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Use of the Intramolecular Heck Reaction for Forming Congested Quaternary Carbon Stereoenters. Stereocontrolled Total Synthesis of (±)-Gelsemine

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Abstract

Intramolecular Heck reactions of α,β-unsaturated 2-haloanilides derived from azatricyclo[4.4.0.0[2,8]]decanone **5** efficiently install the congested spirooxindole functionality of gelsemine. Depending upon the Heck reaction conditions and the nature of the β-substituent, either products having the natural or unnatural configuration of the spirooxindole group are formed predominantly. Efforts to elaborate the hydropyran ring of gelsemine from the endo-oriented nitrile substituent of pentacyclic Heck product **18** were unsuccessful. Important steps in the ultimately successful route to (±)-gelsemine (**1**) are: (a) intramolecular Heck reaction of tricyclic β-methoxy α,β-unsaturated 2-iodoanilide **68** in the presence of silver phosphate to form pentacyclic product **69** having the unnatural configuration of the spirooxindole fragment, (b) formation of hexacyclic aziridine **80** from the reaction of cyanide with intermediate **79** containing an *N*-methoxycarbonyl-β-bromoethylamine fragment, (c) introduction of C17 by ring-opening of the aziridinium ion derived from aziridine **80**, and (d) base-promoted skeletal rearrangement of pentacyclic equatorial alcohol **82** to form the oxacyclic ring and invert the spirooxindole functional group to provide hexacyclic gelsemine precursor **83**.

Introduction

At the time its structure was elucidated,[2] the compact hexacyclic cage structure of gelsemine (**1**) posed implicit challenges to the capabilities of organic synthesis.[3] In the intervening 40 years, a number of approaches to gelsemine have been described and much imaginative chemistry has been developed in this context.[4–16] The first total syntheses of (±)-gelsemine were disclosed in 1994 by the groups of Johnson,[17] Speckamp,[18] and Hart (21-oxogelsemine),[19] additional total syntheses were subsequently reported from the laboratories of Fukuyama,[20] Overman[21] and Danishefsky,[22] and a total synthesis of (+)-gelsemine was disclosed by Fukuyama and co-workers in 2000.[23]

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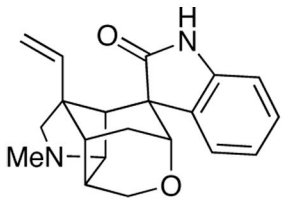


gelsemine (**1**)

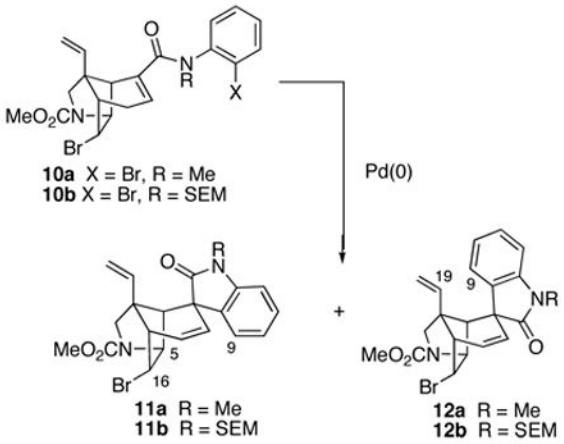
The preceding paper in this series presented full details of the early stages of our gelsemine total synthesis, which resulted in a direct route for preparing azatricyclo[4.4.0.0^{2,8}]decanone **5** from 3-methylanisole (**6**) (Figure 1).[24] The bromide functional group of azatricyclodecanone **5** provides a potential handle for fabricating the hydropyran ring, whereas the ketone carbonyl was seen as a locus for generating the spirooxindole unit. At the outset of these studies, we envisaged that this latter elaboration would be particularly demanding as installation of the spirooxindole on the azatricyclodecane framework introduces a 1,3-diaxial interaction between the oxindole carbonyl group and the angular vinyl group. As events developed, elaboration of the spirooxindole proved to be relatively easy as a result of the remarkable ability, first revealed in these studies,[9a] of intramolecular Heck reactions to form congested quaternary carbon centers.[25] Herein we provide full details of our development of Heck cyclization routes to the spirooxindole unit of gelsemine, our unsuccessful efforts to elaborate the hydropyran ring from pentacyclic intermediates **2**, and the final endgame strategy that allowed (±)-gelsemine (**1**) to be fashioned from **3**.

Results and Discussion

Elaboration of the Spirooxindole Using an Intramolecular Heck Reaction

With a workable synthesis of tricyclic ketone **5** in hand,[24] the next task was to introduce the α,β-unsaturated anilide functionality that would serve as a precursor of the spirooxindole unit. Intermediates **4** wherein Z = H were chosen for our initial attempts to form the spirooxindole functionality, because the projected cyclization was deemed speculative enough without requiring insertion of tetrasubstituted double bonds.[26] To this end, the lithium enolate of ketone **5** was trapped with *N*-phenylbis(trifluoromethanesulfonimide) (**7**) to generate enol triflate **8** in 78% yield (Scheme 1). Palladium-catalyzed carbonylative cross-coupling of triflate **8** with 2-bromoaniline gave 2-bromoanilide **9** in 74% yield.[27] However, this coupling proceeded in poor yield with 2-iodoaniline or *N*-benzyl-2-bromoaniline.[28] Protection of the amide nitrogen of **9** with a methyl or 2-(trimethylsilyl)ethoxymethyl (SEM) group provided α,β-unsaturated amides **10a** and **10b** in good yields.

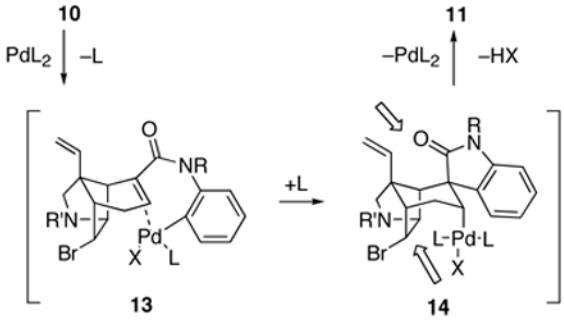
We now were ready to explore generating the critical spiro-fused oxindole fragment of gelsemine by intramolecular Heck reaction. At the time these studies began, we had shown that intramolecular Heck reactions could be employed to elaborate spirooxindole units onto simple, unfunctionalized carbocyclic rings.[9a] However, the projected cyclization of **9** or **10** was far more demanding: these substrates are more highly functionalized, their C-C double bonds are more hindered and two epimeric Heck products could be formed in the Heck cyclizations (equation 1). Migratory insertion from the α-face would lead to spirooxindole **11**, whereas insertion from the β-face would provide the undesired epimer **12**. Molecular mechanics (MM2) calculations indicated that oxindole **11**, wherein the aromatic ring is equatorially disposed, is more stable (~3 kcal/mol); however, it was not clear to what extent at all this preference would be felt in the stereodetermining step.



(1)

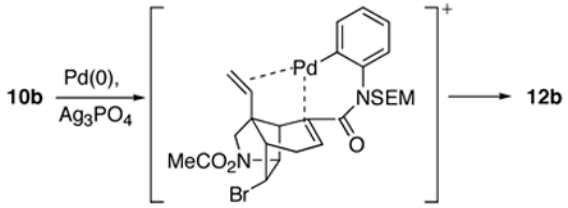
Salient results of our extensive studies of Heck cyclizations in the gelsemine series are summarized in Table 1. Initial attempts to cyclize secondary amide **9** failed, giving only reduction product. This result was not unexpected, because cyclization of a secondary amide requires population of a high-energy *E* amide conformation. In contrast, tertiary anilides **10a,b** cyclized under a variety of Heck reaction conditions. Cyclizations were examined initially using $(Ph_3P)_4Pd$ as the catalyst in refluxing acetonitrile. Changing the amide protecting group from Me to SEM had little effect on the low stereoselectivity observed in the reaction (entries 1 and 2).[29] Cyclization was more sluggish in refluxing tetrahydrofuran; however, stereoselectivity remained unaltered (entries 4 and 5). The configuration of oxindole products **11** and **12** was determined readily by ^{1}H NMR NOE experiments. For diastereomer **11**, a positive NOE is observed between the hydrogens at C9, C5 and C16, whereas for epimer **12**, a positive NOE is seen between the C9 and C19 hydrogens.[30]

With the aim of reducing the severe steric interactions that exist between the phosphine ligands and the two-carbon bridge of the azatricyclic ring in the presumed precursor of spirooxindole **11**, alkylpalladium(II) halide complex **14** (equation 2), we investigated the use of chelating diphosphine ligands. To our surprise, replacing Ph_3P with bis(diphenylphosphino)ethane (dppe) in cyclizations of α,β-unsaturated anilide **10b** carried out in refluxing THF had little effect on stereoselection (entry 4). Stereoselectivity was also poor when the larger 1,1′-bis (diphenylphosphino)ferrocene (dppf) ligand was employed (entry 5). However, cyclizations of α,β-unsaturated anilide **10b** catalyzed by tris(dibenzylideneacetone)dipalladium $[Pd_2(dba)_3]$ without added phosphine ligands were more selective (entries 6 and 7).[31,32,33] Spirooxindoles **11b** and **12b** were generated in a 9:1 ratio, respectively, and in good yield using 10 mol% of $[Pd_2(dba)_3]$ as the catalyst in refluxing toluene.



(2)

In contrast, Heck cyclization of precursor **10b** conducted in the presence of Ag_3PO_4 without phosphine ligands occurred with virtually complete selectivity to give the epimeric oxindole **12b** (entry 8). We attribute the high selectivity (97:3) in this case to coordination of the angular vinyl group during the insertion step (equation 3). Apparently, this coordination is enhanced by the dissociation of the bromide ligand to give a more electrophilic cationic palladium(II) intermediate.[9d] Consistent with this proposal, Heck cyclization under identical conditions of the analog of α,β-unsaturated anilide **10b** in which the angular vinyl group is replaced by an ethyl substituent provided a 1:1 mixture of oxindole diastereomers.[9d]



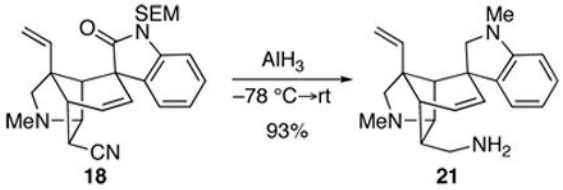
(3)

Attempts to Construct the Tetrahydropyran Ring of Gelsemine from Pentacyclic Intermediate 11b

With five of the six rings of gelsemine assembled, what remained was introduction of one carbon and elaboration of the tetrahydropyran ring. Our anticipation that this task would be straightforward turned out to be a remarkably poor assessment. Our initial plan was to displace the bromide substituent of **11b** with cyanide anion, convert the resulting endo-oriented nitrile to a primary alcohol and engage this group and the alkene to form the final ring of gelsemine. With this strategy in mind, a 9:1 mixture of pentacyclic oxindoles **11b/12b** (formed as described in entry 9 of Table 1) was allowed to react with NaCN in hot dimethylsulfoxide (Scheme 2). To our surprise, this reaction produced aziridines **15/16** in a 9:1 ratio and 85% yield; none of the expected nitrile product was formed. These aziridine epimers could be separated on silica gel, providing the major stereoisomer **15** in 76% yield from the **11b/12b** Heck product. Whether this unusual reaction occurs by an S_N1 process, a double displacement sequence, or another mechanism has not been determined.

The formation of aziridine **15** did not appear to sabotage our plans because the aromatic ring of the oxindole should block backside attack at C5 of this and related intermediates. Thus, we anticipated that nucleophiles would attack an electrophilic aziridinium ion derived from hexacyclic aziridine **15** at the C16 carbon. In practice it was found that reaction of aziridine **15** with methyl trifluoromethanesulfonate at room temperature in CH_2Cl_2 formed the stable *N*-methylaziridinium salt **17**, which, when exposed to an excess of NaCN in dimethylsulfoxide at 90 °C, produced a single pentacyclic nitrile **18** in 84% yield.

We turned to examine elaboration of the endo-oriented nitrile substituent of pentacyclic intermediate **18** to a hydroxymethyl group. Attempted reduction of the nitrile group of **18** with diisobutylaluminum hydride (DIBALH), sodium bis(2-methoxyethoxy)aluminum hydride (RedAl®), $LiAl(OEt)_3H$, $NaBH_4$ or $NaBH_4$•$CoCl_2$ under a wide variety of reaction conditions resulted either in recovery of starting material or production of unidentifiable products. One exception was the reaction of pentacyclic nitrile **18** with $LiAlH_4$ in Et_2O at −78 °C, which delivered indolenine **19** in 80% yield upon aqueous workup (Scheme 2). Further reduction of this product with $LiAlH_4$ in Et_2O at −20 °C provided indoline **20**. It is remarkable that the endo nitrile group was untouched by $LiAlH_4$ under both conditions. The only reagent that reduced the nitrile group of intermediate **18** cleanly was AlH_3[34] which delivered pentacyclic triamine **21** in 93% yield (equation 4).

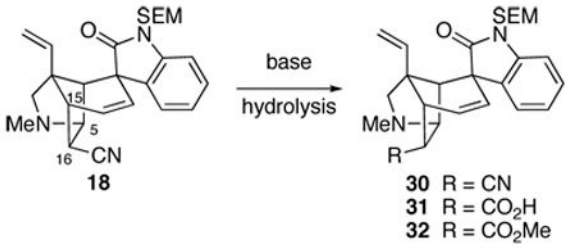


(4)

As a primary amine could plausibly serve as a precursor of a primary alcohol,[35–37] we explored the use of other oxindole protecting groups in the hopes that the nitrile substituent of a congener of pentacyclic intermediate **18** could be selectively converted to the corresponding primary amine without reduction of the oxindole. To examine this issue, the SEM protecting group of **18** was removed by reaction with 6 M HCl, providing pentacyclic oxindole **22** (Scheme 3). This crystalline product yielded single crystals, allowing its structure and the configuration of the major Heck product to be rigorously established. Reaction of unprotected oxindole **22** with triisopropylsilyl (TIPS) trifluoromethanesulfonate in CH_2Cl_2 in the presence of diisopropylethylamine cleanly introduced the TIPS group onto the oxindole nitrogen to give intermediate **23** in 80% yield. Subsequent reduction of **23** with AlH_3•Me_2EtN[38] in THF at room temperature generated primary amine **24**. As we hoped, the bulky TIPS group had shielded the oxindole carbonyl from reduction.[39] This polar intermediate was not purified, but directly acylated with either *N*-(trifluoroacetoxy)succinimide[40] or pentafluorophenyl acetate[41] to give trifluoroacetamide **25** or acetamide **26** in 40–50% overall yields from pentacyclic intermediate **23**. As the TIPS group had been cleaved during these acylation steps, the oxindole nitrogen was reprotected by reaction of amides **25** and **26** with benzoic anhydride to yield imides **27** and **28**.

One of the better methods for converting aliphatic primary amines to alcohols involves thermal rearrangement of *N*-nitrosoamide intermediates. However, all our attempts to convert trifluoroacetamide **27** or acetamide **28** into the corresponding *N*-nitrosoamide failed. For example, reaction of amides **27** or **28** with $NaNO_2$ in Ac_2O-HOAc,[35] or with N_2O_4 in the presence of NaOAc[36] or pyridine[37] only returned unchanged starting material. Subjecting amide **28** to the more electrophilic reagent $NOBF_4$[37] under a variety of reaction conditions resulted only in decomposition of this substrate.

In light of our inability to generate pentacyclic alcohol **29** from an amine precursor, we returned to examine other potentially useful transformations of the nitrile group of pentacyclic intermediate **18**. Initially we explored basic hydrolysis. Reaction of **18** with LiOH in refluxing methanol, or NaOH in refluxing ethanol, resulted only in epimerization of the nitrile group of precursor **18** to give mixtures of **18** and its epimer **30** (equation 5).[42] Hydrolysis of pentacyclic nitrile **18** under more forcing conditions (5 M KOH in ethylene glycol at 150 °C), followed by treating the crude reaction mixture with diazomethane, provided a single methyl ester product in 63% yield. However, it was readily ascertained that this product was the exo ester **32**, most likely resulting from epimerization of the nitrile group prior to hydrolysis. Additionally, treatment of nitrile **18** with basic hydrogen peroxide under phase transfer conditions again yielded an epimerized product, in this case the corresponding primary amide.



(5)

As a last-ditch effort to salvage these intermediates, we explored whether pentacyclic ester **32** could be epimerized by kinetic protonation of its derived enolate.[43] Although such a sequence could be realized with a simpler azatricyclo[4.4.0.0^{2,8}]decyl ester,[44] we never succeeded in accomplishing this epimerization in the pentacyclic series. For example, exposure of ester **32** to excess lithium diisopropylamide (LDA), lithium pyrrolidide, lithium diethylamide, potassium diisopropylamide, potassium bis(trimethylsilyl)amide (KHMDS), lithium hydride or potassium hydride (with or without *N*,*N*′-dimethylpropyleneurea, DMPU), followed by quenching with malononitrile failed to produce C16-epi **32**.[45] In all cases, only the starting ester was obtained. As it was not clear whether deprotonation was taking place, we attempted to prepare the silyl ketene acetal derivative of ester **32**. Screening the same set of bases using *tert*-butyldimethylsilyl chloride as an electrophilic quenching agent also returned only **32**, suggesting that the hindered endo proton at C16 was not being removed.

We also examined acidic conditions for elaborating the hindered endo nitrile group of pentacyclic intermediate **22** in the hopes that epimerization at C16 would be less problematic (Scheme 4). Dissolving this precursor in concentrated H_2SO_4 led, in low yield, to the formation of hexacyclic carboxamide **33**, the structure of which was confirmed by X-ray crystallographic analysis. Although the nitrile group had been converted to a carboxamide without epimerization, these strongly acidic conditions had also promoted cyclization of the oxindole onto the C19 terminal vinyl group.[46] However, all attempts at promoting the cyclization of the γ,δ -unsaturated carboxamide unit of precursor **33** (or the tetracyclic oxindole derived from **33** upon treatment with aqueous HCl) by reaction with I_2,[47] PhSeBr,[48] Br_2,[49] $Hg(OAc)_2$[50] or $Hg(OCOCF_3)_2$[51] were unsuccessful.

With these disheartening results in hand, we abandoned attempts to generate the hydropyran ring of gelsemine from a pentacyclic precursor having an endo-oriented C16 nitrile substituent. We returned to aziridinium ion **17** to examine its opening with other one-carbon nucleophiles. Unfortunately, reactions of hexacyclic aziridinium ion **17** with nucleophiles such as (allyldimethylsilyl)methylmagnesium bromide,[52] (isopropoxydimethylsilyl) methylmagnesium bromide,[53] lithium acetylide, propynyllithium, 1,4-dioxen-2-yl lithium, [54] and the Creger–Silbert dianion, $LiCH_2CO_2Li$,[55] failed to give any identifiable products resulting from ring-opening at C16.

As a final effort to elaborate aziridinium ion **17**, we examined its reaction with the potent one-carbon nucleophile, disodium tetracarbonylferrate (**35**, Collman's reagent).[56] As this reagent reacts with five-and six-carbon unsaturated tosylates and halides to yield cycloalkanones,[57, 58] the expected product of its union with aziridinium ion **17** was hexacyclic ketone **37** (Scheme 5). We conjectured that Baeyer–Villiger oxidation of this product could lead to lactone **38**, which surely would serve as a precursor of gelsemine (**1**).

In the event, reaction of hexacyclic aziridinium ion **17** with Collman's reagent **35** in *N*-methylpyrrolidinone (NMP) at 50 °C under a CO atmosphere did not yield hexacyclic ketone **37**, but instead produced a rearranged product, the isomeric hexacyclic ketone **39**, in 59% yield

(Scheme 6).[9e] A possible mechanism for this unexpected and unprecedented reorganization has been suggested.[9e] Although hexacyclic product **39** was not a useful intermediate *en route* to gelsemine, it did provide one important insight. Exposure of this material to 1 M NaOH solution in acetone at room temperature caused rapid and complete epimerization at the spiro quaternary center to deliver oxindole epimer **42** in 90% yield. Removal of the SEM protecting group from this product gave hexacyclic oxindole **43**, which provided single-crystals suitable for X-ray analysis. Epimerization of the 1,5-dicarbonyl compound **39** likely occurs by retro-Michael fragmentation to generate oxindole enolate **40**, rotation about the C6–C7, and Michael ring closure of rotamer **41** to provide epimer **42**. The driving force for this epimerization is undoubtedly relief of steric interactions between the aromatic ring of the oxindole and the underside of the cup-shaped azatetracyclic moiety of **39**. Base-promoted epimerization of an oxindole intermediate turned out to play an important role in our ultimately successful route to gelsemine (*vide infra*).[59]

Attempts to Elaborate the Tetrahydropyran Ring Prior to Forming the Spirooxindole

Up to this point, our strategy had been to elaborate a hydroxymethyl group at C16 after the spirooxindole was in place (**B** → **44**, Figure 2). This timing of events had been chosen because we anticipated that the presence of an endo substituent at C16 would compromise the stereoselectivity of the intramolecular Heck reaction by shielding the lower face of the cycloalkene. Much to our surprise, in 1994 Speckamp and co-workers[18] reported just such an intramolecular Heck reaction that proceeded with modest stereoselectivity to form the desired spirooxindole using the $Pd_2(dba)_3$ conditions we had introduced.[9d] This disclosure prompted us to investigate installation of the C17 hydroxymethyl group prior to Heck cyclization. We anticipated that the absence of the endo-oriented aryl ring of the oxindole might simplify elaboration of the nitrile to a hydroxymethyl group. Therefore, intermediate **45** became our next sub goal.

The preparation of tricyclic ketone **45** is summarized in Scheme 7. Ketone **5** was readily elaborated to nitrile **48** by way of tetracyclic aziridine **47**.[60] Initial survey experiments showed that reduction of nitrile **48** with diisobutylaluminum hydride (DIBALH) was facile, even at −78 °C. However, hydrolysis of the resulting dialkylaluminum imine was not straightforward, with many standard conditions promoting extensive epimerization of the initially generated endo formyl group. Best results were obtained using aqueous acetic acid. After careful basification, amino aldehyde **49** was obtained as a 4:1 mixture of formyl epimers favoring the desired endo isomer. Reduction of this crude product with $NaBH_4$ and cleavage of the dioxolane group of product **50** gave tricyclic ketone **45** in 56% overall yield from nitrile **48**. However, this sequence, particularly the nitrile reduction step, could not be accomplished successfully on anything larger than exploratory scales. This unsatisfactory outcome forced us to abandon this approach.

The Final Successful Route to (±)-Gelsemine

Up to this point, most of the strategies we had investigated for forming the oxacyclic ring of gelsemine envisaged elaboration of pentacyclic nitrile **2** to intermediates that would allow the hydropyran ring to be constructed by forming the C3–O bond (Figure 1). Two factors, both arising from the sterically congested environment of C17 of the gelsemine ring system, had thwarted these efforts: facile epimerization at C16 when C17 is an electron-withdrawing substituent, and the difficulty in accomplishing common functional-group interconversions at C17 in pentacyclic intermediates. We turned to an alternate strategy that would side step these problems by constructing the tetrahydropyran ring of gelsemine by forming the O–C17 bond. Such an approach could allow the critical functionalization of the hindered endo nitrile to be accomplished in intramolecular fashion as suggested in Figure 3 (**51** → **52**). An attraction of this strategy was the expected ease of reduction of the C3 carbonyl group of intermediates such

as pentacyclic keto nitrile **51** as the reductant could approach from the less-encumbered convex β-face. We entertained the possibility of accessing **51** from pentacyclic enol ethers such as **53**, which might be available from Heck cyclization of α, β-unsaturated anilide **54** having a heteroatom substituent at C3. A pivotal issue would be whether or not the tetrasubstituted double bond of **54** would participate in an intramolecular Heck reaction. Heck insertions of tetrasubstituted double bonds are rare, and none had been described for a substrate approaching the complexity of **54**.[26] Moreover, the double bond of **54** might be a particularly poor ligand because it is part of a delocalized vinylogous carbamate or thiocarbamate.

As preliminary scouting experiments had shown that installing an alkoxy group into the α-position of ketone **5** would be difficult, we examined initially this revised plan in the sulfur series (Scheme 8). After failing to cleanly mono-sulfenylate enolate derivatives of **5**, we developed a novel route to enol triflate intermediate **56**. Tricyclic ketone **5** was initially converted to α,α-dithio derivative **55** by reaction with an excess of potassium hexamethyldisilazide (KHMDS) and methyl methanethiosulfonate. This intermediate was then desulfenylated by reaction with sodium methylmercaptide in THF, and the resulting sodium enolate was trapped with *N*-phenyltriflimide to give enol triflate **56**. Palladium-catalyzed carbonylation of **56** in methanol[27] then provided vinylogous thiocarbonate **57**. As in other Heck reactions investigated in our laboratories, the presence of the β-sulfur substituent did not have a deleterious effect on this palladium-catalyzed reaction.[61] Weinreb aminolysis of ester **57**[62]**Error! Bookmark not defined**. and protection of the resulting secondary amide with a SEM group generated the highly functionalized Heck cyclization substrate **58** in 30% overall yield from azatricyclic ketone **5**.

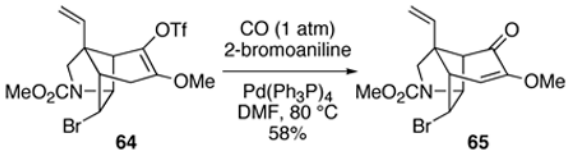
We next examined the propensity of β-methylthio α,β-unsaturated anilide **58** to undergo intramolecular Heck reaction. Cyclization conditions such as those listed in Table 1 that succeed with analogous substituents lacking a β-substituent failed to promote the cyclization of **58**. However, the desired intramolecular Heck reaction was accomplished successfully under forcing conditions (150 °C) using $(Ph_3P)_4Pd$ as the catalyst to give a 1:2 mixture of stereoisomeric tetracyclic products **59** and **60** in a combined yield of 69%. Configurational assignments for these adducts followed from diagnostic signals for the C19 vinyl hydrogens in ^1H NMR spectra.[30] Attempts to improve the diastereoselectivity of this reaction by using $Pd_2(dba)_3$ as the catalyst in the absence of phosphine ligands resulted in no reaction even at 150 °C. At this high temperature, the fine suspension of palladium that is originally present coagulates, a factor that is likely responsible for the unreactivity of substrate **58** under these conditions.

Extensive studies to optimize the Heck cyclization of unsaturated anilide **58** were not carried out because we soon discovered that cleavage of the vinyl sulfide functionality of these adducts would not be straightforward. Preliminary calibration experiments in which **59** was subjected to standard conditions for cleaving a vinylsulfide, for example $Hg(OCOCF_3)_2$–aqueous trifluoroacetic acid (TFA) or TFA alone in several different solvents, resulted in either decomposition or cleavage of the SEM group.[63] Because of these difficulties, we turned to examine the related sequence in the oxygen series.

As alluded to earlier, introduction of an alkoxy group into the α position of ketone **5** proved to be extremely challenging (Scheme 9). Enolization of **5** with KHMDS or LDA, followed by quenching the derived enolate with Davis' oxaziridine[64] returned starting material. Likewise, enolization with LDA followed by attempted oxidation with dimethyldioxirane,[65] MoO_5·pyridine·HMPA[66] or LiOO*t*-Bu[67] returned starting material, as did the reaction of ketone **5** with potassium *tert*-butoxide, molecular oxygen and triethyl phosphite.[68] Treatment of ketone **5** with potassium hydroxide and 2-iodosobenzoic acid or iodosobenzene diacetate[69] led to unidentifiable products, as did attempted oxidation of **5** with *N*-

chlorosuccinimide. [70] Our attempts to oxidize the enoxytriethylsilane derivative **62** (or trimethyl-, or *tert*-butyldimethylsilyl analogs) with *m*-chloroperbenzoic acid (*m*-CPBA),[71] peracetic acid buffered with sodium carbonate, dimethyldioxirane or osmium tetroxide also did not generate the desired α-siloxyketone. We finally discovered that addition of a CH_2Cl_2 solution of crude enoxytriethylsilane **62** to a solution of iodosobenzene and boron trifluoride etherate in methanol at −78 °C and then allowing the temperature to rise to 0 °C[72] produced α-methoxy ketone **63** in useful yield. Although attempted purification of this product on silica gel led to its decomposition, a singlet at δ 3.4 ppm in the ^{1}H NMR spectrum of this crude product left little doubt that a methoxy group had been incorporated. When crude **63** was treated with KHMDS at −78 °C in THF, and the resulting enolate was quenched with 2-[*N*,*N*-bis (trifluoromethylsulfonyl)amino-5-chloropyridine (Comins' reagent),[73] β-methoxy triflate **64** was formed in 61% overall yield from ketone **5**.[74]

To our initial surprise, reaction of **64** with 2–bromoaniline under an atmosphere of carbon monoxide and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in DMF at 80 ° C gave rise to none of the desired anilide, but instead provided α-methoxy enone **65** in 58% (equation 6). This unusual oxidation, which we have shown to be general for enol triflates having alkoxy or thioalkoxy β-substituents, likely involves solvolysis of the β-methoxy vinyl triflate with loss of trifluoromethanesulfinic acid.[75]



(6)

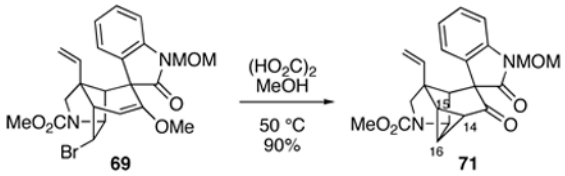
Fortunately, this side reaction could be prevented by carrying out the carbonylation at 80 °C using bis(diphenylphospine)ferrocenylpalladium(II) chloride as the catalyst in DMF-methanol (1:2) under 1 atmosphere of carbon monoxide (Scheme 10). Under these conditions, the crystalline vinylogous carbonate **66** was produced in 94% yield; the structure of this intermediate was confirmed by single-crystal X-ray analysis. Subsequent reaction of vinylogous carbonate **66** with the dimethylaluminum amide of 2-iodoaniline[62] in CH_2Cl_2 at 0 °C and slowly letting the reaction warm to room temperature over a period of 2 hours delivered iodoanilide **67** in 81% yield. It was essential that this reaction be initiated below room temperature, otherwise a significant amount of the vinylogous urea resulting from 1,4 addition of the aluminum amide to **67** was observed as a by-product. Finally protection of the secondary amide with a methoxymethyl (MOM) group provided β-methoxy α,β-unsaturated anilide **68** in 86% yield.

The intramolecular Heck reaction of β-methoxy unsaturated anilide **68** was investigated in detail. We quickly found that Heck cyclization of this intermediate could be accomplished under milder conditions than those required to cyclize the β-methylthio analog **58**. For example, reaction of β-methoxy precursor **68** with 20 mol% $Pd_2(dba)_3$ at 110 °C in the absence of phosphine ligands (conditions of Table 1, entry 9) provided pentacyclic products **69** and **70** in a 5:1 ratio and 60% yield.[30] As was observed in the sulfur series, these conditions favored the formation of the product having the unnatural configuration of the spirooxindole; these results stand in marked contrast to what was observed in the cyclization of the simpler congener having hydrogen as the β substituent (see Table 1).[76] Despite considerable effort, we were never able to find Heck cyclization conditions that provided useful amounts of the natural isomer **70**. However, the unnatural isomer **69** could be produced in high yields by carrying out the Heck cyclization of **68** in the presence of silver salts. Under optimal conditions, β-methoxy α,β-unsaturated anilide **68** was converted to Heck product **69** in yields ranging from 61–78% using 35 mol% $Pd_2(dba)_3$ and 2 equivalents of Ag_3PO_4 in refluxing THF. The high preference for

forming pentacyclic product **69** having the aryl fragment of the oxindole cis to the angular vinyl group presumably arises from coordination of palladium with this latter group (equation 3).[9d]

To prepare gelsemine from pentacyclic Heck product **69**, we needed to invert the configuration of the oxindole as well as fashion the tetrahydropyran ring. Although prospects for the former would have appeared poor at the outset of our investigations, our experience in inverting the spirocyclic oxindole of pentacyclic ketone **39** (Scheme 6), and the significant development of an epimerization strategy by Hart and co-workers,[19b] suggested that epimerization of the spirooxindole should be possible if the enol ether functionality of pentacyclic Heck product **69** could be converted to a C3 ketone or alcohol.

Another example of the unique reactivity engendered by the compact cage structure of gelsemine confronted us when we attempted to hydrolyze pentacyclic enol ether **69** with oxalic acid in MeOH–H_2O at 50 °C or 1 M HCl in acetone at 55 °C. These conditions provided the structurally remarkable hexacyclic cyclopropyl ketone **71** in high yield (equation 7). The structural assignment for **71** followed from its mass spectrum, where the parent peak at 394 amu corresponded to loss of HBr from the expected pentacyclic ketone. The ^{13}C NMR spectrum of cyclopropyl ketone **71** could be fully assigned by an HMQC experiment, showing a carbonyl carbon at 201.6 ppm and signals for C14, C15 and C16 at 24.1, 24.5 and 28.1 ppm, respectively. Of most significance, these cyclopropane carbons had diagnostic C–H coupling constants in the range of 166–180 Hz.[77]



(7)

Fortunately, cyclopropane formation could be avoided by carrying out the hydrolysis of enol ether **69** at room temperature using a 1:2 mixture of concentrated HCl and methanol (Scheme 11). In this way, tetracyclic ketone **72** was obtained in 98% yield, with its structure being confirmed by X-ray crystallographic analysis. In light of our earlier results, it was not surprising to find that product **72** lost HBr when heated at 50 °C in 1 M HCl in methanol, presumably via its enol, to form cyclopropyl ketone **71**.

We were now poised to investigate epimerization of the spirooxindole. Hart had shown that a pentacyclic ketone somewhat analogous to intermediate **72** having a carbonyl group at C3 and the unnatural oxindole stereochemistry undewent epimerization at C7 upon treatment with potassium cyanide.[19b] The mechanism proposed for this oxindole inversion involves initial formation of the C3 cyanohydrin, retro-aldolization to break the C3–C7 bond, rotation about the C6–C7 σ bond, and acylation to regenerate the C3–C7 bond. However in our case, treating ketone **72** with a catalytic amount of KCN in DMF at 50 °C resulted only in forming hexacyclic cyclopropyl ketone **71**. Attempts to form the cyanohydrin derivative of **72** under non-basic conditions by reaction with trimethylsilyl cyanide in the presence of zinc iodide[78] also led to hexacyclic product **71**, whereas attempted reaction of ketone **72** with diethylaluminum cyanide[79] (−30 °C → room temperature in THF) returned starting material.

Influenced by Hart's demonstration that the spirooxindole of a pentacyclic gelsemine precursor having a hydroxyl group at C3 could be inverted by a retro-aldol/aldol process,[19b] we examined the reduction of pentacyclic ketone **72** (Scheme 12). Reaction of this ketone with sodium borohydride and cerium(III) chloride heptahydrate (Luche conditions)[80] in methanol

at −10 °C gave a 3:1 ratio of readily separable alcohol epimers **73** and **74** in 85% combined yield. The selectivity of this transformation could be reversed using triisobutylaluminum as the reductant (−50 °C → room temperature in toluene).[81] These latter conditions provided a 6.5:1 mixture of alcohol epimers with equatorial epimer **74** predominating; after chromatography on silica gel, pentacyclic equatorial alcohol **74** was isolated in 71% yield.

We were once again at a stage to examine the critical epimerization of the spirooxindole fragment. When pentacyclic alcohol **73** or **74** was exposed to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 at room temperature,[19b] epimerization of the oxindole was not realized, but instead the two alcohol epimers were equilibrated (Scheme 12). However, when this mixture of alcohol epimers was heated with DBU at 110 °C in toluene for 4 h, hexacyclic furan **75** was isolated in 57% yield. No trace of the corresponding product having an epimeric oxindole fragment was seen. The stereostructure of **75** followed unambiguously from diagnostic NOE's between the methine hydrogens at C5 and C9. Epimerization of the oxindole, presumably by a retro-aldol fragmentation/aldol condensation sequence, obviously had taken place prior to cyclization of the axial alcohol epimer to form **75**. Why **73** does not undergo similar intramolecular etherification to form the spirooxindole epimer of **75** is less clear. Perhaps the cyclohexyl ring of **73** adopts a boat conformation to minimize steric interaction between the aromatic ring of the oxindole and the neighboring ethenyl group.[82] If so, the C3 hydroxyl group would no longer be positioned appropriately to displace the bromide.

The results summarized in Scheme 12 demonstrated that the nitrile needed to be introduced at C16 prior to attempting epimerization of the spirooxindole. We initially explored this possibility with intermediate **73** after first masking the axial alcohol as an ethoxyethyl ether (Scheme 13). Reaction of this product, **76**, with NaCN in dimethylsulfoxide at 150 °C gave rise to hexacyclic aziridine **77** in 80% yield. Conversion of this product to the corresponding methyl aziridinium ion, and reaction of this salt with NaCN at 90 °C produced hexacyclic furan **78** in high yield. Evidently the methyl aziridinium ion reacts more rapidly with the proximal oxygen of the axial acetal substituent than with external cyanide. This result directed us to the ultimately successful solution: employ equatorial alcohol epimer **74** to introduce C19.

This final sequence began with protection of the equatorial hydroxyl group of pentacyclic intermediate **74** by reaction with pyridinium **p**-toluenesulfonate and ethyl vinyl ether in CH_2Cl_2 to give **79** (Scheme 14). Reaction of this product with NaCN in the usual way provided aziridine **80** in nearly quantitative yield. Activation of **80** by reaction with methyl trifluoromethanesulfonate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) and opening the resulting methyl aziridinium ion with NaCN delivered nitrile **81** in 85% overall yield from hexacyclic aziridine **80**. When the aziridine was activated in the absence of DBMP, the 1-ethoxyethyl group was cleaved prematurely giving hexacyclic tetrahydrofuran **78** as the major product. After removing the 1-ethoxyethyl group of acetal **81** under standard acidic conditions, pentacyclic nitrile **82** was isolated in 71% overall yield from equatorial alcohol **74**.

Three critical conversions remained in order to elaborate hydroxy nitrile **82** to gelsemine: epimerization of the spirooxindole stereocenter C7, epimerization of the C3 alcohol, and intramolecular condensation of the C3 axial alcohol with the endo cyanide. To our delight, we quickly found that all three conversions could be realized by simply heating hydroxy nitrile **82** with DBU in toluene at 110 °C (Scheme 14). After silica gel chromatography, hexacyclic lactone **83** was isolated in 80% yield. A likely mechanism for this multi-faceted conversion is suggested in Scheme 15. Retro-aldol cleavage of **82** would generate oxindole enolate **84**. Rotation about the C6–C7 σ bond and re-aldolization would form spirooxindole epimer **85**, whereas alcohol epimer **86** would be produced by addition of the oxindole enolate to the other prochiral face of the aldehyde. Finally, addition of the axial hydroxyl group of intermediate

86 to the proximal nitrile would generate cyclic imidate **87**. Hydrolysis of this product upon purification on silica gel would give the observed product **83**. Although intermediate **86** was not detected, its equatorial epimer **85** could be isolated when the reaction was stopped prior to completion.

The conversion of hexacyclic lactone **83** to gelsemine (**1**) was straightforward (Scheme 16). The methoxymethyl group of **83** was first discharged by reaction with concentrated HCl in ethylene glycol dimethyl ether (DME) at 55 °C to give the corresponding *N*-hydroxymethyl oxindole; exposure of this intermediate to *N*,*N*-diisopropylethylamine in methanol at 55 °C furnished oxindole lactone **88** in 90% yield. Reduction of this intermediate with excess diisobutylaluminum hydride generated a mixture of lactols **89**, which upon reaction with triethylsilane in trifluoroacetic acid[83] produced (±)–gelsemine (**1**) in 65% yield from hexacyclic lactone **88**. The ^{1}H and ^{13}C NMR and IR spectra, and mass spectral fragmentation patterns of **1** were identical to those of an authentic sample of natural gelsemine.

Conclusion

Structurally unique natural products have long served to benchmark the existing tools of organic synthesis and stimulate the development of new reagents, reactions and synthetic strategies. As gelsemine has no commercial or medicinal value, it was the opportunity to discover and develop new synthetic chemistry that led us to tackle its total synthesis. Discoveries of new chemistry and new modes of reactivity made during our studies, and those of other laboratories working in the area, have broad implications for organic chemistry that transcend the accomplishment of a gelsemine total synthesis.[3f]

The extraordinary ability of intramolecular Heck reactions to construct highly congested quaternary carbon centers is a discovery of fundamental importance made during our efforts in the gelsemine area. At the time we first reported in 1988 that palladium-catalyzed insertions could succeed even in the face of numerous developing syn-pentane (1,3-diaxial) interactions,[9c] Heck reactions were rarely used for ring formation, and never as the key strategic step in the synthesis of complex organic molecules. Today, intramolecular Heck reactions are established as one of the synthetic chemist's most powerful tools for forming C-C bonds in complex, polyfunctional molecules.[25]

This research program also uncovered unique, unexpected reactivity associated with the enforced functional-group proximity engendered by the cage-like gelsemine ring system. Notable examples are: (1) the formation of aziridines from the reaction of *N*-methoxycarbonyl-β-bromoethylamines with cyanide by formal front-side displacement, (2) the unprecedented rearrangement of an alkyl iron intermediate,[9e] (3) the acid-promoted cyclizations of γ-bromoketones to cyclopropyl ketones, and (4) the base-promoted reaction cascade summarized in Scheme 15. Our studies in the gelsemine area revealed also the thermal instability of β-alkoxy enol triflates, providing a caveat to their use in transition metal catalyzed chemistry and foreshadowing our development of a new synthesis of α-thioalkoxy enones.[75] As summarized in some detail in the accompanying paper,[24] our gelsemine studies also provided greater understanding of the scope and limitations of aza-Cope–Mannich transformations.[24]

As for our total synthesis of (±)-gelsemine (**1**), it was accomplished in 1.1% overall yield from 3-methylanisole by the way of 26 isolated intermediates.[84] It is among the most efficient total syntheses of racemic gelsemine reported to date,[85,86] although it is longer than the Speckamp–Hiemstra synthesis, which proceeded in 23 steps from sorbic acid.[18] Despite extensive synthetic work in the gelsemine area over nearly two decades, a short synthesis of gelsemine has yet to emerge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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29. Similar success in this Heck cyclization was observed when the amide protecting group was a benzyl or methoxymethyl group. The iodide analog of 10a cyclized with similar low stereoselectivity.

30. The C19 proton of the terminal vinyl group is observed at lower field in the ^{1}H NMR spectrum of the oxindole isomer that places the carbonyl group proximal to C19 than in its epimer. For example, for epimers **11a/11b** this signal is seen at 6.7 ppm, whereas it is seen at 6.2 ppm in isomers **12a/12b**.

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82. In product **73**, an NOE is observed between the cyclohexyl proton at C3, the vinyl proton at C19, and the aromatic proton at C9. These NOEs are consistent with the cyclohexyl ring of **73** existing in a twist boat conformation.
83. Kursanov DN, Parnes ZN, Loim NM. Synthesis 1974:633–651.
84. The yield of the largest scale reaction we conducted of each step was used in this calculation. For intramolecular Heck reaction of **68** an average yield of 69% was used as this reaction was only carried out on one scale.
85. The first step of our gelsemine synthesis is a Diels–Alder reaction of a 1,3-cyclohexadiene with methyl acrylate.[24] As chiral auxiliaries for acrylate dienophiles have been developed and much progress in asymmetric catalysis of Diels–Alder reactions has been recorded, it would appear likely that an enantioselective version of the opening moves of our gelsemine synthesis could be developed.[85]
86. For selected reviews of asymmetric Diels–Alder reactions, see: (a) Oh T, Reilly M. Org. Prep. Proced. Int 1994;26:129–158. (b) Kagan HB, Riant O. Chem. Rev 1992;92:1007–1019. (c) Corey EJ. Angew. Chem., Int. Ed 2002;41:1650–1667.For a review of the use of the Diels–Alder reaction in natural products total synthesis, see: (d) Nicolaou KC, Snyder SA, Montagnon T, Vassilikogiannakis G. Angew. Chem., Int. Ed 2002;41:1668–1698.

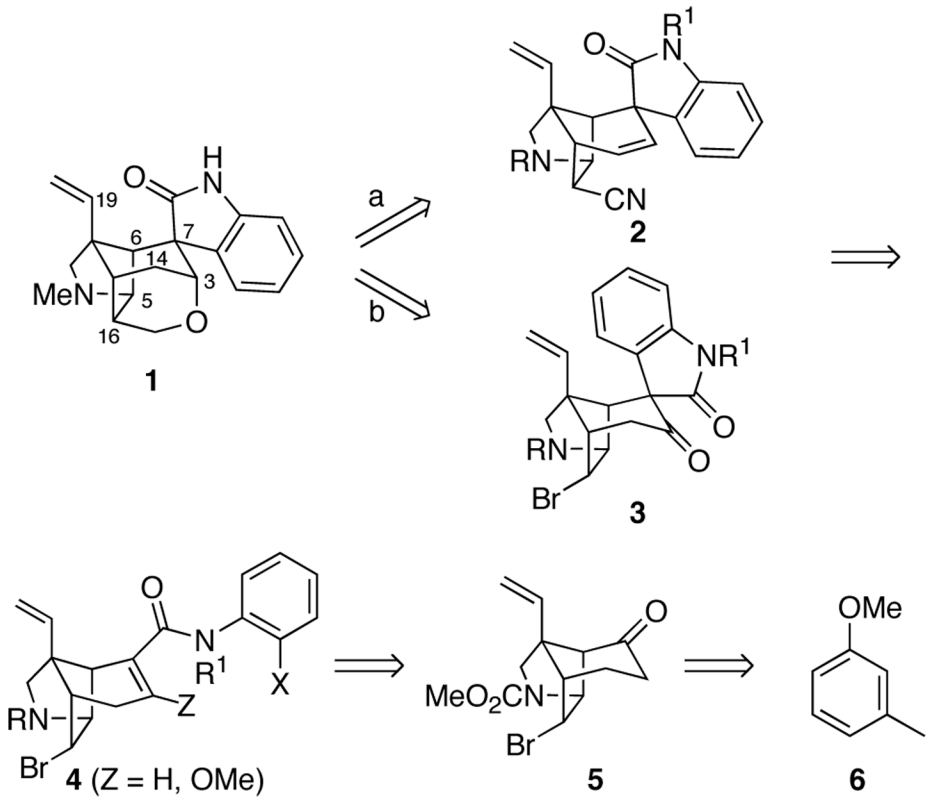


Figure 1.
Synthetic strategy.

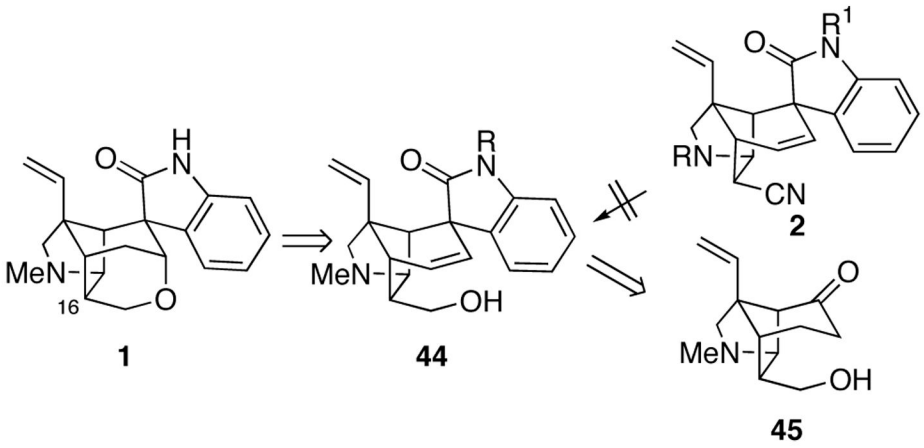


Figure 2.
Potential alternate strategy in which spirooxindole formation is accomplished after elaboration at C16.

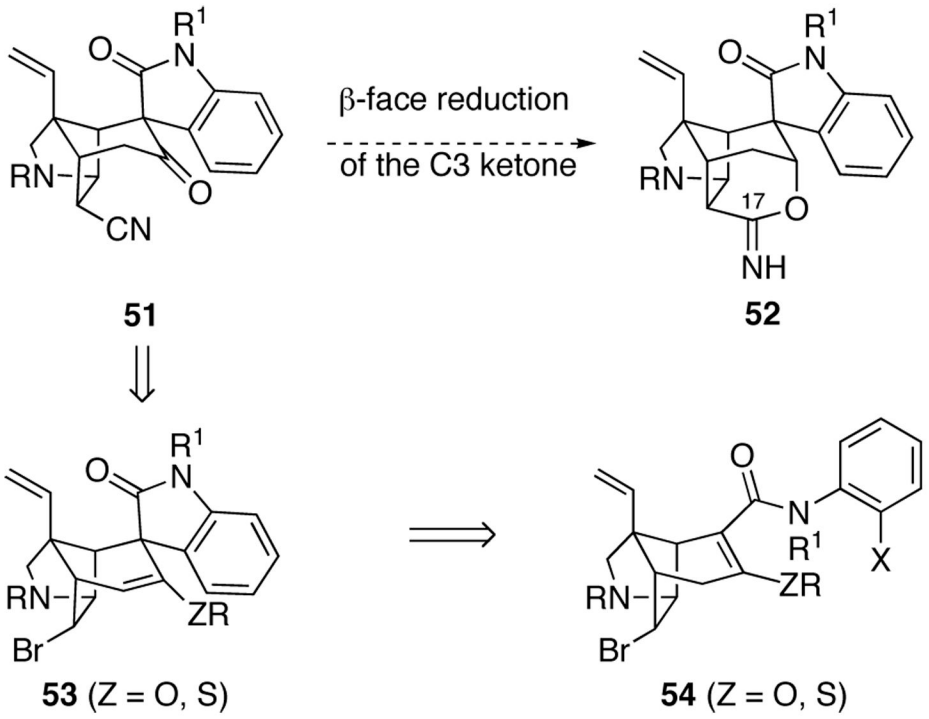
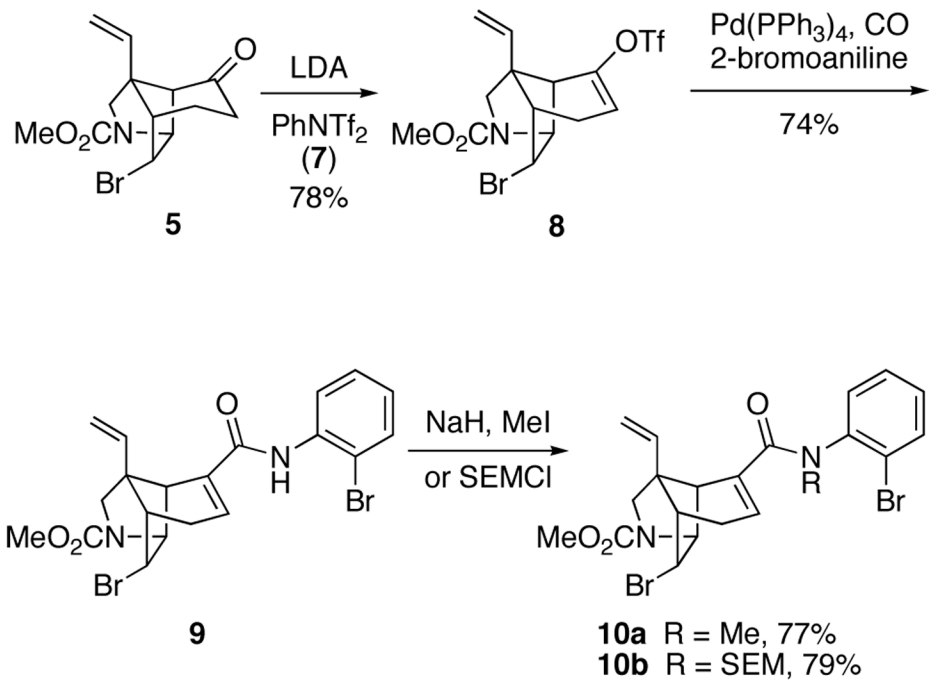
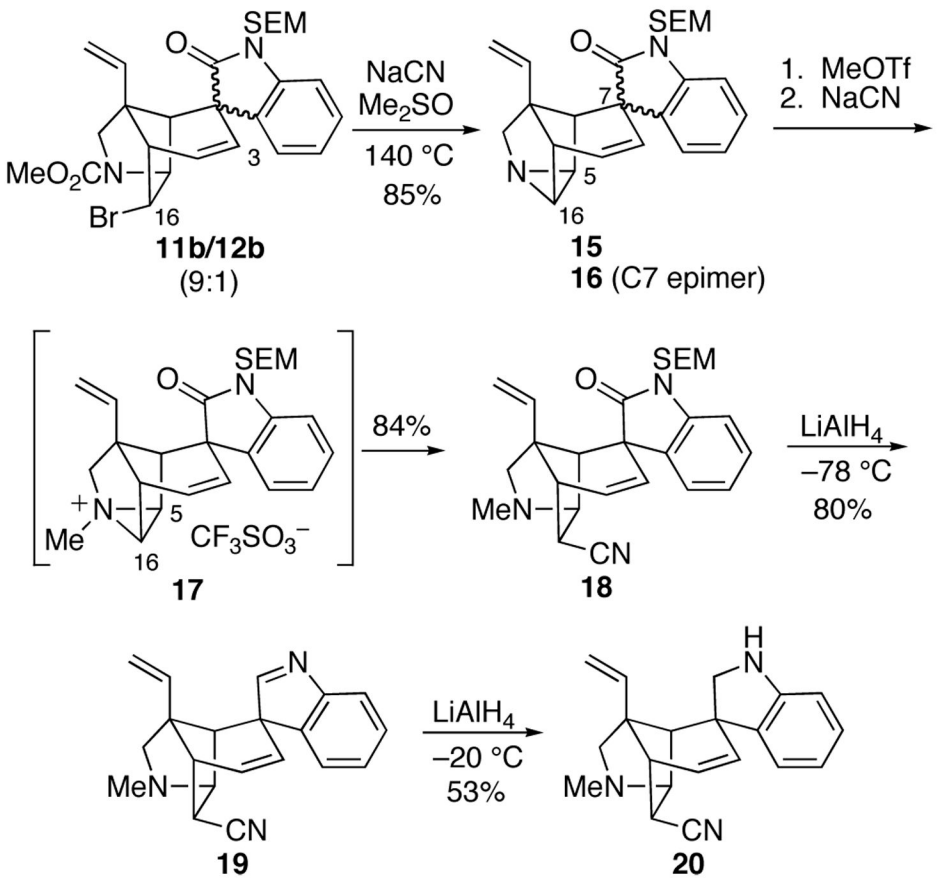


Figure 3.
Revised plan for elaborating the hydropyran ring.



Scheme 1.



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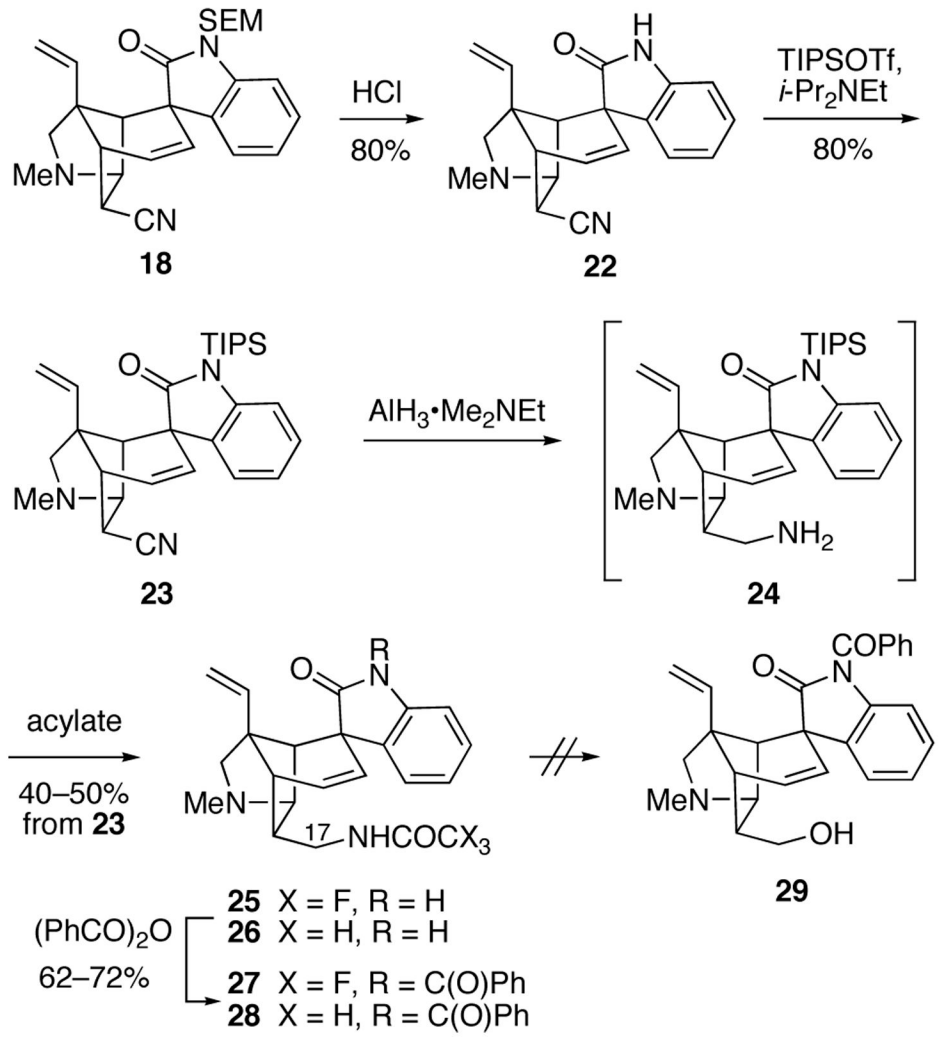

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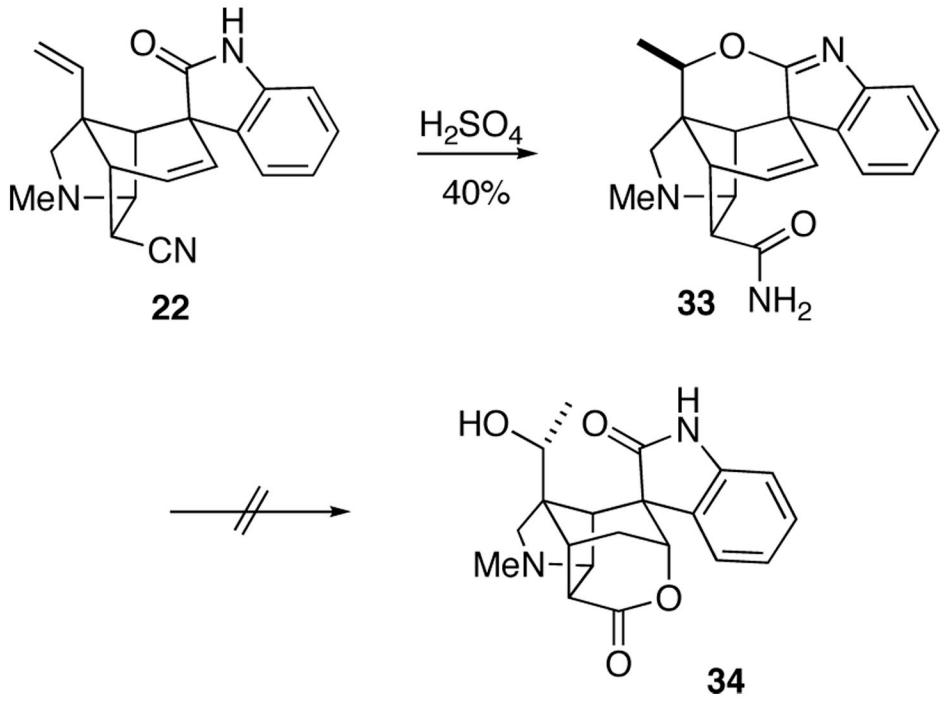

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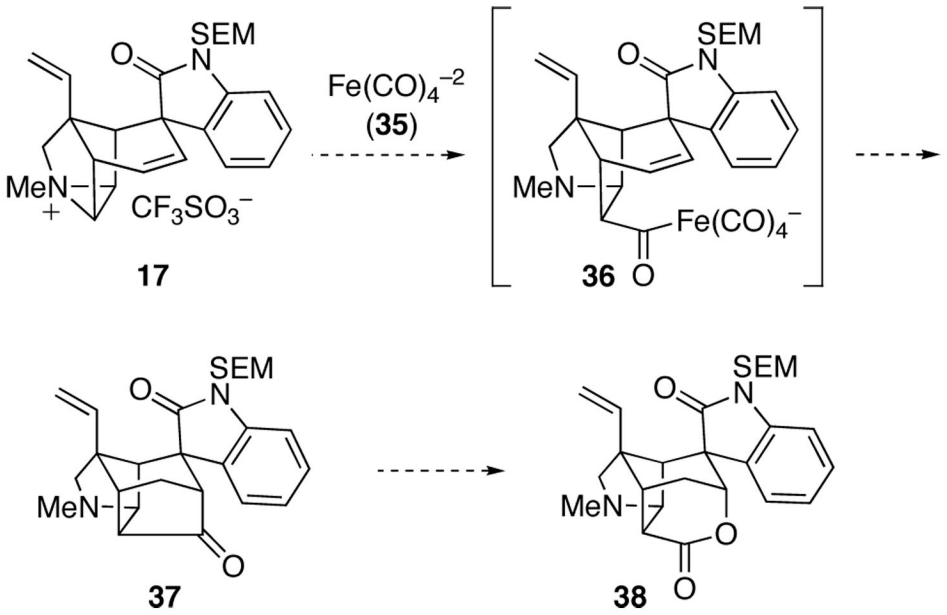

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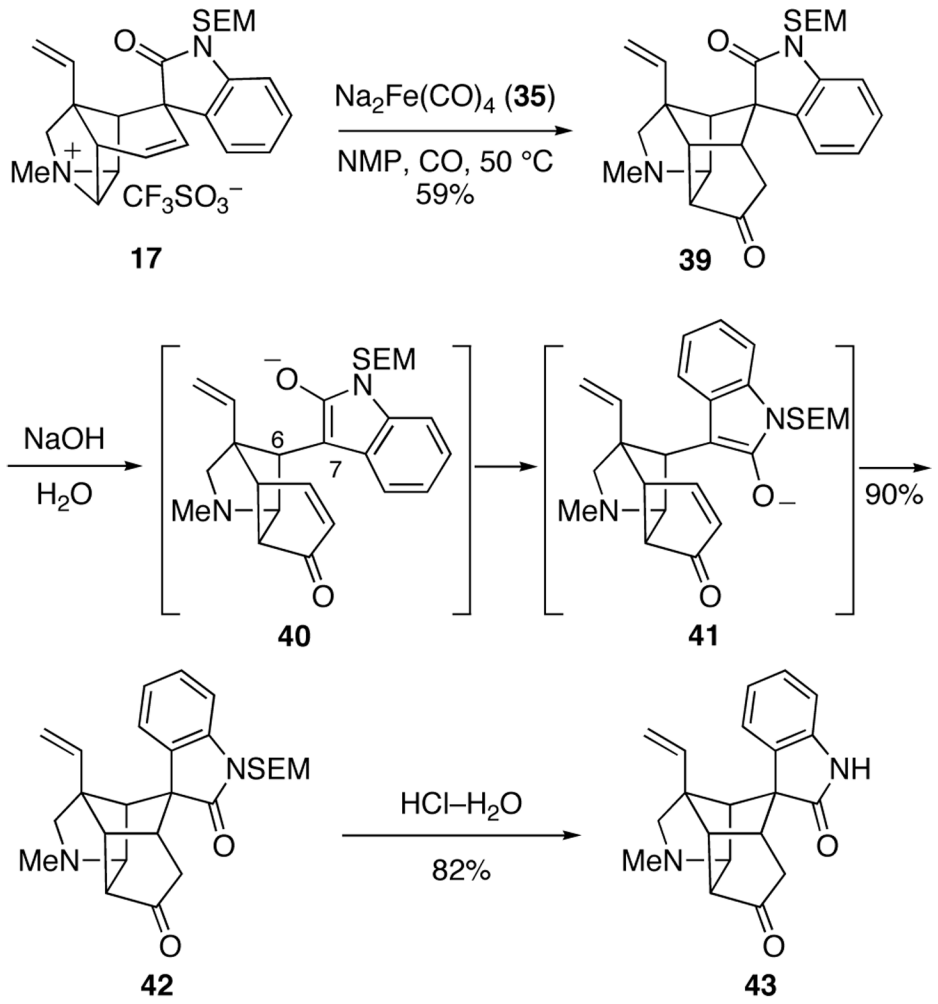

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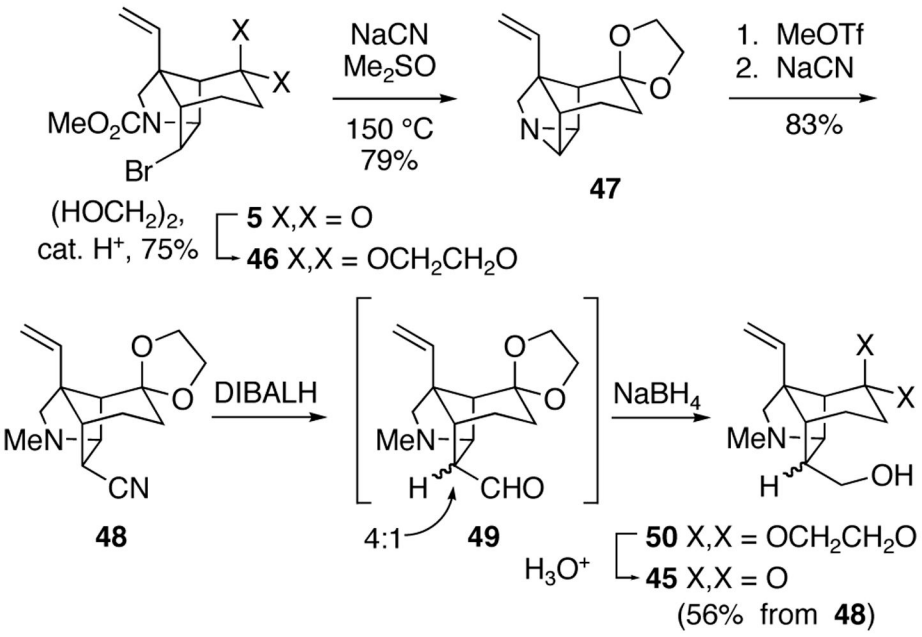

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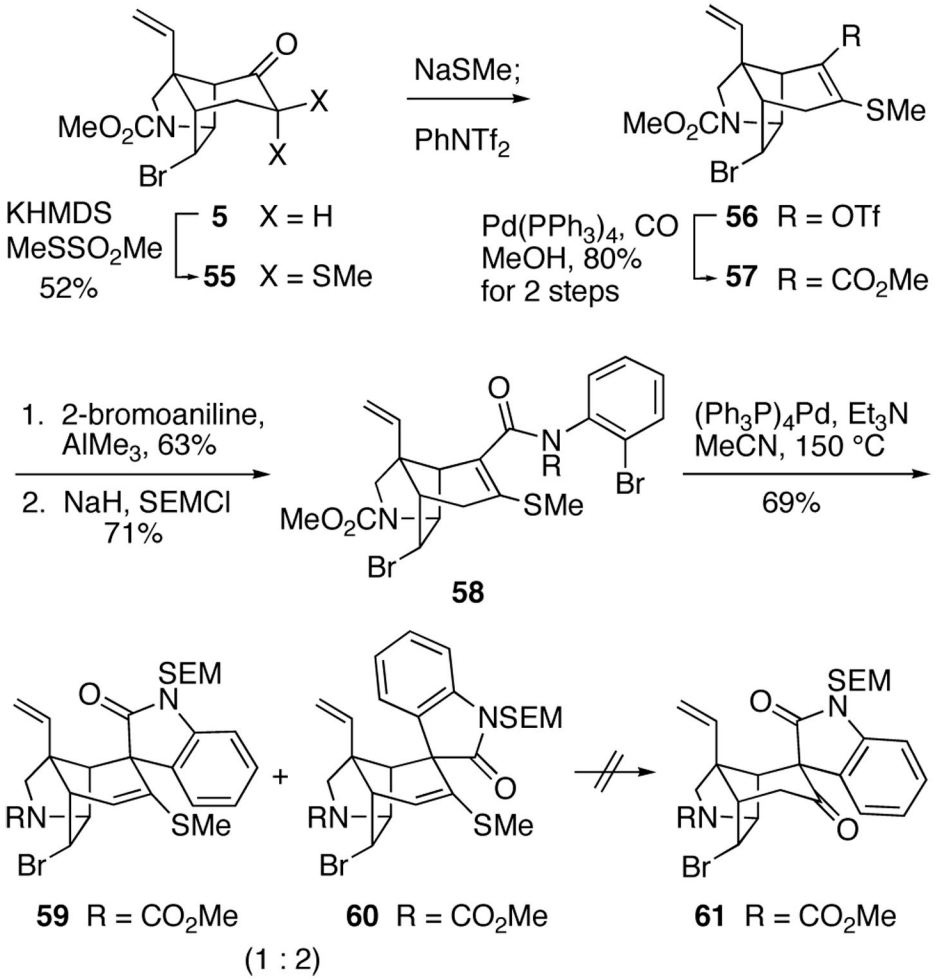

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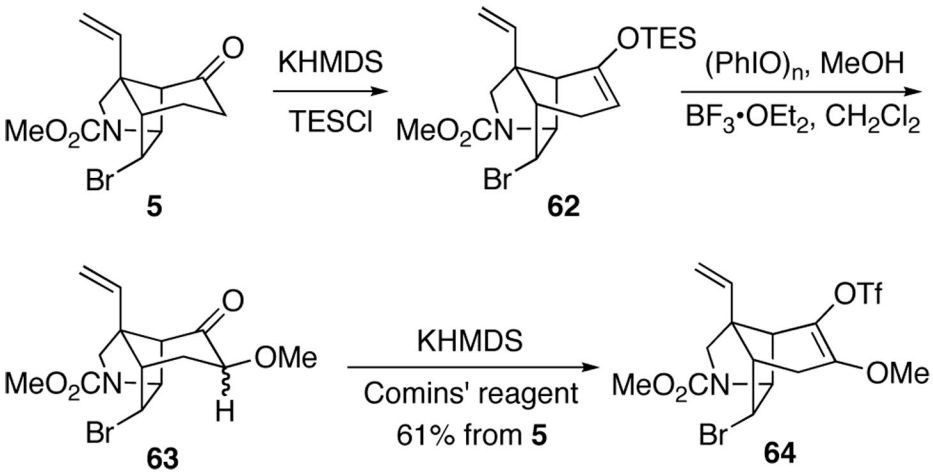

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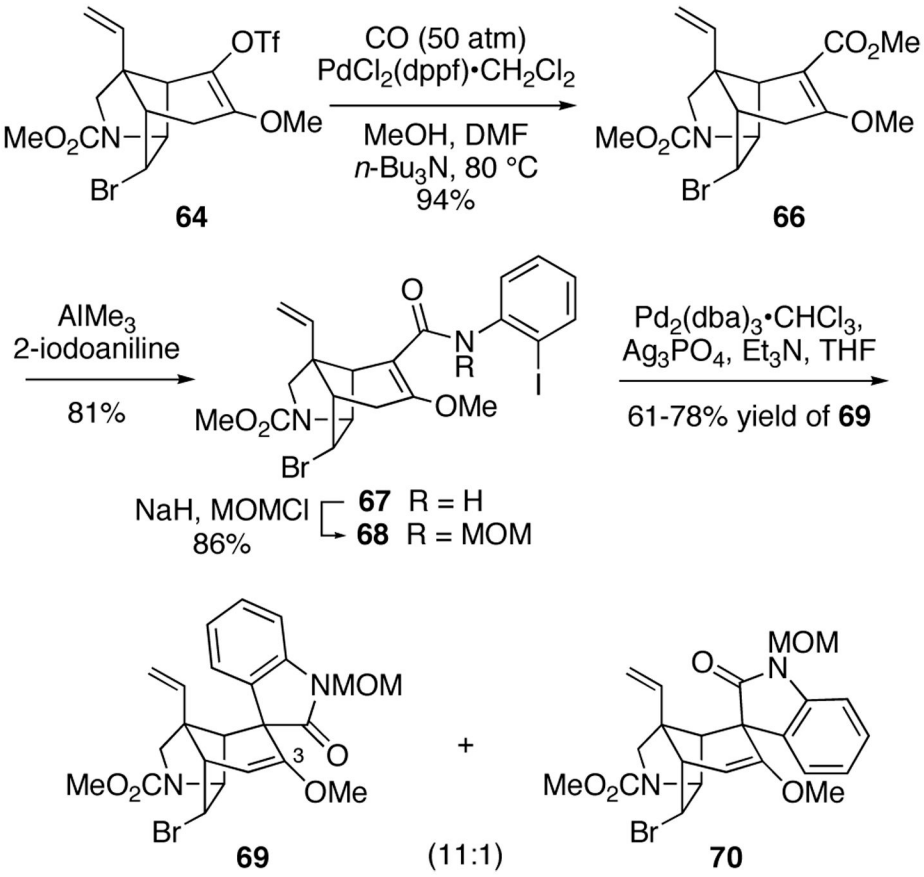

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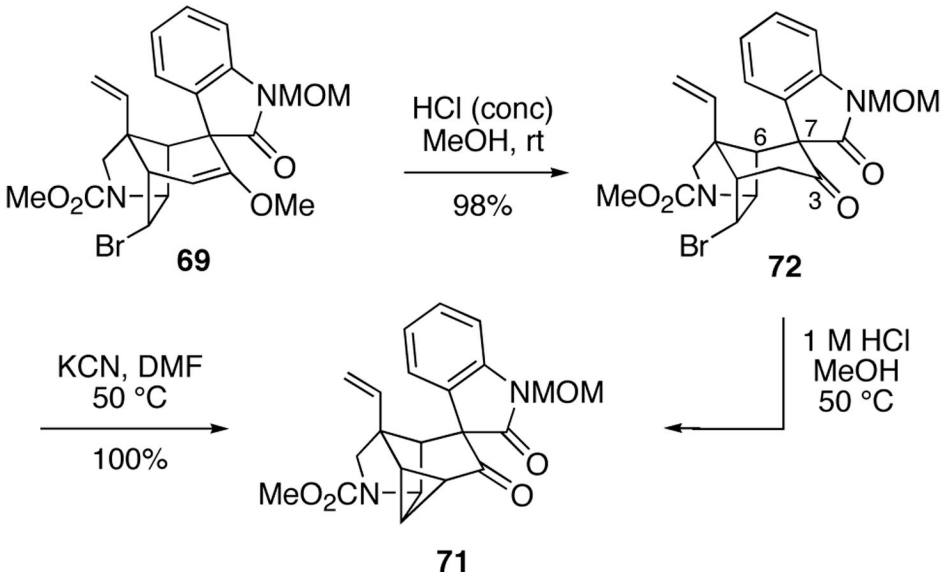
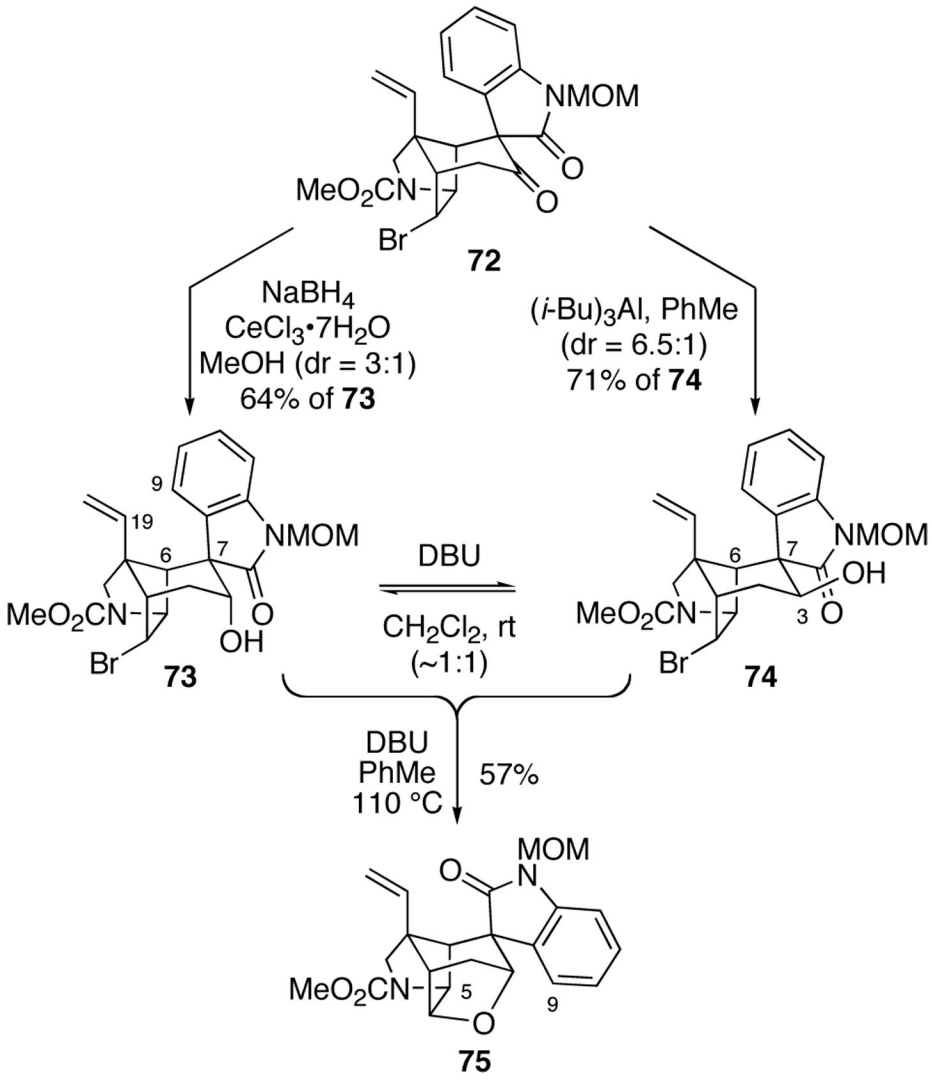


Scheme 11.



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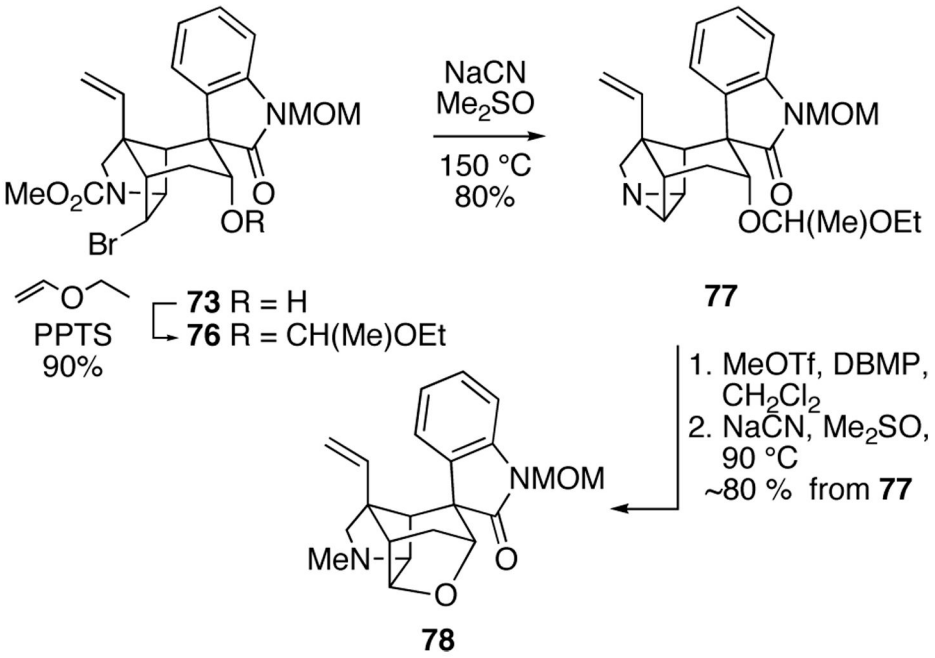
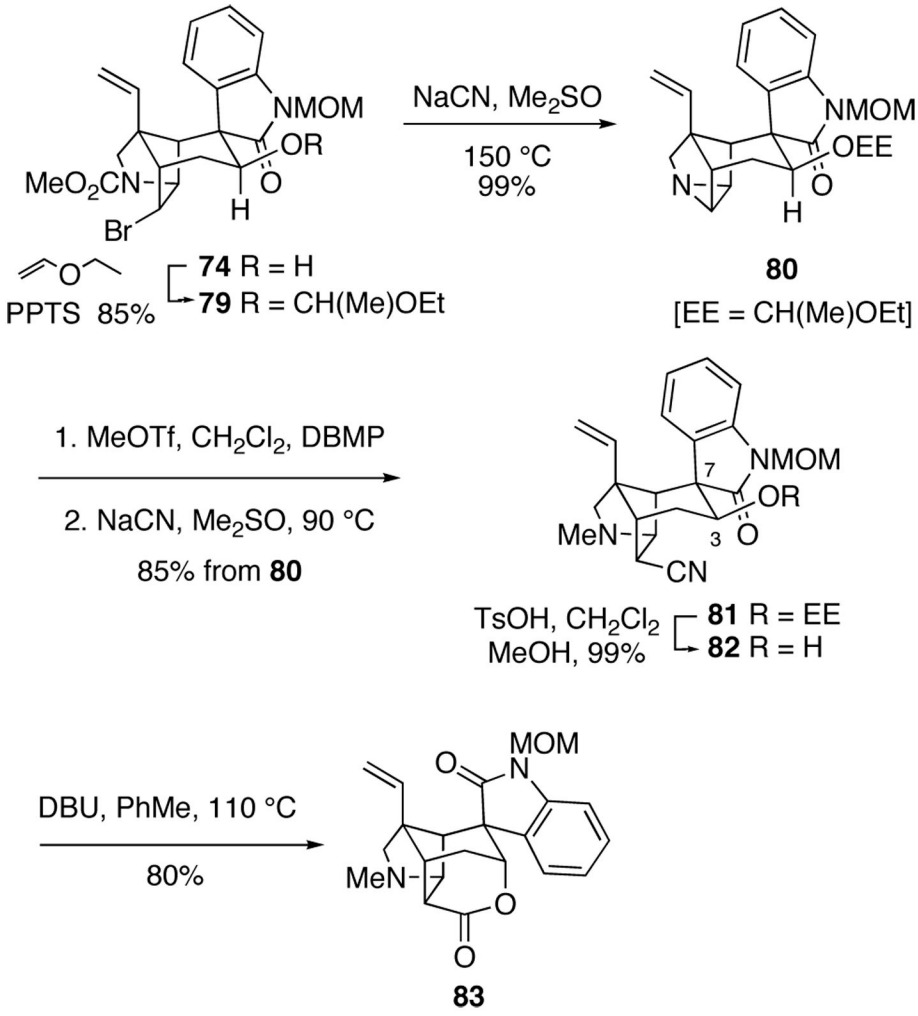


Scheme 13.



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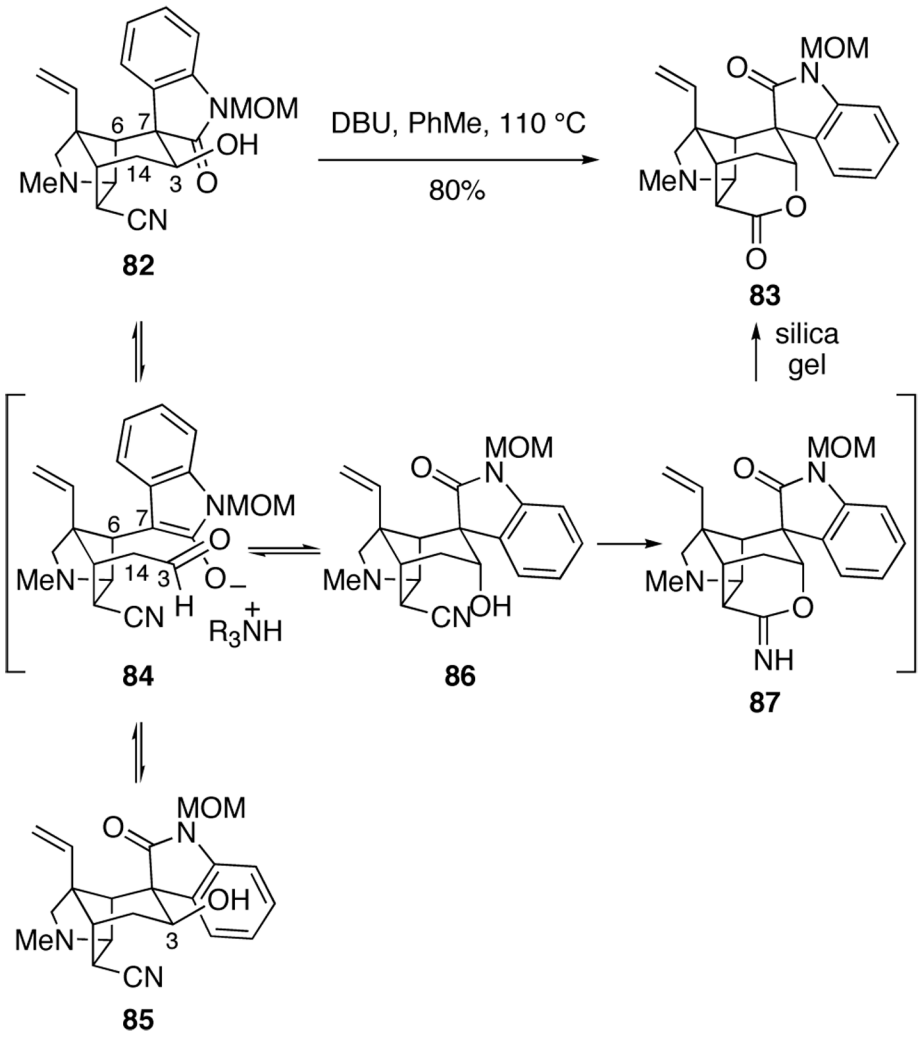

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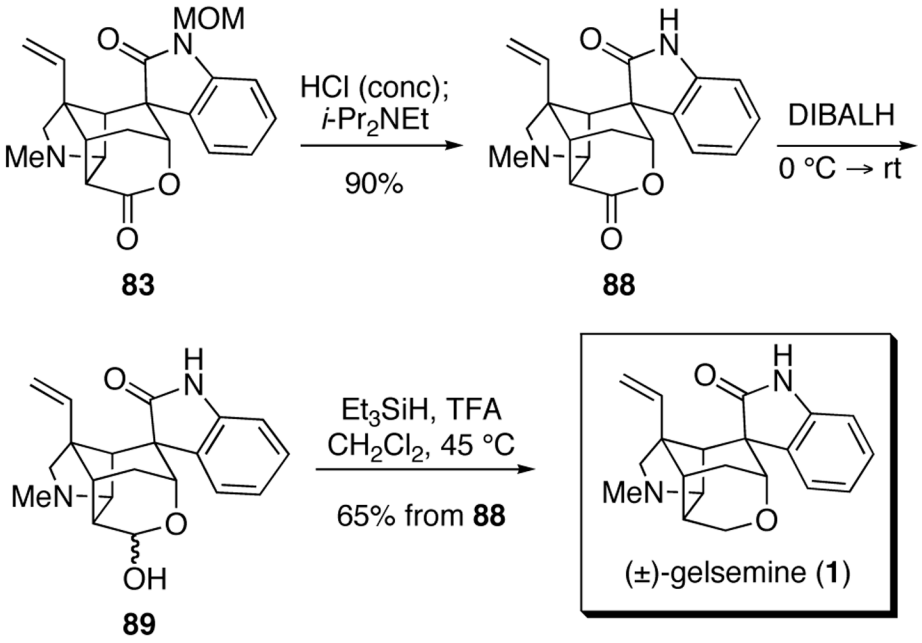

Scheme 16.

Table 1

Heck cyclization of **10** Using Different Palladium Catalysts

		Reaction Conditions					Oxindole	
entry	**substrate**	**catalyst**[a]	**Additive**[b]	**Solvent**	**T (°C)**	**t (h)**	**Yield, %**[c]	**11:12**[d]
1	**10a**	$Pd(Ph_3P)_4$	Et_3N	MeCN	82	18	81	66:34
2	**10b**	$Pd(Ph_3P)_4$	Et_3N	MeCN	82	15	66	60:40
3	**10b**	$Pd(Ph_3P)_4$	Et_3N	THF	66	24	20[f]	60:40
4	**10b**	Pd(dppe)[e]	Et_3N	THF	66	24	46[f]	55:45
5	**10b**	Pd(dppf)[e]	Et_3N	THF	66	36	(18)	50:50
6	**10b**	$Pd_2(dba)_3$	Et_3N	THF	66	24	75[f]	73:27
7	**10b**	$Pd_2(dba)_3$	Et_3N	PhMe	110	1	80–95[g]	89:11
8	**10b**	$Pd_2(dba)_3$	Ag_3PO_4	THF	66	36	77	3:97

[a] 10–20% was employed.

[b] 10–15 equiv of Et_3N or 2 equiv of Ag_3PO_4 (per equiv of **10**) was employed.

[c] Isolated yields of the isomer mixture, yields in parentheses are % conversion by capillary GC analysis (peak area % without calibration).

[d] Capillary GC or 500 MHz ^{1}H NMR analysis; in contrast to the methyl analog, isomers **11b** and **12b** could not be separated on silica gel.

[e] Prepared *in situ* from 1 equiv of $Pd_2(dba)_3$ and 2 equiv of the diphosphine.

[f] The majority of the remaining mass was recovered **10b**

[g] Multiple experiments conducted with 100–300 mg of **10b**.

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