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## Studies on Total Synthesis of the Cylindricine/Fasicularin/ Lepadiformine Family of Tricyclic Marine Alkaloids

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### 1. Isolation and Structure Determination

In three papers that appeared in the early 1990's, Blackman and coworkers described the isolation of a family of eleven structurally related tricyclic alkaloids produced by the marine ascidian (sea squirt) *Clavelina cylindrica*, collected off the east coast of Tasmania.<sup>1</sup> The most abundant of these alkaloids are cylindricines A (**1**) and B (**7**), whose structures were established by spectral analysis, along with X-ray crystallography of the corresponding picrates (Figure 1). The former compound has a pyrrolo[2,1-*j*]quinoline tricyclic framework, whereas the latter possesses a C-ring-expanded pyrido[2,1-*j*]quinoline system. Interestingly, after standing for six days in solution, these compounds produce the same 3:2 equilibrium mixture of **1** and **7**. Since this equilibration occurs only with the free bases of the alkaloids (the corresponding picrates are stable), it was presumed that the interconversion probably occurs via the aziridinium intermediate **6**.<sup>1a</sup>

Subsequent investigations by the Blackman group led to the isolation of some additional minor compounds possessing the cylindricine A pyrroloquinoline framework and stereochemistry, but differing only in the functionality at C(14). The structures of these metabolites were secured mainly by NMR analysis, as well as by a few simple chemical interconversions. Examples of these alkaloids include cylindricines C (**2**), D (**3**), E (**4**) and F (**5**). In addition, a few cylindricine A-type alkaloids were found possessing a butyl chain at C(2) rather than the hexyl group (e.g. cylindricines G (**8**), H (**9**) and I (**10**)). Similarly, a second compound exists in the cylindricine B pyridoquinoline series, but has a C(2) butyl appendage (i.e. cylindricine J (**11**)). Cylindricine K (**12**) is related to cylindricine A, and is the only alkaloid isolated to date with functionality in the A-ring. All of the cylindricine alkaloids possess a *cis*-fused 1-azadecalin A/B-ring system and prefer to exist in the conformations shown in Figure 1, as evidenced by X-ray crystal structure and NMR data, as well as molecular mechanics calculations.<sup>1c</sup>

The absolute configurations of these alkaloids were not established during the structural studies. However, recent enantioselective syntheses of lepadiformine have proven its absolute configuration to be antipodal to those drawn in **1-11** (see sections 5.2.4 and 5.2.5), and this alkaloid is at present the only member of the family for which absolute stereochemistry is definitively known. One might reasonably assume that all the other alkaloids of this family have the same absolute stereochemistry as lepadiformine, but this supposition has not yet been proven. Based upon this assumption and the synthetic work outlined below, structures **1-11** arbitrarily used by Blackman in fact would have the unnatural configuration and correspond to the (-)-cylindricines. The (+)-alkaloids in the natural series would be enantiomeric to the above structures. Unfortunately, optical rotations of the natural cylindricine alkaloids were not taken during the structure work and thus direct comparison with enantiomerically pure synthetic compounds is not possible. Until reisolation of these metabolites, the question of

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their absolute configurations will remain unanswered. For convenience and consistency throughout this review, the enantiomeric series shown by Blackman in the original papers is used for discussions of the racemic syntheses, and the actual antipode which was prepared is shown in the enantioselective syntheses.

In 1997, the tricyclic alkaloid fascicularin (**13**) was isolated by a SmithKline Beecham group from the ascidian *Neptheis fascicularis* collected in Pohnpei, Micronesia (Figure 2).<sup>2</sup> NMR and NOE experiments led to the assignment of the structure, relative stereochemistry and conformation of fascicularin as depicted in **13**. This alkaloid is closely related to the cylindricine B series of pyridoquinolines, but is epimeric at the C(10) quaternary center, thereby rendering a *trans*-1-azadecalin A/B ring fusion. Moreover, this compound lacks the C(4) oxygenation found in all but one of the cylindricine alkaloids. As is the case in the cylindricines, the optical rotation of natural fascicularin was not measured, and thus it has not been possible to compare enantiomerically pure synthetic material with the natural alkaloid to establish its absolute configuration.

In 1994, Biard and coworkers described the isolation of a new marine alkaloid, lepadiformine,<sup>3</sup> obtained by HCl extraction of the methylene chloride-soluble portion of the marine tunicate *Clavelina lepadiformis* (Muller) collected in the Mediterranean off the coast of Tunisia,<sup>3a</sup> and later isolated from *Clavelina moluccensis* (Sluiter) obtained near Djibouti.<sup>3b</sup> Based on proton and carbon NMR analysis, it was suggested that lepadiformine has tricyclic structure **14** which contains an unprecedented zwitterionic vicinal amino alcohol moiety (Figure 3). It should be noted that the A/B-ring system in putative structure **14** is a *cis*-1-azadecalin, thus putting it in the cylindricine class. In addition, the NMR NOE experiments on lepadiformine were interpreted to suggest that this alkaloid had the conformation shown in **14a**. However, based upon synthetic work outlined below, it was found that structure **14** is incorrect, nor does this molecule exist as a zwitterion.<sup>4</sup> Moreover, it was also determined by synthesis that lepadiformine is not a C(2) or C(13) epimer of structure **14**.<sup>5</sup> The constitution and relative configuration of lepadiformine was finally established as shown in **15a** by total synthesis (vide infra).<sup>6,7</sup> Lepadiformine, therefore, is in the fascicularin *trans*-1-azadecalin series, but has a pyrroloquinoline rather than a pyridoquinoline ring system. Moreover, it was found by X-ray crystallography of synthetic material that the alkaloid exists with the B-ring in a boat conformation, thereby avoiding having the hexyl chain in an axial position. As noted above, two subsequent enantioselective total syntheses of lepadiformine determined that the molecule has the absolute configuration shown in **15a**.

Very recently, two additional alkaloids closely related to lepadiformine were isolated from *C. moluccensis*.<sup>3c</sup> These compounds include lepadiformine B (**15b**) which bears a butyl group rather than hexyl at C(2), and lepadiformine C (**15c**), which has lost the hydroxymethyl group at C(13). With these new compounds being isolated, it was proposed that the name of lepadiformine (**15a**) be changed to lepadiformine A. However, since all of the synthetic work described here was done before this latest paper appeared, the name lepadiformine is used throughout to refer to **15a**.

## 2. Biological Activity

No significant biological activity has been reported for any of the cylindricines other than toxicity in a brine shrimp assay. However, fascicularin (**13**) was found to have biological activity against a DNA repair-deficient strain of yeast, as well as cytotoxicity against Vero cells.<sup>2</sup> Recently, Gates et al. investigated the ability of fascicularin to damage DNA by acting as an alkylating agent.<sup>8</sup> In this experiment, mixed-sequence duplex DNA was treated with racemic synthetic fascicularin, and after thermal treatment the guanine alkylation product **17** could be detected (Scheme 1). The assumption was that fascicularin is first converted to the aziridinium

ion **16**, analogous to that proposed for interconversion of cylindricines A and B (Cf. **6**; Figure 1; see also section 4.2). Subsequent attack on intermediate **16** by N(7) of the guanine base led to the observed alkylation product **17**. Although the regiochemistry of the opening of aziridinium ion **16** was not actually proven, it was assumed that nucleophilic attack occurred at the primary carbon as shown in the scheme to give **17** based on results in the cylindricine A and B series.<sup>1b</sup> It was also found in control experiments that the thiocyanate anion formed in the process does not cause DNA strand cleavage.

Lepadiformine (**15a**) has been reported to have moderate *in vitro* cytotoxicity against nasopharynx carcinoma (KB) and non-small-cell lung carcinoma (NSCLC-N6).<sup>3a</sup> In addition, the alkaloid has been investigated *in vivo* for its cardiovascular effects. The alkaloid caused a variety of effects when tested in rats, including induction of bradycardia, prolongation of ECG parameters, and led to a transient fall of blood pressure.<sup>3b</sup> It was also suggested that the alkaloid may have antiarrhythmic properties. Recently, it was reported that alkaloids **15a-c** block cardiac muscle Kir channel.<sup>3c</sup>

### 3. Synthetic Approaches to the Cylindricines

#### 3.1 Snider Synthesis of (±)-Cylindricines A, D and E

The first total synthesis of a cylindricine alkaloid was reported by Snider and Liu in 1997.<sup>9</sup> In this approach, key steps included a double Michael reaction of ammonia with a dienone to form the fused A/B-ring system, and a copper catalyzed *N*-chloroamine/olefin radical cyclization to construct the C-ring. The synthesis commenced with ketone **18**, which underwent addition of 3-butenylmagnesium bromide followed by acid hydrolysis to produce enal **19** (Scheme 2). Addition of 1-octynyllithium to aldehyde **19**, reduction of the resulting propargylic alcohol and allylic alcohol oxidation led to the requisite dienone substrate **20**. It was found that heating this dienone with ammonium hydroxide in methanol under various pH conditions led to only three of the four possible diastereomeric Michael addition products. At high pH, 56% of the desired cylindricine stereoisomer **22** was formed along with 19% of **21** and 6% of **23**. However, at lower pH's, controlled by addition of ammonium chloride to the reaction mixture, the amount of the undesired *trans*-fused 1-azadecalin system **21** increased at the expense of the requisite cylindricine isomer **22**. Based upon some equilibration studies along with molecular mechanics calculations, it was postulated that the ratio of the three products **21-23** is determined by the second kinetically controlled intramolecular Michael step. However, no speculation about the actual details of this process was offered.

To complete the synthesis, bicyclic amine **22** was first treated with NCS, which provided the *N*-chloroamine **24** in high yield (Scheme 3). Exposure of this compound to the Stella conditions for generating aminyl radicals<sup>10</sup> induced a 5-*exo* cyclization which was non-stereoselective, affording a 1:1 mixture of racemic cylindricine A (**1**) and the undesired C(12) epimer **25**. It was possible, however, to recycle unwanted chloride **25** back to amino olefin **22** by a zinc/HCl reduction. Using procedures previously developed by Blackman during structural studies,<sup>1b</sup> it was also possible to convert synthetic (±)-cylindricine A (**1**) to (±)-cylindricine D (**3**) by treatment with sodium methoxide in methanol, and to (±)-cylindricine E (**4**) with sodium acetate in methanol.

#### 3.2 Heathcock Synthesis of (±)-Cylindricines A and B

The Liu/Heathcock approach to the cylindricines is very closely related to the strategy devised by Snider.<sup>11</sup> In fact, their first generation approach was identical to that shown above in Scheme 2, in that it involved the double Michael addition of ammonia to dienone **20** to form a mixture of 1-azadecalins **21-23** in the same proportions as observed by Snider and Liu. Since the stereoselectivity in this process is low, a more efficient second generation strategy was

therefore developed. Enol triflate **26** was first coupled with the second order cuprate derived from 3-butenyllithium to generate ester **27**, which was then converted into  $\beta$ -ketophosphonate **28** (Scheme 4). This intermediate was next deprotonated with NaH and condensed with formaldehyde to form dienone **29**. Heating this compound with ammonia/ammonium hydroxide in ethanol resulted in a double Michael reaction to afford the desired 1-azadecalin **30** in high yield as a 1:1 mixture of *cis* and *trans* isomers. This mixture was *N*-acylated to generate the Teoc-protected system **31**, which was first converted to the corresponding TIPS enol ether and then oxidized with ceric ammonium nitrate to the vinylogous amide **32**.

At this point, the *cis* and *trans* isomers could be separated by HPLC, and each was individually alkylated using the methodology of Comins.<sup>12</sup> Thus, conjugate addition of the cuprate derived from hexylmagnesium bromide to *trans*-1-azadecalin **32** was highly stereoselective and afforded adduct **33** via axial attack of the organometallic reagent (Scheme 5). Similarly, the addition to *cis* isomer **32** gave adduct **34**, once again via axial attack. Removal of the Teoc group from both *trans*-fused isomer **33** and *cis*-fused isomer **34** with tetrabutylammonium fluoride led to the more stable *cis*-1-azadecalin **22**. Conversion of amino olefin **22** to a mixture of ( $\pm$ )-cylindricine A (**1**) and its C(12) epimer **25** was effected as previously done by Snider (Cf. Scheme 3). Synthetic cylindricine A, when dissolved in C<sub>6</sub>D<sub>6</sub>, underwent equilibration to a mixture of cylindricines A and B.<sup>1</sup>

### 3.3 Molander Synthesis of (-)-Cylindricine C

In 1999, Molander and Ronn described an enantioselective total synthesis of (-)-cylindricine C (**2**) which featured an intramolecular double Michael addition of an amine to a dienone.<sup>13</sup> Starting with the known<sup>14</sup> (*S*)-1,2,4-butanetriol-derived tosylate **35** as the source of absolute chirality, the lithium anion of the *N,N*-dimethylhydrazone derivative of cyclohexanone could be alkylated to form ketone **36** (Scheme 6). This ketone was then transformed as shown in three steps to dienone **37**. Hydrolysis of the ketal moiety in **37** proved difficult, but it was found that a palladium-mediated cleavage led to the desired diol, which was processed in three steps to afford azide **38**.

Treatment of azide **38** with chromium(II) chloride under acidic conditions, followed by desilylation of the crude product with tetrabutylammonium fluoride, led to (-)-cylindricine C (**2**) in 37-55% yields. The course of this complex cyclization sequence can best be rationalized as shown in Scheme 7. Initial Michael reaction of the amine derived from reduction of azide **38** can lead to diastereomeric spirocycles **39** and **42**. For stereoelectronic reasons, conjugate addition of the amino group in enone **39** occurs to form tricycle **40** in which the B-ring is a boat, but which has the requisite configuration at C(2) for the cylindricines. Such a ring system is actually relatively stable, as is known to be the case in lepadiformine **15** (vide supra). Subsequent epimerization of ketone **40** at C(5) then produces the thermodynamically more stable cylindricine C system **41** (for a further discussion of the relative stabilities of these ring systems see section 3.5). It is highly unlikely that enone **39** epimerizes at C(5) prior to cyclization since Weinreb and coworkers have shown that this isomeric compound in fact undergoes conjugate addition to produce the C(2) epimer of tricycle **41** (see Scheme 30 below). In the case of diastereomeric spirocycle **42**, the second Michael addition may be precluded for steric reasons due to an unfavorable interaction between the enone and the siloxymethyl group. This intermediate could in principle be reversibly converted to spirocycle **39**, but under these particular reaction conditions may simply decompose, explaining the moderate yields of tricyclic product **2**.

### 3.4 Trost Synthesis of (+)-Cylindricines C, D and E

The strategy in the cylindricine synthesis reported by Trost and Rudd involved an intramolecular double Michael cyclization of an amino dienone which was virtually identical

to that of Molander, but in the antipodal series (Cf. Scheme 7).<sup>15</sup> The Trost approach made use of an efficient ruthenium-catalyzed diyne cyclization to generate the dienone substrate.

Using methodology of Knochel,<sup>16</sup> readily prepared bromo diyne **43** was first coupled with enantiomerically pure iodide **44** derived from (*S*)-serine to produce **45** (Scheme 8). The ester functionality in **45** was then reduced with lithium borohydride, and the resulting alcohol was protected as the TBDPS ether **46**. Using methodology previously developed in the Trost lab,<sup>17</sup> this diyne was found to undergo chemoselective ruthenium-catalyzed hydrative cyclization to afford the desired enone **47** in high yield. This product could next be condensed with heptanal in an aldol reaction and dehydration to yield the requisite dienone **48**. Removal of the Boc protecting group of dienone **48** with TFA, followed by heating the resulting amine salt with potassium carbonate in toluene resulted in a 90% yield of tricyclic product **49**. Subsequent cleavage of the silyl protecting group of this material afforded (+)-cylindricine C (**2**). Of interest is the fact that this cyclization resulted in a significantly higher yield of the desired tricycle **49** than was the case in the Molander synthesis. One possibility is that the reaction conditions used in the cyclization step in the Trost work allowed reversible equilibration of the undesired spirocycle **42** with **39** (Cf. Scheme 7). Using straightforward chemistry, (+)-cylindricine C could be converted to cylindricines D (**3**) and E (**4**).

### 3.5 Kibayashi Syntheses of (+)-Cylindricine C

The Kibayashi group has reported two different enantioselective total syntheses of (+)-cylindricine C. The first synthesis, which was published in 2004, began with lactam **50**, derived from (*S*)-pyroglutamic acid, which underwent Grignard addition to produce ketone **51** (Scheme 9).<sup>18</sup> Removal of the Boc protecting group of **51** with TFA caused cyclization of the resulting ketoamine to the imine, and also resulted in loss of the PMB group, affording the corresponding alcohol. Re-protection of the alcohol functionality as the TBDPS ether then produced ketimine **52**. Based upon the results of some preliminary model studies, it was found that this imine undergoes a highly stereoselective addition of allylmagnesium bromide in the presence of boron trifluoride etherate to afford olefin **53**. This product was processed via the simple four step sequence shown in the scheme to yield aldehyde tosylate **54**.

A number of attempts were made to cyclize the enolate derived from aldehyde **54**, as well as the corresponding iodide, to produce spirocycle **56**. However, substrate **54** is prone to undergo retro-Michael reaction under strongly basic conditions. Alternatively, it was discovered that treatment of aldehyde **54** with pyrrolidine leads to enamine **55** which successfully cyclized (Scheme 10). Hydrolysis of the resulting enamine cyclization product with aqueous acetic acid provided the desired spirocyclic aldehyde **56** in moderate yield as a single stereoisomer. To complete the synthesis, aldehyde **56** was first converted to ynone **57** in two steps, and this compound was then hydrogenated with Lindlar catalyst to produce the *Z*-enone. Removal of the Boc protecting group with TFA, followed by neutralization of the amine salt with aqueous sodium carbonate afforded cylindricine tricycle **59**. This cyclization may in fact involve initial isomerization of the (*Z*)- to the (*E*)-enone, as well as formation of the *trans*-1-azadecalin **58**. Epimerization of **58** at C(5) provided the observed *cis*-1-azadecalin product **59**, which upon reductive debenzoylation yielded (+)-cylindricine C (**2**).

The second Kibayashi synthesis of (+)-cylindricine C involved the convergent preparation of a key advanced intermediate **63** which was also used for both (-)-fasicularin and (-)-lepadiformine (see sections 4.2 and 5.3.5).<sup>19</sup> This approach also started with enantiomerically pure (*S*)-lactam **50**, which was coupled with Grignard reagent **60** to form ketone **61** (Scheme 11). Exposure of **61** to formic acid presumably first generated *N*-acyliminium ion **62**, which cyclized stereoselectively via a chair-like transition state to afford spirocycle **63** in excellent yield. Compound **63** was approximately a 1.6:1 mixture of stereoisomers favoring the  $\alpha$ -formate. The mixture of esters **63** was hydrolyzed to a mixture of allylic alcohols, which was

oxidized to enone **64**. It was found that this ketone could be reduced stereoselectively with (*S*)-BINALH in high yield with a 97% diastereomeric excess in favor of the  $\beta$ -allylic alcohol **65**.

Hydroxyl-directed epoxidation of allylic alcohol **65** with *m*-chloroperbenzoic acid was moderately stereoselective, producing a 4.9:1 mixture of the  $\beta$ -epoxide **66** along with the  $\alpha$ -isomer (Scheme 12). The desired major  $\beta$ -epoxide **66**, which could be isolated in 68% yield, was reduced to 1,3-diol **67** with lithium aluminum hydride. It was possible to selectively form the mesylate of the less hindered C(2) alcohol group of **67**, and following Boc removal, cyclization occurred with inversion to give tricyclic alcohol **68**. Swern oxidation of this alcohol subsequently led to ketone **58**. Molecular mechanics calculation on **58** indicate that the B-ring boat system in the *trans*-1-azadecalin is the lowest energy conformation. Moreover, it was calculated that the *cis*-1-azadecalin **59** is more stable than **58** by 5.5 kcal/mol. In fact, when ketone **58** was exposed to aqueous potassium carbonate, complete epimerization to **59** occurred. Cleavage of the benzyl ether protecting group of **59** as shown in Scheme 10 afforded (+)-cylindricine C (**2**).

### 3.6 Hsung Synthesis of (+)-Cylindricine C

In 2004, Hsung and coworkers reported an approach to (+)-cylindricine C involving a pivotal *N*-acyliminium ion/diene cyclization which is closely related to that of Kibayashi outlined in Scheme 11.<sup>20</sup> In the successful route, iodide **69** was metallated and added to enantiomerically pure (*S*)-lactam **70** to form ketone **71** in moderate yield (Scheme 13). Formic acid induced cyclization of this compound proceeded as in the Kibayashi case (Cf. **61** to **63**)<sup>19</sup> to produce a mixture of spirocyclic formates which was hydrolyzed to a stereoisomeric mixture (ratio unspecified) of allylic alcohols **72**. This alcohol could then be oxidized to enone **73**. All attempts, however, to epimerize this enone at C(5) with base to produce the cylindricine stereochemistry were unsuccessful. It was suggested that the difficulty here is the inability to properly align the C(5) hydrogen with the enone due to severe A<sup>1,3</sup>-strain in the conformations required for deprotonation.

Alternatively, the mixture of alcohols **72** was epoxidized to produce **74**, which was then oxidized to epoxyketone **75** (Scheme 14). This intermediate was subjected to a Wharton rearrangement<sup>21</sup> to yield the transposed allylic alcohol, followed by oxidation to enone **76**. Once again, some unsuccessful attempts were made to epimerize this enone at C(5) with various bases. However, removal of the Boc protecting group of **76** resulted in Michael cyclization of the amino enone as observed in other previously described syntheses (vide supra) to afford *trans*-1-azadecalin **77**. It was found that upon removal of the silyl group of **77** with TBAF, C(5) epimerization also occurs leading to (+)-cylindricine C (**2**).

### 3.7 Ciufolini Synthesis of (-)-Cylindricine C and (-)-2-Epicylindricine C

The Ciufolini group has recently reported a unique synthetic approach to (-)-cylindricine C and its unnatural C(2)-epimer.<sup>22</sup> The route began with (*R*)-homotyrosine derivative **78**, which was oxidized with iodosobenzene diacetate, followed by alcohol protection, to afford the dienone **79** (Scheme 15). Treatment of **79** with KHMDS resulted in conjugate addition of the derived sulfonamide anion to produce adduct **80** with 7:1 diastereoselectivity. The major isomer **80** was then reduced in two steps to afford **81**. The sulfonamide moiety in **81** was deprotonated with *t*-butyllithium, and the resulting anion was alkylated with 1-octene oxide leading to an alcohol which was subsequently oxidized to ketone **82**.

Continuing the synthesis, ketone **82** was exposed to DBU which effected elimination to an isolable  $\alpha,\beta$ -unsaturated ketone, and subjecting of this compound to the Miyaura borylation conditions<sup>23</sup> afforded boronic ester **84** as a single stereoisomer (Scheme 16). The high

stereoselectivity and the rapid rate observed for this reaction suggests that boron delivery to the *Re*-face of the enone occurs internally via a complex like **83**. Reductive amination of aminoketone **84** could be effected with sodium cyanoborohydride, and this step occurred via reduction of iminium compound **85** from the least hindered face to afford tricycle **86**, which is epimeric to cylindricine C at C(2). Finally, oxidative conversion of the boronate to the alcohol, followed by oxidation to the corresponding ketone and silyl group removal provided (-)-2-epicylindricine C (**87**), which had previously been prepared in racemic form by the Weinreb group (see section 5.1.1).<sup>4</sup>

Using advanced intermediate **84**, it was also possible to synthesize (-)-cylindricine C as shown in Scheme 17. In this sequence, the silyl ether protecting group of **84** was first removed to provide the corresponding primary alcohol. Using the Evans protocol,<sup>24</sup> this compound underwent hydroxyl-directed reductive amination (Cf. **85**) to afford tricycle **89** having the desired cylindricine C configuration at C(2). This intermediate was processed as was done in the epimeric series to afford ketone **90**, which upon desilylation yielded (-)-cylindricine C (**2**).

### 3.8 Ishibashi Synthesis of the Cylindricine Ring Skeleton

Ishibashi and coworkers have used a tandem radical cascade protocol to access the tricyclic system of the cylindricines, although none of the natural products were synthesized.<sup>25</sup> Thus, treatment of bromide **91** with tributyltin hydride in the presence of azobis (cyclohexanecarbonitrile) (ACN) afforded tricycle **93** in modest yield as one stereoisomer (Scheme 18). This cyclization presumably occurs via radical intermediate **92**, which undergoes a subsequent stereoselective 5-*endo-trig* cyclization via the conformation shown to provide the product which contains a *cis*-1-azadecaline framework. Similarly, an acyl radical could be employed in this tandem process. For example, cyclization of selenoester **94** was also stereoselective and afforded tricycle **95** in moderate yield.

### 3.9 Hunter Approach to the Cylindricine/Lepadiformine Ring System

Hunter and Richards have reported an approach to the skeleton of the cylindricines and lepadiformine which proved to be lengthy and non-stereoselective.<sup>26</sup> Lactam **96** was first converted to acetal **97**, and following hydrolysis and addition of allylmagnesium chloride, diene alcohol **98** was produced (Scheme 19). Using the first generation Grubbs catalyst, diene **98** underwent ring closing metathesis in high yield to produce cyclohexene **99**. This intermediate was then converted in three simple steps to spirocyclic ketone **100**. Addition of 3-benzyloxypropylmagnesium bromide to this ketone, followed by dehydration yielded olefin **101**. Catalytic hydrogenation of the double bond of **101** was non-stereoselective, and was also accompanied by debenylation. The resulting mixture of alcohols was next converted to the mesylate and cyclized, resulting in a 2:1 mixture of *trans*- and *cis*-1-azadecalins **102** and **103**.

## 4. Synthesis of Fascicularin

### 4.1 Kibayashi Synthesis of (±)-Fascicularin

The Kibayashi group utilized an intramolecular acylnitroso Diels-Alder reaction as a key step in the first total synthesis of racemic fascicularin.<sup>6b</sup> The substrate needed for this cycloaddition was prepared in several steps starting from ketone **104** (Scheme 20). This compound was first converted to a 13:1 mixture of *E:Z* unsaturated nitriles **105**, and the major geometric isomer was reduced to aldehyde **106**. It was then possible to homologate **106** in four straightforward operations into diene alcohol **107**. Three additional steps then served to deliver diene ester **108**.

To set up the system for the hetero Diels-Alder step, ester **108** was first transformed into hydroxamic acid **109** (Scheme 21). This compound could be oxidized with tetrabutylammonium periodate in aqueous DMSO to produce a good yield of a 4.8:1 mixture of isomeric Diels-Alder adducts *A/B-trans* **111** and *A/B-cis* **114**. The cycloaddition proved to be somewhat solvent dependent, and other combinations of aqueous solvents provided slightly poorer ratios of **111:114**. In chloroform as the reaction solvent, the selectivity was significantly lower. The major product **111** of this reaction presumably arises via the transition state conformation shown in **110** where the acylnitroso group is *endo* to the diene but is facially *anti*. The *endo-syn*-facial conformers **112** and **113** would lead to the minor Diels-Alder product **114**, but it was proposed that these conformations are destabilized relative to **110** due to non-bonded interactions between the cyclohexane ring and the acylnitroso tether.

The synthesis of fascicularin continued from the major Diels-Alder adduct **111**, which was hydrogenated to remove the olefinic double bond, leading to tricycle **115** (Scheme 22). At this point it was necessary to replace the MOM protecting group and therefore benzyl ether **116** was prepared. Cleavage of the N-O bond in tricycle **116** was performed with sodium amalgam, and the resulting alcohol was protected as the TBDPS ether **117**. Removal of the benzyl ether and tosylation of the primary alcohol produced **118**, which upon treatment with sodium hydride cyclized to afford **119**.

Tricyclic lactam **119** was reductively ring opened, and the amino group was protected to form alcohol Cbz-derivative **120** (Scheme 23). Oxidation of the primary alcohol to the corresponding aldehyde, addition of hexyl Grignard reagent and oxidation led to ketone **121**. Removal of the Cbz group of **121** and reductive amination of the resulting aminoketone proved to be non-stereoselective. Therefore as an alternative, the silyl group of **121** was removed and the alcohol was inverted by a Mitsunobu procedure yielding alcohol **122**. It was found that the stereochemical course of the catalytic hydrogenation of aminoketone **122** was highly solvent dependent. Using cyclohexane as solvent, a 5.2:1 mixture favoring the desired tricycle **123** along with its C(2) epimer was produced. Presumably the hydroxyl group of **122** is involved in delivery of hydrogen to the *syn*-face of the intermediate iminium ion. With other solvents such as ethyl acetate, ethanol and benzene, the stereoselectivities were lower in the reduction step. To complete the synthesis, it was necessary to introduce a thiocyanate group, and this transformation proved to be surprisingly difficult to effect. For example, attempted displacement of the mesylate derived from alcohol **123** with KSCN gave only elimination and decomposition products. It was finally found that a Mitsunobu reaction of alcohol **123** with thiocyanic acid produced racemic fascicularin (**13**) but in only 20% yield. Although successful, this synthesis of fascicularin was rather long, requiring approximately 29 steps.

## 4.2 Kibayashi Synthesis of (-)-Fascicularin

Spirocyclic enone intermediate **64**, used in the enantioselective synthesis of (+)-cylindricine C described in Schemes 11 and 12, was utilized in a short, efficient total synthesis of (-)-fascicularin.<sup>19</sup> 1,2-Reduction of enone **64** with (*R*)-BINALH proceeded with 9:1 stereoselectivity, and following double bond hydrogenation alcohol **124** was formed (Scheme 24). Removal of the Boc group of **124**, followed by cyclocondensation of the resulting amino alcohol, provided tricycle **125**. Hydrogenolysis of the benzyl ether protecting group of **125** then led to alcohol **126**. To complete the synthesis, alcohol **126** was exposed to Mitsunobu conditions using ammonium thiocyanate to afford a 94% yield of a 1:1 mixture of **128** and (-)-fascicularin (**13**). This transformation presumably involves the aziridinium ion **127** as an intermediate (Cf. Scheme 1). If the undesired isomer **128** is allowed to stand in acetonitrile at room temperature for three days, it is converted into (-)-fascicularin in high yield, once again probably involving intermediate **127**. This total synthesis of (-)-fascicularin (**13**) requires only



about 11 steps from enantiomerically pure pyrrolidinone **50** (Scheme 11), and proceeds in 28% overall yield.

### 4.3 Funk Synthesis of (±)-Fasicularin

Funk and Maeng reported a total synthesis of racemic fascicularin which utilizes a Diels-Alder cycloaddition of a 2-amidoacrolein derivative as a key component of the synthetic strategy.<sup>27</sup> Readily prepared triflamido-1,3-dioxin **129** underwent a retro-Diels-Alder cycloaddition upon heating in toluene to afford 2-triflamidoacrolein **130** along with acetone (Scheme 25). Using unsaturated aldehyde **130**, a regio- and stereoselective [4+2]-cycloaddition with diene **131** could be effected at 12 kbar to afford a single Diels-Alder adduct **132**. Lithium aluminum hydride reduction of **132** served to both reduce the aldehyde and remove the triflamide protecting group, providing amino alcohol **133**. The olefinic double bond and *N*-benzyl group in **133** were then concomitantly removed by catalytic hydrogenation, and the resulting amino alcohol was cyclized with acid to oxazolidine **134**.

Reduction of oxazolidine **134** with sodium borohydride was found to be stereoselective, and proceeded via axial reduction of an intermediate iminium ion, affording amino alcohol **135** having the requisite C(2) stereochemistry for fascicularin (Scheme 26). In order to construct the C-ring of the natural product, intermediate **135** was first acetylated, and the amine was alkylated with 3-iodo-2-(methoxymethoxy)propene to afford **136**. The acetate group of **136** was removed, and the primary alcohol was next oxidized to the corresponding aldehyde. This compound underwent hydrolysis/aldol condensation with aqueous TFA to provide tricyclic enone **137**. Catalytic hydrogenation of the enone double bond of **137**, followed by reduction of the ketone functionality with lithium tri-*tert*-butoxyaluminumhydride afforded a 5.3:1 mixture of alcohols with the desired axial isomer **123** being the major product. As was the case in the Kibayashi synthesis (Scheme 23), conversion of **123** to fascicularin was problematic. In this case, the Mitsunobu procedure used by Kibayashi failed to provide the natural product. However, it was possible to displace the mesylate derived from alcohol **123** with tetrabutylammonium thiocyanate to afford racemic fascicularin (**13**), but only in low yield, along with by-products **138** and **139** which were observed also by Kibayashi.

### 4.4 Dake Enantioselective Formal Synthesis of Fasicularin

Dake and coworkers devised a novel approach to fascicularin which employs siloxyepoxide semipinacol rearrangement as a pivotal transformation.<sup>28,29</sup> The synthesis began with hydroxylactam **140**, which can be obtained in enantiomerically pure form from L-glutamic acid (Scheme 27).<sup>30</sup> Thus, this synthesis is in the antipodal series relative to the Kibayashi work (Cf. Scheme 24). Compound **140** was protected as TBS ether *N*-tosyllactam **141**, and after conversion of the lactam to the enol triflate, palladium(0)-catalyzed coupling was effected with hexamethyldistannane to produce vinyl stannane **142**. Transmetalation of this stannane with methylolithium and magnesium bromide, followed by addition to cyclopentanone led to alcohol **143**. To prepare for the key rearrangement step, enesulfonamide **143** was first stereoselectively epoxidized with dimethyldioxirane. This oxidation probably occurs via axial attack on a half chair conformation of enesulfonamide **143** by DMDO.<sup>29</sup> The alcohol functionality was then silylated to generate **144**. Exposure of compound **144** to titanium tetrachloride promoted a semipinacol rearrangement to afford the desired spirocyclic ketone **145** in high yield. It might be added that the alcohol corresponding to silyl ether **144** does not rearrange cleanly. The hydroxyl functionality of **145** was converted to the mesylate, and eliminated with DBU to alkene **146**. The ketone moiety of **146** was next transformed to the enol triflate **147**.

A number of metal-mediated coupling experiments were conducted with enol triflate **147** in order to incorporate a fragment for construction of the remaining B-ring of the alkaloid. The

route which was ultimately successful involved utilization of (*S*)-allylic ether **149**, which could be prepared in high ee via the Noyori transfer hydrogenation procedure<sup>31</sup> from ynone **148**, followed by some simple transformations (Scheme 28). The alkene **149** was initially hydroborated, and a subsequent Suzuki-Miyaura coupling could then be effected with triflate **147** to produce the requisite alkylated product **150** in good yield. The tosyl and PMB protecting groups of **150** were removed by a dissolving metal reduction to generate the corresponding amino alcohol. A number of hydrogenation conditions were then examined to reduce the double bonds, and it was found that rhodium on carbon was the best catalyst, leading to a 10.5:1 mixture of stereoisomers favoring the desired reduction product **151**. This compound then cyclized with inversion to afford a tricycle, which upon removal of the silyl protecting group provided alcohol **152**. The stereochemistry of this alcohol could be inverted by a two step process involving initial TPAP oxidation to the ketone followed by stereoselective reduction with L-Selectride to **153**, which is enantiomeric to compound **123** synthesized by Kibayashi. Unfortunately, the Dake group was unable to reproduce either the Kibayashi (Scheme 23) or Funk (Scheme 26) procedures for conversion of alcohol **153** to the thiocyanate, which would have led to (+)-fasicularin (**13**).

## 5. Synthesis and Structure Determination of Lepadiformine

### 5.1 Approaches to the Putative Lepadiformine Structure **14** and Related Compounds

**5.1.1 Weinreb Synthesis of Racemic Structure **14****—In 1999, the Weinreb group reported the first synthesis of the structure **14** for lepadiformine which was suggested by Biard.<sup>4</sup> The approach featured an intramolecular nitron/diene 1,3-dipolar cycloaddition. The synthesis commenced with acetone oxime, which was deprotonated and alkylated with epoxide **154** to afford oxime alcohol **155** (Scheme 29). Oxime alcohol **155** was converted to the corresponding trianion, and alkylated with iodo diene **156** to yield **157**. Cleavage of the oxime to the corresponding ketone with TiCl<sub>3</sub> and silylation of the alcohol afforded **158**. The carbonyl group in **158** was then ketalized, and the silyl group was cleaved to afford alcohol **159**. Swern oxidation of **159** to the ketone, followed by oxime formation provided **160**, and reduction of the oxime functionality with sodium cyanoborohydride afforded hydroxylamine **161**.

Treatment of hydroxylamino ketal **161** with aqueous HCl led to the desired cyclic nitron diene **162** in 92% yield (Scheme 30). Thermolysis of **162** in DMSO solution overnight at 195 °C produced cycloadduct **163** in 63% yield as a single stereo- and regioisomer. Cleavage of the N-O bond of this isoxazolidine could be effected with Zn/HOAc to give the amino alcohol, and oxidation with the Dess-Martin reagent led to tricycle **166** via *in situ* cyclization of amino enone **164**. The formation of the C(2) axial epimer occurs for stereoelectronic reasons since conjugate addition of the amino group to the enone functionality in **164** must occur through a transition state initially leading to the boat B-ring **165**, which ring flips to the observed all-chair product **166**. It should be noted that ketone **166** could be protected as its ethylene ketal, and the phenyl protecting group removed by Birch reduction, followed by acid hydrolysis, to afford unnatural (±)-2-epicylindricine C (Cf. Scheme 16).

To complete the synthesis of **14**, tricyclic ketone **166** was reduced under Clemmensen reduction conditions, surprisingly leading to olefin **167** as the major product, along with a small amount of the desired compound **168**. It was possible, however, to stereoselectively reduce alkene **167** by catalytic hydrogenation to produce tricycle **168**. X-ray analysis of the picrate salt of amine **168** showed that the compound exists in the conformation shown, rather than in the flip form **14a** originally suggested by Biard for lepadiformine (see Figure 3). Finally, removal of the phenyl protecting group from **168** afforded racemic **14**, which was found to be different from authentic lepadiformine by a comparison of proton and carbon NMR spectra, and moreover the synthetic compound showed no indication of being a zwitterion.

**5.1.2 Oppolzer Nitrono-Based Approach**—In 2000, Oppolzer and coworkers described intramolecular nitrono/olefin dipolar cycloaddition methodology for synthesis of enantiopure spirocyclic systems like those found in the cylindricines.<sup>32</sup> Their approach is closely analogous to that of the Weinreb group outlined above for preparation of racemic systems. The Oppolzer strategy utilized chiral auxiliary **169** to access enantiomerically pure material for this cycloaddition process (Scheme 31). Thus, readily prepared ester **170** was first converted to the acylsultam **171**.<sup>32a</sup> This compound was deprotonated with sodium hexamethyldisilazide and hydroxylated with 1-nitroso-1-chlorocyclohexane, followed by acid-promoted cyclization to produce nitrono **172** with complete diastereoselectivity. Thermolysis of this nitrono olefin in toluene produced a mixture of regioisomeric cycloadducts **173** and **175**. The minor desired isoxazolidine **173** arises via dipolar cycloaddition through the conformation shown in structure **172**, whereas the major cycloadduct is produced from conformation **174**. It should be noted that the Weinreb group had found similar regiochemical problems in a very closely related intramolecular nitrono/olefin cycloaddition.<sup>4b</sup>

In order to improve regioselectivity in the dipolar cycloaddition, a vinylsilane was investigated as the dipolarophile.<sup>32b</sup> Thus, nitrono *Z*-vinylsilane **176** was prepared using chemistry similar to that shown above (Scheme 32). Thermolysis of this nitrono in benzene for several days provided only cycloadduct **177**, although the yield was not reported. This cycloadduct could be cleaved to aldehyde **178**, once again in unspecified yield.

**5.1.3 Pearson Synthesis of C(2) and C(13) Epimers of 14**—Pearson, et al. synthesized the three diastereomers of structure **14** at C(2) and C(13) utilizing azaallyl anion 1,3-dipolar cycloaddition methodology.<sup>5</sup> In this approach, stannyl amine **180** was first condensed with cyclohexanone **179** to produce imine **181**. Without isolation, this compound was converted to the azaallyl anion with butyllithium, and combined with phenyl vinyl sulfide to stereo- and regioselectively form spirocyclic adduct **182** (Scheme 33). This compound could then be converted in three steps to alcohol **183**. Reductive removal of the thiophenyl group was followed by hydrolytic cleavage of the Cbz and ketal moieties, and the resulting amino ketone underwent reductive amination using sodium borohydride to afford tricycle **184**. This compound was compared with natural lepadiformine and was found to be different.

To prepare two other stereoisomers of **14**, cycloadduct **182** was transformed in three steps to an epimeric mixture of methyl esters **185** (Scheme 34). Three additional steps served to provide pure samples of isomeric compounds **186** and **188**. A deprotection/reductive amination sequence then led to tricycles **187** and **189**, which had spectra that did not match those of lepadiformine.

**5.1.4 Kibayashi Synthesis of Racemic Structure 14**—Kibayashi and coworkers used an intramolecular nitroso Diels-Alder-based strategy for preparation of ( $\pm$ )-**14** similar to that previously discussed for synthesis of racemic cylindricine C (Cf. Schemes 20 and 21).<sup>6a,b</sup> In this approach, it was possible to reverse the stereoselectivity of the key [4+2]-cycloaddition step relative to that in Scheme 21 by introducing a bromine substituent into the diene. Thus, unsaturated aldehyde **190** was first brominated to afford a 1.4:1 mixture of *E:Z* isomers **191** (Scheme 35). This compound was processed via an eight-step sequence, including a separation of the geometric isomers, to eventually produce the bromodiene hydroxamic acid **192** required for the cycloaddition. The best way to conduct the Diels-Alder reaction was to first oxidize hydroxamic acid **192** to the corresponding acylnitroso compound with tetrapropylammonium periodate, and then trap it as a [4+2]-cycloadduct with 9,10-dimethylantracene. Thermal reversion of this reaction, followed by intramolecular cycloaddition led to a 1:5.5 mixture of adducts **194** and **196**. It was suggested that transition state conformation **193**, leading to the minor isomer **194**, is destabilized relative to the alternative conformation **195** by a severe steric

interaction between the bromine on the diene and the tether. Adduct **196** has the requisite A/B-ring *cis*-1-azadecaline stereochemistry for cylindricine-type structures.

Adduct **196** was utilized for the synthesis of **14**, and was first hydrogenated to afford tricyclic alcohol **197** (Scheme 36). The N-O bond of this intermediate was cleaved with sodium amalgam to generate diol lactam **198**, which was next converted to epoxide **199**. Treatment of intermediate **199** with sodium hydride led to intramolecular 5-*exo* attack of the lactam nitrogen on the epoxide to form the C-ring, and after alcohol protection tricyclic lactam **200** was generated in good overall yield. In order to further elaborate the B-ring, this lactam was reduced to the ring-opened amino alcohol, which was protected as Cbz derivative **201** and transformed in three straightforward steps into ketone **202**. Removal of the Cbz protecting group and reductive amination then provided the requisite tricycle **204**. This process occurs via reduction of intermediate iminium salt **203** from the least hindered face. Finally, hydrolytic cleavage of the MOM protecting group afforded racemic compound **14**.

## 5.2 Synthesis of Authentic Lepadiformine 15a

**5.2.1 Kibayashi Synthesis of (±)-Lepadiformine**—Using the key nitroso Diels-Alder-derived intermediate **115** which had been used in their synthesis of fascicularin (Cf. Scheme 22), the Kibayashi group prepared structure **15a** and found that its hydrochloride salt was in fact identical to lepadiformine, thereby unambiguously establishing the structure of this alkaloid.<sup>6b</sup> Oxazine **115** was reduced with sodium amalgam and the resulting alcohol was converted to the mesylate, which upon treatment with potassium *t*-butoxide cyclized with inversion to provide tricyclic lactam **205** (Scheme 37). Reductive ring opening of this lactam, and protection of the resulting amine as its Cbz derivative led to alcohol **206**. The primary alcohol **206** was oxidized to the aldehyde and addition of hexylmagnesium bromide afforded alcohols **207** and **208** in a 1:2 ratio. The minor adduct **207** could be inverted to **208** by a Mitsunobu procedure. Removal of the Cbz group from **208**, followed by cyclization of the resulting amino alcohol with inversion afforded tricycle **209**. Finally, removal of the MOM group with methanolic HCl led to racemic **15a**. The hydrochloride salt of the free base **15a** was prepared and was found to be identical with natural lepadiformine. It should be noted that natural lepadiformine was originally isolated by evaporation of an aqueous HCl solution. In addition, X-ray analysis of the synthetic lepadiformine showed that the B-ring exists as a twist boat.

**5.2.2 Funk Synthesis of (±)-Lepadiformine**—Greshock and Funk applied their 2-amidoacrolein-based methodology to a total synthesis of the lepadiformine structure **15a**.<sup>33</sup> Thus, thermolysis of dioxin **210** produced amidoacrolein **211** via a retro Diels-Alder process (Scheme 38). This compound underwent a [4+2]-cycloaddition reaction with diene **212** under high pressure to afford *endo* adduct **213** as a single regio- and stereoisomer. The aldehyde functionality of **213** was reduced, and catalytic hydrogenation served to both reduce the alkene and remove the *N*-benzyl group. The resulting alcohol sulfonamide was converted to the *N*-tosylaziridine **214** by a Mitsunobu-type process. This compound could then be coupled with excess allylmagnesium bromide, followed by acetal hydrolysis, to generate alkene aldehyde **215** in high overall yield.

The hexyl group was introduced into this aldehyde using hexylmagnesium bromide in the presence of ytterbium triflate to afford **216** as the major product with 10.9:1 stereoselectivity. In the absence of the ytterbium catalyst the stereoselectivity was significantly lower. It was suggested that metal chelation between the aldehyde carbonyl and the sulfonamide was responsible for the good selectivity in this addition. To complete the synthesis, alcohol **216** was first cyclized with inversion, and the tosyl group was removed to lead to bicyclic amino olefin **217**. Finally, treatment of **217** with iodine led to iodomethyl tricycle **218**, which upon

treatment with sodium hydroxide afforded racemic lepadiformine (**15a**). This final step probably proceeds via the aziridinium ion **219**.

**5.2.3 Weinreb Synthesis of (±)-Lepadiformine**—In 2001 Weinreb et al. disclosed an approach to the structure **15a** of lepadiformine which featured a stereoselective intramolecular spirocyclization of an *N*-acyliminium ion with an allylic silane.<sup>34</sup> The substrate **222** for this reaction was easily prepared from cyclic imine **220** by metallation followed by alkylation with allylsilane iodide **221**, then acylation with *o*-nitrobenzoyl chloride (Scheme 39). Exposure of enamides **222** to trifluoroacetic acid led to a single spirocycle **224** in 57% overall yield based upon imine **220**. This cyclization most likely occurs via an *N*-acyliminium ion which cyclizes through the preferred conformation **223** having both the allylsilane and *N*-acylimine groups pseudo-equatorial. The alternative conformation **225**, which would lead to diastereomer **226**, is probably destabilized relative to **223** by a steric interaction between the bulky pseudo-axial *N*-acyl group and the axial hydrogens of the newly forming six-membered ring.

Using the radical transposition methodology previously developed by the Weinreb group,<sup>35</sup> functionalization of compound **224** was next investigated in order to provide a handle for introduction of the hydroxymethyl group of the alkaloid. To effect this transformation, the nitro functionality of **224** was first reduced to the *o*-aminobenzamide **227** which was then subjected to the conditions for conversion of such functionality to an  $\alpha$ -methoxybenzamide, thereby cleanly producing **228** (Scheme 40). It was then possible to alkylate the acyliminium ion **230** derived from  $\alpha$ -methoxybenzamide **228** with the cuprate from (allyldimethylsilyl)methylmagnesium bromide (**229**) to afford an 87% yield of a 7:1 mixture of epimeric products, with the desired silane **231** being the major stereoisomer. This transformation presumably occurs via preferred attack of the cuprate from the least congested face of *N*-acyliminium ion **230**. A Tamao oxidation then allowed conversion of silane **231** to the hydroxymethyl compound **232**. The alkene **232** was hydroformylated, the resulting aldehyde was transformed to the acetal, and the *N*-benzoyl group was removed by basic hydrolysis to give amino alcohol **233**.

The remaining phase of the synthesis involved construction of the lepadiformine B-ring. Thus, amino alcohol **233** was converted to the corresponding amine benzyl ether and then treated with acid to afford the unstable tricyclic enamine **234** (Scheme 41). This enamine could be converted to the more stable  $\alpha$ -amino nitrile **235** which appears to contain a twist boat B-ring. The hexyl chain could be introduced by treating this amino nitrile with hexylmagnesium bromide in the presence of boron trifluoride etherate in THF producing a 3:1 mixture of the desired alkylation product **238** along with its C(2) epimer **240**. The stereoelectronic principles summarized by Stevens were used to rationalize the results of this reaction.<sup>36</sup> Thus, *anti*-periplanar addition of the Grignard reagent to the iminium salt **236** from the preferred “axial” direction (path **A**) will generate an initial chair B-ring as in **237**, and this compound would then undergo conformational inversion to the more stable lepadiformine twist boat conformation **238**. Nucleophilic attack on the iminium ion **236** from the opposite face (path **B**), however, will initially produce an unfavorable B-ring boat **239**, which then flipped to the more stable chair conformer **240** now with an equatorial hexyl group. To complete the synthesis, reductive cleavage of the benzyl ether group from tricycle **238** afforded racemic lepadiformine (**15a**).

**5.2.4 Weinreb Synthesis of (-)-Lepadiformine**—The basic strategy outlined above for synthesis of racemic lepadiformine was extended to achieve an enantioselective total synthesis of the alkaloid, which also established its absolute configuration.<sup>34b</sup> Therefore, readily prepared (*S*)-Boc-lactam **241**, derived from (*S*)-pyroglutamic acid, was coupled with lithio (*Z*)-allylsilane **242** to give adduct **243** (Scheme 41). Without isolation, this intermediate was then exposed to boron trifluoride acetic acid complex in methylene chloride to provide spirocycle **245** as a single stereoisomer in 52% overall yield via selective attack by the

allylsilane onto the less encumbered face of *N*-acyliminium ion **244**. Spirocycle **245** was converted into (-)-lepadiformine (**15a**) as had been done for the racemic compound (Cf. Schemes 40 and 41). Comparison of the optical rotation of the synthetic material with that of the natural product, along with comparison of the proton NMR spectra of their Mosher esters, proved the absolute configuration of the alkaloid to be as shown in structure **15a**.

**5.2.5 Kibayashi Synthesis of (-)-Lepadiformine**—Kibayashi et al. described a total synthesis of (-)-lepadiformine which made use of a common intermediate also utilized in the syntheses of (+)-cylindricine C and (-)-fasicularin described above.<sup>19,37</sup> Thus, enantiopure allylic alcohol **65** was hydrogenated to produce alcohol **246** (Scheme 43). Removal of the Boc group of **246** and cyclization of the resulting amino alcohol with inversion led to tricycle **247**. Finally, hydrogenolysis of the benzyl group yielded (-)-lepadiformine (**15a**). This material was found to be identical to the natural alkaloid by chiral HPLC.

**5.2.6 Hsung Synthesis of (-)-Lepadiformine**—The Hsung group has used intermediate **77**, prepared during their enantioselective total synthesis of (+)-cylindricine C, to complete a synthesis of (-)-lepadiformine.<sup>20</sup> Sodium borohydride reduction of ketone **77** provided the alcohol which was converted into the corresponding xanthate **248** (Scheme 44). Barton-McCombie deoxygenation of **248**, followed by removal of the silyl group then afforded (-)-lepadiformine (**15a**) in good yield.

**5.2.7 Kim Formal Synthesis of (-)-Lepadiformine**—In 2006, Kim et al. reported a new approach to (-)-lepadiformine (**15a**) which uses an amino acid ester-enolate Claisen rearrangement and a ring closing metathesis as key steps.<sup>38</sup> The synthesis made use of enantiomerically pure acid **249**, which can be obtained in eight steps from (*S*)-pyroglutamic acid (Scheme 47). This acid was first converted to (*E*)-allylic ester **250**, which exposed to lithium hexamethyldisilazide and *t*-butyldimethylsilyl chloride to generate the silylketene acetal **251**. This intermediate undergoes a Claisen rearrangement predominantly through the conformation shown to produce an 8:1 mixture of the desired olefin acid **252** along with its diastereomer at C(5, 10). Alkene acid **252** was then esterified, followed by hydroboration with 9-BBN, and the resulting borane was coupled with vinyl bromide to afford the homologated alkene **253**. The ester functionality of **253** could be transformed into alkene **254** in three straightforward steps.

The carbocyclic A-ring of the alkaloid was then formed in high yield by a ring closing metathesis reaction of diene **254** using the second generation Grubbs catalyst, leading to azaspirocyclohexene **255** (Scheme 46). Catalytic hydrogenation of the double bond of **255** produced **256**, and following desilylation, the resulting primary alcohol was oxidized to the corresponding aldehyde **257** using the Dess-Martin periodinane. Finally, treatment of **257** with *p*-toluenesulfonic acid in aqueous acetone led to removal of the Boc protecting group, and subsequent cyclization to the unstable tricyclic enamine **234**, previously prepared by the Weinreb group in their lepadiformine synthesis (Cf. Scheme 41). This enamine was then converted in situ to the more stable amino nitrile **235**, which has been converted to (-)-lepadiformine (**15a**).

## 6. Addendum

### 6.1 Hsung Synthesis of (-)-Cylindricine C

A recent paper from the Hsung group has described a new approach to (-)-cylindricine C which utilizes a pivotal aza-[3+3]-cycloaddition strategy to access the B-ring of the alkaloid.<sup>39</sup> This strategy is different from the one previously used for (+)-cylindricine C (Cf. Schemes 13,14). The source of chirality in this work was (*R*)-vinyl oxazoline **258**, prepared in five steps from L-serine (Scheme 47). Hydroboration of **258** with 9-BBN, followed by a Suzuki-Miyaura

coupling of the resulting borane with vinyl triflate **259** gave unsaturated ester **260**. This intermediate was then converted in three straightforward operations into alcohol **261**. The hydroxyl group of **261** was protected as the corresponding acetate, and the Boc group was subsequently removed. Coupling of the amine product with bromo- $\alpha$ -pyrone **262** led to amino pyrone **263**.

Compound **263** was then converted to aldehyde **264** (Scheme 48). The key step in the synthesis was the intramolecular cycloaddition of amino pyrone aldehyde **264**, which could be effected by heating with piperidinium acetate as catalyst to afford tetracycle **265**. This product was formed in 68% yield as a 9:1 mixture of stereoisomers, with the major isomer having the required configuration at C(10, 13) for the alkaloid. To continue the synthesis, pyrone **265** was treated with NCS in aqueous *t*-butanol to produce chlorohydrin **266** as a single stereoisomer (configuration not determined). Oxidation of alcohol **266** to the corresponding ketone, followed by reductive dechlorination led to ketone **267** having the necessary stereochemistry at C(5) for the cylindricines.  $\alpha$ -Pyrone ketone **267** could subsequently be partially reduced to afford dihydropyrone **268** as a 2:1 mixture of diastereomers. In an interesting transformation, reduction of intermediate **268** with sodium cyanoborohydride in the presence of either HCl or acetic acid led to a reductive decarboxylation product, which after removal of the silyl protecting group yielded vinylogous amide alcohol **269**. Finally, it was found that reduction of this vinylogous amide with sodium triacetoxyborohydride produced (-)-cylindricine C (**2**) stereoselectively in good yield. It might be noted that catalytic hydrogenation of **269** with the Crabtree catalyst afforded C(2)-epicylindricine C.

## 6.2 Renaud Synthesis of ( $\pm$ )-Lepadiformine

Schar and Renaud have recently reported a new approach to racemic lepadiformine which makes use of an interesting free radical carboazidation strategy developed by this group.<sup>40</sup> The synthesis began with cyclohexanone which was converted in a short, straightforward sequence into exo-methylene compound **270** (Scheme 49). Carboazidation of olefin **270** using the conditions shown in the scheme led to a 3:2 mixture of diastereomeric azido esters **271** and **272**. These isomers could be separated here, or used as the mixture for the ensuing reactions. Catalytic hydrogenation of the desired stereoisomeric azide **272** produced the corresponding amino ketone, which under the reaction conditions underwent stereoselective intramolecular reductive amination yielding bicyclic amino ester **273**. This intermediate could then be cyclized to tricyclic lactam **274** in 72% yield starting from the pure azide **272** (43% overall yield from the mixture of **271/272**).

To complete the synthesis it was necessary to introduce C(14) and its attendant stereochemistry into the system. Therefore, the tricyclic lactam **274** was first converted to thiolactam **275** (Scheme 50). This compound was then *S*-methylated, followed by addition of lithium 2-phenylacetylide leading to adduct **276**. Without isolation, this intermediate was exposed to lithium aluminum hydride, affording alkene **277** with high diastereoselectivity in 80% overall yield from thiolactam **275**. Finally, ozonolysis of **277** under acidic conditions, and subsequent reduction of the resulting aldehyde led to racemic lepadiformine (**15a**). This synthesis requires 10 steps starting from cyclohexanone and proceeds in 15% overall yield.

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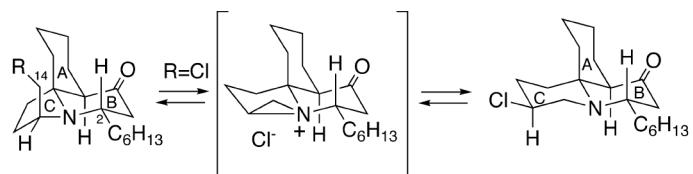
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## Biography

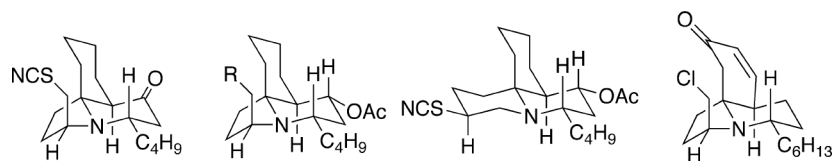




- 1 R=Cl cylindricine A  
 2 R=OH cylindricine C  
 3 R=OMe cylindricine D  
 4 R=OAc cylindricine E  
 5 R=SCN cylindricine F

6

7 cylindricine B



8 cylindricine G

9 R=SCN cylindricine H

10 R=NCS cylindricine I

11 cylindricine J

12 cylindricine K

FIGURE 1.

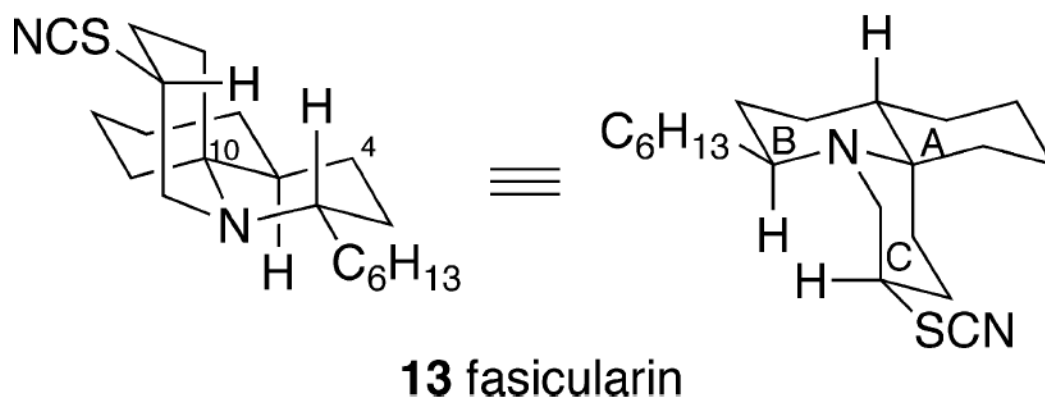


FIGURE 2.

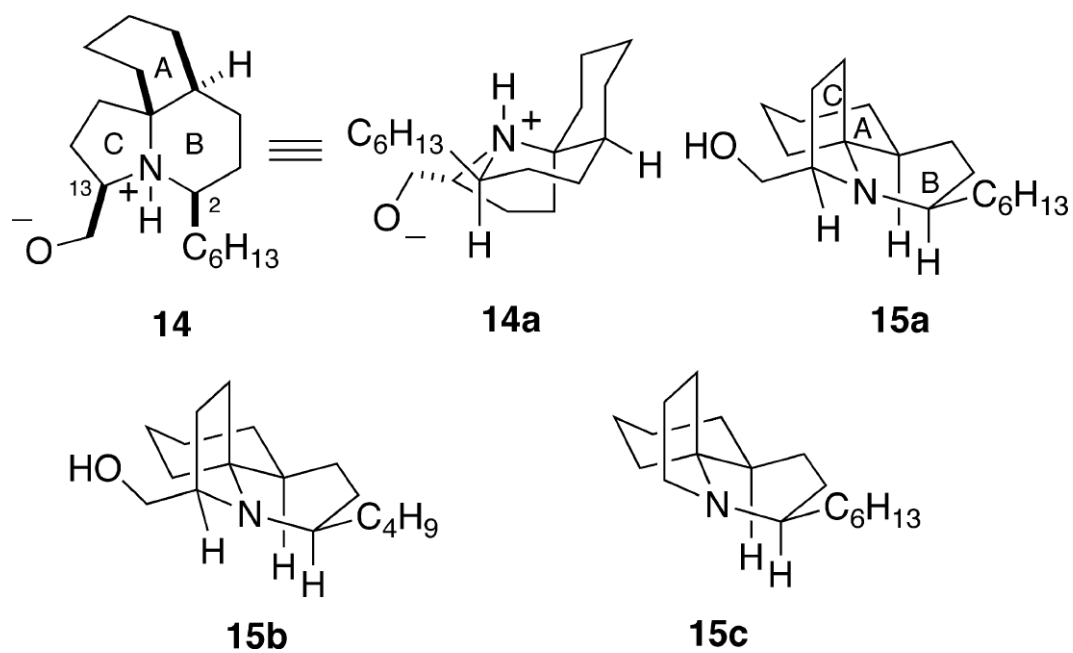
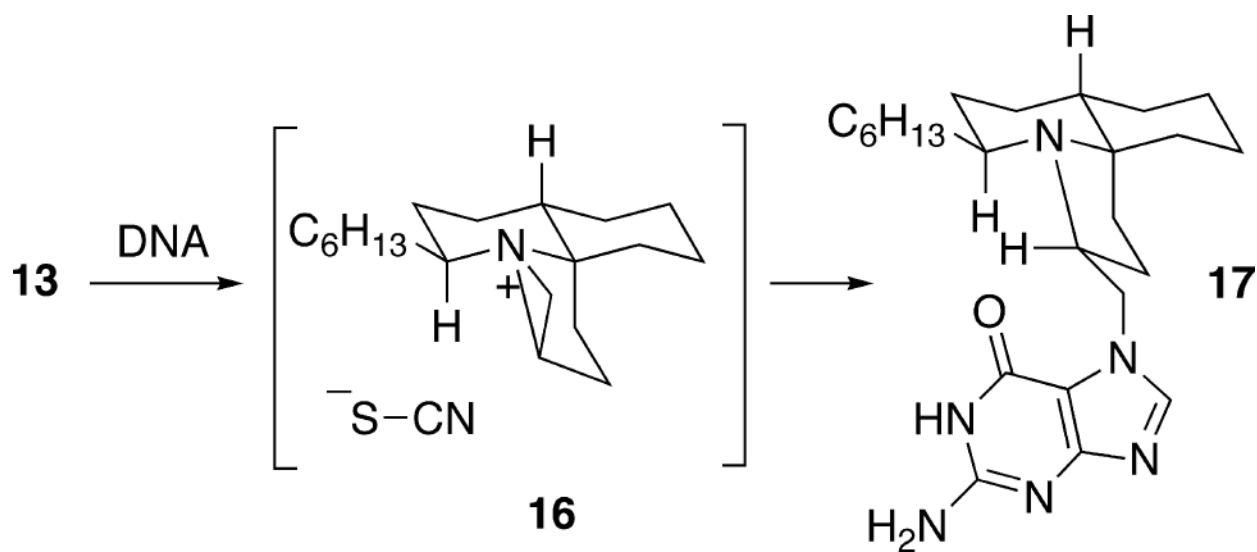
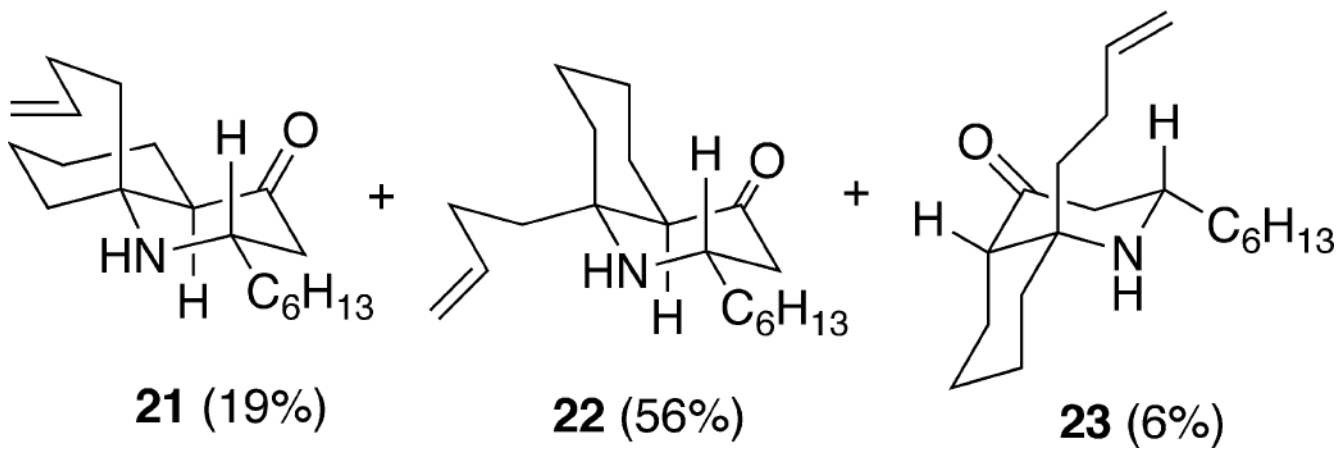
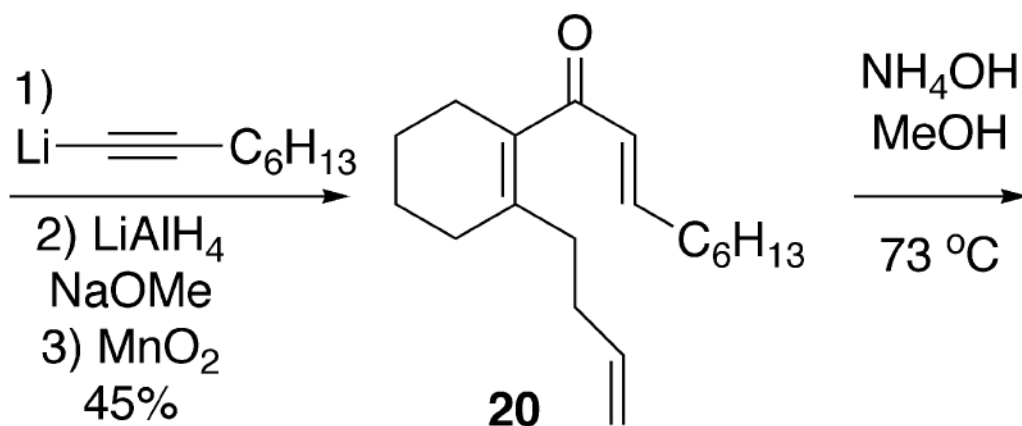
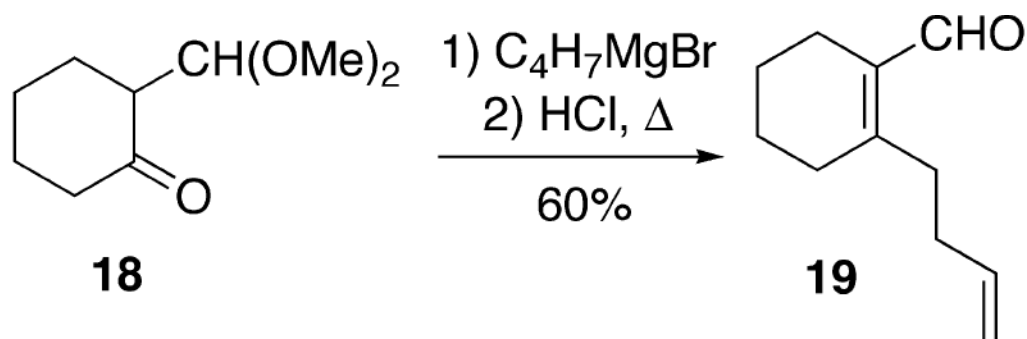


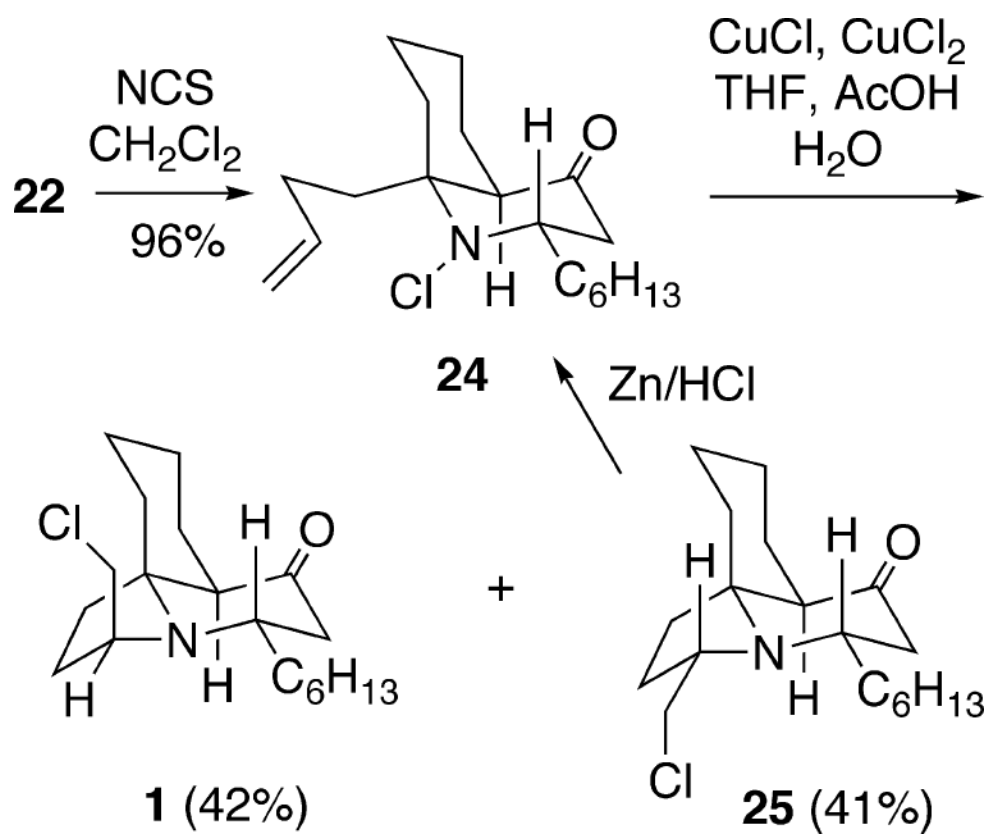
FIGURE 3.



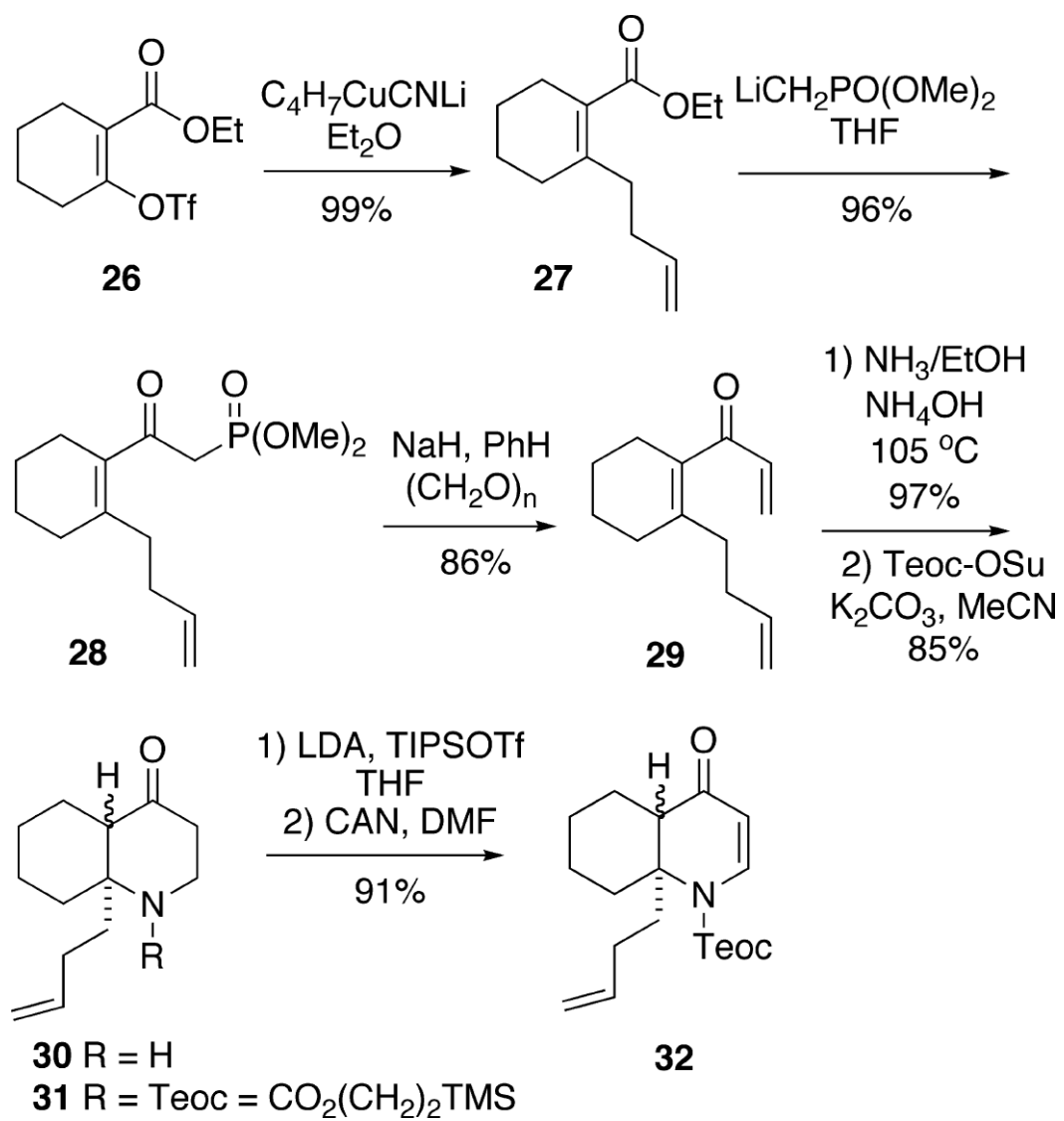
Scheme 1.



Scheme 2.

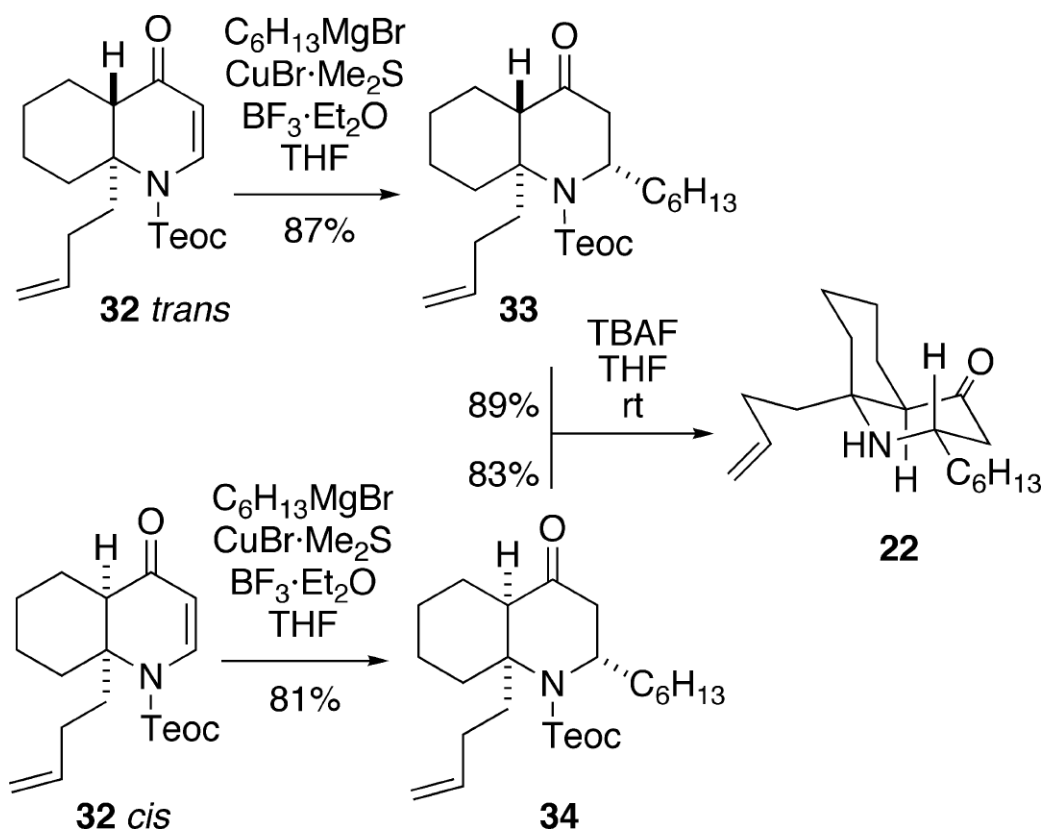


Scheme 3.

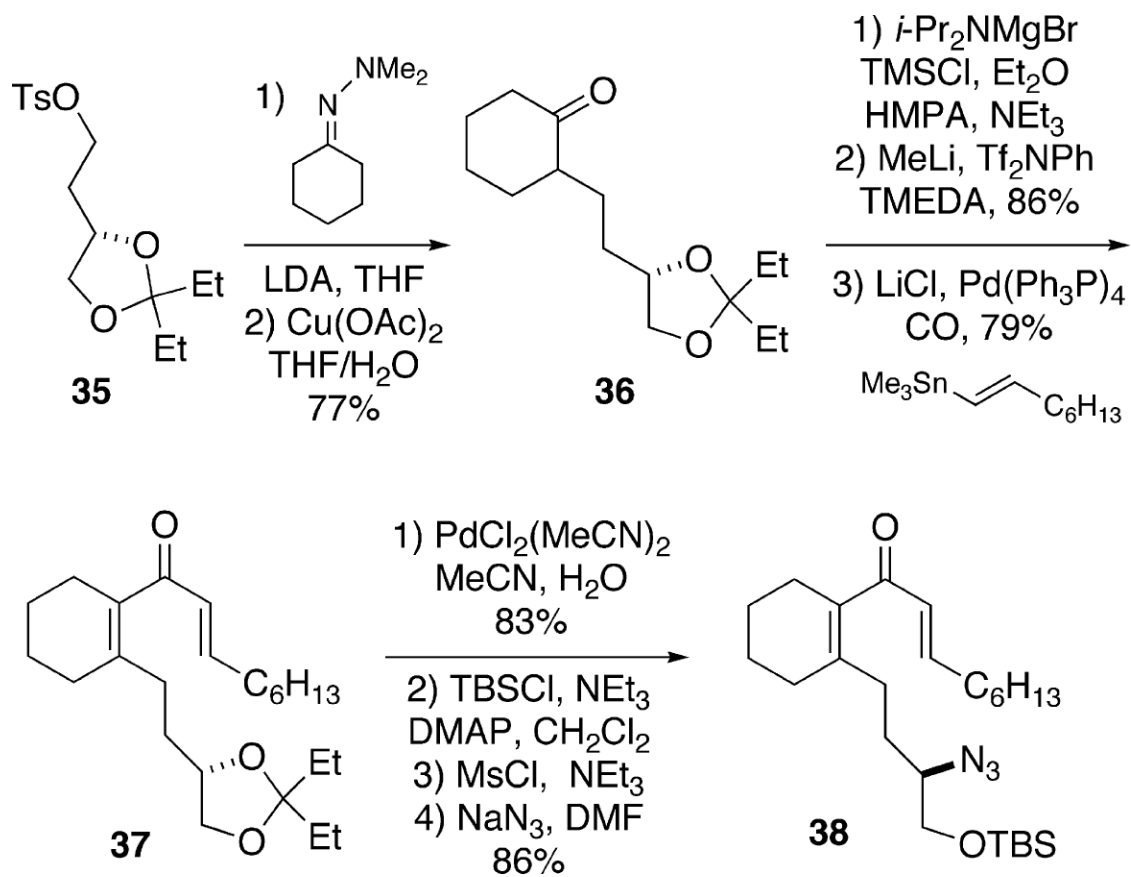


Scheme 4.

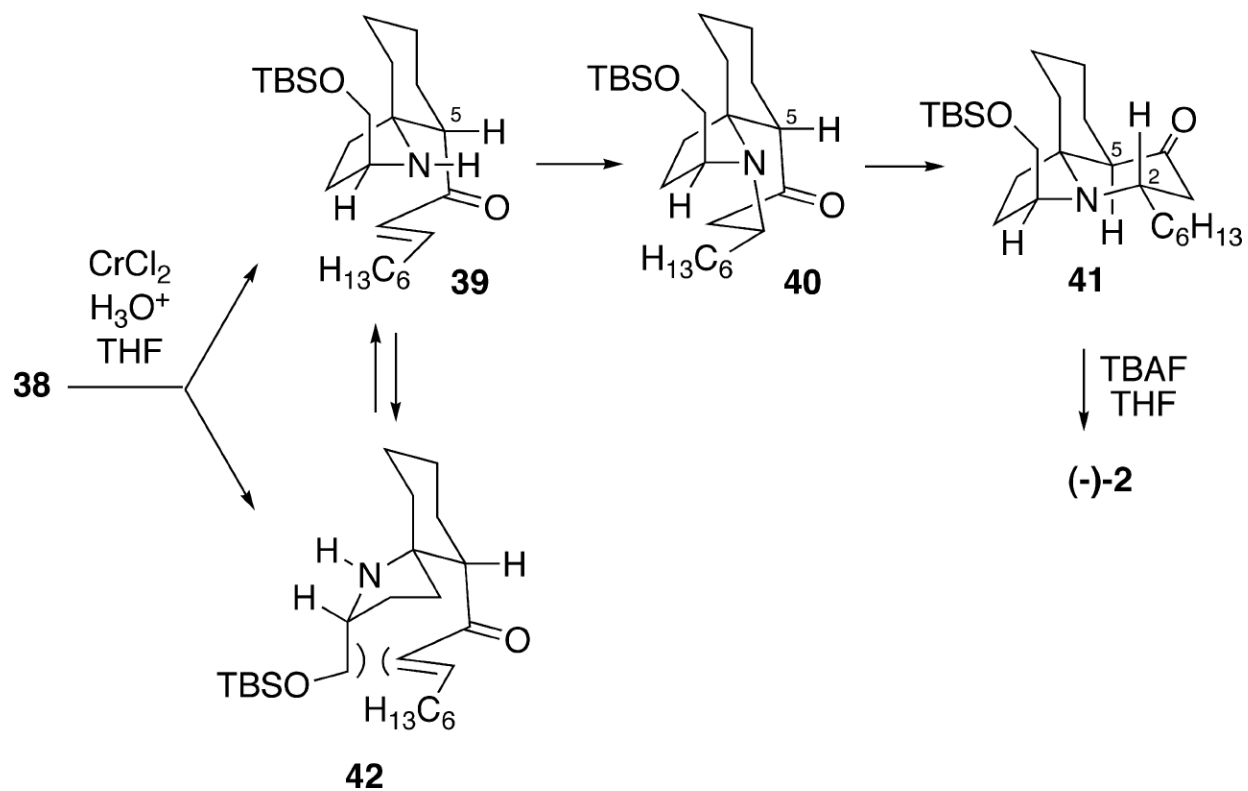




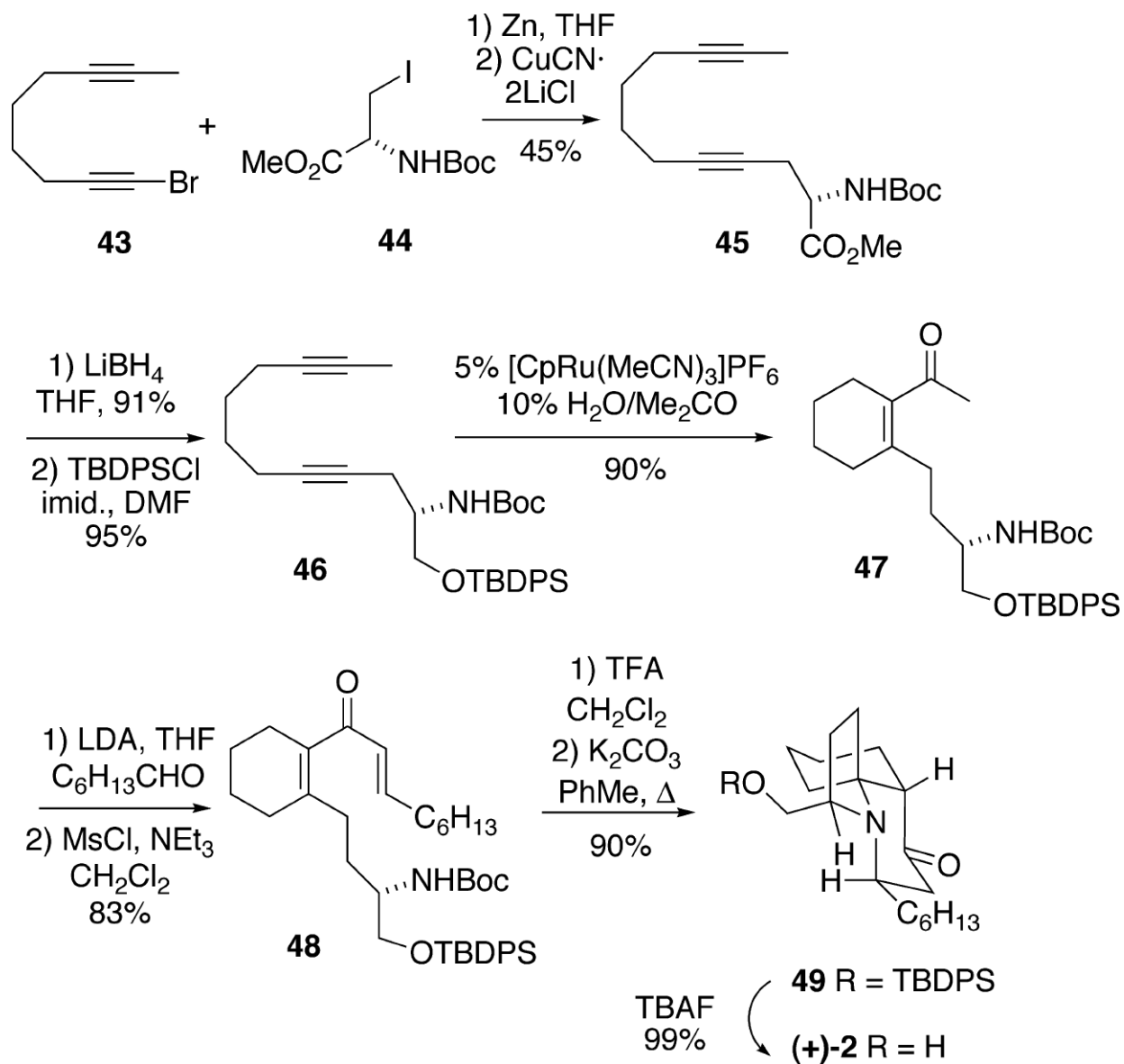
Scheme 5.



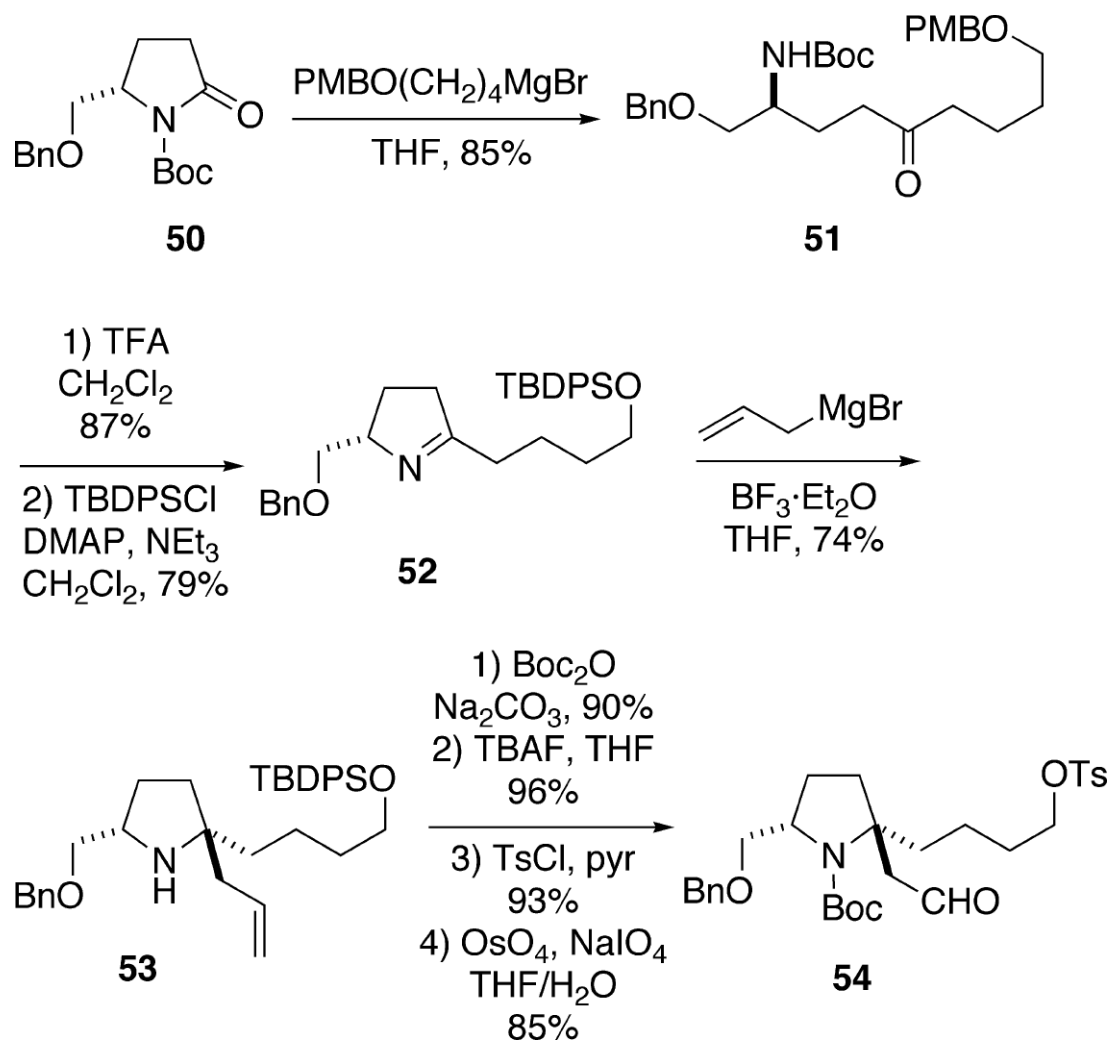
Scheme 6.



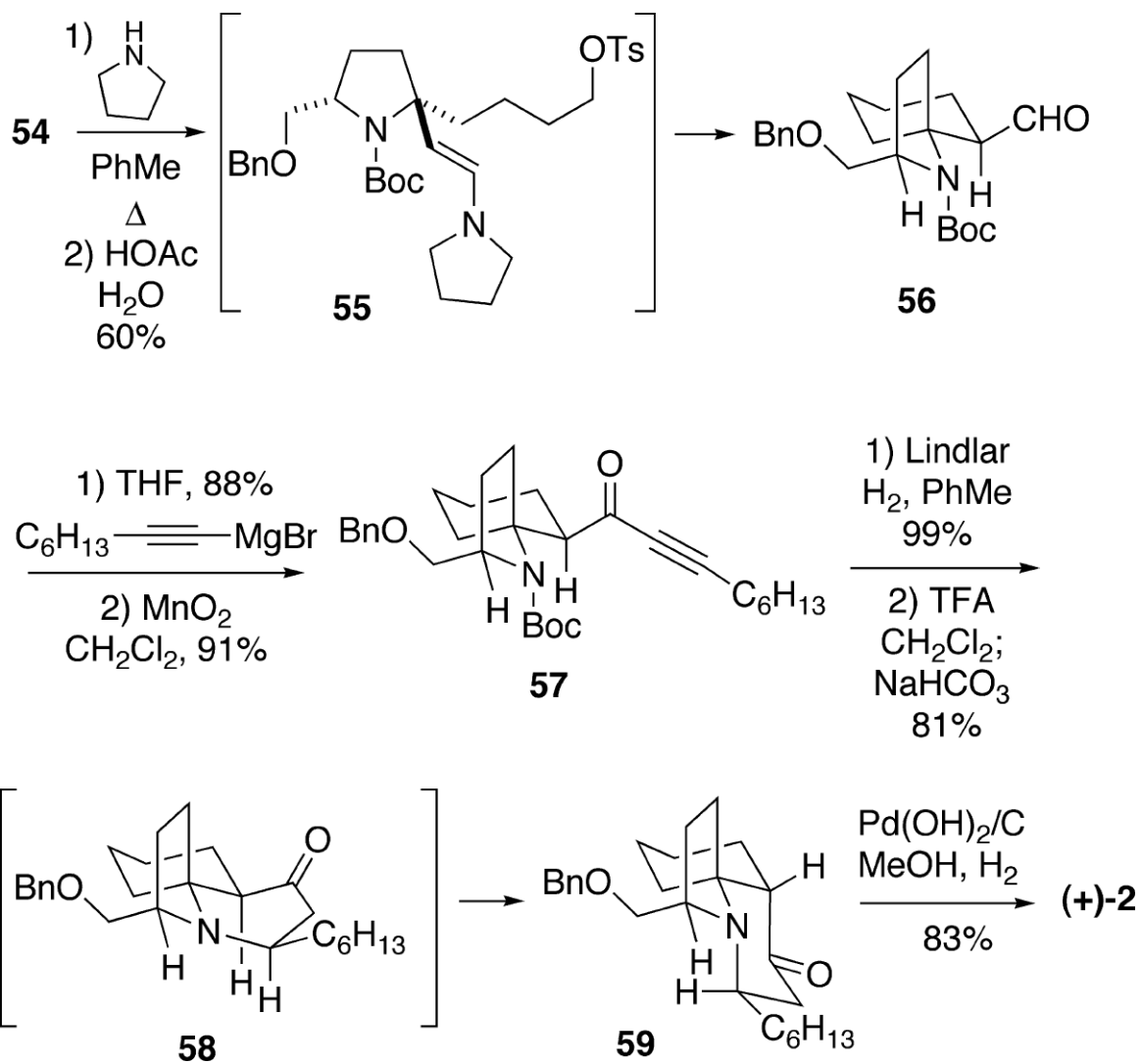
Scheme 7.



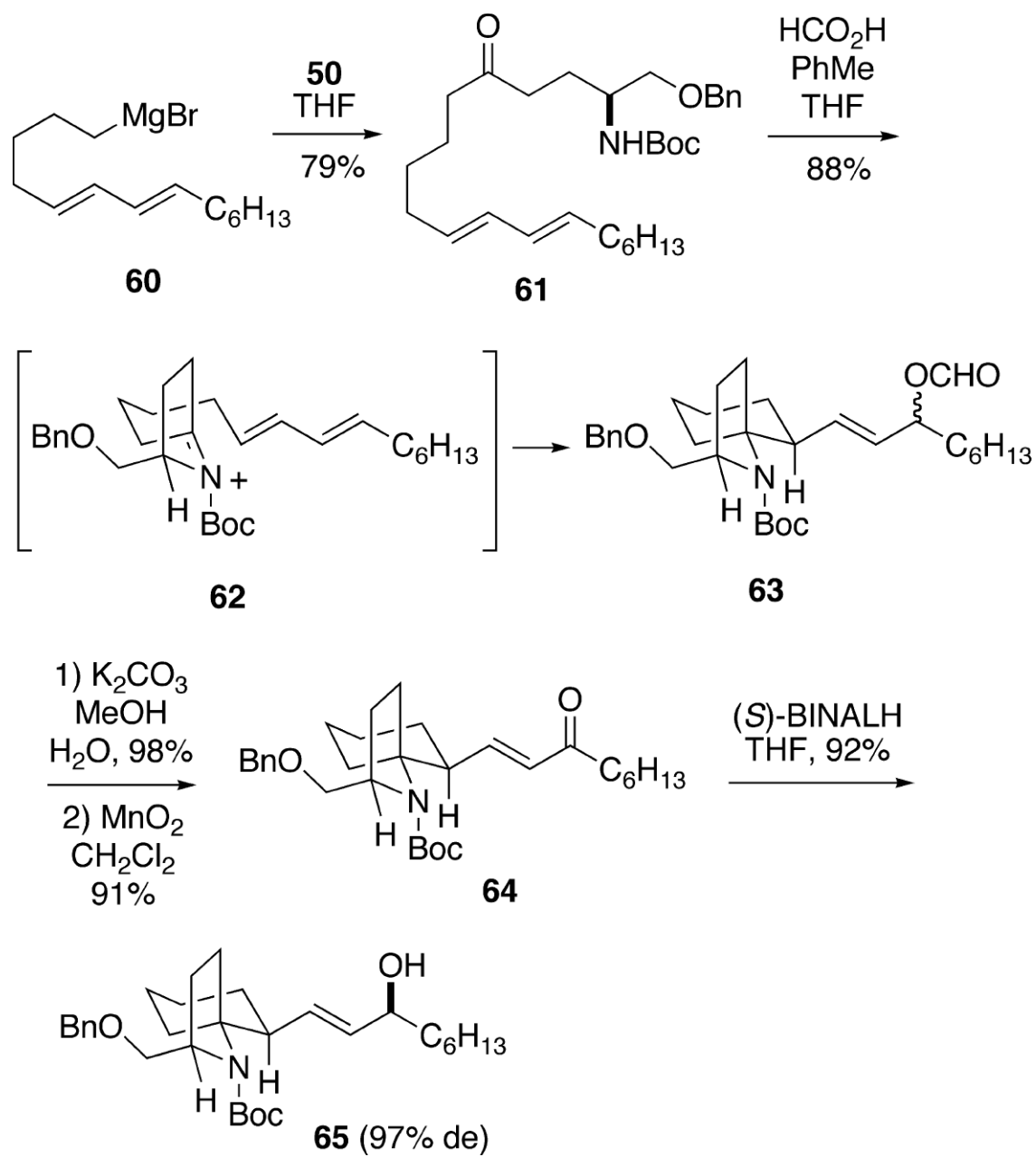
Scheme 8.



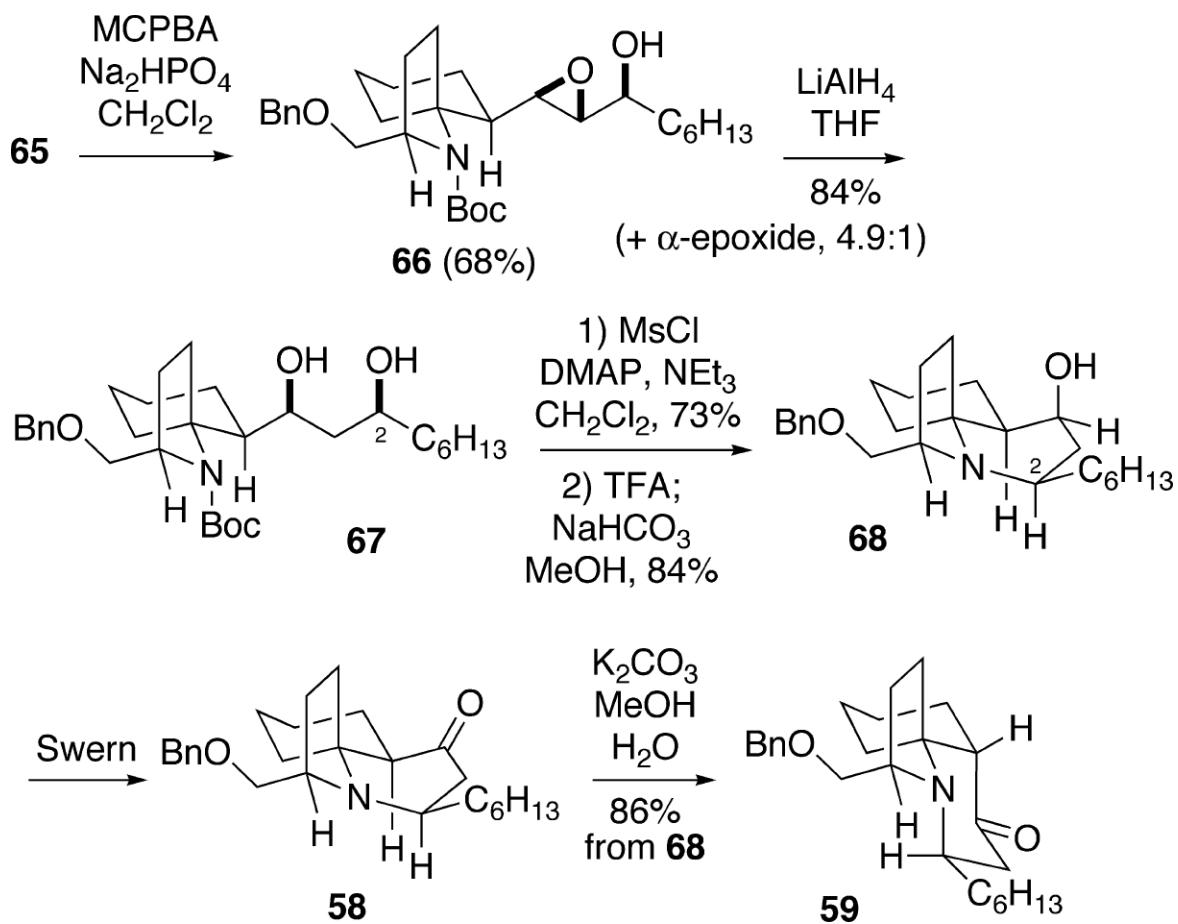
Scheme 9.



Scheme 10.

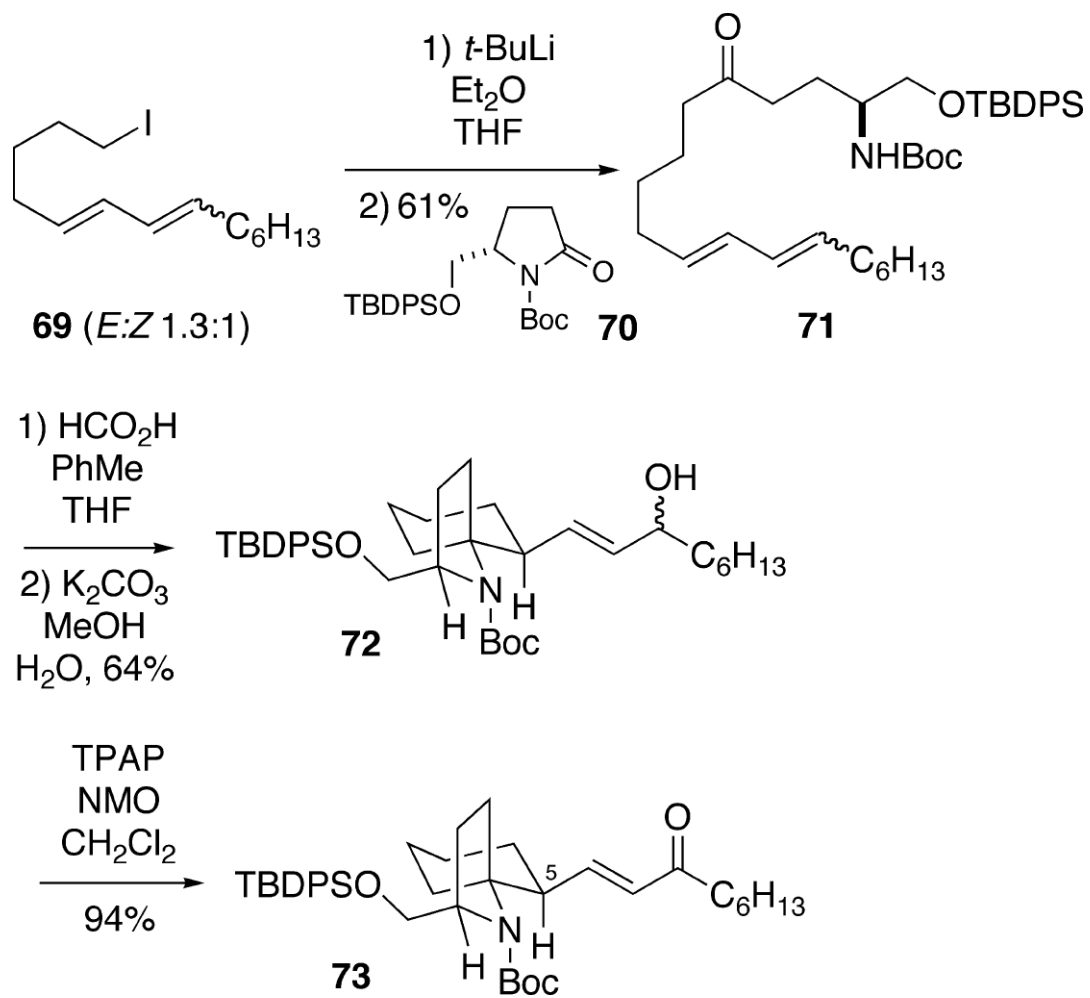


Scheme 11.

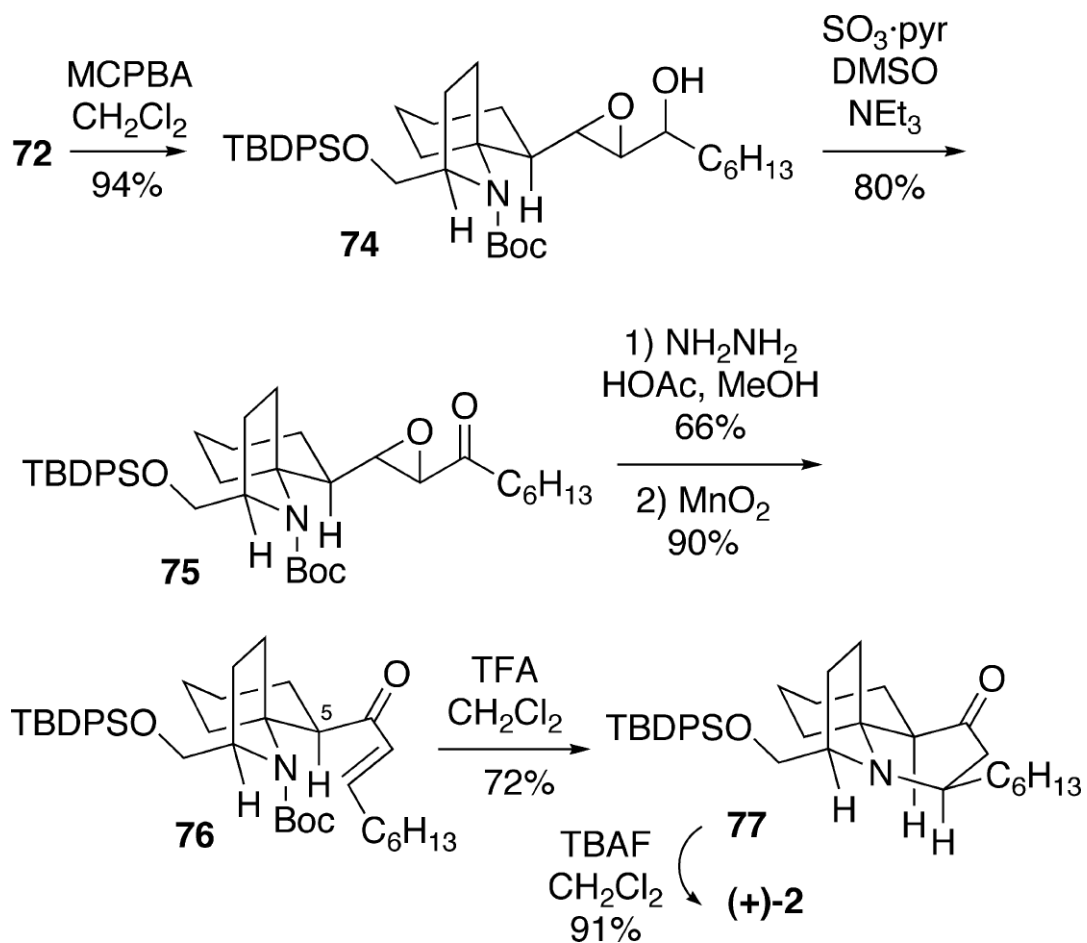


Scheme 12.

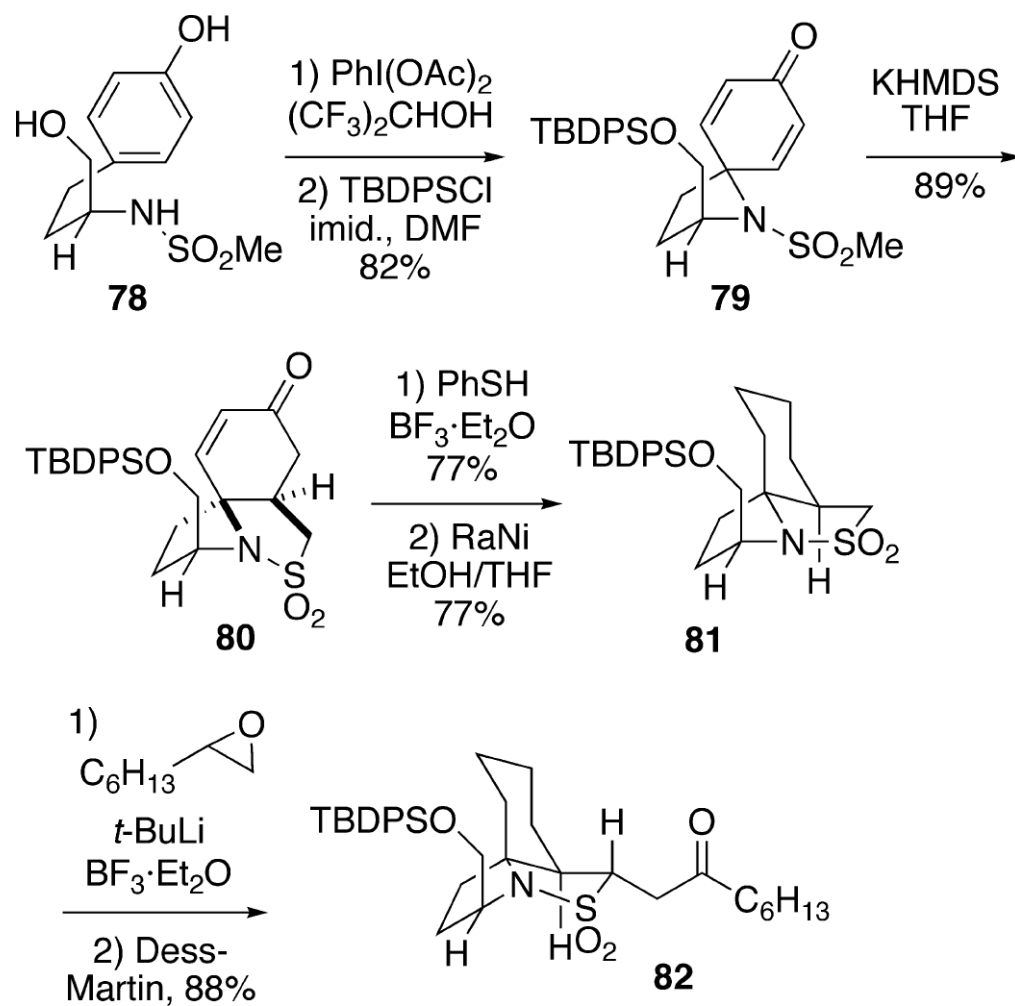




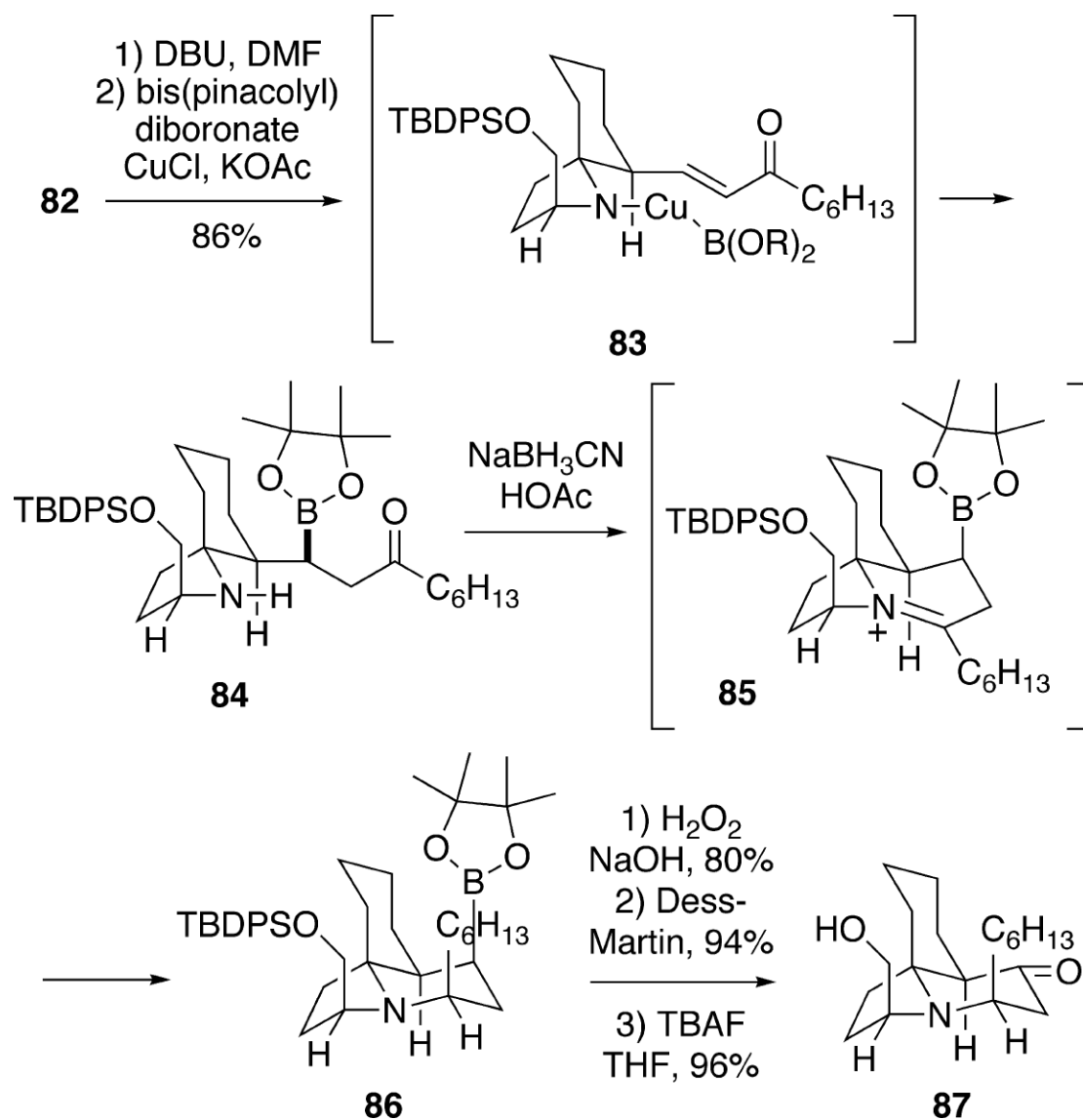
Scheme 13.



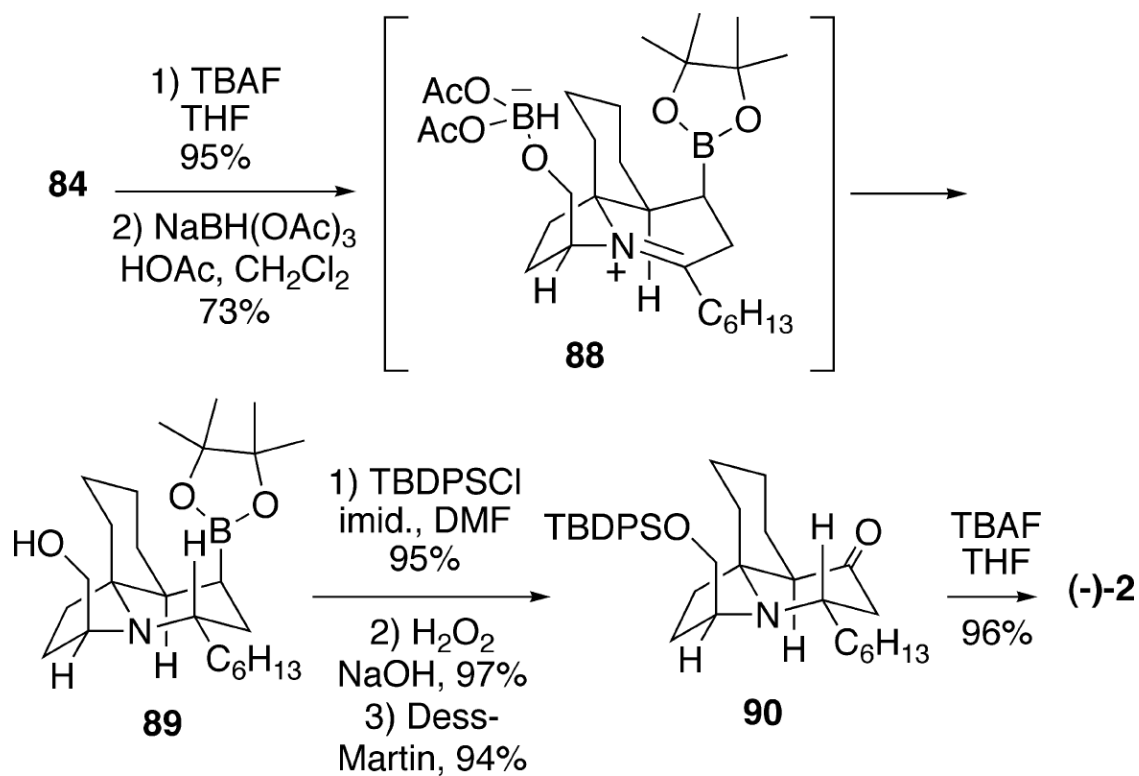
Scheme 14.



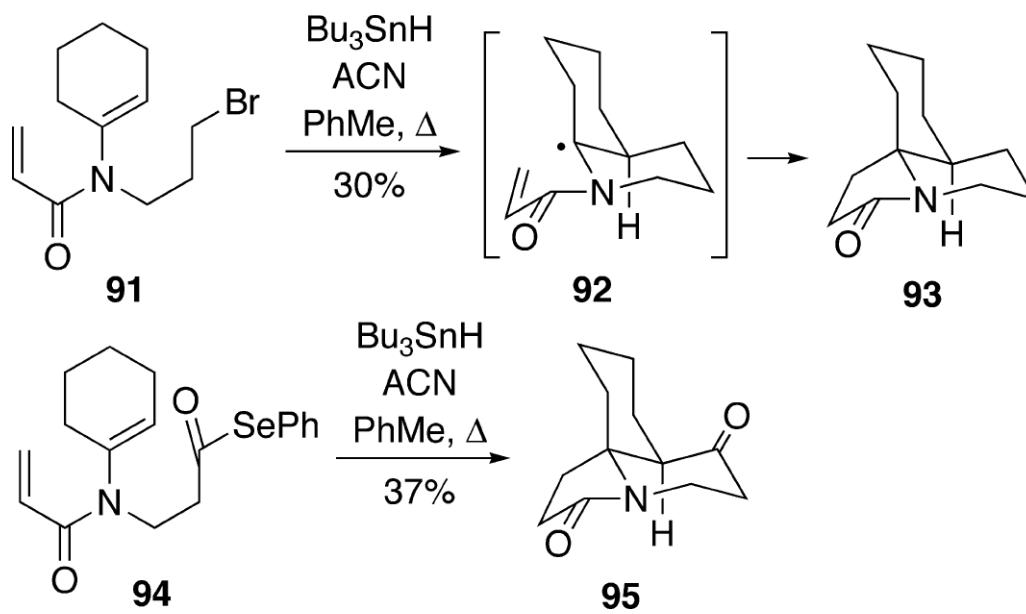
Scheme 15.



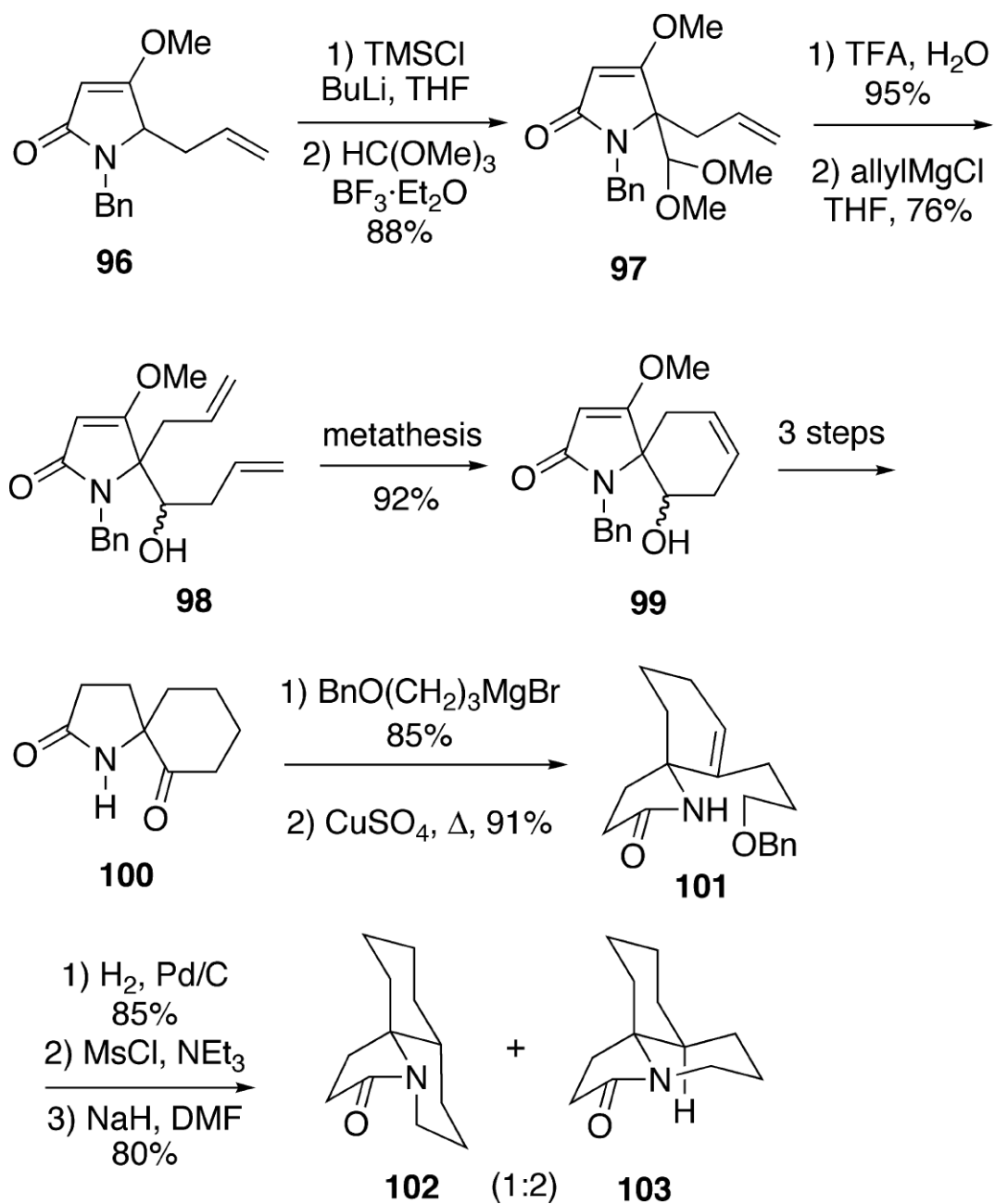
Scheme 16.



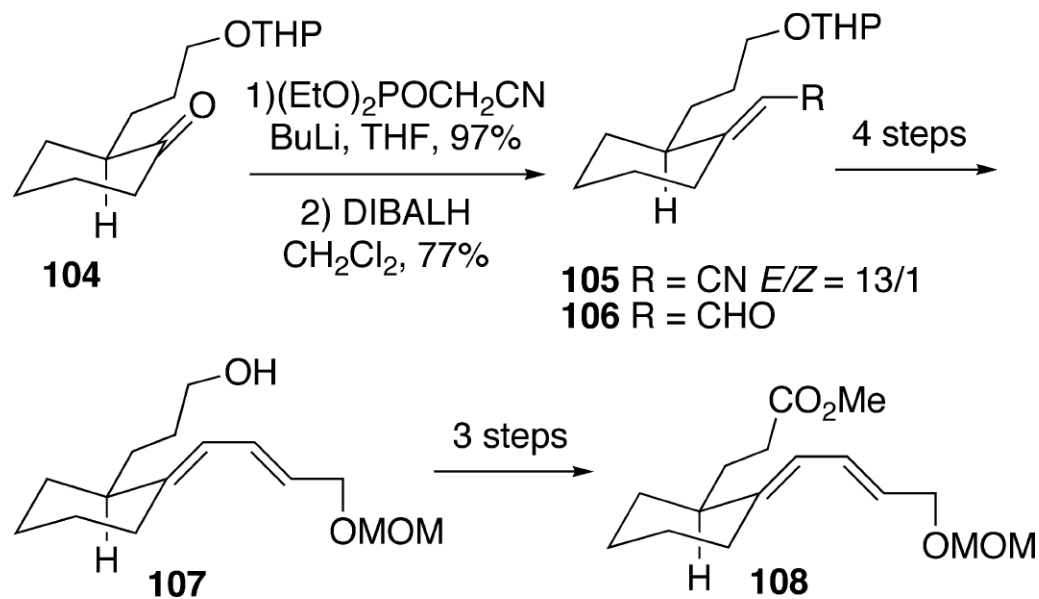
Scheme 17.



Scheme 18.

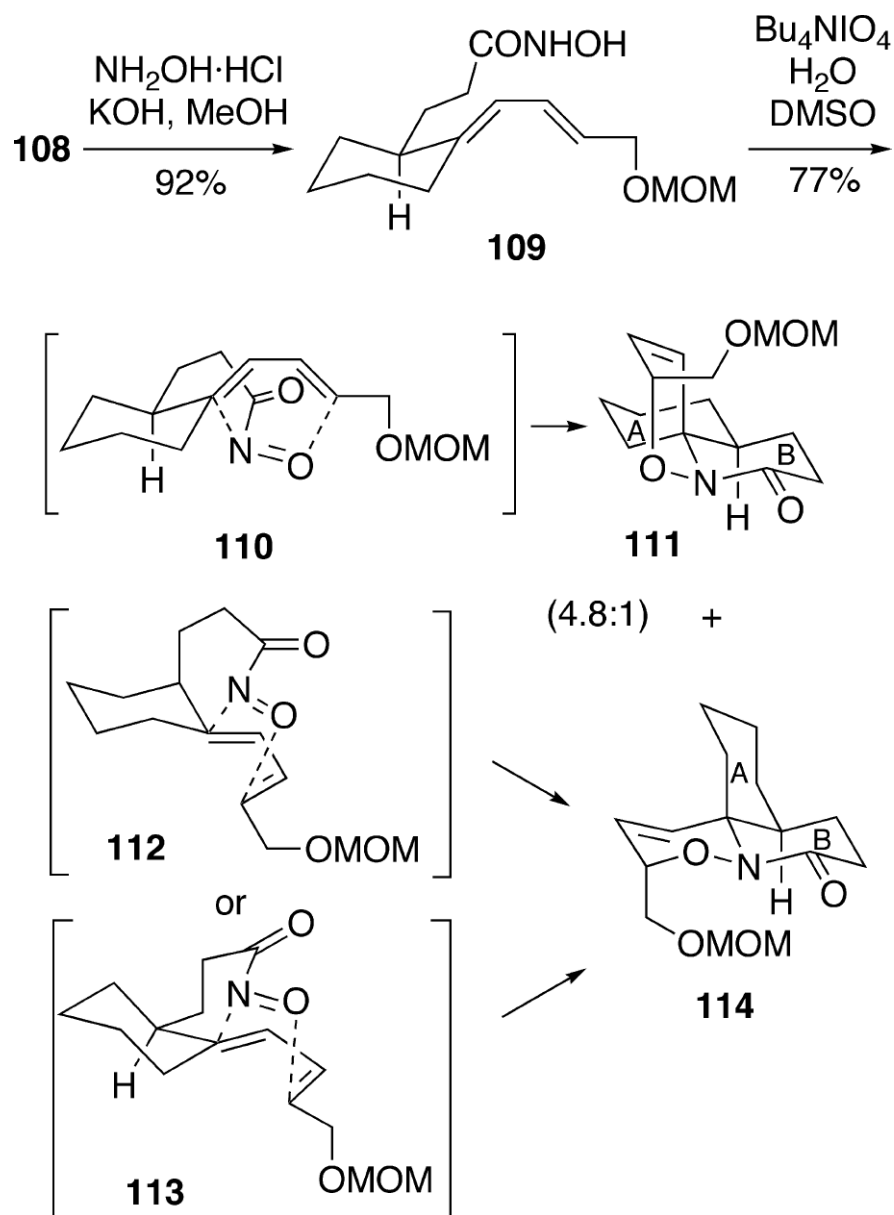


Scheme 19.

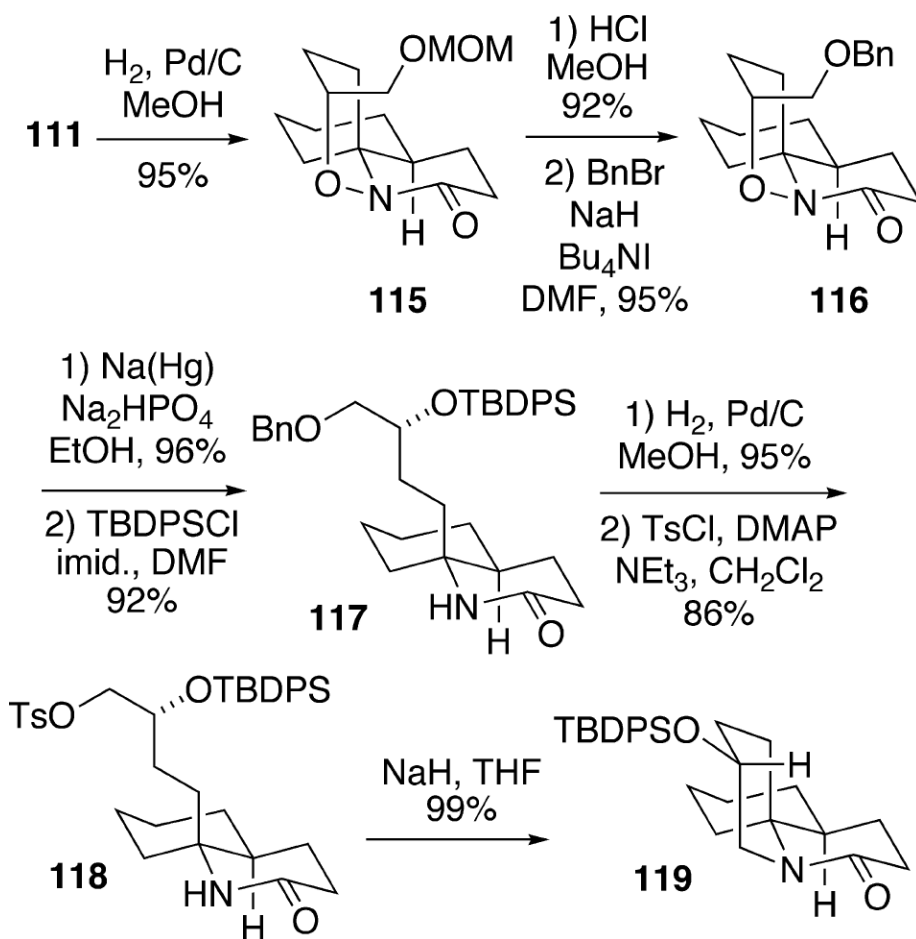


Scheme 20.

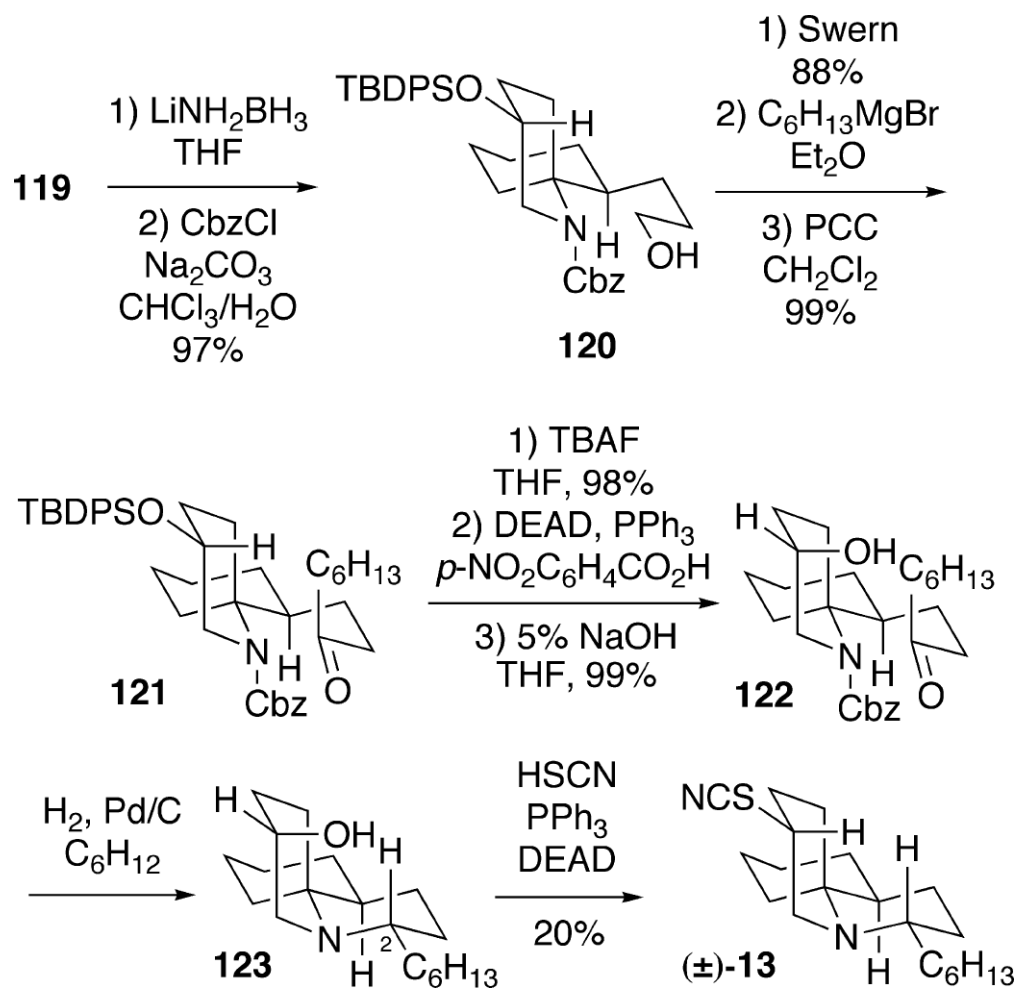




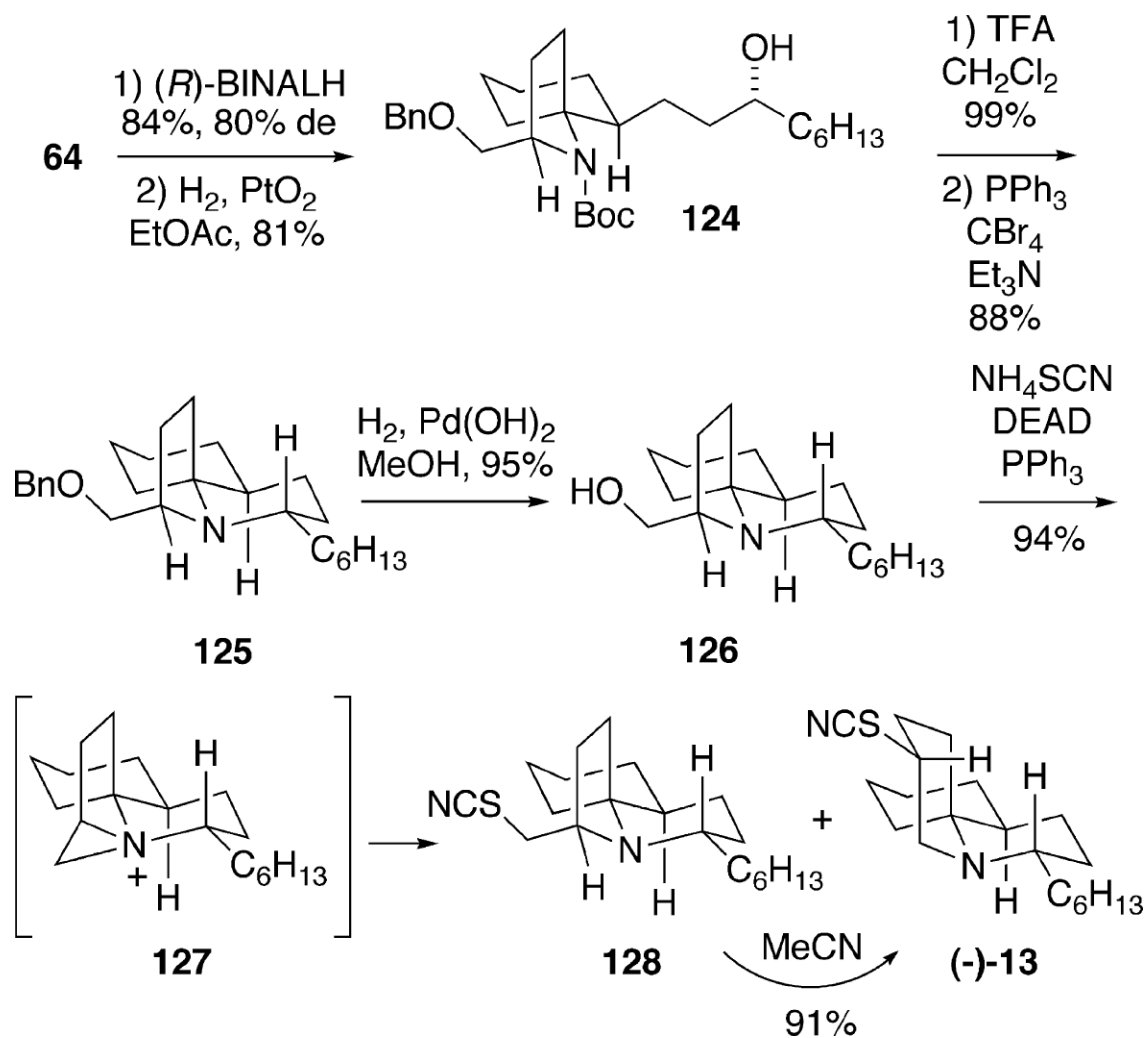
Scheme 21.



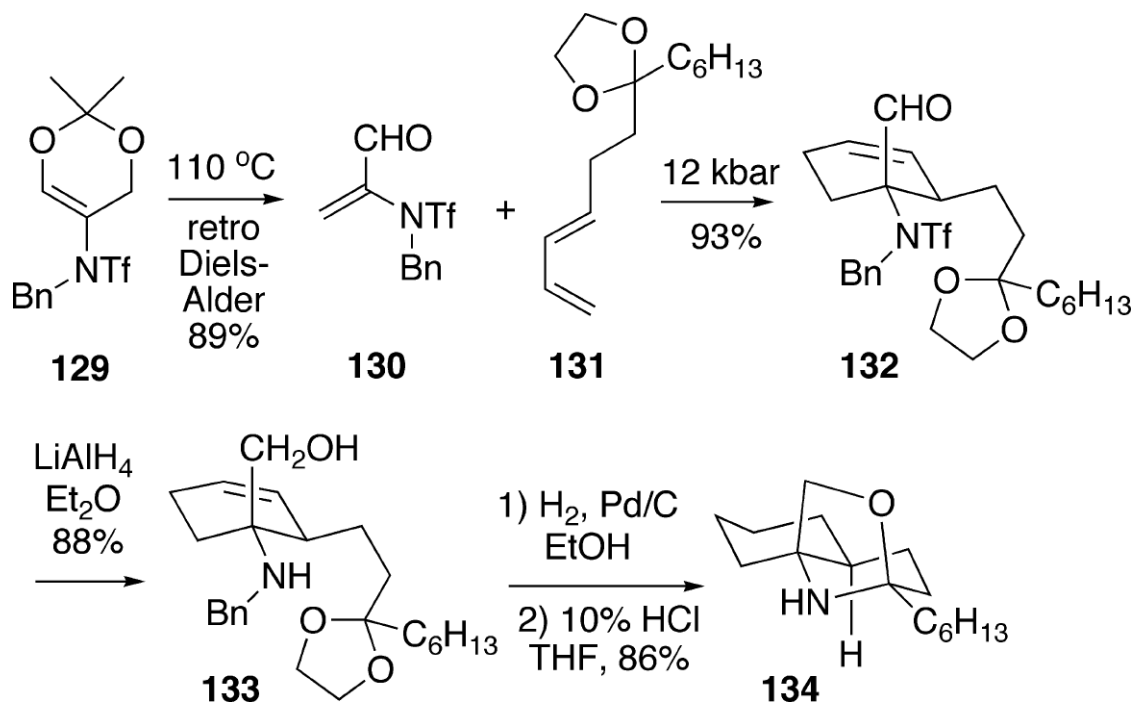
Scheme 22.



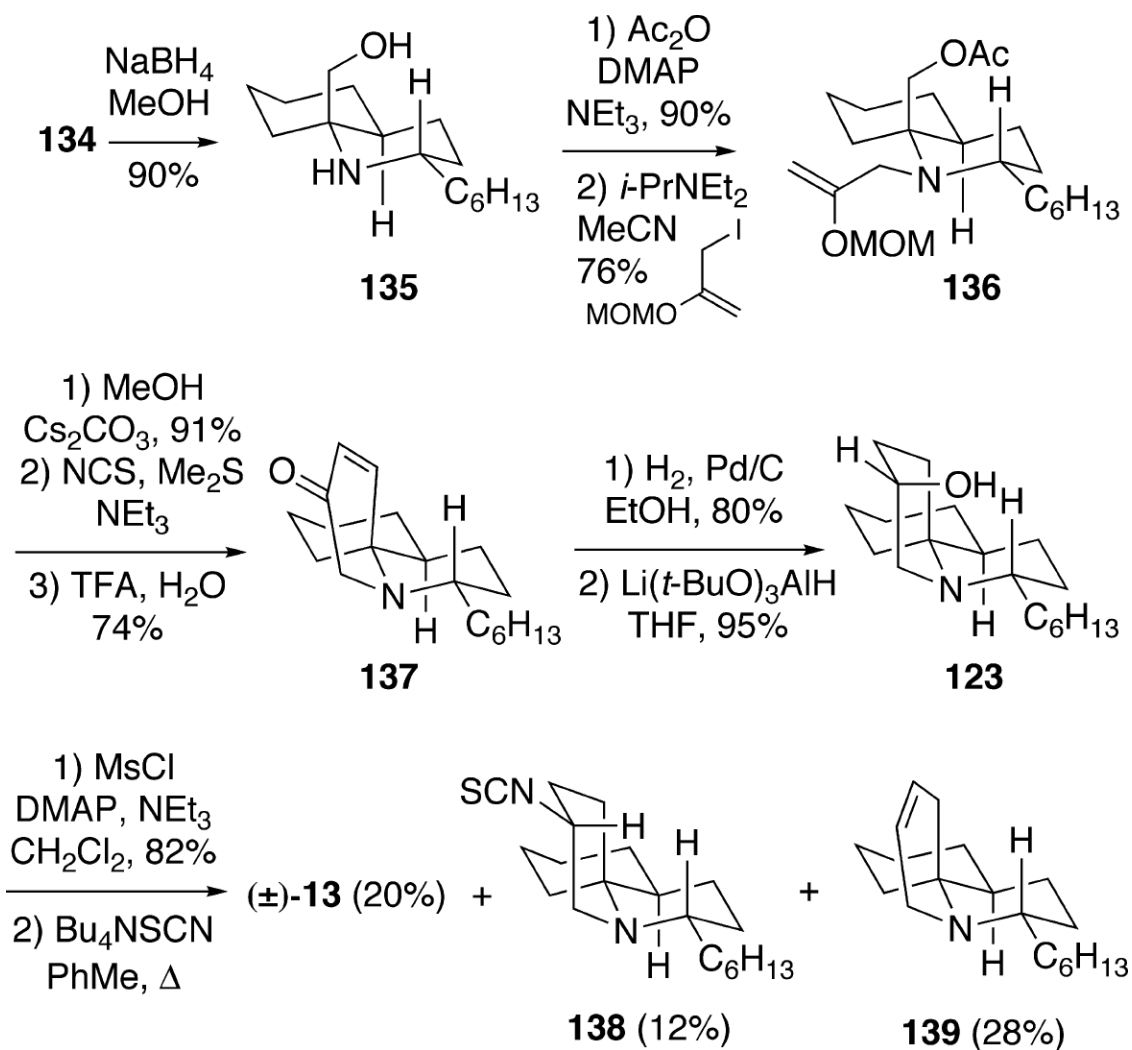
Scheme 23.



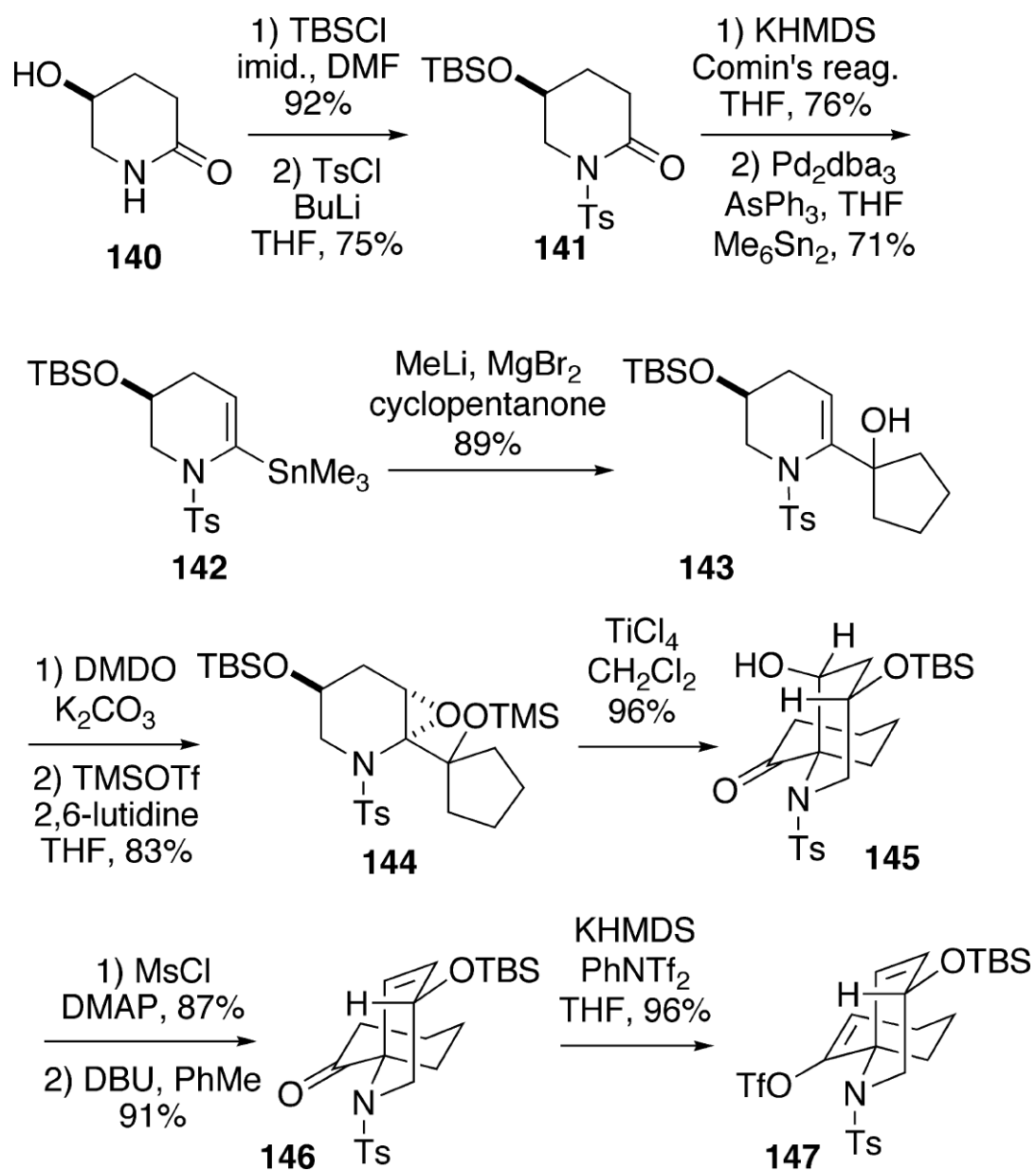
Scheme 24.



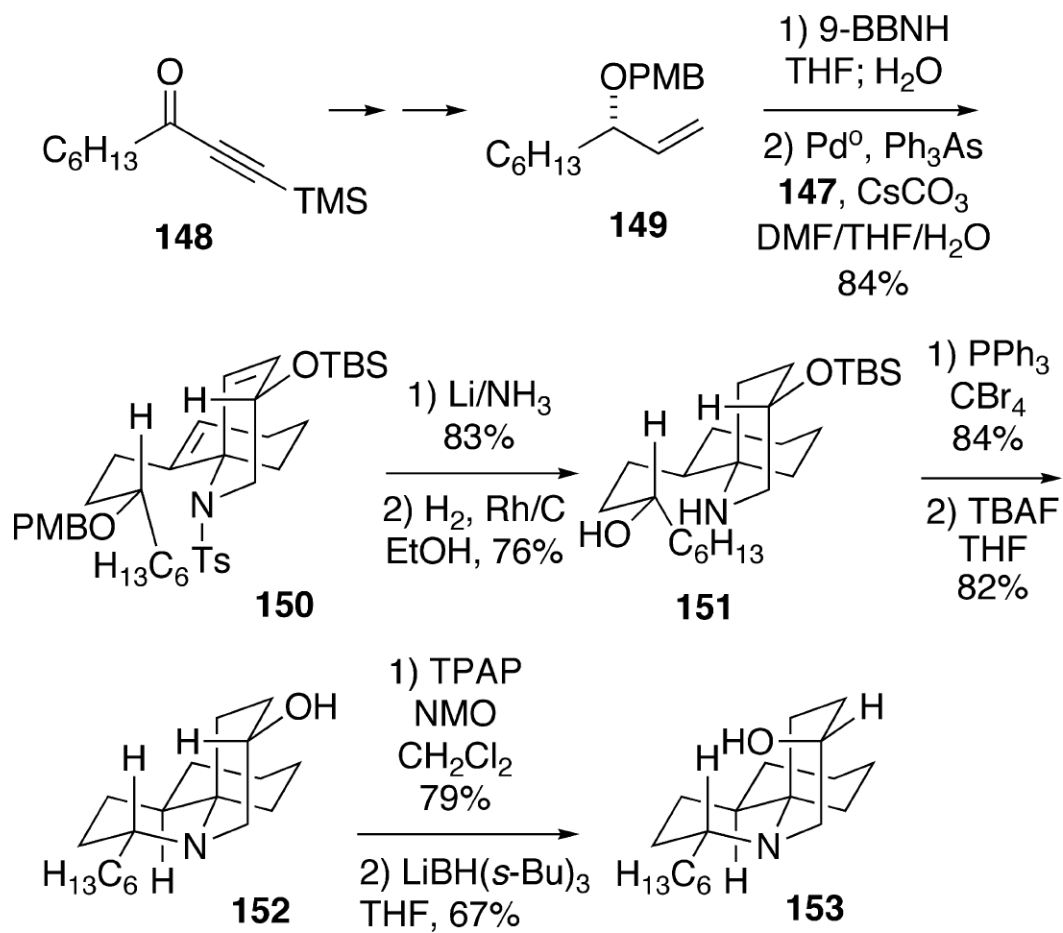
Scheme 25.



Scheme 26.

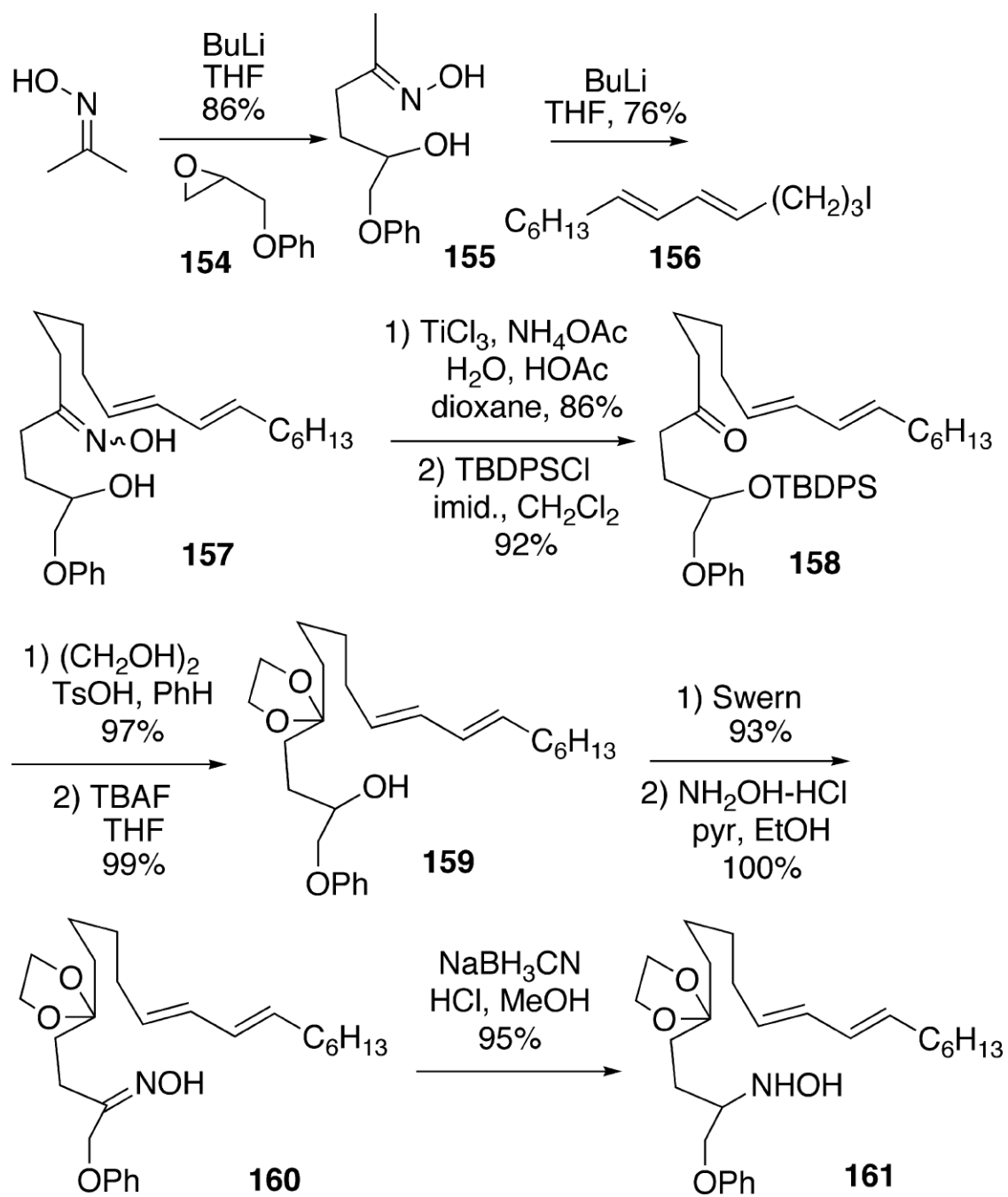


Scheme 27.

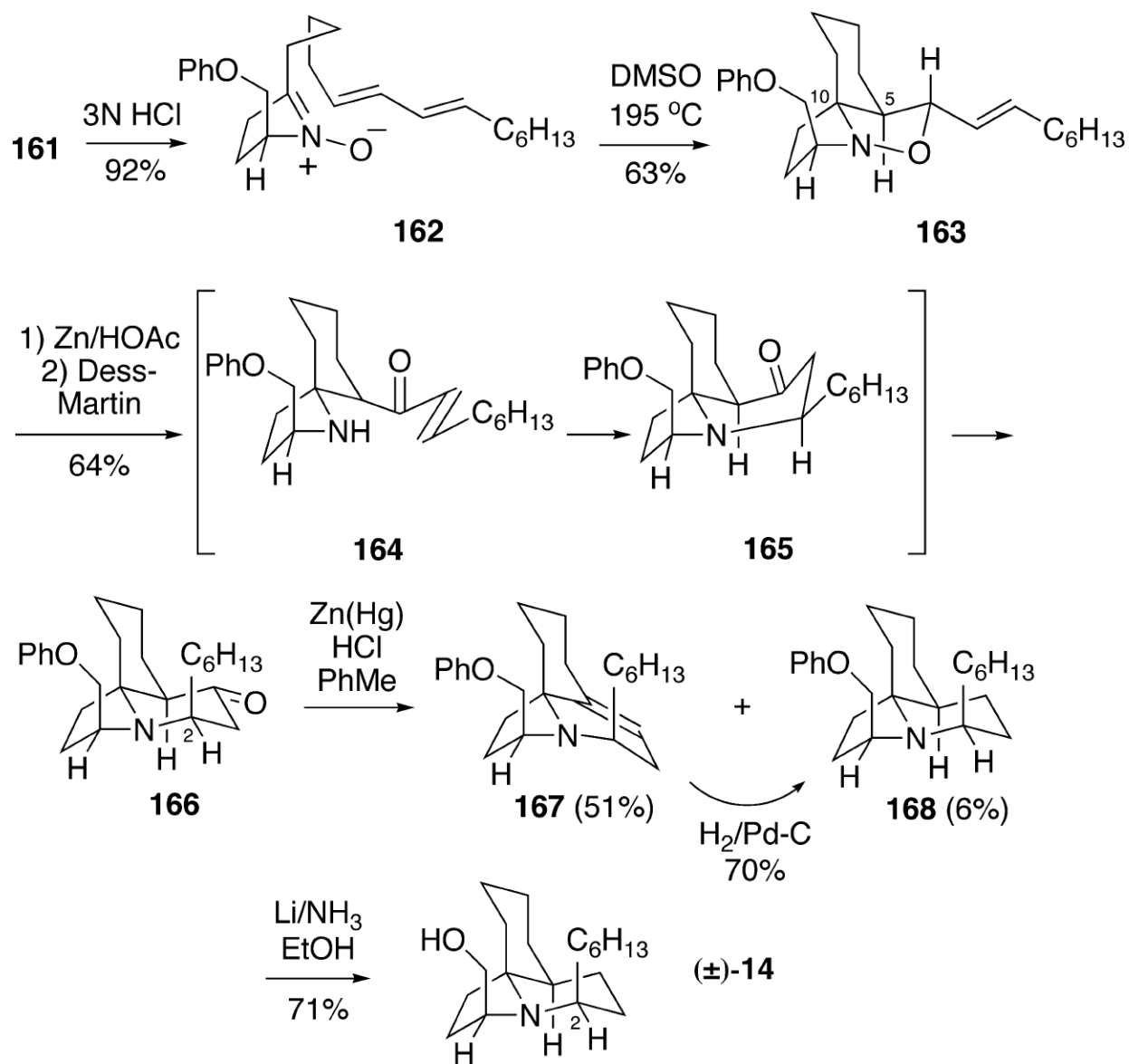


Scheme 28.

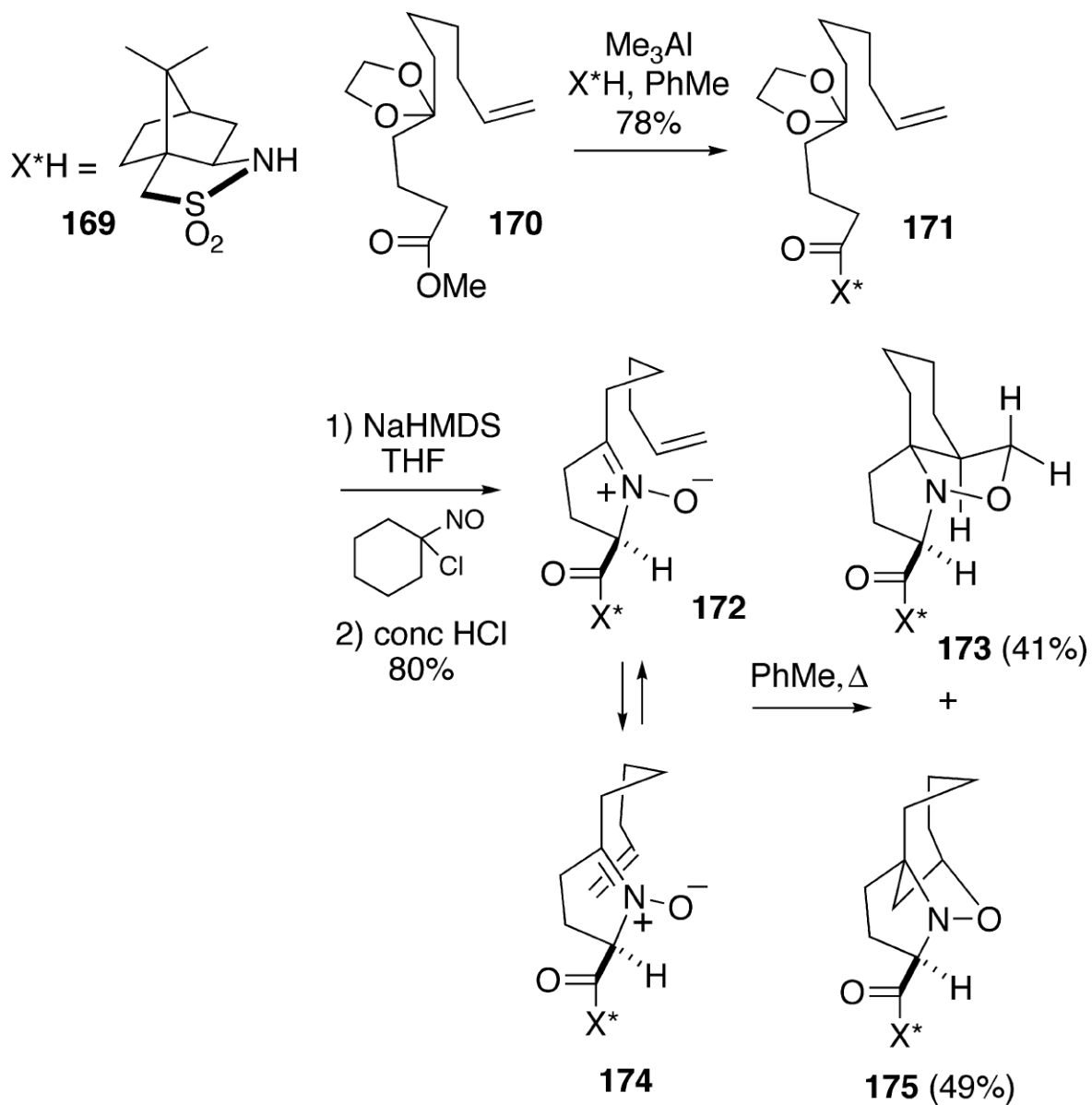




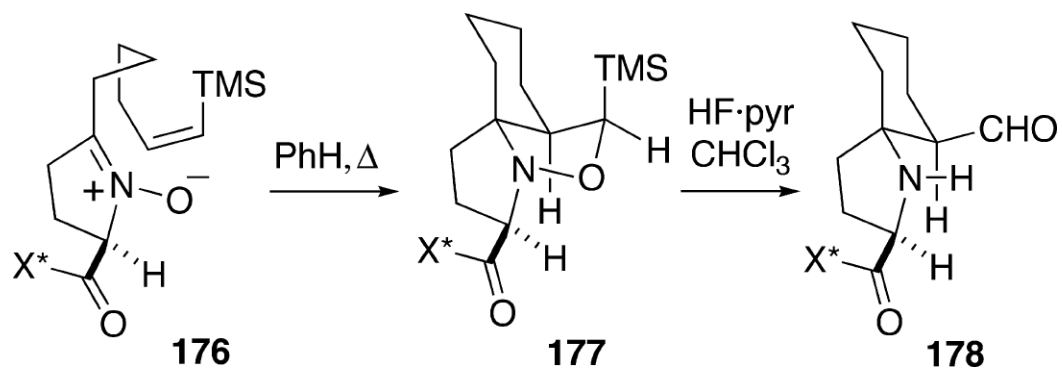
Scheme 29.



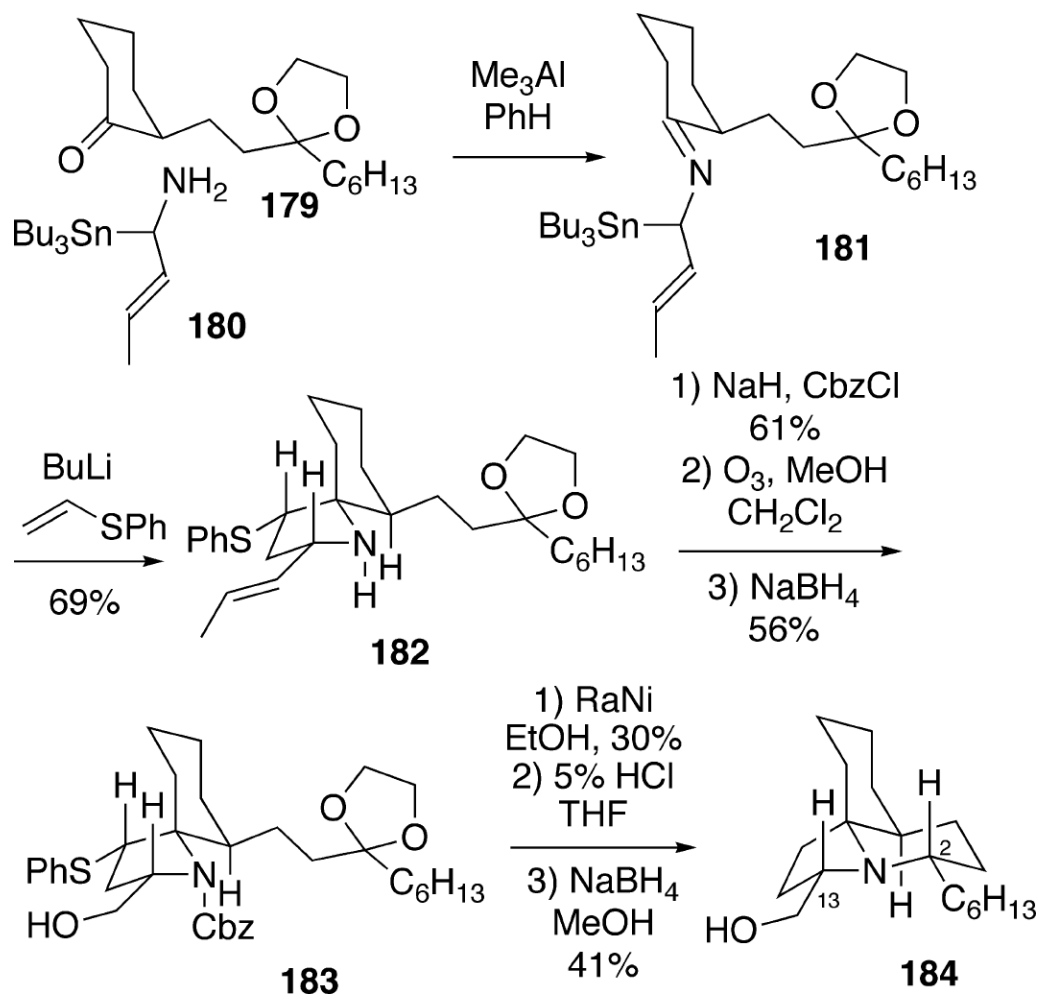
Scheme 30.



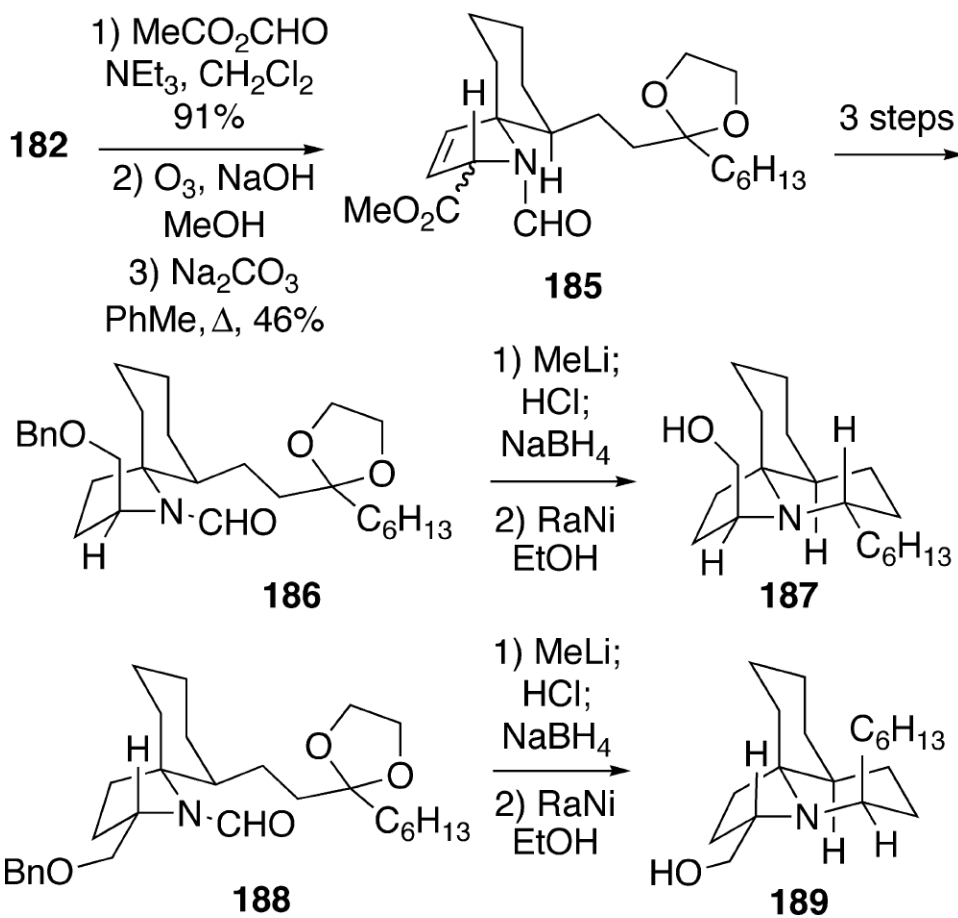
Scheme 31.



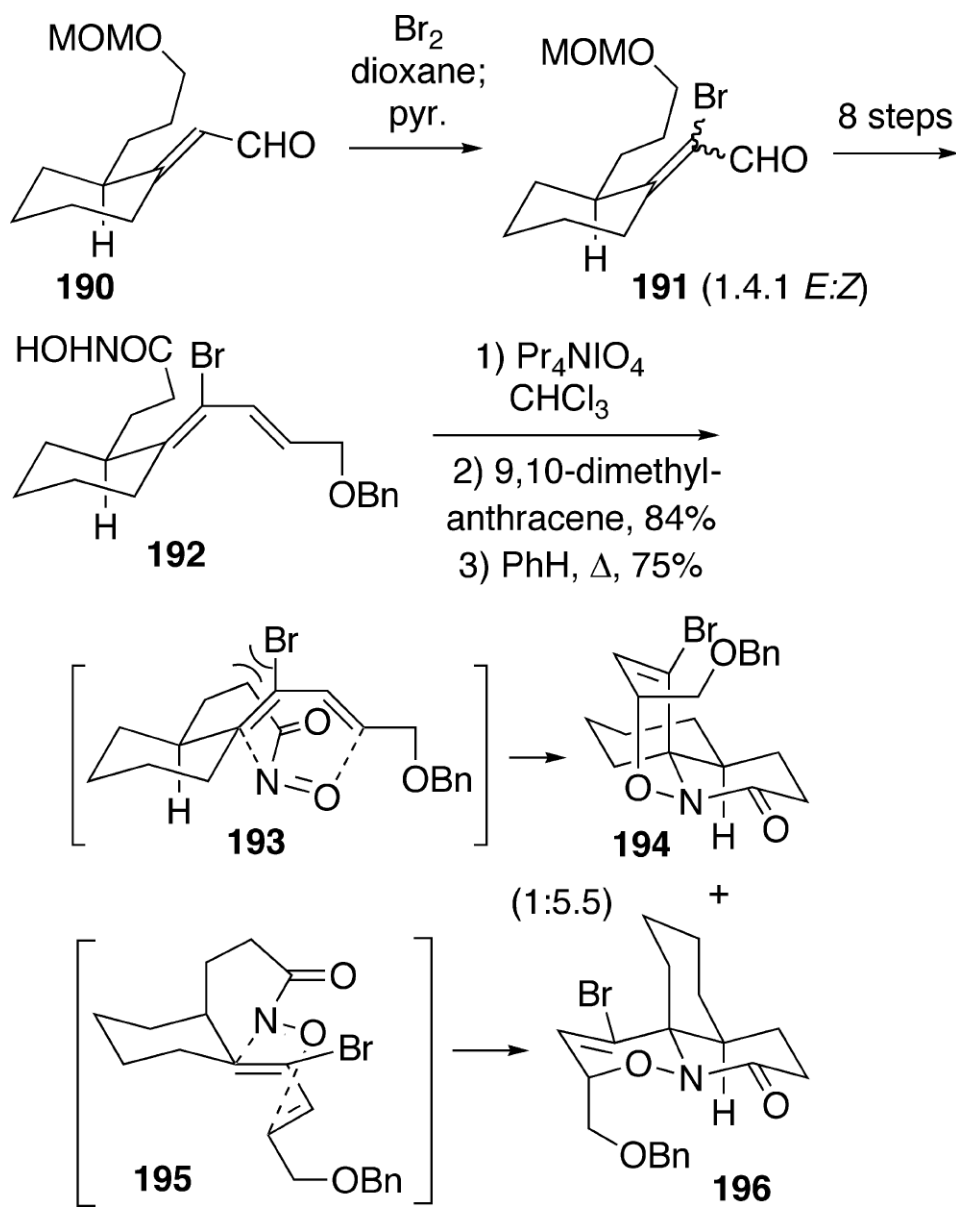
Scheme 32.



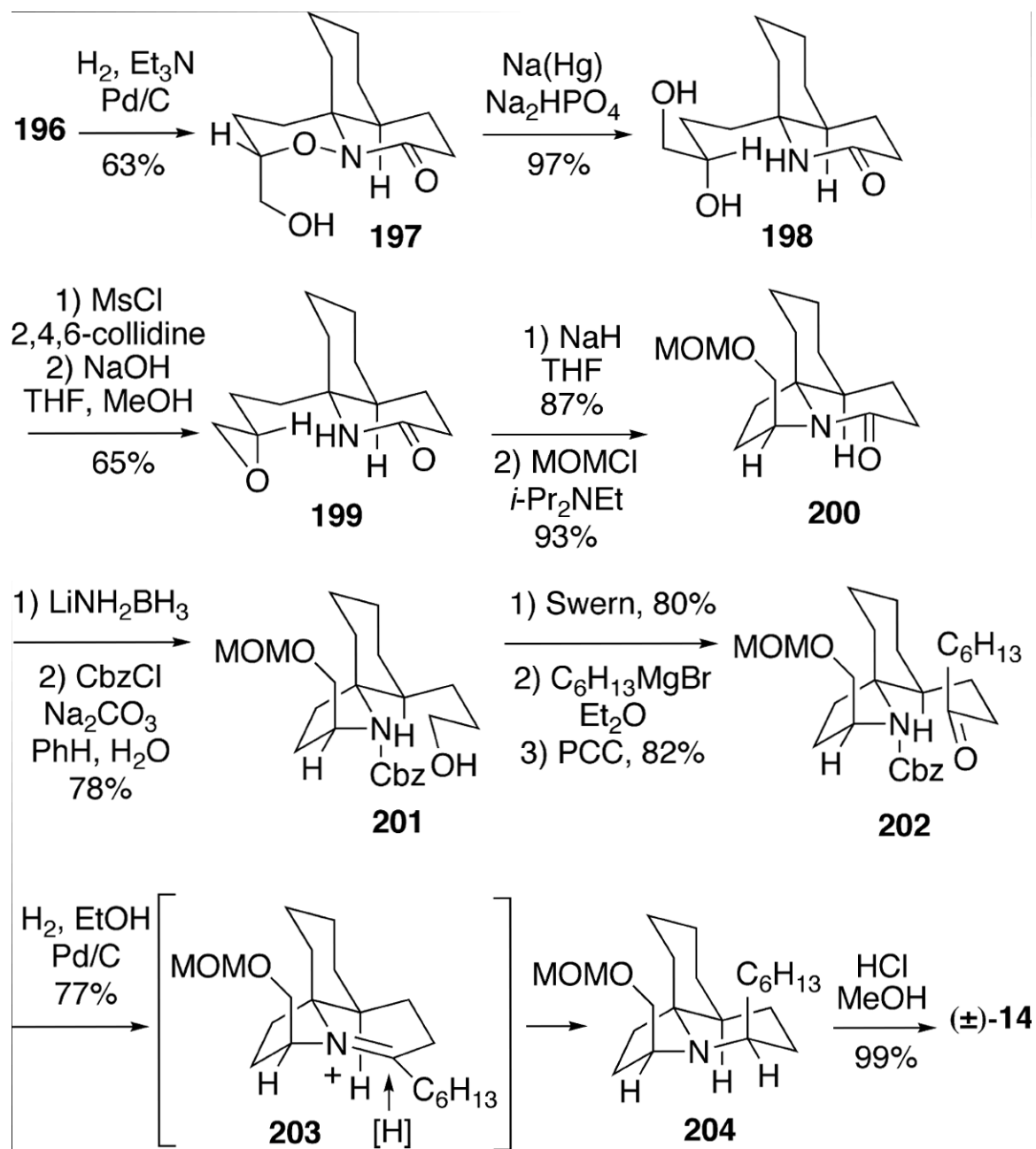
Scheme 33.



Scheme 34.

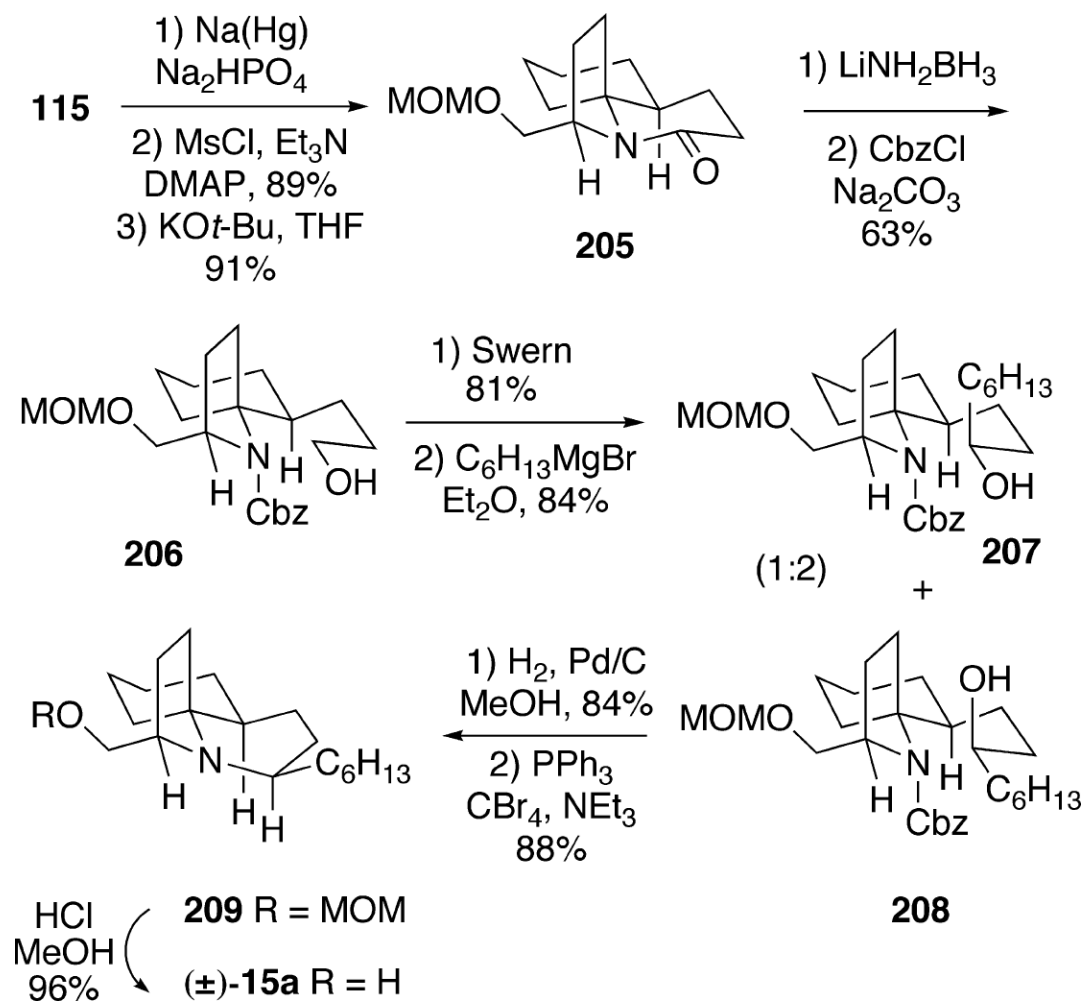


Scheme 35.

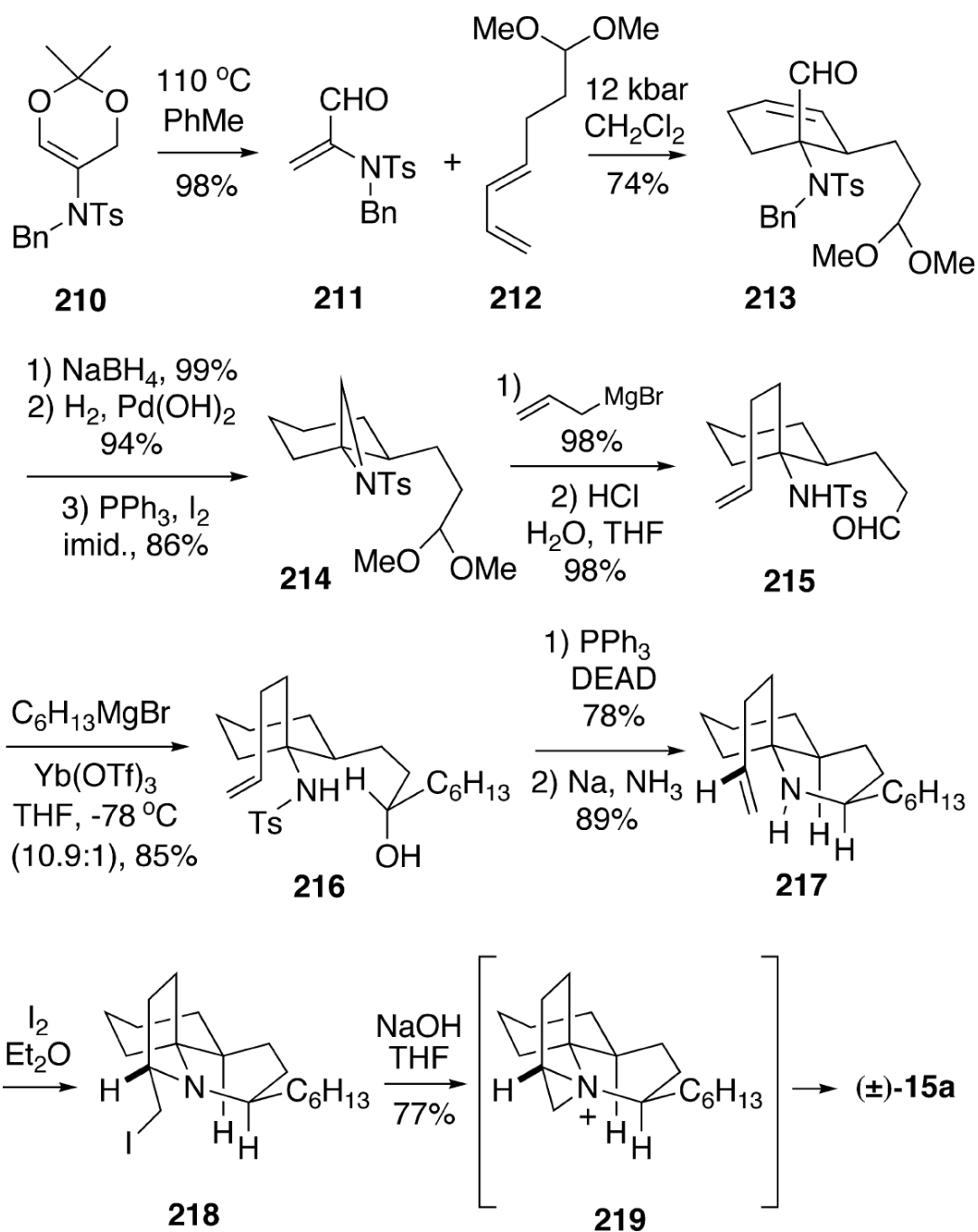


Scheme 36.

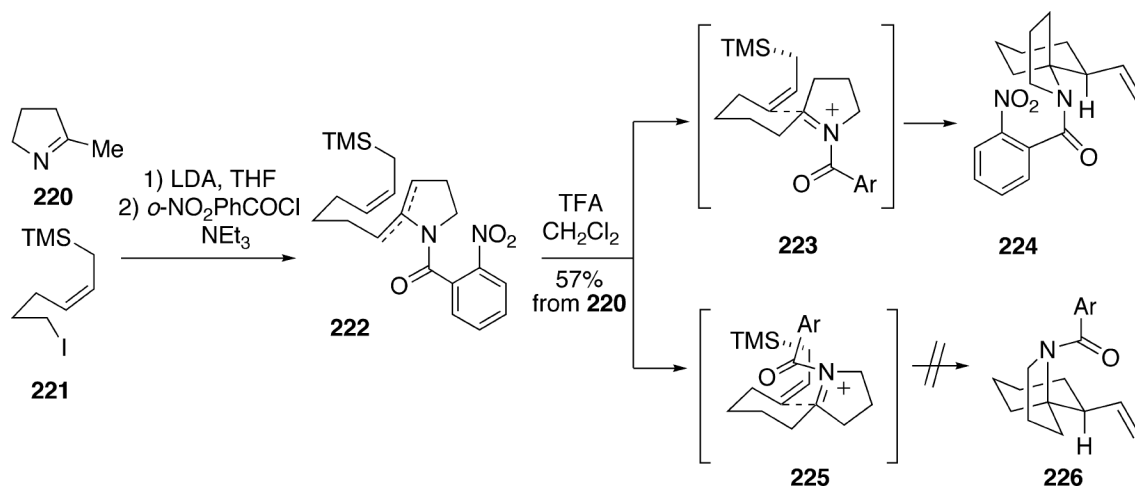




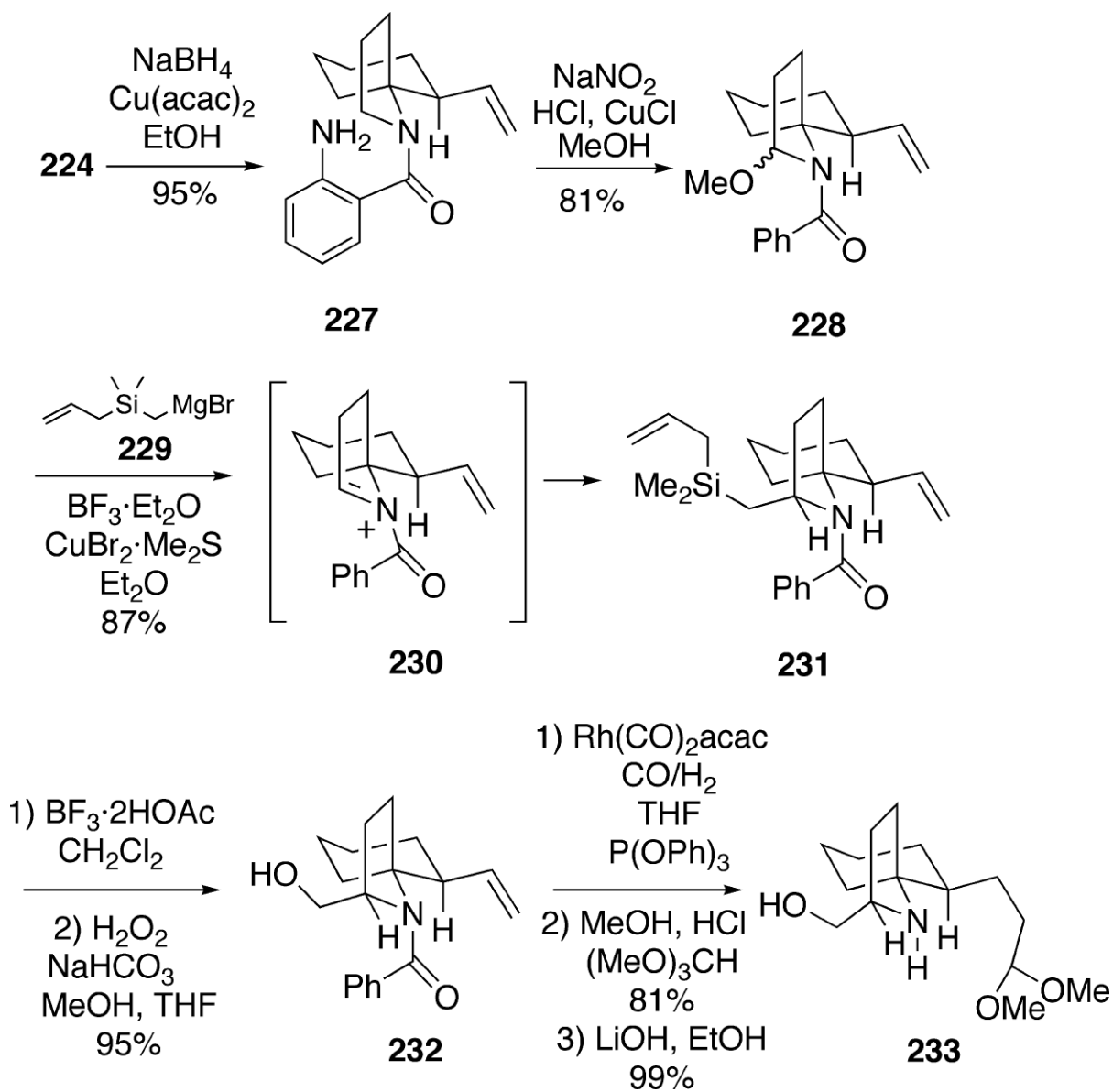
Scheme 37.



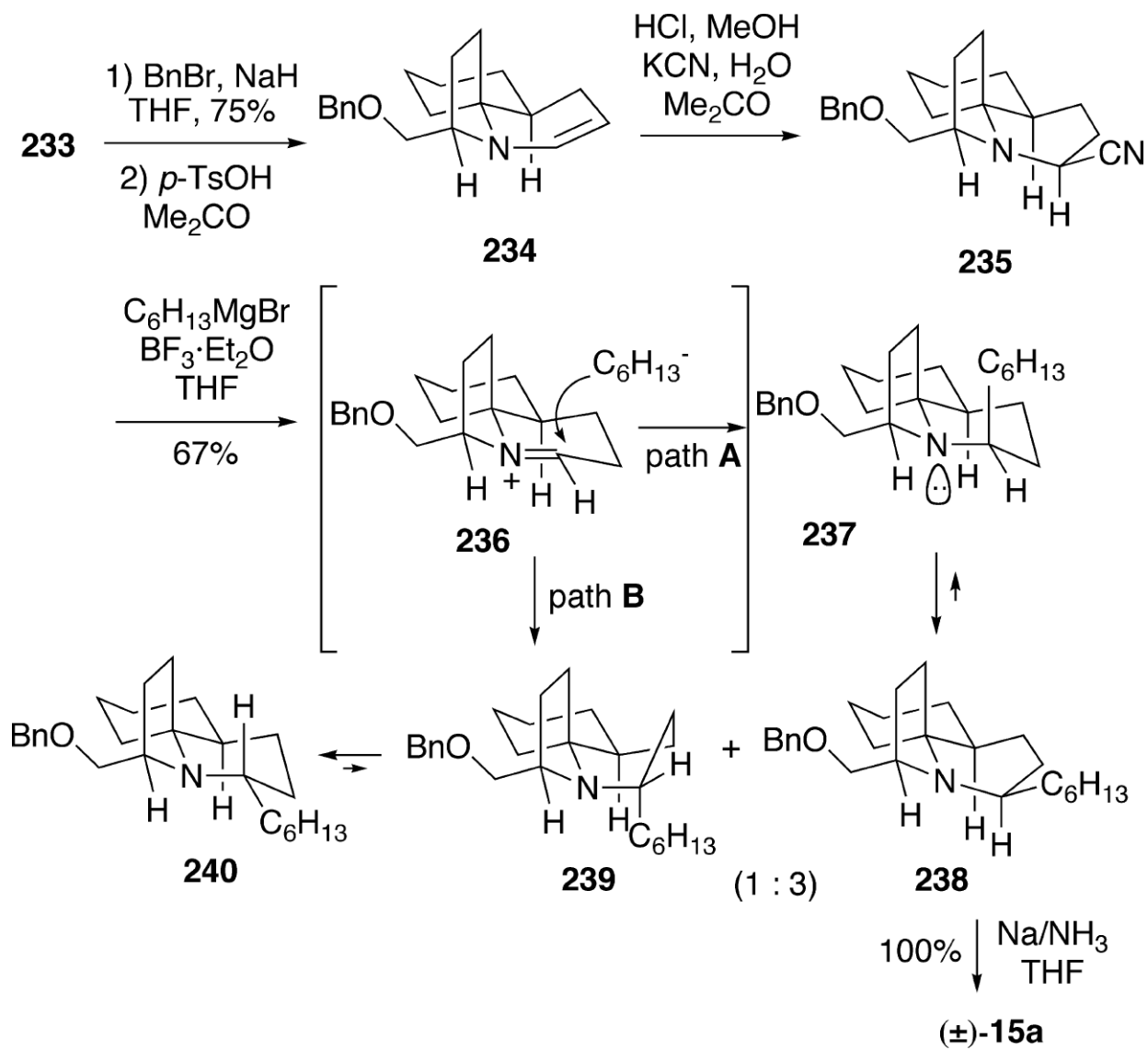
Scheme 38.



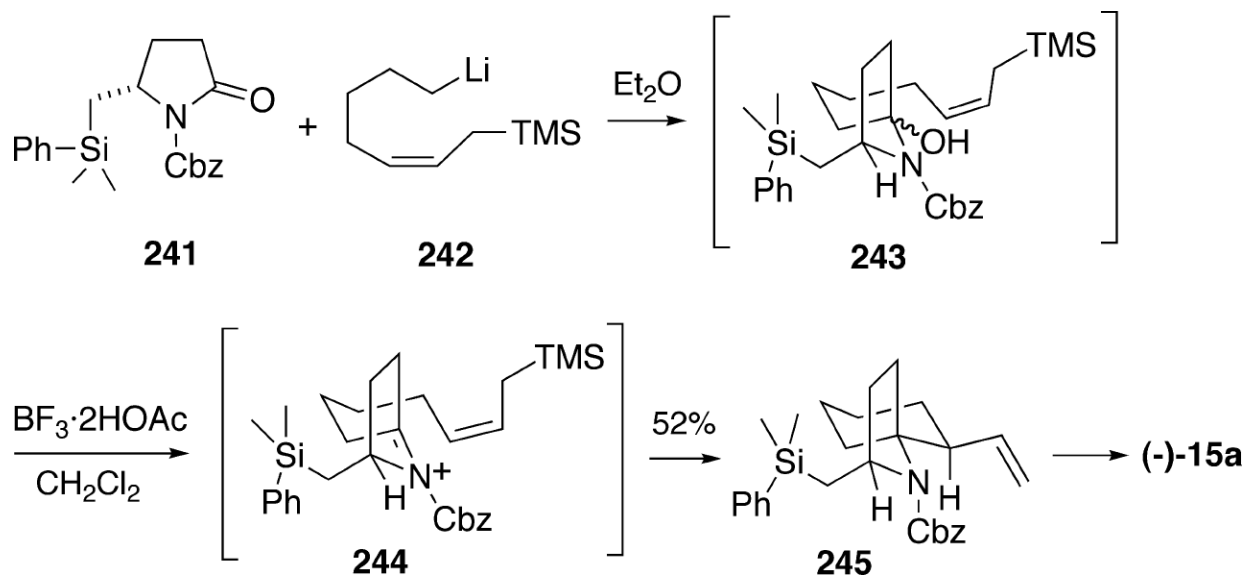
Scheme 39.



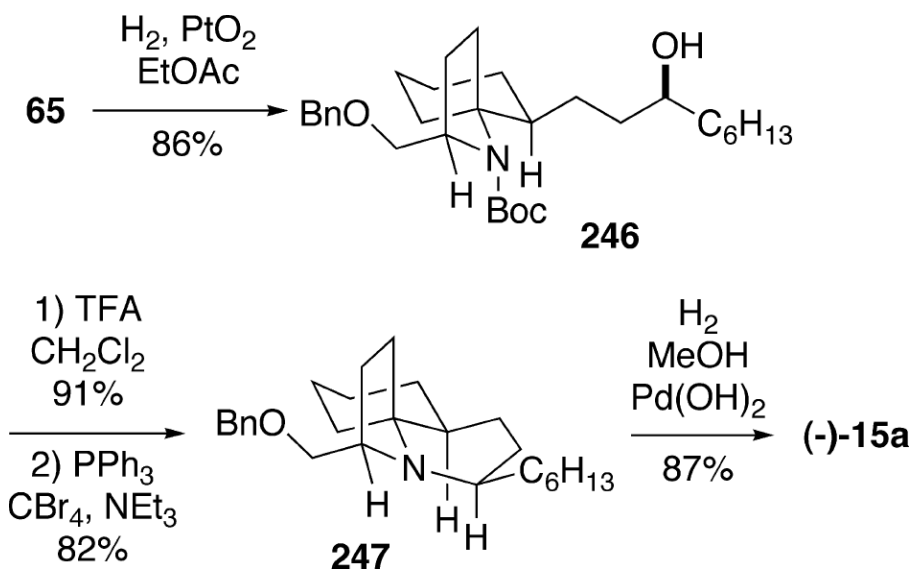
Scheme 40.



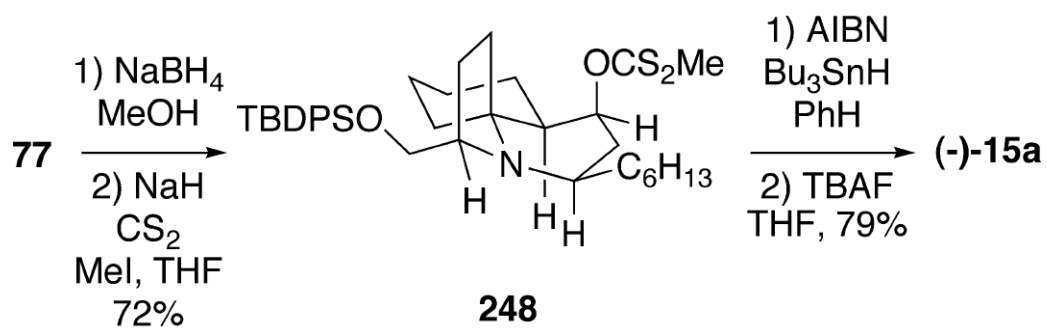
Scheme 41.



Scheme 42.

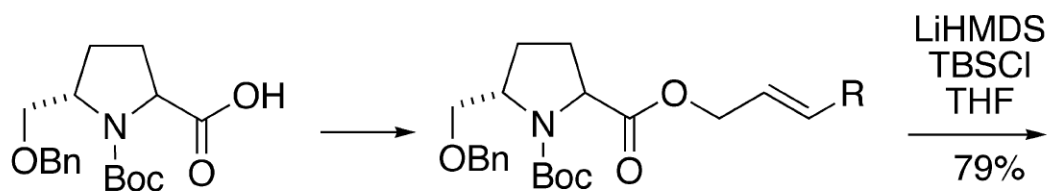
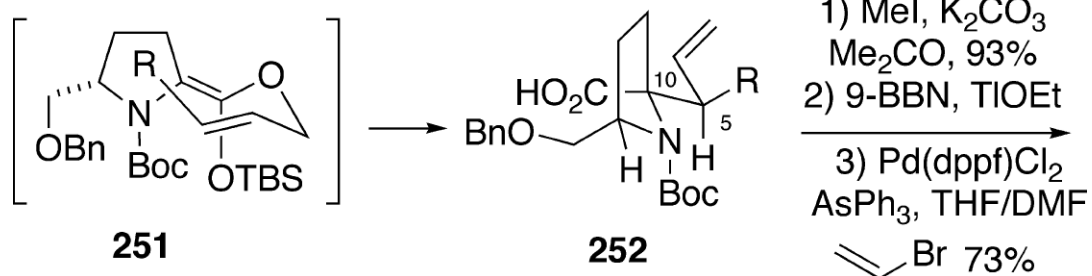
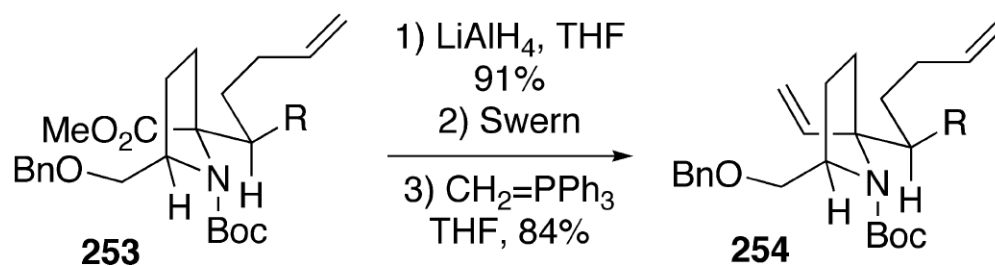


Scheme 43.

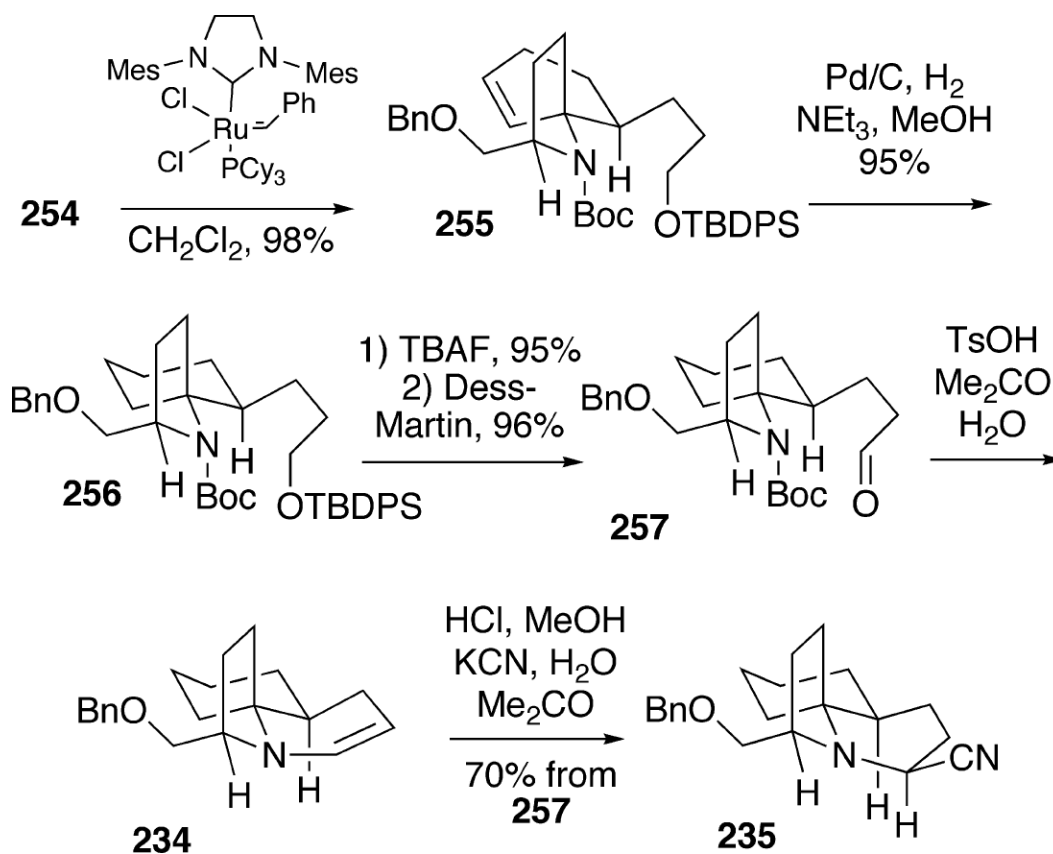


Scheme 44.

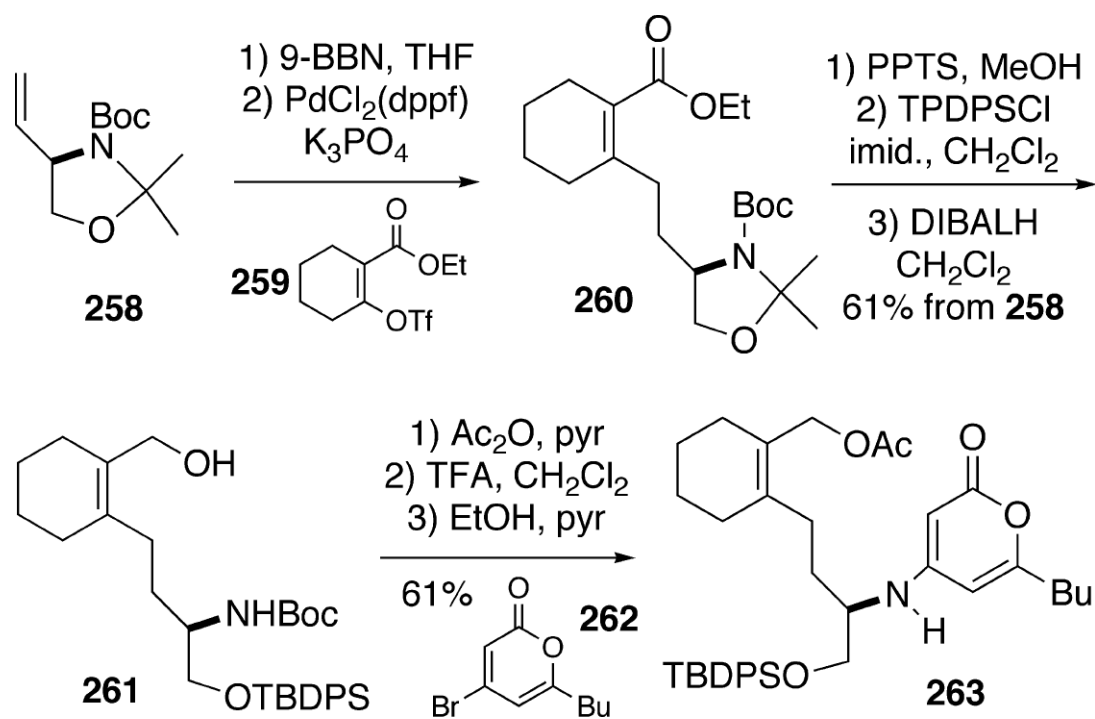


**249**R = (CH<sub>2</sub>)<sub>3</sub>OTBDPS **250****251****252****253****254**

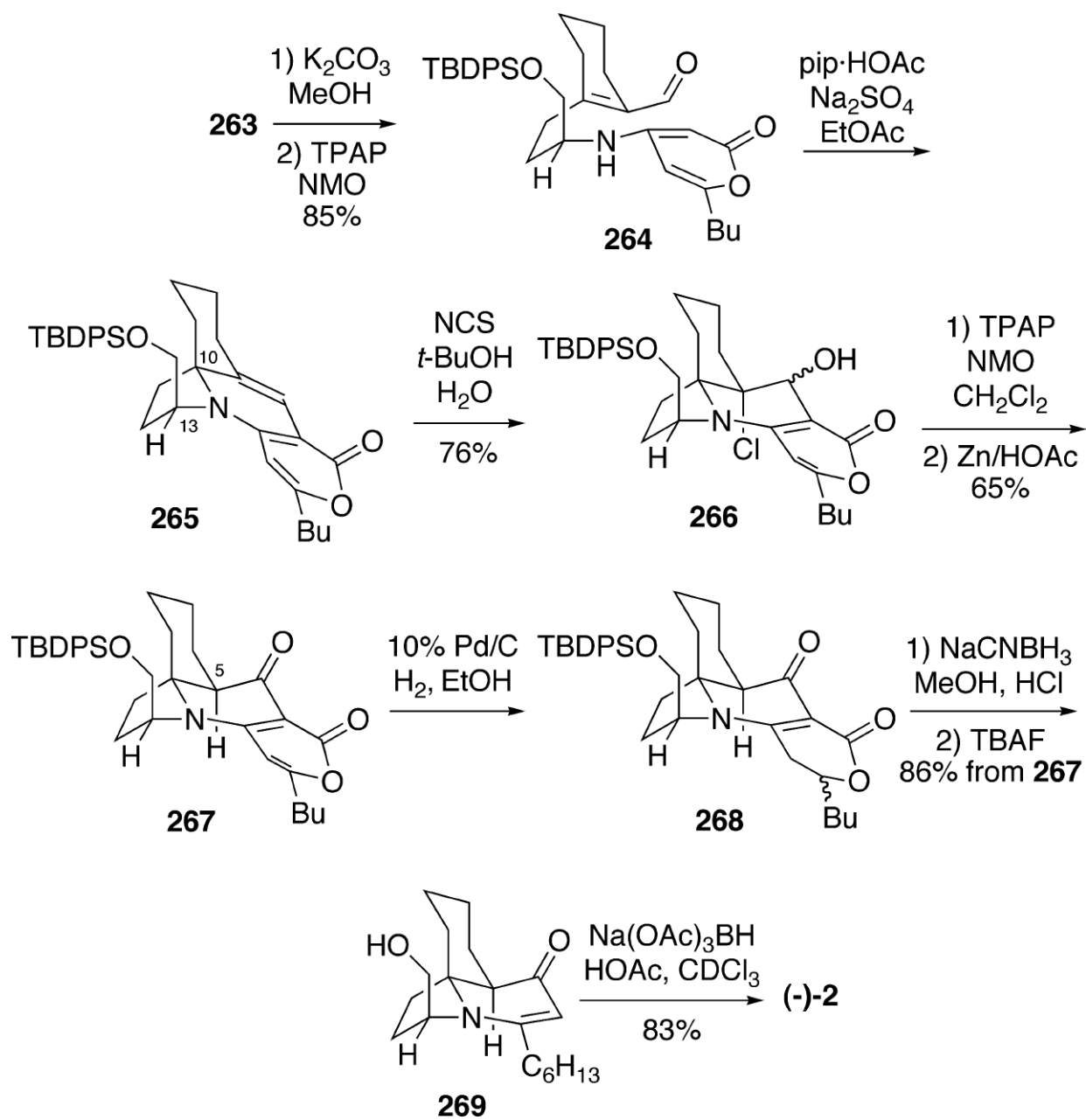
Scheme 45.



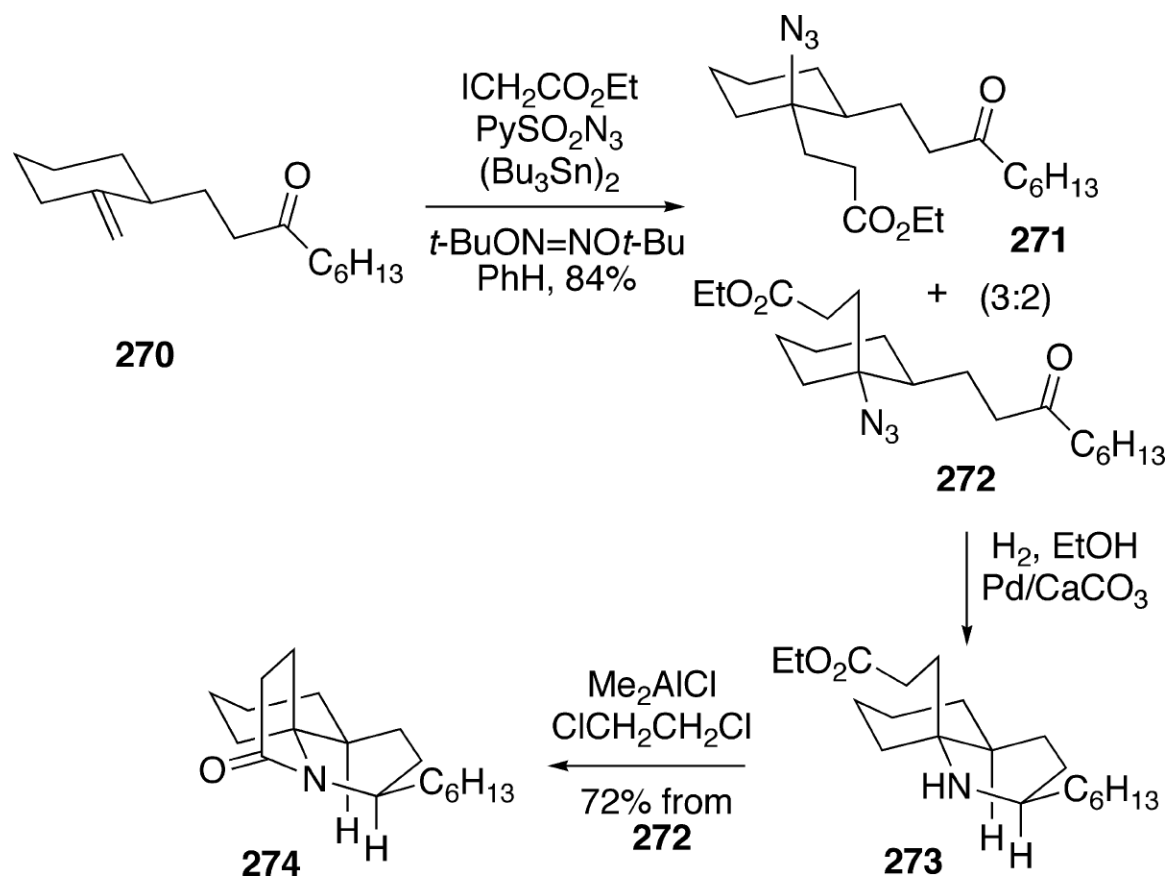
Scheme 46.



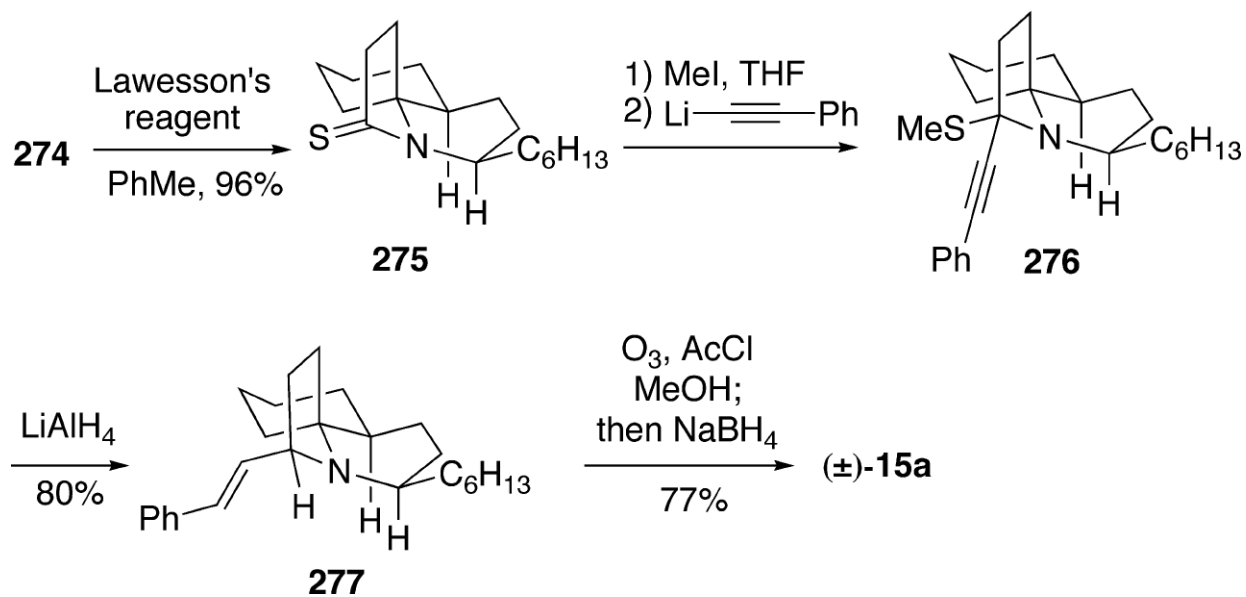
Scheme 47.



Scheme 48.



Scheme 49.



Scheme 50.