—C-5 bond was equatorially disposed on the piperidine ring, as axial disposition of the bond would have been inconsistent with the

```
<table>
<thead>
<tr>
<th>Protons Irradiated</th>
<th>nOe Effect Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>=CH</td>
<td>CH₃ (7.5%)</td>
</tr>
<tr>
<td>NCH₃</td>
<td>H₂ (11.8%)</td>
</tr>
<tr>
<td>H₅a</td>
<td>CH₃ (7.4%)</td>
</tr>
<tr>
<td>H₆a</td>
<td>NCH₃ (5.1%)</td>
</tr>
<tr>
<td>H₇</td>
<td>H₅a (2.8%)</td>
</tr>
<tr>
<td>CH₃</td>
<td>=CH (9.0%)</td>
</tr>
<tr>
<td>H₆e</td>
<td>H₁₀ (3.7%)</td>
</tr>
</tbody>
</table>
```

Fig 2. nOe Studies of Cycloadduct 232.

observation of enhancements at both H-5a and H-5e. Finally, since the signal at δ 1.86 was an apparent triplet (J = 12.9 Hz) and the signal at δ 2.46 was a doublet of doublets (J = 13.1, 4.0 Hz),
these could be assigned to H-5a and H-5e, respectively. By the process of elimination, then, it was clear that the set of methylene protons at 1.52/2.00 was on C-8. Further mapping of the COSY spectra led to the assignment of the C-10 methine as an apparent triplet ($J = 10.1$ Hz) at $\delta 2.16$. The coupling pattern at this proton indicated that it was axially disposed on the piperidine ring and was anti to both H-5a and H-9. The assignments of the methines at H-2, H-7 and H-9 were also straightforward based on COSY spectra. The axial disposition of the cyano group was apparent, as H-2 appeared as a doublet with a coupling constant of only 2.8 Hz. This stereochemical assignment was confirmed by the difference nOe studies, as irradiation of H-2 led to enhancement of 5.1% at the N-methyl group and 9.4% at H-9. In other informative nOe experiments, irradiation of H-7 resulted in an enhancement of 2.9% at H-5a and a combined enhancement of 8.9% at the overlapping signals due to H-8e and H-9, revealing the equatorial

Scheme XXXIX. A Mechanistic Proposal to the Formation of Cycloadduct 232
position of the phenyl group. A 3.7% enhancement at H-10 upon irradiation of H-3a further supported that assignment of trans geometry to the ring juncture of the perhydroisoquinoline.

The formation of perhydroisoquinoline 232 can be rationalized by the mechanism outlined in Scheme XXXIX. It seems reasonable that reaction of 231 with silver fluoride would afford azomethine ylid 234. Since this was not captured by the α,β-unsaturated ketone, it is possible that 234 suffered from protonation to give iminium ion 235 and proton loss to afford enamine 236. An intramolecular Micheal addition of the enamine to the α,β-unsaturated ketone, followed by subsequent trapping of the resulting iminium ion 237 with cyanide anion would then provide 232. Thus, it appeared that the iminium ion-enamine equilibrium problem eluded to earlier in this chapter reared its head with this substrate.

Our next studies were based on the analysis of this problem presented in Scheme XL. It was clear that the desired dipolar cycloaddition could only take place if the C-4 side chain was axially disposed. It was reasoned that the preference of this side chain for an equatorial site (234a) rather than an axial site (234b) was responsible for the inefficiency of the cycloaddition.

**Scheme XL. A Potential Solution to the Problem: Allylic Strain**

![Scheme XL](image-url)
relative to other processes. The presence of a trans fusion between the rings in 232 also indicated that this product was derived from the thermodynamically favored conformation 234a.

A potential solution to this problem involved taking advantage of A¹⁻³-strain. It was imagined that if the double bond in the cyclization substrate had E-geometry, the same geometry that occurs in most Strychnos alkaloids, conformation 238b, in which the dipolarophile-bearing side chain is axially disposed, would be thermodynamically more stable than conformation 238a. Therefore it was decided to attempt to prepare substrates of this type in the hope that they would cyclize to compounds such as 239. This will be the topic of the next section.

V. A Brief Attempt to Modify Substrate 231

In an attempt to examine the solution proposed in Scheme XL while taking advantage of what had been learned from our unsuccessful use of 231, α-cyanotetrahydropyridine 246 was set as the next target for synthesis (Scheme XLII). Although this substrate contained an extra methyl group at the exocyclic double bond, we imagined it could be prepared using the same chemistry used to prepare 231, and it had the allylic strain feature that we hoped would lead to a successful cycloaddition. This project, however, was short-lived. Treatment of 3-acetylpyridine (209) with methyl lithium gave tertiary alcohol 240 in 73% yield. Alkylation of this compound with triflate 189 gave the corresponding pyridinium salt 241 in 92% yield. The usual reductive cyanation afforded the desired α-cyanoamine 242 in 42% yield, but then problems were encountered. In spite of there being precedence for Eschenmoser-Claisen rearrangements of tertiary allylic alcohols,⁶¹⁶ treatment of 242 with N,N-dimethylacetamide dimethyl acetal failed to give the desired product 243. Prolonged reaction times and elevated temperatures only caused decomposition of the starting allylic alcohol. Furthermore, although the corresponding acetate 244 could be prepared in 44% yield, it failed to provide 245 under Ireland-Claisen rearrangement conditions.⁷⁰ Therefore, this approach was abandoned.
VI. Attempted Synthesis of Cycloaddition Substrate 248

We next turned our attention to the synthesis of α-cyanotetrahydropyridine 248, a cycloaddition substrate with E-configuration at the exocyclic double bond, with the hope that the intramolecular cycloaddition reaction would proceed. Retrosynthetically, we envisioned that the
enone unit in 248 could be prepared from aldehyde 249 (Scheme XLII). Two plans were considered for the preparation of 249.

One plan revolved around intramolecular Heck reactions of 250 or 251. It was expected that in the presence of the appropriate palladium catalyst, the vinylic halide and allylic alcohol units

Scheme XLII. Retrosynthetic Analysis of Enone 248
in 250 or 251 might couple to give 249 after elimination of palladium hydride from the initially formed cyclization intermediate.\textsuperscript{71} It was imagined that 250 or 251 could be prepared by alkylation of acetonitrile derivative 252 or 253 with allylic halide of type 254. Furthermore, it was hoped that 252 or 253 could be derived from amine 257 and vinylic halides 255 or 256, respectively. An alternative approach was to access 249 via the corresponding lactam 258. It was imagined that lactam 258 could be prepared from the corresponding lactone 259 and amine 257. It was hoped that a cuprate derived from a vinyl halide of type 261 would conjugate add to an \(\alpha,\beta\)-unsaturated ester of type 260 followed by lactonization to afford 259.\textsuperscript{72} Both plans are reasonably convergent, and stereoselective preparation of the vinyl halides would guarantee the outcome of the double bond geometry in the products.

The starting materials required for the approaches shown in Scheme XLII were prepared as described in Scheme XLIII. Most of them were prepared according to slightly modified literature procedures, with the exception of amine 257. Bromination of methyl crotonate (262) followed by dehydrobromination and reduction of the resulting ester gave bromo alcohol 261\textsuperscript{24c} in 92% yield with a \(Z:E\) ratio of greater than 20:1. The double bond geometry resulted from thermodynamic control in the dehydrobromination step. Alcohol 261 was then transformed into the corresponding mesylate, which was subsequently displaced using lithium bromide to give 255 in 75% yield. The corresponding vinylic iodide was also prepared. Thus, hydrostannylation of 2-butyl-1-ol (263) followed by reaction of the intermediate vinyl stannane with iodine afforded iodo alcohol 264 in 80% yield with a \(Z:E\) ratio of 11:1.\textsuperscript{73} Alcohol 264 was converted to the corresponding bromide 256 in 81% yield by the same procedure used to prepare 255. Allylic bromide 254,\textsuperscript{74} required for the intramolecular Heck approach, was prepared by reduction of commercially available methyl 4-bromocrotonate (265) followed by protection of the resulting alcohol as a tert-butyldimethylsilyl ether. \(\alpha\)-Silylamine 257, also needed for both the Heck and cuprate approaches, was prepared in 97% yield by reaction of triflate 189 with an excess of ammonia in tetrahydrofuran followed by neutralization of the intermediate ammonium triflate with
10% aqueous sodium hydroxide. Finally, unsaturated ester 260, \(^\text{75}\) needed for the cuprate-addition approach, was prepared from 1,3-propanediol (266). Thus, monosilylation of 266 (85%), Swern oxidation of the resulting alcohol (65%), and Wittig olefination of the intermediate aldehyde gave 260 (91%).

We first investigated the approach revolving around the intramolecular Heck reaction. The initial task was preparation of amine 252 and 253 as described in Scheme XLIV. \(N\)-Alkylation of amine 257 with the mesylate derived from alcohol 261 gave 267 in 55% yield. \(N\)-

**Scheme XLIII. Preparation of the Starting Materials**

![Diagram of the reaction scheme](image)

(a) \(\text{Br}_2, \text{CH}_2\text{C}_2, 0^\circ\text{C}\) (b) \(\text{Et}_3\text{N, pentane, } 0^\circ\text{-reflux}\) (c) DIBAL, \(\text{CH}_2\text{C}_2\) (d) \(\text{MsCl, Et}_3\text{N, CH}_2\text{Cl}_2, -20^\circ\text{C}\) (e) \(\text{LiBr, THF}\) (f) \(\text{Bu}_3\text{SnH, AIBN, 85}^\circ\text{C}\) (g) \(\text{I}_2, \text{CCl}_4, 0^\circ\text{C}\) (h) DIBAL, \(\text{CH}_2\text{C}_2\) (i) TBSCI, \(\text{Et}_3\text{N, CH}_2\text{Cl}_2\) (j) excess \(\text{NH}_3, \text{THF}; \text{then } 10\% \text{aq. NaOH}\) (k) TBSCI, \(\text{Et}_3\text{N, CH}_2\text{Cl}_2\) (l) (COCl)\(_2\), DMSO, \(\text{CH}_2\text{Cl}_2\); then \(\text{Et}_3\text{N}\) (m) \(\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et, CH}_2\text{Cl}_2\).
Alkylation of 267 with bromoacetonitrile provided 252 in 99% yield. To avoid over-alkylation of the amine, a large excess of 257 had to be used in this sequence. When attempts to recover the starting material met with difficulties, we opted to change the sequence of the events. Therefore, amine 257 was treated with formaldehyde in the presence of potassium cyanide to afford 268 in 57% yield. N-Alkylation of 268 with allylic bromides 255 and 256 then afforded α-cyanoamines 252 and 253 in 64% and 88% yields, respectively. Only a little more than one equivalent of amine 257 was necessary for these transformations.

Scheme XLIV. Preparation of Amines 252 and 253

![Scheme XLIV](image)

(a) MsCl, Et3N, then 257 (b) BrCH2CN, K2CO3, CH3CN, reflux (c) 37% aq. formaldehyde, Et2O-H2O then KCN (d) 255 or 256, K2CO3, CH3CN, reflux

We next attempted to introduce the olefin-containing side chain (Scheme XLV). When amine 252 was treated with lithium diisopropylamide in THF-HMPA, followed by allylic bromide
254, only elimination product 269 was obtained (85%). When the same reaction was conducted in tetrahydrofuran alone at -78°C, however, the desired alkylation took place. Since the separation was difficult at this stage, the mixture was treated with pyridinium p-toluenesulfonate in methanol to directly provide allylic alcohol 250 in 22% yield (from amine 252). Unfortunately, when 250 was subjected to Heck reaction conditions, none of the desired product was observed. Only amine 267 was isolated in 10% yield. The mechanism responsible for the

Scheme XLV. Synthesis of the Precursors to the Heck Reaction and the Attempted Heck Reaction

(a) LDA, HMPA, THF, -78°C then 254  (b) LDA, THF, -78°C, then 254  (c) PPTS, MeOH, rt  (d) Pd(OAc)$_2$, Ph$_3$P, Et$_3$N

73
formation of this product is not clear, but it is suspected that this may come from ionization of the α-cyanoamine followed by hydrolysis of an intermediate iminium ion or enamine. With the hope that a vinyl iodide would behave better in the Heck reaction, we also attempted to alkylate amine 253 with allylic bromide 254. Unfortunately, the base we used, namely lithium diisopropylamide, only promoted the elimination reaction, as 269 was isolated in 53% yield along with 18% of recovered starting material.

Given the problems associated with the alkylation of 252 and 254, it was decided to introduce the allylic alcohol side chain first and the vinylic halide side chain second, starting with α-cyanoamine 268. Attempts to alkylate the monoanion and dianion derived from 268 at the α-position were not very successful. Therefore, we tried to protect amine 268 before conducting the α-alkylation (Scheme XLVI). Thus, treatment of 268 with benzyl bromide in the presence of potassium carbonate gave 270 in 94% yield. Sequential treatment of 270 with lithium diisopropylamide and allylic alcohol 254 gave 271 in 45% yield, with contamination from allylic bromide 254. Since the separation of 271 from 254 was difficult, we decided to carried the mixture to the next step. Unfortunately, 271 failed to undergo debenzylation with α-chloroethyl chloroformate. At this point, it was decided to abandon this route to aldehyde 249 because concurrent work on the second route was successful (vide infra).

Scheme XLVI. Benzyl Protected Amine 271

\[ \text{Scheme XLVI. Benzyl Protected Amine 271} \]

\[ \begin{align*}
\text{268} & \xrightarrow{(a) \text{K}_2\text{CO}_3, \text{CH}_3\text{CN, BnBr}} \text{270} \\
\text{270} & \xrightarrow{(b) \text{LDA, then 254}} \text{271}
\end{align*} \]
The initial steps in the second route to aldehyde 249 are shown in Scheme XLVII. We began by preparing a mixed cuprate derived from bromide 261, as previously described by Overman,\textsuperscript{34d} and examining its reaction with \(\alpha,\beta\)-unsaturated ester 260. Unfortunately, reaction of 261 with tert-butyllithium, conversion of the resulting dianion to a higher order cuprate, and reaction of this carbanion with 260, gave none of the desired conjugate adduct. This result was not surprising as esters are not particularly good substrate for cuprate conjugate additions.\textsuperscript{72a}

Scheme XLVII. The Cuprate Addition Reaction.

\[
\begin{align*}
\text{CH}_3\text{Br} & \quad \text{OH} & 1. \text{t-BuLi} & 2. (2\text{-thieryl})\text{CuCNLi} & \text{No Reaction} \\
261 & & & & \\
\text{CH}_2\text{Br} & \quad \text{OH} & 1. \text{t-BuLi} & 2. (2\text{-thieryl})\text{CuCNLi} & \text{OTMS} \\
261 & & & & 273 \\
\text{O} & \quad \text{CO}_2\text{Et} & + & \text{O} & \quad \text{CO}_2\text{Et} \\
260 & \quad \text{272} & \quad \text{a} & \text{b or c} & \\
\text{TBS} & \quad \text{RO} & + & \text{TBDPS} & \text{R} = \text{TBS} \\
276 & & & 277 & \text{R} = \text{TBDPS} \\
\text{TBS} & \quad \text{CO}_2\text{Et} & & & \\
260 & & & 272 & \quad \text{275} \\
\text{274} & & & \text{274} & \quad \text{275}
\end{align*}
\]

(a) Acidic Dowex-50 (b) TBSCI, Et$_3$N, DMAP, CH$_2$Cl$_2$ (c) TBDPSCI, imidazole, DMF
Therefore we examined the reaction of the same higher order cuprate with commercially available unsaturated lactone 272, an equivalent to 260 in which the γ-hydroxyl group and ester are tethered. It was hoped that β-elimination, a potential problem with 260, would be geometrically unfavored in 272, and that the unsaturated lactone would be a better Micheal acceptor. In the event, when the cuprate addition was conducted in the presence of two equivalents of trimethylsilyl chloride, lactone 273 could be isolated in low yield after a work-up procedure that hydrolyzed the intermediate silyl enol ether of the lactone. We next set about removing the trimethylsilyl protecting group from 273. All attempts to accomplish this transformation resulted in rearrangement of the lactone skeleton. Thus, acidic conditions, like HCl in tetrahydrofuran, basic conditions, like tetra-n-butylammonium fluoride, or mild conditions, like HF-pyridine complex all led to mixtures of lactones 274 and 275 in ratios ranging from 6:1 to 10:1. The factors that make 274 more stable than 275 are unclear. In summary, it was possible to obtain this mixture of lactones in 32% overall yield from 261 and 272.

Before continuing with this approach to aldehyde 249, a few comments about this conjugate addition are warranted. First, the reaction is technically challenging as it involves manipulations under vigorously anhydrous conditions at low temperature. On top of that, scaling up was a problem because of the need to use three equivalents of tert-butyllithium. For a typical 45 mmol reaction, a total of 78 mL of 1.7 M tert-butyllithium had to be used. It was also discovered that in scaling up, very close monitoring of the internal reaction temperature while adding reagent was crucial to the yield. We had to repeat this time-consuming energy-draining reaction many times to acquire enough material to continue with the synthesis. In addition, it is notable that the starting 5,6-dihydro-2H-pyran-2-one (272) is expensive. In this regard, we preferred to prepare it from the inexpensive starting materials paraformaldehyde and vinylacetic acid (280) according to a literature procedure (Scheme XLVIII).26 With some effort, this procedure was modified into a preparative procedure that required minimal separation and afforded over 10 g of lactone in 39% yield in one run.
Although we had initially planned to work with lactone 275, lactone 274 proved to be useful (vide infra). Treatment of this mixture of alcohols with tert-butyldimethylsilyl chloride in the presence of triethylamine and 4-dimethylaminopyridine in dichloromethane gave a mixture lactones 276 and 277. Lactones 278 and 279 could be prepared in similar manner. In each case, chromatography allowed purification of the major isomers (276 or 278), both in 59% yield. Fractions enriched in the minor isomers (277 or 279) from different runs were combined and subjected to the desilylation/rearrangement conditions and reprotction to generate more pure 276 or 278 in about 40% yield depending on the starting ratios of mixtures. One promising observation made with lactone 276 is that the C-4 side chain clearly occupied an axial site on the six-membered ring. This was apparent from the coupling constants of C-3 methylene protons to

![Fig. 3. Conformation of Lactone 276.](image)
H-4 of 6.1 Hz and 6.4 Hz, respectively. The near identity of those coupling constants indicated that H-4 occupied an equatorial site. Thus, as we had expected, allylic strain was forcing the C-4 substituent to occupy an axial site.

Scheme XLIX. Attempted Transformation of the Lactone to the Lactam

With lactones 276 and 278 in hand, we next set out to prepare the corresponding lactams 258a and 258b using a ring opening-cyclization strategy (Scheme XLIX). Treatment of lactones 276 and with primary amine 257 gave amido alcohol 281a in 93%
Unfortunately, problems were encountered in reclosure of the ring. Initially the hydroxyl group in 281a was converted to the corresponding mesylate, and methyl lithium was then used to deprotonate the nitrogen in an attempt to effect the desired transformation. Quick chromatography of the initial product afforded a 2:1 mixture of the two products, apparent from signals in the vinylic region of the 'H NMR spectrum of the mixture. The minor product was lactone 276. More careful chromatography over silica gel afforded mixtures, with the initial major product present in diminishing amounts. Only pure lactone 276 was ultimately isolated. Apparently O-alkylation had occurred, rather than the desired N-alkylation, and the resulting imidate was eventually hydrolyzed to lactone 276. Other conditions were attempted, such as activation of the alcohol as either a tosylate or bromide and use of potassium hydride and potassium hexamethyldisilazide in place of methyl lithium. None of these conditions led to N-alkylation rather than O-alkylation. We next investigated bringing in the lactam nitrogen through intermolecular alkylation at the allylic alcohol site to give 284, followed by closure of the lactam ring. This required first opening lactones 276 or 278 irreversibly. This was accomplished by treating 276 or 278 with dimethylamine in methanol at reflux, affording amino alcohol 282a and 282b in 75% and 80% yield, respectively. Although alcohol 282b could be protected first, for example to give 283, neighboring group participation unfortunately appeared to interfere with attempts to activate the allylic alcohol. As a result, nucleophilic displacement with amine 257 was never transformed to 284a or 284b, as lactone 276 was always recovered.

It was hoped that addition of an appropriate organometallic to 278 might provide 285, which might be converted to lactam 286 (Scheme L). Whereas treatment of 278 with vinyl lithium reagent derived from α-bromostyrene gave lactol 287, this material underwent elimination of water upon standing to give dihydropyran 288 in 32% yield, along with 68% of recovered starting lactone. Attempts to open 288 to useful substrate 289, for example with 1,3-propanedithiol, did not succeed.
Scheme L. Addition of Vinylic Lithium Reagent to Lactone 276

(a) α-bromostyrene, t-BuLi, THF, -78°C; then 276 (b) 1,3-propanedithiol, BF₃·Et₂O

A more successful plan of attack is outlined in Scheme LI. Reduction of lactone 278 with DIBAL gave lactol 290 in almost quantitative yield. When this lactol and tert-butylidiphenylsilylmethylamine (257) were heated in benzene at reflux in the presence of a catalytic amount of acid, followed by treatment of the crude imine with aqueous potassium cyanide, amino alcohol 291 was obtained in 88% yield as a 3:2 mixture of diastereomers at the newly generated stereogenic center. The piperidine ring closed instantly when the allylic alcohol was activated as both the corresponding bromide and mesylate furnished 292 in 51% and 82% yields, respectively. Treatment of 292 with 1.1 equivalents of tetra-n-butylammonium fluoride, as a 1 M solution in tetrahydrofuran, removed the silicon protecting group to give a diastereomeric mixture of alcohols 293 in 93% yield.
It is notable that all of the 2-cyano-1,2,3,6-tetrahydropyridine derivatives in this sequence were obtained as diastereomeric mixtures. In each case the ratio was determined by integration of the vinylic protons in the \(^1\)H NMR spectra of the mixtures. The diastereomer ratios were generally around 3:1 with the major isomer having the cyano group in an axial position due to the anomeric-
like effect. It is also notable that in the E-olefin series, the "axial-cyano" isomer was not as dominant as in the Z-olefin series (vide supra). Presumably allylic strain in this series forces the C-4 substituent into an axial orientation. This introduces a 1,3-diaxial interaction between this substituent and the cyano group, in turn decreasing the proportion of the isomeric mixture in which the cyano group resides at an axial position. Finally, it is notable that we were able to purify aldehyde 293a, which allowed a detailed analysis of spectral data and a firm assignment of structure. The 'H NMR spectrum of 293a revealed that the coupling constant between H-3a and H-4 was only 5.5 Hz, confirming the axial disposition of the C-4 alkyl group.

Continuing toward the target, treatment of aldehyde 293 with the organocerium reagent derived from α-bromostyrene (225) gave a mixture of four diastereomeric alcohols 294 in 74% yield. The spectra of this material were complicated due to the presence of diastereomers, so we decided to postpone full characterization until after the oxidation step. Unfortunately, we were never able to convert the allylic alcohol to the corresponding enone. This was a big surprise as we had experienced no difficulty with the oxidation of the isomeric allylic alcohols 224 in our early work (vide supra). For example, whereas oxidation of 224 with the Dess-Martin periodinane had provided 231 in 90% yield (see Scheme XXXVIII), similar treatment of 294 gave a complex mixture of materials whose 'H NMR spectrum indicated the presence of only a trace of amount of the desired product (=CH signals at δ 5.90 and 6.15). An array of oxidation conditions were surveyed with 294. Reagents employed included Swern conditions, maganese dioxide, tetra-propyammonium perruthenate (TPAP), and Jones' reagent. In most cases, even though technique checks were performed successfully using allylic alcohol 295 as a model substrate, the oxidation of substrate 294 was just fruitless.

The problems experienced with this oxidation precluded examination of the key cycloaddition reaction (248→239 in Scheme XL) and the project was abandoned at this point. Although the lack of information about the products formed in the attempted oxidation makes substantive speculation impossible, we suggest that the nitrogen lone-pair may be getting
involved with intermediates derived from the allylic alcohol along the oxidation pathway. This would be possible with $295$ (C-4 side chain axial), but not possible with $224$ (C-4 side chain equatorial) and would explain the difference in behavior of these two substrates.

### 7. Summary of Results

In conclusion, this thesis examines a cycloaddition approach to the *Strychnos* family of alkaloids. Although the results were very disappointing to this researcher, and do not look promising for this route, they do not indicate that there is a fatal flaw in the key cycloaddition. They do suggest that an alternative approach to the key azomethine ylid should be examined. One possibility would be to examine the ylid derived from desilylation of $298$. This method of ylid generation would, of course, require a synthesis of thioamide $297$ and also a removal of sulfur at a late stage of the synthesis, in $299$.

### Scheme LII. An Alternative Way of Generation of Azomethine Ylid

In terms of fundamental chemistry, perhaps the most important aspect of this research is the development of an understanding of how to carry potentially labile silicon substituents through a reaction sequence where desilylation is a real possibility. It was demonstrated that by carefully selecting non-nucleophilic counterions (triflate instead of iodide) and the introducing steric hindrance at silicon (TBDPS instead of TMS), it is possible to maintain silicon through a
challenging reaction sequence. In this regard, we note that two extremes at silicon were examined in this work (TMS and TBDPS) and it might be worthwhile to examine silicon groups that lie somewhere between these extremes in terms of steric hindrance (TBS and TIPS).
Experimental Section

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are boiling points. Proton nuclear magnetic resonance spectra (¹H NMR) were recorded on Bruker AC-200, Bruker AM-250, Bruker AC-300 or Bruker AC-500 spectrometers and are recorded in parts per million from internal chloroform and benzene on the δ scale. The ¹H NMR spectra are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz, integration, interpretation]. Carbon-13 nuclear magnetic resonance spectra (¹³C NMR) were obtained with Bruker AC-300 or Bruker AC-500 spectrometers and are recorded in parts per million from internal chloroform or benzene on the δ scale. The ¹³C NMR spectra are reported as follows: chemical shift (multiplicity determined from DEPT spectra). Infrared spectra were taken with a Perkin-Elmer 1600 (FT-IR) instrument. Mass spectra were obtained on a Kratos MS-30 or Kratos VG70-250s instruments at an ionization energy of 70 eV. Compounds for which an exact masses are reported exhibited no significant peaks at m/z greater than that of the parent. Combustion analysis were performed by Atlantic Microlab, Norcross, GA.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl ether and benzene were distilled from sodium metal; dichloromethane, triethylamine, toluene, HMPA, dimethylformamide, and dimethyl sulfoxide were distilled from calcium hydride. Reactions requiring an inert atmosphere were run under argon or nitrogen. Analytical thin-layer chromatography was conducted using EM Laboratoies 0.25 mm thick precoated silica gel 60F-254 plates. Column chromatography was performed over EM Laboratory silica gel (70-230 mesh). All organolithium reagents were titrated prior to use with (+)-menthol.
using 1,10-phenanthroline as the indicator. The abbreviations used in this thesis follow the guidelines suggested by the Journal of Organic Chemistry. The order of experimental procedures follow their order of appearance in the text.

4-Methyl-1-[(trimethylsilyl)methyl]pyridinium trifluoromethanesulfonate (174). To 43 mg (0.46 mmol) of 4-picoline in 2 mL of acetone was added 124 mg (105 μL, 0.52 mmol) of trimethylsilylmethyl trifluoromethanesulfonate dropwise via syringe over a period of 2 min. The reaction mixture was stirred at room temperature for 30 min, and then concentrated in vacuo to give 160 mg brown solid. The solid was dissolved in 2 mL of dichloromethane and hexanes (approximately 0.8 mL) was added dropwise until cloudiness persisted. The resulting white crystalline solid was collected to give 139 mg (92%) of the desired pyridinium salt 174: mp 138-139°C; 1H NMR (CDCl₃, 300 MHz) δ 0.12 (s, 9H, CH₃), 2.61 (s, 3H, CH₃), 4.37 (s, 2H, CH₂), 7.76 (d, J = 6.7 Hz, 2H, H₃ and H₅), 8.64 (d, J = 6.7 Hz, 2H, H₄ and H₆); 19F NMR δ -79.4; 13C NMR (CDCl₃, 75.47 MHz) δ -3.6 (q), 21.72 (q), 53.9 (t), 128.8 (d), 143.2 (d), 156.9 (s); exact mass calcd. for C₇H₁₅F₃O₃NSSi m/z 316.9790, found m/z 316.9839. The quartet corresponding to the CF₃ was not detected conclusively in the ¹³C NMR.
1-[(tert-Butyldiphenylsilyl)methyl]-4-methylpyridinium trifluoromethanesulfonate (175). To 48 mg (50 μL, 0.51 mmol) of 4-picoline in 3 mL of acetonitrile was added 200 mg (0.50 mmol) of crystalline tert-butyldiphenylsilylmethyl triflate. The solution was stirred at room temperature for 2.5 h and then concentrated in vacuo. The solid residue was dissolved in 5 mL of dichloromethane and ether (approximately 1 mL) was added dropwise until cloudiness persisted. The resulting white crystals were collected to give a first crop of 194 mg (79%) and a second crop of 14 mg (6%) of the desired pyridinium salt 175: mp 133-134°C; ¹H NMR (CDCl₃, 250 MHz) δ 1.16 (s, 9H, CH₃), 2.43 (s, 3H, CH₃), 4.94 (s, 2H, CH), 7.73-7.57 (m, 12H, ArH, H3 and H5), 8.16 (d, J = 6.8 Hz, 2H, H4 and H6); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.3 (s), 21.6 (q), 27.4 (q), 49.0 (t), 127.7 (d), 128.5 (d), 128.9 (s), 130.7 (d), 136.0 (d), 143.4 (d), 156.4 (s), the CF₃ was not detected in the ¹³C NMR; Anal. calcd. for C2₄H₂₅F₃O₂NSSi C, 58.16; H, 5.69; found C, 58.13; H, 5.67.
1-[(tert-Butyldiphenylsilyl)methyl]-1,2,3,6-tetrahydro-4-methyl-2-pyridinecarbonitrile (178) and 1-[(tert-Butyldiphenylsilyl)methyl]-1,2,3,6-tetrahydro-4-methylpyridine (181). To 2.07 g (42.3 mmol) of sodium cyanide in 15 mL of methanol, 15 mL of water and 80 mL of diethyl ether was added 354 mg of sodium borohydride (9.3 mmol), followed by 2.6 g (5.3 mmol) of pyridinium salt 175. The mixture was stirred at room temperature for 30 min. The aqueous layer was separated and extracted with three 50-mL portions of diethyl ether. The organic layer was washed with 15 mL of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over 60 g of silica gel (eluted with ethyl acetate-hexanes, 1:50) to give 980 mg (50%) of the desired cyanoamine 178: IR (neat) 1421 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.08 (s, 9H, CH₃), 1.63 (s, 3H, CH₃), 1.86 (d, J = 16.6 Hz, 1H, H₁), 2.31 (dd, J = 16.5, 1.1 Hz, 1H, H₃), 2.78 (AB q, 2H, NCH₂Si), 2.88 (dm, J = 14.6 Hz, 1H, H₅), 3.14 (dd, J = 14.6, 1.65 Hz, 1H, H₆), 3.58 (dd, J = 6.0, 1.5 Hz, 1H, H₇), 5.29 (br s, 1H, H₈), 7.35-7.45 (m, 6H, ArH), 7.66-7.74 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.2 (s), 22.4 (q), 27.9 (q), 33.9 (t), 42.2 (t), 52.5 (t), 52.7 (d), 116.6 (s), 119.7 (d), 127.7 (d), 128.2 (s), 129.39 (d), 129.42 (d), 133.86 (s), 133.95 (s), 135.7 (d), 135.8 (d), (one doublet missing in the aromatic region); exact mass calcd. for C₂₄H₁₉N₂Si m/e 374.2178, found m/e 374.2160.

On one occasion when the reaction was stirred too long at room temperature, the over reduction product 181 was isolated: IR (neat) 1427 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.03 (s, 9H, CH₃), 1.59 (s, 3H, CH₂Cα), 1.88 (br s, 2H, CH₂), 2.37 (t, 2H, NCH₂), 2.57 (s, 2H, NCH₂Si), 2.80 (br s, 2H, NCH₂), 5.20 (s, 1H, CH=), 7.42-7.44 (m, 6H, C₆H₅), 7.66-7.75 (m, 4H, C₆H₅); ¹³C NMR (CDCl₃,
75.47 MHz) 5 18.3 (s), 22.8 (q), 27.8 (q), 31.1 (t), 45.0 (t), 53.7 (t), 57.2 (t), 119.5 (d), 127.4 (d), 128.9 (d), 135.3 (s), 135.9 (d), one singlet downfield from CDCl₃ was not conclusively identified probably due to the poor signal-noise-ratio; exact mass calcd. for C₂₅H₁₇NSi m/e 349.2226, found m/e 349.2221.

1-[(t-Butyldiphenylsilyl)methyl]pyridinium trifluoromethanesulfonate (179). To 0.78 g (0.8 mL, 9.9 mmol) of pyridine in 50 mL of acetonitrile was added 2.7 g (6.8 mmol) of t-butyldiphenylsilylmethyl triflate 189. The solution was stirred at room temperature for 4 h and solvent was then removed in vacuo. The resulting solid was washed with three 25-mL portions of ether and the resulting white solid was collected to give 3.2 g (98%) of pyridinium salt 179: mp 203-204°C; IR (KBr) 1428, 1249, 1166 cm⁻¹; 'H NMR (CDCl₃, 300 MHz) δ 1.16 (s, 9H, CH₃), 5.00 (s, 2H, CH₂), 7.33-7.54 (m, 12H, H₃, H₂ and ArH), 8.07 (t, J =7.8 Hz, 1H, H₄), 8.30, (d, J = 6.7 Hz, 2H, H₂ and H₃); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.4 (s), 27.4 (q), 49.9 (t), 127.2 (d), 128.5 (d), 128.7 (s), 130.7 (d), 135.9 (d), 142.2 (d), 144.2 (d); exact mass calcd. for C₂₅H₂₆F₃NO₃SSi m/e 481.1355, found m/e 481.9578; Anal. calcd. for C₂₅H₂₆F₃NO₃SSi: C, 57.36; H, 5.45; found C, 57.30; H, 5.42.
1-[(tert-Butyldiphenylsilyl)methyl]-1,2,3,6-tetrahydro-2-pyridinecarbonitrile (180): To 1.57 g (32 mmol) of sodium cyanide in a mixture of 15 mL of water, 15 mL of methanol and 50 mL of ether was added 317 mg (8.3 mmol) of sodium borohydride followed by immediate addition of 1.94 g (4.0 mmol) of pyridinium salt 179. The mixture was stirred at room temperature for 20 min. The organic layer was separated and washed with two 10-mL portions of water. The combined aqueous layers were extracted with three 25-mL portions of dichloromethane. The organic phase was washed with 25 mL of brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with ethyl acetate-hexanes, 1:30) to give 428 mg (30%) of the desired α-cyanoamine 180 as a colorless oil: IR (neat) 2223 (CN), 1427 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz), δ 1.12 (s, 9H, CH₃), 2.08 (d, J = 16.7 Hz, 1H, H₃), 2.42 (dd, J = 16.2, 1.8 Hz, 1H, H₃), 2.77-2.90 (AB quartet, 2H, NC(Si)), 2.94 (d, J = 14.5 Hz, 1H, H₃), 3.23 (dd, J = 14.5, 1.6 Hz, 1H, H₃), 3.64 (dd, J = 6.0, 1.3 Hz, 1H, H₃), 5.6 (m, 2H, HC=CH), 7.38-7.45 (m, 6H, ArH), 7.72-7.77 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.3 (s), 27.7 (q), 29.5 (t), 42.6 (t), 52.3 (d), 52.4 (t), 116.5 (s), 120.6 (d), 125.9 (d), 127.8 (d), 129.47 (d), 129.5 (d), 133.9 (d), 135.75 (d), 135.81 (d), one aromatic singlet was not detected: exact mass calcd. for C₂₃H₂₈N₃Si m/z 360.2022, found m/z 360.2020.
(±)-(1R*,2S*,8aS*)-1,2,3,5,8,8a-Hexahydro-N,7-dimethyl-1,2-indolizinedicarboximide (190a) and (±)-(1R*,2S*,8aR*)-1,2,3,5,8,8a-Hexahydro-N7-dimethyl-1,2-indolizinedicarboximide (190b): To a mixture of 99 mg (0.26 mmol) of α-cyanoamine 178 and 32 mg (0.29 mmol) of N-methylmaleimide in 1.2 mL of dry acetonitrile was added 39 mg (0.30 mmol) of silver fluoride. The mixture was stirred in the dark for 24 h, and then filtered through a pipet of Celite. The pipet of Celite was rinsed with approximately 5 mL of diethyl ether. The filtrate was concentrated in vacuo and the residue was chromatographed over 5 g of silica gel (eluted with ethyl acetate-hexanes: 1:1) to give, in sequence, 20 mg (34%) cycloadduct 190a as a colorless oil, and 20 mg (34%) of diastereomer 190b as a pale yellow oil. Cycloadduct 190a gave the following spectral data: IR (neat) 1703, 1432 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.67 (s, 3H, CH₃), 1.86 (d, J = 13.9 Hz, 1H, H₄), 2.21 (dm, J = 13.9 Hz, 1H, H₅), 2.28 (td, J = 10.6, 4.4 Hz, 1H, H₆), 2.47 (dd, J = 9.3, 4.2 Hz, 1H, H₇), 2.86 (br s, 1H, H₈), 2.93 (s, 3H, CH₃), 2.95-3.00 (m, 1H, H₉), 3.12-3.18 (m, 2H, H, and H₉), 3.32 (d, J = 9.5 Hz, 1H, H₀), 5.75 (s, 1H, =CH); ¹³C NMR (CDCl₃, 74.45 MHz) δ 23.0 (q), 24.9 (q), 30.5 (t), 44.0 (d), 46.8 (d), 47.8 (t), 55.6 (t), 63.7 (d), 118.0 (d), 134.1 (s), 175.5 (s), 179.6 (s); exact mass calcd. for C₁₇H₂₄N₂O₂ m/e 220.1212, found m/e 220.1194. Adduct 190b gave the following spectral data: IR (neat) 1702, 1432 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz), δ 1.66-1.71 (s and d, 4H, CH₃ and H₉), 2.16 (m, 1H, H), 2.90-2.98 (m with s at 2.92, 6H, CH₃, H₉, H₂₉, H₃₀), 3.04 (dd, J = 9.4, 2.2 Hz, 1H, H₃₁), 3.10 (t, J = 9.4 Hz, 1H, H₂ₙ), 3.21 (td, J = 7.8, 2.1 Hz, 1H, H₂), 3.88 (br s, 1H, H₈), 5.30 (br s, 1H, =CH); ¹³C NMR (CDCl₃, 300 MHz), δ
(±)-(1'S',2'S',8a'R')-1,2,3,5,8,8a-Hexahydro-7-methyl-1,2-bis(phenylsulfonyl)indolizine (191a) and (±)-(1'R',2'R',8a'R')-1,2,3,5,8,8a-Hexahydro-7-methyl-1,2-bis(phenylsulfonyl)indolizine (191b): To a mixture of 103 mg (0.27 mmol) of α-cyanoamine 178 and 150 mg (0.49 mmol) of trans-1,2-bis(phenylsulfonyl)ethylene in 2.5 mL of acetonitrile and 1 mL of dichloromethane was added 38 mg (0.30 mmol) of silver fluoride. The resulting black slurry was stirred in the dark for 20 h and filtered through a plug of Celite with dichloromethane. The filtrate was concentrated in vacuo and the residue was chromatographed over 4 g of silica gel (eluted with first dichloromethane to remove excess amount of trans-1,2-bis(phenylsulfonyl)ethylene, then with ethyl acetate-hexanes, 1:3) to afford, in sequence, 12 mg (11%) of adduct 191a as a yellow oil and 10 mg (9%) of adduct 191b as a colorless oil. Adduct 191a decomposed while waiting for the spectra to be taken. Mass spectra of 191a gave a parent ion at m/e 417.1074 (calcd. for C_{21}H_{22}S_{2}O_{4}N m/e 417.1068). Adduct 191b gave the following spectral data: 'H NMR (CDCl₃, 500 MHz) δ 1.53 (s, 3H, CH₃), 1.94 (m, 2H, H₃), 2.64 (dq, J = 11.9, 5.5 Hz, 1H, H₃), 2.92 (dq, J = 11.9, 5.4 Hz, 1H, H₃), 3.12 (dd, J = 11.6, 8.5 Hz, 1H, H₃), 3.47 (dd, J = 11.6, 3.3 Hz, 1H, H₃), 3.76 (m, 1H, H₃), 3.93 (dd, J = 7.3, 5.2 Hz, 1H, H₃), 4.14 (m, 1H, H₃), 5.00 (br s, 1H, =CH), 7.5-8.0 (m, 10H, ArH); ¹³C NMR (CDCl₃, 125.8 MHz) δ 23.1 (q), 28.4 (t), 46.0 (t), 53.6 (t), 62.6 (d), 65.7 (d), 68.7 (d), 118.8 (d), 128.6 (d), 128.9 (d), 129.2 (d), 129.5 (d), 134.8 (d), 139.0 (s), 139.7 (s), 140.8 (s), 178.6 (s).
134.3 (d), 135.7 (s), 138.1 (s), 138.6 (s): The assignments of protons are based on careful analysis of \(^1\)H-\(^1\)H COSY, \(^1\)H-\(^{13}\)C COSY, \(^{13}\)C DEPT, and selective difference nOe experiments. Copies of the spectra are attached in the Appendix. Exact mass calcd. for \(C_2H_{22}S_2O_4N\) \(m/e\) 417.1068, found \(m/e\) 417.1061.

\[
\begin{align*}
\text{Ph} & \quad \text{Si-CH}_2\text{OH} \\
\text{Ph} & \\
188
\end{align*}
\]

(\textit{tert-Butyldiphenylisilyl})methanol (188). To 25.5 g (93.0 mmol) of \(t\)-butylchlorodiphenylsilane in 250 mL of THF at 0°C was added 3.6 g (520 mmol) of freshly cut lithium wire in three portions over 20 min. The resulting solution was stirred at 0-4°C for 30 min, during which it turned dark red. The solution was stirred at that temperature for additional 4 h. The solution was cooled to -78°C with a dry-ice-acetone bath. A separate flask containing 5.0 g (169 mmol) of paraformaldehyde was connected to the aforementioned flask through two nitrogen-inlets, a short piece of Tygon tubing and a glass tubing. The tip of the glass tubing was immersed in the anion solution. A strong stream of nitrogen was maintained through the flask containing paraformaldehyde to the anion solution. The powdery paraformaldehyde was then heated with a Bunsen burner and the paraformaldehyde thereby generated was carried to the anion solution by the strong flow of nitrogen. This process took approximately 30 min. The resulting dark green suspension was stirred at -78°C for 10 min and then warmed to room temperature. The reaction mixture was filtered through a plug of glass wool and 100 mL of saturated aqueous ammonium chloride and 300 mL of dichloromethane was added to the filtrate. The organic layer was separated and washed with another 50 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted with three 50-mL portions of dichloromethane. The combined
organic layers were washed with 50 mL of brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was dissolved in 150 mL of dichloromethane and hexanes (approximately 50 mL) was added in small amounts until cloudiness persisted. The resulting white crystals were collected to give a first crop of 15.5 g (62%) and second crop yielded 3.9 g (16%) of 188; mp 83-84°C; IR (KBr) 3321 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.03 (s, 1H, OH), 1.13 (s, 9H, CH₃), 4.08 (s, 2H, CH₂), 7.39-7.42 (m, 6H, ArH), 7.68-7.71 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.45 MHz) δ 18.0 (t), 27.8 (q), 127.8 (d), 129.4 (d), 133.1 (s), 135.8 (d); exact mass calcd. for C₁₇H₁₆Si m/e 270.1440, found m/e 270.1435; Anal. calcd. for C₁₇H₁₆Si C, 75.52; H, 8.21; found C, 75.38; H, 8.11.

(tert-Butyldiphenylsilyl)methanol trifluoromethanesulfonate (189). To 16.8 g (10.0 mL, 59.4 mmol) of triflic anhydride in 75 mL dry dichloromethane cooled in an ice bath was added 4.8 g (4.9 mL, 60.6 mmol) of pyridine dropwise via syringe over a period of 10 min. To the resulting white slurry was added 14.4 g (53.6 mmol) of alcohol 188 in 25 mL dichloromethane via syringe over a period of 10 min. The reaction mixture was stirred at room temperature for 3 h and the resulting slurry was filtered through a pad of 100 g of silica gel (eluted with hexanes). The filtrate was concentrated in vacuo to give 20 g of (93%) the desired triflate 189 as an off-white solid. A small amount was recrystallized from hexanes to provide an analytically pure sample: mp 63-64°C; ¹H NMR (CDCl₃, 300 MHz) δ 1.18 (s, 9H, CH₃), 4.83 (s, 2H, CH₂), 7.39-7.50 (m, 6H, ArH), 7.59-7.62 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.1 (s), 27.6 (q), 67.1 (t), 128.1 (d), 130.2
1-(tert-Butyldiphenylsilyl)methylamine (257). In a three-neck flask equipped with a dry-ice condenser and an additional funnel, and cooled to -78°C was added 50 mL of THF followed by condensation of approximately 300 mL of ammonia. To the solution was added 8.0 g (199 mmol) of tert-butyldiphenylsilylmethyl trifluoromethanesulfonate (189) in 50 mL THF through the additional funnel over a period of 1 h. [After half of the addition was done, the slurry was too thick to stir, the cold bath was removed and the rest of the triflate was added while the slurry was warmed to room temperature]. The mixture was stirred overnight followed by addition of 25 mL of 10% aqueous sodium hydroxide. The solution was stirred at room temperature for 30 min. The aqueous layer was separated and extracted with three 20-mL portions of dichloromethane. The combined organic layers were washed with 20 mL of brine, dried (MgSO₄), concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate) to give 7.6 g (97%) of the desired amine 257 as a pale yellow, viscous oil: IR (neat) 3372 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.98 (s, 2H, NH₂), 1.16 (s, 9H, CH₃), 2.89 (s, 2H, CH₂), 7.36-7.42 (m, 6H, ArH), 7.68-7.75 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.0 (s), 25.4 (t), 27.8 (q), 127.8 (d), 129.3 (d), 133.1 (s), 135.9 (d); exact mass calcd for C₅H₁₃NSi m/e 269.1600, found m/e 269.1591.
3-Pyridyl diethylcarbamate (192).\textsuperscript{80} To a solution of 22 mL of triethylamine in 200 mL of benzene was added 10.0 g (107.6 mmol) of 3-hydroxypyridine followed by addition of 14.2 g (13.3 mL, 105.0 mmol) of diethyl chlorocarbamate over a period of 10 min. The resulting solution was warmed under reflux for 16 h. The dark red slurry was filtered through Celite, the filtrate was concentrated in vacuo and the residue was distilled under reduced pressure (100-115°C/0.95 torr) to give 19.15 g (94%) of carbamate 192 as a yellow oil: \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textdelta 1.20 (t, \textit{J} = 7.1 Hz, 3H, CH\textsubscript{3}), 1.26 (t, \textit{J} = 7.1 Hz, 3H, CH\textsubscript{3}), 3.38 (q, \textit{J} = 7.1 Hz, 2H, NCH\textsubscript{2}), 3.45 (q, \textit{J} = 7.1 Hz, 2H, NCH\textsubscript{2}), 7.29 (dd, \textit{J} = 8.4, 4.8 Hz, 1H, H\textsubscript{5}), 7.50 (m, 1H, H\textsubscript{5}), 8.43 (br s, 2H, H\textsubscript{2} and H\textsubscript{6}).

4-Methyl-3-pyridyl diethylcarbamate (197).\textsuperscript{17b} To a solution of 5.76 g (29.6 mmol) 3-pyridyl diethylcarbamate (192) in 200 mL THF at -78°C under nitrogen was added 29 mL of 1.3 M sec-butyllithium (37.7 mmol) in cyclohexane dropwise over a 60 min period. The internal temperature was not allowed to raise above -65°C during the addition. To the solution was added 4.6 g (6 mL, 39.8 mmol) of TMEDA. The resulting brown solution was stirred at -78°C for 1 h and
3.6 g (1.6 mL, 35.7 mmol) of methyl iodide was added quickly via syringe. The solution was stirred for another hour at -78°C before 25 mL of brine was added slowly, and the mixture was then allowed to warm to room temperature. The inorganic layer was separated and extracted with three 40-mL portions of dichloromethane. The combined organic extract was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate-hexane, 1:3) to give 4.15 g (68%) of carbamate 192 as a yellow oil: 'H NMR δ 1.18 (t. J = 7.1 Hz, 3H, CHj). 1.25 (t. J = 7.0 Hz, 3H, CH,). 2.21 (s, 3H, CH3). 3.36 (q, J = 7.1 Hz, 2H, NCHj). 3.45 (q, J = 7.1 Hz, 2H, NCHj). 7.12 (d, J = 4.8 Hz, 1H, H). 8.28 (d, J = 4.9 Hz, 1H, H). 8.30 (s, 1H, H). Note: In some runs, MPLC (eluted with ethyl acetate-hexanes, 1:8) was used to separate product from unreacted starting material.

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \quad \text{NET}_2 \\
\text{H} & \quad \text{O} \quad \text{NET}_2
\end{align*}
\]

(±)-4-(2-Hydroxy-3-methyl-3-butenyl)-3-pyridyl diethylcarbamate (193) and (±)-4-(2-Formylpropyl)-3-pyridyl diethylcarbamate (201). To a solution of 1.23 g (5.91 mmol) of 4-methyl-3-pyridyl diethylcarbamate in 50 mL of THF at -78°C under nitrogen was added dropwise 4.1 mL of 1.6 M n-BuLi (6.56 mmol) in hexanes over a 10 min period. The resulting red solution was stirred at -78°C for one hour and then 0.50 g (0.59 mL, 7.13 mmol) of methacrolein was added dropwise via syringe. The mixture was stirred at -78°C for another hour, 5 mL of brine was added cautiously, and the light orange slurry was allowed to warm to room temperature. The aqueous layer was decanted and extracted with three 15-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo.
The residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate-hexane, 1:1) to give in sequence 303 mg (18%) of aldehyde 201 and 850 mg (60%) of alcohol 193.

Aldehyde 201: \( \text{IR (CH}_2\text{Cl}_2 \) 1722 cm\(^{-1}\); \( ^1\text{H NMR (CDCl}_3 \) 300 MHz) \( \delta \) 1.08 (d, \( J = 7.1 \) Hz, 3H, CH\(_3\)), 1.15 (t, \( J = 7.1 \) Hz, 3H, NCH\(_3\)), 1.22 (t, \( J = 7.1 \) Hz, 3H, CH\(_3\)), 1.56-1.65 (m, 1H, CH\(_2\)), 1.91-2.04 (m, 1H, CH\(_2\)), 2.33 (m, 1H, CH), 2.56 (dd, \( J = 8.2, 8.0 \) Hz, 2H, CH\(_3\)), 3.33 (q, \( J = 7.1 \) Hz, 2H, NCH\(_3\)), 3.42 (q, \( J = 7.1 \) Hz, 2H, NCH\(_3\)), 7.12 (d, \( J = 4.8 \) Hz, 1H, H\(_3\)), 8.29 (m, 2H, H\(_2\) and H\(_6\)), 9.56 (s, 1H, CHO); \( ^13\text{C NMR (CDCl}_3 \) 75.47 MHz) \( \delta \) 13.17 (q), 13.26 (q), 14.2 (q), 26.6 (t), 29.5 (t), 41.9 (t), 42.3 (t), 45.5 (d), 124.2 (d), 142.5 (s), 144.4 (d), 146.4 (d), 152.3 (s), 203.9 (d) (one of the aromatic singlets was not observed in \( ^13\text{C NMR} \)); exact mass calcd. for C\(_{15}\)H\(_{22}\)N\(_2\)O\(_3\) m/e 278.1630, found m/e 278.1625.

Alcohol 193: \( \text{IR (CH}_2\text{Cl}_2 \) 3412 (broad), 1772 cm\(^{-1}\); \( ^1\text{H NMR (CDCl}_3 \) \( \delta \) 1.15 (t, \( J = 7.1 \) Hz, 3H, CH\(_3\)), 1.25 (t, \( J = 7.1 \) Hz, 3H, CH\(_3\)), 1.73 (s, 3H, CH\(_3\)), 2.66 (dd, \( J = 13.9, 9.1 \) Hz, 1H, CH\(_3\)), 2.80 (dd, \( J = 13.9, 4.1 \) Hz, 1H, CH\(_2\)), 3.33 (q, \( J = 7.1 \) Hz, 2H, NCH\(_3\)), 3.43 (q, \( J = 7.2 \) Hz, 2H, NCH\(_3\)), 3.5 (br s, 1H, OH), 4.23 (dd, \( J = 9.0, 4.0 \) Hz, 1H, CH), 4.8 (br s, 1H), 4.90 (br s, 1H), 7.21 (d, \( J = 5.0 \) Hz, 1H, H\(_5\)), 8.22 (d, \( J = 5.3 \) Hz, 1H), 8.24 (s, 1H); \( ^13\text{C NMR (CDCl}_3 \) \( \delta \) 13.2 (q), 14.2 (q), 17.7 (q), 35.7 (t), 41.9 (t), 42.4 (t), 74.5 (d), 111.2 (t), 125.6 (d), 140.4 (s), 144.3 (d), 146.1 (d), 146.7 (s), 146.9 (s), 153.7 (s); exact mass calcd. for C\(_{15}\)H\(_{22}\)N\(_2\)O\(_3\) m/e 278.1630, found m/e 278.1681. Note: Small signals in \( ^13\text{C NMR} \) spectra indicated the presence of impurities in both 193 and 201.
To 622 mg (2.98 mmol) of 4-methyl-3-pyridyl diethylcarbamate in 20 mL of THF at -78°C under nitrogen was added 2.1 mL of 1.6 M n-BuLi (3.36 mmol) dropwise via syringe over a period of 5 min. The mixture was stirred at -78°C for 1 h and then 0.25 g (0.3 mL, 3.6 mmol) of methacrolein was added via syringe over a 2 min period. The mixture was stirred 30 min and then allowed to warm to 45°C over a period of 30 min. The mixture was heated at 45°C for another 30 min then cooled to room temperature, followed by addition of 3 mL of brine. The aqueous phase was separated and extracted with three 10-mL portions of dichloromethane. The organic layers were combined, dried (MgSO₄), concentrated in vacuo. The residue was chromatographed over 60 g of silica gel (eluted with ethyl acetate) to give, in sequence, 165 mg (20%) of aldehyde 201 as a yellow oil and 540 mg (65%) of 3-pyridinol 205 as another yellow oil, which gave the following spectral data: IR (neat) 3222 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.99 (t, J = 7.0 Hz, 6H, NCH₂), 1.75 (s, 3H, CH₃), 2.95 (dm, J = 12.9 Hz, 2H, CH₂), 3.17 (q, J = 7.0 Hz, 4H, NCH₂CH₃), 4.78-4.82 (m, 2H, CH₂=), 5.34 (dd, J = 7.4, 6.0 Hz, 1H, CH), 7.02 (d, J = 5.9 Hz, 1H, H₄), 7.90 (d, J = 5.9 Hz, 1H, H₄), 8.13 (s, 1H, H₆), the phenolic proton was not detected; ¹³C NMR (CDCl₃, 75.47 MHz), δ 13.2 (q), 13.7 (q), 18.2 (q), 33.7 (t), 41.0 (t), 41.6 (t), 76.5 (d), 112.2 (t), 125.8 (d), 134.2 (s), 136.1 (d), 138.8 (d), 143.3 (s), 153.5 (s), 155.1 (s); exact mass cacld. for C₁₃H₁₂N₂O₃ m/e 278.1630, found m/e 278.1630. This material contained some contamination by ¹³C and ¹H NMR.
(±)-2-Methyl-3-(phenylthio)propionaldehyde (202). To 0.5 mL (0.43 g, 6.04 mmol) of methacrolein was added 0.66 g (0.62 mL, 6.04 mmol) of thiophenol via syringe over a period of 5 min at -78°C. The mixture was stirred at -78°C for 30 min and then at room temperature for 18 h. The residue was chromatographed directly on 70 g of silica gel (eluted with hexanes until thiophenol had eluted, then ethyl acetate-hexanes, 1:10), to give 0.63 g (58%) of desired aldehyde 202 as a yellow oil: IR (CHCl₃) 1723 cm⁻¹; ¹H NMR (CDCl₃) δ 1.23 (d, J = 7.2 Hz, 3H, CH₃), 2.61 (sextet, J = 7 Hz, 1H, CH), 2.91 (dd, J = 13.3, 7.1 Hz, 1H, CH₂), 3.30 (dd, J = 13.3, 6.8 Hz, 1H, CH₂), 7.18-7.28 (m, 5H, C₆H₅), 9.67 (d, J = 1.4 Hz, 1H, CHO); ¹³C NMR (CDCl₃) δ 13.4 (q), 14.6 (t), 45.8 (d), 128.5 (d), 129.0 (d), 129.9 (d), 135.3 (s), 202.8 (d); exact mass calcd. for C₁₀H₁₃O₅ m/e 180.0608, found m/e 180.0605.

(±)-4-[2-Hydroxy-3-methyl-4-(phenylthio)butyl]-3-pyridyldiethyl-carbamate (203). To 0.25 g (0.36 mL, 2.5 mmol) of diisopropylamine in 20 mL THF at -78°C under nitrogen was added 1.5 mL of 1.6 M n-BuLi (2.40 mmol) in hexanes dropwise via syringe
over a period of 5 min. The mixture was stirred at -78°C for 20 min and 418 mg (2.0 mmol) of 4-
methyl-3-pyridyl diethylcarbamate 197 in 0.5 mL of THF was added dropwise via syringe. The
resulting red solution was stirred at -78°C for 1 h and 387 mg (2.1 mmol) of aldehyde 202 in 0.5
mL of THF was introduced dropwise via syringe over 10 min. The solution was stirred at -78°C for
another hour and 5 mL brine was added slowly. The yellow slurry was stirred for 15 min at -78°C
and then warmed to room temperature. The aqueous layer was decanted and extracted with
three 15-mL portions of dichloromethane. The combined organic layers were dried (MgSO4) and
concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with
ethyl acetate-hexanes, 1:1) to afford 701 mg (90%) of a 1:1 mixture of two diastereomeric
alcohols 203 as a light yellow oil: IR (CH2Cl2) 3417, 1722 cm⁻¹; ¹H NMR (CDCl3) δ 0.97 (overlapping
t’s, J = 7.0 Hz, 6H, CH3), 1.12 (d, J = 6.5 Hz, 1.5H, CH3), 1.16 (d, J = 6.5 Hz, 1.5H, CH3), 1.85-2.05
(m, 1H), 2.42-2.51 (m, 1H, CH2), 2.58-2.66 (m, 1H, CH2), 2.77-2.84 (m, 1H, CH2), 2.99-3.26 (m,
4H, CH2), 3.27 (dd, J = 13.1, 6.5 Hz, 0.5H, CH2), 3.44 (dd, J = 12.9, 4.1 Hz, 0.5H, CH2), 3.65-3.75
(m, 1H, CH and OH), 3.82 (br s, 0.5H, OH), 4.05 (dm, J = 13.2 Hz, 0.5H, CH), 6.92 (d, J = 7.8 Hz,
0.5H, H2), 6.88 (d, J = 7.9 Hz, 0.5H, H2), 6.94-7.02 (m, 1H, CH2), 7.08-7.13 (m, 2H, CH2), 7.35-
7.48 (m, 2H, CH2), 8.24 (d, J = 7.8 Hz, 0.5H, H2), 8.28 (d, J = 8.0 Hz, 0.5H, H2), 8.43 (s, 0.5H, H2),
8.49 (s, 0.5H, H2); ¹³C NMR (CDCl3, 75.47 MHz) δ 13.2 (q), 14.2 (q), 15.7 (q), 34.4 (t), 34.8 (t), 36.6
(t), 37.3 (t), 38.3 (d), 39.3 (d), 41.96 (t), 42.0 (t), 42.4 (t), 71.8 (d), 73.6 (d), 125.5 (d), 125.6 (d),
125.7 (d), 125.8 (d), 128.6 (d), 128.7 (d), 128.8 (d), 136.7 (s), 136.8 (s), 141.0 (s), 141.1 (s),
144.2 (d), 146.1 (d), 146.2 (d), 146.9 (s), 147.0 (s), 153.8 (s), 153.9 (s), one triplet and three
quartets in the aliphatic and two doublets in the aromatic regions were not observed; exact mass
calcd. for C21H29N2O3S m/z 388.1821, found m/z 388.1824.

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(±)-1-[(tert-Butyldiphenylsilyl)methyl]-3-[(diethylcarbamoyl)oxy]-4-(2-hydroxy-3-methyl-3-butenyl)pyridinium trifluoromethanesulfonate (207). To 576 mg (2.07 mmol) of alcohol 193 in 8 mL dry acetonitrile was added 833 mg (2.07 mmol) of solid tert-butyldiphenylsilylmethyl triflate 189. The resulting yellow solution was stirred at room temperature for 48 h and then concentrated in vacuo. The residue was recrystallized from dichloromethane and hexanes (5:1) to give 1.11 g (78%) pyridinium salt 207 as an off-white solid. A second crop of 0.28 g (20%) of 207 was also obtained: mp 152-154°C, IR (KBr) 3467, 1723, 1639 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.12-1.22 (two t's, J = 7.2 Hz, 6H, CH₃), 1.15 (s, 9H, CH₃), 1.74 (s, 3H, CH₃), 2.74 (dd, J = 13.6, 9.7 Hz, 1H, CH₂), 2.88 (dd, J = 13.7, 2.8 Hz, 1H, CH₂), 3.32 (q, J = 7.2 Hz, 2H, CH₂), 3.38 (q, J = 7.2 Hz, 2H, CH₂), 4.21 (dm, J = 6.9 Hz, 1H, CH), 4.83 (br s, 3H, CH₂ and CH), 4.93 (br s, 1H, CH), 7.35-7.49 (m, 6H, CH₃ and H,), 7.55-7.60 (m, 5H, CH₃), 7.90 (dd, J = 6.2, 0.8 Hz, 1H, H₃), 8.06 (br s, 1H, H₂), according to the integration of the signals at δ 3.3-3.4, there is another hydrogen underneath, probably due to the OH proton; ¹³C NMR (CDCl₃) δ 12.9 (q), 14.0 (q), 18.0 (s), 18.3 (q), 27.4 (q), 36.4 (t), 42.2 (t), 42.7 (t), 49.8 (t), 72.9 (d), 111.5 (t), 128.5 (d), 128.9 (s), 129.4 (d), 130.6 (d), 136.0 (d), 138.4 (d), 139.4 (d), 146.0 (s), 148.6 (s), 150.2 (s), 151.2 (s); exact mass calc. for C₃₅H₄₅F₃N₃O₈SiS m/e 680.2563, (molecular weight is too high to detect on the mass spectrum); Anal. calcd. for C₃₅H₄₅F₃N₃O₈SiS: C, 58.21; H, 6.36; found C, 58.08; H, 6.31.
(+)-1-[(tert-Butyldiphenylsilyl)methyl]-6-cyano-1,2,5,6-tetrahydro-4-(2-hydroxy-3-methyl-3-butenyl)-3-pyridyl diethylcarbamate (208). To 224 mg (4.57 mmol) of sodium cyanide in a mixture of 10 mL of water, 10 mL of methanol and 20 mL of diethyl ether was added 24.5 mg (0.65 mmol) of sodium borohydride followed by immediate addition of 340 mg (0.50 mmol) of the solid pyridinium salt 207. The two phase mixture was stirred at room temperature for 20 min and then diluted with 20 mL diethyl ether. The aqueous layer was separated and extracted with three 20-mL portions of dichloromethane. The combined organic phases were washed with 15 mL of brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 25 g of silica gel (eluted with ethyl acetate-hexanes, 1:3) to give 112 mg (40%) of a major isomeric α-cyanosilylamine 208 as a colorless oil and 16 mg of a mixture of the two isomers (6%). The major isomer gave the following spectral data: IR (neat) 3427(br), 1713, 1474, 1427 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.08 (s, 9H, CH₃), 1.02-1.27 (m, 6H, two NC₃H₂C₆H₃), 1.67 (s, 3H, CH₃), 1.98 (d, J=14.5 Hz, 1H, CH₂), 2.05 (d, J = 6.9 Hz, 1H, CH₂), 2.35 (dd, J = 14.0, 10.6 Hz, 1H, CH₂), 2.63 (br d, J = 6.7 Hz, 1H, CH₂), 2.78 (AB quartet, 2H), 2.88 (d, J = 16.3 Hz, 1H, CH₂), 3.17-3.37 (m, 5H, two NC₃H₂CH₃ and CH₂), 3.42 (d, J = 4.6 Hz, 1H, CH₂), 3.60 (dd, J = 4.5, 1.5 Hz, 1H), 4.05 (dd, J = 10.3, 3.9 Hz, 1H, OCH), 4.77 (s, 1H, CH₂=), 4.95 (s, 1H, CH₂=), 7.33-7.63 (m, 6H, C₆H₅), 7.62-7.71 (m, 4H, C₆H₅); ¹³C NMR (CDCl₃, 75.47 MHz) δ 13.2 (q), 14.1 (q), 17.6 (q), 18.2 (s), 27.6 (q), 31.4 (t), 35.8 (t), 41.8 (t), 42.0 (t), 42.3 (t), 52.2 (d), 53.2 (t), 72.0 (d), 103
110.2 (t), 116.2 (s), 117.4 (s), 127.8 (d), 129.48 (d), 129.50 (d), 133.4 (s), 133.8 (s), 135.7 (d), 135.8 (d), 141.0 (s), 140.4 (s), 154.2 (s), one of the aromatic doublets was missing, probably due to overlapping in that region; exact mass calcd. for C_{32}H_{42}N_{3}O_{5}Si m/e 559.3230, found m/e 559.3265.

![Chemical Structure](image)

1-[(tert-Butylidiphenylsilyl)methyl]-6-cyano-1,2,5,6-tetrahydro-4-(3-methyl-2-oxo-3-butenyl)-3-pyridyl diethylcarbamate (194). To 36 mg (25 μL, 0.28 mmol) of oxalyl chloride in 0.5 mL of dichloromethane at -78°C was added 66 mg (60 μL, 0.84 mmol) dimethylsulfoxide via syringe. The mixture was stirred at -78°C for 30 min and then a solution of 50 mg (0.09 mmol) of alcohol 208 in 0.6 mL of dichloromethane was added dropwise via syringe over a period of 5 min. The resulting mixture was stirred at -78°C for another 1 h and then 0.87 g (1.2 mL, 8.6 mmol) of triethylamine was added dropwise via syringe over 5 min. The slurry was stirred at -78°C for 30 min, and warmed to room temperature over another 30 min. The mixture was concentrated in vacuo and the residue was chromatographed over 5 g of silica gel (eluted with ethyl acetate-hexanes, 1:5) to afford 33.4 mg (67%) of the desired enone 194 as a bright yellow oil: IR (neat) 1721, 1679, 1427 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.07 (s, 9H, CH₃), 1.00-1.10 (m, 6H, two NCH₂CH₃), 1.82 (s, 3H, CH₃), 1.98 (d, J = 16.8 Hz, 1H, H₃NMe), 2.45 (d, J = 14.2 Hz, 1H, H₃NMe), 2.72-2.84 (AB quartet, 2H, CH₂), 2.97 (dd, J = 15.7, 1.4 Hz, 1H, H₃NMe), 3.19-3.42 (m, 7H, two NCH₂CH₃, CH₂CO and H₃NMe), 3.53 (dd, J = 5.7, 1.7 Hz, 1H, H₂), 5.76 (d, J = 1.3 Hz, 1H,
CH$_2$=), 5.95 (s, 1H, CH$_2$=), 7.32-7.43 (m, 6H, ArH), 7.63 (dm, 2H, J = 7.7 Hz, ArH), 7.69 (dm, 2H, J = 7.7 Hz, ArH); $^1$H NMR (CDCl$_3$, 75.45 MHz) δ 13.3 (q), 14.1 (q), 17.5 (q), 18.2 (s), 27.6 (q), 31.4 (t), 38.2 (t), 41.6 (t), 41.9 (t), 42.0 (t), 52.1 (d), 53.2 (t), 114.0 (s), 115.8 (s), 125.4 (t), 127.8 (d), 129.4 (d), 133.4 (s), 133.8 (s), 135.6 (d), 135.8 (d), 141.0 (s), 144.0 (s), 152.6 (s), 198.4 (s), total of 25 carbons observed. There were eight singlets in the aromatic region, which means that the two phenyl rings were not magnetically equivalent. Therefore these should be two more aromatic doublets that were probably not resolved; exact mass calcd for C$_{33}$H$_{14}$N$_2$O$_2$Si m/e 557.3073, found m/e 557.3102.

$\begin{align*}
\text{216}
\end{align*}$

$\alpha$-Methyl-3-pyridinemethanol (216). To 6.09 g of 3-acetylpyridine (50 mmol) in 50 mL of anhydrous ethanol was added 3.88 g (102 mmol) of sodium borohydride in three portions over a period of 30 min. The resulting mixture was stirred at room temperature for another 30 min and to the reaction mixture was cautiously added 50 mL of brine. The resulting slurry was diluted with 50 mL of dichloromethane. The aqueous layer was separated and extracted with ten 50-mL portions of dichloromethane. The organic layers were combined, dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate-hexanes, 2:1) to give 5.15 g (84%) of the desired alcohol 216 as a colorless oil; $^1$H NMR (CDCl$_3$, 300 MHz) δ 1.51 (d, J = 6.5 Hz, 3H, CH$_3$), 2.88 (br s, 1H, OH), 4.93 (q, J = 6.5 Hz, 1H, CH), 7.30 (dd, J = 7.8, 4.8 Hz, 1H, H$_3$), 7.74 (dt, J = 7.9, 1.7 Hz, 1H, H$_4$), 8.46 (dd, J = 4.8, 1.7 Hz, 1H, H$_5$), 8.51 (dd, J = 2.1 Hz, 1H, H$_6$).
NOTE TO USERS

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1-[(tert-Butyldiphenylsilyl)methyl]-3-(1-hydroxyethyl)pyridinium trifluoromethanesulfonate (217) To 369 mg (3.00 mmol) of α-methyl-3-pyridinemethanol (216) in 20 mL of acetonitrile was added 1.21 g (3.00 mmol) tert-butyldiphenylsilyl)methyl triflate (189). The mixture was stirred at room temperature for 16 h and then concentrated in vacuo. The resulting crude material was dissolved in 10 mL of dichloromethane and hexanes (approximately 2 mL) was added dropwise until cloudiness persisted. The resulting white crystals were collected to give a first crop of 1.25 g (80%) and a second crop of 115 mg (7%) as the desired pyridinium salt 217: mp 155-156°C; IR (KBr) 3446 cm⁻¹ (OH); ¹H NMR (CDCl₃, 300 MHz) δ 1.17 (d and s, 12H, CH₃), 2.60 (br s, 1H, OH), 4.71 (q, J = 6.7 Hz, 1H, CHOH), 4.89 (s, 2H, CH₂), 7.33-7.53 (m, 11H, ArH and H₃), 8.01 (d, J = 9.3 Hz, 1H, H₄ or H₅), 8.03 (d, J = 6.4 Hz, 1H, H₄ or H₅), 8.25 (s, 1H, H₆); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.3 (s), 23.7 (q), 27.4 (q), 49.8 (t), 65.9 (d), 126.7 (d), 128.51 (d), 128.53 (d), 128.70 (s), 128.74 (s), 130.8 (d), 135.84 (d), 135.86 (d), 140.3 (d), 141.5 (d), 142.4 (d), 147.8 (s), one doublet was missing in the aromatic region, probably due to overlapping signals; Anal. calcd. for C₂₅H₂₂F₃NO₃SSi: C, 57.13; H, 5.76; found C, 57.06; H, 5.79.
1-[(tert-Butyldiphenylsilyl)methyl]-1,2,3,6-tetrahydro-5-(1-hydroxyethyl)-2-pyridinecarbonitrile (210). To 160 mg (3.26 mmol) of sodium cyanide in 10 mL of water, 10 mL of methanol and 20 mL of diethyl ether was added 15 mg (0.39 mmol) of sodium borohydride, followed by immediate addition of 200 mg (0.38 mmol) of pyridinium salt 217. The resulting mixture was stirred at room temperature for 10 min and then diluted with 20 mL of diethyl ether. The aqueous layer was separated and extracted with three 15-mL portions of dichloromethane. The combined organic layers were washed with 15 mL of brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (eluted with ethyl acetate-hexanes, 1:3) to give 701 mg (57%) of amino alcohol 210 as a colorless oil: IR (neat) 3419 (broad, OH), 2167 (weak, CN), 1427 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz), δ 1.08 (s, 9H, CH₃), 1.13 (d, J = 6.5 Hz, 3H, CH₃), 1.53 (br s, 0.5H, OH), 1.54 (br s, 0.5H, OH), 2.08 (m, 1H, H₃(b)), 2.36 (d, J = 15.4 Hz, 1H, H₃(a)), 2.8-2.9 (AB quartet and d, 3H, NCH₂Si and H₃(a)), 3.20 (two d’s, J = 16.4 Hz, 1H, H₃(a)), 3.58 (dd, J = 4.6, 1.5 Hz, 1H, H₂), 4.08 (m, 1H, CHOH), 5.53 (br s, 1H, =CH), 7.34-7.45 (m, 6H, ArH), 7.66-7.72 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.2 (s), 21.3 (q), 21.5 (q), 27.0 (q), 29.0 (t), 29.1 (t), 42.54 (t), 42.56 (t), 51.2 (t), 51.9 (t), 52.4 (d), 52.5 (d), 69.2 (d), 69.7 (d), 114.5 (d), 115.3 (d), 116.42 (s), 116.48 (s), 127.7 (d), 129.5 (d), 133.8 (s), 133.9 (s), 135.7 (d), 135.8 (d), 140.4 (s), 140.7 (s), most signals were doubled due to the presence of two diastereomers, except for the singlet and the quartet corresponding to the t-butyl group and two aromatic doublets; exact mass calcd. for C₂₅H₂₃N₂O₃Si m/z 404.2284, found m/z 404.2298.
$(\pm)-(2R^*,4R^*)-1-[(tert-Butyldiphenylsililyl)methyl]-2-cyano-5-[(Z)-ethylidene]-N,N-dimethyl-4-piperidineacetamide (222).$ To 1.00 g (2.48 mmol) of allylic alcohol 210 in 14 mL of xylene was added 2.73 g (3 mL, 20.5 mmol) of $N,N$-dimethylacetamide dimethyl acetal in one portion via syringe. The mixture was warmed under reflux for 1.5 h and then cooled to room temperature. The solvent was removed in vacuo. The residue was chromatographed over 5 g of silica gel (eluted with ethyl acetate-hexanes, 1:1) to afford 969 mg (83%) of 8:1 mixture of the trans and the cis amides as a yellow oil. Recrystallization from dichloromethane and hexanes provided a small, analytically pure sample of 222: mp 131-133°C; IR (neat) 1651, 1427 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.07 (s, 9H, CH$_3$), 1.12 (d, $J = 6.6$ Hz, 3H, CH$_3$), 1.27 (td, $J = 12.6$, 4.4 Hz, 1H, $H_{39}$), 1.73 (dd, $J = 15.1$, 8.5 Hz, 1H, CH$_2$CONMe$_2$), 1.94 (dt, $J = 13.0$, 2.5 Hz, 1H, $H_{39}$), 2.16 (s, 3H, CH$_3$), 2.19 (m, 1H, CH$_2$CONMe$_2$), 2.60 (s, 3H, CH$_3$), 2.67 (d, $J = 14.4$ Hz, 2H, NCH$_2$Si, H$_{39}$), 2.84 (m, 1H, H$_4$), 2.88 (d, $J = 14.8$ Hz, 1H, NCH$_2$Si), 3.39 (t, $J = 3$ Hz, 1H, H$_3$), 3.46 (d, $J = 12.6$ Hz, 1H, $H_{39}$), 4.85 (q, $J = 6.6$ Hz, 1H, =CH), 7.20 (m, 6H, ArH), 7.65 (m, 2H, ArH), 7.75 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 75.47 MHz) $\delta$ 12.5 (q), 18.5 (s), 27.9 (q), 34.2 (d), 34.9 (q), 35.1 (t), 35.8 (t), 36.3 (q), 43.3 (t), 53.0 (t), 57.5 (d), 115.8 (d), 116.4 (s), 127.7 (d), 128.0 (d), 128.3 (d), 129.67 (d), 129.71 (d), 134.9 (s), 136.1 (d), 136.4 (d), 136.6 (s), 170.0 (s); exact mass calcd. for C$_{29}$H$_{30}$N$_2$OSi $m/e$ 473.2862, found $m/e$ 473.2873.
(±)-(1R*,4R*)-1-[(tert-Butyldiphenylsilyl)methyl]-5-[(Z)-ethylidene]-4-(formylmethyl)-2-piperidinecarbonitrile (223): To 471 mg (0.99 mmol) of amide 2 and 204 mg (205 μL, 1.10 mmol) of diphenylsilane in 1.5 mL benzene was added 284 mg (295 μL, 1.00 mmol) of titanium isopropoxide dropwise via syringe over a period of 2 min. The resulting mixture was stirred at room temperature for 18 h. The solution was diluted with 50 mL of THF and 10 mL of 1 N aqueous HCl was added. The reaction mixture was stirred vigorously at room temperature for 15 min and then 20 mL of saturated aqueous sodium bicarbonate was added. The mixture was stirred at room temperature for another 10 min. The aqueous layer was separated and extracted with three 40-mL portions of ether. The combined organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:6) to give 257 mg (60%) of an 8:1 mixture of aldehyde 223 and its cis isomer as a white foam: ¹H NMR (CDCl₃, 300 MHz) δ 1.00 (s, 9H, CH₃), 1.22 (d, J = 6.4 Hz, 3H, CH₃), 1.51 (td, J = 12.7, 4.5 Hz, 1H, H₃β), 1.83 (dt, J = 12.8, 3.0 Hz, 1H, H₃α), 2.26 (dd, J = 16.7, 6.0 Hz, 1H, CH₂CHO), 2.57-2.71 (m, 2H, CH₃CHO, and H₃α), 2.74-2.97 (m and AB quartet, 3H, H₂β and NCH₂Si), 3.54 (d, J = 12.9 Hz, 1H, H₃α), 3.74 (br s, 1H, H₃β), 4.99 (q, J = 6.8 Hz, 1H, =CH), 7.24-7.42 (m, 6H, ArH), 7.62-7.78 (m, 4H, ArH), 9.68 (t, J = 1.7 Hz, 1H, CHO); ¹³C NMR (CDCl₃, 74.47 MHz) δ 12.3 (q), 18.3 (s), 27.7 (q), 32.1 (d), 35.4 (t), 43.0 (t), 45.1 (t), 52.7 (t), 56.8 (d), 116.2 (s), 117.2 (d), 127.7 (d), 129.40 (d), 129.45 (d), 129.9 (d), 133.7 (s), 134.0 (d), 134.1 (d).
134.3 (d), 134.6 (d), 134.7 (s), 135.7 (d), 135.79 (d), 135.85 (d), 201.2 (d). The minor (cis) isomer was visible in both \(^1\)H NMR and \(^{13}\)C NMR spectra. Some of the diagnostic signals in the \(^1\)H NMR include \(\delta 2.9-3.0\) (AB quartet and d, NCH\(_2\)Si and H\(_d\)), 3.59 (t, H\(_b\)), 5.15 (q, =CHMe), and in the \(^{13}\)C NMR \(\delta 12.1\) (q), 26.3 (q), 33.5 (d), 33.8 (t), 43.1 (t), 46.3 (t), 50.4 (t), 54.5 (d), 118.3 (s), 120.1 (d), 200.9 (d). Interpretation of the aromatic region of the \(^{13}\)C NMR was difficult due to the presence of the minor (cis) isomer; exact mass calcd. for C\(_{27}\)H\(_{34}\)N\(_2\)OSi \(m/e 430.2440\), found \(m/e 430.2415\).

1,5-Diphenyl-1-penten-3-ol (230). \(^{44b}\) Method A. A three-neck flask containing 375 mg (3.05 mmol) of chromium chloride and 4 mg (0.03 mmol) of nickel chloride was flame dried and cooled to room temperature under a stream of nitrogen. To the solid was added 4 mL of dry DMSO via syringe, and the resulting slurry was stirred at room temperature for 10 min. To the mixture was added 70.6 mg (0.53 mmol) of hydrocinnamaldehyde followed by 279 mg (1.52 mmol) of \(\alpha\)-iodostyrene via syringe. The resulting mixture was stirred at room temperature for 18 h, and then partitioned between 25 mL of diethyl ether and 5 mL of water. The organic phase was washed with two 5-mL portions of water. The aqueous washes were combined and extracted with three 15-mL portions of diethyl ether. The organic layers were combined, washed with brine (10 mL), dried (MgSO\(_4\)), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with ethyl acetate-hexanes, 1:10) to give 60 mg (48%) of the desired allylic alcohol 230 as a colorless oil. Method B. To a flame-dried three-neck flask containing 263 mg (2.14 mmol) of chromium chloride and 1.3 mg (0.01 mmol) of nickel chloride was added 5 mL of DMF. The resulting green slurry was stirred at room temperature for 10 min, and to it v. s added
68 mg (67 µL, 0.50 mmol) of hydrocinnamaldehyde, followed by 256 mg (1.01 mmol) of vinyl triflate 227 in 2 mL of DMF. The resulting mixture was stirred at room temperature for 20 h, and then partitioned between 20 mL of diethyl ether and 5 mL of water. The organic layer was separated and washed with two 5-mL portions of water. The aqueous washes were combined and extracted with three 15-mL portions of diethyl ether. The organic layers were combined, washed with 15 mL of brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 7 g of silica gel (eluted with ethyl acetate-hexanes, 1:15) to give 62 mg (51%) of the desired allylic alcohol 230 as a yellow oil: ¹H NMR (CDCl₃, 200 MHz) δ 1.8-2.1 (m, 3H, CH₂ and OH), 2.6-2.9 (m, 2H, CH₂), 4.70 (dd, J = 7.4, 4.6 Hz, 1H, CHOH), 5.38 (br s, 1H, =CH₂), 5.43 (br s, 1H, =CH₂), 7.2-7.5 (m, ArH, 10H).

α-Bromostyrene (225). To 14.1 g (135 mmol) of styrene in 20 mL of chloroform in an ice-bath was added 34.3 g (17.5 mL, 340 mmol) of bromine in 20 mL of chloroform dropwise over a period of 20 min. The resulting mixture was warmed to room temperature, stirred for 1 h and then concentrated in vacuo to give a light yellow solid. The crude dibromide was dissolved in 40 mL of benzene and the resulting mixture was added to a well stirred mixture of 35.7 g (892 mmol) of potassium hydroxide and 0.62 g (1.84 mmol) of myristyltrimethylammonium bromide in 40 mL of water. The resulting mixture was heated to reflux for 3 h and cooled to room temperature. The organic layer was separated and washed with, in sequence, 25 mL of water and 25 mL of brine. The aqueous washes were combined and extracted with three 50-mL portions of diethyl ether. The organic layers were combined, dried (MgSO₄), and concentrated in vacuo. The
residue was distilled under reduced pressure to give 20.5 g (83%) of the desired vinyl bromide 225 as a yellow liquid (bp 95-110°C/3.5 torr): \( ^1H \) NMR (CDCl\(_3\), 200 MHz) \( \delta \) 5.78 (d, \( J = 2.0 \) Hz, 1H, \( =CH_2 \)), 6.13 (d, \( J = 2.0 \) Hz, 1H, \( =CH_2 \)), 7.30 -7.45 (m, 3H, ArH), 7.55-7.70 (m, 2H, ArH). The product contains about 3% of the unseparable \( \beta \)-bromostyrene according to the \( ^1H \) NMR spectrum. The diagnostic signals of the minor isomer appear at \( \delta \) 6.67 (d, \( J = 5.6 \) Hz, 1H, \( =CH \)), 7.12 (d, \( J = 15.6 \) Hz, 1H, \( =CH \)), 8.00 (m, 2H, ArH).

\( \text{P h} \)

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\( \alpha \)-iodostyrene (226). A mixture of 4.13 g (34.4 mmol) of acetophenone, 8.27 g (165 mmol) of hydrazine monohydrate and 4 mL of triethylamine in 15 mL of absolute ethanol was heated at 85°C (oil bath temperature) for 16 h. The resulting mixture was cooled to room temperature and partitioned between 10 mL of water and 30 mL of dichloromethane. The aqueous layer was separated and extracted with three 30-mL portions of dichloromethane. The organic layers were combined, washed with brine (15 mL), dried (MgSO\(_4\)), and concentrated in vacuo. The residue was dissolved in 40 mL of tetrahydrofuran, and 60 mL of triethylamine was added. To the resulting mixture in an ice-bath, was added 18.3 g (72.0 mmol) of iodine in 50 mL of THF dropwise over a period of 30 min. The resulting mixture was warmed to room temperature and stirred for 1 h. To the mixture was added 5 g of sodium bisulfite and stirred for 5 min. The resulting mixture was diluted with 100 mL of diethyl ether and washed, in sequence, with 40 mL of saturated aqueous sodium bisulfite, 40 mL of brine, 40 mL of saturated aqueous sodium bicarbonate, 40 mL of brine, 40 mL of 1 N aqueous HCl and 40 mL of brine. The organic layer was dried (MgSO\(_4\)) and concentrated in vacuo. The residue was distilled under reduced pressure to
give 1.8 g of light yellow liquid (bp 35-40°C/0.25 torr). 'H NMR of the distillate showed that it contained about 5% of acetophenone (δ 2.62 (s, CH₃)). The mixture was dissolved in 50 mL of benzene and 10 mg (0.05 mmol) of p-toluenesulfonic acid monohydrate and 0.20 g (1.01 mmol) of 2,4-dinitrophenylhydrazine was added. The resulting mixture was heated to reflux for 1 h, cooled to room temperature and filtered through Celite. The filtrate was concentrated in vacuo and the residue was distilled under reduced pressures to give 1.2 g (48%) of the desired vinyl iodide 226 as a yellow liquid (bp 52-57°C/1.2 torr): 'H NMR (CDCl₃, 200 MHz) δ 6.08 (d, J = 1.8 Hz, 1H, =CH₂), 6.48 (d, J = 1.8 Hz, 1H, =CH₂), 7.2-7.4 (m, 3H, ArH), 7.4-7.6 (m, 2H, ArH).

\[ \text{Ph} \quad \text{OTf} \]

1-Phenylethenyl triflate (227). Method A: ⁶⁷b To a mixture of 6.3 g (30.0 mmol) of acetophenone and 2.7 g (2.6 mL, 32 mmol) of pyridine in 10 mL of pentane at -78°C was added 9.2 g (5.5 mL, 33 mmol) of triflic anhydride dropwise via syringe over a period of 10 min. The resulting slurry was warmed to room temperature, 10 mL pentane was added and stirred for 24 h. The top solution was decanted and the green mass at the bottom was dissolved in approximately 15 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with three 25-mL portions of pentane. The organic layer was combined, dried (K₂CO₃) and concentrated in vacuo. The residue was distilled under reduced pressure to give 1.03 g (16%) of the desired triflate 227 as a yellow oil (bp 68-70°C/1.3 torr). Method B: ⁴⁴b To 5.2 g (5.4 mL, 4.9 mmol) of phenylacetylene in 50 mL of dry hexanes at a methanol-dry-ice bath was added dropwise 4.1 g (2.4 mL, 2.7 mmol) of triflic acid via syringe over a period of 20 min. The resulting brown slurry was so thick that stirring was difficult. The mixture was warm to -30°C and stirred for 30 min. To the resulting mixture was added 10 mL of saturated aqueous sodium bicarbonate dropwise over 10
min. The resulting mixture was warmed to room temperature and the aqueous layer was separated and extracted with two 10-mL portions of hexanes. The organic layers were combined, washed with two 10-mL portions of saturated aqueous sodium bicarbonate, dried (K₂CO₃) and concentrated in vacuo. The residue was distilled under reduced pressure to give 3.1 g (45%) of the desired triflate 227 as a yellow liquid (bp 45-50°C/0.3 torr): ¹H NMR (CDCl₃, 200 MHz) δ 5.37 (d, J = 5.5 Hz, 1H, =CH₂), 5.62 (d, J = 5.5 Hz, 1H, =CH₂), 7.35-7.47 (m, 3H, ArH), 7.48-7.6 (m, 2H, ArH). The product obtained from Method B contained about 4% of 2-phenylethyl triflate (according to ¹H NMR). The diagnostic signals include δ 6.75 (d, J = 15.6 Hz, 1H, =CH), 7.11 (d, J = 15.6 Hz, 1H, =CH), 8.00 (m, 2H, ArH).

1-[(tert-Butyldiphenylsilyl)methyl]-5-[(Z)-ethylidene]-4-(2-hydroxy-3-phenyl-3-butenyl)-2-piperidinonitrile (224). A flask containing 456 mg (1.22 mmol) of cerium chloride was heated slowly to 150°C over a period of 1.5 h under reduced vacuum (0.3-0.4 torr). The oil bath was maintained at that temperature for 15 h. The flask was cooled to room temperature under vacuum and the vacuum line was then quickly changed to aseptum connected to a nitrogen source. The powdery solid was flushed with a strong flow of nitrogen for 5 min and 4 mL of THF was added. The resulting white slurry was stirred at room
temperature for 3 h. To 204 mg (145 µL, 1.12 mmol) of α-bromostyrene in 6 mL THF in a separate
flame-dried three-neck flask at -78°C was added 1.4 mL of 1.7 M (2.38 mmol) t-BuLi in
pentane dropwise via syringe over a period of 3 min. The resulting dark red solution was stirred at -
78°C for additional 30 min. The resulting vinyl lithium solution was then transferred to the cerium
chloride suspension via cannula at -78°C over a period of 10 min. The resulting light pink slurry
was stirred at -78°C for 1 h. To the mixture at -78°C was added 350 mg (0.81 mmol) of aldehyde
223 in 2 mL of THF dropwise via syringe over a period of 5 min. The color of the slurry faded
almost immediately. The resulting off-white slurry was stirred at -78°C for 3.5 h and 2 mL of brine
was added. The resulting mixture was warmed to room temperature and a mixture of 4 mL of water
and 40 mL of diethyl ether was added. The aqueous layer was separated and extracted with three
20-mL portions of diethyl ether. The organic layers were combined, dried (MgSO₄), and
concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with
ethyl acetate-hexanes, 1:6) to give 213 mg (49%) of the desired allylic alcohol 224 as a white
foam. This mixture consisted of four diastereomers that was difficult to characterize, but could be
used directly in the next reaction.

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\text{1-[(\text{tert-Buylidiphenylisilyl})methyl]-5-[(Z)-ethylidene]-4-(2-oxo-3-phenyl-}
\text{3-butenyl)-2-piperidinecarbonitrile (231).}
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To a mixture of 44 mg (0.56 mmol) of pyridine
and 84 mg (0.20 mmol) of Dess-Martin periodinane in 1 mL of dichloromethane was added 75 mg
(0.14 mmol) of alcohol 224 in 1.5 mL dichloromethane dropwise over a period of 5 min via
syringe. The mixture was stirred at room temperature for 2 h and then 1 mL of 20% aqueous
sodium hydroxide was added. The mixture was diluted with 15 mL of dichloromethane. The
aqueous layer was separated and extracted with three 10-mL portions of dichloromethane. The
organic layers were combined, washed with 10 mL brine, dried (MgSO4), and concentrated in
vacuo. The residue was chromatographed over 7 g of silica gel (eluted with ethyl acetate-
hexanes, 1:10) to give 69 mg (90%) of 6:1 mixture of trans and cis enones 231a and 231b as a
light yellow oil: a IR (neat) 1688, 1427 cm−1; 1H NMR (CDCl3, 300 MHz) δ 1.07 (s, 9H, t-Bu), 1.19 (d,
J = 6.5 Hz, 3H, CH3), 1.46 (td, J = 12.6, 4.6 Hz, 1H, H3a), 1.83 (dt, J = 12.8, 3.1 Hz, 1H, H5b), 2.51
(dd, J = 16.2, 7.0 Hz, 1H, CH3CO), 2.60 (d, J = 12.9 Hz, 1H, H6a), 2.71-2.86 (AB quartet and
multiplet, 3H, NCH3Si and H3), 2.98-3.07 (m, 1H, CH3CO), 3.44 (d, J = 12.9 Hz, 1H, H6a), 3.69 (t, J
= 3.2 Hz, 1H, H5), 4.95 (q, J = 6.6 Hz, 1H, =CHCH2), 5.86 (s, 1H, CH=), 6.06 (s, 1H, CH=), 7.22-
7.46 (m, 10H, ArH), 7.63-7.73 (m, 5H, ArH); 13C NMR (CDCl3, 75.47 MHz) δ 12.3 (q), 16.2 (s), 27.7
(q), 33.6 (d), 35.3 (t), 41.3 (t), 42.9 (t), 52.9 (t), 56.8 (d), 116.2 (s), 116.3 (d), 124.2 (t), 127.7 (d),
128.1 (d), 128.17 (d), 128.24 (s), 129.33 (d), 129.37 (d), 134.2 (s), 135.1 (s), 135.7 (d), 135.8
(d), 136.9 (s), 149.4 (s), 200.1 (s), some overlap of signals occurred in the aromatic region. The
aforementioned NMR data are that of the major (trans) isomers; Signals for the minor isomer (cis)
were visible in the 1H NMR spectrum at δ 5.6, 6.1 (singlets, =CH2), 5.15 (q, CH3CH=), and in the
aliphatic region of the 13C NMR spectrum at δ 12.2, 13.6, 22.5, 26.7, 31.8, 35.7, 42.0, 50.0, 55.0;
exact mass calcd. for C35H40N2O5Si m/e 532.2910, found m/e 532.2913.
(±)-(1R*,4aS*,7R*,8aS*)-4-[(Z)-Ethylidene]decahydro-2-methyl-6-oxo-7-phenyl-1-isoquinolinecarbonitrile (232). To 100 mg (0.19 mmol) of enone 231 in 15 mL of acetonitrile at 55°C was added 36 mg (0.28 mmol) of silver fluoride. The mixture was heated to reflux in the dark for 20 h. The resulting black slurry was cooled to room temperature and filtered through a pipet of Celite. The filtrate was concentrated in vacuo and the residue was chromatographed over 8 g of silica gel (eluted with ethyl acetate-hexanes, 1:1, followed straight ethyl acetate) to give 12.0 mg (21%) amino ketone 232 as a yellow oil: IR (neat) 1716, 1456 cm⁻¹; 
¹H NMR (CD₃OD, 500 MHz) δ 1.36 (q, J = 6.6 Hz, 3H, =CHCH₃), 1.48-1.58 (m, 2H, H₁ and H₂), 1.86 (t, J = 12.9 Hz, 1H, H₁), 2.00 (q, J = 12.7 Hz, 1H, H₃), 2.00 (s, 3H, NCH₃), 2.16 (t, J = 10.1 Hz, 1H, H₄), 2.46 (dd, J = 13.1, 4.0 Hz, 1H, H₅), 2.50 (d, J = 13.0 Hz, 1H, H₆), 3.05 (dd, J = 13.0, 4.5 Hz, 1H, H₇), 3.12 (d, J = 2.8 Hz, 1H, H₈), 3.25 (d, J = 13.0 Hz, 1H, H₉), 4.76 (q, J = 6.6 Hz, 1H, CH₂CH=), 7.0-7.3 (m, 5H, ArH); ¹³C NMR (CD₃OD, 125.8 MHz) δ 12.5 (q), 37.0 (t), 41.1 (d), 42.2 (d), 43.0 (t), 43.3 (q), 50.1 (t), 55.8 (d), 59.7 (d), 113.9 (s), 116.1 (d), 127.0 (d), 128.3 (d), 129.0 (d), 135.0 (s), 138.1 (s), 204.9 (s); exact mass calcd. for C₁₉H₂₂N₄O m/e 294.1732, found m/e 294.1722. All the assignments were made based on data obtained from ¹H-¹³C correlation, COSY and nOe studies.

118
α,α-Dimethyl-3-pyridinemethanol (240). To 4.85 g (4.4 mL, 40.4 mmol) of 3-acetyl pyridine in 160 mL of dry THF under nitrogen at -78°C was added 40 mL of 1.4 M (56 mmol) methyllithium in diethyl ether dropwise via syringe over a period of 30 min. The resulting mixture was stirred at -78°C for 30 min, and 25 mL of brine was added over a period of 20 min. The resulting mixture was warmed to room temperature, and then partitioned between 100 mL of diethyl ether and 50 mL of water. The aqueous layer was separated and extracted with three 40-mL portions of dichloromethane. The organic layers were combined, washed with 40 mL of brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 120 g of silica gel (eluted with ethyl acetate-hexanes 1:1) to give 3.94 g (73%) of the desired alcohol 240 as a light yellow liquid: ¹H NMR (CDCl₃, 200 MHz) δ 1.48 (s, 6H, CH₃), 4.98 (br s, 1H, OH), 7.12 (dd, J = 7.9, 4.8 Hz, 1H, H₆), 7.75 (dm, J = 8.4 Hz, 1H, H₄ or H₅), 8.22 (dm, J = 4.7 Hz, 1H, H₄ or H₅), 8.54 (br s, 1H, H₇).

1-[[tert-Butyldiphenylsilyl)methyl]-3-(1-hydroxy-1-methylethyl)pyridinium trifluoromethanesulfonate (241). To 1.38 g (102.2 mmol) of 3-(1-hydroxy-1-methylethyl)pyridine in 40 mL of acetonitrile was added 4.13 g (102.7 mmol) of crystalline tert-
butyldiphenylsilylmethyl triflate 189 in one portion. The resulting solution was stirred at room temperature for 4 h and the mixture was concentrated in vacuo. The yellow residue was dissolved in 100 mL of dichloromethane and hexanes was added in small portions until cloudiness persisted (approximately 15 mL). The resulting crystals were collected to give a first crop of 4.84 g (88%) and a second crop of 195 mg (4%) as the desired pyridinium salt 241: mp 174-175°C; IR (KBr) 3564 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.16 (s, 6H, CH₃), 1.29 (s, 9H, t-Bu), 3.80 (broad s, 1H, OH), 4.94 (s, 2H, NCH₃Si), 7.33 (m, 11H, ArH and H₂), 8.04 (d, J = 8.8 Hz, 1H, H₆ or H₇), 8.10 (d, J = 6.1 Hz, 1H, H₆ or H₇), 8.41 (s, 1H, H₈); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.4 (s), 27.4 (q), 30.4 (q), 49.7 (t), 70.3 (s), 126.7 (d), 128.5 (d), 128.8 (s), 130.7 (d), 135.9 (d), 139.9 (d), 141.4 (d), 141.7 (d), 150.9 (s), the CF₃ signal was not observed; Anal. calcd. for C₂₉H₃₂F₃NO₅SSi: C, 57.87; H, 5.98; found C, 57.80; H, 6.00.

1-[(tert-Butyldiphenylsilyl)methyl]-1,2,3,6-tetrahydro-5-(1-hydroxy-1-methylethyl)-2-pyridinecarbonitrile (242). To a mixture of 1.86 g (37.9 mmol) sodium cyanide of in 20 mL of water, 20 mL of methanol and 40 mL of diethyl ether was added 144 mg (3.7 mmol) of sodium borohydride, followed immediately by addition of 1.98 g (3.9 mmol) of pyridinium salt 33 in one portion. The resulting yellow mixture was stirred at room temperature for 30 min. The organic layer was separated and washed with 10 mL of water. The aqueous layer was extracted with three 20-mL portions of dichloromethane. The organic layers were combined and washed with 20 mL of brine, dried (MgSO₄), and concentrated in vacuo. The residue was
chromatographed over 80 g of silica gel (eluted with ethyl acetate-hexanes, 1:3) to give 647 mg (42%) of the desired α-cyanoamine 242 as a yellow oil: IR (neat) 3453, 2224 (w) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.09 (s, 9H, t-Bu), 1.10 (s, 3H, CH₃), 1.13 (s, 3H, CH₃), 2.12 (dd, J = 17.4, 3.2 Hz, 1H, H₃α), 2.39 (dm, J = 17.6 Hz, 1H, H₉β), 2.74-2.85 (m, 3H, AB quartet of NCH₃Si and H₈β), 3.14 (d, J = 17.2, 1H, H₅β), 3.61 (d, J = 5.2 Hz, 1H, H₂), 5.59 (m, 1H, CH=), 7.3-7.5 (m, 6H, ArH), 7.65-7.75 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.2 (s), 27.7 (q), 28.6 (q), 29.1 (t), 42.9 (t), 51.7 (t), 52.7 (d), 71.6 (s), 112.8 (d), 116.5 (s), 127.7 (d), 129.41 (d), 129.44 (d), 133.9 (s), 134.6 (s), 135.7 (d), 135.8 (d), 143.3 (s), only six out of the seven doublets in the aromatic region were resolved, because overlapping of the signals occurred; exact mass calcd. for C₉₅H₆₇N₆O Si m/e 418.2440, found m/e 418.2446.

![244](image)

5-(1-Acetoxy-1-methylethyl)-1-[(tert-butyldiphenylsilyl)methyl]-1,2,3,6-tetrahydro-2-pyridinecarbonitrile (244). To a mixture of 390 mg (0.93 mmol) of alcohol 242 and 34 mg (0.23 mmol) of 4-pyrrolidinopyridine in 1.5 mL of dichloromethane was added 0.19 g (0.26 mL, 1.86 mmol) of triethylamine followed by addition of 133 mg (123 µL, 1.30 mmol) of acetic anhydride. The resulting mixture was stirred at room temperature for 28 h. The mixture was diluted with 40 mL of dichloromethane and washed with 10 mL of saturated aqueous sodium bicarbonate. The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:8) to give 189 mg (44%) of the desired acetate 244 as a yellow oil: IR (neat) 2218 (w), 1735, 1427 cm⁻¹; ¹H NMR
(CDCl₃, 300 MHz) δ 1.08 (s, 9H, t-Bu), 1.29 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.76 (s, 3H, COCH₃),
2.17 (d, J = 17.3 Hz, 1H, H₃), 2.52 (d, J = 17.2 Hz, 1H, H₃), 2.72 (d, J = 13.8 Hz, 1H, H₃), 2.76
(d, J = 14.5 Hz, 1H, NCH₂Si), 2.83 (d, J = 14.7 Hz, 1H, NCH₂Si), 3.07 (d, J = 16.1 Hz, 1H, H₃), 3.63 (d, J = 5.4 Hz, 1H, H₃), 5.50 (broad s, 1H, =CH), 7.3-7.4 (m, 6H, ArH), 7.6-7.7 (m, 4H, ArH);
¹³C NMR (CDCl₃, 75.47 MHz) δ 18.2 (s), 21.8 (q), 25.3 (q), 26.2 (q), 27.7 (q), 29.2 (l), 43.1 (l), 50.9
(l), 53.0 (d), 81.0 (s), 114.6 (d), 116.4 (s), 127.67 (d), 127.74 (d), 129.36 (d), 129.43 (d), 133.8 (s)
134.2 (s), 135.6 (d), 135.7 (d), 139.8 (s), 169.3 (s); exact mass calculated for C₉₈H₇₆N₄O₂Si m/e
460.2546 found m/e 460.2530.

TBDPS

NC

CH₃

268

[[tert-Butyldiphenylsilyl)methyl]amino]acetonitrile (268). To 2.3 g (8.55 mmol) of tert-butyldiphenylsilylmethylamine 189 in 6.5 mL of diethyl ether and 6.5 mL of water was added 1.8 g (17.3 mmol) of sodium bisulfite, and 1.4 mL (16.5 mmol) of 37% aqueous formaldehyde solution. The resulting mixture was stirred at room temperature for 3 h and then 1.76 g (27.0 mmol) of potassium cyanide was added. The resulting mixture was stirred at room temperature for another 20 h. The mixture was partitioned between 40 mL of diethyl ether and 10 mL of 5% aqueous sodium hydroxide. The aqueous layer was separated and extracted with three 15-mL portions of diethyl ether. The organic layers were combined, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 60 g of silica gel (eluted with ethyl acetate-hexanes, 1:10) to give 1.52 g (57%) of the desired amine 268 as a thick colorless oil which slowly turned into a solid. A small amount was recrystallized from dichloromethane and hexanes to obtain an analytically pure sample: mp 65-67°C; IR (neat) 3070 cm⁻¹; ¹H NMR (CDCl₃,
(Z)-2-Bromo-N-[(tert-butyldiphenylsilylmethyl)-2-butenylamine (267). To a mixture of 1.55 g (10.3 mmol) of (Z)-2-bromo-2-butenol and 1.26 g (1.73 mL, 12.4 mmol) of triethylamine in 20 mL of dichloromethane at -20°C was quickly added 1.30 g (0.88 mL) of methanesulfonyl chloride via syringe. The resulting mixture was warmed to 0°C and stirred at 0°C for 1 h. The resulting white slurry was partitioned in 80 mL of diethyl ether and 15 mL of 1 N aqueous HCl. The organic layer was separated and washed with three additional 15-mL portions of 1 N aqueous HCl. The aqueous layers were combined and extracted with three 25-mL portions of diethyl ether. The combined organic layers were washed in sequence with 15 mL of saturated aqueous sodium bicarbonate and 15 mL of brine, dried (MgSO₄) and concentrated in vacuo to give 2.28 g (97%) of the crude mesylate as a thick oil. To a solution of mesylate in 20 mL of dichloromethane was added a solution of 5.32 g (20 mmol) of t-butyldiphenylsilylmethylamine 257 in 50 mL of dichloromethane over a period of 20 min. The resulting mixture was stirred at room temperature for 60 h. The solution was concentrated in vacuo and the residue was chromatographed over 120 g of silica gel (eluted in sequence with ethyl acetate-hexanes, 1:20,
and 1:3) to give 2.2 g (55%) of amine 267 as a light yellow syrup and an inseparable mixture of starting amine 257 and an unidentified impurity. 267: IR (neat) 3331, 1659 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.13 (s, 9H, t-Bu), 1.34 (broad s, 1H, NH), 1.80 (d, J = 6.5 Hz, 3H, CH₂), 2.66 (s, 2H, CH₂), 3.53 (s, 2H, CH₂), 5.95 (q, J = 6.4 Hz, 1H, CH₃CH=), 7.4-7.5 (m, 6H, ArH), 7.7-7.8 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 16.5 (q), 18.1 (s), 27.9 (q), 31.9 (l), 61.5 (l), 125.7 (d), 127.3 (d), 127.7 (d), 128.0 (s), 128.9 (d), 129.2 (d), 133.6 (s), 135.6 (s), 135.9 (d), 136.2 (d), an extra quartet appeared in the upfield region probably due to impurities; exact mass calcd. for C₂₁H₂₆BrNSi (⁺⁺Br) m/e 403.1154 and 401.1174 (⁺⁺Br), found m/e 403.1144 and 401.1136.

![Structure of 252]

\[
\text{252}
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To 2.23 g (5.58 mmol) of amine 267 in 15 mL of acetonitrile was added 0.33 g (0.19 mL, 2.8 mmol) of bromoacetonitrile. The resulting mixture was heated to reflux for 15 h. The solution was then cooled to room temperature and concentrated in vacuo. The residue was chromatographed over 150 g of silica gel (eluted with ethyl acetate-hexanes, 1:20) to give 1.21 g (99%) amine 252 as a very thick oil, which solidified upon standing.

**Method B:** To a mixture of 205 mg (0.67 mmol) of amine 268 and 183 mg (1.33 mmol) of potassium carbonate in 4 mL of acetonitrile and 4 mL of dichloromethane was added 284 mg (1.34 mmol) of (Z)-1,2-dibromo-2-butene. The resulting white slurry was heated at 60°C for 3 days and then cooled to room temperature. The mixture was partitioned between 20 mL of diethyl ether
and 5 mL of water. The aqueous layer was separated and extracted with three 8-mL portions of diethyl ether. The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:50) to afford 188 mg (64%) of the desired amine 252 as a light yellow oil. An analytically pure sample was obtained by recrystallization from dichloromethane and hexanes: mp 77-78°C; IR (neat) 1658 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.09 (s, 9H, t-Bu), 1.75 (d, J = 6.5 Hz, 3H, CH₃), 2.82 (s, 2H, CH₂), 3.24 (s, 2H, CH₂), 3.35 (s, 2H, CH₂), 6.03 (q, J = 6.5 Hz, 1H, CH₂), 7.37-7.46 (m, 6H, ArH), 7.74-7.78 (m, 4H, ArH); ¹³C NMR δ 16.6 (q), 18.2 (s), 27.7 (q), 40.3 (t), 43.2 (t), 66.7 (t), 114.4 (s), 124.3 (s), 127.8 (d), 128.7 (d), 129.5 (d), 133.4 (s), 135.9 (d); exact mass calcd. for C₂₇H₅₉BrN₂Si m/e 440.1284 (⁷⁹Br) and 442.1263 (⁸¹Br), found m/e 440.1263 and 442.9492; Anal. calcd. for C₂₇H₅₉BrN₂Si: C, 62.57; H, 6.62; found C, 62.51; H, 6.61.

![TBDPS](tbddps.png)

**253**

**[(tert-Butyldiphenylsilyl)methyl][(Z)-2-iodo-2-butenyl]amino]acetonitrile (253).** To a mixture of 280 mg (0.91 mmol) of amine 268 and 264 mg (1.91 mmol) of potassium carbonate in 4 mL of acetonitrile was added 490 mg (1.88 mmol) of (Z)-1-bromo-2-iodo-2-butene. The resulting white slurry was heated to reflux for 26 h and then cooled to room temperature. The mixture was partitioned between 5 mL of water and 25 mL of dichloromethane. The aqueous layer was separated and extracted with two 10-mL portions of dichloromethane. The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with ethyl acetate-hexanes, 1:30), to give 325 mg (88%) of the desired amine.
253 as a yellow oil: IR (neat) 1643 (w), 1469 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.10 (s, 9H, f-Bu), 1.77 (d, \(J = 6.3\) Hz, 3H, CH\(_3\)), 2.84 (s, 2H, CH\(_2\)), 3.21 (s, 2H, CH\(_2\)), 3.36 (s, 2H, CH\(_2\)), 5.59 (q, \(J = 6.4\) Hz, 1H, =CHCH\(_3\)), 7.37-7.47 (m, 6H, ArH), 7.76-7.80 (m, 4H, ArH); \(^13\)C NMR (CDCl\(_3\), 75.47 MHz) \(\delta\) 18.2 (s), 21.7 (q), 27.7 (q), 40.3 (t), 42.9 (t), 69.7 (t), 105.6 (s), 114.25 (s), 127.8 (d), 129.5 (d), 133.3 (s), 135.1 (d), 136.0 (d); exact mass calcd. for C\(_{32}\)H\(_{50}\)N\(_2\)Si m/e 488.1146, found m/e 488.1160.

![Structure of 250](image)

\((E)-2-[[((Z)-2-Bromo-2-butenyl)[(tert-butylphenylsilyl)methyl]amino]-6-hydroxy-4-hexenenitrile (250).\) To 0.12 g (0.16 mL, 1.1 mmol) of diisopropylamine in 6 mL of THF under nitrogen at -78°C was added 0.4 mL of 2.5 M (1.0 mmol) n-BuLi in hexanes dropwise via syringe over a period of 5 min. The resulting solution was stirred at -78°C for 20 min. A solution of 400 mg (0.91 mmol) of amine 252 in 2 mL of THF was then added dropwise via syringe over a period of 2 min. The resulting dark red solution was stirred at -78°C for 1 h. To the mixture was added dropwise a solution of 0.287 g (1.1 mmol) of \(((E)-4-bromo-2-butenyl)oxy]-tert-butylidimethylsilane 254 in 2 mL of THF via syringe over a period of 5 min. The resulting mixture was stirred at -78°C for 1 h and 2 mL of brine was added. The resulting mixture reaction was warmed to room temperature. The aqueous layer was separated and extracted with three 5-mL portions of dichloromethane. The organic layer was dried (MgSO\(_4\)) and concentrated in vacuo. The residue was dissolved in 5 mL of methanol and 223 mg (1.17 mmol) of p-toluenesulfonic acid
monohydrate was added. The resulting mixture was stirred at room temperature for 4 h and concentrated in vacuo. The residue was diluted with 20 mL of diethyl ether and 4 mL of saturated aqueous sodium bicarbonate. The aqueous layer was separated and extracted with 10 mL of diethyl ether. The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:3) to give 102 mg (22%) of aminoalcohol 250 as a colorless oil: IR (neat) 3380, 1427 (w) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.09 (s, 9H, CH₃), 1.55 (broad s, 1H, OH), 1.76 (d, J = 6.5 Hz, 3H, CH₂), 2.33-2.37 (m, 2H, CH₂), 2.57 (d, J = 14.8 Hz, 1H, NCH₂Si), 3.02 (m, 2H, two overlapping doublets of NCH₂Si and NCH₂C), 3.45 (d, J = 14.3 Hz, 1H, NCH₂C=), 3.51 (t, J = 7.8 Hz, 1H, NCHCN), 3.98 (d, J = 5.4 Hz, 2H, CH₂OH), 5.36 (dt, J = 15.4, 6.9 Hz, 1H, HC=), 5.58 (dt, J = 15.4, 5.4 Hz, 1H, =CH), 5.98 (q, J = 6.5 Hz, 1H, MeCH=), 7.37-7.48 (m, 6H, ArH), 7.66-7.70 (m, 2H, ArH), 7.82-7.86 (m, 2H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 16.7 (q), 18.2 (s), 27.6 (q), 34.0 (t), 36.4 (t), 55.8 (d), 63.0 (t), 63.5 (t), 116.6 (s), 124.7 (s), 125.5 (d), 127.6 (d), 127.8 (d), 128.6 (d), 129.5 (d), 132.6 (s), 133.2 (d), 133.8 (s), 135.7 (d), 136.4 (d). Only seven doublets, instead of nine, were observed in the aromatic region, probably because of the magnetic equivalence; exact mass calc'd. for C₂₇H₅₁BrN₂O₂Si m/e 510.1702 (¹⁷Br), and 512.1682 (¹⁹Br) found m/e 509.9731 (¹⁷Br) and 511.9307 (¹⁹Br).
Method A: To 116 mg (0.15 mL, 1.14 mmol) of diisopropylamine in 6 mL of THF at -78°C under nitrogen was added dropwise 0.43 mL of 2.5 M n-BuLi (1.08 mmol) in hexanes over a period of 5 min via syringe. The resulting solution was stirred at -78°C for 30 min, and to the mixture was added 0.8 mL of dry HMPA via syringe. The resulting solution was stirred at -78°C for 5 min and then a solution of 569 mg (1.02 mmol) of amine 252 in 2 mL of THF was added quickly via syringe. The resulting red solution was stirred at -78°C for 1 h, and then a solution of 317 mg (1.20 mmol) of [(E)-4-bromo-2-butenyl]oxy]-tert-butyldimethylsilane (254) in 2 mL of THF was added dropwise over 5 min via syringe. The resulting mixture was stirred at -78°C for 30 min, warmed to room temperature, and stirred for 1 h. To the resulting mixture was added 1 mL of brine, 20 mL of diethyl ether and 5 mL of water. The aqueous layer was separated and extracted with three 15-mL portions of dichloromethane. The organic layers were combined, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with ethyl acetate-hexanes, 1:50), to give in sequence 0.27 g (85%) of the recovered allylic bromide (254), 41 mg (7%) of recovered amine 252, and 272 mg (80%) of amine 269 as a yellow oil.

Method B: To 0.87 g (0.12 mL, 0.95 mmol) of diisopropylamine in 4 mL of THF at -78°C was added dropwise 0.3 mL of 2.5 M n-BuLi (0.75 mmol) in hexanes over a period of 5 min via syringe. The resulting mixture was stirred at -78°C for 20 min and to the mixture was added quickly a solution of 335 mg (0.69 mmol) of amine 253 in 1.5 mL of THF via syringe. The resulting red solution was stirred at -78°C for 1 h, and then a solution of 215 mg (0.81 mmol) of [(E)-4-bromo-2-butenyl]oxy]-tert-butyldimethylsilane (254) in 1 mL of THF was added dropwise over a period of 5 min via syringe. The resulting mixture was stirred at -78°C for 2 h and then warmed to room temperature. To the resulting mixture was added 1 mL of brine, 20 mL of diethyl ether, and 5 mL of water. The aqueous layer was separated and extracted with two 10-mL portions of dichloromethane. The organic layers were combined, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with ethyl acetate-hexanes,
1:40) to give in sequence 206 mg (95%) of recovered [(E)-4-bromo-2-butenyl]oxy]-tert-
butyldimethylsilane (254) as a clear liquid. 61 mg (18%) of the recovered amine 253 as a
colorless oil, and 132 mg (53%) of amine 259 as a yellow oil: IR (neat) 1962 (w) cm⁻¹; ¹H NMR
(CDC₃, 300 MHz) δ 1.11 (s, 9H, t-Bu), 1.83 (t, J = 2.3 Hz, 3H, CH₃), 2.84 (s, 2H, CH₂), 3.22 (q, J =
2.3 Hz, 2H, CH₂), 3.41 (s, 2H, CH₂), 7.37-7.45 (m, 6H, ArH), 7.70-7.75 (m, 4H, ArH); ¹³C NMR δ 3.4
(q), 18.3 (s), 27.7 (q), 39.9 (t), 44.6 (t), 47.3 (t), 73.5 (s), 81.8 (s), 115.1 (s), 127.8 (d), 129.5 (d),
133.6 (s), 135.8 (d); exact mass calcd. for C₃₂H₃₆N₂Si m/e 360.2022, found m/e 360.2008.

[270]

[Benzyl[(tert-butyldiphenylsilyl)methyl]amino]acetonitrile (270). To 422 mg
(1.4 mmol) of amine 268 in 4 mL of acetonitrile was added 378 mg (2.7 mmol) of potassium
carbonate, followed by 467 mg (325 μL, 2.73 mmol) of benzyl bromide. The resulting mixture was
heated to reflux at 90°C (oil bath temperature) for 3 h, and cooled to room temperature. The
mixture was then partitioned between 20 mL of diethyl ether and 5 mL of water. The aqueous
layer was separated and extracted with two 10-mL portions of diethyl ether. The organic layers
were combined, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed
over 15 g of silica gel (eluted with ethyl acetate-hexanes, 1:20) to give 515 mg (94%) of amine
270 as white crystals: mp 92-93°C; ¹H NMR (CDCl₃, 300 MHz) δ 1.11 (s, 9H, CH₃), 2.93 (s, 2H,
CH₂), 3.19 (s, 2H, CH₂), 3.61 (s, 2H, CH₂), 7.16-7.21 (m, 2H, ArH), 7.26-7.30 (m, 3H, ArH), 7.40-
7.47 (m, 6H, ArH), 7.76-7.80 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.2 (s), 27.7 (q), 40.7
(t), 44.2 (t), 62.0 (l), 114.6 (s), 127.6 (d), 127.8 (d), 128.4 (d), 129.1 (d), 129.5 (d), 133.5 (s),

129
135.9 (d), 137.2 (s); exact mass calcd. for C_{20}H_{30}N_{2}Si m/e 398.2178, found m/e 341.1453 (M-\text{-C}_2\text{H}_5).

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\text{\textbf{(E)-2-[Benzyl[(\text{tert-butyldiphenylsilyl)methyl]amino}-6-(\text{tert-butyldimethylsiloxy)-4-hexenenitrile (271):}}
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To 72 mg (93 \(\mu\)L, 0.71 mmol) of \(i\)-Pr\(_2\)NH in 2.5 mL of THF under nitrogen at -78°C was added 0.24 mL of 2.5 M \(n\)-BuLi (0.60 mmol) in hexanes. The resulting mixture was stirred at -78°C for 30 min, and 200 mg (0.50 mmol) of amine 270 in 1 mL of THF was then added dropwise via syringe over a period of 5 min. The resulting mixture was stirred at -78°C for 1 h. To the reaction mixture was added 174 mg (0.66 mmol) of allylic bromide 254 dropwise via syringe over 2 min. The resulting mixture was stirred at -78°C for 30 min and then warmed to room temperature. To the resulting mixture was added 5 mL of water cautiously. The mixture was diluted with 20 mL of diethyl ether. The aqueous layer was separated and extracted with three 10-mL portions of diethyl ether. The organic layers were combined, dried (MgSO\(_4\)), concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with ethyl acetate-hexanes, 1:50) to give 162 mg (57%) of amine 271 as a light yellow oil: \(\text{'H NMR (CDCl}_3, 300 MHz) \delta 0.00 (s, 3H, CH}_3), 0.01 (s, 3H, CH}_3), 0.94 (s, 9H, CH}_3), 1.00 (s, 9H, CH}_3), 2.2-2.5 (m, 2H, CH}_2), 2.64 (d, J = 14.7 Hz, 1H, CH}_2N), 2.94 (d, J = 14.7 Hz, 1H, CH}_2N), 3.14 (d, J = 13.1 Hz, 1H, CH}_2N), 3.43 (dd, J = 7.6, 8.2 Hz, 1H, NCH-CN), 3.81 (d, J = 13.1 Hz, 1H, CH}_2N), 4.06 (dd, J = 4.8, 1.1 Hz, 2H, CH}_3OTBS), 5.31 (dt, J = 15.2, 6.9 Hz, 1H, =CH), 5.54 (dt, J = 15.3, 4.9
Hz, 1H, =CH), 6.9-7.0 (m, 2H, ArH), 7.2-7.2 (m, 3H, ArH), 7.4-7.5 (m, 6H, ArH), 7.7-7.8 (m, 4H, ArH): exact mass calcd. for C_{36}H_{50}N_{2}O_{3}Si m/e 582.3461, found m/e 582.3481.

![Structure of 261](image)

(Z)-2-Bromo-2-buten-1-ol (261). To 15 g (100 mmol) of methyl crotonate in 50 mL of dichloromethane in an ice-bath was added a solution of 62 g (20 mL, 390 mmol) of bromine in 75 mL dichloromethane over a period of 45 min. The resulting red solution was warmed to room temperature and stirred for 1 h. The mixture was concentrated in vacuo and the residue was dissolved in 500 mL pentane and cooled with an ice-bath. To the resulting mixture was added 80 g (100 mL, 789 mmol) of triethylamine dropwise over a period of 45 min. The resulting white slurry was warmed to reflux overnight (oil bath temperature 56-60°C). The mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was diluted with hexanes to 200 mL and washed with three 40-mL portions of 1N aqueous HCl. The aqueous layers were combined and extracted with three 50-mL portions of pentane. The organic layers were combined, washed with 50 mL of brine, dried (MgSO₄), and concentrated in vacuo. The resulting 24.9 g of red residue was dissolved in 750 mL of dichloromethane. To the resulting solution at -78°C, was added 300 mL of 1.0 M (300 mmol) diisobutylaluminum hydride in hexanes dropwise under argon over a period of 1 h. The solution was stirred for an additional hour at -78°C. To the resulting mixture was slowly added 250 mL saturated aqueous potassium tartrate. The white slurry was warmed to room temperature and stirred overnight. The mixture was filtered through a pad of Celite. The filtrate was transferred to a
separatory funnel. The aqueous layer was separated and extracted with three 100-mL portions of dichloromethane. The organic layers were combined, washed with 50 mL brine, dried (MgSO₄) and concentrated. The residue was chromatographed over 400 g of silica gel (eluted with diethyl ether-hexanes, 1:4) to give 13.8 g (92%) of the desired alcohol 261 as a light brown liquid (the mixture Z:E ratio was better than 25:1 according to the ¹H NMR spectrum): ¹H NMR (CDCl₃, 300 MHz) δ 1.74 (dt, J = 6.5, 1.1 Hz, 3H, CH₃), 2.87 (broad s, 1H, OH), 4.25 (s, 2H, CH₂OH), 6.06 (qd, J = 6.5, 1.2 Hz, 1H, CH₃CH=). The NMR data reported above are for the major isomer (Z). The minor isomer (E) was sometimes also visible in ¹H NMR: δ 1.71 (d, J = 6.6 Hz, 3H, CH₃), 4.32 (s, 2H, CH₂OH).

(CH₂)₂C=Br

(Z)-1,2-Dibromo-2-butene (255). To 2.5 g (16.6 mmol) of (Z)-2-bromo-2-buten-1-ol and 2.5 g (3.5 mL, 25.1 mmol) of triethylamine in 30 mL of dichloromethane at -20°C was added quickly 2.4 g (1.6 mL, 20.7 mmol) of methanesulfonyl chloride. The resulting white slurry was stirred at -20°C for 1.5 h. The mixture was partitioned between 30 mL of diethyl ether and 10 mL of 1N aqueous HCl. The organic layer was separated and washed with three 10-mL portions of 1N aqueous HCl. The aqueous layers were combined and extracted with three 25-mL portions of diethyl ether. The organic layers were combined, dried (MgSO₄), and concentrated in vacuo. The residue was dissolved in 15 mL of THF. To the resulting mixture was added 4.4 g (51.2 mmol) of lithium bromide. The resulting slurry was stirred at room temperature for 3 h. The mixture was partitioned between 20 mL of water and 20 mL of diethyl ether. The aqueous layer was separated and extracted with three 20-mL portions of diethyl ether. The organic layers were combined,
dried (MgSO₄), and concentrated in vacuo to give 2.65 g (75%) of dibromide 255 as a yellow liquid: ¹H NMR (CDCl₃, 300 MHz) δ 1.78 (d, J = 6.5 Hz, 3H, CH₃), 4.28 (s, 2H, CH₂Br), 6.18 (q, J = 6.5 Hz, 1H, CH₃CH=).

(Z)-2-iodo-2-buten-1-ol (264).³ To a mixture of 2.25 g (2.4 mL, 32.1 mmol) of 2-butyn-1-ol and 3.14 g (2.9 mL, 10.8 mmol) of tributyltin hydride, was added 54 mg (0.22 mmol) of 1,1'-azobis(cyclohexane-carbonitrile). The mixture was heated at 85°C for 3 h. The resulting mixture was then distilled at reduced pressure to give 1.32 g (59%) of recovered 2-butyn-1-ol as a clear liquid (bp 32°C/0.8-0.9 torr) and 1.65 g (42%) of (Z)-2-tri-n-butylstannyl-2-buten-1-ol as a clear liquid (bp 137-139°C/0.8-0.9 torr). To 1.62 g (4.49 mmol) of (Z)-2-tri-n-butylstannyl-2-buten-1-ol in 25 mL of carbon tetrachloride at 5°C was added 1.14 g (4.50 mmol) of iodine crystals. The resulting mixture was stirred at 5°C for 25 min and was then washed with two 6-mL portions of 10% aqueous sodium bisulfite. The aqueous layer was extracted with two 15-mL portions of diethyl ether. The organic layers were combined, washed with 10 mL of brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 70 g of silica gel (eluted with ethyl acetate-hexanes, 1:8) to give 0.71 g (80%) of an 11:1 mixture (by ¹H NMR) of the desired Z alcohol and its E isomer as a colorless liquid. The major (Z) isomer 264: ¹H NMR (CDCl₃, 200 MHz) δ 1.76 (s, 1H, OH), 1.82 (d, J = 6.5 Hz, 3H, CH₃), 4.25 (s, 2H, CH₃OH), 5.95 (q, J = 6.5 Hz, 1H, CH₃CH=). Signals belong to the minor (E) isomer could be seen at δ 2.21 (d, J = 7.3 Hz, 3H, CH₃), 6.35 (q, J = 7.3 Hz, 1H, CH₃CH=).
To a mixture of 471 mg (2.37 mmol) of 2-iodo-2-buten-1-ol 264 and 0.51 g (0.70 mL, 5.02 mmol) of triethylamine in 5 mL of dichloromethane at 0°C was added 0.44 g (0.30 mL, 3.84 mmol) of methanesulfonyl chloride. The resulting slurry was stirred at 0-10°C for 1 h. The mixture was diluted with 40 mL of diethyl ether and washed with four 5-mL portions of 1 N aqueous of HCl. The aqueous layers were combined and extracted with three 15-mL portions of diethyl ether. The organic layers were combined, washed with 10 mL of brine, dried (MgSO₄) and concentrated in vacuo to give 656 mg of a colorless oil as the crude mesylate. The residue was dissolved in 2.5 mL of THF and 634 mg (7.37 mmol) of lithium bromide was added to the resulting mixture. The mixture was stirred at room temperature for 30 min. The resulting white slurry was partitioned between 30 mL of diethyl ether and 6 mL of water. The aqueous layer was separated and extracted with three 10-mL portions of diethyl ether. The organic layers were combined, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with hexanes) to give 499 mg (81%) of the desired bromide 256 as a colorless liquid: ¹H NMR (CDCl₃, 200 MHz) δ 1.80 (d, J = 6.5 Hz, 3H, CH₃), 4.35 (d, J = 0.95 Hz, 2H, CH₂), 6.05 (q, J = 6.5 Hz, 1H, CH₃CH=). The aforementioned NMR data are for the major (Z) isomer. Diagnostic signals for the minor (E) isomer were also visible in the ¹H NMR spectrum at δ 1.72 (d, J = 7.3 Hz, 3H, CH₃), 4.28 (s, 2H, CH₂), 6.38 (q, J = 7.3 Hz).
To 5.63 g (31.4 mmol) of methyl 4-bromocrotonate in 95 mL of dry dichloromethane at -78°C under argon was added dropwise 95 mL of 1.0 M diisobutylaluminium hydride in hexanes over a period of 30 min. The resulting light yellow solution was stirred at -78°C for 1 h and a mixture of 5 mL of glacial acetic acid and 5 mL of water was added very slowly. The resulting white slurry was warmed to room temperature and stirred for 1 h. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was chromatographed over 60 g of silica gel (eluted with ethyl acetate-hexanes, 1:5) to give 3.63 g (77%) of the desired \((E)\)-4-bromo-2-buten-1-ol as a colorless liquid. To a mixture of 3.63 g (24.2 mmol) of \((E)\)-4-bromo-2-buten-1-ol, 3.11 g (4.2 mL, 24.1 mmol) of \(N,N\)-diisopropylethylamine and 0.32 g (2.6 mmol) of 4-dimethylaminopyridine in 45 mL of dichloromethane was added 7.34 g (48.9 mmol) of tert-butyldimethylsilyl chloride in one portion. The resulting mixture was stirred at room temperature for 45 h. The resulting mixture was diluted with 150 mL of diethyl ether and washed with four 20-mL portions of 1N aqueous HCl. The aqueous layers were combined and extracted with three 75-mL portions of diethyl ether. The organic layers were combined, washed with 30 mL of brine, dried (\(\text{MgSO}_4\)) and concentrated in vacuo. The residue was chromatographed over 150 g of silica gel (eluted with ethyl acetate-hexanes, 1:20) to afford 3.62 g (57%) of the desired bromide \(254\) as a light yellow liquid: \(^1\text{H NMR} \delta 0.41 (s, 6\text{H}, \text{CH}_3), 0.93 (s, 9\text{H}, \text{CH}_3), 4.06 (m, 2\text{H}, \text{CH}_2), 4.21 (m, 2\text{H}, \text{CH}_2), 5.86 (m, 2\text{H}, \text{CH=CH}).\)
5,6-Dihydro-2H-pyran-2-one (272). To 25 g (290 mmol) of vinylacetic acid and 9.9 g (330 mmol) of paraformaldehyde in 80 mL of glacial acetic acid was added 0.6 mL of concentrated sulfuric acid. The mixture was heated to 120-125°C (oil bath temperature) for 15 h. The majority of the acetic acid was removed by distillation at reduced pressure (approximately 50 torr). The resulting brown residue was dissolved in 150 mL of diethyl ether, and to the resulting mixture was added 15 g of potassium carbonate. The resulting slurry was stirred overnight and then filtered through Celite. The filtrate was concentrated and the residue was chromatographed over 120 g of silica gel (eluted with diethyl ether-hexanes, 3:2) to afford 10.9 g (38%) of the desired lactone 272 as a light yellow liquid: 'H NMR (CDCl₃, 200 MHz) δ 2.43 (m, 2H, CH₂), 4.39 (t, J = 6.4 Hz, 2H, CH₂), 5.99 (dt, J = 9.8, 1.8 Hz, 1H, CH=), 6.92 (dt, J = 9.8, 4.2 Hz, 1H, CH=).

To 2.21 g (14.7 mmol) of vinyl bromide 261 in 45 mL of dry diethyl ether under argon at -78°C was added dropwise 26 mL of 1.7 M t-BuLi (44.2 mmol) in pentane over a period of 30 min. The internal temperature was maintained below -65°C during the addition. The resulting bright yellow solution was stirred at -78°C for 20 min, then warmed to 0°C and stirred for 2 h.

In a separate flask, to 1.32 g (1.26 mL, 15.8 mmol) of thiophene in 12 mL THF at 0°C under argon was added dropwise 6 mL of 2.5 M n-BuLi (15.0 mmol) in hexanes over a period of 5 min. The resulting light brown solution was stirred at 0°C for 30 min and was then transferred via cannula to a slurry of 1.41 g (15.6 mmol) of copper cyanide in 30 mL of THF at -78°C over a period of 10 min (the CuCN was azetropically dried with toluene). The resulting light yellow solution was stirred at -78°C for 50 min. To the resulting mixture at -78°C, was added the dianion solution dropwise via cannula over 20 min. The resulting dark green slurry was stirred at -78°C for 30 min, and then 3.33 g (3.90 mL, 30.7 mmol) of trimethylchlorosilane was added in one portion. The solution was stirred for 2 min and 1.42 g (1.25 mL, 14.5 mmol) of 5,6-dihydro-2H-pyran-2-one was added dropwise over a period of 2 min. The color of the mixture lightened almost immediately. The resulting yellow mixture was stirred at -78°C for 2 h and then at -50°C for another 2 h. To the resulting mixture was added 8 mL of a 1:1 (v/v) mixture of 3% aqueous ammonium hydroxide and saturated aqueous ammonium chloride, followed by 10 mL of water. The resulting mixture was warmed to room temperature and stirred for overnight. The aqueous layer was separated and extracted with three 40-mL portions of diethyl ether. The organic layers were combined and washed with 40 mL of brine, dried (MgSO₄), and concentrated in vacuo. The residue was dissolved in 25 mL of methanol and 0.45 g of Dowex-50 was added. The resulting mixture was stirred at room temperature for 4 h. The mixture was filtered and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with ethyl acetate-hexanes, 1:1) to give 765 mg (31%) of a 1:8 mixture of alcohols 274 and 275 as a brown oil: IR 3405, 1731 cm⁻¹; ¹H NMR δ 1.54-1.76 (m, 2H, CH₂CH₂OH), 1.67 (d, J = 6.9 Hz, 3H, CH₃), 2.28 (s, 1H, OH), 2.54 (dd, J = 15.8, 6.0 Hz, 1H, CH₂COO), 2.69 (dd, J = 15.8, 6.5 Hz, 1H, CH₂COO), 3.10 (m, 1H, CH), 3.67
(dd, J = 7.6, 5.8 Hz, 2H, CH$_2$OH), 4.54 (d, J = 12.8 Hz, 1H, COOCH$_3$), 4.74 (d, J = 12.0 Hz, 1H, COOCH$_3$), 5.59 (q, J = 7.0 Hz, 1H, CH$_2$CH=); $^{13}$C NMR 13.3 (q), 29.2 (d), 35.1 (t), 36.8 (t), 59.5 (t), 72.0 (t), 123.9 (d), 133.2 (s), 172.9 (s); The aforementioned NMR data are those of the major isomer 274. The minor isomer 275 was observed in both the $^1$H NMR and $^{13}$C NMR spectra. Some signals in the $^1$H NMR appeared at: δ 2.0 (td, J = 6.9 Hz, 3H, CH$_3$), 4.08 (s, CH$_2$OH), 4.27 (td, J = 10.8, 3.9 Hz, 1H, CH$_2$OH), 4.50 (m, 1H, CH$_2$OCO); some signals appeared in the $^{13}$C NMR spectrum at: δ 12.8 (q), 27.3 (t), 31.3 (d), 34.8 (t), 65.3 (t), 68.9 (t), 125.0 (d), 139.0 (s), 171.8 (s); exact mass calcd. for C$_9$H$_{14}$O, m/e 170.0943, found m/e 170.0946.

![Chemical Structures](image)

(±)-4-[2-(tert-Butyldiphenylsiloxy)ethyl]-5-[(E)-ethylidene]tetrahydro-2H-pyran-2-one (278) and (±)-4-[(E)-1-[(tert-Butyldiphenylsiloxy)methyl]-1-propenyl]tetrahydro-2H-pyran-2-one (279) To a mixture of 1.57 g (9.2 mmol) of alcohol 274 and 275 (8:1, respectively) and 2.77 g (2.62 mL, 10.1 mmol) of t-butyldiphenylchlorosilane in 10 mL of DMF was added 763 mg (11.2 mmol) of imidazole. The resulting mixture was stirred at room temperature for 28 h and was partitioned between 100 mL of diethyl ether and 25 mL of water. The aqueous layer was separated and extracted with three 25-mL portions of diethyl ether. The organic layers were combined, washed with 20 mL of brine, dried (MgSO$_4$) and concentrated.
in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate-
hexanes, 1:10) to give, in sequence, 2.45 g (59%) of lactone 278 as a colorless oil which
solidified upon standing, 0.10 g (2%) of a 1:2.1 mixture of lactones 278 and 279, and 73 mg
(1%) of lactone 279 as a colorless oil. A small amount of lactone 278 was recrystallized from
diethyl ether and hexanes to give an analytically pure sample. Lactone 278: mp 84-85°C; IR
(neat) 1749 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.15 (s, 9H, t-Bu), 1.56 (tt, J = 9.5, 4.8 Hz, 1H,
CH₂CH₂OR), 1.68 (d, J = 6.8 Hz, 3H), 1.88 (m, 1H, CH₂CH₂OR), 2.47 (dd, J = 15.7, 6.1 Hz, 1H,
CH₃COO), 2.66 (dd, J = 15.7, 6.5 Hz, 1H, CH₃COO), 3.20 (m, 1H, CH₂), 3.72 (m, 2H, CH₂OR), 4.53
(d, J = 12.8 Hz, 1H, COOCH₃), 4.71 (d, J = 12.8 Hz, 1H, COOC₂H₅), 5.59 (q, J = 6.9, 1.1 Hz, 1H,
CH₃CH=), 7.3-7.5 (m, 6H, ArH), 7.6-7.7 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 13.3 (q), 19.1
(s), 26.8 (q), 29.0 (d), 34.8 (t), 37.1 (t), 60.7 (t), 71.9 (t), 123.6 (d), 127.67 (d), 127.70 (d), 129.70
(d), 129.75 (d), 133.4 (s), 133.6 (s), 135.4 (d), 172.4 (s), not all the peaks in the aromatic region
were resolved, one singlet and one doublet were not observed; exact mass calcd. for C₃₅H₄ₐO₃Si
m/e 408.2120, found m/e 407.4324 (M+-1); Anal. calcd. for C₃₅H₄ₐO₃Si C, 73.49; H, 7.90; found
C, 73.35; H, 7.90. Lactone 279: 1739 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.05 (s, 9H, t-Bu), 1.85
(d, J = 6.9 Hz, 3H, CH₃), 1.86 (m, 1H, CH₂CH₂O), 2.05 (m, 1H, CH₂CH₂O), 2.60 (ddd, J = 17.4, 6.1,
1.5 Hz, 1H, CH₂COO), 2.72 (dd, J = 17.4, 11.8 Hz, 1H, CH₂COO), 3.09 (m, 1H, CH₂), 4.11 (s, 2H,
CH₂OR), 4.29 (td, J = 11.0, 3.8 Hz, 1H, COOCH₃), 4.45 (ddd, J = 11.0, 5.0, 3.8 Hz, 1H, COOCH₃),
5.52 (q, J = 6.9 Hz, 1H, CH₂CH=), 7.3-7.5 (m, 6H, ArH), 7.6-7.7 (m, 4H, ArH); ¹³C NMR (CDCl₃,
75.47 MHz) δ 12.8 (q), 19.0 (s), 26.7 (q), 27.2 (t), 31.6 (d), 34.8 (t), 66.3 (t), 68.9 (t), 123.8 (d),
127.6 (d), 129.7 (d), 133.1 (s), 133.1 (s), 135.5 (d), 137.9 (s), 171.2 (s), three doublets were not
observed in the aromatic region due to overlapping of signals; exact mass calcd. for C₃₅H₄ₐO₃Si
m/e 408.2120, found m/e 351.1424 (M+-C₄H₈).
(±)-4-[(2-tert-Butyldimethylsiloxy)ethyl]-5-[(E)-ethylidene]tetrahydro-2H-pyran-2-one (276) and (±)-4-[(E)-1-(tert-Butyldimethylsiloxy)methyl]-1-propenyl)tetrahydro-2H-pyran-2-one (277). To a mixture of 112 mg of alcohol 274 and 275 (6:1, respectively) 192 mg (265 μL, 1.90 mmol) of triethylamine and 11 mg (0.09 mmol) of 4-dimethylaminopyridine in 1.5 mL of dichloromethane was added 146 mg (0.97 mmol) of tert-butyldimethylsilyl chloride in one portion. The resulting mixture was stirred at room temperature for 28 h. The resulting mixture was partitioned between 20 mL of diethyl ether and 3 mL of 1 N aqueous HCl. The aqueous layer was separated and extracted with three 10-mL portions of diethyl ether. The organic layers were combined and washed with two 5-mL portions of brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with ethyl acetate-hexanes, 1:10) to give in sequence 111 mg (59%) of lactone 276 as a colorless oil and 24 mg (13%) of a 1:3 mixture (by ¹H NMR) of lactones 276 and 277.

Lactone 276: IR (neat) 1751 cm⁻¹, ¹H NMR (CDCl₃, 300 MHz) δ 0.04 (s, 6H, CH₃), 0.93 (s, 9H, tert-Bu), 1.50-1.58 (m, 1H, CH₂CH₂OR), 1.68 (d, J = 7.0 Hz, 3H, =CHCH₃), 1.76-1.83 (m, 1H, CH₂CH₂OR), 2.53 (ddd, J = 16.7, 6.1, 1.0 Hz, 1H, CH₂COO), 2.69 (ddd, J = 15.8, 6.5, 1.1 Hz, 1H, CH₂COO), 3.12 (m, 1H, CH), 3.64 (dd, J = 5.8, 3.6 Hz, 2H, CH₂OR), 4.54 (d, J = 12.8 Hz, 1H, COOCH₂), 4.74 (d, J = 12.0 Hz, 1H, COOCH₂), 5.58 (q, J = 7.0 Hz, 1H, CH₂=); ¹³C NMR (CDCl₃, 75.47 MHz) δ -5.59 (q), -5.54 (q), 13.3 (q), 18.1 (s), 25.7 (q), 29.0 (d), 35.0 (t), 37.1 (t), 59.7 (t), 72.0 (t), 123.5 (d), 133.6 (s), 172.6 (s); exact mass calcd. For C₂₀H₃₆O₄Si m/z 284.1808, found
m/e 285.1845 (M*+1). Lactone 277: IR 1738 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.05 (s, 6H, CH₃), 0.93 (s, 9H, t-Bu), 1.68 (d, J = 6.8 Hz, 3H, =CHCH₃), 1.87 (dq, J = 15.2, 3.4 Hz, 1H, CH₂CH₂), 2.05 (m, 1H, CH₂CH₂), 2.58 (ddd, J = 17.1, 8.6, 0.9 Hz, 1H, CH₃COO), 2.73 (dd, J = 17.1, 10.3 Hz, 1H, CH₃COO), 3.12 (m, 1H, CH), 4.12 (AB quartet, 2H, CH₂OTBS), 4.31 (td, J = 12.0, 4.3 Hz, 1H, COOCH₃), 4.52 (dt, J = 12.0, 6.8 Hz, 1H, COOCH₂), 5.58 (q, J = 6.8 Hz, 1H, CH₂CH=). The NMR data for lactone 277 were obtained from the 1:3 mixture of 276 and 277. Contamination signals from lactone 276 were visible; exact mass calcd. for C₁₅H₂₉O₃Si m/e 284.1808, found m/e 284.1838.

![Diagram](281a)

(±)-(E)-3-[2-(tert-Butyldimethylsiloxy)ethyl]-N-[(tert-butylidiphenylsilyl)methyl]-4-(hydroxymethyl)-4-hexenamide (281). A mixture of 43 mg (0.15 mmol) of lactone 276, 0.22 g (0.3 mL, 1.72 mmol) of diisopropylethylamine, and 101.8 mg (0.38 mmol) of 1-tert-(butyldiphenylsilyl)methylamine 257 in 1.8 mL of THF was heat to reflux for 24 h. The resulting mixture was cooled to room temperature and partitioned between 20 mL of diethyl ether and 2 mL of 1N aqueous HCl. The organic layer was separated and washed with two 2-mL portions of 1N aqueous HCl. The aqueous layers were combined and extracted with three 10-mL portions of diethyl ether. The organic layers were combined, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (eluted with ethyl acetate-
hexanes, 1:8) to give 77.4 mg (93%) of the desired amide 281a as a colorless oil: IR 3314, 1644 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ -0.01 (s, 6H, CH₃), 0.85 (s, 9H, t-Bu), 1.03 (s, 9H, t-Bu), 1.49 (d, J = 6.9 Hz, 3H, CH₃CH=), 1.57 (t, J = 6.4 Hz, 2H, CH₂CH₂OR), 2.15 (dd, J = 13.5, 5.1 Hz, 1H, CH₂CONH), 2.31 (dd, J = 13.5, 10.8 Hz, 1H, CH₂CONH), 2.6 (br s, 1H, OH), 3.07 (m, 1H, CH), 3.37 (t, J = 6.4 Hz, 2H, CH₂OR), 3.44 (d, J = 8.2 Hz, 1H, SiCH₃NH), 3.45 (d, J = 9.2 Hz, 1H, SiCH₃NH), 3.74 (d, J = 11.7 Hz, 1H, CH₃), 3.91 (d, J = 11.7 Hz, 1H, CH₂), 5.43 (broad s, 1H, NH), 5.46 (q, J = 6.9 Hz, 1H, CH₃CH=), 7.3-7.5 (m, 6H, ArH), 7.6-7.7 (m, 4H, ArH); ¹³C NMR (CDCl₃, 300 MHz) δ -5.5 (q), 13.1 (q), 17.9 (s), 18.1 (s), 23.4 (t), 25.8 (q), 27.4 (q), 33.0 (d), 36.5 (t), 41.4 (t), 61.1 (t), 65.5 (t), 126.8 (d), 128.0 (d), 129.7 (d), 132.1 (s), 135.7 (d), 139.3 (s), 173.2 (s); exact mass cacld. for C₃₂H₅ₙO₇NSi₂ m/e 553.3407, found m/e 553.3447.

(±)-(E)-3-[2-(tert-Butyldimethylsiloxy)ethyl]-4-(hydroxymethyl)-N,N-dimethyl-4-hexenamide (282a). To 414 mg (1.46 mmol) of lactone 276 was added 25 mL of 2M dimethylamine in methanol. The resulting mixture was heated to 75-80°C for 48 h, was concentrated in vacuo, and the residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:1) to give 363 mg (75%) of the desired amide 282a as a colorless oil: IR 3399, 1632 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.00 (s, 6H, CH₃), 0.85 (s, 9H, CH₃), 1.71 (d, J = 6.6 Hz, 3H, CH₃CH=), 1.58 (m, 2H, CH₂CHOR), 2.55 (dd, J = 13.8, 10.9 Hz, 1H, CH₂CONMe₂), 2.66 (dd, J = 13.8, 5.5 Hz, 1H, CH₂CONMe₂), 2.86 (s, 3H, CH₂CONMe₂), 3.01 (s, 3H, CH₂CONMe₂), 142
3.21 (m, 1H, CH), 3.55 (m, 2H, CH₂OR), 3.94 (d, J = 11.7 Hz, 1H, CH₂OH), 4.10 (d, J = 11.7 Hz, 1H, CH₂OH), 5.63 (d, J = 6.9 Hz, 1H, CH₂CH₂), the OH proton was not observed probably due to severe broadening; ¹³C NMR (CDCl₃, 75.47 MHz), δ -5.5 (q), 13.0 (q), 18.1 (s), 25.7 (q), 32.0 (d), 35.2 (q), 36.2 (t), 37.5 (q), 38.0 (t), 60.9 (t), 65.9 (t), 126.0 (d), 140.0 (s), 172.9 (s); exact mass calcd. for C₁₄H₂₉NO₅Si m/e 329.2386, found m/e 329.2400.

The OH proton was not observed probably due to severe broadening. The compound was characterized by ¹³C NMR (CDCl₃, 75.47 MHz), δ -5.5 (q), 13.0 (q), 18.1 (s), 25.7 (q), 32.0 (d), 35.2 (q), 36.2 (t), 37.5 (q), 38.0 (t), 60.9 (t), 65.9 (t), 126.0 (d), 140.0 (s), 172.9 (s); exact mass calcd. for C₁₄H₂₉NO₅Si m/e 329.2386, found m/e 329.2400.

To 215 mg (0.53 mmol) of lactone 278 was added 8 mL of 2 M dimethylamine (16 mmol) in methanol. The resulting mixture was heated to reflux for 22 h. The mixture was cooled to room temperature and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:1, followed by ethyl acetate) to give 194 mg (80%) of the desired amido alcohol 282b as a colorless oil: IR 3376, 1626 cm⁻¹; ¹H NMR (CDCl₃, 300MHz) δ 1.05 (s, 9H, t-Bu), 1.61 (d, J = 6.9 Hz, 3H, CH₃), 1.70-1.81 (m, 2H, CH₂CH₂), 2.58 (dd, J = 13.8, 5.7 Hz, 1H, CH₂CONMe₂), 2.68 (dd, J = 13.8, 10.9, 1H, CH₂CONMe₂), 2.88 (broad s, 3H, NCH₃), 3.00 (broad d, 3H, NCH₃), 3.30 (m, 1H, CH), 3.65 (t, J = 6.1 Hz, 2H, OCHR), 3.92 (d, J = 11.8 Hz, 1H, CH₂OH), 4.12 (d, J = 11.7 Hz, 1H, CH₂OH), 4.88 (broad s, 1H, OH), 5.66 (q, J = 6.9 Hz, 1H, CH₂CH₂), 7.34-7.45 (m, 6H, ArH), 7.62-7.67 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 13.1 (q), 19.0 (s), 26.7 (q), 31.9 (d), 36.1 (t), 37.9 (t), 61.8 (t), 65.8 (t), 126.4 (d), 127.6 (d), 129.6 (d), 133.5 (s), 135.4 (d), 139.6 (s), 173.2 (s). The N-methyl
groups were observed as the broad signals next to δ 36 and 37 in the 13C NMR spectrum; exact
mass calcd. for C27H39O3NSi m/e 453.2699, found m/e 453.2708.

(±)-(E)-3-[2-(tert-Butyldiphenylsiloxyl)ethyl]-4-[[p-methoxybenzyl]-
oxy)methyl]-N,N-dimethyl-4-hexenamide (283). To 182 mg (0.4 mmol) of alcohol 282b
in 2 mL of THF was added 26 mg (0.65 mmol) of sodium hydride (60% dispersion in mineral oil).
The resulting grey slurry was stirred at room temperature for 10 min, and 79 mg (69 μL, 0.51 mmol)
of p-methoxybenzyl chloride was added dropwise. The resulting mixture was stirred at room
temperature for 20 h. To the resulting mixture was added 2 mL of saturated aqueous ammonium
chloride, 2 mL of water and 40 mL of diethyl ether. The aqueous layer was separated and
extracted with three 10-mL portions of dichloromethane. The organic layers were combined and
washed with 10 mL of brine, dried (MgSO4), and concentrated in vacuo. The residue was
chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:5) to give 175 mg
(75%) of the desired amide 283 as yellow oil: IR 1650 cm⁻¹; 1H NMR (CDCl3, 300 MHz) δ 1.05 (s,
9H, t-Bu), 1.69 (d, J = 6.8 Hz, 3H, CH3CH=), 1.74 (m, 2H, CH2CH2R), 2.39 (dd, J = 14.8, 6.2 Hz, 1H,
CH2CONMe2), 2.55 (dd, J = 15.2, 7.9 Hz, 1H, CH2CONMe2), 2.82 (s, 6H, NCH3), 3.38 (m, 1H, CH),
3.62 (m, 2H, CH2CH2OR), 3.75 (s, 3H, OCH3), 3.78 (d, J = 11.6 Hz, 1H, CH2OAr), 3.94 (d, J = 11.6
Hz, 1H, CH2OAr), 4.33 (AB quartet, 2H, OCH2Ar), 5.61 (q, J = 6.8 Hz, 1H, CH3CH=), 6.85 (d, J =
8.7 Hz, 2H, MeOArH), 7.20 (dm, J = 8.7 Hz, 2H, MeOArH), 7.33-7.44 (m, 6H, ArH), 7.55-7.68 (m,
4H, ArH); $^{13}$C NMR (CDCl$_3$, 75.47 MHz) δ 13.2 (q), 19.0 (s), 26.8 (q), 31.8 (d), 36.0 (t), 37.2 (t), 55.1 (q), 62.2 (t), 71.4 (t), 72.8 (t), 113.6 (d), 126.5 (d), 127.5 (d), 129.1 (d), 129.4 (d), 130.6 (s), 133.8 (s), 133.9 (s), 135.4 (d), 135.5 (d), 137.1 (s), 158.9 (s), 172.1 (s), the two $N$-methyl groups appear as broad signals at about δ 36 and 37; not all the peaks were resolved in the aromatic region, as only seven doublets were observed (instead of nine); exact mass calcd. for C$_{35}$H$_{47}$O$_4$NSi m/e 573.3274, found m/e 573.3288.

![Chemical Structure](image)

(±)-[tert-Butyl-[2-[3-[(E)-ethylidene]-3,4-dihydro-6-(1-phenylvinyl)2H-pyran-4-yl]ethoxy]dimethylsilane (288). To 89 mg (63 μL, 0.48 mmol) of α-bromostyrene in 2 mL of THF under argon at -78°C was added dropwise 0.57 mL of 1.7 M t-BuLi in pentane (0.97 mmol) over a period of 5 min via syringe. The resulting red solution was stirred at -78°C for 30 min and was transferred via cannula to a mixture of 110 mg (0.39 mmol) of lactone 276 in 2.5 mL of THF over a period of 5 min at -78°C. The resulting dark yellow solution was stirred at -78°C for 1.5 h followed by dropwise addition of 1 mL of brine. The resulting mixture was then warmed to room temperature. The aqueous layer was separated and extracted with three 5-mL portions of dichloromethane. The organic layers were combined, dried (MgSO$_4$), concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:15, 1:5) to give, in sequence, 75 mg (68%) of recovered lactone 276 as a yellow oil,
and 48 mg (32%) of the addition product 288 as a yellow oil: IR 1593, 1493 cm⁻¹; ¹H NMR δ (CDCl₃, 300MHz) δ -0.03 (s, 3H, CH₃), -0.01 (s, 3H, CH₃), 0.86 (s, 9H, CH₃), 1.62 (q, J = 6.5 Hz, 2H, CH₂CH₂O), 1.70 (dd, J = 6.8, 1.6 Hz, 3H, CH₃), 3.21 (q, J =7.0 Hz, 1H, CH), 3.60 (t, J = 6.4 Hz, 2H, CH₂O), 4.31 (dd, J = 11.3, 1.1 Hz, 1H, CH₂O), 4.45 (dt, J = 11.3, 1.4 Hz, 1H, CH₂O), 4.81 (d, J = 4.8 Hz, 1H, HC=), 5.12 (s, 1H, =CH₂), 5.60 (q, J = 6.8 Hz, 1H, CH₂CH=), 5.61 (broad s, 1H, =CH₂), 7.29-7.36 (m, 5H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ -5.6 (q), -5.5 (q), 13.3 (q), 18.1 (s), 25.8 (q), 30.2 (d), 39.7 (t), 60.1 (t), 69.5 (t), 106.5 (d), 113.5 (t), 122.3 (d), 127.3 (d), 127.8 (d), 128.8 (d), 134.8 (s), 140.2 (s), 144.8 (s), 152.0 (s); exact mass calcd. for C₃₃H₆₉O₂Si m/e 370.2328, found m/e 372.2318.

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4-[(2-tert-Butyldiphenylsiloxy)ethyl]-5-[(E)-ethylidene]tetrahydro-2H-pyran-2-ol (290). To 0.99 g (2.43 mmol) of lactone 278 in 40 mL of diethyl ether at -78°C under argon was added 3.2 mL of 1.0 M diisobutylaluminium hydride (3.20 mmol) in hexanes dropwise via syringe over a period of 5 min. The resulting mixture was stirred at -78°C for 1 h and 20 mL of saturated aqueous potassium tartrate solution was added very slowly over a period of approximately 30 min. The resulting white slurry was warmed to room temperature and stirred for 1 h. The aqueous layer was separated and extracted with three 20-mL portions of diethyl ether. The organic layers were combined, dried (MgSO₄), and concentrated in vacuo to give 1.00 g (100%) of the desired lactol 290 as a colorless, viscous oil (2:3 mixture of cis and trans isomers,
respectively, by $^1$H NMR: IR (neat) 3382, 1589 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ 1.10 (s, 9H, t-Bu), 1.59 (d, $J = 6.3$ Hz, 1.8H, CH$_3$), 1.63 (d, $J = 6.5$ Hz, 1.2H, CH$_3$CH=, 0.4H underneath δ 1.6 for the methylene from the minor (cis) isomer), 1.75 (td, $J = 6.3$ Hz, 1.2H, CH$_3$CH$_2$, and 0.4H, CH$_3$CH$_2$ for the minor (cis) isomer), 1.90 (t, $J = 13.2$ Hz, 1.2H, H$_{2a}$ and H$_{2e}$), 2.06 (q, $J = 6.6$ Hz, 0.8H, H$_{2a}$, and H$_{2e}$), 3.20 (m, 1H, CH), 3.51-3.77 (m, 2H, OCH$_3$Si, and 0.8H, OH and OCH$_3$ of the minor (cis) isomer, 4.02 (d, $J = 12.9$ Hz, 0.6H, OCH$_2$), 4.15 (d, $J = 12.8$ Hz, 0.6H, OCH$_2$), 4.20 (d, $J = 6.1$ Hz, 0.6H, OH), 4.63 (d, $J = 12.2$ Hz, 0.4H, OCH$_2$), 5.00 (t, $J = 6.5$ Hz, 0.6H, HOCHO), 5.29 (s, 0.4H, HOCHO), 5.38 (q, $J = 7.0$ Hz, 0.6H), 5.45 (q, $J = 7.1$ Hz, 0.4H), 7.4-7.7 (m, 6H, ArH), 7.6-7.7 (m, 4H, ArH); $^{13}$C NMR (CDCl$_3$, 75.47 MHz) δ 12.3 (q), 12.7 (q), 19.1 (s), 26.8 (q), 28.2 (d), 29.4 (d), 34.3 (t), 35.4 (t), 36.9 (t), 37.1 (t), 61.8 (t), 62.0 (t), 62.5 (t), 68.0 (t), 92.3 (d), 92.9 (d), 120.4 (d), 120.9 (d), 127.5 (d), 127.6 (d), 129.5 (d), 129.59 (d), 129.61 (d), 133.7 (s), 133.9 (s), 133.95 (s), 139.49 (d), 135.57 (d), 136.4 (d). The NMR data are of a 2:3 mixture of cis and trans isomers. In $^{13}$C NMR spectrum one singlet and one quartet were missing in the aliphatic region. Judging from their intensities, it was speculated that the singlet at δ 19.1 and the quartet at δ 28.8 are probably from both isomers. Due to severe overlapping of signals in the aromatic region, caused by the existence of stereogenic centers, more signals should have been observed; exact mass calcd. for C$_{26}$H$_{32}$O$_3$Si m/e 410.2277, found m/e 392.2188 (M$^+$H$_2$O).
(E)-4-[2-(tert-Butyldiphenylsiloxy)ethyl]-2-[[tert-butyldiphenylsilyl)methyl]amino]-5-(hydroxymethyl)-5-heptenenitrile (291). A mixture of 1.45 g (3.53 mmol) of lactol 290, and 1.33 g (4.94 mmol) of 1-(tert-butyldiphenylsilyl)methylamine (257), and 79 mg (0.31 mmol) pyridinium p-toluenesulfonate in 30 mL of benzene was heated to 95-100°C with a Dean-Stark trap for 3 h. The resulting mixture was cooled to room temperature and to the mixture was added 2.29 g (35 mmol) of potassium cyanide, 765 mg of sodium bisulfite and 6 mL of water. The resulting two-phase mixture was stirred at room temperature for 12 h and 3 mL of saturated aqueous sodium bicarbonate was added. The mixture was stirred for 10 min. The aqueous layer was separated and extracted with three 15-mL portions of diethyl ether. The organic layers were combined, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with ethyl acetate-hexanes, 1:6), to give 2.15 g (88%) of the desired amino alcohol 291 as a white foam: IR (CHCl₃) 3426, 3336, 2236 (w), 1589, 1471 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) The presence of two diastereomers makes a description of this spectrum difficult. The reader is referred to the Appendix where a copy of the spectrum is supplied. The olefinic signals (=CH) for the minor and major isomers appeared as quartets at δ 5.45 (J = 6.8 Hz) and 5.65 (J = 6.7 Hz), respectively; ¹³C NMR (CDCl₃, 75.4 MHz) δ 13.2 (q), 13.3 (q), 18.0 (s), 19.0 (s), 26.8 (q)*, 27.8 (q)*, 31.8 (t), 32.1 (d, t), 32.4 (d), 36.4 (t)*, 36.9 (t), 37.1 (t), 53.0 (d), 53.1 (d), 62.0 (t)*, 64.5 (t), 65.0 (t), 120.3 (s), 120.4 (s), 125.9 (d), 126.0 (d), 127.6 (d), 127.8 (d), 127.9 (d), 129.2 (d), 129.5 (d), 129.6 (d), 132.6 (d), 132.8 (s), 132.9 (s), 133.5 (s), 135.47 (d), 135.53 (d), 135.70 (d), 135.75 (d), 135.83 (d), 139.0 (s), 139.5 (s). Not all the peaks for both diastereomers were resolved. Those peaks in the aliphatic region which are suspected to represent two carbons based on the intensities are marked with an asterisk. Four singlets in the aromatic region were not observed, probably due to magnetic equivalence; exact mass calcd. for C₄₃H₆₆N₂O₂Si₂ m/z 688.3880, found m/z 688.3918.
4-[2-(tert-Butyldiphenylsiloxy)ethyl]-1-[[tert-butyldiphenylsilyl)methyl]-5-[(E)-ethylidene]-2-piperidinecarbonitrile (292). **Method A.** To a mixture of 93 mg (0.14 mmol) of amino alcohol 291 and 68 mg (0.20 mmol) of carbon tetrabromide in 0.8 mL of dichloromethane was added a solution of 36 mg (0.14 mmol) of triphenylphosphine in 0.8 mL of dichloromethane dropwise over a period of 5 min via syringe. The resulting mixture was stirred at room temperature for 2.5 h, and 1 mL of saturated aqueous sodium bicarbonate solution was added. The aqueous layer was separated and extracted with three 5-mL portions of diethyl ether. The organic layers were combined, washed with 1 mL of brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (eluted with ethyl acetate-hexanes, 1:50) to give 46 mg (51%) of the desired piperidine 292 as a yellow oil (4:1 mixture of two diastereomers by 'H NMR).

**Method B.** To a mixture of 0.57 g (0.78 mL, 5.6 mmol) of triethylamine and 2.15 g (3.12 mmol) of amino alcohol 291 in 35 mL of dichloromethane at -20°C was added 0.47 g (0.32 mL, 4.1 mmol) of methanesulfonyl chloride in one portion via syringe. The resulting mixture was warmed to 10°C and stirred for 1 h. The resulting mixture was then warmed to room temperature, diluted with 75 mL of diethyl ether, and washed with three 15-mL portions of water. The aqueous layers were combined and extracted with three 25-mL portions of diethyl ether. The organic layers were combined, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with ethyl acetate-hexanes, 1:8) to
give 1.72 g (82%) of the desired piperidine 292 as a thick white foam (4:1 mixture of cis and trans isomers by \( ^1\)H NMR): IR (neat) 1465 cm\(^{-1}\); The cis isomer: \( ^1\)H NMR (CDCl₃, 300 MHz) \( \delta \) 1.04 (s, 9H, t-Bu), 1.09 (s, 9H, t-Bu), 1.51 (dd, \( J = 6.8, 1.3 \) Hz, 3H, \( =\text{CHCH}_3 \)), 1.75-1.90 (m, 4H, \( \text{CH}_2\text{CH}_2 \)), 2.71 (s, 2H, \( \text{NCH}_2\text{Si} \)), 2.65-2.75 (m, 1H, \( \text{NCH}_2 \)), 3.00 (m, 2H, \( \text{NCH}_2 \)), 3.50-3.65 (m, 3H, \( \text{CH}_2\text{OR} \), and H), 4.98 (q, \( J = 6.8 \) Hz, 1H, \( \text{CH}_2\text{CH} \)), 7.3-7.4 (m, 12H, ArH), 7.6-7.7 (m, 8H, ArH); Some diagnostic signals from the minor (trans) isomer appeared at \( \delta \) 1.04 (s, 9H, t-Bu), 1.14 (s, 9H, t-Bu), 1.42 (dd, \( J = 6.8, =\text{CHCH}_3 \)), 4.70 (q, \( J = 6.8 \) Hz, 1H, \( \text{CH}_2\text{CH}=\)); \(^{13}\)C NMR (CDCl₃, 300 MHz) \( \delta \) 12.5 (q), 18.2 (s), 19.1 (s), 26.8 (q), 27.67 (q), 27.74 (q), 27.9 (d), 31.9 (t), 34.9 (t), 42.5 (t), 53.4 (d), 56.9 (t), 61.2 (t), 118.2 (s), 120.6 (d), 127.49 (d), 127.51 (d), 127.6 (d), 129.3 (d), 139.4 (d), 133.7 (s), 133.8 (s), 134.1 (s), 135.4 (d), 135.7 (s), 135.9 (d), 136.0 (s). The aforementioned \(^{13}\)C NMR spectrum is for the major (cis) isomer. Not all peaks were resolved. Four quartets were observed instead of three in the aliphatic region and only eight doublets were observed instead of thirteen in the aromatic region. Some extra peaks could be those of the minor (trans) isomer; mass calcd. for \( \text{C}_{53}\text{H}_{54}\text{N}_2\text{OSi}_2 \) \( m/e \) 670.3774, found \( m/e \) 670.3810.

![Image](image.png)

1-[(\text{tert-Butyldiphenylsilyl)methyl]-5-[(E)-\text{ethylidene]-4-(2-hydroxyethyl)-2-piperidinecarbonitrile (293)}. To 718 mg (1.07 mmol) of 2-piperidinecarbonitrile 292 in 12 mL of THF at -20°C under argon was added 1.35 mL of 1.0 M TBAF in THF dropwise over a
period of 5 min via syringe. The resulting mixture was warmed to room temperature and stirred for 5 h. The resulting mixture was partitioned between 50 mL of diethyl ether and 10 mL of water. The aqueous layer was separated and extracted with three 15-mL portions of diethyl ether. The organic layers were combined, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:8, then 1:1) to give 432 mg (93%) of the desired amino alcohol 293 as a white foam: IR (neat) 3422 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.18 (s, 9H, t-Bu), 1.54 (dd, J = 6.8, 1.5 Hz, 3H, CH₂)=CH₂), 1.77-2.00 (m, 5H, CH₂CH₂OH, CH₂CH₃OH, CH₂, OH), 2.74-2.82 (s and d, 3H, NCH₃Si, and H₆a), 2.86 (m, 1H, CH), 3.00 (d, 1H, J = 12.9 Hz, H₆a), 3.48-3.65 (m, 3H, CH₂OH and H₂), 5.03 (q, J = 6.8 Hz, 1H, CH₃CH=), 7.34-7.43 (m, 6H, ArH), 7.66-7.76 (m, 4H, ArH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 12.5 (q), 18.3 (s), 27.8 (q), 28.5 (d), 32.5 (t), 35.1 (t), 42.6 (t), 53.4 (d), 56.9 (t), 60.4 (t), 118.4 (s), 120.8 (d), 127.6 (d), 129.2 (d), 129.27 (d), 129.33 (d), 134.10 (s), 134.18 (s), 134.3 (s), 135.6 (s), 135.9 (d), one doublet was missing in the aromatic region probably due to overlapping signals. Some diagnostic signals of the minor (trans) include: ¹H NMR δ 1.14 (s, 9H, t-Bu), 1.48 (dd, J = 6.8, 1.5 Hz, CH₃), 2.43 (d, J =14.3 Hz, 1H, H₆a), 2.52 (d, J=10.2 Hz, 1H, H₆a), 2.86 (m, 1H, H₆a), 3.32 (d, J = 14.3 Hz, 1H, H₆a), 3.42 (dd, J = 10.2, 3.3 Hz, 1H, H₆a); ¹³C NMR δ 18.4 (s), 27.7 (q), 34.3 (t), 34.7 (t), 42.7 (t), 54.45 (d), 58.7 (t), 60.3 (t), 119.8 (s), 121.4 (d), 134.7 (s), 135.5 (s), 136.0 (d); exact mass calcd. for C₂₀H₂₉N₂O₃Si m/e 432.2597, found m/e 432.2595.
(±)-(2R*,4S*)-1-[((tert-Butyldiphenylsilyl)methyl]-5-[(E)-ethyldiene]-4-(formylmethyl)-2-piperidinecarbonitrile (294a) and (±)-(2R*,4R*)-1-[((tert-Butyldiphenylsilyl)methyl]-5-[(E)-ethyldiene]-4-formylmethyl)-2-piperidine-carbonitrile (294b). To 116 mg (80 µL, 0.92 mmol) of oxalyl chloride in 4 mL of dichloromethane at -78°C under argon was added 138 mg (125 µL, 1.76 mmol) of dimethylsulfoxide. The resulting mixture was stirred at -78°C for 1 h and 270 mg (0.63 mmol) of alcohol 293 in 1 mL of dichloromethane was added dropwise over a period of 5 min via syringe. The resulting mixture was stirred at -78°C for 1.5 h, followed by dropwise addition of 0.36 g (0.5 mL, 3.6 mmol) of triethylamine. The resulting slurry was warmed to room temperature and filtered through a plug of glass wool. The filtrate was concentrated and chromatographed over 10 g of silica gel (eluted with ethyl acetate-hexanes, 1:6) to give, in sequence, 126 mg (58%) of the desired cis aldehyde 294a as a white foam, 42 mg (16%) of a 1:1 mixture of cis aldehyde 294a and trans aldehyde 294b and 23 mg (8%) of a 1:4 mixture of cis aldehyde 294a and trans aldehyde 294b, as a light yellow oil. cis-Aldehyde 294a: IR (neat) 1724 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.11 (s, 9H, t-Bu), 1.51 (dd, J = 6.9 Hz, 1.6 Hz, 3H, CH₃), 1.86 (dm, J = 14.2 Hz, 1H, H₂), 1.92 (dt, J = 14.2, 5.5 Hz, 1H, H₃), 2.63 (dd, J = 17.6, 10.1, 1.4 Hz, 1H, CH₂CHO), 2.74 (AB quartet, 2H, Si(CH₃)₂), 2.75 (d, J = 13.6 Hz, 1H, H₃), 2.96 (dd, J = 17.6, 7.5, 1.5 Hz, 1H, CH₂CHO), 3.03 (d, J = 13.6, 1H, H₃), 3.26 (m, 1H, CH), 3.58 (m, 1H, H₂), 5.01 (q, J = 6.6 Hz, 1H, CH₂CHO), 7.34-7.44 (m, 6H, ArH), 7.65-7.68 (m, ArH, 4H), 9.70 (t, J = 1.5 Hz, 1H, CHO); ¹³C NMR
(CDCl₃, 75.47 MHz) δ 12.4 (q), 18.2 (s), 26.1 (d), 27.7 (q), 31.9 (t), 42.6 (t), 46.0 (t), 53.2 (d), 56.8 (t), 118.1 (s), 121.1 (d), 127.7 (d), 129.4 (d), 133.9 (s), 134.4 (s), 135.8 (d), 200.7 (d), the fact that only one singlet and three doublets were observed for the aromatic carbons suggested that the two Ph's were accidentally equivalent; exact mass calcd. for C₂₇H₄₄N₂OSi m/e 430.2440, found m/e 430.2409; The trans aldehyde 294b: IR (neat) 1721 cm⁻¹; 'H NMR (CDCl₃, 300 MHz) δ 1.10 (s, 9H, t-Bu), 1.49 (dd, J = 7.0, 1.5 Hz, 3H, =CHCH₂), 1.84 (dm, J = 15.5 Hz, 1H, H⁻), 2.07 (ddd, J = 15.5, 9.7, 5.8 Hz, 1H, H⁺), 2.46 (dd, J = 7.4, 1.8 Hz, 2H, CH₂CHO), 2.48 (d, J = 13.4 Hz, 1H, H⁻), 2.63 (d, J = 14.6 Hz, 1H, NCH₂Si), 2.84 (d, J = 13.4 Hz, 1H, H⁻), 3.21 (d, J = 14.5 Hz, 1H, NCH₂Si), 3.25 (m, 1H, H₆), 3.35 (dd, J = 9.7, 4.0 Hz, 1H, H₇), 4.81 (q, J = 7.0 Hz, 1H, CH₂CH=), 7.32-7.45 (m, 6H, ArH), 7.61 (dm, J = 7.8 Hz, 2H), 7.83 (dm, J = 7.8 Hz, 2H, ArH), 9.60 (t, J = 1.8 Hz, 1H, CHO); ¹³C NMR (CDCl₃, 75.47 MHz) δ 12.5 (q), 18.6 (s), 27.1 (d), 27.9 (q), 34.2 (t), 42.8 (t), 45.4 (t), 54.5 (d), 59.0 (t), 119.3 (s), 121.4 (d), 128.1 (d), 129.7 (d), 129.7 (d), 133.7 (s), 134.7 (s), 135.1 (s), 136.3 (d), 136.5 (d), 198.8 (d), because of overlapping of the signals, only six doublets were observed in the aromatic region instead of seven. The trans isomer was characterized as a 1:4 mixture of cis and trans isomers. In the ¹³C NMR spectrum of this mixture, the aliphatic region turned out to be straightforward, but interpretation of the aromatic region was difficult.
LIST OF REFERENCES


4. Regnault, V. Ann. 1838, 26, 10.


APPENDIX A: List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-Butyl</td>
</tr>
<tr>
<td>s Bu</td>
<td>sec-Butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
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<tr>
<td>DME</td>
<td>1,2-Dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethyl phosphoric triamide</td>
</tr>
<tr>
<td>Imid</td>
<td>Imidazole</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>LAH</td>
<td>Lithium aluminium hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
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<tr>
<td>m-CPBA</td>
<td>m-Chloroperoxybenzoic acid</td>
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<tr>
<td>MVK</td>
<td>Methyl vinyl ketone</td>
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<td>Acronym</td>
<td>Full Form</td>
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<td>-----------</td>
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<tr>
<td>NMO</td>
<td>N-Methylmorpholine N-oxide</td>
</tr>
<tr>
<td>PPA</td>
<td>Phosphoric acid</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium p-toluenesulfonate</td>
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<td>SEM</td>
<td>2-(Trimethylsilyl)ethoxymethyl</td>
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<tr>
<td>TBAF</td>
<td>Tetrabutyl ammonium fluoride</td>
</tr>
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<td>TBDMS</td>
<td>Tributyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>Tributylphenylsilyl</td>
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<td>Trifluoroacetic acid</td>
</tr>
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<td>Trifluoroacetic anhydride</td>
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<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
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<tr>
<td>TMEDA</td>
<td>N,N,N,N'-Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetrapropylammonium perruthenate</td>
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<tr>
<td>Triton B</td>
<td>N-Benzyltrimethylammonium hydroxide</td>
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</table>
APPENDIX B: $^1$H and $^{13}$C NMR Specta of Selected Compounds
TMS

\[
\text{YH-I-140 (75.47, CDC}_{6}^{1})
\]
YH-I-204 (250 MHz, CDCl₃)

[Chemical structure image]

ppm

9.0  8.0  7.0  6.0  5.0  4.0  3.0  2.0  1.0  0.0
YH-I-204 (75.47 MHz, CDCl₃)
YH-I-210-A (75.47 MHz, CDCl$_3$)
YH-II-96-B (75.47 MHz, CDCl$_3$)
190a

YH-I-241-C (500 MHz, CDCl₃)
YH-1-241-C (75.47 MHz, CDCl₃)
190b
YH-I-241-D (500 MHz, CDCl₃)
190b
YH-1-241-D (75.47 MHz, CDCl₃)
YH-II-106-D (125.8 MHz, CDCl₃)
YH-I-197 (300 MHz, CDCl₃)

Ph

Si-CH₂OH

Ph

188
SI-CH$_2$OTf
Ph
Ph

189
YH-III-188 (300 MHz, CDCl$_3$)
$\text{Ph}_3\text{Si-CH}_2\text{OTf}$

189

YH-III-188 (75.47 MHz, CDCl$_3$)
Ph-Si-CH$_2$NH$_2$

YH-III-226 (300 MHz, CDCl$_3$)
YH-III-226 (75.47 MHz, CDCl₃)
YH-II-163-A (200 MHz, CDCl₃)
YH-183-B (300 MHz, CDCl$_3$)
YH-II-189-A (300 MHz, CDCl₃)
201

YH-II-189-A (75.47 MHz, CDCl₃)
OH

CH₃

OCNEt₂

205

YH-II-261-B (300 MHz, CDCl₃)
YH-II-261-B (75.47 MHz, CDCl₃)
PhS,
CH
202
YH-II-194 (300 MHz, CDCl₃)
PhS
CH₃

202
YH-II-194 (75.47 MHz, CDCl₃)
YH-II-205 (75.47 MHz, CDCl₃)
YH-II-246 (300 MHz, CDCl₃)
YH-II-246 (75.47 MHz, CDCl₃)
YH-II-252-A (300 MHz, CDCl₃)
if

YH-II-252-A (75.47 MHz, CDCl₃)
YH-II-256 (300 MHz, CDCl₃)

TBDPS
TBDPS

\[
\text{YH-II-256 (75.47 MHz, CDCl}_3\text{)}
\]
YH-III-130-B (200 MHz, CDCl₃)
YH-I-251 (300 MHz, CDCl₃)
YH-I-251 (75.47 MHz, CDCl₃)
TBDPS

YH-III-41 (300 MHz, CDCl₃)
YH-III-41 (75.47 MHz, CDCl₃)
YH-III-42 (300 MHz, CDCl₃)
YH-III-42 (75.47 MHz, CDCl$_3$)
YH-III-85-D (75.47 MHz, C₆D₆)
Ph \( \text{Br} \)

225

YH-III-141 (200 MHz, CDCl\(_3\))
Ph\textsubscript{226} YH-III-179 (200 MHz, CDC\textsubscript{3})
Ph\(\text{OTf}\)

YH-III-166 (200 MHz, CDCl\(_3\))
TBDPS
NC/NC

223

YH-III-125-B (300 MHz, CDCl₃)
YH-III-125-B (75.47 MHz, CDCl$_3$)
YH-III-197-B (300 MHz, CDCl₃)
YH-III-197-B (75.47 MHz, CDCl₃)
YH-III-213-C (300 MHz, C₆D₆)
YH-III-213-C (125.8 MHz, C₆D₆)
YH-III-155-C (200 MHz, CDCl₃)
YH-III-167 (300 MHz, CDCl₃)
YH-III-167 (75.47 MHz, CDCl₃)
YH-III-178-B (300 MHz, CDCl₃)

242

TBDPS

NC

2

OH

PPM
YH-III-178-B (75.47 MHz, CDCl₃)
TBDPS
NC
N
\n
244

YH-III-198-A (300 MHz, CDCl₃)
YH-III-198-A (75.47 MHz, CDCl₃)
TBDPS

268

YH-IV-51 (300 MHz, CDCl₃)
YH-IV-51 (75.47 MHz, CDCl₃)
YH-IV-43 (300 MHz, CDCl₃)
YH-IV-31 (300 MHz, CDCl₃)
YH-IV-31 (75.47 MHz, CDCl₃)
YH-IV-117 (300 MHz, CDCl₃)
YH-IV-117 (75.47 MHz, CDCl₃)
YH-IV-60-B (300 MHz, CDCl₃)
YH-IV-60-B (75.47 MHz, CDCl₃)
I V 3

TBDPS

NC  \_ N

269

YH-IV-44-C (300 MHz, CDCl₃)
YH-IV-44-C (75.47 MHz, CDCl₃)
YH-III-250 (300 MHz, CDCl₃)
YH-IV-115-A (200 MHz, CDCl₃)
254
YH-IV-119 (200 Hz, CDCl₃)
YH-IV-132 (75.47 MHz, CDCl₃)
YH-IV-134 (300 MHz, CDCl₃)
YH-III-280 (300 MHz, CDCl₃)
YH-III-280 (75.47 MHz, CDCl₃)
TBDPSO

YH-VI-57-B (300 MHz, CDCl₃)
278
YH-VI-57-B (75.47 MHz, CDCl₃)
OTBDPS

YH-VI-57-C (75.47 MHz, CDCl₃)

279
YH-III-294-A (300 MHz, CDCl₃)
TBSO

276

YH-III-294-A (75.47 MHz, CDCl₃)
YH-III-294-B (300 MHz, CDCl₃)
TBDPS

\[
\begin{align*}
\text{O} & \quad \text{NH} \\
\text{OH} & \\
\text{TBSO} & \quad 281a
\end{align*}
\]

YH-III-303-B (75.47 MHz, CDCl\textsubscript{3})
YH-IV-46-C (75.47 MHz, CDCl3)
Me₂N\text{O} \quad \text{OH}

TBDPSO

282b

YH-IV-67 (300 MHz, CDCl₃)
YH-IV-67 (75.47 MHz, CDCl₃)
Me₂N

\[ \text{Me}_2\text{N} \quad \text{OPMB} \]

\[ \text{TBDPSO} \]

283

YH-IV-69-B (300 MHz, CDCl₃)
YH-IV-69-B (75.47 MHz, CDCl₃)
YH-IV-55-A (75.47 MHz, CDCl₃)
YH-IV-140 (75.47 MHz, CDCl₃)
YH-IV-135 (300 MHz, CDCl₃)
291
YH-IV-135 (75.47 MHz, CDCl₃)
YH-IV-137 (300 MHz, CDCl₃)
YH-IV-137 (75.47 MHz, CDCl₃)
YH-IV-149 (300 MHz, CDCl₃)
YH-IV-155-A (300 MHz, CDCl₃)
294b
YH-IV-155-B (300 MHz, CDCl₃)