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Aza-Cope Rearrangement–Mannich Cyclizations for the Formation of Complex Tricyclic Amines: Stereocontrolled Total Synthesis of (±)-Gelsemine

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Abstract

A detailed examination of the use of aza-Cope rearrangement–Mannich cyclization sequences for assembling the azatricyclo[4.4.0.0^{2,8}]decane core of gelsemine is described. Iminium ions and *N*-acyloxyiminium ions derived from endo-oriented 1-methoxy- or 1-hydroxybicyclo[2.2.2]oct-5-enylamines do not undergo the first step of this sequence, cationic aza-Cope rearrangement to form *cis*-hydroisoquinolinium ions. However, the analogous base-promoted oxy-aza-Cope rearrangement does take place to form *cis*-hydroisoquinolones containing functionality that allows iminium ions or *N*-acyloxyiminium ions to be generated regioselectively in a subsequent step. Mannich cyclization of *cis*-hydroisoquinolones prepared in this way efficiently assembles the azatricyclo[4.4.0.0^{2,8}] decane unit of gelsemine. Using a sequential base-promoted oxy-aza-Cope rearrangement/Mannich cyclization sequence, gram quantities of azatricyclo[4.4.0.0^{2,8}]decanone **18**, a central intermediate in our total of (±)-gelsemine, was prepared from 3-methylanisole in 12 steps and 16% overall yield.

Background

The genus *Gelsemium* (Loganiaceae) is comprised of three species, of which *G. sempervirens* (Carolina or yellow jasmine) has been the most extensively investigated for the presence of alkaloids.[2] This particular plant is indigenous to the southeastern United States and has a long history of medicinal applications. Wormley first detected the presence of alkaloids in extracts of *G. sempervirens* in 1870.[3] In 1876, Sonnenschein isolated the principal component of the species, gelsemine (**1**), as an amorphous base (Figure 1).[4] The correct molecular formula of gelsemine, $C_{20}H_{22}N_2O_2$, was established in 1910 by Moore.[5] More than 70 years of degradative studies failed to elucidate the structure of gelsemine, but demonstrated that gelsemine had the same five functional groups that are present in strychnine.[2] Finally, in 1959, the structure was solved independently by two laboratories: Lovell and co-workers used

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X-ray crystallography to determine the structure of the hydrochloride and hydroiodide salts of gelsemine,[6] whereas Conroy and Chakrabarti derived the same structure from a combination of biosynthetic rationale (attributed to Woodward) and an early application of ^{1}H NMR spectroscopy for structure elucidation.[7,8] Gelsemine's presumed biosynthesis from secologanin suggests the absolute configuration depicted in Figure 1, a supposition verified in 2000 by Fukuyama's enantioselective total synthesis.[9]

Since these early reports, many structurally related *Gelsemium* alkaloids have been reported (Figure 1).[10–15] Among these, gelsemicine (**5**) is the most toxic and appears to be largely responsible for the CNS stimulant activity that is characteristic of the *Gelsemium* extracts.[12] Koumine (**10**), which has enjoyed a long history of use in traditional Chinese medicine, is the most abundant alkaloid found in *G. elegans*.[16] Gelsemine (**1**), gelsevirine (**2**), gelsedine (**6**), gelsenicine (**9**), gelsemine *N*-oxide, 19-(*S*)-hydroxydihydrogelsevirine and 19-(*R*)-hydroxydihydrogelsevirine (**11**) are among the numerous alkaloids isolated from *G. elegans*.[17] The least studied species is *G. rankinii*, from which rankinidine (**14**), 21-oxogelsevirine (**4**), 19-(*R*)-acetoxydihydrogelsevirine (**12**) and 19-(*R*)-hydroxydihydrogelsemine (**13**) have been isolated.[17a,18]

The six diverse rings of gelsemine (**1**) are assembled into a compact cage. The unusual and densely functionalized nature of this hexacyclic structure provoked intense efforts to synthesize gelsemine.[19] These studies stimulated the development of many innovative synthetic methods,[20,21] culminating in total syntheses of (±)-gelsemine by the groups of Johnson,[22] Speckamp,[23] Hart,[24] Fukuyama,[25] Overman,[26] and Danishefsky,[27] and of (+)-gelsemine by Fukuyama and co-workers.[9]

Initial Synthesis Planning

The retrosynthetic analysis that propelled our efforts to synthesize gelsemine is outlined in Figure 2. We envisaged forming the hydropyran ring last, for example by intramolecular etherification of an intermediate such as **15**. It was hoped that the spirooxindole unit of pentacyclic intermediate **15** could be formed by cyclization of an appropriately functionalized α,β-unsaturated amide such as **16**. At the outset, we entertained the possibility that either radical-chain or metal-catalyzed processes might accomplish this conversion. At the time our efforts began, precedent that a sterically congested quaternary carbon center such as C7 could be fashioned by either process was lacking. Nonetheless, we adopted this strategy in part because it would present opportunities for developing new methods to address what still remains a challenging problem in organic synthesis: stereocontrolled construction of quaternary carbon stereocenters.[28] As it happened, the discovery that intramolecular Heck reactions could solve this general problem with remarkable facility is the most significant outcome of our endeavors in this area.[29]

We anticipated that cyclization precursor **16** could be prepared from the azatricyclo [4.4.0.0^{2,8}]decanone **17**. This latter intermediate encodes a 3-acylpyrrolidine unit, suggesting that it might be available by aza-Cope–Mannich reaction of bicyclo[2.2.2]octyliminium ion **19**.[30,31] The projected aza-Cope–Mannich transformation is outlined in more detail in Scheme 1. Although thermal Cope rearrangements of bicyclo[2.2.2]octenes bearing endo alkenyl substituents have high activation barriers,[32] these rearrangements and the corresponding oxy-Cope rearrangements have been employed to prepare functionalized *cis*-decalins.[33] Because of the kinetic activation provided by the positively charged nitrogen atom,[31b] we expected the conversion of iminium cation **19** to *cis*-hydroisoquinolinium cation **21** to occur at significantly lower temperatures than those required for similar sigmatropic reorganizations of hydrocarbons. At the outset, Mannich cyclization of iminium ion **21** to yield azatricyclo [4.4.0.0^{2,8}]decanone **17** was viewed as the potentially problematic step of this sequence for

two reasons: (1) the ring strain of the azatricyclo[4.4.0.0^{2,8}]decane ring system,[34] and (2) the requirement that the tetrahydropyridinium ring adopt a boat conformation (as depicted in conformer **22**) to achieve acceptable orbital overlap for the intramolecular Mannich reaction.[31a,35]

The intramolecular Mannich reaction depicted in Scheme 1 was without precedent; however, the literature provided examples of other cyclizations that form tricyclo[4.4.0.0^{2,8}]decane ring systems.[36] For example, closure of an analogous bond is involved in a tosylate displacement reaction leading to sativene.[37] A more relevant example of this bond construction is found in Woodward's base-promoted conversion of α-santonin (**23**) to santonic acid, which is particularly germane as the intramolecular Michael reaction involved in this sequence, like the Mannich reaction, presumably is reversible (Scheme 2).[38]

With these considerations in mind, we set out to explore the feasibility of the aza-Cope–Mannich reaction to prepare the azatricyclo[4.4.0.0^{2,8}]decane ring system of gelsemine (**1**). At the time our studies began, this cascade reaction had just been invented[30] and never had been examined in the bicyclo[2.2.2]octyl series, nor with a substrate as complex as **19**. Although the direct way to access azatricyclodecanone intermediate **17** depicted in Scheme 1 ultimately proved unworkable, a base-promoted variant of aza-Cope–Mannich chemistry eventually provided access to related intermediate **18** (Figure 2). Full details of our investigations into iminium-ion transformations in the bicyclo[2.2.2]octyl series and the development of a base-promoted 2-aza-Cope rearrangement are the subject of this account.[39] The development of Heck cyclization chemistry to prepare spirooxindoles, and the endgame strategy that ultimately led to (±)-gelsemine (**1**), are presented in the accompanying paper.[40]

Results and Discussion

Attempted Construction of Azatricyclo[4.4.0.0^{2,8}]decane Intermediates by Cationic Aza-Cope–Mannich Cyclizations

Bicyclooctenylamine **29** was chosen for our inaugural investigations of the projected aza-Cope–Mannich transformation (Scheme 3). The synthesis of this amine commenced with the reaction of cyclohexadiene **24**, the Birch-reduction product of 3-methylanisole, with methyl acrylate in the presence of a catalytic amount of dichloromaleic anhydride to provide a separable 2.7:1 mixture of endo, **25**, and exo, **26**, adducts.[41] The methyl ester of the endo product **25** was saponified and the resulting acid was converted to carbamate **28** by a standard Curtius-rearrangement sequence.[42] Reduction of this product with alane[43] provided bicyclooctenylamine **29** in 45% overall yield from Diels–Alder product **25**.

With amine **29** in hand, we turned to examine the proposed cationic aza-Cope–Mannich transformation. Reaction of bicyclooctenylamine **29** with paraformaldehyde and camphorsulfonic acid (CSA) in refluxing benzene for extended periods of time resulted only in the recovery of starting material. The use of higher boiling solvents such as toluene or chlorobenzene was also unsuccessful, as paraformaldehyde sublimed from these reaction mixtures. However, heating bicyclooctenylamine **29** with 1.1 equiv of paraformaldehyde, 0.98 equiv of camphorsulfonic acid and a slight excess of sodium sulfate in acetonitrile at 100 °C provided one major product, which was isolated in 76% yield. The presence of exomethylene and methoxy groups, readily apparent in ^{1}H and ^{13}C NMR spectra, established that this product was not the desired azatricyclo[4.4.0.0^{2,8}]decanone, but rather the 10-methylene-4-azatricyclo[4.3.1.0^{3,7}]decane **32**. Iminium-ion intermediate **30** had not undergone aza-Cope rearrangement, but rather aza-Prins cyclization at the proximal terminus of the alkene double bond to generate tertiary carbenium ion **31** and, ultimately, azatricyclodecane **32**.

We hypothesized that the electron-releasing methyl group at C5 of iminium-ion intermediate **30** was responsible for the undesired cyclization to generate **32**. As a substituent at C5 must ultimately evolve to the angular vinyl group of gelsemine, considerable variation in the electronic properties of this group would be permitted. Therefore, we turned to explore the chemistry of related bicyclo[2.2.2]octenyl formaldiminium ions having less electron-rich carbon-carbon double bonds.

The outcome of generating a formaldiminium ion from a bicyclo[2.2.2]octenylamine having an unsubstituted double bond was explored first. The straightforward preparation of such a precursor, bicyclo[2.2.2]octenylamine **35**, from acid **33**[44] is summarized in Scheme 4. Exposing bicyclooctenylamine **35** to paraformaldehyde and camphorsulfonic acid in acetonitrile or methanol at 100 °C resulted in no reaction. Heating these reactants to 200 °C in toluene in a sealed tube also returned the starting secondary amine **35**, together with its *N*,*N*-dimethylamine congener. As we had recorded considerable success in initiating other aza-Cope–Mannich transformations of formaldiminium ions from cyanomethylamine precursors,[31,45] octenylamine **35** was allowed to react with formalin and potassium cyanide to give cyanomethylamine **36**. Heating this precursor with camphorsulfonic acid and paraformaldehyde also failed to affect the desired aza-Cope–Mannich reaction. The formation of the *N*-methylated product confirmed that a formaldiminium ion was being generated; however, aza-Cope rearrangement or Mannich cyclization of this intermediate was slower than its reduction.[46]

As *N*-acyloxyiminium ions are more reactive than iminium ions and are readily generated by the acid-promoted reaction of formaldehyde with secondary carbamates,[47,48] we also examined the direct reaction of bicyclooctenyl carbamate **34** with paraformaldehyde. When this condensation was carried out in formic acid at 50 °C using 1.3 equiv of paraformaldehyde, azatricyclo[4.3.1.$0^{3,7}$]decyl formate **37**, the product of aza-Prins cyclization, was produced in high yield.

We turned next to explore whether introduction of an electron-withdrawing group at C5 of the bicyclooctenylamine precursor might prevent iminium ion–alkene (aza-Prins) cyclization, thus allowing the desired sigmatropic reorganization to be realized. The synthesis of such a precursor, ester **40**, began with selenium dioxide oxidation of bicyclo[2.2.2]octenyl carbamate **28** in refluxing dioxane to form aldehyde **38** in 89% yield (Scheme 5). Sodium chlorite oxidation of this intermediate provided acid **39** in 83% yield, which, upon reaction with methyl iodide and potassium carbonate, delivered methyl ester **40** in 89% yield.

A new reaction manifold was revealed when carbamate ester **40** was allowed to react at room temperature with paraformaldehyde in trifluoroacetic acid (TFA), a reaction that produced one major tricyclic product, trifluoroacetate **42**. Single-crystal X-ray analysis established that this crystalline product had a rearranged carbon skeleton. Tricyclic diester **42** likely arises by initial aza-Prins cyclization to generate carbocation intermediate **41**, which undergoes Wagner–Meerwein rearrangement and trapping of the resulting carbocation with trifluoroacetic acid.

Construction of Azatricyclo[4.4.0.$0^{2,8}$]decanes by Sequential Base-Promoted Aza-Cope Rearrangement and Iminium Ion Cyclization

General Considerations—The failure to realize the desired aza-Cope reorganization in the bicyclo[2.2.2]octenyl series, even with intermediates having an electron-withdrawing group at C5 of the bicyclooctenylamine precursor, forced us to consider other options.[49] As a result of the high electrophilicity of the iminium ion and *N*-acyloxyiminium ion functional groups, bond formation is likely advanced with respect to bond cleavage in iminium ion and *N*-acyloxyiminium ion [3,3]-sigmatropic rearrangements. In the mechanistic limit, these rearrangements could occur by a stepwise cyclization–Grob fragmentation sequence. Thus, the

energy of the transition state of the cationic aza-Cope rearrangement of **43** → **45** is expected to be influenced strongly by the stability of the tricyclic ring system defined by the sigmatropic rearrangement transition structure **44** (Figure 3). A simplified model for this transition structure would be tricyclo[4.4.0.$0^{0,0}$]decane (**47**, twistane). Molecular mechanics calculations predict that this hydrocarbon is 2.2 kcal/mol higher in energy than tricyclo[4.3.1.$0^{3,7}$]decane (**46**).[34] Thus, the greater strain of the twistane tricyclodecane skeleton provides a rationale why the iminium- and *N*-acyloxyiminium-ion intermediates generated in the reactions summarized in Scheme 3–Scheme 5 cyclize to generate 4-azatricyclo[4.3.1.$0^{3,7}$]decyl carbenium ion intermediates rather than undergo aza-Cope rearrangements.

We hypothesized that a potential way to relieve the constraints imposed by the rigid bicyclo [2.2.2]octenyl ring system would be to alter the electronic nature of the rearranging system in such a way to advance bond cleavage relative to bond formation in the sigmatropic reorganization. The seminal contributions of Evans and Goddard[50] to the origin of base acceleration[51] in the oxy-Cope rearrangement suggested that an analogous base-promoted oxy-aza-Cope rearrangement would have a less constrained transition structure than that of the cationic rearrangement depicted in Figure 3.

Ultimately Successful Synthesis of Azatricyclo[4.4.0.$0^{2,8}$]decane 18—Although rarely used, base-promoted aza-Cope–Mannich reactions are known.[52] To explore this transformation in the azabicyclo[2.2.2]octene ring system, we needed to assemble bicyclo [2.2.2]oct-5-ene-2-amines in which the bridgehead C1 substituent is hydroxyl in order for the powerful activating effect of an alkoxide substituent[51] to be brought into play. Initially we examined demethylation of Diels–Alder products **28** and **29** (see Scheme 3) to gain access to such substrates. However, all attempts to remove the methyl group from these precursors with trimethylsilyl iodide, boron tribromide or boron trifluoride/ethanethiol failed to give the corresponding alcohols.

However, we were able to prepare hydroxyl bicyclooctenylamine **53** quite smoothly by a Diels–Alder strategy using a triisopropylsilyl (TIPS) group to protect what will become the C1 hydroxyl substituent of the bicyclo[2.2.2]octenylamine (Scheme 6). This sequence began with kinetic deprotonation of β,γ-unsaturated ketone **48**[53] with lithium diisopropylamide at −78 °C, followed by quenching with triisopropylsilyl trifluoromethanesulfonate to give siloxy diene **49** in 92% overall yield from 3-methylanisole, the precursor of enone **48**. Diels–Alder cycloaddition of diene **49** with methyl acrylate at −78 °C in the presence of $AlCl_3$ provided an 8:1 mixture of endo/exo cycloadducts in nearly quantitative yield. The major epimer **50** was separated by chromatography and saponified to yield acid **51**. Curtius rearrangement of **51**, with trapping of the resulting isocyanate by ethanol, provided bicyclooctenyl carbamate **52** in 68% yield.[54] Removal of the alcohol protecting group from this intermediate with tetrabutylammonium fluoride, followed by cleavage of the carbamate with potassium hydroxide delivered the hydroxyl bicyclooctenylamine **53** in 64% yield for the two steps.

With hydroxyl bicyclo[2.2.2]octenylamine **53** in hand, we turned to investigate the projected base-promoted aza-Cope–Mannich sequence (Scheme 7). A method for generating the labile formaldehyde imine derivative of **53**[55] under strongly basic conditions that would also deprotonate the bridgehead alcohol was required. Such a method was available, as we had shown earlier that formaldehyde imines could be generated *in situ* by base-promoted fragmentation of secondary cyanomethylamines.[56] Cyanomethylamine **54** was prepared conveniently in 84% yield by reaction of the hydrochloride salt of primary amine **53** with formalin and KCN in aqueous THF. Exposure of this product to an excess of KH at room temperature in THF affected the desired base-promoted oxy-aza-Cope rearrangement to generate *cis*-hydroisoquinoline alkoxide **56**. Upon aqueous workup, the corresponding ketone **57**, albeit impure, was isolated in low yield. We soon discovered that quenching the basic

reaction at low temperature with an aqueous HCN/KCN buffer solution allowed the *cis*-3-cyanohydroisoquinolone **58** to be isolated in 67% yield.[57]

We had succeeded in promoting the desired sigmatropic rearrangement; however, alkoxide imine **56** did not cyclize to generate an azatricyclo[4.4.0.$0^{2,8}$]decane product. This outcome, which contrasts with the formation of 3-acylpyrrolidine and hydroindolone conjugate bases from related base-promoted aza-Cope–Mannich transformations,[52] likely reflects the strain of the azatricyclo[4.4.0.$0^{2,8}$]decane ring system. The increase in basicity that would result when a potassium enolate is transformed to a potassium amide renders the cyclization of imine enolate **56** much less favorable than the related junction of iminium ion and enol functional groups (classical Mannich cyclization).

Decoupling the base-promoted sigmatropic reorganization and the Mannich cyclization step finally allowed the long-sought azatricyclo[4.4.0.$0^{2,8}$]decanones to be constructed. To eventually facilitate the Mannich cyclization, *cis*-3-cyanohydroisoquinolone **58** was converted to its tertiary amine congener **59** by reaction with methyl methanesulfonate and diisopropylethylamine in refluxing chloroform (Scheme 7). To our delight, exposure of this intermediate to excess HCl in methanol at 95 °C brought about the desired intramolecular Mannich reaction to generate azatricyclo[4.4.0.$0^{2,8}$]decanone **61**. This product, whose structure was secured readily by NMR and mass spectrometric analysis, was isolated in 44% yield.

With the successful sequential base-promoted oxy-aza-Cope–Mannich sequence developed we turned to examine the related process with intermediates that contained functionality that plausibly could be employed to fashion the terminal vinyl and hydropyran fragments of gelsemine. We began by examining a sequence in which the hydroxymethylene unit of gelsemine would be present from the outset. This study commenced with the Diels–Alder cycloaddition of siloxy diene **49** with methyl (*E*)-4-benzyloxy-2-butenoate (**62**) (Scheme 8). When conducted in the presence of $AlCl_3$ at −78 °C, this reaction delivered a 7:1 mixture of endo and exo cycloadducts in 71% yield, from which the endo epimer **63** was separated readily by chromatography. Allylic oxidation of adduct **63** with selenium dioxide gave aldehyde **64**, which upon standard Wittig methylenation provided diene **65** in 68% yield for the two steps. Saponification of the methyl ester of **65**, Curtius rearrangement of the derived acid, and alkaline hydrolysis of the resulting isocyanate delivered primary amine **67** in 60% overall yield. The cyanomethyl group was introduced next by reaction of **67** with chloroacetonitrile in the presence of tetrabutylammonium iodide to deliver amino nitrile **68** in 65% yield. Finally the silyl protecting group was removed using TBAF giving the oxy-aza-Cope precursor **69** in 91% yield. However, exposing **69** to KH to initially form formaldimine alkoxide **70** did not effect the desired anionic aza-Cope rearrangement; when this reaction was quenched with methyl chloroformate, only the tricyclic oxazolidine **71** was isolated (43% yield).

Presumably the benzyloxymethyl side chain of **70** is responsible for imine–alkoxide **70** failing to undergo [3,3]-sigmatropic rearrangement. As depicted in Scheme 1, this substituent would emerge after [3,3]-sigmatropic rearrangement on the congested concave face of the *cis*-hydroisoquinoline product. Presumably this extra steric encumbrance is sufficient to prevent the sigmatropic reorganization. We had no choice but to postpone installation of the hydroxymethyl group until after the base-promoted oxy-aza-Cope rearrangement/Mannich cyclization sequence. Bromoazatricyclodecane **18** (Figure 2) emerged as a logical target, foreseeing the exo-oriented bromine at C16 as a handle for eventual installation of the hydroxymethyl group.

The ultimately successful synthesis of rearrangement substrate **18** began with the 8:1 mixture of Diels–Alder cycloadducts **50**, which was prepared on large scale in 90% overall yield from

3-methylanisole (see Scheme 6). Allylic oxidation of **50** provided a mixture of epimeric enals. These products could be separated on large scale by flash chromatography to provide the required endo epimer **72** in 80% yield (Scheme 9). Wittig methylenation of aldehyde **72**, followed by saponification of the diene product delivered acid **74** in 86% yield for the two steps. Curtius rearrangement of acid **74** was effected using triphenylphosphoryl azide in refluxing toluene, and the resulting isocyanate was trapped at room temperature with 4-methoxybenzyl alcohol to give the *p*-methoxybenzyl carbamate (Moz) **75** in 72% yield. Exposure of **75** to trifluoroacetic acid at room temperature in the presence of anisole cleaved the carbamate to provide the corresponding primary amine in high yield.[54] Reaction of this crude primary amine with formalin and KCN in a pH 7 buffer solution then delivered cyanomethylamine **76** in 81% yield for the two steps. Finally, liberation of the hydroxyl group of **76** using TBAF provided the crystalline aza-Cope rearrangement precursor **77** in 90% yield.

Azatricyclo[4.4.0.$0^{2,8}$]decanone **18** was assembled from bicyclooctenylamine **77** in three additional steps. The sequence was initiated by base-promoted aza-Cope rearrangement brought about by exposing **77** to excess potassium hydride and 18-crown-6 at room temperature in THF. Quenching the resulting rearrangement product with methyl chloroformate provided a mixture of regioisomeric carbamate enecarbonates **78**. Selective cleavage of the carbonate functionality of this crude product with methanolic KOH at room temperature gave *cis*-hydroisoquinoline enecarbamate **79** in 81% overall yield from cyanomethylamine **77**. Incorporation of the bromine substituent was realized without complications by reaction of enecarbamate **79** with 1.1 equiv of bromine and excess 1,2,2,6,6-pentamethylpiperidine (PMP) to generate β-bromo enecarbamate **80**. This product was not purified, but directly heated at reflux in trifluoroacetic acid to provide azatricyclo[4.4.0.$0^{2,8}$]decanone **18** as a single stereoisomer in 67% overall yield from enecarbamate **79**.[58] ^{1}H NMR NOE studies suggested that the bromine substituent was oriented on the exo face of the azatricyclic ring system, a conclusion that was confirmed by single crystal X-ray analysis of ethylene ketal derivative **82**. After extensive optimization, the sequence summarized in Scheme 9 allowed gram quantities of azatricyclo[4.4.0.$0^{2,8}$]decanone **18** to be prepared from commercially available 3-methylanisole in an overall yield of 16% for the 12 steps.

The configuration of the bromine substituent in azatricyclic product **18** deserves comment. We assume that β-bromo enecarbamate **80** kinetically protonates from the convex face to deliver initially *N*-acyloxyiminium-ion epimer **83** (Scheme 10). However, Mannich cyclization of this epimer is not observed because the boat conformation of the azacyclic ring that would be required to achieve proper overlap in the cyclization step thrusts the bulky bromine substituent directly under the carbocyclic ring. Thus, **83** equilibrates by way of **80** with epimer **84**, the latter undergoing Mannich cyclization as depicted in transition structure **81** to deliver azatricyclodecanone **18**.

Conclusion

Iminium ions and *N*-acyloxyiminium ions derived from endo-oriented 1-methoxy- or 1-hydroxybicyclo[2.2.2]oct-5-enylamines do not undergo cationic aza-Cope rearrangement to form *cis*-hydroisoquinolinium ions (e.g., **19** → **21**, Scheme 1), a failure that we ascribe to two factors: bond formation being advanced with respect to bond cleavage in this sigmatropic rearrangement, and the tricyclo[4.4.0.$0^{0,0}$]decane-like pericyclic transition state being of high energy.[32,34] However, the analogous base-promoted oxy-aza-Cope rearrangement does take place, which we associate with bond cleavage being advanced over bond formation in this anionic sigmatropic rearrangement.[50] Moreover we demonstrated for the first time that the azatricyclo[4.4.0.$0^{2,8}$]decane core fragment and the C5-C6 bond of gelsemine can be formed by Mannich cyclization of a *cis*-hydroisoquinolone precursor.[59] Using a sequential base-promoted oxy-aza-Cope rearrangement–Mannich cyclization sequence,[26,40] gram quantities

of azatricyclo[4.4.0.0^{2,8}]decanone **18**, a central intermediate in our total synthesis of (±)-gelsemine,[40] was prepared from 3-methylanisole in 12 steps and 16% overall yield.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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55. Formaldehyde imines, unless substituted with extremely bulky substituents on nitrogen, cannot be isolated as they rapidly trimerize to form hexahydro-1,3,5-triazines.[56a]
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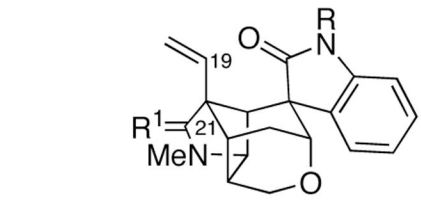
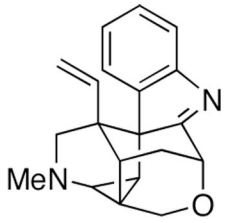
58. The formyl analog (**79**/**80** with R = CHO), which is available from the reaction of **79** with Vilsmeier reagent, does not cyclize under these conditions

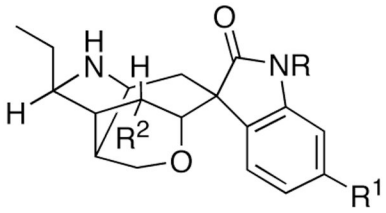
59. Johnson subsequently employed a Mannich cyclization of a more advanced intermediate to form this bond of gelsemine in his inaugural total synthesis of (±)-gelsemine.[22]

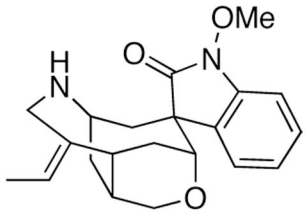


R = H, R^1 = H,H gelsemine (**1**)
R = OMe, R^1 = H,H gelsevirine (**2**)
R = H, R^1 = O 21-oxogelsemine (**3**)
R = OMe, R^1 = O 21-oxogelsevirine (**4**)



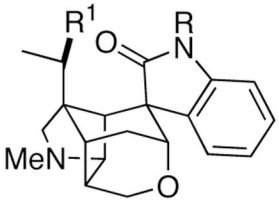
koumine (**10**)





rankinidine (**14**)

R = OMe, R^1 = OMe, R^2 = H gelsemicine (**5**)
R = OMe, R^1 = R^2 = H gelsedine (**6**)
R = R^1 = OMe, R^2 = OH hydroxygelsemicine (**7**)
R = OMe, R^1 = H, R^2 = OH 14β-hydroxygelsedine (**8**)
R = R^1 = R^2 = H gelsenicine (**9**)



R = OMe, R^1 = OH 19-(*R*)-hydroxydihydrogelsevirine (**11**)
R = OMe, R^1 = OAc 19-(*R*)-acetoxydihydrogelsevirine (**12**)
R = H, R^1 = OH 19-(*R*)-hydroxydihydrogelsemine (**13**)

Figure 1.
Gelsemium alkaloids.

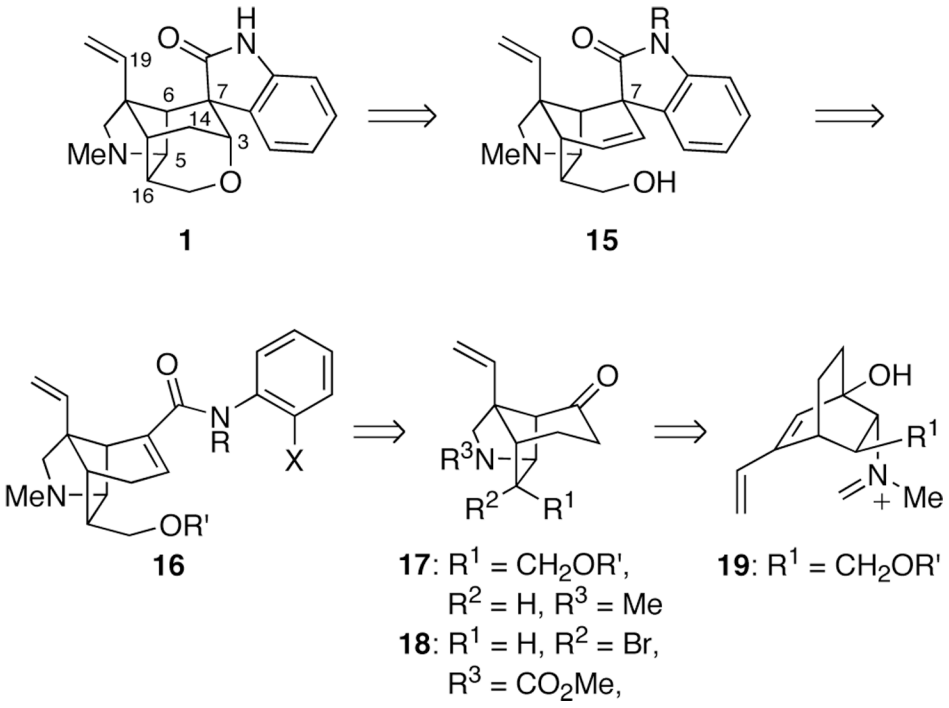


Figure 2.
Initial retrosynthetic analysis.

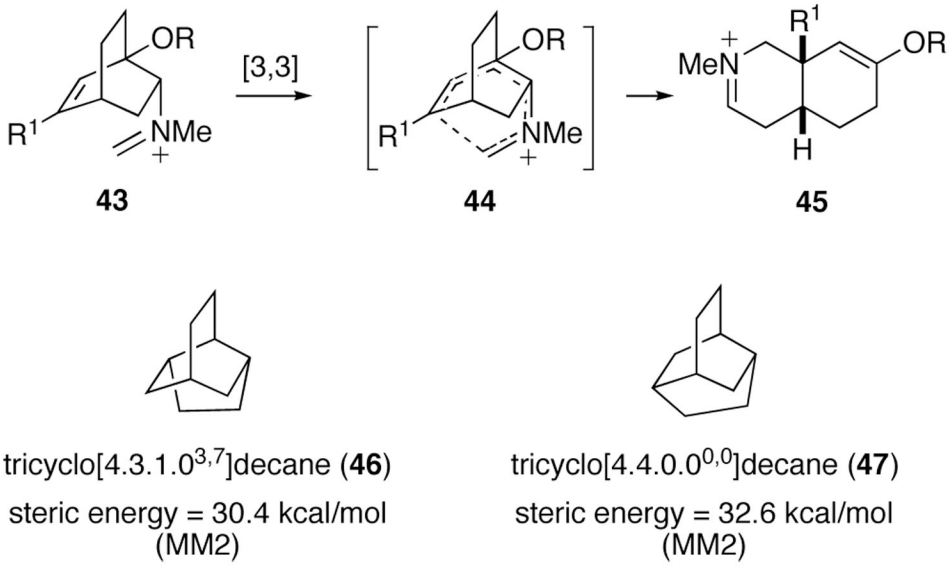
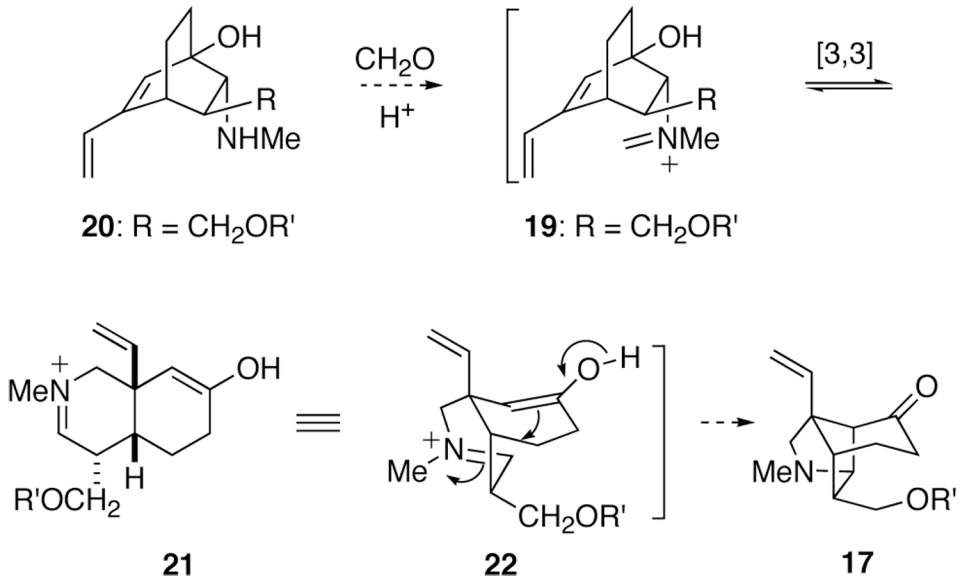
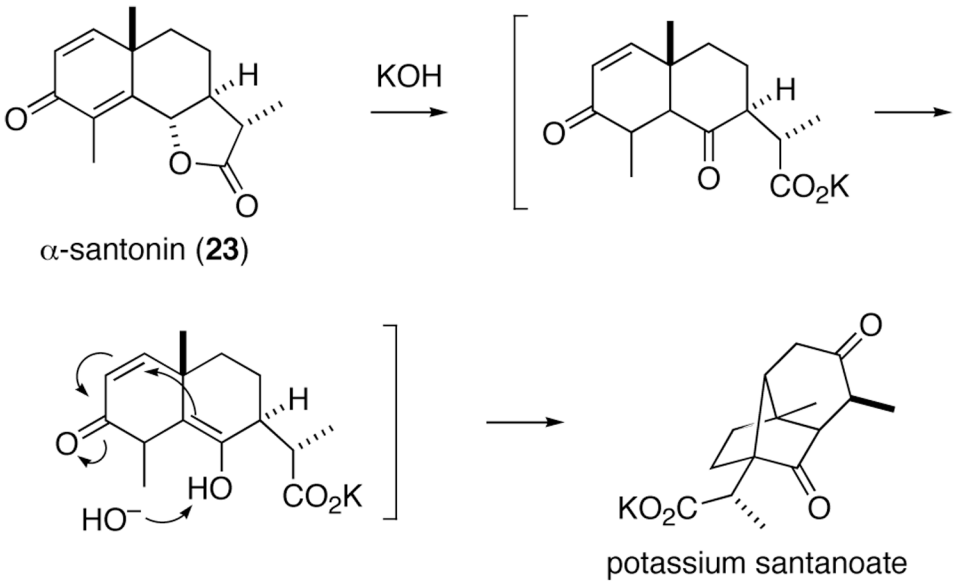


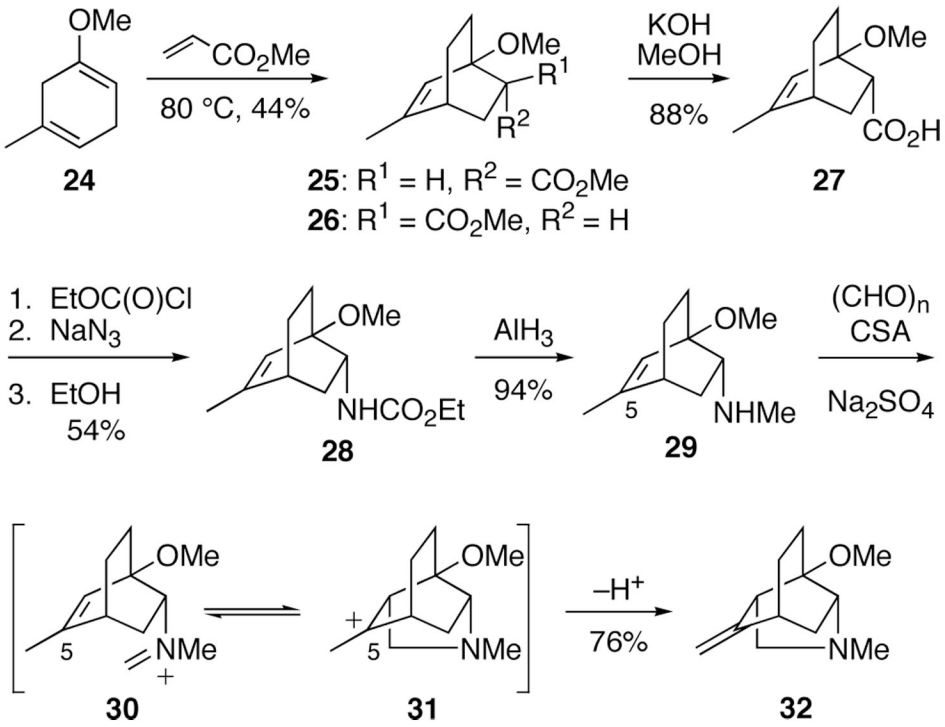
Figure 3.
Transition structure of the cationic aza-Cope rearrangement of **43** and the steric energies of related tricyclodecanes.



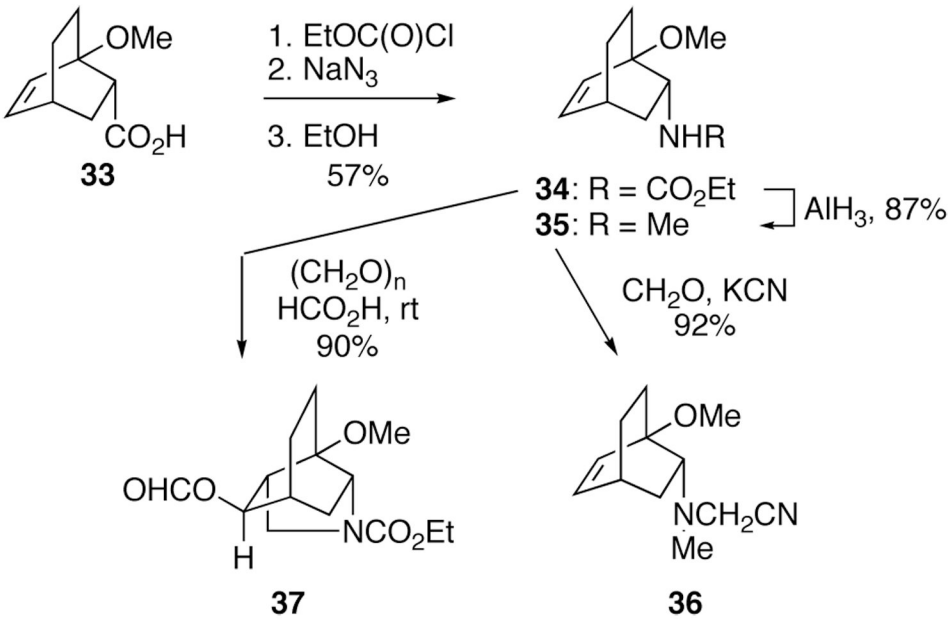
Scheme 1.



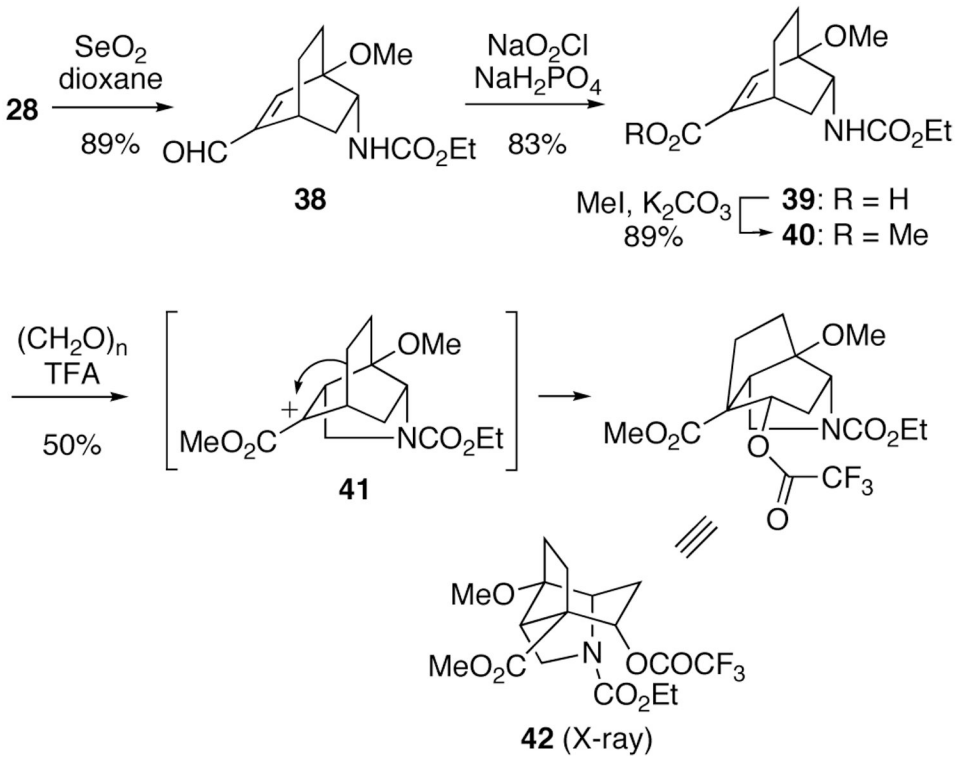
Scheme 2.



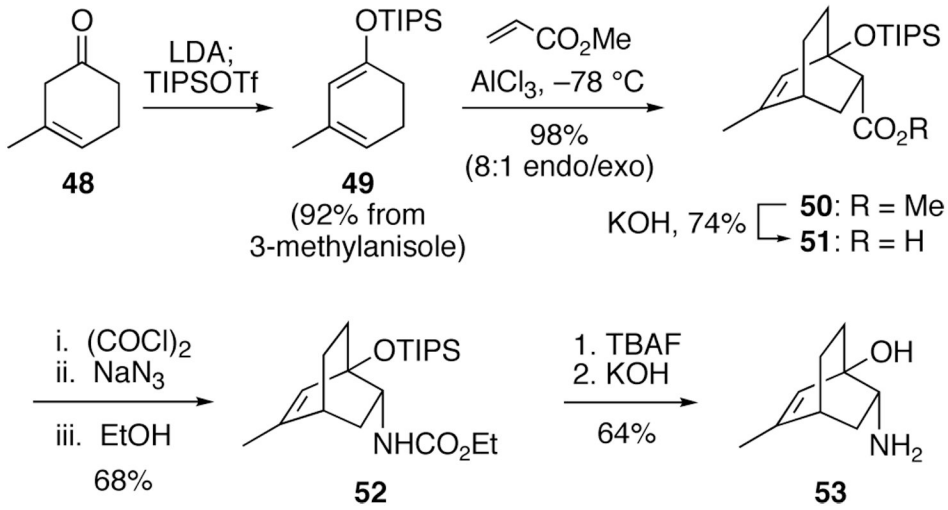
Scheme 3.



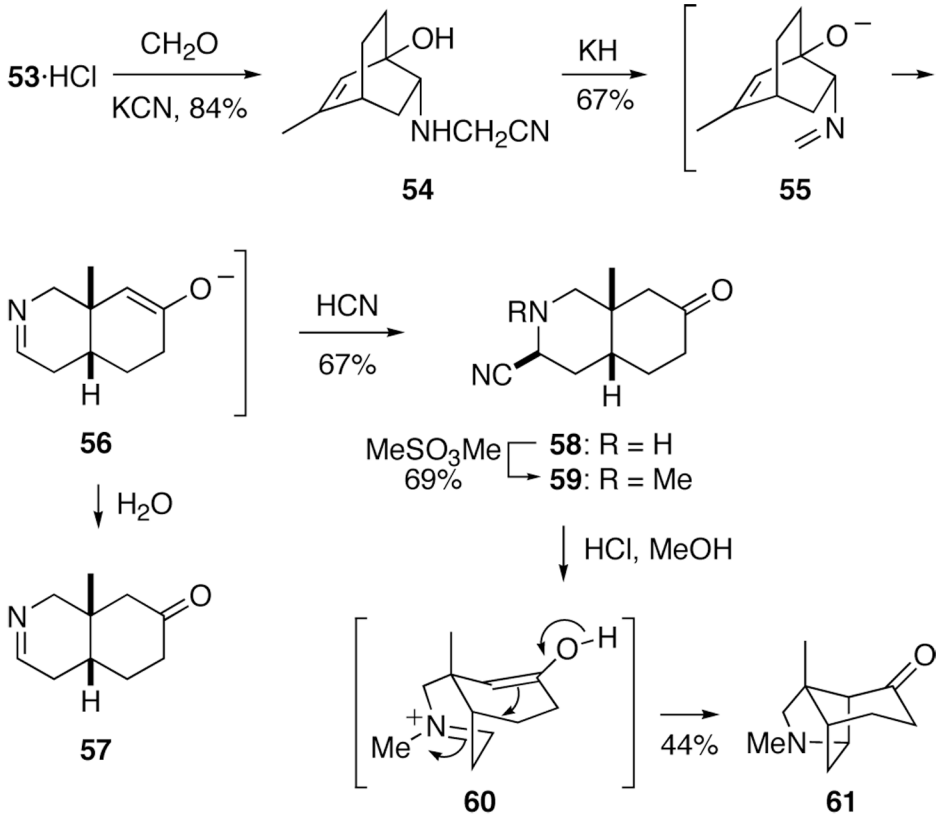
Scheme 4.



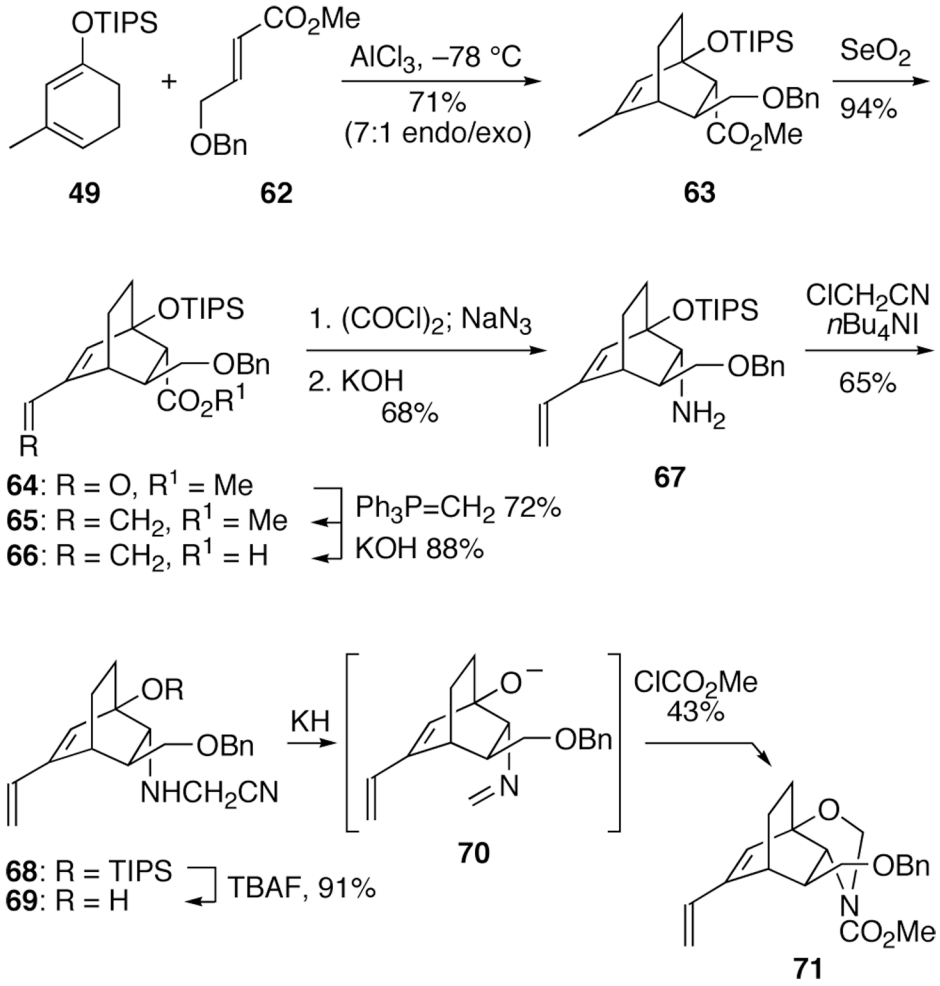
Scheme 5.



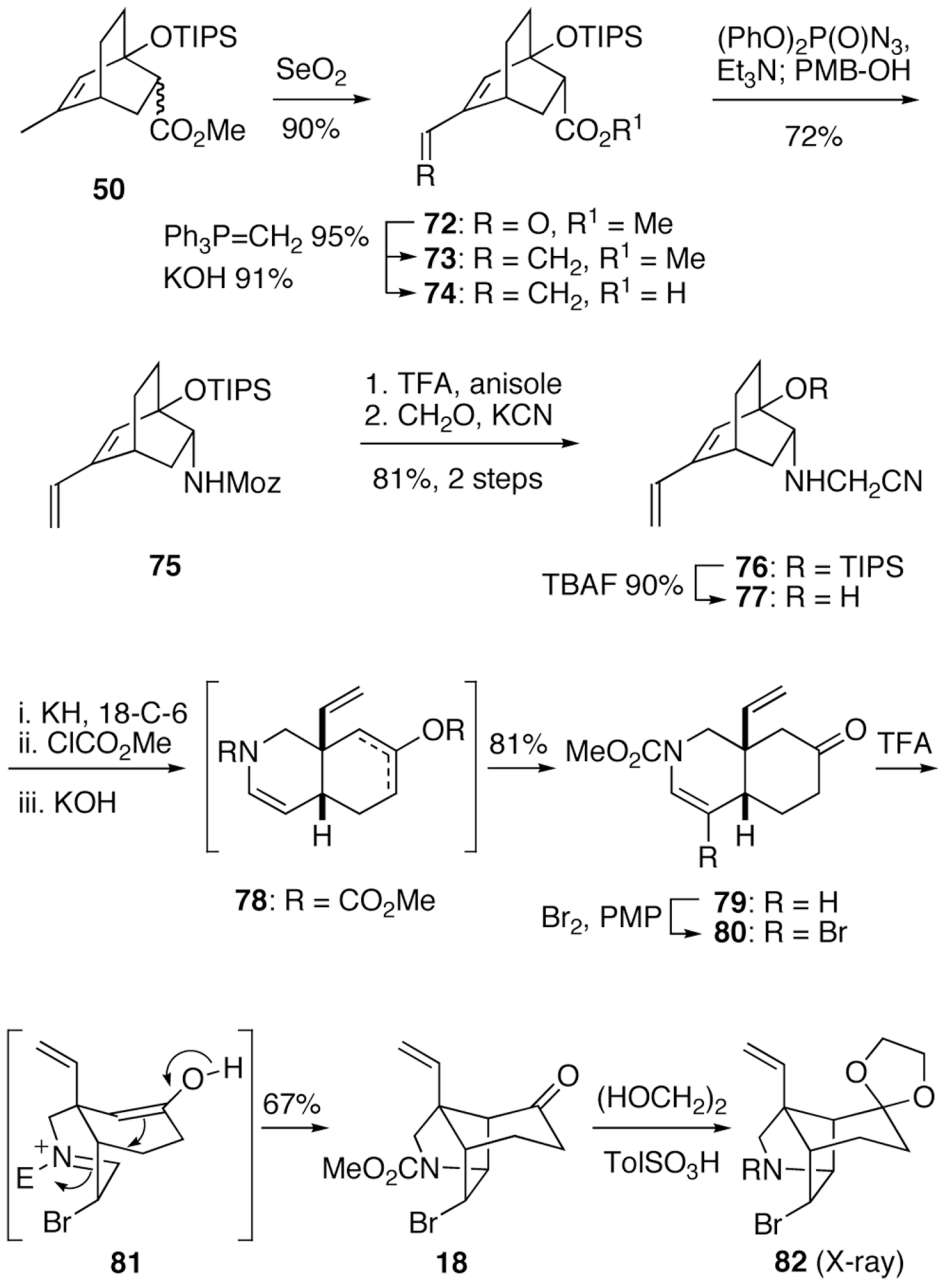
Scheme 6.



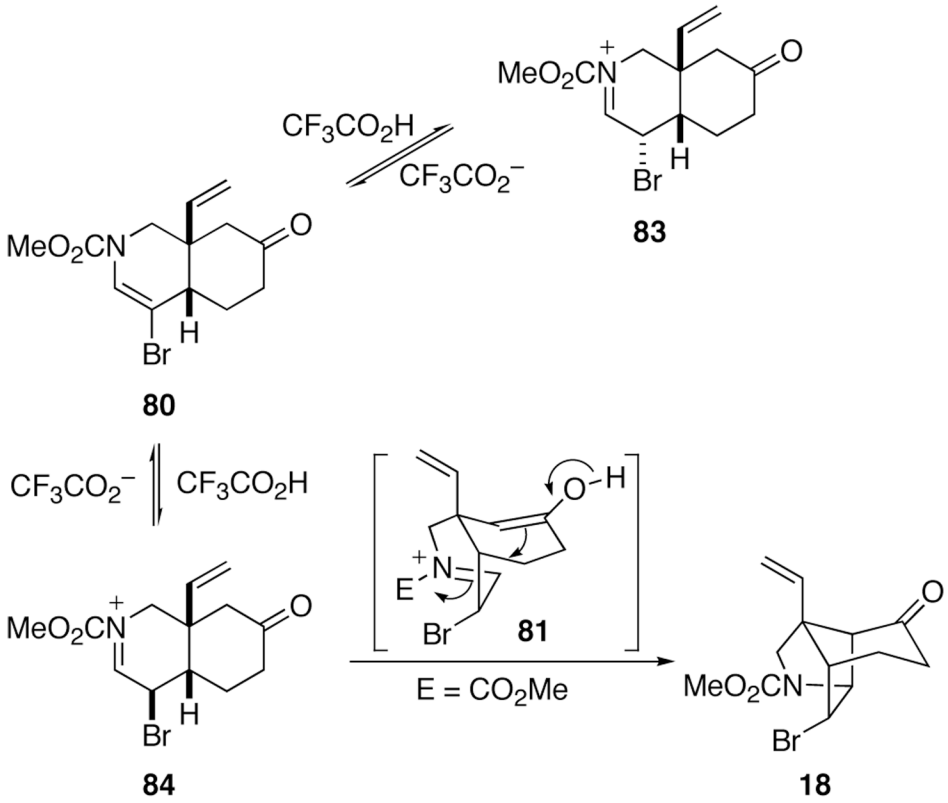
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.